

*Symposium*

# Multiple roles of RNAs and their dysregulations in cancer

September 11<sup>th</sup>-13<sup>th</sup>, 2024

Institut Curie, Paris, France

## KEYNOTE SPEAKERS

Claire ROUGEULLE, FR

Ashok VENKITARAMAN, SG

## SPEAKERS

Laurence CALZONE, FR

Polly CHEN, SG

Pierre-Antoine DEFOSSEZ, FR

Anand JEYASEKHARAN, SG

Loredana MARTIGNETTI, FR

Dennis KAPPEI, SG

Antonin MORILLON, FR

Jason PITT, SG

Yvonne TAY, SG

Hélène SALMON, FR

Thomas WALTER, FR

## ORGANISING COMMITTEE

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Emmanuel BARILLOT (Institut Curie/PSL, FR)

Dennis KAPPEI (SCI/NUS, SG)

Yvonne TAY (CSI/NUS, SG)

Selena GAN (CSI/NUS, SG)



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# Welcome message

Welcome to the Single-Cell Res/volution 2024 a symposium jointly organized by Institut Curie and École normale supérieure, PSL University, France and Cancer Science Institute of Singapore, National University Singapore. We are thrilled to gather outstanding researchers in the fields of single-cell technologies and bioinformatics from both countries, united in our quest to exchange ideas and information for scientific advancement.

Cancer remains one of the most significant global health challenges, responsible for millions of deaths each year. To address this pressing issue, it is imperative that we develop better prognostic and therapeutic tools. Recent breakthroughs in single-cell sequencing technologies have revolutionized our understanding of cancer biology, enabling us to uncover hidden complexities and previously unknown aspects of this multifaceted disease. From illuminating the intricacies of the tumor microenvironment to unravelling tumor heterogeneity and exploring the fascinating realms of cancer plasticity and cancer stem cells, single-cell technologies have propelled our insights to unprecedented heights. Moreover, these techniques have also extended their impact to the realms of immunology and developmental biology, opening up new frontiers of knowledge in biomedical research.

In the spirit of collaborative progress, the core objective of Single-Cell Res/volution 2024 is to foster vibrant scientific discourse and promote fruitful collaborations between researchers in Singapore and France. By bringing together exceptional minds from diverse backgrounds, we aim to facilitate the exchange of ideas, promote interdisciplinary approaches, and ignite ground-breaking scientific discoveries. Beyond nurturing our existing scientific collaborations, we seek to forge new connections and kindle the sparks of inspiration that lead to transformative breakthroughs.

This three-day symposium serves as an exceptional platform for learning and the exchange of insights, where participants can engage in thought-provoking discussions, share their latest research findings, and gain valuable perspectives from esteemed experts in the field. By coming together, we can harness the power of collective knowledge and drive advancements in single-cell technologies and bioinformatics, pushing the boundaries of cancer research and paving the way for improved diagnostic, prognostic, and therapeutic strategies.

We extend our heartfelt gratitude to all the participants and sponsors, who have contributed their unwavering support to bring Single-Cell Res/volution 2024 to fruition.

Together, let us embark on this exciting journey of scientific exploration, collaboration, and discovery. We look forward to your active participation, engaging discussions, and the forging of lifelong connections that will shape the future of cancer research.

*Organizing Committee Single-Cell Res/volution 2024*

# Program

<b>Wednesday Sept 11<sup>th</sup></b>		Amphitheatre H�el�ene Martel-Massignac (BDD)
14h00	Emmanuel Barillot (Curie)	<i>Introduction to the joint symposium.</i>
14h30	Ashok Venkitaraman (CSI)	Keynote lecture: <i>Metabolic triggers for cancer evolution.</i>
15h30	Coffee break	Hall BDD
16h00	Thomas Walter (Curie)	<i>Computer Vision for the analysis of RNA point clouds in cells and tissues.</i>
16h30	Jason Pitt	<i>Leveraging artificial intelligence for conditional generation of cancer genomics profiles.</i>
17h00	Antonin Morillon (Curie)	<i>The cryptic dark transcriptome: an unexplored source of tumour specific antigens.</i>
18h00	Coktail	Hall BDD
20h00	Speaker dinner	Chez L�ena & Mimile

<b>Thursday Sept 12<sup>th</sup></b>		Amphith��atre Constant Burg
9h00	Polly Chen (CSI)	<i>The role of self-derived double-stranded RNA species in tumor immune evasion.</i>
9h30	Dennis Kappel (CSI)	<i>Turning on the lights for the adaptive immunity gene expression program in B-cells.</i>
10h00	Coffee break	Green caf�e
10h30	Yvonne Tay (CSI)	<i>Widespread alterations in 3'UTR processing regulate oncogene expression and cancer development.</i>
11h00	Anand Jeyasekharan (CSI)	<i>The spatial organization of cells expressing MYC and BCL2 affects immune microenvironment composition and prognosis in DLBCL.</i>
11h30	Laurence Calzone (Curie) & Loredana Martignetti (Curie)	<i>From data to mechanistic models.</i>
12h00	Poster, discussion with students and Lunch	Hall BDD
14h00	Platform visits, face to face meetings	
19h30	Speaker dinner (TBC)	Le Perraudin (TBC)

<b>Friday Sept 13<sup>th</sup></b>		Amphith��atre Constant Burg
9h00	Pierre-Antoine Defossez (CNRS/UPC)	<i>DNA methylation: stability, instability, and consequences.</i>
9h30	Claire Rougeulle (Curie)	Keynote lecture: <i>Control of X chromosome activity in early human development.</i>
10h30	Coffee break	Green Caf�e
11h00	H�el�ene Salmon (Curie)	<i>Combining Xenium/Merfish spatial transcriptomics and single-cell RNA sequencing to decipher the tumor-fibroblast crosstalk in lung and head &amp; neck carcinoma.</i>
11h30	Round-table discussion	

# **Presentations of speakers and organisers**

## Keynote Speaker



### Ashok VENKITARAMAN, MD, PhD

Director & Senior Principal Investigator,  
Cancer Science Institute of Singapore, NUS

**Title:** *Metabolic Triggers for Cancer Evolution.*

#### Abstract

Metabolic stresses present ubiquitous challenges to cellular homeostasis, which have been implicated in aging-related diseases such as cancer and neurodegeneration. In this talk, I will discuss recent work from my laboratory revealing unrecognized molecular mechanisms by which small-molecule products of metabolic stress induce alterations in nuclear and mitochondrial DNA that promote cancer evolution (1,2,4) and disease progression (3).

#### References

1. Tan et al (2017). Class of Environmental and Endogenous Toxins Induces BRCA2 Haploinsufficiency and Genome Instability. *Cell* **169**: 1105-18.
2. Renaudin et al (2021). BRCA2 deficiency reveals that oxidative stress impairs RNaseH1 function to cripple mitochondrial DNA maintenance. *Cell Rep* **36**: 109478
3. Ferrer et al (2023). Ketogenic diet promotes tumor ferroptosis but induces relative corticosterone deficiency that accelerates cachexia. *Cell Metab* **35**: 1147-1162.e7.
4. Kong et al (2024). A glycolytic metabolite bypasses 'two hit' tumor suppression by BRCA2. *Cell* **187**: 2269-87.

#### Biosketch

Ashok Venkitaraman is a Distinguished Professor of Medicine at the National University of Singapore, the director of the Cancer Science Institute of Singapore, and a Research Director at the Institute of Molecular & Cell Biology, A\*STAR. He learnt and practiced medicine at the Christian Medical College, Vellore, India before his Ph.D. with Sir Marc Feldmann at the University of London. After his postdoctoral work with Michael Neuberger, Ashok established his research group at the Medical Research Council (MRC) Laboratory of Molecular Biology, Cambridge, prior to his election as the inaugural holder of the Ursula Zoellner Professorship of Cancer Research at the University of Cambridge from 1998-2020. He was the director of the MRC Cancer Unit in Cambridge from 2006-2019.

Ashok's research has contributed fundamentally to our understanding of how human cancer is suppressed by genes that maintain the integrity of the genome. He has pioneered new technologies that enable the precise identification and validation of therapeutic targets, leading to the serial spin-out by Cambridge University of biotechnology firms based on his research.

Ashok's work has been recognized by international awards, and appointments to the advisory boards of leading academic and commercial organizations. He was inducted as a fellow of the Academy of Medical Sciences, one of the UK's four national academies, in 2001, and as a member of EMBO in 2004.

## Invited speaker



### Dennis KAPPEI, PhD

Principal Investigator, Cancer Science Institute of Singapore, NUS  
Assistant Professor, Department of Biochemistry,  
Yong Loo Lin School of Medicine, NUS

**Title:** *Turning on the Lights for the Adaptive Immunity Gene Expression Program in B-cells.*

#### Abstract

CIITA is the master regulator of MHC II gene expression and hence the adaptive immunity gene expression program. CIITA expression is tightly regulated by three lineage-specific promoters, pI, pIII and pIV, and can also be induced by IFN-gamma in non-immune cells. While key regulatory elements have been identified within these promoters, knowledge of transcription factors regulating CIITA is incomplete. Here, we demonstrate that the telomere-binding protein and transcriptional activator ZBTB48 directly binds to the critical activating elements within the B-cell-specific promoter CIITA pIII. ZBTB49 knockout impedes the CIITA-MHC II expression program induced by INF $\gamma$  and loss of ZBTB48 in mice silences MHC II in pro-B- an immature B-cells. The transcriptional regulation is enabled by the ZBTB48-dependent chromatin opening at CIITA pIII upstream of activating H3K4me3 marks. Thus, ZBTB48 primes CIITA pIII by acting as a molecular on-off-switch for B-cell-specific CIITA expression. I will discuss the possible implications of this regulatory mechanism on the tumor microenvironment in B-cell malignancies.

#### Biosketch

Research in the Kappei lab focuses on how telomere-driven genomic instability contributes to carcinogenesis by interrogating changes in telomeric chromatin with cutting-edge quantitative mass spectrometry approaches. Since many telomeric proteins moonlight as transcription factors (as illustrated by the project above), the lab further studies the mechanism and functional impact of their gene regulatory roles.

Dennis Kappei obtained his MSc degree from Ecole Normale Supérieure and University Paris VI and pursued his graduate studies at the Max Planck Institute of Molecular Cell Biology and Genetics under the roof of the Dresden International Graduate School for Biomedicine and Bioengineering. For his graduate work he was awarded the Georg Helm Prize by TU Dresden. Currently, he is a Principal Investigator and the Head of the Quantitative Proteomics Core at the Cancer Science Institute of Singapore (CSI) and an Assistant Professor in the Department of Biochemistry in the Yong Loo Lin School of Medicine at the National University of Singapore. Dr Kappei has been awarded membership to the EMBO Global Investigator Network (GIN) in 2024.

## Invited speaker



### Yvonne TAY, PhD

Principal Investigator, Cancer Science Institute of Singapore, NUS  
Associate Professor, Department of Biochemistry, NUS

#### Title:

*Widespread Alterations in 3'UTR Processing Regulate Oncogene Expression and Cancer Development.*

#### Abstract

Most mammalian genes generate messenger RNAs with variable untranslated regions (UTRs) which are important post-transcriptional regulators. In cancer, 3'UTR shortening via alternative polyadenylation can activate oncogenes. However, 3'UTR splicing remains poorly understood as splicing studies have traditionally focused on protein-coding alterations. Here, we systematically map the pan-cancer landscape of 3'UTR splicing. We find that 3'UTR splicing is widespread, upregulated in cancers, correlated with poor prognosis and more prevalent in oncogenes. Targeted inhibition of 3'UTR splicing efficiently reduces oncogene expression and impedes tumor progression. Notably, we identify CTNNB1 3'UTR splicing as the most consistently dysregulated event across cancers and demonstrate that its spliced 3'UTR variant is the predominant contributor to its oncogenic functions. Overall, our study provides the first compendium of 3'UTR splicing in cancer and may launch new avenues for RNA-based anti-cancer therapeutics.

#### Biosketch

Yvonne began her research career in Bing Lim's lab at the Genome Institute of Singapore, where she studied miRNA function and mechanisms of action (Tay et al, Nature 2008). She then pursued her postdoctoral training in the Pandolfi lab at Harvard Medical School, where she investigated how transcripts can co-regulate each other by competing for shared miRNAs (Tay et al, Cell 2011). Now based at the Cancer Science Institute of Singapore and National University of Singapore, Yvonne's research group studies non-coding RNAs as well as the non-coding regions of protein-coding mRNAs (untranslated regions, UTRs; Chan et al, Nat Cell Biol 2022). As many mRNA populations comprise transcripts with different UTRs, and these UTRs control key processes such as stability, localization and transport, a better understanding of their function may lead to insights into the regulation of key cancer genes.

## Invited speaker



### Polly Leilei CHEN, MD, PhD

Principal Investigator, Cancer Science Institute of Singapore, NUS  
Assistant Professor, Department of Biochemistry,  
Yong Loo Lin School of Medicine, NUS

**Title:** *The Role of Self-derived Double-stranded RNA Species in Tumor Immune Evasion.*

#### **Abstract**

Cancer remains a significant global health concern. One of the main challenges in developing effective treatments for cancer is the ability of tumors to evade the immune system. While substantial progress has been made in understanding how cancers escape immune responses, strategies to overcome this are still lacking. Intriguingly, recent research has shed light on the crucial role of double-stranded RNA (dsRNA) molecules in regulating tumor immunity, identifying it as a novel and critical mechanism in immune evasion in cancer. Identifying which dsRNAs are involved and understanding how they are recognized and modified to facilitate immune evasion will enable the development of new and innovative treatments that address the challenges of unresponsiveness and resistance to immunotherapy. Adenosine-to-inosine (A-to-I) RNA editing, mediated by the enzyme ADAR1, is a recently discovered immune protector that destabilizes self-derived dsRNA species through its editing function to prevent the triggering of interferon responses. In this talk, I would like to share our latest findings, focusing on the intricate interplay between ADAR.

#### **Biosketch**

Dr. Polly Leilei Chen received her Bachelor of Medicine and completed her medical training in China before earning her PhD in 2010 from the University of Hong Kong. In 2014, Dr. Chen joined the National University of Singapore (NUS) as a Principal Investigator at the Cancer Science Institute of Singapore, concurrently assuming the role of Assistant Professor in the Department of Anatomy. She was promoted to Associate Professor in 2021. Dr. Chen is an EMBO Young Investigator and an Asian RNA Research Ambassador. She currently places her research focus on functional and mechanistic investigation of RNA changes (particularly RNA editing, modification, and splicing) leading to cancer initiation and development; and the development of novel cancer therapies targeting these cancer-associated RNA changes.

## Invited speaker



### Anand JEYASEKHARAN, MD, PhD

Principal Investigator & Head of the Microscopy and Multiplexed Assay Core, Cancer Science Institute of Singapore, NUS  
Assistant Professor, Department of Medicine, NUS  
Senior Consultant, Department of Haematology-Oncology, National University Cancer Institute, Singapore

**Title:** *The Spatial Organization of Cells Expressing MYC and BCL2 Affects Immune Microenvironment Composition and Prognosis in DLBCL.*

#### Abstract

Point process analyses are widely used in ecology and geography to understand the impact and relevance of spatial distribution of points in a complex system. To date, only a few studies have explored point process analyses in the context of tumor heterogeneity. Malignancies often show variable patterns of cellular distribution, and the relationship of these topographic variables with underlying biological processes and clinical outcomes is not well understood. Here, we performed spatial point process analyses in diffuse large B-cell lymphoma (DLBCL), leveraging advances in multiplexed immunohistochemistry and cellular phenotyping, with downstream multi-omic and clinicopathological analyses. We have previously demonstrated that cellular co-expression of the oncogenes MYC and BCL2 in the absence of BCL6 (M+2+6-) in DLBCL confers a poor prognosis (Cancer Discovery, 2023). Building on this work, we modeled the spatial organization of M+2+6- cells within DLBCL using x-y coordinate information from multiplexed fluorescent immunohistochemistry (mFHC) in four independent cohorts. We derived spatial point patterns, upon which Geyer point process models were applied, and found that patients could be stratified into “clustered” and “dispersed” groups based on M+2+6- spatial organization. Cases with predominantly “dispersed” M+2+6- cells showed shorter overall survival in all analyzed cohorts. Multi-omics analyses were performed to identify potential biological explanations for this association between topography and clinical outcome: Through the integration of transcriptomic information from digital spatial profiling as well as bulk and single-cell RNA sequencing, we observed that lymphomas with an M+2+6- “dispersed” phenotype had an immunologically cold microenvironment enriched in Tregs and exhausted CD4+ and CD8+ T cell, with malignant B-cells expressing potentially targetable immune checkpoints such as LAG3. This work represents the first demonstration that the spatial distribution of malignant cell subpopulations in lymphoma can embody biological and clinical significance.

#### Biosketch

Anand is a principal investigator at the Cancer Science Institute of Singapore and a senior consultant medical oncologist at the Department of Haematology-Oncology, National University Cancer Institute, Singapore. He obtained his undergraduate medical degree from Christian Medical College Vellore, India and then received a Gates Cambridge Scholarship towards a PhD in Oncology at the University of Cambridge UK, followed by training in Internal Medicine and Medical Oncology at National University Hospital, Singapore. Anand has a special interest in the treatment of lymphomas/sarcomas, as well as personalized therapy for rare and advanced cancers. His research interests are in the use of spatial/ imaging assays to understand drug resistance, and on ex-vivo combination drug testing for personalized medicine. Anand is also a platform lead for a national translational research program in cancer through the Singapore Translational Cancer Consortium (STCC).

## Invited speaker



### Jason PITT, PhD

Principal Investigator, Cancer Science Institute of Singapore, NUS

**Title:** *Leveraging Artificial Intelligence for Conditional Generation of Cancer Genomics Profiles.*

#### **Abstract**

Somatic mutations are a fundamental component of genomic instability underlying cancer development. In precision medicine, predictive models can use the patterns within mutational profiles to stratify patients, aiding recommendations. To achieve optimal performance and generalizability, deep-learning-based predictive models often require large amounts of training data. In the past decade, the pan-cancer consortium efforts (i.e. TCGA, PCAWG) have shown that cancer is highly complex and heterogeneous with heavily underrepresented phenotypes. Predictive models trained on such imbalanced datasets may be biased towards overrepresented patients and show poor performance on underrepresented patients. Generative models have shown to be highly effective in generating images, audio, and textual data. We hypothesize that generative models can also be used to generate cancer mutational profiles. We trained a conditional variational autoencoder on the PCAWG and European breast cancer (BRCA-EU) datasets and generated biologically plausible mutational profiles with specified phenotypes including cancer type and subtype, and gene mutational status. We ask if these generated synthetic data can bolster the training of predictive models in precision oncology. We have also begun to explore if similar approaches can aid the identification of rare cell types from single cell datasets.

#### **Biosketch**

Dr. Jason Pitt received his Ph.D. in Genetics, Genomics, and Systems Biology from the University of Chicago where he used data-intensive computing to explore germline and somatic variation in cancer. He is currently a Principal Investigator and Head of the Genomics and Data Analytics Core at the Cancer Science Institute of Singapore. There his laboratory uses a combination of computation, software engineering, and biological knowledge to analyze and democratize large-scale cancer genomics data. Scientifically, they leverage this data to identify features and correlates of genome instability – a cancer hallmark with therapeutic implications. Their efforts promote precision oncology through both novel biomarker discovery and innovative digital health solutions.

## Keynote Speaker



### Claire ROUGEULLE, PhD

Director of the Research Center of the Curie Institute

**Title:** *Control of X chromosome activity in early human development*

#### **Abstract**

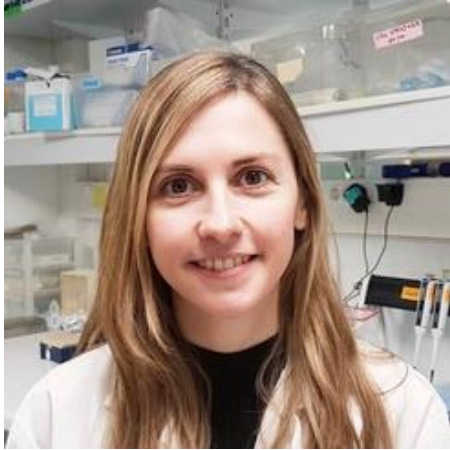
X chromosome inactivation in mammals is an essential epigenetic process involving long non-coding RNAs (lncRNAs), which compensates for X chromosome imbalance between sexes. XCI is established early during female development, at peri-implantation stages, and is triggered by the accumulation of XIST lncRNA, which recruits a plethora of factors leading to transcriptional silencing and chromatin reorganization. This process has been mainly studied in the mouse where embryonic stem cells (ESCs) have been instrumental to characterize the actors of the process, and to unravel the kinetics of the molecular events leading to the transcriptional silencing of one of the two X chromosomes. However, it is now known that X-inactivation initiates through remarkable diverse strategies in different species. We are using primate ESCs as a model system for early primate development, to characterize the early stages of X chromosome inactivation and to identify regulators of the process in primates.

#### **Biosketch**

Claire Rougeulle research focuses on X chromosome inactivation in mammals, as a paradigm of epigenetic regulations. Her team's work interrogates the role played by non-coding RNAs in this process and in the plasticity of epigenetic regulations in evolution. Her group is currently studying the control of X chromosome activity in relation to cell fate in human and non-human primates.

Claire Rougeulle is a CNRS Research Director and the Director of the Institut Curie Centre de Recherche. She is also Deputy Director of the Epigenetics and Cell Fate Unit (CNRS/Université Paris Cité) and Coordinator of the Labex (laboratory of excellence) research consortium "Who Am I?", which addresses, in a multidisciplinary manner, the question of identity. She is EMBO member since 2016 and has been awarded the CNRS bronze and Silver Medals in 2007 and 2019.

## Invited speaker



### H el ene SALMON, MD, PhD

Head of the Team Stroma and immunity,  
Department of Immunity and Cancer at Institut Curie, Paris

**Title:** *Combining Xenium/Merfish spatial transcriptomics and single-cell RNA sequencing to decipher the tumor-fibroblast crosstalk in lung and head & neck carcinoma.*

#### **Abstract**

Cancer-associated fibroblasts (CAF) and the extracellular matrix they produce are key drivers of T cell marginalization in solid tumors. We recently described two CAF states associated with T cell exclusion in human lung cancer. We now aim to investigate the molecular crosstalk between tumor cells and their surrounding fibroblasts that can drive T cell-excluding CAF phenotypes. Here will be presented recent data of Xenium and MERFISH spatial transcriptomics performed on tumor samples from Non Small Cell Lung Carcinoma (NSCLC) as well as Head and Neck Squamous Cell Carcinoma (HNSCC) patients. I will discuss the challenges of cell segmentation to analyze elongated cells such as fibroblasts, and the important contribution of single-cell RNA sequencing data for optimal cell identification and deeper analysis of the molecular interplay between cell types in the tumor microenvironment. The data will include untreated NSCLC resections and HNSCC tumor samples from a clinical trial assessing the effects of combined PD-L1/TGFb therapy.

#### **Biosketch**

H el ene Salmon's research focuses on immune cell dynamics in solid tumors and on cancer immunotherapy strategies modulating the tumor microenvironment. Her prior work shed light on the importance of the stromal extracellular matrix in the control of T cell migration in human solid tumors, and showed that the paucity of activated CD103+ dendritic cells in tumors limits checkpoint blockade efficacy. The main goals of her team's research are to define the contribution of stromal cells to tumor immunity and to develop new strategies to target the stromal compartment and improve tumor response to current immunotherapies.

## Invited speaker



### Antonin MORILLON, PhD

Research Director (1st Class) at the CNRS  
Group leader of the ncRNA, epigenetic and genome fluidity team,  
Institut Curie, Paris

**Title:** *The cryptic dark transcriptome: an unexplored source of tumour specific antigens*

Join work with Dominika Foretek, Marc Gabriel and Olivier Namy, funded by grant ERC DARK, MSCA Marie Curie

#### **Abstract**

Long non-coding (lnc)RNAs regulate multiple cellular processes. Although they were predicted to lack coding potential, recent works have revealed that some lncRNAs can be translated, resulting in the production of lncRNA-derived peptides. However, despite the interest they arouse, 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 reveal 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.

#### **Biosketch**

Our team is interested in understanding long non coding RNA (lncRNA), their processing and functional significance, from yeast to human, by using large scale transcriptomic and genetic engineering strategies. Our approaches use in vitro model organisms to tumor collected from breast cancer, prostate cancer and lung cancer patients in collaboration with hospital teams.

## Invited speaker



### Pierre-Antoine DEFOSSEZ, PhD

Principal Investigator at Université Paris Cité

**Title:** *DNA methylation: stability, instability, and consequences.*

#### **Abstract**

Epigenetic marks ensure genome stability as well as proper transcriptional activity in many species including mammals. Therefore, it is essential for mammalian cells that these marks be properly reproduced when cells divide. Progress has been made towards a mechanistic understanding of this "epigenome replication", yet results by us and others show that the picture is incomplete and that some of the existing models need revision. A first aim of our work is to use our new cellular tools, together with genetics and proteomics, to clarify these mechanisms. The tools we have also allow us to address a different, but related question: how do cells respond and adapt to epigenetic disturbances? This question is the topic of our second research aim. Lastly, our third aim will tackle an important and open problem, which is : "How can we identify epimutagens?", i.e. molecules present in cells or in the environment that decrease epigenome stability. We have built and validated a powerful cellular system that will not only enable the identification of epimutagens, but will also help delineate their mode of action.

Altogether, our three aims will clarify how the epigenome is maintained, how cells respond to epigenome instability, and how the intracellular and extracellular environments can affect epigenome stability. This work has direct implications for human health and diseases, especially cancer.

#### **Biosketch**

Pierre-Antoine Defossez studied biology at Ecole Normale Supérieure. He carried out his PhD work with Dominique Stéhelin and 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.

## Organiser



### Emmanuel BARILLOT, PhD

Director of the Department of Computational Oncology, Institut Curie  
Scientific Director of the Institut Curie Bioinformatics Core Facility

#### Biosketch

Emmanuel Barillot research focuses on Computational Systems Biology of Cancer and aims at understanding tumorigenesis and tumor progression using artificial intelligence for analysing high-throughput multimodal data of tumors like multiomics, imaging and other health record data. Both these data and prior knowledge are combined in frameworks that aim at building digital twins to predict drug response and improve therapeutic strategies. These approaches use machine learning as well as modeling and simulation of signaling networks and of spatial organization.

Emmanuel Barillot heads the Department of Computational Oncology at Institut Curie (U900 INSERM, in partnership with Mines ParisTech). He is also Scientific Director of the Institut Curie Bioinformatics Core Facility, which is expert in biological data integration, omics data analysis, and support for precision medicine. He holds a Chair in Cancer Genomics at the Paris Artificial Intelligence Research Institute (PRAIRIE). Emmanuel Barillot has published ~250 articles in bioinformatics, genomics, systems biology, cancer biology, translational and clinical cancer research, biophysics and computer science.

## Invited speaker



### Thomas WALTER, PhD

Professor at Ecole des Mines de Paris  
Director of the Centre for Computational Biology CBIO at Mines Paris  
Codirector of the Department of Computational Oncology at Institut Curie  
Chair at the Paris Artificial Intelligence Research Institute PRAIRIE

**Title:** *Computer Vision for the analysis of RNA point clouds in cells and tissues.*

#### Abstract

Gene expression is one of the most fundamental processes in living system, tightly controlled by a large variety of signals across space and time. Single Molecule Fluorescence in Situ Hybridization (smFISH) allows to visualize individual RNAs inside cells and is thus the method of choice to investigate spatial gene expression patterns at the cellular and the tissue level.

Subcellular localization of mRNAs is thought of as playing an important role for the spatial control of gene expression. However, the function and mechanism of RNA localization are not yet well understood. In addition, it is still unclear which localization patterns exist and which mRNAs distribute according to which localization pattern. These questions can be addressed by large-scale image-based assays, where individual mRNA molecules are visualized by smFISH. Here, I present an analysis framework to automatically analyze smFISH images for cell-based assays in order to infer the localization patterns according to which mRNA molecules distribute in cells [1-3]. Application of these methods to a dual protein/RNA localization screen revealed the discovery of specialized translation factories, potentially enabling a new gene regulatory mechanism [4].

Variants of smFISH can also be used to study tissue architecture, by analyzing the spatial arrangement of different cell types composing the tissue. This technique is often referred to as image-based spatial transcriptomics or spatial profiling. One of the bottlenecks of these methods is cell segmentation. Here, I present a new method for the segmentation of cells solely based on RNA point clouds, and thus leveraging the differences in the expression profile of cells [5].

Together, these methods provide important tools to reach a deeper understanding of gene expression at the single-cell and the tissue level.

#### References

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5. Defard et al (2024) A Point Cloud Segmentation Framework for Image-Based Spatial Transcriptomics. *Commun Biol* **7**:823.

#### Biosketch

Thomas Walter received his PhD from the Centre for Mathematical Morphology, Mines Paris-Tech. After 6 years of work at the EMBL Heidelberg, he joined the Centre for Computational Biology (CBIO, Mines ParisTech) in 2012.

## Organiser & speaker



### Laurence CALZONE, PhD

Research Engineer at Curie Institute

Co-head of the Computational Systems Biology of Cancer team

**Title:** *From data to mechanistic models*

Joint talk with Loredana Martignetti

#### **Abstract:**

Network models are a common and powerful formalism for studying cell functioning and its deregulations during cancer. They allow the integration of a large number of entities into a single complex network. However, the analysis of these large networks remains a challenge.

Here, we explore a novel topic modeling approach for integrating data from multiple omics. We showcase two examples of this approach: in the first one, we applied topic modeling to examine the transcriptional heterogeneity of breast cancer cells and identifying protein-coding genes and long non-coding RNAs (lncRNAs) that group thousands of cells into biologically similar clusters.

In the second one, we conduct an integrative multi-omics study of medulloblastoma patients to classify patients into molecular similar subgroups.

The output of the topic modeling analyses is interpreted as weighted signatures per cancer subgroups encompassing transcription factors, long non coding RNAs, proteins and phosphorylated states of kinases. Then, we used this information to build network models specific for each disease subgroup. These networks can be used as basis for mathematical modeling and dynamical simulations to predict possible points of intervention.

#### **Biosketch**

Dr Laurence Calzone (Institut Curie, France) is a research scientist at Institut Curie. She has published mathematical models using several formalisms including nonlinear ordinary differential equations, Boolean formalism and agent-based approaches to address specific biological questions related to cancer (cell fate decision processes in response to cell death signals, interplays between MAPK pathways, metastasis process, etc.) with the aim to provide personalized treatments. She has experience in constructing these models based on published articles and in analyzing patient data using these models. She has participated in developing methods and tools to improve the simulations of the mathematical models she builds.

## Organiser & speaker



### Loredana MARTIGNETTI, PhD

Inserm Research Engineer at Curie Institute - U900 Unit

**Title:** *From data to mechanistic models*

Joint talk with Laurence Calzone

**Abstract:**

Network models are a common and powerful formalism for studying cell functioning and its deregulations during cancer. They allow the integration of a large number of entities into a single complex network. However, the analysis of these large networks remains a challenge.

Here, we explore a novel topic modeling approach for integrating data from multiple omics. We showcase two examples of this approach: in the first one, we applied topic modeling to examine the transcriptional heterogeneity of breast cancer cells and identifying protein-coding genes and long non-coding RNAs (lncRNAs) that group thousands of cells into biologically similar clusters.

In the second one, we conduct an integrative multi-omics study of medulloblastoma patients to classify patients into molecular similar subgroups.

The output of the topic modeling analyses is interpreted as weighted signatures per cancer subgroups encompassing transcription factors, long non coding RNAs, proteins and phosphorylated states of kinases. Then, we used this information to build network models specific for each disease subgroup. These networks can be used as basis for mathematical modeling and dynamical simulations to predict possible points of intervention.

**Biosketch**

Loredana Martignetti received her Ph.D. in Bioinformatics from University of Torino, Italy, in 2007. She holds a Master's degree in Physics of Biosystems. After her Ph.D, she joined the Computational Systems Biology of Cancer group (U900) at Institut Curie in Paris as a post-doc researcher, working on microRNA deregulation in pediatric tumors. She is currently a Inserm Research engineer in the same group. Her research interests include gene regulation, non-coding RNAs, systems biology of cancer and comparative genomics.

## Organiser



### Denis THIEFFRY, PhD

Professor at the Ecole Normale Supérieure, Paris  
Senior researcher at Curie Institute, Paris

#### Biosketch

Denis has obtained his Ph. D in 1993 at the Université Libre de Bruxelles, Brussels, Belgium, under the direction of René THOMAS. He is currently Professor (Exceptional Class) of Systems Biology at the Ecole Normale Supérieure (ENS), Paris, France.

Previously, he did postdocs in Mexico (UNAM, 1995-1997), Germany (MPI, Berlin, 1997-1998) and Belgium (Univ. Ghent, 1998-2000), and was appointed as full Professor of Bioinformatics at Aix-Marseille University in France (2000-2010).

Denis research mainly focuses on the following topics:

- 1) Development of computational tools for the integration, the modelling and the dynamical analysis of biological regulatory networks.
- 2) Computational analysis of cis-regulatory DNA sequences.
- 3) Computational analysis of single-cell transcriptomic and epigenomic data.
- 4) Application of these approaches to developmental biology and immunology.
- 5) History and philosophy of biology.

Associate Editor of *PLoS Computational Biology* and *NAR Genomics and Bioinformatics*, Denis has published over 150 articles and book chapters, mostly in international journals, proceedings or books.

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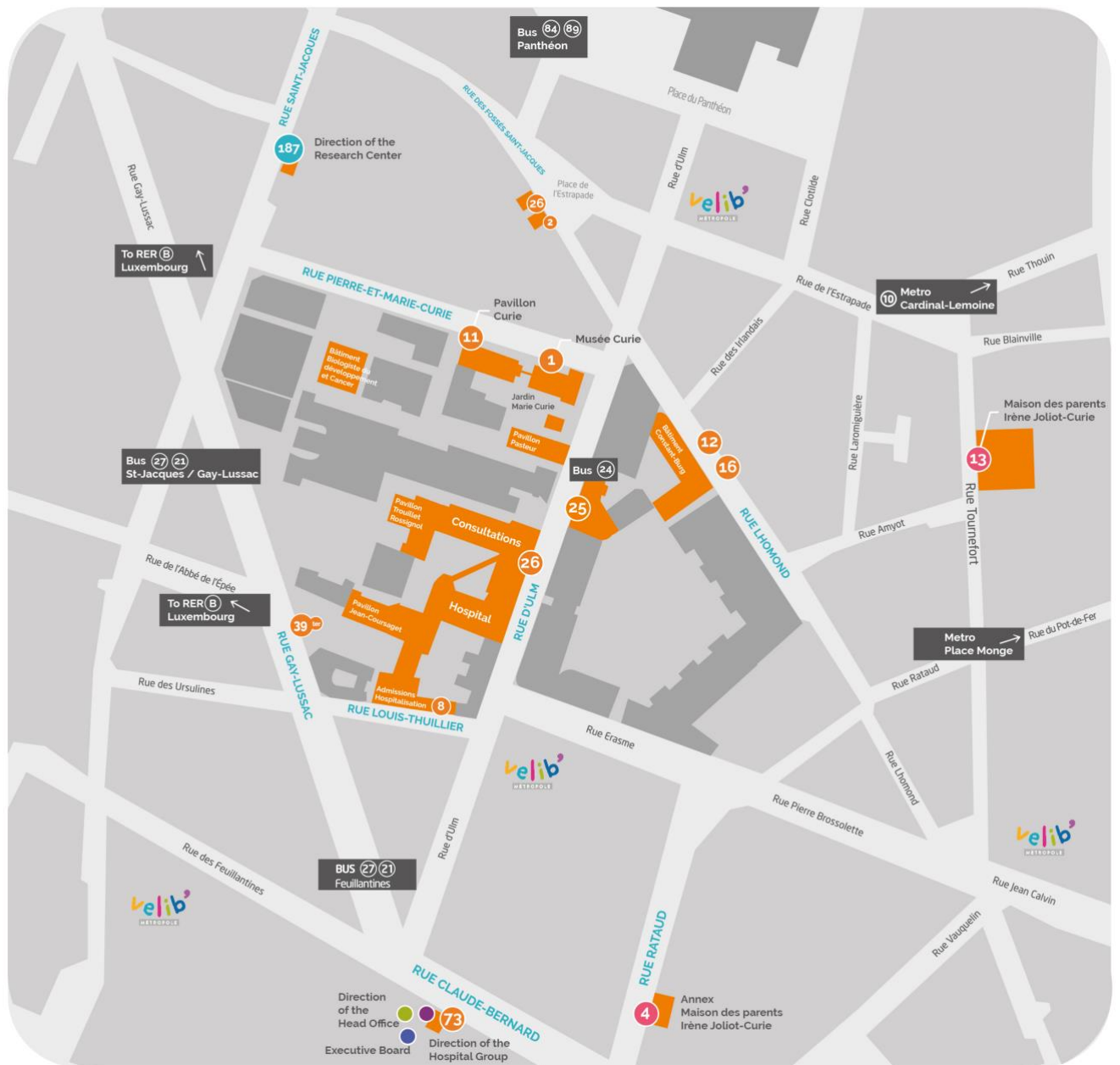
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# Map



Google map itineraries from hotel to meeting sites and restaurants:

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