COLLEGE ED BIOLOGIE DOCTORAL SANTE PAYS DE LA LOIRE

Year 2024/2025

THESIS TOPIC

Subject N° (to be completed by the ED):	**FUNDING:** ☒ **Requested** ☐ **Acquired**	**Funding origin:**
Thesis title: **Interventional immunostimulating implants for inhibition of post-resection relapse of glioblastoma**		3 keywords: Glioblastoma; immunostimulation; nanostructured hydrogels
Unit / team: **CRCI2NA, INSERM U1307, CNRS U6075 – Team GLIAD (Angers University)**		
Supervisor's name: **Dr Emmanuel GARCION (director) / Dr Florence DUMAS (co-supervisor)**		Phone number: 02 44 68 85 43 (EG)/02 41 35 84 79 (FD) Email address: emmanuel.garcion@univ-angers.fr and florence.dumas@univ-angers.fr

Socio-economic and scientific context (approximately 10 lines):
Glioblastomas (GB) are devastating tumors of the central nervous system (CNS). Despite the implementation of standard treatment combining surgical resection and concomitant radiochemotherapy, their prognosis remains poor. The explanations for this failure are tumor heterogeneity and the peritumoral infiltrative niche. Relapse is always observed within 2cm of the peritumoral area. Infiltrating cells explain the relapse. A complex interaction between the initial location of the tumor, its attraction by the peritumoral microenvironment define a heterogeneous pathway which is probably the most relevant target if we want to develop more curative therapies. Although the CNS is considered unique in its structure and barriers, it constantly interacts with the immune system. Advances in cancer treatment with the advent of PD-1/PD-L1 immune checkpoint inhibitors and CAR-T cells suggest that a solution to cancer, including GB, will include an immunotherapeutic component. They also show the limits of monoclonal antibodies (bioavailability, cost, adverse effects associated with their long half-life, reduced action in the CNS by systemic administration).

Working hypothesis and aims (approximately 8 lines):
The engineering of immunomodulatory platforms and/or locoregional immunocompetent tissues is a promising avenue. The intracavitary administration of a peptide PD-1 inhibitor from a nanocomposite hyaluronic acid hydrogel, then immunostimulant, could be directly integrated into the resection without surgical reintervention. It would adapt to the currently unused post-resection time of one month benefiting from a key therapeutic window before conventional radio-chemotherapy. A generic tool dedicated to locoregional immunomedicine will be developed and tested at the preclinical level for the treatment of GB. This thesis project would be ideal for the exploration of immunostimulating brain locoregional implants and could open the way to new trials in humans.

Main milestones of the thesis (approximately 12 lines): The thesis includes three connected stages. ***1) Production of AuNP-12 nanocomposite hydrogels (HA-NP(AUNP-12)).*** Nanocomposite hydrogels loaded with AuNP-12 (human and murine PD-1 antagonist peptide) will be formulated and characterized. The GLIAD team has recently contributed to the development of polymer systems for chemotherapy and delivery of therapeutic proteins, as well as the development of hyaluronic acid hydrogels (HA, HTL Biotechnology). The physicochemical properties of the hydrogels (gelation and injectability) will be characterized as well as the release of AuNP-12 in vitro. ***2) Biological activity in vitro.*** The biological activity of vectorized AuNP-12 will be evaluated on splenocytes, or on peripheral blood mononuclear cells (PBMC), stimulated by PD-L1 and in cocultures with murine GB GL261 cells. The levels of IL-2 and IFNγ in the supernatants will be measured by ELISA. ***3) In vivo effectiveness and synergy with radiotherapy.*** Preclinical evaluation of AuNP-12 hydrogels will be carried out in the GL261 intracavitary model in C57Bl6/J mice. The biodegradability of the developed systems and the distribution of the radiotraced peptide will be explored. The effectiveness will be studied in order to establish the temporality and spatial representation of biological events (tumor growth MRI, Kaplan-Meier, anatomo-pathology, cellular/molecular analyzes of peripheral blood and tumor and microenvironmental responses in situ). The recruitment and activity of immune contingents will be understood using isolated samples. The association with radiotherapies will be discussed (211At-Abs, 188Re-LNC, RX).

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

Bioengineering, Pharmacotechnics, Molecular and cellular biology, In vitro and in vivo experimental models, Teamwork essential! Motivation, autonomy, team spirit, good oral and written expression

3 publications from the team related to the topic (last 5 years):
Molina-Peña R*, Ferreira NH*, Roy C, Roncali L, Najberg M, Avril S, Zarur M, Bourgeois W, Ferreirós A, Lucchi C, Cavallieri F, Hindré F, Tosi G, Biagini G, Valzania F, Berger F, Abal M, Rousseau A, Boury F, Alvarez-Lorenzo C*, **Garcion E***. Implantable SDF-1α-loaded silk fibroin hyaluronic acid aerogel sponges as an instructive component of the glioblastoma ecosystem: Between chemoattraction and tumor shaping into resection cavities. ***Acta Biomaterialia***, 173 (2024) 261–282. (IF: 10.633)
Rinaldi A., **Dumas F.**, Duskey J.T., Imbriano C., Belluti S., Roy C., Ottonelli I., Vandellia M.A., Ruozi B., **Garcion E.**, Tosi G., Boury F. Polymer-lipid Hybrid Nanomedicines to Deliver siRNA in and Against Glioblastoma Cells. ***International Journal of Pharmaceutics***, 654 (2024) 123994. (IF: 5.800).
M. Najberg, M. Haji Mansor, T. Taillé, C. Bouré, R. Molina-Pena, F. Boury, JL. Cenis, **E. Garcion***, C. Alvarez-Lorenzo*. Aerogel sponges of silk fibroin, hyaluronic acid and heparin for soft tissue engineering: composition-properties relationship. ***Carbohydrate Polymers***, 237 (2020) 116107. *ec contributions (IF: 9.381)

National and international collaborations: Marcel Holleinstein, Institut Pasteur, Paris ; Jorge Barbaza, Miguel Abal, Nasasbiotech, Coruna, Spain ; Giovanni Tosi, UNIMORE, Modena ; François Berger, BrainLab, CHUGA, Grenoble ; Carmen Alvarez-Lorenzo, USC, Santiago de Compostela ; Maria Marlow, Nottingham, UK ; Michel Chérel, CRCI2NA team 2 ; Consortium GLIOSILK Euronanomed III ; LABEX IRON ; Projet Ligue National FUSTARG « ARN thérapeutiques » ; CGO. Tereza Manzo, Milano, Italy ; Leila Akkari, Amsterdam, Netherland.