

All living organisms remain in the dynamic equilibrium, with the constant cell production counteracting cellular deterioration. In the adults, this is achieved through activity of the elite set of cells termed stem cells. Due to their remarkable plasticity, stem cells are capable of replenishing every mature cell type of the tissue in which they reside. One of the most astonishing tissue systems in the human organism (as well as in any other complex specie), is the blood. Due to the extreme degree of specialization, blood ensures constant flux of the oxygen and nutrients, prevents bleeding to death after we get wounded and eliminates pathogens during infection. To achieve this, billions of new blood cells must be produced every single day of our lives.

This process is maintained by stem cells of the blood – hematopoietic stem cells. They are extremely rare and typically remain in the inactive state of the quiescence. Upon stimuli such as increased demand for oxygen (e. g. when we start to exercise regularly), bacterial infection or wounding, hematopoietic stem cells are getting activated to produce mature blood cells that are required at the moment. Moreover, as hematopoietic stem cells can be prospectively isolated and transplanted, they offer a unique therapeutic avenue for diseases of the blood system, such as leukemias or bone marrow failure. All of these aspects made hematopoietic stem cells a subject of intense research efforts for more than last 50 years. Despite that, there is still much and more that we need to learn on the mechanisms that govern function of this type of stem cells.

Our new observations indicate that one of the processes critically required for hematopoietic stem cells well-being is splicing. Splicing is a molecular process that acts as an amplifier to boost amount of information encoded in the genome. During splicing parts of the ribonucleic acid (RNA) are cut and stitched to produce new variants and types. That enables creation of multiple mature proteins on the matrix of the single gene. Molecular scissors that are responsible for splicing are complex macromolecular machineries – spliceosomes. Spliceosome is the largest and most complex conglomerate in the cell, composed of hundreds of proteins. In this project, we propose that differential levels of individual proteins from the spliceosome may affect its function. We further posit that this regulation may be preferentially important for the biology of hematopoietic stem cells in the health and in the pre-cancerous disease.

We will start by analysing expression profiles of spliceosome proteins between mature and stem cells of the blood. We will delineate how these regulated levels may impact splicing reaction to determine hematopoietic stem cells function. In the last stage, we will determine how regulation of the splicing impacts transition between normal and diseased blood differentiation. To delineate all of these dependencies, we will employ an ensemble of proteomic approaches, *in vivo* experiments and genome editing technologies.

Through the proposed research program, we hope to understand how individual components of the spliceosome are regulated during specification of the blood system. We envision that in the long range it may ameliorate therapeutic potential of hematopoietic stem cell-based therapies and determine molecular underpinnings of the blood diseases.