BioISI - Biosystems & Integrative Sciences Institute

New antitumor Ru-based compound derivatives optimized using in silico methods

Place of work/: **BioISI & DQB-FCUL (C8, 8.5.50D)**

Supervisors: Miguel Machuqueiro

Contact: (Email): machuque@ciencias.ulisboa.pt

In the last two decades, there has been a remarkable progress in the research of metal-based drugs for cancer therapy. TM34 has shown excellent antitumor properties [1], which is now being optimized by conjugating with small peptides (in the lab of Dr. Tânia Morais, CQE@FCUL) to improve selectivity. TM34 is also known to interact with P-glycoprotein (P-gp) [2], which is a membrane exporter overexpressed in tumors, although its mechanism is unknown. Understanding the molecular details impacting the overall antitumor performance of these derivatizations is the focus of this work plan. This proposal is in line with a recently approved FCT project (PTDC/QUI-QIN/0146/2020) and can be divided in different tasks:

I. Set up an umbrella-sampling (US) protocol coupled to Molecular Dynamics (MD) simulations to sample the complete membrane crossing process of TM34. Using the ISDM method, we can use obtained potential of mean force profile to estimate the compound membrane permeability.

II. Build the TM34-peptide derivatives using the peptide sequences being tested in vivo in Dr. Morais Lab. MD simulations will be used to assess the membrane interaction profiles of all compounds, while the US protocols will allow the estimation of their membrane permeabilities.

III. We will also set up a P-gp/membrane system to explore its interactions with TM34 using Molecular Docking and MD simulations.

IV. Compile all results in a master thesis and prepare a manuscript submission to an international scientific journal.

[1] Machado, J.F., Machuqueiro, M., Marques, F., Robalo, M.P., Piedade, F.M., Garcia, M.H., Correia, J.D.G., Morais, T.S. (2020) "Novel 'ruthenium cyclopentadienyl'-peptide conjugate complexes against human FGFR(+) breast cancer", Dalton Trans., 49, 5974-5987.

[2]Côrte-Real, L. et al. (2019) 'Unprecedented inhibition of P-gp activity by a novel ruthenium-cyclopentadienyl compound bearing a bipyridine-biotin ligand', Eur. J. Med. Chem., 163, 853–863.