Dissecting the cross-talk between normal, leukaemic stem cells and the bone marrow microenvironment

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Hematopoietic stem cells (HSC) sustain the life-long maintenance of mature blood cells. In adult, HSC functions are maintained and tightly regulated in our bone marrow (BM) cavity, where they interact with different types of stromal cells. Recent progresses have been made in our understanding of the contribution of the different stroma cells in the regulation of normal HSCs. In recent years, deregulation of the BM microenvironment has emerged to be an important factor in the development of myeloid malignancies. Indeed, like normal HSC, Leukemic cells remain dependent on signals from the BM niche for survival and proliferation, and niche factors serves as a sanctuary for their chemoresistance. Thus, targeting BM niche factors represents a promising avenue for therapeutic interventions. Determining the niche associated alterations in the composition/ organization and dissecting the interactome of AML cells and their niche is thus fundamental to understand mechanisms of leukaemia initiation, evolution and resistance. In this talk, I will demonstrate how by combining in vivo model (xenotransplantation but also our recently developed in vivo humanised 3D scaffold) with transcriptomic and integrate imaging techniques, we could identify key cell types or molecules in stroma being altered by human myeloid leukemia as well as investigate how leukemia influence the normal residual haematopoietic stem/progenitor cell compartment.

Biography: Dominique Bonnet obtained her PhD degree at University of Paris VII. She then joined the group of Prof. John Dick's laboratory in Toronto, Canada for her post-doctoral training. Four years later, she was accepted as a Group Leader at the Coriell Institute for Medical Research, in New Jersey and became Assistant Professor. In 2001, she moved to Cancer Research UK, London Research Institute where she became a Group Leader in 2006. Since August 2012, she is Professor at the University College of London, division of Biosciences, and a Senior Lecturer at the Institute of Child Health. In 2016, her group moved to the new Francis Crick Institute.

Her group is investigating the molecular program that regulate human normal blood stem cells and how oncogenic events impede the normal development both directly and via the stem cell microenvironment. More recently, she developed humanised niche model to further study the interaction of human HSC/LSC within the BM niche.

Calcium mediated Cell fate dysregulation: A perspective on Cancer

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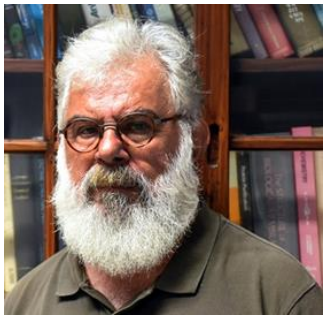
Cell-fate decisions like cell survival, death and senescence are regulated by Ca^{2+} signals arising from the endoplasmic reticulum (ER), which is in close proximity to the mitochondria. These two organelles are linked by Ca^{2+}-transport mechanisms involving the inositol 1,4,5-trisphosphate receptor (IP3R). Basal Ca^{2+} levels resulting from constitutive IP3 signaling in lymphoma and leukemia cells are important for cancer cell survival. They represent a vulnerability, rendering cancer cells dependent on Bcl-2 to limit IP3R activity. A peptide tool (Bcl-2/IP3R Disruptor-2; BIRD-2) was developed to abrogate the interaction of Bcl-2 with IP3Rs by targeting Bcl-2′s BH4 domain. BIRD-2 seems to switch constitutive IP3 signaling from pro-survival into pro-death. Cellular senescence, a state of irreversible growth arrest, is generally regarded as a tumor suppressive process. However, the accumulation of premature senescent cells in tissue microenvironment may contribute to mitochondrial oxygen radical injury and abnormal proliferation. The mechanisms implicated in the alteration of mitochondrial function in oncogene-induced senescence (OIS) is not well understood. Here, we show that the short transient receptor channel (TRPC)3 protein downregulation in senescence occurs regardless the type of senescence inducer. TRPC3 reduces IP3R-mediated Ca^{2+} release from the ER, enhancing cytosolic/mitochondrial Ca^{2+} oscillations and elevated mitochondrial Ca^{2+} load. Cellular senescence evoked by TRPC3 downregulation in stromal cells displays a proinflammatory and tumour-promoting secretome that encourages cancer epithelial cell proliferation and hence, tumour growth in vivo. Moreover, one characteristic of cancer cells is their ability to produce increased numbers of reactive oxygen species (ROS).

Biography: Haidar AKL holds a PhD in Biomedical and Pharmaceutical sciences from the university of Brussels (ULB). He is currently a professor of immunology at the Lebanese University, where he was involved in the setting up of a research lab on covid-19 in collaboration with the Ministry of Health. Dr AKL followed various post-doc positions at well-known laboratories such as Laboratory of Molecular and Cellular Signaling (LMCS), Gasthuisberg campus, KU Leuven and Laboratory of experimental Hematology, Bordet institute, ULB. His research shed the light on the Ca^{2+} signaling dysregulation in Adult T-cell Leukemia (ATL), Chronic Lymphocytic Leukemia (CLL) and Diffuse Large B Cell Lymphoma (DLBCL), which can be targeted in a cell death-based anti-cancer therapy.



Intercellular Communication in hematological Malignancies

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Intercellular communication in the hematopoietic microenvironment plays a critical role in regulating normal and malignant hematopoiesis. Although the role of Connexins, gap junction channels building blocks, their level of expression and function in leukemia development is not fully unraveled, several studies document their function in blood malignancies.

The Bone Marrow environment including fibroblasts, osteoblasts, Mesenchymal Stem Cells, and endothelial cells play a vital role in the development and progression of hematological malignancies and contribute to chemotherapy resistance. Increasing evidence demonstrates that Leukemia Initiating Cells interact with their surrounding BMME, and that intercellular communication with BMSC has a direct impact on leukemic hematopoiesis, and regulates leukemic stem/progenitor cell survival, proliferation, differentiation, and self-renewal.

This talk will highlight the role of intercellular communication whether through gap junctions or Extracellular Vesicles (EVs) in hematological malignancies.

Biography: Marwan El-Sabban is a Professor of Cell Biology, director of Cancer and Stem Cells Center of Excellence and director of Biological Imaging Facility at the Faculty of Medicine at the American University of Beirut. Dr El-Sabban did his post-doc studies at the Nuffield Department of Clinical Biochemistry, Radcliffe Infirmary, Oxford University (1985). His Postdoctoral training included Department of Pharmacology, Cornell University, Ithaca NY (1989) where he continued as a Research Associate in the Cancer Biology program. He was then a Research Associate in the Department of Neuroscience at Albert Einstein College of Medicine, NY, USA (1995) and then an Assistant professor of Medicine at SUNY Stony brook and then the Director of Cell Biology Laboratories at Winthrop-University Hospital, NY, USA (1997). His research interests involve the role of cell-cell and cell-matrix interaction in cellular function with special focus on organ-specificity of cancer metastasis. Interaction between host tissues and cancer cells: Molecular mechanisms of cancer cell extravasation, invasion and metastasis; Hetero-cellular interactions and niche function in cancer development. Also, organ-specific stem cell differentiation: novel approaches to Regenerative Medicine and drug screening.

Search for origins of childhood leukemia: mapping "molecular diary" of nature and nurture

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Cancer is the primary killer among all diseases in children, but causes are not well understood for most of its forms, including leukemia, which is the most common type. Childhood cancer is diverse and rare, so international effort is vital for bringing together data and biospecimen from many countries. Biological resources used in childhood cancer research have mostly been from clinical samples collected after disease onset. However, biological processes and biomarkers identified in these samples can be due to the cancer rather than its cause – what is known as reverse causality. The *in utero* period has a remarkable impact on human development, driven largely by epigenetic mechanisms – the molecular imprint of nature and nurture that shapes the different cells and organs. Unlike genetic mutations, epigenetic changes are potentially reversible, thus, offer interesting targets for disease prevention. For this reason and because childhood cancer may have an *in-utero* origin, we have decided to travel back in time and collect blood samples from babies at birth who then went on to develop leukemia later in life. In collaboration with several countries worldwide, we use large collections of those samples to produce molecular (OMICs) maps of the DNA of newborn babies. Each map can enable scientists to create a molecular snapshot – sort of a diary – of early-life factors that the baby had been exposed to during pregnancy. In this talk, we shall discuss how combining epidemiology, cross-OMICs analyses and cutting-edge laboratory science can provide unprecedented insights into causes of childhood leukemia and guide future preventive strategies and personalized therapy.
Animation: https://www.youtube.com/playlist?list=PLgDB39BFocs1HGX_S7-za4-oEPfs--9GD

Biography: Dr. Akram GHANTOUS is a staff scientist at IARC-WHO. His expertise encompasses epigenomics and cross-omics analysis in cancer research, with applications to cellular, clinical and epidemiological models, including large-scale and inter-disciplinary studies. After having ranked first in Lebanon for the International Fulbright Award for PhD studies at elite universities abroad, he embarked on the challenge to contribute to re-initiating the PhD program in his country through the American University of Beirut, and he became the first PhD graduate from Lebanon after the program had been terminated since decades of regional unrest. He then moved to IARC through its prestigious International Postdoctoral Fellowship, where he secured a staff scientist position as an official of the United Nations. Several of his publications rank top 1% in their fields, including those generated from low-resource settings.

Nucleophosmin-1 in Acute Myeloid Leukemia: A friend or Foe?

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Nucleophosmin-1 (NPM1) is a pleiotropic protein involved in numerous cellular processes. NPM1 shuttles between the nucleus and the cytoplasm, but exhibits a predominant nucleolar localization, where its fate and functions are exquisitely controlled by dynamic post-translational modifications (PTM). Sentrin/SUMO Specific Peptidase 3 (SENP3) and ARF are two nucleolar proteins involved in NPM1 PTMs. SENP3 antagonizes ARF-mediated NPM1 SUMOylation, to promote ribosomal biogenesis. In Acute Myeloid Leukemia (AML), NPM1 is frequently mutated, and exhibits an aberrant cytoplasmic localization (NPM1c). NPM1c mutations define a separate AML entity with good prognosis in some AML patients, rendering NPM1c as a potential therapeutic target. The impact of NPM1 mutations, alone or co-occurring with other mutations namely IDH1/2, DNMT3A or FLT3-ITD, on the clinical management of AML will be summarized. In addition, an overview on targeting NPM1c with a particular focus on the NPM1/SENP3/ARF axis, in different preclinical models will be provided. Collectively, this presentation will assert NPM1c as a druggable entity in certain categories of AML and will provide a strong rationale for testing therapies modulating NPM1c PTMs in the management of NPM1c AML.

Biography: Dr. Hiba El Hajj is an Associate Professor at the Department of Experimental Pathology, Immunology and Microbiology, at the Faculty of Medicine of the American University of Beirut. She attained her doctorate in 2005 in Molecular Parasitology at Montpellier University where she also completed her first post-doctoral fellowship. In 2006 she joined AUB as a post-doctoral scientist in Molecular Oncology at the American University of Beirut. She then joined the professorial ranks as an Assistant Professor with a dual appointment at the Departments of Internal Medicine and Experimental Pathology, Immunology and Microbiology (2012-2019). Her research interests span the fields of Molecular Oncology and Molecular Parasitology. In Oncology, her research focuses on the concept of oncoprotein targeted therapies in human hematological malignancies. In Parasitology, she is investigating innovative strategies for the prevention and treatment of toxoplasmosis and cutaneous leishmaniasis.

Characterizing the role of oncogenic mutations in pre-leukemic hematopoietic stem cells.

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Acute myeloid leukemia (AML) develops through a complex process of clonal evolution and selection from normal hematopoietic stem cells (HSCs) to pre-leukemic HSC clones to full-blown AML. The pre-leukemic HSCs often supplant the healthy blood system and contribute to disease progression and relapse. We identified histone H3-K27 mutations as strong drivers of pre-leukemic clonal expansion of HSCs and leukemogenesis in AML. Mutations in H3 histone variants were initially identified in pediatric brain tumours, followed by sarcomas, and these lead to epigenetic disruption, which is a common feature of cancer. The H3-K27M pre-leukemic HSCs represent a) a defined subject to examine the early stages of leukemic development and b) promising targets for novel anticipation-based treatment strategies. A benefit to examining the H3-K27M mutation is that it can give insight into the role of H3-K27 epigenetic marks in pre-leukemia without the confounding secondary functions of PRC2 genes. By modeling H3-K27M and comparing with other pre-leukemia events such as ASXL1 and IDH2 mutations in human HSCs, we are attempting to determine how such mutations drive the clonal expansion of pre-leukemic HSCs and the mechanisms underlying early events in leukemia development in AML.

Biography: Kolja Eppert is an Associate Professor at the Dept of Pediatrics, McGill University. He holds Canada Research Chair in Cancer Stem Cell Biology, Tier 2. He is also Medical Scientist, Research Institute of the McGill University Health Centre. His lab studies the fundamental biology of acute myeloid leukemia (AML) stem cells in pediatric and adult patients. Projects encompass identifying novel drivers of leukemogenesis, novel regulators of stem cells and the development of therapeutics. The main goal of the Eppert Lab is to better understand the biology of these malignant blood stem cells (leukemic stem cells) as they contribute to disease relapse and resistance to therapy. The Eppert lab is located at the Research Institute of the McGill University Health Centre (RI-MUHC) in Montreal, Quebec, Canada. The RI-MUHC is one of the largest medical institutes in Canada and is affiliated with the Faculty of Medicine at McGill University.

RNA signaling in the bone marrow microenvironment

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Extracellular vesicles (EVs) transfer complex biologic material between cells. However, the role of this process in vivo is poorly defined. Here, we demonstrate that osteoblastic cells in the bone marrow (BM) niche elaborate extracellular vesicles that are taken up by hematopoietic progenitor cells in vivo. Genotoxic or infectious stress rapidly increased stromal-derived extracellular vesicle transfer to granulocyte-monocyte progenitors. The extracellular vesicles contained processed tRNAs (tiRNAs) known to modulate protein translation. 5'-ti-Pro-CGG-1 was preferentially abundant in osteoblast-derived extracellular vesicles and, when transferred to granulocyte-monocyte progenitors, increased protein translation, cell proliferation, and myeloid differentiation. Upregulating EV transfer improved hematopoietic recovery from genotoxic injury and survival from fungal sepsis. Therefore, EV-mediated tiRNA transfer provides a stress-modulated signaling axis in the BM niche distinct from conventional cytokine-driven stress responses.

Biography: Currently, Youmna Kfoury is a senior scientist at Moderna, Tx leading a team focused on developing mRNA therapeutics for hematological diseases. Dr. Kfoury's research focused on the role of the bone marrow (BM) microenvironment in maintaining hematopoeisis in addition to being a critical player in hematological malignancies and solid tumor bone metastases. Dr. Kfoury's work identified the role of extra cellular vesicles as mediators of cellular communication within the BM microenvironment, highlighting the role of stress induced tRNA fragments (tiRNA) in orchestrating the response of myeloid progenitors to genotoxic and infectious stress independent of classical receptor ligand interaction. In the context of malignancy, Dr. Kfoury's work mapped molecular perturbations within the non-hematipoietic stromal compartment of the BM in AML and MDS using bulk and single cell RNA sequencing. Her work demonstrated the ability of specific molecular perturbations to impact disease progression in chimeric animal models. Dr. Kfoury is a member of the Boston bone metastases consortium that mapped the immune microenvironment in bone and BM samples from patients with bone metastatic prostate cancer identifying drivers of the disease. Finally, Dr. Kfoury is the recipient of the Dubai Harvard medical research foundation fellowship and the Aplastic anemia and MDS foundation research award.

Defining the role of DHODH inhibition in the treatment of T-cell ALL

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Acute T-cell lymphoblastic leukemia (T-ALL) is an aggressive hematologic malignancy affecting children and young adults. T-ALL continues to have higher rates of both induction failure as well as relapse as compared to B-ALL, with very poor survival rates in both scenarios. Compared to B-ALL, T-ALL has not benefitted from the same immune-mediated therapies and continues to pose an ongoing treatment challenge as well as an unmet therapeutic need. Here we show that inhibition of dihydroorotate dehydrogenase (DHODH), an enzyme which converts dihydroorotate to orotate as part of the de novo synthesis of uridine, has a robust anti-leukemia effect in both in vitro and in vivo models of T-ALL. DHODH is ubiquitously-expressed, and inhibition of DHODH (DHODHi) leads to rapid depletion of pyrimidine ribo- and deoxyribonucleotides. The cell's ability to tolerate periods of pyrimidine starvation are dependent on a variety of alternative salvage pathways and are not well-understood. DHODH inhibitors are already in clinical trials in a variety of malignancies, including myeloid malignancies, where they are also known to have an anti-leukemic effect. The goal of this project is to understand why T-lymphoblasts are so sensitive to DHODHi, and to develop new therapeutic combinations for patients with T-ALL using DHODH inhibitors.

Biography: Dr. Sexauer is a graduate of the Johns Hopkins University, School of Medicine. She completed her residency at the Children's Hospital of Philadelphia and was followed later a fellowship at the Dana-Farber Cancer Institute and Boston Children's Hospital. She has the American Board Certification in Pediatrics. Dr Sexauer studies the process of normal hematopoietic differentiation and its perturbations in both myeloid and lymphoid malignancies. Her goal as an academic physician-scientist is to continue to develop new combination therapies for children with high-risk leukemias to improve survival and minimize long-term toxicity. Her clinical interests involve: Adolescents and young adult oncology, Hematologic malignancies and Novel therapies and she is specialized in the treatments of Bone Marrow Failure, Childhood Leukemias, Childhood Lymphomas and Childhood Myelodysplastic Syndrome (MDS).

Targeting cellular iron homeostasis in B cell malignancies

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Diffuse large B cell lymphoma (DLBCL) is the most common hematological malignancy. Although more than half of DLBCL patients achieve long-term remission, the majority of remaining patients succumb to the disease. As abnormal iron homeostasis is implicated in carcinogenesis and the progression of many tumors, we searched for alterations in iron metabolism in DLBCL that could be exploited to develop novel therapeutic strategies. Analysis of the iron metabolism gene expression profile of large cohorts of DLBCL patients established the Iron Score (IS), a gene expression-based risk score enabling identification of DLBCL patients with a poor outcome who might benefit from a suitable targeted therapy. In a panel of 16 DLBCL cell lines, ironomycin, a promising lysosomal iron-targeting small molecule, inhibited DLBCL cell proliferation at nanomolar concentrations compared to typical iron chelators. Ironomycin also induced significant cell growth inhibition, ferroptosis, and autophagy. Ironomycin treatment resulted in accumulation of DNA double strand breaks, delayed progression of replication forks, and increased RPA2 phosphorylation, a marker of replication stress. Ironomycin significantly reduced the median number of viable primary DLBCL cells of patients without major toxicity for non-tumor cells from the microenvironment and presented low toxicity in hematopoietic progenitors compared to conventional treatments. Significant synergistic effects were also observed by combining ironomycin with Doxorubicin, BH3 mimetics, BTK inhibitors, or Syk inhibitors. Altogether, these data demonstrate that a subgroup of high-risk DLBCL patients can be identified with the IS that can potentially benefit from targeting iron homeostasis.

Biography: Jerome MOREAUX is associate professor at the university of Montpellier and junior member at Institut Universitaire de France. He is leading a group in the Institute of Human Genetics (Montpellier) "Epigenome modifications and genomic instability in normal and malignant B cells". The laboratory uses genome data, computing, mathematical modeling and specific cellular models to study mature B cells and plasma cells with a focus on epigenome modifications and genomic instability. These approaches work in tandem with technological advancements to study tumorigenesis and to understand the mechanisms of tumor progression and drug resistance to develop new diagnostic and treatment strategies. Jérôme MOREAUX is co-founder of Diag2Tec company created to valorize the research activity of the group.

Adult T cell leukemia as a virus addicted malignancy: implications for therapy

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Adult T cell Leukemia (ATL) is an aggressive lymphoproliferative malignancy secondary to chronic infection by the human T-cell leukemia virus type I (HTLV-I). ATL carries a very poor prognosis because of intrinsic resistance to chemotherapy and severe immunosuppression. In a worldwide meta-analysis, we showed that the combination of two antiviral agents zidovudine (AZT) and Interferon-alpha (IFN) proved highly effective and significantly improved survival in the leukemic chronic and smoldering subtypes of ATL as well as in a subset of the acute subtype with wild type P53. Unfortunately, most patients relapse upon treatment discontinuation. ATL leukemogenesis remains enigmatic. Two viral proteins, Tax and HBZ, play central roles in ATL leukemogenesis. Using Tax and HBZ transgenic fly models, we demonstrated that unlike Tax, which induces NF-κB activation and enhanced PRC2 activity creating an activation loop, HBZ neither induces transformation nor NF-κB activation in vivo. Unraveling this in vivo antagonistic effect of HBZ on Tax-induced transformation and cellular effects, help understanding long-term HTLV-I persistence and cellular transformation and open perspectives for new therapeutic strategies targeting the epigenetic machinery in ATL. In preclinical models, arsenic trioxide and IFN selectively trigger Tax degradation by the proteasome and apoptosis of ATL cells ex vivo. This combination cures Tax-driven murine ATL by clearing leukemia initiating cells (LICs) activity. Chronic ATL patients treated with AS/IFN/zidovudine achieved high response rates and some patients exhibited a sustained response after treatment withdrawal. Therapy-induced abrogation of ATL LIC activity reflects loss of ATL-secreted interleukin-10 and innate immunity-mediated clearance of ATL.

Biography: Ali Bazarbachi, MD, PhD is a Professor of Medicine (Hematology and Oncology), Professor of Anatomy, Cell Biology and Physiological Sciences, and Director of the bone marrow transplantation program at the American University of Beirut-Medical Center. He received his MD and PhD degrees, residency and fellowship training at the University of Paris VII in France. Dr. Ali Bazarbachi's basic and translational research focuses on targeted therapies for hematological malignancies as well as post-transplant pharmacological interventions. He has co-authored more than 350 articles in leading scientific journals including The New England Journal of Medicine, Science, Journal of Experimental Medicine, The Lancet Oncology, Journal of Clinical Oncology, Blood, Nature Communication, and Cancer Research. He is the Chairman of the EMBMT Leukemia Working Party, Chairman of the NCCN Lymphoma Group for Middle East and North Africa, past President of the Lebanese Society of Hematology, past President of the International Association for Comparative Research on Leukemia and Related Disorders, and Associate Editor of Bone Marrow Transplantation. He garnered multiple prestigious national and international awards including the 2008 award of the French National Academy of Medicine.

Targeting SUMOylation in preclinical models of AML

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Acute Myeloid Leukemias (AML) are severe hematomalignancies with dismal prognosis (5-year survival <25%). We have previously shown that SUMOylation, a protein post-translational modification related to ubiquitylation, plays a critical role in AML response to therapies (chemotherapies and differentiation therapies) through its ability to regulate transcription and constitutes an attractive target for AML treatment. A recent breakthrough in the field of SUMOylation is the discovery of the TAK-981, a first in class inhibitor of SUMOylation used in clinical trials for lymphomas and solid tumors. We tested the anti-leukemic potential of TAK-981. We demonstrated that, *in cellulo*, TAK-981 induces the death of AML cell lines and primary blast cells from patient bone marrows with minimal toxicity on normal cells. TAK-981 also showed a strong synergy with drugs used for AML treatments (genotoxics and epidrugs). Those results were confirmed in vivo in NSG mice grafted with luminescent AML cell lines or primary patient blast cells (PDX). To understand the molecular mechanisms underlying the antileukemic activity of TAK-981 and its synergy with AML treatments, we conducted RNA-Seq experiments. This revealed that combining TAK-981 with epidrugs activate genes involved in apoptosis, cell cycle control but also, more surprisingly, immune response, in particular those linked to the activation of Natural Killer cells. The ability of TAK-981 to induce anti-tumor immunity was confirmed both in vitro and in vivo. Altogether, we provide a preclinical demonstration of the therapeutical potential of SUMOylation inhibition, alone or in combination with drugs used for AML treatment. In addition, our data suggest that such treatment could induce an anti-AML immune response, which could further increase its therapeutic efficacy.

Biography: Ludovic Gabellier is a MD, haematologist at the Montpellier University Hospital, France. He is currently a PhD student at the Institut de Génétique Moléculaire de Montpellier (IGMM, CNRS), under the supervision of Guillaume Bossis.