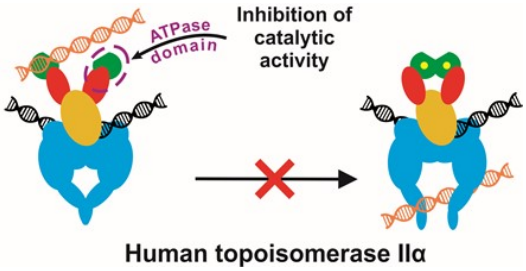
Advancing Type II DNA Topoisomerase Research through QM/MM Simulations and Development of Catalytic Inhibitors

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Human DNA topoisomerase IIα (htIIα) is one of the established anticancer targets due to its role in cell proliferation process. It catalyzes topological changes of the DNA molecule, essential for progression of transcription and translation, and its level is higher in rapidly dividing cells. There are several ways to tackle htIIα, and agents targeting it are divided into two groups. Among the established group of topo II poisons, some molecules are used in clinical practice, such as doxorubicin and etoposide. Due to the frequent occurrence of serious side effects, especially cardiotoxicity and induction of secondary tumors, as well as the observed resistance to topo II poisons, further drug development efforts were initiated, trying to take advantage of other inhibition paradigms available in the topo IIα catalytic cycle. This has led to the development of catalytic inhibitors of htIIα that offer new opportunities to revisit this established target and inhibit it via alternative inhibition mechanisms. Such molecules could, in principle, have an improved safety profile with comparable anticancer efficacy [1].

In our research, we are using available structural information about the htIIα ATPase domain to gain insight into the enzymatic mechanism of ATP hydrolysis and to design novel catalytic htIIα inhibitors that would target the ATP binding site [2]. With multiscale QM/MM calculations and a point mutation study, we investigated the catalytic mechanism of ATP hydrolysis and showed it favors the dissociative substrate-assisted mechanism, with Lys376 acting as a stabilizing residue [3]. Next, we used htIIα as a model target to validate a new virtual screening strategy that incorporates dynamic components of molecular recognition and expanded the known chemical space of flavonoid-based htIIα catalytic inhibitors [4]. Finally, we also discovered a class of substituted 4,5'-bithiazoles acting as ATP competitive htIIα catalytic inhibitors. These molecules arrested the cell in G1 phase, affected cell proliferation, and did not cause DNA double-strand breaks, thus displaying potential for further development to efficient and potentially safer cancer therapies that exploit an alternative topo II inhibition paradigm [5].



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