PhD position in medicinal chemistry:
Inhibition of the drug efflux activity of Ptch1 to overcome chemotherapy resistance

Chemotherapy resistance is one of the major challenges in cancer treatment. Despite scientific advances, cancer remains one of the leading causes of death in developed countries and the search for new treatments a real challenge.
Our team identified the Hedgehog receptor Patched as a drug efflux pump that participates to the resistance of cancer cells to chemotherapy. Thanks to a screening program, Panicein A hydroquinone (PAH), a natural compound purified from a marine sponge, was identified as an inhibitor of drug efflux activity of Patched. The synthesis of PAH allowed us to confirm that PAH increases the cytotoxic effect of several chemotherapeutic agents on melanoma cell lines *in vitro* and *in vivo*. Recently, new original structures derived from PAH have been identified to improve the physicochemical properties of the molecule.

In this context, the PhD work will focus on:
- Synthesis of chemical probes to get further comprehension of the mechanism of action
- Optimization of the new generation of molecules thanks to a combination of *in silico* modelisation and structure-activity relationship (SAR) studies
- Providing proof-of-concept of the efficacy of the best optimized leads on melanoma but also on more Patched-expressing cancer cells (effect of the best PAH analogues on the proapoptotic, anticlonogenic and antiproliferatif effects of vemurafenib on melanoma cells in culture, and on the cytotoxicity of other chemotherapeutic agents on other cancer cell lines in culture)

The use of PAH in combination with chemotherapy may be a novel and innovative way to circumvent drug resistance, recurrence and metastasis of tumors. The final objective is to obtain a clinical candidate that could be considered for clinical testing with a Pharma partner.

This project will be supervised by Pr. S. Azoulay (Institut de Chimie de Nice, France), for the chemical part, and by Dr. I. Mus-Veteau (Institut de Pharmacologie Moléculaire et Cellulaire, Nice, France) for the biological part.

The applicant must be highly motivated and have a solid background in organic chemistry and notions of cell biology. *In silico* notions will be also appreciated.

Applications include a motivation letter, a detailed Curriculum Vitae, transcripts of master and undergraduate studies and the contact of at least one referee to stephane.azoulay@univ-cotedazur.fr . The thesis funded by a ministerial grant will start on 1 October 2023 (net salary 1640€ / month).

References

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