

# ΕΙΣΑΓΩΓΗ ΣΤΟ JAK-STAT PATHWAY

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# Δήλωση συμφερόντων

Τιμητική αμοιβή από τη Sobi

# Introduction to the JAKs

- Not all receptors have cytoplasmic signalling domains, some receptors are dependent on additional proteins with kinase activity<sup>1</sup>
- **Janus kinases (JAKs)** are cytoplasmic, non-receptor tyrosine kinases that transduce signalling for many cytokines and growth factors<sup>2,3</sup>
  - There are four known JAK family members<sup>3</sup>
- JAKs mediate downstream signalling by phosphorylating **Signal Transducer and Activator of Transcription (STAT)** proteins<sup>3</sup>
  - There are seven known STAT proteins (1–4, 5a, 5b and 6)<sup>3</sup>

JAK3 is primarily expressed in haematopoietic cells<sup>4</sup>



JAK1



JAK2



JAK3



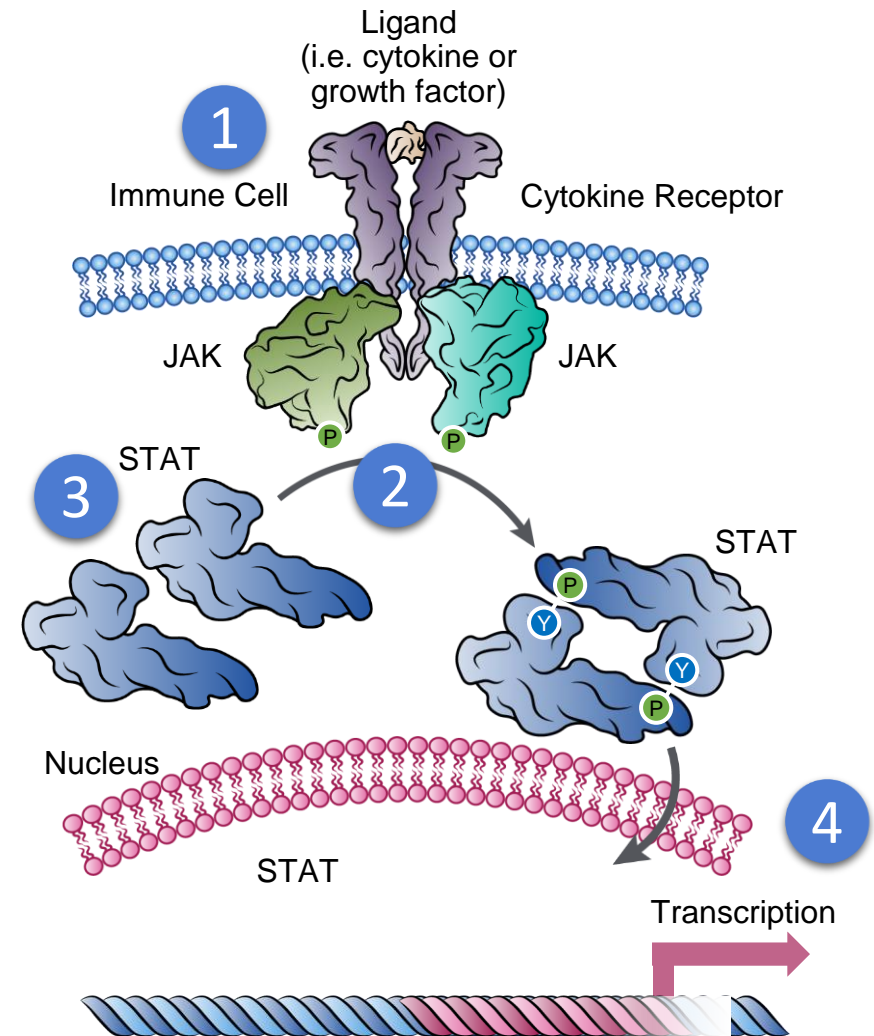
TYK2

TYK: tyrosine kinase 2

References: 1. Heldin CH, et al. Cold Spring Harb Perspect Biol 2016; 8:a005900. 2. Schwartz DM, et al. Nat Rev Drug Discov 2017; 16:843–862. 3. O'Shea JJ, et al. Annu Rev Med 2015; 66:311–328. 4. Choy EH. Rheumatology 2019; 58:953–962.

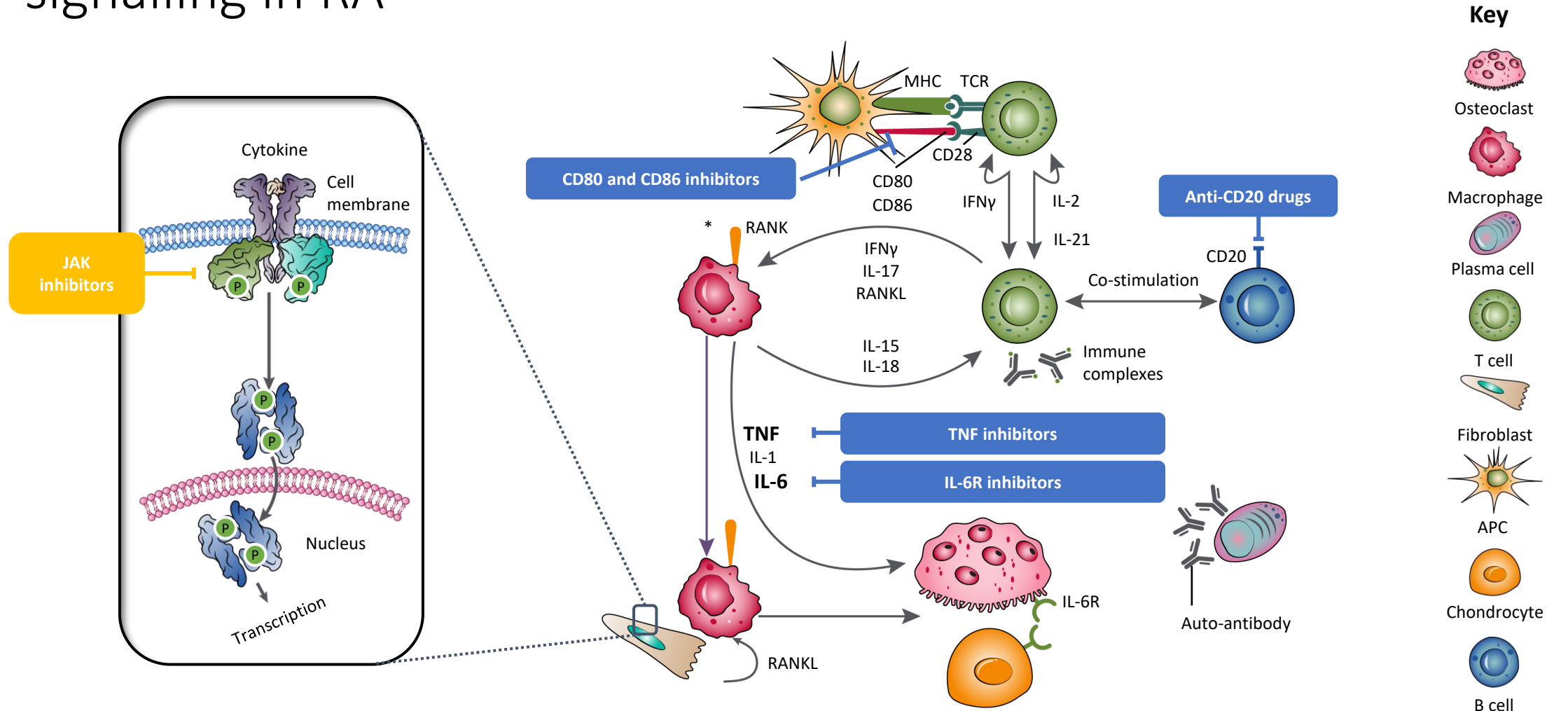
# JAKs pair together to facilitate signalling of specific cytokines

- 1 JAK proteins form homo- or heterogeneous pairs and associate with specific cytokine receptors
- 2 Receptor engagement induces activation of the JAK complex via phosphorylation of specific tyrosine residues on each JAK
- 3 JAK activation leads to the phosphorylation and dimerisation of Signal Transducer and Activator of Transcription (STAT) proteins
- 4 STAT proteins bind to DNA and regulate gene transcription of proteins required for key physiological processes, e.g. immune modulators



References: O'Shea JJ, et al. Annu Rev Med 2015; 66:311–328.

# JAK inhibitors target the JAK-STAT pathway to reduce cytokine signalling in RA<sup>1</sup>

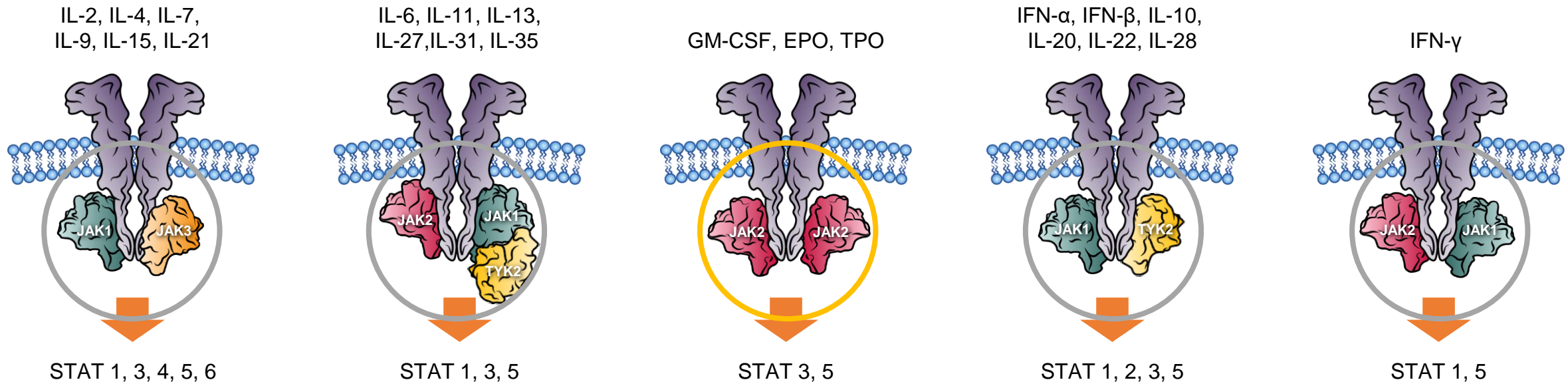


IL-6R: interleukin 6 receptor; MHC: major histocompatibility complex; RANK(L): receptor activator of nuclear factor kappa-B (ligand); TCR: T-cell receptor  
 Figure adapted from Smolen JS, et al. *Nat Rev Dis Primers* 2018; 4:18001 and Virtanen AT, et al. *BioDrugs* 2019; 33:15–32.

References: 1. Virtanen AT, et al. *BioDrugs* 2019; 33:15–32.



# JAK pairs facilitate the signalling of cytokines in ligand-specific combinations<sup>1</sup>



**Excessive cytokine signalling via the JAK-STAT pathway leads to inflammation, autoimmunity, bone erosion and cartilage damage, which are intrinsic to RA pathology<sup>2-10</sup>**

References: 1. Clark JD, et al. *J Med Chem* 2014; 57:5023–50380. 2. Malemud CJ. *Ther Adv Musculoskel Dis* 2018; 10:117–127. 3. Schwartz DM, et al. *Nat Rev Rheumatol* 2016; 12:25–36. 4. Dinesh P, Rasool M. *J Cell Physiol* 2018; 233:3918–3928. 5. Chen Z, et al. *J Immunol* 2013; 190:5256–5266. 6. Srirangan S, Choy EH. *Ther Adv Musculoskel Dis* 2010; 2:247–256.

7. Boettger MK, et al. *Arthritis Res Ther* 2010; 12:R140. 8. Lofti N, et al. *Front Immunol* 2019; 10:1265. 9. Schurgers E, et al. *J Interferon Cytokine Res* 2011; 31:917–926. 10. McHugh J. *Nat Rev Rheumatol* 2018; 14:63.