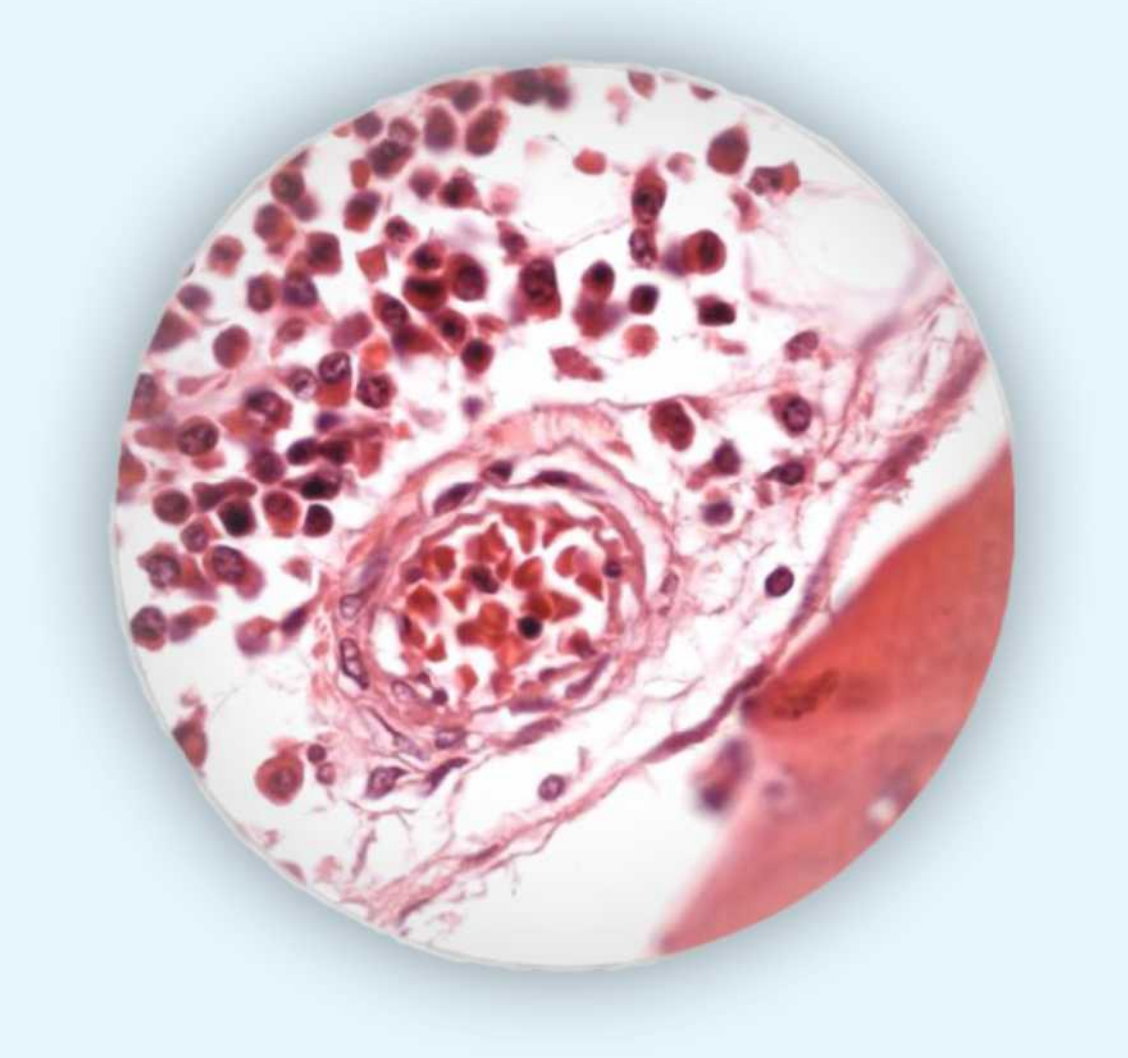
INTERNATIONAL WORKSHOP

HAEMATOPOIETIC STEM CELL

Principles and Applications

PROGRAM



National Program "European Research Networks"

TranStem

PROSPERITAS VESTRA FINIS NOSTRA!

Friday, September 30

Dimyat Hotel

16:00 Registration

18:00 - 18:15 **Igor Resnick**

Welcome address and opening

Session 1

Keynote lecture

18:15 - 19:00 **Tsvee Lapidot**

Metabolic regulation of haematopoietic stem cells and their bone marrow niches.

Will be discussed the role of daily light and darkness cues, chemokines, cytokines, and proteolytic enzymes.

19:00 Evening reception: drinks and hors d'oeuvres

Saturday, October 1

Dimyat Hotel

Session 2

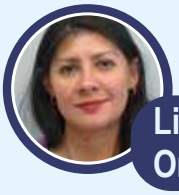
Chair: not defined

09:00 – 09:45 **Mariusz Z. Ratajczak**

Haematopoietic and innate immunity: an inseparable couple for good and bad times, bound together by an hormetic relationship

Haematopoietic and immune cells originate from a common haematopoietic/lymphopoietic stem cell (HSPC) what explains that these different cell types often share the same receptors and respond to similar factors. Accumulating evidence shows that innate immunity modulates several aspects of haematopoietic within the hormetic zone in which the biological response to low exposure to potential innate immunity stressors generally is favorable and benefits trafficking, survival and expansion of HSPCs. Moreover, what is intriguing HSPCs express functional intracellular complement proteins, defined as complosome, that regulate haematopoietic in intracrine-dependent manner.

09:45 – 10:05



Lizeth Alejandra Ordonez-Moreno

The role of lactate in HSPC mobilization

Mobilized haematopoietic stem and progenitor cells (HSPC) are the most widely used source for clinical transplantation of patients with hematological and malignant diseases. Granulocyte colony-stimulating factor (G-CSF, also known as filgrastim), is one of the main mobilizers used in the clinic. However, there is a percentage of people known as "poor mobilizers" who do not respond to treatment. As a consequence, the quality of life decreases while the cost of treatment increases considerably. The mechanism of G-CSF is still poorly understood. Here we show for the first time that G-CSF increases bone marrow lactate levels through neutrophil activation, which is crucial for successful mobilization. Otherwise, neutrophil depletion decreases BM lactate levels and impairs HSPC mobilization. For the first time, we are showing the novel role of lactate as a major player in HSPC mobilization which could then be considered as a marker to detect or even correct poor mobilizers.

10:05 – 10:50

Panagiotis Tsirigotis

Allogeneic Stem Cell Transplantation: Current Challenges and Future Perspectives

Allogeneic stem cell transplantation remains the only therapeutic modality with a curative potential for various hematological malignant and non-malignant disorders. Despite the recent progress, the major limitations associated with the procedure are the significant non-relapse morbidity and mortality and the risk of relapse especially for patients with active disease at the time of transplant. Except for the classic manifestations of graft versus host disease patients present with various other immune-mediated syndromes such as thrombotic microangiopathy, encephalopathy, and non-infectious pulmonary complications that further contribute to morbidity and mortality. Relapse of the malignancy is another obstacle to the success story of allo-SCT. Not rare but underestimated complications, as well as, methods for prevention and treatment of post-transplant relapse will be the topic of this lecture.

10:50 – 11:35

David Kunke

Patient-derived organoids: from benchtop to bedside.

Organoids are a three-dimensional model of organ-specific cell types derived from a single stem or progenitor cells that can be used to model human organ development, homeostasis, and the onset of disease. Patient-derived organoids (PDOs) could complement existing approaches in treatment and improve the prediction of drug responses. Moreover, PDOs can recapitulate patient responses in the clinic and could be implemented in personalized medicine.

11:35 – 12:00 **Coffee break**

Session 3

Chair: not defined

12:00 – 12:45

Dimitrios Mougiakakos

CAR T-Cells: From Lymphoma to Autoimmunity

The CD19 CAR T-cell therapy may induce rapid remission of refractory SLE. The rapid disappearance of dsDNA autoantibodies suggests CD19-expressing plasmablasts as the major source of these antibodies. For details see here. I explain why ended up treat a patient with SLE with CARTs.

12:45 – 13:00

Montaser Haddad

and Khatib-Massalha E, Ordonez-Moreno L-A,Chakrabarti P, Kollet O,Poller WC, Aroca-Crevillén A,Hidalgo A, Swirski F & Lapidot T.

Circadian Rhythms Control the Magnitude of Host Immune Responses to LPS-Induced Inflammation

The diurnal variations of LPS-induced inflammation were studied in wild type mice that were injected with 10 mg/kg LPS intraperitoneally. Mice were sacrificed following 4 or 20 hours of PBS or LPS administration or were monitored for their survival. Biomarkers of inflammatory responses, including cytokine storm, and neutrophil activation status (ROS production, and degranulation) were measured applying ELISA, flow cytometry, image stream, and light-sheet microscopy. Our preliminary results reveal a regulatory network linking light/dark signals, circadian hormones' activity, cytokines/chemokines burst, and consequently neutrophil activation. The levels of this network activation drive the diurnal variations in mice susceptibility to LPS challenge and the consequent mice survival rates.

13:00 – 13:15

Priyasmita Chakrabarti

and Kollet O, Golan K,Ordonez-Moreno L-A,Haddad M, Petrovich-Kopitman E, Kucinski I, Wilson N, Kinston S, Xie S, Dick J, Itkin T, Gottgens B & Lapodot T.

Circadian cues reprogram metabolic pathways in long-term repopulating haematopoietic stem cells

Haematopoietic stem and progenitor cells (HSPCs) are primarily maintained in an undifferentiated, and quiescent state in the mouse bone marrow (BM). We have recently found that circadian cues regulate daily HSPC fate decisions. Daily light and darkness cues induce a fraction of BM HSPCs to differentiate and egress from the BM in daylight to replenish the circulation with mature blood and immune cells. While darkness metabolically elevates their self-renewal to maintain the BM reservoir of undifferentiated HSPC. Previously, we have reported higher competitive long-term HSC (LT-HSC) repopulation at night compared with morning. The dynamic switch between HSPC quiescence and activation involves transient morning increase in their ROS levels. By applying single stem cell RNA sequencing and flow cytometry with functional HSPC assays, we report night LT-HSCs to have lower mitochondrial membrane potential, previously associated with increased LT-HSC competitive repopulation potential.

Darkness cues are associated with enhanced hypoxia and enhanced transcriptional expression of glycolytic pathway genes. We also found both increased expression of the glucose transporter, Glut1 and higher glucose uptake at night in LT-HSCs, pointing to Glut1 as a metabolic mediator of LT-HSC function under circadian regulation. Mechanistically, we found higher levels of the master metabolic transcriptional coactivator, PGC1a at night, known to regulate the Glut1 transcription. These metabolic changes are accompanied with higher LT-HSC mitochondrial ROS and calcium levels at night and an increase in the fatty acid oxidation pathway occurring within the mitochondrial matrix. Moreover, we observed an increase in expression of mitophagy-related genes at night. Thus, a balance between metabolic regulation and mitochondrial dynamics influences LT-HSC function under light and darkness control.

13:15 – 14:00

Manlio Vinciguerra

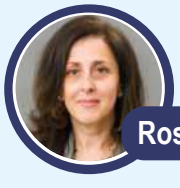
Integrative Cut&Tag/RNA-Seq analysis of histone variant macroH2A1-dependent orchestration of human iPSCs reprogramming

Cleavage under targets and tagmentation (CUT&Tag), is a new method used for epigenomic profiling of small samples. "Multiomics" approaches where the integrated analysis of transcriptional activity and chromatin accessibility via CUT&Tag are still in their infancy. Induced pluripotent stem cells (iPSC) are pluripotent stem cells that can be used in personalized disease modelling. However they are not considered safe for transplant because of inherent iatrogenic tumorigenesis, linked to epigenome stability. Among the epigenetic alterations, the substitution of canonical histones with histone variants appears as an emerging regulator of iPSC identity. MacroH2A1 proteins are histone variants featuring two exon splicing isoforms: macroH2A1.1 and macroH2A1.2 having common and distinct biological functions. We have recently reported that macroH2A1.1 is an enhancer of DNA damage repair and iPSC reprogramming from somatic cells. In this work, we employed human umbilical vein endothelial cells (HUVEC) during their reprogramming into iPSC over-expressing tagged macroH2A1.1 or macroH2A1.2, to perform an integrative Cut&Tag/RNA-Seq analysis of histone variant macroH2A1-dependent orchestration of human iPSCs reprogramming. Our analyses uncover a new exquisite histone variant-based genomic/transcriptomic interplay underlying iPSC reprogramming, which may inform functional and preclinical assays.

14:00 - 14:15 Tsvee Lapidot, Igor Resnick
Closing remarks

14:15 – 15:00 Lunch

Contact:



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