SUPPLEMENTAL INFORMATION

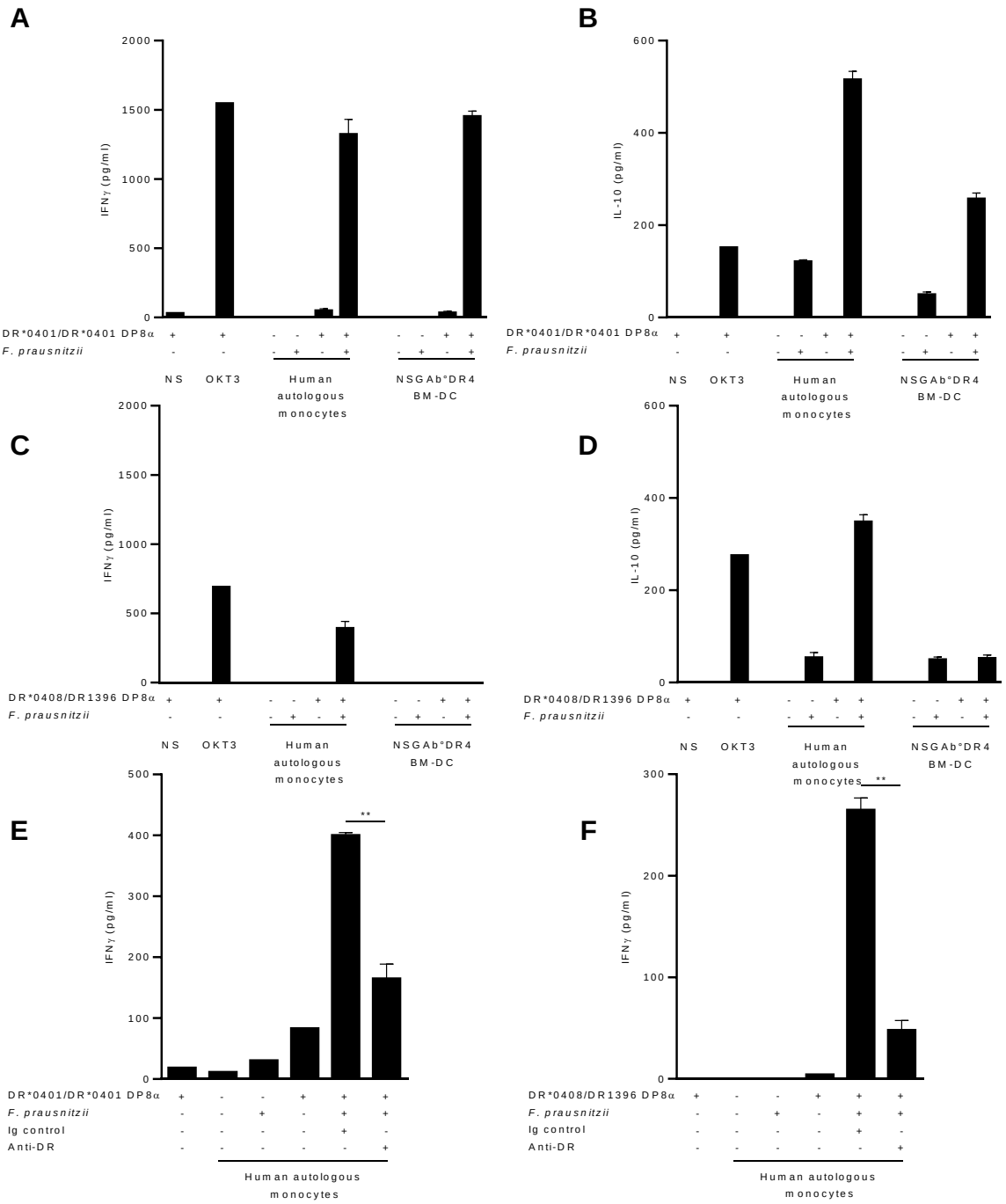
Supplemental Methods

Screening for HLA-restriction. Grown DP8α Treg clones were screened for their HLA-DR restriction using the L243 blocking antibody. To this end, autologous monocytes ($CD14^+$ magnetically purified, Miltenyi Biotec) were loaded overnight with *F. prausnitzii* (ratio 1 monocyte:1 bacterium) before addition of individual DP8α Treg clones (ratio 2 clones:1 monocyte), in the presence or in the absence of the L243 antibody (10µg/ml) or its corresponding control Ig. Selected HLA-DR*04-restricted clones were then extensively expanded for *in vivo* experiments.

Isolation of murine bone-marrow derived dendritic cells. For co-culture with DP8α Treg clones, bone-marrow derived dendritic cells from a 10-week-old NSG-Ab°DR4 mice were differentiated *ex vivo*. Femurs and tibias were collected from the mouse, soaked in 70% ethanol for 5 min and placed in Iscove's Modified Dulbecco's Medium (IMDM) medium supplemented with 10% FBS, 1% L-Glutamine (Gibco), 1% Penicillin/streptomycin (Gibco), 50 µM of betamercaptoethanol (Sigma) (complete medium). Bone marrow was flushed from the bones using a 2 ml syringe and 26G needle, collected in a 50 ml tube and centrifugated 5 minutes at 300g at 4. Supernatant was discarded and the cells were incubated at room temperature with red blood cell lysis solution (Miltenyi Biotec) for 5 minutes. After centrifugation 5 minutes at 300 g at room temperature, the cells were washed and resuspended in complete medium supplemented with 10 ng/ml recombinant mouse granulocyte-macrophage colony-stimulating factor (GM-CSF; Miltenyi Biotec) at the concentration of 5×10^6 cells / ml in non-culture treated bacterial petri dish (Sarstedt) and placed at 37°C 5% CO_2 for 5 days. At day 5, culture medium was replaced. At day 7, BM-DC were detached using cold PBS, counted and frozen in FBS + 10% DMSO before being used for co-culture experiments.

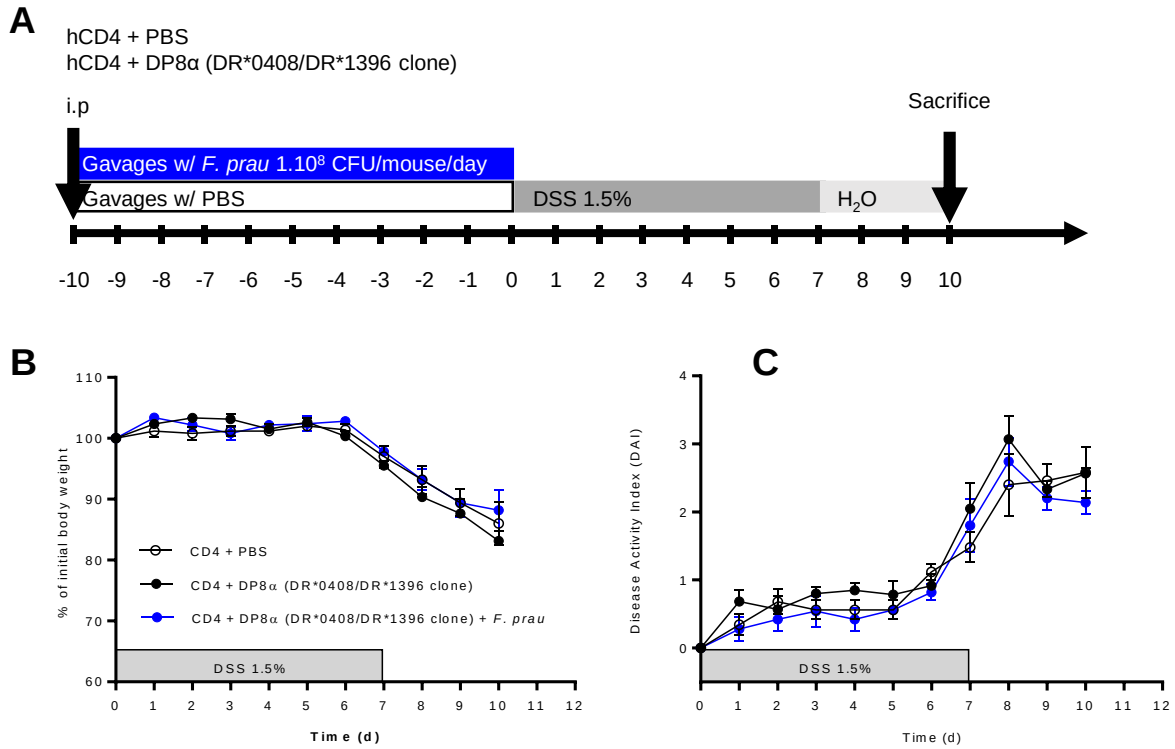
Human IL-10 and IFNγ ELISAs. DP8α Treg clones were stimulated either specifically by APCs: autologous monocytes or murine NSG-Ab°DR4 BM-DC (ratio 2 lymphocytes:1 APC) loaded overnight or not with the A2-165 *F. prausnitzii* strain (multiplicity of infection, MOI 10), or non-specifically using coated anti-CD3 (clone OKT3, 1 µg/ml, eBioscience, San Diego, CA) for 48h at 37°C. Supernatants were harvested at 24h for IFNɣ and 48h for IL-10. Cytokine production was measured using Ready-Set-Go ELISAs (eBioscience) according to the manufacturer's instructions.

SUPPLEMENTAL FIGURES



Supplemental Figure 1. A human DP8α Treg clone from a homozygous DRb1*0401/DRb1*0401 donor responds to bone-marrow derived dendritic cells (BM-DCs) from NSG-Ab°DR4 mice loaded with *F. prausnitzii*. (A, B) HLA-DR restriction of the DRb1*0401 / DRb1*0401 and the DRb1*0408 / DRb1*1396 DP8α clones using an anti-human HLA-DR blocking antibody (L243 clone) or a control Ig. **(C, D)** IFNɣ and **(E, F)** IL-10 production upon co-culture of DP8α Treg clones in non-stimulating conditions (NS), in response to non-specific stimulation (anti-OKT3 antibody), human autologous monocytes or

murine NSG-Ab°DR4 bone marrow derived dendritic cells (BM-DC) loaded or not with *F. prausnitzii*. Results are presented as the mean ± S.E.M (n = 3). Two-tailed Mann-Whitney tests.



Supplemental Figure 2. Human DP8α Treg clone from a DRb1*0408 / DRb1*1396 donor has no protective effect on DSS-induced colitis in NSG-Ab°DR4 mice. (A) Experimental outline: NSG-Ab°DR4 female mice were injected intraperitoneally (i.p.) with 2.10^6 human peripheral CD4 effector T cells alone, or in combination with 2.10^6 human DR*0408/DR*1396 DP8α clones and received daily intragastric gavage with 200 µl PBS 1X or 1.10^8 CFU of *F. prausnitzii* for 10 days before 1.5% DSS supplementation in drinking water for 7 days followed by 3 days of regular drinking water. **(B)** Body weight and **(C)** disease activity index (DAI) were assessed during the protocol in all groups of mice.

SUPPLEMENTAL TABLES

Variable	HC	CD	UC
Group [n]	73	185	65
Age [years]	39 (24.5)	39 (20)	36 (17.5)
BMI [kg/m^2]	-	22.9 (4.8)	21.9 (5.4)
Gender [male]	41 (56.2%)	115 (62.2%)	37 (56.7%)
Intestinal resection	-	72 (38.9%)	2 (3.1%)
Smoking	-	40 (21.6%)	3 (4.6%)

Supplemental Table 1. Clinical characteristics of healthy individuals and inflammatory bowel disease (IBD) patients recruited in the study. Continuous variables are presented as median (interquartile range). Categorical variables are presented as counts (%). Abbreviation: HC: healthy controls, CD: Crohn's disease, UC: ulcerative colitis, BMI: Body mass index.

Variable	CD	UC
Montreal (CD)		
L1	35 (18.9%)	-
L2	42 (22.7%)	-
L3	72 (38.9%)	-
L4	1 (0.5%)	-
L1 + L4	13 (7.0%)	-
L3 + L4	20 (10.8%)	-
Montreal (UC)		
E1	-	2 (3.1%)
E2	-	25 (38.5%)
E3	-	38 (58.5%)
Oral 5'-ASA	21 (11.35%)	28 (43.07%)
AZA/6-MP	41 (22.16%)	18 (27.69%)
Methotrexate	22 (11.89%)	1 (1.54%)
Anti-TNFα	158 (85.41%)	53 (81.54%)
Vedolizumab	18 (9.73%)	12 (18.46%)
Ustekinumab	1 (0.54%)	0 (0%)

Supplemental Table 2. Disease extent, disease severity and medications specific for IBD patients. Disease extent and medications presented as counts (%). Disease activity presented as median (range). Abbreviation: AZA/6-MP: Azathioprine, 6-mercaptopurine; 5-ASA: 5-aminosalicylic acid