

CLAIMS

What is claimed:

1. An RNAi construct for inhibiting expression of a human *MARCI* 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 CAUCUAAUAUCCAG (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 *MARCI* 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 *MARCI* 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.

~~4~~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.

~~2~~13. The RNAi construct of claim ~~4~~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.

~~3. The RNAi construct of claim 2, wherein the duplex region is about 17 to about 24 base pairs in length.~~

~~4~~14. The RNAi construct of ~~any one of~~ claims ~~21 to 13~~, wherein the duplex region is about 19 to about 21 base pairs in length.

~~5~~15. The RNAi construct of any one of claims 1 to ~~4~~14, wherein the sense strand and the antisense strand are each independently about 19 to about 30 nucleotides in length.

~~6~~16. The RNAi construct of claim ~~5~~15, wherein the sense strand and the antisense strand are each independently about 19 to about 23 nucleotides in length.

~~7~~17. The RNAi construct of any one of claims 1 to ~~6~~16, wherein the RNAi construct comprises one or two blunt ends.

~~8~~18. The RNAi construct of any one of claims 1 to ~~6~~16, wherein the RNAi construct comprises one or two nucleotide overhangs of 1 to 4 unpaired nucleotides.

~~9~~19. The RNAi construct of claim ~~8~~18, wherein the nucleotide overhang has 2 unpaired nucleotides.

~~4020~~. The RNAi construct of claim ~~8-18~~ or ~~919~~, 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.

~~4121~~. The RNAi construct of any one of claims 1 to ~~4020~~, wherein the RNAi construct comprises at least one modified nucleotide.

~~4222~~. The RNAi construct of claim ~~4121~~, wherein the modified nucleotide is a 2'-modified nucleotide.

~~4323~~. The RNAi construct of claim ~~4121~~, 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.

~~4424~~. The RNAi construct of claim ~~4121~~, wherein all of the nucleotides in the sense and antisense strands are modified nucleotides.

~~4525~~. The RNAi construct of claim ~~4424~~, wherein the modified nucleotides are 2'-O-methyl modified nucleotides, 2'-fluoro modified nucleotides, or combinations thereof.

~~4626~~. The RNAi construct of any one of claims 1 to ~~4525~~, 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.

~~4727~~. The RNAi construct of claim ~~4626~~, wherein the abasic nucleotide is linked to the adjacent nucleotide through a 3'-3' internucleotide linkage or a 5'-5' internucleotide linkage.

~~4828~~. The RNAi construct of any one of claims 1 to ~~4727~~, wherein the sense strand, the antisense strand, or both the sense and antisense strands comprise one or more phosphorothioate internucleotide linkages.

1929. The RNAi construct of claim ~~1828~~, wherein the antisense strand comprises two consecutive phosphorothioate internucleotide linkages between the terminal nucleotides at both the 3' and 5' ends.

2030. The RNAi construct of claim ~~1828~~ or 1929, wherein the sense strand comprises a single phosphorothioate internucleotide linkage between the terminal nucleotides at the 3' end.

2131. The RNAi construct of claim ~~1828~~ or 1929, wherein the sense strand comprises two consecutive phosphorothioate internucleotide linkages between the terminal nucleotides at the 3' end.

2232. The RNAi construct of any one of claims ~~112~~ to 2131, wherein the antisense strand comprises or consists of a sequence selected from the antisense sequences listed in Table 1 or Table 2.

2333. The RNAi construct of any one of claims ~~112~~ to 2232, 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: 2949~~; SEQ ID NO: 2953; and SEQ ID NO: 2956.

2434. The RNAi construct of any one of claims ~~112~~ to 2333, wherein the sense strand comprises or consists of a sequence selected from the sense sequences listed in Table 1 or Table 2.

2535. The RNAi construct of claim 2434, 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: 391;~~ SEQ ID NO: 409; SEQ ID NO: 2808; and SEQ ID NO: 2820.

~~2636.~~ The RNAi construct of any one of claims ~~1-12~~ to ~~2535~~, 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.

~~2737.~~ The RNAi construct of any one of claims ~~1-12~~ 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;

(~~ii~~) 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;

(iv) 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;

~~(v) 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;~~

(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.

2838. The RNAi construct of claim 2738, 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;

(~~iii~~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;

(iv) 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;

~~(v) 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;~~

(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.

2939. The RNAi construct of any one of claims ~~1-12~~ to **2838**, wherein the RNAi construct is any one of the duplex compounds listed in Tables 1-24.

3040. The RNAi construct of claim **2939**, wherein the RNAi construct is **D-2241**, D-2078, D-2079, D-2081, D-2182, D-2196, D-2238, ~~D-2241~~, 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.

3141. The RNAi construct of claim 30, wherein the RNAi construct is **D-2241**, D-2079, D-2081, D-2196, D-2238, ~~D-2241~~, D-2255, D-2258, D-2317, D-2332, D-2357, or D-2399.

~~32. — An RNAi construct for inhibiting expression of a human *MARCI* 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.~~

~~33. — The RNAi construct of claim 32, 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.~~

~~34. — The RNAi construct of claim 32 or 33, wherein the region of the antisense strand comprises a sequence of CAUCUAAUAUCCAG (SEQ ID NO: 3656).~~

35. — The RNAi construct of claim 32, wherein the RNAi construct is ~~D-2063, D-2066, D-2076, D-2077, D-2078, D-2080, D-2081, D-2108, D-2113, D-2142, D-2240, D-2241, 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.~~

36. — The RNAi construct of claim 35, wherein the RNAi construct is ~~D-2063, D-2066, D-2076, D-2077, D-2078, D-2080, D-2081, D-2108, D-2113, D-2142, or D-2301.~~

37. — An RNAi construct for inhibiting expression of a human *MARCI* 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.

38. — The RNAi construct of claim 37, wherein the region of the antisense strand comprises a sequence of UGGGACAUUGAAGCA (SEQ ID NO: 3657).

39. — The RNAi construct of claim 37, 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.~~

40. — The RNAi construct of claim 39, wherein the RNAi construct is ~~D-2042, D-2043, D-2047, D-2052, D-2304, D-2305, D-2306, D-2307, or D-2308.~~

41. — ~~An RNAi construct for inhibiting expression of a human *MARCI* 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.~~

42. — ~~The RNAi construct of claim 41, 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.~~

43. — ~~The RNAi construct of claim 41 or 42, wherein the region of the antisense strand comprises a sequence of AUCAGAUCUUAGAGU (SEQ ID NO: 3658).~~

44. — ~~The RNAi construct of claim 41, 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.~~

45. — ~~The RNAi construct of claim 44, wherein the RNAi construct is D-2045, D-2065, D-2079, D-2082, D-2105, D-2106, D-2137, D-2143, D-2302, or D-2303.~~

46. — ~~The RNAi construct of any one of claims 32 to 45, wherein the duplex region is about 19 to about 21 base pairs in length.~~

47. — ~~The RNAi construct of any one of claims 32 to 46, wherein the sense strand and the antisense strand are each independently about 19 to about 30 nucleotides in length.~~

~~48. — The RNAi construct of claim 47, wherein the sense strand and the antisense strand are each independently about 19 to about 23 nucleotides in length.~~

~~49. — The RNAi construct of any one of claims 32 to 48, wherein the RNAi construct comprises one or two blunt ends.~~

~~50. — The RNAi construct of any one of claims 32 to 48, wherein the RNAi construct comprises one or two nucleotide overhangs of 1 to 4 unpaired nucleotides.~~

~~51. — The RNAi construct of claim 50, wherein the nucleotide overhang has 2 unpaired nucleotides.~~

~~52. — The RNAi construct of claim 50 or 51, 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.~~

~~53. — The RNAi construct of any one of claims 32 to 52, wherein the RNAi construct comprises at least one modified nucleotide.~~

~~54. — The RNAi construct of claim 53, wherein the modified nucleotide is a 2' modified nucleotide.~~

~~55. — The RNAi construct of claim 54, 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 BNA, a deoxyribonucleotide, or combinations thereof.~~

~~56. — The RNAi construct of claim 53, wherein all of the nucleotides in the sense and antisense strands are modified nucleotides.~~

~~57. — The RNAi construct of claim 56, wherein the modified nucleotides are 2' O-methyl modified nucleotides, 2' fluoro modified nucleotides, or combinations thereof.~~

~~58. — The RNAi construct of any one of claims 32 to 57, 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.~~

~~59. — The RNAi construct of claim 58, wherein the abasic nucleotide is linked to the adjacent nucleotide through a 3' 3' internucleotide linkage or a 5' 5' internucleotide linkage.~~

~~60. — The RNAi construct of any one of claims 32 to 59, wherein the sense strand, the antisense strand, or both the sense and antisense strands comprise one or more phosphorothioate internucleotide linkages.~~

~~61. — The RNAi construct of claim 60, wherein the antisense strand comprises two consecutive phosphorothioate internucleotide linkages between the terminal nucleotides at both the 3' and 5' ends.~~

~~62. — The RNAi construct of claim 60 or 61, wherein the sense strand comprises a single phosphorothioate internucleotide linkage between the terminal nucleotides at the 3' end.~~

~~63. — The RNAi construct of claim 60 or 61, wherein the sense strand comprises two consecutive phosphorothioate internucleotide linkages between the terminal nucleotides at the 3' end.~~

~~6442.~~ The RNAi construct of any one of claims 1 to ~~6341~~, wherein the RNAi construct further comprises a ligand.

~~6543.~~ The RNAi construct of claim ~~6442~~, 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.

~~6644.~~ The RNAi construct of claim ~~6442~~, wherein the ligand comprises galactose, galactosamine, or N-acetyl-galactosamine.

~~6745.~~ The RNAi construct of claim ~~6644~~, wherein the ligand comprises a multivalent galactose moiety or multivalent N-acetyl-galactosamine moiety.

~~6846.~~ The RNAi construct of claim ~~6745~~, wherein the multivalent galactose moiety or multivalent N-acetyl-galactosamine moiety is trivalent or tetravalent.

~~6947.~~ The RNAi construct of any one of claims ~~6442~~ to ~~6846~~, wherein the ligand is covalently attached to the sense strand optionally through a linker.

~~7048.~~ The RNAi construct of claim ~~6947~~, wherein the ligand is covalently attached to the 5' end of the sense strand.

~~7149.~~ A pharmaceutical composition comprising the RNAi construct of any one of claims 1 to ~~7048~~ and a pharmaceutically acceptable carrier or excipient.

~~7250.~~ An RNAi construct of any one of claims 1 to 48 or the pharmaceutical composition of claim 49 for use in therapy method for reducing the expression of mARC1 protein in a patient in need thereof comprising administering to the patient the RNAi construct of any one of claims 1 to 70 or the pharmaceutical composition of claim 71.

~~73.~~—The method of claim 72, wherein the expression level of mARC1 in hepatocytes is reduced in the patient following administration of the RNAi construct or pharmaceutical composition as compared to the mARC1 expression level in a patient not receiving the RNAi construct or pharmaceutical composition.

~~74.~~—The method of claim 72, wherein the patient is diagnosed with or at risk for cardiovascular disease, nonalcoholic fatty liver disease, nonalcoholic steatohepatitis, or cirrhosis.

~~75. — A method for reducing serum cholesterol in a patient in need thereof comprising administering to the patient the RNAi construct of any one of claims 1 to 70 or the pharmaceutical composition of claim 71.~~

~~76. — The method of claim 75, wherein the serum cholesterol is non-HDL cholesterol or LDL cholesterol.~~

~~77. — A method for treating, preventing, or reducing the risk of developing fatty liver disease in a patient in need thereof comprising administering to the patient the RNAi construct of any one of claims 1 to 70 or the pharmaceutical composition of claim 71.~~

~~78. — The method of claim 77, wherein the fatty liver disease is nonalcoholic fatty liver disease or nonalcoholic steatohepatitis.~~

~~79. — The method of claim 77 or 78, wherein the patient is diagnosed with type 2 diabetes, a metabolic disorder, or is obese.~~

~~80. — The method of claim 77 or 78, wherein the patient has elevated levels of non-HDL cholesterol or triglycerides.~~

~~81. — A method for treating, preventing, or reducing liver fibrosis in a patient in need thereof comprising administering to the patient the RNAi construct of any one of claims 1 to 70 or the pharmaceutical composition of claim 71.~~

~~82. — The method of claim 81, wherein administration of the RNAi construct or pharmaceutical composition to the patient prevents or delays cirrhosis.~~

~~83. — The method of claim 81 or 82, wherein the patient is diagnosed with nonalcoholic fatty liver disease or nonalcoholic steatohepatitis.~~

~~84. — The method of any one of claims 72 to 83, wherein the RNAi construct or pharmaceutical composition is administered to the patient via a parenteral route of administration.~~

~~85. — The method of claim 84, wherein the parenteral route of administration is intravenous or subcutaneous.~~

~~86. — An RNAi construct of any one of claims 1 to 70 for use in a method for reducing serum cholesterol in a patient in need thereof.~~

~~87. — The RNAi construct of claim 86, wherein the serum cholesterol is non-HDL cholesterol or LDL cholesterol.~~

~~88. — An RNAi construct of any one of claims 1 to 70 for use in a method for treating, preventing, or reducing the risk of developing fatty liver disease in a patient in need thereof.~~

~~89. — The RNAi construct of claim 88, wherein the fatty liver disease is nonalcoholic fatty liver disease or nonalcoholic steatohepatitis.~~

~~90. — An RNAi construct of any one of claims 1 to 70 for use in a method for treating, preventing, or reducing liver fibrosis in a patient in need thereof.~~

~~91. — The RNAi construct of claim 90, wherein the patient is diagnosed with nonalcoholic fatty liver disease or nonalcoholic steatohepatitis.~~

9251. Use of an RNAi construct of any one of claims 1 to ~~70~~ 48 in the preparation of a medicament for reducing serum cholesterol in a patient in need thereof.

9352. The use of claim 9251, 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.

9454. Use of an RNAi construct of any one of claims 1 to ~~70~~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.

9555. The use of claim 9454, wherein the fatty liver disease is nonalcoholic fatty liver disease or nonalcoholic steatohepatitis.

9656. Use of an RNAi construct of any one of claims 1 to ~~70~~48 in the preparation of a medicament for treating, preventing, or reducing liver fibrosis in a patient in need thereof.

9757. The use of claims 9654 or 56, wherein the patient is diagnosed with or at risk for nonalcoholic fatty liver disease, ~~or~~ nonalcoholic steatohepatitis or cirrhosis.