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Patched-e-ChemBiol: Inhibition of Patched chemotherapy resistance activity (biocomputational, chemical and cellular approaches)

The proposed programme will foster interdisciplinary, intersectoral and international experiences with the objective of contributing to creating a new generation of PhDs equipped for both academic and non-academic careers in e-health and inclined to the great research and innovation challenges of tomorrow.

Cancer drug resistance is a major problem of chemotherapy nowadays. Our team recently 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*. The use of PAH in combination with chemotherapy may be a novel and innovative way to circumvent drug resistance, recurrence and metastasis of tumors.

To get further comprehension of the mechanism of action and synthesize a more potent compound, the PhD student will have to

- Optimize the lead molecule PAH thanks to a combination of *in silico* modelisation and structure-activity relationship (SAR) studies (docking of PAH on Patched structure and drug design to propose PAH modifications, synthesis of PAH analogues, effect of each analogues on the cytotoxicity of a chemotherapeutic agent such as vemurafenib on melanoma cells and IC50 determination).
- Provide 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 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 Dr. 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 have a solid background in organic chemistry and notions of cell biology. *In silico* notions will be appreciated since he/she will have to perform a 6-month internship in the laboratory of Pr. P. Ruggerone at the University of Cagliari in Italy to carry out computational studies (docking and drug design) allowing to guide the synthesis of new and more effective analogues of PAH.

Applications before 12th August at http://univ-cotedazur.fr/fr/recherche/boosturcareer#.XQYIFI8682w

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