université PARIS-SACLAY
FACULTÉ DE PHARMACIE

Graduate School: Health and Drug Research
Master 2 Pharmaceutical Technology and Biopharmacy

**Company/laboratory/public institution:** **Institut Galien Paris-Saclay (IGPS) – UMR 8612**

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**Supervision of trainee:** **LEPETRE Sinda and PONCHEL Gilles**

**Name of tutor:** **LEPETRE Sinda**

**Position:** **Associate Professor**

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Internship period: 20 January - 18 July 2025

**Title of the project:** **Squalene-based nanoparticles for the treatment of cancer-induced bone pain.**

**General context and positioning of the project :**

Osteosarcoma and Ewing's sarcoma are the two most common malignant bone tumors in children, adolescents, and young adults. They affect between 200 and 300 patients aged 5 to 25 years per year in France. Cancer-induced bone pain (CIBP) is often resistant to opioids, making it very challenging to manage due to its physiological complexity, which includes significant osteoclastic activity (bone destruction), an inflammatory component, neuropathic pain due to peripheral nerve or perimedullary space involvement, and nociceptive pain related to the invasion of soft tissues. Animal studies have shown that it is necessary to administer 10 times more morphine to relieve CIBP compared to a similarly intense inflammatory pain.[1]

Recently, a molecule has been identified as playing a major role in the inhibition of multiple voltage-dependent sodium channels (Nav channels), specifically the Nav1.7, Nav1.8, and Nav1.9 isoforms. These isoforms play a crucial role in pain perception. Furthermore, this molecule (molecule X) has been shown to provide pain relief in animal models of acute, inflammatory, and chronic pain (the name of the molecule X is confidential, and a patent application is underway).

These findings open up new perspectives for harnessing the therapeutic potential of this drug in pediatric bone cancer pain and thus offer a promising alternative to the use of opioids. However, it is important to note that the use of molecule X can lead to adverse effects, such as the inhibition of sodium channels in the heart, which can lead to cardiac toxicity. In this context, we hypothesized that the specific delivery of this drug at the tumor site would represent a major advance in the management of these refractory pains. To overcome this challenge and minimize off-target toxicity, the molecule X can be encapsulated in nanoparticles and administered intravenously. This approach would promote drug accumulation at the tumor site through the Enhanced Permeation Effect (EPR). This nanoformulation of molecule X should improve its therapeutic index by favorably altering its biodistribution while reducing cardiac toxicity.

**Objectives of the internship :**

For this approach, we propose to encapsulate molecule X in squalene-based nanoparticles, composed of Leu-enkephalin-squalene (LENK-SQ) prodrug. This prodrug was obtained by coupling the Leu-enkephalin (LENK) neuropeptide to a squalene (SQ) derivative through a biocleavable linkage. LENK-SQ nanoparticles (NPs) have already demonstrated analgesic effects in an inflammatory and post-operative pain model.[2,3] The encapsulation of molecule X in LENK-SQ NPs will result in squalene-based multidrug nanoparticles that can effectively adress CIPB by simultaneously acting on opioid receptors and Nav channels that are both overexpressed in the tumor.

Research in this field is of great importance because it aims to provide effective and safe relief for patients with bone cancer, thereby improving their quality of life and reducing the adverse effects associated with current pain treatments.

**Summary of the scientific/technical program :**

This project is conducted in collaboration with Hôpital Necker Enfants Malades.The master student will be located at Institut Galien Paris-Saclay (IGPS) under supervision of Dr Sinda Lepetre, Pr Gilles Ponchel and the PhD student Adélaïde Le Franc.

The primary objectives of this Master's project are as follows:

1. **Synthesis of LENK-SQ prodrug**
2. **Pre-formulation and formulation of LENK-SQ with Molecule** X (**Hybrid Nanoparticles) and characterization**
   Methodology : Pre-formulation studies will investigate various parameters, including nanoparticles' size, surface charge, drug loading and stability (of the nanoformulation). A stability study over time will be also carried out.
3. **Development of HPLC-Mass Method** to study the drug encapsulation efficiency and to perform a pharmacokinetic study**:** Establish a robust High-Performance Liquid Chromatography-Mass Spectrometry (HPLC-Mass) method for the accurate characterization and quantification of NPs containing molecule X. (IGPS)
   • Methodology : This phase will include sample preparation, method development, validation, and the establishment of standard operating procedures for the HPLC-Mass technique.
4. **Pharmacokinetic Study:** Since the master student does not have authorization for animal experimentation, he will assist the PhD student with in vivo procedures involving mice. The objective of this work is to conduct a comprehensive pharmacokinetic study to understand the bioavailability and metabolism of molecule X on mouse model. (IGPS)
   • Methodology : Blood samples will be collected at various time points post-administration of the nanoparticles in mice, and the pharmacokinetic parameters will be determined.

**Required profile**: Maser 2 pharmaceutical, medical, or scientific

**References :**

1. Urch C.E., Donovan-Rodriguez T., Gordon-Williams R., Bee L.A., Dickenson A.H. Efficacy of chronic morphine in a rat model of cancer-induced bone pain: behavior and in dorsal horn pathophysiology. J Pain. **2005**, 6(12), 837-45. doi: 10.1016/j.jpain.2005.08.005.
2. Feng J, Lepetre-Mouelhi S, Gautier A, Mura S, Cailleau C, Coudore F, Hamon M, Couvreur P. A new painkiller nanomedicine to bypass the blood-brain barrier and the use of morphine. Sci Adv. 2019 Feb 13;5(2):eaau5148. doi: 10.1126/sciadv.aau5148.
3. Hazam H, Prades L, Cailleau C, Mougin J, Feng J, Benhamou D, Gobeaux F, Hamdi L, Couvreur C, Sitbon P, Lepetre-Mouelhi S. A nanomedicine approach for the treatment of long-lasting pain. J Control Release. **2024**, 373, 688-698. doi : 10.1016/j.jconrel.2024.07.033.