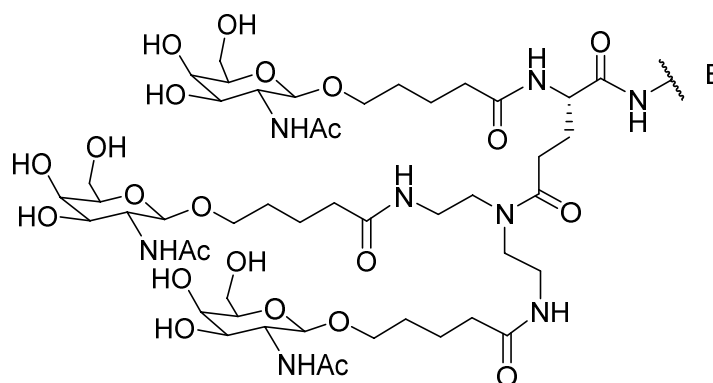


SUMMARY

[005] In one aspect, provided herein is an RNAi agent for reducing FAS gene expression, wherein the RNAi agent comprises a delivery moiety of Formula I conjugated to R, wherein R is a double stranded RNA (dsRNA) comprising an antisense strand and a sense strand:



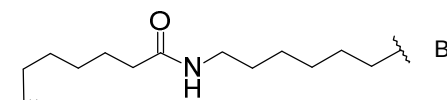
Formula I,

wherein R is conjugated to connection point E of Formula I, optionally via a linker, wherein the sense strand and the antisense strand form a duplex region, and wherein the antisense strand comprises a region of complementarity to a FAS mRNA target sequence of SEQ ID NO: 1, and wherein the sense and antisense strand each optionally comprise one or more modified nucleotides and one or more modified internucleotide linkages. In some examples, Formula I is conjugated to the sense strand, optionally via a linker. In some examples, Formula I is conjugated to the 3' terminal nucleotide of the sense strand, optionally via a linker.

[006] In some examples, the antisense strand is 15 to 50 nucleotides in length. In some examples, the sense strand is 15 to 50 nucleotides in length. In some examples, the antisense strand is between 18 and 23 nucleotides in length. In some examples, the sense strand is between 18 and 21 nucleotides in length. In some examples, the antisense strand is 23 nucleotides in length and the sense strand is 21 nucleotides in length.

[007] In some examples, the sense strand or the antisense strand comprises a sequence selected from Table 2, 3A, 3B, 4A, 4B, 7, or 8 disclosed herein. In some examples, the sense strand and the antisense strand comprises a sequence selected from Table 2, 3A, 3B, 4A, 4B, 7, or 8 disclosed herein.

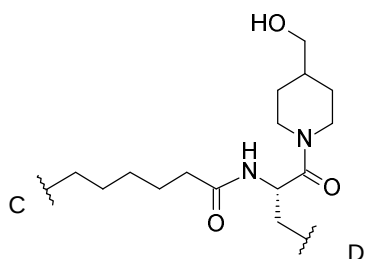
[008] In some examples, R is conjugated to Formula I via a linker. In further examples, the linker comprises a linker of Formula II having connection points A and B or the linker comprises Formula III having connection points C and D, and wherein:



A

B

Formula II;



Formula III;

- a. Formula I conjugated to Formula II at connection point A and Formula II is conjugated to a phosphate group at connection point B, and the phosphate group is further conjugated to R; or
- b. Formula I conjugated to Formula III at connection point C and Formula III is conjugated to a phosphate group at connection point D, and the phosphate group is further conjugated to R.

[009] Also provided herein are pharmaceutical composition comprising the FAS RNAi agent described herein and one or more pharmaceutically acceptable excipients.

[009a] In another aspect, provided herein is a pharmaceutical composition comprising the RNAi agent as described herein, and one or more pharmaceutically acceptable excipients.

[0010] Also provided herein are methods of treating autoimmune hepatitis (AIH) in a patient in need thereof, comprising administering to the patient a FAS RNAi agent or pharmaceutical composition thereof described herein.

[0011] Also provided herein are FAS RNAi agent for use in a therapy. Also provided herein are FAS RNAi agent for use in in the treatment of AIH. Also provided herein are uses of FAS RNAi agent in the manufacture of a medicament for the treatment of AIH.

[0011a] In another aspect, provided herein is the RNAi agent as described herein, for use in therapy.

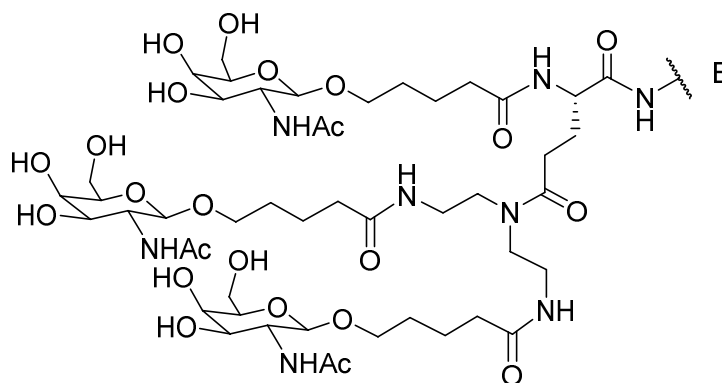
[0011b] In another aspect, provided herein is the RNAi agent as described herein, for use in the treatment of autoimmune hepatitis (AIH).

[0011c] In another aspect, provided herein is the use of the RNAi agent as described herein, in the manufacture of a medicament for the treatment of autoimmune hepatitis (AIH).

[0011d] In another aspect, provided herein is an in vitro method of decreasing FAS expression in a cell, comprising contacting the cell with the RNAi agent as described herein.

What is claimed is:

1. An RNAi agent for reducing FAS gene expression, wherein the RNAi agent comprises a delivery moiety of Formula I conjugated to R, wherein R is a double stranded RNA (dsRNA) comprising an antisense strand and a sense strand:



Formula I,

- wherein R is conjugated to connection point E of Formula I, optionally via a linker, wherein the sense strand and the antisense strand form a duplex region, and wherein the antisense strand comprises a region of complementarity to a FAS mRNA target sequence of SEQ ID NO: 1, and wherein the sense and antisense strand each optionally comprise one or more modified nucleotides and one or more modified internucleotide linkages.
2. The RNAi agent of claim 1, wherein Formula I is conjugated to the sense strand, optionally via a linker.
 3. The RNAi agent of claim 2, wherein Formula I is conjugated to the 3' terminal nucleotide of the sense strand, optionally via a linker.
 4. The RNAi agent of any one of claims 1 to 3, wherein the antisense strand is 15 to 50 nucleotides in length.
 5. The RNAi agent of any one of Claims 1 to 4, wherein the sense strand is 15 to 50 nucleotides in length.

6. The RNAi agent of any one of claims 1 to 5, wherein the antisense strand is between 18 and 23 nucleotides in length.
7. The RNAi agent of any one of claims 1 to 6, wherein the sense strand is between 18 and 21 nucleotides in length.
8. The RNAi agent of any one of claims 1 to 7, wherein the antisense strand is 23 nucleotides in length and the sense strand is 21 nucleotides in length.
9. The RNAi agent of any one of Claims 1 to 8, wherein the region of complementarity is at least 18 nucleotides in length.
10. The RNAi agent of any one of claims 1 to 9, wherein the antisense strand comprises a sequence selected from the group consisting of SEQ ID NO: 2 to SEQ ID NO: 112.
11. The RNAi agent of any one of claims 1 to 10, wherein the antisense strand comprises at least 18 contiguous nucleotides of a sequence selected from the group consisting of SEQ ID NOs: 224 to 334, 337, 338, 573, and 577.
12. The RNAi agent of any one of claims 1 to 11, wherein the antisense strand has a nucleotide sequence selected from the group consisting of SEQ ID NOs: 224 -334, 337, 338, 573, and 577, or a sequence having at least 90% sequence identity thereto.
13. The RNAi agent of any one of claims 1 to 12, wherein the sense strand is selected from the group consisting of SEQ ID NOs: 113 to 223, 335, 336, 572, and 576, or a sequence having at least 90% sequence identity thereto.
14. The RNAi agent of any one of claims 1 to 13, wherein the duplex region between the sense strand and the antisense strand comprises 0, 1, 2, or 3 mismatches between the sense strand and the antisense strand.

15. The RNAi agent of any one of claims 1 to 14, wherein the sense strand comprises a first nucleic acid sequence and the antisense strand comprises a second nucleic acid sequence, wherein the first nucleic acid sequence and the second nucleic acid sequence are selected from the group consisting of:
 - a. the first nucleic acid sequence has at least 95% sequence identity to SEQ ID NO: 129, and the second nucleic acid sequence has at least 95% sequence identity to SEQ ID NO: 240;
 - b. the first nucleic acid sequence has at least 95% sequence identity to SEQ ID NO: 116, and the second nucleic acid sequence has at least 95% sequence identity to SEQ ID NO: 227;
 - c. the first nucleic acid sequence has at least 95% sequence identity to SEQ ID NO: 151, and the second nucleic acid sequence has at least 95% sequence identity to SEQ ID NO: 262;
 - d. the first nucleic acid sequence has at least 95% sequence identity to SEQ ID NO: 128, and the second nucleic acid sequence has at least 95% sequence identity to SEQ ID NO: 239; and
 - e. the first nucleic acid sequence has at least 95% sequence identity to SEQ ID NO: 155, and the second nucleic acid sequence has at least 95% sequence identity to SEQ ID NO: 266.
16. The RNAi agent of any one of claims 1 to 15, wherein the sense strand comprises a first nucleic acid sequence and the antisense strand comprises a second nucleic acid sequence, wherein the first nucleic acid sequence and the second nucleic acid sequence are selected from the group consisting of:
 - a. the first nucleic acid sequence comprises SEQ ID NO: 129, and the second nucleic acid sequence comprises SEQ ID NO: 240;
 - b. the first nucleic acid sequence comprises SEQ ID NO: 116, and the second nucleic acid sequence comprises SEQ ID NO: 227;
 - c. the first nucleic acid sequence comprises SEQ ID NO: 151, and the second nucleic acid sequence comprises SEQ ID NO: 262;
 - d. the first nucleic acid sequence comprises SEQ ID NO: 128, and the second nucleic acid sequence comprises SEQ ID NO: 239; and

- e. the first nucleic acid sequence comprises SEQ ID NO: 155, and the second nucleic acid sequence comprises SEQ ID NO: 266.
- 17. The RNAi agent of any one of claims 1 to 16, wherein the sense strand or the antisense strand each independently comprise one or more modified nucleotides.
 - 18. The RNAi agent of any one of claims 1 to 17, wherein the sense strand or the antisense strand each independently comprise one or more modified nucleotides, and the modified nucleotides are independently 2' fluoro modified nucleotide residues, 2'-O-methyl modified nucleotides, or glycol nucleic acid (GNA) nucleotides.
 - 19. The RNAi agent of any one of claims 1 to 18, wherein the sense strand comprises one or more modified nucleotide residues, and wherein at least one modified nucleotide residue is a GNA nucleotide that is present in an internal position of the sense strand.
 - 20. The RNAi agent of any one of claims 1 to 19, wherein each nucleotide of the sense strand and each nucleotide of the antisense strand is a modified nucleotide.
 - 21. The RNAi agent of any one of claims 1 to 20, wherein the antisense strand is 23 nucleotides in length and wherein each nucleotide of the antisense strand is a modified nucleotide, and 2' fluoro modified nucleotides are present at
 - a. Positions 2, 3, 7, 14, and 16 from the 5' end of the antisense strand; or
 - b. Positions 2, 5, 7, 14, and 16 from the 5' end of the antisense strand; or
 - c. Positions 2, 3, 8, 14, and 16 from the 5' end of the antisense strand; or
 - d. Positions 2, 5, 8, 14, and 16 from the 5' end of the antisense strand; or
 - e. Positions 2, 6, 14, and 16 from the 5' end of the antisense strand.
 - 22. The RNAi agent of any one of claims 1 to 21, wherein the sense strand and antisense strand each independently comprise one or more modified internucleotide linkages, and wherein each modified internucleotide linkage is a phosphorothioate linkage.

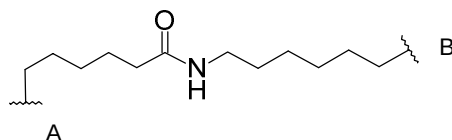
23. The RNAi agent of claim 1 to 22, wherein the sense strand and antisense strand each independently comprise four phosphorothioate linkages.
24. The RNAi agent of any one of claims 1 to 23, wherein the 5' terminal nucleotide of the antisense strand comprises a phosphate group or a phosphate analog.
25. The RNAi agent of any one of claims 1 to 24, wherein the antisense strand comprises a sequence selected from the group consisting of SEQ ID NOs: 340, 342, 344, 346, 348, 350, 352, 354, 356, 358, 360, 362, 364, 366, 368, 370, 372, 374, 376, 378, 380, 382, 384, 386, 388, 390, 392, 394, 396, 398, 400, 402, 404, 406, 408, 410, 412, 414, 416, 418, 420, 422, 424, 426, 428, 430, 432, 434, 436, 438, 440, 442, 444, 446, 448, 450, 452, 454, 456, 458, 460, 462, 464, 466, 468, 470, 472, 474, 476, 478, 480, 482, 484, 486, 488, 490, 492, 494, 496, 498, 500, 502, 504, 506, 508, 510, 512, 514, 516, 518, 520, 522, 524, 526, 528, 530, 532, 534, 536, 538, 540, 542, 544, 546, 548, 550, 552, 554, 556, 558, 560, 562, 563, 566, 567, 569, 570, 571, 575, 579, 581, 583, 585, or a sequence having at least 90% sequence identity thereto, wherein the 5' terminal nucleotide of the antisense strand comprises a vinyl phosphonate, a phosphate, or a hydroxyl group.
26. The RNAi agent of any one of claims 1 to 25, wherein the sense strand comprises a sequence selected from the group consisting of SEQ ID NOs: 339, 341, 343, 345, 347, 349, 351, 353, 355, 357, 359, 361, 363, 365, 367, 369, 371, 373, 375, 377, 379, 381, 383, 385, 387, 389, 391, 393, 395, 397, 399, 401, 403, 405, 407, 409, 411, 413, 415, 417, 419, 421, 423, 425, 427, 429, 431, 433, 435, 437, 439, 441, 443, 445, 447, 449, 451, 453, 455, 457, 459, 461, 463, 465, 467, 469, 471, 473, 475, 477, 479, 481, 483, 485, 487, 489, 491, 493, 495, 497, 499, 501, 503, 505, 507, 509, 511, 513, 515, 517, 519, 521, 523, 525, 527, 529, 531, 533, 535, 537, 539, 541, 543, 545, 547, 549, 551, 553, 555, 557, 559, 561, 564, 565, 568, 574, 578, 580, 582, 584 or a sequence having at least 90% sequence identity thereto, wherein the 5' terminal nucleotide of the antisense strand comprises a vinyl phosphonate, a phosphate, or a hydroxyl group.

27. The RNAi agent of any one of claims 1 to 24, wherein the antisense strand comprises a sequence selected from the group consisting of SEQ ID NOs: 587, 589, 591, 593, 595, 597, 599, 601, 603, 605, 607, 609, 611, 613, 615, 617, 619, 621, 623, 625, 627, 629, 631, 633, 635, 637, 639, 641, 643, 645, 647, 649, 651, 653, 655, 657, 659, 661, 663, 665, 667, 669, 671, 673, 675, 677, 679, 681, 683, 685, 687, 689, 691, 693, 695, 697, 699, 701, 703, 705, 707, 709, 711, 713, 715, 717, 719, 721, 723, 725, 727, 729, 731, 733, 735, 737, 739, 741, 743, 745, 747, 749, 751, 753, 755, 757, 759, 761, 763, 765, 767, 769, 771, 773, 775, 777, 779, 781, 783, 785, 787, 789, 791, 793, 795, 797, 799, 801, 803, 805, 807, 813, 815, 817, 819, or a sequence having at least 90% sequence identity thereto.
28. The RNAi agent of any one of claims 1 to 24 or 27, wherein the sense strand comprises a sequence selected from the group consisting of SEQ ID NOs: 588, 590, 592, 594, 596, 598, 600, 602, 604, 606, 608, 610, 612, 614, 616, 618, 620, 622, 624, 626, 628, 630, 632, 634, 636, 638, 640, 642, 644, 646, 648, 650, 652, 654, 656, 658, 660, 662, 664, 666, 668, 670, 672, 674, 676, 678, 680, 682, 684, 686, 688, 690, 692, 694, 696, 698, 700, 702, 704, 706, 708, 710, 712, 714, 716, 718, 720, 722, 724, 726, 728, 730, 732, 734, 736, 738, 740, 742, 744, 746, 748, 750, 752, 754, 756, 758, 760, 762, 764, 766, 768, 770, 772, 774, 776, 778, 780, 782, 784, 786, 788, 790, 792, 794, 796, 798, 800, 802, 804, 806, 808, 809, 810, 811, 812, 814, 816, 818, or a sequence having at least 90% sequence identity thereto.
29. The RNAi agent of any one of claims 1 to 28, wherein the sense strand comprises a first nucleic acid sequence and the antisense strand comprises a second nucleic acid sequence, wherein the first nucleic acid sequence and the second nucleic acid sequence are selected from the group consisting of:
- a. the first nucleic acid sequence has at least 95% sequence identity to SEQ ID NO: 339, and the second nucleic acid sequence has at least 95% sequence identity to SEQ ID NO: 340;
 - b. the first nucleic acid sequence has at least 95% sequence identity to SEQ ID NO: 341, and the second nucleic acid sequence has at least 95% sequence identity to SEQ ID NO: 342;

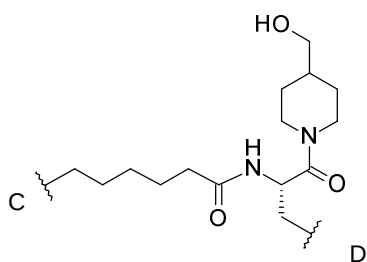
- c. the first nucleic acid sequence has at least 95% sequence identity to SEQ ID NO: 343, and the second nucleic acid sequence has at least 95% sequence identity to SEQ ID NO: 344;
 - d. the first nucleic acid sequence has at least 95% sequence identity to SEQ ID NO: 345, and the second nucleic acid sequence has at least 95% sequence identity to SEQ ID NO: 346;
 - e. the first nucleic acid sequence has at least 95% sequence identity to SEQ ID NO: 347, and the second nucleic acid sequence has at least 95% sequence identity to SEQ ID NO: 348;
 - f. the first nucleic acid sequence has at least 95% sequence identity to SEQ ID NO: 349, and the second nucleic acid sequence has at least 95% sequence identity to SEQ ID NO: 350;
 - g. the first nucleic acid sequence has at least 95% sequence identity to SEQ ID NO: 353, and the second nucleic acid sequence has at least 95% sequence identity to SEQ ID NO: 354;
 - h. the first nucleic acid sequence has at least 95% sequence identity to SEQ ID NO: 363 and the second nucleic acid sequence has at least 95% sequence identity to SEQ ID NO: 364; and
 - i. the first nucleic acid sequence has at least 95% sequence identity to SEQ ID NO: 381, and the second nucleic acid sequence has at least 95% sequence identity to SEQ ID NO: 382.
30. The RNAi agent of any one of claims 1 to 28, wherein the sense strand comprises a first nucleic acid sequence and the antisense strand comprises a second nucleic acid sequence, wherein the first nucleic acid sequence and the second nucleic acid sequence are selected from the group consisting of:
- a. the first nucleic acid sequence has at least 95% sequence identity to SEQ ID NO: 564 or 809, and the second nucleic acid sequence has at least 95% sequence identity to SEQ ID NO: 571;
 - b. the first nucleic acid sequence has at least 95% sequence identity to SEQ ID NO: 568 or 811, and the second nucleic acid sequence has at least 95% sequence identity to SEQ ID NO: 567;

- c. the first nucleic acid sequence has at least 95% sequence identity to SEQ ID NO: 580 or 814, and the second nucleic acid sequence has at least 95% sequence identity to SEQ ID NO: 581 or 815;
 - d. the first nucleic acid sequence has at least 95% sequence identity to SEQ ID NO: 582 or 816, and the second nucleic acid sequence has at least 95% sequence identity to SEQ ID NO: 583 or 817; and
 - e. the first nucleic acid sequence has at least 95% sequence identity to SEQ ID NO: 584 or 818, and the second nucleic acid sequence has at least 95% sequence identity to SEQ ID NO: 585 or 819.
31. The RNAi agent of any one of claims 1 to 28, wherein the sense strand comprises a first nucleic acid sequence and the antisense strand comprises a second nucleic acid sequence, wherein the first nucleic acid sequence and the second nucleic acid sequence are selected from the group consisting of:
- a. the first nucleic acid sequence comprises SEQ ID NO: 564 or 809, and the second nucleic acid sequence comprises SEQ ID NO: 571;
 - b. the first nucleic acid sequence comprises SEQ ID NO: 568 or 811, and the second nucleic acid sequence comprises SEQ ID NO: 567;
 - c. the first nucleic acid sequence comprises SEQ ID NO: 580 or 814, and the second nucleic acid sequence comprises SEQ ID NO: 581 or 815;
 - d. the first nucleic acid sequence comprises SEQ ID NO: 582 or 816, and the second nucleic acid sequence comprises SEQ ID NO: 583 or 817; and
 - e. the first nucleic acid sequence comprises SEQ ID NO: 584 or 818, and the second nucleic acid sequence comprises SEQ ID NO: 585 or 819.
32. The RNAi agent of any one of claims 29-31, wherein the 5' terminal nucleotide of the antisense strand contains a vinyl phosphonate, a phosphate group, or an OH group.
33. The RNAi agent of any one of the claims 1 to 32, wherein R is conjugated to Formula I via a linker.

34. The RNAi agent of claims 1 to 33, wherein R is conjugated to Formula I via a linker, and wherein linker comprises a linker of Formula II having connection points A and B or the linker comprises Formula III having connection points C and D, and wherein:

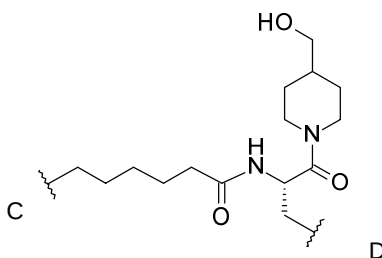


Formula II;



Formula III;

- a. Formula I is conjugated to Formula II at connection point A and Formula II is conjugated to a phosphate group or a phosphorothioate group at connection point B, and the phosphate group or phosphorothioate group is further conjugated to R; or
 - b. Formula I is conjugated to Formula III at connection point C and Formula III is conjugated to a phosphate group or phosphorothioate group at connection point D, and the phosphate group or phosphorothioate group is further conjugated to R.
35. The RNAi agent of any one of claims 1 to 34, wherein R is conjugated to Formula I via a linker, and wherein the linker is a linker comprising Formula III having connection points C and D:



Formula III;

and wherein Formula I is conjugated to Formula III at connection point C and Formula III is conjugated to a phosphate group or a phosphorothioate group at connection point D, and the phosphate group or the phosphorothioate group is further conjugated to R.

36. The RNAi agent of any one of claims 1 to 35, wherein the RNAi agent decreases expression of the FAS gene in a liver cell, as compared to a control.
37. The RNAi agent of any one of claims 1 to 35, wherein the linker is of Formula III and Formula III is conjugated to a phosphate group at connection point D, and wherein the sense strand comprises a first nucleic acid sequence and the antisense strand comprises a second nucleic acid sequence, wherein the first nucleic acid sequence comprises SEQ ID NO: 564, and the second nucleic acid sequence comprises SEQ ID NO: 571.
38. The RNAi agent of any one of claims 1 to 37, for use in therapy.
39. The RNAi agent of any one of claims 1 to 37, for use in the treatment of autoimmune hepatitis (AIH).
40. A pharmaceutical composition comprising the RNAi agent of any one of claims 1 to 37, and one or more pharmaceutically acceptable excipients.
41. The use of the RNAi agent of any one of claims 1 to 37, in the manufacture of a medicament for the treatment of autoimmune hepatitis (AIH).

42. An in vitro method of decreasing FAS expression in a cell, comprising contacting the cell with the RNAi agent of any one of claims 1 to 37.
43. The method of claim 42, wherein the method further comprises incubating the cell for a time sufficient for decreasing the level of FAS mRNA by at least 50% as compared to an untreated or control treated cell.