Master	Title	Institute	Host Laboratory	Name of the PI	Supervisor	Description	Duration	e-mail
M1	Identifying regulators of the pro-inflammatory secretome in senescent cells	CRBM	Dynamics of cell invasion in cancer	Pierre Roux	Véronique Gire	Cellular senescence by halting the proliferation of cells harboring mutations or genomic instability is a potent tumor-suppressive barrier. Paradoxically senescent cells favor also tumor outgrowth in later stage by the secretion of bioactive molecules with pro-inflammatory, immunosuppressive properties. Given the relevance of senescence itself and their secretome in influencing cancer development, to understand how they are regulated is key to target them therapeutically. We are in the process of identifying genes influencing senescence and their secretome. We intend to define the molecular mechanisms underlying the action of these genes and how they relate to core p16/RB and p53 tumour suppressor pathways that implement the senescence programs. To this end, we combine cell culture of normal human fibroblasts, Western Blotting, RT-qPCR, and microscopy experiments.	6 months	veronique.gire@crbm.cnrs.fr
M1	Evaluation of the p53 isoform roles in late endosome/exosome trafficking pathway	CRBM	Migration, invasion and microenvironnement	Pierre Roux	Nikola Arsic	p53 isoforms and particularly Δ133p53β play a critical role in cancer progression. Different aspects of this isoform contribution to oncogenic process are described and particularly promotion of cancer cell migratory capacities. Recently we were able to demonstrate that Δ133p53β activity is regulated through aggregation dependent mechanism. In continuation of this study we demonstrated that these aggregates mostly co-localise with late endosomes and autophagosomes cellular vesicles. Further studies are necessary to evaluate export of Δ133p53β isoform through late endosomes/exosome/extracellular vesicles signalling pathway and its consequence in cancer progression.	4 to 5 months	nikola.arsic@crbm.cnrs.fr
M1	Role of translational control in the colorectal cancer cell plasticity in response to 5-FU: impact on tumor recurrence	IGF	Signaling, plasticity and Cancer	Julie Pannequin	Julie pannequin Olivia Villeronce	Fighting therapeutic resilience is a priority in oncology. Following anti-cancer therapies cell response gives rise to cells tolerant to treatment and responsible for recurrence and metastases. Non-genomic processes support cell plasticity contributing to tolerance, among which those related to transcriptomics and epigenetics are widely studied. However, eukaryotic gene expression proceeds through highly regulated sequential steps, the ultimate of which being translation of mRNA into proteins. We have shown that during tolerance phase following treatment of colorectal cancer cells with 5-FU – a drug widely used in chemotherapy - a strong unexpected activation of translation is observed while cells no longer divide. This activation accompanies induction of cell population heterogeneity including cells exhibiting stem cell features. This phase is then followed by a restart of cell division. The objective of this project is to identify the 5-FU-induced translational reprogramming of each cell populations. Single cell surface proteomics will allow to discriminate and purify the different cell populations that will be submitted to translatome analysis. Expression of proteins coded by translationally deregulated mRNAs during the tolerance phase will be further modulated to determine their impact in recurrence.	4 to 6 months	julie.pannequin@igf.cnrs.fr
M1	Role of micro-RNAs and their cellular signaling pathways in the regulation of colon cancer stem cell phenotype	IGF	Signaling, plasticity and Cancer	Julie Pannequin	Chris Planque	Colorectal cancer (CRC) lethality usually results from the post-treatment relapse in the majority of stage II-IV patients, due to the enhanced resistance of cancer stem cells (CSCs). Targeting CSCs, considered as the root of tumor recurrence, is a major milestone toward the design of effective anti-cancer therapies but is still an unmet challenge. In this project, we propose to characterize the micro-RNAs and their cellular signaling pathways involved in the regulation of the chemoresistance and self-renewal capacities of colon CSCs. Micro-RNAs were previously identified following a high-throughput screening of interfering miRNA libraries regulating the Aldefluor-positive population, a functional phenotypic marker of CSCs. During the internship, the student will pursue the study of miRNA target genes regulating CSC phenotype and associated signaling pathways. The techniques used will be mainly the following: qPCR (RNA and miRNA), Western-blot, flow cytometry, cell culture, proliferation and xenograft assays. Given that CSCs are the chief culprits in the failure of current therapies, it is important to identify innovative approaches that target them to improve clinical outcomes for colon cancer patients.	4 to 6 months	chris.planque@igf.cnrs.fr alexandre.david.igf.cnrs.fr
M1	Oncogenic effects of FGF19 in hepatocellular carcinoma	IGMM	Cancer and inflammation Tumor heterogeneity in liver cancer group	Damien Grégoire	Carine Chavey	A promising therapeutic target in hepatocellular carcinoma, the main liver cancer, is FGF19, an hormone with multiple metabolic effects. Using a mouse model of carcinogenesis based on in vivo transfection of hepatocytes, we showed that FGF19 has a strong protumoral effect in combination with other oncogenic events. The objective of this internship is to characterize the oncogenic effects of FGF19 using classical tumor analysis techniques (molecular biology, biochemistry, immunohistochemistry) combined with high-throughput image analysis.	4 months	damien.gregoire@igmm.cnrs.fr
M1/M2	Regulation of the SRC oncogenic signaling by the SLAP tumor suppressive adaptor protein in colon cancer cells	CRBM	Cancer cell signaling	Serge Roche	Audrey Sirvent	Colorectal cancer (CRC) is one of the leading causes of cancer related deaths worldwide. We identified a new important control mechanism of SRC oncogenic activity in CRC that relies on the onco-suppressive function of the SRC-Like adaptor protein (SLAP). Our data support a model where SLAP functions by ubiquitination of key SRC signaling components in CRC cells. By various biochemical approaches and global proteomics we wanted to better characterize this SLAP action mechanism. Methods: cell culture, transfections, western-blot, pull-down, structure function, interactomics, ubiquination assays.	4 to 6 months	serge.roche@crbm.cnrs.fr audrey.sirvent@crbm.cnrs.fr
M1/M2	Control of chromosome segregation and genome stability by the ubiquitin ligase SCFGrr1	CRBM	Mitotic regulation of chromosome partitioning and cell division	Simonetta Piatti	Simonetta Piatti Alain Devault	Chromosome instability is a common feature of cancer cells and is often linked to gain or loss of chromosomes during mitosis, referred to as aneuploidy. Accurate chromosome segregation is critical to prevent aneuploidy, however our understanding of its underlying mechanisms is still fragmentary. Our lab studies how proper chromosome segregation is achieved in eukaryotic cells, using the budding yeast S. cerevisiae as model system. We have recently identified the ubiquitin ligase complex SCFGrr1 as an important regulator of chromosome segregation and are trying to characterize its critical substrates using multiple approaches that involve genetics, cell biology, biochemistry and mass spectrometry.	2 to 6 months	simonetta.piatti@crbm.cnrs.fr

M1/M2	Characterization of RUVBL1/2, a new therapeutic target in colorectal cancer	CRBM	Regulation of gene expression	Dominique Helmlinger	Bérangère Pradet-Balade	RUVBL1/2 are chaperones important for the assembly of complexes that are essential for gene expression (SAGA, TIP60, RNA polymerases), the response to DNA damage (ATR, DNA-PK, ATM) and cell proliferation and survival (TORC1, TORC2). We showed that a recently developed inhibitor of RUVBL1/2 ATPase activity has a promising therapeutic potential in specific subtypes of colorectal cancer (CMS). We are now investigating (i) the determinants of their sensitivity to RUVBL1/2 inhibition, (ii) the molecular mechanisms of RUVBL1/2 activity. This project holds therapeutic potential, as well as fundamental knowledge about essential cellular chaperones. Techniques: cell culture, proteomics, transcriptomics, high resolution fluorescent microscopy to detect single molecule mRNAs and proteins.	3 to 6 months	pradet@crbm.cnrs.fr
M1/M2	Role of flotillins in exosome/extracellular vesicle production and perturbation of cellular functions.	CRBM	Cytoskeleton and membrane trafficking dynamics in cellular adhesion	Cécile Gauthier Rouvière Anne Blangy	Sylia Chehade Cécile Gauthier-Rouvière	Tumor cell invasion and metastasis formation are the main cause of death in patients with cancer. Flotillins are upregulated in many cancers, and this is associated with poor prognosis. The team demonstrated that flotillin upregulation is sufficient to promote tumor cell invasion. Preliminary data show that high flotillin levels favor the secretion of N-cadherin-carrying exosomes, a subtype of extracellular vesicles promoting metastasis. This project aims to identify the molecular mechanisms by which flotillin upregulation favors the secretion of N-cadherin-containing exosomes, where we anticipate a major role of the sphingolipids. A screening strategy and the use of cutting-edge cell biology techniques will be used to identify molecular actors. This project addresses, for the first time, the role of tumor cell exosomes in the deregulation of cadherin-mediated cell-cell adhesion. Data obtained will increase our knowledge of the molecular mechanisms leading to exosome biogenesis upon flotillin upregulation. The results of this project will have a strong impact on the cancer cell biology field and will also open new therapeutic strategies for aggressive flotillin-positive tumors.	4 to 6 months	Sylia.chehade@crbm.cnrs.fr cecile.gauthier@crbm.cnrs,fr
M1/M2	Development of nanoparticules targeting Pregnane X Receptor	IGF	Signaling, plasticity and Cancer	Jean-Marc Pascussi	Lucile Bansard	Pregnane X receptors (PXR, NR1I2) belong to the nuclear hormone receptor superfamily and function as ligand-dependent transcription factors that regulate xenobiotic and drug metabolism. There is an increasing interest in developing blockers that target PXR activation as PXR has been linked to chemoresistance, metabolic diseases and toxicological bioactivation. However, effective PXR antagonists and inhibitors are yet to be developed. Thus, we aimed to develop PXR degraders (proteolysis targeting chimeras PROTACs against PXR) as a complementary strategy to provide a similar effect to PXR inhibition. We design and synthesis first-in-class PXR-agonist-based PROTACs which exhibit PXR degradation activity *in vitro* via the ubiquitin-proteasome system. In collaboration with Dr M AMBLARD (IBMM, Montpellier) team, we are now developing silica-based nanoparticules (nanoPROTACs) to improve their delivery and activity in vivo. We hope that nanoPROTACs targeting PXR proteins will become novel therapeutic agents for PXR-related diseases or to enhance cancer cells sensitivity to chemotherapy.	M1: 2 months M2: 6 months	jean-marc.pascussi@igf.cnrs.fr
M1/M2	Deregulated replication and cancer: Role of RB tumour suppressor inactivation by viral oncoproteins	IGMM	DNA Replication, Genome Instability & Cell Identity	Etienne Schwob	Vjekoslav Dulic	"High-risk" human papillomaviruses (HPV) are responsible for 5% of all human cancers, including cervical carcinomas. The oncoprotein HPV-16-E7, which inactivates pRb tumor suppressor, has recently been identified as the main contributor to carcinogenesis. The goal of this project is to decipher the mechanisms by which the inactivation of the pRb module by viral oncoproteins compromises the genome stability by causing a replication stress and aberrant mitoses. We use an inducible pRb inactivation system in non-transformed human cells to identify key events responsible for chromosome instability at the early and decisive stages of tumor initiation.	6 months	vjekoslav.dulic@igmm.cnrs.fr
M1/M2	Development of PROTACs for a targeted inhibition of SUMOylation in cancer cells	IGMM	The Ubiquitin Family in Hematologic Malignancies	Guillaume Bossis	Olivier Coux	SUMOylation is a post-translational modification that modifies protein function and fate in a variety of ways and is consequently involved in the regulation of most cellular processes. G. Bossis's team (IGMM) has shown that SUMOylation plays a critical role in Acute Myeloid Leukemias (AML) response to therapies (chemotherapies, differentiation therapies and epigenetic therapies). However, the study of SUMOylation is hampered by the lack of tools to modulate SUMO conjugation to target proteins. To fill this gap, we are, together with M. Amblard's team (IBMM), developing a new kind of SUMOylation inhibitors, based on the use of stapled peptides and targeting SUMO enzymes. We have already designed a series of artificial peptides able to inhibit SUMOylation in vitro. The proposed internship will aim at (1) optimizing these peptides and new PROTAC(*) derivatives of these molecules and to (2) develop cell-based assays to test the inhibitory activities of the compounds. (*) PROTACs are bifunctional molecules able to provoke the degradation of their target (see Alabi & Crews (2021) J Biol Chem. 296, 100647)	2 to 6 months To be discussed with applicants	olivier.coux@cnrs.fr guillaume.bossis@igmm.cnrs.fr
M1/M2	Single-cell quantitative phospho-proteomics analysis of cellular heterogeneity to predict response of metastatic melanoma to MAPK inhibitors	IRCM	Signaling of tumor invasion	Peter Coopman	Romain Larive	Treatment resistance arises from heterogeneous drug-tolerant cancer cells. Metastatic melanoma, which is highly resistant to conventional therapies, is particularly sensitive to targeting protein kinases of the MAPK signaling pathway. However, for 25 % of patients, the tumors are initially unresponsive. Moreover, initially sensitive cancer cells adapt through various mechanisms and become resistant. Our hypothesis is that primary and acquired resistance to treatments can be predetermined by biomarkers related to the initial state of intracellular molecular networks. Our objective is to develop models of resistance to treatments to predict, from the initial cellular characteristics, the tumor evolution during the application of a treatment. By combining experimental analyses (on cell lines and tumor organoids) and clinical validation (retrospective studies), we propose to analyze cellular heterogeneity by quantitative phospho-proteomics on single cell to predict the response of metastatic melanoma to MAPK inhibitors. Anticipating therapeutic failures due to cancer resistance to treatments is crucial to advance towards an efficient personalized medicine.	2 to 6 months	romain.larive@umontpellier.fr

M1/M2	Evaluation of bispecific antibody formats for a new modality of immunotherapy in IL-6 dependent cancers	IRCM	Tumor microenvironnement and cancer	Andreï Turtoi	Marie-Alix Poul	Inhibition of IL-6 signaling is a promising therapy in various cancers, including myeloma, alone or in combination with other treatment (for review, Nat Rev Clin Oncol. 2018 Apr; 15(4): 234–248.). IL-6 is involved in myeloma tumor progression by its effects both on tumor cells and stroma cells. We have designed bispecific antibodies (BsAb) to avoid secondary effects of systemic accumulation of IL-6 by the use of classic neutralizing anti-IL-6 monoclonal antibodies (Rossi, J.-F., et al. 2015. Clin. Cancer Res. 21, 1248–57). These BsAb binds to transferrin receptor-1 TfR1, overexpressed in myeloma cells and to IL-6 in a pH-dependent manner allowing the elimination of IL-6 specifically at the tumor site by a so called “sweeping” activity (Poul, M.-A, et al. brevet, PCT/EP2019/081873, WO/2020/104496). The intern will be in charge of the biochemical and the in vitro functional evaluation of anti-TfR1-anti-IL-6 BsAb in myeloma relevant models (BsAb production, functional cell based assays, Western Blot, RT-qPCR, ELISA).	4 to 6 months	marie-alix.poul@inserm.fr
M1/M2	Roles of AXL and ROR1 in the stemness phenotype of triple negative breast cancers	IRCM	Genetic and phenotypic plasticity of cancer	Claude Sardet	Isabelle Jariel-Encontre	Triple negative breast cancers (TNBCs) are aggressive and metastatic cancers representing 15 % of breast cancers. These cancers of poor prognosis do not currently benefit from any targeted therapy. Chemotherapy treatments lead to the destruction of most cancer cells, but are relatively ineffective on a subtype of cell, called cancer stem cells (CSCs), which are responsible for tumor recurrence. Recent data from the laboratory indicated that AXL and ROR1, two tyrosine kinase receptors (RTKs) belonging to two distinct families of RTKs, are co-expressed in cell subpopulations of TNBC cell lines. Interestingly, analysis of stemness properties by monitoring the cell ability to form spheres (CFS) and sphere self-renewal showed that cells co-expressing AXL and ROR1 receptors (AXL+/ROR1+) could be enriched in CSC, in contrast to AXL-/ROR1- cells. Based on these observations, the project will aim to (i) determine whether the co-expression of the two RTKs is essential for the maintenance of the stemness and (ii) characterize the signaling cascades activated by one and/or the other of these receptors and determine whether their activation is necessary for the stemness.	6 months	Isabelle.jariel@inserm.fr
M1/M2	Protein citrullination in cancer	IRCM	Nuclear signaling and cancer	Priyanka Sharma	Priyanka Sharma	Protein citrullination includes the modification of arginine to the non-coded amino acid citrulline, catalyzed by a family of enzymes called peptidyl arginine deiminases (PADIs). PADI2 is widely expressed among family members and regulates several cellular processes associated with tumor progression. PADI2 is intricately involved in the progression of several tumors while the underlying functional mechanism could differ from one malignancy to another. The potential candidate will elucidate the function of PADI2-directed citrullination to modulate transcription plasticity in breast cancer progression.	6 months	Priyanka.sharma@inserm.fr
M1/M2	Analysis of candidate markers of residual cells (DTPs) in ovarian cancer after chemotherapy by multi-color IF	IRCM	Genetic and phenotypic plasticity of cancer	Stanislas Du Manoir	Stanislas Du Manoir	We have characterised drug tolerant persisters (DTPs) in ovarian cancer PDXs after carboplatin treatment (du manoir et al, J Pathol 2022, PMID: 35302657). These PDXs model well the clinical history of the patients. We have identified three proteins that are over-expressed in residual cells (CEACAM6, CRYAB, SOX2) and in tumours made resistant in vivo. We wish to verify in ovarian cancer samples from patients before and after neo-adjuvant chemotherapy (carbo + taxol, 20 couples) whether these three proteins (and other candidates from the literature) are indeed over-expressed in DTPs and constitute markers allowing the isolation of these cells and possibly their targeting. These experiments will be performed by multi-colour IF on paraffin sections.	6 months	Stanislas.dumanoir@inserm.fr
M1/M2	Search for upstream signaling pathways that activate the Syk tyrosine kinase and mediate its tumor suppressor activity in breast cancer	IRCM	Signaling of tumor invasion	Peter Coopman	Peter Coopman	We discovered that the protein kinase Syk acts as a tumor suppressor in breast cancer (Nature, 2000). The internship will aim to identify upstream signaling pathways that activate Syk in mammary cells, which currently remain unknown. For identification we applied proteomic analysis of the differential interactome of a mutant Syk that no longer localizes nor interacts at the sub-membrane level. Identified candidate proteins will be studied in detail by cancer cell biology assays (proliferation, invasion, and cytotoxicity), immunocytochemistry and biochemistry.	2 to 5 months	peter.coopman@inserm.fr
M1/M2	Role of proteins involved in epithelial integrity and polarity, regulated by (de)phosphorylation by Syk or PTPN13, in mammary tumour invasion	IRCM	Signaling of tumor invasion	Peter Coopman	Marion Peters	In the context of breast cancer, we are studying the signalling pathways controlled by the tyrosine kinase Syk and the tyrosine phosphatase PTPN13, which we have shown to be tumour suppressors. The student will characterise new effectors of Syk and PTPN13, involved in the maintenance of epithelial integrity and polarity. The function of these Syk and PTPN13 target proteins, the consequences of their (de)phosphorylation and their contributions to epithelial integrity will be studied by different approaches, including advanced imaging techniques : confocal and two-photon microscopy, FRET/FLIM.	M1: 2 to 6 months M2: 5 to 6 months	marion.peters@inserm.fr