CLAIMS

1. An expression repressor comprising:

a first targeting moiety that binds a genomic locus comprising at least 16, 17, 18, 19, or 20 nucleotides of the sequence of SEQ ID NO: 83, and

a first effector moiety comprising a DNA methyltransferase.

2. The expression repressor of claim 1, wherein the first targeting moiety comprises:

i) a zinc finger domain; and/or

ii) an amino acid sequence according to SEQ ID NO: 13 or a sequence with at least 80, 85, 90, 95, 99, or 100% identity thereto, or having no more than 20, 19, 18, 17, 16, 15, 14, 13, 12, 11, 10, 9, 8, 7, 6, 5, 4, 3, 2, or 1 positions of difference thereto.

3. The expression repressor of claim 1 or 2, wherein the first effector moiety comprises:

i) MQ1 or a functional variant or fragment thereof;

ii) a sequence of SEQ ID NO: 19 or 87, or a sequence with at least 80, 85, 90, 95, 99, or 100% identity thereto, or having no more than 20, 19, 18, 17, 16, 15, 14, 13, 12, 11, 10, 9, 8, 7, 6, 5, 4, 3, 2, or 1 positions of difference thereto; and/or

iii) a sequence of SEQ ID NO: 30 or 129, or a sequence with at least 80, 85, 90, 95, 99, or 100% identity thereto, or having no more than 20, 19, 18, 17, 16, 15, 14, 13, 12, 11, 10, 9, 8, 7, 6, 5, 4, 3, 2, or 1 positions of difference thereto.

4. A system comprising:

a first expression repressor according to any of claims 1-3, and

a second expression repressor.

5. The system of claim 4, wherein the second expression repressor comprises:

a second targeting moiety that binds a genomic locus, and

a second effector moiety, optionally wherein:

i) the second targeting moiety binds a genomic locus comprising at least 14, 15, 16, 17, 18, 19, or 20 nucleotides of the sequence of SEQ ID NO: 77, 199 or 201;

ii) the second targeting moiety comprises a zinc finger domain;

iii) the second targeting moiety comprises an amino acid sequence according to SEQ ID NO: 7, 169, 171, or a sequence with at least 80, 85, 90, 95, 99, or 100% identity thereto, or having no more than 20, 19, 18, 17, 16, 15, 14, 13, 12, 11, 10, 9, 8, 7, 6, 5, 4, 3, 2, or 1 positions of difference thereto;

iv) the second effector moiety comprises KRAB or a functional variant or fragment thereof;

v) the second effector moiety comprises an amino acid sequence according to SEQ ID NO: 18, or a sequence with at least 80, 85, 90, 95, 99, or 100% identity thereto, or having no more than 20, 19, 18, 17, 16, 15, 14, 13, 12, 11, 10, 9, 8, 7, 6, 5, 4, 3, 2, or 1 positions of difference thereto; or

vi) the second expression repressor comprises an amino acid sequence according to SEQ ID NO: 24, 177, 183, 179, or 185 or a sequence with at least 80, 85, 90, 95, 99, or 100% identity thereto, or having no more than 20, 19, 18, 17, 16, 15, 14, 13, 12, 11, 10, 9, 8, 7, 6, 5, 4, 3, 2, or 1 positions of difference thereto.

6. An expression repression system comprising:

a) a first expression repressor comprising:

i) a first targeting moiety having an amino acid sequence according to SEQ ID NO: 13 or a sequence with at least 80, 85, 90, 95, 99, or 100% identity thereto, or having no more than 20, 19, 18, 17, 16, 15, 14, 13, 12, 11, 10, 9, 8, 7, 6, 5, 4, 3, 2, or 1 positions of difference thereto and

ii) a first effector moiety having an amino acid sequence according to SEQ ID NO: 19 or 87 or a sequence with at least 80, 85, 90, 95, 99, or 100% identity thereto, or having no more than 20, 19, 18, 17, 16, 15, 14, 13, 12, 11, 10, 9, 8, 7, 6, 5, 4, 3, 2, or 1 positions of difference thereto, and

b) a second expression repressor comprising:

i) a second targeting moiety having an amino acid sequence according to SEQ ID NO: 7 or a sequence with at least 80, 85, 90, 95, 99, or 100% identity thereto, or having no more than 20, 19, 18, 17, 16, 15, 14, 13, 12, 11, 10, 9, 8, 7, 6, 5, 4, 3, 2, or 1 positions of difference thereto, and

ii) a second effector moiety having an amino acid sequence according to SEQ ID NO:18, or a sequence with at least 80, 85, 90, 95, 99, or 100% identity thereto, or having no more than 20, 19, 18, 17, 16, 15, 14, 13, 12, 11, 10, 9, 8, 7, 6, 5, 4, 3, 2, or 1 positions of difference thereto.

7. An expression repression system comprising:

a) a first expression repressor comprising:

i) a first targeting moiety having an amino acid sequence according to SEQ ID NO: 13 or a sequence with at least 80, 85, 90, 95, 99, or 100% identity thereto, or having no more than 20, 19, 18, 17, 16, 15, 14, 13, 12, 11, 10, 9, 8, 7, 6, 5, 4, 3, 2, or 1 positions of difference thereto and

ii) a first effector moiety having an amino acid sequence according to SEQ ID NO: 19 or 87 or a sequence with at least 80, 85, 90, 95, 99, or 100% identity thereto, or having no more than 20, 19, 18, 17, 16, 15, 14, 13, 12, 11, 10, 9, 8, 7, 6, 5, 4, 3, 2, or 1 positions of difference thereto, and

b) a second expression repressor comprising:

i) a second targeting moiety having an amino acid sequence according to SEQ ID NO: 169, 171 or a sequence with at least 80, 85, 90, 95, 99, or 100% identity thereto, or having no more than 20, 19, 18, 17, 16, 15, 14, 13, 12, 11, 10, 9, 8, 7, 6, 5, 4, 3, 2, or 1 positions of difference thereto, and

ii) a second effector moiety having an amino acid sequence according to SEQ ID NO:18, or a sequence with at least 80, 85, 90, 95, 99, or 100% identity thereto, or having no more than 20, 19, 18, 17, 16, 15, 14, 13, 12, 11, 10, 9, 8, 7, 6, 5, 4, 3, 2, or 1 positions of difference thereto.

8. The expression repressor or expression repression system of any of the preceding claims, wherein:

i) the expression repressor or expression repression system appreciably decreases expression of MYC for a time period of at least 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, or 25 days, or at least 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10 cell divisions, e.g., as measured by ELISA;

ii) binding of the expression repressor to a MYC locus appreciably decreases expression of MYC at 1, 2, 3, 4, 5, 6, 7, 8, 10, 12, 16, 20, 24, 28, 32, 36, 40, 44, 48, 52, 56, 60, 64, 68, 72, 76, 80, or 96 hours post-transfection with the expression repressor or expression repression system;

iii) contacting a plurality of cells with the expression repressor, expression repressor system, or a nucleic acid encoding the expression repressor, or the first expression repressor and the second expression repressor decreases the viability of the plurality of cells; and/or

iv) administration of the expression repressor or expression repression system results in apoptosis of at least 5%, 6%, 7%, 8%, 9% 10%, 12%, 15%, 17% 20%, 25% 30%, 40%, 45%, 50%, 55%, 60%, 65%, 75% of target cells (e.g., cancer cells).

9. The expression repressor or expression repression system of claim 8, wherein the plurality of cells comprises a plurality of cancer cells and a plurality of non-cancer cells, optionally wherein contacting the plurality of cells with the expression repressor, the system, or a nucleic acid encoding the expression repressor or the system decreases the viability of the plurality of cancer cells more than it decreases the viability of the plurality of non-cancer cells, optionally wherein the viability of the plurality of cancer cells decreases 1.05x (i.e., 1.05 times), 1.1x, 1.15x, 1.2x, 1.25x, 1.3x, 1.35x, 1.4x, 1.45x, 1.5x, 1.6x, 1.7x, 1.8x, 1.9x, 2x, 3x, 4x, 5x, 6x, 7x, 8x, 9x, 10x, 20x, 50x, or 100x more than the viability of the plurality of non-cancer cells.

10. A nucleic acid comprising a sequence encoding the expression repressor or system of any of claims 1-9.

11. The nucleic acid of claim 10, which comprises:

i) a nucleotide sequence encoding the first targeting moiety, wherein the nucleotide sequence encoding the first targeting moiety comprises a sequence according to SEQ ID NO: 46 or 131 or a sequence with at least 80, 85, 90, 95, 99, or 100% identity thereto, or having no more than 20, 19, 18, 17, 16, 15, 14, 13, 12, 11, 10, 9, 8, 7, 6, 5, 4, 3, 2, or 1 positions of difference thereto;

ii) a nucleotide sequence encoding the first effector moiety, wherein the nucleotide sequence encoding the first effector moiety comprises a sequence according to SEQ ID NO: 52 or 132, or a sequence with at least 80, 85,

90, 95, 99, or 100% identity thereto, or having no more than 20, 19, 18, 17, 16, 15, 14, 13, 12, 11, 10, 9, 8, 7, 6, 5, 4, 3, 2, or 1 positions of difference thereto;

iii) a nucleotide sequence according to SEQ ID NO: 63 or 130, or a sequence with at least 80, 85, 90, 95, 99, or 100% identity thereto, or having no more than 20, 19, 18, 17, 16, 15, 14, 13, 12, 11, 10, 9, 8, 7, 6, 5, 4, 3, 2, or 1 positions of difference thereto, wherein a poly-A sequence is optional;

iv) a nucleic acid encoding the first expression repressor and second expression repressor of the system of any of claims 4-6, optionally wherein the nucleic acid comprises a nucleotide sequence according to SEQ ID NO: 113, 196, or 197, wherein a poly-A sequence is optional.

12. The nucleic acid of claim 10 or 11, which comprises a nucleotide sequence of SEQ ID NO: 93, 94, 112, 113, 196, 197, or a sequence with at least 80, 85, 90, 95, or 99% identity thereto, or a sequence with no more than 20, 19, 18, 17, 16, 15, 14, 13, 12, 11, 10, 9, 8, 7, 6, 5, 4, 3, 2, or 1 positions of difference thereto.

13. An expression repressor comprising:

a targeting moiety having an amino acid sequence according to Table 4, or a sequence with at least 80, 85, 90, 95, 99, or 100% identity thereto, or having no more than 20, 19, 18, 17, 16, 15, 14, 13, 12, 11, 10, 9, 8, 7, 6, 5, 4, 3, 2, or 1 positions of difference thereto, and

optionally, an effector moiety.

14. A nucleic acid comprising a sequence according to Table 5, Table 6, Table 8, Table 16, or Table 10, or a sequence with at least 80, 85, 90, 95, 99, or 100% identity thereto, or having no more than 20, 19, 18, 17, 16, 15, 14, 13, 12, 11, 10, 9, 8, 7, 6, 5, 4, 3, 2, or 1 positions of difference thereto.

15. A vector comprising the nucleic acid encoding the system or expression repressor of any of claims 1-9.

16. A pharmaceutical composition comprising the expression repressor, system, nucleic acid, or vector of any of the preceding claims.

17. Use of the expression repressor, the system, or the nucleic acid encoding the expression repressor or the system of any of claims 1-14 in the manufacture of a medicament for the treatment of cancer, the treatment of hepatitis, or reducing tumor growth in a subject in need thereof, optionally wherein the subject has an overexpression of MYC in at least some cells.

18. The expression repressor, the system, or the nucleic acid encoding the expression repressor or the system of any of claims 1-14 for use in the treatment of cancer, or hepatitis, or reducing tumor growth in a subject in need thereof, wherein:

the expression repressor, the system, or the nucleic acid encoding the expression repressor or the system is to be administered, optionally wherein the subject has an overexpression of MYC in at least some cells.

19. The expression repressor, the system, or a nucleic acid encoding the expression repressor or the system of any one of claims 1-14 for use in increasing or restoring sensitivity of a cancer to:

(i) a kinase inhibitor, e.g., sorafenib, wherein the expression repressor or system, or the nucleic acid encoding the expression repressor or the system is to be administered to a subject having the cancer, optionally wherein administration of the expression repressor or system, or the nucleic acid encoding the expression repressor or the system, lowers the IC_{50} of the kinase inhibitor by 10%, 20%, 30%, or 40%, e.g., in a cancer cell viability assay;

(ii) a bromodomain inhibitor, e.g., a BET inhibitor, e.g., JQ1, wherein the expression repressor or system is to be administered to a subject having the cancer, wherein optionally administration of the expression repressor or system, or the nucleic acid encoding the expression repressor or the system, lowers the IC_{50} of the bromodomain inhibitor by 10%, 20%, 30%, 40%, 50%, 60%, 70%, 80%, 90%, or 95%, e.g., in a cancer cell viability assay; and/or

(iii) a MEK inhibitor, e.g., Trametinib, wherein the expression repressor or system, or the nucleic acid encoding the expression repressor or the system is to be administered to a subject having the cancer, wherein optionally administration of the expression repressor or system, or the nucleic acid encoding the expression repressor or the system, lowers the IC_{50} of the MEK inhibitor by 10%, 20%, 30%, 40%, 50%, 60%, 70%, 80%, 90%, or 95%, e.g., in a cancer cell viability assay, and

wherein, optionally wherein the subject has an overexpression of MYC in at least some cells.

20. The use according to any of claims 17-19, wherein:

i) the cancer comprises cells characterized by increased MYC expression relative to a reference level (e.g., relative to a reference cell's MYC expression, e.g., an otherwise similar non-cancerous cell of the subject), and cells not characterized by increased MYC expression relative to a reference level (e.g., relative to a reference cell's MYC expression, e.g., an otherwise similar non-cancerous cell of the subject), e.g., having normal MYC expression;

ii) the use comprises:

a) firstly, a first plurality of doses of an expression repressor or system of any of claims 1-14, to be administered to the subject, wherein optionally each subsequent dose in the first plurality is to be administered 5 days after the previous dose in the first plurality;

b) secondly, withdrawing the expression repressor or system for a period of time (a "drug holiday"), e.g., for about 2 weeks), and

c) thirdly, a second plurality of doses of the expression repressor or system to be administered to the subject, wherein optionally a subsequent dose of the second plurality is to be administered 5 days after the previous dose in the second plurality;

iii) tumor volume declines (e.g., to undetectable levels) after cessation of treatment with the expression repressor or system;

iv) the use further comprises:

a. contacting the cell with a second therapeutic agent; or

b. a second therapeutic agent to be administered to the subject, optionally wherein the second therapeutic agent is not an expression repressor, system, nucleic acid, vector, or pharmaceutical composition of any of claims 1-16 (e.g., an immunotherapy, one or both of immune checkpoint and anti-vascular-endothelial-growth-factor therapy, systemic chemotherapy, a tyrosine kinase inhibitor, e.g., sorafenib, a mitogen-activated protein kinase kinase inhibitor, e.g., trametinib, or a bromodomain inhibitor, e.g., a BET inhibitor, e.g., JQ1, e.g., birabresib), optionally wherein (I) the first and the second therapeutic agent are administered concurrently; or (II) the first and the second therapeutic agent are to be administered sequentially.