PEPTIDE PET TRACERS TARGETING C-MET FOR IMPROVED CANCER IMAGING AND THERAPY

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Aberrant hepatocyte growth factor receptor (HGFR or c-Met) expression is involved in the development and metastatic progression of several tumour types, including breast cancer, ovarian, prostate, colorectal cancer, gastric adenocarcinoma, renal, lung, thyroid, pancreatic carcinomas and melanoma[1-5]. C-Met overexpression is also associated with increasing invasiveness of cancer cells, drug resistance and poor clinical outcome[6]. All of these characteristics indicate that this protein receptor is a key player in cancer initiation and progression, and therefore knowledge of c-Met expression in real-time will be helpful in the diagnosis and in the monitoring of response to therapy.

In this context, we propose, evaluate and select small peptides PET tracers for c-Met imaging as powerful tools for the detection, monitoring and treatment of the most common and lethal cancers worldwide. These sequences should be able to effectively target c-Met and to efficiently bind gallium-68 and/or iodine-124/131 to selectively make the cells visible in the positron emission tomography (PET).

The sequences of peptides were selected from the most promising in literature and a fluorescent probe, i.e. carboxyfluorescein, was used. The synthesis of the peptides was done on a solid support and the fluorescent tag covalently bonded on a residue before the cleavage from the resin support. For the biological evaluation, breast cancer cells expressing respectively high levels of c-Met (MDA-MB-231) and low levels (ZR-75-1 and MCF-7) were employed. An initial cell viability assay (MTT test) and cell morphology analysis (actin filaments staining) were performed to evaluate any cytotoxicity effect attributable to the peptides at different concentrations (from 2.5 μM up to 100 μM). Then using the same sequences tagged with a fluorescent probe, fluorimetry and fluorescence microscopy studies were conducted to establish which one is the best performing in terms of cellular uptake, internalization and stability.

After the synthesis of the peptides, the purification and chemical characterization were made by preparative HPLC and Mass spectroscopy. Their stability was studied over time in serum and phosphate buffer at 37 °C. The biological study revealed no cytotoxic effects attributed to the peptides, and the cell viability and the cell morphology were not negatively affected. Targeting c-Met positive cells was specifically evaluated across all tested sequences. The most promising outcomes were detected with one of the studied sequences, which exhibited a statistically significant presence in c-Met positive cells after 1 hour compared to the other two sequences.

The screening in this study has enabled us to select the most promising and effective peptides, which will be conjugated with gallium-68 and/or iodine-124/131 after a proper functionalization with an appropriate chelating agent to selectively visualize the cells with PET.

Key words: *hepatocyte growth factor receptor (c-Met); positron emission tomography; cancer imaging; theranostics; peptides chemistry.*

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