Master level project proposal
Direct supervisor: Ann-Sofie Jemth, PhD
Main supervisors: Petra Marttila, PhD student and Dimitrios Chioureas, PhD
Place: Helleday Laboratory, SciLifeLab, OnkPat, KI
Timing: 2022/2023; duration at least 6 months
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Investigation of interplay between altered cellular metabolism and genome integrity in cancer

Metabolic reprogramming is a hallmark of cancer which has been therapeutically exploited since the 1950s. The use of antimetabolites targeting cancer metabolism has been shown to effectively kill cancer cells; however, they inhibit enzymes also found in normal tissues, resulting in severe toxicity and limiting their therapeutic potential. It is therefore of great interest to further characterize cancer metabolism to identify better therapeutic strategies. Many cancer cells depend on the *de novo* purine synthesis pathway to ensure rapid proliferation, while healthy cells utilize the purine salvage pathway. At Helleday laboratory, we are interested in improving our understanding about altered cellular metabolism upon cancer transformation which can ultimately lead to better, more cancer-selective therapies.

The overall aim of this project is to investigate in detail two key enzymes in the *de novo* purine synthesis pathway and how these enzymes support DNA replication and repair in cancer cells. Our preliminary data suggests nuclear localization of these enzymes, which is enhanced upon induction of DNA damage. Thus, we will study the involvement of these enzymes in the DNA damage response. Moreover, recent studies suggest the presence of these enzymes at the replisome. To this end, we will pull down active replication forks from established human cancer cell lines to validate any physical interaction of our target enzymes and other components of the replisome. We also aim to identify novel interacting proteins with the *de novo* purine synthesis enzymes.

Skills and competences to be acquired (learning outcomes):
1. Extensive cell culture knowledge, including handling of cytotoxic compounds
2. Western blotting
3. Subcellular fractionations and co-immunoprecipitation
4. Flow cytometry
5. Confocal imaging and immunofluorescence, acquisition of single-cell image data, high-throughput imaging and automated image analysis
6. Theoretical knowledge about metabolic reprogramming in cancer and DNA replication and repair
7. Experimental planning, data analysis and data interpretation

Requirements:
- Bachelor degree in biology, biochemistry, biomedicine or similar subjects
- Experience in basic molecular and cellular techniques (e.g. cell culture, Western blotting, confocal microscopy) is a plus
- The candidate should be highly motivated and pro-active, have good communication skills and ability to interact effectively and work productively in a team
- Fluent in English

The selected student will be a part of the Helleday laboratory that takes a multidisciplinary approach involving close collaboration between biochemists, medicinal chemists, molecular biologists and pharmacologists. The high diversity of methods and competences is a unique chance to acquire a very broad skillset depending on motivation of the chosen candidate.

The research group focuses on understanding basic cellular processes with a special interest in metabolism and DNA repair, as well as developing novel drugs for treating a variety of diseases, including cancer and inflammatory diseases. See our Helleday lab homepage for more information about our research: http://helleday.org/

Are you interested?

Apply by sending your CV and personal letter to petra.marttila@ki.se