SZN-1326, a Wnt Signal Activator, is more Efficacious than Cyclosporine A in an Acute DSS Model

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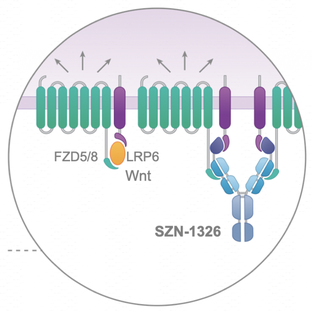
Introduction

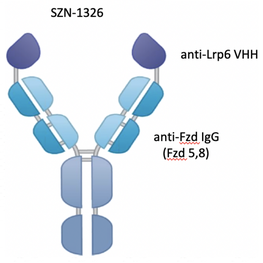
Current Inflammatory bowel disease (IBD) treatments focus on inhibition of excessive inflammation, and clinical remission rates have reached a plateau. There is a clear unmet need for agents that directly repair and regenerate the intestinal epithelial barrier as mucosal healing has been associated with reduced hospitalizations and long-term remission.

Wnt/β-catenin signaling promotes intestinal stem cell renewal, is crucial for intestinal epithelial homeostasis and regeneration, and has been shown to be disrupted in IBD. Fzd5, a Wnt receptor, is highly expressed in intestinal epithelium.

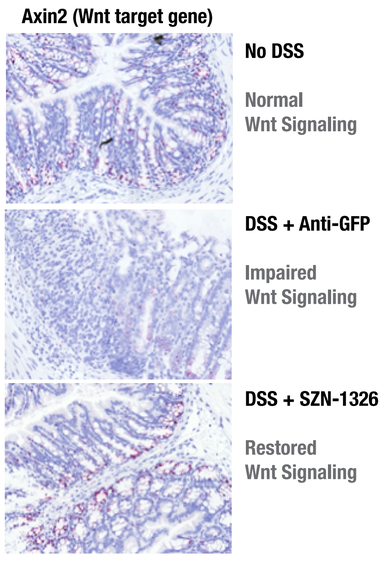
We have engineered a FZD5,8 and LRP6 bi-specific effectorless IgG1 antibody, SZN-1326, which potently induced Wnt signaling in a Super Top Flash (STF) Luciferase reporter assay, stimulated intestinal organoid growth, increased Wnt target gene Axin2 expression in the colon tissue and ameliorated Dextran Sulfate Sodium (DSS)-induced colitis in mice.

Selective Binding Profile





Restores Wnt Signaling in Damaged Intestinal Epithelium



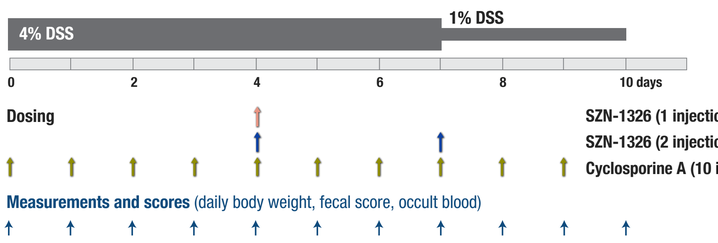
The objective of the current study was to compare the efficacy of SZN-1326 to Cyclosporine A, which has been shown to have activity in an acute DSS-induced colitis mouse model.

Methods

To induce acute colitis, 7- to 8-week-old female C57BL/6 mice were given drinking water containing 4.0% (w/v) DSS for 7 days followed by 1.0% DSS for 3 days.

Groups of mice were treated either with an isotype control antibody (anti-GFP), one intraperitoneal (IP) injection of R2M13-26 (parental version of SZN-1326) at 10 mg/kg, one IP injection of SZN-1326 at 2, 6, 20 mg/kg on day 4 or two injections of SZN-1326 at 1, 3, 10 mg/kg on days 4 and 7, or treated daily with Cyclosporine A by oral gavage at 80 mg/kg on days 0–9, and the mice were taken down on day 10.

Study Design



n	DSS	Dose (mpk)	Treatment	Injections
6	0%		Vehicle	2 Injections at Day 4, 7
10	4%	10	Anti-GFP	2 Injections at Day 4, 7
10	4%	10	R2M13-26	2 Injections at Day 4, 7
10	4%	80	Cyclosporine A	10 Injections at Days 0–9
10	4%	2	SZN-1326	1 Injection at Day 4
10	4%	6	SZN-1326	1 Injection at Day 4
10	4%	20	SZN-1326	1 Injection at Day 4
10	4%	1	SZN-1326	2 Injections at Day 4, 7
10	4%	3	SZN-1326	2 Injections at Day 4, 7
10	4%	10	SZN-1326	2 Injections at Day 4, 7

References

Chen et al. Development of potent, selective surrogate WNT molecules and their application in defining frizzled requirements. Cell Chem Biol, 27:1-12 (2020)

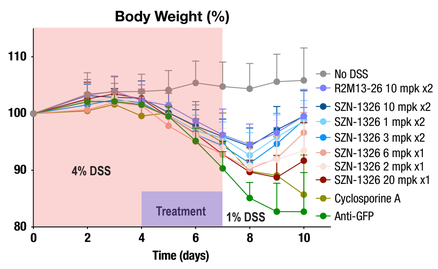
Fowler et al. Development of selective bispecific Wnt mimetics for bone loss and repair. Nat Commun, 31;12(1):3247 (2021)

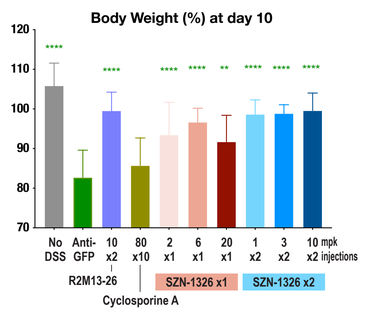
Acknowledgements

We thank Vincent Meador for histological analysis on colon H&E slides.

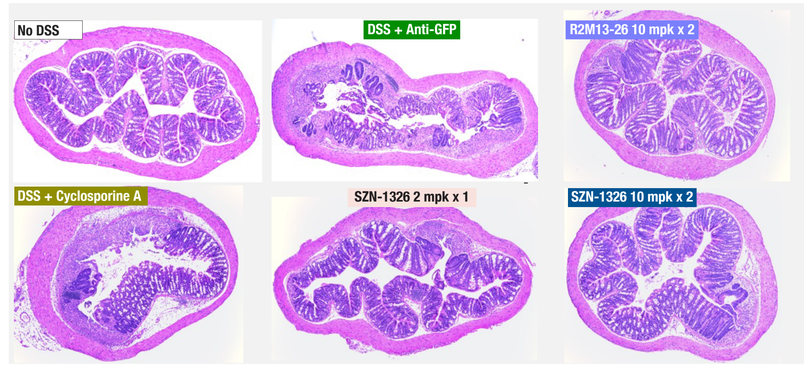
Results

SZN-1326 Treatments Improved Body Weight more than Cyclosporine A

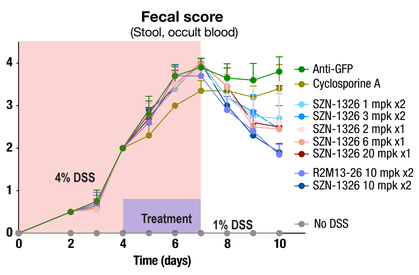


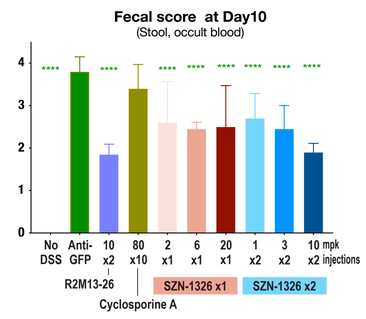


SZN-1326 Treatments Repaired Damaged Colon Epithelium more than Cyclosporine A

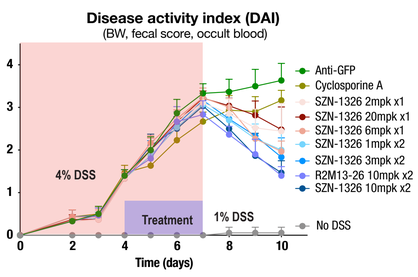


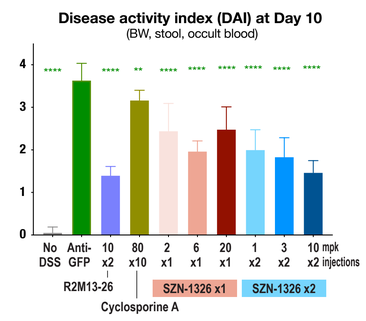
SZN-1326 Treatments Decreased Fecal Score more than Cyclosporine A



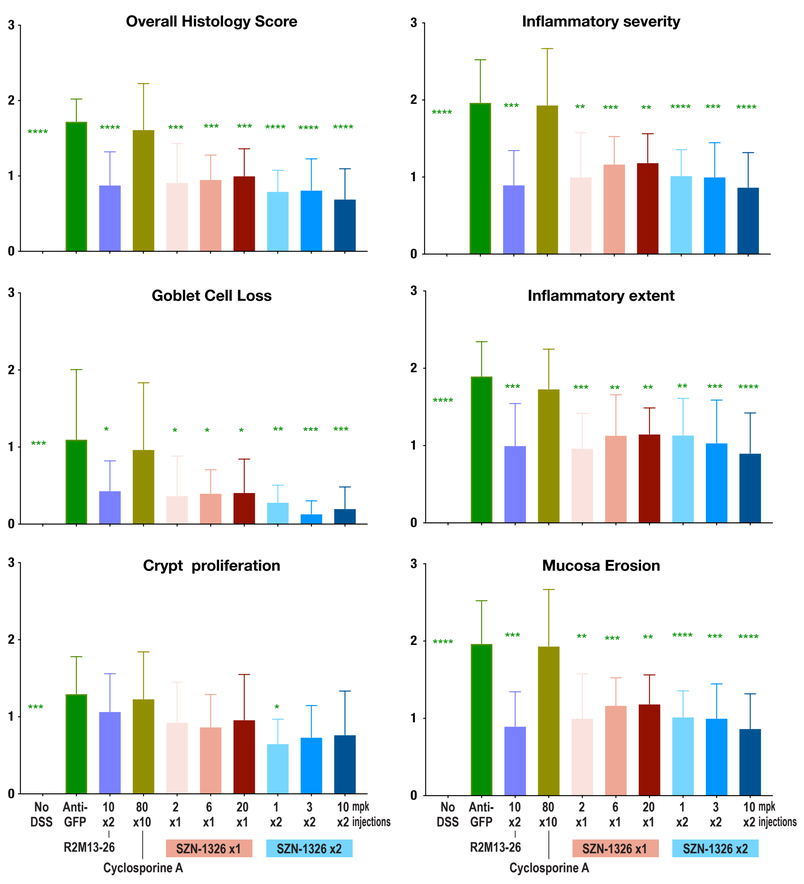


SZN-1326 Treatments Decreased Disease Activity Index (DAI) more than Cyclosporine A





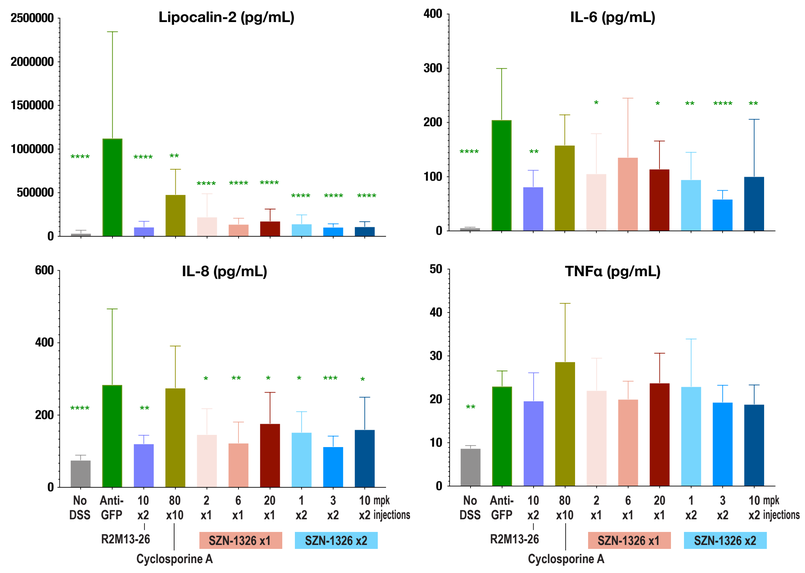
SZN-1326 Treatments Decreased Colon Histology Severity Scores more than Cyclosporine A



Statistical Analyses: One-way ANOVA, Holm-Sidak test (GraphPad Prism). All comparisons made with the anti-GFP group. Error bars: Mean with SD.
* p<0.05, ** p<0.01, *** p<0.001, **** p<0.0001

Histological evaluation showed SZN-1326 treatments repaired the damaged colon epithelium, decreased colon histology scores of inflammation, mucosal erosion, and goblet cell loss, at doses as low as 1 mg/kg dosed twice or a single dose of 2 mg/kg.

SZN-1326 Treatments Decreased Serum Level of Inflammatory Cytokines more than Cyclosporine A



Summay

- There is a clear unmet need for agents that directly repair and regenerate the intestinal epithelial barrier and induce mucosal healing in IBD
- SZN-1326 is a bi-specific effectorless IgG1 antibody that binds to Fzd 5,8 and LRP6 receptors on the intestinal stem and progenitor cells
- In the acute DSS model
  - SZN-1326 repaired the damaged colon epithelium and restored the colon tissue structure
  - SZN-1326 reduced the histology severity score and improved mucosal healing
  - SZN-1326 reduced inflammatory cytokines in the serum
  - SZN-1326 reduced the disease activity index
  - Efficacy was shown at doses as low as 1 mg/kg dosed twice or a single dose of 2 mg/kg
  - Cyclosporine A showed only a mild effect on reducing DAI and lipocalin-2

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