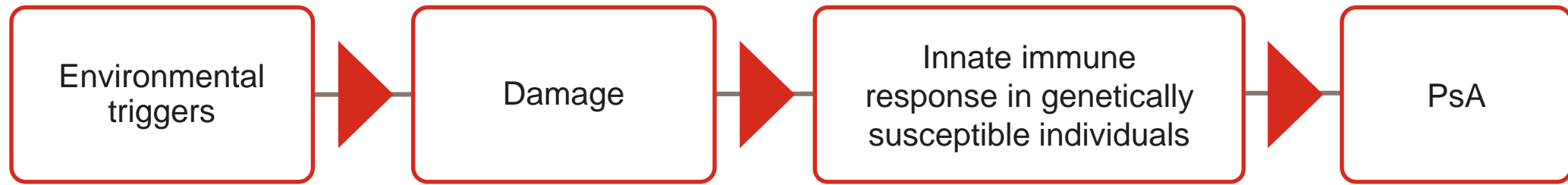


Module 2:

Role of IL-17 in Psoriatic Arthritis (PsA)

What Is the Trigger for PsA?

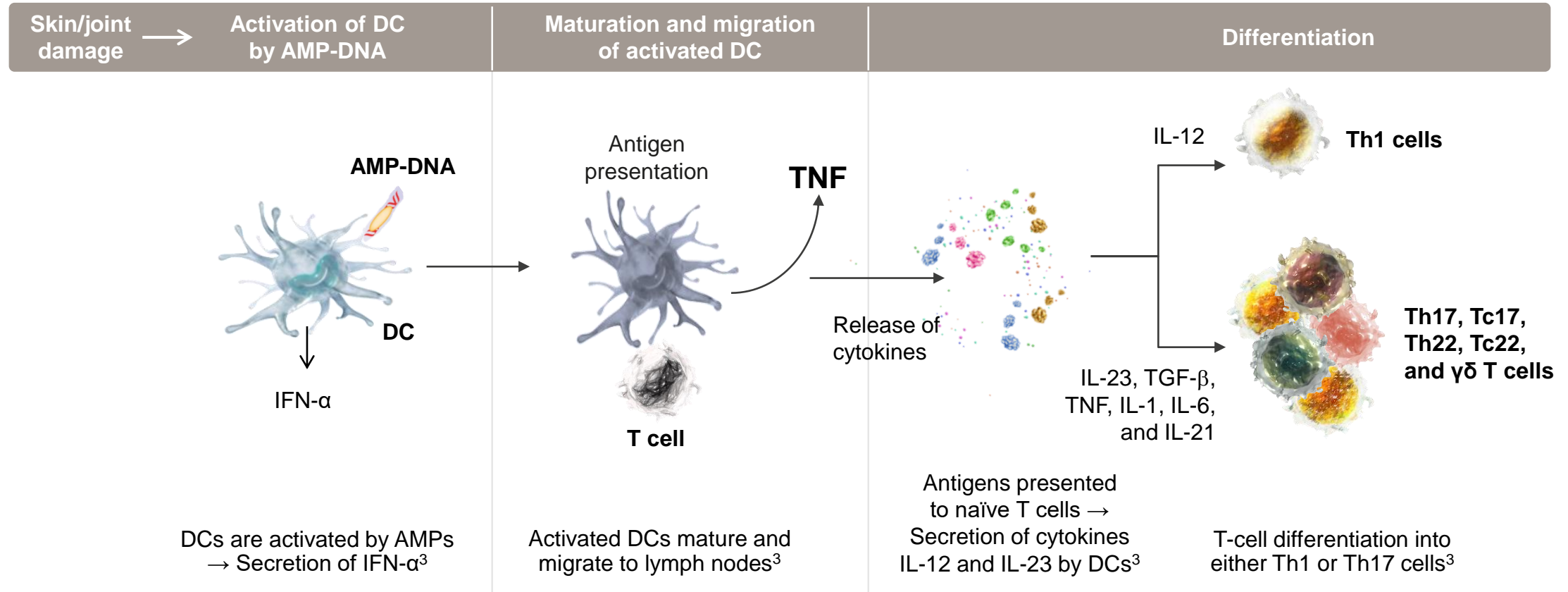
More is known about the pathophysiologic processes in psoriatic skin lesions than in PsA joints, but the processes and cytokines involved may be similar



The Role of Immune Pathways in the Pathogenesis of PsA

The Initial Immune System Response in PsA

In the joint, IL-17A, TNF, and other cytokines affect cell types that participate in inflammatory and joint-damaging processes¹⁻³



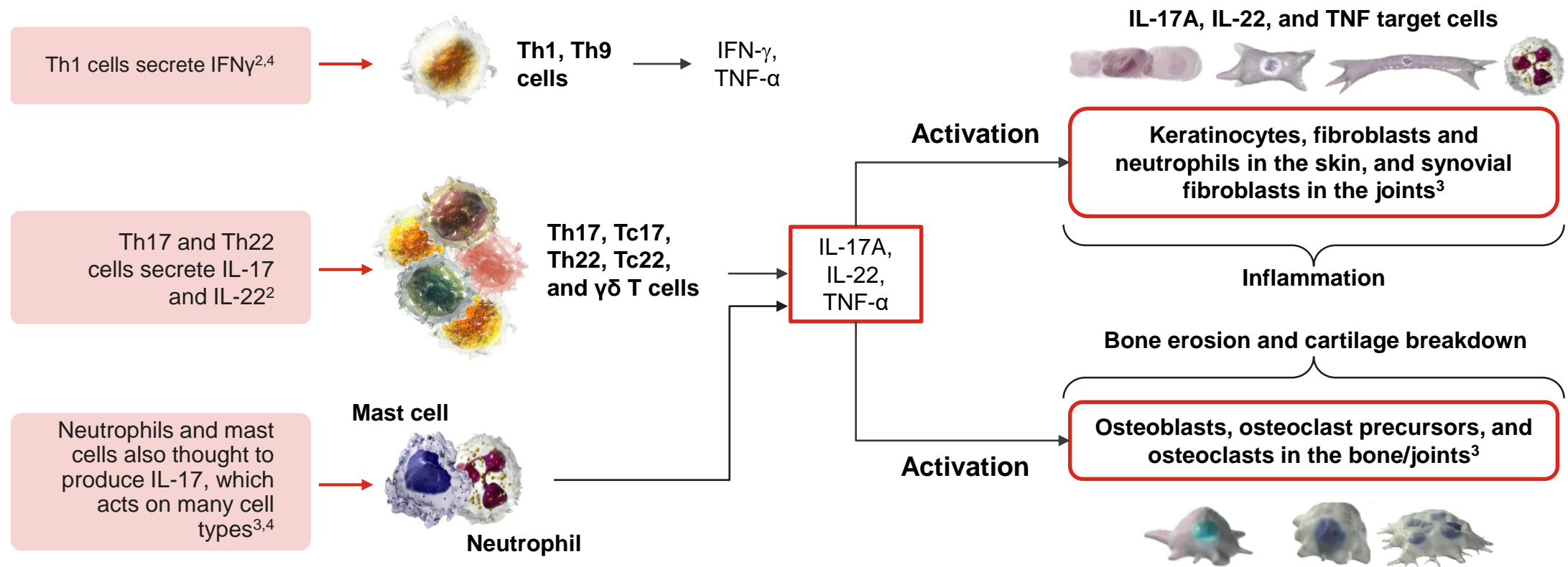
AMP=Antimicrobial Peptide; DC=Dendritic Cell; IFN=Interferon; IL=Interleukin; PsA=Psoriatic Arthritis; Tc=T Cytotoxic; TGF=Transforming Growth Factor; Th=T Helper; TNF=Tumor Necrosis Factor.

1. Carvalho AL, Hedrich CM. *Front Mol Biosci.* 2021;8:662047. 2. Wang EA, et al. *Eur J Rheumatol.* 2017;4(4): 272-277. 3. Vičić M, et al. *Int J Mol Sci.* 2021;22(21):11574.

The Role of Immune Pathways in the Pathogenesis of PsA

T Lymphocytes in PsA

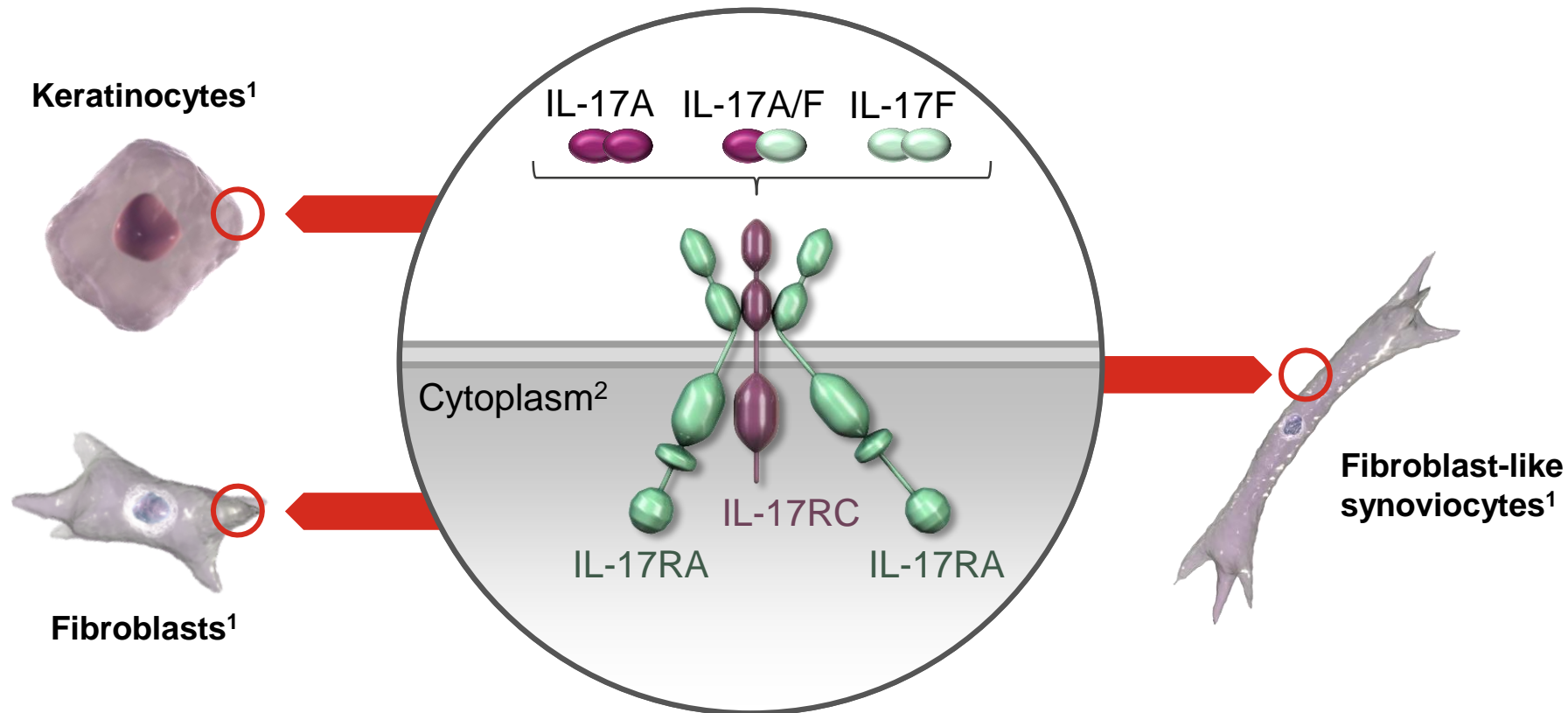
In the joint, IL-17A, TNF, and other cytokines affect cell types that participate in inflammatory and joint-damaging processes¹⁻⁴



IFN=Interferon; IL=Interleukin; PsA=Psoriatic Arthritis; Tc=T Cytotoxic; Th=T Helper; TNF=Tumor Necrosis Factor.

1. Carvalho AL, Hedrich CM. *Front Mol Biosci.* 2021;8:662047. 2. Wang EA, et al. *Eur J Rheumatol.* 2017;4(4): 272-277. 3. Boutet MA, et al. *Int J Mol Sci.* 2018;19(2):530. 4. Schön MP, Erpenbeck L. *Front Immunol.* 2018;9:1323.

The IL-17A Receptor Is Expressed by a Variety of Cells

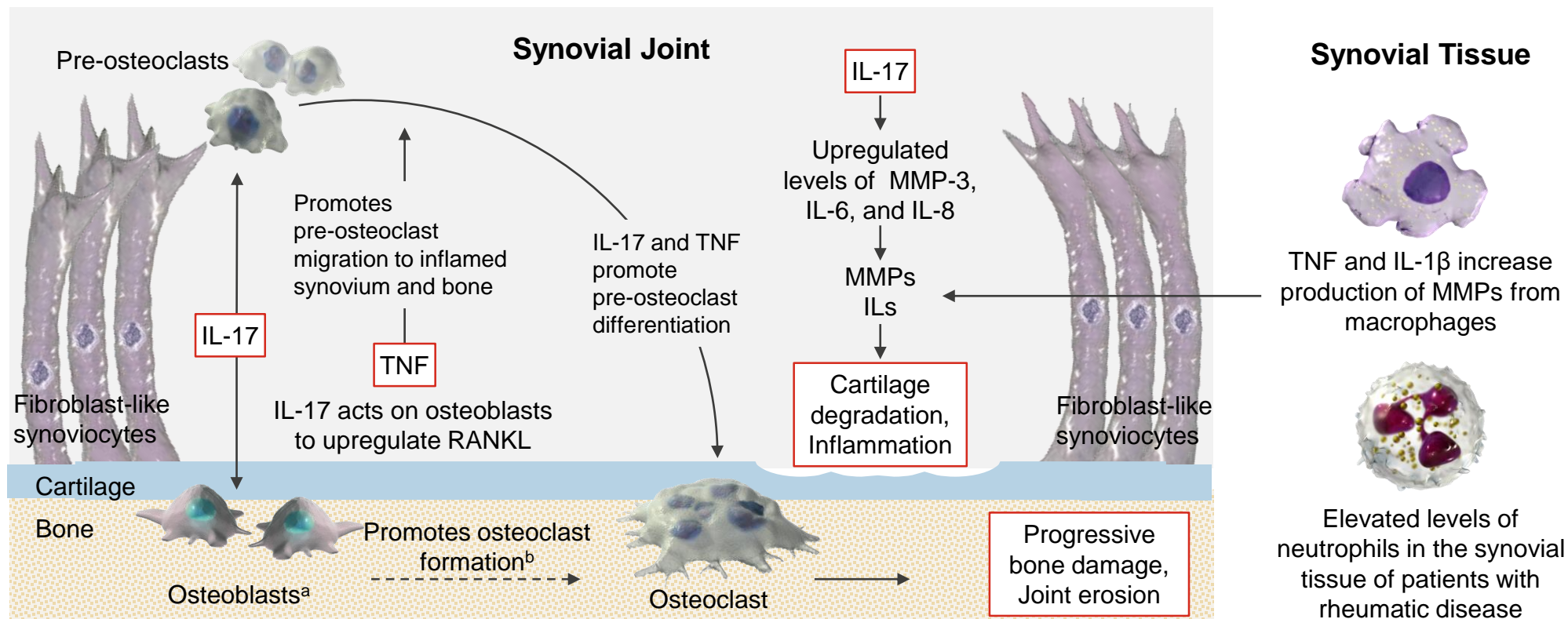


IL=Interleukin.

1. Wang EA, et al. *Eur J Rheumatol.* 2017;4(4): 272-277. 2. Brembilla NC, et al. *Front Immunol.* 2018;9:1682.

The Pivotal Role of IL-17 in Joints

In the joint, IL-17, TNF, and other cytokines affect cell types that participate in inflammatory and joint-damaging processes¹⁻⁴



^aNormally synthesize bone. ^bRANKL binds its receptor (RANK) on pre-osteoclasts, inducing their differentiation into bone-resorbing osteoclasts.

IL=Interleukin; MMP=Matrix Metalloproteinase; RANK=Receptor Activator of Nuclear Factor κ B; RANKL=RANK Ligand; TNF=Tumor Necrosis Factor.

1. Carvalho AL, Hedrich CM. Front Mol Biosci. 2021;8:662047. 2. Wang EA, et al. Eur J Rheumatol. 2017;4(4): 272-277. 3. Tsukazaki H, Kaito T. Int. J. Mol. Sci. 2020;21(17):6401. 4. Blauvelt A, Chiricozzi A. Clin Rev Allergy Immunol. 2018;55(3):379-390.

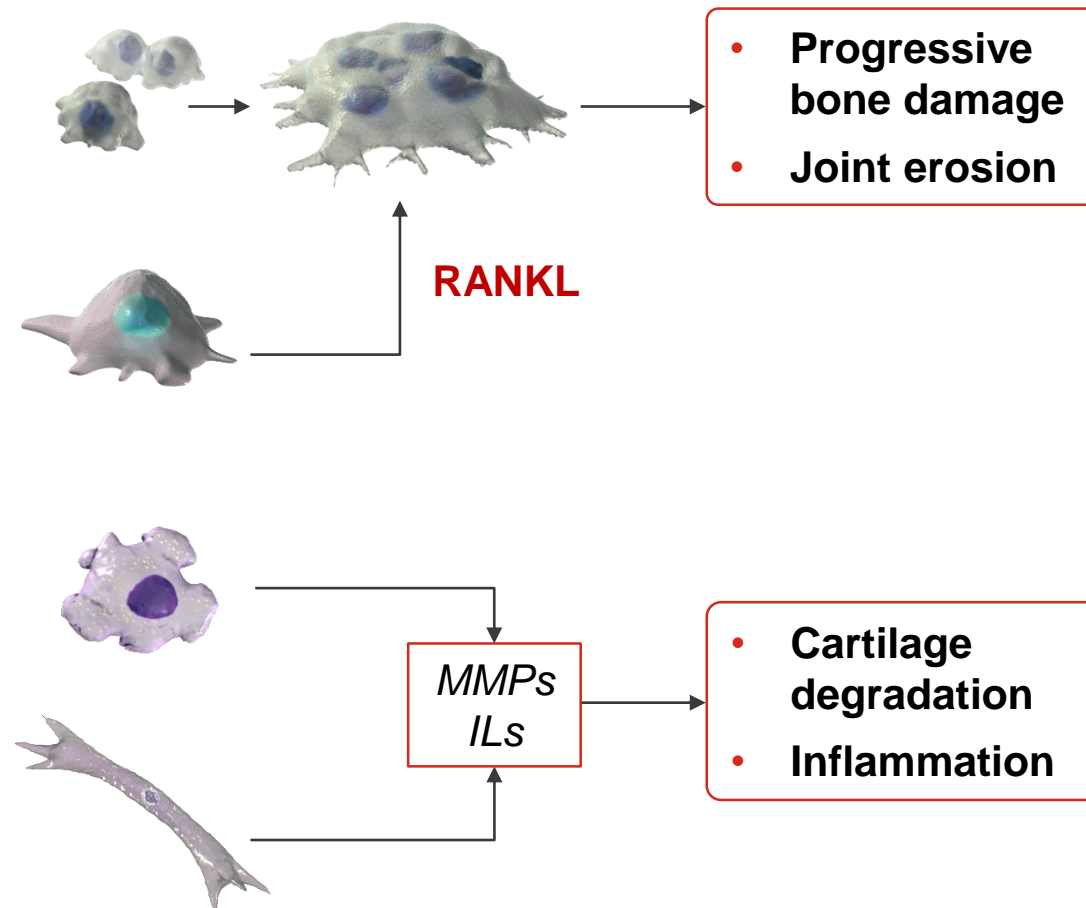
The Pivotal Role of IL-17 in Joints

Osteoclasts: IL-17 and TNF promote osteoclast precursor differentiation and migration to inflamed synovium and bone¹⁻⁴

Osteoblasts: IL-17 acts on osteoblasts (which normally synthesize bone) to upregulate RANKL and thus, promote osteoclast formation¹⁻⁴

Macrophages: TNF and IL-1 β increase the production of MMPs. Neutrophils are elevated in synovial tissue.¹⁻⁴

Fibroblast-like synoviocytes: IL-17 may lead to the upregulation of MMP-3, IL-6, and IL-8¹⁻⁵



IL=Interleukin; MMP=Matrix Metalloproteinase; RANK=Receptor Activator of Nuclear Factor κ B; RANKL=RANK Ligand; TNF=Tumor Necrosis Factor.

1. Carvalho AL, Hedrich CM. *Front Mol Biosci.* 2021;8:662047. 2. Wang EA, et al. *Eur J Rheumatol.* 2017;4(4): 272-277. 3. Tsukazaki H, Kaito T. *Int. J. Mol. Sci.* 2020;21(17):6401. 4. Blauvelt A, Chiricozzi A. *Clin Rev Allergy Immunol.* 2018;55(3):379-390. 5. Raychaudhuri SH, et al. *Clin Rheumatol.* 2015;34:1019-1023.

The Pivotal Role of IL-17 in Skin

In the skin, IL-17 and other cytokines affect different cell types that participate in the inflammatory process¹

Keratinocytes: IL-17 and IL-22 promote aberrant differentiation, hyperproliferation, and secretion of AMPs, chemokines, and other pro-inflammatory cytokines^{1,2}



AMP
cytokines

- Thickening of the skin
- Inflammation

DCs and macrophages: IL-17 and IL-36 lead to the release of TNF- α , IL-12, and IL-23 in a positive feedback loop^{3,4}



IL-12
IL-23
TNF- α

More upstream
cytokine release

Endothelial cells: IL-17 leads to enhanced neutrophil mobilization⁴. TNF increases expression of VEGF contributing to increased vascularity in psoriatic skin.⁵



VEGF

Angiogenesis

Selectins
Integrin
ligands

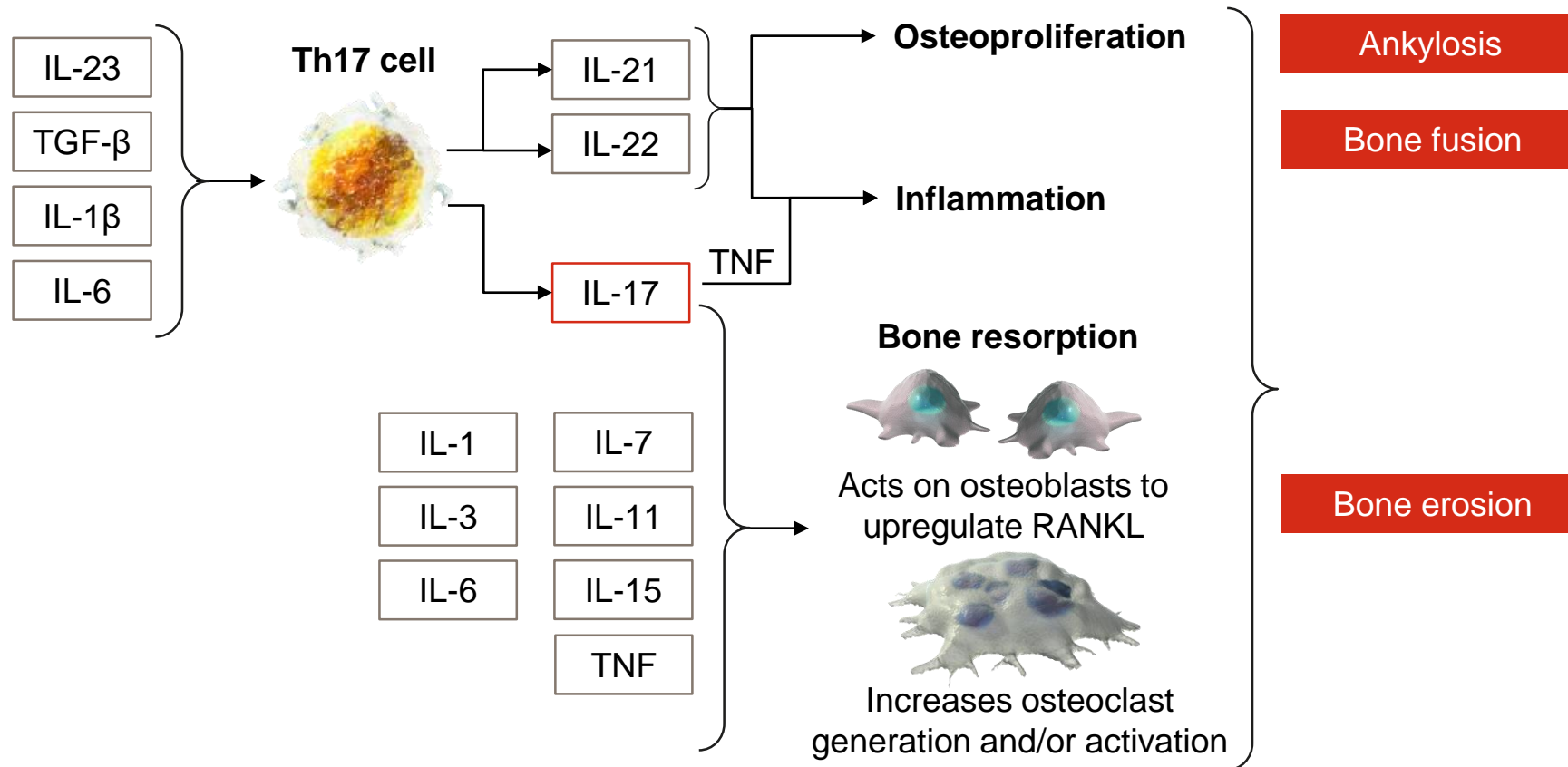
Neutrophil
mobilization

AMP=Antimicrobial Peptide; DC=Dendritic Cell; IL=Interleukin; IL-17R=Interleukin-17 Receptor; TNF=Tumor Necrosis Factor; VEGF=Vascular Endothelial Growth Factor.

1. Brembilla NC, et al. *Front Immunol.* 2018;9:1682. 2. Ekman AK, et al. *J Invest Dermatol.* 2019;139(7):1564-1573.e8. 3. Ten Bergen LL, et al. *Scand J Immunol.* 2020;92(4):e12946. 4. Mercurio L, et al. *PLoS One.* 2020;15(4):e0222969. 5. Marina ME, et al. *Clujul Med.* 2015;88(3):247-252.

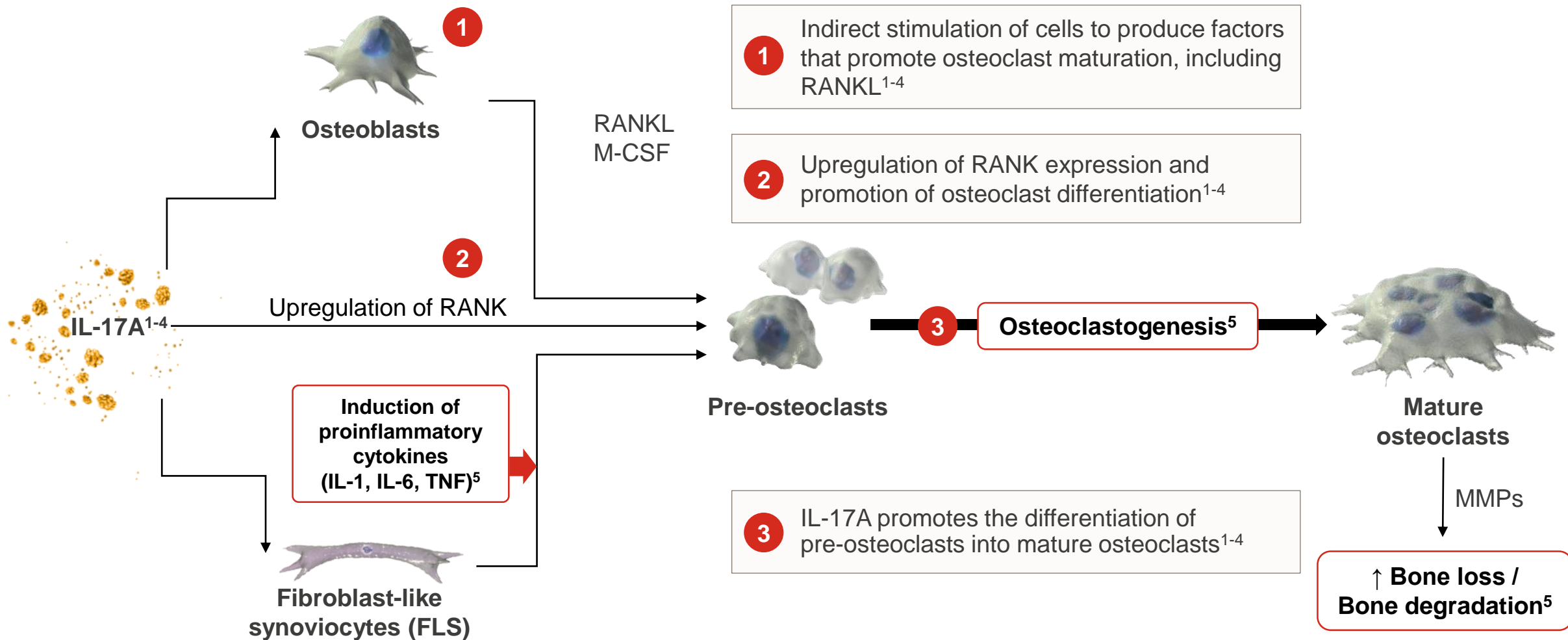
Proinflammatory Cytokines May Have a Pathogenic Role in Spondyloarthritis

Abnormal activation of the immune system can skew the balance between bone formation and resorption



IL=Interleukin; RANKL=Receptor Activator of Nuclear Factor κB Ligand; TGF=Tumor Growth Factor; TNF=Tumor Necrosis Factor.
Raychaudhuri SH, et al. *Clin Rheumatol*. 2015;34:1019-1023.

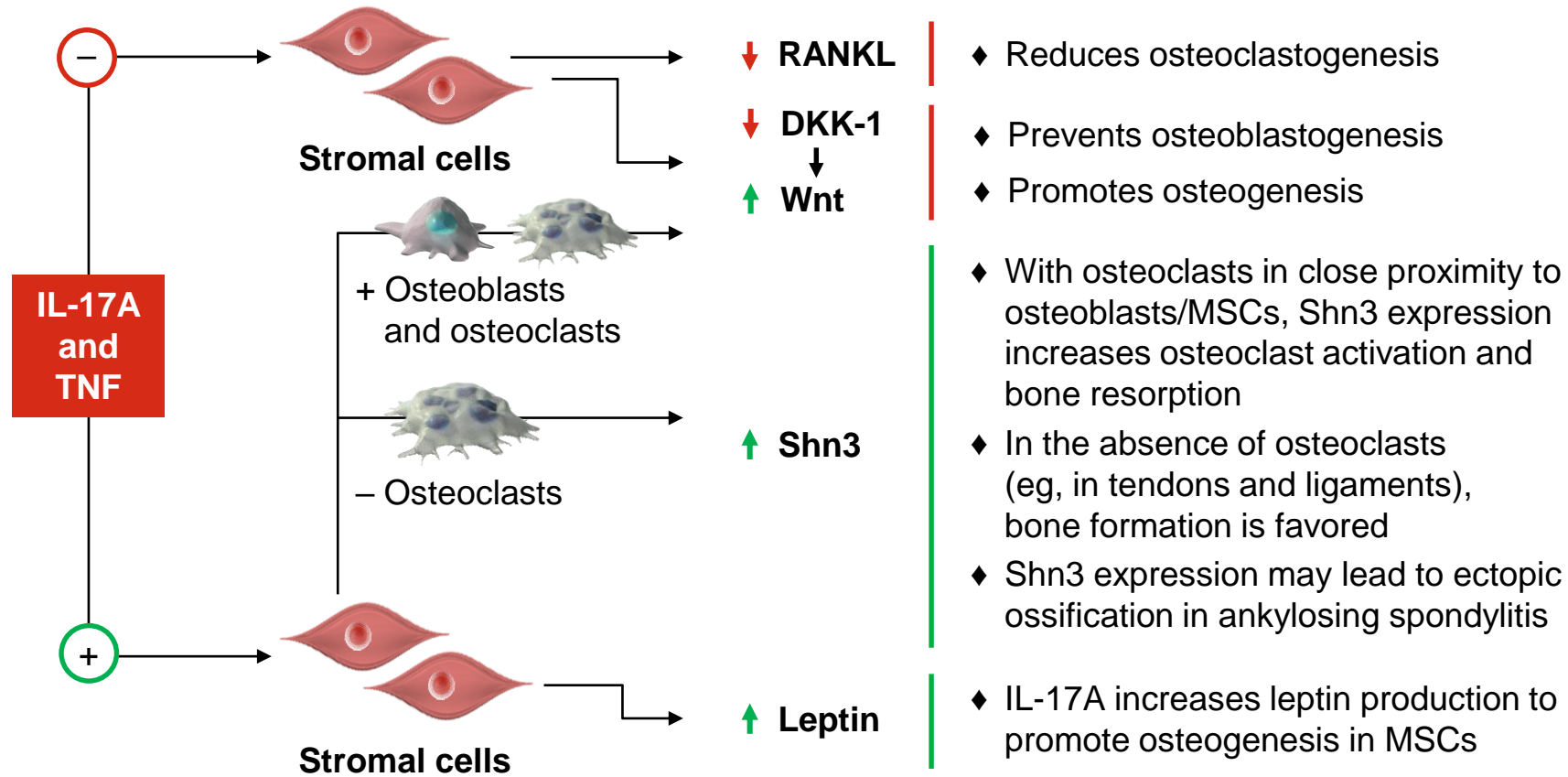
The Role of IL-17A in Pathogenic Bone Remodelling



IL=Interleukin; M-CSF=Macrophage Colony-stimulating Factor; MMP=Matrix Metalloproteinase; RANK=Receptor Activator of Nuclear Factor κB; RANKL=RANK Ligand.

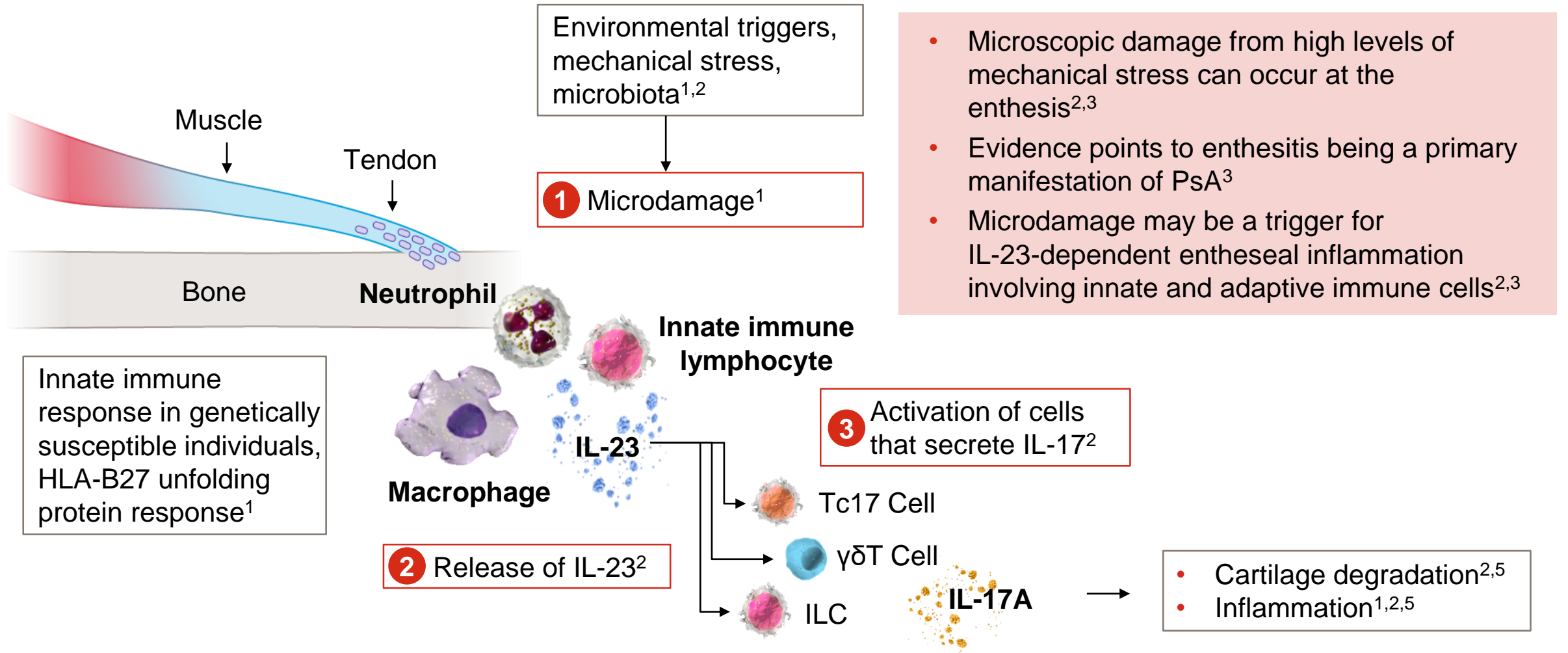
1. Carvalho AL, Hedrich CM. *Front Mol Biosci.* 2021;8:662047. 2. Wang EA, et al. *Eur J Rheumatol.* 2017; 4(4): 272-277. 3. Tsukazaki H, Kaito T. *Int. J. Mol. Sci.* 2020;21(17):6401. 4. Blauvelt A, Chiricozzi A. *Clin Rev Allergy Immunol.* 2018;55(3):379-390. 5. Raychaudhuri SH, et al. *Clin Rheumatol.* 2015;34:1019-1023.

IL-17A May Have a Pathogenic Role in Ectopic Bone Formation



DKK-1=Dickkopf-1; IL=Interleukin; MSC=Mesenchymal Stem Cell; RANKL=Receptor Activator of Nuclear Factor κB Ligand; Shn3=Schnurri-3; TNF=Tumor Necrosis Factor; Wnt=Wingless-related Integration Site. Osta B, et al. *Front Immunol.* 2014;5:1-8.

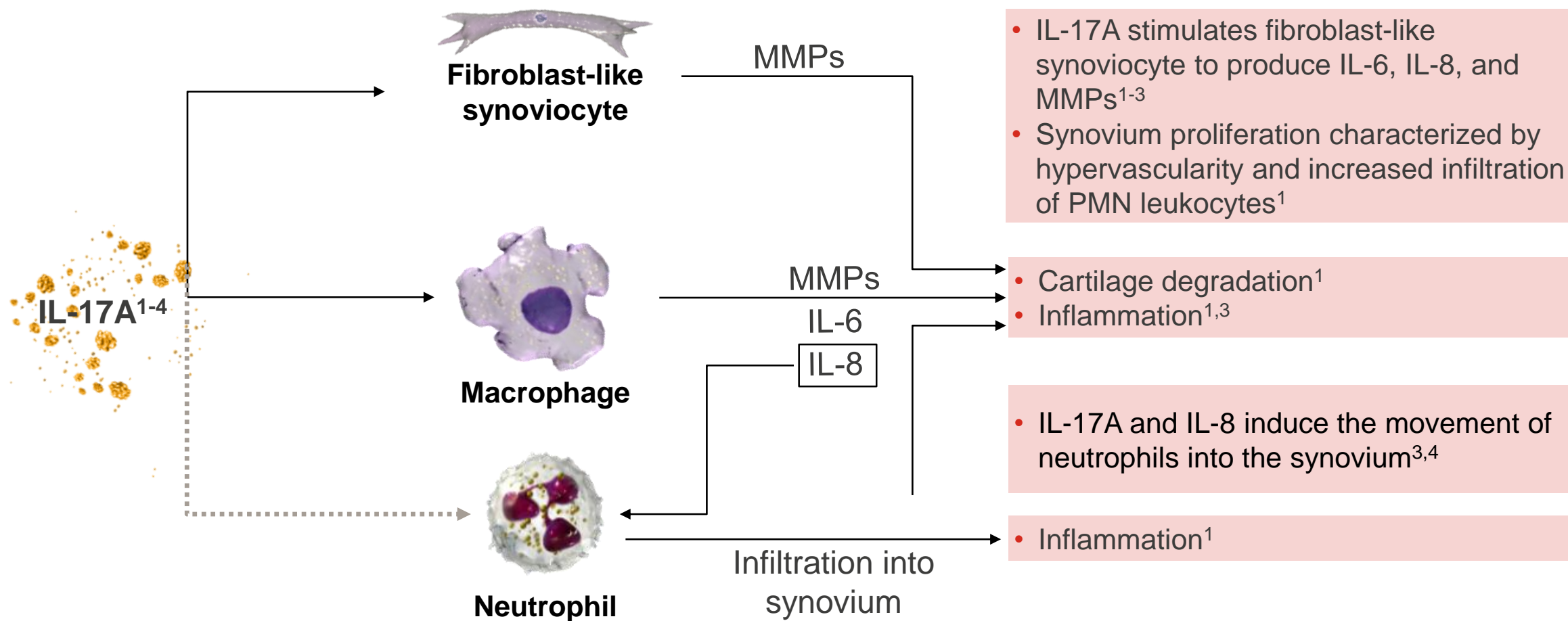
The Role of IL-17A in Enthesitis



HLA=Human Leukocyte Antigen; IL=Interleukin; ILC=Innate Lymphoid Cell; PsA=Psoriatic Arthritis; Tc=T Cytotoxic; Th=T Helper.

1. Boutet MA, et al. *Int J Mol Sci.* 2018;19(2):530. 2. Tsukazaki H, Kaito T. *Int. J. Mol. Sci.* 2020;21(17):6401. 3. Kaeley GS, et al. *Semin Arthritis Rheum.* 2018;48(1):35-43. 4. Blauvelt A, Chiricozzi A. *Clin Rev Allergy Immunol.* 2018;55(3):379-390. 5. Carvalho AL, Hedrich CM. *Front Mol Biosci.* 2021;8:662047

The Role of IL-17A in Synovitis



Note: Dotted arrows indicate indirect action.

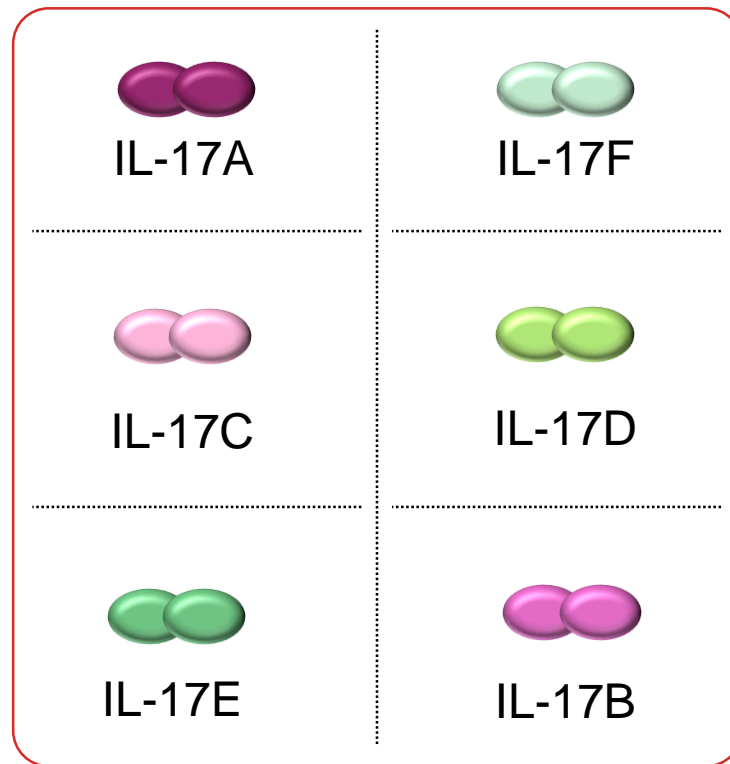
IL=Interleukin; MMP=Matrix Metalloproteinase; PMN=Polymorphonuclear.

1. Carvalho AL, Hedrich CM. *Front Mol Biosci.* 2021;8:662047. 2. Wang EA, et al. *Eur J Rheumatol.* 2017; 4(4): 272-277. 3. Tsukazaki H, Kaito T. *Int. J. Mol. Sci.* 2020;21(17):6401. 4. Blauvelt A, Chiricozzi A. *Clin Rev Allergy Immunol.* 2018;55(3):379-390.

IL-17 Family

IL-17 Family of Cytokines

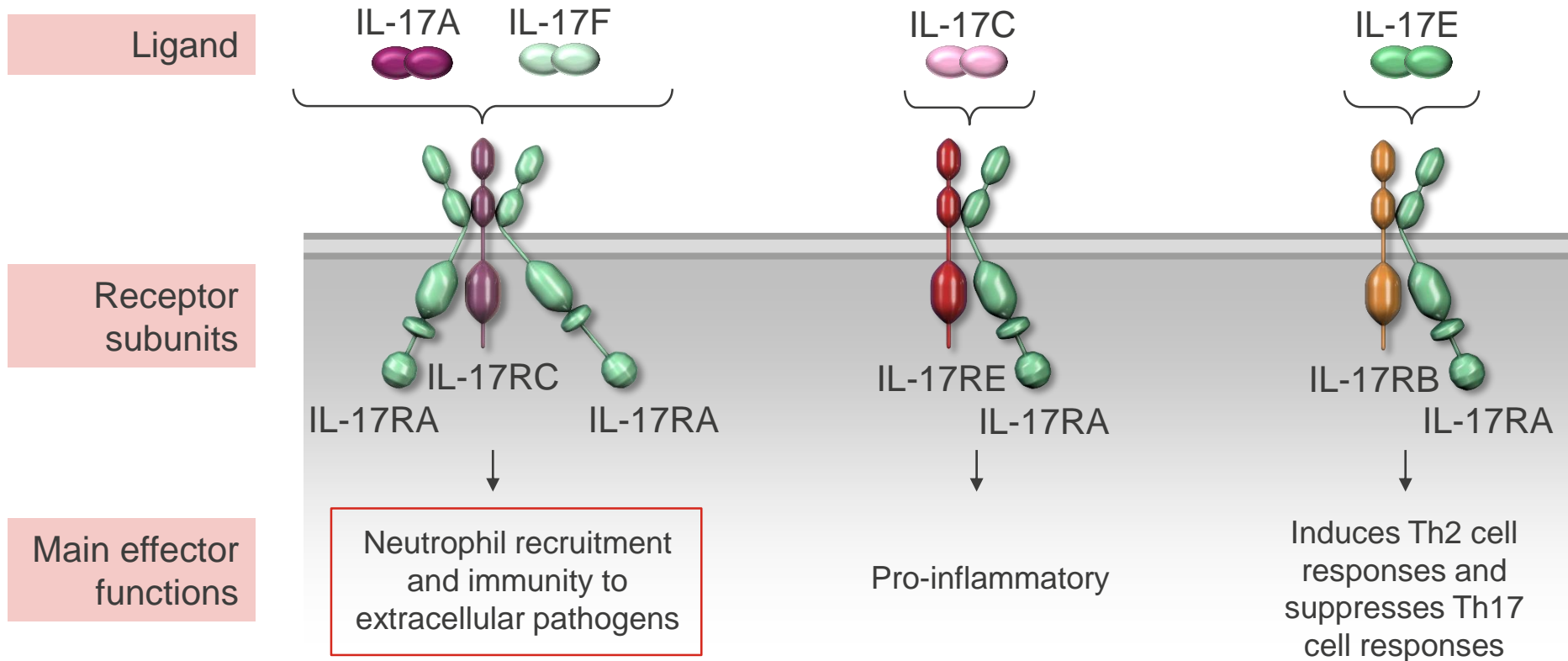
The IL-17 family of cytokines exist as dimers



- A family of cytokine dimers formed from 6 different subunits
- Each IL-17 cytokine exists as a dimer
- IL-17A seems to have a critical role in chronic inflammation and autoimmunity

Signaling and Effector Functions of IL-17 Family Members

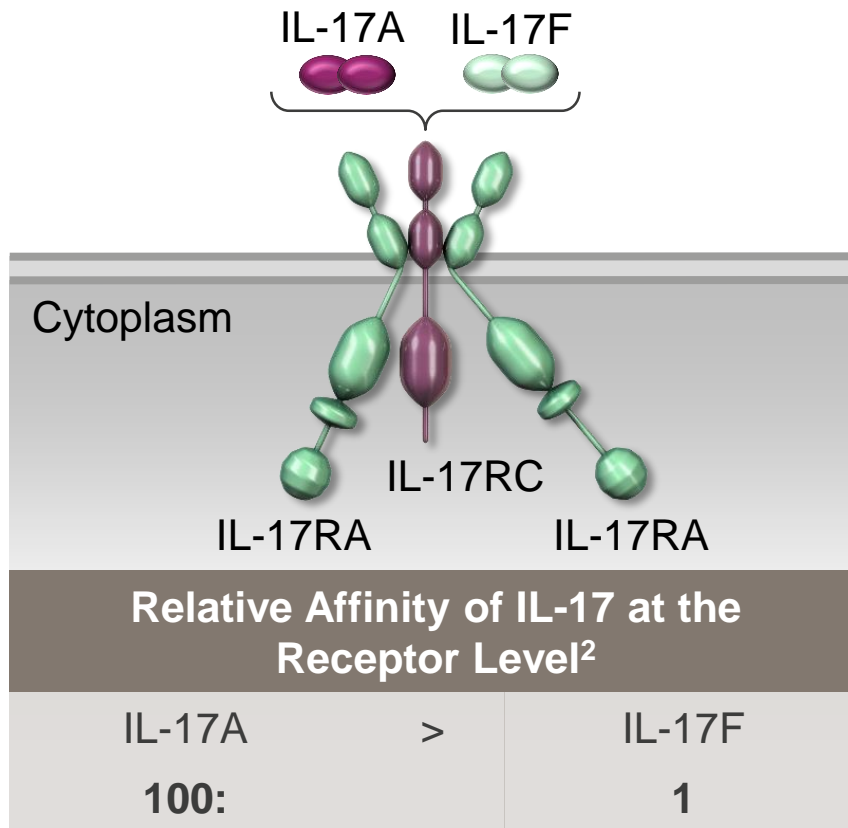
IL-17 family members have multiple immune and inflammatory functions



Note: The effector functions of IL-17B and IL-17D are unknown.
IL=Interleukin; IL-17R=Interleukin-17 Receptor; Th=T Helper.
Brembilla NC, et al. *Front Immunol.* 2018;9:1682.

The Receptor for IL-17A

IL-17A and IL-17F signal through the ubiquitously expressed IL-17 receptor¹



- The signaling that occurs after activation of the IL-17 receptor depends on which form of IL-17 has bound to the receptor³
- In terms of downstream gene activation, responses of IL-17F are 10–30 fold weaker than those of IL-17A³

Note: The effector functions of IL-17B and IL-17D are unknown.

IL=Interleukin; IL-17R=Interleukin-17 Receptor.

1. Brembilla NC, et al. *Front Immunol*. 2018;9:1682. 2. Waters LC, et al. *Cytokine*. 2021;142:155476. 3. Tsoukas A, et al. *Molecular Biology of B Cells* (Second Edition). 2015:527-539.