

2025 Activity Report

RESEARCH CENTRE: Inria Lyon Centre

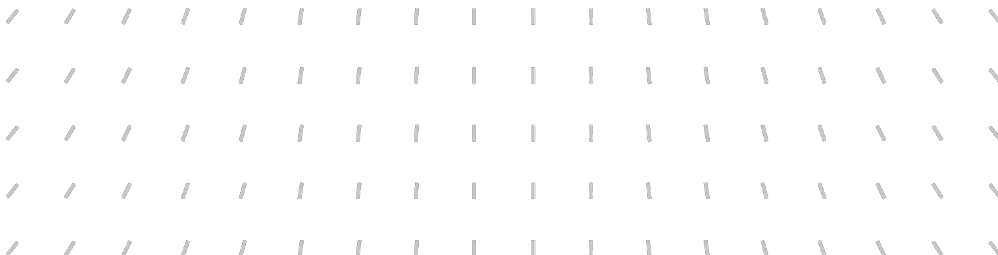
IN PARTNERSHIP WITH: Ecole normale supérieure de Lyon, INSERM, CNRS, Centre Léon Bérard, Université Claude Bernard (Lyon 1)

Project-Team

CASTING

Cancer dynAmicS, adapTation and modelING

In collaboration with Unité de Mathématiques Pures et Appliquées, Centre de Recherche en Cancérologie de Lyon



Project-Team CASTING

Creation of the Project-Team: 2024 June 01

Each year, Inria research teams publish an Activity Report presenting their work and results over the reporting period. These reports follow a common structure, with some optional sections depending on the specific team. They typically begin by outlining the overall objectives and research programme, including the main research themes, goals, and methodological approaches. They also describe the application domains targeted by the team, highlighting the scientific or societal contexts in which their work is situated. The reports then present the highlights of the year, covering major scientific achievements, software developments, or teaching contributions. When relevant, they include sections on software, platforms, and open data, detailing the tools developed and how they are shared. A substantial part is dedicated to new results, where scientific contributions are described in detail, often with subsections specifying participants and associated keywords. Finally, the Activity Report addresses funding, contracts, partnerships, and collaborations at various levels, from industrial agreements to international cooperations. It also covers dissemination and teaching activities, such as participation in scientific events, outreach, and supervision. The document concludes with a presentation of scientific production, including major publications and those produced during the year.

Keywords

Computer sciences and digital sciences

- A6.1.1. – Continuous Modeling (PDE, ODE)
- A6.1.2. – Stochastic Modeling
- A6.1.3. – Discrete Modeling (multi-agent, people centered)
- A6.2.3. – Probabilistic methods
- A6.3.3. – Data processing

Other research topics and application domains

- B1.1.5. – Immunology
- B1.1.6. – Evolutionary biology
- B1.1.8. – Mathematical biology
- B2.2.3. – Cancer
- B2.4.1. – Pharmacokinetics and dynamics
- B2.4.2. – Drug resistance

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1 Team members, visitors, external collaborators

Research Scientists

- Helene Leman [Team leader, INRIA, Researcher, HDR]
- Céline Bonnet [INRIA, ISFP]
- Pierre Martinez [INSERM, Researcher, HDR]
- Sandra Ortiz-Cuaran [Centre Léon Bérard, HDR]

Faculty Members

- Karène Mahtouk [UNIV LYON I, HDR]
- Pierre Saintigny [Centre Léon Bérard, Professor, HDR]
- Loïc Verlingue [CLB, HDR]

Post-Doctoral Fellow

- Charlotte Andrieu [IRD, Post-Doctoral Fellow, until Oct 2025]

PhD Students

- Paul De Lambert [ENS DE LYON, from Sep 2025]
- Imane El Herch [Centre Léon Bérard]
- Fabian Leon-Perez [ADMIR]
- Constance Nicq [UNIV LYON I]

Technical Staff

- Sonia Canjura Rodriguez [Centre Léon Bérard]
- David Coulette [CNRS, Engineer]
- Claire Ecotiere [CLB, from Apr 2025]
- Lucas Michon [Centre Léon Bérard]

Interns and Apprentices

- Matthieu Biragnet [INRIA, Intern, from Sep 2025]
- Clea Soupe–Drouet [INRIA, Intern, from May 2025 until Jul 2025]

Administrative Assistant

- Sylvie Boyer [INRIA]

Visiting Scientist

- Benoit Lecoester [HCL]

2 Overall objectives

The CASTING team is a joint Inria-Inserm research team whose objective is to combine mathematical modeling and computational biology together with *in vitro*, *ex vivo* and *in vivo* experiments to better understand the evolution of different populations of cells within its ecosystem, at all stages of the disease, from normal to preneoplasia, to established malignant tumors, and under the selective pressure of therapy. The team brings together expertise in mathematics, computational biology, bioinformatics, experimental biology, and clinical oncology to address key challenges in precision cancer medicine.

CASTING aims to:

- Understand cancer as an evolving ecosystem, from early pre-neoplastic stages to advanced disease,
- Quantify the impact of systemic therapies on tumor evolution and resistance,
- Develop predictive models that integrate experimental, clinical, and multi-omics data,
- Translate modeling results into clinically relevant strategies for prevention, diagnosis, and treatment.

3 Research program

The research program is structured around mechanistic modeling tightly coupled to experimental and clinical data.

3.1 Evolution under the selective pressure of systemic therapy

This first central research axis focuses on **tumor cell evolution in response to systemic therapies**, including targeted therapy or immunotherapy. In the presence of a drug, tumor cells will tend to evolve to escape the impact of treatment, and to become persistent or resistant, limiting the efficiency of the treatment. The understanding of how a cell evolves under the "pressure of selection" exerted by therapy is a crucial step to optimize therapeutic schemes involving one or more drugs. Mathematical and bio-informatic models are developed to describe the emergence of drug-tolerant, persistent, and resistant cell populations.

This axis is closely connected to experimental *in vitro* systems, allowing calibration and validation of models. The objective is to explore **optimal treatment scheduling and drug combinations** to delay or prevent resistance.

This line of research builds on and extends prior mechanistic oncology models and is aligned with recent work on tumor adaptation and therapeutic failure.

3.2 Early Stages of Carcinogenesis and Tumor Ecosystem Dynamics

CASTING also investigates the **evolutionary dynamics of tissues prior to malignancy**, with a strong emphasis on **head and neck cancers and oral carcinogenesis**. The team develops stochastic and spatial models to describe how normal tissues accumulate somatic mutations and transition toward preneoplastic and malignant states.

Indeed, in some patients, oral lesions may spontaneously disappear or on the contrary evolve into oral cancer. This early evolution remains poorly understood, which limits the development of preventive approaches. By integrating multi-scale heterogeneous data with interdisciplinary approaches, we aim to characterize the ecological context in which these lesions develop, and identify robust markers to evaluate their risk of cancer progression.

This axis is directly connected to large-scale experimental efforts, including:

- Spatial transcriptomics,
- Single-cell RNA sequencing,
- Multispectral immunofluorescence.

3.3 Tumor Microenvironment and Immune Interactions

A major part of the program addresses **tumor-immune interactions**, including the role of stromal components such as **cancer-associated fibroblasts (CAFs)** and immune cell recruitment. CASTING combines bioinformatics analyses with mathematical models to describe how microenvironmental heterogeneity influences tumor progression and response to therapy.

3.4 Theoretical Developments in Ecology and Evolution

Ecology and evolutionary theory, and in particular **tumor ecology and cellular evolution**, give rise to a wide range of challenging mathematical problems in **probability theory and partial differential equations (PDEs)**. These problems are continuously renewed by advances in biological and medical technologies, which generate large, high-quality datasets and raise new questions at multiple spatial and temporal scales. In this axis, CASTING focuses on the **theoretical challenges** emerging from these biological questions. The team develops and studies stochastic models and deterministic PDE-based models, as well as the mathematical links between them, including scaling limits and hybrid formulations. This work aims to provide rigorous foundations for modeling evolutionary dynamics in complex biological systems, while contributing to **advances in both mathematics and life sciences**.

4 Application domains

The main application domains of CASTING research are:

- **Precision and Personalized Oncology**, including genomic medicine integration at the healthcare system level.
- **Cancer Biology**, with a strong focus on head and neck cancers.
- **Immuno-oncology**, through quantitative characterization of immune ecosystems.
- **Clinical Decision Support**, via predictive modeling and data-driven tools for patient stratification and trial eligibility.

5 Social and environmental responsibility

CASTING addresses major public health challenges by targeting cancer prevention, diagnosis, and treatment optimization. The team is deeply embedded in clinical environments (Centre Léon Bérard) and contributes to national and European initiatives in digital health and personalized medicine.

6 Highlights of the year

- Collaboration with ADMIR structured by a CIFRE grant, ANR Laboratoire Commun funding, and regionalized iDemo funding
- Oral presentation at the 2025 annual meeting of the American Association for Cancer Research (gene expression signature as a biomarker of immunotherapy response) of Mehdi Lamkhioued's thesis work
- Pierre Saintigny has been nominated as President of the Auvergne Rhône-Alpes Cancer Research Cluster (CLARA)
- The group of Sandra Ortiz has published a review on the theme: Biology and Clinical Management of Non-V600 BRAF Alterations in NSCLC (non-small cell lung cancer), in JTO - Journal of Thoracic Oncology, online in 2026.

7 Latest software developments, platforms, open data

Open Data

Participants: Martinez pierre.

SuperSeries on single cell transcriptomics (GSE310225), published on the BDD Genome Expression Omnibus (GEO).

Latest software developments

Participants: Michon Lucas, Saintigny Pierre.

Development of an R package for analyzing the spatial organization of cancers: neighborhood, local density, and interaction coefficient.

8 New results

The main new results obtained during the year include:

- Development of quantitative national-scale frameworks for genomic medicine deployment and recommendations to accelerate the future of precision oncology care. [1, 7].
- Identification of distinct molecular and immune patterns in oral lesions and head and neck cancers, with implications for early detection and prevention [2, 5, 14].
- Analysis of multi-omics spatial data to distinguish immune microenvironments in HNSCC and predict immunotherapy response [16].
- Identification of prognosis marker and molecular therapeutic target [10], and Section 8.9.
- New insights into tumor plasticity and stemness mechanisms [12].
- Review on current research in NSCLC [11].
- Methodological advances in stochastic and mechanistic modeling of evolving biological systems [4, 17, 3].

8.1 PFMG2025—integrating genomic medicine into the national healthcare system in France

Participants: Saintigny Pierre.

Abstract [1]: Integrating genomic medicine into healthcare systems is a health policy challenge that requires continuously transferring scientific advances into clinics and ensuring equal access for patients. France was one of the first countries to integrate genome sequencing into clinical practice at a nationwide level, with the ambition to provide more accurate diagnostics and personalized treatments. Since 2016, the French government has invested €239M in the 2025 French Genomic Medicine Initiative (PFMG2025) which has so far focused on patients with rare diseases (RD), cancer genetic predisposition (CGP) and cancers. PFMG2025 has addressed numerous challenges to set up an operational organizational framework. As of

December the 31st 2023, 12,737 results were returned to prescribers for RD/CGP patients (median delivery time: 202 days, diagnostic yield: 30.6%) and 3109 for cancer patients (median delivery time: 45 days). PFMG2025's future priorities encompass ensuring economic sustainability, strengthening links with research, empowering patients and practitioners, and fostering collaborations with European partners. Funding : as of December the 31st 2023, €239M have been invested by the French government.

8.2 Worldwide Innovative Network (WIN) Consortium in Personalized Cancer Medicine: Bringing next-generation precision oncology to patients

Participants: Saintigny Pierre.

Abstract [7]: The human genome project ushered in a genomic medicine era that was largely unimaginable three decades ago. Discoveries of druggable cancer drivers enabled biomarker-driven gene- and immune-targeted therapy and transformed cancer treatment. Minimizing treatment not expected to benefit, and toxicity—including financial and time—are important goals of modern oncology. The Worldwide Innovative Network (WIN) Consortium in Personalized Cancer Medicine founded by Drs. John Mendelsohn and Thomas Tursz provided a vision for innovation, collaboration and global impact in precision oncology. Through pursuit of transcriptomic signatures, artificial intelligence (AI) algorithms, global precision cancer medicine clinical trials and input from an international Molecular Tumor Board (MTB), WIN has led the way in demonstrating patient benefit from precision-therapeutics through N-of-1 molecularly-driven studies. WIN Next-Generation Precision Oncology (WINGPO) trials are being developed in the neoadjuvant, adjuvant or metastatic settings, incorporate real-world data, digital pathology, and advanced algorithms to guide MTB prioritization of therapy combinations for a diverse global population. WIN has pursued combinations that target multiple drivers/hallmarks of cancer in individual patients. WIN continues to be impactful through collaboration with industry, government, sponsors, funders, academic and community centers, patient advocates, and other stakeholders to tackle challenges including drug access, costs, regulatory barriers, and patient support. WIN's collaborative next generation of precision oncology trials will guide treatment selection for patients with advanced cancers through MTB and AI algorithms based on serial liquid and tissue biopsies and exploratory omics including transcriptomics, proteomics, metabolomics and functional precision medicine. Our vision is to accelerate the future of precision oncology care.

8.3 Strategies for early detection and detailed characterization of oral lesions and head and neck squamous cell carcinoma in Fanconi anemia patients

Participants: Saintigny Pierre, Martinez Pierre.

Abstract [2]: Fanconi Anemia (FA) is an inherited disorder associated with profound DNA repair defects, marked by failure to thrive, congenital malformations, progressive bone marrow failure (BMF), and an increased susceptibility to cancer. Clinical manifestations of FA vary widely, with BMF and clonal evolution predominantly affecting younger individuals, while adults are more frequently presenting with solid tumors. Individuals with FA are at a 500-fold increased risk of developing head and neck squamous cell carcinoma (HNSCC), which tends to appear at a median age of 30 years, often at advanced stages with only a 57% two-year survival rate. The DNA repair deficiency prohibits the use of cisplatin and radiation therapy, limiting the treatment options for FA patients. Given the critical importance of early HNSCC detection in FA patients, innovative and less invasive diagnostic techniques are needed. This review discusses the role of brush biopsy-based cytology combined with molecular and morphometric analyses, as well as next-generation sequencing. Cytology alone demonstrated significant potential for detecting high-grade oral epithelial dysplasia and early-stage HNSCC, achieving sensitivities and specificities of 97.7% and 84.5%, respectively. Such techniques allow for stringent surveillance of the oral cavity in FA patients, essential given the aggressive nature of HNSCC in FA and the limited treatment options. In the absence of oral mucosal

lesions, a six-month follow-up is recommended. For oral lesions persisting beyond three weeks, diagnostic evaluation is warranted, with clinical follow-up every three months for low-grade dysplasia and treatment of high-grade dysplasia. Integrating modern diagnostic tools within a comprehensive screening framework, alongside patient participation, is essential for personalized care, improved surveillance, and developing preventive measures to enhance FA patient care.

8.4 Advanced Stage Head and Neck Cancer Diagnosis: HEADSpAcE Consortium Health Systems Benchmarking Survey

Participants: Saintigny Pierre.

Abstract [5]: Background – Globally, most people with head and neck cancers (HNCs) are diagnosed with advanced-stage disease. HNC diagnostic stage has multifactorial explanations, with the role of health system factors not yet fully investigated.

Methods – HNC centres (n =18) from the HEADSpAcE Consortium were surveyed via a bespoke health system questionnaire covering a range of factors. Centres were compared using the least square means for the presence/absence of each health system factor to their proportion of advanced-stage HNC.

Results – Health system factors associated with lower proportion in advanced-stage diagnosis were formal referral triaging (14%, 95% CI-0.26, -0.03), routine monitoring of time from referral to diagnosis (16%, 95% CI-0.27, -0.05), and fully publicly funded systems (17%, 95% CI-0.29, -0.06). Several health systems factors had no routinely available data.

Conclusions – Through identifying and monitoring health systems factors associated with lower proportions of advanced stage HNC, interventions could be developed, and systems redesigned, to improve early diagnosis.

8.5 Mechanisms of Adaptive Resistance to Targeted Therapy in RET-Aberrant Cancers

Participants: Ortiz Sandra.

Abstract [14]: The success of targeted therapies in oncogene-driven cancer is limited by adaptive or acquired treatment resistance, leading to disease progression. A recent study reports that YAP-dependent human epidermal growth factor receptor 3 (HER3) activation constitutes a therapeutic vulnerability of adaptive resistance to RET-targeted therapies in RET-altered cancers, highlighting a promising strategy to improve RET inhibitor tumor responses.

8.6 LIBELULE: A Randomized Phase III Study to Evaluate the Clinical Relevance of Early Liquid Biopsy in Patients With Suspicious Metastatic Lung Cancer

Participants: Ortiz Sandra, Saintigny Pierre.

Abstract: Genomic profiling is a major component for first-line treatment decisions in patients with NSCLC and the timeliness of biomarker testing is essential to improve time to treatment initiation (TTI) or avoid inappropriate treatment.

8.7 Mapping immune activity in HPV-negative head and neck squamous cell carcinoma: a spatial multiomics analysis

Participants: Saintigny Pierre.

Abstract [16]: Background – Head and neck squamous cell carcinoma (HNSCC) exhibits low response rates to immunotherapies, with only about 15-25% of patients responding to monotherapy and 30-45% to combination therapy. This limited effectiveness is attributed to significant intertumor and intratumor heterogeneity, which affects the immunological activity of individual tumors and their regions, thereby influencing immunotherapy outcomes. Various biomarkers at the gene and protein expression levels have been identified to predict the response to immunotherapy in HNSCC.

Methods – In this study, we evaluated intertumor heterogeneity using a 27-gene expression signature to stratify tumors by their immunologic activity status. We investigated intertumor heterogeneity at the molecular and cellular level and further analyzed intratumor spatial heterogeneity within and across these subgroups by using spatial multiomics approaches.

Results – Immunologically active tumors showed increased interferon- γ and interferon- α signaling and upregulation of major histocompatibility complex-I signaling and genes involved in antigen presentation. Chemokines such as CXCL8 and CXCL9, which are crucial for immune cell recruitment, were differentially regulated. The spatial analysis revealed that active tumors tended to show higher autocorrelation of homogeneous regions with immune cell infiltration compared with inactive tumors. Proximity measures showed an increased colocalization of immune cells, particularly CD8+ T cells, T helper cells, and regulatory T cells, near tumor cells in active tumors. Despite this high immune infiltration, HNSCC often has an immunosuppressive microenvironment, which we observed as a colocalization of programmed cell death protein-1+ (PD-1+) cytotoxic T cells and cytotoxic T cells, indicating regional differences in active and exhausted cell ratios. Furthermore, upregulation of JAK-STAT3 signaling in active tumors was potentially associated with immune evasion.

Conclusions – The spatial analysis at multiple omics levels allowed for a detailed investigation of molecular and cell type markers to further distinguish between immunologically active and immunosuppressive microenvironments and their spatial heterogeneity. Our study demonstrates that, besides gene expression signatures, cell colocalization signatures can infer immunological activity in HNSCC, thus predicting immunotherapy response.

8.8 Frizzled 7 drives amplification of cancer stem-cell subpopulations and the aggressiveness and poor differentiation of human hepatocellular carcinoma

Participants: Saintigny Pierre.

Abstract [10]: FZD7 is one of the key players in the subset of WNT-TGF β -activated hepatocellular carcinomas (HCC), but the consequences of its abnormal expression on hepatocarcinogenesis remain to be better understood. Herein, we aimed to investigate the role of the FZD7-mediated signaling in immature phenotype and aggressiveness of HCC. Firstly, 499 human HCCs were used for clinical and molecular comparisons regarding the expression of FZD7 and stemness-associated markers. We showed that FZD7 overexpression was associated with poor differentiation and, in combination with CD133, predicted a poor outcome of patients with aggressive recurrence. Next, the impact of WNT3/FZD7 signaling on the differentiation of hepatic cells was assessed in HCC cell lines, as well in the non-transformed progenitor HepaRG cell line and in primary human hepatocytes, transduced with WNT3 and FZD7-expressing lentiviruses. We demonstrated that the ectopic expression of WNT3 and FZD7 inhibited the differentiation behavior of HepaRG cells and human primary hepatocytes, amplified the pool of EpCAM (+), CD90 (+) and CD133 (+) subsets of HCC cell

lines, and increased their cancer stem cell features. Moreover, we found that WNT3/FZD7-mediated stemness properties of cancer cells were independent of the stemness-associated marker NANOG. In conclusion, we identified the FZD7 (+) /CD133 (+) signature as a potential prognosis marker and molecular therapeutic target, and we strengthened the hypothesis for the involvement of FZD7 in the enrichment of a cancer stem cell pool in HCC.

8.9 Chromosome centromere copy number amplification associated with exceptional response in HER2-positive metastatic breast cancer patients

Participants: Andrieu Charlotte.

Abstract: Metastatic breast cancer (MBC) is generally an incurable neoplasm. A small cohort of patients with HER2-positive MBC, however, achieve such prolonged remission without relapse following anti-HER2 therapy and chemotherapy, that it is speculated they might be cured. The genomes of these patients might provide insights into the underlying mechanisms for their successful treatment. Here, a total of 243 HER2-positive patients diagnosed with MBC between 2000 and 2015 were studied. Of these, 29 patients were identified as exceptional responders (ExR) with an overall survival (OS) > 60 months and no evidence of relapse, 54 patients with an OS > 60 months but who relapsed or developed progressive disease were defined as exceptional survivors (ExS), and 160 patients with an OS < 60 months were identified as short-term responders (STR). Whole-Genome Sequencing and centromere copy number (CCN) analysis was performed on 27 patients (12 ExR; 4 ExS; 11 STR). A significant amplification was observed in the centromeric regions of ExR, exhibiting higher CCN compared to the ExS and STR. Digital PCR validation of chromosome 4 centromere region D4Z1 copy number was not associated with ExR OS. Our results suggest that the amplification of centromere regions are associated with very prolonged remission and survival in patients with HER2-positive MBC.

8.10 EMT-driven plasticity prospectively increases cell–cell variability to promote therapeutic adaptation in breast cancer

Participants: Saintigny Pierre, Martinez Pierre, Coutant Angèle.

Abstract [12]: Cellular plasticity enables cancer cells to adapt non-genetically, thereby preventing therapeutic success. The epithelial-mesenchymal transition (EMT) is a type of plasticity linked to resistance and metastasis. However, its exact impact on population diversity and its dynamics under chemotherapy is unknown. We used single-cell transcriptomics to investigate phenotypic diversity dynamics upon treatment in two in vitro models of triple negative breast cancer (TNBC), where EMT-driven plasticity is either induced or spontaneously occurring. We report that EMT-driven plasticity confers higher phenotypic cell-cell variability ($p = 0.001$) while enriching for stem-like cells. Genetic and phenotypic cell-cell variability were not consistently correlated. High-plasticity populations displayed more pre-adapted cells before treatment ($p = 0.03$). In a population displaying spontaneous EMT and phenotypic variation, pre-adapted cells were a rare minority of high-scoring outliers whose expression patterns correlated with survival in TNBC patients subjected to chemotherapy ($p = 0.03$). Higher plasticity was not associated with a partial EMT status. Our results provide novel insights on how EMT-driven plasticity promotes a prospective diversification process increasing population phenotypic diversity, which can yield rare pre-adapted states before treatment. This highlights the need to tackle phenotypic diversity prior to treatment in high-plasticity tumours.

8.11 Advances in Lung Cancer Basic and Translational Research in 2025 - Overview and Perspectives Focusing on NSCLC

Participants: Ortiz Sandra.

Abstract [11]: Basic and translational research in lung cancer is a rapidly evolving field with a transformational impact on early detection, diagnosis, therapeutic development, and personalization of care. Recent advances have greatly increased our understanding of the molecular genomics, proteomics, pathogenesis, and cellular biology of this deadly malignancy. The International Association for the Study of Lung Cancer (IASLC) recently formed a Basic and Translational Science (BaTS) Committee to further enhance the scientific leadership of IASLC in thoracic cancer research. This review by members of the committee highlights the breadth of current research in NSCLC, with a focus on molecular risk factors and processes in tumorigenesis, heterogeneity, phenotypic plasticity, metabolic reprogramming, immunobiology, the immune microenvironment, and microbiome. This review also identifies future research areas that may lead to further improvement in survival outcomes and curative therapies especially for patients with advanced NSCLC.

8.12 Continuous limits of large plant-pollinator random networks and some applications

Participants: Leman H el ene.

Abstract [4]: We study a stochastic individual-based model of interacting plant and pollinator species through a bipartite graph: each species is a node of the graph, an edge representing interactions between a pair of species. The dynamics of the system depends on the between- and within-species interactions: pollination by insects increases plant reproduction rate but has a cost which can increase plant death rate, depending on the densities of pollinators. Pollinators reproduction is increased by the resources harvested on plants. Each species is characterized by a trait corresponding to its degree of generalism. This trait determines the structure of the interaction graph and the quantities of resources exchanged between species. Our model includes in particular nested or modular networks. Deterministic approximations of the stochastic measure-valued process by systems of ordinary differential equations or integro-differential equations are established and studied, when the population is large or when the graph is dense and can be replaced with a graphon. The long-time behaviors of these limits are studied and central limit theorems are established to quantify the difference between the discrete stochastic individual-based model and the deterministic approximations. Finally, studying the continuous limits of the interaction network and the resulting PDEs, we show that nested plant-pollinator communities are expected to collapse towards a coexistence between a single pair of species of plants and pollinators.

8.13 Evolution of a trait distributed over a large fragmented population: Propagation of chaos meets adaptive dynamics

Participants: Leman H el ene.

Abstract [17]: We consider a metapopulation made up of K demes, each containing N individuals bearing a heritable quantitative trait. Demes are connected by migration and undergo independent Moran processes with mutation and selection based on trait values. Mutation and migration rates are tuned so that each deme receives a migrant or a mutant in the same slow timescale and is thus essentially monomorphic at all times for the trait (adaptive dynamics). In the timescale of mutation/migration, the metapopulation can then be seen as a giant spatial Moran model with size K that we characterize. As $K \rightarrow \infty$ and physical space becomes continuous, the empirical distribution of the trait (over the physical and trait spaces) evolves deterministically according to an integro-differential evolution equation. In this limit, the trait of every migrant is drawn from this global distribution, so that conditional on its initial state, traits from finitely many

demes evolve independently (propagation of chaos). Under mean-field dispersal, the value X_t of the trait at time t and at any given location has a law denoted μ_t and a jump kernel with two terms: a mutation-fixation term and a migration-fixation term involving μ_{t-} (McKean-Vlasov equation). In the limit where mutations have small effects and migration is further slowed down accordingly, we obtain the convergence of X , in the new migration timescale, to the solution of a stochastic differential equation which can be referred to as a new canonical equation of adaptive dynamics. This equation includes an advection term representing selection, a diffusive term due to genetic drift, and a jump term, representing the effect of migration, to a state distributed according to its own law.

8.14 Some topics in random walks

Participants: Bonnet Céline.

Abstract [3]: We collect a few recent results on random walks, which are ubiquitous in probability theory. The topics covered are: persistence problems for stochastic processes, large fluctuations in multi-scale modeling for rest hematopoiesis, and fine properties of the elephant random walk.

9 Bilateral contracts and grants with industry

ADMIR

Participants: Saintigny Pierre, Léon Fabian.

Partners:

- Inserm
- CLB, Centre Léon Bérard

description: Use of multispectral infrared tissue imaging for tissue segmentation in oral cancers, study of tumor heterogeneity in upper aerodigestive tract cancers

Additional information: Laboratoire Commun ANR

SmartCatch

Participants: Saintigny Pierre, Ortiz Sandra.

Partners:

- CLB, Centre Léon Bérard

description: Development of a workflow for the automatic quantification of circulating tumor cells and their phenotypic characterization as single cells

DeepLife

Participants: Saintigny Pierre.

Partners:

- DeepLife, France

description: Development of an atlas of one million single cells including laboratory and public domain data (GEO)

10 Partnerships and cooperations

10.1 European initiatives

INTERCEPTOR (COST)

Participants: Saintigny Pierre.

Description: coordination of a European network on the prevention of oral cancers through multidisciplinary research into oral conditions with malignant potential.

PI: submitter & chair (P Saintigny)

CGI CLINICS (HORIZON, Europe)

Participants: Saintigny Pierre, Verlingue Loïc.

Description: Development and evaluation of a tool for interpreting variants discovered through NGS sequencing

Partner: CLB, Centre Léon Bérard.

IMMUCAN (IMI2, Europe)

Participants: Saintigny Pierre, Michon Lucas, Canjura Sonia.

Description: understand the tumor microenvironment, particularly in its spatial dimensions, in order to identify new biomarkers

Partner: CLB, Centre Léon Bérard.

Partner in the ERC Starting Grant: GAMEchange

Participants: David Coulette.

Description: Mathematical modeling and numerical simulation for the study of soil bacteria ecological and evolutionary dynamics in the context of global climate change.

PI: Elsa Abs (CNRS, LSCE)

10.2 National initiatives

ANR JCJC SIFREP

Participants: Leman H el ene, C eline Bonnet, Pierre Martinez, David Coulette.

Title: Site Frequency Spectrum of rescued populations,

Date/Duration: 2025-2029

Montant: 170 000  

Additional info/keywords: Cancer represents a substantial challenge to society, with current treatments being both physically taxing and financially costly. Despite these efforts, treatments can be ineffective, in part due to "rescue events". A rescue event occurs when cells initially respond to a treatment but, over time, some undergo mutations that confer resistance, allowing a subpopulation to survive and proliferate despite ongoing therapy. The objective of this project is thus to investigate the composition and behavior of a cell population undergoing such event, by developing and analyzing stochastic models that represent these dynamics, aiming to gain deeper insights into how resistance develops and spreads.

More precisely, models will be developed using stochastic processes which will represent the events of division, death, acquisition of a resistant mutation, and of neutral mutations (i.e., those that do not affect individual growth) for each cell. The interest lies in a multi-scale context, wherein the initial sensitive population is large and the probability of acquiring resistance is low.

The aim is to study the Site Frequency Spectrum (SFS), a method for analysing the distribution of neutral mutations within a population, which is accessible through DNA sequencing. There will be a focus on neutral mutations that are shared by a significant proportion of the population, a topic that has been relatively understudied. Moreover, the aim is to establish convergence in law for the SFS, providing reliable predictions that account for limited in vivo or experimental realizations. Ultimately, the objective is to develop estimators of the population growth, the mutation rates, and the occurrence time of resistance from SFS data, reducing reliance on computationally intensive methods generally used to study these data.

INCa PLBIO TransPlaCer

Participants: Pierre Martinez.

Title: Transdifferentiation and Plasticity in rare breast canCers: underlying causes, evolutionary dynamics and molecular biomarkers

Additional info/keywords: Institut National du Cancer, Projet Libre en Biologie (Coordonnateur, 180K , 598K  total, 5  quipes).

Members recruited to join CASTING: Pierre Giroux, postdoctoral researcher starting April 1, 2026; Alex Buteau, M2 intern starting February 2, 2026.

Abstract: Triple negative breast cancers (TNBC) face a lack of therapeutic options and a high mortality. Metaplastic breast carcinomas (MpBC) are a rare subtype of TNBC, characterized by high cellular plasticity and the presence of at least one transdifferentiated tumor compartment. These compartments

can be of different non-epithelial types, the presence of which is determined histologically. Due to their rarity and complexity, the biology of MpBCs is poorly understood and patients are still poorly managed.

The objectives of the TransPlaCer project are to better understand the emergence of transdifferentiated compartments in MpBC, in order to better diagnose and treat these tumors. In mixed histology MpBCs, we will analyze pairs of phenotypically different compartments using multi-omics technologies: spatial and single-cell transcriptomics ; post-microdissection exome and methylome analyses. This will allow us to better understand the origin of different types of transdifferentiation (spindle, squamous, chondroid, osteoid), the genetic/non-genetic mechanisms underlying them, as well as their evolutionary dynamics. We will validate the diagnostic utility of biomarkers specific to each type of transdifferentiation by immunohistochemical analyses in an independent cohort. We will also analyze the impact of key identified alterations, as well as pharmacological perturbations for therapeutic purposes, in in vitro patient-derived models (xenografts and patient/xenograft-derived organoids).

This project will produce spatially resolved multi-omics data, providing the scientific community with a level of precision never achieved so far in MpBC. It will also allow, for these cancers that still cruelly lack adequate clinical options, to identify potential therapeutic targets and molecular diagnostic solutions.

INCa PRTK-25

Participants: Ortiz Sandra.

Title: Unravelling immunotherapy resistance in pulmonary sarcomatoid carcinomas: mechanistic insights and therapeutic targeting of the CD70/CD27 axis.

Participating teams: • Co-PI : Marie Wislez, CHU Cochin

- Eric Tartour, HEGP, Paris
- Paul Hofman, CHU Nice
- Julien Mazieres, CHU Toulouse
- Charlotte Domblides, CHU Bordeaux

Funding from Intersiric between Sirics In-situ in Paris and Lyrican+ in Lyon

Participants: Bonnet Céline, Ecotière Claire, Leman Hélène, Saintingy Pierre, Ortiz Sandra. .

Title: Modelling for oral mucosal cancers and Acute Myeloid Leukemia

Participating teams: Raphaël Itzykson and Vincent Bansaye

Additional information: The latter funding has enabled the recruitment of a research engineer (Claire Ecotière) for 2 years from April 2025.

INCa PLBIO-25

Participants: Ortiz Sandra. .

Title: Elucidating the mechanisms of cancer cell plasticity in BRAF-mutant non-small cell lung cancer.

Participating teams:

- Dr Friboulet Luc Équipe Adaptation génétique aux inhibiteurs de kinase / INSERM U981 Université Paris-Saclay, Inserm U981, Gustave Roussy, Villejuif
- Olivier Calvayrac, Cancer Research Center of Toulouse
- Anton Crombach, Centre Inria de Lyon, Villeurbanne
- Gabriel Ichim, INSERM, CRCL, Lyon

Partner in INCA PLBIO24-161

Participants: Coulette David.

Description: Development of image analysis pipelines and mathematical modeling for the quantification of PC and IF microscopy images for the study of the impact of the *TRα1* hormone in Colorectal Cancer.

PI: Michela Plateroti (Inserm-IGBMC)

Montant: a 18-month post-doc for our team.

MIRFLECT

Participants: Saintigny Pierre.

Call: BPI France ; iDemo régionalisé

Partners:

- CLB, Centre Léon Bérard, France
- CYPATH

Description: development of a reflective optical architecture that will enable MIRSTAIN & MIRDIAG devices to be used on a very large scale, involving the adaptation of its deep learning algorithms

MECANIC, Characterization of pre-neoplastic lesions and stratification of their evolutionary risks

Participants: Saintigny Pierre.

Partners:

- Inserm, France
- IARC, "plateforme Génomique des Cancers"

Description: In-depth description of the genomic and microenvironmental determinants of the formation and progression of leukoplakia (precancerous lesion) according to different exposure contexts.

Partner in ANR INFOGENETICS

Participants: Saintigny Pierre.

Call: BPI France ; iDemo régionalisé

Partners: • CLB, Centre Léon Bérard, France

Description: research related to the humanities and social sciences

ISEBIO (INCa PREV-BIO)

Participants: Saintigny Pierre, Martinez Pierre.

Call: BPI France ; iDemo régionalisé

Partners: • CLB, Centre Léon Bérard, France

Description: Description of the heterogeneity of (erythro)leukoplakia in a European multicenter cohort (INTERCEPTOR network)

FRAILIMMUNEBIO (SIGN'IT Fondation ARC)

Participants: Saintigny Pierre, Michon Lucas, Canjura Sonia.

Call: BPI France ; iDemo régionalisé

Partners: • CLB, Centre Léon Bérard, France

Description: Identification of spatial organization parameters as biomarkers of clinical benefit to immunotherapy in the context of a clinical trial

10.3 Regional initiatives

Partner in ShapeMed projet: MitoMove

Participants: Coulette David.

Description: Development of a microscopy timelapse image analysis pipeline for the study of the impact of mitochondria on cell movement in the context of Cancer research.

Link: [link](#).

PI: Gabriel Ichim (CRLCL) and Clara Gil (CRCL)

Collaboration with "Service National de Police Scientifique" (SNPS, LPS69)

Participants: Coulette David, Bonnet Céline, Leman Hélène.

Description: Data analysis on correlations between gene methylation levels and age for criminal forensics applications.

Contact: M. Gabut

Collaboration between IRD Montpellier and CRCL Lyon

Participants: Andrieu Charlotte.

Description: developing an analysis workflow for the detection of somatic variants in normal tissues using high-depth whole-exome sequencing data, contributing to methodological advances in the study of somatic mutations outside of overt cancer.

10.4 Public policy support**CLARA , OncoStarter Thématisé « Expérience Patient »: FancoGPS**

Participants: Martinez Pierre, Saintigny Pierre, Andrieu Charlotte.

Title: FancoGPS : Maladie de Fanconi et Généralisation des brosses Pour la Surveillance.

Additional info/keywords: 38K€ total, Partnership with the "Association Française de la Maladie de Fanconi"

11 Dissemination**11.1 Promoting scientific activities****11.1.1 Scientific events: organisation****Organization of the "Séminaire de modélisation du vivant"**

Participants: Bonnet Céline, Leman Hélène.

Information: These meetings take place on Thursday mornings once every three months and consist of two presentations per session, primarily by local speakers.

In addition, there are three days of meetings (Grenoble, Lyon, Marseille) throughout the year.

link: [link](#)

11.1.2 Scientific events: selection

Andrieu Charlotte: selection for the competitive training programme EBEC 2025 (Evolutionary Biology and Ecology of Cancer) at the Wellcome Sanger Institute (UK)

11.1.3 Talks and Poster

Andrieu Charlotte: Poster "Somatic Evolutionary Dynamics and Oncogenesis in the Oral Mucosa" at the CRCL International Cancer Symposium 2025

Ortiz Sandra: Invited speaker, European Lung Cancer Congress. Paris (France).

Ortiz Sandra: Poster, CRCL Symposium, January 2025. Activating PIK3CA mutations in resistance to BRAF-targeted therapies in BRAF V600E mutant non-small cell lung cancer cell.

Ortiz Sandra: Poster, EACR Meeting - Persister Cells: from Bacteria to Cancer. Transcriptomic analyses of treatment-persistent residual disease in BRAF-mutant lung adenocarcinoma.

Ortiz Sandra: Poster, IASLC World Conference in Lung Cancer Clinical and genomic landscape of BRAF-mutant NSCLC patients from the AACR GENIE BPC cohort.

Leman H el ene: Talk at the Probability seminar of Lille University.

Leman H el ene: Invited talk at the conference "Interacting populations and beyond" in Travem unde (Germany).

Leman H el ene: Invited talk at the conference "Mathematical Biology Modelling days of Besan on 2025".

11.1.4 Research administration

Leman H el ene: Member of the "Conseil de Laboratoire" at UMPA

11.2 Teaching - Supervision - Juries - Educational and pedagogical outreach

11.2.1 Supervision

Martinez Pierre : 1 PhD student (Ang le Coutant, viva successfully passed in May 2025) ; 1 Master student (Jordan Dutel, M2 bioinformatics, 6 months) ; 1 post-doc (Charlotte Andrieu, since August 2024).

Leman H el ene & Saintigny Pierre : 1 master student (Cl a Soupe, 3 months), 1 PhD student (Paul de Lambert, since sept 2025)

Leman H el ene & Bonnet C eline : 1 L3 student (2 months, Esther Aubin)

Leman H el ene : 1 PhD student (Alice Fohr) in collaboration with F. Cl ement (Inria Saclay, Musca TEAM).

Saintigny Pierre: 1 post-doc (Daniel Cs ury) in digital pathology; 3 co-direction of PhD students (Leon Fabian, Straub Flavie, Lamkhioued Mehdi); 1 international internship (Vitoria Scavacini Possebon).

Saintigny Pierre & Michon Lucas & Canjura Sonia: supervision of students in dual degree in medicine and engineering school (Centrale Lyon) (Colin Aubonnet, Youssef Malouf, Matthieu Biragnet).

11.2.2 Educational and pedagogical outreach

Mahtouk Karen: lecturer in immunology, UBCL1, **192h per year** from L2 to M2, in particular with courses within the PASS program (Parcours d'Accès Spécifique Santé).

Coulette David: Cours du Diplôme ENS de Lyon : IA pour les sciences - ENS de Lyon - 6h CM

Bonnet Céline & Leman Hélène : M2 course, Scaling limits for stochastic processes : application to biology - ENS de Lyon - 18h CM

Leman Hélène : M2 course, Ecologie spatiale - Lyon1 - 9h CM

Bonnet Céline : lecturer for the french "Agrégation" preparation - ENS de Lyon.

Martinez Pierre : Evolutionary trajectories in cancer in 2 Masters (M1 Santé Publique, UBCL; M2 de Génétique, Université Paris Cité). 1.5 to 2 hours per lecture.

Saintigny Pierre: Head of the Oncology Unit for students at the Lyon East Faculty of Medicine (DFGSM3, 3rd year), UCBL1.

Saintigny Pierre: Head of Doctoral School Announcement of bad news in oncology for students at the Lyon East Faculty of Medicine (DFASM1, 4th year), UCBL1

Saintigny Pierre: Head of the CLB's ECOS (Standardized Objective Clinical Examination) working group for CLB hospital students

Saintigny Pierre: Coordinator of the Specialized Studies Diploma (DES) in Oncology for the Lyon subdivision, UCBL1

11.3 Popularization

11.3.1 Specific official responsibilities in science outreach structures

Leman Hélène: Director of the scientific committee of the "Maison des Mathématiques et de l'Information" [link](#): The aim of MMI is to raise public awareness of mathematics and computer science and to inspire scientific vocations through a lively, playful, and interdisciplinary approach, offering workshops, exhibitions, and events for all audiences.

Bonnet Céline: member of the scientific committee of the MMI.

11.3.2 Participation in Live events

Leman Hélène & Bonnet Céline: Participation in numerous activities at MMI in front of middle and high school students: exhibition visits, magic workshops, research discovery workshops...

Leman Hélène: Talk for high school students for the Rhône-Alpes Mathematics Olympiad awards ceremony.

Leman Hélène: Visit to the mathematics laboratory for young high school girls as part of the day "Sciences, un métier de femmes".

12 Scientific production

12.1 Publications of the year

International journals

- [1] C. Abadie, A. Abderrahmane, O. Abdous, C. Abel, O. Ackermann, C. Acquaviva, F. Ader, S. Adham, D. Adjaoud, A. Afenjar et al. ‘PFMG2025—integrating genomic medicine into the national healthcare system in France’. In: *The Lancet Regional Health - Europe* 50 (6th Jan. 2025). doi: [10.1016/j.lanepe.2024.101183](https://doi.org/10.1016/j.lanepe.2024.101183). URL: <https://hal.science/hal-04988732> (cit. on p. 8).
- [2] A. Beddok, E. Velleuer, F. Sicre de Fontbrune, R. Brakenhoff, J.-H. Dalle, C. Dufour, S. Faivre, C. Genet, J. Klijanienko, C. Krieg, T. Leblanc, P. Martinez, R. Peffault de Latour, A. Rigolet, P. Saintigny, D. S. Lyonnet, J. Soulier, J. Surralles, M. Schramm and J. Thariat. ‘Strategies for early detection and detailed characterization of oral lesions and head and neck squamous cell carcinoma in Fanconi anemia patients’. In: *Cancer Letters* 617 (2025), p. 217529. doi: [10.1016/j.canlet.2025.217529](https://doi.org/10.1016/j.canlet.2025.217529). URL: <https://hal.science/hal-04984529> (cit. on pp. 8, 9).
- [3] Q. Berger, C. Bonnet, L. Laulin and K. Raschel. ‘Some topics in random walks’. In: *ESAIM: Proceedings and Surveys*. Journées MAS 2022 - Dynamic and Stochastic Modelling Rouen, France, August 29–31, 2022 80 (2025), pp. 51–71. doi: [10.1051/proc/202580051](https://doi.org/10.1051/proc/202580051). URL: <https://hal.science/hal-05210861> (cit. on pp. 8, 14).
- [4] S. Billiard, H. Leman, T. Rey and V.-C. Tran. ‘Continuous limits of large plant-pollinator random networks and some applications’. In: *MathematicS In Action* (2025). URL: <https://cnrs.hal.science/hal-03525607> (cit. on pp. 8, 13).
- [5] G. Creaney, M. de Aquino Goulart, A. McMahon, C. Paterson, J. Mccaul, S. Perdomo, L. Mendoza, L. Alemany, L. M. R. Arantes, P. A. R. Urrego, T. Dudding, M. Pring, M. Vilenky, C. Cuffini, S. A. L. de Blanc, J. C. de Oliveira, S. Pervez, P. Saintigny, M. Cuello, J. Betka, L. F. R. Pinto, M. P. Curado, K. Zendehdel, L. Richiardi, M. Popovic, J. R. de Podesta, S. V. von Zeidler, R. M. Rocha, S. Alwaheidi, P. Brennan, S. Virani, A. Ross and D. Conway. ‘Advanced Stage Head and Neck Cancer Diagnosis: HEADSpAcE Consortium Health Systems Benchmarking Survey’. In: *Head & Neck* 47.7 (24th Feb. 2025), pp. 1977–1988. doi: [10.1002/hed.28094](https://doi.org/10.1002/hed.28094). URL: <https://hal.science/hal-05112070> (cit. on pp. 8, 10).
- [6] W. C. Cross, S. Nowinski, G. Cresswell, M. Mossner, A. Banerjee, B. Lu, M. Williams, G. Vlachogiannis, L. Gay, A.-M. Baker et al. ‘Negative Selection Maintains Grossly Altered but Broadly Stable Karyotypes in Metastatic Colorectal Cancer’. In: *Cancer Discovery* (21st Jan. 2026), OF1–OF17. doi: [10.1158/2159-8290.CD-24-0813](https://doi.org/10.1158/2159-8290.CD-24-0813). URL: <https://hal.science/hal-05471470>.
- [7] W. S. El-Deiry, C. Bresson, F. Wunder, B. A. Carneiro, D. S. Dizon, J. L. Warner, S. L. Graff, C. G. Azzoli, E. T. Wong, L. Cheng et al. ‘Worldwide Innovative Network (WIN) Consortium in Personalized Cancer Medicine: Bringing next-generation precision oncology to patients’. In: *Oncotarget* (12th Mar. 2025). URL: <https://hal.science/hal-05022607> (cit. on pp. 8, 9).
- [8] C. Dupain, N. Jacquin, A. Latouche, Z. Nevière, P. Gestraud, A. Hamza, K. Nedara, V. Cockenpot, J. Selves, Y. Allory, L. Chanas, M. Milder, I. Soubeyran, H. Blons, A. Patrikidou, A. de Bernardi, J. Masliah-Planchon, O. Mariani, E. Rouleau, F. Escande, S. Boyault, P. Saintigny, F. de Fraipont, P. Blanc, J. Wong, C. Tlemsani, I. Guillou, J. Flavius, N. Fuentealba, M. Kamal, I. Bièche, N. Servant, C. Le Tourneau and S. Watson. ‘Management and survival of patients with cancer of unknown primary discussed by a French national multidisciplinary tumour board: a retrospective analysis’. In: *The Lancet Regional Health - Europe* 60 (Jan. 2026), p. 101524. doi: [10.1016/j.lanepe.2025.101524](https://doi.org/10.1016/j.lanepe.2025.101524). URL: <https://hal.science/hal-05471797>.
- [9] E. Ebrahimi, A. Sangphukieo, H. A. Park, V. Gaborieau, A. Ferreiro-Iglesias, B. Diergaard, W. Ahrens, L. Alemany, L. M. Arantes, J. Betka et al. ‘Cross-ancestral GWAS identifies 29 variants across head and neck cancer subsites’. In: *Nature Communications* 16 (2nd Oct. 2025). doi: [10.1038/s41467-025-63842-z](https://doi.org/10.1038/s41467-025-63842-z). URL: <https://hal.science/hal-05471780>.

- [10] A. Lopez, A. Paturel, N. Fares, F. Pez, G. Wang, P. Gifu, L. Lefrançois, J. Chouaref, P. Saintigny, J. Selves, J.-M. Peron, M. Rivoire, P. Merle and C. Caron de Fromental. ‘Frizzled 7 drives amplification of cancer stem-cell subpopulations and the aggressiveness and poor differentiation of human hepatocellular carcinoma’. In: *PLoS ONE* 20 (7th Oct. 2025). doi: [10.1371/journal.pone.0332768](https://doi.org/10.1371/journal.pone.0332768). URL: <https://hal.science/hal-05308248> (cit. on pp. 8, 11).
- [11] C. Mascaux, T. Sen, M. Sanchez-Cespedes, S. Ortiz-Cuaran, Y. Bossé, F. Dammeijer, M. Cavic, M. P. Barr, S. Arulananda, R. Armisen, A. H. Berger, F. Bianchi, D. P. Carbone, F. Cerciello, W. W. Lockwood, T. Mitsudomi, S. Ohara, K. Politi, S. Qin, L. C. Roisman, R. Samstein, F. Skoulidis, A. C. Tan, A. Thomas, J. Zhang, M. W. Wynes, T. John and M. S. Tsao. ‘Advances in Lung Cancer Basic and Translational Research in 2025 – Overview and Perspectives Focusing on NSCLC’. In: *Journal of Thoracic Oncology* 20.10 (3rd June 2025), pp. 1369–1391. doi: [10.1016/j.jtho.2025.05.024](https://doi.org/10.1016/j.jtho.2025.05.024). URL: <https://univoak.hal.science/hal-05444856> (cit. on pp. 8, 13).
- [12] L. Muller, F. Fauvet, C. Chassot, F. Angileri, A. Coutant, C. Dégletagne, L. Tonon, P. Saintigny, A. Puisieux, A.-P. Morel, M. Ouzounova and P. Martinez. ‘EMT-driven plasticity prospectively increases cell–cell variability to promote therapeutic adaptation in breast cancer’. In: *Cancer Cell International* 25 (3rd Feb. 2025). doi: [10.1186/s12935-025-03637-w](https://doi.org/10.1186/s12935-025-03637-w). URL: <https://inria.hal.science/hal-04928815> (cit. on pp. 8, 12).
- [13] S. Ortiz-Cuaran, L. Dupriez, C. Nicq, C. Lindsay, J. Mazieres, D. Santamaría, C. Ambrogio, O. Calvayrac, C. Teixido, L. Friboulet, S. Novello, F. Tabbò, A. Swalduz, E. Nadal, D. Planchard, L. Mezquita and M.-J. Nokin. ‘Biology and Clinical Management of Non-V600 BRAF Alterations in NSCLC’. In: *Journal of Thoracic Oncology* (Jan. 2026), p. 103531. doi: [10.1016/j.jtho.2025.12.001](https://doi.org/10.1016/j.jtho.2025.12.001). URL: <https://hal.science/hal-05471095>.
- [14] S. Ortiz-Cuaran and C. Leonce. ‘Mechanisms of Adaptive Resistance to Targeted Therapy in RET -Aberrant Cancers’. In: *Clinical Cancer Research* 31.6 (17th Mar. 2025), pp. 958–959. doi: [10.1158/1078-0432.CCR-24-3734](https://doi.org/10.1158/1078-0432.CCR-24-3734). URL: <https://hal.science/hal-05471401> (cit. on pp. 8, 10).
- [15] I. Ray-Coquard, M.-C. Kaminsky-Forrett, R. Ohkuma, A. de Montfort, F. Joly, I. Treilleux, S. Ghamry-Barrin, D. Bello-Roufai, P. Saintigny, A. Angelergues, L. Michon, A.-C. Hardy-Bessard, V. Attignon, J. Auclair, G. Chemin, A. Lainé, H. Péré, D. Veyer, A.-M. Savoye, J. Berthet, C. Caux, F. Lecuru, B. Dubois and S. Bétrian. ‘Neoadjuvant immune checkpoint blockade before chemoradiation for cervical squamous carcinoma (GINECO window-of-opportunity COLIBRI study): a phase II trial’. In: *Nature Communications* (5th Jan. 2026). doi: [10.1038/s41467-025-67646-z](https://doi.org/10.1038/s41467-025-67646-z). URL: <https://hal.science/hal-05471803>.
- [16] N. Zwing, L. Voith von Voithenberg, L. Alberti, S. M. Gabriel, J. Monné Rodriguez, R. Feddersen, J.-P. Foy, F. Damiola, N. Gadot, P. Saintigny and B. Gomes. ‘Mapping immune activity in HPV-negative head and neck squamous cell carcinoma: a spatial multiomics analysis’. In: *Journal for Immunotherapy of Cancer* 13.6 (25th June 2025), e011851. doi: [10.1136/jitc-2025-011851](https://doi.org/10.1136/jitc-2025-011851). URL: <https://hal.science/hal-05193518> (cit. on pp. 8, 11).

Reports & preprints

- [17] A. Lambert, H. Leman, H. Morlon and J. Tchouanti. *Evolution of a trait distributed over a large fragmented population: Propagation of chaos meets adaptive dynamics*. 8th Jan. 2025. URL: <https://hal.science/hal-04873740> (cit. on pp. 8, 13).