

**Supplementary Table S4. Mechanisms involved in the therapeutic effects of MSC-based therapy using different molecule-silencing approaches (listed in chronological order)**

Reference	Animal model	Specie, Strain, Gender	MHC context	Source of MSCs	Administration route	MSC Dose	No. of infusions	Molecule silenced in MSCs	Day of infusion (D)	Parameters analysed for IBD progression	Therapeutic effect of MSC therapy
Akiyama K, 2012 (38)	10-day DSS cycle	Mouse, C57BL6/J, F	A	BM	IV	1x10 <sup>6</sup>	1	-WT MSCs -FASL <sup>-/-</sup> MSCs	D3	-DAI (Body weight, stool consistency & rectal bleeding) -AnxV <sup>+</sup> 7-AAD <sup>+</sup> CD3 <sup>+</sup> cells (PB) -Th17 & Treg (colon)	-Yes, WT MSCs -No, FASL <sup>-/-</sup> MSCs
An JH, 2020b (43)	7-day DSS cycle	Mouse, C57/BL6, M	X	AD	IP	100 µg	3	-EVs from WT MSCs -EVs from TSG-6 <sup>-/-</sup> MSCs	D1, D3 & D5	-DAI (Body weight, stool consistency, rectal bleeding & general activity) -Colon length & H/E staining -Arg, CD11b, CD11c CD206, COX-2, FOXP3, IFNγ, IL6, IL10, IL17, iNOS, TGF-β, TNF-α & TSG-6, (colon) -Body weight, stool consistency & rectal bleeding	-Yes, EVs from WT MSCs -No, EVs from TSG-6 <sup>-/-</sup> MSCs
Fan H, 2012 (44)	7-day DSS cycle	Mouse, C57/BL6, M	X	UC	IV	2x10 <sup>6</sup>	1	-WT MSCs -IL1β-pretreated MSCs -IL1R1 <sup>-/-</sup> MSCs	D1	-Colon length, weight & H/E staining -M1 & M2 macrophages (PC) -Th1, Th2, Th17 & Treg (SP & mLNs)	Yes, IL1β-pretreated MSCs>IL1R1 <sup>-/-</sup> MSCs>WT MSCs

Feng Y, 2018 (50)	TNBS	Mouse, BALB/C, M	A	BM	IP	2x10 <sup>6</sup>	1	-WT MSCs -MGP <sup>-/-</sup> MSCs	12h	-Body weight, stool consistency & survival -Colon length & H/E staining -CD3, CD4, CD8, IFN $\gamma$ , IL1 $\beta$ , IL6, IL10, IL17 & TNF $\alpha$ (colon)	Yes, WT MSCs>MGP <sup>-/-</sup> MSCs
Giri J, 2020 (51)	6-day DSS cycle	-Mouse, C57BL6, F -Mouse, IL10 KO, F	S	BM	IP	1x10 <sup>7</sup>	2	-WT MSCs -IFN $\gamma$ -pretreated MSCs -CCL2 <sup>-/-</sup> MSCs	D2 & D4	-DAI (Body weight) -Colon H/E staining	-Yes, IFN $\gamma$ - pretreated MSCs>WT MSCs -No, CCL2 <sup>-/-</sup> MSCs
Kang J, 2019 (56)	10-day DSS cycle	Mouse, BALB/C, NA	X	UC	IP	3x10 <sup>6</sup>	3	-WT MSCs -WT MSCs+miR148b-5p inhibitor -WT MSCs+15-lox-1 -miR148b-5p-MSCs	D3, D6 & D9	-DAI (Body weight & stool consistency) -Colon length, H/E staining & IHC (PCNA) -caspase 3, IL1 $\beta$ , IL6, 15lox1, PCNA, & TNF $\alpha$ (colon)	-Yes, miR148b- 5p-MSCs=15- lox-1-WT MSCs=WT MSCs -No, WT MSCs+miR148 b-5p inhibitor
Liao Y, 2016 (48)	TNBS	Mouse, C57/BL6, NA	S	BM	IP	2x10 <sup>6</sup>	1	-WT MSCs -IGFBP7 <sup>-/-</sup> MSCs	12 h	-Body weight & survival -Colon length & H/E staining - IFN $\gamma$ & TNF $\alpha$ in CD4 & CD8 T cells (mLN)	-Yes, WT MSCs -No, IGFBP7 <sup>-/-</sup> MSCs
Nemoto Y, 2013 (204)	Adoptive transfer	-Mouse, RAG1 KO, NA -Mouse, RAG1 & IL7 KO,	S	BM	IV	1x10 <sup>6</sup>	1	-WT MSCs -IL7 <sup>-/-</sup> MSCs	-D-28 -D0 -D1 & D28	-DAI (Body weight, stool consistency & rectal bleeding) -Colon length & H/E staining -IFN $\gamma$ , IL17 & TNF $\alpha$ in	-Yes, WT MSCs -No, IL7 <sup>-/-</sup> MSCs

		NA -mouse, RAG2 KO, NA							CD4 T cells (colon, mLN & SP)		
Parekkadan B, 2012 (47)	Adoptive transfer	Mouse, RAG1 KO, NA	S	BM	IV	2x10 <sup>5</sup>	2	-WT MSCs -Aire <sup>-/-</sup> MSCs	-D0 & D21	-DAI (Body weight) -Colon H/E staining -TNFα (serum) -IL6, IL10, Th1 Tr1, Treg & TNFα (colon)  -Yes, WT MSCs -No, Aire <sup>-/-</sup> MSCs  -Yes, Poly (I:C)-pretreated MSCs>IFNγ- pretreated MSCs>LPS- pretreated MSCs=TNFα- pretreated MSCs=WT MSCs -Yes, S=X -Yes, 12h & D4 -No, WT- MSCs+DAPT, TLR3 <sup>-/-</sup> MSCs,Jagged- 1 <sup>-/-</sup> MSCs & Notch-1 <sup>-/-</sup> MSCs	
Qiu Y, 2017 (46)	TNBS	Mouse, BALBC, NA	-X -S	UC	IP	1x10 <sup>6</sup>	1	-WT MSCs -Poly (I:C)-pretreated MSCs -TNFα-pretreated MSCs -IFNγ-pretreated MSCs -LPS-pretreated MSCs -WT MSCs+DAPT -TLR3 <sup>-/-</sup> MSCs -Jagged-1 <sup>-/-</sup> MSCs -Notch-1 <sup>-/-</sup> MSCs	-2 h -D4	-DAI (Body weight, stool consistency & survival) -Colon H/E staining & MPO activity -COX2, IFNγ, IL4, IL6, IL10, IL17A, IL21, IL23, PGE2 & TNFα (colon & serum) -Th1, Th17 & Treg (mLN & SP)	
Sala E, 2015 (20)	-10-day DSS cycle -TNBS	-Mouse, C57BL6, F -Mouse,	-S -A	-BM -AD	-IV -IP -SC	3x10 <sup>6</sup>	-5 -4	-WT MSCs -TSG6 <sup>-/-</sup> MSCs -Encapsulated MSCs -TSG-6	-D5-D9 -D1-D4	-DAI (Body weight, stool consistency & rectal bleeding) -Colon length & H/E	-Yes, TSGW>T MSCs=encapsu lated MSCs -No, TSG6 <sup>-/-</sup>

		BALB/C, F									staining -Arg-II, B220 <sup>+</sup> , CCL22, CD3 <sup>+</sup> , CD11b <sup>+</sup> F4/80 <sup>+</sup> , CD11 <sup>+</sup> Ly6G <sup>+</sup> Foxp3, HEMO-1, IL10, IL12, TGF-β & TNFα (colon & P) -TSG-6 (serum) -DAI (Body weight, stool consistency & rectal bleeding)	MSCs
Song WJ, 2017 (42)	7-day DSS cycle	Mouse, C57BL6, M	X	AD	IP	2x10 <sup>6</sup>	1	-WT MSCs -TSG6 <sup>-/-</sup> MSCs	D1	-Colon H/E staining & IHC (CD11b & CD206) -Arg1, CD206, Fizz1, IFNγ, IL1β IL10, IL17, TNFα & Ym1 (colon)	-Yes, WT MSCs -No, TSG6 <sup>-/-</sup> MSCs	
Song WJ, 2018 (41)	7-day DSS cycle	Mouse, C57BL6, M	X	AD	IP	2x10 <sup>6</sup>	-1	-WT MSCs -TSG6 <sup>-/-</sup> MSCs	D1	-DAI (Body weight, stool consistency & rectal bleeding) -Colon H/E staining & IHC (AnxV, CD11b, CD206 & PI) -IL6, IL10 & TNFα (colon) -Body weight -Colon length & H/E staining -colon, mLN, & SP IHC (GFP) -CD4, CD11c, CD51, CD103 & Foxp3 (colon, mLN & SP)	-Yes, WT MSCs -No, TSG6 <sup>-/-</sup> MSCs	
Takeyama H, 2017 (49)	DSS	Mouse, C57BL6, M	S	AD	IP	2x10 <sup>6</sup>	1	-WT MSCs -TSP-1 <sup>-/-</sup> MSCs	D2		-Yes, WT MSCs -No, TSP-1 <sup>-/-</sup> MSCs	

Tian J, 2020 (57)	10-day DSS cycle	Mouse, C57BL6, NA	S	BM	IV	0.5 x 10 <sup>6</sup>	1	-WT MSCs -Pitsopt2-pretreated MSCs -Colivelin-pretreated MSCs -siRNA-BECN1-MSCs	D3	-DAI (Body weight, stool consistency & rectal bleeding) -Colon length & H/E staining -Th17 & Treg (SP) -BECN1, Corticosterone, IFN $\gamma$ , CD4, CD8, CD9, CD63, CD81, LC3-I, LC3-II, pSTAT3, STAT3 & TNF $\alpha$ (PB)	-Yes, WT MSCs>colivelin-pretreated MSCs -No, Pitsopt2-pretreated MSCs & siRNA-BECN1-MSCs
Wang C, 2014 (54)	7-day DSS cycle	Mouse, C57BL6, M	S	BM	IV	1x10 <sup>6</sup>	1	WT MSCs WT MSCs+SB431542	D8	-DAI (Body weight, stool consistency & rectal bleeding) -Colon H/E staining -CD206, F4/80 IFN $\gamma$ , IL6, IL17, pSMAD, pTFG $\beta$ & TNF $\alpha$ (colon)	-Yes, WT MSCs -No, WT MSCs+SB431542
Wu T, 2015 (138)	9-day DSS cycle	Mouse, C57BL6, M	X	BM	IV	1x10 <sup>6</sup>	1	-WT MSCs -mir21-/- MSCs	D3	-DAI (Body weight) -Colon length & H/E staining -Treg (colon)	Yes, Mir21-/- MSCs > WT MSCs
Xu J, 2020 (55)	3x5-day DSS cycle every 10 days	Mouse, C57BL6, M	X	E	IV	5x10 <sup>5</sup>	3	-WT MSCs -WT MSCs+OSI906 -WT MSCs+PPP -IGF-1	D3, D18 & D33	-DAI (Body weight, stool consistency & rectal bleeding) -Colon H/E staining & IHC (Ki67) -Liver IF (F4/80) -Lung IF (CD31) -ACE, Adiponectin, BLC, CXCL1, CXCL2, IGF1, Igfbp 1, 2 3 & 4, IL5, IL6,	-Yes, WT MSCs>IGF-1 -No, WT MSCs+OSI906 & WT MSCs+PPP

											IL17BR, IL17F, ITAC, MCP1, PDGFaa, pentraxin3, SDF & e-selectin (serum) - AKT, pAKT, PI3K IGF-1R, pIGF-1R $\beta$ , p44/42 MAPK, mTOR, pmTOR, & p70s6 Kinase (colon) -RNA sequencing analysis (colon)	
Yang R, 2018 (45)	10-day DSS cycle	Mouse, C57BL6, NA	S	G	IV	0.2x10 <sup>6</sup>	1	-WT MSCs -NaHS-pretreated MSCs -Cbs <sup>-/-</sup> MSCs	Cbs <sup>-/-</sup> D3	-DAI (Body weight & stool consistency) -Colon H/E staining -Th17 & Treg (colon)	-Yes, WT MSCs=NaHS-pretreated Cbs <sup>-/-</sup> MSCs -No, Cbs <sup>-/-</sup> MSCs	
Yang S, 2021 (39)	-7-day DSS cycle -TNBS	-Mouse, C57BL6, M -Mouse, BALB/C, M	X	UC	IP	200 $\mu$ g	1	-EVs from WT MSCs -siTSG-6 MSCs-EVs -rhTSG-6	-D5 -24h	-DAI (Body weight, stool consistency, rectal bleeding & survival) -Colon length, FITC, H/E & PAS staining, MPO activity & IHC (Claudin-1, Occludin & ZO-1) -Claudin-1, CXCL14, IL-1 $\beta$ , IL-4, IL-11, IL-12 Occludin, TGF- $\beta$ , TSG6 & ZO-1 (colon) -Th2 & Th17 (mLN & SP)	-Yes, EVs from WT MSCs=TSG6 -No, siTSG-6 MSCs-EVs	
Zhang S, 2021 (40)	7-day DSS cycle	Mouse, C57BL6, NA	X	Musc	IV	2.5x10 <sup>5</sup>	1	-WT MSCs -IFN- $\gamma$ +TNF $\alpha$ -pretreated MSCs -IDO <sup>-/-</sup> MSCs	D2	-Body weight -Colon H/E staining -IL6 (serum)	Yes, WT MSCs=TSG6>IDO <sup>-/-</sup> MSCs+TSG6=I	

									-TSG6 <sup>-/-</sup> MSCs		DO <sup>-/-</sup>
									-TSG6		MSCs+KYN=I
									- IDO <sup>-/-</sup> MSCs+KYN		DO <sup>-/-</sup>
									- IDO <sup>-/-</sup> MSCs+KYNA		MSCs+KYNA>
											IDO <sup>-/-</sup>
											MSCs=TSG6 <sup>-/-</sup>
											MSCs
										-DAI (Body weight, stool consistency, rectal bleeding & survival)	
										-Colon length, H/E & Masson's trichrome staining, MPO activity &	-Yes, BM-
		-Mouse, C57BL/6,								IHC (IFN-γ, IL-10 & IL-17)	MSCs=U-
Zhou C, 2020 (205)	-2x7-day DSS cycle -TNBS	F -Mouse, BALB/C, M	X	-U -BM	IP	1x10 <sup>6</sup>	-1 -2	-WT MSCs -siCOX2-MSCs	-D1 -D7 -D7 & D16	- GCSF, IFN-γ, IL1β, IL2, IL3, IL6, IL7, IL-10, IL12p70, IL15, IL-17, IL23, PGE2 & TNFα (colon)	MSCs>siCOX2
										-Th1, Th17, Tr1 & Treg (mLN)	
										-PGE2 (PB)	

Therapeutic effect; > better than, =similar to; <less than