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BIOBASED NANOEMULSION FOR BLOCKING COVID-19 FROM ACCELERATING ALZHEIMER'S DISEASE

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An effective therapeutic strategy to delay dementia could be based upon nanotargeting drug(s), using lipid nanocarriers (*i.e.*, biobased nanoemulsion technology), toward a major serum amyloid A (SAA) receptor responsible for certain proinflammatory, SAA-mediated, cell signaling events. For example, other investigators have already confirmed that SR-BI receptors (or its human ortholog CLA-1) function as proinflammatory cell-surface SAA receptors, and additionally report that various ligands for CLA-1/SR-BI "efficiently compete" with SAA for CLA-1/SR-BI binding. A similar benefit (of "competitive binding") may well accompany the clinical intravenous use of the ("HDL-like") lipid nanocarriers (*i.e.*, biobased nanoemulsion [see above]), which have already been repeatedly described in the peer-reviewed literature as a targeted (and SR-BI mediated) drug-delivery agent. To conclude, the above-proposed "competitive binding", between SAA and such biobased nanoemulsion(s), could assist/enhance the protective (ordinarily anti-inflammatory) role of HDL — as well as provide targeted drug-delivery to the (human) brain cells bearing CLA-1/SR-BI receptors. The first resulting advantage is that this (intravenous) colloidal-nanocarrier therapeutic makes it possible for various cell types, all potentially implicated in Alzheimer's disease and/or (late-onset) dementia, to be simultaneously sought out and better reached for localized drug treatment of brain tissue *in vivo*. A second major advantage is that this therapeutic-target approach has particular relevance to the current COVID-19 human pandemic; namely, immune response and excessive inflammation in COVID-19 infection may accelerate the progression of brain inflammatory neurodegeneration which, if effectively halted, might play a major role in reducing Alzheimer's disease pathology.

Keywords: Alzheimer's disease, dementia, drug nanotargeting, inflammation, nanocarrier, nanoemulsion.

Conflict of interest: The author declares the following potential conflicts of interest:
1. Joseph S. D'Arrigo 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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НАНОЭМУЛЬСИЯ БИОЛОГИЧЕСКОГО ПРОИСХОЖДЕНИЯ ДЛЯ ПРЕДОТВРАЩЕНИЯ СТИМУЛИРУЮЩЕГО ВЛИЯНИЯ COVID-19 НА РАЗВИТИЕ БОЛЕЗНИ АЛЬЦГЕЙМЕРА

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Эффективная стратегия лечения, направленного на замедление прогрессирования деменции, может быть основана на применении таргетных нанопрепаратов, созданных с использованием липидных наноперенос чиков (технологии получения наноэмульсий биологического происхождения). Эти наноперенос чики должны доставлять препарат к основному рецептору сывороточного амилоида А (SAA), который обеспечивает активацию определенных провоспалительных сигнальных путей внутри клеток. В ряде исследований было показано, что рецепторы SR-BI (или их человеческий ортолог CLA-1) действуют так же, как и провоспалительные рецепторы SAA, расположенные на поверхности клеток. Помимо этого, в литературе дополнительно сообщается, что различные лиганды CLA-1/SR-BI «эффективно конкурируют» с SAA за связывание с CLA-1/SR-BI. Подобное преимущество («конкурентного связывания») может также наблюдаться при внутривенном введении в клинических условиях липидных (ЛПВП-подобных) наноперенос чиков (вышеупомянутой наноэмульсии биологического происхождения), которые были неоднократно описаны в рецензируемых изданиях как один из способов таргетной (в том числе SR-BI-опосредованной) доставки лекарственных препаратов. В итоге такое «конкурентное связывание» SAA с соответствующими наноэмульсиями может поддерживать/усиливать защитную (как правило, противовоспалительную) функцию ЛПВП, а также обеспечивать адресную доставку лекарственных средств в клетки головного мозга (в том числе и человека), несущие рецепторы SR-BI (в случае человека – CLA-1). Первым преимуществом этого подхода является то, что при внутривенном введении препарата с наноперенос чиком можно оказывать эффекты на потенциально вовлеченные в развитие болезни Альцгеймера и/или сенильной деменции клетки различных типов, обеспечивая прицельное воздействие на ткань головного мозга *in vivo*. Второе важное преимущество заключается в том, что этот таргетный терапевтический подход имеет особое значение в контексте текущей пандемии COVID-19, так как именно иммунный ответ и избыточная воспалительная реакция при COVID-19 могут ускорить прогрессирование процесса воспалительной нейродегенерации в головном мозге. Эффективное блокирование данного процесса может значительным образом ограничить развитие патологических изменений, характерных для болезни Альцгеймера.

Ключевые слова: болезнь Альцгеймера, деменция, таргетный нанопрепарат, воспаление, наноперенос чик, наноэмульсия.

Конфликт интересов: Автор заявляет о следующем потенциальном конфликте интересов:
1. Дж. С. Д'Арриго является сотрудником Cav-Con. Inc.
2. Описанная в настоящем обзоре наноэмульсия (наночастица) LCM/ND не является готовым/производимым продуктом и не доступна для приобретения на розничном рынке.

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1. Introduction: Recent research (*e.g.*, [1, 2]) indicates that chronic inflammatory stimulus in the gut may induce (*e.g.*, via serum amyloid A (SAA)) the release of proinflammatory cytokines. At the same time, increased blood-brain barrier (BBB) permeability due to aging (or dysfunction), in turn, allows these proinflammatory cytokines to enter the brain, inducing glia reactivity [1, 2]. These recent findings, and various past studies, indicate that inflammation plays an important role in the process of amyloid-β (Aβ) deposition and, therefore, the inhibition of inflammatory cascades may attenuate amyloidogenic processes — such as Alzheimer's disease [3] (*cf.* [4]). Hence, an effective preventive and therapeutic strategy could be based upon nanotargeting drug(s) toward a major SAA receptor responsible for numerous SAA-mediated cell signaling events leading to cognitive decline and eventually Alzheimer's disease or (late-onset) dementia [5, 6].

2. Serum Amyloid A (SAA) versus SR-BI Targeting, and Cognitive Impairment. Earlier research [5-9] has already confirmed that SR-BI receptors (or its human ortholog CLA-1) function as cell-surface SAA receptors — which bind, internalize, and mediate SAA-induced proinflammatory effects (*cf.* [8]). However, Baranova *et al.* additionally report that (in cell culture) ligands for CLA-1/SR-BI "efficiently compete" with SAA for CLA-1/SR-BI binding [7]. (For example, it has already been documented in the literature that both apoA-1 and SAA are substrates for SR-BI, which indicates that SR-BI could mediate the transport of both proteins across the blood-brain barrier (*e.g.*, [9]).) Not surprisingly, therefore, Robert *et al.* have recently asserted that many lines of evidence suggest a protective role for high-density lipoprotein (HDL), as well as this lipoprotein particle's major apolipoprotein (apo)A-1, in Alzheimer's disease [10]. Accordingly, a similar benefit (of "competitive binding" to SR-BI receptors) may well accompany the clinical intravenous use of the ("HDL-like") LCM/ND lipid nanoemulsion vehicle (*cf.* [5]) — which has already been repeatedly described in the peer-reviewed literature (based upon numerous *in vivo* animal studies) as a targeted, apoA-1-based, (SR-BI mediated) drug-delivery agent (*e.g.*, [5, 11]). Moreover, by incorporating drug molecules into the LCM/ND lipid nanoemulsion type, one is likely to obtain a multitasking "combination therapeutic" capable of targeting cell-surface SR-BI. This (intravenous) colloidal-nanocarrier therapeutic would make it possible for various cell types, all potentially implicated in Alzheimer's disease [12, 13] and/or (late-onset) dementia, to be simultaneously sought out and better reached for localized drug treatment of brain tissue *in vivo* [5, 11, 14-16].

3. COVID-19, ("HDL-like") LCM/ND Nanoemulsion, and (late-onset) Dementia. From the descriptions provided in Sections 1 & 2 above, it is already apparent that SAA accumulation in HDL reduces this lipoprotein's "anti-inflammatory capacity" — due to the accumulated SAA activating proinflammatory signaling pathways. Since it plays a key role in decreasing HDL functionality, SAA represents an interesting therapeutic target for influencing the fate of cardiovascular-related disease [17]. Finally, as concerns this concept of an HDL-related therapeutic target, the above Sections also explained why anticipated "competitive binding" between

SAA and (HDL-like) LCM/ND nanoemulsion particles, occurring at above-described "(human) CLA-1/(rodent)SR-BI receptors" (*cf.* Sect. 2), may well accompany clinical intravenous use of such nanoemulsion (which is repeatedly described in the literature as a targeted, apoA-1-based, (SR-BI mediated) drug-delivery agent [5, 11]) (*cf.* [18]).

Meanwhile, much evidence indicates a protective (*i.e.*, ordinarily anti-inflammatory) role for HDL, and its major apolipoprotein (apoA-1), in Alzheimer's disease (*e.g.*, [5, 11, 18-20]) (*cf.* [21]). Hence, the above-proposed "competitive binding", between SAA and the LCM/ND nanoemulsion, could assist/enhance the "protective (ordinarily anti-inflammatory) role" of HDL — as well as provide targeted drug-delivery to the (human) brain cells bearing (CLA-1/)SR-BI receptors. This novel therapeutic-target approach has particular relevance to the current COVID-19 human pandemic. Namely, immune response and excessive inflammation in COVID-19 infection may accelerate the progression of brain inflammatory neurodegeneration, which plays a major role in Alzheimer's disease pathology. In addition, individuals with type 2 diabetes are at increased risk for Alzheimer's disease, as well as for severe outcomes after COVID-19 infection [22]. Severely affected COVID-19 cases experience high levels of proinflammatory cytokines and acute respiratory dysfunction. All these COVID-19-related homeostatic disruptions have the potential to cause cognitive decline (resulting from direct negative effects of the immune reaction, acceleration or aggravation of pre-existing cognitive deficits, and/or *de novo* induction of a neurodegenerative disease). Accordingly, patients surviving COVID-19 are at risk for subsequent development of neurological disease and in particular Alzheimer's disease [23].

4. Concluding Remarks: Recent reviews (*e.g.*, [5, 24-26]) of human Alzheimer's-disease studies have noted a significant elevation in inflammatory mediators in the cerebral microcirculation; crucially, inflammation has a key role in linking several types of vascular and neuronal damage (in Alzheimer's-disease brain) with cardiovascular risk factors, such as arterial stiffness and hypertension [24]. In addition, various past studies (*cf.* [5]) indicate that inflammation also plays an important role in the actual process of Aβ deposition and, therefore, the inhibition of inflammatory cascades may attenuate amyloidogenic processes — such as Alzheimer's disease. Hence, an effective preventive and therapeutic strategy could be based upon nanotargeting drug(s), using lipid nanocarriers, toward a major SAA receptor responsible for numerous SAA-mediated cell signaling events leading to cognitive decline and eventually Alzheimer's disease or (late-onset) dementia. Lastly, it has been reconfirmed in the current literature that receptor-mediated endocytosis/transcytosis via lipoprotein receptors, particularly scavenger receptors including SR-BI, remains a major route of drug delivery across the blood-brain barrier; namely, recently published work has demonstrated that (blood-borne) nanocomplexes can be readily transported into brain capillary endothelial cells (bovine and porcine) via SR-BI receptor-mediated endocytosis [27] (see also [28-30]). Accordingly, the effects of the various cell types targeted (via SR-BI) may be additive, multiplicative, or otherwise synergistic. Moreover, recent research (*e.g.*, [5, 31-34]) repeatedly indicates for several age-related diseases, including cardiovascular and neurodegenerative disease, that accompanying the aging process there is often a decreased ability for fine control of systemic inflammation (*i.e.*, the human immune system often displays a progressive and chronic tendency toward a proinflammatory phenotype, also called "inflamm-aging" [31]) (*cf.* [35]). At the same time, the immune response and excessive inflammation (which is commonly observed in the very recent human coronavirus (COVID-19) pandemic [36-41]) may actually accelerate the progression of brain inflammatory neurodegeneration [22, 42, 43]; furthermore, the hippocampus is reported to be particularly vulnerable to coronavirus infections — which increases the probability of post-infection memory impairment

and accelerating progression of Alzheimer's disease [43]. Hence, the proposed multitasking combination therapeutic, using (biobased) LCM/ND nanoemulsion(s), may also display greater effectiveness at different stages of Alzheimer's disease; as a result, this multitasking (drug-delivery) therapeutic could represent a promising way to treat, delay, or even prevent the disease in the future (*cf.* [44-46]). In addition, very recent (detailed, animal) data indicates such proinflammatory cytokine production and, hence, prolonged inflammation is an underlying cause of "long Covid" (*i.e.*, the inducing of long-term effects from COVID-19 infection) [47].

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