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Review

Next-generation immunotherapeutic strategy and clinical advances of vaccines against nicotine addiction

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ABSTRACT

Smoking causes death of millions of people every year. However, available therapies for nicotine addiction are partially effective and exhibit frequent side effects. Thus vaccines targeted at drug nicotine not brain offer a promising strategy to treat nicotine addiction. They cannot pass blood-brain barrier, avoiding serious side effects relevant with central nervous system. The specific nicotine antibody produced by vaccines would convert to complex after combined with nicotine in serum, decreasing or even blocking the distribution of nicotine in brain. This review summarizes the pre-clinical and clinical advances of nicotine vaccines and then addresses future directions of nicotine vaccine and the practical aspects of deployments.

1. Introduction

Smoking is responsible for death of millions of people [1,2]. Over 8 million people die from illness directly related to smoking every year [3]. Smoking promotes the occurrence of various diseases, particularly in chronic respiratory and cardiovascular system [4,5]. The use of tobacco products increased the growth of the global mortality and brought a great burden for domestic economy. It is known that nicotine is one of the main components in tobacco, which is highly addictive [6]. It combines with acetylcholine receptor to change the normal value of dopamine in brain and even structural and functional change in brain [7,8].

Nicotine dependence has been estimated as a chronic addictive disease [9]. Nicotine addiction usually depend on the self-report of smokers by some questions, such as when, where, how often, methods or others. Various assessment scales have been reported to measure nicotine addiction [10–12] . Currently, available pharmacotherapy for clinical smoking cessation mainly contains two types: nicotine replacement therapy (NTR) and non-nicotine drugs [13,14]. In various forms of NTR, e-cigarette is the most popular and potential to achieve smoking cessation. However, the study by Hajek et al. [15,16] showed the 1-year abstinence rate was only 18.0 % in the e-cigarette group and 9.9 % in the nicotine-replacement group. Whether NTR is truly effective for smoking cessation still remains unclear [17]. And the first line drugs varenicline displayed an increase of depression, as well as the risk of instability and possible suicidal behavior [18–20]. These side effects limited the scope of application on smoking cessation.

Thus nicotine vaccine targeting at drug nicotine rather than brain was explored as a promising strategy [21]. Considering nicotine molecule is too small to be recognized by the immune system, nicotine hapten has been designed and prepared by conjugate with a foreign carrier protein to render immunogenic, which can activate immune reaction of immune cells and finally induce specific antibody (Fig. 1). The antibody combines with nicotine with a high affinity and blood-brain barrier would sequester the oversize antigen-antibody complex in serum or extracellular fluid, which eventually reduces the distribution of nicotine in brain. This unique mechanism can avoid serious side effects on central nervous system, such as depression, anxiety, and even suicidal tendencies. To this day, no serious adverse reactions related to nicotine vaccines has been found in existing animal and clinical studies [22–25], encouraging researchers to be involved in exploration of nicotine vaccine.

The present review addresses the pre-clinical and clinical studies on nicotine vaccines. Starts from a summary of pre-clinical advances in nicotine vaccines, ranging from the design of hapten optimization, linker modifications, formulations of carrier and adjuvant to the strategies of multivalent vaccine and nanoparticle packaging, their influences on immune effectiveness are analyzed. Then a detailed description of clinical aspects relevant to seven nicotine vaccines is given. Future directions of nicotine vaccine and the practical aspects of deployments are illustrated in the end.

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2. Advances in pre-clinical nicotine vaccines

In order to better play the full potential of active immunization in treatment of smoking cessation, improvements and modulations on drug-immune response strategies are very important to improve the immune effectiveness. This section focuses on the new pre-clinical progress of nicotine vaccines.

2.1. Advances in design of pre-clinical nicotine vaccines

In order to provoke immune system response, nicotine scaffold must be covalently attached to carrier protein through a linker or direct combination. A great number of nicotine haptens, linkers, carriers and adjuvants were designed and applied to improve the consistency and effectiveness of immunogenicity.

Hapten Chemical modifications on nicotine molecule are significant to progress of screening antigen series. The flexibility of nicotine is mostly formed by rotatable bond between pyridine and pyrrolidine rings [26]. The impacts of hapten stability on vaccine efficacy were studied and constrained haptens with stable conformation were found to be related with more moderate affinity antibodies under the same adjuvant [27]. Similar result was also observed in the report on cocaine vaccine [28]. These reductions in degrees of freedom in molecular structure might be able to contribute to enhancing consistency of nicotine antibody, thereby maximizing immunogenicity of vaccines. Furthermore, enantiomers of nicotine haptens should not be ignored in design of nicotine hapten, owing to only the (*S*)-nicotine serving as active ingredient in nicotine addiction. The enantiomers of a leading nicotine hapten 3′-aminomethylnicotine have been proved to be more conducive to production of specific antibodies compared to the racemic mixture [29].

Hapten clustering has been an alternative strategy to potentiate immune response with the increase of hapten density. This approach aims at improving immune reaction by adjusting antigenic spatial arrangement and promoting activation signaling transmission mediated by B-cell receptor. It suggested the introduction of nicotine trivalent hapten (triAM1) could contribute to limiting variability of immune response [30]. The hapten clustering has become a potential strategy to chemically define antigenic structure and enhance the efficacy of vaccine.

Linker Linker is indispensable to connect active nicotine hapten to macromolecular carrier. Besides structural connection function, linkers help to maintain a necessary distance for presentation of target structure to immune cells [31]. Most linkers usually are deemed to be a simple and unsubstituted chain with 5–15 carbon atoms. The optimization of linker length, lipophilicity and flexibility are incorporated in design consideration to provide better immunogenicity and efficacy. Haptens with too short linker would hamper exposure of epitopes owing to increase of steric effect and conversely haptens with too long linker are likely to form into some fold with the increasing of linker flexibility. Linker length, rigidity and polarity have been reported to be influential on recognition and binding of nicotine haptens by immune cells [32–34]. Hence, optimization of the linker composition should be considered for developing nicotine vaccines.

Carrier Carrier facilitates presentation of antigen and induce immune cells to regulate antibody production and immunological memory [35]. A set of carriers have been utilized for the nicotine vaccine. The traditional carriers such as keyhole limpet hemocyanin (KLH) have been proved widely effective [36]. However, these carriers derived from bacteria or virus, including *Pseudomonas aeruginosa* exoprotein A [37], recombinant cholera toxin-B subunit, tetanus toxoid (TT) and virus-like particles (VLP) from Bacteriophage Qb, exhibited poor response to treatment of nicotine addiction and relapse in clinical trials. Nicotine vaccine formulated with purified hexon of recombinant serotype 5

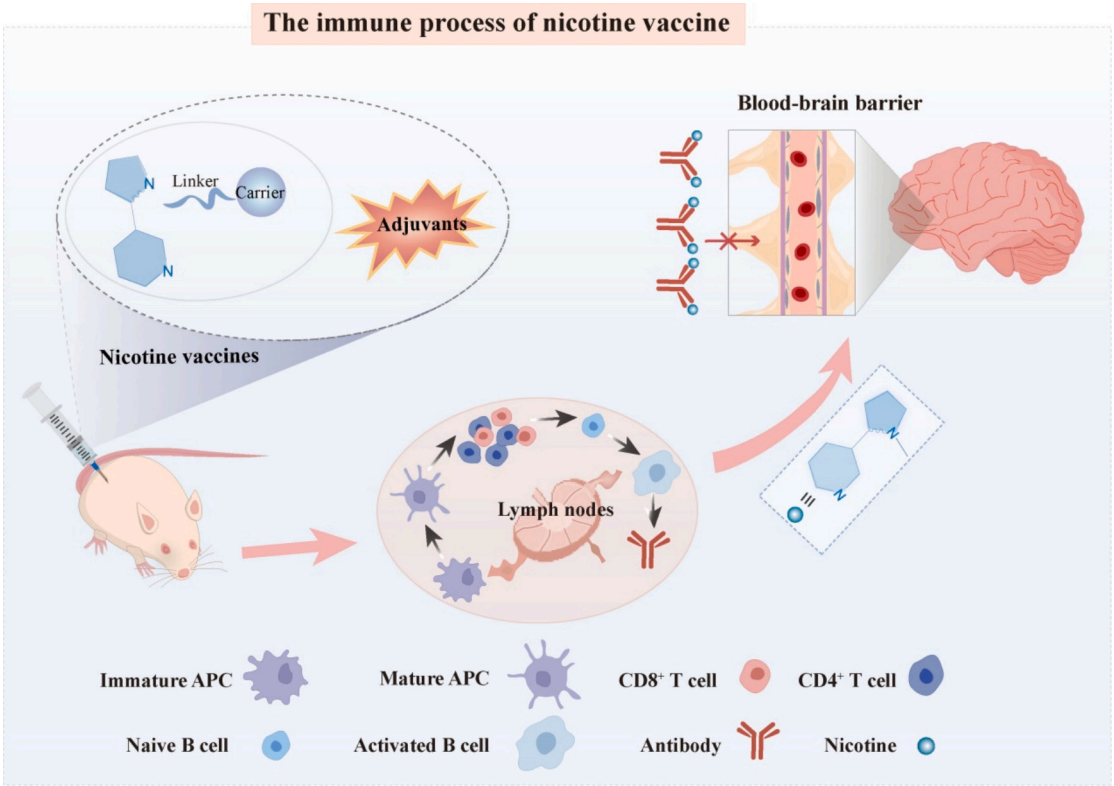

Fig. 1. Schematic illustration of immune responses induced by nicotine vaccines. Nicotine vaccines were composed of haptens, linkers, carriers and adjuvants. After immunization, antigen-presenting cells (APCs) within lymph nodes became mature, the interaction between APCs and T and B cells increased, naive B cells were activated to memory B cells, a large number of antibodies were generated and released into blood. Antibodies became into antigen-antibody complex, which were too big to cross blood-brain barrier.

adenovirus (E1-E3-Ad5) was demonstrated to evoke sufficient high level of antibodies to inhibit nicotine-induced pathophysiology in rodents [38]. Moreover, carriers with adjuvant-like property have been adopted into nicotine vaccine [39,40]. Diphtheria toxin crossreactive material (CRM197) has been successfully used as carrier in nicotine vaccine, which has advanced toward clinical evaluation (NIC7–001 in Table 1). The carrier protein flagellin conjugated with a nicotine hapten with 4-position attached by an aminopropyl linker (N4N2) was explored in the vaccine formulation and the result showed an enhanced antibody affinity [40].

With the development of vaccine technology, peptides are gradually favored by researchers as carrier of vaccine because of the advantages of high safety, low immunogenicity and exact structure [41–43]. An additional benefit of peptides is quite convenient to be synthetized according any amino acid sequence combination and consequently carriers are composed more readily and predictably directed against multiple pathogen epitopes or different subtype epitopes of same pathogen. The application of peptides as carrier in nicotine vaccine showed great advantages [44,45]. For example, in order to circumvent interference of carrier epitopes, a novel peptide-based carrier trimetri coiled-coil (TCC) was designed to increase hapten density for improvement of antigen presentation [45]. Peptides were also used in the field of multivalent nicotine vaccine. On the foundation of coiled-coil peptide carrier, together with enantiopure nicotine haptens and multivalent formulations, a nicotine vaccine with two-fold higher antibody response and substantially increased antibody affinity was developed [46].

The studies of carriers demonstrate that the carriers with adjuvant-like property are in favor to maximize the efficient immune response for nicotine vaccines. Better clarity of carriers in structure is helpful to engineer more promising and applicable vaccine candidates for nicotine relapse and addiction cessation.

Table 1
Composition of nicotine vaccines in clinical trial stage.

Vaccine	Manufacturer	Composition	Reference
NicVAX	Nabi Biopharmaceuticals	3′-amino-methyl-nicotine hapten conjugated to carrier *Pseudomonas aeruginosa* exoprotein A with a succinic acid linker, adjuvanted with aluminum hydroxide	[85]
NicQb/ NIC002	Cytos Biotechnology/ Novartis	3′-hydroxy-methyl-nicotine hapten conjugated to carrier virus-like particle from Bacteriophage Qb with a succinic acid linker, adjuvanted with complete Freund's adjuvant	[86,87]
TA-NIC	Celtic Pharma	1-butryic acid - nicotine hapten conjugated to carrier cholera toxin-B subunit, adjuvanted with aluminum hydroxide	[88]
SEL-068	Selecta Biosciences	A polymer matrix, a toll-like receptor agonist adjuvant, a T-cell helper peptide, and nicotine hapten covalently conjugated to the nanoparticle surface	[89]
Niccine	Independent Pharmaceutica AB	Nicotine hapten conjugated to carrier tetanus toxoid, adjuvanted with aluminum hydroxide	[90]
NIC7–001	Pfizer	5-aminoethoxy-nicotine hapten conjugated to carrier CRM_{197}, a single amino acid mutant of diphtheria toxoid, adjuvanted with aluminum hydroxide and toll-like receptor 9 agonist CpG	[32]
SELA-070	Selecta Biosciences	–	–

— No available information at this time.

Adjuvant Purpose of adjuvants used in vaccines is to strengthen the immune response to antigens [47]. They can create a local immune environment by continuously released antigens at injection site, thus extending action time and simultaneously reducing the dosage of immune substance to save production cost [48]. The quality and quantity of immune response bolster by adjuvants suggest their performance. The Freund's adjuvant was frequently-used and effective in the animal immunity of nicotine vaccines [33,34,37,49]. However, it is not ratified in human body. Aluminum hydroxide has been approved to use in human vaccine by FDA due to its acceptable safety and strong ability to generate immune response, which is the most commonly used adjuvant in the development of nicotine vaccine [50–52]. Currently four nicotine vaccines have entered clinical experiment under the formulation of aluminum hydroxide (Table 1). Its mechanism was poorly defined except the facilitation on the presentation of antigen to immune cells by strong adsorption capacity, differentiation of related immune cells, as well as secretion of proinflammatory factor [53,54]. However, strong adsorption of microparticle aluminum hydroxide also brought some limitation for biological function of antigen presenting cells (APCs) and application in nanoparticle vaccine [55,56]. The application of traditional aluminum hydroxide in nicotine nanovaccine has been reported not effective for treatment of nicotine addiction [57]. There is increasing evidence that aluminum hydroxide at nanometer scale is more likely to show superior adjuvant activity [55,56,58].

Liposomes which are formed by closed vesicles and aggregated phospholipid bilayers have developed into delivery systems for many years [59]. Compared with other vaccine adjuvants, liposome have its own unique advantages in active adaptation on molecular weight and charge of antigen, composition of cell membrane analogue with good biocompatibility, protecting antigens from destruction and mediating antigens uptake by macrophages through the structure of encapsulation and particle [60,61]. A series of liposomes and their combination with other materials such as Adjuvant Finlay Proteoliposome 1 (AFPL1) from the *Neisseria meningitidis* serogroup B, Sigma Adjuvant System® (SAS), as well as squalene emulsion (GLA-SE) have been initiated for addressing the immunogenicity challenge in nicotine vaccine [30,46,62–64]. In the comparison of aluminum hydroxide and GLA-SE adjuvants, nicotine vaccine formulating a TCC-based GLA-SE adjuvant was proved to be far superior in generating immune response and affinity [45].

Various adjuvant molecules specifically binding to Toll-like receptors (TLRs) or other innate immune receptors have been studied for nicotine vaccines, including CpG oligodeoxynucleotides (CpG ODNs), monophosphoryl lipid A, Resiquimod (R848) and α-galactosylceramide (αGalCer) [65–67]. CpG ODNs is a TLR9 agonist with several GpG dinucleotide motifs, which is considered to be the adjuvant with the clearest mechanism of action at present. Benefited from its highly effective immunostimulatory activity in nicotine vaccine, CpG ODNs is usually indispensable in the formulations of combined adjuvants [32,39,65,68]. The combination of CpG and aluminum hydroxide as adjuvant showed significantly higher antibody level and antibody affinity for nicotine than alone aluminum hydroxide as adjuvant, which is in agreement with the reports on other vaccines against drug addiction [69,70]. This approach in nicotine vaccine NIC7–001 has been evaluated by Pfizer in a phase I trial (NCT01672645) with no available result [71]. The combination adjuvants of monophosphoryl lipid A with Resiquimod (R848) and ODN 1826 better enhanced the immunological efficacy of nicotine vaccines than single TLR adjuvant in the study of a hybrid nanoparticle nicotine vaccine [66]. The nicotine vaccine after adjuvanted with αGalCer (a kind of iNKT cell agonist) induced higher nicotine specific antibody in mice, compared with the frequently used lipopeptide adjuvant Pam3CSK4 (a kind of TLR agonist) [68].

In addition, four stabilizing non-natural peptides were designed and formulated into nicotine vaccine as adjuvant delivery system together with a microbial derived adjuvant to test the response of 1 L-1β in a dendritic cell line and the induced nicotine-specific antibody levels in

mice, and the result indicated that peptides could enhance immune response significantly [72].

Collectively, all these data suggest that every hapten requires tailored adjuvant to maximize the efficient immune response. Some new approaches including the addition of TLR-based adjuvant, liposome adjuvant and peptide into vaccine formulation and rational incorporation of different adjuvants might break the limitation of immune effectiveness.

2.2. Other new progress on pre-clinical nicotine vaccine

Nanovaccine The design of nanovaccine has been approved feasible and make great progress in nicotine vaccine [25,73]. Nanomaterials have been developed extensively as delivery system or immune synergist for vaccines which could protect antigen from being destroyed and present them to APCs after arriving target site [74,75]. Compared with traditional conjugate vaccine, nanovaccines more efficiently stimulate dendritic cells to ingest, process and present antigens, as well as activate initial T cells to maintain the immune response [76,77]. Based on this design, it is expected to break the restrictions of conjugate vaccines and improve immune effects by approach of nanoparticle-based vaccines. A nicotine nanovaccine has been reported to be composed of spherical nanoparticles structured by a poly(lactic-*co*-glycolic acid) core wrapped with lipid shell and some nicotine antigens located on the surface of nanoparticles [50]. The immunogenicity of nicotine vaccine was effective enhanced by the nanoparticle-based design in hapten density, modulating hapten localization and adjuvants [50,65,78]. Besides spherical core-shell structure, the nicotine nanovaccine assembled with negatively charged carbon nanohorn and cationic liposomes was developed and showed no apparent toxicity as well as much better stability [79]. Nicotine vaccine based on assembly of lipid-PLA hybrid nanoparticle produced higher stability and longer half-life period compared with lipid-PLGA [25]. Most of these nicotine nanovaccines are still at the stage of laboratory research. SEL-068 is the only one reaching the stage of phase I trial, which is developed by Selecta Biosciences. There was no available information for the results [80].

Multivalent vaccine Among preclinical studies, strategy of multivalent vaccine has emerged in treatment of nicotine addiction as the means of enhancing the antibody response [62]. The design of multivalent vaccine is based on the concurrent administration of several structurally distinct nicotine antigens which can elicit independent immune responses. The aim of this strategy is to maximize vaccine response by activating several B cell populations and generating additive antibody response [81]. Generally, structural differences of the nicotine antigens reflect in the sites for attachment, chemical modifications, linker composition and selection of carrier [34,82]. These differences conduce to production of non-overlapping antibodies and further increase of total immune response, remedying intrinsic shortcomings of traditional monovalent conjugate vaccines. For instance, antigens generating non cross-reacting nicotine-specific antibodies were

Table 2
Review of clinical trials of nicotine vaccines.*

Vaccine	NTC Number	Duration	Phase	Enrollment	Age / Sex	Reference	Results
NicVAX	NCT00598325	Jan 2008-Oct 2010	I-II	74	18–65/ All	–	–
	NCT00318383	May 2006-Dec 2007	II	313	18-older/All	[85]	Succeeded to elicit antibodies associated with higher continuous abstinence rates
	NCT00995033	Oct 2009-Sep 2012	II	558	18–65/ All	[23,91]	Only a subgroup of the top 30 % antibody responders achieved higher abstinence rates than placebo
	NCT00218413	Oct 2004-Aug 2006	II	51	18-older/All	–	–
	NCT00996034	Sep 2009-Feb 2011	II	14	18–50/ All	[92]	The β2-nAChR occupancy by nicotine was significantly reduce which provided evidence for the mechanisms of vaccination against nicotine dependence
	NCT01318668	Feb 2011-Jue 2012	I-II	38	25–40/ Male	[93]	No significant effects of immunization on brain activity in response
	NCT01375933	May 2011-Oct 2011	III	260	18–55/ All	–	–
	NCT01304810	Jan 2011-Aug 2011	III	300	18–65/ All	–	–
	NCT01102114	Mar 2010-Nov 2011	III	1000	18–65/ All	–	–
	NCT00836199	Oct 2009-Jul 2011	III	1000	18–65 /All	–	–
	NCT01178346	Jul 2010-Nov 2011	III	500	18–65/ All	–	–
NicQb (NIC002)	–		I	40	18–45/ All	[86]	The vaccine was safe and well tolerated; Succeeded to elicit nicotine-specific IgM and IgG antibodies at day 7 and 14
	NCT00369616	Dec 2003- Oct 2005	II	341	18–70/ All	[87]	Significant increased continuous abstinence rates were only observed when sufficiently high antibody levels are achieved
	NCT00736047	Aug 2008-Oct 2009/	II	200	18–65/ All	–	–
	NCT01280968	Dec 2010-Apr 2013	II	52	18–55/ All	–	–
TA-NIC	NCT00633321	May 2007-Feb 2009	II	522	18-older/All	–	–
SEL-068	NCT01478893	Nov 2011-Mar 2013	I	82	18–60/ All	–	–
Niccine	–		II	335	25–50/ All	[90]	The vaccine was well tolerated but ineffective among cigarette smokers
NIC7–001	NCT01672645	Jun 2012-Dec 2015	I	277	18–60/ All	–	–
SELA-070	NCT03148925	May 2017-Oct 2018	I	72	18–60/ All	–	–

* Available clinical trial registration (clinicaltrials.gov or PubMed) or other publications. β2-containing nicotinic acetylcholine receptors (β2-nAChR), Immunoglobulin M (IgM), Immunoglobulin G (IgG). — No information available at this time.

engineered to enhance additive vaccine efficacy [83], which indicated the potential of multivalent vaccine in reducing variability in human immune response [49]. Studies on multivalent nicotine vaccine mainly focus on bivalent [49,84] and multivalent concurrent administration [62,66,82]. These results demonstrate that design of multivalent nicotine vaccine is feasible to enhance the immune response and circumvent limitation of traditional conjugate vaccine.

3. Clinical trials on nicotine vaccines

So far, seven candidate vaccines for nicotine have entered human clinical testing: NicVAX, NicQb/ NIC002, TA-NIC, SEL-068, Niccine, NIC7–001 and SELA-070. Most of the vaccines have reached phase I / II, and only NicVAX has reached phase III (see Tables 1 and 2). The vaccines were aimed to prevent first-time drug use, drug dependence or smoking relapse. Muscle injection is the most commonly used form of administration. Inclusion criteria usually include healthy smoker and a certain number of cigarettes per day. Subjects were vaccinated repeatedly over a period of time. Except the phase II clinical trial NCT00995033, other nicotine vaccines were conducted as stand-alone medication. The hapten structures of these nicotine vaccines were shown in Fig. 2.

The vaccine NicVAX, developed by Nabi Biopharmaceuticals, has a 3-amino-methyl-nicotine hapten conjugated to the carrier *Pseudomonas aeruginosa* exoprotein A with a succinic acid linker, and was adjuvanted with aluminum hydroxide to enhance immunogenicity [85]. A phase II clinical trial (NCT00318383) was conducted for NicVAX on 301 smokers to evaluate the efficacy of nicotine vaccine at the doses of 200 μg and 400 μg [85]. Obvious higher abstinence rates compared with placebo were observed in the high-dose group. However, in the subsequent phase II clinical trial (NCT00995033), these optimistic abstinence rates were only replicated in the top 30 % antibody responders of a subgroup [23]. Though the proof of concept study (NCT00996034) proved that NicVAX could reduce the nicotine binding to beta2-containing nicotinic acetylcholine receptors in brain [92], the clinical fmri study (NCT01318668) of NicVAX on the brain activity of 38 smokers concluded that the vaccine was unlikely to cease smoking than placebo [93]. To date, five phase III clinical trials for NicVAX have all completed and the results were not posted and reported. NicQb (NIC002) vaccine consists of a hapten 3-hydroxy-methyl-nicotine, which is connected to the carrier virus-like particle Bacteriophage Qb by a succinic acid linker [86,87]. It was initially developed by Cytos Biotechnology and subsequently acquired by Novartis. Its phase I and II clinical trials have been completed (Table 2). In the phase I clinical trials (NTC Number was not available), 40 non-smokers were enrolled to investigate the safety and immunogenicity of the vaccine for treating nicotine dependence [86]. Besides good safety and tolerability, high affinity for nicotine was also observed, indicating NicQb might provide a promising effective in promoting smoking cessation. Results of phase II trial (NCT00369616) for the vaccine NicQb showed that though 100 % antibody response rates were induced, significant continuous abstinence rates were only observed in the participants with high antibody response in subgroup analysis [87]. This meant higher levels of antibodies generated by nicotine vaccine were positive relevant with higher success rates of smoking cessation. Nevertheless, the high variable in individual immune response finally resulted in the undesirable effect on smoking cessation.

Besides, three other nicotine vaccines (TA-NIC, SEL-068, Niccine) have finished their phase II clinical trials (Table 2). The vaccine TA-NIC belonging to Celtic Pharma utilized 1-butryic acid-nicotine as hapten and cholera toxin-B subunit as carrier [88]. Differently, the SEL-068 vaccine was developed by Selecta Biosciences on the basics of nanotechnology [89]. The clinical trials of TA-NIC and SEL-068 both had no reported outcomes. The vaccine Niccine (Independent Pharmaceutica AB) utilized tetanus-toxoid as a carrier. Its phase II clinical trial (no available NTC Number) on 355 smokers appeared well tolerated but ineffective in quitting smoking and relapse prevention [90]. This phenomenon was together with the later results of NicVAX and NicQb. A phase I clinical trial (NCT01672645) of NIC7–001 which containing a 5-aminoethoxy-nicotine as hapten and a single amino acid mutant of diphtheria toxoid (CRM_{197}) as carrier was evaluated in Canada after being adjuvanted with combination of aluminum hydroxide and toll-like receptor (TLR) 9 agonist CpG [39], the results of which have not been disclosed. In addition, Selecta Biosciences has recently conducted a phase I clinical study to evaluate safety and pharmacodynamics of the second nicotine vaccine SELA-070 in Belgium (NCT03148925). The relevant study has actually finished in 2018 with no results posted [94].

Taken together, good safety and immunogenicity were often observed, but subsequent clinical studies on effectiveness found that

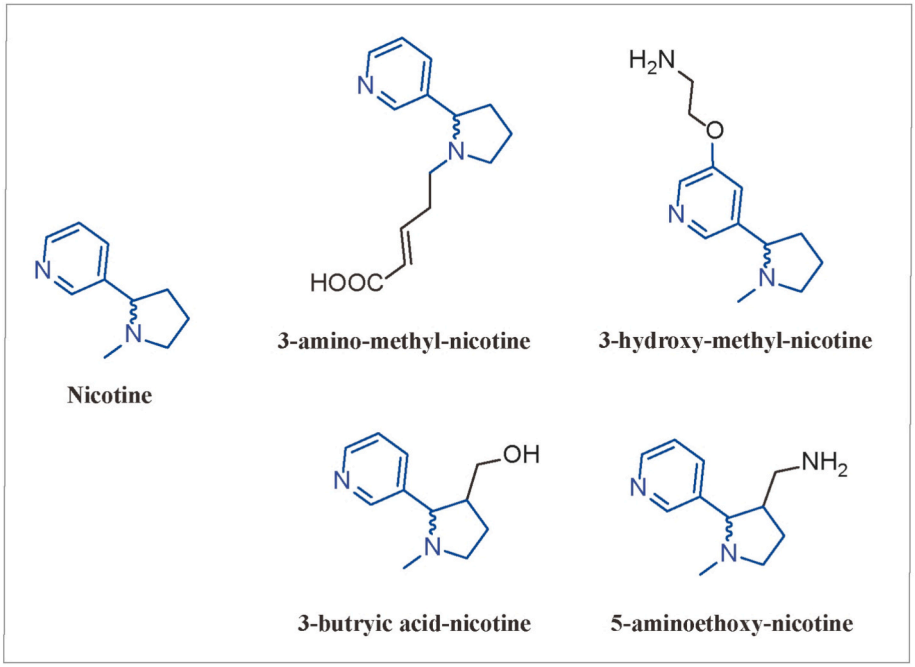

Fig. 2. The hapten structures of nicotine vaccines in clinical stage.

none of these nicotine vaccines maintained the expected effects in pre-clinical studies [85,87,91,93].

There are several collective explanations to the limited efficacy in clinical results. Firstly, physiological differences between human subjects cause different immune responses. The individual differences of antibody levels were large, so it is difficult to prove the therapeutic effect of vaccines on elimination of addiction [73]. This similar wide range of variability in human immune response was also noticed in clinical studies of other addiction vaccines [95,96]. In the second place, most researchers attributed these unsatisfactory results to the not high enough antibody responses elicited by vaccines to eliminate the effects of the inhaled nicotine in human body [87,97,98]. Besides, shortcomings and limitations of the animal models on nicotine addiction might be partially responsible for the failure in clinical studies [98]. The difference between species might induce discrepancies on the immune response after nicotine vaccine injection.

4. Future directions

These pre-clinical and clinical data provide better insight for rational development of nicotine vaccines with higher therapeutic efficacy. Although none of vaccines against nicotine has achieved ultimate success, these studies provided vital information to point out the directions of future research.

The success or failure of nicotine vaccine mainly relies on combination of hapten, linker, carrier and adjuvant. Apart from traditional mindset in hapten design, hapten deuteration might be useful to revive the success in clinical trials, which has been proved in a study of heroin vaccine [99]. In the past, various proteins have been extensively used as immunogenic carrier for nicotine vaccine. However, some other carriers, such as polysaccharides [100], have not been explored. Emphasis should be placed to exploration of new design strategies for high level antibody to enhance the chance of success.

The adequacy of animal models is very important in design of clinical studies. Many candidate vaccines targeting addictive drugs have shown strong antibody responses in pre-clinical tests on animals, but failed to repeat the same effect in human clinical trials. The administration of simple nicotine injection in animal models ignores the possible behavioral effects from thousands of compounds in tobacco smoke. Thus it is possible that efficacy of vaccines in smoking abstinence is overrated in these studies on animal models.

Another key question in nicotine vaccine development is how to accurately assess vaccine immunogenicity and efficacy. And whether the varying levels of antibodies in different studies are conformable is still doubtful due to the poor consistency of ELISA results between different times, animal models and investigators. No specific guideline for evaluating antibody titers has been set as a reference. Analysis of biomarkers such as B cells and IL-4, as an indicator of vaccine efficacy, is the most promising approach to overcome the difference in antibody production between different models [101,102].

Besides, personal motivation of abandoning treatment causing by the complexities related to addiction should be noted. The vaccination strategy should be combined with a program of science education to minimize treatment misunderstanding and maximize the conversion of patients into subjects.

Of course, the search for novel treatment strategies such as nicotine catalytic enzyme [103–105] should also be considered when the current treatments are ineffective.

It is worth noting that recently the company Cessation Therapeutics, Inc. conducted a preliminary clinical trial on the amonoclonal antibody CSX-1004 for fentanyl overdose, and the result showed significant safety (NCT06005402). It is expected to begin the second phase of efficacy trials later. If the results are valid, the company will seek accelerated FDA approval within a few years. This indicates that it still exists the company that maintains optimistic views and continues to invest in development of vaccines for substance use disorders.

5. Conclusions

Although many nicotine vaccines have showed promising effect in pre-clinical stages, the efforts in clinical trials have only obtained qualified success. These failures help us to understand the complexity of clinical trials for vaccines against drug abuse, encouraging researchers to draw a lesson and continue to persist in improving vaccines and experimental designs. The comprehensive application of different strategies might help to get a higher success rate of nicotine vaccines. Once approved, the strategy of nicotine vaccine would be expected to circumvent the side effects associated with central nerve system and provide a safe and effective solution for nicotine addiction.

CRediT authorship contribution statement

Kun Yan: Writing – original draft, Project administration, Methodology, Funding acquisition. **Shan Xu:** Methodology, Data curation. **Hufeng Fang:** Investigation. **Hao Yang:** Investigation. **Dan Su:** Writing – review & editing, Supervision, Conceptualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Data availability

Data will be made available on request.

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