Universität Zürich[UZH]

IMCR INSTITUTE OF MOLECULAR CANCER RESEARCH

Master's Thesis Project

Biochemical and Biophysical Characterization of Small-Molecule Inhibitors Targeting DNA Repair

Institute of Molecular Cancer Research, University of Zurich

Background

DNA repair pathways ensure genome stability, which is crucial for cellular survival and the prevention of cancer. On the other hand, DNA repair enzymes are attractive targets to improve the efficacy of current cancer therapy regimens. Human FAN1 is a DNA nuclease involved in the processing of DNA interstrand crosslinks induced by platinum-based chemotherapy. Moreover, genetic evidence has implicated FAN1 as a major risk modifier of Huntington's disease, an incurable neurodegenerative disorder.

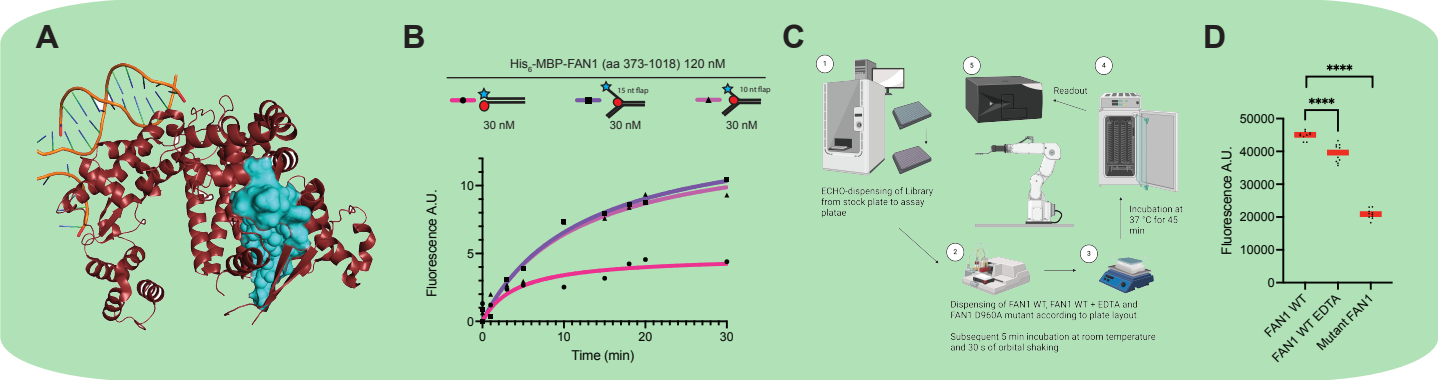

Figure 1: Working pipeline for the High Throughput Screen (HTS)
A Crystal structure of FAN1. The nuclease domain is colored in blue. **B** Established method to perform HTS. Three DNA substrates were engineered to release fluorescence upon catalytic digestion by FAN1. **C** HTS automation pipeline. **D** results from initial quality control experiment. FAN1 WT is able to cleave the substrate, leading to fluorescence release, while the catalytic mutant is not.

Project Outline

We are currently in the process of conducting high-throughput screens with chemical libraries to identify small molecule inhibitors of FAN1. The MSc thesis project entails detailed characterization of hit molecules resulting from the screening. Results from this work will help establish the potential of FAN1 inhibitors as research tools and as a therapeutic strategy for the treatment of human pathologies.

Techniques

The MSc student will learn an array of biochemical, biophysical and cellular method designed to determine the binding affinity, selectivity, and efficacy of small-molecules targeting FAN1. This project also involves *in silico* computational tools to complement the results of *in vitro* experiments and to suggest ways to improve the chemistry of the lead molecules.

Qualifications

The ideal candidate has a strong interest in molecular cancer biology, DNA repair mechanisms, and therapeutic innovation. A high level of motivation and responsability for this project is essen tial. While direct and daily supervision is provided by a third-year PhD student, the progress of the project is closely monitored by Prof. Sartori. The MSc student should be prepared to work with increasing independence and demonstrate effective communication skills. Practical experience in molecular biology and protein biochemistry approaches is definitively a plus.

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