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.

GM-CSF

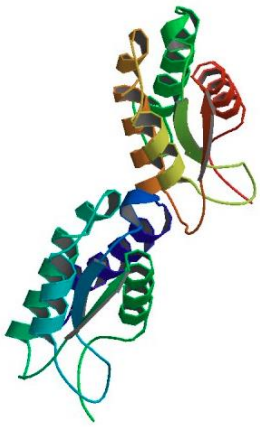
Evidence Summary

Pilot clinical studies show that GM-CSF can modulate the immune system in neurodegenerative disease patients, but the consistency and clinical utility of these changes is unclear. Long-term safety in this population needs to be established.

Neuroprotective Benefit: GM-CSF can modulate peripheral immune profiles in patients with neurodegenerative disease. Some of these changes may be neuroprotective, but the conditions to reliably produce beneficial effects have not been established, and may vary with disease, stage, or individual factors.

Aging and related health concerns: GM-CSF's effects on certain age-related disease can be beneficial or detrimental, depending on the disease due to its context-dependent nature.

Safety: GM-CSF has hematological effects and some well-known side effects that can be mitigated, though the long-term side effects in elderly individuals is not clear.

Availability: Available with a prescription as sargramostim (Leukine) or molgramostim with IV or subcutaneous administration	**Dose**: 250 µg/m^2 per day (s.c.) in Alzheimer's trial, 6 µg/kg or 3 µg/kg per day (s.c.) in Parkinson's trials	**Chemical formula:** $C_{639}H_{1006}N_{168}O_{196}S_8$ **MW:** 14434.5 Da  **Source:** Drugbank
Half-life: 162 minutes (subcutaneous)	**BBB**: Penetrant (in animals)	
Clinical trials: GM-CSF has been tested in hundreds of clinical trials, with the majority as an adjunct to cancer drugs. Sargramostim was also tested in two small trials in Parkinson's (n=20; n=5) and one in Alzheimer's disease (n=40).	**Observational studies**: Elevated GM-CSF levels have been found to be associated with disease severity in several inflammatory conditions.	

What is it?

Granulocyte-macrophage colony stimulating factor (GM-CSF) is a secreted glycoprotein that promotes the proliferation and differentiation of hematopoietic stem cells to myeloid cells (macrophages and dendritic cells). It is one of four colony-stimulating factors (macrophage-CSF, granulocyte-CSF, and IL-3 are the other three). It is used to promote white blood cell recovery after bone marrow transplant. Other uses of GM-CSF include improvement of neutrophil recovery after chemotherapy in patients with acute myeloid leukemia and to improve survival in patients exposed to myelosuppressive doses of radiation (sargramostim label). Pharmaceutical-grade GM-CSF drugs include sargramostim (Leukine) and molgramostim (Leucomax).

Neuroprotective Benefit: GM-CSF can modulate peripheral immune profiles in patients with neurodegenerative disease. Some of these changes may be neuroprotective, but the conditions to reliably produce beneficial effects have not been established, and may vary with disease, stage, or individual factors.

Types of evidence:

- One observational study in cancer patients
- One pilot study in Alzheimer's disease
- Two pilot studies in Parkinson's disease
- Multiple biomarker studies
- Multiple preclinical studies

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

Cancer-related cognitive impairment:
In cancer patients undergoing hematopoietic cell transplantation, a situation which can cause cognitive decline, patients concurrently taking recombinant GM-CSF plus granulocyte-colony stimulating factor (G-CSF) had greater cognitive improvement at six months (but not 12 months) than those taking only G-CSF. At 12 months, both groups had improved about equally (Jim et al, 2012).
A prospective, longitudinal cohort study examined the relationship between plasma cytokines, brain derived neurotrophic factor (BDNF), and cognitive trajectories in patients with breast cancer (n=136) (Yap et al., 2021). While IL-6 was the only cytokine to show a significant association, there were trends for an inverse relationship between IFN-γ, IL-1β, IL-4, IL-8, and GM-CSF with BDNF, such that the patients with the worst cognitive trajectories showed high levels of these inflammatory cytokines and low levels of BDNF. However, it is unclear whether the elevation in GM-CSF contributes to the negative impacts on BDNF and cognition, or whether it acts as a compensatory protective factor to counter the effects of the other pro-inflammatory cytokines.

Human research to suggest benefits to patients with dementia

Alzheimer's disease: GM-CSF CAN MODULATE THE PERIPHERAL IMMUNE RESPONSE
GM-CSF and its receptor, GM-CSF Rα, were expressed throughout the brain in Alzheimer's patients and non-Alzheimer's patients, primarily in neurons with some expression in astrocytes, ependymal cells, and

cells in the choroid plexus. Although there was no change in GM-CSF expression, GM-CSF Rα expression was reduced in the hippocampus of Alzheimer's patients and slightly reduced in the cortex (Ridwan et al, 2012).

In a study examining multiple cerebrospinal fluid (CSF)inflammatory biomarkers, Taipa et al (2019) reported that GM-CSF CSF levels were not increased in patients with Alzheimer's disease or frontotemporal dementia. However, there was an inverse correlation with disease progression, suggesting that higher levels were more beneficial. Llano et al (2012) also reported no difference in CSF levels of GM-CSF in Alzheimer's patients or controls. However, Tarkowski et al (2001) reported an increase in CSF and serum levels of GM-CSF in patients with Alzheimer's and vascular dementia. The differences in the results could be due to variability of the assays or the different characteristics of the patients. Each of the previous studies was small (~20 patients per group).

In a double-blind, placebo-controlled RCT testing sargramostim at a dose of 250 mcg/m^2/day via subcutaneous injection (s.c.) five days/week for three weeks in patients with mild to moderate Alzheimer's disease (n=40) (NCT01409915), treatment led to statistically significant alterations to the peripheral immune profile (Potter et al., 2021). These changes include increases in the absolute numbers of monocytes, lymphocytes, and neutrophils, as well as increases in the plasma cytokines IL-2, IL-6, IL-10, and tumor necrosis factor alpha (TNF-α), and a decrease in IL-8. These immunomodulatory effects of sargramostim are reflective of the broad-spectrum of immune-related effects that can be elicited by GM-CSF, as it influences classically pro- or anti-inflammatory cytokines, as well as those with context-dependent functions. Although underpowered for its secondary outcomes on cognition, there was a statistically significant increase in cognitive function based on MMSE score relative to placebo at the end of the trial, with a mean difference of 1.80. The change in MMSE was correlated with the log change in immune cells. An improvement relative to baseline was seen in 70% of sargramostim-treated patients, compared to 35% placebo-treated patients, at this time point. By the 90-day follow-up, the number of patients showing improvement relative to baseline dropped to 55% of sargramostim and 25% of placebo-treated patients. No significant treatment effects were seen on the ADAS-Cog13 or ADCS-ADL. In an exploratory biomarker analysis, sargramostim treatment was associated with a 10% increase in plasma Aβ40, a 24% decrease in total tau, and 42% decrease in UCH-L1, a biomarker of neurodegeneration.

Overall, this study suggests that sargramostim can impact the peripheral immune profile in patients with Alzheimer's disease, but it is unclear whether it is driving the immune system into a more pro-inflammatory, anti-inflammatory, tolerogenic, or into some hybrid state of activation. The current evidence suggests it may be the latter. It is also unclear how much GM-CSF is getting into the CNS, and

the impact it is having on immune cell numbers/activation in the CNS either through direct activity or via its effects in the periphery. More work is needed to determine whether the potential effect on cognition is meaningful and sustainable, and whether it is linked to specific changes to the immune system.

Parkinson's disease: GM-CSF CAN MODULATE THE PERIPHERAL IMMUNE RESPONSE
In an RCT of 20 Parkinson's patients, 56-day treatment with sargramostim (6 µg/kg per day) increased the number of regulatory T cells, altered immune-linked plasma metabolites, and improved scores of motor function. (Gendelman et al, 2017).
In a follow-up unblinded, open-label Phase 1b trial (NCT03790670), five male patients with Parkinson's disease were treated with 3 µg/kg/day sargramostim (five days on, two days off s.c.) for one year (Olson et al., 2021). As a proof-of-concept study, it does not adequately address the therapeutic potential of this intervention, but offers insights towards its mechanism of action for potential benefit. Treatment altered the peripheral immune profile. Levels of white blood cells increased, including lymphocytes, monocytes, eosinophils, and neutrophils. Sixty percent (3 out of 5) of the patients showed a decrease in MDS-UPDRS Part III scores relative to baseline, though there was wide variability across individuals. While there was no significant increase in overall CD4+ T cells, there were changes to certain subpopulations, namely a sustained increase in CD4+CD127lowCD25+ T regulatory cells (Tregs) and a transient increase in CD4+CD127highCD25+ T effector cells. There were also increases in surface and costimulatory molecules associated with enhanced Treg function, such as ItgB7, FOXP3, FAS, CD27, and CD45RA. The inverse association between MDS-UPDRS Part III scores and levels of Tregs with markers of elevated suppressive activity suggests that the potential neurological benefits of GM-CSF stem from its immunomodulatory activity, particularly its tolerogenic effects. Considering the heterogeneity seen in this small sample, it may be that a certain subpopulation of patients, likely those with a particular dysregulated immune profile, may be most likely to benefit from this intervention. More work is needed to determine this patient subpopulation.

Mechanisms of action for neuroprotection identified from laboratory and clinical research:
The hypothesis for its use in Alzheimer's disease stems from the observation that patients with rheumatoid arthritis (RA) have a reduced risk for Alzheimer's disease. At first it was thought that the anti-inflammatory medications taken by individuals with RA may reduce the risk for Alzheimer's. However, after the failure of many NSAID trials, some investigators thought there might be something intrinsic in RA for reducing risk. GM-CSF is increased in joints in RA, and research begun to look at the link between GM-CSF and Alzheimer's.

Later research suggested that GM-CSF may also be a neurotrophic factor in the brain. GM-CSF and its receptor, GM-CSF R, are expressed in the brain, and GM-CSF may be involved in the proliferation and differentiation of neural stem cells, astrocytes, and microglia. GM-CSF signals through a heterodimeric receptor with an α-binding subunit (GM-CSFRα) and a β-signaling subunit (GM-CSFRβ) (Ridwan et al, 2012).

Labeled GM-CSF was reported to cross the blood brain barrier in rodents (McLay et al, 1997). However, the GM-CSF used in the study was murine, recombinant GM-CSF. Sargramostim has a leucine instead of a proline at position 23 and is produced in yeast, thus it has a different glycosylation pattern. Molgramostim is produced in *E. Coli* and is un-glycosylated. It is not clear whether these differences would alter the blood brain barrier penetration in humans. Glycosylated GM-CSF shows less immunogenicity and greater pharmacokinetic availability.

Cerebral small vessel disease: GM-CSF IS ELEVATED WITH DISEASE SEVERITY
Microscopic polyangiitis (MPA) is a form of anti-neutrophil cytoplasmic antibody-associated vasculitis which can lead to stroke. In a study looking at the relationship between serum cytokines and disease severity (n=50), serum levels of GM-CSF were significantly higher in those with high-grade white matter hyperintensities (WMH) compared to those with low-grade WMH (1.47, 95% CI 0.25 to 12.1 pg/mL vs. 0.25, 95% CI 0.25 to 1.60 pg/mL) (Ota et al., 2021). As a result, high serum GM-CSF levels were associated with a diagnosis of high-grade WMH (odds ratio [OR] 5.59, 95% CI 1.16 to 27.02; P = 0.032). High serum GM-CSF was also associated with several scales for disease severity. It is unclear whether the increased GM-CSF plays a detrimental role, or whether its upregulation is indicative of a protective response toward the inflammation driving the cerebrovascular damage.

Alzheimer's disease: In an *ex vivo* study of brain explants from aged Alzheimer's mice, treatment of slices with GM-CSF, but not other molecules (IL-10, TGF-B, IL-6, IL-12/p40), reduced the amyloid halo around plaques, leaving only a core amyloid plaque. This was accompanied by the proliferation and accumulation of microglia around amyloid plaques. Additionally, co-culturing microglia from young mice, as well as young GM-CSF knockout mice, also reduced the amyloid halo around plaques, suggesting that other young factors besides GM-CSF can increase microglia uptake of amyloid (Daria et al, 2017). In an Alzheimer's animal model, mouse recombinant GM-CSF (50ug/kg – once/day for ten days followed by two rounds of five injections) increased the number of regulatory T cells in the plasma. There were no effects on the number of amyloid plaques, though amyloid beta oligomers were decreased in the brain. GM-CSF also improved cognition and increased the number of microglia (Iba1

expression), increased synaptic density, and increased neurogenesis (Kiyota et al, 2018). In another study in an Alzheimer's animal model, a single intrahippocampal injection of GM-CSF reduced amyloid burden one week later. Twenty daily subcutaneous injections reduced amyloid load, increased microglial markers (Iba1 expression), increased synaptic density, and improved cognition (Boyd et al, 2010). In the APP/PSEN1 mouse model, GM-CSF was found to be the second-most upregulated cytokine in the brain (5.47-fold increase) next to IL-17A (6.31-fold increase). A similar increase in GM-CSF was not seen in the context of healthy aging in the rodent brain (Varga-Medveczky et al., 2021).

On the other hand, Shang et al (2016) reported that GM-CSFRβ (but not GM-CSFRα) mRNA was increased in Alzheimer's patients' monocytes. In an *in vitro* model of the blood brain barrier, monocytes with high GM-CSFRβ had increased permeability through the barrier and reduced the expression of tight junction proteins. Intracerebral injection of a GM-CSF neutralizing antibody reduced the infiltration of peripheral monocytes into an Alzheimer's mouse brain. In addition, Manczak et al (2009) reported that five days after intracerebral injection of an GM-CSF neutralizing antibody in an Alzheimer's animal model there was a reduction in amyloid plaques, a non-significant reduction in AB42, a non-significant increase in AB40, and reductions in a number of inflammatory cytokines (IL-6, IL-1) and inflammation markers (CD40, CD11b).

The reason for these mixed results is unclear. Both Kiyota et al (2018) and Manczak et al (2009) used older Alzheimer's animals while Boyd et al (2010) started treating animals at a younger age. The doses or types of administration could be responsible for some of the opposing effects.

Non-Alzheimer's animal models

Intracerebral ventricular injection of GM-CSF also increased neuroinflammation which was prevented by co-injection of a GM-CSF neutralizing antibody (Reddy et al, 2009). In addition, intrahippocampal injection of GM-CSF was used as a model of schizophrenia. It increased inflammation and behavioral deficits, results that were partially reduced by coadministration of minocycline (Zhu et al, 2014).

GM-CSF knockout mice were reported to have cognitive deficits. Although there were no gross structural changes in GM-CSF knockout mice hippocampi, there were microstructural alterations, including a reduction in dendrite length and spine density, though this did not result in a reduction of hippocampal long-term potentiation. AAV-viral reduction or enhancement of GM-CSF Rα expression in the hippocampus slightly reduced or increased cognition, respectively (Krieger et al, 2012). Similarly,

GM-CSF-enriched human umbilical cord plasma improved cognition in aged mice, though it did not alter levels of neurogenesis (Castellano et al, 2017).

In hippocampal slice cultures from male rats, GM-CSF induced the proliferation of microglia. In contrast to priming with the pro-inflammatory cytokine IFNγ, treatment with GM-CSF did not induce inflammatory neuroinflammation in the presence of LPS (Dikmen et al., 2020). However, chronic GM-CSF treatment did trigger network dysfunction, as evidenced by disturbances in gamma oscillations. The proposed mechanism is a loss of excitation-inhibition balance. Due to the context-dependent nature of GM-CSF signaling, it is unclear whether a similar network dysfunction would occur *in vivo*. Additionally, it is unclear whether these conditions, i.e., sustained high concentrations of GM-CSF within the hippocampus, would occur *in vivo* outside of an infection or injury. Systemic administration of GM-CSF as a therapeutic is unlikely to result in chronically high local concentrations in the CNS.
In the context of a sciatic nerve crush injury in mice, innate immune cell activity is important for nerve regeneration. Myeloid cells in the injured nerve were found to upregulate expression of the receptors for GM-CSF, and GM-CSF regulates the inflammatory milieu of the nerve in a manner that promotes repair (Kalinski et al., 2020). The infiltration of these myeloid cells is important for the induction of inflammation resolution. In the absence of GM-CSF, the resolution of inflammation is delayed, and there is a failure of nerve regeneration. Notably, this GM-CSF-associated innate immune response does not occur in the context an axotomy injury, in which regeneration is inefficient or absent. This suggests that GM-CSF may promote a neuroprotective immune response, at least under certain conditions.

Conclusion
The results from preclinical studies are conflicting. However, GM-CSF treatment appears to increase markers of inflammation in animal models. There is an ongoing debate whether markers of inflammation are beneficial (they are a sign of microglial uptake of amyloid) or detrimental (a sign of the release of pro-inflammatory cytokines).

The conflicting results seen in preclinical studies are a reflection of the heterogeneity of immune responses that can be elicited in response to GM-CSF. GM-CSF is best understood as an immunomodulatory cytokine because it can promote either a pro- or anti-inflammatory immune response based on the overall immune landscape (Zhan et al., 2019). In this way, the activity of GM-CSF cannot be considered in isolation, as its downstream effects are dependent on its environment. The prevailing hypothesis is that the effects are based on the signaling strength of GM-CSF, which is influenced by the local concentration, the presence of its cognate receptor and on which cell types it is

present, and the presence or absence of other immunomodulatory signals, such as cytokines, chemokines, and co-stimulatory molecules (Zhan et al., 2019). Thus, the potential for the induction of a neuroprotective immune response will likely vary across diseases, disease stages, and even across individuals depending on the nature of their immune landscape.

It is clear from clinical studies that GM-CSF can alter the peripheral immune profile in patients with neurodegenerative diseases, and from preclinical studies that it can promote an environment conducive for neural repair in some contexts. The major outstanding question is whether the conditions which steer GM-CSF to induce a neuroprotective response are present in patients with neurodegenerative diseases. The optimal immune response may differ across different diseases and/or disease stages. GM-CSF can induce an alternative state in macrophages and microglia which promotes phagocytic activity which may be beneficial for the clearance of toxic proteins and fostering a repair-oriented environment. In Parkinson's patients, the induction of suppressive Tregs appears to be important for shaping a neuroprotective environment. The induction of Treg stems from the induction of tolerogenic dendritic cells by GM-CSF (Bhattacharya et al., 2015). In mice, these tolerogenic dendritic cells are found in the CD11c+CD8a- subset, and some studies suggest that the presence of the co-stimulatory molecule OX40L is an important mediator in this process (Marinelarena et al., 2018).
To determine patient populations who may benefit from GM-CSF studies will need to assess baseline immune profiles and analyze whether there is an association between the immune profile induced following treatment relative to baseline. Additionally, since the downstream effects are influenced by the level of GM-CSF, the dose needed for an optimal response may vary across patients/indications, and will need to be carefully considered.

APOE4

None reported

Aging and related health concerns: GM-CSF's effects on certain age-related disease can be beneficial or detrimental, depending on the disease due to its context-dependent nature.

Types of evidence:

- 4 meta-analyses or systematic reviews in cancer
- 1 clinical study in coronary artery disease
- 3 clinical studies in peripheral arterial disease
- Multiple reviews on GM-CSF and immune responses
- Multiple preclinical studies of cardiovascular disease and stroke

Cardiovascular Disease: MIXED

The potential effects of GM-CSF on atherosclerosis are mixed with one study in hyperlipidemic rabbits suggesting a reduction in plaque size (45% vs. 74% for GM-CSF vs. placebo) (Shindo et al, 1999) and another study suggesting an increase in plaque size in ApoE-/- mice on a high fat diet (25% vs. 10% for GM-CSF vs. placebo) (Haghighat et al, 2007). Similarly, injection of GM-CSF increases the proliferation of cells in an atherosclerotic lesion in a mouse model of atherosclerosis while injection of an anti-GM-CSF antibody reduces proliferation (Zhu et al, 2009). Other preclinical cardiovascular models suggest that GM-CSF promotes myeloid and dendritic cell infiltration, proliferation and pro-inflammatory cytokine release (Mindur and Swirski, 2019). A summary of the effects of GM-CSF (and the related IL-3) in different inflammatory diseases can be found in (Borriello et al, 2019).

However, GM-CSF (and G-CSF) may be beneficial in certain cardiovascular complications (such as ischemia or myocardial infarction), as they can also promote arteriogenesis and neovascularization in preclinical studies (Kovacic et al, 2007). In addition, a small clinical study reported that local administration of GM-CSF over two weeks improved coronary collateral flow in patients with advanced coronary artery disease (Seiler et al, 2001).

In support of these studies, multiple studies of ischemic stroke have reported that administration of GM-CSF reduces infarct size, reduces cell death, and improves neurological outcomes. CSF levels of GM-CSF are increased in humans after acute stroke, though levels were not correlated with improved neurological outcomes (Lanfranconi et al, 2011).

Peripheral arterial disease: Peripheral arterial disease (PAD) is an obstruction of the arteries, often as a result of atherosclerosis. GM-CSF has been shown to play a role in the mobilization of hematopoietic

and endothelial progenitor cells involved in vascular repair. GM-CSF has been tested in several clinical trials for this indication. In the Phase 1 GPAD-1 study (n=45), GM-CSF promoted the mobilization of these progenitor cells into the circulation. In the Phase 2 GPAD-2 RCT (NCT01041417) (n=159), increases in progenitor cell mobilization were associated with increased performance on a treadmill walking task. In the PROPEL study (NCT01408901) (n=210), the combination of GM-CSF with exercise training did not improve treadmill walking distance. A Phase 2 GPAD-3 double-blind, placebo-controlled RCT (NCT03304821) is underway to further test the ability of GM-CSF to improve walking distance and quality of life measures in this patient population (Mehta et al., 2020).

Autoimmune disease: MIXED

The pro-inflammatory properties of GM-CSF are most closely tied to its role in disease progression in rheumatoid arthritis, where it is elevated in the synovial fluid of affected joints, and associated with pain worsening (Zhan et al., 2019). GM-CSF is also implicated as a disease driver in multiple sclerosis. However, GM-CSF is associated with protective effects in some other autoimmune diseases and their associated preclinical models. A key distinction between these effects may be the relative contribution of T cell activity (cellular response) compared to humoral responses, in driving disease activity (Lofti et al., 2019). GM-CSF can be secreted by multiple cell types, and the signaling strength may vary depending on the cell type and conditions under which it is produced (Zhan et al., 2019). The direct effects of GM-CSF are primarily on myeloid cells. The GM-CSF-induced changes to these cells can influence the overall immune response, and in doing so has indirect effects on a variety of other immune cell types. The conditions under which GM-CSF will drive particular immune responses has not been well characterized, though some broad generalizations have been described.

Both rheumatoid arthritis and multiple sclerosis are typically classified as T-cell driven inflammatory diseases, and the indirect effects of GM-CSF on T cells may differ based on the level of T cell activation in a given environment. In the context of highly inflammatory activated T cells, GM-CSF tends to trigger the activation of pro-inflammatory NF-kB signaling in macrophages, and the induction of mature antigen-presenting dendritic cells, which will lead to a further exacerbation of inflammatory damage (Zhan et al., 2019) (Bhattacharya et al., 2015). Alternatively, GM-CSF can induce immature tolerogenic dendritic cells, which promote the expansion of Tregs, under conditions of low inflammation and antigen loads. Consequently, GM-CSF and anti-GM-CSF approaches have both been used in the context of different autoimmune diseases, to varying degrees of success (Lofti et al., 2019). More work is needed to determine the conditions under which GM-CSF promotes tolerance or inflammation, so that treatments can be tailored more effectively.

Cancer: MIXED

The therapeutic potential for GM-CSF has been most widely tested in the context of cancer. These studies highlight the heterogeneity in the immune responses that can be triggered by GM-CSF. While often considered a proinflammatory cytokine, GM-CSF can produce pro-inflammatory, anti-inflammatory, or tolerogenic responses depending on environment. The effect is likely dictated by the combination of the local abundance of GM-CSF and the milieu of other immunomodulatory cytokines and signaling receptors present in a given tissue (Zhan et al., 2019).

Immunostimulation: GM-CSF has been used as adjunct to immunotherapies and cancer vaccines to try to boost the anti-tumor immune response (Lazarus et al., 2021). The results have been mixed. The reasons for the disparate results across trials appears to be related to dose, the type of combination therapy, and the type or stage of cancer. In this context, the role of GM-CSF is to prime the immune response so that the immunotherapies may have a more potent response. One mechanism by which GM-CSF can achieve this is through the maturation of dendritic cells, which present cancer neoantigens to T cells and activate them via costimulatory molecules, and thus may boost the anti-tumor T cell response (Tarhini et al., 2021). Some studies have shown that GM-CSF treatment was associated with increases in circulating levels of mature dendritic cells, and of tumor-infiltrating T cells (Tarhini et al., 2021). Use of GM-CSF in melanoma is associated with some of the best results of this approach, thus far, though potential benefits have been inconsistent (Lazarus et al., 2021) (Tarhini et al., 2021). The success of this approach in some patients is likely because melanomas are known to be highly immunogenic tumors.

A meta-analysis of six trials including 445 patients found that the combination of GM-CSF (sargramostim) with the checkpoint inhibitor ipilimumab, which targets cytotoxic T-lymphocyte-associated antigen 4 (CTLA-4), an inhibitory signal on T cells, was associated with improved overall survival (Hazard Ratio [HR] 0.70, 95% CI 0.60 to 0.82) (Chen et al., 2018). However, there were trends, but no significant improvements to response rate or progression-free survival. These findings suggest that benefits to survival may stem from the mitigation of immunotherapy-related adverse events, rather than from enhanced anti-tumor activity, per se. Patients using the combination had a lower incidence of gastrointestinal disorders (RR 0.25 to 0.34), relative to those taking ipilimumab alone (Chen et al., 2018), which may be related to the protective role of GM-CSF in the maintenance of the intestinal homeostasis (Dabritz 2015). One of the primary clinical uses of GM-CSF is to accelerate recovery from radiation treatment. Furthermore, a meta-analysis of 15 studies including 1043 cancer patients found that GM-CSF significantly accelerated the recovery of hematological parameters following chemotherapy (Yu et al., 2018).

Immunosuppression: GM-CSF has been shown to be secreted by a variety of tumor cell lines (Zhan et al., 2019). High concentrations of GM-CSF within the tumor microenvironment serve to promote the reprogramming of macrophages into myeloid-derived suppressor cells (MDSCs), leading to an anergic, immunosuppressive response to the tumor (Zhan et al., 2019). When used as an adjuvant at high doses GM-CSF has also shown immunosuppressive effects that promote tumor growth (Lazarus et al., 2021). Meanwhile, when administered at a low-dose, GM-CSF was able to potentiate anti-tumor immune responses, at least in some patients. Since the effects of GM-CSF are highly dependent on the local concentration and environmental immune milieu, a personalized approach may be needed, such that the treatment strategy can be tailored to the immune profile of a given cancer patient.

Covid-19: MIXED

GM-CSF and anti-GM-CSF have both been proposed as potential therapeutic strategies for Covid-19. Elevated GM-CSF was found to be associated with severe Covid-19 in the ISARIC4C study, which included 471 patients requiring hospitalization and 39 patients with mild disease (Thwaites et al., 2021). Principal components analysis indicated a central role for GM-CSF in Covid-19 pathogenesis. However, since the samples were collected an average of nine days following symptom onset, this association may be a sign of an impaired (late) immune response, such that an early elevation of GM-CSF may foster pathogen clearance, while a late elevation is indicative of a delayed pro-inflammatory response which is more harmful than beneficial. An RCT (MASH-COVID) (NCT04399980) (n=40) testing the anti-GM-CSF, mavrilimumab (6 mg/kg i.v.), found that this treatment has no significant effect on outcomes (Cremer et al., 2021). GM-CSF is also being tested in clinical trials for Covid-19. In one of the trials (n=81) (NCT04326920), treatment with inhaled sargramostim for five days improved lung oxygenation (54% vs 26% in placebo group), and did not lead to induction of a cytokine storm (Press release). It is likely that efficacy of either strategy is contingent on the stage of infection (early vs late), as the effects of GM-CSF will vary in accordance with the phase of the overall immune response.

Safety: GM-CSF has hematological effects and some well-known side effects that can be mitigated, though the long-term side effects in elderly individuals is not clear.

Types of evidence:

- 1 meta-analysis of RCTs in Crohn's disease
- 1 meta-analysis of trials in cancer
- 1 meta-analysis of RCTs in burn patients
- 2 pilot trials in Parkinson's disease
- 1 pilot trial in Alzheimer's disease

In a meta-analysis of RCTs for Crohn's disease more patients in the sargramostim group experienced a serious adverse event than patients in the placebo group (2 studies, 251 participants; pooled RR = 2.17; 95%CI 0.82-5.70). Adverse events include injection site reactions (90% vs 12% in drug vs. placebo), bone pain (37% vs. 7%), musculoskeletal chest pain (36% vs. 5%), and dyspnea (13% vs. 0%) (Roth et al, 2012). Other reported adverse events include hypersensitivity reactions (anaphylactic reactions), risk of myelosuppression when administered within 24 hours of chemotherapy, edema and capillary leak syndrome, supraventricular arrhythmias (reversible after discontinuation), leukocytosis (an increase in white blood cell count), possibly myeloid malignancies, and induction of neutralizing anti-drug antibodies (sargramostim label). In a meta-analysis of studies looking at GM-CSF following chemotherapy, GM-CSF treatment was associated with an increased risk for fever (RR 3.44, 95% CI 1.43 to 8.28), and the distribution of other adverse events was highly variable across patients, likely due to patient-specific factors (Yu et al., 2018). GM-CSF was not associated with systemic adverse events in patients with second-degree burns based on an analysis of seven RCTs, but increased swelling and pain at the wound sites were common (Li et al., 2020).

Although long-term effects of sargramostim are not known, in a Parkinson's trial side effects at a dose of 6 µg/kg per day included injection site reactions (100% of treated, 40% of non-treated), abnormal laboratory values (increased white blood cell count – 100% of treated, 30% non-treated), and abnormal pain at non-injection sites (e.g. bone extremities, chest-tightening – 70% of treated, 30% non-treated) (Gendelman et al, 2017). Lowering the dose to 3 µg/kg/day was associated with better tolerability, with fewer reports of pain, rashes, muscle soreness and weakness, and itching than at the higher dose (Olson et al., 2021). Elevated white blood cell counts were seen in all patients, and the majority (80%) had injection site reactions. There were no serious adverse events in this 12-month study.

In patients with mild to moderate Alzheimer's disease, sargramostim, at a dose of 250 mcg/m^2/day s.c. (5 days/week for 3 weeks), was not associated with any drug-related serious adverse events or amyloid-related imaging abnormalities (Potter et al., 2021). The most common sargramostim-associated adverse events were dermatological (16 sargramostim vs. 5 for placebo), gastrointestinal (8 vs. 5), and headache (8 vs. 2).

Sargramostim should not be used in those who have a hypersensitivity to GM-CSF or yeast-derived products. A formulation containing benzyl alcohol is toxic to babies, and sargramostim has not been tested in pregnant women (sargramostim label).

Drug interactions:
Sargramostim is associated with many moderate drug interactions, most of which are cancer drugs (drugs.com).

Sources and dosing:
GM-CSF is available as sargramostim or margramostim. Sargramostim is typically used at a dose of 250 µg/m^2/day i.v. or s.c. for approved indications (drugs.com). Doses used in clinical trials include 250 µg/m^2 of sargramostim per day for five days in Alzheimer's trial, 6 µg/kg or 3 µg/kg of sargramostim per day in Parkinson's trial. The optimal dosing is likely to vary with disease indication, and possibly from person to person.

Research underway:
According to Clinicaltrials.gov, there are currently over 450 active clinical trials involving GM-CSF. This includes a Phase 2 trial for sargramostim in Alzheimer's disease (NCT04902703).

Search terms:
granulocyte-macrophage colony stimulating factor +
alzheimer, aging, atherosclerosis, lifespan, cardiovascular
sargramostim

Websites:

- Clinicaltrials.gov
- Pubchem
- Drugbank
- Drugs.com

***Disclaimer**: Cognitive Vitality Reports® do not provide, and should not be used for, medical advice, diagnosis, or treatment. You should consult with your healthcare providers when making decisions regarding your health. Your use of these reports constitutes your agreement to the **Terms & Conditions**.*

If you have suggestions for drugs, drugs-in-development, supplements, nutraceuticals, or food/drink with neuroprotective properties that warrant in-depth reviews by ADDF's Aging and Alzheimer's Prevention Program, please contact INFO@alzdiscovery.org. To view our official ratings, visit Cognitive Vitality's Rating page.