Radiolabeled bombesin and gastrin analogs in cancer theranostics: Developments at NCSR "Demokritos"

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The overexpression of peptide receptors on tumors cells as opposed to their lack of expression in healthy surrounding tissues has been elegantly exploited in recent years to direct diagnostic and therapeutic radionuclides to tumor sites using peptide carriers. The advent of radiolabeled somatostatin analogs represents a first breakthrough in this venture, allowing for theranostic (diagnosis and therapy) management of patients with neuroendocrine tumors showing high levels of somatostatin subtype 2 receptor expression. The concept of theranostics in nuclear oncology has been gaining momentum and has been rapidly expanding to other cancer types, characterized by the overexpression of alternative peptide receptors. Thus, a wide range of radiolabeled peptide analogs, targeting the gastrin-releasing peptide receptor (GRPR) for patients with prostate cancer or mammary carcinoma, or the cholecystokinin subtype 2 receptor (CCK_2R) for medullary thyroid carcinoma (MTC) and lung cancer patients, are two such examples.

The Molecular Radiopharmacy team at NCSR “Demokritos” has been engaged since 1995 in the development and preclinical screening of radiolabeled peptides, “radiopeptides”, to select candidates for clinical evaluation in cancer patients. A major part of these activities have been focused on the GRPR and the CCK_2R systems with a considerable number of the corresponding bombesin (BBN) and gastrin analogs developed by coupling suitable chelators for stable binding of ^{99m}Tc and trivalent radiometals of medical interest, such as ^{111}In, $^{67/68}$Ga and ^{177}Lu. The resulting peptide radioligands have been evaluated in GRPR-positive cells (e.g. prostate PC-3 or breast T-47D cells) and CCK_2R-positive cells (e.g. AR4-2J, transfected A431-CCK_2R, or HEK293-CCK_2R cells), respectively. The shift from GRPR-radioagonists to antagonists was initiated by the introduction of ^{99m}Tc-Demobesin 1 as early as 2003 and was recently concluded with the theranostic ^{68}Ga/^{177}Lu-NeoBOMB1 pair, currently undergoing multi-center clinical evaluation in prostate, breast cancer and GIST patients. Likewise, we have recently introduced ^{99m}Tc-DGA1, a new promising CCK_2R-antagonist-based peptidomimetic radiotracer, and conducted a head-to-head preclinical comparison with the respective agonist-based ^{99m}Tc-Demogastrin 2, that was successfully tested in MTC patients previously.

Last but not least, we have directed our forces in elucidating the impact of in vivo metabolic stability of peptide radioligands from several peptide families, including the GRPR- and CCK_2R-targeting analogs, on tumor uptake and pharmacokinetics. We were able to reveal the prominent role of neprilysin, an ectoenzyme anchored in epithelial tissues of the body, in the rapid catabolism of many radiopeptides, whereas in a few cases angiotensin converting enzyme (ACE) was implicated as well. By treatment of mice with a NEP (and an ACE) inhibitor we were able to stabilize these radiopeptides in circulation and induce marked increases of their uptake in experimental tumors in mice and very recently also in patients.