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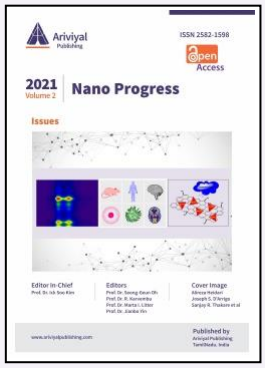

Biobased Nanoemulsion Methodology Aimed at Nanotargeted Drug Delivery for Dementia

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Abstract: Microvascular endothelial dysfunction precedes often by decades, the cognitive decline associated with Alzheimer's disease. Potential treatment is practicable via incorporating appropriate drug(s) into biobased (lipid cubic phase) nanocarriers, yielding a multitasking combination therapeutic which targets certain cell-surface scavenger receptors (mainly SR-BI), and then crosses the blood-brain barrier (BBB). The SR-BI receptor is amply expressed by endothelial cells – including those comprised within the BBB – and this receptor is involved in the endothelial protective effects of high-density lipoproteins (HDL). These HDL-associated protective effects on the endothelial-cell lining of the vasculature include antioxidant and anti-inflammatory properties, which are mostly due to HDL's proteome. Meanwhile, the actual targeting function of the biobased nanocarrier is facilitated by documented similarities in lipid composition, between naturally occurring HDL and the colloidal-nanocarrier particles, which effectively simulate or mimic the known heterogeneity (i.e., subpopulations or subspecies) of HDL particles. Such colloidal drug-nanocarrier targeting can potentially be extended to the treatment of complex medical disorders like dementia, and allows for various Alzheimer's-related cell types to be simultaneously searched in a holistic integrative approach. This (nanocarrier-) targeting advantage, in vivo, may be particularly important when delivering pleiotropic natural substances (e.g., a stilbenoid) or for repurposing an FDA-approved drug.

Keywords: Alzheimer's disease; Cognitive impairment; Nanoemulsion; SR-BI; Vascular dementia

1. Introduction

Vascular brain lesions occur frequently in people over 70 years old, and recent reviews[1,2] provide much evidence that a large percentage of dementia cases may be associated with cerebrovascular disease.[3,4] Accordingly, vascular cognitive impairment is the second leading cause of dementia behind Alzheimer's disease, and often is a co-morbidity in the Alzheimer's patient.[5,6] Furthermore, growing data from various animal models indicate that cerebrovascular dysfunction often precedes cognitive impairment as well as the onset of neurodegenerative changes in Alzheimer's disease.[2,4]

In pathological states, members of the scavenger receptor family of proteins (including class A receptors and class B receptors) mediate the recruitment, activation and transformation of macrophages, and other cells which appear to be related to the development of not only Alzheimer's disease but also atherosclerosis.[2] Lipid accumulation in the blood vessel wall depends on the intracellular uptake by macrophages, which transform into foam cells. Overloaded foam cells finally degenerate, leaving extracellular lipid deposits. The lipid overload of macrophages is brought about by several classes of cell-surface scavenger receptors. As one example, a major type of class B scavenger receptor is reported to be upregulated; hence, binding followed by uptake perpetuates a cycle of lipid accumulation and receptor expression. Both class B and class A scavenger receptors are expressed in the lipid-laden macrophages in atherosclerotic lesions. Furthermore, the differential distribution of the scavenger receptor types within human atherosclerotic lesions has already been reported in the literature.[2] In view of the detailed published information available on the presence, functional characteristics and localization of scavenger receptor populations in atherosclerotic lesions, localized drug delivery to such lesions may offer a means for targeted drug-delivery therapy of atherosclerosis and, potentially also (cf. above), late-onset Alzheimer's disease.

2. Endothelial Dysfunction, and Targeted Nanotherapy for Late-Onset Dementia

Small-vessel disease is commonly found in patients who have other brain pathologies, such as plaques and tangles associated with neurodegenerative disease. Accordingly, the most common cause of clinical dementia in the elderly has been ascribed to mixed pathology, displaying both Alzheimer's disease and vascular abnormalities. Bennett et al.[5] have recently pointed to much

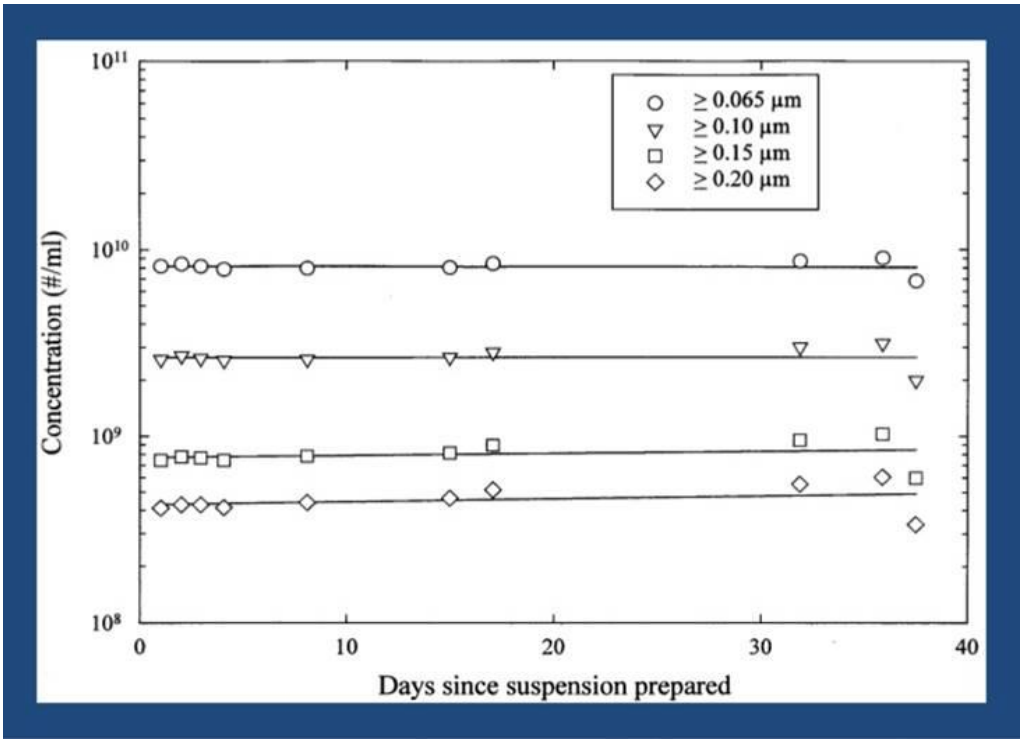

Fig. 1. LCM/ND nanoemulsion stability over time. (Adapted from ref. 2).

evidence that, as observed in the clinic by MRI scans or at autopsy by neuropathological evaluation, "pure" Alzheimer's disease is substantially less common than mixed dementias – where protein tau tangles (in neurons) and (extracellular amyloid-beta) plaques are accompanied by vascular changes. These authors' own published work provides evidence that tau pathological changes (in neurons) can impact brain endothelial-cell biology which, in turn, induces changes in the brain's microvasculature (including abnormal spiraling morphologies, reduced blood vessel diameters, and increased overall blood vessel density in the cerebral cortex) separate from the effects of senile plaques on vasculature; hence, these observations indicate a previously unknown pathway by which pathological tau tangles may accelerate cognitive decline in Alzheimer's disease.[5] In Alzheimer's disease itself, the characteristic lesions that develop, called senile plaques, are extracellular deposits principally composed of insoluble aggregates of amyloid-β protein (Aβ) fibrils, infiltrated by reactive microglia and astrocytes. Aβ fibrils exert a cytotoxic effect on neurons and stimulate microglia to produce neurotoxins, such as reactive oxygen species. Mononuclear phagocytes, including microglia, express scavenger receptors that mediate adhesion and/or endocytosis; in particular, microglia have been shown to be intimately associated with amyloid deposits, and have also been implicated as scavengers responsible for clearing Aβ fibril deposits of Alzheimer's disease. Accordingly, microglial scavenger receptors have already been described as novel targets for therapeutic interventions in Alzheimer's disease; specifically, it is believed that microglia play a major role in the cellular response associated with the pathological lesions of Alzheimer's disease and, furthermore, that pharmacological agents which suppress microglial activation may prove a useful strategy to slow the progression of Alzheimer's disease.[2] The vascular changes associated with small-vessel disease of the cerebral microvasculature include morphological alterations and resultant blood-brain barrier (BBB) breakdown. It is not surprising, therefore, that multiple epidemiological studies have revealed a marked overlap among risk factors for small-vessel cerebrovascular disease and late-onset Alzheimer's disease.[2]

It has been reported continually that endothelial modulation and/or repair is practicable by pharmacological targeting[1,2,7-13] via cell-surface scavenger receptors (mainly class B type I, i.e., SR-BI).[13-15] Since SR-BI has already been identified as a major receptor for high-density lipoprotein or 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.[16-18] Documented similarities in the lipid composition of HDL versus these nanoemulsion (drug-carrier) particles may enable such LCM/ND nanoemulsions to mimic, in part, HDL-particle heterogeneity.[1,2]

This targeted-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[1,19-29] and an apparent *endothelium* dysfunction[2,17,18,25,30-36] in both Alzheimer's disease and its major risk factors.[1,2,29-41] Incorporating certain drug molecules into the LCM/ND lipid nanoemulsion type (yielding particle sizes mostly < 0.1 µm in diameter – see Fig. 1), known to be a successful drug carrier,[2,42,43] would make the following possible: Various cell types, all potentially implicated in Alzheimer's disease,[1] can be simultaneously nanotargeted via cell-surface SR-BI.[42,43]

3. LCM/ND Lipid Nanoemulsion: Particle Size Distribution and Safety Studies

Physical characterization of the actual size distribution, of the LCM/ND lipid nanoemulsion particles, has been described in detail earlier.[2] Basically, collaborative multidisciplinary analyses of the nanoemulsion particle sizes, particularly in the submicron range, were carried out at CT Associates, Inc. LCM/ND nanoemulsion size distributions were measured using three different techniques, i.e., optical particle counting (see below), dynamic light scattering, and scanning electron microscopy; the first of these techniques yielded the most data. Five different optical particle counters, all manufactured by Particle Measuring Systems (Boulder, CO), were used to measure the scattered light over different collection angles. (The five counters utilize different light sources and measure the scattered light over different collection angles. Hence the raw data collected may vary between these counters, over short data-collection periods, and prior to further statistical analysis, since the amount of light scattered is a complicated function of the illuminating light properties, scattering angle, and refractive index. Nonetheless, detailed statistical analyses of the resulting data confirmed that the five instruments all measured similar particle concentrations.) The filtered LCM/ND lipid nanoemulsion contained close to 10^{10} particles < 0.10 µm per ml, with most (~90%) of the nanoemulsion particles being smaller than 0.2 µm in diameter (cf. Fig. 1).[2] The effect of concentration on the nanoemulsion size distributions was also determined using the S100 optical particle counter. It was thought that if the total concentration of LCM/ND nanoemulsion material changed, the size distribution might also change as a new equilibrium condition was achieved. (The experiment was performed by preparing different dilutions of nanoemulsion material, then injecting the various dilutions into water at different rates using the dilution/flow system set up for the S100 instrument. In this way, multiple concentrations could be obtained in both the injecting and final suspensions.) All of the measurements were found to be essentially identical, indicating that the LCM/ND lipid nanoemulsion did *not* change particle size when subjected to the different concentration conditions. In addition, the effect of LCM/ND nanoemulsion age on the particle size distribution was determined by measuring the nanoemulsion size distribution at different times over 37 days, using the M65 optical particle counter. *No* change in the size distribution with time (over at least 1 month) was evident.[2] In summary, the LCM/ND nanoemulsion size distribution in deionized water was measured using several analytical techniques. This nanoemulsion was found to contain close to 10^{10} particles < 0.1 µm per ml, when measured using optical particle counters. A large majority (~90%) of the nanoemulsion particles were smaller than 0.2 µm in diameter.

With regard to safety considerations, the LCM/ND lipid nanoemulsion particles have neither been found to agglomerate nor coalesce into any "superparticle or microbubble-like" structure larger than 5 µm, either in vitro or in vivo, thus the risk of embolus is negligible.[2] More specifically, past quality assurance (Q/A) testing of the LCM/ND lipid nanoemulsion has involved other particle size analyses, by electroimpedance-sensed volumetric sizing using a Coulter Multisizer, which consistently yielded the following results: using a Coulter aperture tube with a 50-µm orifice [giving the instrument a nominal particle-diameter detection range from ~1.0 to 30.0 µm], more than 99% of the detected nanoemulsion particle population is under 4.5 µm, and all nanoemulsion particles are less than 5.0 µm in diameter. Furthermore, one-by-one nonoptical counting of the LCM/ND lipid nanoemulsion particles (i.e., those having diameters larger than ~ 1.0 µm) by the Coulter Multisizer consistently resulted in a calculated total concentration of approximately 5 x 10^5 particles/ml in the nanoemulsion samples. All of the above product specifications remain constant for many months when the LCM/ND nanoemulsion agent is stored at room temperature and for over 1 year when the nanoemulsion agent is stored refrigerated (but not frozen). Moreover, when the entire particle size analysis (Q/A testing) was repeated on many LCM/ND lipid nanoemulsion batches using subsequent, more sensitive models of the Coulter Multisizer (Models II and IIe), maximum nanoemulsion particle size remained under 5.0 µm. However, these newer Coulter instruments uncovered evidence that the *vast majority* of the LCM/ND-lipid-nanoemulsion particle poulation exhibits diameters *less* than 1.0 µm (cf. previous paragr.).[2]

Also, acute intravenous toxicity studies of this (isotonic) LCM/ND nanoemulsion agent in rabbits and dogs were conducted at an independent GLP contractor. [Note that the acronym "GLP" indicates that studies conducted by aforesaid contractor are in compliance with the Good Laboratory Practices Regulations as stated in 21 CFR Part 58, for submission to the U.S. Food and Drug Administration in support of an Investigational New Drug Application (INDA). Accordingly, this statement carries the expectation that there are no deviations from the GLP regulations which would affect the quality or integrity of the study.]

The acute intravenous LD_{50} in both rabbits and dogs was found to be greater than 4.8 ml/kg. (From the data summarized in the first two paragraphs of this Sect. 3, the apparent concentration of LCM/ND nanoemulsion particles that were injected intravenously at 4.8 ml/kg was approximately 10^{10} particles/ml.) Furthermore, no signs of gross toxicity or mortality were observed at a dosage of 4.8 ml/kg. More specifically, in the first study, ten rabbits (five males and five females) were intravenously administered LCM/ND lipid nanoemulsion at a dose level of 4.8 ml/kg. Signs observed during this study included increased respiration and decreased activity. None of the animals died during the study. Terminal necropsy revealed pale lungs in one animal. No other visible lesions were observed in any of the remaining animals at terminal necropsy. Separately, in the latter study, four dogs (two males and two females) were administered LCM/ND lipid nanoemulsion by intravenous injection at a dose level of 4.8 ml/kg. No clinical signs were observed during the study. None of the animals died at the 4.8 ml/kg dose level. No visible lesions were observed in any animal at terminal necropsy.[2]

It has also been found in other animal (range-finding subchronic intravenous) toxicology studies, using this same (isotonic) lipid nanoemulsion agent, that at intravenous doses of 0.14 ml/kg given three times per week for 6 weeks in rats and, separately, at intravenous doses of 0.48 ml/kg given three times per week for 3 months in rabbits, the following toxicology results were observed:

There were no untoward changes in serum chemistry, liver functions, haematology, or clotting profile or histological changes in adrenals, bladder, brain, heart, kidney, liver, lungs, marrow, pituitary, spleen, testes, thyroid, or ureters.[2] Finally, the lipids present in the LCM/ND nanoemulsion agent are similar to those found in the clinical products Intralipid and Liposyn III, except at extremely smaller concentrations and dosages employed than with these two human-approved clinical products. Intralipid is a fat emulsion for intravenous administration; in particular, the saturated fatty acids and neutral triglycerides and/or di- and monoglycerides present are metabolized by the same metabolic pathways. Hence, a comparison of the lipid composition of LCM/ND nanoemulsion agent with that of the intravenous fat-emulsion products (Intralipid and Liposyn), and their respective (intended clinical) dosages, indicate enormous margins of safety for the LCM/ND nanoemulsion in its intended clinical application for targeted drug-delivery therapy in humans.

4. LCM/ND Nanoemulsion Type, and Targeting via Lipid Cubic Phases

Monoglyceride is the largest fraction (by wt. %) of the lipids used to produce (Filmix®) LCM/ND nanoemulsions. As a group, monoglycerides exhibit the ability to self-assemble into varied and useful dispersed cubic phases (among other liquid-crystalline phases) when placed in contact with water.[2,44,45] The (lyotropic or solvent-induced) cubic liquid-crystalline phases can be grouped into two distinct classes: bicontinuous cubic phases[46] *and* micellar or *dis*continuous (e.g., type *Fd3m*) cubic phases.[47] A noteworthy lipid cubic phase of the latter category is based upon packings of discrete inverse micellar aggregates and is formed by a variety of lipid systems.[47] Seddon et al.[48] point out that the most frequently observed such (inverse micellar cubic) structure is a cubic phase of crystallographic space group *Fd3m*, which requires a heterogeneous mixture of polar lipids.[49,50] The *dispersed Fd3m* cubic phase is particularly relevant to the earlier-described LCM/ND lipid nanoemulsion; specifically, both above-described structures often specifically include cholesterol and three categories of (saturated) glycerides, that is, tri-, di-, and monoglycerides.[51,52]

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, including notably apoA-I, toward the appropriate receptors on the target-cell surface. This likely adsorption of apoA-I and, hence, targeting success of these nanoemulsion particles is understandable.[2] When the above information is combined with the known heterogeneity of HDL particles as well as the well-documented multiligand capability of SR-BI, then again SR-BI emerges as the prime candidate (of all lipoprotein receptors) for major involvement in the enhanced endocytosis of LCM/ND nanoemulsion particles into, and transcytosis across, the endothelial-cell layer of the BBB.[2]

5. Brain Injury, Edaravone, Resveratrol, and Alzheimer's disease

Besides considerations about amyloid pore formation (regarding calcium fluxes and Alzheimer's disease) described in the literature, (e.g., [53-58]) an especially important pathophysiological overlap exists between traumatic brain injury (TBI) and Alzheimer's-disease brain. Interestingly, the drug Edaravone has been used successfully, in past TBI research, due to its neuroprotective and antioxidative effects on the brain after TBI. These pharmacological effects lead to a decreased inflammatory response and decreased glial activation, thereby reducing neuronal death and improving neurological function.[59,60] [Edaravone continues to be used clinically to aid patient recovery from ischemic stroke in Japan since 2001, and this drug was also approved for the treatment of amyotrophic lateral sclerosis (ALS) in the USA. The drug is thought to reduce oxidative stress in cells by lowering intracellular levels of free radicals; it is administered by intravenous infusion and is primarily excreted in the urine. Edaravone is available commercially as a clear, colorless liquid provided as a sterile injection solution. The drug is metabolized to pharmacologically inactive sulfate and glucuronide conjugates. The pharmacokinetics of Edaravone were not affected by age in the geriatric population during clinical trials, and no significant differences were observed between Japanese and Caucasian subjects (cf.[59,60]).]

In view of the above description of TBI, the effects of the drug Edaravone, and the pathophysiological overlap of TBI with many characteristics of Alzheimer’s disease brain (cf. above), it is logical and consistent that Jiao et al.[61] have recently reported that Edaravone can also ameliorate Alzheimer’s disease-type pathologies and cognitive deficits of a mouse model of Alzheimer’s disease. These investigators further state that their above findings suggest that Edaravone is a promising drug candidate for Alzheimer’s disease by targeting multiple key pathways of the disease pathogenesis[61] (cf. [62]).

While the risk factors for dementia trigger widespread inflammation and oxidative stress (e.g., [63,64]), it is also true that these two processes can result in more biological effects than enhanced calcium load in brain tissue and neurodegeneration (cf. [65-67]). In fact, oxidative stress and inflammation each involve pathophysiological cascades associated with a wide range of pathologies and especially *aging*.[67] Accordingly, Khalil et al.[68] found that Alzheimer's disease impaired the interaction of HDL (and apoA-I) with the SR-BI receptor, and their experimental results indicated that such patients had higher levels of oxidative stress.[68,69]

Lastly, in addition to the above-described repurposing of the FDA-approved drug Edaravone (cf. Abstract and this Section, paragr. 1&2), it was alluded to earlier that targeted delivery of pleiotropic natural substances (cf. Abstract) -- such as docosahexaenoic acid (DHA),[42] astaxanthin,[70] and resveratrol (e.g.,[71-73]) -- fit well with the initial drug candidates (for incorporation into the LCM/ND lipid nanoemulsion) already suggested elsewhere.[1] These suggested drug candidates, chosen on the basis of their low-molecular-weight and sufficient lipophilicity (as again proposed here), would be intended for use in the targeted treatment of Alzheimer's disease and late-onset dementia. As particularly concerns resveratrol, Broderick et

al.[71] have recently emphasized that this plant polyphenol has gained interest as a nonpharmacological (dietary) approach for the treatment and prevention of Alzheimer's disease. (Resveratrol is a major ingredient found in red wine, grape seeds, and certain nuts and berries;[e.g.,71] this plant compound is a type of natural phenol [i.e., a stilbenoid polyphenol] commonly used as a dietary supplement.) Broderick et al. cite published evidence that resveratrol attenuates learning impairment and delays the onset of neurodegeneration in transgenic murine models of Alzheimer's disease; moreover, a significant reduction in the number of activated microglia and decreased inflammation in APP/PS1 mice following resveratrol treatment has been reported.[71] In summary, the above-described targeting advantage, using the LCM/ND lipid nanoemulsion, may be particularly important when delivering pleiotropic natural substances or for repurposing an FDA-approved drug in order to now treat late-onset dementia.

6. Conclusions

A desirable feature for a parenteral lipid nanoemulsion is the ability to avoid "reticuloendothelial system" (RES) capture and hence circulate for a prolonged period in the bloodstream, thereby allowing the opportunity for cell-selective targeting of drugs. Accordingly, it is interesting to consider much evidence in the literature, reviewed elsewhere,[2] which indicates that a sizable portion of intravenously injected LCM/ND lipid nanoemulsion bypasses the RES to then become endocytosed by target cells. One probable reason for this repeated experimental observation is that the colloidal nanoparticles employed are uncharged (in such lipid nanoemulsions) and, hence, these dispersed liquid-crystalline phases are all unlikely to be captured easily by the RES during circulation (prior to adsorption of plasma apoA-I and subsequent receptor-mediated endocytosis).[2] More specifically, in vivo biodistribution studies (using micellar nanoparticles) have demonstrated that undesirable liver uptake was very large for highly positively or negatively charged (blood-borne) nanoparticles; based on these studies, the authors conclude that very low charge at the nanoparticle surface reduces the undesirable clearance by the reticuloendothelial system (RES) and improves the blood compatibility.[74] This conclusion is consistent with earlier published work, by other investigators, indicating that charge neutrality at the surface of blood-borne nanoparticles greatly increases their blood-tissue compatibility.[75] Another factor which can prolong the half-life in the bloodstream, of a circulating lipid nanoemulsion, relates to particle size; namely, the size of the lipid emulsion particles themselves is known to influence the RES uptake of intravenous lipid emulsions. Various investigators have reported that "*small*-particle" (~0.10 µm in diameter) lipid emulsions displayed: (1) a reduced hepatic uptake; and (2) a much slower plasma clearance, or a significantly greater area under the plasma concentration-time curve. Accordingly, the above trend would help explain why LCM/ND lipid nanoemulsion formulations (cf. Fig. 1) have been found capable of largely avoiding RES capture and display a prolonged circulation in the bloodstream.[2]

As specifically concerns neurodegenerative disease, vascular dementia (similarly to Alzheimer's disease) is a common cause of cognitive impairment – where there is an increased risk with aging, a rapid step-wise disease progression, and a high mortality rate.[76] The known cardiovascular risk factors driving vascular dementia include diabetes and hypertension. Accordingly, both clinical and experimental data indicate that associated cerebrovascular disease can lead to cerebral hypoperfusion, thereby altering brain metabolism and leading to cognitive impairment[76] (cf.[77]). Past studies (e.g.,[78,79]) have already shown that low-grade inflammation and endothelial dysfunction contribute to reduced information processing speed and executive functioning in an older population. Biomedical application of colloidal drug-nanocarriers, capable of crossing the BBB, can potentially be extended to the treatment of complex medical disorders like vascular dementia and (late-onset) Alzheimer's disease.[78-82] Recent published work has demonstrated that nanocomplexes can be readily transported into brain capillary endothelial cells (bovine and porcine) via SR-BI receptor-mediated endocytosis[7] (see also[83-85]). Accordingly, endothelial modulation and repair become feasible by pharmacological targeting [8-12,86-90] via SR-BI receptors (cf. [13,90]). While SR-BI is a major receptor highly expressed in the liver, SR-BI is also amply expressed by endothelial cells – including those comprised within the BBB – and this receptor is involved in the endothelial protective effects of HDL. These protective effects on the endothelial-cell lining of the vasculature include antioxidant and anti-inflammatory properties.[90-92] (More specifically, the vasculoprotective effects of HDL are mostly due to its proteome, where apoA-I is the most abundant protein constituent.[91] HDL are heterogeneous and multimolecular complexes of hundreds of different molecules (e.g., proteins). Inflammatory conditions modify both the composition and the structural components of HDL, resulting in dysfunctional HDL particles.[93] Growing preclinical evidence suggests that loss of HDL-associated proteins may be a feature of Alzheimer's disease, even at early stages.[92]) The proposed multitasking combination therapeutic, described herein, appears likely to display greater efficacy at different stages of Alzheimer's disease (cf. [41]). Note also that this multitasking drug-nanocarrier approach (i.e., multitasking drug-delivery vehicle)[2] can also serve to reduce the size and/or extent of the "multidrug cocktail"[94] that the clinician would otherwise need to employ for adequate, or fully effective, treatment of the varied etiology of Alzheimer's-disease symptoms (i.e., the "multiple aging pathways"[94;cf.95] or various pathogenic cascades involved). Moreover, the effects of the various cell types targeted (via SR-BI[90]) may be additive, multiplicative, or otherwise synergistic. As explained by clinical chemists[93] studying HDL function, any successful clinical exploitation of HDL (and/or HDL-like colloidal drug-nanocarriers) will depend upon the identification of the most relevant (dys)functions and their structural correlates. The most relevant agonists carried by these HDL-like particles and their cellular receptors are interesting targets for drug development.[93]

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Conflicts of Interest

Author(s) declare the following potential conflicts of interest:

1) J.S.D. is employed at Cav-Con Inc.

2) The actual "LCM/ND nanoemulsion (nanoparticle)" described in this review is not a finished/manufactured product, and is not on the retail market for sale.

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