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Review Article

# Facilitation of the Brain Hepatocyte Growth Factor/C-Met Receptor System: A New Approach to Treat Alzheimer's Disease?

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**Abstract**

Alzheimer's disease (AD) is a major neurodegenerative disorder presently without adequate treatment that is increasing in frequency as life expectancy increases. New therapeutic approaches are needed to slow and hopefully reverse disease progression. Neurotrophic agents such as nerve growth factor and brain-derived neurotrophic factor have received research attention concerning their potential to treat AD but have not progressed to clinical trials due to their reasonably large size, inability to penetrate the blood-brain barrier (BBB), and the high cost of synthesis. This review focuses on one over looked neuro trophin, hepatocyte growth factor (HGF) that acts via the Type 1 tyrosine kinase receptor c-Met to mediate stem cell differentiation, synaptogenesis, neurogenesis, and protect against tissue insults in a wide range of cell types including neurons. We have determined that the brain angiotensin and HGF/c-Met systems interact in such a way that angiotensin IV (Ang IV)-based analogs including Nle$^1$-AngIV, Dihexa and others stimulate HGF dimerization which is a prerequisite to binding at the c-Met receptor. These analogs have shown the ability to facilitate the formation of new functional synaptic connections in hippocampal slices, promote neurogenesis, and augment memory consolidation and retrieval in animal models of AD. This family of compounds represents a new class of drugs with lead candidates that are orally active, penetrate the BBB sufficiently to reach therapeutic concentrations, and reverse memory deficits seen in animal models of dementia.

**Keywords:** Alzheimer's disease, Angiotensin IV, Nle$^1$-Angiotensin IV, Dihexa, $AT_4$ receptor subtype, Hepatocyte growth factor, c-Met receptor

## Abbreviations

Aβ: Amyloid Beta Protein; ACE: Angiotensin Converting Enzyme; Ach: Acetylcholine; ACSF: Artificial Cerebrospinal Fluid; AD: Alzheimer's Disease; Ang: Angiotensin; Ang(3-7): Angiotensin II(3-7); AngI: Angiotensin I; AngII: Angiotensin II; AngIII: Angiotensin III; AngIV: Angiotensin IV; AP-A: Aminopeptidase A; AP-N: Aminopeptidase N; ARBs: Angiotensin Receptor Blockers; $AT_1$: Angiotensin Receptor Subtype 1; $AT_2$: Angiotensin Receptor Subtype 2; $AT_4$: Angiotensin Receptor Subtype 4; BBB: Blood-Brain Barrier; BDNF: Brain-Derived Neurotrophic Factor; Carb-P: Carboxypeptidase P; CBF: Cerebral Blood Flow; CIP: Chromatin Immunoprecipitation; c-Met: Met Type 1 Receptor Tyrosine Kinase; D: Aspartate; ERK: Extracellular Signaling-Regulated Kinase; F: Phenylalanine; FDA: Federal Drug Administration; H: Histidine; HGF: Hepatocyte Growth Factor; HIV: Human Immunodeficiency Virus; I: Isoleucine; Ile: Isoleucine; K: Lysine; L: Leucine; LTP: Long-Term Potentiation; LVV-H7: Leucine-Valine-Valine-Hemorphin-7; MAPK: Mitogen Activated Protein Kinase; MCI: Mild Cognitive Impairment; N: Asparagine; NGF: Nerve Growth Factor; Nle: Norleucine; NMDA: N-Methyl-D-Aspartate; NO: Nitric Oxide; NSAIDs: Non-Steroidal Anti-Inflammatory Drugs; NT3: Neurotrophin-3; NT4: Neurotrophin-4; P: Proline; Phe: Phenylalanine; ψ: $CH_2$-$NH_2$; PO: Propyl Oligopeptidase; Pro: Proline; P13K: Phosphatidylinositol 3-Kinase; R: Arginine; RAS: Renin-Angiotensin System; SK: Scatter Factor; SPH: Serine Proteinase Homology; Tyr: Tyrosine; V: Valine; Y: Tyrosine

## Introduction

Alzheimer's disease (AD) is characterized by elevated levels of amyloid plaques and neurofibrillary tangles that predispose progressive neuron losses in memory related structures including neocortex, piriform cortex, hippocampus and the nucleus basalis of Meynert [1,2]. AD currently afflicts approximately 5.3-6 million Americans with annual treatment and care costs estimated at $70-100 billion [3,4]. These patients respond only marginally to presently available FDA approved drugs [5,6]. In the absence of a breakthrough in treatment the number of AD patients is predicted to reach 16 million in the U.S. by mid-century with associated health care costs in excess of $500 billion [4,7]. Such costs will cripple our health care system. The goal of providing an effective treatment for AD has been elusive due to the complexity of the disease process and resulting inability to identify reliable biomarkers. In addition, AD diagnostic indicators are present in other clinical conditions including vascular disease, frontotemporal dementia, Parkinson's disease and HIV infection induced dementia, as well as normal aging [8-11]. These considerations make drug development to treat AD a very challenging task. A treatment designed to delay the onset




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**Table 1:** FDA approved drugs to treat Alzheimer's disease and AngIV-based analogs that interact with the HGF/c-Met receptor system.

| Drug/Compound | Mechanism of Action | Clinical Target | Reference |
|---|---|---|---|
| Namenda | NMDA receptor antagonist | Mid-stage AD | [15-17] |
| Cholinesterase inhibitors | Interfere with degradation of Ach | Early- mid-stage AD | [5,6] |
| Monoclonal antibodies against Aβ | Block intracellular accumulation of Aβ1-42 | Early-stage AD | [18-20] |
| Anti-inflammatories | Reduce inflammation, promote neuro protection | Early- mid-stage AD | [21-24] |
| Nle$^1$-AngIV, Dihexa | Increase HGF dimerization and facilitate binding to c-Met | Proposed early-stage AD | [45,81,93] |
| Norleual-AngIV | Reduce HGF dimerization and inhibit binding to c-Met | Proposed treatment against carcinomas | [29,30,78] |

of symptoms would prolong and maintain the patient's quality of life and significantly reduce health care costs. De la Torre [12] has calculated that postponing the onset of AD by 5 years could reduce patient numbers by upwards of 50%. Recently it has been reported that the presence of two positive biomarkers for AD, β-amyloid and neuro degeneration, and the use of in vivo amyloid imaging agents, offer pre-diagnostic predictive value regarding the trajectory of cognitive change [13,14]. These findings promise to be of major importance regarding diagnosis but not prevention of AD.

## Current drugs to treat Alzheimer's disease

Available FDA approved drugs to treat AD fall into two major classes (Table 1): 1) Namenda (memantine HCl) acts as an N-methyl-D- aspartate (NMDA) receptor antagonist designed to limit glutamate excitotoxicity and resulting neuronal damage [15-17]. Namenda has shown positive results in some patients particularly if given in combination with acetylcholinesterase inhibitors [5,6]. 2) Cholinesterase inhibitors such as Razadyne, Exelon, Cognex and Aricept disrupt the degradation of acetylcholine (Ach) thus extending the half-life and availability of this neurotransmitter acting at central cholinergic muscarinic and nicotinic receptors. Additional treatment approaches being vigorously pursued include monoclonal antibodies designed to attenuate and block the production and deposition of insoluble amyloid β (Aβ) protein fragments resulting from amyloid precursor protein proteolysis. It is suggested that dysfunction between Aβ production and clearance causes damaging accumulations of cellular Aβ, coupled with hyper phosphorylation of neuronal tau protein resulting in neurofibrillary tangle formation [18-20]. Anti-inflammatories and anti-oxidants are also being tested including non-steroidal anti-inflammatory drugs (NSAIDs, eg. naproxen, rofecoxib, ibuprofen, indomethacin, tarenflurbil, diclofenac/misoprostol), luteolin, ferulic acid to protect against neurotoxicity [21-24].

An interim treatment strategy designed to offset neuron losses by stimulating synaptogenesis in existing neurons and the formation of new functional neurons would be advantageous in slowing disease progression. The neurotrophic agents capable of facilitating synaptogenesis and neurogenesis include nerve growth factor (NGF), brain-derived neurotrophic factor (BDNF), neurotrophin-3, and neurotrophin-4 [25,26]. To date BDNF has received the most attention [27]. Our laboratory has focused on an overlooked neurotrophic factor, hepatocyte growth factor (HGF), and found it to be more potent than BDNF when activated by angiotensin IV (AngIV)-based analogs [28]. These analogs allosterically mimic dimerization/activation, a prerequisite to binding to the Type 1 tyrosine kinase receptor c-Met [29,30]. This review initially describes the renin-angiotensin system's (RAS) role in memory formation followed by descriptions of neurotrophic agents and the HGF/c-Met system. We conclude with details concerning the development and testing of AngIV-based analogs that activate the brain HGF/c-Met receptor system and show promise as anti-dementia agents in animal models of AD. We also detail the limitations of these molecules.

## The renin-angiotensin system and memory

The classic RAS is recognized for its role in regulating blood pressure and body water balance as mediated by the octapeptide angiotensin II (AngII) acting at the G-protein coupled $AT_1$ receptor subtype(40-42 kDa; [31]). This AngII/$AT_1$ receptor system has been a major focus regarding the development of antihypertensive drugs and its role in inflammation, oxidative stress and tissue remodeling [32,33]. These latter processes contribute to the "neuronal inflammation response" a key factor in neurodegenerative diseases including AD [34-36]. A role for AngII in memory was suggested some time ago focused on AngII interacting with the $AT_1$ receptor subtype (reviewed in [2,37-39]). More recently members of our laboratory discovered the $AT_4$ receptor protein (160-190 kDa) and the importance of the hexapeptide AngIV acting at this receptor subtype in the facilitation of memory acquisition and retrieval [28,40,41]. Subsequent findings indicated that the learning and memory enhancing effects originally attributed to AngII acting at the $AT_1$ receptor were due to the enzymatic conversion of AngII to AngIII and then to AngIV acting at the $AT_4$ receptor (Figure 1) [42-44]. It is now clear that AngII interferes with performance by animal models of AD on most memory tasks while AngIV facilitates performance.

The analogNle$^1$-AngIV (Norleucine-YIHPF) overcomes the memory impairments evidenced by animal models of AD. Specifically, intracerebroventricular treatment with Nle$^1$-AngIV reverses memory deficits due to: 1) application of the cholinergic muscarinic receptor antagonist scopolamine; 2) kainic acid-induced lesions of the hippocampus; 3) perforant path knife-cuts; 4) embolic stroke due to carotid artery injection of microspheres; 5) treatment with the angiotensin receptor blocker (ARB) losartan; and 6)ischemia resulting from transient four-vessel occlusion (reviewed in [45]). This latter finding is particularly important given the possibility that cerebral hypoperfusion may act as a precursor to the development of mild cognitive impairment (MCI), a condition that often precedes the onset of AD [46]. To date we have not tested an AngIV-based analog for efficacy in a transgenic mouse model of AD. Consistent with the above behavioral results [$^{125}$I] AngIV has been auto radiographically localized within structures known to mediate cognitive processing including human neocortex, hippocampus, and the basal nucleus of Meynert [2,47].

## Neurotrophic agents

Over the past 60 years several neurotrophic agents have been identified in the mammalian brain and their roles in neurogenesis, neurite outgrowth and neural protection have been studied (reviewed in [48]). Nerve growth factor (NGF) was the first to be discovered

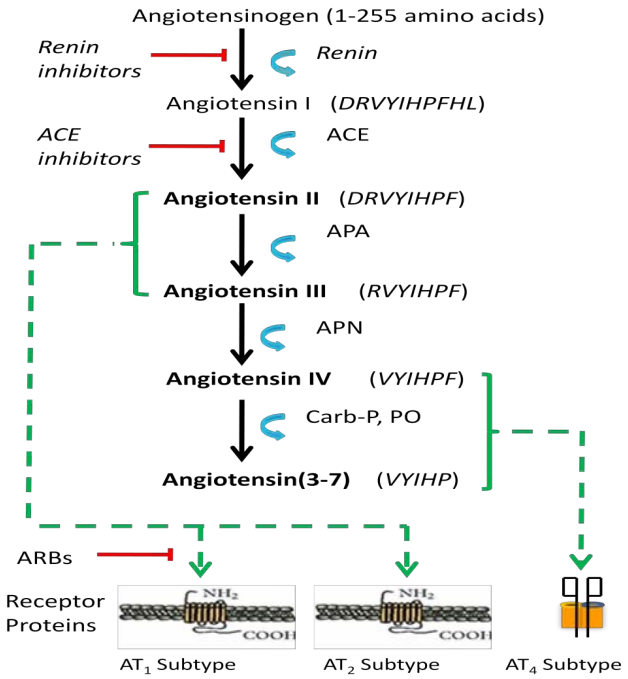


**Figure 1:** Angiotensin structures and synthesis pathway to produce biologically active ligands. The angiotensin synthesis pathway is presented indicating biologically active ligands (bold font), enzymes, and receptors involved in mediating related physiologies and behaviors. Angiotensinogen is converted to the decapeptide angiotensin I by renin. Angiotensin I is converted to the octapeptide angiotensin II by angiotensin converting enzyme (ACE). Aminopeptidase A (APA) converts angiotensin II to the heptapeptide angiotensin III that is converted to the hexapeptide angiotensin IV by aminopeptidase N (APN). Angiotensins II and III bind at the $AT_1$and $AT_2$receptor subtypes; while angiotensin IV binds at the $AT_4$ receptor subtype. Antihypertensive drugs such as ACE inhibitors act to interfere with conversion of angiotensin I to the biologically active form angiotensin II, and angiotensin receptor blockers (ARBs) act as antagonists at the $AT_1$ receptor thus preventing angiotensin II binding.

[49] followed by the purification of BDNF [50]. Most recently neurotrophin-3 (NT3) and neurotrophic-4 (NT4) have been isolated in the mammalian brain; while HGF was first isolated from the liver [51] and has now been identified in the brain [52-54].

Neurotrophic agents promote brain neuronal survival while decreases in their levels have been measured in several neurodegenerative diseases [55,56]. Thus, neurotrophins have been suggested as potential treatments against AD, Parkinson's disease and other neurodegenerative diseases [57]. BDNF has received the most attention due to its importance in the development and ongoing maintenance of normal brain functioning. Significant declines in BDNF expression have been seen in several neurodegenerative diseases [58-60] and BDNF has been implicated as important in Alzheimer's [61] and Huntington's diseases [62]. BDNF has been shown to overcome learning deficits in animal models of AD [63], and reveals increased expression with treadmill exercise [64]. NGF is synthesized in the hippocampus and neocortex and is transported to cholinergic neurons located in the forebrain. Since AD patients suffer from deficits in axonal transport NGF has been suggested as a treatment strategy [65,66]. Somewhat less attention has been given to NT3 and NT4, although their roles as brain neurotrophic agents are important (reviewed in [67-69].

## The hepatocyte growth factor/c-Met receptor system

The plasminogen family member HGF, also known as "scatter factor", has been shown to promote liver regeneration [52-54]. HGF acts at the c-Met receptor to stimulate mitogenesis, motogenesis and morphogenesis in a number of cellular targets including epithelial, endothelial and neurons [51,70,71]. This system has received considerable research attention related to its role in solid tumor cancers and possible therapies [72-74]. As the name implies HGF was originally isolated from the liver and shown to promote liver regeneration [75]. The c-Met receptor is made up of disulfide bond-linked alpha (45 kDa) and beta (145 kDa) subunits (Figure 2) [76]. c-Met's molecular weight agrees with our estimated weight for the $AT_4$ receptor calculated some years ago and suggests that they are the same protein. The alpha-chain of c-Metis extracellular while the beta-chain is transmembrane. HGF dimerization precedes binding to the c-Met receptor which then undergoes phosphorylation. Once phosphorylated the tyrosine residues of the beta subunit serve as docking sites for downstream signaling mediators including extracellular signal-regulated kinase (ERK) and the phosphatidylinositol-3-kinase (P13K) pathway [75].

The hypothesis that brain AngIV interacts with and activates the HGF/c-Met system is supported by the observation that AngIV-associated behavioral and physiological functions closely match those mediated by HGF [77-79]. These functions include augmentation of dendritic arborization and synaptogenesis, neurogenesis, facilitation of hippocampal long-term potentiation (LTP) and calcium signaling (hypothesized building blocks of memory consolidation), angiogenesis and facilitation of cerebral blood flow and cerebro protection. Such overlapping functions suggest that AngIV-induced activities are via activation of the HGF/c-Met system.

Recently we reported that the $AT_4$ receptor antagonist Norleual-AngIV (Nle-YI-ψ-($CH_2$-$NH_2$)-HPF) inhibited HGF binding to c-Met and in turn HGF-dependent signaling, proliferation, invasion, and scattering [78]. Norleual-AngIV's mechanism of action as a c-Met receptor antagonist is by inhibiting the dimerization of HGF, a necessary prerequisite for binding and activation of the c-Met receptor. This dimerization process is dependent upon a short HGF domain located between its N-terminal and first kringle domain referred to as the "hinge region" (Figure 2) [80]. The importance of this hinge region was confirmed by the synthesis and utilization of a hexapeptide mimic (Hinge: KDYIRN) that bound to HGF with high affinity and blocked HGF dimerization [29]. The application of Hinge did not interfere with memory in normal functioning animals [81], a finding consistent with an earlier report that noted no impact on learning and memory in cognitively intact animals treated with AngIV and AngIV analogs [44]. Given these results we hypothesized that AngIV analogs mimic this hinge region and behave as allosteric activators by emulating the change in HGF's conformation that normally results from its dimerization. Imaging data from cultured neonatal rat hippocampal neurons indicate that $Nle^1$-AngIV stimulates dendritic spine numbers and size, as well as overall dendritic arborization, suggesting a plausible mechanism for enhanced synaptic plasticity, connectivity among neurons, and facilitation of memory [28]. HGF activation of the c-Met receptor has also been shown to mediate dendritic arborization and neurogenesis in cultured hippocampal neurons [82] and facilitate memory

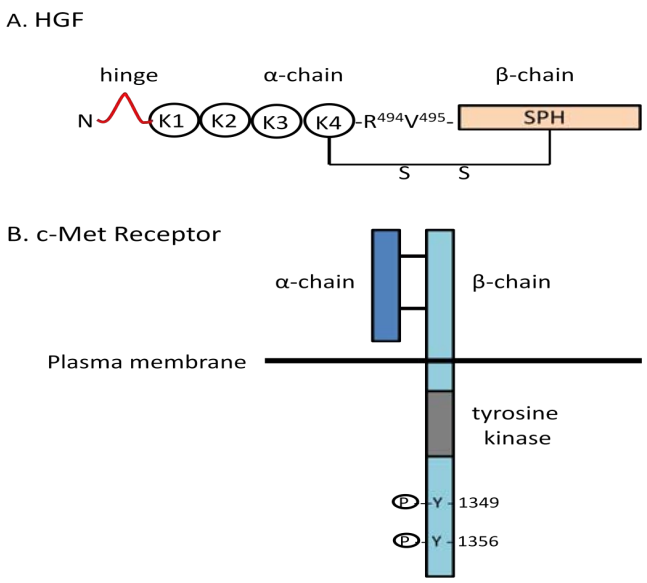


**Figure 2:** The structures and functions of the HGF/c-Met receptor system. (A) The structure of hepatocyte growth factor (HGF) includes a α-chain (69 kDa) of four Kringle domains and a β-chain (43 kDa) consisting of a serine proteinase homology (SPH) domain linked by disulfide bonds. (B) The c-Met receptor consists of a α-chain (50 kDa) and a β-chain (140 kDa) linked by disulfide bonds. HGF binds to c-Met resulting in tyrosine phosphorylation leading to a number of biological activities as listed. Nle[1]-AngIV and Dihexa act at the "hinge" region of HGF to facilitate dimerization which is a prerequisite to c-Met receptor binding and activation.

consolidation and retrieval in memory compromised animal models [83-86]. Elevated CNS levels of HGF have been measured in patients diagnosed with multiple sclerosis, Parkinson's disease, amyotrophic lateral sclerosis and spinal cord injury [87-90]. Unfortunately these increases in HGF are not maintained with disease progression, and the hippocampal HGF/c-Met system appears to be down regulated in AD patients [91]. Thus, the brain HGF/c-Met system appears to initially respond to neurodegenerative disease-induced injury by facilitating synaptic plasticity and neurogenesis; however these elevations in HGF are not sustained as the disease progresses.

### Development of AngIV-based analogs

Given the above research findings regarding Nle[1]-AngIV's ability to facilitate synaptogenesis and memory consolidation via stimulating the HGF/c-Met system in animal models of AD AngIV-based pharmaceuticals have been proposed as therapeutic agents to treat AD (reviewed in [45,92]). In an effort to develop such a drug members of our laboratory synthesized a number of AngIV-based compounds possessing extended half-lives by utilizing reduced peptide bonds ($CH_2$-$NH_2$) between residues. However, two critical physiochemical properties hindered drug development: 1) a lack of metabolic stability resulting in short circulating half-lives (eg. Nle[1]-AngIV = 1.42 min.; and 2) an inability to penetrate the blood-brain barrier (BBB) [93]. This latter limitation of AngIV-related peptides results from considerations of molecular size, overall hydrophobicity, and hydrogen-bonding potential as reflected by the size of the encompassing hydration sphere. We next determined that the memory facilitating effects of intra cerebroventricularly delivered Nle[1]-AngIV derived from its N-terminal region given that N-directed fragments as small as tetra- and tripeptides retained the ability to overcome scopolamine-induced amnesia [2,28]. Further, Nle[1]-AngIV and these shorter fragments augmented hippocampal synaptic connectivity via the formation of new synapses. Functionality of these synapses was confirmed by the presence of analog-induced spino genesis and colocalization of synaptic markers in newly formed dendritic spines, coupled with the recording of enhanced miniature excitatory postsynaptic currents. These results encouraged the possibility that a clinically useful drug could be designed possessing oral efficacy, increased metabolic stability, and BBB penetrability offering facilitated cognitive functioning. Subsequent efforts yielded the parent compound Dihexa and a related family of molecules possessing increased hydrophobicity, decreased hydrogen bonding potential, and increased metabolic stability (plasma half-life = 335 min [93]). Dihexa and its analogs bind with high affinity to HGF, induce c-Met phosphorylation in the presence of subthreshold levels of HGF, stimulate hippocampal spinogenesis and synaptogenesis equivalent with HGF [81], and promote neurogenesis and cerebro protection (data in preparation for publication). Intact Dihexa has been retrieved in cerebrospinal fluid samples taken from rats following both oral and parenteral treatment (data in preparation for publication). Treatment with the HGF antagonist, Hinge as well as a short hairpin RNA directed at c-Met, significantly inhibited these processes. These compounds penetrate the BBB in sufficient quantity to facilitate memory consolidation and retrieval in aged rats, and the scopolamine-induced amnesic rat model of AD, as measured employing the Morris water maze task of spatial memory [93].

### Therapeutic prospective and limitations

Limiting side effects is of particular importance regarding angiotensin-based antihypertensive drugs given the documented problems of dry mouth, nausea and dizziness, muscle soreness, and diuresis that may occur with ACE inhibitors and ARBs (Figure 1). Each member of these classes of drugs is designed to reduce $AT_1$ receptor activation and control hypertension. However, the AngII/$AT_1$ receptor system influences multiple functions beyond blood pressure, including body water balance, control of vasopressin and oxytocin release and sexual reproduction and behavior, thus undesirable drug-induced effects are possible. Dihexa-based compounds do not interact with central or peripheral $AT_1$ receptors, are highly target specific, exhibit little interaction with cardiac channel proteins and hepatic CIP isoforms, and reveal no acute toxicity following a 6x effective dose of Dihexa. More extensive safety studies are currently underway. These data predict that the greatest clinical impact will be in individuals with compromised brain HGF/c-Met systems as present in early-stage AD. The combined neuroprotective, synaptogenic, and neurogenic mechanisms proposed for these compounds encourage the possibility that they may be a treatment option for neurodegenerative and neuro-traumatic disorders beyond AD. Despite the potential to attenuate and possibly reverse deleterious molecular events common to many neurodegenerative diseases, we do not foresee this approach as a "cure" because the underlying etiologies will likely persist. We do believe that damage due to ongoing neurodegenerative processes will be significantly slowed and attenuated.

## Conclusion

New pharmacological approaches to treat AD include anti-

amyloid and anti-Tau drugs to clear cellular Aβ and Tau proteins respectively, NSAIDs, selective COX-2 inhibitors, Gamma-secretase modulators, and anti-amyloid antibodies to block β-amyloid storage. While harnessing the regenerative capacity of neurotrophic factors has been considered as a treatment approach to dementia practical implementation of this concept has been lacking. Recently, HGF-directed molecules have been synthesized that are orally active and possess sufficient BBB permeability to facilitate improved cognitive function in animal models of AD. The therapeutic value of this approach lies in its capacity to encourage the formation of new functional synaptic connections among existing neurons, and facilitate the replacement of damaged and lost neurons from available neural stem cell populations. These treatment outcomes would benefit patients afflicted with AD and perhaps individuals with other neurodegenerative diseases.

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