Cancéropôle grand ouest

Epigenetics and cancer

EpiNANTES

www.epinantes2024.com

September 24-25, 2024

IRS1, 8 quai Moncousu, Nantes, France

EDITO

Thank you for attending this 7th edition of the EpiMeetings. After EpiNantes-2013, EpiNantes-2015, EpiBrest-2016, EpiNantes-2018, e-EpiMeeting-2021 and EpiBesançon 2022, it is a great pleasure for us to welcome you back to Nantes.

It is with great enthusiasm that we invite you to take place in this amphitheater to live together this 7th edition of our EpiMeetings around the themes of epigenetics and epitranscriptomics in oncology.

With a rich program of oral and poster presentations covering both fundamental and translational areas, we hope that this meeting will be an opportunity for everyone to discuss current and future projects, and to establish new collaborations between our laboratories.

Thank you to our institutional and industrial partners who, remained faithful to us and without forgetting those who trusted us this year for the first time.

We look forward to meeting you all in a casual atmosphere of researchers passionate about epigenetics and epitranscriptomics.

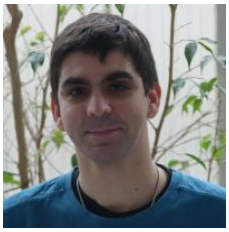
We wish you a very pleasant EpiMeeting!

Pierre-François Cartron (CRCI2NA, Nantes), Delphine Fradin (CRCI2NA, Nantes), Benjamin Ory (CRCI2NA, Nantes) and David Roulois (Mobidic, Rennes)

The scientific organizers

Dr Pierre-François Cartron obtained his PhD from Ecole Pratique des Hautes Etudes (EPHE) Paris La Sorbonne from his work on the structure-function interaction of the pro-apoptotic protein Bax in glioblastoma multiforme. He joined the Memorial Sloan Kettering Cancer Center (New York) in the EC Holland's lab to study the role of DNA methylation dysregulation occurring during gliomagenesis (initiation, progression and relapse). Since 2005 he is permanent researcher at INSERM CRCI2NA. He develops research aiming to characterize the epigenetic and epitranscriptomic mechanisms in order to derive innovative molecules selectively directed against epigenetic and epitranscriptomic players. In cancer area, he focuses its researches on the deciphering of DNA and miRNA methylation patterns to develop biomarkers and therapeutic options for individualized and precision medicine. He has authored 79 peer-reviewed publications.

Dr Delphine Fradin obtained her PhD from the Université Paris Cité (René Descartes) for her work on genetic and epigenetic factors in childhood obesity. She joined then Pr Andrew Feinberg's lab in the Epigenetics Center of Johns Hopkins University (Baltimore, USA) where she studied epigenetic mark changes throughout life. Since 2015, she joined the CRCI2NA to develop projects about the impact of treatments on tumor cells, from molecular mechanisms to clinically relevant biomarkers, by focusing on non-coding RNAs (miRNAs and lncRNAs). She has authored 43 peer-reviewed publications.



Dr David Roulois obtained his PhD from the University of Nantes for his work on T cell responses in malignant pleural mesothelioma. He then joined the team of Dr. Daniel De Carvalho at the Princess Margaret Cancer Centre (Toronto, Canada), to study the mechanism of "viral mimicry" induction by DNA methyltransferase inhibitors. Since 2016, he joined the U1236-MOBIDIC unit to study the role of epigenetic mechanisms in the regulation of lymphoid stromal cell polarization and response to inflammation, as well as the deregulation of these mechanisms in the context of follicular lymphoma. He has authored 20 peer-reviewed publications.

Pr Benjamin Ory obtained his PhD degree in 2007 from Nantes Medical School studying primary bone tumors biology and the potential therapeutic role of bisphosphonates in Osteosarcoma. He then worked 3 years (2008 to 2010) at the HARVARD Medical School Cancer Center studying microRNAs implication in the p63 family in squamous cell carcinoma. Pr ORY came back to France in 2011 to study the role of microRNAs in Osteosarcoma. In 2017, Pr ORY headed the "Epistress" team of the INSERM UMR1238 focused on the genetic and epigenetic aspects of primary bone tumors. Since January 2022, Pr Ory is leading team CHILD "Chromatin and transcriptional deregulation "in pediatric bone sarcoma of CRCI2NA (Centre de Recherche en Cancérologie et Immunologie Intégrée de Nantes Angers).

EpiNantes 2024

Program

Tuesday, September 24, 2024 – Wednesday September 25, 2024

IRS UN, 8 quai Moncousu, Nantes

Day one _ September 24, 2024

9:20 – 9:50 – Reception

9:50 – 10:00 - Opening

Keynote Lecture

10:00 – 11:00 – Mathieu Lupien, Senior scientist, Princess Margaret Cancer Centre, University Health Network, Professor University of Toronto, Canada

- *Decoding intra-tumour heterogeneity from chromatin variants*

SESSION 1 - Epigenetic players of cancer gene regulation

11:00 - 11:30 - Pierre-Antoine Defossez, Group leader, CNRS, Research Scientist, Epigenetics and cell fate Lab, Paris, France

- *Dynamics and interpretation of DNA methylation in mammals*

11:30 – 11:45 Short oral communication
Fabien Foucher, INSERM, UMR 1317, Nutrition, Métabolisme et Cancer, University of Rennes, France

- *Impact of histone modifications and DNA methylation on cell plasticity and tumor heterogeneity of human hepatocellular carcinomas*

11:45 - 11:55 – Clément Proux, Active Motif sponsor talk
11:55 - 12:05 – Jessica Apulei, Diagenode sponsor talk
12:05 - 12:10 – Société Française du Cancer sponsor talk

12:10 - 1:15 - Lunch break and meet the speakers

1:15 - 1:45 – Posters session

1:45 - 2:15 - Charlotte Proudhon, INSERM Investigator, Group leader, IRSET, Research Institute for Environmental and Occupational Health, Rennes, France

- *Non-invasive multi-cancer detection using DNA hypomethylation of LINE-1 retrotransposons*

2:15 - 2:45 -Short oral communications
Silvia Anna Ciafrè, PhD, Dept. of Biomedicine and Prevention, University of Rome Tor Vergata, via Montpellier, Rome, Italy

- *MEOX2 interaction with PRC2 and nuclear lamina components in glioblastoma stem cells suggests its possible role in the modulation of chromatin state*

Joséphine Briand, PhD, Laboratoire Sensibilité des Cancers aux Traitements (SCaT), Institut de Cancérologie de l'Ouest, Site d'Angers, France

- *A breast-on-chip to link oxidative stress-mediated epigenetic changes in adipose tissue and breast cancer risk*

2:45 - 2:55 – Emeric Roux, Stilla sponsor talk

SESSION 2 - When Epigenetics met Chemistry?

2:55 - 3:25 - Marie Lopez, Institut des biomolécules Max Mousseron (IBMM), CNRS-Univ. Montpellier-ENSCM UMR5247, France

- *Multifunctional chemical compounds to target epigenetic mechanisms in cancer*

3:25 - 3:40 – Short oral communication
Jules Durand, Univ. Bourgogne Franche-Comté, INSERM, EFS BFC, UMR1098, Interactions Hôte-Greffon-Tumeur/Ingénierie Cellulaire et Génique, Besançon, France

- *Identification of novel partner proteins of EZH2 and KDM6B in Epithelial to Mesenchymal Transition*

3:40 - 4:10 – *Coffee break and posters session*

4:10 - 4:40 - Elena Bochenkova, Research Intern at Department of Biochemistry, University of Zurich, Switzerland

- *Targeting METTL3 as a novel therapeutic strategy for acute myeloid leukemia*

4:40 - 4:55 – Short oral communication
Jean-Maxime Besson, Institut des biomolécules Max Mousseron (IBMM), CNRS-Univ. Montpellier-ENSCM UMR5247, France

- *Targeting DNA methylation in cancers by selective dissociation of their protein complexes*

SESSION 3 - Making sequencing reads readable

4:55 - 5:25 - Luca Cozzuto, Senior Bioinformatician at the Bioinformatics Technology Unit, Barcelona, Spain

- *MasterOfPores3: a suite of pipelines for nanopore sequencing data*

5:25 - 5:40 - Short oral communication
Slim Karkar, PhD, University of Bordeaux, France

- *Decomics, a user-friendly application for unsupervised cell type deconvolution and biological interpretation from tumor bulk methylome or transcriptomic data*

Rendez-vous at 8pm at "Lieu Unique" for Gala Dinner (an option at the time of registration)

Day Two _ September 25, 2024

Keynote Lecture

9:00 - 10:00 – Maite Huarte, Director of DNA and RNA Medicine Division and Head of the Noncoding RNA and Cancer Genome Lab at CIMA, Univ. of Navarra, Pamplona, Spain

- *Noncoding RNA roles in the coordination of DNA replication and stress signaling*

SESSION 4 - Epiregulation by non coding RNAs in cancer

10:00 - 10:30 - Eleonora Leucci, Professor at KU Leuven, Belgium

- *Contribution of lncRNAs to the generation of drug-tolerant persister cells*

10:30 - 10:45 - Short oral communication
Thomas Papazyan, Medical oncology, Centre Hospitalier Universitaire Nantes, Inserm UMR 1307, CNRS UMR 6075, Université d'Angers, CRCI2NA, Nantes, France

- *Identification of the lncRNAs involved in resistance to KRAS G12C inhibitors in lung cancer*

10:45 - 11:15 - Coffee break and posters session

11:15 - 11:45 - Rory Johnson, Associate professor, University College of Dublin, Ireland

- *Non-protein coding RNA drivers of tumorigenesis*

11:45 - 12:15 - Isabel Barragan, Ph.D. Scientist and Group Leader of Translational Research in Cancer Immunotherapy and Epigenetics in Research Institute of Malaga and BIONAND platform and Group of Pharmacoepigenetics at Karolinska Institutet, Stockholm, Sweden

- *Non coding RNA regulation of the clinical response to Immune Checkpoint Blockade*

12:15 - 12:25 – Paola Vecino, MedChemExpress sponsor talk

12:25 - 1:50 - Lunch break and meet the speakers

1:50 - 2:20 Antonin Morillon, Research scientist, Group leader at Institut Curie, CNRS, Sorbonne University, PSL, UMR3244, Paris

- *Dark genome and cancer*

2:20 - 2:35 - Short oral communication
Yuna Blum, Univ Rennes, CNRS, INSERM, IGDR (Institut de Génétique et Développement de Rennes) - UMR 6290, ERL U1305, Equipe Labellisée Ligue Nationale contre le Cancer, Rennes, France

- *Identification of sponge mechanisms involving circular RNAs associated to cutaneous melanoma treatment resistance*

SESSION 5 - Epitranscriptomics and Cancer

2:35 - 3:05 - Sandra Blanco, Research Scientist, CSIC, Head of Epitranscriptomics and Cancer Lab, Salamanca, Spain

- *Targeting tRNA methylases in cancer*

3:05 - 3:20 - Short oral communication
Jana Jeschke, Applied Cancer Epigenomics and Epitranscriptomics Group, Institut Jules Bordet, Brussels, Belgium

- *Mining the human breast cancer epitranscriptome: opportunities for personalized medicine*

3:20 - 3:45 - Coffee break

3:45 - 4:15 - Francesco Nicassio, Center Coordinator - Senior Researcher Tenured, Center for Genomic Science of IIT@SEMM (CGS), Milan, Italy

- *Cellular and molecular heterogeneity in human cancer*

4:15 - 4:45 - Short oral communications
Alexandre Gaspar Maia, PhD, Laboratory of Functional Epigenomics, Mayo Clinic, Rochester, USA

- *Comprehensive single cell analysis of the epigenome of ovarian cancer*

Alessandro Fatica, Department of Biology and Biotechnologies “Charles Darwin”, Sapienza University of Rome, Italy

- *Enhancing sensitivity of Triple Negative Breast Cancer to DNA Damaging Therapy through chemical inhibition of the m6A methyltransferase METTL3*

4:45 - 5:00- Concluding remarks and prizes for young researchers

End of the congress

Mathieu Lupien, Senior scientist, Princess Margaret Cancer Centre, University Health Network, Professor University of Toronto, Canada

Dr. Mathieu Lupien is a Senior Scientist at the Princess Margaret Cancer Centre, a Professor at the University of Toronto. His research is demonstrating that cancer is a disease of the chromatin. Amongst key discoveries, Dr. Lupien's research identified chromatin variants as a form of heritable variation complementary to genetic variants. His work showed that cancer-specific chromatin variants support oncogenesis independently of genetic variants and reflect opportunities for epigenetic therapy.

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Decoding intra-tumour heterogeneity from chromatin variants

Precision medicine for cancer patients is entering a new phase where chromatin variants are to play a central role. Chromatin, the complex of DNA and proteins within cells, regulates gene expression by controlling the accessibility of DNA to transcription factors and other regulatory proteins. Chromatin variants, which include segments of the genome that adopt a different chromatin state in different cell and tissue types based on histone modifications, chromatin accessibility or DNA methylation, strongly influence the behavior of cancer cells.

Emerging technologies allow for the identification of these chromatin variants with unprecedented precision. Here we identified chromatin variants in early and advance prostate cancer to identify drivers of tumor evolution. These drivers populate the repetitive genome and provides new targets for therapy development.

Pierre-Antoine Defossez, Group leader, CNRS, Research Scientist, Epigenetics and cell fate Lab, Paris, France

Pierre-Antoine Defossez carried out his PhD work with Yvan de Launoit on oncogenic transcription factors of the ETS family, during which he took part in the discovery and characterization of a new ETS family member, ETV5

He was a postdoctoral scientist in the lab of Lenny Guarente at MIT, where he made key contributions to the relationship between chromatin and cellular senescence in yeast.

He entered the French research system in 2000 as a senior scientist in the lab of Eric Gilson, working on chromatin and telomeres in yeast. Shortly afterwards (2003) he established his junior research group at the Curie Institute in Paris, then his senior research group at the University of Paris (2009). The Defossez lab has been investigating mammalian epigenetics, and more specifically DNA methylation, in the context of stem cells and cancer.

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Dynamics and interpretation of DNA methylation in mammals

DNA methylation is a key epigenetic mark involved in transcriptional regulation and genome stability in many eukaryotic species. This mark is essential for mammalian development and cellular survival, and is altered in many prevalent human diseases as well as during aging.

DNA methylation patterns are initially set up by "de novo" DNA methyltransferases. Then, at every subsequent cell division, the replicated DNA undergoes "maintenance" DNA methylation, involving the proteins DNMT1 and UHRF1. Despite their importance, the mechanisms of DNA methylation establishment and maintenance, and the underlying machinery, are still incompletely understood.

To elucidate the biological functions of UHRF1 and DNMT1 in DNA methylation and beyond, we have used the auxin-inducible degron (AID) system, which allows the rapid degradation of tagged proteins. As will be explained in the talk, this system has allowed us to show that UHRF1 has roles in DNA methylation besides stimulating DNMT1, and it has also helped us delineate the cellular response to loss of UHRF1 and/or DNMT1, with implications for cancer.

Charlotte Proudhon, INSERM Investigator, Group leader Circulating (Epi)Markers Lab, IRSET, Research Institute for Environmental and Occupational Health, Rennes, France

Charlotte Proudhon is an INSERM researcher in genetics and epigenomics, with expertise in liquid biopsy research and the development of non-invasive tests for precision oncology. Charlotte Proudhon completed her PhD in molecular genetics at the Institut Curie in Paris under the supervision of Déborah Bourc'his. During this period, she trained in the study of DNA methylation, and in particular its role as an epigenetic vector of information between generations in the mouse model. She then completeḋ a post-doctorate at New York University in Jane Skok's laboratory, where she specialized in three-dimensional genome analysis in immune system cells. She obtains a position as a research fellow at INSERM in 2020. In 2022, she sets up her research team on Circulating (Epi)Markers at IRSET in Rennes, supported by a Starting Grant from the European Research Council (ERC).

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Non-invasive multi-cancer detection using DNA hypomethylation of LINE-1 retrotransposons

The detection of circulating tumor DNA allows to non-invasively retrieve tumor molecular profiles and follow disease evolution. It promises optimal and individualized management of patients with cancer. However, despite remarkable progress, several technological obstacles still limit liquid biopsy widespread application. Indeed, detecting small fractions of tumor DNA released when the tumor burden is reduced remains a challenge and detectable recurrent mutations do not cover all patients.

We aimed to assess the universal potential of DNA methylation as circulating tumor biomarker using new highly sensitive strategies to detect common cancer-specific signatures in blood. We targeted hypomethylation of LINE-1 elements, a shared feature of multiple cancers, using a multiplex PCR-based targeted bisulfite method coupled to deep sequencing, together with computational tools to accurately align sequencing data in a genome reference-free manner. We implemented machine learning-based classifiers, integrating methylation patterns at single CpG sites and at the single molecule level, to discriminate cancer from healthy plasma samples.

We detected 30-40,000 LINE-1 elements scattered throughout the genome, covering abound 100,000 CpG sites. Methylation of these LINE-1 elements showed an extremely performant ability to discriminate between healthy and tumor plasmas from 6 different types of cancers, including colorectal, breast, lung, ovarian, gastric cancers and uveal melanoma.

Our method allows to dramatically increase the sensitivity of ctDNA detection in a cost-effective manner, providing an optimal trade-off between the number of targeted regions and sequencing depth. These results have important biomedical implications and should lead to the development of more efficient non-invasive diagnostic tests adapted to all types of cancers, based on the universality of these factors.

Marie Lopez, Institut des biomolécules Max Mousseron (IBMM), CNRS-Univ. Montpellier-ENSCM UMR5247, France

Dr Marie Lopez obtained her Ph.D. in 2007 in chemo-enzymatic synthesis of oligosaccharides under the supervision of Drs H. Driguez and A. Buléon. In 2008, she joined Poulsen's group (GRIDD, Brisbane) to work on glycosylated carbonic anhydrase inhibitors. In 2011 she then worked on anti-infectious agents developing strategy to target virulence factors. She was then recruited as a CNRS research scientist in 2013 to work at the ETaC laboratory in Toulouse on DNA methylation through enzyme inhibition and chemical probe strategies. She is currently at the IBMM in Montpellier, managing projects in chemistry and chemical biology to decipher and target epigenetic modifications in pathological contexts.

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Multifunctional chemical compounds to target epigenetic mechanisms in cancer

Epigenetic enzymes control gene expression without modification of the DNA sequence and are known to be involved in the deregulation of gene expression in cancers. Several epi-drugs, i.e., five HDAC, two DNMT and one HMT (EZH2) inhibitors were approved as anticancer treatments, which demonstrates the interest of targeting such epigenetic modifications in cancer. However, these therapies are only used in third line treatment and/or in combination due to their important toxicity.

In this context, we are interested in applying innovative strategies to identify new "epi-drug" candidates with improved activity, selectivity and bioavailability targeting DNA methyltransferases (DNMTs) and histones deacetylases (HDACs) and methyltransferases (HMTs).

One of these strategies is to exploit the multivalence using homo- and hetero-multifunctional inhibitors. The work presented here will first show the interest of targeting HDACs using homo-functionalised multivalent HDAC inhibitors to strongly improve the inhibition activity. In a second approach, based on previous inhibitors identified in our laboratory, we designed and synthesised bifunctional inhibitors against DNMTs and HMTs, where both active moieties are in a single molecule. These compounds showed low micromolar range activity on purified enzymes and a significant impact on cellular viability in HMT inhibitor-resistant multiple myeloma patient-derived cell line XG7.

We hope that these results will open new opportunities to target epigenetic mechanisms in cancer and to improve our understanding of the implication of epigenetic mechanisms in cancer formation and proliferation.

Elena Bochenkova, Research Intern at Department of Biochemistry, University of Zurich, Switzerland

Elena Bochenkova received her degree in General Medicine in 2017. Since then, she has gained laboratory experience through several internships in biomedical research. In 2019, Elena joined the Caflisch group at the University of Zurich to study how epitranscriptomic modifications regulate different cellular processes and to investigate proteins involved in RNA methylation as novel targets for anticancer drugs.

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Targeting METTL3 as a novel therapeutic strategy for acute myeloid leukemia

Epitranscriptomics is a rapidly growing field that studies co- and post-transcriptional RNA modifications. To date, over 160 distinct RNA modifications have been identified. Among these, N6-methyladenosine (m6A) is the most prevalent modification in eukaryotic messenger RNA (mRNA). m6A has been shown to play a significant role in various cellular processes, including oncogenesis.

N6-methyladenosine (m6A) is the most abundant post-transcriptional modification in eukaryotic messenger RNA. It has a significant impact on a variety of cellular processes, including cancer development and progression. The METTL3-14 complex is the major enzyme for m6A deposition, where METTL3 acts as the catalytic subunit and METTL14 promotes mRNA binding. METTL3 knockout studies have highlighted its crucial role in blood cancer progression, making it a promising target for therapy. In my talk, I will review current strategies to target METTL3 with small molecules and discuss recent advances in this field.

The complex of methyltransferase-like proteins 3 and 14 (METTL3-14) is the major enzyme that deposits m6A on mRNA. METTL3 serves as the catalytic subunit, while METTL14 is involved in mRNA binding.

Several METTL3 knockout studies have demonstrated its crucial role in the development and progression of blood cancers, particularly acute myeloid leukemia. Thus, targeting METTL3 has emerged as a promising therapeutic strategy.

In my presentation, I will summarize ongoing efforts to target the METTL3 enzyme using small molecules, providing insights into their effectiveness and potential as therapeutic agents. Additionally, I will highlight recent advancements in the development of these inhibitors.

Luca Cozzuto, Senior Bioinformatician at the Bioinformatics Technology Unit, Barcelona, Spain

Luca Cozzuto is a senior bioinformatician working at the Bioinformatics Technology Platform of the Centre for Genomics Regulation in Barcelona, Spain. He has a degree in Biotechnology and a Ph.D. in molecular medicine. His work primarily focuses on the analysis of high-throughput sequencing data in areas such as genomics, transcriptomics, epigenomics, and metagenomics.
Throughout his career, Cozzuto has collaborated with various international research teams and has published more than 40 peer-reviewed papers in scientific journals. Luca Cozzuto has contributed to the development of numerous Nextflow pipelines, which are designed to automate and streamline complex bioinformatics tasks, making large-scale data analysis more efficient and accessible to researchers worldwide. In addition to his research, Luca Cozzuto is actively involved in mentoring and teaching, contributing to the education and training of both biologists and bioinformaticians. From this year he is a Nextflow ambassador.

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MasterOfPores3: a suite of pipelines for nanopore sequencing data

I will present Master of Pores 3: a suite of Nextflow-based pipelines for fully reproducible processing and analysis of the Nanopore sequencing data, both cDNA and RNA, with a focus on in-depth analysis of direct RNA-seq data.
The package is composed of 4 pipelines: the first one (mop_preprocess) is for pre-processing of raw fast5 / pod5 files applying base calling (using either CPU or GPU) and read demultiplexing, filtering, aligning and assembling, producing a comprehensive report. The second pipeline (mop_mod) is used for predicting modified RNA bases applying four different approaches that can be chosen independently. The third pipeline (mop_tail) was developed to estimate the length of polyA tails using two independent methods. The fourth pipeline allows the calculation of a consensus of predictions output from the mop_mod pipeline, improving the sensitivity.
MoP3 is completely modular and scalable up to the amount of data produced by a PromethION flowcell. For small datasets, the integrated pipelines can be run on a laptop, and, for large datasets, in different HPC or cloud environments.

References:
"Nanopore Direct RNA Sequencing Data Processing and Analysis Using MasterOfPores" Cozzuto L, Delgado-Tejedor A, Hermoso Pulido T, Novoa EM, Ponomarenko J. N. Methods Mol Biol. 2023;2624:185-205. doi: 10.1007/978-1-0716-2962-8_13.

"MasterOfPores: A Workflow for the Analysis of Oxford Nanopore Direct RNA Sequencing Datasets" Luca Cozzuto, Huanle Liu, Leszek P. Pryszcz, Toni Hermoso Pulido, Anna Delgado-Tejedor, Julia Ponomarenko, Eva Maria Novoa. Front. Genet., 17 March 2020. https://doi.org/10.3389/fgene.2020.00211

Maite Huarte, Director of DNA and RNA Medicine Division and Head of the Noncoding RNA and Cancer Genome Lab at CIMA, Univ. of Navarra, Pamplona, Spain

Maite Huarte, current Director of the DNA and RNA Medicine Division at CIMA, Univ. of Navarra, Spain, earned her PhD at Autonomous Univ. of Madrid, focusing on the influenza virus interaction with the infected cell. During her postdoctoral tenure at Harvard Medical School, she identified novel histone demethylase enzymes, uncovering their impact on chromatin and cell identity. Later, at the Broad Institute of Harvard and MIT, she pioneered research on long noncoding RNAs (lncRNAs) in gene regulation. Since 2011, her group explores the contributions of lncRNAs to gene regulatory mechanisms, revealing their pivotal roles in cancer pathways such as p53 and their influence on chromatin and cell homeostasis. In recent years, they have explored the noncoding functions of RNA in the regulation of DNA replication, revealing RNA significance in preserving genomic stability.

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Noncoding RNA roles in the coordination of DNA replication and stress signaling

Regardless of their coding or noncoding nature, RNAs transcribed in the nucleus spend part of their life in the close environment of the chromatin, intervening in chromatin-associated processes. However, the impact that these nuclear RNAs play in different aspects of DNA replication and genomic stability is poorly understood. We recently found that RNAs are implicated in the initiation of DNA replication. ORC1, the pioneering subunit of the human Origin Recognition Complex, interacts with RNAs transcribed from genes with origins in their transcription start sites. By interacting with the IDR of ORC1, RNA regulates its phosphorylation and chromatin release, which is required for optimal activation of replication origins. Furthermore, we explored the association of RNAs with the nascent DNA beyond the step of initiation, identifying a new class of repetitive long noncoding RNAs that are specifically enriched at replication forks. The association of these lncRNAs has a negative effect on the efficiency and speed of DNA synthesis. I will elaborate on our new research findings, revealing distinct noncoding functions of RNA within chromatin, dynamically coordinating transcription and replication in human cells.

Eleonora Leucci, Professor at KU Leuven, [1]Laboratory for RNA Cancer Biology, Department of Oncology, KU Leuven, Leuven, Belgium. [2]Trace, Leuven Cancer Institute, KU Leuven, Leuven, Belgium

Eleonora Leucci obtained her PhD in Medical Biotechnology from the University of Siena (Italy) in 2007. She then moved to BRIC, University of Copenhagen (Denmark) where she worked on small and long non-coding RNAs in the lab of Anders Lund as a postdoctoral fellow. Since 2012, she moved to Belgium, where she was first a Marie Curie/VIB postdoctoral fellow in Chris Marine's lab and then an FNRS research associate at ULB, studying the role of lncRNAs in skin cancer. She received several national and international prizes in 2016 for her work on the lncRNA SAMMSON and she is the recipient of the MRA young investigator award 2018. Since 2017 Eleonora Leucci leads the laboratory for RNA cancer biology and heads the PDX platform TRACE at KU Leuven. Her lab studies RNA metabolism in cancer with particular focus on the characterization of long non-coding RNAs important for therapy resistance.

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Contribution of lncRNAs to the generation of drug-tolerant persister cells

Long non-coding RNAs (lncRNAs) generated from remote areas of the human genome constitute a major source of innovation for the adaptation to the numerous stresses encountered by cancer cells during progression and development of resistance. As such, research in this field offers a unique opportunity to study cancer evolution and unveil potentially novel biology. Over the years we have characterised several novel transcripts interacting with the translational machinery, either in the mitochondria or in the cytosol, and affecting the generation of drug-tolerant cells. These transcripts represent previously unexplored cancer-specific vulnerabilities and thus extend the palette of therapeutic opportunities to include RNA-based medicines.

Rory Johnson, Associate professor, University College of Dublin, Ireland

Rory Johnson is Associate Professor at University College Dublin (Ireland) and Adjunct Faculty at the University Hospital of Bern (Switzerland). The focus of his research is to understand the role of long noncoding RNAs in human health and disease by means of genomic and bioinformatic techniques. He received his MSc in Physics from Imperial College, London, in 2000. He won a Wellcome Trust PhD scholarship at the University of Leeds (UK), where he wrote a thesis on gene regulation in neurodegenerative disease (2007). He carried out postdoctoral work at the Genome Institute of Singapore into the application of next generation sequencing in mapping gene regulatory networks in embryonic stem cells. As a Ramon y Cajal fellow at the Centre for Genomic Regulation (Barcelona), he worked with the GENCODE consortium to develop comprehensive annotations of lncRNAs that formed the basis for thousands of studies. In 2016, he established the Laboratory for Genomics of LncRNAs (GOLD Lab), presently numbering 15 experimental and bioinformatic researchers. The lab also participates in international consortia including Genomics England and FANTOM.

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Non-protein coding RNA drivers of tumorigenesis

Tumours originate and grow through the acquisition of 'driver mutations', which alter gene function to enhance cell fitness. With the recent availability of thousands of tumour genome sequences, we have the opportunity to search for driver mutations and genes, both at scale and with high resolution. Amongst the most interesting yet poorly understood class of cancer genes are long noncoding RNAs (lncRNAs). Do driver mutations act through lncRNAs, and if so, how? To address this, we have developed improved driver discovery analysis pipeline, ExInAtor-PS, and applied it to the largest available cohort of 16,000 tumours from Genomics England. I will present the landscape of mutated lncRNAs and their clinical and genomic properties. Experimental inhibition of these lncRNAs reduces cancer cell viability. I will also present a new high-resolution driver methodology that sheds light on the molecular mechanisms linking mutations to cell fitness. Overall, driver analysis sheds light on how mutations in the non-coding genome contributes to tumorigenesis and may lead to future RNA-targeting therapies.

Isabel Barragan, Ph.D. Scientist and Group Leader of Translational Research in Cancer Immunotherapy and Epigenetics in Research Institute of Malaga and BIONAND platform and Group of Pharmacoepigenetics at Karolinska Institutet, Stockholm, Sweden

My current appointment is Principal Investigator at Institute of Biomedical Investigation, Málaga, Group Leader of CIMO2: Translational Research in Cancer Immunotherapy and Epigenetics. After returning to Spain from period of seven years of formation to become an independent group leader at Karolinska Institutet, I returned to Spain with a Marie Curie Fellowship and gained a position as a Principal Investigator at the Andalusian Public Health System. I am also affiliated at Karolinska Institutet as external lecturer and Master supervisor. I have a combined expertise in Pharmacology, Human Genetics and Cancer Epigenetics. My current line of research on Cancer Immunotherapy has a strong translational component and is based on clinical samples and data. My aim is to stand at the forefront of the genetic and epigenetic characterization of biomarkers in cancer, and the introduction of new regulatory layers for unveiling the mechanisms of resistance and for generating new therapeutic options.

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Non coding RNA regulation of the clinical response to Immune Checkpoint Blockade

Immune Checkpoint Blockade (ICB) constitutes a promising cancer treatment strategy that consists of reactivating the silenced T-cell cytotoxicity. In the pivotal trials, ICB demonstrated durable responses and acceptable toxicity, resulting in the regulatory approval of eight checkpoint inhibitors for 15 cancer indications. Indeed, in metastatic melanoma, anti-PD1 is a standard choice for first-line treatment (Checkmate-066, Keynote006). However, up to ~85% of patients present innate or acquired resistance to ICB, limiting its clinical utility. The identification of resistance and prognosis biomarkers for patient selection arises has become critical. Although FDA has approved PD-L1 expression, tumor gene mutation burden, and DNA repair defects as ICB response predictive biomarkers for several tumor types, the performance in melanoma is not sufficient. Our and others latest research shows the high complexity of the interaction between the host immune system and the tumor. Moreover, the best prediction models highlight the utility of the combination of several clinical and molecular layers. In an attempt to understand and decipher the role of the non coding RNA regulation on the response and prognosis in the context of ICB, we explored the relationship between non coding RNAs (lncRNAs), and circular RNAs (circRNAs). RNA-seq from 12 formalin-fixed paraffin-embedded (FFPE) samples from the metastatic biopsies of cutaneous metastatic melanoma patients treated with nivolumab was used to identify response-associated transcripts. Our findings indicate that specific lncRNAs and circRNAs, probably acting as competitive endogenous RNAs (ceRNAs), are involved in the regulatory networks of the immune response against the tumor. Moreover, we established a predictive risk score on overall survival (OS) and progression-free survival (PFS). This proof-of-principle work provides a possible insight into the function of ceRNAs, contributing to efforts to decipher the complex molecular mechanisms of ICB cancer treatment response.

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After completing a thesis at IBPC in Paris and a postdoc at Oxford, Antonin Morillon established a research team at CGM in Gif in 2005, later moving to Institut Curie for studying the noncoding genome in human cancer. As a CNRS Research Director and EMBO YIP since 2010, he now leads a research unit. thanks to national and international fundings, his team studies the Dark genome, aiming to understand its role in gene expression and to identify novel therapeutical tools.

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Dark genome and cancer

Long non-coding (lnc)RNAs regulate multiple cellular processes. Although they were predicted to lack coding potential, recent works revealed that lncRNAs can be translated, resulting in the production of lncRNA-derived peptides. However, despite the interest, the potential of these peptides and the mechanisms controlling their synthesis have been poorly characterized.
Here, we investigated the functional impact of non-canonical translation events on cytoplasmic lncRNAs in human cells.
We have recently shown that Xrn1-sensitive cytoplasmic lncRNAs (XUTs) in yeast are translated even in NMD-competent cells, suggesting that despite the cryptic nature of the transcript, its translation results in a detectable product. In human cells, we identified DIS3, and not Xrn1, as the main exonuclease restricting accumulation of lncRNAs in the cytoplasm and revealed thousands of DIS3-sensitive lncRNAs (DISTs). We show that DISTs also display active translation, producing peptides predicted to be high-affinity antigens in multiple myeloma patients carrying DIS3 mutations. Finally, immunogenic tests revel that the resulting neoAntigens can be recognized by T cell collected from patients' samples, opening new strategies for the next generation of immunotherapies.
Overall, our work highlights the central role of translation in the metabolism of cytoplasmic lncRNAs, with different potential outcomes. While the resulting peptides could constitute raw material exposed to the natural selection in yeast, we propose that some of them could be part of the cell-to-cell communication through tumor-specific antigen presentation in human cells.

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Dr Sandra Blanco is group leader at the Epitranscriptomics and Cancer Lab, in the Cancer Research Centre (National Council Research and University of Salamanca) and associate researcher at the Biomedicine Research Institute of Salamanca (Spain). Throughout her training at the Stem Cell Institute, Cambridge University, CIC-bioGUNE and CIC, she became expert in stem cell biology, pre-clinical models, epitranscriptomics, cancer, immunology, the development of novel tools to determine RNA modifications genome-wide. Her research has demonstrated how methylation of tRNAs regulate essential functions for stem cell maintenance and differentiation, migration and survival to stress in humans and mice. Her research has also established that mutations or aberrant expression of the writers of tRNAs can lead to cancer, and their inhibition are a promising strategy to eliminate cancer stem cells or to modulate the tumour immune microenvironment.

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Targeting tRNA methylases in cancer

Non-mutational events, particularly RNA post-transcriptional modifications, are emerging as key players in tumour development and progression in several cancer types. Emerging evidence show that self-renewal, survival and migration are regulated by epitranscriptomic marks, which may be a potential therapeutic target to specifically eliminate cancer cells.

By using genomic screenings, epitranscriptomic tools, CRISPR/Cas9 technology, proteomics, cell and mouse models and patient samples we aim to decipher the epitranscriptome in prostate cancer in order to implement novel therapeutic strategies. We found that overexpression of novel transfer RNA (tRNA) methyltransferases correlated with poor prostate cancer prognosis. Loss-of-function analyses resulted in reduced protein synthesis. Mechanistically reduced tRNA methylation resulted in reduced global protein synthesis of cell cycle and metabolic genes, but increased expression secretion and interferon signalling pathways regulators, resulting in increased infiltration of pro-inflammatory immune cells in tumours, cell proliferation and invasion *in cellulo*, and tumour formation and metastasis *in vivo*. In summary, we find that tRNA modifications regulate cell proliferation and invasion, metabolic pathways and the tumour microenvironment crosstalk by adapting the translational machinery.

Targeting tRNA methylation is emerging as an effective therapeutic tool to eliminate cancer cells. Whether targeting tRNA methylation alone, or in combination with agents targeting metabolic pathways or immunotherapy can be used as effective therapeutic tools needs further validation.

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Cellular and molecular heterogeneity in human cancer

Cancer is a highly heterogeneous disease, where phenotypically distinct subpopulations coexist and can be primed to different fates. Both genetic and epigenetic factors may drive cancer evolution, however little is known about whether and how such a process is pre-encoded in cancer clones. Using single-cell multi-omic lineage tracing and phenotypic assays, we investigate the predictive features of either tumour initiation or drug tolerance within the same cancer population. In Triple-Negative Breast Cancer models, we found that cancer evolution can be driven by a limited subset of clones within the parental population. Clones primed to tumour initiation *in vivo* display two distinct transcriptional states at baseline. Remarkably, these states share a distinctive DNA accessibility profile, highlighting an epigenetic basis for tumour initiation. The drug tolerant niche is also largely pre-encoded, but only partially overlaps the tumour-initiating one and evolves following two genetically and transcriptionally distinct trajectories. Our study highlights coexisting genetic, epigenetic and transcriptional determinants of cancer evolution, unravelling the molecular complexity of pre-encoded tumour phenotypes.

Short talks

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Impact of histone modifications and DNA methylation on cell plasticity and tumor heterogeneity of human hepatocellular carcinomas.

Hepatocellular carcinoma (HCC) is the third deadliest cancer in the world. Cell proliferation/differentiation ratios define two major HCC classes: *Proliferative HCCs* are poorly differentiated, highly invasive, enriched in cancer stem/progenitor cells, with a poor patient outcome; *Non-proliferative HCCs* are well-to-moderately differentiated, preserve the metabolic program of normal hepatocytes, with a better outcome.

The HepaRG human HCC cell line is a model of HCC heterogeneity. Upon low-density seeding, they exhibit an immature proliferative liver cell phenotype for 7 days. After 30 days in culture, they develop the morphology and metabolic functions typical of normal adult hepatocytes.

We applied full-genome Chromatin Immunoprecipitation Sequencing (ChIPSeq) to pull down histones H3K4me1, H3K27ac, H3K4me3 and H3K27me3 in immature proliferative (day 7) and differentiated hepatocyte-like (day 30) HepaRG cells. Also, we carried out DNA methylation sequencing by Nanopore MiniON on stem cell spheroids and day-30 cells. ChIPSeq results were integrated with publicly available ChIPseq data from 3 human HCCs. Nanopore results were compared with publicly available DNA methylation data from 370 human HCCs (TCGA). Both ChIPSeq and Nanopore results were validated with publicly available transcriptomics from 1750 HCCs (TCGA, GSE14520; GSE237977).

Activating histone modifications, DNA hypomethylation and upregulated RNA expression targeted oncofetal genes in immature proliferative cells and, conversely, hepatocyte-specific metabolism in differentiated hepatocyte-like cells. ChIPSeq and DNA methylation signatures of immature proliferative and differentiated hepatocyte-like cells matched *Proliferative* and *Non-proliferative* HCCs, respectively. Epigenetically activated genes in immature proliferative cells predicted overall and disease-free patient survival.
In conclusion, the data highlight the importance of epigenetic regulation on functional heterogeneity in human HCCs.

Keywords: Hepatocellular carcinoma, histone modification, DNA methylation, transcriptomics, tumor heterogeneity

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MEOX2 interaction with PRC2 and nuclear lamina components in glioblastoma stem cells suggests its possible role in the modulation of chromatin state

Glioblastomas (GBM) are primary brain tumours, currently incurable and characterized by a very short survival time from diagnosis. Years of research on the origin of GBM have led to the identification of glioblastoma stem cells (GSC), which are held responsible not only for the onset but also for resistance to therapies and for the spread of GBM. We previously performed RNA-seq and proteomic characterization in a cohort of patient-derived GSC lines, which led us to identify the extreme and specific overexpression of MEOX2 mRNA and protein in GSCs versus healthy brain tissue, cultured healthy astrocytes, and also versus human glioblastoma non-stem cell lines. We demonstrated that MEOX2 knock-down (KD) strongly reduced the survival and self-renewal capacity of GSCs, and produced a large perturbation of gene expression. Interestingly, among the large number of genes modulated in two distinct GSC lines KD for MEOX2, only a few overlapped, while the majority was different. In addition, reports published by other groups working on MEOX2 in GBM and specifically in GSCs, always failed to find a common set of genes consistently modulated by MEOX2, suggesting that this protein might play a role wider than that of a specific transcription factor, simply recognizing a defined consensus sequence in a common set of target genes. To investigate the molecular basis of the role of Meox2 in GSCs, we have performed a mass-spec analysis on proteins that were found to co-immunoprecipitate with Meox2 in a GSC line, and validated some of them by reverse co-IP in the same GSC line and in additional ones. Among them, we have found members of the nuclear lamina, known to play roles in the modulation of chromatin state, and members of the PRC2 complex. These protein interactions offer insights into the potential role of MEOX2 in the modulation of chromatin remodelling in GSCs, and might explain the dynamic and context-dependent effects of MEOX2.

Keywords: MEOX2, glioblastoma, stem cells, PRC2, nuclear lamina

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A breast-on-chip to link oxidative stress-mediated epigenetic changes in adipose tissue and breast cancer risk

Understanding the mechanisms underlying risk elevation is an essential pillar for cancer prevention. Yet, the contribution of the environment to increased cancer risk, by influencing the epigenome, is seldom understood. Among many environmental factors, we have begun by studying their common denominator: oxidative stress (OS), responsible for cellular aging, the strongest risk factor for breast cancer.

We are building a breast-on-chip model, recreating the architecture of the three compartments of the breast, to test the epigenetic effects of the exposome under physiological contexts. Cells in the microenvironment may influence breast cancer onset, notably adipocytes, themselves impacted by exposure-mediated OS. Our hypothesis is that exposome factors leading to OS induce epigenetic aging of the adipocytes, in turn changing the content of extracellular vesicles (EVs) released in the microenvironment.

As a first approach, we investigated differences in the phenotype of adipocytes upon aging. Mixed effects statistical models applied to six shape descriptors of chromatin morphometry of breast adipose cells on archival tissue sections demonstrate that bulk chromatin area is significantly increased in older women. To study OS effects *in vitro*, we have designed a pre-adipocyte differentiation method that best reflects *in vivo* tissue architecture, with a pre-adipocyte/adipocyte ratio of around 50/50, as indicated by the number and size of lipid vesicles. Treatment of adipose tissue with 25 µM of H_2O_2 for 10 days to induce chronic OS reveals an increase in adipocyte differentiation by approximately 10% in the cell population, and induces epigenetic aging, as shown by methylation of epigenetic clock genes.

We are currently studying the influence of EV content from epigenetically modified adipose tissue on the breast epithelium, and testing whether microRNAs from this major circulating EVs producer include biomarkers for breast cancer risk stratification.

Keywords: exposome, risk stratification, epigenetics, tissue-on-chip, aging

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Identification of novel partner proteins of EZH2 and KDM6B in Epithelial to Mesenchymal Transition

Epithelial to mesenchymal transition (EMT) is a progressive and reversible mechanism through which cells with an epithelial phenotype switch to a mesenchymal one. This mechanism has been linked to the formation of metastases in cancer. This switch in phenotype is the consequence of a wide reprogramming of gene expression that include, but is not limited to, adherence proteins such as E-Cadherin and N-Cadherin, these protein expression changes are tightly controlled by epigenetics. In particular, the methylation level of the Lysine 27 of the Histone H3 (H3K27) has been shown to vary significantly on the promoters of key genes during EMT. The methylation of H3K27 is regulated by the methyltransferase EZH2 (Enhancer of Zest Homolog 2) and the demethylase KDM6B (Lysine Demethylase 6 B). Interestingly, despite having opposite catalytic activities, both enzymes induce EMT when overexpressed in cancerous cells. This could be due to the recruitment of these enzymes towards different sets of genes by partner proteins. To investigate this, we used Rapid Immunoprecipitation Mass spectroscopy to identify proteins interacting with EZH2 or with KDM6B and associated with chromatin while using a TGFβ/TNFα treatment to induce EMT. We identified, in A549 cells (non-small cell lung carcinoma), 93 putative partners of KDM6B and 77 putative partners of EZH2. We then validated these interactions by Proximity Ligation Assay and co-immunoprecipitation and studied the importance of these proteins in establishing a mesenchymal phenotype using siRNA knockdowns. Investigating these proteins and the importance of their interaction with EZH2 and KDM6B during EMT could shed light on the way EZH2 and KDM6B activities are regulated during EMT as well as unravel new targets for cancer

Keywords: EMT, EZH2, KDM6B, H3K27me3, Interactome

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Targeting DNA methylation in cancers by selective dissociation of their protein complexes

Most of anticancer therapies face challenges due to resistance development, low efficacy, and lack of selectivity. Among them, epi-drugs, including DNA methyltransferase inhibitors (DNMTi), first appeared as a possible alternative to cytotoxic treatment but their lack of selectivity limit their use. DMNTs were shown to be involved in tumor suppressor gene (TSG) silencing and two nucleoside analogues, *i.e.* 5-azacitidine and 5-aza-2'-deoxycitidine, are FDA-approved DNMTi. However, their mode of action, *i.e.* DNA incorporation, lead to unselective targeting and non-nucleoside analogues are, to date not potent enough.

In this context, our project aims at exploring a new strategy to enhance DNMT inhibition selectivity and activity. Thus, we propose an innovative approach combining a DNMTi, interacting in the catalytic pocket, with a peptide sequence, disrupting DNMT complexes. Using AlphaFold2 Multimer (AF2M), an AI tool for protein structure prediction, we designed peptide-based DNMT inhibitors. Peptides mimicking interaction domains were then synthesized by solid-phase peptide synthesis. Their effectiveness was evaluated in a glioblastoma cell model, focusing on potential pro- or anti-tumoral effects. Global DNA methylation was assessed, qMSRE assays evaluated the specificity of synthesized peptides on protein-protein disruption and their impact on cancer hallmarks (cellular invasion, doubling time, and cell lysis) was measured. We identified a peptide that disrupts DNMT1/DMAP1 interactions without causing global DNA hypomethylation, selectively inhibits DNA methylation at specific sites and reduces cancer hallmarks. This peptide was linked to a DNMT inhibitor using a click chemistry reaction. The hybrid inhibitor is currently tested in glioblastoma models.

We believe that this strategy combining DNMTi and protein complex disruptor will offer a novel approach to selectively inhibit DNMT activity, enhancing the efficacy and specificity of existing DNMTi.

Keywords: DNA methyltransferases, protein-protein interactions, peptide, anti-cancer strategy, AlphafoldMultimer-2

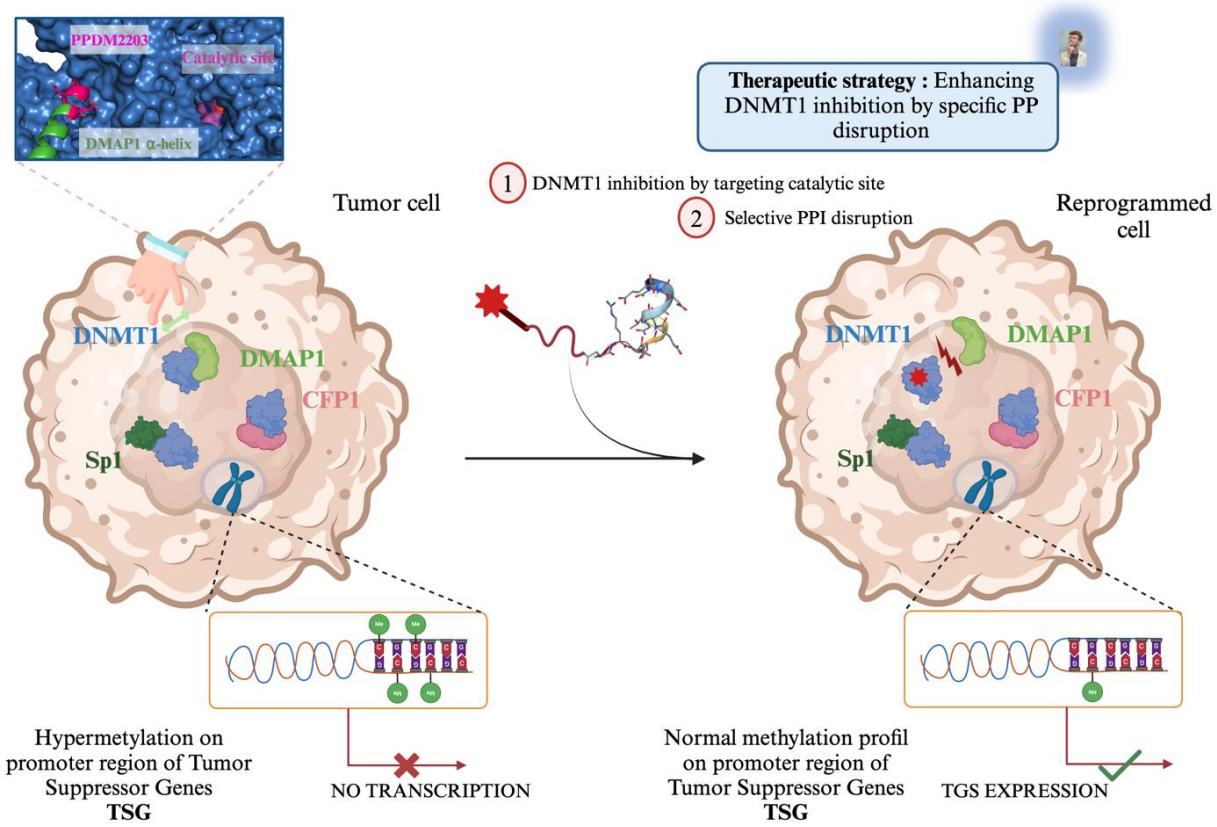

Figure 1. A new therapeutic strategy for targeting DNMT1 by peptide-based inhibitors

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DECOMICS, a user-friendly application for unsupervised cell type deconvolution and biological interpretation from tumor bulk methylome or transcriptomic data

Identification of the cell composition contributing to bulk molecular signals is a major challenge in molecular cancer analysis. The development of in silico deconvolution methods has made it possible to revisit existing bulk omic data from large patient cohorts with regard to intra-sample heterogeneity, and thus to compare sample cell composition with available clinical annotations such as treatment response.

Unsupervised deconvolution algorithms are often used to estimate cell composition from bulk tumor samples as unlike supervised methods, they can identify new cell populations or populations that would not have been taken into account a priori. However, applying unsupervised cell type deconvolution and interpreting the results remains a challenge, even more without prior training in bioinformatics.

Here we propose DECOMICS, a user-friendly shiny interactive web application designed to perform unsupervised deconvolution on methylome and transcriptomic data. Six different unsupervised methods are implemented in DECOMICS, including the most commonly used (ICA and NMF), and more recent algorithms (CDSeq, debCAM and PREDE, EDec). Our tool also provides guidance during the process and helps with the biological interpretation of the results. Decomics is highly adaptable, allowing for easy updates and redeployment as new reference-free methods or enrichment analysis databases become available. This flexibility ensures that Decomics remains at the cutting edge, capable of incorporating the latest technical and methodological advancements. We illustrate the significance and usefulness of our tool on different use cases involving transcriptomic and methylome data with known cell type proportions.

In conclusion, we propose an open-source and easy to use tool for estimating and identifying cell type composition from bulk methylome or transcriptomic data using cutting edge methodologies, which should be of significant interest for both bioinformaticians and clinicians.

Keywords: Tumor heterogeneity, deconvolution, unsupervised approaches, methylome, transcriptomic data

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Identification of the lncRNAs involved in resistance to KRAS G12C inhibitors in lung cancer

Background
Lung cancer is the leading cause of cancer-related mortality worldwide. KRAS mutations are present in 30% of lung adenocarcinomas with the KRAS G12C variant the most common. The development of covalent inhibitors targeting this variant is a recent clinical breakthrough. However, despite promising phase I/II clinical trial results, only 40% of patients initially respond to these treatments and most of them will develop resistance. Current research on resistance mechanisms is limited and predominantly focuses on genetic factors. Non-genetic mechanisms, including those involving long non-coding RNAs (lncRNAs), remain largely unexplored.
Our objective is to identify lncRNAs involved in resistance mechanisms to KRAS G12C inhibitors in non-small cell lung cancer (NSCLC).

Experimental Design
Using the ADCA72 cell line derived from a KRAS G12C-mutated patient, we generated adagrasib-sensitive and -resistant cells. Then, we conducted two types of long-read nanopore sequencing (direct RNA and cDNA) to identify differentially expressed lncRNAs between sensitive and resistant cells. Next, we performed a lncRNA CRISPR activator screen with a large sgRNA library targeting 10,000 lncRNAs in ADCA72 cells along with a deadCas9 coupled to a transcription activator.

Results
Long-read nanopore sequencings identified 19 significantly differentially expressed lncRNAs between sensistive and resistant cells using the cDNA approach and 2 lncRNAs by the direct RNA approach. Among them, one was common. Cross-referencing the results revealed that some candidates were associated with resistance using both the nanopore technology and the CRISPR screens. Interestingly, our analysis highlighted some lncRNAs previously described in resistance to chemotherapy but also uncharacterized lncRNAs.

Conclusion
Our study highlights the role of lncRNAs in resistance mechanisms to KRAS G12C inhibitors in NSCLC. It suggests that non-genetic mechanisms involving lncRNAs contribute to the development of resistance. Further functional research into these lncRNAs could provide new therapeutic targets and strategies.

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Identification of sponge mechanisms involving circular RNAs associated to cutaneous melanoma treatment resistance

Cutaneous melanoma, an increasingly prevalent skin cancer, is frequently associated with the BRAFV600E activating mutation. Despite the availability of BRAF inhibitors (BRAFi), resistance to treatment appears in most cases. To better understand these resistance mechanisms, our study focuses on the role of non-coding RNAs, recently described for their involvement in cancer. Among these, circular RNAs (circRNAs) have recently been discovered for their microRNA (miRNA) sponge function, which allows them to modulate the expression of miRNA target genes: they take on the role of competitive endogenous RNAs.

In this study, we present Cirscan (CIRcular RNA Sponge CANdidates), an interactive Shiny application that automatically infers circRNA–miRNA–mRNA networks from transcriptomic data from two biological conditions, in order to identify on a large-scale potential sponge mechanisms active in a specific condition. Cirscan ranks each circRNA–miRNA–mRNA subnetwork according to a sponge score that integrates multiple criteria based on interaction reliability and expression level. Finally, the top ranked sponge mechanisms can be visualized as networks and a functional enrichment analysis is performed to help the biological interpretation.
Applied to melanoma cell lines resistant or sensitive to BRAFi, Cirscan identified a dozen of sponge mechanisms associated to BRAFi resistance that we validated experimentally, providing novel potential therapeutic targets.

Keywords: Circular RNAs, Sponge mechanism, Transcriptomic data, Regulation network, Melanoma

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Mining the Human Breast Cancer Epitranscriptome: Opportunities for personalized medicine

Completely unsuspected features were recently discovered that gave impetus to a new field, termed 'Epitranscriptomics'. The exciting potential of RNA modifications to fine-tune complex functions of mRNAs is changing our perception of epigenetics. The most prevalent and best studied mRNA modification is N6-methyladenosine (m6A), which has been shown to influence mRNA stability, splicing, and protein translation. The importance of m6A in cancer is emerging. A recent study from our lab as well as others uncovered in preclinical models of breast and other cancers a new m6A-based layer of dysregulation of major oncogenic pathways driving cancer progression and therapy resistance. These studies point to a potential clinical value for m6A and warrant the study of this new epigenetic mark in human tumors. However, classic technologies do currently not allow for systematic m6A mapping in human tumor biopsies. We therefore explore Oxford Nanopore Direct RNA Sequencing for the detection of m6A in human samples. This unique and unprecedented analysis of the m6A methylome in human tumor samples could provide invaluable new insights into unknown epigenetic characteristics of cancer that could revolutionize how we diagnose and treat this disease. This presentation will focus on the challenges we encountered and the progress we have made in bringing RNA epigenetics to the clinic and we will share first insights from mapping m6A in clinical breast cancer samples.

Keywords: Epitranscriptomics, RNA modifications, m^6A, breast cancer

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Comprehensive single cell analysis of the epigenome of ovarian cancer

High-grade serous ovarian cancer, also known as high-grade serous carcinoma (HGSC), is the most common and deadliest type of ovarian cancer. Here we used a single cell epigenomic profiling that includes expression (scRNA) and chromatin accessibility (scATAC) from the same cells in order to expand our understanding of the microenvironment in fallopian tube epithelium (non-malignant) when compared with HGSC patients were the tumors have been surgically removed from two groups: naive and neoadjuvant chemotherapy.

We identified important differences between BRCA mutants and wild type especially in cancer stem cell signatures which are then associated with the up-regulation of immunosuppressive pathways. We also identified transcription factors that are associated with the expression of transposable elements, a key feature of malignancy that has yet to be defined at the single cell level. Using co-culturing systems, we were able to validate regulatory pathways and also model the immunosuppressive phenotypes.

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Enhancing sensitivity of Triple Negative Breast Cancer to DNA Damaging Therapy through chemical inhibition of the m6A methyltransferase METTL3

Triple-negative breast cancer (TNBC) is the most aggressive breast cancer subtype with a poor prognosis and high recurrence rate. Conventional chemotherapy and DNA damaging agents are the main treatment for this cancer. However, for patients with mutations in genes like BRCA1 or BRCA2 that impair the homologous recombination (HR) repair pathway, targeted therapies like PARP inhibitors offer a more promising response. N6-methyladenosine (m6A) is the most abundant internal mRNA modification, critically regulating mRNA processing and function. METTL3, the catalytic subunit of the m6A methyltransferase complex, installs m6A marks on mRNAs and is often upregulated in cancers, promoting tumorigenesis and drug resistance. Notably, TNBC exhibits high METTL3 activity, correlating with increased invasiveness and metastasis. Here, we demonstrate that STM2457, a selective METTL3 inhibitor, potently suppresses TNBC cell proliferation and migration in vitro and in vivo. Furthermore, STM2457 strongly synergizes with DNA damaging agents utilized in TNBC therapy, such as platinum-salts and the PARP1/2 inhibitor olaparib. Importantly, using patient-derived TNBC organoids with wild-type BRCA1 and BRCA2 genes, we show that METTL3 inhibition significantly enhances the efficacy of DNA-damaging chemotherapy and, crucially, sensitizes TNBC organoids to olaparib treatment. These findings suggest that incorporating small-molecule METTL3 inhibitors into standard TNBC therapy holds great promise. This approach could pave the way for innovative combination targeted therapies with improved anti-tumour efficacy and potentially reduced treatment-associated toxicities.

Keywords: METTL3, m^{6}A, TNBC, STM2457

Sponsor talks

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EpiNantes 2024 Active Motif - New advances in chromatin research, Clément Proux – Key Account Manager – France & South Switzerland

Active Motif is the industry leader in developing and delivering innovative tools to enable epigenetics and gene regulation research. Chromatin-associated proteins play critical roles in regulating various cellular processes such as gene expression, DNA replication, DNA repair, and cell differentiation. Understanding the binding patterns of these proteins can provide insight into how these cellular processes are regulated. CUT&RUN is a valuable tool for studying chromatin-associated proteins because it is sensitive, specific, and requires fewer cells than ChIP, making it ideal for identifying binding patterns of chromatin-associated proteins such as transcription factors or histone modifications genome-wide.
Active Motif has developed a complete and optimized CUT&RUN workflow including the CUT&RUN assay kit and the DNA Library Prep Kit for Illumina® designed to generate high complexity DNA libraries for NGS sequencing on Illumina® platforms.
In addition, identification of differences between data sets can be challenging when global modification changes occur. Inaccurate quantification of starting material or technical variation during processing can also results in variation across sample data. To overcome this challenges, Active Motif offers Spike-In reagents for ChIP-Seq and CUT&Tag data normalization, and has now
introduced a similar approach for CUT&RUN

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The Tn5 transposase unique properties have revolutionized the field of epigenomics. In this talk, we will focus on how it can be exploited in ATAC-seq to study global chromatin accessibility, as well as in CUT&Tag, a cheaper and faster alternative to ChIP-seq.
Diagenode's compatible solutions will be presented, and key technical points will be provided to ensure the best quality of results.

Emeric Roux, Alexandra Martin

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7-Color Instruments, more than 20-plex Assays: How Stilla Technologies is reinventing digital PCR

Stilla Technologies is the digital PCR company transforming complex genomic data into actionable insights across a wide range of research and clinical applications including cancer and liquid biopsy studies, cell and gene therapies, infectious disease detection, and food and environmental testing. Stilla's solutions include the industry's first 7-color digital PCR system, providing biomedical researchers and clinicians the highest multiplexing and detection capacity on the market.

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Epigenetics and the quality of procurement – MEDCHEMEXPRESS

A deep understanding of epigenetic mechanisms and their dysregulation is essential for developing innovative therapeutic strategies, particularly in areas such as cancer treatment. These strategies rely on epigenetic drugs, which target key areas of epigenetic dysregulation, focusing on three main pillars:

1. Chromatin & Histones (Acetylation): Histone modifications, such as acetylation, methylation, phosphorylation, and ubiquitination, play a central role in gene regulation. Acetylation is mediated by histone acetyltransferases (HATs) and deacetylation by histone deacetylases (HDACs). Histone demethylation is performed by the LSD (lysine-specific demethylase) family proteins (LSD1 and LSD2) and JmjC domain-containing histone demethylase (JHDM).
2. DNA Methylation: DNA methylation is primarily regulated by DNA-methyltransferases (DNMTs), with two main types: DNMT1, which maintains existing methylation patterns during cell replication, and DNMT3A/B, known as "de novo" DNMTs, which add methylation marks to previously unmethylated DNA.
3. Short Non-Coding RNA: Epigenetic-modifying enzymes can also be regulated by microRNAs (miRNAs). For instance, miR-34a inhibits the activity of SIRT1, thereby influencing cholesterol homeostasis.

At MedChemExpress, we offer a comprehensive range of cutting-edge compounds such as DNMT inhibitors (DNMTi), HDAC inhibitors (HDACi), and BET inhibitors (BETi), which are constantly evolving in the field of epigenetic therapies and are already making an impact in clinical settings.

Epigenetic alterations are commonly observed in cancer, leading to the formation of new cellular identities, which reveal specific biomarkers that can be targeted through immunotherapies. Recent studies highlight that combining epigenetic therapies with immunotherapies is a highly promising approach in combating cancer.

MedChemExpress supports epigenetics research by providing a wide selection of high-quality epigenetic inhibitors and antibody-drug conjugates (ADCs) targeting epigenetic markers. Our compounds are designed to be fast, efficient, and cost-effective solutions for researchers pushing the frontiers of cancer treatment and beyond.

Posters

P01

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MicroRNAs of small-extracellular vesicles derived from NSCLC cells dampen the CD8+ T cell response against tumor

Despite the development of immune checkpoint inhibitors therapy (ICI) in non-small cell lung cancer (NSCLC) patients, most of them eventually experience relapse, caused by impaired immune response. Antitumoral immune response is mainly promoted by CD8+ T lymphocyte (CD8 T cells). However malignant cells can escape this immune surveillance due to microRNAs (miRNAs) loaded into small extracellular vesicles (sEV) secreted by malignant cells. In this project we investigate the immunosuppressive effects of miRNAs of sEV derived from NSCLC on CD8 T cell immune response. To do so, NSCLC-sEV were purified from NSCLC patient-derived cell lines or from tumor resection. Their immunosuppressive effects were studied by exposing healthy or tumorinfiltrated CD8+ T cells to NSCLC-sEV, where their activation, proliferation, and viability were assessed. By NGS, the miRNAs cargo of NSCLC-sEV were investigated. Using bioinformatic analysis, we identified potential immunosuppressive miRNAs load into NSCLC-sEV that were tested by direct transfection in CD8+ T cells. First, we showed that CD8 T cells exposed to NSCLC's sEV were able to internalize sEV. CD8+ T cells exposed to NSCLC-sEV showed reduced expression of their activation markers CD25 and CD45, and decreased secretion of antitumoral TNFα, granzyme B, and perforin-1, suggesting that they are unable to conduct an efficient anti-tumoral response. NSCLC-sEV also upregulated the CD8+ immune checkpoint markers, such as PD-1, TIGIT, and TIM-3, and decreased the viability and proliferation of exposed CD8+ T cells. We showed that there was a common enriched miRNAs's profile in sEV derived from the different NSCLC cell lines. Transfection of our candidate miRNAs, miR-29c-3p and miR-181b-5p, into CD8+ T cells induced an inhibition similar to that induced by native NSCLC-sEV.

Overall, our results describe the immunosuppressive functions of NSCLC-sEV, that could be supported by their immunosuppressive miRNAs cargo.

Keywords: NSCLC, microRNAs, small extracellular vesicles, CD8 T cell

P02

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Role of the Sirtuin SIRT1 in the response to hypoxia in a colon cancer model

The Sirtuin SIRT1 acts as an epigenetic regulator through the modulation of the acetylation state of histones. It regulates the expression of genes involved in cellular processes such as cell survival and metabolism. It also deacetylates lysine residues of other non-histone and non-nuclear proteins. In colon cancer, SIRT1 is described as being overexpressed in early stages I, II and III compared to normal tissues, but downregulated in stage IV metastatic tumours. On the other side, studies carried-out on colon cancer models, have reported a tumour suppressor role of SIRT1 due to its ability to prevent the migratory and invasive potential of cancer cells.
Recent results from our laboratory have shown that SIRT1 is overexpressed, both at the mRNA and protein levels, in colon cancers compared to adjacent non-cancer tissue, and more intensely in right than left colon tumours. In addition, low expression of SIRT1 in the primary tumour is associated with a number of criteria of aggressiveness.
Several studies have shown the role of SIRT1 in the stabilization of HIF-1α which is associated with promotion of tumour aggressiveness under hypoxic conditions. In this study, we demonstrated that *SIRT1* mRNA expression is positively correlated with *HIF1A* mRNA expression, but negatively correlated to its target genes, in particular *ENO1* and *SLC2A1* in colon tumours with high hypoxia scores, using data from TCGA databases. We also studied the kinetics of HIF-1α protein stabilisation in correlation with SIRT1 in HT29 and HCT116 primary or SW620 and LoVo metastatic colon cancer cell lines subjected to either normoxic (21% O2) or hypoxic (1% O2) conditions. 5 to 16 hours exposure to hypoxia stabilized the HIF-1α protein and this was correlated with a downregulation of the SIRT1 protein in the SW620 and LoVo metastatic cell lines, but not in non-metastatic cell lines. Eventually, we investigated the consequences of SIRT1 downregulation in SW620 and HT29 subjected to both normoxic and hypoxic conditions on the invasive and migratory potential and epithelial-mesenchymal transition. Interestingly, invalidation of SIRT1 induced an increase of invasiveness in normoxia and hypoxia in both lines, but with different amplitudes.
The goals of our study are to determine whether SIRT1 serve as a prognostic marker in colon cancer and to identify its mechanisms of action.

Keywords: Sirtuin 1, HIF-1α, Hypoxia, Epithelio-mesenchymal Transition, Colon cancer

P03

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Characterization of long non-coding RNAs in TNBC using multiple orthogonal approaches

Long non-coding RNAs (lncRNAs) are regulatory RNAs involved in different molecular mechanisms. A major characteristic of lncRNAs is that their expression is highly context-specific, suggesting they may contribute in finely regulating gene expression in a cell-specific manner.
We recently exploited an approach combining single-cell multi-omic and lineage tracing in a triple-negative breast cancer (TNBC) model to investigate pre-encoded factors driving cancer evolution, as in the paper Nadalin F. et al, BioRxiv (2023). By this approach, we uncovered specific transcriptional states and DNA accessibility profiles typical of a cancer subpopulation (S1) with tumor-initiation capacity in vivo. The multiomic analysis of S1 highlighted the involvement of EMT-related protein coding genes but the contribution of lncRNAs to these tumor-initiating cells (TICs) specific gene regulatory networks (GRNs) remains elusive. We aimed at identify and functionally characterize those lncRNAs associated with TIC exploiting multiple high-throughput approaches in order to investigate their impact on global gene expression and their contribution to cancer initiation.
The functional characterization of the most likely candidates presents a significant challenge: while various silencing approaches are available, each tool has intrinsic limitations. CRISPRi showed high knockdown efficiencies but, as it is acting on the DNA locus, it cannot distinguish between locus- and transcript-dependent mechanisms. Transfection-based tools (ASOs or siRNAs) allow for transient knockdown at RNA level, while RNA-targeting CRISPR tools, such as the newly discovered CRISPR-Cas13 system, produce a stable silencing of the transcript, allowing for a permanent depletion of the molecule. Using some lncRNA candidates in a proof of principle study, we identified their respective advantages and limitations, allowing us to exploit their specific characteristics for functional validation of the candidates.
In conclusion, we advocate for the use of orthogonal approaches in studying lncRNAs, as this strategy enables discrimination between different molecular features underlying distinct mechanisms. This comprehensive approach is essential for a thorough understanding of the regulatory roles of lncRNAs sustaining cancer plasticity.

Keywords: lncRNAs, tumor initiating cells, triple negative breast cancer

P04

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Identification of circulating non-genic RNAs as novel early and multi-cancer biomarkers

Circulating tumor RNAs (ctRNAs) hold promise for cancer management as altered transcriptional states reflect tumor identity and evolution. Transcripts of retrotransposons, which are often reactivated in cancer, can provide a multi-cancer signature. In addition, deregulated expression of non-coding RNAs, such as long non-coding RNAs (lncRNAs), occurs in many cancers. ctRNAs can be found in the blood, notably in extracellular vesicles (EVs) which protect them from degradation and reflect molecular events in tumors. Many studies have highlighted the potential of miRNAs included in EVs as biomarkers for diagnosis, prognosis and monitoring response to treatment, but few have explored the biomarker potential of lncRNAs, whose expression is highly tissue- and condition- specific. Furthermore, the presence of circulating retrotranscripts following cancer-associated DNA hypomethylation remains largely unexplored. We postulated that non-genic transcripts could be sensitive and specific biomarkers of cancer, and that EVs could help to detect them. Here, we investigated whether Human Specific Long Interspersed Nuclear Element-1 (L1HS) RNA is associated to EVs-derived from cancer cell lines.

First, by bisulfite pyrosequencing, we examine the DNA methylation level of L1 in breast- and prostate-cancer cell lines, as well as in normal-like cell lines to identify those in which L1HS could be reactivated. We then produced and characterized EVs from these cells. We are now investigating whether L1HS RNA is re-expressed in hypomethylated L1HS elements in cancer cells, and whether L1HS RNA is associated with EVs. We will also focus on lncRNAs especially chimeric lncRNAs initiated from reactivated retrotransposons. We will then investigate this in EV-enriched, EV-depleted and unprocessed plasma samples to evaluate the best source of transcript biomarkers.

This study should identify highly specific circulating transcripts as biomarkers for better patient management in different cancer types.

Keywords: liquid biopsies, cell free RNAs, transposable elements, lncRNAs, extracellular vesicles

P05

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Characterization of the organized structure of the chromatin in human monocytes

French service members have a specific vaccine schedule all along their carrier. Mandatory vaccines aim to prevent infectious diseases outbreaks in specific military settings and preserve operational capacity. Immunization procedures and schedule must be constantly revised and optimized to adapt to emerging threats.
Vaccination is known to stimulate the memory of the adaptive immune system, including T and B lymphocytes, resulting in an enhanced and faster immune reaction against pathogens. Vaccination was also shown to stimulate and promote “a memory” of the innate immune system by involving epigenetic reprogramming. Understanding of epigenetic mechanisms and dynamics underlying this phenomenon may help to optimize vaccination strategies especially for service members who gets multiple vaccines.
This study was conducted to understand the chromatin architecture involved in the “epigenetic memory” of innate cells as monocytes. For this, we combined chromatin immunoprecipitation (ChIP)-qPCR and Assay for Transposase-Accessible Chromatin with high-throughput sequencing (ATAC-seq) technics.
First, peripheral mononuclear cells were purified from human whole-blood samples by density gradient centrifugations. Monocytes were enriched with Miltenyi CD14+ beads, then cultured and stimulated for 24h, before collection for ChIP-qPCR. We focused on two specific epigenetic marks, i.e. on trimethylation of histone H3 lysine 4 (H3k4me3) and acetylation of histone 3 lysine 27 (H3k27ac). Accumulation of these two marks at promoter site is associated with the positive transcription of the following gene. We aim to assess the enrichment of these marks in promoter regions of inflammatory genes in monocytes, under antigenic stimulations. The second experiment was designed, to evaluate vaccination effects on the chromatin structure. After enrichment, monocytes were directly collected for ATACseq. Open chromatin regions were assessed on monocytes from service members before and 1 month after heterologous prime boost SARS-COV-2 vaccination.
Our first results are a preview of the monocytes’ response after stimulations. Further experiments will analyze the hallmarks of the chromatin changes and their persistence among a prospective cohort of service members vaccinated with one or more mandatory vaccines.

Keywords: Monocytes, ChIP-qPCR, ATACseq, innate immune system

P06

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Unveiling gene regulatory networks (GRNs) in TNBC

Our lab focuses on investigating the transcriptional and epigenetic mechanisms underlying cancer phenotypes. We recently exploited an approach combining single-cell multi-omic analysis plus lineage tracing in a triple-negative breast cancer (TNBC) model to investigate pre-encoded factors driving cancer evolution in a heterogeneous cancer population, as described in the paper "Nadalin et al. bioRxiv"*. By this approach, we uncovered specific transcriptional states and DNA accessibility profiles associated with tumor initiation in vivo and drug tolerance in vitro. Notably, one of these transcriptional/epigenetic programs resembles a “hybrid EMT” state, recurrent in various cancer types and frequently associated with and responsible for tumor progression and metastasis outcome.
An outstanding and unresolved question is how this “hybrid EMT” state is regulated at the transcriptional and epigenetic level in human cancer (and specifically in TNBC). Integrating transcriptional and epigenetic data of cancer clones, we identified modules characterizing the Gene Regulatory Networks (GRNs) of cancer cells, composed of genes and their regulatory regions, classified as promoter-like or distal/proximal enhancer-like. A particular module (Module 1) stood out as the most characteristic for the cells with tumor-initiating capacity that are in the hybrid EMT state.
To explore the functional relevance of the regulatory elements within Module 1, we designed a CRISPRi library screening to target the components of key GRNs. This approach allowed us to repress candidate regulatory elements and assess their impact on cancer cell survival and proliferation. Hits were prioritized based on their significant effects on cellular functions and proliferation in both 2D and 3D conditions. By integrating CROP-seq and individual validation assays, we uncovered the importance of several enhancers proximal to Collagen genes. We started from a specific region near COL1A1 and its repression by CRISPRi platform led to a significant reduction in COL1A1 expression.
Integrating multi-omic data with functional genomics reveals the transcriptional, epigenetic, and genetic factors driving cancer evolution. This comprehensive approach enhances our understanding of cancer biology and uncovers the pre-existing states that contribute to tumor development.

* Multi-omic lineage tracing predicts the transcriptional, epigenetic and genetic determinants of cancer evolution
F. Nadalin, M.J. Marzi, M. Pirra Piscazzi, P. Fuentes, S. Procaccia, M. Climent, P. Bonetti, C. Rubolino, B. Giuliani, I. Papatheodorou, J.C. Marioni, F. Nicassio

Keywords: Enhancers – Subpopulations – TNBC – hybrid EMT - CRISPRi

P07

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Gene regulatory network analysis of an atlas of lymphoid stromal cells from follicular lymphoma patients revealed key transcription factors driving the polarization in cancer associated fibroblasts

Follicular lymphoma (FL) is an incurable and indolent liquid cancer originating from B cells, localized in the lymph nodes and invading the bone marrow in 70% of cases. In France alone, between 3000 and 5000 patients are diagnosed each year and 10% of patients do not survive up to 5 years after diagnosis, with relapses more frequent 5 years after diagnosis.
The tumour microenvironment (TME) is increasingly recognized as a critical factor in cancer prognosis and outcome. In FL, our team and others have extensively demonstrated the importance and modification of the TME in FL, particularly the stromal compartment. However, the molecular mechanism involved in the transition of the resident lymphoid stromal cells (LSC) to follicular lymphoma cancer-associated fibroblasts (FL-CAF), is still not fully understood yet. In this study, we studied the regulation/dysregulation of the gene regulatory network (GRN) composed of transcription factors and associated target genes during CAF commitment. To this end, we build an atlas of LSC and FL-CAF, including samples generated by our team and published dataset of both LSC and FL-CAF. Using UMAP of regulon activity, we were able to distinguish several clusters based on both LSC heterogeneity and tumour involvement (Figure 1). Furthermore, analysis of the GRN revealed a highly heterogeneous stromal landscape driven by key transcription factors such as STAT1 and STAT2. By investigating the impact of these STATs pathways, we demonstrated an implication of these transcription factors in the acquisition of the FL-CAF protumour phenotype.

Keywords: follicular lymphoma; cancer associated fibroblast; gene regulatory network; transcription factors

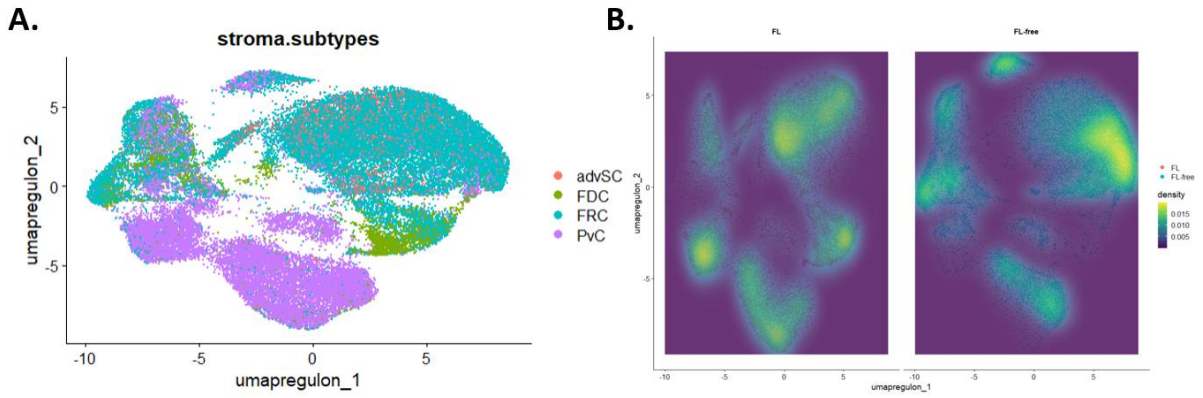

Figure 1 : UMAP of stromal cells Atlas, made with SCENIC GRN expression data
A. UMAP with each cells colored on cell type based on RNA expression
B. UMAP with differential density of points by pathological status

P08

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Effect of epigenetic dysregulations due to IDH2^{R140Q} expression on expression and splicing of inflammatory pathway genes

Myeloproliferative Neoplasms are chronic hematological malignancies characterized by an overproduction of blood cells. This disease is caused by acquired mutations activating proliferation pathways, particularly the JAK2-STAT5 pathway. The most typical and frequent mutation is JAK2^{V617F}. This disease can evolve to acute myeloid leukemia due to additional mutations affecting different mechanisms, mainly the epigenetics and particularly IDH2 which is often considered as epigenetic regulator.

Previous RNA-seq data from our team have shown the effect of IDH2^{R140Q} mutation. This mutation leads to a biphasic expression dysregulation of CCL2 and CD69 genes which are under-expressed at day 7 and subsequently over-expressed at day 14 of IDH2^{R140Q} expression. Along this dysregulation, the RNA-seq have shown a splicing dysregulation of ITGB3BP, particularly an increase of exon 10 exclusion.

In that context, we focus on verifying and increasing this dysregulation in alternative models.

To address that issue, the UT-7 and HL-60 cell lines were used. These cell lines inducibly (Doxycyclin) express the mutated alleles JAK2^{V617F} and IDH2^{R140Q}. Flow cytometry allowed to monitor inflammatory marks (CD69) and qRT-PCR expression of CCL2 and CD69 and splicing of ITGB3BP.

The results of qPCR on UT-7 cell line showed a reduction of CD69 expression of 7% at day 7, followed by and overexpression of 340% at day 14 and a reduction of CCL2 expression of 50% at day 7 followed by an overexpression of 380%. The results also showed an 70%-increase of ITGB3BP-exon 10 exclusion. Regarding HL-60 cell line, the flow cytometry showed a significant reduction of CD69- expression of 30% followed by and overexpression of 30%. Similarly, the qPCR showed a significant reduction of CD69-expression of 40% at day 7 followed by a significant overexpression at day 18.

These results confirm the expression dysregulation of CCL2 and CD69 as well as the increase of exon 10 exclusion of ITGB3BP in response to IDH2^{R140Q}. These results highlight the stability of our data on different cell lines models and reinforce the link between epigenetic, inflammation and cancer. Further efforts will focus on confirming these data on primary cells and study the epigenetic mechanisms involved in gene dysregulation.

Keywords: Epigenetics, MPN, AML, IDH2, inflammation

P09

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Identification of the role of circRNAs in BRAFi resistance in metastatic melanoma treatment

50% of the patients diagnosed with metastatic melanoma harbor the driver mutation V600E of the kinase BRAF, resulting in an uncontrolled cell growth. BRAF inhibitors (BRAFi) combined with MEK inhibitors (MEKi) are the main treatment in this case. However the majority of patients develop resistance. This resistance is linked to melanoma plasticity, which can be influenced by various noncoding RNAs, including long noncoding RNAs and circular RNAs (circRNAs). CircRNAs are abundant in the eukaryotic transcriptome and can act as miRNA sponges, preventing miRNAs from degrading their target mRNAs.

This project aims to decipher the role of the circRNA-miR-mRNA network in regulating BRAFi resistance genes in melanoma using comprehensive bioinformatics approaches. We particularly focused on the regulation of critical metastasis and BRAFi resistance regulators such as AhR, AXL, and EGFR. Using luciferase reporter assays, we identified miR-MRE interactions on the 3'UTRs of AhR, AXL, and EGFR, as well as on circRNAs.

Parallel overexpression of specific miRNAs through transfection of synthetic miRNA mimics led to the specific downregulation of AhR and AXL, as confirmed by qPCR and Western blot analysis. Additionally, depletion of specific circRNAs, such as circ_443 and circ_2805, resulted in decreased levels of AhR and EGFR.

We further explored the impact of each circRNA and miRNA on BRAFi sensitivity (sensitivity assay) and metastatic phenotype switch (spheroid assay) to propose new therapeutic strategies.

Keywords: Melanoma, BRAFi resistance, miRNA, circRNA, Interacting network

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Unraveling Metastatic Mechanisms in Osteosarcoma: Insights from Single-Cell RNA Sequencing of Osteoblastic and Chondroblastic Subtypes

Osteosarcoma is the most common primary malignant bone tumor. As with many cancers, the presence of metastases at the time of diagnosis leads to a significant decrease in survival rates. To identify the mechanisms associated with tumor dissemination, samples from both osteoblastic and chondroblastic subtypes were sequenced, including primary tumors metastases, using single-cell RNAseq. Analysis of these data revealed a group of chromosomally proximal genes overexpressed in a cell cluster characterized by a poor prognosis signature. Moreover, this same cluster appears to contain both osteoblasts and chondroblasts, which could indicate a convergence of the metastatic mechanism between osteosarcoma subtypes.

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Study of leptin impact on the global methylome of mammary epithelial cells

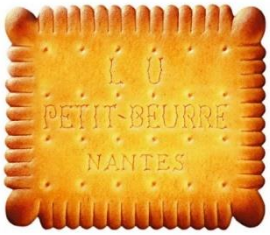
The search for the molecular causes of cancer occurrence represents a major challenge in the implementation of primary prevention policies and actions. In the context of the occurrence of breast cancers, two molecular causes can be identified: a high level of leptin linked to obesity and global DNA hypomethylation. Based on this dual observation, we sought to determine whether a high level of leptin could not be the cause of global DNA hypomethylation likely to induce or initiate tumor transformation of mammary epithelial cells.
To this end, MCF10A cells were treated with 5ng/ml (leptin level associated with a normal BMI) and 100ng/ml (leptin level associated with a BMI reflecting obesity) of leptin for 72 hours. Our results showed that the 100ng/ml leptin treatment of MCF10A cells induced global DNA hypomethylation, global DNA hyperoxidation (8-oxodG), global DNA hyperhydroxymethylation (5hmC) and ROS overproduction. The same correlation between these parameters was also observed from plasma samples of 30 women who donated their blood. Our study then identified the loss of DNMT1, DNMT3B expression and the elevation of alpha-ketoglutarate (αKG) level as 3 molecular actors responsible for the global DNA hypomethylation and hyperhydroxymethylation observed in MCF10A cells treated with 100ng/ml of leptin. Next, we wanted determine whether this global DNA hypomethylation affects the expression of genes regulating the epithelial-mesenchymal transition (EMT) of these cells. Our results showed no impact of leptin on the expression of genes associated to the EMT suggesting the absence of EMT in our model. Further, we showed that global DNA hypomethylation can be reversed by the use of nutricaments acting on DNA methylation, thus responding to the concept of nutriepigenetics. This result could be used as a starting point in the proposal of a preventive action to people at risk.

Keywords: Leptin, breast cancer, global DNA hypomethylation, DNA oxidation, Nutricaments.

Notes :

A bit of history….

Do you know this little cookie emblematic of Nantes?

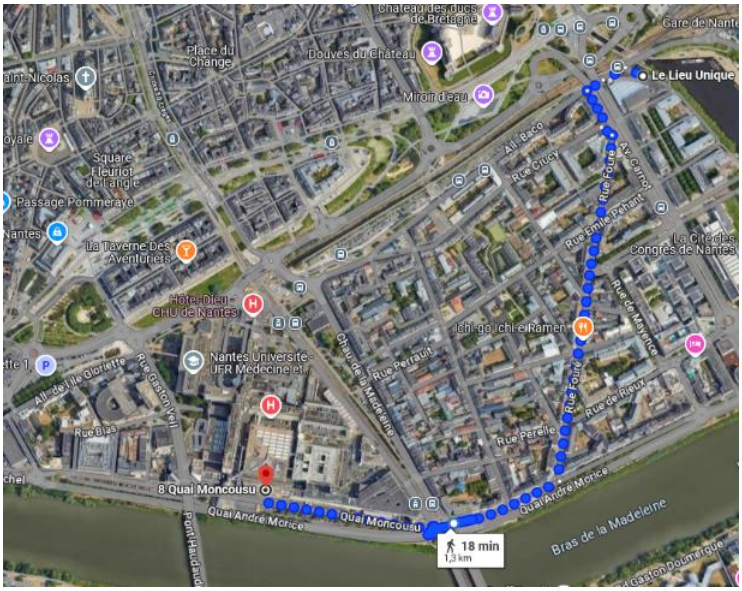


We've all, at least once, savored this little rectangular cake with its singular pattern. Children love to crunch the little teeth of the cookie before devouring it whole. However, you may not be aware of the anecdotes surrounding the designs of this seemingly unchanging Nantes cake, which has evolved over time. In 1886, in Nantes, Louis Lefèvre-Utile, who had modernized his family's traditional cookie factory in the heart of the city, imagined a typically Nantes shortbread cookie: Petit-Beurre LU was born.

Mr. Lefèvre-Utile's original idea was to create a cake that could be eaten every day. He came up with the original idea of incorporating time measurements into the design of the cookie itself:

- Originally, the Petit-Beurre measured 7 cm, or 1 cm for each day of the week.
- Its 52 teeth represented the 52 weeks of the year.
- The 4 corners of the cookie symbolized the 4 seasons.
- And the 24 small dots on its surface represented the 24 hours of the day.

Over time, the shape of the Petit-Beurre changed slightly: its dimensions were redesigned to optimize packaging, transport and storage. Tin cans, once used to promote the product, have been replaced by more practical packages. In fact, between the 19th century and today, Petit-Beurre LU has grown from a small-scale production to more than... 1 billion cookies sold every year!



Today, the LU factory in downtown Nantes has disappeared, but one of the towers has been symbolically preserved and transformed into a landmark of Nantes life, housing a café, a bar-restaurant and a concert hall: the Lieu Unique, the LU of modern times.

All this to say that we're looking forward to seeing you on Tuesday evening for the gala dinner at 8pm in the former LU factory at 2 rue de la biscuiterie in Nantes.

THANKS to all participants

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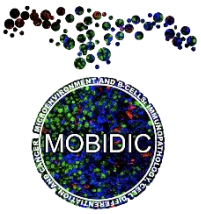
Our conviction: research will beat cancer.
Our ambition: to unleash the extraordinary potential of French cancer research.
Our goal: to one day succeed in curing cancer, all cancers.

In a world where cancer remains one of the first causes of mortality, we believe that **only research progress will allow us to cure all cancers !** That is the reason why research is at the core of our mission : research against all cancers, people-oriented, dynamic and positive, accessible to all.

Even if there are still a lot of challenges ahead of us, our every day mission is to draw the strategic orientations of research in oncology, to support the most innovative initiatives of today for tomorrow, to foster the most innovative projects, to detect, bring together and promote the most talented researchers, and to disseminate the knowledge that will allow us to face the disease.

Thanks to the discoveries of the scientists, boosted by the **surge of solidarity from donors,** we are now contributing to cure 60% of cancers. By 2025, we aim to bring this number to 2 cancers out of 3. Then, in the nearest possible future, we hope to win the battle: **succeed in curing cancer, every cancer.**

THANKS to the sponsors and partners



Rendez-vous at EpiBreizh 2026!
Keep in touch!