Gene Therapy for Hypertension

The Preclinical Data

M. Ian Phillips

Abstract—Despite several drugs for the treatment of hypertension, there are many patients with poorly controlled high blood pressure. This is partly because all of the available drugs are short-lasting (≤24 hours), have side effects, and are not highly specific. Gene therapy offers a possibility of producing longer-lasting effects with precise specificity based on the genetic design. Preclinical studies on gene therapy for hypertension have taken 2 approaches. Chao et al have performed extensive studies on gene transfer to increase vasodilator proteins. They have transferred kallikrein, atrial natriuretic peptide, adrenomedullin, and endothelin NO synthase into different rat models. Their results show that blood pressure can be lowered for 3 to 12 weeks with the expression of these genes. The antisense approach, which we began by targeting angiotensinogen and the angiotensin type 1 (AT1) receptor, has now been tested independently by several different groups in multiple models of hypertension. Other genes targeted include the β1-adrenoceptor, thyrotropin-releasing hormone, angiotensin gene-activating elements, carboxypeptidase Y, c-fos, and CYP4A1. There have been 2 methods of delivering antisense: one is by oligodeoxynucleotides, and the other is with full-length DNA in viral vectors. All the studies show a decrease in blood pressure lasting several days to weeks or months. Oligos are safe and nontoxic and could be delivered orally or eventually by skin patches. Systemic delivery of recombinant adeno-associated virus with DNA antisense to AT1 receptors in adult rodents decreases hypertension for up to 6 months. We conclude that there is sufficient preclinical data to give serious consideration to phase I trials for testing some of the antisense oligodeoxynucleotides, although testing the viral vectors needs much more work. (Hypertension. 2001;38[part 2]:543-548.)

Key Words: genes ■ drug therapy ■ kallkrein ■ renin angiotensin system ■ adrenergic receptor blockers ■ oligonucleotides ■ antisense ■ adeno-associated virus

Although many excellent pharmacological agents are commercially available for the treatment of hypertension, the problems of cardiovascular disease related to hypertension continue to affect millions of people throughout the world. Hypertension is a multifactorial, multigenic disease, but the drugs aimed at controlling hypertension are aimed at relatively few targets. They target the renin-angiotensin system, β-adrenergic or α-adrenergic receptors, and calcium channels. They should be very effective, but then why is hypertension so widespread and morbid in our society and the world?

Many of the drugs are expensive and therefore unavailable to poor segments of all societies. Another problem is detection. Hypertension is undetected in ≈31.6% of the population of the United States, according to the sixth report of the Joint National Committee.1 Of those in whom hypertension has been detected, 53.6% receive treatment. The problem is further compounded because it is estimated that only 27.4% of those hypertensive patients who receive treatment fully comply with their treatment and have their hypertension controlled.1 Clearly, there is a need for rethinking our approach to the treatment of hypertension. Detection could be increased by education. Nonpharmacologic treatment—such as exercise, weight loss, and low-salt diets—could provide inexpensive treatment, but it has proven very difficult to achieve compliance for these approaches. For treating hypertension on a worldwide scale, we need something akin to an immunization against hypertension. Because hypertension is polygenic and not a single-gene disease, except in very few cases,2 it cannot be immunized against.

We need to develop ways that would improve hypertension control by providing longer-lasting effects with a single dose and reducing side effects that lead to poor compliance. To do this, we began developing a somatic gene therapy approach in 1993,3,4 with the goal of producing prolonged control of hypertension. There have been 2 strategies taken. One used by Chao and colleagues5 is to increase genes for vasodilation, and the other by Phillips and colleagues6 is to decrease genes for vasoconstriction. They represent the 2 sides to transferring DNA into cells: one is the sense approach (ie, the normal DNA sequence direction), and the other is the antisense approach (ie, the opposite DNA sequence direction).
Sense to Vasodilation Genes

Chao et al have an extensive series of studies on gene transfer to genes that act to increase vasodilator proteins (Table 1). They have used genes such as kallikrein, atrial natriuretic peptide, adrenomedullin, and endothelial NO synthase. In different rat models of hypertension (spontaneously hypertensive [SHR], Dahl salt-sensitive, deoxycorticosterone acetate–salt [DOCA]), they showed that they could achieve blood pressure–lowering effects for 3 to 12 weeks with the overexpression of these genes. The fall in pressure resulting from these vasodilator proteins was from −21 to −41 mm Hg. The results of this group are consistent and impressive. Even though the effects were not very prolonged, there were reductions in end-organ damage with these therapeutics. However, this strategy has no obvious applicability to hypertension, because the cause of the disease lies in the reaction of blood vessels, not in one specific tissue. Even the heart, kidney, and brain are obviously very important in hypertension. The in vivo approach is challenging. One challenge is to provide sufficient antisense DNA, either alone or in a vector, to produce a sufficient concentration for uptake in a large number of cells. To do this, we have developed 2 different strategies for hypertension gene therapy based on antisense (1) antisense oligonucleotides (Table 2) and (2) viral vectors to deliver antisense DNA (Table 3).

Antisense to Vasoconstrictor Genes

To counter overexpression of a gene as a critical factor contributing to hypertension, we introduced antisense somatic gene therapy. Antisense provides a highly specific biological approach to produce attenuation of the sense DNA expression, which produces too much protein (eg, angiotensin II, which is responsible for increased vasoconstriction). Antisense gene therapy involves recombinant antisense DNA to express an antisense RNA or antisense oligonucleotides to inhibit mRNA designed to specifically reduce an overexpressed protein that is critical to the disease. Because hypertension is a multigene disease, how can we decide on candidate genes for gene therapy? Several genes have been targeted by antisense oligodeoxynucleotides (AS-ODNs) (see Table 1). We have ignored the difficulties of defining all of the candidate genes by concentrating on those genes that have already been shown to be successful targets by experience with current drugs. These include β-receptors, ACE, and angiotensin type 1 receptors (AT1, Rs). Other targets follow logically, including angiotensinogen (AGT). Transfer of the antisense genes to somatic cells is achieved by an in vivo approach. It would be possible to try an ex vivo approach in which target cells are removed from the host, transduced in vivo, and then reimplanted as genetically modified cells. However, this strategy has no obvious applicability to hypertension, because the cause of the disease lies in the reaction of blood vessels, not in one specific tissue. Even the heart, kidney, and brain are obviously very important in hypertension. The in vivo approach is challenging. One challenge is to provide sufficient antisense DNA, either alone or in a vector, to produce a sufficient concentration for uptake in a large number of cells. To do this, we have developed 2 different strategies for hypertension gene therapy based on antisense with (1) antisense oligonucleotides (Table 2) and (2) viral vectors to deliver antisense DNA (Table 3).

Nonviral Delivery

Antisense Oligonucleotides

Antisense oligonucleotides are short lengths of synthetically made nucleotides (DNA) designed to hybridize with a specific sequence of mRNA. The hybridization has several effects. It stimulates RNase H, sterically inhibits the mRNA from translating its message in the read-through process at the ribosome, and/or prevents ribosome assembly.

Delivery of AS-ODNs can be performed with direct injection of naked DNA. We have found that direct injection is effective, but the efficiency of uptake is greatly increased by delivering the ODN in cationic liposomes, provided the correct ratio has been calculated.

β1-Adrenoceptor Antisense

Nonviral gene delivery, using cationic liposomes such as DOTAP and DOPE, have been successfully used by our group to deliver β1-adrenoceptor AS-ODNs (β1-AS-ODNs) to act as novel β-blockers with prolonged effects. By optimizing the liposome/ODN ratio and the incubation procedure, we are able to produce antihypertensive effects with β1-AS-ODN for up to 33 to 40 days with a single dose. The beauty of the β1-AS-ODN is its specificity. The β1-AS-ODN reduces β1-adrenoceptors but does not affect β2-
adrenoceptors. Second, the β1-AS-ODN does not cross the blood brain barrier, and therefore, the novel β1-blocker, based on antisense, will have no central nervous system side effects. The strongest uptake sites are in the heart and kidney, where the β1-adrenoceptors play a significant role. In the heart, they control the force of contraction, and this is reduced by the β1-adrenoceptor. However, the heart rate is not affected by the β1-AS-ODN.29 This is in contrast to the effects of currently available β1-blockers that have both β1 and β2 actions and, second, reduce heart rate as well as heart contractility. Therefore, the specificity offered by the ODN provides a more precise and accurate way of controlling the mechanisms contributing to high blood pressure without the side effects of bradycardia.28 Furthermore, because the effect lasts for 30 to 40 days with a single injection, the AS-ODN is greatly superior to the currently available drugs, all of which have to be taken on a daily basis. Repeated injections of β1-AS-ODN intravenously at intervals of 3 to 4 weeks produce prolonged control of high blood pressure without any toxic effects in the liver, blood, or organs.

**TABLE 2. Preclinical Data of Gene Therapy for Hypertension Vasoconstrictor Genes: AS-ODNs**

<table>
<thead>
<tr>
<th>Target Gene</th>
<th>Delivery</th>
<th>Model</th>
<th>Max Δ BP, mm Hg</th>
<th>Duration of Effect</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>AT1R</td>
<td>AS-ODN ICV</td>
<td>SHR</td>
<td>−30</td>
<td>Unknown</td>
<td>Gyurko et al3</td>
</tr>
<tr>
<td>AGT</td>
<td>AS-ODN ICV</td>
<td>SHR</td>
<td>−35</td>
<td>Unknown</td>
<td>Phillips et al4</td>
</tr>
<tr>
<td>AT1R</td>
<td>AS-ODN PVN microinjection</td>
<td>MRen2</td>
<td>−24</td>
<td>4 days</td>
<td>Li et al14</td>
</tr>
<tr>
<td>TRH receptor</td>
<td></td>
<td>SHR</td>
<td>−20</td>
<td>6 days</td>
<td>Morishita et al17</td>
</tr>
<tr>
<td>TRH</td>
<td>AS-ODN intrathecal</td>
<td>SHR</td>
<td>−28</td>
<td>7 days</td>
<td>Nishii et al18</td>
</tr>
<tr>
<td>AGE-2</td>
<td>AS-ODN portal vein</td>
<td>SHR</td>
<td>−20</td>
<td>4 days</td>
<td>Tomita et al23</td>
</tr>
<tr>
<td>Carboxypeptidase Y</td>
<td>AS-ODN</td>
<td>DOCA-salt</td>
<td>−15</td>
<td>4 days</td>
<td>Hyashi et al19</td>
</tr>
<tr>
<td>c-fos</td>
<td>AS-ODN microinjection in RVLM</td>
<td>WKY</td>
<td>−16</td>
<td>4 to 6 hours</td>
<td>Suzuki et al20</td>
</tr>
<tr>
<td>CYP4A1</td>
<td>AS-ODN continuous Infusion</td>
<td>SHR</td>
<td>−16</td>
<td>Unknown</td>
<td>Wang et al21</td>
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<tr>
<td>AGT</td>
<td>AS-ODN IV</td>
<td>SHR</td>
<td>−25</td>
<td>Unknown</td>
<td>Wielbo et al22</td>
</tr>
<tr>
<td>AGT</td>
<td>AS-ODN hepatic vein</td>
<td>SHR</td>
<td>−20</td>
<td>4 days</td>
<td>Tomita et al23</td>
</tr>
<tr>
<td>AT1R</td>
<td>AS-ODN ICV</td>
<td>SHR</td>
<td>−30</td>
<td>7 days</td>
<td>Gyurko et al3</td>
</tr>
<tr>
<td>AT1R</td>
<td>AS-ODN with asialoglycoprotein IV</td>
<td>SHR</td>
<td>−30</td>
<td>7 days</td>
<td>Makino et al24</td>
</tr>
<tr>
<td>AT1R</td>
<td>AS-ODN IV</td>
<td>2K1C acute</td>
<td>−30</td>
<td>&gt;7 days</td>
<td>Galli et al25</td>
</tr>
<tr>
<td>AT1R</td>
<td>AS-ODN ICV</td>
<td>2K1C 6 months</td>
<td>−30</td>
<td>&gt;5 days</td>
<td>Kagiya et al26</td>
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<tr>
<td>AT1R</td>
<td>AS-ODN IV in liposomes</td>
<td>CII</td>
<td>−38</td>
<td>Unknown</td>
<td>Peng et al27</td>
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<tr>
<td>β1AR</td>
<td>AS-ODN IV in liposomes</td>
<td>SHR</td>
<td>−35</td>
<td>30 to 40 days</td>
<td>Zhang et al28,29</td>
</tr>
</tbody>
</table>

ICV indicates intracerebroventricular; Unknown, recovery of pressure not recorded; THR, thyrotropin-releasing hormone; AGE, angiotension gene-activating element; IV, intravenous; and CIH, cold-induced hypertension.

**TABLE 3. Preclinical Data of Gene Therapy for Hypertension Vasoconstrictor Genes: Viral Vector Delivery of Antisense**

<table>
<thead>
<tr>
<th>Target Gene</th>
<th>Delivery</th>
<th>Model</th>
<th>Max Δ BP, mm Hg</th>
<th>Duration of Effect</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>AGT</td>
<td>AAV-based plasmid</td>
<td>SHR</td>
<td>−22.5</td>
<td>8 Days</td>
<td>Tang et al30</td>
</tr>
<tr>
<td>AT1R</td>
<td>AAV ICV</td>
<td>SHR adult</td>
<td>−40</td>
<td>9 weeks plus</td>
<td>Phillips31</td>
</tr>
<tr>
<td>AT1R</td>
<td>AAV IC</td>
<td>SHR young</td>
<td>−30</td>
<td>2 months</td>
<td>Phillips31</td>
</tr>
<tr>
<td>AT1R</td>
<td>LNSV IC</td>
<td>SHR neonates</td>
<td>−40</td>
<td>90 days</td>
<td>Iyer et al32</td>
</tr>
<tr>
<td>ACE</td>
<td>LNSV IC</td>
<td>SHR neonates</td>
<td>−15</td>
<td></td>
<td>Reaves et al33</td>
</tr>
<tr>
<td>AGT</td>
<td>AAV IC</td>
<td>SHR neonates</td>
<td>−30</td>
<td>6 months</td>
<td>Kimura et al34</td>
</tr>
<tr>
<td>AT1R</td>
<td>AAV IV</td>
<td>Double transgenic mice (adult)</td>
<td>−40</td>
<td>6 months</td>
<td>Phillips et al35</td>
</tr>
</tbody>
</table>

ICV indicates intracerebroventricular; IC, intracardiac; and IV, intravenous.

AGT-AS-ODN
We have also established that AGT-iAS-ODN is effective for AS-ODN for hypertension therapy. In human hypertension, the AGT gene has been shown to be linked to and play a role in the disease.36 However, there are no currently available drugs to inhibit AGT. We have designed antisense targeted to AGT mRNA and tested it in vivo and in vitro.22 When given
intravenously, the AGT-AS-ODN reduces blood pressure significantly when delivered with a liposome. These studies have been confirmed by others independently, showing that AGT-AS-ODN reduces blood pressure for up to 7 days with a single systemic dose.24

**AT1R AS-ODN**

A similar story is true for the effects of AT1R-AS-ODN. This has been tested centrally with intracerebroventricular and intravenous injections. It has been tested in SHR37 and also in 2-kidney, 1-clip (2K1C) animals26 and environmentally induced hypertension.27 In these 3 different models of hypertension—genetic, surgical, and environmental—the antisense produces a decrease in blood pressure within 24 hours of administration. The effect lasts for up to 7 days, and there is no effect on heart rate.27 The distribution of antisense is in blood vessels, kidney, liver, and heart.27 The majority of uptake is in the kidney and liver.27 A reduction in AT1Rs after treatment with the AT1R-AS-ODN reveals reductions in the protein in kidney, aorta, and liver.27

In summary, AS-ODNs have proved to be useful in demonstrating in the preclinical setting because of the power of AS-ODN to target specific genes and reduce blood pressure for several days (or weeks) with a single administration. Laboratory data indicate that these effects are the result of rapid uptake of the AS-ODN into cells,31 where they migrate to the nucleus and inhibit the production of protein, mostly likely through translational inhibition of messenger RNA.38,39 This could occur by the hybridization of ODN with specific mRNA, preventing the passage of the mRNA through the ribosome. Alternatively, DNA hybridization to mRNA will stimulate in some tissues the production of RNase H for the specific sequence of mRNA bound to the ODN. RNase H destroys the RNA that is hybridized to DNA and thereby releases the oligo for further hybridization. This recycling action induced by RNase H may account for the long action of AS-ODNs.

Another useful feature that can make oligos attractive for hypertension therapy is that they can be produced relatively cheaply, rapidly, and in large quantities. The demand for oligos and primers has reduced the cost per base to a few cents. Second, they do not cross the blood brain barrier and therefore will not have central effects when given peripherally.28 Third, they are most effective when delivered in the right combination of ODN to cationic liposome.28,29 Treatment of rats with liposome ODN complexes has not shown any toxicity in our experience.

**Viral Vector Delivery**

To produce very prolonged effects (ie, several months) with a single injection, we use antisense DNA delivery by viral vector. Several viral vectors are available, but the adeno-associated virus (AAV) is both safe for use in humans and large enough to carry antisense genes with tissue-specific promoters.40 The AAV is not to be confused with the adenovirus. Adenoviruses, although easy to use in laboratory animals, have been associated with a death in a human because of multiple-organ failure.41 AAV is a parvovirus that does not replicate and does not induce inflammatory reactions. The AAV can be stripped of its rep and gag genes to carry up to 4.5 kb and deliver it to the nuclei of cells, where it integrates into the genome.42 When antisense DNA is used, the AAV allows the continuous production of an RNA that is in the antisense direction. This antisense RNA hybridizes to specific mRNA and inhibits translation. Therefore, we are developing antisense therapy using the AAV as a vector. To construct a viral vector requires the design and production of plasmids and gene packaging into the vector.

**Delivery by Plasmids**

Plasmids are effective vectors but last for a shorter time than the viral vector because they do not allow integration into the genome. This is illustrated with the adeno-associated vector for AGT antisense cDNA.30 A plasmid containing AAV terminal repeats was prepared with a cassette, consisting of a cytomegalovirus (CMV) promoter, the rat AGT cDNA based on the sequence by Lynch et al.43 The cDNA is oriented in the antisense direction. In addition, the cassette contains an internal ribosome entry site and, as a marker, the green fluorescent protein gene.44 At 48 hours after transfection into pAAV-AGT-AS, there was clear dominant expression of green fluorescent protein in the H-4 cells. There was a significant reduction of AGT (120 ± 14 versus 230 ± 20 ng/mg protein, P < 0.01). Transgene expression detected by reverse transcription–polymerase chain reaction in the H-4 cells started at 2 hours and continued for at least 72 hours. The plasmid was then tested in vivo by injecting the sense and antisense plasmids intravenously into SHR.30 AGT-AS expression was positive in heart and lung at 3 days and at 7 days. Expression in the kidney was weak or absent. When injected with 3 mg/kg plasmid, pAAV-AGT-AS produced a significant drop in blood pressure (P < 0.01) for 6 to 8 days in SHR. The drop in blood pressure correlated to a drop in plasma AGT levels, which was significant at days 3 and 5 after injection. The decrease in blood pressure with injection of plasmid could be prolonged by injecting the plasmid with cationic liposome (DOTAP/DOPE).

Plasmids are useful for delivery of antisense to produce an antihypertensive effect lasting about 1 week. They do not require the more complex packaging needed for recombinant AAV (rAAV).

**Delivery by Recombinant AAV Vector**

To produce long-term decreases in hypertension, we developed rAAV to deliver antisense to AT1Rs in SHR.40,30 The results showed that single intracardiac injection of rAAV-AT1R-AS effectively reduced blood pressure by 30 mm Hg for at least 5 weeks compared with controls.

To test whether an AAV delivery of AT1R-AS would inhibit development of hypertension, we injected 5-day-old SHR. Hypertension in SHR develops between the eighth and tenth week after birth. Therefore, injecting in 5-day-old SHR allowed us to observe if the development of hypertension would be reduced. A single injection of AAV-AGT-AS in 5-day-old SHR significantly attenuated the full development44 and level of hypertension for up to 6 months. In 3-week-old SHR, rAAV-AT1R-AS significantly reduced hypertension by ≈30 mm Hg for at least 5 weeks (the length of...
the study). However, unlike the reports of the effect of retrovirus delivery of an AT1R-AS in 5-day-old SHR “curing” hypertension, we did not find a complete inhibition of the rise in blood pressure.

In rAAV-AGT-AS–treated SHR, measures of plasma AGT levels showed a corresponding lack of increase in AGT in the antisense–treated groups compared with the significant increase of AGT in the control animals. Correlation of AGT versus blood pressure was significant ($P < 0.05$) in the control–treated animals and not significant in the antisense–treated animals. This shows that AGT in the SHR is correlated with an increase in blood pressure. The AAV was expressed in kidney, heart, and liver throughout the time of the reduction in blood pressure. Thus, we concluded that the early treatment with a single dose of rAAV-AGT-AS, given systemically, prevents the full development of hypertension in adult SHR by a prolonged reduction in AGT levels. Similarly, the results with the rAAV-AT1-AS showed a reduction in hypertension development correlated with a consistent reduction in AT1Rs in vascular smooth muscle cells. No toxicity was noted. To prove the potential therapeutic value of rAAV, we have recently used a mouse model of hypertension that clearly depends on an overactive renin-angiotensin system. In this model, which has human renin and human AGT transgenes, rAAV-AS-AT1R reduced high blood pressure for up to 6 months with a single systemic injection. These latest data with rAAV-AT1R-AS confirm the results in adult SHR and give an even clearer picture that the AAV as vector has many advantages for hypertension therapy.

Other Vectors

Other vectors are being tested for hypertension gene therapy. As noted above, adenovirus vectors have been used with kallikrein gene insertion, and recently they have been used to deliver calcitonin in gene-related peptide for hypoxia-induced pulmonary hypertension in mice. However, the adenovirus synthesizes proteins that trigger the immune system and cause inflammation, which limits use in human therapy (eg, the clinical trial in Philadelphia). The Lesch-Nyhan simian virus (LNSV), a retrovirus, has been used to deliver antisense to AT1R by injection into newborn SHR to prevent the development of hypertension in the adults. Retroviruses are appropriate only for dividing cells and therefore are not suitable for hypertension therapy in adults. The LNSV could not be used to injection infants with AT1R-AS on the chance they might become hypertensive. Retroviruses may be useful in treating cardiomyopathy, restenosis, and vascular remodeling, in which cells are actively dividing, but retroviruses integrate randomly into the genome and the possibility of tumorigenesis is an unknown risk. Lentivirus vectors, which can infect dividing cells, are just beginning to be explored for therapeutic use. They offer large gene-carrying capacity, are stable, and are easily produced. The disadvantage is the risk of uncontrolled infection and the potential for neoplastic changes. Other vectors, such as herpes simplex virus and Japan Sendai virus, are being tested as vectors, but as yet, these vectors are only in limited use by certain labs.

Engineering Viruses

In addition to the choice of vectors, the control of transgene needs to be engineered and new promoters need to be explored before viral vectors can be used in humans. The ideal promoter will be active for prolonged periods to maintain transgene expression and specific for a tissue cell type. The vector will need mechanisms to switch them on or off as required (eg, in shock or hypotension). This is being tested with the tetracycline transactivator system, by which a transgene can be activated in the presence (or absence) of tetracycline. Ultimately the promoters and transactivating factors will have to be so specific that the antisense can be turned on in a specific tissue when the need arises.

Conclusion

There are 2 distinct approaches to gene therapy hypertension being developed with antisense inhibition. The ODNs offer the most druglike approach. They can be designed for action that lasts for a few days or a few weeks, depending on how they are delivered. They are gene specific for a target protein and reduce overactive proteins. Because antisense inhibition is never total, the oligos permit normal physiology. ODNs are not toxic at therapeutic doses, and there is no tachyphylaxis. At present we are using intravenous injections, but eventually they may be delivered orally or by skin patches and aerosol.

The AAV vector with antisense DNA has a very prolonged action (weeks or months, possibly years) with a single dose. The AAV is safe, nonpathogenic, noninflammatory, and extremely stable. There are many challenges before they can be used clinically. One is technical, including the production of large amounts at reasonable cost and the further engineering of the control of the vector, as described above. The other is the concern for the prolonged presence in the body of a rAAV. Will there be times when it needs to be rapidly switched off? Will the public accept it? Will companies support the development of a 1-shot therapeutic? Hypertension is often treated by drugs aimed at several targets, so the effect of combining antisense targets will also have to be tested.

This brief review of some of the preclinical data shows that gene therapy for hypertension is possible. It seems that of the 2 strategies, the AS-ODNs will be clinically acceptable first, because of our familiarity with drug treatments and their targets. The viral vector approach may come much later, when all the basic science has been done to assure that the patient is safe.

References


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