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Current Opinion in
Immunology

Vaccines against non-communicable diseases

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Chronic non-communicable diseases (NCDs) are increasingly recognized as the major cause of morbidity and mortality worldwide. Effective, affordable and broadly accessible medicines for their treatment are much sought after. Therapeutic B-cell vaccines aim at inducing neutralizing auto-reactive antibodies against important mediators of such diseases. Numerous animal models have demonstrated that active immunotherapy can induce disease-modifying levels of auto-antibodies. Recent findings from clinical trials have indicated that self-reactive antibodies can also be readily induced in humans; therapeutic efficacy, however, has not always been achieved. To date, clinical experience with vaccines against self-molecules is limited. Choice of the right target, proper vaccine design, optimal vaccine dose and regimen remain the major challenges to achieve clinical efficacy and safety for this novel class of biotherapeutics.

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Current Opinion in Immunology 2010, 22:1–6

This review comes from a themed issue on
Vaccines

Edited by Hildegund Ertl and Antonio Lanzavecchia

0952-7915/\$ – see front matter

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DOI [10.1016/j.coi.2010.02.009](https://doi.org/10.1016/j.coi.2010.02.009)

Introduction

The most effective medical intervention in human history has been prophylactic vaccination against infectious diseases. Indeed, vaccines against viral and bacterial pathogens have contributed greatly to the 30-year increase in life expectancy achieved during the 20th century [1]. At the start of the 21st century, however, risk factors for morbidity and mortality have changed. Today, non-communicable disease (NCDs) like hypertension, obesity, autoimmune and chronic inflammatory diseases such as diabetes and chronic obstructive pulmonary disease, cancer and neurodegenerative diseases like Alzheimer's disease (AD) are the major cause of death and disability worldwide and the global burden continues to grow with an ageing society [2]. Immunotherapy based on active vaccination against disease-

associated self-molecules may offer a means to effectively and affordably treat such diseases [3].

The immune system has evolved central and peripheral self-tolerance checkpoints to remove or silence auto-reactive lymphocytes. Central B-cell tolerance mechanisms which take place during B-cell development in the bone marrow (BM) remove some self-reactive B-cells or induce B-cell receptor editing to decrease self-reactivity. A considerable number of auto-reactive B-cells, however, can become anergic (i.e. functionally silenced) or remain ignorant of the self-antigen, and leave the BM. These B-cells remain dormant in the periphery [4]. In order to proliferate, undergo isotype switching and produce antibodies, naïve B-cells need to interact with activated T-helper cells recognizing antigen-derived peptides on MHC class II molecules presented by these B-cells. Hence T-cell tolerance is a second and often more important mechanism to avoid self-specific B-cell responses and is the major obstacle to be overcome for induction of auto-antibody production by ignorant self-reactive B-cells [5]. Auto-reactive T-cells that escaped thymic deletion and reached peripheral lymphoid organs also exist. Activation of these self-specific T-cells may be achieved by antigenic stimulation in the presence of strong stimulators of innate immunity such as Complete Freund's Adjuvant (CFA) [6]. Activation of auto-reactive T-cell responses during active immunotherapy, however, may be harmful as this can lead to strong auto-inflammatory responses (see below) [7]. Hence, the preferred strategy in the development of B-cell vaccines for NCDs targeting self-molecules is to circumvent T-cell tolerance rather than break it [5]. This can be achieved by either introducing a foreign T-helper cell epitope into the sequence of the self-protein of interest [8] or by linking the self-protein to a foreign carrier protein [9–12]. In this way, T-cell responses that are readily induced against the foreign carrier epitopes of the vaccine can provide help to self-reactive B-cells presenting these epitopes on their MHC class II molecules. Numerous studies in animal models and even clinical trials conducted in the last couple of years have demonstrated feasibility of this approach [13•]. They have furthermore demonstrated that auto-antibody responses induced via circumvention of T-cell tolerance are reversible, an important safety requirement, and can only be boosted in the presence of carrier derived T-cell epitopes.

This review focuses on latest advances in the development and clinical testing of therapeutic B-cell vaccines for the treatment of AD, hypertension, chronic inflammatory and autoimmune diseases.

Vaccines for Alzheimer's disease

AD is the main cause of dementia in elderly people. As the population of the world is ageing AD is becoming an ever-increasing problem. It is a complex disease with two principal hallmarks: first, deposition of amyloid beta (A β) plaques formed by misfolded and aggregated A β -peptide and second, aggregation of the microtubule binding protein tau within neurones giving rise to neurofibrillary tangles [14].

Treatments to reverse, stop or ameliorate disease do not yet exist. However, numerous preclinical studies targeting A β -aggregates with antibodies have demonstrated antibody-mediated clearance of plaques, possibly via antibody-induced phagocytosis of A β -deposits, direct antibody-mediated disruption of aggregates or a shift in equilibrium towards efflux of A β from the brain and its stabilization in the serum. Antibodies may also neutralize toxic activities of A β . Considerable effort has hence been directed towards the development of a vaccine for AD [15*].

The first clinical trial employing active immunotherapy for AD was conducted by Elan Pharmaceuticals with the vaccine AN1792. The vaccine consisted of pre-aggregated synthetic A β _{1–42} peptide formulated in the saponine-based adjuvant QS-21. A phase II clinical trial with AN1792 was halted because of a serious safety issue: meningoencephalitis attributed to A β -specific T-cells infiltrating the brain in 6% of patients. As this vaccine contained A β -peptide without a carrier protein, successful induction of an anti-A β -IgG response had to rely on the induction of A β -reactive CD4⁺ T-cells which presumably then triggered meningoencephalitis in some patients [7,16]. In this case, T-cell tolerance to A β was broken with the strong adjuvant QS-21 in order to overcome B-cell unresponsiveness. Despite the severe safety issues which prevented its further development, AN1792 provided clinical proof-of-concept that A β -specific antibodies induced by active vaccination can lead to substantial amyloid clearance [17,18].

This finding triggered the development of second generation vaccines for AD currently undergoing clinical testing (Table 1). These vaccines are designed to minimize the risk of auto-reactive T-cell induction. They are characterized by short (mostly N-terminal) A β -peptides

devoid of possible T-cell epitopes linked to non-self carrier proteins for provision of T-cell help. Or they make use of A β mimetics as immunogens as for the Affiris/GSK vaccine for which safety and tolerability has recently been reported (http://www.affiris.com/html/en/presse_medien/pressemeldungen.html). Safety in phase I clinical trials was also reported for vaccines CAD106 of Cytos/Novartis and ACC-001 of Elan/Wyeth which currently undergo phase II trials (<http://www.clinicaltrials.gov>).

Next to active vaccination against A β , novel immunotherapy approaches focussing on the microtubule protein tau are being investigated as well [19]. Reductions in insoluble tau and improved behavioural performance were observed in mice. Hence, the future may see AD immunotherapies targeting tau protein entering clinical trials as well [20*].

Vaccines against hypertension

Persistent hypertension is the most common risk factor for cardiovascular disease and stroke, and one of the most important preventable causes of death worldwide. The prevalence of hypertension in the adult population is estimated to be close to 30% [21]. Despite the existence of effective drugs to control blood pressure (BP) only about one in four hypertensive patients have their BP controlled successfully [22]. This is due to the symptomless nature of hypertension and poor compliance with prescribed medication use [23]. In addition, unfavourable pharmacokinetics of oral anti-hypertensive drugs lead to lowest circulating drug concentrations in early morning hours, a time when cardiovascular events are most likely to occur [24]. Hence, a therapeutic B-cell vaccine may not only help resolving the compliance problem but also lead to smoother and improved diurnal BP control by nearly constant levels of circulating therapeutic antibodies. Moreover, an anti-hypertension vaccine could be an affordable and convenient treatment option for the more than 600 million hypertensive patients in economically developing countries [21].

The renin–angiotensin aldosterone system (RAAS) is a coordinated hormonal cascade that governs the regulation of arterial BP. Angiotensin-converting enzyme inhibitors are very successful in managing hypertension. Interestingly, even at high doses these drugs do not reduce BP

Table 1

Clinical trials with therapeutic B-cell vaccines for Alzheimer's disease

Company	Vaccine	Therapeutic agent	Stage
Elan Pharmaceuticals	AN1792	A β (1–42) + QS-21	Aborted
United Biomedical	UB 311	N-terminal A β peptide (1–14)–CpG oligonucleotide immunocomplex	Phase I
Affiris/GSK	Affitope AD01/AD02	A β mimetic peptide	Phase I
Merck	V950	A β -peptide $\pm$ Iscomatrix	Phase I
Cytos/Novartis	CAD106	N-terminal A β -peptide attached to VLP	Phase II
Elan Pharmaceuticals/Wyeth	ACC-001	N-terminal A β -peptide attached to carrier protein	Phase II

below normal levels, which makes RAAS components an attractive target for active immunotherapy [25^{••}]. Several attempts to use the immune system to suppress the activity of components of RAAS have been undertaken in animals and humans. Renin inhibition interferes with the initial and rate limiting step of angiotensin II production. Attempts to reduce BP by vaccination against renin in animal experiments made use of heterologous renins formulated in CFA. These trials not only achieved a significant and sustained reduction in BP but also resulted in autoimmune inflammation in the kidney [26,27]. High levels of renin in kidneys led to the deposition of anti-renin immune complexes and triggered autoimmune renal disease [27]. These safety concerns discouraged further development of anti-renin vaccines and highlighted the importance of choosing the right target for active immunotherapy.

Current anti-hypertension vaccines under evaluation include angiotensin I, angiotensin II and AT₁ receptor peptides chemically coupled to protein carriers or VLPs. In each case a robust antibody response against these antigens could be induced and none of the vaccines produced autoimmune disease in animal models or human studies conducted to date [25^{••}].

Angiotensin I vaccines have been tested in animal models and humans but did not result in significant lowering of BP. PMD-3117 is an angiotensin I vaccine developed by Protherics (now BTG) and consists of angiotensin I coupled to KLH formulated in Alum. It did not reduce BP in hypertensive patients probably because induced antibody titers were insufficient [28]. To increase antibody titers, the vaccine is currently tested in a new formulation which includes the adjuvant 'Covaccine HT' in a phase II clinical trial (<http://www.clinicaltrials.gov>) (Table 2).

The only angiotensin II vaccine tested in clinical trials so far is AngQb consisting of a modified angiotensin II peptide N-terminally coupled to VLPs of the bacteriophage Q β , formulated in Alum [29]. The vaccine induced a strong angiotensin II specific IgG response in humans and remains the only anti-hypertension vaccine so far that has demonstrated clinical efficacy. A 300 μ g dose of the

vaccine administered at weeks 0, 4 and 12 reduced mean ambulatory daytime BP at week 14 by $-9.0/-4.0$ (systolic/diastolic) mm Hg. Especially early morning BP, which surges when RAAS is stimulated before wake-up, was reduced by up to $-25/-13$ mm Hg [30^{••}]. In an attempt to induce higher antibody titers and to further reduce BP, a larger dose of vaccine and more frequent immunizations in shorter intervals were employed in a follow-up phase II clinical trial. Although higher antibody titers were indeed induced, weaker reduction in BP was observed with the modified vaccine regimen. Whether reduced efficacy observed in the second trial was caused by lower antibody affinities induced by the new regimen or a counterbalance by renin is currently investigated [31].

Anti-cytokine vaccines for chronic inflammatory and autoimmune diseases

All inflammatory autoimmune diseases involve cytokine cascades in their development. By acting during innate and cognate phases of the inflammatory process, cytokines play numerous important roles in enhancing, regulating and amplifying autoimmune pathogenesis. Passive administration of high affinity anti-cytokine mAbs has proven very effective in neutralizing overproduced cytokines and blocking their pathogenic effects in autoimmune diseases as demonstrated in numerous clinical trials with mAbs against TNF, IL-1, IL-12/23, IL-15, IL-17 and others. Although effective, immunotherapy with mAbs is also subject to limitations: if chronic diseases are to be treated, frequent mAb administrations are required. This makes treatment expensive and cumbersome for patients and may hamper compliance. Furthermore, frequent administration, even when using fully human mAbs, may increase the risk of inducing anti-antibody responses which can lead to secondary unresponsiveness to the treatment [32].

Active immunization aimed at inducing neutralizing anti-cytokine antibodies offers an alternative approach which has the potential to overcome these limitations. The longevity of antibody responses induced by active vaccination supersedes the need for frequent administration. Proof-of-concept for active vaccination against cytokines has come from numerous animal models of autoimmune and chronic inflammatory diseases and has been reviewed in detail elsewhere [33,34[•]].

Few therapeutic anti-cytokine B-cell vaccines for the treatment of autoimmune and chronic inflammatory diseases have entered clinical trials so far (Table 3). They are directed against the cytokines TNF and IL-1 β , for which long-term neutralization with biotherapeutics has proven to be safe. Thus, both cytokines are clinically validated targets for autoimmune and chronic inflammatory conditions with well-known safety profiles [35,36]. These vaccines consist of full-length cytokines or cytokine derived peptides coupled to KLH or VLPs. A phase I/

Table 2

Clinical trials with therapeutic B-cell vaccines for hypertension

Company	Vaccine	Therapeutic agent	Stage
Protherics	PMD-3117	Angiotensin I coupled to KLH	Aborted
Protherics/BTG	Angiotensin therapeutic vaccine (ATV)	Angiotensin I coupled to KLH + 'Covaccine HT'	Phase II
Cytos	AngQb	Angiotensin II coupled to VLP	Phase II

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Table 3**Clinical trials with therapeutic anti-cytokine B-cell vaccines for autoimmune diseases**

Company	Vaccine	Therapeutic agent	Stage
Pharmexa	TNF AutoVac	TNF with inserted foreign T-helper epitope	Aborted
Cytos	TNFQb	TNF-peptide coupled to VLP	Aborted
Neovacs	TNF α -kinoid	TNF coupled to KLH	Phase I/IIa
Cytos	IL1bQb	IL-1 β mutant coupled to VLP	Phase I/IIa

IIa study in psoriasis patients with a vaccine composed of a TNF-peptide coupled to the VLP Q β demonstrated safety and tolerability of the vaccine. All patients mounted an antibody response against TNF but only a temporary non-significant improvement of disease symptoms was reported [37]. Whilst safe, the use of peptides as immunogens for the induction of high affinity neutralizing antibodies against full-length proteins may be problematic. Owing to the conformational flexibility of short peptides, antibodies may be induced that either fail to recognize the epitope in context of the full-length protein or do so only weakly. Indeed, more than 50 mAbs generated from patients immunized with TNF-peptide coupled to VLPs recognized the peptide but failed to effectively neutralize native TNF protein (M Bachmann, unpublished observation). Use of full-length proteins as antigen for the induction of anti-cytokine antibodies is hence preferable. Furthermore, full-length proteins have the advantage of inducing polyclonal antibody responses and may trigger the formation of small, non-pathogenic immune complexes that contribute to rapid clearance of the cytokine from the circulation [38]. The downside of using full-length proteins as antigens can be potentially toxic effects of the vaccine caused by the potent bioactivity of native cytokines. Therefore, anti-cytokine vaccines currently tested in clinical trials make use of detoxified cytokine-antigens. Neovacs' TNF-kinoid vaccine consists of chemically detoxified TNF cross-linked to the carrier KLH and induces neutralizing antibodies [39]. A phase I/IIa clinical trial with the TNF-kinoid vaccine is currently performed in Crohn's disease patients. Preliminary data have demonstrated safety of the vaccine and signs of clinical remission in treated patients [40]. The IL-1 β vaccine IL1bQb developed by Cytos consists of an IL-1 β mutant with strongly reduced bioactivity coupled to VLPs. The vaccine is currently tested in a phase I/IIa clinical trial in type II diabetes patients and first results are awaited in 2010.

In order to reach therapeutic efficacy, anti-cytokine vaccines have to induce sufficiently high antibody titers and affinities. In murine models of autoimmune diseases, very high anti-cytokine antibody titers can be induced

which readily leads to therapeutic benefit [9,39,41,42]. In humans, however, antigen specific titers after therapeutic vaccination are usually 1–2 logs lower (Bachmann *et al.*, unpublished observation). According to the law of mass action, at lower concentrations, antibody affinity becomes more crucial to achieve sufficient neutralization. Anti-cytokine mAbs currently used in the clinic or clinical trials have affinities in the low pM to even fM range and achieve therapeutic efficacy with serum concentrations in the low μ g/ml range [43]. Whether average affinities of polyclonal antibody responses after vaccination need to reach similar affinities to become therapeutically effective is currently unclear. Average affinities of polyclonal antibody responses induced against cytokines in mice show affinities in the pM range. Preclinical data with IL1bQb have demonstrated that affinities and concentrations in sera of immunized primates are compatible with clinical efficacy.

Conclusions

Therapeutic B-cell vaccines hold potential as affordable and effective therapeutic option for NCDs. Numerous animal studies and first clinical trials performed with second generation vaccines have demonstrated that induced auto-antibody responses are reversible and auto-reactive T-cell responses are limited or absent. Due care should also be taken in selecting suitable targets as from a safety perspective not all molecules are suitable for therapeutic vaccination. Proper understanding of the biology of the target molecule and potential consequences of its long-term neutralization are essential. Most molecules targeted by therapeutic vaccination to date have been previously clinically validated with, for example mAb-therapies. The risk/benefit ratio for therapeutic vaccination will have to be assessed, however, on an individual target basis. So far, experience with therapeutic vaccines in humans is limited. Lessons learned from current trials, however, will provide the foundation for efficacy and safety as we seek to expand the use of vaccines to widespread non-communicable chronic diseases.

Disclosures

TA Röhn, and MF Bachmann are employees of, and hold stocks or stock options with, Cytos Biotechnology.

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