Master	Title	Institute	Host Laboratory	Name of the PI	Supervisor	Description	Duration	e-mail
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

M2	Targeting collagen receptor DDR1 activity to reduce tumor progression and immune exclusion in metastatic colorectal cancer	CRBM	Cancer cell signaling	Serge Roche	Audrey Sirvent	Several recent reports including ours point to the tyrosine kinase receptor DDR1 as an essential receptor mediating collagens tumor promoting effects associated with metastatic colorectal cancer (mCRC) progression and therapeutic resistance. The objective of this project is to evaluate the contribution of DDR1 kinase activity in tumor progression/immune evasion and to explore the interest of targeting DDR1 activity with kinase inhibitors in mCRC using various in cellulo, biochemical and in vivo experiments. Methods: 2D and 3D cell culture, western-blot, Q-PCR, plasmid and siRNA transduction, co-cultures, mouse sub-cutaneous xenografts, FACS, IHC…	4 to 6 months	serge.roche@crbm.cnrs.fr audrey.sirvent@crbm.cnrs.fr
M2	Regulation of Src tumor activity in intestinal cancer by its unstructured region	CRBM	Cancer cell signaling	Serge Roche	Serge Roche	While unstructured regions are thought to be intrinsically disordered, our NMR study reveals a fuzzy intramolecular complex made by the unstructured region of the Src oncogene (Structure 2017). We then showed that this fuzzy complex has an important function in cancer with potential therapeutic opportunity (Oncogene 2022). We now with decipher this mechanism by functional screening a synthetic library of Src mutants focused on this region to develop specific inhibitors.	6 months	serge.roche@crbm.cnrs.fr
M2	Exosomal regulation of Src metastatic activity in colon cancer	CRBM	Cancer cell signaling	Serge Roche	Serge Roche	Cancer exosomes are produced by the primary tumor for long-range communication, enabling metastatic development. We could show that the Src oncogene is a key inducer of exosome biogenesis (Imjeti et al PNAS 2017), to mediate metastatic activity in colon cancer. We now wish to decipher the underlying mechanism by showing that Src induces cancer exosomes full of active receptor tyrosine kinases to initiate metastasis development.	6 months	serge.roche@crbm.cnrs.fr
M2	Targeting a novel receptor pathway induced by the tumor microenvironment to overcome therapeutic resistance in colon cancer	CRBM	Cancer cell signaling	Serge Roche	Julie Nguyen	Colon cancer cell communication with its microenvironment plays a key role in metastatic dissemination and therapeutic resistance. The aim of this project is to address whether our new developed therapeutic antibody, which inhibits cancer stem cell traits induced by the tumor microenvironment, can overcome resistance to chemotherapy. For this, we will combine cell biological methods with several intestinal cancer models, including nude mice xenografts and genetically modified mouse models, patients derived organoids and others.	6 months	serge.roche@crbm.cnrs.fr julie.nguyen@crbm,cnrs,fr
M2	Mechanisms regulating the dynamics of osteoclast cyloskeleton as targets against osteoporosis	CRBM	cytoskeleton and membrane trafficking dynamics in cellular adhesion	Anne Blangy	Anne Blangy	Osteoclasts hyperactivity causes osteoporosis, a major public health problem, and is also associated with bone metastases, causing severe pain and fractures. 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 cutting edge fluorescence microscopy, laser capture microdissection, transcriptomics, proteomics, RNA interference, CRISPR/Cas9…	Up to 6 months	anne.blangy@crbm.cnrs.fr
M2	Targeting the Epitranscriptome in Cancer	IGF	Signaling, plasticity and Cancer	Alexandre David	Françoise Macari	This project intends to decipher the molecular mechanism by which the N6, 2'-O-dimethyladenosine (m6Am) RNA mark regulates Cancer Stem Cell (CSC) abilities and steers colorectal cancer cell fate. Building on this outcome, this project seeks to determine whether m6Am dynamic could be exploited for diagnostic/prognosis purpose and for preventing colorectal cancer dissemination and recurrence through adjuvant-based therapy. This project involves five teams covering specific areas of expertise such as RNA epigenetic (A. David, IGF), bioinformatics (E. Rivals, LIRMM), mass spectrometry (C. Hirtz), clinics (E. Crapez, ICM) and chemistry (M. Etheve-Quelquejeu, LCBPT).	4 to 6 months	francoise.macari@igf.cnrs.fr alexandre.david@igf.cnrs.fr
M2	Crosstalk between nucleic acid immunity and fatty acid metabolism in hepatocellular carcinoma	IGH	Molecular Basis of Inflammation Team, IGH & Tumor microenvironnement and resistance to treatment, IRCM	Nadine Laguette Andreï Turtoi	Nadine Laguette Andreï Turtoi	Immune responses and metabolic rewiring are deeply interconnected and cooperate to dictate tumour fate. We have recently established that nucleic acid immunity regulate polyunsaturated fatty acid metabolism. We wish to uncover how this crosstalk is regulated in cancer cells and how it impacts on the tumour microenvironment to promote tumorigenesis. To this aim, hepatocellular carcinoma (HCC), the 4th leading cause of mortality from cancer worldwide will be our primary model of cancer. The Master 2 project will focus on the identification of nucleic acid detection pathways in HCC and their regulation of PUFA metabolism, using proteomics, transcriptomics and metabolomics approaches. The student will be primarily hosted in the IGH for molecular biology and biochemistry approaches while metabolic analysis will be performed in the premises of the IRCM.	6 months	Nadine.laguette@igh.cnrs.fr Andrei.turtoi@inserm.fr
M2	Alternative mechanisms of telomere protection	IGH	Biology of repetitive sequences	Jerome Dejardin	Mathieu Tardat Joey Dufourd	Telomeres are crucial structures which protect chromosome ends from unwanted DNA damage response. Loss of telomere protection results in genome instability, and has the potential to transform cells. In addition, all cancer cells must re-activate a telomere maintenance mechanism to ensure cell proliferation. We identified a novel mechanism and novel players involved in telomere protection. The work proposed will consist in characterizing this mechanism by performing state of the art molecular biology, microsocopy and biochemistry.	6 months	Jerome.dejardin@igh.cnrs.fr
M2	Understanding Enhancer activation during a metastasis-like cellular transition	IGH	Chromatin and splicing	Andrew Oldfield	Andrew Oldfield	Promoter-distal regulatory elements (such as enhancers) regulate the spatio-temporal control of gene expression and are thus critical determinants of development and disease. Here, using the epithelial-to-mesenchymal transition of human mammary cells as a model, we aim to identify the actors and understand the mechanisms that lead to enhancer activation during cell-identity changes. Genome-wide techniques such as ChIP-seq, ATAC-seq and RNA-seq will be complemented by CRISPRi/CRISPRa and knock-down/overexpression experiments to tease apart the roles of the lab's candidate proteins. Funding for a PhD position (starting 10/23) is available.	6 months	andrew.oldfield@igh.cnrs.fr
M2	Understanding the molecular basis of glioblastoma cancer stem cells resistance to DNA damaging agents	IGH	Genome surveillance and stability	Domenico Maiorano	Nour Benbahouche	Glioblastoma (GBM) is an aggressive brain cancer for which current therapeutic treatments have failed. It is admitted that GBM resistance to therapy is due to the presence of cancer stem cells (CSCs) which characterize the heterogeneity of this tumor. The objective of this internship is to study the implication of a gene identified in the host team in GBM CSCs proliferation and resistance to DNA damaging agents using GBM cell lines and organoïds models.	6 months	domenico.maiorano@igh.cnrs.fr
M2	DNA replication & Cancer	IGMM	DNA Replication, Genome Instability & Cell Identity	Etienne Schwob	Vincent Coulon	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 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	Etienne Schwob	Nicolas Talarek 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
M2	Molecular mechanisms of the crosstalk between colonic epithelial cells and fibroblasts induced by PTK7	IGMM	Inflammation and cancer	Michael Hahne	Michael Hahne Bénédicte Lemmers	Protein Tyrosine Kinase 7 (PTK7) receptor expression is associated with bad prognosis in colorectal cancer (CRC) and has been accordingly suggested as a drug target. Our immunohistological analysis of mouse colons displayed PTK7 expression in both colonic epithelial cells (CEC) and fibroblasts, which is increased during chemically induced colitis associated colon carcinogenesis (CAC). PTK7 appears therefore to regulate potentially colon pathology via different cellular compartments. To explore this finding, we have generated cell type specific knock-out mice, deleting PTK7 in either CEC or colonic fibroblasts. We have subjected those mouse strains to CAC and acute colitis to explore the cell type specific function of PTK7 in pathological conditions. We found only moderate alterations in mice caused by PTK7-deficiency in CEC, but more important ones in mice with PTK7-deficient colonic fibroblasts. We are now focusing on understanding the role of PTK7 in the fibroblast compartment using immunohistochemical, RNAISA).voke the degradation of	6 months	michael.hahne@igmm.cnrs.fr
M2	Tumor microenvironment shaping by p53 mutants in liver cancer	IGMM	Cancer and inflammation Tumor heterogeneity in liver cancer group	Damien Grégoire	Damien Grégoire	Hepatocellular carcinoma (HCC) is characterized by considerable genetic and phenotypic inter-patient heterogeneity, including at the level of the immune tumor microenvironment. Understanding how the mutational profile of the tumor shapes the immune microenvironment is key for optimization of therapeutic approaches targeting the immune response.Using a mouse model of carcinogenesis based on in vivo transfection of hepatocytes, we generated a biobank of liver tumors driven by eight distinct p53 mutants. We observed differences in tumoral microenvironment. The objective of this internship is to characterize the impact of specific p53 mutants on tumoral microenvironment using state of the art analysis techniques (Imagine mass spectrometry, high-throughput image analysis).	5 to 6 months	damien.gregoire@igmm.cnrs.fr
M2	Search for new therapeutic targets in KRAS-associated signaling pathways in lung adenocarcinoma.	IRCM	Signaling of tumor invasion	Gilles Freiss Peter Coopman	Gilles Freiss	In non-small-cell lung cancers (NSCLC), mutations of the KRAS gene are characterized by their frequency and the difficulty in developing effective inhibition strategies. We seek to identify new signaling pathways interconnected with KRAS pathways. We have identified the tyrosine kinase Syk and the tyrosine phosphatase PTPN13 which seem to be specifically involved in NSCLC tumorigenesis. We modulated the expression (stable transfection or KO by CRISPR/Cas9) of SYK and PTPN13 in cellular models of NSCLC carrying a KRAS mutation (A549, H2009, H358). The objectives are now: i. to confirm in our genetically modified models the importance of PTPN13 and SYK in modulating the aggressiveness of mutated KRAS tumours: effect of PTPN13 and Syk on the growth, mobility and invasive capacity of the cellular models developed. ii. to identify the signaling networks linking KRAS, Syk and PTPN13 from (phospho)proteome analyzes on the same cellular models associated with a bioinformatics approach.	5 to 6 months	gilles.freiss@inserm.fr
M2	Targeting the CXCL5/neutrophil axis in lung cancer to improve immunotherapy treatment.	IRCM	Immunity and Cancer	Nathalie Bonnefoy	Dr Julien Faget Dr Laurent Gros Chiara Ursino (PhD Student)	The selected candidate will be responsible to carryout experimentations on the function of the CXCL5 chemokine that is expressed by lung cancer cells. We have accumulated evidences suggesting that CXCL5 could be responsible of neutrophil accumulation in lung tumors and our previous publications showed that tumor-infiltrated neutrophils can be responsible for disease progression and refractoriness to immunotherapy. Thus, we have developed mouse models in which the cancer cells are deficient for CXCL5 and we are generating antibodies against the human CXCL5. The research project will consist in the characterization of the tumor microenvironment in our mouse models as well as of an evaluation of the biological activity of our new antibodies (patent release?). We will offer the best possible conditions for successful application to the doctoral school in Jun.	6 months	Julien.faget@inserm.fr
M2	Role of tumor environment reprogramming in liposarcomagenesis	IRCM	Metabolism and sarcomas	Laetitia Linares	Laetitia Linares	Liposarcomas (LPS) are tumors of mesenchymal origin. The most common subtypes, well-differentiated (WD-LPS) and dedifferentiated (DD-LPS), are characterized by the amplification of the q13-15 region on chromosome 12 containing the Mdm2 gene. This quasi-systematic amplification of Mdm2 gene is such that it is used clinically to distinguish WD/DD-LPS from other sarcoma types. These observations raise essential questions regarding the strong selection pressure that leads to MDM2 amplification during the development of LPSs. MDM2 is an oncoprotein whose roles in the degradation of the tumor suppressor p53 are widely described. However, data from our laboratory have proven that MDM2, through atypical functions, also plays an important role in metabolism to influence LPS development. Indeed, we have recently shown that MDM2 is recycled to chromatin during oxidative stress, independently of p53 (Riscal et al., Mol. Cell. 2016). A pan-genomic analysis showed that MDM2 in chromatin targets a transcriptional program involved in amino acid transfer and in particular that of serine. Our results also show that modulation of MDM2-dependent serine metabolism influences liposarcoma development (Cissé et al., Sci. Trans. Med. 2020). In addition, we were able to observe that LPS influence their environment to facilitate tumor growth. The goal of the stage is to understand tumor environment reprogramming to the advantage of the tumor. Cell biology (conditioned media, co-cultures (tumor cells and cells from surrounding tissues), etc…) will be set up in order to identify signals emitted by the LPSs that will impact by their microenvironment. These signals will be analyzed by classical techniques of biochemistry and molecular biology but also by “omics” approaches.	6 months	Laetitia.linares@inserm.fr

M2	Evaluation of new therapeutic drug combinations for EGFR-driven lung cancer patients relapsing after Osimertinib therapy	IRCM	Oncogenic pathways in lung cancer	Antonio Maraver	Maicol Mancini	In EGFR-driven lung cancer targeted therapy provides a clear advantage compared to standard chemotherapy; but unfortunately the occurrence of resistance is the main limitation. Today, in Osimertinib (a currently use EGFR inhibitor) –treated patients MET amplification is the main relapsing mechanism. Our lab, aim to prove that single drug treatment have limited value but a strategy based on a combinational drug therapy, could be more effective. The student will be involved in validating a panel of previously identified molecules to abolish and/or prevent the occurrence of MET-induced Osimertinib resistance in-vitro. He/She will acquire a good knowledge of basic molecular biology techniques. Previous tissue culture experience is required.	6 months	maicol.mancini@inserm.fr
M2	Generation of non-genetically modified CAR-like NK cells	IRMB	Lymphocyte differentiation, tolerance and metabolism: basis for biotherapies and engraftment	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 are the mediators of antibody-dependent cell cytotoxicity (ADCC) and can be used in an allogeneic context. We have patented an NK expansion technique (eNK). These eNKs can be "armed" with monoclonal antibodies (mAbs) modified using our new technology (NKAb). The eNKs NKAb-armed (NKAb-eNK) acquire their selectivity via the mAbs to lyse the target cells. These eNKs are not GMOs and can easily be armed with one or more mAbs chosen according to the tumor. This offers the possibility of targeting several antigens (Ags), at different times in the evolution of the disease, and should reduce the phenomena of tumor resistance linked to the loss of the targeted Ag as described after the anti- CD19 CAR-Ts. In addition, they could have better selectivity. Our objectives are: 1) To develop an "armed" eNK cell with several mAbs giving it selectivity towards several Ags expressed by a tumor. 2) Develop a preclinical protocol to eliminate target cells by NKAb-eNKs. We will test these hypotheses using target cells expressing different levels of Ags, e.g. CD20, CD38. We will produce NKAb modified AcMs: rituximab, daratumumab. Our objective is to demonstrate that we can make the cytotoxicity of NK cells more selective and effective without genetic modification and thus develop an immunotherapy product coupling antibodies and NK cells that can be used at the patient's bedside.	6 months	martin.villalba@inserm.fr