Objective of the project. Hematopoietic transplantation is since 50 years a well establish procedure to treat patients suffering from malignant and non-malignant hematological disorders that could be cured by transplantation of hematopoietic stem/progenitor cells (HSPCs). These patients are transplanted with own autologous or donor derived (allogeneic) HSPCs. Patients are prepared for transplantation using myeloablative or non-myeloablative conditioning to destroy old hematopoiesis and suppress immune system. Cells during transplantation procedure are infused intravenously with intention that they will find their way to bone marrow (BM), where they will subsequently home and permanently engraft supplying hematopoietic cells (e.g., red blood cells, leucocytes and platelets). In order to ensure proper long-term reconstitution after transplantation a required "threshold number" of HSPCs has to be infused into the patient. This number for human hematopoietic transplantations is based on a proper number of CD34+ cells present in the graft per kilogram of patient body weight. However, to harvest the sufficient number of CD34+ cells is often problematic in case of transplantations with low number of harvested BM cells, donors that are poor mobilizers of HSPCs and finally in case of umbilical cord blood (UCB) transplants when a number of HSPCs is not sufficient to perform this procedure in adult patient. Moreover, it has been calculated that only 10-20% of HSPCs infused into PB home to BM microenvironment what is reflected by so called "seeding efficiency factor". Therefore, it is so important to develop strategies that will enhance homing/seeding efficiency of transplanted HSPCs. Therefore, this proposal will seek to develop new strategies to enhance optimal homing and engraftment of transplanted HSPCs. This will lead to both better clinical results as well as will help to reduce costs of this costly procedure.

Research to be carried out. These investigations will be first performed and optimized in murine model of hematopoietic transplants where mice will be transplanted with murine HSPCs and subsequently verified in immunodeficient mice transplanted with human HSPCs. In order to develop optimal homing strategies of transplanted cells we propose to: *1)* increase formation of membrane lipid rafts on HSPCs to enhance homing potential of transplanted cells and/or by coating HSPCs with blood platelet derived extracellular microvesicles (ExMVs) that will transfer to HSPCs platelet surface receptors enhancing adhesion of cells in BM; *2)* modulate cell surface- and intracellular-expressed enzymes that regulate responsiveness of HSPCs to BM-expressed homing factors and *3)* increase BM-concentration of chemoattractants for HSPCs.

Reasons for choosing the research topic. Transplantation of HSPCs is well established and in many cases lifesaving clinical procedure. However, delayed engraftment of HSPCs and even worse its lack is still an important clinical problem in particular in situations when a number of HSPCs in graft is low (e.g., poor harvest of HSPCs from donor BM, poor mobilizers of HSPCs, UCB transplants). We envision that this research will follow path from "the bench to the clinic" and will improve clinical outcomes from hematopoietic transplantations. Faster engraftment of HSPCs and hematopoietic recovery is also an important aspect reducing costs of this expensive procedure (e.g., less antimicrobial treatment, platelet infusions and red cell infusions). Therefore every day of accelerated recovery after hematopoietic transplantation, that is in great extend function of number of HSPCs that engraft in BM will put a patient on lower risk of some post-transplant related complications and allow to lower costs of this procedure. In sum data generated in this proposal will allow us to propose new therapeutic strategies based on simple modulation of HSPCs before infusion into the patient that will enhance responsiveness of HSPCs to chemoattractants secreted in BM.