ONM-400, A NOVEL APPROACH FOR INTERLEUKIN-2 THERAPY USING A PH-ACTIVATED NANOPARTICLE TARGETING METABOLIC ACIDOSIS IN SOLID CANCERS

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Background Interleukin-2 (IL-2) is a potent immunotherapy for treatment of metastatic melanoma and renal cell cancers. However, the clinical application has been hindered by immunosuppressive stimulation and unfavorable pharmacological properties that can induce life-threatening toxicities. Although strategies including ‘no-alpha’ muteins have been developed to provide target specificity at the molecular level, little has been done to improve tumor specificity and accumulation at tissue level. We developed ONM-400, a novel IL-2 encapsulating pH-activated nanoparticle that targets metabolic acidosis of cancer to improve the therapeutic index of IL-2 therapy. During circulation, IL-2 activity is sequestered within the nanoparticles. Upon entering the tumor microenvironment, IL-2 release is precisely and instantly triggered by acidic tumor pH, resulting in the selective deposition of active IL-2 at the site of disease.

Methods A tumor-agnostic pH-activated nanoparticle with pH responsiveness similar to ONM-100, a cancer imaging agent currently in a Phase 2 clinical trial, has been developed for cytokine delivery. IL-2 was encapsulated within the nanoparticle using a proprietary method to produce ONM-400 and the physical properties were characterized. Activity of IL-2 in ONM-400 was evaluated using a bioluminescent cell-based assay for both its encapsulated (inactive) state and activated format. Tumor accumulation and biodistribution following intravenous injection (I.V.) of ONM-400 were evaluated in mice bearing head and neck tumors using fluorescent imaging. In vivo antitumor efficacy of ONM-400 after I.V. injection was studied in MC38 colon cancer-bearing mice and compared with unencapsulated IL-2 at the same dose.

Results Quantitative analysis shows high encapsulation efficiency and drug loading density of IL-2 in ONM-400. At neutral pH, IL-2 bioactivity is effectively sequestered in ONM-400 through encapsulation which avoids IL-2 toxicity in normal tissue. Upon acid-triggered release, IL-2 bioactivity is rescued without compromise compared to unencapsulated IL-2 control. Significantly higher tumor accumulation and lower renal elimination were observed with ONM-400 in biodistribution studies as compared to free IL-2 control suggesting an alteration of pharmacokinetics of IL-2 after encapsulation. ONM-400 induced strong antitumor efficacy as a monotherapy in MC38 colon cancer-bearing mice (figure 1). After ONM-400 treatment 60% of the animals showed complete tumor regression and remained tumor free 60 days. Following a secondary MC38 challenge, 5/6 animals resisted tumor growth.

Conclusions Tumor acidosis-driven accumulation and activation of ONM-400 provide a high local concentration of IL-2 within tumors resulting in strong antitumor response as a monotherapy. Tumor metabolic targeting pH-activatable nanoparticles provides a novel strategy to deliver immunomodulators for cancer treatment.

Ethics Approval All animal experiments were reviewed and approved, and performed in accordance with, by Pennsylvania State College of Medicine Institutional Animal Care and Use Committee under Animal Protocol Number: 47682.

REFERENCES

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REGRESSION BY HETIL-15 MONOTHERAPY IN DIFFERENT MOUSE BREAST CANCER MODELS CORRELATES WITH INTRATUMORAL INFILTRATION OF A NOVEL POPULATION OF DENDRITIC CELLS

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Background IL-15 is a cytokine which stimulates the proliferation and cytotoxic function of CD8+ T and NK cells. We have produced and applied the native heterodimeric IL-15 (hetIL-15) on several preclinical models, which have supported the anti-tumor activity of hetIL-15. Based on these results, hetIL-15 has advanced to clinical trials. The objectives of this study were to explore how hetIL-15 shapes the tumor microenvironment and to characterize the interactions between tumor-infiltrating lymphoid and myeloid cells.

Methods We studied the efficacy of locoregional administration of heterodimeric IL-15 (hetIL-15) in two different orthotopic triple-negative breast cancer (TNBC) mouse models, syngeneic for C57BL/6 and Balb/c, respectively. The effects of hetIL-15 on immune cells were analyzed by flow cytometry, immunohistochemistry (IHC) and gene expression profiling. The profile of the novel infiltrated dendritic cell populations was further explored by bulk and single cell RNAseq.

Results hetIL-15 resulted in tumor eradication in 40% of treated mice and reduction of metastasis. Subsequent challenges with the same cell line failed to generate tumor

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Anti-tumor efficacy of ONM-400

ONM-400 induces strong antitumor response in MC38 tumor bearing mice as a monotherapy. Mice received I.V. injections of PBS, 50 ug of rhIL-2 or ONM-400 with 50 ug of encapsulated rhIL-2 on Day 0, 2, 4 and 6. A-C, individual tumor growth curve of animals treated with PBS (A), rhIL-2 (B) or ONM-400 (C); CR = complete response. D. Kaplan-Meier curves of animals after the treatment. Statistical significance was analyzed by Log-rank test. **P<0.01