Zacks Small-Cap Research

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# Neurotrope, Inc. (NTRP - OTC)

## *NTRP: Initiating coverage of Neurotrope, Inc.; Battling Alzheimer's Disease with a Natural Compound*

| | |
|---|---|
| **Current Recommendation** | **Buy** |
| Prior Recommendation | N/A |
| Date of Last Change | 10/20/2014 |
| Current Price (10/20/14) | $0.65 |
| **Target Price** | **$1.50** |

### INITIATION

We are initiating coverage of Neurotrope, Inc. (OTC: NTRP) with a Buy rating and a $1.50 price target.

Neurotrope is developing therapeutics for neurodegenerative diseases such as Alzheimer's Disease (AD), and orphan drug indications including Neimann Pick Type C and Fragile X Syndrome. The company's lead compound, bryostatin-1, is currently in a Phase 2a clinical trial for the treatment of AD.

Neurotrope is also developing a simple AD diagnostic test that uses a skin biopsy sample with results showing sensitivity ≥ 97% and specificity ≥ 96%, suggesting a low risk of incorrect diagnosis.

## SUMMARY DATA

| | |
|---|---|
| **52-Week High** | **$1.15** |
| **52-Week Low** | **$0.50** |
| **One-Year Return (%)** | **N/A** |
| **Beta** | **N/A** |
| **Average Daily Volume (sh)** | **14,181** |
| **Shares Outstanding (mil)** | **22** |
| **Market Capitalization ($mil)** | **$14** |
| **Short Interest Ratio (days)** | **N/A** |
| **Institutional Ownership (%)** | **0** |
| **Insider Ownership (%)** | **N/A** |
| **Annual Cash Dividend** | **$0.00** |
| **Dividend Yield (%)** | **0.00** |
| **5-Yr. Historical Growth Rates** | |
| **Sales (%)** | **N/A** |
| **Earnings Per Share (%)** | **N/A** |
| **Dividend (%)** | **N/A** |
| **P/E using TTM EPS** | **N/A** |
| **P/E using 2013 Estimate** | **N/A** |
| **P/E using 2014 Estimate** | **N/A** |

| | |
|---|---|
| **Risk Level** | **Above Average** |
| **Type of Stock** | **Small-Growth** |
| **Industry** | **Med-Biomed/Gene** |

## ZACKS ESTIMATES

### Revenue

(In millions of $)

| | Q1 (Mar) | Q2 (Jun) | Q3 (Sep) | Q4 (Dec) | Year (Dec) |
|---|---|---|---|---|---|
| 2013 | 0 A | 0 A | 0 A | 0 A | 0 A |
| 2014 | 0 A | 0 A | 0 E | 0 E | 0 E |
| 2015 | | | | | 0 E |
| 2016 | | | | | 0 E |

### Earnings per Share

(EPS is operating earnings before non-recurring items)

| | Q1 (Mar) | Q2 (Jun) | Q3 (Sep) | Q4 (Dec) | Year (Dec) |
|---|---|---|---|---|---|
| 2013 | -$0.00 A | -$0.00 A | -$0.21 A | -$0.14 A | -$0.35 A |
| 2014 | -$0.08 A | -$0.09 A | -$0.10 E | -$0.10 E | -$0.37 E |
| 2015 | | | | | -$0.39 E |
| 2016 | | | | | -$0.45 E |

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## WHAT'S NEW

**Initiating Coverage**

We are initiating coverage of Neurotrope, Inc. (OTC: NTRP) with a Buy rating and a $1.50 price target.

Neurotrope is seeking to commercialize technology developed at and exclusively licensed from the Blanchette Rockefeller Neurosciences Institute (BRNI) for therapeutic and diagnostic applications in Alzheimer's Disease (AD) and other neurodegenerative disorders.

AD is a debilitating neurodegenerative disorder that results in dementia, a decline in memory or thinking skills that adversely affects an individual's life and well-being. The disease is caused by the death of neurons in the brain, which leads to the typical phenotypes associated with AD such as memory loss, confusion, and behavioral changes. A number of drugs have been developed that target a multitude of factors associated with AD. Unfortunately, none of these experimental compounds have shown significant efficacy in Phase 3 clinical trials. Thus, a new way of thinking about AD and therapeutic targets is warranted.

Investigations at BRNI into memory formation revealed that Protein Kinase C (PKC) is vital to memory acquisition and storage. These results led to the notion that PKC may be involved in AD, as memory loss is the first clinical sign of the disease. Scientists later discovered that activating PKC resulted in lower levels of beta-amyloid and an increase in learning performance in a mouse model of the disease.

PKC is activated by a number of compounds. One such compound is bryostatin-1, a natural product that is isolated from the marine organism *Bugula neritina*. Bryostatin-1 was initially tested in clinical trials as a cancer therapeutic. The drug was studied in over 1,200 patients, however results were not strong enough to warrant its continued development as a cancer treatment. With the discovery that bryostatin-1 activates PKC and that PKC has a central role in a number of AD-related cellular processes, attention has now turned to testing bryostatin-1 as an AD therapeutic.

Neurotrope just recently initiated a Phase 2a clinical trial in AD patients testing a single dose of bryostatin-1. The primary endpoint of the study is safety and tolerability, with secondary endpoints examining various neurological outcomes. Data from the trial is expected in the first quarter of 2015.

In addition to bryostatin-1, the company is developing an AD diagnostic test based on biomarkers that are regulated by PKC. Using fibroblasts from a simple skin biopsy, a series of *in vitro* tests are used to amplify the expression of these biomarkers. The skin fibroblast displays the same basic pathophysiology indicative of AD as a neuron in the brain. Preliminary studies in 140 patients with Alzheimer's Dementia, dementia of other etiologies, and age-matched controls, including 51 patients with autopsy-confirmed diagnoses, were reported to show sensitivity ≥ 97% and specificity ≥ 96%, suggesting a low risk of incorrect diagnosis.

With so many clinical trial failures for AD therapeutics, a new treatment option is clearly needed. We are encouraged by the results from preclinical work with bryostatin-1 in AD models, and are looking forward to seeing the results from the ongoing Phase 2a trial, which is the first-in-human study of bryostatin-1 for the treatment of AD. We believe a safe and efficacious AD drug would easily generate sales in excess of $1 billion.

As of June 30, 2014, the company held $12.0 million in cash and investments and is only burning around $1.5 million per quarter. That means cash as of September 30, 2014 is still above $10 million. We find this to be sufficient to fund operations well into 2016.

## INVESTMENT THESIS

**Dementia**

Dementia is the generic term to describe a decline in memory or other thinking skills that negatively impacts a person's ability to perform everyday tasks. It is caused by damage to neurons, the nerve cells in the brain. The damage renders the cells unable to function normally, and oftentimes leads to their death. A significant loss of neurons can lead to changes in a person's ability to think clearly, remember things, and act normally.

There are a number of conditions that cause dementia, and it is important to clinically differentiate between the different conditions for treatment purposes. The conditions include:

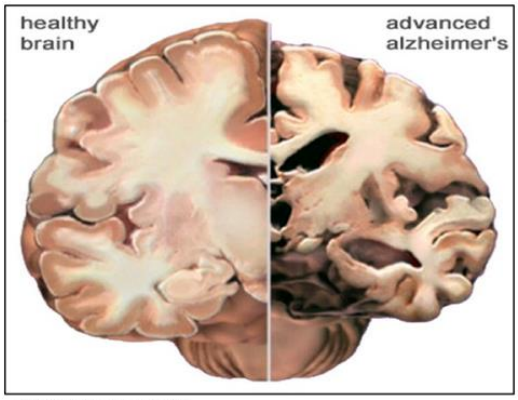
- Alzheimer's disease
- Vascular dementia
- Dementia with Lewy bodies (DLB)
- Frontotemporal lobar degeneration (FTLD)
- Parkinson's disease dementia
- Creutzfeldt-Jakob disease
- Normal pressure hydrocephalus

In addition to the dementias listed above, there are a host of conditions that can mimic dementia that are the result of depression, delirium, medication side effects, thyroid problems, and excessive use of alcohol. While those conditions are reversible, currently there are no treatments that will reverse dementia caused by the conditions listed above.

***…Alzheimer's disease…***

Alzheimer's disease (AD) is the most common form of dementia in older adults. The disease is named after Dr. Alois Alzheimer, who identified the first case in a 50-year-old woman named Auguste Deter in 1902. Dr. Alzheimer followed her case until her death in 1906, at which point he first publicly reported on it (Alzheimer, 1907).

After Ms. Deter's death, Dr. Alzheimer examined her brain and found many abnormal clumps (now known as amyloid plaques) and tangled bundles of fibers (now known as neurofibrillary tangles). Over the next five years, 11 similar cases were reported in the medical literature, with some of them already using the term Alzheimer's disease (Berchtold *et al*., 1998).



*Source:* thebrightdirection.com

For much of the 20th century, an AD diagnosis was reserved for those between the ages of 45-65 who developed symptoms of dementia. The terminology changed following an AD conference where a conclusion was reached that the clinical and pathological manifestations of presenile and senile dementia were almost identical, leading to the use of the term Alzheimer's disease independent of age (Boller *et al*., 1998).

The most common early symptom of AD is a gradually worsening ability to remember new information. This is due to neurons associated with forming new memories dying off first. As neurons in other parts of the brain die, individuals experience different symptoms, which include:

- ✓ Memory loss that disrupts daily life
- ✓ Inability to plan or solve problems
- ✓ Difficulty completing familiar tasks
- ✓ Confusion with location and time
- ✓ Difficulty with visual images and spatial relationships
- ✓ Problems with words in speaking or writing
- ✓ Withdrawal from social activities
- ✓ Changes in mood, including apathy and depression

Each person progresses through AD at a different rate, and little is known about how or why there is such a marked variation, thus predicting how it will affect someone is quite difficult. One thing that is common to everyone diagnosed with AD is that his or her cognitive and functional abilities will gradually decline. As the disease progresses symptoms can include confusion, irritability, aggression, mood swings, and long-term memory loss. In the final advanced stage of the disease, people need help with the basic activities of living (e.g., bathing, dressing, eating, and using the restroom), they lose the ability to communicate, fail to recognize loved ones, and eventually become bed bound and reliant on round-the-clock care (Förstl *et al*., 1999). The inability to move makes them more prone to infections, including pneumonia, which are often a contributing factor to the death of those with AD.

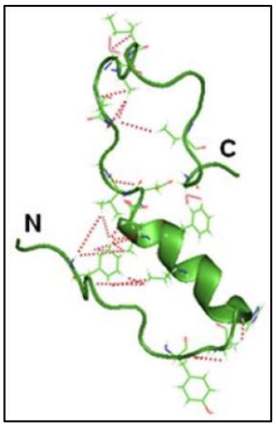
***…Many competing theories for the cause of Alzheimer's…***

The root cause of Alzheimer's is still unknown; however, it is likely to involve a number of different factors as opposed to being due to one single cause. These factors are likely a combination of genetic, environmental, and lifestyle. There are a number of hypotheses that exist to explain the cause of the disease:

- Genetic: A rare form of the disease, known as Familial Alzheimer's Disease (FAD), typically strikes early in life, before the age of 65, and is inherited in an autosomal dominant fashion. This form of the disease is the only one for which there is a clear understanding of the cause. FAD is caused by mutations in one of at least three genes: presenilin 1, presenilin 2, and amyloid precursor protein (Bertram *et al*., 2008). However, the vast majority of Alzheimer's cases do not exhibit autosomal-dominant inheritance and instead are termed sporadic AD. Even so, there are known genetic risk factors, the best studied of which is the inheritance of the ε4 allele of the apolipoprotein E (APOE) gene (Mahley *et al*., 2006). The APOEε4 allele increases the risk of the disease by three times in heterozygotes (having one copy of the allele) and by 15 times in homozygotes (having two copies of the allele; Blennow *et al*., 2006). In addition, mutations in the TREM2 gene are associated with a three to five times higher risk of developing AD (Jonsson *et al*., 2012).

- Cholinergic hypothesis: This is the oldest theory, and the one for which most of the current AD treatments are based on. It proposes that AD is caused by reduced synthesis of the neurotransmitter acetylcholine. A number of studies from the mid-1970s showed substantial deficits in the enzyme responsible for the synthesis of acetylcholine in the brains of patients with AD (Davies *et al*., 1976). However, this theory has fallen out of favor since it was originally proposed, as medications to treat acetylcholine deficiency have not shown strong efficacy in treating AD patients.

- Amyloid hypothesis: This hypothesis proposes that extracellular beta-amyloid deposits are the fundamental cause of the disease (Hardy *et al*., 1991). Beta-amyloid is a fragment of the larger protein amyloid precursor protein (APP), mutations of which are known to cause FAD. Several lines of evidence support the amyloid hypothesis: 1) the location of APP is on chromosome 21, while those with Down Syndrome (trisomy 21) almost all show signs of AD by 40 years of age (Lott *et al*., 2005); 2) APOEε4 is a major genetic risk factor for AD, and while apolipoproteins enhance the breakdown of beta-amyloid, some isoforms are less capable of performing this task than others, leading to more beta-amyloid buildup on the brain (Polvikoski *et al*., 1995); 3) mice that harbor a mutant form of APP develop amyloid plaques and Alzheimer's-like pathology (Games *et al*., 1995). Lastly, amyloid plaques are readily identifiable by microscopy in the brains of AD patients (Tiraboschi *et al*., 2004). While the brains of many older individuals develop some plaques, the brains of AD patients show severe pathological changes specifically within the temporal neocortex (Bouras *et al*., 1994).



Beta-amyloid
*Source*: Vivekanandan *et al*., 2011

- Tau hypothesis: Tau is a protein located mainly within the axonal compartment of neurons and is an important element in microtubule stabilization and neurite outgrowth. In AD, a proportion of tau protein becomes abnormally phosphorylated, dissociates from axonal microtubules, and accumulates in paired helical filaments inside the neuron (Goedert *et al*., 1991). When this occurs, the microtubules disintegrate causing the collapse of the neuron's transport system (Igbal *et al*., 2005). Just as with beta-amyloid plaques, tau tangles are readily observable in the brains of those affected by AD.

The exact mechanism for how production and aggregation of beta-amyloid peptide results in the pathology of AD is still unclear. It is also unknown how all the other factors conspire to impair neuronal function and survival or what the ultimate initiating factor is for the disease.

***…Diagnosis of AD…***

A patient's primary care physician generally diagnoses AD. It is based on a medical and family history, including a history of cognitive and behavioral changes. Imaging techniques such as magnetic resonance imaging (MRI) or positron emission tomography (PET) can be utilized to exclude other brain abnormalities or different dementias. Memory testing and other assessments of intellectual functionality can help further characterize the disease.

In 2011, the National Institute on Aging (NIA) and the Alzheimer's Association proposed revised guidelines for diagnosing AD (McKhann *et al*., 2011). The criteria and guidelines were an updated version of the diagnostic criteria and guidelines published in 1984 by the Alzheimer's Association and the National Institute of Neurological Disorders and Stroke (McKann *et al*., 1984). In 2012, the NIA and Alzheimer's Association also proposed new guidelines to help pathologists characterize the brain changes due to AD and other dementias (Hyman *et al*., 2012).

The 1984 guidelines were based chiefly on a primary care physician's judgment about the cause of the individual symptoms, results of cognitive tests, and general neurological assessment. The updated guidelines incorporated two noteworthy changes:

1. They identify Alzheimer's as a three-stage disease, with the first stage of Alzheimer's occurring before there are any symptoms such as memory loss. The 1984 guidelines stated that memory loss and a decline in thinking abilities had to already have occurred;
2. They incorporate biomarker tests. A biomarker is a biological factor that can be measured and utilized to indicate the presence or absence of a disease.

The three stages of AD proposed by the 2011 guidelines are: Preclinical AD, Mild Cognitive Impairment (MCI) due to AD, and Dementia due to AD.

- Preclinical AD: At this stage individuals have changes in brain, cerebrospinal fluid, and/or blood biomarkers that indicate the earliest signs of disease, but they have not yet developed clinical symptoms. This preclinical stage reflects the current understanding of Alzheimer's disease that brain changes may occur up to 20 years before symptoms occur (Villemagne *et al*., 2013). An important note about this stage of the disease is that there are no diagnostic criteria available at this point, but rather the guidelines state that additional research is necessary before this stage of Alzheimer's can be identified. The biomarker test(s) will need to be validated to determine the most effective test to diagnose the disease with a high degree of accuracy.

- MCI due to AD: Individuals with MCI have mild but noticeable changes in thinking abilities, but are still able to function on a day-to-day basis. It is thought that as many as 10 to 20% of people ages 65 and older have MCI (Lopez *et al*., 2003). After reliable and accurate biomarker tests are available, the 2011 guidelines recommend biomarker testing for people with MCI to learn whether they have biological changes that put them at risk of developing AD and other dementias. If biomarker testing shows changes that are similar to the changes in AD, the 2011 criteria and guidelines recommend a diagnosis of MCI due to AD. However, just as a diagnosis of preclinical AD cannot currently be made, neither can a diagnosis of MCI due to AD be made as additional research is necessary to validate the 2011 criteria before they can be used in a clinical setting.

- Dementia due to AD: The 2011 criteria and guidelines describe this stage as including quite noticeable memory, thinking, and behavioral symptoms that, unlike MCI, limit the person's ability to function in daily life.

***…Current Treatment Options for AD…***

Pharmacologic Therapy: There are five medications that are currently approved by the Food and Drug Administration (FDA) to specifically treat AD: donepezil (Aricept®), galantamine (Razadyne®/Razadyne® ER), rivastigmine (Exelon® Patch), tacrine (Cognex®), and memantine (Namenda®/Namenda® ER). The first four drugs listed are all acetylcholinesterase inhibitors, while memantine is an NMDA receptor antagonist.









A reduction in the activity of the cholinergic neurons is a well-known characteristic of AD (Geula *et al*., 1995). Acetylcholinesterase inhibitors are designed to reduce the rate at which acetylcholine, a chemical messenger in the brain that transmits information from one nerve cell to another, is broken down. This then increases the concentration of acetylcholine that would otherwise be lower due to the death of cholinergic neurons. Unfortunately, the neurons that make acetylcholine are also slowly destroyed by AD, thus this class of drugs eventually becomes ineffective.

There is evidence for the efficacy of acetylcholinesterase inhibitors in patients with mild to moderate AD (Birks, 2006). Only donepezil is approved for treatment in advanced AD. The side effects for these medications are usually mild and include nausea, vomiting, diarrhea, headache, and insomnia. The exception to this is the potential for liver damage caused by tacrine, thus while available that drug is rarely prescribed.

The neurotransmitter glutamate is needed for proper memory function; however, excessive amounts of glutamate in the brain can lead to cell death through a process called excitotoxicity, which as an overstimulation of glutamate receptors, of which the NMDA receptor is an example. Memantine works as a noncompetitive NMDA receptor antagonist, whereby it prevents glutamate from over stimulating the receptor. The drug has been shown to be moderately efficacious in the treatment of moderate to severe AD (Areosa Sastre *et al*., 2004). Side effects due to treatment with memantine are generally mild, and include hallucinations, confusion, dizziness, headache, and fatigue.

Pfizer's Aricept®, the leading acetylcholinesterase inhibitor, had peak sales of $3.3 billion before losing patent protection in 2010. Forest Labs' Namenda® posted sales of $1.5 billion in 2013. Sales of all AD medications have declined in recent years as they are now available as generics, with the exception of tacrine, with total revenues expected to be approximately $5 billion in 2014. However, the market for AD therapeutics is expected to continue to grow due to the aging populations of the developed world.

Non-Pharmacologic Therapy: These therapies employ approaches other than medication, such as physical therapy and reminiscence therapy (showing old photos or other family items that can sometimes elicit recall). These treatments have not been shown to alter the course of AD, rather their goal is to maintain cognitive function or to help the brain compensate for impairments. They have also been used to improve quality of life or reduce negative behavioral symptoms such as depression, apathy, wandering, agitation, and aggression.

While a number of non-pharmacologic therapies have been utilized, few have sufficient evidence to support their effectiveness. Of the high quality studies that are available, cognitive training, cognitive stimulation, and training in activities of daily living appeared to be most successful in reaching the aims of the interventions (Olazarán *et al*., 2010).

***…Multiple clinical trial failures point to a flawed AD drug development modality…***

The development of new and novel AD therapeutics has proven to be quite difficult. No new medications have been approved by the FDA for the treatment of AD since 2003. To examine the AD drug development process, a recent study examined all AD clinical trials since 2002 along with all currently ongoing trials and active compounds (Cummings *et al*., 2014). The results of this study are quite discouraging, with the authors noting the overall success rate for approval from trials conducted from 2002 to 2012 being 0.4%.

A total of 413 trials representing 244 unique compounds were conducted between 2002 and 2012. The pharmaceutical industry sponsored the vast majority of the trials (322 of 413), with almost half of the trials being conducted in the United States. The tested drugs were classified into six therapeutic categories, with symptomatic agents aimed at improving cognition being utilized in the most trials (36.5%), followed by disease-modifying small molecules (35.1%) and disease-modifying immunotherapies (18.4%).

Anti-beta-amyloid therapies have dominated AD trials, with 70 of 146 (combined small molecules and immunotherapies) compounds targeted against beta-amyloid, compared with 13 compounds against tau-related mechanisms and 62 compounds with neuroprotective approaches. During the period reviewed, 54 compounds were tested in Phase 3 with only one compound advancing to the FDA for review and approval (1.8% success rate). Overall, 244 compounds were tested from 2002-2012 with one approved for marketing. Excluding the 14 compounds that are still currently being tested, AD drug development during the reviewed time period had a failure rate of 99.6%.

Some notable trial failures involving anti-beta-amyloid therapeutics include:

- Solanezumab (Eli Lilly): This compound is a humanized monoclonal antibody that preferentially binds to soluble forms of amyloid and in preclinical studies was shown to clear amyloid from the brain. Two Phase 3, randomized, double-blind, placebo controlled trials were performed where patients with mild to moderate AD received either placebo or solanezumab every 4 weeks for 18 months (Doody *et al*., 2014). Results showed no statistically significant difference between groups in the Alzheimers's Disease Assessment Scale (ADAS) and the Alzheimer's Disease Cooperative Study-Activities of Daily Living Scale (ADCS-ADL).

- Bapineuzumab (Pfizer): This compound is a humanized anti-beta-amyloid monoclonal antibody that was shown in preclinical mouse models to reduce the amount of beta-amyloid in the brain and improve memory. Two double-blind, randomized, placebo controlled Phase 3 trials were conducted in patients with mild to moderate AD (Salloway *et al*., 2014). Results showed no significant difference between groups in the ADAS or the Disability Assessment for Dementia.

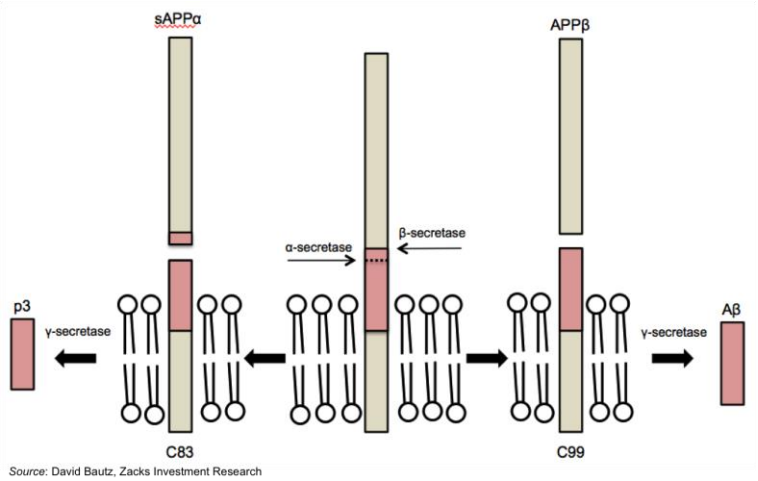
- Crenezumab (Genentech): This compound is a humanized monoclonal antibody that targets beta-amyloid. This drug was selected in 2012 to be tested in a five-year trial that is currently ongoing against early-onset AD, in a partnership between Genentech, Banner Alzheimer's Institute, and the National Institutes of Health. In a separate Phase 2 clinical trial (ABBY), results showed no significant difference in ADAS or the Clinical Dementia Rating-Sum of Boxes in patients with mild to moderate AD.

Therapeutics targeting beta-amyloid was an intense area of research over the past decade. However, targeting beta-amyloid has not proven to be a successful approach to treating AD based on the multiple clinical trial failures. Thus, a new paradigm in treating the disease is necessary through identification of novel treatment targets and medications, as the current AD drug development platform has proven ineffective.

***…A novel AD treatment target…***

Memory loss is the most characteristic clinical manifestation of AD and occurs early in the course of the disease when an inability to retain recent information is primarily affected (Petersen *et al*., 1994). Past research into memory formation has shown that the enzyme Protein Kinase C (PKC) activates multiple targets during memory acquisition and storage (Olds *et al*., 1993). Interestingly, PKC is also responsible for processing APP (Jolly-Tornetta *et al*., 2000) and levels of PKC are decreased in the brains of patients with AD (Cole *et al*., 1988).

APP is a protein that is critical to neuron growth, survival, and post-injury repair (Turner *et al*., 2003). The processing of APP and its metabolic products plays a fundamental role in AD pathophysiology, and targeting this pathway has been an intense area of pharmacological research for potential AD treatments, as discussed above. APP is a large, transmembrane protein that can be cleaved in three distinct sites by proteolytic enzymes called secretases (Selkoe, 2001). The α-secretase cleaves APP to generate a large soluble fragment (sAPPα) and a smaller intracellular fragment C83. These fragments appear to have no pathological significance and in fact may have some neuroprotective properties. The β-secretase cleaves APP to generate APPβ and a cell-bound fragment C99. The cell-bound fragment is the precursor of beta-amyloid peptide that is generated from cleavage by a third secretase, γ-secretase, which yields the plaque-forming and neurotoxic beta-amyloid (Aβ) fragment.



*Source:* David Bautz, Zacks Investment Research

Since the α- and β-secretase both utilize APP, one therapeutic approach to treating AD would be to promote expression of the former or decrease expression of the latter, which in theory would promote the formation of the sAPPα and decrease formation of the pathogenic beta-amyloid peptide (Skovronsky *et al*., 2000). The "α-processing" of APP is enhanced by activation of PKC as was originally shown with phorbol esters (natural substrates of PKC) along with additional PKC activators resulting in an increase in the secretion of sAPPα (Desdoults *et al*., 1996). Unfortunately, phorbol esters cannot be utilized as AD therapeutics as they are tumor promoters (Blumberg, 1988). Therefore, novel compounds that induce activation of PKC offer an alternative therapeutic approach to increasing the α-processing of APP.

***…A natural PKC activator…***

The National Cancer Institute (NCI) sponsored a program to discover antitumor agents from natural resources from the 1950s through the 1980s. As part of that program, marine organisms were collected at random, processed, and sent to the NCI where extracts were tested against mouse leukemia cell lines. The tests showed that a particular marine organism, *Bugula neritina*, a filter-feeding creature approximately 1 mm in length that resides in ocean waters around the world, harbored compounds that exhibited anticancer activity. These compounds, known as bryostatins, are a family of 20 highly complex molecules, with the most thoroughly characterized being bryostatin-1.

It took a number of years from the time that *B. neritina* extracts were shown to have antineoplastic activity to the isolation of the responsible compound. In 1991, the NCI initiated a massive isolation of bryostatin-1 by collecting upwards of 14 tons of the organism, from which researchers were able to isolate 18 g of bryostatin-1 (Schaufelberger *et al*., 1991). The NCI was attempting to acquire enough compounds to run clinical trials in various types of cancer. Due to the high potency of bryostatin-1, the 18 g have been enough to supply all clinical trials using the compound up until the present time.

Bryostatin-1 is one of a number of compounds that work by modulating the activities of PKC, a family of fifteen isozymes in humans that are responsible for the activation of a host of other proteins and signaling cascades in various cells throughout the body (Mellor *et al*., 1998). Once activated, PKC plays an important role in intracellular signaling cascades. PKC has been known to cancer biologists for a long time due to it being activated by phorbol esters, which are known tumor promoters. However, while phorbol esters cause tumors to grow, bryostatin-1 was shown to suppress tumor growth, even though both compounds bind to the same portion of PKC to activate it.

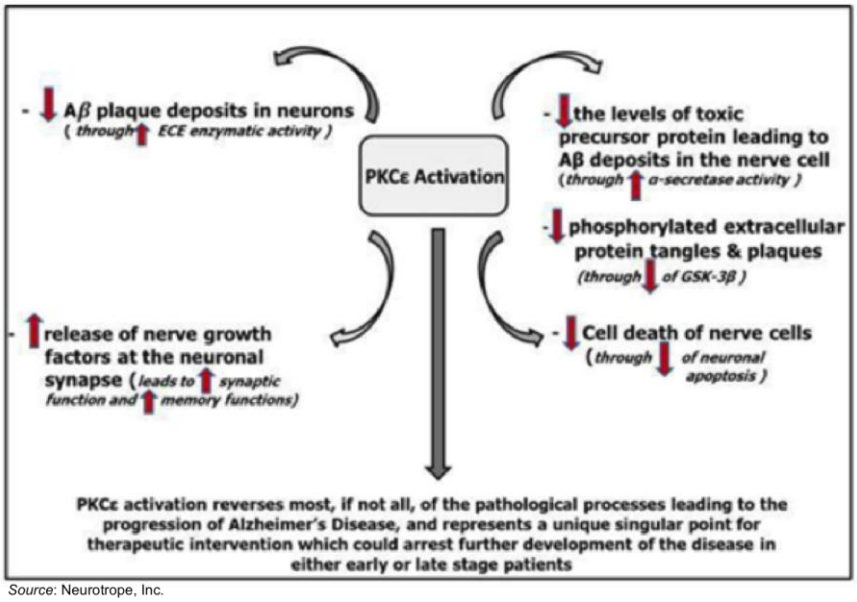
The initial excitement over bryostatin-1 as an anti-cancer agent has since faded due to a number of clinical trial failures. Bryostatin-1 has failed to show significant activity as a single agent or in combination with other chemotherapies despite the fact that the drug has been tested in close to 1,200 patients thus far in over thirty Phase 1 and Phase 2 clinical trials. However, these trials have provided a wealth of information on the safety, pharmacokinetics, and toxicity of the drug.

***…PKC, Bryostatin-1, and AD…***

As mentioned earlier, PKC activation is vital for memory formation along with the formation of new synapses, which are the structures that allow neurons to form connections with other neurons. With this understanding, researchers began to investigate whether PKC might be relevant to the memory loss seen in AD patients.

Synaptic loss is the only pathological finding in the brain's of AD patients that is closely correlated with the degree of dementia (Terry *et al*., 1991). In fact, the two pathological marks of AD, amyloid plaques and neurofibrillary tangles, are only weakly correlated with the degree of dementia in AD patients. Amyloid-beta has been shown to degrade PKC in cultured fibroblasts as well as brain endothelial cells (Favit *et al*., 1998; Pakaski *et al*., 2002) and to downregulate PKC by binding to it (Lee *et al*., 2004).

The PKC isozymes PKCα and PKCε are important for synaptogenesis. There is a high abundance of PKCε in the presynaptic nerve fibers, suggesting the protein plays an important role in neurite outgrowth, synapse formation, and neurotransmitter release (Shirai *et al*., 2008). In addition, activation of PKCα and PKCε has been shown to prevent synaptic loss in pathogenic mouse models (Sun *et al*., 2008, 2009). Using specific PKC isozyme inhibitors showed that PKCε as the isozyme that most effectively suppresses the production of beta-amyloid (Zhu *et al*., 2001). Bryostatin-1 is able to selectively activate PKCε, and to a lesser extent PKCα, which is believed to affect multiple different mechanisms to stop the progression of AD.




*Source*: Neurotrope, Inc.

***…Preclinical research supports the use of bryostatin-1 in AD…***

There have been a number of preclinical studies published that support the use of bryostatin-1 as a treatment for AD. A selection of these publications is summarized below:

- Etcheberrigaray *et al*., 2004: This study provided evidence that bryostatin-1 enhanced the secretion of the α-secretase product sAPPα in fibroblasts from AD patients. In addition, it was shown that bryostatin-1 was effective in reducing toxic beta-amyloid peptide and reducing the rate of premature death in transgenic mice harboring a mutation in the APP protein.

- Choi *et al*., 2006: This study utilized a mouse model that overexpressed PKCε and showed that PKCε overexpression reduced the number of amyloid plaques and the level of beta-amyloid peptide in the brains of transgenic mice that harbored a mutant APP protein. The authors also showed that the results were due to an increase in the activity of endothelin-converting enzyme (ECE), a protease that degrades APP.

- Khan *et al*., 2009: This study confirmed the findings of the Etcheberrigaray study showing that bryostatin-1 increased the secretion of sAPPα from AD skin fibroblasts, and in fact was more potent than a synthetic analog molecule. In addition, results showed that bryostatin-1 was able to convert a peripheral AD biomarker (Erk1/2 phenotype, Khan *et al*., 2006) of the AD fibroblasts into the phenotype of "normal" control fibroblasts. Lastly, bryostatin-1 was shown to prevent the beta-amyloid induced abnormalities of the AD biomarker in normal fibroblasts.

- Hongpaisan *et al*., 2011: This study examined the effects of bryostatin-1 on the formation of bety-amyloid peptide, synaptic structures and numbers, amyloid plaques, and memory functions. Administration of bryostatin-1 significantly improved the learning performance and prevented memory deficits in Tg2576 mice, which are a model of slowly progressive AD. In addition, it was shown that bryostatin-1 prevented an increase in beta-amyloid peptide, prevented a decrease in PKCα and PKCε protein levels, and prevented the loss of the total number of synapses.

- Khan *et al*., 2014: This study examined PKCε and amyloid-beta in the brains of autopsy confirmed AD patients and age matched controls as well as in skin fibroblasts from AD, non-AD dementia, and age-matched controls. PKCε was found to be significantly lower in the hippocampus and temporal pole areas of AD patients, whereas beta-amyloid peptide levels were significantly higher. In addition, skin fibroblasts from AD patients also demonstrated a deficit in PKCε compared to controls, with the change in PKCε holding the possibility of being utilized as an accurate, non-invasive peripheral AD biomarker.

The results from these and other studies point to a central role of PKCε in maintaining neuron structure and function. Specifically, activation of PKCε results in a decreased level of beta-amyloid peptide by increasing the rate of amyloid degradation by ECE and induction of α-secretase cleavage of APP.

Thus, activators of PKCε, such as bryostatin-1, may work not just to alleviate the symptoms of AD, but could delay the progression of the disease through both synaptogenesis (formation of new synapses in the brains of AD patients) and through a decrease in the amount of beta-amyloid.

***…Bryostatin-1 enters the clinic…***

On July 29, 2014, Neurotrope announced the initiation of a Phase 2a clinical trial (NCT02221947) to evaluate bryostatin-1 for the treatment of patients with AD. This is a randomized, double-blind, placebo controlled, single dose study with a total of 15 patients expected to be enrolled. Ten patients will be randomized to receive bryostatin-1 through intravenous infusion and five will receive a matching placebo control. The primary objective of the trial is to assess the safety and tolerability of a single dose of bryostatin-1. The secondary objectives of the study are the preliminary evaluation of the efficacy of a single dose of bryostatin-1, the pharmacokinetics of the drug, and to correlate the changes in PKCε with plasma levels of bryostatin-1 and with improvement in cognitive function. Top-line results are expected to be reported by the end of the first quarter of 2015. The company is also in talks with the FDA to add an additional 30 patients to the trial. The trial expansion is subject to FDA approval of an amended protocol. In addition, some of those patients will be on a multiple dose regimen. Depending upon when the company is able to start the multiple dose study those results could be available by the summer of 2015.

The study will consist of screening evaluations and on study evaluations divided into two segments, an inpatient segment and an outpatient segment. The four-day inpatient segment will consist of baseline evaluations and a 1-hour IV infusion of study drug followed by multiple evaluations over the first 72 hours post dose. During the outpatient segment, patients will be followed for adverse events and have a final evaluation 2 weeks post dose and a 4-week telephone safety follow up.

Males and females between the ages of 50-85 are eligible for the study if they have had a cognitive deficit present for at least one year and meet diagnostic criteria for AD dementia. In addition, the mini mental state exam score must be between 16 and 26. The mini mental state exam is a 30-point questionnaire test that is used to screen for cognitive impairment (Folstein *et al*., 1975). It includes simple questions and problems in a number of areas (arithmetic, language use and comprehension, basic motor skills) and is scored on a 30-point scale. A score greater than 27 indicates normal cognition, 19-26 points indicates mild cognitive impairment, 10-18 points indicates moderate cognitive impairment, and scores ≤ 9 indicate severe cognitive impairment (Mungas, 1991). Thus, Neurotrope is selecting patients with mild to moderate cognitive impairment for inclusion in the Phase 2a trial.

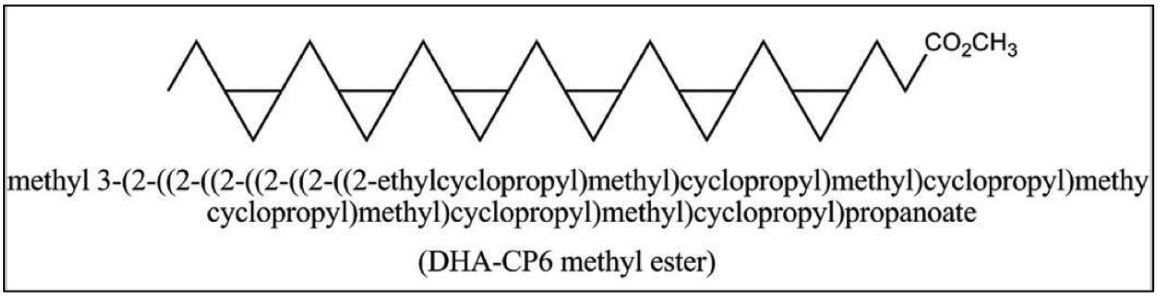
To determine preliminary efficacy of the drug, the study subjects will be evaluated using the Hopkins Verbal Learning Test-Revised™ (HVLT-R™; Brandt, 1991; Benedict *et al*., 1998). This test is utilized to assess both verbal learning and memory and is composed of a 12-item word list that is read to subjects on three successive learning trials. As soon as the 12 words are read each time the subject is asked to recall as many items as possible in any order (“Free recall scores”). Following the third learning trial, there is a 20-25 min interval filled with unrelated tasks after which the subject is asked to recall as many of the 12 words as possible. Following that, the subject is read a total of 24 words, the 12 target words used in the learning trials and 12 non-target words. For each word, the patient is asked to say “yes” if the word was on the target list and “no” if the word was not previously presented.

The dosage of bryostatin-1 used in this study is quite small, and is similar to that seen in cancer trials with the drug. For this trial, bryostatin-1 will be administered as a single IV dose of 25 μg/$m^2$. Many drugs are dosed according to the size of the patient’s body, represented as either their weight (in kg) or their body surface area (BSA) in square meters ($m^2$). BSA is estimated through the use of one of a few formulas that takes into account a patient’s height and weight. For illustrative purposes, a 170 pound male who is 5’ 9” tall would have a BSA of 1.94 $m^2$. Were this patient to be in the Phase 2a clinical trial they would be administered 48.5 μg of bryostatin-1. To put that into perspective, Aricept® (donepezil) is dosed at 5, 10, or 23 mg, which is approximately 100-500 times more than a bryostatin-1 dose! This is indicative of the fact that bryostatin-1 is highly potent, and very little of the drug is necessary to see a physiologic effect. This is also the reason that the 18 g (18,000,000 μg) of bryostatin-1 isolated in 1991 has been enough for all the clinical trials performed thus far with the compound.

In addition to the Phase 2a clinical trial, bryostatin-1 has also been utilized in a compassionate use basis for three patients thus far suffering from advanced AD, as there are little to no treatment options available to these patients. While the FDA does not allow Neurotrope to discuss the details of these cases, it should be noted that the company is planning on expanding the use of bryostatin-1 in these patients through the compassionate use mechanism.

***…DHA-CP6 is a follow-on PKC activator…***

Given the fact that bryostatin-1 is both difficult to purify and produce synthetically, researchers have devoted a large amount of time to developing other PKC activators. Researchers at BRNI have developed a new chemical family of polyunsaturated fatty acid (PUFA) analogs, which appear to be effective in the activation of PKC. One such compound, DHA-CP6, is a derivative of docosahexaenoic acid and has been shown to specifically activate PKCε (Nelson *et al*., 2009).




*Source*: Nelson *et al*., 2009

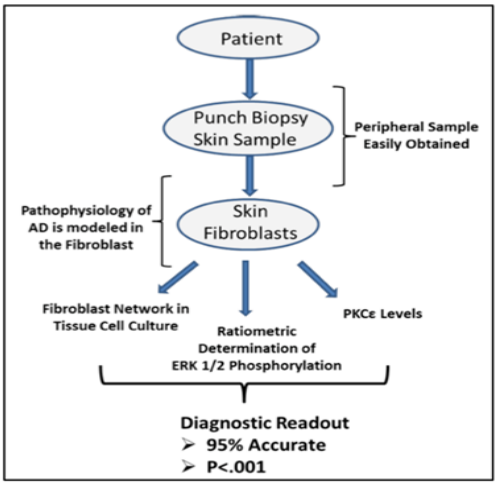
The compound was tested *in vitro* against cells that express large quantities of beta-amyloid with results showing that DHA-CP6 reduced the intracellular and secreted levels of beta-amyloid by 60-70%. These results appeared to be due to an increase in the activity of ECE, and not by activating nonamyloidogenic APP metabolism.

Additional preclinical work is continuing with DHA-CP6 and other PUFA analogs. Neurotrope believes that the PUFA analogs represent a potential source for follow-on drug candidates and they have identified DHA-CP6 as a second clinical compound. The company plans to initiate clinical trials with DHA-CP6 in 2015.

**Development of an AD Diagnostic Test**

The 2011 revised guidelines for diagnosing AD incorporate the use of biomarkers to aid in the diagnosis of the disease. Currently there are no validated biomarkers that have been proven to differentiate AD patients from those healthy individuals or from those suffering from other forms of dementia.

As part of the research into the role of PKC in AD, scientists at BRNI have identified a series of three peripheral biomarkers whose expression is mediated by PKC that are highly correlated with the presence of AD. Utilizing fibroblasts obtained from a small skin biopsy, a series of *in vitro* tests are performed to amplify the expression of the biomarkers. Research shows that skin fibroblasts display the same basic pathophysiology indicative of AD as neurons in the central nervous system. The three biomarkers are: PKC, Erk1/2 phosphorylation ratios, and the fibroblast morphology test.



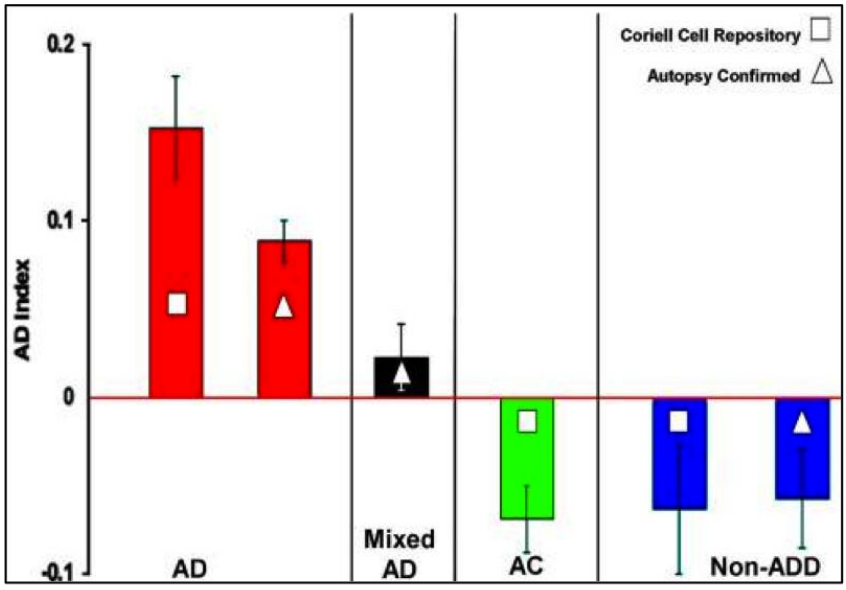

*Source*: Neurotrope, Inc.

Based on these biomarkers, an AD index was developed that takes into account quantified phosphorylated Erk1/2 ratios from skin fibroblasts after stimulation with bradykinin, which activates PKC pathways. The AD index is calculated as follows:

$$\text{AD index} = [\text{P-Erk1/P-Erk2}]^{BK+} - [\text{P-Erk1/P-Erk2}]^{BK-}$$

*Source*: Khan *et al*., 2006

Representative results of the AD index are shown below utilizing samples from patients with AD, mixed AD, age-matched controls (AC), and non-AD dementia patients (i.e., Parkinson's disease and Huntington's disease). The difference between AD and AC samples was highly significant ($P < 0.00001$).




*Source*: Khan *et al*., 2006

To date, there have been four studies of the diagnostic test in a total of 140 individuals, including AD patients, patients with mixed dementia, patients with non-AD dementia, and healthy controls, including 51 patients with autopsy-confirmed diagnoses, were reported to show sensitivity (correctly diagnosing AD) >= 97% and specificity (correctly identifying individuals without AD) >= 96%. These results compare favorably with other published diagnostic tests, and represent one of the largest evaluations to include autopsy-confirmed diagnoses. The company is currently evaluating the market potential for the diagnostic test and whether it is feasible to produce the test without a therapeutic product approved to go along with it (i.e. a companion diagnostic or standalone diagnostic).

**AD market analysis**

Using U.S. Census data along with a population based study (Hebert *et al*., 2013), we estimate that there are approximately five million individuals suffering from AD in the U.S. in 2014. There are another approximately 200,000 individuals who have Familial Alzheimer's Disease. In the next ten years the number of patients with AD is forecasted to increase to approximately six million. Interestingly, only about half of those who meet the diagnostic criteria for having AD have received a diagnosis from a physician (Boustani *et al*., 2003).

As mentioned previously, there are five compounds that are approved for the treatment of AD. Revenues from these five drugs are expected to total $5.2 billion in revenue in 2014, which is a decrease from revenues of $5.9 billion in 2009. The market is expected to continue to decrease over the next few years as all of the available AD therapeutics have lost patent protection and are available as generics. The current medications cost anywhere from $650 to $4000 per year, with the difference mostly due to generic versus branded versions of the drugs.

With Phase 2 studies occurring in 2014 and 2015, we forecast Phase 3 studies to commence in 2016 with approval of the drug in 2019. A number of drugs approved for treating AD have generated in excess of $1 billion per year in revenue. With strong clinical trial results that show clear and robust efficacy in treating patients with AD, bryostatin-1 would be a blockbuster with at least $1 billion, and perhaps as much as $5 billion, per year in revenue.

**Additional Orphan Indications**

Neurotrope has signed a world-wide, exclusive license agreement with the Icahn School of Medicine at Mount Sinai for the use of bryostatin-1 in the treatment of Niemann-Pick Type C Disease (NPC), a rare disease that mostly affects children who are afflicted with Alzheimer's-like symptoms. NPC is an orphan disease as it affects approximately 3,000 individuals in the U.S. The disease is part of a group of inherited metabolic disorders known as lysosomal storage diseases. Normally, lipids are broken down to provide energy, however in NPC harmful quantities of lipids accumulate in the spleen, liver, lungs, and brain. Symptoms include brain degeneration, loss of muscle tone, feeding and swallowing difficulties, and slurred speech. Since PKC is involved in synaptogenesis, bryostatin-1 treatment has the potential to obviate the neuronal degeneration seen in NPC patients.

Neurotrope is also investigating the use of bryostatin-1 in other neurodegenerative diseases such as Fragile X syndrome (FXS), a genetic condition that results in a range of developmental problems including learning disabilities and cognitive impairment. The condition affects approximately 1 in 4,000 men and 1 in 8,000 women in the U.S. Nearly all cases of FXS are caused by a mutation in the FMR1 gene, which encodes the fragile X mental retardation protein (FMRP). FMRP is thought to play a role in synaptic plasticity, which is the ability of synapses to form new connections in the processes of learning and memory. Activation of PKC by bryostatin-1 could represent a novel treatment option for these patients through the induction of synaptogenesis.

**Intellectual Property**

Neurotrope was started in 2012 to commercialize technology developed at BRNI. The company has entered into a Technology License and Services Agreement with BRNI, whereby Neurotrope was granted an exclusive, non-transferable, world-wide, royalty-bearing license to certain patents owned by BRNI to develop, use, manufacture, market, and sell products or services for therapeutic or diagnostic applications for AD or other cognitive dysfunctions. The license provides for BRNI to continue to use the licensed intellectual property to engage in research and development and other non-commercial activities.

The license calls for Neurotrope to pay BRNI a royalty up to 5% of revenues collected in connection with the licensed technology, depending upon the percentage of Neurotrope that is owned by Neuroscience Research Ventures, Inc., which is an affiliate of BRNI. The amount of the royalty increases as the percentage ownership by Neuroscience Research Ventures, Inc. decreases according to the following table. According to the company's 10-K, Neuroscience Research Ventures, Inc. currently owns 43.5% of outstanding common stock.

| Percentage of NRV I's Equity Ownership of Neurotrope | Royalty Rate |
|---|---|
| Greater than or equal to 47.5% | 2.0% |
| Greater than or equal to 45.0% and less than 47.5% | 2.5% |
| Greater than or equal to 40.0% and less than 45.0% | 3.0% |
| Greater than or equal to 35.0% and less than 40.0% | 3.5% |
| Greater than or equal to 30.0% and less than 35.0% | 4.0% |
| Greater than or equal to 25.0% and less than 30.0% | 4.5% |
| Less than 25.0% | 5.0% |

**Financial Position**

As of June 30, 2014, the company held $12.0 million in cash and investments and is only burning around $1.5 million per quarter. That means cash as of September 30, 2014 is still above $10 million. We find this to be sufficient to fund operations well into 2016.

**Potential Risks to our Thesis**

Bryostatin-1 does not show efficacy in clinical trials. As mentioned previously, the failure rate for AD treatments is above 99%, thus any compound entering the clinic as a potential AD therapeutic faces very steep odds for eventually gaining approval. Thus, an investment in Neurotrope is extremely high risk, albeit with the potential for an extremely high reward if bryostatin-1 is shown to be efficacious in treating AD. This risk is somewhat mitigated by the fact that Neurotrope will also be pursuing orphan drug indications including Neimann Pick Type C and Fragile X Syndrome. In addition, should bryostatin-1 not prove effective in treating AD, the company does have the AD diagnostic test that has shown impressive results in early testing. We have not included this asset in our valuation but it is something that the company could monetize in the future.

DHA-CP6 does not show efficacy or has serious adverse side effects in clinical trial testing. DHA-CP6 is the follow on chemical to bryostatin-1 with preclinical tests showing that DHA-CP6 selectively activates PKCε. However, the compound is still in the preclinical stage, thus the company has no clinical data at this point and thus there is the chance that the compound could perform differently in clinical subjects than it does *in vitro*.

## MANAGEMENT PROFILES

**Charles S. Ramat – Chief Executive Officer**
Mr. Ramat is currently a private investor and has extensive operational and general business experience in several industries including: biotechnology, medical devices, commercial finance, real estate and mobile communications. Until December 2013, Mr. Ramat was a principal investor and consultant to Continental Home Loans, the third largest FHA mortgage originator in New York State, with operations in 22 states and with annual originations and servicing portfolio both in excess of $1 billion. Since 2006, he has developed land, principally 1,000 acres of private gated communities, with a strong emphasis on environmentally friendly practices, in upstate New York. From 2002 to 2005, Mr. Ramat was the President and Chief Executive Officer of Kushner Companies, managing 25,000 apartment units and a commercial portfolio exceeding five million square feet. Mr. Ramat has served on various business company boards, philanthropies and trade organizations. Mr. Ramat graduated cum laude with a B.A. from Yeshiva University and earned a Juris Doctor degree from Columbia Law School.

**Paul E. Freiman – Chairman**
Mr. Freiman has extensive pharmaceutical and biotechnology industry operating experience as a board member and Chief Executive Officer of private and publicly traded companies and is a pharmacist. Mr. Freiman is currently an independent pharmaceutical and biotechnology industry consultant. He serves as Chairman of Chronix BioMedical and is a member of the NovaBay Pharmaceutical Board of Directors. In the past, Mr. Freiman served on the Boards of Otsuka America, Inc. and several biotechnology companies based in the United States and Singapore. Prior to his current consulting and board member roles, Mr. Freiman was a partner of Burrill Brasil Investimentos based in Rio de Janiero. He also served as President and Chief Executive Officer of Neurobiological Technologies, Inc. and as a member of its Board of Directors. Mr. Freiman also served as Chairman and Chief Executive Officer of Syntex Corporation which was sold to The Roche Group for $5.3 billion during his tenure. He is credited with much of the marketing success of Syntex's lead product, Naprosyn®, and was responsible for moving the product to over-the-counter status, marketed as Aleve®. Aleve® currently generates approximately $400 million in annual revenues worldwide. Mr. Freiman served on the Board of the Pharmaceutical Research and Manufacturers Association of America (PhRMA) and was its Chairman. Mr. Freiman received a B.S. in pharmacy from Fordham University and an honorary doctorate from the Arnold & Marie Schwartz College of Pharmacy.

**Robert Weinstein – Chief Financial Officer**
Mr. Weinstein joined the company in June 2013 as its acting Chief Financial Officer. He has extensive accounting and finance experience, spanning more than 25 years, as a public accountant, investment banker, healthcare private equity fund principal and Chief Financial Officer. From September 2011 to current, Mr. Weinstein has been an independent consultant for several healthcare companies in the pharmaceutical and biotechnology industries. From March 2010 to August 2011, he was the Chief Financial Officer of Green Energy Management Services Holdings, Inc., a publicly-traded energy consulting company. From August 2007 to February 2010, Mr. Weinstein served as Chief Financial Officer of Xcorporeal, Inc., a publicly-traded, development-stage medical device company which was sold in March 2010 to Fresenius Medical USA, the largest provider of dialysis equipment and services worldwide. Mr. Weinstein received his MBA degree in finance and international business from the University of Chicago Graduate School of Business, is a Certified Public Accountant (inactive), and received his BS degree in accounting from the State University of New York at Albany.

**Dr. Daniel Alkon, Chief Scientific Officer**
Dr. Alkon received his undergraduate degree in chemistry in 1965 at the University of Pennsylvania. After earning his M.D. at Cornell University and finishing an internship in medicine at the Mt Sinai Hospital in New York, he joined the staff of the National Institutes of Health where during his 30-year career he became a Medical Director in the U.S. Public Health Service at the NINDS and Chief of the Laboratory of Adaptive Systems. In 1999, Dr. Alkon then became the founding Scientific Director of the Blanchette Rockefeller Neurosciences Institute and occupies the Toyota Chair in Neuroscience at the Institute. In this position he and his team conduct multidisciplinary research on the molecular and biophysical mechanisms of memory and memory dysfunction in psychiatric and neurological disorders, particularly Alzheimer's disease. He is also a Professor at BRNI and a Professor of Neurology at West Virginia University. As an internationally recognized pioneer in research on brain-based neural networks and the molecular basis of memory, he has authored hundreds of scientific articles as well as several books including Memory Traces in the Brain by Cambridge University Press, and the popular book Memory's Voice by Harper Collins.

## VALUATION AND RECOMMENDATION

We are initiating coverage of Neurotrope, Inc. (OTC: NTRP) with a Buy rating and a price target of $1.50.

Neurotrope is currently focused on developing bryostatin-1 for the treatment of Alzheimer's disease (AD) and has recently initiated a Phase 2a clinical trial to test the compound in AD patients. The company also has a diagnostic test for AD that has been tested in a total of 140 individuals, including AD patients, patients with mixed dementia, patients with non-AD dementia, and healthy controls. The total also includes 51 patients with autopsy-confirmed diagnoses. Results showed sensitivity (correctly diagnosing AD) ≥ 97% and specificity (correctly identifying individuals without AD) ≥ 96%, both of which compare quite favorably with other published diagnostic tests.

We have not included the AD diagnostic test in our valuation model as Neurotrope has limited resources and thus it is unclear to us at this time whether the company will move forward with development. However, particularly given the impressive data shown thus far, we believe this asset decreases the risk associated with an investment in Neurotrope and offers some upside should the company decide to focus on its development or otherwise monetize it through a licensing or partnership deal.

***…A novel AD treatment target…***

Recent research into developing AD therapeutics has focused on eliminating beta-amyloid, the toxic protein aggregate that accumulates in the brains of Alzheimer's patients and is thought to contribute to the disease mechanism. A number of high profile drugs that were designed to specifically eliminate beta-amyloid have failed Phase 3 trials, most notably solanezumab (Eli Lilly), bapineuzamab (Pfizer), and crenezumab (Genentech). In addition, from 2002-2012 the failure rate for AD drugs in clinical trials (i.e., the percentage of drugs that entered clinical testing but did not go on to get approved by the FDA) was 99.6%. Clearly, the current thinking in regards to AD therapeutics needs changing and alternate treatment targets will be necessary to find successful AD treatments.

Pre-clinical data has shown that protein kinase C (PKC) is vital for memory formation, thus a significant amount of research has gone into understanding if PKC is involved with AD, as the first clinical manifestation of AD is memory loss. Interestingly, PKC was shown to be involved in amyloid precursor protein (APP) processing, which is the protein that ultimately gives rise to beta-amyloid. In addition, activation of PKC promotes the non-amyloidogenic processing of APP and was shown to decrease levels of beta-amyloid in pathogenic mouse models of AD. These results lead investigators to develop novel PKC activators that could be tested as AD treatments.

***...A novel AD therapeutic …***

Neurotrope is developing bryostatin-1, a natural compound isolated from the marine organism *Bugula neritina*, for the treatment of AD. The compound activates PKC, specifically the isoforms PKCα and PKCε, both of which have been shown to be important for synaptogenesis (the creation of new synapses in the brain) and could potentially alleviate a number of the pathological processes of AD by decreasing the levels of beta-amyloid, decreasing neuron death, and increasing synaptic function.

Bryostatin-1 was originally developed as a cancer therapeutic, however it did not show the efficacy necessary in Phase 2 trials to advance to Phase 3 testing as either a single agent or in combination with various chemotherapies. Nevertheless, the compound was tested in over 1200 patients, thus there is a significant amount of data related to toxicity, dosing, and pharmacokinetics.

A number of preclinical studies have shown the potential for bryostatin-1 as an AD therapeutic. The results of those studies pointed to a central role of PKCε in maintaining neuron structure and function as well as decreasing the overall level of beta-amyloid. Thus, activators of PKCε, including bryostatin-1, may work through multiple mechanisms in treating AD, and could lead to not just the alleviation of symptoms but also delaying or even stopping the progression of the disease.

***…Little downside risk, with the potential for tremendous upside…***

A novel approach to treating AD is certainly warranted, and the preclinical data generated thus far appears to support the notion of utilizing bryostatin-1 to activate PKCε. We are encouraged by the preclinical data that has been generated thus far, and there is certainly enough data to justify moving bryostatin-1 into the clinic as an AD therapeutic.

Neurotrope has just begun Phase 2a testing with bryostatin-1 in AD patients, thus there is no clinical data available on the compound as an AD treatment. Thankfully, we will not have to wait too long for clinical data, as topline results from the single-dose Phase 2a trial will be available in the first quarter of 2015. In addition, data from the multiple-dose Phase 2a study could be available by the summer of 2015. Thus, it should be known in a relatively short amount of time whether bryostatin-1 holds promise as an AD treatment, however we do not necessarily expect to see signs of efficacy from these early studies.

Neurotrope currently has a market cap of only $14 million on a non-diluted basis, thus there is very little downside risk to investing in the company at this juncture. As of June 30, 2014, the company held $12.0 million in cash and investments and is only burning around $1.5 million per quarter. That means cash as of September 30, 2014 is still above $10 million. We find this to be sufficient to fund operations well into 2016. Should bryostatin-1 prove to be an effective AD treatment the upside potential is enormous, as there are few treatment options available for AD patients. We believe a safe and efficacious AD drug would easily generate sales in excess of $1 billion. Thus, while an investment in Neurotrope is very high risk, the potential return on an investment at this point is enormous.

***…Valuation methodology for Neurotrope…***

We model that upon successful completion of the Phase 2a study, Neurotrope would initiate a Phase 2b study in 2015, with a Phase 3 trial commencing in 2016, and an NDA filing in 2018 with approval of bryostatin-1 in 2019. We apply a 25% discount rate to future earnings and give a probability of success at 20%. While a 20% probability of success may be optimistic in some people's opinions based on the 99% past failure rate of AD treatments in the clinic, we believe it is warranted due to:

1) The novel mechanism of action of bryostatin-1 in treating AD. No other compound tested as a treatment for AD has targeted PKC, thus it may not be appropriate to think of success probabilities for bryostatin-1 in terms of past failures, as this approach to treating AD has not been attempted previously.
2) The large amount of positive preclinical data. The use of bryostatin-1 in treating AD is supported by a significant amount of preclinical data that has been accumulated for a number of years. Thus, there is both a theoretical and a data driven justification for testing a PKC modulator as an AD therapeutic.
3) The continued use of bryostatin-1 in a compassionate use basis for patients suffering from advanced AD. The company is not allowed to discuss the results seen with compassionate use, however the fact that the program is continuing to enroll patients is a positive sign.

We forecast that bryostatin-1 would cost $5000 per year, which is a slight premium to the branded AD treatments that are currently available. Lastly, we forecast free cash flow as 60% of gross revenues. This leads to a value of approximately $80 million for bryostatin-1. Neurotrope currently has approximately 21.9 million common shares outstanding with 23 million shares of convertible preferred stock and 8.5 million warrants. This leads to a fully diluted share count of approximately 53.4 million. Dividing the value we assign to bryostatin-1 by the fully diluted share count leads us to a fair value of approximately $1.50 per share and we are assigning a 'Buy' rating to the stock.

## PROJECTED FINANCIALS

**Neurotrope, Inc.**
Income Statement

| Neurotrope, Inc. | 2013 A | Q1 A | Q2 A | Q3 E | Q4 E | 2014 E | 2015 E | 2016 E |
|---|---|---|---|---|---|---|---|---|
| **Bryostatin** | **$0** | **$0** | **$0** | **$0** | **$0** | **$0** | **$0** | **$0** |
| *YOY Growth* | - | - | - | - | - | - | - | - |
| **Licensing & Other Revenues** | **$0** | **$0** | **$0** | **$0** | **$0** | **$0** | **$0** | **$0** |
| *YOY Growth* | - | - | - | - | - | - | - | - |
| **Total Revenues** | **$0** | **$0** | **$0** | **$0** | **$0** | **$0** | **$0** | **$0** |
| CoGS | $0 | $0 | $0 | $0 | $0 | $0 | $0 | $0 |
| *Product Gross Margin* | - | - | - | - | - | - | - | - |
| R&D | $1.4 | $0.7 | $0.8 | $0.8 | $0.9 | $3.2 | $3.7 | $4.5 |
| *% R&D* | - | - | - | - | - | - | - | - |
| SG&A | $6.2 | $1.0 | $1.2 | $1.3 | $1.4 | $5.0 | $6.0 | $9.0 |
| *% SG&A* | - | - | - | - | - | - | - | - |
| Other expenses | $0 | $0 | $0 | $0 | $0 | $0 | $0 | $0 |
| Operating Income | ($7.6) | ($1.7) | ($2.0) | ($2.1) | ($2.3) | ($8.1) | ($9.7) | ($13.5) |
| *Operating Margin* | - | - | - | - | - | - | - | - |
| Total Other Income | $0.0 | $0.0 | $0.0 | $0.0 | $0.0 | $0.0 | $0.0 | $0.0 |
| Pre-Tax Income | ($7.6) | ($1.7) | ($2.0) | ($2.1) | ($2.3) | ($8.1) | ($9.7) | ($13.5) |
| Taxes & Other | $0.0 | $0.0 | $0.0 | $0.0 | $0.0 | $0.0 | $0.0 | $0.0 |
| *Tax Rate* | *0%* | *0%* | *0%* | *0%* | *0%* | *0%* | *0%* | *0%* |
| Net Income | ($7.6) | ($1.7) | ($2.0) | ($2.1) | ($2.3) | ($8.1) | ($9.7) | ($13.5) |
| | | | | | | | | |
| **Reported EPS** | **($0.35)** | **($0.08)** | **($0.09)** | **($0.10)** | **($0.10)** | **($0.37)** | **($0.39)** | **($0.45)** |
| *YOY Growth* | - | - | | | | - | | - |
| Shares Outstanding | 21.7 | 21.9 | 21.9 | 22.0 | 22.2 | 22.0 | 25.0 | 30.0 |

*Source: Zacks Investment Research, Inc.* *Jason Napodano, CFA*

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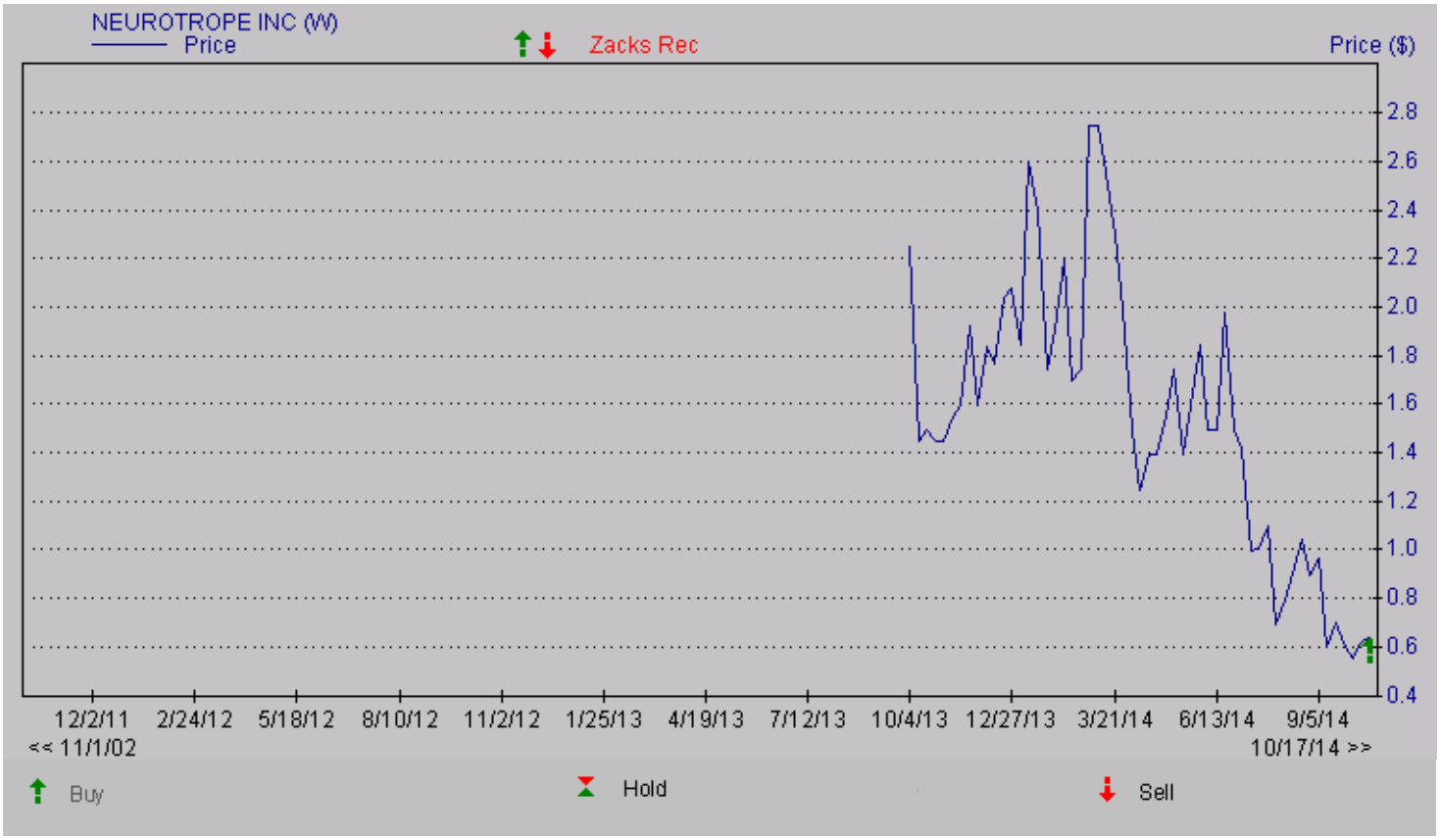


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