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.

NNI-362

Evidence Summary

NNI-362 was discovered through cell culture screens for the ability to promote neurogenesis. In mouse models, NNI-362 restores cognitive function and increases the number of new neurons.

Neuroprotective Benefit: NNI-362 promoted neurogenesis and improved cognitive function in rodent models. It remains to be seen whether NNI-362 shows efficacy in Alzheimer's patient.

Aging and related health concerns: Although NNI-362 is under development for "age-related disorders", there is no evidence for any indications other than the preclinical studies in Alzheimer's and Parkinson's models.

Safety: NNI-362 has undergone IND-enabling safety studies and is undergoing a phase 1a clinical trial as of September 2021. No safety data have been published to date.

Availability: in clinical development	**Dose**: not established. A phase 1a dose-escalation study in healthy aged volunteers is testing NNI-362 doses of 10 mg, 20 mg, 60 mg, and 120 mg (NCT04074837).	**Chemical formula:** not published **MW**: not published
Company: NeuroNascent, Inc.		
Half life: not documented	**BBB**: penetrant based on studies in rodents	
Clinical trials: A phase 1a dose-escalation study of NNI-362 is ongoing in 56 healthy aged volunteers (NCT04074837).	**Observational studies**: None	

What is it? NNI-362 is under development by NeuroNascent Inc., a privately-held company developing therapeutics aimed at neuronal regeneration. NNI-362 is a lead candidate identified through a phenotypic screen for its ability to promote proliferation of human neuronal progenitor cells and to promote differentiation into mature neurons in a dose dependent manner. NNI-362 exerts these actions through stimulation of p70S6 kinase phosphorylation, which in turn, promotes proliferation and differentiation of neural progenitor cells to neurons (Sumien et al., 2021). NeuroNascent has now completed all IND-enabling safety studies, submitted IND application, and received clearance from the FDA; in August 2019, NeuroNascent initiated a phase 1a study of NNI-362 in healthy older volunteers (NCT04074837). NNI-362 is being developed for mild to moderate Alzheimer's disease, early Parkinson's disease, and other age-related disorders (NeuroNascent Inc., pipeline).

Neuroprotective Benefit: NNI-362 promoted neurogenesis and improved cognitive function in rodent models. It remains to be seen whether NNI-362 shows efficacy in Alzheimer's patients.

Types of evidence:

- 0 clinical trials
- Several laboratory studies, though none published in peer-reviewed journals

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:
NNI-362 was identified through a phenotypic screen of small-molecule synthetic libraries that possessed properties conducive to blood brain barrier penetrance and oral administration (NeuroNascent Inc.). These molecules were screened by NeuroNascent for their ability to promote proliferation of human neuronal progenitor cells and to promote differentiation into mature neurons in a dose-dependent manner. These molecules were further optimized with changes to the chemical structure to improve potency in cell culture. These molecules then underwent a secondary screen in cell culture to evaluate whether the molecules were neuroprotective in addition to having neurogenic properties. NNI-362 emerged as the lead candidate. In the *in vitro* screening, NNI-362 at a concentration of 1000 nM promoted neural progenitor cell proliferation on days in vitro (DIV) 3 and increased the ratio of mature neurons to total cells at DIV12/13 (Sumien et al., 2021).

In old mice treated with NNI-362 (1, 3, or 10 mg/kg/day, orally) for 4 weeks, performance on the novel object recognition test was comparable to that of young control mice (Sumien et al., 2021). Old mice had lower numbers of new neurons (BrdU+ cells), while the old mice treated with 10 mg/kg/day NNI-362 had higher numbers of BrdU+ cells than the old vehicle-treated mice. The number of new neurons in the NNI-362-treated mice were not significantly different from the young control mice.

Old mice treated with NNI-362 at 10 mg/kg/day for 4 weeks also showed an improvement in memory function while this treatment did not reverse age-related motor dysfunction (Sumien et al., 2021). Similarly, in a mouse model of Down Syndrome (Ts65Dn mice), NNI-362 treatment (3 mg/kg/day) reversed the impairment in recognition memory and restored the number of BrdU+ cells surviving in the hippocampal dentate gyrus.

A pilot study also showed that in a model of chronic progressive Parkinson's disease, administration of NNI-362 for a very short duration showed a trend toward regeneration of neuron connections in the caudate putamen while increasing the number of new neuronal progenitors (NeuroNascent Inc., Parkinson's disease).

NNI-362 promotes phosphorylation of the p70S6 kinase, which in turn, promotes proliferation and differentiation of neural progenitor cells to neurons (Sumien et al., 2021). Out of a panel of 151 kinases, NNI-362 exclusively stimulated the p70S6 kinase and allosterically targeted the p70S6 kinase. NNI-362 phosphorylated p70S6 at the neuron regenerative concentration (≥ 1000 nM) and only during the early dividing and beginning differentiation phase (e.g., DIV6), while having no effect in fully differentiated neurons on DIV12. NNI-362 acts at Ser411, the auto-inhibitory pseudosubstrate site, where CDK5 phosphorylates p70S6 kinase during the mitogenic translational stage.

In postmortem studies of Alzheimer's disease patients, neurogenesis has been shown to be reduced in the hippocampal dentate gyrus (Moreno-Jimenez et al., 2019). However, there is continued presence of neural progenitor cells in older people, suggesting that these cells are potential targets for neuroprotection and neuronal regeneration.

Although preclinical studies have so far shown that NNI-362 stimulates neurogenesis, proliferation, survival, and migration of new neurons, future studies are needed to demonstrate that NNI-362 promotes integration of newly formed neurons and synapses with the neurocircuit (Sumien et al., 2021).

APOE4 interactions: Unknown.

Aging and related health concerns: ***Rated N/A for potential and N/A for evidence.*** Although NNI-362 is under development for "age-related disorders", there is no evidence for any indications other than the preclinical studies in Alzheimer's and Parkinson's models.

Types of evidence:

- 0 clinical trials
- 0 laboratory studies

Given that NNI-362 was identified through a phenotypic screen for its ability to promote proliferation of human neuronal progenitor cells, NNI-362 is not likely to have benefits for age-related health conditions outside of the brain.

Safety: ***Rated B for potential and D for evidence.*** NNI-362 has undergone IND-enabling safety studies and is undergoing a phase 1a clinical trial as of September 2021. No safety data have been published to date.

Types of evidence:

- 0 clinical trials, 1 phase 1a study ongoing
- Several laboratory studies, though none published in peer-reviewed journals

NNI-362 has undergone IND-enabling safety studies, IND application, and received clearance from the FDA. As of September 2021, NNI-362 is undergoing a phase 1a study in 56 healthy older volunteers (NCT04074837). Safety, tolerability, and pharmacokinetics of single and multiple doses of NNI-362 are being investigated. Results of this clinical trial have not been published as of 9/7/2021.

In studies with mice, NNI-362 treatment was suggested to not show toxic or off-target effects after up to 6 weeks of administration; however, details of toxicology and safety data were not presented in the manuscript (Sumien et al., 2021).

Drug interactions: Drug interactions have not been documented.

Sources and dosing: NNI-362 is under clinical development by NeuroNascent Inc. for mild to moderate Alzheimer's disease, early Parkinson's disease, and other age-related disorders (Neuronascent Inc., pipeline). An ongoing phase 1a dose-escalation study in healthy aged volunteers is testing NNI-362 doses of 10 mg, 20 mg, 60 mg, and 120 mg (NCT04074837). In mouse models, NNI-362 has been tested at doses ranging between 1-10 mg/kg/day, orally, for up to 6 weeks (Sumien et al., 2021).

Research underway: Clinical development of NNI-362 for Alzheimer's disease is currently supported by an R01 grant from the National Institute on Aging (R01AG056561). A phase 1a dose-escalation study of NNI-362 is ongoing in healthy aged volunteers (NCT04074837). This randomized controlled study is enrolling 56 participants to test single and multiple doses, dose-escalation, and to evaluate the safety, tolerability, and pharmacokinetics of oral NNI-362 in healthy people (50-72 years old). The primary outcome measure is the number of treatment-related events. Secondary outcomes include maximum plasma concentration and area under the curve with single or multiple dosing. Doses that will be tested are 10 mg, 20 mg, 60 mg, and 120 mg in liquid suspension. This study is scheduled to be completed in December 2020. Results of this clinical trial have not been published as of 9/7/2021.

Intellectual property: NeuroNascent has submitted patent applications for the composition and use of families of structures that promote neurogenesis and neuronal regeneration for neurodegenerative diseases (NeuroNascent Inc.). In 2008, a national patent was filed on lead families for composition and use, including NNI-362. In 2011, USPTO has allowed claims for its patent, "Methods and Compositions for Stimulating Neurogenesis and Inhibiting Neuronal Degeneration", covering composition of NeuroNascent's lead therapeutics (e.g., NNI-362) and chemical family.

Search terms:
Pubmed, Google: NNI-362

Websites visited for NNI-362:

- Clinicaltrials.gov
- DrugAge (0)
- Geroprotectors (0)
- Drugs.com (0)
- WebMD.com (0)
- PubChem (0)
- DrugBank.ca (0)
- Cafepharma (0)
- Pharmapro.com (0)