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.

SULT2B1b Inhibitors

Evidence Summary

SULT2B1b is a regulator of cholesterol metabolism and has a variety of context-dependent roles in brain health, immune responses, and cancer risk. Inhibitor development is at a very early stage.

Neuroprotective Benefit: SULT2B1b is implicated in pathways associated with AD, including LXR signaling, neurosteroid hormone regulation, and cell survival. The impact of SUL2B1b inhibition on AD risk or outcomes is not yet clear.

Aging and related health concerns: Altered SULT2B1 expression is associated with patient outcomes in cancer, though the direction is cancer-type dependent. Inhibition may also have context-dependent effects on metabolic and immune responses.

Safety: The potential safety profile is unclear due to the limited understanding of the specific contribution of SULT2B1b to biological activities across tissues in humans. Based on genetic variants, inhibitors may affect skin turnover and cancer risk.

Availability: Not available/in development	**Dose**: N/A	**Chemical formula:** N/A **MW**: N/A
Half-life: N/A	**BBB**: N/A	
Clinical trials: None	**Observational studies**: Altered SULT2B1 expression is associated with poor prognosis in a variety of cancers.	

What is it?

Sulfotransferase 2B1b (SULT2B1b) is an enzyme that carries out the sulfation of cholesterol as well as related sterols, including dehydroepiandrosterone (DHEA) and pregnenolone [1]. The sulfation process initiates with the 3'-phosphoadenosine 5'-phosphosulfate (PAPS) synthase complex and concludes with the transfer of the sulfate group from PAPS to the 3β- hydroxyl group of cholesterol (or sterol/oxysterol) by the sulfotransferase (SULT2B1b) [1]. The sulfate can be removed from cholesterol/sterol through the enzyme steroid sulfatase (STS). Thus, the balance of SULTs and STS determines the relative level of free to sulfated cholesterol/sterol in a given tissue.
The SULT2B1 gene encodes for both SULT2B1a and SULT2B1b via alternative splicing [1]. SULT2B1b is generally expressed more broadly and at higher levels. They vary based on the length of the N terminus, which in 15 resides longer in SULT2B1b [2]. The substrate selectivity preferences also vary, with SULT2B1a showing preferred sulfation of pregnenolone and SULT2B1b showing more activity toward sulfating cholesterol [1]. With blood levels in the order of 1.3 to 2.6 µg/mL, cholesterol sulfate is one of the most abundant steroid sulfates in circulation [1]. The sulfation of cholesterol makes it water soluble to allow for hydrophilic excretion [1]. Cholesterol sulfate has a variety of additional biological activities via the regulation of cholesterol homeostasis, membrane composition and function, and immune responses [1]. Therefore, a major mechanism by which SULT2B1b impacts physiological and pathological responses is through the regulation of cholesterol sulfate production. SULT2B1b is also involved in the sulfation of oxysterols, which impacts their functional properties [3].

Due to the multitude of substrates, which may vary in prevalence from tissue to tissue, SULT2B1b has been shown to have a variety of different context-dependent roles [2]. It has been the most well studied

in the context of cancer, where it exerts oncogenic properties in many tumor types [2]. As such, SULT2B1 inhibition is considered a potential therapeutic strategy. However, the development of SULT2B1 inhibitors is at a very early stage, and no clinically viable inhibitors have been developed yet.

The unique N terminus of 1b has been proposed as a way to allow isoform specific development of a SULT2B1b inhibitor [2]. In silico studies demonstrated that the N terminus forms an allosteric binding pocket which confers its selectivity for cholesterol as a substrate, relative to the 1a isoform [4]. The flavonoid quercetin was identified as a partial allosteric inhibitor of SULT2B1b. Modeling and structural analysis may facilitate the development of novel inhibitors. Another study identified the bile acid 3β-OH-5-Chln as an inhibitor of SULT2B1b [5].
Additionally, the development of a novel label-free assay based on high-throughput (>1 Hz) desorption electrospray ionization mass spectrometry (DESI-MS) may facilitate the testing of SULT2B1b inhibitors [6].

Neuroprotective Benefit: SULT2B1b is implicated in pathways associated with AD, including LXR signaling, neurosteroid hormone regulation, and cell survival. The impact of SUL2B1b inhibition on AD risk or outcomes is not yet clear.

Types of evidence:

- 2 reviews on the role of neurosteroids in brain health and disease
- Several laboratory studies (none specifically for inhibitors)

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

We do not yet have a clear understanding of the role of SULT2B1b in the development of dementia or its progression, though it is implicated in several biological processes associated with neurodegenerative disease [2]

Human research to suggest benefits to patients with dementia:

SULT2B1b inhibitors have not yet been developed or clinically tested in dementia patients.

Mechanisms of action for neuroprotection identified from laboratory and clinical research:
Alzheimer's disease: POTENTIAL MIXED (preclinical/theoretical)
The potential impact of inhibiting SULT2B1b in the context of Alzheimer's disease (AD) is mixed, as it is involved in processes associated with the potentiation of neuropathology, as well as processes associated with neuroprotection. It is currently difficult to determine whether the net effect would be beneficial, neutral, or harmful because the outcomes associated with SULT2B1 deletion or overexpression have been shown to be very context dependent. Without information specifically related to how SULT2B1b expression and activity is impacted in human AD patients, including the degree of variability and how it relates to alterations in the different processes downstream of SULT2B1b, the therapeutic potential of SULT2B1b inhibition is challenging to predict. The development of bioavailable SULT2B1b inhibitors is expected to enhance our understanding of how SULT2B1b impacts disease processes in a variety of cellular and *in vivo* AD models.

Potential neuropathological mechanisms of SULT2B1b

Aβ aggregation: The aggregation of beta amyloid is one of the neuropathological hallmarks of AD. Cholesterol dysregulation has been observed in the context of AD [7]. Cholesterol is an important component of cell membranes, particularly within the brain, such that alterations in cellular cholesterol levels can impact the structure and function of cell membranes, which, in turn, impacts a wide range of cell activities. Membranes enriched in cholesterol facilitate the aggregation of Aβ [8]. *In vitro* studies indicate that membranes enriched in the sulfated derivative of cholesterol, cholesterol sulfate, which confers a negative charge, have an even stronger propensity toward facilitating Aβ aggregation [9]. The effect was concentration dependent, such that low levels of cholesterol sulfate had a moderate facilitating effect, while high levels (≥ 0.25 µg/mL) had a strong effect [9]. One study found that cholesterol sulfate accelerated Aβ fibril formation 13-fold relative to cholesterol [10]. Additionally, at presumed disease-relevant concentrations, it was estimated that around half of Aβ oligomers contain cholesterol sulfate [10].

Liver X receptor (LXR) activation: LXR plays important roles in processes implicated in AD pathology, including cholesterol metabolism, inflammatory responses, reducing Aβ and tau pathology, and neurogenesis [2; 11]. The accumulation of intracellular cholesterol is a driver of pathological activity in AD, including mitochondrial dysfunction and neuroinflammation [12]. LXR lowers intracellular cholesterol by promoting efflux and reducing uptake [11]. LXR also acts as a regulator of inflammatory signaling through repression of proinflammatory mediators, including NF-kB. As such, LXR agonists show

protective effects in AD models [2; 11]. However, LXR has been challenging to target clinically [11]. LXRβ is ubiquitously expressed, but enriched in the brain, whereas LXRα is enriched in the liver. Pan-LXR agonists are not clinically viable because they induce LXRα-driven lipogenic side effects [11]. LXRβ-selective agonists have also experienced clinical setbacks, to date [11; 13].
An alternative approach is to target inhibitors/activators of LXR that have more tissue-restricted expression/activity [2]. Oxidized derivatives of cholesterol, called oxysterols, have been shown to act as regulators of LXR [14]. 24-hydroxycholesterol (24-OHC) is produced by the oxidization of carbon 24 in cholesterol by the enzyme CYP46A1 [14]. 24-OHC is the primary cholesterol metabolite produced in the brain [14]. It is able to cross the BBB such that its formation allows for the removal of excess cholesterol from the brain. As a rise in 24-OHC levels is an indication of excess cholesterol, 24-OHC activates LXR to facilitate cholesterol efflux from the brain [14]. The sulfation of 24-OHC by sulfotransferases, including SULT2B1b, reduces its permeability and changes it from a modest agonist to a potent antagonist of LXR [14]. Consequently, inhibiting SULT2B1b is expected to facilitate LXR activation by reducing sulfation of 24-OHC, thus reducing levels of a predominantly brain localized LXR inhibitor [14].

Potential neuroprotective mechanisms of SULT2B1b

Neurosteroid regulation: Neurosteroids play important roles in brain function [15]. Sulfate conjugation by sulfotransferases, such as SULT2B1b, can impact the properties of the neurosteroids, by increasing their water solubility and increasing their half-lives [15]. Changes in the ratio of sulfated to unconjugated neurosteroids have been observed in the context of AD and other neurodegenerative conditions, and may be reflective of and/or contribute to pathological processes [15]. Two key neurosteroids that undergo sulfation are DHEA and pregnanolone [15]. Both of these can be sulfated in the brain by SULT2B1b. Like DHEA, the sulfated form, DHEAS promotes neurogenesis, neuronal survival, and has anti-inflammatory effects [15]. DHEA and DHEAS have been shown to counteract the negative impact of cortisol on working memory [16]. DHEAS also has neuromodulatory effects by potentiating NMDA-mediated Ca2+ currents and inhibiting GABAAR-mediated chloride currents [16].
Sulfated pregnenolone has a neuromodulatory role as a potent positive allosteric modulator of NMDAR-mediated synaptic transmission, and as a negative allosteric modulator of GABA, glycine, kainate, and AMPA receptors [16]. The sulfation of pregnenolone is expected to primarily be catalyzed by SULT2B1a [1], but the relative degree of sulfation by different sulfotransferases in the human brain under physiological or disease contexts has not been fully characterized. Decreased levels of DHEAS and pregnenolone-S have been observed in AD brain tissue [15; 16]. One study observed an inverse correlation between levels of cortical Aβ with levels of pregnenolone-S in the striatum and cerebellum,

as well as an inverse correlation between levels of p-Tau and DHEAS in the hypothalamus [17]. Another study found that higher plasma DHEAS levels were associated with better memory performance [18]. Numerous studies have found that plasma levels of DHEAS are reduced in AD patients, including a reduction in the ratio of DHEAS to unconjugated DHEA [15]. This may be reflective of a broader reduction in sulfotransferase activity, as other studies have observed a reduction in the overall ratio of circulating conjugated/sulfated steroids to unconjugated/free steroids in AD patients [15; 19]. Together these studies suggest that sulfotransferase activity may be decreased in the context of AD, leading to the reduction of neuroprotective conjugated neurosteroids. However, it is not clear whether these effects are driven by changes in the activity of SULT2B1b or other sulfotransferases in the brain or periphery. There is also evidence to suggest potential changes in steroid sulfatase (STS), the complementary enzyme that removes sulfates, which could also cause the altered sulfation levels in AD [15]. As such, it is unclear the degree to which SULT2B1b inhibition would contribute to the further decline of sulfated neurosteroids in AD.

Cell survival: The neurosteroid DHEA, and its sulfated form DHEAS, promote neuron survival [15]. They have been shown to induce the anti-apoptotic factor Bcl-2 via the AKT signaling pathway [20]. In cultured astrocytes, treatment with cholesterol sulfate protected against glutamate-induced toxicity and rotenone-induced cell death [20]. The protective effect may stem from the conversion of cholesterol sulfate to DHEAS [20]. Since SULT2B1b is involved in the formation of both cholesterol sulfate and DHEAS, it could play a neuroprotective role irrespective of which sterol mediates the effect. Cholesterol sulfate treatment also improved mitochondrial efficiency in the astrocytes, which preserved energy production and may have mediated the reduction in reactive oxygen species (ROS) in response to these cell stressors [20]. A study assessing a different sulfotransferase (SULT1C2) in the kidney found that increased levels of cholesterol sulfate in mitochondrial membranes protected against mitochondrial membrane collapse and cellular injury in the context of ischemia [21]. This suggests that in the context of cellular damage, enhanced production of cholesterol sulfate via increased sulfotransferase activity may drive mechanisms related to resistance and cell survival. The relevance of this mechanism in the brain is supported by the protective effect of cholesterol sulfate in a mouse model of ischemic stroke. SULT2B1 deficiency exacerbated neuronal loss, while cells treated with cholesterol sulfate upregulated protective processes by activating AMPK-CREB signaling and had decreased levels of ROS in response to ischemic injury [22].

Oxysterol regulation: Oxysterols, oxidized derivatives of cholesterol, are produced enzymatically through CYP P450 enzymes or through free radial attack [3]. The oxysterols can be sulfated by

sulfotransferases, including SULT2B1b, to oxysterol sulfates, which can have different biological properties. Our current understanding of the role of oxysterol sulfates is quite limited, due in large part to a lack of consistent information regarding oxysterol sulfate levels under physiological and disease conditions [23]. One study assessed the composition of oxysterols and oxysterol sulfates in AD brain tissue [24]. Levels of the oxysterols, 26-OHC, 25-OHC, and 27-OHC were elevated in AD brain tissue, whereas levels of the sulfated counterpart 25-OHCS were reduced. Some studies suggest that oxysterols and oxysterol sulfates can act as paired regulators of lipid metabolism, cell survivals/death, and inflammatory responses [3; 25]. Several oxysterols, such as 27-OHC and 25-OHC have been associated with neuroinflammation, impaired neuronal viability, and impaired neuronal metabolism [23; 26]. As such, increased sulfation of these potentially damaging oxysterols could be neuroprotective. Due to its expression in the human brain [27], SULT2B1b is a major candidate for regulating the balance of oxysterol sulfates in the brain.

APOE4 interactions: Not established.

Aging and related health concerns: Altered SULT2B1 expression is associated with patient outcomes in cancer, though the direction is cancer-type dependent. Inhibition may also have context-dependent effects on metabolic and immune responses.

Types of evidence:

- 1 review of the association of SULT2B1 gene variants with disease risk/phenotypes
- 8 studies assessing SULT2B1b expression in human cancer tissue
- Numerous laboratory studies for SULT2B1 (not for specifically for inhibitors)

Cancer: MIXED

SULT2B1b inhibitors are expected to have the greatest utility in the context of cancer due to the relationship between elevated SULT2B1 expression and poor prognosis observed in many types of cancer [2; 28]. SULT2B1 plays complex, multi-faceted roles in cancer, influencing mechanisms related to cell growth, cell survival, immune responses, drug resistance, and metastasis [28]. While it is primarily considered oncogenic, SULT2B1 can also act as a tumor suppressor in some cancer types due to context dependent factors, including the responsiveness of the tissue to steroid hormones.

Oncogenic mechanisms of SULT2B1

Inhibiting tumor infiltration by effector T cells: Cholesterol sulfate, a product of SULT2B1b, acts as an inhibitor of DOCK2, which plays an essential role in the migration and activation of lymphocytes [5]. Cancer-derived cholesterol sulfate prevents tumor infiltration by effector T cells in preclinical models [5; 29]. High levels of cholesterol sulfate have been associated with lower levels of tumor CD8+ T cell infiltration in colon cancer [29]. The presence of cholesterol sulfate may also confer resistance to immunotherapy. 3β-OH-5-Chln, a component of fetal bile acids, was identified in a screen to act as an inhibitor of SULT2B1b [5]. In mice, treatment with 3β-OH-5-Chln, promoted T cell infiltration into cancer tissue, and restored the sensitivity of anti-PD1 immunotherapy in refractory tumors [5].

Metabolic regulation: Glycolytic metabolism promotes cancer cell proliferation and chemoresistance [30]. c-Myc is an important oncogene that acts as a master regulator of cellular metabolism. It can be induced downstream of AKT/mTOR signaling [30]. c-Myc can promote glycolytic metabolism in tumor cells through induction of pyruvate kinase M2 (PKM2) [31]. In colon cancer cells, SULT2B1 was found to promote glycolysis by inducing AKT/mTOR signaling [30; 31].
Lipid metabolism also plays an important role in tumor cell growth, by providing the building blocks for cell membranes and fuel for energy [32]. In colon cancer cells, SULT2B1 was shown to interact with the stearoyl-CoA desaturase SCD1 to facilitate lipid metabolism [32].

Epithelial-mesenchymal transition (EMT): The EMT involves the transition from stationary to migratory cells, and is implicated in tumor cell migration and metastasis [33]. SULT2B1 was found to promote EMT in human liver cells in response to TGF-β1 via the Wnt/β-catenin/ matrix metalloproteinase-7 (MMP7) pathway [34]. This is consistent with evidence that cholesterol sulfate, the byproduct of SULT2B1b, can enhance MMP7 activity to degrade the extracellular matrix [35]. That this drives metastasis in human cancer is supported by metabolomic studies showing that cholesterol sulfate is upregulated in tumor metastases compared with primary tumors [36].

Cell survival: SULT2B1 activity is associated with the induction of numerous signaling pathways associated with cell survival, including the AKT/mTOR pathway [28]. Through activation of AKT, sulfated sterol byproducts of SULT2B1, including cholesterol sulfate, promote cell survival by increasing the ratio of anti-apoptotic factors, such as Bcl-2 [20; 37]. Protein Kinase C (PKC) can promote cancer growth in a complex isoform-related manner [38]. Cholesterol sulfate has been shown to induce different PKC isoforms [39], which may impact tumor growth and metastasis [40].

Tumor suppressor mechanisms of SULT2B1

Oxysterol inactivation: SULT2B1 is also known to sulfate and inactivate oxysterols, cholesterol-oxidized products that have been shown to favor tumor growth by directly promoting tumor cell growth and indirectly by dampening anti-tumor immune responses [29; 41]. The presence or absence of tumor promoting oxysterols could be one of the determinants of whether SULT2B1b activity promotes or suppresses tumor growth [29].

Steroid hormone regulation: DHEA is a precursor for the production of androgens and estrogens, the major steroid sex hormones [42]. Sulfation of DHEA transforms it into a largely inactive precursor, which can then serve as a reservoir. Changes in the activities of SULT2B1 and steroid sulfatase can influence the balance between DHEA and DHEAS. In cancers where sex hormones drive tumor growth, such as prostate cancer, lower levels of the active (DHEA) form relative to the inactive (DHEAS) form may be beneficial.

Association of SULT2B1 in cancers

Prostate cancer**:** LOSS OF SULT2B1 ASSOCIATED WITH WORSE PROGNOSIS
The role of SULT2B1 as a tumor suppressor has been best studied in the context of prostate cancer. Several intronic genetic variants in the SULT2B1 gene have been associated with risk for prostate cancer progression and prognosis [28]. The variants rs10426628 (Hazard Ratio [HR]: 0.49, 95% Confidence Interval [CI] 0.26 to 0.91) and rs2665582 (HR: 0.38, 95% CI 0.13 to1.09) were associated with reduced risk of progression and lower levels of circulating steroid hormones, while the variant rs12460535 had the opposite effect and was associated with worse progression (HR: 2.44, 95% CI 1.10 to 5.41) in a cohort of 739 Caucasian men [43].
SULT2B1 is highly expressed in the prostate epithelium under physiological conditions, but its expression has been shown to be reduced in prostate cancer tissue [44]. Lower levels of SULT2B1 were associated with more aggressive cancers and shorter patient survival [44]. Expression was lowest in metastatic cancer cells, and nearly absent in metastasized castration-resistant prostate cancer [44; 45]. In castration-resistant prostate cancer, aldo-keto reductase IC3 (AKRIC3) can promote the conversion of DHEA to active androgens, activate the androgen receptor, and drive pro-survival ERK signaling [45; 46]. Loss of SULT2B1 expression is associated with upregulated AKRIC3 and reactivated androgen receptor signaling [46].

However, one group found that loss of SULT2B1 activity may also enhance tumor cell death in castration-resistant prostate cancer cells by facilitating TNF-mediated apoptosis [47]. An inverse association between SULT2B1 expression and the expression of TNF-related genes TNF, CD40LG, FADD, and NFKB1, was observed in human prostate cancer datasets [47]. Additionally, a study assessing gene variants associated with time to androgen deprivation therapy failure in men of Chinese ancestry with prostate cancer found that the intronic variant in SULT2B1, rs71179009, was associated with increased risk for androgen deprivation therapy failure (HR: 2.16, 95% CI 1.44 to 3.22) [48]. While the impact of this variant is not clear, it is in the linkage disequilibrium region of a synonymous exonic variant that increases SULT2B1 expression [48].
These studies suggest that SULT2B1 plays multi-faceted, potentially opposing, roles in prostate cancer and treatment response. The predominant effects may vary based on stage, tumor environment, and treatment conditions.

Breast cancer: SULT2B1 EXPRESSION IS ELEVATED
The impact of SULT2B1 activity on breast cancer appears to be complex. Estrogen facilitates the growth of the majority of breast cancers [49]. DHEA can be converted to estrogens and androgens, and following menopause, DHEA becomes the major source for the synthesis of these sex hormones [42]. Consequently, the impact of SULT2B1 may differ based on menopausal status. Low DHEA has been associated with increased risk for breast cancer in premenopausal women, but decreased risk in post-menopausal women [50]. By turning it into an inactive form, the sulfation of DHEA by SULT2B1 would be expected to reduce the pool of circulating sex hormones [50]. One study found racial differences in SULT2B1 expression in breast tissue between Caucasian and African American women [50]. SULT2B1 expression was higher in African American women, which is consistent with epidemiological trends indicating a higher incidence of breast cancer during pre-menopausal years and a lower incidence during post-menopausal years [50].
The expression of SULT2B1 has been shown to be upregulated in breast cancer tissue, especially in estrogen-receptor positive tumors [28]. This may stem from a compensatory response to mitigate the conversion of DHEA to estrogen, though the net effect may be to drive further growth due to the numerous pro-tumorigenic effects of SULT2B1 [50].

***Esophageal cancer*:** LOW SULT2B1 ASSOCIATED WITH POOR PROGNOSIS
The intronic SULT2B1variant, rs4149455 (IVS6-436 C>T) (per allele Odds Ratio [OR]: 0.81, 95% CI 0.72 to 0.91) as well as the T allele of the synonyms variant rs1052131 (g.Ex7+122C>T; p.D316D) (per allele OR: 0.84, 95% CI 0.70 to 0.99) were found to be associated with reduced risk of esophageal squamous cell

carcinoma (ESCC) [51]. This study assessed the impact of sex hormone-related variants on ESCC risk because esophageal tissue expresses estrogen and androgen receptors [51].
The expression of SULT2B1 was found to be low or absent in ESCC patient tissue and cell lines, with lower expression associated with worse survival [52]. Lower expression was associated with more advanced stages, a greater degree of invasion, and lymph node metastasis. The loss of SULT2B1 was also associated with the down regulation of the core circadian clock gene Per1 [52]. The dysregulation of clock genes may play a role in driving cancer cell growth in ESCC.

***Colorectal cancer**:* HIGH SULT2B1 ASSOCIATED WITH POOR PROGNOSIS
SULT2B1 was found to be highly expressed in colon/colorectal cancer tissues and cell lines [30; 31; 53]. Higher expression was observed in more advanced stages, and associated with poor prognosis [31; 53]. Elevated SULT2B1 was associated with the presence of distant and lymph node metastases, suggesting that SULT2B1 activity may be a driver of metastasis in colon cancer [31; 53].

Hepatocellular carcinoma: ELEVATED SULT2B1 IN CANCER TISSUE
The expression of SULT2B1b was found to be associated with the rate of cell proliferation in a variety of hepatocellular carcinoma cell lines [54]. SULT2B1 was upregulated in hepatocarcinoma tumor tissues relative to non-cancerous liver tissue [54].

Atherosclerosis: POTENTIAL BENEFIT (preclinical)
Due to its role in facilitating reverse cholesterol transport to remove excess cholesterol from cells, the activation of LXR signaling is considered to be anti-atherogenic [11]. As such, the activity of SULT2B1b, which produces metabolites that antagonize LXR signaling would be expected to be pro-atherogenic [2]. The evidence to date suggests that SULT2B1b may play a role in adverse cardiovascular outcomes in individuals with atherosclerosis but well-managed LDL-C levels, and thus contribute to residual cardiovascular risk. The negative impact to cardiovascular health appears to stem from the polarization of immune cells toward a pro-inflammatory/pro-atherogenic state by driving the accumulation/preventing the efflux of cholesterol from the immune cells.

Trimethylamine N-oxide (TMAO) is a microbiota-derived metabolite [55]. Elevated plasma levels of TMAO are associated with increased risk for adverse cardiovascular events [55]. In a cohort of 71 individuals with or without atherosclerotic coronary artery disease (CAD) but adequately managed LDL-C levels (< 1.8 mmol/L), plasma TMAO levels were higher in CAD patients, and inversely associated with levels of PSRC1 expression [55]. PRSC1 was found to be a cardioprotective factor by upregulating LXR-

mediated reverse cholesterol transport and inactivating pro-inflammatory NF-kB signaling [55]. TMAO was found to induce SULT2B1b, resulting in the inhibition of LXR, and the facilitation of pro-inflammatory macrophages and foam cell formation. This suggests that SULT2B1b may be a mediator of TMAO-related cardiovascular risk. Notably, along with higher TMAO, neutrophils were also elevated in CAD patients, consistent with a more pro-inflammatory profile.

Similarly, a study including 20 participants with or without CAD and acute myocardial infarction, but low plasma LDL-C found that the cholesterol content of lymphocytes was elevated in CAD patients, stemming from reduced cholesterol efflux [56]. This was accompanied by elevated levels of pro-inflammatory mediators TNF-α and IFN-γ. These effects were attributed to the inhibition of LXR signaling due to the upregulation of SULT2B1b expression in CAD lymphocytes.

One study identified a variant in the promoter region of SULT2B1 rs2665580, which influenced SULT2B1b expression in monocytes from patients with CAD [57]. Higher SULT2B1expression related to the GG genotype was associated with a more pro-inflammatory profile and more unstable coronary plaques.

These clinical findings are supported by mechanistic work in macrophage cell culture indicating that knockdown of SULT2B1b suppressed proliferation and proinflammatory IKKβ/NF-κB signaling in response to stimulation with oxidized-LDL [58]. The knockdown of SULT2B reduces levels of oxysterol sulfates that act as LXR antagonists, resulting in the activation of LXR in macrophages [57].

However, there is also evidence related to the biology of cholesterol sulfate that could support a protective role for SULT2B1b in the context of atherosclerosis. Cholesterol sulfate has been shown to promote the degradation of HMG-CoA reductase (HMGCR), the rate-limiting step in the synthesis of cholesterol [59]. HMGCR is the enzyme targeted by statins, the most widely used therapies for the prevention/management of atherosclerosis.
While supporting evidence is currently limited, cholesterol sulfate deficiency has been proposed as a novel hypothesis for atherosclerosis [60]. This hypothesis posits that the negatively charged sulfates are important for the maintenance of the glycocalyx, the carbohydrate-rich lining of the vascular endothelium.

Metabolic disease: POTENTIAL MIXED
Protection from adverse metabolic phenotypes, such as obesity and fatty liver, have been observed in the context of both SULT2B1 overexpression and deficiency in different studies [61; 62]. This highlights the multifaceted roles for SULT2B1 in different cell types. Though, it could also be confounded by differential expression of SULT2B1a and SULT2B1b across tissues. Consequently, the SULT2B1b inhibition could potentially induce opposing metabolic phenotypes in different tissues.

Diabetes: POTENTIAL PROTECTIVE ROLE FOR SULT2B1b
Elevated gluconeogenesis in the liver is a driver of insulin resistance and hyperglycemia in type 2 diabetes. SULT2B1b has been identified as a transcriptional target of Hepatocyte Nuclear Factor 4-alpha (HNF4α), an important regulator of liver fat storage and gluconeogenesis [61; 63]. SULT2B1b acts as part of a negative feedback loop to limit gluconeogenesis [63].
Cholesterol sulfate, the major byproduct of SULT2B1b activity, was found to exert a protective effect in pancreatic β-cells [64]. Cholesterol sulfate protected against stress-induced β-cell loss by enhancing mitochondrial integrity, resulting in increased energy production and decreased oxidative stress (ROS production) [64]. β-cell signaling was also enhanced by cholesterol sulfate via activation of the AKT and CREB pathways. The upregulation of cholesterol sulfate may be a compensatory protective pathway, as cholesterol sulfate levels were found to be increased in the plasma from patients with type 1 diabetes, as well as in type 2 diabetes, with a greater effect in men [64].

Obesity: POTENTIAL BENEFIT (preclinical)
Transgenic hepatic overexpression of SULT2B1 protected against high-fat diet induced weight gain, insulin resistance, and induction of gluconeogenic and lipogenic genes in mice, similar to what was observed following treatment with cholesterol sulfate [61]. Interestingly, a similar degree of protection from the adverse metabolic effects of a high-fat diet were also observed in the context of whole body SULT2B1 knockout mice [62]. In this context, the protective metabolic effects were related to the loss of SULT2B1 in extrahepatic tissues, including adipose tissue and the intestines [62]. SULT2B1 deficiency was associated with increased thermogenic brown fat activation, as well as the attenuation of inflammatory macrophage infiltration into adipose tissue. Lipid levels were kept low despite a high-fat diet through the suppression of dietary lipid absorption in the intestines.
This indicates that SULT2B1 has a variety of effects in different metabolically active tissues, such that the impact of an inhibitor may depend on which tissues are preferentially targeted and the baseline levels in those tissues.

Immune system: SULT2B1b HAS CONTEXT DEPENDENT ROLES
SULT2B1 plays context dependent roles in immune system regulation. Cholesterol sulfate, the major product of SULT2B1b activity, generally shows anti-inflammatory/immunosuppressive properties in experimental systems [1]. However, immune cell polarization is highly impacted by the microenvironment, particularly the metabolic state of a cell or tissue [65]. Baseline cholesterol/lipid levels may be an important factor in determining whether SULT2B1 activity induces downstream pro- or anti-inflammatory responses.

Macrophage polarization: In the context of injury/cell stress, whether the induction of SULT2B1b activity has a protective/productive effect largely depends on whether the type of triggered immune response facilitates or hinders healing in that particular environment. In a mouse stroke model, SULT2B1 promoted the polarization of monocytes toward a type 2 anti-inflammatory profile, which had a neuroprotective effect [22]. In contrast, in a mouse model of laser-induced macular degeneration, SULT2B1-mediated polarization of M2 macrophages was associated with angiogenesis resulting in pathological neovascularization [66].
An injury setting generally results in increased energy demand. In contrast, excess levels of glucose/lipids can result in a different kind of metabolic stress. Under these conditions, such as models of obesity and atherosclerosis, SULT2B1 has been associated with the polarization of macrophages into a pro-inflammatory state [57; 58; 62]. Thus, the type of polarization may vary depending on the metabolic status and overall signaling milieu.

DOCK2 inhibition: One of the major mechanisms by which SULT2B1 exerts immunosuppressive effects is via the regulation of DOCK2 [1]. The DOCK2-Rac pathway is a critical mediator of the activation and migration of leukocytes, such that genetic mutations in DOCK2 are associated with severe immunodeficiency [67]. Cholesterol sulfate acts as an inhibitor of DOCK2 [67]. The production of cholesterol sulfate in the Hadrian gland of the eye socket may be a mechanism to mitigate inflammation in the eye [67]. In mice, loss of SULT2B1 was associated with increased ocular inflammation [67]. However, whether or not this is beneficial depends on context. Another study found that cholesterol sulfate inhibition of DOCK2 delayed corneal wound healing by limiting the recruitment of leukocytes (neutrophils and eosinophils) to the injury site [68]. In the context of cancer, inhibiting the migration of cytotoxic T cells to the tumor facilitates unchecked tumor growth [5].

T cell activation: Cholesterol sulfate has also been shown to inhibit T cell activation by displacing the cholesterol binding to the T cell receptor (TCR) [69]. It was also found to play a role in thymic selection,

such that in the absence of cholesterol sulfate, T cells are more sensitive to self-antigens [69]. This suggests that cholesterol sulfate levels, mediated in part through SULT2B1 activity may influence the survival of developing T cells, and autoimmunity.

Skin disorders

Congenital Ichthyosis: MIXED

Cholesterol sulfate plays an important role in keratinocyte differentiation in the epidermis of the skin [70]. SULT2B1b is expressed in the skin and is responsible for the formation of cholesterol sulfate in the epidermis [70]. Alterations to the level of cholesterol sulfate in the epidermis can impact the process of desquamation, which is the shedding of the outermost layer of the skin [70]. Ichthyosis refers to a group of rare skin disorders characterized by excess scaling of the skin due to disruption in the skin turnover process, such as through disturbed cholesterol metabolism [70].

Congenital forms of ichthyosis have been associated with both excess cholesterol sulfate and a deficiency of cholesterol sulfate in the skin. Recessive x-linked ichthyosis occurs from loss-of-function mutations in steroid sulfatase (STS), resulting in excess levels of cholesterol sulfate [71]. Meanwhile, loss-of-function mutations in SULT2B1 have been identified in several cases of autosomal-recessive congenital ichthyosis [28]. One study identified the homozygous missense mutation, c.446C>T (p.Pro149Leu), as well as another missense mutation c.821G>A (p.Arg274Gln) that alter highly conserved residues in the region of SULT2B1 that binds to PAPS. A homozygous splice site mutation, c.71+2T>A predicted to affect intron retention, and a hypothetical stop mutation p.Ser24Argfs∗42, were also identified in families with congenital ichthyosis [72]. Additional missense variants in SULT2B1, p.Glu78Lys, p.Arg100Trp, p.Ala140Val, and p.Met304Ile, have also been associated with autosomal recessive ichthyosis [28].

This suggests that topical SULT2B1b inhibitors may be beneficial for forms of ichthyosis linked to excess cholesterol sulfate [2].

Psoriasis: SULT2B1 ASSOCIATED WITH SKIN RESPONSE TO INFLAMMATION

Cholesterol sulfate levels were shown to be elevated in the skin of psoriasis patients [73]. This may be a compensatory response to reduce the inflammatory response in the skin, since SULT2B1 was induced in human epidermal keratinocytes in response to inflammatory stimuli [73].

Safety: The potential safety profile is unclear due to the limited understanding of the specific contribution of SULT2B1b to biological activities across tissues in humans. Based on genetic variants, inhibitors may affect skin turnover and cancer risk.

Types of evidence:

- 1 review of the association of SULT2B1 gene variants with disease risk/phenotypes
- Numerous laboratory studies of SULT2B1 knockout mice

Clinically viable SULT2B1b inhibitors have not yet been developed. As such, the prospective safety profile of these inhibitors is unclear.

SULT2B1 knockout mice may provide some insights, however, there are several caveats that limit the translatability of the phenotypes present or absent in these mice. SULT2B1 mice are viable, and have reduced levels of cholesterol sulfate, indicating that while SULT2B1b plays a major role in the production of cholesterol sulfate, other sulfotransferases can partially compensate for its absence [1]. Consistent with the context-dependent roles of SULT2B1b, phenotypes only tend to emerge upon challenge conditions. These mice present with altered metabolic and immune responses in a highly context-dependent manner [62; 67; 69]. This context dependency of SULT2B1b presents the greatest challenge in terms of assessing its prospective therapeutic and safety profile.
Caution is warranted in the interpretation of the findings in SULT2B1 whole-body knockout mice. Since SULT2B1 produces both SULT21a and SULT21b via alternative splicing, genetic knockout of SULT2B1 impacts both isoforms, such that selective loss of SULT2B1b may have slightly different effects. Some of the phenotypes may be milder with selective SULT2B1b loss due to partial compensation, at least in some tissues, by SULT2B1a. The major caveat is the difference between mice and humans with respect to sterol biology. There are species differences in relative expression of SULT2B1b across tissues, as well as the levels of different sterol substrates [74; 75].

Genetic variants may provide additional information about potential effects of SULT2B1 inhibition. Variants that alter expression have been associated with altered risk for certain cancers [28]. Homozygous loss of function variants in SULT2B1 are associated with the skin disorder autosomal-recessive congenital ichthyosis [28; 72]. While the impacts of lifelong changes in expression may not be comparable to the use of an inhibitor, these genetic associations suggest that there could be impacts to cancer risk/responses, particularly with chronic use. Due to its role in keratinocyte turnover [70], SULT2B1 may increase the risk for disruptions to the skin barrier and other skin-related side effects.

A variety of other variants have been identified that impact the sulfation rate of DHEA and pregnenolone *in vitro*, though the physiological impact of these variants in humans is not yet clear [76].

Animal and cell models support a role for SULT2B1b in immune response modulation, particularly the promotion of immunosuppressive responses [1; 69]. Consequently, SULT2B1b inhibition could potentially increase the risk for inflammatory disorders or altered immune responses. Metabolic effects have also been observed in preclinical models, including effects on gluconeogenesis and insulin sensitivity [61; 62].

The overall safety profile will likely vary based on the degree of specificity, the degree of inhibition, as well as the bioavailability/activity profile across different tissue types.

Drug interactions: Interactions with SULT2B1b inhibitors have not been established, but due to the variety of pathways that interact with SULT2B1b, drug interactions are likely. Steroidal antiandrogen developed for prostate cancer treatment, such as galeterone and abiraterone, have been shown to inhibit SULT2B1b [6; 77]. Due to its role in the sulfonation of DHEA, SULT2B1b inhibitors may also interact with other drugs that impact estrogens and androgens. Cholesterol sulfate, a byproduct of SULT2B1b activity, has been shown to be a negative regulator of HMGCR, an enzyme involved in cholesterol synthesis that is also targeted by cholesterol-lowering therapies, including statins [59]. SULT2B1b inhibitors may also interact with acetaminophen, since SULT2B1b is involved in its detoxification, and SULT2B1b expression modulated the sensitivity to acetaminophen-induced liver injury in a rodent model [78].

Sources and dosing:

Clinically usable SULT2B1b inhibitors have not yet been developed.

Research underway:

The development of SULT2B1b inhibitors is still in the early preclinical stage.

Search terms:
Pubmed, Google: SULT2B1

- Alzheimer's disease, neurodegeneration, brain, cardiovascular, cancer, inhibitor, metabolism, genetic variants

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