

CLAIMS

1. A modular RNA molecule, comprising:

- a. a 5' region comprising a sensor domain comprising a stretch of consecutive nucleotides that is complementary to a corresponding stretch of consecutive nucleotides of a cellular RNA, wherein said sensor domain comprises a stop codon editable by ADAR; and
- b. a 3' region comprising a first protein coding domain, wherein said first protein coding domain is downstream of and in-frame with said sensor domain,

wherein, upon introduction of said modular RNA into a cell comprising an Adar enzyme, said stretch of consecutive nucleotides of said sensor domain and said corresponding nucleotide stretch of said cellular RNA form an RNA duplex comprising said stop codon, wherein said stop codon comprised in said RNA duplex is edited by ADAR in said cell, thereby to permit translation of said protein, optionally wherein said modular RNA molecule is encoded by a DNA vector.

2. The modular RNA molecule of claim 1, wherein:

- (a) said stretch of consecutive nucleotides of said sensor domain is able to form an RNA duplex with at least a portion of an mRNA;
- (b) said first protein coding domain encodes an effector protein; or
- (c) said molecule further comprises consecutive nucleotides encoding a self-cleaving 2A peptide positioned between said sensor domain and said effector domain, optionally wherein said self-cleaving 2A peptide is selected from the group consisting of one or more of T2A peptide, P2A peptide, E2A peptide, and F2A peptide.

3. A composition comprising:

- a) a first nucleic acid comprising a modular RNA molecule according to claim 1, wherein the first protein-coding domain encodes an effector protein, and
- b) a second nucleic acid comprising a second protein coding domain.

4. The composition of claim 3, wherein:
 - (a) said first and second nucleic acids comprise a single nucleic acid molecule;
 - (b) said first and second nucleic acids comprise two nucleic acid molecules;
 - (c) said first and second nucleic acid are covalently linked;
 - (d) said second protein coding domain is comprised within a gene comprising a transcription control element, optionally, a promoter, optionally wherein said effector protein binds to said gene;
 - (e) expression of said second protein coding domain is modulated by said effector protein;
 - (f) the first protein-coding domain encodes a transcriptional activator;
 - (g) the first protein-coding domain encodes a DNA recombinase; or
 - (h) the first protein-coding domain encodes a cell killing protein selected from the group consisting of: thymidine kinase (TK) and cytosine deaminase (CD) , a programmed cell death protein selected from the group consisting of CASP3, CASP9, BCL, GSDME, GSDMD, GZMA and GZMB, a neural activating protein selected from the group consisting of: Chr2 and DREADD-M3Dq, an immunity enhancer protein selected from the group consisting of IFNB, IFNG, TNFA, IL2, IL12, IL15 and CD40L, a physiological editing protein selected from the group consisting of NaChBac and Kir2.1, a protein synthesis inhibition protein including ricin, a neural inhibitor protein selected from the group consisting of DREADD-hM4D, NpHR and GtACR1, a protein involved in neural cell fate such as NEUROD, a protein involved with cell regeneration including Epidermal growth factors.
5. A nucleic acid delivery vehicle comprising the modular RNA molecule of claim 1 or the composition of claim 3.
6. A delivery vehicle according to claim 5:
 - (a) selected from the group consisting of a nanoparticle, a liposome, a vector, an exosome, a micro-vesicle, a gene-gun, and a Selective Endogenous encapsulation for cellular Delivery (SEND) system; or

- (b) comprising a viral vector, optionally wherein the viral vector is selected from the group consisting of adeno-associated virus (AAV), adenovirus, retrovirus, lentivirus, herpes virus.
7. A pharmaceutical composition comprising the modular RNA molecule of claim 1, the composition of claim 3, or the delivery vehicle of claim 5, and a pharmaceutically acceptable carrier, excipient and/or diluent.
 8. A cell comprising the modular RNA molecule of claim 1, the composition of claim 3, or the delivery vehicle of claim 5, optionally wherein the cell is a mammalian cell.
 9. A kit comprising the modular RNA molecule of claim 1, the composition of claim 3, or the delivery vehicle of claim 5, and packaging therefore.
 10. An agent comprising a modular RNA molecule according to claim 1 or a nucleic acid composition according to claim 3 or a delivery vehicle according to claim 5 for use as a medicament in treating a disease or disorder in a mammal, wherein said agent is to be administered to said mammal in a therapeutically effective amount to permit translation of said effector protein in selected cells of said mammal, thereby to produce said protein in said cells, wherein production of said protein in said cells is used as a medicament for the treatment of said disease or disorder in said mammal.
 11. The use of the agent according to claim 10, wherein said agent comprises said composition of claim 3 or said delivery vehicle of claim 5 and said first protein coding region encoding said effector protein comprised in said agent encodes a transactivator protein that activates expression of said second protein coding region, and wherein expression of said second protein coding region in said selected cells is therapeutically effective in treating said disease or disorder, optionally wherein said protein coding region of said modular RNA encodes a transactivator, and wherein said select cell of said mammal further comprises a VEGFa gene under the control of said transactivator.
 12. The use of the agent according to claim 10, wherein said cell is a cancer cell, optionally wherein:
 - (a) said cancer cell is a metastatic cancer cell; or
 - (b) said selected cell RNA encodes HER2, and wherein said sensor domain comprising said stretch of consecutive nucleotides is complementary to a corresponding stretch of

consecutive nucleotides of said HER2 cell RNA, optionally wherein said protein coding domain of said modular RNA encodes a protein selected from the group consisting of CASP3, CASP9, BCL, GSDME, GSDMD, GZMA and GZMB.

13. The use of the agent according to claim 10, wherein:

(a) said mammal is infected with a pathogen and wherein said selected cell RNA is expressed by said pathogen in said selected cell;

(b) said mammal comprises a defective protein encoded by and expressed from a cellular RNA, and wherein said modular RNA molecule comprises a stretch of consecutive nucleotides of said sensor domain complementary to a corresponding stretch of consecutive nucleotides of said cellular RNA encoding said defective protein, and a protein coding domain encoding an effector protein that is a wild type functional protein of said defective protein, and

wherein upon introduction of said agent to said mammal said stretch of consecutive nucleotides of said sensor domain of said modular RNA molecule forms a duplex with said corresponding stretch of consecutive nucleotides of said cellular RNA, said duplex is edited by ADAR in said cell and said wild type functional protein is produced in said mammal;

(c) a selected cell comprises a border zone (BZ) cell surrounding an infarct zone of cardiac tissue, and wherein said selected cell RNA is selected from the group consisting of: NPPB, MYH7, ANKRD1, DES, UCHL1, JUN, and FOXP1 RNA, optionally wherein said protein coding domain of said modular RNA encodes VEGFA or said selected cell RNA is a NPPB RNA;

(d) said mammal is human and is afflicted with glioblastoma, wherein said selected cell is a cancerous glioblastoma cell, wherein said selected cell RNA is a SPARC and/or a VIM RNA, and wherein said modular RNA molecule comprises a sensor domain comprising a stretch of consecutive nucleotides complementary to a stretch of consecutive nucleotides of said selected cell SPARC and/or VIM RNA and said protein coding domain comprises caspase, optionally wherein

said modular RNA molecule comprises two tandem in-frame sensor domains, the first of said two tandem in-frame sensor domains comprising a stretch of consecutive nucleotides complementary to a stretch of consecutive nucleotides of said selected cell SPARC RNA, and

the second of said two tandem in-frame sensor domains comprising a stretch of consecutive nucleotides complementary to a stretch of consecutive nucleotides of said selected cell VIM RNA, wherein a first RNA duplex forms between a said modular RNA molecule and said selected cell SPARC RNA and a second RNA duplex forms between a said modular RNA molecule and said selected cell VIM RNA, and wherein said effector protein is expressed only in the presence of both said SPARC RNA and said VIM RNA; or

said protein coding domain of said modular RNA molecule is selected from the group consisting of: a suicide gene coding region, a cell death inducing gene coding region, a tumor suppressor gene coding region, and a gene enhancing anti-tumor immunity coding region, optionally wherein:

(i) said protein coding domain of said modular RNA molecule comprises a coding region of a gene encoding a protein that enhances anti-tumor immunity or encoding Interferon β ; or

(ii) said protein coding domain of said modular RNA molecule comprises a protein coding region of a suicide gene, wherein the suicide gene is selected from the group consisting of thymidine kinase and cytosine deaminase, optionally wherein said suicide gene is cytidine kinase and comprises the sequence of SEQ ID NO:150 or wherein said suicide gene is thymidine kinase1 and comprises the sequence of SEQ ID NO:151; or

(iii) said protein coding domain of said modular RNA molecule comprises a protein coding region of a cell death inducing gene, wherein the cell death inducing gene is selected from the group consisting of Caspase3, Caspase9, Bcl 2 and GSDMs, optionally wherein the cell death inducing gene is caspase 3 and comprises the sequence of SEQ ID NO:152, the cell death inducing gene is caspase 9 and comprises the sequence of SEQ ID NO:153, the cell death inducing gene is BCL2 and comprises the sequence of SEQ ID NO:154, or the cell death inducing gene is GSDMD and comprises the sequence of SEQ ID NO:155; or

(iv) said protein coding domain of said modular RNA molecule comprises a protein coding region of a tumor suppressor gene, wherein the tumor suppressor gene is selected from the group consisting of Rb and PTEN;

(e) said patient is afflicted with Diffuse large B cell lymphoma (B NHL), wherein the efRNA encodes an antiCD19-CAR and the sesRNA is CD3E, optionally wherein the PCAG-

sesRNA^{CD3E-CD19-CAR} plasmid or *in vitro* transcribed mRNA is delivered by CD5-targeting LNPs through i.v. injection to enhance T cell orientated uptake; (f) said patient is afflicted with Crigler-Najjar Syndrome (CNS), wherein the SES targets are directed against RNA transcribed by ApoA2 (Apolipoprotein A-2), AHSB (Alpha 2-HS Glycoprotein) and Albumin (Alb) genes, and the efRNA encodes functional UGT1A1 gene; or

- (g) said disease or disorder is a monogenic disorder selected from the group consisting of: muscular dystrophy, cystic fibrosis, congenital deafness, Duchenne muscular dystrophy, familial hypercholesterolemia, Hemochromatosis, Neurofibromatosis type 1 (NF1), Sickle cell disease and Tay-Sachs disease and wherein the protein coding region of the modular RNA molecule encodes a wild type protein.
14. A modular RNA molecule for use in a method of detecting expression of a protein in a cell of a subject, the method comprising:
- a) introducing into said cell a modular RNA molecule under conditions in which said modular RNA is comprised in said cell, said modular RNA comprising (i) a 5' region comprising a sensor domain comprising a stretch of consecutive nucleotides that is complementary to a corresponding stretch of consecutive nucleotides of said selected cellular RNA, wherein said sensor domain comprises a stop codon editable by ADAR; and (ii) a 3' region comprising a domain encoding said protein, wherein said protein coding region is downstream of and in-frame with said sensor domain, wherein upon introduction of said modular RNA molecule to said cell, an RNA duplex is formed in said cell between said stretch of consecutive nucleotides of said sensor domain and said corresponding stretch of consecutive nucleotides of said cellular RNA, wherein said RNA duplex comprises said ADAR-editable stop codon, and wherein ADAR edits said stop codon comprised in said RNA duplex, thereby permitting translation of said protein, and wherein said protein is produced in said cell; and
 - b) detecting said protein in said cell.

15. An in vitro method of detecting expression of a protein in a cell, the method comprising:
- a) introducing into said cell, in vitro, a modular RNA molecule under conditions in which said modular RNA is comprised in said cell, said modular RNA comprising (i) a 5' region comprising a sensor domain comprising a stretch of consecutive nucleotides that is complementary to a corresponding stretch of consecutive nucleotides of said selected cellular RNA, wherein said sensor domain comprises a stop codon editable by ADAR; and (ii) a 3' region comprising a domain encoding said protein, wherein said protein coding region is downstream of and in-frame with said sensor domain,
- wherein upon introduction of said modular RNA molecule to said cell, an RNA duplex is formed in said cell between said stretch of consecutive nucleotides of said sensor domain and said corresponding stretch of consecutive nucleotides of said cellular RNA, wherein said RNA duplex comprises said ADAR-editable stop codon, and wherein ADAR edits said stop codon comprised in said RNA duplex, thereby permitting translation of said protein, and wherein said protein is produced in said cell; and
- b) detecting said protein in said cell.