Master	Title	Institute	Host Laboratory	Name of the PI	Supervisor	Description	Duration	e-mail
M1/M2	**Pathological role of cell division defects in kidney cancer**	CRBM	Centrosome, cilia and pathologies	Dr Bénédicte DELAVAL	Dr Bénédicte DELAVAL	Epithelial tubular organisation is a common feature of many tissues including the kidney. This epithelial organisation is disrupted in various pathologies and in particular in kidney cancer. Cell division plays a key role in maintaining the integrity of proliferative tissues. We have recently shown that defects in division orientation are observed during the cystic phases that precede the appearance of certain kidney cancers. We propose here to combine 3-dimensional cell culture microscopy approaches with the zebrafish as an in vivo model to characterise the contribution of perturbations in the geometry of cell division to the early phases of cellular disorganisation observed in kidney cancers.	5 months	benedicte.delaval@crbm.cnrs.fr
M1/M2	**How do overexpressed-flotillins disrupt vesicular trafficking in cancer cells to deregulate AXL? Identification of a potential target to improve the efficacy of anti-AXL antibodies.**	CRBM	Cytoskeleton and membrane trafficking dynamics in cellular adhesion	Dr Anne BLANGY Dr Cécile GAUTHIER-ROUVIERE	Dr Stéphane BODIN	Overexpression of flotillins is detected in a fraction of all solid cancers and participates in metastatic development. It promotes their oligomerisation and the formation of membrane microdomains initiating an endocytosis and vesicular trafficking pathway, named UFIT (Upregulated Flotillin Induced Trafficking pathway). This pathway favors the formation of non-degradative late endosomes with a recycling and signalling functions activating oncogenic signals. Recently we identified the tyrosine kinase receptor AXL as being a cargo of the UFIT pathway. AXL is overexpressed in many tumours and promotes invasion and resistance to therapy. We recently show that the UFIT pathway can participate in AXL stabilization and consequently to its overexpression.	4 months with potential possibility to extend to 5 months	stephane.bodin@crbm.cnrs.fr
M1/M2	**Vesicular trafficking in cell invasion**	CRBM	Cytoskeleton and membrane trafficking dynamics in cellular adhesion	Dr Anne BLANGY Dr Cécile GAUTHIER-ROUVIERE	Dr Daniel BOUVARD	Dysregulation of cell adhesion to the ECM is a major event associated with tumour progression. In this project, we aim at deciphering the emerging role of vesicular trafficking of late endosomes (LE) in normal and tumour cells. LE are intracellular vesicles that were originally identified to clear cellular component, but their role in cell signaling has recently been shed to light. In particular, we showed that a strong connection linked cell adhesion and integrin's signaling to their dynamic. Using cells derived from the osteogenic lineage (normal but also tumor cells also named osteosarcoma) we will address the role of proteins (flotillin, Lamtors) involved in LE dynamics as new regulators of cell migration/invasion. We will use state of the art cell imaging technics (FRAP, high speed videomicroscopy, etc…) to address how trafficking of LE affects cell migration machinery.	6 months	Daniel.bouvard@crbm.cnrs.fr
M1/M2	**How flotillin upregulation generates exosomes in cancer cells**	CRBM	Cytoskeleton and membrane trafficking dynamics	Dr Cécile GAUTHIER ROUVIERE	Dr Sylia CHEHADE	Metastasis formation is under the control of small extracellular vesicles called exosomes, that are lipid-enriched structures containing proteins and nucleic acids which are released by live cells. These exosomes modify the cell environement and support cell invasion and the formation of the pre-metastatic niche. The group works on proteins named flotillins, that are upregulated in many cancers, which is associated to metastasis formation. The group showed that upregulated flotillin derails the cellular membrane trafic to secrete exosomes and the student will participate to the elucidation of the mechanisms.	5 months	Sylia.chehade@crbm.cnrs.fr cecile.gauthier@crbm.cnrs.fr
M1/M2	**Mechanisms regulating the dynamics of osteoclast cyloskeleton as targets against osteoporosis**	CRBM	Cytoskeleton and membrane trafficking dynamics in cellular adhesion	Dr Anne BLANGY	Dr Anne BLANGY	Osteoclasts hyperactivity causes osteoporosis, a major public health problem, and is associated with bone metastases. We study the molecular mechanisms controlling cytoskeleton dynamics to allow osteoclast adhesion on bone and bone resorption. Our proteomic and transcriptomic data identified new candidate proteins controlling bone resorption. Our general scientific approach is to decipher the signaling pathways taken by candidate proteins to influence cytoskeleton dynamics in osteoclasts and bone resorption activity. Techniques used are cell culture, RNA interference, CRISPR, cutting edge fluorescence microscopy approaches.	Up to 6 months	anne.blangy@crbm.cnrs.fr
M2	**Transcription regulation by co-activator complexes in cancer cells**	CRBM	Regulation of gene expression	Dr Dominique HELMLINGER	Dr Dominique HELMLINGER	Many studies have established that aberrant gene expression is a hallmark of tumor initiation and maintenance. As a consequence, the dependency of certain cancers on specific transcriptional regulators, such as c-MYC, has emerged as a novel therapeutic opportunity. However, such dependencies are typically not identified by cancer genome sequencing, but, rather, through focused mechanistic studies. The overall objective of the project is to characterize the contribution of the SAGA and TIP60 co-activator complexes to c-MYC oncogenic activities, in the context of colorectal tumorigenesis. The goal of the Master student will be to characterize new mutant alleles that affect the ability of c-MYC to recruit either SAGA or TIP60. Techniques: Molecular and cellular biology. CRISPR-Cas9-mediated genome editing. Nascent transcription analyses. Native chromatin binding analyses.	Up to 6 months	dhelmlinger@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	Dr Simonetta PIATTI	Dr Simonetta PIATTI	Chromosome instability is a common feature of cancer cells and is characterised by a gain or loss of chromosomes during mitosis, referred to as aneuploidy. Changes in chromosome number can lead to the abnormal expression of oncogenes or tumour suppressors, and be instrumental for tumour onset and development. Furthermore, it can confer a selective advantage that could be exploited by cancer cells to exceedingly proliferate under challenging conditions. Although accurate chromosome segregation is critical for enome stability, our understanding of the mechanisms underlying this process is still fragmentary. Our lab studies how balanced chromosome segregation is achieved, using the budding yeast Saccharomyces cerevisiae as model system. In particular, we are trying to decipher the mechanism of action of the conserved protein kinase Mps1, which is essential for accurate chromosome segregation and also triggers the "Spindle Assembly Checkpoint", the surveillance device that delays mitotic progression until all chromosomes are correctly attached to spindle microtubules. Through a genetic screen, we have recently identified a ubiquitin ligase called SCFGrr1 as an antagonist of Mps1 in both chromosome segregation and the Spindle Assembly Checkpoint. Our preliminary data suggest that SCFGrr1 opposes the function of Mps1 by promoting the degradation of an unknown substrate. Aim of this project is to identify the critical target of SCFGrr1 in the control of chromosome segregation, using multiple approaches that involve genetics, cell biology, biochemistry and mass spectrometry. Altogether, the project will contribute to our understanding of the mechanisms ensuring genome stability in eukaryotes.	6 months	simonetta.piatti@crbm.cnrs.fr
M2	**Targeting collagens receptor DDR1 in metastatic colorectal cancer**	CRBM	Tyrosine kinase signalling in human cancer	Dr Serge ROCHE	Dr Audrey SIRVENT	Several recent reports including ours point to DDR1 as an essential receptor mediating collagens tumor promoting effects associated to development of metastatic colorectal cancer (mCRC). Therefore, targeting DDR1 activity may reduce metastasis development and improve treatment of mCRC. Our collaborator, Bruno Robert (IRCM) recently developed ph-dependent anti-DDR1 antibodies that specifically recognized the receptor in the acidic tumor microenvironment context. The objective of this project is to evaluate the specificity and the functional effects of these antibodies using biochemistry and various in cellulo assays. Methods: cell culture, western-blot, proliferation, invasion & colospheres formation assays.	5 to 6 months	audrey.sirvent@crbm.cnrs.fr serge.roche@crbm.cnrs.fr

M2	**Deorphanization of a tumor micro-environment factor to target colon cancer**	CRBM	Tyrosine kinase signalling in human cancer	Dr Serge ROCHE	Dr Julie NGUYEN	Metastatic colorectal cancer is one of the leading causes of death from cancer. Current therapies show clinical benefit, but they only prolong the survival of these patients by a few months. Thus, there is an urgent need to identify new therapies targeting these invasive tumors. Factors in the tumor microenvironment play an essential role in the aggressiveness of these cancers. We have identified an orphan receptor that plays an essential role in the malignant activities of an important factor in this microenvironment. Our goal is to confirm this factor-dependent tumor activity and to develop therapeutic antibodies against this receptor to reduce metastatic activity from this microenvironment.	5 to 6 months	julie.nguyen@crbm.cnrs.fr serge.roche@crbm.cnrs.fr
M1/M2	**Gene expression regulation by chaperones in colorectal cancer cells**	CRBM	Regulation of gene expression	Dr Dominique HELMLINGER	Dr Bérengère PRADET BALADE	HSP90, R2TP and TTT are essential for the proliferation of both normal and cancer cells. This chaperone machinery controls an essential step in gene expression by assembling newly synthesized proteins into active complexes, such as the SAGA and TIP60 transcription co-activators. We recently discovered that R2TP and TTT are implicated in colorectal tumor maintenance. The goal of this internship is to characterize how R2TP and TTT regulate SAGA and TIP60 biogenesis in cancer cells. For this, we will use a combination of proteomics and single-molecule imaging in colorectal cancer cell lines. We expect this work to eventually lead to the design of specific inhibitors of R2TP and TTT for cancer treatment.	6 months	pradet@crbm.cnrs.fr dhelmlinger@crbm.cnrs.fr
M2	**Characterization of the lipid effectors of the DNA damage response**	CRBM	Cytoplasmic Control of Genome Stability	Dr María MORIEL-CARRETERO	Dr María MORIEL-CARRETERO	The nuclear membrane is a continuum with the Endoplasmic Reticulum, a key organelle ensuring calcium homeostasis, correct protein folding and synthesis of many lipid species. We wanted to ask whether the dual role of the nuclear membrane as the shield of the genome and in the biology of lipids would imply a crosstalk between these two otherwise unconnected cell processes. Our laboratory has uncovered, in the past three years, a strong link by which DNA lesions trigger a lipid metabolism reprogramming that, in turn, finetunes the processes of DNA damage sensing and repair. At this stage, we are investigating many aspects of this relationship: which genome harms trigger which specific lipid changes, what are the consequences for genome integrity of preventing such modifications and which are the main players needed to make all this happen. The currently proposed project aims at unraveling a very specific set of these actors: which are the proteins of the metabolism of lipids that are the direct targets and then the effectors of the apical sensing kinases of the DNA Damage Response ATM and ATR?	6 months	maria.moriel@crbm.cnrs.fr
M2	**A chemical biology strategy to unravel molecular targets of a potential cancer stem cell targeted therapy**	IGF	Signaling, Plasticity and Cancer	Dr Julie PANNEQUIN	Dr Jean-Marc PASCUSSI	Epithelial cancers are heterogeneous due to a hierarchical organization of tumor tissues where several subpopulations of self-renewing cancer stem cells (CSCs) sustain the long-term oligoclonal maintenance of the neoplasm, drive disease progression and fuel therapeutic resistance. Thus, developing CSC-targeting therapies is of major interest to improve cancer care. In order to identify new anti-CSC therapies, we carried out a chemical library screen to identify FDA-approved compound able to target efficiently the CSC population. We identified a 5-nitrofuran drug widely used in human for over 40 years, with a potent anti-CSC effect in breast, colon, pancreatic, and gastric cancer models. Recently it has been confirmed as having an anti-CSC activity in melanoma. However, the molecular mechanism sustaining the CSCs killing effect of this compound remains unknown as well as the opportunity of positioning this drug as adjuvant therapy to prevent colon and breast cancer relapse. The aims of this research proposal are to 1) to decipher its killing molecular mechanism of action in cancer stem cells thanks to the use of metabolites and clickable analogs preserving its functional integrity but amenable to bio-orthogonal chemical ligation, and 2) perform pre-clinical trials to challenge this drug as a valid therapeutic approach to eradicate breast and colon CSC burden and overcome tumor relapse in combination with conventional treatments.	6 months	Jean-marc.pascussi@inserm.fr
M2	**Deciphering early dissemination in colorectal cancer**	IGF	Signaling, Plasticity and Cancer	Dr Julie PANNEQUIN	Dr Julie PANNEQUIN	Though the vast majority of cancer death is due to metastasis, the mechanisms underlying this process remain poorly described. The literature on the topic is mainly focused on the later stages of tumorigenesis, ignoring early dissemination, notably in the context of colorectal cancer. In order to fill this void and to decipher early dissemination mechanisms, we exploit a transgenic mouse model that recapitulates those very early steps of colorectal tumorigenesis and validate our findings on patient samples. Single cell RNA sequencing, mass cytometry based on CyTOF/hyperion technology and cell biology in general will be the main used techniques.This innovative project should greatly improve our knowledge about the crucial initial events of metastatic dissemination.	6 months	Julie.pannequin@igf.cnrs.fr
M2	**RNA methylation and FTO activity steer colorectal cancer cell phenotype**	IGF	Signaling, Plasticity and Cancer	Dr Julie PANNEQUIN	Dr Alexandre DAVID	Cancer stem cell (CSC) represents a minor subpopulation of tumor cells endowed with self-renewal and multi-lineage differentiation capacity, which can escape from chemotherapies, disseminate and seed metastasis. N6-methyladenosine (m6A) is the most prevalent internal modification in mammalian messenger RNA (mRNA). We identified the Fat mass and Obesity-associated protein (FTO), a nuclear m6A demethylase, as the sole m6A effector capable of tempering CSC phenotype in colorectal cancer (CRC) (Nature Communications 2021). Our consortium SMART aims at deciphering the underlying molecular mechanism.	6 months	alexandre.david@igf.cnrs.fr
M1/M2	**Role of micro-RNAs modifications dynamic in the regulation of cancer stem cell properties**	IGF	Signaling, Plasticity and Cancer	Dr Julie PANNEQUIN	Dr Chris PLANQUE	These last three years, chemical modifications of RNA emerged as a novel key variable in gene expression control and fine-tuning of biological functions. In a tumoral context, these modifications favor tumor evolution, dissemination, acquisition of resistance to therapy and disease relapse. For now, the presence and the role of chemical modifications in mature micro-RNAs (miRNAs) have been poorly studied, even though these molecules are involved in the regulation of gene expression essential to the maintenance of cancer stem cell (CSC) phenotype, particularly in colon cancer. This innovative project proposes to identify and quantify by mass spectrometry miRNAs chemical modifications from cell populations with cancer stem properties. Thus, miRNA modifications will be sought from models of primary colorectal cancer cultures established in the laboratory and treated by chemotherapy or from cell populations sorted according to their ALDH activity, a functional and metabolic marker of CSCs. In addition to their potential use as biomarkers, these modifications could open up new therapeutic perspectives through the targeting of the enzymatic actors involved in their regulation. This innovative project stems from an ongoing study of SMART (Spectrométrie de masse des Modifications des ARN Totaux) from Montpellier and is conducted within the framework of the «EPITRAN» COST that promotes the development of epitranscriptomic in Europe. The main techniques used during the internship by the student will be the following : molecular biology (RNA extraction from cells and samples), cell biology (cell culture, functional tests), cytometry, mass spectrometry and bioinformatics.	6 months	chris.planque@igf.cnrs.fr alexandre.david@igf.cnrs.fr

M1/M2	**Developing organoïd cultures from brain tumors**	IGF	Brain plasticity, stem cells and diffuse low-grade gliomas	Dr Jean-Philippe HUGNOT	Dr Jean-Philippe HUGNOT	Gliomas are incurable brain tumors. Our research team, located at the IGF focuses on IDH1 mutant tumors that mainly affect young adults (18-30 years). There is no good model for these tumors which poses a real problem for the development of biomarkers of progression and innovative therapies. The development of cultures in the form of 3D organoids is a recent advance in the field and the internship project aims at implementing this mode of 3D cultures to form glioma "tumoroids". These cellular structures will be studied according to several modalities: tumoral cell diversity, interactions of tumor cells with their microenvironment, canonical signalling pathways (Notch) and cancer stem cell genes.	M1: 2 months M2: 6 months	jean-philippe.hugnot@umontpellier.fr
M2	**Functional analysis of RNA granules: example of *Drosophila* germ granules**	IGH	mRNA regulation and Development	Dr Martine SIMONELIG	Dr Anne RAMAT	Many recent data have highlighted the importance of phase separation in the assembly of membraneless condensates or granules that play a key role in organizing biological reactions within the cell. Some of these membraneless condensates are RNA granules that assemble from RNAs and RNA binding proteins and are involved in mRNA regulation. Specific RNA granules such as processing bodies and stress granules have an important role in cancer progression and chemoresistance. The relationships between the organization of these RNA granules and their functions are poorly understood. The project aims at analyzing germ granules in Drosophila, whose functions are better understood, to decipher the links between organization and functions of RNA granules. The project involves innovative single molecule imaging approaches to record ongoing translation at germ granules in various contexts. **Methods and approaches**: Drosophila molecular genetics; CRISPR knock-in; RNA molecular biology; single molecule imaging: smFISH, SunTag; live imaging. **Key-words**: mRNA regulation; Phase separation; RNA granule; Translational regulation; Single molecule imaging	4 to 6 months	martine.Simonelig@igh.cnrs.fr
M2	**Role of H3K27 marks in the epithelial-to-mesenchymal transition: a splicing story**	IGH	Chromatin and Splicing	Dr Reini LUCO	Dr Reini LUCO Dr Andrew OLDFIELD	Cancer cells take advantage of normal cells transcriptome to gain new phenotypic traits through a process called alternative splicing. However, little is known on how these cancer-specific splicing programs are regulated. We have found that H3K27ac and H3K27me3 histone marks are drivers of the changes in splicing necessary for the Epithelial-to-Mesenchymal Transition (EMT). This chromatin-induced changes in splicing are sufficient to induce an EMT and increase cell migration and invasiveness, which could have a direct impact in tumor metastasis. We want now to better understand the role of these H3K27 marks in alternative splicing regulation and metastasis. One of our hypothesis is that H3K27-marked exons could be in close contact with enhancer sequences that impact the recruitment of splicing regulators to the pre-mRNA via interaction with chromatin-binding adaptor proteins. Using proteomics and CRISPRi/CRISPRa tools, we will study the role of these long-range 3D interactions in splicing regulation and identify the protein factors involved. With this internship, the student will acquire knowledge on cell culture and EMT models, CRISPR technologies and basic molecular biology with the possibility of continuing the internship with a PhD and develop more genome-wide global approaches.	6 months	reini.luco@igh.cnrs.fr
M2	**Unravelling the role of the Rad18 ubiquitin ligase in glioblastoma development and resistance to therapy**	IGH	Genome surveillance and stability	Dr Maiorano DOMENICO	Dr Nour BENBAHOUCHE	Glioblastoma is the most frequent and aggressive primary brain tumour. The mean survival time of patients affected by this disease is of less than 1 year. This is due to a strong resistance to the therapy. The aim of this project is to identify the molecular pathways regulated by Rad18 that sustain glioblastoma proliferation and resistance to therapy. This will achieved through the analysis of the gene expression and proteomic landscape of glioblastoma cancer stem cells underexpressing Rad18 and through the identification of novel Rad18 substrates in glioblastoma.	6 months	domenico.maiorano@igh.cnrs.fr
M1/M2	**Genome manipulation by CRISPR/Cas9 to explore functional interactions between microRNAs and their targets**	IGH	Systemic impact of small regulatory RNAs	Dr hervé SEITZ	Dr Isabelle BUSSEAU Dr Hervé HEITZ	The project aims at using CRISPR/Cas9/HDR technology to introduce in vivo small sequence changes on the seed of a miRNA of interest, as well as, on a compensatory basis, on its complementary sites in one or more of its target RNAs, to question their function in development and disease. This approach is suitable for application to any miRNA in a wide variety of organisms. The project will suit a candidate willing to use a variety of complementary technologies that are part of the team's areas of expertise: bioinformatics, molecular biology, cell cultures and/or Drosophila genetics.	To be discussed with candidate.	Isabelle.busseau@igh.cnrs.fr Herve.seitz@igh.cnrs.fr
M2	**DNA replication & Cancer**	IGMM	DNA Replication, Genome Instability & Cell Identity	Dr Etienne SCHWOB	Dr Philippe COULOMBE Dr Vjekoslav DULIC	Chromosome rearrangements are hallmarks of cancer cells and usually a consequence of replication defects. Our lab studies how replication origins are selected and how oncogenes disturb the spatio-temporal replication programs of cancer cells. We use a variety of techniques going from single molecule analysis of DNA replication to cell biology, biochemistry and long-read genome sequencing. Ongoing projects aim at identifying the mode of action of the Obi1 regulator of origin firing, and how inactivation of Retinoblastoma family proteins leads to chromosome instability, aneuploidy and micronuclei formation.	4 to 6 months	etienne.schwob@igmm.cnrs.fr
M2	**Mitotic DNA synthesis of under-replicated chromosomes**	IGMM	DNA Replication, Genome Instability & Cell Identity	Dr Etienne SCHWOB	Dr Nicolas TALAREK Dr Philippe COULOMBE	The plasticity of chromosome replication programs allows for adaptation to cellular stress, cell-type specific gene expression and genome evolution. Chromosomal regions that replicate late during S phase or in G2 evolve more rapidly through a variety of mechanisms. Our lab designed a genetic system in yeast for inducible late DNA replication and identified a replisome protein whose phosphorylation at mitotic entry is required for the completion of chromosome replication in mitosis (MiDAS), using break-induced replication (BIR). Ongoing efforts aim at characterizing, using proteomics, how replication forks are remodeled upon mitotic entry and what triggers chromosome rearrangements. We found that cancer cells replicate parts of their genome very late, and that the protein identified in yeast is regulated similarly in human cells. Targeting this mechanism may thus affect cancer cells selectively.	4 to 6 months	etienne.schwob@igmm.cnrs.fr
M1/M2	**Deregulated replication and cancer: Roles of HPV16-E7 oncoprotein and RB tumor suppressor inactivation**	IGMM	DNA Replication, Genome Instability & Cell Identi	Dr Etienne SCHWOB	Dr Vjekoslav DULIC	"High-risk" human papillomaviruses (HPV) are responsible for 5% of all human cancers, including cervical carcinomas. The HPV-16-E7 oncoprotein (E7), which inactivates RB tumour suppressor, has been identified as the main contributor to carcinogenesis. The aim of this project is to decipher the mechanisms whereby RB inactivation by viral oncoproteins compromises genome stability in human cells. Using an inducible RB inactivation model and E7-expressing cells we seek to identify key events responsible for deregulated replication leading to genotoxic stress and chromosome instability at the early and decisive stages of tumour initiation.	5 months	vjekoslav.dulic@igmm.cnrs.fr

M2	**The role of posttranslational modifications in colorectal cancer**	IGMM	Inflammation and cancer	Dr Michael HAHNE	Dr Valérie PINET	A prime target in cancer chemotherapy are microtubules (MTs). Tubulin-binding agents, such as Taxol, are successfully employed to treat a range of solid cancers. Until now, however, these drugs are inefficient in colorectal cancer (CRC), which could be related to specific MT properties in colon cells. Crucial in the modulation of MT properties are post-translational modifications (PTMs). In this frame, we focus on PTMs that are restricted to tubulin, such as glycylation and glutamylation. To explore their implication in CRC we are using tissue specific knock out mice, animal models for CRC, immunohistochemistry, organoid cell cultures, biochemistry and RNAseq. Moreover, we collaborate with different clinical centers in Europe for the analysis of patient biopsies. Our recent publications illustrate our experimental strategy (Guo et al. J. Clin Invest, 2021; Maurizy et al. bioRxiv 10.1101/2019.12.19.882712, now in press at Nat Commun).	6 months	michael.hahne@igmm.cnrs.fr
M2	**Deciphering the role of the Protein Tyrosine Kinase receptor PTK7 in colon homeostasis and carcinogenesis**	IGMM	Cancer and Inflammation	Dr Michael HAHNE	Dr Bénédicte LEMMERS Dr Michael HAHNE	The orphan tyrosine kinase receptor PTK7 has been associated with metastatic outcome and reduced survival in non-metastatic colorectal cancer patients. PTK7 has been therefore suggested as a drug target and potential biomarker. Nevertheless, the role of PTK7 in CRC is still poorly understood. In addition, no mouse models to explore the impact of PTK7 deletion in adult tissues homeostasis and carcinogenesis has been developed so far. This project addresses this deficit by evaluating the role of PTK7 on colon homeostasis and carcinogenesis using relevant mouse models and *ex vivo* co-culture systems. We established protocols for PTK7 immunostainings in mouse paraffin embedded tissue displaying PTK7 expression in both colonic epithelial cells (CEC) and fibroblasts, which is increased during colon cancer. This suggests that PTK7 can regulate carcinogenesis via different cellular compartments, which has been so far overlooked. We generated tissue-specific PTK7 KO mice by crossing floxed (fl) PTK7 mice with two Cre-strains to evaluate the contribution of PTK7 in the epithelium and fibroblastic colonic compartment on colon homeostasis, colitis and carcinogenesis. We are characterizing the PTK7 expressing colonic fibroblasts, the impact of PTK7 deletion in both cell compartments on colon homeostasis and carcinogenesis using an established mouse model, and the underlying molecular mechanisms by which PTK7 modulates the cross-talk between colonic epithelial cells and fibroblast. The Master student will familiarize with the different techniques and focus on the immunohistological analysis done in collaboration with the pathologist. B. Riviere (CHU, Montpellier).	6 months	benedicte.lemmers@igmm.cnrs.fr michael.hahne@igmm.cnrs.fr
M2	**Structure-function studies of the cell proliferation antigen Ki-67**	IGMM	Nuclear control of cell proliferation	Dr Daniel FISHER	Dr Liliana KRASINSKA	Ki-67 is a universal cell proliferation marker in cancer and is essential for multiple steps of carcinogenesis, including metastasis. However, its molecular mechanisms of action are not well understood. In this project we will focus on its biochemical properties and their regulation. Our hypothesis is that Ki-67 is an intrinsically disordered protein that can form molecular condensates by liquid-liquid phase separation, thereby organizing heterochromatin, a prominent feature of cancer cell nuclei. We will study this using an optogenetic system in cells to dissect the Ki-67 gene. We will thus identify the parameters governing phase separation, and the effects of manipulating cell cycle kinases.	4-6 months	daniel.fisher@igmm.cnrs.fr
M2	**Targeting SUMOylation to induce an anti-tumor immune response in Acute Myeloid Leukemias**	IGMM	The Ubiquitin Family in Hematologic Malignancies	Dr Guillaume BOSSIS	Dr Denis TREMPÉ	Acute Myeloid Leukemia (AML) are severe hematological malignancies. Their treatment mostly relies on an intensive chemotherapy. Relapses are however very frequent and the prognosis dark, in particular in elderly (around 20% 5-years survival). It is therefore essential to identify new therapeutic targets. Our recent work has shown that SUMOylation, a post-translational modification related to Ubiquitylation, plays a critical role in AML response to chemotherapies and differentiation therapies (Bossis et al, Cell Reports, 2014; Baik et al, Cancer Research, 2018). The objectives of the project will consist in exploring the role of SUMOylation in AML, in particular in the control of gene expression, and determine the therapeutic benefit of its inhibition, in particular in the induction of an anti-AML immune response. This project will rely on the use of cell lines, patient samples (ongoing collaboration with the clinical hematology department of the Montpellier hospital) and murine models : xenografts of chemoluminescent AML cell lines and PDX(Patient-derived xenografts).	6 months	guillaume.bossis@igmm.cnrs.fr
M1/M2	**Transcriptional control of the tumor immune ecosystem**	IRCM	Nuclear signaling and cancer	Dr Vincent CAVAILLES	Dr Marion LAPIERRE Dr Vincent CAVAILLES	The transcriptional coregulator RIP140 is involved in key steps of colorectal carcinogenesis. Our results clearly indicate that RIP140 controls the remodeling of the immune microenvironment of these tumors. Indeed, histological analysis of the colon of RIP/APCKOint mice shows important differences in particular concerning tertiary lymphoid structures when Rip140 is no longer expressed in intestinal epithelial cells. The objectives of this internship are therefore to study the effect of RIP140 on the remodeling of the immune microenvironment of intestinal tumors by deciphering the underlying signaling pathways and by clarifying its role in vivo in the antitumor immune response.	6 months	vincent.cavailles@inserm.fr
M2	**Protein citrullination regulates transcription plasticity in cancer**	IRCM	Nuclear signaling and cancer	Dr Vincent CAVAILLES	Dr Priyanka SHARMA	Arginine citrullination is the post-translational 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 the 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. Our work spotlights the PADI2-mediated citrullination of the arginine1810 Cit1810 of RNA polymerase II (RNAP2) as a key player in the transcription plasticity of breast cancer cells. Now, we are aiming to understand the functional implications of citrullination in the distinct stage of transcription and RNA processing. Towards this goal, the potential candidate will elucidate the function of citrullination in transcription plasticity in breast cancer progression.	6 months	priyanka.sharma@inserm.fr
M1/M2	**Transcriptional Regulation of the inflammatory phenotype in Ulcerative Colitis**	IRCM	Nuclear signaling and cancer	Dr Vincent CAVAILLES	Dr Marion LAPIERRE Dr Vincent CAVAILLES	This project aims to study the impact of the transcription factor RIP140 on the inflammatory process in the intestinal mucosa. The objective is to clarify its biological role in the inflammatory response and to study its impact on signaling pathways deregulated during inflammation. This will be addressed by *in vitro* approaches on cancer cell lines and *in vivo* using transgenic mouse models, and validated on biopsies from patients with chronic inflammatory bowel diseases.	2 à 6 months	marion.lapierre@inserm.fr
M1/M2	**Detection and characterization of the RIP140 mutation in patients with microsatellite instable colorectal cancer**	IRCM	Nuclear signaling and cancer	Dr Audrey CASTET-NICOLAS	Dr Marion LAPIERRE	In colorectal cancer (CRC) with microsatellite instability (MSI), a truncative mutation of RIP140 (RIPMSI) exerts a dominant negative effect and is associated with a significant decrease in the survival of patients. The RIPMSI mutation thus represents a new potential prognosis/predictive marker. The goal is to further characterize this mutant and develop new detection techniques. We will set up its detection on circulating cell-free DNA (cfDNA) from blood samples and by immunohistochemistry on tissue sections using a specific anti-RIPMSI antibody. We will compare the sensibility and specificity of these techniques and validate the correlation with patient survival.	6 months	audrey-castet@chu-montpellier.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	Dr Peter COOPMAN	Dr Marion PETER	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 in particular by advanced imaging approaches : confocal and two-photon microscopy, FRET/FLIM.	M1: 2 to 6 months M2: 5 to 6 months	marion.peter@inserm.fr
M1/M2	**Proteomic and phenotypic study of melanoma sensitivity to protein kinases inhibitors**	IRCM	Signaling of tumor invasion	Dr Peter COOPMAN	Dr Romain LARIVE	Metastatic melanoma is resistant to classical chemotherapies, but highly sensitive to drugs targeting the proteins kinases of the canonical signaling pathway MAPK. Nevertheless, melanoma cells acquire resistance to these new treatments, by various cellular mechanisms and molecular plasticity of cell signaling. Using our quantitative phosphoproteomic data, we modelize the intracellular molecular signaling of melanoma cells that are sensitive or resistant to MAPK inhibitors. During his/her internship, the student trainee will evaluate the value of these mathematical models to predict the sensibility of melanoma cells to new combinations of inhibitors in order to link cell sensitivity to the inhibitors (cellular phenotype) to intracellular signaling dynamic.	2 to 6 months	romain.larive@umontpellier.fr
M1/M2	**Search for new therapeutic targets in KRAS-associated signalling pathways in lung adenocarcinoma**	IRCM	Signaling of tumor invasion	Dr Peter COOPMAN	Dr Gilles FREISS	Within the theranostic biomarkers of lung cancer KRAS gene mutations are characterised by their frequency and the difficultý in developing effective inhibition strategies. We seek to identify novel signalling pathways interconnected with KRAS pathways. We have identified two signalling proteins, the tyrosine kinase Syk and the tyrosine phosphatase PTPN13 that appear to be specifically involved in lung adenocarcinoma tumorigenesis. We aim to identify the signalling networks linking KRAS, SYK and PTPN13 from interactome and (phospho)proteome analyses combined with bioinformatics studies. To this end, cell and mouse models of KRAS mutated lung cancers expressing or not PTPN13 or SYK have been developed or are under development. These models will allow us to evaluate the effects of the expression of these two enzymes on the aggressiveness of KRAS mutated lung tumours and to study the interactions between their signalling pathways and that of KRAS.	6 months	gilles.freiss@inserm.fr
M1/M2	**Metabolic analysis of effector and regulatory γδ T cell populations and impact on anti-tumor immune response**	IRCM	Immunity and Cancer team	Dr Virginie LAFONT	Dr Ghita CHABAB	Cellular metabolism comprises a series of interconnected biochemical pathways that use energy-rich molecules to produce ATP either by oxidative phosphorylation (OXPHOS) or by performing glycolysis. T cell activation is generally linked to a metabolic switch from OXPHOS to glycolysis. While naive T cells rely on OXPHOS to maintain energy demand; activated T cells engage increased glycolysis and glutaminolysis consuming massive amount of glucose and glutamine, to generate their functions. In contrast, the metabolic profile of regulatory T cells relies on OXPHOS and fatty acid oxidation (FAO) to support their survival and differentiation. γδ T cells participate to the immune response against many tumors through their direct cytotoxic activity against cancer cells and their capacity to regulate the biological functions of other immune cells. Nevertheless, their presence in the tumor microenvironment has also been associated with poor prognosis in several cancers suggesting that γδ T cells may also display pro-tumoral activities. Accordingly, we recently described that γδ T cell subsets expressing CD73 display regulatory functions through the production of immunosuppressive molecules, such as IL-10, adenosine and the chemotactic factor IL-8. In parallel, we showed that in human breast and ovarian tumors, γδ T cells were present and that ~20% of tumor-infiltrating γδ T cells expressed CD73 and displayed suppressive functions. The project will aim at providing the characterization and comparison of metabolic programs used by CD73- (effector) and CD73+ (regulatory) γδ T cell subsets with the final goal to identify mechanisms able to boost the anti-tumor immune response. The metabolic program of γδ T cells will be analyzed by an innovative protocols: the SCENITH, a flow cytometry-based method to functionally profile energy metabolism with single cell resolution. From these data, new therapeutic approaches could be proposed to improve the anti-tumoral functions of effectors γδ T cells.	M1: 2-4 months M2: 5-6 months	Virginie.lafont@inserm.fr
M2	**Antitumor immune response and cytotoxicity characterization of small extracellular vesicles released by irradiated tumors in patients treated by targeted radionuclide therapy**	IRCM	Radiobiology for targeted and personalized radiotherapy	Dr Jean-Pierre POUGET	Dr Julie CONSTANZO Dr Emmanuel DESHAYES	Context. To date, 50% of cancers are treated with radiotherapy worldwide. While it has been for long considered that only irradiated cells would die, it is now clear that cell-to-cell communication play a central role in radiation response and lead to death of cells located at distance from the irradiated cells. Short distance communications (called bystander effects) involve the release of soluble factors, such as small extracellular vesicles (sEVs) by irradiated cells or transfer of signals molecules via gap junctions (1). Long distance communications (called abscopal or systemic effects) involve activation of an immune response (2). sEVs have an endocytic origin and are formed by invagination of the multivesicular body membrane before being released by the fusion of the latter with the plasma membrane (3,4). Structurally, sEVs have a phospholipid bilayer containing surface and transmembrane proteins, and they can enclose proteins and nucleic acids mostly RNA species such as small RNAs, as well as DNA from genomic or mitochondrial origin. In addition, one of the major pathways that mediate the immune response to DNA is governed by the enzyme cGAS. cGAS is activated upon binding to double-stranded DNA (dsDNA), which will lead to the activation of the stimulator of interferon genes (STING) pathway, inducing an immune response and tumor clearance in preclinical models (5). Therefore, dsDNA-containing sEVs may prime antitumor immunity. We therefore focused on sEVs as a second messenger released by cancer cells that may activate an antitumor immune response through the STING pathway. One our recent study (6) showed that sEVs were released by tumor cells exposed to targeted radionuclide therapy (TRT). Then, we demonstrated that these sEVs released by cells exposed to TRT were cytotoxic for recipient cells in vitro and were delaying tumor growth in vivo after their intra-tumoral injection (6). In addition, this project supported by SIRIC Montpellier Cancer, will benefit from the ICM Nuclear Medicine Biobank BCBRIV set up by Dr. E. Deshayes, which collects patients' blood samples before, during and after TRT within a prospective registered clinical trial (NCT04104529). Objectives. These 6 months of training will offer the candidate to characterize the therapeutic potential of sEVs released into patients' blood following TRT, mainly in inducing an antitumor immunity. Cytotoxic, genotoxic and immunostimulatory properties of patients' sEVs will be determined in vitro.	6 months	julie.constanzo@inserm.fr emmanuel.constanzo@icm.unicancer.fr
M1/M2	**Role of autophagy in the dialogue between neurons and cancer cells in colorectal cancer**	IRCM	Tumor microenvironnement and resistance to treatment	Dr Andrei TURTOI	Dr Sophie PATTINGRE	The presence of perineural invasions within tumors is a sign of the aggressiveness of the tumor and resistance to treatments. Autophagy, that allows the lysosomal degradation of intracellular material, is frequently activated in cancer, favoring the cancer cell survival during stress. The aim of this project is to study the role of autophagy, in the dialogue between neurons and cancer cells, in the formation of perineural invasions and their pro-tumor functions.	6 months	sophie.pattingre@inserm.fr

M2	**Roles of AXL and ROR1 in the stemness phenotype of triple negative breast cancers**	IRCM	Genetic and phenotypic plasticity of cancer	Dr Claude SARDET	Dr 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 ti the destruction of most cancer cells, but are relatively ineffective on a subtype of cell, called cancer stem cell (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 the contrast to AXL-/ROR1- cells. Based on these observations, the project will aim to (i) determine wheter 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	**Targeting the breast tumor microenvironment with anti-cathepsin D hydrophilic Antibody Drug Conjugates (ADC) with high Drug Antibody Ratio (DAR)**	IRCM	Breast Cancer, microenvironment and Immunotar	Dr Emmanuelle LIAUDET COOPMAN	Dr Valérie LAURENT-MATHA	Few targeted therapies are available for recurrent and treatment-resistant breast cancer. The aspartyl protease, cathepsin D (Cath-D), a poor prognostic marker is overexpressed and hypersecreted by different subtypes of breast cancer, both hormono-dependent (HR+) expressing and not expressing HER2 (HER2+/-), and triple-negative (TNBC, HR-/HER2-). Works of the team have shown that Cath-D secreted in the tumour microenvironment displays oncogenic actions. With the support of Labex MAbImprove, the immunotargeting of secreted Cath-D with human anti-Cath-D (F1) antibodies (Ab) led to a significant decrease of tumour growth in vivo in nude mice xenografted with the TNBC line, MDA-MB-231, and with PDXs (Ashraf*, Mansouri* et al., JITC, 2019). Hypersecreted Cath-D is thus a new target opening new therapeutic perspectives. In view of the growing interest of ADCs (Antibody Drug Conjugate) in the treatment of recurrent cancer, we are developping an anti-Cath-D ADC with a high DAR 8 (Drug to Antibody Ratio), hydrophilic, coupled via a cleavable arm to a topoisomerase I inhibitor, Deruxtecan, using the same technology as those used for the development of the ADC "Enhertu" approved as third line treatment in recurrent HER2+ breast cancer. As Cath-D is internalised by different tumour cells (epithelial cells and fibroblasts), as well as the Cath-D/ADC-anti-Cath-D complex, a strong tumour regression should be induced. This approach is original because the target is both secreted and associated with cell membranes from tumor and stromal cells, contrary to available ADCs which are only directed against membrane receptors. This anti-Cath ADC should strongly amplify the therapeutic impact of the observed naked Ab. The objectives of this master's degree course are to study the cytotoxic activity of this anti-Cath-D ADC in vitro in comparaison with a control ADC in the MDA-MB231 and Sum159 TNBC cell lines, and the hormone-resistant (HR+) MCF-7-LCC2 line. We will test the effect of anti-cath-D ADC on cell survival in two-dimensional (2D) and three-dimensional (3D) culture in spheroid models. Internalization experiments of the ADC/CathD complex will be performed on cancer cells and stromal cells. The immuno-targeting of the massively secreted Cath-D in the breast tumour microenvironment with a human ADC-anti-Cath-D biomedicine should open up new treatment perspectives for patients resistant to currently available treatments with fewer side effects than conventional chemotherapy.	4 to 6 months	valerie.laurent2@umontpellier.fr
M2	**Identification of a novel strategy to improving T--cells homing to brain tumors**	IRCM	Molecular oncogenesis	Dr Laurent LE CAM	Dr Alexandre GARANCHER	Medulloblastoma is the most common malignant brain tumor in children. We are interested in the modulation of the immune microenvironment of this disease in order to identify new therapeutic strategies that are more effective and less toxic. Single cell RNA sequencing studies performed on human tumors, as well as flow cytometric analyzes in our murine models of Medulloblastoma indicate a very low proportion of cytotoxic T lymphocytes within the tumor. We hypothesize that increasing the localization of T lymphocytes to these brain tumors could significantly improve the efficacy of immunotherapies. The objective of this project is to identify and validate new surface molecules of T cells from candidate molecules, which would promote their infiltration within the tumor. To this purpose, the student will have to isolate primary lymphocytes from mouse lymph nodes and infect them with retroviruses encoding for these candidate genes in order to force their expression. Once the expression of these candidates has been verified, functional tests will be performed in vitro to validate their potential before validation in vivo. In parallel, infiltrating lymphocytes from murine medulloblastomas will be isolated and characterized in terms of expression of surface molecules and state of activation by whole genome approaches (RNA seq). Trainee activities: • Carry out all the experimental protocols planned for the project: o Cell culture: - Maintenance of HEK293T cells and production of murine retroviruses - Purification, culture and transduction of primary murine lymphocytes and tumors o Functional in vitro tests (migration, proliferation, activation and cell death test) o Molecular biology (RT-qPCR, flow cytometry, immunofluorescence).	6 months	Alexandra.garancher@inserm.fr
M2	**Metabolic reprogramming during cellular senescence**	IRCM	Molecular oncogenesis	Dr Laurent LE CAM	Dr Pierre-François ROUX Dr Laurent LE CAM	Cellular senescence is a potent anti-tumor barrier which is also implicated in organismal aging. Senescent cells undergo a profound metabolic reprogramming but the molecular consequences of these metabolic changes remain poorly understood. Our project aims at further understanding how changes in pyruvate as well as in amino-acid metabolism influence the epigenome and the epitranscriptome to control gene expression during senescence.	6 months	Laurent.lecam@inserm.fr
M2	**Generation of non-genetically modified CAR-like NK cells**	IRMB	Natural killer cell based immunotherapies: monoclonal antibodies and metabolism	Dr Martin VILLALBA	To be defined	CAR-NK cells are a less toxic alternative to CAR-T cells, but these therapies share the problem of being GMOs. NK cells mediate antibody-dependent cell cytotoxicity (ADCC) and can be used in an allogeneic setting. We have patented an NK expansion technique (eNK). These eNKs can be "armed" with modified monoclonal antibodies (mAbs) using our new technology (NoCar). The armed eNKs (NC-eNKs) acquire their selectivity via the mAbs to lyse the target cells. These NC-eNKs are not GMO and can easily be armed by one or more mAbs chosen according to the tumor. This offers the possibility to target several antigens (Ags), at different times of the disease progression, and should decrease the tumor resistance phenomena related to the loss of the targeted Ag as described after anti-CD19 CAR-Ts, and could allow a better selectivity. Our objectives are: 1) To develop an eNK cell "armed" with several mAbs conferring selectivity towards several Ags expressed by a tumor. 2) To develop a preclinical protocol to eliminate target cells by NC-eNK. We will test these hypotheses using target cells expressing different levels of Ags, e.g. CD20,CD38. We will produce the modified NoCar mAbs: rituximab, daratumumab. Our goal is to demonstrate that we can make the cytotoxicity of NK cells more selective and efficient without genetic modification and thus develop an immunotherapy product coupling antibodies and NK cells that can be used at the patient's bed.	6 months	martin.villalba@inserm.fr

M2	**A knowledge base in immunogenetics for the discovery of new scientific knowledge, Immuno-Gnosis**	IGMT	IMGT®, the international ImMunoGeneTics information system®	Pr Sofia KOSSIDA	Dr Gaoussou SANOU Dr Patrice DUROUX Dr Konstantin TODOROV Pr Sofia KOSSIDA	Ontologies are today major technological components in the context of Open and Big Data. They allow the federation, integration and structuring of data into knowledge graphs (KG). KG improve data access and information retrieval. The field of life sciences abounds in complex and sometimes subjective terms, making their computer formalization difficult. Indeed, it is difficult to respond to complex queries without the presence of a centralized, structured and semantic database that will facilitate access to data for experts. IMGT® is today the international reference in the field of immunogenetics and contains seven relational databases, seventeen analysis tools and a large number of web pages. Its strength lies in particular in the construction over time of an ontology. The foundations of IMGT-ONTOLOGY were published in 1999 and a first implementation in OWL language was made available in 2010. In the field of immunogenetics, antibody engineering for therapeutic purposes is a booming branch that requires the structuring of knowledge in the form of knowledge graphs. For this, a database of monoclonal antibodies (artificial or natural) IMGT/mAb-DB exists within IMGT. The amino acid sequences of their protein chains are also integrated into the IMGT/3Dstructure-DB database. It is the result of time-consuming and manual work that requires searching through various unstructured and heterogeneous resources. The main objective of the project is to offer tools to help the expert to extract information and knowledge from structured (KG) and unstructured data (other data within IMGT) and thus provide support to generate and validate scientific hypotheses in the field of antibodies for therapeutic purposes.	6 months	sofia.kossida@igh.cnrs.fr
M1/M2	**The mitochondrial network, a reflection of cellular "health status": Applications in Oncology**	ISEM	Isem, équipe EVAS	Dr Mylène WEILL	Dr Sophie CHARASSE Dr Abdel AOUACHERIA	The abundance, morphology and dynamics of mitochondria allow a reading critical of the internal cellular state. The maintenance of structurally integrated and metabolically active is a condition sine qua non to the proper functioning of cells and survival and "good health" of organisms (Aouacheria et al., 2017). In response to various intracellular and extracellular, mitochondria adapt their number, shape, position, shape, connectivity and their movement. Cells containing tubular mitochondria or elongated, networked and energy-producing are generally viable and perform their functions. Conversely, stressed cells often have mitochondria fragmented, isolated, with low membrane potential and mitochondrial functions compromises. This «MITOMATIQUE» project proposes to analyze and quantify mitochondrial networks, by confocal microscopy screening in: •Various cancer versus normal cell types •Different tumour stages (tumour progression, cell invasion) •Test the efficacy of new therapeutic molecules (single or combined).	5 mois	sophie.charrasse@umontpellier.fr