RESTORING IMMUNE FITNESS WITH ORAL SALMONELLA TYPHI ZH9 TO UNLOCK THE POTENTIAL OF CANCER IMMUNOTHERAPIES
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Background Most patients still fail to benefit from immunotherapy approaches and innovative orthogonal strategies targeting the myeloid compartment may unlock deep and durable responses to approved therapies.

We recently demonstrated the preclinical safety and efficacy of live-attenuated Salmonella Typhi ZH9 as a novel, locally delivered microbial immunotherapy for bladder cancer. In those studies, we observed that systemic priming with ZH9 prior to local therapy improved tumour control and enhanced recruitment of innate and adaptive immune cells to the bladder. We hypothesized, in light of the emerging concept of trained immunity, that this immune priming effect in bladder cancer results from Salmonella-induced systemic reprogramming of myeloid cells leading to alleviation of immune suppression within the tumour microenvironment. Here we investigate the potential of oral Salmonella treatment to restore immune fitness in patients through myeloid reprogramming, leading to enhanced efficacy of existing cancer therapies.

Methods The effects of oral Salmonella on myeloid cells were examined by phenotyping splenic myeloid cells using flow cytometry. The impact on tissue immunosurveillance was measured in syngeneic subcutaneous (MC38) and experimental metastasis (4T1) models. Potential synergy with established therapies was examined utilizing an in vitro co-culture system with cancer patient samples and by demonstrating treatment efficacy in syngeneic murine models, in combination with anti-PD-L1 or gemcitabine and cyclophosphamide chemotherapies.

Results Oral Salmonella treatment of mice induced long-term phenotypic and functional myeloid changes, including upregulation of co-stimulatory and MHC molecules on dendritic cells, monocytes and macrophages, and increased responsiveness of CD11c+ splenocytes to secondary stimuli, suggesting Salmonella can reprogramme systemic myeloid cells. As a monotherapy, oral Salmonella enhanced tissue immunosurveillance, resulting in delayed tumour growth in subcutaneous and experimental metastasis models, indicating that this trained myeloid phenotype may translate to changes in the myeloid compartment of the TME. Additionally, immune training by Salmonella complemented the effects of other cancer therapies. In vitro, Salmonella-trained human monocytes from patients overcame a cytokine-induced suppressive M2 phenotype, synergizing with anti-PD-L1 to drive T-cell proliferation. In vivo, oral Salmonella synergized with anti-PD-L1 to suppress the growth of checkpoint-refractory subcutaneous MC38 tumours and with chemotherapy to reduce tumour growth and metastasis.

Conclusions These exciting findings open new avenues for combination therapy, leveraging reprogramming of myeloid cells to improve immune fitness in cancer patients and broaden the reach of current treatments. As immunotherapy moves into earlier therapeutic settings, Salmonella-mediated immune training holds significant potential for enhancing cancer interception strategies and warrants clinical investigation.

Ethics Approval Studies were conducted with approval from United Kingdom Home Office (Project License PP8366809); Labcorp Drug Development PCO’s Animal Care and Use Committee; and Health Research Authority, London - Stanmore Research Ethics Committee (19/LO/0179; 257743).

http://dx.doi.org/10.1136/jitc-2023-SITC2023.1088