Peptide-Based Vaccines for Neurodegenerative Diseases

Subjects: Immunology | Neurosciences
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Neurodegenerative diseases are associated with a progressive loss of neurons in the central nervous system (CNS) and are characterized by severe clinical deficits, especially cognitive, motor, and psychiatric ones. The most common neurodegenerative disease is Alzheimer's disease (AD), while other well-known neurodegenerative diseases include Parkinson's disease (PD), amyotrophic lateral sclerosis (ALS), Huntington's disease (HD), etc.

During the last two decades several research endeavors have been devoted to the development of peptide-based active immunotherapies/vaccines for fighting neurodegenerative diseases -aiming, eventually, at clinical application. The most significant among the aforementioned peptide-based candidate vaccines for neurogenerative diseases have been based on specific epitopes of certain biomolecular targets associated with neurodegeneration, especially beta-amyloid peptide (Aβ), tau protein (tau) and α-synuclein (α-syn), as will be presented below.

Keywords: vaccines ; neurodegenerative diseases ; peptide epitopes ; beta-amyloid-based peptide-vaccines ; tau-protein-based peptide-vaccines ; α-synuclein-based peptide-vaccines

1. Treatment of AD and other Neurodegenerative Diseases: Short History

AD and other neurodegenerative diseases [1] have a high socioeconomic impact. Treatment of AD is a very important issue for health care systems worldwide [2]. Until recently, treatment for AD patients relied on the pharmacological intervention of cholinergic and glutamatergic neurotransmission. Thus, a few drugs for AD have been approved by the US Food and Drug Administration (FDA), including donepezil, rivastigmine, and galantamine (cholinesterase inhibitors), memantine (an N-methyl-D-aspartate receptor partial antagonist), and acombination of donepezil and memantine. All these drugs, however, have limited effectiveness and they do not reverse the progression of the disease or improve cognitive dysfunction, but they rather delay the deterioration of AD symptoms for a limited time period [3]. In 2021 a passive immunotherapeutic agent, i.e. a fully human monoclonal antibody was approved by the FDA as a treatment for AD, but some controversy has surrounded this decision [4][5][6][7][8]. Overall, investigation and development of more successful therapeutic/preventive strategies to fight AD and other neurodegenerative diseases is still a goal of utmost importance [9]. Several research endeavors have been focused on the development of peptide-based active immunotherapies/vaccines for neurodegenerative diseases [10][11] and this approach seems to be an interesting perspective in the field.

2. Biomolecular Targets of Vaccines for Neurodegenerative Diseases

Significant efforts toward the development of active immunotherapies/vaccines for neurodegenerative diseases have focused on targeting pathologic species of Aβ, tau, and, to a lesser extent α-syn since aberrant aggregation of these biomolecules is considered to play a major role in the disease pathophysiology [12]. Immunization targeting these peptides/proteins has been expected to result in the generation of antibodies that might facilitate clearance or prevent the formation of neurotoxic forms of the parental targets [10]. However, there are some issues that should be taken into account and appropriately addressed, in order to achieve optimal results: Aβ, as well as tau and α-syn, are probably conceived as "self" molecules by the host organism; thus, they may be either non-immunogenic or induce a detrimental auto-immune reaction [2] and this aspect should be carefully taken into consideration when designing such a vaccine. Another issue is how the antibodies induced after immunization can cross the blood–brain barrier and access the pathologic spots [10]. However, antibodies against Aβ that had been peripherally administered were reported to enter CNS in mouse models of AD, and in human subjects participating in clinical trials [2][13]. In vivo access of the pathologic loci is even more complicated, when intracellular proteins are targeted, such as tau. Previous experimental data have shown, however, that intracellular "neurodegenerative" proteins may be also present extracellularly [14]. Moreover, recent

technological advances, especially in the field of formulation/delivery systems, have facilitated successful in vivo accessibility of pathologic targets and stimulated new efforts to develop active immunotherapies targeting Aβ, tau, and α-syn [14].

According to recently accumulated evidence, neurotoxic species of Aβ, tau, and α-syn may exert their toxicity at least in part through binding to cellular prion protein (PrP) on the surface of neurons [15][16][17]. Thus, PrP rather than individual disease-associated proteins might be (immuno)therapeutically targeted. Moreover, a few additional molecular targets have been reported in the literature, e.g., TAR DNA-binding protein 43 (TDP-43), dipeptide repeat proteins (DPRs), superoxide dismutase 1, and huntingtin protein [1][14][18][19][20], but little data on the development of vaccines against these targets are currently available.

3. Peptides Epitopes: General Concepts

Peptide vaccines are based on specific B- (and T-) cell peptide epitopes. The epitope choice is a crucial step in the vaccine design, since the peptide epitopes should be able to induce strong, long-lasting humoral and/or cellular immunity against the biomolecular target [21].

A B-cell epitope is a specific fragment of the antigen/immunogen which is recognized by the B-cell receptors present on the surface of B-cells of a unique clone; B-cell epitopes are subsequently bound to the antibodies generated upon B-cell stimulation/maturation. B-cell epitopes can be linear and may be as short as pentapeptides, but they are mostly conformational [11][22]. T-cell epitopes are linear peptide fragments that can be bound to major histocompatibility complex proteins (MHC I, MHC II), through which they are presented on the surface of appropriate cells and subsequently recognized by T-cell receptors on CD8+ (cytotoxic T-cells) and CD4+ (helper T-cells), respectively [11][22]. Cytotoxic T-cell epitopes are usually 8- to 12-mer peptides, whereas helper T-cell epitopes (Th) are usually 12- to 17-mers [2][22].

Identifying epitopes in disease-associated immunogens is of great interest for designing epitope-based vaccines. NMR and X-ray crystallographic methods have been used for this purpose. T-cell and B-cell epitope computational prediction methods and tools (immunoinformatics), which are faster and less expensive than NMR and X-ray crystallography, have also been employed [22][23][24]. Moreover, antibodies have been often utilized as a template for vaccine design, following the concept that if a particular epitope is related to certain B- cell responses, then it will probably induce similar responses when administered in the form of a vaccine [10].

4. Peptide Epitopes Used in Aβ-Vaccines

The first therapeutic approach for AD through active immunization was based on full-length pre-aggregated Aβ(1-42) [25]. However, the first clinical trials with the so-called AN1792 vaccine (**Table 1**), based on Aβ(1-42), failed, since meningoencephalitis appeared in some of the immunized AD patients; this severe side-effect was attributed to a cell-mediated inflammatory response caused by the T cell epitopes of Aβ(1-42) -and also the adjuvant used (QS-21). Moreover, the AN1792 vaccine induced rather insufficient antibody titer, probably due to the weak immunogenicity of Aβ [2][9][26].

Despite the serious safety issues and the rather low efficacy, results of the initial clinical trials with AN1792 along with follow-up data inspired further research toward the development of vaccines targeting Aβ. Special efforts were focused on how to avoid autoreactive T cells against Aβ and to generate relatively high titers of antibodies. Biochemical assays have identified the first N-terminal 15 amino acids of Aβ as the site of the principal B-cell epitope [27], whereas the T-cell epitopes are believed to localize in the C-terminus. Thus, second-generation Aβ vaccines were developed by selecting peptide fragments of the N terminus of Aβ, and suitably formulating [28] these fragments with foreign carriers/delivery systems and adjuvants, so as to enhance the immunogenicity of B-cell epitopes [2][10].

Second-generation Aβ vaccines that have subsequently been tested in clinical trials (**Table 1**) include CAD106, ACC-001 (vanutide cridificar), Lu AF20513, UB-311, ACI-24, V-950, ABvac40, AD01, AD02, and AD03 [2][9][10][14][28][29]. CAD106 [1][2][9][10][14][28][29][30][31] is based on the first 6 amino acids of Aβ, ACC-001 [1][2][9][14][28][29][32] is based on the first 7 amino acids, Lu AF20513 [2][9][10][28][29] is based on the first 12 amino acids, UB-311 [2][9][10][14][28][29][33] is based on the first 14 amino acids, and ACI-24 [1][2][9][14][28][29] is based on the first 15 amino acids, whereas V-950 also employs an N-terminal Aβ peptide fragment [9][28][29], reported to be Aβ(1-15) [33]. On the other hand, it should be noticed that ABvac40 vaccine [1][2][9][10][14][28][34] has employed a short C-terminal fragment of Aβ, i.e., Aβ(33-40), based on the observation that antibodies raised against the C-terminus of Aβ seem to affect Aβ aggregation [34][35]. Moreover, AD01 [9], AD02 and AD03 [2][9][14][28][29][36] are based on epitopes mimicking the Aβ N-terminus [9][29]. Though none of the second-generation vaccines have

induced meningoencephalitis, a few antibody-mediated adverse effects did appear, while these vaccines could not lead to a dramatically improved therapeutic outcome [37]; therefore, clinical trials have continued only for a few of them, i.e., CAD106, ACI-24, UB-311, and ABvac40, as recently reported [2].

In addition to vaccines that have undergone clinical trials, many other peptide-based Aβ-vaccines have been developed and tested in rodents, mostly transgenic mice. Most of these vaccines focus on the Aβ N-terminus. More specifically (**Table 1**), Aβ(3-10) [37][38][39] and Aβ(1-6) were among the peptide epitopes used [40]; different copy numbers of the latter were used in another attempt to develop new Aβ- vaccines [41]. In addition, Aβ(1-6) and Aβ(1-15) were used for the synthesis of 4-branched multiple-antigen peptides (MAP)4 and subsequently administered to mice to develop Aβ specific antibodies [42]. Aβ(1-15) was also used in a cholera toxin B subunit/silkworm pupa vaccine [43] as well as in a yeast-based vaccine (Y-5A15) [44]. Aβ(1-11) was used in a combination vaccine (AV-1959R/AV-1980R) targeting both Aβ and tau [45]. Moreover, Aβ(1-11) was used in a DNA vaccine (AB-1959D), which encoded for a fusion protein containing three copies of Aβ(1-11) [46]. Aβ(1-11) was also part of a fusion protein containing the bacterial protein domain E2, (1-11)E2, which was further used in animal vaccination [47]. Vaccines based on small cyclic peptides, i.e., cyclo[Aβ(22-28)-YNGK'], cyclo[Aβ(23-29)-YNGK'], and cyclo[Aβ(22-29)-YNGK'], mimicking the specific molecular turn in the structure of oligomeric Aβ were reported [48]. In a recent paper, a series of several synthetic Aβ epitope-peptides, linear or cyclic, including Aβ(1-6), Aβ(1-6)3, Aβ(1-15), cyclo[Aβ(1-7)], cycloEP1 and cycloEP2 (where EP1 and EP2 are special peptide epitopes of Aβ oligomers, selected with phage display from random peptide libraries), have been appropriately formulated and subsequently tested in animal preclinical studies [49]. Interestingly, intact Aβ(1-42) was specially formulated and tested in animals a few years ago, without inducing neuroinflammation [50]. Moreover, a DNA vaccine based on Aβ(1-42) trimer and targeting amyloid plaques and tau protein was also reported [51]. Since soluble Aβ oligomers and protofibrils are now considered as the most toxic forms of Aβ and the ideal target of an Aβ-vaccine may be a discontinuous conformational epitope formed by soluble Aβ oligomers [18][28][35], one more vaccine (AOE1) based on specific conformational epitope(s) of Aβ oligomers has been recently described [52].

5. Peptide Epitopes Used in Tau-Vaccines

Targeting therapeutically relevant epitopes on tau proteins in a safe manner is a very interesting and highly challenging objective [53]. Identification of the most effective tau epitopes for vaccine development is still a matter of debate since many modifications of tau, mainly phosphorylation along with truncation, oligomerization, etc., have been demonstrated to contribute to neurodegenerative disease pathogenesis. Moreover, it should be noticed that tau contains more than eighty potential serine, threonine, and tyrosine phosphorylation sites, while many phosphorylated epitopes of tau are also present in healthy human brains; which epitope will be chosen and targeted is therefore very critical [54][55].

Two tau vaccines have been tested in clinical trials with AD patients, AADvac1 and ACI-35 (**Table 1**). AADvac1 [1][9][10][14][28][54][56][57][58] is based on tau(294-305). This sequence was approximated through experimental immunization of transgenic mice with mis-disordered tau(151-391/4R) followed by isolation of antibodies and screening for in vitro disruption of tau-tau interaction [10]; tau(294-305) epitope was determined by X-ray crystallography [59] and then tested in an AD-animal model [60]. AADvac1 induces specific antibodies targeting three or four conformational epitopes on mis-disordered tau protein with an exposed microtubule-binding repeat domain (MTBR), which seems to be actively involved in tau aggregation [14][57][58]. Initial clinical trials have proved vaccine safety, thus encouraging further trials with larger numbers of participants[10]. On the other hand, vaccine ACI-35 [1][9][10][14][54][57] is based on the synthetic C-terminal peptide tau(393-408); more specifically, it consists of 16 copies of the aforementioned tau fragment, phosphorylated at Ser^{396} and Ser^{404} [10][53][57]. The rationale is that the antibodies induced will attack tau conformers containing the pathologic phosphorylation residues rather than the non-pathologic tau species [54]. A few years ago, a phase Ib/IIa trial was conducted to validate the safety, tolerability, and immunogenicity of an advanced version of this vaccine, i.e., ACI-35.030 [1][9][14].

In addition to the vaccines that have undergone clinical trials, other tau-vaccines have been developed and tested in animal preclinical studies (**Table 1**). More specifically, the N-terminal region tau(2-18), also known as phosphatase activating domain (PAD), has been appropriately formulated and used for vaccinating transgenic mice, since PAD becomes exposed in pathologic tau and plays an essential role in tau polymerization [45][61][62][63]. Moreover, the epitope tau(294-305), i.e., that used in vaccine AADvac-1, has been specially formulated (T294-HBcVLP) and the vaccine was tested in AD transgenic mice [64]. On the other hand, many vaccines recently tested in animals target phosphorylated tau (phospho-tau) epitopes [55][65][66][67]. Pathologic phosphorylation is a crucial event in tau pathogenicity and it is believed that by eliminating such toxic tau species, the degenerative process may be blocked [68]. Thus, a series of peptides from tau protein, including the so-called T294, pTau(396-404), and pTau422, have been used in a recent preclinical study; more specifically, two phosphorylated epitopes of tau, pTau(396-404) and pTau422, along with T294, i.e., tau(294-305), were

appropriately formulated using the so-called SpyCatcher/SpyTag technology and administered to AD transgenic mice; as shown, the vaccine based on pTau422 peptide alleviated cognition deficits and blocked neuropathology progression in animals [49]. In another recent preclinical study, three phosphorylated tau peptides (pTau peptides) bearing a combination of up to four AD-related epitopes were designed and synthesized. pTau30 has been phosphorylated at residues Ser^{202}/Thr^{205}/Ser^{238}/Ser^{262}; pTau31 has been phosphorylated at residues Ser^{202}/Thr^{205}/Ser^{396}/Ser^{404}; pTau35 has been phosphorylated at Ser^{238}/Ser^{262}/Ser^{396}/Ser^{404}. Mice immunization has shown that only pTau31-induced antibodies could recognize all carried four epitopes. Furthermore, pTau31 could neither elicit non-phosphorylated Tau31-specific antibodies nor stimulate tau-specific T-cell activation [67]. Moreover, other tau peptides containing tauopathy-related phosphorylated epitopes, i.e., tau(195-213)/p202/205, tau(207-220)/p212/214, and tau(224-238)/p231, were used for animal vaccination in preclinical studies, leading to results supporting the alleviation of both, tau and Aβ pathologies [65]. Similarly, in a previous work, tau(379-408)/p396/404 was tested in preclinical studies leading to a reduction in both, tau and Aβ pathologies [1][69].

6. Peptide Epitopes Used in α-Syn Vaccines

In order to identify surface-exposed regions of in vitro and in vivo formed aggregates of α-syn, polyclonal IgY antibodies were raised against short linear peptides of α-syn and used in suitable immunochemical studies [70]; as revealed, the N-terminal α-syn(1-10) and C-terminal α-syn(90-140) fragments were surface-exposed [70] and may, therefore, be considered as putative epitopes of α-syn. Following a rather similar approach, the C-terminal fragments α-syn(111-140)/α-syn(121-140), which are recognized by human anti-α-syn antibodies isolated from PD patients [71], have also been considered putative epitopes of α-syn. On the other hand, the secondary structural features of α-syn in an aqueous environment have been studied with computer simulation [72], revealing information that may be exploited when new peptide-based α-syn-vaccines are to be designed.

The only α-syn vaccines that have been tested in clinical trials (**Table 1**) are based on short synthetic peptide fragments that mimic C-terminal residues of α-syn(110-130) (PD01A and PD03A, Affiris) [14][73][74][75][76][77][78]. PD01A and PD03A have shown promising efficacy and safety in phase I clinical trials with multiple system atrophy (MSA) patients. Interestingly, peptides from the C-terminus of α-syn have been reported to induce in vitro both helper and cytotoxic T cell autoimmune responses in patients with PD [79]; the still adequately good safety features of PD01A/PD03A, which target the α-syn C-terminus, may be attributed to two main reasons, (i) the C-terminal peptides used are too short for inducing a T-cell autoimmune response, and, (ii) the vaccines developed do not bear the exact native epitope, but rather a mimicking sequence [14][73][78]. In July 2021, the AC Immune Company announced that it would begin a phase II clinical trial of an optimized formulation of the PD01 vaccine, called ACI-7104 [78].

In addition to the aforementioned vaccines tested in clinical trials, other α-syn vaccines have been developed and evaluated in animal preclinical studies [80][81].

7. Future Perspectives - Conclusions

Future Perspectives: After two decades of research in the field, the development of successful peptide-based vaccines for neurodegenerative diseases seems to be a very ambitious, but not impossible goal to achieve. Further research on the design and selection of appropriate B-cell peptide epitopes of Aβ (including safe conformational epitopes of Aβ oligomers), tau, and α-syn, which would be capable of inducing antibodies of high titer and optimal features, and prevent any undesirable T-cell autoimmune responses, may eventually result in vaccines of great efficacy and safety. Moreover, using simultaneously multiple peptide epitopes of Aβ, tau, and α-syn may enhance the overall vaccine efficacy, in comparison with monotherapy, as several literature reports have pointed out [2][14]. Peptide-based vaccines targeting biomolecules other than Aβ, tau, or α-syn [1][14][18] may also prove to be successful, while combinations of vaccines and passive immunotherapies (antibodies) might be advantageous [14]. Research achievements in other related areas are expected to stimulate and greatly assist research toward novel peptide-based vaccines for neurodegenerative diseases. Thus, results of passive immunotherapy with anti-Aβ monoclonal antibodies are expected to provide valuable information concerning the immunochemical features, such as the epitope specificity and subclass that the vaccine-induced antibodies should ideally show [2]. Moreover, valuable information is expected to be gathered and exploited via numerous peptide-based vaccines, e.g. vaccines targeting acquired immune deficiency syndrome (AIDS), malaria, and, most recently, coronavirus disease 2019 (COVID-19 [11]), as well as peptide-based anti-cancer vaccines [82], which are currently under development. It should also be noted that promising new adjuvants have been recently proposed in vaccine research, including, interestingly, short peptides that target Toll-like receptors [83][84]. In addition, a deeper insight into less-studied risk factors for neurodegenerative diseases [85] and a better understanding of the biological mechanisms through which nutritional, environmental, and lifestyle parameters may affect neuropathology (similar with their influence on pathology/epidemiology

of, e.g., neoplastic diseases [86]), are expected to broaden the array of putative therapeutic targets for fighting neurodegeneration. On the other hand, preliminary findings that associate gut microbiome with brain diseases [87][88], e.g., PD, through several ways including the production of proteins similar to misfolded α-syn by the intestine microbes (which may further serve as a human-protein misfolding-template), are just an example of how diverse future perspectives in this area may be. Moreover, recent research efforts have focused on the discovery of novel biomarkers, eventually including personalized markers, for assessing onset and/or progression of neurodegenerative diseases [1][3][89], while much research has been directed toward developing improved analytical methods for reliable measurement of established biomarkers, each one alone or often in combination, in easily available biological fluids, such as plasma, urine, or saliva [1][90][91][92]. Thus, success in the discovery of novel biomarkers, especially in the area of synucleinopathies [14], and development of highly reliable and easy to perform methods for biomarker analysis will definitely facilitate the evaluation of candidate peptide-based vaccines for neurodegenerative diseases and accelerate further progress.

Conclusions: Neurodegenerative diseases are very complex and heterogeneous in nature, and their treatment remains a great challenge for the community. Interest in immunotherapeutic approaches has been rekindled after recent FDA-approval (even amid some controversy) of a monoclonal antibody as the first, passive, immunotherapy against AD. Efforts to develop active immunotherapies, i.e., vaccines, on the other hand, have actually never been abandoned, despite initial setbacks. The vast majority of vaccines under development are peptide-based ones and employ specific peptide epitopes (or, specially designed mimotopes) of biomolecular targets associated with the neurodegeneration onset/progress, such as the polypeptide Aβ, or the proteins tau and α-syn. The overall efficacy and safety of peptide-based vaccines are greatly influenced by specific factors, such as the exact peptide epitope and the formulation components used. Further advances, including the discovery of novel biomolecular targets linked with neurodegeneration, identification of peptide-epitopes on the former through high-resolution structural biology methods or immunoinformatics, and the development of improved formulation systems are expected to accelerate/facilitate research in this particulate area of immunotherapy, aiming ultimately at clinical exploitation.

Table 1. Peptide-based Aβ-, tau-, and α-syn vaccines for neurodegenerative diseases: Peptide epitopes and main formulation components used.

Target/Vaccine	Peptide Epitope	Carrier Protein/Delivery System	Adjuvant	Type of Study	Reference
Aβ/AN1792	**Aβ(1-42)**	**Pre-aggregated peptide**	**QS-21**	**Clinical**	[2][9][26][28][29]
Aβ/CAD106	**Aβ(1-6)**	**Qβ-VLPs [1]**	**Alum or MF59**	**Clinical**	[1][2][9][10][14][28][29][30][31]
Aβ/ACC-001	**Aβ(1-7)**	**CRM197 [2]**	**QS-21**	**Clinical**	[1][2][9][14][28][29][32]
Aβ/Lu AF20513	**Aβ(1-12)**	**Tetanus toxoid**	**-**	**Clinical**	[2][9][10][28][29]
Aβ/UB-311	**Aβ(1-14)**	**UBITh [3]**	**Alum + CpG [4]**	**Clinical**	[2][9][10][14][28][29][33]
Aβ/ACI-24	**Aβ(1-15)**	**Liposomes**	**MLPA [5]**	**Clinical**	[1][2][9][14][28][29]
Aβ/V950	**Aβ(1-15)**	**ISCOMATRIX**	**Quil A**	**Clinical**	[9][28][29][33]
Aβ/ABvac40	**Aβ(33-40)**	**KLH [6]**	**Alum**	**Clinical**	[1][2][9][10][14][28][34]
Aβ/AFFITOPE AD01	**Aβ N-terminus mimotope**	**KLH**	**Alum**	**Clinical**	[9]
Aβ/AFFITOPE AD02	**Aβ N-terminus mimotope**	**KLH**	**Alum**	**Clinical**	[2][9][14][28][29][36]
Aβ/AFFITOPE AD03	**Aβ N-terminus mimotope**	**KLH**	**Alum**	**Clinical**	[9][29]
Tau/AADvac1	**Tau(294-305)**	**KLH**	**Alum**	**Clinical**	[1][9][10][14][28][54][56][57][58]
Tau/ACI-35	**Tau(393-408) [p[7]396/p404]**	**Liposomes**	**MLPA**	**Clinical**	[1][9][10][14][54][57]

Target/Vaccine	Peptide Epitope	Carrier Protein/Delivery System	Adjuvant	Type of Study	Reference
α-Syn/AFFITOPE PD01A	α-syn C-terminus mimotope	KLH	Alum	Clinical	[14][73][74][75][76][77]
α-Syn/ AFFITOPE PD03A	α-syn C-terminus mimotope	KLH	Alum	Clinical	[14][73][74][75][76]
Aβ	Aβ(1-6)	BLPs [8] fused with peptidoglycan anchoring domain (PA)	-	Preclinical	[41]
Aβ	Aβ(1-6)	Norovirus P Particles	CpG [5]	Preclinical	[40]
Aβ	Aβ(3-10)	KLH	CFA/IFA	Preclinical	[37][38][39]
Aβ	Aβ(1-11)	Bacterial protein domain E2	Alum	Preclinical	[47]
Aβ/AV-1959D DNA vaccine	Aβ(1-11)	MultiTEP [9]	-	Preclinical	[46]
Aβ/Y-5A15	Aβ(1-15)	Yeast cells (EBY-100)		Preclinical	[44]
Aβ	Aβ(1-15)	Silkworm pupae	Cholera toxin B subunit	Preclinical	[43]
Aβ	Aβ(1-6), Aβ(1-15)	Multiple antigenic peptide system	CFA/IFA [10]	Preclinical	[42]
Aβ	cyclo[Aβ(22-28)-Y [11]NGK'] cyclo[Aβ(23-29)-YNGK'], cyclo[Aβ(22-29)-YNGK']	Tetanus toxoid	Alum+MLPA	Preclinical	[48]
Aβ/AOE1	Oligomer-specific Aβ mimotope peptide	Yeast cell (EBY-100)	-	Preclinical	[52]
Aβ	Aβ(1-42)		CFA+bvPLA2 [12]	Preclinical	[50]
Aβ/ DNA vaccine	Aβ(1-42)	Gold particles	-	Preclinical	[51]
Aβ, Tau	Aβ(1-11), Tau(2-18)	MultiTEP	Advax [13]+CpG	Preclinical	[45]
Aβ, Tau	Linear Aβ(1-6), Aβ(1-6)3, Aβ(1-15), Tau(294-305), p[7]Tau(396-404), pTau422 cycloAβ(1-7), cycloEP1 [14], cycloEP2 [14]	HBc-VLPs conjugated with peptides via SpyCatcher/SpyTag technology [15]	Alum	Preclinical	[49]
Tau	Tau(2-18)	MultiTEP	Advax+CpG	Preclinical	[61][63]
Tau	Tau(294-305)	HBc-VLPs [16]	Alum	Preclinical	[64]
Tau	Tau(175-190)[p181]	Qβ-VLPs		Preclinical	[66]
Tau	Tau(195-213) [p202/205], Tau(207-220) [p212/214], Tau(224-238) [p231]	-	CFA+pertussis toxin	Preclinical	[65]
Tau	Tau(379-408) [p396/404]		Alum	Preclinical	[69]
Tau	pTau30 [p202/205/238/262], pTau31 [p202/205/396/404] pTau35 [p238/262/396/404]	Norovirus P particles	CpG+AS01	Preclinical	[67]
α-Syn	α-Syn(85-99) α-Syn(109-126) α-Syn(126-140)	Tetanus toxoid	Quil A	Preclinical	[81]
α-Syn	middle region: C[11]GGKNEEGAPQ (PD1) N-terminal: MDVFMKGLGGC (PD2) C-terminal: CGGEGYQDYEPEA (PD3)	Qβ-VLPs	-	Preclinical	[80]

[1] Qβ-VLP: Virus-like particles from capsid proteins of Qβ bacteriophage. [2] CRM197: Nontoxic mutant of diphtheria toxin. [3] UBITh: Two different helper T cell peptide epitopes, MvF5 Th and HBsAg3 Th. [4] CpG: Cytosine phosphoguanosine motif. [5] MLPA: Monophosphoryl lipid A. [6] KLH: Keyhole limpet hemocyanin. [7] p: Phosphorylated amino acid residue(s) at a specific site in the protein sequence. [8] BLPs: Bacterium-like particles. [9] MultiTEP: A platform composed of 12 foreign helper T (Th) cell epitopes. [10] CFA/IFA: Complete Freund's Adjuvant/Incomplete Freund's Adjuvant. [11] Amino acids shown with the one-letter code. [12] bvPLA2: Bee venom phospholipase A2. [13] Advax: A novel polysaccharide-based adjuvant derived from crystalline particles of delta inulin, a natural plant sugar comprised of fructose and glucose units. [14] EP1, EP2: Special peptide epitopes of Aβ oligomers selected with phage display from random peptide libraries. [15] SpyCatcher/SpyTag technology: A novel method to load particulate epitopes on virus-like particles through the formation of an iso-peptide bond between the SpyCatcher protein and SpyTag peptide. [16] HBc VLP: Virus-like particles from hepatitis B virus core protein.

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