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## Findings questioning the involvement of Sigma-1 receptor in the uptake of anisamide-decorated particles

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### Abstract

Anisamide is a small benzamide previously suggested as a tumor-targeting ligand for nanocarriers and it has been shown to enhance tumor uptake *in vitro* as well as *in vivo* when grafted on the nanoparticle surface. Anisamide has been hypothesized to interact with the Sigma-1 receptor, based on the binding of larger benzamides, which contain anisamide in their structure, to this receptor. However, the interaction between anisamide and Sigma-1 receptor has never been thoroughly studied. We developed fluorescent PEGylated particles decorated with anisamide, which were preferentially taken up *in vitro* by melanoma cells compared to macrophages. The anisamide-decorated particles were used to study their interaction with the Sigma-1 receptor. The absence of competition of Sigma-1 receptor ligands for the particle uptake was a first indication that the receptor might not be involved in the uptake process. In addition, the extent of particle uptake did not correlate with the levels of cellular expression of Sigma-1 receptor in the cell models tested. Immunostaining of the receptor on melanoma cells revealed intracellular localization, indirectly excluding the possibility of anisamide binding to the receptor when grafted on the particles. All these data question the previously suggested Sigma-1 receptor-mediated uptake of the anisamide-decorated particles, a finding which may have an impact on the use of anisamide as a targeting ligand.

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