*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.*

# SHIP1 Modulators

**Evidence Summary**

SHIP1 is a context-dependent immune regulator. SHIP1 dysregulation is implicated in various diseases, but determining whether activity should be turned up or down to provide benefit has been challenging.

**Neuroprotective Benefit:** SHIP1 gene variants are associated with Alzheimer's disease risk. These variants may drive altered innate immune responses, but it is currently unclear which direction SHIP1 should be modulated for therapeutic benefit.

**Aging and related health concerns:** SHIP1 has many context-dependent effects on immune function. Elevated and reduced SHIP1 are both associated with inflammation. The therapeutic profile of SHIP modulators will need to be determined empirically.

**Safety:** The safety profile of SHIP1 modulators may vary based on compound properties and disease indication as well as the dosing regimen. Intermittent dosing of SHIP1 inhibitors may be needed to avoid serious bone and immune-related side effects.

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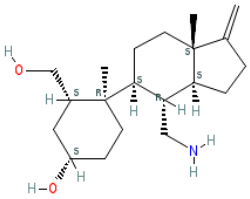
|---|---|---|
| **Availability**: Research use | **Dose**: Not established.<br>SHIP1 inhibitors may require intermittent dosing. | AQX-1125 (rosiptor)<br>**Chemical formula:** $C_{20}H_{35}NO_2$<br>**MW**: 321.50 g/mol<br>  <br>Source: IUPHAR/BPS Guide |
| **Half-life**: AQX-1125: > 5 h | **BBB**: Varied | |
| **Clinical trials**: The SHIP1 agonist AQX-1125 was tested in clinical trials for interstitial cystitis/bladder pain syndrome (n=69; n=385), asthma (n=22), COPD (n=400), and atopic dermatitis (n=54). | **Observational studies**: Genetic variants in SHIP1 (INPP5D) are associated with risk for Alzheimer's disease. | |

**What is it?**

Src homology-2 domain-containing inositol 5-phosphatase 1 (SHIP1), which is encoded by the gene INPP5D, is primarily expressed in hematopoietic lineage cells [1]. It plays important roles in the regulation of immune function by influencing the differentiation of different immune cell subsets in the bone marrow and impacts signaling cascades that influence immune cell activation and polarization [2]. SHIP1 is a phosphatase that is regulated by a variety of inputs and impacts a variety of downstream signaling cascades in a phosphatase-dependent or phosphatase independent manner [1]. The most well studied aspect of SHIP1 is its role as a regulator of phosphoinositol signaling. SHIP1 is a negative regulator of phosphoinositol 3-kinase (PI3K), a critical signaling coordinator of cell growth and survival. The kinase activity of PI3K produces the membrane-derived lipid second messenger phosphatidylinositol-3,4,5-trisphosphate [PI(3,4,5)P3], while the phosphatase activity of SHIP1 reduces levels of this important lipid second messenger by removing a phosphate, thereby converting it to PI(3,4)P2 [1]. The Src-homology-2 (SH2) domain of SHIP1 acts as an important scaffold for the recruitment of various cell surface receptors. Several SHIP1 isoforms have been identified, some of which lack either the SH2 or phosphatase domain, leading to different activity profiles [3]. As a result, the effects of SHIP1 activity are highly context dependent. SHIP1 has been implicated in exacerbating and mitigating inflammation in different contexts, thus SHIP1 activators and inhibitors are being developed for diseases with immune-related dysregulation [4]. In some cases, such as with Alzheimer's disease, SHIP1 activators and inhibitors are being developed for the same condition. The properties may also differ depending on whether they target the phosphatase-dependent or phosphatase-independent functions of SHIP1.

Only one SHIP1 modulator, a SHIP1 agonist, AQX-1125 (rosiptor) has been tested in clinical trials. This compound was in clinical development by Aquinox Pharmaceuticals , but development was discontinued after the failure of a Phase 3 trial in interstitial cystitis/bladder pain syndrome in 2018 [5]. The clinical failure of AQX-1125 may have been related to properties of the compound rather than a reflection of the SHIP1 activator class. Despite good oral bioavailability, AQX-1125 was found to exhibit only weak binding to SHIP1 and marginal phosphatase activating capacity [6; 7].

**Neuroprotective Benefit:** SHIP1 gene variants are associated with Alzheimer's disease risk. These variants may drive altered innate immune responses, but it is currently unclear which direction SHIP1 should be modulated for therapeutic benefit.

*Types of evidence:*

- 1 review INPP5D gene variant associations with Alzheimer's disease
- Numerous laboratory studies

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

SHIP1, encoded by the gene INPP5D, has been identified as a genetic risk factor for Alzheimer's disease (AD) [8]. The single nucleotide variants (SNPs) rs35349669 and rs10933431, located in intronic regions of INPP5D, have been associated with AD risk. The minor allele of rs35349669, located in intron 10, is associated with increased AD risk ($p= 4.85 \times 10^{9}$, minor allele frequency [MAF]= 0.498, Z-score = 5.85), while the minor allele of rs10933431, located in intron 2, is associated with decreased AD risk ($p = 8.92 \times 10^{10}$, MAF = 0.220, Z-score = −6.13) [8]. INPP5D is considered to be a major genetic risk factor, with the rs35349669 variant accounting for 3.8% of AD genetic risk [3]. Although it has not yet been established the degree to which these SNPs impact INPP5D expression and/or SHIP function, it has been speculated that rs35349669 may increase expression because the minor allele of this SNP has been found to be associated with increased INPP5D expression in whole blood ($p = 2.2 \times 10^{-12}$) in the GTEx consortium atlas [8]. It is not yet clear exactly how these variants modify AD risk. As a gene associated with hematopoietic lineage cells, microglia constitute the dominant source of INPP5D expression in the brain, thus, SHIP1 is thought to impact AD risk via the modulation of microglial function and/or activation.

There are multiple isoforms of INPP5D, which can differ in terms of transcriptional start site and inclusion or exclusion of various domains [3]. As a result, differences in the isoform profile could alter

the ability of SHIP1 to act as a scaffold for downstream signaling as well as its phosphatase activity. The full-length isoform contains 27 exons and includes both the SH2 domain, which is important for the recruitment of SHIP1 to the plasma membrane to interact with other proteins, as well as the phosphatase domain, which can act on phospholipids and phosphoproteins. While the expression of INPP5D in general has been found to be increased in the AD brain [9], differences have been detected in the isoform profile [8; 10]. One study found that isoforms with transcriptional start sites at exon 1 (ENSEMBL 201, 204, and 205) and in intron 14 (the truncated 213 isoform) were elevated in conjunction with AD pathology, while there was no change in expression of the 202-isoform lacking the SH2 domain, relative to the full-length gene [8]. The 213 isoform lacks a complete phosphatase domain, though the potential impact this has on AD pathology is currently unclear. This study also identified a novel isoform lacking the initial 47bp of exon 12, leading to a premature termination codon that produces a protein containing the SH2 domain but lacking the phosphatase domain. The expression of this novel isoform was also increased in conjunction with AD pathology. This phosphatase domain-lacking isoform was found to account for around 13% of the total INPP5D expression in the AD brain, and may be a substrate for nonsense-mediated decay, suggesting that despite higher levels of expression, there may be lower levels of functional SHIP1 protein in the AD brain.
There is additional evidence to support a reduction in SHIP1 activity in AD [10; 11]. One study found a reduction in levels of full-length soluble SHIP1 [10]. There was a shift away from phosphatase-containing forms toward more truncated forms lacking the phosphatase domain and particularly of truncated C-terminus containing peptides.

***Human research to suggest benefits to patients with dementia***:

SHIP1 modulators have not yet been tested in dementia patients.

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

**Alzheimer's disease**: UNCLEAR, LIKELY CONTEXT DEPENDENT
The preclinical studies investigating the role of SHIP1 in AD have been mixed in terms of concluding whether SHIP1 inhibitors or activators would be more therapeutically beneficial [12]. This is likely a function of the highly context dependent nature of SHIP1 activity, which has been observed across a wide range of indications. This context dependency appears to be a natural extension of its role as an immune system modulator that is generally involved in maintaining homeostasis by acting as a negative regulator of immune signaling [2]. The degree of SHIP1 activity can also bias immune cell differentiation,

with higher SHIP1 typically opposing the expansion of regulatory populations. As a result, the inhibition of SHIP1 can promote both the induction of pro-inflammatory mediators and the expansion of more anti-inflammatory immune subsets [2]. The end result depends on the conditions within a given tissue, such that the impact of modulating SHIP1 in a particular model/disease-setting needs to be determined empirically. In this way, the potential translatability of SHIP1 modulators in preclinical models remains very unclear. In young adult (10-12 weeks of age) C57BL/6 mice, SHIP1 was found to regulate neuroinflammation and microglial activation [11]. In the steady-state brain, SHIP1$^{-/-}$ microglia were found to have a modestly activated phenotype, involving increased expression of some inflammation-associated surface markers without changes in morphology or induction of peripheral leukocytes. However, these microglia were also hyperresponsive to pro-inflammatory lipopolysaccharide (LPS) stimulation, suggesting that the impact of altered SHIP1 varies depending on the environmental/inflammatory milieu.
As described above, while expression of SHIP1 at both the gene and protein levels appears to be elevated in the AD brain [8; 9; 10], there are still questions regarding whether SHIP1-related activity is increased or decreased. To further complicate matters, SHIP1 interacts with multiple pathways implicated in AD pathophysiology.

***TREM2 and phagocytosis***: SHIP1 is a negative regulator of TREM2 [12]. The SH2 domain of SHIP1 interacts with the adaptor protein DAP12 to inhibit TREM2-DAP12 downstream signaling. The activated TREM2-DAP12 complex recruits spleen tyrosine kinase (SYK). This, in turn, results in the activation of other downstream signaling pathways, including PI3K and PLCγ, which are involved in cell growth, proliferation, and survival. The activation of TREM2 and SYK is involved in the transition of microglia from a resting homeostatic state to the disease-associated microglia (DAM) state with enhanced phagocytic capacity [13]. The loss of function R47H TREM2 variant is associated with increased AD risk, while the P522R variant that enhances the activity of PLCγ2 appears to be protective [8; 12]. This would suggest that relieving the inhibition of TREM2 by SHIP1 should be neuroprotective. However, preclinical studies suggest that the situation is more complex, in part because SHIP1 also impacts a variety of other signaling pathways, and because the biology of TREM2 itself is complex and context dependent. TREM2 is implicated in the clearance of Aβ and the microglial-mediated compaction of amyloid plaques from diffuse to dense-core type, which is thought to limit the neurotoxicity of Aβ [12]. Expression of INPP5D has been found to be lower in phagocytic microglia relative to non-phagocytic microglia [9]. SHIP1 deficiency has been shown to promote the recruitment of plaque-associated microglia [14]. A study using 5XFAD mice with germline SHIP1 haploinsufficiency observed a reduction in overall plaque burden coupled with a shift from diffuse to more dense-core type plaques [15]. These mice also showed a

preservation of cognitive function and an altered microglial response skewed toward activation of the TREM2-SYK signaling pathway and lower inflammatory cytokine production. However, a separate study using a conditional deletion of SHIP1 in microglia (as well as some peripheral monocyte/macrophage populations) using the Cx3cr1 promoter, induced at three months of age, in the PSAPP AD mouse model found increased recruitment of microglia to plaques that was coupled with increased plaque burden [16]. But this increased plaque burden was not associated with enhanced synaptic toxicity, suggesting that the amyloid may be converted to a less toxic state. These studies highlight the unpredictability of SHIP1 modulation *in vivo*, and the need for more studies in human tissue.

While expression of INPP5D appears to increase in AD in conjunction with increasing neuropathology, there is evidence to suggest that microglia in the AD brain show a profile more consistent with low SHIP1 [10]. Spatial transcriptomics identified a plaque-associated glial cluster in AD mice following INPP5D knockdown that was similar to the profile seen in human AD postmortem brain tissue [16].

The timing of SHIP1 modulation may be a crucial factor, as the genetic studies suggest that impacts on pathology could differ depending on whether SHIP1 is inhibited/depleted before or after the induction of amyloid, and over time compensatory changes to immune cell function could alter the potential benefit profile of SHIP1 inhibition. This is consistent with what has been seen with TREM2 and PLCγ2, in which stage of disease appears to impact the outcomes associated with modulation of these genes in animal models [8].

***NLRP3 inflammasome***: Activation of the NLRP3 inflammasome has been implicated in AD pathophysiology [12]. Analysis of human postmortem brain tissue found evidence of NLRP3 inflammasome activation in microglia with reduced SHIP1 activity [12]. The treatment of iPSC-derived human microglia with the SHIP1 inhibitor 3AC enhanced NLRP3 inflammasome activation and the production of pro-inflammatory cytokines, particularly, IL-1β, in response to LPS stimulation [7]. iPSC-derived human microglia with heterozygous loss of function of INPP5D showed evidence of impaired autophagic flux and sub-lytic inflammasome activation. The chronic inflammasome activation with reduced INPP5D may have triggered a negative feedback mechanism resulting in a reduction in IL1B mRNA levels. In AD brain tissue, microglia with higher levels of ASC speck formation, an indicator of inflammasome activation, had lower levels of INPP5D. Additionally, the expression profile of INPP5D loss of function microglia was highly similar to that of microglia in AD postmortem brain tissue.

SHIP1 also acts as an inhibitor of NF-kB inflammatory signaling [12]. A novel class of SHIP1 agonists in which the activation does not require the C2 domain of SHIP1 was found to inhibit the production of the inflammatory cytokines, TNF-α and IL-6, in BV2 microglial cells following LPS stimulation [17]. While SHIP1 inhibitors have been shown to promote the phagocytic uptake of Aβ, the novel SHIP1 agonist

K306 was found to enhance the phagocytic degradation of lipid-rich cargo, such as synaptosomes, but not protein-rich cargo like Aβ.

Overall, these studies suggest that the role of SHIP1 in AD pathophysiology is complex and likely stage-dependent, such that SHIP1 inhibitors and activators may preferentially benefit at different stages of disease.

***APOE4 interactions***: Not established.

**Aging and related health concerns:** SHIP1 has many context-dependent effects on immune function. Elevated and reduced SHIP1 are both associated with inflammation. The therapeutic profile of SHIP modulators will need to be determined empirically.

*Types of evidence:*

- 5 clinical trials for AQX-1125 in asthma, atopic dermatitis, COPD, and interstitial cystitis/bladder pain syndrome
- 2 observational studies on relation of SHIP1 expression with inflammatory autoimmune conditions (rheumatoid arthritis and inflammatory bowel disease)
- Numerous laboratory studies

**Immune modulation/pathogen control**: POTENTIAL BENEFIT for SHIP1 INHIBITOR (Preclinical)
SHIP1 has been implicated as a mediator of trained innate immunity, and studies in animal models suggest that SHIP1 inhibitors may boost immunity to certain pathogens. This stems from the role of SHIP1 as a negative regulator of pattern recognition receptor-induced inflammatory responses [2]. Pathogens trigger pattern recognition receptors via the release of pathogen-associated molecular patterns (PAMPs). The activation of these receptors then triggers an innate immune response. SHIP1 restrains these responses to help ensure that the inflammatory immune response to the pathogen does not also harm the host, however, excessive SHIP1 activity could also hinder the ability of the host to mount a sufficient immune response to the pathogen.
SHIP1 restrains IFN-I mediated immune responses during malaria (*Plasmodium* infection) by promoting the autophagic degradation of IRF3 [18]. Mice with SHIP1 deficient bone marrow exhibited a stronger IFN-1 response and greater antimalarial immunity during *Plasmodium yoelii nigeriensis* N67 infection. Treatment with the SHIP1 inhibitior, 3AC, reduced parasite load in BALB/c mice following *Leishmania*

*major* and *Leishmania donovani* infections, due to increased anti-leishmanial cytokine (IL-12) production [19].
SHIP1 may also impact trained immunity by modulating the cytokine response to pathogen-derived stimuli. SHIP1 was shown to modulate the degree of trained immunity in macrophages induced by β-glucan, which are components of the fungal cell wall [20]. SHIP1 deficient macrophages that had previously been exposed to β-glucan exhibited a more robust cytokine response toward second pathogen challenge. This translated to increased survival toward a lethal infection of *Candida albicans* in mice with SHIP1 deficient myeloid cells with prior low dose *Candida*/ β-glucan exposure. The 'trained' response of the macrophages involved epigenetic modification and metabolic reprogramming. SHIP1 activity may also impact the degree of non-specific trained immunity induced by the Bacille Calmette-Guérin (BCG) vaccine because SHIP1 shows inhibitor function toward one of the signaling pathways (NOD2) implicated in mediating BCG's effects on trained immunity. Therefore, pairing a SHIP1 inhibitor with administration of the BCG vaccine could potentially boost its non-specific immune protective effects [20].

However, these immune stimulating effects may require acute or intermittent inhibition of SHIP1, as chronic SHIP1 inhibition is associated with changes that could lead to anergy or impair adaptive immunity [4]. SHIP1 is primarily expressed in hematopoietic lineage cells and plays important roles in immune cell differentiation and activation. The loss of SHIP1 in the hematopoietic stem cell compartment results in a myeloid cell bias that becomes more pronounced with age. Aged mice lacking SHIP1 in mesenchymal stem cells have a high proportion of myeloid and granulocytic populations in their bone marrow, coupled with decreased lymphoid output [21]. This may stem from chronic G-CSF production, since SHIP1 typically acts to limit the production of G-CSF. SHIP1 deficiency in the bone marrow also hinders the production of bone marrow-derived dendritic cells, leading to excessive macrophage production and defective dendritic cell differentiation in mice [22].

**Obesity**: POTENTIAL BENEFIT WITH SHIP1/2 INHIBITOR (Preclinical)
Inhibitors of SHIP1 and SHIP2 have been shown to protect against and reverse diet-induced obesity in rodent models. SHIP2 is implicated in metabolic control because it is a negative regulator of insulin signaling, while SHIP1 plays a role in adipose tissue inflammation [4]. SHIP1 was shown to be upregulated in the context of diet-induced obesity in mice, and the infiltration of the SHIP1 expressing macrophages was correlated with fat mass [23].
Treatment with the SHIP1/2 inhibitor K118 (10 mg/kg, twice per week) reversed diet-induced obesity in mice. The reduction in adiposity was related to the mitigation of visceral adipose tissue inflammation

[24]. Treatment with the SHIP inhibitor increased the frequency of IL-4 producing eosinophils, myeloid derived suppressor cells, and alternatively activated (M2-like) macrophages in visceral fat tissue. SHIP inhibition was also protective against age-related adiposity in mice, as K118 treatment was associated with a lower body fat percentage in 8–12-month-old mice, but had no impact on body weight in young healthy mice. There was a shift toward a Th2-like cytokine profile and bias away from IFN-γ producing T cells towards more immunosuppressive T regulatory cells. Similar protection against diet-induced and age-related adiposity were seen with the SHIP1/2 inhibitor K161 [25]. Notably, these effects were replicated by use of the combination, but not by SHIP1 or SHIP2 selective inhibitors alone. These effects of SHIP inhibition appear to be mediated by the promotion of ILC2 cells, which are important for eosinophil proliferation and function. Improvements in blood glucose and insulin sensitivity were also observed with SHIP1/2 inhibition. The pulsative administration of the SHIP inhibitors may have been an important feature of the immune regulatory effects in the adipose tissue, as acute and chronic SHIP1 inhibition can have different and even opposing effects on immune system function [24].

**Cancer**: CONTEXT DEPENDENT (Preclinical)
Phosphoinositide 3-kinase (P13K) signaling can promote cancer cell survival via downstream activation of Akt [26]. PI3K is a driver of phosphoinositol (PI) signaling by converting the inositol phospholipid PI(4,5)P2 to PI(3,4,5)P3 As such, negative regulators of PI3K would be expected to act as tumor suppressors. This is true for PTEN, which is a phosphatase involved in the conversion of PI(3,4,5)P3 back to P1(4,5)P2. However, SHIP1 converts PI(3,4,5)P3 to PI(3,4)P2. According to the 'Two PIP Hypothesis', both PI(3,4,5)P3 and PI(3,4)P2 are involved in the activation of Akt and cancer cell malignancy [4]. Therefore, the effect of SHIP1 may depend on the balance of these phosphoinositol species as well as the presence of downstream signaling mediators.
Additionally, SHIP1 modulation may impact the immune-related control of cancer. Acute SHIP1 inhibition may promote tumor responsive NK cells and T cells, while overstimulation stemming from chronic inhibition may lead these cells to become anergic and unresponsive [26]. As a result, pulsatile administration of a SHIP1 inhibitor may help potentiate anti-tumor immune responses [4].
However, both SHIP1 inhibitors and activators have been shown to have cytotoxic effects against tumor cells in preclinical studies, suggesting that the tumor microenvironment, particularly the milieu of signaling mediators and immune cells, may determine the type of SHIP modulator needed for a given tumor type [4]. The overexpression of SHIP2 has also been found to be associated with poor prognosis in a variety of cancers, suggesting that targeting both SHIP1 and SHIP2 may offer more therapeutic utility [26].

**Rheumatoid arthritis**: UNCLEAR, LIKELY CONTEXT DEPENDENT (Preclinical)
Neutrophils derived from patients with rheumatoid arthritis (RA) were found to exhibit enhanced expression of SHIP1 and neutrophil extracellular trap production (NETosis) [27]. SHIP1 is a regulator of NETosis. *Ex vivo* treatment with the SHIP1 inhibitor 3AC was shown to reduce the induction of the p38MAPK/TNF-α signaling mediated NETosis in patient-derived neutrophils [27]. Similarly, SHIP1 inhibition mitigated NETosis in the collagen-induced arthritis mouse model, which was accompanied by a reduction in immune cell infiltration and cartilage destruction in the synovial joints. A separate study found that the SHIP1 inhibitor 3AC led to expansion of myeloid-derived suppressor cells (MDSCs) and T regulatory cells, which is consistent with the role of SHIP1 in regulating the reciprocal balance between Th17 cells and T regulatory cells [28]. The expansion of these regulatory immune populations can blunt the inflammatory response and thus mitigate disease progression in the collagen-induced arthritis model. Protective effects were seen with pretreatment using 3AC as well as with adoptive transfer of bone marrow from 3AC-treated mice. Consistent with this, diminished induction of miR-155, a negative regulator of SHIP1, was associated with abnormal pro-inflammatory T regulatory cells in RA patients [29].
However, SHIP1 may play different roles in different cell types involved in disease-associated inflammation, and there are discrepancies across studies regarding whether SHIP1 and miR-155, which are in a reciprocal negative feedback loop, are upregulated or downregulated in arthritis. Furthermore, both miR-155 overexpression and knockdown appear to protect against different aspects of disease pathophysiology in animal models [30]. Small clinical trials have found that β-D-mannuronic acid (M2000), a monosaccharide with anti-inflammatory properties, reduced joint stiffness and pain in patients with RA [31]. A biomarker assessment in peripheral blood mononuclear cells (PBMCs) was performed in a subset of study participants (n=12) [31]. Prior to treatment, SHIP1 expression was found to be non-significantly lower in the RA patients (0.75-fold), relative to a subset of healthy individuals, but increased by 1.54-fold following treatment. The inverse pattern was seen with miR-155, a negative regulator of SHIP1, which was found to be elevated in RA patients at baseline and then reduced with treatment. The inflammatory mediator, NF-kB was also reduced with treatment in this study.
The conflicting studies on whether SHIP1 and miR-155 levels are increased or decreased in RA depending on the cell type and compartment suggest that their activity may impact disease activity and progression in a variety of ways, such that the impact of SHIP1 modulators may vary depending on the model or subtype, which may be difficult to predict *a priori*.

**Inflammatory bowel disease**: POTENTIAL BENEFIT WITH SHIP1 ACTIVATOR (Preclinical)
SHIP1 deficient mice die prematurely due to excessive inflammation in the lung and gut. These mice develop severe ileitis characterized by a reduction in CD4 and CD8 T cells coupled with hyperresponsive neutrophils and macrophages [26].
SHIP1 deficiency has also been observed in patients with inflammatory bowel disease (IBD). In a cohort of IBD patients including 44 with Crohn's disease and 45 with ulcerative colitis, 14.6% were found to be SHIP1 deficient. SHIP1 deficiency was characterized by having SHIP1 levels in PBMCs less than 10% (range 0.5 to 8.0%, mean ± SD, 4.5 ± 2.8%) of normal levels [32]. The reduction in SHIP1 levels was not due to variants in the INPP5D gene, but rather, were associated with a novel SHIP1:ATG16L1 fusion transcript. The presence of the SHIP1:ATG16L1 fusion transcript was associated with a SHIP1 deficient phenotype (OR: 606.3, 95% CI 22.76 to 16,150; P < 0.0001), characterized by low levels of circulating CD4 T cells and more severe IBD requiring multiple surgeries. This suggests that IBD patients, or at least a subset of them, may benefit from the augmentation of SHIP1 activity.
In a mouse model of colitis stemming from IL-10 deficiency, treatment with the SHIP1 allosteric activator ZPR-MN100 (2 mg/kg i.p.) reduced levels of pathology and inflammation to a similar degree as the corticosteroid, dexamethasone [7]. The anti-inflammatory cytokine IL-10 can induce the formation of a complex between SHIP1 and STAT3. ZPR-MN100 could mimic the activity of IL-10 by inducing the formation of this complex, and downstream anti-inflammatory signaling.

**Interstitial Cystitis/Bladder Pain Syndrome**: NO BENEFIT WITH SHIP1 ACTIVATOR
The SHIP1 activator, AQX-1125, was tested in two clinical trials in patients with moderate to severe interstitial cystitis/bladder pain syndrome (IC/BPS). Clinical development of AQX-1125 was discontinued following the failure of the Phase 3 trial in this indication. In a Phase 2 RCT, AQX-1125 was tested in a dose of 200 mg/day orally for six weeks in comparison with placebo in 69 women with moderate to severe IC/BPS [33]. Relative to placebo, AQX-1125 was associated with a reduction in O'Leary-Sant interstitial cystitis symptom indices ICSI (by 3.8 points vs 1.4; P=0.005), interstitial cystitis problem indices (ICPI) (by 3.6 vs 1.6; P=0.014) and bladder pain interstitial cystitis symptom score (BPIC-SS) (by 8.8 points vs 4.0; P=0.011). Due to the potentially promising results in this pilot trial, AQX-1125 was tested in a larger Phase 3 trial including 298 female and 87 male participants with moderate to severe IC/BPS at a dose of 100 or 200 mg/day orally for 12 weeks [5]. Relative to placebo, treatment with AQX-1125 was not associated with any significant differences in bladder pain, ICSI, BPIC-SS, or urinary voiding frequency. It was determined that it may not be possible to develop a mechanistic-based therapy for IC/BPS at this time due to a lack of clarity on the underlying etiology.

**Lung inflammation**: POTENTIAL MINOR BENEFIT WITH SHIP1 ACTIVATOR
SHIP1 deficiency in mice is associated with an aggressive form of type-2 dominated lung inflammation. Group 2 innate lymphoid cells, ILC2 cells, are strong inducers of this type-2 inflammation, driven by the inflammatory cytokines IL-5 and IL-13 [34]. SHIP1 may maintain lung homeostasis by tempering the PI3K signaling that drives ILC2 cell development. SHIP1 is also involved in mediating cellular responses to allergens by regulating the threshold of IgE-induced signaling for degranulation in mast cells and basophils [2]. The degree of SHIP1 activation has been shown to be inversely associated with the degree of basophil histamine production. This suggests that SHIP1 activation may be best suited to the dampening of allergen-driven excessive type-2 mediated lung inflammation.
***Asthma***: The SHIP1 activator AQX-1125 was tested in a small (n=22) randomized, double-blind, placebo-controlled, two-way crossover study clinical trial in patients with mild to moderate asthma [35]. It is not clear whether these patients were screened for having the type-2 inflammation asthma subtype. Patients were treated with 450 mg/day oral AQX-1125 for seven days, and an allergen challenge was conducted on day six. Relative to placebo, AQX-1125 treatment was associated with an attenuated late phase (4-10 h) response as measured by the forced expiratory volume in one second (FEV1) (mean difference 150 mL, 20%; P = 0.027), as well as an increase in the minimum FEV1 during the late phase response. There was also a non-significant trend toward a reduction in sputum eosinophils, neutrophils and macrophages, though the study was not powered to detect a difference on these measures. There were no significant differences on the early phase response or on responses to a methacholine challenge. Clinical development of AQX-1125 has been discontinued, and it is unclear whether a next-generation SHIP1 agonist will be tested/developed for this indication.
***COPD***: AQX-1125 was tested in a placebo-controlled Phase 2 RCT including 400 patients with acute exacerbations of chronic obstructive pulmonary disease (COPD) [36]. Patients receiving AQX-1125 at an oral dose of 200 mg/day for 12 weeks showed no significant differences on the primary outcome of EXACT score (415.4 vs. 391.7) or on any the spirometry measures, relative to placebo, indicating a lack of efficacy in this population.

**Atopic dermatitis**: NO BENEFIT WITH SHIP1 ACTIVATOR AQX-1125
The SHIP1 activator AQX-1125, tested at a dose of 200 mg/day orally for 12 weeks in patients with atopic dermatitis (n=54) failed to show efficacy on its primary endpoint of total lesions symptoms in a Phase 2 RCT (Press release).

**Safety:** The safety profile of SHIP1 modulators may vary based on compound properties and disease indication as well as the dosing regimen. Intermittent dosing of SHIP1 inhibitors may be needed to avoid serious bone and immune-related side effects.

*Types of evidence:*

- 5 clinical trials for AQX-1125
- Numerous laboratory studies

SHIP1 inhibitors have not yet been clinically tested. Preclinical studies highlight the highly context-dependent nature of SHIP1 activity, such the therapeutic profile for SHIP modulators needs to be tested empirically, which may differ depending on the underlying inflammatory profile and environment of a given disease state. Studies in mice using genetic SHIP1 deficiency reveal potential concerns related to chronic loss of SHIP1 activity [26]. SHIP1 knockout mice have shortened lifespans, succumbing to complications related to massive lung and gut inflammation during young adulthood. While it has many context and tissue-type dependent effects, SHIP1 primarily acts to restrain immune activation, thus the complete loss of this brake could result in a lethal inflammatory response [2]. The intended effect on a target tissue may differ from overall systemic effects. Another concern with chronic SHIP1 inhibition is osteoporosis, as SHIP1 plays a role in regulating the balance between bone forming osteoblasts and bone reabsorbing osteoclasts due to its ability to impact mesenchymal stem cells [26]. SHIP1 deficient mice exhibit a severe osteoporosis phenotype due to the impaired development of osteoblasts [37]. Lower bone mass has also been observed with chronic use of the SHIP1 inhibitor 3AC.
However, the use of SHIP inhibitors via an intermittent/pulsatile administration scheme in mice has not been associated with any of these phenotypes, suggesting that it will likely be possible to find clinically safe dosing strategies for SHIP inhibitors [24].

To date, AQX-1125 is the only clinically tested SHIP1 agonist. It has generally been well-tolerated in clinical trials, though it should be noted that AQX-1125 is a weak SHIP1 agonist [7], and due to the context-dependent nature of SHIP1 activity, its safety profile may or may not be reflective of what would be expected with other more potent SHIP1 activators.
In patients with Interstitial Cystitis/Bladder Pain Syndrome, the adverse event profile was similar between AQX-1125 and placebo, with gastrointestinal events and headache as the most common events in both groups [5]. A similar profile was seen in asthma patients [35]. In patients with COPD, similar levels of adverse events were reported between groups, though fewer serious adverse events were observed in those treated with AQX-1125 (13/200) relative to placebo (23/200) [36].

***Drug interactions***: Drug interactions have not been established for SHIP1 modulators, and exact interactions will likely depend on compound properties. Due to its roles in the modulation of networks of pleiotropic signaling cascades, such as PI3K, SHIP1modulators may interact with other drugs that impact these signaling networks. Additionally, due to the role of SHIP1 in immune system regulation, modulators may interact with other immunomodulatory agents.

**Sources and dosing:**

To date SHIP1modulators have not been approved for any indication, and none are currently in clinical testing. Various SHIP inhibitors and activators are in preclinical development for a variety of indications. Preclinical studies suggest that intermittent/pulsatile administration of SHIP1 inhibitors may be needed to maximize desired immune modulatory activity while minimizing the potential safety risks associated with chronic SHIP1 inhibition, as observed in genetic models [26].

**Research underway:**

There are currently no ongoing clinical trials testing SHIP1 modulators, but there are several research groups developing them [4] [17] [25][7][38].

**Search terms:**

Pubmed, Google: SHIP1

- Alzheimer's disease, neurodegeneration, cognition, inflammation, cancer, clinical trials

Websites visited for SHIP1 Inhibitors:

- Clinicaltrials.gov (AQX-1125)
- DrugBank.ca (AQX-1125)

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