

Master 2 Internship in Organic and Medicinal Chemistry

Design, synthesis and optimization of new GRP78 inhibitors with anti-melanoma activity

Laboratory: Institut de Chimie de Nice, UMR7272.

Institute : Université Nice Sophia Antipolis, Parc Valrose 06108 Nice cedex 2, France

Team : Equipe Molécules Bioactives.

Contacts : Dr. Cyril Ronco, Dr. Rachid Benhida

Position: 6 months

Application deadline: **30/09/2017**

Starting date for the training in the lab: **January 2018**

Melanoma is an aggressive form of skin cancer that occurred in more than 230000 people and resulted in 55000 deaths in 2012, mainly in developed countries. Despite significant progress brought by the new anti-Braf and anti-PD1 targeted therapies, patients in the metastatic phase have a median life expectancy of only 8 - 9 months, because of the rapid emergence of resistance to these treatments. Thus it is of utmost importance to find new therapeutic approaches to treat these diseases.

GRP78 is a chaperone enzyme responsible for helping the proper folding of proteins synthesized in the ribosomes. It also acts as a molecular sensor of non-/misfolded protein accumulation, and triggers a cellular protection mechanism called UPR (Unfolded Protein Response) slowing down protein synthesis, and aiding the proper folding or the evacuation of these malformed proteins.

Recently, we demonstrated, in collaboration with biologist partners from the Mediterranean Centre of Molecular Medicine (C3M) that the inhibition of GRP78 and UPR allowed circumventing these resistance phenomena by selectively inducing cell death in melanoma cells, without causing side effects or toxicity in non-cancerous cells. Therefore, we have developed new compounds inhibiting GRP78, active *in vitro* and *in vivo*, and whose pharmacological properties need to be optimized.

The objective of the internship will be to continue the medicinal chemistry program (strategy 'Hit-to-Lead'), focusing on the creation of new analogs to establish the structure activity relationships and to optimize the pharmacological properties. New synthetic methodologies will be used to open access to innovative structures. The biological activity of the synthesized compounds will be systematically evaluated by our partners of the C3M.

Profile: The candidate should have strong skills in organic synthesis and synthetic methodology. An interest for Chemistry-Biology interface and knowledge of biochemistry, pharmacology, and bioanalytical methods will be appreciated.

Application: Please send your cover letter and CV to cyril.ronco@unice.fr and rachid.benhida@unice.fr