Identifying unique adaptive responses of red pulp macrophages to iron deficiency

In mammals, iron is an essential trace element for life. Each cell needs it for key metabolic functions. In the bone marrow, 2×10^{15} iron atoms every second are utilized for the hemoglobin synthesis during the daily production of around 200 billion red blood cells (RBCs) in a process called **erythropoiesis**. Hemoglobin-containing RBCs that deliver oxygen to our tissues **undergo natural aging** and after approximately 120 days need to be removed from the circulation. Macrophages are cells that are proficient in phagocytosing ('eating') other cells or pathogens. These cells are spread through the body and have distinct roles for the correct functioning of our organism. One type of macrophages that is localized in the spleen (so-called **red pulp macrophages or RPMs**) is responsible for the **removal of aged erythrocytes**. This process is as intense as erythropoiesis: up to five million RBCs are engulfed each second. Following erythrocyte lysis, RPMs release iron back to the bloodstream to sustain continuous erythropoiesis. Thus, they handle most of the iron pool in our body and play a key role in the so-called '**iron-recycling**' that enables **RBCs turnover**. In sum, the **'making' of RBCs and their 'breaking' by RPMs are key processes in our physiology**.

Iron deficiency represents one of the leading global health issues. It is currently estimated that above 1.9 billion people worldwide suffer from anemia, which is mostly caused by iron deficiency. Iron deficits lead also to adverse pregnancy outcomes, impaired child development, low work productivity in adults, and increased mortality risk in the elderly. Still**, little is known about how functions of specialized cells in the body are affected by low iron levels**.

We knew that RPMs react to limited iron supply: **they increase the rate of iron export** when the organism is iron deficient to liberate iron for erythropoiesis. This physiological 'adaptation' is enabled by low levels of the liver-derived hormone called hepcidin. However, it was not known if the intensity of erythrocyte uptake and digestion by RPMs are regulated by iron availability, and specifically, if these processes may be affected by iron deficiency. **By using a mouse model of dietary iron deficiency we uncovered that iron-poor RPMs enhance their ability to remove and lyse erythrocytes.** We observed that this **'functional acceleration'** of iron-deficient RPMs is accompanied by increased mass and activity of mitochondria, cellular power plants. **Such a boost of metabolic activity in iron-poor RPMs is unique** in comparison to other cell types which typically 'slow down' their metabolism when iron levels drop. We hypothesized that this **well-orchestrated response of RPMs to iron deficiency** likely contributes to the 'adaptation' of the whole organism to limited iron supplies. Moreover, our preliminary work revealed that hepcidin, the same hormone that controls iron release from RPMs, may also regulate RBC uptake, thus likely coordinating these two processes. Within this project, we will apply both *in vivo* and *in vitro* approaches to **understand in detail how this newly discovered 'adaptation program' of RPMs in iron deficiency is triggered (Aim I), how hepcidin controls it as an endocrine factor (Aim II), and investigate how perturbation of these responses would affect whole-body physiology when iron supplies are limited (Aim III).**

Taken together, the characterization of these new physiological responses to iron deficiency at three levels: **cellular, endocrine, and organismal**, will significantly advance our understanding of the body's adaptation to limited iron supply.