ACTM-838, a Novel Immunotherapy that Enriches in Solid Tumors after IV Dosing and Comprehensively Reverses the Immunosuppressive TME to Promote Durable Anti-tumor Immunity

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Background

- ACTM-838 is a genetically engineered bacterial immunotherapy that encodes an engineered IL-15 (IL-15pex) and a constitutively active STING variant (eSTING). The ACTM-838 strain is a highly modified, attenuated S. Typhimurium that lacks several major inflammatory and immunomodulatory components on the surface of the microbe and is designed to naturally and specifically enrich in the tumor microenvironment (TME) via (1) obligate nutrient dependency for adenylate kinase (AK) for extracellular proliferation and (2) intracellular uptake by phagocytic APCs for payload delivery, both of which are highly elevated in the immunosuppressive TME.

- Human macrophage uptake of labeled ACTM-838 led to acidic lysosomes and nuclear delivery with a concomitant increase in expression of encoded IL-15pex and eSTING payloads such as IL-15, IFNγ reporter activity and IFNγ secretion, respectively (Udyavar et al. 2022).

- ACTM-838 treated tumors exhibited a significant increase in human IL-15pex protein payload. ACTM-838 as a single agent induced profound immune reprogramming and remodeling of the tumor microenvironment through increased infiltration and activation of myeloid, NK, and cytotoxic CD8 T cells, MHC class I and II, antigen presentation activity as well as increased CD8+ PD-1+ Lag3+ exhausted CD8 T cells, and a reconstituted stromal signature, as assessed by bulk RNAscope, and confirmed by flow cytometry (Udyavar et al. 2022).

- Synergic anti-tumor activity was observed in multiple tumor models when ACTM-838 was dosed in combination with anti-PD1, safely inducing complete durable memory responses (Udyavar et al. 2022).

Biodistribution, Tumor-Specific Payload Delivery and Cellular Specificity of ACTM-838

- Figure 1. ACTM-838 biodistribution, cellular specificity and tumor-specific payload delivery post single IV dose in EMT6 tumor-bearing Balb/c mice. (A) ACTM-838 biodistribution on Day 3 post-treatment (D3 PT). (B) ACTM-838 payload delivery to other healthy tissues. (C) Human IL-15pex and IFNγ (eSTING target) are detected only in tumor and not in other healthy tissues at D7 post-treatment, with an increase in tumor density at D15 post-treatment. (D) ACTM-838 (macrophages, neutrophils, DCs and macrophages) internalized ACTM-838 in TME and neutrophils in spleen, suggesting cell type uptake specifically.

ACTM-838 Exhibits Durable Anti-tumor Immunity in Syngeneic Breast and Colon Tumor Models

- Figure 2. ACTM-838 induces a dose-dependent durable memory anti-tumor response in syngeneic tumor models. (A) EMT6 treated cancer and (B, C) MCF7 colon cancer cells were implanted orthotopically in 6-8 week old female BALB/c or C57BL/6 mice, respectively. Mice received a single IV dose of ACTM-838 when tumors reached 50-100mm3 volume. ACTM-838 induced a dose-dependent anti-tumor effect both tumor models. (C-D) ACTM-838 cured mice relapsed with 1-65 tumor cells 30 days after initial tumor remission exhibited durable anti-tumor immunity with the dosing of ACTM-838 in both tumor models.

ACTM-838 Reprograms TME in MC38 Colon Tumor Model

- ACTM-838 Reprograms TME in MMTV-PyMT Model

- Figure 3. ACTM-838 exhibited anti-tumor responses in MMTV-PyMT breast cancer GEMM. A single IV dose (8e7 CFU) of ACTM-838 or PBS was given to 8 week old female MMTV-PyMT mice. (A) The total number of tumors per animal. (B) Cumulative tumor volume and (C) lung metastasis were significantly reduced in response to ACTM-838 day 35 post-treatment.

ACTM-838 Lowers CD73 Expression on Immune Cells in TME

- Figure 7. Adenosine generating enzyme CD73 decreased on myeloid cells and T cells across multiple tumor models with ACTM-838 treatment. CD73, an enzyme that generates adenosine from AMP, expressed on immune cells, is strongly associated with immunosuppression. ACTM-838 use adenosine pathway metabolites for its extracellular payload in the TME, and thereby reduces proportions of (A) CD73 myeloid and (B) CD73 T cells across EMT6, MC38 and MMTV-PyMT tumor models.

Summary

- ACTM-838 shows tumor-specific enrichment where phagocytic APCs take up ACTM-838 and deliver and express IL-15pex and eSTING payloads in the TME.

- ACTM-838 internalization and payload delivery significantly reprograms the immunosuppressive microenvironment leading to the increase in antigen presentation (MHCs), costimulatory marker CD80 and reduced phagocytic marker CD206 in monocytes and macrophages.

- ACTM-838 activated APCs present tumor antigens to T cells leading to an increase in activated CD8+ T cells and a decrease in exhausted CD8 T cells and Tregs, resulting in durable anti-tumor efficacy in multiple syngeneic and GEMM tumor models.