Cognitive Vitality Reports® are reports written by neuroscientists at the Alzheimer's Drug Discovery Foundation (ADDF). These scientific reports include analysis of drugs, drugs-in-development, drug targets, supplements, nutraceuticals, food/drink, non-pharmacologic interventions, and risk factors. Neuroscientists evaluate the potential benefit (or harm) for brain health, as well as for age-related health concerns that can affect brain health (e.g., cardiovascular diseases, cancers, diabetes/metabolic syndrome). In addition, these reports include evaluation of safety data, from clinical trials if available, and from preclinical models.

Anti-IL-11

Evidence Summary

IL-11 is associated with pro-fibrotic signaling, and IL-11 blocking antibodies protect against fibrosis and show good safety in preclinical models. Early stage clinical trials are underway.

Neuroprotective Benefit: IL-11 may have distinct protective roles in the CNS relative to the periphery, but does not appear to play a role in cognition. The contribution of IL-11 to neurodegenerative conditions is unclear.

Aging and related health concerns: IL-11 is a key driver of fibrotic signaling and upregulated in a variety of fibrotic conditions. IL-11 neutralizing antibodies have shown anti-fibrotic and metabolic effects in preclinical models, but clinical trials are needed.

Safety: IL-11 blocking antibodies have been safe and well-tolerated in short Phase 1 trials and preclinical studies. Based on low expression in healthy tissue and minor phenotypes in knockout mice, targeting IL-11 is expected to have good safety.

Availability: In clinical trials	**Dose**: Not established. Antibodies in clinical testing are i.v. formulations.	**Chemical formula:** N/A **MW**: N/A
Half-life: Varies LASN01 ~11 days (at a dose of 1,200 mg)	**BBB**: Current antibodies are in development for peripheral indications and likely have low to no penetrance.	
Clinical trials: Three anti-IL-11 (9MW3811 and BI 765423) or anti-IL-11Rα (LASN01) antibodies are currently being tested in small Phase 1 trials.	**Observational studies**: IL-11 is elevated in several fibrotic diseases, including idiopathic pulmonary fibrosis, cirrhosis, and chronic heart failure. Elevated IL-11 is associated with worse prognosis in several cancers.	

What is it?

Interleukin-11 (IL-11) is a cytokine in the IL-6 family, which all signal through the ubiquitously expressed receptor gp130 [2]. The specificity comes from the expression of the cognate receptor that is part of a complex with gp130, which for IL-11 is IL-11Rα. IL-11 is a stromal cell derived cytokine, and the expression of IL-11Rα is primarily on stromal cells, namely fibroblasts, and epithelial cells. IL-11 is implicated in mechanisms of tissue repair and regeneration in lower vertebrates, but is associated with tissue fibrosis in mammals. IL-11 is induced by TGF-β, considered to be the primary driver of fibrotic signaling, and promotes fibrosis-associated signaling pathways, including JAK/STAT and ERK. Targeting TGF-β directly is not a viable therapeutic strategy due to its pleiotropic effects, which has led to interest in the development of IL-11 targeting therapies for the prevention and treatment of fibrotic diseases. There are currently three antibodies in clinical development that target IL-11 or its receptor, IL-11Rα, from Boehringer Ingelheim, Mabwell Biosciences, and Lassen Therapeutics.

Neuroprotective Benefit: IL-11 may have distinct protective roles in the CNS relative to the periphery, but does not appear to play a role in cognition. The contribution of IL-11 to neurodegenerative conditions is unclear.

Types of evidence:

- 1 observational biomarker study in stroke patients
- A few laboratory studies

Human research to suggest prevention of dementia, prevention of decline, or improved cognitive function:

Anti-IL-11 antibodies have not been clinically tested for neurological indications, and human mutations in IL-11Rα are not associated with neurological phenotypes, thus there is limited information available as to how the inhibition of IL-11 may impact cognition [2]. One biomarker study suggests that IL-11 may play a protective role in the brain in the context of cerebral ischemia. A study assessing serum IL-11 levels, found that IL-11 was lower in patients with cerebral infarction (n=102) relative to healthy controls (n=64), and that low IL-11 was a marker of poor prognosis [3]. Low IL-11 levels were more common in patients who experienced early neurological deterioration (END). NIH Stroke Scale (NIHSS) score (r = -0.613) and infarction volume (r = −0.679) were inversely associated with serum IL-11 levels, while the neurotrophic growth factor, BDNF, was positively associated with IL-11.

Human research to suggest benefits to patients with dementia:

Anti-IL-11 antibodies have not been tested in dementia patients.

Mechanisms of action for neuroprotection identified from laboratory and clinical research:

IL-11 has not been extensively studied in the nervous system, but the preclinical studies conducted thus far suggest that the expression of IL-11 may play a neuroprotective role within cells of the CNS, such as neurons and glia, but it could also be associated with damaging inflammation when highly expressed by immune cells [4].
Consistent with the association between serum IL-11 levels and better neurological outcomes in the context of cerebral infarction, the mRNA expression of IL-11 in neurons was reduced following cerebral ischemia in the mouse model of middle cerebral artery occlusion (MCAO) [5]. Treatment of the mice

with recombinant mouse IL-11 (i.v.) ten minutes prior to reperfusion was associated with less cell death, a lower infarction volume, and better neurological scores. This was accompanied by a reduction in pro-inflammatory cytokines, glial activation, and oxidative stress, which may have been mediated through the inhibition of AMPK.
IL-11 has also been implicated as a mediator of myelin growth and repair through the enhancement of oligodendrocyte survival and maturation [4]. The facilitation of myelin repair would be beneficial in the context of multiple sclerosis (MS), however, there is evidence that IL-11 is elevated in the serum and cerebrospinal fluid (CSF) of MS patients, due to the increased presence of IL-11+CD4+ T cells, which contribute to the development of inflammatory lesions [6]. Consequently, peripheral IL-11 neutralization would likely offer greater benefit in the context of MS.
It has not yet been established whether IL-11 contributes to mechanisms of cognitive aging.

APOE4 interactions: Not established

Aging and related health concerns: IL-11 is a key driver of fibrotic signaling and upregulated in a variety of fibrotic conditions. IL-11 neutralizing antibodies have shown anti-fibrotic and metabolic effects in preclinical models, but clinical trials are needed.

Types of evidence:

- Several observational studies of IL-11 expression in pathological conditions
- Numerous laboratory studies

Healthspan: POTENTIAL BENEFIT (Preclinical)
Preclinical studies have identified IL-11 as a senescence associated secretory phenotype (SASP) factor involved in inflammaging. IL-11 drives senescence through the activation of ERK and mTOR signaling and treatment with IL-11Rα neutralizing antibodies can attenuate the induction of replicative senescence markers in cultured fibroblasts, such as p16 and p18, as well as promote the maintenance of telomere length, basal metabolic rate, and mitochondrial DNA copy number [7].
IL-11 was found to be elevated in aged (two-year-old) mice, particularly in the metabolic tissues of liver, fat, and skeletal muscle [7]. Mice lacking IL-11 showed greater preservation of lean mass, less adiposity, and lower frailty scores in old age, along with a reduction in liver triglyceride content [7]. A partial reversal of these aging phenotypes was also observed with the administration of an IL-11 neutralizing antibody (X203) (40 mg/kg every three weeks) for 25 weeks starting at 75 weeks of age (~1.5 years) [7].

Aged mice treated with the IL-11 antibody showed a preservation of muscle strength and the respiratory exchange ratio, a measure of metabolic flexibility, compared to IgG control treated aged mice, though these measures were still lower than what is typically seen in young mice. Serum cholesterol, triglycerides and IL6 levels were lowered with the IL-11 antibody, and markers of liver damage, hepatic triglyceride content were reduced or reversed with X203 treatment in the aged mice, along with a reversal of age-related visceral adiposity and sarcopenia. A reversal of tissue fibrosis was observed in adipose tissue, skeletal muscle, and liver, which was accompanied by a lowering of epigenetic clock age by approximately 30 weeks and 50 weeks in the muscle and liver, respectively. The inhibition of cellular senescence was most apparent in the white adipose tissue, which was coupled with a reduction in lipid droplet accumulation.

Together, these studies suggest that the inhibition of IL-11 may improve healthspan through the mitigation of age-related tissue dysfunction stemming from fibrosis, inflammation, and metabolic dysfunction. Clinical trials are needed to confirm whether a similar degree of benefit could be achieved in humans, and whether there is an optimal window of administration to protect against aging-related phenotypes.

Fibrotic diseases: POTENTIAL BENEFIT (Preclinical)

IL-11 expression is generally very low in healthy tissue, but is induced by TGF-β, a major driver of fibrosis pathology, in response to tissue damage [8]. It plays a role in tissue remodeling in the context of wound healing. IL-11 appears to facilitate tissue regeneration in fish and amphibians, but does not appear to be critical for normal tissue homeostasis [2]. These animals form a blastema, or a regenerative bud, at the site of injury, in which IL-11 drives the tissue remodeling required to rebuild the tissue (i.e. limb/fin). Mammals, however, do not form a blastema and are not capable of this type of regeneration such that the induction of IL-11 may lead to maladaptive tissue remodeling rather than repair.

Classical IL-11 signaling through the IL-11Rα and gp130 receptors leads to the transient induction of JAK/STAT signaling, which may play an acute role in mechanisms of repair [2; 9]. Alternative signaling in the context of Y759 phosphorylation of gp130 can lead to the induction of prolonged MEK/ERK signaling which drives a sustained cycle of pro-fibrotic and pro-inflammatory signaling [9].

IL-11 can induce extracellular matrix proteins and meditators of fibrosis, such as collagen type 1 [8]. IL-11 facilitates the fibroblast to myofibroblast transition [8]. The production of myofibroblasts is one of the main mechanisms of pathological fibrosis since these cells secrete excessive amounts of extracellular matrix proteins like α-SMA and collagen. IL-11 has been found to be upregulated in a variety of fibrotic tissues and preclinical studies suggest that IL-11 neutralizing antibodies may mitigate fibrosis, however, there is likely to be a therapeutic window, with preferential benefit at early stages relative to later

stages of fibrotic tissue remodeling. A recent study suggests that while IL-11 is a downstream pro-fibrotic mediator of TGF-β, neutralizing IL-11 alone may be insufficient to effectively dampen fibrotic processes in the context of elevated TGF-β [10]. Ongoing clinical trials with IL-11 neutralizing antibodies will provide information about the translatability of this approach.

Idiopathic pulmonary fibrosis: POTENTIAL BENEFIT (Preclinical)
IL-11 is highly induced in lung tissue from patients with idiopathic pulmonary fibrosis (IPF), and has been linked to disease pathogenesis by facilitating the fibroblast to myofibroblast transition, extracellular matrix remodeling, and disrupting communication between fibroblasts with other cell types, such as epithelial cells and macrophages [10; 11; 12]. TGF-β 1/IL-11/MEK/ERK (TIME) signaling promotes the epithelial to mesenchymal transition of lung epithelial cells and may mediate cell senescence in lung fibroblasts [13]. IL-11 was found to be increased 100-fold in fibroblasts from patients with IPF, while treatment with anti-IL-11 reduced expression of IL-11, p16, and collagen 1 [13]. The induction of IL-11 has been recapitulated in a variety of models of lung fibrosis, while neutralizing IL-11 antibodies have consistently shown therapeutic benefit [12].
In the bleomycin mouse model of lung fibrosis, the IL-11 neutralizing antibody, X203, inhibited ERK and SMAD signaling, and mitigated myofibroblast activation, lung scarring, immune cell infiltration and parenchymal disruption [11]. In a mouse model of silica particle-induced lung fibrosis and inflammation, a neutralizing IL-11 antibody reduced the expression of pro-inflammatory cytokines and fibrotic extracellular matrix proteins, but was less efficacious at later stages of silicosis, as the antibody could mitigate ongoing fibrotic activity, but not repair the damage related to the long-term persistence of the silica in the lungs [14]. LASN01, an IL-11Rα blocking antibody in clinical development, reduced the expression of pro-fibrotic (collagen, fibronectin, and TIMP-1) and inflammatory (IL-8 and MCP-1) markers in precision cut lung slices from patients with IPF [15].These studies suggest that the utility of anti-IL-11 therapies may be best suited to early stages, to prevent disease progression. Due to the consistent evidence of IL-11 as a mediator of lung fibrosis, IPF is generally the first indication for novel anti-IL-11 therapies currently in clinical development [2].

Renal fibrosis: POTENTIAL BENEFIT (Preclinical)
Urinary IL-11 levels are elevated in the context of IgA nephropathy and lupus nephritis, and correlate with proteinuria [16]. IL-11 is also one of the most highly upregulated genes in tissue slices from patients with end-stage kidney disease [16]. IL-11 neutralizing antibodies have shown protective effects in rodent models of kidney disease [2]. IL-11 is upregulated in the kidney in response to acute injury, and the kidneys of mice lacking IL-11 are protected against the induction of fibrosis following acute injury [17].

Treatment with the IL-11 neutralizing antibody, X203, three days after injury, mitigated the induction of pro-fibrotic genes, as well as markers of renal damage, inflammation, and fibrosis [17]. The protective effects may be mediated by the prevention and reversal of the epithelial to mesenchymal transition of renal tubular epithelial cells. In a model of chronic kidney disease, when treatment with X203 was initiated three weeks after injury, anti-IL-11 was associated with a progressive increase in kidney mass, coupled with a progressive decrease in collagen content and histological fibrosis. This IL-11 neutralizing antibody also reduced ERK activation, collagen content, fibrosis, inflammation, and tubule damage in a mouse model of Alport disease, a genetic disorder due to a mutation in type IV collagen that leads to end-stage kidney failure [18]. Notably, treatment with the IL-11 neutralizing antibody prolonged the lifespan of these mice by 44%, even when administered after the onset of proteinuria and detectable renal pathology.

Liver fibrosis: POTENTIAL BENEFIT (Preclinical)
Many therapeutics are in clinical development for metabolic dysfunction-associated steatotic liver disease (MASLD), some of which show promise toward reducing levels of hepatic lipotoxicity. However, impacts to liver fibrosis have generally been lackluster, and effective anti-fibrotic therapies are a major unmet clinical need. IL-11 targeted therapies show promise in preclinical studies toward addressing both the metabolic and fibrotic aspects of liver disease.
IL-11 may be a driver of liver fibrosis in both alcohol-related cirrhosis and non-alcoholic steatohepatitis (NASH). Serum levels of IL-11 were found to be elevated in two cohorts of patients with alcoholic hepatitis and/or cirrhosis (n=179; n=186), such that levels above 6.4 pg/mL were a predictor of model of end-stage liver disease and worse transplant-free survival at six months with a sensitivity of 59.4% and a specificity of 93.3% [19]. A similar association was observed in a mouse model, such that hepatic IL-11 and IL-11-Rα expression was positively correlated with the severity of alcohol-induced liver inflammation [19]. Treatment of ethanol-fed mice with anti-IL-11Rα reduced the infiltration of pro-inflammatory cells in the liver along with hepatic expression of the inflammatory mediators, TNFα, TIMP1, IL-10, CXCL1, IL-1ß, and MIP-2. Serum IL-11 levels were progressively increased in patients with liver fibrosis based on the degree of liver damage.
Expression of IL-11 was also found to be increased in fibrotic liver tissue from patients with hepatocellular carcinoma, and from patients with NASH [20; 21]. Hepatic IL-11 was found to be elevated in a variety of NASH mouse models, while the use of anti-IL-11 (X203) and anti-IL-11Rα (X209) antibodies showed the capacity to prevent, slow, or reverse signs of hepatic steatosis and fibrosis, depending on the model and timing of antibody treatment relative to the severity of liver damage [21]. The most substantial benefit was observed when used in combination with dietary modification in a high-fat,

methionine- and choline-deficient diet model in which severe fibrosis had developed over a 10-week period, and then the mice were converted to normal chow while initiating treatment with IL-11 neutralizing antibodies. The degree of fibrosis was unchanged in those undergoing the dietary change alone, which is consistent with metabolic interventions for NASH, while the hepatic collagen content decreased around 20% by three weeks, and by about 40% by six weeks with the addition of anti-IL-11. This was associated with a reversal of the profibrotic and pro-inflammatory expression signature as well as the destruction of transformed hepatic stellate cells. IL-11 stimulation plays a role in the transformation of hepatic stellate cells into pro-inflammatory myofibroblasts [22]. The rodent models suggest that IL-11 signaling plays a role in steatosis as well as fibrosis. IL-11 signaling was shown to impact lipid metabolism in the liver, such that it impairs fatty acid beta-oxidation and triggers mitochondrial dysfunction [22]. The secretion of IL-11 by lipid-loaded hepatocytes may trigger metabolic dysfunction as well as the transformation of hepatic stellate cells into myofibroblasts. Clinical studies are needed to determine how well these preclinical findings translate into meaningful benefit for patients.

Cardiac fibrosis: POTENTIAL BENEFIT (Preclinical)
IL-11 was initially implicated in platelet production, such that recombinant IL-11 was approved for the treatment of chemotherapy-related thrombocytopenia in 1998 [2]. Eventually, IL-11 was understood to be redundant for hematopoiesis, and the acute platelet induction to high-dose IL-11 is considered to stem from the non-specific activation of gp130, and is not characteristic of endogenous IL-11 [23].
IL-11 has been found to be elevated in the arterial blood of patients with coronary artery disease, in the plasma and thoracic aorta in patients with acute thoracic aortic dissection, and in the serum of patients with chronic heart failure [24]. IL-11 had originally been thought to be cardioprotective, but subsequent studies suggest that it is cardiotoxic [2]. The use of recombinant IL-11 for thrombocytopenia was found to be associated with adverse cardiac effects, including elevations of serum B-natriuretic peptide levels, atrial arrhythmias, and heart failure [23].
The confusion stemmed from the species-specific responses toward recombinant IL-11 [2]. Human IL-11 does not activate IL-11 signaling in rodents, but rather, works to block endogenous IL-11 signaling. Consequently, the protective responses observed with recombinant human IL-11 (rhIL-11) were due to the blocking of IL-11 signaling, such that similar protective effects have been observed with IL-11 neutralizing antibodies.
IL-11 neutralizing antibodies were found to dampen pro-fibrotic/extracellular matrix gene expression, ERK signaling, cardiac fibrosis, and collagen content in mouse models of pressure overload-induced cardiac fibrosis [25; 26]. However, the IL-11 antibodies did not alleviate cardiac hypertrophy, left

ventricular wall thickening, or diastolic dysfunction in these models, suggesting that the overall impact to clinical measures may be modest, particularly at later stages of disease [24].

Cancer: IL-11 IS A PROGNOSTIC BIOMARKER; POTENTIAL BENEFIT IN COMBINATION (Preclinical)
IL-11 has been found to be overexpressed in a variety of cancers, and is considered a marker of poor prognosis [27]. Additionally, IL-11 appears to be a driver of bone metastasis in breast cancer [28]. The secretion of IL-11 by cancer-associated fibroblasts has been associated with tumor growth and chemoresistance in several cancers. In non-small cell lung cancer (NSCLC), fibroblast activation and high IL-11 expression are associated with worse survival [27]. While not all lung cancer patients have detectable serum levels of IL-11, concentrations generally increase progressively with disease severity, and those with elevated levels tend to have lower rates of survival. Serum IL-11 is also a predictive marker for bone metastasis in patients with breast cancer, and is associated with shorter survival [28]. IL-11 was found to be one of the most abundantly expressed osteolytic factors in breast cancer cells through the induction of osteoclastogenesis [28].
The effect of IL-11 on tumor growth is thought to be partially mediated through an effect on immune cells, including macrophages and T-cells. Blocking IL-11 may help reverse T cell exhaustion and overcome resistance to anti-PD-1 therapy. The IL-11 blocking antibody, 9MW3811, inhibited tumor cell growth in a xenograft model of NSCLC using A549 cells, as well as in lung squamous cell carcinoma models [29]. 9MW3811 also worked synergistically with anti-PD-1 to increase tumor growth inhibition in syngeneic models from 45% to 83% in a model using colon cancer cells (MC38), and from 34% to 75% in a model using liver cancer cells (Hepa1-6). Notably, the combination of 9MW3811 with anti-PD-1 exerted tumor growth inhibition of 67% in a model using CT26 colon cancer cells which are typically resistant to anti-PD-1 monotherapy. The inhibition of tumor growth was associated with an increase in tumor infiltrating cytotoxic CD8 T cells. 9MW381 is currently in clinical development in Phase 1 trials, including a Phase 1 dosing trial in patients with advanced solid tumors (NCT05911984).

Osteoporosis: UNCLEAR (Preclinical)
IL-11 plays a role in bone development and remodeling, though the contribution to age-related bone loss remains unclear [2]. Individuals heterozygous for a loss of function mutation in IL-11Rα show bone growth-related phenotypes, including craniosynostosis, conductive hearing loss, underdevelopment of the jaw, eye protrusion, delayed tooth eruption, scoliosis and joint laxity, suggesting that IL-11 plays a role in proper bone growth, at least during development [4; 30]. These phenotypes occur with variable penetrance and severity, suggesting that there are other compensatory mechanisms involved, such as altered signaling through the gp130 receptor [2]. Mice lacking IL-Rα show a similar range of phenotypes,

while mice lacking IL-11 do not display these skeletal alterations. It is unclear whether IL-11 plays a similar role in bone growth and maintenance during adulthood, though it does have an established role as an osteolytic factor in cancer cells that promotes bone metastasis [28].
Preclinical studies suggest that IL-11 is involved in the production of both osteoblasts, or bone forming cells, and osteoclasts, which are involved in bone reabsorption [30]. As a result, *in vivo* conditions, such as interactions with hormones, growth factors, and other signaling pathways, may determine which process dominates. This is reflected in the literature, by the mix of studies showing that both IL-11 and anti-IL-11 can promote bone growth. For example, one study found that anti-IL-11 blocked mechanical loading-induced osteoblastogenesis and bone growth [31], while another study found that in the context of estrogen-deficiency, anti-IL-11 reversed bone loss by reducing rates of bone reabsorption [32]. Due to the potential for opposing context-dependent effects in bone, IL-11 targeted therapies may not be well-suited to the treatment or prevention of bone loss, aside from cancer-related osteolysis.

Safety: IL-11 blocking antibodies have been safe and well-tolerated in short Phase 1 trials and preclinical studies. Based on low expression in healthy tissue and minor phenotypes in knockout mice, targeting IL-11 is expected to have good safety.

Types of evidence:

- 2 Phase 1 clinical trials
- Numerous laboratory studies

Anti-IL-11 and anti-IL-11Rα antibodies are currently in Phase 1 clinical trials in healthy volunteers. To date, only topline results are available from a Phase 1 single and multiple ascending dose (SAD and MAD) trial in healthy volunteers testing the anti-IL-11Rα monoclonal antibody, LASN01 (NCT05331300). It is reported that LASN01 was generally well-tolerated, with dose linear pharmacokinetics, and dose proportional inhibition of pSTAT3 that was >95% at day 70 for the 600 mg and 1,200 mg doses [15]. A half-life of 11 days supports monthly dosing for the 1,200 mg dose (Press release). BI 765423, an anti-IL-11 antibody, was recently tested in a Phase 1 SAD trial in healthy men (NCT05658107). Results have not yet been made available, but the antibody has progressed into a MAD study. Ongoing studies will provide a better sense of the short and long-term safety profile of IL-11 neutralizing therapies in healthy populations, patients with fibrotic conditions, and patients with cancer.

As the master regulator of fibrotic signaling, targeting TGF-β would be the most potent anti-fibrotic strategy [26]. However, due to its pleiotropic effects, the inhibition of TGF-β results in a variety of on-target side effects, and thus is not a therapeutically viable target. Targeting IL-11 is considered the next best alternative, as it is a major downstream target of TGF-β, that is induced in the context of tissue fibrosis in a variety of settings. Critically, IL-11 appears to be dispensable for normal tissue function, such that its inhibition does not incur the same safety concerns as TGF-β.

Preclinical studies with IL-11 neutralizing antibodies, as well as phenotypic analysis of mice with genetic deletions in IL-11 or IL-11Rα and humans with mutations in IL-11Rα suggest that the inhibition of IL-11 should be safe and well-tolerated, with a low risk for side effects [2]. The variable penetrance of the mild bone/skeletal defects, including craniosynostosis, scoliosis, and delayed tooth eruption, with loss of IL-11Rα suggests that these effects may stem from an altered profile of gp130 signaling due to compensatory responses or higher availability by other IL-6 family members during development [2]. Additionally, these effects generally stem from a lack of IL-11Rα during development. The expression of IL-11 during adulthood is generally low or undetectable in serum and most tissues in healthy individuals, and only induced during the context of tissue stress/injury. This suggests that IL-11 does not play a role in tissue homeostasis. Preclinical studies in rodents targeting IL-11 or IL-11Rα during adulthood have not been associated with adverse effects.

Drug interactions: Interactions have not been established for IL-11 neutralizing antibodies. Due to its roles in the modulation of JAK/STAT and ERK signaling, IL-11 antibodies may interact with other drugs that modulate those pathways.

Sources and dosing:

Anti-IL-11 and anti-IL-11Rα monoclonal antibodies are currently in clinical development for fibro-inflammatory and oncologic indications, but have not yet been approved for any indication. Currently, anti-IL-11 antibodies are in development by Mabwell Bioscience and Boehringer Ingelheim, while an anti-IL-11Rα antibody is in development by Lassen Therapeutics. They are currently being administered as intravenous injections.

Research underway:

LASN01 is an anti-IL-11Rα monoclonal antibody in clinical development for fibro-inflammatory diseases by Lassen Therapeutics. It is currently being tested in a Phase 1/2 trial (NCT 05331300). The Phase 1 SAD/MAD study in healthy volunteers has been completed, and is now being tested in patients with idiopathic pulmonary fibrosis (IPF) or progressive fibrosing interstitial lung disease or thyroid eye disease. This study has an estimated completion date in 2025. Additionally, LASN01 is being tested in a Phase 2 proof of concept trial in patients with thyroid eye disease who have previously received teprotumumab treatment (NCT06226545), which also has an expected completion date in 2025.

9MW3811 is a humanized anti-IL-11 monoclonal antibody in clinical development for fibrotic and oncologic indications by the Chinese biotech, Mabwell Bioscience (Shanghai Stock Exchange: 688062)(Market Cap: 12.30B CNY). It is currently being tested in two Phase 1 SAD study to assess safety, tolerability, pharmacokinetics, pharmacodynamics and immunogenicity in healthy volunteers (NCT05740475 and (NCT05912049), which had expected completion dates in 2023, and a Phase 1 dose finding study in patients with advanced solid tumors (NCT05911984), which has an expected completion date in 2024.

BI 765423 is an anti-IL-11 antibody in clinical development for fibrotic diseases by Boehringer Ingelheim, who acquired the anti-IL-11 portfolio from the Singapore-based biotech, Enleofen. It was recently tested in a Phase 1 SAD study in healthy men (NCT05658107), and is currently being tested in Phase 1 MAD study in healthy men (NCT06232252), which has an estimated completion date in 2025.

To enhance the clinical utility of these therapies, there are efforts underway to develop formulations that can be administered subcutaneously [7]. To date, mouse targeted anti-IL-11 antibodies have been developed which will be used to compare the safety and efficacy relative to intravenously administered anti-IL-11 antibodies in preclinical models.

Search terms:

Pubmed, Google: Anti-IL-11

- Fibrosis, inflammation, cancer, bone, lifespan/healthspan, clinical trials, neurodegeneration, safety

Websites visited for Anti-IL-11:

- Clinicaltrials.gov (LASN01, 9MW3811, BI 765423)

References:

1. Myzithras M, Lin S, Radden L *et al.* (2022) Development of novel ultra-sensitive IL-11 target engagement assays to support mechanistic PK/PD modeling for an anti-IL-11 antibody therapeutic. *mAbs* **14**, 2104153https://www.ncbi.nlm.nih.gov/pmc/articles/PMC9348130/.

2. Cook SA (2023) Understanding interleukin 11 as a disease gene and therapeutic target. *The Biochemical journal* **480**, 1987-2008https://www.ncbi.nlm.nih.gov/pmc/articles/PMC10754292/.

3. Guo X, Zhu X, Zhou S *et al.* (2024) Serum levels of IL-9 and IL-11 serve as predictors for the occurrence of early neurologic deterioration in patients with cerebral infarction. *Clinica chimica acta; international journal of clinical chemistry* **558**, 119683https://pubmed.ncbi.nlm.nih.gov/38643817/.

4. Airapetov MI, Eresko SO, Ignatova PD *et al.* (2023) Interleukin-11 in Pathologies of the Nervous System. *Molecular biology* **57**, 1-6https://www.ncbi.nlm.nih.gov/pmc/articles/PMC10062686/.

5. Zhang B, Zhang HX, Shi ST *et al.* (2019) Interleukin-11 treatment protected against cerebral ischemia/reperfusion injury. *Biomedicine & pharmacotherapy = Biomedecine & pharmacotherapie* **115**, 108816https://pubmed.ncbi.nlm.nih.gov/31096144/.

6. Seyedsadr M, Wang Y, Elzoheiry M *et al.* (2023) IL-11 induces NLRP3 inflammasome activation in monocytes and inflammatory cell migration to the central nervous system. *Proceedings of the National Academy of Sciences of the United States of America* **120**, e2221007120https://www.ncbi.nlm.nih.gov/pmc/articles/PMC10293805/.

7. Widjaja AA, Lim W-W, Viswanathan S *et al.* (2023) Inhibition of an immunometabolic axis of mTORC1 activation extends mammalian healthspan. *bioRxiv*, 2023.2007.2009.548250https://www.biorxiv.org/content/biorxiv/early/2023/07/09/2023.07.09.548250.full.pdf.

8. Corden B, Adami E, Sweeney M *et al.* (2020) IL-11 in cardiac and renal fibrosis: Late to the party but a central player. *British journal of pharmacology* **177**, 1695-1708https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7070163/.

9. Elshoff D, Mehta P, Ziouzenkova O (2024) Chronic Kidney Disease Diets for Kidney Failure Prevention: Insights from the IL-11 Paradigm. *Nutrients* **16**https://www.ncbi.nlm.nih.gov/pmc/articles/PMC11085624/.

10. Tan Y, Mosallanejad K, Zhang Q *et al.* (2024) IL11-mediated stromal cell activation may not be the master regulator of pro-fibrotic signaling downstream of TGFβ. *Frontiers in immunology* **15**, 1293883https://www.ncbi.nlm.nih.gov/pmc/articles/PMC10917968/.

11. Ng B, Dong J, D'Agostino G *et al.* (2019) Interleukin-11 is a therapeutic target in idiopathic pulmonary fibrosis. *Science translational medicine* **11**https://pubmed.ncbi.nlm.nih.gov/31554736/.

12. Kortekaas RK, Burgess JK, van Orsoy R *et al.* (2021) Therapeutic Targeting of IL-11 for Chronic Lung Disease. *Trends in pharmacological sciences* **42**, 354-366https://pubmed.ncbi.nlm.nih.gov/33612289/.

13. Chen H, Chen H, Liang J *et al.* (2020) TGF-β1/IL-11/MEK/ERK signaling mediates senescence-associated pulmonary fibrosis in a stress-induced premature senescence model of Bmi-1 deficiency. *Experimental & molecular medicine* **52**, 130-151https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7000795/.

14. Ma J, Xie Y, Xu Y *et al.* (2023) Neutralization of interleukin-11 attenuates silica particles-induced pulmonary inflammation and fibrosis in vivo. *Journal of environmental sciences (China)* **126**, 772-783https://pubmed.ncbi.nlm.nih.gov/36503802/.

15. Swaney J, Jun T, Horlick RAA *et al.* A First-in-Class IL-11 Receptor Blocking Antibody as a Treatment for Pulmonary Fibrosis. In *D19 NEW PERSPECTIVES ON TRANSLATIONAL STUDIES FOR LUNG FIBROSIS*, pp. A6262-A6262https://www.atsjournals.org/doi/abs/10.1164/ajrccm-conference.2023.207.1_MeetingAbstracts.A6262.

16. Widjaja AA, Cook SA (2023) The Pathobiology of IL-11 in Kidney Disease: From Epithelial Cell to Fibroblast and Back Again. *The American journal of pathology* **193**, 1910-1913https://pubmed.ncbi.nlm.nih.gov/37816442/.

17. Widjaja AA, Viswanathan S, Shekeran SG *et al.* (2022) Targeting endogenous kidney regeneration using anti-IL11 therapy in acute and chronic models of kidney disease. *Nature Communications* **13**, 7497https://doi.org/10.1038/s41467-022-35306-1.

18. Widjaja AA, Shekeran SG, Adami E *et al.* (2022) A Neutralizing IL-11 Antibody Improves Renal Function and Increases Lifespan in a Mouse Model of Alport Syndrome. *Journal of the American Society of Nephrology : JASN* **33**, 718-730https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8970448/.

19. Effenberger M, Widjaja AA, Grabherr F *et al.* (2023) Interleukin-11 drives human and mouse alcohol-related liver disease. *Gut* **72**, 168-179https://pubmed.ncbi.nlm.nih.gov/35365572/.

20. Jiang L-F, Yang M, Meng H-W *et al.* (2023) The effect of hepatic stellate cell derived-IL-11 on hepatocyte injury in hepatic fibrosis. *Life Sciences* **330**, 121974https://www.sciencedirect.com/science/article/pii/S0024320523006094.

21. Widjaja AA, Singh BK, Adami E *et al.* (2019) Inhibiting Interleukin 11 Signaling Reduces Hepatocyte Death and Liver Fibrosis, Inflammation, and Steatosis in Mouse Models of Nonalcoholic Steatohepatitis. *Gastroenterology* **157**, 777-792.e714https://pubmed.ncbi.nlm.nih.gov/31078624/.

22. Dong J, Viswanathan S, Adami E *et al.* (2021) Hepatocyte-specific IL11 cis-signaling drives lipotoxicity and underlies the transition from NAFLD to NASH. *Nature Communications* **12**, 66https://doi.org/10.1038/s41467-020-20303-z.

23. Sweeney M, O'Fee K, Villanueva-Hayes C *et al.* (2023) Interleukin 11 therapy causes acute heart failure and its use in patients should be reconsidered. *bioRxiv*, 2023.2009.2030.560259https://www.biorxiv.org/content/biorxiv/early/2023/10/01/2023.09.30.560259.full.pdf.

24. Wu J, Ma W, Qiu Z *et al.* (2023) Roles and mechanism of IL-11 in vascular diseases. *Frontiers in cardiovascular medicine* **10**, 1171697https://www.ncbi.nlm.nih.gov/pmc/articles/PMC10250654/.

25. Lim WW, Corden B, Ye L *et al.* (2021) Antibody-mediated neutralization of IL11 signalling reduces ERK activation and cardiac fibrosis in a mouse model of severe pressure overload. *Clinical and experimental pharmacology & physiology* **48**, 605-613https://pubmed.ncbi.nlm.nih.gov/33462828/.

26. Corden B, Lim WW, Song W *et al.* (2021) Therapeutic Targeting of Interleukin-11 Signalling Reduces Pressure Overload-Induced Cardiac Fibrosis in Mice. *Journal of cardiovascular translational research* **14**, 222-228https://pubmed.ncbi.nlm.nih.gov/32592090/.

27. Leung JH, Ng B, Lim WW (2022) Interleukin-11: A Potential Biomarker and Molecular Therapeutic Target in Non-Small Cell Lung Cancer. *Cells* **11**https://www.ncbi.nlm.nih.gov/pmc/articles/PMC9318853/.

28. Maroni P, Bendinelli P, Ferraretto A *et al.* (2021) Interleukin 11 (IL-11): Role(s) in Breast Cancer Bone Metastases. *Biomedicines* **9**https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8228851/.

29. Wang S, Zhang C, Jiao S *et al.* (2024) Abstract 2365: Disrupting IL-11/IL-11R signaling by an efficacious anti-IL-11 antibody 9MW3811 enhances T cell tumor infiltration and synergizes with anti-PD-1 therapies in vivo. *Cancer Research* **84**, 2365-2365https://doi.org/10.1158/1538-7445.AM2024-2365.

30. Dong B, Zhu J, Chen X *et al.* (2023) The Emerging Role of Interleukin-(IL)-11/IL-11R in Bone Metabolism and Homeostasis: From Cytokine to Osteokine. *Aging and disease* **14**, 2113-2126https://www.ncbi.nlm.nih.gov/pmc/articles/PMC10676798/.

31. Kido S, Kuriwaka-Kido R, Imamura T *et al.* (2009) Mechanical stress induces Interleukin-11 expression to stimulate osteoblast differentiation. *Bone* **45**, 1125-1132https://pubmed.ncbi.nlm.nih.gov/19665600/.

32. Shaughnessy SG, Walton KJ, Deschamps P *et al.* (2002) Neutralization of interleukin-11 activity decreases osteoclast formation and increases cancellous bone volume in ovariectomized mice. *Cytokine* **20**, 78-85https://pubmed.ncbi.nlm.nih.gov/12445802/.