

College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. *J Am Coll Cardiol*. 2017 Nov 7. pii: S0735-1097(17)41517-8. doi: 10.1016/j.jacc.2017.11.004; and Whelton *et al.* (2017 ACC/AHA/AAPA/ABC/ACPM/AGS/APhA/ASH/ASPC/NMA/PCNA Guideline for the Prevention, Detection, Evaluation, and Management of High Blood Pressure in Adults: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. *J Am Coll Cardiol*. 2017 Nov 7. pii: S0735-1097(17)41519-1. doi: 10.1016/j.jacc.2017.11.006).

Despite the number of anti-hypertensive drugs available for treating hypertension, more than two-thirds of subjects are not controlled with one anti-hypertensive agent and require two or more anti-hypertensive agents selected from different drug classes. This further reduces the number of subjects with controlled blood pressure as adherence is reduced and side-effects are increased with increasing numbers of medications.

SUMMARY OF THE INVENTION

The present invention provides iRNA compositions which effect the RNA-induced silencing complex (RISC)-mediated cleavage of RNA transcripts of a gene encoding angiotensinogen (AGT). The AGT gene may be within a cell, *e.g.*, a cell within a subject, such as a human subject. The present invention also provides methods of using the iRNA compositions of the invention for inhibiting the expression of an AGT gene and/or for treating a subject who would benefit from inhibiting or reducing the expression of an AGT gene, *e.g.*, a subject suffering or prone to suffering from an AGT-associated disorder, *e.g.*, hypertension.

Accordingly, in an aspect, the invention provides a double stranded ribonucleic acid (dsRNA) agent for inhibiting expression of angiotensinogen (AGT) in a cell, wherein the dsRNA agent comprises a sense strand and an antisense strand forming a double stranded region, wherein the sense strand comprises at least 15, *e.g.*, 15, 16, 17, 18, 19, or 20, contiguous nucleotides differing by no more than 0, 1, 2, or 3 nucleotides from the nucleotide sequence of SEQ ID NO:1 or SEQ ID NO:3 and the antisense strand comprises at least 15, *e.g.*, 15, 16, 17, 18, 19, or 20, contiguous nucleotides differing by no more than 1, 2, or 3 nucleotides from the corresponding portion of the nucleotide sequence of SEQ ID NO:2 or SEQ ID NO:4.

In another aspect, the present invention provides a double stranded ribonucleic acid (dsRNA) agent for inhibiting expression of angiotensinogen (AGT) in a cell, wherein the dsRNA agent comprises a sense strand and an antisense strand forming a double stranded region, wherein the antisense strand comprises a region of complementarity to an mRNA encoding AGT, and wherein the region of complementarity comprises at least 15 contiguous nucleotides differing by no more than 3 nucleotides from any one of the antisense nucleotide sequences in any one of Tables 2-7.

In another aspect, the present invention provides a cell containing the dsRNA agent as described herein.

In another aspect, the present invention provides a pharmaceutical composition for inhibiting expression of a gene encoding angiotensinogen (AGT) comprising the dsRNA agent as described herein and a pharmaceutically acceptable carrier.

In another aspect, the present invention provides a use of the dsRNA agent as described herein, or the pharmaceutical composition as described herein in the manufacture of a medicament for inhibiting expression of an angiotensinogen (AGT) gene in a cell, wherein the medicament is to be contacted with the cell, thereby inhibiting expression of the AGT gene in the cell.

In another aspect, the present invention provides a use of the dsRNA agent as described herein, or the pharmaceutical composition as described herein in the manufacture of a medicament for treating a subject having a disorder that would benefit from reduction in angiotensinogen (AGT) expression, wherein the medicament is to be administered to the subject in a therapeutically effective amount.

In another aspect, the present invention provides a use of the dsRNA agent as described herein, or the pharmaceutical composition as described herein in the manufacture of a medicament for preventing at least one symptom in a subject having a disorder that would benefit from reduction in angiotensinogen (AGT) expression, wherein the medicament is to be administered to the subject in a prophylactically effective amount.

In another aspect, the present invention provides a kit comprising the dsRNA agent as described herein or the pharmaceutical composition as described herein.

In another aspect, the present invention provides a vial comprising the dsRNA agent as described herein or the pharmaceutical composition as described herein.

In another aspect, the present invention provides a syringe comprising the dsRNA agent as described herein or the pharmaceutical composition as described herein.

In another aspect, the present invention provides an RNA-induced silencing complex (RISC) comprising an antisense strand as described herein.

In another aspect, the present invention provides an in vitro method of inhibiting expression of an angiotensinogen (AGT) gene in a cell, the method comprising contacting the cell with the dsRNA agent as described herein, or the pharmaceutical composition as described herein, thereby inhibiting expression of the AGT gene in the cell.

In another aspect, the present invention provides the dsRNA agent as described herein, or the pharmaceutical composition as described herein for use in therapy.

In another aspect, the present invention provides a double stranded ribonucleic acid (dsRNA) for inhibiting expression of angiotensinogen (AGT) in a cell, wherein said dsRNA comprises a sense strand and an antisense strand forming a double stranded region, wherein the antisense strand comprises a region of complementarity to an mRNA encoding AGT, and wherein the region of complementarity comprises at least 15, *e.g.*, 15, 16, 17, 18, 19, or 20, contiguous nucleotides differing by no more than 0, 1, 2, or 3 nucleotides from any one of the antisense nucleotide sequences in any one of Tables 2-7.