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NANOTHERAPY TO DELAY COGNITIVE IMPAIRMENT: USING COLLOIDAL NANOCARRIERS TO BLOCK AMYLOID-β-INDUCED DAMAGE IN BRAIN CELL MEMBRANES

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Review

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ABSTRACT

Background: Numerous published studies indicate that microvascular endothelial dysfunction precedes cognitive decline in Alzheimer's disease, and that preservation of a healthy cerebrovascular endothelium can be an important therapeutic target.

Methods: 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. Documented similarities in lipid composition between high-density lipoproteins (HDL) and the biomimetic (nanoemulsion) nanocarrier particles can partially simulate or mimic the known heterogeneity (i.e., subpopulations or subspecies) of HDL particles. Moreover, the above-described type BI scavenger receptor (i.e., either SR-BI (rodent) and/or CLA-1 (human) orthologs) has been shown to be a multifunctional receptor able to bind a broad variety of ligands, including HDL and chylomicron remnants.

Results: Such colloidal-nanocarrier targeting allows for various Alzheimer's-related cell types to be simultaneously searched out, in vivo, for localized drug treatment. Using various lipids and their mixtures to form self-assembled non-lamellar 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. In particular, within the range of self-assembled phases in model surfactant-like lipid systems, various investigators further emphasize that monglyceride-based lyotropic liquid-crystalline phases are relatively unique owing to their rich polymorphism in water and potential application as drug nanocarriers.

Conclusion: This (colloidal-nanocarrier) 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 animals models of Alzheimer's disease (e.g., the anticancer drug bexarotene). Bexarotene (and several analogs or other candidate-repurposing drugs) 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, dementia, drug targeting, lipid cubic phases, nanoemulsion, scavenger receptors, SR-BI

BACKGROUND

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. It is no surprise, therefore, that 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. As a result, vascular cognitive impairment and dementia (VCID) is the second leading cause of dementia behind Alzheimer's disease [4,10,11].

Endothelial Dysfunction as a Therapeutic Target for Cognitive Impairment

It has been reconfirmed in the current literature (see below) 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. [27-31]). Recently, Fung et al. [32] specifically reported that SR-BI mediates the uptake and transcytosis of 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 [2,29,31,33-37] (cf. [38-43]).

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 [1,44–51] and an apparent *endothelium* dysfunction [2,28–36,52–61] in both Alzheimer's disease and its major risk factors [1,2,62-71]. Furthermore, 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. [72,73]), to be simultaneously sought out and better reached for localized drug treatment of brain tissue in vivo [73] (cf. [74]).

Consistent with the above considerations concerning endothelial dysfunction in Alzheimer's disease, ApoA -I has very recently been reported by Camacho et al. [75] to play a special role in cerebral amyloid angiopathy (CAA). CAA is observed in more than 90% of patients with Alzheimer's disease, although it additionally has an independent contribution to the cognitive deterioration associated with age. CAA can be neuropathologically classified as CAA type I or type II, where type I is characterized by amyloid-β deposition in cerebral capillaries (versus type II where cerebral capillaries are not involved). The human data (from autopsy brains of 20 post-mortem cases), reported by Camacho et al., revealed that the ApoA-I immunohistochemical staining was localized strongly toward capillary walls with CAA (i.e., especially toward CAA type I pathology) [75].

Also, as alluded to above (see Abstract), the previously documented similarities in lipid composition among HDL (as well as native low-density lipoproteins (LDL) and modified LDL) and LCM/ND nanoemulsion particles can partially simulate or mimic the known heterogeneity (i.e., subpopulations or subspecies) of HDL particles (see [73] for a review). Moreover, the above-described type BI scavenger receptor (i.e., either SR-BI (rodent) and/or CLA-1 (human) orthologs) has been shown to be a multifunctional receptor able to bind a broad variety of ligands, including HDL, LDL, oxidized LDL (OxLDL), very-low-density lipoproteins (VLDL), and chylomicron remnants. The presence of amphipathic helices is a common feature of "exchangeable apolipoproteins", which are known to be the primary ligands (including notably apoA-I) for SR-BI [3]. In view of all the above considerations, SR-BI emerges

as the most plausible candidate (of all lipoprotein receptors) for major involvement in the enhanced endocytosis of LCM/ND nanoemulsion(s) for targeted drug delivery [73].

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

The self-assembling LCM/ND lipid nanoemulsion class comprises nonionic lipids exclusively (e.g., [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., 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 [73].

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. [78-81]). In agreement with numerous other investigators, Kaasgaard and Drummond [82] 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. [83-89]).

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 [73]. There is great interest to utilize these *dispersed cubic* phases for the administration of drugs, or for the formulation of new delivery systems [73,87]. The (lyotropic or solvent-induced) cubic liquid-crystalline phases may be classified into two distinct classes: *bi*continuous cubic phases [90-94] *and* micellar or *dis*continuous (e.g., type *Fd3m*) cubic phases [89,90]. As reviewed by Garg et al. [77], 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 [77] (see also [73,95-105]).

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., [89]). Luzzati and coworkers have reported that this *Fd3m* cubic phase evidently requires a heterogeneous mixture of polar lipids [91]: Using the lipid examples they cite (and the lipid classification system of Small [81]), this *Fd3m* phase apparently must include *both* at least one (sufficiently polar) *insoluble swelling amphiphilic* lipid (e.g., monoglyceride) and at least one (weakly polar) *insoluble nonswelling amphiphilic* lipid (e.g., diglyceride and/or cholesterol) (e.g., [3]; cf. [73]) 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 [76]) specifically include cholesterol and three categories of (saturated) glycerides, that is, tri-, di-, and monoglycerides (see [76]). 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 [73] 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 [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 [106]. In addition, Kuntsche et al. [107,108] 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 [73].

To conclude, self-assembled (colloidal mesophase) lipid nanoemulsions (e.g., [92-98]), particularly those predominantly containing dispersed cubic-phase lipid nanoparticles (e.g., [3,73,99-105]), 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 (cf. [3]). 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]).

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 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. 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 [109,110].

Historical support for the above amyloid-β ion channel hypothesis, or so-called "calcium hypothesis", has also been observed at the clinical level [111]. 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 [112]. (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 [112].

As summarized by Di Scala et al. [111], the structure of amyloid pores has been extensively studied by ul-

trastructural 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: 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 [113]. (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 [113]. Very recently, a different research group reported very similar findings [114]. 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 [114] 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 [114].

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) [111]. 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 [115]. However, when *oral* administration of bexarotene was employed subsequently in a Phase Ib (proof of mechanism) clinical trial [116], 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 [116](cf. [117])).

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 [118,119] (cf. [120,121]). 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. [122] 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 [122]. (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. [123] 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 [123].

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. [124,125]). In the most recently published study, Kamp et al. [126] 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 [126]. The longer, neurotoxic, Aβ(1-42) peptide is highly aggregation prone and represents the major Aβ species deposited in the brain [126-129]. Cholesterol promotes Aβ(1-42) aggregation by enhancing its primary nucleation rate by up to 20-fold [129].) Kamp et al. argue that their data [126] suggest that bexarotene is a pleiotropic molecule that interferes with Aβ metabolism through multiple mechanisms. More specifically, earlier work by Di Scala et al. [115] 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 [115]. 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 [130], and thereby prevent reaching higher levels of BBB breakdown associated with cognitive impairment (and/or eventually dementia) in late-onset Alzheimer's disease [130-132].

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 biomimetic-nanoemulsion targeting allows for various Alzheimer's-related cell types to be simultaneously searched out, in vivo, for localized drug treatment. The proposed multitasking nanocarrier therapeutic appears likely to display greater efficacy at different stages of Alzheimer's disease. This (colloidal-nanocarrier) in vivo targeting advantage may be particularly important for repurposing an FDA-approved drug, especially one (such as the anticancer drug bexarotene) which has shown the added ability to restore some cognitive functions in certain animal models of Alzheimer's disease.

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Conflicts of Interest

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

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