

The New and Evolving Science of IL-6 in Rheumatoid Arthritis

# The Contributions of IL-6 to Disease Manifestations of RA



**Leonard H. Calabrese, DO**

Co-Editor

Professor of Medicine  
Cleveland Clinic

Cleveland Clinic  
Lerner College of Medicine  
of Case Western Reserve University



**Ernest Choy, MD**

Co-Editor

Head of Rheumatology and  
Translational Research

Cardiff University

SANOFI GENZYME 

**REGENERON**

Dear Colleagues,

This is a very exciting time in the field of rheumatoid arthritis (RA). The more we understand from basic and clinical research about the pathogenesis of RA, the more equipped we are to understand this disease. We now know that cytokines play many key roles in the inflammation that drives RA. One such example is interleukin-6 (IL-6), a multifunctional cytokine that contributes to chronic inflammation in patients with RA.

Regeneron Pharmaceuticals and Sanofi Genzyme are excited to bring you additional educational material describing some of the fundamental immunology as well as clinical pathology we see in RA patients through a series of scientific monographs entitled *The New and Evolving Science of IL-6 in Rheumatoid Arthritis*. In the first installment, we reviewed the signaling mechanisms of IL-6 that allow it to have widespread effects in RA. In the second installment, we reviewed the contributions of the IL-6 pathway to bone resorption, both at the joint and more systemically, in RA. In this installment, we discuss in greater detail how persistently elevated IL-6 signaling may contribute to both articular and systemic manifestations of RA.

We hope you find this latest installment informative and engaging.

Sincerely,

**Leonard H. Calabrese, DO**

Co-Editor

Cleveland Clinic  
Cleveland Clinic Lerner College of Medicine  
of Case Western Reserve University

**Ernest Choy, MD**

Co-Editor

Head of Rheumatology and  
Translational Research  
Cardiff University

Dr Calabrese and Dr Choy were provided honoraria by Sanofi Genzyme and Regeneron Pharmaceuticals.

Provided by Sanofi Genzyme and Regeneron Pharmaceuticals.

# Introduction

Rheumatoid arthritis (RA) is a chronic, progressive, autoimmune disease characterized by debilitating articular and systemic manifestations.<sup>1</sup> Articular manifestations include pain, tender and swollen joints, and morning stiffness. Although the disease course varies among patients, RA leads to progressive joint destruction and loss of function in most cases, and may lead to physical disability.<sup>1,3</sup> Systemic manifestations may include anemia, fatigue, osteoporosis, rheumatoid nodules, and vasculitis. These manifestations may negatively impact prognosis and survival of patients with RA.<sup>1,4</sup>

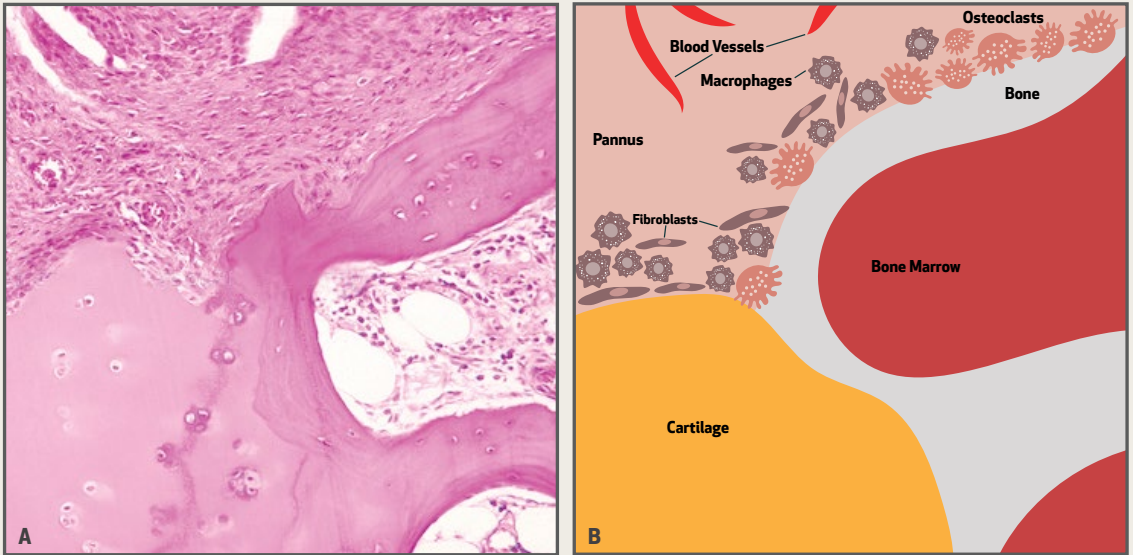
It has been established that RA and other inflammatory diseases are driven by a complex network of cytokines, including tumor necrosis factor- $\alpha$  (TNF- $\alpha$ ), interleukins (IL)-1, 4, 6, 12, 13, and 17, and interferons (IFN).<sup>1,5</sup> IL-6 is a multifunctional cytokine that performs many diverse functions, including vital pro-inflammatory roles, in response to infection or injury.<sup>1,5</sup> Persistently elevated IL-6 signaling may play a role in disrupting homeostasis in multiple physiologic processes, which can contribute to pathologic conditions observed in autoimmunity and chronic inflammation conditions such as RA.<sup>6,7</sup> Elevated IL-6 signaling plays an important role in RA, and may contribute to both articular and systemic manifestations of the disease.<sup>1,8-11</sup> IL-6 is one of the most abundant cytokines in the serum and synovial fluid of patients with RA and correlates with both disease activity and articular destruction.<sup>1,12,13</sup>

The signaling features of IL-6 allow it to interact with a broad range of cells and tissues including immune cells, fibroblast-like synoviocytes (FLS), hematopoietic stem cells, hepatocytes, adipocytes, endothelial cells, and pancreatic islets.<sup>5,8,14-17</sup> IL-6 can signal through both a membrane-bound receptor and a soluble receptor.<sup>1</sup> The latter differentiates IL-6 signaling from other cytokines such as TNF- $\alpha$  and IL-1, which are also implicated in driving inflammation in RA.<sup>3,18</sup>

This monograph will describe how the broad cell and tissue distribution of IL-6 signaling allows for its contributions to the articular and systemic manifestations seen in RA.

## Elevated IL-6 Signaling Plays a Critical Role in Driving Articular Manifestations of RA<sup>1,9,19</sup>

**Synovial joint damage is mediated by cells of the pannus.** In RA, there is a marked increase in proliferation, or hyperplasia, of cells of the synovial intimal lining, which include FLS, osteoclasts, and macrophages.<sup>20</sup> As a result, the lining increases from a depth of 1 to 2 cells to a depth of 10 to 20 cells.<sup>21</sup> This expansive synovial tissue is referred

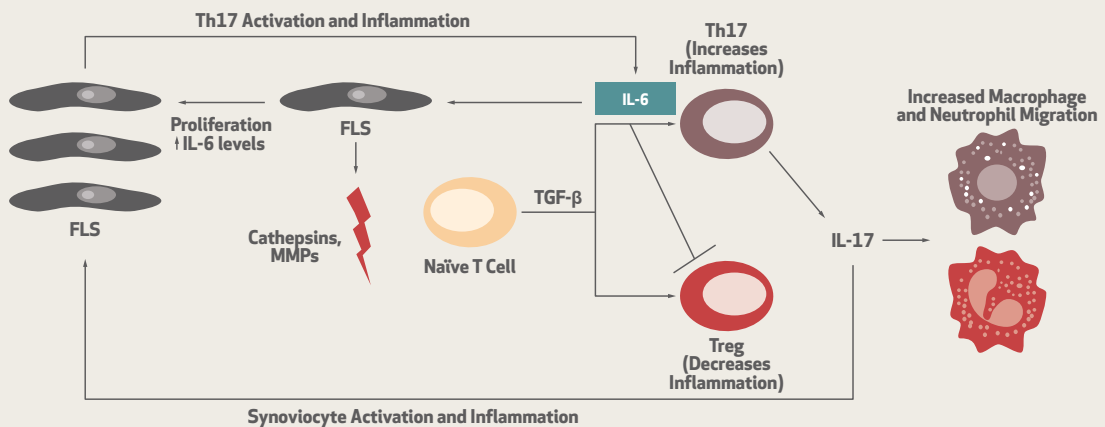


**Figure 1. Pathology in a rheumatoid joint. A)** A section through the ankle pannus of a patient with rheumatoid arthritis. **B)** Schematic representation. The synovial lining interfaces directly with the cartilage and bone, providing access to effector cells which mediate cartilage and bone destruction. Reprinted from the Clinical Slide Collection on the Rheumatic Diseases, © 1991, 1995, 1997. Used by permission from the American College of Rheumatology.

to as *pannus* and directly interfaces with both cartilage and bone of the joint with pathological consequences. During RA progression, FLS along with chondrocytes degrade cartilage, and the pannus invades bone, causing erosion through increased osteoclast activity (**Figure 1**).<sup>21,22</sup>

**FLS of the synovial intimal, or inner, lining play a key role in chronic inflammation and joint destruction in RA.**<sup>15-23,24</sup> The invasive properties of FLS have been shown to correlate with radiographic and histological damage in RA.<sup>25</sup> Under normal conditions, FLS secrete proteins that help build the extracellular collagen network, which is responsible for cushioning in joints.<sup>20</sup> In RA, however, FLS:

- Promote inflammatory cell recruitment and activation, as well as angiogenesis, through expression of immunomodulating cytokines and mediators, including IL-6<sup>15,21,23,24</sup>
- Are the main effectors of cartilage breakdown due to their unique invasive properties and the production of large amounts of matrix metalloproteinases (MMPs)<sup>21,26</sup>
- Contribute to bone erosion and systemic osteoporosis through secretion of factors such as receptor activator of nuclear factor kappa B ligand (RANKL), which promotes osteoclast differentiation, survival, and activity<sup>27,28</sup>



**Figure 2. IL-6 forms a positive feedback loop through its effects on FLS and Th17 cells.** FLS release cathepsins and matrix metalloproteases (MMPs), which degrade cartilage. In concert with TGF- $\beta$ , IL-6 can induce naïve T-cells to differentiate into Th17 cells instead of Treg cells. Th17 cells in turn secrete IL-17, which has proinflammatory effects on macrophages and neutrophils. IL-17 also stimulates FLS to produce more IL-6, enhancing a feedback loop that increases inflammation.

Elevated IL-6 contributes to chronic inflammatory synovitis and promotes joint damage in RA by:

- **Activating pro-inflammatory cells and mediators both at the joint and extra-articularly**, such as neutrophils, macrophages, FLS, T cells, and B cells, and increasing the production of pro-inflammatory molecules, such as cytokines and chemokines<sup>12,15,23,24,29-36</sup>
- **Activating and increasing proliferation of FLS.** IL-6 both activates and is produced by FLS, establishing a positive feedback loop.<sup>15,23,24</sup> FLS in the intimal lining are the primary source of IL-6 in synovial joints, as shown by *in situ* hybridization and immunohistochemistry studies.<sup>21</sup> Because most synovial cells do not express transmembrane IL-6R in the joint, it is thought that *trans*-signaling mediates IL-6 effects on synovioytes<sup>37</sup>
- **Activating Th17 cells, in combination with effects on FLS, sets up a positive feedback loop of IL-6 expression.** The combined

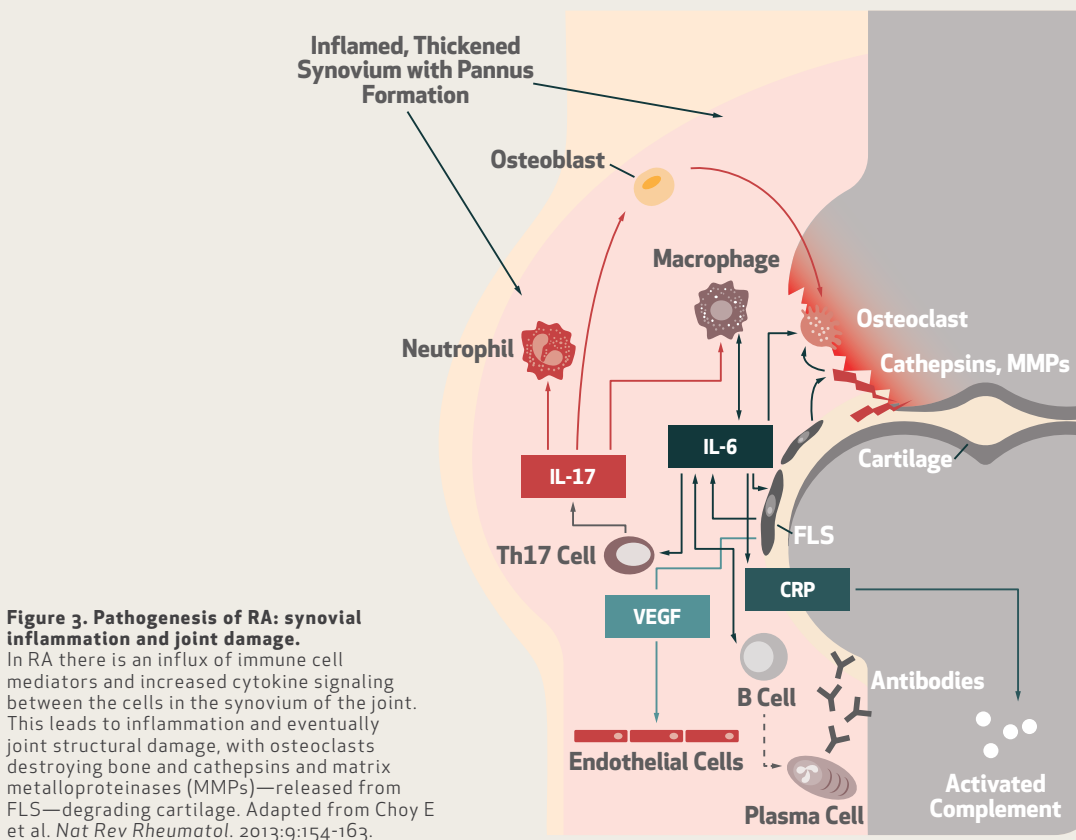
presence of IL-6 and TGF- $\beta$  stimulates naïve T cells to differentiate into Th17 cells.<sup>38</sup> Th17 cells in turn release more IL-6, which further promotes Th17 differentiation.<sup>39</sup> Th17 cells produce IL-17, which also contributes to RA pathogenesis, in part by increasing RANKL expression on osteoblasts (Figure 2)<sup>5,40</sup>

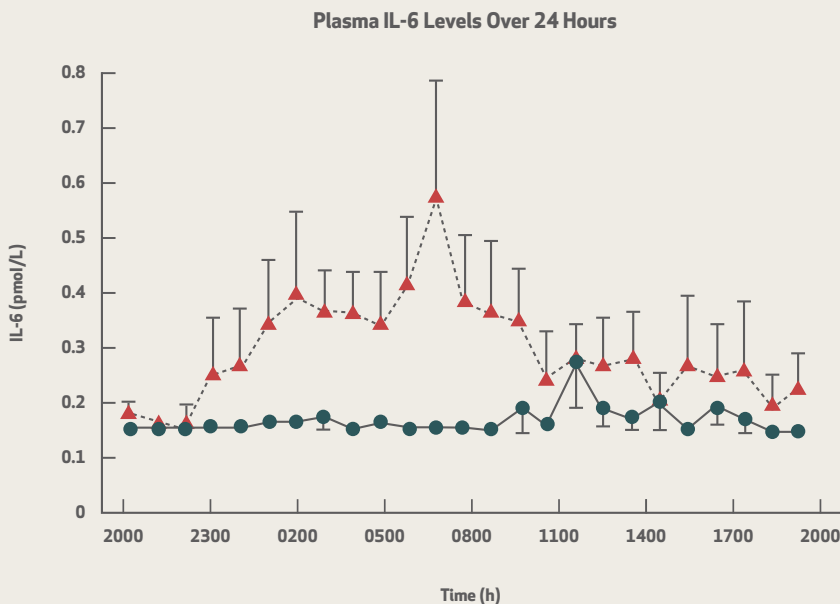
- **Stimulating osteoclastogenesis and osteoclast activity, leading to structural damage through bone resorption.** There is also evidence that IL-6 and/or sIL-6R may be implicated in the regulation of osteoclast precursors in the bone marrow (hematopoietic stem cells) before and during inflammatory arthritis<sup>12,41,42</sup>
- **Increasing VEGF levels synergistically with TNF- $\alpha$  and IL-1 $\beta$ .** VEGF is central to the formation and maintenance of the pannus through stimulation of angiogenesis<sup>1,43,44</sup>
- **Contributing to the shift from acute to chronic inflammation in RA.** The transition from acute to chronic inflammation in RA is

characterized by a shift from neutrophil to monocyte infiltration of the synovia. During acute inflammation, IL-6 is initially released by monocytes, macrophages, and endothelial cells; IL-6 signaling mediates neutrophil recruitment through activation of a subset of chemokines by endothelial cells, and by increasing expression of adhesion molecules on these cells. Soluble IL-6 receptor is in turn released from neutrophils, which increase the amounts of monocyte-specific, but not neutrophil-specific, chemoattractants secreted by endothelial cells.<sup>45-48</sup> It has been proposed that IL-6 and its soluble receptor may regulate the leukocyte recruitment transition through a shift in chemokine

production. During acute inflammation, IL-6 may favor the resolution of the neutrophilic infiltrate and the initiation of the immune response; in chronic inflammation, IL-6 may increase the mononuclear cell infiltrate and participate in disease pathogenesis<sup>1,49,50</sup>

- **Regulating B-cell differentiation and autoantibody production.** IL-6 stimulates plasmablasts to differentiate into mature plasma cells.<sup>29,51</sup> IL-6 can also stimulate antibody production by increasing the production of IL-21 to provide CD4<sup>+</sup> T cell-mediated B-cell help.<sup>52,53</sup> These functions increase B-cell interactions, sustain B-cell survival, and lead to ectopic germinal-center





**Figure 4. Diurnal variation in plasma IL-6 concentrations in 5 normal subjects (●) and 5 RA patients (▲).** Samples were taken every hour over a 24-hour period.<sup>32</sup> Exaggerated circadian variation with respect to amplitude and timing in serum IL-6 levels was seen in patients with RA when compared with healthy subjects. The data showed that serum IL-6 levels significantly increased and were at their highest in the early morning. Adapted from Crofford LJ et al. *J Clin Endocrinol Metab.* 1997;82:1279-1283.

formation in synovial tissue.<sup>54</sup> Activated mature B cells trigger inflammatory and mesenchymal cells to produce cytokines, chemokines, and other pro-inflammatory factors. They also produce autoantibodies that contribute to chronic inflammation<sup>15</sup>

- **Activating and targeting the complement system to healthy tissue.** Abundant, activated complement is found in the synovial fluid of RA patients.<sup>55</sup> C-reactive protein (CRP), a major acute-phase protein induced by IL-6, enhances sIL-6R shedding and can activate the complement system.<sup>56</sup> Complement, in conjunction with autoantibody immune complexes, places a target on healthy tissues for destruction.<sup>57</sup> The complement cascade also contributes to inflammation by increasing cytokine production<sup>58</sup>

Through these diverse mechanisms, IL-6 contributes significantly to the articular pathology associated with RA (summarized in **Figure 3**).

### Elevated IL-6 levels in diurnal sway and morning stiffness

Serum IL-6 levels are at their highest in the early morning hours when patients with RA particularly experience articular pain and stiffness, as well as functional disability (**Figure 4**).<sup>32,59,60</sup> This morning stiffness is related to both increased levels of IL-6 and decreased levels of cortisol.<sup>61</sup> Diurnal variation of IL-6 levels is thought to be controlled at a systemic level through signaling pathways originating from the central circadian clock, and at a local level by autonomous clocks in inflammatory cells and tissues.<sup>60</sup> In

vitro, macrophages and synoviocytes both demonstrate rhythmic IL-6 responses or circadian oscillations.<sup>62,63</sup>

In humans, levels of cortisol are downregulated during the evening and upregulated in the early morning. In patients with RA, the ratio of serum cortisol to serum pro-inflammatory cytokines is reduced compared with healthy subjects, leading to articular pain and stiffness in the early morning, when IL-6 levels are increased. In healthy subjects and cancer patients, investigational administration of exogenous IL-6 leads to a dose-dependent increase in plasma cortisol levels; however, repeated IL-6 administration leads to a blunting of this response.<sup>61</sup>

## Elevated IL-6 Signaling and Its Potential Correlation With Systemic Manifestations of RA

As mentioned, IL-6 is one of the most abundant cytokines in the serum and synovial fluid of patients with RA.<sup>1,12,13</sup> In RA, IL-6 is synthesized and secreted by cells of the synovia of

inflamed joints including FLS, monocytes/macrophages, and neutrophils.<sup>5,16,19</sup> IL-6 originating from articular sources can then diffuse into circulation and affect a broad range of distal cells/tissues due to its dual signaling mechanism. Consistent with this, increased IL-6 levels may be associated with systemic manifestations of RA, which are described below (**Figure 5**).

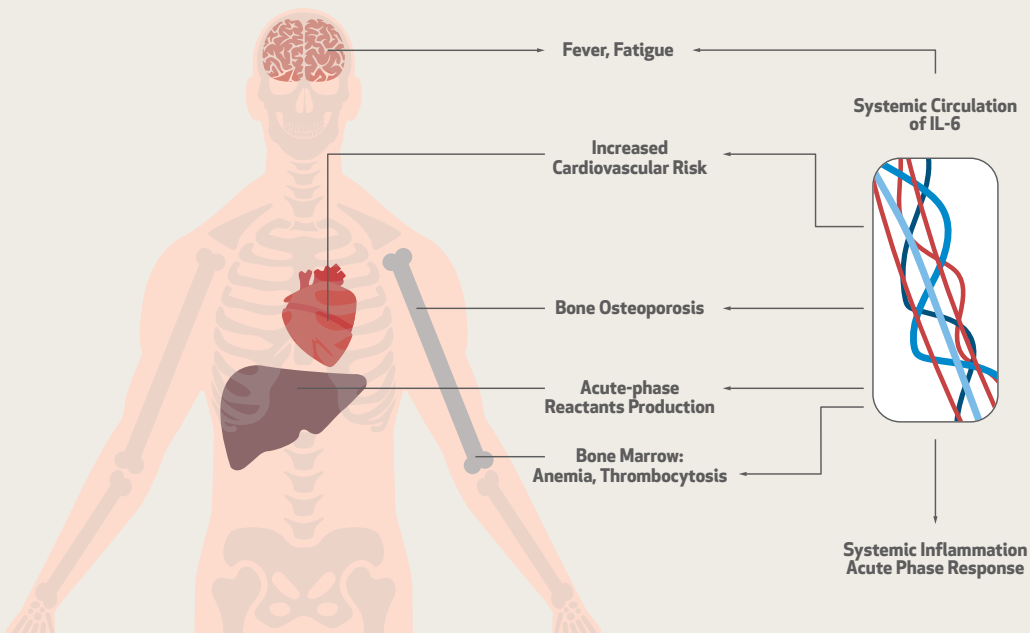
### Induction of acute-phase proteins

#### **C-reactive protein (CRP)**

**IL-6 signaling is a major contributor to induction of CRP and other acute-phase proteins.** The acute-phase response is the change in the concentration of certain plasma proteins, such as CRP, hepcidin, and serum amyloid A, which are produced by the liver in response to infection, tissue injury, neoplastic growth, or immunological disorder.<sup>1,8,64,65</sup> IL-6 is a major inducer of acute phase protein levels, although other cytokines such as IL-1, TNF- $\alpha$ , TGF- $\beta$ 1, and IFN- $\gamma$  also have stimulatory effects.<sup>4,64</sup> Peak values of CRP usually occur within 24 to 72 hours after experimental induction with IL-6 and last for several days, although circulating levels remain elevated in cases of chronic inflammation.<sup>64</sup>

A prospective study found that an elevated baseline CRP level was a significant predictive factor for radiographic damage at 3 years in patients with RA.<sup>66</sup> Several studies investigating the relationship between CRP levels and cardiovascular disease (CVD)





**Figure 5. Potential association of IL-6 and RA systemic effects.**

Persistently elevated IL-6 signaling may be associated with several systemic manifestations of RA.

have found that CRP is associated with an increased risk of myocardial infarction, stroke, sudden death from cardiac causes, and peripheral arterial disease. RA patients are at higher risk for cardiovascular illness (standardized mortality rate, ~1.5) which includes myocardial infarction, cerebrovascular events, and heart failure.<sup>67</sup> Data suggest that CRP levels are a strong predictor of cardiovascular events, as evidenced by improved clinical outcomes in a general patient population with lowered CRP levels following statin therapy compared to those with higher CRP levels, regardless of the resultant level of low-density lipoprotein (LDL) cholesterol.<sup>4,5,68-70</sup>

### **Hepcidin**

#### **Elevated IL-6 signaling may lead to hypoferrremia through induction of hepcidin.**

IL-6 increases production of hepcidin, an acute-phase protein that is a key regulator of iron homeostasis with antimicrobial properties.<sup>71-73</sup> In a study of six healthy human volunteers infused with IL-6, urinary hepcidin levels rose 7.5-fold within 2 hours.<sup>72</sup> IL-6 induces hepcidin expression in the liver via the JAK-STAT signaling pathway. Hepcidin reduces iron bioavailability, which is critical for new hemoglobin synthesis, by inhibiting iron uptake in the duodenum and iron release from macrophages in the spleen and elsewhere.<sup>1,5,72</sup> As a result, when hepcidin levels are increased, concentrations of iron in the blood are limited, a condition referred to as hypoferrremia.<sup>65</sup>

## Effects of persistent elevated hepcidin levels in RA and the prevalence of anemia, sleep disturbances, and fatigue

Hepcidin is a potential contributing cause of anemia in patients with chronic inflammatory disease.<sup>1,65</sup> Anemia is one of the most frequent systemic manifestations of RA, occurring in approximately one-third of patients, and has been associated with more severe joint disease.<sup>74,75</sup> In addition, anemic patients with RA tend to have greater radiographic progression than non-anemic patients.<sup>76,77</sup> In humans, serum hepcidin levels have been shown to be highest in patients with RA and anemia, whereas healthy adults have been reported to have the lowest levels.<sup>78</sup> Baseline hepcidin levels also correlated with CRP levels.<sup>79,80</sup>

Anemia is a common contributor to fatigue.<sup>4,81</sup> 40% to 80% of rheumatoid arthritis patients report fatigue as their most disabling symptom.<sup>82</sup> In addition to its role in hepcidin production, IL-6 has also been associated with other causes of fatigue.<sup>83</sup> IL-6-induced effects have been linked to functions of the HPA (hypothalamic-pituitary-adrenal) axis, including fatigue, and elevated levels of IL-6 have been positively correlated with fatigue in RA.<sup>1,4,84,85</sup> Studies have also shown that circulating levels of IL-6 may contribute to sleep disturbances in several different patient populations.<sup>83</sup>

## Contributing effects of elevated IL-6 signaling on energy homeostasis in RA

### IL-6 functions as an energy sensor.

Prolonged myocyte activation during sustained exercise depletes glycogen stores, thus triggering a cascade of compensatory responses. Glycogen depletion induces myocytes to produce and secrete IL-6 into plasma.<sup>86</sup> Following exercise, plasma IL-6 concentration may increase up to 100-fold, but less dramatic increases are more frequent.<sup>86</sup> Circulating IL-6 promotes the conversion of hepatic glycogen into glucose, and subsequent glucose uptake and utilization by skeletal muscle. In contrast, TNF- $\alpha$  levels are not increased by myocytes in response to sustained exercise.<sup>87,88</sup> In the context of muscle tissue, IL-6 also stimulates the production of anti-inflammatory cytokines and actually suppresses TNF- $\alpha$  production, which suggests IL-6 offers protection against TNF-induced insulin resistance.<sup>89-91</sup> A recent study also suggests that IL-6 may have a beneficial role in the prevention of obesity-associated insulin resistance through a polarization of macrophages from a pro-inflammatory to an anti-inflammatory phenotype.<sup>92</sup>

IL-6 plays important roles in the endocrine functions of pancreatic islet cells, specifically  $\alpha$  and  $\beta$  cells.<sup>93</sup> The IL-6 receptor is expressed by  $\alpha$  cells, and IL-6 treatment of  $\alpha$  cells promotes their proliferation and acutely regulates pro-glucagon gene expression and glucagon secretion.<sup>93</sup>  $\beta$  cells are a source of IL-6, and experimental models have shown

that IL-6 protects the  $\beta$ -cell population from TNF- $\alpha$ - and IFN- $\gamma$ -induced apoptosis, and preserves insulin secretory functions.<sup>14,94</sup>

Adipose tissue stores triglycerides and is an active endocrine organ with a central role in maintaining normal energy homeostasis.<sup>95,96</sup> Adipocytes communicate with other cells involved in energy homeostasis through release of adipokines—cytokines secreted by adipose tissue—such as leptin and adiponectin.<sup>97,98</sup> IL-6 also functions as an adipokine; it can increase adipose cell size, and modulate leptin production and lipid metabolism.<sup>99,100</sup>

The persistently elevated levels of circulating cytokines such as IL-6 in RA could be one of the contributing factors to muscle and adipose tissues becoming insulin-resistant during chronic inflammation, a condition referred to as an “inflammatory metabolic” state.<sup>67,101,102</sup> In addition, the biochemical composition of lipids is altered in response to chronic inflammation. Rheumatoid arthritis is associated with reduced serum levels of total, high-density lipoprotein (HDL), and low-density lipoprotein (LDL), cholesterol. Although effective therapies raise HDL, LDL, and total cholesterol levels as a consequence of reducing inflammation, these therapies also reduce the risk of cardiovascular events in patients with RA.<sup>67,103</sup>

Circulating levels of IL-6 are elevated in some insulin-resistant states such as obesity.<sup>104</sup> Higher inflammatory activity and a reduced functional activity are associated with obesity in RA patients.<sup>105</sup> Growing evidence suggests that IL-6 is not only produced by adipocytes

but is also capable of inducing insulin resistance in these cells.<sup>106-110</sup>

## Effects of elevated IL-6 signaling on bone metabolism in RA

RA leads to increased bone destruction, which places patients at risk for fractures.<sup>111</sup> In the clinical evaluation of synovial fluid from patients with RA, it was determined that the ratio of RANKL to osteoprotegerin (OPG), a protein that binds directly to RANKL and inhibits it from interacting with its receptor, reflects osteoclast function, and a higher ratio of RANKL to OPG is correlated to osteoclast hyperactivity and bone resorption in joints in patients with RA.<sup>23,42,112-115</sup>

Similar to more general cases of inflammation, IL-6 can affect the RANKL/OPG ratio through two mechanisms during RA inflammation. First, IL-6 directly stimulates osteoblasts to increase expression of RANKL, which can be bound by osteoclasts and drive their activation. Second, IL-6 directly stimulates Th17 cells, which produce IL-17; IL-17 levels are significantly higher in the synovial fluid of patients with RA.<sup>116,117</sup> IL-6 induces macrophages/monocytes to produce IL-1 and TNF- $\alpha$ . IL-17, IL-1, and TNF- $\alpha$  all stimulate effector T-cell proliferation and activation, which contribute to tissue damage in patients with RA. Importantly, these newly formed, activated T cells can express RANKL.<sup>118</sup> Therefore, the increased number of T cells expressing RANKL increases the ratio of RANKL to OPG and thereby enhances osteoclast function.<sup>119,120</sup> The increased

osteoclast function shifts the balance of bone resorption/formation toward resorption, resulting in reduced bone mineral density in patients with RA. Elevated IL-6 signaling also inhibits bone regeneration by affecting osteogenesis.<sup>1,23,112,113,115</sup> The increased bone resorption activity associated with RA translates to articular bone damage and systemic bone loss.<sup>121-123</sup>

**Elevated IL-6 levels are associated with generalized bone mineral density loss, a common systemic manifestation of RA.**<sup>1,5,124-126</sup>

The prevalence of bone mineral density loss in the overall RA patient population has been reported as between 20% and 56%.<sup>123,124,127-129</sup> The disruption of homeostasis caused by elevated IL-6 signaling, and the resultant increase in bone resorption, can lead to overall bone mineral density loss, bone weakening, cartilage destruction, and an increased susceptibility to fracture.<sup>130</sup>

Bone mineral density loss is especially prevalent in postmenopausal women with RA; generalized bone mineral density loss occurs in >50% of this population compared with ~15% in postmenopausal women without RA.<sup>131</sup> Studies have shown that estrogen blocks the synthesis of IL-6 by bone-forming osteoblasts and may also interfere with expression of IL-6 receptors. Elevated serum levels of IL-6 and sIL-6R have also been associated with bone mineral density loss in postmenopausal women with RA, independent of glucocorticoid (GC) use.<sup>132</sup> Elevated serum levels of sIL-6R have also been shown to be the main predictor of bone mineral density loss in a study of postmenopausal women with RA, independent

of well-known risk factors of generalized bone loss such as age, disease duration, low body mass index, and cumulative GC dose.<sup>125,133</sup>

## Conclusions

IL-6 is a multifunctional cytokine mediating key functions within the complex cytokine network.<sup>15</sup> The broad range of IL-6 activities is due in large part to its ability to signal through both transmembrane and soluble forms of its receptors, allowing for interaction with cells that do not express the IL-6 receptor, resulting in expanded biological activity.<sup>1</sup> As a result, IL-6 performs many diverse functions, including vital pro-inflammatory functions, in response to infection or injury under normal physiological conditions. Conversely, persistent elevated IL-6 signaling may have a negative impact that can disrupt homeostasis across multiple physiologic processes. Particularly in RA, IL-6 contributes to articular destruction and may be associated with systemic manifestations that culminate in functional disability.<sup>1,3-5,9,134</sup> Continued research on the many functions of IL-6 may further delineate the pathological origins and underpinnings of RA.

# References

1. Dayer JM, Choy E. Therapeutic targets in rheumatoid arthritis: the interleukin-6 receptor. *Rheumatology (Oxford)*. 2010;49:15-24.
2. Fleming A, Benn RT, Corbett M, Wood PH. Early rheumatoid disease. II. Patterns of joint involvement. *Ann Rheum Dis*. 1976;35:361-364.
3. Colmegna I, Ohata BR, Menard HA. Current understanding of rheumatoid arthritis therapy. *Clin Pharmacol Ther*. 2012;91:607-620.
4. Choy E. Understanding the dynamics: pathways involved in the pathogenesis of rheumatoid arthritis. *Rheumatology (Oxford)*. 2012;51(suppl 5):v3-11.
5. McInnes IB, Schett G. Cytokines in the pathogenesis of rheumatoid arthritis. *Nat Rev Immunol*. 2007;7:429-442.
6. Janeway CJ, Travers P, Walport M, Shlomchik M. *Immunobiology: The Immune System in Health and Disease*. 5th ed. New York: Garland Science; 2001.
7. O'Shea J, Sims J, Siegel R, Farber J. Cytokines. In: Hochberg M, Silman AJ, Smolen JS, Weinblatt ME, Weisman MH, eds. *Rheumatology (Oxford)*, 5th ed. Philadelphia, PA: Mosby Elsevier; 2001.
8. Bode JG, Albrecht U, Häussinger D, Heinrich PC, Schaper F. Hepatic acute phase proteins—regulation by IL-6- and IL-1-type cytokines involving STAT3 and its crosstalk with NF- $\kappa$ B-dependent signaling. *Eur J Cell Biol*. 2012;91:496-505.
9. Choy EH, Kavanaugh AF, Jones SA. The problem of choice: current biologic agents and future prospects in RA. *Nat Rev Rheumatol*. 2013;9:154-163.
10. Liang KP, Myasoedova E, Crowson CS, et al. Increased prevalence of diastolic dysfunction in rheumatoid arthritis. *Ann Rheum Dis*. 2010;69:1665-1670.
11. Rho YH, Chung CP, Oeser A, et al. Inflammatory mediators and premature coronary atherosclerosis in rheumatoid arthritis. *Arthritis Rheum*. 2009;61:1580-1585.
12. Wong PK, Quinn JM, Sims NA, van Nieuwenhuijze A, Campbell IK, Wicks IP. Interleukin-6 modulates production of T lymphocyte-derived cytokines in antigen-induced arthritis and drives inflammation-induced osteoclastogenesis. *Arthritis Rheum*. 2006;54:158-168.
13. Kotake S, Sato K, Kim KJ, et al. Interleukin-6 and soluble interleukin-6 receptors in the synovial fluids from rheumatoid arthritis patients are responsible for osteoclast-like cell formation. *J Bone Miner Res*. 1996;11:88-95.
14. Campbell IL, Cutri A, Wilson A, Harrison LC. Evidence for IL-6 production by and effects on the pancreatic  $\beta$ -cell. *J Immunol*. 1989;143:1188-1191.
15. Ito A, Itoh Y, Sasaguri Y, Morimatsu M, Mori Y. Effects of interleukin-6 on the metabolism of connective tissue components in rheumatoid synovial fibroblasts. *Arthritis Rheum*. 1992;35:1197-1201.
16. Jansen JH, Kluin-Nelemans JC, Van Damme J, Wientjens GJ, Willemze R, Fibbe WE. Interleukin 6 is a permissive factor for monocytic colony formation by human hematopoietic progenitor cells. *J Exp Med*. 1992;175:1151-1154.
17. Okada A, Yamasaki S, Koga T, et al. Adipogenesis of the mesenchymal stromal cells and bone oedema in rheumatoid arthritis. *Clin Exp Rheumatol*. 2012;30:332-337.
18. Sha Y, Markovic-Plese S. A role of IL-1R1 signaling in the differentiation of Th17 cells and the development of autoimmune diseases. *Self Nonself*. 2011;2:35-42.
19. Calabrese LH, Rose-John S. IL-6 biology: implications for clinical targeting in rheumatic disease. *Nat Rev Rheumatol*. 2014;10:720-727.
20. Bottini N, Firestein GS. Duality of fibroblast-like synoviocytes in RA: passive responders and imprinted aggressors. *Nat Rev Rheumatol*. 2013;9:24-33.
21. Bartok B, Firestein GS. Fibroblast-like synoviocytes: key effector cells in rheumatoid arthritis. *Immunol Rev*. 2010;233:233-255.
22. Pope RM. Apoptosis as a therapeutic tool in rheumatoid arthritis. *Nat Rev Immunol*. 2002;2:527-535.
23. Hashizume M, Hayakawa N, Mihara M. IL-6 trans-signalling directly induces RANKL on fibroblast-like synovial cells and is involved in RANKL induction by TNF- $\alpha$  and IL-17. *Rheumatology (Oxford)*. 2008;47:1635-1640.
24. Choe JY, Park KY, Park SH, Lee SJ, Kim SK. Regulatory effect of calcineurin inhibitor, tacrolimus, on IL-6/sIL-6R-mediated RANKL expression through JAK2-STAT3-SOCS3 signaling pathway in fibroblast-like synoviocytes. *Arthritis Res Ther*. 2013;15:R26.
25. Tolboom TC, van der Helm-van Mil AH, Nelissen RG, Breedveld FC, Toes RE, Huizinga TW. Invasiveness of fibroblast-like synoviocytes is an individual patient characteristic associated with the rate of joint destruction in patients with rheumatoid arthritis. *Arthritis Rheum*. 2005;52:1999-2002.
26. Firestein GS. Fibroblast-like synoviocytes in rheumatoid arthritis. Passive responders or transformed aggressors? *Arthritis Rheum*. 1996;39:1781-1790.
27. Shigeyama Y, Pap T, Kunzler P, Simmen BR, Gay RE, Gay S. Expression of osteoclast differentiation factor in rheumatoid arthritis. *Arthritis Rheum*. 2000;43:2523-2530.
28. Muller-Ladner U, Kriegsmann J, Franklin BN, et al. Synovial fibroblasts of patients with rheumatoid arthritis attach to and invade normal human cartilage when engrafted into SCID mice. *Am J Pathol*. 1996;149:1607-1615.
29. Muraguchi A, Hirano T, Tang B, et al. The essential role of B cell stimulatory factor 2 (BSF-2/IL-6) for the terminal differentiation of B cells. *J Exp Med*. 1988;167:332-344.
30. Schroder AE, Greiner A, Seyfert C, Berek C. Differentiation of B cells in the nonlymphoid tissue of the synovial membrane of patients with rheumatoid arthritis. *Proc Natl Acad Sci U S A*. 1996;93:221-225.
31. Li J, Kuzin I, Moshkani S, et al. Expanded CD23(+)/CD21(hi) B cells in inflamed lymph nodes are associated with the onset of inflammatory-erosive arthritis in TNF-transgenic mice and are targets of anti-CD20 therapy. *J Immunol*. 2010;184:6142-6150.
32. Crofford LJ, Kalogeras KT, Mastorakos G, et al. Circadian relationships between interleukin (IL)-6 and hypothalamic-pituitary-adrenal axis hormones: failure of IL-6 to cause sustained hypercortisolism in patients with early untreated rheumatoid arthritis. *J Clin Endocrinol Metab*. 1997;82:1279-1283.
33. Nakamura I, Omata Y, Naito M, Ito K. Blockade of interleukin 6 signaling induces marked neutropenia in patients with rheumatoid arthritis. *J Rheumatol*. 2009;36:459-460.
34. van Leeuwen MA, Westra J, Limburg PC, van Riel PL, van Rijswijk MH. Interleukin-6 in relation to other proinflammatory cytokines, chemotactic activity and neutrophil activation in rheumatoid synovial fluid. *Ann Rheum Dis*. 1995;54:33-38.
35. Mihara M, Moriya Y, Kishimoto T, Ohsugi Y. Interleukin-6 (IL-6) induces the proliferation of synovial fibroblastic cells in the presence of soluble IL-6 receptor. *Br J Rheumatol*. 1995;34:321-325.
36. Mitani H, Katayama N, Araki H, et al. Activity of interleukin 6 in the differentiation of monocytes to macrophages and dendritic cells. *Br J Haematol*. 2000;109:288-295.
37. Cronstein BN. Interleukin-6—a key mediator of systemic and local symptoms in rheumatoid arthritis. *Bull NYU Hosp Jt Dis*. 2007;65 (suppl 1):S11-15.
38. Kimura A, Kishimoto T. IL-6: regulator of Treg/Th17 balance. *Eur J Immunol*. 2010;40:1830-1835.
39. Ogura H, Murakami M, Okuyama Y, et al. Interleukin-17 promotes autoimmunity by triggering a positive-feedback loop via interleukin-6 induction. *Immunity*. 2008;29:628-636.
40. Ota M, Yanagisawa M, Tachibana H, et al. A significant induction of neutrophilic chemoattractants but not RANKL in synoviocytes stimulated with interleukin 17. *J Bone Miner Metab*. 2015;33:40-47.
41. Palmqvist P, Persson E, Conaway HH, Lerner UH. IL-6, leukemia inhibitory factor, and oncostatin M stimulate bone resorption and regulate the expression of receptor activator of NF- $\kappa$ B ligand, osteoprotegerin, and receptor activator of NF- $\kappa$ B in mouse calvariae. *J Immunol*. 2002;169:3353-3362.
42. Ishimi Y, Miyaura C, Jin CH, et al. IL-6 is produced by osteoblasts and induces bone resorption. *J Immunol*. 1999;163:3297-3303.
43. Nakahara H, Song J, Sugimoto M, et al. Anti-interleukin-6 receptor antibody therapy reduces vascular endothelial growth factor production in rheumatoid arthritis. *Arthritis Rheum*. 2003;48:1521-1529.
44. Hashizume M, Hayakawa N, Suzuki M, Mihara M. IL-6/sIL-6R trans-signalling, but not TNF- $\alpha$  induced angiogenesis in a HUVEC and synovial cell co-culture system. *Rheumatol Int*. 2009;29:1449-1454.

45. Alesci S, Martinez PE, Kelkar S, et al. Major depression is associated with significant diurnal elevations in plasma interleukin-6 levels, a shift of its circadian rhythm, and loss of physiological complexity in its secretion: clinical implications. *J Clin Endocrinol Metab.* 2005;90:2522-2530.
46. Hurst SM, Wilkinson TS, McLoughlin RM, et al. IL-6 and its soluble receptor orchestrate a temporal switch in the pattern of leukocyte recruitment seen during acute inflammation. *Immunity.* 2001;14:705-714.
47. Modur V, Li Y, Zimmerman GA, Prescott SM, McIntyre TM. Retrograde inflammatory signaling from neutrophils to endothelial cells by soluble interleukin-6 receptor alpha. *J Clin Invest.* 1997;100:2752-2756.
48. Lindemann SW, Yost CC, Denis MM, McIntyre TM, Weyrich AS, Zimmerman GA. Neutrophils alter the inflammatory milieu by signal-dependent translation of constitutive messenger RNAs. *Proc Natl Acad Sci U S A.* 2004;101:7076-7081.
49. Kaplanski G, Marin V, Montero-Julian F, Mantovani A, Farnarier C. IL-6: a regulator of the transition from neutrophil to monocyte recruitment during inflammation. *Trends Immunol.* 2003;24:25-29.
50. Gabay C. Interleukin-6 and chronic inflammation. *Arthritis Res Ther.* 2006;8(suppl 2):S3.
51. Jego G, Bataille R, Pellat-Deceunynck C. Interleukin-6 is a growth factor for nonmalignant human plasmablasts. *Blood.* 2001;97:1817-1822.
52. Dienz O, Eaton SM, Bond JP, et al. The induction of antibody production by IL-6 is indirectly mediated by IL-21 produced by CD4+ T cells. *J Exp Med.* 2009;206:69-78.
53. Kuchen S, Robbins R, Sims GP, et al. Essential role of IL-21 in B cell activation, expansion, and plasma cell generation during CD4+ T cell-B cell collaboration. *J Immunol.* 2007;179:5886-5896.
54. Gommerman JL, Browning JL. Lymphotoxin/light, lymphoid microenvironments and autoimmune disease. *Nat Rev Immunol.* 2003;3:642-655.
55. Ballanti E, Perricone C, di Muzio G, et al. Role of the complement system in rheumatoid arthritis and psoriatic arthritis: relationship with anti-TNF inhibitors. *Autoimmun Rev.* 2011;10:617-623.
56. Jones SA, Novick D, Horiuchi S, Yamamoto N, Szalai AJ, Fuller GM. C-reactive protein: a physiological activator of interleukin 6 receptor shedding. *J Exp Med.* 1999;189:599-604.
57. Banda NK, Levitt B, Wood AK, et al. Complement activation pathways in murine immune complex-induced arthritis and in C3a and C5a generation in vitro. *Clin Exp Immunol.* 2010;159:100-108.
58. Lee H, Whitfield PL, Mackay CR. Receptors for complement C5a. The importance of C5aR and the enigmatic role of C5L2. *Immunol Cell Biol.* 2008;86:153-160.
59. Arvidson NG, Gudbjornsson B, Elfman L, Ryden AC, Totterman TH, Hallgren R. Circadian rhythm of serum interleukin-6 in rheumatoid arthritis. *Ann Rheum Dis.* 1994;53:521-524.
60. Gibbs JE, Ray DW. The role of the circadian clock in rheumatoid arthritis. *Arthritis Res Ther.* 2013;15:205.
61. Spies CM, Straub RH, Cutolo M, Buttgerit F. Circadian rhythms in rheumatology—a glucocorticoid perspective. *Arthritis Res Ther.* 2014;16 Suppl 2:S3.
62. Gibbs JE, Blaikley J, Beesley S, et al. The nuclear receptor REV-ERB $\alpha$  mediates circadian regulation of innate immunity through selective regulation of inflammatory cytokines. *Proc Natl Acad Sci U S A.* 2012;109:582-587.
63. Haas S, Straub RH. Disruption of rhythms of molecular clocks in primary synovial fibroblasts of patients with osteoarthritis and rheumatoid arthritis, role of IL-1 $\beta$ /TNF. *Arthritis Res Ther.* 2012;14:R122.
64. Panichi V, Migliori M, De Pietro S, et al. The link of biocompatibility to cytokine production. *Kidney Int Suppl.* 2000;76:S96-103.
65. Ganz T. Hepcidin, a key regulator of iron metabolism and mediator of anemia of inflammation. *Blood.* 2003;102:783-788.
66. Combe B, Dougados M, Goupille P, et al. Prognostic factors for radiographic damage in early rheumatoid arthritis: a multiparameter prospective study. *Arthritis Rheum.* 2001;44:1736-1743.
67. McInnes IB, Schett G. The pathogenesis of rheumatoid arthritis. *N Engl J Med.* 2011;365:2205-2219.
68. Ridker PM, Rifai N, Stampfer MJ, Hennekens CH. Plasma concentration of interleukin-6 and the risk of future myocardial infarction among apparently healthy men. *Circulation.* 2000;101:1767-1772.
69. Ridker PM, Rifai N, Rose L, Buring JE, Cook NR. Comparison of C-reactive protein and low-density lipoprotein cholesterol levels in the prediction of first cardiovascular events. *N Engl J Med.* 2002;347:1557-1565.
70. Ridker PM, Cannon CP, Morrow D, et al. C-reactive protein levels and outcomes after statin therapy. *N Engl J Med.* 2005;352:20-28.
71. Nemeth E, Valore EV, Territo M, Schiller G, Lichtenstein A, Ganz T. Hepcidin, a putative mediator of anemia of inflammation, is a type II acute-phase protein. *Blood.* 2003;101:2461-2463.
72. Nemeth E, Rivera S, Gabayan V, et al. IL-6 mediates hypoferrremia of inflammation by inducing the synthesis of the iron regulatory hormone hepcidin. *J Clin Invest.* 2004;113:1271-1276.
73. Lombardi L, Maisetta G, Batoni G, Tavanti A. Insights into the antimicrobial properties of hepcidins: advantages and drawbacks as potential therapeutic agents. *Molecules.* 2015;20:6319-6341.
74. Gonzalez-Lopez L, Rocha-Munoz AD, Ponce-Guameros M, et al. Anti-cyclic citrullinated peptide (anti-CCP) and anti-mutated citrullinated vimentin (anti-MCV) relation with extra-articular manifestations in rheumatoid arthritis. *J Immunol Res.* 2014;2014:536050.
75. Nikolaisen C, Figenschau Y, Nossent JC. Anemia in early rheumatoid arthritis is associated with interleukin-6-mediated bone marrow suppression, but has no effect on disease course or mortality. *J Rheumatol.* 2008;35:380-386.
76. Moller B, Scherer A, Forger F, Villiger PM, Finckh A. Swiss Clinical Quality Management Program for Rheumatic D. Anaemia may add information to standardised disease activity assessment to predict radiographic damage in rheumatoid arthritis: a prospective cohort study. *Ann Rheum Dis.* 2014;73:691-696.
77. van Steenberg HW, van Nies JA, van der Helm-van Mil AH. Anaemia to predict radiographic progression in rheumatoid arthritis. *Ann Rheum Dis.* 2013;72:e16.
78. Demirag MD, Haznedaroglu S, Sancak B, et al. Circulating hepcidin in the crossroads of anemia and inflammation associated with rheumatoid arthritis. *Intern Med.* 2009;48:421-426.
79. Sellam J, Kotti S, Fellahi S, et al. Serum hepcidin level is not an independent surrogate biomarker of disease activity or of radiographic progression in rheumatoid arthritis: results from the ESPOIR cohort. *Ann Rheum Dis.* 2013;72:312-314.
80. Song C, Merali Z, Anisman H. Variations of nucleus accumbens dopamine and serotonin following systemic interleukin-1, interleukin-2 or interleukin-6 treatment. *Neuroscience.* 1999;88:823-836.
81. Hewlett S, Chalder T, Choy E, et al. Fatigue in rheumatoid arthritis: time for a conceptual model. *Rheumatology (Oxford).* 2011;50:1004-1006.
82. Balsamo S, Diniz LR, dos Santos-Neto LL, da Mota LM. Exercise and fatigue in rheumatoid arthritis. *Isr Med Assoc J.* 2014;16:57-60.
83. Kapsimalis F, Basta M, Varouchakis G, Gourgoulialis K, Vgontzas A, Kryger M. Cytokines and pathological sleep. *Sleep Med.* 2008;9:603-614.
84. Davis MC, Zautra AJ, Younger J, Motivala SJ, Attrep J, Irwin MR. Chronic stress and regulation of cellular markers of inflammation in rheumatoid arthritis: implications for fatigue. *Brain Behav Immun.* 2008;22:24-32.
85. Motivala SJ, Sarfatti A, Olmos L, Irwin MR. Inflammatory markers and sleep disturbance in major depression. *Psychosom Med.* 2005;67:187-194.
86. Fischer CP. Interleukin-6 in acute exercise and training: what is the biological relevance? *Exerc Immunol Rev.* 2006;12:6-33.
87. Febbraio MA, Hiscock N, Sacchetti M, Fischer CP, Pedersen BK. Interleukin-6 is a novel factor mediating glucose homeostasis during skeletal muscle contraction. *Diabetes.* 2004;53:1643-1648.
88. Steensberg A, Keller C, Starkie RL, Osada T, Febbraio MA, Pedersen BK. IL-6 and TNF- $\alpha$  expression in, and release from, contracting human skeletal muscle. *Am J Physiol Endocrinol Metab.* 2002;283:E1272-E1278.



89. Petersen AM, Pedersen BK. The anti-inflammatory effect of exercise. *J Appl Physiol* (1985). 2005;98:1154-1162.
90. Plomgaard P, Bouzakri K, Krogh-Madsen R, Mittendorfer B, Zierath JR, Pedersen BK. Tumor necrosis factor- $\alpha$  induces skeletal muscle insulin resistance in healthy human subjects via inhibition of Akt substrate 160 phosphorylation. *Diabetes*. 2005;54:2939-2945.
91. Starkie R, Ostrowski SR, Jauffred S, Febbraio M, Pedersen BK. Exercise and IL-6 infusion inhibit endotoxin-induced TNF- $\alpha$  production in humans. *FASEB J*. 2003;17:884-886.
92. Mauer J, Chaurasia B, Goldau J, et al. Signaling by IL-6 promotes alternative activation of macrophages to limit endotoxemia and obesity-associated resistance to insulin. *Nat Immunol*. 2014;15:423-430.
93. Ellingsgaard H, Ehses JA, Hammar EB, et al. Interleukin-6 regulates pancreatic  $\alpha$ -cell mass expansion. *Proc Natl Acad Sci U S A*. 2008;105:13163-13168.
94. Choi SE, Choi KM, Yoon IH, et al. IL-6 protects pancreatic islet beta cells from pro-inflammatory cytokines-induced cell death and functional impairment in vitro and in vivo. *Transpl Immunol*. 2004;13:43-53.
95. Flier JS. Obesity wars: molecular progress confronts an expanding epidemic. *Cell*. 2004;116:337-350.
96. Onate B, Vilahur G, Ferrer-Lorente R, et al. The subcutaneous adipose tissue reservoir of functionally active stem cells is reduced in obese patients. *FASEB J*. 2012;26:4327-4336.
97. Ahima RS. Adipose tissue as an endocrine organ. *Obesity (Silver Spring)*. 2006;14 (suppl 5):242S-249S.
98. Monzillo LU, Hamdy O, Horton ES, et al. Effect of lifestyle modification on adipokine levels in obese subjects with insulin resistance. *Obes Res*. 2003;11:1048-1054.
99. Ryan AS, Berman DM, Nicklas BJ, et al. Plasma adiponectin and leptin levels, body composition, and glucose utilization in adult women with wide ranges of age and obesity. *Diabetes Care*. 2003;26:2383-2388.
100. Trujillo ME, Sullivan S, Harten I, Schneider SH, Greenberg AS, Fried SK. Interleukin-6 regulates human adipose tissue lipid metabolism and leptin production in vitro. *J Clin Endocrinol Metab*. 2004;89:5577-5582.
101. Bastard JP, Maachi M, Van Nhieu JT, et al. Adipose tissue IL-6 content correlates with resistance to insulin activation of glucose uptake both in vivo and in vitro. *J Clin Endocrinol Metab*. 2002;87:2084-2089.
102. Cojocaru M, Cojocaru IM, Silosi I, Vrabie CD. Metabolic syndrome in rheumatoid arthritis. *Maedica (Buchar)*. 2012;17:148-152.
103. Sattar N, McCarey DW, Capell H, McInnes IB. Explaining how "high-grade" systemic inflammation accelerates vascular risk in rheumatoid arthritis. *Circulation*. 2003;108:2957-2963.
104. Khaodhiar L, Ling PR, Blackburn GL, Bistrian BR. Serum levels of interleukin-6 and C-reactive protein correlate with body mass index across the broad range of obesity. *JPEN J Parenter Enteral Nutr*. 2004;28:410-415.
105. Stavropoulos-Kalinoglou A, Metsios GS, Koutedakis Y, Kitas GD. Obesity in rheumatoid arthritis. *Rheumatology (Oxford)*. 2011;50:450-462.
106. Fernandez-Real JM, Vayreda M, Richart C, et al. Circulating interleukin 6 levels, blood pressure, and insulin sensitivity in apparently healthy men and women. *J Clin Endocrinol Metab*. 2001;86:1154-1159.
107. Omoigui S. The interleukin-6 inflammation pathway from cholesterol to aging—role of statins, bisphosphonates and plant polyphenols in aging and age-related diseases. *Immun Ageing*. 2007;4:1.
108. Rotter V, Nagaev I, Smith U. Interleukin-6 (IL-6) induces insulin resistance in 3T3-L1 adipocytes and is, like IL-8 and tumor necrosis factor- $\alpha$ , overexpressed in human fat cells from insulin-resistant subjects. *J Biol Chem*. 2003;278:45777-45784.
109. Wang SW, Lin TM, Wang CH, Liu HH, Hwang JY. Increased toll-like receptor 2 expression in peptidoglycan-treated blood monocytes is associated with insulin resistance in patients with nondiabetic rheumatoid arthritis. *Mediators Inflamm*. 2012;2012:690525.
110. Wildman RP, Kaplan R, Manson JE, et al. Body size phenotypes and inflammation in the Women's Health Initiative Observational Study. *Obesity (Silver Spring)*. 2011;19:1482-1491.
111. Goldring SR. Inflammatory signaling induced bone loss. *Bone*. 2015; 80:143-149.
112. Kudo O, Sabokbar A, Pocock A, Ittonaga I, Fujikawa Y, Athanasou NA. Interleukin-6 and interleukin-11 support human osteoclast formation by a RANKL-independent mechanism. *Bone*. 2003;32:1-7.
113. Kaneshiro S, Ebina K, Shi K, et al. IL-6 negatively regulates osteoblast differentiation through the SHP2/MEK2 and SHP2/Akt2 pathways in vitro. *J Bone Miner Metab*. 2014;32:378-392.
114. Haynes DR, Crotti TN, Loric M, Bain GI, Atkins GJ, Findlay DM. Osteoprotegerin and receptor activator of nuclear factor kappaB ligand (RANKL) regulate osteoclast formation by cells in the human rheumatoid arthritic joint. *Rheumatology (Oxford)*. 2001;40:623-630.
115. Tamura T, Udagawa N, Takahashi N, et al. Soluble interleukin-6 receptor triggers osteoclast formation by interleukin 6. *Proc Natl Acad Sci U S A*. 1993;90:11924-11928.
116. Camporeale A, Poli V. IL-6, IL-17 and STAT3: a holy trinity in auto-immunity? *Front Biosci (Landmark Ed)*. 2012;17:2306-2326.
117. Kotake S, Udagawa N, Takahashi N, et al. IL-17 in synovial fluids from patients with rheumatoid arthritis is a potent stimulator of osteoclastogenesis. *J Clin Invest*. 1999;103:1345-1352.
118. Page G, Miossec P. RANK and RANKL expression as markers of dendritic cell-T cell interactions in paired samples of rheumatoid synovium and lymph nodes. *Arthritis Rheum*. 2005;52:2307-2312.
119. Kotake S, Nanke Y, Mogi M, et al. IFN- $\gamma$ -producing human T cells directly induce osteoclastogenesis from human monocytes via the expression of RANKL. *Eur J Immunol*. 2005;35:3353-3363.
120. Harvey BP, Gee RJ, Haberman AM, Shlomchik MJ, Mamula MJ. Antigen presentation and transfer between B cells and macrophages. *Eur J Immunol*. 2007;37:1739-1751.
121. Sinigaglia L, Nervetti A, Mela Q, et al. A multicenter cross sectional study on bone mineral density in rheumatoid arthritis. Italian Study Group on Bone Mass in Rheumatoid Arthritis. *J Rheumatol*. 2000;27:2582-2589.
122. Laan RF, Buijs WC, Verbeek AL, et al. Bone mineral density in patients with recent onset rheumatoid arthritis: influence of disease activity and functional capacity. *Ann Rheum Dis*. 1993;52:21-26.
123. Haugeberg G, Uhlig T, Falch JA, Halse JI, Kvien TK. Bone mineral density and frequency of osteoporosis in female patients with rheumatoid arthritis: results from 394 patients in the Oslo County Rheumatoid Arthritis register. *Arthritis Rheum*. 2000;43:522-530.
124. Forsblad D'Elia H, Larsen A, Waltbrand E, et al. Radiographic joint destruction in postmenopausal rheumatoid arthritis is strongly associated with generalised osteoporosis. *Ann Rheum Dis*. 2003;62:617-623.
125. Oelzner P, Franke S, Lehmann G, Eider T, Hein G, Wolf G. The balance between soluble receptors regulating IL-6 trans-signaling is predictive for the RANKL/osteoprotegerin ratio in postmenopausal women with rheumatoid arthritis. *Rheumatol Int*. 2012;32:199-206.
126. Giuliani N, Sansoni P, Girasole G, et al. Serum interleukin-6, soluble interleukin-6 receptor and soluble gp130 exhibit different patterns of age- and menopause-related changes. *Exp Gerontol*. 2001;36:547-557.
127. Xu S, Wang Y, Lu J, Xu J. Osteoprotegerin and RANKL in the pathogenesis of rheumatoid arthritis-induced osteoporosis. *Rheumatol Int*. 2012;32:3397-3403.
128. Gonzalez-Lopez L, Gamez-Nava JI, Vega-Lopez A, et al. Performance of risk indices for identifying low bone mineral density and osteoporosis in Mexican Mestizo women with rheumatoid arthritis. *J Rheumatol*. 2012;39:247-253.
129. Mobini M, Kashi Z, Ghobadifar A. Prevalence and associated factors of osteoporosis in female patients with rheumatoid arthritis. *Caspian J Intern Med*. 2012;3:447-450.
130. De Benedetti F, Rucci N, Del Fattore A, et al. Impaired skeletal development in interleukin-6 transgenic mice: a model for the impact of chronic inflammation on the growing skeletal system. *Arthritis Rheum*. 2006;54:3551-3563.
131. Ahlberg HG, Rosengren BE, Jarvinen TL, et al. Prevalence of osteoporosis and incidence of hip fracture in women—secular trends over 30 years. *BMC Musculoskelet Disord*. 2010;11:48.
132. Kroger H, Honkanen R, Saarikoski S, Alhava E. Decreased axial bone mineral density in perimenopausal women with rheumatoid arthritis—a population based study. *Ann Rheum Dis*. 1994;53:18-23.
133. Scheidt-Nave C, Bismar H, Leidig-Bruckner G, et al. Serum interleukin 6 is a major predictor of bone loss in women specific to the first decade past menopause. *J Clin Endocrinol Metab*. 2001;86:2032-2042.
134. Gabriel SE, Crowson CS, Kremers HM, et al. Survival in rheumatoid arthritis: a population-based analysis of trends over 40 years. *Arthritis Rheum*. 2003;48:54-58.

SANOFI GENZYME



**REGENERON**