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Peptide-tagged nanocarriers for targeted delivery of cytokines to the tumor vasculature

A Corti[1,4], F Curnis[1], AM Gasparri[1], M Ghitti[1], A Sacchi[1], F Sudati[1], M Fiocchi[1], A Gori[2], S Valtorta[1], MR Moresco[1], F Pastorino[3], M Ponzoni[3] and **G Musco[1]**
[1]San Raffaele Scientific Institute, Italy
[2]CNR, Milan
[3]Istituto G Gaslini, Italy
[4]Vita-Salute San Raffaele University, Italy

Statement of the Problem: Peptides containing the NGR motif have proven useful for delivering cytokines and other compounds to tumors. For example, we have previously shown that NGR peptides can be used for delivering TNF-alpha (TNF) to CD13-positive tumor vessels, either in the form of peptide-protein fusion product (called NGR-TNF, currently tested in Phase II and III clinical studies with evidence of activity), or in the form of TNF-bearing gold nanoparticles. The good results obtained with these drugs in preclinical and clinical studies highlight the usefulness and versatility of NGR peptides for the development of tumor-homing cytokines. A major problem associated with the use of NGR is that its asparagine residue has a strong propensity to undergo rapid deamidation. This reaction, converts NGR into isoDGR, causing receptor switching from CD13 to integrins, with potentially important pharmacological and toxicological implications. Thus, the development of stable CD13 ligands and nanoparticles is desirable.

Methodology: To prevent asparagine deamidation, we have chemically modified NGR peptides and investigated their CD13 binding properties. Furthermore, using conventional and chemically modified NGR peptides we have developed peptide-tagged nanodrugs, including TNF-bearing nanogold, and investigated their therapeutic properties in animal models.

Findings: Biochemical and structural studies showed that chemical modification of NGR completely prevents asparagine deamidation without impairing CD13 recognition. Studies in animal models showed that the modified peptide can be exploited for delivering radio- and fluorescent-labeled compounds, liposomal doxorubicin and TNF-bearing nanogold to tumors, with an efficiency similar to that of a conventional NGR.

Conclusion & Significance: These findings suggest that NGR can be chemically modified to obtain a stable and efficient CD13 ligand, which can be used for the development of tumor-homing gold nanoparticles. The novel peptide-tagged gold nanoparticles could be exploited as a stable platform for delivering TNF and other cytokines to tumor vasculature.

corti.angelo@hsr.it