DESCRIPTION FOR THE GENERAL PUBLIC

1. Research project objectives/Research hypothesis

Hematopoietic stem cell (HSC) give raise to every blood cell in our bodies. However, the precision of HSC's action requires an efficient supervision of cell divisions. Our studies conducted on mice show that one of the cell cycle's key regulators may be heme oxygenase-1 (HO-1).

HSC lacking HO-1 enter cell cycle more often and increase significantly their population in murine bone marrow. What is more, HO-$1^{-/-}$ HSC have impaired functions and show higher level of DNA damage. **We suspect that HO-1 may play a crucial role in controlling HSC's divisions. One of its tasks may be influencing a decision if a cell should progress with a cell cycle or be removed due to accumulated DNA damage.** Proposed project aims to verify this hypothesis and study mechanisms governing proliferation of HSC.

2. Research project methodology

In order to verify the influence of HO-1 on a cell cycle, firstly, we plan to compare the level of activated cell cycle regulator between HO-$1^{-/-}$ and HO-$1^{+/+}$ animals. Our initial studies show that the level of expression of given genes is changed in HO-$1^{-/-}$ HSC, however we do not know how protein level is affected.

Moreover, we suspect that lack of HO-1 may lead to perturbations in HSC cell cycle length and that more HO-$1^{-/-}$ HSC enter cell cycle each day. Changes in duration of a cell cycle would explain higher level of DNA damage in HO-$1^{-/-}$ HSC – those cells would not have enough time to verify amplified DNA material. To test this hypothesis we plan to perform *in vivo* experiment in which mice from both genotypes will incorporate DNA intercalating molecule (BrdU) into their cells. By analysing the percentage of cells positive for the presence of this compound we will be able to define the number of HSC divisions and duration of a cell cycle. Additionally, we will define the level of HSC supposed to be cleared from organism because of contained DNA damage.

We also suspect that increased proliferation of HO-$1^{-/-}$ HSC may lead to faster telomere shortening, structures responsible for protection of chromosomes ends. We want to compare telomere length between HO-$1^{-/-}$ and HO-$1^{+/+}$ HSC. To do so, we will use innovative approach, measuring telomere length in single-cell HSC and by applying telomere marking with fluorescent probes.

All of proposed methods were matched to the proposed research model and consider the low number of HSC available for analysis.

3. Expected impact of the research project on the development of science

Studying HO-1 involvement in a regulation of cell cycle in HSC is an innovative approach. Although there are some studies showing possible interaction between HO-1 and DNA repair proteins such as PARP-1 or influencing transcription factors no one noticed the connection between HO-1 and regulation of such basic process as a cell cycle.

Our results could successfully be adapted by other researchers interested in cell cycle regulations. Insights into the mechanisms governing cell divisions in HSC can beyond doubt lead to a better understating of the stem cell biology. The ability to influence cell cycle progression in HSC could also affect modern approaches to treat hematopoietic malignancies.