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-CD33

Evidence Summary

High CD33 surface expression impairs the phagocytic capacity of microglia and may contribute to risk for Alzheimer's disease, but it is also important for immune self-tolerance.

Neuroprotective Benefit: CD33 alleles that reduce CD33 surface expression on microglia are associated with decreased risk for Alzheimer's because high CD33 impairs phagocytic capacity and Aβ clearance. Anti-CD33 antibodies can reduce CD33 surface expression, but have poor BBB penetrance.

Aging and related health concerns: CD33 is important for self-tolerance, so blocking CD33 can increase immunosurveillance against cancer cells, but may also increase systemic inflammation and promote autoimmunity.

Safety: The only approved anti-CD33 therapy, the drug-antibody conjugate gemtuzumab, is associated with liver toxicity. Unconjugated anti-CD33 antibodies have shown good safety in patients with CD33⁺ cancer, but the side effect profile in other populations has not been determined.

What is it? CD33, also known as sialic acid binding Ig-lectin 3 (Siglec-3), is a transmembrane receptor expressed on the surface of certain classes of hematopoietic and immune cells [1]. It belongs to the family of CD33 related siglecs (CD33rSiglecs), which has shown expansion in long-lived primates [2]. CD33rSiglec family members bind glycoproteins and show species specificity in terms of their binding partners and intracellular domain properties, thus the functions attributed to CD33 in other species may not be applicable to humans [1]. CD33 is primarily expressed on cells of myeloid lineage, especially monocytes and dendritic cells, and to a lesser extent on some lymphoid cells, including activated T cells and natural killer cells, but not on hematopoietic stem cells. It preferentially binds to α-2,6 linked sialic acids with potency in the micromolar to millimolar range.

Siglec expression is typically low under homeostatic conditions, and is induced in response to immune cell activating stimuli. CD33 is expressed on myeloid-derived suppressor cells, which are important for mediating self-tolerance and preventing autoimmunity [3]. Accordingly, its best understood function is as **a mediator of immune response inhibition** on monocytes. Ligand binding leads to the recruitment of inhibitory proteins via its immunoreceptor tyrosine-based inhibition motif (ITIM) domains which initiates signaling cascades that inhibit functions associated with cell activation, such as cytokine release and phagocytosis [1]. However, **the functions of CD33 have not been fully characterized, and are dependent upon the sialic acid microenvironment** [4]. Different patterns of CD33 glycosylation have also been detected in different CD33 expressing immune cell lineages, which could influence binding partners and downstream function [5]. Consequently, the role of CD33 in the context of a given disease is driven by both changes in CD33 expression and how the disease affects the environmental milieu.

The association with disease is also influenced by the distribution of CD33 isoforms. There are **two isoforms of CD33 generated through alternative splicing.** The full-length form, CD33M, and the shorter form that skips exon 2, CD33m, which lacks the siglec binding V-set domain [5]. The shorter form generally does not localize to the cell surface and is considered to be inactive.

Neuroprotective Benefit: CD33 alleles that reduce CD33 surface expression on microglia are associated with decreased risk for Alzheimer's because high CD33 impairs phagocytic capacity and Aβ clearance. Anti-CD33 antibodies can reduce CD33 surface expression, but have poor BBB penetrance.

Types of evidence:
- 2 meta-analyses (CD33 SNPs and AD risk)
- 8 gene association studies (CD33 and AD)
- 7 cell culture studies

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

Alzheimer's Disease:

CD33 is one of the top 10 hits on Alzgene, which identifies genes associated in Alzheimer's risk based on GWAS studies. The primary SNP associated with Alzheimer's disease (AD) risk is rs3865444, which is located 373 bp upstream of the promoter [1]. **The major allele, rs3865444C, is associated with increased risk, whereas the minor allele, rs3865444A is associated with protection**. Microglia from the brains of AD patients were found to have increased expression of CD33 [6]. While some neurons also expressed CD33, these levels were not found to be altered in the AD brain, and the total amount of neuronal CD33 was negligible relative to the level of microglial CD33 [6]. With respect to the CD33 SNP, **the surface expression of CD33 was found to be higher in those with the C risk allele** with or without AD, relative to those with the protective A allele [7]. This allele was found to account for approximately 70% of the variance in CD33 surface expression. The difference in levels of CD33 surface expression between the alleles has been attributed to differences in the ratio of the two splice isoforms. The presence of the **protective A allele leads to higher levels of the alternatively spliced short CD33m isoform**, which does not interact with sialic acids or localize to the cell surface. Although, the rs3865444 SNP is located in a non-coding region, it is in linkage disequilibrium with the SNP rs112459419, which is located in exon 2 at a predicted binding site for a splicing factor [8]. This SNP promotes the skipping of exon 2, leading to higher levels of the short exon 2-lacking (CD33m) isoform. The full-length form (CD33M) was found to be decreased 25.2% in heterozygotes, and by 46.4% in those homozygous for the protective allele [8].

The protective allele is associated with a relatively modest risk reduction of approximately 10%. A meta-analysis including 12,714 AD patients and 13,367 individuals without AD showed an odds ratio (OR): 0.87 for heterozygotes (rs3865444CA) and OR: 0.82 for protective allele homozygotes (rs3865444AA) [8]. The

overall frequency of the protective allele is 0.21, and varies widely across ethnicities ranging from 0.05 in Africans to 0.48 in Native Americans [9]. The majority of studies examining the role of the CD33 in genetic risk for AD have been performed in populations of European descent, which has a relatively high protective allele frequency of 0.31. In a meta-analysis of 22 case-controlled studies, the reduction in AD incidence was only found to be significant in Caucasians (OR: 0.92; 95% CI, 0.90–0.94, P=0.05) [10].

The A allele is a human-derived allele not found in other primates, and is hypothesized to have evolved for its ability to improve post-reproductive fitness by reducing the risk for late-onset AD (LOAD) [9]. Relative to other primates, such as chimpanzees, humans have higher expression of the full-length CD33M isoform, and the presence of the A allele restores the isoform balance to the levels seen in other primates [9]. Changes in cellular microenvironment associated with human aging, such as inflammation or altered patterns of glycosylation, may alter the function of CD33 in a way that becomes pathological. Reducing levels of the form of CD33 (CD33M) that interacts with these external signals could then potentially mitigate the onset of pathology.

Human research to suggest benefits to patients with dementia: None

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

Increased surface expression of CD33 is thought to increase risk of LOAD by **reducing the phagocytic capacity of microglia**. In cell culture, CD33 expression was found to be sufficient for inhibiting microglial uptake of Aβ42, and monocytes from individuals with the risk allele show reduced phagocytic capacity relative to those with the protective allele in *in vitro* assays [6; 11]. **A positive correlation has been found between CD33 surface expression levels and Aβ plaque burden** [6]. Individuals with the risk allele are also more likely to be PiB+ (amyloid+) on PET or have a higher neuritic plaque burden in postmortem tissue [7]. Additionally, the surface of Aβ plaques is coated with glycoproteins, including sialic acid, so binding of CD33 to these glycoproteins may help shield Aβ from immunosurveillance [1]. The importance of microglial phagocytic function to risk for AD is supported by the association of TREM2 variants with AD [12]. TREM2 is important for promoting microglial phagocytosis, thus the **proper balance of CD33 and TREM2 is critical for regulating phagocytosis**. A protein quantitative trait analysis found that CD33 expression influenced levels of TREM2 expression [13]. In an *in vitro* assay of microglial aging, the presence of Aβ stimulated the expression of TREM2, but Aβ internalization was limited when CD33 was elevated [14]. Furthermore, aged microglia which had the highest levels of CD33 failed to upregulate TREM2 at all, and had the lowest levels of Aβ clearance. This suggests that CD33 and TREM2 may influence risk through the same mechanism.

CD33 may also influence LOAD risk through other gene interactions or mechanisms. One study in individuals of European descent found that the CD33 risk allele was associated with smaller intracranial volume, but the effect size was no longer significant after correcting for multiple testing [15]. The protective allele was found to be associated with decreased expression of immediate early response 2 (IER2) in the temporal cortex [16]. Although the significance of this association is unclear, IER2 expression was found to be increased in the AD brain [16].

Due to the lack of the sialic acid binding domain, the short isoform (CD33m) is hypothesized to be inactive in terms of immune cell repression, however, it may have additional undiscovered functions. CD33 contains a peroxisome targeting sequence near its C-terminus and the **short isoform was found to localize to peroxisomes** in human blood-derived monocytes and microglial cell line [17]. LOAD is associated with increased oxidative stress and a decrease in peroxisomes. CD33rSiglecs have been implicated in protection against oxidative stress [2], however, it is unknown whether the short isoform of CD33 can stimulate peroxisome proliferation, or whether it has any other protective antioxidant functions.

APOE4 interactions:

ApoE and CD33 are both projected to affect glial functions, including phagocytic capacity. One study examining the Health and Retirement Study cohort of 7,451 Caucasians found that the presence of the CD33 risk allele was associated with increased risk for cognitive decline in ApoE4 carriers, based on a modified Telephone Interview for Cognitive Status (HRS TICS-m) measure of cognitive function [18]. The group with ApoE4 and the CD33 risk allele (rs3865444C) had more decline than those with ApoE4 without the CD33 risk allele, but this distinction was only apparent in the oldest participants (>80 years old). It is not clear whether the effect is driven by accelerated decline from the CD33 risk allele or a mitigation in decline from the protective allele.

Aging and related health concerns: CD33 is important for self-tolerance, so blocking CD33 can increase immunosurveillance against cancer cells, but may also increase systemic inflammation and promote autoimmunity.

Types of evidence:

- 2 meta-analyses (n=11 RCTs for gemtuzumab, and n=5 Phase 3 RCT for gemtuzumab)
- 2 laboratory studies

Cancer: CD33 inhibitors may have benefit

CD33 expressing myeloid-derived suppressor cells increase with age, which decreases the capacity for immunosurveillance and is thought to contribute to the increased risk for cancer with age [19]. Therefore**,** therapies that reduce levels of CD33 would be expected to reduce cancer risk. **High levels of CD33 are associated with certain types of cancer**, especially acute myeloid leukemia (AML). The currently available CD33 targeted therapies were developed for the treatment of AML [20]. Gemtuzumab ozogamicin is the only anti-CD33 therapy that is FDA-approved for AML. It has a cytotoxic agent conjugated to an anti-CD33 antibody in order to induce targeted killing of the CD33^{+} cancer cells and is typically used as an adjunct to induction chemotherapy [20]. Based on meta-analyses of RCTs, gemtuzumab was found to improve relapse-free survival relative to chemotherapy alone (Hazard ratio (HR): 0.90, 95 % confidence interval (CI) 0.84–0.98, p = 0.01), but the benefits were largely restricted to patients who had favorable cytogenetics [21; 22]. The response to therapy was not dependent on overall tumor cell CD33 expression, but on the level of the full-length (CD33M) isoform [23]. Tumors that contained the rs3865444 and rs11245941 SNPs which lead to the production of higher levels of the smaller exon 2 lacking (CD33m) variant were more resistant to anti-CD33 treatment [8]. The antibody targets the sialic acid binding V-set domain located in exon 2, thus the exon 2 lacking isoform will not be recognized/targeted by the antibody.

Inflammation/Autoimmunity: CD33 inhibitors may cause harm

Since CD33 is important for inhibiting immune responses and mediating self-tolerance, systemic CD33 inhibition could potentially induce inflammatory autoimmune diseases. Patients with Type 2 diabetes were found to have decreased monocyte CD33 expression, and higher circulating levels of inflammatory cytokines (TNFα, IL-8, IL-12p70). The decrease in CD33 may stem from increased exposure to oxidative stress stemming from chronically high glucose levels [24]. Culturing monocytes from healthy controls under high glucose conditions led to the generation of reactive oxygen species (ROS), which induced expression of SOCS3, a negative regulator of CD33 [24]. The CD33rSiglecs are hypothesized to influence susceptibility to oxidative stress damage. One study found a positive correlation between a species' number of CD33rSiglec genes and its lifespan [2]. Mice lacking their most highly expressed CD33rSiglec (Siglec-E) showed increased sensitivity to oxidative stress, accelerated aging, and reduced lifespan. It is not known how or whether CD33 specifically contributes to this process.

Safety: The only approved anti-CD33 therapy, the drug-antibody conjugate gemtuzumab, is associated with liver toxicity. Unconjugated anti-CD33 antibodies have shown good safety in cancer patients, but the side effect profile in other populations has not been determined.

Types of evidence:

- 2 meta-analyses (gemtuzumab +chemotherapy in AML)
- 6 RCT (Phase 3 fractionated dose gemtuzumab +chemotherapy n=280; Phase 1 high dose lintuzumab n=35; Phase 2b (n=211) and Phase 3 (n=191) lintuzumab + chemotherapy; Phase 1 vadastuximab + chemotherapy n=131; Phase 1b BI836858 + chemotherapy n=31)
- Several laboratory studies

CD33 targeted therapies

As of this point, **no CD33 targeted therapies have been tested in AD patients** or in animal models of AD. Due to the species specificity of CD33, preclinical testing would need to be done in animal models containing humanized versions of CD33. Since the functions of CD33 have not been fully elucidated, therapies that lead to full inhibition or severe downregulation of its expression could potentially have unforeseen negative effects. Instead, a partial reduction of the full-length isoform in individuals with a genetic predisposition toward higher full-length CD33 surface expression may allow for the best benefit to side effect ratio. However, individuals with the CD33 risk allele have elevated CD33 surface expression throughout life [7], which may contribute to the buildup of amyloid over time. It is not clear how early a CD33 targeted intervention would need to be administered in order to achieve clinical benefit, but it is likely to be prior to the onset of pathology.

Anti-CD33 antibodies:

The currently available **therapeutic antibodies against CD33 are targeted against the V-set domain in exon 2, thus they exclusively target the full length-form** (CD33M) [20]. This is an attractive target because the AD protective allele is associated with a decrease in the expression of the full-length form and an associated increase of the short-form (CD33m). Since there is no evidence that the short-form exerts any detrimental functions, and it is possible that the short-form exerts some type of beneficial function [17], it is most prudent to selectively target the full-length form whose increased surface expression is associated with increased risk for AD. However, these antibodies **have low BBB penetrance** of ~0.1%, and thus are not ideal for targeting CD33 on microglia in the CNS [1]. Since CD33 is primarily expressed on circulating monocytes, systemically administered anti-CD33 antibodies are **likely**

to be subject to a peripheral sink effect. These antibodies would be best for targeting the peripheral monocyte-derived macrophages recruited into the CNS, as these cells are important phagocytes that contribute to repair. Stimulating the phagocytic capacity of these cells, then, could enhance Aβ clearance provided that they were recruited into the CNS in sufficient numbers. On the other hand, they may also promote inflammation.

Conjugated antibodies

This type of therapy involves the combination of an **anti-CD33 antibody with a cytotoxic agent**, which allows for targeted killing of CD33$^+$ cancer cells. While this approach is necessary for eliminating cancer cells, it **may lead to excessive toxicity** in individuals without CD33$^+$ cancer. The safety of these antibodies has only been tested in populations with CD33$^+$ blood cancers, therefore the side effect profile in other patient populations is unknown, but would be expected to exert higher systemic toxicity. In the context of AD, the goal is the downregulation of microglial CD33, not the destruction of the CD33$^+$ cells, thus these antibodies are not well-suited to repurposing for AD.

Gemtuzumab ozogamicin, marketed under the brand name Mylotarg®, is the only FDA-approved anti-CD33 therapy. It is comprised of a humanized IgG4 anti-CD33 antibody conjugated to N-acetyl-γ calicheamicin 1,2-dimethyl hydrazine dichloride [20]. It is internalized upon antigen binding, which leads to the release of the cytotoxic agent calicheamicin. It was approved in 2000 for use as a monotherapy in older AML patients (>age 60), who are not good candidates for standard chemotherapy due to heightened risk for treatment-induced toxicity, since the benefit to side effect ratio was not found to be affected by age [23]. However, it is more commonly used as an adjunct to induction chemotherapy, and a meta-analysis of RCTs indicates that gemtuzumab use increases the rate of treatment-induced mortality [21]. Gemtuzumab is associated with **myelosuppression**, persistent thrombocytopenia, and prolonged neutropenia [23; 25]. Gemtuzumab was voluntarily withdrawn from the market in 2010 due to **increased risk for serious liver injury**, including sinusoidal obstruction syndrome (Press release). RCTs indicated that 20-30% of patients experienced increases in liver enzymes (bilirubin or transaminases) [22; 23]. It was approved and re-introduced to the market in 2017 for patients with CD33$^+$ AML over age 2 with a black box warning for hepatotoxicity (FDA Press Release).

Vadastuximab talirine (SGN-CD33A) was being developed by Seattle Genetics. It is a humanized monoclonal anti-CD33 antibody linked to pyrrolobenzodiazepine dimers [20]. In a Phase 1 trial, vadastuximab was associated with dose dependent myelosuppression and thrombocytopenia [26]. In 2016, the FDA placed a hold on other early-stage clinical trials for vadstuximab over **concerns for excessive liver toxicity** (Press release). Hepatoxicity, including sinusoidal obstruction syndrome, was

observed in 6 patients, leading to 4 deaths [27]. After the suspension, the company discontinued a Phase 3 trial based on safety concerns due to **increased mortality**, including fatal infections (Press release).

Unconjugated antibodies

These therapies showed promise in preclinical trials, but have thus far failed to show significant clinical benefits in patients with myeloproliferative cancers due to low cytotoxicity *in vivo* [20]. Unlike the drug-antibody conjugates, the unconjugated anti-CD33 antibodies are not associated with increased risk for hepatotoxicity. However, since they have not been tested in patients without CD33$^+$ blood cancers, the **potential for adverse events in other patient populations has not been established**, and could be much higher.

Lintuzumab (HuM195) is a humanized monoclonal IgG1 anti-CD33 antibody that showed good antibody dependent mediated cell toxicity *in vitro*, but not *in vivo* [20]. It failed to improve remission or survival rates when used in combination with chemotherapy in a Phase 3 RCT at a dose of 12 mg/m^2 (IV) [28]. Lintuzumab showed a good safety profile, with transient infusion related reactions (chills, fever, hypotension) as the primary adverse events. Higher doses were tested (up to 8 mg/kg IV) in a Phase 1 trial and showed a similar safety profile, with no evidence of cytokine release syndrome or grade 4 toxicities [29]. At the highest dose a few patients showed grade 3 toxicities of rectal hemorrhage or febrile neutropenia. Lintuzumab also failed to improve survival in a subsequent Phase 2b trial using a 600 mg dose (IV) in combination with chemotherapy [30]. Notably, the higher dose did not increase the incidence of non-infusion related reaction adverse events, which is consistent with lintuzumab having good safety but poor efficacy for AML.

The feasibility of lintuzumab for AD was tested in cell culture. Doses of lintuzumab (10 ng/ml) in range of the projected concentrations in the CNS previously tested in clinical trials, based on BBB penetrance of 0.1% [1], were found to be sufficient to decrease expression of CD33 by 80% on PMA-treated U937 cells [8]. However, it is unclear whether the CD33 expressing microglia in the brain would show the same level of sensitivity as inflammation (PMA) induced CD33 on cancer derived myeloid cells. Due to a peripheral sink effect, it is also not clear how much of the antibody would actually reach the CNS. Furthermore, the trials conducted thus far may have underestimated the potential for systemic side effects, since antibody binding would primarily occur on CD33$^+$ cancer cells, rather than on healthy tissue resident CD33$^+$ myeloid cells.

BI836858 (mAb33.1) is a fully human monoclonal IgG1 anti-CD33 antibody developed by Boehringer Ingelheim. It has received orphan designations from the FDA for AML and myelodysplastic syndromes (Press release). It has been **glycoengineered to have increased antibody dependent cell mediated toxicity** based on *in vitro* studies [31]. BI836858 is currently being tested in a dose escalation Phase 1b/2 clinical trial for previously untreated patients >60 years old with AML (n=31) in combination with the chemotherapeutic azacytidine (NCT02240706). Of the 25 patients assessed for dose limiting toxicities thus far, one had grade 4 neutropenia, and one had grade 3 portal hypertension [32]. Other common grade 3/4 toxicities were largely known to be associated with azacytidine, including anemia, low platelet count, and low white blood cell count. While the increased antibody dependent cytotoxicity may increase efficacy for AML, it makes BI836858 a less attractive therapeutic agent for AD.

Small Molecules

Various high throughput screens have been developed to identify CD33 targeted small molecules. CD33 is a challenging drug target because the sialic acid binding domain does not have clear binding pockets and is **highly polar**, which is unfavorable for BBB penetrance [1]. Recent developments in determining the crystal structure are expected to facilitate the drug discovery process (MMDB). Systemically administered small molecules that block CD33 also carry the risk of inducing inflammation and/or autoimmunity.

In the context of cancer, CD33 binding nanoparticles have been developed using medicinal chemistry efforts. These nanoparticles contain a disubstituted sialic acid ligand that has ~350-fold increased affinity for CD33 over the natural sialic acid ligand, and could potentially be used for targeted drug delivery to CD33 expressing cells [33].

An *in vitro* assay using human monocyte derived microglia-like cells which recapitulates certain microglial phenotypes and functions, such as phagocytosis, has been developed to identify CD33 targeting drugs [11; 34]. Using this assay, they tested a panel of 1200 FDA-approved compounds and found 2 (LDNX49 and LDN755) that reduced CD33 expression on monocytes from people with the AD risk allele and increased Aβ clearance *in vitro*. Following an expanded screen of 9000 compounds, they identified 3 small molecules for further study (LDN- 0022404, LDN-X0022446, and LDN-X0022461) (Slides).

Sources and dosing:

Gemtuzumab ozogamicin is marketed by Pfizer under the brand name Mylotarg®, is available by prescription as part of chemotherapy treatment for CD33+ AML, and is administered intravenously.

Vadastuximab talirine and lintuzumab were developed by Seattle Genetics Inc, but neither are currently in clinical use due to discontinuation of development. A radioimmunoconjugate form of lintuzumab, [255]Ac-lintuzumab, continues to be tested in clinical trials for leukemia. BI836858 is currently being tested by Boehringer Ingelheim in a clinical trial for AML. The CD33 small molecules are still in medicinal chemistry and preclinical testing phases.

Research underway:

Based on [Clinicaltrials.gov](), the majority of anti-CD33 therapies in development are focused on improving the cytotoxicity toward CD33⁺ cancer cells and involve CAR-T therapy, bispecific or trispecific antibodies. Gemtuzumab ozogamicin is being tested in combination with a variety of other therapies for AML and myelodysplastic syndrome. [255]Ac-lintuzumab is being tested in 4 clinical trials for AML or multiple myeloma. There are 4 active trials testing BI836858 in AML or myelodysplastic syndrome.

A novel anti-CD33 monoclonal antibody, AL003, being developed by Alector Inc. will be tested for safety and tolerability in healthy adults, and in participants with mild to moderate AD in a Phase 1 clinical trial that is expected to be completed in mid-2020 ([NCT03822208]()). Preclinical evidence is sparse, but suggests that it may have higher BBB penetrance than other previously tested anti-CD33 therapies.

[PHAGO]() was created as a research project to foster the development of immunomodulatory therapies for AD by the Innovative Medicines Initiative in collaboration with various industry partners led by Janssen Pharmaceutica NV. It includes 8 pharmaceutical companies, 3 small/medium size enterprises, and 8 universities. Their goal is to increase understanding of the biology of TREM2 and CD33 and foster cross-talk between academia and industry in order to speed up the development of assays and identification of compounds/tools to effectively target TREM2 and CD33 related functions. The project is funded for 5 years until October 2021. To date the majority of the published research stemming from this project has been focused on TREM2.

CD33 as an imaging biomarker:

Preclinical proof-of-principle studies have been conducted to determine the feasibility of **developing anti-CD33 antibodies for immuno-PET**. A Cu-64 radiolabeled murine anti-human CD33 antibody (p67.6) conjugated to DOTA was used in PET-CT imaging to detect CD33⁺ cells in AML tumor cell bearing mice [35]. A newly generated humanized antibody was also able to detect CD33⁺ cells in AML cell lines and a patient sample. The goal of this type of imaging is to allow for more targeted radiation therapy and to monitor treatment responses in AML. It is not clear whether this type of PET ligand would be useful for measuring levels of CD33 on non-cancerous cells. Since it is antibody based, its low BBB penetrance may

limit its utility as a reliable readout of CD33$^+$ microglia. Additionally, since CD33 is typically involved in immune suppression in the periphery, it is not clear whether increased levels of CD33 in the CNS would reflect increased or decreased levels of neuroinflammation.

Search terms:

Pubmed, Google: CD33 or anti-CD33 or Gemtuzumab ozogamicin or Vadastuximab talirine or Lintuzumab or BI836858 +

Alzheimer's disease, dementia, aging, lifespan, cancer, inflammation, clinical trials, safety, biomarker

Websites visited for CD33 therapies:

- Clinicaltrials.gov
- Treato.com (Mylotarg)
- Drugs.com (Gemutzumab ozogamicin)
- WebMD.com (Mylotarg)
- DrugBank.ca (Gemtuzmuab), (Vadastuximab)

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