1227 ORAL INULIN GEL FORMULATION MODULATES THE GUT MICROBIOME AND IMPROVES THE SAFETY AND EFFICACY OF IMMUNE CHECKPOINT BLOCKERS

[1]Jin Xu, [1]Kai Han, [2]Xuehui Huang, [1]James J Moon*. [1]*University of Michigan, Ann Arbor, MI, USA*; [2]*College of Pharmacy, University of Michigan, Ann Arbor, Ann Arbor, MI, USA*

Background The dysregulated gut microbiota found in cancer patients is emerging as the new therapeutic target. Here, we have engineered inulin – a widely consumed dietary fiber – into an oral gel formulation to modulate the gut microbiota and the host immune responses. We show that inulin gel improves the safety and anti-tumor efficacy of immune checkpoint blockers (ICBs) in various murine tumor models.

Methods We have optimized the scale-up production of inulin gel. In tumor-bearing mice, inulin gel was orally administered starting day 7 after tumor inoculation, while anti-PD-1 was intraperitoneally injected from day 10. The gut microbiota profile in fecal samples was examined by 16s rRNA gene sequencing, and the metabolites in feces and serum were tested by ion- or liquid-chromatography. Tumor-infiltrating lymphocytes were measured via flow cytometry. In addition, inulin gel was tested on the mouse ICBs-associated colitis model, where 3% dextran sulphate sodium (DSS) was supplied in the drinking water.

Results After oral gavage in mice, inulin gel formulation was retained longer in the colon, thus increasing the cumulative inulin exposure and fermentation in the colon. Consequently, inulin gel increased the frequencies of *Akkermensia* as well as other commensal microbes known to modulate the systemic and colonic immune responses. Oral administration of inulin gel markedly augmented the antitumor efficacy of anti-PD-1 and anti-CTLA-4 ICBs in multiple tumor models, including CT26 colon carcinoma, B16F10 melanoma, and DSS-accelerated colon tumour model in *CDX2-cre NLS-APC*fl/fl mice. Notably, colitis is one of the most frequently observed immune-related adverse events (irAEs) associated with ICB therapy in the clinic. Our results showed that oral administration of inulin gel ameliorated DSS-induced, ICBs-exacerbated colitis, suggesting that inulin gel can also improve the safety profiles of ICB therapy. Metabolomics analysis revealed that inulin gel plus anti-PD-1 increased the concentrations of short-chain-fatty-acids, which promoted the differentiation of stem-like $Tcf1^{+}PD\text{-}1^{+}CD8^{+}$ T cells, conferring long-lasting protection against tumor re-growth. Meanwhile, inulin gel plus anti-PD-1 decreased the concentrations of ATP and L-Phenylalanine that could exacerbate colitis. Toward the goal of initiating a human clinical study, we have optimized the scale-up manufacturing of inulin gel.

Conclusions Orally administered inulin gel formulation normalizes the dysregulated gut microbiome, improves the host immune responses, and decreases the ICB-associated colitis. Based on this work, we are initiating a Phase I study to examine the impact of inulin gel consumption in healthy volunteers.

Acknowledgements This work was supported by NIH (R01AI127070, R01CA210273, U01CA210152, R01DK108901, R01DE026728, R01DE030691, R01DE031951) and the University of Michigan Rogel Cancer Center Support Grant (P30CA46592).

Ethics Approval The University of Michigan, Ann Arbor is an AAALAC international accredited institution, and all work conducted on animals was in accordance with and approved by the Institutional Animal Care and Use Committee (IACUC).

http://dx.doi.org/10.1136/jitc-2023-SITC2023.1227