

2025 Activity Report

RESEARCH CENTRE: Inria Centre at Université Côte d'Azur

IN PARTNERSHIP WITH: INSERM, Aix-Marseille Université, CNRS, CAC4 MARSEILLE
- Institut Paoli-Calmettes

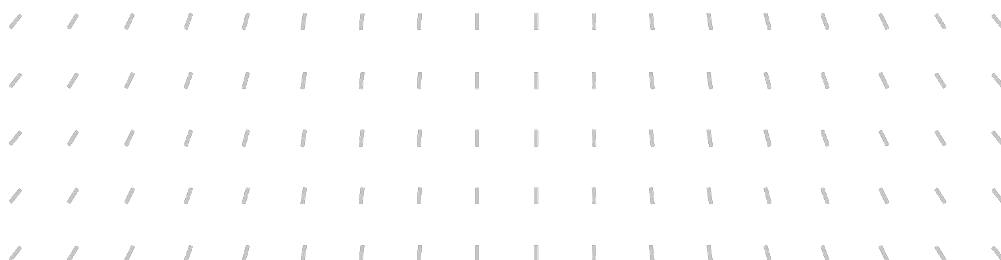

Project-Team

COMPO

COMPUtational pharmacology and clinical Oncology



In collaboration with Centre de Recherche en Cancérologie de Marseille



Project-Team COMPO

Creation of the Project-Team: 2021 May 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

- A3.1.1. – Modeling, representation
- A3.1.10. – Heterogeneous data
- A3.1.11. – Structured data
- A3.2.3. – Inference
- A3.3.2. – Data mining
- A3.3.3. – Big data analysis
- A3.4. – Machine learning and statistics
- A6.1.1. – Continuous Modeling (PDE, ODE)

Other research topics and application domains

- B1.1.2. – Molecular and cellular biology
- B1.1.7. – Bioinformatics
- B1.1.8. – Mathematical biology
- B1.1.10. – Systems and synthetic biology
- B2.2.3. – Cancer
- B2.2.7. – Virtual human twin
- B2.4.1. – Pharmacokinetics and dynamics
- B2.4.2. – Drug resistance

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1 Team members, visitors, external collaborators

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- Thibaut Reichert [AMU]
- Geoffroy Venton [APHM]
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2 Overall objectives

The Inria-Inserm COMPO joint project-team develops novel mathematical, statistical, and computational tools to model data in oncology, with a focus on clinical data from clinical studies and routine care. The team's objectives are: 1) to improve the quantitative understanding of cancer diseases, 2) to assist drug development through biomarker identification, dosing regimen optimization, and clinical trials decision support, and 3) to develop personalized medicine by providing clinicians with digital decision tools.

To achieve these goals, the team uniquely brings together mathematicians, computer scientists, pharmacologists, and medical oncologists. It is integrated into the Center of Cancer Research of Marseille (Inserm U1068, CNRS UMR7258, Aix-Marseille Université UM105, Institut Paoli-Calmettes) and located on the La Timone Health Science campus of the University Hospitals of Marseille (AP-HM), close to the INCa-labeled center for early phase clinical trials (CLIP2).

Built on strong expertise in mathematical modeling, pharmacometrics, and experimental and clinical oncology, the project-team is committed to developing novel methodologies combining mechanistic and statistical learning ("mechanistic learning", see Figure 1) to be ultimately applied at bedside.

Of note, in the Research Priorities document released by the American Society of Clinical Oncology in February 2021, "Developing and Integrating Artificial Intelligence in Cancer Research", "Identifying Strategies That Predict Response and Resistance to Immunotherapies" and "Optimizing Multimodality Treatment for Solid Tumors" are listed as top-priorities, which fit quite well with our research program.

3 Research program

We address problems that (1) are clinically or biologically relevant, (2) come with accessible clinical and / or biological data, and (3) where the mechanistic learning methodology is necessary or clearly beneficial.

The planned methodological advances span mechanistic learning for clinical data (axis 1), modeling multi-omics data (axis 2) and pharmacometrics (axis 3).

The main challenges are linked to data heterogeneity, high dimensionality, and the difficulty of validating complex models in clinical settings.

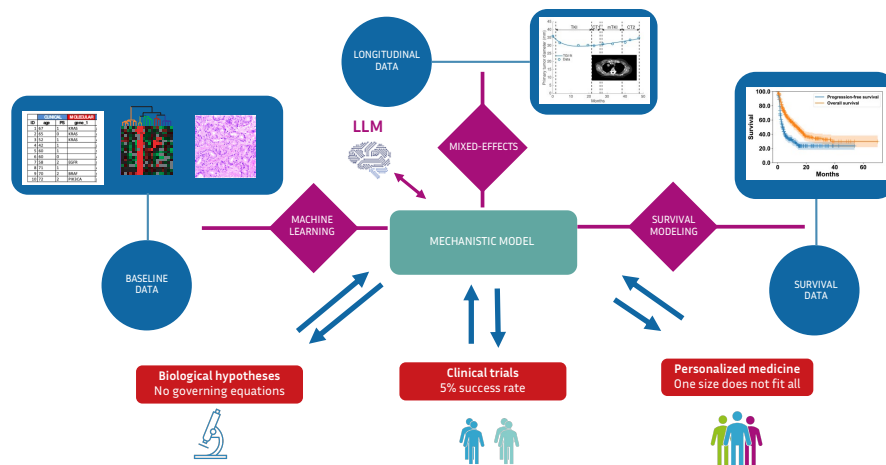


Figure 1: Mechanistic modeling and statistical learning for pharmacological and clinical oncology.

3.1 Axis 1: Mechanistic learning for clinical data (SB, QM)

3.1.1 (Automated) mechanistic modeling for longitudinal data

A major current open question in quantitative modeling in oncology is the establishment of governing equations providing foundations for the derivation of more advanced models or even, so-called "digital twins". We will continue our efforts in the discovery of such fundamental laws, written as ordinary or partial differential equations. A specific domain of interest will be immuno-oncology. Two approaches will be undertaken in parallel. The first is knowledge-driven and will benefit not only from the medical and pharmacological knowledge in the team but also, crucially, from the triple expertise of Quentin Marcou (QM) in computational modeling, immunology, and medicine. The second is data-driven and will explore recent advances in the field of scientific machine learning [56, 60, 59]. In particular, we will further pursue ongoing efforts – based on initial work by van der Schaar [58] – that use agentic large language models to discover not only structural forms of mechanistic models but also the statistical model. Example of an open problem in this area is to integrate such algorithms within the context of nonlinear mixed-effects modeling.

3.1.2 Causal inference and mechanistic modeling for time-to-event data

Traditional data-centric machine learning approaches, despite their ability to integrate complex data have at identifying high-order correlations, including with confounding factors, they fall short in generalizing findings beyond specific cohorts, impeding their use in a clinical setting. Causal inference offers promising solutions to these challenges, potentially addressing issues related to explainability, robustness and generalizability. While causal discovery (or causal graph inference) methods from observational data have been developed and used by systems biology researchers to infer large gene networks from observational data, they have been seldom applied to clinical and longitudinal data. Their development in clinical oncology is an open avenue and has emerged as a primary objective for COMPO.

In particular, time-to-event (survival) data in the presence of censoring or competing risks, constitutes a special type of compound data that could trigger artifactual causal structures or loss of statistical power upon using off-the-shelf causal discovery algorithms. Leveraging QM's knowledge in statistical causal inference, we aim to investigate how causal discovery methods can be adapted to more effectively handle such data. A further objective is to combine these with the novel methods developed by Sébastien Benzekry (SB) that proposed a mechanistic modeling approach to such data [12, 77] [NPP+20]. More broadly, clarifying the relationships between causal inference and mechanistic modeling – two fields that have so far remained isolated – is an avenue we want to research.

3.2 Axis 2: Multi-omics modeling (EV, QM)

3.2.1 Dynamic single-cell modeling and causal inference

A crucial challenge in systems oncology is to unravel how individual cells respond dynamically to therapeutic perturbations. Time series of single-cell data provide a unique window to capture cellular trajectories under treatment and to infer the regulatory mechanisms driving phenotypic adaptation. In previous work, Elias Ventre (EV) has developed methodologies to reconstruct signaling networks by calibrating mechanistic dynamic models at the single-cell level from longitudinal transcriptomics datasets. By joining COMPO, EV aims to extend these methods to learn from more complex datasets, containing multi-omics and/or spatial information, by combining optimal transport with statistical inference and machine learning to design causal discovery algorithms consistent with mechanistic models. These novel methods will be applied on tumoroids and clinical data to address two central open questions in the single-cell community:

- how to robustly link molecular alterations to phenotypic changes,
- how to account for inter-patient variability and integrate clinical covariates to derive predictive signatures.

These applications will be carried in collaboration with the CRCM (E. Pasquier) and the CRCL in Lyon (L. Broutier, M. Castets) on pediatric cancer tumoroids, and A.-S. Chrétien (CRCM) to identify causal drivers of immune response heterogeneity.

3.2.2 Analysis of the immune repertoire response to cancer

Cancer neoantigens, generated by non-synonymous somatic mutations in tumor cells, must be presented on major histocompatibility complexes (MHC) and specifically recognized by T cell receptors (TCRs) to trigger cytotoxic immune responses. Thus, identifying which neoantigens drive such recognition is essential to understand tumor immuno-editing, predict immune responses, and guide targeted therapies such as cancer vaccines or adoptive T cell therapies. Yet, despite the advances in protein structure and function prediction, Protein Language Models have shown limited predictive power for T cell recognition beyond a few viral antigens and well-characterized MHC haplotypes. Drawing from his expertise in building mechanistic statistical models capturing TCRs random generation process, QM aims to develop mechanistic and unsupervised machine learning approaches to decode the adaptive immune response to cancer from patients cohorts and longitudinal sequencing of the adaptive immune repertoire and cancer genome (tumor biopsy or tumor circulating nucleic acids). The developed approaches aim to address key questions in cancer immuno-oncology:

- Can we associate frequent neoantigens with their corresponding responsive T-cells?
- Using these neoantigen-T cell pairings, can we explain part of the heterogeneity in response to Immune Checkpoint Inhibitor therapies? Can these associations be leveraged to develop large coverage vaccines and Adoptive T Cell Therapies based on public neoantigens?
- Can we develop pan-cancer immune repertoire sequencing signatures for cancer screening and diagnostic?
- Can we quantify immune-selection pressure (immuno-editing) in early and late-stage tumors?

This line of research will be pursued in synergy with ongoing COMPO projects on the LUCA-pi and PIONeeR RHUs, in close collaboration with the CRCM bioinformatics community and Marseille's immunoinformatics researchers at CIML (P. Milpied and T. Dupic).

3.3 Axis 3: Pharmacometrics and individualized dosing (JC, FG, AR, RF, SB)

3.3.1 Pharmacokinetic (PK) / Pharmacodynamic (PD) modeling (AR, SB)

PK/PD modeling will remain as a central research axis of our team, with a strong emphasis on its application to innovative therapeutic entities such as liposomes, ADCs (antibody drug conjugates), antibody fragments,

or nanoparticles, using real-world data from the APHM and the Paoli Calmettes Institute. In such complex formulations, modeling efforts must often be structurally adapted to account for multiple kinetic entities, requiring linked or semi-mechanistic models with multiple compartments and inter-component transformations (e.g., cleavage, activation).

3.3.2 Physiologically-based Pharmacokinetic (PBPK) modeling (FG)

COMPO is involved in projects aiming to provide relevant PBPK models guiding drug development. First, the international consortium built to develop the TORNADO project will continue to collaborate and apply to European grants, and systemic and tumoral *in vivo* PK data will continue to be collected as a basis to further develop the PBPK model for nanotherapeutics, with a focus on the tumor compartment. Second, the PBPK model for mAbs will be extended by adding a more predictive sub-cutaneous absorption module in PK-Sim platform. Another project aims to contribute to the challenge of predicting drugs' renal elimination, currently in its infancy. We will combine evaluation of renal elimination of small drugs and nanotherapeutics on an innovative kidney-on-a-chip (KoC) system with its modeling to provide a translational PBPK model bridging the KoC data with *in vivo* PK.

3.3.3 Individualized dosing for clinical Oncology (JC, RF, AR)

Understanding the sources of pharmacokinetic variability and tailoring dosages, particularly in oncology, is a significant challenge. Based upon the gained expertise over the past 5 years, we propose to further apply this strategy to the aforementioned newest entities in clinical oncology. The latter also have complex inter-relationships with the immune system that impact pharmacokinetics and, ultimately, treatment response. Understanding their pharmacokinetics and identifying exposure covariates will enable us to develop state-of-the-art PK/PD/PGx models to personalize dosing, thus optimizing the toxicity/efficacy ratio in patients. Such models will require extra-skills due to the very nature of those entities, such as the joint-PK of both intact ADCs and released payload for instance, plus the intrinsic characteristics of new entities such as bispecific monoclonal antibodies, plus the rise of novel scaffolds such as peptide-drug conjugates, trispecific antibodies, BITEs, DuoBodies, bispecific ADCs – each coming with new challenges to model their PK and to decipher their PK/PD relationships, both as single agents or as part of combinatorial strategies, such as the ADC/immunotherapy combinations emerging in breast or in urothelial cancers. This will be achieved through both real-world studies and dedicated clinical trials, using customized compartmental analysis to ensure a good identifiability of the parameters and an efficacious transposition to bedside application.

4 Application domains

The COMPO research team's projects all focus on a serial of complementary and inter-related domains described in an itemized fashion below:

- **Health:** all the models to be developed within the framework of the COMPO team are related to improving healthcare;
- **Cancer:** in particular, the models will be developed to address specific issues related to cancerous diseases;
- **Precision Medicine:** in particular, in cancer the developed models will be part of the implementation of precision medicine in oncology focusing on the following items;
- **Combinatorial regimen:** developing model-informed strategies to determine the optimal modalities when combining several treatments altogether. With the increasingly diversified arsenal of therapeutic approaches to treat cancers (surgery, radiotherapy, chemotherapy, targeted and anti-angiogenic therapy and immunotherapy), defining optimal combination protocols is highly challenging [57]. This spans the issues of sequencing, scheduling and dosing of those therapies, which are to date largely addressed using a trial-and-error approaches. Consequently, too many combinatorial trials fail, and attrition rate with combinatorial immunotherapy is now a rising issue in clinical oncology and we hypothesize that extensive modeling and pharmacometrics could help refining the way anticancer drugs are combined;

- **Tools for decision-making:** developing model-informed strategies to forecast clinical outcome, i.e., during clinical trials. Assessing the predictive power of markers not only at baseline but also in their change over time is a current challenge. The information available, on the basis of which decision is made, includes clinico-demographic variables, classical biomarkers (e.g., blood counts, thyroglobulin, lactate dehydrogenase levels, etc...) but also an increasing amount of data from other sources (e.g., immuno-monitoring, anatomical functional imaging or genomics) that require state-of-the-art modeling to analyze extremely dense and longitudinal data;
- **Adaptive dosing strategies:** developing model-informed strategies to customize dosing so as to ensure an optimal toxicity-efficacy ratio. All anticancer agents are approved upon registration trials performed in highly selected patients (i.e., with controlled lifestyle, little comorbidities, controlled poly medication and restricted range of age), thus smoothing the interindividual variability. In real-world practice however, patients are all heavily co-treated with a wide variety of other drugs plus herbal medications, likely to interact with drug metabolism and transport, and are frequently older than in clinical trials. In addition, genetic polymorphisms affecting genes coding for drug transport proteins or drug-metabolizing enzymes in the liver, or transcriptional factors can impact as well on dose-exposure relationships. Consequently, standard dosing may not be suitable in non-standard patients to reach the adequate drug exposure levels associated with optimal toxicity/efficacy balance;
- **Nanomedicines:** developing model-informed strategies to conceptualize drug-loaded nanoparticles likely to improve the toxicity-efficacy ratio over conventional treatments. As of today, the biodistribution phase of anticancer agents is totally aspecific, making "on-target off-site" actions an issue because it is associated with drug-related side effects affecting healthy tissues. Nanoparticles present unique features likely to deliver specifically a high amount of payload directly on a tumor site, thus improving the antiproliferative action while sparing healthy tissues. In addition, nanoparticles are expected to reshape the tumor micro-environment, making them good candidates to be further associated with immunotherapy (see **Combinatorial Regimen** above).

5 Social and environmental responsibility

5.1 Impact of research results

Due to its unique composition including medical oncologists, clinical pharmacologists and mathematical modelers, COMPO is at stake with important social challenges: oncology healthcare and innovation in drug development. The software and results developed by COMPO are devoted to these challenges and aim to be directly used by medical and pharmaceutical oncologists or by the biotech and pharmaceutical industry to help drug development and biomarker discovery.

To give a few examples:

- the *KineticsPro* software historically developed by Pr Iliadis is used daily by pharmacists to individually adapt the dose of anti-cancer drugs (e.g., for methotrexate, cisplatin or busulfan);
- the *compo.EDA* package is used by physicians and biologists to produce automated statistical reports, helping to analyze the data collected for specific medical questions;
- COMPO is in charge of the biostatistical, machine learning and mechanistic modeling analysis of the large-scale **PIONeeR RHU** project to identify biomarker signatures predictive of the resistance to immunotherapy in lung cancer;
- the LUCA-pi RHU, led by COMPO member Pr Boulate, will conduct research to implement lung cancer screening in France (currently not performed).

6 Highlights of the year

- The results of the RHU **PIONeeR** (Precision Immuno-Oncology for advanced Non-Small Cell Lung Cancer Patients with PD1(L1) ICI Resistance) biomarker study have been published as a preprint [38].

This is the achievement of a **5-years** long effort with many COMPO members involved. The dataset is one of the world's largest multi-modal dataset on this topic. The main result is an **18-biomarkers** signature that **outperforms both standard-of-care** clinical markers (e.g., PDL1 expression) and **state-of-the-art** results of multi-modal machine learning models for prediction of primary resistance to immunotherapy in lung cancer. The paper is published together with a **companion website**, which contains an **interactive dashboard**. Additionally, PIONeeR helped to identify a threshold in Pembrolizumab plasma exposure which proved to be a strong, independant predictor of clinical efficacy, paving the way for implementation of PK-guided dosing at bedside.

- The results of the VENETACIBLE Project which is a collaboration between COMPO, the APHM and the University Hospital of Nice, has demonstrated that Venetoclax administred as a 14-days regime, outperforms the 28 days regimen in patients with accute myeloid leukemia in terms of efficacy and toxicity. Additionally, a threshold associated with efficacy has been identified (trough levels 2500 ng/mL), and allowed to perform PK-guided individualized dosing in real-world patients ([23]).
- The CETUXiMAX project is now completed. This multicentric PK study, led by Sebastien Salas with several COMPO students and senior members, established a relationship between cetuximab exposure and disease control rate in head and neck cancer patients, and allowed to build an original pop-PK model describing the pharmacometrics of this drug that could be used next to customize dosing or scheduling.
- The TORNADO project has made an important step forward, with the publication of a PBPK model for intact lipid nanocapsules labeled with a specific signal ([16]), in partnership with the MINT group in the university of Angers. The COMPO PhD student Jessica OU, who defended her PhD thesis in 2024 was co-first author of the work, which also involved a previous COMPO M2 intern and F. Gattacceca who supervised the development of the PBPK model.

6.1 Awards

- Linh Nguyen-Phuong received the Lewis Sheiner award at the 33th PAGE (Population Approach Group in Europe) conference

7 Latest software developments, platforms, open data

7.1 Latest software developments

7.1.1 ROOFS

Name: RObust biOmarker Feature Selection

Keyword: Feature selection

Functional Description: ROOFS is a Python package for benchmarking feature selection (FS) methods, designed to help researchers choose the most suitable FS method for their predictive task. ROOFS executes bootstrap-based machine learning pipelines that include the FS step and generates comprehensive reports summarizing key evaluation metrics: downstream predictive performance estimated with optimism correction, stability, reliability of individual features, and true positive and false positive rates assessed on semi-synthetic data with simulated outcomes. ROOFS includes 30+ FS methods from different algorithmic families.

News of the Year: Initial development of the package.

URL: <https://gitlab.inria.fr/compo/roofs>

Publication: [hal-05241230](https://hal.archives-ouvertes.fr/hal-05241230)

Contact: Sebastien Benzekry

Participants: Sebastien Benzekry, Anastasiia Bakhmach, Mohamed Boussena

7.1.2 compo.EDA

Name: Exploratory Data Analysis and Biostatistics for Clinical Oncology Data

Keywords: Data Exploration, Biostatistics

Scientific Description: This library implements as an R package:

- Exploratory analysis:
 - Clinical characteristics table
 - Kaplan-Meier estimation of the progression-free and overall survival
 - Clinical and biological features distribution
- Classification analysis:
 - Univariate and multivariate logistic regression
 - Odds ratio
 - Area under ROC curve
 - t test / chi2 test
- Survival analysis:
 - Univariate and multivariate Cox regression
 - Hazard ratio
 - Area under ROC curve
 - log-rank test
- Data visualization:
 - Correlation plots (Pearson correlation)
 - Volcano plots (p-value and adjusted p-value)
 - Boxplots (quantitative features) and barplots (qualitative feaures)
 - Kaplan-Meier curves
 - Automatic comprehensive and customizable statistical reports

Functional Description: The package compoEDA aims to provide a comprehensive exploratory analysis of data from clinical studies in oncology. These studies commonly investigate biological markers able to reveal and distinguish different tumor profiles, in order to early adapt the therapeutic strategy for patients.

The objective of this software is to provide a simplified tool for both computational scientists and clinical researchers to easily generate a graphical results and automatic reports containing the following analyses:

- overview and visualization of clinical data and biological markers
- univariate and multivariate classification analysis (logistic regression)
- univariate and multivariate survival analysis (Cox regression, Kaplan-Meier analysis)
- correlation analysis
- statistical tests
- visualization of markers (boxplots, barplots, volcano plots, forest plots ...).

Release Contributions: Version 1.1 Summary - compo.EDA

Major updates:

- interactive tables
- new dataset
- improved book generation.

Code quality improvements

- parameter normalization,
- extensive documentation
- CI/CD
- Docker support

Bug fixes: Windows compatibility, dumification, p-value calculations, and plot display issues.

News of the Year: Key accomplishments:

- Large repository cleanup with notation harmonization and deprecated function removal
- Unified logistic and Cox regression outputs into single `results_table()` function
- Integrated new toy dataset from Zenodo
- Established comprehensive GitLab CI/CD with Docker containers and ARM64 support
- Improved code quality, reduced warnings, enhanced documentation and README
- Contributors (340 commits): Benzekry (architecture/documentation), Vaglio (refactoring/CI/CD), Nguyen (regression/visualization)

URL: <https://gitlab.inria.fr/compo/compo.eda>

Contact: Sebastien Benzekry

Participants: Sebastien Benzekry, Linh Nguyen Phuong, Celestin Bigarre, Paul Dufosse, Melanie Karlsen, Andrea Vaglio

7.1.3 `compo.tidyML`

Name: Machine learning with tidymodels

Keywords: Survival analysis, Machine learning, Data analysis, Oncology

Scientific Description: This software maximizes the use of the R package tidymodels.

Functional Description: This package provides multiple functions to perform machine learning analysis using the ‘tidymodels’ framework. Tasks include: feature selection, plot feature importances, train, cross-validate, apply supervised machine learning algorithms (classification or survival analyses) and unsupervised machine learning, evaluate metrics of predictive performances, compute learning curves.

Initial development was part of the ‘stats_pioneer’ package (also called ‘pioneerPackage’) and ‘ml.tidy’ evolved as a standalone package only in February 2023.

Release Contributions: MAJOR ADDITIONS:

- Complete ML pipeline with automated report generation (`create_ml_report`, `render_ml_report`)
- New models: XGBoost (classification & survival), GBM, Logistic LASSO
- Feature selection: BoBoLASSO, BOLASSO, improved stepwise methods, LOO-CV
- SHAP analysis integration for XGBoost models with patient profiling

VISUALIZATION ENHANCEMENTS:

- Stratified Kaplan-Meier plots with optimal cutpoint methods
- Single marker predictive metrics plotting with class proportions
- Custom color palettes, enhanced heatmaps, interactive tables (`reactable`)

INFRASTRUCTURE:

- CI/CD pipeline (GitLab), Docker support (multi-architecture)
- Removed Pioneer dependencies, comprehensive documentation overhaul - R 4.2.2+ compatibility, improved package structure

TOTAL: 516 commits over 3 years | Contributors: Andrea Vaglio, Sebastien Benzekry

News of the Year: - Complete ML pipeline with automated reporting

- XGBoost/GBM models with SHAP analysis
- Single marker predictive metrics plotting
- CI/CD pipeline
- Docker and dev container
- Dependency cleanup and R 4.2.2+ compatibility

Total: 123 commits. Contributors: Andrea Vaglio, Sebastien Benzekry

URL: <https://gitlab.inria.fr/compo/compo.tidyml>

Publications: [hal-03478003](#), [hal-03926538](#), [hal-03928784](#)

Contact: Sebastien Benzekry

Participants: Andrea Vaglio, Sebastien Benzekry

7.1.4 compo.NLME

Name: R package for fitting and analyzing Non-Linear Mixed Effects (NLME) models using Monolix.

Keywords: Monolix, Nonlinear mixed effects models, Lixoft, Population approach

Scientific Description: Available features:

- Structural models
 - constant
 - linear
 - double exponential
 - double exponential with dropout
 - hyperbolic
- preprocess blood marker datasets
- preprocess tumor kinetics datasets
- fit NLME models using monolix API
- post-process of results

Available data:

- **Tumor Kinetics with dropout data.** A simulated dataset of tumor kinetics following the double-exponential model, with parameters obtained from (Benzekry et al., PAGE 20, 2022), which deals with the RECIST-based sum of largest diameters (SLD, in mm) of lung cancer treated with immune-checkpoint blockade (anti-PDL1 drug atezolizumab). Dropout was also simulated using a Weibull survival model.
- **Tumor and Blood marker Kinetics with dropout data.** A simulated dataset of joint tumor and blood markers (albumin C-reactive protein, lactate dehydrogenase, neutrophils) kinetics following the models and parameters established in (Benzekry et al., PAGE 20, 2022). These are monitoring data during immune-checkpoint blockade (anti-PDL1 drug atezolizumab) in lung cancer. Dropout was also simulated using a Weibull survival model.

Functional Description: This R package implements a framework to work with Non-linear Mixed effects models in the context of clinical oncology to predict relapse and survival using longitudinal data.

News of the Year: Total commits: 42

Contributors: 2 (BENZEKRY Sebastien, Linh Nguyen)

- Multivariate and joint modeling: adapted BICC table for MV modeling, time-to-event files, and observation type selection
- Enhanced run_monolix: new parameters for correlations, covariates, and random effects removal
- Improved postprocessing: standard errors table with condition numbers, plotting functions with customizable aesthetics
- Documentation and licensing: improved vignette, updated LICENSE with IDDN, added Pandoc dependency
- Bug fixes: double exponential for concave curves, aesthetics issues, lixoftConnectors >=2023 requirement

URL: <https://gitlab.inria.fr/compo/compo.nlme>

Publications: [hal-04375606](#), [hal-03921394](#)

Contact: Sebastien Benzekry

Participants: Sebastien Benzekry, Celestin Bigarre, Linh Nguyen Phuong, Ruben Taieb

7.1.5 SChISMModeling

Name: SChISM modeling

Keywords: SChISM, Statistical analysis, Biostatistics, Mechanistic modeling, Cancer

Scientific Description: • Preprocess

- Exploratory data analysis
- Classification analysis (logistic regression)
- Survival analysis (Cox regression)
- Mixed-effects modeling analysis
- Simulation for ODE models for mechanistic modeling

Functional Description: SChISMModeling aims to analyze SChISM data (Size CfDNA Immunotherapies Signature Monitoring). SChISM is a clinical study that introduces an innovative approach to quantify circulating free DNA in cancer patients treated with immunotherapy. The study's objective is to early predict response to immunotherapy in patients at an advanced/metastatic stage according to these quantitative cfDNA data.

This software corresponds to the very first step of the data analysis, which is the statistical analysis. Some of its functions aim at:

- preprocessing the data (creation of clinical variables, dictionary, outcome variables, clinical biomarkers, treatment of the variables types)
- computing statistical tests, logistic or Cox regression, performing a correlation analysis
- visualizing the data (boxplots, barplots, survival curves, ROC curves, volcano plots)
- providing detailed and interactive statistical reports on the data
- simulation for ODE models for mechanistic modeling

News of the Year: • Creation of data loading function and update of data preprocessing functions

- Unsupervised analysis of baseline cfDNA data (e.g., heatmaps)
- Longitudinal visualization tools (spaghetti plots, etc.)
- Visualization of mechanistic model outputs (individual fits, goodness-of-fit diagnostics, etc.)

- Functions for generating figures and tables for two research articles and the thesis manuscript

URL: <https://gitlab-int.inria.fr/schism/schism>

Contact: Sebastien Benzekry

Participants: Sebastien Benzekry, Linh Nguyen Phuong, Romain Zakrajsek, Lucie Della-Negra

7.1.6 metamats

Keyword: Mechanistic modeling

Functional Description: This R package is the implementation of a general framework to build and use models of the metastatic process based on the initial model of Iwata et al. (2000). The family of model that can be built describe the metastatic disease with a partial differential equation (pde) on the size structured distribution of the tumors. These models have three components, a function that characterize the growth of the primary tumor, a function that characterize the growth of the metastases, and a dissemination function that describes how new metastases are produced.

Release Contributions: Features:

- Model structure
- Direct computation of $N(t)$ (C++)
- Individual fit of cumulative size distribution (direct only)
- Many diagnostic plots

News of the Year: 1. Release v1.0.0 (Dec 14): Major milestone with significant improvements across the package.

2. Package Merge: Consolidated metamatsModels into metamats, including all growth and dissemination models (Gompertz, Exponential, Logistic, Power-law variants).

3. Documentation Suite: Added comprehensive vignettes covering Getting Started, predefined models, parameter fitting, visualization, and custom model building.

4. Testing Framework: Implemented testthat test suite with comprehensive coverage of core functionality across all major components.

5. Error Handling: Established error class hierarchy with 25+ dedicated stop_* functions organized by domain (param, model, data, api, fit, domain errors).

6. New Features: Added simulate() method for generating patient data, as_tibble() for DataIndiv conversion, cpp_compute_N wrapper, and parameter ownership model.

7. Code Quality: Migrated from deprecated tidyverse functions, replaced variadic args with explicit parameters, and added comprehensive input validation.

8. Data Assets: Included three simulated breast cancer datasets (breast_simple, breast_followup, breast_fitting) for educational examples.

9. Architecture: Documented comprehensive system architecture in ARCHITECTURE.md explaining design patterns and class hierarchies.

10. Bug Fixes: Resolved ggplot2 import issues, parameter handling edge cases, and CSD plotting for various data configurations.

URL: <https://gitlab.inria.fr/compo/metamats/metamats>

Contact: Celestin Bigarre

Participants: Sebastien Benzekry, Celestin Bigarre

8 New results

8.1 Axis 1: Mechanistic learning for clinical data

8.1.1 An integrative multimodal machine learning signature of primary resistance to immunotherapy in advanced non-small cell lung cancer: biomarker analysis from the PIONeeR study

Participants: Laurent Greillier, Joseph Ciccolini, Anastasiia Bakhmach, Paul Dufossé, Andrea Vaglio, Mélanie Karlsen, Mohamed Boussena, Celestin Bigarre, Mourad Hamimed, Sébastien Benzekry.

Funding and data: RHU PIONeeR

Preprint: [38]

Background: Immune checkpoint inhibitors (ICIs) have transformed the treatment landscape for advanced non-small cell lung cancer (NSCLC), yet primary resistance remains common, with only 50% of patients responding to first-line chemo-immunotherapy and 20–30% to monotherapy. Existing biomarkers such as PD-L1 expression and tumor mutational burden (TMB) demonstrate limited predictive accuracy, underscoring the need for more comprehensive, integrative approaches.

Methods: We conducted a prospective, multicenter study involving 439 patients with advanced NSCLC treated with anti-PD-(L)1 ICI across first- and later-line settings. A total of 443 pre-treatment tumor and blood-derived biomarkers—including genomic alterations, immune cell phenotypes, proteomic markers, and routine laboratory tests—were profiled. Both traditional biostatistics and a rigorously benchmarked machine learning (ML) pipeline were applied to identify predictors of primary resistance (PrR).

Results: Single biomarkers showed limited predictive utility, with PD-L1 (AUC 0.62), TMB (AUC 0.55), and key gene mutations (e.g., STK11, KEAP1) failing to achieve significance after multiple testing correction. A gradient boosting ML model integrating 18 features yielded a corrected AUC of 0.73 and a positive predictive value (PPV) of 60% for PrR, outperforming standard biomarkers. In first-line patients, the model achieved a PPV of 51% and negative predictive value (NPV) of 79% (baseline PrR rate: 29.9%); in subsequent-line patients, PPV reached 64% (PrR rate: 55.1%). Importantly, the signature also stratified progression-free survival (PFS): high-risk patients had a median PFS of 3.9 vs. 14.6 months in low-risk patients (HR 0.307, $p < 0.0001$). Features from routine blood tests—such as serum chloride, albumin, C-reactive protein, and monocyte-to-lymphocyte ratio (MLR)—accounted for half of the final model and demonstrated independent associations with both PrR and PFS (e.g., chloride: OR 0.616, AUC 0.626; HR 0.685, C-index 0.61). SHAP-based individual-level model explainability revealed heterogeneous and nonlinear biomarker contributions, including cases where high CRP, low albumin, or elevated MLR overrode favorable PD-L1 or Treg profiles.

Conclusions: Multimodal machine learning integration of clinical, genomic, immune, and laboratory data enables improved prediction of ICI resistance in NSCLC beyond current biomarkers. This approach not only captures the multifaceted nature of tumor–host interactions but also highlights the underrecognized predictive value of accessible blood-based markers, offering a path toward individualized immunotherapy decision-making.

8.1.2 The SChISM study: Circulating cell-free DNA size profiles as predictors of progression in advanced carcinoma treated with immune-checkpoint inhibitors

Participants: Linh Nguyen Phuong, Laurent Greillier, Romain Zakrasjek, Lucie Della-Negra, Sébastien Benzekry, Sébastien Salas.

Funding and data: SChISM study. Trial registration NCT05083494.

Preprint: [44]

Background: Circulating cell-free DNA (cfDNA) offers a promising noninvasive way to predict resistance to immune-checkpoint inhibitors (ICI), for which robust biomarkers are still lacking.

Methods: The SChISM (Size CfDNA Immunotherapy Signature Monitoring) proof-of-concept study (NCT05083494) collected baseline plasmatic cfDNA size profiles from 126 ICI-treated advanced carcinomas,

quantified using the innovative, patented and standardized BIABooster device (Adelis). Fragmentome-derived variables and standard clinical variables (including neutrophils-to-lymphocyte ratio, NLR) were analyzed for univariable associations with early progression (EP, progression at first imaging) and progression-free survival (PFS). Multivariable analysis was carried through both unsupervised and supervised learning. Twenty-six variable selection methods combined with 11 models were benchmarked to derive a multivariable predictive model relying on a minimal subset of variables.

Results: Higher cfDNA concentration and high quantities of short fragments (111–240 base pairs (bp)) were associated with poor response and reduced PFS, unlike long fragments (> 300 bp). The proportion of fragments longer than 1650 bp exhibited the strongest association, with non-EP odds ratio = 0.39 [95% CI: 0.25–0.62] and PFS hazard ratio = 0.54 [95% CI: 0.42–0.68]. Unsupervised learning identified four patient clusters significantly associated with EP ($p = 0.004$, Pearson's Chi-squared test) and PFS ($p = 0.001$, log-rank test). The multivariable machine learning analysis identified a subset of nine variables that shown greater performances in a logistic regression model ($AUC_{\text{signature}} = 88.5 \pm 3.3\%$, EP positive predictive value $PPV_{\text{signature}} = 69.4 \pm 7.49\%$) compared to single marker ($AUC_{R>1650} = 73.6 \pm 3.70\%$, $PPV_{R>1650} = 55.8 \pm 7.46\%$, $AUC_{\text{NLR}} = 68.9 \pm 5.02\%$, $PPV_{\text{NLR}} = 52.6 \pm 8.75\%$).

Conclusion: The cfDNA size profiles were significantly associated with progression and PFS during ICI, and outperformed routinely used markers.

8.1.3 Mechanistic Modeling of cfDNA Fragmentome Dynamics Predicts Progression to Immunotherapy

Participants: Linh Nguyen Phuong, Frédéric Fina, Laurent Greillier, Pascale Tomasini, Jean-Laurent Deville, Audrey Boutonnet, Frédéric Ginot, Jean-Charles Garcia, Sebastien Salas, Sébastien Benzekry.

Funding and data: SChISM study. Trial registration NCT05083494.

Preprint: [45]

Background: Plasma cell-free DNA (cfDNA) shows promise as predictive cancer biomarker, but mechanisms governing cfDNA production/fragmentation/elimination dynamics, and their relationships with tumor burden and disease progression, remain poorly understood.

Methods: We developed a mechanistic model jointly describing short (75-<580 bp) and long (≥ 580 -1650 bp) cfDNA dynamics alongside tumor kinetics in 112 advanced cancer patients receiving immune checkpoint inhibition, using a population approach.

Results: The model successfully described complex cfDNA patterns, including treatment-initiation spikes. It revealed large inter-patient variability in kinetic cfDNA parameters, and a 7.4-fold higher shedding rate for short versus long fragments. A model-derived parameter from 6-weeks data — reflecting enhanced release or reduced elimination of short fragments — was significantly associated with progression-free survival (PFS) (HR=1.6 [95% confidence interval (CI): 1.2-2.2], $p=0.001$). Notably, adding this parameter to baseline clinical prognostic variables improved PFS prediction (C-index 0.78 [95% CI: 0.73-0.89] vs 0.80 [95% CI: 0.74-0.90], $p<0.0001$).

Conclusion: Our model provides quantitative insights into cfDNA biology and offers a non-invasive way to monitor and predict resistance before imaging.

8.1.4 Metamats: A mechanistic software for the simulation, inference and prediction of clinical metastasis

Participants: Célestin Bigarré, Alice Daumas, Laurent Greillier, Xavier Muracciole, Laeticia Padovani, Sébastien Benzekry.

Funding and data: Inria-Inserm, AP-HM

Publication: [40]

The development of metastases is a complex process that can be better understood and predicted using mathematical mechanistic models. We propose "METAMATS", a ready-to-use modeling framework

implementing a semi-mechanistic model for simulating the time dynamics of metastatic development, including a primary tumor and a population of metastatic tumors. It relies on a reduced set of mathematical parameters: α (tumor proliferation rate), μ (dissemination rate), and γ (fractal scale parameter). "METAMATS" supports both individual and population-level analyses.

At the individual level, it can simulate metastatic dynamics, infer parameters from longitudinal metastasis size data, and predict the natural history of cancer both retrospectively and prospectively. At the population level, leveraging nonlinear mixed effects modeling, "METAMATS" performs inference of parameter distributions and assessment of biologically interpretable covariate effects on proliferation and/or dissemination, from distant metastasis-free survival data. "METAMATS" also serves as a generative model for simulating virtual patients or populations.

We demonstrate its applicability for modeling, inference, prediction, and simulation in a clinical setting: the dynamics of brain metastases (BM) in small-cell lung cancer patients and the impact of prophylactic cranial irradiation (PCI). Data included two cohorts: 103 patients from Assistance publique-Hôpitaux de Marseille with longitudinal individual measurements of BM sizes, and 100 patients from the CONVERT study (NCT00433563). PCI was found to have an impact on BM by significantly reducing metastatic appearance (parameter μ), rather than metastatic growth (parameter α), a biological finding impossible to obtain by means of classical survival analysis only.

8.1.5 ROOFS: RObust biOmarker Feature Selection

Participants: Anastasiia Bakhmach, Paul Dufossé, Andrea Vaglio, Laurent Greillier, Sébastien Benzekry.

Funding and data: RHU PIONeeR

Preprint: [37]

Feature selection (FS) is essential for biomarker discovery and in the analysis of biomedical datasets. However, challenges such as high-dimensional feature space, low sample size, multicollinearity, and missing values make FS non-trivial. Moreover, FS performances vary across datasets and predictive tasks. We propose ROOFS, a Python package available at [webpage](#), designed to help researchers in the choice of FS method adapted to their problem. ROOFS benchmarks multiple FS methods on the user's data and generates reports that summarize a comprehensive set of evaluation metrics, including downstream predictive performance estimated using optimism correction, stability, reliability of individual features, and true positive and false positive rates assessed on semi-synthetic data with a simulated outcome. We demonstrate the utility of ROOFS on data from the PIONeeR clinical trial, aimed at identifying predictors of resistance to anti-PD-(L)1 immunotherapy in lung cancer. The PIONeeR dataset contained 374 multi-source blood and tumor biomarkers from 435 patients. A reduced subset of 214 features was obtained through iterative variance inflation factor pre-filtering. Of the 34 FS methods gathered in ROOFS, we evaluated 23 in combination with 11 classifiers (253 models in total) and identified a filter based on the union of Benjamini-Hochberg false discovery rate-adjusted p-values from t-test and logistic regression as the optimal approach, outperforming other methods including the widely used LASSO. We conclude that comprehensive benchmarking with ROOFS has the potential to improve the robustness and reproducibility of FS discoveries and increase the translational value of clinical models.

8.2 Axis 2: Multi-omics modeling

8.2.1 Cell Trajectory Inference based on Schrödinger Problem and a Mechanistic Model of Stochastic Gene Expression

Participants: Elias Ventre, Olivier Gandrillon (*ENS Lyon*), Fabien Crauste (*MAP5*), Clémence Fournié (*MAP5*), Aymeric Baradat (*UCBL1*), Ulysse Herbach (*Inria Nancy*).

Publication: Submitted in *Systems Biology and Applications* [43]

Cellular differentiation is the biological process that leads a cell to opt for a particular cellular identity. Recently, single-cell RNA-sequencing has enabled the simultaneous measurement of gene expression levels at specific times for a large number of individual cells and a large number of genes. Repeating such measurements at different time points gives then access to the temporal variation, or transport, of a distribution on a gene expression space. The whole temporal trajectory of distributions thus characterizes the differentiation process at population level, but trajectories of individual cells are still out of reach since most measurement techniques are destructive.

The optimal transport theory that has been used so far to infer cellular differentiation trajectories from time-stamped single-cell RNA-seq data involves solving the so-called Schrödinger problem in its most common version. This implies assuming that cells move, in the gene expression space, by diffusion. Yet, real gene dynamics are much more complex.

In the present work, we assume that mRNA dynamics are characterized by brief and important production of RNA, with long periods of inactivity in between, and consider the so-called Bursty model of gene dynamics. We use this model to define a reference process for the Schrödinger problem. By comparing the solutions of the Schrödinger problems with a Diffusive and a Bursty reference process, under different conditions, we show that the Bursty model provides a better approximation of the underlying gene dynamics than the standard Diffusive process when inferring cell trajectories.

8.2.2 Global StationaryOT: Trajectory inference for aging time courses of single-cell snapshots

Participants: Elias Ventre, Geoffrey Schiebinger (*UBC*), Cole Boyle (*UBC*).

Publication: Submitted in *Bioinformatics* [41]

Trajectory inference (TI) methods for single-cell snapshots of developmental systems have yielded numerous insights into the gene regulatory networks (GRNs) that control cell differentiation. Many TI algorithms have been proposed for recovering cell trajectories from single samples containing cells spanning a spectrum of differentiation states; however, these methods cannot leverage temporal information when a time course of such diverse samples is available. As interest grows in understanding how GRNs change as an organism ages, current TI theory and methods must be adapted to take advantage of all information in aging time courses of single-cell data. In this paper, we present our novel age-conscious method, Global StationaryOT, which exploits the temporal information in aging time courses to simultaneously reconstruct debiased cell trajectories at all ages. We demonstrate that this first-of-its-kind method achieves more accurate, biologically consistent trajectories in synthetic and real biological contexts where data sparsity produces significant noise in the outputs of current TI methods when they are applied to time course samples independently.

8.3 Axis 3: Pharmacokinetic Modeling for drug delivery

8.3.1 THERMONANO

Participants: Anne Rodallec, Sophie Marolleau, Sébastien Benzekry.

Publication: communicated at PAGE [55] and CRS Benelux & France LC [36]

Data: PK and PD data on breast cancer bearing mice, Paris-Sud.

Background Commercial Paclitaxel (PTX) formulations such as Taxol are associated with adverse drug toxicities related to the added emulsifier. Therefore, PTX formulations have been explored as they could increase efficacy and have improved pharmacokinetic (PK) properties. Recently our partners have developed a new polymer prodrug of PTX for which we proposed that metronomic dosing could result in an effective and tolerable anticancer treatment that is simultaneously convenient for patients as it allows for subcutaneous (SC) administration.

Objective The objective of this study was to develop a PK/PD model of a novel polymer prodrug subcutaneously injectable to predict the best administration scheme.

Methods Pharmacokinetics and pharmacodynamics (PD) studies were done on MCF-7 bearing mice using Monolix software. The PK model was developed on both intravenous (IV) Ptx and SC Ptx-PAAm (7mg/kg) data. The PD model was developed on three PD data sets (control, IV Ptx, SC Ptx-PAAm 15mg/kg), and validated on an independent group (SC Ptx-PAAm 60mg/kg). Simulations explored multiple treatment schedules, and the most effective ones were tested in vivo.

Results The optimal model included a two-compartment PK structure and drug resistance in the PD component. The in vivo results demonstrated excellent agreement with the model predictions. A loading dose followed by daily administration achieved 60% complete response, outperforming previous internal results (tumor volume reduced to 60 versus 1350 mm³), without additional toxicity.

Conclusion : Our PK/PD model showed SC Ptx-PAAm with optimized regimens significantly increased efficacy over standard schedules.

8.3.2 Injectable Gel-Based Subcutaneous Delivery of Antibody-Drug Conjugates

Participants: Anne Rodallec, Yacine Gomari, Joseph Ciccolini.

Publication: communicated at Canceropole [51]

Data: PK and PD data on breast cancer bearing mice, Strasbourg.

Background : Antibody Drug Conjugates (ADCs) are increasingly used in oncology but are currently limited to intravenous (IV) delivery. Subcutaneous (SC) administration could improve patient quality of life and was previously developed for large molecules. However, hyaluronidase, the only SC option for monoclonal antibodies (mAbs), has limitations for ADCs SC delivery (local inflammation, toxicity, cold storage) which were addressed in this project by developing a novel polymeric formulation.

Objective : The objective of this study was to develop a PK/PD model of a innovative subcutaneously injectable to predict the best administration scheme.

Methods : To evaluate its potential and guide further development, a population pharmacokinetic (popPK) model of trastuzumab emtansine (T-DM1) polymeric formulation was developed using experimental pharmacokinetic data from 60 BALB/c mice (4 T-DM1 groups: IV, SC, SC-polymer at two doses). Total trastuzumab was quantified by HTRF (Homogeneous Time-Resolved Fluorescence) on plasma samples. Data were analyzed using MonolixSuite™ through non-compartmental (NCA) and stepwise compartmental analyses (CA).

Results NCA showed IV parameters were consistent with literature and SC-polymer absorption was saturated (bioavailability: 66% at 17.5 mg/kg; 55% at 30 mg/kg). A one-compartment model with linear elimination, absorption lag time and a dose-dependent bioavailability term for SC-polymer was developed. This term accounted for saturation by reducing bioavailability as dose increased. Goodness of fit was assessed through graphical diagnostics, numerical observations and model robustness.

Conclusion : This validated model will support future PK/PD modeling integrating tumor growth data to optimize T-DM1 SC-polymer administration scheduling.

8.3.3 Preclinical Pharmacokinetic-Pharmacodynamic Modeling of Antibody Nanoconjugates for Breast Cancer Treatment

Participants: Anne Rodallec, Sebastien Benzekry, Joseph Ciccolini, Raphaelle Fanciullino.

Publication: Preprint available [47]

Data: Biodistribution and PD data on breast cancer bearing mice.

Background : Over the past five years, the number of antibody–drug conjugates (ADCs) entering the oncology market has surged. By contrast, the clinical use of immunoliposomes—nanoparticles that also employ antibodies as targeting agents (i.e., antibody–nanoconjugates, ANCs)—has yet to receive approval. One possible reason is the limited understanding of the relationship between ANC exposure and efficacy.

Objective : The objective of this study was to develop a PK/PD model of an immunoliposome to predict the best administration scheme.

Methods : To address this gap, we developed a pharmacokinetic/pharmacodynamic (PK/PD) model for a docetaxel–trastuzumab ANC. PK and PD studies were conducted in MDA-MB-231 tumor–bearing mice, divided into three treatment groups: (i) control, (ii) free docetaxel + free trastuzumab, and (iii) docetaxel–trastuzumab ANCs. PK data were obtained by fluorescence imaging and captured systemic and tumor distribution of ANCs, while PD data were based on tumor growth measurements. The PK model was built using data from the ANC group, and the PD model was developed across all three treatment groups, with a leave-one-out cross validation strategy for predictive evaluation. Treatment schedule simulations were then performed.

Results : Using a population nonlinear mixed-effects (NLME) approach, the final PK model included a central and a tumor compartment, each with independent elimination rates. Tumor growth dynamics were best described by a reduced Gompertz model coupled with a Simeoni resistance model. This model demonstrated strong predictive performance. Using only data from the first two treatment cycles (4 time points) and Bayesian estimation in the test set, it accurately predicted systemic and tumor ANC concentrations across the subsequent four treatment cycles, with a relative error (RE) below 15%. Prediction precision was further improved (RE <5%) when data from one additional treatment cycle were incorporated. Similar performance was achieved for PD data, with tumor volume predictions exhibiting RE < 15% and RE <7.5% when implementing data from two and three treatment cycles, respectively. The model was then applied to simulate alternative treatment schedules. Interestingly, while systemic exposure remained comparable across regimens, weekly administration yielded the greatest tumor exposure compared to daily, every-5-day, and every-35-day dosing (mean \pm SD tumor AUC: 55.4 \pm 10.9 mg/kg-day vs. 47.6 \pm 9.38 mg/kg-day, 51.4 \pm 11.5 mg/kg-day, and 44.6 \pm 10.028 mg/kg-day, respectively, one-way ANOVA, $p < 0.001$), highlighting the importance of dosing frequency.

Conclusion : Overall, these results illustrate how PK/PD modeling can refine intra-tumor PK understanding and support preclinical development of innovative formulations such as ANCs.

8.3.4 Adaptive dosing of high-dose busulfan in real-world adult patients undergoing haematopoietic cell transplant conditioning

Participants: Dorian Protzenko, Joseph Ciccolini.

Background To evaluate the effectiveness of a Bayesian adaptive dosing strategy in achieving target busulfan exposure in adult patients undergoing haematopoietic cell transplantation (HCT).

Patients and Methods This study included 71 adult patients scheduled to receive high-dose busulfan. Busulfan was administered to achieve a cumulative area under the curve (AUC) of 66.0 mg/L/h (16 000 μ M/min), 82.60 mg/L/h (20 000 μ M/min) or 87.6 mg/L/h (21 200 μ M/min) depending on the regimen. Individual pharmacokinetic (PK) parameters of busulfan were estimated from three blood samples using a one-compartment model and Bayesian estimation after the first standard dose. Individual PK parameters were used to adjust subsequent doses to achieve the target exposure.

Results All patients had their dose adjusted after the first dose administration. The final deviation from the target AUC was significantly improved compared to the initial deviation after standard mg/kg dosing (mean absolute deviation 19.5% vs 11.7%, $P < .01$). In addition, the proportion of patients with marked deviation from target exposure (ie, $> 25\%$) decreased significantly from 31% after standard dosing to 10% after PK-guided dosing ($P < .01$). Canonical busulfan-related toxicity, specifically veno-occlusive disease, was observed in 5% of patients who achieved successful PK-guided dosing. In contrast, one-third of patients with off-target exposure with poor dosing experienced toxicity.

Conclusion The Bayesian adaptive dosing strategy significantly improves the accuracy of achieving the target busulfan AUC in patients undergoing HCT. This approach not only reduces marked deviations from target exposure, but also reduces the incidence of busulfan-related toxicity, thereby maintaining a favorable toxicity/efficacy ratio.

8.3.5 Overcoming immuno-resistance by rescheduling anti-VEGF/cytotoxics/anti-PD-1 combination in lung cancer model

Participants: Guillaume Sicard, Dorian Protzenko, Sarah Giacometti, Joseph Ciccolini, Raphaëlle Fanciullino.

Background Many tumors are refractory to immune checkpoint inhibitors, but their combination with cytotoxics is expected to improve sensitivity. Understanding how and when cytotoxics best re-stimulate tumor immunity could help overcome resistance to immune checkpoint inhibitors.

Methods In vivo studies were performed in C57BL/6 mice grafted with immune-refractory LL/2 lung cancer model. A longitudinal immunomonitoring study on tumor, spleen, and blood after multiple treatments including Cisplatin, Pemetrexed, and anti-VEGF (either alone or in combination) was performed, spanning a period of up to 21 days, to determine the optimal time window during which immune checkpoint inhibitors should be added. Finally, an efficacy study was conducted comparing the antiproliferative performance of various schedules of anti-VEGF, Pemetrexed-Cisplatin doublet, plus anti-PD-1 (i.e., immunomonitoring-guided scheduling, concurrent dosing or a random sequence), as well as single agent anti-PD1.

Results Immunomonitoring showed marked differences between treatments, organs, and time points. However, harnessing tumor immunity (i.e., promoting CD8 T cells or increasing the T CD8/Treg ratio) started on day 7 and peaked on day 14 with the anti-VEGF followed by cytotoxics combination. Therefore, a 14-day delay between anti-VEGF/cytotoxic and anti-PD1 administration was considered the best sequence to test. Efficacy studies then confirmed that this sequence achieved higher antiproliferative efficacy compared to other treatment modalities (i.e., -71% in tumor volume compared to control).

Conclusions Anti-VEGF and cytotoxic agents show time-dependent immunomodulatory effects, suggesting that sequencing is a critical feature when combining these agents with immune checkpoint inhibitors. An efficacy study confirmed that sequencing treatments further enhance antiproliferative effects in lung cancer models compared to concurrent dosing and partly reverse the resistance to cytotoxics and anti-PD1.

8.3.6 Pegylated liposome encapsulating docetaxel using microfluidic mixing technique: Process optimization and results in breast cancer models

Participants: Mathilde Dacos, Anne Rodallec, Benoit Immordino, Sarah Giacometti, Guillaume Sicard, Joseph Ciccolini, Raphaëlle Fanciullino.

Background The development of nanoparticles could help to improve the efficacy/toxicity balance of drugs. This project aimed to develop liposomes and immunoliposomes using microfluidic mixing technology.

Patients and Methods Various formulation tests were carried out to obtain liposomes that met the established specifications. The liposomes were then characterized in terms of size, polydispersity index (PDI), docetaxel encapsulation rate and lamellarity. Antiproliferative activity was tested in human breast cancer models ranging from near-negative (MDA-MB-231), positive (MDA-MB-453) to HER2 positive. Pharmacokinetic studies were performed in C57BL/6 mice. Numerous batches of liposomes were synthesized using identical molar ratios and by varying the microfluidic parameters total flow rate (TFR), flow rate ratio (FRR) and buffer.

Results All synthesized liposomes have a size < 200 nm, but only Lipo-1, Lipo-6, Lipo-7, Lipo-8 have a PDI < 0.2, which meets our initial requirements. The size of the liposomes was correlated with the total FRR, for a 1:1 FRR the size is 122.2 ± 12.3 nm, whereas for a 1:3 FRR the size obtained is 163.4 ± 34.0 nm ($p = 0.019$). Three batches of liposomes were obtained with high docetaxel encapsulation rates > 80 %. Furthermore, in vitro studies on breast cancer cell lines demonstrated the efficacy of liposomes obtained by microfluidic mixing technique. These liposomes also showed improved pharmacokinetics compared to free docetaxel, with a longer half-life and higher AUC (3-fold and 3.5-fold increase for the immunoliposome, respectively).

Conclusions This suggests that switching to the microfluidic process will produce batches of liposomes with the same characteristics in terms of in vitro properties and efficacy, as well as the ability to release the encapsulated drug over time in vivo. This time-efficiency of the microfluidic technique is critical, especially in the early stages of development.

8.3.7 Body mass index affects imatinib exposure: Real-world evidence from TDM with adaptive dosing

Participants: Paul Maroselli, Joseph Ciccolini, Raphaëlle Fanciullino.

Background Imatinib is the treatment of elderly or frail patients with chronic myeloid leukemia (CML). Trough levels of around 1000 ng/ml are considered as the target exposure.

Methods We searched for baseline parameters associated with imatinib pharmacokinetics, and studied the clinical impact of subsequent adaptive dosing. We present data from 60 adult CML patients upon imatinib with therapeutic drug monitoring (TDM) and adaptive dosing.

Results Mean trough levels after treatment initiation were 994.2 ± 560.6 ng/ml (with 56% inter-patient variability). Only 29% of patients were in the therapeutic range. Body weight, height, body surface area, body mass index (BMI), and age were associated with imatinib plasma levels on univariate analysis. Age and BMI remained the only parameters associated with imatinib trough levels on multivariate analysis. As severe toxicities have been previously reported in patients with low BMI treated with standard imatinib, we evaluated the extent to which low BMI may lead to plasma overexposure. We found a statistically significant difference in trough imatinib levels in patients with BMI < 18.5 kg/m², with exposure +61.5% higher than

in patients with $18.5 < \text{BMI} \leq 24.9$ and +76.3% higher than in patients with $\text{BMI} \geq 25$. After TDM with adaptive dosing, a statistically significant difference in dosing between patients was observed, with doses ranging from 200 to 700 mg. No difference in toxicity or efficacy was observed regardless of BMI after adaptive dosing.

Conclusion Our data suggest that low BMI has a significant impact on imatinib exposure but that pharmacokinetically-guided dosing limits its clinical impact in patients.

8.3.8 Life-threatening toxicities upon Pembrolizumab intake: could pharmacokinetics be the bad guy?

Participants: Mourad Hamimed, Sophie Marolleau, Joseph Ciccolini.

Background We report the case of an adult patient diagnosed with Hodgkin's lymphoma who was scheduled for Pembrolizumab after failure of standard therapy. After three well-tolerated courses of Pembrolizumab, a PET scan showed a favorable outcome and a fourth course of Pembrolizumab was started. Unexpectedly, extremely severe toxicities (i.e., autoimmune peripheral hypothyroidism, rhabdomyolysis and severe acute renal failure) occurred after this last course, requiring transfer to the intensive care unit.

Methods Therapeutic drug monitoring was performed to measure residual Pembrolizumab levels at intervals from the last dose (i.e., 120 and then 170 days), as well as pharmacogenetics investigations on the FC γ R gene.

Results Pembrolizumab plasma concentrations that were still pharmacologically active months after the last administration, suggesting impaired elimination of Pembrolizumab in this patient. Further pharmacokinetic modeling based on the population approach showed that both half-life (47.8 days) and clearance (0.12 L/day) values were significantly different from the standard values usually reported in patients. Further in silico simulations showed that pharmacologically active concentrations of Pembrolizumab were maintained for up to 136 days after the last dose. The search for possible polymorphisms affecting the genes coding for FC γ R (i.e., rs1801274 on FCGR2A and rs396991 on FCGR3A gene) was negative. Further TDM showed that Pembrolizumab could be detected up to 263 days after the last administration.

Conclusion This case report suggests that persistent overexposure in plasma could lead to life-threatening toxicities with Pembrolizumab.

8.3.9 Poor prognosis of SRSF2 gene mutations in patients treated with VEN-AZA for newly diagnosed acute myeloid leukemia

Participants: Raphaelle Fanciullino.

Background Mutations in spliceosome genes (SRSF2, SF3B1, U2AF1, ZRSR2) correlate with inferior outcomes in patients treated with intensive chemotherapy for Acute Myeloid Leukemia. However, their prognostic impact in patients treated with less intensive protocols is not well known.

Methods This study aimed to evaluate the impact of Spliceosome mutations in patients treated with Venetoclax and Azacitidine for newly diagnosed acute myeloid leukemia (AML). 117 patients treated in 3 different hospitals were included in the analysis.

Results Thirty-four harbored a mutation in at least one of the spliceosome genes (splice-mut cohort). K/NRAS mutations were more frequent in the splice-mut cohort (47% vs 19%, $p=0.0022$). Response rates did not differ between splice-mut and splice-wt cohorts. With a median follow-up of 15 months, splice mutations were associated with a lower 18-month LFS ($p=0.0045$). When analyzing splice mutations separately, we found SRSF2 mutations to be associated with poorer outcomes ($p=0.034$ and $p=0.037$ for OS and LFS respectively). This negative prognostic impact remained true in our multivariate analysis.

Conclusion We believe this finding should warrant further studies aimed at overcoming this negative impact.

9 Bilateral contracts and grants with industry

9.1 Research contracts

CIFRE PhD of S. Benamara

Title: Predicting monoclonal antibody pharmacokinetics using PBPK modeling: towards an integrated strategy to support first-in-human (FIH) clinical trials

Partner Institutions: • D. Teutonico (Sanofi, Paris)

Date/Duration: 2023 - 2026

Funding: 120k€, CIFRE

Principal investigator: D. Teutonico (Sanofi, Paris)

COMPO members involved: F. Gattacceca (co-supervisor).

NANOSTAP

Title: Development of dual nanoparticles in PDAC models

Partner Institution: • Pancreas Team CRCM

• EsqLabs

Date/Duration: 2025-2028

Funding: 30 K€ Canceropole + CIFRE Grant

Principal investigator: J.Ciccolini

COMPO members involved: J. Ciccolini, A. Rodallec, R. Fanciullino, E. Diroff (Ph.D. student)

9.2 Clinical trials

Participants: Joseph Ciccolini, Raphaëlle Fanciullino, Laurent Greillier, Sébastien Salas.

CetuxiMAX

- Registration: NCT4218136
- Partner: Merck Serono
- Title: Maximizing Cetuximab efficacy in head and neck cancer patients through PK/PD modeling
- Funding: 40 k€
- Duration: 2020 - 2025
- Principal investigator: Sébastien Salas

ALTER

- Registration: in progress
- Partner: IPC
- Title: A multicenter, randomized, open-label phase II trial evaluating alternating sacituzumab govitecan and trastuzumab deruxtecan in patients with metastatic or locally advanced HER2-low triple-negative breast cancer.
- Funding: PHRC-K (INCa)
- Duration: 2025-2028
- COMPO Investigator: Joseph Ciccolini

PEMBOV

- Registration: NCT03596281
- Partner: INCa
- Title: Pembrolizumab in Combination With Bevacizumab and Pegylated Liposomal Doxorubicin in Patients With Ovarian Cancer (PEMBOV)
- Funding: 700 k€
- Duration: 2020-2025
- Principal investigator: Judith Mitchels (IGR)
- COMPO investigator: Joseph Ciccolini

REZOLVE

- Registration: ANZGOG-1101
- Partner: Sydney Medical Center Australia
- Title: Pembrolizumab in Combination With Bevacizumab and Pegylated Liposomal Doxorubicin in Patients With Ovarian Cancer (PEMBOV)
- Funding: Aus\$ 800k
- Duration: 2018-2026
- Principal investigator: Sonia Yip (Sydney University)
- COMPO investigator: Joseph Ciccolini

ZEN-CLL

- Registration: ongoing
- Partner: IUCT Toulouse, University Hospital of Lyon, University Hospital of Clermont Ferrand
- Title: Search for Predictive Marker of Zanibrutinib in CLL patients.
- Funding: 300 K€ (BeiGene)
- Duration: 2025-2028
- Principal investigator: Eloise Perrot (Lysarc Lyon)
- COMPO investigator: Joseph Ciccolini

PERSEE

- Registration: EudraCT 2020-002626-86
- Partner: CHRU de Brest
- Title: A trial comparing the pembrolizumab platinum based chemotherapy combination with pembrolizumab monotherapy in first line treatment of non small-cell lung cancer (NSCLC) patients
- Starting year: 2020
- Principal investigator: Renaud Descourt, Chantal Decroisette, Christos Chouaid
- COMPO investigator: Laurent Greillier

ELEVATE HNSCC

- Registration: NCT04854499
- Partner: Gilead Sciences
- Title: Study of Magrolimab Combination Therapy in Patients With Head and Neck Squamous Cell Carcinoma
- Duration: 2021-2025
- COMPO investigator: Sébastien Salas

Iintune-1

- Registration: NCT04420884
- Partner: Takeda
- Title: A Study of Dazostinag as Single Agent and Dazostinag in Combination With Pembrolizumab in Adults With Advanced or Metastatic Solid Tumors
- Duration: 2020-2026
- COMPO investigator: Sébastien Salas

ADAPTABLE

- Registration: NCT05781308
- Partner: Intergroupe Francophone de Cancerologie Thoracique
- Title: Combination of Paclitaxel-bevacizumab \pm Atezolizumab in Patients With Advanced NSCLC Progressing After Immunotherapy & Chemotherapy
- Duration: 2023-2026
- COMPO investigator: Laurent Greillier

10 Partnerships and cooperations**10.1 International research visitors****10.1.1 Visits of international scientists**

Nov-Dec 2025: COMPO hosts Shav Chakraborty from Perth University Medical School (Australia)

10.1.2 Visits to international teams

Nov. 2025: Joseph Ciccolini was an invited-speaker at Hanoi Oncology Hospital, VietNam, as part of the initiation of a collaborative project on clinical pharmacokinetics and clinical pharmacology of anticancer agents.

Nov. 2025: Joseph ciccolini was an invited speaker at Leiden Medical Center, Netherlands (Dirk Jan Moes Lab) as part of the initiation of collaborative projects on the clinical pharmacokinetics of antibody drug conjugates.

10.2 National initiatives

Note: COMPO seniors (respectively, juniors) are permanent (respectively, non-permanent) researchers.

10.2.1 Axis 1: Mechanistic learning for clinical data

Participants: Sebastien Benzekry, David Boulate, Xavier Muracciole.

LUCA-pi RHU

Title: Lung cancer prevention and interception

Partner Institutions:

- Gustave Roussy Institute (G. Kroemer, L. Zitvogel)
- Therapanacea (N. Paragios)
- CIML (P. Milpied)

Date/Duration: 2023 - 2028

Funding: \approx 10 M€, ANR

Principal investigator: D. Boulate (COMPO)

COMPO seniors: D. Barbolosi, S. Benzekry

COMPO juniors: L. Nguyen-Phuong, A. Vaglio, R. Zakrasjek

DIGPHAT PEPR Digital Health

Title: Digital pharmacological twin

Partner Institutions:

- JB Woillard (CHU Limoges)
- C. Battail (CEA Grenoble)
- M. Ursino + S. Zohar (HEKA, Inria, Paris)
- J. Josse (PREMEDICAL, Inria, Montpellier)
- E. Chatelut + M. White-Koning (IUCT, Toulouse)

Date/Duration: 2023 - 2028

Funding: Total 1.8 M€, COMPO 251k€

Principal investigator: JB Woillard (CHU Limoges)

COMPO senior: S. Benzekry.

COMPO juniors: A. Bakhmach, S. Charpigny

LABreX COALA

Title: Cure Oncogene-Addicted Lung Adenocarcinoma

Partner Institutions: 15 constitutive national teams + 9 associated

Date/Duration: 2024 - 2029

Funding: Total 3M€, COMPO 130k€

Principal investigator: J. Mazières (CRCT, Toulouse)

COMPO senior: S. Benzekry.

COMPO junior: A. Pottier

SChISM

Title: Size CfDNA Immunotherapies Signature Monitoring

Partner Institutions:

- APHM
- M. Lavielle (XPOP – Inria)
- Adelis
- F. Fina (ID-Solutions Oncology)

Date/Duration: 2022 - 2025

Funding: ≈ 120k€, APHM + PhD grant ICI - Laennec

Principal investigator: S. Benzekry, S. Salas

COMPO junior: L. Nguyen Phuong

METAMATS**Title:** Mechanistic modeling for the prediction of metastatic relapse in breast cancer**Partner Institutions:**

- F. Bertucci (IPC, Marseille)
- G. MacGrogan (Institut Bergonié , Bordeaux)

Date/Duration: 2020 - 2025**Funding:** \approx 100k€, Inria-Inserm PhD grant**Principal investigator:** S. Benzekry, X. Muracciole**COMPO members involved:** C. Bigarre**AML****Title:** Prédiction de la Toxicité du Venetoclax dans la Population de Patients Agés traités pour une LAM**Partner Institutions:**

- AP-HM, Marseille

Date/Duration: 2023 - 2026**Funding:** \approx 30k€, GIRCI**Principal investigator:** Sylvain Garciaz (IPC, Marseille)**COMPO members involved:** S. Benzekry, R. Fanciullino, A. Bakhmach**Prevalung****Title:** Epidemiological Study to Assess the Prevalence of Lung Cancer in patients with smoking-associated atherosclerotic cardiovascular diseases**Partner Institution:**

- APHM, Gustave Roussy Institute

Date/Duration: 2019-2025**Funding:** \approx 7M€ Horizon Europe**Principal investigator:** D. Boulate**COMPO members involved:** D. Boulate, D. Barbolosi, C. Buton**10.2.2 Axis 2: Multi-omics modeling****Participants:** Sebastien Benzekry, Elias Ventre.**South-ROCK****Title:** South-research on cancer for kids**Partner Institutions:** 28 constitutive teams

- P. Mehlen (Centre Léon Bérard + Hospices Civils de Lyon)
- E. Pasquier (CRCM, Marseille)
- M. Castets (CRCL, Lyon)

Date/Duration: 2023 - 2028

Funding: Total 2 M€

Principal investigators: P. Mehlen (CLB + HCL, Lyon), E. Pasquier (CRCM, Marseille), M. Castets (CRCL, Lyon)

COMPO seniors: S. Benzekry, F. Gattacceca, J.Ciccolini

COPYCAT

Title: Combining Organoid technology with Mathematics to develop innovative models mimicking tumor cellular heterogeneity and plasticity for pediatric oncology

Partner Institutions: • L. Broutier (CRCL, Inserm, CNRS, UCBL, Lyon)

• E. Pasquier (CRCM)

• R. Mounier (INMG, Inserm, CNRS, UCBL, Lyon)

Date/Duration: 2023 - 2027

Funding: Total 922k€, COMPO 115k€ (INCa)

Principal investigator: L. Broutier (CRCL, Inserm, CNRS, UCBL, Lyon)

COMPO seniors: S. Benzekry, E. Ventre, G. Fiandaca

COMPO junior: G. Fiandaca

PhD H. Hamdache

Title: Improving therapeutic efficacy and managing side effects and sequelae in pediatric cancer through improved and personalized nutritional programs using computer simulations

Partner Institutions: • V. Pancaldi (IUCT, Inserm, Toulouse)

Date/Duration: 2023 - 2026

Funding: 120k€, Inria-Inserm PhD grant

Principal investigator: V. Pancaldi (IUCT, Inserm, Toulouse)

COMPO members involved: S. Benzekry (co-supervisor).

10.2.3 Axis 3: Pharmacometrics and individualized dosing

Participants: Sebastien Benzekry, Joseph Ciccolini, Raphaelle Fanciullino, Florence Gattacceca, Anne Rodallec.

THERMONANO

Title: Nanoassemblies for the subcutaneous self-administration of anticancer drugs

Partner Institution: • Institut Galien Paris-Saclay (UMR CNRS 8612)

Date/Duration: 2019 - 2024

Funding: 1.8 M€, ERC

Principal investigator: J. Nicolas (Institut Galien, Paris-Sud)

COMPO members involved: A. Rodallec, S. Benzekry, S. Marolleau.

ZEN-CLL

Title: Zanubrutinib in chronic Lymphoid Leukemia: search for predictive biomarkers.

Partner Institution: • CHU Toulouse, CHU Clermont-Ferrand, CHU Lyon

Date/Duration: 2025-2027

Funding: 300 K€, BeiGene

Principal investigator: E. Perrot (Lysarc, Lyon South Hospital)

COMPO members involved: J. Ciccolini

ALTER

Title: Testing Two Different Drugs (Sacituzumab-govitecan and Trastuzumab-deruxtecan) Combinations Prescribed in an Alternating Pattern to Patients With Metastatic or Locally Advanced Triple-negative Breast Cancer

Partner Institution: • Institut Paoli Calmettes

Date/Duration: 2025-2027

Funding: 700 K€, PHRC-K (INCa)

Principal investigator: A. de Nonneville (IPC)

COMPO members involved: J. Ciccolini

BAP1

Title: A phase II trial evaluating the efficacy of temozolomide in patients with advanced BAP1-mutant cutaneous melanoma.

Partner Institution: • APHM

Date/Duration: 2025-2027

Funding: 700 K€, PHRC-K (INCa)

Principal investigator: N. Mallissen

COMPO members involved: J. Ciccolini

PEMBOV

Title: Pembrolizumab in Combination With Bevacizumab and Pegylated Liposomal Doxorubicin in Patients With Ovarian Cancer

Partner Institution: • Institut Gustave Roussy (IGR)

Date/Duration: 2021-2024

Funding: 400 K€, PHRC-K (INCa)

Principal investigator: J. Michels (IGR)

COMPO members involved: J. Ciccolini, M. Hamimed

REZOLVE

Title: A phase 2 trial of intraperitoneal bevacizumab to treat symptomatic ascites in patients with chemotherapy-resistant, epithelial ovarian cancer

Date/Duration: 2020-2025

Funding: total funding undisclosed, COMPO funding 40 K€

Principal investigator: S. Yip (Sydney Medical Center Australia), J.Ciccolini

COMPO senior: J.Ciccolini

COMPO junior: C. Marin

COMPLICITY

Title: COMPutational tools for NanoBooster In Cancer ImmunoTherapY

Partner Institution: • Pharmaceutical Institute, Bonn University, GERMANY: A Lamprecht M Shetab Boushehri

Date/Duration: 2023-2026

Funding: 25k€ (Amidex Pepiniere), 30K€ (ARC), 2K€ (DAAD), 3K€ (Institut LAENNEC)

Principal investigator: A. Rodallec

COMPO senior: A. Rodallec, F. Gattacceca

COMPO junior: A. Aubert, Z. Benslimane

MIPP Project Paris Saclay Cancer Cluster

Title: Clinical Pharmacokinetics Platform MIPP

Partner Institution: • Paris Saclay - APHM

Date/Duration: 2025-2029

Funding: 3.2 M€ (PSCC)

Principal investigator: E. Vivier (PSCC)

COMPO members involved: J. Ciccolini

TheranoImmuno

Title: Injectable Hydrogel for Subcutaneous Delivery of ADCs to Improve the Treatment of Solid and Hematological Tumors

Partner Institution: • ICANS (Strasbourg), Gustave Roussy institute (Paris)

Date/Duration: 2023-2028

Funding: \approx 1.5M€ ERC

Principal investigator: A. Detappe (ICANS, Gustave Roussy Institute)

COMPO members involved: A. Rodallec, J. Ciccolini, Y. Gomari

METOXIM

Title: Early Prediction of impaired elimination of high dose Methotrexate in neuro-oncology

Partner Institution: • APHM - PetraNetwork

Date/Duration: 2025-2027

Funding: 80 K€ (GIRCI + AORC)

Principal investigator: E. Mamessier (APHM)

COMPO members involved: J. Ciccolini

NanImmuno

Title: Immunomodulating properties of anti-Her2 nanoparticles in breast cancer models

Partner Institution: • Institut Roche - Genentech

Date/Duration: 2022-2026

Funding: 80 K€ (Institut Roche)

Principal investigator: R. Fanciullino

COMPO members involved: J. Ciccolini, M. Dacos (Ph;D. student)

MOIO

Title: A non-inferiority randomized phase III trial of standard immunotherapy by checkpoint inhibitors vs. reduced dose intensity in responding patients with metastatic cancer: the MOIO protocol study.

Partner Institution: • Institut Paoli Calmettes + 10 recruiting centers

Date/Duration: 2023-2027

Funding: 800 K€, PHRC-K (INCa)

Principal investigator: G. Gravis (IPC)

COMPO members involved: J. Ciccolini

VENETACIBLE

Title: PK/PD relationships of Venetoclax in Leukemia patients

Partner Institution: • University Hospital of Nice, APHM

Date/Duration: 2023-2026

Funding: 80 K€ AORC (APHM)

Principal investigator: R. Fanciullino

COMPO members involved: J. Ciccolini, L. Osanno (Ph.D. student)

PROVIN

Title: Phase I study of a propranolol (hemangirol®) and oral metronomic vinorelbine (navelbine®) combination for children and teenagers with refractory, relapsing solid tumors

Partner Institution: • APHM + recruiting centers

Date/Duration: 2016-2026

Funding: 400 K€ PHRC-K (INCa)

Principal investigator: N. André

COMPO members involved: J. Ciccolini.

CEREAL

Title: Cladribine Dose Escalation in Conditioning Regimen Prior to Allo-HSCT for Refractory Acute Leukemia and Myelodysplastic Syndromes (CEREAL)

Partner Institution: • IPC

Date/Duration: 2018-2028

Funding: INCa

Principal investigator: S. Furts (IPC)

COMPO members involved: J. Ciccolini, D. Protzenko (Ph.D. student)

DPDMAX

Title: DPD-MAX study: an open-label prospective cohort study aiming to analyze the influence of the DPD phenotype on response to capecitabine treatment in patients with metastatic breast cancer.

Partner Institution: • Centre Antoine Lacassagne Nice

Date/Duration: 2020-2026

Funding: INCa

Principal investigator: A. Creisson (CAL)

COMPO members involved: J. Ciccolini, G. Kallee (Ph.D. student)

11 Dissemination

Participants: Sebastien Benzekry, Joseph Ciccolini, Raphaëlle Fanciullino, Florence Gattacceca, Quentin Marcou, Anne Rodallec, Elias Ventre.

11.1 Promoting scientific activities

11.1.1 Scientific events: organization

General chair, scientific chair

- F. Gattacceca: President of GEPK (French Group of Lecturers in PK), organized the 2025 annual meeting, Marseille, France, July 7-8, 2025
- J.Ciccolini:
 - President of the PAMM (Pharmacokinetics and Molecular Mechanism) at EORTC (European Organization of Research and Treatment for Cancer)
 - Board Member of the Cours St Paul in Digestive Oncology.
 - Board Member of the ADC & Bispecifics Task Force at EORTC (European Organization of Research and Treatment for Cancer)
 - Board Member of the Copil HN at Unicancer.
 - Board Member of TRANSFORM-O (Recherche Translationnelle et Formation Scientifique en Oncologie) at the SFC (Société Française du Cancer).
- R.Fanciullino: Head of the Clinical Pharmacy Workgroup at SFPO (Société Française des Pharmaciens Oncologues)

Member of the organizing committees

- F. Gattacceca:
 - GMP (Group of Metabolism and Pharmacokinetics) symposium (Paris, October 2025), Chair of sessions "Replacing and refining in vivo pharmacokinetic experiments" and "Artificial Intelligence and Machine Learning shaping the Future of Drug Development"
 - F. Gattacceca: OSP community conference (Paris, September 2025), Chair of session "Clinical applications/Development"
- J.Ciccolini:
 - Organizing Committee, XXth GPCO-Unicancer symposium, Paris November 27-28, 2025
 - Organizing Committee, PAMM EORTC 2025 annual meeting, La Laguna, Spain, April 4-5, 2025
 - Organizing Committee, 4th Cours St Paul, Nice, France, November 19-22, 2025
 - Organizing Committee, TRANSFORM-O 2025 Edition, Sete France, October 3-5 2025
- A. Rodallec: CRS, CRS Benelux & France LC
- E. Ventre: Mathematics of single-cell datasets, CIRM

11.1.2 Journal

Member of the editorial boards

- S. Benzekry: JCO: Clinical Cancer Informatics, Mathematical Biosciences
- J.Ciccolini: Cancer Chemotherapy and Pharmacology (Springer), Frontiers in Pharmacology (Frontiers).

Reviewer - reviewing activities

- S. Benzekry: Bioinformatics, Clinical Pharmacology and Therapeutics, JCO: Clinical Cancer Informatics, Journal of the Royal Society Interface
- J.Ciccolini: Cancer Chemotherapy and Pharmacology, Clinical Pharmacology and Therapeutics; Clinical Pharmacology and Therapeutics psp; Bone Marrow Transplant, British Journal of Cancer; Fundamental and clinical Pharmacology; Clinical Pharmacokinetics; Frontiers in Immunology; Bioanalysis; Expert Review of Anticancer Therapy; Scientific Reports; Expert Opinion On Drug Safety; Bulletin du Cancer; Frontiers in Pharmacology; BMJ Case Reports; Cancer Immunology, Immunotherapy; British Journal of Clinical Pharmacology; Clinical Chemistry and Laboratory Medicine; Cancer Drug Resistance; The Journal of Thoracic Disease; Frontiers in Toxicology; Journal for Immunotherapy of Cancer.
- F. Gattacceca: Advances in therapy
- Q. Marcou: Immunoinformatics
- E. Ventre: Bioinformatics, Communications Biology, Science Advances, Systems Biology and applications

11.1.3 Invited talks

- S. Benzekry:
 - November, 2025. **SophIA summit**. Côte d'Azur, France.
 - October, 2025. **CRCT workshop: Innovations in immuno-oncology: from data to therapeutic insights**. Toulouse, France.
 - July, 2025. **Cancéropôle PACA**. Machine learning for prediction of resistance to immunotherapy. Saint-Raphael, Marseille.
 - May, 2025. AI in healthcare. EPFL, Lausanne, Switzerland.
- J.Ciccolini:
 - January 2025: "ADCs et bispécifiques en oncologie digestive: mythe ou réalité?", Journées ABCD, UCGI-Unicancer, Paris France.
 - January 2025: "Impaired elimination of HD MTX: The METOXIM trial", PETRA Network Symposium, Marseille France.
 - March 2025: "Pharmacometrics as a decision-making tool with immune checkpoint inhibitors: finding the perfect blend?", PAMM-EORTC Winter Meeting La Laguna Spain.
 - March 2025: "Dosage pharmacologique avec les inhibiteurs des points de contrôle de l'immunité, quel intérêt ?", Symposium Scientifique Astra Zeneca, Nîmes France.
 - October 2025: "Clinical Pharmacology of Antibody Drug Conjugates", Annual conference on Hospital Pharmacy, Hanoi, Vietnam.
 - November 2025: "Update on TDM in oncology: a focus on innovative therapies in cancer", IATDMCT Local Chapter, Leiden Netherlands.
 - November 2025: "Innovations Pharmacologiques dans le Digestif", 4ème Cours St Paul en Oncologie Digestive, Nice France.
 - November 2025: "Precision Dosing in oncology: where do we stand?", Hanoi 50th Anniversary Oncology Hospital conference, Hanoi, Vietnam.
 - December 2025: "ADCs in Oncology: debunking the myth", Scientific Symposium Servier Paris Saclay, Paris France.
 - December 2025: "Innovative drugs in lung cancer: PK and PK/PD considerations", Atrium Thorax, Paris France.

- R. Fanciullino:
 - October 2025: "Clinical Pharmacy and Pharmaceutical Intervention", XVeme Journées Nationales Actualités en Oncologie - Société Française du Pharmacien Oncologue (SFPO), St Malo France.
- E. Ventre:
 - July 2025: "Dynamical Optimal transport for trajectory inference from single-cell data", CIRM, Marseille
 - October 2025: "Simulation and inference of gene regulatory networks", CompSysBio, Aussois
 - December 2025: "Characterizing cell state dynamics in rhabdomyosarcoma tumoroid models", SouthRock congress, Lyon

11.1.4 Leadership within the scientific community

- J. Ciccolini: "National Reference Laboratory For the Therapeutic Drug Monitoring of Monoclonal antibodies in Oncology" Label by the French Ministry of Health (JORF n°0167 du 21 juillet 2021).

11.1.5 Scientific expertise

- F. Gattacceca: Scientific expert at ANSM (Agence Nationale de Sécurité du Médicament, national drug agency), member of the permanent scientific committee "Quality and safety of drugs" and of the working group "IA and organs-on-chips"
- J. Ciccolini: Scientific Expert at ZonMw - Clinical Fellows Grant Application, the Netherlands.
- J. Ciccolini: Scientific Expert at John Hopkins Cancer Center - Professorship Application, Baltimore USA.
- J. Ciccolini: Scientific Expert at INCa (Institut National du Cancer) -ANSM - Agence Nationale de Sécurité du Médicament, national drug agency) "Déficit DPD et adaptation posologique des fluoropyrimidines" Working Group Boulogne Billancourt France.
- J. Ciccolini: Scientific Expert at Canceropole IDF - Emergence Grant Applications. Paris France.
- J. Ciccolini: Member of the DSMB (Data Safety and Monitoring Board) of the Revert Phase 2 clinical trial (SwissEthics) and the ONUVEN phase 2 clinical trial (Groupe Francophone des Myelodysplasies).
- J. Ciccolini: President of the HCERES (Evaluation recherche Enseignement supérieur) Evaluation committee, IntheRes unit application, Ecole Nationale Vétérinaire de Toulouse and Toulouse University.

11.1.6 Research administration

- F. Gattacceca: Member of the scientific committee of the school of pharmacy
- J. Ciccolini
 - Member of the Scientific Committee of the School of Pharmacy
 - Member of the Commission Paritaire d'Etablissement of the School of Pharmacy
 - co-Director of the TRANSLATE-IT Department at CRCM.
 - Director of the SMARTc platform at CRCM.
 - Co-Director of the MIPP joint-platform at APhM-Paris Saclay Cancer Cluster.

11.2 Teaching - Supervision - Juries - Educational and pedagogical outreach

11.2.1 Teaching

- S. Benzekry:
 - M2 Biologie Santé – Parcours IA biomarqueurs (6h). M2 "Pharmacokinetics" (6h).
 - M2 PK "Fundamentals for modeling and simulation in pharmacokinetics/pharmacodynamics" (6h).
- A. Rodallec
 - Lectures in MSc in Pharmacokinetics, MSc in Digipharm, MSc in Innovative Diagnostic and therapeutic Drug Products, DESU "Advances courses in pharmacometrics", DESU in animal experiments, Pharm.D. studies (2nd, 3rd, 4th and 6th year), odontology studies -> 200 h a year
 - Teaching outside of AMU: additional lectures at University of Paris Saclay and Wuhan University (China).
- J. Ciccolini
 - Lectures at Aix Marseille Univ in: MSc (2nd year) in Oncology, MSc (2nd year) in Oncogenetics, MSc (2nd year) in Pharmacokinetics, MSc (2nd year) in Digipharm, MSc (1st year) in Drugs & Health Products, D.U. in Animal Experiments, D.U. in Genetic Counseling, Master Class in Lung Cancer, Pharm.D. studies (2nd, 3rd, 4th and 6th year), CESU "Innovative immunotherapy" -> 230 h a year.
 - Teaching outside of AMU: additional lectures in pharmacokinetics at Université Catholique de Lyon, Leiden Medical Center (NL), and the International School of Metronomics. Lectures for Cours National Approfondissement DES Oncologie Médicale and Phase d'Approfondissement Docteur Junior, Paris Saclay University.
 - Founder and co-Chair of the "Digital Tools for Pharmaceutical Sciences (Digipharm)" Master Degree, Aix Marseille Univ.
- R. Fanciullino
 - Lectures in: MSc (2nd year) in Pharmacokinetics, MSc (2nd year) in Digipharm, CESU in Oncogeriatrics, DES in PK Variability, Pharm.D. studies (3rd, 4th and 5th year) -> 190 h a year.
 - Head of the CESU "Pharmacokinetics variability in Oncology".
- F. Gattacceca
 - Lectures in pharmacokinetics and pharmacometrics at Aix-Marseille University school of pharmacy (305h), teaching in other universities (Nîmes, Angers, Montpellier): 90% at a post-graduate level.
 - Director of the master program "Pharmacokinetics".
 - Director of two international post-graduate university diplomas: "Modeling and simulation: population approaches in pharmacokinetics/pharmacodynamics" and "Modeling and simulation: physiologically-based pharmacokinetic modeling for pharmacology and toxicology".
 - Member of the national reflection committee for the industry pharmacy studies and the training steering committee of ICI (Immunology Cancer Institute).
 - Tutor of 3 sessions in the second (2025) edition of the "Pharmacometrics Africa" training in French.
 - CIVIS International Summer School "Drug Design and Discovery", Madrid, Spain 2025 (Lectures and hands-ons).
- L. Greillier
 - Lectures in M2 Recherche clinique et Simulation en Santé.

- Lectures in oncology and pulmonology for 3rd–11th year medical students.
- Q. Marcou
 - M2 Artificial Intelligence for Public Health (AI4PH) (9h).
 - M2 Digipharm (3h).
- X. Muracciole
 - DIU radio-urology for resident medical students.
 - DCIU radio surgery for resident medical students.
- L. Nguyen Phuong
 - CESU "Fundamentals for modeling and simulation in pharmacokinetics/pharmacodynamics" and Introduction to R for pharmacokinetic modeling (9h).
 - M2 PK: Introduction to R for pharmacokinetic modeling (20h).
- S. Salas
 - Medical study/initial training: Seminary in palliative care, Therapeutic module in pains, Oncodigestive module, Cancerology (44h), for 3rd–6th year medical students.
 - Medical and paramedical study: DU Supportive care in oncology and palliative medicine, DU Wounds and healing, DIU Supportive care in oncology and palliative medicine, Master's in Advanced Practice Nursing (Cancerology, General, and pains modules), CEU Service providers at home, Home-based cancer care, DU Ambulatory shift Oncology module (37h).

11.2.2 Supervision

- Postdoc
 - S. Benzekry and E. Ventre
 - G. Fiandaca, 2025-2027: "Characterizing cell state dynamics in rhabdomyosarcoma tumoroid models"
 - J. Ciccolini
 - M. Centanni, 2025-2027: "PK-guided dand MIPD in oncology" co-supervision with L. Friberg Uppsala University Sweden
- Engineers
 - S. Benzekry
 - S. Charpigny (PEPR DIGPHAT)
 - L. Nguyen-Phuong (RHU LUCA-pi)
 - A. Vaglio (RHU PIONeeR)
 - Q. Marcou
 - Mehdi Mansour (PharmIAge, hosted by the SESSTIM lab)
- PhD students
 - S. Benzekry
 - A. Bakhmach (PEPR Santé Numérique DIGPHAT), 2023 - 2026: "Modeling and statistical learning for pharmacology in oncology", co-supervision with R. Fanciullino (COMPO, APHM) and S. Garciaz (IPC)

- M. Boussena (Institut Laënnec, AMU), 2023 - 2026: "Machine learning methods for clinical oncology data: application to the prediction of immunotherapy response in lung cancer", co-supervision with J. Josse (Premedical, Inria) and L. Greillier (COMPO, APHM)
- C. Bigarré, 2020 - 2024: "Mathematical modeling for prediction of metastatic relapse in breast cancer", co-supervision X. Muracciole, funding Inria – Inserm
- L. Nguyen Phuong, 2022 - 2025, SChISM: "Mechanistic modeling of circulating DNA combined to machine learning for prediction of response and survival following immunotherapy", co-supervision S. Salas, funding Amidex ICI (Institute for Cancer Immunotherapy) and Laënnec (Institute for AI and health)
- R. Ferrara, 2025 - 2028: "Découverte automatique de modèles mécanistiques pour la pharmacocologie par apprentissage automatique : application à la radiothérapie interne vectorisée"
- H. Hamdache, 2023 - 2026: "Improving therapeutic efficacy and managing side effects and sequelae in pediatric cancer through improved and personalized nutritional programs using computer simulations", co-supervision V. Pancaldi (IUCT, Inserm, Toulouse), funding Inria–Inserm.
- D. Boulate
 - C. Buton (Institut Laënnec, AMU), 2024-2027: "Development of interactive expert software stratifying the risk of lung cancer diagnosis in the setting of lung cancer screening based on mathematical modeling and machine learning approaches", co-supervision with D. Barbolosi (COMPO)
 - A. Todesco (CRCM - E19 - SMARTc), 2023-2026: "Study of the maintenance of pulmonary and systemic vascular permeability: from physiology to pathology", co-supervision with P. Habert (APHM)
 - E. Armand (CRCM), 2023-2026: "French screening programme: development of risk stratification tools"
- J. Ciccolini
 - A. Ronda, "Pembro Monitoring in real-world patients", funding APHM
 - G. Kallee, "DPD status and clinical outcome", funding APHM
 - D. Protzenko, "PK-guided dosing in HCT conditioning", funding APHM
 - L. Wirtz, "Improving the drug delievery of natural products in oncology", funding APHM co-supervision A. Rodallec.
 - E. Diroff, "development of smart nanoparticles in PDAC", funding CIFRE, EsQlabs. co-supervision A. Rodallec.
 - B. Son Nhat, "PK/PD of immunosuppressive drugs in leukemia patients", funding USTH Hanoi co-supervision Nguyen Thi Van Anh, University of Science and Technology of Hanoi (USTH) and Vietnam Academy of Science and Technology (VAST)
- F. Gattacceca
 - S. Benamara, 2023-2026: "Prediction of monoclonal antibody pharmacokinetics in humans using PBPK modeling: towards an integrated strategy to support First-in-human (FIH) clinical trials", co-supervision with D. Teutonico (SANOFI), funding CIFRE
- R. Fanciullino
 - M. Dacos, Development of nanoparticles in HER2+ breast cancer, funding APHM
 - L. Osanno, PK/PD of nucleoside analogs in oncology-hematology, funding APHM
 - Q. Gerbault, Pharmacometrics in leukemia patients, funding APHM
- E. Ventre

- C. Berthaud (CRCL), 2024-2027: "Bioinformatic approach to the impact of modulation of the respiratory chain SDH complex on cell states dynamics in pediatric gliomas and rhabdomyosarcomas", co-supervision M. Castets (Inserm, CRCL), funding Ligue contre le cancer
- Y. Maugé, 2025-2028: "Generative mechanistic models for subpopulations, trajectories and GRN inference from single-cell datasets", co-supervision A-S. Chrétien (CRCM), funding ENS Lyon.
- Interns (Master 2)
 - S. Benzekry
 - L. Della-Negra (ENSC, Bordeaux)
 - R. Ferrara (M2 AIOH, Grenoble)
 - R. Fanciullino
 - Quentin Gerbeault M2RPK AMU
 - F. Gattacceca
 - Catherine Dubois (M2 PK, Lyon)
 - Ester Tonon (pharmacy master, Torino, Italy)
 - Q. Marcou
 - Roufeida Segaula (M2 MIAS Centrale Lille, hosted by the SESSTIM lab)
 - Mehdi Mansour (M2 MALIA, Université Lyon 2, hosted by the SESSTIM lab)
 - A. Rodallec
 - Yacine Gomari (M2 PK, Marseille)
 - Zakaria Benslimane (M2 IA & Biomarkers, Marseille)

11.2.3 Juries

- S. Benzekry
 - Reviewer PhD: L. Vuduc (Paris Saclay Univ., CentraleSupélec); A. Pitoy (Univ. Paris Cité)
 - Jury PhD: A. Gabaut (Bordeaux Univ.)
- J. Ciccolini
 - President of PharmD Dissertation Jury: >20 thesis/year (AMU)
 - Reviewer of PhD Defense: P. Claraz (Toulouse University), Dimitrios Papakonstantinou (Paris Saclay University)
 - Reviewer of PhD scientific evaluation committee: Stefan Nicolescu (Montpellier University), Agnes Ducoulmombier (Nice University), M. Vahabi (Amsterdam University NL).
- F. Gattacceca
 - Reviewer in PhD committee: M. Boulanger (Université de Toulouse)
 - Member of PhD scientific evaluation committees: M. Godard (Université de Montpellier), B. Cardozo (Aix Marseille Université), A. Baillot (Université de Poitiers)
 - President of PharmD committee: Q. Renou (Aix Marseille Université)
- Q. Marcou
 - Member of PhD scientific evaluation committees: E. Hector (Aix Marseille Université)
- A. Rodallec

- Member of PharmD committees (5-10 per year)
- E. Ventre
 - Member of PhD committee: N. Ben Boina (Aix Marseille Université)

11.2.4 Educational and pedagogical outreach

- F. Gattacceca
 - PK Docs, creation and organization of the international online monthly event for PK PhD students
 - Organization of PK national Masters Class (Every Thursday, November-December 2025)
 - Tutor of 3 sessions in the second (2025) edition of the "Pharmacometrics Africa" training in French

11.3 Popularization

11.3.1 Productions (articles, videos, podcasts, serious games, ...)

- J. Ciccolini:
 - Serious Game "Translational Research in Oncology" TRANSFORM-O Société Française du Cancer: 20 selected resident in Medical Oncology and Radiation Therapy/year.
 - Jury at the Pharm'Innov Serious Game, School of Pharmacy of Marseille.
- S. Benzekry: Two online articles from an interview with a journalist at the SophIA summit
 - About the [KineticPro software](#)
 - About the [PIONeeR RHU and mechanistic learning](#)
- F. Gattacceca:
 - Coordinator and co-author of the book: "Pharmacie galénique - Pharmacocinétique - L'enseignement en fiches", published in September 2025
 - Coach and jury at the Pharm'Innov Serious Game, School of Pharmacy of Marseille.
- A. Rodallec:
 - Coordinator of the podcast "The POSTDOC Chronicles" by the BNLFCRS LC, to dive into the science, stress, and success that shape your journey as an early-career scientist (4 episodes per year)
 - Jury at the Pharm'Innov Serious Game, School of Pharmacy of Marseille.

11.3.2 Participation in Live events

- G. Fiandaca:
 - September 3-4, 2025: Contribution and participation to the "dose-effect" game of the "Fête de la science" in Aix en Provence
- F. Gattacceca:
 - September 3-4, 2025: Creation and participation to the "dose-effect" game of the "Fête de la science" in Aix en Provence
 - October 6-7, 2025: Participation to the "Rencontres étudiants-chercheurs" (Meetings between students and researchers) in Aix en Provence (Montperrin campus)
 - November 22, 2025: Representation of the school of pharmacy at "Salon de l'Etudiant" (Aix en Provence)

- Q. Marcou: "Data, nouveaux outils et Règlementation" round table, organized by the Amicale des Actuaire du Sud
- A. Rodallec
 - Participation to "Contre le Cancer j'apporte ma Pierre" to popularize cancer in schools
 - Participation to "The talented researcher step on strategies" at Cancerpole Seminaire in Saint-Raphael, France

11.3.3 Others science outreach relevant activities

- E. Ventre: Participation to the programm CHICHE Inria (2h in Lycée Marseilleveyre in November 2025 and and 4h in Lycée Saint Exupéry in December 2025)

12 Scientific production

12.1 Major publications

- [1] A. Bakhmach, P. Dufossé, A. Vaglio, F. Monville, L. Greillier, F. Barlési and S. Benzekry. *ROOFS: RObust biOmarker Feature Selection*. 2026. DOI: [10.48550/arXiv.2601.05151](https://doi.org/10.48550/arXiv.2601.05151). URL: <https://inria.hal.science/hal-05241230>.
- [2] F. Barlesi, F. Monville, L. Greillier, N. Ngoi, J. Ciccolini, S. Garcia, J.-P. Dales, F. Sabatier, L. Arnaud, A. Pouchin, F. Vely, S. Bokobza, A. Bakhmach, P. Dufossé, A. Vaglio, M. Karlsen, M. Boussena, C. Bigarre, M. Hamimed, R. Malkoun, L. Ghezali, M. Le Ray, M. Roumieux, J. Mazieres, M. Perol, E. Vivier, J. Fieschi-Meric and S. Benzekry. *An integrative multimodal machine learning signature of primary resistance to immunotherapy in advanced non-small cell lung cancer: biomarker analysis from the PIONeR study*. 2025. URL: <https://inria.hal.science/hal-05241459>.
- [3] S. Benzekry. 'Artificial Intelligence and Mechanistic Modeling for Clinical Decision Making in Oncology'. In: *Clinical Pharmacology and Therapeutics* (18th June 2020). DOI: [10.1002/cpt.1951](https://doi.org/10.1002/cpt.1951). URL: <https://inria.hal.science/hal-02916941>.
- [4] S. Benzekry, M. Karlsen, C. Bigarré, A. E. Kaoutari, B. Gomes, M. Stern, A. Neubert, R. Bruno, F. Mercier, S. Vatakuti, P. Curle and C. Jamois. 'Predicting Survival in Patients with Advanced NSCLC Treated with Atezolizumab Using Pre- and on-Treatment Prognostic Biomarkers'. In: *Clinical Pharmacology and Therapeutics* 116.4 (12th July 2024), pp. 1110–1120. DOI: [10.1002/cpt.3371](https://doi.org/10.1002/cpt.3371). URL: <https://hal.science/hal-04647230>.
- [5] S. Benzekry, M. Matri, C. Nicolò and J. Ebos. 'Machine-learning and mechanistic modeling of primary and metastatic breast cancer growth after neoadjuvant targeted therapy'. In: *PLoS Computational Biology* 20.5 (3rd May 2024), e1012088. DOI: [10.1371/journal.pcbi.1012088](https://doi.org/10.1371/journal.pcbi.1012088). URL: <https://hal.science/hal-04384182>.
- [6] C. Bigarré, F. Bertucci, P. Finetti, G. Macgrogan, X. Muracciole and S. Benzekry. 'Mechanistic modeling of metastatic relapse in early breast cancer to investigate the biological impact of prognostic biomarkers'. In: *Computer Methods and Programs in Biomedicine* 231 (Apr. 2023), p. 107401. DOI: [10.1016/j.cmpb.2023.107401](https://doi.org/10.1016/j.cmpb.2023.107401). URL: <https://inria.hal.science/hal-04008520>.
- [7] R. Elfatairi, J. Ou, V. Lebreton, M. Mahdjoub, N. Kaeokhamloed, J. Bejaud, G. Hilairat, F. Gattacceca, E. Roger and S. Legeay. 'Specific quantification of intact lipid nanocapsules in rats using FRET: biodistribution and PBPK model development'. In: *Nanomedicine* 20.10 (24th Apr. 2025), pp. 1101–1112. DOI: [10.1080/17435889.2025.2492537](https://doi.org/10.1080/17435889.2025.2492537). URL: <https://hal.science/hal-05242719>.
- [8] F. Ferrer, R. Fanciullino, G. Milano and J. Ciccolini. 'Towards Rational Cancer Therapeutics: Optimizing Dosing, Delivery, Scheduling, and Combinations'. In: *Clinical Pharmacology and Therapeutics* 108.3 (2nd Aug. 2020), pp. 458–470. DOI: [10.1002/cpt.1954](https://doi.org/10.1002/cpt.1954). URL: <https://hal.science/hal-04869551>.

- [9] L. Nguyen Phuong, F. Fina, L. Greillier, P. Tomasini, J.-L. Deville, R. Zakrasjek, L. Della-Negra, A. Boutonnet, F. Ginot, J.-C. Garcia, S. Benzekry and S. Salas. *The SChISM study: Cell-free DNA size profiles as predictors of progression in advanced carcinoma treated with immune-checkpoint inhibitors*. 3rd Sept. 2025. URL: <https://inria.hal.science/hal-05238567>.
- [10] L. Nguyen Phuong, F. Fina, L. Greillier, P. Tomasini, J.-L. Deville, A. Boutonnet, F. Ginot, J.-C. Garcia, S. Salas and S. Benzekry. *Mechanistic Modeling of cfDNA Fragmentome Dynamics Predicts Progression to Immunotherapy*. 2025. URL: <https://inria.hal.science/hal-05241421>.
- [11] A. Rodallec, R. Lee, J. Cao, S. Marolleau, J. Nicolas and S. Benzekry. *Model-Driven Scheduling of Nanocarriers: Application to an Anticancer Polymer Prodrug Administered Subcutaneously*. 2025. URL: <https://inria.hal.science/hal-04937053>.

12.2 Publications of the year

International journals

- [12] S. Benamara, E. Sjögren, F. Gattacceca, M. Chenel, A. Deslandes, L. Nguyen and D. Teutonico. ‘Prediction of Monoclonal Antibodies Pharmacokinetics in Human: Identification of a Reference Neonatal Fc Receptor (FcRn) Binding Affinity Using Physiologically Based Pharmacokinetic (PBPK) Modeling’. In: *ACS Pharmacology & Translational Science* (22nd Dec. 2025). DOI: [10.1021/acspsci.5c000674](https://doi.org/10.1021/acspsci.5c000674). URL: <https://hal.science/hal-05441327>.
- [13] S. Benamara, C. Troisi, F. Gattacceca, E. Sjögren, L. Nguyen and D. Teutonico. ‘Cross-Species Extrapolation of Neonatal Fc Receptor (FcRn) Binding Affinity to Predict Monoclonal Antibody Pharmacokinetics in Humans Using Physiologically Based Pharmacokinetic Modeling (PBPK): Are We There Yet?’ In: *ACS Pharmacology & Translational Science* 8.9 (5th Aug. 2025). DOI: [10.1021/acspsci.5c000356](https://doi.org/10.1021/acspsci.5c000356). URL: <https://hal.science/hal-05238046>.
- [14] M. Brunini, J.-M. Forel, X. Muracciole, A. Roch, D. Barbolosi and L. Papazian. ‘Heterogenous treatment effect of neuromuscular blocking agents for moderate-to-severe ARDS: a post hoc Markov model re-analysis of the ACURASYS trial’. In: *Intensive Care Medicine* 51.9 (6th Aug. 2025), pp. 1615–1627. DOI: [10.1007/s00134-025-08064-z](https://doi.org/10.1007/s00134-025-08064-z). URL: <https://hal.science/hal-05240898>.
- [15] E. Collomb, L. Bourguignon, A. Tichadou, P. Roche, G. Berton, J. Ciccolini, J. Colle, L. Farnault, R. Costello, R. Fanciullino and G. Venton. ‘Impact of CDA Dynamics on Clinical Outcome of Patients With AML or High-Risk MDS Treated With Nucleoside Analogs’. In: *Hematological Oncology* 43.2 (15th Mar. 2025). DOI: [10.1002/hon.70057](https://doi.org/10.1002/hon.70057). URL: <https://hal.science/hal-05240068>.
- [16] R. Elfatairi, J. Ou, V. Lebreton, M. Mahdjoub, N. Kaeokhamloed, J. Bejaud, G. Hilairat, F. Gattacceca, E. Roger and S. Legeay. ‘Specific quantification of intact lipid nanocapsules in rats using FRET: biodistribution and PBPK model development’. In: *Nanomedicine* 20.10 (24th Apr. 2025), pp. 1101–1112. DOI: [10.1080/17435889.2025.2492537](https://doi.org/10.1080/17435889.2025.2492537). URL: <https://hal.science/hal-05242719> (cit. on p. 12).
- [17] A. Géraud, P. Gougis, A. de Nonneville, M. Beaufiles, F. Bertucci, E. Billon, G. Brisou, G. Gravis, L. Greillier, M. Guerin, E. Mezni, E. Mitry, R. Noel, J. Pignon, R. Sabatier, L. Seguin, J.-P. Spano, C. Vicier, F. Viret, A. Goncalves and J. Ciccolini. ‘Pharmacology and pharmacokinetics of antibody-drug conjugates, where do we stand?’ In: *Cancer Treatment Reviews* 135 (Apr. 2025), p. 102922. DOI: [10.1016/j.ctrv.2025.102922](https://doi.org/10.1016/j.ctrv.2025.102922). URL: <https://hal.science/hal-05240065>.
- [18] G. Kallee, G. Milano and J. Ciccolini. ‘Dihydropyrimidine Dehydrogenase-Guided Dosing of 5-Fluorouracil: Prioritizing Precision Over Dose Reduction’. In: *JCO precision oncology* 9 (Oct. 2025). DOI: [10.1200/PO-25-00657](https://doi.org/10.1200/PO-25-00657). URL: <https://inria.hal.science/hal-05468739>.
- [19] G. Kallee, G. Milano, F. Duffaud, L. Dahan and J. Ciccolini. ‘DPD Ultra-Rapid Metabolizer Status and Efficacy of 5-Fluorouracil Treatment: A Real-World Study’. In: *Fundamental & Clinical Pharmacology* 39.4 (7th July 2025). DOI: [10.1111/fcp.70035](https://doi.org/10.1111/fcp.70035). URL: <https://hal.science/hal-05240066>.
- [20] L. Karlsson, J. Ciccolini, R. ter Heine and M. Centanni. ‘Eco Friendly and Budget Smart: An Economic and Environmental Evaluation of Alternative PD-1 and PD-L1 Inhibitor Dosing Regimens’. In: *PharmacoEconomics* 43.12 (10th Sept. 2025), pp. 1433–1449. DOI: [10.1007/s40273-025-01535-7](https://doi.org/10.1007/s40273-025-01535-7). URL: <https://inria.hal.science/hal-05468373>.

- [21] F. de Kermenguy, D. Morel, M. El-Aichi, D. Barbolosi, E. Deutsch and C. Robert. ‘Radiation-Induced Lymphopenia: From Mathematical Modeling Toward Mechanistic Learning’. In: *International Journal of Radiation Oncology, Biology, Physics* (Aug. 2025). DOI: [10.1016/j.ijrobp.2025.07.1429](https://doi.org/10.1016/j.ijrobp.2025.07.1429). URL: <https://hal.science/hal-05240899>.
- [22] L. Nguyen Phuong, S. Salas and S. Benzekry. ‘Computational modeling for circulating cell-free DNA in clinical oncology’. In: *JCO Clinical Cancer Informatics* 9 (Mar. 2025). DOI: [10.1200/CCI-24-00224](https://doi.org/10.1200/CCI-24-00224). URL: <https://hal.science/hal-04481689>.
- [23] L. Osanno, L. Brocque, L. Bourguignon, C. Delpech, L. Farnault, J. Colle, P. Roche, J. Chiaroni, C. Izard, R. Costello, M. Dacos, C. Solas, C. Djeddar, J. Ciccolini, T. Cluzeau, G. Venton and R. Fanciullino. ‘Predicting the toxicity-efficacy ratio of venetoclax in real-world patients’. In: *Annals of Hematology* 104.12 (11th Dec. 2025), pp. 6327–6337. DOI: [10.1007/s00277-025-06531-7](https://doi.org/10.1007/s00277-025-06531-7). URL: <https://inria.hal.science/hal-05469523> (cit. on p. 12).
- [24] C. Plazy, M. Boussena, L. Nguyen Phuong, B. Assié Jean, E. Grolleau, V. Gounant, N. Chaabane, C. Decroisette, E. Dansin, H. Babey, C. Daniel, G. Leprieur Etienne, D. Planchard, M. Riuvadets, A. Canellas, Y. Oulkhair, M. Pérol, A.-C. Toffart, S. Benzekry and E. Gobbi. ‘The Rechallenge Benefit Score: A Clinical Decision Tool for Patients Progressing After Immunotherapy’. In: *European Journal of Cancer* (Nov. 2025). URL: <https://inria.hal.science/hal-05240613>.
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