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Improving the tumor microenvironment with liposomal gemcitabine, FF-10832, enhances the effects of immune checkpoint blockade

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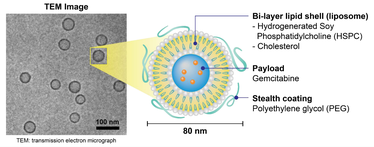
Background:

Cancer immunotherapy, including immune checkpoint blockade (ICB), is a type of cancer treatment that achieves tumor regression in various types of cancer. However, more than half of patients are resistant to ICB therapy. As the tumor microenvironment (TME) is different in each cancer patient, it is important to understand the state of immune cells in the tumor and develop strategies, including combination therapies. In the TME, immunosuppressive cells such as regulatory T cells (Treg), tumor associated macrophages (TAM) and myeloid derived suppressor cells (MDSC) work in correlation with ICB resistance. These immunosuppressive cells are promising targets for ameliorating resistance to ICB treatment and a lot of drugs targeting these cells have been developed.
We previously developed liposomal nanoparticle FF-10832, the liposomal nanoparticles encapsulated the cytotoxic anti-tumor drug, gemcitabine, preferentially distributed to the tumor and localized in the phagocytes not in the tumor cells in TME (Int J Pharm. 2022 Nov 5;627:122250., Pharm Res. 2021 Jun;38(6):1093-1106., Cancer Sci. 2019 Sep;110(9):2933-2940.). Moreover, Phase I clinical trial indicated that FF-10832 was well-tolerated in heavily pre-treated patients with advanced solid tumors (NCT03440450, Borazanci et al., ASCO 2022). Therefore, this study investigated the application of FF-10832 as an immunomodulator in combination therapy with ICB.

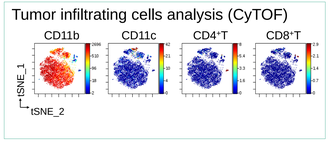
① FF-10832

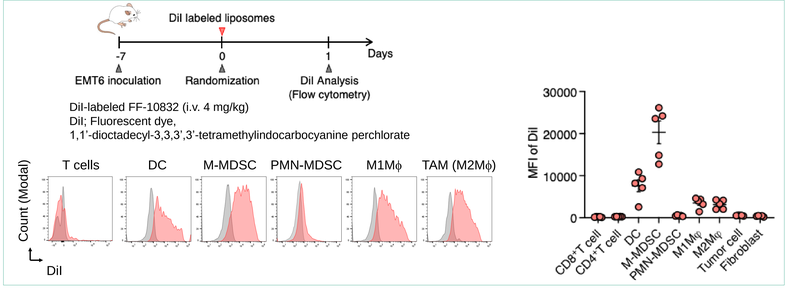


- Prolonged plasma half-life with stable encapsulation of gemcitabine
- Improved safety and efficacy via preferential tumor exposure
- Clinical investigations are ongoing with monotherapy or in combination with pembrolizumab in the US (NCT03440450 and NCT05318573)
- Encouraging clinical activity even in patients progressed on or after gemcitabine-based therapies

② FF-10832 was internalized by DC, M-MDSC, M1Mϕ and M2Mϕ in the TME of EMT6 tumor

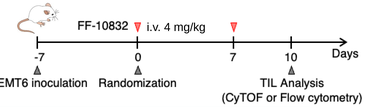
EMT6 tumor-bearing mice which has balanced infiltrating the various types of myeloid lineage cells was employed for this study.
Flow cytometry analysis showed that the DiI fluorescent-labeled FF-10832 was detected in DC, M-MDSC, M1Mϕ and M2Mϕ in the TME of EMT6 tumor.

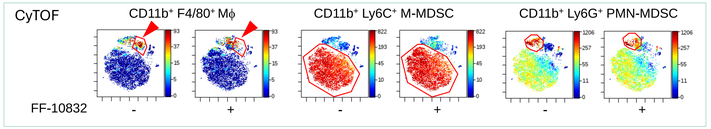


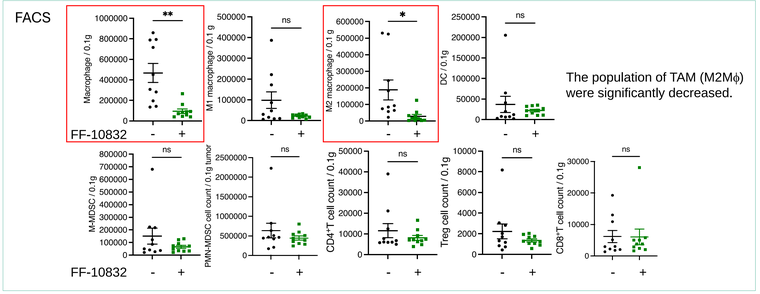


③ TAM were preferentially decreased in TME after FF-10832 administration.

To determine immune landscape after FF-10832 administration, tumor infiltrating lymphocytes (TIL) analysis was performed using CyTOF and flow cytometry.

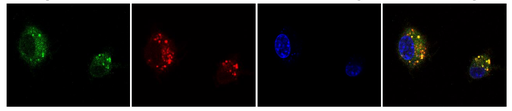






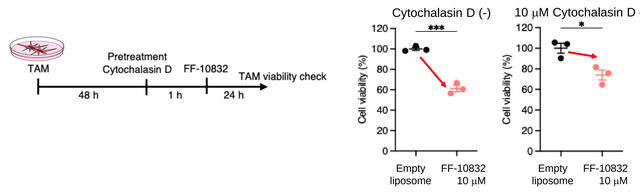
The population of TAM (M2Mϕ) were significantly decreased.

④ DiI labeled liposomes was colocalized with the Lyso Tracker, lysosome indicator in TAM.



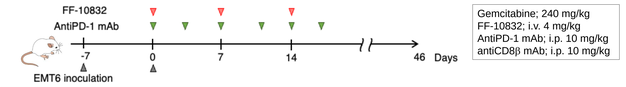
TAM Isolated from DiI-labeled FF-10832-treated EMT6 tumor

⑤ The decrease of TAM was induced not only by the effect of gemcitabine but also the engulfment of FF-10832.

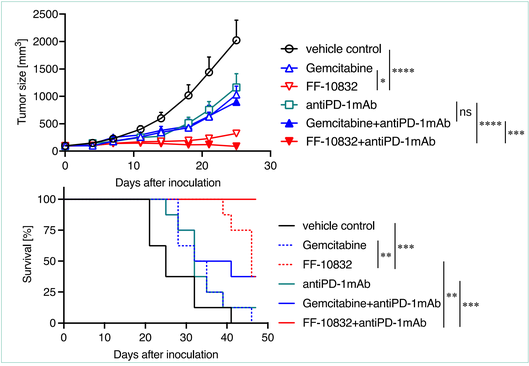


Cytochalasin D, an endocytosis inhibitor, inhibited the engulfment of liposome and decreased the cell death of TAM induced by FF-10832 treatment.

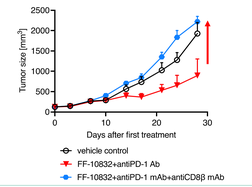
⑥ FF-10832 and anti-PD-1 mAb combination treatment showed enhanced anti-tumor efficacy.



Gemcitabine; 240 mg/kg
FF-10832; i.v. 4 mg/kg
AntiPD-1 mAb; i.p. 10 mg/kg
antiCD8β mAb; i.p. 10 mg/kg

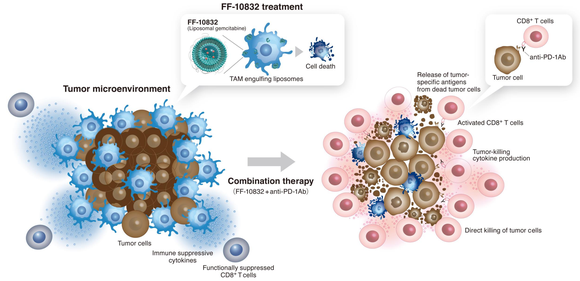


The antitumor effect of the FF-10832 and anti-PD-1mAb combination treatment was abolished by depletion of CD8+ T cells indicating that CD8+ T cells are indispensable for the antitumor efficacy of the combination treatment.



Conclusion:

FF-10832 was taken up by TAM, killing them and modulating immune landscape, which may lead to the enhanced anti-tumor effect of anti-PD-1 mAb treatment. In the future, liposomalization could be applied to other chemotherapies and molecular targeted therapies, leading to a wider choice of combination therapies. A phase 2a clinical study is ongoing with FF-10832 monotherapy or in combination with pembrolizumab for non-small cell lung cancer and urothelial cancer in the US (NCT05318573, Langer et al., ASCO 2024).



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