# THESIS TOPIC

<table>
<thead>
<tr>
<th>Subject N° (to be completed by the ED):</th>
<th>FUNDING:</th>
<th>Requested</th>
<th>Acquired</th>
<th>Funding origin:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thesis title: Study of Cytokine's signal propagation: A new way to deliver signaling.</td>
<td></td>
<td></td>
<td></td>
<td>3 keywords: Cytokine Exosome Cell communication</td>
</tr>
</tbody>
</table>

**Unit / team:** CRCINA, University of Nantes, Inserm UMR1232, CNRS ERL6001

**Supervisor’s name:** Erwan MORTIER

**N° de tél :** 02 28 08 03 04  
**Mail :** erwan.mortier@univ-nantes.fr

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

Intercellular communication is the basis of the cohesion of organisms. Immune cells have different modes of communication in order to fight against cancers. As such, the cytokines interleukin (IL-2) and IL-15 are essential molecules for anti-tumor immune surveillance, notably promoting the survival and functions of cytotoxic CD8 T cells and Natural Killer (NK). However, the involvement of these cytokines in several T cell malignancies has been well established. Indeed, the unusual expression of IL-15 has been implicated in the etiopathology and deterioration of several subtypes of hematological malignancies via an autocrine/paracrine mechanism. IL-15 is therefore an ambivalent cytokine that can be both anti- and pro-tumor. Regulation of the IL-2/15 signal of lymphocytes is therefore critical both for an optimal cytolytic immune response and for the prevention of a malignant lymphocyte disorders. Therefore, improving our knowledge of the regulation of the IL-15 and IL-2 systems and the mechanisms by which they ensure the development of NK and CD8 T cells may lead to the optimization of the anti-cancer immune response as well as to the treatment of certain types of leukemia.

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

Over this thesis, we propose to study the "non-soluble” component of cytokines. Preliminary experiments conducted in the laboratory have shown that cells pre-stimulated with IL-15 or IL-2 "use" these cytokines until their signaling machinery is saturated, then disperse the signal to neighboring cells. This phenomenon is observable even though no cytokine is detectable in the culture supernatant. We hypothesized that these cells pre-stimulated with cytokines were able to recycle the molecules or keep them on the surface and then redistribute them to propagate the signal: by cell contact? and/or via the cytokines associated with extracellular vesicles? In order to answer these questions, we will analyze the responses of different cell types (NK and T cells) to IL-15 and IL-2 stimuli, both healthy and pathological (ATL, CTL).

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

This thesis is based on preliminary results generated in the laboratory and will consist of two complementary but independent parts.

1/ Study of the propagation of the IL-2 and IL-15 cytokine signal by cellular contact.

2/ Regulation of the cytokine signal by extracellular vesicles.

Initially, the student will be in charge of studying and analyzing the mechanisms of action of delivery of the original cytokine signals recently demonstrated, allowing the propagation of the signal in the absence of soluble cytokine in the surrounding environment. This will require the mastery of techniques for culturing healthy and pathological immune cells as well as the isolation of extracellular microvesicles. In vitro functional and characterization tests will be performed in flow cytometry, alphaScreen technology, western blot and SPR using biological tools derived from cytokines generated in the laboratory (IL-15 and IL-2 mutants). In parallel, we propose to visualize the fate of these cytokines inside cells by confocal microscopy. Throughout this work, we will analyze in comparison the so-called healthy cells (NK and T cells) with pathological cells of leukemic type (ATL, CTL). Based on these results, we will attempt to validate these observations made in vitro and in vivo in mice in order to show the physiological and/or pathological impact of this pool of non-detectable but biologically active cytokines in an organism.

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

- Cell culture
- Flow cytometry

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


**National and international collaborations:**