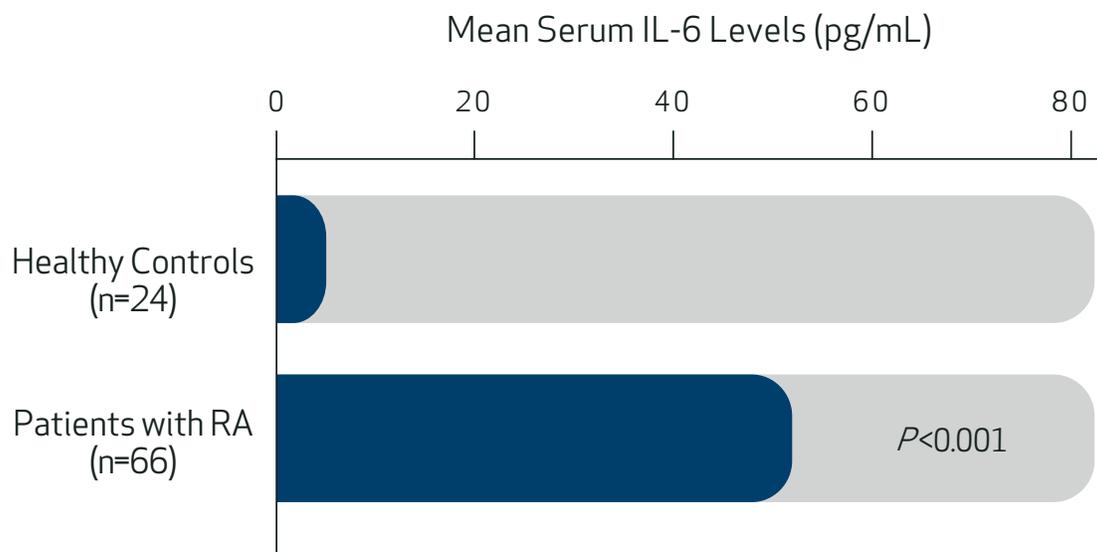


# The Importance of IL-6 in Rheumatoid Arthritis

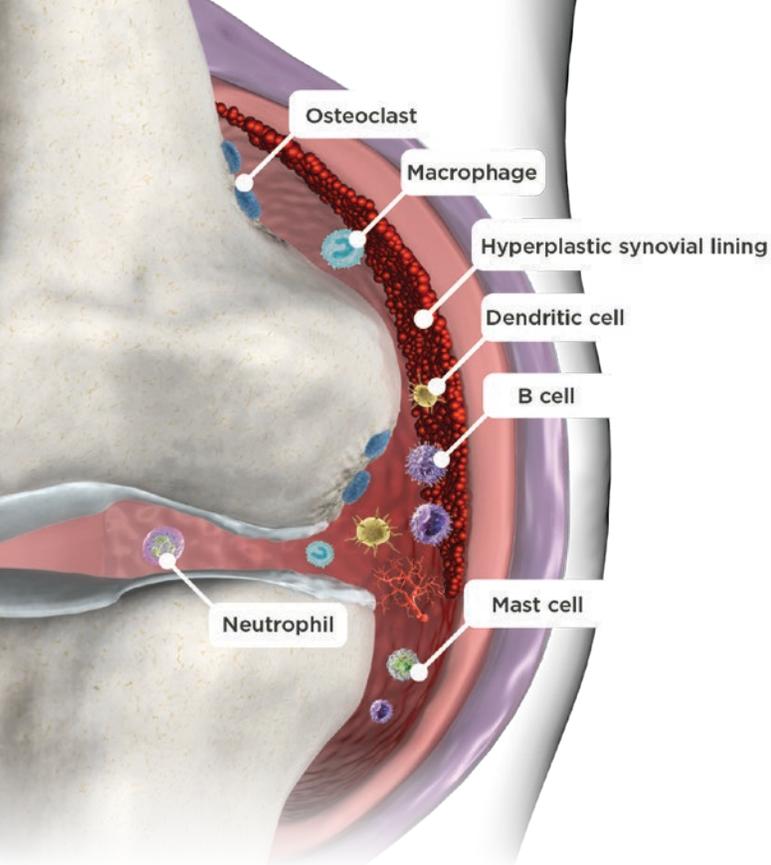
## A Key Driver of Articular and Systemic Manifestations

Interleukin-6 (IL-6) is one of the most abundant cytokines in the serum and synovial fluid of patients with rheumatoid arthritis (RA) and plays a pivotal role in chronic inflammation<sup>1-3</sup>

Mean serum IL-6 levels were approximately 10 times higher in patients with RA<sup>4</sup>



In a single-center controlled study, serum concentrations of IL-6 were measured in healthy subjects and adult RA patients, and the levels were correlated with disease activity<sup>4</sup>

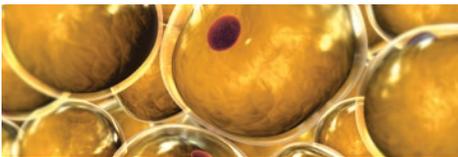


## Elevated IL-6 perpetuates chronic synovitis and promotes joint destruction through<sup>1,5</sup>:

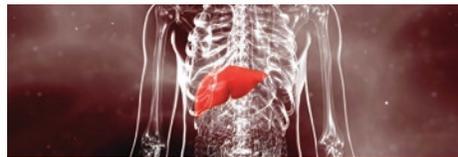
- Activation of proinflammatory cells and mediators within the joints, such as neutrophils, macrophages, fibroblast-like synoviocytes (FLS), T cells, and B cells<sup>1,6-10</sup>
- Activation of FLS and chondrocytes, leading to degradation of cartilage<sup>1,5</sup>
- Stimulation of osteoclastogenesis and osteoclast activity, leading to structural damage through bone resorption<sup>1,6</sup>

Adapted from Choy 2012.<sup>5</sup>

Persistently elevated IL-6 levels may contribute to structural damage, fatigue, morning stiffness, and other systemic manifestations of RA<sup>5,10,11</sup>



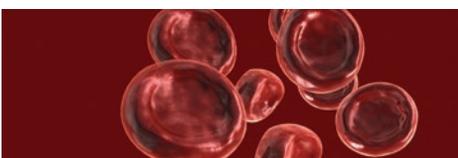
- Lipid metabolism through interactions with adipose tissue<sup>12,13</sup>



- Increased hepatocyte production of C-reactive protein (CRP) and serum amyloid A (SAA)<sup>5</sup>



- Contributes to vascular endothelial dysfunction<sup>1,14</sup>



- Induction of hepcidin, leading to hypoferremia<sup>5</sup>
- Lower hemoglobin levels and fatigue<sup>5</sup>



- Osteoclast activation that leads to bone resorption<sup>5,15</sup>

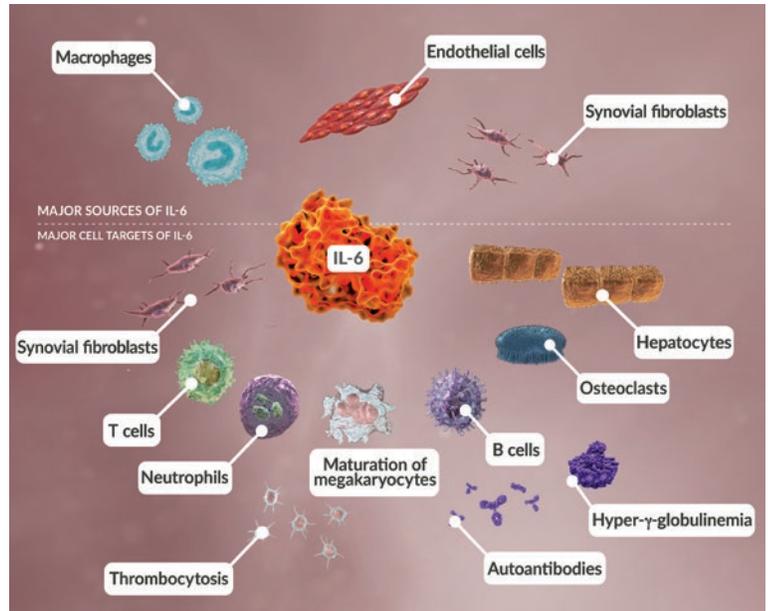


- Regulation of T cells and B cells<sup>1,15</sup>
- Autoantibody production<sup>1</sup>

## IL-6 Is a Multifunctional Cytokine That Is Vital for Maintaining Immunological Homeostasis<sup>16</sup>

### In the Inflammatory Process, IL-6 Has Various Roles, Including<sup>2</sup>:

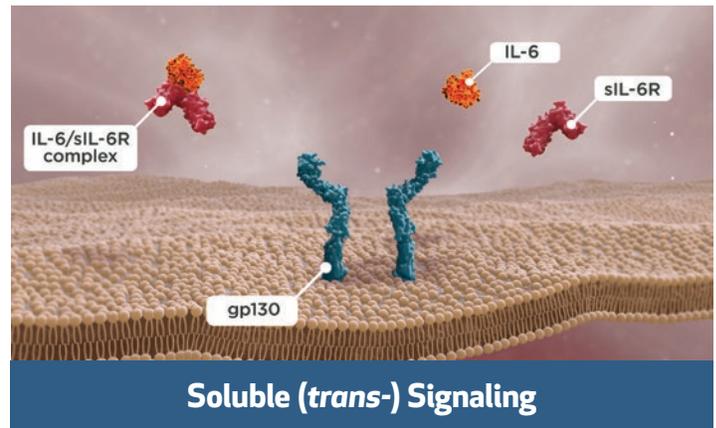
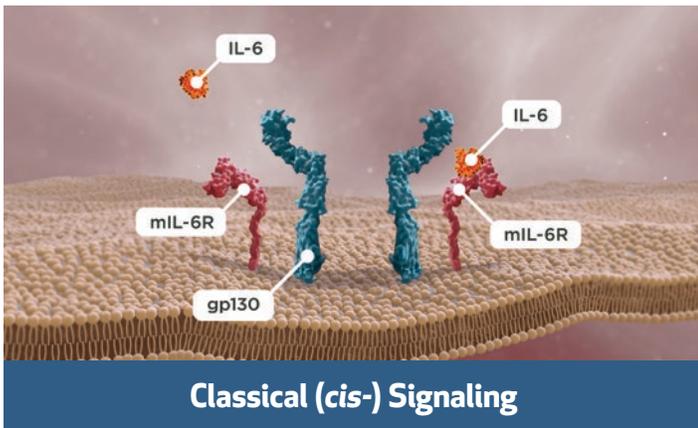
- IL-6 levels are greatly increased in response to infection or injury, helping to promote and coordinate the proinflammatory activities of cells throughout the body<sup>16,17</sup>
  - Once the infection or injury is resolved, circulating IL-6 levels are restored to basal levels<sup>16</sup>
- In RA, persistently elevated IL-6 may disrupt homeostasis in multiple physiologic processes through its actions on a broad range of cells<sup>1,5</sup>



Adapted from Choy 2004.<sup>18</sup>

### IL-6 signals through 2 distinct mechanisms<sup>3</sup>

- IL-6 can signal through *membrane-bound* receptors (classical or *cis*-signaling)
- IL-6 can also signal through *soluble* forms of its receptors (*trans*-signaling)
- These 2 distinct signaling mechanisms allow IL-6 to expand its range of biological activity and interact with cells that do or do not express the IL-6 membrane-bound receptor (mIL-6R)



In RA, the widespread effects of elevated IL-6 stem from its ability to signal via both soluble and membrane-bound receptors, thereby impacting a wide variety of cells<sup>1</sup>

# IL-6—a multifunctional cytokine that:

- Is one of the most abundant cytokines in the serum and synovial fluid of patients with RA<sup>1</sup>
- At normal levels, is vital for maintaining immunological homeostasis<sup>16</sup>
- Has various roles in the inflammatory process<sup>2</sup>
- At persistently elevated levels, is a key driver of articular and systemic manifestations and chronic inflammation of RA<sup>1,5</sup>
- Impacts a wide variety of cells and physiologic processes throughout the body due to its unique dual signaling mechanism<sup>1,5</sup>

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