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.

OGG1 Agonists

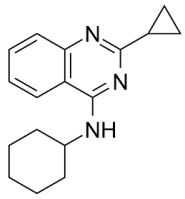
Evidence Summary

OGG1 protects cells against oxidative stress damage, and its reduction with aging may promote cellular aging. Augmenting its activity could mitigate age-related cell damage, but more studies are needed.

Neuroprotective Benefit: Reduced OGG1 activity is seen in neurodegenerative disease and may serve as a risk factor. It needs to be determined whether increasing OGG1 activity can mitigate age or disease-related cognitive decline.

Aging and related health concerns: OGG1 activity decreases with aging leading to increased oxidative stress damage and cancer risk. The augmentation of OGG1 activity may help preserve genomic integrity during aging.

Safety: Very limited safety data is available from cell culture studies. Safety profiles will be dependent on drug-specific properties, but target-related safety concerns are low.

Availability: Research use	**Dose**: Not established	**TH10785** **Chemical formula:** $C_{17}H_{21}N_3$
Half-life: Not established	**BBB**: Not established	**MW**: 267.37 g/mol
Clinical trials: None	**Observational studies**: Variants in OGG1 that reduce its function are associated with increased risk for mortality, cancer, and neurodegenerative diseases.	 Source: MedChemExpress

What is it?

8-oxoguanine DNA glycosylase 1 (OGG1) is a base excision repair enzyme that helps protect the integrity of the genome by catalyzing the removal of oxidized guanine (8-oxoG) from DNA. 8-oxoG is one of the most common DNA base lesions and is formed in the presence of reactive oxygen species (ROS) under oxidative conditions [1]. 8-oxoG tends to accumulate in aged cells, and can be mutagenic due to misreading by DNA polymerases. The glycosylase OGG1 initiates the base excision repair process to remove oxidized guanine [2]. OGG1 is the major glycosylase involved in the removal of 8-oxoG, however, additional glycosylases are present which can facilitate the removal of oxidized guanine, thus major accumulation of 8-oxoG and phenotypic effects regarding OGG1 deficiency are typically only seen when the activity of several of these glycosylases are reduced and/or under conditions of high oxidative stress. Reductions in OGG1 base excision repair activity is seen in the context of aging, especially in the brain, where decreased OGG1 activity has been associated with several neurodegenerative diseases. Due to these associations, OGG1 agonists are currently in preclinical development for neurodegenerative diseases [1]. Reduced OGG1 activity has also been implicated as a risk factor for some types of cancer, due to the mutagenic potential of 8-oxoG [2]. However, in the context of cancer, elevated OGG1 activity could promote the viability of tumor cells that would otherwise be targeted for removal, thus OGG1 antagonists are also being developed as potential anti-cancer therapeutics.
In addition to its base excision repair activity, OGG1 can act in concert with 8-oxoG as an epigenetic regulator of the response to oxidative stress [2]. Under low to moderate levels of ROS, the base excision repair activity of OGG1 will dominate. However, under conditions of high ROS, post-translational modifications temporarily inhibit the enzymatic activity of OGG1, allowing it to instead act as a transcriptional enhancer to support the recruitment of transcription factors that mediate pro-inflammatory responses, such as the NF-kB and MAPK signaling cascades. This can support the removal

of highly oxidatively damaged cells, which may pose a threat for oncogenic transformation. In pathological settings, chronically high ROS may result in a shift in the balance toward high inflammation and low repair.
As a result, the OGG1 activators and inhibitors in development are generally targeted toward certain aspects of its activity. Different indications will likely benefit from certain types of OGG1 modulators. Base excision repair activators are expected to have the widest utility for the prevention/mitigation of age-related diseases.

Neuroprotective Benefit: Reduced OGG1 activity is seen in neurodegenerative disease and may serve as a risk factor. It needs to be determined whether increasing OGG1 activity can mitigate age or disease-related cognitive decline.

Types of evidence:

- 11 biomarker studies for OGG1 and Alzheimer's disease
- 1 biomarker study for OGG1 and Parkinson's disease
- 2 gene association studies for OGG1 variants and Alzheimer's disease
- 4 gene association studies for OGG1 variants and Parkinson's disease
- 2 gene association studies for OGG1 variants and Huntington's disease
- Numerous laboratory studies of OGG1 biology

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

OGG1 agonists have not yet been clinically tested, however, there is evidence from gene association studies to suggest that reduced function of OGG1 is associated with a higher risk for several neurodegenerative diseases, including Alzheimer's disease (AD).
Several genetic variants in OGG1 which appear to reduce its enzymatic activity have been identified. The most common and best studied variant is Ser326Cys, where C is the major allele, and G is the minor allele (rs1052133) [3]. The minor allele has been shown to occur at frequencies ranging from 25 to 40% in Caucasian populations, and from 40 to 60% in Asian populations [4]. This variant has reduced catalytic activity, especially under oxidizing conditions, where the enzymatic activity is reduced around 40% in *in vitro* assays [4]. Various studies have found that the presence of this variant can result in higher levels of oxidatively damaged DNA, however, the net effect, in terms of disease risk, appears to be highly

dependent on the overall genetic landscape in combination with exposure to environmental stressors. As a result, the effect of the Ser326Cys variant on disease risk can vary from person to person, which can lead to inconsistencies in gene association studies across different populations. The impact of Ser326Cys and other OGG1 variants appears to be greatest under conditions where the function of other genes involved in base excision repair is suboptimal due to either genetic variants or modifications, and when an individual is exposed to mitochondria-damaging toxins. In addition to gene variants, OGG1 activity can be influenced by the methylation status of its promoter as well as post-translational modifications to the protein [2]. Although the mechanism by which OGG1 enzymatic activity is reduced may vary, the totality of the evidence suggests that low OGG1 activity is a common feature of neurodegenerative disease, and likely serves as a predisposition factor.

Alzheimer's disease: REDUCED OGG1 ACTIVITY IS ASSOCIATED WITH INCREASED RISK

The levels of oxidized DNA, as measured by the most common oxidative DNA lesion, 8-oxo-7,8-dihydroguanine (8-oxoG), have been shown to be increased in the blood and plasma of patients with AD, which is indicative of increased levels of oxidative damage and/or reduced levels of DNA repair. Levels of 8-oxoG in the DNA from blood lymphocytes was found to be 20.5 pg/mL for AD patients, relative to 9.1 pg/mL for age-matched controls [5]. Similarly, plasma levels of 8-hydroxy-2'-deoxyguanosine (8-OHdG) were 0.61- 0.73 ng/mL in AD patients, relative to 0.2-0.24 ng/mL in controls [6]. The increase is seen early in the disease course and may trigger compensatory changes in the levels of DNA repair enzymes. This may account for fluctuations in levels of oxidized guanine over the course of disease progression. The levels of proteins involved in DNA repair, including OGG1, have been shown to decrease in peripheral blood lymphocytes after age 60 [7]. There are eight major isoforms of OGG1, three of which are classified as type 1, 1a, 1b, and 1c; the first primarily localizing to the nucleus, while the latter two are localized to mitochondria and generally expressed at a higher level [8]. The OGG1-1b isoform tends to be a major driver of OGG1 protein levels. In the context of aging, there is a decline in the expression of both mitochondrial isoforms, with levels of OGG1-1b decreasing approximately two-fold, leading to a related decline in protein levels [9]. In AD patients, there is a drastic decline in OGG1-1b by approximately 100-fold, coupled with the massive upregulation of the other type 1 isoforms early in the disease course, which wanes with disease progression [10]. Due to the additional non-enzymatic activity of OGG1 to act as a transcriptional enhancer regulating the expression of inflammatory mediators, the upregulation of the nuclear OGG1 isoform could be counterproductive by contributing to the induction of pro-inflammatory signaling cascades.

The degree of oxidized DNA damage in AD patients can be subject to modification depending on the activity status of OGG1. Several studies have found that levels of oxidized DNA damage were higher in

AD patients carrying the Ser326Cys variant of OGG1, whereas these variant differences were not always present in control populations [6; 8; 11]. Similarly, a small study (n=24) found that AD patients were more likely to have mutations in OGG1 (Ser326Cys and others) which reduce its catalytic activity [12]. A role for OGG1 promoter hypermethylation has been less clear, due to differences across studies assessing different populations. Hypermethylation of the OGG1 promoter in blood cells was not seen in cohorts of AD patients in Italy (n=111) [13] or in patients with mild cognitive impairment (MCI) of Chinese Uyghur descent (n=168) [14], however an association was seen in ApoE4 carriers from a separate study of Uyghurs with AD (n=51) [15].

A study of postmortem brain tissue found that individuals with preclinical AD (n=10) had levels of 8-hydroxyguanosine (8-OHG) in nuclear DNA from the hippocampus/parahippocamapal gyri and superior/middle temporal gyri that were 1039.4% (range 123.4 to 2931.1%) higher than brain tissue from age-matched controls (n=8) [16]. The increase in 8-OHG was accompanied by a presumed compensatory increase in the expression of OGG1. A separate study examining the expression of base excision repair genes, including OGG1, in blood (n=166) or postmortem brain tissue (n=51) in relation to AD trajectory found that while base excision repair gene expression was generally higher in the brain than the blood, mRNA expression of OGG1 was reduced in the blood in individuals with clinical cognitive impairment (AD and MCI), but a clear separation with disease status in the brain regions studied was not apparent [17]. Notably, the association was with cognition rather than AD pathology, as there were no clear associations of OGG1 with CSF Aβ or tau. The inconsistent associations of disease state with OGG1 expression may be a reflection of a greater contribution to post-translational changes in OGG1 activity in the context of dementia. Levels of 8-OHdG were found to be elevated in postmortem brain tissue (n=21) from patients with AD or MCI, relative to controls [18]. The levels of this oxidized DNA marker were inversely correlated with activity levels of OGG1 in the brain. While this appeared to be driven by a reduction in levels of the OGG1 protein in the nuclear compartment, the impairment to OGG1's enzymatic activity in the mitochondrial compartment appeared to be driven by the modification of OGG1 by the lipid peroxidation product 4-hydroxynonenal (HNE), which is formed under conditions of oxidative stress.

Overall, these studies suggest that the expression and activity of OGG1 is altered in AD, and these changes occur early in the disease course. Genetic variants or modifications that reduce the enzymatic activity of OGG1 may mediate susceptibility to oxidative stress-related pathology.

Parkinson's disease: ELEVATED OXIDIZED DNA DAMAGE IS ASSOCIATED WITH RISK

Exposure to mitochondrial toxins is a well-established risk factor for Parkinson's disease (PD), however, the effect is mediated by genetic susceptibility. Gene association studies suggest that variation in base excision repair genes, including OGG1, may moderate the risk associated with toxin exposure. Elevated serum levels of 8-OHdG have been seen in PD patients, and this increase in 8-OHdG appears to be a risk factor [9]. There are numerous mechanisms by which levels of oxidized guanine could be increased, with reduced activity of base excision repair proteins representing one possibility. There are inconsistencies across studies regarding whether certain base excision repair gene variants on their own are associated with increased risk for PD, likely because the impact of these variants depends on the oxidation state, and tend not to appreciably influence phenotypes outside of oxidative conditions [19; 20]. In support of this, a study including 619 PD patients and 854 controls found that carriers of the Ser326Cys OGG1 variant did not show elevated risk unless they were also exposed to mitochondria-damaging/oxidative stress-inducing toxins (Odds Ratio [OR]: 1.79, 95% Confidence Interval [CI] 1.22 to 2.64), while individuals without this variant (CC genotype) who were exposed to toxins did not show an elevated risk for PD [21]. Likewise, an enhanced vulnerability to dopaminergic loss following exposure to mitochondrial toxins (MPTP) is seen in OGG1 deficient rodents [10].

Similar to the compensatory changes seen in AD, an upregulation of mitochondrial isoform OGG1-2a, has been seen in the substantia nigra in postmortem brain tissue from patients with early-stage PD, with levels 1.6 to 2.9-fold higher than age-matched controls [22]. This protective response to increased oxidative stress damage tapers off with advanced disease progression.

Huntington's disease: ASSOCIATION WITH OGG1 IS UNCLEAR

Huntington's disease (HD) results from the expansion of the CAG repeat in the Huntingtin gene, leading to a loss of function. The size of the repeat is associated with age of onset, such that longer repeats are associated with an earlier age of disease onset. In addition to errors in DNA replication, mechanisms involved in base repair can also result in the lengthening of DNA tracts, referred to as somatic expansion. The 'toxic oxidation cycle' model proposes that age-related increases in oxidative DNA damage in neurons could lead to an increase in base excision and single strand break repair mechanisms, resulting in CAG expansion, which could contribute to HD onset and progression [23]. While there was no difference in the presence of the Ser326Cys OGG1 variant between HD patients and controls, one study in Italy (91 cases; 211 controls) found that HD variant carriers tended to have longer CAG expansions and an earlier age of onset [23]. However, a separate study including 419 German HD patients did not replicate this finding [24], and a study in a rodent model of HD (R6/1) found that age-

related CAG expansion was reduced in the absence of OGG1 [25]. Together these studies suggest that if oxidative stress-related CAG expansion is clinically relevant, it likely involves multiple DNA repair genes, such that the contribution of OGG1 may be minimal and depend on the activity status of other DNA repair enzymes.

Human research to suggest benefits to patients with dementia:

OGG1 agonists have not been tested in dementia patients. While they could potentially be useful to slow disease progression, they would likely be most beneficial for prevention and during the preclinical phase.

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

Alzheimer's disease and brain aging: POTENTIAL BENEFIT (Preclinical)
Preclinical rodent models support a role for altered OGG1 activity in the context of aging and AD. The function of OGG1 is most consequential under oxidative conditions, which is a common feature of aging. The brain has one of the lowest capacities for mitochondrial base excision repair, thus it is particularly vulnerable to decreases in the expression and/or activity of the major players in this process, as occurs during aging [26]. Furthermore, the capacity for mitochondrial base excision repair differs across brain regions, such that those with lower capacities, like the hippocampus, show greater vulnerability to age-related oxidative damage, while regions with higher capacity, like the cerebellum, are more resistant.

In the brains of male mice, the OGG1 promoter was found to be increasingly methylated with age, along with a reduction in base excision repair activity [27]. OGG1 was found to be mutated (p.R304W) in all strains of senescence accelerated mice (SAMP), though on its own this mutation was not sufficient to shorten lifespan [28]. Furthermore, relative to a strain of mice that does not show accelerated senescence, brain levels of OGG1, especially mitochondrial-targeted OGG1, declined more precipitously with age, leading to an accumulation of mitochondrial DNA damage [29]. While neurons lacking OGG1 can develop normally under physiological conditions, they show a deficit in neurite growth under oxidative conditions stemming from dysfunctional mitochondria [30].

OGG1 is dynamically regulated under conditions of oxidative stress. Aerobic exercise is a paradigm that leads to transient elevation of ROS, leading to a transient reduction in OGG1 activity, which appears to be mediated by a change in acetylation status. Since aerobically trained animals show cognitive benefits,

it is unclear whether this adaptive regulation of OGG1 activity is important for cognition. In mice, exercise training was shown to reduce the acetylation of OGG1, which was driven by the activity of the deacetylase SIRT3 [31]. Similarly, a study in rats found that exercise training reduced acetylated OGG1 levels via the induction of the deacetylase SIRT1, while the expression of OGG1 was ultimately increased by training [32]. The trained rats also showed better spatial memory performance. The deacetylation of OGG1via treatment with the HDAC1 activator, exifone, reduced 8-oxoG levels and enhanced measures of synaptic plasticity in both 5XFAD mice and aged (14–17-month-old) wildtype mice [33]. Together these suggest that OGG1 activators may need to allow for the dynamic regulation of physiological OGG1 activity to help preserve age-related cognition, as chronic OGG1 activation may not produce the desired effect. Ultimately, OGG1 activators will need to be tested *in vivo*.

Similar to what has been seen in AD patients, AD models show that a reduction in OGG1 which enhances vulnerability to oxidative stress damage, and the expression of OGG1 is altered in an attempt to compensate for the loss of activity. Transgenic ArcSwe mice show increased expression of OGG1 during the stage of pre-plaque Aβ deposition, likely as a response to elevated levels of oxidative stress [34]. OGG1 deficiency accelerated the accumulation of 8-oxoG and microgliosis in the brains of AD (AppNL-G-F/NL-G-F knock-in) mice [35]. In the 3xTg-AD, OGG1 deficiency increased 8-oxoG accumulation, microglial activation, and neuronal loss, leading to an acceleration of symptomatic cognitive impairment [1].

APOE4 interactions: Not established

Aging and related health concerns: OGG1 activity decreases with aging leading to increased oxidative stress damage and cancer risk. The augmentation of OGG1 activity may help preserve genomic integrity during aging.

Types of evidence:

- 3 meta-analyses of gene association studies on OGG1 variants and lung cancer
- 3 meta-analyses of gene association studies on OGG1 variants and gastrointestinal cancer
- 3 meta-analyses of gene association studies on OGG1 variants and breast cancer
- 2 meta-analyses of gene association studies on OGG1 variants and overall cancer risk
- 2 meta-analyses of gene association studies on OGG1 variants and cataracts
- 1 meta-analysis of gene association studies on OGG1 variants and pancreatic cancer

- 1 meta-analysis of gene association studies on OGG1 variants and bladder cancer
- 1 gene association study on OGG1 variants and all-cause mortality
- 1 biomarker study on OGG1 expression and cancer prognosis
- 1 biomarker study on OGG1 expression and atherosclerosis
- 3 preclinical studies on OGG1 agonists
- Numerous laboratory studies on OGG1 biology

Aging: ELEVATED 8-OXOG AND REDUCED OGG1 ARE ASSOCIATED WITH AGING AND MORTALITY
Base excision repair is critical to the maintenance of genomic integrity throughout the lifespan of an organism [26]. The accumulation of oxidatively damaged DNA following ROS exposure can lead to increased mutational burden which hampers cell function. Telomeres are especially sensitive to ROS-mediated damage. Chronic induction of 8-oxoG lesions can lead to telomere shortening and hinder cell survival [36]. Under oxidative conditions, deficiency of the base excision repair enzyme OGG1 can trigger replicative stress, telomere loss, and chromosomal fusion.
The first step of base excision repair involves the enzymatic activity of DNA glycosylases. OGG1 is the primary glycosylase to catalyze the removal of oxidized guanine [2]. Its activity is especially important in mitochondria, which have fewer mechanisms to cope with DNA damage relative to the nucleus and are thus highly reliant on base excision repair [26]. One study found that the ratio of oxidized guanine to unmodified guanine (8-oxodG/dG) in mitochondrial DNA from brain and heart tissue was inversely correlated with maximum lifespan in mammals [37]. This suggests that the accumulation of oxidative damage in mitochondria is a key driver of aging. Consistent with this finding, individuals homozygous (Cys/Cys) for the Ser326Cys variant which reduces the enzymatic activity of OGG1 were found to have a higher risk for all-cause mortality (Hazard Ratio [HR]: 1.69, 95% CI 1.09 to 2.62) and cardiovascular mortality (HR 3.31; 95% CI 1.68 to 6.53) in a study of 7,170 older adults (age 55 to 80) from Spain at risk for cardiovascular disease [38].
OGG1 mutations were found to be present in senescence accelerated (SAMP) mice [28]. These mice show 1.5 to 1.9-fold higher levels of oxidized hepatic nuclear DNA, though on its own these OGG1 mutations did not significantly shorten lifespan [39]. OGG1 knockout mice also show an increased (2.8-fold) steady state level of oxidized DNA in hepatocytes, which increased over the lifespan [40]. Similar effects were not seen in splenocytes, spermatocytes, kidney cells, or fibroblasts from these mice, suggesting that particular tissue types, namely those with slow proliferation rates and high oxidative metabolism, are more vulnerable to the accumulation of oxidative damage in the absence of OGG1. In cultured skin cells (keratinocytes), a 19.42-fold increase in levels of 8-OH-dG was detected in cells from older (age 60-82) donors relative to those from younger (age 2-45) donors [41]. This was accompanied

by a significant decline in the expression of base excision repair genes, including OGG1, as well as an increase in pro-inflammatory NLRP3 activation and IL-1β levels. These studies suggest that enhancement of OGG1 enzymatic activity could mitigate age-related declines in mitochondrial and cellular function, though this remains to be tested.
Thus far, OGG1 activators have only been tested in cell culture. The small molecule OGG1 activator TH10785 interacts with the phenylalanine-319 and glycine-42 amino acids to lead to a 10-fold increase in the catalytic activity of OGG1, and an enhancement of cellular DNA repair [42]. A series of allosteric small molecule OGG1 activators reduced paraquat-induced mitochondrial dysfunction, by enhancing the integrity of the mitochondrial DNA and membrane dynamics [43]. Similarly, a series of small molecule OGG1 enhancers, augmented the repair activity of OGG1 and protected against paraquat-induced mitochondrial toxicity in lung cells [4]. The different tool compounds had differential activity for the wildtype OGG1 and the Ser326Cys variant forms. Compounds that have preferential activity for Ser326Cys could help to normalize OGG1 activity in variant carriers, which may mitigate their risk for aging-related oxidative stress-related diseases.

Although the enzymatic activity of OGG1 is important for genomic integrity, its non-enzymatic activity can also be protective by playing a role in triggering the removal of cells with excessive oxidative damage through the induction of senescence and inflammatory programs [44]. OGG1 can act as an epigenetic regulator of the cellular response to oxidative stress [2]. This role is particularly relevant in the lungs, which experience a highly oxidative environment [45]. In a high ROS environment, the enzymatic activity of OGG1 is transiently reduced via post-translational modifications. In this setting, OGG1 primarily binds to 8-oxoG and acts as an enhancer to facilitate the recruitment of transcriptional regulators. As such, the presence of chronically high levels of catalytically inactive OGG1 can promote inflammation in sensitive tissues. Indeed, OGG1 knockout mice, and mice treated with OGG1 inhibitors, which prevent the binding of OGG1 to the promoters of pro-inflammatory genes (i.e NF-kB), show resistance to LPS-induced lung inflammation [2; 46]. It has not yet been established whether OGG1 enzymatic activators, which are still in early preclinical development [4; 42; 43], can also help reduce lung inflammation by restoring the balance between base excision repair and pro-inflammatory signaling.

Cancer: REDUCED OGG1 FUNCTION IS ASSOCIATED WITH INCREASED RISK
Oxidative stress can facilitate oncogenic mutations. The 8-oxoG modification can lead to CG→AT transversion mutations during DNA replication if the modified guanine is incorrectly read as a thymidine [47]. 8-oxodGTP can also be mistakenly incorporated into DNA in place of thymidine by polymerases

resulting in AT→CG mutations. Under physiological conditions, there are approximately 10^3 8-oxoG per cell per day, whereas in cancer cells, this is increased to approximately 10^5 [47]. This is indicative of an environment with elevated levels of ROS and reduced levels of DNA damage repair. As such, differential expression and/or activity of DNA damage repair genes is associated with cancer risk and prognosis. With respect to OGG1, the directionality of the association can vary for risk and prognosis, in a tissue-specific manner, due to differential oncogenic potential of the enzymatic and transcriptional/epigenetic activities of OGG1 [2]. In general, reduced OGG1 activity appears to be a predisposition factor for various types of cancer, but its relevance is generally dependent on other genetic and environmental factors. As part of a blood biomarker analysis in the Normative Aging Study involving 582 men who were cancer-free at baseline, the methylation status of OGG1 was associated with increased risk for all-cancer (HR: 1.43, 95% CI 1.15 to 1.78) and for prostate cancer (HR: 1.52, 95% CI 1.03 to 2.25) [48]. Similarly, a systematic review and meta-analysis of 109 studies (34,041 cases; 42,730 controls) found that the Ser326Cys variant allele was associated with an increased risk for cancer (OR: 1.071, 95 % CI 1.019 to 1.125), with Cys/Cys showing greater risk relative to Cys/Ser or Ser/Ser genotypes (OR: 1.159, 95 % CI 1.076 to 1.248) [3]. When stratified by cancer type, the associations were strongest for lung cancer, head and neck cancer, and digestive cancer.

Lung cancer: Altered OGG1 activity shows the clearest association with lung cancer due to the preferential importance of OGG1 in lung tissue homeostasis [45]. The lung interfaces with the environment and is exposed to the highest concentration of oxygen. While OGG1 activity is dispensable under low oxygen conditions, it becomes essential for cell survival under high oxygen conditions, such as those present in lung tissue. OGG1 is important for regulating the balance between levels of DNA repair and inflammation, which is important for the maintenance of tissue barrier integrity. Excessive levels of ROS can disrupt this balance by shifting the balance away from DNA repair and towards the induction of inflammatory signaling cascades. Notably, enzymatically inactive OGG1 can pair with 8-oxoG to function as a guanine exchange factor (GEF), leading to the activation of oncogenic RAS proteins and MAPK signaling cascades. OGG1 variants with reduced enzymatic (base repair) activity may result in higher levels of oxidized DNA damage, such as 8-oxoG, under conditions of elevated ROS, which increases the risk for oncogenic mutations. But because the impact of reduced OGG1 activity is most relevant under conditions of high ROS/mitochondrial dysfunction, and because ROS can reduce OGG1 activity via post-translational modifications, the contribution of OGG1 variants on their own to cancer risk is likely small, thus the ability to detect the effect in populations with heterogenous environmental-related risk can be marginal, leading to discrepancies across studies.

A meta-analysis examining the genetic susceptibility to lung cancer posed by 246 variants of 138 genes found 22 variants from 21 genes that showed strong cumulative epidemiological evidence for an association, one of which was the OGG1 Ser326Cys variant [49]. A meta-analysis of 30 studies including 22,475 individuals found that the Ser326Cys variant was not associated with lung cancer susceptibility in the total population, but there were significant differences in risk in particular subpopulations, such as studies using hospital-based controls [50]. A meta-analysis of 202 case-control studies looking at base excision repair variants, found an increased risk for lung cancer with the Ser326Cys variant using the recessive model [51].

Gastrointestinal cancers: Meta-analyses indicate preferential associations between OGG1 variants and risk for specific types of cancers along the gastrointestinal tract. A meta-analysis of 17 studies including 5,533 cases and 6,834 controls found that that the Ser326Cys allele was associated with increased risk for the cancers of the upper aero-digestive and gastrointestinal tract (OR: 1.22, 95 % CI 1.05 to 1.41) [52]. A meta-analysis of case-control studies assessing 22 gene variants from 17 genes found that the Ser326Cys variant was associated with an increased risk for rectal cancer (OR: 1.18, 95% CI 1.03 to 1.34), but not for colon cancer (OR: 0.93, 95% CI 0.81 to 1.06) [53]. A meta-analysis of 11 studies (2,028 cases; 3,302 controls) found that Cys/Cys homozygotes had increased risk for esophageal cancer (OR:1.40, 95% CI 1.12 to 1.74), especially esophageal squamous cell carcinoma [54].

Breast cancer: A meta-analysis examined 62 studies involving 32,626 participants to assess the relevance of different risk gene variants to breast cancer susceptibility [55]. In the pooled analysis of OGG1 variants, there was a positive association between OGG1 mutations and cancer in 60.1% of individuals, while 39.3% individuals showed no association, and there was an inverse or protective role of OGG1 mutations in 0.7% of individuals. In a mutational analysis involving 925 subjects, 15 different types of OGG1 mutations were observed, several of which were associated with a significantly increased cancer risk. These include the splice site variant g.9800972T>G (OR: 28.85, 95% CI 3.87 to 207.7), 3'UTR variant g.9798848G>A (OR: 29.20, 95% CI 33.98 to 213.74), the intronic variant g.9793680G>A (OR: 14.65, 95% CI 1.95 to 109.9), the nonsense variant Trp375STOP (OR: 12.90, 95% CI 1.71 to 97.28), as well as the missense variants Val159Gly (OR: 13.68, 95% CI 1.82 to 102.9), Gly221Arg (OR: 16.85, 95% CI 2.26 to 125.53), and Ser326Cys (OR: 18.45, 95% CI 2.49 to 136.99) [55]. Additionally, there was a risk interaction between several of these OGG1 variants and a history of smoking. A meta-analysis of 19 studies (9,417 cases; 11,087 controls) did not find a significant association between the OGG1 Ser326Cys variant with breast cancer [56]. While a separate meta-analysis of 17 studies (9,040 cases; 10,042

controls) also did not find a significant association for the Ser326Cys allele within the pooled analysis, it did find an increased risk in Asian populations and menopausal patients, in subgroup analysis [57].

Hepatocellular carcinoma: The expression of OGG1 was found to be higher in liver tissue from patients with hepatocellular carcinoma [58]. Those with higher OGG1 expression had lower rates of five-year overall survival (HR: 1.6) and disease-free survival (HR: 1.4). The change in expression is likely driven by reduced OGG1 promoter methylation, as a lower degree of methylation was associated with more severe disease (i.e. higher grade). The pro-oncogenic effect appears to stem from the stimulation of cell proliferation. Although the mechanism was not assessed, it may be related to the non-enzymatic role of OGG1 as a transcriptional regulator capable of activating Ras-MAPK cell survival-promoting signaling.

Pancreatic cancer: A meta-analysis of five case-control studies including 1,690 cases and 3,650 controls did not find an association between the OGG1 Ser326Cys allele and pancreatic cancer susceptibility [59].

Bladder cancer: A meta-analysis of 10 studies (4,319 cases; 4,716 controls), four of which examined smoking exposure, did not find an association between in the Ser326Cys variant and bladder cancer in the overall population, or in smokers [60].

Age-related cataracts: REDUCED OGG1 FUNCTION IS ASSOCIATED WITH INCREASED RISK
Oxidative stress plays a key role in the alterations of proteins in the lens in a manner which reduces transparency, resulting in the development of cataracts. Case-control studies have found an association between the Ser326Cys variant of OGG1, which has reduced enzymatic activity, and the incidence of age-related cataracts. In a cohort from China (415 cases; 386 controls), the presence of the Cys allele was associated with an increased risk for cataracts (OR: 1.517, 95% CI 1.204 to 1.911), with the risk highest for Cys/Cys homozygous (OR: 2.06, 95% CI 1.171 to 3.624) [61]. Similarly, in a cohort from Egypt (150 cases; 50 controls), individuals with the Cys allele were more likely to have age-related cataracts (OR: 1.85, 95% CI 1.07 to 3.20), especially in those with two copies of the Cys allele (OR: 4.13, 95% CI 0.93 to 18.21) [62].

Atherosclerosis: OGG1 IS REDUCED WITH LESION PROGRESSION
Atherosclerotic lesions show increased levels of oxidized mitochondrial DNA and mitochondrial damage [63]. This is accompanied by a progressive decrease in the expression of OGG1 with disease severity. AMPK is an important regulator of metabolism and energy homeostasis and helps maintain the proper

level of functional mitochondria. As such, it helps regulate mitochondrial DNA damage repair, in part through the enhancement of OGG1. The microRNA miR-33, which is upregulated in atherosclerotic tissue, reduces levels of OGG1 via inhibition of AMPK. In a mouse model of atherosclerosis (Ldlr-/- with high fat diet), OGG1 deficiency increases levels of mitochondrial DNA damage in macrophages, atherosclerotic plaque size, and serum levels of the inflammatory cytokine IL-1β [63]. The pro-inflammatory response is driven by the induction of the NLRP3 inflammasome. Oxidized mitochondrial DNA binds and activates NLRP3. Although OGG1 is one of the primary mechanisms by which oxidized mitochondrial DNA is repaired, alternative pathways can be engaged in the absence of OGG1. It was shown in mice that in the absence of OGG1, oxidized mitochondrial DNA was cleaved by the endonuclease FEN1, leading to the production of 500–650 bp fragments which exited mitochondria [64]. Within the cytosol, these mitochondrial DNA fragments activate the GAS-STING cytosolic DNA sensor and the NLRP3 inflammasome, ultimately resulting in a pro-inflammatory response.

Safety: Very limited safety data is available from cell culture studies. Safety profiles will be dependent on drug-specific properties, but target-related safety concerns are low.

Types of evidence:

- 3 laboratory studies on OGG1 agonists
- 2 laboratory studies on OGG1 inhibitors

OGG1 activators have not yet been tested *in vivo*. Additionally, there is minimal safety data from the studies conducted in cell culture with tool compounds, other than that they protect against mitochondrial toxins [4; 42; 43]. The selective, active-site OGG1 inhibitor, TH5487, was shown to be metabolically stable and well-tolerated in mice, when administered intraperitoneally [46]. Similarly, computational modeling of a compound library of OGG1 inhibitors suggests that they have little to no toxicity [65].

The safety profile for OGG1 activators will likely be dependent on their specificity, binding site, mode of action, and compound-specific pharmacokinetic properties. Ideally, these compounds would target the catalytic activity of OGG1 to normalize it, in order to restore the balance between its enzymatic and non-enzymatic functions. Other than in the context of pathological conditions where the non-catalytic activity of OGG1 predominates, there is currently no clear evidence that augmentation of the base excision repair activity of OGG1 is harmful. Extensive *in vivo* testing will be needed to determine whether OGG1 activators have acceptable safety profiles.

Drug interactions: Not established

Sources and dosing:

OGG1 activators are not available for *in vivo* use, though some are available for research use. These compounds are currently under development by several academic research labs, as well as by GSK.

Research underway:

OGG1 activators are currently in early preclinical development.

Search terms:

Pubmed, Google: OGG1

- Alzheimer's disease, Parkinson's disease, neurodegenerative disease, aging, lifespan, cardiovascular, cancer, agonists

References:

1. Oka S, Leon J, Sakumi K *et al.* (2021) MTH1 and OGG1 maintain a low level of 8-oxoguanine in Alzheimer's brain, and prevent the progression of Alzheimer's pathogenesis. *Scientific reports* **11**, 5819https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7988129/.

2. Sampath H, Lloyd RS (2019) Roles of OGG1 in transcriptional regulation and maintenance of metabolic homeostasis. *DNA repair* **81**, 102667https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6939861/.

3. Zhou PT, Li B, Ji J *et al.* (2015) A systematic review and meta-analysis of the association between OGG1 Ser326Cys polymorphism and cancers. *Medical oncology (Northwood, London, England)* **32**, 472https://pubmed.ncbi.nlm.nih.gov/25588927/.

4. Baptiste BA, Katchur SR, Fivenson EM *et al.* (2018) Enhanced mitochondrial DNA repair of the common disease-associated variant, Ser326Cys, of hOGG1 through small molecule intervention. *Free radical biology & medicine* **124**, 149-162https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6098717/.

5. Sliwinska A, Kwiatkowski D, Czarny P *et al.* (2016) The levels of 7,8-dihydrodeoxyguanosine (8-oxoG) and 8-oxoguanine DNA glycosylase 1 (OGG1) - A potential diagnostic biomarkers of Alzheimer's disease. *Journal of the neurological sciences* **368**, 155-159https://pubmed.ncbi.nlm.nih.gov/27538622/.

6. Dinçer Y, Akkaya Ç, Mutlu T *et al.* (2019) DNA repair gene OGG1 polymorphism and its relation with oxidative DNA damage in patients with Alzheimer's disease. *Neuroscience letters* **709**, 134362https://pubmed.ncbi.nlm.nih.gov/31299287/.

7. Dezor M, Dorszewska J, Florczak J *et al.* (2011) Expression of 8-oxoguanine DNA glycosylase 1 (OGG1) and the level of p53 and TNF-αlpha proteins in peripheral lymphocytes of patients with Alzheimer's disease. *Folia neuropathologica* **49**, 123-131https://pubmed.ncbi.nlm.nih.gov/21845541/.

8. Dorszewska J, Kempisty B, Jaroszewska-Kolecka J *et al.* (2009) Expression and polymorphisms of gene 8-oxoguanine glycosylase 1 and the level of oxidative DNA damage in peripheral blood lymphocytes of patients with Alzheimer's disease. *DNA and cell biology* **28**, 579-588https://pubmed.ncbi.nlm.nih.gov/19630534/.

9. Karahalil B, Miser Salihoğlu E, Elkama A *et al.* (2022) Individual susceptibility has a major impact on strong association between oxidative stress, defence systems and Parkinson's disease. *Basic & clinical pharmacology & toxicology* **130**, 158-170https://pubmed.ncbi.nlm.nih.gov/34582115/.

10. Cardozo-Pelaez F, Sanchez-Contreras M, Nevin AB (2012) Ogg1 null mice exhibit age-associated loss of the nigrostriatal pathway and increased sensitivity to MPTP. *Neurochemistry international* **61**, 721-730https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3468700/.

11. Kwiatkowski D, Czarny P, Toma M *et al.* (2016) Associations between DNA Damage, DNA Base Excision Repair Gene Variability and Alzheimer's Disease Risk. *Dementia and geriatric cognitive disorders* **41**, 152-171https://pubmed.ncbi.nlm.nih.gov/27011006/.

12. Mao G, Pan X, Zhu BB *et al.* (2007) Identification and characterization of OGG1 mutations in patients with Alzheimer's disease. *Nucleic acids research* **35**, 2759-2766https://www.ncbi.nlm.nih.gov/pmc/articles/PMC1885677/.

13. Coppedè F, Tannorella P, Stoccoro A *et al.* (2017) Methylation analysis of DNA repair genes in Alzheimer's disease. *Mechanisms of ageing and development* **161**, 105-111https://pubmed.ncbi.nlm.nih.gov/27080585/.

14. Zou T, Chen W, Zhou X *et al.* (2019) Association of multiple candidate genes with mild cognitive impairment in an elderly Chinese Uygur population in Xinjiang. *Psychogeriatrics : the official journal of the Japanese Psychogeriatric Society* **19**, 574-583https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6899574/.

15. Chen W, Zhou X, Duan Y *et al.* (2018) Association of OGG1 and DLST promoter methylation with Alzheimer's disease in Xinjiang population. *Experimental and therapeutic medicine* **16**, 3135-3142https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6125839/.

16. Lovell MA, Soman S, Bradley MA (2011) Oxidatively modified nucleic acids in preclinical Alzheimer's disease (PCAD) brain. *Mechanisms of ageing and development* **132**, 443-448https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3188850/.

17. Lillenes MS, Rabano A, Støen M *et al.* (2016) Altered DNA base excision repair profile in brain tissue and blood in Alzheimer's disease. *Molecular brain* **9**, 61https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4884418/.

18. Shao C, Xiong S, Li GM *et al.* (2008) Altered 8-oxoguanine glycosylase in mild cognitive impairment and late-stage Alzheimer's disease brain. *Free radical biology & medicine* **45**, 813-819https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2745061/.

19. Aslan NS, Orhan G, Karahalil B (2020) The impacts of prominent gene polymorphisms in DNA repair enzymes on Parkinson's disease. *Neuroscience letters* **735**, 135203https://pubmed.ncbi.nlm.nih.gov/32603833/.

20. Coppedè F, Ceravolo R, Migheli F *et al.* (2010) The hOGG1 Ser326Cys polymorphism is not associated with sporadic Parkinson's disease. *Neuroscience letters* **473**, 248-251https://pubmed.ncbi.nlm.nih.gov/20193742/.

21. Sanders LH, Paul KC, Howlett EH *et al.* (2017) Editor's Highlight: Base Excision Repair Variants and Pesticide Exposure Increase Parkinson's Disease Risk. *Toxicological sciences : an official journal of the Society of Toxicology* **158**, 188-198https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6075191/.

22. Fukae J, Takanashi M, Kubo S *et al.* (2005) Expression of 8-oxoguanine DNA glycosylase (OGG1) in Parkinson's disease and related neurodegenerative disorders. *Acta neuropathologica* **109**, 256-262https://pubmed.ncbi.nlm.nih.gov/15841414/.

23. Coppedè F, Migheli F, Ceravolo R *et al.* (2010) The hOGG1 Ser326Cys polymorphism and Huntington's disease. *Toxicology* **278**, 199-203https://pubmed.ncbi.nlm.nih.gov/19857538/.

24. Taherzadeh-Fard E, Saft C, Wieczorek S *et al.* (2010) Age at onset in Huntington's disease: replication study on the associations of ADORA2A, HAP1 and OGG1. *Neurogenetics* **11**, 435-439https://pubmed.ncbi.nlm.nih.gov/20512606/.

25. Kovtun IV, Liu Y, Bjoras M *et al.* (2007) OGG1 initiates age-dependent CAG trinucleotide expansion in somatic cells. *Nature* **447**, 447-452https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2681094/.

26. Gredilla R (2010) DNA damage and base excision repair in mitochondria and their role in aging. *Journal of aging research* **2011**, 257093https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3018712/.

27. Langie SA, Cameron KM, Ficz G *et al.* (2017) The Ageing Brain: Effects on DNA Repair and DNA Methylation in Mice. *Genes* **8**https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5333064/.

28. Tanisawa K, Mikami E, Fuku N *et al.* (2013) Exome sequencing of senescence-accelerated mice (SAM) reveals deleterious mutations in degenerative disease-causing genes. *BMC genomics* **14**, 248https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3637625/.

29. Tian F, Tong TJ, Zhang ZY *et al.* (2009) Age-dependent down-regulation of mitochondrial 8-oxoguanine DNA glycosylase in SAM-P/8 mouse brain and its effect on brain aging. *Rejuvenation research* **12**, 209-215https://pubmed.ncbi.nlm.nih.gov/19594329/.

30. Leon J, Sakumi K, Castillo E *et al.* (2016) 8-Oxoguanine accumulation in mitochondrial DNA causes mitochondrial dysfunction and impairs neuritogenesis in cultured adult mouse cortical neurons under oxidative conditions. *Scientific reports* **6**, 22086https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4766534/.

31. Bo H, Kang W, Jiang N *et al.* (2014) Exercise-induced neuroprotection of hippocampus in APP/PS1 transgenic mice via upregulation of mitochondrial 8-oxoguanine DNA glycosylase. *Oxidative medicine and cellular longevity* **2014**, 834502https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4236906/.

32. Sarga L, Hart N, Koch LG *et al.* (2013) Aerobic endurance capacity affects spatial memory and SIRT1 is a potent modulator of 8-oxoguanine repair. *Neuroscience* **252**, 326-336https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3856236/.

33. Pao PC, Patnaik D, Watson LA *et al.* (2020) HDAC1 modulates OGG1-initiated oxidative DNA damage repair in the aging brain and Alzheimer's disease. *Nature communications* **11**, 2484https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7235043/.

34. Lillenes MS, Støen M, Gómez-Muñoz M *et al.* (2013) Transient OGG1, APE1, PARP1 and Polβ expression in an Alzheimer's disease mouse model. *Mechanisms of ageing and development* **134**, 467-477https://pubmed.ncbi.nlm.nih.gov/24121118/.

35. Mizuno Y, Abolhassani N, Mazzei G *et al.* (2022) Deficiency of MTH1 and/or OGG1 increases the accumulation of 8-oxoguanine in the brain of the App(NL-G-F/NL-G-F) knock-in mouse model of Alzheimer's disease, accompanied by accelerated microgliosis and reduced anxiety-like behavior. *Neuroscience research* **177**, 118-134https://pubmed.ncbi.nlm.nih.gov/34838904/.

36. Fouquerel E, Barnes RP, Uttam S *et al.* (2019) Targeted and Persistent 8-Oxoguanine Base Damage at Telomeres Promotes Telomere Loss and Crisis. *Molecular cell* **75**, 117-130.e116https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6625854/.

37. Barja G, Herrero A (2000) Oxidative damage to mitochondrial DNA is inversely related to maximum life span in the heart and brain of mammals. *FASEB journal : official publication of the Federation of American Societies for Experimental Biology* **14**, 312-318https://pubmed.ncbi.nlm.nih.gov/10657987/.

38. Corella D, Ramírez-Sabio JB, Coltell O *et al.* (2018) Effects of the Ser326Cys Polymorphism in the DNA Repair OGG1 Gene on Cancer, Cardiovascular, and All-Cause Mortality in the PREDIMED Study: Modulation by Diet. *Journal of the Academy of Nutrition and Dietetics* **118**, 589-605https://pubmed.ncbi.nlm.nih.gov/29305130/.

39. Mori M, Toyokuni S, Kondo S *et al.* (2001) Spontaneous loss-of-function mutations of the 8-oxoguanine DNA glycosylase gene in mice and exploration of the possible implication of the gene in senescence. *Free radical biology & medicine* **30**, 1130-1136https://pubmed.ncbi.nlm.nih.gov/11369503/.

40. Osterod M, Hollenbach S, Hengstler JG *et al.* (2001) Age-related and tissue-specific accumulation of oxidative DNA base damage in 7,8-dihydro-8-oxoguanine-DNA glycosylase (Ogg1) deficient mice. *Carcinogenesis* **22**, 1459-1463https://pubmed.ncbi.nlm.nih.gov/11532868/.

41. Tinaburri L, D'Errico M, Sileno S *et al.* (2018) miR-200a Modulates the Expression of the DNA Repair Protein OGG1 Playing a Role in Aging of Primary Human Keratinocytes. *Oxidative medicine and cellular longevity* **2018**, 9147326https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5889889/.

42. Michel M, Benítez-Buelga C, Calvo PA *et al.* (2022) Small-molecule activation of OGG1 increases oxidative DNA damage repair by gaining a new function. *Science (New York, NY)* **376**, 1471-1476https://pubmed.ncbi.nlm.nih.gov/35737787/.

43. Tian G, Katchur SR, Jiang Y *et al.* (2022) Small molecule-mediated allosteric activation of the base excision repair enzyme 8-oxoguanine DNA glycosylase and its impact on mitochondrial function. *Scientific reports* **12**, 14685https://www.ncbi.nlm.nih.gov/pmc/articles/PMC9424235/.

44. German P, Saenz D, Szaniszlo P *et al.* (2017) 8-Oxoguanine DNA glycosylase1-driven DNA repair-A paradoxical role in lung aging. *Mechanisms of ageing and development* **161**, 51-65https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5177546/.

45. Vlahopoulos S, Adamaki M, Khoury N *et al.* (2019) Roles of DNA repair enzyme OGG1 in innate immunity and its significance for lung cancer. *Pharmacology & therapeutics* **194**, 59-72https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6504182/.

46. Visnes T, Cázares-Körner A, Hao W *et al.* (2018) Small-molecule inhibitor of OGG1 suppresses proinflammatory gene expression and inflammation. *Science (New York, NY)* **362**, 834-839https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6645780/.

47. Markkanen E (2017) Not breathing is not an option: How to deal with oxidative DNA damage. *DNA repair* **59**, 82-105https://pubmed.ncbi.nlm.nih.gov/28963982/.

48. Gao T, Joyce BT, Liu L *et al.* (2016) DNA methylation of oxidative stress genes and cancer risk in the Normative Aging Study. *American journal of cancer research* **6**, 553-561https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4859680/.

49. Wang J, Liu Q, Yuan S *et al.* (2017) Genetic predisposition to lung cancer: comprehensive literature integration, meta-analysis, and multiple evidence assessment of candidate-gene association studies. *Scientific reports* **7**, 8371https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5567126/.

50. Xu Z, Yu L, Zhang X (2013) Association between the hOGG1 Ser326Cys polymorphism and lung cancer susceptibility: a meta-analysis based on 22,475 subjects. *Diagnostic pathology* **8**, 144https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3853705/.

51. Liu S, Xiao Y, Hu C *et al.* (2020) Associations between polymorphisms in genes of base excision repair pathway and lung cancer risk. *Translational cancer research* **9**, 2780-2800https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8799111/.

52. Das S, Nath S, Bhowmik A *et al.* (2016) Association between OGG1 Ser326Cys polymorphism and risk of upper aero-digestive tract and gastrointestinal cancers: a meta-analysis. *SpringerPlus* **5**, 227https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4771670/.

53. Aggarwal N, Donald ND, Malik S *et al.* (2017) The Association of Low-Penetrance Variants in DNA Repair Genes with Colorectal Cancer: A Systematic Review and Meta-Analysis. *Clinical and translational gastroenterology* **8**, e109https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5539343/.

54. Wang Z, Gan L, Nie W *et al.* (2013) The OGG1 Ser326Cys polymorphism and the risk of esophageal cancer: a meta-analysis. *Genetic testing and molecular biomarkers* **17**, 780-785https://pubmed.ncbi.nlm.nih.gov/23909557/.

55. Ali K, Mahjabeen I, Sabir M *et al.* (2015) OGG1 Mutations and Risk of Female Breast Cancer: Meta-Analysis and Experimental Data. *Disease markers* **2015**, 690878https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4452349/.

56. Sanjari Moghaddam A, Nazarzadeh M, Noroozi R *et al.* (2016) XRCC1 and OGG1 Gene Polymorphisms and Breast Cancer: A Systematic Review of Literature. *Iranian journal of cancer prevention* **9**, e3467https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4922200/.

57. Peng Q, Lu Y, Lao X *et al.* (2014) Association between OGG1 Ser326Cys and APEX1 Asp148Glu polymorphisms and breast cancer risk: a meta-analysis. *Diagnostic pathology* **9**, 108https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4064811/.

58. Zhang H, Jiang PJ, Lv MY *et al.* (2022) OGG1 contributes to hepatocellular carcinoma by promoting cell cycle-related protein expression and enhancing DNA oxidative damage repair in tumor cells. *Journal of clinical laboratory analysis* **36**, e24561https://www.ncbi.nlm.nih.gov/pmc/articles/PMC9279955/.

59. Yan Y, Chen X, Li T *et al.* (2014) Association of OGG1 Ser326Cys polymorphism and pancreatic cancer susceptibility: evidence from a meta-analysis. *Tumour biology : the journal of the International Society for Oncodevelopmental Biology and Medicine* **35**, 2397-2402https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3967056/.

60. Wenjuan C, Jianzhong L, Chong L *et al.* (2016) The hOGG1 Ser326Cys gene polymorphism and susceptibility for bladder cancer: a meta-analysis. *International braz j urol : official journal of the Brazilian Society of Urology* **42**, 883-896https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5066884/.

61. Zhang Y, Zhang L, Song Z *et al.* (2012) Genetic polymorphisms in DNA repair genes OGG1, APE1, XRCC1, and XPD and the risk of age-related cataract. *Ophthalmology* **119**, 900-906https://pubmed.ncbi.nlm.nih.gov/22306120/.

62. Gharib AF, Dabour SA, Etewa RL *et al.* (2014) Polymorphisms of DNA repair genes OGG1 and XPD and the risk of age-related cataract in Egyptians. *Molecular vision* **20**, 661-669https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4029483/.

63. Tumurkhuu G, Shimada K, Dagvadorj J *et al.* (2016) Ogg1-Dependent DNA Repair Regulates NLRP3 Inflammasome and Prevents Atherosclerosis. *Circulation research* **119**, e76-90https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5010464/.

64. Xian H, Watari K, Sanchez-Lopez E *et al.* (2022) Oxidized DNA fragments exit mitochondria via mPTP- and VDAC-dependent channels to activate NLRP3 inflammasome and interferon signaling. *Immunity* **55**, 1370-1385.e1378https://pubmed.ncbi.nlm.nih.gov/35835107/.

65. Muhseen ZT, Ali MH, Jaber NR *et al.* (2021) Determination of Novel Anti-Cancer Agents by Targeting OGG1 Enzyme Using Integrated Bioinformatics Methods. *International journal of environmental research and public health* **18**https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8706639/.