



Targeting Beta-Amyloid at the CSF: A New Therapeutic Strategy in Alzheimer's Disease

Manuel Menendez-Gonzalez^{1,2,3*}, Huber S. Padilla-Zambrano⁴, Gabriel Alvarez⁵, Estibaliz Capetillo-Zarate^{6,7,8,9}, Cristina Tomas-Zapico^{3,10} and Agustin Costa¹¹

¹ Servicio de Neurología, Hospital Universitario Central de Asturias, Oviedo, Spain, ² Department of Cellular Morphology and Biology, University of Oviedo, Oviedo, Spain, ³ Instituto de Investigación Sanitaria del Principado de Asturias, Oviedo, Spain, ⁴ Centro de Investigaciones Biomedicas (CIB), University of Cartagena, Cartagena, Colombia, ⁵ HealthSens, S.L., Oviedo, Spain, ⁶ Departamento de Neurociencias, Universidad del País Vasco (UPV/EHU), Leioa, Spain, ⁷ El Centro de Investigación Biomédica en Red sobre Enfermedades Neurodegenerativas, Madrid, Spain, ⁸ Achucarro Basque Center for Neuroscience, Leioa, Spain, ⁹ Ikerbasque, Basque Foundation for Science, Bilbao, Spain, ¹⁰ Department of Functional Biology, University of Oviedo, Oviedo, Spain, ¹¹ Department of Physical and Analytical Chemistry, University of Oviedo, Oviedo, Spain

OPEN ACCESS

Edited by:

Mohammad Amjad Kamal,
King Abdulaziz University,
Saudi Arabia

Reviewed by:

Fabrizio Piazza,
Università degli Studi di Milano
Bicocca, Italy
Alessandro Stefani,
Università degli Studi di Roma Tor
Vergata, Italy

*Correspondence:

Manuel Menendez-Gonzalez
manuelmenendezgonzalez@gmail.com

Received: 31 October 2017

Accepted: 26 March 2018

Published: 16 April 2018

Citation:

Menendez-Gonzalez M, Padilla-Zambrano HS, Alvarez G, Capetillo-Zarate E, Tomas-Zapico C and Costa A (2018) Targeting Beta-Amyloid at the CSF: A New Therapeutic Strategy in Alzheimer's Disease. *Front. Aging Neurosci.* 10:100. doi: 10.3389/fnagi.2018.00100

Although immunotherapies against the amyloid- β (A β) peptide tried so date failed to prove sufficient clinical benefit, A β still remains the main target in Alzheimer's disease (AD). This article aims to show the rationale of a new therapeutic strategy: clearing A β from the CSF continuously (the "CSF-sink" therapeutic strategy). First, we describe the physiologic mechanisms of A β clearance and the resulting AD pathology when these mechanisms are altered. Then, we review the experiences with peripheral A β -immunotherapy and discuss the related hypothesis of the mechanism of action of "peripheral sink." We also present A β -immunotherapies acting on the CNS directly. Finally, we introduce alternative methods of removing A β including the "CSF-sink" therapeutic strategy. As soluble peptides are in constant equilibrium between the ISF and the CSF, altering the levels of A β oligomers in the CSF would also alter the levels of such proteins in the brain parenchyma. We conclude that interventions based in a "CSF-sink" of A β will probably produce a steady clearance of A β in the ISF and therefore it may represent a new therapeutic strategy in AD.

Keywords: Alzheimer disease, amyloid beta-peptides, cerebrospinal fluid, immunotherapy, "CSF sink hypothesis"

PHYSIOLOGICAL CLEARANCE OF A β

Amyloid beta (A β) denotes peptides of 36–43 amino acids that are intrinsically unstructured, meaning that in solution it does not acquire a unique tertiary fold but rather populates a set of structures. These peptides derive from the amyloid precursor protein (APP), which is cleaved by beta- (BACE) and gamma-secretases to yield A β (Menendez-Gonzalez et al., 2005; O'Nuallain et al., 2010).

Amyloid beta is cleared from the brain by several independent mechanisms (Malm et al., 2010; Diem et al., 2017; Zuroff et al., 2017), including drainage to the vascular and glymphatic systems (DeMattos et al., 2001; Iliff et al., 2012, 2013; Tarasoff-Conway et al., 2015; Bakker et al., 2016; Zuroff et al., 2017), and *in situ* degradation by glial cells (Ries and Sastre, 2016; Zuroff et al., 2017). Astrocytes and microglia can produce A β degrading proteases like neprilysin, as well as chaperones involved in the clearance of A β . There is also a receptor mediated

endocytosis, where receptors located in the surface of glial cells are involved in the uptake and clearance of A β , like lipoprotein receptor-related protein 1 (LRP), receptor for advanced glycation end products (RAGE) and others (Ries and Sastre, 2016). In transcytosis, A β is removed from ISF across the blood brain barrier (BBB) by LRP (Yamada et al., 2009). LRP binds A β in the brain and then transports it across the BBB into the systemic blood. The LRP extracellular domain is cleaved allowing the LRP bound to A β . RAGE protein brings unbound A β back into the CNS. The whole process is regulated by PICALM (Zhao et al., 2015). A perivascular pathway facilitates CSF flow through the brain parenchyma and the clearance of interstitial solutes, including A β (Iliff et al., 2012, 2013). It was thought that changes in arterial pulsatility may contribute to accumulation and deposition of toxic solutes, including A β , in the aging brain (Iliff et al., 2012, 2013). However, mathematical simulation showed that arterial pulsations are not strong enough to produce drainage velocities comparable to experimental observations and that a valve mechanism such as directional permeability of the intramural periarterial drainage pathway is necessary to achieve a net reverse flow (Diem et al., 2017).

ALTERED CLEARANCE OF A β IN ALZHEIMER'S DISEASE

The pathophysiology of Alzheimer's disease (AD) is characterized by the accumulation of A β and phospho-tau protein in the form of neuritic plaques and neurofibrillary tangles, respectively (Braak and Braak, 1991; Atwood et al., 2002). A β molecules can aggregate to form flexible soluble oligomers, which exist in several forms and are toxic to neurons (Haass and Selkoe, 2007), and finally into diffuse and dense plaques. Moreover, variable amounts of misfolded oligomers (known as "seeds") are taken up by neurons then transmitted from neuron to neuron via the extracellular milieu and can propagate aggregates by a 'seeding' or "prion like" mechanism (Walker et al., 2016; Lei et al., 2017). Tau also forms such prion-like misfolded oligomers, and there is some evidence that misfolded A β can induce tau misfolding (Pulawski et al., 2012; Nussbaum et al., 2013).

Amyloid- β accumulation has been hypothesized to result from an imbalance between A β production and clearance. An overproduction is probably the main cause of the disease in the familial AD where a mutation in the *APP*, *PSEN1*, or *PSEN2* genes is present (presenilins are postulated to regulate APP processing through their effects on gamma-secretase) while altered clearance is probably the main cause of the disease in sporadic AD. A good amount of studies reporting altered clearance of A β in AD have been published in recent years (Atwood et al., 2002; Mawuenyega et al., 2010; Tarasoff-Conway et al., 2015; Ries and Sastre, 2016; de Leon et al., 2017; Zuroff et al., 2017), becoming one of the "hot-topics" in AD research today.

The different clearance systems probably contribute to varying extents on A β homeostasis. Any alteration to their function may trigger the progressive accumulation of A β (Morrone et al., 2015; Tarasoff-Conway et al., 2015; de Leon et al., 2017), which is the fundamental step in the hypothesis of the amyloid cascade

(Lambert et al., 1998; Quan and Banks, 2007; Mawuenyega et al., 2010; Bateman et al., 2012; Fagan et al., 2014; Fleisher et al., 2015). There is a relationship between the decrease in the rate of turnover of amyloid peptides and the probability of aggregation due to incorrect protein misfolding (Patterson et al., 2015) resulting in its accumulation. As soluble molecules can move in constant equilibrium between the ISF and the CSF, A β monomers and oligomers can be detected in the CSF. The AP42, and A β oligomer/protofibril levels in cortical biopsy samples are higher in subjects with insoluble cortical A β aggregates than in subjects without aggregates, and brain tissue levels of AP42 are negatively correlated with CSF AP42 (Patel et al., 2012; Cesarini and Marklund, 2018). Indeed, measuring the levels of A β in the CSF is one of the main proposed biomarkers already accepted in the diagnostic criteria of AD (McKhann et al., 2011). It has been reported that levels of A β in the CSF vary with time. Results from cross-sectional analysis in familial AD demonstrate higher levels of A β in the CSF from mutation carriers compared to controls very early in the disease process (~20–30 years prior to estimated symptom onset), which then drop with disease progression, becoming significantly lower than controls ~10–20 years prior to symptom onset (Morrone et al., 2015; Tarasoff-Conway et al., 2015). These low levels then begin to plateau with the development of cognitive symptoms (Iliff et al., 2013). In sporadic AD at very early preclinical stage (transitional stage) there might be either elevations or reductions in CSF AP42 (Clark et al., 2018; de Leon et al., 2018).

THERAPEUTIC CLEARANCE OF A β

Different approaches have been investigated with the aim of removing brain A β . Decreasing A β production might be the first approach that one can think of to reduce ISF A β . For instance, the inhibition BACE is one of the first therapeutic strategies formulated after the amyloid cascade hypothesis, and it is still being explored today. Alternatively, increasing the elimination of A β by enzymatic degradation or by clearance enhancement may be able to slow down both the aggregation and the spread processes of the disease given the relevance of A β as a substrate in AD (Ryan et al., 2010). Among all strategies to enhance the clearance of A β , immunotherapy is the most explored approach so far.

A β Immunotherapy

Peripheral A β Immunotherapy and the Mechanism of Action of "Peripheral-Sink"

The A β immunotherapy consist on activating the immune system against A β through the induction (active immunotherapy) or administration (passive immunotherapy) of A β -antibodies (Menendez-Gonzalez et al., 2011). Passive immunotherapy can be either monoclonal (mAbs) or polyclonal (immunoglobulins). Active immunization activates the immune system to produce specific antigen antibodies. In AD, A β or fragments of A β can be used as an antigen, conjugated to a T-cell epitope-bearing protein, together with a booster of the immune system (adjuvant). Passive immunization avoids the need to activate and initiate

an immune response to produce antigen-specific antibodies. In both active and passive immunization, A β -antibodies bind to A β , potentially promoting the clearance of the peptide (Georgievska et al., 2015).

Some interventions have been shown to produce some positive changes on brain A β , both in animal models and in human subjects. Unfortunately, these neuropathological benefits were not accompanied by sufficient clinical benefit; therefore, none of these therapies have been transferred to the clinic. One of the reasons may be that effective development of AD therapeutic strategies targeting A β require very early administration (before amyloid-plaques are in place) and consideration of the age- and ApoE-specific changes to endogenous A β clearance mechanisms in order to optimize efficacy (Morrone et al., 2015).

Understanding how A β -antibodies remove A β from the brain is a key in the design of A β immunotherapies for AD. Two distinct but not mutually exclusive mechanisms have been proposed: The “microglial phagocytosis” would require the antibodies to enter the brain, where they mediate the uptake of A β into local microglia. The “peripheral sink” mechanism of action relies only on peripheral antibodies to sequester A β in the systemic blood, lowering the level of free A β and inducing the brain to release its store of the peptide. This sequestration of circulating A β produces a shift in the concentration gradient of A β between the brain and the blood causing an efflux of A β out of the brain. Thus, it has been hypothesized that reducing A β peptides in the periphery would be a way to diminish A β levels and plaque load in the brain (Xiang et al., 2015). However, controversy still remains, with evidence both in favor and against the peripheral sink mechanism (Deane et al., 2009; Yamada et al., 2009). Studies with transgenic AD mice seem to validate the hypothesis of the peripheral sink as the main mechanism of A β removal after immunization. Some others showed that little or no antibody enters the brain (Vasilevko et al., 2007) and that peripheral anti-A β antibody alters CNS and plasma A β clearance decreasing brain A β burden (DeMattos et al., 2001). Additionally, mice with the Dutch and Iowa mutations have an A β peptide that is a poor substrate for the efflux transporter LRP, and so accumulates to high levels in the brain. Indeed, these mice have no peripheral sink effect, and despite a massive buildup of vascular amyloid and parenchymal plaque in brain, A β remains undetectable in their blood (Deane et al., 2004; Davis et al., 2006). Direct measurements of brain extracts revealed that little or no antibody was able to enter the brain from the periphery (Ryan et al., 2010). Sagare et al. (2007) showed that infusing in the blood a recombinant version of LRP (sLRP) binding A β lowers plaque burden in these mice, producing the peripheral sink effect. Authors also proved that A β shifted out of the CNS into the blood (Sagare et al., 2007).

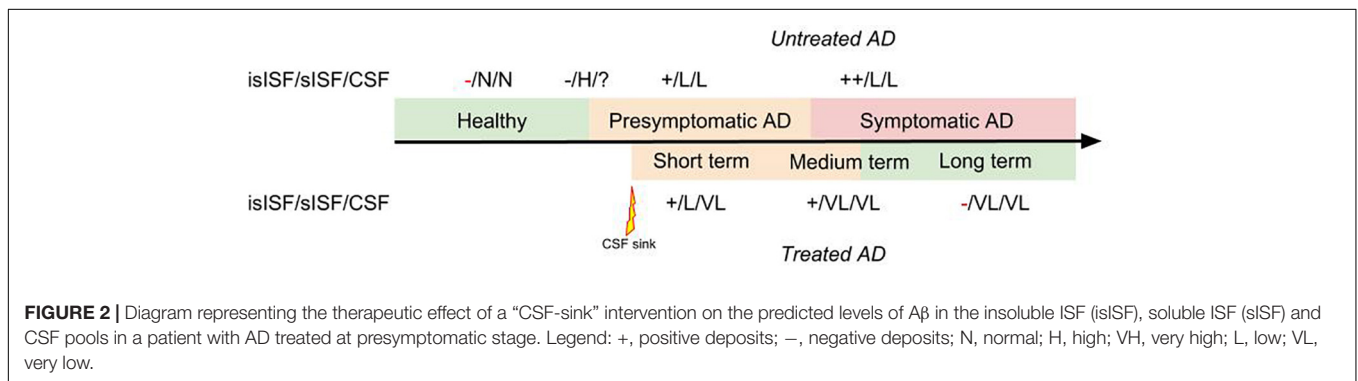
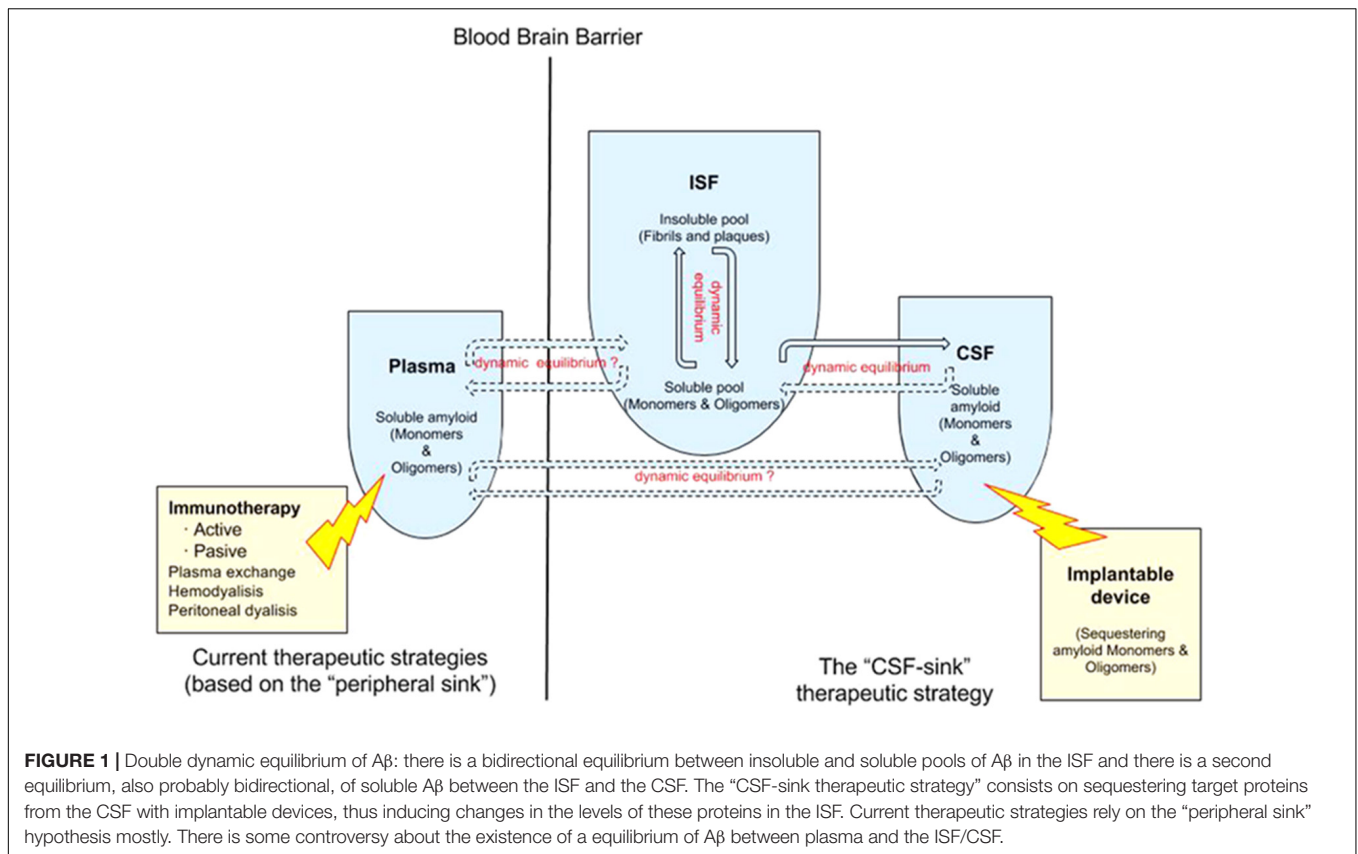
On the other hand, sustained peripheral depletion of A β with a new form of neprilysin, which fuses with albumin to prolong plasma half-life, is designed to confer increased A β degradation activity and does not affect central A β levels in transgenic mice, rats and monkeys (Henderson et al., 2014). In other report (Deane et al., 2009), authors tested the peripheral sink hypothesis by investigating how selective inhibition of A β production in the periphery, using a BACE inhibitor or

reducing BACE gene dosage, affects A β load in the brain. Selective inhibition of peripheral BACE activity in wildtype or transgenic mice reduced A β levels in the periphery but not in the brain, even after chronic treatment over several months. In contrast, a BACE inhibitor with improved brain disposition reduced A β levels in both brain and periphery already after acute dosing. BACE heterozygous mice displayed an important reduction in plasma A β , whereas A β reduction in the brain was much lower. These data suggest that reduction of A β in the periphery is not sufficient to reduce brain A β levels and that BACE is not the rate-limiting enzyme for A β processing in the brain (Georgievska et al., 2015). Recent research suggests that CSF naturally occurring antibodies against A β seem to have a protective effect for AD, while serum naturally occurring antibodies against A β do not seem to have any effect (Kimura et al., 2017; Menendez Gonzalez, 2017a). In line with this, Piazza et al. (2013) reported the first evidence about the participation of natural anti-A β autoantibodies in cerebral amyloid-related angiopathy (CAA) and the possible elimination mechanism of soluble A β in the CSF by antibodies. Today, CSF anti-A β autoantibodies are known to play a key role in the development of amyloid-related imaging abnormalities (ARIA) (DiFrancesco et al., 2015; Chen et al., 2016; Piazza and Winblad, 2016), which are MRI signal changes representing vasogenic edema (VE) and microhemorrhages (mH). VE and mH share some common underlying pathophysiological mechanisms, both in the natural history of AD and in immunotherapies (Sperling et al., 2011). Furthermore, this ARIA has been associated with a massive release of soluble A β , plaques and vascular deposits during the acute inflammatory phase (DiFrancesco et al., 2015; Chen et al., 2016; Piazza and Winblad, 2016).

Administered monoclonal antibodies also showed molecular effect, but clinical benefit in humans was not significant. For instance, Solanezumab increases the elimination of soluble A β and decreases the deposition of cerebral amyloid plaque in AD mice. In clinical trials, the administration of Solanezumab in patients with mild to moderate AD generated an increase of unbound A β in CSF, suggesting that the antibody has a direct peripheral effect with central indirect effect. However, clinical trials showed not improvement of the cognitive and functional capacities of patients (Doody et al., 2014; Chen et al., 2016; Siemers et al., 2016). Similarly, Bapineuzumab modifies A β accumulation and CSF biomarkers, but none of the trials showed a significant clinical benefit (Salloway et al., 2014).

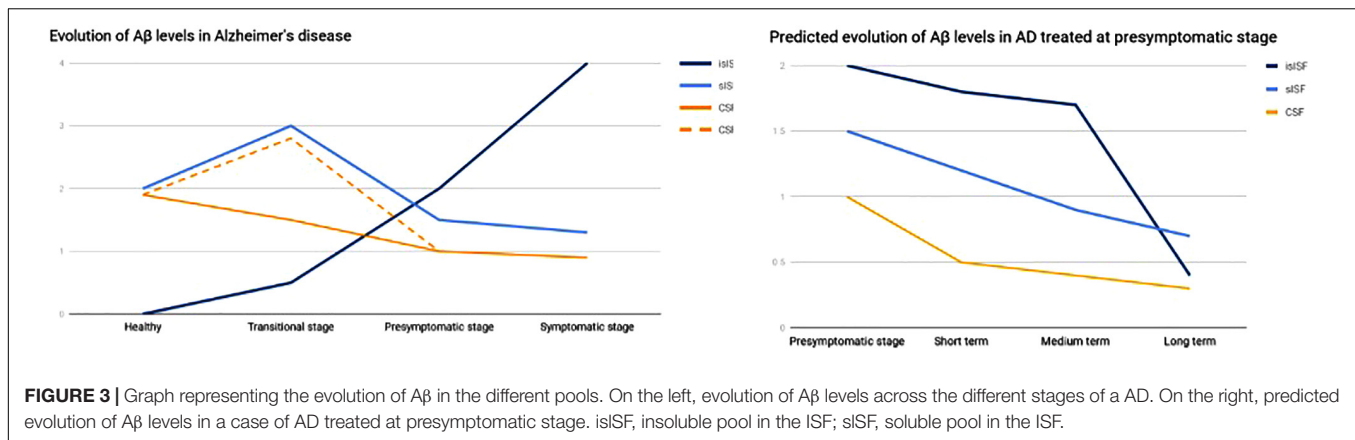
A β -Immunotherapy Into the CNS

Many investigators have indicated that peripheral clearance through the BBB is not recommended in elderly people, in whom the normal transport of A β may present alterations. In addition, the risk of antibody-mediated hemorrhage in sites of cerebral amyloid angiopathy decreases the authors' interest in peripheral passive as well as in active reduction mediated by CNS A β antibodies. Due to this, it has been considered that the direct administration of immunotherapy to the CNS is more efficient than the peripheral one, but the intrinsic characteristics of the BBB make the pharmacological approach difficult. This has led to the search for strategies to overcome



the BBB. These approaches were divided into two categories: the first comprises techniques that facilitate the passage of drugs through the BBB (for example, molecular “Trojan horses,” oligopeptides transporters coupled to protons, exosomes, liposomes, nanoparticles, chimeric peptides, prodrugs); and the second consists on techniques that avoid BBB through direct delivery to the SNC. In this last category, the techniques have been investigated include the interruption of BBB (for example, with ultrasound and microbubbles) and intrathecal, intracerebroventricular and intranasal administration (Wilcock et al., 2003; Carty et al., 2006). Although much less explored, passive Aβ-immunotherapy into the CNS has been tested on animal models. Several groups have reported to have achieved clearance of brain Aβ after intracerebral or intraventricular

injection of either Aβ antibodies (Wilcock et al., 2003, 2004; Oddo et al., 2004; Carty et al., 2006; Levites et al., 2006), antibodies to oligomeric assemblies of Aβ (Chauhan, 2007) or promoting cellular expression of Aβ-specific antibodies, delivered using viral vectors (Ryan et al., 2010). In most cases, the clearance was rapid (within a few days), but the benefits of the injections were transient because the decrease in amyloid plaques approached reversion at 30 days (Sevigny et al., 2016). Authors also observed a decrease in tau hyperphosphorylation, an increase in the number of microglia counts and an improved learning behavior (Doody et al., 2014). In different reports, the level of clearance achieved by this method varies significantly and ranges from what appears to be elimination throughout the CNS (Sakai et al., 2016) to the limited elimination of diffuse



amyloid around the site of antibody injection (Ostrowitzki et al., 2012).

Some human monoclonal antibodies have been shown to enter the brain even when administered peripherally. In a transgenic mouse model of AD, Aducanumab is shown to enter the brain, bind parenchymal Aβ, and reduce soluble and insoluble Aβ in a dose-dependent manner. In patients with prodromal or mild AD, 1 year of monthly intravenous infusions of Aducanumab reduces brain Aβ in a dose- and time-dependent manner. This is accompanied by a slowing of clinical decline. The main safety issues are amyloid-related imaging abnormalities (Sevigny et al., 2016). Phase 3 clinical trials are ongoing. Gantenerumab preferentially interacts with aggregated brain Aβ, both parenchymal and vascular. This antibody acts centrally to disassemble and degrade amyloid plaques by recruiting microglia and activating phagocytosis (Ostrowitzki et al., 2012) but it does not alter plasma Aβ (Bohrmann et al., 2012). As with Adenacumab, trials showed positive trends in clinical scales, main safety worries are amyloid-related imaging abnormalities and clinical trials in different phases are ongoing.

In conclusion, no Aβ immunotherapy has demonstrated significant efficacy in humans to date. A meta-analysis of immunotherapies (Penninkilampi et al., 2017) found no significant treatment differences for typical primary outcome measures. Clinical benefits of peripheral immunotherapy in humans are limited, while the benefits of central immunotherapy in animal models are transient.

Alternative Therapeutic Strategies

Despite Aβ immunotherapy showed not conclusive results to date, Aβ remains the main target in AD. A study using an image biomarker determined that a 15% decrease in Aβ is related to a cognitive improvement of 15–20% (Liu et al., 2015). For all that, there is an urgent need to find alternative methods to achieve a depletion of Aβ in the brain.

A number of studies showed that blood dialysis and plasmapheresis reduces Aβ levels in plasma and CSF in humans and attenuates AD symptoms and pathology in AD mouse models (58,6165), suggesting that removing Aβ from the plasma seems to be an effective -albeit indirect- way of removing Aβ. Different methodologies, from peritoneal dialysis (Jin et al., 2017)

to hemodialysis (Kitaguchi et al., 2015; Sakai et al., 2016; Tholen et al., 2016) and plasma exchange (Boada et al., 2009), reported some extent of success removing Aβ from the plasma, which in turn reduces Aβ in the CSF and in the ISF -this last compartment has been confirmed in animals only-. Again, the “peripheral-sink hypothesis” adds new sources of support from these alternative strategies (Figure 1).

However, there might be a much more direct way of removing Aβ from the ISF than clearing it from the plasma: clearing it from the CSF. A starting rationale is that there is an equilibrium of Aβ levels between the ISF and plasma in AD transgenic mice before developing Aβ deposits (DeMattos et al., 2002; Cirrito et al., 2003; Hong et al., 2011; Nag et al., 2011). However, this equilibrium is lost once Aβ deposits are in place while the equilibrium of Aβ between the ISF and the CSF still persists (DeMattos et al., 2002). Some studies also found a relationship between the load of cortical deposits and levels in the CSF in humans who underwent neurosurgery (ventriculo-peritoneal shunt) (Seppala et al., 2012; Pyykko et al., 2014; Herukka et al., 2015; Abu Hamdeh et al., 2018). At equilibrium, Aβ remains predominantly monomeric up to 3 pM, above which forms large aggregates (Nag et al., 2011). Once aggregated are in place, amyloid deposits can rapidly sequester soluble A from the ISF (Cirrito et al., 2003; Hong et al., 2011). Aβ in the ISF in plaque-rich mice is thought to be derived not from new A biosynthesis but rather from the large reservoir of less soluble Aβ in brain parenchyma (Cirrito et al., 2003). Moreover, a portion of the insoluble Amyloid pool is in dynamic equilibrium with ISF Amyloid. *In vitro* studies have shown that A aggregates contain a readily dissociable pool of Aβ, or “docked Aβ” as well as a long-lasting or stable “locked” pool of Aβ (Maggio et al., 1992; Esler et al., 2000). *In vitro*, as the concentration of Aβ in solution decreases, this docked pool can quickly dissociate from fibrils. *In vivo*, when Aβ production is inhibited and ISF Aβ levels begin to decrease, it is likely that this associated docked pool can return to solution over a finite period of time, as occurs *in vitro*, causing this pool of Aβ to dissociate from fibrils and become soluble. This results in a prolonged apparent half-life of ISF Aβ in animals with Aβ deposition (Cirrito et al., 2003).

We previously posed the hypothesis that soluble proteins can be cleared from the brain with interventions where soluble proteins are continuously removed from the CSF (Liu et al., 2015;

Menendez Gonzalez, 2017c). This is since soluble proteins are in constant equilibrium between the ISF and the CSF. Therefore, clearing A β from the CSF continuously will probably promote the efflux of A β from the ISF to the CSF (Figure 2).

The “CSF-sink” therapeutic strategy consists on sequestering A β from the CSF (Figure 2). Today, we can conceive several ways of accessing the CSF with implantable devices (Menendez Gonzalez, 2017b). These devices can be endowed with different technologies able to capture target molecules, such as A β , from the CSF. Thus, these interventions would work as a central sink of A β , reducing the levels of CSF A β , and by means of the CSF-ISF equilibrium would promote the efflux of A β from the ISF to the CSF (Figure 2).

A study on the A β clearance kinetics suggests that the speed and efficiency of A β clearance pathways may influence the effect on A β deposits (Yuede et al., 2016). A therapeutic strategy aimed at rapid clearance at only high concentrations may be different from a strategy that is designed for a sustained, possibly larger, suppression of A β . The “CSF-sink” therapeutic strategy is expected to provide an intense and sustained depletion of A β in the CSF and, in turn, a steady decrease A β in the ISF, preventing the formation of new aggregates and deposits in the short term and potentially reversing the already existing deposits in the medium and long terms (Figure 3).

REFERENCES

- Abu Hamdeh, S., Virhammar, J., Sehlin, D., Alafuzoff, I., Cesarini, K. G., and Marklund, N. (2018). Brain tissue Abeta42 levels are linked to shunt response in idiopathic normal pressure hydrocephalus. *J. Neurosurg.* doi: 10.3171/2017.7.JNS171005 [Epub ahead of print].
- Atwood, C. S., Martins, R. N., Smith, M. A., and Perry, G. (2002). Senile plaque composition and posttranslational modification of amyloid-beta peptide and associated proteins. *Peptides* 23, 1343–1350. doi: 10.1016/S0196-9781(02)00070-0
- Bakker, E. N., Bacskai, B. J., Arbel-Ornath, M., Aldea, R., Bedussi, B., Morris, A. W. J., et al. (2016). Lymphatic clearance of the brain: perivascular, paravascular and significance for neurodegenerative diseases. *Cell Mol. Neurobiol.* 36, 181–194. doi: 10.1007/s10571-015-0273-8
- Bateman, R. J., Xiong, C., Benzinger, T. L. S., Fagan, A. M., Goate, A., Fox, N. C., et al. (2012). Clinical and biomarker changes in dominantly inherited Alzheimer's disease. *N. Engl. J. Med.* 367, 795–804. doi: 10.1056/NEJMoa1202753
- Boada, M., Ortiz, P., Anaya, F., Hernandez, I., Munoz, J., Nunez, L., et al. (2009). Amyloid-targeted therapeutics in Alzheimer's disease: use of human albumin in plasma exchange as a novel approach for Abeta mobilization. *Drug News Perspect.* 22, 325–339. doi: 10.1358/dnp.2009.22.6.1395256
- Bohrmann, B., Baumann, K., Benz, J., Gerber, F., Huber, W., Knoflach, F., et al. (2012). Gantenerumab: a novel human anti-Abeta antibody demonstrates sustained cerebral amyloid-beta binding and elicits cell-mediated removal of human amyloid-beta. *J. Alzheimers Dis.* 28, 49–69. doi: 10.3233/JAD-2011-110977
- Braak, H., and Braak, E. (1991). Neuropathological staging of Alzheimer-related changes. *Acta Neuropathol.* 82, 239–259. doi: 10.1007/BF00308809
- Carty, N. C., Wilcock, D. M., Rosenthal, A., Grimm, J., Pons, J., Ronan, V., et al. (2006). Intracranial administration of deglycosylated C-terminal-specific anti-A β antibody efficiently clears amyloid plaques without activating microglia in amyloid-depositing transgenic mice. *J. Neuroinflammation* 3:11. doi: 10.1186/1742-2094-3-11
- Albeit AD is a complex disease, and targeting one single molecule might not be enough to hinder the whole neurodegenerative process, we consider this strategy is worth trying, since it is feasible and potentially efficient.
- Finally, we would like to mention this strategy might also be valid for other neurodegenerative and neuroimmune diseases where target molecules are well identified and present in the CSF in equilibrium with the ISF. A series of studies in cellular and animal models are needed to prove this hypothesis.

CONCLUSION

We introduce the rationale basis for the “CSF-sink” hypothesis and conclude that continuous depletion of A β in the CSF will probably produce a steady clearance of A β in the ISF. Implantable devices aimed at sequestering A β from the CSF may represent a new therapeutic strategy in AD.

AUTHOR CONTRIBUTIONS

MM-G is the author of the hypothesis and wrote the whole manuscript. All the other authors revised the existing literature and critically reviewed the manuscript.

- Cesarini, K. G., and Marklund, N. (2018). Brain tissue A β 42 levels are linked to shunt response in idiopathic normal pressure hydrocephalus. *J. Neurosurg.* doi: 10.3171/2017.7.JNS171005 [Epub ahead of print].
- Chauhan, N. B. (2007). Intracerebroventricular passive immunization with anti-oligoAbeta antibody in TgCRND8. *J. Neurosci. Res.* 85, 451–463. doi: 10.1002/jnr.21110
- Chen, Y. F., Ma, X., Sundell, K., Alaka, K., Schuh, K., Raskin, J., et al. (2016). Quantile regression to characterize solanezumab effects in Alzheimer's disease trials. *Alzheimers Dement.* 2, 192–198. doi: 10.1016/j.trci.2016.07.005
- Cirrito, J. R., May, P. C., O'Dell, M. A., Taylor, J. W., Parsadanian, M., Cramer, J. W., et al. (2003). In vivo assessment of brain interstitial fluid with microdialysis reveals plaque-associated changes in amyloid-beta metabolism and half-life. *J. Neurosci.* 23, 8844–8853.
- Clark, L. R., Berman, S. E., Norton, D. L., Kosciak, R., Jonaitis, E., Blennow, K., et al. (2018). Age-accelerated cognitive decline in asymptomatic adults with CSF β -amyloid. *Neurology.* doi: 10.1212/WNL.0000000000005291
- Davis, J., Xu, F., Miao, J., Previti, M. L., Romanov, G., Ziegler, K., et al. (2006). Deficient cerebral clearance of vasculotropic mutant Dutch/Iowa Double A beta in human A betaPP transgenic mice. *Neurobiol. Aging* 27, 946–954. doi: 10.1016/j.neurobiolaging.2005.05.031
- de Leon, M. J., Li, Y., Okamura, N., Tsui, W. H., Saint-Louis, L. A., Glodzik, L., et al. (2017). Cerebrospinal fluid clearance in Alzheimer disease measured with dynamic PET. *J. Nucl. Med.* 58, 1471–1476. doi: 10.2967/jnumed.116.187211
- de Leon, M. J., Pirraglia, E., Osorio, R. S., Glodzik, L., Saint-Louis, L., Kim, H.-J., et al. (2018). The nonlinear relationship between cerebrospinal fluid Abeta42 and tau in preclinical Alzheimer's disease. *PLoS One* 13:e0191240. doi: 10.1371/journal.pone.0191240
- Deane, R., Bell, R. D., Sagare, A., and Zlokovic, B. V. (2009). Clearance of amyloid-beta peptide across the blood-brain barrier: implication for therapies in Alzheimer's disease. *CNS Neurol. Disord. Drug Targets* 8, 16–30. doi: 10.2174/187152709787601867
- Deane, R., Wu, Z., Sagare, A., Davis, J., Du Yan, S., Hamm, K., et al. (2004). LRP/amyloid beta-peptide interaction mediates differential brain efflux of Abeta isoforms. *Neuron* 43, 333–344. doi: 10.1016/j.neuron.2004.07.017
- DeMattos, R. B., Bales, K. R., Cummins, D. J., Dodart, J. C., Paul, S. M., and Holtzman, D. M. (2001). Peripheral anti-A beta antibody alters CNS and plasma

- A beta clearance and decreases brain A beta burden in a mouse model of Alzheimer's disease. *Proc. Natl. Acad. Sci. U.S.A.* 98, 8850–8855. doi: 10.1073/pnas.151261398
- DeMattos, R. B., Bales, K. R., Parsadanian, M., O'Dell, M. A., Foss, E. M., Paul, S. M., et al. (2002). Plaque-associated disruption of CSF and plasma amyloid-beta (Abeta) equilibrium in a mouse model of Alzheimer's disease. *J. Neurochem.* 81, 229–236. doi: 10.1046/j.1471-4159.2002.00889.x
- Diem, A. K., MacGregor Sharp, M., Gatherer, M., Bressloff, N. W., Carare, R. O., and Richardson, G. (2017). Arterial pulsations cannot drive intramural periarterial drainage: significance for A β drainage. *Front. Neurosci.* 11:475. doi: 10.3389/fnins.2017.00475
- DiFrancesco, J. C., Longoni, M., and Piazza, F. (2015). Anti-Abeta autoantibodies in amyloid related imaging abnormalities (ARIA): candidate biomarker for immunotherapy in Alzheimer's disease and cerebral amyloid angiopathy. *Front. Neurol.* 6:207. doi: 10.3389/fneur.2015.00207
- Doody, R. S., Thomas, R. G., Farlow, M., Iwatsubo, T., Vellas, B., Joffe, S., et al. (2014). Phase 3 trials of solanezumab for mild-to-moderate Alzheimer's disease. *N. Engl. J. Med.* 370, 311–321. doi: 10.1056/NEJMoa1312889
- Esker, W. P., Stimson, E. R., Jennings, J. M., Vinters, H. V., Ghilardi, J. R., Lee, J. P., et al. (2000). Alzheimer's disease amyloid propagation by a template-dependent dock-lock mechanism. *Biochemistry* 39, 6288–6295. doi: 10.1021/bi992933h
- Fagan, A. M., Xiong, C., Jasielec, M. S., Bateman, R. J., Goate, A. M., Benzinger, T. L. S., et al. (2014). Longitudinal change in CSF biomarkers in autosomal-dominant Alzheimer's disease. *Sci. Transl. Med.* 6:226ra30. doi: 10.1126/scitranslmed.3007901
- Fleisher, A. S., Chen, K., Quiroz, Y. T., Jakimovich, L. J., Gutierrez Gomez, M., Langois, C. M., et al. (2015). Associations between biomarkers and age in the presenilin 1 E280A autosomal dominant Alzheimer disease kindred: a cross-sectional study. *JAMA Neurol.* 72, 316–324. doi: 10.1001/jamaneuro.2014.3314
- Georgievska, B., Gustavsson, S., Lundkvist, J., Neelissen, J., Eketjall, S., Ramberg, V., et al. (2015). Revisiting the peripheral sink hypothesis: inhibiting BACE1 activity in the periphery does not alter beta-amyloid levels in the CNS. *J. Neurochem.* 132, 477–486. doi: 10.1111/jnc.12937
- Haass, C., and Selkoe, D. J. (2007). Soluble protein oligomers in neurodegeneration: lessons from the Alzheimer's amyloid beta-peptide. *Nat. Rev. Mol. Cell Biol.* 8, 101–112. doi: 10.1038/nrm2101
- Henderson, S. J., Andersson, C., Narwal, R., Janson, J., Goldschmidt, T. J., Appelkvist, P., et al. (2014). Sustained peripheral depletion of amyloid- β with a novel form of neprilysin does not affect central levels of amyloid- β . *Brain* 137, 553–564. doi: 10.1093/brain/awt308
- Herukka, S.-K., Rummukainen, J., Ihalainen, J., von Und Zu Fraunberg, M., Koivisto, A. M., Nerg, O., et al. (2015). Amyloid-beta and tau dynamics in human brain interstitial fluid in patients with suspected normal pressure hydrocephalus. *J. Alzheimers Dis.* 46, 261–269. doi: 10.3233/JAD-14-2862
- Hong, S., Quintero-Monzon, O., Ostaszewski, B. L., Podlisny, D. R., Cavanaugh, W. T., Yang, T., et al. (2011). Dynamic analysis of amyloid beta-protein in behaving mice reveals opposing changes in ISF versus parenchymal Abeta during age-related plaque formation. *J. Neurosci.* 31, 15861–15869. doi: 10.1523/JNEUROSCI.3272-11.2011
- Illiff, J. J., Wang, M., Liao, Y., Plogg, B. A., Peng, W., Gundersen, G. A., et al. (2012). A paravascular pathway facilitates CSF flow through the brain parenchyma and the clearance of interstitial solutes, including amyloid beta. *Sci. Transl. Med.* 4:147ra111. doi: 10.1126/scitranslmed.3003748
- Illiff, J. J., Wang, M., Zeppenfeld, D. M., Venkataraman, A., Plog, B. A., Liao, Y., et al. (2013). Cerebral arterial pulsation drives paravascular CSF-interstitial fluid exchange in the murine brain. *J. Neurosci.* 33, 18190–18199. doi: 10.1523/JNEUROSCI.1592-13.2013
- Jin, W.-S., Shen, L.-L., Bu, X.-L., Zhang, W.-W., Chen, S.-H., Huang, Z.-L., et al. (2017). Peritoneal dialysis reduces amyloid-beta plasma levels in humans and attenuates Alzheimer-associated phenotypes in an APP/PS1 mouse model. *Acta Neuropathol.* 134, 207–220. doi: 10.1007/s00401-017-1721-y
- Kimura, A., Takemura, M., Saito, K., Yoshikura, N., Hayashi, Y., and Inuzuka, T. (2017). Association between naturally occurring anti-amyloid β autoantibodies and medial temporal lobe atrophy in Alzheimer's disease. *J. Neurol. Neurosurg. Psychiatry* 88, 126L–131. doi: 10.1136/jnnp-2016-313476
- Kitaguchi, N., Hasegawa, M., Ito, S., Kawaguchi, K., Hiki, Y., Nakai, S., et al. (2015). A prospective study on blood Abeta levels and the cognitive function of patients with hemodialysis: a potential therapeutic strategy for Alzheimer's disease. *J. Neural. Transm.* 122, 1593–1607. doi: 10.1007/s00702-015-1431-3
- Lambert, M. P., Barlow, A. K., Chromy, B. A., Edwards, C., Freed, R., Liosatos, M., et al. (1998). Diffusible, nonfibrillar ligands derived from Abeta1-42 are potent central nervous system neurotoxins. *Proc. Natl. Acad. Sci. U.S.A.* 95, 6448–6453. doi: 10.1073/pnas.95.11.6448
- Lei, Y., Han, H., Yuan, F., Javed, A., and Zhao, Y. (2017). The brain interstitial system: anatomy, modeling, in vivo measurement, and applications. *Prog. Neurobiol.* 157, 230–246. doi: 10.1016/j.pneurobio.2015.12.007
- Levites, Y., Das, P., Price, R. W., Rochette, M. J., Kostura, L. A., McGowan, E. M., et al. (2006). Anti-Abeta42- and anti-Abeta40-specific mAbs attenuate amyloid deposition in an Alzheimer disease mouse model. *J. Clin. Invest.* 116, 193–201. doi: 10.1172/JCI25410
- Liu, Y.-H., Xiang, Y., Wang, Y.-R., Jiao, S.-S., Wang, Q.-H., Bu, X.-L., et al. (2015). Association between serum amyloid-beta and renal functions: implications for roles of kidney in amyloid-beta clearance. *Mol. Neurobiol.* 52, 115–119. doi: 10.1007/s12035-014-8854-y
- Maggio, J. E., Stimson, E. R., Ghilardi, J. R., Allen, C. J., Dahl, C. E., Whitcomb, D. C., et al. (1992). Reversible in vitro growth of Alzheimer disease beta-amyloid plaques by deposition of labeled amyloid peptide. *Proc. Natl. Acad. Sci. U.S.A.* 89, 5462–5466. doi: 10.1073/pnas.89.12.5462
- Malm, T., Koistinaho, M., Muona, A., Magga, J., and Koistinaho, J. (2010). The role and therapeutic potential of monocytic cells in Alzheimer's disease. *Glia* 58, 889–900. doi: 10.1002/glia.20973
- Mawuenyega, K. G., Sigurdson, W., Ovod, V., Munsell, L., Kasten, T., Morris, J. C., et al. (2010). Decreased clearance of CNS beta-amyloid in Alzheimer's disease. *Science* 330:1774. doi: 10.1126/science.1197623
- McKhann, G. M., Knopman, D. S., Chertkow, H., Hyman, B. T., Jack, C. R. J., Kawas, C. H., et al. (2011). The diagnosis of dementia due to Alzheimer's disease: recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease. *Alzheimers Dement.* 7, 263–269. doi: 10.1016/j.jalz.2011.03.005
- Menendez Gonzalez, M. (2017a). Association between naturally occurring anti-amyloid β autoantibodies and medial temporal lobe atrophy in Alzheimer's disease. *J. Neurol. Neurosurg. Psychiatry* 88, 96–97. doi: 10.1136/jnnp-2016-314136
- Menendez Gonzalez, M. (2017b). Implantable systems for continuous liquorpheresis and CSF replacement. *Cureus* 9:e1022. doi: 10.7759/cureus.1022
- Menendez Gonzalez, M. (2017c). Mechanical dilution of beta-amyloid peptide and phosphorylated tau protein in Alzheimer's disease: too simple to be true? *Cureus* 9:e1062. doi: 10.7759/cureus.1062
- Menendez-Gonzalez, M., Perez-Pinera, P., Martinez-Rivera, M., Calatayud, M. T., and Blazquez Menes, B. (2005). APP processing and the APP-KPI domain involvement in the amyloid cascade. *Neurodegener. Dis.* 2, 277–283. doi: 10.1159/000092315
- Menendez-Gonzalez, M., Perez-Pinera, P., Martinez-Rivera, M., Muniz, A. L., and Vega, J. A. (2011). Immunotherapy for Alzheimer's disease: rational basis in ongoing clinical trials. *Curr. Pharm. Des.* 17, 508–520. doi: 10.2174/138161211795164112
- Morrone, C. D., Liu, M., Black, S. E., and McLaurin, J. (2015). Interaction between therapeutic interventions for Alzheimer's disease and physiological A β clearance mechanisms. *Front. Aging Neurosci.* 7:64. doi: 10.3389/fnagi.2015.00064
- Nag, S., Sarkar, B., Bandyopadhyay, A., Sahoo, B., Sreenivasan, V. K. A., Kombrabail, M., et al. (2011). Nature of the amyloid-beta monomer and the monomer-oligomer equilibrium. *J. Biol. Chem.* 286, 13827–13833. doi: 10.1074/jbc.M110.199885
- Nussbaum, J. M., Seward, M. E., and Bloom, G. S. (2013). Alzheimer disease: a tale of two prions. *Prion* 7, 14–19. doi: 10.4161/pri.22118
- Oddo, S., Billings, L., Kesslak, J. P., Cribbs, D. H., and LaFerla, F. M. (2004). Abeta immunotherapy leads to clearance of early, but not late, hyperphosphorylated tau aggregates via the proteasome. *Neuron* 43, 321–332. doi: 10.1016/j.neuron.2004.07.003
- O'Nuallain, B., Freir, D. B., Nicoll, A. J., Risse, E., Ferguson, N., Herron, C. E., et al. (2010). Amyloid beta-protein dimers rapidly form stable synaptotoxic protofibrils. *J. Neurosci.* 30, 14411–14419. doi: 10.1523/JNEUROSCI.3537-10.2010

- Ostrowitzki, S., Deptula, D., Thurfjell, L., Barkhof, F., Bohrmann, B., Brooks, D. J., et al. (2012). Mechanism of amyloid removal in patients with Alzheimer disease treated with gantenerumab. *Arch. Neurol.* 69, 198–207. doi: 10.1001/archneurol.2011.1538
- Patel, S., Lee, E. B., Xie, S. X., Law, A., Jackson, E. M., Arnold, S. E., et al. (2012). Phosphorylated tau/amyloid beta 1-42 ratio in ventricular cerebrospinal fluid reflects outcome in idiopathic normal pressure hydrocephalus. *Fluids Barriers CNS* 9:7. doi: 10.1186/2045-8118-9-7
- Patterson, B. W., Elbert, D. L., Mawuenyega, K. G., Kasten, T., Ovod, V., Ma, S., et al. (2015). Age and amyloid effects on human central nervous system amyloid-beta kinetics. *Ann. Neurol.* 78, 439–453. doi: 10.1002/ana.24454
- Penninkilampi, R., Brothers, H. M., and Eslick, G. D. (2017). Safety and efficacy of anti-amyloid-beta immunotherapy in Alzheimer's disease: a systematic review and meta-analysis. *J. Neuroimmune Pharmacol.* 12, 194–203. doi: 10.1007/s11481-016-9722-5
- Piazza, F., Greenberg, S. M., Savoirdo, M., Gardinetti, M., Chiapparini, L., Raicher, I., et al. (2013). Anti-amyloid β autoantibodies in cerebral amyloid angiopathy-related inflammation: implications for amyloid-modifying therapies. *Ann. Neurol.* 73, 449–458. doi: 10.1002/ana.23857
- Piazza, F., and Winblad, B. (2016). Amyloid-related imaging abnormalities (ARIA) in immunotherapy trials for Alzheimer's disease: need for prognostic biomarkers? *J. Alzheimer's Dis.* 52, 417–420. doi: 10.3233/JAD-160122
- Pulawski, W., Ghoshdastider, U., Andrisano, V., and Filipek, S. (2012). Ubiquitous amyloids. *Appl. Biochem. Biotechnol.* 166, 1626–1643. doi: 10.1007/s12010-012-9549-3
- Pyykko, O. T., Lumela, M., Rummukainen, J., Nerg, O., Seppala, T. T., Herukka, S.-K., et al. (2014). Cerebrospinal fluid biomarker and brain biopsy findings in idiopathic normal pressure hydrocephalus. *PLoS One* 9:e91974. doi: 10.1371/journal.pone.0091974
- Quan, N., and Banks, W. A. (2007). Brain-immune communication pathways. *Brain Behav. Immun.* 21, 727–735. doi: 10.1016/j.bbi.2007.05.005
- Ries, M., and Sastre, M. (2016). Mechanisms of A β clearance and degradation by glial cells. *Front. Aging Neurosci.* 8:160. doi: 10.3389/fnagi.2016.00160
- Ryan, D. A., Mastrangelo, M. A., Narrow, W. C., Sullivan, M. A., Federoff, H. J., and Bowers, W. J. (2010). A β -directed single-chain antibody delivery via a serotype-1 AAV vector improves learning behavior and pathology in Alzheimer's disease mice. *Mol. Ther.* 18, 1471–1481. doi: 10.1038/mt.2010.111
- Sagare, A., Deane, R., Bell, R. D., Johnson, B., Hamm, K., Pendu, R., et al. (2007). Clearance of amyloid-beta by circulating lipoprotein receptors. *Nat. Med.* 13, 1029–1031. doi: 10.1038/nm1635
- Sakai, K., Senda, T., Hata, R., Kuroda, M., Hasegawa, M., Kato, M., et al. (2016). Patients that have undergone hemodialysis exhibit lower amyloid deposition in the brain: evidence supporting a therapeutic strategy for Alzheimer's disease by removal of blood amyloid. *J. Alzheimer's Dis.* 51, 997–1002. doi: 10.3233/JAD-151139
- Salloway, S., Sperling, R., Fox, N. C., Blennow, K., Klunk, W., Raskind, M., et al. (2014). Two phase 3 trials of bapineuzumab in mild-to-moderate Alzheimer's disease. *N. Engl. J. Med.* 370, 322–333. doi: 10.1056/NEJMoa1304839
- Seppala, T. T., Nerg, O., Koivisto, A. M., Rummukainen, J., Puli, L., Zetterberg, H., et al. (2012). CSF biomarkers for Alzheimer disease correlate with cortical brain biopsy findings. *Neurology* 78, 1568–1575. doi: 10.1212/WNL.0b013e3182563bd0
- Sevigny, J., Chiao, P., Bussiere, T., Weinreb, P. H., Williams, L., Maier, M., et al. (2016). The antibody aducanumab reduces A β plaques in Alzheimer's disease. *Nature* 537, 50–56. doi: 10.1038/nature19323
- Siemers, E. R., Sundell, K. L., Carlson, C., Case, M., Sethuraman, G., Liu-Seifert, H., et al. (2016). Phase 3 solanezumab trials: secondary outcomes in mild Alzheimer's disease patients. *Alzheimers Dement.* 12, 110–120. doi: 10.1016/j.jalz.2015.06.1893
- Sperling, R. A., Jack, C. R. J., Black, S. E., Frosch, M. P., Greenberg, S. M., Hyman, B. T., et al. (2011). Amyloid-related imaging abnormalities in amyloid-modifying therapeutic trials: recommendations from the Alzheimer's association research roundtable workgroup. *Alzheimers Dement.* 7, 367–385. doi: 10.1016/j.jalz.2011.05.2351
- Tarasoff-Conway, J. M., Carare, R. O., Osorio, R. S., Glodzik, L., Butler, T., Fieremans, E., et al. (2015). Clearance systems in the brain—implications for Alzheimer disease. *Nat. Rev. Neurol.* 11, 457–470. doi: 10.1038/nrneuro.2015.119
- Tholen, S., Schmaderer, C., Chmielewski, S., Forstl, H., Heemann, U., Baumann, M., et al. (2016). Reduction of amyloid-beta plasma levels by hemodialysis: an anti-amyloid treatment strategy? *J. Alzheimer's Dis.* 50, 791–796. doi: 10.3233/JAD-150662
- Vasilenko, V., Xu, F., Previti, M. L., Van Nostrand, W. E., and Cribbs, D. H. (2007). Experimental investigation of antibody-mediated clearance mechanisms of amyloid-beta in CNS of Tg-SwDI transgenic mice. *J. Neurosci.* 27, 13376–13383. doi: 10.1523/JNEUROSCI.2788-07.2007
- Walker, L. C., Schelle, J., and Jucker, M. (2016). The prion-like properties of amyloid-beta assemblies: implications for Alzheimer's disease. *Cold Spring Harb. Perspect. Med.* 6:a024398. doi: 10.1101/cshperspect.a024398
- Wilcock, D. M., DiCarlo, G., Henderson, D., Jackson, J., Clarke, K., Ugen, K. E., et al. (2003). Intracranially administered anti-A β antibodies reduce beta-amyloid deposition by mechanisms both independent of and associated with microglial activation. *J. Neurosci.* 23, 3745–3751.
- Wilcock, D. M., Munireddy, S. K., Rosenthal, A., Ugen, K. E., Gordon, M. N., and Morgan, D. (2004). Microglial activation facilitates A β plaque removal following intracranial anti-A β antibody administration. *Neurobiol. Dis.* 15, 11–20. doi: 10.1016/j.nbd.2003.09.015
- Xiang, Y., Bu, X.-L., Liu, Y.-H., Zhu, C., Shen, L.-L., Jiao, S.-S., et al. (2015). Physiological amyloid-beta clearance in the periphery and its therapeutic potential for Alzheimer's disease. *Acta Neuropathol.* 130, 487–499. doi: 10.1007/s00401-015-1477-1
- Yamada, K., Yabuki, C., Seubert, P., Schenk, D., Hori, Y., Ohtsuki, S., et al. (2009). A β immunotherapy: intracerebral sequestration of A β by an anti-A β monoclonal antibody 266 with high affinity to soluble A β . *J. Neurosci.* 29, 11393–11398. doi: 10.1523/JNEUROSCI.2021-09.2009
- Yuede, C. M., Lee, H., Restivo, J. L., Davis, T. A., Hettinger, J. C., Wallace, C. E., et al. (2016). Rapid in vivo measurement of β -amyloid reveals biphasic clearance kinetics in an Alzheimer's mouse model. *J. Exp. Med.* 213, 677–685. doi: 10.1084/jem.20151428
- Zhao, Z., Sagare, A. P., Ma, Q., Halliday, M. R., Kong, P., Kisler, K., et al. (2015). Central role for PICALM in amyloid-beta blood-brain barrier transcytosis and clearance. *Nat. Neurosci.* 18, 978–987. doi: 10.1038/nn.4025
- Zuroff, L., Daley, D., Black, K. L., and Koronyo-Hamaoui, M. (2017). Clearance of cerebral A β in Alzheimer's disease: reassessing the role of microglia and monocytes. *Cell Mol. Life Sci.* 74, 2167–2201. doi: 10.1007/s00018-017-2463-7

Conflict of Interest Statement: GA is employed by HealthSens, S.L.

The other authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Copyright © 2018 Menendez-Gonzalez, Padilla-Zambrano, Alvarez, Capetillo-Zarate, Tomas-Zapico and Costa. This is an open-access article distributed under the terms of the Creative Commons Attribution License (CC BY). The use, distribution or reproduction in other forums is permitted, provided the original author(s) and the copyright owner are credited and that the original publication in this journal is cited, in accordance with accepted academic practice. No use, distribution or reproduction is permitted which does not comply with these terms.