Structural biology of genome guarding: Making sure we never loose a chromosome

The Sekulic group is interested in understanding molecular mechanisms that are assuring genomic stability during cell division. During mitosis DNA is duplicated, resulting in two identical chromosomes. These are held together at a special part of the chromosome, called the centromere. On the top of the centromere, a protein megacomplex – the kinetochore – forms to connect duplicated chromosomes to microtubules that emanate from opposite poles of the dividing cell. Only when all the chromosomes attach correctly to microtubules, are the sister chromatids separated. These then travel to the poles of the dividing cell. Making sure that each chromosome is attached correctly is very challenging – it can be likened to making sure that 23 pairs of kindergarteners are all holding hands whilst being dragged in opposite directions. The accuracy with which cells control this elaborate process, which happens at least a billion times a day in our organism, is intriguing. Mistakes resulting in inaccurate chromosome segregation are either detrimental, or typical of cancer cells. Furthermore, in cases of unequal division in germ cells, the results are congenital genomic disorders, such as Down syndrome. Thus, a better understanding of the molecular mechanisms that guard the genome during these numerous cell divisions also means a better understanding of the basics of genetics and heredity itself. Also, further research in this field holds promise to initiate new therapies for health conditions connected to erroneous cell divisions (cancer and congenital polysomies).

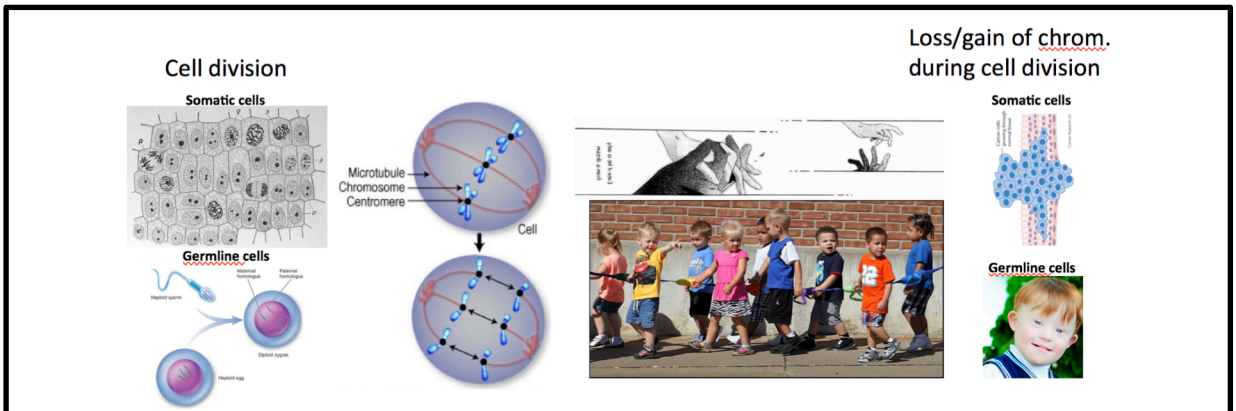

Photo adapted from web resources by Nikolina Sekulic

Our research focuses on centromeres. We want to understand 1) What are the structural determinants of centromere formation and maintenance? 2) How does centromere recruits major effector proteins in mitosis? and 3) What is the molecular basis for the activation of central mitotic kinase, Aurora B?

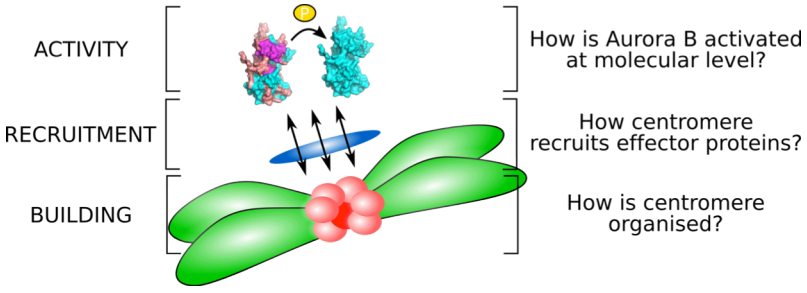

Photo credit: Nikolina Sekulic

Different levels of complexity that are studied to get the insight into mechanisms of maintenance of genomic stability during cell division.

MASTER – Project: COMPUTATIONAL PROTEIN MODELING

A master thesis project is available at The University of Oslo. The project is a collaboration between the Sekulic lab at NCMM (Norwegian Center for Molecular Medicine) (http://www.med.uio.no/ncmm/english/groups/sekulic-group/index.html) and the Cascella group at UiO The Department of Chemistry (https://www.mn.uio.no/kjemi/english/people/aca/michelec/). The project is at the interface of chemistry, biology, physics and computational techniques. The major goal is computational modelling of an enzyme, Aurora B, that is a cancer drug target. The student is expected to explore molecular dynamics of the enzyme (protein kinase) in phosphorylated (active) and unphosphorylated (inactive) form. We use hydrogen-deuterium exchange to experimentally measure dynamic differences between the two different forms of the enzyme. The knowledge gained from computational modeling, together with the collected experimental data will contribute to understanding process of enzyme activation and it will serve as basis for generation of new more potent cancer therapies. The project is expected to last for 6 – 12 months. If you are interested please consider applying for Erasmus+ program (http://www.unizg.hr/nc/vijest/article/1-krug-natjecaja-za-mobilnost-studenata-erasmus-strucna-praksa-akademska-godina-201819/) and contact Nikolina Sekulic (Nikolina.sekulic@ncmm.uio.no).

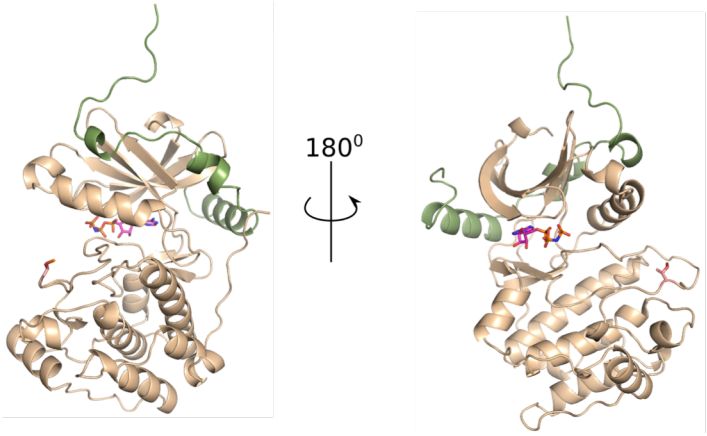

Photo credit: Dario Segura

Understanding the role of flexibility in the enzyme activity might be exploited in engineering effective drugs for specific cancer targeted therapy.

Literature:

1. Zaytsev AV, Segura-Peña D, Godzi M, Calderon A, Ballister ER, Stamatov R, Mayo AM, Peterson L, Black BE, Ataullakhanov FI, Lampson MA, Grishchuk EL. Bistability of a coupled Aurora B kinase-phosphatase system in cell division. Elife. 2016 Jan 14;5:e10644. doi: 10.7554/eLife.10644.

The University of Oslo is Norway's oldest and highest ranked educational and research institution, with 28 000 students and 7000 employees. With its broad range of academic disciplines and internationally recognised research communities, UiO is an important contributor to society.

Centre for Molecular Medicine Norway (NCMM) was established in 2008 and is the Norwegian node in the Nordic EMBL Partnership for Molecular Medicine. NCMM is a joint venture between the University of Oslo, Health Region South-East and the Research Council of Norway. From 2017 NCMM is merged with the Biotechnology Centre of Oslo and now has altogether 11 research groups. The overall objective of NCMM is to conduct cutting edge research in molecular medicine and biotechnology as well as facilitate translation of discoveries in basic medical research into clinical practice.