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REVIEW

Immunization against angiotensins for the treatment of hypertension

Patrik Maurer, Martin F. Bachmann*

Cytos Biotechnology AG, Wagistr. 25, CH-8952 Schlieren, Switzerland

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Abstract Current vaccination approaches against hypertension target angiotensin I and angiotensin II, key components of the renin–angiotensin system. The effectiveness and long-term safety of blockade of the renin–angiotensin system with antihypertensive small-molecule drugs is well documented. Phase I/II testing of the angiotensin I vaccine PMD3117 demonstrated safety and immunogenicity in humans. While angiotensin I-specific antibodies were induced blood pressure was not lowered, presumably due to insufficient antibody levels. A second vaccine, which targets angiotensin II, has been clinically tested. Administration of CYT006-AngQb to subjects with mild to moderate hypertension was safe and well tolerated. After three administrations of 300 μg of the vaccine, ambulatory blood pressure was significantly reduced compared to placebo. The vaccine was particularly effective early in the morning as systolic and diastolic blood pressure were lowered by −25 mm Hg and −13 mm Hg, respectively. Further studies are required to show long-term safety and to assess how robust and long-lived the blood pressure reduction is. It will also be important to ascertain whether the strong reduction of blood pressure in the early morning, when most cardiovascular events occur, might result in long-term benefits over current therapies.

Contents

* Corresponding author.
E-mail address: martin.bachmann@cytos.com (M.F. Bachmann).

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Hypertension

High blood pressure is the most common treatable risk factor for cardiovascular diseases. Stroke and ischemic heart disease result in 7.6 million premature deaths worldwide [1]. Approximately half of these events can be attributed to high blood pressure. Prevalence of hypertension varies between 5% in rural India and 70% in Poland. Interestingly, even within western countries there are substantial differences in disease prevalence. In the US and Canada 28% of the adult population are hypertensive (defined as a blood pressure of 140/90 or higher or current use of antihypertensive medication) while 44% of Europeans living in Finland, Italy, England, Sweden, Spain or Germany are affected [2]. The reasons for this difference are not clear. Multiple factors such as nutrient intake, obesity, physical activity and genetic susceptibility contribute to high blood pressure. The high incidence of disease results in a substantial burden to the health care system. A contributing factor to disease outcome and health care cost is the fact only a small proportion of hypertensives are treated (~30% in Europe) and of those treated only a minority (30%) achieves blood pressure control. Accordingly, adequate control of hypertension control is alarmingly low; about 9% in Europe and 30% in the US [3]. One reason for poor control of hypertension is lack of compliance to intake of medications [4]. Patients often do not take their prescribed medication; it has been estimated that 50–80% are non-compliant. A majority of patients have reservations about long-term drug therapy and compliance is further worsened when patients experience medication side effects such as dry cough, peripheral oedema and sexual dysfunction. In contrast, hypertension is for the most part asymptomatic.

Blood pressure and the renin–angiotensin system

Blood pressure is principally influenced by three factors: 1) cardiac output regulated by sympathetic nerve system activation, 2) sodium and fluid retention in the kidney and 3) vascular resistance. The latter is tightly regulated by the renin–angiotensin system (RAS), a hormone system that regulates blood pressure by constricting blood vessels. The active component of the system is angiotensin II, an eight amino acid peptide that binds the AT1 receptors (Fig. 1). The AT1 receptor is a G-protein coupled receptor located on vascular smooth muscle cells. Receptor engagement by angiotensin II results in vasoconstriction of arterioles. Angiotensin II also induces aldosterone secretion in adrenal cortex which leads to sodium resorption in the kidney. Accordingly, blood pressure is increased when angiotensin II levels are high. Angiotensin II is derived from the precursor protein angiotensinogen via the action of two proteases. Angiotensinogen is constitutively produced by the liver and cleaved in the serum by renin to form angiotensin I, a ten amino acid peptide. This precursor peptide is further cleaved by angiotensin-converting enzyme (ACE) to form angiotensin II (Fig. 1).

Hypertension has long been successfully treated by small-molecule drugs that target various components of the renin–angiotensin system: renin inhibitors block the production of angiotensin I, ACE inhibitors interfere with the production of angiotensin II and angiotensin-receptor blockers (ARBs) inhibit the signalling of angiotensin II via the AT1 receptor. Additionally, diuretics, beta-blockers and calcium-channel blockers are also used for the long-term reduction of blood pressure.

Therapeutic vaccination

Despite the availability of numerous effective drugs for treating hypertension, reduction of the global burden of disease has not been achieved. National health agencies are in agreement that new approaches and further measures are needed. Therapeutic active vaccination targeting components of the RAS is a potential option. It offers the possibility for reduction of blood pressure with two to three immunizations per year. Such an approach could circumvent the need for daily medication and substantially reduce the issue of patient compliance. In the following, we review different active vaccination approaches for immunotherapy against hypertension.

Vaccination against renin

To date, vaccines tested for their ability to treat hypertension have solely targeted components of the renin–angiotensin

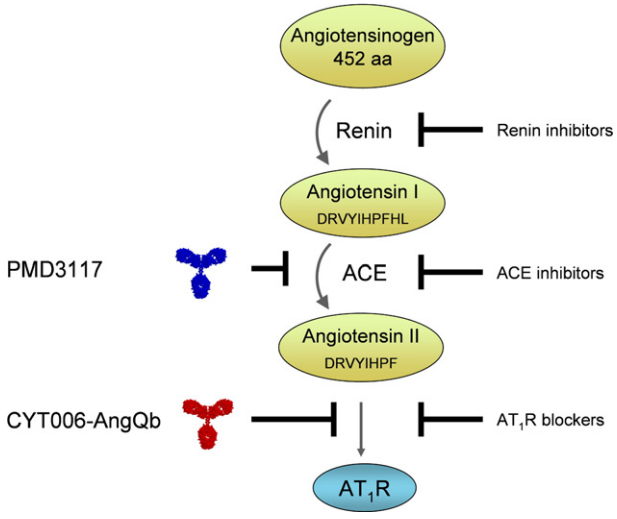

Figure 1 Renin–angiotensin system (RAS). A proteolytic cascade with the enzymes renin and ACE cleaves the precursor protein angiotensinogen and leads to the formation of the 10 amino acid peptide angiotensin I and the 8 amino acid peptide angiotensin II which binds to AT1 receptors (AT_1R) on vascular smooth muscle cells and increases blood pressure. Small-molecule drugs interfering with the RAS are shown on the right. Vaccines in clinical development are shown on the left.