MODULATING THE TUMOR MICROENVIRONMENT VIA HYPOXIA ACTIVATED PRODRUG CPD100LI INDUCED CELL DEATH SYNERGISTICALLY ENHANCES ANTI-CTLA-4 IMMUNOTHERAPY

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Background The industry is diverting from chemotherapy because of side-effects, primarily immunosuppressive – but not so fast, it could hold immunostimulatory properties. CPD100, a prodrug, is activated in the hypoxic regions of the tumor microenvironment. The liposome formulation, CPD100Li, targets the prodrug to the tumor following the enhanced permeability and retention effect (EPR). Our hypothesis suggests that indiscriminate cell death induced in the hypoxic regions of solid tumors by activating a potent cytotoxin could effectively remodel the tumor microenvironment from tumor directed immunosuppression to modulated immunity under the control of one or more checkpoint molecules. Combining CPD100Li therapy with a checkpoint inhibitor could then unleash activated T cells to kill the cancer selectively.

Methods Subcutaneous CT26 murine colon carcinoma in female BALB/c mice were assessed for the effects of CPD100Li on the immunophenotype of implanted tumors compared to Vehicle by multiparametric flow cytometry. Additional treatment groups included three anti-checkpoint inhibitors mCTLA-4, mPD-L1 and mVISTA, alone and in combinations with CPD100Li to assess anti-cancer effects compared to isotype control.

Results Flow cytometry demonstrated CPD100Li decreased cell viability in the tumors compared to Vehicle and triggered an increase in the percentage of CD45+ among total live cells (figure 1). CPD100Li treatment also led to decreased absolute cell counts of Tregs, M-MDSC and M2 macrophages, compared to Vehicle but maintained the percentage of M1 macrophages (figure 2). Furthermore, the ratio of M1/M2 tumor-associated macrophages increased, suggesting that CPD100Li enhances the persistence of immune cells in the tumor (figure 3). Finally, a reduction in the expression of PD-1 exhaustion marker on CD8+ T cells was observed (figure 4). None of the checkpoint inhibitors alone demonstrated a strong response to delaying tumor growth whereas the combination of CPD100Li and CTLA-4 showed a significant synergistic response delaying tumor growth – an increase in time to progression of >200%, and a >60% incidence of complete tumor regressions with 25% remaining as tumor-free survivors at the end of the study (figure 5).

Conclusions Taken together, these data provide evidence that CPD100 inhibits CT26 tumor growth by attenuating T cell exhaustion, possibly by a mechanism that promotes M1 macrophage activity. Feasibly, that CPD100Li induces changes in the tumor microenvironment that can convert ‘cold’ tumors into ‘hot’, promoting a strong anti-tumor response in combination with CTLA-4. This study demonstrates a novel and effective combination strategy for cancer immunotherapy, making it a potent candidate for cancer therapy in near future.

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