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Improvement of pyrazolo[3,4-d]pyrimidines pharmacokinetic properties: Nanosystem approaches for drug delivery

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Pyrazolo [3, 4-d] pyrimidines are a class of compounds with a good antitumor activity against several cancer cell lines. The activity of pyrazolo[3,4-d]pyrimidines has been related to the inhibition of some TKs families, such as Abl and Src. Recently, remarkable results have been obtained in several xenograft mouse models.[2]

Despite the promising anticancer activity, these molecules showed a poor aqueous solubility. This issue could limit the future development of pyrazolo[3,4-d]pyrimidines as clinical drug candidates.

With the aim of improving solubility profile and consequently the pharmacokinetic properties of our compounds, we have explored albumin nanoparticles and stealth liposomes as possible nanocarrier systems.[1]

For this study, we have chosen four compounds (1–4), previously characterized for their activity against neuroblastoma by enzymatic, cytotoxic and *in vivo* assays.[2-4]

For each selected compound (1-4), albumin nanoparticles (AL 1-4) and stealth liposomes (LP 1-4) were prepared and characterized regarding size and ζ-potential distribution, polidispersity index, entrapment efficiency and activity against SH-SY5Y human neuroblastoma cell line. The most promising nanosystem, namely LP-2, was chosen to perform further studies: confocal microscopy, *in vitro* stability and drug release in physiological conditions, and 24 hours biodistribution test in male Sprague-Dawley rats.

Herein we demonstrated that the cytotoxic activity of 1-4 compounds against SH-SY5Y cell line is likely to be exerted by their encapsulation in liposomes, thanks to the release of the active compound in the cellular cytoplasm after the nanoparticles uptake. Importantly, the liposomal system resulted stable in physiological conditions.

Finally, the 24 hours biodistribution assay proved the beneficial properties of LP-2 (longer circulation residential time). Further preclinical *in vivo* studies will allow the determination of the full pharmacokinetic profile and the therapeutic efficacy of this novel formulation.

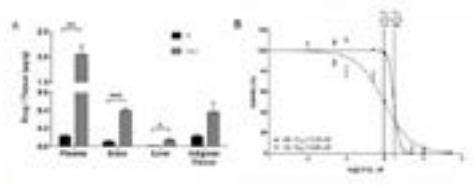

Figure 1A. Concentration of compound 2 determined in plasma, brain, liver and adipose tissue, after the administration of the free drug 2 (black) and the liposomal formulation LP-2 (grey).

Figure 1B. Viability of SH-SY5Y human NB cells evaluated at 48 and 72h after treatment with: A) Empty liposomes, B) Free compound 2 and C) LP-2.

Biography

Arianna Mancini has her expertise in drug delivery and nanomedicine in oncology. The principal field of her research is about anticancer compounds, especially pyrazolo[3,4-d]pyrimidines compounds, that represent a valid approach against several cancer types (i.e. glioblastoma, neuroblastoma). Her work covers the preparation and the characterization of pharmaceutical nanotechnologies (i.e. liposomes, albumin nanoparticles, carbon nanodots) and their *in vivo* administration and pharmacokinetic parameters evaluation. Her knowledge includes elements of biophysics and molecular imaging (magnetic resonance), as instruments for real time monitoring of gadolinium-loaded liposomal nanotechnology.

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