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.

Pexidartinib (PLX3397)

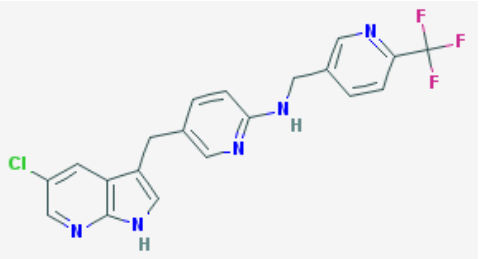
Evidence Summary

Potentially beneficial adjunct to cancer therapy. May either exacerbate or ameliorate brain injury by depleting microglia depending on the inflammatory microenvironment.

Neuroprotective Benefit: Has potential to both exacerbate acute neural injury and prevent neuronal damage associated with chronic microglia-associated inflammation. Effects are context dependent.

Aging and related health concerns: May be useful as an adjunct to potentiate antitumor responses to immunotherapy in some cancers, but has minimal benefits as a monotherapy.

Safety: Side effects of long-term microglial depletion in humans have not been established. Has potential to cause liver toxicity at high doses.

Availability: In clinical trials	**Dose:** 1000mg/day orally in cancer patients	**Chemical formula:** $C_{20}H_{15}ClF_3N_5$ **MW:** 417.82 g/mol  Source: Pubchem
Half-life: ~20 hours	**BBB:** Penetrant	
Clinical trials: Cancer: RCTs: Phase 1 (n=41), 2 (n=23), 3 (n=120) for Tenosynovial giant cell tumor, Phase 2 for glioblastoma (n=61), Phase 1b for solid tumors (n=52)	**Observational studies:** None	

What is it? Pexidartinib (PLX3397) is an orally available, CNS permeable, selective tyrosine kinase inhibitor that preferentially targets the macrophage colony stimulating factor-1 receptor (CSF-1R), but also inhibits closely related family members c-Kit and FLT3 [1]. CSF-1R is primarily expressed on monocytes and signaling through this receptor regulates the proliferation, survival, and function of a subset of myeloid cells including macrophages, microglia, osteoclasts, and mast cells. Depending on the dosage, pexidartinib can either deplete macrophages/microglia or modify their function and possibly their polarization. Pexidartinib was developed by Plexxikon Inc., and has primarily been tested for use in various types of cancer. It has shown benefits for treating Tenosynovial giant cell tumors, but has been largely unsuccessful as a monotherapy for other types of cancer, and is now being tested as an adjunct therapy.

Neuroprotective Benefit: Has potential to both exacerbate acute neural injury and prevent neuronal damage associated with chronic microglia-associated inflammation. Effects are context dependent.

Types of evidence:

- Several laboratory studies

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

Chronically reduced CSF-1R signaling, due to CSF-1R haploinsufficiency leads to a form of dementia called adult-onset leukoencephalopathy with axonal spheroids and pigmented glia (ALSP) which

involves aberrant microglial distribution and white matter degeneration [2; 3]. Since CSF-1R signaling is important during brain development [4], it is unclear whether the pathology is related to a neurodevelopmental defect or impaired CSF-1R signaling during adulthood. Preclinical studies support a role for microglia in myelin maintenance and the homeostasis of oligodendrocyte progenitors in adulthood [5], suggesting that chronic microglial depletion could accelerate white matter damage or inhibit repair.

Human research to suggest benefits to patients with dementia: None

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

Neurogenerative disease: Potential mixed benefit/harm (context dependent)

Due to the pleiotropic functions of both microglia and CSF-1R signaling, the inhibition of CSF-1R or depletion of microglia could either be beneficial by reducing neuroinflammation and protecting synapses, or could accelerate neural damage through the loss of neurotrophic support and induction of reactive astrogliosis [1] . **Effects are highly dependent on the brain microenvironment**, which vary based on the mechanism of neuropathology and the stage of the disease.

Alzheimer's disease: Potential mixed benefit (chronic phase, rodents)

The expression of CSF-1 and CSF-1R has been found to be increased in the brain tissue of people with Alzheimer's disease (AD) [6], which is hypothesized to contribute to the augmented and aberrant chronic inflammatory microglial activation typically seen in this patient population. Additionally, there is evidence that CSF-1R dynamics may change over the course of the disease, as AD patients were found to have significantly higher levels of CSF-1 in their cerebrospinal fluid (CSF) than those with mild cognitive impairment (MCI) (441.5 ± 188.6 vs 319.9 ± 71.6 pg/ml; p=0.003) [7]. The differences highlight the ***changing roles for microglia over the course of disease, and how the timing and nature of any microglial-targeted intervention is likely to be a critical aspect to its potential efficacy.*** Furthermore, genetic studies have found no genetic association between various CSF-1 SNPs and AD incidence [8], suggesting that the dysregulation of CSF-1R signaling may be a downstream effect, rather than a primary cause of neuropathology.

Cognitive enhancing benefits have been demonstrated for both recombinant CSF-1 and CSF-1R inhibitors in various rodent AD models [1]. While primarily expressed on microglia, CSF-1R has been shown to be expressed on a small subset (1-2%) of neurons in the hippocampus and cortex. Expression levels increase in response to neuronal injury. CSF-1R ligands (CSF-1 and IL-34) can enhance neuronal

survival through the activation of neuronal CSF-1R. Therefore, augmenting neuronal CSF-1R signaling could be neuroprotective. Meanwhile, activation of CSF-1R on microglia could contribute to pathological chronic neuroinflammation, thus CSF-1R inhibition has also been shown to be neuroprotective by protecting against inflammation-associated neuronal loss. While microglia do exhibit some neuroprotective functions, the microglia in AD patients appear to be dysfunctional, thus it is hypothesized that depleting them may be beneficial [9]. In the 5XFAD (amyloid pathology), 3xTg, and Tg4510 (tau overexpressing) models, microglial depletion (80-90%) or reduction (30%) with PLX3397 starting before or after the onset of pathology, offered minor cognitive benefits on some memory tasks, and reduced microglial association with plaques, but generally had no effect on Aor tau pathology [10; 11; 12; 13]. However, microglial depletion with PLX3397 reduced the transmission of tau in an AAV-mediated rapid tau propagation model [14]. In this model, tau transmission between neurons in different regions of the hippocampus was mediated through microglia derived exosomes.

Parkinson's disease: Potential harm (acute phase, rodents)

Pretreatment with PLX3397 (40mg/kg daily by oral gavage for 21 days) depleted microglia in mice by approximately 90%. The microglia depletion prior to MPTP induced dopaminergic cell damage **exacerbated MPTP mediated toxicity** [15]. It worsened motor deficits, and enhanced inflammation by promoting the infiltration of leukocytes ($CD4^+$ and $CD8^+$ T cells) and augmenting local inflammatory responses by astrocytes. This work supports the finding of other studies that microglial depletion is detrimental during acute neural injury, but does not indicate whether it may be beneficial in a chronic phase, as has been demonstrated with other neurodegenerative disease models.

Amyotrophic lateral sclerosis: Potential harm/mixed (etiology dependent, rodents)

Patients with sporadic ALS have less spinal microglia than those with the familial SOD1 driven disease, which may explain the disparate effects of CSF-1R inhibitors in different models of the disease. In the classic SOD^{G93A} familial mouse model, use of the selective CSF-1R inhibitor, GW2580, reduced microglial proliferation, attenuated motor neuron death, and extended survival [16]. In contrast, in a mouse model of sporadic ALS (rNLS8) involving prominent hTDP-43 mediated pathology, microglial activity was necessary for the clearance of neuronal TDP-43, and microglial depletion with PLX3397 (1000 mg/kg) resulted in worse motor function [17]. The discrepancy may also be related to the differential effects of the two CSF-1R inhibitors in terms of timing and potency. GW2580 primarily affected proliferation, only leading to a 30% reduction in microglial number, which was restricted to the chronic phase, whereas PLX3397 produced a substantial depletion of microglia starting in the acute phase.

Stroke: Potential mixed benefit/harm (context dependent, rodents)

Modulation of microglial numbers and/or function has been shown to **either ameliorate or exacerbate neural injury** in various stroke models. In stroke patients, there is an increase in the level of pro-inflammatory (IL-1β+) microglia in the brain 24 hours after intracerebral hemorrhage. In a mouse model of intracerebral hemorrhage, pre-treatment with PLX3397 (40 mg/kg by oral gavage for 21 days) reduced microglia by 90%, reduced neuroinflammation, prevented brain edema, and attenuated neurological deficits [18]. However, the same pretreatment regimen augmented the production of inflammatory mediators, leukocyte infiltration, stroke severity, and worsened neurological deficits in an ischemic stroke model, middle cerebral artery occlusion (MCAO) [19]. These studies suggest that the effects of microglial modulation therapy could greatly vary from patient to patient, but it is unclear whether these studies are even relevant to humans, who likely would not receive treatment until after stroke onset.

Radiation protection: Potential benefit (rodents)

Microglial activation has been implicated in the induction of cognitive function-related side effects of cancer treatments, such as radiation therapy. Mice treated with PLX3397 (1.2 mg per day) while undergoing whole brain irradiation (IRR 3.3 Gy) were spared from radiation induced monocyte accumulation, declines in synaptic spine density, and cognitive deficits [20]. In a hippocampal-dependent novel object recognition task, PLX3397 treated mice performed similarly to non-radiated sham controls (sham = 30.34 ± 5.67 %; PLX IRR = 27.37 ± 4.50 %; $p > 0.05$; control IRR = 1.145 ± 4.24 %; $p < 0.05$). Since PLX3397 treatment has also been shown to potentiate the antitumor response to radiation therapy in preclinical models [21], it may be useful in boosting the benefit-to-side effect profile in cancer treatment.

APOE4 interactions: Unknown

Aging and related health concerns: May be useful as an adjunct to potentiate antitumor responses to immunotherapy in some cancers, but has minimal benefits as a monotherapy.

Types of evidence:

- 4 RCTs (Cancer: Phase 1/2, 3 for TGCT, Phase 2 for glioblastoma, Phase 1b for solid tumors)
- 1 case report (TGCT)
- Numerous laboratory studies

Cancer: Potential benefit

Immunosuppressive (M2-like) tumor associated macrophages are linked with poor outcome in various cancers. They can modulate the tumor microenvironment in a manner that limits the ability of the immune system to remove the cancerous tissue. Cancer patients with the CSF-1R c.1085A>G SNP have less M2-like tumor associated macrophages and better disease-free survival [22]. The production of CSF-1 by tumor cells promotes the infiltration and proliferation of these immunosuppressive macrophages, therefore CSF-1R inhibitors, such as pexidartinib, have been proposed as a method of preventing/relieving this immunosuppression. Since tumor-mediated immunosuppression involves multiple mechanisms, targeting the macrophages alone is insufficient. Pexidartinib is most beneficial when used in combination with other immunosuppressive targets such as checkpoint inhibitors, which remove co-inhibitory molecules (i.e. PD-1) on anti-tumor T cells.

Monotherapy

Tenosynovial giant cell tumor: Benefit

Tenosynovial giant cell tumor (TGCT) is a type of cancer of the joints (synovium) in which mass formation is driven by the recruitment of macrophages to the joint [23]. It can be localized or diffuse, and occurs around the knee in approximately 75% of cases. The diffuse form is also called Pigmented Villonodular Synovitis (PVNS). In many cases surgical resection would worsen joint function. Pexidartinib (oral 1000 mg daily) was demonstrated to have **clinically beneficial effects in Phase 1, 2, and 3 trials for TGCT**. In a Phase 1/2 trial (NCT01004861) 23% of patients had disease stabilization and one patient had a partial response in the dose-escalation study (n=41), while 52% had a partial response and 31% had disease stabilization in the Phase 2 extension study (n=23) [24]. In the recent 24-week Phase 3 ENLIVEN trial (n=120), pexidartinib (1000 mg/day for 2 weeks followed by 800 mg/day for 22 weeks) significantly reduced tumor size with a 39% overall tumor response rate versus placebo ($P<0.0001$), and no further progression after a 6-month median follow-up.

Pexidartinib has been granted Breakthrough Therapy designation for TGCT or PVNS where surgical resection may worsen outcome. Based on these positive results, Daiichi Sankyo (Plexxikon parent company) is planning to submit a New Drug Application to the FDA for TGCT (Press release).

Glioblastoma: No benefit

Although pexidartinib (oral 1000 mg daily) could successfully cross the blood-tumor barrier, it showed no efficacy in the treatment of patients with recurrent glioblastoma (n=61, average age 58.5 years) [25].

Only 8.8% (90% CI, 3.5%–21.6%) of patients reached the primary endpoint of 6-months progression-free survival in the multicenter Phase 2 RCT. In patients with surgical resection, 58% (7/12) were found to have a decrease in the number of tumor localized Iba1+ microglia, but across all patients there was no overall difference in tumor microglia in the treated population. While it is unclear whether the lack of efficacy was related to the incomplete microglial depletion, preclinical studies suggest that PLX3397 is only likely to offer clinical benefits when used in combination with immunotherapy and checkpoint inhibitors (i.e. anti-PD-1) [26; 27].

Adjunct therapy

Combination with Chemotherapy: Potential benefit

In a Phase 1b open label trial, patients with advanced solid tumors (n=52, age range 36-82) taking between 600-1600 mg of oral pexidartinib per day in conjunction with paclitaxel (i.v.), 14% of patients had a partial response and 36% had disease stabilization. The responders had breast, squamous cell, bladder, or ovarian cancer. A multicenter Phase 2 (I-SPY2) trial is being planned to follow-up on this dosing study.

In preclinical models, PLX3397 was able to augment the response to chemotherapeutic agents. In castration-resistant prostate cancer, the combination with PLX3397 reduced tumor growth significantly more than docetaxel alone (tumor volume 1130± 399 vs 2763 ± 537 mm^3, P<0.01)[28]. PLX3397 may also be beneficial in preventing relapse for malignant melanoma driven by BRAF mutations. The combination of PLX3397 with a BRAF inhibitor improved survival (88% survival rate for 250 days vs median survival of 70 days for control group), and antitumor efficacy through potentiation of tumor infiltrating lymphocytes ($CD8^+$ T cells)[29; 30]. Efficacy was further enhanced by the addition of a checkpoint inhibitor (anti-PD-1) [29].

Combination with Immunotherapy: Potential benefit (preclinical)

The modulation of tumor associated macrophages has been shown to potentiate the responses to immunotherapy in preclinical models by promoting the infiltration and activation of antitumor cytotoxic $CD8^+$ T cells. The greatest efficacy was found with triple combination therapy involving modulation of the macrophages with PLX3397, removal of inhibitory signaling through anti-PD-1, and direct immune cell modification using oncolytic viruses, dendritic cell vaccination, or adoptive T-cell transfer [26; 31; 32; 33; 34].

Regeneration/Healing: Potential harm (preclinical)

Monocyte (macrophage/microglial) mediated processes have been shown to be important for the proliferation of precursor cells associated with regenerative processes [35; 36]. In a zebrafish model, phagocytic monocytes were found to be necessary for cardiac cell proliferation and heart regeneration following injury [36]. Therefore, chronic microglial depletion may impair healing processes following acute tissue damage.

Safety: Side effects of long-term microglial depletion in humans have not been established. Has potential to cause liver toxicity at high doses.

Types of evidence:

- 4 clinical trials
- 1 case report (TGCT)
- Numerous laboratory studies

The short-term safety of pexidartinib has been tested in several RCTs involving cancer patients, primarily those with TGCT. In all trials the most common adverse events were fatigue (48%-65%), change in hair color, nausea, anemia, and decreased white blood cell counts [24; 37]. Fatigue was the most common reason for dose reduction. The most common serious adverse event was liver toxicity. In the Phase 3 ENLIVEN trial for TGCT, eight patients discontinued pexidartinib due to hepatic adverse events, of whom four had serious nonfatal events involving increased bilirubin. Two of the cases involved severe nonfatal liver toxicity that led to the temporary suspension of the trial. While adverse effects have not been reported in adult animals treated with PLX3397 for several months, it is unknown how chronic CSF-1R inhibition and microglial depletion would impact human health.

Sources and dosing:

Pexidartinib (PLX3397) is manufactured by Plexxikon Inc., which was acquired by Daiichi Sankyo in 2011. It is currently available for human use in clinical trials, and can be obtained by Plexxikon for research use. It has been granted Breakthrough Therapy and Orphan Drug designation by the FDA and Orphan drug status by the European Commission for TGCT/PVNS, and Daiichi Sankyo is planning to submit a New Drug Application to the FDA. In cancer trials, 1000 mg per day, in the form of 200 mg oral capsules was determined to be the tolerated effective dose [24]. The therapeutic dose for AD or other indications has not been established.

Research underway:

According to Clinicaltrials.gov, there are currently 10 active or recruiting clinical trials in various types of cancer. Pexidartinib is being tested as a monotherapy in KIT-mutated melanoma, TGCT, and solid tumors in adults, and refractory leukemia and neurofibromas in pediatric patients. It is also being tested as a combination therapy with chemotherapy for metastatic breast cancer (with Eribulin), advanced solid tumors (with Sunitinib), and unresectable sarcoma (with rapamycin). It is also being tested in combination with radiation and chemotherapy (temozolomide) for glioblastoma, and with a PD-1 inhibitor for pancreatic and colorectal cancer.

A Phase 2a trial has been registered in Denmark by Plexxikon to test the safety, tolerability, and pharmacokinetics of pexidartinib in patients with mild to moderate Alzheimer's disease. The primary goal of the trial is to determine a therapeutic dose; however, the trial was temporarily halted in 2016 for unknown reasons.

Search terms:

Pubmed, Google: Pexidartinib or PLX3397 +

Alzheimer's disease, dementia, neuroprotection, aging, cancer, clinical trials, safety

Websites visited for Pexidartinib:

- Clinicaltrials.gov
- Clinicaltrialsregister.eu
- PubChem
- DrugBank.ca

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