CLAIMS

What is claimed:

1. An RNAi construct for inhibiting expression of a human *MARC1* gene in a cell, said RNAi construct comprising a sense strand and an antisense strand that hybridize to form a duplex region of about 15 to about 30 base pairs in length, and wherein the antisense strand comprises a region having a sequence that is substantially complementary to the sequence of at least 15 contiguous nucleotides of nucleotides 1205 to 1250 of SEQ ID NO: 1.

2. The RNAi construct of claim 1, wherein the region of the antisense strand comprises a sequence that is substantially complementary to the sequence of at least 15 contiguous nucleotides of nucleotides 1209 to 1239 of SEQ ID NO: 1.

3. The RNAi construct of claim 1 or 2, wherein the region of the antisense strand comprises a sequence of CAUCUAAUAUUCCAG (SEQ ID NO: 3656).

4. The RNAi construct of claim 1, wherein the RNAi construct is D-2241, D-2063, D-2066, D-2076, D-2077, D-2078, D-2080, D-2081, D-2108, D-2113, D-2142, D-2240, D-2243, D-2245, D-2246, D-2248, D-2250, D-2251, D-2253, D-2255, D-2256, D-2258, D-2259, D-2261, D-2264, D-2265, D-2268, D-2269, D-2270, D-2271, D-2301, D-2309, D-2311, D-2312, D-2314, D-2316, D-2317, D-2319, D-2321, D-2322, D-2324, D-2326, D-2327, D-2329, D-2331, D-2332, D-2334, D-2336, D-2337, D-2339, D-2341, D-2342, D-2344, D-2346, D-2347, D-2349, D-2351, D-2352, D-2354, D-2356, D-2357, D-2376, D-2380, D-2393, D-2395, D-2396, D-2431, D-2436, D-2437, D-2440, D-2441, D-2444, D-2445, D-2447, D-2453, D-2518, D-2519, D-2520, D-2521, D-2522, D-2523, D-2524, D-2525, D-2526, D-2527, D-2528, D-2529, D-2530, D-2531, D-2532, D-2533, D-2534, or D-2535.

5. An RNAi construct for inhibiting expression of a human *MARC1* gene in a cell, said RNAi construct comprising a sense strand and an antisense strand that hybridize to form a duplex region of about 15 to about 30 base pairs in length, and wherein the antisense strand comprises a region having a sequence that is substantially complementary to the sequence of at least 15 contiguous nucleotides of nucleotides 1345 to 1375 of SEQ ID NO: 1.

6. The RNAi construct of claim 5, wherein the region of the antisense strand comprises a sequence of UGGGACAUUGAAGCA (SEQ ID NO: 3657).

7. The RNAi construct of claim 5, wherein the RNAi construct is D-2042, D-2043, D-2047, D-2052, D-2158, D-2162, D-2169, D-2182, D-2183, D-2184, D-2185, D-2186, D-2187, D-2189, D-2211, D-2213, D-2304, D-2305, D-2306, D-2307, D-2308, D-2384, D-2384, D-2385, D-2386, D-2387, D-2388, D-2389, D-2390, D-2391, D-2392, D-2399, D-2400, D-2401, D-2402, D-2403, D-2488, D-2494, D-2500, D-2506, D-2512, D-2538, D-2539, D-2540, or D-2541.

8. An RNAi construct for inhibiting expression of a human *MARC1* gene in a cell, said RNAi construct comprising a sense strand and an antisense strand that hybridize to form a duplex region of about 15 to about 30 base pairs in length, and wherein the antisense strand comprises a region having a sequence that is substantially complementary to the sequence of at least 15 contiguous nucleotides of nucleotides 2039 to 2078 of SEQ ID NO: 1.

9. The RNAi construct of claim 8, wherein the region of the antisense strand comprises a sequence that is substantially complementary to the sequence of at least 15 contiguous nucleotides of nucleotides 2048 to 2074 of SEQ ID NO: 1.

10. The RNAi construct of claim 8 or 9, wherein the region of the antisense strand comprises a sequence of AUCAGAUCUUAGAGU (SEQ ID NO: 3658).

11. The RNAi construct of claim 8, wherein the RNAi construct is D-2045, D-2065, D-2079, D-2082, D-2105, D-2106, D-2137, D-2143, D-2166, D-2173, D-2193, D-2242, D-2247, D-2252, D-2257, D-2260, D-2262, D-2266, D-2272, D-2273, D-2302, D-2303, D-2310, D-2313, D-2315, D-2318, D-2320, D-2323, D-2325, D-2328, D-2330, D-2333, D-2335, D-2338, D-2340, D-2343, D-2345, D-2348, D-2350, D-2353, D-2355, D-2358, D-2394, D-2397, D-2454, D-2455, D-2456, D-2457, D-2458, D-2459, D-2460, D-2463, D-2465, D-2465, D-2468, D-2470, D-2472, D-2473, D-2477, D-2487, D-2493, D-2499, D-2505, D-2511, D-2552, D-2553, D-2554, D-2555, D-2556, or D-2557.

12. An RNAi construct comprising a sense strand and an antisense strand, wherein the antisense strand comprises a region having a sequence that is substantially complementary to a mARC1 mRNA sequence, and wherein said region comprises at least 15 contiguous nucleotides from an antisense sequence listed in Table 1 or Table 2.

13. The RNAi construct of claim 12, wherein the sense strand comprises a sequence that is sufficiently complementary to the sequence of the antisense strand to form a duplex region of about 15 to about 30 base pairs in length.

14. The RNAi construct of any one of claims 1 to 13, wherein the duplex region is about 19 to about 21 base pairs in length.

15. The RNAi construct of any one of claims 1 to 14, wherein the sense strand and the antisense strand are each independently about 19 to about 30 nucleotides in length.

16. The RNAi construct of claim 15, wherein the sense strand and the antisense strand are each independently about 19 to about 23 nucleotides in length.

17. The RNAi construct of any one of claims 1 to 16, wherein the RNAi construct comprises one or two blunt ends.

18. The RNAi construct of any one of claims 1 to 16, wherein the RNAi construct comprises one or two nucleotide overhangs of 1 to 4 unpaired nucleotides.

19. The RNAi construct of claim 18, wherein the nucleotide overhang has 2 unpaired nucleotides.

20. The RNAi construct of claim 18 or 19, wherein the RNAi construct comprises a nucleotide overhang at the 3′ end of the sense strand, the 3′ end of the antisense strand, or the 3′ end of both the sense strand and the antisense strand.

21. The RNAi construct of any one of claims 1 to 20, wherein the RNAi construct comprises at least one modified nucleotide.

22. The RNAi construct of claim 21, wherein the modified nucleotide is a 2′-modified nucleotide.

23. The RNAi construct of claim 21, wherein the modified nucleotide is a 2′-fluoro modified nucleotide, a 2′-O-methyl modified nucleotide, a 2′-O-methoxyethyl modified nucleotide, 2′-O-alkyl modified nucleotide, a 2′-O-allyl modified nucleotide, a bicyclic nucleic acid (BNA), a deoxyribonucleotide, or combinations thereof.

24. The RNAi construct of claim 21, wherein all of the nucleotides in the sense and antisense strands are modified nucleotides.

25. The RNAi construct of claim 24, wherein the modified nucleotides are 2′-O-methyl modified nucleotides, 2′-fluoro modified nucleotides, or combinations thereof.

26. The RNAi construct of any one of claims 1 to 25, wherein the sense strand comprises an abasic nucleotide as the terminal nucleotide at its 3′ end, its 5′ end, or both its 3′ and 5′ ends.

27. The RNAi construct of claim 26, wherein the abasic nucleotide is linked to the adjacent nucleotide through a 3′-3′ internucleotide linkage or a 5′-5′ internucleotide linkage.

28. The RNAi construct of any one of claims 1 to 27, wherein the sense strand, the antisense strand, or both the sense and antisense strands comprise one or more phosphorothioate internucleotide linkages.

29. The RNAi construct of claim 28, wherein the antisense strand comprises two consecutive phosphorothioate internucleotide linkages between the terminal nucleotides at both the 3′ and 5′ ends.

30. The RNAi construct of claim 28 or 29, wherein the sense strand comprises a single phosphorothioate internucleotide linkage between the terminal nucleotides at the 3′ end.

31. The RNAi construct of claim 28 or 29, wherein the sense strand comprises two consecutive phosphorothioate internucleotide linkages between the terminal nucleotides at the 3′ end.

32. The RNAi construct of any one of claims 12 to 31, wherein the antisense strand comprises or consists of a sequence selected from the antisense sequences listed in Table 1 or Table 2.

33. The RNAi construct of any one of claims 12 to 32, wherein the antisense strand comprises or consists of a sequence selected from SEQ ID NO: 2949; SEQ ID NO: 715; SEQ ID NO: 732; SEQ ID NO: 733; SEQ ID NO: 738; SEQ ID NO: 754; SEQ ID NO: 761; SEQ ID NO: 763; SEQ ID NO: 764; SEQ ID NO: 766; SEQ ID NO: 809; SEQ ID NO: 810; SEQ ID NO: 814; SEQ ID NO: 841; SEQ ID NO: 848; SEQ ID NO: 851; SEQ ID NO: 862; SEQ ID NO: 916; SEQ ID NO: 1057; SEQ ID NO: 1078; SEQ ID NO: 2919; SEQ ID NO: 2926; SEQ ID NO: 2946; SEQ ID NO: 2953; and SEQ ID NO: 2956.

34. The RNAi construct of any one of claims 12 to 33, wherein the sense strand comprises or consists of a sequence selected from the sense sequences listed in Table 1 or Table 2.

35. The RNAi construct of claim 34, wherein the sense strand comprises or consists of a sequence selected from SEQ ID NO: 391; SEQ ID NO: 46; SEQ ID NO: 63; SEQ ID NO: 64; SEQ ID NO: 69; SEQ ID NO: 85; SEQ ID NO: 92; SEQ ID NO: 94; SEQ ID NO: 95; SEQ ID NO: 97; SEQ ID NO: 140; SEQ ID NO: 141; SEQ ID NO: 145; SEQ ID NO: 172; SEQ ID NO: 179; SEQ ID NO: 182; SEQ ID NO: 193; SEQ ID NO: 247; SEQ ID NO: 388; SEQ ID NO: 390; SEQ ID NO: 409; SEQ ID NO: 2808; and SEQ ID NO: 2820.

36. The RNAi construct of any one of claims 12 to 35, wherein:

(i) the sense strand comprises or consists of the sequence of SEQ ID NO: 46 and the antisense strand comprises or consists of the sequence of SEQ ID NO: 715;

(ii) the sense strand comprises or consists of the sequence of SEQ ID NO: 63 and the antisense strand comprises or consists of the sequence of SEQ ID NO: 732;

(iii) the sense strand comprises or consists of the sequence of SEQ ID NO: 64 and the antisense strand comprises or consists of the sequence of SEQ ID NO: 733;

(iv) the sense strand comprises or consists of the sequence of SEQ ID NO: 69 and the antisense strand comprises or consists of the sequence of SEQ ID NO: 738;

(v) the sense strand comprises or consists of the sequence of SEQ ID NO: 85 and the antisense strand comprises or consists of the sequence of SEQ ID NO: 754;

(vi) the sense strand comprises or consists of the sequence of SEQ ID NO: 92 and the antisense strand comprises or consists of the sequence of SEQ ID NO: 761;

(vii) the sense strand comprises or consists of the sequence of SEQ ID NO: 94 and the antisense strand comprises or consists of the sequence of SEQ ID NO: 763;

(viii) the sense strand comprises or consists of the sequence of SEQ ID NO: 95 and the antisense strand comprises or consists of the sequence of SEQ ID NO: 764;

(ix) the sense strand comprises or consists of the sequence of SEQ ID NO: 97 and the antisense strand comprises or consists of the sequence of SEQ ID NO: 766;

(x) the sense strand comprises or consists of the sequence of SEQ ID NO: 140 and the antisense strand comprises or consists of the sequence of SEQ ID NO: 809;

(xi) the sense strand comprises or consists of the sequence of SEQ ID NO: 141 and the antisense strand comprises or consists of the sequence of SEQ ID NO: 810;

(xii) the sense strand comprises or consists of the sequence of SEQ ID NO: 145 and the antisense strand comprises or consists of the sequence of SEQ ID NO: 814;

(xiii) the sense strand comprises or consists of the sequence of SEQ ID NO: 172 and the antisense strand comprises or consists of the sequence of SEQ ID NO: 841;

(xiv) the sense strand comprises or consists of the sequence of SEQ ID NO: 179 and the antisense strand comprises or consists of the sequence of SEQ ID NO: 848;

(xv) the sense strand comprises or consists of the sequence of SEQ ID NO: 182 and the antisense strand comprises or consists of the sequence of SEQ ID NO: 851;

(xvi) the sense strand comprises or consists of the sequence of SEQ ID NO: 193 and the antisense strand comprises or consists of the sequence of SEQ ID NO: 862; or

(xvii) the sense strand comprises or consists of the sequence of SEQ ID NO: 247 and the antisense strand comprises or consists of the sequence of SEQ ID NO: 916.

37. The RNAi construct of any one of claims 12 to 25, wherein:

(i) the sense strand comprises or consists of the sequence of SEQ ID NO: 391 and the antisense strand comprises or consists of the sequence of SEQ ID NO: 2949;

(ii) the sense strand comprises or consists of the sequence of SEQ ID NO: 409 and the antisense strand comprises or consists of the sequence of SEQ ID NO: 1078;

(iii) the sense strand comprises or consists of the sequence of SEQ ID NO: 388 and the antisense strand comprises or consists of the sequence of SEQ ID NO: 1057;

(iv) the sense strand comprises or consists of the sequence of SEQ ID NO: 2808 and the antisense strand comprises or consists of the sequence of SEQ ID NO: 2926;

(v) the sense strand comprises or consists of the sequence of SEQ ID NO: 2820 and the antisense strand comprises or consists of the sequence of SEQ ID NO: 2946;

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(vi) the sense strand comprises or consists of the sequence of SEQ ID NO: 390 and the antisense strand comprises or consists of the sequence of SEQ ID NO: 2956;

(vii) the sense strand comprises or consists of the sequence of SEQ ID NO: 179 and the antisense strand comprises or consists of the sequence of SEQ ID NO: 2919;

(viii) the sense strand comprises or consists of the sequence of SEQ ID NO: 388 and the antisense strand comprises or consists of the sequence of SEQ ID NO: 2953; or

(ix) the sense strand comprises or consists of the sequence of SEQ ID NO: 388 and the antisense strand comprises or consists of the sequence of SEQ ID NO: 1057.

38. The RNAi construct of claim 38, wherein:

(i) the sense strand comprises or consists of the sequence of modified nucleotides according to SEQ ID NO: 3076 and the antisense strand comprises or consists of the sequence of modified nucleotides according to SEQ ID NO: 3472;

(ii) the sense strand comprises or consists of the sequence of modified nucleotides according to SEQ ID NO: 3078 and the antisense strand comprises or consists of the sequence of modified nucleotides according to SEQ ID NO: 3337;

(iii) the sense strand comprises or consists of the sequence of modified nucleotides according to SEQ ID NO: 3080 and the antisense strand comprises or consists of the sequence of modified nucleotides according to SEQ ID NO: 3339;

(iv) the sense strand comprises or consists of the sequence of modified nucleotides according to SEQ ID NO: 3163 and the antisense strand comprises or consists of the sequence of modified nucleotides according to SEQ ID NO: 3441;

(v) the sense strand comprises or consists of the sequence of modified nucleotides according to SEQ ID NO: 3183 and the antisense strand comprises or consists of the sequence of modified nucleotides according to SEQ ID NO: 3469;

(vi) the sense strand comprises or consists of the sequence of modified nucleotides according to SEQ ID NO: 3077 and the antisense strand comprises or consists of the sequence of modified nucleotides according to SEQ ID NO: 3484;

(vii) the sense strand comprises or consists of the sequence of modified nucleotides according to SEQ ID NO: 2051 and the antisense strand comprises or consists of the sequence of modified nucleotides according to SEQ ID NO: 3545;

(viii) the sense strand comprises or consists of the sequence of modified nucleotides according to SEQ ID NO: 3080 and the antisense strand comprises or consists of the sequence of modified nucleotides according to SEQ ID NO: 3481;

(ix) the sense strand comprises or consists of the sequence of modified nucleotides according to SEQ ID NO: 3188 and the antisense strand comprises or consists of the sequence of modified nucleotides according to SEQ ID NO: 3339;

(x) the sense strand comprises or consists of the sequence of modified nucleotides according to SEQ ID NO: 3080 and the antisense strand comprises or consists of the sequence of modified nucleotides according to SEQ ID NO: 3476; or

(xi) the sense strand comprises or consists of the sequence of modified nucleotides according to SEQ ID NO: 3223 and the antisense strand comprises or consists of the sequence of modified nucleotides according to SEQ ID NO: 3517.

39. The RNAi construct of any one of claims 12 to 38, wherein the RNAi construct is any one of the duplex compounds listed in Tables 1-24.

40. The RNAi construct of claim 39, wherein the RNAi construct is D-2241, D-2078, D-2079, D-2081, D-2182, D-2196, D-2238, D-2243, D-2246, D-2255, D-2258, D-2301, D-2316, D-2317, D-2329, D-2332, D-2341, D-2344, D-2356, D-2357, D-2399, or D-2510.

41. The RNAi construct of claim 30, wherein the RNAi construct is D-2241, D-2079, D-2081, D-2196, D-2238, D-2255, D-2258, D-2317, D-2332, D-2357, or D-2399.

42. The RNAi construct of any one of claims 1 to 41, wherein the RNAi construct further comprises a ligand.

43. The RNAi construct of claim 42, wherein the ligand comprises a cholesterol moiety, a vitamin, a steroid, a bile acid, a folate moiety, a fatty acid, a carbohydrate, a glycoside, or antibody or antigen-binding fragment thereof.

44. The RNAi construct of claim 42, wherein the ligand comprises galactose, galactosamine, or N-acetyl-galactosamine.

45. The RNAi construct of claim 44, wherein the ligand comprises a multivalent galactose moiety or multivalent N-acetyl-galactosamine moiety.

46. The RNAi construct of claim 45, wherein the multivalent galactose moiety or multivalent N-acetyl-galactosamine moiety is trivalent or tetravalent.

47. The RNAi construct of any one of claims 42 to 46, wherein the ligand is covalently attached to the sense strand optionally through a linker.

48. The RNAi construct of claim 47, wherein the ligand is covalently attached to the 5′ end of the sense strand.

49. A pharmaceutical composition comprising the RNAi construct of any one of claims 1 to 48 and a pharmaceutically acceptable carrier or excipient.

50. An RNAi construct of any one of claims 1 to 48 or the pharmaceutical composition of claim 49 for use in therapy.

51. Use of an RNAi construct of any one of claims 1 to 48 in the preparation of a medicament for reducing serum cholesterol in a patient in need thereof.

52. The use of claim 51, wherein the serum cholesterol is non-HDL cholesterol or LDL cholesterol.

53. The use of claim 51, wherein the patient is diagnosed with or at risk for cardiovascular disease.

54. Use of an RNAi construct of any one of claims 1 to 48 in the preparation of a medicament for treating, preventing, or reducing the risk of developing fatty liver disease in a patient in need thereof.

55. The use of claim 54, wherein the fatty liver disease is nonalcoholic fatty liver disease or nonalcoholic steatohepatitis.

56. Use of an RNAi construct of any one of claims 1 to 48 in the preparation of a medicament for treating, preventing, or reducing liver fibrosis in a patient in need thereof.

57. The use of claims 54 or 56, wherein the patient is diagnosed with or at risk for nonalcoholic fatty liver disease, nonalcoholic steatohepatitis or cirrhosis.