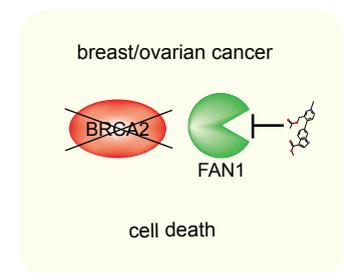
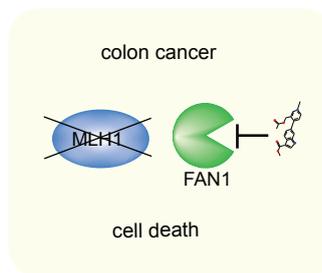
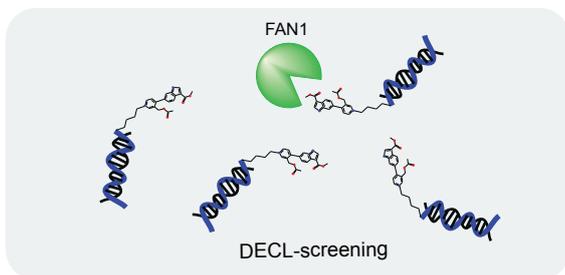
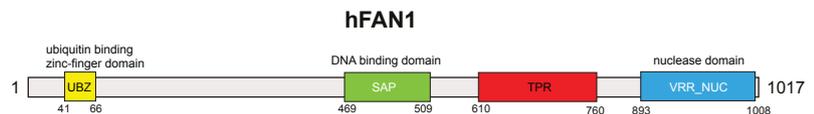
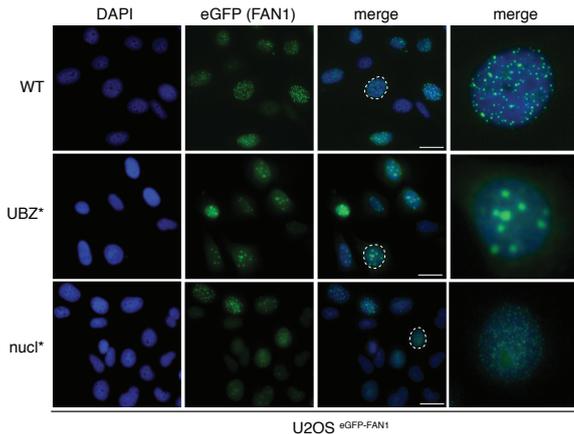


MASTER THESIS

Exploring the DNA repair nuclease FAN1 as a novel anti-cancer target

Sartori Lab, Irchel Campus, University of Zurich



Background: DNA repair is essential for maintaining genome integrity and cancer avoidance. On the other hand, defects associated with DNA repair pathways are also ideal molecular targets for therapeutic interventions in the fight against cancer. Human FAN1 is a multi-functional DNA repair nuclease involved in diverse genome maintenance mechanisms. FAN1 variants have been associated with cancer predisposition. FAN1 was originally identified by its direct interaction with MLH1, a protein implicated in the repair of base pair mismatches that arise during DNA replication. Importantly, MLH1 deficiency is a common feature of Lynch-syndrome, formerly known as hereditary non-polyposis colorectal cancer (HNPCC).

Our recent work implicates a crucial role for FAN1-MLH1 interaction in preserving genome integrity. Specifically, our data suggests that the physical association of MLH1 with FAN1 is required to guide FAN1 nuclease activity. We therefore speculate that MLH1 deficiency may result in inappropriate FAN1 hyperactivation, potentially driving genomic instability and tumorigenesis. Moreover, we have recently reported that FAN1 becomes essential for the survival of cells lacking the BRCA2 tumor suppressor gene. Based on these findings, we propose that FAN1 may represent a therapeutic target to selectively eliminate MLH1- and BRCA2-mutated tumors.

Project outline and techniques: By performing high-throughput screening of DNA-encoded chemical libraries in collaboration with Prof. Dario Neri (Department of Chemistry and Applied Biosciences, ETH Zurich) we have identified potential small-molecules inhibitors (SMI) of FAN1. You will extend from these findings and validate selected SMIs employing in vitro biochemistry and a variety of cell-based techniques combined with clonogenic survival assays. Furthermore, you will be engaged in the characterization of novel signalling networks responsible for controlling FAN1 activity.

Environment: You will be part of a young and dynamic international research group embedded in the interactive and supportive environment of the Institute of Molecular Cancer Research. You will be able to participate in weekly group meetings, progress report seminars and literature sessions and enjoy a comprehensive scientific education in a vibrant research environment.

Qualifications: You should have a genuine interest in molecular cancer research and a high level of motivation. While you will be directly supervised by a senior scientist, you should be comfortable and confident when working in the lab and strive to become rather independent. In addition, you should have good communication skills.

Applications: Interested candidates should send their CV and a brief motivational letter to : sartori@imcr.uzh.ch

Starting date: Negotiable

