 doi:10.20944/preprints201808.0204.v1

Targeted Nanotherapy for Cognitive Impairment: Blocking Amyloid-B-Induced Membrane Damage in Brain Tissue

Author: **Joseph S. D'Arrigo, Ph.D.**[1]

Affiliation: **Cavitation-Control Technology Inc.**, Farmington, CT 06032, USA
[1] Present address: Cav-Con Inc., Bellevue, WA 98007, USA

Abstract: A frequent co-morbidity of cerebrovascular pathology and Alzheimer's disease pathology has been observed over past decades. Accordingly, much evidence has been reported which indicates that microvascular endothelial dysfunction, due to cerebrovascular risk factors (e.g., atherosclerosis, obesity, diabetes, smoking, hypertension, aging), precedes cognitive decline in Alzheimer's disease and contributes to its pathogenesis. By incorporating appropriate drug(s) into biomimetic (lipid cubic phase) nanocarriers, one obtains a multitasking combination therapeutic which targets certain cell-surface scavenger receptors, mainly class B type I (i.e., SR-BI), and crosses the blood-brain barrier (BBB). Such targeting allows for various Alzheimer's-related cell types to be simultaneously searched out, in vivo, for localized drug treatment. This in vivo targeting advantage may be particularly important for repurposing an FDA-approved drug, especially one which has shown the added ability to restore some cognitive functions in certain animal models of Alzheimer's disease (e.g., the anticancer drug bexarotene); this (candidate repurposing) drug up to now, by itself (i.e, without nanocarrier), displayed poor CNS penetration in human subjects.

Keywords: Alzheimer's disease; blood-brain barrier; cognitive aging; cognitive impairment; dementia; drug targeting; nanoemulsion; nanocarriers; scavenger receptors

1. Introduction

Vascular brain lesions are very common in people over 70 years old, and recent reviews (e.g., [1,2]) provide much evidence that a large proportion of dementia cases may be attributable to cerebrovascular disease. Accordingly, vascular cognitive impairment and dementia (VCID) is the second leading cause of dementia behind Alzheimer's disease, and is a frequent co-morbidity in the Alzheimer's patient [3-9]. On a worldwide basis, 47 million people had dementia in 2016; of these dementia patients, 60%-80% have Alzheimer's disease [4,10,11].

 doi:10.20944/preprints201808.0204.v1

2. Endothelial Dysfunction, and Targeted Treatment for Early Dementia

It has been reconfirmed in the current literature that receptor-mediated endocytosis/transcytosis via lipoprotein receptors, particularly scavenger receptors (including class B type I, i.e., SR-BI), remains a major route for drug delivery across the blood-brain barrier (BBB). Accordingly, endothelial-cell modulation and repair is feasible by pharmacological targeting [1,2,12-26] via SR-BI receptors (cf. [25]): As the detailed review by Mahringer et al. [27] points out, the BBB is equipped with several endocytic receptors at the luminal surface (i.e., the capillary endothelial membrane), including SR-BI . Furthermore, very recently published experimental work has demonstrated in detail [28] that high-density lipoproteins (HDL), acting via SR-BI, block amyloid-β uptake into endothelial cells both in experimental monolayers and probably in the intact human cerebrovascular endothelium (cf. [3,29-31]). These authors also observed that inhibiting SR-BI binding with a specific blocking antibody *abolished* the ability of HDL to suppress "amyloid-β-induced" monocyte adhesion to (human microvascular) endothelial cells [28].

Almer et al. [14] explain in their recent review that the integration of lipoprotein-related or apolipoprotein-targeted nanoparticles, as drug carriers, is an expanding concept in nanomedicine to exploit the intrinsic characteristics of lipoprotein particles as being the natural transporter of lipophilic compounds in human circulation. Discrete lipoprotein assemblies and lipoprotein-based biomimetics offer a versatile nanoparticle platform for constructing drug loaded, reconstituted or artificial lipoprotein particles for specific medical applications. As naturally occurring nanoassemblies, lipoprotein particles are not readily (nor rapidly) cleared by the mononuclear phagocyte system (of the liver and spleen) and remain in circulation for a longer period of time [3,14]. More recently, Fung et al. [32] separately reported that SR-BI mediates the uptake and transcytosis of HDL across brain microvascular endothelial cells (i.e., across the BBB). These investigators further argue that manipulation of HDL transcytosis across the BBB to increase delivery of plasma apolipoprotein A-I (apoA-I) may, in turn, facilitate increasing the transport of "*HDL-like synthetic particles*" containing therapeutic drug across the BBB to treat neurodegenerative disorders such as Alzheimer's disease [32]. Since SR-BI has already

 doi:10.20944/preprints201808.0204.v1

been identified as a major receptor for HDL (with their major apolipoprotein *(apo)A-I) as well as for* the recently reviewed [1,2] "lipid-coated microbubble/nanoparticle-derived" *(LCM/ND) nanoemulsion* (see below), this multitasking lipid nanoemulsion can arguably serve as a targeted, apoA-I-based, (SR-BI mediated) therapeutic agent for common (late-onset) dementias [2,28,33-35] (cf. [36-42]).

This targeted-drug-delivery approach, using the proposed LCM/ND lipid nanoemulsion for treating the more common (late-onset) dementias, receives added impetus from continual findings of cerebrovascular pathology [1,43–53] and an apparent *endothelium*-dysfunction [2,33–41,49,54–60] in both Alzheimer's disease and its major risk factors [1,2,53–72]. By incorporating drug molecules into the LCM/ND lipid nanoemulsion type (yielding particle sizes mostly < 0.1 μm in diameter), known to be a successful drug carrier [73,74], one is likely to obtain a multitasking combination therapeutic capable of targeting cell-surface SR-BI. This combination therapeutic would make it possible for various cell types, all potentially implicated in Alzheimer's disease (see [1,2] for reviews; cf. [71,72]), to be simultaneously sought out and better reached for localized drug treatment of brain tissue in vivo [73].

3. LCM/ND Nanoemulsion Type, Lipid Cubic Phases, and Biomimetic Nanocarriers

The self-assembling LCM/ND lipid nanoemulsion class comprises nonionic lipids exclusively (cf. [75,76]) throughout its coated microbubble's and/or related nanoparticle's (i.e., related lipid polymorphs') supramolecular structures(s). This biobased lipid composition of LCM/ND nanoemulsions (i.e., glycerides and cholesterol compounds) is similar to lipids contained in several types of plama lipoproteins; accordingly, when these LCM/ND nanoemulsion particles are injected into the bloodstream, they likely acquire (i.e., bind) plasma apolipoprotein(s) – including notably apoA-I [73]. Hence, the molecular composition of the LCM/ND nanoemulsion particles resulted in both microbubble/nanoparticle stability and marked targeting toward tumors and certain hyperproliferative-disease lesions/sites; this very rapid targeting has been demonstrated to occur by an "active uptake" process, i.e., "endocytosis" – which likely involves certain "lipoprotein receptor"-mediated endocytic pathways [2].

 doi:10.20944/preprints201808.0204.v1

Importantly, monoglyceride is the largest single-lipid fraction (by wt. %) of the powdered solid lipid surfactants used to produce the (Filmix®) LCM/ND nanoemulsions [73]. As a group, monoglycerides exhibit different phase behaviors when they are exposed to water [77] (cf. [78,79]). The ability to exist in several different phases is an important property of pure lipids and lipid mixtures; it depends upon temperature, hydration, and lipid class [77]. Although monoglycerides typically have poor water solubility, they have free hydroxyl groups which can hydrogen bond with water, surfactants, cosolvents, etc. As polar lipids, monoglycerides typically: (1) are better solvents for drugs; (2) act as "cosurfactants" which promote mutual solubility between excipients (i.e., inactive ingredients); (3) enhance water uptake; and (4) promote self-dispersibility of lipid formulations [80]. The above properties of monoglycerides place them in a lipid class known as "insoluble swelling amphiphiles". These lipid molecules form stable monolayers (at the air/water interface), but also swell in water to form liquid-crystalline phases [81]. In their detailed review, Kaasgaard and Drummond [82] explain that these lyotropic (i.e., solvent induced) liquid-crystalline phases of monoglycerides include the one-dimensional lamellar phase, which has been widely studied and employed as a model system for biomembranes and drug-delivery applications. More recently studied are the structurally more complex two- and three-dimensional ordered (lyotropic) liquid-crystalline phases, of which inverse hexagonal and cubic phases are two prominent examples. In agreement with numerous other investigators, Kaasgaard and Drummond also state that all these types of liquid-crystalline phases are frequently stable in excess water, which facilitates the preparation of nanoparticle dispersions and makes them suitable candidates for the encapsulation and controlled release of drugs ([82]; cf. [83-89]).

The self-assembly of varied and useful *dispersed cubic* phases (among other liquid-crystalline phases) depends heavily on the acyl chain length of the glycerides (primarily monoglycerides) placed in contact with water [73]. As Yaghmur et al. [89] point out, the significant interest in the formulation and the characterization of these complex and varied, self-assembled, liquid-crystalline *cubic* phases is driven by both fundamental and

 doi:10.20944/preprints201808.0204.v1

practical considerations: They offer many advantages compared to conventional dispersed systems (such as simple emulsions or double emulsions) because of their confined equilibrium nanostructures with high interfacial area, their low viscosity, and their capabilities to solubilize a wide variety of active molecules. Therefore, there is great interest to utilize these *dispersed cubic* phases for the administration of drugs, or for the formulation of new delivery systems [89].

Besides certain glyceride-based liquid-crystalline systems displaying colloidal stability in excess water, the same important attribute has been documented for cholesterol and cholesterol esters – all of which are present in LCM/ND nanoemulsion formulations [73]. For example, cholesterol and its esters change the packing structure of lipids, and in high concentrations they are known to induce the formation of a liquid-crystal phase [90]. In addition, Kuntsche et al. [91,92] have prepared lipid nanoparticles in the (mesomorphic or) liquid-crystalline phase from cholesterol esters with saturated acyl chains. These investigators were motivated by the knowledge that many cholesterol esters are physiologic lipid compounds which can form liquid-crystalline phases (thermotropic mesophases) and, hence, they were interested in their potential for the development of liquid-crystalline nanoparticles as a carrier system for lipophilic drugs [92]. In accord with the above observations and considerations, the substantial concentrations of cholesterol esters and cholesterol in the LCM/ND nanoemulsion formulation likely further contribute to the known long-term stability of this nanoemulsion's (liquid-crystalline) lipid nanoparticles in excess water, thereby providing a persistent carrier matrix upon exposure to liquids such as blood plasma [73].

To conclude, self-assembled (colloidal mesophase) lipid nanoemulsions (e.g., [93-98]), particularly those predominantly containing dispersed cubic-phase lipid nanoparticles (e.g., [99-103]), continue to receive growing attention in pharmaceutical and/or biological fields. The main reason behind much of this attention is the fact that nonlamellar lipid nanostructures, such as cubic liquid-crystalline phases, have wide potential as delivery systems for numerous drugs, cosmetics, and food applications (e.g., [104-106]). Namely, using various lipids and their mixtures to form self-assembled non-lamellar

Preprints (www.preprints.org) | NOT PEER-REVIEWED | Posted: 10 August 2018 doi:10.20944/preprints201808.0204.v1

nanostructures, it has continually been reported possible to successfully obtain stable colloidal dispersions of (liquid-crystalline) lipid cubic phases with well-defined particle size and morphology (e.g., [105,106]). In particular, within the range of self-assembled phases in model surfactant-like lipid systems, Yaghmur et al. [107] further emphasized that the monoglyceride-based lyotropic liquid-crystalline phases are relatively unique owing to their rich polymorphism in water and potential application as drug nanocarriers (cf. [108]). A recurring example of a largely monoglyceride-based drug-delivery agent category is the multitasking LCM/ND nanoemulsion formulation (cf. above). In this particular targeted-delivery approach, the self-assembled "lipid particle" structure itself (upon intravenous injection of the LCM/ND nanoemulsion) is apparently successfully utilized as the "active" targeting ligand – which is directed via (adsorption of) plasma lipoproteins toward the appropriate receptors on the target-cell surface. These dispersed liquid-crystalline lipid particles, of the LCM/ND nanoemulsion formulation, are colloidally stable nanocarriers which very likely represent liquid-crystalline inverse-topology nanotransporters (nanocarriers), i.e., dispersed lipid cubic phases (cf. [73]).

4. Calcium Dyshomeostasis, and the Amyloid-β Ion Channel Hypothesis of Alzheimer's Disease

As explained in many reviews (e.g., [109,110]) by different investigators, it has been recognized for over two decades that disturbance of the intracellular calcium homeostasis is central to the pathophysiology of neurodegeneration. In Alzheimer's disease, it is believed by many researchers that enhanced calcium load may be brought about by extracellular accumulation of amyloid-β in the brain. Such studies have laid the foundation for the popular idea that amyloid-β peptides (Aβ; 39-42 amino acid molecules) are, in part, toxic to brain tissue because they form aberrant ion channels in cellular membranes and thereby disrupt Ca^{2+} homeostasis in brain tissue and increase intracellular Ca^{2+}. More specifically, later studies indicated that soluble forms of Aβ facilitate influx through calcium-conducting ion channels in the plasma membrane, leading to excitotoxic neurodegeneration [109,110].

 doi:10.20944/preprints201808.0204.v1

The precise cellular pathway(s) by which the amyloid-β peptides bring about excitotoxic neurodegeneration has been much debated. A common cellular picture used to explain the disruptive effect of calcium dyshomeostasis within brain tissue, appearing often in the literature (e.g., [111,112]), involves a central role for the tripartite glutamatergic synapse in the pathophysiology of Alzheimer's disease. Under this hypothesis, perturbations in the glutamatergic tripartite synapse (comprised of a presynaptic neuron terminal, a postsynaptic neuron terminal, and an astrocytic process) are believed to underlie the pathogenic mechanisms of Alzheimer's disease. Glutamate is the primary excitatory neurotransmitter in the brain and plays an important role in cognition and memory, but alterations in glutamatergic signaling can lead to excitotoxicity. This "Ca^{2+} dyshomeostasis"-induced excitotoxicity occurs when uncontrolled glutamate release surpasses the capacity of astrocytic clearance mechanisms, and is linked to several neurodegenerative disorders including Alzheimer's disease [111](cf. [112]).

Historical support for the above amyloid-β ion channel hypothesis, or so-called "calcium hypothesis", has also been observed at the clinical level [113]. Namely, there is little correlation between the amounts of fibrillar (insoluble) deposit at autopsy and the clinical severity of Alzheimer's disease. In contrast, a good correlation exists between early cognitive impairment and levels of soluble forms of Aβ in the brain [114]. (Aggregation of Aβ proceeds from formation of soluble (low molecular weight) spherical oligomers toward eventually assuming a final and stable conformation as insoluble fibrils from which amyloid-β plaques are constituted. Neurotoxicity is associated with soluble aggregates (i.e., oligomers) of Aβ rather than with the plaques themselves.) Accordingly, related experimental work has already shown that application of soluble Aβ oligomers (but not monomers or fibrils) to cultured neuroblastoma cells evoked large increases in cytosolic calcium that arise largely through Ca^{2+} influx across the plasma membrane [114].

As summarized by Di Scala et al. [113], the structure of amyloid pores has been extensively studied by ultrastructural methods. In particular, one group of investigators recently applied strategies (widely used to examine the structure of membrane proteins)

 doi:10.20944/preprints201808.0204.v1

to study the two major Aβ variants, namely, Aβ(1-40) and Aβ(1-42). Under the optimized detergent micelle conditions: 1) Aβ(1-40) aggregated into amyloid fibrils; 2) contrariwise, Aβ(1-42) assembled into oligomers that inserted into lipid bilayers as well-defined pores [115]. (These amyloid pores adopted characteristics of a β-barrel arrangement.) Because Aβ(1-42), relative to Aβ(1-40), has a more prominent role in Alzheimer's disease, the higher propensity of Aβ(1-42) to form β-barrel pore-forming oligomers is an indication of their importance in Alzheimer's disease [115]. Very recently, a different research group reported very similar findings [116]. As background for their study, these latter authors point out that: elevated Aβ(1-42) plasma levels have been correlated with the progression of late-onset forms of Alzheimer's disease; Aβ(1-42) is significantly more neurotoxic than Aβ(1-40) both in vivo and in neuronal cell culture; and memory impairment is believed to be driven by Aβ(1-42) disruption of long-term (hippocampal) potentiation. In accordance with these considerations, the authors' own detailed experimental data [116] indicated that Aβ(1-42) assemblies in oligomeric preparations form ion channels (in membranes excised from cells of neuronal origin). In contrast, Aβ(1-40) oligomers, fibrils, and monomers did not form channels. Moreover, ion channel conductance results suggested that Aβ(1-42) oligomers, but not monomers and fibrils, formed pore structures. The authors concluded that their findings demonstrate that only Aβ(1-42) contains unique structural features that facilitate membrane insertion and channel formation, now aligning ion channel formation with the neurotoxic effect of Aβ(1-42) compared to Aβ(1-40) in Alzheimer's disease [116].

5. Renewed Promise of Bexarotene (or analogs) to Inhibit Cognitive Decline in Humans

The preceding discussion of amyloid pore formation, in the cellular membranes of brain tissue, leads to another important consideration – the role of cholesterol. Namely, cholesterol is required for the assembly of amyloid pores formed by Aβ(1-42) [113]. Therefore, an amphipathic drug (such as bexarotene) which competes with cholesterol for binding to Aβ(1-42) would be capable of preventing oligomeric channel formation (at least in vitro). Such a strategy has already been contemplated for the treatment of Alzheimer's and other neurodegenerative diseases that involve cholesterol-dependent

 doi:10.20944/preprints201808.0204.v1

toxic oligomers [117]. However, when *oral* administration of bexarotene was employed subsequently in a Phase Ib (proof of mechanism) clinical trial [118], bexarotene displayed poor CNS penetration in normal human subjects. (Hence, the observed absence of an effect on Aβ metabolism was likely reflective of the low CNS-levels of bexarotene achieved [118](cf. [119])).

Nonetheless, at least two recently published reports (both in 2017) on bexarotene indicate a continuing interest in the ability of this FDA-approved (anticancer) drug to: 1) bind free Aβ peptide as well as 2) bexarotene's previously reported positive effects in Alzheimer's-disease mouse models [120,121] (cf. [122,123]). Such past studies in animal models of Alzheimer's disease, concerning the beneficial effects of bexarotene, have also motivated a detailed analysis by Fantini et al. [124] that utilized a combination of molecular, physicochemical, and cellular approaches to elucidate the mechanisms underlying the anti-Alzheimer properties of bexarotene in brain cells. These investigators demonstrated that bexarotene shares structural analogy with cholesterol: both bexarotene and cholesterol are amphipathic compounds, with a large apolar part consisting of a succession of hydrocarbon rings and a small polar headgroup (hydroxyl for cholesterol, carboxylate for bexarotene). Molecular dynamics simulations gave structural insights into the role of cholesterol in amyloid channel formation and explained the inhibitory effect of bexarotene. Because it is the first drug that can both inhibit the binding of cholesterol to Aβ(1-42) and prevent calcium-permeable amyloid pore formation in the plasma membrane of brain cells, bexarotene might be considered as the prototype of a new class of anti-Alzheimer compounds [124]. (Note that because bexarotene shares structural analogy with cholesterol, and the above-described LCM/ND nanoemulsion contains substantial concentrations of cholesterol esters and cholesterol (see Sect. 3), incorporation of the bexarotene molecule into the LCM/ND nanocarrier is expected to represent an uncomplicated, straightforward formulation procedure commercially.) Moreover, Casali et al. [125] have very recently reported that treatment of an Alzheimer's-disease mouse model with (this FDA-approved anticancer drug) bexarotene resulted in enhanced cogniton in the APP/PS1 mice which resembled earlier findings. Strikingly, the authors observed sustained cognitive improvements in the mice even when bexarotene treatment

 doi:10.20944/preprints201808.0204.v1

was discontinued for 2 weeks. Also, they observed a sustained reduction in microgliosis and plaque burden, following drug withdrawal, exclusively in the hippocampus. Casali et al. concluded that bexarotene selectively modifies aspects of neuroinflammation in a region-specific manner to reverse hippocampal-dependent cognitive deficits in Alzheimer's-disease (APP/PS1) mice [125].

Additional molecular aspects, concerning the membrane-related mechanisms for the known neuroprotective effect, of bexarotene action on brain tissue continue to be suggested and/or described in the recent literature (cf. [126,127]). In the most recently published study, Kamp et al. [128] show by NMR and CD spectroscopy that bexarotene directly interacts with the transmembrane domain of the amyloid precursor protein (APP) in a region where cholesterol binds. (Note that Aβ peptides are derived from APP, by the sequential action of β- and γ-secretases. γ-Secretase cleavage occurs in the transmembrane domain, of the C-terminal fragment left by β-secretase cleavage, and results in the release of Aβ peptides of various lengths. The longer, neurotoxic, Aβ(1-42) peptide is highly aggregation prone and represents the major Aβ species deposited in the brain [128]. See also [129-131].) These authors argue that their data [128] suggest that bexarotene is a pleiotropic molecule that interferes with Aβ metabolism through multiple mechanisms. The authors point out that one promising strategy is the use of small molecules, that interfere with protein aggregation and the formation of amyloid structures. In reviewing the related literature, Kamp et al. [128] explain that based on molecular modeling, monolayer experiments, and binding assays for bexarotene, it has been hypothesized by some investigators that bexarotene binds to extracellular Aβ peptides and inhibits the cholesterol-driven insertion of these peptides into the cellular membranes of brain tissue, thereby preventing oligomerization and subsequent neurotoxic pore formation [128].

6. Conclusion

The proposed multitasking combination therapeutic appears likely to display greater efficacy at different stages of Alzheimer's disease (cf. [72]). It is also possible that the effects on various cell types targeted may be additive, multiplicative, or otherwise

synergistic [26]. As a result, this multitasking (drug-delivery) therapeutic could represent a promising way to treat, delay, or even prevent the disease in the future [1,2]. By incorporating the appropriate drug(s) into biomimetic (lipid cubic phase) nanocarriers, one obtains a multitasking combination therapeutic which targets certain cell-surface scavenger receptors, mainly class B type I (SR-BI), and crosses the BBB. Such targeting allows for various Alzheimer's-related cell types to be simultaneously searched out, in vivo, for localized drug treatment. This in vivo targeting advantage may be particularly important for repurposing an FDA-approved drug (such as the anticancer drug bexarotene) which up to now, by itself (i.e., without nanocarrier), has previously displayed poor CNS penetration in human subjects.

Acknowledgements: This research did not receive any specific grant from funding agencies in the public, commercial, or nonprofit sectors.

Conflicts of Interest: The authors declare no conflict of interest. J.S.D. is employed at Cav-Con Inc.

References

1. D'Arrigo, J.S. Alzheimer's disease, brain injury, and CNS nanotherapy in humans: Sonoporation augmenting drug targeting. *Med. Sci.* **2017**, *5*, 29.

2. D'Arrigo, J.S. Nanotherapy for Alzheimer's disease and vascular dementia: Targeting senile endothelium. *Adv. Colloid Interface Sci.* **2018**, *251*, 44–54.

3. D'Arrigo, J.S. Targeting early dementia: Using lipid cubic phase nanocarriers to cross the blood-brain barrier. *Biomimetics* **2018**, *3*, 4.

4. Dichgans, M.; Leys, D. Vascular cognitive impairment. *Circ. Res.* **2017**, *120*, 573–591.

5. Greenberg, S.M. Vascular disease and neurodegeneration: Advancing together. *Lancet Neurol.* **2017**, *16*, 333.

6. Kalaria, R.N. Neuropathological diagnosis of vascular cognitive impairment and vascular dementia with implications for Alzheimer's disease. *Acta Neuropathol.* **2016**, *131*, 659–685.

7. Duncombe, J.; Kitamura, A.; Hase, Y.; Ihara, M.; Kalaria, R.N.; Horsburgh, K. Chronic cerebral hypoperfusion: A key mechanism leading to vascular cognitive impairment and dementia. Closing the translational gap between rodentmodels and human vascular cognitive impairment and dementia. *Clin. Sci.* **2017**, *131*, 2451–2468.

8. Perrotta, M.; Lembo, G.; Carnevale, D. Hypertension and dementia: Epidemiological and experimental evidence revealing a detrimental relationship. *Int. J. Mol. Sci.* **2016**, *17*, 347.

9. Sudduth, T.L.;Weekman, E.M.; Price, B.R.; Gooch, J.L.;Woolums, A.; Norris, C.M.; Wilcock, D.M. Time-course of glial changes in the hyperhomocysteinemia model of vascular cognitive impairment and dementia (VCID). *Neuroscience* **2017**, *341*, 42–51.

10. Bhat, N.R. Vasculoprotection as a convergent, multi-targeted mechanism of anti-AD therapeutics and interventions. *J. Alzheimers Dis.* **2015**, *46*, 581–591.

11. Alzheimer's Disease International. *World Alzheimer Report 2016*; Alzheimer's Disease International: London, UK, 2016. Available online: www.alz.co.uk/worldreport2016 (accessed on 20 February 2018).

12. Srimanee, A.; Regberg, J.; Hallbrink, M.; Vajragupta, O.; Langel, U. Role of scavenger receptors in peptide-based delivery of plasmid DNA across a blood–brain barrier model. *Int. J. Pharm.* **2016**, *500*, 128–135.

13. De Boer, A.G.; van der Sandt, I.C.J.; Gaillard, P.J. The role of drug transporters at the blood–brain barrier. *Annu. Rev. Pharmacol. Toxicol.* **2003**, *43*, 629–656.

14. Almer, G.; Mangge, H.; Zimmer, A.; Prassl, R. Lipoprotein-related and apolipoprotein-mediated delivery systems for drug targeting and imaging. *Curr. Med. Chem.* **2015**, *22*, 3631–3651.

15. Preston, J.E.; Abbott, J.; Begley, D.J. Transcytosis of macromolecules at the blood–brain barrier. *Adv. Pharmacol.* **2014**, *71*, 147–163.

16. Di Marco, L.Y.; Venneri, A.; Farkas, E.; Evans, P.C.; Marzo, A.; Frangi, A.F. Vascular dysfunction in the pathogenesis of Alzheimer's disease—A review of endothelium-mediated mechanisms and ensuing vicious circles. *Neurobiol. Dis.* **2015**, *82*, 593–606.

17. Salmina, A.B.; Inzhutova, A.I.; Malinovskaya, N.A.; Petrova, M.M. Endothelial dysfunction and repair in Alzheimer-type neurodegeneration: Neuronal and glial control. *J. Alzheimers Dis.* **2010**, *22*, 17–36.

18. Tong, X.K.; Hamel, E. Simvastatin restored vascular reactivity, endothelial function and reduced string vessel pathology in a mouse model of cerebrovascular disease. *J. Cereb. Blood Flow Metab.* **2015**, *35*, 512–520.

19. Carradori, D.; Gaudin, A.; Brambilla, D.; Andrieux, K. Application of nanomedicine to the CNS diseases. *Int. Rev. Neurobiol.* **2016**, *130*, 73–113.

20. Koster, K.P.; Thomas, R.; Morris, A.W.; Tai, L.M. Epidermal growth factor prevents oligomeric amyloid-induced angiogenesis deficits in vitro. *J. Cereb. Blood Flow Metab.* **2016**, *36*, 1865–1871.

21. Zenaro, E.; Piacentino, G.; Constantin, G. The blood–brain barrier in Alzheimer's disease. *Neurobiol. Dis.* **2016**, *107*, 41–56.

22. Qosa, H.; Mohamed, A.; Al Rihani, S.B.; Batarseha, Y.S.; Duong, Q.V.; Keller, J.N.; Kaddoumi, A. High-throughput screening for identification of blood–brain barrier integrity enhancers: A drug repurposing opportunity to rectify vascular amyloid toxicity. *J. Alzheimers Dis.* **2016**, *53*, 1499–1516.

23. Hostenbach, S.; D'haeseleer, M.; Kooijman, R.; De Keyser, J. The pathophysiological role of astrocytic endothelin-1. *Prog Neurobiol.* **2016**, *144*, 88–102.

24. Koizumi, K.;Wang, G.; Park, L. Endothelial dysfunction and amyloid--induced neurovascular alterations. *Cell. Mol. Neurobiol.* **2016**, *36*, 155–165.

25. Goldwaser, E.L.; Acharya, N.K.; Sarkar, A.; Godsey, G.; Nagele, R.G. Breakdown of the cerebrovasculature and blood–brain barrier: A mechanistic link between diabetes mellitus and Alzheimer's disease. *J. Alzheimers Dis.* **2016**, *54*, 445–456.

26. Bredesen, D.E. Reversal of cognitive decline: A novel therapeutic program. *Aging (Albany, NY)* **2014**, *6*, 707–717.

27. Mahringer, A.; Reichel, V.; Ott, M.; MacLean, C.; Reimold, I.; Hollnack-Pusch, E.; Fricker, G. Overcoming the blood brain barrier: The challenge of brain drug targeting. *J. Nanoneurosci.* **2012**, *2*, 5–19.

28. Robert, J.; Button, E.B.; Stukas, S.; Boyce, G.K.; Gibbs, E.; Cowan, C.M.; Gilmour, M.; Cheng, W.H.; Soo, S.K.; Yuen, B.; et al. High-density lipoproteins suppress Aβ-induced PBMC adhesion to human endothelial cells in bioengineered vessels and in monoculture. *Mol. Neurodegener.* **2017**, *12*, 60.

29. Vishnyakova, T.G.; Bocharov, A.V.; Baranova, I.N.; Chen, Z.; Remaley, A.T.; Csako, G.; Eggerman, T.L.; Patterson, A.P. Binding and internalization of lipopolysaccharide by CLA-1, a human orthologue of rodent scavenger receptor B1. *J. Biol. Chem.* **2003**, *278*, 22771–22780.

30. Darlington,D.; Li, S.; Hou, H.; Habib, A.; Tian, J.; Gao, Y.; Ehrhart, J.; Sanberg, P.R.; Sawmiller, D.; Giunta, B.; et al. Human umbilical cord blood-derived monocytes improve cognitive deficits and reduce amyloid-pathology in PSAPP mice. *Cell Transplant.* **2015**, *24*, 2237–2250.

31. Chang, E.H.; Rigotti, A.; Huerta, P. Age-related influence of the HDL receptor SR-BI on synaptic plasticity and cognition. *Neurobiol. Aging* **2009**, *30*, 407–419.

32. Fung, K.Y.;Wang, C.; Nyegaard, S.; Heit, B.; Fairn, G.D.; Lee,W.L. SR-BI mediated transcytosis of HDL in brain microvascular endothelial cells is independent of caveolin, clathrin, and PDZK1. *Front. Physiol.* **2017**, *8*, 841.

33. Robert, J.; Stukas, S.; Button, E.; Cheng, W.H.; Lee, M.; Fan, J.; Wilkinson, A.; Kulic, I.; Wright, S.D.; Wellington, C.L. Reconstituted high-density lipoproteins acutely reduce soluble brain A levels in symptomatic APP/PS1 mice. *Biochim. Biophys. Acta* **2016**, *1862*, 1027–1036.

34. Armstrong, S.M.; Sugiyama, M.G.; Fung, K.Y.Y.; Gao, Y.; Wang, C.; Levy, A.S.; Azizi, P.; Roufaiel,M.; Zhu, S.N.; Neculai, D.; et al. A novel assay uncovers an unexpected role for SR-BI in LDL transcytosis. *Cardiovasc. Res.* **2015**, *108*, 268–277.

35. Hottman, D.A.; Chernick, D.; Cheng, S.; Wang, Z.; Li, L. HDL and cognition in neurodegenerative disorders. *Neurobiol. Dis.* **2014**, *72*, 22–36.

36. Velagapudi, S.; Yalcinkaya, M.; Piemontese, A.; Meier, R.; Norrelykke, S.F.; Perisa, D.; Rzepiela, A.; Stebler, M.; Stoma, S.; Zanoni, P.; et al. VEGF-A regulates cellular localization of SR-BI as well as transendothelial transport of HDL but not LDL. *Arterioscler. Thromb. Vasc. Biol.* **2017**, *37*, 794–803.

37. Choi, H.J.; Seo, E.H.; Yi, D.; Sohn, B.K.; Choe, Y.M.; Byun, M.S.; Lee, J.M.; Woo, J.I.; Lee, D.Y.Amyloid-independent amnestic mild cognitive impairment and serum apolipoprotein A1 levels. *Am. J. Geriatr. Psychiatry* **2016**, *24*, 144–153.

38. Kitamura, Y.; Usami, R.; Ichihara, S.; Kida, H.; Satoh, M.; Tomimoto, H.; Murata, M.; Oikawa, S. Plasma protein profiling for potential biomarkers in the early diagnosis of Alzheimer's disease. *Neurol. Res.* **2017**, *39*, 231–238.

39. Lazarus, J.; Mather, K.A.; Armstrong, N.J.; Song, F.; Poljak, A.; Thalamuthu, A.; Lee, T.; Kochan, N.A.; Brodaty, H.; Wright, M.J.; et al. DNA methylation in the apolipoprotein-A1 gene is associated with episodic memory performance on healthy older individuals. *J. Alzheimers Dis.* **2015**, *44*, 175–182.

40. Ma, C.; Li, J.; Bao, Z.; Ruan, Q.; Yu, Z. Serum levels of apoA1 and apoA2 are associated with cognitive status in older men. *Biomed. Res. Int.* **2015**, *2015*, 481621.

41. Slot, R.E.; Van Harten, A.C.; Kester, M.I.; Jongbloed, W.; Bouwman, F.H.; Teunissen, C.E.; Scheltens, P.; Veerhuis, R.; van der Flier,W.M. Apolipoprotein A1 in cerebrospinal fluid and plasma and progression to Alzheimer's disease in non-demented elderly. *J. Alzheimers Dis.* **2017**, *56*, 687–697.

42. Yin, Z.G.; Li, L.; Cui, M.; Zhou, S.M.; Yu, M.M.; Zhou, H.D. Inverse relationship between apolipoprotein A-I and cerebral white matter lesions: A cross-sectional study in middle-aged and elderly subjects. *PLoS ONE* **2014**, *9*, e97113.

43. Weekman, E.M.; Sudduth, T.L.; Caverly, C.N.; Kopper, T.J.; Phillips, O.W.; Powell, D.K.; Wilcock, D.M. Reduced efficacy of anti-A immunotherapy in a mouse model of amyloid deposition and vascular cognitive impairment comorbidity. *J. Neurosci.* **2016**, *36*, 9896–9907.

44. Nelson, A.R.; Sweeney, M.D.; Sagare, A.P.; Zlokovic, B.V. Neurovascular dysfunction and neurodegeneration in dementia and Alzheimer's disease. *Biochim. Biophys. Acta* **2016**, *1862*, 887–900.

45. Kapasi, A.; Schneider, J.A. Vascular contributions to cognitive impairment, clinical Alzheimer's disease, and dementia in older persons. *Biochim. Biophys. Acta* **2016**, *1862*, 878–886.

46. McAleese, K.L.; Alafuzoff, I.; Charidimou, A.; De Reuck, J.; Grinberg, L.T.; Hainsworth, A.H.; Hortobagyi, T.; Ince, P.; Jellinger, K.; Gao, J.; et al. Post-mortem assessment in vascular dementia: Advances and aspirations. *BMC Med.* **2016**, *14*, 129.

47. Noh, Y.; Seo, S.W.; Jeon, S.; Lee, J.M.; Kim, J.S.; Lee, J.H.; Kim, J.H.; Kim, G.H.; Ye, B.S.; Cho, H.; et al. The role of cerebrovascular disease in amyloid deposition. *J. Alzheimers Dis.* **2016**, *54*, 1015–1026.

48. Hishikawa, N.; Fukui, Y.; Sato, K.; Kono, S.; Yamashita, T.; Ohta, T.; Deguchi, K.; Abe, K. Cognitive and affective functions in Alzheimer's disease patients with metabolic syndrome. *Eur. J. Neurol.* **2016**, *23*, 339–345.

49. Gutierrez, J.; Honig, L.; Elkind, M.S.; Mohr, J.P.; Goldman, J.; Dwork, A.J.; Morgello, S.; Marshall, R.S. Brain arterial aging and its relationship to Alzheimer dementia. *Neurology* **2016**, *86*, 1507–1515.

50. Nagata, K.; Yamazaki, T.; Takano, D.; Maeda, T.; Fujimaki, Y.; Nakase, T.; Sato, Y. Cerebral circulation in aging. *Ageing Res. Rev.* **2016**, *30*, 49–60.

51. Calabrese, V.; Giordano, J.; Signorile, A.; Ontario, M.L.; Castorina, S.; de Pasquale, C.; Eckert, G.; Calabrese, E.J. Major pathogenic mechanisms in vascular dementia: Roles of cellular stress response and hormesis in neuroprotection. *J. Neurosci. Res.* **2016**, *94*, 1588–1603.

52. Toth, P.; Tarantini, S.; Csiszar, A.; Ungvari, Z.I. Functional vascular contributions to cognitive impairment and dementia: Mechanisms and consequences of cerebral autoregulatory dysfunction, endothelial impairment, and neurovascular uncoupling in aging. *Am. J. Physiol. Heart Circ. Physiol.* **2017**, *312*, H1–H20.

53. Devraj, K.; Poznanovic, S.; Spahn, C.; Schwall, G.; Harter, P.N.; Mittelbronn, M.; Antoniello, K.; Paganetti, P.; Muhs, A.; Heilemann, M.; et al. BACE-1 is expressed in the blood–brain barrier endothelium and is upregulated in a murine model of Alzheimer's disease. *J. Cereb. Blood Flow Metab.* **2016**, *36*, 1281–1294.

54. Chao, A.C.; Lee, T.C.; Juo, S.H.; Yang, D.I. Hyperglycemia increases the production of amyloid -peptide leading to decreased endothelial tight junction. *CNS Neurosci. Ther.* **2016**, *22*, 291–297.

55. Khalil, R.B.; Khoury, E.; Koussa, S. Linkingmultiple pathogenic pathways in Alzheimer's disease.*World J. Psychiatry* **2016**, *6*, 208–214.

56. Festoff, B.W.; Sajja, R.K.; van Dreden, P.; Cucullo, L. HGMB1 and thrombin mediate the blood–brain barrier dysfunction acting as biomarkers of neuroinflammation and progression to neurodegeneration in Alzheimer's disease. *J. Neuroinflamm.* **2016**, *13*, 194.

57. Gangoda, S.V.; Butlin, M.; Gupta, V.; Chung, R.; Avolio, A. Pulsatile stretch alters expression and processing of amyloid precursor protein in human cerebral endothelial cells. *J. Hypertens.* **2016**, *34*, e24.

58. Roberts, A.M.; Jagadapillai, R.; Vaishnav, R.A.; Friedland, R.P.; Drinovac, R.; Lin, X.; Gozal, E. Increased pulmonary arteriolar tone associated with lung oxidative stress and nitric oxide in a mouse model of Alzheimer's disease. *Physiol. Rep.* **2016**, *4*, e12953.

59. Shang, S.; Yang, Y.M.; Zhang, H.; Tian, L.; Jiang, J.S.; Dong, Y.B.; Zhang, K.; Li, B.; Zhao,W.D.; Fang,W.G.; et al. Intracerebral GM-CSF contributes to transendothelial monocyte migration in APP/PS1 Alzheimer's disease mice. *J. Cereb. Blood Flow Metab.* **2016**, *36*, 1987–1991.

60. Austin, S.A.; Katusic, Z.S. Loss of endothelial nitric oxide synthase promotes p25 generation and tau phosphorylation in amurinemodel of Alzheimer's disease. *Circ. Res.* **2016**, *119*, 1128–1134.

61. Katusic, Z.S.; Austin, S.A. Neurovascular protective function of endothelial nitric oxide. *Circ. J.* **2016**, *80*, 1499–1503.

62. Wang, L.; Du, Y.; Wang, K.; Xu, G.; Luo, S.; He, G. Chronic cerebral hypoperfusion induces memory deficits and facilitates A generation in C57BL/6J mice. *Exp. Neurol.* **2016**, *283*, 353–364.

63. Kyrtsos, C.R.; Baras, J.S. Modeling the role of the glymphatic pathway and cerebral blood vessel properties in Alzheimer's disease pathogenesis. *PLoS ONE* **2015**, *10*, e0139574.

64. Kalaria, R.N.; Akinyemi, R.; Ihara, M. Stroke injury, cognitive impairment and vascular dementia. *Biochim. Biophys. Acta* **2016**, *1862*, 915–925.

65. Khan, A.; Kalaria, R.N.; Corbett, A.; Ballard, C. Update on vascular dementia. *J. Geriatr. Psychiatry Neurol.* **2016**, *29*, 281–301.

66. Austin, S.A.; Santhanam, A.V.; d'Uscio, L.V.; Katusic, Z.S. Regional heterogeneity of cerebral microvessels and brain susceptibility to oxidative stress. *PLoS ONE* **2015**, *10*, e0144062.

67. Toda, N.; Okamura, T. Cigarette smoking impairs nitric oxide-mediated cerebral blood flow increase: Implications for Alzheimer's disease. *J. Pharmacol. Sci.* **2016**, *131*, 223–232.

68. Uiterwijk, R.; Huijts, M.; Staals, J.; Rouhl, R.P.; De Leeuw, P.W.; Kroon, A.A.; van Oostenbrugge, R.J. Endothelial activation is associated with cognitive performance in patients with hypertension. *Am. J. Hypertens.* **2016**, *29*, 464–469.

69. Kamat, P.K.; Kyles, P.; Kalani, A.; Tyagi, N. Hydrogen sulfide ameliorates homocysteine-induced Alzheimer's disease-like pathology, blood–brain barrier disruption, and synaptic disorder. *Mol. Neurobiol.* **2016**, *53*, 2451–2467.

70. Iadecola, C. Untangling neurons with endothelial nitric oxide. *Circ. Res.* **2016**, 119, 1052–1054.

71. Wang, Y.J. Lessons from immunotherapy for Alzheimer's disease. *Nat. Rev. Neurol.* **2014**, *10*, 188–189.

72. Krstic, D.; Knuesel, I. Deciphering the mechanism underlying late-onset Alzheimer's disease. *Nat. Rev. Neurol.* **2013**, *9*, 25–34.

73. D'Arrigo, J. *Stable Nanoemulsions: Self-Assembly in Nature and Nanomedicine*; Elsevier: Amsterdam, The Netherlands, 2011; 415p, ISBN 978-0-444-53798-0.

74. Barbarese, E.; Ho, S.Y.; D'Arrigo, J.S.; Simon, R.H. Internalization of microbubbles by tumor cells in vivo and in vitro. *J. Neurooncol.* **1995**, *26*, 25–34.

75. D'Arrigo, J. Surfactant Mixtures, Stable Gas-in-Liquid Emulsions, and Methods for the Production of such Emulsions from Said Mixtures. U.S. Patent No. 4,684,479A, 4 August 1987.

76. D'Arrigo, J. Method for the Production of Medical-Grade Lipid-Coated Microbubbles, Paramagnetic Labeling of such Microbubbles and Therapeutic Uses of Microbubbles. U.S. Patent No. 5,215,680A, 1 July 1993.

77. Garg, G.; Saraf, Sh.; Saraf, Sw. Cubosomes: An overview. *Biol. Pharm. Bull.* **2007**, *30*, 350–353.

78. Tanford, C. *The Hydrophobic Effect: Formation of Micelles and Biological Membranes*; Wiley: New York, NY, USA, 1973; 200p.
79. Boyd, B.J.; Whittaker, D.V.; Khoo, S.M.; Davey, G. Lyotropic liquid crystalline phases formed from glycerate surfactants as sustained release drug delivery systems. *Int. J. Pharm.* **2006**, *309*, 218–226.

80. Pouton, C.W. Properties and uses of common formulation lipids, surfactants and cosurfactants. In Proceedings of the AAPSWorkshop, Effective Utilization of Lipid-Based Systems to Enhance the Delivery of Poorly Soluble Drugs: Physicochemical, Biopharmaceutical and Product Development Considerations, Bethesda, MD, USA, 5–6 March 2007; Constantinides, P.P., Porter, C.J.H., Eds.; AAPS: Arlington, VA, USA, 2007.

81. Small, D.M. The behavior of biological lipids. *Pure Appl. Chem.* **1981**, *53*, 2095–2103.

82. Kaasgaard, T.; Drummond, C.J. Ordered 2-D and 3-D nano-structured amphiphile self-assembly materials stable in excess solvent. *Phys. Chem. Chem. Phys.* **2006**, *8*, 4957–4975.

83. Shearman, G.C.; Khoo, B.J.; Motherwell, M.L.; Brakke, K.A.; Ces, O.; Conn, C.E.; Seddon, J.M.; Templer, R.H. Calculations of and evidence for chain packing stress in inverse lyotropic bicontinuous cubic phases. *Langmuir* **2007**, *23*, 7276–7285.

84. Rizwan, S.B.; Dong, Y.D.; Boyd, B.J.; Rades, T.; Hook, S. Characterization of bicontinuous cubic liquid crystalline systems of phytantriol and water using cryo field emission scanning electron microscopy (cryo FESEM). *Micron* **2007**, *38*, 478–485.

85. Yaghmur, A.; de Campo, L.; Sagalowicz, L.; Leser, M.E.; Glatter, O. Emulsified microemulsions and oil-containing liquid crystalline phases. *Langmuir* **2005**, *21*, 569–577.

86. Yaghmur, A.; de Campo, L.; Sagalowicz, L.; Leser, M.E.; Glatter, O. Control of the internal structure of MLO-based isasomes by the addition of diglycerol monooleate and soybean phosphatidylcholine. *Langmuir* **2006**, *22*, 9919–9927.

87. Gustafsson, J.; Ljusberg-Wahren, H.; Almgren, M.; Larsson, K. Submicron particles of reversed lipid phases in water stabilized by a nonionic amphiphilic polymer. *Langmuir* **1997**, *13*, 6964–6971.

88. De Campo, L.; Yaghmur, A.; Sagalowicz, L.; Leser, M.E.; Watzke, H.; Glatter, O. Reversible phase transitions in emulsified nanostructured lipid systems. *Langmuir* **2004**, *20*, 5254–5261.

89. Yaghmur, A.; de Campo, L.; Salentinig, S.; Sagalowicz, L.; Leser, M.E.; Glatter, O. Oil-loaded monolinolein-based particles with confined inverse discontinuous cubic structure (Fd3m). *Langmuir* **2006**, *22*, 517–521.

90. Amselem, S.; Friedman, D. Solid Fat Nanoemulsions. U.S. Patent No. 5,662,932A, 2 September 1997.

91. Larsson, K. Aqueous dispersions of cubic lipid–water phases. *Curr. Opin. Colloid Interface Sci.* **2000**, *5*, 64–69.

92. Luzzati, V. Biological significance of lipid polymorphism: The cubic phases. *Curr. Opin. Struct. Biol.* **1997**, *7*, 661–668.

93. Lacko, A.G.; Nair, N.; Prokai, L.; McConathy, W.J. Prospects and challenges of the development of lipoprotein-based formulations for anti-cancer drugs. *Expert Opin. Drug Deliv.* **2007**, *4*, 665–675.

94. Azeem, A.; Rizwan, M.; Ahmad, F.J.; Iqbal, Z.; Khar, R.K.; Aqil, M.; Talegaonkar, S. Nanoemulsion components screening and selection: A technical note. *AAPS Pharm. Sci. Tech.* **2009**, *10*, 69–76.

95. Sagar, G.H.; Arunagirinathan, M.A.; Bellare, J.R. Self-assembled surfactant nano-structures important in drug-delivery: A review. *Indian J. Exp. Biol.* **2007**, *45*, 133–159.

96. Anton, N.; Benoit, J.P.; Saulnier, P. Design and production of nanoparticles formulated from nano-emulsion templates: A review. *J. Control. Release* **2008**, *128*, 185–199.

97. Bansal, T.; Mustafa, G.; Khan, Z.I.; Ahmad, F.J.; Khar, R.K.; Talegaonkar, S. Solid self-nanoemulsifying delivery systems as a platform technology for formulation of poorly soluble drugs. *Crit. Rev. Ther. Drug Carrier Syst.* **2008**, *25*, 63–116.

98. Sadurni, N.; Solans, C.; Azemar, N.; Garcia-Celma, M.J. Studies on the formation of O/W nano-emulsions, by low-energy emulsification methods, suitable for pharmaceutical applications. *Eur. J. Pharm. Sci.* **2005**, *26*, 438–445.

99. Tresset, G. The multiple faces of self-assembled lipidic systems. *PMC Biophys.* **2009**, *2*, 3.

100. Hato, M.; Yamashita, J.; Shiono, M. Aqueous phase behavior of lipids with isoprenoid type hydrophobic chains. *J. Phys. Chem. B* **2009**, *113*, 10196–10209.

101. Barauskas, J.; Cervin, C.; Tiberg, F.; Johnsson, M. Structure of lyotropic self-assembled lipid nonlamellar liquid crystals and their nanoparticles in mixtures of phosphatidyl choline and -tocopherol (vitamin E). *Phys. Chem. Chem. Phys.* **2008**, *10*, 6483–6485.

102. Efrat, R.; Aserin, A.; Garti, N. On structural transitions in a discontinuous micellar cubic phase loaded with sodium diclofenac. *J. Colloid Interface Sci.* **2008**, *321*, 166–176.

103. Yaghmur, A.; Laggner, P.; Almgren, M.; Rappolt, M. Self-assembly in monoelaidin aqueous dispersions: Direct vesicles to cubosomes transition. *PLoS ONE* **2008**, *3*, e3747.

104. Yaghmur, A.; Glatter, O. Characterization and potential applications of nanostructured aqueous dispersions. *Adv. Colloid Interface Sci.* **2009**, *147–148*, 333–342.

105. Vandoolaeghe, P.; Rennie, A.R.; Campbell, R.A.; Nylander, T. Neutron reflectivity studies of the interaction of cubic phase nanoparticles with phospholipid bilayers of different coverage. *Langmuir* **2009**, *25*, 4009–4020.

106. Vandoolaeghe, P.; Barauskas, J.; Johnsson, M.; Tiberg, F.; Nylander, T. Interaction between lamellar (vesicles) and nonlamellar lipid liquid-crystalline nanoparticles as studied by time-resolved small-angle X-ray diffraction. *Langmuir* **2009**, *25*, 3999–4008.

107. Yaghmur, A.; Kriechbaum, M.; Amenitsch, H.; Steinhart, M.; Laggner, P.; Rappolt, M. Effects of pressure and temperature on the self-assembled fully hydrated nanostructures of monoolein–oil systems. *Langmuir* **2010**, *26*, 1177–1185.

108. Fong, W.K.; Hanley, T.; Boyd, B.J. Stimuli responsive liquid crystals provide “on-demand” drug delivery in vitro and in vivo. *J. Control. Release* **2009**, *135*, 218–226.

109. Nimmrich, V.; Eckert, A. Calcium channel blockers and dementia. *Brit. J. Pharmacol.* **2013**, *169*, 1203-1210.

110. Shirwany, N.A.; Payette, D.; Xie, J.; Guo, Q. The amyloid beta ion channel hypothesis of Alzheimer's disease. *Neuropsychiatr. Dis. Treat.* ***2007****, 3*, 597-612.

111. Rudy, C.C.; Hunsberger, H.C.; Weitzner, D.S.; Reed, M.N. The role of the tripartite glutamatergic synapse in the pathophysiology of Alzheimer's disease. *Aging Dis.* **2015**, *6*, 131-148.

112. Zhang, Y.; Li, P.; Feng, J.; Wu, M. Dysfunction of NMDA receptors in Alzheimer's disease. *Neurol. Sci.* **2016**, *37*, 1039-1047.

113. Di Scala, C.; Yahi, N.; Boutemeur, S.; Flores, A.; Rodriguez, L; Chahinian, H.; Fantini, J. Common molecular mechanism of amyloid pore formation by Alzheimer's β-amyloid peptide and α-synuclein. *Sci. Rep.* **2016**, *6*, 28781.

114. Demuro, A.; Smith, M.; Parker, I. Single-channel Ca^{2+} imaging implicates Aβ1-42 amyloid pores in Alzheimer's disease pathology. *J. Cell Biol.* **2011**, *195*, 515-524.

115. Serra-Batiste, M.; Ninot-Pedrosa, M.; Bayoumi, M.; Gairi, M.; Maglia, G.; Carulla, N. Aβ42 assembles into specific β-barrel pore-forming oligomers in membrane-mimicking environments. *Proc. Natl. Acad. Sci. USA* **2016**, *113*, 10866-10871.

116. Bode, D.C.; Baker, M.D.; Viles, J.H. Ion channel formation by amyloid-β_{42} oligomers but not amyloid-β_{40} in cellular membranes. *J. Biol. Chem.* **2017**, *292*, 1404-1413.

117. Di Scala, C.; Chahinian, H.; Yahi, N.; Garmy, N.; Fantini, J. Interaction of Alzheimer's β-amyloid peptides with cholesterol: Mechanistic insights into amyloid pore formation. *Biochemistry* **2014**, *53*, 4489-4502.

118. Ghosal, K.; Haag, M.; Verghese, P.B.; West, T.; Veenstra, T.; Braunstein, J.B.; Bateman, R.J.; Holtzman, D.M.; Landreth, G.E. Arandomized controlled study to evaluate the effect of bexarotene on amyloid-β and apolipoprotein E metabolism in healthy subjects. *Alzheimers Dement. (NY)* **2016**, *2*, 110-120.

119. Pierrot, N.; Lhommel, R.; Quenon, L.; Hanseeuw, B.; Dricot, L.; Sindic, C.; Maloteaux, J.M.; Octave, J.N.; Ivanoiu, A. Targretin [bexarotene] improves cognitive and biological markers in a patient with Alzheimer's disease. *J. Alzheimer's Dis.* **2016**, *49*, 271-276.

120. Mirza, Z.; Beg, M.A. Possible molecular interactions of bexarotene – a retinoid drug and Alzheimer's Aβ peptide: A docking study. *Curr. Alzheimer Res.* **2017**, *14*, 327-334.

121. Huy, P.D.Q.; Thai, N.Q.; Bednarikova, Z.; Phuc, L.H.; Linh, H.Q.; Gazova, Z.; Li, M.S. Bexarotene does not clear amyloid beta plaques but delays fibril growth: Molecular mechanisms. *ACS Chem. Neurosci.* **2017**, *8*, 1960-1969.

122. Mariani, M.M.; Malm, T.; Lamb, R.; Jay, T.R.; Neilson, L.; Casali, B.; Medarametla, L.; Landreth, G.E. Neuronally-directed effects of RXR activation in a mouse model of Alzheimer's disease. *Sci. Rep.* **2017**, *7*, 42270.

123. Habchi, J.; Arosio, P.; Perni, M.; Costa, A.R.; Yagi-Utsumi, M.; Joshi, P.; Chia,S.; Cohen, S.I.A.; Muller, M.B.D.; Linse, S.; et al. An anticancer drug suppresses the primary nucleation reaction that initiates the production of the toxic Aβ42 aggregates linked with Alzheimer's disease. *Sci. Adv.* **2016**, *2*, e1501244.

124. Fantini, J.; Di Scala, C.; Yahi, N.; Troadec, J.D.; Sadelli, K.; Chahinian, H.; Garmy, N. Bexarotene blocks calcium-permeable ion channels formed by neurotoxic Alzheimer's β-amyloid peptides. *ACS Chem. Neurosci.* **2014**, *5*, 216-224.

125. Casali, B.T.; Reed-Geaghan, E.G.; Landreth, G.E. Nuclear receptor agonist-driven modification of inflammation and amyloid pathology enhances and sustains cognitive improvements in a mouse model of Alzheimer's disease. *J. Neuroinflamm.* **2018**, *15*, 43.

126. Tu, L.; Yang, X.L.; Zhang, Q.; Wang, Q; Tian, T.; Liu, D.; Qu, X.; Tian, J.Y. Bexarotene attenuates early brain injury via inhibiting microglia activation through PPARγ after experimental subarachnoid hemorrhage. *Neurol. Res.* **2018**, doi:10.1080/01616412.2018.1463900 .

127. Dheer, Y.; Chitranshi, N.; Gupta, V.; Abbasi, M.; Mirzaei, M.; You, Y; Chung, R.; Graham, S.L.; Gupta, V. Bexarotene modulates retinoid-X-receptor expression and is protective against neurotoxic endoplasmic reticulum stress response and apoptotic pathway activation. *Mol. Neurobiol.* **2018**, doi:10.1007/s12035-018-1041-9 .

128. Kamp, F.; Scheidt, H.A.; Winkler, E.; Basset, G.; Heinel, H.; Hutchison, J.M.; LaPointe, L.M.; Sanders, C.R.; Steiner, H.; Huster, D. Bexarotene binds to the amyloid precursor protein transmembrane domain, alters its α-helical conformation, and inhibits γ-secretase nonselectivity in liposomes. *ACS Chem. Neurosci.* **2018**, doi:10.1021acschemneuro.8b00068 .

129. Serra-Batiste, M.; Tolchard, J.; Giusti, F.; Zoonens, M.; Carulla, N. Stabilization of a membrane-associated amyloid-β oligomer for its validation in Alzheimer's disease. *Front. Mol. Biosci.* **2018**, *5*, 38.

130. Xiang, N.; Lyu, Y.; Zhu, X.; Narsimhan, G. Investigation of the interaction of amyloid-β peptide (11-42) oligomers with a 1-palmitoyl-2-oleoyl-sn-glycero-3-phosphocholine (POPC) membrane using molecular dynamics simulation. *Phys. Chem. Chem.Phys.* **2018***, 20*, 6817-6829.

131. Habchi, J.; Chia, S.; Galvagnion, C.; Michaels, T.C.T.; Bellaiche, M.M.J.; Ruggeri, F.S.; Sanguanini, M.; Idini, I.; Kumita, J.R.; Sparr, E.; et al. Cholesterol catalyses Aβ42 aggregation through a heterogeneous nucleation pathway in the presence of lipid membranes. *Nat. Chem.* **2018**, *10*, 673-683.