PhD project proposal:

Elucidating SMC functions in chromosome segregation and in DNA immunity

SMC (Structural Maintenance of Chromosomes) complexes are ATP-powered DNA motors that organize chromosomal DNA by forming large loops through a process called loop extrusion. In eukaryotes, three types of SMC complexes—cohesin, condensin, and Smc5/6—facilitate chromosome segregation during mitosis and meiosis. In most bacteria, a single SMC complex serves this role. Additionally, some SMC complexes have functions in DNA defense or are exclusively dedicated to this task. For instance, the human Smc5/6 complex is vital for both chromosome segregation and antiviral defense, whereas the SMC Wadjet complex in bacteria and archaea is dedicated to anti-plasmid defense.

This PhD project aims to uncover how SMC complexes support maintenance of chromosomal DNA on the one hand and restriction of invasive DNA on the other hand, and how they recognize nonself-DNA to avoid auto-immune reactions. We will generate chimeric SMC proteins with the goal to generate SMC complexes that can support both activities (similar to Smc5/6 in humans) or to interconvert an anti-plasmid SMC complex to a chromosome organizing SMC complex and vice versa.

We will utilize laboratory strains of *E. coli* as genetically tractable experimental system studying the endogenous SMC complex (called MukBEF) as well as Wadjet complexes from related strains. We will employ cloning strategies (2) to generate chimeric complexes and test functions both *in vivo* by plasmid loss assays (3) and *in vitro* using purified preparations of proteins by plasmid DNA cleavage assays (3, 4).

This project will advance our understanding of SMC complexes' dual roles in chromosome segregation and DNA immunity, providing insights into their mechanisms and potential applications in biotechnology and medicine.

References

(1) https://doi.org/10.1042/BST20221395
(2) https://www.biorxiv.org/content/10.1101/2024.06.17.599295v1
(2) https://doi.org/10.1016/j.molcel.2022.11.015
(3) https://doi.org/10.1016/j.molcel.2024.01.009