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.

SPG-302

Evidence Summary

No studies on SPG-302 have been published; an older generation compound, SPG-101, increased dendritic spine density and improved cognitive functions in wild-type mice as well as AD and TBI mice.

Neuroprotective Benefit: A previous generation SPG compound has shown increased dendritic spine density and improved cognitive functions in wild-type mice as well as models of AD and TBI, though no studies using SPG-302 have been published yet.

Aging and related health concerns: This compound has not been investigated for age-related health conditions.

Safety: No safety data or studies specific to SPG-302 have been published.

Availability: in clinical development	**Dose**: unknown	**Chemical formula:** proprietary/undisclosed **MW**: undisclosed
Half life: unknown; a previous generation SPG compound, SPG-101, has a plasma half-life of 14 minutes	**BBB**: unknown; a previous generation SPG compound, SPG-101, is penetrant, but no data has been published for SPG-302	
Clinical trials: none	**Observational studies**: none	

What is it? Synaptic loss and dendritic spine retraction occur in mild cognitive impairment and appear to be early events in the disease process that precede neuronal loss in Alzheimer's (Scheff et al., 2006). SPG-302 is a third-generation tetraethylene glycol derivative of benzothiazole aniline that was developed by Spinogenix, Inc. The previous generation of these benzothiazole aniline derivatives (BTA/SPG10X) bound to Aβ and had potent spine-inducing activity in wild-type mouse neurons *in vitro* and *in vivo* (R43AG058278). SPG-302 targets fascin, which regulates the interior architecture of neurons to rebuild retracted dendritic spines.

Neuroprotective Benefit: A previous generation SPG compound has shown increased dendritic spine density and improved cognitive functions in wild-type mice as well as models of AD and TBI, though no studies using SPG-302 have been published yet.

Types of evidence:

- A few laboratory studies of previous generation SPG compounds

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

Human research to suggest benefits to patients with dementia: None available.

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

Wild-type mice: No studies have tested SPG-302 specifically, but one study tested an earlier generation compound. In wild-type mice, treatment with a benzothiazole aniline compound, SPG-101(formerly known as BTA-EG4; 30 mg/kg/day, i.p.), was blood-brain-barrier penetrant (10 mg/kg; brain-to-plasma ratio of 2.63;), decreased Aβ levels, altered cell surface expression of APP, and improved memory (Megill et al., 2013). The SPG-101-mediated memory improvement was not correlated with synaptic plasticity as measured by LTP, but with increased spinogenesis. The higher dendritic spine density reflected an increase in the number of functional synapses (as measured by increased mEPSC frequency). Also, SPG-101 increased spine density through APP, which interacts with RasGRF1 to regulate Ras signaling.

Although strong benefits are seen in wild-type mice, it remains unclear if having too many spines is beneficial, as autism and Fragile-X mental retardation are associated with an overabundance of spines.

AD mice: No studies have tested SPG-302 specifically, but one study tested an earlier generation compound. In a mouse model of Alzheimer's (3xTg mice), treatment with SPG-101 (formerly known as BTA-EG4; 30 mg/kg/day, i.p.) for 2 weeks increased dendritic spine density and cognitive function in an age-dependent manner (Song et al., 2014). In 6-10-month old 3xTg mice, SPG-101 treatment increased dendritic spine density in cortical layers II/III and in the hippocampus compared to vehicle. However, at 13-16 months of age, only cortical spine density was increased. The increase in spine density in this older group was under 20% and did not reach levels observed in the younger 6-10-month-old mice. A caveat to this study is that spine density and size were measured by Golgi staining, which is not ideal as the method lacks z-plane resolution (unable to visualize spines that lie underneath the dendritic shaft or discern spines that lie in close proximity to the dendritic shaft).

In the cortex and hippocampus of SPG-101-injected 3xTg AD mice, the increase in dendritic spine density correlated with increased Ras activity when the mice were 6-10 months old. However, in 13-16-month-old mice, there was only a trend toward an increase in Ras activity in the cortex.

In 6-10-month-old 3xTg AD mice, SPG-101 treatment resulted in improved learning and memory as measured by the Morris water maze; however, only minimal improvement was observed at 13-16 months of age (Song et al., 2014). The behavioral improvement corresponded to decreased levels of soluble Aβ40. Based on these findings, it is possible that SPG-101 or related compounds would only be neuroprotective early in Alzheimer's disease, before levels of Aβ become significantly elevated.

In contrast, in a more recent study in brain slice cultures from 3xTg mice, SPG-101 treatment did not alter APP processing, Aβ40 levels, Aβ42 levels, or the Aβ-42/Aβ-40 ratio (Croft CL et al., 2017). However, this study found that SPG-101 treatment decreased tau phosphorylation at 1 out of the 3 phosphorylation sites: decreased CP13 (p-Ser202), but not PHF-1 (p-Ser396/404) or Tau-1 (dephospho-Ser199/202/205). Reduced tau phosphorylation was associated with an inactivation of the major tau kinase, GSK-3.

Traumatic brain injury (TBI) model: In a mouse model of TBI (controlled cortical impact), SPG-101 treatment (30 mg/kg/day, i.p.) started 1 hour post-injury and once daily for the next 34 days significantly improved sensorimotor functional recovery (modified Neurological Severity Score, mNSS; days 7-35, $p < 0.0001$), spatial learning (days 32-35, $p < 0.0001$), novel object recognition (days 14 and 35, $p < 0.0001$), and social recognition (days 14 and 35, $p < 0.0001$) (Zhang Y et al., 2019). Also, the treatment significantly increased dendritic spine density in the injured cortex ($p < 0.05$), while no spine density changes were observed in the hippocampus (CA1 or dentate gyrus). In this model, SPG-101 was

beneficial in improving both sensorimotor and cognitive functional recovery by acting as a spinogenic agent in the injured cortex.

APOE4 interactions: Unknown.

Aging and related health concerns: This compound has not been investigated for age-related health conditions.

Types of evidence:

- None available

No studies have tested whether SPG-302 has benefits for age-related health concerns. Given that the compound promotes the growth of retracted spines in neurons, it is unlikely the compound has benefits for peripheral conditions. However, it is not known how SPG-302 affects fascin expressed in peripheral tissues including cancer cells (Zhang et al., 2008).

Safety: No safety data or studies specific to SPG-302 have been published.

Types of evidence:

- No published studies

Based on ongoing work funded by the NIH (described in "Research underway"), Spinogenix is performing *in vitro* screens to establish compounds for toxicity and pharmacokinetic testing in normal mice (R43AG058278). A previous generation SPG compound, SPG-101 (formerly known as BTA-EG4), was reported to have no toxicity, though details of the data could not be found (Song et al., 2014).

Drug interactions are unknown.

Sources and dosing: SPG-302 is a third-generation tetraethylene glycol derivative of benzothiazole aniline that was developed by Spinogenix from prototype compounds in-licensed from University of California San Diego (BioCentury article).

Research underway: Vincent Simmon, PhD, Chief Operating Officer of Spinogenix is the principal investigator on an NIH SBIR grant titled "Novel small molecules that target Alzheimer's disease by increasing spinogenesis and decreasing Aβ toxicity" (R43AG058278). The 3 aims are: 1) to develop a

detailed analysis of the pharmacological properties of the best BAM (SPG-203) to understand how it can be improved; 2) to screen the derivatives to establish a structure-activity relationship of the compounds to identify ones that have better stability, enhanced Aβ binding affinity, improved fascin targeting, and increased spinogenic activity with an acceptable toxicity profile; and 3) to characterize lead compound SPG30X- induced memory, cognition, and spinogenesis *in vivo* in 3xTg AD mice using super-resolution imaging methods. The total funding amount is $314,511 and the project is scheduled to end on April 30, 2019.

Spinogenix plans to start a phase I trial in Alzheimer's in 2020 (BioCentury article). They are also developing efficacy markers, based on *in vivo* imaging and molecular techniques amenable to use in clinical trials, though details of these markers are not disclosed.

Patents: Spinogenix has filed 2 international patents.

"Benzothiazole and related compounds" was filed on 8/1/2018 with a publication date of 2/7/2019 (WO/2019/028164). The international application number is: PCT/US2018/044852. This patent application discloses compounds that promote spinogenesis, reduce neural toxicity of beta-amyloid peptides, and/or reduce the symptoms of traumatic brain injury in a patient.

"Use of benzothiazole amphiphiles for treating traumatic brain injury" was filed on 6/25/2018 with a publication date of 1/3/2019 (WO/2019/005682). The international application number is PCR/US2018/039322. The invention is directed to methods of reducing symptoms of traumatic brain injury in patients by administering a therapeutically effective amount of a benzothiazole amphiphile compound within 0 to 72 hours of incurring the injury.

Search terms:
Pubmed, Google: SPG, SPG-302, BTA-EG4 (=SPG-101)

Websites visited for SPG-302:

- Clinicaltrials.gov (0)
- ProjectReporter

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