Every second of our life the body produces 2 millions of new blood cells. They need to replace worn, damaged, old or lost cells (e.g. after bleeding). Production of blood cells takes place in the bone marrow. Specialized bone marrow cells able to produce all types of blood cells throughout entire human life are called **hematopoietic stem cells**. Scientists believe that stem cells divide in an asymmetric manner. It means that after the division one daughter cell remains stem cell while the other differentiates (maturates) and becomes a progenitor cell that is able to produce blood cells but loses self-renewal properties. In consequence, progenitor cell differentiates more and more and after a few weeks stops producing new blood cells. Therefore, if all the stem cells in the bone marrow died because of some reason (e.g. irradiation), with time, blood production would completely stop because all progenitor cells would become mature, differentiated blood cells. How stem cells become progenitor cells? Can we reverse this process? We will try to answer these questions in the experiment planned in this project.

All cells in the body have the same set of genes, so-called **genome**. Even though the genome is the same, the cells differ from each other, because they use different genes from the genome. During differentiation, to enable special properties of the cell, some of the genes are blocked while the others are “in use”. This process, called **epigenetics**, does not require any changes in genes, it simply makes the DNA accessible or not. It is known, that epigenetics is involved in the transformation of stem cells into mature cells, but the details underlying this process remain unclear. In this project, we want to find exact epigenetic mechanisms responsible for the constant renewal of stem cell population in the bone marrow and their differentiation to progenitor cells during asymmetric divisions.

We performed an experiment that allowed us to switch off some of the epigenetic genes and check if it can reverse the differentiation process. We used a library of more than 500 shRNAs, molecules able to block protein synthesis and switch off their function. We introduced this library to progenitor cells and used those modified cells in bone marrow transplants for irradiated mice who lost their own stem cells. If the transplanted cells remained progenitors, after a few weeks there would be no mature blood cells in the mouse because there would be no stem cells in the bone marrow. However, if switching of the epigenetic factors in some of the progenitors reversed differentiation to stem cell stage, blood cells will be produced normally by long-living stem cells. This method allowed us to find 12 factors that might be involved in the differentiation of hematopoietic stem cells into progenitor cells.

This experiment is only a beginning of the project, showing us a direction in which the further study should go. In the current project, we plan to perform a series of advanced studies allowing us to confirm the role of those factors in the differentiation of stem cells. Moreover, we want to study the mechanism of action of these factors using many advanced methods, including analysis of proteins produced by a single cell. Finally, because all these studies are performed in laboratory mice, we plan to check if the same processes can be observed in human cells cultured in a laboratory dish.

Finding factors governing blood production at the earliest stages has tremendous significance, both scientific and practical. Abnormal differentiation of blood cells is a cause of many human diseases, e.g. leukemias, immunodeficiencies or some anemias. The possibility to reverse differentiation of stem cells creates a technological possibility to develop new therapies and new opens fascinating paths for research.