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Rethinking the approach to treat Alzheimer's disease

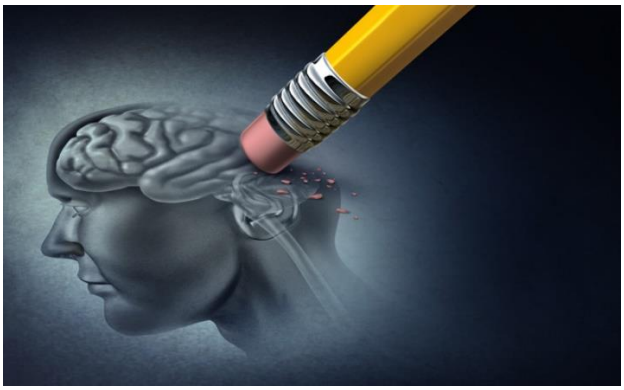
Both scientists and physicians are still wrestling with the idea of how to identify the biological drivers that are responsible for the early onset of neurodegenerative diseases. Alzheimer's disease (AD), in particular, is extremely challenging to treat because it develops slowly and by the time the symptoms manifest, it is too late to initiate therapy.

Several companies are rethinking their approach to treat this debilitating disease; looking beyond the usual suspects and trying to identify therapeutic agents that could provide beneficial therapeutic outcomes. One such company, Neurotez Inc., is focused on developing recombinant leptin to address AD in its early stages. Preclinical studies have shown favorable results but the candidate needs to be further investigated in clinical studies. Since leptin is an already approved drug that is being repurposed for the treatment of AD, it could follow an accelerated development pathway, given the known mechanism of action and well-established safety and toxicity profile. A safe drug with proven efficacy could potentially garner a significant market share, if and when commercialized.

We have provided an in depth discussion on the etiology of Alzheimer's disease and elaborate on the currently available and developing treatment options, with a focus on Neurotez and its drug candidate.

Alzheimer's Disease

Exhibit 1: Alzheimer's Disease



(Source: Shutterstock)

AD is a degenerative neurological disease that results in the irreversible loss of neurons, specifically from the cortex and hippocampal area of the brain. The three stages of AD proposed by the guidelines from National Institute on Aging (NIA) and the Alzheimer's Association are: preclinical AD, Mild Cognitive Impairment (MCI), and dementia[1]. The root cause of AD remains unknown as this neurodegenerative disease exhibits pleiotropic effects. It is likely that a combination of genetic, environmental and lifestyle factors cause AD. The clinical characteristics of AD include episodic memory loss, cognitive deficits, aphasia, disorientation to

[1] Dementia is a neurocognitive disorder caused by a significant damage to neurons. It interferes with cognitive function resulting in declining memory and thinking skills and a person's ability to perform every day activities.

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physical surroundings, paranoia, aggression, hallucinations and limitations in social behavior. Early symptoms are caused by synaptic dysfunction and loss are key features in AD as the disease progresses, thus initiating successive memory loss. The gradual degeneration and death of neurons is accompanied by the accumulation of pathological proteins in the brain. The brain of patients with advanced AD show inflammation, dramatic shrinkage from cell loss and widespread debris from dead and dying neurons. In advanced stages of the disease, the patient is non-ambulatory and has trouble functioning independently.

Studies have been conducted to investigate whether AD is caused by reduced synthesis of the neurotransmitter acetylcholine. Although the studies in the brains of patients with AD showed substantial deficits in the enzyme responsible for the synthesis of acetylcholine, medications to treat acetylcholine deficiency have not shown strong efficacy in treatment. Genetic mutations result in the formation of Aβ plaques and its accumulation is believed to trigger inflammation, tau-tangle formation, synapse dysfunction and eventually cell death, which ultimately leads to dementia. The ε4 allele of the apolipoprotein E (APOE) gene is the most studied genetic factor proposed to cause AD. The one copy of the APOEε4 increases the risk of the disease by 3x and having two copies by 15x. In addition, mutations in the TREM2 gene are associated with a three to five times higher risk of developing AD.

Although scientists are still trying to determine the underlying cause of this disease, amyloid beta (Aβ) and phospho-tau are widely viewed as two of the key factors in AD etiology. Scientists believed that the disease evolves from the extracellular accumulation of Aβ in the form of proteinaceous plaques as well as from hyperphosphorylation of tau proteins intracellularly. Accumulation of Aβ is known to interfere with synaptic communication while neurofibrillary tangles disrupt the function of microtubules. Further, the microtubules disintegrate causing the collapse of the neuron's transport system. Just as with Aβ plaques, tau tangles are readily observable in brains of those affected by AD. Both these effects compromise the synaptic integrity resulting in increasing impairment in cognitive function and insidious memory loss. Consequently, scientists hypothesized that Aβ is the primary culprit causing the disease and developed drugs to address its removal. However, there has been a long list of failures in late-stage drug development because Aβ is *not* the first step in disease progression for different forms of AD.

Diagnosis and treatment…

The spectrum of symptoms associated with AD remains an enigma to the physicians and the scientists likewise. Diagnosis is based on a comprehensive medical evaluation of cognitive and behavioral changes as well as understanding family history. The pathological signs in AD include neuronal loss, neuroinflammation, insulin resistance or mitochondrial dysfunction. Physicians also use radiologic scans to determine the cause of the disease.

Researchers believe that early detection of AD is critical to slowing, stopping and even preventing the disease. Better efficacy in treatment could be obtained when therapy commences at the time the neurons begin to dysfunction. Treating the patient in late stages of the disease, where the patient has significant neuronal damage, has proven ineffective.

The FDA has approved two types of pharmacologic treatments — cholinesterase inhibitors (donepezil (Aricept®), galantamine (Razadyne®/Razadyne® ER), rivastigmine (Exelon® Patch), tacrine (Cognex®)) and memantine (Namenda®) — to treat the cognitive symptoms of AD. A reduction in the activity of the cholinergic neurons is a well-known characteristic of AD. Acetylcholinesterase inhibitors are designed to reduce the rate at which acetylcholine 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. 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.

The efficacies of the approved therapies are somewhat limited in magnitude due to the heterogeneity in patient groups as well as disease being in the late stage. Current modes of therapy attempt to remove/reduce lesions but have not been entirely successful due to the inability of such agents to therapeutically address ongoing synaptic loss. Further, these medications are toxic at the high doses.

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. There are a few companies who are attempting to address AD by employing novel mechanisms. Neurotrope, Inc. (NASDAQ: NTRP), a biopharmaceutical company, is focusing on the development of a product platform for the treatment of AD. Its lead product candidate is bryostatin, a natural product isolated from a marine invertebrate organism, a bryozoan called Bugula neritina. The company also develops bryostatin for other neurodegenerative or cognitive diseases and dysfunctions, such as Fragile X syndrome, multiple sclerosis, and niemann-pick type C diseases. Studies conducted using 20 mcg Brystostatin-1 showed overall good tolerance and a 5.0 improvement in SIB score compared to baseline in the Moderate Stratum cohort in the non-Namenda group. This score was maintained throughout the treatment period and for four weeks after completion of the study. INmune Bio, Inc. (NASDAQ: INMB) is developing an inhibitor of soluble TNF-α for which it has received a $1 million grant from the Alzheimer's Association to conduct a Phase I clinical trial in Alzheimer's patients with mild to moderate disease. A number of preclinical studies have shown an association between inflammation and AD pathology in several animal models of AD. Elevated levels of TNF are found in the serum of AD patients. An elevated TNF serum levels are associated with an increased risk of conversion from MCI to AD. Their candidate XPro 1595 can cross the blood-brain barrier to selectively inhibit sTNF and alleviate inflammation to lower the risk for AD. Resverlogix Corp. (RVX.TO), the Calgary-based company developing the drug, apabetalone, that blocks the expression of pro-inflammatory cytokines, particularly chemokines and cell adhesion receptors known to rev up vascular inflammation. Apabetalone is being developed to quell vascular inflammation by targeting TNFα-driven inflammatory responses. Apabetalone targets several genes that are downstream of TNFα, a primary regulator of inflammation. ProMIS Neurosciences Inc. (PMN.TO) is developing a monoclonal antibody (mAb) that targets epitopes specific to toxic oligomers implicated in the development of AD. Its lead product candidates include PMN310, a monoclonal antibody (mAb); PMN350, a mAb targeting on toxic amyloid beta oligomers (AßO); and PMN330, a monoclonal antibody targeting toxic prion-like forms of AßO for AD. PMN310 has demonstrated a high degree of binding to toxic oligomers without binding to non-toxic forms of Aß. Clinical studies have also shown that PMN310 has the potential for greater therapeutic potency versus other Aß-directed antibodies. The company is also developing therapeutics targeting the neurotoxic form of the tau protein in AD.



Snapshot

Neurotez, a spin-off from Columbia University, was founded in 2005 by Dr. Nikolaos Tezapsidis, a veteran in the field of biomedical research. Dr. Tezapsidis served as a faculty member in New York University Medical School and at Mount Sinai School of Medicine before becoming the President & CEO of Neurotez. The company is developing an analog of leptin, Memtin™, as a hormone replacement therapy for AD patients or as a prophylactic therapy for those at risk. Memtin could have the potential to impact a significant number of patients with AD where there is currently an unmet medical need.

Mounting evidence suggests that leptin, a naturally occurring hormone and metabolically active compound previously tested in obesity, is decreased in patients suffering from AD. Also, cognitive deterioration in AD patients correlates strongly with a decline in circulating leptin levels. Scientists at Neurotez view AD as a metabolic disorder, and are developing a recombinant leptin in the treatment of AD. Thus far, Dr. Tezapsidis has recruited industry experts on the advisory board, conducted R&D programs and established a strong patent portfolio (more than 20 patents globally issued and pending) for their compound.

It has been shown in studies that administration of leptin in preclinical models inhibits both the production of Aβ and the phosphorylation of tau protein, both *in vitro* and *in vivo*. In 2009, the National Institutes of Health (NIH) awarded a Small Business Innovation Research (SBIR) grant to Neurotez in the amount close to $3M to initiate the clinical development of Memtin as a novel therapy for AD. In preclinical studies using transgenic mouse models of AD, trials have demonstrated that the administration of leptin significantly improves cognition. The preclinical findings strongly support the likelihood that leptin supplementation could retard or halt the progression of AD and may even preclude or delay the onset of cognitive decline in prodromal AD individuals.

The firm is planning to meet with the regulatory authorities to seek guidance on the continued development of Memtin. Memtin, a repurposed candidate, protected by intellectual property for their active pharmaceutical ingredient (API) could have a potentially cheaper and quicker route to market. Once Memtin studies demonstrate efficacy, established safety and low cost (can be manufactured without post-translational modification for activity) over the current standard of care, both patients and Neurotez are likely to benefit. While we think the company could potentially obtain partial governmental support or other grants from disease-focused associations to continue development, we anticipate Neurotez will require ~$10M as Memtin moves into the clinic. The company also has other candidates in the discovery stages; however, we believe that they will garner attention once management gets Memtin off the ground.

Neurotez's drug candidate is currently in relatively early development stages. However, considering the huge unmet need that exists in the AD space, we would not be surprised to see Neurotez strike a partnership deal with a bigger industry player. This could provide financing upfront that could help Neurotez with furthering development plans for other candidates.

Leptin replacement therapy offers new hope for Alzheimer's

Several studies have been conducted to study the relation between obesity and dementia. Adipose tissue increases in obesity, causing decrease in cerebral vascularization, especially to the hippocampal regions of the brain. The hippocampus has a high baseline metabolic activity and is most vulnerable to ischemia, resulting in declining loss of memory. Leptin, a polypeptide endocrine hormone released by the adipose tissue, is responsible for fat mobilization and regulation of energy homeostasis. Growing evidence indicates that leptin is a pleiotropic hormone that exhibits diverse central actions including its ability to regulate hippocampal synaptic plasticity; more specifically, cellular events including synaptogenesis, neurogenesis, axon growth and neuroprotection.

Exhibit 2: 3D Structure of Leptin



(Source: Shutterstock)

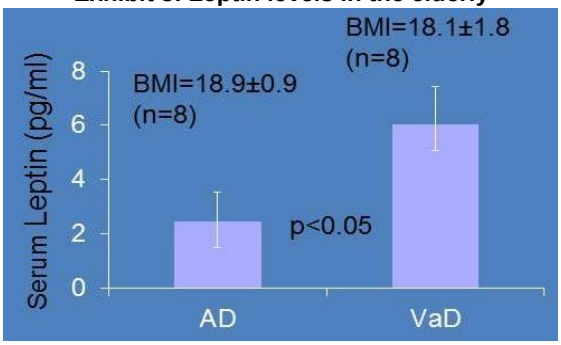
…Preclinical research supports the use of leptin in AD…

There have been a number of preclinical studies published that have shown the association between leptin and cognitive function. A selection of these publications is discussed below.

- *Serum Leptin levels in elderly*
  Low leptin levels have been implicated as a direct cause of cognitive impairment, particularly in AD. Consequently, the absence of beneficial effects of leptin in the central nervous system (CNS) would predispose to cognitive impairment. Epidemiological studies on a small group of patients[2], have clearly shown alterations in the circulating levels of leptin in the elderly, as AD patients exhibit significantly lower levels of leptin in serum than normal people. The results have since been corroborated with larger patient populations. In a prospective study with 2,871 elderly people, followed over 4 years, demonstrated that those in the high leptin group had lesser likelihood of developing cognitive decline than those in the lower group[3].

[2] Power DA, Noel J, Collins R et al. Circulating leptin levels and weight loss in Alzheimer's disease patients. Dement. Geriatr. Cogn. Disord. 12, 167–170 (2001).
[3] Holden KF, Lindquist K, Tylavsky FA et al. Serum leptin level and cognition in the elderly: findings from the Health ABC study. Neurobiol. Aging 30(9), 1483–1489 (2009).

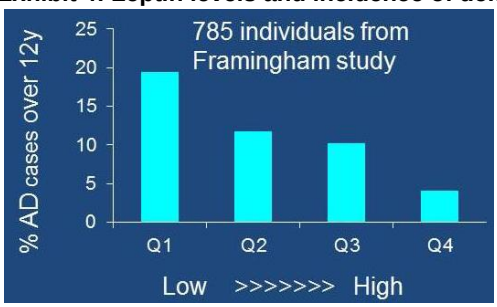
Exhibit 3: Leptin levels in the elderly



(Source: Neurotez Presentation)

Another small study in 41 patients provided the first evidence that increased leptin levels in serum are associated with a reduced number of CD34(+) progenitor cells in AD patients. These findings demonstrate the combined involvement of leptin and CD34(+) progenitor cells in the pathogenesis of AD. The study clearly showed the correlation between low circulating plasma leptin levels and circulating CD34(+) progenitor cells which suggests important molecular link between vascular risk factors and early AD[4].

Exhibit 4: Leptin levels and incidence of dementia



(Source: Neurotez Presentation)

A third study followed 785 healthy individuals from the Framingham cohort for 8.3 years and showed that individuals with lower circulating leptin also have a greater risk of developing dementia[5]. In addition, the incidence of dementia decreases gradually across increasing leptin quartiles; thus a person with a baseline leptin level in the lowest quartile (Q1) had a 25% risk of developing AD, whereas the corresponding risk for a person in the top quartile (Q4) was only 6%. These data underscore the significance of leptin in cognition and AD pathology.

- *Leptin targets amyloid beta, tau protein and improves memory*

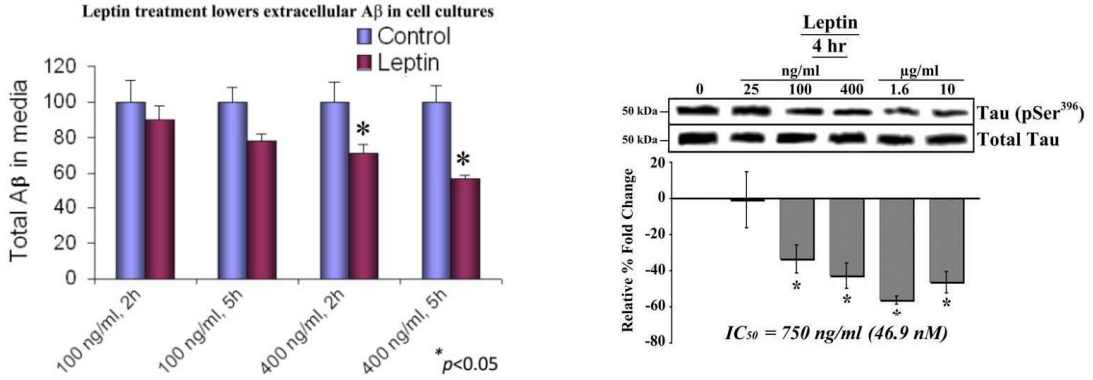
  Leptin has been shown to directly regulate both in vitro and in vivo levels of Aβ[6,7]. Leptin is reported to attenuate Aβ levels in neurons by inhibiting β-secretase activity and thereby reducing Aβ production. Chronic leptin administration has been reported to increase apolipoprotein E–dependent Aβ uptake into the cell and modulate bidirectional Aβ kinesis, reducing concentrations extracellularly[8]. Leptin also has the capacity to alter the levels of hyperphosphorylated tau. By inhibiting GSK3β (a tau kinase), leptin reduces protein tau phosphorylation, reducing the formation

[4] Bigalke B, Schreitmuller B, Sopova K et al. Adipocytokines and CD34+ progenitor cells in Alzheimer's disease. PLoS ONE 6(5), e20286 (2011).
[5] Lieb W, Beiser AS, Vasan RS et al. Association of plasma leptin levels with incident Alzheimer disease and MRI measures of brain aging. JAMA 302(23), 2565–2572 (2009).
[6] Fewlass DC, Noboa K, Pi-Sunyer FX et al. Obesity-related leptin regulates Alzheimer's Ab. FASEB J. 18(15), 1870–1878 (2004).
[7] Greco SJ, Bryan KJ, Sarkar S et al. Leptin reduces pathology and improves memory in a transgenic mouse model of Alzheimer's disease. J. Alzheimers Dis. 19(4), 1155–1167 (2010).
[8] S. J. Greco, S. Sarkar, J. M. Johnston et al., "Leptin reduces Alzheimer's disease-related tau phosphorylation in neuronal cells," Biochemical and Biophysical Research Communications, vol. 376, no. 3, pp. 536–541, 2008.

and accumulation of neurofibrillary tangles in neuronal cells[9,10]. The ability of leptin to reduce both Aβ accumulation and hyperphosphorylation of tau, independently and directly, underscores the underlying therapeutic potential[11].

Hippocampus is a key area implicated in memory processing and AD pathology. Contextual fear conditioning is a form of learning that is generally thought to be hippocampus-dependent whereas cued fear conditioning is thought to be hippocampus-independent. Since it has been proven that leptin has neurotrophic and neuroprotective properties, it is hypothesized that leptin signaling deficits may lead to susceptibility to AD-related neurotoxic conditions. Leptin primarily target hippocampus, and plays an important role in synaptic plasticity process, in memory preservation, and has pro-cognitive effects[12]. These effects are mediated by modulating glutamate receptors: the ionotropic α-amino-3-hydroxy-5-methyl-4- isoxazolepropionic acid (AMPA) and N-methyl-D-aspartate (NMDA), that are involved in long-term potentiation (LTP) and in long-term depression (LTD). Leptin enhances LTP and decreases LTD, increasing the efficacy of excitatory synaptic transmission[13], increasing the synaptic density and rescuing memory deficits. In addition to ameliorating AD pathology, treatment of CRND8 transgenic mice with leptin improved cognitive performance in object recognition and contextual and cued fear conditioning tests compared to saline-treated littermates[14].

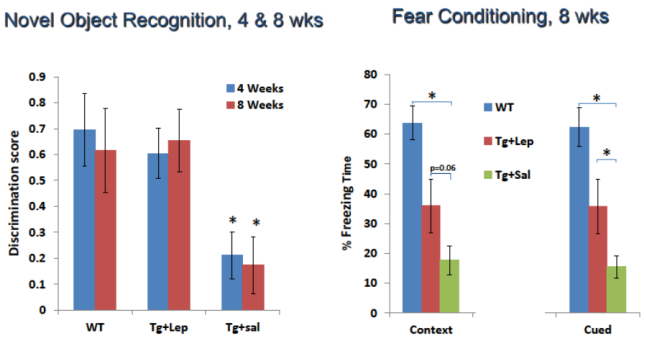
Exhibit 5: Leptin targets Aβ and tau protein



(Source: Neurotez Presentation)

[9] S. J. Greco, S. Sarkar, G. Casadesus et al., "Leptin inhibits glycogen synthase kinase-3β to prevent tau phosphorylation in neuronal cells," Neuroscience Letters, vol. 455, no. 3, pp. 191– 194, 2009.
[10] Greco SJ, Sarkar S, Johnston JM et al. Leptin reduces Alzheimer's disease-related tau phosphorylation in neuronal cells. Biochem. Biophys. Res. Comm. 376(3), 536–541 (2008).
[11] S. J. Greco, K. J. Bryan, S. Sarkar et al., "Leptin reduces pathology and improves memory in a transgenic mouse model of Alzheimer's disease," Journal of Alzheimer's Disease, vol. 19, no. 4, pp. 1155–1167, 2010.
[12] Harvey J (2013) Leptin regulation of neuronal morphology and hippocampal synaptic function. Front. Synaptic Neurosci. 5:3
[13] McGregor, G., et al (2018b). Regulation of hippocampal synaptic function by the metabolic hormone, leptin: Implications for health and neurodegenerative disease. Front. Cell. Neurosci. 12:340.
[14] S. A. Farr, W. A. Banks, and J. E. Morley, "Effects of leptin on memory processing," Peptides, vol. 27, no. 6, pp. 1420–1425, 2006.

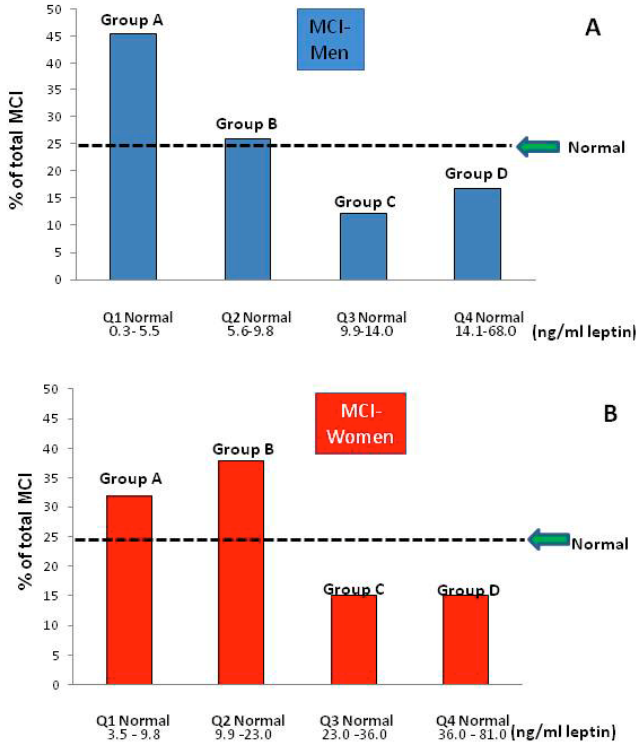
Exhibit 6: Leptin therapy improves memory in animal models



(Source: Neurotez Presentation)

Researchers at Neurotez pooled data from the Alzheimer's Disease Neuroimaging Initiative (ADNI) program[15]. Analysis revealed that plasma leptin levels were lower in individuals with MCI or AD than for normals. Approximately 70% of subjects with MCI had plasma leptin levels lower than the median values of normal subjects. Additionally, half of these subjects carried at least one APOEε4. The data suggested that plasma leptin deficiency offers an indication of potential CNS leptin deficiency, further supporting the hypothesis that plasma leptin levels could be used as a diagnostic marker for MCI or AD.

Exhibit 7: Low Plasma Leptin Levels are Associated with MCI and AD



(Source: Neurotez Presentation)

[15] Johnston JM, et al. Low plasma leptin in cognitively impaired ADNI subjects: gender differences and diagnostic and therapeutic potential. Curr Alzheimer Res. 2014;11(2):165-174.

A few interventional trials were conducted in order to investigate whether leptin administration could help to diminish or reverse the detrimental changes in patients.

- *Cognitive benefits after leptin supplement*
  Within 2 weeks of initiation of leptin replacement, patients exhibited a change in behavior and interpersonal attitudes from a baseline of infantile and docile to assertive and adult-like[16]. Matochik's team conducted a study that showed increase in gray matter tissue in the anterior cingulate gyrus, the inferior parietal lobule, and the cerebellum after 6 months of leptin replacement therapy. The increase in leptin levels were maintained for over 18 months[17]. In a study conducted over a three-year period by London et all[18], results revealed that withholding and restoration of leptin resulted in gray matter increase in the posterior half of the left thalamus, particularly in the pulvinar nucleus. Another study[19] which followed a patient for two years, found that leptin treatment improved neurocognition.

The findings from the above discussed studies suggest that leptin can have sustained effects on tissue composition in the human brain and broaden the potential spectrum of leptin's influence beyond feeding behavior and endocrine function. Leptin has also been shown to have proliferative effects on neurons[20] increasing hippocampal volume and neuronal progenitor number, as well as reducing neurodegeneration caused by AD-related mutations. Thus, leptin, 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 Aβ and tau tangles.

[16] Licinio J, et al, (2004) Phenotypic effects of leptin replacement on morbid obesity, diabetes mellitus, hypogonadism, and behavior in leptin-deficient adults. Proc Natl Acad Sci U S A 101, 4531-4536.
[17] Matochik, JA, Effect of Leptin Replacement on Brain Structure in Genetically Leptin-Deficient Adults, The Journal of Clinical Endocrinology & Metabolism, Volume 90, Issue 5, 1 May 2005, Pages 2851–2854
[18] London ED, Short-term plasticity of gray matter associated with leptin deficiency and replacement J. Clin. Endocrinol. Metab., 96 (2011), pp. E1212-E1220
[19] Paz-Filho GJ, Leptin replacement improves cognitive development PLoS ONE, 3 (2008), p. e3098
[20] Paz-Filho G, Wong ML, Licinio J. The procognitive effects of leptin in the brain and their clinical implications. Int. J. Clin. Pract. 64(13), 1808–1812 (2010).

Development and Regulatory Process

Neurotez has developed a human recombinant leptin, called Memtin, and investigating it as a potential therapeutic molecule in the treatment of neurodegeneration. The company also has two additional products in the discovery stage. Neurons depend on presenilin 1 (PS1) and Cytoplasmic linker protein 170 (CLIP 170) to generate Aβ. Peptides, NT1 and NT2, disrupt the PS1/CLIP-170 interaction which is associated with both decreased secretion of endogenous Aβ and decreased uptake of exogenous Aβ and could ultimately become valuable preventative therapies for early-onset familial AD cases. Additionally, the company is developing two screening platforms, Screen A and Screen B, to identify new molecular entities that can be adapted to repurpose drug candidates at all stages of development. Neurotez intends to explore these and other opportunities as soon as capital becomes available.

Exhibit 8: Development Pipeline



(Source: Neurotez Presentation)

Memtin to enter clinic

The company has raised about $4.5M, including support from NIH SBIR grant. The financial resources have thus far been used to conduct mechanism of action studies, filing for intellectual property and manufacturing of a clinical-grade leptin product. The drug candidate is now ready for GMP studies. The company anticipates the need of another $10M to conduct drug manufacturing using CMOs, IND-enabling studies as well as to file an IND application over the course of the next one year. Management intends to use a CRO to leverage their expertise to streamline the efficiencies for developing their candidate.

The preclinical studies have already demonstrated that leptin can reduce levels of Aβ and phosphorylated tau protein in neuronal cells within hours in culture. Accumulating evidence from numerous sources strongly supports that leptin therapies for a number of CNS disorders are being developed. Currently, in order to gain partnership or collaborate, the company is in need of clinical data for validation of their candidate.

Based on the criteria implemented in studies, Memtin can be developed to treat a subgroup of Alzheimer's patients who have low leptin levels. People with MCI are at a higher risk for progressing to AD. In fact, MCI has been shown to develop into AD at a rate of 12%–15% per year.

The initial clinical trial would entail enrolling early stage patients, a small group of MCIs, to be treated for 28 days and evaluated for CSF biomarker changes. In order to demonstrate that the drug candidate is effective, an impact in cognitive parameters need to be recorded. Biomarkers have scientific and regulatory value as they might improve the accuracy of diagnosis of AD and could serve indirectly to measure disease severity. Due to this reason biomarkers need to have a scientific rationale, should change with disease progression in longitudinal observational studies and must be measurable and reproducible. In a slowly progressing disease such as AD, biomarker readout is normally slow. For this reason, Neurotez is using a digital application called MemTrax, a memory test developed by Dr. Ashford that allows scoring of episodic memory levels

easily. The test is associated with age and could reveal indications of possible MCI, dementia, or AD. It is proposed to be part of the trial to track and monitor the patient's progress.

Management intends to seek approval for the use of Memtin as a treatment for hypoleptinemia in AD patients. This could provide the basis for accelerated and/or conditional approval following short clinical trials that demonstrate the drug candidate's ability to safely increase a surrogate endpoint. Post-marketing surveillance could be implemented to assess Memtin's potential as a long-term therapy or preventive approach for those at risk.

Regulatory scenario

There is an emerging question regarding AD drug development as to whether the treatment failed due to the drugs being administered too late in the disease progression to reverse the pathological damage in patients. Perhaps the trial inclusion criteria needed to be revised. Indeed, in 2018, the FDA released guidance to include patients with very early-stage AD in studies and with appropriate endpoints. To support marketing approval, the regulatory authority suggests demonstrating a biomarker evidence that likely predicts clinical benefit, employing surrogate markers as well as having a single endpoint.

Neurotez has made a concerted effort to repurpose the drug candidate which enables an accelerated development pathway as compared to traditional drug discovery, given the known mechanism of action and well-established, already proven safety and toxicity profile. Literature reports reveal that drug repurposing has lower attrition rate than *de novo* development. The success rates from Phase I to marketing approval for pre-approved drugs is 33%, a huge improvement over their *de novo* counterparts, whose rates are only at 10%[21,22]. Since leptin is an already approved medication with an established safety profile, Memtin can enter clinic directly in a Phase II study to assess its effectiveness in MCI patients, via the 505(b)(2) regulatory pathway. This approval pathway was established in 1984 under the Drug Price Competition and Patent Term Restoration Act (Hatch-Waxman Act). The regulatory approval relies on published literature and the FDA's notes regarding safety of the approved product, fewer supporting studies are required, resulting in shorter timelines and reduced expenses. Also, this process completely eliminates any attrition rate associated with the discovery, preclinical and Phase I stages in development. Memtin could then traverse a single positive pivotal trial for regulatory clearance and marketing approval followed by a Phase IV study, which is a post marketing surveillance study, to gather clinical data from a broad patient population. Additionally, the entire process from Phase II until approval significantly reduces the time to market. For instance, sildenafil (Viagra) was originally tested for treating coronary artery disease (CAD), hypertension and angina pectoris but two years later was approved by the FDA to treat erectile dysfunction. Similarly, exenatide (Byetta) was prescribed used for Type 2 diabetes, but later repurposed to treat non-diabetic obese patients. Another drug, Crizotinib, was investigated as a repurposed drug based on its ALK-inhibiting properties in non-small cell lung cancer (NSCLC) in just a four-year timeframe. In 1960, amantadine was developed as an antiviral drug to treat influenza but eventually came to be utilized for early symptomatic treatment of Parkinson's disease (PD). The above-mentioned cases have led to new treatments, thus helping in the fight against AD.

Additionally, researchers at Neurotez have developed modified versions of leptin, and are developing further novel IP for Memtin as a new molecular entity. Consequently, repurposing an approved drug such as leptin, for a secondary indication in AD patients, with reformulation or other modifications would definitely benefit Neurotez as they own the IP for Memtin.

Leptin is currently approved in the U.S. and Japan as a drug for generalized lipodystrophy, a rare, complex and clinically heterogeneous disorder characterized by the widespread loss of adipose tissue and associated metabolic abnormalities including hyperglycemia, dyslipidemia, fatty liver and hypertriglyceridemia. Despite the potentially abbreviated clinical development path for repurposed drugs, there remains a significant commitment in the need to demonstrate the efficacy of Memtin in this new indication and safety if higher doses Memtin are required for treatment. Further, since Memtin is Neurotez's own product, it would gain 12 years of market exclusivity as per the Biologics Act in the U.S. We think Memtin could well be shielded from

[21] Neuberger A (2019) Drug Discovery Today. 24(1): 1-3

[22] Ashburn TT, Thor KB. Drug repositioning: identifying and developing new uses for existing drugs. Nat Rev Drug Discov (2004) 3(8):673–83

competitors using the regulatory exclusivities provided by the Hatch-Waxman Act as well as the protection from IP. Based upon the benefits provided by repurposed drug candidate, Memtin could also enjoy sufficient market exclusivity to profit from initial investments.

Outlook

MCI is a term used to describe individuals who fall between the cognitive changes of aging and early dementia. Annual incidence for MCI ranges between 12% and 18% in persons older than 60 years of age, with prevalence increasing with age. Persons with MCI have a heightened risk for further cognitive decline. There are currently 5.7M people with AD in the U.S. and a staggering 14M globally. Researchers are of the belief that MCI is the prodromal stage of AD. The U.S. Census Bureau projects that the U.S. population aged 85 years and older, are most likely to have AD. Total Medicare and Medicaid spending, including medical expenses and supportive care, for people with AD and other dementias is estimated to be about $200 billion.

A total of 244 unique compounds, including symptomatic agents (36.5%), disease-modifying small molecules (35.1%) and immunotherapies (18.4%), were investigated in a total of 413 trials conducted between 2002 and 2012 in the U.S. Anti-Aβ therapies have dominated AD trials, with 70 of 146 (combined small molecules and immunotherapies) compounds, compared with 13 compounds against tau-related mechanisms and 62 compounds with neuroprotective approaches. During the period reviewed, 54 compounds progressed to Phase III studies with only one compound receiving the FDA nod (1.8% success rate). Overall, 244 compounds were tested from 2002-2012 with one approved for marketing. Excluding the 14 compounds that were still in clinic, *AD drug development during the reviewed time period had a failure rate of 99.6%.*

Current pharmacological therapies are limited in their ability to manage the symptoms or slow the progression of the disease. Further, they sometimes can lead to some severe side effects. Greater efficacy remains to be the top unmet need in Alzheimer's treatment.

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. Despite the sales of all AD medications declining due to patent expiration, the market for AD therapeutics is expected to continue to grow due to the aging populations in the developed economies. The current medications cost anywhere from $650 to $4000 per year, with the difference mostly due to generic versus branded versions of the drugs.

Currently, there are a few players investigating their candidates in this space. Swiss AC Immune has developed an Abeta-focused vaccine called ACI-24, which has been both effective and safe in pre-clinical models of AD. Aducanumab, from Biogen, is a human monoclonal antibody that is being studied for the treatment of AD in a Phase IIIb clinical trial. Eisai and Biogen's joint investigational asset, BAN2401, is a humanized monoclonal antibody for AD, that binds to large oligomers, called protofibrils, and neutralizes their damage to brain cells. BAN2401 treatment demonstrated brain amyloid reduction in the core Phase II study. Cotexyme’s asset, COR388, is a novel bacterial protease inhibitor designed to target a specific bacterium, Porphyromonas gingivalis (P. gingivalis), which has been identified in the brain tissue and cerebrospinal fluid of Alzheimer’s patients. It is currently in the Phase II/III GAIN trial for treatment of mild to moderate AD.

Neurotez’s candidate Memtin is still in an early developmental stage. Although substantial effect has been demonstrated in preclinical studies, it remains to be seen whether Memtin will be effective in humans. As per the Pharmaceutical Research and Manufacturers of America (PhRMA), clinical trial processes are typically both expensive and time-consuming and could take six to seven years to complete. Although Neurotez’s drug candidate is a repurposed drug which offers accelerated approval pathway, it is yet to enter the clinic and might be a few years before it reaches commercialization stage. Whether the disease-modifying properties of leptin therapy will produce a clinically relevant reduction in cognitive decline remains to be seen.

Management has indicated that they believe an IND filing could potentially occur in 2H 2020. We expect that cash required for IND-enabling studies, IND application and toxicology studies will be in the $2.5 million - $4 million range. We like to note that Memtin, being a biologic, would require expertise and are expensive to manufacture. The firm expects to engage third-party contract manufacturers for production of Memtin for clinical studies in accordance with cGMP standards.

We believe that Memtin would likely be categorized as a BLA. Phase I studies could commence in 2021, depending on timing of IND approval. We believe there are a number of inflection points that could occur over the next two years, which could trigger a development and/or commercialization partnership for Neurotez's drug candidate. If Neurotez can continue to show that Memtin can improve cognitive function, especially the ability to improve performance in various memory tasks, it may have meaningful potential for the treatment of prodromal AD patients. If eventually approved and commercialized, this could command superior labeling and pricing.

As it relates to other indications, Neurotez is still in discovery stage and primarily focused on getting Memtin off the ground. Therefore, other programs may sit on the back burner until management finds a partner who is interested in pushing forward. As the initial focus is with Memtin, most expenses are expected to be related to this program.

Partnerships and Collaborations

Dr. Wesson Ashford has been a collaborator and advisor to Neurotez since 2006. Dr. Ashford is a Senior Research Scientist at the Stanford/VA Aging Clinical Research Center and Alzheimer's Center, a Clinical Professor affiliated with the Department of Psychiatry and Behavioral Sciences at Stanford University, the Director of the WRIISC at the VA Palo Alto Health Care System and a staff psychiatrist at the VAPAHCS. Dr. Ashford is an authority on AD, MCI and traumatic brain injury (TBI). He is experienced in the recognition, diagnosis, and treatment of these and numerous other neuropsychiatric disorders. He has contributed major innovations to the fields of cognitive testing, brain imaging and dementia treatment. Neurotez intends to use a digital application called MemTrax, a memory test developed by Dr. Ashford to score episodic memory levels easily, in their clinical trials.

Neurotez also signed a Memorandum of Understanding (MOU) with Cytox Group Limited to optimize the design of the clinical trial involving Memtin. Additionally, the company will use Cytox's help in developing a genetic screen to identify suitable candidates for Memtin treatment and understand the influence of genetic backgrounds on treatment responses.

Summary

Leptin, a naturally occurring hormone with a pluripotent and well-established safety profile, offers an alternative therapy for AD patients and those presenting low leptin levels. Neurotez is developing its patented compound Memtin, a recombinant leptin for the treatment of AD.

As of May 31, 2020, the company has limited amount of cash with minimum burning rate. We think the company definitely needs financial assistance of approximately $10M to fund operations well into 2021.

A number of preclinical studies have shown the potential for leptin as an AD therapeutic. The results of those studies point to a central role of leptin in maintaining neuron structure and function as well as decreasing the overall level of beta-amyloid. Thus, leptin replacement therapy may work in treating AD, and could lead to not just the alleviation of symptoms but also delaying or even stopping the progression of the disease. We are encouraged by the preclinical data that has been generated thus far, and there is certainly enough data to justify moving Memtin into the clinic as an AD therapeutic.

As Neurotez has limited financial resources, it is unclear at this time when the company will move forward with clinical development. However, particularly given the favorable preclinical data obtained from studies thus far, we believe this asset offers some upside.

Valuation Based on Comps…
The neuroscience sector remains attractive for dealmaking, despite the multitude of expensive late-stage clinical trial failures, particularly for AD. Despite the mounting failures with amyloid-focused approaches to AD, Biogen (NASDAQ: BIIB) is investigating its candidate, aducanumab (an anti-amyloid antibody), in a Phase III trial. Cognitive improvements have been demonstrated using a small trial and has raised some expectations that this candidate might succeed where others have failed. The antibody was licensed at the discovery phase from Neurimmune Therapeutics in 2007 for $380 million in upfront and potential milestone payments, as well as royalties on net sales. Biogen expanded its AD portfolio through a 2014 collaboration with Eisai in which the company gained rights to two of Eisai's assets in return for funding and options on Biogen programs. In 2017, Biogen spread its Alzheimer's bets by bringing in a Phase I anti-tau antibody from Bristol-Myers Squibb (NASDAQ: BMY) for $300 million upfront and a total projected deal value of more than $1.2 billion.

In 2016, Allergan Plc (NYSE: AGN) acquired Chase Pharmaceuticals, a clinical-stage biopharmaceutical company developing treatment for AD, for an upfront payment of $125 million and additional potential regulatory and sales milestone payments for CPC-201, a cocktail consisting of acetylcholinesterase inhibitor (AChEI), donepezil, and the peripherally acting cholinergic blocker, solifenacin.

In 2019, AbbVie (NYSE: ABBV) paid $205 million in cash and made a $20 million equity investment to collaborate with Alector (NASDAQ: ALEC) to generate new Alzheimer's drug. If AbbVie opts to take on development of AL003 from Phase III stage, Alector could receive up to $986 million in additional milestone payments.

Therefore, we would not be surprised if in the future Neurotez were to strike a favorable partnership deal with an industry giant. We remain positive on Neurotez for three reasons: First, it is pursuing a new avenue to treat AD. While no precedent exists, new understanding of the biology of the disease makes the approach reasonable. Secondly, Memtin has a few advantages over other AD candidates in that it is a repurposed drug and has an established safety and toxicity profile. Consequently, the development costs are reduced, which could accelerate the path to approval. Memtin is well protected with patents surrounding its formulation. Therefore, combining the intellectual property (IP) and regulatory exclusivities, Memtin could be successful commercially. Lastly, the huge unmet need and potential market for a disease-modifying drug is tremendous. We think that any drug candidate that yields favorable clinical trial results to treat AD could potentially gain substantial market share once approved. There is a significant unmet need for an effective

AD treatment and large addressable market for Neurotez. The presence of a solid leadership team as well as strategic advisory board provides credibility to Neurotez's mission.

In 2016. the Securities and Exchange Commission (SEC) had made revisions to the JOBS (Jump-Start Our Business Start-Ups) Act which allows anyone to purchase equity shares in small businesses that advertise their investment opportunities on crowdfunding platforms. Investors are not required to be accredited, but some limits apply. We note that in order to help meet the need for working capital and grow the business, Neurotez's founder and CEO, Dr. Tezapsidis, is using Netcapital, a crowdfunding platform to raise up to $2.5 million through Reg. CF and Reg D. Boston, MA-based Netcapital is an online private securities platform that helps emerging companies raise capital through investment opportunities to the public. Management is exploring other opportunities and is in conversation with prospective investors about raising additional financing of the order of $10M+.

Leadership Team

Nikolaos Tezapsidis, PhD
Chief Executive Officer
James Harris, MBA
Chief Financial Officer
J. Wesson Ashford, MD, PhD
Chief Medical Officer
George Perry, PhD
Chief Scientific Officer
Jukka Karjalainen, MD, PhD
Chief Operating Officer
Hamish McArthur, PhD
Manufacturing Chief Officer
Jane M. Johnston, PhD
VP of Operations

Board of Directors

Bob Oliver, MBA

Thomas J. Humphries, MD, FACP, FACG, AGAF

Nikolaos Tezapsidis, PhD

J. Wesson Ashford, MD, PhD

George Perry, PhD

James Harris, MBA

Advisory Board

Lex Van der Ploeg, PhD

Arthur Klausner, MBA

Nikolaos Robakis, PhD

Robert Winkler, MD

Julio Licinio, MD, FRANZCP

Daniel P. Van Kammen, MD, PhD, FACNP

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