Unravelling the broader complexity of IL-6 involvement in health and disease

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Highlights–

1. IL-6 controls tissue and immune homeostasis in both health and disease.
2. The IL-6 signalling cassette is complex and regulated at multiple levels.
3. IL-6 controls immune regulation, cell metabolism, neuroendocrine function, pain, tissue repair and regeneration, and psychological wellbeing.
4. Specific genetic mutations identify important roles for IL-6 in human physiology.
5. Biological drugs used to inhibit IL-6 in pathophysiology target disease processes and the wider aspects of IL-6 bioactivity.

Abstract–

The classification of interleukin-6 (IL-6) as a pro-inflammatory cytokine undervalues the biological impact of this cytokine in health and disease. With broad activities affecting the immune system, tissue homeostasis and metabolic processes, IL-6 displays complex biology. The significance of these involvements has become increasingly important in clinical settings where IL-6 is identified as a prominent target for therapy. Here, clinical experience with IL-6 antagonists emphasises the need to understand the context-dependent properties of IL-6 within an inflammatory environment and the anticipated or unexpected consequences of IL-6 blockade. In this review, we will describe the immunobiology of IL-6 and explore the gamut of IL-6 bioactivity affecting the clinical response to biological drugs targeting this cytokine pathway.

Keywords: Cytokines, biological drugs, inhibition, inflammation, health, disease

1. Introduction–

Initially described as a cytokine involved in the control of lymphocyte and hepatic responses, the activities of IL-6 now extend beyond these early definitions. Besides the involvement of IL-6 in innate and adaptive immunity, IL-6 elicits broad-reaching effects on various physiological processes. These include impacts on tissue homeostasis, metabolism, neuroendocrine function, fatigue, and mental wellbeing (Figure-1)[1-8]. Thus, IL-6 is a truly pleiotropic cytokine, and biological drugs inhibiting IL-6 in pathophysiology often alters the physiological regulation of these processes[9-15]. In this review, we will explore the properties of IL-6 in health and disease by offering a perspective of IL-6 biology beyond its role in immune regulation.

Characterisation of the IL-6-like cytokine system in Drosophila melanogaster identifies roles for this ancestral pathway in development, tissue homeostasis, metabolism, and innate immunity (Figure-1)[16-19]. These functions echo those described for IL-6, and other members of the IL-6 cytokine family, in higher mammals and humans[9,12,20]. For example, studies of murine macrophages and Drosophila plasmacytes identify roles for IL-6 (unpaired-3 in Drosophila) in glucose metabolism, with mouse models evidencing the ability of IL-6 to promote glucose intolerance and resistance to obesity-driven changes in insulin sensitivity[21,22]. Here, the capacity of IL-6 to engage a receptor system that signals *via* specific Janus-activated kinases (Jak) and members of the Signal Transducer and Activator of Transcription (STAT) family help explain how cells sense and interpret cytokine cues to elicit alternate functions or cell-specific responses[20,23,24]. In this regard, the expression and bioactivity of IL-6 are tightly regulated, ensuring both its physiological involvement in homeostasis and rapid induction following immune challenge.

Almost all haematopoietic and non-haematopoietic cells express IL-6, with changes in gene regulation occurring in response to various inflammatory stimuli. These include cytokines (e.g., IL-1β, TNFα, IL-17), Toll-like receptor agonists, prostaglandins, adipokines and cellular stress[12,20]. Serum IL-6 levels in humans are typically low (1-5 pg/ml). However, physiological levels of IL-6 rapidly increase following infection, trauma, or injury to reach quantities in the high ng/ml or μg/ml range[25]. The regulation of IL-6 gene expression occurring via a complex array of intracellular and extracellular factors, which help to limit IL-6 bioavailability or contain IL-6 bioactivity[12]. For example, microRNAs (e.g., let-7a), RNAases and RNA-binding proteins (e.g., regnase-1, Arid5a, Lin28B). IL-6 expression is also subject to coordinated circadian rhythms, including seasonal variations in IL-6 bioavailability between winter and summer months[26-31].

Moreover, circulating IL-6 levels often provide an index of systemic inflammation in infection, autoimmunity, and cancer, and increases in IL-6 frequently contribute to cytokine response syndromes and associated patient mortality[32,33]. In this regard, IL-6 is often a better predictor of disease activity than C-reactive protein[34-37]. Consequently, is IL-6 a biomarker of systemic inflammatory or a primary driver of pathophysiology? The clinical benefits associated with biological drugs that target IL-6 or its receptor are significant and identify IL-6 as a keystone cytokine responsible for evolving or maintaining adverse inflammatory reactions[11-13,38]. However, these therapies are not always successful, and patients with the same underlying disease often show differing therapeutic responses, and IL-6 blockade is not suitable for all diseases[39-41]. Building on the narrative of several excellent reviews of IL-6 biology in disease[6,9-13,20,38,42-44], we will now discuss the broader actions of IL-6 to offer some thoughts on the context-dependent properties of IL-6 in health and disease.

2. The IL-6 signalling cassette–

The composition and biological activities of the IL-6 receptor has been described elsewhere[24,45-48]. Briefly, the IL-6 receptor comprises an 80kDa type-1 cytokine receptor subunit (IL-6R, CD126) and a 130kDa signal-transducing receptor subunit (gp130, CD130; encoded by IL6ST). The binding of IL-6 to IL-6R facilitates a ligand-dependent interaction with gp130, with structure-function studies predicting that a signalling IL-6 receptor requires an IL-6-IL-6R-gp130 complex arranged in a dimer structure (termed classical IL-6 receptor signalling) (Figure-2A)[45,46,48].

Although initially characterised as the signalling subunit of the IL-6 receptor, gp130 also functions as the β-cytokine receptor for IL-11, IL-27, oncostatin-M, ciliary neurotrophic factor, leukaemia inhibitory factor, cardiotrophin-1, and cardiotrophin-like cytokine[9,20,49]. All cells of the body express gp130. While deletion of *gp130* in mice results in embryonic lethality, the introduction of genetic mutations into the gp130 sequence identify essential roles in development, haematopoiesis, tissue homeostasis, cell survival and growth, and immune regulation[9,20,49]. In contrast, IL-6R is more restricted in its cellular expression. Cells expressing IL-6R include leukocytes, hepatocytes, megakaryocytes, and certain mesenchymal cells[9,20,49]. While *Il6ra*$^{-/-}$ and *Il6*$^{-/-}$ mice are viable[50-52], these mice show differences in wound healing, susceptibility to colitis and alterations in glucose tolerance[22,53-55]. These phenotypic differences have raised questions about potential alternate ligands for IL-6R. Ligands that display a low affinity for IL-6R include ciliary neurotrophic factor, p28IL-27 (IL-30) and heterodimeric cytokine-like factors[12,56-59]. Conversely, IL-6 reportedly binds CD5

to amplify STAT3 signals in mouse tumour models[60]. The relevance or biological need for these additional interactions is not overtly obvious and requires further investigation.

The cellular expression of a specific receptor system typically shapes the biological functions of a cytokine[61]. However, the discovery of a soluble IL-6R (sIL-6R) in human urine and plasma and the identification that IL-6 binding to sIL-6R creates an agonistic complex capable of triggering gp130 signalling (termed IL-6 trans-signalling) has added to the mystic surrounding IL-6 biology (Figure-2A)[49,62-64]. In this regard, the IL-6-sIL-6R complex resembles a heterodimeric cytokine (e.g., IL-12, IL-23, IL-27) and sIL-6R shares close sequence identity with IL-12p40 and EBI3[65,66]. There is now a large body of research demonstrating the regulation of sIL-6R in inflammation. Investigations in various mouse models describe central roles for IL-6 trans-signalling in colitis, tissue fibrosis, allergy, infectious disease, arthritis, cancer-associated inflammation, neuroinflammation and vascular disease[51,67-85].

Beyond the characterisation of classical IL-6 receptor signalling and IL-6 trans-signalling, a recent report described a mode of IL-6 signalling termed IL-6 trans-presentation[86]. Mechanistically equivalent to a form of signalling described from IL-15, IL-6 trans-presentation may arise in immune privileged sites where the cellular presentation of IL-6 and IL-6R to a neighbouring gp130-positive cell type supports local immune reactions (Figure-2A)[86,87]. Further work is still required to identify the significance of IL-6 trans-presentation in health and disease.

3. Contextualisation of IL-6 activities in disease–

Cytokines quintessentially deliver cellular signals affecting proliferation, differentiation, survival, and cell type-specific effector functions[61]. These broad activities epitomise the contribution of IL-6 to infectious disease, cancer, and immune-mediated inflammatory diseases. Interleukin-6 often receives bad press in these settings. Here, the benefits afforded by blocking IL-6 in clinical settings endorse the pro-inflammatory attributes of this cytokine. It is easy to forget that IL-6 contributes to protective immunity (e.g., B-cell antibody production) and control of inhibitory signals essential for the dampening of innate immunity (e.g., deactivation of macrophage responses). These activities are essential for anti-microbial host defense[12,22,50,88,89]. Thus, IL-6 involvement in disease progression typically arises through distortion or skewing of these processes, altering the course of innate and adaptive immunity and a transition towards inflammation-induced tissue damage. This level of complexity potentially explaining the mixed patient outcomes reported with IL-6 blocking

therapies in SARS-CoV2 infections[32]. Several excellent articles have recently reviewed the role of IL-6 in disease[6,9-13,20,38,42-44]. To support the narrative in the forthcoming sections, we will focus on some key features of IL-6 receptor signalling relevant to the subsequent discussion (Figure-2B).

Cells sense and interpret IL-6 signals through receptor-associated cytoplasmic tyrosine kinases (Jak-1, Jak-2, and non-receptor tyrosine-protein kinase 2 [Tyk2]) and signalling intermediates downstream of the tyrosine-protein phosphatase SHP2. The activation of Jak-1, Jak-2 and Tyk2 affecting distinct patterns of tyrosine and serine phosphorylation linked with control of the activation of latent transcription factors (namely, STAT1, STAT3 and to a lesser extent STAT5)[20,24]. In contrast, SHP2 promotes activation of the Ras-Raf pathway and the Src-YAP-Notch pathway, regulating transcriptional activators including NF-IL-6 (a CAAT-enhancer binding protein; C/EBP), activator protein 1 (AP-1) and mitogen-activated protein kinases (MAPKs)[34,44,90]. Receptor activation of the Ras-Raf pathway primarily controls IL-6 responses affecting proliferation, differentiation, and tissue regeneration (Figure-2B)[20,47,91]. However, most of the biological activities assigned to IL-6 occur through activation of Jak-STAT signalling and the transcriptional properties of STAT1 and STAT3. Genetic ablation studies emphasising the importance of these transcription factors in determining haematopoiesis, immune cell recruitment, activation and survival, and stromal cell responses affecting tissue remodelling and chronic disease progression (Figure-2B)[20]. In this regard, the transcriptional output of STAT1 and STAT3 often provides valuable insights into the role of IL-6 in autoimmunity and cancer, and their activities serve as clinical predictors of patient outcomes.

4. IL-6 in tissue homeostasis, regeneration, and repair–

Experience with IL-6 antagonists in the clinic illustrates that these therapies are less successful in indications affecting barrier surfaces[12,20,39]. Patients with IL-6 autoantibodies or genetic mutations affecting the IL-6 receptor cassette or associated Jak-STAT pathway also develop complications at barrier surfaces. These include subcutaneous abscesses, staphylococcal cellulitis, and eczematoid dermatitis[92-98]. Some of these mutations also promote connective tissue abnormalities and immunedeficiencies[96-99]. For patients receiving IL-6 blocking drugs, infections typically occur at epithelial surfaces and mucosal barriers, and gastric perforations and the associated incidence of diverticulitis are significant clinical considerations when applying these therapies[20,38,39]. These clinical phenotypes evidence the importance of IL-6 in maintaining barrier immunity and tissue homeostasis.

Various studies identify roles for IL-6 in maintaining tissue homeostasis. These include activities that affect adipose tissues, bone turnover, liver regeneration, haematopoiesis, neurones, and epithelial barriers. Most of these involvements originate from the capacity of IL-6 to control cellular proliferation, differentiation, or survival. The ability of IL-6 to promote hepatocyte proliferation epitomises these activities, contributing to liver regeneration following hepatic injury[100,101]. A similar scenario exists in the bone. Here, IL-6 promotes osteoclastogenesis through the regulation of RANK ligand and osteoprotegerin essential for bone formation[102]. Indeed, IL-6 levels and IL6 polymorphisms often impact bone mineral density during inflammatory disease[103]. Similar changes occur in mice where Il6 deficiency results in impaired bone remodelling[104-106]. *Il6*$^{-/-}$ mice display marked protection from osteopenia and postmenopausal bone loss following oestrogen depletion[104]. Extending these findings to mucosal barrier surfaces, IL-6 maintains the functional integrity of epithelial surfaces[107-109]. These latter observations explain the increased susceptibility of gastric perforations seen in patients on IL-6 therapy[110]. It is, therefore, apparent that IL-6 plays a pivotal role in governing stromal tissue physiology essential for immune homeostasis and barrier immunity. For example, through influences on the cell properties and effector characteristics of resident tissue and inflammatory infiltrating immune cells. These functions illustrate how IL-6 activities encourage communication between the stromal tissue compartment and the immune system. In this regard, IL-6 supports a transition from innate to adaptive immunity[12,44,68,111,112]. Thus, the impact of IL-6 on tissue homeostasis and barrier immunity often appears intrinsically connected. In wound healing and fibrosis, IL-6 coordinates inflammation, proliferative signals, and the remodelling of extracellular matrix[77,113-118]. Compromised IL-6 signalling frequently contributing to aberrant healing and tissue scaring in patients[119-121]. A similar scenario occurs in atopic dermatitis. Here, IL-6 affects the expansion of IL-4 and IL-13-secreting Th2 CD4+ T cells and changes in IL-22Rα on keratinocytes[122,123]. The mechanistic involvement of IL-6 in atopic dermatitis is not fully understood. Clinical trials of atopic dermatitis show that tocilizumab improved erythema, induration, excoriation and lichenenifcation[124]. However, the study also noted an increase in bacterial skin infections in the treatment group. Thus, supporting a role for IL-6 in both barrier immunity and the maintenance of tissue integrity.

In this regard, IL-6 antagonists typically fail in disease settings where IL-6 controls the physiological maintenance of tissue homeostasis. IL-6 blockade occasionally exacerbating the symptoms of any pre-existing condition. These include diseases of the skin (e.g., psoriasis), gut (e.g., Crohn's disease), and ankylosing spondylitis[39,125-128]. However, in these inflammatory settings, IL-6 still contributes to

the underlining pathology. For example, IL-6 activities in the gut lamina propria control the infiltration and maintenance of effector T-cells. Thus, contributing to diseases such as Crohn's disease, inflammatory bowel disease, ulcerative colitis, and diverticulitis[52,67,129-131]. Thus, IL-6 maintains the local inflammatory reaction by supporting the activities of other cytokines (e.g., TNFα, IL-4, IL-5, IL-13, IL-17, and IL-23), including those targeted for the treatment of diseases affecting the skin, gut, and lung. Currently, it is unclear how IL-6 coordinates the balance between tissue and immune homeostasis and the transition towards tissue injury and chronic disease within these clinical settings. Additional research addressing the balance of classical IL-6 receptor signalling versus IL-6 trans-signalling is anticipated[51,132-134]. A further consideration is also required to understand how IL-6 transmits signals via the Jak-STAT pathway[23]. Control of the intracellular cytokine signalling is complex, and subtle alternations in the delivery of STAT1 and STAT3 signals profoundly alters the transcriptional output of IL-6 in target cells[23,135,136]. Similar, chronic disease progression is often associated with episodic bouts of inflammation. These are likely to modify the way IL-6 contributes to pathology. Studies assessing the impact of recurrent inflammation show that IL-6 compromises tissue repair and drives fibrosis through the expansion of pro-fibrotic Th1 cells as a response to repeated inflammatory activation[77].

Investigations of IL-6 *trans*-signalling *in vitro* and *in vivo* first described activities responsible for leukocyte recruitment and adhesion[44,68,69,111,112]. Whilst these reports commonly identify mechanisms affecting the control of local tissue inflammation, the impact of IL-6 *trans*-signalling in endothelial cells, fibroblasts, and smooth muscle cells emphasises the importance of IL-6 in regulating vascular function[83,137-143]. Such activities impact endothelial dysfunction, complement activation and deposition, vascular calcification, coagulation, plaque formation, and the expression of inflammatory chemokines (e.g., CCL2) affecting atherosclerosis[112,143-148]. In this regard, genome-wide association studies and related Mendelian randomisation studies commonly identify genetic determinants of the IL-6 receptor cassette linked with cardiovascular risk[149-155]. These hallmarks may explain the systemic consequences of IL-6 bioactivity in chronic disease and associated multimorbidity[156-158]. For example, cardiovascular complications in COVID-19 patients[32].

5. Metabolism–

The pleiotropic functions of IL-6 include effects on lipids, glucose, iron, and mitochondrial bioactivity[12,20,159]. Patients receiving IL-6 antagonists often show clinical signs and symptoms

attributed to the disruption of these biochemical processes. For example, IL-6 reduces appetite, delays gastric emptying, decreases postprandial glycemia and regulates adiposity[160,161].

Interestingly, IL-6 activities are often enhanced by exercise or as a consequence of an active lifestyle[162-164]. Systemic changes in IL-6 following physical exercise affects glucose disposal and insulin sensitivity[165-167]. Patients on IL-6 antagonists frequently experience hyperlipidaemia and increased body mass[168-171]. Studies of maturity-onset obesity, hyperlipidaemia and insulin resistance in animal models highlight the importance of IL-6 in regulating these metabolic processes[172-174]. The administration of IL-6 in mouse models of obesity (e.g., high-fat diet) or type-2 diabetes led to reduced body mass, suppressed appetite, and improved insulin sensitivity *via* the production of glucagon-like peptide[175-178]. While the precise mechanisms involved require further investigation, changes in appetite and increases in energy expenditure may occur *via* IL-6 trans-signalling in the paraventricular nucleus of the hypothalamus[173,177]. Here, studies in cell type-specific *Il6*$^{-\backslash-}$ or *Il6ra*$^{-\backslash-}$ mouse models of obesity reveal the complexity of these cell and tissue-dependent mechanisms. Adipocyte-specific *Il6*$^{-\backslash-}$ mice demonstrate decreased adipose tissue inflammation and increased energy expenditure, with no effect on glucose tolerance or insulin sensitivity[179,180]. In comparison, myeloid-specific *Il6*$^{-\backslash-}$ or *Il6ra*$^{-\backslash-}$ mice develop increased insulin resistance, reduced energy expenditure, hepatic steatosis, and enhanced macrophage-driven inflammation of adipose tissues[22,179]. Moreover, T-cell specific *Il6ra*$^{-\backslash-}$ mice initially display improved insulin sensitivity and reduced adipose tissue inflammation that reverses over time, potentially due to compensatory IL-6 trans-signalling mechanisms[181].

IL-6 also regulates the master switch of iron homeostasis, hepcidin (Figure-3). Hepatic changes in hepcidin expression in response to IL-6 promote iron-restricted erythropoiesis and inflammatory anaemia during infection, autoimmune disease, and cancer[3,182,183]. IL-6 antagonism improves inflammatory anaemia in patients with rheumatoid arthritis, multicentric Castleman disease or undergoing haemodialysis[2,184,185]. These activities reflect the role of IL-6 as a hepatocyte stimulating factor that accounts for the control of acute phase reactants and serum lipids[186,187]. Studies in rheumatoid arthritis or patients with a high risk of atherothrombosis demonstrate that IL-6 inhibitors reduce various biomarkers of systemic inflammation or thrombosis. These include C-reactive protein, serum amyloid-A, haptoglobin, fibrinogen, secretory phospholipase A2, and lipoprotein-a[188,189]. Focussing more specifically on lipid metabolism, patients on tocilizumab typically display enhanced levels of low-density and high-density lipoprotein C[186]. Tocilizumab

intervention alters the lipid composition to lower cholesterol-associated biomarkers of cardiovascular risk[189]. These studies emphasise the potential benefit of IL-6 or IL-6R inhibition in cardiovascular disease and pulmonary arterial hypertension. However, reports of stroke, myocardial infarction and aneurysms following tocilizumab treatment in patients with Kawasaki disease or serious infections suggest that the underlining health status of a patient may ultimately influence the clinical outcome[190-192].

Integral to the IL-6 regulation of metabolic processes is its ability to regulate mitochondria bioactivity. These include influences affecting changes in oxidative capacity, reactive oxygen species production, calcium mobilisation and mitochondrial remodelling in response to obesity, type-2 diabetes, and cancer cachexia[172,193-197]. Again, we see interesting links with studies performed during exercise. Acute administration of IL-6 to trained athletes impairs performance and promotes chronic fatigue[198]. Here, IL-6 regulates glucose metabolism and hypothalamic neuropeptides involved in energy homeostasis[160]. Whilst much of this work has been conducted in healthy volunteers during normal physiology or exercise, the relevance of these discoveries to chronic diseases where patients suffering from debilitating fatigue requires further consideration. Future studies will establish how pathophysiology distorts the metabolic properties of IL-6.

6. Psychoneuroimmunology–

Patients with chronic disease or cancer suffer from complex clinical symptoms and comorbidities that influence their clinical management and long-term treatment. For a significant proportion of patients, chronic illness has a profound impact on their psychological wellbeing. Approximately 30-40% of patients display symptoms of depression, and patients with chronic illness frequently suffer with mental fatigue, anxiety, alterations in mood and insomnia[199,200]. These symptoms dramatically affect the quality of life of patients and significantly impact their long-term clinical outcomes. For example, medical outpatients with depression show almost twice as many days of restricted activity or missed work due to illness than patients without depression. Here, data from clinical trials and patient recorded outcomes support the view that inflammatory mediators activate processes affecting psychopathology and behaviour[199-207]. Studies in humans and rodents show that endotoxin administration promotes changes in cognitive function, social behaviour and anhedonia[199]. Patients with anxiety, major depressive disorders, schizophrenia, or neurodegenerative disease show similar behaviours[207]. Here, signs of acute psychosocial stress and depression, and feelings of fatigue, insomnia, and anger (or hostility) often correlate with systemic markers of inflammation[199-201,208].

These include cytokines, acute phase reactants, prostaglandins, and changes in lipid peroxidation and mitochondrial activity[199,201-206]. While these and other studies have identified new and exciting ideas on the development of psychopathology (e.g., alterations in endothelial blood-brain barrier function or metabolic dysfunction), the underpinning biology remains unclear[199-201].

Cytokines, including IL-6, control various hormone-like activities that are subject to tight circadian regulation during health[12,209]. These include seasonal variations and daily oscillations in circulating IL-6 and sIL-6R levels, which reflect physiological sleep patterns. Chronic illness and heightened systemic inflammation will distort these circadian processes to impact physical and mental wellbeing. These would be akin to the effects seen in shift workers and frequent flyers experiencing jet lag. Gross changes in sleep behaviours often contribute to non-communicable diseases[210,211]. These include systemic arterial hypertension, dyslipidaemia, and type-2 diabetes. Here, biological drugs, including adalimumab, etanercept and tocilizumab, often improve patient wellbeing in chronic disease[12,15,209,212,213]. For example, treatment of rheumatoid arthritis with IL-6 antagonists reduces symptoms of depression, fatigue, and anhedonia[214-216]. While the mode-of-action of these drugs and how they improve these patient outcomes remain unknown, parallel studies in *Il6*$^{-/-}$ mice emphasise their resistance to depression-like symptoms and show behaviours reflecting enhanced hedonic motivation[8,217-219]. Treatment of mice with MR16-1 (a mouse surrogate antibody for tocilizumab) demonstrates a rapid and long-lasting anti-depressive action in susceptible mice[220]. Genetic studies further identify various risk alleles in *IL6* and *IL6R* associated with major depressive disorders[221-226]. For example, the IL-6R single polymorphism rs228145 variant[226]. This mutation encodes an Asp^{358}Ala amino acid substitution, which affects the proteolytic cleavage of IL-6R and increases circulating sIL-6R[227]. Emphasising a link between inflammation, stress, and depression, this polymorphism increases the risk of cardiovascular disease and enhances susceptibility for insulin resistance and type-2 diabetes, but a more favourable outcome in COVID-19[153,226-228].

Current models used to study depression in patients include treatment with type-1 interferon (e.g., IFNα), commonly prescribed in viral hepatitis and malignant melanoma[229]. Clinical depression is a significant adverse outcome of IFNα therapy and typically occurs in 30-50% of patients[230]. Neuroimaging of patients treated with IFNα shows that type-1 interferons promote hyperactivity of the basal ganglia and controls dopamine metabolism and dopamine receptor signalling through induction of several interferon target genes[231,232]. Thus, cytokine therapy may activate localised transcriptional events within the brain. It is, however, uncertain whether this accounts for the

clinical impact biological drugs have on patient wellbeing and psychopathology in the treatment of chronic disease[8]. For example, patients typically receive large quantities of tocilizumab (infusion of 4-8mg/kg). However, only small amounts of the drug are detectable within the central nervous system[233]. Thus, IL-6 antagonists may improve depression, fatigue, and anhedonia by inhibiting physiological processes under systemic control. Examples would include the blockade of cytokine actions on the liver, vasculature, or neuroendocrine system[8]. As reflected by the impact on the blood-brain barrier, organs of the hypothalamus-pituitary-adrenal cortex (HPA) axis, or biochemical pathways linked with lipid peroxidation, and amino acid catabolism (Figure-3)[234-239]. Studies with tocilizumab support links between IL-6 activity, changes in hepcidin regulated iron metabolism, anaemia, and fatigue[11,12,15]. Advancing this concept, mouse studies of depressive behaviours show that the anti-depressive effect of IL-6 inhibition only occurs when drugs are administered intravenously but not intracerebroventricularly[14,240]. Thus, a sustained or heightened change in systemic inflammation may negatively impact psychological wellbeing and mental health commonly associated with infectious disease, immune-mediated inflammatory disorders, and cancer. However, translating IL-6 discoveries from mouse to human remains challenging and currently limited to patient recorded outcomes in defined patient groups on IL-6 antagonists[216,241-244].

7. Pain perception–

Early papers describing the biological properties of IL-6 identified IL-6 as a neurotrophic factor[245]. With wide-ranging effects on neuronal survival and differentiation, neurons, astrocytes, microglia, and endothelial cells provide a cellular source of IL-6 within the central nervous system[246]. The cell targets for IL-6 are mainly astrocytes and microglia, which express the cognate IL-6R. However, many studies evidence the importance of IL-6 trans-signalling and potentially IL-6 trans-presentation. For example, in nerve regeneration and remyelination in normal physiology and deleterious outcomes associated with neurodegeneration[246,247]. These include the formation of sympathetic and sensory neurons from neonatal superior cervical ganglia and the embryonic dorsal root ganglia and the expansion of Schwann cell progenitors expressing myelin basic protein[248-250]. The neurotrophic properties of neurotrophins often becoming augmented by IL-6 signalling. Here, IL-6 signals acting *via* the Jak-STAT pathway work in combination with nerve growth factor[251]. How IL-6 signalling determines the balance between neurodegeneration and regeneration is unclear. So, how do IL-6 responses become distorted in neuroinflammation? To address this question, it is now essential to understand how the epigenetic and transcriptional landscape changes to bring out alternate cell functions or fates.

The contribution of IL-6 to neuronal biology also depends on the location of IL-6 involvement within the periphery or central nervous system. Cytokine signalling affecting the generation of neuronal precursors such as acetylcholine from noradrenaline or 5-hydroxytryptamine. Similar involvements include a dampening of neuron excitation and synaptic transmission within the central system (e.g., via metabotropic glutamate receptors and TRPM7) and enabling neuron excitation and sensitivity within the periphery (e.g., via TRPV1, TRPA1)[252-260]. Thus, IL-6 elicits responses affecting higher central nervous system processing and includes activities linked with sensory (nociceptive) and neuropathic pain[4]. In this regard, *Il6*$^{-/-}$ mice often show signs of sensory impairment, and intrathecal administration of IL-6 in rats promotes animal behaviours indicative of pain perception[261,262].

Pain is a major factor affecting the quality of life for patients with debilitating chronic diseases. Recent advances in experimental medicine and fundamental discovery science have strived to distinguish the IL-6 control of pain from inhibition of inflammatory processes following therapeutic intervention with IL-6 blocking strategies[4,263,264]. Observational studies in patients with wounds show that the degree of injury correlates with increases in IL-6 and the magnitude of the pain response[265]. Moreover, rats administered with IL-6 show hypersensitivity to mechanical and thermal stimuli[266]. During inflammation, changes in systemic and local IL-6 concentrations affect distinct processes affecting pain perception[264]. Here, systemic changes in IL-6 activity drives an amplification of pain signalling, which includes increased dorsal root ganglia activity and inhibition of feedback mechanisms that would curtail pain conduction[4,263,264]. These activities are augmented by IL-6 locally generated within inflamed tissues, which increases nociceptive plasticity and nerve fibre regrowth and the persistence of pain signals from sensitized peripheral neurons[263,264].

The involvement of IL-6 in pain is a rapidly evolving area of research with highly complex biology. However, extensive evidence from literature clearly defines the role of IL-6 in both inflammatory and neuropathic pain[246,263,267-269]. Future research is now needed to understand the neuronal cell targets for IL-6, the mode of cellular activation adopted (e.g., classical IL-6 receptor signalling vs IL-6 trans-signalling vs IL-6 trans-presentation), and their relevance to human physiology and disease.

8. Complexities of IL-6 antagonism–

Early studies of IL-6 characterised the biological activities of IL-6 as a lymphokine. The original cytokine nomenclature classified its activity as interferon-β2, cytotoxic T-cell differentiation factor, B-cell differentiation factor and B-cell stimulatory factor-2. Thus, IL-6 was highly associated with the proliferative expansion, survival and activation of T-cells and the differentiation of B-cells[12].

Simultaneous investigations performed by researchers working on liver regeneration and the acute phase response identified IL-6 as a hepatocyte stimulating factor. For example, with impacts on C-reactive protein, haptoglobin, hepcidin and fibrinogen[100]. Thus, identifying the relevance of IL-6 to the control of infectious disease, immune-mediated diseases, and cancer[10,50]. These initial studies pioneered rapid advances in biological drug development, leading to the clinical approval of tocilizumab in 2009. The spectrum of drugs that target this cytokine now includes inhibitors of IL-6, the IL-6R or IL-6 trans-signalling. These are in various stages of clinical development, whilst others are in routine clinical practice. Most are monoclonal antibodies. These include clazakizumab, olokizumab, sirukumab, siltuximab and ziltivekimab, which bind IL-6 and tocilizumab and sarilumab targeting IL-6R. These drugs display subtle differences in pharmacodynamics or pharmacokinetics and clinical efficacy against several diseases[9-15]. IL-6 antagonists are now routinely prescribed for rheumatoid arthritis, other rheumatic-like disorders (e.g., juvenile idiopathic arthritis, adult-onset Still's disease, giant cell arteritis, Takayasu arteritis), Castleman disease, and cytokine release syndromes[11]. While experimental medicine continues to identify other indications tractable to IL-6 inhibition (e.g., uveitis, neuromyelitis optica, systemic sclerosis-associated interstitial lung disease), patients often display differences in therapeutic response with clinical trials evidencing scenarios in which IL-6 inhibition fails[11,12,20,32,39,270]. For example, tocilizumab is less effective in conditions where IL-6 orchestrates barrier immunity or the maintenance of epithelial homeostasis[12,20,32,39,40]. Notable examples include psoriasis, atopic dermatitis and systemic sclerosis-associated skin fibrosis, and gastrointestinal diseases (e.g., Crohn's disease, inflammatory bowel disease, colitis). These features of IL-6 inhibition also reflect contraindications associated with drug intervention. For example, gastrointestinal perforations and associated diverticulitis are recognised complications in rheumatoid arthritis patients on IL-6 antagonsts[12,39]. However, this view of IL-6 involvement in disease processes comes from biological drugs targeting the IL-6 receptor. Clinical trials with tocilizumab remain the most widely studied mechanism of IL-6 inhibition[11]. There is now a need to understand whether therapies targeting IL-6 offer different clinical outcomes to biological drugs against IL-6R. Clazakizumab, olokizumab, siltuximab, and ziltivekimab potentially managing any inflammatory flare in IL-6 production[12]. In stark contrast, IL-6 receptor inhibitors require more sustained concentrations to maintain a blockade of both membrane and soluble forms of the IL-6R[12]. Thus, in clinical indications where IL-6 maintains tissue homeostasis, IL-6R inhibition may negatively impact physiological processes essential for more tissue function. Here, the publication of clinical data for olamkicept (an engineered variant of sgp130) in patients with active inflammatory

bowel disease showcases how the blockade of IL-6 trans-signalling, representing the major pathway for IL-6 involvement in disease, adds a degree of selectivity to the clinical inhibition of IL-6[132]. Further clinical investigations are required to advance this therapeutic application of olamkicept as a selective IL-6 antagonist. However, these promising data open possibilities to entrap inflammatory IL-6 in a complex with sIL-6R, leaving classical membrane-bound IL-6R signalling intact[49].

Biological drugs that target IL-6 possess different pharmacodynamics and pharmacokinetics. They should not be considered like-for-like substitutes and often show differing behaviours when administered to patients. There is complexity here that highlights the need to differentiate the biological properties of these drugs. For example, the inhibition of IL-6 by clazakizumab and olokizumab are mechanistically very different, targeting functional epitopes within Site-1 and Site-3 of the IL-6 sequence[12,24,46]. Clazakizumab inhibits IL-6 binding to IL-6R (Site-1), while olokizumab blocks the docking of IL-6 to gp130 (Site-3) and the formation of a signalling IL-6 receptor complex[12,46,271]. This fundamental difference affects the bioavailability of circulating IL-6, with antibodies targeting Site-1 causing sustained increases in systemic IL-6 levels when administered to patients[272]. Whilst increases in IL-6 are also seen with other IL-6 blockers, this effect appears less prominent with Site-3 IL-6 blockers or anti-IL-6R monoclonal antibodies such as tocilizumab[273,274]. It is currently unclear whether these changes impact the control of physiological processes governed by IL-6. Current studies evaluating the impact of IL-6 antagonists on conditions such as depression and anxiety have focussed on diseases where IL-6 inhibition improves clinical symptoms and promotes disease remission (e.g., rheumatoid arthritis)[214-216]. Clinical improvements were not, however, seen in hematopoietic cell transplantation patients. Here, tocilizumab contributed to a worsening of depressive symptoms[275]. Thus, there is a need to reflect on the clinical context and the mode of IL-6 inhibition when reviewing biological drugs that target IL-6.

9. Concluding remarks–

Research involving animals have significantly enhanced our understanding of IL-6 biology in health and disease. Here, cytokine and cytokine receptor-deficient mice, genetic knock-in strains and pharmaceutical agents including antibodies, soluble receptors, engineered fusion proteins have contributed to studies of classical IL-6 receptor signalling, IL-6 trans-signalling and the characterisation of receptor signalling mechanisms. These discoveries explain how IL-6 drives pathology and pioneering the development of biological drugs and small molecule inhibitors. Many of these agents are in routine clinical practice, and the real-world experiences obtained with these

agents continue to broaden our appreciation of IL-6 biology. For example, tissue regeneration, metabolism (e.g., glucose, lipid, iron), neuroendocrine activity, sleep, and psychological wellbeing[15,237,238]. Clinical correlates often place IL-6 at the centre of these conditions. These include involvements in associated comorbidities and patient multimorbidity in chronic disease. Here, IL-6 contributes to increased cardiovascular risk (e.g., alterations in endothelial dysfunction, cellular adhesion, clot formation, and vascular tone), and processes affecting anaemia, fatigue, acute psychosocial stress, and depression. So, what does the future hold for IL-6 research?

In clinical studies, the measurement of IL-6 provides a blunt marker of inflammation. However, interpretations often ignore the contribution of sIL-6R, the impact of sgp130, circadian differences in IL-6 expression, and genetic traits that affect IL-6 bioactivity and bioavailability[12,32,43,78,276]. When considering the physiological role of IL-6 in health and disease, it is essential to gain as much information as possible about the biology of the cytokine. Such insights will determine whether IL-6 is simply a biomarker of inflammation (akin to measures of C reactive protein) or a keystone cytokine supporting the architecture of the disease process[12]. Here, the complex nature of human diseases emphasises the need to consider at least two interconnecting inflammatory reactions. One that drives tissue-specific pathology and, a second, affecting the systemic features of chronic disease. For instance, available data from COVID-19 patients treated with IL-6 antagonists often made it difficult to understand whether IL-6 drives immune pathology or the containment of viral infection and anti-microbial immunity[32,78,276]. Thus, we need to become less fixated on defining IL-6 as a pro-inflammatory cytokine. Current investigator-led studies are exploring the benefits of IL-6 antagonists in various conditions. Examples include diseases of the eyes, schizophrenia, Schnitzler syndrome, graft-versus-host disease, erosive osteoarthritis, familial Mediterranean fever, and myocardial infarction. The primary endpoint of these studies is an improvement in disease activity. However, extending these outcome measures to identify the impact of IL-6 inhibition on common comorbidities within these conditions may provide additional insights into the physiological properties of IL-6 in health and disease. Here, advances in clinical trial design (e.g., bucket or umbrella trials) provide new and exciting opportunities to explore new features of cytokine biology that reflect changes in systemic inflammation or altered normal physiology.

10. References–

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Figure Legends–

Figure-1. IL-6 activities beyond the control of immune regulation.

(A) The ancestral IL-6-like system in *Drosophila melanogaster* comprising Unpaired (IL-6-like), Domeless (gp130-like), hopscotch (Janus-activated kinase) and STAT92E (STAT transcription factor) coordinates cytokine-like responses relevant to human physiology. **(B)** Summary of the contributions of IL-6 biology to human health and disease.

Figure-2. The receptor mechanisms coordinating IL-6 activity.

(A) Cartoons depicting the three modes of IL-6 receptor signalling. Classical IL-6 receptor signalling occurs in cells expressing the cognate IL-6 receptor (IL-6R) and the signal-transducing receptor subunit gp130. Circulating sIL-6R retains the capacity to bind IL-6, forming a cytokine-cytokine receptor complex that can activate cells expressing gp130, but lacking IL-6R (e.g., endothelial cells, fibroblasts, mesothelial cells, and smooth muscle cells). This mode of IL-6 signalling is termed IL-6 trans-signalling. Finally, IL-6 *trans*-presentation represents a juxtracrine-form of cellular activation. Here, IL-6 presented in complex with IL-6R activates cell responses in adjacent cells expressing gp130. **(B)** Focussing on the intracellular pathways coordinated by gp130 activation, the cartoon shows the various signalling intermediates controlled by IL-6 and the cellular responses elicited by their activation.

Figure-3. IL-6 activities relevant to physiology and pathophysiology.

The biological properties of IL-6 are summarised and colour-coded to identify involvements in metabolic processes (blue), links to functional processes (orange) and clinical outcomes (white). Activities are focussed on the IL-6 responses in the liver, brain, bone, muscle, and organs of the HPA axis (hypothalamus, H; pituitary gland, P; adrenal cortex, A). The connecting red lines identify how IL-6 activities coordinated within these organs potentially link to deliver wholesale physiological changes.

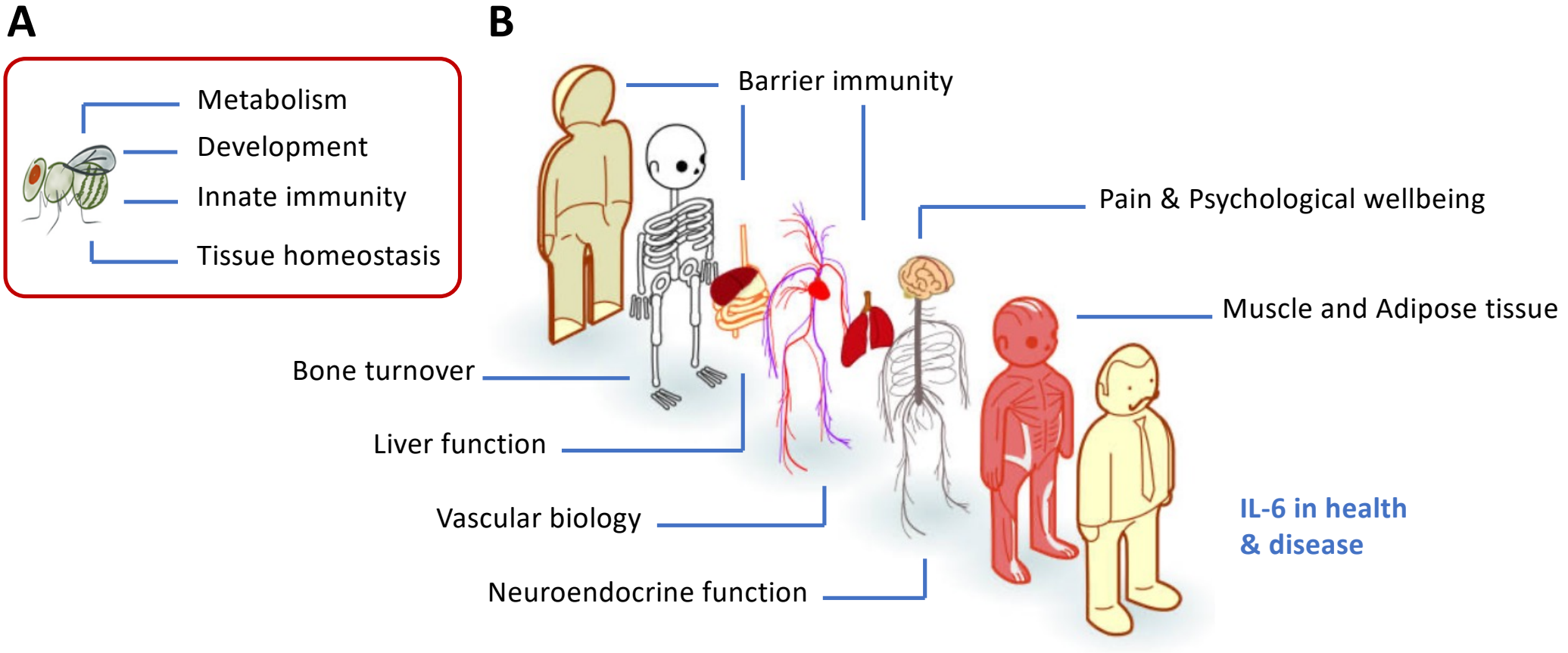
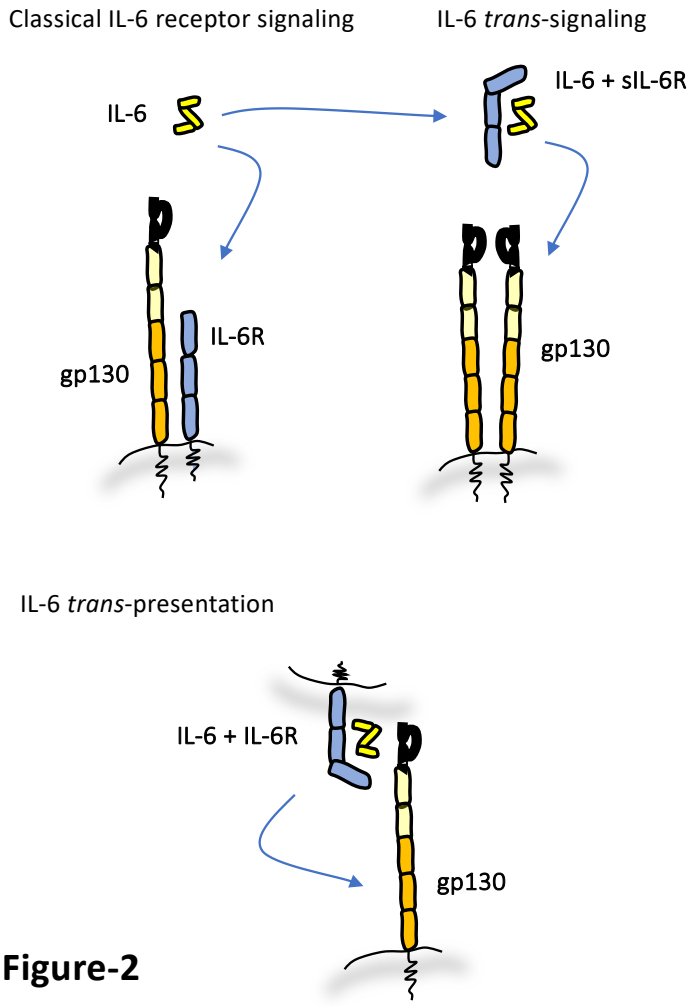

A
Metabolism
Development
Innate immunity
Tissue homeostasis
B
Barrier immunity
Pain & Psychological wellbeing
Muscle and Adipose tissue
Bone turnover
Liver function
Vascular biology
Neuroendocrine function
IL-6 in health
& disease

Figure-1

A. Modes of IL-6 signaling



B. IL-6 signaling pathways

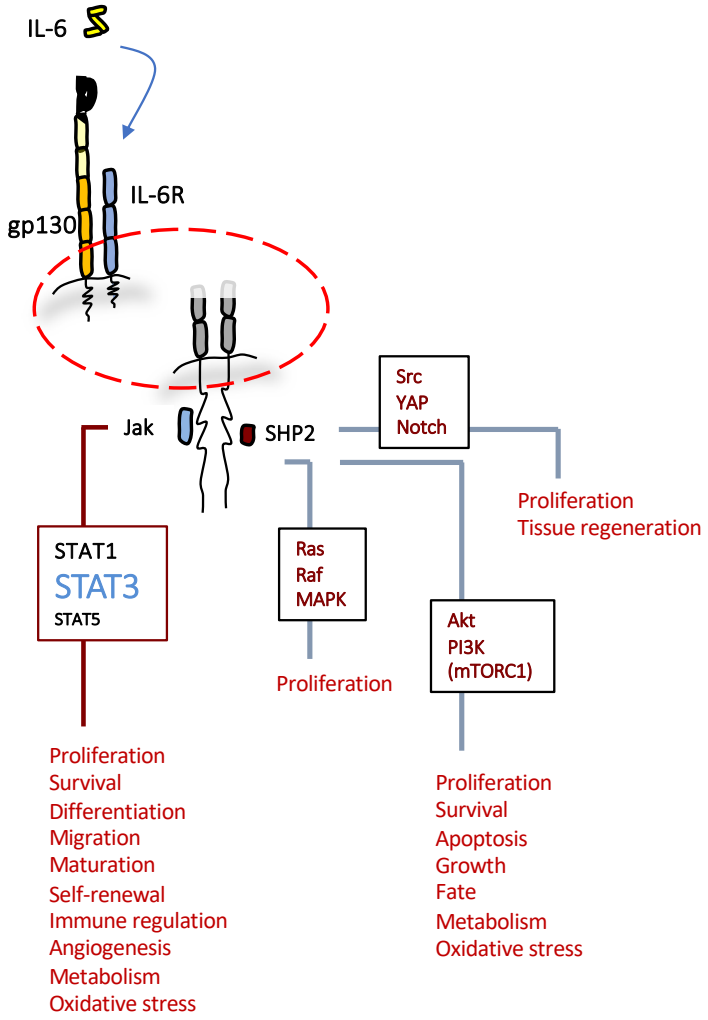


Figure-2

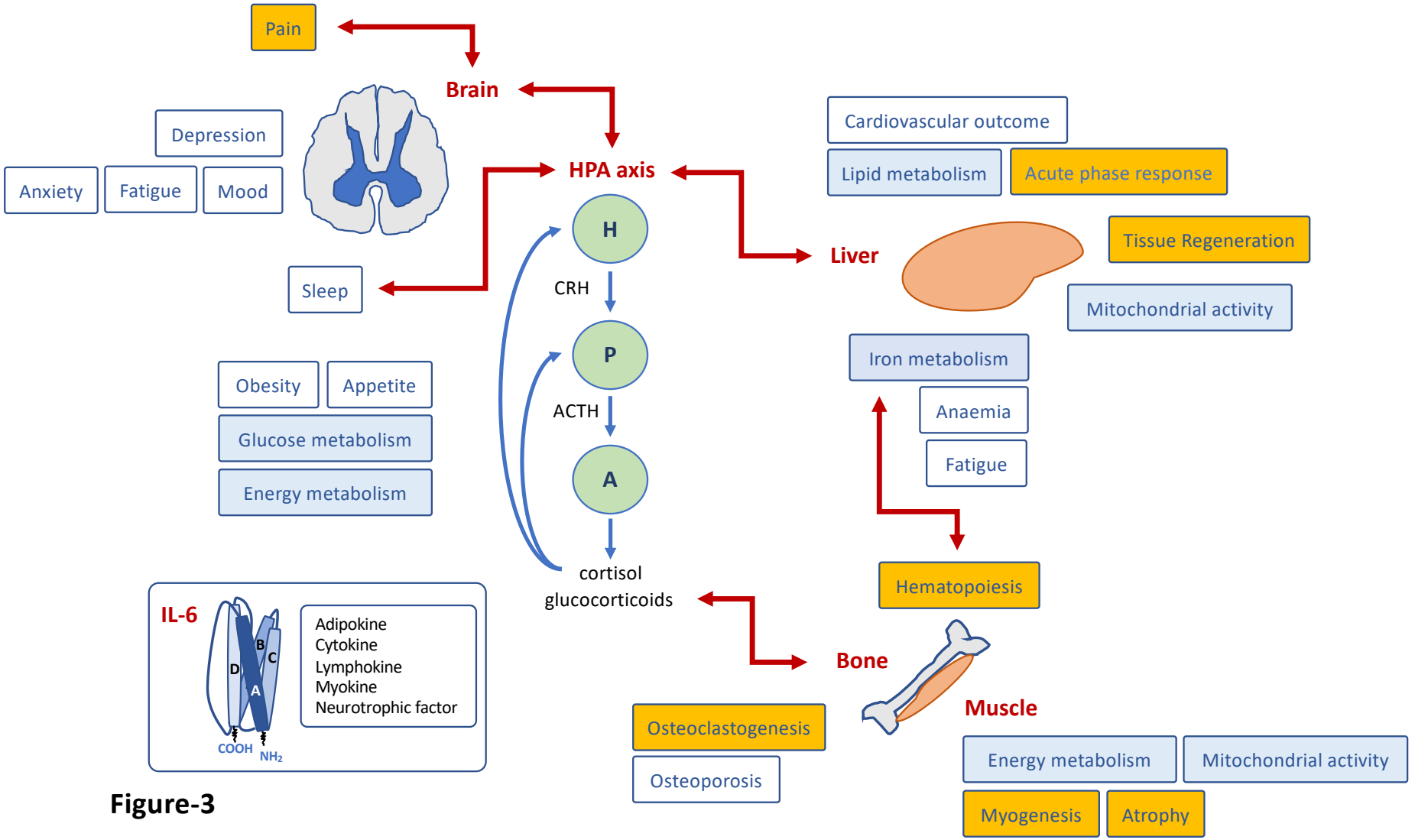

Pain
Brain
Depression
Anxiety
Fatigue
Mood
Sleep
HPA axis
H
CRH
P
ACTH
A
cortisol
glucocorticoids
Obesity
Appetite
Glucose metabolism
Energy metabolism
Cardiovascular outcome
Lipid metabolism
Acute phase response
Liver
Tissue Regeneration
Mitochondrial activity
Iron metabolism
Anaemia
Fatigue
Hematopoiesis
Bone
Osteoclastogenesis
Osteoporosis
Muscle
Energy metabolism
Mitochondrial activity
Myogenesis
Atrophy
IL-6
A
B
C
D
COOH
NH2
Adipokine
Cytokine
Lymphokine
Myokine
Neurotrophic factor

Figure-3