DOCTORAT BIOLOGIE BRETAGNE SANTE LOIRE

Year 20 /20

THESIS TOPIC

Subject N° (to be completed by the ED):	**FUNDING:** ☒ **Requested** ☐ **Acquired**	**Funding origin:**
Thesis title: **Identification of the mechanisms involved in cell-to-cell communication in cancer stem-like cells**		3 keywords: glioblastoma extracellular vesicles centriollar satellites
Unit / team: **CRCI2NA, Team Signaling in Oncogenesis, Angiogenesis, and Permeability**		
Supervisor's name: **Gavard, Julie**		Phone number: 0228080327 Email address: julie.gavard@inserm.fr

Socio-economic and scientific context (approximately 10 lines):

Glioblastoma Multiforme (GBM) represents the most lethal adult primary brain tumors, with a median survival time of 15 months following diagnosis. Within these highly heterogeneous tumors exists a subpopulation of tumor cells named Glioblastoma Stem-like Cells (GSCs). Although the molecular and functional definition of GSCs is still a matter of debate, there is compelling evidence that these cells can promote resistance to conventional therapies, invasion into the normal brain, and angiogenesis. As such, they are suspected to play a role in tumor initiation and progression, as well as recurrence and therapeutic resistance. In this context, extracellular vesicles (EVs) emerge as important mediators of cell-to-cell communication within the tumor soil. These nanosized particles ranging from 30–100 nm to a few micrometers haul proteins, lipids, and nucleic acids. EVs are suspected to support cancer growth and dissemination by mediating both local (autocrine, paracrine) and at-distance signaling. The main objectives are to explore the mechanisms involved in GSC expansion in interaction with their environment and to do so, we will detail the molecular basis for EV production in life-and-death decisions.

Working hypothesis and aims (approximately 8 lines):

Because EVs are released from different cellular sources (membrane, cytosol, and cilia), we aimed at investigating whether centriolar satellites (CS) can ignite EV genesis in GSCs. CS are indeed cytoplasmic granules that are localized in clusters around the centrosome and cilia, the centrosome being the main center of microtubule organization in cells. CS have been described to allow the transport of proteins to the centrosome and the primary cilium. In addition, recent lines of research have identified satellites as regulators of many cellular processes, such as autophagy, neurogenesis, and ciliogenesis. Recently, more than 65 proteins have been identified via proteomic analysis within CS, further illustrating the highly complex nature of these structures. The exact functions of CS in GSCs and EV release are not fully elucidated.
The thesis project will be dedicated to answering these biological questions in the course of cancer progression: What are the organization and composition of CS in GSCs? Beside ciliogenesis, what are the roles of CS in vesicle genesis and trafficking? Are CS regulating GSC properties?

Main milestones of the thesis (approximately 12 lines):

In the course of the thesis project, CS will be examined in details using complementary approaches (confocal imagery, proteomics, biochemistry) using patient-derived glioblastoma cells, cultured in 2D and 3D, in favorable conditions and under hostile challenge (chemotherapy, radiations, starvation). Next, CS will be dismantled using genetic targeting (siRNA silencing and CRISPR-mediated deletion) in order to study how they contribute to EV release, using standardized methodologies available in the team. Finally, how CS modulate GSC properties will be studied in vitro (self-renewal, viability, stemness, differentiation, resistance to treatments) and in vivo (tumor growth).
This project is based on the expertise of the team in characterizing and manipulating patient cells, as well as studying cellular biology of extracellular vesicles and CS. Core-facilities in the vicinity will be instrumental for the success of the project.

Scientific and technical skills required by the candidate (2 lines):

- Scientific skills: cell biology, cancer,
- Technical skills: culture, imagery, biochemistry

3 publications from the team related to the topic (last 5 years):

- Trillet K, Jacobs KA, André-Grégoire G, Thys A, Maghe C, Cruard J, Minvielle S, Gonzales Diest S, Montagnac G, Bidère N, Gavard J. The glycoprotein GP130 governs the surface presentation of the G-protein coupled receptor APLNR. **J Cell Biol** 2021; 220(9): e202004114
- Douanne T, André-Grégoire G, Thys A, Trillet K, Gavard J, Bidère N. CYLD Regulates Centriolar Satellites Proteostasis by Counteracting the

E3 Ligase MIB1. **Cell Reports** 2019; 27(6): 1657-65.

- Harford-Wright, Andre-Gregoire G, Jacobs KA, Treps L, Le Gonidec S, Leclair HM, Gonzalez-Diest S, Roux Q, Guillonneau F, Loussouarn D, Oliver F, Vallette FM, Foufelle F, Valet P, Davenport AP, Glen RC, Bidere N, Gavard J. Pharmacological targeting of apelin impairs glioblastoma growth. **Brain** 2017; 11(1): 2939–54.

National and international collaborations:

- Jacky Goetz, Strasbourg

- Guillaume Van Niel, Paris

- SFR François Bonamy