

Objective of the project

Development of hematopoietic cells is an exciting and studied for many years physiological phenomenon. Nevertheless, recent evidence points out that apart from cytokines, growth factors and bioactive lipids—some **extracellular nucleotides (EXN)**, when released from cells, act as signaling molecules and emerged as new and potent group of hematopoietic regulatory factors being involved in a process of so called purinergic signaling. These small molecules are released from the cells under steady-state conditions in response to certain stimuli, but what is important for this project they may also be secreted from damaged, leaky cells in bone marrow during inflammation, oxidative stress or radio-therapy as danger-associated molecular pattern (**DAMP**). Deciphering the role/involvement of EXN operating in hematopoietic stem/progenitor cells will be important not only to get a broader picture of the regulation of proliferation and expansion of hematopoietic stem cells (HSCs) residing in the bone marrow, but in addition will shed more light on the role of EXN during pharmacological mobilization of HSCs to the circulation and during their homing/engraftment after injection into recipient of the hematopoietic transplant.

Research to be carried out

These investigations will employ *i)* unique mutant mice with defects in purinergic signaling, *ii)* testing of available and newly synthesized modulators of purinergic signaling, *iii)* murine models of hematopoietic stem cell mobilization and *iv)* transplantation assays where mice will be transplanted with murine HSPCs. Subsequently some of the data will be verified by employing immunodeficient mice transplanted with human HSPCs. In order to understand the potential role of nucleotides in regulation of normal and pathological hematopoiesis we propose to: *i) study the role of nucleotides in proliferation and expansion of bone marrow stem cells; ii) evaluate the pivotal role of EXN signaling in mobilization of bone marrow stem cells* and finally *iii) determine involvement of EXN and purinergic signaling in homing and engraftment of bone marrow stem cells after hematopoietic transplantation.*

Reasons for choosing the research topic

A long series of crucial discoveries demonstrated beyond doubt that EXN are critical molecules involved in several biological processes. However, their role in proliferation and expansion of bone marrow stem cells is still very limited and often controversial. In proposed research, we will study the role EXN on proliferation and expansion of hematopoietic stem cells in bone marrow, their mobilization into the circulation and pharmacological induction and finally their potential involvement in the homing of injected cells into BM after transplantation. This multidisciplinary approach based on the modulation of EXN purinergic signaling may provide new therapeutic approaches in hematology, hematopoietic transplants, and treatment of hematopoietic diseases. This work will be performed in close collaboration between investigators with unique and complementary expertise including Prof. Ulrich Henning (University of Sao Paulo, Brazil), renowned specialist in nucleotide signaling, Prof. Wiesław Jędrzejczak (Medical University of Warsaw) pioneer of hematopoietic transplants in Poland and Dr hab. Grzegorz Basak (Medical University of Warsaw, Department of Hematology, Oncology and Internal Diseases) to evaluate the role of nucleotide in the mobilization and homing of bone marrow stem cells.

In sum, we want to shed more light on the role of nucleotides in normal and malignant hematopoiesis to develop new therapeutic strategies that will lead to crucial advances in basic and clinical hematology. These goals will be achieved by execution of research proposal driven by specialists with the complementary areas of expertise. Knowledge gained in this proposal will be also relevant to other areas of medicine beyond hematology and oncology, in which EXN play an important role including cardiology, pulmonology and neurology.