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.

Anti-CD22

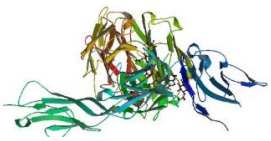
Evidence Summary

Available anti-CD22 mAbs primarily target peripheral B cells via IV administration. Better safety profile than other B-cell targeted mAbs, but would require intrathecal delivery for CNS, and benefit is unclear.

Neuroprotective Benefit: Acute CD22 upregulation in the CNS may have a protective response, but during aging chronic upregulation may signal microglial dysregulation. Systemic administration would primarily target peripheral B cells and not reach the CNS.

Aging and related health concerns: Anti-CD22 antibodies are used as immunotoxins in B-cell cancer therapy, but there is no evidence that CD22 plays an important role in immune aging.

Safety: Unconjugated anti-CD22 mAb, epratuzumab, was well-tolerated with only minor B cell depletion in clinical trials.

Availability: Clinical trials/ Research	**Dose**: 360 to 1200 mg every other week IV in clinical trials for Epratuzumab in Lupus. Therapeutically efficacious dose not established.	**Chemical formula:** **MW**: 135 kDa (for CD22)  Complex CD22 with epratuzumab Source: Protein data bank
Half-life: 13- 24 days depending on dosing (consistent with IgG1 half-life)	**BBB**: Not penetrant	
Clinical trials: Tested in B-cell cancers. Epratuzumab also tested in Lupus (including two Phase 3 n=786, n=788) and Sjogren's (Phase 1/2 n=16)	**Observational studies**: CD22 expression upregulated in AD brain tissue (1 study).	

What is it? CD22, also known as Siglec 2, is a transmembrane sialoglycoprotein, or a protein coated with sialic acid and sugar molecules, that belongs to the siglec family of lectins and binds α2,6 sialic acid [1]. It is primarily found on the surface of mature B cells, and typically serves as an inhibitory receptor for conventional B cells (B2), which are part of the adaptive immune system (B1 cells are part of the innate immune system). CD22 regulates B cell receptor signaling. It contains an inhibitory ITIM domain which recruits the protein tyrosine phosphatase SHP-1 to inhibit cell signaling. Monoclonal antibodies have been developed against CD22 for therapeutic use in B-cell cancers [2] and for autoimmune diseases with B-cell etiology [1]. These therapies are designed to deplete the pathogenic CD22 expressing B-cells and/or alter their signaling. Anti-CD22 therapies have been less effective for these conditions than other B-cell depleting therapies, such as anti-CD20 biologics.

Neuroprotective Benefit: Acute CD22 upregulation in the CNS may have a protective response, but during aging chronic upregulation may signal microglial dysregulation. Systemic administration would primarily target peripheral B cells and not reach the CNS.

Types of evidence:

- 3 observational studies (CD22 expression in Niemann Pick Disease, Menopausal women, and Alzheimer's disease)
- 1 laboratory study for anti-CD22 treatment

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

Human research to suggest benefits to patients with dementia: None

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

Cognitive Aging: Potential benefit (preclinical models)

CD22 plays a role in maintaining the quiescent or 'resting' state of microglia. The CD22-CD45 interaction and the CD200-CD200R interaction are primarily involved in retaining microglia in the resting surveillance state and inhibit their transformation to an activated state [3]. Polysialyated proteins on the surface of cells engage siglecs, such as CD33 and CD22, to inhibit phagocytosis. CD22 is upregulated in response to an inflammatory stimulus in order to dampen the immune response and prevent immune mediated damage. While this may be protective in the context of an acute event, chronic inflammation can lead to a maladaptive increase in CD22 which prevents appropriate activation responses, leading to microglial dysregulation.

In patients with Niemann Pick Disease, a neurodegenerative condition, CD22 was found to be elevated in the cerebrospinal fluid (CSF) relative to age-matched controls, and was associated with microglial dysregulation [4]. In an ovariectomized rat model of menopause, there was a shift in the microglial transcriptional profile including an upregulation of CD22 (2.5 fold) and CD45 (1.2 fold) [5]. Notably, the increase in CD45 was exacerbated by estrogen (E2) treatment, whereas the upregulation in CD22 was unaffected by E2 replacement. A similar upregulation in CD22 and CD45 was seen in a microarray analysis comparing pre and post-menopausal women.

CD22 has been found to be upregulated on the microglia of mice in the context of aging [6; 7]. A recent study using intrathecal administration of anti-CD22 (Cy34, BioXCell) via an osmotic pump for 28 days (steady concentration of 10 ug/ml) in aged (20-22 months) mice found that **blocking CD22 restored microglial homeostasis and induced a shift in the transcriptional profile of microglia** [8]. CD22 knockout mice, or mice treated intrathecally with anti-CD22 had improved spatial memory on the forced alternation Y maze and associative memory in the contextual fear conditioning test. Notably, these effects on cognition do not appear to be related to the effect of CD22 on B cells, since intraperitoneal administration, which primarily affects peripheral B cells, was not protective against cognitive aging, and B cell infiltration into the CNS was not significantly affected by intrathecal antibody administration.

The beneficial effects appear to be related to the **improved phagocytic clearance of cellular debris in the absence of CD22**, as the clearance of labelled myelin is enhanced in the brains of the treated mice [8]. The specific benefit in the context of aging may stem from age related changes in microglial subpopulations and in the expression of the co-receptors for CD22.

Alzheimer's Disease: Unclear

CD22 expression has been found to be upregulated in the brain tissue of patients with Alzheimer's disease (AD) [9]. This could be a compensatory response designed to mitigate neuroinflammation and phagocytosis of stressed neurons (phagoptosis) which then becomes maladaptive by inhibiting clearance of Aβ and cellular debris. In culture, stressed neurons have been shown to secrete CD22, which binds to CD45 on microglia to inhibit their activation and the production of the pro-inflammatory cytokine TNFα [10].

Rodent and cell culture studies suggest that blocking CD45 on microglia is detrimental for AD by promoting neuron loss and inhibiting the clearance of Aβ [11; 12; 13]. The seeming contradiction with respect to phagocytosis/clearance for CD45 may arise due to different functions for different isoforms of CD45, or stem from interactions between CD45 and molecules other than CD22 that promote microglia toward to a pro-phagocytic state. Alternatively, it could stem from heterogeneity within the CD45 expressing microglia. The vast majority of microglia express low levels of CD45 ($CD45^{lo}$), but a small subset that increases with age expresses high levels ($CD45^{hi}$) [14]. The $CD45^{hi}$ microglia were found to have superior phagocytosis capacity toward clearing Aβ, while the $CD45^{lo}$ cells had higher levels of expression for genes involved in pathological neuronal phagoptosis. This suggests that inhibition via engagement of CD22 on $CD45^{lo}$ cells may be neuroprotective, whereas it could drive pathology when it engages with $CD45^{hi}$ cells. It is not yet clear whether blocking CD22 would be neuroprotective in the context of AD.

APOE4 interactions: Unknown

Aging and related health concerns: Anti-CD22 antibodies are used as immunotoxins in B-cell cancer therapy, but there is no evidence that CD22 plays an important role in immune aging.

Types of evidence:

- Numerous clinical trials for anti-CD22 therapies in cancer
- 1 observational study (CD22 B cell expression with aging)

Cancer: Benefit for B-cell malignancies

CD22 regulates the survival of both normal and malignant B cells, and is highly upregulated in many types of B-cell cancers [15]. Soluble CD22 also serves as a tumor marker for B cell malignancies [16]. Monoclonal anti-CD22 antibodies (mAbs) have been developed as therapeutic agents to inhibit the survival of malignant B-cells [2]. The most effective of the anti-CD22 anti-cancer therapeutics are antibody conjugates. Since CD22 is an endocytic receptor, anti-CD22 mAbs can be used to target a cytotoxic agent to CD22 expressing cells, where it can be taken up by the cell [17]. Inotuzumab ozogamicin (Besponsa) is anti-CD22 conjugated to the chemotherapeutic agent ozogamicin, and is approved for refractory B cell acute lymphoblastic leukemia (Product insert). Similar to the anti-CD33 drug-antibody conjugate, gemtuzumab ozogamicin, it is associated with the risk for severe liver toxicity (see CD33 report). Moxetumomab pasudotox (Lumoxiti) is an immunotoxin containing anti-CD22 conjugated to Pseudomonas exotoxin and was approved for refractory hairy cell leukemia in 2018 (Product insert).

Immunosenesence: No clear benefit or harm (preclinical)

Aging is associated with an impairment in humoral immunity involving changes into the distribution of naïve and memory B cell subsets, and changes to the pattern of receptor expression on B cells [18]. Since CD22 is involved in regulating B cell signaling and survival, changes in its levels could potentially contribute to this process. However, a study comparing receptor expression on B cells from young (age 25-40, n=20) and elderly (age 78-90, n=20) people found no significant difference in CD22 expression, suggesting that CD22 is unlikely to be a major contributor to B cell immunosenescence [19]. IgG+IgD-CD27- B cells, commonly called double-negative cells, expand with aging [20] and this population was found to be lower in people that were genetically advantaged for longevity, based on having a centenarian parent, compared to their age-matched counterparts [19]. These individuals also had higher levels of telomerase reactivation in their B cells following *ex vivo* stimulation.

Safety: Unconjugated anti-CD22 mAb, epratuzumab, was well-tolerated with only minor B cell depletion in clinical trials.

Types of evidence:

- 9 clinical trials (Epratuzumab for Non-Hodgkin's Lymphoma Phase 1/2 n=56; Sjogren's Phase 1/2 n=16; Lupus: Phase 2 n=14, n=20, n=90, n=203, n=277; Phase 3 n=786, n=788)

Anti-CD22 mAbs have been tested clinically in B cell cancers and autoimmune diseases. The mAbs for cancer are conjugates, and their side effect profile stems from the effects of the conjugated cytotoxic agent. These are meant to kill CD22 expressing cells, and thus are not therapeutically relevant for neurodegenerative diseases where the goal is to reduce CD22 expression, not eliminate cells.

Epratuzumab is a humanized anti-CD22 mAb that has been tested in clinical trials for B cell cancers and the autoimmune diseases systemic lupus erythematosus and Sjogren's syndrome. Epratuzumab does not induce complement dependent cytotoxicity (CDC) and only induces a moderate amount of antibody dependent cell-mediated cytotoxicity (ADCC), consequently, it is not a strong B cell (CD22 expressing cell) depleting agent. Its therapeutic mechanism of action has not been fully determined, but is thought to stem from its ability to modulate B-cell receptor (BCR) signaling and regulate B-cell activity [21]. Epratuzumab has primarily been tested in the context of cancer as a combination therapy with the potent B cell depleting agent rituximab (an anti-CD20 mAb), or for targeted delivery with chemotherapeutics, or as a radioimmunotherapy. The side effects attributable to epratuzumab cannot be conclusively determined in these combination studies.

Epratuzumab was tested as a monotherapy in a Phase 1/2 open-label trial for refractory Non-Hodgkin's Lymphoma (n=56), where 120-1000 mg/m^2 was administered once weekly for 4 weeks intravenously (IV). It was found to be well-tolerated with no dose-limiting toxicity [22; 23]. All adverse events were mild, and were generally infusion related. Fatigue (23%) was the most common adverse event. The serum half-life was consistent with human IgG, and it had no significant effect on levels of T cells.

Most of the trials involving epratuzumab as a monotherapy have taken place in moderate to severe lupus patients plus one trial in Sjogren's, ranging from 12 to 48 weeks with dosing up to 1200 mg every other week [24; 25; 26; 27; 28; 29; 30; 31]. These trials report a comparable incidence of adverse events between the epratuzumab and placebo treated groups, with respiratory and urinary tract infections being the most common. There were no significant changes in T cells, immunoglobulins, or routine hematological parameters. Patients experienced a reduction in total numbers of B cells (by 30-50%), which is much less than the level of reduction seen with CD20 targeted therapies, with a greater effect on naïve cells than memory B-cells, and a reduction in surface expression of CD22 [24; 27; 32]. This profile suggests that epratuzumab carries a lower risk for infection than other more potent B-cell targeted therapies. However, CD22 may be important for the immune system response for a subset of pathogens. For example, CD22 may be required for protection against West Nile Virus [33].

As a large mAb, epratuzumab is unlikely to appreciably cross the BBB, and systemic IV injection would primarily affect peripheral B cells. Therefore, intrathecal administration would be necessary to target CD22 expression on microglia in the context of neurodegenerative disease. It is not yet clear whether this would significantly affect B cell function in the CNS or contribute to a higher risk for brain infection.

Sources and dosing:

Epratuzumab is administered IV, with doses in clinical trials for autoimmune disease ranging from 360 to 1200 mg. It has not been tested for intrathecal administration in humans. It is unclear whether epratuzumab will be approved for any clinical indication. Its failure in several Phase 3 trials for lupus has led UBS to withdraw its collaboration with Immunomedics to develop epratuzumab for non-cancer indications (Press release). It is currently in clinical development by Immunomedics for Acute Lymphoblastic Leukemia (ALL).

Research underway:

Epratuzumab is currently being tested in a trial for childhood ALL (NCT01802814). ADCT-602 is a drug-antibody conjugate of pyrrolobenzodiazepine with anti-CD22 being tested in relapsed B-cell ALL (NCT03698552). Moxetumomab pasudotox will be tested in combination with rituximab for relapsed Hairy B-cell Leukemia (NCT03805932). Inotuzumab ozogamicin is also being tested, primarily in combination with chemotherapy, in several clinical trials for ALL.

Search terms:

Pubmed, Google: CD22, or anti-CD22, or Epratuzuamb

- Alzheimer's disease, cogniton, neurodegeneration, aging, cancer, autoimmune, immunosenescene, safety, clinical trials

Websites visited for CD22:

- Clinicaltrials.gov (Epratuzumab)
- PubChem (CD22)
- DrugBank.ca (Epratuzumab)

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