The IL-17 Story: All in the Family

SLIDES FOR PROACTIVE USE BY MEDICAL TEAM ONLY

September 2024

Inspired by patients.
Driven by science.

US-DA-2400852

Objectives

1. Understand the biology, structure, and function of the IL-17 family

2. Understand how the IL-17 family of cytokines can play a role in health and protection against disease

3. Highlight the emerging evidence that supports a role of the IL-17 family cytokines in immune-mediated inflammatory diseases and other conditions

IL, interleukin

An introduction to the IL-17 family of cytokines

The IL-17 family includes 6 structurally related cytokines

IL-17A **IL-17B** **IL-17C** **IL-17D** **IL-17E** **IL-17F**

IL-17A: prototypic member – first documented in 1993, in T cells[1,2]

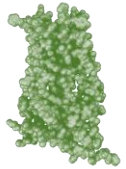
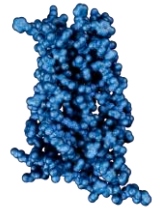
IL-17A and IL-17F: Most widely studied.
Well established role in the development of SpA and other inflammatory diseases[2,3]

IL-17B, IL-17C, IL-17D, and IL-17E: More recently characterized.
Emerging evidence on their role in inflammatory disease, but still largely unknown

IL, interleukin; SpA, spondyloarthritis

1. Liu X, et al. Int Arch Allergy Immunol. 2020;181:618–623. 2. Brembilla NC, et al. Front Immunol. 2018;9.doi:10.3389/fimmu.2018.01682. 3. Navarro-Compán V, et al. Front Immunol. 2023;14. https://doi.org/10.3389/fimmu.2023.1191782

The IL-17 family includes 6 structurally related cytokines

IL-17A	IL-17B	IL-17C	IL-17D	IL-17E	IL-17F
					
	29%	23%*	25%*	17%*	~50%*

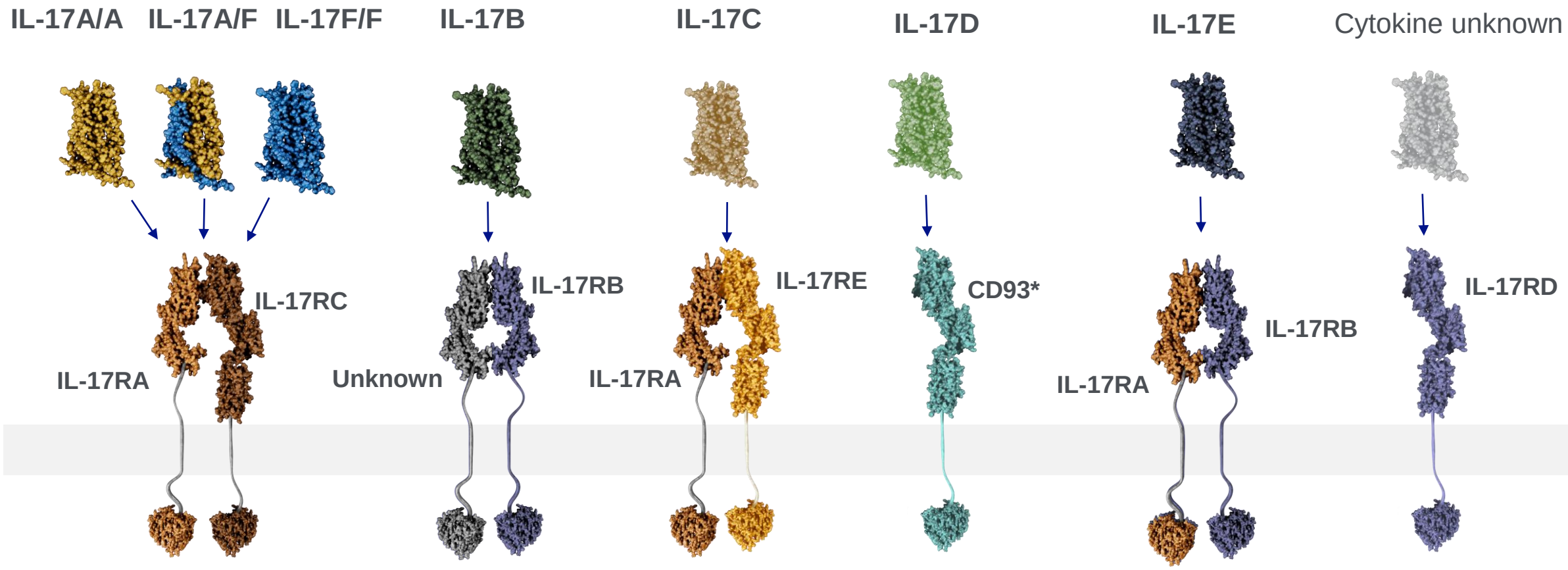
IL-17F shares the highest homology to IL-17A (~50%)[1,2]

*The percentages denote **structural homology** each family member shares with IL-17A[1]

IL, interleukin

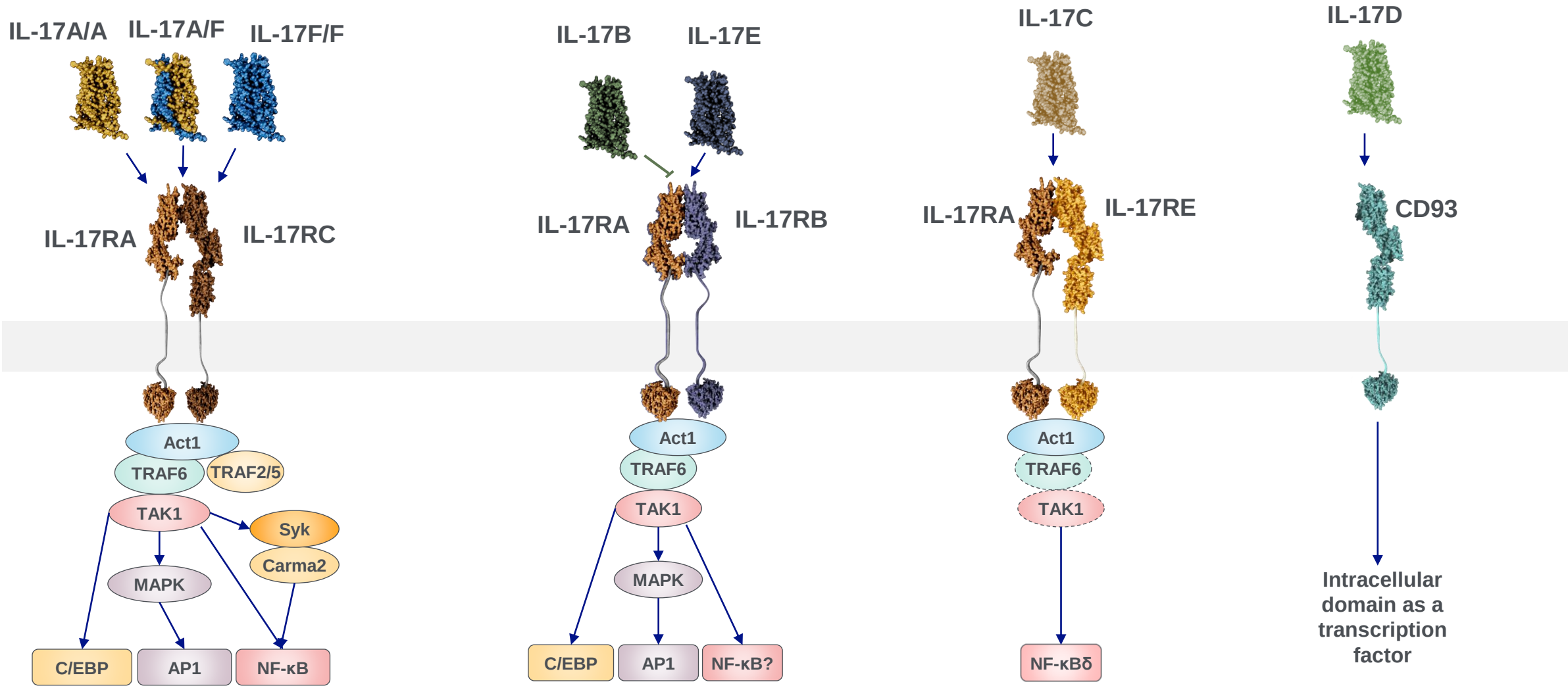
1. Liu X, et al. Int Arch Allergy Immunol. 2020;181:618–623. 2. Brembilla NC, et al. Front Immunol. 2018;9.doi:10.3389/fimmu.2018.01682

Each IL-17 cytokine binds to one or more receptors[1–4]



*CD93 receptor identified as a receptor for IL-17D involved in gastrointestinal tissues/cells but receptors in other cells are unknown
CD93, Cluster of Differentiation 93; IL, interleukin; IL-17R, interleukin 17 receptor
1. Liu X, et al. Int Arch Allergy Immunol. 2020;181:618–623. 2. Brembilla NC, et al. Front Immunol. 2018;9:1682. 3. Gaffen SS. Nat Rev Immunol. 2009;9:556. 4. Ruiz de Morales JMG, et al. Autoimmun Rev. 2020;19:102429

The IL-17 family act via both shared and distinct intracellular secondary signaling pathways



Act1, actin 1; AP1, activator protein 1; C/EBP, CCAAT/enhancer binding proteins; CD93, Cluster of Differentiation 93; IL, interleukin; IL-17R, interleukin 17 receptor; MAPK, mitogen-activated protein kinases; NF-κB, nuclear factor kappa light chain enhancer of activated B cells; Syk, spleen tyrosine kinase; TAK1, transforming growth factor β-activated kinase 1; TRAF, tumor necrosis factor receptor associated factor

Chung S-H, et al. Int Immunol. 2021;12:723–729

IL-17 cytokines play a key role in both health and disease

Health

Protection from infection[1]

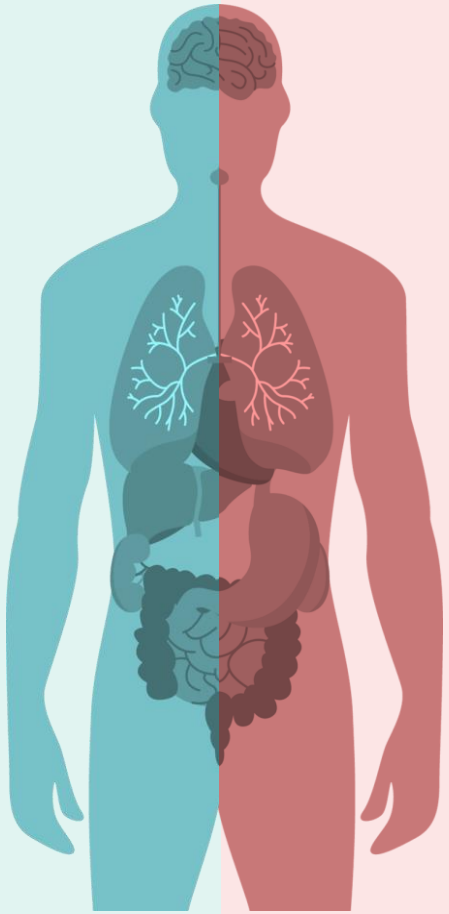
- Mediate immune response
- Microbiota homeostasis

Other protective functions[1]

- Wound healing
- Epithelial proliferation
- Barrier function
- Protection against some diseases

Metabolism/homeostasis[1]

- Metabolism
- Thermogenesis
- Adipose regulation



Disease

SpA[1,2]

- Chronic inflammation
- Tissue remodelling
- Bone erosion

Other IMIDs[1,2]

- PSO, HS
- SLE, RA
- IBD

Other diseases/conditions[1]

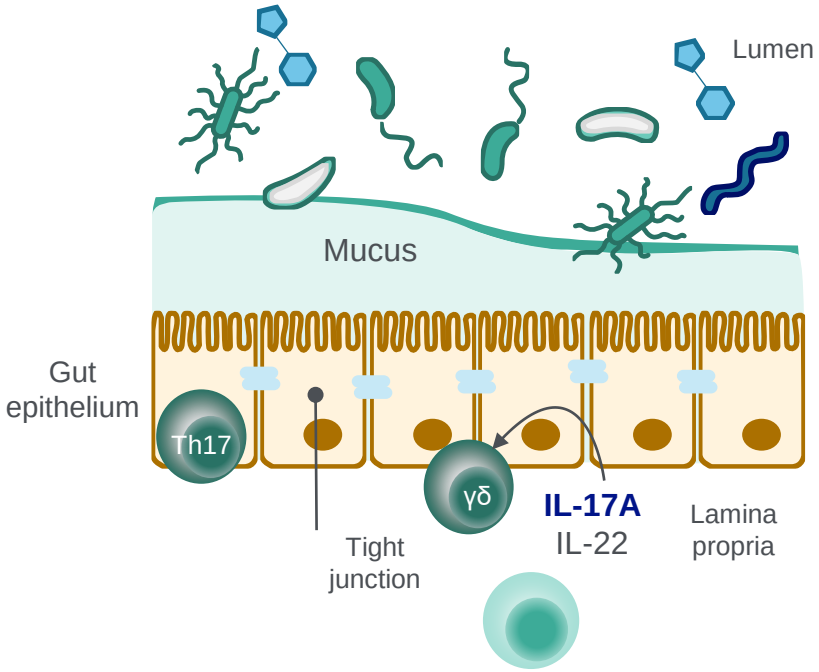
- Obesity
- Cancer
- Asthma
- Neurodegeneration, MS, depression

Figure adapted from McGeachy MJ, et al. Immunity. 2019;50:892-906. Copyright 2019, with permission from Elsevier
HS, hidradenitis suppurativa; IBD, inflammatory bowel disease; IL, interleukin; IMID, immune-mediated inflammatory disease; MS, multiple sclerosis; PSO, psoriasis; RA, rheumatoid arthritis; SLE, systemic lupus erythematosus; SpA, spondyloarthritis

1. McGeachy MJ, et al. Immunity. 2019;50:892–906. 2. Davydova A, et al. Biomedicines. 2023;11:1328

There are shared immune pathways in both health and disease

Healthy gut



Inflammation (e.g., gut-joint axis in SpA)

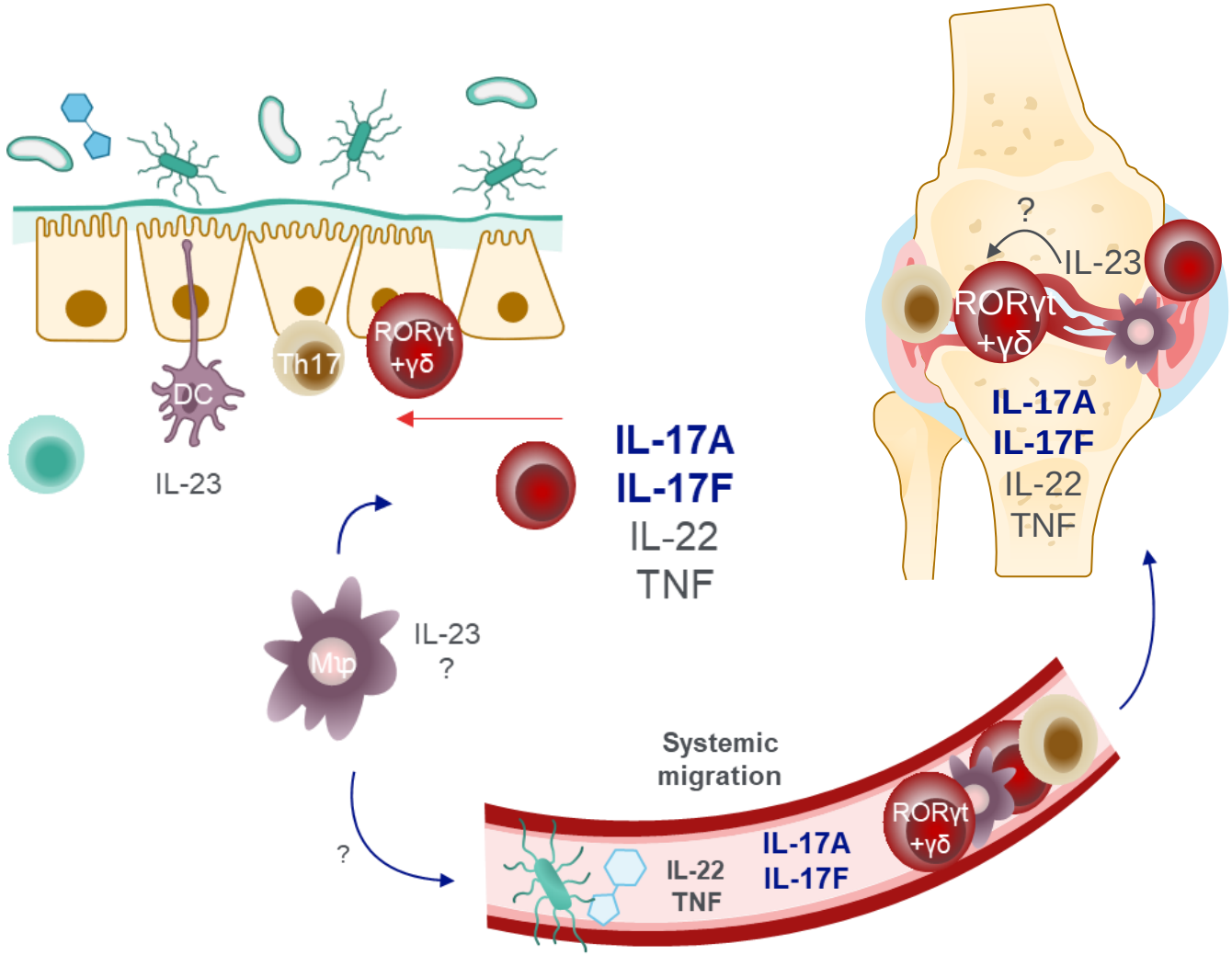
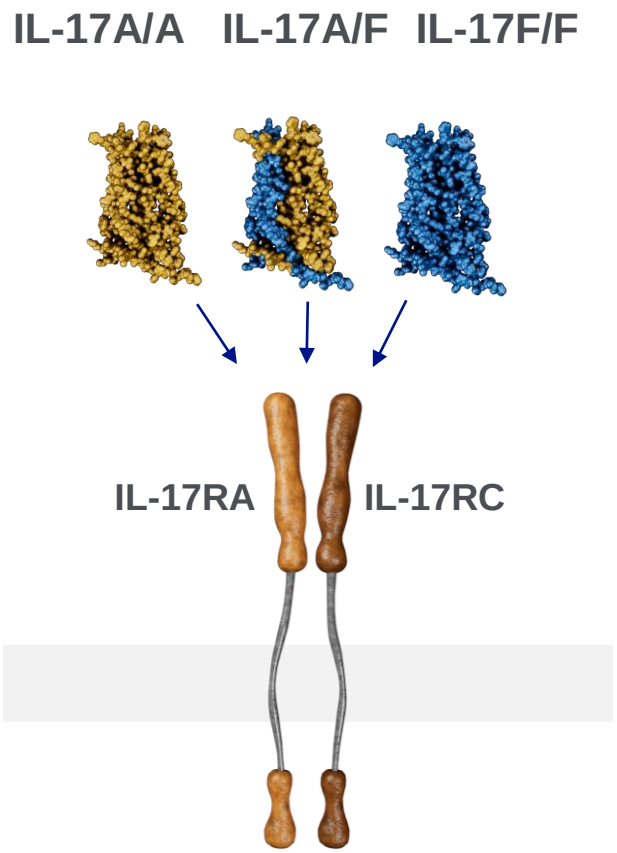


Figure courtesy of Dr Elewaut
DC, dendritic cell; IL, interleukin; SpA, spondyloarthritis; Th17, T helper 17; TNF, tumor necrosis factor

The role of IL-17 family in health and disease

IL-17A and IL-17F form homodimers and heterodimers



2x homodimers and 1x heterodimer

Use the same receptor complex

Different receptor binding affinities to the three dimers correlate with biological potencies

IL, interleukin; IL-17R, interleukin 17 receptor
Sánchez-Rodríguez, G. Int J Mol Sci. 2023;24:10305

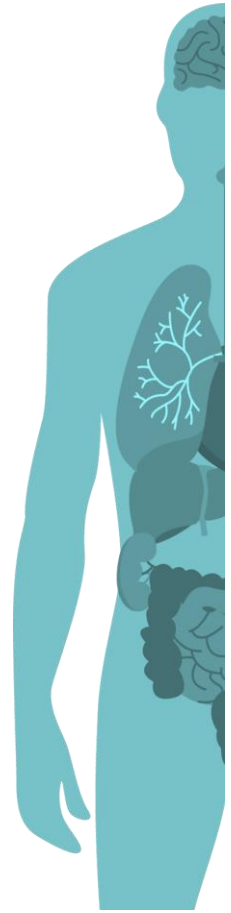
IL-17A vs IL-17F: Shared roles in health[1-5]

IL-17A

- Maintenance of gut epithelium[1-3]
- Protection against IBD[1,2]
- Skin/wound healing[2,3,5]
- Adipogenesis regulation and glucose homeostasis[3]

IL-17F

- Remain to be elucidated



IBD, inflammatory bowel disease; IL, interleukin

1. Chung SH, et al. Int Immunol. 2021;33:723–729. 2. Meehan EV, Wang K. Genes 2022;13:1643. 3. Davydova A, et al. Biomedicines. 2023;11:1328. 4. Navarro-Compán V, et al. Front. Immunol. 2023;14. https://doi.org/10.3389/fimmu.2023.1191782. 5. Bechara R, et al. J Exp Med. 2021;218:10.1084/jem.20202191

IL-17A and IL-17F play an important role in protection against fungal and bacterial infections

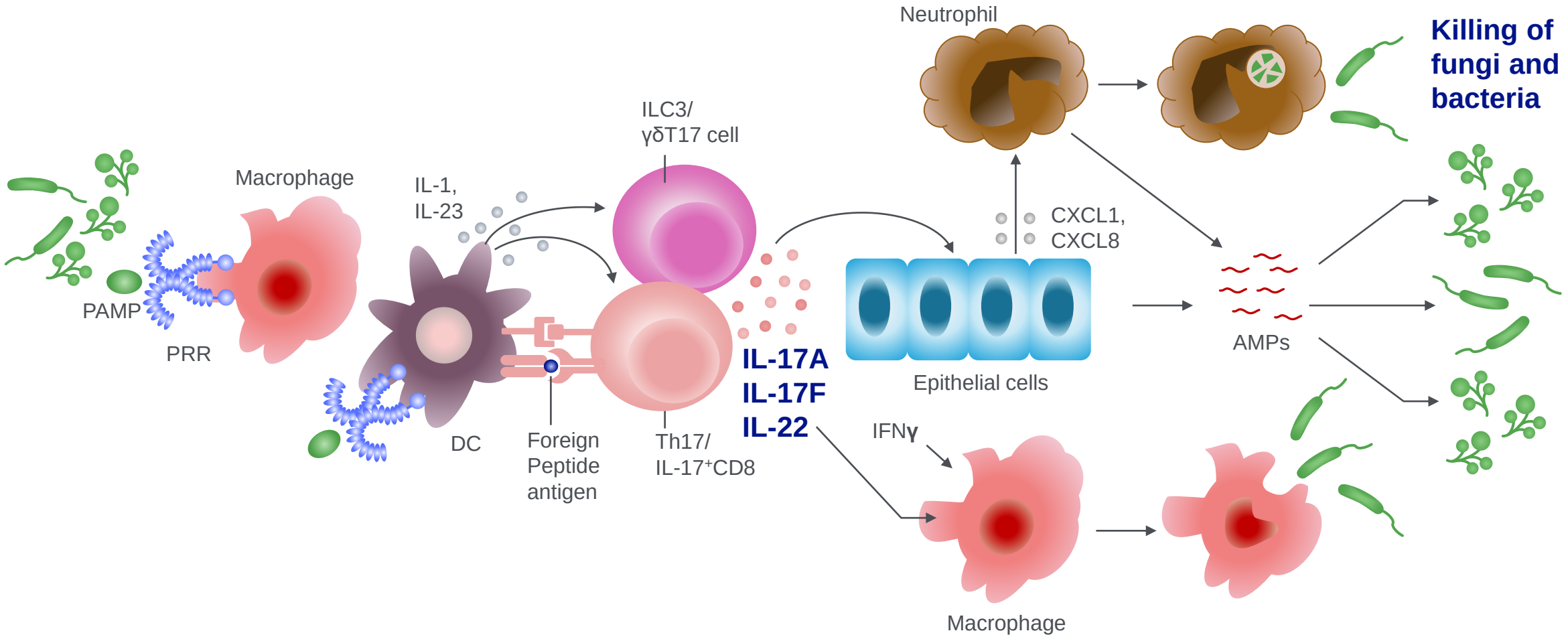


Figure from Mills et al. Nat Rev Immunol 2023;23:38–54, Springer Nature, 2023, adapted with permission from SNCSC
AMP, adenosine monophosphate; CXCL, chemokine ligand 1; DC, dendritic cell; IFN, interferon; IL, interleukin; ILC3;Type 3 innate lymphoid cells; PAMP, pathogen-associated molecular patterns; PRR, Pattern Recognition Receptors; Th17, T helper 17
Mills KHG, et al. Nat Rev Immunol. 2023;23:38–54

IL-17A and IL-17F play a role in protection against mucocutaneous candida infections

Protective immunity after epidermal *Candida* colonization requires both IL-17A and IL-17F

Candida albicans **CFUs in the skin of WT, *Il17a* $^{-/-}$, *Il17f* $^{-/-}$, and *Il17af* $^{-/-}$ mice on Day 7 after inoculation**

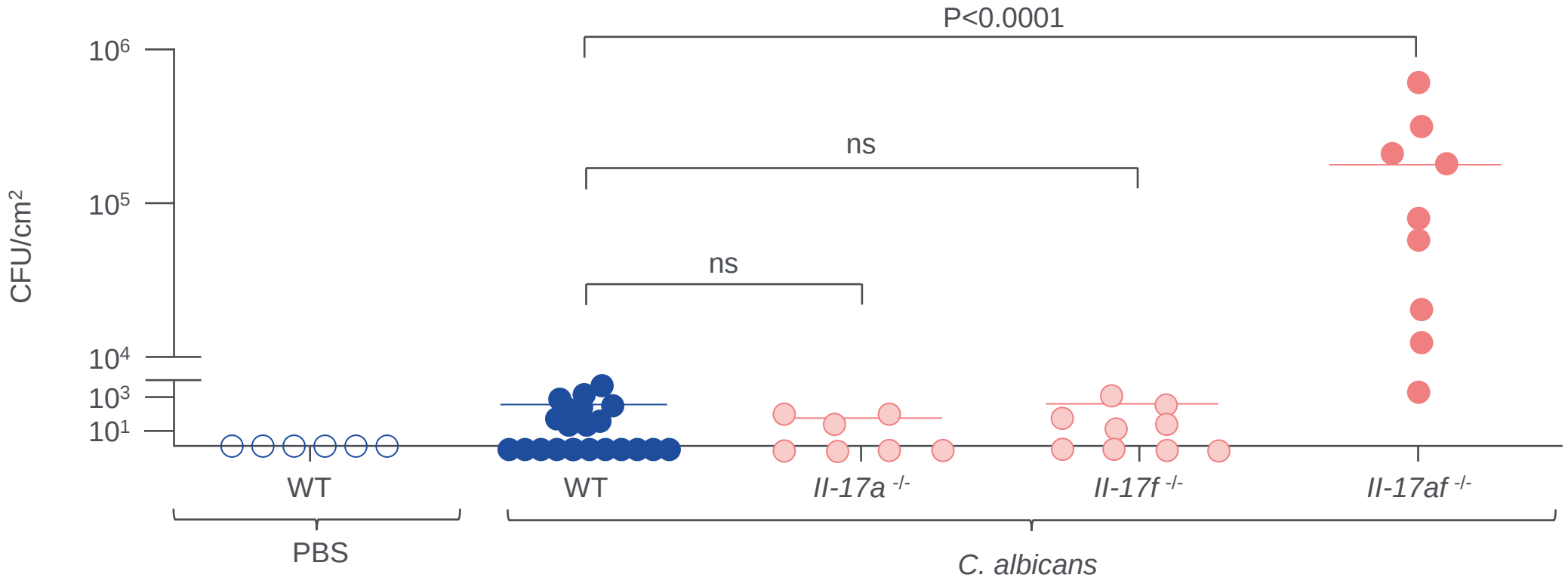
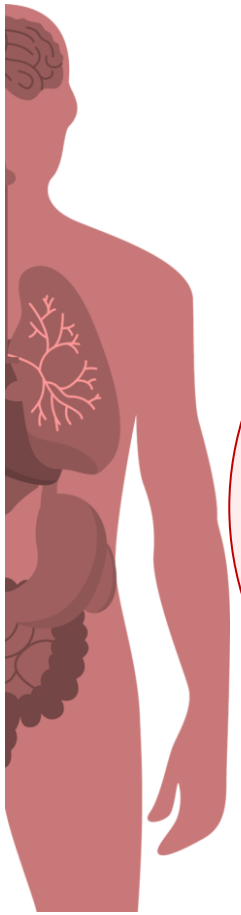


Figure adapted from Iwasawa MT et al. International Immunology. 2022;34(8)409-420
CFU, colony-forming units; IL, interleukin; ns, not significant; PBS, phosphate-buffered saline; WT, wild-type
Iwasawa MT, et al. Int Immunol. 2022;34:409-420

IL-17A and IL-17F: Shared roles in mediating disease



IL-17A

Rheumatic disease
- SLE[1]

Other conditions
- Neurocognitive disorders (i.e., MS)[2,4,5]
- Chronic pain[6]

IL-17F

Rheumatic disease
- PsA, axSpA[4]
- RA[2]

Other IMIDs
- Psoriasis[4,5]
- HS[4]

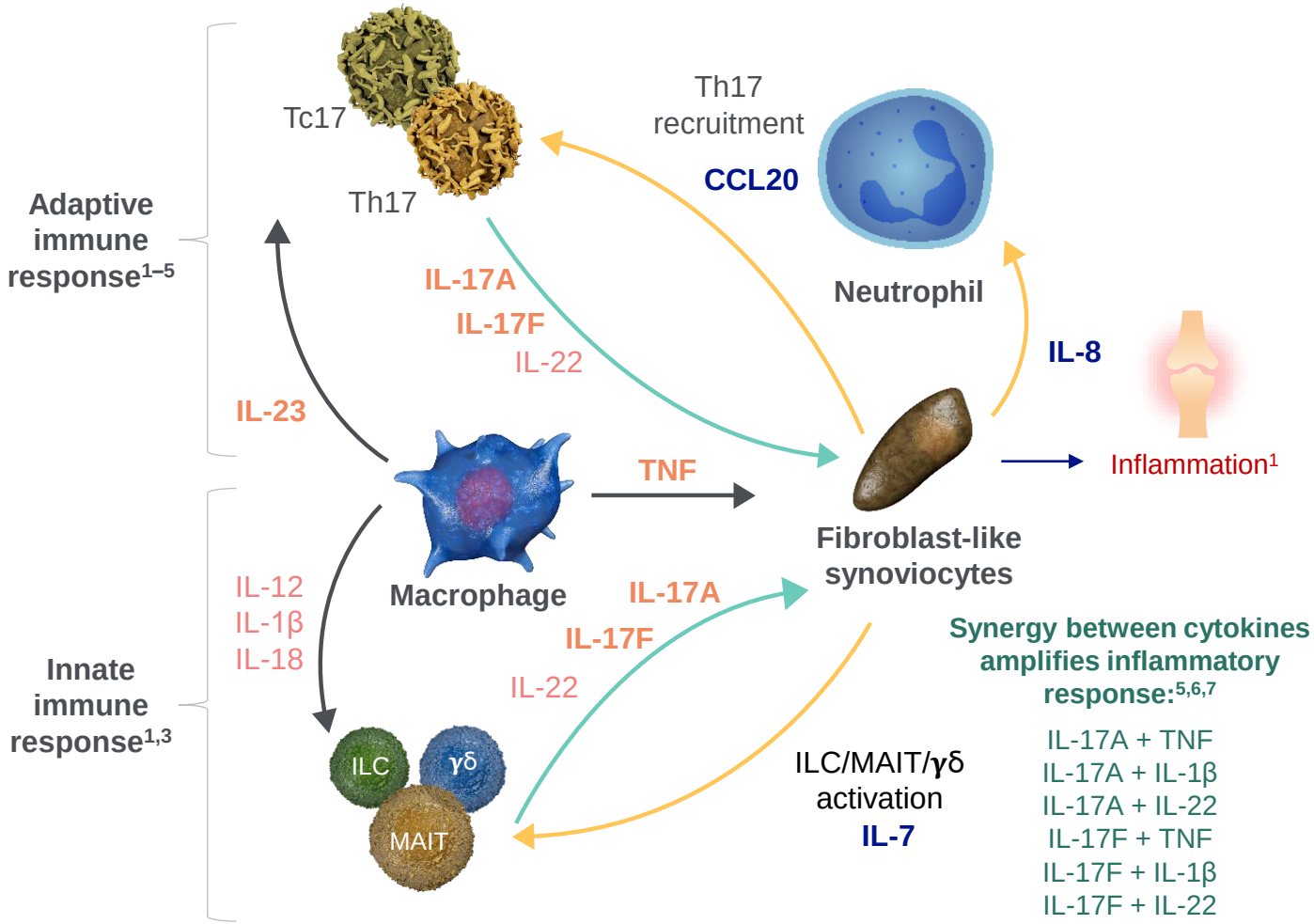
Other conditions
- Tumors[3]
- Obesity[7]
- Asthma[4]

- Remain to be elucidated

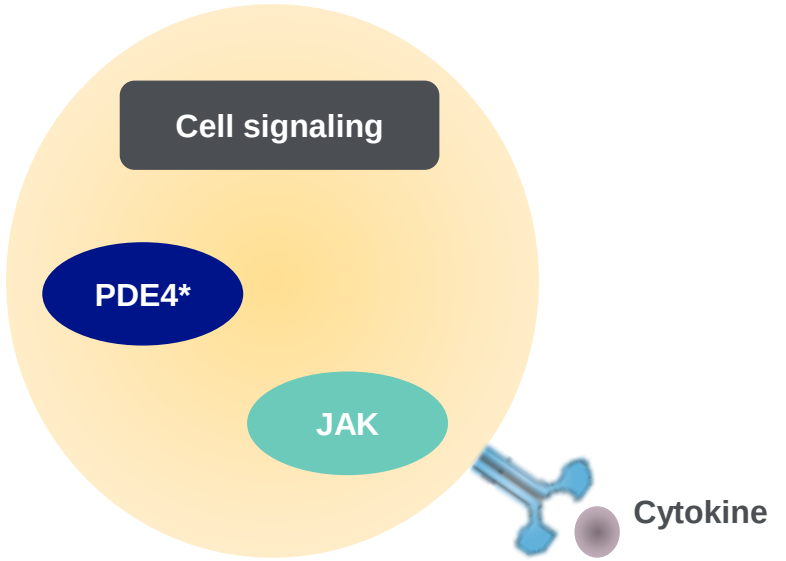
axSpA, ankylosing spondyloarthritis; HS, hidradenitis suppurativa; IBD, inflammatory bowel disease; IL, interleukin; IMID, immune-mediated inflammatory disease; MS, multiple sclerosis; PsA, psoriatic arthritis; RA, rheumatoid arthritis; SLE, systemic lupus erythematosus

1. Koga T, et al. Front Immunol. 2021;11:624971. 2. Chung SH, et al. Int Immunol. 2021;33:723–729. 3. Meehan EV, Wang K. Genes. 2022;13:1643. 4. Navarro-Compán V, et al. Front Immunol. 2023;14. 5. Davydova A, et al. Biomedicines. 2023;11:1328. 6. Jiang X, et al. Front. Immunol. 2022.13:999407. 7. Polak-Szczybyło E, et al. Nutrients. 2022;14:643.

Key inflammatory pathways involved in the pathobiology of PsA and axSpA



Other factors that regulate cytokine production[8–10]



*PDE4 has been shown to play a role in PsA (but not axSpA)

APC, antigen-presenting cell; axSpA, axial spondyloarthritis; CCL,C-C motif chemokine ligand; IL, interleukin; ILC, innate lymphoid cell; JAK, Janus kinase; MAIT, mucosal-associated invariant T cells; PDE4, phosphodiesterase 4; PsA, psoriatic arthritis; Tc, CD8+ T cell; Th, T helper; TNF, tumor necrosis factor. Figure adapted from Smith J and Colbert R. Arthritis Rheumatol. 2014;66:231–241

1. Tsukazaki H, Kaito T. Int J Mol Sci. 2020;21:6401. 2. Blanco P, et al. Cytokine Growth Factor Rev. 2008;19:41–52. 3. Rosine N, Miceli-Richard C. Front Immunol. 2021;11:553742. 4. Cole S, et al. Front Immunol. 2020;11:585134. 5. Taams L, et al. Nat Rev Rheum. 2018;14:453–466. 6. Noack M, et al. Front Immunol. 2019;10:1726. 7. Onishi RM, Gaffen SL. Immunology. 2010;129:311–321. 8. Crispino N, Ciccia F. Clin Exp Rheumatol. 2021;39:668–675. 9. Picchianti-Diamanti A, et al. Int J Mol Sci. 2021;22:2638. 10. Hammitzsch A, et al. Front Immunol. 2020;11:591176.

IL-17A and IL-17F are both drivers of inflammation and new bone formation in models of PsA and axSpA[1-3]

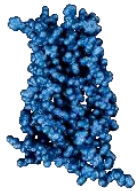
Innate immunity-driven pathology[1]

Innate lymphocytes

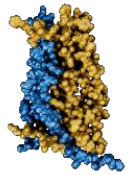
Adaptive immunity-driven pathology[1]

IL-23

Adaptive lymphocytes



IL-17F/F

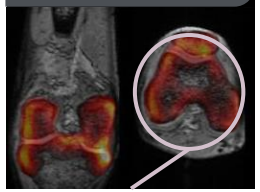


IL-17A/F

IL-17A/A

Inflammation and new bone formation in SpA[3]

Peripheral Joint[6]*

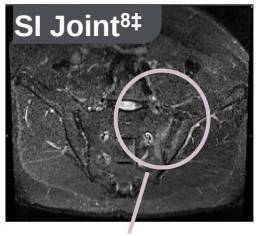


Hypermetabolic Activity

Skin[7]†

Epidermal hyperplasia

SI Joint[8]‡



Bone marrow edema

Spine[9]§

Non-bridging syndesmophytes

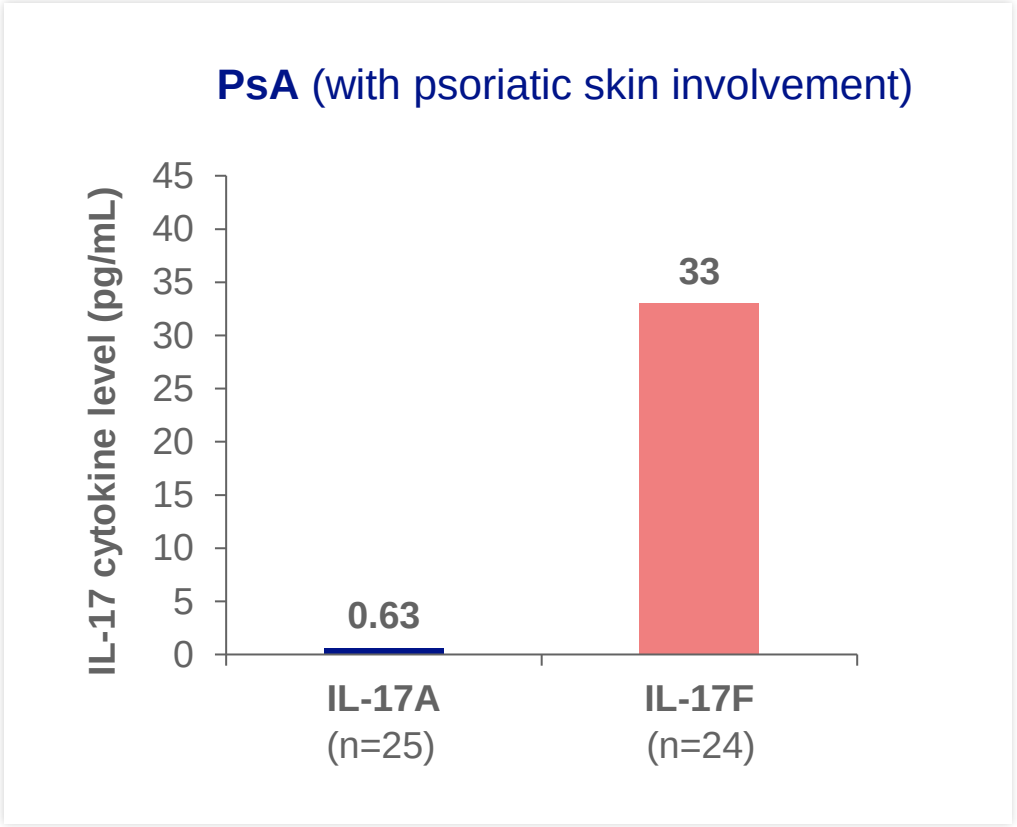
IL-17 production by innate lymphocytes can be independent of IL-23[4,5]

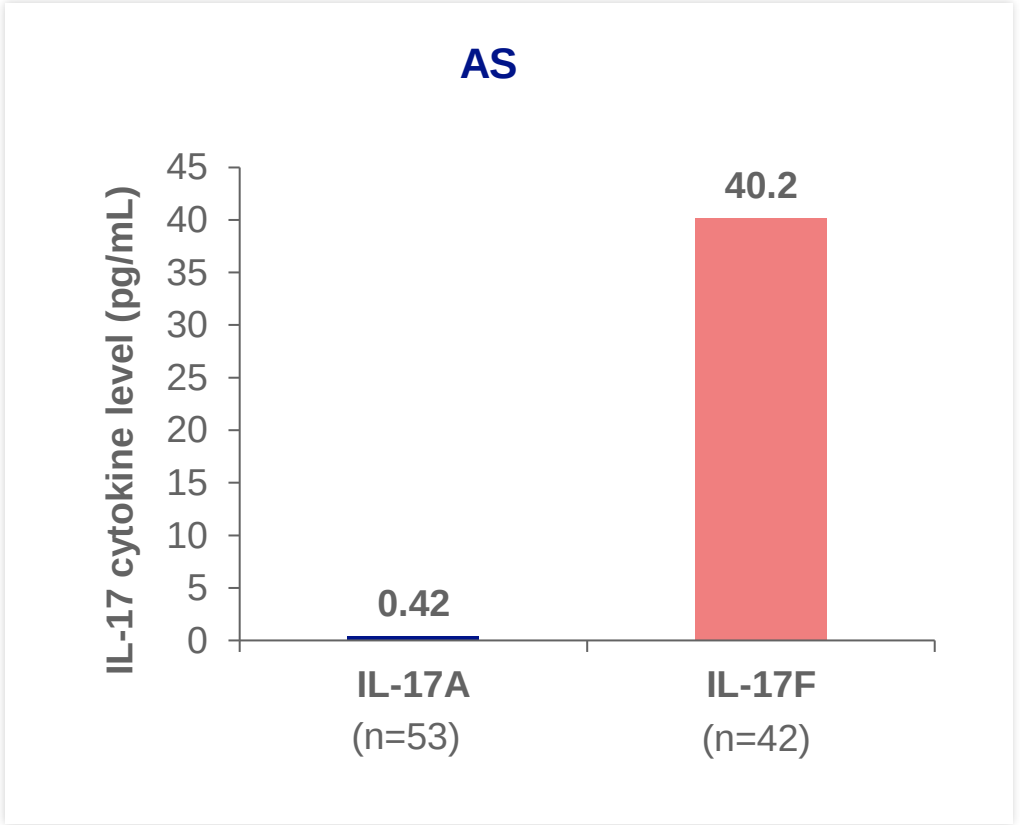
*Images on right: Reproduced from Soldati et al. PLoS One. 2021;16(5):e02517885 under the Creative Commons Attribution License (CC BY 4.0), (https://creativecommons.org/licenses/by/4.0/).
†Reproduced from Gottlieb A et al. PLoS One. 2015;10:e0134703 under CC BY 4.0. ‡Reproduced from Nicolaes et al. ACR Convergence 2021, Poster 0157 with permission of the author.
§Reproduced from Laloo et al. Insights Imaging 10, 67 (2019), under CC BY 4.0
axSpA, axial spondyloarthritis; IL, interleukin; PsA, psoriatic arthritis; SI, sacroiliac; SpA, spondyloarthritis

1. Tsukazaki H, Kaito T. Int J Mol Sci. 2020;21:6401. 2. Glatt S, et al. Ann Rheum Dis. 2018;77:523–532. 3. Shah M, et al. RMD Open. 2020;6:e001306. 4. Cole S, et al. Front Immunol. 2020;11:585134.
5. Łukasik Z, et al. Rheumatology (Oxford). 2021;60(Suppl 4):iv16-iv27. 6. Soldati E, et al. PLoS One. 2021;16:e0251788. 7. Gottlieb A, et al. PLoS One. 2015;10:e0134703.
8. Nicolaes J, et al. ACR Convergence 2021. Poster 0157. 9. Poddubnyy D and Sieper J. Curr Rheumatol Rep. 2017;19:55

IL-17F is more abundant than IL-17A in serum from patients with PsA and AS

Expression of IL-17A and IL-17F in patient serum

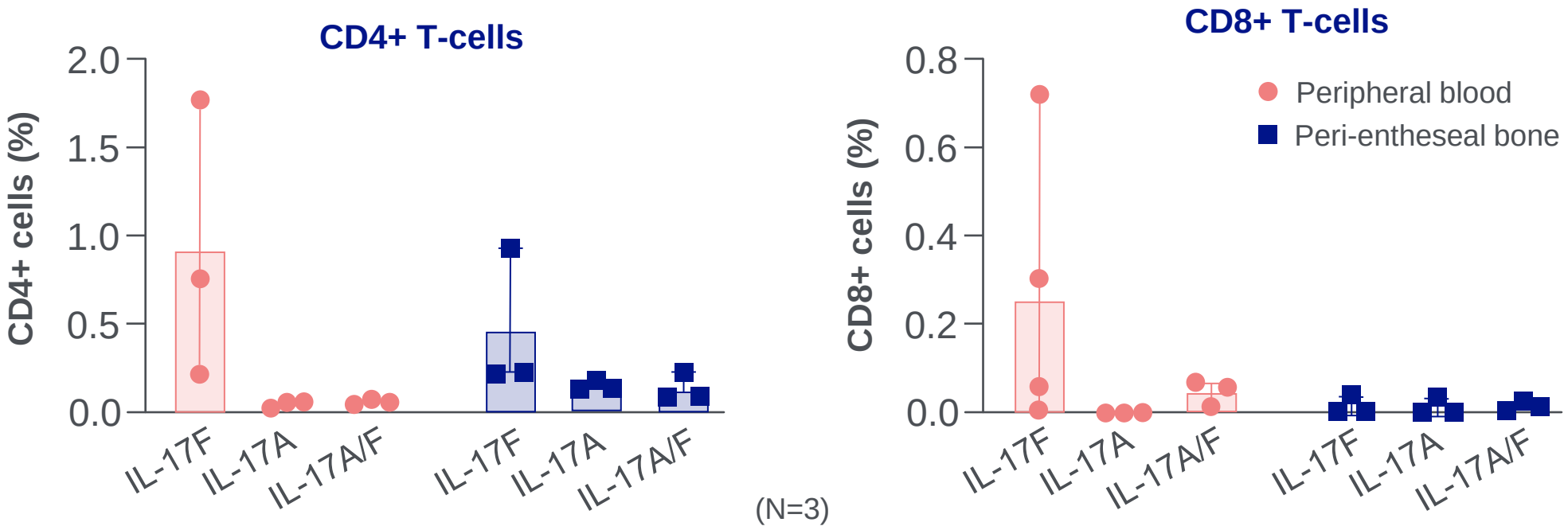




Figures created using data from Kolbinger et al. J Allergy Clin Immunol. 2017;139:923–932
AS, ankylosing spondylitis; IL, interleukin; PsA, psoriatic arthritis
Kolbinger F, et al. J Allergy Clin Immunol. 2017;139:923–932

IL-17F is the dominant IL-17 isoform expressed by innate and adaptive lymphocytes, at the enthesis

Percentage of IL-17F, IL-17A, and IL-17A/F co-expression via flow cytometry after 72 hours of inflammatory activation

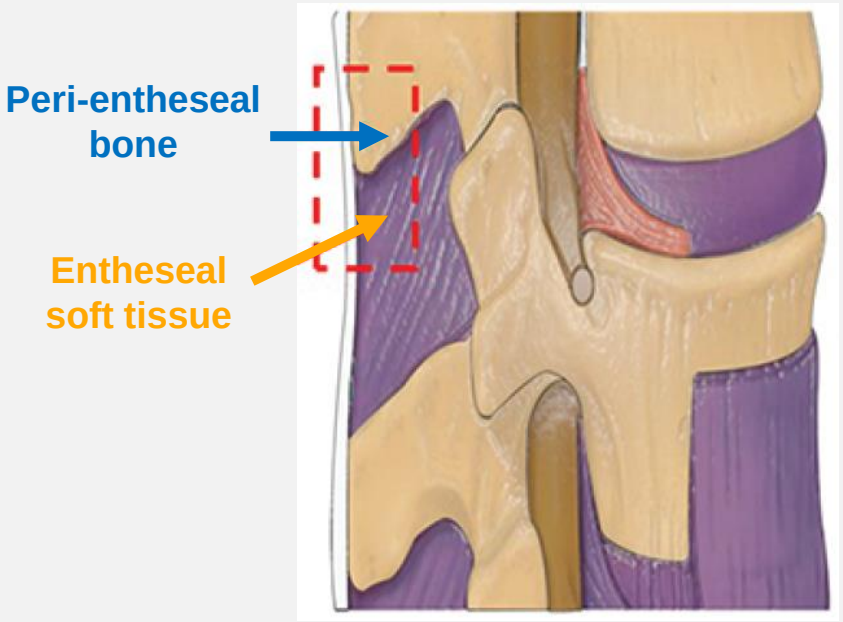


In peripheral blood and enthesis, **IL-17F was preferentially expressed** over IL-17A by CD4+ and CD8+ T-cells

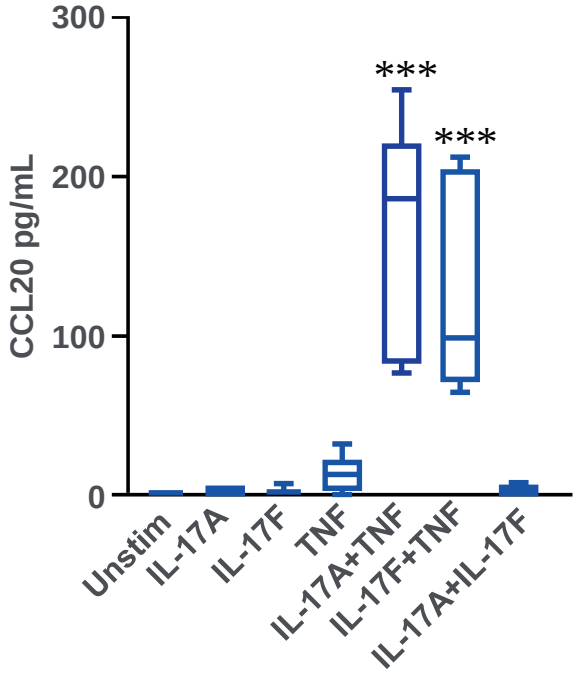
IL-17 expression by CD4 & CD8 T-cells in peripheral blood & peri-entheseal bone was measured following 72hrs stimulation with anti-CD3 & CD28 (100 ng/ml).
Error bars are representative of the mean with range. N=3
Figure reproduced from McDermott N et al. Ann Rheum Dis. 2023;82(Suppl 1):1184 with permission from BMJ Publishing Group Ltd.
CD, Cluster of Differentiation; CyTOF, cytometry by time-of-flight; IL, interleukin; PBMC, peripheral blood mononuclear cell
McDermott N et al. Ann Rheum Dis. 2023;82(Suppl 1):1184. Abstract AB0011

IL-17A and IL-17F are produced by entheseal T cells and synergize with TNF to drive inflammation

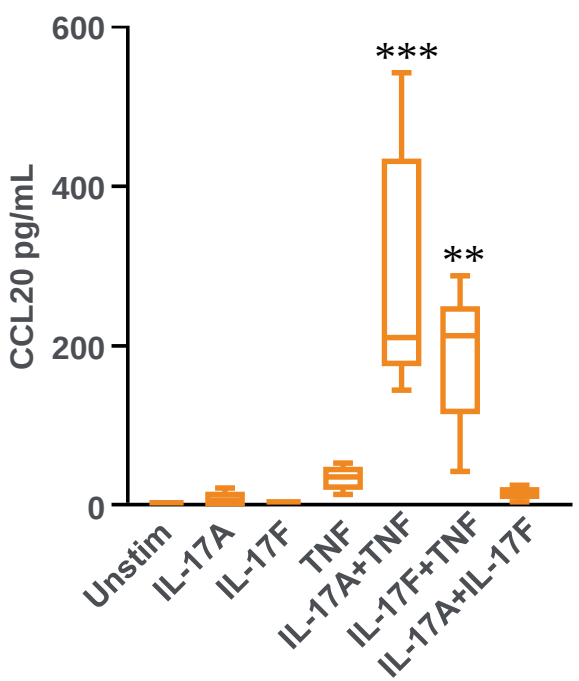
Inflammation of tendon/ligament anchorage points is the cardinal lesion in SpA



Peri-entheseal bone stromal cells



Soft tissue stromal cells



IL-17A and IL-17F synergize with TNF to induce CCL20 from enthesis stromal cells, potentially driving further migration of IL-17–producing lymphocytes to entheseal tissues

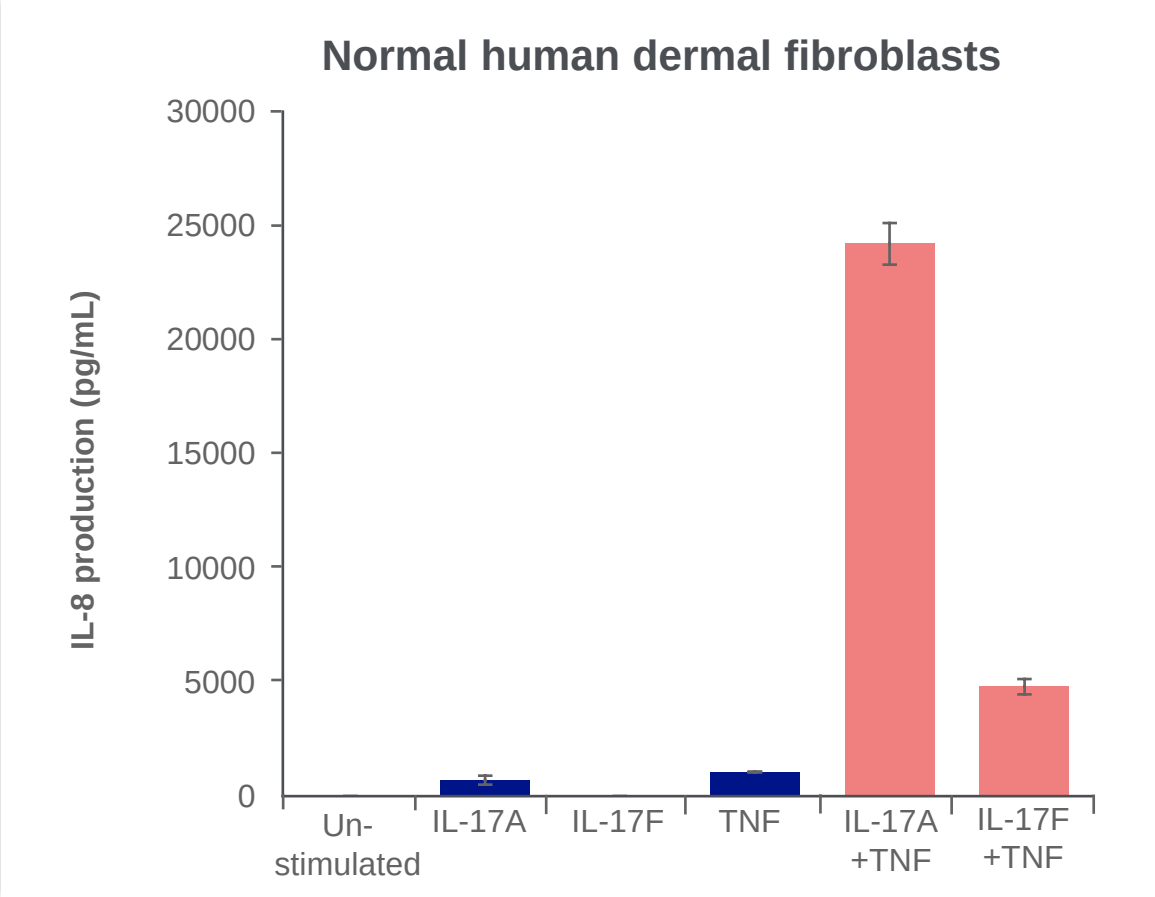
*P<0.05, **p<0.01, ***P<0.001 (one-way ANOVA). Stromal cells from patients undergoing spinal decompression or surgery for scoliosis correction were isolated from both PEB and ST and were stimulated for 48 hr with combinations of IL-17A, IL-17F, and TNF. CCL20 was subsequently measured by ELISA

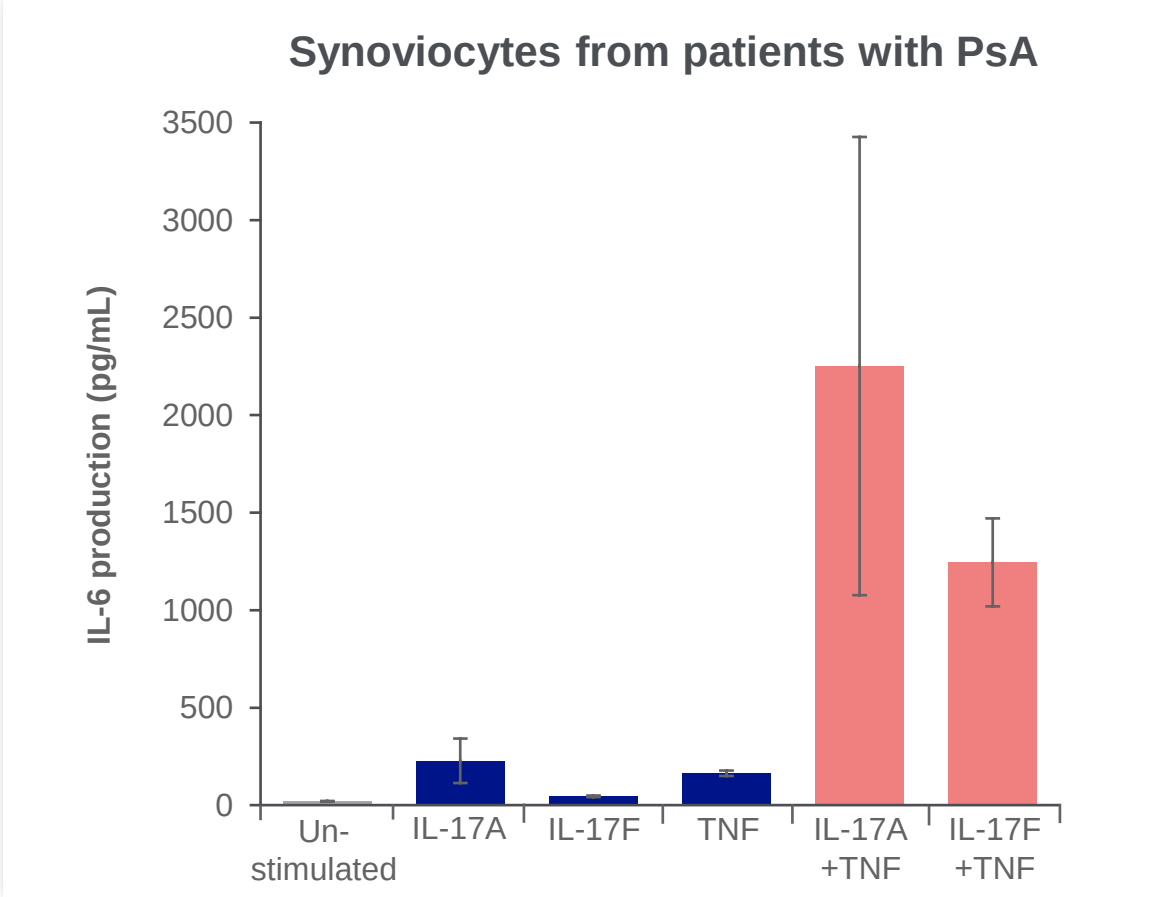
Figures adapted from Bridgewood et al. Ann Rheum Dis. 2019;78:274. Abstract THUR0013 with permission from BMJ Publishing Group Ltd.

ANOVA, analysis of variance; CCL, chemokine ligand; IL, interleukin; PEB, Peri-entheseal bone; SpA, spondyloarthritis; ST, soft tissue; TNF, tumor necrosis factor

Bridgewood, et al. Ann Rheum Dis. 2019;78:274. Abstract THUR0013

IL-17A and IL-17F are drivers of inflammation in *in vitro* models of SpA

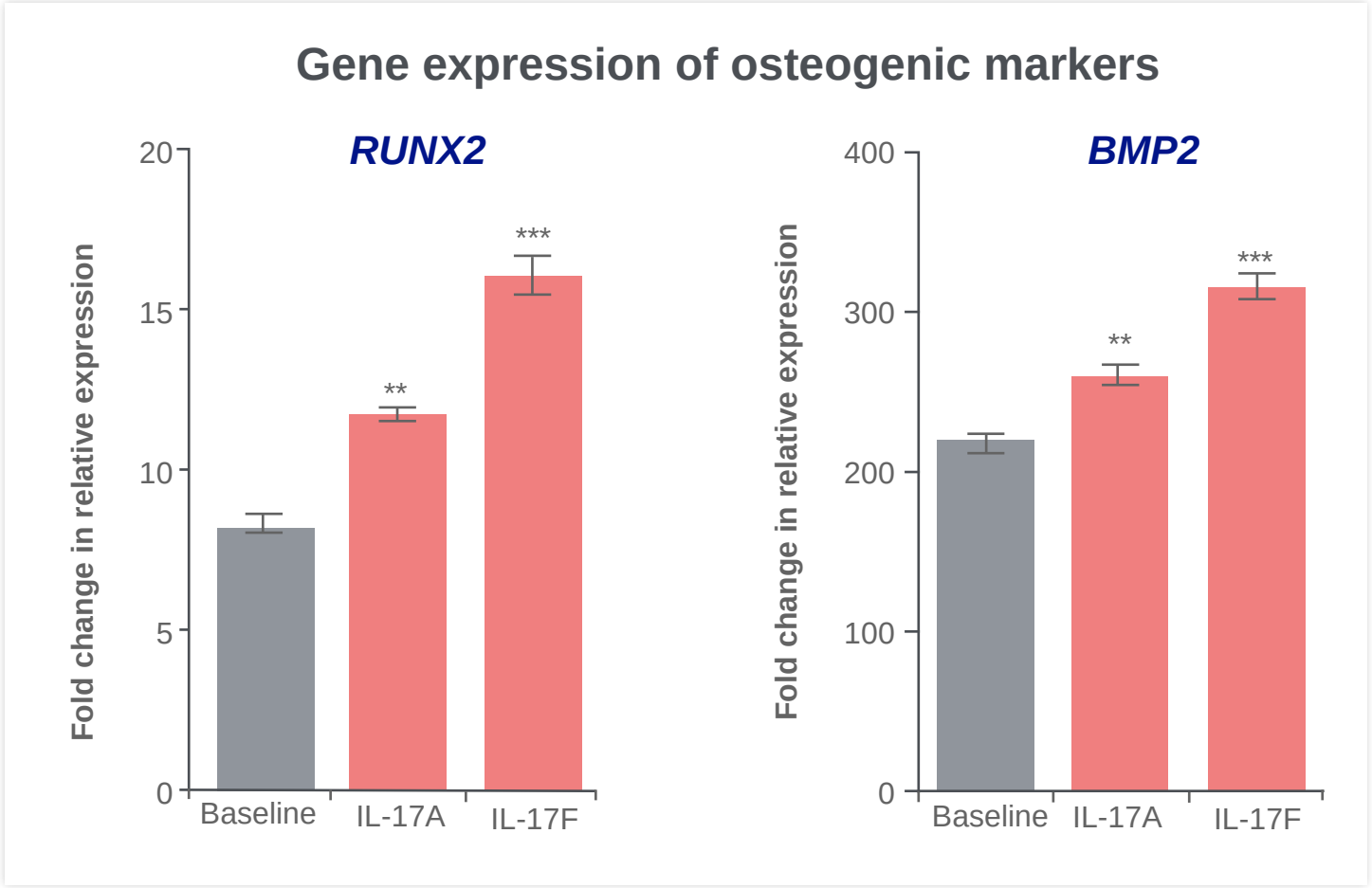


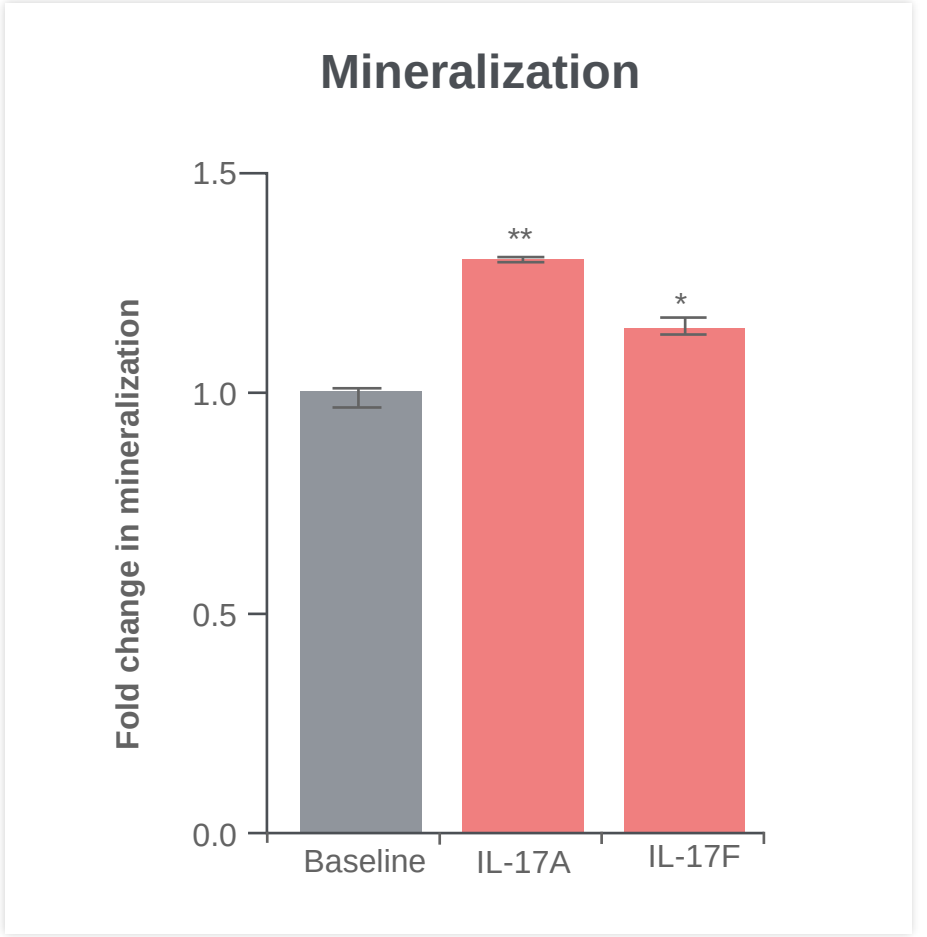


IL-17A and IL-17F independently cooperate with TNF to drive inflammation (amplify production of IL-8 and IL-6)

Normal human dermal fibroblasts and synoviocytes from patients with PsA: data are mean ± SEM. TNF at 1 ng/ml. IL-17A and IL-17F at 100 ng/ml
Figures adapted from Glatt et al. Ann Rheum Dis. 2018;77:523-532 with permission from BMJ Publishing Group Ltd.
IL, interleukin; PsA, psoriatic arthritis; SEM, standard error of the mean; TNF, tumor necrosis factor
Glatt S, et al. Ann Rheum Dis. 2018;77:523–532

IL-17A and IL-17F are drivers of new bone formation in *in vitro* models of SpA





IL-17A and IL-17F drive osteogenic differentiation of human periosteal stem cells

Inspired by patients. Driven by science.

**P<0.01; ***P<0.001 vs Baseline.
Figures adapted from Shah M et al. RMD Open. 2020;6(2):e001306 with permission from BMJ Publishing Group Ltd.
BMP2, bone morphogenetic protein 2; IL, interleukin; RUNX2, runt-related transcription factor 2
Shah M, et al. RMD Open. 2020;6(2):e001306

Role of IL-17A and IL-17F in SpA may differ across sites of inflammation

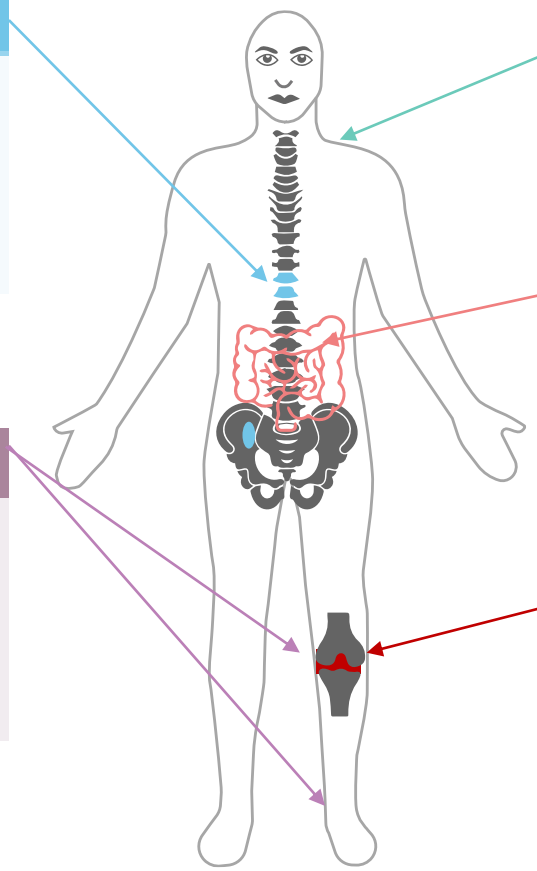
Summary of findings from pre-clinical and translational studies

Bone (axSpA and PsA)

- IL-17A & IL-17F: equal potency in promoting osteogenic differentiation[1]
- IL-17A & IL-17F can drive osteoproliferation in AS[1]

Peripheral and axial enthesis

- IL-17F > IL-17A expression[2]
- IL-17A & IL-17F produced by entheseal T cells and synergize with TNF[3]



Skin

- IL-17F > IL-17A in lesional skin and serum[4]

Gut (IBD)

- IL-17A is protective[5]

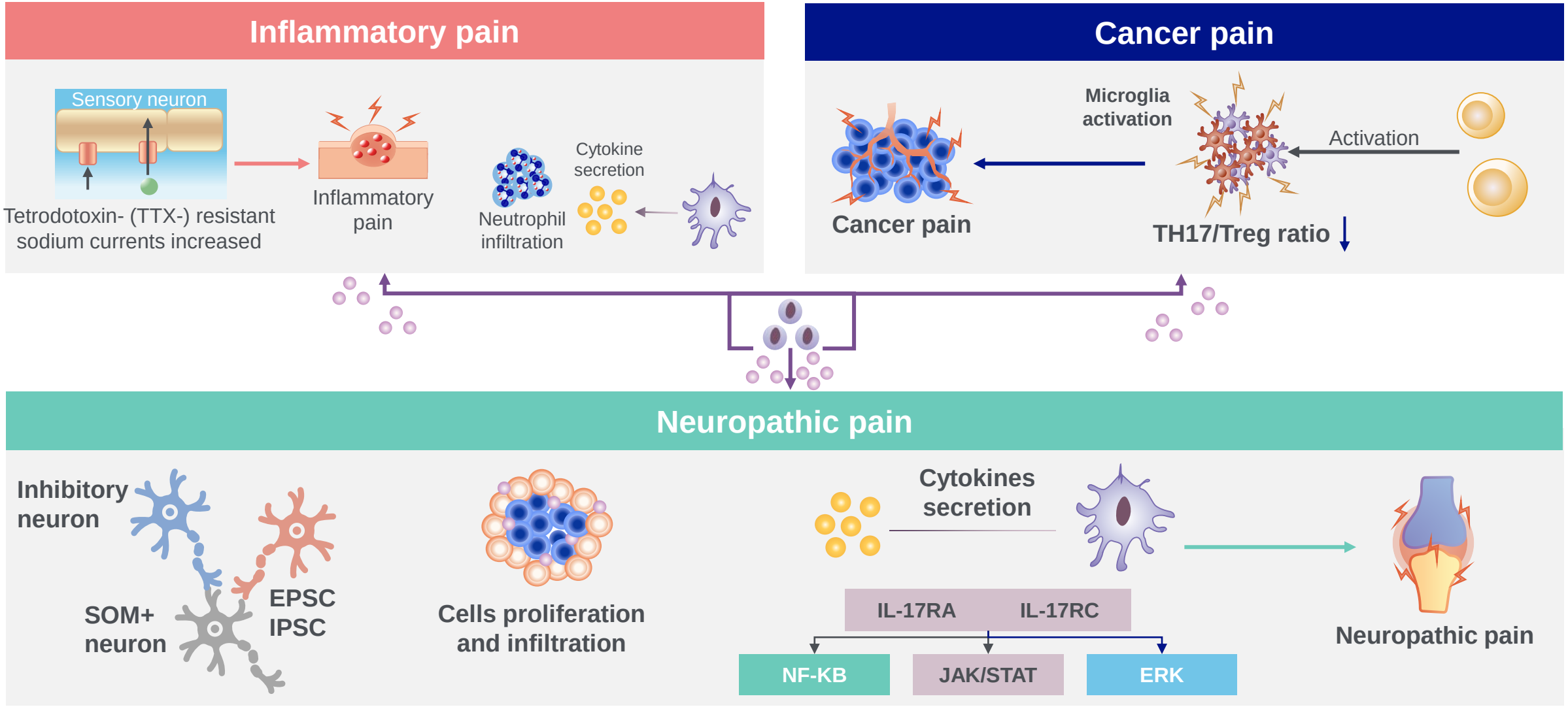
Joint (axSpA and PsA)

- IL-17A > IL-17F in SpA synovitis[4,6]
- ↑ IL-17F (not IL-17A) in synovial tissue in PsA vs OA[7,8]

AS, ankylosing spondylitis; IL, interleukin; ILC, innate lymphoid cells; OA, osteoarthritis; PsA, psoriatic arthritis; PSO, psoriasis; SpA, spondyloarthritis; TNF, tumor necrosis factor

1. Shah M, et al. RMD Open. 2020; 6:e001306. 2. McDermott N et al. Ann Rheum Dis. 2023;82(Suppl 1):1184. Abstract AB0011. 3. Bridgewood, et al. Ann Rheum Dis. 2019;78:274. Abstract THUR0013. 4. Yeremenko N. Curr Opin Rheumatol. 2021;33:333–340. 5. Zhou C, et al. Cytokine. 2021;148:155715. 6. Chen S, et al. J Rheumatol. 2020; 47:1606–1613. 7. Taams L, et al. Nat Rev Rheum. 2018;14:453–466. 8. Burns LA, et al. Eur J Immunol. 2020; 50:568–580

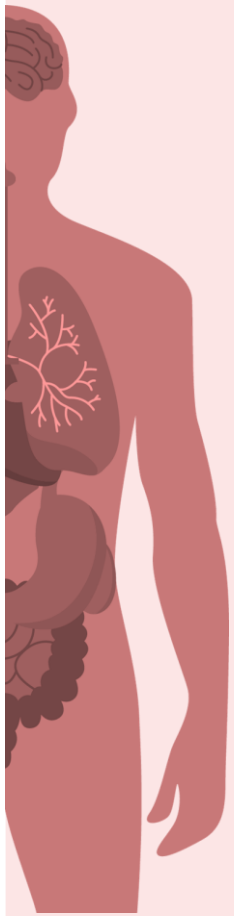
IL-17A plays an important role in chronic pain



EPSC, enhance excitatory postsynaptic currents; ERK, extracellular signal-regulated kinase; IL, interleukin; IPSC, reduce inhibitory postsynaptic currents; JAK, Janus kinase; NF-KB, nuclear factor-kappaB; SOM, somatostatin; STAT, signal transducers and activators of transcription; TH17, T helper 17; Treg, regulatory T cells
Jiang X, et al. Front Immunol. 2022;13:999407

The IL-17 Family: Additional insights on role in health and disease

IL-17B: Role in mediating disease



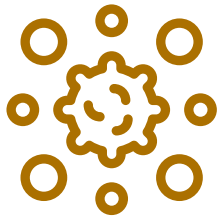
SpA

- Remains to be elucidated *(Established role in inflammation)*[1]

Other IMIDs

- Inflammatory arthritis (RA)[2,3]
- SLE[2]

Other diseases/conditions

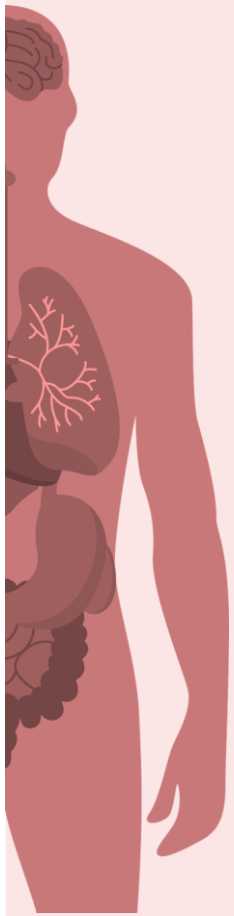


- Various cancers[2,3]
- Lung fibrosis[3]

IL, interleukin; IMID, immune-mediated inflammatory disease; RA, rheumatoid arthritis; SLE, systemic lupus erythematosus

1. Reynolds JM, et al. Immunity. 2015;42:692–703. 2. Davydova A, et al. Biomedicines. 2023;11:1328. 3. Fletcher JM, et al. Clin Exp Immunol. 2020;201:121–134

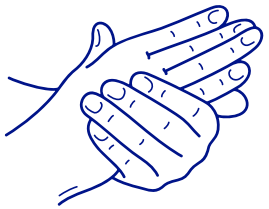
IL-17C: Role in mediating disease



SpA

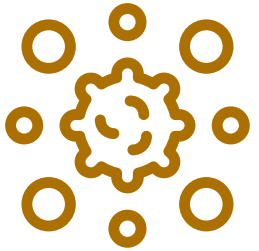
- Remains to be elucidated *(established role in inflammation)*[1]

Other IMIDs



- PSO[1]
- HS[2]
- IBD[3]

Other diseases/conditions

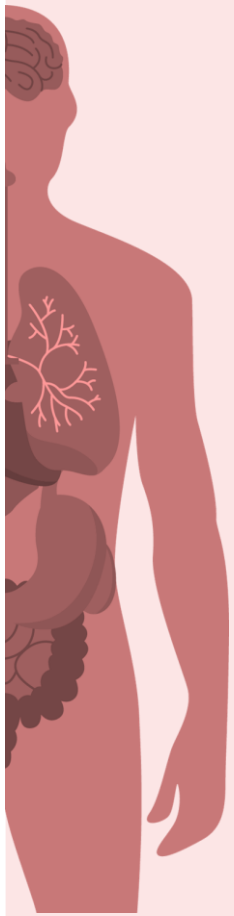


- Various cancers[1,3]
- Kidney disease[4]
- Kidney damage in SLE[5]

HS, hidradenitis suppurativa; IBD, inflammatory bowel disease; IL, interleukin; IMID, immune-mediated inflammatory disease; PSO, psoriasis; SLE, systemic lupus erythematosus

1. Meehan EV, Wang K. Genes. 2022;13:1643. 2. Fletcher JM, et al. Clin Exp Immunol. 2020;201:121–134. 3. Nies JF, Panzer U. Front Immunol. 2020;11:341. 4. Zhang, F. et al. eBioMedicine. 2023;92: 104607. 5. Davydova A, et al. Biomedicines. 2023;11:1328

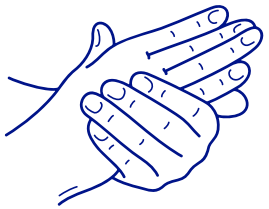
IL-17D: Role in mediating disease



SpA

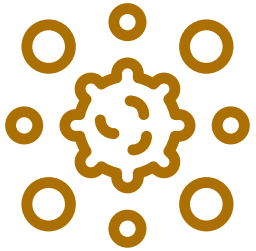
- **Protective role[1]**

Other IMIDs



- RA (detected in rheumatoid nodules)[2]

Other diseases/conditions

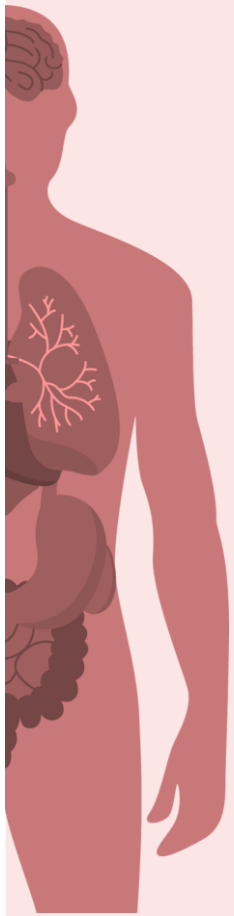


- Severe sepsis[3]
- Cancer[2]
  - Pathogenic role remains to be elucidated

IL, interleukin; IMID, immune-mediated inflammatory disease; RA, rheumatoid arthritis

1. Yeremenko N. Curr Opin Rheumatol. 2021;33:333–340. 2. Liu X, et al. Int Arch Allergy Immunol. 2020;181:618–623. 3. Davydova A, et al. Biomedicines. 2023;11:1328

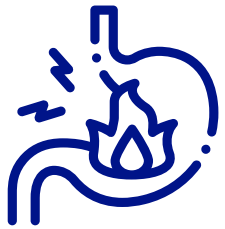
IL-17E: Role in mediating disease



SpA

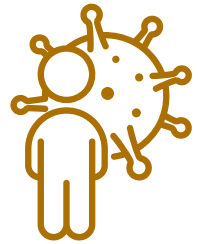
- Remains to be elucidated
  - May have an immune-modulatory effect in RA[1]

Other IMIDs



- PSO[1,2]

Other diseases/conditions



- Allergic responses[2,3]
- Asthma (bronchial)[2]
- Obesity[4]

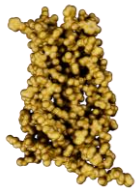
IL, interleukin; PSO, psoriasis; RA, rheumatoid arthritis

1. Liu Y, et al. J Immunol Res. 2018;2018:6519465. 2. Davydova A, et al. Biomedicines. 2023;11:1328. 3. Navarro-Compán V, et al. Front Immunol. 2023;14. (Supplementary material); doi.org/10.3389/fimmu.2023.1191782. 4. Polak-Szczybyło E, et al. Nutrients. 2022;14:643

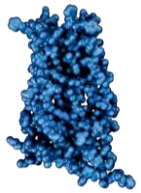
Summary and conclusion

The role of the IL-17 family in health and disease

IL-17A



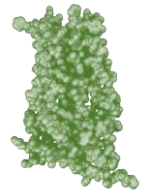
IL-17F



IL-17B

IL-17C

IL-17D



IL-17E

IL-17A and IL-17F have emerged as key drivers of SpA and belong to a larger family of cytokines that include IL-17B, IL-17C, IL-17D, and IL-17E (IL-25)

Recent studies have revealed the wide-ranging roles of the IL-17 family in both health and disease. However, the precise functions of many IL-17 members are yet to be elucidated

Future research on IL-17 cytokines may hold the key to therapeutic advances across a range of diseases

IL, interleukin; SpA, spondyloarthritis

Chung SH, et al. Int Immunol. 2021;33:723–729

Questions?