Selective Janus Kinase 1 inhibitor targets monocytes and tissue macrophages during DSS colitis

Leonie de Vries[1,2], Jose Duarte[1], Francisca Hilbers[1], Menno de Winther[4], Perry Moerland[5], Mike Woodrow[3], Martin Sims[3], Valerie Ludbrook[3], Geert D'Haens[2], Wouter de Jonge[1,2]

1 Tytgat Institute for Liver and Intestinal Research, AMC, Amsterdam, Netherlands 2 Department of Gastroenterology and Hepatology, AMC, Amsterdam, Netherlands 3 Kinase DPU, GlaxoSmithKline, Stevenage, United Kingdom 4 Department of Medical Biochemistry, AMC, Amsterdam, Netherlands 5 Department of Clinical Epidemiology, Biostatistics and Bioinformatics, AMC, Amsterdam, Netherlands **Contact: l.c.devries@amc.uva.nl**

WWW.IBD-AMC.NL

Background

Non-selective Janus Kinase inhibitors (JAKi) have shown efficacy in treatment of inflammatory bowel diseases (IBD). However, side effects such as increased viral susceptibility and hypercholesterolemia are observed. A selective JAK1 inhibitor (formerly known as GLPG0555, in licensed by GSK from Galapagos) interferes with cytokine signaling important in IBD.

Aim investigate the ability of JAK1i to protect mice from an acute Dextran Sulphate Sodium (DSS) colitis, or to ameliorate a chronic DSS colitis. In addition, cellular targets of JAK1i were examined in vitro and in vivo.

Methods

A transcription array (Illumina Mouse WG-6 v2) was performed on murine bone marrow derived macrophages (BMDM) stimulated with LPS (100 ng/ml) and IFNγ (10 ng/ml) (n=6) of which 3 mice were stimulated in the presence of 1000 nM JAK1i (figure 2). IFNγ-induced genes downregulated by JAK1i were validated in vitro by qPCR (figure 3). In the DSS experiments C57/Bl6 mice were given 2% DSS in drinking water, combined with oral gavage of JAK1i (figure 1). Clinical and histological inflammation scoring was performed the day of sacrifice.

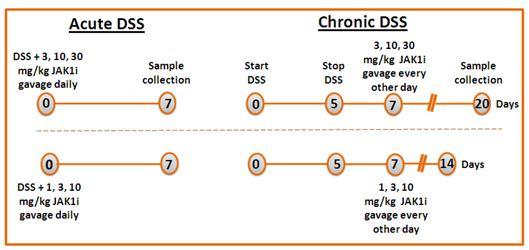

Fig.1| Schematic overview of acute and chronic DSS-induced colitis experiments

Conclusion

In vivo, JAK1i did not reduce colitis symptoms and mucosal inflammation in acute and chronic DSS colitis. In vitro, JAK1i affects mediators of the tryptophan catabolism in IFNγ/LPS triggered BMDM, which might attribute to compromised bacterial clearance in this colitis model.

Results

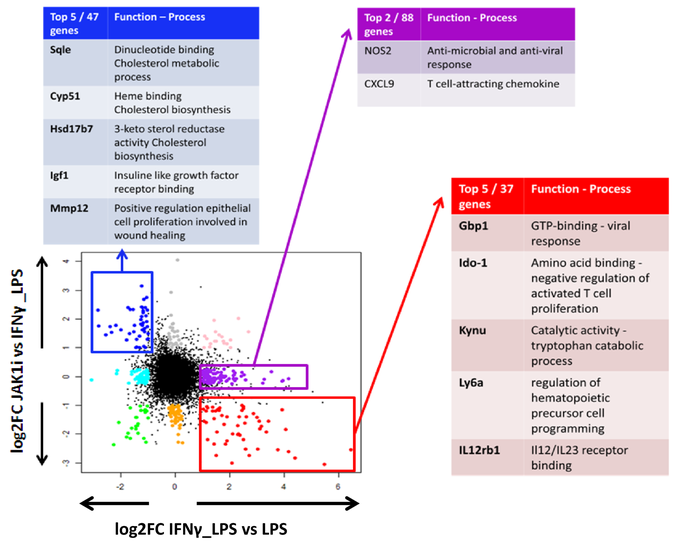

Fig.2| Transcription array: JAK1i attenuated 37 IFNγ inducible genes (1-3 log2 fold change). JAK1i upregulated 47 genes, showing a decreased expression in presence of IFNγ alone (1-4 log2 fold change) in BMDM stimulated with LPS/IFNγ. JAK1i left 88 genes unaffected.

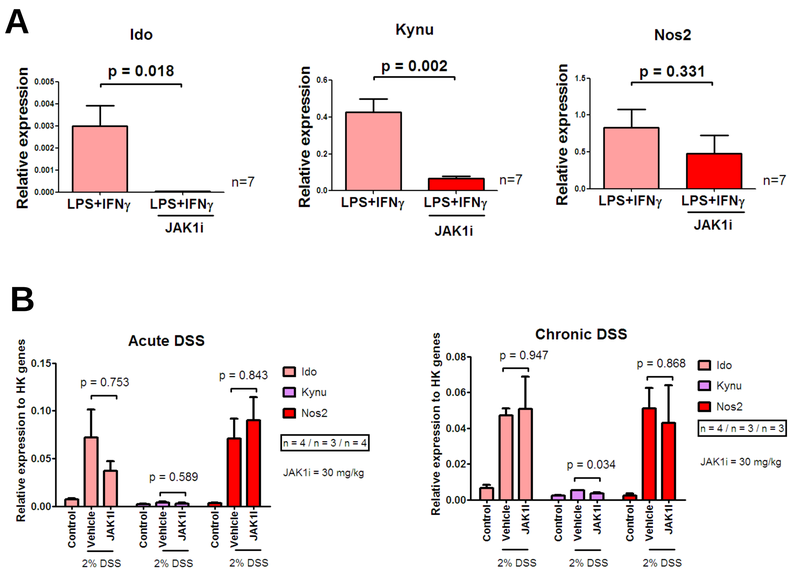

Fig.3| (A) qPCR validation: JAK1i (1000 nM) downregulated indoleamin 2,3-dioxygenase (IDO1) and kynureninase (KYNU) in vitro. Nitric oxide synthase 2 (NOS2) was unaffected, replicating the transcription array outcomes. (B) JAK1i downregulated KYNU in chronic DSS colitis in total RNA from colon specimens. Error bars represent ± SD; p = <0.05

Results

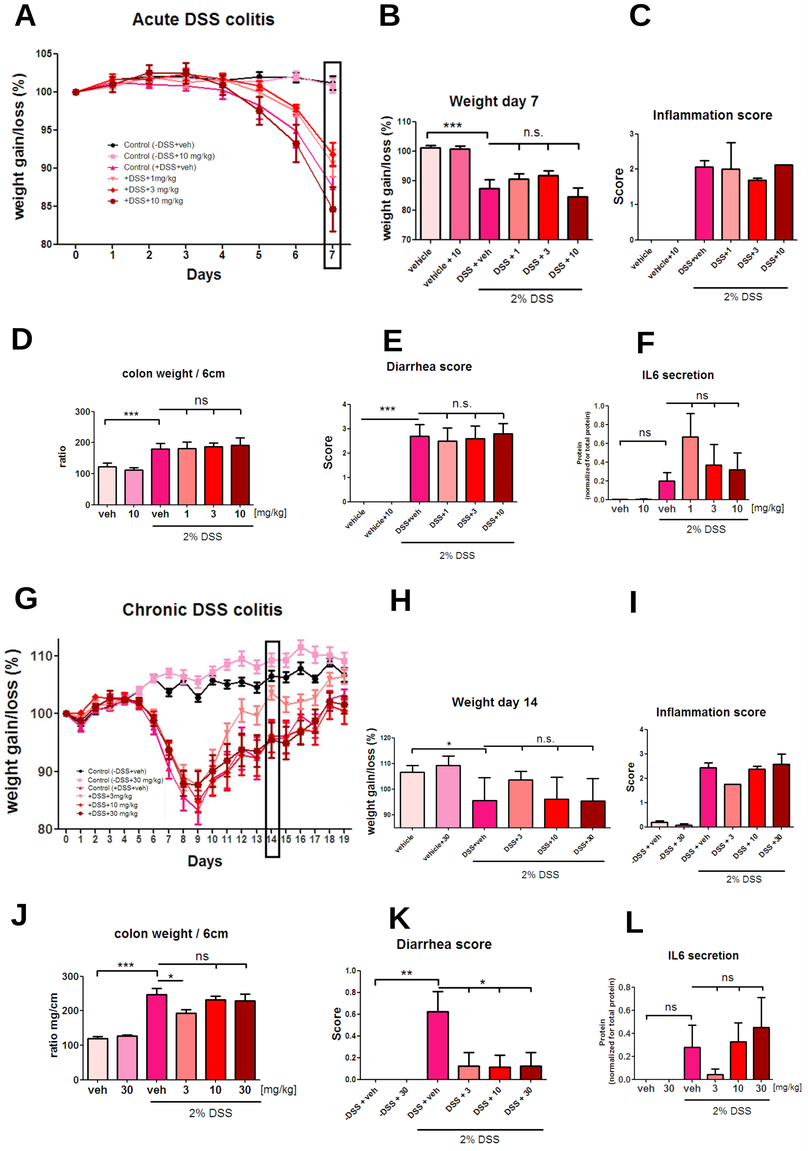

Fig.4| (A) Acute DSS: 1, 3, 10 mg/kg JAK1i did not protect mice from weight loss comparison to animals treated with DSS alone. Data of 2nd experiment is shown. (G) Chronic DSS: a trend of faster recovery was seen at 3 mg/kg JAK1i. However, at repetition this was not seen (data not shown). (B+H) Body weight was monitored daily and is depicted as a % of initial body weight that is defined as 100%; (C+I) Histological inflammation score (D+J) Colon weight-length ratio/6 cm (E+K) Dhiarrhea score (F+L) An increase of IL6 secretion in colon homogenates was observed in both experiments. Error bars represent SD; *** p<0.001; ** 0.001≤p≤0.01; * 0.01<p≤0.05; ns, not significant.