ENCAPSULATION OF IL-12 WITH AN ULTRA PH-SENSITIVE TUMOR DELIVERY PLATFORM IMPROVES TOLERABILITY AND PROMOTES ANTITUMOR RESPONSE IN A PRECLINICAL MODEL

Qingtai Su, Stephen Gutowski, Austin Burcham, Irina Kalashnikova, Bhargavi Allu, Zirong Chen, Kartik Krishnan, Ruolan Han, Jason B Miller*, Tian Zhao.

1OncoNano Medicine, Inc., Southlake, TX, USA; 2OncoNano Medicine, Prosper, TX, USA; 3OncoNano Medicine Inc., Allen, TX, USA

Background Interleukin-12 is a potent proinflammatory cytokine that proliferates and activates T cells, NK cells and differentiates Th1 cells, but its clinical translation has been hindered by toxicities such as cytokine release syndrome. Strategies to reduce systemic IL-12 toxicity include activity-attenuating mutations, protease-cleavable masking, and local administration but these efforts often result in lower potency or low tumor specificity. To minimize the severe toxicities while maintaining potency for a potential IL-12 treatment modality, we have developed ON-BOARD, an ultra-pH sensitive nanoparticle tumor delivery platform for masked and targeted delivery of payloads to the acidic tumor microenvironment. Herein we report encapsulation and delivery of IL-12 using ON-BOARD in immunocompetent mice, demonstrating tolerability, potent anti-tumor efficacy in mice bearing MC38 colorectal tumors, and potential for clinical translation.

Methods IL-12Fc fusion proteins were formulated in ON-BOARD nanoparticles. The properties and stability profiles were characterized. In vitro pH-specific bioactivity was determined in cell-based reporter assays and IFNγ induction assays. The release of ON-BOARD formulated IL-12 was compared to a protease-cleavable IL-12 prodrug. Efficacy and tolerability of ON-BOARD encapsulated mouse IL-12 were studied in vivo after intravenous injection. Pharmacodynamic response was evaluated by measuring systemic plasma cytokine levels and immunophenotyping the tumor microenvironment. Toxicity was measured by body weight loss and clinical chemistry for liver and kidney functions. Anti-tumor efficacy of ON-BOARD/IL-12 formulations was performed in MC38 tumor-bearing mice with an unencapsulated IL-12 control.

Results ON-BOARD/IL-12 formulations showed high encapsulation efficiency (>85%) in uniformly distributed particles (Dh<50nm) for both human and mouse IL-12Fc and showed 6-month storage stability. pH-specific release was confirmed in vitro with >100-fold activation window between the acid-activated and intact formulations by a HEK IL-12 reporter assay and an IFNγ induction assay. ON-BOARD showed complete recovery of IL-12 bioactivity in <40 minutes after acid-activation compared to MMP demasked prodrug which required overnight incubation with compromised potency. In vivo, ON-BOARD/IL-12 formulations demonstrated significantly improved tolerability compared to unencapsulated IL-12, with reduced body weight loss, decreased liver toxicity, and reduced systemic cytokines including >1,000-fold reduction in plasma IFNγ level. ON-BOARD/IL-12 treatment induced immune remodeling of the tumor with increased IFNγ and GzmB positive CD8+ T and NK cells and demonstrated strong anti-tumor efficacy in MC38 tumor-bearing animals with >95% TGI and complete responders.

Conclusions The ON-BOARD platform demonstrated potential for masking toxicity and facilitating tumor-specific delivery of IL-12 for anti-cancer therapy.

Ethics Approval Animal studies reported in this abstract were conducted in accordance with protocol number 47682, Syngeneic tumor models utilized for the development of new human anti-cancer therapies’ which was approved by the Pennsylvania State College of Medicine Institutional Animal Care and Use Committee.

http://dx.doi.org/10.1136/jitc-2023-SITC2023.1147-B