Claims

1. **A combination** comprising or consisting of
(i) at least one first component comprising at least one therapeutic RNA; and
(ii) at least one second component comprising at least one antagonist of at least one RNA sensing pattern recognition receptor,
wherein the at least one therapeutic RNA of the first component is selected from a coding RNA.

2. Combination of **claim 1**, wherein the at least one RNA sensing pattern recognition receptor induces cytokines upon binding of an RNA agonist and/or
wherein the at least one RNA sensing pattern recognition receptor inhibits translation upon binding of an RNA agonist.

3. Combination of **any of the preceding claims**, wherein the at least one antagonist of the second component reduces cytokine induction by the at least one RNA sensing pattern recognition receptor upon binding of an RNA agonist and/or reduces translation inhibition by the at least one RNA sensing pattern recognition receptor upon binding of an RNA agonist and/or
wherein the combination of the at least one therapeutic RNA of the first component and the at least one antagonist of at least one RNA sensing pattern recognition receptor of the second component to be administered leads to a reduced innate immune response compared to the at least one therapeutic RNA of the first component without combination with the at least one antagonist of at least one RNA sensing pattern recognition receptor of the second component to be administered.

4. Combination of **any of the preceding claims**, wherein the at least one RNA sensing pattern recognition receptor is a receptor for single stranded RNA (ssRNA) and/or a receptor for double stranded RNA (dsRNA).

5. Combination of **any of the preceding claims**, wherein the at least one RNA sensing pattern recognition receptor is selected from a Toll-like receptor (TLR), a Retinoic acid-inducible gene-I-like receptor (RLR), a NOD-like receptor, PKR, OAS, SAMHD1, ADAR1, IFIT1 and/or IFIT5, preferably wherein the at least one Toll-like receptor is selected from TLR3, TLR7, TLR8 and/or TLR9, more preferably wherein the at least one Toll-like receptor is selected from TLR8 and/or TLR9, most preferably from a TLR7 and /or TLR8, and, optionally,
wherein the Retinoic acid-inducible gene-I-like receptor (RLR) is selected from RIG-1, MDA5, LGP2, cGAS, AIM2, NLRP3, NOD2, preferably RIG1 and/or MDA5.

6. Combination of **any one of the preceding claims**, wherein the at least one antagonist of the second component is a nucleic acid, preferably a single stranded nucleic acid, and/or
wherein the nucleic acid of the second component comprises or consists of nucleotides selected from DNA nucleotides, RNA nucleotides, PNA nucleotides, and/or LNA nucleotides, or analogs or derivatives of any of these.

7. Combination of **claim6**, wherein the nucleic acid of the second component comprises at least one modified nucleotide and/or at least one nucleotide analogue or nucleotide derivative,

wherein the at least one modified nucleotide and/or at least one nucleotide analogues is preferably selected from a backbone modified nucleotide, a sugar modified nucleotide and/or a base modified nucleotide, or any combination thereof, more preferably, wherein the least one modified nucleotide and/or the at least one nucleotide analog is selected from 1-methyladenosine, 2-methyladenosine, N6-methyladenosine, 2'-O-methyladenosine, 2-methylthio-N6-methyladenosine, N6-isopentenyladenosine, 2-methylthio-N6-isopentenyladenosine, N6-threonylcarbamoyladenosine, 2-methylthio-N6-threonyl carbamoyladenosine, N6-methyl-N6-threonylcarbamoyladenosine, N6-hydroxynorvalylcarbamoyladenosine, 2-methylthio-N6-hydroxynorvalyl carbamoyladenosine, inosine, 3-methylcytidine , 2'-O-methylcytidine, 2-thiocytidine, N4-acetylcytidine, lysidine, 1-methylguanosine, 7-methylguanosine, 2'-O-methylguanosine, queuosine, epoxyqueuosine, 7-cyano-7-deazaguanosine, 7-aminomethyl-7-deazaguanosine, pseudouridine, dihydrouridine, 5-methyluridine, 2'-O-methyluridine, 2-thiouridine, 4-thiouridine, 5-methyl-2-thiouridine, 3-(3-amino-3-carboxypropyl)uridine´, 5-hydroxyuridine, 5-methoxyuridine, uridine 5-oxyacetic acid, uridine 5-oxyacetic acid methyl ester, 5-aminomethyl-2-thiouridine, 5-methylaminomethyluridine, 5-methylaminomethyl-2-thiouridine, 5-methylaminomethyl-2-selenouridine, 5-carboxymethylaminomethyluridine, 5-carboxymethylaminomethyl- 2'-O-methyluridine, 5-carboxymethylaminomethyl-2-thiouridine, 5-(isopentenylaminomethyl)uridine, 5-(isopentenylaminomethyl)- 2-thiouridine, or 5-(isopentenylaminomethyl)- 2'-O-methyluridine.

8. Combination of claim 7, wherein the at least one modified nucleotide is a sugar modified nucleotide, preferably a 2' ribose modified RNA nucleotide, more preferably a 2'-O-methylated RNA nucleotide, wherein the 2'-O-methylated RNA nucleotide is more preferably selected from 2'-O-methylated guanosine (Gm), a 2'-O-methylated uracil (Um), a 2'-O-methylated adenosine (Am), a 2'-O-methylated cytosine (Cm), or a 2'-O-methylated analogue of any of these nucleotides.

9. Combination of **any one of claims 6 to 8**, wherein the nucleic acid of the second component comprises at least one or more trinucleotide M-X-Y motifs,
wherein M is selected from Gm, Um, or Am, preferably wherein M is Gm;
wherein X is selected from G, A, or U, *preferably* wherein X is G; and
wherein Y is selected from G, A, U, C, or dihydrouridine, *preferably* wherein Y is C, and/or
wherein the nucleic acid of the second component comprises or consists of a nucleic acid sequence according to formula I:

$$N_W\text{-}M\text{-}X\text{-}Y\text{-}N_Z \qquad \text{(Formula I)}$$

wherein N is independently selected from G, A, U, C, Gm, Am, Um, Cm, or a modified nucleotide;
wherein W is 0 or an integer of 1 to 15;
wherein Z is 0 or an integer of 1 to 15;
wherein M, X, and Y are selected as defined before, optionally
wherein the nucleic acid of the second component comprises or consists of at least 2, 3, 4, 5, 6, 7, 8, 9, 10 or more nucleic acid sequences according to formula I, wherein each of the at least 2, 3, 4, 5, 6, 7, 8, 9, 10 or more nucleic acid sequences according to formula I are identical or independently selected from each other, and/or
the nucleic acid of the second component contains a 5′ end that is devoid of a triphosphate group.

10. Combination of **any one of claims 6 to 9**, wherein the nucleic acid of the second component has a length of about 3 to about 50 nucleotides, about 5 to about 25 nucleotides, about 5 to about 15, or about 5 to about 10 nucleotides, *preferably* about 5 to about 15 nucleotides, optionally wherein the nucleic acid of the second component has a length of 5 nucleotides, 6 nucleotides, 7 nucleotides, 8 nucleotides, 9 nucleotides, 10 nucleotides, 11 nucleotides, 12 nucleotides, or 13 nucleotides, *preferably* 9 nucleotides.

11. Combination of **any one of claims 6 to 10**, wherein the nucleic acid of the second component is a single stranded oligonucleotide, preferably wherein the single stranded oligonucleotide is a single stranded RNA oligonucleotide.

12. Combination of **any one of claims 6 to 11**, wherein the nucleic acid of the second component, comprises or consists of a nucleic acid sequence derived from a bacterial tRNA, preferably a bacterial $tRNA^{Tyr}$, optionally wherein the nucleic acid sequence is or is derived from a bacterial $tRNA^{Tyr}$, preferably from the D-Loop of a bacterial $tRNA^{Tyr}$, most *preferably* the D-Loop of Escherichia coli $tRNA^{Tyr}$.

13. Combination of **any one of claims 6 to 12**, wherein the nucleic acid of the second component comprises or consists of a nucleic acid sequence identical or at least 70%, 80%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% identical to a nucleic acid sequence selected from the group consisting of **SEQ ID NOs: 85-212**, or fragments of any of these sequences, preferably wherein the nucleic acid of the second component comprises or consists of a nucleic acid sequence identical or at least 70%, 80%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% identical to a nucleic acid sequence selected from the group consisting of **SEQ ID NOs: 85-87, 149-212**, or fragments of any of these sequences, more *preferably* wherein the nucleic acid of the second component comprises or consists of a nucleic acid sequence identical or at least 70%, 80%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% identical to a nucleic acid sequence according to 5'-GAG CGmG CCA-3' (**SEQ ID NO: 85**), or a fragment thereof.

14. Combination of **any of the preceding claims**, wherein the at least one therapeutic RNA of the first component is an in vitro transcribed RNA, preferably wherein the in vitro transcribed RNA is obtainable by RNA in vitro transcription using a sequence optimized nucleotide mixture, and/or wherein at least one therapeutic RNA of the first component is a purified RNA, wherein the purified RNA is more *preferably* purified by RP-HPLC and/or TFF and/or Oligo d(T) purification.

15. Combination of **any of the preceding claims,** wherein the coding RNA is selected from an mRNA, a self-replicating RNA, a circular RNA, a viral RNA, or a replicon RNA, preferably from an mRNA, wherein the coding RNA or the mRNA comprises at least one coding sequence encoding at least one peptide or protein, preferably wherein the expression of the encoded at least one peptide or protein of the coding RNA or the mRNA is increased or prolonged by the combination with the at least one antagonist of at least one RNA sensing receptor of the second component to be administered into

cells, a tissue or an organism compared to the expression of the encoded at least one peptide or protein of the coding RNA or the mRNA
without combination with the at least one antagonist of at least one RNA sensing pattern recognition receptor of the second component, wherein the at least one peptide or protein is or is derived from a therapeutic peptide or protein, wherein the therapeutic peptide or protein preferably is or is preferably derived from an antibody, an intrabody, a receptor, a receptor agonist, a receptor antagonist, a binding protein, a CRISPR-associated endonuclease, a chaperone, a transporter protein, an ion channel, a membrane protein, a secreted protein, a transcription factor, an enzyme, a peptide or protein hormone, a growth factor, a structural protein, a cytoplasmic protein, a cytoskeletal protein, a viral antigen, a bacterial antigen, a protozoan antigen, an allergen, a tumor antigen, or fragments, variants, or combinations of any of these, wherein the at least one coding sequence is more *preferably* a codon modified coding sequence, wherein the at least one codon modified coding sequence is most *preferably* selected from C maximized coding sequence, CAI maximized coding sequence, human codon usage adapted coding sequence, G/C content modified coding sequence, and G/C optimized coding sequence, or any combination thereof.

16. Combination of **any one of the preceding claims**, wherein the at least one therapeutic RNA of the first component, *preferably* the mRNA, comprises a 5'-cap structure, preferably wherein the 5'-cap structure is a cap0, cap1, cap2, a modified cap0 or a modified cap1 structure, more preferably the 5'-cap structure is a cap1 structure.

17. Combination of **any one of the preceding claims**, wherein the at least one therapeutic RNA of the first component comprises at least one modified nucleotide or a modified nucleotide analogue, wherein the at least one modified nucleotide is preferably selected from pseudouridine (ψ), N1-methylpseudouridine (m1ψ), 5-methylcytosine, and/or 5-methoxyuridine.

18. Combination of **any one of the preceding claims**, wherein the at least one therapeutic RNA of the first component, *preferably* the mRNA, comprises at least one poly(A) sequence, and/or at least one poly(C) sequence, and/or at least one histone stem-loop sequence/structure, preferably wherein the poly(A) sequence is located at the 3' terminus of the therapeutic RNA, and/or wherein the 3' terminus of the RNA consists of a poly(A) sequence terminating with an A nucleotide and/or
wherein the at least one therapeutic RNA of the first component, *preferably* the mRNA, comprises at least one heterologous 5'-UTR and/or at least one heterologous 3'-UTR,
wherein the at least one heterologous 3'-UTR comprises a nucleic acid sequence preferably derived from a 3'-UTR of a gene selected from PSMB3, ALB7, alpha-globin, CASP1, COX6B1, GNAS, NDUFA1 and RPS9, or from a homolog, a fragment or a variant of any one of these genes or
wherein the at least one heterologous 5'-UTR comprises a nucleic acid sequence preferably derived from a 5'-UTR of a gene selected from HSD17B4, RPL32, ASAH1, ATP5A1, MP68, NDUFA4, NOSIP, RPL31, SLC7A3, TUBB4B and UBQLN2, or from a homolog, a fragment or variant of any one of these genes.

19. Combination of **any one of the preceding claims**, wherein the at least one antagonist of the second component, *preferably* the nucleic acid, and/or the at least one therapeutic RNA of the first component is complexed or associated with or at least partially complexed or partially associated with one or more

cationic or polycationic compound, *preferably* cationic or polycationic polymer, cationic or polycationic polysaccharide, cationic or polycationic lipid, cationic or polycationic protein, or cationic or polycationic peptide, or any combinations thereof, preferably wherein the at least one antagonist of the second component, *preferably* the nucleic acid, and/or the at least one therapeutic RNA of the first component is complexed, partially complexed, encapsulated, partially encapsulated, or associated with one or more lipids, thereby forming liposomes, lipid nanoparticles (LNP), lipoplexes, and/or nanoliposomes, *preferably* lipid nanoparticles (LNP), wherein the LNP more preferably comprises
(i) at least one cationic lipid, *preferably* lipid III-3;
(ii) at least one neutral lipid, *preferably* 1,2-distearoyl-sn-glycero-3-phosphocholine (DSPC);
(iii) at least one steroid or steroid analogue, *preferably* cholesterol; and
(iv) at least one PEG-lipid, *preferably* a PEGylated lipid of formula (IVa),
preferably wherein (i) to (iv) are in a molar ratio of about 20-60% cationic lipid; 5-25% neutral lipid; 25-55% sterol; 0.5-15% PEG-lipid.

20. **Pharmaceutical composition** comprising or consisting of a combination as defined in **any one of claims 1 to 19**, and *optionally* at least one pharmaceutically acceptable carrier, preferably wherein the at least one therapeutic RNA and the at least one antagonist are formulated separately, wherein the at least one therapeutic RNA and the at least one antagonist are more preferably co-formulated to increase the probability that they are both present in one particle to ensure that the at least one therapeutic RNA and the at least one antagonist are uptaken by the same cell.

21. Pharmaceutical composition of **claim 20**, wherein the molar ratio of the at least one antagonist, *preferably* the nucleic acid, to the at least one therapeutic RNA ranges from about 1:1, to about 100:1, or ranges from about 20:1, to about 80:1 and/or
wherein the weight to weight ratio of the at least one antagonist, *preferably* the nucleic acid, to the at least one therapeutic RNA ranges from about 1:1, to about 1:30, or ranges from about 1:2, to about 1:10.

22. Pharmaceutical composition of **any one of claims 20 and 21**, wherein the composition is to be administered to a cell, tissue, or organism results in essentially the same or at least a comparable activity of the therapeutic RNA as compared to a corresponding therapeutic RNA to be administered only, or wherein the composition is to be administered to a cell, tissue, or organism results in increased activity of the therapeutic RNA *for example* as compared to a corresponding therapeutic RNA to be administered only wherein activity of the therapeutic RNA is preferably expression of an encoded peptide or protein, more *preferably* protein expression.

23. Pharmaceutical composition of **any one of claims 20 to 22**, wherein the composition is to be administered to a cell, tissue, or organism results in a reduced (innate) immune stimulation as compared to the corresponding therapeutic RNA to be administered only.

24. Kit or kit of parts comprising at least one first and at least one second component as defined in **any one of claims 1 to 19**, and/or at least one pharmaceutical composition as defined in **any one of claims 20 to 23**, *optionally* comprising a liquid vehicle for solubilising, and, *optionally*, technical instructions providing information on administration and/or dosage of the components.

25. Combination of **any one of claims 1 to 19**, pharmaceutical composition of **any one of claims 20 to 23**, or kit or kit of parts of **claim 24** for use as a medicament.

26. Combination of **any one of claims 1 to 19**, pharmaceutical composition of **any one of claims 20 to 23**, or kit or kit of parts of **claim 24** for use in a chronic medical treatment, or for use in the treatment or prophylaxis of an infection, *preferably* a virus infection, a bacterial infection, or a protozoan infection, or use in the treatment or prophylaxis of a tumour disease, or of a disorder related to such tumour disease or for use in the treatment or prophylaxis of a genetic disorder or condition or for use in the treatment or prophylaxis of a protein or enzyme deficiency.