A small molecule selective integrin α4β7 inhibitor demonstrates efficacy in a chronic model of inflammatory bowel disease

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BACKGROUND

- The integrin α4β7 regulates the recruitment of T cells to intestinal mucosa through binding to mucosal addressin cell adhesion molecule (MAdCAM)-1.
- Disruption of this interaction has been clinically validated for the treatment of inflammatory bowel diseases (IBD) by the anti-α4β7 antibody vedolizumab.
- Using potent and selective α4β7 small molecule inhibitors (SMi) including the clinical compound MORF-057, our oral α4β7 antagonist in Phase 2 for ulcerative colitis (UC), we have previously shown their robust impact on B and T lymphocyte trafficking to the gut of healthy rodents including receptor occupancy (RO) and gut homing model[1], Peyer's patches decellularity[2], and exposure-driven RO and circulating $\beta7^{high}$ T memory cells biomarker increase in non-human primates[3].
- In healthy volunteer phase 1 clinical studies, MORF-057 demonstrated a favorable PK profile, safety, target engagement, and a clear PK/PD leading to increase in peripheral $\beta7^{+}$ T memory and B switched memory lymphocyte subsets as biomarkers[4, 5, 6].
- The current study aimed to elucidate the preclinical efficacy of MT-103, a highly potent and selective α4β7 SMi in the clinically-relevant $CD4^{+}CD45RB^{hi}$ T cell transfer (TCT) colitis mouse model that was initially used to validate α4β7 targeting during the development of vedolizumab[7].

METHODS

$CD4^{+}CD45RB^{hi}$ T cell transfer (TCT) colitis model

Female RAG2 KO mice (n=10-15 except for naïve group where n=5) were administered either:

1) Vehicle (50% DMSO in normal saline), or α4β7 SMi, MT-103, via subcutaneously implanted osmotic minipumps (continuous flow; swapped at 4 weeks) across 3 dose cohorts (3, 10, or 30 mg/ml) from weeks -1 to 7, or
2) Anti-IL12p40 mAb (25 mg/kg, weekly/QW, intraperitoneally/i.p., weeks 0-7), or
3) Anti-α4β7 mAb (DATK32 clone - mouse surrogate of vedolizumab, 30 mg/kg, Q3D, i.p., weeks 0-7), or Vehicle (PBS, Q3D, i.p., weeks 0-7).

$CD4^{+}CD45RB^{hi}$ T cell adoptive transfer was performed on week 0 (day 0) and colitis development was evaluated as outlined below.

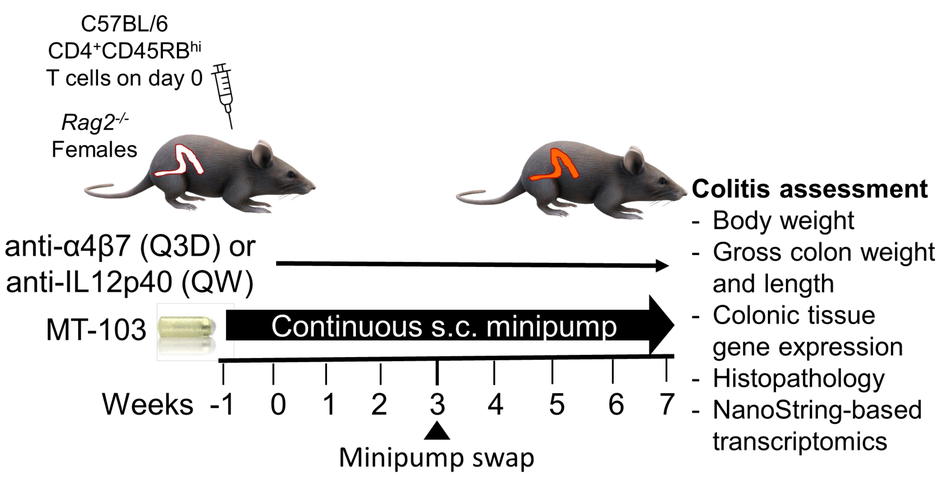

Figure 1: *Study design using mouse $CD4^{+}$ T cell transfer colitis model.*

RESULTS

α4β7 SMi MT-103 robustly improves macroscopic colon readouts in TCT colitis

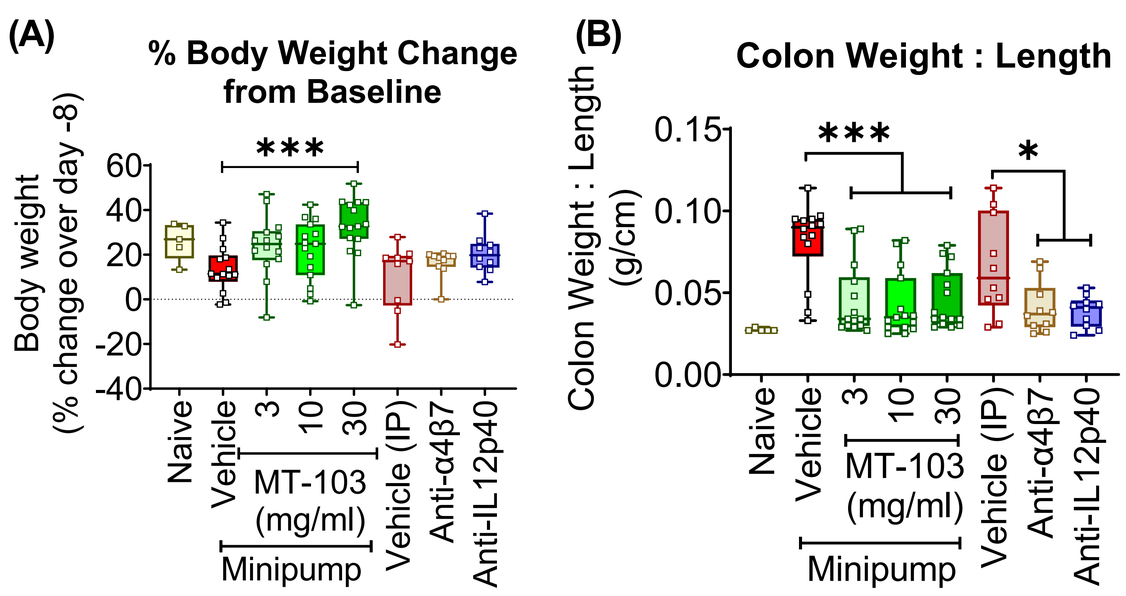

Figure 2: ***(A)*** *% body weight change on day 49 relative to pre-minipump surgery day (day -8), post $CD4^{+}CD45RB^{hi}$ T cell adoptive transfer. ***p<0.001 compared to vehicle (minipump) group; 1-way ANOVA with Tukey's Multiple Comparisons Tests.* ***(B)*** *Gross colon weight/length ratios at necropsy. *p<0.05, ***p<0.001, relative to vehicle groups as shown; Mann-Whitney test.* ***(C)*** *Plasma PK of MT-103 on day 49 showing linear relationship between dosing cohorts.*

α4β7 blockade ameliorates histopathology of TCT colitis

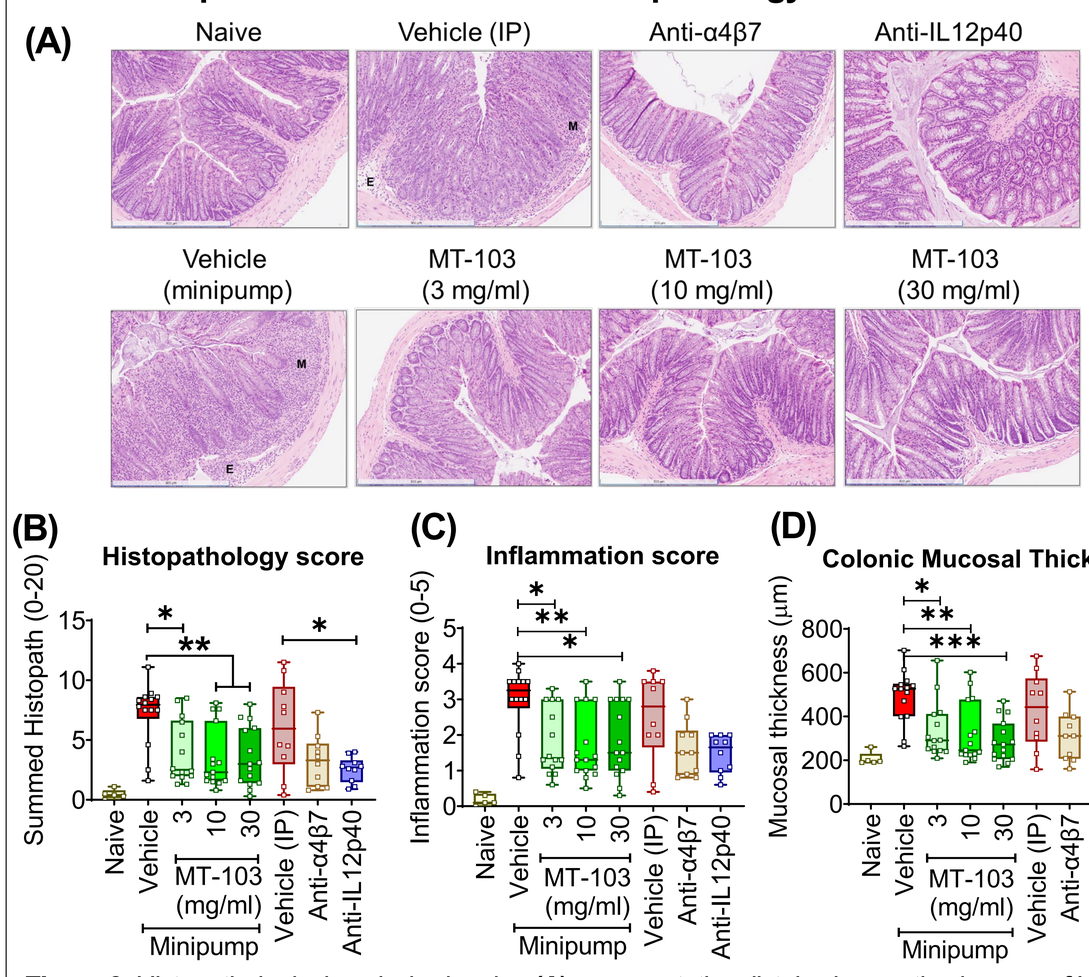

Figure 3. *Histopathological analysis showing* ***(A)*** *representative distal colon section images of H&E staining (scale 500μm). E, edema, M, most severely affected mucosa. Graphical summary of pooled proximal and distal colon scores of* ***(B)*** *histopathology (range 0-20) resulting from the sum of inflammation score* ***(C)****, gland loss, erosion, and hyperplasia (0-5 each criteria); and* ***(D)*** *colonic mucosal thickness (μm). *p<0.05, **p <0.01, ***p <0.001; One-way ANOVA with Tukey's Multiple Comparisons Test.*

α4β7 inhibition reveals distinct molecular signatures associated with colitis amelioration

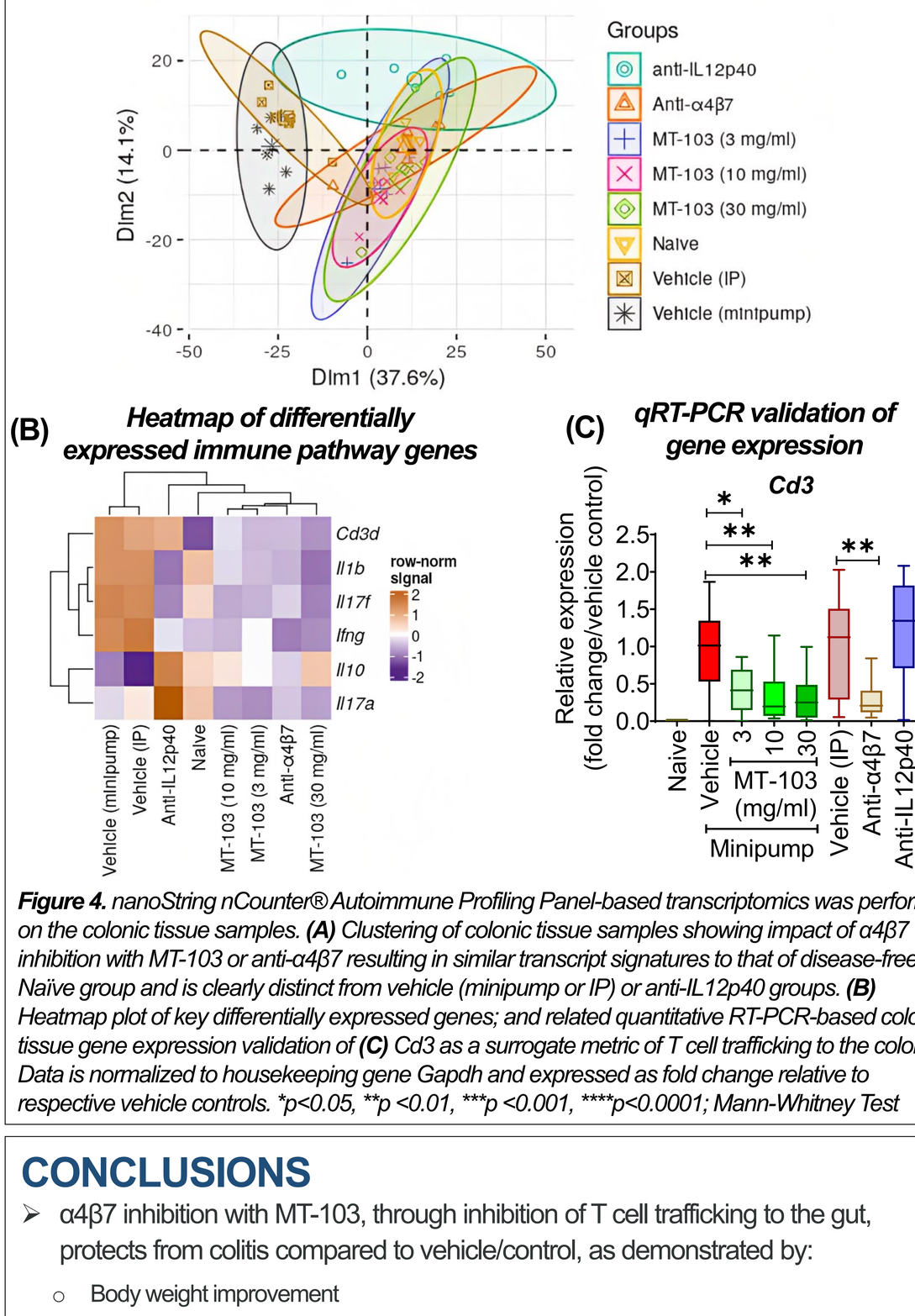

Figure 4. *nanoString nCounter® Autoimmune Profiling Panel-based transcriptomics was performed on the colonic tissue samples.* ***(A)*** *Clustering of colonic tissue samples showing impact of α4β7 inhibition with MT-103 or anti-α4β7 resulting in similar transcript signatures to that of disease-free Naïve group and is clearly distinct from vehicle (minipump or IP) or anti-IL12p40 groups.* ***(B)*** *Heatmap plot of key differentially expressed genes; and related quantitative RT-PCR-based colonic tissue gene expression validation of* ***(C)*** *Cd3 as a surrogate metric of T cell trafficking to the colon. Data is normalized to housekeeping gene Gapdh and expressed as fold change relative to respective vehicle controls. *p<0.05, **p <0.01, ***p <0.001, ****p<0.0001; Mann-Whitney Test*

CONCLUSIONS

- α4β7 inhibition with MT-103, through inhibition of T cell trafficking to the gut, protects from colitis compared to vehicle/control, as demonstrated by:
  - Body weight improvement
  - Decrease in terminal colon weight/length ratios
  - Reduction in colonic gene expression signatures for T cells (*Cd3*) and inflammatory effector cytokines (*Ifng, Il1b, Il17a*), and reciprocal increase in anti-inflammatory *Il10*
  - Histopathological resolution of intestinal inflammation, and improved mucosal healing
- Efficacious small molecule inhibition of α4β7 in TCT colitis model mechanistically mirrors blockade of colitis by an α4β7-specific antibody.
- These proof-of-concept data validate the mechanism of action of Morphic Therapeutic's small molecule inhibitors of the α4β7 integrin.

Conflict of Interest Statement

All authors are employed by Morphic Therapeutic for the duration of the study. A.S.R. is a past employee of Morphic Therapeutic.

References: *[1]Redhu et al, AAI 2021; [2]Redhu et al, DDW 2022; [3]Wong et al, ECCO 2022; [4]Ray et al, ECCO 2021; [5]Hussain et al, UEG 2022; [6]Chavan et al, ACG 2022; [7]Picarella et al, J Immunol 1997.*