Biodegradable Photoluminescent Nanoparticles for Immune Cell-Mediated Melanoma Targeting and Theranostic Drug Delivery

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Statement of Purpose: Although there have been tremendous efforts in developing nanomedicine and targeting strategies for cancer management, nanocarriers still suffer from short circulating time and limited targeting efficiency. Theranostic nanomedicine has the potential to promote therapeutic outcomes in cancer therapy and diagnostics. Advances in imaging techniques such as fluorescence imaging have allowed earlier detection of cancer and real-time monitoring drug delivery process. Cell-mediated drug/nanoparticle delivery is another emerging field where cells such as immune cells can act as drug delivery carriers. In this study, by taking advantage of immune cells' innate ability to target to tumor cells, we have developed a novel immune cell-mediated drug delivery system. Macrophages, as an example, are carriers and guiders for biodegradable fluorescent nanoparticles to achieve live melanoma-specific delivery. The design is illustrated in Fig.1.

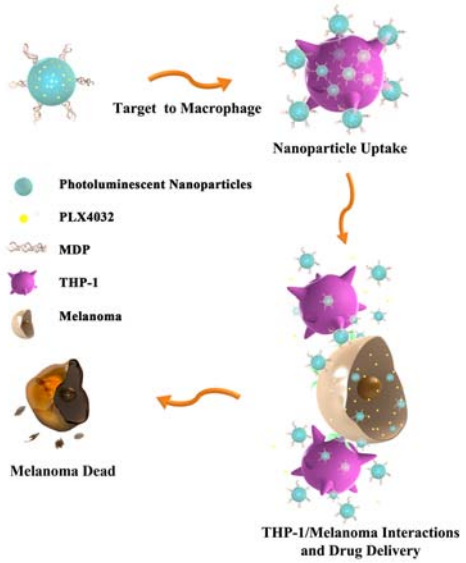

Fig. 1 Illustration of THP-1 mediated theranostic nanoparticle delivery to melanomas.

Methods: Biodegradable photoluminescent poly (lactic acid) (BPLP-PLA) was fabricated into nanoparticles by a single-emulsion method[1,2]. To increase macrophage targeting efficiency, BPLP-PLA nanoparticles were conjugated with muramyl dipeptide (MDP) via the EDC/NHS chemistry, and then characterized by DLS, and SEM. THP-1 cells, which were differentiated into macrophages, were incubated with MDP-BPLP-PLA nanoparticles on a rocker for 2 hours. The nanoparticle uptake was studied by fluorescent confocal microscopy and flow cytometry. Nanoparticles-carrying macrophages were then co-cultured with melanoma cells (WM35 and 1205Lu) in both static and dynamic conditions to examine the macrophage/melanoma binding. B-RAF mutant melanoma selective drug, PLX4032, was loaded into BPLP-PLA nanoparticles. Pharmaceutical studies were conducted by incubating PLX4032-nanoparticles-carrying macrophages with melanoma cells for various times and tested by CCK-8 assay.

Results: MDP-BPLP-PLA nanoparticles were successfully fabricated with an average size of 217.2 nm. They are stable in physiological solutions and non-toxic to THP-1 cells. The fluorescence emission of the nanoparticles can be tuned up to 700 nm. THP-1-derived macrophages were able to internalize more MDP-BPLP-PLA nanoparticles than BPLP-PLA nanoparticles. *In vitro* studies showed macrophages delivered nanoparticles to the melanoma cells in both static and dynamic conditions with shear rates from $50s^{-1}$ to $200s^{-1}$. The intrinsic photoluminescence of nanoparticles was utilized to monitor the targeting and binding process. Pharmaceutical studies indicated that MDP-BPLP-PLA-PLX4032 nanoparticles showed no significant cytotoxicity to macrophages and effectively killed both WM35 and 1205Lu melanomas in 7 days suggesting that drugs can be released from macrophages and kill tumor cells.

Conclusions: We have demonstrated that MDP-BPLP-PLA nanoparticles can selectively bind to macrophages, which enabled a live targeting to melanoma cells under both static and dynamic conditions. The released drugs from nanoparticle-bearing macrophages were also effective to kill melanoma cells. The immune-cell mediated nanoparticle drug delivery strategy enables a true live-targeting drug delivery for the treatment of cancers.

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References: 1. Xie, Z., et al., Adv. Mater., 2014. 26: p4491–4496. 2. Yang, J., et al., Proc. Nat. Acad. Sci., 2009. 106: p10086.