Research project title	**Role of cholangiocarcinoma-derived extracellular vesicles containing EGFR in the tumor stroma crosstalk: new opportunities for therapy and diagnosis**
Call of interest description	The Marie S. Curie Postdoctoral Fellowship (MSCA-PF) programme is a highly renowned EU-funded scheme. It offers talented scientists the unique chance to set up 2-year research projects on their own with the support of a supervising team. Besides providing an attractive grant, it represents a major opportunity to boost the career of promising researchers. The **Centre de recherche Saint-Antoine (CRSA)**, UMR-S 938 **Inserm**-Sorbonne Université (joint research unit)**,** is thus looking for **excellent postdoctoral researchers** with an international profile to write a persuasive proposal to apply for a **Marie S. Curie Postdoctoral Fellowship grant in 2021 (deadline of the EU call set on** October 12th**, 2021)**. The topic and research team presented below have been identified in this regard.
Main Research Field	Life Sciences (LIF)
Sub Research Field	Cancer, cell biology, experimental models
Key words	Liver cancer, tumor microenvironment, cell signaling
Research project description	**Background:** cholangiocarcinoma (CCA) is a malignant tumor with asymptomatic behavior leading to a late diagnosis when tumor has usually reached to an advanced stage. CCA is highly refractory to therapies, probably due to its molecular heterogeneity and prominent stroma that contribute to the growth and survival of cancer cells. Epidermal growth factor receptor (EGFR) is a growth factor that favors CCA growth and progression, and plays a key role in the interplay between cancer and stroma cells. In the last years, the relevance of extracellular vesicles (EVs) in cell-cell communication and cancer pathophysiology was highlighted. Interestingly, CCA cell-derived EVs exhibit an upregulation of several oncogenic proteins including EGFR and show pro-tumorigenic properties on cholangiocytes and stroma cells. **Hypothesis:** CCA cells are able to deliver EGFR through EVs to the surrounding microenvironment cells, thereby participating in stroma activation and tumor growth. Therefore, targeting CCA cell-derived EVs production may provide a new therapeutic approach for this deadly cancer. **Objectives:** 1. Isolate and characterize EVs derived from CCA cells and from the plasma of i/ mice carrying CCA xenografts and ii/ CCA patients;

	2. Investigate the role of EGFR in EVs derived from CCA in the crosstalk between tumor and stroma cells both *in vitro* and *in vivo* in CCA xenograft mouse model using human CCA cells expressing ectopic EGFR tagged with mCherry or invalidated for EGFR by the CRISP/Cas9 technology. 3. Analyze the expression and activation status of EGFR in EVs from blood plasma of mice carrying CCA xenografts and CCA patients; correlate this status with patient's survival and CCA tumor stage. The fellow will work on all aspects of the projects from preclinical models to human. Since Laura Fouassier is a member committee of an e-COST action on CCA (Euro-Cholangio-Net website https://eurocholangionet.eu), the fellow will benefit of the network, grant to support participation to international meetings and training school. 1. Arbelaiz A, et al. Serum extracellular vesicles contain protein biomarkers for primary sclerosing cholangitis and cholangiocarcinoma. Hepatology. 2017 Oct;66(4):1125-1143. 2. Zanetti-Domingues LC, et al. Cooperation and Interplay between EGFR Signalling and Extracellular Vesicle Biogenesis in Cancer. Cells. 2020 8;9(12):2639. 3. Claperon, A., et al., EGF/EGFR axis contributes to the progression of cholangiocarcinoma through the induction of an epithelial-mesenchymal transition. J Hepatol, 2014. 61(2): p. 325-32. 4. Claperon, A., et al., Hepatic myofibroblasts promote the progression of human cholangiocarcinoma through activation of epidermal growth factor receptor. Hepatology, 2013. 58(6): p. 2001-11.
Supervisor(s)	Laura Fouassier (PhD) is a full-time permanent researcher at Inserm since 2005. She has expertise and track record in liver cancer biology with a specific focus on EGFR and ZEB1, cell plasticity, tumor microenvironment and cancer treatment and resistance. **Area of expertise:** Liver carcinogenesis, cholangiocarcinoma (CCA), tumor microenvironment, cell plasticity, physical-based therapies, drug resistance **Academic education:** PhD thesis in pathophysiology, Sorbonne Université (1998); post- doctoral training at Denver, USA (1999-2001); Habilitation to supervise research (HDR), Univ. Paris-Descartes (2008). **Mentoring activities:** Supervision of 3 post-doctoral fellows, 3 PhD theses, 19 Master students. **Editorial activities & evaluation of research:** Invitation to join the editorial board of Livers. She is regularly solicited to review manuscripts (Hepatology, J. Hepatol., Liver Int., Oncogene) and to evaluate grant applications, both for

	national (e.g. AFEF) and international associations or governmental institutions (e.g. Biotech Research and Innovation Centre (BRIC) from University of Copenhagen, Belgian Foundation against Cancer, Medical Research Council, UK). **Publications:** 96 publications referenced in Web of Science (H-index 27) and international patents. - Nicolas Boluda, A; Vaquero, J; Laurent, G; Renault, G; Bazzi, R; Donnadieu, E; Roux, S; Fouassier, L*; Gazeau, F* (* co-leadership). Photothermal Depletion of Cancer-Associated Fibroblasts Normalizes Tumor Stiffness in Desmoplastic Cholangiocarcinoma. ASC Nano 2020 26;14(5):5738-5753. - J Vaquero, F Judée, M Vallette, H Decauchy, A Arbelaiz, L Aoudjehane, O Scatton, E Gonzalez-Sanchez, F Merabtene, J Augustin, C Housset, T Dufour , L Fouassier. Cold-atmospheric plasma induces tumor cell death in preclinical in vivo and in vitro models of human cholangiocarcinoma. Cancers 2020 19;12(5):1280. - Vaquero J, Lobe C, Tahraoui S, Clapéron A, Mergey M, Merabtene F, Wendum D, Housset C, Coulouarn C, Desbois-Mouthon C, Praz F, Fouassier L. IGF2/IR/IGF1R pathway in tumor cells and myofibroblasts mediates resistance to EGFR inhibition in cholangiocarcinoma. Clin Cancer Res 2018 24(17):4282-4296. **ORCID:** 0000-0001-6377-5610 **Google Scholar:** link here
Department/ Research	The **UMR_S 938 CRSA** (Dir: Prof. Bruno Fève) is conceived to optimize the major translational research potential of the groups in the rapidly moving areas of onco-hematology and metabolism-inflammation. The CRSA connects investigators from a wide spectrum of skills that includes cellular and molecular biology, preclinical experimentation in whole animals, investigator-initiated clinical research, and translational research that brings discoveries from the bench to the bedside. https://www.crsa.fr/ The "**Fibro-Inflammatory Diseases of Metabolic and Biliary Origin**" research team is focused on liver physiology and pathology (NASH, liver cancer). Within this team, Laura Fouassier is leading a group with a research focus on cholangiocarcinoma, tumor microenvironment and cell signaling (*i.e.* EGFR). The group works on several pre-clinical models (2D/3D cell culture and murine models) and on human samples (liver, biliary and CCA). **Facilities available**: The CRSA benefits from a common administrative unit, L1, L2, and L3 culture rooms, and high-level small animal housing facilities. Otherwise, we have a privileged access to other technologies in strong connection with dedicated platforms for cell imaging, histology, flow cytometry (UMS 30 LUMIC), and biostatistics and bioinformatics platforms (UMS 29 OMICS). The platform HumanHep Cell, ICAN (lead by Lynda Aoudjehane) is

	of a great value, providing cell types from human healthy liver and human cholangiocarcinoma.
Suggestion for interdisciplinary / intersectoral secondments	This project is part of a collaborative work with **Prof Jesus Banales** (Biodonostia Institute -Donostia Univ. Hospital-, San Sebastian, Spain) to perform the experiments on the human specimen, and of collaborative networks (**ENS-CCA** and **e-COST Euro-Cholangio-Net**) to which Laura Fouassier belong.
Skills Requirements	**Specific Skill Requirements:** cell biology (cell culture), Biochemistry (protein detection by immunostaining and immunoblotting…), molecular biology (RT-QPCR…), animal experimentation (with certificate if possible), Statistics, English writing. **Publications:** At least one in first author in high impact journal and other (2-3) in second or third position. **Required Languages:** English **Other skills:** must be well organized with excellent capacity to communicate and interact with our collaborators
Eligibility criteria for applicants	**Academic qualification:** By the MSCA-PF call deadline (September 15th, 2021), applicants must be in possession of a doctoral degree, defined as a successfully defended doctoral thesis, even if the doctoral degree has yet to be awarded. **Research experience:** Applicants must have a maximum of 8 years full-time equivalent experience in research, measured from the date applicants were in possession of a doctoral degree. Years of experience outside research and career breaks (e.g. due to parental leave), will not be taken into account. **Nationality & Mobility rules*:*** Applicants can be of any nationality but must not have resided more than 12 months in France in the 36 months immediately prior to the MSCA-PF call deadline (October 12th, 2021).
Application process	We encourage all motivated researchers **to apply directly through email**, before June 30th to laura.fouassier@inserm.fr. Your application has to include: - a CV including: (i) the exact date of your stay in each position and country and (ii) a list of publications; - a research outline (up to 2 pages) identifying the research synergies with the faculty members and pre-identified topics described above. **Please indicate [your name + CRSA MSCA PF application] in the subject of your email**

	Estimated timetable: - Deadline to apply to the present call of interest: 30th June 2021 - Selection of the most promising application(s): July 2021 - Writing the MSCA-PF proposal with the support of the above-mentioned supervisor(s): July–October 2021 MSCA-PF 2021 call deadline: 12th October 2021