Lauroyl-gemcitabine loaded lipid nanocapsules for the treatment of metastases in mediastinal lymph nodes
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Lauroyl-gemcitabine loaded lipid nanocapsules for the treatment of metastasised medistinal lymph nodes.

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INTRODUCTION
Lymph nodes remain the leading cause of cancer-related mortality around the world (Siegel et al., CA Cancer J. Clin., 2013). Once diagnosed, non-small cell lung cancers (NSCLC) 5-year survival rate reaches globally 15% with the different therapeutic modalities such as surgery, radiotherapy and chemotherapy. For most patients, NSCLC has spread in mediastinal and supraclavicular lymph nodes (II2 disease, stage III) or in the contralateral lung, pleural cavity or beyond lung (M1 disease, stage IV) (Rung et al., J. Thorac. Oncol., 2012). In aim to protect the drug until the site of action, target the lymph nodes invaded by metastases and decrease the related systemic toxicities, nanomedicine could be a very great tool (Schoeder et al., Nat. Rev. Cancer., 2012).

Lipid nanoparticles (LNC) loaded with a lauroyl-modified gemcitabine (Gem-C12) have been developed and demonstrated the ability to form a hydrogel by nanoparticle assembly (Moyyan et al, Soft Matter, 2013). These nanocarriers could be delivered as a gel by subcutaneous (sc) route or as a suspension (after dilution) for intravenous (iv) administration. The purpose of this study is to reach passively the lymph nodes in vivo, and to evaluate the antitumor efficacy of this new system in a human NSCLC metastatic model, which mimics the spreading of metastases in mediastinum from the primary tumor implanted in the lung of mice. The tolerance (myelosuppression and hepatotoxicity) of this new treatment delivered either as a gel by sc route or as a suspension by iv route was also investigated.

LAUROYL-MODIFIED GEMCITABINE–LOADED LIPID NANO CAPSULES
Lauroyl-modified Gemcitabine (Gem-C12) was trapped at the lipid nanocapsule (LNC) surface during formulation process and hydrogel was obtained with inter LNC association.

IN VIVO BIODISTRIBUTION IN HEALTHY AND TUMOR-BEARING MICE
In vivo biodistribution of DIO-LNC in healthy nude mice, after intravenous (iv) or intraperitoneal (ip) injection of DIO-LNC in suspension (no encapsulated Gem-C12) (A and B) and subcutaneous injection (behind the ears) of DIO-Gem-C12 (C and D). Time-response of fluorescent signals of the removed live spleen and inguinal, axillary cervical and brachial lymph nodes (LM) using fluorescence images (10 minute integration time) at various times post LNC administration (1, 4, 6, 8 and 16h) (in vivo, mean ± SD).

An immediate accumulation in liver and spleen, and in all lymph nodes was observed with DIO- loaded LNC suspension intravenously delivered. DIO-Gem-C12 loaded LNC in gel form subcutaneously delivered accumulated exclusively in the lymph nodes close to the injection site and presented a very low systemic exposition.

With tumor-bearing SCID-CB17 mice, DIO-LNC were visible in the entire lung of the three mice after iv injection. On the contrary, DIO-Gem-C12 administered by sc route emitted an intense accumulation in mediastinal lymph nodes in the pictures.

IN VIVO ANTITUMOR EFFICACY AND TOLERANCE OF TREATMENTS
The Kaplan-Meier survival curves and the weight evolution of mice (n=10 per group) grafted with Me3K-3 cells after various gemcitabine treatments (total dose of 40mg/kg, equal equivalent gemcitabine hydrochloride).

Significant level (p < 0.05, log-rank test) was reached with all gemcitabine treatments in comparison to controls (treatment without drug). However, there was no significant difference between the survival rates of groups treated by gemcitabine regardless of the route of administration. The weight evolution of different groups of mice remained similar during the experiment with a short duration during the treatment period. Treatment with non-encapsulated Gemcitabine presented significant decreases (p < 0.05, Kruskal-Wallis test) of platelet count and alkaline phosphatase. No difference was measured for plasma biochemical parameters and complete blood counts when Gem-C12 was encapsulated inside LNCs, regardless of the route of administration.

CONCLUSION
The lipid nanocapsules loaded with a lipophilic derivative of gemcitabine were able to target the lymph nodes and more specifically the mediastinal lymph nodes, displaying a similar antitumor efficacy as the conventional systemic gemcitabine in the lymphogenous metastatic preclinical model with a treatment schedule of twice a week ic in comparison to three times a week iv for the standard drug. Moreover, LNC loaded with Gem-C12 and delivered iv or sc did not induce myelosuppression unlike the conventional systemic gemcitabine. This latter feature shows clearly the advantage brought by a nanostructured formulation of gemcitabine.

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REFERENCES
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