Development of anti-cancer therapies targeting the tumor microenvironment

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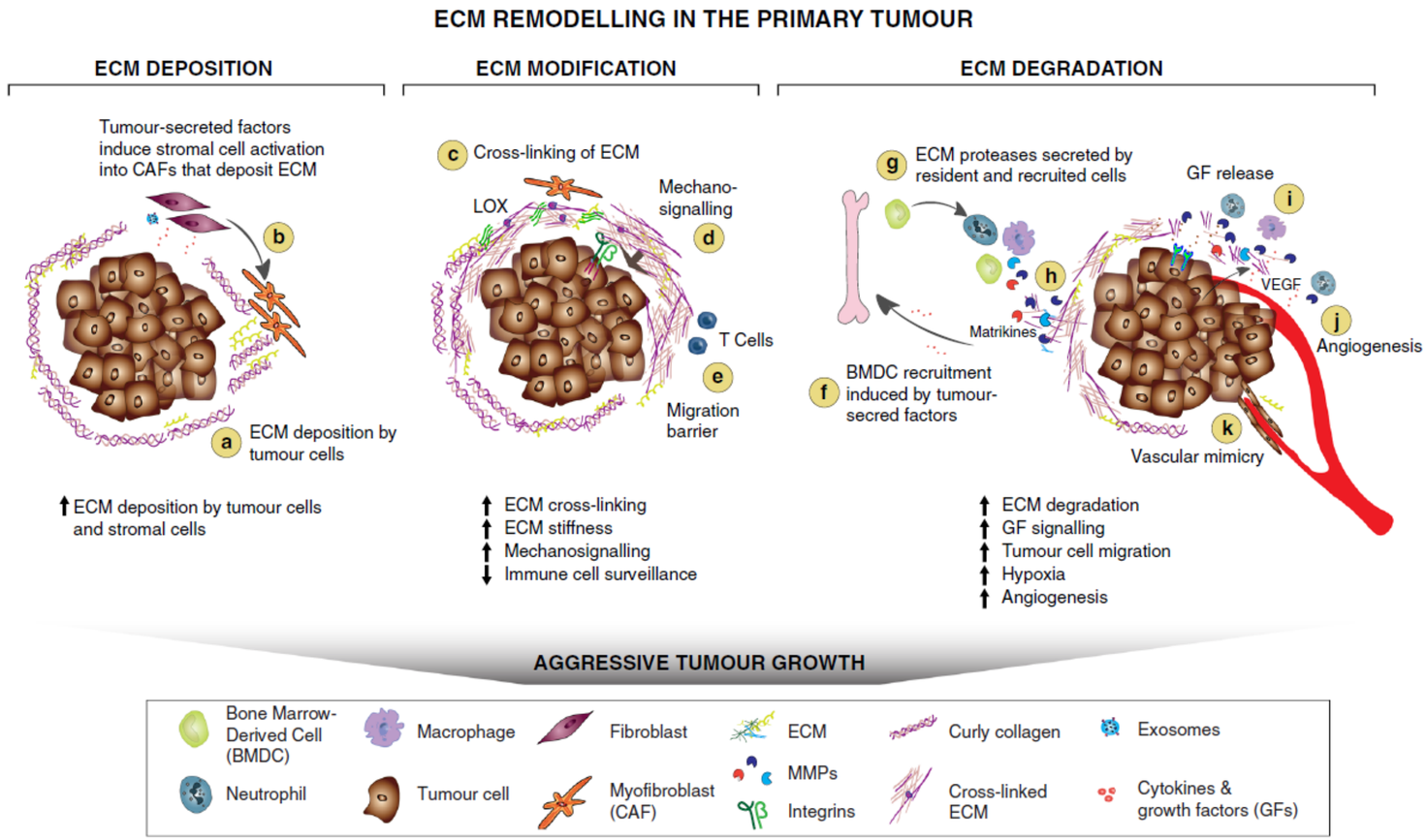
APMONIA THERAPEUTICS

CANCÉROPÔLE Est
Régions Bourgogne-Franche-Comté / Grand Est

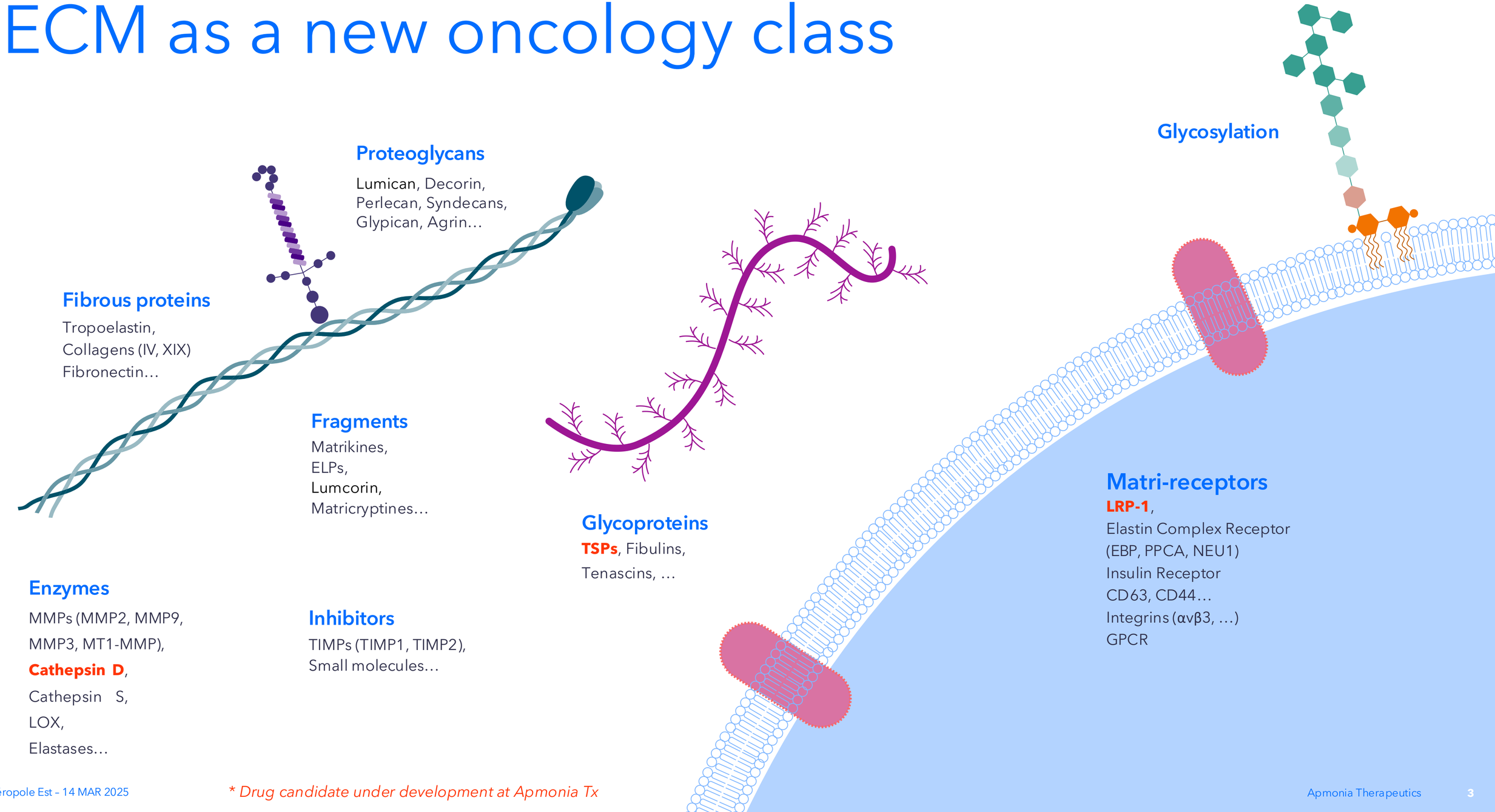
The ExtraCellular Matrix (ECM) in cancer

- A highly complex and dynamic structural network of macromolecules
- Surrounding cells and supporting tissues
- Long time wrongly regarded as inert
- A key regulator of cell communication
- Regulates and fine- tunes every cellular process in the body



ECM affects the behavior of cancer and stroma cells …
… which in turn influences the composition, organization, and stiffness of the ECM

ECM as a new oncology class



Proteoglycans

Lumican, Decorin,
Perlecan, Syndecans,
Glypican, Agrin…

Fibrous proteins

Tropoelastin,
Collagens (IV, XIX)
Fibronectin…

Fragments

Matrikines,
ELPs,
Lumcorin,
Matricryptines…

Glycoproteins

TSPs, Fibulins,
Tenascins, …

Glycosylation

Matri-receptors

LRP-1,
Elastin Complex Receptor
(EBP, PPCA, NEU1)
Insulin Receptor
CD63, CD44…
Integrins (αvβ3, …)
GPCR

Enzymes

MMPs (MMP2, MMP9,
MMP3, MT1-MMP),
Cathepsin D,
Cathepsin S,
LOX,
Elastases…

Inhibitors

TIMPs (TIMP1, TIMP2),
Small molecules…

** Drug candidate under development at Apmonia Tx*

Apmonia Tx: Versatile & Unique Platform to Target ECM in Oncology

Combining unique knowledge of ECM, cancer biology and molecular modeling

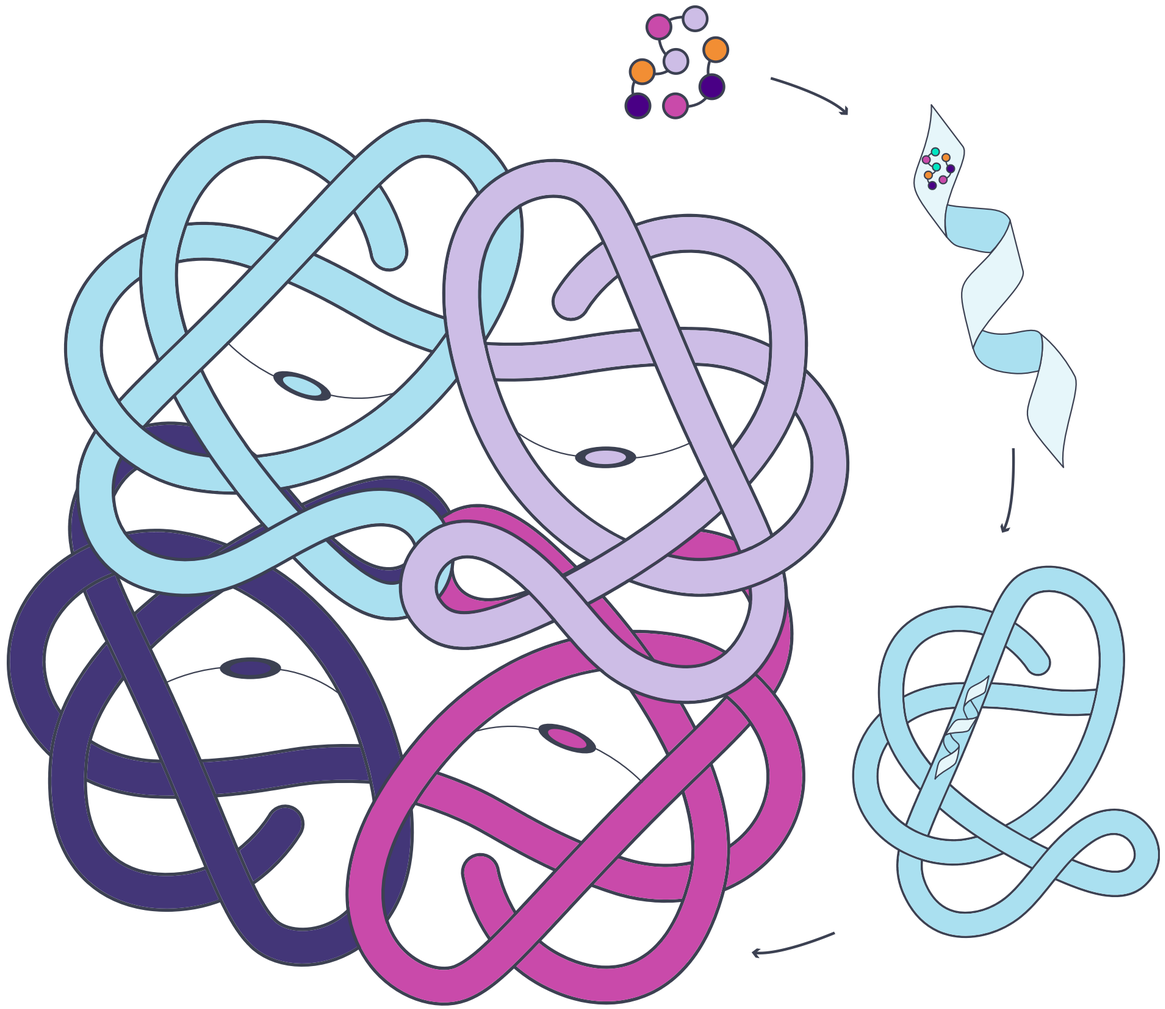
High performance computational engineering

- A powerful supercomputing platform to study the ECM (speed > 8 PetaFLOP):
- Structure-based drug discovery & development (screening & modeling)
- Validating the best pattern of interacting molecules w/ biological targets

Small peptides as extremely potent & selective drugs

- Tumor Stroma strongly differs from Normal
  One: Identify-Screen-Target Strategy
- Peptides can Selectively Address the Tumor with
  No Need to Enter the Cells

Using computation, biochemistry and cell biology, we take our proprietary candidates from non-clinical to early clinical validation.



Apmonia Tx core team

Management

Albin JEANNE
CEO & CSO / Co-Founder
Ph.D. Biochemistry
Management & Business

Sylvie GODEFROY
Chief Operating Officer
Ph.D. Immunology
Operational Management

Clinical Department

Hafedh HADDAD
Medical Director
M.D.
>20y Clinical Development

Estelle GEFFARD
Clinical Project Manager
M.Sc. Biomedical sciences
>25y Clinical Expertise

Linda LEBON
Chief Regulatory Officer
M.Sc., M.B.A.
25y Science & Regulatory

R&D Department

Non-clinical Team

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Matrix Biology

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M.Sc. Molecular & Cell Biology

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Lab Associate
Biology Bachelor's degree

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Discovery Project Manager
Ph.D. Immunology
>10y Biotech exp. (Discovery)

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Vascular Biology

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Molecular Docking & Dynamics

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Ph.D. Biophysics
Molecular Docking & Dynamics

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University Professor

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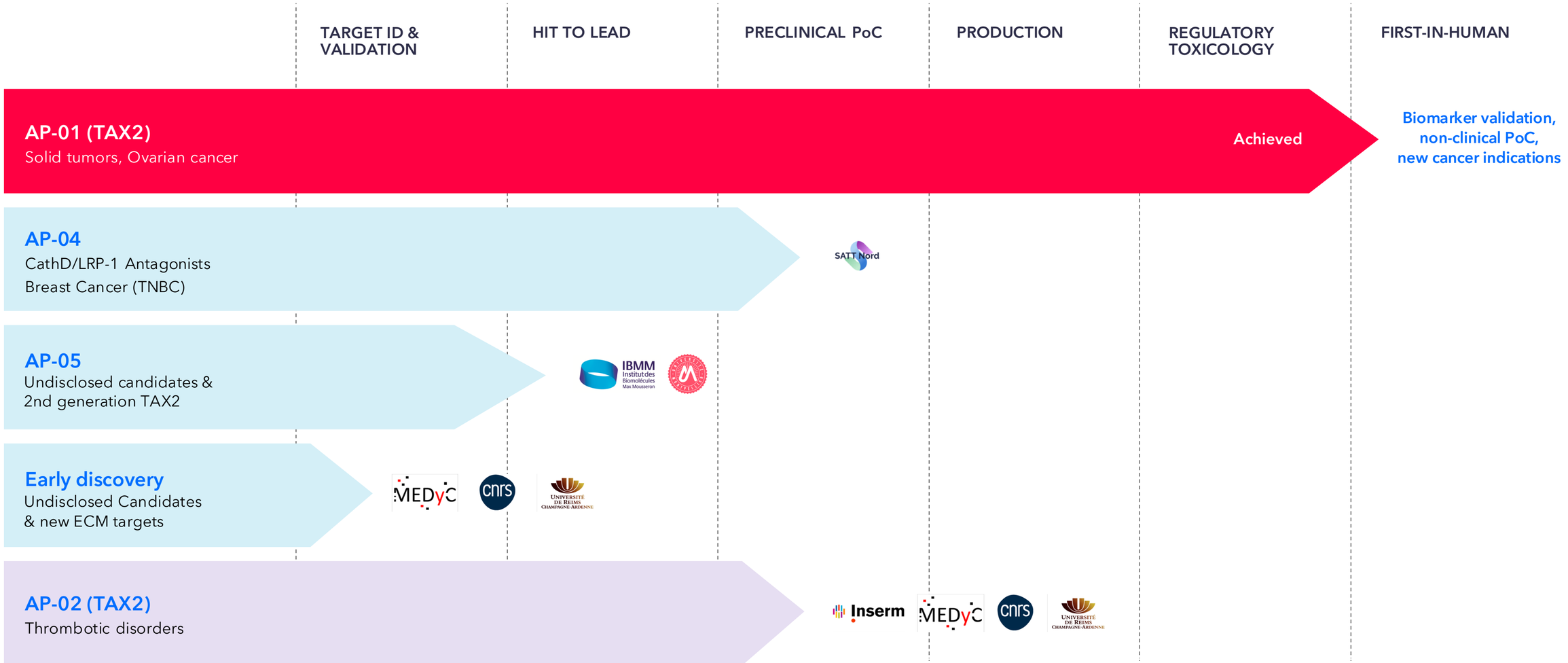
Immuno-Oncology
PhD Life Sciences
Research Director

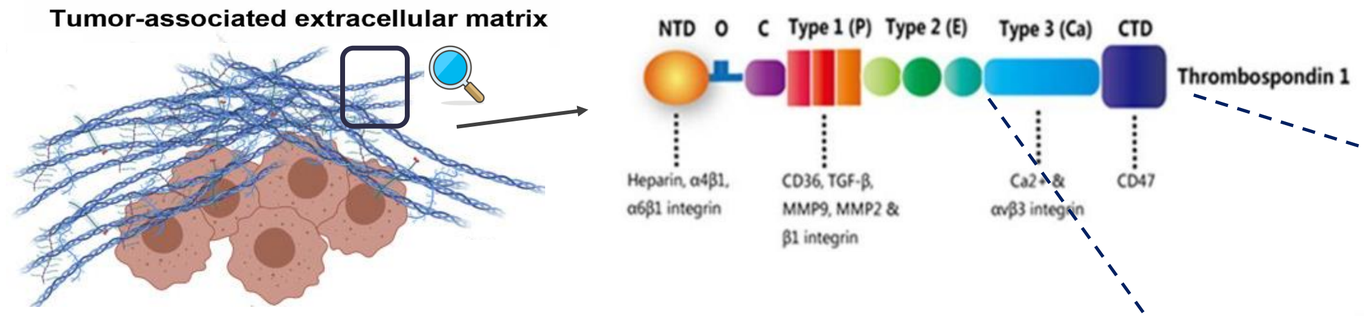
Pr. Olivier BOUCHE
Digestive Oncology
Medical oncologist

Pipeline of drug candidate development

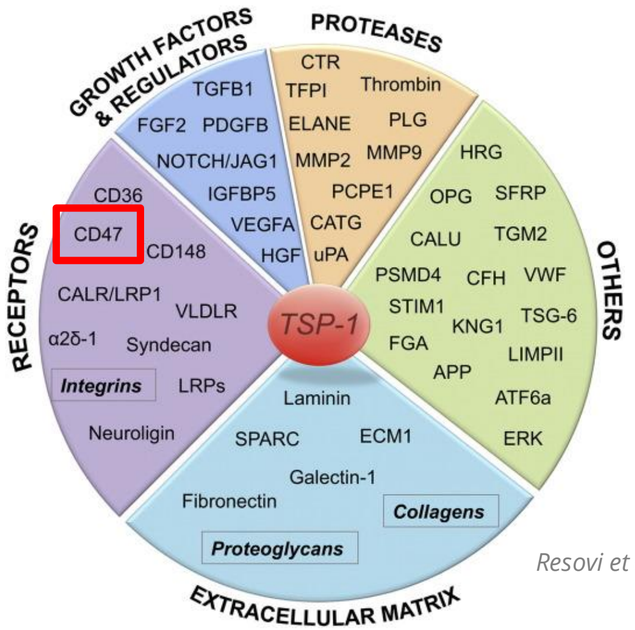
Our collaborations have already generated several peptide-based potential drugs



Thrombospondin-1 (TSP-1): a main (complex) actor within tumor microenvironment

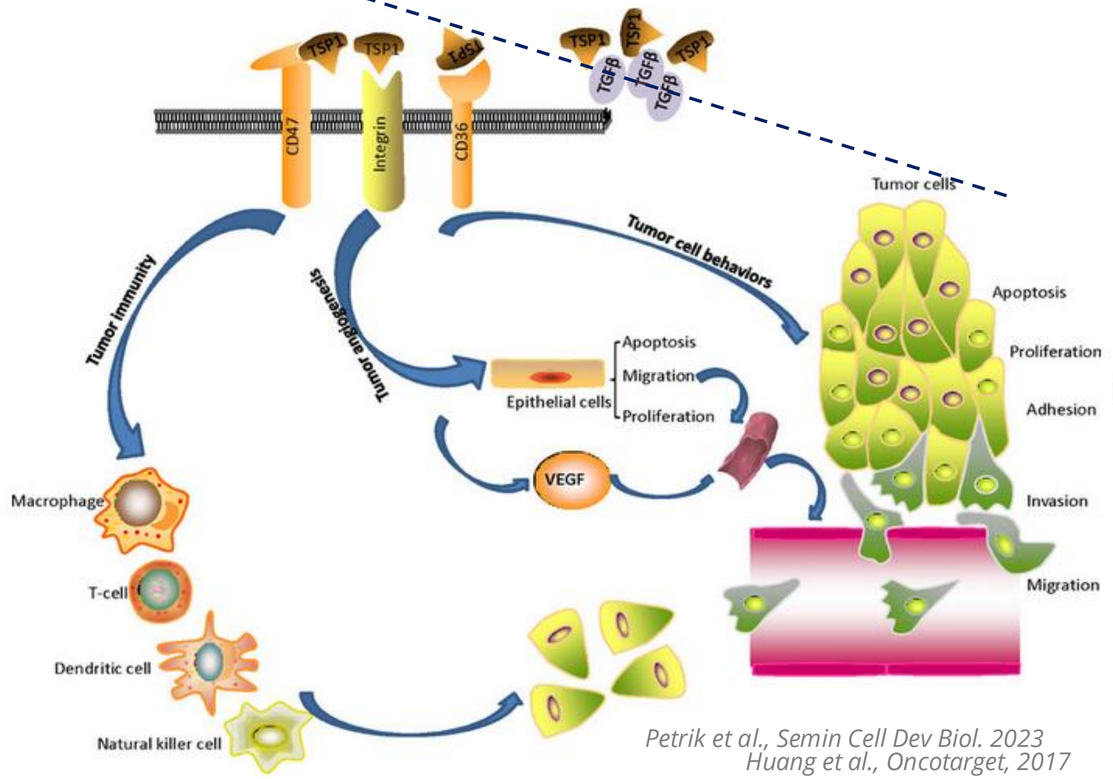


- A trimeric multi-modular and multifunctional protein
- A wide variety of ligands



Resovi et al., Matrix Biol, 2014

Pleiotropic activities on cancer progression

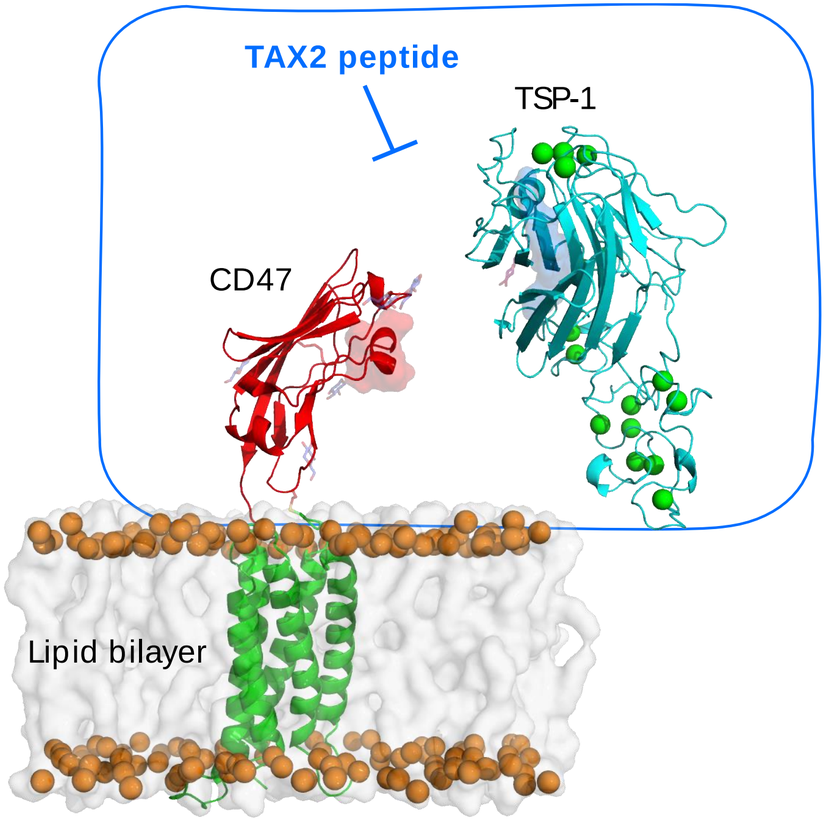


Petrik et al., Semin Cell Dev Biol. 2023
Huang et al., Oncotarget, 2017

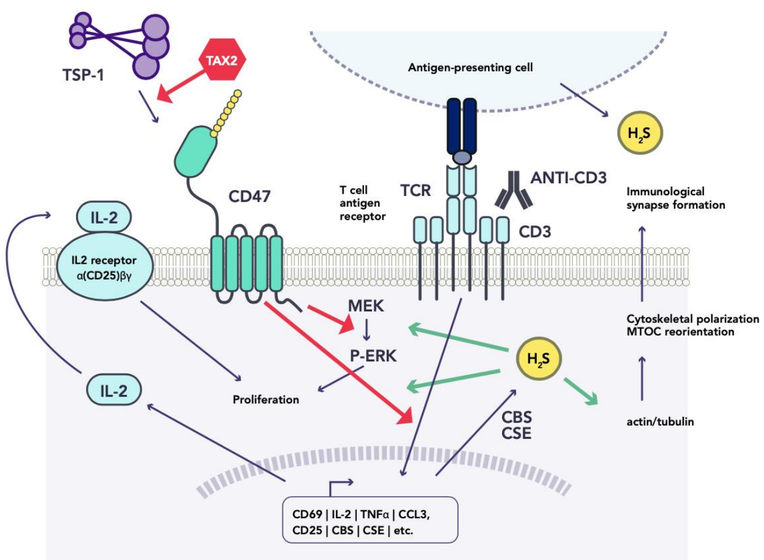
⚠ **TSP-1 concentration, origin, temporality…**

A new approach of TSP-1:CD47 antagonization

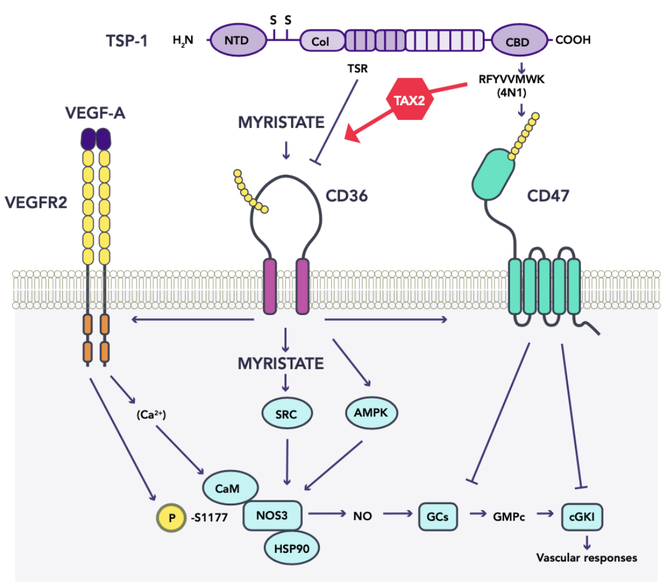
TAX2 peptide is the first-ever selective antagonist for CD47 receptor activation by thrombospondin-1 (TSP-1), with multiple proof-of-concept in tumor animal models



Mechanism of Action



TAX2 peptide stimulates T lymphocytes differentiation, activation and proliferation



TAX2 peptide redundantly inhibits tumor-associated vascularization

TAX2 displays a high pan-cancer anti-tumor activity

Overview of non-clinical data

	Model	Doses	Treatment schedule	Tumor response
Human xenografts *(inbred & outbred mice)*	A375 melanoma	30 mg/kg BW - i.p.	3X/w (4 w) from tumor volume > 200 mm^3	↘ tumor infiltration, ↗necrosis, altered blood flow
	SK-N-BE(2) & SK-N-SH neuroblastoma	**30 to 100 mg/kg BW - i.p.**	3X/w (3 w) from **tumor volume > 500 mm^3**	↘ tumor growth (**15% CR** ; 30% SD), ↗ survival, altered blood flow
	Capan-1 & MIA PaCa-2 pancreatic carcinoma	**10 mg/kg BW - i.p.**	3X/w (4-5 w) from tumor volume > 200 mm^3	- 50 % tumor growth, inhibition of vascularization
	A2780 & SK-OV-3 ovarian carcinoma	10 mg/kg BW - i.p.	**3X/w (3-7 w)**	- 50 % tumor growth, increased survival **(several w post-treatment)**
PDX	P3 & NCH421k glioblastoma	10 mg/kg BW - i.p.	3X/w (3 w)	↘ tumor invasion, ↗necrosis, inhibition of vascularization
Syngeneic tumors *(heterotopic & orthotopic)*	B16F1 melanoma (s.c.)	10 mg/kg BW - i.p.	**days 3, 5 and 7 post tumor cells inoculation**	**+ 130 % lymphocytic infiltration**, tumor necrosis, inhibition of vascularization
	B16F10 melanoma (i.v.)	10 mg/kg BW - i.p.	3X/w (3 w)	**inhibition of metastatic dissemination, inhibition of pre-established metastases growth**
	ID8 ovarian carcinoma (s.c.)	30 mg/kg BW - i.p.	3X/w (4 w)	↗ **CD4+ and CD8+ tumor infiltration**, - 40 % tumor growth, tumor necrosis
	ID8 ovarian carcinoma (i.p.)	30 mg/kg BW - i.p.	3X/w (8 w)	↗ **CD4+ and CD8+ recruitment**, IFN-γ ascites production, **inhibition of metastatic dissemination**
	Genetically engineered ID8 ovarian carcinoma	30 mg/kg BW - **i.v.**	3X/w (4 w)	Significant improvement of anti-PD1 treatment when combined with TAX2 (**Survival**)
	Genetically engineered ID8 ovarian carcinoma	30 mg/kg BW - **i.v.**	3X/w (4 w)	**Improved survival** both as a stand-alone and as a second-line post PARPinh recurrence

Selected publications:

Moniot et al, Molecular Cancer 2024

Jeanne et al, Cancers 2021

Daubon et al, Nature Communications 2019

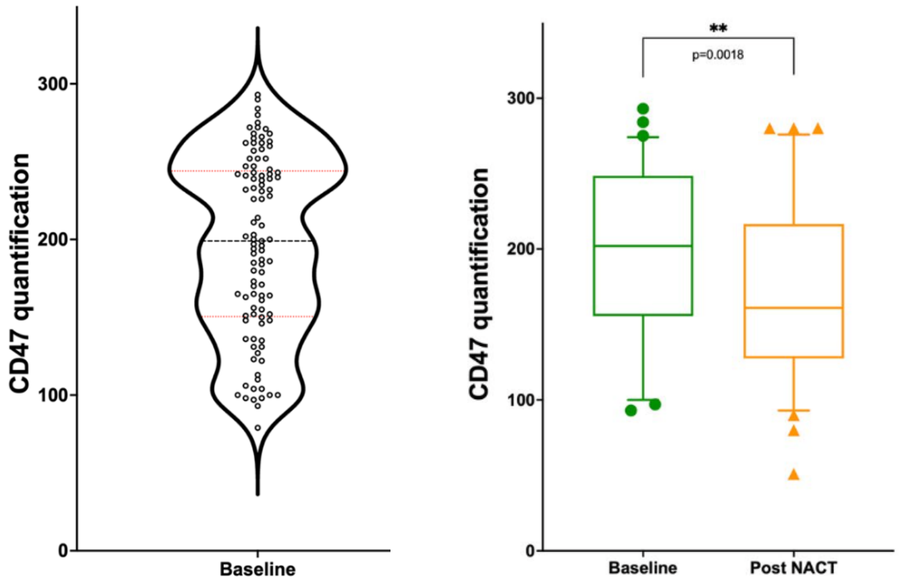
Jeanne et al, Scientific Reports 2017

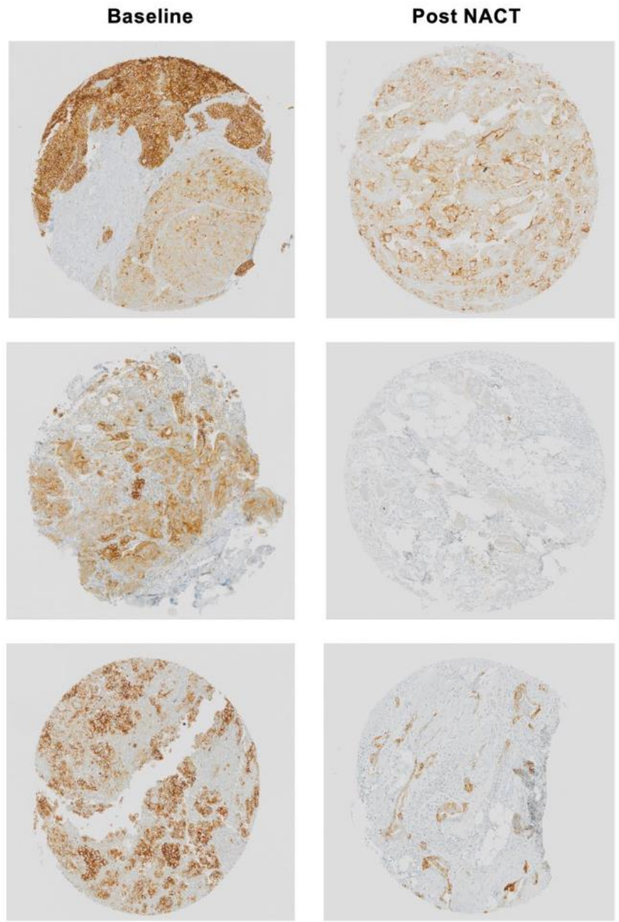
Jeanne et al, Pediatric Research 2017

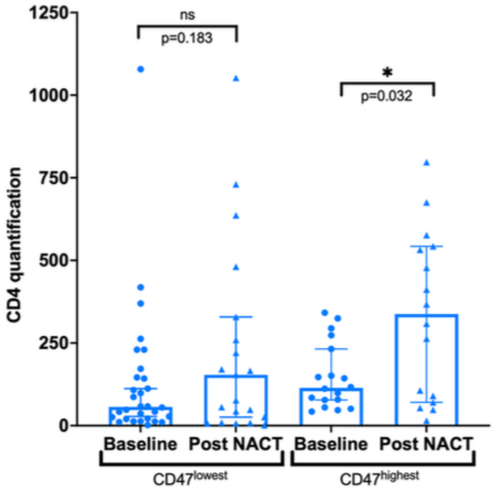
Jeanne et al, Clin Exp Metastasis 2016

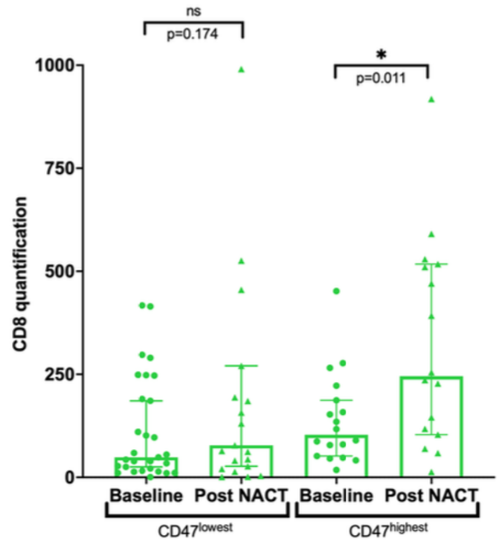
Jeanne et al, Oncotarget 2015

Biomarker identification from retrospective clinical cohorts





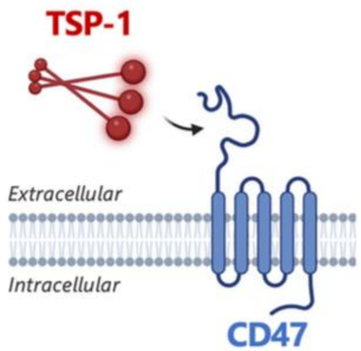


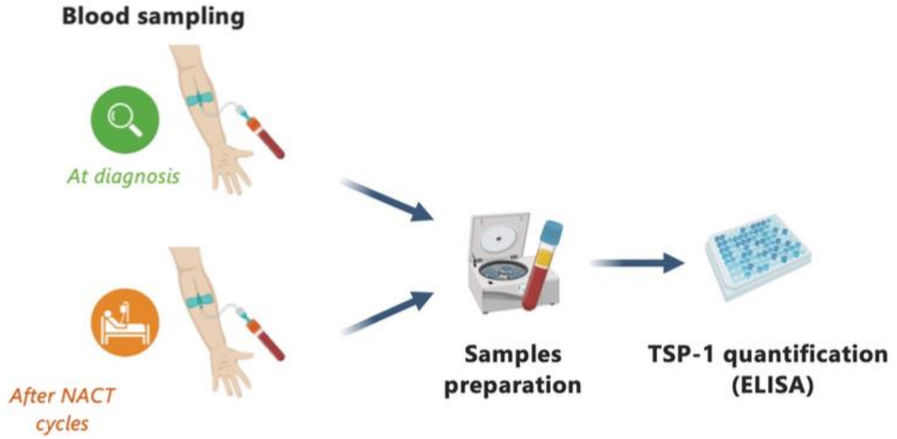


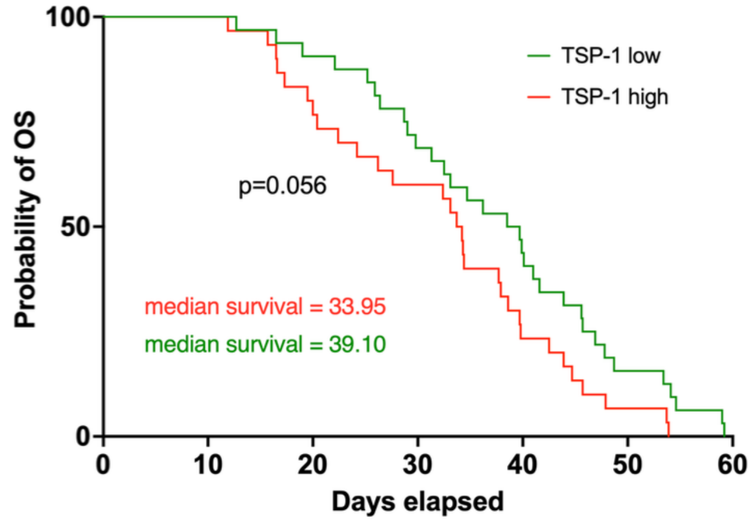
Moniot et al, Molecular Cancer 2024

CD47 levels correlate with CD8 and CD4 infiltration after NACT only in the population with highest CD47 expression

Biomarker identification from retrospective clinical cohorts







Moniot et al, Molecular Cancer 2024

Lower overall patient survival correlated with elevated plasma TSP-1 levels

TAX2 activates Adaptive Immune Response in OC

ID8 OVARIAN CARCINOMA (OC): a late-stage model of syngeneic epithelial OC

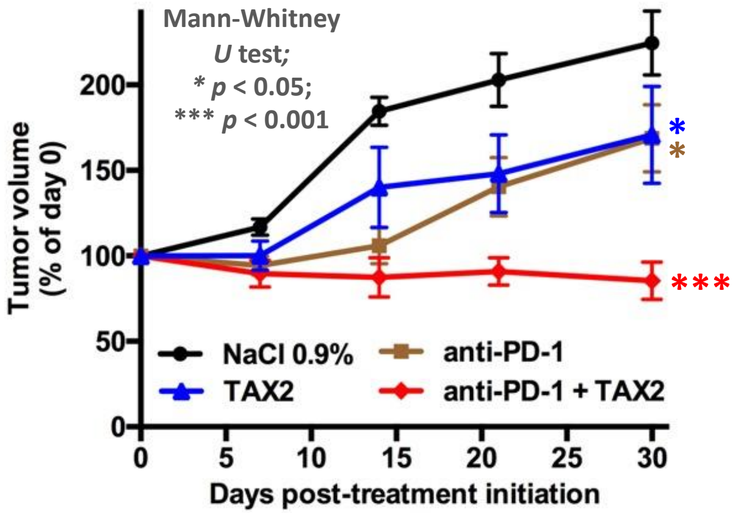
TAX2 treatment starts after 21 weeks tumor growth, for a 4 weeks duration *(30 mg.kg^{-1} BW ; 3X/w)*

Day 0: Mouse ovarian carcinoma cell inoculation (5×10^6 cells)

ID8 SUBCUTANEOUS ALLOGRAFTS

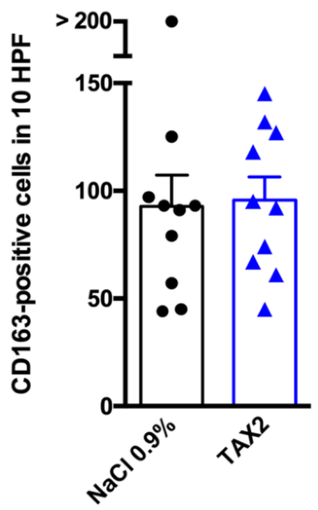
TUMOR ANALYSIS

TUMOR GROWTH

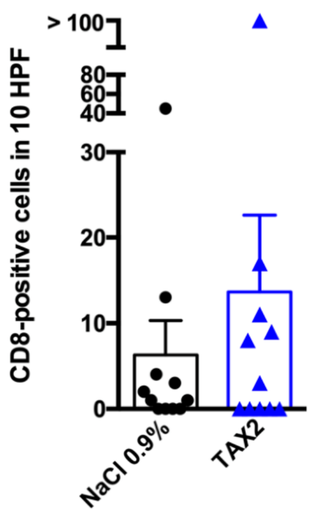


TUMOR ANALYSIS

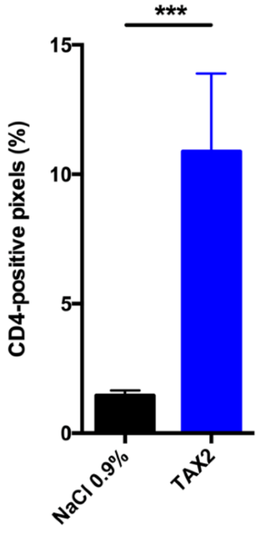
Macrophages (no effect)



Cytotoxic T-cells (increased)

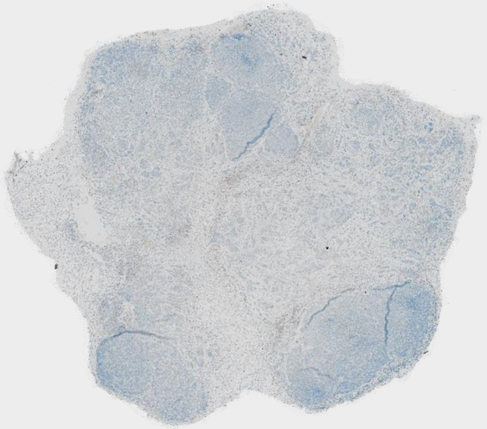


Helper T-cells (increased)

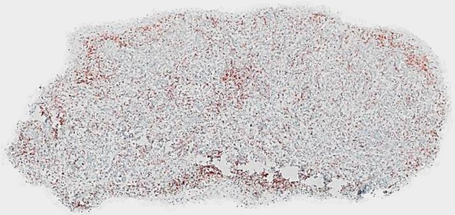


Tumor-infiltrating lymphocytes (TILs)

Ctrl



TAX2



TAX2 activates Adaptive Immune Response in OC

ID8 Orthotopic Implantation: a very aggressive translational model

Peritoneal carcinomatosis due to ID8 i.p. dissemination mimicks stage IV ovarian cancer settings

Day 0: Mouse ovarian carcinoma cell inoculation (5×10^6 cells)

ID8 PERITONEAL CARCINOMATOSIS

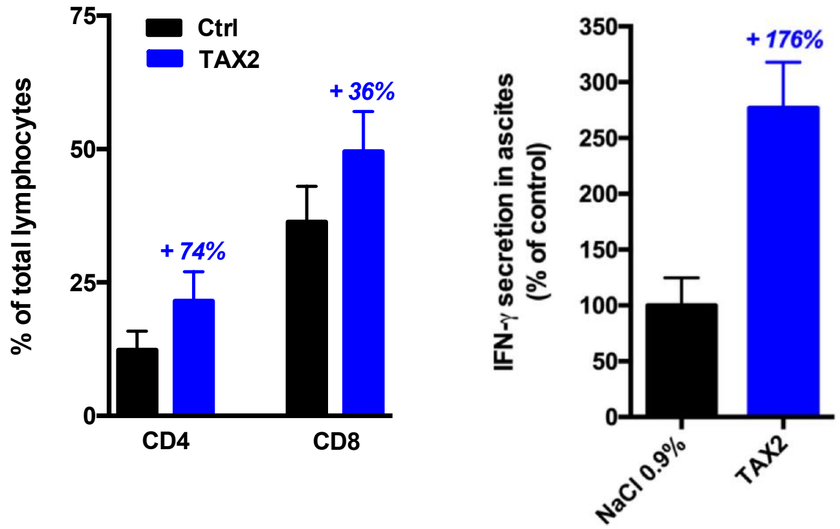
Day 14 — Day 74 — Day 94

TAX2 (30 mg.kg^{-1} BW ; 3X/w)

ASCITES ANALYSIS & NECROPSY

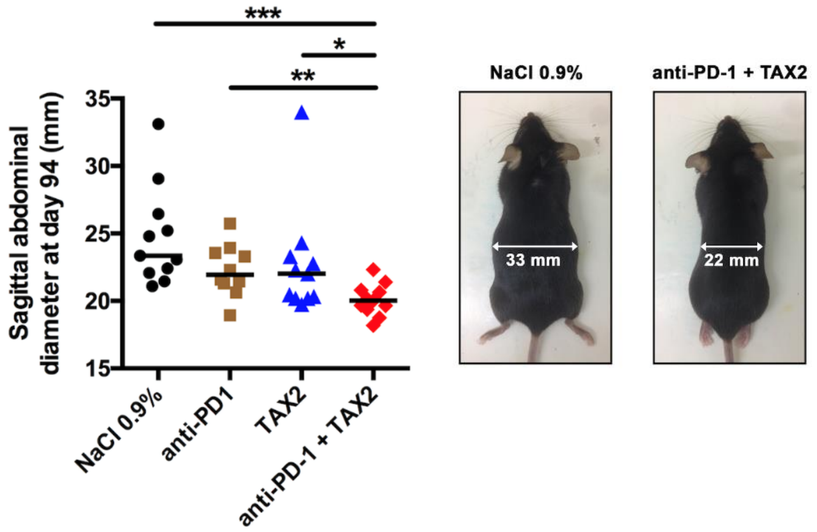
ASCITES COMPOSITION

Helper T cells (increased) | Cytotoxic T cells (increased) | Interferon gamma (increased)



ASCITES FLUID PRODUCTION

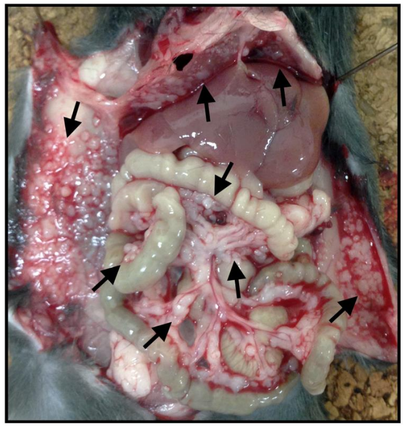
Abdominal volume (reduced)



NECROPSY

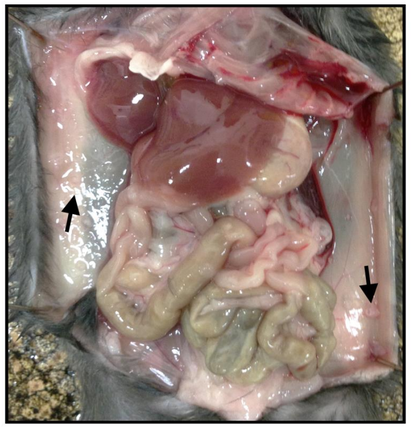
Wide tumor spread

NaCl 0.9%



Reduced tumor spread

anti-PD-1 + TAX2

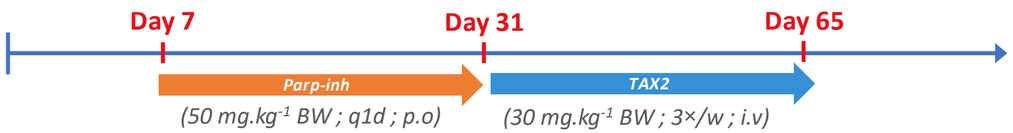


Efficacy : ID8 *Trp*53$^{-/-}$ *Brca2*$^{-/-}$ OC Allograft Model

There is still a high unmet medical need for OC patients experiencing post-PARPinh recurrence

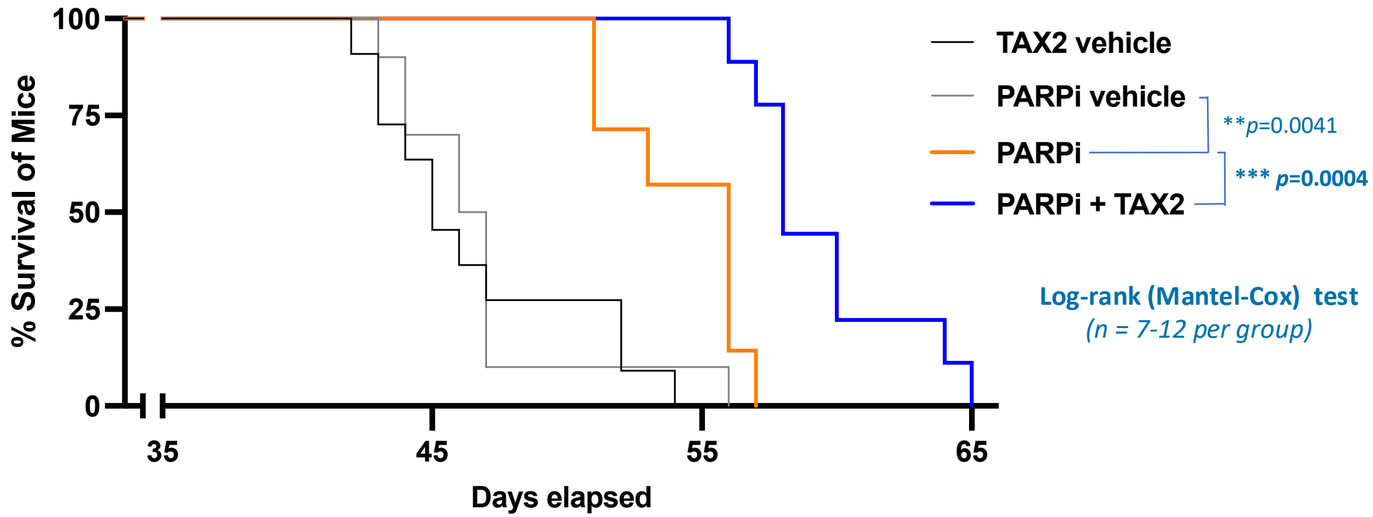
Day 0: Mouse ovarian carcinoma cell inoculation (2×10^6 cells)

ID8 PERITONEAL CARCINOMATOSIS



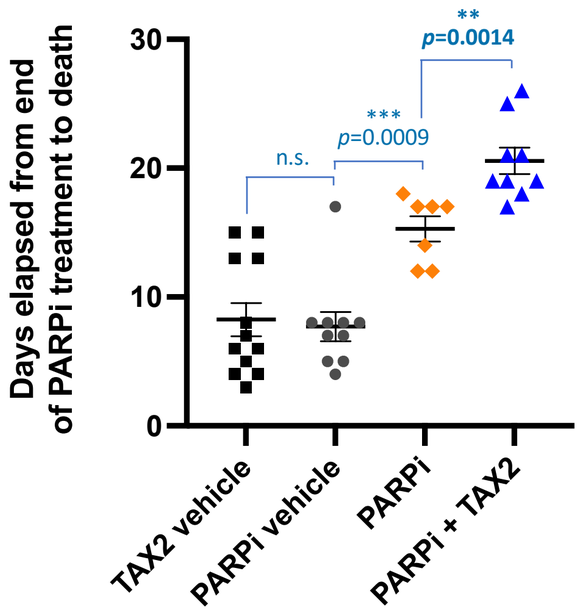
OVERALL SURVIVAL ANALYSIS

Kaplan-Meier Overall Survival Analysis



Log-rank (Mantel-Cox) test
(n = 7-12 per group)

Time to Death



Mann-Whitney *U* test
(n = 7-12 per group)

Mouse survival is significantly improved for PARPi + TAX2 combination therapy arm relative to PARPi monotherapy

AP-01: Optimized & druggable first-in-class NCE

A competing 12 a.a. Cyclic Peptide (i.v. administration)

Completed CMC

GMP-ready process (kg scale)
GLP-validated analytical & bioanalytical methods

Favorable Safety profile

GLP toxicology and safety pharmacology performed in rats & dogs

Proven Efficacy in 15 mouse models

Strong non-clinical data package (PoC, PK/PD, Biodistribution) w/established MoA

Clinical Relevance

Validated clinical biomarkers & rationale for patient stratification

Regulatory Plan

Preclinical & clinical (FiH) strategy has been endorsed by reg. agency (FAMHP)

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APMONIA THERAPEUTICS

Co-funded by the European Union

FRANCE 2030

Targeting the ECM is a frontier of discovery.
We are breaking new boundaries in the fight against cancer, join us.

THANK YOU FOR YOUR ATTENTION