**THESIS TOPIC**

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<th>Subject N° (to be completed by the ED):</th>
<th>FUNDING:</th>
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<tr>
<td>Thesis title: Study of the migration in the niche of childhood acute B lymphoblastic leukemia</td>
<td>3 keywords: Leukemia Microenvironment Chemoresistance</td>
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**Unit / team:** IGDR UMR6290 CNRS / Expression des gènes et oncogenèse (GEO)

**Supervisor's name:** Dr. Frédéric Mazurier (DR INSERM)
**Cosupervisor:** Pr. Virginie Gandemer (PU-PH)

**Socio-economic and scientific context (approximately 10 lines):**
Pediatric cancers account for 1,700 new cases per year (France) among which leukemias are the most common (29%). Acute lymphoblastic leukemias (ALL) represent the majority of leukemias, and 85% affect the B lineage (B-ALL). Therapeutic advances have greatly improved survival by 10% to 80%, but relapse often occurs as early as 18 months, but also up to 10 years after the end of treatment. The tumor microenvironment is now considered as a key element of chemoresistance. The relapse from niches of extramedullary origin, frequent in ALL, requires local treatments with considerable consequences. At diagnosis, leukemia cells are detected in the central nervous system in 5 to 10% of cases, and in 35% of cases that do not receive prophylactic treatment. The testis and ovaries are frequently colonized sites and are sanctuaries of late relapse. Studying the migration mechanisms of ALL is a challenge to prevent relapse and identify mechanisms for escaping adult and pediatric tumors.

**Working hypothesis and aims (approximately 8 lines):**
B-ALL is characterized by an accumulation of blasts in the bone marrow and blood, but also in extramedullary niches. The presence of clones with different or additional mutations compared to the original clone may explain the resistance to treatment. Our team has hypothesized for several years that the trafficking of malignant cells in low oxygenized (hypoxic) tissues would induce the expression of CD9 and migration into extramedullary niches, which could explain the relapse in the longer or shorter term. The team’s results showed that CD9 is involved in B-ALL cell migration and regulated by hypoxia. There comes the question of migration in a more complex microenvironment. Can an in vitro surrogate niche model be established? What about in vivo? What are the mechanisms involved?

**Main milestones of the thesis (approximately 12 lines):**
To answer the questions, the thesis will be carried out in six tasks:
1. Assess and monitor migration of B-lymphoblasts in a co-culture model with MSCs;
2. Study the expression of CD9 and CXCR4 in the cell fractions and their involvement in the migration;
3. Determine HIF contribution;
4. Assess resistance to treatment (asparaginase, daunorubicin) and the involvement of CD9 and HIF;
5. Determine the ability to initiate leukemia in vivo of the different cell fractions and the testicular colonization in immune-deficient NSG mice;
6. Search for the mechanisms involved and validate the expression of the most relevant targets.

**Scientific and technical skills required by the candidate (2 lines):**
Scientific or medical program. Skills (M2 level) in cellular and molecular biology, genomics and post-genomics techniques: cell culture, microscopy, western-blot, PCR, immunohistochemistry...

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

**National and international collaborations:**
The scientific research project in the field of tumor/microenvironment relationship perfectly fits into one of the objectives of the FHU CAMIn «cancer microenvironment innovation». The laboratory is in close collaboration with the pediatric hematology clinical department of the Rennes CHU as well as with the other pediatric hematology centers of “Région Grand Ouest” through the interregional organization GOCE (interregional network defined by the INCa) and the interregional FHU GOAL on acute leukemia in children and adults. In addition, the GEO team is part of the REACT-4KIDS network whose mission is to federate French laboratories on oncopediatric research.