Instituts thématiques

Institut national de la santé et de la recherche médicale

Modéli métastatique : le isme

X. Muracciole

C. Bigarré

CRCM Centre de Recherche en Cancérologie de Marseille

cnrs

Aix*Marseille université

AP-HM Assistance Publique Hôpitaux de Marseille

Inria – Inserm project-team

COMPO - COMPutational pharmacology and clinical Oncology: Optimization of therapeutic strategies by mechanistic and statistical modeling

S. Benzekry

COMPO: COMPutational pharmacology and clinical Oncology

MATHEMATICAL MODELING

Mechanistic modeling	Pharmacometrics	Statistics Data science
D. Barbolosi S. Benzekry	D. Barbolosi, S. Benzekry F. Gattacceca	S. Benzekry

PHARMACOLOGY

Experimental	Clinical
J. Ciccolini R. Fanciullino A. Rodallec	J. Ciccolini R. Fanciullino B. Lacarelle

MEDICINE

Pr L. Greillier Dr X. Muracciole
Pr S. Salas

Historical context

A. Iliadis

- Pioneering work of A. Iliadis and D. Barbolosi in pharmacokinetics and pharmacodynamic modeling in the 1980's

- SMARTc (Simulation and Modeling for Adaptive Response for Therapeutics in Cancer) platform of the CRCM

- Strong collaboration with S. Benzekry from Inria MONC for 7+ years (17 publications, one Inria-Inserm joint PhD, co-supervision of MD theses)

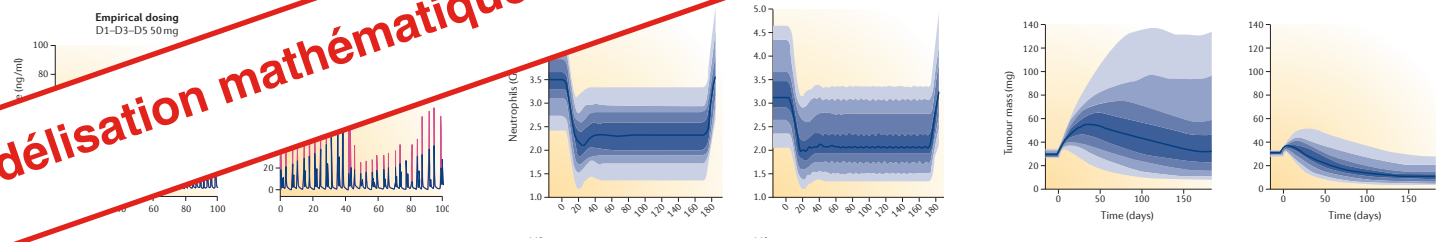
June 2020: laureate of the Inria-Inserm call for joint project-teams

Previous scientific achievements

Essais cliniques basés sur la modélisation mathématique : l'expérience marseillaise

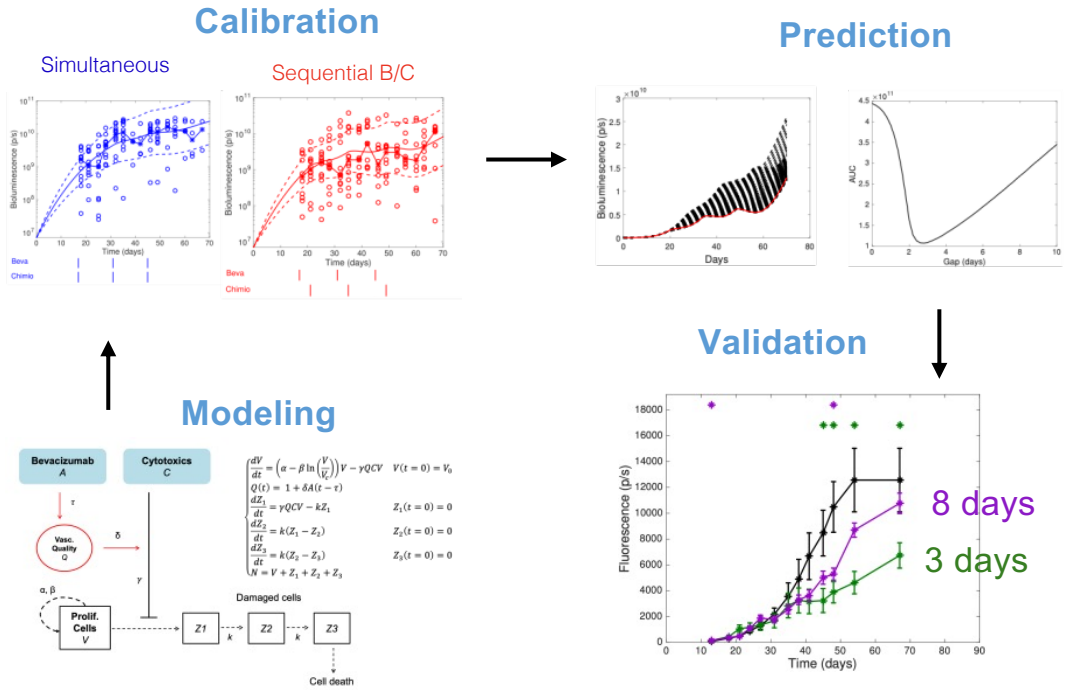
- **MODEL1**: world first mo[illegible]nical trial in oncology
  - Modeling toxicities
  - Safe densification of chemothera[illegible]
  - Adaptive, personali[illegible]
  - Media[illegible]20 to 55 months

D. Barbolosi



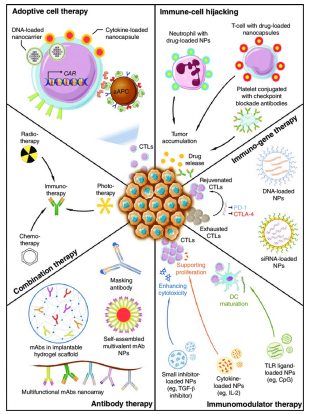
Meille et al. (Iliadis), Clin Pharmacokinet 2016, Barbolosi et al., Nat Rev Clin Oncol, 2016

- **Antiangiogenics + cytotoxics sequence**
  - Biological rationale: bevacizumab-induced vasculature normalization
  - Modeling tumor kinetics
  - Calibration from experimental data
  - Validation of model predictions

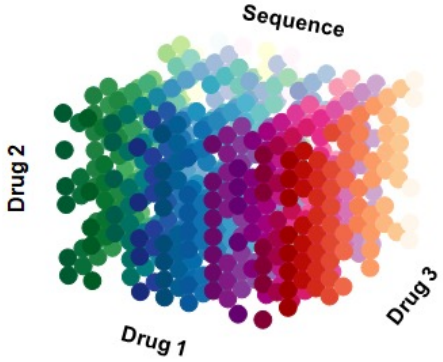


Mollard et al., Oncotarget 2017
Imbs et al., CPT: PSP, 2018, Schneider et al., CPT:PSP, 2019

Current challenges in clinical oncology and pharmacology



Therapeutic strategies are increasingly complex



Curse of dimensionality

Ever-increasing amount of information for decision-making

Qualitative, quantitative and longitudinal ‘big’ data from: demographics, radiology, functional imaging, molecular biology, histology, immune-monitoring, biomarkers, blood counts

Trial-and-error approaches unfit for current challenges

Lack of appropriate numerical softwares that could support decision-making for determining the best strategy: Treating or not? To what extent? Which drugs? Which dosing/scheduling/sequencing?

Math onco, machine learning and pharmacometrics

MATHEMATICAL ONCOLOGY

- Theoretical models for complex behaviours
- Dynamic models

Limitations

- No clinical application
- Few validation of models
- Few models of metastasis

MACHINE LEARNING

- Focus on prediction rather than inference
- Integrates high-dimensional data
- Success for genomic and imaging data

Limitations

- No application in clinical oncology (yet?)
- Lack of interpretability
- Longitudinal data

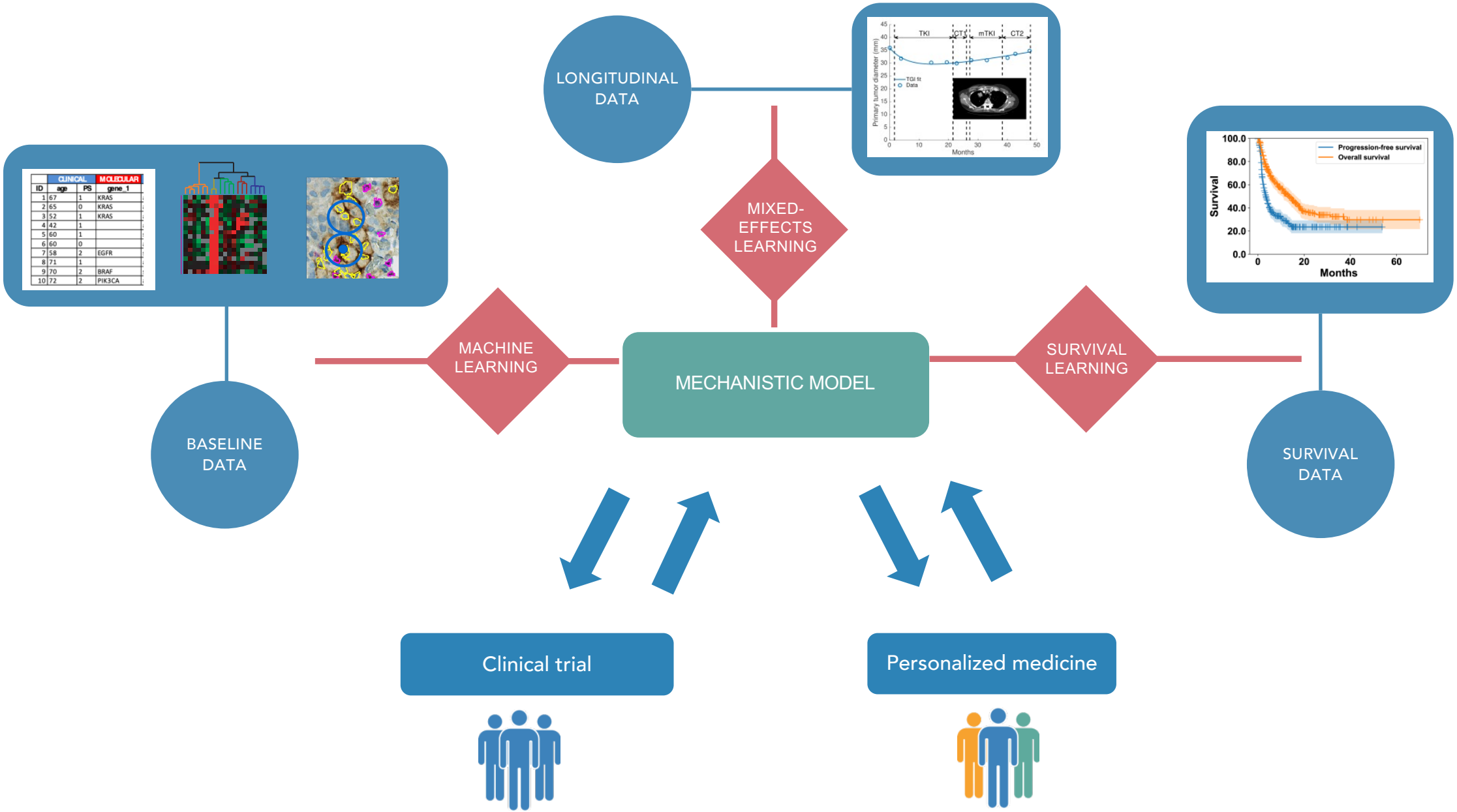
PHARMACOMETRICS

- Quantitative methods to PK/PD data
- Success for applications to clinical trials and drug development

Limitations

- Limited use in routine
- Coarse-grained modeling
- Lack of integration of ‘big’ data

Mechanistic learning



Research axes

- **Axis 1**: Modeling clinical biomarkers for personalized decision-making
- **Axis 2**: Individualizing anticancer drugs regimen
- **Axis 3**: Optimizing combinatorial strategies

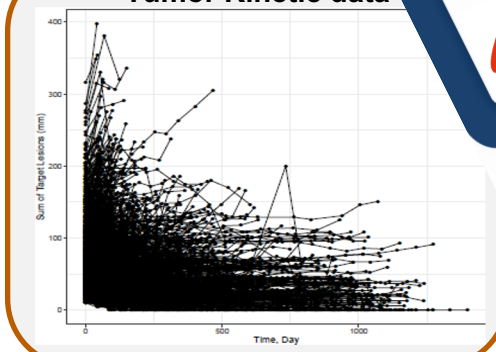
Axis 1: D-Light project (… 5 patients)

Goal = predict respon… …ibition in NSCLC

INPUTS … LS | OUTPUTS

8,635 measurements

Tumor Kinetic data



Model parameters
p ≃ 15

Baseline clinical factors and biomarkers
p ≃ 120

RNAseq
p ≃ 50,000

+

Machine Learning and Mechanistic Modeling for the prediction of Overall Survival on the basis of 1st line Tumor Dynamics in HNSCC

K. Atsou[1], A. Auperin[2], J. Guigay[3], S. Salas[1,4], S. Benzekry[1]
[1] COMPutational pharmacology and clinical Oncology Team, Inria Sophia Antipolis - Méditerranée, Cancer Research Center of Marseille, Inserm, CNRS, Aix Marseille University, Marseille, France.
[2] Biostatistical and Epidemiological Division, Institut Gustave Roussy, Villejuif, France.
[3] Clinical Oncology, Centre Antoine Lacassagne, Nice, France
[4] Clinical Oncology, Hôpital Timone, Aix-Marseille University, Marseille, France.

OBJECTIVES

- Propose the best **mathematical model** for the description of the longitudinal measurement of the patients individual SLDs (Sum of the Largest Diameters)
- Predict the **Overall Survival** using the kinetic data of first line and some baseline data

BACKGROUND

- Prediction of **Overall Survival** and **Response to 2nd line** is a **major challenge** in treatment of HNSCC
- **Tumor kinetics during first line** may provide interesting **predictive metrics** for Overall Survival

MATERIAL AND METHODS

Clinical data
- EXTREME (cetuximab, 5-…
- vs TPEx (cetuximab, do…
- **Phase 2 clinical trial**
- **528 patients** enrolle… (EXTREME)).

Tumor Growth Inhi…

Tumor Growth … treatment effect

Nonlinear Mixed Effects Modeling (NLMEM)

Biexponential model

$SLD(t) = SLD_0\left(e^{KGt} + e^{-KSt} - 1\right)$

μ fixed effects, η_i random effects

combined error model

K. Atsou

S. Salas

RESULTS

The Biexponential model provides the best Fit (AIC and Identifiability)[3]

KG is the most important parameter for predicting OS

Tumor Kinetic Parameters Outperform All Others

CONCLUSION AND PERSPECTIVES

- A **mechanistic** mathematical model was able to fit the **clinical data** of SLD measurements in a mCRC clinical trial
- Modeling and Machine learning algorithms were combined to predict **Overall Survival**
- **only modest so far** but only the SLD measurements was considered
- model **individual lesions kinetics**

Model parameters
(e.g. KG, KS, TTG, …)

…iction of phase III trial …come from phase I/II …and early data

…al prediction of …tcome

QUANTitative modeling combined to

esistance to Immune-checkpoint inhibition

Assistance Publique Hôpitaux de Marseille

THE PIONEER PROJECT

Instituts thématiques Inserm Institut national de la santé et de la recherche médicale

INSTITUT NATIONAL DU CANCER

aviesan alliance nationale pour les sciences de la vie et de la santé ITMO Cancer

Inria

Machine learning for prediction of immunotherapy efficacy in cell lung cancer from simple clinical and biological data

Sébastien Benzekry [1,*], Mathieu Grangeon [2,*], Mélanie Karlsen [1], Pauline Fleury [1], Maria Alexa [1], Isabella Bicalho-Frazeto [1], Solène Chaleat [2], Pascale Tomasini [1,2,3], Dominique Barbolosi [1], Fabrice Barlesi [3,4], Laurent Greillier [1,2]

1 COMPutational pharmacology and clinical Oncology Team, Inria Sophia Antipolis - Méditerranée, Cancer Research Center of Marseille, Inserm, CNRS, Aix Marseille University, Marseille, France. 2 Multidisciplinary Oncology and Therapeutic Innovations Department, Assistance Publique - Hôpitaux de Marseille, Aix Marseille University, Marseille, France. 3 Aix Marseille University, CNRS, INSERM, CRCM, Marseille, France. 4 Gustave Roussy Cancer Campus, International Center of Thoracic Cancers, Université Paris-Saclay, Villejuif, France.
* = these authors contributed equally

OBJECTIVES

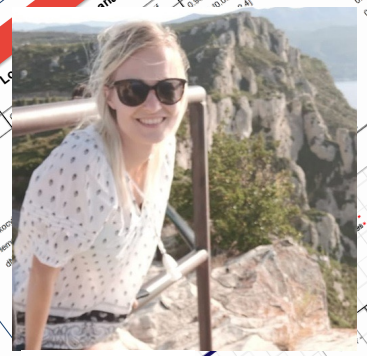
- Study the predictive power of **blood counts** before the start of
- Assess the utility of classical machine learning algorithms to **establish a predictive model of response**

BACKGROUND

- Immune checkpoint inhibitors (ICIs) are now a therapeutic standard in stage IV non-small cell lung cancer (NSCLC).
- However, 4 out of 5 patients don't respond to single agent ICI.
- Strong predictive markers for ICIs efficiency are still lacking.

MATERIAL AND METHODS

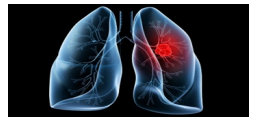
RESULTS

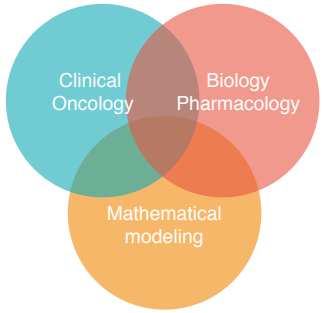


M.Karlsen

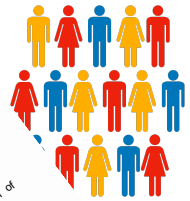
L. Greillier

P. Fleury





n = 450 pts



CONCLUSION AND PERSPECTIVES

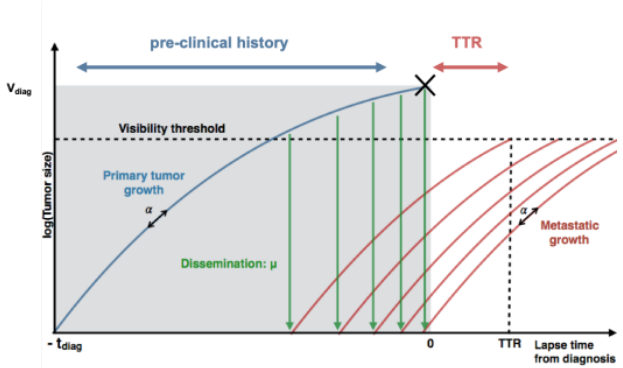
Blood counts prior to ICIs (elevation of hemoglobin, decrease of NLR, leukocytes or neutrophils) and clinical status (good PS) were **significantly associated with better DCR** in multivariable analysis. The practical application of these associations using machine learning algorithms was able to **accurately predict individual response to treatment**. This could be improved further by increasing the number of variables in the model and should be further validated in an independent cohort.

S., Grangeon, M., ... Barlesi, F., Greillier, L.: et al. Machine learning for prediction of efficacy in non-small cell lung cancer from simple clinical and biological data. Artificial Intelligence and Mechanistic Modeling for clinical Decision Making in Oncology, Clinical Therapeutics (2020)

...si, L. Greillier

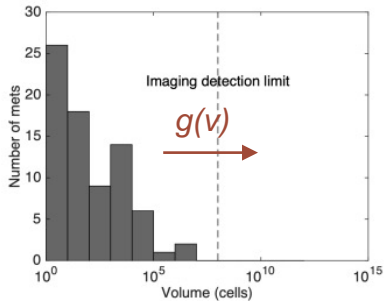
Axis 1: Modeling metastatic relapse in early-stage breast cancer

Mechanistic modeling

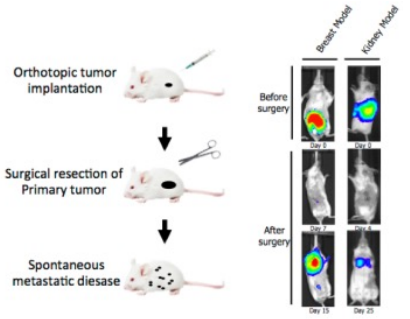


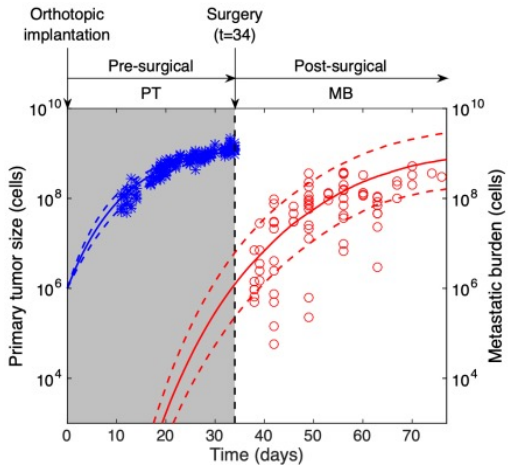
Size-structured PDE

$$\begin{cases} \partial_t \rho(t,v) + \partial_v(g(v)\rho(t,v)) = 0 \\ g(V_0)\rho(t,V_0) = d(V_p(t)) \\ \rho(0,v) = \rho^0 \end{cases}$$



Experimental validation





Benzekry et al., Cancer Res, 2016
Benzekry et al., Cancer Res, 2017

Clinical prediction of relapse

21 biomarkers

Mechanistic learning

x_1
x_2
.
.
.
x_{21}

Machine learning

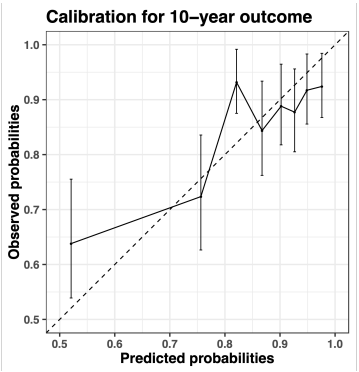
Feature selection

Ki67
Tumor size
Age
EGFR
CD44

μ
α

Time to relapse

Algorithm	AUROC	Accuracy	Sensitivity	Specificity
5-year				
Mechanistic model	0.73	0.68	**0.75**	0.67
Random survival forest	0.73	0.69	0.64	0.70
Random forest	**0.75**	0.66	0.71	0.66
Logistic regression	**0.75**	0.83	0.42	0.87
k-Nearest neighbor	0.62	**0.91**	0.02	**1.00**
Gradient boosting	0.71	0.90	0.11	0.98
Support vector machine	0.64	0.87	0.09	0.95
Cox	0.71	0.72	0.66	0.73
10-year				
Mechanistic model	0.67	**0.67**	0.62	**0.68**
Random survival forest	**0.69**	0.62	**0.71**	0.60
Cox	0.65	0.65	0.61	0.65



Nicolò et al., JCO: Clin Cancer Inform, 2020

Axis 2: Individualizing anticancer drugs regimen

Modèles mathématiques et Médecine de Précision en Oncologie : individualisation des traitements en pratique clinique de routine

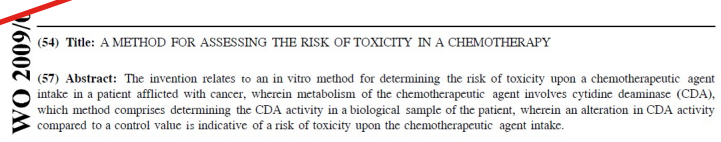
J. Ciccolini

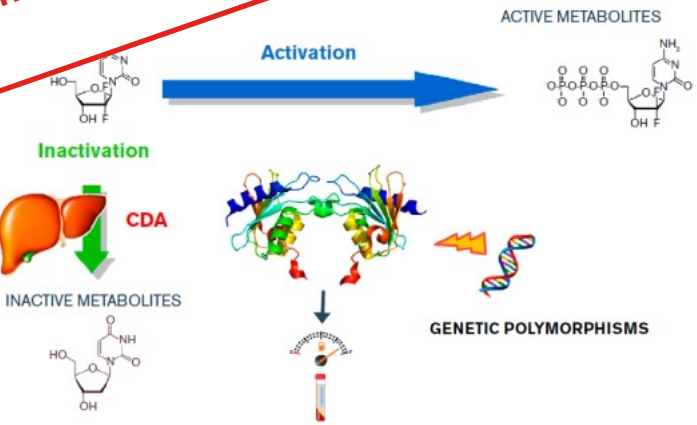
✓ **A PK/PD/PGx model f… …alizing the dosing of nucleosides analogs in leu…**

Demonstration of errati… …n liver CDA because of PGx syn…

Possible impact on PK/… …nships with sever…

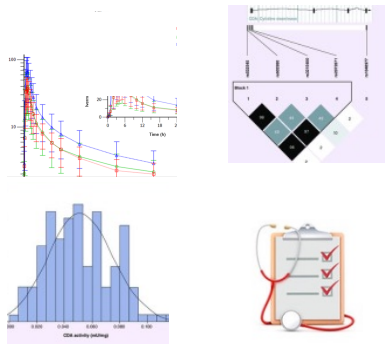
Development and validation of a ph… …um to determine CDA status



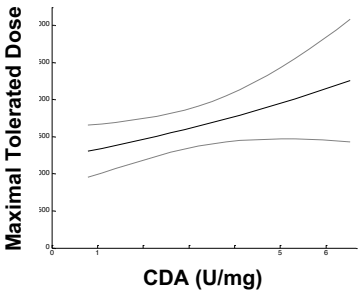


Ciccolini et al. J Clin Oncol 2010;
Fanciullino et al., Blood Adv 2017

- O… …n clinical trials in adult AML patients with cytarabine, liposomal cytarabine and azacytidine with full PK and PG… …port to build a PK/PD/PGx model to tailor dosing.

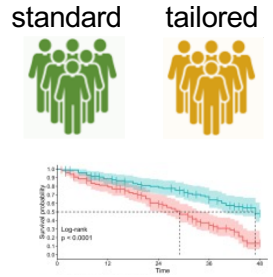


PK/PD/PGx Model Building



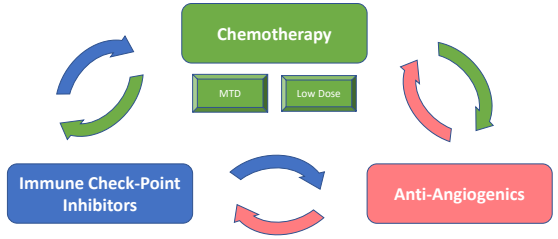
Dose tailoring tool

Comparative Phase 2 trials



Axis 3: Optimizing combinatorial strategies with immunotherapy

- Combining cytotoxics, anti-angiogenics and anti-PD1 pembrolizumab is a mainstay in NSCLC
- Concomitant dosing is the standard of care, regardless of possible sequence-effects.

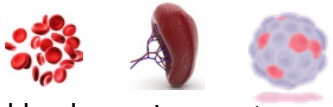


- Objectives: semi-mechanistic, mathematical model for driving this combination

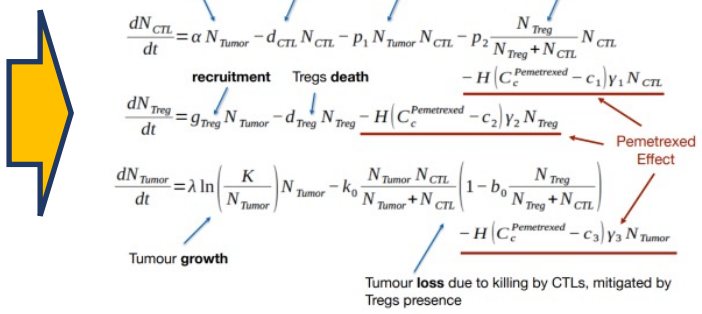
CTL **CDDP** **PTXD** **CDDP + PTXD + anti-VEGF**

MTD VS. Low MTD VS. Low MTD VS. Low

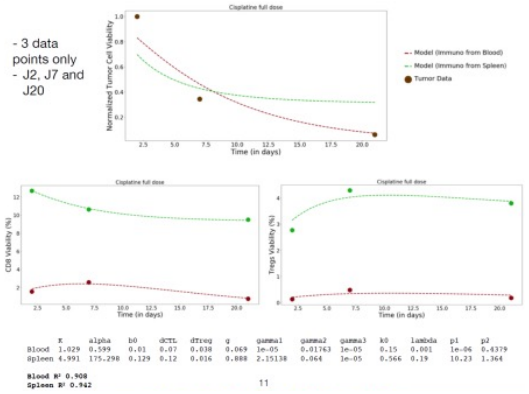
CD4+ CD8+ NK Tregs MDSCs Leuco



blood spleen tumor



Model Calibration



Modeling & Simulation

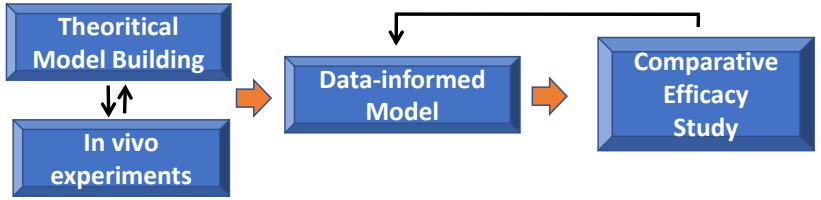
CDDP + PTXD + anti-VEGF + anti-PD1

Standard **Model**

VS.

- ✓ Efficacy
- ✓ Survival
- ✓ Safety

- Modeling the data of the GFPC phase III clinical trial pembro vs pembro + chemo

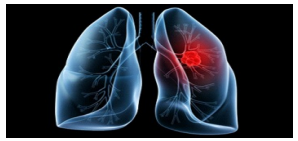


- Mid-term objective: model-based prospective, phase 2 trial

Take home message

WHO?

A muldisciplinary team
Bedside -> model -> bench -> bedside

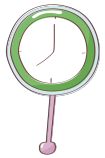


- 5 *in house* ongoing clinical trials

WHAT?

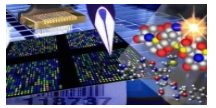
Drug combinations

Treatment schedules



Computational Oncology

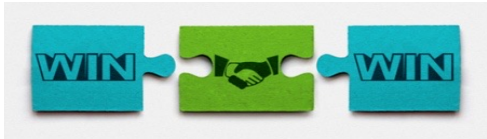
Mechanistic Learning



Clinical Trials

WHY?

Inria – Inserm :
a win-win strategy



- Data analysis and modeling
- Powerful clinical and experimental resources

Thank you for your attention!