



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.

cGAS-STING Inhibitors

Evidence Summary

Chronic overactivation of cGAS-STING promotes inflammation that accelerates a variety of aging-related diseases, but inhibition of this pathway could increase vulnerability to infection.

Neuroprotective Benefit: Inhibiting cGAS-STING may protect neurons by mitigating chronic inflammation in the context of mitochondrial stress and autophagic dysregulation, but the effects are likely to be context dependent.

Aging and related health concerns: cGAS-STING inhibition may protect against inflammation driven diseases of aging, but may promote cancer by limiting cellular senescence in cells with genomic instability/DNA damage.

Safety: The safety profile has not been established, but there are potential risks for infection and cancer based on its mechanism of action.



What is it? Cyclic GMP-AMP synthase (cGAS) is a cytosolic DNA sensor that acts as a pattern recognition receptor and **stimulates an innate immune pathway to promote pathogen clearance** [1]. cGAS is primarily activated by long double stranded DNA, as it will only be activated once it interacts with the level of nucleic acids capable of inducing into a conformation where the active site is suitably structured [2]. In this way, there is a threshold effect that can prevent activation in the presence of normal low levels of DNA [3]. The organization of DNA into chromatin prevents cGAS activation within the nucleus of a healthy cell, but the presence of micronuclei, such as in a genetically unstable cancer cell, can activate it [2]. Activation of cGAS leads to its catalytic activity, the synthesis of the second messenger cyclic GMP-AMP (cGAMP), which goes on to activate the transmembrane receptor, stimulator of interferon genes (STING) [2]. The cGAMP signal can be spread through cellular syncytium via gap junctions. The activation of STING induces a signaling platform that leads to the recruitment and activation of TANK binding kinase 1 (TBK1), which then leads to the activation (phosphorylation) of the transcription factor interferon regulatory factor 3 (IRF3), leading to its dimerization and translocation to the nucleus where **it induces the expression of type 1 interferons** and other interferon responsive genes.

The cGAS-STING-IRF3 pathway is important for defense against DNA viruses and intracellular bacteria. cGAS-STING is an ancient defense pathway, that utilized the activation of autophagy to clear pathogens [4]. In vertebrates, the pathway utilizes both inflammatory (interferon) and autophagic mechanisms. In healthy organisms, activation of this pathway is protective with anti-viral and anti-cancer properties, however, chronic overactivation can lead to deleterious inflammation, and can promote aging-related diseases, neurodegenerative diseases, and autoimmunity [2]. Since cGAS-STING signaling interacts with a variety of other signaling pathways, **the effects of its activation can be context dependent**, which could complicate therapeutic development [5]. cGAS-STING inhibitors are still in preclinical development, while cGAS-STING activators have been developed, and some have been clinically tested for cancer [6].

Neuroprotective Benefit: Inhibiting cGAS-STING may protect neurons by mitigating chronic inflammation in the context of mitochondrial stress and autophagic dysregulation, but the effects are likely to be context dependent.

Types of evidence:

- Numerous laboratory studies



Human research to suggest prevention of dementia, prevention of decline, or improved cognitive function? None

Human research to suggest benefits to patients with dementia: None

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

Neuroinflammation: The cGAS-STING pathway acts as an intermediary in the process of how mitochondrial stress and impaired proteostasis induce pathological neuroinflammation and lead to neurodegeneration. cGAS is negatively regulated by apoptosis, so the release of DNA from apoptotic cells should not trigger this pathway, however, it can be activated by intact cells that release DNA due to cellular stress [5]. Metabolic stress that damages mitochondria can lead to the release of mitochondrial DNA (mtDNA) into the cytosol, which then triggers the cytosolic DNA sensor cGAS, activation of STING, and ultimately induction of the type 1 interferon (IFN) and interferon responsive genes [7]. The interferon-mediated pro-inflammatory response is designed to be transient, and is primarily directed at pathogen clearance [1]. To avoid immune overactivation, there are regulatory feedback loops built into the pathway [8]. Depending on which part of the regulatory pathway is disrupted and the cellular conditions, chronic overactivation can have different effects ranging from autoimmune disease to immune exhaustion.

One of the key regulatory mechanisms involves autophagy, as there is **extensive cross-talk between the autophagy and interferon pathways** [9]. The association of cGAS with the autophagy protein beclin-1, leads to the removal of a negative regulator, leading to the induction of autophagy [10]. This promotes the autophagic degradation of both cytosolic DNA and cGAS itself, which dampens cGAS activity by removing the source of stimulation. The interaction with beclin-1 also inhibits the production of cGAMP, the second messenger that drives IFN production. This regulatory process can be circumvented by type 1 IFN, which induces the E3 ligase TRIM14 to stabilize cGAS and prevent its degradation [11]. Therefore, cGAS-STING signaling is sensitive to the cellular environment, and this pathway can become chronically activated in the context of elevated inflammation and disrupted autophagy, as is common in many neurodegenerative diseases.

STING is also regulated in an autophagy dependent manner. Activation of STING can activate autophagy independently of IFN production, which plays a role in pathogen clearance. STING dependent autophagy is dependent on some classical autophagy machinery (WIP12, ATG5), but is independent of other key



players (ULK, beclin-1, ATG9A, p62) [4; 12]. STING itself also becomes a target for degradation, which prevents overactivation.

This suggests that in the context of high mitochondrial stress resulting in an accumulation of cytosolic mtDNA as well as an impairment in autophagy, that there can be chronic, unrestrained activation of the cGAS-STING-IFN pathway and associated inflammation [8]. The compensatory responses to the chronic activation could lead to exhaustion, which further exacerbates autophagy dysfunction, and ultimately leads to cell death. Based on its role as a mediator of cellular/mitochondrial stress-related neuroinflammation, cGAS-STING could be a central target applicable to a variety of neurodegenerative conditions [1]. However, due to its context dependent nature, it is important to know the specific mechanisms driving cGAS-STING activation as well as the impact of compensatory effects for each disease in order to target it in a safe and effective manner.

Alzheimer's disease: MIXED (Preclinical)

There is conflicting data from animal models as to whether inhibition of cGAS-STING could be beneficial for Alzheimer's disease (AD), which likely stems from the context dependency of cGAS-STING signaling. In a mouse model of chronic neurodegeneration, an upregulation of cytosolic DNA sensors, including cGAS, were found to drive type 1 IFN and pro-inflammatory cytokine production in microglia [13]. In 5 month old APP/PS1 AD mice, stimulation of the STING-IRF3 pathway with cGAMP was neuroprotective by inducing TREM2 [14]. In this model, cGAMP reduced pro-inflammatory cytokines (IL-1 β , TNF α), augmented anti-inflammatory cytokines (IL-10, IL-4), and shifted the microglial phenotype to a more M2-like state, via TREM2 upregulation. STING activation was also found to be protective in two models (muMT strain; intracerebroventricular injection of streptozotocin) of endogenous retrovirus-related hippocampal memory impairment, where it may protect against retrotransposon-mediated DNA damage [15]. Reduced cGAS-STING activation through the genetic variant, STING R293Q was associated with reduced risk for cognitive impairment (Odds ratio OR: 0.439, 95% Confidence Interval [CI] 0.199 to 0.972, $p = 0.042$) in a subgroup of smokers ($n=69$) [16], but similar cognitive protection was not seen in the entire cohort ($n=3397$) or in a subpopulation of obese ($n=931$) [16; 17]. Since the protective effects in this population were primarily related to cardiovascular disease, the impact on cognition may have been related to vascular dementia. These studies suggest that due to the heterogeneity within the clinical AD population, the response to cGAS-STING inhibitors may vary amongst patients, depending on their particular pathological profile.



Parkinson's Disease: POTENTIAL BENEFIT (Preclinical)

In mouse models of Parkinson's disease that involve the loss of Pink1 or Parkin, overactivation of the cGAS-STING pathway is associated with dopaminergic neuron degeneration [18]. The loss of Pink/Parkin disrupts mitochondrial homeostasis, so these animals are more susceptible to mitochondrial stress damage. The mitochondrial stress leading to release of mtDNA into the cytosol can lead to the activation of cGAS-STING, and downstream inflammatory processes. Notably, STING deficient mice are protected from dopaminergic cell loss and associated neurological phenotypes, while STING deficient flies are not. Since, cGAS-STING couples to the inflammatory interferon pathway in vertebrates, but not invertebrates, it suggests that the innate immune inflammatory response may be mediating the neuronal damage in mammals [19].

Traumatic brain injury: POTENTIAL BENEFIT (Preclinical)

STING was found to be upregulated (within 6 hours) in the brains of individuals who died from traumatic brain injury (TBI) in areas both ipsilateral (fold change 2.73 ± 0.51 ; $p = 0.0003$) and contralateral (fold change 2.19 ± 0.41 ; $p = 0.0139$) to the injury site [20]. A similar elevation in STING was detected in the controlled cortical impact brain injury model in mice [20]. STING deficient mice had a reduced inflammatory response (TNF α , IL-6, IL-1 β , IFN) and lesion volume. The lack of STING normalized autophagic flux following TBI, which may have contributed to the improved neurological outcome.

Ischemic stroke: POTENTIAL BENEFIT (Preclinical)

In the transient middle cerebral artery occlusion (tMAO) model of ischemic stroke, ischemia led to the release of DNA into the cytosol, triggering the activation of the cGAS-STING-IFN pathway, in male mice [21]. This led to the induction of pro-inflammatory cytokines, inflammasome activation, and a form of inflammatory cell death called pyroptosis. Treatment with a cGAS antagonist (A151 Synthetic oligonucleotide 300 μg i.p. starting after reperfusion) reduced immune cell infiltration, neuronal loss, and infarct volume. cGAS-STING inhibition may be best suited for minimizing pathological inflammation following acute brain trauma, since acute treatment is unlikely to compromise immunity or lead to long-lasting (mal)adaptive compensatory changes to immune responses.

Huntington's Disease: POTENTIAL BENEFIT (Preclinical)

cGAS and phosphorylated TBK1 have been found to be increased in the striatum in postmortem brain tissue from patients with Huntington's disease [22]. The elevated cGAS promotes autophagy by enhancing autophagosome formation, and may contribute to the increased autophagic flux in (mHTT) Huntington's disease cells [22]. Huntington's disease model mice (mHTT R6/2) were found to have



increased levels of cytosolic mtDNA, which accumulated with disease progression [23]. This led to activation of cGAS-STING-IFN mediated inflammation. The increase in mitochondrial stress and cytosolic mtDNA may have been related to decreased levels of endogenous melatonin, as treatment with exogenous melatonin was able to prevent activation of this pathway. This suggests that increases in levels of reactive oxygen species (ROS) and other mitochondrial stressors and/or a decline in endogenous antioxidant mediators may be the catalyst for pathological inflammation and autophagic dysregulation in Huntington's disease.

APOE4 interactions: Not known

Ageing and related health concerns: cGAS-STING inhibition may protect against inflammation driven diseases of aging, but may promote cancer by limiting cellular senescence in cells with genomic instability/DNA damage.

Types of evidence:

- 1 gene variant association study for STING and aging-related diseases (n=3397)
- Numerous laboratory studies

Cellular senescence/Aging: POTENTIAL BENEFIT (Preclinical)

cGAS is an important inducer of the senescence associated secretory phenotype (SASP) in response to DNA damage, particularly through the production of type 1 IFNs [24]. The pro-inflammatory cytokine response can trigger 'inflammaging'. In cell culture, cGAS deficiency prevents the expression of senescence-associated inflammatory genes in response to DNA damaging agents, in both human and mouse cells. STING deficient mice also show a reduced SASP phenotype [24]. Innate immunity signaling via cGAS-STING is associated with a variety of aging-related diseases. In a study of 3,397 older adults (aged 65-103), **the STING R293Q variant allele (rs7380824), which has impaired function, was found to be associated with reduced risk for aging-related diseases** (OR: 0.823, 95% CI 0.683 to 0.89, $p = 0.038$), especially chronic lung disease, likely due to a reduction in 'inflammaging' [16]. The protective effect was strongest in individuals who experience high levels of DNA damage and mitochondrial/metabolic stress, such as cigarette smokers (OR: 0.391, 95% CI 0.222 to 0.686, $p = 0.001$) and the obese (OR: 0.651, 95% CI 0.462 to 0.917, $p = 0.014$) [16; 17]. In these subgroups the variant was primarily protective against cardiovascular disease.



The cGAS-STING-IFN pathway may also play a role in transposable element induced aging-related inflammation. In mice, de-repression of the transposable element LINE1 can induce DNA damage and lead to the accumulation of cytosolic LINE1 DNA, which triggers cGAS and the type 1 IFN inflammatory response [25]. However, there is also evidence that cGAS acts within the nucleus to monitor and protect against genomic instability [2], so it is unclear whether cGAS-STING inhibition could potentially lead to a higher overall level of DNA damage, but reduce the inflammatory response to it.

Cancer: MIXED/POTENTIAL HARM

The induction of cellular senescence by the cGAS-STING pathway in response to the accumulation of DNA damage typically acts to prevent cells from becoming cancerous. cGAS-STING signaling interacts with a variety of cell death pathways, including apoptosis, necroptosis, pyroptosis, and autophagy-induced cell death [5]. Additionally, the cGAS-STING-IFN response can stimulate both innate and adaptive immune cells to recognize and attack cancerous cells [6]. Consequently, cGAS-STING activating therapies are being developed for cancer. **In most cases, cGAS-STING acts as a tumor suppressor.** For example, in lung adenocarcinoma, low cGAS expression and low STING expression are associated with poor survival (Hazard ratio HR: 1.85, 95% CI 1.4 to 2.5; HR: 1.52, 95% CI 1.1 to 2, respectively) [24].

The cGAS-STING pathway is part of the innate immune response that recognizes cancer cells, stimulates type 1 IFN production, and allows for the antigen cross-priming that drives the anti-cancer adaptive immune response [26]. cGAS-STING-IFN activation plays a crucial role in the activation of antigen-presenting dendritic cells. CD8+ T cells primed with cGAMP can drive anti-tumor immunity [6]. However, the effects of cGAS-STING signaling are context dependent, and certain types of tumors can co-opt this pathway to stimulate tumor growth and invasion [6]. Chronic activation of STING can drive an anti-inflammatory immunosuppressive response, which promotes carcinogenesis, and in this environment, STING can drive malignant transformation and metastasis. Therefore, cGAS-STING agonists will need to be used in a selective, personalized manner.

A variety of cGAS-STING agonists have been developed and have been tested alone or in combination with other immunotherapies, primarily checkpoint inhibitors, in clinical trials for cancer [26]. The initial trials had been largely unsuccessful, but this may be because the agonists used were not well suited for human use or the downregulation of cGAS and/or STING in the tumor tissue prevented an adequate response.



Obesity/metabolic disease: POTENTIAL BENEFIT (Preclinical)

There are strong interactions between metabolism and immunity. Metabolic stress can induce inflammation. A high fat diet can induce mitochondrial damage leading to the release of mtDNA into the cytosol, and activation of the cGAS-STING-IFN sterile inflammation response [7]. This chronic inflammation contributes to accelerated aging and increased risk for a variety of aging-related diseases, especially cardiovascular disease [17]. **cGAS-STING activation can promote inflammation** in the vasculature and adipose tissue by enhancing the recruitment of pro-inflammatory monocytes to these tissues [27]. Activation of this pathway also promotes high-fat diet induced metabolic dysfunction, as STING deficient mice fed a high-fat diet have improved insulin sensitivity [27]. cGAS-STING acts as a negative regulator of thermogenesis in adipose tissue, thus chronic activation can lead to the storage rather than the utilization of excess fuel, contributing to obesity [28]. This regulatory pathway may be designed to prevent mitochondrial overloading and mitigate mitochondrial dysfunction-related cell damage [28]. Consequently, blocking this pathway could potentially have both protective and deleterious effects on mitochondrial function and integrity in a context dependent manner.

Cardiovascular disease: POTENTIAL BENEFIT (Preclinical)

cGAS-STING driven inflammatory responses are associated with cardiac damage, adverse remodeling, and fibrosis. In obese individuals (n=931), the STING R293Q variant allele was associated with reduced risk for cardiovascular disease (OR: 0.490, 95% CI 0.285 to 0.841, $p = 0.010$) [17]. Obesity is typically associated with increased systemic inflammation, but relative to non-carriers, the STING allele carriers had reduced levels of c-reactive protein (CRP) (4.41 $\mu\text{g/L}$ vs 5.11 $\mu\text{g/L}$) and IL-6 (2.98 ng/L vs 3.30 ng/L), suggesting that cGAS-STING activation contributes to obesity-related inflammation. In mice, inhibition of cGAS-STING attenuated high-fat diet (palmitic acid)-induced cardiomyocyte contractile dysfunction [29]. Similarly, cGAS-STING inhibition preserved left ventricular contractile function and protected against cardiac hypertrophy, fibrosis, and apoptosis in a mouse model of traverse aortic constriction [30]. It also reduced the infiltration of immune cells and inflammatory cytokine expression in cardiac tissue. Suppression of the interferon response via treatment with an IFNAR neutralizing antibody (MAR1-5A3 500 μg i.p at 8 and 48 hours after ligation) reduced inflammatory immune cell infiltration, improved cardiac function, and improved survival after myocardial infarction in mice [31]. The interferon response may be one of the key drivers of cardiac inflammation after myocardial infarction, as interferon-responsive genes were found to be among the most upregulated classes following myocardial infarction in mice [31].



Liver disease: POTENTIAL BENEFIT (Preclinical)

The cGAS-STING-IFN pathway is associated with both alcoholic and non-alcoholic-related liver inflammation and injury [7]. An analysis of liver tissue from patients with alcoholic liver disease (n=51), found that the expression of cGAS-STING-IFN pathway related genes (STING and IRF3) correlated with disease severity. In mice, alcohol consumption increased hepatic expression of the cGAS-STING-IFN pathway, which is likely driven by an increase in the level of cytosolic mtDNA [32]. Metabolic stress, such as through consumption of a high-fat diet, can disrupt mitochondrial stability and lead to the release of mtDNA into the cytosol, and subsequent activation of the cGAS-STING-IFN pathway. In mouse models of high-fat diet induced liver disease, STING deficiency mitigates hepatic steatosis, fibrosis, and inflammation [7]. Loss of STING also improves the overall metabolic phenotype. These metabolic effects may be related to the crosstalk between the cGAS-STING and mTOR pathways [7].

Lung disease: POTENTIAL BENEFIT (Preclinical)

The cGAS-STING pathway is triggered in response to DNA damage and cellular stressors that induce mitochondrial damage in lung cells, and can promote pulmonary fibrosis. The reduced function STING R293Q variant allele was found to offer protection against chronic lung disease (OR: 0.730, 95% CI 0.576 to 0.924, $p = 0.009$), and carriers with lung disease had lower levels of inflammation markers, such as CRP [16]. Cigarette smoke can induce the release of DNA from damaged lung cells, which recruits immune cells and activates the cGAS-STING-IFN inflammatory pathway [33]. In cell culture, lung fibroblasts from patients with idiopathic pulmonary fibrosis had higher levels of cytosolic mtDNA [34]. Elevated cGAS was detected in fibrotic lung tissue, and was associated with the induction of cellular senescence. In culture, treatment of control lung fibroblasts with STING activator cGAMP promoted a senescence phenotype, while treatment of patient-derived fibrotic lung fibroblasts with cGAS siRNA or the cGAS inhibitor RU.521 reduced their expression of senescence markers (p16, p21) and production of inflammatory cytokines (IL-6).

Kidney disease: POTENTIAL BENEFIT (Preclinical)

cGAS-STING mediated inflammation may contribute to renal inflammation and fibrosis. In tissue samples from patients with chronic kidney disease (n=433), cGAS and STING expression were correlated with kidney fibrosis [35]. STING inhibition (C-176) can also alleviate fibrosis in a mouse model of kidney disease.

Autoimmune disease: MIXED- DISEASE DEPENDENT

The cGAS-STING pathway is primarily an innate immune pathway to help the body detect and clear pathogens. Activation relies on the detection of pathogen (viral, bacterial, etc.) DNA (nucleic acids) in the cytosol, however, the cGAS sensor cannot distinguish between self-DNA and foreign DNA in the cytosol [3]. Therefore, events such as cell trauma or mutations in proteins that degrade cytosolic self-DNA or lead to mitochondrial/DNA damage can result in excess activation of the cGAS-STING-IFN pathway, resulting in autoimmune disease [36]. Autoimmune diseases associated with overactivation of this pathway include Bloom syndrome, Wiskott-Aldrich syndrome, Aicardi-Goutieres syndrome, systemic lupus erythematosus, and STING-associated vasculopathy with onset in infancy. However, not all autoimmune diseases are driven by overactivation of the interferon inflammatory pathway, and in some conditions, activation of this pathway can mitigate disease [37]. For example, type 1 IFNs are therapeutic in multiple sclerosis and IFN- β was one of the first FDA approved therapies for the treatment of relapsing-remitting multiple sclerosis due to its anti-inflammatory effects in this condition.

Safety: The safety profile has not been established, but there are potential risks for infection and cancer based on its mechanism of action.

Types of evidence:

- Several laboratory studies

Clinically suitable cGAS-STING inhibitors have not yet been developed, so all of the studies conducted thus far, using a variety of research grade inhibitors, have involved preclinical models [1]. These proof-of-concept studies primarily used acute treatment and did not test short or long-term safety.

Based on its endogenous functions in pathogen defense and the induction of cellular senescence, the **major safety concerns for a prospective cGAS-STING inhibitor would be increased risks for infection and cancer**. It has been suggested that inhibition of cGAS-STING would not lead to the same degree of immunosuppression as agents that target common downstream inflammatory targets, because it leaves other pattern recognition receptor systems intact [1]. Additionally, while they are more vulnerable to infection from DNA viruses, cGAS knockout mice appear generally healthy [24]. This suggests that cGAS-STING inhibitors may increase susceptibility to a specific subset of pathogens and risks for both infection and cancer may vary from person to person due to the context dependent nature of cGAS-STING signaling. While likely best suited for acute conditions, it may be possible to use them for chronic



conditions with an intermittent dosing schedule, as is done with some other immunosuppressive agents [1].

Drug interactions: Interactions have not been established, but cGAS-STING inhibitors will likely interact with other immunosuppressant drugs.

Sources and dosing: There are currently no cGAS-STING inhibitors available for human use, though some are available for preclinical research use.

Research underway: The cGAS-STING inhibitors identified thus far have suffered from poor drug properties, and thus work is underway to develop clinically viable cGAS-STING inhibitors.

Search terms:

Pubmed, Google: cGAS/STING + Inhibitor

- Alzheimer's disease, Parkinson's disease, neurodegeneration, aging, senescence, cardiovascular, cancer, inflammation, fibrosis, autophagy, immunity

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