

Targeting IL-6 trans-signalling: past, present and future prospects

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Abstract

Interleukin-6 (IL-6) is a key immunomodulatory cytokine that affects the pathogenesis of diverse diseases, including autoimmune diseases, chronic inflammatory conditions and cancer. Classical IL-6 signalling involves the binding of IL-6 to the membrane-bound IL-6 receptor α -subunit (hereafter termed ‘mIL-6R’) and glycoprotein 130 (gp130) signal-transducing subunit. By contrast, in IL-6 trans-signalling, complexes of IL-6 and the soluble form of IL-6 receptor (sIL-6R) signal via membrane-bound gp130. A third mode of IL-6 signalling – known as cluster signalling – involves preformed complexes of membrane-bound IL-6–mIL-6R on one cell activating gp130 subunits on target cells. Antibodies and small molecules have been developed that block all three forms of IL-6 signalling, but in the past decade, IL-6 trans-signalling has emerged as the predominant pathway by which IL-6 promotes disease pathogenesis. The first selective inhibitor of IL-6 trans-signalling, sgp130, has shown therapeutic potential in various preclinical models of disease and olamkicept, a sgp130Fc variant, had promising results in phase II clinical studies for inflammatory bowel disease. Technological developments have already led to next-generation sgp130 variants with increased affinity and selectivity towards IL-6 trans-signalling, along with indirect strategies to block IL-6 trans-signalling. Here, we summarize our current understanding of the biological outcomes of IL-6-mediated signalling and the potential for targeting this pathway in the clinic.

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Introduction

In 1986, the group of Tadimitsu Kishimoto cloned a cDNA coding for B cell stimulatory factor 2, which later was renamed interleukin-6 (IL-6)¹. The amino acid sequence of IL-6 revealed that other factors such as hepatocyte-stimulating factor², hybridoma growth factor³, interferon β ² and a 26-kDa protein identified from fibroblasts⁵ were identical to IL-6, indicating the pleiotropic activity of this cytokine⁶. Today, IL-6 is seen as one of the major immunomodulatory cytokines controlling health and disease⁷. Strategies to inhibit global IL-6 signalling based on antibodies and small molecules directed against IL-6, the IL-6 receptor (IL-6R) or downstream signalling effectors such as Janus kinases (JAKs) have entered the clinic and shown success, including as treatments for chronic inflammatory diseases, for COVID-19 and for preventing fatal cytokine storms associated with CAR T cell therapy in patients with cancer^{8,9}. Importantly, our growing understanding of IL-6 biology has led to the description of three distinct modes of IL-6-mediated signalling: classic IL-6 signalling, IL-6 trans-signalling and IL-6 cluster signalling (Fig. 1). In turn, this has guided new strategies to selectively inhibit these specific signalling modes of IL-6. In classic signalling, IL-6 binds to membrane-bound IL-6R (mIL-6R) to induce a signal-transducing homodimer of the glycoprotein 130 (gp130) receptor chain¹⁰. In contrast, in the case of IL-6 trans-signalling, soluble forms of IL-6R (sIL-6R), generated either by alternative splicing or limited proteolytic processing, form complexes with IL-6 to activate membrane-bound gp130^{11,12}. Finally, in IL-6 cluster signalling, IL-6–mIL-6R complexes formed on a transmitter cell activate gp130 subunits on a neighbouring receiver cell^{13,14}. Of note, the closest relative of IL-6, IL-11, also signals via gp130 homodimers, but initially binds to the membrane-bound or soluble IL-11

receptor (IL-11R) as an α -receptor. Accordingly, IL-11 classic signalling and trans-signalling have been described in vivo, whereas IL-11 cluster signalling has only principally been shown in cell cultures^{15–19}.

Although sIL-6R-mediated IL-6 trans-signalling has emerged as the pathological mode of IL-6 signalling underlying various disease states, classic signalling via mIL-6R and the signal-transducing receptor gp130 has homeostatic, protective and acute inflammatory functions. Cluster signalling appears to play a role in the priming of pathogenic T helper 17 (T_H17) cells¹⁴, but selective inhibitors of IL-6 cluster signalling have not yet been developed. Considering the broad impact of IL-6 trans-signalling on disease, in this Review, we focus on this mode of IL-6 signalling. We first provide a historic overview of the discovery of IL-6 trans-signalling and then we consider the strategies that have been used to selectively interfere with this mode of IL-6 signalling and the potential use of these drugs in the clinic.

The advent of IL-6 trans-signalling

In a seminal article, Bazan hypothesized that cytokines such as growth hormone, prolactin, IL-6, granulocyte stimulating factor and erythropoietin belonged to a four-helical cytokine family²⁰ (Fig. 2). Although the amino acid sequence homology of these proteins is extremely low, they shared structural similarities, which was underlined by a conserved exon–intron organization around the sequences encoding their shared helical structures²¹.

When the DNA coding for IL-6R was cloned in 1988, the type I transmembrane protein it encoded appeared to have no signalling potential, and also bound IL-6 with only low affinity²². It emerged in 1989 that classic IL-6 signalling relied on a second protein, gp130. This

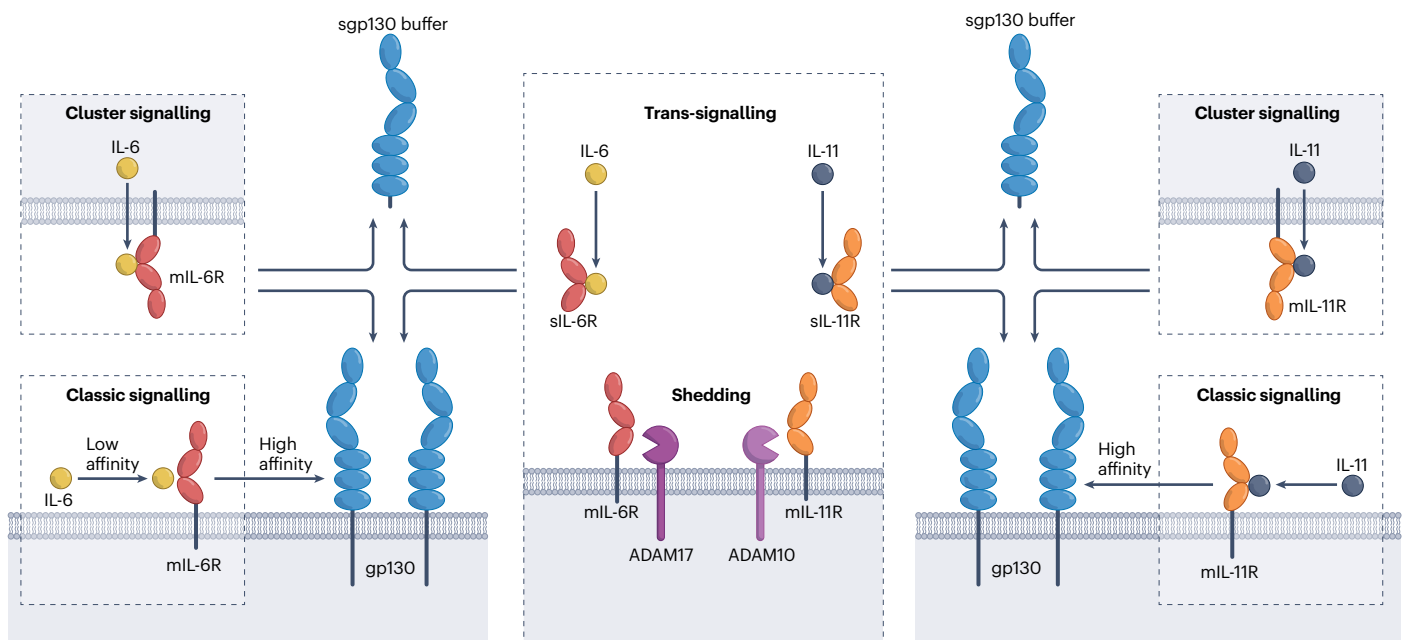


Fig. 1 | Principles of IL-6 and IL-11 classic and trans-signalling. In classic signalling, interleukin-6 (IL-6) and IL-11 bind to membrane IL-6 receptor (mIL-6R) and mIL-11R, respectively, and immediately recruit the high-affinity complex with the signal-transducing glycoprotein 130 (gp130) receptor. Soluble IL-6 receptor (sIL-6R) and sIL-11R can be generated by the proteases ADAM17 (a disintegrin and metalloproteinase 17) and ADAM10, respectively. In cluster signalling, a transmitter cell presents IL-6–mIL-6R complexes to cells expressing gp130.

Cluster signalling has only been described for IL-6, but in principle it is also possible for IL-11. Low-affinity complexes of IL-6–sIL-6R and IL-11–sIL-11R can induce trans-signalling by the formation of high-affinity complexes with gp130. For the sake of simplicity, IL-6 complexes are shown as tetramers (IL-6–IL-6R–2×gp130), although experimental evidence suggest hexamers (2×IL-6–2×IL-6R–2×gp130). The same holds true for IL-11 signalling. Naturally occurring sgp130 might serve as an IL-6 trans-signalling and IL-6 cluster-signalling buffer system (see Box 1).

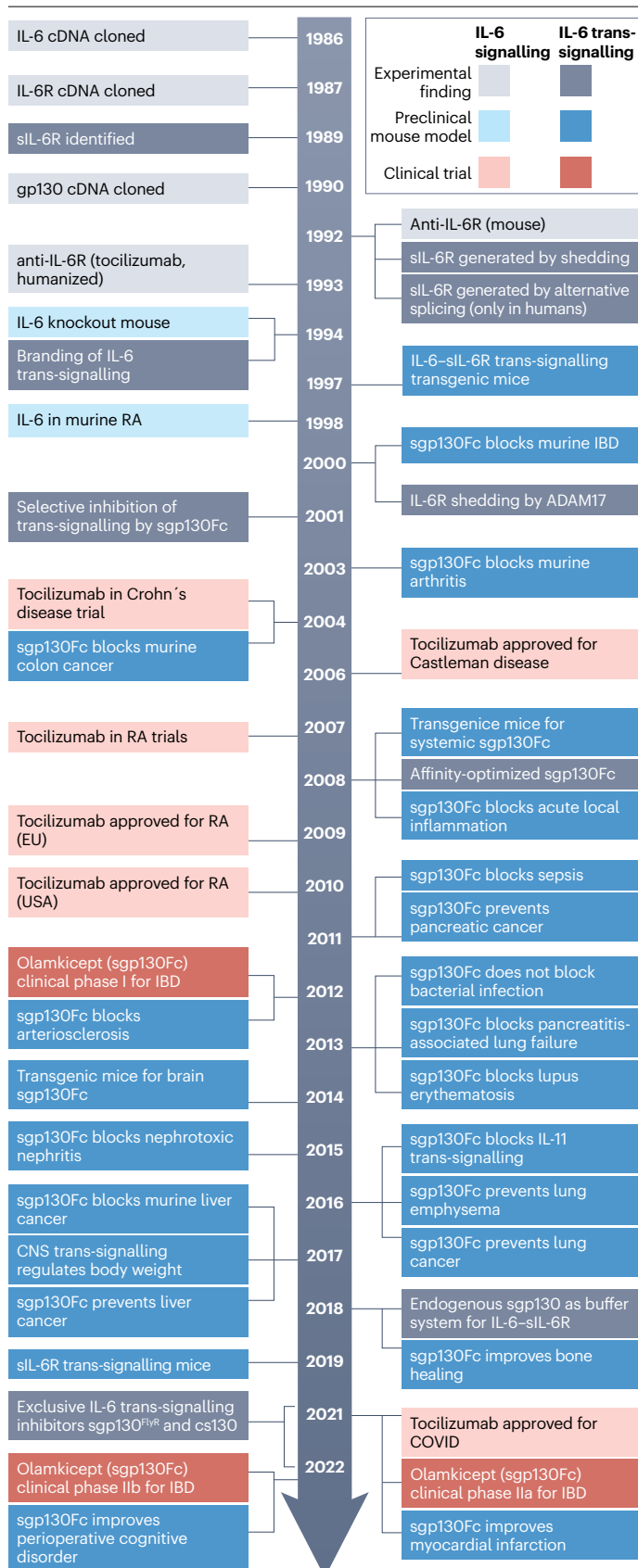


Fig. 2 | Timeline of IL-6 trans-signalling – from discovery to targeted therapies. The timeline shows the discovery milestones for interleukin-6 (IL-6) trans-signalling and compares the development of IL-6-targeted therapies for combined classic and trans-signalling inhibition. The key studies defining the IL-6 trans-signalling pathway took place between 1989 and 1994, and preclinical studies began in the early 2000s, with clinical trials for olamkicept starting in 2012. ADAM17, a disintegrin and metalloproteinase 17; CNS, central nervous system; cs130, chimeric soluble gp130; gp130, glycoprotein 130; IBD, inflammatory bowel disease; IL-6, interleukin-6; IL-6R, IL-6 receptor; RA, rheumatoid arthritis; sgp130Fc, soluble gp130-Fc fusion protein; sIL-6R, soluble IL-6R.

membrane-bound protein formed a high-affinity receptor complex with mIL-6R and IL-6, whereas no binding of mIL-6R to gp130 could be detected in the absence of IL-6^{10,23}. When the structure of the IL-6-mIL-6R-gp130 complex was solved, it became clear that the contribution of IL-6 to the buried area between the IL-6-mIL-6R complex and site II of gp130 formed by the elbow between domain 2 and domain 3 was modestly larger for IL-6 (1272 Å², site IIa) than for the IL-6R (1078 Å², site IIb). For the assembly at site III of gp130 formed by domain 1, the contribution of IL-6 (1276 Å², site IIIa) was substantially larger than that of the IL-6R (473 Å², site IIIb). The binding energy of IL-6 or IL-6R alone was not sufficient to allow binding to gp130²⁴ (Fig. 3).

Further cDNAs of homologous cytokines with partly overlapping but clearly distinct biological activities were cloned²¹. These included IL-11²⁵, leukaemia inhibitory factor (LIF)²⁶, ciliary neurotrophic factor (CNTF)²⁷, oncostatin M (OSM)²⁸, cardiotrophin 1 (CT1)²⁹, cardiotrophin-like cytokine (CLC)³⁰ and IL-27, the last a dimeric cytokine consisting of a cytokine moiety (p28) and a soluble receptor moiety (EBI3)³¹. All of these cytokines used gp130 as an obligatory receptor subunit³². Importantly, it was shown that gp130 mRNA is expressed in virtually all cells, with the only exception reported so far being granulocytes³³. In contrast, mIL-6R is only expressed by hepatocytes, subsets of epithelial cells and leukocytes^{8,34}, and the expression of specific receptors for IL-11 (IL-11R) and CNTF (CNTFR) is also restricted to only a few cell types³⁵, including cardiomyocytes³⁶, fibroblasts³⁷ and epithelial cells³⁸.

In the early 1990s, our group found that mIL-6R was subject to limited proteolysis, leading to the generation of sIL-6R consisting of the extracellular portion of the IL-6R^{39,40}. The major protease involved in the shedding of sIL-6R during inflammation is the membrane-bound metalloproteinase ADAM17 (a disintegrin and metalloproteinase 17), although ADAM10 is also involved to a minor extent (Fig. 4). The cleavage site in mIL-6R targeted by both of these inflammatory ADAM proteases is close to the membrane, located between Pro355 and Val356⁴¹. In humans but not in mice, a soluble form of the IL-6R can also be generated by translation from a differentially spliced mRNA, although this only accounts for about 15% of the sIL-6R found in the blood^{42,43}. Other proteases such as meprin- α and meprin- β ⁴⁴, rhomboid-related protein 2^{45,46}, cathepsin S⁴⁷ and cathepsin G⁴⁸ are capable of mediating the shedding of the sIL-6R, although the biological importance of these secondary sheddases has not been analysed. The sIL-6R was shown to bind IL-6 with similar affinity as mIL-6R^{39,40}. We demonstrated that cells that express gp130 but not mIL-6R are not responsive to IL-6, but they become responsive to IL-6 in the presence of sIL-6R^{39,49}. This mode of signalling was named IL-6 trans-signalling¹¹. As almost all cells express gp130 on their cell surface³⁴, the switch to IL-6 trans-signalling would make virtually all cells responsive to IL-6¹¹.

To analyse the consequences of IL-6 trans-signalling in vitro and in vivo, the designer cytokine 'hyper-IL-6' was developed. This protein consists of IL-6 covalently bound to the sIL-6R via a flexible peptide

linker⁵⁰. Comparing stimulation of cells with IL-6 versus hyper-IL-6 showed that IL-6-mediated stimulation of many cell types, including neural cells⁵¹, adult haematopoietic stem cells and embryonic stem cells^{52,53}, depended on the presence of sIL-6R⁵⁴. Additionally, the presence of sIL-6R augmented the response of mIL-6R-expressing cells to IL-6 in terms of increased signalling intensity, as measured by phosphorylation of STAT3 or cytokine-induced proliferation^{55,56}. As gp130 levels on cells that co-express mIL-6R – including hepatocytes and immune cells – are about 10–20 times higher than mIL-6R levels, stimulation with IL-6 only led to restricted activation of gp130 receptors⁵⁴. In contrast, stimulation with the complex of IL-6 and sIL-6R activated all gp130 receptors on the cell surface. Moreover, stimulation with IL-6 alone led to the rapid internalization of the IL-6–mIL-6R–gp130 signalling complex, whereas stimulation with the IL-6–sIL-6R complex led to reduced gp130 internalization and therefore longer signalling duration; however, no qualitative differences between intracellular IL-6 classic signalling and trans-signalling pathways (for example, in terms of JAK–STAT and MAPK activation) were detected^{57,58}. We concluded that cells stimulated via IL-6 trans-signalling showed a more sustained IL-6 response with a higher amplitude than cells expressing mIL-6R when stimulated with IL-6 in the absence of sIL-6R⁵⁴.

To clarify the pathophysiological role of sIL-6R *in vivo*, we generated mice that expressed the human sIL-6R as a transgene⁵⁵. As mouse IL-6 does not interact with the human sIL-6R, these mice did not show a

discernible phenotype. Importantly, upon injection of human IL-6 into these mice, the presence of sIL-6R prolonged the half-life of IL-6 and led to increased activation of gp130 receptors. Thus, IL-6 target cells – such as hepatocytes – were hypersensitized⁵⁵. When the human sIL-6R-expressing transgenic mice were bred with human IL-6 transgenic mice to generate IL-6–sIL-6R double-transgenic mice, we observed extramedullary expansion of haematopoietic progenitor cells in the liver that resembled the fetal liver, which is the site of haematopoiesis in the embryo⁵⁶. The IL-6–sIL-6R double-transgenic mice were markedly smaller than IL-6 or sIL-6R single-transgenic mice and showed enlarged livers and spleens⁵⁴. These data for the first time demonstrated the difference in outcome between classical IL-6 signalling and trans-signalling, as IL-6 single-transgenic mice showed no liver phenotype even though hepatocytes express the IL-6R and can therefore respond to IL-6 alone⁵⁶.

Interestingly, extramedullary haematopoiesis and hepatocyte proliferation were not seen in mice that expressed a constitutively active gp130 variant (L-gp130)⁵⁹ in hepatocytes⁶⁰, indicating that gp130 stimulation in other liver cell populations contributed to the complex phenotype of the IL-6–sIL-6R double-transgenic mice⁵⁶. Additionally, we detected hepatocellular hyperplasia in close to 100% of the hepatocytes, resembling liver regeneration⁶¹. A dominant role of sIL-6R in liver regeneration was confirmed using recombinant hyper-IL-6 treatment⁶² or using mice in which mIL-6R was exchanged for sIL-6R⁶³.

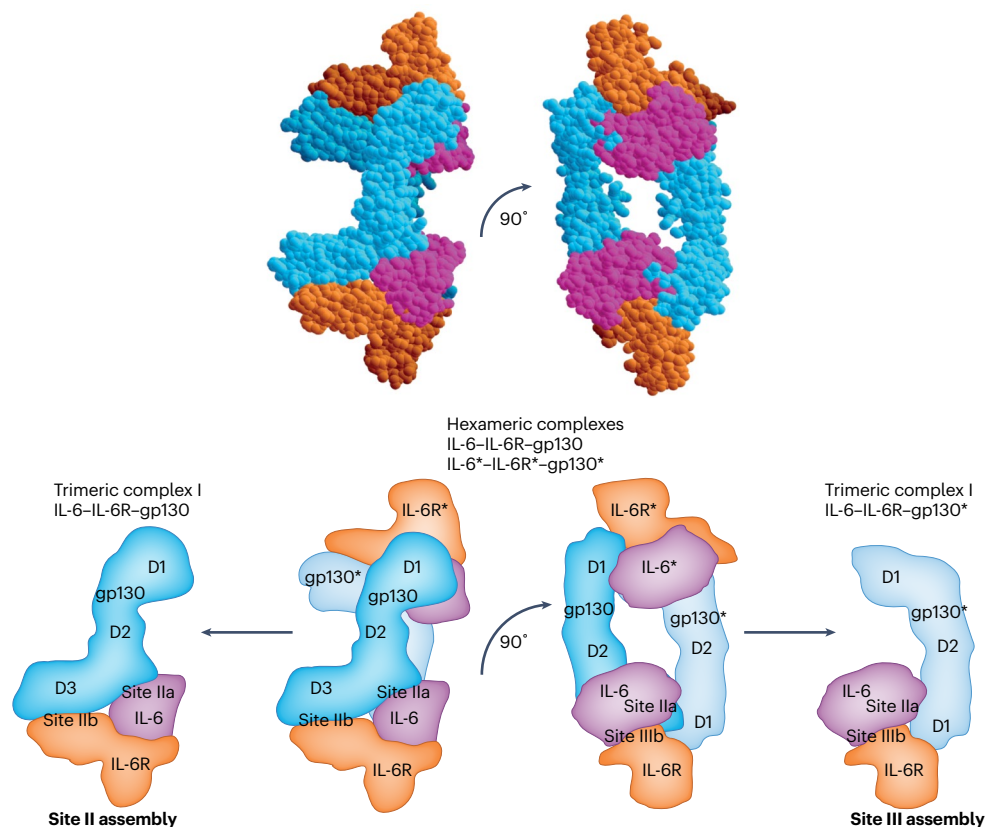


Fig. 3 | Assembly of the IL-6–IL-6R–gp130 complex via site II and site III. Hexameric assembly of glycoprotein 130 (gp130)–gp130* with interleukin-6 (IL-6)–soluble IL-6 receptor (sIL-6R) and IL-6*–IL-6R* complexes via site II and site III. The asterisks indicate the second gp130, IL-6 and IL-6R in the assembly

of two trimeric complexes. A trimeric complex of gp130 and IL-6–sIL-6R is formed between site IIa of IL-6, site IIb of IL-6R and domain D2–D3 of gp130²⁴. A second trimeric complex of gp130* and IL-6–sIL-6R is formed between site IIIa of IL-6, site IIIb of IL-6R and domain D1 of gp130²⁴.

These transgenic sIL-6R mice showed liver regeneration that was indistinguishable from control mice⁶³.

In summary, the mechanistic separation of IL-6 trans-signalling from classic signalling has provided an opportunity to develop small molecules and antibody-based strategies that either globally block IL-6 activity *in vivo*^{64,65}, or else selectively block pathological IL-6 trans-signalling¹¹, as will be discussed in the following sections.

Development of IL-6 signalling inhibitors

Studies in IL-6-deficient mice showed that IL-6 contributes to the pathogenesis of many inflammatory diseases, including bacterial and viral infections⁶⁶, arthritis^{67,68}, experimental colitis⁶⁹ and multiple sclerosis⁷⁰. Therefore, IL-6 inhibition emerged as an attractive therapeutic avenue to translate to the clinic. In principle, inhibition of IL-6 signalling can be achieved by the application of antibodies to any component of the receptor signalling complex; blockade of IL-6, IL-6R or gp130 alone is sufficient to completely silence IL-6-mediated signalling (Fig. 4). Small-molecule inhibitors targeting JAKs, which act downstream of gp130, represent another viable approach, and such molecules have

been used in the clinic to treat rheumatoid arthritis and other inflammatory diseases^{71–73}. However, JAKs are not exclusively activated by IL-6, so targeting these signalling molecules does not enable selective inhibition of IL-6.

Although expression levels of mIL-6R and gp130 are only marginally upregulated during inflammation, IL-6 levels in the circulation dramatically rise from virtually undetectable (lower picograms-per-millilitre range) in healthy individuals to several nanograms per millilitre in inflammatory diseases and up to micrograms-per-millilitre levels in patients who develop fatal sepsis⁷⁴. This is an important consideration from a therapeutic point of view, as rather high amounts of antibodies blocking gp130 or the IL-6R (see Box 1) would be needed to saturate all membrane-bound and soluble IL-6 receptors in order to attain a clinical response. In contrast, lower amounts of antibodies that block IL-6 directly might be sufficient, and the application of an IL-6-neutralizing antibody could be rather easily adapted to the amount of IL-6 measured in patient serum samples.

In practice, only antibodies blocking IL-6 or the IL-6R have made their way into the clinic^{8,75}. The fact that gp130 is generally used by

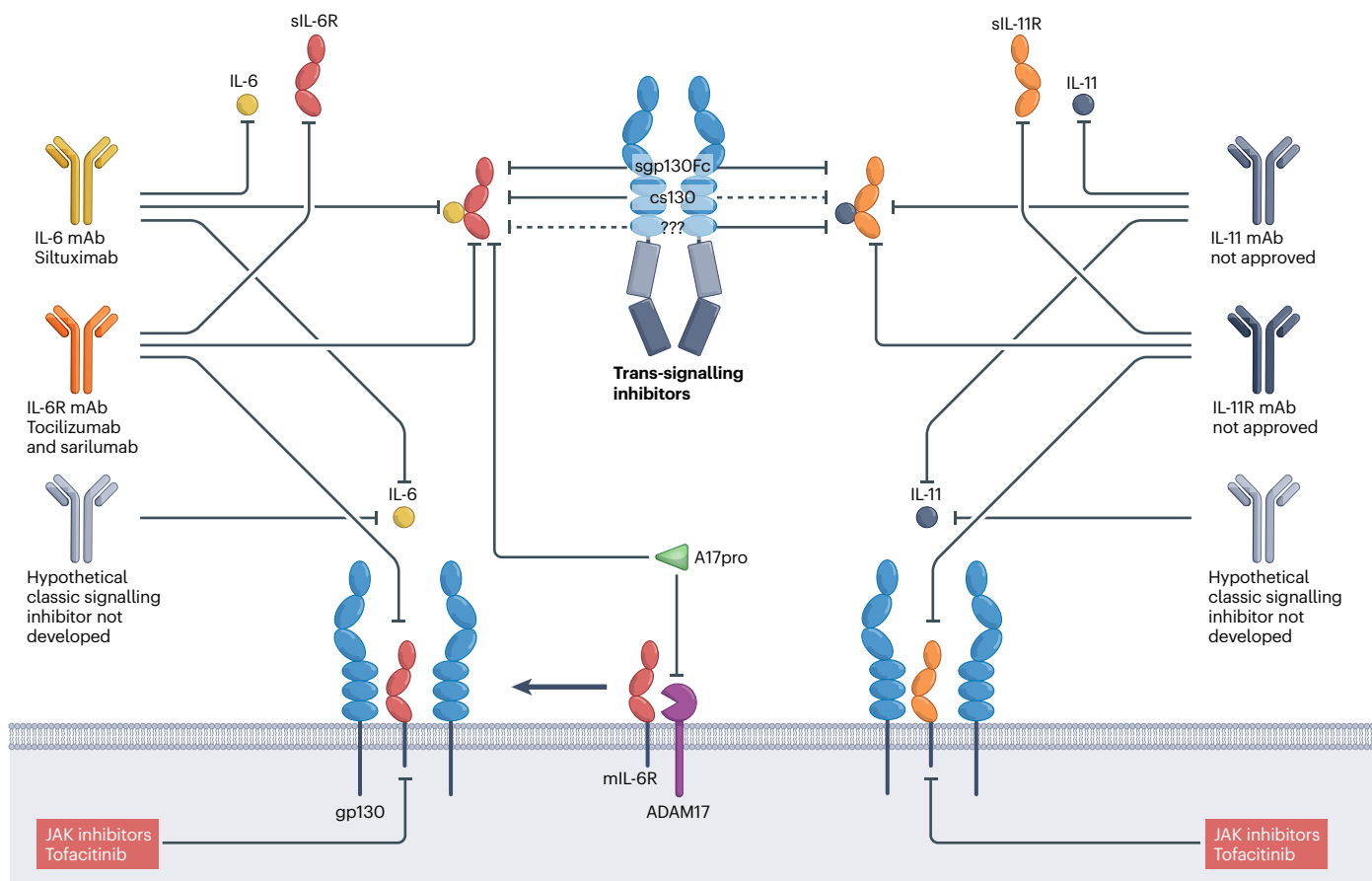


Fig. 4 | Inhibitory principles of IL-6 and IL-11 classic and trans-signalling. Classic and trans-signalling of interleukin-6 (IL-6) and IL-11 can be inhibited by antagonistic substances (for example, antibodies and small molecules) directed against the cytokine, the α -receptors, or glycoprotein 130 (gp130)-associated Janus kinases (JAKs). Antibodies to gp130 are currently not in clinical development. Trans-signalling is inhibited by variants of soluble gp130. Sgp130Fc (soluble gp130–Fc fusion protein) inhibits IL-6 and IL-11

trans-signalling, chimeric soluble gp130 (cs130) inhibits IL-6 trans-signalling, and the autoinhibitory N-terminal ADAM17 (a disintegrin and metalloproteinase 17) pro-domain (A17pro) inhibits the release of soluble IL-6 receptor (sIL-6R), prevents IL-6 trans-signalling and might increase classic signalling because mIL-6R level might increase. A selective IL-11 trans-signalling inhibitor has not been described. Selective classic-signalling inhibitors have also not been developed thus far.

Box 1

The IL-6 buffer in the blood is formed by sIL-6R and sgp130

In healthy individuals, interleukin-6 (IL-6) levels in the blood are in the range of 1–5 pg/ml. These levels increase during inflammatory states around 1,000 fold²¹. In sepsis, IL-6 levels of up to several micrograms per millilitre have been reported⁷⁴. Under homeostatic conditions, levels of soluble IL-6 receptor (sIL-6R) are in the range of 40–75 ng/ml and have been shown to increase between 2-fold and 10-fold during inflammatory diseases²¹. It is not clear whether sIL-6R levels correlate with disease severity, as this has not been studied systematically. However, recent studies in patients with inflammatory bowel disease²⁰³ and COVID-19²⁰⁴ reported conflicting results. Levels of sgp130 in healthy individuals have been observed to be in the range of 250–400 ng/ml. Interestingly, it was first reported that sgp130 was generated by differential splicing²⁰⁵. Unexpectedly, it was recently found that about 50% of the sgp130 in the blood is generated by the protease BACE via limited proteolysis²⁰⁶. Levels of sgp130 remain unaltered during inflammation²¹ (Fig. 5a,b). IL-6 secreted by cells will bind to the sIL-6R with an affinity of around 1 nM. The complex of IL-6 and sIL-6R binds to sgp130 with considerably higher affinity and will thereby be neutralized⁹⁴. Thus, sIL-6R and sgp130 in the blood can be seen as a buffer for IL-6, serving as a protection from

overstimulation⁷⁴ (Fig. 5). The capacity of the buffer is determined by the level of the sIL-6R because sgp130 levels exceed sIL-6R levels on the molar level. A single-nucleotide polymorphism has been found in the gene coding for the human IL-6R, which leads to a change of Asp358 to Ala358 close to the ADAM17 cleavage site of the IL-6R protein⁴¹. The Ala358 variant of the IL-6R leads to its more efficient cleavage²⁰⁷ and therefore to about 50% higher levels of sIL-6R in the blood^{182,188}. Consequently, carriers of the Ala358 variant of the IL-6R are less susceptible to several inflammatory conditions, such as congestive heart disease, abdominal aortic aneurism and rheumatoid arthritis²⁰⁸. A likely explanation of this phenomenon is the higher buffer capacity of the IL-6 buffer in the blood brought about by the higher levels of sIL-6R²⁰⁹. Disturbance of the buffer has been reported (for example, in patients with type 2 diabetes²¹⁰) and might contribute to pathophysiology in this and other inflammatory diseases. In our view, the demonstrated beneficial role of sgp130Fc (olamkicept) is on the one hand explained by the selective blockade of IL-6 trans-signalling. On the other hand, the sgp130Fc protein increases the IL-6 buffering capacity, which might be limited in autoimmune diseases.

IL-6 family cytokines^{76,77} and that gp130 knockout mice are not viable hindered the clinical development of gp130 antibodies. In 1997, antibodies to gp130, which neutralized IL-6 activity but not the activity of LIF, OSM and CNTF, were described⁷⁸. Unfortunately, these antibodies were not evaluated in further in vivo studies and were not tested for cross-reactivity to IL-11, IL-27 and CLC.

The first clinical trial for an IL-6-specific inhibitor was performed in a patient with plasma cell leukaemia because IL-6 had previously been identified as a potent growth factor for this cancer^{79,80}. The trial was conducted with a mouse monoclonal antibody to human IL-6 and showed very promising initial results, including suppression of myeloma cell proliferation in the bone marrow and reduced C-reactive protein (CRP) levels⁸¹. However, owing to the formation of IL-6-antibody complexes that were not efficiently cleared via the kidney, IL-6 levels, although biologically inactive, accumulated in the circulation and reached high concentrations of up to 14 ng/ml⁸² in some patients and up to 1.7 µg/ml in a patient who developed sepsis during therapy⁸³. In a second case report, treatment of a patient with Castleman disease with the same antibody led to the resolution of disease symptoms and improved laboratory parameters. However, increased IL-6 levels, probably due to the formation of complexes with the antibody, were detected and the treatment was finally discontinued⁸⁴. Thus, despite the initial positive clinical response of the two patients, which clearly underlined that IL-6 can be successfully targeted therapeutically in IL-6-driven diseases, this approach was not further pursued.

Instead, the humanized monoclonal antibody tocilizumab, an antibody to IL-6R that prevents binding of IL-6 to the IL-6R, was developed and is currently in clinical use, for example, to treat rheumatoid arthritis, Castleman disease and cytokine release syndrome⁸. Recently, tocilizumab was shown to improve survival in hospitalized

adult patients with COVID-19 with both hypoxia and systemic inflammation⁹, and was subsequently approved for this indication in several countries. Interestingly, IL-6 levels also slightly increased in patients treated with tocilizumab^{85,86}, which can be explained by lack of IL-6 internalization and degradation by IL-6R-expressing cells⁸⁷. Interestingly, the reported increases in sIL-6R are much smaller than the increases in IL-6 during anti-IL-6 therapy, because tocilizumab does not form a complex with IL-6, which is therefore still cleared via the kidney. However, sIL-6R levels were increased up to 10-fold in patients treated with tocilizumab (27.7 ± 4.4 ng/ml at baseline versus 251.4 ± 24.7 ng/ml after 6 weeks of tocilizumab treatment) owing to the prolonged half-life of sIL-6R-tocilizumab complexes⁸⁵. In addition to tocilizumab, the fully humanized anti-IL-6R monoclonal antibody sarilumab was approved for the treatment of rheumatoid arthritis⁸⁸, whereas the chimeric anti-IL-6 monoclonal antibody siltuximab was approved for patients with idiopathic multicentric Castleman disease⁸. Several other therapeutics targeting either IL-6 or the IL-6R are currently at different stages of clinical or preclinical development⁸.

Although inhibition of IL-6 or IL-6R was considered to result in comparable signalling outcomes, a recent publication using a single side-by-side administration protocol for siltuximab and tocilizumab in patients with type 1 diabetes reported differences between the two antibodies⁸⁹. The authors describe distinct influences on T cell function, because siltuximab but not tocilizumab enhanced the suppression of effector T cells by regulatory T cells⁸⁹. As this is the first in vivo study addressing this issue, it might simply be related to differences in dosing and pharmacokinetics⁸⁹. However, it might also, at least in part, be caused by IL-6 family cytokine crosstalk. It has been shown that CNTF⁹⁰ and the p28 subunit (also known as IL-30) of IL-27^{91,92} also signal via the IL-6R, and such signals could be blocked by tocilizumab

but not by siltuximab. However, both CNTF and p28 have a much lower affinity for the IL-6R compared to IL-6 itself, and a functional role for these other IL-6R ligands in vivo has yet to be established. Crosstalk for IL-6, however, has not been described to date.

Of note, none of these IL-6 signalling inhibitors can discriminate between classic signalling and trans-signalling, and they block both pathways simultaneously. As already mentioned, and described in detail in the next section, IL-6 trans-signalling has turned out to be the pathological arm of IL-6, whereas classic IL-6 signalling often seems to be protective and anti-inflammatory. Therefore, interfering with classic IL-6 signalling might give rise to a negative benefit–risk scenario.

An IL-6 trans-signalling inhibitor: sgp130Fc

The designer cytokine hyper-IL-6 was the first biological tool to specifically activate cells via IL-6 trans-signalling, but not by classic IL-6 signalling via mIL-6R⁵⁰. From a molecular three-dimensional model of IL-6 bound to the sIL-6R, we estimated that the distance between the COOH-terminus of IL-6 and the NH₂-terminus of the sIL-6R was about 40 Å. We connected the cDNA coding for the sIL-6R to the cDNA coding for IL-6 by a stretch of nucleotides coding for 13 amino acids. These amino acids formed a flexible linker between sIL-6R and IL-6, allowing the natural interaction between the ligand and the receptor⁵⁰. This designer cytokine enabled the identification of a variety of potential target cells for IL-6 trans-signalling, including neuronal cells⁵¹, adult haematopoietic stem cells and embryonic stem cells^{52,53}. A limitation was that these experiments did not prove that IL-6 trans-signalling actually occurred in vivo and drove pathophysiological responses. It came to our notice that most soluble receptors were competitive inhibitors of their cognate membrane-bound versions⁹³ and that the powerful agonistic activity of sIL-6R was a prominent exception. To design an alternative to the antibody IL-6 inhibitor, we generated a fusion protein of the extracellular portion of gp130 fused to the Fc portion of a human IgG1 antibody (Fig. 4). As neither IL-6 nor sIL-6R alone bind to gp130, this fusion protein – sgp130Fc – was a selective inhibitor of IL-6 trans-signalling but did not interfere with classic signalling⁹⁴. We were rather surprised by this finding, because sgp130Fc interacts not only with IL-6–sIL-6R complexes⁹⁴ but also with IL-6–mIL-6R complexes¹³.

This might be explained by the receptor activation mode of IL-6, which might allow binding of naturally occurring sgp130 or sgp130Fc to membrane-bound IL-6–IL-6R complexes in the absence (but not in the presence) of cell surface gp130. Gp130 has been described to assemble as preformed dimers, most likely to enable rapid signal induction after IL-6 binding^{87,95}. It was, however, not analysed whether IL-6R or IL-11R are also included in these preformed receptor complexes. Of note, we recently deciphered the apical and basolateral sorting code of IL-6R, IL-11R and gp130 in polarized cells. Although we have not analysed this directly, our results suggest that IL-6R and IL-11R are either in complex with gp130 or within the same micro-membrane localization, either directly after translocation to the membrane of the endoplasmic reticulum or after transport to the Golgi apparatus⁹⁶.

Such preformed receptor complexes might prevent sgp130Fc accession and inhibition of classic IL-6 signalling. As already explained, neither IL-6 nor IL-6R alone bind to gp130. Therefore, the first step of activation is the formation of the complex of IL-6 and IL-6R. Thereafter, this complex binds the low-affinity site of gp130, which is formed by the elbow between domain 2 and domain 3 of gp130 (Fig. 3). Only then will contact of the tip of IL-6 to the high-affinity site of gp130 (formed by domain 1 of gp130) be established¹⁹. Apparently, once binding of

the complex of IL-6 and IL-6R has been established, sgp130Fc has no access to the complex of IL-6 and IL-6R.

This might, however, not be the full explanation. IL-6–IL-6R–gp130 complexes might be additionally stabilized by other, so far unknown factors. For example, it is unclear the extent to which signalling by IL-6–IL-6R–gp130 complexes is initiated directly at the plasma membrane, or if signalling by these complexes is specifically continued or even boosted after endocytosis⁹⁷. For other cytokines, such as tumour necrosis factor (TNF), signalling from endosomes plays an important role in signal transduction⁹⁸. At least to some extent, activation of STAT3 involves endosomal trafficking of the receptor complex⁹⁹.

Having discussed the general features of sgp130 in the inhibition of IL-6 trans-signalling, in the following section we will detail the preclinical and clinical development of the sgp130Fc variant olamkicept.

Preclinical and clinical development of olamkicept

The generation of sgp130Fc (named olamkicept by the World Health Organization in 2016) was a welcome addition to the arsenal of IL-6 inhibitors and has enabled us to define the physiological and pathophysiological roles of IL-6 trans-signalling in numerous mouse models of inflammatory or neoplastic diseases (Table 1 and Fig. 5a–c). The experimental blueprint included comparing global blockade of IL-6 in anti-IL-6-treated mice or IL-6-deficient mice to selective inhibition of IL-6 trans-signalling in sgp130 transgenic mice¹⁰⁰ or animals treated with recombinant sgp130Fc. Surprisingly, in many disease models, treatment with sgp130Fc was more beneficial than global blockade by IL-6-neutralizing antibodies. Such disease models included sepsis¹⁰¹, cerulein-induced acute pancreatitis¹⁰², bone fracture healing^{103,104} and myocardial infarction¹⁰⁵. In the cerulein-induced acute pancreatitis model, *Il6*^{-/-} mice showed more inflammation-associated damage in the pancreas than wild-type mice, but no subsequent lung failure. In contrast, sgp130Fc transgenic mice administered with cerulein were completely protected against pancreatic damage and lung failure, and therapeutic treatment of cerulein-administered wild-type mice with sgp130Fc protein attenuated severe acute pancreatitis and led to 100% survival¹⁰². Further, in a mouse model for uneventful bone fracture healing, the global blockade of IL-6 with a neutralizing antibody reduced systemic inflammation, the hepatic acute-phase reaction and immune-cell infiltration to the fracture site, but led to delayed fracture healing. In contrast, specific blockade of IL-6 trans-signalling with recombinant sgp130Fc had minor effects on the immune response but did not impede bone fracture healing^{103,104}. In a rat model of reperfused myocardial infarction, treatment with an IL-6-neutralizing antibody did not alter the infarct size, whereas treatment with sgp130Fc reduced the infiltration of neutrophils and mononuclear phagocytes into the myocardium and reduced the infarct size by about 50%, thereby preserving cardiac function 28 days after the myocardial infarction¹⁰⁵.

A potential caveat with the use of anti-inflammatory therapies is the common burden of increased frequency of infections, with incidence rates for serious infections (patients with events per 100 patient–years) ranging from 7.59 for the anti-TNF blocker certolizumab pegol, to over 5.45 for tocilizumab, to 2.93 for the JAK inhibitor tofacitinib¹⁰⁶. In other words, if a physician treats 100 patients for one year with these inhibitors, approximately 3–8 patients will acquire a serious infection¹⁰⁶. This is an important issue because treatment of autoimmune diseases with anti-cytokine drugs need to be continued for years if not for life, leading to an accumulation of the infection risk.

A reduced capacity to cope with infections was also seen in IL-6-deficient mice after *Listeria monocytogenes* infection. Global blockade of IL-6 activity in mice infected with *L. monocytogenes* reduced hepatic induction of acute-phase proteins and led to significantly higher titres of bacterial colony-forming units in spleen and liver^{66,107}. In contrast, infected sgp130Fc transgenic mice or infected wild-type mice treated with recombinant sgp130Fc did not show reduced induction of hepatic acute-phase proteins or increased bacterial colony-forming units in spleen and liver¹⁰⁷, suggesting that inhibition of IL-6 trans-signalling did not interfere with bacterial defence mechanisms. The beneficial consequences of selectively blocking IL-6 trans-signalling in inflammatory bowel disease (IBD) and cardiovascular disease might point to known effects of trans-signalling on T cells endothelial cells and smooth muscle cells. It has been shown that IL-6-mediated apoptotic resistance in T cells is based on IL-6 trans-signalling^{69,94}. Furthermore, it has been demonstrated that the differentiation of T cells into T_H17 cells, which is induced by TGFβ and IL-6, is by far more efficient in the presence of sIL-6R¹⁰⁸. Endothelial cells and smooth muscle cells have been shown to express gp130 but not IL-6R^{109,110}. These cells cannot respond to IL-6 alone but can be stimulated by the combination of IL-6 and sIL-6R to express various chemokines and ICAM1. These changes might contribute to the vascular injuries observed in patients with sepsis^{109,110}. Interfering with IL-6 trans-signalling would dampen these effects and thereby act in an anti-inflammatory manner.

These data suggest that the pro-inflammatory activities of IL-6 are predominantly mediated by trans-signalling, whereas classic IL-6 signalling is primarily pro-inflammatory in the acute stage of an inflammatory responses but later acts in a protective, regenerative manner¹¹¹. Therefore, it might be reasonable to selectively block the IL-6 trans-signalling pathway rather than block IL-6 globally via neutralizing antibodies^{8,112}.

In phase I clinical trials of olamkicept in healthy individuals in 2013 and 2014, no serious adverse events were encountered. A small open-label phase IIa clinical trial was subsequently performed involving 16 patients with IBD (EudraCT No 2016-000205-36). Similar to the results in the phase I study, olamkicept was well tolerated and induced clinical response in 44% and clinical remission in 19% of the patients. Molecular profiling confirmed that clinical remission was associated with distinct changes in mucosal levels of phosphorylated STAT3 in intestinal epithelium and lamina propria of the treated patients¹¹³.

In a second double-blind placebo-controlled phase IIb clinical study, 91 patients with moderate-to-severe ulcerative colitis that had shown inadequate response to conventional therapy were enrolled. Olamkicept was well tolerated and showed dose-dependent high efficacy with regards to clinical response, clinical remission and mucosal healing¹¹⁴ (NCT03235752). Most of the patients (94.5%) had previously not been treated with biologics. After 12 weeks with injections every second week, clinical remission was seen in 0% (placebo), 6.7% (olamkicept 300 mg/injection) and 20.7% (olamkicept 600 mg/injection) of the patients. At the same time, mucosal healing occurred in 3.4% (placebo), 10% (olamkicept 300 mg/injection) and 34.5% (olamkicept 600 mg/injection) of the patients¹¹⁵. Based on the positive results of these phase II clinical trials, phase III clinical trials are being planned for the near future.

In addition to IBD, compassionate use of olamkicept has been undertaken in a single patient with very high-risk atherosclerotic cardiovascular disease. After 11 weeks of olamkicept treatment every second week (600 mg/injection), the patient showed reduced arterial wall inflammation¹¹⁶. This was not unexpected because in low-density lipoprotein

Table 1 | Efficacy of sgp130Fc-mediated blockade of IL-6 trans-signalling in preclinical models of inflammation and cancer

Year	Disease Model	Study Outcome	Refs.
2000, 2006, 2009	Intestinal inflammation	Suppression of inflammatory bowel disease	69,182,187
2003, 2006, 2009	Rheumatoid arthritis	Improvement of established arthritis	169,188,189
2004, 2009, 2010, 2018	Colon cancer	Reduction of tumour load	182,190,191
2007, 2008	Acute local inflammation	Suppression of acute local inflammation	100,192
2011	Pancreatic cancer	Inhibition of tumour progression, reduction of ductal adenocarcinoma	164
2011, 2012	Sepsis	Up to 100% survival in sepsis models	186,193
2012	Mycobacteria infection	No increase of bacterial burden	194
2012	Atherosclerosis	Regression of atherosclerosis plaques	117
2013	<i>Listeria</i> infection	No increase or reduction of bacterial burden	107
2013	Pancreatitis-associated lung failure	100% survival of severe, acute experimental pancreatitis	102
2013	Lupus erythematosus	Suppression of inflammation and renal pathology	195
2015, 2016	Nephrotoxic nephritis	Amelioration of disease	196,197
2016	Lung emphysema	Improvement of disease by blockade of alveolar apoptosis	198
2016	Lung cancer	Reduction of tumour load	166
2017	Liver cancer	Reduction of tumour load	199,200
2018	Bone healing	Improvement of bone healing	103,104
2019	Abdominal aortic aneurysm	Improved survival	201
2021	Myocardial Infarction	Reduction of infarct size and preserving of cardiac function	105
2022	Perioperative neurocognitive disorder	Prevention of surgery-induced cognitive decline	202

receptor-deficient (*Ldlr*^{-/-}) mice on a high-fat, high-cholesterol diet, sgp130Fc treatment not only prevented mouse atherosclerosis but also strongly reduced existing atherosclerotic plaque burden¹¹⁷.

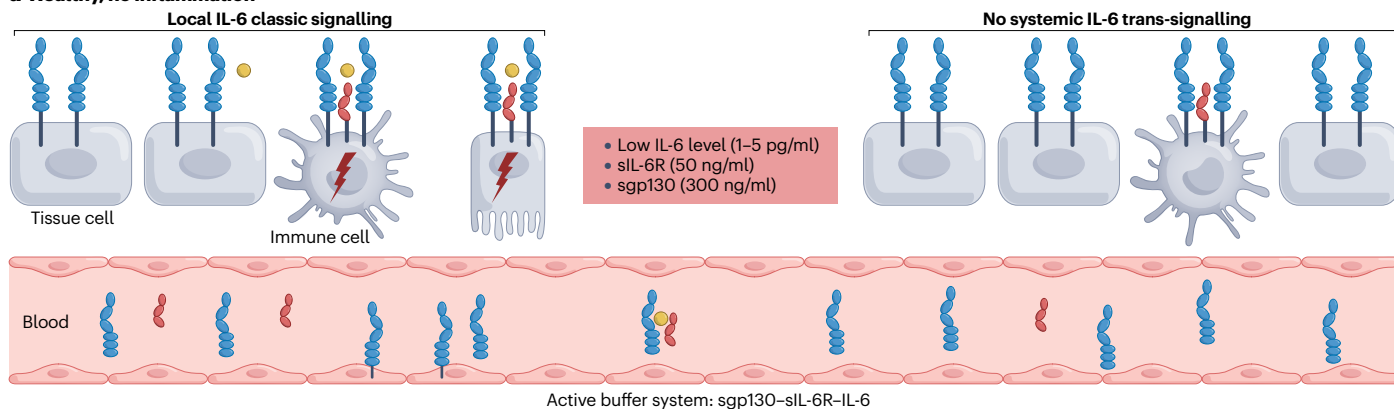
The results with olamkicept in the described clinical trials are encouraging. As mentioned, we have performed numerous preclinical trials in animal models of human autoimmune and neoplastic diseases (Table 1). In all disease models, we noted that specific blockade of IL-6 trans-signalling with the sgp130Fc protein was at least as efficient as treatment with anti-IL-6 or anti-IL-6R monoclonal antibodies, which lead to global blockade of IL-6 activity. However, in animal models of sepsis, pancreatitis, bone fracture healing and myocardial infarction,

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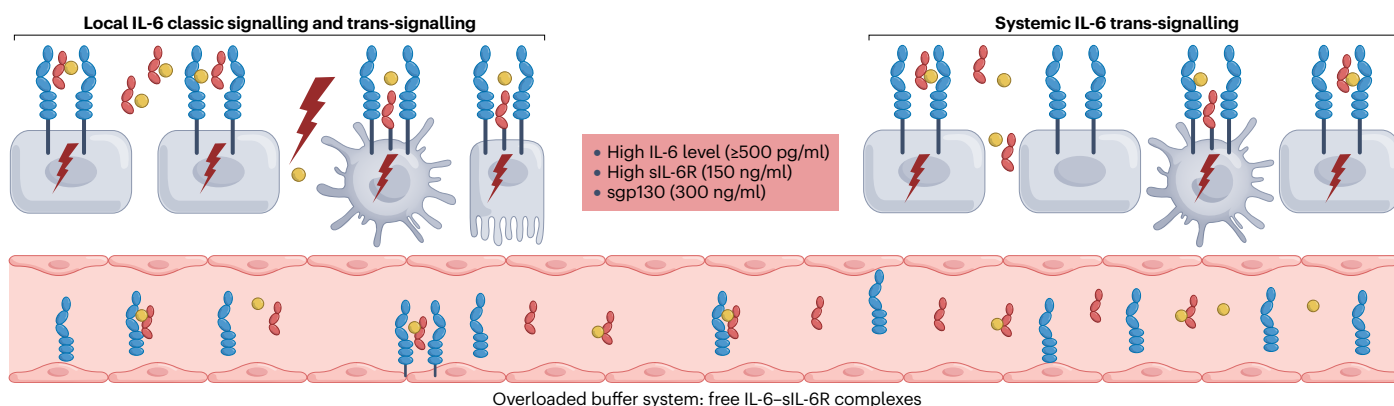
a clear advantage in the specific blockade of IL-6 trans-signalling was demonstrated over global blockade of IL-6 activity^{94–103}. These diseases are therefore good candidates for further clinical trials with olamkicept.

Taken together, the promising clinical potential of olamkicept as an efficacious anti-inflammatory drug provides the rationale to further refine sgp130Fc for the development of next-generation inhibitors of IL-6 trans-signalling with higher affinity, specificity and bioavailability.

a Healthy, no inflammation



b Acute and chronic inflammation



c Contained chronic inflammation

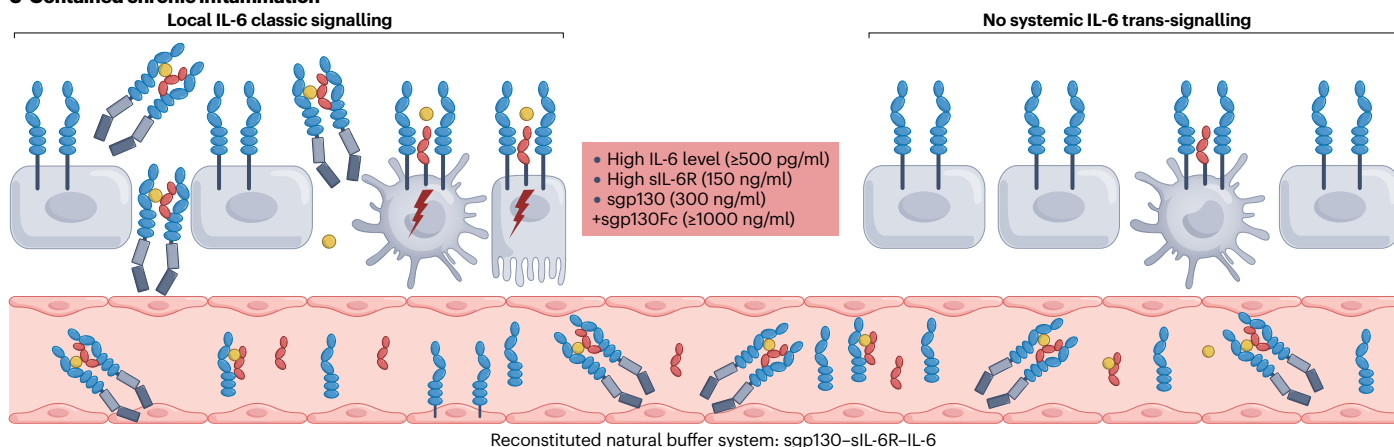


Fig. 5 | Endogenous and therapeutic buffer system to limit IL-6 signalling.

The buffer for interleukin-6 (IL-6) in the blood is formed by soluble IL-6 receptor (sIL-6R) and sgp130 (Box 1). **a**, Under healthy, noninflammatory conditions, the buffer system allows local homeostatic signalling mainly in immune cells and hepatocytes but not in typical tissue cells, smooth muscle cells and endothelial cells. A low level of IL-6 and the buffer system prevents

systemic IL-6 signalling. **b**, Under acute and chronic inflammatory conditions, the buffer system is overloaded and allows systemic IL-6 trans-signalling. **c**, Therapeutic application of sgp130Fc (soluble gp130–Fc fusion protein) under acute and chronic inflammatory conditions reinforces the buffer system and prevents systemic IL-6 trans-signalling. Coloured shapes have the same meanings as in Fig. 4.

Next-generation inhibitors of IL-6 trans-signalling

Considering that sgp130Fc is derived from the common signal-transducing gp130 receptor used by many members of the IL-6 cytokine family⁷⁶, it is no surprise that the inhibitory activity of sgp130Fc extends to other family members. This includes IL-11, a cytokine that affects physiological processes including haematopoiesis¹¹⁸, thrombopoiesis¹¹⁹, bone metabolism¹²⁰, plasma cell proliferation¹²¹ and T cell-dependent development of antibody-producing B cells²⁵. Protective effects of IL-11 were described following myocardial infarction^{122,123}, stroke¹²⁴ and during tissue regeneration¹²⁵. However, IL-11 also promotes gastric cancer¹²⁶, and recent work suggests a crucial role of IL-11 in promoting cardiac³⁷, kidney³⁷, liver^{127–129} and lung fibrosis¹³⁰. In analogy to the sIL-6R, a soluble form of the IL-11R (sIL-11R) has been detected in human serum¹⁹. The sIL-11R has also been detected in tumour tissue from patients with gastric cancer and mouse models of this disease¹³¹, which suggests that IL-11 trans-signalling operates *in vivo*. Furthermore, IL-11 trans-signalling was demonstrated to be induced by the designer cytokine hyper-IL-11 or by naturally occurring IL-11–sIL-11R complexes^{15–19}. However, definitive pathophysiological roles for IL-11 trans-signalling that are distinguishable from IL-6 trans-signalling *in vivo* remain elusive, the complexities of which might be compounded by differential expression patterns of mIL-11R and mIL-6R. Although only a few cell types express mIL-6R at high levels and all other cell types have either low or no mIL-6R expression at all, the distribution of mIL-11R throughout the body appears to be more balanced. When many cell types already respond to classic signalling, it is difficult to demonstrate an (additional) functional role for trans-signalling.

Importantly, the activity of other gp130-dependent cytokines including OSM, LIF and IL-27 can only be inhibited by more than 100 times higher concentrations of sgp130Fc than those needed to inhibit IL-6 trans-signalling^{94,132}. The promiscuous inhibitory effect of sgp130Fc on several IL-6 family cytokines suggests that its therapeutic use may inadvertently induce side effects. For instance, targeting pathological IL-6 trans-signalling with sgp130Fc could simultaneously inhibit homeostatic and protective functions of other IL-6 family members, such as IL-11. However, it is notable that treatment of patients with IBD with the sgp130 variant olamkcept was found to be safe and efficacious in the above-mentioned phase 2 clinical trials¹¹³.

A solution to limiting potential side effects in disease states in which only targeting of pathological IL-6 trans-signalling is desired may be provided by second-generation sgp130Fc variants (Fig. 6). One such variant, sgp130^{FLY}Fc, was generated by the substitution of amino acids Q113F or T102Y, Q113F and N114L (FLY) at site III of sgp130Fc. The sgp130^{FLY}Fc variant showed enhanced binding affinity for hyper-IL-6 and more potently inhibited IL-6 trans-signalling, but showed strongly diminished inhibition of IL-11 trans-signalling^{15–17}. Interestingly, a gp130 single-nucleotide polymorphism (SNP) (842G>A) – encoding an R281Q substitution at site IIb in the protein – was observed in a patient presenting with craniofacial malformations. This mutation has been associated with selective abrogation of IL-11-mediated responses but intact responses of other gp130-dependent cytokines (including IL-6, IL-27, OSM and LIF)¹³³. Importantly, this discovery guided engineering of the R281Q substitution in sgp130Fc, which selectively augmented specificity for IL-6 inhibition to a level comparable to that observed for the sgp130^{FLY}Fc variant. Moreover, the combination of R281Q and FLY mutations in another sgp130Fc variant, sgp130^{FLYR}Fc, completely abrogated its inhibitory effects on IL-11 trans-signalling without impacting inhibition of IL-6 trans-signalling¹⁶.

The third generation of trans-signalling inhibitors use alternative overall structural assemblies. Cs130Fc is a chimeric sgp130 molecule containing the cytokine-binding domains D1–D3 of gp130 fused to a noninhibitory single-domain antibody (nanobody, VHH) recognizing an intermolecular, nonlinear epitope of the IL-6–sIL-6R complex, along with the human IgG1 Fc fragment¹⁵. Compared to sgp130Fc, cs130Fc is smaller (185 kDa versus 240 kDa), displays enhanced specificity for inhibition of IL-6 trans-signalling (2-fold improved IC₅₀ for IL-6 trans-signalling inhibition, 8-fold reduction in activity against IL-11 trans-signalling), and can be produced without the Fc fragment as an even smaller fully active 75-kDa molecule to enhance bioavailability and tissue penetration (Fig. 6). The improved binding kinetics (mainly *k_{off}*-rate) and overall activity of cs130Fc relative to the first-generation sgp130Fc is due to its high affinity for the IL-6–sIL-6R complex (mediated via the single-domain antibody VHH6) leading to a more stable association with IL-6 trans-signalling complexes than sgp130Fc¹⁵. The potential to further augment the selective inhibitory actions of cs130Fc on IL-6 trans-signalling has been indicated by the incorporation of site III FLY mutations into cs130Fc to generate cs130^{FLY}Fc, which enhanced IL-6 trans-signalling blockade by 3-fold versus sgp130Fc, whereas inhibitory effects on IL-11 trans-signalling were completely abrogated¹⁵.

Despite the advantages of selectively applying sgp130Fc or its next-generation derivatives in inflammation-associated diseases (including cancer) in which IL-6 trans-signalling contributes to disease pathogenesis, it is likely that other cytokines (for example, TNF, IL-1, IL-17 and IL-23) and/or growth factors (such as TGFβ and amphiregulin) concurrently drive such disease states⁸. Therefore, the blockade of IL-6 trans-signalling in concert with other known molecular drivers of the disease may provide a more favourable clinical outcome than targeting IL-6 trans-signalling alone. For instance, in mouse models of colitis, rheumatoid arthritis and allergic asthma, simultaneous inhibition of IL-6R and TNF proved more effective than single-target-directed treatment^{69,134,135}. Similarly, dual blockade of IL-6 and IL-17 signalling using a bispecific antibody demonstrated increased efficacy in inflammatory disease models compared to IL-6 or IL-17 blockade alone¹³⁶.

Dysregulated IL-6 signalling is a hallmark of infections, including SARS-CoV-2, that are characterized by hyperinflammation^{137–145}, with high IL-6 levels in patients with COVID-19 being implicated in the depletion of CD4⁺ T cells, CD8⁺ T cells and natural killer cells¹⁴⁶. Moreover, recent evidence suggested a key role of IL-6 trans-signalling, but not classic signalling, in the development of hyperinflammatory states in severe COVID-19^{138,141,142}, resulting in respiratory failure and multi-organ damage¹³⁷. Indeed, increased ADAM17-mediated IL-6R shedding was observed in epithelial cells following SARS-CoV-2 infection or upon overexpression of spike protein, accelerating the inflammatory spiral¹⁴². Interestingly, studies on CAR T cell-induced hyperinflammation suggested a rate-limiting role of sIL-6R serum concentrations¹³⁸. COVID-19-induced dysregulated IL-6 trans-signalling seems to be associated with liver damage¹⁴¹ and abnormalities in the coagulation cascade, including increased tissue factor, thrombin and platelet activity^{147–149} finally leading to endothelial dysfunction¹⁴⁷ and immunothrombotic processes¹⁵⁰. Such IL-6 trans-signalling-mediated increases in coagulation factors were efficiently inhibited by sgp130Fc in liver sinusoidal endothelial cells¹⁴¹. These findings, coupled with accumulating evidence that the IL-6R-targeted antibodies tocilizumab and sarilumab demonstrated beneficial effects on survival rates in severe COVID-19 cases^{151–154}, have led to the generation of a bispecific functionalized sgp130Fc variant, c19s130Fc (Fig. 6). This sgp130 variant is composed of cs130Fc functionalized with an additional neutralizing

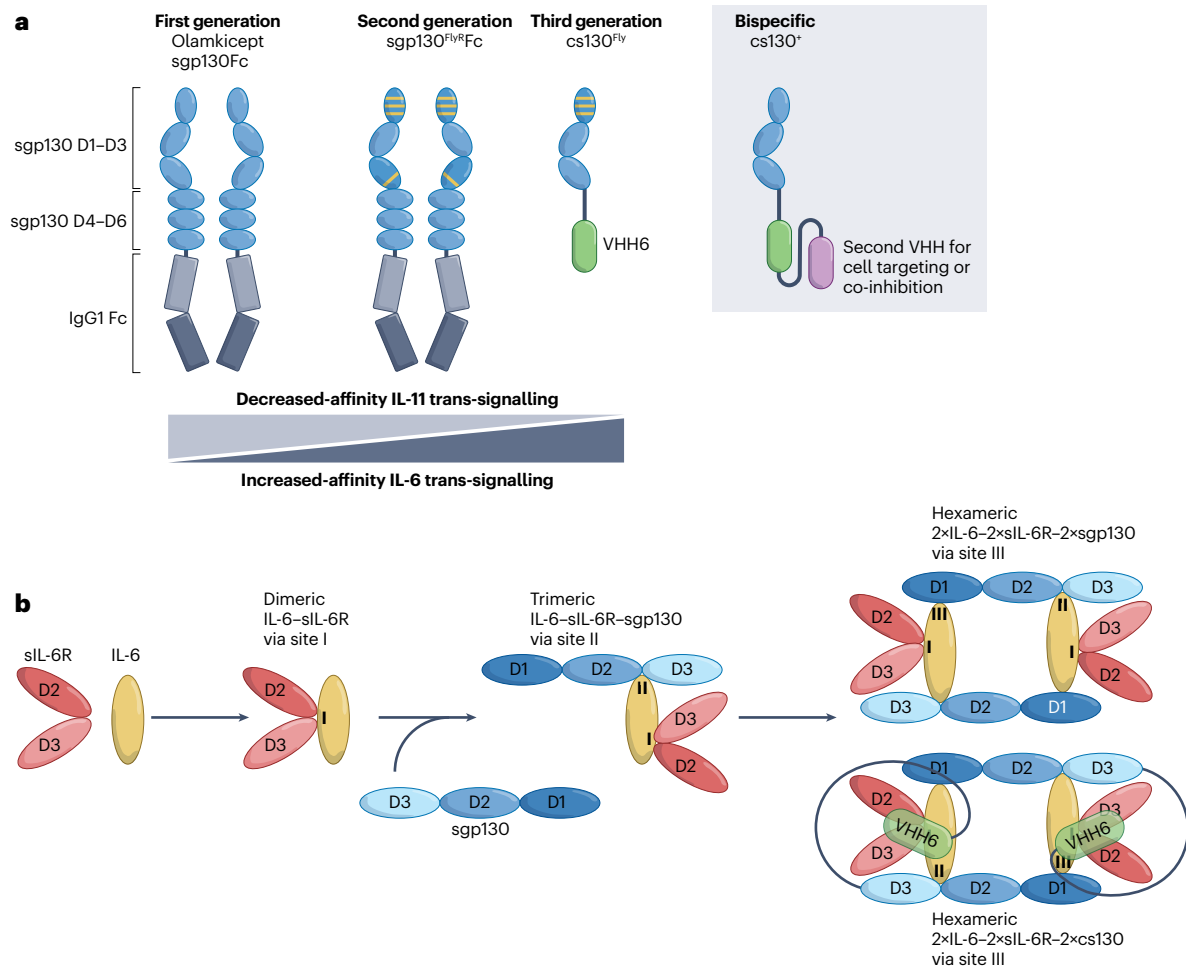


Fig. 6 | Next-generation IL-6 trans-signalling inhibitors. **a**, First-generation sgp130Fc (soluble gp130–Fc fusion protein) is composed of domains D1–D6 of glycoprotein 130 (gp130; blue) fused to a human IgG1 Fc (grey). The first-generation trans-signalling inhibitor efficiently inhibits interleukin-6 (IL-6) and IL-11 trans-signalling and, with lower efficiency, oncostatin M (OSM) and leukaemia inhibitory factor (LIF) signalling. The second-generation sgp130 variants have improved IL-6 trans-signalling activity and/or reduced effects on the signalling of IL-11, LIF and OSM. Point mutations in domains D1 and D3 that improve the activity and specificity of sgp130Fc are indicated by yellow lines. Third-generation inhibitors such as chimeric soluble gp130 (cs130) are composed of the domains D1–D3 of gp130 (blue) fused to the single-domain

antibody VHH6 (green), an antibody to the complex of IL-6 and soluble IL-6 receptor (IL-6–sIL-6R) (yellow and red). Bispecific cs130* variants are based on cs130 fused to VHH6 and a second nanobody (purple) enabling additional functions including SARS-CoV-2-neutralization, inhibition of other inflammatory cytokines or cell-specific targeting. **b**, Proposed tetrameric and hexameric assembly mode of sgp130 and cs130 with IL-6–sIL-6R complexes. According to Boulanger et al.²⁴, the initial trimeric complex of gp130 and IL-6–sIL-6R is formed between site IIa of IL-6, site IIb of IL-6R and domain D2–D3 of gp130. Subsequently, hexameric complexes are formed by binding of two trimeric IL-6–sIL-6R–sgp130 complexes via site IIIa of IL-6, site IIIb of IL-6R and domain D1 of gp130.

single-domain antibody to the SARS-CoV-2 spike protein, yielding an IL-6 trans-signalling inhibitor with high binding affinity for both IL-6–sIL-6R complexes and the SARS-CoV-2 spike protein¹⁵⁵. Importantly, c19s130Fc was shown to inhibit SARS-CoV-2 infection of cells and to improve the therapeutic efficacy of sgp130Fc, indicating that c19s130Fc may provide synergistic therapeutic effects on containing viral infection and the resulting hyperinflammation. Collectively, these observations pave the way for future approaches involving bispecific biologics that target IL-6 trans-signalling and other inflammatory cytokines, such as IL-1 and TNF.

Moreover, the multifunctional type I transmembrane inflammatory protease ADAM17 has emerged as a key regulator of the ectodomain

shedding of more than 80 known membrane-tethered substrates, including IL-6R^{156,157}. ADAM17 is expressed in most tissues as a catalytically inactive full-length precursor that is predominantly stored in the endoplasmic reticulum. Although the transcriptional regulation of ADAM17 is static in both physiological and pathological settings, the mechanisms governing ADAM17 surface expression as a mature and biologically active enzyme are complex and remain to be fully elucidated: they involve a series of steps including the cleavage by the furin convertase of the autoinhibitory ADAM17 N-terminal pro-domain in the Golgi apparatus, which triggers its transport to the cell membrane that is dependent on the iRhom intramembrane rhomboid proteases^{157–160}. Considering that upregulated production of sIL-6R and other processed ADAM17 substrates, in particular

TNF and EGFR ligands (for example, TGF α and amphiregulin), is a feature of numerous inflammatory conditions (for example, colitis, rheumatoid arthritis, sepsis and pancreatitis) and cancers (such as colorectal, lung and pancreatic cancers), ADAM17 presents as an attractive therapeutic target to simultaneously block inflammatory IL-6 trans-signalling and co-existent disease-associated ADAM17-regulated pathways^{69,101,102,161–169}. This notion is supported by recent studies employing ADAM17-neutralizing monoclonal antibodies that act via several modalities, including allosteric perturbation of the binding ability of its catalytic active site, or steric hindrance leading to competitive or noncompetitive inhibition of protein substrate binding^{170,171} (Fig. 5b). In mouse models of pancreatic ductal adenocarcinoma or polymicrobial sepsis, the selective antibody-mediated blockade of ADAM17 suppressed the onset and/or progression of disease^{172,173}. Curiously, circulating sIL-6R levels were either unchanged or not investigated in these studies, raising the questions as to whether such antibody-mediated targeting of ADAM17 will be sufficient to indirectly block IL-6 trans-signalling in these disease settings, and whether other IL-6R sheddases, such as ADAM10¹⁷⁴ or meprin- α/β ¹⁷⁴, can substitute for ADAM17 activity.

Importantly, an alternative therapeutic strategy against ADAM17 to target IL-6 trans-signalling has arisen via the autoinhibitory N-terminal pro-domain of ADAM17 (Fig. 4), which serves as a powerful template to generate a recombinant protein that selectively blocks ADAM17 biological activity with high affinity¹⁷⁵. The pro-domain of ADAM17 is an independent folding unit comprising ~200 amino acids, which specifically interacts with and inhibits the catalytic domain of ADAM17. Indeed, the ADAM17 pro-domain inhibitor (A17pro), engineered as a stable recombinant protein, exhibits robust therapeutic efficacy in numerous preclinical mouse inflammatory disease and inflammation-associated cancer models, including rheumatoid arthritis, IBD, sepsis, acute pancreatitis, kidney fibrosis and lung adenocarcinoma^{161,167,175,176}. Notably, in acute pancreatitis and lung adenocarcinoma, sIL-6R was the predominant substrate employed by ADAM17 for its pathological activity, and in the preclinical *Kras*^{G12D} lung adenocarcinoma mouse model, A17pro exhibited greater anticancer activity than sgp130Fc^{166,167}. These observations suggest that inhibitor-based targeting of the ADAM17 protease may provide an effective rationale for targeting inflammatory IL-6 trans-signalling in certain disease settings. From a clinical and safety perspective, it is noteworthy that the above-mentioned ADAM17 pro-domain and antibody-based inhibitors are highly selective for ADAM17, and are therefore advantageous compared to earlier small-molecule inhibitors against ADAM17, which also targeted other related proteases (for example, ADAM10) leading to an unfavourable toxicity profile in the clinic¹⁷⁷.

Conclusions and future prospects

Today, IL-6 trans-signalling is recognized as a biologically important independent pathway of cytokine receptor activation. This has led to the clinical development of the first selective inhibitor of IL-6 trans-signalling – olamkicept – as well as to the next-generation inhibitors that we have discussed above. Virtually all cells of the body are responsive to IL-6 trans-signalling. In our opinion, this finding is key to explaining the incredibly far-reaching role of IL-6 in autoimmune diseases, chronic inflammatory conditions and cancer. For more than a decade, antibodies and small molecules that block global IL-6 signalling have served as therapeutic gold standards. However, we will soon know whether selective targeting of IL-6 trans-signalling by olamkicept can show therapeutic benefit while reducing the side effects typically observed with current anti-IL-6 therapies.

In the Western world, at least 0.5% of people have IBD¹⁷⁸. Although some biologics have entered the clinic, anti-TNF therapeutics still dominate the treatment regimen for IBD. Therefore, it might seem obvious to select IBD for the first phase II clinical study of olamkicept. In truth, this was a risky decision because IL-6 and IL-6R antibodies failed in phase II clinical trials for IBD due to intolerable side effects, including intestinal perforations^{179,180}, which were also observed for anti-IL-6R therapy for rheumatoid arthritis¹⁸¹. A possible explanation is that classic IL-6 signalling via mIL-6R is involved in the intestinal regeneration response, which is largely blocked in IL-6 knockout mice¹⁸² as well as by IL-6 and IL-6R antibodies^{180,183,184}. However, this regenerative response is not affected when only IL-6 trans-signalling is inhibited, as IL-6 activities via mIL-6R are not affected by olamkicept¹⁰⁷. Alternatively, it might be that the anti-IL-6 or anti-IL-6R antibodies lead to reduced T_H17 responses, which are required for barrier function in the intestine. Blocking IL-17

Glossary

ADAM

(A disintegrin and metalloproteinase). Proteases in a family of single-pass transmembrane proteins structurally related to snake venom disintegrins that contain both catalytic inactive and active members; in particular, ADAM10 and ADAM17 have been characterized over the last decades as the principal proteases for important membrane-anchored proteins such as EGFR ligands, Notch receptors, IL-6R and TNF.

Castleman disease

A spectrum of heterogeneous lymphoproliferative disorders characterized by common lymph node histopathologic features (including abnormal germinal centre architecture with prominent follicular dendritic cell), with IL-6 overproduction considered as a key mechanism (particularly for multicentric Castleman disease).

Cerulein

A oligopeptide of ten amino acids long that shows homology to cholecystokinin, stimulates smooth muscle cells and is used to induce pancreatitis in experimental animal models.

Listeria monocytogenes

A facultative anaerobic, Gram-positive bacterium that reproduces inside the host cells and, when ingested via contaminated food, causes the human disease listeriosis, a severe illness characterized by meningitis, encephalitis and sepsis.

Single-domain antibody (nanobody)

An antibody fragment consisting of a single monomeric variable domain (VH) naturally occurring in the Camelidae family or synthetically derived from the heavy chain of an antibody, combining high antigen affinity with the absence of complement-dependent or cell-mediated cytotoxicity due to the lack of a constant (Fc) region.

STAT3

(Signal transducer and activator of transcription 3). A transcription factor that is latent associated with the signal-transducing β -receptor gp130 and translocates to the nucleus after being phosphorylated at tyrosine 705 in response to several cytokines and growth factors, including IL-6 and IL-11.

TNF

(Tumour necrosis factor). A transmembrane protein that can act as either a pro-inflammatory cytokine or an important adipokine that promotes insulin resistance, which can further either be cleaved into a soluble form and signal pro-inflammatory and apoptotic via TNFR1, or act as a membrane-bound cytokine anti-inflammatory and cell proliferation-promoting fashion mainly through signalling via TNFR2.

activity with the antibody secukinumab indicated that IL-17 exhibits protective functions in the intestine¹⁸⁵.

We have also delineated second-generation and third-generation therapeutics, based on size-reduced IL-6-selective trans-signalling inhibitors or ADAM17-specific inhibitors with increased bioavailability compared to olamkicept. With the introduction of IL-6 trans-signalling-selective point mutations in sgp130Fc and the size-reduced cs130Fc, inhibition of IL-11 trans-signalling was abrogated. It will be interesting to see whether IL-11 affinity-increasing mutations will lead to IL-11 trans-signalling-selective sgp130 variants, which are needed to identify IL-11 trans-signalling-driven diseases in vivo. The IL-6-sIL-6R binding VHH6 nanobody, which we used in cs130Fc, showed that composite epitopes exist, making the generation of inhibitory trans-signalling nanobodies another future prospect. Size-reduced trans-signalling inhibitors will ease the generation of bispecific drugs, for instance to simultaneously block IL-6 trans-signalling and TNF signalling or enable cell-type-restricted inhibition of IL-6 trans-signalling. This, however, also comprises strategies for the cell-type-restricted abrogation of IL-6R shedding to specifically prevent the local production of inflammatory sIL-6R. Despite the obvious focus on the clinical utility of targeting IL-6 trans-signalling, we also note that in the future, it will be of interest to generate a selective IL-6 classic-signalling inhibitor, not only as a tool but eventually leading to alternative clinical applications.

With respect to pharmacokinetics and pharmacodynamics, we realized from our mouse studies that far less sgp130Fc was needed to completely block IL-6 trans-signalling than to inhibit global IL-6 signalling. Albeit not addressed in the initial phase II clinical studies, this might open up the appealing opportunity to eventually reduce olamkicept dosing for patients who experience an unfavourable ratio of therapeutic benefit to side effects. Moreover, only limited dosing of sgp130 was able to prevent fatal sepsis in mice¹⁸⁶, independently suggesting that lower amounts of sgp130 in comparison to standard antibody doses might be beneficial and should be included in future clinical trial design, once olamkicept has been approved for therapy.

We consider the role of endogenous sgp130 as a safety system to limit overshooting systemic IL-6 trans-signalling activities (see Box 1 and Fig. 5). From this, it follows that therapeutic sgp130Fc assists the natural solution to overshooting local IL-6 trans-signalling. Therefore, limiting the pharmaco-dosing practically may define sgp130Fc as a pioneer in the development of natural therapeutics.

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Author contributions

The authors contributed equally to all aspects of the article.

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C.G. has received a research grant from Corvidia Therapeutics (Waltham, MA, USA) and has acted as a consultant/speaker for AbbVie and NovoNordisk. J.M.M. and J.S. declare that they have applied for a patent covering cs130Fc and c19s130Fc. J.M.M. has acted as a consultant for Ferring Pharmaceuticals. S.R.-J. has acted as a consultant and speaker for AbbVie, Chugai, Genentech Roche, Regeneron, Pfizer and Sanofi. He also declares that he is an inventor on patents owned by CONARIS Research Institute, which develops the sgp130Fc protein olamkcept together with Ferring Pharmaceuticals and I-Mab Biopharma. S.R.-J. has stock ownership in CONARIS. B.J.J. declares no competing interests.

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