Novel approach in the treatment of anaplastic thyroid cancer using EGFR- and PIP3-targeted synthetic peptides to inhibit the PI3K/AKT/mTOR signaling pathway

[1*]Zehra-Cagla Kahvecioglu, [1]Samuel Vandecasteele, [1]Marine Bougard, [2]Sarah Peeters,[1,4]Sophie Laurent, [3]Sven Saussez, [1]Carmen Burtea

[1] Department of General, Organic and Biomedical Chemistry, NMR and Molecular Imaging Laboratory, Faculty of Medicine and Pharmacy, University of Mons

[2] Cellular and Molecular Microbiology, Faculté des Sciences, Université Libre de Bruxelles

[3] Department of Human Anatomy and Experimental Oncology, Faculty of Medicine and Pharmacy, University of Mons

[4] Center for Microscopy and Molecular Imaging (CMMI), Faculty of Medicine and Pharmacy, University of Mons

* E-mail : ZEHRACAGLA.KAHVECIOGLU@umons.ac.be

Although rare, anaplastic thyroid carcinoma (ATC) represents the most aggressive and deadliest TC in humans. The overall survival of patients with ATC is about 4 months following diagnosis. Nowadays, this malignancy has no known effective cure. With a high morbidity rate and the paucity of treatment options, it is crucial to investigate novel therapeutic approaches. Mainly dysregulated signaling pathways in ATC are those of MAP kinase and PI3K/AKT/mTOR (PAM).

The proposed peptide-based targeted therapy is developed in our lab and aims to inhibit the aberrant PAM pathway, essentially responsible of cell division, growth and survival. EGFR overexpression and overactivation in oncologic processes and its endocytosis represent a driving element in our strategy, whereas phosphatidylinositol (3,4,5)-trisphosphate (PIP3) represents the therapeutic target due to its involvement in PAM triggering and cell survival.

In this context, an EGFR-targeted peptide (vector peptide, VP) was coupled to a PIP3-targeted therapeutic peptide (TP) via a scaffold molecule in a peptide complex (PC) to enable specific drug delivery to ATC cells. Once associated with EGFR, PT is endocytosed and induces apoptosis specifically in cancer cells by targeting intracellular PIP3.

The molecular mechanism of PV binding to EGFR has been analyzed *in silico* by peptide-protein docking studies using the HPEPDOCK web server. VP has a long half-life and binds to the interface between domains I and III of EGFR, in the large hydrophobic pocket exposing the binding sites to EGF. VP is endocytosed independently of the EGF presence and without activating the EGFR. Within cells, VP is colocalized with EGFR, following its trafficking pathway. Moreover, 10 µM of PC induces cell apoptosis after 1h of incubation. To conclude, our studies confirmed that VP is a good EGFR-targeting candidate to deliver TP to cancer cells.