A novel peptide-based therapeutic strategy for anaplastic thyroid carcinoma: Dual targeting of EGFR and PIP3.

Zehra-Cagla Kahvecioglu[1], Samuel Vandecasteele[1], Marine Bougard[1], Olivia Rasson[1], Céline Martens[1], Maurine Appels[1], Sophie Laurent[1,2], Sven Saussez [3], Carmen Burtea[1]

[1]NMR and Molecular Imaging Laboratory, General, Organic and Biomedical Chemistry Unit, Faculty of Medicine, Pharmacy and Biomedical Sciences, University of Mons, B-7000 Mons, Belgium
[2]Center for Microscopy and Molecular Imaging (CMMI), Charleroi, Belgium
[3]Human Anatomy and Experimental Oncology Unit, Faculty of Medicine, Pharmacy and Biomedical Sciences, University of Mons, B-7000 Mons, Belgium

zehracagla.kahvecioglu@umons.ac.be

Anaplastic thyroid carcinoma (ATC) is one of the deadliest forms of cancer, notorious for its swift progression and resistance to treatment, although it accounts for only 2% of thyroid cancer cases. ATC has a dismal prognosis, with an average survival time of only 4 months post-diagnosis. Conventional treatments, including surgery, chemotherapy, and radiotherapy, show limited effectiveness due to ATC's rapid progression and early metastasis. Therefore, novel treatment options are urgently needed. A key feature of ATC is the dysregulation of signaling pathways, particularly the PI3K/AKT/mTOR (PAM) pathway, which promotes cancer cell survival and proliferation. Our study introduces a targeted peptide-based therapy designed to inhibit the PAM pathway by targeting epidermal growth factor receptor (EGFR) and phosphatidylinositol (3,4,5)-trisphosphate (PIP3), thereby providing a potentially effective strategy to combat ATC.

The therapy consists of a peptide complex (PC) comprising a vector peptide (VP) that targets EGFR and a therapeutic peptide (TP) targeting PIP3. Tests conducted on ATC cell lines demonstrated that the VP promotes PC endocytosis and induces apoptosis in tumor cells within one hour. Preliminary studies of tumor biodistribution were carried out by fluorescence lifetime imaging (FLI) using VP coupled to a fluorochrome (PV-IRDye800), which was injected at various doses (0.8, 1.2 and 2.4 µmol/kg) in a murine model of ATC developed in athymic nude mice.

These findings suggest that the PC could represent a promising peptide-based therapeutic strategy for ATC by inhibiting the PAM pathway. Additional *in vivo* studies are necessary to validate this approach and explore its potential clinical applications.