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REVIEW

IL-6 Signaling in Immunopathology: From Basic Biology to Selective Therapeutic Intervention

Tim Schumertl, Juliane Lokau, Christoph Garbers

Institute of Clinical Biochemistry, Hannover Medical School, Hannover, 30625, Germany

Correspondence: Christoph Garbers, Institute of Clinical Biochemistry, Hannover Medical School, Carl-Neuberg-Strasse 1, Hannover, 30625, Germany, Tel +49 511 532 9802, Email garbers.christoph@mh-hannover.de

Abstract: Interleukin-6 (IL-6) is a cytokine with pro- and anti-inflammatory functions. Interestingly, its divergent biological activities are mediated by different signaling pathways: In IL-6 classic signaling, which is associated with the regenerative and anti-inflammatory properties of the cytokine, IL-6 binds to and signals via the membrane-bound IL-6 receptor (IL-6R) on its target cells. In contrast, the pro-inflammatory properties of IL-6 are mediated via the soluble (s)IL-6R (IL-6 trans-signaling). Recently, a third mode of IL-6 signaling was revealed, which was termed cluster signaling and is required for the generation of pathogenic Th17 cells. In all pathways, intracellular signaling cascades are activated via the formation of a gp130 homodimer. The involvement of IL-6 in the pathogenesis of inflammatory diseases, autoimmune diseases and even cancer has made IL-6 and the IL-6R important therapeutic targets. Consequently, antibodies that block either IL-6 itself or the IL-6R are in clinical use and have been approved for different inflammatory diseases, including rheumatoid arthritis (RA). This review gives an overview about the complex biology of this important cytokine, summarizes the current usage of anti-IL-6 therapeutics in clinical use and highlights the pre-clinical and clinical development of novel therapeutic agents that specifically block only the trans-signaling pathway of IL-6.

Keywords: interleukin-6, interleukin-6 receptor, trans-signaling, gp130, olamkicept

Introduction

The cytokine interleukin-6 (IL-6) is a member of the IL-6 family of cytokines and consists of 184 amino acids.[1] The protein is glycosylated[2] and consists of four anti-parallel α-helices which are arranged in an up-up-down-down topology.[3] IL-6 is produced by different immune cells such as B cells, T cells, dendritic cells or macrophages but also by other cell types such as fibroblasts or myocytes.[4,5] Its release is induced e.g. by the activation of pattern recognition receptors or in response to stress, leading to a significant increase of IL-6 levels.[6–9] IL-6 is not only involved in a number of physiological processes that are essential for human health, but it is also critically involved in basically all inflammatory diseases and thus an important therapeutic target. The rather unique feature of IL-6 in this regard is the fact that its biological activities in health and disease are mediated via two different ways of signaling: Physiological, regenerative and anti-inflammatory activities of IL-6 are mediated via the membrane-bound IL-6R (classic signaling), while the pathological, pro-inflammatory and tumor-promoting activities of IL-6 are mediated via the soluble IL-6R (trans-signaling). Via classic signaling, IL-6 is involved in the regulation of different aspects of the immune system, for example by inducing the production of acute phase proteins in the liver[10,11] or by regulating the differentiation of B[12] or T cells.[13] In addition, the cytokine contributes to different aspects of the metabolism[14,15] as well as bone remodeling.[16] Furthermore, involvement of IL-6 in neural differentiation[17] as well as in the regeneration of different organs like liver[18] or intestine[19] was reported.

In addition to this high number of physiological functions, IL-6 critically contributes to inflammatory diseases, including several autoimmune diseases, and to different cancer entities.[5,20,21] The upregulation of IL-6 in these diseases makes the cytokine and its receptor, the IL-6 receptor (IL-6R), attractive targets for therapeutic interventions.[22] The antibody tocilizumab, which binds to the IL-6R and thus prevents binding of IL-6 to the IL-6R and the following

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activation of intracellular signaling cascades, was the first approved specific IL-6 inhibitor and has proven clinical benefit in multiple inflammatory diseases, including rheumatoid arthritis (RA).[22,23] Since then, several other antibodies and designer proteins have been developed that are either already in clinical use or are currently investigated in clinical trials (see Inhibition of IL-6 Signaling for details). Furthermore, inhibitors which target only selected aspects of the complex biology of IL-6 have been developed, which are promising next-generation IL-6 inhibitors that promise more specificity and less side effects.[24]

The present review gives an overview of the multi-faceted biology of IL-6 and summarizes recent developments regarding its specific inhibition in inflammatory diseases.

Different Modes of IL-6 Signaling

IL-6 can activate its target cells via three different modes called classic signaling,[25] trans-signaling[24,26] and cluster signaling[22,27,28] (Figure 1). Interestingly, despite the different roles of these signaling modes in physiology and pathophysiology, intracellular signaling pathways are always activated by a complex consisting of the cytokine IL-6, the membrane-bound or soluble (s)IL-6R and a homodimer of the β-receptor glycoprotein 130 (gp130).[22] In the first step of complex formation IL-6 binds to the (s)IL-6R.[25] While the single components IL-6 and (s)IL-6R possess no affinity to gp130, the IL-6/(s)IL-6R complex is able to bind to gp130 with high affinity, resulting in the activation of the IL-6

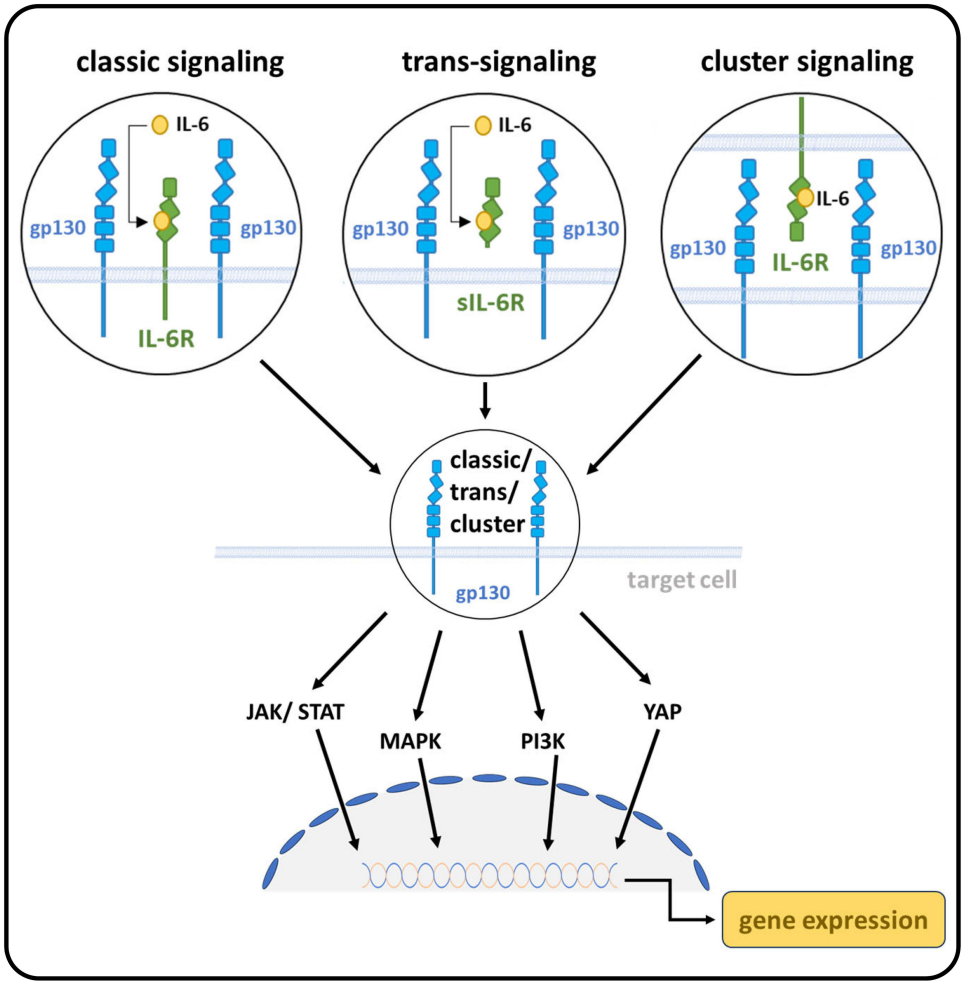

Figure 1 Three different modes of IL-6 signaling. IL-6 signaling is induced by a complex of IL-6, IL-6R and a gp130 homodimer. The IL-6R in this complex can be located on the target cell (left, classic signaling), as a soluble form (sIL-6R) in the extracellular space (middle, trans-signaling) or on a cell that is not the target cell (right, cluster signaling). Gp130 of the signaling complex is always located on the target cell. The formation of the signaling complex results in the activation of the JAK/STAT, MAPK, PI3K and YAP pathway, which regulate the expression of different target genes.

signaling cascade.[25,29] This two-step mechanism is crucial, because the (s)IL-6R is only able to bind the cytokine and not capable of activating intracellular signal cascades on its own. The expression of the β-receptor gp130 in basically all cells ensures that they can be activated by IL-6.[25,30] Irrespective of the extracellular composition of the signaling complex, dimerization of two gp130 molecules results in the activation of the same intracellular signaling pathways: the Janus kinase/ Signal Transducer and Activator of Transcription (JAK/STAT), Mitogen-Activated Protein Kinase (MAPK), Phosphoinositide 3-kinases (PI3K) and YES-associated protein (YAP) pathway, which regulate the activity of different target genes involved for example in the regulation of apoptosis, differentiation, proliferation and survival of the cell (Figure 1).[31,32]

Despite these similarities, the functional outcomes of the three signaling modes are fundamentally different. In classic signaling, IL-6 binds to the membrane-bound IL-6R (Figure 1). This means that expression of the IL-6R by the target cells is a prerequisite for classic signaling and that cells lacking IL-6R on their surface do not respond to IL-6 classic signaling.[25,30] Cells expressing the IL-6R include most immune cells, eg, monocytes, macrophages, dendritic cells, B cells or T cells but also other cells such as hepatocytes and osteoclasts.[33–36] IL-6 classic signaling is associated with the regenerative and anti-inflammatory functions of the cytokine, most prominently the hepatic acute phase response.[37]

In contrast to classic signaling, trans-signaling uses a sIL-6R for the formation of the receptor complex (Figure 1).[26] This means that IL-6 trans-signaling can activate many more cell types than IL-6 classic signaling because the β-receptor is expressed on almost all cells of the human body with the exception of granulocytes.[25,26,38] The sIL-6R is generated by alternative splicing,[39] released on microvesicles[33] or generated by proteolysis of the membrane-bound IL-6R[40] (see the next section for details). In addition to the formation of the sIL-6R, proteolysis also reduces the amount of the membrane-bound IL-6R on the cell surface.[40,41] Thus, IL-6R proteolysis can be envisioned as a molecular switch which not only induces IL-6 trans-signaling, but also downregulates the amount of IL-6R on the cell surface and thereby limits IL-6 classic signaling.[42] IL-6 trans-signaling is primarily associated with chronic inflammation and inflammatory diseases and thus accounts for the pro-inflammatory properties of IL-6.[24] Additionally, trans-signaling is the main IL-6 pathway associated with cancer as well as autoimmune diseases.[24] However, also an association of trans-signaling and liver regeneration was reported.[43]

The third mode of IL-6 signaling uses again the membrane-bound IL-6R (Figure 1).[27] In IL-6 cluster signaling, however, the IL-6R is located on a cell that is not the target cell that expresses gp130.[27] Here, the IL-6/IL-6R complex on dendritic cells activates the IL-6 signaling cascade in cognate T cells by interacting with gp130 on the T cells. This pathway is relevant for the formation of pathogenic T_H17 cells that are involved in the development of multiple sclerosis.[27] Whether cluster signaling is also involved in other diseases in addition to the autoimmune disease multiple sclerosis has yet to be investigated.

Interestingly, multiple modes of IL-6 signaling can occur in parallel in the same cell.[44–46] Cells expressing the membrane-bound IL-6R and gp130 can be activated by IL-6 classic signaling as well as IL-6 trans-signaling when the number of gp130 molecules exceed the number of membrane-bound IL-6R molecules.[44–47] So activation of these cells by the membrane-bound IL-6R alone or by the membrane-bound IL-6R and the sIL-6R in combination results in a different number of activated gp130 molecules, resulting in different signaling strengths that can lead to different cellular responses like increased cellular proliferation. For example, simultaneous activation of IL-6 classic and trans-signaling leads to higher cell proliferation than IL-6 classic signaling alone.[44,46,48]

Another level of complexity is added by the existence of the other IL-6 family cytokines IL-11, cardiotrophin 1 (CT-1), cardiotrophin-like cytokine (CLC), ciliary neurotrophic factor (CNTF), leukemia inhibitory factor (LIF), oncostatin M (OSM) and IL-27.[1,38] These cytokines also use gp130 as part of their signaling complex, which results in overlapping activation of intracellular signaling molecules. Additionally, these cytokines alter the amount of available gp130 molecules, which might affect the different IL-6 signaling modes, allowing further modulations of the cellular response by these cytokines.[49]

Generation of the Soluble IL-6 Receptor

Soluble cytokine receptors can be generated via different mechanisms.[50] One of the first studies regarding the sIL-6R reported the isolation of an mRNA that encodes a soluble IL-6R.[39] The underlying mechanism is termed alternative mRNA splicing (Figure 2), which in case of the sIL-6R means the excision of the exon encoding the transmembrane

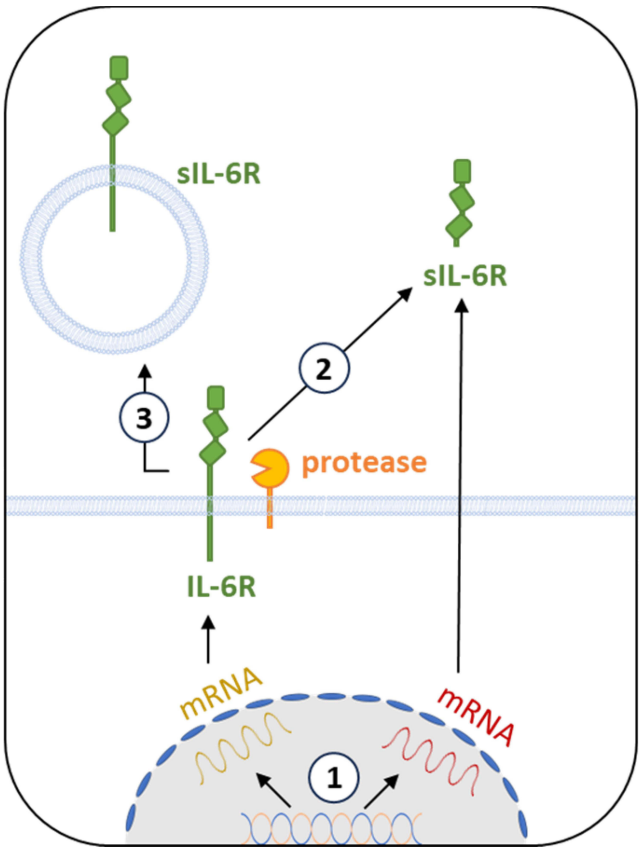

Figure 2 Different mechanisms to generate soluble IL-6R. The sIL-6R is generated by three different modes: (1) In addition to mRNA coding for the full-length IL-6R cells can also generate mRNA coding for a soluble form of the receptor. This process is called alternative mRNA splicing and occurs when the mRNA is processed by the spliceosome. (2) The majority of the sIL-6R is generated by proteolytic cleavage of the full-length IL-6R on the cell surface. This event is catalyzed by proteases, most notably by ADAM17. (3) Moreover, the full-length IL-6R can be released on extracellular vesicles. This is the only mode in which the sIL-6R is not a truncated version of the full-length receptor.

region of the IL-6R. This splicing event results in a frameshift and a unique C-terminus of the sIL-6R that includes ten novel amino acids which are not part of the full-length IL-6R sequence.[39,51] After generation of an antibody directed against this particular C-terminus and the development of an ELISA, we could show that ~15% of the sIL-6R present in the serum of healthy humans contains this C-terminus and thus is generated via alternative splicing of the *IL6R* mRNA.[51]

The majority of the sIL-6R, however, stems from proteolytic cleavage of the membrane-bound IL-6R precursor (Figure 2), as shown by mass spectrometry-based detection of a novel C-terminal peptide that was generated by a protease.[51] Using mutagenesis of the cleavage site, chemical inhibitors and protease-deficient cell lines, we have identified the metalloprotease ADAM17 as the major protease that cleaves the IL-6R.[42,51–53] Importantly, by mapping the IL-6R cleavage site we could for the first time explain why human individuals homozygous for the minor allele of the single nucleotide polymorphism (SNP) rs2228145 have doubled levels of sIL-6R in their serum. This SNP results in an exchange of the aspartic acid residue at position 358 of the IL-6R, to an alanine residue. This position is in close proximity to the cleavage site and the exchange renders the IL-6R more susceptible towards proteolytic cleavage.[54]

Of note, in addition to ADAM17 several other proteases have been identified in recent years that are, at least in vitro, capable of IL-6R proteolysis and thus sIL-6R generation. These are ADAM10,[41] RHBDL2,[55,56] meprins[57] and cathepsin S.[58] With the exception of ADAM10,[51] the cleavage site used by the other proteases has not been determined and compared to the cleavage site found in vivo, and it is thus unclear whether these proteases contribute to sIL-6R serum levels, whether they might be important IL-6R sheddases under inflammatory conditions, or whether they cleave the IL-6R in vivo at all. Irrespective of the protease that cleaves the IL-6R or whether it originates from alternative splicing, all

mentioned sIL-6R variants contain the IL-6 binding site and thus do not differ in their ability to perform IL-6 trans-signaling on cells that do not express the IL-6R.

Lastly, we could show that the IL-6R can also be released from cells via extracellular vesicles (Figure 2).[33] In contrast to alternative splicing and proteolytic cleavage, extracellular vesicles contain a full-length IL-6R and not a truncated protein. The functional relevance of this pathway is only poorly understood, but there is some evidence that the extracellular vesicles containing the IL-6R can fuse with other cells, including cells that lack the IL-6R on their surface, and thus transform a cell that cannot respond to IL-6 classic signaling into a cell that can directly be activated by IL-6.[59] Thus, the third mode of sIL-6R generation does not lead to IL-6 trans-signaling, but might represent another layer of regulation of IL-6 signaling. Interestingly, ADAM proteases are also part of extracellular vesicles,[60–62] so IL-6R cleavage might occur even after release of the vesicles in a cell autonomous manner, although there is no published evidence for such a mechanism to date.

Interestingly, also gp130 exists in different soluble forms which are all able to bind IL-6/sIL-6R complexes. However, the generation of sgp130 differs from sIL-6R generation and is explored in much less detail. Differential splicing events and alternative intronic polyadenylation of the gp130 mRNA give rise to at least three different sgp130 variants with different molecular weights.[63–66] These sgp130 variants are expressed in a cell-type specific manner, bind IL-6/sIL-6R with different efficacy, and are believed to allow endogenous fine-tuning of IL-6 trans-signaling.[67] Additionally, sgp130 can also be generated by proteolysis. While ADAM10 and ADAM17 can shed gp130 from the cell surface,[67] the majority of proteolysis-derived sgp130 is generated by the protease BACE1.[68]

The sIL-6R/sgp130 Buffer System

We have described in the previous section how sIL-6R and sgp130 are generated. While this has been investigated in much detail, the biological function and functional relevance of the two proteins for IL-6 biology remains controversial and under intense investigation and debate.

There is good evidence that all receptors of the IL-6 family exist not only as membrane-bound proteins, but also as soluble forms.[50] This is not an exclusive feature of the IL-6 family, as soluble cytokine receptors have also been described for other cytokine families, eg, the IL-2/common gamma chain family.[50] Thus, soluble cytokine receptors, which are antagonistic decoy proteins in most cases, might represent an additional mechanism how the biological activity of cytokines is controlled and thus contribute to the prevention of overshooting cytokine activities. However, one could even envision that all membrane-bound proteins undergo proteolytic cleavage, which might be one mechanism by which a cell can control and regulate the amount of a particular protein on its surface. In this case, the generated soluble proteins would rather be waste products than molecules with distinct properties and functions.

While it is not possible to definitely answer this question in general, there is ample evidence that at least sIL-6R and sgp130 fulfill meaningful and important biological functions that are relevant for human health. The serum levels of sIL-6R in healthy individuals are between 20 and 80 ng/mL, while sgp130 serum levels are around 400 ng/mL.[69] Thus, IL-6 that enters the bloodstream will most likely bind to a sIL-6R molecule and form an IL-6/sIL-6R complex. This bipartite complex can either bind to gp130 expressed on a cell, thus performing IL-6 trans-signaling, or it will be inactivated by binding to a sgp130 molecule. Our hypothesis is therefore that sIL-6R and sgp130 constitute a natural buffer system that eliminates IL-6, as the tripartite IL-6/sIL-6R/sgp130 complex cannot bind to a cell anymore, but will instead be removed from the circulation (Figure 3A). There is little hard information about the percentage of free IL-6 and soluble receptors, active IL-6/sIL-6R dimers, and inactive IL-6/sIL-6R/sgp130 trimers in the blood, but the proportions can be calculated. Due to the rather weak affinity of IL-6 to the (s)IL-6R, which is around 1nM, and the much higher affinity of the IL-6/sIL-6R complex to (s)gp130 of about 10pM,[30] it is quite clear that no significant amount of free IL-6/sIL-6R complexes can exist in healthy individuals. Furthermore, sgp130 is present in molar excess over sIL-6R, which emphasizes that the amount of sIL-6R determines the capacity of the buffer system, because more sIL-6R will be able to bind more free IL-6, ultimately leading to more inactive IL-6/sIL-6R/sgp130 complexes. Whenever more IL-6 is generated than sIL-6R is present, the buffer will be exhausted and systemic IL-6 classic signaling will occur (Figure 3B). Increased IL-6 concentrations are reported in a variety of different diseases and can even reach several micrograms per milliliter in patients with bacterial sepsis,[70] which significantly exceed the capacity of the buffer. Similarly, inflammatory events are

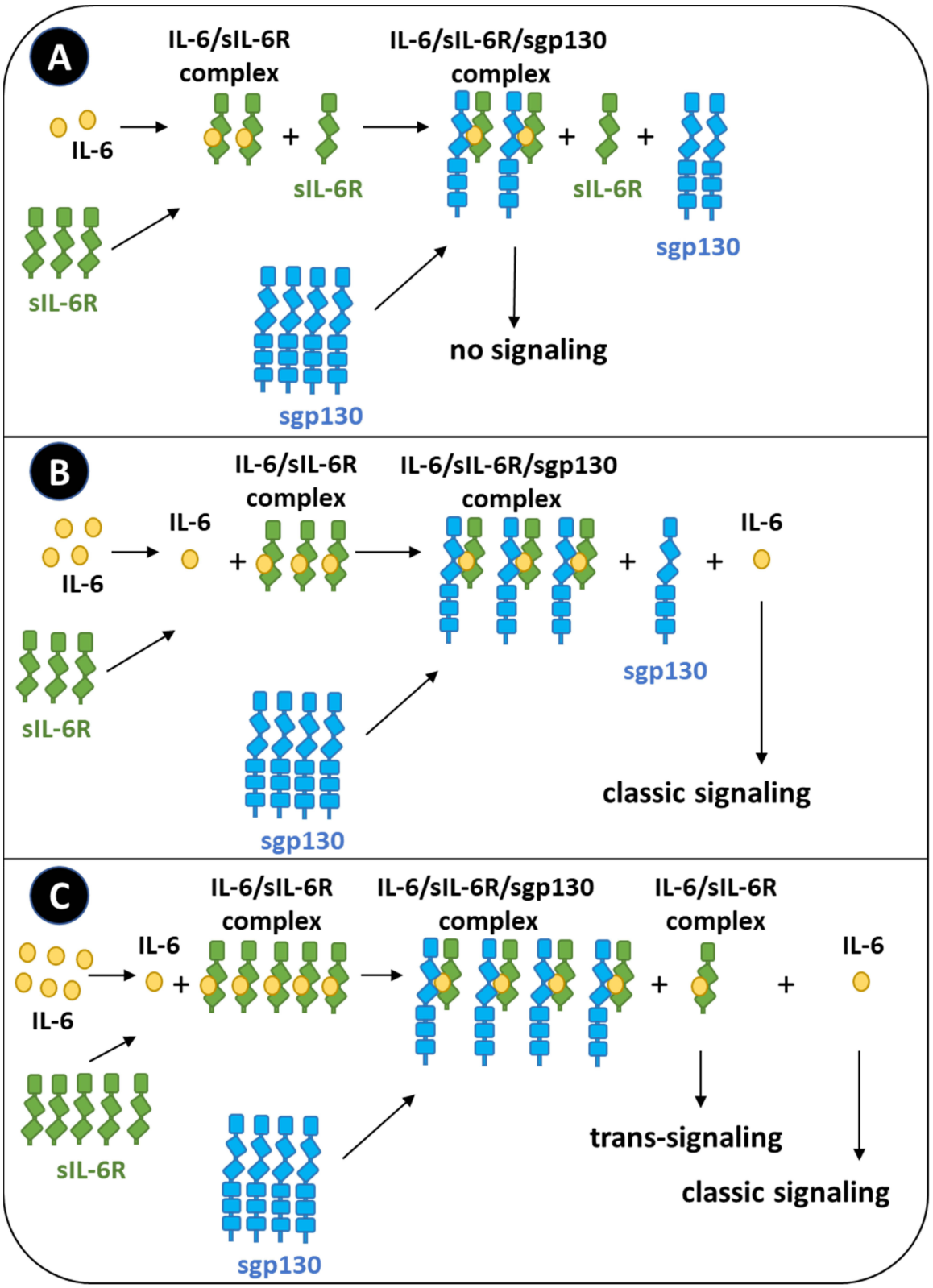

Figure 3 An endogenous buffer system for IL-6. (**A**) In the blood of healthy individuals, the amount of IL-6 is below the amount of the sIL-6R, and the amount of sgp130 exceeds the levels of both IL-6 and sIL-6R. All IL-6 that is released into the blood can bind to sIL-6R and the excess of sgp130 inactivates the resulting IL-6/sIL-6R complexes. Thus, neither classic signaling nor trans-signaling can occur. (**B**) Whenever the number of IL-6 molecules exceeds the number of sIL-6R molecules, free IL-6 exists in the blood due to the lack of sIL-6R that is required to form IL-6/sIL-6R complexes. Free IL-6 can initiate classic signaling. IL-6 that binds to the sIL-6R is again inactivated by the excessive amount of sgp130. (**C**) In cases in which the number of IL-6/sIL-6R complexes exceeds the number of sgp130 molecules, IL-6 trans-signaling can occur, as IL-6/sIL-6R complexes that are not bound by sgp130 are present besides the inactive IL-6/sIL-6R/sgp130 complexes. Additionally, classic signaling can occur if the number of IL-6 molecules exceeds the number of sIL-6R molecules as already shown in (**B**).

often accompanied not only by an increase in IL-6, but also increased sIL-6R, in which case the amounts of sgp130 are not sufficient to neutralize all IL-6/sIL-6R complexes, and systemic classic and trans-signaling will occur (Figure 3C).

The best evidence for the existence and high relevance of this buffer comes from two meta analyses that described a causal association between coronary heart disease and the IL-6R.[71,72] Both studies analyzed data from more than 100,000 patients and found that the SNP rs2228145, which results in the exchange of an aspartic acid to an alanine residue at position 358 of the IL-6R,[73] was associated with higher sIL-6R concentrations, lower amounts of C-reactive protein and most importantly decreased odds of coronary heart disease events.[71,72] We have described in the previous section that the exchange of this amino acid increases proteolysis by ADAM proteases and thus leads to higher amounts of sIL-6R and lower amounts of membrane-bound IL-6R.[54,74] The increased sIL-6R levels allow more free IL-6 to be bound and inactivated, contributing to reduced systemic inflammation, which results in reduced odds to experience coronary heart disease.[75,76] Using recombinant proteins at concentrations that mimic the conditions found in vivo, we could indeed show in vitro the enhanced neutralizing capacity of the buffer system when sIL-6R amounts are increased.[69]

This is not only relevant for coronary heart disease, but most likely also for several other inflammatory diseases. We could show that sIL-6R and sgp130 serum levels were lower and IL-6 levels were higher in patients with type 2 diabetes compared to healthy controls, indicating a lower buffer capacity which might be accompanied by higher IL-6 induced pro-inflammatory signals. We observed this also in patients with both type 2 diabetes and atherosclerosis, but not in patients with atherosclerosis alone.[69] Besides this, a systematic analysis of this phenomenon has not been conducted to date, but warrants further investigation.

Inhibition of IL-6 Signaling

The IL-6 signaling complex and its downstream signaling cascades offer multiple avenues of therapeutic intervention, and all of them have been explored. In order to block IL-6 signaling from the outside of the cell, antibodies directed against either IL-6, the IL-6R, or the signal-transducing β-receptor gp130 can be used. IL-6 complex formation is elicited via three different binding sites of IL-6. First, IL-6 binds to the soluble or membrane-bound IL-6R via site I, whereas the binding of the two gp130 molecules is facilitated through site II and site III, respectively.[77,78] Inhibition of gp130 is not a suitable mechanism to block IL-6 signaling due to the shared usage of gp130 with the other cytokines of the IL-6 family.[49] The importance of this cytokine family is easiest visualized by a knock-out of gp130 in mice, which results in embryonic lethality.[79] In line with that, human individuals with loss-of-function variants in *IL6ST* (the human gene encoding gp130) have lethal Stüve-Wiedemann-like syndrome, characterized by neonatal lung dysfunction and skeletal abnormalities among other features.[80] Accordingly, although monoclonal antibodies against gp130 have been developed that target cytokine-specific epitopes on this receptor,[81–83] none of these have reached clinical studies.[22]

Instead, the first clinically approved antibody to block IL-6 signaling was tocilizumab, which targets the IL-6R contact site to which IL-6 would bind via site I[84] and thus prevents binding of IL-6, the subsequent formation of the signaling complex and finally the activation of intracellular signaling pathways (Figure 4). Tocilizumab has been first approved for the treatment of Castleman disease,[85,86] a rare lymphoproliferative disorder. Nowadays, tocilizumab is used for several other inflammatory diseases, including RA, systemic juvenile idiopathic arthritis, giant cell arteritis and neuromyelitis optica spectrum disorder.[22,87] Typical adverse effects of tocilizumab are an increased risk for infection and elevations of laboratory parameters like lipids and transaminases, the latter ones often described as transient.[88,89]

During the recent pandemic, IL-6 was early on recognized as a crucial factor of inflammation during the SARS-CoV -2 infection,[90,91] and several studies evaluated tocilizumab in the treatment of COVID-19 patients, albeit with rather mixed results.[92–99] Nevertheless, tocilizumab was approved, but only for the treatment of severe COVID-19 pneumonia.[87] Interestingly, also alterations in sIL-6R levels in patients with COVID-19 were noted.[100,101] Another application of tocilizumab is the CAR T cell therapy, a cancer immunotherapy in which T cells of the patient are engineered to recognize and thus eliminate tumor cells.[102] Here, a critical side effect is the induction of a so-called cytokine release syndrome, meaning the massive production of different pro-inflammatory cytokines, including IL-6, induced by the CAR T cells. Application of tocilizumab has been proven beneficial in these patients.[103,104] Of note, tocilizumab binds to both membrane-bound and soluble IL-6R forms and is not able to discriminate between the different modes of IL-6 signaling (Figure 4).

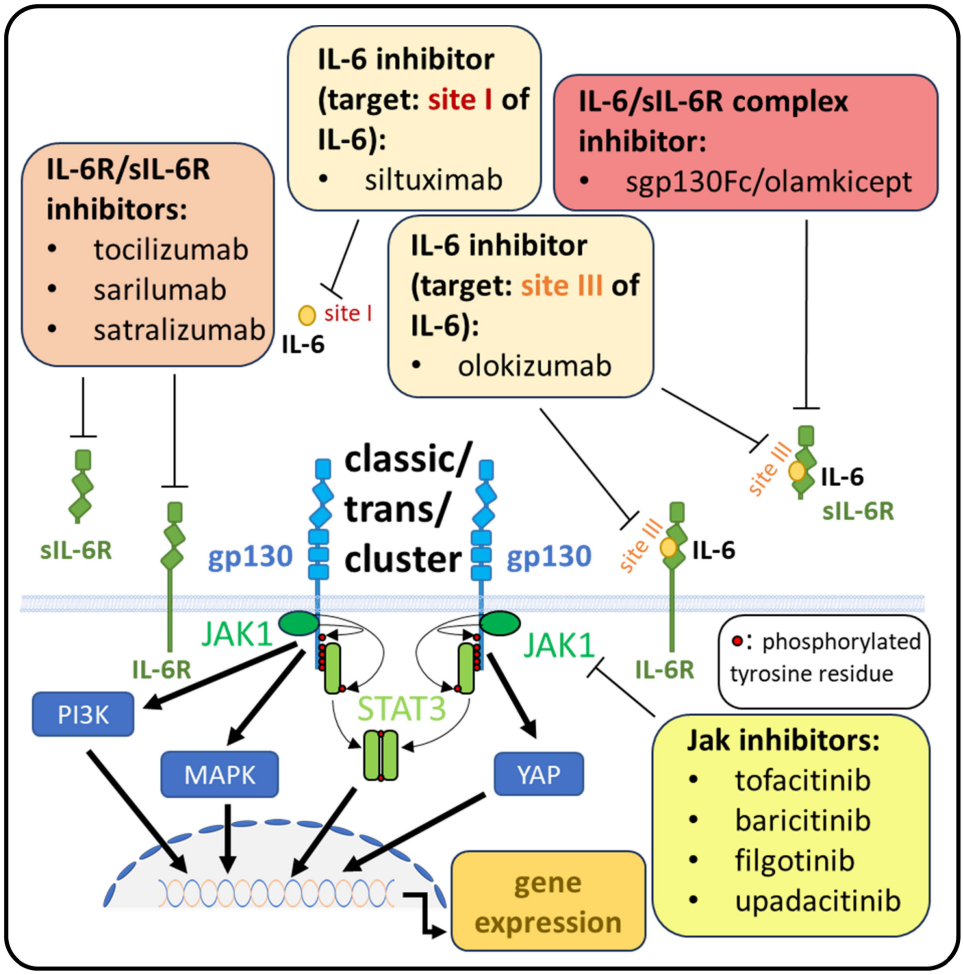

Figure 4 IL-6 inhibitors in clinical use. IL-6 inhibitors that are approved for clinical use include the anti-IL-6 antibodies siltuximab and olokizumab. While the interaction with siltuximab blocks site I in IL-6 and consequently formation of the IL-6/(s)IL-6R complex, olokizumab does not prevent this complex formation. Instead, olokizumab interacts with site III of IL-6, thereby inhibiting binding of the IL-6/(s)IL-6R complex to gp130. Tocilizumab, sarilumab and satralizumab target the IL-6R. All antibodies do not discriminate between classic and trans-signaling. In contrast, the designer protein sgp130Fc/olamkicept is a selective inhibitor of IL-6 trans-signaling. Further approaches target the Janus kinases (JAKs) as part of the intracellular signaling cascade. JAK inhibitors that are already approved include tofacitinib (selective for JAK1- and JAK3), baricitinib (selective for JAK1- and JAK2), filgotinib and upadacitinib (both selective for JAK1).

Besides tocilizumab, two other antibodies targeting the IL-6R are approved and in clinical use (Figure 4). Sarilumab, which binds to the same part of the IL-6R as tocilizumab,[84] has been proven to be effective in treating patients with RA[105–108] and has therefore been approved for clinical use. The newest addition is satralizumab, which showed promising results in phase 3 trials[109,110] and is approved for the treatment of neuromyelitis optica spectrum disorder. Long-term studies have shown that the antibody retains its efficacy over more than 3.5 years of treatment.[111] A recent randomised, double-blind, multicentre, placebo-controlled phase 3 trial of satralizumab in patients with generalised myasthenia gravis showed small improvements in patient-reported and clinician-reported outcomes compared with placebo.[112]

In addition to the three anti-IL-6R antibodies, two anti-IL-6 antibodies have been approved for clinical use (Figure 4). Siltuximab, which binds to site I of IL-6 and thus prevents binding of IL-6 to the IL-6R, is approved for Castleman disease in the United States and the EU.[22] The second antibody is olokizumab, which targets site III of IL-6 and thus allows the initial binding of IL-6 to the IL-6R, but interferes with the formation of the gp130 homodimer. Olokizumab has been evaluated successfully in several phase III clinical trials, eg, versus placebo or the TNFα blocking antibody adalimumab in RA patients,[113] in combination with methotrexate in RA patients which did not respond to anti-TNFα

therapy[114] or methotrexate therapy.[115] Currently, olokizumab is approved for clinical use in Russia, but not in the United States or the EU.

None of the antibodies mentioned above is able to discriminate between the different modes of IL-6 signaling. Therefore, another therapeutic option to target IL-6 extracellularly is the specific inhibition of IL-6 trans-signaling.[24] We describe the mode of action of sgp130Fc/olamkicept and the current status of its clinical evaluation in detail in the following section.

Lastly, it is possible to interfere with the activation of the downstream signaling cascades in order to block IL-6 signaling. While different compounds and approaches have been developed to target the transcription factor STAT3, none of these have reached the clinic. Instead, several small molecules that target the JAK kinases, which phosphorylate gp130 and STAT3, have been developed and are in clinical use since many years (Figure 4). Besides their usage as therapeutics in different forms of blood cancer, JAK inhibitors are also used to treat inflammatory, IL-6-driven diseases like RA and inflammatory bowel disease.

JAK kinases are a family of four different proteins (JAK1, JAK2, JAK3 and TYK2), and JAK1 appears to be the kinase that is predominantly activated by IL-6.[116–118] Due to the structural similarities of the four kinases, the development of selective inhibitors that target a single kinase and do not cross-react with the other three is challenging.[119,120] In order to inhibit IL-6-mediated signaling, an inhibitor selective for JAK1 would be desirable. However, the first inhibitor that was approved by the FDA in 2012 for the treatment of RA patients was tofacitinib, which is selective for JAK1 and JAK3.[121] In 2017, the JAK1- and JAK2-selective inhibitor baricitinib was approved in Europe, also for the treatment of RA patients,[122] and in 2020 for the systemic treatment of atopic dermatitis.[123] Interestingly, two JAK1-selective inhibitors have been approved in recent years after undergoing phase 3 clinical trials.[124] These are filgotinib, which can be used to treat patients with RA or colitis ulcerosa[125,126] and upadacitinib, which is approved for RA, colitis ulcerosa, Morbus Crohn and other inflammatory diseases.[127] It will be interesting to see whether the JAK1-selective inhibitors have a measurable advantage over the other inhibitors. What needs to be considered: IL-6 is by far not the only cytokine that signals via JAK1, and JAK inhibitors are therefore not selective IL-6 inhibitors. Selective inhibition of IL-6 signaling can therefore only be achieved by blocking IL-6 or the IL-6R from outside of the cell. Inhibition of intracellular signaling cascades will always affect other proteins.

Specific Blockade of IL-6 Trans-Signaling

Although the global blockade of IL-6 signaling has proven to be beneficial for patients with different inflammatory diseases (see previous section for details), side effects like increased numbers of bacterial infections occur in treated patients.[89] As the pro-inflammatory activities of IL-6 are mediated via trans-signaling and classic signaling is responsible eg, for the beneficial hepatic acute phase response, the development of sgp130Fc, a compound that binds the IL-6/sIL-6R complex and thus specifically and selectively inhibits IL-6 trans-signaling (Figure 4), holds the promise to be an IL-6 blocker with less side effects (the history of sgp130Fc development is covered in several recent reviews).[24,128,129]

Sgp130Fc, which has been named olamkicept recently, is currently undergoing evaluation in clinical trials for patients with inflammatory bowel disease. Regarding the randomized, placebo-controlled phase I trials, no severe or serious treatment-emergent adverse events were reported.[130] In these trials, different intravenous doses (0.75–750 mg) and one subcutaneous (60 mg) dose were applied once to 64 healthy subjects. Single injections of three of these doses (75 mg, 300 mg, and 750 mg) were further evaluated in 24 patients with Crohn's disease. In order to mimic actual treatment of patients, three different doses (75, 300, and 600 mg) were given once weekly for 4 weeks to 24 healthy subjects. Olamkicept serum levels of 1–5 µg/mL were sufficient to inhibit STAT3 phosphorylation in blood cells, which was used as readout for a successful inhibition of IL-6 trans-signaling.[130] Given the fact that numerous cytokines, growth factors and other signaling molecules are known to activate STAT3 signaling, it is rather surprising that the selective inhibition of IL-6 trans-signaling results in less STAT3 phosphorylation in blood cells.

In addition, olamkicept was further evaluated in two independent phase II clinical trials. The first trial called FUTURE was a 12-week, open-label, prospective phase 2a trial conducted in Germany, which enclosed 16 patients with active inflammatory bowel disease (nine patients with ulcerative colitis and seven patients with Crohn's disease).[131] The study used 600 mg olamkicept every 2 weeks, and the patients received up to seven infusions. The study reported

a clinical response in 44% and clinical remission in 19% of the patients along with a reduction of STAT3 phosphorylation, which resulted in changes on the transcriptional level in the inflamed mucosa of the patients.[131] The second trial was a randomized, double-blind, placebo-controlled phase 2 trial including 91 patients with active ulcerative colitis and conducted at 22 clinical study sites in East Asia.[132] Patients received infusions every second week of either 300 mg olamkicept, 600 mg olamkicept or placebo for 12 weeks in total. Interestingly, only 600 mg olamkicept resulted in a greater likelihood of clinical response at 12 weeks compared with placebo, whereas this was not the case for 300 mg olamkicept. Treatment-related adverse events were not dramatically different in the three groups: (600 mg olamkicept: 53%; 300 mg olamkicept: 58%; placebo: 50%), although the most common adverse events like bilirubin in urine, hyperuricemia and increased aspartate aminotransferase levels occurred more often in the two groups receiving olamkicept.[132]

In addition, there is a recent report on compassionate use of infusion of 600 mg olamkicept every 14 days for ten weeks in a patient with very-high-risk atherosclerotic cardiovascular disease.[133] The treatment reduced arterial wall inflammation, did not interfere with lipoprotein metabolism, and no side effects were observed, suggesting that inhibition of IL-6 trans-signaling might be a suitable therapeutic option also for this disease.[133] IL-6 trans-signaling is crucial for several other inflammatory diseases, which opens other opportunities for treatment with olamkicept, but to our knowledge no trials or compassionate use treatments are currently ongoing.

Although sgp130Fc/olamkicept does selectively bind IL-6/sIL-6R complexes and thus does not directly interfere with IL-6 classic signaling,[44] we could show that sgp130Fc is also a potent and selective inhibitor of IL-11 trans-signaling.[134] Similar to IL-6 trans-signaling, IL-11 can bind to soluble forms of the IL-11R (sIL-11R), and the resulting IL-11/sIL-11R complex can activate cells expressing gp130.[55,134] Interestingly, the interfaces between gp130 and IL-6 or IL-11 differ at the site III contact site. Modification of three amino-acid residues including Q113 of sgp130Fc resulted in an improved inhibitor that blocked IL-6 trans-signaling, but did not interfere with IL-11 trans-signaling anymore.[135,136] There are several approaches to inhibit IL-6 trans-signaling currently in development,[137–139] and it can be expected that future studies will further improve the selectivity and features of sgp130Fc, which can later be used as next-generation inhibitors in the clinic.

Conclusions and Outlook

Several hundred studies over the last 35 years have unraveled in molecular detail the complicated biology of IL-6. This led not only to a profound understanding of the biological actions of this cytokine, but also paved the way to use this knowledge for the clinical benefit of millions of people with inflammatory diseases that are treated with anti-IL-6 therapeutics worldwide. Besides the clinically approved antibodies and small molecules targeting IL-6/(s)IL-6R and the Janus kinases, several novel antibodies and designer proteins are currently in development and will hopefully result in next-generation therapeutics that are as efficient as the current treatment options, but provoke less side effects.

As the pathogenic role of IL-6 in inflammatory diseases, autoimmune diseases and cancer unfolds more and more, one important question remains: What are the physiological roles of IL-6 or is it just involved in disease but not in health? Mice deficient for IL-6 show no gross abnormalities as long as they are not infected, and it was unclear for a long time what IL-6 does in a healthy human. The answer was recently provided by the identification of two human patients with a loss-of-function mutation within *IL6R*, the gene encoding the IL-6R. The patients suffer from recurrent infections and abnormal acute-phase responses, symptoms that align well with data from knock-out mice and adverse effects seen in patients under anti-IL-6(R) therapy.[140] Furthermore, elevated IgE antibodies, eczema, and eosinophilia were reported.[140] In a second study comprising four patients, repeated invasive microbial infections and varying degrees of eczema were reported, mostly matching the symptoms of the first study.[141]

In the future, the development of novel compounds that provide safe IL-6 inhibition without interfering with the above mentioned functions of IL-6 will be of high importance. Olamkicept, which blocks IL-6 trans-signaling while preserving the hepatic acute phase response, is a first step in this direction.[24]

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Disclosure

The authors report no conflicts of interest in this work.

References

1. Tanaka T, Narazaki M, Kishimoto T. IL-6 in inflammation, immunity, and disease. *Cold Spring Harb Perspect Biol*. 2014;6(10):a016295. doi:10.1101/cshperspect.a016295
2. Reif A, Lam K, Weidler S, et al. Natural glycoforms of human interleukin 6 show atypical plasma clearance. *Angew Chem Int Ed Engl*. 2021;60 (24):13380–13387. doi:10.1002/anie.202101496
3. Grötzinger J. Molecular mechanisms of cytokine receptor activation. *Biochim Biophys Acta*. 2002;1592(3):215–223. doi:10.1016/S0167-4889(02)00316-6
4. Kamimura D, Ishihara K, Hirano T. IL-6 signal transduction and its physiological roles: the signal orchestration model. *Rev Physiol Biochem Pharmacol*. 2003;149:1–38. doi:10.1007/s10254-003-0012-2
5. Wolf J, Rose-John S, Garbers C. Interleukin-6 and its receptors: a highly regulated and dynamic system. *Cytokine*. 2014;70(1):11–20. doi:10.1016/j.cyto.2014.05.024
6. Hunter CA, Jones SA. IL-6 as a keystone cytokine in health and disease. *Nat Immunol*. 2015;16(5):448–457. doi:10.1038/ni.3153
7. Maes M, Song C, Lin A, et al. The effects of psychological stress on humans: increased production of pro-inflammatory cytokines and a Th1-like response in stress-induced anxiety. *Cytokine*. 1998;10(4):313–318. doi:10.1006/cyto.1997.0290
8. Kurt-Jones EA, Popova L, Kwinn L, et al. Pattern recognition receptors TLR4 and CD14 mediate response to respiratory syncytial virus. *Nat Immunol*. 2000;1(5):398–401. doi:10.1038/80833
9. Flynn CM, Garbers Y, Lokau J, et al. Activation of Toll-like Receptor 2 (TLR2) induces Interleukin-6 trans-signaling. *Sci Rep*. 2019;9(1):7306. doi:10.1038/s41598-019-43617-5
10. Andus T, Geiger T, Hirano T, et al. Regulation of synthesis and secretion of major rat acute-phase proteins by recombinant human interleukin-6 (BSF-2/IL-6) in hepatocyte primary cultures. *Eur J Biochem*. 1988;173(2):287–293. doi:10.1111/j.1432-1033.1988.tb13997.x
11. Depraetere S, Willems J, Joniau M. Stimulation of CRP secretion in HepG2 cells: cooperative effect of dexamethasone and interleukin 6. *Agents Actions*. 1991;34(3–4):369–375. doi:10.1007/BF01988730
12. Kishimoto T, Hirano T. Molecular regulation of B lymphocyte response. *Annu Rev Immunol*. 1988;6:485–512. doi:10.1146/annurev.iy.06.040188.002413
13. Uyttenhove C, Coulie PG, Van Snick J. T cell growth and differentiation induced by interleukin-HP1/IL-6, the murine hybridoma/plasmacytoma growth factor. *J Exp Med*. 1988;167(4):1417–1427. doi:10.1084/jem.167.4.1417
14. Mauer J, Denson JL, Brüning JC. Versatile functions for IL-6 in metabolism and cancer. *Trends Immunol*. 2015;36(2):92–101. doi:10.1016/j.it.2014.12.008
15. Giraldez MD, Carneros D, Garbers C, et al. New insights into IL-6 family cytokines in metabolism, hepatology and gastroenterology. *Nat Rev Gastroenterol Hepatol*. 2021;18(11):787–803. doi:10.1038/s41575-021-00473-x
16. Poli V, Balena R, Fattori E, et al. Interleukin-6 deficient mice are protected from bone loss caused by estrogen depletion. *EMBO J*. 1994;13 (5):1189. doi:10.1002/j.1460-2075.1994.tb06368.x
17. März P, Herget T, Lang E, et al. Activation of gp130 by IL-6/soluble IL-6 receptor induces neuronal differentiation. *Eur J Neurosci*. 1997;9 (12):2765–2773. doi:10.1111/j.1460-9568.1997.tb01705.x
18. Cressman DE, Greenbaum LE, DeAngelis RA, et al. Liver failure and defective hepatocyte regeneration in interleukin-6-deficient mice. *Science*. 1996;274(5291):1379–1383. doi:10.1126/science.274.5291.1379
19. Kuhn KA, Manieri NA, Liu T-C, et al. IL-6 stimulates intestinal epithelial proliferation and repair after injury. *PLoS One*. 2014;9(12):e114195. doi:10.1371/journal.pone.0114195
20. Rose-John S. Local and systemic effects of interleukin-6 (IL-6) in inflammation and cancer. *FEBS Lett*. 2022;596(5):557–566. doi:10.1002/1873-3468.14220
21. Runge J, Garbers C, Lokau J. The role of interleukin-6 classic and trans-signaling and interleukin-11 classic signaling in gastric cancer cells. *Contemp Oncol*. 2024;28(2):105–113. doi:10.5114/wo.2024.142211
22. Garbers C, Heink S, Korn T, et al. Interleukin-6: designing specific therapeutics for a complex cytokine. *Nat Rev Drug Discov*. 2018;17 (6):395–412. doi:10.1038/nrd.2018.45
23. Narazaki M, Kishimoto T. Current status and prospects of IL-6-targeting therapy. *Expert Rev Clin Pharmacol*. 2022;15(5):575–592. doi:10.1080/17512433.2022.2097905
24. Rose-John S, Jenkins BJ, Garbers C, et al. Targeting IL-6 trans-signalling: past, present and future prospects. *Nat Rev Immunol*. 2023;23 (10):666–681. doi:10.1038/s41577-023-00856-y
25. Taga T, Hibi M, Hirata Y, et al. Interleukin-6 triggers the association of its receptor with a possible signal transducer, gp130. *Cell*. 1989;58 (3):573–581. doi:10.1016/0092-8674(89)90438-8
26. Rose-John S, Heinrich PC. Soluble receptors for cytokines and growth factors: generation and biological function. *Biochem J*. 1994;300(Pt 2):281–290. doi:10.1042/bj3000281
27. Heink S, Yogev N, Garbers C, et al. Trans-presentation of IL-6 by dendritic cells is required for the priming of pathogenic TH17 cells. *Nat Immunol*. 2017;18(1):74–85. doi:10.1038/ni.3632

28. Lamertz L, Rummel F, Polz R, et al. Soluble gp130 prevents interleukin-6 and interleukin-11 cluster signaling but not intracellular autocrine responses. *Sci Signal*. 2018;11(550). doi:10.1126/scisignal.aar7388
29. Jostock T, Müllberg J, Özbek S, et al. Soluble gp130 is the natural inhibitor of soluble IL-6R transsignaling responses. *Eur J Biochem*. 2001;268 (1):160–167. doi:10.1046/j.1432-1327.2001.01867.x
30. Hibi M, Murakami M, Saito M, et al. Molecular cloning and expression of an IL-6 signal transducer, gp130. *Cell*. 1990;63(6):1149–1157. doi:10.1016/0092-8674(90)90411-7
31. Schaper F, Rose-John S. Interleukin-6: biology, signaling and strategies of blockade. *Cytokine Growth Factor Rev*. 2015;26(5):475–487. doi:10.1016/j.cytogfr.2015.07.004
32. Heinrich PC, Behrmann I, Haan S, et al. Principles of interleukin (IL)-6-type cytokine signalling and its regulation. *Biochem J*. 2003;374(Pt 1):1–20. doi:10.1042/bj20030407
33. Schumacher N, Meyer D, Mauermann A, et al. Shedding of endogenous interleukin-6 receptor (IL-6R) is governed by A Disintegrin and Metalloproteinase (ADAM) proteases while a full-length IL-6R isoform localizes to circulating microvesicles. *J Biol Chem*. 2015;290 (43):26059–26071. doi:10.1074/jbc.M115.649509
34. Luig M, Kluger MA, Goerke B, et al. Inflammation-induced IL-6 functions as a natural brake on macrophages and limits GN. *J Am Soc Nephrol*. 2015;26(7):1597–1607. doi:10.1681/ASN.2014060620
35. Bauer J, Bauer TM, Kalb T, et al. Regulation of interleukin 6 receptor expression in human monocytes and monocyte-derived macrophages. comparison with the expression in human hepatocytes. *J Exp Med*. 1989;170(5):1537–1549. doi:10.1084/jem.170.5.1537
36. Zola H, Flego L. Expression of interleukin-6 receptor on blood lymphocytes without in vitro activation. *Immunology*. 1992;76(2):338–340.
37. Kopf M, Baumann H, Freer G, et al. Impaired immune and acute-phase responses in interleukin-6-deficient mice. *Nature*. 1994;368 (6469):339–342. doi:10.1038/368339a0
38. Wilkinson AN, Gartlan KH, Kelly G, et al. Granulocytes are unresponsive to IL-6 due to an absence of gp130. *J Immunol*. 2018;200 (10):3547–3555. doi:10.4049/jimmunol.1701191
39. Lust J, Donovan KA, Kline MP, et al. Isolation of an mRNA encoding a soluble form of the human interleukin-6 receptor. *Cytokine*. 1992;4 (2):96–100. doi:10.1016/1043-4666(92)90043-Q
40. Müllberg J, Schooltink H, Stoyan T, et al. The soluble interleukin-6 receptor is generated by shedding. *Eur J Immunol*. 1993;23(2):473–480. doi:10.1002/eji.1830230226
41. Garbers C, Jänner N, Chalaris A, et al. Species specificity of ADAM10 and ADAM17 proteins in interleukin-6 (IL-6) trans-signaling and novel role of ADAM10 in inducible IL-6 receptor shedding. *J Biol Chem*. 2011;286(17):14804–14811. doi:10.1074/jbc.M111.229393
42. Schumertl T, Lokau J, Rose-John S, et al. Function and proteolytic generation of the soluble interleukin-6 receptor in health and disease. *Biochim Biophys Acta Mol Cell Res*. 2022;1869(1):119143. doi:10.1016/j.bbamcr.2021.119143
43. Drucker C, Gewiese J, Malchow S, et al. Impact of interleukin-6 classic- and trans-signaling on liver damage and regeneration. *J Autoimmun*. 2010;34(1):29–37. doi:10.1016/j.jaut.2009.08.003
44. Garbers C, Thaiss W, Jones GW, et al. Inhibition of classic signaling is a novel function of soluble glycoprotein 130 (sgp130), which is controlled by the ratio of interleukin 6 and soluble interleukin 6 receptor. *J Biol Chem*. 2011;286(50):42959–42970. doi:10.1074/jbc.M111.295758
45. Reeh H, Rudolph N, Billing U, et al. Response to IL-6 trans- and IL-6 classic signalling is determined by the ratio of the IL-6 receptor alpha to gp130 expression: fusing experimental insights and dynamic modelling. *Cell Commun Signal*. 2019;17(1):46. doi:10.1186/s12964-019-0356-0
46. Peters M, Müller A, Rose-John S. Interleukin-6 and soluble interleukin-6 receptor: direct stimulation of gp130 and hematopoiesis. *Blood*. 1998;92(10):3495–3504. doi:10.1182/blood.V92.10.3495
47. McGregor NE, Murat M, Elango J, et al. IL-6 exhibits both cis- and trans-signaling in osteocytes and osteoblasts, but only trans-signaling promotes bone formation and osteoclastogenesis. *J Biol Chem*. 2019;294(19):7850–7863. doi:10.1074/jbc.RA119.008074
48. Garbers C, Spudy B, Aparicio-Siegmund S, et al. An interleukin-6 receptor-dependent molecular switch mediates signal transduction of the IL-27 cytokine subunit p28 (IL-30) via a gp130 protein receptor homodimer. *J Biol Chem*. 2013;288(6):4346–4354. doi:10.1074/jbc.M112.432955
49. Garbers C, Hermanns HM, Schaper F, et al. Plasticity and cross-talk of interleukin 6-type cytokines. *Cytokine Growth Factor Rev*. 2012;23 (3):85–97. doi:10.1016/j.cytogfr.2012.04.001
50. Lokau J, Garbers C. Biological functions and therapeutic opportunities of soluble cytokine receptors. *Cytokine Growth Factor Rev*. 2020;55:94–108. doi:10.1016/j.cytogfr.2020.04.003
51. Riethmueller S, Somasundaram P, Ehlers JC, et al. Proteolytic origin of the soluble human IL-6R In vivo and a decisive role of N-glycosylation. *PLoS Biol*. 2017;15(1):e2000080. doi:10.1371/journal.pbio.2000080
52. Riethmueller S, Ehlers JC, Lokau J, et al. Cleavage site localization differentially controls interleukin-6 receptor proteolysis by ADAM10 and ADAM17. *Sci Rep*. 2016;6(1):25550. doi:10.1038/srep25550
53. Baran P, Nitz R, Grötzinger J, et al. Minimal interleukin (IL-)6 receptor stalk composition for IL-6R shedding and IL-6 classic signaling. *J Biol Chem*. 2013;288(21):14756–14768. doi:10.1074/jbc.M113.466169
54. Garbers C, Monhasery N, Aparicio-Siegmund S, et al. The interleukin-6 receptor Asp358Ala single nucleotide polymorphism rs2228145 confers increased proteolytic conversion rates by ADAM proteases. *Biochim Biophys Acta*. 2014;1842(9):1485–1494. doi:10.1016/j.bbadis.2014.05.018
55. Koch L, Kespohl B, Agthe M, et al. Interleukin-11 (IL-11) receptor cleavage by the rhomboid protease RHBDL2 induces IL-11 trans-signaling. *FASEB J*. 2021;35(3):e21380. doi:10.1096/fj.202002087R
56. Johnson N, Březinová J, Stephens E, et al. Quantitative proteomics screen identifies a substrate repertoire of rhomboid protease RHBDL2 in human cells and implicates it in epithelial homeostasis. *Sci Rep*. 2017;7(1):7283. doi:10.1038/s41598-017-07556-3
57. Sammel M, Peters F, Lokau J, et al. Differences in shedding of the interleukin-11 receptor by the proteases ADAM9, ADAM10, ADAM17, meprin alpha, meprin beta and MT1-MMP. *Int J Mol Sci*. 2019;20(15):3677. doi:10.3390/ijms20153677
58. Flynn CM, Garbers Y, Düsterhöft S, et al. Cathepsin S provokes interleukin-6 (IL-6) trans-signaling through cleavage of the IL-6 receptor in vitro. *Sci Rep*. 2020;10(1):21612. doi:10.1038/s41598-020-77884-4
59. Arnold P, Lückstädt W, Li W, et al. Joint reconstituted signaling of the IL-6 receptor via extracellular vesicles. *Cells*. 2020;9(5):1307. doi:10.3390/cells9051307

60. Lee JH, Schierer S, Blume K, et al. HIV-Nef and ADAM17-containing plasma extracellular vesicles induce and correlate with immune pathogenesis in chronic HIV infection. *EBioMedicine*. 2016;6:103–113. doi:10.1016/j.ebiom.2016.03.004
61. Groth E, Pruessmeyer J, Babendreyer A, et al. Stimulated release and functional activity of surface expressed metalloproteinase ADAM17 in exosomes. *Biochim Biophys Acta*. 2016;1863(11):2795–2808. doi:10.1016/j.bbamcr.2016.09.002
62. Hugendieck G, Lettau M, Andreas S, et al. Chemotherapy-induced release of ADAM17 bearing EV as a potential resistance mechanism in ovarian cancer. *J Extracell Vesicles*. 2023;12(7):e12338. doi:10.1002/jev2.12338
63. Richards PJ, Nowell MA, Horiuchi S, et al. Functional characterization of a soluble gp130 isoform and its therapeutic capacity in an experimental model of inflammatory arthritis. *Arthritis Rheum*. 2006;54(5):1662–1672. doi:10.1002/art.21818
64. Tanaka M, Kishimura M, Ozaki S, et al. Cloning of novel soluble gp130 and detection of its neutralizing autoantibodies in rheumatoid arthritis. *J Clin Invest*. 2000;106(1):137–144. doi:10.1172/JCI7479
65. Sommer J, Garbers C, Wolf J, et al. Alternative intronic polyadenylation generates the interleukin-6 trans-signaling inhibitor sgp130-E10. *J Biol Chem*. 2014;289(32):22140–22150. doi:10.1074/jbc.M114.560938
66. Wolf J, Waetzig GH, Reinheimer TM, et al. A soluble form of the interleukin-6 family signal transducer gp130 is dimerized via a C-terminal disulfide-bridge resulting from alternative mRNA splicing. *Biochem Biophys Res Commun*. 2016;470(4):870–876. doi:10.1016/j.bbrc.2016.01.127
67. Wolf J, Waetzig GH, Chalaris A, et al. Different soluble forms of the interleukin-6 family signal transducer gp130 fine-tune the blockade of interleukin-6 trans-signaling. *J Biol Chem*. 2016;291(31):16186–16196. doi:10.1074/jbc.M116.718551
68. Muller SA, Shmueli MD, Feng X, et al. The Alzheimer's disease-linked protease BACE1 modulates neuronal IL-6 signaling through shedding of the receptor gp130. *Mol Neurodegener*. 2023;18(1):13. doi:10.1186/s13024-023-00596-6
69. Aparicio-Siegmund S, Garbers Y, Flynn CM, et al. The IL-6-neutralizing sIL-6R-sgp130 buffer system is disturbed in patients with type 2 diabetes. *Am J Physiol Endocrinol Metab*. 2019;317(2):E411–E420. doi:10.1152/ajpendo.00166.2019
70. Waage A, Brandtzaeg P, Halstensen A, et al. The complex pattern of cytokines in serum from patients with meningococcal septic shock. Association between interleukin 6, interleukin 1, and fatal outcome. *J Exp Med*. 1989;169(1):333–338. doi:10.1084/jem.169.1.333
71. Sarwar N. Interleukin-6 receptor pathways in coronary heart disease: a collaborative meta-analysis of 82 studies. *Lancet*. 2012;379 (9822):1205–1213.
72. Swerdlow D. The interleukin-6 receptor as a target for prevention of coronary heart disease: a mendelian randomisation analysis. *Lancet*. 2012;379(9822):1214–1224.
73. Rafiq S, Frayling TM, Murray A, et al. A common variant of the interleukin 6 receptor (IL-6r) gene increases IL-6r and IL-6 levels, without other inflammatory effects. *Genes Immun*. 2007;8(7):552–559. doi:10.1038/sj.gene.6364414
74. Ferreira R, Freitag DF, Cutler AJ, et al. Functional IL6R 358Ala allele impairs classical IL-6 receptor signaling and influences risk of diverse inflammatory diseases. *PLoS Genet*. 2013;9(4):e1003444. doi:10.1371/journal.pgen.1003444
75. Scheller J, Rose-John S. The interleukin 6 pathway and atherosclerosis. *Lancet*. 2012;380(9839):338. doi:10.1016/S0140-6736(12)61246-X
76. Garbers C, Aparicio-Siegmund S, Rose-John S. The IL-6/gp130/STAT3 signaling axis: recent advances towards specific inhibition. *Curr Opin Immunol*. 2015;34:75–82. doi:10.1016/j.coi.2015.02.008
77. Skiniotis G, Boulanger MJ, Garcia KC, et al. Signaling conformations of the tall cytokine receptor gp130 when in complex with IL-6 and IL-6 receptor. *Nat Struct Mol Biol*. 2005;12(6):545–551. doi:10.1038/nsmb941
78. Boulanger MJ, Chow D-C, Brevnova EE, et al. Hexameric structure and assembly of the interleukin-6/IL-6 alpha-receptor/gp130 complex. *Science*. 2003;300(5628):2101–2104. doi:10.1126/science.1083901
79. Yoshida K, Taga T, Saito M. Targeted disruption of gp130, a common signal transducer for the interleukin 6 family of cytokines, leads to myocardial and hematological disorders. *Proc Natl Acad Sci U S A*. 1996;93(1):407–411. doi:10.1073/pnas.93.1.407
80. Chen YH, Grigelioniene G, Newton PT, et al. Absence of GP130 cytokine receptor signaling causes extended Stuve-Wiedemann syndrome. *J Exp Med*. 2020;217(3). doi:10.1084/jem.20191306
81. Gu ZJ, Wijdenes J, Zhang X-G, et al. Anti-gp130 transducer monoclonal antibodies specifically inhibiting ciliary neurotrophic factor, interleukin-6, interleukin-11, leukemia inhibitory factor or oncostatin M. *J Immunol Methods*. 1996;190(1):21–27. doi:10.1016/0022-1759(95)00232-4
82. Wijdenes J, Heinrich PC, Müller-Newen G, et al. Interleukin-6 signal transducer gp130 has specific binding sites for different cytokines as determined by antagonistic and agonistic anti-gp130 monoclonal antibodies. *Eur J Immunol*. 1995;25(12):3474–3481. doi:10.1002/eji.1830251240
83. Chevalier S, Clement C, Robledo O, et al. Monoclonal antibodies define different functional epitopes on gp130 signal transducer. *Ann N Y Acad Sci*. 1995;762(1):482–484. doi:10.1111/j.1749-6632.1995.tb32375.x
84. Wang M, Chen L, He J, et al. Structural insights into IL-6 signaling inhibition by therapeutic antibodies. *Cell Rep*. 2024;43(3):113819. doi:10.1016/j.celrep.2024.113819
85. Nishimoto N, Kanakura Y, Aozasa K, et al. Humanized anti-interleukin-6 receptor antibody treatment of multicentric Castleman disease. *Blood*. 2005;106(8):2627–2632. doi:10.1182/blood-2004-12-4602
86. Nishimoto N, Kishimoto T, Yoshizaki K. Anti-interleukin 6 receptor antibody treatment in rheumatic disease. *Ann Rheum Dis*. 2000;59(Suppl 1):p.i21–7. doi:10.1136/ard.59.suppl_1.i21
87. Kishimoto T, Kang S. IL-6 revisited: from rheumatoid arthritis to CAR T cell therapy and COVID-19. *Annu Rev Immunol*. 2022;40:323–348. doi:10.1146/annurev-immunol-101220-023458
88. Campbell L, Chen C, Bhagat SS, et al. Risk of adverse events including serious infections in rheumatoid arthritis patients treated with tocilizumab: a systematic literature review and meta-analysis of randomized controlled trials. *Rheumatology*. 2011;50(3):552–562. doi:10.1093/rheumatology/keq343
89. Lang VR, Englbrecht M, Rech J, et al. Risk of infections in rheumatoid arthritis patients treated with tocilizumab. *Rheumatology*. 2012;51 (5):852–857. doi:10.1093/rheumatology/ker223
90. Del Valle DM, Kim-Schulze S, Huang -H-H, et al. An inflammatory cytokine signature predicts COVID-19 severity and survival. *Nat Med*. 2020;26(10):1636–1643. doi:10.1038/s41591-020-1051-9
91. Coomes EA, Haghbayan H. Interleukin-6 in Covid-19: a systematic review and meta-analysis. *Rev Med Virol*. 2020;30(6):1–9. doi:10.1002/rmv.2141
92. Chilimuri S, Sun H, Alemam A, et al. Tocilizumab use in patients with moderate to severe COVID-19: a retrospective cohort study. *J Clin Pharm Ther*. 2021;46(2):440–446. doi:10.1111/jcpt.13303

93. Eimer J, Vesterbacka J, Svensson A-K, et al. Tocilizumab shortens time on mechanical ventilation and length of hospital stay in patients with severe COVID-19: a retrospective cohort study. *J Intern Med*. 2021;289(3):434–436. doi:10.1111/joim.13162
94. Group RC. Tocilizumab in patients admitted to hospital with COVID-19 (RECOVERY): a randomised, controlled, open-label, platform trial. *Lancet*. 2021;397(10285):1637–1645.
95. Xu X, Han M, Li T, et al. Effective treatment of severe COVID-19 patients with tocilizumab. *Proc Natl Acad Sci U S A*. 2020;117 (20):10970–10975. doi:10.1073/pnas.2005615117
96. Guaraldi G, Meschiari M, Cozzi-Lepri A, et al. Tocilizumab in patients with severe COVID-19: a retrospective cohort study. *Lancet Rheumatol*. 2020;2(8):e474–e484. doi:10.1016/S2665-9913(20)30173-9
97. Kewan T, Covut F, Al–Jaghbeer MJ, et al. Tocilizumab for treatment of patients with severe COVID-19: a retrospective cohort study. *EClinicalMedicine*. 2020;24:100418. doi:10.1016/j.eclinm.2020.100418
98. Campochiaro C, Della-Torre E, Cavalli G, et al. Efficacy and safety of tocilizumab in severe COVID-19 patients: a single-centre retrospective cohort study. *Eur J Intern Med*. 2020;76:43–49. doi:10.1016/j.ejim.2020.05.021
99. Rosas IO, Bräu N, Waters M, et al. Tocilizumab in hospitalized patients with severe covid-19 pneumonia. *N Engl J Med*. 2021;384 (16):1503–1516. doi:10.1056/NEJMoa2028700
100. Rodriguez-Hernandez MA, Carneros D, Núñez-Núñez M, et al. Identification of IL-6 signalling components as predictors of severity and outcome in COVID-19. *Front Immunol*. 2022;13:891456. doi:10.3389/fimmu.2022.891456
101. Lokau J, Garbers Y, Vicente MM, et al. Long-term increase in soluble interleukin-6 receptor levels in convalescents after mild COVID-19 infection. *Front Immunol*. 2024;15:1488745. doi:10.3389/fimmu.2024.1488745
102. Brudno JN, Kochenderfer JN. Current understanding and management of CAR T cell-associated toxicities. *Nat Rev Clin Oncol*. 2024;21 (7):501–521. doi:10.1038/s41571-024-00903-0
103. Grupp SA, Kalos M, Barrett D, et al. Chimeric antigen receptor-modified T cells for acute lymphoid leukemia. *N Engl J Med*. 2013;368 (16):1509–1518. doi:10.1056/NEJMoa1215134
104. Teachey DT, Lacey SF, Shaw PA, et al. Identification of predictive biomarkers for cytokine release syndrome after chimeric antigen receptor T cell therapy for acute lymphoblastic leukemia. *Cancer Discovery*. 2016;6:664–679. doi:10.1158/2159-8290.CD-16-0040
105. Boyce EG, Rogan EL, Vyas D, et al. Sarilumab: review of a second IL-6 receptor antagonist indicated for the treatment of rheumatoid arthritis. *Ann Pharmacother*. 2018;52(8):780–791. doi:10.1177/1060028018761599
106. Huizinga T, Choy E, Praestgaard A, et al. Clinical efficacy of sarilumab versus upadacitinib over 12 weeks: an indirect treatment comparison. *Rheumatol Ther*. 2023;10(3):539–550. doi:10.1007/s40744-022-00521-1
107. Strand V, Kosinski M, Chen C-I, et al. Sarilumab plus methotrexate improves patient-reported outcomes in patients with active rheumatoid arthritis and inadequate responses to methotrexate: results of a phase III trial. *Arthritis Res Ther*. 2016;18(1):198. doi:10.1186/s13075-016-1096-9
108. Huizinga TW, Fleischmann RM, Jasson M, et al. Sarilumab, a fully human monoclonal antibody against IL-6Ralpha in patients with rheumatoid arthritis and an inadequate response to methotrexate: efficacy and safety results from the randomised SARIL-RA-MOBILITY Part A trial. *Ann Rheum Dis*. 2014;73(9):1626–1634. doi:10.1136/annrheumdis-2013-204405
109. Yamamura T, Kleiter I, Fujihara K, et al. Trial of satralizumab in neuromyelitis optica spectrum disorder. *N Engl J Med*. 2019;381 (22):2114–2124. doi:10.1056/NEJMoa1901747
110. Traboulsee A, Greenberg BM, Bennett JL, et al. Safety and efficacy of satralizumab monotherapy in neuromyelitis optica spectrum disorder: a randomised, double-blind, multicentre, placebo-controlled phase 3 trial. *Lancet Neurol*. 2020;19(5):402–412. doi:10.1016/S1474-4422(20) 30078-8
111. Kleiter I, Traboulsee A, Palace J, et al. Long-term efficacy of satralizumab in AQP4-IgG-seropositive neuromyelitis optica spectrum disorder from SAkuraSky and SAkuraStar. *Neurol Neuroimmunol Neuroinflamm*. 2023;10(1). doi:10.1212/NXI.0000000000200071
112. Habib AA, Zhao C, Aban I, et al. Safety and efficacy of satralizumab in patients with generalised myasthenia gravis (LUMINESCE): a randomised, double-blind, multicentre, placebo-controlled phase 3 trial. *Lancet Neurol*. 2025;24(2):117–127. doi:10.1016/S1474-4422(24) 00514-3
113. Smolen JS, Feist E, Fatenejad S, et al. Olokizumab versus placebo or adalimumab in rheumatoid arthritis. *N Engl J Med*. 2022;387(8):715–726. doi:10.1056/NEJMoa2201302
114. Feist E, Fatenejad S, Grishin S, et al. Olokizumab, a monoclonal antibody against interleukin-6, in combination with methotrexate in patients with rheumatoid arthritis inadequately controlled by tumour necrosis factor inhibitor therapy: efficacy and safety results of a randomised controlled phase III study. *Ann Rheum Dis*. 2022;81(12):1661–1668. doi:10.1136/ard-2022-222630
115. Nasonov E, Fatenejad S, Feist E, et al. Olokizumab, a monoclonal antibody against interleukin 6, in combination with methotrexate in patients with rheumatoid arthritis inadequately controlled by methotrexate: efficacy and safety results of a randomised controlled phase III study. *Ann Rheum Dis*. 2022;81(4):469–479. doi:10.1136/annrheumdis-2021-219876
116. Rodig SJ, Meraz MA, White JM, et al. Disruption of the Jak1 gene demonstrates obligatory and nonredundant roles of the jaks in cytokine-induced biologic responses. *Cell*. 1998;93(3):373–383. doi:10.1016/S0092-8674(00)81166-6
117. Guschin D, Rogers N, Briscoe J, et al. A major role for the protein tyrosine kinase JAK1 in the JAK/STAT signal transduction pathway in response to interleukin-6. *EMBO J*. 1995;14(7):1421–1429. doi:10.1002/j.1460-2075.1995.tb07128.x
118. Aparicio-Siegmund S, Sommer J, Monhasery N, et al. Inhibition of protein kinase II (CK2) prevents induced signal transducer and activator of transcription (STAT) 1/3 and constitutive STAT3 activation. *Oncotarget*. 2014;5(8):2131–2148. doi:10.18632/oncotarget.1852
119. Wu P, Nielsen TE, Clausen MH. FDA-approved small-molecule kinase inhibitors. *Trends Pharmacol Sci*. 2015;36(7):422–439. doi:10.1016/j.tips.2015.04.005
120. Chrencik JE, Patny A, Leung IK, et al. Structural and thermodynamic characterization of the TYK2 and JAK3 kinase domains in complex with CP-690550 and CMP-6. *J Mol Biol*. 2010;400(3):413–433. doi:10.1016/j.jmb.2010.05.020
121. Winthrop KL. The emerging safety profile of JAK inhibitors in rheumatic disease. *Nat Rev Rheumatol*. 2017;13(5):320. doi:10.1038/nrrheum.2017.51
122. Dougados M, van der Heijde D, Chen Y-C, et al. Baricitinib in patients with inadequate response or intolerance to conventional synthetic DMARDs: results from the RA-BUILD study. *Ann Rheum Dis*. 2017;76(1):88–95. doi:10.1136/annrheumdis-2016-210094

123. Reich K, Kabashima K, Peris K, et al. Efficacy and safety of baricitinib combined with topical corticosteroids for treatment of moderate to severe atopic dermatitis: a randomized clinical trial. *JAMA Dermatol*. 2020;156(12):1333–1343. doi:10.1001/jamadermatol.2020.3260
124. Mysler E, Lizarraga A. Phase III trials of JAK1 selective inhibitors in rheumatoid arthritis. *Rheumatology*. 2021;60(Suppl 2):ii17–ii23. doi:10.1093/rheumatology/keaa823
125. Tanaka Y, Matsubara T, Atsumi T, et al. Efficacy and safety of filgotinib in combination with methotrexate in Japanese patients with active rheumatoid arthritis who have an inadequate response to methotrexate: subpopulation analyses of 24-week data of a global phase 3 study (FINCH 1). *Mod Rheumatol*. 2022;32(2):263–272. doi:10.1093/mr/roab030
126. Mannucci A, D'Amico F, El Saadi A, et al. Filgotinib for moderately to severely active ulcerative colitis. *Expert Rev Gastroenterol Hepatol*. 2022;16(10):927–940. doi:10.1080/17474124.2022.2138857
127. Damianos JA, Osikoya O, Brennan G. Upadacitinib for acute severe ulcerative colitis: a systematic review. *Inflamm Bowel Dis*. 2024;2024:1.
128. Rose-John S. Therapeutic targeting of IL-6 trans-signaling. *Cytokine*. 2021;144:155577. doi:10.1016/j.cyto.2021.155577
129. Rose-John S. Blocking only the bad side of IL-6 in inflammation and cancer. *Cytokine*. 2021;148:155690. doi:10.1016/j.cyto.2021.155690
130. Wagner FD, Schreiber S, Bagger Y, et al. Safety, tolerability, and pharmacokinetics of single- and multiple-ascending doses of olamkicept: results from randomized, placebo-controlled, first-in-human phase I trials. *Clin Transl Sci*. 2024;17(5):e13832. doi:10.1111/cts.13832
131. Schreiber S, Aden K, Bernardes JP, et al. Therapeutic IL-6 trans-signalling inhibition by olamkicept (sgp130Fc) in patients with active inflammatory bowel disease. *Gastroenterology*. 2021;160(7):2354–2366.e11. doi:10.1053/j.gastro.2021.02.062
132. Zhang S, Chen B, Wang B, et al. Effect of induction therapy with olamkicept vs placebo on clinical response in patients with active ulcerative colitis: a randomized clinical trial. *JAMA*. 2023;329(9):725–734. doi:10.1001/jama.2023.1084
133. Schulte DM, Waetzig GH, Schuett H, et al. Case report: arterial wall inflammation in atherosclerotic cardiovascular disease is reduced by olamkicept (sgp130Fc). *Front Pharmacol*. 2022;13:758233. doi:10.3389/fphar.2022.758233
134. Lokau J, Nitz R, Agthe M, et al. Proteolytic cleavage governs interleukin-11 trans-signaling. *Cell Rep*. 2016;14(7):1761–1773. doi:10.1016/j.celrep.2016.01.053
135. Lokau J, Garbers Y, Grötzinger J, et al. A single aromatic residue in sgp130Fc/olamkicept allows the discrimination between interleukin-6 and interleukin-11 trans-signaling. *iScience*. 2021;24(11):103309. doi:10.1016/j.isci.2021.103309
136. Heise D, Derrac Soria A, Hansen S, et al. Selective inhibition of IL-6 trans-signaling by a miniaturized, optimized chimeric soluble gp130 inhibits T H 17 cell expansion. *Sci Signal*. 2021;14(696):p.eabc3480. doi:10.1126/scisignal.abc3480
137. Berg AF, Ettich J, Weitz HT, et al. Exclusive inhibition of IL-6 trans-signaling by soluble gp130(FlyR)Fc. *Cytokine X*. 2021;3(4):100058. doi:10.1016/j.cytox.2021.100058
138. Ettich J, Werner J, Weitz HT, et al. A hybrid soluble gp130/spike-nanobody fusion protein simultaneously blocks interleukin-6 trans -signaling and cellular infection with SARS-CoV-2. *J Virol*. 2022;96(4):e0162221. doi:10.1128/jvi.01622-21
139. Gesiorowski A, Ettich J, Werner J, et al. Bispecific soluble cytokine receptor-nanobody fusions inhibit interleukin (IL-)6 trans-signaling and IL-12/23 or tumor necrosis factor (TNF) signaling. *J Biol Chem*. 2023;299(11):105343. doi:10.1016/j.jbc.2023.105343
140. Spencer S, Köstel Bal S, Egner W, et al. Loss of the interleukin-6 receptor causes immunodeficiency, atopy, and abnormal inflammatory responses. *J Exp Med*. 2019;216(9):1986–1998. doi:10.1084/jem.20190344
141. Nahum A, Sharfe N, Broides A, et al. Defining the biological responses of IL-6 by the study of a novel IL-6 receptor chain immunodeficiency. *J Allergy Clin Immunol*. 2020;145(3):1011–1015e6. doi:10.1016/j.jaci.2019.11.015