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Review

Treating Dementia Early: Limiting Cellular Damage in Brain Tissue

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Abstract

Much evidence has been published which indicates that microvascular endothelial dysfunction, due to cerebrovascular risk factors (e.g., atherosclerosis, hypertension, obesity, diabetes, smoking, 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, 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 FDA-approved drug(s), especially one which has shown the added ability to restore some cognitive functions in certain animal models of Alzheimer's disease.

Keywords

Dementia; cognitive impairment; blood-brain barrier; Alzheimer's disease; drug targeting; nanoemulsion

1. Background

Cognitive impairment late in life is associated with two dominant diseases in humans, i.e., Alzheimer's disease and small vessel cerebrovascular disease, both causing brain atrophy years before clinical symptoms are detected. In fact, vascular brain lesions are very common in people over 70 years old, and recent reviews (e.g., [1, 2] for background information) provide much evidence that a large proportion of dementia cases may be attributable to cerebrovascular disease (see also [3, 4] and below). These vascular lesions include alterations in density and morphology of cerebral microvasculature, and a blood-brain barrier (BBB) breakdown with leakage of blood-borne molecules (see [4] for recent animal data, and a description of human data contained in citations 4-6 therein). 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 (e.g., [5, 6]; cf. [7-12]; see also below). On a worldwide basis, 47 million people had dementia in 2016; of these dementia patients, 60%-80% have Alzheimer's disease (e.g., [8, 9, 13, 14]: cf. below). It is no surprise, therefore, that multiple epidemiological studies have shown a marked overlap among risk factors for small vessel cerebrovascular disease and late-onset Alzheimer's disease. Furthermore, growing data from brain imaging studies and various animal models suggest that cerebrovascular dysfunction may well preceed cognitive impairment and the onset of neurodegenerative changes in Alzheimer's disease [2, 4].

Also consistent with all the above considerations, clinicians have recently reported [15] (after a detailed review of studies examining current strategies for dementia prevention) that human studies to date suggest that multifactorial intervention, emphasizing particularly physical exercise and amelioration of vascular risk factors, may hold the most promise for the prevention of cognitive decline. As recently reviewed by Barnes and Corkery [16], aging and cardiovascular disease risk factors have long been associated with diminished vascular function, often having clinical implications which can include brain health. Nevertheless, these authors report that the age-associated increase in blood pressure and impairment in vascular function often may be lessened or even reversed through changes in lifestyle behaviors. Greater amounts of habitual exercise and higher cardiorespiratory fitness are correlated with measurable beneficial effects on cerebrovascular health and cognition [15, 16].

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 (see below). Accordingly, endothelial-cell modulation and repair is feasible by pharmacological targeting [1, 2, 17-36] via SR-BI receptors (cf. [30]). Recently, Fung et al. [37] specifically reported that SR-BI mediates the uptake and transcytosis of high-density lipoprotein (HDL) across brain microvascular endothelial cells (i.e., across the BBB). Since SR-BI has already 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, 33, 38-40] (cf. [41-47]).

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, 48-58] and an apparent endothelium-dysfunction [2, 38-46, 54, 59-65] in both Alzheimer's disease and its major risk factors [1, 2, 58-77]. This (intravenous) combination therapeutic would make it possible for various cell types, all potentially implicated in Alzheimer's disease (see [1, 2] for reviews; cf. [76, 77]), to be simultaneously sought out and better reached for localized drug treatment of brain tissue in vivo [78] (cf. [79]).

Note also that various published findings, reviewed earlier [78], supply further (indirect) evidence indicating that SR-BI may well provide an effective route for receptor-mediated (endocytic) drug delivery. For example, SR-BI is known to mediate the cellular uptake of cholesterol esters from HDL. When combined with various factors concerning the heterogeneity of HDL particles as well as the well-documented multiligand capability of SR-BI, then SR-BI emerges as the most plausible candidate (of all lipoprotein receptors) for major involvement in the enhanced endocytosis of LCM/ND lipid nanoemulsion(s) for targeted drug delivery. The parallel which exists is that the previously documented similarities in lipid composition between HDL and LCM/ND nanoemulsion(s) can partially simulate or mimic the above-mentioned heterogeneity (i.e., subpopulations or subspecies) of HDL particles [78].

In addition, the "lipid-coated microbubble/nanoparticle" population(s), within the LCM/ND lipid nanoemulsion, have neither been found to agglomerate nor coalesce into any "microbubble/particle" structure larger than 5 μm, either in vitro or in vivo, thus the risk of air embolus is negligible. Acute intravenous toxicity studies of this (isotonic) LCM/ND nanoemulsion agent in rabbits and dogs were conducted at an independent GLP contractor. The acute intravenous LD_{50} in both species was found to be greater than 4.8 mL/kg (i.e., well beyond all intended clinical dosages). Furthermore, no signs of gross toxicity or mortality were observed at the dosage of 4.8 mL/kg. It has also been found in other animal toxicology studies that at (intended clinical) intravenous LCM/ND lipid nanoemulsion doses of 0.14 mL/kg given three times per week for 6 weeks in rats and (much higher intravenous doses of) 0.48 mL/kg given three times per week for 3 months in rabbits, there were no untoward changes in serum chemistry, liver functions, hematology, or clotting profile or histological changes in adrenals, bladder, brain, heart, kidney, liver, lungs, marrow, pituitary, spleen, testes, thyroid, or ureters [78].

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

The self-assembling LCM/ND lipid nanoemulsion class comprises nonionic lipids exclusively (cf. [80, 81]) 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., comprising 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 [78]. While most early studies with LCM/ND nanoemulsions focused on its "lipid-coated microbubble (LCM) subpopulation" which rapidly targeted various tumors and neuroinjury sites, the same targeted drug-delivery attributes can logically be expected also from a colloidal (liquid-crystalline) "lipid nanoparticle subpopulation" in the LCM/ND nanoemulsion–since both categories of stable colloidal species (i.e., LCM and

nanoparticles) are formed simultaneously in the stable nanoemulsion using the same (earlier-patented) mixture of powdered solid lipid surfactants. Basically, this patented mixture of lipid compounds comprises saturated glycerides (with acyl chain lengths greater than 10 carbons) combined with cholesterol and cholesterol esters. Moreover, later studies (using improved versions of various particle-sizing instruments) uncovered evidence that the vast majority of the LCM/ND nanoemulsion's lipid "microbubble/nano-particle" population exhibits diameters less than 1.0 μm [78].

Importantly, monoglyceride is the largest single-lipid fraction (by wt. %) of the powdered solid lipid surfactants used to produce the (Filmix®) LCM/ND nanoemulsions [78]. As a group, monoglycerides exhibit different phase behaviors when they are exposed to water [82] (cf. [83-86]). In agreement with numerous other investigators, Kaasgaard and Drummond [87] 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 (cf. [88-94]).

In particular, 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 [78]. There is great interest to utilize these dispersed cubic phases for the administration of drugs, or for the formulation of new delivery systems [94]. The (lyotropic or solvent-induced) cubic liquid-crystalline phases may be classified into two distinct classes: Bicontinuous cubic phases [95-99] and micellar or discontinuous (e.g., type *Fd3m*) cubic phases [94]. As reviewed by Garg et al. [82], monoglycerides spontaneously form bicontinuous cubic phases upon the addition of water, are relatively insoluble (allowing the formation of colloidal dispersions of cubic phases), and are resistant to changes in temperature. Accordingly, lipid nanoparticles comprising interior liquid-crystalline structures of curved lipid membranes (i.e., dispersed cubic phases) have been used to solubilize, encapsulate, and deliver medications to disease areas within the body [82] (see also [100-111]).

In addition to the above-described category of various bicontinuous cubic phases, the other above-named category referred to as "micellar or discontinuous" cubic phases is also worthy of comment at this point. Of particular interest within this latter category is the well-studied micellar cubic structure of the type *Fd3m* (which is often denoted by the number Q^{227}) (e.g., [94, 112]). Luzzati and coworkers have reported that this *Fd3m* cubic phase evidently requires a heterogeneous mixture of polar lipids [112, 113]: Using the lipid examples they cite (and the lipid classification system of Small [86]), this *Fd3m* phase apparently must include *both* at least one (sufficiently polar) insoluble swelling amphiphilic lipid (e.g., monoglyceride [112, 113]) and at least one (weakly polar) insoluble nonswelling amphiphilic lipid (e.g., diglyceride and/or cholesterol [112-114]; see also [115-118]) in order to self-assemble properly in (excess) water. Hence, the dispersed *Fd3m* cubic phase can represent a lipid/water system which is particularly relevant to the earlier-described (Filmix®) LCM/ND lipid nanoemulsion formulation(s) on account of the fact that the patent claims describing the precise lipid composition of such nanoemulsion formulations (see especially Claim #1 in [80, 81]) specifically include cholesterol and three categories of (saturated) glycerides, that is, tri-, di-, and monoglycerides (see [80, 81]). In view of all the advantageous attributes of monoglycerides (recounted in the preceding paragraphs), and since (saturated) monoglyceride represents the largest single-lipid fraction of the LCM/ND lipid nanoemulsion type, the monoglyceride content probably plays a dominant role in supporting the

evident long-term stability of the liquid-crystalline lipid nanoparticles in such nanoemulsions (see also [78] for a detailed review).

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 [78]. 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 [119]. In addition, Kuntsche et al. [120, 121] have prepared lipid nanoparticles in the (mesomorphic or) liquid-crystalline phase from cholesterol esters with saturated acyl chains. 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 [78].

To conclude, self-assembled (colloidal mesophase) lipid nanoemulsions (e.g., [95-100]), particularly those predominantly containing dispersed cubic-phase lipid nanoparticles (e.g., [101-105]), 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., [106-108]). 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. [78]).

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

As explained in many reviews (e.g., [122-124]) by different investigators, it has been recognized for over two decades that disturbance of the intracellular calcium homeostasis is deeply involved in various aspects of the pathophysiology of several neurodegenerative disorders. As concerns Alzheimer's disease, it is believed by many researchers that enhanced calcium load may be brought about by extracellular accumulation of amyloid-β(Aβ) in the brain [122, 123]. (In a subsequent review by Liao et al. [125], it is explained that this loss of calcium homeostasis is known to cause both the hyperphosphorylation of tau, resulting in neurofibillary tangles, and eventual neurodegeneration. Moreover, these authors further provide evidence supporting an updated amyloid cascade hypothesis, framing tau hyperphosphorylation as a cellular event between Aβ triggering and final synaptic deficits–which are strongly correlated with cognitive decline [125]. Therefore, blocking of the initial (soluble-)Aβ triggering event can be seen as a crucial goal in treating dementia early (see below).) Such studies have laid the foundation for the popular idea that amyloid-β peptides (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 [122, 123].

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., [126, 127]), involves a central role for the tripartite glutamatergic synapse in the pathophysiology 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 [126] (cf. [127]). (More generally, it should also be noted that various other alterations of intracellular signaling can lead to neurovascular degeneration. For example, Calabrese and coworkers [56] describe the major pathogenic factors involved in vascular cognitive impairment, emphasizing the relevance of cerebrocellular stress and neurohormetic responses to neurovascular insult. Similarly, this research group has recently [128] discussed various cellular mechanisms (e.g., oxidant/antioxidant status, oxidative stress, and the vitagene network) underlying Alzheimer's-disease neuroinflammatory pathogenesis that are contributory to Alzheimer's disease [56, 128, 129].)

Historical support for the above amyloid-β ion channel hypothesis, or so-called "calcium hypothesis", has also been observed at the clinical level [130]. 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 [131]. (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 [131]. Moreover, recent studies [132, 133] have found that the concentration of soluble Aβ oligomers (in aqueous brain lysates) from patients with early Alzheimer's-disease dementia was significantly higher than (in aqueous brain lysates) from patients with comparable Aβ-plaque burden but no dementia. These authors hypothesized that Aβ plaques could serve as binding reservoirs (sinks) or buffers for toxic soluble Aβ oligomers, sequestering them from other targets in the extracellular space and thereby preventing their toxicity. At early stages, the Aβ plaques could adequately buffer soluble oligomers, thereby protecting nearby neuropil from toxicity; whereas at later times if buffering capacity was lost or overwhelmed, soluble Aβ oligomers could be free to diffuse in the extracellular space and exert toxicity [132, 133].) 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 [131].

As summarized by Di Scala et al. [130], 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) to study the two major Aβ variants, namely, Aβ(1-40) and Aβ(1-42). Under the optimized detergent-micelle conditions employed: 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 [134]. (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 [134]. Very recently, a different research group reported very similar findings [135]. 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, these authors' own detailed experimental data [135] 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 [135]. (In addition, very recent in vivo experiments in rodents [136] have shown that cerebrospinal fluid enters the brain tissue along arterial perivascular spaces, and this flow plays a vital role in driving the clearance of toxic proteins such as Aβ(1-42) [137] from the interstitial fluid at more downstream locations. Detailed data analysis confirms that pumping of the heart, along with vascular wall kinetics (perivascular pumping), directly drive pulsatile cerebrospinal fluid bulk flow through the spaces between brain cells–thus clearing potentially toxic proteins into the bloodstream [136, 137]. There is a decline in such clearance activity throughout the normal older adult lifespan, allowing buildup of Aβ(1-42) in brain tissue [137]; this buildup can accordingly be expected to facilitate membrane insertion of Aβ(1-42) and subsequent amyloid pore formation.

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) [130]. 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 toxic oligomers [138]. However, when *oral* administration of bexarotene was employed subsequently in a Phase Ib (proof of mechanism) clinical trial [139], 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 [139] (cf. [140]).)

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 [141, 142] (cf. [143-145]). 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. [146] 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). 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 [146]. (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 above), incorporation of the bexarotene molecule into the LCM/ND nanocarrier is expected to represent an uncomplicated, straightforward formulation procedure commercially.) Moreover, Casali et al. [147] 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 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 [147].

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. [148, 149]). In the most recently published study, Kamp et al. [150] 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 [150]. The longer, neurotoxic, Aβ(1-42) peptide is highly aggregation prone and represents the major Aβ species deposited in the brain [150-153]. Cholesterol promotes Aβ(1-42) aggregation by enhancing its primary nucleation rate by up to 20-fold [153].) Kamp et al. argue that their data [150] suggest that bexarotene is a pleiotropic molecule that interferes with Aβ metabolism through multiple mechanisms. More specifically, earlier work by Di Scala et al. [138] provided evidence that bexarotene competed with cholesterol for binding to Aβ and prevented oligomeric channel formation. Di Scala et al. argue that their findings indicate that it is possible to prevent the generation of neurotoxic oligomers by targeting the cholesterol-binding domain of Aβ peptides [138]. Note that such blocking of amyloid-β-induced neurotoxic pore formation can be expected to avoid exacerbation of blood-brain barrier breakdown, already occurring at lower levels in aged humans with cognitive decline [154], and thereby prevent reaching higher levels of BBB breakdown associated with cognitive impairment (and/or eventually dementia) in late-onset Alzheimer's disease [154-156]. The known neuroprotective effect of beraxotene action on brain tissue has also recently stimulated expanded research into the use of a bexarotene derivative (i.e., an analog), which demonstrated the successful attenuation of Alzheimer's disease-related

pathologies and cognitive impairments in an Alzheimer's-disease mouse model [157] (see also [158, 159]).

Lastly, when considering the entire literature on oligomeropathics as well as the pathogenesis of Alzheimer's disease as a whole, Forloni et al. [160] point out in their review that the molecular mechanisms of oligomer-related toxic effects can be summarized under three different types of interactions (that are not necessarily mutually exclusive): amyloid-pore channel formation; direct or indirect action on specific cellular receptors; and nonspecific perturbance of cellular and intracellular membranes. Accordingly, very recently Mroczko et al. [161] have asserted that the causative role of Aβ(1-42) aggregation in the pathogenesis of Alzheimer's disease has been under debate for over 25 years. Strikingly, however, further analysis by Evangelisti et al. [162] has revealed the existence of a linear correlation between the level of the influx of Ca^{2+} across neuronal membranes, that triggers cellular damage, and the fraction of Aβ(1-42) oligomers bound to the membrane ([162]; cf. [134, 135]).

6. Conclusion

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.

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Author Contributions

Joseph S. D'Arrigo did all works.

Conflicts of Interest

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

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