COLLEGE ED BIOLOGIE DOCTORAL SANTE PAYS DE LA LOIRE

Year 2023/2024

THESIS TOPIC

Subject N° (to be completed by the ED):	**FUNDING:** **X Requested** ☐ **Acquired**	**Funding origin:**
Thesis title: **C-NU-Study of oncolytic viruses interactions with non-malignant cells of the tumor microenvironment**		3 keywords**: antitumor virotherapy** **oncolytic viruses** **tumor microenvironnement**
Unit / team: **CRCI2NA, team 1 : Immunomodulation of the Tumor Microenvironment and Immunotherapy of Thoracic Cancers**		
Supervisor's name: **Jean-François Fonteneau**		Phone number: **(+33) 02 28 08 02 36** Email address: **jean-francois.fonteneau@inserm.fr**

Socio-economic and scientific context (approximately 10 lines):
Lung adenocarcinoma and neuroblastoma are cancer for which a proportion of patients do not respond to current therapies. It is therefore necessary to propose new therapeutic strategies. To this end, our team is studying oncolytic immunotherapy. This therapeutic approach is based on the use of attenuated oncolytic viruses (OVs) that replicate only in tumor cells and induce a form of immunogenic cell death that stimulate the anti-tumor immune response. Oncolytic immunotherapy is currently experiencing its first successes with the authorization by the FDA and EMA in 2015 of a first OV, Imlygic for the treatment of melanoma and the evaluation in phase III clinical trials of several other OVs including Pexa-Vec vaccinia virus.
Our team is studying several different OVs, including the attenuated Schwarz vaccine strain of measles virus (MV) in collaboration with Dr. Frédéric Tangy of the Pasteur Institute who produces this virus. We also study the vaccinia virus or the vesicular stomatitis virus (VSV) which allows us to test this approach in animal models. We characterize the mechanisms of sensitivity of tumor cells to OVs, their effects on the non-malignant cells of the tumor microenvironment (macrophages, fibroblast …) and the anti-tumor immune response. This study should lead to new strategies to improve viral oncolytic activity against cancers.

Working hypothesis and aims (approximately 8 lines):
Recently we showed that the permissiveness of tumor cell lines to MV replication depends on defects of the type I interferon antiviral response (IFN I) in cancer cells. However, tumors are made of tumor cells and different non-malignant cell types (macrophages, fibroblasts…) that may interfere in the oncolytic virus replication. Recently, we develop a 3D culture model of cancer cell lines under the form of spheroid with tumor cells alone or with non-malignant cells to mimic a tumor. The aims of this study are:
1. To study the replication and spreading of MV and other OVs in the spheroid model to better understand what the virus does to cells of the tumor microenvironment (TME) and reciprocally how non-malignant cells from the TME affect the oncolytic activity.
2. To study the replication and spreading of MV and other OVs in cultured tumor biopsies from lung cancer patients to identify and assess new strategies to increase replication in tumor cells.

Main milestones of the thesis (approximately 12 lines):
Main steps of the thesis will be:

1. To study the replication and spreading of fluorescent protein encoding OVs in tumor spheroids containing or not non-malignant cells (macrophages, fibroblasts…) by confocal microscopy, cytometry and viral titration. In parallel, replication and spreading will be studied in cultured tumor biopsies from lung cancer patients by the same techniques.
2. To study effects of the OVs on non-malignant cells of the TME (macrophages, fibroblasts…) after spheroid or tumor biopsies dissociation by multiparametric flow cytometry, transcriptomic study and cytokine multiplex assays.
3. We will assess strategies to increase viral replication in tumor cells notably by arming the virus with transgene encoding immunomodulatory proteins

Scientific and technical skills required by the candidate (2 lines):
cell culture, cytometry, microscopy, molecular biology

3 publications from the team related to the topic (last 5 years):
Grard M, Chatelain C, Delaunay T, Pons-Tostivint E, Bennouna J, Fonteneau, Homozygous Co-Deletion of Type I Interferons and CDKN2A Genes in Thoracic Cancers: Potential Consequences for Therapy*, Front Oncol,* 11 (2021) 695770.
Delaunay T, Achard C, Boisgerault N, Dutoit S, Blanquart C, Royer PJ, Combredet C, Minvielle S, Quetel L, Meiller C, Jean D, Fradin D, Bennouna J, Magnan A, Cellerin L, Tangy F, Grégoire M and Fonteneau JF. Frequent bi-allelic deletions of type I interferon genes in mesothelioma confer sensitivity to oncolytic measles virus. *J Thorac Oncol*. 2020 Jan 13. pii: S1556-0864(20)30019-8. doi: 10.1016/j.jtho.2019.12.128. [Epub ahead of print]
Delaunay T, Nader J, Grard M, Farine I, Hedwig V, Foloppe J, Blondy T, Violland M, Pouliquen D, Gregoire M, Boisgerault N, Erbs P, Fonteneau JF, High Oncolytic Activity of a Double-Deleted Vaccinia Virus Copenhagen Strain against Malignant Pleural Mesothelioma, *Mol Ther Oncolytics*, 18 (2020) 573-578.

National and international collaborations:
Dr Frédéric Tangy, Institut Pasteur, Paris, France.
Dr Mireia Pelegrin and Gilles Uzé, Institute for Regenerative Medicine and Biotherapy (IRMB), Montpellier, France.