Title: Therapeutic potential against metastatic melanoma of a copper-based aquaporin inhibitor nanoformulated

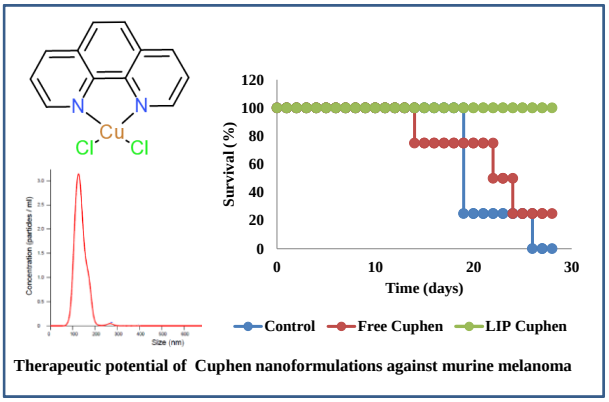
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Statement: Clinical and preclinical studies evidence the overexpression of aquaporins (AQPs) in a high number of cancers. In this sense, the development of selective AQP inhibitors represents an alternative therapeutic strategy for these pathologies. Metallodrugs of copper and gold are potential candidates to fulfill this need. However to promote a preferential targeting to tumor sites *in vivo*, the design and development of novel technologies based on nanostructured materials such as liposomes acting mainly as vectors for metallodrugs delivery represents a stimulating research area. Cuphen, a potent copper-based aquaporin inhibitor, was the selected metallodrug in the present work to be nanoformulated in liposomes.

Methodology: Cuphen was incorporated in liposomes by the dehydration-rehydration method. CuPhen liposomes were characterized in terms of mean size, polydispersion index, zeta potential and encapsulation parameters using different lipid compositions. The ability of Cuphen to induce cancer cell death was evaluated by MTS and ViaCount assays against several human and mouse cell lines (A431, MNT-1, HaCaT, B16F10 and C26). The hemolytic activity of Cuphen in free and liposomal forms using EDTA-preserved peripheral human blood from voluntary donors was carried out. *In vivo* toxicity studies were performed in healthy mice and the therapeutic effect was evaluated in a murine melanoma xenograft model.

Findings: *In vitro* studies illustrated the antiproliferative effects of Cuphen in different cancer cell lines. *In vivo* studies revealed no toxic effects after parenteral administration in healthy mice. A higher anti-cancer effect in a murine melanoma xenograft model in terms of survival rate was observed for the metallodrug nanoformulated in long circulating liposomes.

Conclusion: Cuphen liposomes are considered a very attractive nanoformulation with therapeutic potential against melanoma due to their preferential extravasation and accumulation in solid tumors.



Therapeutic potential of Cuphen nanoformulations against murine melanoma

Recent Publications

- Nave M, Castro RE, Cecília MP Rodrigues CMP, Casini A, Soveral G, Gaspar MM (2016) Nanoformulations of a potent copper-based aquaporin inhibitor with cytotoxic effect against cancer cells. Nanomedicine UK 11 (4): 1817-1830.
- Calado S, Eleutério C, Mendes E, Rocha MJ, Francisco AP, Gaspar MM (2016) Nanoformulations of a triazene analogue with specific affinity to human melanoma. J. Nanosci. Adv. Tech 1(4): 1-9.
- Gaspar MM, Calado S, Pereira J, Ferronha H, Correia I, Castro H, Tomás AM, Cruz MEM (2015) Targeted Delivery of Paromomycin in Murine Infectious Diseases Through Association to Nano Lipid Systems. Nanomedicine: NBM Nanotechnology, Biology, and Medicine 11(7): 1851-1860.
- Silva JM, Zupancic E, Vandermeulen G, Oliveira VG, Salgado A, Videira M, Gaspar MM, Graca L, Préat V, Florindo HF (2015) *In vivo* delivery of peptides and Toll-like receptor ligands by mannose-functionalized polymeric nanoparticles induces prophylactic and therapeutic anti-tumor immune responses in a melanoma model. J. Control. Release 198: 91-103.
- Gaspar MM, Radomska A, Gobbo OL, Bakowsky U, Radomski MW, Ehrhardt C (2012) Targeted Delivery of transferring-conjugated liposomes to an orthotopic model of lung cancer in nude rats. J. Aerosol Med. Pulm. Drug Delivery 25(6): 310-318.



Biography

Maria Manuela Gaspar has completed her PhD in 2005 in Pharmaceutical Technology in the University of Lisbon and in 2007/2008 has done post-doctoral studies in the University of Dublin, Trinity College. She is a researcher in the Research Institute for Medicines, iMed.ULisboa, University of Lisbon. The area of research has been focused on design, development and biological evaluation of drug delivery systems for improving the therapeutic index of incorporated molecules in infectious, inflammatory and cancer animal models. She is co-author of numerous patents, papers in peer-reviewed journals and book chapters.

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Notes/Comments