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**Review Article**

# Therapeutic renin–angiotensin vaccines for the treatment of hypertension

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**CONTENTS**



**Abstract**

Hypertension is a pathophysiological state of persistently high blood pressure and is a major risk factor for stroke, coronary heart disease, heart failure, renal failure and arterial aneurysm. Despite recent success in the use of traditional chemical drugs for the management of hypertension, the incidence of this condition is on the rise and has reached epidemic proportions by all estimates. A new class of therapies targeting the renin–angiotensin system (RAS) based on vaccine approaches are now in clinical trials and hold promise for the long-term control of hypertension. In this review, we discuss the role of the RAS in hypertension, the different RAS components as targets for vaccination, the efficient and safe immune response to self-antigens in the RAS vaccine, and the future of RAS vaccines.

## Introduction

Hypertension is a pathophysiological state of persistently high blood pressure (BP). It contributes to serious health complications, such as stroke, coronary heart disease, heart failure, renal failure and arterial aneurysm (1, 2). The major goal of current hypertension therapy is to control BP and prevent the complications (i.e., end-organ damage) associated with the disorder. Despite the availability of chemical agents that are highly effective at lowering BP, successful control of BP is only observed in a small percentage of patients. Half of the patients with hypertension in the United States reported receiving drugs for lowering BP, but only 30% had their BP controlled to the conventionally recommended target of < 140/90 mmHg (3). The situation is much worse in developing countries, where the prevalence of hypertension is high and BP control rates are extremely low —for example, only 6.1% in China (4). These data have led many to conclude that traditional pharmacotherapy has reached a plateau and that novel approaches must be sought for the control of hypertension. As a result, our group and many other researchers have explored the use of vaccination strategies for the long-term control of hypertension.

Vaccination is an effective and economic form of medical intervention for the treatment of communicable diseases. The use of vaccines, where infrequent doses induce a long-term and smooth biological response, may provide benefits over the use of traditional pharmacotherapy, such as: 1) noncompliance by patients can be significantly reduced because of the fact that infrequent doses could remain effective for months or even years; 2) with the ability to induce long-term antibody responses, the vaccine approach may produce long-term beneficial outcomes in end-organ damage in hypertension; and 3) in comparison to chemical drugs used every day, infrequent vaccination is a more economic therapy for chronic hypertension, which is a huge burden for health systems, especially in developing countries.

## The renin–angiotensin system and pharmacological or immunological inhibition

Since the discovery of renin as a pressor substance in 1898, the renin–angiotensin system (RAS) has been extensively studied because it remains the most important regulator of systemic BP (5). The classic RAS cascade begins with the secretion of renin, the rate-limiting enzyme that catalyzes the hydrolysis of angiotensin (Ang) I from the *N*-terminus of angiotensinogen. Ang I is hydrolyzed by angiotensin-converting enzyme (ACE) to form Ang II, a potent vasoconstrictor and the primary

active product of the RAS. Ang II mainly acts at two cell transmembrane receptors: the type 1 receptor ($AT_1$) and the type 2 receptor ($AT_2$). The $AT_1$ receptor mediates the best-understood actions of Ang II, including its hemodynamic and trophic effects (6). The $AT_2$ receptor mediates cellular differentiation and growth, thus opposing the actions of Ang II via the $AT_1$ receptor (7). In the past few years, the RAS has been newly recognized. Many novel components and angiotensin metabolic pathways have been discovered (8). A scheme describing the RAS, including some of the latest developments, new peptides and enzymes participating in this system, is shown in Figure 1. These advances have led to a better understanding of the role of the RAS in hypertension.

The RAS can be inhibited at various points by chemical agents. Renin inhibitors interfere with the first and rate-limiting step in the cascade: the interaction of renin with its substrate angiotensinogen. ACE inhibitors block the conversion of Ang I to Ang II. $AT_1$ receptor blockers (ARBs) interfere with the interaction of the hormone Ang II with the $AT_1$ receptor, but do not oppose stimulation of the $AT_2$ receptor. Active and passive immunization against the components of the RAS was also investigated. Immunization against renin interrupts the metabolism of angiotensin peptides (Ang I and Ang II). Immunization against angiotensin peptides or the $AT_1$ receptor blocks the receptor–ligand interaction. Renin synthesis and secretion are inhibited in negative feedback loops by Ang II, high BP, salt and volume overload. Both chemical drugs and vaccination interrupt the normal feedback suppression of renin secretion from the kidneys. However, there are differences in the effects on the RAS cascade that interrupt different steps (Table I). For example, immunization against renin interfered with the initial and rate-limiting step to inhibit the entire cascade (9, 10). Conversely, active immunization against Ang II led to a decrease of free Ang II in plasma, which augmented renin activity and led to a consequent increase in Ang I and total Ang II (antibody-bound and free) in plasma (13-17). Immunization against the $AT_1$ receptor was hypothesized to antagonize the binding of Ang II to the receptor (18, 19). During $AT_1$ receptor blockade, there is also a reactive rise in Ang II due to increased activity of renin. This may result in excessive $AT_2$ receptor stimulation. Such stimulation exerts opposite effects on the $AT_1$ receptor, which has been proposed to contribute to the more beneficial effects (7, 20).

### Lessons learned from vaccination against renin: safety of vaccines against self-antigens

Vaccination against the RAS with the aim of decreasing BP in hypertensive patients was first performed by Goldblatt et al. (21). Although antirenin to heterologous renin can inactivate renin of animals, it has no effect on human renin or the BP of hypertensive patients. Further

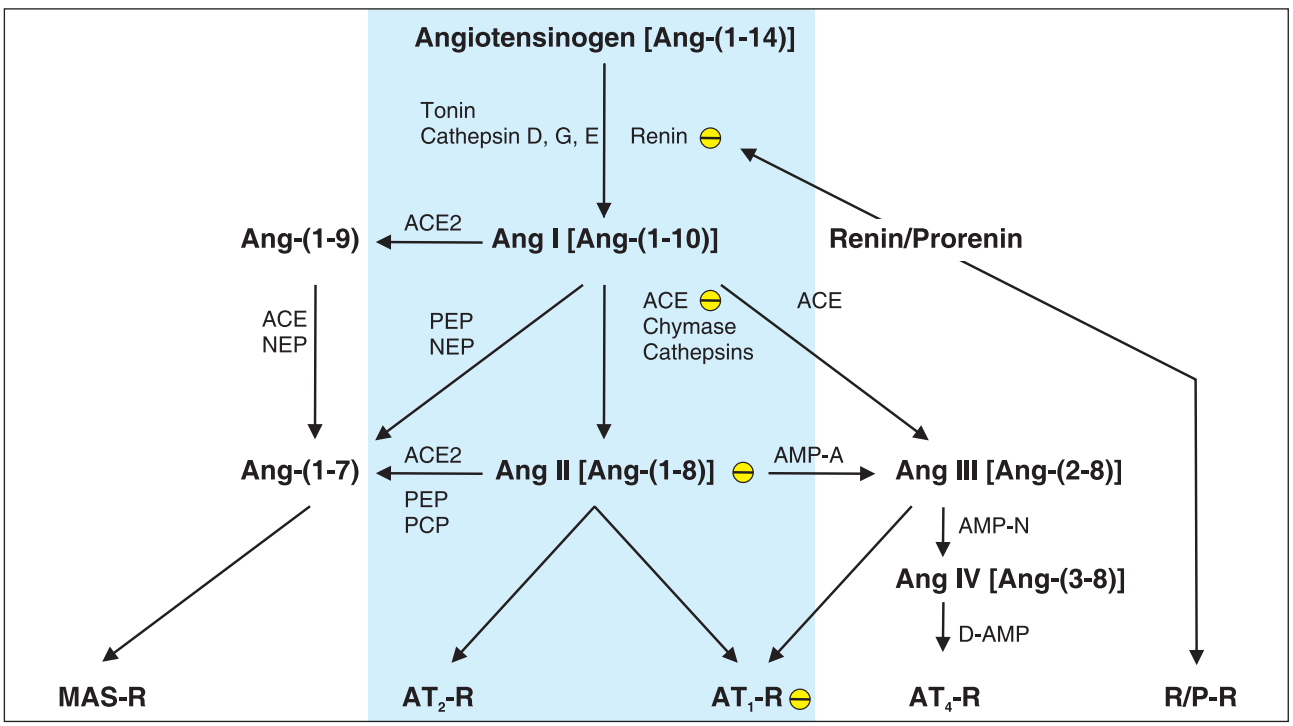


Fig. 1. Simplified overview of the components of the renin–angiotensin system (RAS). The classic pathway is shaded in light blue. Yellow circles represent therapeutic targets of the RAS for hypertension. ACE, angiotensin-converting enzyme; R/P-R, renin/prorenin receptor; AMP-A, aminopeptidase A; AMP-N, aminopeptidase N; D-AMP, dipeptidylaminopeptidase; PEP, prolylendopeptidase; PCP, prolylcarboxypeptidase; NEP, neutral endopeptidase 24.11; $AT_1$-R, angiotensin II type 1 receptor; $AT_2$-R, angiotensin II type 2 receptor; $AT_4$-R, angiotensin IV receptor; MAS-R, Mas-related G protein-coupled receptor (MAS1L).

*Table I: Impact of different classes of antihypertensive agents on activity of the RAS in plasma.*

| Treatment | PRA | PRC | Ang | Ang I | Ang II | Ald | Ref. |
|---|---|---|---|---|---|---|---|
| Renin inhibitors | ↓ | ↑ | NA | ↓ | ↓ | ↓ | 11 |
| ACE inhibitors | ↑ | ↑ | ↓ | ↑ | ↓ | ↓ | 11 |
| ARBs | ↑ | ↑ | ↓ | ↑ | ↑ | ↓ | 11 |
| Renin vaccine | ↓ | ↓ | ↑ | NA | ↓ | ↓ | 9, 10 |
| Ang I vaccine | NA | – | NA | NA | NA | – | 12 |
| Ang II vaccine* | ↑ | ↑ | NA | ↑ | ↑ | – | 13-17 |

RAS, renin–angiotensin system; PRA, plasma renin enzymatic activity; PRC, plasma renin concentration; Ang, angiotensin; Ald, aldosterone; ACE, angiotensin-converting enzyme; ARBs, angiotensin $AT_1$ receptor blockers; NA, not available. ↑ = increase, ↓ = decrease, – = no change. *The data for the Ang II vaccine are from articles published by different research groups using different vaccination methods against Ang II. Ang II in plasma includes free Ang II and antibody-bound Ang II. No data are available for vaccination against the $AT_1$ receptor.

research found that altering the antigenicity of dog renin by acetylation could produce an antirenin that neutralized dog renin as well as human renin (22). In these early studies, renin was proven to be antigenic. The efficiency of the immunization depended on the homology between the species-specific heterologous renin used as antigen and the endogenous form. In early studies, interpretation of such results was limited by the fact that renin was not completely purified. With the development of affinity chromatography technology, pure renin was purified from pig, dog and human kidneys (23, 24). Michel et al. examined the effects of active immunization against pure renin and chronic blockade of the renin substrate reaction in marmosets and rats (9, 10). Renin protein immunization successfully led to complete blockade of the system: decreased renin enzyme activity, suppressed generation of angiotensin peptides and decreased urinary aldosterone excretion rate. The increase in renin antibodies was associated with a significant drop in BP not only in normotensive animals but also in spontaneously hypertensive rats (SHR). Moreover, cardiac protection of target organs was evidenced by the significantly decreased ratio of left ventricular weight to body weight in SHR.

For renin, self-tolerance can be completely overcome by multiple immunizations in the presence of Freund's adjuvant, although it causes a kidney-specific autoimmune disease and granulomatous formation in the lung and the kidney (9, 10). However, in an early study of active immunization against hog renin in dogs or rabbits without Freund's adjuvant, no evidence of autoimmune disease was found in kidneys upon microscopic examination (25, 26). This raises the question of the role of Freund's adjuvant in the development of autoimmune disease against renin (see Ref. 27 for a detailed review of the role of Freund's adjuvant in experimental autoimmune diseases). Freund's adjuvant can induce strong inflammatory Th1 responsiveness and delayed-type hypersensitivity against self-antigen. Therefore, it is suggested that a RAS vaccine be formulated in a Th2-type adjuvant (i.e., alum). A vaccine for hypertension based on a self-antigen aims to induce antibody responses to renin. Activation of antibody responses (B-cell responses) requires T-cell help. If a large-molecule self-antigen (human renin, a 406-amino-acid protein) is vaccinated alone, the T-cell help required for the induction of strong IgG antibody responses will be, by necessity, directed against the antigen itself. Unwanted T-cell-mediated cytotoxicity against self-antigen should be considered, as it can cause autoimmune disease.

Similar safety concerns were also present in the research of a vaccine against β-amyloid peptide (Aβ, a 40- to 43-amino-acid peptide) for Alzheimer's disease (AD) (28, 29). A phase IIa clinical trial of an AD vaccine was halted due to meningoencephalitis developing in approximately 6% of the patients (30). It is hypothesized that the immunogen, full-length $A\beta_{1-42}$, may have led to unwanted T-cell-mediated cytotoxicity and caused an autoimmune response. By using low doses of vaccines, avoiding adjuvant and using small peptides devoid of self T-cell epitopes, it might be possible to overcome this issue. Lemere et al. developed novel peptide immunogens targeting Aβ B-cell epitopes (within $A\beta_{1-15}$) and avoiding Aβ-specific T-cell epitopes ($A\beta_{16-42}$ peptide) (31). These short Aβ immunogens induced robust antibody titers that were able to clear cerebral Aβ in the absence of Aβ-specific T-cell reactivity. Alternative approaches that bias the immune response toward a Th2 phenotype and/or combine a short B-cell epitope with a foreign T-cell epitope or a carrier protein may reduce self T-cell-mediated inflammation and prevent the development of autoimmune disease.

Renin is an aspartate protease that consists of two homologous lobes with the active site located in the cleft between the two lobes (32). The cleft between the lobes contains the active site with two catalytic aspartic residues. A key component of the active site is a distinct subpocket (S3sp), which is specific to renin and unique among the aspartate proteases (33). The active site can accommodate seven amino acid units of the substrate angiotensinogen and cleaves the Leu10–Val11 peptide bond within angiotensinogen to generate Ang I. An x-ray crystallographic representation of human renin is presented in Figure 2.

With the knowledge of the structure of renin, the epitopes for blocking antibodies were defined. Evin et al.

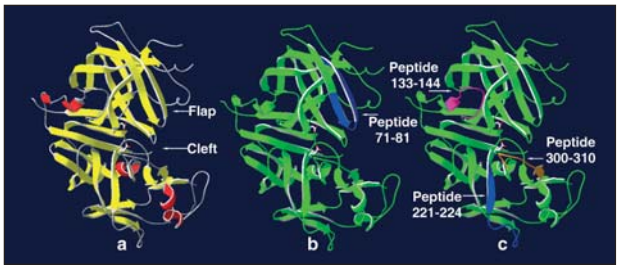


Fig. 2. Ribbon models of renin. Two catalytic residues are indicated by ball-and-stick drawings and shown in blue and red, respectively. **a.** The flap and cleft structures are indicated. **b.** A probable blockade epitope, 78-91, representing the renin flap structure is indicated in deep blue. **c.** Two blockade epitopes, 133-144 and 211-224, located near the catalytic sites of renin, are indicated in purple and deep blue; another blockade epitope, 300-310, located at the edge of the cleft opposite flap, is indicated in orange.

identified two renin epitopes (Y-211-224 and C-180-188) for the renin antibodies (34). Further research by this group found antibodies directed against three epitopes (Y-133-144, Y-211-224 and Y-300-310), which were related to the substrate binding cleft and the enzyme catalytic site, that were able to inhibit renin activity (35). Bouhnik et al. found that renin epitope 81-90, which corresponds to the flap region holding the substrate in the catalytic site, was able to produce antibodies that bound the native renin molecule and inhibited its enzymatic activity (36). A similar epitope was also identified by Fehrentz et al. (37). All these epitopes identified in relation with the catalytic site and the flap region may be used to develop a synthetic antirenin vaccine in the future.

### Failure of Ang I vaccines and success of Ang II vaccines: immunogenicity and efficiency of epitope-based vaccines

Active immunization against Ang I was proposed to induce blocking antibodies, preventing the generation of Ang II and the subsequent increase in BP (12, 38). PMD-3117, a complex of Ang I coupled with keyhole limpet hemocyanin (KLH) in the presence of alhydrogel, was the first vaccine for hypertension tested in humans (12). Ang I, a decapeptide, may contain only one B-cell epitope. KLH provides foreign T-cell epitopes to T-cell responses. Alhydrogel, a relatively weak adjuvant, is used for antibody induction (39). This vaccine has successfully broken immunosilence and has been demonstrated to have good tolerability and safety in humans. However, the vaccine had no effect on BP. Antibodies will never lead to the complete blockade of a particular molecule, because there will always be an equilibrium between free and antibody-bound molecules (40). According to the law of mass action, a higher concentration and greater affinity of the antibodies are required to inhibit the physiological activity of the target molecule. It is presumed that the formulation of the Ang I vaccine was not efficient to provide sufficient antibodies to inhibit angiotensin production or action. Moreover, despite a powerful blockade of Ang II generation within the plasma compartment, the tissue conversion of Ang I to Ang II was not blocked by immunization against Ang I. The half-life of Ang I is short, so its presence is transitory within the tissue; therefore plasma antibodies to Ang I do not diffuse sufficiently into the interstitium to efficiently block Ang I conversion at the tissue level (41).

Christlieb et al. first showed that experimental renal hypertension in rats could be ameliorated after the successful in vivo production of antibodies against Ang II by a complex of Ang II coupled to albumin with Freund's adjuvant (42). However, the results of previous work on Ang II immunization were not consistent. Active immunization against Ang II had no effect on hypertension in other studies using renal hypertension models (43-45). The Ang II vaccine was actively immunized to generate high-titer anti-Ang II antibodies to bind Ang II in plasma. Once free Ang II in plasma has fallen, the stimulus for renin activity is augmented, resulting in a further increase in Ang II and saturation of the antibodies (46). The excess angiotensin would thereby produce renewed hypertension. Therefore, a sufficient amount of antibody in plasma is required to absorb the increase in Ang II in plasma.

Recent work showed that an Ang II vaccine based on virus-like particles (VLPs), which produced high-affinity and high-titer antibodies, was successful in reducing the BP of SHR (13). This vaccine, referred to as CYT006-AngQb, was constructed by linking a modified Ang II peptide to the surface of the RNA bacteriophage Qb VLPs. AngQb demonstrated good immunogenicity, safety and efficacy in humans. VLPs are a highly repetitive antigen structure (47). The structural components of some VLPs have also proven amenable to the insertion or fusion of foreign antigenic sequences, allowing the production of chimeric VLPs exposing the foreign antigen on their surface. For proper B-cell activation and subsequent antibody production, a crucial factor for immunogenicity is the repetitiveness and order in which antigens are presented to the immune system (48). By way of chemical, physical or genetic engineering modification, self-antigens arrayed in a repetitive fashion at appropriate density on the surface of VLPs can induce strong B-cell responses in the absence of adjuvants (46, 49). The VLP platform can also serve as a source of foreign T-helper epitopes. Data for a vaccine against A$\beta$ peptide and a vaccine against TNF-$\alpha$ based on VLPs showed that T-cell responses were mainly directed against viral components (50, 51). Thus, VLPs that amplify humoral B-cell responses and minimize inflammatory T-cell responses against self-antigens represent an ideal platform to be applied in RAS vaccines against self-antigens.

In the past few years, many novel angiotensin peptides of the RAS have been discovered that are metabolites of Ang I or Ang II. Their amino acid sequences are described in Table II. Despite their very similar amino acid sequences, they may have opposite biological functions (6, 8, 52-60) (Table II). For example, Ang-(1-7), a heptapeptide fragment of Ang II, acts as a vasodilator

*Table II: Amino acid sequences of angiotensin peptides and vaccines.*

| | Sequence | Main function of active angiotensin peptides | Ref. |
|---|---|---|---|
| Angiotensinogen | Asp-Arg-Val-Tyr-Ile-His-Pro-Phe-His-Leu-Leu-Val-Tyr-Ser | | |
| Ang I [Ang-(1-10)] | Asp-Arg-Val-Tyr-Ile-His-Pro-Phe-His-Leu | | |
| Ang-(1-9) | Asp-Arg-Val-Tyr-Ile-His-Pro-Phe-His | | |
| Ang II [Ang-(1-8)] | Asp-Arg-Val-Tyr-Ile-His-Pro-Phe | Vasoconstriction/proliferation (via $AT_1$-R) | 6 |
| Ang-(1-7) | Asp-Arg-Val-Tyr-Ile-His-Pro | Vasodilatation/antiproliferation (via MAS-R) | 52, 53 |
| Ang III [Ang-(2-8)] | Arg-Val-Tyr-Ile-His-Pro-Phe | Vasoconstriction (via $AT_1$-R) | 54 |
| Ang IV [Ang-(3-8)] | Val-Tyr-Ile-His-Pro-Phe | Vasodilatation/antiproliferation, enhancing memory (via $AT_4$-R/IRAP)* | 55-57 |
| Ang V [Ang-(3-7)] | Val-Tyr-Ile-His-Pro | Enhancing memory | 58 |
| Des-Asp-Ang I [Ang-(2-10)] | Arg-Val-Tyr-Ile-His-Pro-Phe-His-Leu | Antiproliferation | 59 |
| Ang A (Des-Asp1-Ala1-Ang II) | Ala-Arg-Val-Tyr-Ile-His-Pro-Phe | Vasoconstriction (via $AT_1$-R) | 60 |
| PMD-3117 (Ang I vaccine) | KLH-acetylcysteine-glycine-Asp-Arg-Val-Tyr-Ile-His-Pro-Phe-His-Leu | | |
| CYT006-AngQb (Ang II vaccine) | VLP-Cys-Gly-Gly-Asp-Arg-Val-Tyr-Ile-His-Pro-Phe | | |

*The high-affinity Ang IV binding site ($AT_4$ receptor) has been identified as the transmembrane enzyme insulin-regulated membrane aminopeptidase (IRAP).

and counterregulates the actions of Ang II (52). The antibodies raised by immunization with the Ang I analogue vaccine were found to cross-react with angiotensinogen (38) and the antibodies induced by the Ang II vaccine (AngQb) cross-reacted with Ang III (Ang-[2-8]) and Ang I (13). Antibodies raised against AngQb bound most strongly to Ang II, followed by Ang III; binding to Ang I was an order of magnitude lower. However, it is not clear whether or not the antibodies against Ang I or Ang II will cross-react with the angiotensin peptides which counter the functions of Ang II, such as Ang-(1-7), Ang-(3-8) and Ang-(2-10).

### Immunization against the $AT_1$ receptor

As already noted, Ang II acts at four angiotensin receptor subtypes (6). The $AT_1$ receptor mediates most of the established physiological and pathophysiological effects of Ang II, including hemodynamic and trophic actions on the cardiovascular system (vasoconstriction, increased BP, increased cardiac contractility, vascular and cardiac hypertrophy). Therefore, specific antagonism of Ang II action at the $AT_1$ receptor is a logical therapeutic target. The $AT_1$ receptor belongs to the family of G protein-coupled receptors (GPCRs) which are transmembrane proteins. Autoimmunity of GPCRs was also previously documented in thyroid diseases (61). Autoantibodies against the TSH receptor (thyrotropin receptor) ectodomain protein are the primary cause of thyroid diseases. Davies et al. have reviewed different antibodies against extracellular components of the thyrotropin receptor and reported that they display different pharmacological characteristics, including stimulant, blocking and neutral effects on the TSH receptor (62). Epitope study of monoclonal antibodies (mAbs) against the TSH receptor found that blocking mAbs recognized different epitopes of the receptor, one of which is indistinguishable from the thyroid-stimulating epitope (63, 64). Thus, immunization aimed at a specific epitope of a receptor acting as an agonist or antagonist has the potential to be developed for clinical use.

Zelezná's group was the first to report that preimmunization with the *N*-terminal sequence 14-23 of the $AT_1$ receptor completely prevented the development of two-kidney, one-clip renal hypertension in rats (65). Immunization against this peptide also attenuated the development of genetic hypertension in young SHR, but did not modify established hypertension in adult SHR (19, 66). Our group has developed a peptide vaccine against the rat $AT_{1A}$ receptor comprised of a complex of 181-187 from the second extracellular component of the $AT_{1A}$ receptor, tetanus toxoid and Freund's adjuvant (18). Active immunization with this peptide reduced systolic BP and ameliorated remodeling of target organs of SHR over 64 weeks (67).

The $AT_1$ receptor is a membrane-bound protein. Abundant membrane-bound proteins are supposed to be particularly susceptible to destructive mechanisms, such as antibody-dependent cellular cytotoxicity (ADCC). However, there were no signs of autoimmune damage in the main organs of vaccinated animals in experiments with an epitope-based $AT_1$ receptor vaccine (18, 67). Extensive therapeutic experience with mAb therapies has largely resolved the possible issue of ADCC in RAS vaccination, as it has not occurred systemically in patients treated with anti-TNF-$\alpha$ antibodies (68). It would appear

that ADCC is more of a theoretical concern than a practical issue.

## Future directions and conclusions

To achieve BP control, most hypertensive patients will require two or more different types of antihypertensive drugs (3). For example, in a recent large-scale trial in high-risk hypertension, approximately 9 of 10 patients were given two or more antihypertensive drugs in order to reduce BP to < 140/90 mmHg (69). ACE inhibitors or ARBs used alone achieve the target BP values in only 20-30% of the overall hypertensive population, except in subjects with grade 1 hypertension (70, 71). Vaccination against multiple other target molecules must be tried in an attempt to improve the therapeutic outcome. Xu et al. showed that antibodies against the third extracellular region of TRCP5, a member of the transient receptor potential calcium channel family, bound to and led to inhibition of the channel (72). This strategy, immunotherapy to inhibit a specific domain of an ion channel, may also be used in the design of a vaccine against $Ca^{2+}$ channels in the vasculature. The $\alpha_1$-adrenoceptor, another member of the GPCR family, is also an important target for the therapy of hypertension. Epitope studies of the receptor may find a blocking epitope for a hypertension vaccine. Thus, $Ca^{2+}$ channels and $\alpha_1$-adrenoceptors in the vasculature both offer interesting possibilities as potential sites for immunotherapy.

It is evident from the above discussion that a safe and effective vaccine against a component of the RAS requires a delicate balance between providing a specific and adequate humoral immune response, and reducing or eliminating unwanted adverse events that may induce excess inflammation or an autoimmune response. Besides the VLPs, many approaches, including plasmid DNA vaccines, live viral vectors, recombinant phages and conjugate vaccines with strong and promiscuous T-cell epitopes, have the potential to be developed as safe and effective RAS vaccines. Plasmid DNA vaccines are based on bacterial plasmids that have been engineered to express the antigen using promoter elements that are active in mammalian cells. Fused with molecular adjuvant genes, for example the IL-4 cytokine gene, vaccination against encoding self-antigens can lead the immune response to be driven to a more Th2-like phenotype (73, 74). Recombinant virus vectors, for example recombinant adeno-associated virus (AAV), in which genetic information derived from the B epitope of the self-antigen has been incorporated, can induce an ideal humoral immune response without T-cell proliferative responses to self-antigen (75, 76). The genome of filamentous bacteriophages can be engineered to allow foreign peptide to be displayed in the exposed *N*-terminal segment of the major coat protein in the virus particle (77). Administration of filamentous phages induces a strong immunological response to the phage proteins in all animals tested, without any evidence of toxic effects (78, 79). The high immunogenicity of filamentous phages enables the raising of antibodies against self-peptides (80). Recently, a novel multicomponent antigen display and delivery system based on bacteriophage T4 capsid protein was tested in vaccines against human immunodeficiency virus (HIV) and anthrax (81-83). Because recombinant bacteriophage T4 can display foreign peptides or proteins at high copy numbers on the phage capsid surface, it is a highly efficient antigen delivery system. Moreover, multiple antigens fused to outer capsid proteins of this phage can be displayed on the same capsid and such particles can elicit broad immunological responses. These unique features may lend bacteriophage T4 to the development of a multicomponent vaccine for hypertension. In synthetic vaccines, the B-cell epitope of a target molecule can be coupled to a promiscuous T-cell epitope to make it immunogenic (84). In the study of the AD vaccine, a promiscuous T-cell epitope could provide strong T-cell support to promote a potent humoral response to the self B-cell epitope (85). This strategy can also be used in the design of a vaccine for hypertension.

The RAS plays a key role in the regulation of fluid and electrolyte balance and BP. Therapeutic vaccination against the RAS is a promising new strategy in the treatment of hypertension, and the first steps in clinical development have been made. With the increasing understanding of the pharmacology of the RAS and developing techniques in vaccinology, new vaccine formations should become available in the future.

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