SUMMARY ~~OF THE INVENTION~~

[0006] Provided herein are compositions, methods and kits useful for modulating expression of target genes in the Toll-like receptor pathway. In various ~~aspects~~ embodiments provided are nucleic acid molecule inhibitors of a mammalian gene selected from the group consisting of TLR2, TLR4, MYD88, TICAM1 and TIRAP, having mRNA polynucleotide sequences set forth in SEQ ID NOS: 1-12 which include SEQ ID NO:1 (TLR2 mRNA); SEQ ID NO:2-4 (TLR4 mRNA), SEQ ID NO:5-9 (MYD88 mRNA), SEQ ID NO:10 (TICAM1 mRNA) or SEQ ID NO:11-12 (TIRAP mRNA).

[0006a] In one aspect, there is provided a double stranded nucleic acid molecule comprising a sense strand and an antisense strand wherein the strands are described as TLR2_34 (SEQ ID NOS:20613 and 20620).

[0007] In particular embodiments provided herein are novel double stranded nucleic acid molecules, in particular double-stranded RNA (dsRNA), that inhibit, down-regulate or reduce expression of a gene selected from the group consisting of TLR2, TLR4, MYD88, TICAM1 and TIRAP, and pharmaceutical compositions comprising one or more such oligonucleotides or a vector capable of expressing the oligonucleotide. Further provided herein are methods for treating inflammation and inflammatory diseases and graft rejection associated with organ transplantation, such as lung transplantation, in which expression of one or more of the TLR2, TLR4, MYD88, TICAM1 and TIRAP genes is associated with the etiology or progression of inflammation and graft rejection associated with organ transplantation.

[0008] In some ~~aspects and~~ embodiments the double stranded oligonucleotides are chemically modified dsRNA compounds. In some embodiments the dsRNA sense and antisense oligonucleotides are selected from sense oligonucleotides and corresponding antisense oligonucleotides set forth in SEQ ID NOS:13-5846 (targeting TLR2), SEQ ID NOS:5847-12144 (targeting TLR4), SEQ ID NOS:12145-16332 (targeting MYD88), SEQ ID NOS:16333-18242 (targeting TICAM1) and SEQ ID NOS:18243-20606 (targeting TIRAP) .

[0009] Accordingly, in one ~~aspect~~ embodiment provided herein is a nucleic acid molecule having the following double-stranded Structure:

(A1) 5' (N)x – Z 3' (antisense strand)

3' Z'-(N')y –z" 5' (sense strand)

[0091] In one embodiment the double stranded nucleic acid molecule comprises an antisense strand and a sense strand selected from pairs of oligonucleotides set forth in set forth in SEQ ID NOS:13-5846 (targeting TLR2), SEQ ID NOS:5847-12144 (targeting TLR4), SEQ ID NOS:12145-16332 (targeting MYD88), SEQ ID NOS:16333-18242 (targeting TICAM1) and SEQ ID NOS:18243-20606 (targeting TIRAP), or preferably oligonucleotide pairs set forth in Tables 1-5, *infra*, the sense strand includes at least one 2'-OMe sugar modified pyrimidine ribonucleotide, a C3OH or C3Pi non-nucleotide moiety covalently attached at the 3' terminus and a cap moiety such as an inverted abasic deoxyribonucleotide moiety covalently attached at the 5' terminus; and the antisense strand includes at least one 2'-OMe sugar modified pyrimidine ribonucleotide, a 2'5' ribonucleotide in position 6; and a nucleotide or C3Pi-C3OH moiety covalently attached at the 3' terminus.

[0092] In some embodiments the nucleotide moiety covalently attached at the 3' terminus comprises the dinucleotide dTdT.

[0093] According to one ~~aspect~~embodiment, the present ~~invention~~disclosure provides a method of generating a double stranded RNA molecule consisting of a sense strand and an antisense strand having oligonucleotide sequences forth in SEQ ID NOS:13-3060 to target TLR2; SEQ ID NOS:5847-8612 to target TLR4; SEQ ID NOS:12145-13924 to target MYD88; SEQ ID NOS:16333-16882 to target TICAM1; or SEQ ID NOS:18243-19046 to target TIRAP, the method comprising the steps

a) synthesizing a sense strand;

b) synthesizing an antisense strand;

c) annealing the sense strand to the antisense strand;

thereby generating a double stranded RNA molecule. In some embodiment the synthesis includes synthesis of a chemically unmodified dsRNA strand. In some embodiments synthesis includes incorporation of modified nucleotides including 2'-OMe sugar modified ribonucleotides or unconventional moieties including 2'5' linked nucleic acid, abasic and inverted abasic moieties and the like.

[0094] In some embodiments, neither (N)x nor (N')y are phosphorylated at the 3' and 5' termini. In other embodiments either or both (N)x and (N')y are phosphorylated at the 3' termini.

[0094a] In one aspect, there is provided a pharmaceutical composition comprising the double stranded nucleic acid molecule as defined herein in an amount effective to inhibit gene expression, and a pharmaceutically acceptable carrier, wherein the gene encodes an RNA having a polynucleotide sequence set forth in SEQ ID NOS:1.

[0095] In ~~a second aspect~~ one embodiment, provided herein are pharmaceutical compositions comprising one or more double stranded molecules as disclosed herein, in an amount effective to inhibit target gene expression, and a pharmaceutically acceptable carrier wherein the target gene is selected from a gene having a mRNA set forth in SEQ ID NOS:1-12.

[0096] In another ~~aspect~~embodiment provided is a cell comprising one or more double stranded molecule as disclosed herein in an amount effective to inhibit target gene expression.

[0097] In various embodiments the compound comprises an antisense oligonucleotide (N)x and a corresponding sense oligonucleotide, the oligonucleotide pairs set forth in SEQ ID NOS:13-5846 (targeting TLR2), SEQ ID NOS:5847-12144 (targeting TLR4), SEQ ID NOS:12145-16332 (targeting MYD88), SEQ ID NOS:16333-18242 (targeting TICAM1) and SEQ ID NOS:18243-20606 (targeting TIRAP), or preferably oligonucleotide pairs set forth in Tables 1-5, *infra*.

[0098] In other ~~aspects~~embodiments disclosed are oligonucleotide compounds useful in preventing or treating chronic or acute aseptic inflammation, neuropathic pain, primary graft failure, ischemia-reperfusion injury, reperfusion injury, reperfusion edema, allograft dysfunction, pulmonary reimplantation response and/or primary graft dysfunction (PGD) in organ transplantation, such as lung transplantation in a subject in need thereof.

[0099] In another ~~aspect~~embodiment, provided is a method for the treatment of a subject in need of treatment for a disease or disorder or symptom or condition associated with the disease or disorder, associated with the expression of a target gene comprising administering to the subject an amount of a double stranded molecule as disclosed herein which reduces or inhibits expression of a target gene. In preferred embodiments the double stranded molecule is chemically modified as described herein.

[00100] Also provided is a double stranded molecule as described herein for the treatment of a disease or injury selected from chronic or acute aseptic inflammation, neuropathic pain, primary graft failure, ischemia-reperfusion injury, reperfusion injury, reperfusion edema, allograft dysfunction, pulmonary reimplantation response and/or primary graft dysfunction (PGD) in organ transplantation, such as lung transplantation.

[00101] Further provided is a double stranded molecule as described herein for the preparation of a medicament for the treatment of a disease or injury selected from chronic or

acute aseptic inflammation, neuropathic pain, primary graft failure, ischemia-reperfusion injury, reperfusion injury, reperfusion edema, allograft dysfunction, pulmonary reimplantation response and/or primary graft dysfunction (PGD) in organ transplantation, such as lung transplantation.

[00101a] In one aspect, there is provided the use of the double stranded nucleic acid molecule as defined herein in preparing a medicament for the treatment of a subject in need of treatment for a posttransplantational disease or disorder or symptom or condition associated with the expression of a target gene, wherein the target gene encodes an RNA having a polynucleotide sequence set forth in SEQ ID NO:1.

[00101b] In one aspect, there is provided the use of a composition as defined herein in preparing a medicament for the treatment of a subject in need of treatment for a posttransplantational disease or disorder or symptom or condition associated with the expression of a target gene, wherein the target gene encodes an RNA having a polynucleotide sequence set forth in SEQ ID NO:1.

[00101c] In one aspect, there is provided the use of a double stranded nucleic acid molecule as defined herein in preparing a medicament for treating or preventing the incidence or severity of a posttransplantational complication selected from the group consisting of primary graft failure, ischemia-reperfusion injury, reperfusion injury, reperfusion edema, allograft dysfunction, pulmonary reimplantation response, primary graft dysfunction (PGD), in a subject in need thereof wherein the complication is associated with expression of a gene encoding an RNA having a polynucleotide sequence set forth in SEQ ID NO:1.

[00101d] In one aspect, there is provided the use of a composition as defined herein in preparing a medicament for treating or preventing the incidence or severity of a posttransplantational complication selected from the group consisting of primary graft failure, ischemia-reperfusion injury, reperfusion injury, reperfusion edema, allograft dysfunction, pulmonary reimplantation response, primary graft dysfunction (PGD), in a subject in need thereof wherein the complication is associated with expression of a gene encoding a RNA having a polynucleotide sequence set forth in SEQ ID NO:1.

[00102] In other ~~aspects~~ embodiments the disclosure relates to methods for treating or preventing the incidence or severity of a posttransplantational (e.g. following lung transplantation) complication selected from, without being limited to, primary graft failure, ischemia-reperfusion injury, reperfusion injury, reperfusion edema, allograft dysfunction, pulmonary reimplantation response and/or primary graft dysfunction (PGD), in a subject in need thereof wherein the complication is associated with expression of a gene selected from a gene set forth in Table A1. Such methods involve administering to a mammal in need of such treatment a prophylactically or therapeutically effective amount of one or more double stranded molecules disclosed herein to inhibit or reduce expression or activity of at least one such gene. In other ~~aspects~~embodiments the disclosure relates to methods for reducing acute or chronic inflammation in a subject in need thereof wherein the inflammation is associated with expression of a gene selected from a gene set forth in Table A1. Such methods involve

administering to a mammal in need of such treatment a prophylactically or therapeutically effective amount of one or more double stranded molecules disclosed herein to inhibit or reduce expression or activity of at least one such gene.

[00103] In some embodiments posttransplantational complication is present in an organ transplant recipient (such as a lung transplantation recipient) and the target gene is selected from TLR2, TLR4, MYD88, TICAM1 and TIRAP, having mRNA polynucleotide sequences set forth in SEQ ID NOS: 1-12. Sense and antisense oligonucleotide pairs useful in preparing dsRNA for inhibiting expression of TLR2, TLR4, MYD88, TICAM1 and TIRAP are set forth in SEQ ID NOS: 13-5846 (targeting TLR2), SEQ ID NOS:5847-12144 (targeting TLR4), SEQ ID NOS: 12145-16332 (targeting MYD88), SEQ ID NOS: 16333-18242 (targeting TICAM1) and SEQ ID NOS: 18243-20606 (targeting TIRAP) or preferably oligonucleotide pairs set forth in Tables 1-5, infra.

[00104] The methods, materials, and examples that will now be described are illustrative only and are not intended to be limiting; materials and methods similar or equivalent to those described herein can be used in practice or testing of the ~~invention~~disclosure. Other features and

advantages of the ~~invention~~disclosure will be apparent from the following detailed description, and from the claims.

[00105] This disclosure is intended to cover any and all adaptations or variations of combination of features that are disclosed in the various embodiments herein. Although specific embodiments have been illustrated and described herein, it should be appreciated that the invention encompasses any arrangement of the features of these embodiments to achieve the same purpose. Combinations of the above features, to form embodiments not specifically described herein, will be apparent to those of skill in the art upon reviewing the instant description.

DETAILED DESCRIPTION OF THE INVENTION

[00106] The present invention relates in general to compounds which down-regulate expression of certain target genes associated with posttransplantational (e.g. following lung transplantation) complications and their use in treating a subject suffering from diseases or disorders associated with such posttransplantational complications. Inhibition of expression of the one or more of the target genes selected from TLR2, TLR4, MYD88, TICAM1 and TIRAP is now shown to be beneficial in treating a subject suffering from an adverse effect of organ transplantation, for example lung transplantation; more specifically from a posttransplantational (e.g. following lung transplantation) complication selected from, without being limited to, primary graft failure, ischemia-reperfusion injury, reperfusion injury, reperfusion edema, allograft dysfunction, pulmonary reimplantation response and/or primary graft dysfunction (PGD). The present invention relates in particular to small double stranded RNA compounds, such as interfering RNA (siRNA) compounds which inhibit expression of TLR2, TLR4, MYD88, TICAM1 and TIRAP, and to the use of these siRNA compounds in the treatment of certain diseases and disorders. Preferred sense and antisense oligonucleotides useful in the preparation of dsRNA compounds are set forth in SEQ ID NOS:13-5846 (targeting TLR2), SEQ ID NOS:5847-12144 (targeting TLR4), SEQ ID NOS:12145-16332 (targeting MYD88), SEQ ID NOS:16333-18242 (targeting TICAM1) and SEQ ID NOS:18243-20606 (targeting TIRAP).

[00107] Compounds, compositions and methods for inhibiting target genes having mRNA set forth in any one of SEQ ID NOS:1-12 are discussed herein at length, and any of said compounds and/or compositions are beneficially employed in the treatment of a patient

CLAIMS

1. A double stranded nucleic acid molecule comprising a sense strand and an antisense strand wherein the strands are described as TLR2_34 (SEQ ID NOS:20613 and 20620).

2. The double stranded nucleic acid molecule according to claim 1 having the following structure:

(A2) 5' N^1-(N)x - Z 3' (antisense strand)

3' Z'-N^2-(N')y –z" 5' (sense strand)

wherein each N^2, N and N' is an unmodified or modified ribonucleotide, or an unconventional moiety;

wherein each of (N)x and (N')y is an oligonucleotide in which each consecutive N or N' is joined to the adjacent N or N' by a covalent bond;

wherein each of x and y is independently an integer between 17 and 24;

wherein the sequence of (N')y is complementary to the sequence of (N)x and (N)x is complementary to a consecutive sequence in a target RNA set forth in SEQ ID NO:1 (TLR2 mRNA);

wherein N^1 is covalently bound to (N)x and is mismatched to the target RNA;

wherein z" may be present or absent, but if present is a capping moiety covalently attached at the 5' terminus of N^2- (N')y;

wherein each of Z and Z' is independently present or absent, but if present is independently 1-5 consecutive nucleotides, consecutive non-nucleotide moieties or a combination thereof covalently attached at the 3' terminus of the strand in which it is present; and

wherein N^1 -(N)x and N^2- (N')y are the oligonucleotides described as TLR2_34 (SEQ ID NOS:20613 and 20620).

3. The double stranded nucleic acid molecule of claims 2 wherein Z is covalently attached to the 3' terminus of N^1-(N)x and comprises a non-nucleotide moiety selected from the group consisting of C3OH, C3Pi, C3Pi-C3OH and C3Pi-C3Pi.

4. The double stranded nucleic acid molecule of claim 3 wherein z" is covalently attached to the 5' terminus of N^2-(N')y and is selected from the group consisting of: an inverted abasic deoxyribose moiety, an inverted abasic ribose moiety, an abasic deoxyribose moiety, an abasic ribose moiety, a C3 moiety, L-DNA or L-RNA.

5. The double stranded nucleic acid molecule of claim 4 wherein Z' comprises a C3 moiety or a 3' terminal phosphate (Pi).

6. The double stranded nucleic acid molecule claim 5 wherein N' in at least one of positions 7, 8, 9 or 10 from the 5' terminus of N^2-(N')y is selected from a threose nucleic acid moiety, a 2'5' nucleotide and pseudoUridine.

7. The double stranded nucleic acid molecule of claim 2 wherein the sense strand includes at least one 2'-OMe sugar modified pyrimidine ribonucleotide, a C3OH moiety covalently attached at the 3' terminus, and a cap moiety covalently attached at the 5' terminus; and wherein the antisense strand includes at least one 2'-OMe sugar modified pyrimidine ribonucleotide, a TNA or 2'-5' ribonucleotide at position 7 (5'>3'); and a nucleotide or C3Pi-C3OH non-nucleotide moiety covalently attached at the 3' terminus.

8. A pharmaceutical composition comprising the double stranded nucleic acid molecule of any of claims 1-7 in an amount effective to inhibit gene expression, and a pharmaceutically acceptable carrier, wherein the gene encodes an RNA having a polynucleotide sequence set forth in SEQ ID NOS:1.

9. Use of the double stranded nucleic acid molecule of any of claims 1-7 in preparing a medicament for the treatment of a subject in need of treatment for a posttransplantational disease or disorder or symptom or condition associated with the expression of a target gene, wherein the target gene encodes an RNA having a polynucleotide sequence set forth in SEQ ID NO:1.

10. Use of a composition according to claim 8 in preparing a medicament for the treatment of a subject in need of treatment for a posttransplantational disease or disorder or symptom or condition associated with the expression of a target gene, wherein the target gene encodes an RNA having a polynucleotide sequence set forth in SEQ ID NO:1.

11. The use of claim 9 or 10, wherein posttransplantational disease or disorder or symptom or condition is disease or disorder or symptom or condition following lung transplantation.

12. The use of claim 9 or 10, wherein the disease or injury is selected from the group consisting of primary graft failure, ischemia-reperfusion injury, reperfusion injury, reperfusion edema, allograft dysfunction, pulmonary reimplantation response and primary graft dysfunction (PGD) in organ transplantation.

13. The use of claim 12, wherein the disease or injury comprises primary graft dysfunction (PGD) in organ transplantation.

14. The use of claim 13, wherein said organ transplantation comprises lung transplantation.

15. Use of a double stranded nucleic acid molecule of any of claims 1-7 in preparing a medicament for treating or preventing the incidence or severity of a posttransplantational complication selected from the group consisting of primary graft failure, ischemia-reperfusion injury, reperfusion injury, reperfusion edema, allograft dysfunction, pulmonary reimplantation response, primary graft dysfunction (PGD), in a subject in need thereof wherein the complication is associated with expression of a gene encoding an RNA having a polynucleotide sequence set forth in SEQ ID NO:1.

16. Use of a composition according to claim 8 in preparing a medicament for treating or preventing the incidence or severity of a posttransplantational complication selected from the group consisting of primary graft failure, ischemia-reperfusion injury, reperfusion injury, reperfusion edema, allograft dysfunction, pulmonary reimplantation response, primary graft dysfunction (PGD), in a subject in need thereof wherein the complication is associated with expression of a gene encoding a RNA having a polynucleotide sequence set forth in SEQ ID NO:1.

17. The use of claim 15 or 16, wherein the posttransplantational complication is complication following lung transplantation.

CLAIMS

1. A double stranded nucleic acid molecule comprising a sense strand and an antisense strand wherein the strands are selected from the oligonucleotides described as TLR2_25 (SEQ ID NOS:20607 and 20614), TLR2_28 (SEQ ID NOS:20608 and 20615), TLR2_42 (SEQ ID NOS:20609 and 20616), TLR2_43 (SEQ ID NOS:20610 and 20617), TLR2_47 (SEQ ID NOS:20611 and 20618), TLR2_31 (SEQ ID NOS:20612 and 20619), TLR2_34 (SEQ ID NOS:20613 and 20620).

2. A double stranded nucleic acid molecule comprising a sense strand and an antisense strand wherein the strands are selected from the oligonucleotides described as TLR4_08 (SEQ ID NOS:20621 and 20630), TLR4_10 (SEQ ID NOS:20622 and 20631), TLR4_11 (SEQ ID NOS:20623 and 20632), TLR4_14 (SEQ ID NOS:20624 and 20633), TLR4_15 (SEQ ID NOS:20625 and 20634), TLR4_28 (SEQ ID NOS:20626 and 20635), TLR4_29 (SEQ ID NOS:20627 and 20636), TLR4_31 (SEQ ID NOS:20628 and 20637), TLR4_33 (SEQ ID NOS:20629 and 20638).

3. A double stranded nucleic acid molecule comprising a sense strand and an antisense strand wherein the strands are selected from the oligonucleotide described as MYD88_11 (SEQ ID NOS:12178 and 12660)

4. A double stranded nucleic acid molecule comprising a sense strand and an antisense strand wherein the strands are selected from the oligonucleotides described as TICAM1_20 (SEQ ID NOS:20644 and 20655), TICAM1_15 (SEQ ID NOS:20639 and 20650), TICAM1_16 (SEQ ID NOS:20640 and 20651), TICAM1_17 (SEQ ID NOS:20641 and 20652), TICAM1_18 (SEQ ID NOS:20642 and 20653); TICAM1_19 (SEQ ID NOS:20643 and 20654); TICAM1_21 (SEQ ID NOS:20645 and 20656), TICAM1_22 (SEQ ID NOS:20646 and 20657), TICAM1_23 (SEQ ID NOS:20647 and 20658), TICAM1_24 (SEQ ID NOS:20448 and 20659), TICAM1_25 (SEQ ID NOS:20649 and 20660).

5. A double stranded nucleic acid molecule comprising a sense strand and an antisense strand wherein the sense and antisense strands are selected from the oligonucleotides described as TIRAP_16 (SEQ ID NOS:20661 and 20673), TIRAP_17 (SEQ ID NOS:20662 and 20674), TIRAP_18 (SEQ ID NOS:20663 and 20675); TIRAP_19 (SEQ ID NOS:20664 and 20676); TIRAP_20 (SEQ ID NOS:20665 and 20677), TIRAP_21 (SEQ ID NOS:20666 and 20678), TIRAP_22 (SEQ ID NOS:20667 and 20679), TIRAP_23 (SEQ ID NOS:20668

and 20680), TIRAP_24 (SEQ ID NOS:20669 and 20681), TIRAP_25 (SEQ ID NOS:20670 and 20682), TIRAP_26 (SEQ ID NOS:20671 and 20683) and TIRAP_27 (SEQ ID NOS:20672 and 20684).

6. A double stranded nucleic acid molecule comprising a sense strand and an antisense strand wherein the strands are selected from oligonucleotide pairs set forth in SEQ ID NOS:13-5846 (targeting TLR2), SEQ ID NOS:5847-12144 (targeting TLR4), SEQ ID NOS:12145-16332 (targeting MYD88), SEQ ID NOS:16333-18242 (targeting TICAM1) and SEQ ID NOS:18243-20606 (targeting TIRAP).

7. A double stranded nucleic acid molecule having the following structure:

(A1) 5' (N)x – Z 3' (antisense strand)

3' Z'-(N')y –z" 5' (sense strand)

wherein each N and N' is a nucleotide which may be unmodified or modified, or an unconventional moiety;

wherein each of (N)x and (N')y is an oligonucleotide in which each consecutive N or N' is joined to the next N or N' by a covalent bond;

wherein each of Z and Z' is independently present or absent, but if present independently comprises 1-5 consecutive nucleotides or non-nucleotide moieties or a combination thereof covalently attached at the 3' terminus of the strand in which it is present;

wherein z" may be present or absent, but if present is a capping moiety covalently attached at the 5' terminus of (N')y;

wherein each of x and y is independently an integer between 18 and 25;

wherein the sequence of (N')y is complementary to the sequence of (N)x; and (N)x comprises an antisense sequence to a target RNA set forth in any one of SEQ ID NO:1 (TLR2 mRNA); SEQ ID NO:2-4 (TLR4 mRNA), SEQ ID NO:5-9 (MYD88 mRNA), SEQ ID NO:10 (TICAM1 mRNA) or SEQ ID NO:11-12 (TIRAP mRNA).

8. The double stranded nucleic acid molecule of claim 7 wherein (N)x and (N')y comprise the sense sequence and complementary antisense sequence set forth in SEQ ID NOS:13-1448 or 1449-3060 (targeting TLR2); or SEQ ID NOS:5847-8320 or 8321-8612 (targeting TLR4); or SEQ ID NOS:12145-13108 or 13109-13924 (targeting MYD88); or SEQ ID

NOS:16333-16866 or 16867-16882 (targeting TICAM1); or SEQ ID NOS:18243-19010 or 19011-19046 (targeting TIRAP).

9. The double stranded nucleic acid molecule of claim 8 wherein (N)x and (N')y are selected from the oligonucleotides described as TLR2_25 (SEQ ID NOS:20607 and 20614), TLR2_28 (SEQ ID NOS:20608 and 20615), TLR2_42 (SEQ ID NOS:20609 and 20616), TLR2_43 (SEQ ID NOS:20610 and 20617), TLR2_47 (SEQ ID NOS:20611 and 20618).

10. The double stranded nucleic acid molecule of claim 8 wherein (N)x and (N')y are selected from the oligonucleotides described as TLR4_08 (SEQ ID NOS:20621 and 20630), TLR4_10 (SEQ ID NOS:20622 and 20631), TLR4_11 (SEQ ID NOS:20623 and 20632), TLR4_14 (SEQ ID NOS:20624 and 20633), TLR4_15 (SEQ ID NOS:20625 and 20634), TLR4_28 (SEQ ID NOS:20626 and 20635), TLR4_29 (SEQ ID NOS:20627 and 20636), TLR4_31 (SEQ ID NOS:20628 and 20637), TLR4_33 (SEQ ID NOS:20629 and 20638).

11. The double stranded nucleic acid molecule of claim 8 wherein (N)x and (N')y are selected from the oligonucleotides described as MYD88_11 (SEQ ID NOS:12178 and 12660); TICAM1_20 (SEQ ID NOS:20644 and 20655); or TIRAP_16 (SEQ ID NOS:20661 and 20673).

12. The double-stranded molecule of claim 7 wherein the molecule comprises a mismatch to the target mRNA at the 5' terminal nucleotide of (N)x (antisense strand).

13. The double stranded nucleic acid molecule of claim 12 having the following structure:

(A2) 5' N^1-(N)x - Z 3' (antisense strand)

3' Z'-N^2-(N')y –z" 5' (sense strand)

wherein each N^2, N and N' is an unmodified or modified ribonucleotide, or an unconventional moiety;

wherein each of (N)x and (N')y is an oligonucleotide in which each consecutive N or N' is joined to the adjacent N or N' by a covalent bond;

wherein each of x and y is independently an integer between 17 and 24;

wherein the sequence of (N')y is complementary to the sequence of (N)x and (N)x is complementary to a consecutive sequence in a target RNA set forth in any one of SEQ ID NO:1 (TLR2 mRNA); SEQ ID NO:2-4 (TLR4 mRNA), SEQ ID NO:5-9 (MYD88 mRNA),

~~SEQ ID NO:10 (TICAM1 mRNA) or SEQ ID NO:11-12 (TIRAP mRNA);~~

wherein N^1 is covalently bound to (N)x and is mismatched to the target RNA or is a complementary DNA moiety to the target RNA;

wherein N^1 is a moiety selected from the group consisting of unmodified or modified nucleotides selected from uridine (rU), deoxyribouridine (dU), ribothymidine (rT), deoxyribothymidine (dT), adenosine (rA) and deoxyadenosine (dA);

wherein z" may be present or absent, but if present is a capping moiety covalently attached at the 5' terminus of N^2- (N')y; and

wherein each of Z and Z' is independently present or absent, but if present is independently 1-5 consecutive nucleotides, consecutive non-nucleotide moieties or a combination thereof covalently attached at the 3' terminus of the strand in which it is present.

14. The double stranded nucleic acid molecule of claim 13 wherein (N)x and (N')y comprise the sense sequence and complementary antisense sequence set forth in SEQ ID NOS:3061-5260 or 5261-5846 (targeting TLR2); SEQ ID NOS:8613-12040 or 12041-12144 (targeting TLR4); SEQ ID NOS:13925-15910 or 15911-16332 (targeting MYD88); SEQ ID NOS:16883-18236 or 18237-18242 (targeting TICAM1) or SEQ ID NOS:19047-20590 or 20591-20606 (targeting TIRAP).

15. The double stranded nucleic acid molecule of claim 13 wherein N^1 -(N)x and N^2- (N')y are selected from the oligonucleotides described as TLR2_31 (SEQ ID NOS:20612 and 20619), TLR2_34 (SEQ ID NOS:20613 and 20620).

16. The double stranded nucleic acid molecule of claim 13 wherein N^1 -(N)x and N^2- (N')y are selected from the oligonucleotides described as TICAM1_15 (SEQ ID NOS:20639 and 20650), TICAM1_16 (SEQ ID NOS:20640 and 20651), TICAM1_17 (SEQ ID NOS:20641 and 20652), TICAM1_18 (SEQ ID NOS:20642 and 20653); TICAM1_19 (SEQ ID NOS:20643 and 20654); TICAM1_21 (SEQ ID NOS:20645 and 20656), TICAM1_22 (SEQ ID NOS:20646 and 20657), TICAM1_23 (SEQ ID NOS:20647 and 20658), TICAM1_24 (SEQ ID NOS:20448 and 20659), TICAM1_25 (SEQ ID NOS:20649 and 20660).

17. The double stranded nucleic acid molecule of claim 13 wherein N^1 -(N)x and N^2- (N')y are selected from the oligonucleotides described as TIRAP_17 (SEQ ID NOS:20662 and

20674); TIRAP_18 (SEQ ID NOS:20663 and 20675); TIRAP_19 (SEQ ID NOS:20664 and 20676); TIRAP_20 (SEQ ID NOS:20665 and 20677), TIRAP_21 (SEQ ID NOS:20666 and 20678), TIRAP_22 (SEQ ID NOS:20667 and 20679), TIRAP_23 (SEQ ID NOS:20668 and 20680), TIRAP_24 (SEQ ID NOS:20669 and 20681), TIRAP_25 (SEQ ID NOS:20670 and 20682), TIRAP_26 (SEQ ID NOS:20671 and 20683) and TIRAP_27 (SEQ ID NOS:20672 and 20684).

18. The double stranded nucleic acid molecule of any of claims 7-17 wherein the covalent bond joining each consecutive N or N' is a phosphodiester bond.

19. The double stranded nucleic acid molecule of claim 7 wherein x = y and each of x and y is 19, 20, 21, 22 or 23.

20. The double stranded nucleic acid molecule of claim 19 wherein x = y =19.

21. The double stranded nucleic acid molecule of claim 13 wherein x = y and each of x and y is 18, 19, 20, 21 or 22.

22. The double stranded nucleic acid molecule of claim 21 wherein x = y =18.

23. The double stranded nucleic acid molecule of claim 7–12 wherein the sequence of (N')y is fully complementary to the sequence of (N)x.

24. The double stranded nucleic acid molecule of claim 13 wherein the sequence of N^2-(N')y is fully complementary to the sequence of N^1-(N)x.

25. The double stranded nucleic acid molecule of claim 13 wherein N^1 and N^2 form at least one hydrogen bond.

26. The double stranded nucleic acid molecule of claim 25 wherein N^1 and N^2 form a Watson-Crick base pair.

27. The double stranded nucleic acid molecule of claim 13 wherein N^1 and N^2 form a non-Watson-Crick base pair.

28. The double stranded nucleic acid molecule of claim 26 or 27 wherein N^1 and N^2 form a base pair between a ribonucleotide and a deoxyribonucleotide.

29. The double stranded nucleic acid molecule of claim 28 wherein N^1 is covalently bound to (N)x and comprises a DNA moiety complementary to the target RNA.

30. The double stranded nucleic acid molecule of claim 13 wherein N^1 is selected from an unmodified or modified adenosine, deoxyadenosine, deoxyuridine, ribothymidine or deoxythymidine, and the pairing nucleotide in the target RNA is adenosine.

31. The double stranded nucleic acid molecule of claim 13 wherein N^1 is selected from an unmodified or modified adenosine, deoxyadenosine, uridine, deoxyuridine, ribothymidine or deoxythymidine and the pairing nucleotide in the target RNA is cytidine.

32. The double stranded nucleic acid molecule of claim 13 wherein N^1 is selected from an unmodified or modified adenosine, deoxyadenosine, uridine, deoxyuridine, ribothymidine or deoxythymidine and the pairing nucleotide in the target RNA is guanosine.

33. The double stranded nucleic acid molecule of claim 13 wherein N^1 is selected from an deoxyadenosine, deoxyuridine, ribothymidine or deoxythymidine and wherein the nucleotide in the pairing nucleotide in the target RNA is uridine.

34.The double stranded nucleic acid molecule of claim 13 wherein N^1 is selected from adenosine and deoxyadenosine and N^2 is uridine and N^1 and N^2 form a base pair.

35. The double stranded nucleic acid molecule of claim 13 wherein N^1 is selected from uridine or deoxyuridine and N^2 is selected from deoxyadenosine or adenosine and N^1 and N^2 form a base pair.

36. The double stranded nucleic acid molecule of claim 28 wherein N^1 comprises adenosine and N^2 comprises uridine and N^1 and N^2 form a base pair.

37. The double stranded nucleic acid molecule of any of claims 7-36 wherein at least one of N or N' comprises a modified nucleotide or an unconventional moiety.

38. The double stranded nucleic acid molecule of claim 37 wherein at least one of the pyrimidine ribonucleotides in (N)x or N^1-(N)x comprises a 2' sugar modified pyrimidine ribonucleotide.

39. The double stranded nucleic acid molecule of claim 38 the 2' sugar modified ribonucleotide comprises a 2'-OMe sugar modified ribonucleotide.

40. The double stranded nucleic acid molecule of any of claims 7-39 wherein in (N)x or N^1-(N)x, N in positions 1, 3, 5, 9, 11, 13, 15, 17 and 19 (5'>3') comprises 2'-OMe sugar

modified ribonucleotides and N in positions 2, 4, 6, 8, 10, 12, 14, 16, and 18 (5'>3') comprises unmodified ribonucleotides.

41. The double stranded nucleic acid molecule of any of claims 7-39 wherein in (N)x or N^1-(N)x, N in positions 2, 4, 6, 8, 11, 13, 15, 17 and 19 (5'>3') comprises 2'-OMe sugar modified ribonucleotides.

42. The double stranded nucleic acid molecule of any of claims 7-41 wherein Z is covalently attached to the 3' terminus of (N)x or N^1-(N)x and comprises a non-nucleotide moiety selected from the group consisting of C3OH, C3Pi, C3Pi-C3OH and C3Pi-C3Pi.

43. The double stranded nucleic acid molecule of any of claims 7-41 wherein Z is covalently attached to the 3' terminus of (N)x or N^1-(N)x and comprises a dinucleotide dTdT.

44. The double stranded nucleic acid molecule of any of claims 7-43 wherein N' in at least one of positions 7, 8, 9 or 10 from the 5' terminus of (N')y or N^2-(N')y is selected from a threose nucleic acid moiety, a 2'5' nucleotide and pseudoUridine.

45. The double stranded nucleic acid molecule of any of claims 7-44 wherein N' comprises a threose nucleic acid (TNA) moiety or a 2'5' nucleotide in 4, 5, or 6 consecutive positions starting at the 3' terminal or 3' penultimate positions in (N')y or N^2-(N')y.

46. The double stranded nucleic acid molecule of any of claims 7-45 wherein z" is covalently attached to the 5' terminus of (N')y or N^2-(N')y and is selected from the group consisting of an inverted abasic deoxyribose moiety, an inverted abasic ribose moiety, an abasic deoxyribose moiety, an abasic ribose moiety, a C3 moiety, L-DNA or L-RNA.

47. The double stranded nucleic acid molecule of any of claims 7-46 wherein Z' is covalently attached to the 3' terminus of (N')y or N^2-(N')y and is selected from the group consisting of an C3OH, C3Pi, C3Pi-C3OH, and C3Pi-C3Pi.

48. The double stranded nucleic acid molecule of claims 7-47 comprises a TNA moiety in position 5, a TNA moiety in position 6, a TNA moiety in position 7, a TNA moiety in position 8, a TNA moiety in position 9, TNA moieties in positions 5-6, TNA moieties in positions 6-7, TNA moieties in positions 7-8, TNA moieties in positions 8-9, TNA moieties in positions 5-7, TNA moieties in positions 6-8, TNA moieties in positions 7-9, TNA moieties in positions 5-8, TNA moieties in positions 6-9 or TNA moieties in positions 5-9.

49. The double stranded nucleic acid molecule of any of claims 7-47 wherein (N)x or N^1-(N)x comprises a 2'-5' nucleotide in position 5, a 2'-5' nucleotide in position 6, a 2'-5' nucleotide in position 7, a 2'-5' nucleotide in position 8, a 2'-5' nucleotide in position 9, 2'-5' nucleotides in positions 5-6, 2'-5' nucleotides in positions 6-7, 2'-5' nucleotides in positions 7-8, 2'-5' nucleotides in positions 8-9, 2'-5' nucleotides in positions 5-7, 2'-5' nucleotides in positions 6-8, 2'-5' nucleotides in positions 7-9, 2'-5' nucleotides in positions 5-8, 2'-5' nucleotides in positions 6-9 or 2'-5' nucleotides in positions 5-9.

50. The double stranded nucleic acid molecule of any of claims 7-47 wherein (N)x or N^1-(N)x comprises a mirror nucleotide in position 5, a mirror nucleotide in position 6, a mirror nucleotide in position 7, a mirror nucleotide in position 8, a mirror nucleotide in position 9, mirror nucleotides in positions 5-6, mirror nucleotides in positions 6-7, mirror nucleotides in positions 7-8, mirror nucleotides in positions 8-9, mirror nucleotides in positions 5-7, mirror nucleotides in positions 6-8, mirror nucleotides in positions 7-9, mirror nucleotides in positions 5-8, mirror nucleotides in positions 6-9 or mirror nucleotides in positions 5-9.

51. The double stranded nucleic acid molecule of any of claims 7-47 wherein N' in at least one of positions 9 or 10 from the 5' terminus of the sense strand is selected from a threose nucleic acid (TNA) moiety, a 2'5' nucleotide, a pseudoUridine or a combination thereof.

52. The double stranded nucleic acid molecule of any of claims 7-47 wherein (N')y or N^2-(N')y comprises a threose nucleic acid (TNA) moiety in position 9 and/or in position 10.

53. The double stranded nucleic acid molecule of any of claims 7-47 wherein (N')y or N^2-(N')y comprises a 2'5' nucleotide in position 9 and/or in position 10.

54. The double stranded nucleic acid molecule of any of claims 7-47 wherein (N')y or N^2-(N')y comprises a pseudoUridine in position 9 and/or in position 10.

55. The double stranded nucleic acid molecule of any of claims 7-47 wherein N' comprises 4, 5, or 6 consecutive 2'5' nucleotides starting at the 3' terminal or penultimate position of the sense strand.

56. The double stranded nucleic acid molecule of any of claims 7-47 wherein the sense strand further comprises Z'.

57. The double stranded nucleic acid molecule of claim 56 wherein Z' comprises a C3 moiety or a 3' terminal phosphate (Pi).

~~58. The double stranded nucleic acid molecule of any of claims 7-57 wherein the sense~~ strand comprises four or five consecutive 2'5' nucleotides starting at the 3' terminal or penultimate position.

59. The double stranded nucleic acid molecule of claim 58 wherein each strand is 19 nucleotides in length and (N')y comprises 2'5' nucleotides in positions 15, 16, 17 and 18, or in positions 16, 17, 18, and 19 or in positions 15, 16, 17, 18, and 19.

60. The double stranded nucleic acid molecule of claim 58 wherein x=y=19;

N in at least one of positions 5, 6, 7, 8, or 9 from the 5' terminus of the antisense strand is selected from a threose nucleic acid moiety, a 2'5' nucleotide or a mirror nucleotide;

N' in at least one of positions 9 or 10 from the 5' terminus of the sense strand is selected from a threose nucleic acid moiety, a 2'5' nucleotide and a pseudoUridine; and

at least one pyrimidine ribonucleotide in the antisense strand is substituted.

61. The double stranded nucleic acid molecule of claim 58 wherein x=y=19; comprising a 2'5' nucleotide in position 9 of the antisense strand and a 2'5' nucleotide in position 5 or 6 in the sense strand.

62. The double stranded nucleic acid molecule of claim 61 further comprising at least one 2'-OMe modified pyrimidine ribonucleotide.

63. The double stranded nucleic acid molecule of claim 58 wherein x=y=19;

N in at least one of positions 5, 6, 7, 8, or 9 from the 5' terminus of the antisense strand is selected from a threose nucleic acid moiety, a 2'5' nucleotide or a mirror nucleotide; and

N' in 4, 5, or 6 consecutive positions starting at the 3' terminal or penultimate position of the sense strand comprises a 2'5' nucleotide.

64. The double stranded nucleic acid molecule of claim 37 wherein at least one of N' comprises a mirror nucleotide.

65. The double stranded nucleic acid molecule of claim 64 wherein (N')y or N^2-(N')y comprises at least one mirror nucleotide at one or both termini.

66. The double stranded nucleic acid molecule of claim 65 wherein (N')y or N^2-(N')y comprises two consecutive mirror nucleotides, one at the 3' penultimate position and one at the 3' terminus.

67. The double stranded nucleic acid molecule of claim 64 wherein the at least one mirror nucleotide is selected from an L-ribonucleotide and an L-deoxyribonucleotide.

68. The double stranded nucleic acid molecule of claim 67 wherein the mirror nucleotide is an L-deoxyribonucleotide.

69. The double stranded nucleic acid molecule of any of claims 7-12 wherein the (N)x or and the (N')y are non-phosphorylated at the 3' termini and the 5' termini or are phosphorylated at the 3' termini or at both the 3' termini and 5' termini.

70. The double stranded nucleic acid molecule of any of claims 13-17 wherein the N^1-(N)x and N^2-(N')y are non-phosphorylated at the 3' termini and the 5' termini or are phosphorylated at the 3' termini or at both the 3' termini and 5' termini.

71. The double stranded nucleic acid molecule of any of claims 7-36 wherein each N and each N' comprise an unmodified ribonucleotide.

72. A pharmaceutical composition comprising a double stranded nucleic acid molecule of any of claims 1-71 in an amount effective to inhibit gene expression, and a pharmaceutically acceptable carrier wherein the gene encodes a RNA having a polynucleotide sequence set forth in any one of SEQ ID NOS:1-12.

73. A cell comprising a double stranded nucleic acid molecule of any of claims 1-71 in an amount effective to inhibit gene expression, wherein the gene encodes a RNA having a polynucleotide sequence set forth in any one of SEQ ID NOS:1-12.

74. A double stranded nucleic acid molecule of any of claims 1-71 or a composition according to claim 72 for use in therapy.

75. The use of claim 74, wherein said therapy is treatment of a disease or injury selected from the group consisting of chronic or acute aseptic inflammation, neuropathic pain, primary graft failure, ischemia-reperfusion injury, reperfusion injury, reperfusion edema, allograft dysfunction, pulmonary reimplantation response and primary graft dysfunction (PGD) in organ transplantation.

76. A method for the treatment of a subject in need of treatment for a disease or disorder or symptom or condition associated with the expression of a target gene comprising administering to the subject an amount of a double stranded nucleic acid molecule of any of claims 1-71, or a composition according to claim 72 in an amount effective to down regulate gene expression, wherein the gene encodes a RNA having a polynucleotide sequence set forth in any one of SEQ ID NOS:1-12.

77. The method of claim 76, wherein the disease or injury is selected from the group consisting of chronic or acute aseptic inflammation, neuropathic pain, primary graft failure, ischemia-reperfusion injury, reperfusion injury, reperfusion edema, allograft dysfunction, pulmonary reimplantation response and primary graft dysfunction (PGD) in organ transplantation.

78. The method of claim 77, wherein the disease or injury comprises primary graft dysfunction (PGD) in organ transplantation.

79. The method of claim 78, wherein said organ transplantation comprises lung transplantation.

80. A method for treating or preventing the incidence or severity of a posttransplantational complication selected from the group consisting of primary graft failure, ischemia-reperfusion injury, reperfusion injury, reperfusion edema, allograft dysfunction, pulmonary reimplantation response, primary graft dysfunction (PGD), in a subject in need thereof wherein the complication is associated with expression of a gene encoding a RNA having a polynucleotide sequence set forth in any one of SEQ ID NOS:1-12, the method comprising administering to the subject a prophylactically or therapeutically effective amount of a double stranded nucleic acid molecule of any of claims 1-71, or a composition according to claim 72 in an amount effective to down regulate the gene expression.

81. A method for reducing acute or chronic inflammation in a subject in need thereof wherein the inflammation is associated with expression of a gene encoding a RNA having a polynucleotide sequence set forth in any one of SEQ ID NOS:1-12, the method comprising administering to the subject a therapeutically effective amount of a double stranded nucleic acid molecule of any of claims 1-71, or a composition according to claim 72 in an amount effective to down regulate gene expression.