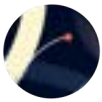
RÉPUBLIQUE FRANÇAISE

FRANCE 2030

RESEARCH PROGRAM
Cellular Identities and Destinies



cea cnrs Inserm

Cellular Identities and Destinies

France 2030 Research Program

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Cellular Identities and Destinies Research Program (PEPR Cell-ID)

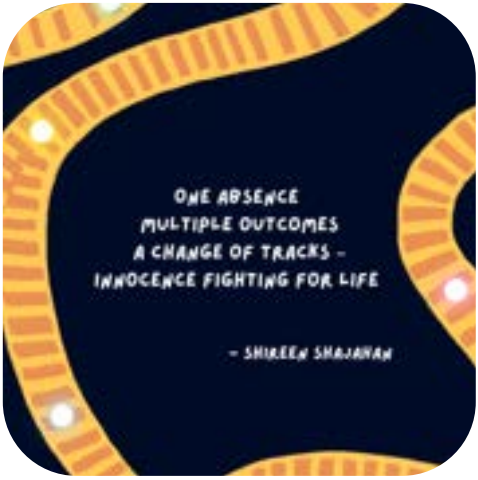
The "Cellular identities and destinies" exploratory research program (PEPR Cell-ID) aims to deploy **interceptive medicine** in the field of **pediatric brain cancer research**. The French State has entrusted its management to two major national research organisations: the **CNRS** and **Inserm**; and its scientific direction to **Geneviève Almouzni** (CNRS). Cell-ID is funded by **France 2030** over **7 years** and has a budget of **€50 million** operated by the National Research Agency (**ANR**).

The Cell-ID program explores crucial questions in developmental biology:

- **How do cells acquire their identity?** Every cell has a dynamically functioning genome, making it essential to understand how cell trajectories are generated over time
- **How do diverse cell populations contribute to the three-dimensional organization of brain tissue?** How each cell interacts in time and space with its neighbors and environment is an important issue in the formation of healthy tissue. Characterizing this blueprint, along with the distinct cell populations required for neurological development, remains a key challenge.
- **How non-physiological deviations contribute to the onset and progression of brain tumors in children?** Currently, children with brain tumors are often diagnosed at an advanced stage, when tumor cells have already spread extensively throughout the central nervous system. Advancements are needed to provide earlier, non-invasive diagnostic methods and detect the disease before disabling symptoms appear, as well as to monitor patients at risk and prevent relapses.

Cell-ID's mission

Understand the **mechanisms that govern cell identities and fates**, and determine **when and how cells go off the rails**. This involves studying the physiological development of the nervous system, and in parallel, certain pediatric brain cancers, whose origin is thought to be due to a deregulation of cell fate during embryonic development.



Haiku written by Shireen Shajahan at Cell-ID's Next-ID 4Y, an event dedicated to students - Sept 2025

Governance

Cell-ID's governance is composed with **representatives of the institutions** and **universities** involved, of a **steering committee** composed of the program director and the heads of the targeted projects, and of an **International Scientific Advisory board** chaired by Professor Wendy Bickmore, Director of the MRC Human Genetics Unit at the University of Edinburgh.

SAB members

- Pr. Wendy Bickmore, University of Edinburgh, UK
- Dr. Sarah Teichmann, CSCI (Cambridge Stem Cell Insititute), UK
- Dr. Denis Duboule, Collège de France, FR
- Pr. Maria-Elena Torres Padilla, Helmhotz, DE
- Dr. Marc Marti-Renom, Center for Genomic Regulation, SP
- Pr. Stefan Pfister, DKFZ, DE
- Dr. Hervé Chneiweiss, Sorbonne Université, FR

The Cell-ID Team

Coordination

Geneviève Almouzni
DR, CNRS
Cell-ID Scientific Director and Scientific leader of PC4

Giacomo Cavalli
DR, CNRS
Scientific leader of PC1

Marcelo Nollmann
DR, CNRS
Scientific co-leader of PC1

Gaëlle Legube
DR, CNRS
Scientific leader of PC2

Stéphane Nedelec
DR, Inserm
Scientific co-leader of PC2

Daniel Jost
DR, CNRS
Scientific leader of PC3 Data

Thomas Walter
PR, Mines
Scientific co-leader of PC3 Data and PC4

David Castel
DR, Inserm
Scientific leader of PC3 Med

Laure-Bally-Cuif
DR, CNRS
Scientific leader of PC3 Med

Sophie Jarriault
DR, CNRS
Scientific co-leader of PC4

Support Team

Therese Wilhelm
CNRS
Governance, Cell Context & Cell Exp

Susana Abreu Ribeiro
Inserm
Cell Next

David Sitbon
Institut Curie
Data Med

Julien Destrade
CNRS
Finance & Administration

Ana Garre Debiès
Inserm
Communication

Emna Chabaane
Institut Curie
Data

Ana Boranijasevic
Training Advisory Board

Iris Unterweger
Training Advisory Board

Cristina Fracassi
Training Advisory Board

Find the full list of researchers involved in Cell-ID on our website

pepr-cell-id.fr/about/team

What we do

Community Animation & Structuring

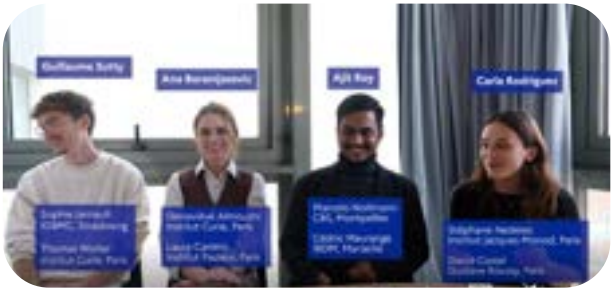
Scientific Events

- Annual Cell-ID Scientific Meeting to share our knowledge and expertise
- Annual pre-event dedicated to students Next-ID4Y
- Monthly webinars, seminars and conferences

Workshop on Science and Art, Sept 2025
Writing haikus to reflect on their work, creating visual metaphors to translate complex science into accessible images, and more!

The Cell-ID community at the 2025 Annual Meeting in the Institut Jacques Monod, Paris

Outreach

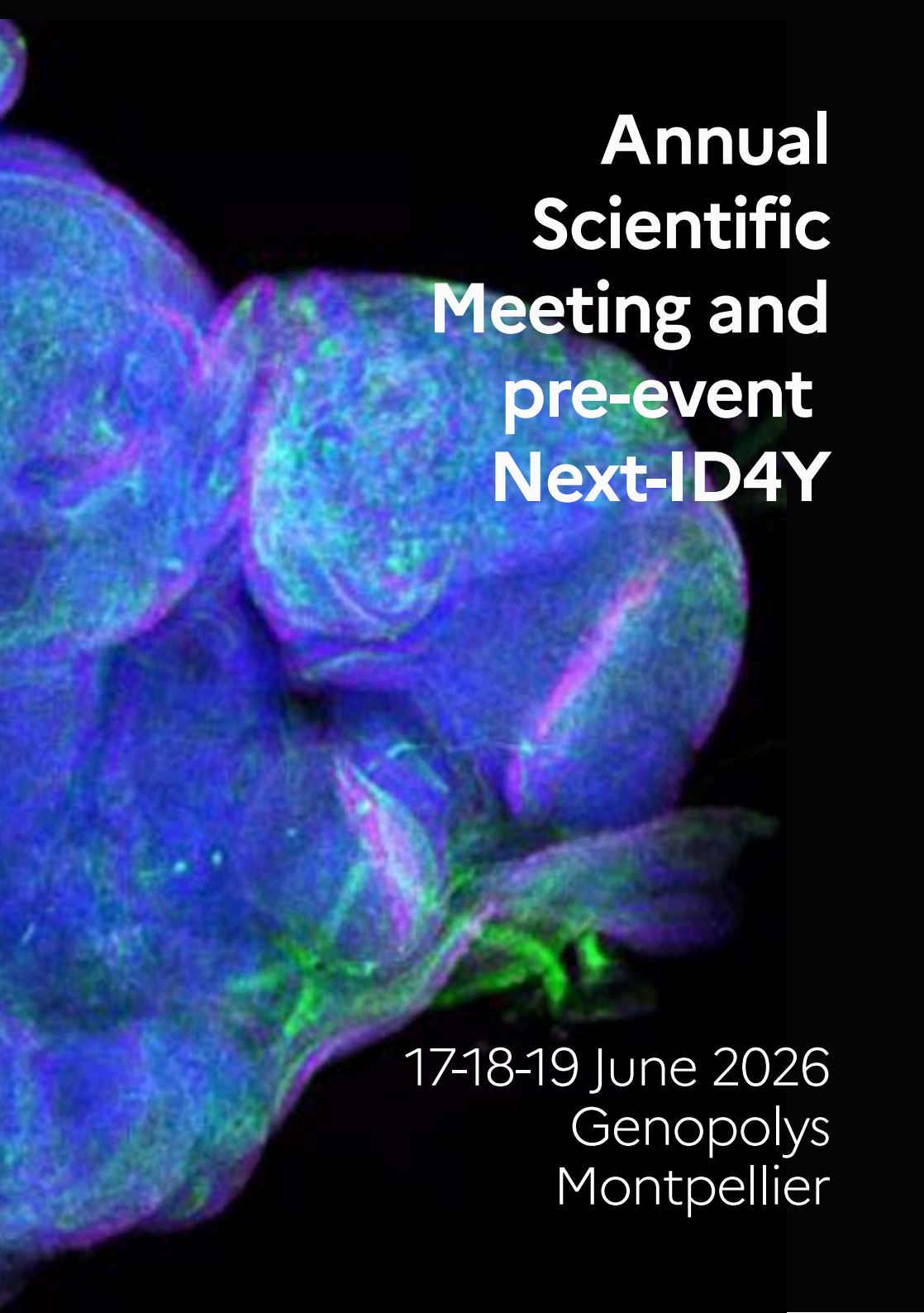


Interview of 4 of the new Cell-ID PhD students in the form of a 2 minute video

Sharing Cell-ID news on LinkedIn, on our dedicated website, and in our newsletter

1300
followers on LinkedIn

200
suscribers to our newsletter



Annual Scientific Meeting and pre-event Next-ID4Y

17-18-19 June 2026
Genopolys
Montpellier

Next-ID 4Y

France 2030 Research Programme Cell Identity and Destiny **(PEPR Cell-ID),** Genopolys Montpellier

17 & 18 June 2026

Wednesday 17 June

12:00	**Welcome lunch**
13:30	Opening Remarks - Genevieve Almouzni Presentation of new members and TAB's ideas - Training Advisory Board
14:00	**Intro round**

14:30	**Selected talks**
	• 2 long talks
	  ◦ *Mapping Human Choroid Plexus Development and Its Connection to Pediatric Tumor Biology* - **Nada Abdelgawad** (DFKZ Heidelberg)
	  ◦ *Understanding and modulating cell trajectory in a Drosophila model of AT/RT* - **Julien Leclercq** (IBDM, Marseille)
	• 5 flash talks
	  ◦ *Nuclear organization of transcription factors in embryos: origins and consequences* - **Shaswati Sarbagna** (CRBM Montpellier)
	  ◦ Cell state reporters - **Alan Jiao** (Ludwig Institute Oxford University)
	  ◦ *Mosaic expression of EFNB1 leads to patterning defect in human cerebral organoids* - **Cassandra Konan** (CBI-MCD Toulouse)
	  ◦ *Exploiting DNA Repair Vulnerabilities in H3-Mutant Pediatric High-Grade Gliomas* - **Delphine Burlet** (University of Paris)
	  ◦ *Modeling cell state plasticity in pediatric gliomas* - **Cherubin Manokaran** (Ludwig Institute Oxford Universiry)

15:30	**Coffee Break & Group Picture**
16:00	*Invited speaker: career path and outlooks* - **Charlene Boumendil** (IGH)
17:00	*Scientific workshop: hands-on session on drafting a preLight* - **Reinier Prosée** (The Company of Biologists) The goal is to learn how engaging with preprints can help disseminate and contextualize new research, while gaining experience in science writing and editing, staying up to date with recent work in their field.
19:00	**Drinks and poster session**
20:30	**Dinner**

Next-ID 4Y

France 2030 Research Programme Cell Identity and Destiny **(PEPR Cell-ID),** Genopolys Montpellier

17 & 18 June 2026

Thursday 18 June

08:30 — Welcome coffee

09:00

Selected talks

- 2 long talks
  - *Perturbation of X Chromosome Inactivation Affects Early Neural Fate in Human Cerebral Organoids* - **Carla Piqueras** (Institut Curie)
  - *Development of human hindbrain organoid models to investigate gliogenic lineage derailment in diffuse midline gliomas* - **Carla Rodriguez-Villa** (Institut Jacques Monod)
- 5 flash talks
  - *Exploring the role of m6a RNA modification during early development* - **Iryna Mohylyak** (IGMM, Montpellier)
  - *Spatial organization of chromatin accessibility states in human cancer tissues revealed by spatial multiomics network analysis* - **Joel Herrera Martinez** (CRCT, Toulouse)
  - *Developmentally programmed loss of long-range Polycomb interactions is regulated by cohesin* - **Valeriia Smialkovska** (DKFZ, Heidelberg)
  - *Using mammalian gastruloids to study the regulatory landscape of Cyp26a1* - **Anaïs Le Nabec** (Collège de France)
  - *Integrating replication timing as a new layer of single-cell multi-omics* - **Jane Schadtler-Law** (Institut Curie)

10:00

Outreach workshop: creating games to communicate Cell-ID concepts - Cell-ID TAB, Asya Sayin and Ana Debiès

The goal is to develop an interactive game that introduces non-scientific audiences to the concept of PEPR Cell-ID and highlights its importance. Participants will work collaboratively to design a simple and educational game that effectively communicates these ideas in an accessible and engaging way.

12:00 — Lunch

Annual Scientific Meeting

France 2030 Research Programme Cell Identity and Destiny **(PEPR Cell-ID),** Genopolys Montpellier

18 & 19 June 2026

Thursday 18 June

12:00 — Welcome lunch | Registration | Poster Display

13:30 — **Opening Remarks**
- Welcome from the Coordination Team & Welcoming Newcomers
- Outcomes of the previous NextID4Y meeting
- PC0 progress

14:00 — *Developmental hallmarks of pediatric brain tumors* – **Stefan Pfister** (Kitz, Heildelberg)

14:30 — Scientific Progress Session | PC Updates
- PC1 Scientific Updates
- PC2 Scientific Updates

14:55 — Coffee Break & Group Picture

15:20
- PC3 Data Scientific Updates
- PC3 Med Scientific Updates
- PC4 Updates

16:00 — **Breakout Sessions | Parallel**
- Conclusion from last year's break-out session
- Topic 1: New Cell-ID technologies
- Topic 2: Emerging model systems
- Topic 3: AI & research

17:30 — **Governance** | Participation restricted to SAB members, PC coordinators and pilot institution representatives

Poster Session all participants

Transit (19:00)

20:00 — Evening Museum Visit MO.CO. Montpellier & Restaurant Faune

Annual Scientific Meeting

France 2030 Research Programme Cell Identity and Destiny **(PEPR Cell-ID),** Genopolys Montpellier

18 & 19 June 2026

Friday 19 June

08:30	Welcome Coffee
09:00	*Invited Speaker* - **Vincent Calvez** (PEPR Maths Vives)
09:30	*Invited Speaker* - **Tasnime Akbaraly** & **Laure Cayrefourcq** (PEDIACRIEX CIRCLE & CIRCUNEUR)
10:00	Scientific Progress Session | Highlighted Research Talks Session 1 | 3 short talks • *Real-time visualization of the single-cell transcriptome by live-fixed correlative imaging to understand human diseases* - **Camille Bacquié** (IGH Montpellier) • Histone H3 variants and their chaperones in paediatric brain cancers - **Ana Boranijasevic** (Institut Curie Paris) • Expanding the functional landscape of PRC2 in cell fate transitions - **Cristina Fracassi** (IGH Montpellier)
10:45	Coffee Break & Group Picture
11:15	Session 2 | 4 short talks • *TPR disorder coiled-coils orchestrate chromatin organization and define a new permeability barrier at the nuclear pore basket* - **Stefany Figueroa** (IGH Montpellier) • *Unraveling the link between chromatin organization and chromatin mobility during Drosophila ZGA* - **Pablo Garcia Idieder** (IGMM Montpellier) • *Aquarius RNA helicase Protects Pluripotent Stem Cell Identity* - **Maxime Lalonde** (Helmholtz Munich) • *Elucidating the cis-regulatory code of cell types involved in sex determination using deep learning models* - **Ivan Barberá Aura** (IGBMC Strasbourg)
12:00	**Breakout Session Synthesis | Plenary** • Discussion and consolidation of results from Thursday's breakout session
12:30	**Closing Remarks and SAB feedback - Wendy Bickmore** • Wrap-up • Next steps for the consortium • Best Poster Award - SAB
13:10	Lunch Break
14:30	Departure

Nada Abdelgawad (DKFZ, Heidelberg)

Mapping Human Choroid Plexus Development and Its Connection to Pediatric Tumor Biology

The choroid plexus (ChP) is among the earliest functional brain structures, producing cerebrospinal fluid and forming the blood-CSF barrier. Despite its role in neurodevelopment and link to pediatric tumors, the regulatory landscape of human ChP development remains poorly understood. Here, we present the first single-nuclei multiomic atlas of the human embryonic ChP, spanning telencephalic (TChP) and hindbrain (HChP) regions from 7 to 20 postconceptional weeks. We identify a conserved epithelial differentiation trajectory of four sequential states shared across regions. Integrating gene expression and chromatin accessibility reveals stage-specific regulatory programs, including transient metabolic activation linked to ciliogenesis. TChP and HChP engage distinct developmental programs underpinned by divergent chromatin accessibility and transcription factor activity, converging toward a shared secretory identity in adult tissue. Mapping pediatric choroid plexus tumors onto the atlas shows tumor cells resemble embryonic TChP states, suggesting a reactivation of early developmental programs. This work provides a framework for understanding ChP development, regional specification, and links to pediatric tumor susceptibility.

Julien Leclercq (IBDM, Marseille)

Understanding and modulating cell trajectory in a Drosophila model of AT/RT

Atypical teratoid rhabdoid tumor (AT/RT) is a rare pediatric brain tumor affecting young children and with a very poor prognosis. This cancer stems from inactivation of the SMARCB1 gene, a member of the SWI-SNF chromatin remodeler complex. Since AT/RTs are developmental tumors, knowing the cell of origin is crucial to better understand the formation and progression of the tumor. However, the cell of origin is inaccessible in human patient and still remains elusive in mouse models. To circumvent this issue and gain information about the mechanisms that drive ATRTs from their cell-of-origin, we use Drosophila as a model. Indeed, it is possible to generate AT/RT-like tumor by knock-down of Snr1, the ortholog of SMARCB1 from a very well-defined subset of neural stem cells. Single-cell transcriptomics revealed that the tumor recapitulates the developmental trajectory observed in normal condition (temporal progression of the progenitors as well as the differentiation trajectory into neurons). Moreover, manipulation of the Notch pathway promotes fly survival by preventing tumor progression. Overall, this model offers a unique opportunity to study the mechanisms underlying the formation, composition and progression of AT/RTs.

Shaswati Sarbagna (CRBM-CNRS, Montpellier)

Nuclear organization of transcription factors in embryos: origins and consequences.

Nuclear organization of transcription factors in embryos: origins and consequences.Embryo development involves progressive spatial refinement to form a functional organism, accompanied by nuclear reorganization as cells differentiate into diverse tissues. Transcription factors (TFs) regulate gene expression essential for cellular identity. We investigate how nuclear organization of TFs contributes to the precision and robustness of gene expression during embryogenesis. We characterize the shapes, sizes, spatial distributions, and connectivity of TF clusters, and perturb them to assess their role in transcriptional regulation. Using Drosophila melanogaster embryos and the Hox TF Ultrabithorax (Ubx) as a model, we combine super-resolution microscopy (3D-STED, expansion microscopy, lattice light-sheet microscopy) with spatial analyses grounded in physics and mathematics. Our preliminary results reveal long-range correlations in TF distributions, suggesting a system with memory and stochasticity. Nuclear size and shape alone do not determine TF organization. We now use optogenetic perturbations to test whether TF distributions and cluster properties recover after disruption.

Alan Jiao (Ludwig Cancer Research, Oxford University)

Cell state reporters

One of the most significant obstacles to effective cancer treatment is intra-tumor heterogeneity. This heterogeneity arises in part from the ability of cancer cells to adopt different states, a property known as phenotypic plasticity. For many cancers, including incurable childhood brain tumors known as diffuse midline gliomas (DMGs), the molecular and genetic drivers of plasticity remain incompletely understood. An important missing tool to identify such novel regulators is a simple in vitro readout of plasticity. Here we establish prolonged differentiation as a powerful tool to uncover regulators of pediatric glioma cell states. Using this system, we show that the most frequent mutation in DMGs, H3K27M, as well as the pioneer transcription factor ASCL1, enhance phenotypic plasticity. Loss of H3K27M or ASCL1 minimally affected cell proliferation but abrogated tumorigenesis in vivo. Our findings suggest that prolonged differentiation to model and manipulate cell state plasticity in pediatric gliomas may reveal new tumor vulnerabilities.

Cassandra Konan (CBI-MCD, Toulouse)

Mosaic expression of EFNB1 leads to patterning defect in human cerebral organoids

Mutations in the EFNB1 gene are implicated in the CranioFrontoNasal Syndrom (CFNS), a rare congenital X-linked disorder characterized by multiple midline defects and skeletal abnormalities. Interestingly, CFNS exhibits an unusual pattern of phenotypic expression: heterozygous females are more severely affected than hemizygous males. In addition to cranial and skeletal phenotypes, patients exhibit brain abnormalities and cognitive deficits.

To understand how mutations in EFNB1 may lead to cognitive deficits in humans, we established a 3D in vitro model of CFNS by deriving cerebral organoids (CO) from hiPSCs carrying pathogenic variant in EFNB1. We generated mimics of male (full mutant CO) and female (mosaic CO) conditions and have already confirmed two distinct roles in human cerebral development. First, we observed an acceleration of neurogenesis in mutant and mosaic CO which exhibit an imbalance in neuronal subtypes. Second, in mosaic CO, we observed alterations of tissue patterning at early stages of development. We now aim to deepen the characterization of these phenotypes and identify the molecular cascades acting downstream of EPHRIN-B1 signaling and its contribution to these phenotypes

Delphine Burlet (Epigenetics and Cell Fate Center, Paris)

Exploiting DNA Repair Vulnerabilities in H3-Mutant Pediatric High-Grade Gliomas

Exploiting DNA Repair Vulnerabilities in H3-Mutant Pediatric High-Grade Gliomas Pediatric high-grade gliomas (pHGG) are aggressive, incurable brain tumors characterized by infiltrative growth and resistance to therapy. Recurrent heterozygous mutations in histone H3 variants, particularly H3.3 define major pHGG subgroups. Emerging evidence indicates that these mutations impair DNA repair processes and contribute to genomic instability. We demonstrated that H3.3 mutations alter the repair of replication-associated DNA damage via PNKP-dependent non-homologous end joining. PNKP depletion selectively impairs proliferation of H3.3-mutant pHGG cells, revealing a therapeutic vulnerability. Our current work aims to further characterize the synthetic interaction between histone H3.3 mutations and PNKP loss-of-function in cellular models of pHGG and to identify potent PNKP inhibitors with preclinical relevance. We also investigate PNKP-associated partners in DNA end processing and fork protection to uncover additional druggable targets. These studies will elucidate how H3.3 mutations disrupt DNA repair and promote novel therapies to overcome treatment resistance in pediatric gliomas.

Cherubin Manokaran (Ludwig Cancer Research, Oxford University)

Modeling cell state plasticity in pediatric gliomas

Modeling cell state plasticity in pediatric gliomas - One of the most significant obstacles to effective cancer treatment is intra-tumor heterogeneity. This heterogeneity arises in part from the ability of cancer cells to adopt different states, a property known as phenotypic plasticity. For many cancers, including incurable childhood brain tumors known as diffuse midline gliomas (DMGs), the molecular and genetic drivers of plasticity remain incompletely understood. An important missing tool to identify such novel regulators is a simple in vitro readout of plasticity. Here we establish prolonged differentiation as a powerful tool to uncover regulators of pediatric glioma cell states. Using this system, we show that the most frequent mutation in DMGs, H3K27M, as well as the pioneer transcription factor ASCL1, enhance phenotypic plasticity. Loss of H3K27M or ASCL1 minimally affected cell proliferation but abrogated tumorigenesis in vivo. Our findings suggest that prolonged differentiation to model and manipulate cell state plasticity in pediatric gliomas may reveal new tumor vulnerabilities.

Carla Piqueras (Institut Curie, Paris)

Perturbation of X Chromosome Inactivation Affects Early Neural Fate in Human Cerebral Organoids

Neurodevelopmental disorders (NDDs) show a strong sex bias: males often display higher incidence and severity, whereas females appear relatively protected. Beyond hormonal and sociocultural influences, regulation of the sex chromosomes, particularly the X chromosome, enriched in brain related genes and frequently implicated in intellectual disability, offers an additional source of divergence. In females, X chromosome inactivation (XCI) balances X linked gene dosage, yet some genes escape silencing in a cell type specific manner, potentially shaping sex biased vulnerability to NDDs. Using a clonal female hESC line (H9) with an inactive X, we generated cerebral organoids and disrupted XCI through CRISPR mediated deletion of XIST. Complementary 2D neural progenitor models enabled high resolution allelic profiling of gene reactivation. XIST loss in organoids produced an early telencephalic bias and altered neural composition, as revealed by scRNA seq, indicating that X linked dosage influences fate decisions. In hNPCs, we identified X linked genes reactivated upon XIST deletion, suggesting their contribution to developmental divergence. Overall, perturbing XCI reshapes early neural specification and may underlie sex biased NDD risk.

Carla Rodriguez-Villa (IJM, Paris)

Development of human hindbrain organoid models to investigate gliogenic lineage derailment in diffuse midline gliomas

Diffuse Midline Gliomas (DMGs) are aggressive, incurable pediatric brain tumors arising preferentially in the developing pontine hindbrain, frequently associated with K27M mutations in histone H3 genes. Tumor cell identities range from OPC-like to oligodendrocyte- and astrocyte-like states, suggesting disruption of hindbrain gliogenic lineages. To model this derailment, we are generating organoids that recapitulate neural and OPC lineages arising sequentially from ventral hindbrain progenitors. Combined activation of Wnt and SHH signaling under neuralizing conditions differentiates hPSCs into ventral progenitors expressing OLIG2 and/or NKX2.2, which generate cranial motor neurons and later OPCs in vivo. Further differentiation produces cranial motor neurons ($PHOX2B^+$, $ISL1^+$) expressing HOXB1 and HOXB4, markers of the hindbrain, while lacking the spinal cord marker HOXA5. Through a targeted screening, we identified conditions promoting OPC emergence ($SOX10^+$, $OLIG2^+$). Collectively, these results establish a physiologically relevant hindbrain organoid platform to dissect the mechanisms driving DMG pathogenesis.

Iryna Mohylyak (IGMM, Montpellier)

Exploring the role of m6a RNA modification during early development

M6A is a prevalent RNA modification known to modulate gene expression via RNA stability and protein interactions. While its role in mRNA decay is established, its impact on translational efficiency remains poorly understood. We utilised the Drosophila early embryo to conduct high-resolution analysis of how deposition modulates translation in vivo. We characterised the endogenous expression of the Methyltransferase Complex, revealing that zygotic expression initiates after gastrulation. While writers and the YTHDC1 reader maintain uniform expression, the cytoplasmic YTHDF reader is enriched in muscle and neuronal tissues. Using direct Nanopore sequencing, we mapped the landscape with single-nucleotide resolution and stoichiometry during the ZGA. Our analysis confirmed a 5'UTR deposition bias and identified model mRNAs to investigate stability and translation efficiency using quantitative imaging of the SunTag system. By modulating writers and readers with novel optogenetic tools we identified critical action windows in cell fate specification and tissue-specific depletion revealed how m6A machinery affects myogenesis and neurogenesis. This work establishes how the pathway contributes to embryonic patterning and tissue development.

Joel Herrera Martinez (CRCT, Toulouse)

Spatial organization of chromatin accessibility states in human cancer tissues revealed by spatial multiomics network analysis

Spatial organization of chromatin accessibility states in human cancer tissues revealed by spatial multiomics network analysis Chromatin accessibility (CA) is a key indicator of the cell's regulatory state in normal and cancerous tissues. However, whether it is shaped by the local cellular context remains unexplored. Spatial multiomics technologies make it possible to address this question. We analyzed a published dataset comprising spatially resolved paired snRNA-seq and snATAC-seq profiles. We characterized CA in 2,529 spatially resolved cells by defining gene-centric accessibility profiles from the ATAC-seq signal in promoter-proximal regions. Unsupervised clustering of these profiles identified nine CA profiles that partially, but not entirely, recapitulate RNA-based cell type annotations. To assess whether these profiles exhibit spatial structure, we reconstructed the tissue's cellular network using tysserand and applied mosna to quantify spatial co-localization patterns. These analyses revealed that CA states are spatially organized and provide initial evidence that CA is not only linked to cell identity, but is also spatially structured.

Valeriia Smialkovska (DKFZ, Heidelberg)

Developmentally programmed loss of long-range Polycomb interactions is regulated by cohesin

Distal regulatory elements, such as enhancers, can regulate genes across megabase-long distances via coming into close spatial proximity. During cell type transitions, the genome undergoes extensive rewiring while establishing new transcriptional programmes, which involves gain and loss of chromatin interactions.

Extensive scientific effort has been spent in understanding how chromatin interactions are formed during development, yet the mechanisms underlying their developmentally programmed loss remain largely unclear. By leveraging chromatin accessibility-assisted footprinting, acute protein degradation and chromatin conformation capture we show that loss of promoter interactions cannot be explained with reduced binding of sequence-specific transcription factors. Instead, we identify a subset of interactions that depend on cohesin for developmental disruption. These sites are characterized by high Polycomb levels and extensive differentiation-dependent rewiring. Preventing interaction loss by cohesin degradation results in downregulation of associated genes. These results suggest that cohesin indirectly regulates developmental loss of Polycomb interactions by assisting the gain of other regulatory contacts.

Anaïs Le Nabec (Collège de France, Paris)

Using mammalian gastruloids to study the regulatory landscape of Cyp26a1

During gastrulation of the mammalian embryo, several genes and signalling pathways play critical roles. In particular retinoic acid (RA) signalling in posterior cells of the elongating trunk, which requires a precise regulation to reach proper RA levels. This is achieved by the Aldh1a2-mediated production and Cyp26a1-mediated degradation of RA in these posterior cells, establishing an anterior-posterior gradient in the embryo. CYP26A1 protects posterior NMP cells from inappropriate RA signalling, preventing severe congenital malformations that result from Cyp26a1 misregulation or excessive RA signalling. To better understand the regulatory mechanisms underlying Cyp26a1 transcription and its role in embryonic development, we used pseudo-embryos or gastruloids, an alternative model to early posterior embryos. We initially deleted the RA binding domain in the Cyp26a1 gene and scRNA-seq analysis combined with in-situ hybridization allowed us to confirm the imbalance between neural and mesodermal progenitors associated with the reported anomalies in developing trunk structures. Further analyses (ATAC-seq, ChIP-seq, CHiC) are underway to improve our understanding of Cyp26a1 regulation in gastruloids.

Jane Schadtler-Law (Institut Curie, Paris)

Integrating replication timing as a new layer of single-cell multi-omics

To ensure faithful genome duplication, DNA replication follows a coordinated yet stochastic program in which genomic regions replicate in a defined order. Replication timing (RT) is cell-type specific and correlates with chromatin accessibility and transcriptional activity, contributing to epigenetic regulation and genome stability. Consequently, integrating RT analysis into single-cell studies provides a valuable readout to disentangle its interplay with other cellular processes. RT heterogeneity may underlie cell-to-cell variability in transcription and genome integrity. We developed Kronos 2.0, a scalable Nextflow pipeline for extracting RT profiles from single-cell WGS and Hi-C data. This redesigned framework uses a containerized environment for reproducibility. Preprocessing relies on standard alignment tools and a batched CNV strategy enabling parallel analysis of thousands of cells. Kronos 2.0 integrates MnM, a deep-learning classifier for accurate cell-cycle phase assignment and supports inputs from FASTQ to CNV profiles, enabling flexible RT analysis without cell sorting. Applied to cancer cell lines and primary tissues, Kronos 2.0 reveals subpopulation-specific RT heterogeneity.

Camille Bacquié (IGH, Montpellier)

Real-time visualization of the single-cell transcriptome by live-fixed correlative imaging to understand human diseases

Cells adopt different fates, and single-cell sequencing has revealed that this occurs via 'cellular trajectories,' where a cell's transcriptome evolves from one state to another in a defined manner. This dynamic view is reconstructed retrospectively from numerous cells, isolated at different stages of their evolution. Therefore, the way an individual cell moves along these trajectories in real time is not known. Here, we will address this question by developing new methods to visualize the transcription of 4 genes in real-time in living cells. Using a mathematical approach, these data will be integrated with single-cell sequencing and multiplexed smFISH to model dynamic gene regulatory networks and estimate the transcriptome of single cells in real time.
The goal will be to develop mathematical models to integrate these data into gene regulatory networks that describe cellular trajectories. Applied to live cells, these models will estimate the transcriptome of individual cells in real time.

Ana Boranijasevic (Institut Curie, Paris)

Histone H3 variants and their chaperones in paediatric brain cancers

This project aims to investigate how histone H3 variants with their network partners contribute to cell identity determination during human brain development in both physiological and pathological conditions. In particular, we wish to explore cell fate derailment in pediatric brain tumors due to “oncohistones” and alterations in associated proteins. Within the Cell-ID PEPR consortium, I will use both human brain organoids and cell lines to compare normal and perturbed development in space and time. Combining imaging and OMICS data, I will monitor at multiple scales features affecting chromatin in different cell types over time. To capture changes at the single-cell level, I will implement the most advanced analytical tools on both published and new data generated within the consortium.

Cristina Fracassi (IGH)

Histone H3 variants and their chaperones in paediatric brain cancers

Epigenetic regulation of gene expression is a well-established mechanism underlying cell identity, yet it operates through transient changes whose stabilization into heritable states remains poorly understood. To investigate how epigenetic information is maintained we focus on Polycomb repressive complex 2 (PRC2), a key epigenetic regulator of developmental gene expression programs. We examine its role during the transition from pluripotency to early neuronal progenitors. Transcriptomic profiling across developmental stages shows that transient PRC2 depletion in mESC rewires transcriptional dynamics during differentiation, altering both the timing and amplitude of gene expression. Deregulated genes are enriched for lineage programs, reflecting loss of lineage restriction and ectopic activation of alternative fates.

While part of these changes is reversible, a subset of genes remains constantly deregulated, indicating PRC2-dependent epigenetic memory. These effects coincide with disrupted H3K27me3 dynamics. Together, these results indicate that PRC2 regulates gene expression during differentiation by establishing epigenetic memory during early cell fate decisions, shedding light on the mechanisms stabilizing epigenetic information.

Stefany Figueroa (IGH, Montpellier)

TPR disorder coiled-coils orchestrate chromatin organization and define a new permeability barrier at the nuclear pore basket

Nuclear pore complexes (NPCs) regulate nucleocytoplasmic transport through a size-dependent permeability barrier classically attributed to intrinsically disordered FG-repeat nucleoporins within the central channel. Here, we investigate the non-FG nucleoporin TPR, the principal component of the nuclear basket, whose role in transport and heterochromatin exclusion has remained unclear. Using disorder prediction analyses, in vivo super-resolution imaging of TPR mutants, chromocenter targeting with the iCRISPR-GHoST system, and LEXY export assays, we demonstrate that TPR contains interspersed disorderd coiled-coil regions that drive biomolecular condensate formation. These condensates mechanically exclude heterochromatin, maintain heterochromatin-free zones at NPCs, and contribute to global nuclear architecture. In addition, the disordered coiled-coil domain restricts CRM1-mediated protein export, establishing a previously unrecognized permeability barrier at the nuclear basket. Together, our findings reveal unconventional biophysical properties of TPR disrodered coiled-coil domain and redefine the nuclear basket as an active regulator of transport selectivity, chromatin spatial organization, and nuclear architecture.

Pablo Garcia Idieder (IGMM, Montpellier)

Unraveling the link between chromatin organization and chromatin mobility during Drosophila ZGA

Zygotic genome activation is a crucial developmental transition in which the silent genome becomes transcriptionally active though chromatin remodelling and specific enhancer–promoter interactions. Yet, how enhancers find their targets within the crowded nuclear environment remains unclear. Here, we investigated how molecular and biophysical constraints shape chromatin mobility during ZGA in early Drosophila embryos. Using quantitative live imaging, we explored the mobility of identical snail enhancer reporters inserted at distinct chromosomal locations before and during ZGA. Chromatin motion was globally subdiffusive and consistently decreased from nuclear cycle 13 to 14, indicating reduced chromatin dynamics during ZGA. At this stage, chromosomes adopt a polarized Rabl configuration, with centromeres and telomeres occupying opposite nuclear regions. While most loci displayed similar dynamics, regions near centromeres and telomeres showed more constrained motion. We further examined the contributions of pioneer factors, heterochromatin, insulators, and transcriptional activity to chromatin motion. We provide a quantitative framework linking nuclear organization, chromatin, and enhancer dynamics during ZGA.

Maxime Lalonde (Hamperl lab, IES, Helmholtz Munich)

Aquarius RNA helicase Protects Pluripotent Stem Cell Identity

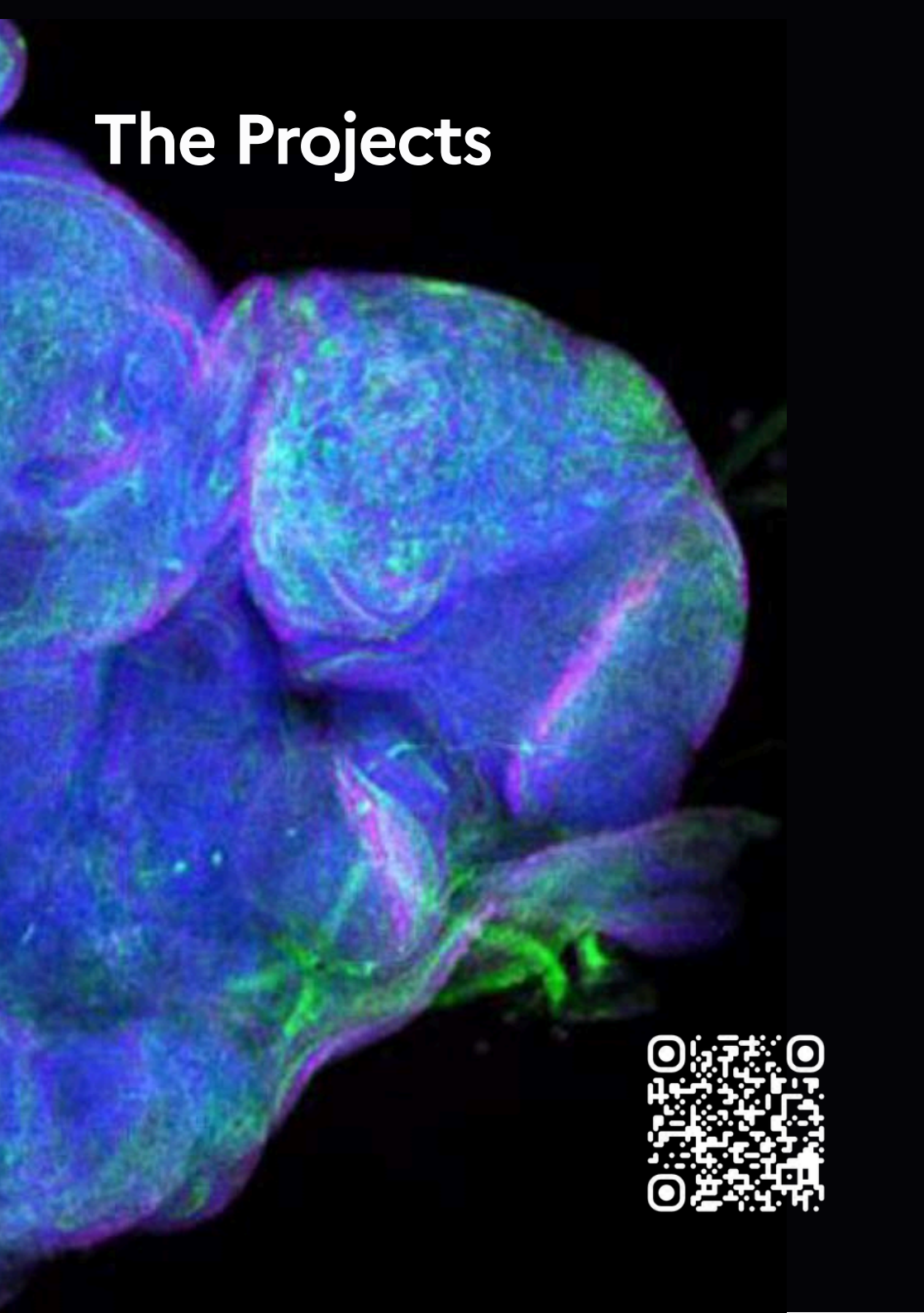
Pluripotent stem cells must reconcile rapid replication with a highly dynamic transcriptional program, creating an inherent susceptibility to transcription–replication conflicts (TRCs). We demonstrate that embryonic stem cells (ESCs) operate in a "resilient" replication mode, tolerating high genomic traffic through the constitutive upregulation of R-loop and TRC resolution pathways. Through a targeted functional screen, we identify the RNA helicase Aquarius (AQR) as an essential safeguard of this state. AQR depletion downregulates these resolution factors, collapsing this stress-resistant program and driving ESCs into unstable, heterogenous states, marked by increased transcriptional entropy and cell-to-cell noise. Mechanistically, we show that key identity-defining genes are preferentially located within R-loop and TRC prone regions, making them uniquely vulnerable to AQR depletion. Our findings establish AQR as a critical governor of transcriptional fidelity, demonstrating that genomic resilience is fundamental to maintaining pluripotent cell identity.

Ivan Barbera Aura (IGBMC, Illkirch-Graffenstaden)

Elucidating the cis-regulatory code of cell types involved in sex determination using deep learning models

Recent advances have highlighted the importance of the non-coding genome in regulating sex determination. However, the underlying rules, patterns, and sequence features underlying this activity are largely unknown. In this poster, I will present our recent efforts to decode the cis- regulatory code of cell types driving sex determination by applying sequence-to-function models to single-cell omics data. These approaches can uncover broad sequence motifs that pinpoint key transcriptional regulators and, most importantly, the combinatorial syntax through which they act. Beyond deciphering regulatory logic, deep learning models allow the design of synthetic cis-regulatory elements that can drive transcription in specific cell types, with spatial and temporal precision. All in all, these advances enable bottom-up strategies for dissecting and engineering the regulatory programs that control the identity of cell types implicated in sex determination.

The Projects



CELL CONTEXT

Access to the identity of individual cells in their original spatial context

The Cell Context project is developing innovative spatial and single-cell multi-omics approaches to study physiological neural and brain development and selected pediatric brain tumors. These technologies enable the analysis of transcriptomic, proteomic, epigenetic, and genetic variations at the single-cell level while maintaining the spatial organization of the tissues.

Giacomo Cavalli
DR, CNRS
Scientific leader of PC1

Marcelo Nollmann
DR, CNRS
Scientific co-leader of PC1

Key objectives are to develop technologies based on sequencing, imaging and single-cell proteomics.

Key actions:

- Integration of sequencing and single-cell multi-omics imaging applied to neurodevelopment and pediatric cancer:
- Spatial imaging Development of multi-omic spatial imaging adapted to neurodevelopment
- Proteomics for neurodevelopment and single-cell profiling of pediatric brain tumors

Expected results:

- Progress in single-cell multi-omics and sequencing techniques
- Improving spatial genomics and imaging technologies
- Making progress with single-cell proteomics methods

This project will contribute to the development of multi-omics techniques that can be used to better understand the mechanisms of human neurodevelopment and the changes taking place in pediatric cancer models.

CELL EXP

Specialized experimental systems

The ambition of the Cell-Exp project is to develop dedicated models to study physiological and pathological embryonic development, focusing on brain development. These models will be used to identify, at the cellular level, physiological trajectories and detect early cellular and molecular signs of alterations leading to the development of these pediatric brain cancers.

Gaëlle Legube
DR, CNRS
Scientific leader of PC2

Stéphane Nedelec
DR, Inserm
Scientific co-leader of PC2

Key objectives are to identify cell diversity, develop and improve neural organoids and provide reference maps for cancer model analyses

Expected results:

- A 3D atlas of cell diversity dynamics in cancer-prone regions of the human nervous system. A reference atlas for studies of neural organoids.
- High-resolution multiparametric mapping of cell diversity and differentiation trajectories in organoids.
- Analysis of genetic networks specifying neuronal diversity
- Robust protocols for the generation of reliable and reproducible regional neural organoids
- Establishing robust pipelines for modeling pediatric tumors using regional neural organoids

This project will contribute to the study of the mechanisms of human neurodevelopment and the development of relevant ex vivo models for the study of pediatric brain cancers, while meeting the objective of reducing animal experimentation in biomedical research.

DATA

Harnessing the power of data to understand pediatric cancers

The Cell-ID Data sub-project addresses the challenges posed by the analysis of the massive, complex and heterogeneous data generated in the Cell-ID project. These data, characterizing the single cell within its spatial and temporal context, are essential for deciphering the mechanisms that disrupt cell fate and trigger the development of pediatric cancers.

Daniel Jost
DR, CNRS
Scientific leader of PC3 Data

Thomas Walter
PR, Mines
Scientific co-leader of PC3 Data and PC4

Key objectives are to create a data management infrastructure capable of storing, sharing and securing data Develop AI-based analysis tools

Resources deployed:

- Data management infrastructure
- Analysis and integration tools
- Sharing and dissemination of results

Expected results:

The Data sub-project will provide a unique resource for pediatric cancer research, including :

- A centralized database of cell profiles.
- Pipelines and algorithms accessible to the scientific community.
- Predictive models to identify early anomalies and propose therapeutic interception strategies.

By combining infrastructure, AI and international collaborations, Cell-ID's Data project aims to transform data into actionable knowledge to improve the management of pediatric cancers.

MED Intercepting pediatric brain tumors

The Med sub-project aims to understand and intercept the onset and progression of pediatric brain tumors, specifically: Atypical Rhabdoid teratoid Tumors (ATRT), Medulloblastoma (MB), High-grade pediatric gliomas (pHGG), including Diffuse Midline Gliomas (DMG) and Hemispheric Gliomas (DHG) with histone H3.3 mutations

David Castel
DR, Inserm
Scientific leader of PC3 Med

Laure-Bally-Cuif
DR, CNRS
Scientific leader of PC3 Med

Why these tumors ?
Complexity of the "cell of origin", common epigenetic alterations, early development

Key objectives

- Map the early stages of tumor development
- Validate the hypotheses in human models
- Identify "second hits" that promote tumor progression
- Translate discoveries into clinical interventions.

The results of the MED sub-project will enable:

- Earlier diagnosis thanks to the identification of specific molecular signatures.
- New therapeutic approaches to improve follow-up and management of pediatric brain tumors.
- Expanded applications for other types of pediatric cancer and related neurodevelopmental disorders.

CELL NEXT

Training and career development & innovation

Tailor-made training and career development program, combining cutting-edge research and training in molecular, cellular and epigenetic sciences applied to cancer. Cell-Next will also invest in interdisciplinary knowledge to address major societal challenges such as sustainability, diversity, equity and inclusion (DEI), as well as communication with the public. The program will also foster opportunities for innovative early-stage research with direct applications.

Geneviève Almouzni
DR, CNRS
Cell-ID Scientific Director and Scientific leader of PC4

Sophie Jarriault
DR, CNRS
Scientific co-leader of PC4

Thomas Walter
PR, Mines
Scientific co-leader of PC3 Data and PC4

Cell Next, an initiative of the Cell-ID program, aims to train researchers and clinicians capable of adopting an integrative and collaborative research model. To meet complex scientific challenges, such as generating high-resolution molecular data and integrating it into sophisticated biological systems — the project takes an interdisciplinary approach. Cell Next also responds to a growing demand for more responsible and socially aware research practices, and will build on scientific innovations to foster early-stage projects with tangible societal impact.

Expected Results

- Creating a community of collaborative researchers
- Promoting scientific excellence in France
- Preparing a new generation of committed researchers
- Enhancing scientific innovation

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FRANCE 2030

RESEARCH PROGRAM

Cellular Identities and Destinies

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