TITLE OF RESEARCH TOPIC: DYNAMICAL MODEL OF A TYPE II DNA TOPOISOMERASE BIOLOGICAL NANOMACHINE AND DEVELOPMENT OF CATALYTIC INHIBITORS FOR SAFER FUTURE CHEMOTERAPY

Summary:
The PhD student will study type II topoisomerases that regulate DNA topology and are targets of chemotherapeutic agents. In the first part, molecular simulations will be performed to gain deeper insight into the inner workings of these molecular motors and their catalytic cycle. In the second part, computational drug design tools will be used to design and optimize catalytic inhibitors of topoisomerase IIα that bind to the ATP binding site of their ATPase domain and are suitable for subsequent preclinical development. Exploration of an alternative, clinically unused topo II inhibition paradigm could potentially yield safer and comparably effective molecules for cancer therapies. For the experimental interpretation and validation of the computational results of both parts of the research, a PhD student will collaborate in a feedback loop with synthetic chemists and biochemists from various Slovenian and international research institutions such as FU Berlin, Germany, National Institute of Biology, Ljubljana, Faculty of Pharmacy, Ljubljana, and Inspiralis, UK.

Research techniques used:
The PhD student will primarily focus on the application of advanced computational chemistry techniques, such as all-atom molecular dynamics simulations, multiscale QM/MM approaches, and computational molecular design tools (e.g., molecular docking, pharmacophore models, dynophore models, water-based pharmacophores, etc.). The computationally intensive molecular simulations will be performed using the facilities of the Azman HPC Centre at the National Institute of Chemistry in Ljubljana, which has more than 6000 CPU /GPU units.

The reason why the topic is innovative:
1.Simulations of type II topoisomerases provide an understanding of their mechanisms of action at the atomic level.
2.Catalytic inhibition of topoisomerase IIα paves the way for a new generation of safer chemotherapies that have a better therapeutic profile than existing topo II drugs.

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