

Toward the development of peptide inhibitors targeted to PI3K/AKT signalling pathway for the therapy of anaplastic thyroid carcinoma

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Introduction: Thyroid cancer is the most common endocrine cancer worldwide. Anaplastic thyroid cancer (ATC) represents one of the most aggressive cancers in humans. The death of patients generally occurs within 2-6 months from diagnosis. Consequently, there is an urgent need for novel therapeutic approaches. The PI3K/AKT pathway is overactivated in many cancer types including ATC. PIP3 acts as a docking site for the AKT protein, which once phosphorylated will activate or inhibit different cellular targets. The purpose of this project is to develop a peptide able to inhibit the PI3K/AKT pathway by targeting the PIP3.

Materials and Methods: A phage display library of randomized linear dodecapeptides fused to the pIII proteins of the M13 bacteriophage capsid was screened against PIP3. The dissociation constant and the half maximal inhibitory concentration of the selected peptide clones were determined by ELISA. The DNA was sequenced by the Sanger's method. The abundance of PIP3, the phosphorylation of AKT and the binding of selected peptides to the target were confirmed on ATC biopsies by immunohistochemistry (IHC).

Results: The affinity and specificity of the selected peptide clones was evaluated against PIP3 and other phospholipids. The DNA sequencing revealed 3 different peptide sequences, which present a high specificity against PIP3 and are able to block AKT binding to PIP3. The presence of PIP3 and phosphorylated AKT was validated by a high staining level in ATC cases, suggesting their overactivation. The labelling observed with synthesized peptides by IHC is comparable to PIP3 distribution, suggesting their specific binding to this biomarker.

Conclusion/Perspectives: One of the 3 selected peptides presented optimal PIP3-binding affinity and specificity. Prospectively, the present study will be consecrated to the *in vitro* and *in vivo* pharmacological characterization of the selected peptide to finally obtain a confident therapeutic agent, which may find applications in ATC and any cancer types presenting a similar biomarker configuration.