1st Edition

ABSTRACTS BOOK

CRCM
CANCER RESEARCH CENTER
Marseille

# CRCM Symposium

## CANCER RESEARCH CENTER MARSEILLE

Comet
Cell communication & Microenvironment dpt.

Translate-IT
Translational research & Innovative therapies dpt.

**4 - 6 February 2026**

**MARSEILLE**
Palais du Pharo

### CONFIRMED SPEAKERS

**Frédéric Bard** *(Marseille, France)*
**Martin Bergö** *(Stockholm, Sweden)*
**René Bernards** *(Amsterdam, The Netherlands)*
**François Bertucci** *(Marseille, France)*
**Brice Chanez** *(Marseille, France)*
**Raffaele Colombo** *(Vancouver, Canada)*
**Nelson Dusetti** *(Marseille, France)*
**Greta Mattavelli** *(Germany)*
**Patrick Mehlen** *(Lyon, France)*
**Gérard Milano** *(Nice, France)*
**Javad Nazarian** *(Zurich, Switzerland)*
**Angela Nieto** *(Alicante, Spain)*
**Thales Papagiannakopoulos** *(New York, USA)*
**Gabriel Revon-Riviere** *(Marseille, France)*
**Giorgio Seano** *(Paris, France)*
**Sophie Tartare-Deckert** *(Nice, France)*
**Alissa Weaver** *(Nashville, USA)*
**Mattia Zampieri** *(Basel, Switzerland)*

### TOPICS/SESSIONS

**Innovative therapies**
**Tumor microenvironment & cellular cross-talk**
**Challenging sites of tumorigenesis: junior scientist session**
**Cancer progression and treatments**

This event is supported by the City of Marseille.

### ORGANIZING COMMITTEE

**Joseph Ciccolini, Nelson Dusetti, Christophe Ginestier, Luca Lignitto, Emilie Mamessier, Eddy Pasquier, Sophie Vasseur**

*With the valuable support of the junior researchers:*
***Agathe Cohendet, Georgios Efthymiou, Julie Lafont, Raphael Leblanc, Shuheng Lin, Maëlle Picard, Celia Sequera-Hurtado, Romain Zakrajsek***

With the institutional support of

1st Edition
CRCM Symposium
CANCER RESEARCH CENTER MARSEILLE
CRCM CANCER RESEARCH CENTER Marseille
Comet Cell communication & Microenvironment dpt.
Translate-IT Translational research & Innovative therapies dpt.
4 - 6 February 2026
MARSEILLE
Palais du Pharo

## SESSION 2 : - TUMOR MICROENVIRONMENT AND CELLULAR CROSS-TALK - Part 2

### CO01 : Assessing the spatial interplay of Tumor Heterogeneity and its microenvironment in Breast Cancer

*Zeinab Homayed*

**Authors:**
Zeinab Homayed (1), Martin Castagne (1), Maria Victoria Regge (2), Julien Wicinski (1), Olivier Rosnet (1), Geoffrey Guittard (2), Christophe Ginestier (1), Emmanuelle Charafe (1)

*1. COMET, CRCM, Marseille, France*
*2. Ohio, CRCM, Marseille, France*

**Keywords:** Intratumor heterogeneity, immune escape, spatial transcriptomics

**Introduction:**
Intratumoral heterogeneity (ITH), encompassing both genetic and non-genetic variation, is a key driver of tumor evolution and therapeutic resistance. It leads to the coexistence of phenotypically and functionally distinct tumor cell populations within a single lesion, each governed by specific transcriptional programs. In parallel, the fate of tumor cells is not solely determined by intrinsic features but is also shaped by interactions with the surrounding tumor microenvironment (TME), which plays a central role in tumor progression and treatment resistance. Deciphering the spatial organization and functional interplay between ITH and the TME is essential to understand mechanisms of immune escape and therapeutic failure. Thus, we aim to characterize how intratumoral heterogeneity is spatially organized within the TME and to determine whether these spatial relationships drive immune evasion and contribute to failure of anti-tumor immune responses.

**Method:**
We employ complementary approaches to dissect the interplay between intratumoral heterogeneity and the immune microenvironment. First, we use breast cancer cell line models recapitulating intratumoral heterogeneity to interrogate tumor–immune interactions through functional co-culture assays. Second, spatial transcriptomic analysis of patient tumor sections is used to map distinct tumor cell states and immune cell populations within the TME, revealing how immune infiltration patterns correlate with specific tumor cell states.

**Results:**
Functional co-culture assays identify differential immune susceptibility across tumor cell populations, enabling the derivation of a resistanceassociated transcriptional signature. In parallel, spatial omics analysis reveals organized immune infiltration patterns aligned with distinct tumor cell identities. Moreover, this resistance signature is expressed by a specific tumor cell state that spatially correlates with immune exclusion and altered immune infiltration patterns, validating the biological relevance of the signature and supporting its use in a CRISPRi screen to identify novel mediators of immune escape.

**Discussion:**
The spatial interplay between tumor heterogeneity and immune cell distribution is a key determinant of immune evasion, yet remains poorly characterized. By revealing which tumor cell states drive immune escape, we can decode mechanisms underlying resistance and identify new therapeutic targets.

**Conclusion:**
By integrating complementary functional and spatial approaches, this work elucidates mechanisms by which intratumoral heterogeneity facilitates immune escape in breast cancer and highlights candidate targets for overcoming resistance.

1st Edition
CRCM Symposium
CANCER RESEARCH CENTER MARSEILLE
CRCM CANCER RESEARCH CENTER Marseille
Comet Cell communication & Microenvironment dpt.
Translate-IT Translational research & Innovative therapies dpt.
4 - 6 February 2026
MARSEILLE
Palais du Pharo

## SESSION 2 : - TUMOR MICROENVIRONMENT AND CELLULAR CROSS-TALK - Part 2

# CO02 : A humanized in vitro model to explore neuron-cancer interactions

*Teraraina Flavie Chung Shing*

**Authors:**
Teraraina Flavie Chung Shing (1), Alex Chauvin (2), Philippe Soubeyran (2), Ana Maria Borges Correia (3), Robson Francisco Carvalho (4), Nelson Dusetti (2), Maxime Cazorla (3), Fanny Mann (5), Sophie Chauvet (5)

*1. Institute of Developmental Biology of Marseille, Marseille, France*
*2. CRCM, Marseille, France*
*3. Institut de Neurosciences de la Timone, Marseille, France*
*4. Institute of Biosciences, Sao Paulo, Brazil*
*5. Institute of Developmental Biology of Marseille, Marseille, France*

**Keywords:** CANCER NEUROSCIENCE, PDAC, ORGAN-ON-CHIP, AXON GROWTH

**Introduction**
Advances in cancer neuroscience demonstrate that the peripheral nervous system actively contributes to cancer progression, rather than passively responding to it. Tumors reshape the surrounding neuronal circuits, and sensory neurons promote tumor growth through direct interactions and bioactive signals. This bidirectional crosstalk is particularly evident in pancreatic ductal adenocarcinoma (PDAC). Our team has demonstrated that sensory neurons undergo extensive remodeling within PDAC lesions. Although targeting this neuronal plasticity could limit PDAC progression, the molecular cues driving PDAC innervation remain largely unknown. Given the close interaction between axons and PDAC cells, we hypothesized that PDAC cells actively promote sensory innervation by releasing factors that attract axons within the tumor.

**Method :**
Rodent dorsal root ganglia (DRG)-like nociceptors and mechanoreceptors were cultured in a bicompartmentalized organ-on-a-chip device and exposed to conditioned media (CM) from the human PDAC cell lines Panc1 and MiaPaCa2. Candidate secreted factors were identified via multi-omics meta-analysis, which combined secretomic and transcriptomic data. We validated secretion levels using ELISA and tested axon outgrowth with neutralizing antibodies on rodent and human induced pluripotent stem cell (iPSC)-derived sensory neurons. In parallel, we used patient-derived PDAC lines to evaluate whether our system could capture differential sensory neuron responses to clinically relevant tumor variants.

**Results :**
We found that the CM of Panc1, but not MiaPaCa2, cells promotes the growth of sensory axons in nociceptor-like neuron cell lines, but not mechanoreceptor-like ones. We identified GDF15 (growth differentiation factor 15) and DKK1 (Dickkopf-1) as potential candidates for inducing sensory axon outgrowth. These proteins are overexpressed by Panc1 cells compared to MiaPaCa2 cells. Functional validation of the two candidates revealed that recombinant GDF15 and DKK1 proteins increase the axon length of rodent nociceptors. Furthermore, blocking GDF15 and DKK1 specifically in Panc1 CM but not in MiaPaCa2 CM reduced the axon length of rodent and human iPSC-derived sensory nociceptor neurons. Screening of patient-derived PDAC lines confirmed GDF15 and DKK1 as relevant clinical candidates. GDF15 is broadly overexpressed and strongly associated with classical PurIST/PAMG signatures, while DKK1 correlates with gemcitabine resistance. Next, we will test how these patient-derived lines affect human sensory neurons differently.

**Discussion :**
Our results demonstrate that PDAC cells stimulate pro-tumor sensory axon remodeling by secreting GDF15 and DKK1. Since both factors promote tumor growth and their expression in patient-derived lines correlates with classical signatures and chemoresistance, targeting them could limit tumor progression and the pro-tumor influence of sensory neurons simultaneously.

1st Edition
CRCM Symposium
CANCER RESEARCH CENTER MARSEILLE
CRCM CANCER RESEARCH CENTER Marseille
Comet Cell communication & Microenvironment dpt.
Translate-IT Translational research & Innovative therapies dpt.
4 - 6 February 2026
MARSEILLE
Palais du Pharo

## SESSION 2 : - TUMOR MICROENVIRONMENT AND CELLULAR CROSS-TALK - Part 2

### CO03 : Evaluation of the predictive value of Organoid-derived Extracellular Vesicles for tumor progression and Microenvironment-mediated resistance to FOLFIRINOX

*Christopher Rovera*

**Authors:**
C. Ravera, C. Montenegro, P. Bertrand, D. Belghoula, Z. Hussain, H. Benistant, T. Bremont, M-E. Acioli, S. Tubiana, F. Matrand, J. Roques, N. Dusetti, S. Audebert, L. Camoin, F. Guillaumond, S. Vasseur, R. Tomasini

Resistance to chemotherapy in pancreatic ductal adenocarcinoma (PDAC) is due to molecular alterations in tumour cells and their microenvironment. Tumour cells modify and educate neighbouring and distant cells to create a supportive microenvironment. This stroma is composed of cancer-associated fibroblasts (CAFs) and the extracellular matrix they produce or degrade, regulating tumour proliferation, invasion and chemoresistance. There is growing evidence that extracellular vesicles (EVs) play a key role in tumour intercellular dialogue and may be effective biomarkers of cancer progression. However, few studies take into account the intra-tumour and inter-patient heterogeneity of tumour cells and CAFs, resulting in a lack of tools for predicting the onset of metastasis and response to treatment.

We took advantage of the availability, here in Marseille, of a large cohort of PDAC-patient-derived tumor cells organoids (Pacaomics), and our own biobank of CAFs we have in the lab. By combining in vitro models of inter-cellular dialogue and mass spectrometry proteomics (LC-MS/MS), we aim to identify biomarkers of tumor progression and chemotherapeutic resistance.

First, we characterized the composition of the EVs (vesiculome) from 26 different organoids. The analysis of this vesiculome clusterize together non-detected metastasis patients with a poor survival (« borderline patients ») and patients with metastasis, at the contrary of resected patients, suggesting that organoid EVs can have a predictive value.

Second, we analyzed the response of CAF treated with organoid EVs and the proteomic composition of the matrix they produce (matrisome). Interestingly, the analysis of this matrisome clusterize together again the matrices of CAF treated with the borderline patients organoid-derived EVs and the one from patients with metastasis. Our results suggest that the content of organoid EVs is efficiently processed by CAF in the matrix and that the matrix can also be a source of specific signature related to the clinical picture of patients.

Using a tumour spheroid model, we analysed the sensitivity of tumour cells to FOLFIRINOX when exposed to organoid EVs. This test identifies two groups of EVs, one protecting against the cytostatic effects of FOLFIRINOX and the other not, which differ from the clinical classification. Moreover, we directly co-cultured organoids in the matrix of CAFs treated with organoid EVs and analysed their response to FOLFIRINOX. This test also identifies two groups of matrices linked to different levels of sensitivity to FOLFIRINOX.

Using these different models, we identify extracellular vesicles and matrices associated with chemoresistance that enable patients to be classified differently from the usual clinical diagnosis. We are now reimposing this new clustering on the proteomics data in order to identify and validate vesicular and matrix signatures specific to the response to chemotherapy. Finally, this work could identify new biomarkers and therapeutic targets to prevent PDAC progression and give clinicians new tools to guide patients towards the best treatment they need.

1st Edition
CRCM Symposium
CANCER RESEARCH CENTER MARSEILLE
CRCM CANCER RESEARCH CENTER Marseille
Comet Cell communication & Microenvironment dpt.
Translate-IT Translational research & Innovative therapies dpt.
4 - 6 February 2026
MARSEILLE
Palais du Pharo

## SESSION 2 : - TUMOR MICROENVIRONMENT AND CELLULAR CROSS-TALK - Part 2

### CO04 : Metastatic potential of colorectal cancer is regulated by an EphA2-PTK7 crosstalk

*Charlotte Dessaux*

**Authors:**
Charlotte Dessaux (1), Constantin Semenchenko (2), Laëtitia Ganier (2), Ab dessamad ElKaoutari (2), Avais Daulat (2), Stéphane Audebert (3), Luc Camoin (3), Rémy Castellano (4), Armelle Goubard (4), Bingsheng Wang (5), Xiaojun Shi (5), Flavio Maina (2), Jean-Paul Borg (2)

*1. Centre de Recherche en Cancérologie de Marseille, Marseille, France*
*2. Centre de Recherche en Cancérologie de Marseille, Marseille, France*
*3. Proteomics, Centre de Recherche en Cancérologie de Marseille, Marseille, France*
*4. TrGET, Centre de Recherche en Cancérologie de Marseille, Marseille, France*
*5. MetroHealth Medical Center, Cleaveland, USA*

**Keywords:** Pseudokinase, PTK7, EphA2, Integrins, cell adhesion

**Introduction**
Despite the lack of catalytic activity, pseudokinases contribute to cell signalling and have pivotal functions in physiology and diseases. Bulk analyses of many cancer types, including colorectal cancer, have frequently correlated high expression of the pseudokinase PTK7 receptor to poor prognosis and resistance to treatment. However how it intervenes in heterogenous cancer cell populations at the pronostic and molecular levels is yet unknown. Here we uncover a previously unrecognized mechanism by which PTK7 controls signaling and functions of EphA2, an active tyrosine kinase receptor which plays a key role in cell-cell communication and metastasis.

**Results :**
Heterogenous co-expression of PTK7 and EphA2 assessed at the single cell level is observed in malignant colorectal tumors and associated to distinct pathways. Molecularly, we show that PTK7 regulates the oligomeric state of EphA2 through a direct interaction. PTK7 loss stabilizes active EphA2 dimers resisting to K63 ubiquitin and lysosomal-dependent degradation, and perturbs integrin functions. PTK7-deficient cells with loose adhesive properties to extracellular matrices have a more pronounced metastatic potential in mice. Likewise, PTK7low/EphA2high expression in tumors predicts poorer clinical outcome of patients.

**Conclusion :**
Our findings establish the PTK7-EphA2 axis as an essential regulator of integrin-driven adhesion and reveal the duality of PTK7 functions in the prometastatic program and probably in the response to treatment.

1st Edition
CRCM Symposium
CANCER RESEARCH CENTER MARSEILLE
CRCM CANCER RESEARCH CENTER Marseille
Comet Cell communication & Microenvironment dpt.
Translate-IT Translational research & Innovative therapies dpt.
4 - 6 February 2026
MARSEILLE
Palais du Pharo

## SESSION 3: - CHALLENGING SITES OF TUMORIGENESIS: JUNIOR SCIENTIST SESSION - Part 1

### CO05 : High-throughput drug screening reveals metabolic vulnerabilities in patient-derived diffuse midline glioma models

*Julie Lafont*

**Authors:**
Julie Lafont (1), Kévin Müller (1), Maria Tsoli (2), David Ziegler (2), Samuel Meignan (3), Nicolas André (1, 4), Marion Le Grand (1), Eddy Pasquier (1)

*1. Translate-It, CRCM, Marseille, France*
*2. Children's Cancer Institute, Sydney, Australia*
*3. Lille Cancer Research Institute , Lille, France*
*4. Pediatric Hematology and Oncology Department, La Timone Children's Hospital, AP-HM, Marseille, France*

**Keywords:** Diffuse Midline Glioma, metabolic vulnerability, drug screening, spectral cytometry

**Introduction**
Diffuse Midline Glioma (DMG) is a fatal type of pediatric brain tumor. It represents one of the biggest challenges in pediatric oncology with a median overall survival of 9-11 months. After decades of clinical trial failure, the imipridone ONC-201 has just been approved by the FDA for patients with recurrent H3K27M-mutant tumors. While most patients temporarily respond to this molecule, tumor growth inevitably restarts, highlighting the need to identify combination therapies to enhance (or prolong) its efficacy. Approximately 80% of DMG harbour a recurrent somatic mutation on histone H3, the H3K27M mutation. It has been identified as a key driver of DMG, due to the major epigenetic dysregulation it induces. Indeed, recent data support the view that at least two different epigenetic cell states coexist within DMG tumors, thereby creating a specific and high level of intratumoral heterogeneity. Moreover, several studies have identified a metabolic reprogramming of DMG tumors and highlighted their dependencies on cholesterol biosynthesis, TCA cycle and de novo pyrimidine biosynthesis.

**Method :**
We hypothesize that the metabolic reprogramming occurring in DMG cells constitutes a targetable vulnerability that could be exploited to develop innovative combination therapies and increase our knowledge of DMG biology. To test this hypothesis, we performed a high-throughput drug screening using a 110-drug focused library in combination with ONC-201 or its derivatives in 8 different models of patient-derived DMG.

**Results :**
Amongst the 330 tested pairwise combinations, the association of ONC-201 (and its derivatives) with NAMPT inhibitors was identified as the most potent. Using a matrix of 6x5 different drug concentrations, we validated the potency of the drug combination in 4 different models, using different NAMPT inhibitors. By calculating the Bliss score, we were able to define the association as highly synergistic. Furthermore, a second highthroughput screening using a dedicated library of 152 metabolic inhibitors confirmed that NAMPT inhibition efficiently impacts DMG neurosphere growth.

**Discussion :**
Functional validation is currently underway to ascertain ON-target mechanism involved in the synergy between imipridones and NAMPT inhibitors.

**Conclusion :**
Thus, using high-throughput drug screening we identified a metabolic vulnerability in DMG which can be therapeutically exploited by combining ONC compounds with NAMPT inhibitors. To go further, we will study the impact of this combination on the different cell sub-populations using spectral cytometry, to investigate the level of complexity between epigenetic and metabolic reprogramming heterogeneity and identify vulnerabilities as a step towards the development of better tailored treatments for DMG.

1st Edition
CRCM Symposium
CANCER RESEARCH CENTER MARSEILLE
CRCM CANCER RESEARCH CENTER Marseille
Comet Cell communication & Microenvironment dpt.
Translate-IT Translational research & Innovative therapies dpt.
4 - 6 February 2026
MARSEILLE
Palais du Pharo

## SESSION 3: - CHALLENGING SITES OF TUMORIGENESIS: JUNIOR SCIENTIST SESSION - Part 1

### CO06 : Molecular heterogeneity, a key component in glioblastoma cells molecular dynamics under metabolic pressure

*Mélanie Laurent-Blond*

**Author:**
Mélanie Laurent-Blond (1)

*1. CRCI2NA UMR1307, Nantes, France*

**Introduction**
Glioblastoma (GBM) is the most aggressive primary brain tumor in adults, with less than 5% survival at 5 years (Stupp 2005). This poor prognosis is due to its multi-layer intra-tumoral heterogeneity. In particular, three main molecular states have been identified, namely the mesenchymal (MES), astrocyte-like (AC) and OPC-like (OPC) state (Neftel 2019). Importantly, GBM cells can shift between molecular states, in particular from OPC to MES state, allowing them to adapt, resist and escape treatments (Schmitt 2021, Hara 2021). In this context, understanding the dynamics of these molecular shifts is crucial to improve GBM outcomes. However, transition monitoring is currently limited by the lack of a specific marker of each state and the limited diversity of molecular states in primary GBM cultures. Here, we designed a complex tumoroid model integrating a defined ratio of molecular states with dynamic dual tools monitoring both OPC and MES states.

**Method :**
Primary GBM cells were transduced with both OPC and MES genetic tracers. Tumoroids were generated with either OPC cells, MES cells or an equal mixture of both. Dynamic molecular transitions were performed using western blot, flow cytometry and videomicroscopy.

**Results :**
We initially validated the specific expression of OPC- and MES- genetic tracer according to the established molecular subtype using OPC and MES cells, respectively. Then, we evaluated the cell state transition upon TNFα. We observed a dynamic transition from an OPC state toward MES state.
Finally, since spatial molecular state organization is associated with the metabolic landscape, we investigate whether metabolic restriction impacts GBM molecular dynamics. Both glucose or glutamine restriction triggered the emergence of a hybrid OPC/MES state in OPC tumoroids. Strikingly, similar experiments performed in the presence of MES cells induced a complete transition of OPC cells into MES state.

**Discussion :**
Since molecular transition has been reported in response to radiotherapy and chemotherapy, this innovative model will allow a better understanding of the temporal dynamics of this process, the molecular mechanisms involved and the identification of potential strategies preventing this dynamic.

**Conclusion :**
This innovative GBM model allows the dynamic monitoring of molecular transition, a crucial step in understanding tumor adaptation to treatment involved in systematic GBM recurrence and poor prognosis.

1st Edition
CRCM Symposium
CANCER RESEARCH CENTER MARSEILLE
CRCM CANCER RESEARCH CENTER Marseille
Comet Cell communication & Microenvironment dpt.
Translate-IT Translational research & Innovative therapies dpt.
4 - 6 February 2026
MARSEILLE
Palais du Pharo

## SESSION 3: - CHALLENGING SITES OF TUMORIGENESIS: JUNIOR SCIENTIST SESSION - Part 2

### CO07 : Tuft cells remodel the mucosal immune microenvironment to promote intestinal tumourigenesis

*Imène Gasmi*

**Authors:**
Imène Gasmi (1), Emmanuelle Sidot (2), Nathalie Coutry (2), François Gerbe (2), Philippe Jay (2)

*1. IGF-UMR5203-Montpellier, Montpellier, France*
*2. IGF-UMR5203-Montpellier, Montpellier, France*

**Keywords:** Tumor initiation, Tuft cells, Immune microenvironment, Cox-2

**Introduction**
Colorectal cancer remains a major public health concern in France, ranking among the most common cancers and representing the second leading cause of cancer-related mortality. Extensive research has focused on genetic alterations in epithelial cells, particularly allelic losses of the tumor suppressor gene APC (Adenomatous Polyposis Coli), identified as the initiating event in 80–85% of sporadic CRC cases. Over the past decade, the tumor microenvironment has emerged as a critical determinant of cancer initiation, progression, and therapeutic response. Among the components of the TME, the immune system plays a dual role in both restraining and promoting tumor development. Understanding the mechanisms leading to the establishment of a pro-tumoral immune microenvironment could facilitate the discovery of novel prognostic biomarkers and foster the development of immune-based therapy. We hypothesized that intestinal tuft cells, a specialized population of epithelial cells with immunomodulatory functions, influence tumor initiation by shaping the immune microenvironment during colorectal tumorigenesis.

**Method :**
To test this hypothesis, we used a mouse model of intestinal tumorigenesis (ApcΔ14/+) combined with tuft cell deficiency (Pou2f3$^{-/-}$). The immune cell infiltrate in the non-tumoral intestinal mucosa was analyzed to determine how absence of tuft cells affects immune composition. We also employed the DEREG mouse model to specifically deplete regulatory T cells (Tregs) in vivo during tumorigenesis. To identify the mediators through which tuft cells modulate the immune microenvironment, we focused on prostanoids—pro-inflammatory lipid mediators synthesized by COX-2. For this purpose, we generated a conditional Cox-2 knockout in tuft cells (Cox2fl/fl ; Villin-Cre ; ApcΔ14/+) to assess the impact of COX-2 loss on immune infiltration and tumor initiation.

**Results :**
Tuft cell deficiency in ApcΔ14/+ mice led to a significant reduction in tumor numbers, accompanied by a decrease in Treg infiltration in the nontumoral mucosa compared with controls. Specific depletion of Tregs in DEREG mice similarly resulted in a drastic reduction in tumor initiation, highlighting the essential role of Tregs during early tumorigenesis. We further found that tuft cells are the only epithelial population expressing Cox-2 in the context of Apc heterozygosity. In addition, the specific genetic deletion of Cox2 in tuft cells phenocopied tuft cell deficiency, both in terms of reduced tumor initiation and decreased Treg infiltration.

**Conclusion :**
Overall, our findings demonstrate that tuft cells promote tumor initiation through COX-2-dependent modulation of the immune microenvironment, notably via recruitment of immunosuppressive Tregs. This work highlights tuft cells and COX-2 signaling as promising targets for preventive and therapeutic interventions in colorectal cancer.

1st Edition
CRCM Symposium
CANCER RESEARCH CENTER MARSEILLE
CRCM CANCER RESEARCH CENTER Marseille
Comet Cell communication & Microenvironment dpt.
Translate-IT Translational research & Innovative therapies dpt.
4 - 6 February 2026
MARSEILLE
Palais du Pharo

## SESSION 3: - CHALLENGING SITES OF TUMORIGENESIS: JUNIOR SCIENTIST SESSION - Part 2

### CO08 : BRD4 inhibition creates a permissive state for breast cancer initiation

*Anaïs Grandon*

**Authors:**
Anaïs Grandon (1), Shuheng Lin (2), Caroline Bonnet (2), Julien Wicinski (2), Martin Castagné (2), Eddy Pasquier (2), Rémy Castellano (2), Olivier Rosnet (2), Emmanuelle Charafe-Jauffret (2), Christophe Ginestier (2)

*1. Centre de Recherche en Cancérologie de Marseille, Marseille, France*
*2. Centre de Recherche en Cancérologie de Marseille, Marseille, France*

**Keywords:** breast cancer, tumor initiation, epigenetic priming, cellular pliancy, BRD4

**Introduction**
Breast cancer screening strategies lead to an increase in the detection of diverse preneoplastic lesions, raising the risk to overdiagnosis and/or overtreatment due to the uncertainty about their evolution to cancer. Understanding the early steps of breast cancer initiation is therefore essential. Tumor initiation theories differ: some base on genetics, with a single somatic mutation driving tumor formation, while others highlight epigenetic changes as a priming event. Together, these findings suggest that epigenetic perturbations may raise cell susceptibility to transformation, promoting additional mutations and tumor development. In the mammary gland, a complex tissue whose epithelium is structured into a cell hierarchy, our lab demonstrated that epigenetic perturbations can disrupt mammary epithelial differentiation and homeostasis, thereby enhancing tumorigenesis. Altogether, this supports our hypothesis that epigenetic priming can represent an initiating event in tumorigenesis, increasing mammary epithelial cell susceptibility to acquire genetic alterations and drive cancer development, while genetic alterations alone are insufficient to initiate tumor.

**Method :**
To decipher these early events, normal human mammary epithelial (HME) cells were used as a model. HME cells reveals a continuum from mammary stem cells (MaSC) to luminal cells (LC), tracing a simplified mammary hierarchy. An epidrug screen was performed to identify epigenetic perturbations disrupting differentiation of MaSC-sorted cells, validated by mammosphere assays. Using colony formation assays and xenotransplantation into humanized fat pads of immunodeficient mice, we tested whether epigenetic priming was sufficient to increase HME cell susceptibility to transformation following an oncogenic stress. Finally, scRNAseq and CUT&RUNseq were performed to study how this epigenetic perturbation impairs differentiation and cell susceptibility.

**Results :**
The epidrug screen revealed an enrichment of bromodomain inhibitors among the drugs with the greatest impact on MaSC differentiation. We selected a BRD4i, a demonstrate that HME treatment with this compound increased MaSC proportion by impairing differentiation, confirmed by an increase in MaSC-module genes in scRNAseq. Then, PIK3CAH1047R was expressed in BRD4i-treated cells. In vitro and in vivo, BRD4i-PIK3CAH1047R cells showed increased growth and formed tumor, whereas PIK3CAH1047R-only cells formed fibrocystic non-tumoral gland. CUT&RUNseq showed perturbation activated enhancers leading to deregulation of gene expression which could explain this impairment of differentiation and increase of cell susceptibility to be transformed.

**Discussion :**
BRD4i alters MaSC differentiation and primes cells for PIK3CAH1047R-induced transformation. These results support that epigenetic perturbation can act as an early event in breast tumorigenesis and suggest that specific gene expression changes contribute to increased cell susceptibility.

1st Edition
CRCM Symposium
CANCER RESEARCH CENTER MARSEILLE
CRCM CANCER RESEARCH CENTER Marseille
Comet Cell communication & Microenvironment dpt.
Translate-IT Translational research & Innovative therapies dpt.
4 - 6 February 2026
MARSEILLE
Palais du Pharo

## SESSION 3: - CHALLENGING SITES OF TUMORIGENESIS: JUNIOR SCIENTIST SESSION - Part 2

### CO09 : Investigating tumor-trained immunity in pancreatic cancer

*Fanny Matrand*

**Authors:**
Fanny Matrand (1), Melissa Giroudoux (1), Fanny Hidalgo-Villeda (1), Julien Vernerey (2), Pierre Bertrand (1), Elena Lo Presti (3), Richard Tomasini (1), Erinn Soucie (1)

*1. COMET, CRCM, Marseille, France*
*2. CIBI, CRCM, Marseille, France*
*3. University of Palermo, Palermo, Italy*

**Keywords:** PDAC , Trained-Immunity , Epigenetic , Immune suppression , Tumor microenvironment

**Introduction**
The incidence of pancreatic ductal adenocarcinoma (PDAC) has risen significantly in recent years and, although considered rare, it is projected to become the second deadliest cancer by 2030 due to the lack of early biomarkers and high resistance to current therapies. Immunotherapy has brought new hope for other cancers. However, PDAC is characterized by a highly developed stroma, and crosstalk between tumor cells and the numerous stromal cell types within the tumor microenvironment (TME) coordinates the suppression of anti-tumor immune responses and promotes resistance to current immune therapies. Tumor-associated macrophages dominate the PDAC immune landscape and play a central role in shaping this immunosuppressive barrier.

**Method :**
Tumor- and stromal cell–secreted factors circulate beyond the PDAC TME and reach the bone marrow. To investigate the impact of this systemic signalling on adaptive immunity and hematopoietic niche remodeling, we analysed bone marrow–derived stem and progenitor cells, as well as bone marrow–derived macrophages (BMDMs), from mice with PDAC compared to controls. In parallel, we assessed the functional consequences of this potential immune training on tumor progression in vivo using chimeric mouse models.

**Results :**
We show a series of epigenetic changes in bone marrow–derived populations that correlate with immune reprogramming in tumor-bearing mice. It appears that this reprogramming is heritable, supporting a model of tumor-trained immunity. We show that BMDMs from these tumor-bearing mice displayed a pro-tumor phenotype upon ex vivo stimulation with PDAC-secreted factors. Functionally, our data suggest that this training was associated with increased tumor growth and reduced infiltration of pro-inflammatory tumor-infiltrating lymphocytes (TILs) and tumor-associated macrophages (TAMs). Epigenetic signatures identified in circulating monocytes from PDAC patients support the existence of this model in humans and suggest a potential biomarker for earlier detection.

**Discussion :**
These findings suggest that systemic signals originating from the tumor microenvironment can remodel the hematopoietic compartment and shape immune responses that favor tumor progression. The identification of heritable epigenetic changes supports a model in which trained immunity contributes to the establishment of an immunosuppressive environment in PDAC.

**Conclusion :**
Taken together, we propose a new model of trained-immunity to explain how the immune system adapts in response to circulating tumor factors. Epigenetic reprogramming associated to this training could provide a therapeutic target to regulate the anti-tumor immune response in PDAC at both primary and metastatic sites, and to prevent relapse in patients.

1st Edition
CRCM Symposium
CANCER RESEARCH CENTER MARSEILLE
CRCM CANCER RESEARCH CENTER Marseille
Comet Cell communication & Microenvironment dpt.
Translate-IT Translational research & Innovative therapies dpt.
4 - 6 February 2026
MARSEILLE
Palais du Pharo

## SESSION 3: - CHALLENGING SITES OF TUMORIGENESIS: JUNIOR SCIENTIST SESSION - Part 2

### CO10 : Model-driven scheduling of nanocarriers: application to an anticancer polymer prodrug administered subcutaneously

*Anne Rodallec*

**Authors:**
Anne Rodallec (1), Randy Lee (2), Jingming Cao (3), Sophie Marolleau (4), Nicolas Julien (3), Sebastien Benzekry (5)

*1. COMPO/SMARTc-CRCM - Aix Marseille University, Marseille, France*
*2. COMPO-CRCM - Inria Sophi Antipolis, marseille, France*
*3. CNRS, Institut Galien Paris-Saclay, Orsay, France*
*4. COMPO/SMARTc-CRCM - Aix Marseille University, marseille, France*
*5. COMPO-CRCM - Inria Sophi Antipolis, Marseille, France*

**Introduction**
The limitations of chemotherapy (e.g., toxicities, limited efficacy) have led to the development of nanocarriers for drug delivery to improve pharmacokinetics (PK) and therapeutic outcomes. However, optimizing dosing regimens remains challenging. Moreover, since chemotherapy are mainly administered intravenously (IV), this results in patient discomfort and high treatment cost.

**Method :**
To address these issues, we used PK/pharmacodynamics (PD) modeling and applied it to subcutaneously (SC) injectable polymer prodrug based on paclitaxel (Ptx) and polyacrylamide (PAAm).

**Results :**
PK/PD studies were performed on MCF-7 tumor-bearing mice. The PK model was developed on IV Ptx and SC Ptx-PAAm data. The PD model was developed on control, IV Ptx, and SC Ptx-PAAm groups (15 mg/kg), and validated on an independent group (SC Ptx-PAAm 60 mg/kg). Optimal dosing regimens identified in silico were then validated in vivo with excellent agreement. A dosing regimen combining a loading dose and daily injections achieved a 60% complete response rate without added toxicity, outperforming prior results.

**Conclusion :**
This is the first validated PK/PD model for nanocarriers, offering a framework for more effective, cost-efficient, and ethically refined drug development.

1st Edition
CRCM Symposium
CANCER RESEARCH CENTER MARSEILLE
CRCM CANCER RESEARCH CENTER Marseille
Comet Cell communication & Microenvironment dpt.
Translate-IT Translational research & Innovative therapies dpt.
4 - 6 February 2026
MARSEILLE
Palais du Pharo

## SESSION 4 : - CANCER PROGRESSION AND TREATMENTS

# CO11 : Single-cell analysis of treatment-associated dynamics in PDAC reveals drug-response programs and plasticity mechanisms driving chemoresistance

*Nicolas Fraunhoffer*

**Authors:**
Nicolas Fraunhoffer (1, 2), Vladimir Chocoloff (3), Brice Chanez (4), Alice Boilève (5), Philippe Soubeyran (3), Loïc Moubri (3), Analia Meilerman (3), Pascal Hammel (6), Thierry Conroy (7), Jerome Cros (8), Juan Iovanna (3), Nelson Dusetti (3), PRODIGE-24/MOSAPAC Consortium (9)

1. *TRANSLATE-IT, Centre de Recherche en Cancérologie de Marseille (CRCM), Marseille, France*
2. *Center for Pharmacological and Botanical Studies, Faculty of Medicine, National Council for Scientific and Technical Research, Buenos Aires, Argentina*
3. *Centre de Recherche en Cancérologie de Marseille (CRCM), INSERM U1068, Marseille, France*
4. *Institut Paoli-Calmettes, Marseille, France*
5. *Medical Oncology Department, Gustave Roussy, Villejuif, France*
6. *Digestive and Medical Oncology, Paul Brousse Hospital, Assistance Publique-Hôpitaux de Paris (AP-HP), Université Paris-Saclay, Villejuif.*
7. *Medical Oncology Department, Institut de Cancérologie de Lorraine, Vandoeuvre-lès-Nancy; Université de Lorraine, INSERM, INSPIIRE, Nancy, France*
8. *Université Paris Cité, Department of Pathology, FHU MOSAIC, Beaujon/Bichat University Hospital (AP-HP), Paris, France*
9. *Unicancer, Paris, France*

**Keywords:** Pancreatic cancer, chemoresistance, cell plasticity, single cell

**Introduction**
Pancreatic ductal adenocarcinoma (PDAC) is a highly lethal cancer with a five-year survival rate under 12%. Chemotherapy, including mFOLFIRINOX or gemcitabine-based regimens, is the main treatment for unresectable cases but achieves tumor regression in only 10%-30% of patients. Nearly all patients experience recurrence or progression, driven by preexisted (primary) or acquired (secondary) chemoresistant cells. The hypothesis of this study is that the drug-response profile and phenotypic evolution dynamics of PDAC tumors are determined by the tumor cell phenotype at the niche level, which in turn drives the tumor's drug response and the patient's outcome.

**Method :**
Intratumoral cell phenotypes were identified through the integration of bulk and single-cell transcriptomic data. The identified cell phenotypes were validated in single-cell RNA sequencing (scRNA-seq) cohorts of patients. Additionally, the treatment-associated dynamics of the identified phenotypes was evaluated in three patient-derived organoids (PDO) treated with five chemotherapeutic agents: gemcitabine, paclitaxel, 5- fluorouracil (5-FU), oxaliplatin, and SN38. Lastly the enrichment of the cell phenotypes in bulk RNAseq of patients was assessed across three independent cohorts: 343 resectable cases (PRODIGE-24), 65 primary tumors from metastatic patients, and 29 paired samples collected before and after neoadjuvant treatment.

**Results :**
Five phenotype modules were identified: two associated with pancreatic differentiation, an epithelioid phenotype, a squamous phenotype, and an EMT phenotype. Validation in single-cell cohorts of patients showed significant enrichment of squamous and EMT-related cell clusters in the metastatic stage ($P<0.001$) and after neoadjuvant treatment ($P<0.001$). Treatment-associated dynamics showed that the effect varied depending on the initial phenotype. Gemcitabine and paclitaxel showed the most pronounced transcriptomic changes, inducing a phenotypic shift toward more aggressive phenotypes. Analysis of bulk RNA-seq data revealed that patient prognosis was associated with the dominant cell phenotype. In the PRODIGE-24 cohort, patients enriched in the Differentiated 1 phenotype exhibited a better prognosis in both treatment arms: gemcitabine (stratified HR: 0.38; 95% CI, 0.19–0.75; P=0.005) and FOLFIRINOX (stratified HR:0.40; 95% CI, 0.20–0.79; P=0.009), whereas those enriched in squamous had the worst prognosis. A similar pattern was observed in metastatic patients. In the neoadjuvant setting, treatment led to a shift toward more unfavorable phenotypes.

**Discussion :**
Characterizing intratumoral heterogeneity and treatment-associated dynamics in PDAC reveals tumor cells as key drivers of patient outcome. Patient stratification by tumor cell composition enables improved treatment allocation and identification of resistance pathways for personalized treatment strategies.

**Conclusion :**
This study highlights a link between PDAC cell phenotypes and drug response, suggesting plasticity-driven mechanisms underlying acquired chemoresistance.

1st Edition
CRCM Symposium
CANCER RESEARCH CENTER MARSEILLE
CRCM CANCER RESEARCH CENTER Marseille
Comet Cell communication & Microenvironment dpt.
Translate-IT Translational research & Innovative therapies dpt.
4 - 6 February 2026
MARSEILLE
Palais du Pharo

## SESSION 4 : - CANCER PROGRESSION AND TREATMENTS

# CO12 : ORGANOTREAT-01: a pioneering multicenter trial of organoid-driven precision medicine in refractory colorectal cancers

*Jerome Cartry*

**Author:**
Jerome Cartry (1)

*1. Paris, France*

**Keywords:** patient-derived organoids; functional precision medicine; metastatic colorectal cancer, personalized therapy; organoid drug testing

**Introduction**
Patient Tumor-Derived Organoids (PDTOs) provide an ex vivo platform to test drug sensitivity and guide individualized treatment decisions within functional personalized medicine (FPM). Observational studies show PDTOs can recapitulate clinical responses, but their operational implementation and clinical utility remain largely untested in prospective interventional trials. The primary objective was to assess the feasibility of generating PDTOs and a drug sensitivity profile (chemogram) within 10 weeks in more than 50% of evaluable patients. Secondary objectives were to determine the proportion of patients receiving PDTO-guided treatment and to evaluate treatment efficacy.

**Method :**
In this multicenter phase I/II trial, patients with heavily pretreated metastatic colorectal cancer underwent tumor biopsy for PDTO generation. Each PDTO was tested against a 25-drug panel including off-label CRC treatments. The chemograms generated were reviewed by a dedicated tumor board, which issued personalized treatment recommendations.

**Results :**
A total of 61 patients were enrolled, and 54 biopsied, forming the per-protocol evaluable population. The PDTO take-on rate was 78%, the highest reported in a prospective solid-tumor FPM study. The chemograms were generated within 10 weeks for 39 patients (72%), meeting the primary endpoint. Nineteen patients (35%) received PDTO-guided treatment. Clinical benefit, evaluated in the PDTO-guided population, was observed in four patients (21%), achieving durable disease control lasting between 5.6 and 12.9 months.

**Conclusion :**
ORGANOTREAT-01 demonstrates that PDTO-based drug testing is feasible and can be integrated into routine clinical workflows. The unprecedented take-on rate enabled drug testing in most patients, resulting in durable disease control in a subset. These findings support further optimization of FPM strategies and the expansion of PDTO-guided approaches to other solid tumors.

1st Edition
CRCM Symposium
CANCER RESEARCH CENTER MARSEILLE
CRCM CANCER RESEARCH CENTER Marseille
Comet Cell communication & Microenvironment dpt.
Translate-IT Translational research & Innovative therapies dpt.
4 - 6 February 2026
MARSEILLE
Palais du Pharo

## Posters Session 1 - Precision oncology, targeted therapies and strategies for refined drug delivery

# S1CA01 : XON11: a novel multimodal polyclonal antibody to overcome tumor heterogeneity in pancreatic cancer

*Ophélie Dauphouy*

**Authors:**
Ophélie DAUPHOUY (1, 2), Carine Ciron (2), Gwenaëlle Evanno (2), Pierre-Joseph Royer (2), George Graur (3), Hoa Le Mai (1), Odile Duvaux (4), Sophie Brouard (1), Firas Bassissi (2)

*1. Research, INSERM CR2TI UMR 1064, Nantes, France*
*2. Research and Development , Xenothera, Nantes, France*
*3. Bioproduction, Xenothera, Nantes, France*
*4. CEO, Xenothera, Nantes, France*

**Keywords:** Pancreas cancer, Immunotherapy, tumor heterogeneity, resistance

**Introduction**
Pancreatic cancer remains a malignancy characterized by an exceptionally high mortality rate, primarily driven by significant intratumoral heterogeneity and a profound immunosuppressive tumor microenvironment. To date, the limited efficacy of current standard-of-care chemotherapy and single-agent immunotherapy underscores an urgent, unmet clinical need for innovative therapeutic strategies. XON11, a new developed polyclonal antibody, targets simultaneously multiple synergistic antigens expressed by pancreatic cancer cells. The aim of these studies was to assess the anti-tumoral efficacy of XON11 and characterize mechanistic impact on cancer stem cell (CSC)-driven tumor heterogeneity, in nonclinical pancreatic cancer models.

**Method :**
Pancreatic cancer heterogeneity was investigated in a panel of five phenotypically diverse human PDAC cell lines (MiaPaca-2, Aspc-1, Capan-1, Panc-1 and BxPC-3). CSC subpopulations were defined and monitored using established markers, including EpCam, CD24, CD44, CD133. We quantified XON11's ability to induce Complement Dependent Cytotoxicity (CDC) and apoptosis over 24- and 72-hour incubation periods, comparing its activity against gemcitabine. The functional capacity of XON11 to impair tumorsphere formation and growth, a key indicator of stemness, was tested over 10 days. In vivo XON11 tolerance and efficacy were evaluated in AsPC-1 and BxPC-3 xenograft mice models after intraperitoneal dosing at 40 mg/kg twice a week or gemcitabine over an 8- to 9-week period.

**Results :**
Flow cytometric analysis confirmed strong cellular heterogeneity among the PDAC cell lines. Mechanistically, XON11 selectively reduced the proportion of the highly aggressive EpCam+ CD24+ CD44+ subpopulation in the BxPC-3 and Panc-1 lines, an effect that was absent following gemcitabine treatment in all tested lines. XON11 exhibited potent and selective anti-proliferative activity across the panel, notably retaining efficacy in cell lines demonstrating resistance to gemcitabine. Crucially, XON11 significantly decreased tumorsphere viability in Aspc-1, Panc-1, and Mia- Paca-2 cells following treatment, achieving complete inhibition of sphere formation at concentrations as low as 33 µg/ml. Translational findings were confirmed in vivo: XON11 demonstrated significant efficacy against tumor growth in both xenograft models. Furthermore, in the BxPC-3 model, XON11 exhibited superior efficacy and tolerance compared to gemcitabine, achieving a Tumor Growth Inhibition (TGI) of 61.9% ± 1.9% versus 34.2% ± 4.1% for gemcitabine.

**Conclusion :**
Based on its potent anti-proliferative and CSC-targeting mechanisms, coupled with its observed superior in vivo efficacy and favorable tolerance profile, XON11 represents a highly promising, novel multimodal therapeutic strategy for overcoming tumor heterogeneity and chemoresistance in recurrent pancreatic cancer.

1st Edition
CRCM Symposium
CANCER RESEARCH CENTER MARSEILLE
CRCM CANCER RESEARCH CENTER Marseille
Comet Cell communication & Microenvironment dpt.
Translate-IT Translational research & Innovative therapies dpt.
4 - 6 February 2026
MARSEILLE
Palais du Pharo

## Posters Session 1 - Precision oncology, targeted therapies and strategies for refined drug delivery

# S1CA02 : Identification of a fibroblast subtype associated with early-relapse in metastatic colorectal cancer by single-nuclei rna sequencing

*Maelle Picard*

**Author:**
Maelle Picard (1)

*1. Translate-It, CRCM, Marseille, France*

**Keywords:** Microenvironment, Fibroblast, Single-nuclei RNA sequencing, liver metastasis of colorectal cancer, relapse

**Introduction**
The era of single-cell analysis has demonstrated the importance of accurate characterization of all organ-specific cell subtypes. In the context of malignancies, this has greatly improved our understanding of cell interactions and reciprocal influence. However, metastatic tissues are often forgotten, even though they are the real cause of cancer-related mortality, especially for colorectal cancer (CRC), whose prognosis is directly related to the presence of liver metastases (lm). One reason for this is the inherent difficulties in analyzing lm-CRC tissues with single-cell resolution: first, the liver is composed of cells that are extremely fragile and poorly recoverable after enzymatic digestion; second, most surgical specimens are from patients who have received chemotherapy and are therefore highly necrotic, fibrotic, and fragile. Due to these limitations, most studies have focused on the immune system characterization, ignoring the role of the other components of a however very rich and complex ecosystem.

**Method :**
To address this gap, we performed one of the first in-depth and representative characterizations of the ecosystem of lm-CRC using single-nuclei RNA sequencing. The global landscape, subpopulation composition, cell-cell interactions, tumor cell inference were analyzed in the entire population and regarding relapse.

**Results :**
We generated more than 26,000 high-quality cells from 9 patients for a total of 30 clusters, including malignant epithelial cells from CRC, immune cells, fibroblasts, and normal liver cells. We found a subset of cancer-associated fibroblasts (CAF) that was positively correlated with early-relapse risk. These CAFs expressed extracellular matrix remodeling and hypoxia features and interacted strongly with the immune, endothelial and epithelial clusters. These preliminary results lay the foundation for an accurate description of a pro-metastatic, immunosuppressive, and chemotherapy-resistant microenvironment that may be the cause of relapse.

**Conclusion :**
Some of the identified populations could serve as relapse-biomarkers and could lead to a reconsideration of therapeutic strategy.

1st Edition
CRCM Symposium
CANCER RESEARCH CENTER MARSEILLE
CRCM CANCER RESEARCH CENTER Marseille
Comet Cell communication & Microenvironment dpt.
Translate-IT Translational research & Innovative therapies dpt.
4 - 6 February 2026
MARSEILLE
Palais du Pharo

## Posters Session 1 - Precision oncology, targeted therapies and strategies for refined drug delivery

# S1CA03 : Disarming radioresistant breast cancer cells by targeting yap pathway

*Claire Zobouyan*

**Author:**
Claire Zobouyan (1)

*1. Equipe Charafe/Ginestier, CRCM, Marseille, France*

**Keywords:** Tumor heterogeneity, radioresistance, cellular plasticity, yap signaling, breast cancer

**Introduction**
Breast cancer remains the most common cancer in women and the leading cause of death among women, despite recent therapeutic advances. Radiotherapy is a standard treatment, but recurrences persist after irradiation, revealing the existence of radiation-resistant tumour cells such as cancer stem cells (CSCs). These cells have a high capacity for survival and plasticity and are derived from the dedifferentiation of non-stem cancer cells into CSCs known as therapy-induced cancer stem cells (iCSCs). This radio-induced cellular plasticity is a process in which the Hippo pathway, and in particular the LRP4-YAP axis, seems to play a central role. This work aims to explore the precise role of the YAP protein in the radioresistance of breast cancer cells. Inhibiting YAP could make breast cancer cells more sensitive to radiotherapy, thereby reducing the risk of recurrence.

**Method :**
The experiments were performed on the SUM159 cell line, derived from triple-negative human breast carcinoma. Radiosensitivity was tested by genetic (siRNA) and pharmacological (Verteporfin) inhibition of YAP, followed by colony formation assays after irradiation at different doses. The expression of YAP target genes was quantified by RT-qPCR. The efficacy of the YAP inhibitor on the cell line was determined by an MTS assay to calculate the IC50. The proportion of CSCs after exposure to Verteporfin was assessed by an Aldefluor assay (ALDH activity) and by the ability of cells to form spheres under non-adherent conditions. YAP activation after irradiation was monitored by immunolabelling and image analysis.

**Results :**
Genetic inhibition of YAP leads to a significant decrease in colony formation after irradiation, in a dose dependent manner. Pharmacological inhibition of YAP by Verteporfin at its IC50 of 0.8 µM decreases the expression of YAP target genes, reduces the pool of ALDH+ CSCs and abolishes their ability to form spheres, confirming its effectiveness on this cell pool, by targeting YAP. Combination tests with Verteporfin + Irradiation show a synergistic effect on colony formation, even with the addition of low doses of radiotherapy. Inhibition of YAP, whether genetic or pharmacological, radiosensitises breast cancer cells. YAP activation is an early post-irradiation event, supporting its role in the emergence of radioresistant cells.

**Discussion :**
These results identify YAP as a regulator of radiation-induced cellular plasticity and a promising target for sensitising breast tumours to radiotherapy. However, in vivo validation is still needed before clinical strategies combining radiotherapy and YAP inhibition can be considered.

**Conclusion :**
YAP appears to play a central role in breast cancer radioresistance.

1st Edition
CRCM Symposium
CANCER RESEARCH CENTER MARSEILLE
Comet
Cell communication & Microenvironment dpt.
Translate-IT
Translational research & Innovative therapies dpt.
4 - 6 February 2026
MARSEILLE
Palais du Pharo

## Posters Session 1 - Precision oncology, targeted therapies and strategies for refined drug delivery

### S1CA04 : Dendrimer nanosystems hijack in situ tumor-secreted extracellular vesicle for RNA delivery

*Christina Galanakou*

**Author:**
Christina Galanakou (1)

*1. Centre Interdisciplinaire de Nanoscience de Marseille (CINaM, UMR 7325 CNRS), Marseille, France*

**Introduction**
RNA-based therapeutics hold significant promise for precision cancer therapy thanks to their ability to modulate disease-relevant genes. However, effective RNA delivery remains a major challenge, particularly in the context of tumor heterogeneity and the dynamic evolution of the tumor microenvironment. Conventional delivery systems often fail to achieve deep tumor penetration, stability, and efficient cellular uptake, limiting their clinical translation. We report here that self-assembling dendrimer nanosystems can serve as an adaptable RNA delivery platform by hijacking in situ tumor-secreted extracellular vesicles (EVs), thereby enhancing RNA stability, cellular uptake, and propagation throughout heterogeneous and evolving tumors via intrinsic endogenous EV-mediated inter-cellular delivery for effective treatment.

**Method :**
Extracellular vesicles (EVs) were isolated from cells treated with dendrimer/RNA complexes and characterized using TEM and biomarkers. The presence and delivery of RNA within these EVs were evaluated using fluorescence imaging and flow cytometry (FACS) to confirm successful repackaging. EV-mediated propagation of RNA delivery to neighboring cells was analyzed using fluorescently labeled RNA and imaging assays in cocultured 2D- and 3D cancer cell models. In vivo tumor-xenograft models were employed to assess biodistribution, EV-mediated RNA dissemination, and therapeutic efficacy of RNA-loaded dendrimer nanomicelles.

**Results :**
Following cellular uptake of dendrimer/RNA complexes, RNA was successfully repackaged into tumor-derived EVs, which were isolated and analyzed for their RNA cargo using fluorescence imaging and FACS, confirming effective loading. These EVs mediated further transfer of RNA to neighboring cells, establishing a self-propagating delivery network. In vivo studies demonstrated deep tumor penetration and widespread dissemination of RNA within tumors, correlating with improved therapeutic outcomes.

**Discussion :**
By combining dendrimer-nanotechnology based nucleic acid delivery with tumor EV trafficking, we developed a smart, self-amplifying RNA delivery platform. This system overcomes key limitations of conventional RNA therapeutics, including instability, poor and inefficiency penetration in heterogeneous tumors. The successful repackaging of RNA into EVs and their propagation to neighboring cells via intrinsic endogenous delivery mechanism demonstrates a natural amplification mechanism, enabling deep tumor penetration and adaptive delivery.

**Conclusion :**
The dendrimer-EV platform protects and propagates RNA effectively, adapts to tumor heterogeneity and evolution, and improves therapeutic outcomes. This strategy represents a versatile and promising avenue for the development of personalized RNA therapeutics.

1st Edition
CRCM Symposium
CANCER RESEARCH CENTER MARSEILLE
CRCM CANCER RESEARCH CENTER Marseille
Comet Cell communication & Microenvironment dpt.
Translate-IT Translational research & Innovative therapies dpt.
4 - 6 February 2026
MARSEILLE
Palais du Pharo

## Posters Session 1 - Precision oncology, targeted therapies and strategies for refined drug delivery

### S1CA05 : Uncovering Stage-Specific Vulnerabilities in Recurrent Breast Tumors

*Emma Der Kazarian*

**Authors:**
Emma Der Kazarian (1), Caroline Bonnet (2), Aurelien Bore (3), Mauro Vedelago (2), Martin Castagne (2), Julien Wicinski (2), Raphaël Margueron (3), Emmanuelle Charafe (2), Christophe Ginestier (2)

*1. Inserm, Marseille, France*
*2. Inserm, Marseille, France*
*3. Inserm, Paris, France*

**Keywords:** TNBC, Resistance, Recurrence, PDX, scRNAseq, CRISPR

**Introduction**
Tumor recurrence remains a major challenge in cancer treatment, often associated with acquired resistance to conventional chemotherapy. Patientderived xenografts (PDX) provide a physiologically relevant in vivo model to investigate tumor evolution and the mechanisms underlying therapy resistance. Understanding these mechanisms is critical to identify potential therapeutic vulnerabilities in resistant tumors.

**Method :**
PDX models were analyzed at three stages: treatment-naïve tumors, early recurrence, and advanced resistant recurrence. Single-cell RNA sequencing combined with CITE-seq was performed to characterize transcriptional states at single-cell resolution. InferCNV was applied to predict major genomic alterations. Additionally, an in vivo CRISPR screen was implemented to identify stage-specific molecular dependencies and essential survival pathways.

**Results :**
Transcriptomic analysis revealed that cells from the advanced resistant recurrence exhibit a distinct transcriptional profile, while cells from treatment-naïve and early recurrence stages remain transcriptionally similar. InferCNV analysis showed that the dominant clone in the resistant recurrence was already prevalent in the naïve tumor, indicating that resistance is not strictly driven by genomic selection but rather by non-genetic adaptive mechanisms. Preliminary results from the scRNAseq analysis suggest that specific survival pathways become essential in the advanced resistant stage

**Discussion :**
These findings demonstrate that tumor resistance evolves primarily through transcriptional and metabolic adaptation under therapeutic pressure, independent of strict clonal selection. The distinction between transient and stabilized resistance highlights the importance of single-cell resolution analyses. Integration of transcriptomic and functional screening approaches provides a powerful framework to uncover stage-specific vulnerabilities that could be therapeutically exploited.

**Conclusion :**
Our study emphasizes that resistance in recurrent tumors is driven by adaptive non-genetic mechanisms rather than exclusive genomic selection. Single-cell analyses combined with in vivo functional screens in PDX models will reveal potential molecular targets and pathways that could be leveraged to overcome or reverse resistance in advanced recurrent tumors, providing a roadmap for the development of precision therapeutic strategies.

1st Edition
CRCM Symposium
CANCER RESEARCH CENTER MARSEILLE
CRCM CANCER RESEARCH CENTER Marseille
Comet Cell communication & Microenvironment dpt.
Translate-IT Translational research & Innovative therapies dpt.
4 - 6 February 2026
MARSEILLE
Palais du Pharo

## Posters Session 1 - Precision oncology, targeted therapies and strategies for refined drug delivery

# S1CA06 : Identifying Therapeutic Vulnerabilities in Drug-Tolerant Persister Cells of Triple-Negative Breast Cancer Through Boolean Network Inference

*Min Wu*

**Authors:**
Min Wu (1), Mauro VEDELAGO (2), Julien Wicinski (2), Martin Castagné (2), Emmanuelle Charafe-Jauffret (3), Christophe Ginestier (3)

*1. MARSEILLE, France*
*2. none, MARSEILLE, France*
*3. corresponding author, none, MARSEILLE, France*

**Keywords:** Drug-tolerant persisters, Triple-negative breast cancer, Cellular plasticity, Boolean networks, REVERT, Therapeutic vulnerabilities

**Introduction**
Triple-negative breast cancer (TNBC) remains the most aggressive breast cancer subtype with limited treatment options and high recurrence rates. Drug-tolerant persister (DTP) cells, a rare subpopulation that survives chemotherapy through phenotypic plasticity, are increasingly recognized as the seed of relapse. However, systematic approaches to identify molecular vulnerabilities in DTPs and reverse their tolerant state remain lacking, representing a critical gap in developing effective anti-relapse strategies.

**Method :**
We induced a DTP model in SUM159 cells (doxorubicin: docetaxel = 1:1000 dosing), capturing naive, DTP, and relapse states, and performed singlecell RNA sequencing. We adapted the REVERT (REVerse Transitions) framework to infer Boolean regulatory networks and identify attractor states representing stable cellular phenotypes. This systems biology approach enables computational prediction of perturbation targets that can destabilize DTP states, thereby restoring drug sensitivity.

**Results :**
Boolean network inference identified a 20-gene regulatory network governing naive-to-DTP transitions, encompassing cell cycle regulators (E2F1/2/7, TFDP1, BRCA1, RAD21), chromatin modifiers (EZH2), transcriptional regulators (MYC, NFKB1, NFE2L2), and plasticity factors (ZEB1, JUNB, FOXP4). Attractor analysis revealed 12 stable states with basin distributions ranging from 6-13%, suggesting a complex multistable landscape. Key nodes, including E2F family members, MYC, NFKB1, and ZEB1, exhibited high state-switching variability across attractors, marking them as potential intervention targets.

**Discussion :**
This study provides a systems-level map of regulatory vulnerabilities underlying DTP formation and plasticity in TNBC. The identified network nodes represent candidate targets for experimental validation to develop combination strategies that collapse persister states and prevent relapse. Our REVERT-based approach offers a generalizable framework for rational therapeutic target discovery in chemoresistant cancers.

**Conclusion :**
The REVERT-based approach offers a generalizable framework for rational therapeutic target discovery in TNBC drug-tolerant persister cells.

1st Edition
CRCM Symposium
CANCER RESEARCH CENTER MARSEILLE
CRCM CANCER RESEARCH CENTER Marseille
Comet Cell communication & Microenvironment dpt.
Translate-IT Translational research & Innovative therapies dpt.
4 - 6 February 2026
MARSEILLE
Palais du Pharo

## Posters Session 1 - Precision oncology, targeted therapies and strategies for refined drug delivery

# S1CA07 : Validation and molecular study of new ubiquitination type theranostic markers in pancreatic cancer

*Hery Dinah Ratovonindnrina*

**Authors:**
Hery Dinah Ratovonindnrina (1), Philippe Soubeyran (1), Odile Gayet (1), Marion Rubis (1), Julie Roques (1), Juan Iovanna (1), Nelson Dusetti (1)

*1. Translate IT, CRCM, Marseille, France*

**Keywords:** Pancreatic ductal adenocarcinoma (PDAC); chemoresistance; ubiquitination; post-translational modifications (PTMs); theranostic markers

**Introduction**
Pancreatic ductal adenocarcinoma (PDAC) remains one of the most aggressive malignancies, with a median survival of approximately six months and a five-year survival rate of only 5–7%. Post-translational modifications (PTMs), such as ubiquitination, play key roles in protein function regulation, yet their involvement in PDAC chemoresistance remains poorly understood. Mass spectrometry analysis of 60 PDAC samples identified 37 ubiquitination profiles associated with resistance to gemcitabine, 5-FU, oxaliplatin, and irinotecan. We hypothesized that these ubiquitination profiles could serve as theranostic markers and molecular targets in PDAC and aimed to validate their functional relevance.

**Method :**
Seven candidate proteins were selected based on their biological function and reported association with chemoresistance. The type of ubiquitination (mono-, multi- or polyubiquitination) was characterized using nickel pull-down, immunoprecipitation, and western blot analyses. The correlation between ubiquitination and drug resistance was assessed by PLA on TMAs derived from PDX models sensitive or resistant to chemotherapy. Sitedirected mutagenesis (lysine-to-arginine substitution) was used to inactivate specific ubiquitination sites, and functional effects were evaluated by overexpression in primary PDAC cell lines.

**Results :**
PSMD2, RPS20, and SLC3A2 were validated as potential theranostic markers. Their ubiquitination was increased in resistant tumor cells, correlating positively with chemoresistance for PSMD2 and RPS20, and negatively for SLC3A2. Inactivation of two critical ubiquitination sites, including RPS2 K58R and CDC42 K133R, partially restored chemosensitivity, highlighting a functional role of ubiquitination in maintaining the resistant phenotype

**Discussion :**
The identified ubiquitination events appear to modulate protein stability and signaling pathways essential for maintaining chemoresistance in PDAC. The functional rescue observed after site-specific ubiquitination loss suggests that these PTMs actively regulate cellular stress responses and survival mechanisms, positioning them as key drivers of resistance biology.

**Conclusion :**
These findings reveal novel resistance mechanisms involving ubiquitination and support a theranostic and personalized treatment approach in PDAC through the targeting of specific PTMs

1st Edition
CRCM Symposium
CANCER RESEARCH CENTER MARSEILLE
CRCM CANCER RESEARCH CENTER Marseille
Comet Cell communication & Microenvironment dpt.
Translate-IT Translational research & Innovative therapies dpt.
4 - 6 February 2026
MARSEILLE
Palais du Pharo

## Posters Session 1 - Precision oncology, targeted therapies and strategies for refined drug delivery

# S1CA08 : Identification and characterization of atypical circulating cells during neoadjuvant chemotherapy in early breast cancer patients

*Agathe Cohendet*

**Authors:**
Agathe Cohendet (1), Lucas Usclade (1), Claire Germier (1), Emilie Denicolaï (1), Quentin Da Costa (1), Marine Makoa-Meng (1), François Bertucci (1, 2), Emilie Mamessier (1)

*1. Oncologie Prédictive, Centre de Recherche en Cancérologie de Marseille, Marseille, France*
*2. Département d'Oncologie Médicale, Institut Paoli-Calmettes, Marseille, France*

**Keywords:** circulating tumor cell, liquid biopsy, breast cancer, biomarker

**Introduction**
Breast cancer patients can benefit from different treatment options depending on the stage and type of tumor. Despite similar indications, not all tumors respond equally well to a particular treatment, and patients who respond poorly are at higher risk of early recurrence. Therefore, there is an urgent need to develop tools to identify the appropriate "tumor/treatment response" pair early after treatment initiation. The search for easily accessible and sensitive biomarkers of early response to cancer therapies is one of the promises of liquid biopsy.

**Method :**
This is the focus of the Neo-R clinical trial, in which blood samples were collected from 70 patients with early breast cancer before, during, and after neoadjuvant chemotherapy. Assuming that the number of circulating tumor cells (CTCs) remains stable or increases at all time points in nonresponsive patients, we isolated these cells using size-based and low-deformability methods. We then counted and characterized them at the cytological, phenotypic, and molecular levels.

**Results :**
Surprisingly, in addition to "classical" CTCs, we also observed isolated subsets of atypical circulating cells (aCCs). In the literature, these are anecdotally referred to as "giant cells," and two hypotheses have been proposed, but not yet tested in detail, regarding their possible origin: aCCs could be either cancer-associated macrophage-like cells or megakaryocytes. Interestingly, these aCCs occur more frequently in patients who do not respond to neoadjuvant treatment.

**Conclusion :**
Using ex vivo (multiplex immunofluorescence), molecular (single-cell RNA sequencing), and in silico approaches, my work aims to provide new insights into these aCCs with the goal of elucidating their role during the metastatic cascade.

1st Edition
CRCM Symposium
CANCER RESEARCH CENTER MARSEILLE
CRCM CANCER RESEARCH CENTER Marseille
Comet Cell communication & Microenvironment dpt.
Translate-IT Translational research & Innovative therapies dpt.
4 - 6 February 2026
MARSEILLE
Palais du Pharo

## Posters Session 1 - Precision oncology, targeted therapies and strategies for refined drug delivery

# S1CA09 : Combining innate Vδ2 and CAR-mediated targeting to overcome glioblastoma heterogeneity

*Julianne Ceroni*

**Author:**
Julianne Ceroni (1)

*1. Translate IT, CRCM, Marseille, France*

**Keywords:** Glioblastoma, heterogeneity, molecular state, cellular state, γδ CAR T cells

**Introduction**
Despite aggressive and multimodal treatments, Glioblastoma (GBM) remains the deadliest primary brain tumor with a median overall survival of approximately 18 months and a 5-year survival rate below 5%. Multiple mechanisms contribute to therapeutic failure, including the great intratumoral heterogeneity of GBM. Three major molecular states have been described, namely the mesenchymal-like (MES), the astrocyte-like (AC) and the oligodendrocyte progenitor (OPC) states, each of them displaying either stem-like (GSC) or differentiated-like (DGC) features. Among these subpopulations, MES state and GSC cells are considered the most aggressive and seems associated with GBM recurrence. In this context, we developed an immunotherapy approach based on engineered Vδ2 T lymphocytes expressing a Chimeric Antigen Receptor (CAR) targeting the ganglioside GD2 or its O-acetylated form OGD2, with the aim of targeting all GBM subpopulations.

**Method :**
To address GBM heterogeneity, we used human GBM cell lines cultured under GSC- or DGC-promoting conditions, as well as primary GBM cultures representing distinct molecular states. GD2 and OGD2 expression were assessed by flow cytometry. Vδ2 CAR-T cell activation was evaluated by degranulation assay and tumor cell killing, using flow cytometry and live-cell videomicroscopy, respectively.

**Results :**
We first confirmed that Vδ2 T cells recognized and killed MES GBM cells through innate immunoreactivity involving Vδ2 TCR recognition of butyrophilins. Depending on the cell line, innate recognition was also observed with some GSC and DGC cells. We then demonstrated that all GSC cells, as well as AC/OPC cells, express significant levels of GD2, and to a lesser extent, OGD2, allowing their recognition and killing by Vδ2-CAR T cells targeting either ganglioside. Specific CAR-mediated recognition was supported by the loss of Vδ2-CAR T cell cytotoxicity upon abrogation of GD2 or OGD2 expression by genetic silencing of the respective biosynthetic enzymes. In contrast, DGC cells were not efficiently recognized by either innate nor CAR-mediated targeting.

**Discussion :**
Our results indicate that innate Vδ2 T cell cytotoxicity combined with CAR-mediated ganglioside targeting overcomes most of GBM heterogeneity. Importantly, aggressive subpopulations as MES cells and GSC cells subpopulation were efficiently eliminated. However, our strategy remains ineffective against some DGC cells, highlighting a potential niche for relapse and the need for complementary approaches.

**Conclusion :**
In conclusion, our results support the use of Vδ2-CAR T cells as a promising approach to improve immunotherapy efficiency in GBM.

1st Edition
CRCM Symposium
CANCER RESEARCH CENTER MARSEILLE
CRCM CANCER RESEARCH CENTER Marseille
Comet Cell communication & Microenvironment dpt.
Translate-IT Translational research & Innovative therapies dpt.
4 - 6 February 2026
MARSEILLE
Palais du Pharo

## Posters Session 1 - Precision oncology, targeted therapies and strategies for refined drug delivery

### S1CA10 : Cadherin X: new target to fight pancreatic cancer ?

*Amandine Lopez*

**Authors:**
Amandine Lopez (1), Sébastien Germain (1), Rénaté Bonier (1), Philippe Guigue (1), Stéphane Audebert (2), Luc Camoin (2), Juan Iovanna (1), Nelson Dusetti (1), Véronique Rigot (1), Frédéric Andre (1)

*1. Translate-IT, Centre de Recherche en Cancérologie de Marseille (CRCM), Marseille, France*
*2. Protéomique et Spectrométrie de Masse, Centre de Recherche en Cancérologie de Marseille (CRCM), Marseille, France*

**Keywords:** Aggregation, Cell-cell interaction, Invasion, Migration, Signaling pathway

**Introduction**
Due to their variable expression during pancreatic carcinogenesis, cadherins could serve as markers for pancreatic ductal adenocarcinoma (PDAC). A poorly studied cadherin named CDHX for confidentiality, not detected in most healthy tissues is expressed early in pancreatic ductal cancer. High level expression of this molecule is associated with reduced patient survival. CDHX may be used as a tool for prognostic, diagnostic, and therapeutic of PDAC. CDHX could drive gene dysregulation and disrupt signaling pathways, contributing to tumor invasion and promoting cancer aggressiveness.

**Method :**
CDHX expression was forced in the pancreatic cancer cell lines PANC-1 and MIA PaCa-2. Aggregation assays were performed to assess the adhesive potential of CDHX. Invasion and migration assays were performed in order to determine the impact of CDHX on PDAC aggressiveness. Finally, proteomic analysis was conducted to identify CDHX-interacting proteins, potentially involved in cell adhesion and invasion.

**Results :**
CDHX expression slightly alters the adhesive capabilities of cells. However, it affects their invasive properties by promoting the invasion of isolated cells. Expression of several genes involved in cell invasion is deregulated upon CDHX expression potentially explaining the observed changes in invasion.

**Discussion :**
Further validation in primary cultures and in vivo models is planned. The study indicates novel stage-specific signaling pathways and biomarkers, which could help define a molecular signature of tumor invasion and guide development of CDHX-targeted therapies.

**Conclusion :**
These findings suggest that CDHX may contribute to PDAC aggressiveness and represent a potential therapeutic target.

1st Edition
CRCM Symposium
CANCER RESEARCH CENTER MARSEILLE
CRCM CANCER RESEARCH CENTER Marseille
Comet Cell communication & Microenvironment dpt.
Translate-IT Translational research & Innovative therapies dpt.
4 - 6 February 2026
MARSEILLE
Palais du Pharo

## Posters Session 1 - Precision oncology, targeted therapies and strategies for refined drug delivery

# S1CA11 : Bispecific engineered aptamers for ADAMTSL5 silencing confer druggable AXL addiction to liver cancer

*Celia Sequera Hurtado*

**Authors:**
Ines Barahona (1), Aurelie Dobric (1), Abdessamad El Kaoutari (1), Margherita Grattarola (1), Nicolas Pons (1), Shayan Ahmed (2), Caroline Bonnet (1), Lukas Kubler (3), Sandro Nuciforo (3), Muge Kaya (4), Nils Collinet (4), Anne Farina (5), Markus Heim (6), Remy Castellano (1), Jean-Paul Borg (6), Laurence Choulier (2), Celia Sequera Hurtado (1), Flavio Maina (1)

1. *Aix Marseille Univ, CNRS, Inserm, Institut Paoli-Calmettes, CRCM (Centre de Recherche en Cancérologie de Marseille), Marseille, France*
2. *UMR7021 Laboratory of Bioimaging and Pathologies, CNRS University of Strasbourg, Illkirch, France*
3. *Department of Biomedicine, University Hospital Basel, University of Basel, Basel, Switzerland*
4. *Aix Marseille Univ, Experimental Histopathology ICEP Platform, CNRS, INSERM, Institut Paoli-5 Calmettes, CRCM (Centre de Recherche en Cancérologie de Marseille), Marseille, France*
5. *CRCM (Centre de Recherche en Cancérologie de Marseille), Marseille, France*
6. *COMET, CRCM (Centre de Recherche en Cancérologie de Marseille), Marseille, France*

**Keywords:** Hepatocellular carcinoma, ADAMTSL5, nucleic-acid aptamer based therapy, Nucleolin, receptor tyrosine kinase inhibitors, AXL, anti-AXLADC, drug resistance, precision oncology, nanomedicine in cancer therapy, patient signature.

**Introduction**
The molecular heterogeneity of hepatocellular carcinoma (HCC) and the lack of oncogenic addictions are among the features underlying unsatisfactory treatment options in the clinic.

**Method :**
Transcriptomic data from distinct cancer patient cohorts were bioinformatically analysed to assess gene expression and explore pathway enrichments in different groups. A targeted delivery system was engineered to silence the ADAMTSL5 oncogene and its stability was determined under biological conditions. Its effects on HCC cells, tumoroids, and xenografts were evaluated using a range of approaches, including RT-qPCR, immunostaining, flow cytometry, and viability assays, both alone and in combination with anticancer agents. Tumour microarrays were used to assess ADAMTSL5 and NCL protein levels.

**Results :**
We report that approximately half of HCC patients exhibit simultaneous upregulation of two oncogenes, ADAMTSL5 and Nucleolin (NCL). This molecular signature also characterises large proportions of patients with other cancer types. As increased NCL levels result in its localisation to the membrane of cancer cells, we engineered a targeted delivery system, named aptAdamtsl5, based on the conjugation of a nucleic acid aptamer targeting NCL with a shRNA sequence targeting ADAMTSL5. We show that aptAdamtsl5 selectively targets ADAMTSL5 in cancer cells expressing NCL at the plasma membrane, leading to marked cellular and molecular changes and reduced proliferative capacity. We further demonstrate that aptAdamtsl5 sensitises cancer cells to receptor tyrosine kinase inhibitors, to which the cells are otherwise resistant. Moreover, aptAdamtsl5 confers druggable AXL addiction to liver cancer. The increased stability of aptAdamtsl5 in biological samples enables evaluation of its therapeutic effectiveness on mouse and patient-derived tumoroids as well as in HCC in vivo models. A subgroup of HCC patients potentially responsive to aptAdamtsl5 can be identified based on elevated ADAMTSL5 and NCL levels.

**Conclusion :**
Our results identify a new subgroup of cancer patients with elevated ADAMTSL5 and NCL, who could benefit from the therapeutic potential of aptAdamtsl5 to overcome resistance to current clinical treatments.


## Posters Session 1 - Precision oncology, targeted therapies and strategies for refined drug delivery

# S1CA12 : Lipid and cell cycling perturbations driven by the HDAC inhibitor romidepsin render liver cancer vulnerable to RTK targeting and immunologically active

*Margherita Grattarola*

**Authors:**
Margherita Grattarola (1), Celia Sequera (2), Floriane Cannet (3), Aurélie Dobric (4), Paula Michea Veloso (5), Abdessamad El Kaoutari (5), Paraskevi Kousteridou (5), Delphine Debayle (6), Lukas Kübler (7), Sandro Nuciforo (7), Frédéric Saltel (8), Markus H. Heim (7), Sophie Vasseur (5), Xavier Adhoute (9), Fabienne Guillaumond (5), Jean-Paul Borg (5), Christian Morel (10), Flavio Maina (5)

*1. CRCM, Marseille, France*
*2. CRCM, Marseille, France*
*3. Aix Marseille Univ, CNRS/IN2P3, CPPM, CERIMED, Marseille, France*
*4. Aix Marseille Univ, CNRS, Inserm, Institut Paoli-Calmettes, UCL, London, United Kingdom*
*5. Aix Marseille Univ, CNRS, Inserm, Institut Paoli-Calmettes, Marseille, France*
*6. IPMC-CNRS, Plateforme d'analyse des biomolécules PAB-Azur, Valbonne, France*
*7. Department of Biomedicine, University Hospital Basel, University of Basel, Basel, Switzerland*
*8. Bordeaux University, Inserm, Oncoprot, UMS 005, UMR1312, BRIC, BoRdeaux Institute in onCology, Bordeaux, France*
*9. Department of Gastroenterology and Hepatology, Hôpital Saint-Joseph, Marseille, France*
*10. Aix Marseille Univ, CNRS/IN2P3, CPPM, Marseille, France*

**Introduction**
Histone deacetylases (HDACs) are epigenetic regulators frequently altered in cancer. The relevance of their targeting is highlighted by the use of HDAC inhibitors (HDACi) for anticancer treatment in preclinical and clinical investigations for solid tumours. Among complex cancer types, hepatocellular carcinoma (HCC), the most common type of liver cancer, is characterised by aggressiveness and resistance to available therapies, and displays several epigenetic alterations whose functional relevance has been reported in recent studies. We hypothesised that epigenetic drugs targeting HDACs may confer vulnerability to HCC, including to clinically relevant agents as receptor tyrosine kinase inhibitors (RTKi).

Method :
We bioinformatically evaluated the relevance of class-I HDACs in HCC patients using available datasets. The effects of romidepsin, a class-I HDACi, were assessed in HCC cells, patient-derived tumoroids, and HCC mouse models. Molecular alterations were determined using proteomics, biochemistry, lipidomics, and immunostaining.

Results :
We showed that overexpression of HDAC1 and HDAC2 occurs in HCC patients across eight cohorts and is correlated with decreased overall survival. We documented that romidepsin perturbs cell cycle and survival signals in HCC cells. Romidepsin alters the expression of lipid metabolism regulators, reshaping the composition of distinct lipid species. Additionally, romidepsin affects the mitotic spindle machinery, leading to monopolar spindle formation and cell cycle arrest. These alterations render HCC cells vulnerable, conferring dependency on RTK support. Combined treatment of HCC cells with romidepsin and the RTKi cabozantinib (RomiCabo) converts the cytostatic effect of romidepsin, into apoptosis. We reported the therapeutic effectiveness of RomiCabo treatment on HCC-patient derived tumoroids and on the Alb-R26Met mouse model, which recapitulates HCC resistance and heterogeneity. Furthermore, we documented that RomiCabo leads to immune remodelling in the tumour microenvironment, conferring an immune-stimulatory profile.

Conclusion :
Our findings highlight the intricate crosstalk between epigenetics, metabolism, and immune response in cancer. The broad action of romidepsin on distinct cellular functions underscores its therapeutic potential for HCC treatment.

1st Edition
CRCM Symposium
CANCER RESEARCH CENTER MARSEILLE
CRCM CANCER RESEARCH CENTER Marseille
Comet Cell communication & Microenvironment dpt.
Translate-IT Translational research & Innovative therapies dpt.
4 - 6 February 2026
MARSEILLE
Palais du Pharo

## Posters Session 1 - Precision oncology, targeted therapies and strategies for refined drug delivery

# S1CA13 : Deciphering the mechanism of action of ML-IAP and its inhibitors in glioblastoma: towards therapeutic optimization

*Théo Vialatte*

**Authors:**
Théo Vialatte (1), Alessandra Pagano (1), Claude Villard (1), Eddy Pasquier (2), Emeline Tabouret (1, 3), Aurélie Tchoghandjian (1)

*1. Institut de Neurophysiopathologie, Aix Marseille université, Marseille, France*
*2. Centre de recherche en cancérologie de Marseille, Inserm, Marseille, France*
*3. Department of Neuro-oncology, Hopitaux de Marseille, Marseille, France*

**Keywords:** Glioblastoma, Inhibitor of Apoptosis Protein, ML-IAP, interactome, Smac mimetics, Therapeutic strategies

**Introduction**
Glioblastoma is the most aggressive primary brain tumor in adults. The overexpression of anti-apoptotic mechanisms and the presence of cancer stem cells (CSCs) impair treatments efficiency. Among the family of inhibitor of apoptosis proteins (IAPs), we have shown that ML-IAP is a marker of poor prognosis in glioblastoma patients and is overexpressed in CSCs (Tchoghandjian, 2016). The anti-apoptotic activity of ML-IAP relies on caspase inhibition and the sequestration of endogenous SMAC. However, its precise mechanism of action has not yet been fully characterized. To target IAPs, inhibitors called SMAC mimetics (SMs) have been developed. We have demonstrated that GDC-0152, a SM with high affinity for ML-IAP, enhances apoptosis and improves survival in glioblastoma mouse models. It also induces a remodelling of the tumor microenvironment (Snacel- Fazy,2024). In order to optimize its efficacy for a potential therapeutic application, we aim to determine whether its effects are primarily due to a specific interaction with IAPs or if other protein targets are also involved. The objective of this study is to better characterize the anti-apoptotic mechanism of ML-IAP and the mode of action of its inhibitors.

**Method :**
To explore ML-IAP interactome we transfected a Flag-ML-IAP cDNA sequence into a CSC line and we performed an anti-Flag immunoprecipitation followed by proteomic analysis via mass spectrometry. To identify additional potential protein targets of GDC-0152 and its oral derivative GDC-0917 (GDCs), a Thermal Proteome Profiling (TPP) experiment was conducted. This technique is based on the principle that ligand binding to its target can alter the protein's denaturation temperature. Cell lysates treated with GDCs or vehicle were subjected to a temperature gradient and then ultracentrifuged. The supernatant, containing folded proteins, was collected and analysed by mass spectrometry to identify GDCs protein targets.

**Results :**
Flag-ML-IAP overexpression increased proliferation and clonogenicity in a CSC line but did not alter the response to GDCs. Proteomic analysis of the immunoprecipitated proteins identified potential ML-IAP partners. Among them, BIRC2, HADHB, HTR2, and PGAM5 are already known as partners of other IAP family members, validating our experimental approach. CPT1A and DCLK2 have been identified as potential new partners. TPP revealed 22 proteins with significant changes, suggesting that they may constitute potential targets of GDCs treatment. Their functional implications are now under investigation.

**Conclusion :**
By identifying both the ML-IAP interactome and the proteins potentially modulated by the GDC compounds, this study provides a foundation to improve the development of therapeutic strategies targeting ML-IAP.

1st Edition
CRCM Symposium
CANCER RESEARCH CENTER MARSEILLE
CRCM CANCER RESEARCH CENTER Marseille
Comet Cell communication & Microenvironment dpt.
Translate-IT Translational research & Innovative therapies dpt.
4 - 6 February 2026
MARSEILLE
Palais du Pharo

## Posters Session 1 - Precision oncology, targeted therapies and strategies for refined drug delivery

### S1CA14 : Diagnostic and Therapeutic Potential of Nanobodies against ADAMTSL5 to Target Cancer Communities

*Saliha Lagsier*

**Authors:**
Saliha Lagsier (1), Ines Barahona (1), Celia Sequera (1), Pascale Marchot (2), Flavio Maina (1, 3), Jean -Paul Borg (1, 4)

*1. Aix Marseille Univ, CNRS, Inserm, Institut Paoli-Calmettes, Centre de Recherche en Cancérologie de Marseille (CRCM), Marseille, France.*
*2. Aix Marseille Univ, CNRS, Architecture et Fonction des Macromolécules Biologiques (AFMB), Marseille, France, Marseille, France*
*3. Turing Center for Living Systems (CENTURI), Marseille, France, Marseille, France*
*4. Institut Universitaire de France (IUF), Marseille, France*

**Keywords:** ADAMTSL5, Cancer communities, Cellular interactions, Tumour microenvironment, Cellular identity, Cellular functions, Signalling pathways, Tumour aggressiveness, Molecular interactions, Targeted therapies

**Introduction**
Homeostasis preserves tissue function through the coordinated regulation of cells and their interactions. Although essential for physiological balance, its plasticity can favour deregulated (epi)genetic and signalling programmes that initiate and sustain cancer. These alterations remodel the tissue environment to form “cancer communities” composed of malignant, immune, endothelial, and stromal cells, whose reciprocal crosstalk drives heterogeneity and adaptation. At the centre lies the tumour microenvironment and its extracellular matrix (ECM), which controls tissue composition and mechanics. Cancer and stromal cells reshape the ECM through proteases and matricellular proteins that influence signalling, proliferation, invasion, and immune and vascular responses. Such ECM-centred dynamics define key therapeutic vulnerabilities. Hepatocellular carcinoma (HCC), a leading cause of cancer mortality, exemplifies this complexity. HCC displays marked molecular heterogeneity sustained by diverse (epi) genetic changes. ADAMTSL5, a matricellular protein overexpressed in most HCCs, correlates with poor outcomes. Its inhibition suppresses oncogenic pathways, tumour aggressiveness, and drug resistance, while modulating tumour immune interactions. We hypothesise that the matricellular protein ADAMTSL5 ensures the functionality of cancer communities. We have generated engineered agents, such as nanobodies for ADAMTSL5 detection and targeting. We hypothesise that agents targeting ADAMTSL5 perturb the functionality of cancer communities.

**Method :**
Recombinant ADAMTSL5 was used to generate llama nanobodies. Their ability to bind ADAMTSL5 is assessed by ELISA, western blot, immunostaining, and immunohistochemistry. Their ability to block ADAMTSL5 function is explored by testing their effects on HCC cells using viability assays.

**Results :**
Among several nanobodies against ADAMTSL5 that we have generated, seven targeting the C-terminus and four targeting the N-terminus were selected for further characterisation. All detect ADAMTSL5 on cancer cells. Two exhibit blocking functions, shown by altered cell morphology, exemplified by changes in stress fibre formation. These blocking nanobodies impair cancer cell viability when used alone and induce AXL dependency, as demonstrated by increased sensitivity to the AXL inhibitor bemcentinib.

**Discussion :**
These ongoing studies underline the diagnostic and therapeutic relevance of these nanobodies against ADAMTSL5. Furthermore, they represent unique tools to uncover how ADAMTSL5 functions to regulate cancer communities.

1st Edition
CRCM Symposium
CANCER RESEARCH CENTER MARSEILLE
CRCM CANCER RESEARCH CENTER Marseille
Comet Cell communication & Microenvironment dpt.
Translate-IT Translational research & Innovative therapies dpt.
4 - 6 February 2026
MARSEILLE
Palais du Pharo

## Posters Session 1 - Precision oncology, targeted therapies and strategies for refined drug delivery

# S1CA15 : Combinatorial effects of romidepsin with inhibitors of anti-apoptotic signals on hepatocellular carcinoma and its immune microenvironment

*Filippo Castagna*

**Authors:**
Filippo Castagna (1), Margherita Grattarola (2), Nicolas Pons (2), Paula Michea Veloso (2), Jean-Paul Borg (2), Celia Sequera-Hurtado (2), Flavio Maina (2)

*1. Marseille, France*
*2. CRCM, Marseille, France*

**Keywords:** Hepatocellular carcinoma (HCC), romidepsin, anti-apoptotic signals, tumour heterogeneity, tumour immune microenvironment

**Introduction**
Hepatocellular carcinoma (HCC) is a leading cause of cancer mortality, characterised by extensive heterogeneity at the (epi) genetic and immune microenvironment levels. This heterogeneity contributes to HCC resistance and the limited benefit of current therapies. Previous work from our laboratory has identified key vulnerabilities in HCC following blockade of signals such as MEK, BCL-XL, HDACs, and receptor tyrosine kinases (RTKs). We designed an experimental setting to assess whether combined inhibition of HDAC1/2 (by romidepsin) and anti-apoptotic signals (by navitoclax or venetoclax) elicits therapeutic effects on HCC cells while specifically remodelling the tumour immune microenvironment.

**Method :**
Viability of HCC cells and Alb-R26Met tumoroids was assessed following romidepsin plus navitoclax or venetoclax (RomiNavi/Vene) treatments. Mechanistic effects were analysed by Western blot. Drug-induced immune remodelling was investigated by spectral cytometry.

**Results :**
We found that the viability of heterogeneous human HCC lines, primary murine Alb-R26Met HCC cells and tumoroids is severely affected by RomiNavi and RomiVene at relatively low doses. Preliminary mechanistic studies reveal that romidepsin increases p21 while decreasing MYC, Cyclin-D1, and CDK1 phosphorylation, consistent with disrupted cell cycle progression. Romidepsin also reduces multiple anti-apoptotic proteins (including BCL-XL, Survivin, XIAP), while upregulating MCL1, likely as an attempt to counteract unbalanced anti-apoptotic signals. Notably, DNA damage signalling, monitored by γH2AX, is robustly induced only in RomiNavi and RomiVene conditions, indicating that only these combinations induce strong DNA damage. Further mechanistic aspects are currently being explored through -omics. Spectral cytometry revealed that each regimen induces distinct remodelling of immune cell type populations in control livers. RomiNavi prominently increases monocytes, while all treatments reduce B cells, most markedly under RomiNavi or RomiVene. Furthermore, both combinations expand cDC1s and decrease pDCs, whereas only RomiVene elevates cDC2s. Macrophages are decreased in navitoclax- and venetoclax-treated groups, whereas CD44 and PD1 levels on CD90.2$^+$ cells remain stable. The remodelling process triggered by RomiNavi/Vene in the tumour microenvironment is ongoing.

**Discussion :**
Our findings reveal a dual mechanism elicited by RomiNavi/Vene: direct induction of tumour cell cytotoxicity and reshaping of immune cell types. The latter offers the possibility to pair RomiNavi/Vene with optimal immunotherapies.

**Conclusion :**
RomiNavi/Vene elicit dual antitumor effects: direct cytotoxicity via cell cycle arrest, apoptosis, and DNA damage in heterogeneous HCC models, plus distinct liver immune remodeling (e.g., cDC1 expansion, macrophage reduction). Tumor microenvironment validation will guide immunotherapy pairings.

1st Edition
CRCM Symposium
CANCER RESEARCH CENTER MARSEILLE
CRCM CANCER RESEARCH CENTER Marseille
Comet Cell communication & Microenvironment dpt.
Translate-IT Translational research & Innovative therapies dpt.
4 - 6 February 2026
MARSEILLE
Palais du Pharo

## Posters Session 1 - Precision oncology, targeted therapies and strategies for refined drug delivery

### S1CA16 : Targeting MINK1 in triple negative breast cancer with a kinase inhibitor

*Giulia Delacourt*

**Authors:**
Giulia Delacourt (1), Sébastien Letard (2), Etienne Rebuffet (2), Armelle Goubard (2), Jean Ly (3), Patrice Dubreuil (2), Avais Daulat (1), Jean-Paul Borg (1)

*1. COMET, Centre de Recherche en Cancérologie de Marseille, Marseille, France*
*2. AB Science, Paris 75008, France, Marseille, France*
*3. Centre de Recherche en Cancérologie de Marseille, Marseille, France*

**Keywords:** Kinase, inhibor, Triple Negative Breast Cancer

**Introduction**
The Wnt/PCP (Planar Cell Polarity) pathway is highly deregulated in TNBC, thereby promoting tumor proliferation and migration. We have identified the serine-threonine kinase MINK1, as a key regulator of this pathway and shown that MINK1 hyperactivates this pathway by phosphorylating PRICKLE1 and LL5β, two pro-metastatic proteins associated with poor prognosis in TNBC. My project aims to characterize the functions and molecular organization of MINK1 and its pro-metastatic complex, as well as to assess its potential as a therapeutic target in TNBC. To do this, an inhibitor of MINK1's catalytic activity has been developed. This inhibitor is referred to here as "Compound2"

**Method :**
The efficiency of Compound2 was validated thanks to functional assays, including western blots, immunoprecipitations, and cell migration assays performed on TNBC cell lines. Its effect was also confirmed in 3D cellular models, including spheroids formed from TNBC cell lines and organoids generated from primary breast tumors xenografted into humanized mammary glands (PDX). Moreover, proteomic and phosphoproteomic approaches were also carried out to validate the selectivity of Compound2 for MINK1.

**Results :**
Compound2 belongs to the family of ATP analogs, therefore it binds to the kinase domain of MINK1, specifically within the ATP-binding pocket. The crystal structure of the MINK1 kinase domain bound to Compound2 has been resolved, providing invaluable insights into the mechanism of inhibition. Functional and signaling assays have demonstrated that Compound2 inhibits the phosphorylation of MINK1 substrates (PRICKLE1, LL5β and AKT) and significantly reduces the migration of TNBC cells. Its effectiveness was also confirmed in 3D cellular models. A strong and significant correlation was observed between MINK1 expression levels and the response of TNBC cell lines to Compound2. Moreover, the selectivity of Compound2 for MINK1 was confirmed by proteomic and phosphoproteomic analyses. These approaches have also identified pathways regulated by MINK1, thereby opening the door to new combinatorial therapeutic strategies.

**Discussion :**
The main objective focuses on the generation of MINK1 mutants able to make MINK1 constitutively active or inactive, to better understand its function and role in the tumorigenic process. Other mutations will be introduced within the MINK1 sequence to further confirm the selectivity of Compound2. Another objective is to investigate combination therapy strategies with Compound2 to enhance its efficiency, given MINK1's involvement in therapeutic resistance.

**Conclusion :**
This project demonstrates the therapeutic potential of targeting MINK1 in TNBC.

1st Edition
CRCM Symposium
CANCER RESEARCH CENTER MARSEILLE
CRCM CANCER RESEARCH CENTER Marseille
Comet Cell communication & Microenvironment dpt.
Translate-IT Translational research & Innovative therapies dpt.
4 - 6 February 2026
MARSEILLE
Palais du Pharo

## Posters Session 1 - Precision oncology, targeted therapies and strategies for refined drug delivery

### S1CA17 : UBE2N inhibition to sensitize ovarian cancers to PARP inhibitors by induction of HRD phenotype

*Léonie Ibazizene*

**Authors:**
Léonie Ibazizene (1), Shafi Ullah Khan (2), Steven Lohard (3), Nicolas Elie (4), Laurent Poulain (5), Matthieu Meryet-Figuiere (5), Louis-Bastien Weiswald (5)

1. *Université de Caen Normandie, INSERM, ANTICIPE U1086, Interdisciplinary Research Unit for Cancer Prevention and Treatment, Comprehensive Cancer Center F. Baclesse, 14000 Caen, France, INSERM, ANTICIPE U1086, Caen, France*
2. *Université de Caen Normandie, INSERM, ANTICIPE U1086, Interdisciplinary Research Unit for Cancer Prevention and Treatment, Comprehensive Cancer Center F. Baclesse, 14000 Caen, France, INSERM, ANTICIPE U1086,, Caen cedex 05., France*
3. *Université de Caen Normandie, INSERM, ANTICIPE U1086, Interdisciplinary Research Unit for Cancer Prevention and Treatment, Comprehensive Cancer Center F. Baclesse, 14000 Caen, France, INSERM, ANTICIPE U1086, Caen cedex 05., France*
4. *Université de Caen Normandie, Services Unit PLATON "support platforms for preclinical and translational research in oncology", Virtual'His, 14000 Caen, France , Université de Caen Normandie, Caen cedex 05., France*
5. *UNICANCER, Comprehensive Cancer Center F. Baclesse, 14000 Caen, France, INSERM, ANTICIPE U1086, Caen cedex 05., France*

**Keywords:** Homologous recombination, UBE2N, ovarian cancer, sensitization, PARP inhibitors

**Introduction**
Ovarian cancers (OC) represent the leading cause of death from gynecological cancers worldwide. First-line treatment combines surgery with carboplatin-based chemotherapy, and PARP inhibitors (PARPi) for eligible patients. PARPi efficacy rely on defects in the Homologous Recombination DNA repair pathway (HRD), present in 50% of OC cases. Double stranded DNA breaks can be repaired by either Non-Homologous End Joining (NHEJ) or Homologous Recombination (HR) pathways. While HR is considered faithful, NHEJ is error-prone and can lead to cell death. Thus, HRD increases tumor sensitivity to DNA-damaging agents. Our project aims to induce an HRD-like phenotype by inhibiting UBE2N, a key HR mediator, to sensitize ovarian tumors to carboplatin and PARPi.

**Method :**
We used an ovarian cancer cell line and PDTO (Patient-Derived Tumor Organoids) models generated from tumor of patients grown in 3D in extracellular matrix. UBE2N was inhibited either pharmacologically (NSC697923) or genetically (Cas9 knockout). HR proficiency following UBE2N inhibition (UBE2Ni) was assessed using multiple complementary approaches: comet assay (DNA damage), RECAP test (HR activation), DR-GFP reporter assay (effective HR DNA repair), and micronuclei quantification (genomic instability). In parallel, we investigated a potential correlation between the increase in DNA damage and/or the decrease in DNA repair by HR induced by UBE2N inhibition and its ability to sensitize cells to the action of DNA-damaging therapies (carboplatin, PARPi). Sensitization was assessed by monitoring cell morphology using the IncuCyte S3 and CellDiscoverer 7 real-time imaging systems, as well as through viability assays and colony-forming assays.

**Results :**
UBE2N inhibition, through NSC697923 or knockout, increased micronuclei and DNA damage while decreasing HR DNA repair. In addition, UBE2Ni sensitized an ovarian cancer cell line and multiple HR-proficient PDTO models to PARPi.

**Discussion :**
These findings support the therapeutic potential of UBE2Ni. Further validation in additional PDTO models is ongoing and the effects on DNA repair will be more finely characterized.

**Conclusion :**
Furthermore, this strategy could be extended to other cancer locations where DNA-damaging therapies are currently used such as pancreatic cancer (oxaliplatin-based chemotherapy and PARPi), breast cancer (carboplatin, PARPi), and head and neck cancers (radiotherapy and cisplatin), broadening its relevance in oncology.

1st Edition
CRCM Symposium
CANCER RESEARCH CENTER MARSEILLE
CRCM CANCER RESEARCH CENTER Marseille
Comet Cell communication & Microenvironment dpt.
Translate-IT Translational research & Innovative therapies dpt.
4 - 6 February 2026
MARSEILLE
Palais du Pharo

## Posters Session 1 - Precision oncology, targeted therapies and strategies for refined drug delivery

# S1CA18 : Which antibody-drug conjugate with limited off-target toxicities can be used to treat metastatic colorectal cancer?

*Lisa Malard*

**Authors:**
Lisa Malard (1), Alix Frejafon (1), Maëlle Picard (1), Pascal Finetti (1), Arnaud Guille (1), Olivier Cabaud (1), Sara Santi (2), Nadiya Belfil (1), François Bertucci (1), David Birnbaum (1), Emilie Mamessier (2)

*1. Predictive Oncology, CRCM, IPC, AP-HM, Marseille, France*
*2. Predictive Oncology, CRCM, Marseille, France*

**Keywords:** Antibody-drug conjugates, ADC, expression, colorectal cancer metastases, toxicity

**Introduction**
Colorectal cancer (CRC) is among the most common cancers. When it progresses to the metastatic stage (mCRC), especially with liver involvement, it becomes particularly difficult to treat. Perioperative therapies are often nonspecific, highly toxic, and frequently fail to eliminate all cancer cells. However, a new class of drugs, called antibody-drug conjugates, offers hope for more effective treatment of aggressive tumors. Their effectiveness depends on the expression of the ADC target in cancer tissues. These treatments have already improved outcomes for certain solid tumors, but in mCRC, their potential remains largely unexplored.

**Method :**
We analyzed the transcriptomic expression of 56 potential ADC targets, whose corresponding ADCs are used in the clinic or are currently in development. We examined their expression in bulk and at the single-cell level (by single nucleus RNAseq) in precancerous stages (inflammatory bowel diseases, polyps), primary CRC, and mCRC (liver and lung). ADC target expression in each type was compared with their expression in normal colon tissue, as well as in other normal tissues. We then assessed their expression at the single-cell level in our cohort of mCRC (B-Org cohort NCT05384184). To confirm the results at the protein level, we performed immunostaining for the ADC targets of interest on samples from the B-Org cohort.

**Results :**
Although transcriptomic expression profiles varied across the tissues analyzed, some genes, such as CD276, NECTIN4, PTK7, LGR5 and MET, emerged as promising targets. Their marked overexpression in mCRC highlights them as new potential therapeutic opportunities, which have not always been explored in clinical trials. We then refined our analysis using single-"cell" data, revealing interesting expression patterns of ADC targets. Some ADC targets showed clear differential expression compared to normal epithelial colon cells, positioning them as key candidates; others were unexpectedly expressed in the stromal compartment rather than in malignant cells, introducing a new microenvironment-based tumortargeting strategy. Immunostaining of selected ADC targets on mCRC samples confirmed these expression patterns.

**Conclusion :**
Our assessment of ADC targets landscape based on in-silico analysis allows us to identify ADC targets of potential interest for treating mCRC, a cancer urgently in need of innovative and less toxic therapies. The next step will be to test their efficacy in preclinical models of mCRC using our biobank of patient-derived mCRC organoids (n>50) and patient-derived liver organoids. This screening strategy across different expression levels and tissue types will build the preclinical rationale for selecting ADCs with strong efficacy and reduced toxicity in mCRC.

1st Edition
CRCM Symposium
CANCER RESEARCH CENTER MARSEILLE
CRCM CANCER RESEARCH CENTER Marseille
Comet Cell communication & Microenvironment dpt.
Translate-IT Translational research & Innovative therapies dpt.
4 - 6 February 2026
MARSEILLE
Palais du Pharo

## Posters Session 1 - Precision oncology, targeted therapies and strategies for refined drug delivery

### S1CA19 : Physiologically Relevant Drug Screening in PDAC Using Organoid–CAF Co-cultures

*Jérémy Ariey-Bonnet*

**Authors:**
Jérémy Ariey-Bonnet (1), Enza Scarlato (2), Loïc Moubri (3), Alex Chauvin (3), Vladimir Chocoloff (3), Pauline Moussard (3), Odile Gayet (3), Julie Roques (3), Nicolas Fraunhoffer (3), Nicolas Molinie (4), Nelson Dusetti (3)

*1. Translational and Therapeutic Research in Pancreatic Cancer, Cancer Research Center of Marseille, Marseille Cedex 9, France*
*2. Department of Medicine, Verona University, Verona, Italy*
*3. Translational and Therapeutic Research in Pancreatic Cancer, Cancer Research Center of Marseille, Marseille, France*
*4. Target discovery - Cancer biology, Servier, Saclay, France*

**Keywords:** Tumor plasticity, Stromal-tumor crosstalk, Desmoplastic stroma, Therapeutic resistance, Cellular state dynamics

**Introduction**
Pancreatic ductal adenocarcinoma (PDAC) is characterized by an abundant desmoplastic stroma enriched in cancer-associated fibroblasts (CAFs), which profoundly influence tumor growth, extracellular matrix remodeling, immune exclusion, and therapeutic resistance. However, the functional heterogeneity of CAF subtypes and their dynamic interactions with tumor cells remain insufficiently understood due to limitations of conventional 2D culture systems that exclude key components of the tumor microenvironment. Developing in vitro co-culture models for high-throughput ex vivo drug testing is therefore essential to identify actionable therapeutic targets in a physiologically relevant context and to dissect stromal-induced tumor plasticity.

**Method :**
We established a 3D co-culture system combining patient-derived PDAC organoids with primary CAF populations isolated from a matched tumor specimen. Organoids and CAFs were embedded in defined extracellular matrix conditions and maintained in optimized media supporting both cell types. To uncover actionable vulnerabilities, publicly available CRISPR screen datasets were mined, yielding an initial list of 181 druggable targets. A compound library is being assembled and will be tested using acoustic dispensing on fluorescent co-cultures, while drug effects on both cell populations will be quantified through a high-content imaging workflow. For functional validation, organoid models were engineered to express GFPtagged RNA barcodes, and CAFs were labeled with RFP via lentiviral transgenesis, enabling dynamic monitoring of cell states and plasticity under therapeutic pressure.

**Results :**
Co-culture of PDAC organoids with primary CAFs was successfully established using media compatible with the growth of both components. Initial optimization steps confirmed the feasibility of maintaining fluorescently labeled tumor cells and CAFs in a shared 3D matrix environment. Mining of DepMap CRISPR datasets and the Pharos portal identified 1,048 vulnerabilities, including 181 prioritized candidates, which are currently being integrated into a focused compound library for high-throughput testing. The generation of GFP-barcoded organoids and RFP-labeled CAFs was achieved and will enable forthcoming analyses of cell-state dynamics and therapeutic responses within the co-culture system. Additional functional and transcriptomic characterizations are ongoing.

**Discussion :**
This advanced co-culture platform provides a powerful tool to identify actionable vulnerabilities in PDAC while integrating the complexity of stromaltumor interactions. The model enables long-term evaluation of cellular state plasticity driven by CAFs and offers a physiologically relevant framework for testing therapeutic strategies targeting both tumor cells and their microenvironment.

1st Edition
CRCM Symposium
CANCER RESEARCH CENTER MARSEILLE
CRCM CANCER RESEARCH CENTER Marseille
Comet Cell communication & Microenvironment dpt.
Translate-IT Translational research & Innovative therapies dpt.
4 - 6 February 2026
MARSEILLE
Palais du Pharo

## Posters Session 1 - Precision oncology, targeted therapies and strategies for refined drug delivery

# S1CA20 : Trastuzumab deruxtecan (T-DXd) as a new therapeutic option in pancreatic ductal adenocarcinoma (PDAC)

*Chiara Dall'Ara*

**Authors:**
Chiara Dall'Ara (1), Giulia Madonini (1), Alberta Locatelli (1), Lucia Viganò (1), Barbara Galbardi (1), Matteo Dugo (1), Giorgia Foggetti (2), Tiziana Daniele (3), Giulia Orsi (1), Giampaolo Bianchini (1), Michele Reni (1), Marina Macchini (1)

*1. Medical Oncology, Compehensive Cancer Center, IRCCS San Raffaele Hospital, Milan, Italy*
*2. Experimental Oncology, Comprehensive Cancer Center, IRCCS San Raffaele Hospital, Milan, Italy*
*3. Experimental Imaging Centre, IRCCS San Raffaele Hospital, Milan, Italy*

**Keywords:** Oncology, Cancer therapy, Pancreatic cancer

**Introduction**
Pancreatic ductal adenocarcinoma (PDAC) is a highly aggressive disease with few therapeutic options. Antibody-Drug Conjugates (ADCs) are emerging anticancer agents composed of a monoclonal antibody targeting specific tumor antigens combined with high-potency cytotoxic payload. Trastuzumab Deruxtecan (T-DXd) is an ADC consisting of an anti-HER2 antibody linked to a topoisomerase-I inhibitor (DXd) active in HER2 high and low expressing solid tumors. In PDAC patients, HER2 is expressed in up to 61% of cases, playing a prognostic role. Given the broad expression of HER2 in PDAC samples, we hypothesize that T-DXd, alone and in combination with synergistic compounds, could represent an effective treatment for PDAC patients.

**Method :**
Six PDAC cell lines were analyzed (CAPAN1, PANC1005, ASPC1, PANC1, HS766T, PSN1) according to ERBB2/HER2 expression level by RNA-seq, IF, IHC, WB and FC. Whole exome sequencing was also performed. Each cell line was treated with single agents and combinations of T-DXd, PARP and KRAS inhibitors (PARPi; KRASi) and cell viability was measured by MTT assay. Changes in DNA damage markers and KRAS signalling pathway were investigated by WB (pH2AX/totH2AX, pCHK1/totCHK1, pERK/totERK, pAKT/totAKT, p-p70/tot-p70, p4EBP1/tot4EBP1). Cell cycle distribution was assessed by FC (PI assay).

**Results :**
According to ERBB2 expression level CAPAN1, ASPC1, and PANC1005 were labeled as HER2high cell lines while HS766T, PANC1, and PSN1 as HER2low. KRAS mutations were found in 6/6 lines (KRASmut), BRCA1-2 in 4/6 (BRCA1/2mut). CAPAN1 showed the highest level of total HER2 with highest membrane localization. Accordingly, CAPAN1 (HER2high-KRASmut-BRCA2mut) showed the highest sensitivity to T-DXd single agent (IC50 10 µg/mL), improved by the addition of gemcitabine and cisplatin chemotherapy. Similarly, in HER2high-BRCA1/2mut cells the association of PARPi to
T-DXd reduced cell viability increasing DNA damage (pH2AX and pCHK1) and G2-phase cell cycle arrest as compared to monotherapies. In HER2high-KRASmut cells the addition of KRASi to T-DXd promoted cytotoxic activity enhancing the AKT pathway blockage, as showed by the decrease of pERK, pAKT, p-p70, and p4EBP1.

**Discussion :**
T-DXd based combinations promoted antitumoral effect in HER2high cells. To validate these findings, treatments will be tested in patient-derived organoids (PDO) and primary cells (PDC), and in an orthotopic mouse model. Additionally, transcriptomic analysis of PDO and PDC will be performed to generate response signatures to T-DXd and selected combinations, based on each drug response profiles.

**Conclusion :**
Preliminary findings suggest that T-DXd based combinations are effective in HER2-positive PDAC in vitro models, supporting further validation in preclinical models.

1st Edition
CRCM Symposium
CANCER RESEARCH CENTER MARSEILLE
CRCM CANCER RESEARCH CENTER Marseille
Comet Cell communication & Microenvironment dpt.
Translate-IT Translational research & Innovative therapies dpt.
4 - 6 February 2026
MARSEILLE
Palais du Pharo

## Posters Session 1 - Precision oncology, targeted therapies and strategies for refined drug delivery

### S1CA21 : Use case of the EPITHOR database in the LUCA-pi project

*Romain Zakrajsek*

**Authors:**
Romain Zakrajsek (1, 2), Andrea Vaglio (1, 2), David Boulate (1, 3), Sébastien Benzekry (1, 2)

*1. Translate-it, CRCM, Marseille, France*
*2. COMPO, INRIA, Nice, France*
*3. Chirurgie thoracique et des maladies de l'oesophage, AP-HM, Marseille, France*

**Keywords:** data, lung cancer, recurrence, biostatistics, machine learning

**Introduction**
The EPITHOR ("EPIdémiologie en chirurgie THORacique") database, created in 2003, is a national thoracic surgery registry including more than 250,000 patients from over 100 centers. The LUng CAncer – Prevention and Interception (LUCA-pi) RHU, launched in 2024, aims to develop biological biomarkers and AI-based tools to improve lung cancer prevention and early detection. In this context, the LUCA-pi RETRO database was defined as a subset of EPITHOR, including patients who underwent lung cancer surgery at Hôpital Nord (Marseille) between 2011 and 2024. Despite curative-intent surgery, 20–30% of patients experience cancer recurrence. Predicting recurrence could guide follow-up strategies and (neo-)adjuvant treatment, associated with a lot of adverse effects and a high cost.

**Method :**
As of December 2025, complete clinical, pathological, imaging, and follow-up data are available for 1,938 patients. Only patients with non-small cell lung cancer (NSCLC) were included, with 279 post-preprocess variables. Three cohorts were defined: all patients, stage I patients, and stage II patients. Disease-free survival (DFS), defined as time to recurrence, was the main outcome, with loss to follow-up right-censored. A GitLab-based continuous integration / continuous deployment (CI/CD) data science pipeline was implemented for continuous integration of patient batches. It comprises: preprocessing, statistical analyses (Cox regressions), machine learning predictive analyses and deployment of the reports to a website. An interactive dashboard was also developed and deployed to enable easy exploration of all statistical results.

**Results :**
For all stages, post-operative TNM (Tumor, Nodule, Metastasis) stage was the strongest predictor (C-index = 0.742, HR = 7.08, $p < 0.00001$). Tumor size and staging variables were consistently significant. Angioinvasion also showed strong predictive value (C-index = 0.667; HR = 3.16; $p < 0.00001$). In stage I patients, THORACOSCORE was the best predictor (C-index = 0.644; HR = 1.33; $p < 0.05$), followed by forced expiratory volume in one second (FEV1) (C-index = 0.641; HR = 0.673; $p < 0.005$). In stage II patients, hospitalization duration was most predictive (C-index = 0.625; HR = 1.49; $p < 0.01$).

**Discussion :**
So far, these results confirm the predictive ability of some known variables but the main strength of this dataset lies in enabling deeper investigation. We are currently integrating machine learning methods to identify a predictive signature from these variables.

**Conclusion :**
Future work will incorporate a mechanistic model of tumor growth and metastatic spread to anticipate distant relapse. The long-term goal is to build a practical clinical tool to support decisions on adjuvant therapy and recurrence prevention.

1st Edition
CRCM Symposium
CANCER RESEARCH CENTER MARSEILLE
CRCM CANCER RESEARCH CENTER Marseille
Comet Cell communication & Microenvironment dpt.
Translate-IT Translational research & Innovative therapies dpt.
4 - 6 February 2026
MARSEILLE
Palais du Pharo

## Posters Session 1 - Precision oncology, targeted therapies and strategies for refined drug delivery

# S1CA22 : Combination therapy with YAP/TEAD and RAS inhibitors overcomes phenotypic cell plasticity-driven resistance in NRAS-mutated melanoma

*Mira Kahil*

**Authors:**
Mira Kahil (1), Walaa Mohager (1), Frédéric Larbret (1), Nicolas Dumaz (2), Lionel Larue (3), Marcel Deckert (1), Sophie Tartare-Deckert (1)

*1. Université Côte d'Azur,C3M, INSERM U1065, NICE, France*
*2. INSERM U976, Hôpital Saint Louis (Paris), Paris, France*
*3. Institut Curie , Institut Curie , Orsay, France*

**Keywords:** Cutaneous melanoma, NRAS mutation, therapeutic resistance, RMC-6236, IAG933

**Introduction**
Melanoma is the most aggressive skin cancer, characterized by remarkable cancer cell plasticity, contributing to intra-tumoral heterogeneity and therapeutic resistance. NRAS-mutant melanoma remains a clinical problem, particularly in patients who do not respond to immunotherapies. As a second-line option, MEK inhibitors as single agents fail to provide a significant overall survival benefit. Therefore there is an unmet need for new therapeutic strategies to improve the management of NRAS-mutant melanoma. Here we assessed in vitro and in vivo the response of NRAS-mutant melanoma cells to RMC-6236, a novel non-covalent inhibitor of both oncogenic and wild type RAS isoforms currently undergoing clinical investigation in various cancers.

**Method :**
Loss-of-function approaches using RMC-6236, IAG933 (a YAP-TEAD interaction inhibitor), or siRNAs were employed to evaluate the impact of NRAS inhibition on phenotypic adaptation (RNA-seq, RT-qPCR, western blot analyses) as well as cell proliferation and survival (colony formation assay, flow cytometry) in human and murine NRAS-mutant cell line models. A murine melanoma model using MaNRAS cells grafted into syngeneic C57BL/6 mice was used to assess the effect of RMC-6236 on tumor growth and mouse survival.

**Results :**
Our transcriptomic and proteomic analyses revealed that the anti-proliferative effect of RMC-6236 on NRAS-mutant melanoma cell lines is characterized by a phenotypic transition towards a less differentiated state, with increased expression of mesenchymal and extracellular matrix remodeling markers, along with the activation of a YAP-driven transcriptional signature and focal adhesion kinase (FAK) signaling. In vivo RMC-6236 slowed tumor growth and improved mouse survival. Melanoma cells treated with RMC-6236 in vivo exhibited reduced pigmentation and expressed mesenchymal and neural crest stem cell markers and YAP-target genes. The combination of RMC-6236 and IAG933 synergistically reduced proliferation, prevented phenotypic transition, and induced apoptosis in NRAS-mutant cells. These findings suggest that YAP-TEAD pathway inhibition by IAG933 targets the adaptive response induced by RMC-6236 and enhances treatment efficacy in vitro and in vivo.

**Discussion :**
RMC-6236 inhibits NRAS-mutant melanoma growth but induces an adaptive phenotypic transition toward a less differentiated, YAP-driven mesenchymal state. YAP–TEAD inhibition with IAG933 blocks this adaptive response, prevents dedifferentiation, and synergistically enhances apoptosis and antitumor efficacy in vitro and in vivo.

**Conclusion :**
NRAS inhibition in melanoma cells induces a mesenchymal phenotypic transition linked to YAP pathway activation. YAP/TEAD inhibition can overcome resistance to NRAS inhibition by preventing adaptive phenotype switching and inducing tumor cell death. This work provides a scientific rationale for treating NRAS-mutant melanomas with a combination of RAS and YAP-TEAD inhibitors.

1st Edition
CRCM Symposium
CANCER RESEARCH CENTER MARSEILLE
CRCM CANCER RESEARCH CENTER Marseille
Comet Cell communication & Microenvironment dpt.
Translate-IT Translational research & Innovative therapies dpt.
4 - 6 February 2026
MARSEILLE
Palais du Pharo

## Posters Session 1 - Precision oncology, targeted therapies and strategies for refined drug delivery

# S1CA23 : MET and SRC kinases promote NRF2 activity in Triple-Negative Breast Cancer: a novel vulnerability to enhance Paclitaxel sensitivity

*Irene Taddei*

**Authors:**
Irene Taddei (1, 2), Claudia Cirotti (3, 2), Fabienne Lamballe (4), Olivier Castellanet (4), Flavio Maina (4), Vanessa Medici (5), Fabrizio Fierro (6), Giacomo Corleone (6), Francesca De Nicola (6), Maurizio Fanciulli (6), Eleonora Cesari (5), Alba Di Leone (7), Claudio Sette (5, 8), Daniela Barilà (9, 2)

1. *PhD Program in Cellular and Molecular Biology, Department of Biology, University of Rome Tor Vergata, Rome, Italy*
2. *Laboratory of Cell Signalling, IRCCS-Fondazione Santa Lucia, Rome, Italy*
3. *Department of Biology, University of Rome tor Vergata, Rome, Italy*
4. *CNRS, INSERM, Institut Paoli-Calmettes, Centre de Recherche en Cancérologie de Marseille (CRCM), Turing Center for Living Systems, Aix Marseille Univ, Marseille, France*
5. *GSTeP Organoids Research Core Facility, Fondazione Policlinico Universitario Agostino Gemelli IRCCS, Rome, Italy*
6. *Gene Expression and Cancer Models Unit, IRCCS Regina Elena National Cancer Institute, Rome, Italy*
7. *Breast Unit, Department of Women, Children and Public Health Sciences, Fondazione Policlinico Universitario Agostino Gemelli IRCCS, Rome, Italy*
8. *Department of Neuroscience, Section of Human Anatomy, Catholic University of the Sacred Heart, Rome, Italy*
9. *Department of Biology, University of Rome Tor Vergata, Rome, Italy*

**Keywords:** MET, NRF2, Triple-Negative Breast Cancer, Paclitaxel, Therapy resistance

**Introduction**
Triple-negative breast cancer (TNBC) accounts for 10-15% of all breast cancer cases. It is a highly aggressive and heterogeneous cancer characterized by the absence of Hormone Receptors (HR) and Human Epidermal Growth Factor Receptor 2 (HER2). These molecular characteristics limit the treatment options for TNBC patients resulting in a poor prognosis and frequently relapses. Therefore, the identification of new vulnerabilities to overcome chemotherapy resistance are urgently needed. Nuclear Factor Erythroid 2-related factor 2 (NRF2) is a transcription factor that plays a central role in the response to oxidative stress. It is frequently overactivated in cancer, including TNBC, and it is associated with resistance to therapy allowing for metabolic rewiring. However, pharmacological approaches to block NRF2 are still missing. Despite in some tumours the constitutive activation of NRF2 is mainly caused by NRF2 and KEAP1 genes mutations, its hyperactivation can be achieved also independently of these, suggesting that other signalling pathways can sustain NRF2 activity. Protein Tyrosine kinases (PTKs), often overactivated in cancer and influencing several signalling pathways, are promising candidates to explore for their potential impact on NRF2.

**Method :**
Bioinformatic analyses using TCGA and GEO databases were performed to investigate the survival probability of TNBC and non-TNBC patients stratified them based on different expression levels of RTKs and NRF2. Immunoblotting, immunofluorescence, RT-qPCR and RNAseq experiments were used to confirm the interplay between MET and NRF2. Moreover, cell viability and flow cytometry assays were performed to evaluate the efficacy of combinatorial treatments with paclitaxel and specific inhibitors of the MET–NRF2 axis in TNBC cellular models and patient-derived organoids.

**Results :**
Here, we identify a novel MET–SRC signalling axis that regulates NRF2 expression and activity, and demonstrate that its pharmacological targeting sensitizes TNBC cells and patient-derived organoids to the standard Paclitaxel treatment.

**Discussion :**
Our study shows that RTKs regulate NRF2 expression and activation in TNBC providing a proof of principle for the ability of Tyrosine Kinase Inhibitors (TKIs) to impinge on NRF2 signalling.

**Conclusion :**
Our findings also uncover the value of the MET-SRC-NRF2 interplay as exploitable vulnerability in NRF2-hyperactivated TNBC, paving the way for the repositioning of TKIs as modulators of NRF2 signalling.

1st Edition
CRCM Symposium
CANCER RESEARCH CENTER MARSEILLE
CRCM CANCER RESEARCH CENTER Marseille
Comet Cell communication & Microenvironment dpt.
Translate-IT Translational research & Innovative therapies dpt.
4 - 6 February 2026
MARSEILLE
Palais du Pharo

## Posters Session 1 - Precision oncology, targeted therapies and strategies for refined drug delivery

# S1CA24 : Establishment of a mouse hepatocellular carcinoma tumoroid panel recapitulating inter- and intra-tumour heterogeneity for disease modelling and combinatorial drug discovery

*Nicolas Pons*

**Authors:**
Nicolas Pons (1), Margherita Grattarola (2), Floriane Cannet (3), Müge Kaya (4), Abdessamad El Kaoutari (2), Christian Morel (3), Aurélie Dobric (2), Jean-Paul Borg (2), Flavio Maina (2)

*1. oncogénétique, Institut Paoli Calmettes, Marseille, France*
*2. Ciblage des réseaux de signalisation et du microenvironnement dans le cancer, CRCM, Marseille, France*
*3. imXgam, CPPM, Marseille, France*
*4. Anatomopathology, Institut Paoli Calmettes, Marseille, France*

**Keywords:** Cancer mouse model, Tumoroid, Organoid, Hepatocellular carcinoma, 3D drug testing, Liver cancer, Cancer heterogeneity, Resistance, Disease modelling, Drug discovery, Primary HCC cells

**Introduction**
Hepatocellular carcinoma (HCC) is a highly aggressive malignancy characterized by pronounced inter- and intra-tumoral heterogeneity, which contributes to poor treatment responses and limited therapeutic options. Traditional two-dimensional cell lines fail to capture the molecular diversity and structural complexity of primary tumours, limiting their translational relevance. Three-dimensional tumoroid models better preserve tissue architecture and cellular interactions, but remain challenging to establish systematically from patient samples. Genetically engineered mouse models, such as the Alb-R26Met mice, develop spontaneous liver tumours that recapitulate key features of aggressive human HCC. These models therefore offer a valuable intermediary system for generating physiologically relevant tumoroids and exploring drug response variability in a controlled background.

**Method :**
Primary tumour cells were isolated from spontaneously arising HCCs in Alb-R26Met mice. We established and characterized a panel of independent primary cell lines and optimized protocols for generating corresponding three-dimensional (3D) tumoroids. Morphological, histological, and molecular profiling were performed using imaging, immunostaining, and transcriptional analyses. Functional assays assessed proliferation rates and sensitivity to targeted therapies, including tyrosine kinase inhibitors (TKIs). The resulting tumoroid panel was then used to test single-agent and combinatorial treatments.

**Results :**
We established eight distinct primary cell lines displaying heterogeneous growth properties, molecular signatures, and pathway activation profiles. All lines efficiently generated robust 3D tumoroids that retained key histopathological features of the tumours of origin. Drug-response assays revealed marked variability in TKI sensitivity, consistent with the biological heterogeneity observed in vivo. Combination treatments further highlighted distinct response patterns across tumoroids, demonstrating the utility of this platform for identifying synergistic effects and resistant phenotypes.

**Discussion :**
Discussion and conclusion: We present a reproducible workflow for generating a diversified panel of mouse-derived HCC tumoroids that faithfully reflects tumour heterogeneity. This platform provides a tractable and physiologically relevant tool for disease modelling and for accelerating combinatorial drug discovery in HCC.

1st Edition
CRCM Symposium
CANCER RESEARCH CENTER MARSEILLE
CRCM CANCER RESEARCH CENTER Marseille
Comet Cell communication & Microenvironment dpt.
Translate-IT Translational research & Innovative therapies dpt.
4 - 6 February 2026
MARSEILLE
Palais du Pharo

## Posters Session 1 - Precision oncology, targeted therapies and strategies for refined drug delivery

# S1CA25 : Single-cell analysis of patient-derived organoids reveals treatment-induced clonal dynamics in pancreatic cancer

*Vladimir Chocoloff*

**Authors:**
Vladimir Chocoloff (1), Loïc Moubri (1), Julie Roques (1), Odile Gayet (1), Philippe Soubeyran (1), Juan Iovanna (1), Nelson Dusetti (1), Nicolas Fraunhoffer (1)

*1. CRCM, U1068, Marseille, France*

**Keywords:** PDAC, organoid, chemotherapy, scRNA-seq, clonal plasticity

**Introduction**
Pancreatic ductal adenocarcinoma (PDAC) has a 5-year survival rate of 12%, with nearly all patients experiencing recurrence or progression due to pre-existing (primary) or acquired (secondary) chemoresistant cells. This underscores the urgent need to understand PDAC heterogeneity and the effects of treatment on tumor cell populations.

**Method :**
This study aimed to characterize treatment-associated cellular dynamics in PDAC at single-cell resolution. Three patient-derived organoids (PDOs), representing both classical and basal-like transcriptional profiles, were treated with five chemotherapeutic agents : gemcitabine, paclitaxel, 5- fluorouracil (5-FU), oxaliplatin, and SN38. Single-cell RNA sequencing was performed before and after treatment, and clonal tracking was assessed using MitoTrace.

**Results :**
Treatment effects varied depending on the initial phenotype. Gemcitabine and paclitaxel showed the most pronounced transcriptomic changes, inducing a phenotypic shift toward more aggressive, basal-like programs. In contrast, 5-FU, oxaliplatin, and SN38 had comparatively minor effects on gene expression.

**Discussion :**
Notably, phenotype transitions were clone-specific, suggesting the presence of predetermined phenotypic landscapes that shape treatment-induced plasticity.

**Conclusion :**
These findings highlight chemotherapy-induced clonal plasticity as a mechanism driving resistant phenotypes in PDAC, offering insights for therapeutic stratification and resistance monitoring.

1st Edition
CRCM Symposium
CANCER RESEARCH CENTER MARSEILLE
CRCM CANCER RESEARCH CENTER Marseille
Comet Cell communication & Microenvironment dpt.
Translate-IT Translational research & Innovative therapies dpt.
4 - 6 February 2026
MARSEILLE
Palais du Pharo

## Posters Session 1 - Precision oncology, targeted therapies and strategies for refined drug delivery

# S1CA26 : Kinetic analysis of nanobody binding to integral membrane proteins on extracellular vesicles

*Lorena Mejia*

**Authors:**
Oksana Reznichenko (1), Alexis Dogliani (2), Clara Bouyx (3), Aymeric Audfray (1), Alain Roussel (4)

*1. Application Scientist, Malvern Panalytical, Vénissieux, France*
*2. PhD Biochimiste, LISM, CNRS, Aix-Marseille Université, UMR 7255, Marseille, France, Marseille, France*
*3. IE,CDD, LISM, CNRS, Aix-Marseille Université, UMR 7255, Marseille, France, Marseille, France*
*4. Research Director, CNRS, LISM, CNRS, Aix-Marseille Université, UMR 7255, Marseille, France, Marseille, France*

**Keywords:** Extracellular vesicles, nanoparticles, Grating-Coupled Interferometry (GCI)

**Introduction**
Extracellular vesicles (EVs) are biological nanoparticles that have attracted increasing attention for diverse applications, including diagnostics and therapeutic vectorization [1]. EVs also provide an excellent platform for studying membrane proteins (MPs) in their native lipid environment [2]. Owing to their high stability, EVs allow long-term storage of MPs and enable the investigation of interactions between cell-surface MPs and ligands without the need for detergent-based membrane protein extraction. These properties make EVs particularly suitable for direct analysis of membrane protein–ligand interactions. This work focuses on the kinetic analysis of nanobody binding to integral membrane proteins displayed on extracellular vesicles.

**Method :**
We present a highly sensitive approach to study the kinetics of interactions between extracellular vesicles and nanobodies using the advanced surface-based, label-free biosensing technique known as Grating-Coupled Interferometry (GCI) [3]. The method incorporates novel non-clogging microfluidics that ensure stable baselines and uninterrupted flow, which are essential for accurate kinetic measurements in complex EV samples. The platform employs the waveRAPID assay, an innovative approach that enables full kinetic characterization from a single injection by applying repeated analyte pulses of increasing duration at a constant concentration [4]. This design significantly accelerates data acquisition and enhances experimental throughput.

**Results :**
Using the GCI platform combined with the WaveRAPID assay, we achieved precise kinetic measurements of nanobody interactions with EVassociated membrane proteins. The approach demonstrated high sensitivity and accuracy, even for tight, high-affinity interactions such as nanobody binding to the EV membrane protein SNMP1 [5]. The ability to extract complete kinetic parameters from a single injection substantially reduced assay time while maintaining data robustness.

**Discussion :**
The combination of non-clogging microfluidics and WaveRAPID-based GCI biosensing addresses key challenges in EV analysis, particularly baseline instability and limited throughput. By preserving membrane proteins in their native EV context, this approach avoids artifacts associated with detergent solubilization and enables physiologically relevant interaction studies. The method is especially advantageous for analyzing high-affinity nanobody–membrane protein interactions, which are often difficult to characterize using conventional techniques.

**Conclusion :**
This study highlights a robust, rapid, and highly sensitive platform for kinetic profiling of nanobody binding to membrane proteins on extracellular vesicles. The integration of GCI technology with WaveRAPID assays enables detailed interaction analysis with minimal sample consumption and high throughput. These advances provide a powerful tool for membrane protein research and support the development of sensitive EV-based diagnostic applications.

1st Edition
CRCM Symposium
CANCER RESEARCH CENTER MARSEILLE
CRCM CANCER RESEARCH CENTER Marseille
Comet Cell communication & Microenvironment dpt.
Translate-IT Translational research & Innovative therapies dpt.
4 - 6 February 2026
MARSEILLE
Palais du Pharo

## Posters Session 1 - Precision oncology, targeted therapies and strategies for refined drug delivery

# S1CA27 : Repositioning metabolic drugs to target metabolic pathways promoting chemoresistance in pancreatic adenocarcinoma

*Afaf Hamame*

**Authors:**
Afaf Hamame (1), Elodie Metay (1), Claudio Montenegro (1), Pierre Bertrand (1), Paraskevi Kousteridou (1), Richard Tomasini (1), Fabienne Marchai (1), Sophie Vasseur (1)

*1. crcm, Marseille, France*

**Keywords:** Pancreatic ductal adenocarcinoma (PDAC) FOLFIRINOX Chemoresistance Metabolic reprogramming Cancer-associated fibroblasts (CAFs) Tumor microenvironment Transcriptomic signatures Therapeutic synergy

**Introduction**
Pancreatic ductal adenocarcinoma (PDAC) is one of the most aggressive solid tumors, characterized by late diagnosis, rapid metastatic spread, and limited response to systemic therapies. FOLFIRINOX (FFX) is currently the standard first-line chemotherapy for eligible patients and improves survival compared to gemcitabine. However, its efficacy is strongly limited by treatment-associated toxicity and, more importantly, by the frequent emergence of chemoresistance. Metabolic reprogramming is a hallmark of PDAC and may play a central role in tumor adaptation to chemotherapy. This study aimed to characterize FOLFIRINOX-induced metabolic alterations associated with resistance in PDAC.

**Method :**
Patient-derived xenograft (PDX) models were generated from tumors of six PDAC patients and treated with escalating doses of FOLFIRINOX to obtain sensitive (FFX-S), resistant (FFX-R), and untreated (NT) tumor phenotypes. Transcriptomic profiling was performed using Agilent microarrays, followed by standardized preprocessing and normalization. Differential expression analysis was conducted using the Limma framework with correction for patient and batch effects. A curated metabolic gene filter integrating Gene Ontology annotations, expert-curated datasets, and literature-derived pathways was applied to focus on metabolism-related genes. Functional enrichment analyses, network visualization, and in silico validation were performed using EnrichR, DAVID, Cytoscape, and public bulk and single-cell RNA sequencing datasets.

**Results :**
Comparative transcriptomic analysis between FFX-resistant and FFX-sensitive tumors identified 141 deregulated metabolic genes, including 47 upregulated and 94 downregulated. Enrichment revealed disruptions in fucosylation, and bilirubin biosynthesis. Applying a stricter threshold narrowed the set to 52 key metabolic genes, with FUOM and BLVRA emerging as prominent candidates. FUOM, involved in fucose metabolism, and BLVRA, a regulator of heme metabolism and oxidative stress, were strongly modulated by FOLFIRINOX. Single-cell RNA-seq showed induction of both genes mainly in tumor cells, with distinct regulation in fibroblasts and macrophages.

**Discussion :**
These findings demonstrate that FOLFIRINOX resistance in PDAC is associated with profound metabolic reprogramming affecting carbohydrate and heme-related pathways. The identification of FUOM and BLVRA highlights metabolic adaptations that may support tumor survival under chemotherapeutic stress through enhanced glycosylation and oxidative stress regulation. The compartment-specific regulation observed at the single-cell level underscores the importance of tumor–stroma interactions in shaping metabolic resistance mechanisms. Together, these results provide a mechanistic rationale for targeting metabolic pathways in combination with FOLFIRINOX to overcome resistance.

**Conclusion :**
This study identifies novel metabolic signatures associated with FOLFIRINOX resistance in PDAC and proposes FUOM and BLVRA as potential biomarkers and therapeutic targets. Targeting these metabolic adaptations may represent a promising strategy to enhance FOLFIRINOX efficacy and improve patient outcomes.

1st Edition
CRCM Symposium
CANCER RESEARCH CENTER MARSEILLE
CRCM CANCER RESEARCH CENTER Marseille
Comet Cell communication & Microenvironment dpt.
Translate-IT Translational research & Innovative therapies dpt.
4 - 6 February 2026
MARSEILLE
Palais du Pharo

## Posters Session 1 - Precision oncology, targeted therapies and strategies for refined drug delivery

# S1CA28 : The ROSALIND Study: Revealing the Cellular and Spatial Architecture of Exceptional Cancer Survival to Enable Therapeutic Discovery

*Paloma Cejas*

**Authors:**
Julieta Rodriguez (1), Olivia Le Saux (2), David Gentien (1), Auzias Elisabeth (3), Nick Riddiford (3), Naouel Zerrouk (3), Aleksandr Kotov (3), Quentin Blampley (3), Adrien Paix (3), Alexandre Yazigi (3), Cécile Badoual (4), Ludovic Lacroi (4), Nathalie Droin (4), Gina Dörpholz (5), Rodrigo Dienstmann (6), Jean-Yves Blay (2), Josep Tabernero (6), Olivier Elemento (7), Ulrich Keilhoz (8), Remy Nicolle (9), Cejas Paloma (3), Andre Fabrice (1)

*1. Drug Development Department, Gustave Roussy Cancer Campus,, Villejuif, France*
*2. Medical Oncology Department, Centre Léon Bérard, Lyon, France*
*3. Cure51, Paris, France*
*4. Laboratory Medicine and Pathology, Gustave Roussy Cancer Campus,, Villejuif, France*
*5. Institute of Chemistry and Biochemistry, Charité Cancer Comprehensive Center, Berlin, Germany*
*6. Medical Oncology Department, Vall d'Hebron Barcelona Hospital, Barcelona, Spain*
*7. Englander Institute for Precision Medicine, Weill Cornell Medicine, New York, USA*
*8. Medical Oncology Department, Charité Cancer Comprehensive Center, Berlin, Germany*
*9. Inflammation Research Center (CRI), Paris-Cité University, Paris, France*

**Keywords:** Long-term cancer survivors, Multi-Omics, Spatial transcriptomics, single cell, PDAC, GBM, SCLC

**Introduction**
Long-term survival in cancers with dismal prognosis, such as metastatic pancreatic ductal adenocarcinoma (mPDAC), IDH–wild-type glioblastoma (GBM-IDHwt), and extensive-stage small cell lung cancer (ES-SCLC), is exceptionally rare. Nonetheless, a small subset of patients achieves durable survival without clearly identified clinical or molecular features. These "exceptional survivors" represent a unique opportunity to uncover biological mechanisms underlying effective disease control. The ROSALIND study was designed to systematically dissect the molecular determinants of exceptional survival. The goal is to identify actionable vulnerabilities that could be leveraged to improve survival in patients with standard outcome.

**Method :**
ROSALIND is a retrospective, international, multicenter case-control study encompassing three cohorts: mPDAC, GBM-IDHwt, and ES-SCLC. Longterm survivors are defined as patients surviving more than five years for mPDAC and ES-SCLC, and more than three years for GBM-IDHwt. Controls are matched for tumor stage, age, sample type, and treatment history, with overall survival centered around the median survival reported in pivotal clinical trials for each tumor type. The analytical multi-omics pipeline includes whole-exome sequencing (WES), single-cell RNA sequencing, 10x Genomics Xenium spatial transcriptomics, proteomics, microbiome profiling (16S rRNA), and radiomics.

**Results :**
As of December 2025, 329 patients have been enrolled, including 244 long-term survivors, across the three cohorts: 52 ES-SCLC, 91 GBM-IDHwt, and 101 mPDAC. Patients were recruited through a global network of 87 centers across 34 countries, with an additional 1,466 exceptional survivors identified for potential inclusion. To date, 256 cases have been fully profiled. Preliminary results from the PDAC cohort show pronounced differences in stromal composition distinguishing exceptional survivors from standard survivors, with cancer cells displaying distinct relationships with the immune infiltrate and cancer-associated fibroblasts between the two groups.

**Discussion :**
ROSALIND extends beyond tumor-intrinsic alterations to incorporate spatial features of the tumor microenvironment as a critical determinant of outcome. Spatially resolved analyses suggest that standard survival in PDAC may be associated with a potentially more permissive immune niche compared with exceptional survivors. These findings point to context-dependent vulnerabilities within the tumor microenvironment. By integrating deeply annotated clinical data with high-resolution molecular and spatial profiling, ROSALIND is uncovering strategies to reprogram tumors toward long term-like states in patients with standard outcomes.

**Conclusion :**
ROSALIND represents the largest systematic efforts to characterize exceptional survival in aggressive cancers using state-of-the-art multi-omic and spatial technologies. Our data provide a rational framework for developing precision oncology strategies aimed at improving survival in patients with otherwise lethal malignancies.

1st Edition
CRCM Symposium
CANCER RESEARCH CENTER MARSEILLE
CRCM CANCER RESEARCH CENTER Marseille
Comet Cell communication & Microenvironment dpt.
Translate-IT Translational research & Innovative therapies dpt.
4 - 6 February 2026
MARSEILLE
Palais du Pharo

## Posters Sessions 2 - Cellular crosstalk and molecular mechanisms of cancer progression

### S2CA29 : Bystander killing of antigen-negative tumor cells by CD8 CAR-T cells in patient-derived colorectal organoids

*Raphael Merand*

**Authors:**
Raphael MERAND (1), Jérome Cartry (2), Sabrina Bedja (2), Jacques Mathieu RR (2), Béatrice Corre (3), Fabrice Lemaitre (3), Flavien Berthou (4), Philippe Bousso (3), Fanny Jaulin (2)

*1. Institut Gustave Roussy, VilleJuif, France*
*2. U1279, Institut Gustave Roussy, VilleJuif, France*
*3. Unité dynamique des réponses immunitaires, Institut Pasteur, Paris, France*
*4. PFIC, Institut Gustave Roussy, VilleJuif, France*

**Keywords:** CAR-T cells; Bystander killing; Tumor heterogeneity; Patient-derived organoids

**Introduction**
CAR-T cell therapy has transformed the treatment of hematologic malignancies but remains largely ineffective in solid tumors, mainly because of limited infiltration, immunosuppressive environments, and strong intratumoral heterogeneity. This heterogeneity promotes antigen escape, a major cause of relapse. One way the immune system can compensate is through bystander killing, where activated T cells eliminate neighboring antigennegative ($Ag^-$) tumor cells. Although this phenomenon has been described, most existing models fail to capture the cellular architecture and complexity of human tumors. Patient-derived organoids (PDOs) retain these key features, making them a powerful system to explore bystander killing in a human context.

**Method :**
We engineered colorectal cancer PDOs to express a defined CAR target antigen and combined them at controlled $Ag^+$:$Ag^-$ ratios to generate mosaic tumors. CD8 CAR-T cells (CAR8) were co-cultured with these PDOs from three patients. We tracked tumor cell death by real-time caspase-3 imaging and endpoint viability assays, quantified cytokine release, and performed time-course bulk RNA-seq on sorted $Ag^-$ cells. To functionally dissect the mechanism, we disrupted IFNGR1, TNFR1, and FAS individually or in combination using CRISPR-Cas9.

**Results :**
CAR8 cells showed strong antigen-specific killing, eliminating up to 90% of $Ag^+$ tumor cells in a dose-dependent manner. In mosaic PDOs, $Ag^-$ cell death followed after a ~10-hour delay, coinciding with high IFNγ and TNFα levels. RNA-seq revealed early induction of IFNγ- and TNFα-responsive genes in $Ag^-$ cells, detectable within 4 hours. Knocking out IFNGR1, TNFR1, or FAS each partially reduced $Ag^-$ killing, and triple disruption provided greater but incomplete protection, suggesting multiple converging cytokine pathways.

**Discussion :**
Our data show that CAR8-mediated bystander killing is driven by cytokine signaling through IFNγ, TNFα, and Fas, but also likely involves additional non-redundant factors. The PDO platform captures the spatial and molecular complexity of human tumors, enabling mechanistic insights that are difficult to obtain in conventional models.

**Conclusion :**
Using patient-derived colorectal cancer organoids to model antigen heterogeneity, we show that CD8 CAR-T cells can eliminate $Ag^-$ tumor cells through multifactorial cytokine-driven bystander killing. We now aim to identify other contributors to this process, including the role of epithelial architecture, to guide next-generation CAR-T therapies against heterogeneous solid tumors.

1st Edition
CRCM Symposium
CANCER RESEARCH CENTER MARSEILLE
CRCM CANCER RESEARCH CENTER Marseille
Comet Cell communication & Microenvironment dpt.
Translate-IT Translational research & Innovative therapies dpt.
4 - 6 February 2026
MARSEILLE
Palais du Pharo

## Posters Sessions 2 - Cellular crosstalk and molecular mechanisms of cancer progression

### S2CA30 : Deciphering the Role of FAN1 in Chemoresistance to Anthracycline/Taxane Therapy in Breast Cancer

*Román Martí Díaz*

**Authors:**
Román Martí Díaz (1), Gemael Cedrick Taty (1), Violette Azzoni (1), Elena Martinez Balsalobre (1), Gilles Audoly (1), Lara Lee (1), Pascal Finetti (2), Stephane Audebert (3), Luc Camoin (3), Samuel Granjeaud (3), Francois Bertucci (2), Christophe Lachaud (1)

*1. Dommages de l'ADN et pathologies sanguines, CRCM, Marseille, France*
*2. Oncologie prédictive, CRCM, Marseille, France*
*3. Protéomique et Spectrométrie de Masse, IPC, Marseille, France*

**Keywords:** FAN1, breast cancer, chemoresistance, doxorubicin, paclitaxel, replication stress, mitotic stress.

**Introduction**
Resistance to anthracycline- and taxane-based chemotherapy remains a major hurdle in breast cancer treatment. Building on previous work linking FAN1 overexpression to residual disease in ER–/HER2– tumors treated with anthracycline/taxane combinations, we reanalyzed eight public datasets (1,148 patients) receiving anthracycline-based neoadjuvant chemotherapy. High FAN1 expression was associated with poor response only when taxanes were included, particularly in HER2+ and triple-negative breast cancers (TNBC), suggesting a role for FAN1 in dual replication and mitotic stress adaptation.

**Method :**
FAN1 function was investigated using genetic and biochemical approaches. FAN1 knockout and mutant cell lines lacking the ubiquitin-binding (UBZ) or nuclease (NUC) domains were generated. Cells were exposed to doxorubicin or paclitaxel to induce replication or mitotic stress. Proximitydependent biotinylation (BioID) and mass spectrometry were performed to identify FAN1-interacting partners, followed by biochemical validation.

**Results :**
FAN1 knockout cells exhibited increased chromosomal instability and hypersensitivity to doxorubicin and paclitaxel. Complementation assays revealed that both the UBZ and NUC domains are essential for replication fork protection and mitotic stress tolerance. BioID and mass spectrometry identified ANLN, a cytokinesis-associated actin-binding protein, as a novel FAN1 interactor upon paclitaxel treatment. This FAN1–ANLN pathway appears to safeguard cells against paclitaxel-induced mitotic catastrophe.

**Discussion :**
Our findings identify FAN1 as a crucial regulator of genome stability and chemotherapeutic response. By preserving chromosomal integrity under replication and mitotic stress, FAN1 contributes to resistance against combined anthracycline and taxane treatment. The dual role of FAN1—mediating replication fork protection and mitotic resilience—highlights its importance as a molecular determinant of treatment outcome in breast cancer.

**Conclusion :**
FAN1 expression represents a potential predictive biomarker of chemoresistance in breast cancer. Targeting FAN1 or its functional domains may offer a novel therapeutic approach to sensitize tumors to anthracycline/taxane-based chemotherapy and improve clinical response.

1st Edition
CRCM Symposium
CANCER RESEARCH CENTER MARSEILLE
CRCM CANCER RESEARCH CENTER Marseille
Comet Cell communication & Microenvironment dpt.
Translate-IT Translational research & Innovative therapies dpt.
4 - 6 February 2026
MARSEILLE
Palais du Pharo

## Posters Sessions 2 - Cellular crosstalk and molecular mechanisms of cancer progression

# S2CA31 : How does o-glycosylation drive topological inversion and cell surface expression of calnexin?

*Haiyang Dong*

**Author:**
Haiyang Dong (1)

*1. CRCM - CNRS UMR 7258, MARSEILLE, France*

**Keywords:** Calnexin, O-glycosylation, topology, endoplasmic reticulum

**Introduction**
Tumor growth and metastasis depend on tissue remodeling, a process driven by extracellular matrix (ECM) degradation. Glycosylation plays a key role in regulating ECM remodeling, primarily through the activation of the GALA pathway which could relocate GalNAc Transferases (GALNTs) from the Golgi to the endoplasmic reticulum (ER) and then drive protein hyperglycosylation. One of these proteins is the ER resident protein Calnexin (Cnx) essential for proper protein folding and also vital to ECM degradation in cancer cells. The importance of Cnx in tumor progression is highlighted by findings that anti-Cnx antibodies inhibit liver tumor growth and lung metastasis in breast and liver cancers. Interestingly, antibodies targeting the intracellular C-terminal region of Cnx also block ECM degradation, suggesting that this portion of the protein is exposed on the cell surface. Thus, we hypothesize that O-glycosylation induces a topology shift in Calnexin, transitioning from an «I-type» topology to a «U-type» topology.

**Method :**
To explore the topological change of cell surface glycosylated Calnexin, and the mechanisms underlying this phenomenon, we attempted to detect the extracellularly exposed C-terminus of Calnexin through IF and WB experiments. HaloTag (HT) was inserted at the C-terminus of Calnexin as a marker for the Calnexin C-terminal (Cnx-HT), while HaloTag can be recognized by its specific HaloTag ligands (HL). The pancreatic ductal adenocarcinoma cell line, KPC, was used as a cellular model. GALA levels were controlled by expressing an ER-localized GALNT1 under the control of a doxycycline (DOX) inducible promoter (ER-G1) to simulate high and low GALA conditions.

**Results :**
We investigated the presence of 'U-type' topology of Calnexin by using C-terminal HaloTag and the cell impermeant ligand HL-Alexa Fluor 660. Through the results, we can clearly say that induction of GALA (ER-G1) increased signal from the cell-impermeant ligand, which was not observed in WT, non-induced cells or by expression of HaloTag alone, suggesting an increase in 'U-type' calnexin at the cell surface and a link between this topological change and O-glycosylation.

**Discussion :**
1. How does CHX lead to a significant decrease in CS Cnx levels? 2. Glycosylation might regulate the ribosome translocon complex (RTC)

**Conclusion :**
Calnexin undergoes a significant change in its topology after O-glycosylation. We provide preliminary evidence that the topology change of glycosylated Calnexin occurs, with both the N-terminal and C-terminal domains localized outside the cell membrane. This surprising and unique topological change of glycosylated Cnx indicates a structural alteration that may be key to its escape to the cell surface.

1st Edition
CRCM Symposium
CANCER RESEARCH CENTER MARSEILLE
CRCM CANCER RESEARCH CENTER Marseille
Comet Cell communication & Microenvironment dpt.
Translate-IT Translational research & Innovative therapies dpt.
4 - 6 February 2026
MARSEILLE
Palais du Pharo

## Posters Sessions 2 - Cellular crosstalk and molecular mechanisms of cancer progression

# S2CA32 : GALNT relocalisation reshapes the glycoproteome in pancreatic cancer and activates integrin beta 1

*Eugénie Lohmann*

**Authors:**
Rebecca Bennion (1), Malgorzata Kowalczewska (2), Eugénie Lohmann (3), Eric Mas (1), Nelson Dusetti (1), Sergey Vakhrushev (4), Martin Humphries (5), Frédéric BARD (6)

*1. Centre de Recherche en Cancérologie de Marseille, INSERM, MARSEILLE, France*
*2. Centre de Recherche en Cancérologie de Marseille, AMU, MARSEILLE, France*
*3. Centre de Recherche en Cancérologie de Marseille, INSERM, Marseille, France*
*4. Cellular and Molecular Medicine, University of Copenhagen, COPENHAGUE, Denmark*
*5. Wellcome Centre for Cell-Matrix Research, University of Manchester, MANCHESTER, United Kingdom*
*6. Centre de Recherche en Cancérologie de Marseille, CNRS, MARSEILLE, France*

**Keywords:** GALA pathway, Tn antigen, PDAC, ECM, tumor biomarkers, glycoproteomics

**Introduction**
Aberrant glycosylation drives tumour progression and metastasis. The GalNAc transferase activation (GALA) pathway, where O-GalNAc glycosyltransferases (GALNTs) relocate from Golgi to endoplasmic reticulum (ER), uniquely glycosylates ER-resident proteins. GALA is active in breast and liver cancers, contributing to ECM degradation, tumour growth, and invasion. This study investigates GALA in pancreatic ductal adenocarcinoma (PDAC), focusing on tumour growth and defining a GALA-driven glyco-signature for disease detection.

**Method :**
Pancreatic tumour tissues and cell lines were analysed for GALA activity. Human tumour microarrays were stained with Vicia villosa and Helix pomatia lectins to detect Tn antigen, a GALA hallmark. Genetic models included ER-localised GALNT1 (ER-G1), GALNT1-overexpressing (WT-G1), wild-type (WT), and GALA-inhibited (ER-2Lec) cells. Orthotopic injections of KPC47 cells evaluated tumour growth and metastasis. Glycoproteomic profiling using jacalin-agarose lectin weak affinity chromatography followed by data-independent acquisition mass spectrometry identified glycopeptides with T and Tn glycans. Eighteen patient-derived xenografts (PDXs) from the PaCaOmics cohort validated findings.

**Results :**
Pancreatic tumours showed elevated Tn levels with ER-like distribution versus normal tissue, indicating GALA activation. Tn localised primarily in CK19-positive epithelial cells, though some patients showed high stromal Tn expression, suggesting microenvironment heterogeneity. GALNT2 colocalised with ER marker GRP78, and calnexin was O-glycosylated, confirming GALA activity. ER-localised GALNT1 increased Tn levels more than overexpression alone, indicating ER localisation, not expression level, drives hyperglycosylation. GALA promoted ECM degradation in vitro, and ERG1 cells enhanced tumour growth and metastasis in orthotopic models, while GALA-inhibited tumours failed to establish. Glycoproteome profiling identified a distinct signature driven by ER-localised GALNT1. Hyperglycosylation targeted ER-resident proteins, ECM components, and membrane proteins. GALA increased Tn glycopeptides and poly-T/poly-Tn structures, indicating clustered ER O-glycosylation. PDX tumours validated the ER-like glyco-signature.

**Discussion :**
This study highlights GALA's role in driving a unique pancreatic cancer glyco-signature. Hyperglycosylation of ER-resident, extracellular, and membrane proteins contributes to ECM degradation and tumour progression. Cleaved hyperglycosylated proteins could serve as serum biomarkers for PDAC detection.

**Conclusion :**
Future work will assess this glyco-signature's cancer specificity and diagnostic utility in patient serum.

1st Edition
CRCM Symposium
CANCER RESEARCH CENTER MARSEILLE
CRCM CANCER RESEARCH CENTER Marseille
Comet Cell communication & Microenvironment dpt.
Translate-IT Translational research & Innovative therapies dpt.
4 - 6 February 2026
MARSEILLE
Palais du Pharo

## Posters Sessions 2 - Cellular crosstalk and molecular mechanisms of cancer progression

# S2CA33 : The tumour lung microenvironment affects the functional properties and the expression of immune-checkpoints of endothelial cells: an in vitro study to reverse such unfavourable conditioned milieu

*Laura Finato*

**Authors:**
Laura Finato (1), Antonella Maria Nogara (1), Bruno Lorusso (1), Raffaella Zamponi (1), Gregorio Monica (1), Giovanni Roti (1, 2), Pellegrino Crafa (1), Federico Quaini (1), Costanza Anna Maria Lagrasta (1)

*1. Dept of Medicine and Surgery, University of Parma, Parma, Italy*
*2. Hematology and BMT Unit, University Hospital of Parma, Parma, Italy*

**Keywords:** tumor lung microenvironment, endothelial cell lines, adenocarcinoma cell lines, CD274/PD-L1, HLA-DR, ICAM-1, CD275/ICOS-L

**Introduction**
Growing evidence highlights the primary role of endothelial cells (ECs), fibroblasts, and stromal cells, in regulating the tumour microenvironment (TME) to control tumour growth and modulate immune responses. Furthermore, ECs are considered non-professional antigen-presenting cells due to the expression of adhesion molecules and immune checkpoint proteins, positioning them as critical intermediaries in cancer immunosurveillance.

**Method :**
In this study, we exposed human lung microvascular endothelial cells (HLMVECs) and human umbilical vein endothelial cells (HUVECs) to conditioned media (CM) derived from A549 (CM-A549) and Calu-3 (CM-Calu-3), two lung adenocarcinoma cell lines, to mimic the humoral cancerendothelium crosstalk. Endothelial cell functional properties were evaluated through capillary-like tube formation and wound-healing migration assays. The phenotypic profile was characterized by flow cytometric analysis of key immunoregulatory molecules.

**Results :**
Our results demonstrated that both CM-A549 and CM-Calu-3 significantly enhanced the migratory capacity and promoted capillary-like structure formation on Matrigel® of both endothelial cell types, indicating pro-angiogenic effects. Notably, neither EC line expressed HLA-DR constitutively or following CM treatment, suggesting no antigen presentation capacity under these experimental conditions. HLMVECs exhibited increased PD-L1 and ICAM-1 expression following exposure to both CM, with CM-A549 inducing more pronounced PD-L1 upregulation. HUVECs exposed to CM-Calu-3 demonstrated significant upregulation of both PD-L1 and ICAM-1 proteins, while a negligible rise was observed following CM-A549 exposure, unveiling distinct responsiveness patterns among endothelial cell populations derived from anatomically distinct circulatory districts. CD275/ICOSL expression levels remained consistently low or undetectable across all conditions, indicating that this co-stimulatory pathway is not modulated by the tested tumour secretomes. Furthermore, the addition of 5μM ruxolitinib, a JAK1/2 inhibitor, effectively reduced PD-L1 and normalized ICAM-1 expression in both EC types across all experimental conditions. Similarly, 1μM niclosamide, a STAT3 inhibitor, showed potent inhibitory effects, particularly in suppressing CM-induced PD-L1 upregulation and completely preventing ICAM-1 modulation.

**Discussion :**
Our findings demonstrate that lung cancer secretomes significantly alter endothelial cell functional and immunoregulatory properties in a cell typespecific manner, promoting pro-angiogenic behaviours while inducing immunosuppressive phenotypes. The differential responsiveness between HUVEC and HLMVEC populations highlights the heterogeneity in cancer-endothelium interactions. The efficacy of both ruxolitinib and niclosamide documents the critical role of JAK/STAT signalling in reversing these tumour-induced alterations and suggests that their combination with targeted therapy drugs could represent a promising strategy to restore endothelial function and enhance the effectiveness of cancer immunotherapy.

**Conclusion :**
These culture-based approaches provide valuable tools for exploring novel therapeutic compounds to advance current immunotherapeutic outcomes.

1st Edition
CRCM Symposium
CANCER RESEARCH CENTER MARSEILLE
CRCM CANCER RESEARCH CENTER Marseille
Comet Cell communication & Microenvironment dpt.
Translate-IT Translational research & Innovative therapies dpt.
4 - 6 February 2026
MARSEILLE
Palais du Pharo

## Posters Sessions 2 - Cellular crosstalk and molecular mechanisms of cancer progression

# S2CA34 : A Novel Lineage Tracing System to Reconstruct the Early Steps of Breast Tumorigenesis

*Shuheng Lin*

**Authors:**
Shuheng LIN (1), Anaïs Grandon (2), Olivier Rosnet (2), Caroline Bonnet (2), Julien Wicinski (2), Emmanuelle Charafe (2), Christophe Ginestier (2)

*1. Cancer Research Center of Marseille, Marseille, France*
*2. Cancer Research Center of Marseille, Marseille, France*

**Keywords:** lineage tracing, lineage plasticity, breast cancer, tumor initiation, organoid

**Introduction**
Breast cancer screening reveals many pre-neoplastic lesions, yet their risk of progression remains unpredictable due to limited understanding of early tumorigenesis. Cellular plasticity is increasingly considered as a key driver of tumor initiation, but its molecular mechanisms—studied mainly in transgenic mouse models—remain poorly defined. Lineage-tracing studies suggest that early lineage infidelity increases susceptibility to oncogenic transformation and contributes to intertumoral heterogeneity. However, the human mammary gland is more complex and displays greater diversity of pre-neoplastic lesions than murine tissue, underscoring the need for human-relevant systems. Currently, no experimental model faithfully captures how oncogenes reprogram the cell of origin during the earliest stages of human breast tumorigenesis, representing a major barrier and an opportunity for innovation

**Method :**
In this project, we address this gap by implementing the first lineage tracing strategy in human mammary epithelium. This system allows direct tracking of luminal cells and luminal progenitors (LCs)—the presumed cells of origin for multiple breast cancer subtypes—after activation of oncogenes such as PIK3CAH1047R, MYC, ERBB2, and H-RASG12V. By combining organoid culture with mouse mammary fat pad transplantation, we model oncogene-induced lineage plasticity, preneoplastic lesion formation, and tumor initiation both in vitro and in vivo.

**Results :**
We identified Mucin 4 (MUC4) as a faithful promoter to target LCs in the human mammary epithelium. Using CRISPR-knock in strategy, we developed a new lineage tracing system: MUC4:CreERT2. In the control condition, upon tamoxifen administration, reporter GFP is specifically expressed in LCs in 2D, 3D organoids and in vivo mouse mammary fat pad transplantation. In contrast, oncogene expression such as H-RASG12V induced lineage plasticity and tumor formation.

**Discussion :**
This new lineage-tracing model provides a powerful framework to dissect the molecular drivers of lineage plasticity and early transformation using single-cell multi-omics. The identified candidates will offer a valuable resource of targets to intercept tumor initiation. As a next step, CRISPR-based functional screens in organoids carrying this system will directly test their roles. Overall, this work is expected to reveal biomarkers for risk stratification of pre-malignant lesions and establish a unique platform for developing innovative strategies for breast cancer interception and prevention

**Conclusion :**
This new lineage tracing system is an indispensable tool It will provide fundamental insights into the cellular and molecular mechanisms underlying malignant transformation of mammary epithelial cells, while identifying key regulators of oncogene-induced plasticity.

1st Edition
CRCM Symposium
CANCER RESEARCH CENTER MARSEILLE
CRCM CANCER RESEARCH CENTER Marseille
Comet Cell communication & Microenvironment dpt.
Translate-IT Translational research & Innovative therapies dpt.
4 - 6 February 2026
MARSEILLE
Palais du Pharo

## Posters Sessions 2 - Cellular crosstalk and molecular mechanisms of cancer progression

# S2CA35 : Heme acts as a molecular degrader linking CRL2FEM1B to substrate proteolysis and ferroptosis regulation in lung cancer

*Bashir Ahmed*

**Authors:**
Bashir Ahmed (1), Bashir Ahmed (2)

*1. PHD student, CRCM, Marseille , France*
*2. CRCM, Marseielle France, France*

**Keywords:** Lung cancer, Ferroptosis, Heme, protein degradation

**Introduction**
To sustain their growth, cancer cells often increase their demand for iron, which also makes them more vulnerable to ferroptosis—a form of ironcatalyzed cell death driven by lipid peroxidation. Drugs that target ferroptosis, such as sulfasalazine and sorafenib, have shown promise in enhancing the effectiveness of chemotherapy and immunotherapy, offering a potential strategy to eliminate therapy resistant cancer cells . However, lung cancers frequently activate pathways that enable them to evade ferroptosis. In particular, protective mechanisms like GPX4 and SLC7A11 play a critical role in shielding cancer cells from this form of cell death, supporting their survival. Developing new strategies to sensitize lung tumors to ferroptosis is therefore crucial for improving the efficacy of patient therapies. The Ubiquitin Proteasome System (UPS) is the primary pathway responsible for protein degradation, with E3 ubiquitin ligases recognizing specific target substrates. The hypothesis of my project starts off recent evidence suggesting that Cullin ligases are involved in regulating iron metabolism and oxidative stress, thereby influencing ferroptosis sensitivity. During my training, I identified the Cullin ligase complex CUL2-FEM1B as a novel regulator of ferroptosis in lung cancer by degrading BACH1, a transcription factor that maintains redox and iron homeostasis. In particular, BACH1 represses the expression of ferroptosis-protective genes such as SLC7A11, HMOX1, and FERRITIN, thereby sensitizing cells to ferroptosis. My goal is to investigate the CUL2-FEM1B – BACH1 axis as a therapeutic target to enhance the efficacy of ferroptosis inducers, offering new strategies to overcome lung cancer resistance.

**Method :**
Animal Experiments Transcriptomics Proteomics CRISPR, ShRNA, SiRNA Protein Purification and Pull Down Assay Immunohistochemistry Immunofluorescence and Stereomicroscopy Lentivirus- and Retrovirus- Mediated Gene Transfer Cell Viability Assay Lipid Peroxidation Measurement Quantitative PCR Cell Fractionation GSH Quantification

**Results :**
My findings are -CUL2 regulates ferroptosis in lung cancer heme-dependent degradation -FEM1B binds and degrades BACH1 via a heme-binding motif in BACH1's C-Terminal region -The FEM1B-BACH1 pathway controls the expression of ferroptosis regulators -FEM1B knockdown sensitizes lung tumors to ferroptosis inducers in mouse

**Discussion :**
Heme binding enables a degron for direct E3 ligase recruitment and proteolysis. The CRL2FEM1B–BACH1 axis as a therapeutic target to elicit ferroptosis in lung cancer.

**Conclusion :**
Our study identifies the CRL2FEM1B–BACH1 axis as a potential therapeutic target to enhance ferroptosis induction in vivo. These findings provide new opportunities to increase the effectiveness of ferroptosis-inducing treatments that, in combination with standard therapies, may help improve patient outcomes.

1st Edition
CRCM Symposium
CANCER RESEARCH CENTER MARSEILLE
CRCM CANCER RESEARCH CENTER Marseille
Comet Cell communication & Microenvironment dpt.
Translate-IT Translational research & Innovative therapies dpt.
4 - 6 February 2026
MARSEILLE
Palais du Pharo

## Posters Sessions 2 - Cellular crosstalk and molecular mechanisms of cancer progression

### S2CA36 : Melanoma-reprogrammed fibroblasts promote tumor progression and immune evasion in the lymph node niche

*Melissa Chapeau*

**Authors:**
Melissa Chapeau (1), Christopher Rovera (2), Cassandre Tavernier (2), Lindsay Delhaye (2), Daisy Graça (2), Frédéric Larbret (2), Marie Irondelle (2), Marcel Deckert (2), Sophie Tartare-Deckert (2), Virginie Prod'homme (2)

*1. C3M, Nice, France*
*2. C3M, Nice, France*

**Keywords:** Fibroblastic Reticular Cells, Pre-metastatic niche, Melanoma

**Introduction**
Melanoma is an aggressive skin cancer that metastasizes if not detected early, starting by the invasion of the lymph nodes. This lymphatic invasion is a critical step in melanoma progression, as it allows cancer cells to enter the bloodstream and spread to other organs. Understanding the mechanisms underlying lymph node invasion could lead to earlier and more effective interventions. During the pre-metastatic phase, lymph nodes are reprogrammed by factors secreted by melanoma cells in the skin, creating a niche favorable to tumor invasion and proliferation. During this phase, lymph node fibroblasts, known as Fibroblastic Reticular Cells (FRCs), are reprogrammed. In healthy lymph nodes, FRCs play a key role in organizing the structure of lymph nodes and in regulating T cell recruitment, survival, and activation. In many tissues, fibroblasts in the tumor microenvironment, also known as cancer-associated fibroblasts, are known to promote cancer progression, but little is known about the role of FRCs in the lymph node.

**Method :**
To mimic pre-metastatic reprogramming in the lymph node, healthy human FRCs are incubated with melanoma-secreted factors. The reprogrammed FRCs are then cocultured with T cells or tumor cells to assess dysregulated interactions using flow cytometry and real-time microscopy. In parallel, a murine model is used in which melanoma-secreted factors are injected into healthy mice. Draining lymph nodes are then collected and analyzed by flow cytometry to characterize stromal and immune remodelling.

**Results :**
We identified by RNAseq analysis that FRCs are transcriptionally reprogrammed by factors secreted by melanoma cells. Indeed, our previous work demonstrated that IL-1 secreted by dedifferentiated melanoma cells inhibit the contractility of reprogrammed FRCs, facilitating melanoma cell invasion. My research also reveals that reprogrammed FRCs enhance the proliferation of tumor cells, their motility and their resistance to targeted therapies used in the clinic. Additionally, these reprogrammed FRCs disrupt the anti-tumor immune response by altering T cell motility and upregulating immune checkpoint molecules (PD1, LAG3, and CTLA4) on T cells.

**Discussion :**
These results show the role of reprogrammed FRCs in the initiation of the pre-metastatic niche. Future studies will focus on deciphering the molecular mechanisms by which FRCs acquire their tumor-promoting phenotype and on identifying potential targets that could be used to prevent lymph node reprogramming.

**Conclusion :**
These findings highlight the critical role of FRCs in creating a tumor-permissive microenvironment in early melanoma progression, and suggest new therapeutic approaches based on targeting the interactions between reprogrammed FRCs, tumor cells, and immune cells.

1st Edition
CRCM Symposium
CANCER RESEARCH CENTER MARSEILLE
CRCM CANCER RESEARCH CENTER Marseille
Comet Cell communication & Microenvironment dpt.
Translate-IT Translational research & Innovative therapies dpt.
4 - 6 February 2026
MARSEILLE
Palais du Pharo

## Posters Sessions 2 - Cellular crosstalk and molecular mechanisms of cancer progression

### S2CA37 : Role of the BMP pathway in mammary stem cells transformation and basal-like breast cancer initiation

*Boris Guyot*

**Authors:**
Simon Aho (1), Emmanuel Delay (2), Marie Perbet (3), Sandrine Jeanpierre (3), Isabelle Treilleux (1), Boris Guyot (4), Véronique Maguer-Satta (3)

*1. CRCL, Centre Léon Bérard, Lyon, France*
*2. Centre Léon Bérard, Centre Léon Bérard, Lyon, France*
*3. CRCL, CRCL, Lyon, France*
*4. CRCL, CNRS, Lyon, France*

**Keywords:** BMP, BRCA1, Basal breast cancer, DNA repair, Transformation

**Introduction**
Breast cancer is the leading cause of cancer death in women worldwide. It is an heterogeneous disease with several molecular subtypes. The basallike subtype has the poorest prognosis. It is characterized by increased expression of basal differentiation markers and genetic instability, frequently due to alterations in homologous recombination. Mutations in the BRCA1 gene are the best-known risk factor for developing a basal breast tumor. The basal subtype is also enriched in cancer stem cells. These cells appear to be involved in the early stages of carcinogenesis but also in resistance to cytotoxic treatment and relapse. Several signaling pathways influence their biology, notably the bone morphogenetic protein (BMP) pathway. Dysregulation of this pathway has been demonstrated in certain luminal tumors, but its involvement in the emergence of basal-like tumors remains to be explored.

**Method :**
Using primary samples and public databases, we searched for BMP pathway abnormalities in basal-like tumors and BRCA1-mutated predisposed tissues. We also used the MCF10A human mammary epithelial stem cell line to model in vitro stem cell tumor initiation processes in the mammary gland.

**Results :**
We show that BMPR1A receptor and BMP4 ligand expression are deregulated in basal-like tumors and predisposed tissues. In addition, we demonstrate an inverse correlation between the level of BMPR1A protein and BRCA1 mRNA in BRCA1 WT basal breast tumors from patients. Using a human mammary stem cell model, we show that BMP4 signals through BMPR1A to repress the BRCA1 gene transcription. The functional consequences of this BRCA1 repression include preferential differentiation toward the basal phenotype, increased stemness and alterations in the homologous recombination pathway associated with an increased sensitivity to PARP inhibitors, genomic instability and transformation.

**Discussion :**
The regulation by BMP4/BMPR1A signaling of BRCA1 expression and consequently of homologous recombination could be a new mechanism of BRCAness, i.e. any situation mimicking a BRCA1 mutation. Further studies are required to understand the function of the BMP4/BMPR1A/BRCA1 axis in the physiology of the normal mammary gland as well as the precise molecular mechanisms that could favor basal breast cancer formation when BMP4/BMPR1A signaling is altered. Identifying BRCA1 WT patients with basal breast cancer showing a BRCAness phenotype due to altered BMP4/BMPR1A could make them eligible to PARPi therapies.

**Conclusion :**
We suggest a role for the BMP4-BMPR1A axis in the early stages of basal-like breast tumor carcinogenesis, through a phenocopy of BRCA1 mutations inducing basal differentiation of stem cells and promoting the genetic instability necessary for their transformation.

1st Edition
CRCM Symposium
CANCER RESEARCH CENTER MARSEILLE
CRCM CANCER RESEARCH CENTER Marseille
Comet Cell communication & Microenvironment dpt.
Translate-IT Translational research & Innovative therapies dpt.
4 - 6 February 2026
MARSEILLE
Palais du Pharo

## Posters Sessions 2 - Cellular crosstalk and molecular mechanisms of cancer progression

### S2CA38 : Investigating the role of PTK7 nuclear localization in Colorectal cancer development

*Louis Guiraud*

**Authors:**
Louis Guiraud (1), Charlotte Dessaux (2), Avais Daulat (2), Stéphane Audebert (2), Luc Camoin (2)

*1. Centre de Recherche en cancérologie de Marseille, Marseille, France*
*2. Centre de Recherche en cancérologie de Marseille, Marseille, France*

**Keywords:** Colon cancer, Cell fractionation, nuclear translocation, PTK7, pseudokinase

**Introduction**
Colorectal cancer (CRC) represents the 2nd deadliest cancer in the world. There is therefore a real necessity to identify new biomarkers to promote the development of more efficient therapies. The Wnt/β-catenin signaling pathway has a major role in CRC due to frequent dysregulations. PTK7 (Protein Tyrosine Kinase 7), a transmembrane receptor required during embryo development and involved in Wnt/β-catenin and Planar Cell Polarity (PCP) pathways, has been identified both as a poor prognosis marker and a therapeutic target in CRC . As a cell surface protein, PTK7 oncogenic properties have mainly been associated with its membrane localization. Indeed, cell surface PTK7 has already been characterized to act as a positive activator of Wnt pathways by interacting with Wnt ligands and membrane components, such as LRPs and Frizzled. Recently, other studies described PTK7 membrane activity through its interaction with key surface receptors, including EGFR and FGFR1, and interfering with their signaling. Despite their surface location, some tyrosine kinase receptors have been described to translocate into the nucleus, and to interact with transcription factors for regulating gene expression and promoting tumor progression in various cancers. Here, using cell fractionation followed by western blot and mass spectrometry analyses, we have evidence for PTK7 basal localization in both soluble nuclear and chromatin bound fractions in colon cancer cell lines. Additionally, mass spectrometry data suggest HMGA1, a transcription factor positively regulating Wnt/β-catenin pathway by initiating LRP5 transcription, as a potential PTK7 nuclear interactor. Finally, thanks to bulk/single-cell RNAseq analyses, we propose a model in which nuclear PTK7 interacts with HMGA1 at the LRP5 promotor region in order to potentially enhance the Wnt/β-catenin signaling in CRC.

**Results :**
We used cell fractionation followed by western blot to detect PTK7 in CRC cell lines nuclear compartment. Mass spectrometry/ BioID was used to identify PTK7 nuclear interactors including transport proteins such as XPO1, KPNB1, KPNA2, transcription factor such as HMGA1. To confirm the implication of those proteins in PTK7 nuclear transport, we used inhibitors selectively directed against KPNB1 and XPO1 activities. To evaluate the correlation of co-expression between LRP5, HMGA1 and PTK7, we analyzed bulk/single cell RNA seq data extracted from publically available sequenced CRC tumors. Then, we additionally confirmed the implication of both PTK7 and HMGA1 in the positive regulation of LRP5 expression in CRC cell lines by using si-RNA strategies followed by Western-Blot and qRT-PCR analysis.

1st Edition
CRCM Symposium
CANCER RESEARCH CENTER MARSEILLE
CRCM CANCER RESEARCH CENTER Marseille
Comet Cell communication & Microenvironment dpt.
Translate-IT Translational research & Innovative therapies dpt.
4 - 6 February 2026
MARSEILLE
Palais du Pharo

## Posters Sessions 2 - Cellular crosstalk and molecular mechanisms of cancer progression

### S2CA37 : Role of the BMP pathway in mammary stem cells transformation and basal-like breast cancer initiation

*Boris Guyot*

**Authors:**
Simon Aho (1), Emmanuel Delay (2), Marie Perbet (3), Sandrine Jeanpierre (3), Isabelle Treilleux (1), Boris Guyot (4), Véronique Maguer-Satta (3)

*1. CRCL, Centre Léon Bérard, Lyon, France*
*2. Centre Léon Bérard, Centre Léon Bérard, Lyon, France*
*3. CRCL, CRCL, Lyon, France*
*4. CRCL, CNRS, Lyon, France*

**Keywords:** BMP, BRCA1, Basal breast cancer, DNA repair, Transformation

**Introduction**
Breast cancer is the leading cause of cancer death in women worldwide. It is an heterogeneous disease with several molecular subtypes. The basallike subtype has the poorest prognosis. It is characterized by increased expression of basal differentiation markers and genetic instability, frequently due to alterations in homologous recombination. Mutations in the BRCA1 gene are the best-known risk factor for developing a basal breast tumor. The basal subtype is also enriched in cancer stem cells. These cells appear to be involved in the early stages of carcinogenesis but also in resistance to cytotoxic treatment and relapse. Several signaling pathways influence their biology, notably the bone morphogenetic protein (BMP) pathway. Dysregulation of this pathway has been demonstrated in certain luminal tumors, but its involvement in the emergence of basal-like tumors remains to be explored.

**Method :**
Using primary samples and public databases, we searched for BMP pathway abnormalities in basal-like tumors and BRCA1-mutated predisposed tissues. We also used the MCF10A human mammary epithelial stem cell line to model in vitro stem cell tumor initiation processes in the mammary gland.

**Results :**
We show that BMPR1A receptor and BMP4 ligand expression are deregulated in basal-like tumors and predisposed tissues. In addition, we demonstrate an inverse correlation between the level of BMPR1A protein and BRCA1 mRNA in BRCA1 WT basal breast tumors from patients. Using a human mammary stem cell model, we show that BMP4 signals through BMPR1A to repress the BRCA1 gene transcription. The functional consequences of this BRCA1 repression include preferential differentiation toward the basal phenotype, increased stemness and alterations in the homologous recombination pathway associated with an increased sensitivity to PARP inhibitors, genomic instability and transformation.

**Discussion :**
The regulation by BMP4/BMPR1A signaling of BRCA1 expression and consequently of homologous recombination could be a new mechanism of BRCAness, i.e. any situation mimicking a BRCA1 mutation. Further studies are required to understand the function of the BMP4/BMPR1A/BRCA1 axis in the physiology of the normal mammary gland as well as the precise molecular mechanisms that could favor basal breast cancer formation when BMP4/BMPR1A signaling is altered. Identifying BRCA1 WT patients with basal breast cancer showing a BRCAness phenotype due to altered BMP4/BMPR1A could make them eligible to PARPi therapies.

**Conclusion :**
We suggest a role for the BMP4-BMPR1A axis in the early stages of basal-like breast tumor carcinogenesis, through a phenocopy of BRCA1 mutations inducing basal differentiation of stem cells and promoting the genetic instability necessary for their transformation.

1st Edition
CRCM Symposium
CANCER RESEARCH CENTER MARSEILLE
CRCM CANCER RESEARCH CENTER Marseille
Comet Cell communication & Microenvironment dpt.
Translate-IT Translational research & Innovative therapies dpt.
4 - 6 February 2026
MARSEILLE
Palais du Pharo

## Posters Sessions 2 - Cellular crosstalk and molecular mechanisms of cancer progression

### S2CA38 : Investigating the role of PTK7 nuclear localization in Colorectal cancer development

*Louis Guiraud*

**Authors:**
Louis Guiraud (1), Charlotte Dessaux (2), Avais Daulat (2), Stéphane Audebert (2), Luc Camoin (2)

*1. Centre de Recherche en cancérologie de Marseille, Marseille, France*
*2. Centre de Recherche en cancérologie de Marseille, Marseille, France*

**Keywords:** Colon cancer, Cell fractionation, nuclear translocation, PTK7, pseudokinase

**Introduction**
Colorectal cancer (CRC) represents the 2nd deadliest cancer in the world. There is therefore a real necessity to identify new biomarkers to promote the development of more efficient therapies. The Wnt/β-catenin signaling pathway has a major role in CRC due to frequent dysregulations. PTK7 (Protein Tyrosine Kinase 7), a transmembrane receptor required during embryo development and involved in Wnt/β-catenin and Planar Cell Polarity (PCP) pathways, has been identified both as a poor prognosis marker and a therapeutic target in CRC . As a cell surface protein, PTK7 oncogenic properties have mainly been associated with its membrane localization. Indeed, cell surface PTK7 has already been characterized to act as a positive activator of Wnt pathways by interacting with Wnt ligands and membrane components, such as LRPs and Frizzled. Recently, other studies described PTK7 membrane activity through its interaction with key surface receptors, including EGFR and FGFR1, and interfering with their signaling. Despite their surface location, some tyrosine kinase receptors have been described to translocate into the nucleus, and to interact with transcription factors for regulating gene expression and promoting tumor progression in various cancers. Here, using cell fractionation followed by western blot and mass spectrometry analyses, we have evidence for PTK7 basal localization in both soluble nuclear and chromatin bound fractions in colon cancer cell lines. Additionally, mass spectrometry data suggest HMGA1, a transcription factor positively regulating Wnt/β-catenin pathway by initiating LRP5 transcription, as a potential PTK7 nuclear interactor. Finally, thanks to bulk/single-cell RNAseq analyses, we propose a model in which nuclear PTK7 interacts with HMGA1 at the LRP5 promotor region in order to potentially enhance the Wnt/β-catenin signaling in CRC.

**Results :**
We used cell fractionation followed by western blot to detect PTK7 in CRC cell lines nuclear compartment. Mass spectrometry/ BioID was used to identify PTK7 nuclear interactors including transport proteins such as XPO1, KPNB1, KPNA2, transcription factor such as HMGA1. To confirm the implication of those proteins in PTK7 nuclear transport, we used inhibitors selectively directed against KPNB1 and XPO1 activities. To evaluate the correlation of co-expression between LRP5, HMGA1 and PTK7, we analyzed bulk/single cell RNA seq data extracted from publically available sequenced CRC tumors. Then, we additionally confirmed the implication of both PTK7 and HMGA1 in the positive regulation of LRP5 expression in CRC cell lines by using si-RNA strategies followed by Western-Blot and qRT-PCR analysis.

1st Edition
CRCM Symposium
CANCER RESEARCH CENTER MARSEILLE
CRCM CANCER RESEARCH CENTER Marseille
Comet Cell communication & Microenvironment dpt.
Translate-IT Translational research & Innovative therapies dpt.
4 - 6 February 2026
MARSEILLE
Palais du Pharo

## Posters Sessions 2 - Cellular crosstalk and molecular mechanisms of cancer progression

# S2CA39 : Determination of the structure of the extracellular domain of the PTK7 receptor by cryo-electron microscopy to unveil its biological functions

*Jules Caron*

**Authors:**
Jules Caron (1), Charlotte Dessaux (2), Denis Ptchelkine (3), Avais Daulat (2), Stéphane Audebert (2), Flavio Maina (2), Juan Reguera (3), Jean-Paul Borg (2)

*1. CRCM/AFMB, Marseille, France*
*2. CRCM, Marseille, France*
*3. AFMB, Marseille, France*

**Keywords:** PTK7, cryo-electron microscopy, EPHA2, protein:protein interaction

**Introduction**
The Wnt/β-catenin and planar cell polarity (PCP) signaling pathways are involved in various physiological processes and are often dysregulated in cancer. Within the Wnt pathway, the receptor tyrosine kinase (RTK) PTK7 (Protein Tyrosine Kinase 7) is associated with metastasic progression and reduced survival in patients with colorectal cancer (CRC). The receptor is now considered both a poor diagnostic marker and as a promising therapeutic target in CRC. Although PTK7 lacks catalytic activity, it ensures key biological functions through protein-protein interactions. At the cell surface, its pseudokinase domain acts as a scaffold for cytoplasmic partners such as β-catenin or Rack1, while its extracellular domain (ECD) serves as a co-receptor for proteins including Ror2 or Vangl1/2. The structure of the pseudokinase domain has recently been solved by crystallography. In contrast, the structure of the PTK7 ECD is currently only predicted by AlphaFold. The elucidation of this structure will be crucial to understand how PTK7 engages its various co-receptors. The PTK7 ECD consists in seven immunoglobulin-like domains that undergo alternative splicing events, giving rise to different isoforms whose specific functions remain unknown. Several structures of PTK7 co-receptors have recently been elucidated by crystallography or cryo-electron microscopy (cryo-EM). This includes EphA2, an active RTK involved in cancers and identified by the J.-P. Borg team as a partner of the PTK7 ECD. PTK7 negatively regulates EphA2 activity and modulates its oligomerization state.

**Results :**
The strategy consists in producing a soluble form of the PTK7 ECD, fused to a Twin-Strep-Tag, in human HEK293T cells, followed by purification on Strep-Tactin resin. The successful purification of the recombinant protein was confirmed by SDS-PAGE and mass spectrometry, allowing us to perform initial cryo-EM assays. The resulting medium-resolution structure of the PTK7 ECD suggests a trimeric organization, consistent with Blue Native PAGE data and with an AlphaFold3 model. In parallel, co-immunoprecipitation experiments allowed us to map the PTK7:EphA2 complex, identifying the EphA2 ligand-binding domain (LBD) and Cystein-rich domain as key regions involved in the interaction. Now, the objective is to characterize, using the same workflow, the structures of the different PTK7 ECD isoforms and subsequently the structure of the PTK7:EphA2 complex. Additionally, in order to validate the formation of this complex and complete the mapping of the interaction interface, we will conduce biophysical assays such as Bio-Layer Interferometry.

1st Edition
CRCM Symposium
CANCER RESEARCH CENTER MARSEILLE
CRCM CANCER RESEARCH CENTER Marseille
Comet Cell communication & Microenvironment dpt.
Translate-IT Translational research & Innovative therapies dpt.
4 - 6 February 2026
MARSEILLE
Palais du Pharo

## Posters Sessions 2 - Cellular crosstalk and molecular mechanisms of cancer progression

# S2CA40 : Syntenin orchestrates matrix degradation by controlling MT1-MMP secretion in small extracellular vesicles and invadopodia formation

*Sylvie Thuault*

**Authors:**
Marie Huber (1), Rania Ghossoub (1), Raphael Leblanc (1), Guido David (2), Pascale Zimmermann (3, 1), Sylvie Thuault (1)

*1. Extracellular Vesicles: from signaling mechanistic to therapeutic engineering, Cancer Research Center of Marseille, Marseille, France*
*2. KU Leuven, Department of Human Genetics, Leuven, Belgium*
*3. Department of Human Genetics , KU Leuven, Leuven, Belgium*

**Keywords:** MT1-MMP, small extracellular vesicles, invadopodia, syntenin, syndecans

**Introduction**
Matrix metalloproteinases (MMP) play a crucial role in the remodelling of the extracellular matrix (ECM) during cancer progression. The membranetype 1 MMP (MT1-MMP) in particular, is thereby strongly associated with poor prognosis. MT1-MMP localizes at invadopodia, specialized actin-rich structures developed by cancer cells to degrade the ECM, and at the surface of secreted small extracellular vesicles (sEV). The role of sEVassociated MT1-MMP in ECM degradation and the mechanisms supporting MT1-MMP loading into sEV are unknown. We previously established that the PDZ protein syntenin and the syndecan heparan sulfate proteoglycans (SDC) syntenin associates with, are major players controlling sEV biogenesis.

**Method :**
The interaction between syntenin and MT1-MMP was assessed by surface plasmon resonance using the BIAcore technology.Their localization was analyzed by immunofluorescence in MDA-MB-231 triple negative breast cancer (TNBC) cells. MT1-MMP surface levels and endocytosis were examined by biotinylation of cell surface proteins following syntenin or SDC depletion using siRNA. In addition, sEV collected by sequential ultracentrifugation of conditioned media from MDA-MB-231 cells depleted of syntenin or SDC were used to evaluate the impact of the syntenin-SDC pathway on MT1-MMP sorting into sEV. Finally, the effect of syntenin depletion on the matrix degrading activity of MDA-MB-231 cells and their immunocaptured sEV was determined using a gelatin degradation assay.

**Results :**
In present study, we demonstrate that ECM degradation via invadopodia depends on syntenin. We also show that syntenin colocalizes with MT1- MMP in late endosomes, the cellular compartment from which sEV in part originate, and that syntenin directly interacts with MT1-MMP. Interestingly, this interaction does not involve the PDZ-binding motif, but a PRR sequence in MT1-MMP. Moreover, we demonstrate that syntenin and SDC are essential determinants of the sorting of MT1-MMP to sEV. Additionally, sEV contribute to ECM degradation through MT1-MMP activity, a process dependent on syntenin.

**Conclusion :**
These findings provide evidence that syntenin-SDC-MT1-MMP complexes orchestrate ECM degradation in a TNBC model and pave the way for innovative rational approaches to control cancer cell invasion.

1st Edition
CRCM Symposium
CANCER RESEARCH CENTER MARSEILLE
CRCM CANCER RESEARCH CENTER Marseille
Comet Cell communication & Microenvironment dpt.
Translate-IT Translational research & Innovative therapies dpt.
4 - 6 February 2026
MARSEILLE
Palais du Pharo

## Posters Sessions 2 - Cellular crosstalk and molecular mechanisms of cancer progression

### S2CA41 : Function and Regulation of Protein Tyrosine Kinase-7 in Dendritic Cells

*Lisy Collette*

**Authors:**
Lisy Collette (1), Paula Michea (2), Alix Jaeger (2), Jean-Paul Borg (2)

*1. Marseille, France*
*2. CRCM, Marseille, France*

**Keywords:** PTK7; Dendritic cells (DC); Inflammation

**Introduction**
PTK7 is a pseudo-tyrosine kinase involved in cell adhesion, polarity, and migration. Its overexpression is associated with tumor progression, metastatic dissemination and poor prognosis in multiple cancers, including hepatocellular carcinoma, melanoma, and triple-negative breast cancer. A PTK7-targeting antibody–drug conjugate has demonstrated therapeutic efficacy by inducing durable tumor regression (Damelin et al., Sci. Transl. Med., 2017). This study also highlighted PTK7 expression on plasmacytoid dendritic cells (pDCs) in both blood and non-small cell lung carcinoma samples, leading our team to investigate the role of PTK7 in dendritic cells (DCs). We have shown that PTK7 is physiologically expressed mainly by Langerhans cells (LCs), while other DC subsets, particularly cDC2 can express it within B16F10 melanoma tumors, suggesting regulation by the tumor microenvironment. Moreover, our in vitro data indicate that PTK7$^+$ DCs display impaired T-cell priming ability, characterized by reduced proliferation of CD4$^+$ and CD8$^+$ T cells and increased differentiation of regulatory T cells (Jaeger, PhD thesis 2024; Jaeger et al.). These findings suggest that PTK7 expression may contribute to the establishment of an immunosuppressive microenvironment and to the induction of immune tolerance. Given the central role of DCs in activating antitumor T-cell responses, it is plausible that cancers exploit escape mechanisms by altering DC functionality. Previous studies have described tumor-infiltrating DCs capable of supporting tumor progression (Hanks et al., 2013; Scarlett et al., 2012), although the underlying mechanisms remain poorly defined. In light of this and based on our preliminary observations, we hypothesize that PTK7 expression in DCs is modulated by the tumor microenvironment, thereby promoting an immunosuppressive state conducive to cancer progression. To address this hypothesis, our project is structured around three main objectives: 1. Evaluate in vivo the impact of PTK7 deficiency on DC function in physiopathological contexts (cancer, aging). 2. Identify inflammatory signals in the microenvironment regulating PTK7 expression in DCs. 3. Define the PTK7 interactome and associated signaling pathways in DCs under inflammatory conditions.

1st Edition
CRCM Symposium
CANCER RESEARCH CENTER MARSEILLE
CRCM CANCER RESEARCH CENTER Marseille
Comet Cell communication & Microenvironment dpt.
Translate-IT Translational research & Innovative therapies dpt.
4 - 6 February 2026
MARSEILLE
Palais du Pharo

## Posters Sessions 2 - Cellular crosstalk and molecular mechanisms of cancer progression

### S2CA42 : Unravelling the role of Ptk7 in hepatic carcinogenesis

*Guillaume Desandre*

**Authors:**
Guillaume Desandre (1), Castagna Filippo (1), Celia Sequera (1), Abdessamad El Kaoutari (1), Jean-Paul Borg (1), Flavio Maina (1)

*1. INSERM, Marseille, France*

**Keywords:** Ptk7,Tumorigenesis,Mice,Cooperation, HTVi

**Introduction**
Hepatocellular carcinoma (HCC) is the most common primary liver tumour and represents a major public health concern. Its incidence continues to rise, notably with the increasing prevalence of metabolic-associated steatohepatitis. HCC is characterized by pronounced heterogeneity, both interand intra-tumoural, which poses significant challenges for the development of effective therapeutic strategies. Protein Tyrosine Kinase 7 (PTK7) is a pseudo-tyrosine kinase whose functions have been extensively studied in several biological contexts, notably by our team. In cancer, PTK7 has been associated with therapeutic resistance, metastatic progression, and overall poor prognosis. Despite its well-established roles in other cancers, limited data are available regarding PTK7 involvement in HCC. The few existing studies suggest that PTK7 overexpression may correlate with worse clinical outcomes in HCC and the activation of pro-metastatic pathways. In this project, we aim to elucidate the role of PTK7 in HCC tumorigenesis, disease progression, and therapeutic resistance.

**Method :**
This study is structured around four major axes. First, we analyzed public datasets to characterize the status of PTK7 across liver disease and cancer. Second, in relation to pathways relevant to PTK7 functions, we employed hydrodynamic tail-vein injection (HTVi)-based mouse models to reconstitute these signaling circuits in vivo and evaluate their capacity to trigger and drive liver cancer. Third, we will apply state-of-the-art -omics approaches in order to better elucidate the mechanism by which PTK7 induces tumoral growth and treatment resistance. Finally, we will assess the therapeutic efficacy of anti-PTK7 CAR-T cells we have developed as therapeutic agents for HCC treatments.

**Results :**
While PTK7 is poorly expressed in HCC compared to other malignancies, its expression is greatly increased in damaged liver, and correlates with the level of fibrosis in patients. This increased expression spikes in cirrhotic and liver tumours, where elevated PTK7 levels are found in distinct patient clusters, distinguished by specific gene expression patterns, pathway enrichments, and prognosis. In mice, we found that PTK7 triggers HCC formation and progression by cooperating with other oncogenic signals, such as MYC and WNT/β-Catenin. Intriguingly, these PTK7-driven tumours are composed of distinct cellular subtypes, whose characterization is currently ongoing.

**Discussion :**
This study aims to decipher the mechanism by which PTK7 induces HCC development, and support treatment resistance. Using our expertise, study the ability of anti-PTK7 CAR Tcells to induce tumoral regression, that could help establish a robust preclinical framework and potentially support the stratification of patients based on PTK7-associated co-alterations, ultimately paving the way towards more personalized therapeutic strategies.

1st Edition
CRCM Symposium
CANCER RESEARCH CENTER MARSEILLE
CRCM CANCER RESEARCH CENTER Marseille
Comet Cell communication & Microenvironment dpt.
Translate-IT Translational research & Innovative therapies dpt.
4 - 6 February 2026
MARSEILLE
Palais du Pharo

## Posters Sessions 2 - Cellular crosstalk and molecular mechanisms of cancer progression

# S2CA43 : Multi-omics profiling uncovers immune-molecular clusters with distinct chemo- immunotherapeutic vulnerabilities in a mouse model of triple-negative breast cancer

*Nathan Corvaisier*

**Authors:**
Nathan Corvaisier (1), Jean Monatte (2), Olivier Castellanet (3), Abdessamad El Kaoutari (3), Muge Kaya (4), Lorène Ferreira (4), Stephane Audebert (3), Alexandre Tassin De Nonneville (5), Anthony Gonçalves (5), Jean-Paul Borg (3, 6), Paula Michea Veloso (3), Flavio Maina (3), Fabienne Lamballe (3)

*1. CRCM, Marseille, France*
*2. CRCM, CRCM, Marseille, France*
*3. CRCM, Marseille, France*
*4. Experimental Histopathology ICEP Platform, CRCM, Marseille, France*
*5. Medical oncology Institut Paoli-Calmettes, CRCM, Marseille, France*
*6. Institut Universitaire de France (IUF), Paris, France*

**Keywords:** TNBC classification, Chemo/immuno combo, Immune micro-environment, tumoroids, chemokines

**Introduction**
Triple-negative breast cancer (TNBC) is an aggressive and heterogeneous disease in which immune checkpoint inhibitors (ICI) provide inconsistent benefit. Understanding how tumor-immune interactions shape therapeutic responses is crucial for developing treatment strategies. We hypothesized that the MMTV-R26Met spontaneous TNBC model could help uncover how immune microenvironmental features contribute to differential sensitivity to chemo/immunotherapy.

**Method :**
We performed histological analyses, multi-omics profiling (transcriptomics, genomics, proteomics), and immune characterization of spontaneous MMTV-R26Met tumors, and established syngeneic grafts derived from primary tumors. Results were compared with patient datasets and tissue microarrays from human TNBC cohorts. We evaluated the efficacy of epirubicin and anti-PD-1 in MMTV-R26Met syngeneic models. We explored mechanisms driving the recruitment of specific immune cell populations by analyzing cytokine and chemokine expression profiles in cell lines established from MMTV-R26Met tumors, while immune infiltrates were characterized in tumors arising from orthotopic grafts of these cell lines or tumoroids.

**Results :**
Multi-parametric analysis identified four molecular-immune clusters, each characterized by specific immune features: lymphocyte-, macrophage-, neutrophil-, or dendritic cell-enriched. These immune infiltrates were conserved across serial syngeneic transplantations, indicating that tumorintrinsic properties dictate the recruitment of specific immune subsets. This classification aligned with immune signatures found in TNBC patients. In vitro cell and tumoroid models established from MMTV-R26Met primary tumors maintained stable inflammatory identities, reflected by cytokine and chemokine expression patterns characteristic of their dominant immune subtype. Their orthotopic engraftments recapitulated the same immune infiltrates as the original tumors, demonstrating that they intrinsically encode signals capable of driving selective immune recruitment in vivo. Focusing on neutrophil- and macrophage-enriched tumors, immunosuppressive subtypes associated with poor prognosis, we found marked differences in sensitivity to ICI, alone or combined with epirubicin. Specifically, epirubicin induced a myeloid subtype-specific remodeling of the immune microenvironment, with variable ability to convert immunologically “cold” tumors into “hot” ones.

**Discussion :**
Our findings show that the immune microenvironment is a key determinant of therapeutic outcome in TNBC. The dominant myeloid context - neutrophil- or macrophage-enriched - shapes chemotherapy efficacy and its ability to potentiate ICI responses. This myeloid-driven heterogeneity provides a mechanistic basis for interpatient variability and supports immune-informed therapeutic stratification. Ongoing work aims to map the temporal dynamics of myeloid infiltration to understand how shifts in immune states influence treatment sensitivity.

1st Edition
CRCM Symposium
CANCER RESEARCH CENTER MARSEILLE
CRCM CANCER RESEARCH CENTER Marseille
Comet Cell communication & Microenvironment dpt.
Translate-IT Translational research & Innovative therapies dpt.
4 - 6 February 2026
MARSEILLE
Palais du Pharo

## Posters Sessions 2 - Cellular crosstalk and molecular mechanisms of cancer progression

# S2CA44 : A human pathophysiological 3D-bone marrow model reveals immune and stromal cell heterogeneity

*Gulia Campione*

**Authors:**
Gulia Campione (1), Mariette Giannini (2), Léa Torcq (2), Sylvain Donadelli (2), Maroua Bencheikh (2), Sophia Bounaud (2), Sandrine Jeanpierre (2), Kevin Geistlich (2), Sylvain Lefort (2), Julie Leca (2)

*1. CRCL, Lyon, France*
*2. CRCL, Lyon 08, France*

**Keywords:** 3D model, bone marrow, acute myeloid leukemia, microenvironment

**Introduction**
The bone marrow (BM) niche is a complex and dynamic microenvironment composed of diverse cell types, including stromal, endothelial, immune, and hematopoietic cells. Dysregulation of the interactions occurring between cells influence malignant transformation. Existing in vitro and in vivo models incompletely recapitulate human BM physiology, due to species-specific differences, limited immune representation, and poor preservation of cellular heterogeneity. To overcome these limitations, we developed a standardized three-dimensional human bone marrow model (3D-BOM) capable of mimicking key structural and functional features of the BM niche and we assessed its capacity to reproduce physiological and pathological interactions, including those occurring in acute myeloid leukemia (AML).

**Method :**
The 3D-BOM system was generated culturing HMEC-1 endothelial cells and mesenchymal stromal cells (HS27A or primary MSCs) with biphasic calcium phosphate beads in osteogenic medium for 3 weeks allowing self-assembly of the 3D structure. THP-1 monocytic cell line, primary CD14+ monocytes, hematopoietic progenitors cell line or primary HSPCs from normal or AML samples were subsequently introduced. Flow cytometry, ELISA, tubules formation assays, long-term serial 3D cultures, and single-cell RNA sequencing were performed after enzymatic dissociation of the disk.

**Results :**
Single-cell transcriptomics revealed stromal heterogeneity comparable to native human BM, identifying MSCs, osteochondral progenitors, osteoblasts, and chondrocyte progenitors, along with sinusoidal and type S endothelial cells. Long-term culture preserved endothelial functionality, while endothelial cells grown in 3D with AML progenitors exhibited enhanced tubule formation, mirroring the increased angiogenesis observed in AML-BM. In addition, HSPCs maintained stemness features across serial 3D culture. THP-1 and iPSC-derived macrophages spontaneously adopted pro-inflammatory features within the 3D-BOM. Importantly, THP-1 and primary CD14+ cultured with AML progenitors acquired anti-inflammatory phenotype such as increased IL-10 secretion and CD209 expression.

**Discussion :**
3D-BOM faithfully recreates key features of the human BM niche, including stromal and endothelial heterogeneity, long-term maintenance of hematopoietic progenitors and endothelial cells functions, and supporting functional immune activation. Its ability to capture niche remodeling in AML context highlights its relevance as a human physiopathological tool for dissecting mechanisms of leukemic transformation and for preclinical testing of therapies targeting both AML cells and their microenvironment, while reducing reliance on animal models.

**Conclusion :**
The 3D-BOM functions as a self-organizing human BM niche, supporting stromal, endothelial, immune, and hematopoietic dynamics, and reproducing AML-driven niche alterations observed in patients BM.

1st Edition
CRCM Symposium
CANCER RESEARCH CENTER MARSEILLE
CRCM CANCER RESEARCH CENTER Marseille
Comet Cell communication & Microenvironment dpt.
Translate-IT Translational research & Innovative therapies dpt.
4 - 6 February 2026
MARSEILLE
Palais du Pharo

## Posters Sessions 2 - Cellular crosstalk and molecular mechanisms of cancer progression

### S2CA45 : KRAS allelic imbalance reveals adaptive metabolic states in pancreatic cancer

*Alex Chauvin*

**Authors:**
Alex CHAUVIN (1), Alex CHAUVIN (1), Françoise Silvy (1), Julie Roques (1), Loïc Moubri (1), Pauline Moussard (1), Odile Gayet (1), Emilie Mamessier (2), Nicolas Fraunhoffer (1), Eric Mas (1), Nelson Dusetti (1)

1. *Centre de Recherche en Cancérologie de Marseille (CRCM), INSERM U1068, Marseille, France*
2. *Centre de Recherche en Cancérologie de Marseille (CRCM), INSERM U1068, Aix-Marseille University, CNRS, Institut Paoli-Calmettes, Predictive Oncology Laboratory, Ligue Contre le Cancer, Marseille, France*

**Keywords:** Pancreatic Cancer, KRAS mutation, genomic analysis, transcriptomics, allelic imbalance

**Introduction**
Pancreatic ductal adenocarcinoma (PDAC) remains among the most lethal malignancies, with a 5-year overall survival of ~12%, largely due to late diagnosis, limited resectability, and resistance to standard therapies. Over 90% of PDACs harbor oncogenic KRAS mutations, which arise early and are key drivers of tumour initiation and maintenance. Recent studies reveal that quantitative differences in KRAS mutant dosage through allelic gain, loss of wild-type allele or copy-number imbalance may amplify oncogenic signaling and reshape tumour cell behaviour, potentially favouring evolution toward more aggressive and therapy-resistant states.

**Method :**
We hypothesised that comparing KRAS-balanced versus KRAS-imbalanced PDAC models would reveal evolutionary and adaptive mechanisms underlying tumour aggressiveness and treatment resistance, beyond subtype association. Specifically, we aimed to determine whether allelic imbalance generates distinct metabolic and transcriptional programs. KRAS allelic imbalance was quantified using droplet digital PCR (ddPCR) across 333 preclinical PDAC models derived from 219 patients, encompassing patient-derived xenografts (PDXs, n=125), primary cell cultures (PDCs, n=51), and organoids (PDOs, n=157). Transcriptomic subtyping was performed using bulk RNA-seq. To specifically assess the biological effect of allelic dosage, differential expression analyses were conducted within tumours models. Gene Set Enrichment Analysis (GSEA), along with pathway enrichment, was employed to explore metabolic distinctions.

**Results :**
KRAS allelic imbalance was conserved across model types from the same patient, indicating clonal stability. Imbalance was significantly enriched in basal-like PDX (p=0.00037), but intriguingly, we also identified a subset of classical PDAC models exhibiting KRAS imbalance. Within these classical models, GSEA revealed significant up-regulation lipid transport (p-adj.=0.009), and mitotic spindle (NES=1.8 , p-adj.=0.003) while pro-inflammatory pathways (N=-1.78, p-adj.=0.007) are down-regulated. Complementary pathway analyses reinforced enrichment in lipoprotein particle organisation, acylglycerol metabolism, and lipid remodeling, independently of basal-like markers.

**Discussion :**
These results suggest that KRAS allelic imbalance may act as an evolutionary driver shaping metabolic rewiring beyond canonical subtype boundaries. The enrichment of lipid uptake and fatty acid metabolic programs in KRAS-imbalanced classical tumours suggests subtype-transcending metabolic reprogramming. This highlights the need for therapeutic strategies tailored not only to transcriptomic subtype but also to specific metabolic vulnerabilities.

**Conclusion :**
KRAS dosage should therefore be considered as a complementary stratification layer to transcriptomic subtype, and metabolic rewiring particularly lipid-dependent programs may represent exploitable vulnerabilities in KRAS-imbalanced classical PDAC.

1st Edition
CRCM Symposium
CANCER RESEARCH CENTER MARSEILLE
CRCM CANCER RESEARCH CENTER Marseille
Comet Cell communication & Microenvironment dpt.
Translate-IT Translational research & Innovative therapies dpt.
4 - 6 February 2026
MARSEILLE
Palais du Pharo

## Posters Sessions 2 - Cellular crosstalk and molecular mechanisms of cancer progression

### S2CA46 : Role of the WNT/PCP CELSR2 receptor in triple-negative breast cancer progression

*Julia Koren*

**Authors:**
Julia KOREN (1), Yanis Nour Islem (2), Samad El Kaoutari (2), Avais Daulat (3), Fabienne Lamballe (3), Flavio Maina (3), Jean-Paul Borg (3, 4), Alexandra Walton (3)

*1. CRCM, MARSEILLE, France*
*2. CRCM, MARSEILLE, France*
*3. CRCM, Marseille, France*
*4. Institut Universitaire de France, Marseille, France*

**Keywords:** TNBC, aGPCR, CELSR2, tumor growth, EMT, WNT/PCP

**Introduction**
Several studies on breast cancer have shown a link between activation of the WNT/Planar Cell Polarity (WNT/PCP) pathway, tumor development, and resistance to treatment. CELSR2 is a receptor in the WNT/PCP pathway that belongs to the family of G protein-coupled receptors involved in cell adhesion. This receptor has a very large extracellular N-terminal region that includes a proteolytic site where the receptor is cleaved in an autoproteolytic manner, leading to its activation. We have demonstrated, through two transcriptomic analyses, that CELSR2 overexpression is associated with reduced metastasis-free survival and decreased response to treatment in triple negative breast cancer (TNBC), a subtype of breast cancer. TNBC, which affects about 15% of patients, is the most aggressive subtype due to its strong propensity to develop metastases. Moreover, lacking hormone receptors and HER2, TNBC does not benefit from hormone therapy or Trastuzumab. It is therefore essential to identify new therapeutic targets to optimize its treatment and prevent metastatic development.

**Method :**
To investigate how CELSR2 may contribute to TNBC progression, we examined its role in tumor growth (in vitro, in vivo), in cell migration and epithelial–mesenchymal transition (EMT). We also sought to elucidate the molecular mechanisms through which CELSR2 promotes tumor cell aggressiveness.

**Results :**
Here, we experimentally demonstrate that CELSR2 promotes cancer cell proliferation by contributing to tumor growth in orthotopic xenografts of TNBC cell lines implanted in immunodeficient mice, through activation of the cAMP/PKA/p-CREB signaling pathway. We further show that, via this pathway, the transcription factor p-CREB induces the expression of genes involved in oxidative phosphorylation, which may underlie the enhanced proliferation of primary tumors overexpressing CELSR2. In contrast, CELSR2 does not appear to play a role in cell migration. However, CELSR2 is highly expressed in epithelial cells and is downregulated during EMT, becoming less expressed in mesenchymal cells.

**Discussion :**
Taken together, these results suggest that CELSR2 overexpression in TNBC patients is associated with tumor growth through enhanced oxidative phosphorylation, and its underexpression may facilitate tumor cell detachment from the primary tumor. The receptor is no longer expressed in circulating tumor cells but is re-expressed in metastatic lesions, to promote tumor growth. It is therefore important to further investigate the potential of CELSR2 as a predictive biomarker of patient survival and/or treatment response in TNBC, by using of blood-based assays to monitor soluble CELSR2 in pre-neoplastic lesions or to track residual disease.

1st Edition
CRCM Symposium
CANCER RESEARCH CENTER MARSEILLE
CRCM CANCER RESEARCH CENTER Marseille
Comet Cell communication & Microenvironment dpt.
Translate-IT Translational research & Innovative therapies dpt.
4 - 6 February 2026
MARSEILLE
Palais du Pharo

## Posters Sessions 2 - Cellular crosstalk and molecular mechanisms of cancer progression

### S2CA48 : Analysis of automated phosphopeptide enrichment capacity

*Emilie Baudelet*

**Authors:**
Emilie Baudelet (1), Carla Maillet (1), Stephane Audebert (1), Luc Camoin (1)

*1. Marseille Proteomique - MaP, CRCM, Marseille, France*

**Keywords:** Phoshoproteome, automated sample preparation, enrichment capacity, oncology research

**Introduction**
Protein phosphorylation is one of the most common and important post-translational modification. This reversible mechanism drives various cellular processes such as cell-cycle regulation, intracellular signaling, cell proliferation and metabolic regulation. Thus aberrant phosphorylation-mediated signaling networks can contribute to cancer progression and aggressiveness. This is the reason why phoshoproteome studies became an important field to make the research going further.

**Method :**
To overcome the challenges of low stoichiometry of phosphoproteins compared to non-phosphoproteins and peptide loss during enrichment, we use an automated sample preparation with the AssayMap Bravo from Agilent. Our study aimes at determining the capacity of Fe(III)-NTA cartridges to enrich phosphopeptides with a dilution series of breast cancer line (SKBR3) lysates quantity from microgram to milligram.

**Results :**
The Fe(III)-NTA cartridges effectively captured phosphorylated peptides at input quantities ranging from 50µg to 500µg, with a reduction in efficiency observed beyond 500µg due to cartridges saturation. The results showed robust performance with high sensitivity and reproductibility, enabling the identification of thousands of phosphopeptides even with low starting material.

**Discussion :**
Future optimization could futher enhance efficiency, particulary for low-abondance samples.

**Conclusion :**
These advancements hold promise for oncology research.

1st Edition
CRCM Symposium
CANCER RESEARCH CENTER MARSEILLE
CRCM CANCER RESEARCH CENTER Marseille
Comet Cell communication & Microenvironment dpt.
Translate-IT Translational research & Innovative therapies dpt.
4 - 6 February 2026
MARSEILLE
Palais du Pharo

## Posters Sessions 2 - Cellular crosstalk and molecular mechanisms of cancer progression

### S2CA49 : PTK7 identifies a regulatory dendritic cell state and is modulated in inflammation and cancer

*Paula Michea*

**Authors:**
Alix Jaeger (1), Lisy Collette (1), Anne-laure Bailly (1), Sylvie Marchetto (1), Flavio Maina (1, 2), Jean-Paul Borg (1, 3), Paula Michea (4)

*1. Aix Marseille Univ, CNRS, Inserm, Institut Paoli-Calmettes, Centre de Recherche en Cancérologie de Marseille (CRCM), Marseille, France.*
*2. Turing Center for Living Systems (CENTURI), Marseille, France, MARSEILLE, France*
*3. Institut Universitaire de France (IUF), MARSEILLE, France*
*4. CRCM - AMU, Marseille, France*

**Keywords:** PTK7, dendritic cell, immune rgulation,

**Introduction**
Protein Tyrosine Kinase 7 (PTK7) is a Wnt pathway co-receptor whose overexpression is associated with poor prognosis in several cancers, making it an attractive therapeutic target. Although PTK7 expression has recently been reported in dendritic cells (DCs), its functional role in these cells remains unknown.

**Method :**
Here by using multiparametric flow cytometry, bulk RNA-seq analysis and functional experiments in vitro and in vivo, we provide the first comprehensive study of PTK7 expression and function in dendritic cells.

**Results :**
At steady state, PTK7 expression was restricted to a subset of DCs: the Langerhans cells, in the skin and cutaneous lymph nodes (CLNs). PTK7⁺DCs displayed increased CCR7 expression and were enriched among recently migrated DCs in CLNs in a skin sensitization model. Functionally, PTK7⁺ DCs showed a reduced capacity to activate CD4⁺ and CD8⁺ T cells and to induce their proliferation, while promoting regulatory T cell differentiation. In inflammatory conditions, particularly in melanoma and hepatocellular carcinoma models or during aging, PTK7 expression was acquired by additional DC subsets, potentially including recently described mreg DCs, suggesting modulation by the tumor microenvironment. Using a DCspecific PTK7-deficient mouse model, we further observed that PTK7 may contributes to immune regulation, as its deletion leads to increased inflammation in aged mice. RNA-seq analyses revealed altered expression of antigen presentation-related genes, providing mechanistic insight.

**Conclusion :**
Altogether, our data identify PTK7 as a novel marker of regulatory dendritic cells involved in immune homeostasis and cancer-associated inflammation.

1st Edition
CRCM Symposium
CANCER RESEARCH CENTER MARSEILLE
CRCM CANCER RESEARCH CENTER Marseille
Comet Cell communication & Microenvironment dpt.
Translate-IT Translational research & Innovative therapies dpt.
4 - 6 February 2026
MARSEILLE
Palais du Pharo

## Posters Sessions 2 - Cellular crosstalk and molecular mechanisms of cancer progression

### S2CA50 : Effects of GALA on the secretion of proteins in liver cancer

*Sahar El Amrani*

**Authors:**
Sahar El Amrani (1), Eugénie Lohmann (2), Saba Goodarzi (2), Rebecca Bennion (2), Stephane Audebert (2), Emilie Baudelet (2), Frederic Bard (2)

*1. CRCM INSERM, MARSEILLE, France*
*2. CRCM INSERM, MARSEILLE, France*

**Introduction**
O-glycosylation is a post-translational modification catalyzed by N-acetylgalactosaminyltransferases (GALNTs) in the Golgi apparatus, where a glycan is added to proteins to regulate their maturation and function. In some cancers, GALNTs are aberrantly translocated from the Golgi to the endoplasmic reticulum (ER), leading to enhanced glycosylation of newly synthesized proteins. This shift alters the global glycosylation landscape and is known as the GalNAc transferase activation (GALA) pathway. Reported in several solid tumors, including liver cancer, GALA-driven hyperglycosylation can profoundly impact protein secretion, cellular signaling, and interactions within the tumor microenvironment.

**Method :**
This project investigates how increased O-glycosylation modulates protein secretion in liver cancer cells. To this end, secretome analysis was performed using two HUH7-derived cell lines differing in GALA activity. The first, HUH7 ERG1-GFP, expresses an inducible ER-targeted GALNT enzyme that elevates O-glycosylation upon induction, modeling GALA activation. The second, HUH7-GFP, serves as a control with low GALA activity. Mass spectrometry-based proteomic analysis was carried out on the secreted proteins from both cell lines to determine how O-glycosylation influences secretion profiles.

**Results :**
Analysis of five biological replicates revealed that GALA alters the secretion of nearly 400 proteins, with both increases and decreases observed. Notably, angiotensin-converting enzyme (ACE) was highly and exclusively secreted by high-GALA cells, suggesting that hyperglycosylation can selectively enhance the secretion of specific proteins. Such differential secretion may result from increased shedding of membrane-associated or surface receptors, potentially enhancing cell–cell communication and contributing to tumor progression. To understand these phenomena further, we propose that hyperglycosylation modifies the conformation or trafficking behavior of proteins, thereby influencing their secretion or degradation. Excessive glycosylation could target some proteins for degradation while stabilizing or enhancing the release of others, reflecting a fine balance between secretion and turnover. Interestingly, several key regulators of secretion and intracellular trafficking also displayed hyperglycosylation, indicating that GALA might broadly disrupt the cellular secretory machinery.

**Discussion :**
Future investigations will aim to manipulate glycosylation patterns to delineate their effects on protein stability, secretion, and degradation. Understanding how GALA-mediated hyperglycosylation shapes the secretome will provide new insights into tumor biology and may uncover novel targets for modulating cell–cell signaling and microenvironment interactions in liver cancer.

1st Edition
CRCM Symposium
CANCER RESEARCH CENTER MARSEILLE
CRCM CANCER RESEARCH CENTER Marseille
Comet Cell communication & Microenvironment dpt.
Translate-IT Translational research & Innovative therapies dpt.
4 - 6 February 2026
MARSEILLE
Palais du Pharo

## Posters Sessions 2 - Cellular crosstalk and molecular mechanisms of cancer progression

### S2CA51 : NUPR1 - Taking Control of Iron Metabolism to Target PDAC

*Emma Cossialls*

**Authors:**
Emma Cosialls (1), Matias Estaras (2), Josephine Shabani (2), Patricia Santofimia (2), Juan Iovanna (2)

*1. INSERM U1068, Marseille, France*
*2. inserm crcm, MARSEILLE, France*

**Keywords:** iron, ferroptosis, PDAC, NUPR1

**Introduction**
Pancreatic ductal carcinoma (PDAC) is one of the most aggressive and lethal malignancies, largely due to its late diagnosis and resistance to chemotherapy. Nuclear protein 1 (NUPR1), a stress-inducible transcription factor, is overexpressed in many cancers and associated with poor prognosis, making it a promising therapeutic target. We have developed a NUPR1 inhibitor, ZZW-115, which demonstrates strong anticancer effects both in vitro and in vivo. Recent studies, including our own, have shown that ZZW-115 induces ferroptosis in a mitochondria-dependent manner, ferroptosis is an iron- and lipid-dependent cell death that is particularly effective against cancer cells resistant to conventional therapies. Given that dysregulated iron metabolism has been described as marker of poor prognosis PDAC, we investigated the role of iron in tumor progression and in ZZW-115-mediated cell death.

**Method :**
Experiments were conducted using the pancreatic cancer cell line MiaPaCa-2. Functional studies for iron homeostasis and lysosomal activity were performed using microscopy, flow cytometry, and Western blotting measuring various parameters. Mitochondrial respiration was assessed using Seahorse XF technology.

**Results :**
We found that, unexpectedly, iron supplementation tends to attenuate ZZW-115-induced cell death. Mechanistically, NUPR1 inhibition alters lysosomal function and induces the accumulation of ferritin, the iron storage protein, within lysosomes, independently of cellular iron level. This leads to iron imbalance within the cells, and ultimately affects mitochondrial functions which mainly rely on iron level, ultimately leading to cell death. Importantly, iron supplementation might fuel mitochondria and rescue mitochondrial damages caused by ZZW-115.

**Discussion :**
Targeting NUPR1 emerge as a novel strategy to disrupt both iron homeostasis and autophagy, and offering a promising strategy to modulate metabolism and treat PDAC.

**Conclusion :**
In summary, our study highlights a critical connection between NUPR1, lysosomal activity, and the regulation of iron homeostasis in PDAC. We demonstrate that intracellular iron level plays a protective role against damages resulting from NUPR1 inhibition. Our results uncover an exploitable iron-dependent metabolic vulnerability in PDAC that could be targeted to improve therapeutic outcomes

1st Edition
CRCM Symposium
CANCER RESEARCH CENTER MARSEILLE
CRCM CANCER RESEARCH CENTER Marseille
Comet Cell communication & Microenvironment dpt.
Translate-IT Translational research & Innovative therapies dpt.
4 - 6 February 2026
MARSEILLE
Palais du Pharo

## Posters Sessions 2 - Cellular crosstalk and molecular mechanisms of cancer progression

### S2CA52 : Glutaminase mechanosensitive glutamylation in breast cancer

*Célia Jardin*

**Authors:**
Célia Jardin (1), Lara Nasr (2), Cecilia Colson (2), Lucille Barban (2), Nathan Glise (2), Anne-Sophie Gay (3), Véronique Henriot (4), Stephan Clavel (2), Carsten Janke (4), Luc Camoin (5), Thomas Bertero (2), Stéphanie Torrino (2), Stéphane Audebert (5)

*1. Plateforme Protéomique MaP, CRCM, Marseille, France*
*2. IHU RespirERA, IPMC, Valbonne, France*
*3. IPMC, IPMC, Valbonne, France*
*4. CNRS, UMR3348, Institut Curie, Paris, France*
*5. Plateforme Protéomique MaP, CRCM, MARSEILLE, France*

**Keywords:** Glutaminase, Glutamylation, Breast Cancer, Stiff, Mass spectrometry

**Introduction**
Glutamylation is a post-translational modification which adds glutamate side chains onto the γ-carboxyl groups of glutamic acid residues in the primary sequence of target proteins. The glutamate required for this mechanism can be produced by glutaminolysis, the conversion of glutamine to glutamate by glutaminase enzyme (GLS), feeding biosynthesis and energy production which has emerged as a key metabolic route in mechanodependent diseases such as breast cancer and pulmonary hypertension. Although discovered in the 1990s, glutamylation has mainly been reported as a post-translational modification of tubulin. Yet, glutamylation is not restricted to tubulin, and whether mechano-induced glutamine catabolism drives protein glutamylation to promote cancer cell aggressiveness remains unknown.

**Method :**
Using mass spectrometry, we reported that matrix stiffening may induce the glutamylation of several metabolic enzymes, such as GLS. We first determined the precise glutamylated sites on GLS and then identify enzymes mediating the GLS glutamylation by performing a siRNA screening of tubulin tyrosine ligase-like (TTLL) enzymes, which adds glutamate on the protein, and cytosolic carboxypeptidase (CCP) enzymes which remove them.

**Results :**
We demonstrated that knockdown of TTLL5 or TTLL9 significantly reduce GLS glutamylation, whereas knockdown of CCP4, CCP5, or CCP6 increased it. In addition, we showed that mutations preventing GLS glutamylation impair its function, reduce glutamine catabolism and blunt cancer cell's aggressiveness.

1st Edition
CRCM Symposium
CANCER RESEARCH CENTER MARSEILLE
CRCM CANCER RESEARCH CENTER Marseille
Comet Cell communication & Microenvironment dpt.
Translate-IT Translational research & Innovative therapies dpt.
4 - 6 February 2026
MARSEILLE
Palais du Pharo

## Posters Sessions 2 - Cellular crosstalk and molecular mechanisms of cancer progression

# S2CA53 : Identify metabolic vulnerabilities that drive dissemination and metastatic expansion of pancreatic ductal adenocarcinoma

*Georgios Efthymiou*

**Authors:**
Georgios EFTHYMIOU (1), Paraskevi Kousteridou (1), Pierre Bertrand (1), Stéphane Audebert (1), Luc Camoin (1), Richard Tomasini (1), Fabienne Guillaumond (1), Sophie Vasseur (1)

*1. Centre de Recherche en Cancérologie de Marseille, Marseille, France*

**Keywords:** Pancreatic ductal adenocarcinoma, metabolism, metabolic reprogramming, metastasis

**Introduction**
The high metabolic adaptability of pancreatic ductal adenocarcinoma (PDAC) is a key factor that drives tumor evolution in disseminating cells throughout the metastatic cascade and contributes to successful colonization of the liver. We hypothesize that metastatic tumor cells modify their metabolism to establish a bi-directional pro-tumoral crosstalk with resident liver cells, especially with hepatocytes, the most abundant and metabolically active cell population in the liver. We theorize that this intercellular metabolite exchange between hepatocytes and tumor cells promotes tumor cell survival in the new environment and facilitates metastatic expansion.

**Method :**
To explore the global metabolic alterations in liver metastases compared to primary PDAC tissue we performed transcriptomic analysis on bulk RNA extracted from liver metastases and from the primary tumor of a murine PDAC model. This approach was coupled with integration of RNAseq and semi-targeted metabolomics in tumor cells extracted from liver metastases or from primary PDAC and cultivated in vitro to identify alterations specific to tumor cells. To simulate the hepatocyte – tumor cell metabolic crosstalk, we used an in vitro co-culture model of medium exchange, accompanied by proteomic analysis and steady state metabolic tracing. Key elements of the identified metabolic pathway were finally genetically and pharmacologically inhibited in functional assays in vitro to better discern the metabolite exchange between hepatocytes and tumor cells.

**Results :**
Using our high-throughput integration analysis alongside the tissue transcriptomics we identified that tyrosine metabolism is a major metabolic dependency of metastatic cells in the liver. More specifically, we found that hepatocytes convert phenylalanine to tyrosine, which is then secreted and absorbed by tumor cells. Tumor cells then break down tyrosine into simple compounds like fumarate which feeds the TCA cycle promoting metastatic cell growth and ultimately metastatic expansion. Pharmacological inhibition or genetic ablation of the tyrosine degradation enzyme HPD in metastatic tumor cells hinders their tumorigenic and metastatic potential.

**Discussion :**
These results demonstrate the cooperating action between hepatocyte and tumor cell metabolism in the liver: Tumor cells re-wire hepatocytes to produce more tyrosine which tumor cells use to promote cell growth. Interestingly, high expression of enzymes involved in tyrosine metabolism correlates with worse survival of PDAC patients. Pharmacological targeting of tyrosine metabolism may be an attractive approach to improve patient outcomes.

1st Edition
CRCM Symposium
CANCER RESEARCH CENTER MARSEILLE
CRCM CANCER RESEARCH CENTER Marseille
Comet Cell communication & Microenvironment dpt.
Translate-IT Translational research & Innovative therapies dpt.
4 - 6 February 2026
MARSEILLE
Palais du Pharo

## Posters Sessions 2 - Cellular crosstalk and molecular mechanisms of cancer progression

### S2CA54 : Hyper O-glycosylation drives cell competition in liver tumors

*Saba Goodarzi*

**Authors:**
Saba Goodarzi (1), Frederic Bard (2)

*1. Centre de Recherche en Cancérologie de Marseille (CRCM) - Université Aix-Marseille )-, Marseille, France*
*2. Centre de Recherche en Cancérologie de Marseille (CRCM) - Université Aix-Marseille )-, Marseille, France*

**Keywords:** cell competition, GALA pathway, glycosylation

**Introduction**
The interface between normal and transformed epithelial cells at the tumor edge remains poorly understood. In solid tissues, cancer cells outcompete normal cells for space, but the mechanisms behind this process remain unknown. Cell competition, observed in multicellular organisms, is thought to eliminate defective cells and may act as an «epithelial defense against cancer». However, cancer cells function as «super-competitors,» allowing them to form tumor nodules. The molecular processes underlying cell competition implicate various known pathways and oncogenes, such as the Hippo and/or Wnt pathways, the Myc, Src and EGF-R oncogenes and others. Cell surface proteins are in their vast majority glycoproteins, carrying various N- and O-glycans. Cancer is associated with massive changes in glycosylation. Cell surface protein glycosylation occurs in the secretory pathway, a complex and compartmentalized system composed of two main organelles: the ER and the Golgi apparatus. GALNTs, that normally localised in the Golgi, are relocated to the ER upon activation of signaling molecules such as the Src and EGF-R kinases. This relocation leads to increased O-glycosylation and higher cellular Tn levels. We nicknamed GALA pathway, this highly regulated activation of O-glycosylation.

**Discussion :**
We discovered that when the GALA pathway is activated, tumor growth accelerates as compared to tumors with lower GALA levels. In contrast, decreasing both GALNT1 and 2 greatly reduces the risk of developing liver cancers. In contrast, activating the GALA pathway across the liver protected it from tumor growth. As a result, GALA greatly boosts growth when activated only in tumor cells but inhibits tumor development when expressed in surrounding, non-transformed cells. These findings suggest that GALA promotes a type of cell competition required for tumor growth: high GALA cells outcompete low GALA cells. To examine the nature of this competition, we attempted to duplicate it in an in vitro environment. We began coculture of high and low GALA cells to see if low GALA cells exhibit an enhanced rate of apoptosis when cocultured with high GALA cells, as opposed to situations when they are cocultured with cells with equivalent levels of GALA. In timelapse microscopy, we observed distinct interactions between high GALA and low GALA cells, which resulted in apoptosis in the latter.

**Conclusion :**
Our findings revealed that when low GALA cells are exposed to high GALA cells, they undergo more apoptosis than when cocultured with cells with
the same level of glycosylation. Additional research is needed to determine the molecular actors in these interactions..

1st Edition
CRCM Symposium
CANCER RESEARCH CENTER MARSEILLE
CRCM CANCER RESEARCH CENTER Marseille
Comet Cell communication & Microenvironment dpt.
Translate-IT Translational research & Innovative therapies dpt.
4 - 6 February 2026
MARSEILLE
Palais du Pharo

## Posters Sessions 2 - Cellular crosstalk and molecular mechanisms of cancer progression

### S2CA55 : In vitro model to study Circulating Tumor Cells metastatic potential

*Claire Acquaviva*

**Authors:**
Léa Girondier (1), Claire Acquaviva (1), Emilie Mamessier (1)

*1. CRCM, INSERM, Marseille, France*

**Keywords:** Metastase-on-chip, tumor heterogeneity

**Introduction**
In most cancers, death is caused by metastases rather than the primary tumour. This is the case with colorectal cancer, where metastases account for over 90% of mortality. This cancer metastasizes to the liver in over 50% of cases, making it an interesting model for the study of metastatic spread and our choice for this project. Metastases occur when certain cells break away from the tumour, enter the bloodstream, where they are known as Circulating Tumour Cells (CTCs), before eventually leaving and nestling in new organs. CTCs form a heterogeneous population, many of which will not survive exposure to the stressful conditions of the bloodstream (flow, frictional forces, lack of contact with other epithelial and matrix cells, ...). Nor are all surviving cells have the capacity to leave the bloodstream (extravasation), migrate into a new tissue, and proliferate. Only some CTCs are therefore at the origin of metastases, but there is currently no marker that can distinguish CTCs according to their metastatic potential. The impact of CTC analysis could be enhanced by ability to distinguish cells with metastatic potential from harmless cells.

**Method :**
I will present an in vitro model I implement to determine the metastatic potential of CTCs and study its characteristics.

**Results :**
This in vitro test is based on 1- the cells' ability to survive in a flow similar to the bloodstream mimicked by a fluidic system, 2- their ability to cross a physical barrier and migrate to a host site mimicked by a porous membrane, 3- to invade and proliferate in a host tissue represented by a matrix where invasion and proliferation are assessed. I will present the early work on establishing and testing of this system.

**Conclusion :**
We have laid the foundations for a simple fluidic system that can mimic the escape of CTCs from circulation to reach a host compartment. The relevance of the system to reflect the metastatic potential of the cells needs to be confirmed by further experiments with other cell lines. The simple system presented here will also be refined to better reflect the physiological situation.