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MicroRNA silencing: A promising therapy for Alzheimer's disease

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Abstract

Alzheimer's disease (AD) is a global health crisis currently afflicting ~6 million Americans (and ~40 million people worldwide). By the middle of the century, these numbers will stagger by ~16 million Americans (and ~152 million people worldwide) suffering from AD, if breakthrough disease-modifying treatments are not discovered. Currently, there are no treatments to prevent, halt or cure the disease. Multiple independent studies on brain gene expression patterns have indicated that in AD about 1/3rd of the genes are upregulated while the rest 2/3rd of the genes are downregulated. In that regard, AD therapeutics focused on antagomiR-mediated silencing of"upregulated"microRNAs (miRs) may be more feasible since upregulated miRs in AD continue to increase with the disease progression, as opposed to agomiR-mediated overexpression of down-regulated miRs with unpredictable reduced presence and relative short-life of 1–3h under pathological conditions in AD brain. Studies reported thus far indicate that most of the upregulated pathogenic genes in AD are regulated by pro-inflammatory microRNAs (miRs). Given the precedence of chronic neuroinflammation in triggering AD-like neurodegeneration and multifactorial nature of AD, silencing inflammation-specific micro-RNAs using antisense-microRNAs may be an effective adjuvant therapeutic strategy to prevent, halt or cure AD.

Keywords

Alzheimer's disease; MicroRNA; AntagomiRs; Neuroinflammation

Introduction

Alzheimer's disease (AD) is a global health crisis currently afflicting ~6 million Americans (and ~40 million people worldwide). By the middle of the century, these numbers will escalate to ~16 million Americans (and ~152 million people worldwide) with AD, if breakthrough disease-modifying treatments are not discovered [1]. Currently, there are no treatments to prevent, halt or cure the disease. The FDA-approved symptomatic

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pharmacotherapy for AD include acetylcholinesterase inhibitors (AChEi) (Rivastigmine, Donepezil, Galantamine) and N-methyl-D-aspartate (NMDA) glutamate receptor modulator (Memantine) [2]. Investigational therapies for AD include antihypertensive drugs, anti-inflammatory drugs, secretase inhibitors, anti-diabetic insulin resistance drugs, brain-derived neurotrophic factor (BDNF), and immunization. Nutritional and botanical therapies include huperzine A, polyphenols, ginkgo, *panax ginseng*, *Withania somnifera* (Ashwagandha), phosphatidylserine, alpha-lipoic acid, omega-3 fatty acids, acetyl L-carnitine, coenzyme Q10, and melatonin, along with various vitamins and minerals. Other alternatives include physical exercise, cognitive training, leisure activities and socialization [3]. FDA-approved symptomatic pharmacotherapy provides only modest benefits without halting the progression of the disease and is associated with adverse effects [2,4,5] while other investigational therapies are not conclusive [3]. Given the lack of effective disease-modifying treatment(s) for AD [6], there is an unmet medical need in validating effective treatments with least/no side effects for treating AD [4,6]. There is a growing consensus that Alzheimer's is a multifactorial disease involving a dysregulated interplay of multiple "aging" factors occurring much earlier than the actual onset of the disease [7], among which oxidative damage [8–10] constitutes one of the prime factors resulting from high energy requirement of brain with its modest anti-oxidant defense, and hence vulnerable to oxidative damage caused by reactive oxygen species (ROS) [11], along with chronic inflammation [12–14], cholinergic dysfunction [15–17], insulin resistance [18–20] and other factors. Recently, it has been implicated that increase in cerebral ß-amyloid (Aß) in the aging brain either due to reduced Aß clearance, influx of peripheral Aß resulting from age-dependent blood brain barrier (BBB)/blood cerebrospinal fluid barrier (BCSFB) breach, age-related oxidative damage and inflammation-PKR (Protein kinase RNA activated protein) induced Aß production [21], or Aß overproduction due to familial mutations, all leading to cerebral Aß accumulation that tend to destroy synaptic integrity fundamental to cognitive decline observed in prodromal AD and/or mild cognitive impairment (MCI) [7]. Oxidative stress and chronic neuroinflammation constitute the earliest biochemical changes triggering AD [11]. Emerging evidence indicates that these early biochemical changes in AD, are regulated by small non-coding microRNAs (miR/MiRs) [22]. MiRs are highly conserved ~22-nucleotide (nt) long non-coding RNAs that function as post-transcriptional regulators of gene expression shaping the transcriptome of a cell [23,24]. MiRs regulate gene expression by interfering with translation of their target messenger RNAs (mRNAs) via binding to the 3'-untranslated regions (UTR) of mRNAs to induce repression or degradation of target mRNA [25], thus blocking translation of target mRNA(s) into specific proteins [26,27]. Increasing evidence indicates crucial role played by miRs in human health and diseases [28,29]. There are about >3000 mature miRs currently characterized in human brain, of which only ~50 miRs have been found to be enriched within selective anatomical compartment(s) of the brain [23]. Increasing number of studies indicate that the dysregulation of miRs is fundamental to the etiology of neurodegenerative diseases including AD [7,30]. Multiple independent studies on brain gene expression patterns have indicated that in AD, about 1/3rd of the genes are upregulated while the rest 2/3rd of the genes are downregulated [31]. Interestingly, most of the upregulated pathogenic genes in AD are known to be under the transcriptional control of a pro-inflammatory mediators

[31]. Inflammation-inducible miRs are found be significantly upregulated in AD-specific anatomic brain regions [32].

Early upregulation of neuroinflammation in AD and its persistence during the disease process in AD is characterized with the upregulation of NFkB as p50/p65 complex that controls diverse biological functions [33]. NFkB activation and binding to the promoters of NFkB-sensitive genes via miRs, facilitates transcriptions of many pathogenic genes altered in different neurodegenerative conditions including AD [32]. MiRs conventionally bind to the complementary RNA sequences in the 3'-UTR on mRNA and thereby repress the expression of target mRNA [32]. NFkB regulated miRs have been shown to be significantly elevated in AD brain, among which common to aging brain and AD brain i.e. miR-125b and miR-146a, are significantly upregulated [32]. Bioinformatics and multiple analytical techniques including RT-PCR, DNA-Array, Western blots, etc. have confirmed that both miR-125b and miR-146a target the 3'-UTR of several AD-related mRNAs [31,32]. MiR-125b was first shown to be upregulated in both stressed and differentiating mouse and human neurons, and has been implicated in neuronal development, cell-signaling and neurodegeneration [34]. NFkB-regulated miR-125b has been shown to be induced by neurotoxic aluminum sulfate that generates oxidative stress and ROS in human brain cells [35]. Consistent upregulation of miR-125b is associated with astrogliosis in various neurodegenerative conditions including AD [36]. MiR-125b is known to regulate neuronal synaptic functions, synaptic vesicle trafficking and neurotransmitter release, which when impaired in conditions such as AD, is reported to impair synaptic signaling and neurotransmitter release [37]. In addition, miR-125b is known to regulate cell cycle arrest and arachidonate 15-lipoxygenase (ALOX15) essential for conversion of docosahexaenoic acid (DHA) to neuroprotection D1 (NPD1), and therefore dysregulation of miR-125b leads to the down-regulation of cell cycle control and deficits in neurotrophic omega-3 fatty acids in the brain which in turn upregulates ß-secretase, prevents neurotrophic cleavage of ß-amyloid precursor protein (ßAPP) and increases Aß production [38].

On the other hand, miR-146a regulates complement factor H (CFH) and inactivates innate immune response in the brain, hence dysregulation of miR-146a leads to deficits in innate immune control and its chronic stimulation leading to pro-inflammatory signaling [39,40]. Additionally, miR-146a regulates interleukin-1 receptor-associated kinase 1 (IRAK-1), initiates innate immune response and activates NFkB signaling [39]. Moreover, miR-146a regulates transmembrane 4 superfamily member 12 (a regulator of cell surface receptor signal transduction), activates ADAM10-dependent neurotrophic cleavage of ßAPP, therefore when dysregulated, results in a shift from non-amyloidogenic to amyloidogenic processing of ßAPP [39]. In addition to the regulation of innate immunity, studies have shown that miR-146a also affects other biological functions such as hematopoiesis and cell differentiation [41]. Recently, Mai et al. have reported that although mir-146a was upregulated in hippocampus and temporal cortical brain regions critically involved in AD, its expression was unchanged in unaffected areas of AD brain, and showed that intranasal administration of miR-146a agomiR rescued pathological process and improved cognition in a mouse model of AD [42]. Another study by Salta et al. have shown that miR-132 involved in various aspects of central nervous system (CNS) functions, exhibited robust and consistent down-regulation in AD and that the therapeutic use of agomiR to miR-132 has

a great potential in restoring AD-like pathogenesis [42]. Considering the therapeutic use of miRs in AD, it is logical to avoid overexpression of down-regulated miRs since for the most part, their down-regulation may be relevant to the relative short-life to the maximum of ~3h in AD brain and their reduced presence under pathological conditions which may promote rapid degradation [31,43]. Therefore, focusing AD therapeutics with the consideration of "upregulated" miRs may be more justifiable since upregulated miRs in AD continue to be upregulated with disease progression. Therefore, compared to agomiR-mediated overexpression of down-regulated miRs, antagomiR-mediated silencing of upregulated miRs may hold better therapeutic promise in treating AD.

Anti-microRNA (AntagomiR) Strategies

The use of antisense complementary ribonucleotide sequences against the sequences of miR of interest (AntagomiRs) to lower the abundance of upregulated miRs for neutralizing down-stream pathogenic gene expression is coined as "AntagomiR strategy". The activity of any given miR can be experimentally inhibited by an antisense oligos using locked nucleic acid (LNA), also known as 2'-O-Methyl nucleic acid (2MOE) modifications [44]. Of all, the LNA/2MOE RNA modification results in enhanced hybridization to target mRNA with increased sensitivity/selectivity/accuracy [31,45–47], traditionally confirmed by quantitative reverse transcriptase polymerase chain reaction (Q-RTPCR) quantitation of selected miR/mRNA [48]. Additional stability is attained by incorporating phosphorothioate linkage at the 5'-start and 3'-end nucleotides and cholesterol linkage to 3'-prime end, adds to the accuracy and reliability to LNA/2MOE modifications [47,49–51].

AntagomiRs have been successfully validated for their silencing efficacy of target mRNA in various *in vitro* and i*n vivo* systems [32]. PubMed literature search showed only four *in vivo* reports on the use of antagomiRs. Lee et al. showed that intraventricular administration of antagomiR-206 into the third ventricle of Tg2576 AD-mice, prevented detrimental effects of Aß42 on brain-derived neurotrophic factor (BDNF) cerebral levels and dendritic spine degeneration in neurons. Intraventricular delivery of AntagomiR-206 in Tg2576 mice increased BDNF levels, improved memory function, enhanced hippocampal synaptic density and neurogenesis [52]. These authors also attempted in parallel, intranasal administration of antagomiR-206 as a non-invasive delivery, which was found to reach the brain, increased cerebral levels of BDNF and improved memory function [52]. Another study by Zhang et al. showed that miR-299–5p treatment resulted in the attenuation of autophagy protein 5 (Atg5) antagonizing caspase-dependent apoptosis in the primary neurons from APPswe/PS1dE9 mice, N2a cells and SH-SY5Y cells, whereas antagomiR-299–5p enhance autophagy [53]. Another report by Wang et al. showed that intra-hippocampal delivery of antagomiR-146a into 5XFAD mice showed enhanced hippocampal levels of rho-associated coiled-coil containing protein kinase 1 (ROCK1) protein and repressed tau phosphorylation, partly restoring memory function in 5XFAD mice [54]. Lastly, Zhang et al. showed that overexpression of miR-214–3p in primary neurons from SAMP8 mice inhibited autophagy, and conversely, antagomiR-214–3p promoted autophagy and apoptosis in neurons from SAMP8 mice [55]. These reported studies indicate utilization of different routes of administration of miRs. Although intracranial, intrathecal, and intraventricular routes have an advantage of direct delivery of neurotherapeutics to the brain, the invasive nature of these

routes poses practical limitations [56]. In that regard, intranasal route of drug delivery has gained considerable interest by virtue of being a safe, non-invasive route of administration that has proven efficiency of brain targeting [2,42,57–61].

Despite reported beneficial effects of various antagomiRs used in different *in vitro* and *in vivo* systems, the association of possible undesirable down-stream effects of miRs cannot be ruled out. As mentioned earlier, there are about >3000 mature miRs currently characterized in human brain, of which only selected ~50 miRs have been found to be enriched the brain [23] that have a potential to regulate a transcriptome of ~22,000–27,000 mRNAs [47]. Most miRs exhibit tightly regulated tissue- and cell-specific expression pattern and have an ability to potentially target the mRNA encoded by multiple genes simultaneously [31,60,62]. Even then, with a targeted delivery to the brain and advanced modifications of antagomiRs including 3' adenylation, LNA modification with bicyclic furanose unit locked in an RNA-mimicking sugar conformation or other RNA chemical modifications increase the stability and specificity, and complementary binding 3'-UTR mRNA-miR ensures specificity [47]. Moreover, custom tailoring of short half-life of 3'-UTR mRNA-miR hybrid, significantly reduces the possibility of miR off-target undesirable effects [47]. Nevertheless, given the multifactorial heterogeneity of AD, therapeutic interventions for AD should be more of a combinational nature that would not only include RNA interference but also pharmacotherapy, alternative therapy and/or lifestyle/dietary changes [47].

Conclusion

The use of antagomiR silencing therapeutic strategies in human neurological diseases such as Alzheimer's disease are emerging. Advanced designing of miRs towards specific hybridization-affinity to targeted miR/mRNA, LNA nucleotide technology and nuclease resistance, along with relevant chemical modifications such as phosphorothioate backbone and cholesterol moiety inclusion have shown limited but proven success with least side effects under both *in vitro* and *in vivo* conditions. Considering the multifactorial nature of AD, therapeutic interventions of a combinational nature including tailored antagomiR strategies along with effective pharmacotherapy may ensure successful clinical outcome for Alzheimer's cure.

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References

1. 2020 Alzheimer's disease facts and figures. Alzheimers Dement. 2020; 16: 391–460.
2. Wong KH, Riaz MK, Xie Y, Zhang X, Liu Q, Chen H, et al. Review of current strategies for delivering Alzheimer's disease drugs across the blood-brain barrier. International Journal of Molecular Sciences. 2019 Jan;20(2):381.
3. Wollen KA. Alzheimer's disease: the pros and cons of pharmaceutical, nutritional, botanical, and stimulatory therapies, with a discussion of treatment strategies from the perspective of patients and practitioners. Altern Med Rev. 2010 Sep 1;15(3):223–44. [PubMed: 21155625]
4. Oboudiyat C, Glazer H, Seifan A, Greer C, Isaacson RS. Alzheimer's disease. Semin Neurol. 2013;33(4):313–29. [PubMed: 24234352]

5. Casey DA, Antimisiaris D, O'Brien J. Drugs for Alzheimer's disease: are they effective?. Pharmacy and Therapeutics. 2010 Apr;35(4):208. [PubMed: 20498822]
6. Atri A Current and future treatments in Alzheimer's disease. InSeminars in neurology 2019 Apr (Vol. 39, No. 02, pp. 227–240). Thieme Medical Publishers. [PubMed: 30925615]
7. Reddy PH, Tonk S, Kumar S, Vijayan M, Kandimalla R, Kuruva CS, et al. A critical evaluation of neuroprotective and neurodegenerative MicroRNAs in Alzheimer's disease. Biochemical and Biophysical Research Communications. 2017 Feb 19;483(4):1156–65. [PubMed: 27524239]
8. Caracciolo B, Xu W, Collins S, Fratiglioni L. Cognitive decline, dietary factors and gut–brain interactions. Mechanisms of Ageing and Development. 2014 Mar 1;136:59–69. [PubMed: 24333791]
9. S Panickar K, Jang S. Dietary and plant polyphenols exert neuroprotective effects and improve cognitive function in cerebral ischemia. Recent Patents on Food, Nutrition & Agriculture. 2013 Aug 1;5(2):128–43.
10. Butterfield DA, Di Domenico F, Barone E. Elevated risk of type 2 diabetes for development of Alzheimer disease: a key role for oxidative stress in brain. Biochimica et Biophysica Acta (BBA)-Molecular Basis of Disease. 2014 Sep 1;1842(9):1693–706. [PubMed: 24949886]
11. Prasad KN. Oxidative stress and pro-inflammatory cytokines may act as one of the signals for regulating microRNAs expression in Alzheimer's disease. Mechanisms of Ageing and Development. 2017 Mar 1;162:63–71. [PubMed: 27964992]
12. Norden DM, Muccigrosso MM, Godbout JP. Microglial priming and enhanced reactivity to secondary insult in aging, and traumatic CNS injury, and neurodegenerative disease. Neuropharmacology. 2015 Sep 1;96:29–41. [PubMed: 25445485]
13. Rosenberg GA, Bjerke M, Wallin A. Multimodal markers of inflammation in the subcortical ischemic vascular disease type of vascular cognitive impairment. Stroke. 2014 May;45(5):1531–8. [PubMed: 24692476]
14. Lim A, Krajina K, Marsland AL. Peripheral inflammation and cognitive aging. InInflammation in Psychiatry 2013 (Vol. 28, pp. 175–187). Karger Publishers.
15. Anand P, Singh B. A review on cholinesterase inhibitors for Alzheimer's disease. Archives of Pharmacal Research. 2013 Apr 1;36(4):375–99. [PubMed: 23435942]
16. Lendvai B, Kassai F, Szájli Á, Némethy Z. α7 nicotinic acetylcholine receptors and their role in cognition. Brain Research Bulletin. 2013 Apr 1;93:86–96. [PubMed: 23178154]
17. M Hernandez C T Dineley K. α7 Nicotinic acetylcholine receptors in Alzheimer's disease: neuroprotective, neurotrophic or both?. Current Drug Targets. 2012 May 1;13(5):613–22. [PubMed: 22300028]
18. Suzanne M Metabolic derangements mediate cognitive impairment and Alzheimer's disease: role of peripheral insulin resistance diseases. Panminerva Medica. 2012 Sep;54(3):171. [PubMed: 22801434]
19. Ho N, Sommers MS, Lucki I. Effects of diabetes on hippocampal neurogenesis: links to cognition and depression. Neuroscience & Biobehavioral Reviews. 2013 Sep 1;37(8):1346–62. [PubMed: 23680701]
20. Blázquez E, Velázquez E, Hurtado-Carneiro V, Ruiz-Albusac JM. Insulin in the brain: its pathophysiological implications for States related with central insulin resistance, type 2 diabetes and Alzheimer's disease. Frontiers in Endocrinology. 2014 Oct 9;5:161. [PubMed: 25346723]
21. Nillert N, Pannangrong W, Welbat JU, Chaijaroonkhanarak W, Sripanidkulchai K, Sripanidkulchai B, et al. Neuroprotective effects of aged garlic extract on cognitive dysfunction and neuroinflammation induced by β-amyloid in rats. Nutrients. 2017 Jan;9(1):24.
22. Hernandez-Rapp J, Rainone S, Hébert SS. MicroRNAs underlying memory deficits in neurodegenerative disorders. Progress in Neuro-Psychopharmacology and Biological Psychiatry. 2017 Feb 6;73:79–86. [PubMed: 27117821]
23. Hill JM, Lukiw WJ. MicroRNA (miRNA)-mediated pathogenetic signaling in Alzheimer's disease (AD). Neurochemical Research. 2016 Feb 1;41(1–2):96–100. [PubMed: 26441222]
24. Karnati HK, Panigrahi MK, Gutti RK, Greig NH, Tamargo IA. miRNAs: key players in neurodegenerative disorders and epilepsy. Journal of Alzheimer's Disease. 2015 Jan 1;48(3):563–80.

25. Keifer J, Zheng Z, Ambigapathy G. A microRNA-BDNF negative feedback signaling loop in brain: implications for Alzheimer's disease. MicroRNA. 2015 Aug 1;4(2):101–8. [PubMed: 26456533]
26. Fabian MR, Sonenberg N, Filipowicz W. Regulation of mRNA translation and stability by microRNAs. Annual Review of Biochemistry. 2010 Jul 7;79:351–79.
27. Jung HJ, Suh Y. Circulating miRNAs in ageing and ageing-related diseases. Journal of Genetics and Genomics. 2014 Sep 20;41(9):465–72. [PubMed: 25269672]
28. Codocedo JF, Ríos JA, Godoy JA, Inestrosa NC. Are microRNAs the molecular link between metabolic syndrome and Alzheimer's disease?. Molecular Neurobiology. 2016 May 1;53(4):2320–38. [PubMed: 25976367]
29. Basavaraju M, De Lencastre A. Alzheimer's disease: presence and role of microRNAs. Biomolecular Concepts. 2016 Aug 1;7(4):241–52. [PubMed: 27505094]
30. Deraredj Nadim W, Simion V, Bénédetti H, Pichon C, Baril P, Morisset-Lopez S, et al. MicroRNAs in neurocognitive dysfunctions: new molecular targets for pharmacological treatments?. Current Neuropharmacology. 2017 Feb 1;15(2):260–75. [PubMed: 27396304]
31. Zhao Y, Alexandrov PN, Lukiw WJ. Anti-microRNAs as novel therapeutic agents in the clinical management of Alzheimer's disease. Frontiers in Neuroscience. 2016 Feb 25;10:59. [PubMed: 26941600]
32. Lukiw WJ. NF-κB-regulated, proinflammatory miRNAs in Alzheimer's disease. Alzheimer's Research & Therapy. 2012 Dec 1;4(6):47.
33. Granic I, Dolga AM, Nijholt IM, van Dijk G, Eisel UL. Inflammation and NF-κB in Alzheimer's disease and diabetes. Journal of Alzheimer's Disease. 2009 Jan 1;16(4):809–21.
34. Cui JG, Li YY, Zhao Y, Bhattacharjee S, Lukiw WJ. Differential regulation of interleukin-1 receptor-associated kinase-1 (IRAK-1) and IRAK-2 by microRNA-146a and NF-κB in stressed human astroglial cells and in Alzheimer disease. Journal of Biological Chemistry. 2010 Dec 10;285(50):38951–60.
35. Kawahara M, Kato-Negishi M. Link between aluminum and the pathogenesis of Alzheimer's disease: the integration of the aluminum and amyloid cascade hypotheses. International Journal of Alzheimer's Disease. 2011 Jan 1;2011.
36. Pogue AI, Cui J, Li YY, Zhao Y, Culicchia F, Lukiw WJ, et al. Micro RNA-125b (miRNA-125b) function in astrogliosis and glial cell proliferation. Neuroscience Letters. 2010 May 26;476(1):18–22. [PubMed: 20347935]
37. Bykhovskaia M Synapsin regulation of vesicle organization and functional pools. InSeminars in cell & developmental biology 2011 Jun 1 (Vol. 22, No. 4, pp. 387–392). Academic Press.
38. Zhao Y, Calon F, Julien C, Winkler JW, Petasis NA, Lukiw WJ, et al. Docosahexaenoic acid-derived neuroprotectin D1 induces neuronal survival via secretase-and PPARγ-mediated mechanisms in Alzheimer's disease models. PloS one. 2011 Jan 5;6(1):e15816.
39. Lukiw WJ. Amyloid beta (Aβ) peptide modulators and other current treatment strategies for Alzheimer's disease (AD). Expert Opinion on Emerging Drugs. 2012 Mar 1;17(1):43–60.
40. Gupta P, Bhattacharjee S, Sharma AR, Sharma G, Lee SS, Chakraborty C, et al. miRNAs in Alzheimer disease–a therapeutic perspective. Current Alzheimer Research. 2017 Nov 1;14(11):1198–206. [PubMed: 28847283]
41. Labbaye C, Testa U. The emerging role of MIR-146A in the control of hematopoiesis, immune function and cancer. Journal of Hematology & Oncology. 2012 Dec;5(1):1–0. [PubMed: 22272800]
42. Mai H, Fan W, Wang Y, Cai Y, Li X, Chen F, et al. Intranasal administration of miR-146a agomir rescued the pathological process and cognitive impairment in an AD mouse model. Molecular Therapy-Nucleic Acids. 2019 Dec 6;18:681–95. [PubMed: 31707205]
43. Sethi P, Lukiw WJ. Micro-RNA abundance and stability in human brain: specific alterations in Alzheimer's disease temporal lobe neocortex. Neuroscience Letters. 2009 Aug 7;459(2):100–4. [PubMed: 19406203]
44. Flynt AS, Li N, Thatcher EJ, Solnica-Krezel L, Patton JG. Zebrafish miR-214 modulates Hedgehog signaling to specify muscle cell fate. Nature Genetics. 2007 Feb;39(2):259–63. [PubMed: 17220889]

45. Kaur H, Arora A, Wengel J, Maiti S. Thermodynamic, counterion, and hydration effects for the incorporation of locked nucleic acid nucleotides into DNA duplexes. Biochemistry. 2006 Jun 13;45(23):7347–55. [PubMed: 16752924]
46. Stenvang J, Petri A, Lindow M, Obad S, Kauppinen S. Inhibition of microRNA function by antimiR oligonucleotides. Silence. 2012 Dec 1;3(1):1.
47. Jaber VR, Zhao Y, Sharfman NM, Li W, Lukiw WJ. Addressing Alzheimer's disease (AD) neuropathology using anti-microRNA (AM) strategies. Molecular Neurobiology. 2019 Dec 1;56(12):8101–8. [PubMed: 31183807]
48. Kumar S, Vijayan M, Bhatti JS, Reddy PH. MicroRNAs as peripheral biomarkers in aging and age-related diseases. InProgress in Molecular Biology and Translational Science 2017 Jan 1 (Vol. 146, pp. 47–94). Academic Press.
49. Smith CE, Zain R. Therapeutic oligonucleotides: state of the art. Annual Review of Pharmacology and Toxicology. 2019 Jan 6;59:605–30.
50. Yamamoto T, Nakatani M, Narukawa K, Obika S. Antisense drug discovery and development. Future Medicinal Chemistry. 2011 Mar;3(3):339–65. [PubMed: 21446846]
51. Yamashita S, Nishida K, Osawa T, Nakanishi A, Ito Y, Hari Y, et al. Synthesis of Oligonucleotides Containing 2'-N-alkylaminocarbonyl-2'-amino-LNA (2'-urea-LNA) Moieties Using Post-Synthetic Modification Strategy. Molecules. 2020 Jan;25(2):346.
52. Lee ST, Chu K, Jung KH, Kim JH, Huh JY, Yoon H, et al. miR-206 regulates brain-derived neurotrophic factor in Alzheimer disease model. Annals of Neurology. 2012 Aug;72(2):269–77. [PubMed: 22926857]
53. Zhang Y, Liu C, Wang J, Li Q, Ping H, Gao S, et al. MiR-299–5p regulates apoptosis through autophagy in neurons and ameliorates cognitive capacity in APPswe/PS1dE9 mice. Scientific Reports. 2016 Apr 15;6(1):1–4. [PubMed: 28442746]
54. Wang G, Huang Y, Wang LL, Zhang YF, Xu J, Zhou Y, et al. MicroRNA-146a suppresses ROCK1 allowing hyperphosphorylation of tau in Alzheimer's disease. Scientific Reports. 2016 May 25;6:26697.
55. Zhang Y, Li Q, Liu C, Gao S, Ping H, Wang J, et al. MiR-214–3p attenuates cognition defects via the inhibition of autophagy in SAMP8 mouse model of sporadic Alzheimer's disease. Neurotoxicology. 2016 Sep 1;56:139–49. [PubMed: 27397902]
56. Dupoiron D Targeted Drug Delivery (Intrathecal and Intracranial) for Treatment of Facial Pain. Neuromodulation for Facial Pain. 2020;35:155–67.
57. Chauhan NB, Davis F, Xiao C. Wheat germ agglutinin enhanced cerebral uptake of anti-Aβ antibody after intranasal administration in 5XFAD mice. Vaccine. 2011 Oct 13;29(44):7631–7. [PubMed: 21840361]
58. Xiao C, Davis FJ, Chauhan BC, Viola KL, Lacor PN, Velasco PT, et al. Brain transit and ameliorative effects of intranasally delivered anti-amyloid-β oligomer antibody in 5XFAD mice. Journal of Alzheimer's Disease. 2013 Jan 1;35(4):777–88.
59. Chauhan MB, Chauhan NB. Brain uptake of neurotherapeutics after intranasal versus intraperitoneal delivery in mice. Journal of Neurology and Neurosurgery. 2015;2(1).
60. Alexander A, Agrawal M, Uddin A, Siddique S, Shehata AM, Shaker MA, et al. Recent expansions of novel strategies towards the drug targeting into the brain. International Journal of Nanomedicine. 2019;14:5895. [PubMed: 31440051]
61. Agrawal M, Saraf S, Saraf S, Antimisiaris SG, Chougule MB, Shoyele SA, et al. Nose-to-brain drug delivery: An update on clinical challenges and progress towards approval of anti-Alzheimer drugs. Journal of Controlled Release. 2018 Jul 10;281:139–77. [PubMed: 29772289]
62. Satoh JI. Molecular network of microRNA targets in Alzheimer's disease brains. Experimental Neurology. 2012 Jun 1;235(2):436–46. [PubMed: 21945006]