**THESIS TOPIC**

<table>
<thead>
<tr>
<th>Subject N° (to be completed by the ED):</th>
<th>FUNDING:</th>
<th>x Requested [ ] Acquired</th>
<th>Funding origin: ARED/Ligue or contrat doctoral</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thesis title:</td>
<td></td>
<td></td>
<td>3 keywords:</td>
</tr>
<tr>
<td>Interactions between B lymphocytes and lymphoid stromal cells: role in lymphomagenesis</td>
<td></td>
<td></td>
<td>- Tumor niche</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>- Cancer-Associated Fibroblasts</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>- Cell interactions</td>
</tr>
</tbody>
</table>

**Unit / team:** UMR U1236_MICMAC

**Supervisor’s name:** Karin TARTE

**Phone number:** 0223234512

**Email address:** karin.tarte@univ-rennes1.fr

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

Follicular lymphoma (FL) is characterized by a long preclinical stage, an indolent clinical course with multiple relapses, and remains a fatal neoplasia. Interestingly, FL is a good paradigm of an hematological malignancy strongly dependent on its specific permissive microenvironment including in particular CD4<sup>+</sup> T cells harboring a follicular helper phenotype (Tfh) and cancer-associated fibroblasts (CAF) with lymphoid stromal cell phenotype. We have demonstrated that FL-Tfh and FL-CAF display specific phenotypic, transcriptomic, and functional features and that the bidirectional crosstalk between tumor B cells, FL-Tfh, and FL-CAF supports lymphomagenesis and is influenced by tumor genetic profile. However, very few data are available on FL-CAF heterogeneity and function in situ. The current project will provide new insights on the interactions between FL B cells and FL CAF owing to the recent development of innovative tools allowing the study of stromal cells in situ and ex vivo, the coculture of stromal cells and B cells in alginate spheroids reproducing FL biology and the set up of new transgenic mouse models.

**Working hypothesis and aims (approximately 8 lines):**

Our main hypothesis is that the differentiation and organization of FL stromal niche rely on the direct interactions between stromal precursors, tumor B cells and FL-Tfh. Our objectives are to i) define how FL-CAF differentiate and organize tumor niche; ii) how they could directly support malignant B-cell growth.

**Main milestones of the thesis (approximately 12 lines):**

The project is organized in 2 complementary WP

**WP1) In vitro characterization of B-cell/stromal cell crosstalk.** We plan to use our newly developed alginate spheroid model reproducing in 3D co-culture the dependence of FL B cells to supportive stromal cells (patent PCT/FR2018/050855). We will in particular evaluate the dynamic of stromal cell niche organization, the mechanisms of stroma polarization into protumoral CAF in vitro (in comparison with purified FL-CAF recently characterized by RNaseq and in situ microscopy) and the impact of FL-Tfh-derived factors on B-cell/stromal cell interactions.

**WP2) In vivo characterization of B-cell/stromal cell crosstalk.** We will study CAF features in our new lymphoma mouse models and will compare the impact of 2 recurrent genetic alterations in double transgenic mouse models. We have also access to tumor samples from large series of FL patients included in clinical trials making it possible to correlate the modifications of stroma phenotype with genetic profile and to validate the relevance of the data obtained in vitro and in mouse models.

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

Scientific background in cancerology and/or immunology

Technical background in cell culture and molecular biology

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


**National and international collaborations:**

- Fatima Mechta-Grigoriou, Curie
- Francesca Barone, Birmingham
- Laurence Bepoldin/Pierre Nassoy, Bordeaux