### Fiche sujet de thèse

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<th>Sujet N° (à remplir par l’ED)</th>
<th>FINANCEMENT : xDemandé □ Acquis</th>
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<td>Study of oncolytic activity of the attenuated measles virus for the treatment of thoracic cancers</td>
<td>3 Key-words : Oncolytic viruses Mesothelioma Lung cancer</td>
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### Contexte sociéconomique et scientifique (env. 10 lignes) :

Malignant pleural mesothelioma (PML) and lung cancer are aggressive cancers that are refractory to conventional treatments (surgery, chemotherapy and radiotherapy). It is therefore necessary to propose new therapeutic strategies. For this purpose, our team is studying oncolytic immunotherapy. This therapeutic approach is based on the use of oncolytic viruses (OV) that replicate only in tumor cells and induce a form of immunogenic cell death that will stimulate the anti-tumor immune response. Oncolytic immunotherapy is meeting its first success with the launch in 2015 of a first OV, the Imlygic for the treatment of melanoma and the evaluation in phase III clinical trial of several other OV.

Our team is studying several different OV, including the attenuated Schwarz vaccine strain of the measles virus (MV) in collaboration with Dr. Frédéric Tangy of the Institut Pasteur who produces this virus. We are also studying the vesicular stomatitis virus (VSV), which is used to evaluate this approach in animal models. We study mechanisms of sensitivity of tumor cells to OV. We also study the effect of OV on the anti-tumor immune response.

### Hypothèses et questions posées (env. 8 lignes) :

Recently we showed that the sensitivity of mesothelioma and melanoma to MV depends on defects of the type I interferon antiviral response (IFN I). Most of the tested tumor cell lines have defects in this response upstream of the IFN I receptor (IFNAR). They are therefore probably sensitive to IFN I produced by healthy cells in response to MV. We collected preliminary data that support this hypothesis. Thus, the thesis project will consist of:

1. Confirm in 3D culture models (spheroids and explants) that the IFN I response of healthy cells decrease replication and propagation of the MV in the tumor.
2. In collaboration with the team of Dr. Gilles Uzé of Montpellier, develop IFNAR inhibitors that will target only the tumor cells to make Them sensitive to OV.

### Grandes étapes de la thèse (env. 12 lignes) :

The main steps of the thesis will be:

1. Study the replication and propagation of MV in models of tumor spheroids containing or not healthy cells. 18 mesothelioma and lung cancer cell lines form spheroids on the 28 that we tested so far in our biocollection.
2. Confirm that the presence of healthy cells inhibits the spread of MV and that this is due to the IFN I response (use of IFNAR broad inhibitor: ruxolitinib, anti-IFNAR monoclonal antibodies)
3. In vivo and in vitro testing of an inhibitor that only targets IFNAR tumor cells to make them susceptible to OV.

This project, if it worked, would be an important advance for oncolytic immunotherapy because the tumor IFNAR inhibitor could potentially be used to improve the efficacy of all OV in clinical evaluation currently.

### Compétences scientifiques et techniques requises par le candidat (2 lignes) :

-Molecular Biology, 3D cell culture, cytometry, confocale microscopy, RNAseq,…

### Collaborations nationales et internationales :

- Dr Frédéric Tangy, Institut Pasteur, Paris, France. Virus oncolytique de la rougeole souche vaccinale Schwarz.
- Dr Philippe Erbs, société Transgene, Illkirch Graffenstaden, France. Virus oncolytique modifié de la vaccine, VVtk-rR, souche copenhague.
- Dr E Antonio Chiocca, Harvard University, Boston, USA. Virus Herpes simplex type 1 oncolytique modifié, qRNestin34.5.
- Dr JC Bell, Ottawa Hospital Research Institute, Ottawa, Canada. Virus de la stomatite vésiculaire oncolytique modifié, VSV-delta51.
- Dr Gilles Uzé, Université Montpellier (labex Mabimprove) : inhibiteur spécifique du IFNAR tumoral.