

**Supplement table 1**

Characteristics of natural occurring TH<sup>+</sup> cells and of *in vitro* generated induced TH<sup>+</sup> cells.

**Natural occurring TH<sup>+</sup> neuronal cells *in vivo***

<i>Feature</i>	<i>Phenotype or impact</i>	<i>Reference</i>
Regulation of TH	phosphorylation status of subunits, environmental pH value, tetrahydrobiopterin (BH <sub>4</sub> ), bivalent iron (Fe <sup>2+</sup> ), product feedback inhibition, proteasomal degradation, hypoxia	1-7
Marker expression	human TH <sup>+</sup> : TH, vesicular monoamine transporter 2 (VMAT-2), CD163, CD19, prolyl-4-hydroxylase, dopamine-β-hydroxylase (DBH), 3,4-dihydroxyphenylalanine (DOPA) decarboxylase murine TH <sup>+</sup> : TH, VMAT-2, intracellular catecholamines	8 9
Appearance <i>in vivo</i>	human TH <sup>+</sup> : in patients with chronic rheumatoid arthritis, osteoarthritis and multiple sclerosis murine TH <sup>+</sup> : highest at the beginning of chronic collagen-induced arthritis (CIA)	8, 10-12 9
Organ specificity	human TH <sup>+</sup> : synovial tissue and >>blood murine TH <sup>+</sup> : joint, lymph nodes, thymus, bone marrow, spleen,	8, 10, 11 9
Effect <i>in vitro</i>	human TH <sup>+</sup> : anti-inflammatory (inhibition of TNF); release of norepinephrine	8, 11
Sensitivity	murine TH <sup>+</sup> : targeted killing by 6-hydroxydopamine (6-OHDA)	9

***in vitro* generated induced TH<sup>+</sup> neuronal cells (iTH<sup>+</sup>)**

Differentiation factors	human iTH <sup>+</sup> : sonic hedgehog (SHH), human fibroblast growth factor 8 (FGF8), basic fibroblast growth factor (bFGF), brain-derived neurotrophic factor (BDNF) murine iTH <sup>+</sup> : B27 supplement, SHH, FGF8, murine bFGF, human BDNF	13 14, 15
Morphology	human iTH <sup>+</sup> : neural tube-like structures; cell-connected rosette-like patterns murine iTH <sup>+</sup> : neuron-like; cell-connected rosette-like patterns	16 14
Marker expression	human iTH <sup>+</sup> : TH, β-III-tubuline, VMAT-2, nuclear receptor related 1 (Nurr1) murine iTH <sup>+</sup> : TH, β-III-tubuline, VMAT-2, Nurr1	13 14
Secretion	human iTH <sup>+</sup> : dopamine murine iTH <sup>+</sup> : norepinephrine, dopamine	13 14
Effect <i>in vivo</i>	murine iTH <sup>+</sup> : CIA: anti-inflammatory (decreased clinical arthritis score, less cell infiltration into synovial tissue)	14
Sensitivity	human iTH <sup>+</sup> : reduced release of norepinephrine by TNF treatment murine iTH <sup>+</sup> : targeted killing by 6-OHDA	17 14

## References Supplement table 1

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## Supplement table 2

Summary of direct pro-/ anti-inflammatory and direct pro-/ anti-nociceptive effects mediated by selected cytokines and chemokines in antigen-induced arthritis and other experimental arthritis models

<i>Cytokine/ Chemokine</i>	<i>Model, Species</i>	<i>Effect on inflammation</i>	<i>nociception</i>	<i>Reference</i>
IL-4	<b>AIA, m</b>	<b>anti-inflammatory</b>	n.d.	1
	CIA, m	anti-inflammatory	n.d.	2
	K/BxN, m	pro-inflammatory (requirement for induction)	n.d.	3
	AA, m	pro-inflammatory (requirement for induction)	n.d.	4
	AA, r	anti-inflammatory	n.d.	5
IL-6	<b>AIA, m/r</b>	<b>pro-inflammatory</b>	<b>pro-nociceptive (mechanical hyperalgesia)</b>	6-9
	CIA, m	pro-inflammatory	n.d.	10
	K/BxN, m	no influence	n.d.	11
IL-17A	<b>AIA, m/r</b>	<b>no influence</b>	<b>pro-nociceptive (mechanical hyperalgesia)</b>	12-14
	CIA, m	pro-inflammatory	n.d.	15, 16
	K/BxN, m	pro-inflammatory	n.d.	17
TNF $\alpha$	<b>AIA, m/r</b>	<b>pro-inflammatory</b>	<b>pro-nociceptive (thermal &amp; mechanical hyperalgesia)</b>	18, 19
	CIA, m	pro-inflammatory	pro-nociceptive (thermal & mechanical hyperalgesia)	20, 21
	K/BxN, m	pro-inflammatory	pro-nociceptive (mechanical hyperalgesia)	11, 22
	TNFtg, m	pro-inflammatory	pro-nociceptive (thermal & mechanical hyperalgesia)	23, 24
	CFA, r	pro-inflammatory	pro-nociceptive (thermal & mechanical hyperalgesia)	25
	AA, r	anti-inflammatory (by exogenous TNF $\alpha$ only)	n.d.	26
CXCL1 (GRO- $\alpha$ )	<b>AIA, m</b>	<b>pro-inflammatory</b>	<b>pro-nociceptive (mechanical hyperalgesia)</b>	14, 27-29
	CIA, m	pro-inflammatory	pro-nociceptive (mechanical hyperalgesia)	30
	K/BxN, m	pro-inflammatory	n.d.	31, 32
	CAIA, m	pro-inflammatory	n.d.	33
	AA, r	pro-inflammatory	n.d.	34
CXCL2 (GRO- $\beta$ )	<b>AIA, m</b>	<b>pro-inflammatory</b>	<b>pro-nociceptive (mechanical hyperalgesia)</b>	29
	CIA, m	pro-inflammatory (on bone erosion only) & anti-inflammatory	n.d.	35, 36
CCL5 (RANTES)	CIA, m	pro-inflammatory	n.d.	37
	AA, r	pro-inflammatory	n.d.	38, 39

*IL* interleukin, *TNF* tumor necrosis factor, *CCL* Chemokine (C-C motif) ligand, *RANTES* regulated on activation normal T cell expressed and secreted, *CXCL* chemokine (C-X-C motif) ligand, *GRO* growth-regulated oncogene, **AIA** antigen-induced arthritis, *CIA* collagen-induced arthritis, *K/BxN* K/BxN serum transfer arthritis, *AA* adjuvant arthritis, *TNFtg* TNF $\alpha$  transgenic mice spontaneous arthritis, *CFA* complete Freund's adjuvant-induced arthritis, *CAIA* anti-collagen antibody-induced arthritis, *m* murine, *r* rat, *n.d.* no data

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