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(54)名稱

以 ATN1 mRNA 或 pre-mRNA 作為標的之反義寡核苷酸

(57)摘要

在本說明書中，提供一種反義寡核苷酸或其醫藥上可容許之鹽或此等的水合物，該反義寡核苷酸係由與包含序列編號 471 之鹼基序列之特定標的區域中之至少 15 個連續鹼基之核酸互補的 15 至 22 個核苷酸構成者。

Provided in this specification are antisense oligonucleotides consisting of 15-22 nucleotides complementary to a nucleic acid comprising at least 15 contiguous bases in a specific target region of the base sequence of SEQ ID NO: 471, or a pharmaceutically acceptable salts thereof or hydrates thereof.

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【發明摘要】

【中文發明名稱】 以 ATN1 mRNA 或 pre-mRNA 作為標的之反義寡核苷酸

【英文發明名稱】 ANTISENSE OLIGONUCLEOTIDES TARGETING ATN1 mRNA OR pre-mRNA

【中文】

在本說明書中，提供一種反義寡核苷酸或其醫藥上可容許之鹽或此等的水合物，該反義寡核苷酸係由與包含序列編號 471 之鹼基序列之特定標的區域中之至少 15 個連續鹼基之核酸互補的 15 至 22 個核苷酸構成者。

【英文】

Provided in this specification are antisense oligonucleotides consisting of 15-22 nucleotides complementary to a nucleic acid comprising at least 15 contiguous bases in a specific target region of the base sequence of SEQ ID NO: 471, or a pharmaceutically acceptable salts thereof or hydrates thereof.

【指定代表圖】 無。

【代表圖之符號簡單說明】

本案無圖式。

【特徵化學式】 無。

【發明說明書】

【中文發明名稱】 以 ATN1 mRNA 或 pre-mRNA 作為標的之反義寡核苷酸

【英文發明名稱】 ANTISENSE OLIGONUCLEOTIDES TARGETING ATN1 mRNA OR pre-mRNA

【技術領域】

【0001】本發明係關於以 ATN1 mRNA 或 pre-mRNA 作為標的之反義寡核苷酸或其醫藥上可容許之鹽或此等的水合物，及包含該反義寡核苷酸或其醫藥上可容許之鹽或此等的水合物之醫藥組成物等。

【先前技術】

【0002】齒狀紅核蒼白球路易氏體萎縮症(Dentatorubral–pallidoluysian atrophy，DRPLA)，在小兒方面，發生運動失調、稱為肌躍症(myoclonus)之不隨意運動、癲癇、及進行性之智力退化等，在成人方面，發生運動失調、舞蹈指痙病(choreoathetosis)、失智症、或性格變化等進行性之疾病(非專利文獻 1)。

【0003】DRPLA 係由於存在於特定基因之基因體的重複序列異常地伸長，導致 RNA 或蛋白質產生功能異常因而發病的疾病(重複序列病(repeat disease))。DRPLA 已知為在重複序列病中，蛋白質顯示毒性之疾病。DRPLA 係依據發病時期，分為 20 歲以後發病的成人型及 20 歲以前發

病的小兒型，重複序列數約為 65 以上之患者為早期發病之小兒型，嚴重度變高。

【0004】現今，在 DRPLA 之症狀中，雖有針對癲癇、精神症狀、運動失調等之對症療法藥存在，然而其治療滿意度低， 而且無法解決 DRPLA 之根本的分子機制。

[先前技術文獻]

[非專利文獻]

【0005】

[非專利文獻 1] Liana Veneziano et al., GeneReviews [Internet] 1999 Aug 6 [updated 2016 Jun 9], 1993-2021.

【發明內容】

【0006】在如此之狀況中，期望提供一種發揮更優異之治療效果的 DRPLA 治療劑。

【0007】本發明係提供以下記載的以 ATN1 mRNA 或 pre-mRNA 作為標的之反義寡核苷酸或其醫藥上可容許之鹽或此等的水合物，及包含該反義寡核苷酸或其醫藥上可容許之鹽或此等的水合物之醫藥組成物等。

【0008】

(1-1) 一種反義寡核苷酸或其醫藥上可容許之鹽或此等的水合物，其係由 15 至 22 個核苷酸構成，並且與包含標的區域中之至少 15 個連續鹼基之核酸互補，該標的區域係選自由序列編號 471 之鹼基序列之第 1 至 84 位、第 142 至 168 位、第 197 至 224 位、第 286 至 317 位、第 324 至 370

位、第 391 至 434 位、第 519 至 540 位、第 623 至 643 位、第 690 至 780 位、第 824 至 855 位、第 860 至 897 位、第 948 至 987 位、第 1044 至 1072 位、第 1125 至 1174 位、第 1181 至 1213 位、第 1228 至 1255 位、第 1265 至 1327 位、第 1334 至 1356 位、第 1416 至 1440 位、第 1447 至 1631 位、第 1638 至 1667 位、第 1675 至 1705 位、第 1748 至 1823 位、第 1838 至 1861 位、第 1870 至 1913 位、第 1920 至 1941 位、第 2000 至 2040 位、第 2047 至 2075 位、第 2086 至 2120 位、第 2129 至 2187 位、第 2194 至 2415 位、第 2451 至 2497 位、第 2592 至 2759 位、第 2766 至 2870 位、第 2928 至 2948 位、第 2955 至 2989 位、第 3021 至 3086 位、第 3133 至 3209 位、第 3217 至 3284 位、第 3295 至 3350 位、第 3384 至 3436 位、第 3562 至 3771 位、第 3858 至 3905 位、第 3931 至 4039 位、第 4067 至 4134 位、第 4170 至 4232 位、第 4241 至 4283 位、及第 4286 至 4355 位所構成之群組。

(1-2) 如(1-1)記載之反義寡核苷酸或其醫藥上可容許之鹽或此等的水合物，其係與包含標的區域中之至少 15 個連續鹼基之核酸互補，該標的區域係選自由序列編號 471 之鹼基序列之第 1 至 84 位、第 142 至 168 位、第 391 至 434 位、第 697 至 780 位、第 962 至 980 位、第 1125 至 1174 位、第 1181 至 1213 位、第 1228 至 1255 位、第 1265 至 1320 位、第 1454 至 1631 位、第 1682 至 1705 位、第 1748 至 1816 位、第 1870 至 1913 位、第 2015 至 2040 位、第 2086 至 2120 位、第 2129 至 2187 位、第 2201 至 2408 位、第 2592 至 2759 位、第 2773 至 2870 位、第 2955 至 2982 位、第 3028 至 3079 位、第 3133 至 3209 位、第 3224 至 3277 位、第 3295 至

3350 位、第 3391 至 3429 位、第 3562 至 3771 位、第 3865 至 3898 位、第 3938 至 4032 位、第 4074 至 4127 位、及第 4170 至 4225 位所構成之群組。

(2-1) 如(1-1)記載之反義寡核苷酸或其醫藥上可容許之鹽或此等的水合物，其係與包含標的區域中之至少 15 個連續鹼基之核酸互補，該標的區域係選自由序列編號 471 之鹼基序列之第 1 至 69 位、第 331 至 363 位、第 398 至 427 位、第 697 至 773 位、第 867 至 890 位、第 955 至 980 位、第 1132 至 1167 位、第 1272 至 1320 位、第 1454 至 1624 位、第 1682 至 1705 位、第 1748 至 1816 位、第 1877 至 1906 位、第 2007 至 2033 位、第 2093 至 2113 位、第 2136 至 2180 位、第 2201 至 2408 位、第 2458 至 2490 位、第 2599 至 2752 位、第 2773 至 2863 位、第 2962 至 2982 位、第 3028 至 3079 位、第 3140 至 3202 位、第 3224 至 3277 位、第 3302 至 3343 位、第 3391 至 3429 位、第 3569 至 3764 位、第 3865 至 3898 位、第 3938 至 4032 位、第 4074 至 4127 位、第 4177 至 4225 位、第 4248 至 4276 位、及第 4293 至 4355 位所構成之群組。

(2-2) 如(1-1)記載之反義寡核苷酸或其醫藥上可容許之鹽或此等的水合物，其係與包含標的區域中之至少 15 個連續鹼基之核酸互補，該標的區域係選自由序列編號 471 之鹼基序列之第 1 至 69 位、第 398 至 427 位、第 697 至 773 位、第 1132 至 1167 位、第 1272 至 1320 位、第 1454 至 1624 位、第 1682 至 1705 位、第 1748 至 1816 位、第 1877 至 1906 位、第 2093 至 2113 位、第 2136 至 2180 位、第 2201 至 2408 位、第 2599 至 2752 位、第 2773 至 2863 位、第 2962 至 2982 位、第 3028 至 3079 位、

第 3140 至 3202 位、第 3224 至 3277 位、第 3302 至 3343 位、第 3391 至 3429 位、第 3569 至 3764 位、第 3865 至 3898 位、第 3938 至 4032 位、及第 4177 至 4225 位所構成之群組。

(3) 如(1-1)記載之反義寡核苷酸或其醫藥上可容許之鹽或此等的水合物，其係與包含標的區域中之至少 15 個連續鹼基之核酸互補，該標的區域係選自由序列編號 471 之鹼基序列之第 14 至 33 位、第 34 至 53 位、第 54 至 73 位、第 148 至 167 位、第 397 至 432 位、第 723 至 742 位、第 747 至 778 位、第 965 至 984 位、第 1127 至 1146 位、第 1148 至 1173 位、第 1182 至 1213 位、第 1228 至 1254 位、第 1270 至 1308 位、第 1484 至 1564 位、第 1578 至 1629 位、第 1686 至 1705 位、第 1748 至 1767 位、第 1768 至 1787 位、第 1794 至 1813 位、第 1870 至 1913 位、第 2015 至 2034 位、第 2086 至 2118 位、第 2129 至 2148 位、第 2151 至 2184 位、第 2206 至 2225 位、第 2239 至 2272 位、第 2287 至 2336 位、第 2337 至 2373 位、第 2387 至 2406 位、第 2598 至 2757 位、第 2775 至 2809 位、第 2826 至 2866 位、第 2959 至 2982 位、第 3032 至 3051 位、第 3052 至 3071 位、第 3136 至 3155 位、第 3168 至 3187 位、第 3188 至 3207 位、第 3232 至 3270 位、第 3298 至 3344 位、第 3408 至 3427 位、第 3563 至 3582 位、第 3590 至 3728 位、第 3739 至 3769 位、第 3877 至 3896 位、第 3949 至 4030 位、及第 4170 至 4225 位所構成之群組。

(4) 如(3)記載之反義寡核苷酸或其醫藥上可容許之鹽或此等的水合物，其係與包含標的區域中之至少 15 個連續鹼基之核酸互補，該標的區域係選自由序列編號 471 之鹼基序列之第 14 至 33 位、第 34 至 53 位、第 54

至73位、第148至167位、第397至416位、第398至417位、第399至418位、第400至419位、第401至420位、第402至421位、第403至422位、第404至423位、第405至424位、第406至425位、第407至426位、第408至427位、第413至432位、第723至742位、第747至766位、第756至775位、第759至778位、第965至984位、第1127至1146位、第1148至1167位、第1151至1170位、第1154至1173位、第1182至1201位、第1185至1204位、第1188至1207位、第1191至1210位、第1194至1213位、第1228至1247位、第1231至1250位、第1235至1254位、第1270至1289位、第1289至1308位、第1484至1503位、第1488至1507位、第1491至1510位、第1493至1512位、第1506至1525位、第1517至1536位、第1531至1550位、第1545至1564位、第1578至1597位、第1579至1598位、第1580至1599位、第1581至1600位、第1582至1601位、第1583至1602位、第1584至1603位、第1585至1604位、第1586至1605位、第1587至1606位、第1588至1607位、第1589至1608位、第1590至1609位、第1591至1610位、第1592至1611位、第1593至1612位、第1594至1613位、第1595至1614位、第1596至1615位、第1597至1616位、第1598至1617位、第1599至1618位、第1600至1619位、第1601至1620位、第1602至1621位、第1603至1622位、第1604至1623位、第1605至1624位、第1607至1626位、第1610至1629位、第1686至1705位、第1748至1767位、第1768至1787位、第1794至1813位、第1870至1889位、第1871至1890位、第1874至1893位、第1877至1896位、

第1878至1897位、第1879至1898位、第1880至1899位、第1881至1900位、第1882至1901位、第1883至1902位、第1884至1903位、第1885至1904位、第1886至1905位、第1887至1906位、第1889至1908位、第1894至1913位、第2015至2034位、第2086至2105位、第2093至2112位、第2094至2113位、第2097至2116位、第2099至2118位、第2129至2148位、第2151至2170位、第2165至2184位、第2206至2225位、第2239至2258位、第2253至2272位、第2287至2306位、第2301至2320位、第2317至2336位、第2337至2356位、第2354至2373位、第2387至2406位、第2598至2617位、第2613至2632位、第2614至2633位、第2615至2634位、第2616至2635位、第2617至2636位、第2618至2637位、第2619至2638位、第2620至2639位、第2621至2640位、第2622至2641位、第2623至2642位、第2624至2643位、第2625至2644位、第2626至2645位、第2627至2646位、第2628至2647位、第2629至2648位、第2630至2649位、第2631至2650位、第2632至2651位、第2633至2652位、第2634至2653位、第2635至2654位、第2636至2655位、第2637至2656位、第2638至2657位、第2639至2658位、第2640至2659位、第2641至2660位、第2642至2661位、第2643至2662位、第2644至2663位、第2645至2664位、第2646至2665位、第2647至2666位、第2648至2667位、第2649至2668位、第2663至2682位、第2672至2691位、第2673至2692位、第2674至2693位、第2675至2694位、第2676至2695位、第2677至2696位、第2678至2697位、第2679至2698位、

第2680至2699位、第2681至2700位、第2682至2701位、第2683至2702位、第2684至2703位、第2685至2704位、第2686至2705位、第2687至2706位、第2688至2707位、第2689至2708位、第2690至2709位、第2691至2710位、第2692至2711位、第2693至2712位、第2694至2713位、第2695至2714位、第2696至2715位、第2697至2716位、第2698至2717位、第2699至2718位、第2700至2719位、第2701至2720位、第2702至2721位、第2703至2722位、第2704至2723位、第2705至2724位、第2706至2725位、第2707至2726位、第2708至2727位、第2709至2728位、第2710至2729位、第2711至2730位、第2712至2731位、第2713至2732位、第2714至2733位、第2715至2734位、第2716至2735位、第2717至2736位、第2718至2737位、第2719至2738位、第2720至2739位、第2721至2740位、第2722至2741位、第2723至2742位、第2724至2743位、第2725至2744位、第2726至2745位、第2727至2746位、第2728至2747位、第2729至2748位、第2730至2749位、第2731至2750位、第2732至2751位、第2733至2752位、第2738至2757位、第2775至2794位、第2790至2809位、第2826至2845位、第2827至2846位、第2828至2847位、第2829至2848位、第2830至2849位、第2831至2850位、第2832至2851位、第2833至2852位、第2834至2853位、第2835至2854位、第2836至2855位、第2837至2856位、第2838至2857位、第2839至2858位、第2840至2859位、第2841至2860位、第2842至2861位、第2843至2862位、第2844至2863位、第2847至2866位、

第2959至2978位、第2962至2981位、第2963至2982位、第3032至3051位、第3052至3071位、第3136至3155位、第3168至3187位、第3188至3207位、第3232至3251位、第3251至3270位、第3298至3317位、第3302至3321位、第3303至3322位、第3304至3323位、第3305至3324位、第3306至3325位、第3307至3326位、第3308至3327位、第3309至3328位、第3310至3329位、第3311至3330位、第3312至3331位、第3313至3332位、第3314至3333位、第3315至3334位、第3316至3335位、第3317至3336位、第3318至3337位、第3319至3338位、第3320至3339位、第3321至3340位、第3322至3341位、第3323至3342位、第3324至3343位、第3325至3344位、第3408至3427位、第3563至3582位、第3590至3609位、第3608至3627位、第3617至3636位、第3618至3637位、第3619至3638位、第3620至3639位、第3621至3640位、第3622至3641位、第3623至3642位、第3624至3643位、第3625至3644位、第3626至3645位、第3627至3646位、第3628至3647位、第3629至3648位、第3630至3649位、第3631至3650位、第3632至3651位、第3633至3652位、第3634至3653位、第3635至3654位、第3636至3655位、第3637至3656位、第3638至3657位、第3639至3658位、第3640至3659位、第3641至3660位、第3642至3661位、第3643至3662位、第3644至3663位、第3645至3664位、第3646至3665位、第3647至3666位、第3648至3667位、第3649至3668位、第3650至3669位、第3651至3670位、第3652至3671位、第3653至3672位、第3654至3673位、

第3671至3690位、第3672至3691位、第3673至3692位、第3674至3693位、第3675至3694位、第3676至3695位、第3677至3696位、第3678至3697位、第3679至3698位、第3680至3699位、第3681至3700位、第3682至3701位、第3683至3702位、第3684至3703位、第3685至3704位、第3686至3705位、第3687至3706位、第3688至3707位、第3689至3708位、第3690至3709位、第3691至3710位、第3692至3711位、第3693至3712位、第3694至3713位、第3695至3714位、第3696至3715位、第3697至3716位、第3698至3717位、第3699至3718位、第3700至3719位、第3701至3720位、第3702至3721位、第3703至3722位、第3704至3723位、第3705至3724位、第3706至3725位、第3707至3726位、第3708至3727位、第3709至3728位、第3739至3758位、第3740至3759位、第3741至3760位、第3742至3761位、第3743至3762位、第3744至3763位、第3745至3764位、第3750至3769位、第3877至3896位、第3949至3968位、第3964至3983位、第3965至3984位、第3966至3985位、第3967至3986位、第3968至3987位、第3969至3988位、第3970至3989位、第3971至3990位、第3972至3991位、第3973至3992位、第3974至3993位、第3975至3994位、第3976至3995位、第3977至3996位、第3978至3997位、第3979至3998位、第3980至3999位、第3981至4000位、第3982至4001位、第3983至4002位、第3984至4003位、第3985至4004位、第3986至4005位、第3987至4006位、第3988至4007位、第3989至4008位、第3990至4009位、第3991至4010位、

第 3992 至 4011 位、第 3993 至 4012 位、第 3994 至 4013 位、第 3995 至 4014 位、第 3996 至 4015 位、第 3997 至 4016 位、第 3998 至 4017 位、第 3999 至 4018 位、第 4011 至 4030 位、第 4170 至 4189 位、第 4173 至 4192 位、第 4176 至 4195 位、第 4177 至 4196 位、第 4178 至 4197 位、第 4179 至 4198 位、第 4180 至 4199 位、第 4181 至 4200 位、第 4182 至 4201 位、第 4183 至 4202 位、第 4184 至 4203 位、第 4185 至 4204 位、第 4186 至 4205 位、第 4187 至 4206 位、第 4188 至 4207 位、第 4189 至 4208 位、第 4190 至 4209 位、第 4191 至 4210 位、第 4192 至 4211 位、第 4193 至 4212 位、第 4194 至 4213 位、第 4195 至 4214 位、第 4196 至 4215 位、第 4197 至 4216 位、第 4198 至 4217 位、第 4199 至 4218 位、第 4200 至 4219 位、第 4201 至 4220 位、第 4202 至 4221 位、第 4203 至 4222 位、第 4204 至 4223 位、第 4205 至 4224 位、及第 4206 至 4225 位所構成之群組。

(5) 如(2-1)或(3)記載之反義寡核苷酸或其醫藥上可容許之鹽或此等的水合物，其係與包含標的區域中之至少 15 個連續鹼基之核酸互補，該標的區域係選自由序列編號 471 之鹼基序列之第 14 至 33 位、第 34 至 53 位、第 398 至 427 位、第 723 至 742 位、第 747 至 766 位、第 1148 至 1167 位、第 1289 至 1308 位、第 1484 至 1564 位、第 1578 至 1624 位、第 1686 至 1705 位、第 1748 至 1767 位、第 1768 至 1787 位、第 1794 至 1813 位、第 1877 至 1906 位、第 2093 至 2113 位、第 2151 至 2170 位、第 2206 至 2225 位、第 2239 至 2272 位、第 2287 至 2336 位、第 2337 至 2373 位、第 2387 至 2406 位、第 2613 至 2752 位、第 2775 至 2809 位、第 2826 至

2863 位、第 2962 至 2982 位、第 3032 至 3051 位、第 3052 至 3071 位、第 3168 至 3187 位、第 3232 至 3270 位、第 3302 至 3343 位、第 3408 至 3427 位、第 3590 至 3728 位、第 3739 至 3764 位、第 3877 至 3896 位、第 3949 至 4030 位、及第 4177 至 4225 位所構成之群組。

(6) 如(5)記載之反義寡核苷酸或其醫藥上可容許之鹽或此等的水合物，其係與包含標的區域中之至少 15 個連續鹼基之核酸互補，該標的區域係選自由序列編號 471 之鹼基序列之第 14 至 33 位、第 34 至 53 位、第 398 至 417 位、第 399 至 418 位、第 400 至 419 位、第 401 至 420 位、第 402 至 421 位、第 403 至 422 位、第 404 至 423 位、第 405 至 424 位、第 406 至 425 位、第 407 至 426 位、第 408 至 427 位、第 723 至 742 位、第 747 至 766 位、第 1148 至 1167 位、第 1289 至 1308 位、第 1484 至 1503 位、第 1488 至 1507 位、第 1491 至 1510 位、第 1493 至 1512 位、第 1506 至 1525 位、第 1517 至 1536 位、第 1531 至 1550 位、第 1545 至 1564 位、第 1578 至 1597 位、第 1579 至 1598 位、第 1580 至 1599 位、第 1581 至 1600 位、第 1582 至 1601 位、第 1583 至 1602 位、第 1584 至 1603 位、第 1585 至 1604 位、第 1586 至 1605 位、第 1587 至 1606 位、第 1588 至 1607 位、第 1589 至 1608 位、第 1590 至 1609 位、第 1591 至 1610 位、第 1592 至 1611 位、第 1593 至 1612 位、第 1594 至 1613 位、第 1595 至 1614 位、第 1596 至 1615 位、第 1597 至 1616 位、第 1598 至 1617 位、第 1599 至 1618 位、第 1600 至 1619 位、第 1601 至 1620 位、第 1602 至 1621 位、第 1603 至 1622 位、第 1604 至 1623 位、第 1605 至 1624 位、第 1686 至 1705 位、第 1748 至 1767 位、第 1768 至 1787 位、第 1794 至

1813位、第1877至1896位、第1878至1897位、第1879至1898位、第1880至1899位、第1881至1900位、第1882至1901位、第1883至1902位、第1884至1903位、第1885至1904位、第1886至1905位、第1887至1906位、第2093至2112位、第2094至2113位、第2151至2170位、第2206至2225位、第2239至2258位、第2253至2272位、第2287至2306位、第2301至2320位、第2317至2336位、第2337至2356位、第2354至2373位、第2387至2406位、第2613至2632位、第2614至2633位、第2615至2634位、第2616至2635位、第2617至2636位、第2618至2637位、第2619至2638位、第2620至2639位、第2621至2640位、第2622至2641位、第2623至2642位、第2624至2643位、第2625至2644位、第2626至2645位、第2627至2646位、第2628至2647位、第2629至2648位、第2630至2649位、第2631至2650位、第2632至2651位、第2633至2652位、第2634至2653位、第2635至2654位、第2636至2655位、第2637至2656位、第2638至2657位、第2639至2658位、第2640至2659位、第2641至2660位、第2642至2661位、第2643至2662位、第2644至2663位、第2645至2664位、第2646至2665位、第2647至2666位、第2648至2667位、第2649至2668位、第2663至2682位、第2672至2691位、第2673至2692位、第2674至2693位、第2675至2694位、第2676至2695位、第2677至2696位、第2678至2697位、第2679至2698位、第2680至2699位、第2681至2700位、第2682至2701位、第2683至2702位、第2684至2703位、第2685至2704位、第2686至2705位、第2687至

2706位、第2688至2707位、第2689至2708位、第2690至2709位、第2691至2710位、第2692至2711位、第2693至2712位、第2694至2713位、第2695至2714位、第2696至2715位、第2697至2716位、第2698至2717位、第2699至2718位、第2700至2719位、第2701至2720位、第2702至2721位、第2703至2722位、第2704至2723位、第2705至2724位、第2706至2725位、第2707至2726位、第2708至2727位、第2709至2728位、第2710至2729位、第2711至2730位、第2712至2731位、第2713至2732位、第2714至2733位、第2715至2734位、第2716至2735位、第2717至2736位、第2718至2737位、第2719至2738位、第2720至2739位、第2721至2740位、第2722至2741位、第2723至2742位、第2724至2743位、第2725至2744位、第2726至2745位、第2727至2746位、第2728至2747位、第2729至2748位、第2730至2749位、第2731至2750位、第2732至2751位、第2733至2752位、第2775至2794位、第2790至2809位、第2826至2845位、第2827至2846位、第2828至2847位、第2829至2848位、第2830至2849位、第2831至2850位、第2832至2851位、第2833至2852位、第2834至2853位、第2835至2854位、第2836至2855位、第2837至2856位、第2838至2857位、第2839至2858位、第2840至2859位、第2841至2860位、第2842至2861位、第2843至2862位、第2844至2863位、第2962至2981位、第2963至2982位、第3032至3051位、第3052至3071位、第3168至3187位、第3232至3251位、第3251至3270位、第3302至3321位、第3303至3322位、第3304至

3323位、第3305至3324位、第3306至3325位、第3307至3326位、第3308至3327位、第3309至3328位、第3310至3329位、第3311至3330位、第3312至3331位、第3313至3332位、第3314至3333位、第3315至3334位、第3316至3335位、第3317至3336位、第3318至3337位、第3319至3338位、第3320至3339位、第3321至3340位、第3322至3341位、第3323至3342位、第3324至3343位、第3408至3427位、第3590至3609位、第3608至3627位、第3617至3636位、第3618至3637位、第3619至3638位、第3620至3639位、第3621至3640位、第3622至3641位、第3623至3642位、第3624至3643位、第3625至3644位、第3626至3645位、第3627至3646位、第3628至3647位、第3629至3648位、第3630至3649位、第3631至3650位、第3632至3651位、第3633至3652位、第3634至3653位、第3635至3654位、第3636至3655位、第3637至3656位、第3638至3657位、第3639至3658位、第3640至3659位、第3641至3660位、第3642至3661位、第3643至3662位、第3644至3663位、第3645至3664位、第3646至3665位、第3647至3666位、第3648至3667位、第3649至3668位、第3650至3669位、第3651至3670位、第3652至3671位、第3653至3672位、第3654至3673位、第3671至3690位、第3672至3691位、第3673至3692位、第3674至3693位、第3675至3694位、第3676至3695位、第3677至3696位、第3678至3697位、第3679至3698位、第3680至3699位、第3681至3700位、第3682至3701位、第3683至3702位、第3684至3703位、第3685至3704位、第3686至

3705位、第3687至3706位、第3688至3707位、第3689至3708位、第3690至3709位、第3691至3710位、第3692至3711位、第3693至3712位、第3694至3713位、第3695至3714位、第3696至3715位、第3697至3716位、第3698至3717位、第3699至3718位、第3700至3719位、第3701至3720位、第3702至3721位、第3703至3722位、第3704至3723位、第3705至3724位、第3706至3725位、第3707至3726位、第3708至3727位、第3709至3728位、第3739至3758位、第3740至3759位、第3741至3760位、第3742至3761位、第3743至3762位、第3744至3763位、第3745至3764位、第3877至3896位、第3949至3968位、第3964至3983位、第3965至3984位、第3966至3985位、第3967至3986位、第3968至3987位、第3969至3988位、第3970至3989位、第3971至3990位、第3972至3991位、第3973至3992位、第3974至3993位、第3975至3994位、第3976至3995位、第3977至3996位、第3978至3997位、第3979至3998位、第3980至3999位、第3981至4000位、第3982至4001位、第3983至4002位、第3984至4003位、第3985至4004位、第3986至4005位、第3987至4006位、第3988至4007位、第3989至4008位、第3990至4009位、第3991至4010位、第3992至4011位、第3993至4012位、第3994至4013位、第3995至4014位、第3996至4015位、第3997至4016位、第3998至4017位、第3999至4018位、第4011至4030位、第4177至4196位、第4178至4197位、第4179至4198位、第4180至4199位、第4181至4200位、第4182至4201位、第4183至4202位、第4184至

4203 位、第 4185 至 4204 位、第 4186 至 4205 位、第 4187 至 4206 位、第 4188 至 4207 位、第 4189 至 4208 位、第 4190 至 4209 位、第 4191 至 4210 位、第 4192 至 4211 位、第 4193 至 4212 位、第 4194 至 4213 位、第 4195 至 4214 位、第 4196 至 4215 位、第 4197 至 4216 位、第 4198 至 4217 位、第 4199 至 4218 位、第 4200 至 4219 位、第 4201 至 4220 位、第 4202 至 4221 位、第 4203 至 4222 位、第 4204 至 4223 位、第 4205 至 4224 位、及第 4206 至 4225 位所構成之群組。

(7) 如(3)記載之反義寡核苷酸或其醫藥上可容許之鹽或此等的水合物，其係與包含標的區域中之至少 15 個連續鹼基之核酸互補，該標的區域係選自由序列編號 471 之鹼基序列之第 14 至 33 位、第 34 至 53 位、第 54 至 73 位、第 148 至 167 位、第 397 至 432 位、第 747 至 778 位、第 965 至 984 位、第 1127 至 1146 位、第 1148 至 1173 位、第 1182 至 1213 位、第 1228 至 1254 位、第 1270 至 1308 位、第 1484 至 1564 位、第 1578 至 1629 位、第 1686 至 1705 位、第 1748 至 1767 位、第 1768 至 1787 位、第 1794 至 1813 位、第 1870 至 1913 位、第 2015 至 2034 位、第 2086 至 2118 位、第 2129 至 2148 位、第 2151 至 2170 位、第 2206 至 2225 位、第 2239 至 2272 位、第 2287 至 2336 位、第 2337 至 2373 位、第 2387 至 2406 位、第 2598 至 2632 位、第 2633 至 2668 位、第 2672 至 2691 位、第 2699 至 2757 位、第 2775 至 2809 位、第 2826 至 2866 位、第 2959 至 2978 位、第 3032 至 3051 位、第 3052 至 3071 位、第 3136 至 3155 位、第 3168 至 3187 位、第 3188 至 3207 位、第 3232 至 3270 位、第 3298 至 3317 位、第 3325 至 3344 位、第 3408 至 3427 位、第 3590 至 3690 位、

第 3691 至 3728 位、第 3739 至 3769 位、第 3877 至 3896 位、第 3949 至 3983 位、第 3984 至 4030 位、及第 4170 至 4198 位所構成之群組。

(8) 如(7)記載之反義寡核苷酸或其醫藥上可容許之鹽或此等的水合物，其係與包含標的區域中之至少 15 個連續鹼基之核酸互補，該標的區域係選自由序列編號 471 之鹼基序列之第 14 至 33 位、第 34 至 53 位、第 54 至 73 位、第 148 至 167 位、第 397 至 416 位、第 413 至 432 位、第 747 至 766 位、第 756 至 775 位、第 759 至 778 位、第 965 至 984 位、第 1127 至 1146 位、第 1148 至 1167 位、第 1151 至 1170 位、第 1154 至 1173 位、第 1182 至 1201 位、第 1185 至 1204 位、第 1188 至 1207 位、第 1191 至 1210 位、第 1194 至 1213 位、第 1228 至 1247 位、第 1231 至 1250 位、第 1235 至 1254 位、第 1270 至 1289 位、第 1289 至 1308 位、第 1484 至 1503 位、第 1488 至 1507 位、第 1491 至 1510 位、第 1493 至 1512 位、第 1506 至 1525 位、第 1517 至 1536 位、第 1531 至 1550 位、第 1545 至 1564 位、第 1578 至 1597 位、第 1586 至 1605 位、第 1589 至 1608 位、第 1592 至 1611 位、第 1595 至 1614 位、第 1598 至 1617 位、第 1601 至 1620 位、第 1604 至 1623 位、第 1607 至 1626 位、第 1610 至 1629 位、第 1686 至 1705 位、第 1748 至 1767 位、第 1768 至 1787 位、第 1794 至 1813 位、第 1870 至 1889 位、第 1871 至 1890 位、第 1874 至 1893 位、第 1877 至 1896 位、第 1880 至 1899 位、第 1883 至 1902 位、第 1886 至 1905 位、第 1889 至 1908 位、第 1894 至 1913 位、第 2015 至 2034 位、第 2086 至 2105 位、第 2097 至 2116 位、第 2099 至 2118 位、第 2129 至 2148 位、第 2151 至 2170 位、第 2206 至 2225 位、第 2239 至 2258 位、

第 2253 至 2272 位、第 2287 至 2306 位、第 2301 至 2320 位、第 2317 至 2336 位、第 2337 至 2356 位、第 2354 至 2373 位、第 2387 至 2406 位、第 2598 至 2617 位、第 2613 至 2632 位、第 2633 至 2652 位、第 2649 至 2668 位、第 2672 至 2691 位、第 2699 至 2718 位、第 2702 至 2721 位、第 2705 至 2724 位、第 2708 至 2727 位、第 2711 至 2730 位、第 2714 至 2733 位、第 2717 至 2736 位、第 2720 至 2739 位、第 2723 至 2742 位、第 2726 至 2745 位、第 2729 至 2748 位、第 2738 至 2757 位、第 2775 至 2794 位、第 2790 至 2809 位、第 2826 至 2845 位、第 2829 至 2848 位、第 2832 至 2851 位、第 2835 至 2854 位、第 2838 至 2857 位、第 2841 至 2860 位、第 2847 至 2866 位、第 2959 至 2978 位、第 3032 至 3051 位、第 3052 至 3071 位、第 3136 至 3155 位、第 3168 至 3187 位、第 3188 至 3207 位、第 3232 至 3251 位、第 3251 至 3270 位、第 3298 至 3317 位、第 3325 至 3344 位、第 3408 至 3427 位、第 3590 至 3609 位、第 3608 至 3627 位、第 3617 至 3636 位、第 3635 至 3654 位、第 3654 至 3673 位、第 3671 至 3690 位、第 3691 至 3710 位、第 3709 至 3728 位、第 3739 至 3758 位、第 3750 至 3769 位、第 3877 至 3896 位、第 3949 至 3968 位、第 3964 至 3983 位、第 3984 至 4003 位、第 3999 至 4018 位、第 4011 至 4030 位、第 4170 至 4189 位、第 4173 至 4192 位、第 4176 至 4195 位、及第 4179 至 4198 位所構成之群組。

(9) 如(5)或(7)記載之反義寡核苷酸或其醫藥上可容許之鹽或此等的水合物，其係與包含標的區域中之至少 15 個連續鹼基之核酸互補，該標的區域係選自由序列編號 471 之鹼基序列之第 14 至 33 位、第 34 至 53 位、第

747至766位、第1148至1167位、第1289至1308位、第1484至1564位、第1578至1623位、第1686至1705位、第1748至1767位、第1768至1787位、第1794至1813位、第1877至1905位、第2151至2170位、第2206至2225位、第2239至2272位、第2287至2336位、第2337至2373位、第2387至2406位、第2613至2632位、第2633至2668位、第2672至2691位、第2699至2748位、第2775至2809位、第2826至2860位、第3032至3051位、第3052至3071位、第3168至3187位、第3232至3270位、第3408至3427位、第3590至3690位、第3691至3728位、第3739至3758位、第3877至3896位、第3949至3983位、第3984至4030位、及第4179至4198位所構成之群組。

(10-1) 如(9)記載之反義寡核苷酸或其醫藥上可容許之鹽或此等的水合物，其係與包含標的區域中之至少15個連續鹼基之核酸互補，該標的區域係選自由序列編號471之鹼基序列之第14至33位、第34至53位、第747至766位、第1148至1167位、第1289至1308位、第1484至1503位、第1488至1507位、第1491至1510位、第1493至1512位、第1506至1525位、第1517至1536位、第1531至1550位、第1545至1564位、第1578至1597位、第1586至1605位、第1589至1608位、第1592至1611位、第1595至1614位、第1598至1617位、第1601至1620位、第1604至1623位、第1686至1705位、第1748至1767位、第1768至1787位、第1794至1813位、第1877至1896位、第1880至1899位、第1883至1902位、第1886至1905位、第2151至2170位、第2206至2225位、第2239至2258位、第2253至2272位、第2287至2306位、

第 2301 至 2320 位、第 2317 至 2336 位、第 2337 至 2356 位、第 2354 至 2373 位、第 2387 至 2406 位、第 2613 至 2632 位、第 2633 至 2652 位、第 2649 至 2668 位、第 2672 至 2691 位、第 2699 至 2718 位、第 2702 至 2721 位、第 2705 至 2724 位、第 2708 至 2727 位、第 2711 至 2730 位、第 2714 至 2733 位、第 2717 至 2736 位、第 2720 至 2739 位、第 2723 至 2742 位、第 2726 至 2745 位、第 2729 至 2748 位、第 2775 至 2794 位、第 2790 至 2809 位、第 2826 至 2845 位、第 2829 至 2848 位、第 2832 至 2851 位、第 2835 至 2854 位、第 2838 至 2857 位、第 2841 至 2860 位、第 3032 至 3051 位、第 3052 至 3071 位、第 3168 至 3187 位、第 3232 至 3251 位、第 3251 至 3270 位、第 3408 至 3427 位、第 3590 至 3609 位、第 3608 至 3627 位、第 3617 至 3636 位、第 3635 至 3654 位、第 3654 至 3673 位、第 3671 至 3690 位、第 3691 至 3710 位、第 3709 至 3728 位、第 3739 至 3758 位、第 3877 至 3896 位、第 3949 至 3968 位、第 3964 至 3983 位、第 3984 至 4003 位、第 3999 至 4018 位、第 4011 至 4030 位、及第 4179 至 4198 位所構成之群組。

(10-2) 如(7)記載之反義寡核苷酸或其醫藥上可容許之鹽或此等的水合物，其係與包含標的區域中之至少 15 個連續鹼基之核酸互補，該標的區域係選自由序列編號 471 之鹼基序列之第 397 至 416 位、第 759 至 778 位、第 1127 至 1146 位、第 1148 至 1173 位、第 1182 至 1213 位、第 1488 至 1525 位、第 1586 至 1629 位、第 1686 至 1705 位、第 1768 至 1787 位、第 1870 至 1908 位、第 2097 至 2118 位、第 2151 至 2170 位、第 2239 至 2258 位、第 2287 至 2306 位、第 2317 至 2336 位、第 2633 至 2652 位、

第 2702 至 2745 位、第 2832 至 2866 位、第 2959 至 2978 位、第 3298 至 3317 位、第 3635 至 3654 位、第 3671 至 3690 位、第 3691 至 3710 位、第 3750 至 3983 位、第 3984 至 4003 位、及第 4170 至 4198 位所構成之群組。

(10-3) 如(7)或(8)記載之反義寡核苷酸或其醫藥上可容許之鹽或此等的水合物，其係與包含標的區域中之至少 15 個連續鹼基之核酸互補，該標的區域係選自由序列編號 471 之鹼基序列之第 397 至 416 位、第 759 至 778 位、第 1127 至 1146 位、第 1148 至 1167 位、第 1151 至 1170 位、第 1154 至 1173 位、第 1182 至 1201 位、第 1185 至 1204 位、第 1194 至 1213 位、第 1488 至 1507 位、第 1491 至 1510 位、第 1506 至 1525 位、第 1586 至 1605 位、第 1589 至 1608 位、第 1595 至 1614 位、第 1598 至 1617 位、第 1601 至 1620 位、第 1604 至 1623 位、第 1607 至 1626 位、第 1610 至 1629 位、第 1686 至 1705 位、第 1768 至 1787 位、第 1870 至 1889 位、第 1871 至 1890 位、第 1874 至 1893 位、第 1877 至 1896 位、第 1886 至 1905 位、第 1889 至 1908 位、第 2097 至 2116 位、第 2099 至 2118 位、第 2151 至 2170 位、第 2239 至 2258 位、第 2287 至 2306 位、第 2317 至 2336 位、第 2633 至 2652 位、第 2702 至 2721 位、第 2705 至 2724 位、第 2708 至 2727 位、第 2711 至 2730 位、第 2714 至 2733 位、第 2717 至 2736 位、第 2720 至 2739 位、第 2726 至 2745 位、第 2832 至 2851 位、第 2835 至 2854 位、第 2841 至 2860 位、第 2847 至 2866 位、第 2959 至 2978 位、第 3298 至 3317 位、第 3635 至 3654 位、第 3671 至 3690 位、第 3691 至 3710 位、第 3750 至 3769 位、第 3964 至 3983 位、第 3984 至

4003 位、第 4170 至 4189 位、第 4173 至 4192 位、第 4176 至 4195 位、及第 4179 至 4198 位所構成之群組。

(10-4) 如(7)記載之反義寡核苷酸或其醫藥上可容許之鹽或此等的水合物，其係與包含標的區域中之至少 15 個連續鹼基之核酸互補，該標的區域係選自由序列編號 471 之鹼基序列之第 397 至 416 位、第 1194 至 1213 位、第 1506 至 1525 位、第 1586 至 1626 位、第 1870 至 1896 位、第 2097 至 2116 位、第 2317 至 2336 位、第 2633 至 2652 位、第 2702 至 2739 位、第 2841 至 2978 位、第 3298 至 3317 位、第 3635 至 3654 位、第 3691 至 3710 位、第 3750 至 3769 位、第 3984 至 4003 位、及第 4170 至 4198 位所構成之群組。

(10-5)如(7)或(8)記載之反義寡核苷酸或其醫藥上可容許之鹽或此等的水合物，其係與包含標的區域中之至少 15 個連續鹼基之核酸互補，該標的區域係選自由序列編號 471 之鹼基序列之第 397 至 416 位、第 1194 至 1213 位、第 1506 至 1525 位、第 1586 至 1605 位、第 1595 至 1614 位、第 1598 至 1617 位、第 1604 至 1623 位、第 1607 至 1626 位、第 1870 至 1889 位、第 1871 至 1890 位、第 1874 至 1893 位、第 1877 至 1896 位、第 2097 至 2116 位、第 2317 至 2336 位、第 2633 至 2652 位、第 2702 至 2721 位、第 2708 至 2727 位、第 2711 至 2730 位、第 2714 至 2733 位、第 2717 至 2736 位、第 2720 至 2739 位、第 2841 至 2860 位、第 2959 至 2978 位、第 3298 至 3317 位、第 3635 至 3654 位、第 3691 至 3710 位、第 3750 至 3769 位、第 3984 至 4003 位、第 4170 至 4189 位、第 4173 至 4192 位、第 4176 至 4195 位、及第 4179 至 4198 位所構成之群組。

(11) 如(7)記載之反義寡核苷酸或其醫藥上可容許之鹽或此等的水合物，其係與包含標的區域中之至少 15 個連續鹼基之核酸互補，該標的區域係選自由序列編號 471 之鹼基序列之第 1598 至 1626 位、第 1870 至 1890 位、第 2097 至 2116 位、第 2711 至 2736 位、第 2841 至 2860 位、及第 4170 至 4198 位所構成之群組。

(12) 如(7)或(8)記載之反義寡核苷酸或其醫藥上可容許之鹽或此等的水合物，其係與包含標的區域中之至少 15 個連續鹼基之核酸互補，該標的區域係選自由序列編號 471 之鹼基序列之第 1598 至 1617 位、第 1604 至 1623 位、第 1607 至 1626 位、第 1870 至 1889 位、第 1871 至 1890 位、第 2097 至 2116 位、第 2711 至 2730 位、第 2714 至 2733 位、第 2717 至 2736 位、第 2841 至 2860 位、第 4170 至 4189 位、第 4173 至 4192 位、及第 4179 至 4198 位所構成之群組。

(12'-1) 如(5)記載之反義寡核苷酸或其醫藥上可容許之鹽或此等的水合物，其係與包含標的區域中之至少 15 個連續鹼基之核酸互補，該標的區域係選自由序列編號 471 之鹼基序列之第 400 至 425 位、第 1581 至 1624 位、第 1878 至 1898 位、第 2094 至 2113 位、第 2629 至 2656 位、第 2700 至 2741 位、第 2839 至 2863 位、第 2962 至 2981 位、第 3302 至 3325 位、第 3631 至 3658 位、第 3687 至 3714 位、第 3745 至 3764 位、第 3980 至 4007 位、第 4177 至 4199 位、及第 4204 至 4223 位所構成之群組。

(12'-2) 如(5)或(6)記載之反義寡核苷酸或其醫藥上可容許之鹽或此等的水合物，其係與包含標的區域中之至少 15 個連續鹼基之核酸互補，該標的區域係選自由序列編號 471 之鹼基序列之第 400 至 419 位、第 403 至

422 位、第 406 至 425 位、第 1581 至 1600 位、第 1582 至 1601 位、第 1583 至 1602 位、第 1584 至 1603 位、第 1585 至 1604 位、第 1587 至 1606 位、第 1588 至 1607 位、第 1590 至 1609 位、第 1591 至 1610 位、第 1592 至 1611 位、第 1593 至 1612 位、第 1594 至 1613 位、第 1596 至 1615 位、第 1597 至 1616 位、第 1599 至 1618 位、第 1600 至 1619 位、第 1602 至 1621 位、第 1603 至 1622 位、第 1605 至 1624 位、第 1878 至 1897 位、第 1879 至 1898 位、第 2094 至 2113 位、第 2629 至 2648 位、第 2637 至 2656 位、第 2700 至 2719 位、第 2701 至 2720 位、第 2703 至 2722 位、第 2704 至 2723 位、第 2706 至 2725 位、第 2707 至 2726 位、第 2709 至 2728 位、第 2710 至 2729 位、第 2712 至 2731 位、第 2713 至 2732 位、第 2715 至 2734 位、第 2716 至 2735 位、第 2718 至 2737 位、第 2719 至 2738 位、第 2721 至 2740 位、第 2722 至 2741 位、第 2839 至 2858 位、第 2840 至 2859 位、第 2842 至 2861 位、第 2843 至 2862 位、第 2844 至 2863 位、第 2962 至 2981 位、第 3302 至 3321 位、第 3306 至 3325 位、第 3631 至 3650 位、第 3632 至 3651 位、第 3633 至 3652 位、第 3634 至 3653 位、第 3636 至 3655 位、第 3637 至 3656 位、第 3638 至 3657 位、第 3639 至 3658 位、第 3687 至 3706 位、第 3695 至 3714 位、第 3745 至 3764 位、第 3980 至 3999 位、第 3988 至 4007 位、第 4177 至 4196 位、第 4178 至 4197 位、第 4180 至 4199 位、及第 4204 至 4223 位所構成之群組。

(12'-3) 如(5)記載之反義寡核苷酸或其醫藥上可容許之鹽或此等的水合物，其係與包含標的區域中之至少 15 個連續鹼基之核酸互補，該標的區

域係選自由序列編號 471 之鹼基序列之第 400 至 425 位、第 1581 至 1624 位、第 1878 至 1898 位、第 2637 至 2656 位、第 2700 至 2741 位、第 2839 至 2863 位、第 2962 至 2981 位、第 3302 至 3325 位、第 3631 至 3658 位、第 3687 至 3706 位、第 3745 至 3764 位、第 4177 至 4199 位、及第 4204 至 4223 位所構成之群組。

(12'-4) 如(5)或(6)記載之反義寡核苷酸或其醫藥上可容許之鹽或此等的水合物，其係與包含標的區域中之至少 15 個連續鹼基之核酸互補，該標的區域係選自由序列編號 471 之鹼基序列之第 400 至 419 位、第 403 至 422 位、第 406 至 425 位、第 1581 至 1600 位、第 1582 至 1601 位、第 1583 至 1602 位、第 1584 至 1603 位、第 1585 至 1604 位、第 1587 至 1606 位、第 1588 至 1607 位、第 1591 至 1610 位、第 1592 至 1611 位、第 1593 至 1612 位、第 1594 至 1613 位、第 1596 至 1615 位、第 1597 至 1616 位、第 1600 至 1619 位、第 1602 至 1621 位、第 1603 至 1622 位、第 1605 至 1624 位、第 1878 至 1897 位、第 1879 至 1898 位、第 2637 至 2656 位、第 2700 至 2719 位、第 2701 至 2720 位、第 2703 至 2722 位、第 2704 至 2723 位、第 2706 至 2725 位、第 2707 至 2726 位、第 2709 至 2728 位、第 2710 至 2729 位、第 2712 至 2731 位、第 2713 至 2732 位、第 2715 至 2734 位、第 2716 至 2735 位、第 2718 至 2737 位、第 2719 至 2738 位、第 2721 至 2740 位、第 2722 至 2741 位、第 2839 至 2858 位、第 2840 至 2859 位、第 2842 至 2861 位、第 2843 至 2862 位、第 2844 至 2863 位、第 2962 至 2981 位、第 3302 至 3321 位、第 3306 至 3325 位、第 3631 至 3650 位、第 3632 至 3651 位、第 3633 至 3652 位、第 3634 至 3653 位、

第 3636 至 3655 位、第 3637 至 3656 位、第 3638 至 3657 位、第 3639 至 3658 位、第 3687 至 3706 位、第 3745 至 3764 位、第 4177 至 4196 位、第 4178 至 4197 位、第 4180 至 4199 位、及第 4204 至 4223 位所構成之群組。

(12'-5) 如(5)記載之反義寡核苷酸或其醫藥上可容許之鹽或此等的水合物，其係與包含標的區域中之至少 15 個連續鹼基之核酸互補，該標的區域係選自由序列編號 471 之鹼基序列之第 1581 至 1624 位、第 2703 至 2740 位、第 3633 至 3655 位、及第 4177 至 4199 位所構成之群組。

(12'-6) 如(5)或(6)記載之反義寡核苷酸或其醫藥上可容許之鹽或此等的水合物，其係與包含標的區域中之至少 15 個連續鹼基之核酸互補，該標的區域係選自由序列編號 471 之鹼基序列之第 1581 至 1600 位、第 1582 至 1601 位、第 1584 至 1603 位、第 1585 至 1604 位、第 1587 至 1606 位、第 1588 至 1607 位、第 1594 至 1613 位、第 1596 至 1615 位、第 1597 至 1616 位、第 1602 至 1621 位、第 1603 至 1622 位、第 1605 至 1624 位、第 2703 至 2722 位、第 2707 至 2726 位、第 2709 至 2728 位、第 2710 至 2729 位、第 2712 至 2731 位、第 2713 至 2732 位、第 2715 至 2734 位、第 2716 至 2735 位、第 2718 至 2737 位、第 2719 至 2738 位、第 2721 至 2740 位、第 3633 至 3652 位、第 3634 至 3653 位、第 3636 至 3655 位、第 4177 至 4196 位、第 4178 至 4197 位、及第 4180 至 4199 位所構成之群組。

(12'-7) 如(5)記載之反義寡核苷酸或其醫藥上可容許之鹽或此等的水合物，其係與包含標的區域中之至少 15 個連續鹼基之核酸互補，該標的區

域係選自由序列編號 471 之鹼基序列之第 1587 至 1616 位、第 2712 至 2735 位、及第 4180 至 4199 位所構成之群組。

(12'-8) 如(5)或(6)記載之反義寡核苷酸或其醫藥上可容許之鹽或此等的水合物，其係與包含標的區域中之至少 15 個連續鹼基之核酸互補，該標的區域係選自由序列編號 471 之鹼基序列之第 1587 至 1606 位、第 1597 至 1616 位、第 2712 至 2731 位、第 2716 至 2735 位、及第 4180 至 4199 位所構成之群組。

(13) 如(1)至(12)中任一項記載之反義寡核苷酸或其醫藥上可容許之鹽或此等的水合物，其係與包含前述標的區域之至少 20 個連續鹼基的核酸互補。

(14) 如(3)或(4)記載之反義寡核苷酸或其醫藥上可容許之鹽或此等的水合物，其係包含下列(i)、(ii)或(iii)之鹼基序列：

(i) 選自由序列編號 1 至 6、8、9、11、14 至 24、26、29、31 至 60、66 至 67、73 至 75、79 至 82、86 至 89、92 至 111、115 至 136、138 至 145、147 至 158、及 160 至 464 所構成之群組中的鹼基序列，

(ii) 在選自由序列編號 1 至 6、8、9、11、14 至 24、26、29、31 至 60、66 至 67、73 至 75、79 至 82、86 至 89、92 至 111、115 至 136、138 至 145、147 至 158、及 160 至 464 所構成之群組中的鹼基序列中，1 個或複數個鹼基經附加、缺失、或置換而成之鹼基序列，或

(iii) 相對於序列編號 1 至 6、8、9、11、14 至 24、26、29、31 至 60、66 至 67、73 至 75、79 至 82、86 至 89、92 至 111、115 至 136、138 至

145、147至158、及160至464所構成之群組中的鹼基序列，具有90%以上之序列一致性的鹼基序列。

(15) 如(5)或(6)記載之反義寡核苷酸或其醫藥上可容許之鹽或此等的水合物，其係包含下列(i)、(ii)或(iii)之鹼基序列：

(i) 選自由序列編號1、5、6、14至24、31至35、37至40、42至45、47至50、52至59、73、92至100、103、107至110、120至136、138至143、150至153、155至158、及163至464所構成之群組中的鹼基序列，

(ii) 在選自由序列編號1、5、6、14至24、31至35、37至40、42至45、47至50、52至59、73、92至100、103、107至110、120至136、138至143、150至153、155至158、及163至464所構成之群組中的鹼基序列中，1個或複數個鹼基經附加、缺失、或置換而成之鹼基序列，或

(iii) 相對於選自由序列編號1、5、6、14至24、31至35、37至40、42至45、47至50、52至59、73、92至100、103、107至110、120至136、138至143、150至153、155至158、及163至464所構成之群組中的鹼基序列，具有90%以上之序列一致性的鹼基序列。

(16) 如(7)或(8)記載之反義寡核苷酸或其醫藥上可容許之鹽或此等的水合物，其係包含下列(i)、(ii)或(iii)之鹼基序列：

(i) 選自由序列編號1至4、6、8、9、11、14至24、26、29、31至37、39至50、52至60、66至67、73至75、79至82、86至89、92至111、115至118、120至136、138至145、147至158、及160至163所構成之群組中的鹼基序列，

(ii) 在選自由序列編號 1 至 4、6、8、9、11、14 至 24、26、29、31 至 37、39 至 50、52 至 60、66 至 67、73 至 75、79 至 82、86 至 89、92 至 111、115 至 118、120 至 136、138 至 145、147 至 158、及 160 至 163 所構成之群組中的鹼基序列中，1 個或複數個鹼基經附加、缺失、或置換而成之鹼基序列，或

(iii) 相對於選自由序列編號 1 至 4、6、8、9、11、14 至 24、26、29、31 至 37、39 至 50、52 至 60、66 至 67、73 至 75、79 至 82、86 至 89、92 至 111、115 至 118、120 至 136、138 至 145、147 至 158、及 160 至 163 所構成之群組中的鹼基序列，具有 90%以上之序列一致性的鹼基序列。

(17-1) 如(9)或(10-1)記載之反義寡核苷酸或其醫藥上可容許之鹽或此等的水合物，其係包含下列(i)、(ii)或(iii)之鹼基序列：

(i) 選自由序列編號 1、6、14 至 24、31 至 35、37、39、40、42 至 45、47 至 50、52 至 59、73、92 至 100、103、107 至 110、120 至 136、138 至 143、150 至 153、155 至 158、及 163 所構成之群組中的鹼基序列，

(ii) 在選自由序列編號 1、6、14 至 24、31 至 35、37、39、40、42 至 45、47 至 50、52 至 59、73、92 至 100、103、107 至 110、120 至 136、138 至 143、150 至 153、155 至 158、及 163 所構成之群組中的鹼基序列中，1 個或複數個鹼基經附加、缺失、或置換而成之鹼基序列，或

(iii) 相對於選自由序列編號 1、6、14 至 24、31 至 35、37、39、40、42 至 45、47 至 50、52 至 59、73、92 至 100、103、107 至 110、120 至 136、138 至 143、150 至 153、155 至 158、及 163 所構成之群組中的鹼基序列，具有 90%以上之序列一致性的鹼基序列。

(17-2) 如(10-2)或(10-3)記載之反義寡核苷酸或其醫藥上可容許之鹽或此等的水合物，其係包含下列(i)、(ii)或(iii)之鹼基序列：

(i) 選自由序列編號 9、11、16、17、22、31、60、67、73、74、75、79、80、92、95 至 107、110、111、116、117、120 至 122、126、128 至 134、136、140、141、143 至 145、148、151 至 154、156、157、及 160 至 163 所構成之群組中的鹼基序列，

(ii) 在選自由序列編號 9、11、16、17、22、31、60、67、73、74、75、79、80、92、95 至 107、110、111、116、117、120 至 122、126、128 至 134、136、140、141、143 至 145、148、151 至 154、156、157、及 160 至 163 所構成之群組中的鹼基序列中，1 個或複數個鹼基經附加、缺失、或置換而成之鹼基序列，或

(iii) 相對於選自由序列編號 9、11、16、17、22、31、60、67、73、74、75、79、80、92、95 至 107、110、111、116、117、120 至 122、126、128 至 134、136、140、141、143 至 145、148、151 至 154、156、157、及 160 至 163 所構成之群組中的鹼基序列，具有 90%以上之序列一致性的鹼基序列。

(17-3) 如(10-4)或(10-5)記載之反義寡核苷酸或其醫藥上可容許之鹽或此等的水合物，其係包含下列(i)、(ii)或(iii)之鹼基序列：

(i) 選自由序列編號 11、60、92、95、97、98、100、101、104 至 107、116、122、126、128、130 至 134、143、145、148、151、153、154、157、及 160 至 163 所構成之群組中的鹼基序列，

(ii) 在選自由序列編號 11、60、92、95、97、98、100、101、104 至 107、116、122、126、128、130 至 134、143、145、148、151、153、154、157、及 160 至 163 所構成之群組中的鹼基序列中，1 個或複數個鹼基經附加、缺失、或置換而成之鹼基序列，或

(iii) 相對於選自由序列編號 11、60、92、95、97、98、100、101、104 至 107、116、122、126、128、130 至 134、143、145、148、151、153、154、157、及 160 至 163 所構成之群組中的鹼基序列，具有 90%以上之序列一致性的鹼基序列。

(18) 如(11)或(12)記載之反義寡核苷酸或其醫藥上可容許之鹽或此等的水合物，其係包含下列(i)、(ii)或(iii)之鹼基序列：

(i) 選自由序列編號 98、100、101、104、105、116、131 至 133、143、160、161、及 163 所構成之群組中的鹼基序列，

(ii) 在選自由序列編號 98、100、101、104、105、116、131 至 133、143、160、161、及 163 所構成之群組中的鹼基序列中，1 個或複數個鹼基經附加、缺失、或置換而成之鹼基序列，或

(iii) 相對於選自由序列編號 98、100、101、104、105、116、131 至 133、143、160、161、及 163 所構成之群組中的鹼基序列，具有 90%以上之序列一致性的鹼基序列。

(19-1) 如(12'-1)或(12'-2)記載之反義寡核苷酸或其醫藥上可容許之鹽或此等的水合物，其係包含下列(i)、(ii)或(iii)之鹼基序列：

(i) 選自由序列編號 21、164 至 222、233、234、及 350 至 355 所構成之群組中的鹼基序列，

(ii) 在選自由序列編號 21、164 至 222、233、234、及 350 至 355 所構成之群組中的鹼基序列中，1 個或複數個鹼基經附加、缺失、或置換而成之鹼基序列，或

(iii) 相對於選自由序列編號 21、164 至 222、233、234、及 350 至 355 所構成之群組中的鹼基序列，具有 90%以上之序列一致性的鹼基序列。

(19-2) 如(12'-3)或(12'-4)記載之反義寡核苷酸或其醫藥上可容許之鹽或此等的水合物，其係包含下列(i)、(ii)或(iii)之鹼基序列：

(i) 選自由序列編號 21、164 至 171、173 至 177、179 至 184、187 至 214、216、219 至 222、233 至 234、及 350 至 355 所構成之群組中的鹼基序列，

(ii) 在選自由序列編號 21、164 至 171、173 至 177、179 至 184、187 至 214、216、219 至 222、233 至 234、及 350 至 355 所構成之群組中的鹼基序列中，1 個或複數個鹼基經附加、缺失、或置換而成之鹼基序列，或

(iii) 相對於選自由序列編號 21、164 至 171、173 至 177、179 至 184、187 至 214、216、219 至 222、233 至 234、及 350 至 355 所構成之群組中的鹼基序列，具有 90%以上之序列一致性的鹼基序列。

(19-3) 如(12'-5)或(12'-6)記載之反義寡核苷酸或其醫藥上可容許之鹽或此等的水合物，其係包含下列(i)、(ii)或(iii)之鹼基序列：

(i) 選自由序列編號 167 至 171、175 至 177、180 至 182、190、193 至 202、219 至 221、233、及 351 至 353 所構成之群組中的鹼基序列，

(ii) 在選自由序列編號 167 至 171、175 至 177、180 至 182、190、193 至 202、219 至 221、233、及 351 至 353 構成之群組的鹼基序列中，1 個或複數個鹼基經附加、缺失、或置換而成之鹼基序列，或

(iii) 相對於選自由序列編號 167 至 171、175 至 177、180 至 182、190、193 至 202、219 至 221、233、及 351 至 353 所構成之群組中的鹼基序列，具有 90%以上之序列一致性的鹼基序列。

(20) 如(12'-7)或(12'-8)記載之反義寡核苷酸或其醫藥上可容許之鹽或此等的水合物，其係包含下列(i)、(ii)或(iii)之鹼基序列：

(i) 選自由序列編號 170、177、196、199、及 221 所構成之群組中的鹼基序列，

(ii) 在選自由序列編號 170、177、196、199、及 221 所構成之群組中的鹼基序列中，1 個或複數個鹼基經附加、缺失、或置換而成之鹼基序列，或

(iii) 相對於選自由序列編號 170、177、196、199、及 221 所構成之群組中的鹼基序列，具有 90%以上之序列一致性的鹼基序列。

(21) 如(14)至(20)中任一項記載之反義寡核苷酸或其醫藥上可容許之鹽或此等的水合物，其係包含(i)之鹼基序列。

(22) 一種反義寡核苷酸或其醫藥上可容許之鹽或此等的水合物，其係由 15 至 22 個核苷酸構成，並且與包含標的區域中之至少 15 個連續鹼基的核酸互補，該標的區域係選自由序列編號 471 之鹼基序列之第 468 至 487 位、第 474 至 493 位、第 583 至 602 位、第 586 至 605 位、第 619 至 638 位、第 770 至 789 位、第 774 至 793 位、第 775 至 794 位、第 778 至 797

位、第 804 至 823 位、第 851 至 870 位、第 1160 至 1179 位、第 1162 至 1181 位、第 1170 至 1189 位、第 1173 至 1192 位、第 1205 至 1224 位、第 1210 至 1229 位、第 1216 至 1235 位、第 1217 至 1236 位、第 1219 至 1238 位、第 1385 至 1404 位、第 1441 至 1460 位、第 1818 至 1837 位、第 1902 至 1921 位、第 1905 至 1924 位、第 1908 至 1927 位、第 1914 至 1933 位、第 1931 至 1950 位、第 2117 至 2136 位、第 2749 至 2768 位、第 3100 至 3119 位、及第 4125 至 4144 位所構成之群組。

(23) 如(22)記載之反義寡核苷酸或其醫藥上可容許之鹽或此等的水合物，其係包含下列(i)、(ii)或(iii)之鹼基序列：

(i) 選自由序列編號 7、10、12、13、25、27、28、30、61 至 65、68 至 72、76 至 78、83 至 85、90、91、112 至 114、137、146、及 159 所構成之群組中的鹼基序列，

(ii) 在選自由序列編號 7、10、12、13、25、27、28、30、61 至 65、68 至 72、76 至 78、83 至 85、90、91、112 至 114、137、146、及 159 所構成之群組中的鹼基序列中，1 個或複數個鹼基經附加、缺失、或置換而成之鹼基序列，或

(iii) 相對於選自由序列編號 7、10、12、13、25、27、28、30、61 至 65、68 至 72、76 至 78、83 至 85、90、91、112 至 114、137、146、及 159 所構成之群組中的鹼基序列，具有 90%以上之序列一致性的鹼基序列。

(24) 如(23)記載之反義寡核苷酸或其醫藥上可容許之鹽或此等的水合物，其係包含(i)之鹼基序列。

(25) 如(1)至(24)中任一項記載之反義寡核苷酸或其醫藥上可容許之鹽或此等的水合物，其中，該反義寡核苷酸係由 20 個核苷酸構成。

(26) 如(1)至(25)中任一項記載之反義寡核苷酸或其醫藥上可容許之鹽或此等的水合物，其中，構成前述寡核苷酸之至少 1 個核苷酸之糖部分及/或磷酸鍵部分經修飾。

(27-1) 如(26)記載之反義寡核苷酸或其醫藥上可容許之鹽或此等的水合物，其中，該反義寡核苷酸為包含中央之間隔(gap)區域、及與間隔區域之 5'末端側及 3'末端側鄰接的 2 個翼部(wing)區域(5'翼部區域及 3'翼部區域)之間隔子(gapmer)。

(27-2) 如(27-1)記載之反義寡核苷酸或其醫藥上可容許之鹽或此等的水合物，其中該反義寡核苷酸係從 5'側向 3'側，由核苷酸長度 5 之 5'翼部區域、核苷酸長度 10 之間隔區域、及核苷酸長度 5 之 3'翼部區域構成。

(28) 如(27-1)或(27-2)記載之反義寡核苷酸或其醫藥上可容許之鹽或此等的水合物，其中，核苷間之鍵結全部為硫代磷酸酯(phosphorothioate)鍵。

(29) 如(27-1)或(27-2)記載之反義寡核苷酸或其醫藥上可容許之鹽或此等的水合物，其中，從 5'翼部區域之 5'側算起第 2 與第 3 核苷間之鍵結、第 3 與第 4 核苷間之鍵結、及第 4 與第 5 核苷間之鍵結的一個以上為磷酸二酯(phosphodiester)鍵，及/或從 3'翼部區域之 5'側算起第 1 與第 2 核苷間之鍵結、第 2 與第 3 核苷間之鍵結、及第 3 與第 4 核苷間之鍵結的一個以上為磷酸二酯鍵，且其他核苷間之鍵結全部為硫代磷酸酯鍵。

(30) 如(29)記載之反義寡核苷酸或其醫藥上可容許之鹽或此等的水合物，其中，從 5’翼部區域之 5’側算起第 2 與第 3 核苷間之鍵結及第 4 與第 5 核苷間之鍵結為磷酸二酯鍵，及/或從 3’翼部區域之 5’側算起第 1 與第 2 核苷間之鍵結及第 3 與第 4 核苷間之鍵結為磷酸二酯鍵，且其他核苷間之鍵結全部為硫代磷酸酯鍵。

(31) 如(29)記載之反義寡核苷酸或其醫藥上可容許之鹽或此等的水合物，其中，從 5’翼部區域之 5’側算起第 2 與第 3 核苷間之鍵結、第 3 與第 4 核苷間之鍵結、及第 4 與第 5 核苷間之鍵結為磷酸二酯鍵，及/或從 3’翼部區域之 5’側算起第 1 與第 2 核苷間之鍵結、第 2 與第 3 核苷間之鍵結、及第 3 與第 4 核苷間之鍵結為磷酸二酯鍵，且其他核苷間之鍵結全部為硫代磷酸酯鍵。

(32) 如(27-1)至(31)中任一項記載之反義寡核苷酸或其醫藥上可容許之鹽或此等的水合物，其中，翼部區域包含 2’-OMe(2’-O-CH_3)基及/或 2’-O-MOE(2’-O-$CH_2CH_2OCH_3$)基。

(33) 一種醫藥組成物，其係包含(1)至(32)中任一項記載之反義寡核苷酸或其醫藥上可容許之鹽或此等的水合物。

(34) 如(1)至(32)中任一項記載之反義寡核苷酸或其醫藥上可容許之鹽或此等的水合物、或(33)記載之醫藥組成物，其係用以治療及/或預防齒狀紅核蒼白球路易氏體萎縮症(DRPLA)。

(35) 一種齒狀紅核蒼白球路易氏體萎縮症(DRPLA)之治療及/或預防方法，其係包含向對象投予(1)至(32)中任一項記載之反義寡核苷酸或其醫藥上可容許之鹽或此等的水合物、或(33)或(34)記載之醫藥組成物之步驟。

【0009】根據本發明，可提供一種以 ATN1 mRNA 或 pre-mRNA 作為標的之反義寡核苷酸或其醫藥上可容許之鹽或此等的水合物，及包含該反義寡核苷酸或其醫藥上可容許之鹽或此等之水合物的組成物等。

【0010】在本發明中，由於直接抑制屬於 DRPLA 之原因基因的突變 ATN1，因而可提供治療滿足度高之 DPLA 治療劑。在本發明中，由於能以屬於 DRPLA 之原因基因的突變 ATN1 作為標的設計反義寡核苷酸，因此根據本發明之較佳態樣，可提供副作用少的 DRPLA 治療劑。根據本發明之一態樣，亦可基於各個患者之基因資料，提供量身訂製(tailor made)的治療。

【實施方式】

【0011】在一實施型態中，本發明係關於一種反義寡核苷酸或其醫藥上可容許之鹽或此等的水合物，其係由 15 至 22 個核苷酸構成，並且與包含標的區域中之至少 15 個連續鹼基的核酸互補，該標的區域係選自由序列編號 471 之鹼基序列之第 1 至 84 位、第 142 至 168 位、第 197 至 224 位、第 286 至 317 位、第 324 至 370 位、第 391 至 434 位、第 519 至 540 位、第 623 至 643 位、第 690 至 780 位、第 824 至 855 位、第 860 至 897 位、第 948 至 987 位、第 1044 至 1072 位、第 1125 至 1174 位、第 1181 至 1213 位、第 1228 至 1255 位、第 1265 至 1327 位、第 1334 至 1356 位、第 1416 至 1440 位、第 1447 至 1631 位、第 1638 至 1667 位、第 1675 至 1705 位、第 1748 至 1823 位、第 1838 至 1861 位、第 1870 至 1913 位、第 1920 至 1941 位、第 2000 至 2040 位、第 2047 至 2075 位、第 2086 至

2120 位、第 2129 至 2187 位、第 2194 至 2415 位、第 2451 至 2497 位、第 2592 至 2759 位、第 2766 至 2870 位、第 2928 至 2948 位、第 2955 至 2989 位、第 3021 至 3086 位、第 3133 至 3209 位、第 3217 至 3284 位、第 3295 至 3350 位、第 3384 至 3436 位、第 3562 至 3771 位、第 3858 至 3905 位、第 3931 至 4039 位、第 4067 至 4134 位、第 4170 至 4232 位、第 4241 至 4283 位、及第 4286 至 4355 位所構成之群組。

【0012】序列編號 471 為人類 Atrophin-1(ATN1)之 mRNA 的序列(Gen Bank:NM_001007026)。序列編號 471 之序列係包含 4355 個鹼基之鹼基序列，序列編號 1 之中，由第 1691 至 1747 位構成之區域係包含 CAG/CAA 重複序列的重複區域。在一實施型態中，本發明之反義寡核苷酸的標的序列不包括包含 CAG/CAA 重複序列的重複區域。

【0013】在一實施型態中，本發明之反義寡核苷酸係與包含標的區域中之至少 15 個、至少 16 個、至少 17 個、至少 18 個、至少 19 個、至少 20 個，例如 20 個之連續鹼基，或由此等鹼基構成之核酸互補。

【0014】在本說明書中，所謂與某核酸「互補的」反義寡核苷酸，不限定與成為對象之核酸形成沃森-克里克(Watson-Crick)型鹼基對之反義寡核苷酸，亦包含形成搖擺鹼基對(Wobble base pair)的反義寡核苷酸。在此，所謂沃森-克里克型鹼基對意指在腺嘌呤-胸腺嘧啶、腺嘌呤-脲嘧啶、及鳥糞嘌呤-胞嘧啶間形成氫鍵的鹼基對，所謂搖擺鹼基對意指在鳥糞嘌呤-脲嘧啶、肌苷-脲嘧啶、肌苷-腺嘌呤、及肌苷-胞嘧啶間形成氫鍵的鹼基對。又，所謂「互補的鹼基序列」亦可不與成為對象之鹼基序列具有 100%之互補性，例如，相對於成為對象之鹼基序列，可包含 1 鹼基、2 鹼基、3 鹼基、

4 鹼基、或 5 鹼基之非互補的鹼基，又，亦可相對於成為對象之鹼基序列，為短 1 鹼基、2 鹼基、3 鹼基、4 鹼基、或 5 鹼基的鹼基序列。在一實施型態中，與某核酸「互補」之反義寡核苷酸，係相對於該核酸，具有至少 90%、91%、92%、93%、94%、95%、96%、97%、98%、99%、或 100%的互補性。只要是所屬技術領域具有通常知識者則可容易地決定互補性，例如，可藉由將 2 個序列比對(alignment)，計數於序列間形成沃森-克里克型鹼基對或搖擺鹼基對的鹼基數目，將形成了鹼基對的鹼基數目除以序列中鹼基的總數，再對其乘以 100 而算出。

【0015】與某核酸「互補」的反義寡核苷酸之例，係可列舉例如對該核酸可以嚴苛條件雜交的反義寡核苷酸。在本說明書中，所謂「嚴苛條件」可為低嚴苛條件、中嚴苛條件、及高嚴苛條件之任一者。「低嚴苛條件」係例如為 5×SSC、5×登哈特溶液(Denhardt's solution)、0.5%SDS、50%甲醯胺、32℃之條件。又，「中嚴苛條件」係例如為 5×SSC、5×登哈特溶液、0.5%SDS、50%甲醯胺、42℃或 5×SSC、1%SDS、50mM Tris-HCl(pH7.5)、50%甲醯胺、42℃之條件。「高嚴苛條件」係例如為 5×SSC、5×登哈特溶液、0.5%SDS、50%甲醯胺、50℃或 0.2×SSC、0.1%SDS、65℃之條件。在此等條件中，越提高溫度，越可期待能有效率地得到具有高序列一致性的鹼基序列。但是，影響雜交之嚴苛性的要素認為有溫度、探針濃度、探針之長度、離子強度、時間、鹽濃度等複數個要素，只要是所屬技術領域具有通常知識者，則可藉由適當地選擇此等要素，而實現同樣之嚴苛性。

【0016】再者，在雜交時使用市售之套組時，可使用例如 AlkPhos (AlkPhos Direct Labelling and Detection System(GE Healthcare 公司)。

此時，依照附加於套組之操作指南(protocol)，與經標識之探針培養(incubation)一晚後，將膜於 55℃之條件下以包含 0.1%(w/v)SDS 之 1 次洗淨緩衝液洗淨後，可檢測出雜交。或者是，在以標的序列為基礎製作探針時，使用市售之試藥(例如，PCR 標記混合物(PCR Labeling Mix)(Roche Diagnostics 公司)等)，將該探針以地高辛(digoxigenin)(DIG)標識的情況，可使用 DIG 核酸檢測套組(Roche Diagnostics 公司)等檢測出雜交。

【0017】此外，鹼基序列之一致性可藉由使用 Carlin 及 Authur 之演算法(Algorithm) BLAST (基本局部比對搜索工具(Basic Local Alignment Search Tool))(Proc. Natl. Acad. Sci. USA 872264-2268, 1990; Proc Natl Acad Sci USA 90: 5873, 1993)來決定。已開發以 BLAST 之演算法為基礎，被稱為 BLASTN 或 BLASTX 的程式 (Altschul SF, et al: J Mol Biol 215: 403, 1990)。在使用 BLASTN 解析鹼基序列時，參數設為例如 score=100、wordlength=12。在使用 BLAST 及 Gapped BLAST 程式時，使用各程式之預設(defult)參數。

【0018】在一實施型態中，本發明之反義寡核苷酸，可為例如 15 個核苷酸長以上、16 個核苷酸長以上、17 個核苷酸長以上、18 個核苷酸長以上、19 個核苷酸長以上、20 個核苷酸長以上、21 個核苷酸長以上、22 個核苷酸長以上、23 個核苷酸長以上、24 個核苷酸長以上、25 個核苷酸長以上、26 個核苷酸長以上、27 個核苷酸長以上、28 個核苷酸長以上、29 個核苷酸長以上、或 30 個核苷酸長，可為 30 個核苷酸長以下、29 個核苷酸長以下、28 個核苷酸長以下、27 個核苷酸長以下、26 個核苷酸長以下、25 個核苷酸長以下、24 個核苷酸長以下、23 個核苷酸長以下、22 個核苷

酸長以下、21 個核苷酸長以下、20 個核苷酸長以下、19 個核苷酸長以下、18 個核苷酸長以下、17 個核苷酸長以下、16 個核苷酸長以下、或 15 個核苷酸長。本發明之反義寡核苷酸例如可由 15 至 30 個核苷酸、15 至 25 個核苷酸、15 至 24 個核苷酸、15 至 23 個核苷酸、15 至 22 個核苷酸、15 至 21 個核苷酸、15 至 20 個核苷酸、16 至 25 個核苷酸、17 至 25 個核苷酸、18 至 25 個核苷酸、19 至 25 個核苷酸、20 至 25 個核苷酸、16 至 24 個核苷酸、17 至 23 個核苷酸、18 至 22 個核苷酸、19 至 21 個核苷酸，例如 20 個核苷酸構成。

【0019】本發明之反義寡核苷酸的醫藥上可容許之鹽之例可列舉：如鈉鹽、鉀鹽、鋰鹽之鹼金屬鹽；如鈣鹽、鎂鹽之鹼土金屬鹽；如鋁鹽、鐵鹽、鋅鹽、銅鹽、鎳鹽、鈷鹽等金屬鹽；銨鹽；如第三辛基胺鹽、二苄基胺鹽、嗎啉鹽、葡萄糖胺鹽、苯基甘胺酸烷基酯鹽、乙二胺鹽、N-甲基還原葡糖胺鹽、胍鹽、二乙基胺鹽、三乙基胺鹽、二環己基胺鹽、N,N'-二苄基乙二胺鹽、氯普魯卡因鹽、普魯卡因鹽、二乙醇胺鹽、N-苄基-苯乙基胺鹽、哌啡鹽、四甲基銨鹽、參(羥基甲基)胺基甲烷鹽之有機胺鹽；如氫氟酸鹽、鹽酸鹽、氫溴酸鹽、氫碘酸鹽之鹵氫酸鹽；如硝酸鹽、過氯酸鹽、硫酸鹽、磷酸鹽等無機酸鹽；如甲磺酸鹽、三氟甲磺酸鹽、乙磺酸鹽之低級烷磺酸鹽；如苯磺酸鹽、對甲苯磺酸鹽之芳基磺酸鹽；如乙酸鹽、蘋果酸鹽、富馬酸鹽、琥珀酸鹽、檸檬酸鹽、酒石酸鹽、草酸鹽、馬來酸鹽等有機酸鹽；如甘胺酸鹽、離胺酸鹽、精胺酸鹽、鳥胺酸鹽、麩胺酸鹽、天門冬胺酸鹽之胺基酸鹽等。此等之鹽可依照周知的方法製造。或者是，本發明之反義寡核苷酸亦可為其水合物的形態。

本發明之反義寡核苷酸係以核苷酸為構成單元，該核苷酸可為核糖核苷酸、去氧核糖核苷酸、或修飾核苷酸之任一者。

【0020】所謂修飾核苷酸意指構成核糖核苷酸或去氧核糖核苷酸之核酸鹼基、糖部分、及磷酸鍵部分的全部或一部分經修飾者。

【0021】核酸鹼基可列舉例如：腺嘌呤、鳥糞嘌呤、次黃嘌呤(hypoxanthine)、胞嘧啶、胸腺嘧啶、脲嘧啶、或此等之修飾鹼基。該修飾鹼基可列舉例如：假脲嘧啶、3-甲基脲嘧啶、二氫脲嘧啶、5-烷基胞嘧啶(例如，5-甲基胞嘧啶)、5-烷基脲嘧啶(例如，5-乙基脲嘧啶)、5-鹵脲嘧啶(例如，5-溴脲嘧啶)、6-氮雜嘧啶(6-Azapyrimidine)、6-烷基嘧啶(例如，6-甲基脲嘧啶)、2-硫脲嘧啶、4-硫脲嘧啶、4-乙醯基胞嘧啶、5-(羧基羥基甲基)脲嘧啶、5-羧甲基胺基甲基-2-硫脲嘧啶、5-羧甲基胺基甲基脲嘧啶、1-甲基腺嘌呤、1-甲基次黃嘌呤、2,2-二甲基鳥糞嘌呤、3-甲基胞嘧啶、2-甲基腺嘌呤、2-甲基鳥糞嘌呤、N6-甲基腺嘌呤、7-甲基鳥糞嘌呤、5-甲氧基胺基甲基-2-硫脲嘧啶、5-甲基胺基甲基脲嘧啶、5-甲基羰基甲基脲嘧啶、5-甲氧基脲嘧啶、5-甲基-2-硫脲嘧啶、2-甲基硫-N6-異戊烯基腺嘌呤、脲嘧啶-5-氧基乙酸、2-硫胞嘧啶、嘌呤、2,6-二胺基嘌呤、2-胺基嘌呤、異鳥糞嘌呤、吲哚、咪唑、黃嘌呤等，然而不以此等為限。

【0022】在本說明書中，胸腺嘧啶「T」與脲嘧啶「U」可相互交換，由於「T」及「U」皆不會對本發明之反義寡核苷酸的活性造成本質上的影響，因此在本說明書所示之鹼基序列中，亦包含「T」為「U」的情況，以相同之序列編號表示。又，在本說明書中，包含修飾鹼基之序列係與不含修飾鹼基之序列以相同之序列編號表示，例如「胞嘧啶」與「甲基胞嘧啶」

可相互交換，在「胞嘧啶」為「甲基胞嘧啶」時，亦可以相同之序列編號表示。

【0023】糖部分之修飾可列舉例如：核糖之 2'位之修飾及糖之其他部分的修飾。核糖之 2'位的修飾可列舉例如：將核糖之 2'位之-OH 基取代成-OR、-ORORR、-R、-R'OR、-SH、-SR、-NH_2、-NHR、-NR_2、-N_3、-CN、-F、-Cl、-Br、-I、例如-OMe(-O-CH_3)或-O 甲氧基乙基(-O-MOE：-O-$CH_2CH_2OCH_3$)的修飾。在此，R 表示烷基、環烷基、醯基或芳基。R'表示伸烷基。

【0024】糖之其他部分的修飾可列舉例如：將核糖或去氧核糖之 4'位之 O 取代成 S 者、糖之 2'位及 4'位經交聯者，例如，LNA(鏈核酸(Locked Nucleic Acid))或 ENA(2'-O,4'-C-乙烯基交聯核酸(2'-O,4'-C-Ethylene-bridged Nucleic Acids))等，然而不以此等為限。

【0025】磷酸鍵部分之修飾可列舉例如：將磷酸二酯鍵置換成硫代磷酸酯鍵、二硫代磷酸酯(phosphorodithioate)鍵、烷基膦酸酯(alkyl phosponate)鍵、胺基磷酸酯(phosphoramidate)鍵、硼磷酸酯(boranophosphate)鍵(例如，參照 Enya et al: Bioorganic & Medicinal Chemistry,2008, 18, 9154-9160)的修飾(參照例如日本再公表專利公報第 2006/129594 號及再公表專利公報第 2006/038608 號)。

【0026】在本說明書中，烷基較佳為直鏈狀或分枝鏈狀之碳數 1 至 6 的烷基。具體而言，可列舉例如：甲基、乙基、正丙基、異丙基、正丁基、異丁基、第二丁基、第三丁基、正戊基、異戊基、新戊基、第三戊基、正己

基、異己基。該烷基可經取代，該取代基可列舉例如：鹵素、烷氧基、氰基、硝基，可經此等 1 至 3 個取代。

【0027】在本說明書中，環烷基較佳為碳數 3 至 12 之環烷基。具體而言，可列舉例如：環丙基、環丁基、環戊基、環己基、環庚基、環辛基、環癸基、環十二烷基。

【0028】在本說明書中，鹵素可列舉：氟、氯、溴、碘。

【0029】在本說明書中，烷氧基為直鏈狀或分枝鏈狀之碳數 1 至 6 的烷氧基，可列舉例如：甲氧基、乙氧基、正丙氧基、異丙氧基、正丁氧基、異丁氧基、第二丁氧基、第三丁氧基、正戊氧基、異戊氧基、正己氧基、異己氧基等。特佳為碳數 1 至 3 之烷氧基。

【0030】在本說明書中，芳基較佳為碳數 6 至 10 之芳基。具體而言，可列舉例如：苯基、α-萘基、β-萘基，特佳為苯基。該芳基可經取代，該取代基可列舉例如：烷基、鹵素、烷氧基、氰基、硝基，此等亦可經 1 至 3 個取代。

【0031】在本說明書中，伸烷基較佳為直鏈狀或分枝鏈狀之碳數 1 至 6 的伸烷基。具體而言，可列舉例如：亞甲基、伸乙基、三亞甲基、四亞甲基、五亞甲基、六亞甲基、2-(乙基)三亞甲基、1-(甲基)四亞甲基。

【0032】在本說明書中，醯基可列舉直鏈狀或分枝鏈狀之烷醯基或芳醯基。烷醯基可列舉例如：甲醯基、乙醯基、2-甲基乙醯基、2,2-二甲基乙醯基、丙醯基、丁醯基、異丁醯基、戊醯基、2,2-二甲基丙醯基、己醯基等。芳醯基可列舉例如：苄醯基、甲苯甲醯基、萘甲醯基。該芳醯基可在可取代的位置經取代，亦可經烷基取代。

【0033】在一實施型態中，本發明之反義寡核苷酸為包含中央之間隔(gap)區域、及與間隔區域鄰接之 5’末端側及 3’末端側的 2 個翼部區域(亦分別記載為 5’翼部區域及 3’翼部區域)的間隔子(gapmer)。間隔區域意指藉由 RNase H 識別的區域，糖部以未經修飾之去氧核糖核苷酸構成。翼部區域至少包含一個修飾核苷酸，例如其全部皆以修飾核苷酸(例如核糖之 2’位經修飾的核糖核苷酸)構成。在一實施型態中，5’翼部區域及 3’翼部區域之核苷可為包含分別至少一個，例如二個以上、三個以上、四個以上、五個以上之糖部分的修飾，例如 2’-OMe 基及/或 2’-O-MOE 基，亦可為例如 5’翼部區域及 3’翼部區域之核苷全部包含 2’-OMe 基及/或 2’-O-MOE 基者。又，5’翼部區域及 3’翼部區域之核苷，亦可於鹼基部分包含修飾，例如可包含至少一個甲基胞嘧啶。

【0034】間隔區域之長度無限定，例如可為 5 至 15、8 至 12、9 至 11 或 10 個鹼基長。5’翼部區域及 3’翼部區域之長度無限定，例如可各自獨立地為 2 至 10、3 至 8、4 至 6 或 5 個鹼基長。在一實施型態中，間隔區域之長度為 10 個鹼基長，5’翼部區域及 3’翼部區域之長度分別為 5 個鹼基長。

【0035】在一實施型態中，本發明之間隔子包含一個以上磷酸鍵部分的修飾，例如硫代磷酸酯鍵，亦可例如核苷酸間之鍵結一個以上、二個以上、三個以上、四個以上、五個以上、十個以上、十五個以上為硫代磷酸酯鍵，亦可例如全部為硫代磷酸酯鍵。在一實施型態中，本發明之間隔子係核苷間之鍵結全部為硫代磷酸酯鍵。在一實施型態中，本發明之間隔子係於例如 5’翼部區域及/或 3’翼部區域中含有一個以上、二個以上、三個以上、四個以上、五個以上、六個以上、七個以上、八個以上、九個以上、或

十個以上(例如二個至六個)磷酸二酯鍵，且其他核苷間之鍵結全部為硫代磷酸酯鍵。在一實施型態中，5'翼部區域之 5'側算起第 2 與第 3 核苷間之鍵結、第 3 與第 4 核苷間之鍵結、及第 4 與第 5 核苷間之鍵結的一個以上為磷酸二酯鍵，及/或 3'翼部區域之 5'側算起第 1 與第 2 核苷間之鍵結、第 2 與第 3 核苷間之鍵結、及第 3 與第 4 核苷間之鍵結的一個以上為磷酸二酯鍵，且其他核苷間之鍵結全部為硫代磷酸酯鍵。在一實施型態中，5'翼部區域之 5'側算起第 2 與第 3 核苷間之鍵結及第 4 與第 5 核苷間之鍵結為磷酸二酯鍵，及/或 3'翼部區域之 5'側算起第 1 與第 2 核苷間之鍵結及第 3 與第 4 核苷間之鍵結為磷酸二酯鍵，且其他核苷間之鍵結全部為硫代磷酸酯鍵。在一實施型態中，5'翼部區域之 5'側算起第 2 與第 3 核苷間之鍵結、第 3 與第 4 核苷間之鍵結、及第 4 與第 5 核苷間之鍵結為磷酸二酯鍵，及/或 3'翼部區域之 5'側算起第 1 與第 2 核苷間之鍵結、第 2 與第 3 核苷間之鍵結、及第 3 與第 4 核苷間之鍵結為磷酸二酯鍵，且其他核苷間之鍵結全部為硫代磷酸酯鍵。在一實施型態中，5'翼部區域之 5'側算起第 2 與第 3 核苷間之鍵結、及第 3 與第 4 核苷間之鍵結為磷酸二酯鍵，及/或 3'翼部區域之 5'側算起第 2 與第 3 核苷間之鍵結、及第 3 與第 4 核苷間之鍵結為磷酸二酯鍵，且其他核苷間之鍵結全部為硫代磷酸酯鍵。在一實施型態中，5'翼部區域之 5'側算起第 3 與第 4 核苷間之鍵結、及第 4 與第 5 核苷間之鍵結為磷酸二酯鍵，及/或 3'翼部區域之 5'側算起第 1 與第 2 核苷間之鍵結、及第 2 與第 3 核苷間之鍵結為磷酸二酯鍵，且其他核苷間之鍵結全部為硫代磷酸酯鍵。在一實施型態中，5'翼部區域之 5'側算起第 2 與第 3 核苷間之鍵結為磷酸二酯鍵，及/或 3'翼部區域之 5'側算起第 3 與第 4 核苷

間之鍵結為磷酸二酯鍵，且其他核苷間之鍵結全部為硫代磷酸酯鍵。在一實施型態中，5'翼部區域之 5'側算起第 3 與第 4 核苷間之鍵結為磷酸二酯鍵，及/或 3'翼部區域之 5'側算起第 2 與第 3 核苷間之鍵結為磷酸二酯鍵，且其他核苷間之鍵結全部為硫代磷酸酯鍵。在一實施型態中，5'翼部區域之 5'側算起第 4 與第 5 核苷間之鍵結為磷酸二酯鍵，及/或 3'翼部區域之 5'側算起第 1 與第 2 核苷間之鍵結為磷酸二酯鍵，且其他核苷間之鍵結全部為硫代磷酸酯鍵。在一實施型態中，本發明之間隔子亦可不包含磷酸鍵部分之修飾，核苷酸間鍵結全部為磷酸二酯鍵。

【0036】在一實施型態中，本發明之反義寡核苷酸係與包含標的區域中之至少 15 個連續鹼基的核酸互補，該標的區域係選自由序列編號 471 之鹼基序列之第 1 至 84 位、第 142 至 168 位、第 197 至 224 位、第 286 至 317 位、第 324 至 370 位、第 391 至 434 位、第 519 至 540 位、第 623 至 643 位、第 690 至 780 位、第 824 至 855 位、第 860 至 897 位、第 948 至 987 位、第 1044 至 1072 位、第 1125 至 1174 位、第 1181 至 1213 位、第 1228 至 1255 位、第 1265 至 1327 位、第 1334 至 1356 位、第 1416 至 1440 位、第 1447 至 1631 位、第 1638 至 1667 位、第 1675 至 1705 位、第 1748 至 1823 位、第 1838 至 1861 位、第 1870 至 1913 位、第 1920 至 1941 位、第 2000 至 2040 位、第 2047 至 2075 位、第 2086 至 2120 位、第 2129 至 2187 位、第 2194 至 2415 位、第 2451 至 2497 位、第 2592 至 2759 位、第 2766 至 2870 位、第 2928 至 2948 位、第 2955 至 2989 位、第 3021 至 3086 位、第 3133 至 3209 位、第 3217 至 3284 位、第 3295 至 3350 位、第 3384 至 3436 位、第 3562 至 3771 位、第 3858 至 3905 位、第 3931 至

4039 位、第 4067 至 4134 位、第 4170 至 4232 位、第 4241 至 4283 位、及第 4286 至 4355 位所構成之群組。

【0037】在一實施型態中，本發明之反義寡核苷酸係與包含標的區域中之至少 15 個連續鹼基的核酸互補，該標的區域係選自由序列編號 471 之鹼基序列之第 1 至 84 位、第 142 至 168 位、第 391 至 434 位、第 697 至 780 位、第 962 至 980 位、第 1125 至 1174 位、第 1181 至 1213 位、第 1228 至 1255 位、第 1265 至 1320 位、第 1454 至 1631 位、第 1682 至 1705 位、第 1748 至 1816 位、第 1870 至 1913 位、第 2015 至 2040 位、第 2086 至 2120 位、第 2129 至 2187 位、第 2201 至 2408 位、第 2592 至 2759 位、第 2773 至 2870 位、第 2955 至 2982 位、第 3028 至 3079 位、第 3133 至 3209 位、第 3224 至 3277 位、第 3295 至 3350 位、第 3391 至 3429 位、第 3562 至 3771 位、第 3865 至 3898 位、第 3938 至 4032 位、第 4074 至 4127 位、及第 4170 至 4225 位所構成之群組。

【0038】在一實施型態中，本發明之反義寡核苷酸係與包含標的區域中之至少 15 個連續鹼基的核酸互補，該標的區域係選自由序列編號 471 之鹼基序列之第 1 至 69 位、第 331 至 363 位、第 398 至 427 位、第 697 至 773 位、第 867 至 890 位、第 955 至 980 位、第 1132 至 1167 位、第 1272 至 1320 位、第 1454 至 1624 位、第 1682 至 1705 位、第 1748 至 1816 位、第 1877 至 1906 位、第 2007 至 2033 位、第 2093 至 2113 位、第 2136 至 2180 位、第 2201 至 2408 位、第 2458 至 2490 位、第 2599 至 2752 位、第 2773 至 2863 位、第 2962 至 2982 位、第 3028 至 3079 位、第 3140 至 3202 位、第 3224 至 3277 位、第 3302 至 3343 位、第 3391 至 3429 位、

第 3569 至 3764 位、第 3865 至 3898 位、第 3938 至 4032 位、第 4074 至 4127 位、第 4177 至 4225 位、第 4248 至 4276 位、及第 4293 至 4355 位所構成之群組。

【0039】在一實施型態中，本發明之反義寡核苷酸係與包含標的區域中之至少 15 個連續鹼基的核酸互補，該標的區域係選自由序列編號 471 之鹼基序列之第 1 至 69 位、第 398 至 427 位、第 697 至 773 位、第 1132 至 1167 位、第 1272 至 1320 位、第 1454 至 1624 位、第 1682 至 1705 位、第 1748 至 1816 位、第 1877 至 1906 位、第 2093 至 2113 位、第 2136 至 2180 位、第 2201 至 2408 位、第 2599 至 2752 位、第 2773 至 2863 位、第 2962 至 2982 位、第 3028 至 3079 位、第 3140 至 3202 位、第 3224 至 3277 位、第 3302 至 3343 位、第 3391 至 3429 位、第 3569 至 3764 位、第 3865 至 3898 位、第 3938 至 4032 位、及第 4177 至 4225 位所構成之群組。

【0040】在一實施型態中，本發明之反義寡核苷酸係與包含標的區域中之至少 15 個連續鹼基的核酸互補，該標的區域係選自由序列編號 471 之鹼基序列之第 14 至 33 位、第 34 至 53 位、第 54 至 73 位、第 148 至 167 位、第 397 至 432 位、第 723 至 742 位、第 747 至 778 位、第 965 至 984 位、第 1127 至 1146 位、第 1148 至 1173 位、第 1182 至 1213 位、第 1228 至 1254 位、第 1270 至 1308 位、第 1484 至 1564 位、第 1578 至 1629 位、第 1686 至 1705 位、第 1748 至 1767 位、第 1768 至 1787 位、第 1794 至 1813 位、第 1870 至 1913 位、第 2015 至 2034 位、第 2086 至 2118 位、第 2129 至 2148 位、第 2151 至 2184 位、第 2206 至 2225 位、第 2239 至

2272位、第2287至2336位、第2337至2373位、第2387至2406位、第2598至2757位、第2775至2809位、第2826至2866位、第2959至2982位、第3032至3051位、第3052至3071位、第3136至3155位、第3168至3187位、第3188至3207位、第3232至3270位、第3298至3344位、第3408至3427位、第3563至3582位、第3590至3728位、第3739至3769位、第3877至3896位、第3949至4030位、及第4170至4225位所構成之群組。

在一實施型態中，本發明之反義寡核苷酸係與包含標的區域中之至少15個連續鹼基的核酸互補，該標的區域係選自由序列編號471之鹼基序列之第14至33位、第34至53位、第54至73位、第148至167位、第397至416位、第398至417位、第399至418位、第400至419位、第401至420位、第402至421位、第403至422位、第404至423位、第405至424位、第406至425位、第407至426位、第408至427位、第413至432位、第723至742位、第747至766位、第756至775位、第759至778位、第965至984位、第1127至1146位、第1148至1167位、第1151至1170位、第1154至1173位、第1182至1201位、第1185至1204位、第1188至1207位、第1191至1210位、第1194至1213位、第1228至1247位、第1231至1250位、第1235至1254位、第1270至1289位、第1289至1308位、第1484至1503位、第1488至1507位、第1491至1510位、第1493至1512位、第1506至1525位、第1517至1536位、第1531至1550位、第1545至1564位、第1578至1597位、第1579至1598位、第1580至1599位、第1581至1600位、第1582至

1601位、第1583至1602位、第1584至1603位、第1585至1604位、第1586至1605位、第1587至1606位、第1588至1607位、第1589至1608位、第1590至1609位、第1591至1610位、第1592至1611位、第1593至1612位、第1594至1613位、第1595至1614位、第1596至1615位、第1597至1616位、第1598至1617位、第1599至1618位、第1600至1619位、第1601至1620位、第1602至1621位、第1603至1622位、第1604至1623位、第1605至1624位、第1607至1626位、第1610至1629位、第1686至1705位、第1748至1767位、第1768至1787位、第1794至1813位、第1870至1889位、第1871至1890位、第1874至1893位、第1877至1896位、第1878至1897位、第1879至1898位、第1880至1899位、第1881至1900位、第1882至1901位、第1883至1902位、第1884至1903位、第1885至1904位、第1886至1905位、第1887至1906位、第1889至1908位、第1894至1913位、第2015至2034位、第2086至2105位、第2093至2112位、第2094至2113位、第2097至2116位、第2099至2118位、第2129至2148位、第2151至2170位、第2165至2184位、第2206至2225位、第2239至2258位、第2253至2272位、第2287至2306位、第2301至2320位、第2317至2336位、第2337至2356位、第2354至2373位、第2387至2406位、第2598至2617位、第2613至2632位、第2614至2633位、第2615至2634位、第2616至2635位、第2617至2636位、第2618至2637位、第2619至2638位、第2620至2639位、第2621至2640位、第2622至2641位、第2623至2642位、第2624至2643位、第2625至

2644位、第2626至2645位、第2627至2646位、第2628至2647位、第2629至2648位、第2630至2649位、第2631至2650位、第2632至2651位、第2633至2652位、第2634至2653位、第2635至2654位、第2636至2655位、第2637至2656位、第2638至2657位、第2639至2658位、第2640至2659位、第2641至2660位、第2642至2661位、第2643至2662位、第2644至2663位、第2645至2664位、第2646至2665位、第2647至2666位、第2648至2667位、第2649至2668位、第2663至2682位、第2672至2691位、第2673至2692位、第2674至2693位、第2675至2694位、第2676至2695位、第2677至2696位、第2678至2697位、第2679至2698位、第2680至2699位、第2681至2700位、第2682至2701位、第2683至2702位、第2684至2703位、第2685至2704位、第2686至2705位、第2687至2706位、第2688至2707位、第2689至2708位、第2690至2709位、第2691至2710位、第2692至2711位、第2693至2712位、第2694至2713位、第2695至2714位、第2696至2715位、第2697至2716位、第2698至2717位、第2699至2718位、第2700至2719位、第2701至2720位、第2702至2721位、第2703至2722位、第2704至2723位、第2705至2724位、第2706至2725位、第2707至2726位、第2708至2727位、第2709至2728位、第2710至2729位、第2711至2730位、第2712至2731位、第2713至2732位、第2714至2733位、第2715至2734位、第2716至2735位、第2717至2736位、第2718至2737位、第2719至2738位、第2720至2739位、第2721至2740位、第2722至2741位、第2723至

2742位、第2724至2743位、第2725至2744位、第2726至2745位、第2727至2746位、第2728至2747位、第2729至2748位、第2730至2749位、第2731至2750位、第2732至2751位、第2733至2752位、第2738至2757位、第2775至2794位、第2790至2809位、第2826至2845位、第2827至2846位、第2828至2847位、第2829至2848位、第2830至2849位、第2831至2850位、第2832至2851位、第2833至2852位、第2834至2853位、第2835至2854位、第2836至2855位、第2837至2856位、第2838至2857位、第2839至2858位、第2840至2859位、第2841至2860位、第2842至2861位、第2843至2862位、第2844至2863位、第2847至2866位、第2959至2978位、第2962至2981位、第2963至2982位、第3032至3051位、第3052至3071位、第3136至3155位、第3168至3187位、第3188至3207位、第3232至3251位、第3251至3270位、第3298至3317位、第3302至3321位、第3303至3322位、第3304至3323位、第3305至3324位、第3306至3325位、第3307至3326位、第3308至3327位、第3309至3328位、第3310至3329位、第3311至3330位、第3312至3331位、第3313至3332位、第3314至3333位、第3315至3334位、第3316至3335位、第3317至3336位、第3318至3337位、第3319至3338位、第3320至3339位、第3321至3340位、第3322至3341位、第3323至3342位、第3324至3343位、第3325至3344位、第3408至3427位、第3563至3582位、第3590至3609位、第3608至3627位、第3617至3636位、第3618至3637位、第3619至3638位、第3620至3639位、第3621至

3640位、第3622至3641位、第3623至3642位、第3624至3643位、第3625至3644位、第3626至3645位、第3627至3646位、第3628至3647位、第3629至3648位、第3630至3649位、第3631至3650位、第3632至3651位、第3633至3652位、第3634至3653位、第3635至3654位、第3636至3655位、第3637至3656位、第3638至3657位、第3639至3658位、第3640至3659位、第3641至3660位、第3642至3661位、第3643至3662位、第3644至3663位、第3645至3664位、第3646至3665位、第3647至3666位、第3648至3667位、第3649至3668位、第3650至3669位、第3651至3670位、第3652至3671位、第3653至3672位、第3654至3673位、第3671至3690位、第3672至3691位、第3673至3692位、第3674至3693位、第3675至3694位、第3676至3695位、第3677至3696位、第3678至3697位、第3679至3698位、第3680至3699位、第3681至3700位、第3682至3701位、第3683至3702位、第3684至3703位、第3685至3704位、第3686至3705位、第3687至3706位、第3688至3707位、第3689至3708位、第3690至3709位、第3691至3710位、第3692至3711位、第3693至3712位、第3694至3713位、第3695至3714位、第3696至3715位、第3697至3716位、第3698至3717位、第3699至3718位、第3700至3719位、第3701至3720位、第3702至3721位、第3703至3722位、第3704至3723位、第3705至3724位、第3706至3725位、第3707至3726位、第3708至3727位、第3709至3728位、第3739至3758位、第3740至3759位、第3741至3760位、第3742至3761位、第3743至

3762位、第3744至3763位、第3745至3764位、第3750至3769位、第3877至3896位、第3949至3968位、第3964至3983位、第3965至3984位、第3966至3985位、第3967至3986位、第3968至3987位、第3969至3988位、第3970至3989位、第3971至3990位、第3972至3991位、第3973至3992位、第3974至3993位、第3975至3994位、第3976至3995位、第3977至3996位、第3978至3997位、第3979至3998位、第3980至3999位、第3981至4000位、第3982至4001位、第3983至4002位、第3984至4003位、第3985至4004位、第3986至4005位、第3987至4006位、第3988至4007位、第3989至4008位、第3990至4009位、第3991至4010位、第3992至4011位、第3993至4012位、第3994至4013位、第3995至4014位、第3996至4015位、第3997至4016位、第3998至4017位、第3999至4018位、第4011至4030位、第4170至4189位、第4173至4192位、第4176至4195位、第4177至4196位、第4178至4197位、第4179至4198位、第4180至4199位、第4181至4200位、第4182至4201位、第4183至4202位、第4184至4203位、第4185至4204位、第4186至4205位、第4187至4206位、第4188至4207位、第4189至4208位、第4190至4209位、第4191至4210位、第4192至4211位、第4193至4212位、第4194至4213位、第4195至4214位、第4196至4215位、第4197至4216位、第4198至4217位、第4199至4218位、第4200至4219位、第4201至4220位、第4202至4221位、第4203至4222位、第4204至4223位、第4205至4224位、及第4206至4225位所構成之群組。

【0041】屬於上述與包含標的序列中之至少 15 個連續鹼基之核酸互補的反義寡核苷酸之例可列舉包含下列(i)、(ii)或(iii)之鹼基序列，例如(i)之鹼基序列，或由其構成的反義寡核苷酸：

(i) 選自由序列編號 1 至 6、8、9、11、14 至 24、26、29、31 至 60、66 至 67、73 至 75、79 至 82、86 至 89、92 至 111、115 至 136、138 至 145、147 至 158、及 160 至 464 所構成之群組中的鹼基序列，

(ii) 在選自由序列編號 1 至 6、8、9、11、14 至 24、26、29、31 至 60、66 至 67、73 至 75、79 至 82、86 至 89、92 至 111、115 至 136、138 至 145、147 至 158、及 160 至 464 所構成之群組中的鹼基序列中，1 個或複數個鹼基經附加、缺失、或置換而成之鹼基序列，或

(iii) 相對於序列編號 1 至 6、8、9、11、14 至 24、26、29、31 至 60、66 至 67、73 至 75、79 至 82、86 至 89、92 至 111、115 至 136、138 至 145、147 至 158、及 160 至 464 所構成之群組中的鹼基序列，具有 90%以上之序列一致性的鹼基序列。

【0042】在本說明書中，1 個或複數個鹼基經附加、缺失、或置換而成之鹼基序列中的複數個意指 2 個、3 個、4 個、5 個、6 個、7 個、8 個、9 個、或 10 個。

【0043】在一實施型態中，本發明之反義寡核苷酸係與包含標的區域中之至少 15 個連續鹼基的核酸互補，該標的區域係選自由序列編號 471 之鹼基序列之第 14 至 33 位、第 34 至 53 位、第 398 至 427 位、第 723 至 742 位、第 747 至 766 位、第 1148 至 1167 位、第 1289 至 1308 位、第 1484 至 1564 位、第 1578 至 1624 位、第 1686 至 1705 位、第 1748 至 1767

位、第 1768 至 1787 位、第 1794 至 1813 位、第 1877 至 1906 位、第 2093 至 2113 位、第 2151 至 2170 位、第 2206 至 2225 位、第 2239 至 2272 位、第 2287 至 2336 位、第 2337 至 2373 位、第 2387 至 2406 位、第 2613 至 2752 位、第 2775 至 2809 位、第 2826 至 2863 位、第 2962 至 2982 位、第 3032 至 3051 位、第 3052 至 3071 位、第 3168 至 3187 位、第 3232 至 3270 位、第 3302 至 3343 位、第 3408 至 3427 位、第 3590 至 3728 位、第 3739 至 3764 位、第 3877 至 3896 位、第 3949 至 4030 位、及第 4177 至 4225 位所構成之群組。

【0044】在一實施型態中，本發明之反義寡核苷酸係與包含標的區域中之至少 15 個連續鹼基的核酸互補，該標的區域係選自由序列編號 471 之鹼基序列之第 14 至 33 位、第 34 至 53 位、第 398 至 417 位、第 399 至 418 位、第 400 至 419 位、第 401 至 420 位、第 402 至 421 位、第 403 至 422 位、第 404 至 423 位、第 405 至 424 位、第 406 至 425 位、第 407 至 426 位、第 408 至 427 位、第 723 至 742 位、第 747 至 766 位、第 1148 至 1167 位、第 1289 至 1308 位、第 1484 至 1503 位、第 1488 至 1507 位、第 1491 至 1510 位、第 1493 至 1512 位、第 1506 至 1525 位、第 1517 至 1536 位、第 1531 至 1550 位、第 1545 至 1564 位、第 1578 至 1597 位、第 1579 至 1598 位、第 1580 至 1599 位、第 1581 至 1600 位、第 1582 至 1601 位、第 1583 至 1602 位、第 1584 至 1603 位、第 1585 至 1604 位、第 1586 至 1605 位、第 1587 至 1606 位、第 1588 至 1607 位、第 1589 至 1608 位、第 1590 至 1609 位、第 1591 至 1610 位、第 1592 至 1611 位、第 1593 至 1612 位、第 1594 至 1613 位、第 1595 至 1614 位、第 1596 至

1615位、第1597至1616位、第1598至1617位、第1599至1618位、第1600至1619位、第1601至1620位、第1602至1621位、第1603至1622位、第1604至1623位、第1605至1624位、第1686至1705位、第1748至1767位、第1768至1787位、第1794至1813位、第1877至1896位、第1878至1897位、第1879至1898位、第1880至1899位、第1881至1900位、第1882至1901位、第1883至1902位、第1884至1903位、第1885至1904位、第1886至1905位、第1887至1906位、第2093至2112位、第2094至2113位、第2151至2170位、第2206至2225位、第2239至2258位、第2253至2272位、第2287至2306位、第2301至2320位、第2317至2336位、第2337至2356位、第2354至2373位、第2387至2406位、第2613至2632位、第2614至2633位、第2615至2634位、第2616至2635位、第2617至2636位、第2618至2637位、第2619至2638位、第2620至2639位、第2621至2640位、第2622至2641位、第2623至2642位、第2624至2643位、第2625至2644位、第2626至2645位、第2627至2646位、第2628至2647位、第2629至2648位、第2630至2649位、第2631至2650位、第2632至2651位、第2633至2652位、第2634至2653位、第2635至2654位、第2636至2655位、第2637至2656位、第2638至2657位、第2639至2658位、第2640至2659位、第2641至2660位、第2642至2661位、第2643至2662位、第2644至2663位、第2645至2664位、第2646至2665位、第2647至2666位、第2648至2667位、第2649至2668位、第2663至2682位、第2672至2691位、第2673至2692位、第2674至

2693位、第2675至2694位、第2676至2695位、第2677至2696位、第2678至2697位、第2679至2698位、第2680至2699位、第2681至2700位、第2682至2701位、第2683至2702位、第2684至2703位、第2685至2704位、第2686至2705位、第2687至2706位、第2688至2707位、第2689至2708位、第2690至2709位、第2691至2710位、第2692至2711位、第2693至2712位、第2694至2713位、第2695至2714位、第2696至2715位、第2697至2716位、第2698至2717位、第2699至2718位、第2700至2719位、第2701至2720位、第2702至2721位、第2703至2722位、第2704至2723位、第2705至2724位、第2706至2725位、第2707至2726位、第2708至2727位、第2709至2728位、第2710至2729位、第2711至2730位、第2712至2731位、第2713至2732位、第2714至2733位、第2715至2734位、第2716至2735位、第2717至2736位、第2718至2737位、第2719至2738位、第2720至2739位、第2721至2740位、第2722至2741位、第2723至2742位、第2724至2743位、第2725至2744位、第2726至2745位、第2727至2746位、第2728至2747位、第2729至2748位、第2730至2749位、第2731至2750位、第2732至2751位、第2733至2752位、第2775至2794位、第2790至2809位、第2826至2845位、第2827至2846位、第2828至2847位、第2829至2848位、第2830至2849位、第2831至2850位、第2832至2851位、第2833至2852位、第2834至2853位、第2835至2854位、第2836至2855位、第2837至2856位、第2838至2857位、第2839至2858位、第2840至2859位、第2841至

2860位、第2842至2861位、第2843至2862位、第2844至2863位、第2962至2981位、第2963至2982位、第3032至3051位、第3052至3071位、第3168至3187位、第3232至3251位、第3251至3270位、第3302至3321位、第3303至3322位、第3304至3323位、第3305至3324位、第3306至3325位、第3307至3326位、第3308至3327位、第3309至3328位、第3310至3329位、第3311至3330位、第3312至3331位、第3313至3332位、第3314至3333位、第3315至3334位、第3316至3335位、第3317至3336位、第3318至3337位、第3319至3338位、第3320至3339位、第3321至3340位、第3322至3341位、第3323至3342位、第3324至3343位、第3408至3427位、第3590至3609位、第3608至3627位、第3617至3636位、第3618至3637位、第3619至3638位、第3620至3639位、第3621至3640位、第3622至3641位、第3623至3642位、第3624至3643位、第3625至3644位、第3626至3645位、第3627至3646位、第3628至3647位、第3629至3648位、第3630至3649位、第3631至3650位、第3632至3651位、第3633至3652位、第3634至3653位、第3635至3654位、第3636至3655位、第3637至3656位、第3638至3657位、第3639至3658位、第3640至3659位、第3641至3660位、第3642至3661位、第3643至3662位、第3644至3663位、第3645至3664位、第3646至3665位、第3647至3666位、第3648至3667位、第3649至3668位、第3650至3669位、第3651至3670位、第3652至3671位、第3653至3672位、第3654至3673位、第3671至3690位、第3672至3691位、第3673至

3692位、第3674至3693位、第3675至3694位、第3676至3695位、第3677至3696位、第3678至3697位、第3679至3698位、第3680至3699位、第3681至3700位、第3682至3701位、第3683至3702位、第3684至3703位、第3685至3704位、第3686至3705位、第3687至3706位、第3688至3707位、第3689至3708位、第3690至3709位、第3691至3710位、第3692至3711位、第3693至3712位、第3694至3713位、第3695至3714位、第3696至3715位、第3697至3716位、第3698至3717位、第3699至3718位、第3700至3719位、第3701至3720位、第3702至3721位、第3703至3722位、第3704至3723位、第3705至3724位、第3706至3725位、第3707至3726位、第3708至3727位、第3709至3728位、第3739至3758位、第3740至3759位、第3741至3760位、第3742至3761位、第3743至3762位、第3744至3763位、第3745至3764位、第3877至3896位、第3949至3968位、第3964至3983位、第3965至3984位、第3966至3985位、第3967至3986位、第3968至3987位、第3969至3988位、第3970至3989位、第3971至3990位、第3972至3991位、第3973至3992位、第3974至3993位、第3975至3994位、第3976至3995位、第3977至3996位、第3978至3997位、第3979至3998位、第3980至3999位、第3981至4000位、第3982至4001位、第3983至4002位、第3984至4003位、第3985至4004位、第3986至4005位、第3987至4006位、第3988至4007位、第3989至4008位、第3990至4009位、第3991至4010位、第3992至4011位、第3993至4012位、第3994至4013位、第3995至

4014 位、第 3996 至 4015 位、第 3997 至 4016 位、第 3998 至 4017 位、第 3999 至 4018 位、第 4011 至 4030 位、第 4177 至 4196 位、第 4178 至 4197 位、第 4179 至 4198 位、第 4180 至 4199 位、第 4181 至 4200 位、第 4182 至 4201 位、第 4183 至 4202 位、第 4184 至 4203 位、第 4185 至 4204 位、第 4186 至 4205 位、第 4187 至 4206 位、第 4188 至 4207 位、第 4189 至 4208 位、第 4190 至 4209 位、第 4191 至 4210 位、第 4192 至 4211 位、第 4193 至 4212 位、第 4194 至 4213 位、第 4195 至 4214 位、第 4196 至 4215 位、第 4197 至 4216 位、第 4198 至 4217 位、第 4199 至 4218 位、第 4200 至 4219 位、第 4201 至 4220 位、第 4202 至 4221 位、第 4203 至 4222 位、第 4204 至 4223 位、第 4205 至 4224 位、及第 4206 至 4225 位所構成之群組。

【0045】上述與包含標的序列中之至少 15 個連續鹼基之核酸互補的反義寡核苷酸之例可列舉包含下列(i)、(ii)或(iii)之鹼基序列，例如(i)之鹼基序列，或由其構成的反義寡核苷酸：

(i) 選自由序列編號 1、5、6、14 至 24、31 至 35、37 至 40、42 至 45、47 至 50、52 至 59、73、92 至 100、103、107 至 110、120 至 136、138 至 143、150 至 153、155 至 158、及 163 至 464 構成之群組的鹼基序列，

(ii) 在選自由序列編號 1、5、6、14 至 24、31 至 35、37 至 40、42 至 45、47 至 50、52 至 59、73、92 至 100、103、107 至 110、120 至 136、138 至 143、150 至 153、155 至 158、及 163 至 464 構成之群組的鹼基序列中，1 個或複數個鹼基經附加、缺失、或置換而成之鹼基序列，或

(iii) 相對於選自由序列編號 1、5、6、14 至 24、31 至 35、37 至 40、42 至 45、47 至 50、52 至 59、73、92 至 100、103、107 至 110、120 至 136、138 至 143、150 至 153、155 至 158、及 163 至 464 構成之群組的鹼基序列，具有 90%以上之序列一致性的鹼基序列。

【0046】在一實施型態中，本發明之反義寡核苷酸係與包含標的區域中之至少 15 個連續鹼基的核酸互補，該標的區域係選自由序列編號 471 之鹼基序列之第 14 至 33 位、第 34 至 53 位、第 54 至 73 位、第 148 至 167 位、第 397 至 432 位、第 747 至 778 位、第 965 至 984 位、第 1127 至 1146 位、第 1148 至 1173 位、第 1182 至 1213 位、第 1228 至 1254 位、第 1270 至 1308 位、第 1484 至 1564 位、第 1578 至 1629 位、第 1686 至 1705 位、第 1748 至 1767 位、第 1768 至 1787 位、第 1794 至 1813 位、第 1870 至 1913 位、第 2015 至 2034 位、第 2086 至 2118 位、第 2129 至 2148 位、第 2151 至 2170 位、第 2206 至 2225 位、第 2239 至 2272 位、第 2287 至 2336 位、第 2337 至 2373 位、第 2387 至 2406 位、第 2598 至 2632 位、第 2633 至 2668 位、第 2672 至 2691 位、第 2699 至 2757 位、第 2775 至 2809 位、第 2826 至 2866 位、第 2959 至 2978 位、第 3032 至 3051 位、第 3052 至 3071 位、第 3136 至 3155 位、第 3168 至 3187 位、第 3188 至 3207 位、第 3232 至 3270 位、第 3298 至 3317 位、第 3325 至 3344 位、第 3408 至 3427 位、第 3590 至 3690 位、第 3691 至 3728 位、第 3739 至 3769 位、第 3877 至 3896 位、第 3949 至 3983 位、第 3984 至 4030 位、及第 4170 至 4198 位所構成之群組。

【0047】在一實施型態中，本發明之反義寡核苷酸係與包含標的區域中之至少 15 個連續鹼基的核酸互補，該標的區域係選自由序列編號 471 之鹼基序列之第 14 至 33 位、第 34 至 53 位、第 54 至 73 位、第 148 至 167 位、第 397 至 416 位、第 413 至 432 位、第 747 至 766 位、第 756 至 775 位、第 759 至 778 位、第 965 至 984 位、第 1127 至 1146 位、第 1148 至 1167 位、第 1151 至 1170 位、第 1154 至 1173 位、第 1182 至 1201 位、第 1185 至 1204 位、第 1188 至 1207 位、第 1191 至 1210 位、第 1194 至 1213 位、第 1228 至 1247 位、第 1231 至 1250 位、第 1235 至 1254 位、第 1270 至 1289 位、第 1289 至 1308 位、第 1484 至 1503 位、第 1488 至 1507 位、第 1491 至 1510 位、第 1493 至 1512 位、第 1506 至 1525 位、第 1517 至 1536 位、第 1531 至 1550 位、第 1545 至 1564 位、第 1578 至 1597 位、第 1586 至 1605 位、第 1589 至 1608 位、第 1592 至 1611 位、第 1595 至 1614 位、第 1598 至 1617 位、第 1601 至 1620 位、第 1604 至 1623 位、第 1607 至 1626 位、第 1610 至 1629 位、第 1686 至 1705 位、第 1748 至 1767 位、第 1768 至 1787 位、第 1794 至 1813 位、第 1870 至 1889 位、第 1871 至 1890 位、第 1874 至 1893 位、第 1877 至 1896 位、第 1880 至 1899 位、第 1883 至 1902 位、第 1886 至 1905 位、第 1889 至 1908 位、第 1894 至 1913 位、第 2015 至 2034 位、第 2086 至 2105 位、第 2097 至 2116 位、第 2099 至 2118 位、第 2129 至 2148 位、第 2151 至 2170 位、第 2206 至 2225 位、第 2239 至 2258 位、第 2253 至 2272 位、第 2287 至 2306 位、第 2301 至 2320 位、第 2317 至 2336 位、第 2337 至 2356 位、第 2354 至 2373 位、第 2387 至 2406 位、第 2598 至 2617 位、第 2613 至

2632 位、第 2633 至 2652 位、第 2649 至 2668 位、第 2672 至 2691 位、第 2699 至 2718 位、第 2702 至 2721 位、第 2705 至 2724 位、第 2708 至 2727 位、第 2711 至 2730 位、第 2714 至 2733 位、第 2717 至 2736 位、第 2720 至 2739 位、第 2723 至 2742 位、第 2726 至 2745 位、第 2729 至 2748 位、第 2738 至 2757 位、第 2775 至 2794 位、第 2790 至 2809 位、第 2826 至 2845 位、第 2829 至 2848 位、第 2832 至 2851 位、第 2835 至 2854 位、第 2838 至 2857 位、第 2841 至 2860 位、第 2847 至 2866 位、第 2959 至 2978 位、第 3032 至 3051 位、第 3052 至 3071 位、第 3136 至 3155 位、第 3168 至 3187 位、第 3188 至 3207 位、第 3232 至 3251 位、第 3251 至 3270 位、第 3298 至 3317 位、第 3325 至 3344 位、第 3408 至 3427 位、第 3590 至 3609 位、第 3608 至 3627 位、第 3617 至 3636 位、第 3635 至 3654 位、第 3654 至 3673 位、第 3671 至 3690 位、第 3691 至 3710 位、第 3709 至 3728 位、第 3739 至 3758 位、第 3750 至 3769 位、第 3877 至 3896 位、第 3949 至 3968 位、第 3964 至 3983 位、第 3984 至 4003 位、第 3999 至 4018 位、第 4011 至 4030 位、第 4170 至 4189 位、第 4173 至 4192 位、第 4176 至 4195 位、及第 4179 至 4198 位所構成之群組。

【0048】上述與包含標的序列中之至少 15 個連續鹼基之核酸互補的反義寡核苷酸之例可列舉包含下列(i)、(ii)或(iii)之鹼基序列，例如(i)之鹼基序列，或由其構成的反義寡核苷酸：

(i) 選自由序列編號 1 至 4、6、8、9、11、14 至 24、26、29、31 至 37、39 至 50、52 至 60、66 至 67、73 至 75、79 至 82、86 至 89、92 至

111、115至118、120至136、138至145、147至158、及160至163所構成之群組中的鹼基序列，

(ii) 在選自由序列編號1至4、6、8、9、11、14至24、26、29、31至37、39至50、52至60、66至67、73至75、79至82、86至89、92至111、115至118、120至136、138至145、147至158、及160至163所構成之群組中的鹼基序列中，1個或複數個鹼基經附加、缺失、或置換而成之鹼基序列，或

(iii) 相對於序列編號1至4、6、8、9、11、14至24、26、29、31至37、39至50、52至60、66至67、73至75、79至82、86至89、92至111、115至118、120至136、138至145、147至158、及160至163所構成之群組中的鹼基序列，具有90%以上之序列一致性的鹼基序列。

【0049】在一實施型態中，本發明之反義寡核苷酸係與包含標的區域中之至少15個連續鹼基的核酸互補，該標的區域係選自由序列編號471之鹼基序列之第14至33位、第34至53位、第747至766位、第1148至1167位、第1289至1308位、第1484至1564位、第1578至1623位、第1686至1705位、第1748至1767位、第1768至1787位、第1794至1813位、第1877至1905位、第2151至2170位、第2206至2225位、第2239至2272位、第2287至2336位、第2337至2373位、第2387至2406位、第2613至2632位、第2633至2668位、第2672至2691位、第2699至2748位、第2775至2809位、第2826至2860位、第3032至3051位、第3052至3071位、第3168至3187位、第3232至3270位、第3408至3427位、第3590至3690位、第3691至3728位、第3739至

3758 位、第 3877 至 3896 位、第 3949 至 3983 位、第 3984 至 4030 位、及第 4179 至 4198 位所構成之群組。

【0050】在一實施型態中，本發明之反義寡核苷酸係與包含標的區域中之至少 15 個連續鹼基的核酸互補，該標的區域係選自由序列編號 471 之鹼基序列之第 14 至 33 位、第 34 至 53 位、第 747 至 766 位、第 1148 至 1167 位、第 1289 至 1308 位、第 1484 至 1503 位、第 1488 至 1507 位、第 1491 至 1510 位、第 1493 至 1512 位、第 1506 至 1525 位、第 1517 至 1536 位、第 1531 至 1550 位、第 1545 至 1564 位、第 1578 至 1597 位、第 1586 至 1605 位、第 1589 至 1608 位、第 1592 至 1611 位、第 1595 至 1614 位、第 1598 至 1617 位、第 1601 至 1620 位、第 1604 至 1623 位、第 1686 至 1705 位、第 1748 至 1767 位、第 1768 至 1787 位、第 1794 至 1813 位、第 1877 至 1896 位、第 1880 至 1899 位、第 1883 至 1902 位、第 1886 至 1905 位、第 2151 至 2170 位、第 2206 至 2225 位、第 2239 至 2258 位、第 2253 至 2272 位、第 2287 至 2306 位、第 2301 至 2320 位、第 2317 至 2336 位、第 2337 至 2356 位、第 2354 至 2373 位、第 2387 至 2406 位、第 2613 至 2632 位、第 2633 至 2652 位、第 2649 至 2668 位、第 2672 至 2691 位、第 2699 至 2718 位、第 2702 至 2721 位、第 2705 至 2724 位、第 2708 至 2727 位、第 2711 至 2730 位、第 2714 至 2733 位、第 2717 至 2736 位、第 2720 至 2739 位、第 2723 至 2742 位、第 2726 至 2745 位、第 2729 至 2748 位、第 2775 至 2794 位、第 2790 至 2809 位、第 2826 至 2845 位、第 2829 至 2848 位、第 2832 至 2851 位、第 2835 至 2854 位、第 2838 至 2857 位、第 2841 至 2860 位、第 3032 至 3051 位、

第 3052 至 3071 位、第 3168 至 3187 位、第 3232 至 3251 位、第 3251 至 3270 位、第 3408 至 3427 位、第 3590 至 3609 位、第 3608 至 3627 位、第 3617 至 3636 位、第 3635 至 3654 位、第 3654 至 3673 位、第 3671 至 3690 位、第 3691 至 3710 位、第 3709 至 3728 位、第 3739 至 3758 位、第 3877 至 3896 位、第 3949 至 3968 位、第 3964 至 3983 位、第 3984 至 4003 位、第 3999 至 4018 位、第 4011 至 4030 位、及第 4179 至 4198 位所構成之群組。

【0051】上述與包含標的序列中之至少 15 個連續鹼基之核酸互補的反義寡核苷酸之例可列舉包含下列(i)、(ii)或(iii)之鹼基序列，例如(i)之鹼基序列，或由其構成的反義寡核苷酸：

(i) 選自由序列編號 1、6、14 至 24、31 至 35、37、39、40、42 至 45、47 至 50、52 至 59、73、92 至 100、103、107 至 110、120 至 136、138 至 143、150 至 153、155 至 158、及 163 所構成之群組中的鹼基序列，

(ii) 在選自由序列編號 1、6、14 至 24、31 至 35、37、39、40、42 至 45、47 至 50、52 至 59、73、92 至 100、103、107 至 110、120 至 136、138 至 143、150 至 153、155 至 158、及 163 所構成之群組中的鹼基序列中，1 個或複數個鹼基經附加、缺失、或置換而成之鹼基序列，或

(iii) 相對於選自由序列編號 1、6、14 至 24、31 至 35、37、39、40、42 至 45、47 至 50、52 至 59、73、92 至 100、103、107 至 110、120 至 136、138 至 143、150 至 153、155 至 158、及 163 所構成之群組中的鹼基序列，具有 90%以上之序列一致性的鹼基序列。

【0052】在一實施型態中，本發明之反義寡核苷酸，依照本案說明書之實施例記載之方法測定時，投予至 A204 細胞時的 ATN-1 基因表現量相對於投予屬於陽性對照反義寡核苷酸之 OMe-6 或 NRH-71 時之 ATN-1 基因表現量的比(平均值)，在任一個實施例中皆為選自 1.0 以下者。如此之反義寡核苷酸之例可列舉由 15 至 22 個核苷酸構成之反義寡核苷酸，其係與包含標的區域中之至少 15 個連續鹼基之核酸互補者，該標的區域係選自由序列編號 471 之鹼基序列之第 397 至 416 位、第 759 至 778 位、第 1127 至 1146 位、第 1148 至 1173 位、第 1182 至 1213 位、第 1488 至 1525 位、第 1586 至 1629 位、第 1686 至 1705 位、第 1768 至 1787 位、第 1870 至 1908 位、第 2097 至 2118 位、第 2151 至 2170 位、第 2239 至 2258 位、第 2287 至 2306 位、第 2317 至 2336 位、第 2633 至 2652 位、第 2702 至 2745 位、第 2832 至 2866 位、第 2959 至 2978 位、第 3298 至 3317 位、第 3635 至 3654 位、第 3671 至 3690 位、第 3691 至 3710 位、第 3750 至 3983 位、第 3984 至 4003 位、及第 4170 至 4198 位所構成之群組。又，可列舉由 15 至 22 個核苷酸構成之反義寡核苷酸，其係與包含標的區域中之至少 15 個連續鹼基之核酸互補者，該標的區域係選自由序列編號 471 之鹼基序列之第 397 至 416 位、第 759 至 778 位、第 1127 至 1146 位、第 1148 至 1167 位、第 1151 至 1170 位、第 1154 至 1173 位、第 1182 至 1201 位、第 1185 至 1204 位、第 1194 至 1213 位、第 1488 至 1507 位、第 1491 至 1510 位、第 1506 至 1525 位、第 1586 至 1605 位、第 1589 至 1608 位、第 1595 至 1614 位、第 1598 至 1617 位、第 1601 至 1620 位、第 1604 至 1623 位、第 1607 至 1626 位、第 1610 至 1629 位、第 1686 至 1705 位、

第 1768 至 1787 位、第 1870 至 1889 位、第 1871 至 1890 位、第 1874 至 1893 位、第 1877 至 1896 位、第 1886 至 1905 位、第 1889 至 1908 位、第 2097 至 2116 位、第 2099 至 2118 位、第 2151 至 2170 位、第 2239 至 2258 位、第 2287 至 2306 位、第 2317 至 2336 位、第 2633 至 2652 位、第 2702 至 2721 位、第 2705 至 2724 位、第 2708 至 2727 位、第 2711 至 2730 位、第 2714 至 2733 位、第 2717 至 2736 位、第 2720 至 2739 位、第 2726 至 2745 位、第 2832 至 2851 位、第 2835 至 2854 位、第 2841 至 2860 位、第 2847 至 2866 位、第 2959 至 2978 位、第 3298 至 3317 位、第 3635 至 3654 位、第 3671 至 3690 位、第 3691 至 3710 位、第 3750 至 3769 位、第 3964 至 3983 位、第 3984 至 4003 位、第 4170 至 4189 位、第 4173 至 4192 位、第 4176 至 4195 位、及第 4179 至 4198 位所構成之群組。

【0053】上述與包含標的序列中之至少 15 個連續鹼基之核酸互補的反義寡核苷酸之例可列舉包含下列(i)、(ii)或(iii)之鹼基序列，例如(i)之鹼基序列，或由其構成的反義寡核苷酸：

(i) 選自由序列編號 9、11、16、17、22、31、60、67、73、74、75、79、80、92、95 至 107、110、111、116、117、120 至 122、126、128 至 134、136、140、141、143 至 145、148、151 至 154、156、157、及 160 至 163 所構成之群組中的鹼基序列，

(ii) 在選自由序列編號 9、11、16、17、22、31、60、67、73、74、75、79、80、92、95 至 107、110、111、116、117、120 至 122、126、128 至 134、136、140、141、143 至 145、148、151 至 154、156、157、及 160

至 163 所構成之群組中的鹼基序列中，1 個或複數個鹼基經附加、缺失、或置換而成之鹼基序列，或

(iii) 相對於選自由序列編號 9、11、16、17、22、31、60、67、73、74、75、79、80、92、95 至 107、110、111、116、117、120 至 122、126、128 至 134、136、140、141、143 至 145、148、151 至 154、156、157、及 160 至 163 所構成之群組中的鹼基序列，具有 90%以上之序列一致性的鹼基序列。

【0054】在一實施型態中，本發明之反義寡核苷酸，依照本案說明書之實施例記載之方法測定時，投予至 A204 細胞時之 ATN-1 基因表現量相對於投予屬於陽性對照反義寡核苷酸之 OMe-6 或 NRH-71 時之 ATN-1 基因表現量的比(平均值)，在任一實施例中，皆為選自 0.75 以下者。如此之反義寡核苷酸之例可列舉由 15 至 22 個核苷酸構成之反義寡核苷酸，其係與包含標的區域中之至少 15 個連續鹼基之核酸互補者，該標的區域係選自由序列編號 471 之鹼基序列之第 397 至 416 位、第 1194 至 1213 位、第 1506 至 1525 位、第 1586 至 1626 位、第 1870 至 1896 位、第 2097 至 2116 位、第 2317 至 2336 位、第 2633 至 2652 位、第 2702 至 2739 位、第 2841 至 2978 位、第 3298 至 3317 位、第 3635 至 3654 位、第 3691 至 3710 位、第 3750 至 3769 位、第 3984 至 4003 位、及第 4170 至 4198 位所構成之群組。又，可列舉由 15 至 22 個核苷酸構成之反義寡核苷酸，其係與包含標的區域中之至少 15 個連續鹼基之核酸互補者，該標的區域係選自由序列編號 471 之鹼基序列之第 397 至 416 位、第 1194 至 1213 位、第 1506 至 1525 位、第 1586 至 1605 位、第 1595 至 1614 位、第 1598 至 1617 位、

第 1604 至 1623 位、第 1607 至 1626 位、第 1870 至 1889 位、第 1871 至 1890 位、第 1874 至 1893 位、第 1877 至 1896 位、第 2097 至 2116 位、第 2317 至 2336 位、第 2633 至 2652 位、第 2702 至 2721 位、第 2708 至 2727 位、第 2711 至 2730 位、第 2714 至 2733 位、第 2717 至 2736 位、第 2720 至 2739 位、第 2841 至 2860 位、第 2959 至 2978 位、第 3298 至 3317 位、第 3635 至 3654 位、第 3691 至 3710 位、第 3750 至 3769 位、第 3984 至 4003 位、第 4170 至 4189 位、第 4173 至 4192 位、第 4176 至 4195 位、及第 4179 至 4198 位所構成之群組。

【0055】上述與包含標的序列中之至少 15 個連續鹼基之核酸互補的反義寡核苷酸之例可列舉包含下列(i)、(ii)或(iii)之鹼基序列，例如(i)之鹼基序列，或由其構成的反義寡核苷酸：

(i) 選自由序列編號 11、60、92、95、97、98、100、101、104 至 107、116、122、126、128、130 至 134、143、145、148、151、153、154、157、及 160 至 163 所構成之群組中的鹼基序列，

(ii) 在選自由序列編號 11、60、92、95、97、98、100、101、104 至 107、116、122、126、128、130 至 134、143、145、148、151、153、154、157、及 160 至 163 所構成之群組中的鹼基序列中，1 個或複數個鹼基經附加、缺失、或置換而成之鹼基序列，或

(iii) 相對於選自由序列編號 11、60、92、95、97、98、100、101、104 至 107、116、122、126、128、130 至 134、143、145、148、151、153、154、157、及 160 至 163 所構成之群組中的鹼基序列，具有 90%以上之序列一致性的鹼基序列。

【0056】在一實施型態中，本發明之反義寡核苷酸，依照本案說明書之實施例記載之方法測定時，投予至 A204 細胞時的 ATN-1 基因表現量相對於投予屬於陽性對照反義寡核苷酸之 OMe-6 或 NRH-71 時之 ATN-1 基因表現量的比(平均值)，在任一實施例中，皆為選自 0.5 以下者。如此之反義寡核苷酸之例可列舉由 15 至 22 個核苷酸構成之反義寡核苷酸，其係與包含標的區域中之至少 15 個連續鹼基之核酸互補者，該標的區域係選自由序列編號 471 之鹼基序列之第 1598 至 1626 位、第 1870 至 1890 位、第 2097 至 2116 位、第 2711 至 2736 位、第 2841 至 2860 位、及第 4170 至 4198 位所構成之群組。又，可列舉由 15 至 22 個核苷酸構成之反義寡核苷酸，其係與包含標的區域中之至少 15 個連續鹼基之核酸互補者，該標的區域係選自由序列編號 471 之鹼基序列之第 1598 至 1617 位、第 1604 至 1623 位、第 1607 至 1626 位、第 1870 至 1889 位、第 1871 至 1890 位、第 2097 至 2116 位、第 2711 至 2730 位、第 2714 至 2733 位、第 2717 至 2736 位、第 2841 至 2860 位、第 4170 至 4189 位、第 4173 至 4192 位、及第 4179 至 4198 位所構成之群組。

【0057】上述與包含標的序列中之至少 15 個連續鹼基之核酸互補的反義寡核苷酸之例可列舉包含下列(i)、(ii)或(iii)之鹼基序列，例如(i)之鹼基序列，或由其構成的反義寡核苷酸：

(i) 選自由序列編號 98、100、101、104、105、116、131 至 133、143、160、161、及 163 所構成之群組中的鹼基序列，

(ii) 在選自由序列編號 98、100、101、104、105、116、131 至 133、143、160、161、及 163 所構成之群組中的鹼基序列中，1 個或複數個鹼基經附加、缺失、或置換而成之鹼基序列，或

(iii) 相對於選自由序列編號 98、100、101、104、105、116、131 至 133、143、160、161、及 163 所構成之群組中的鹼基序列，具有 90%以上之序列一致性的鹼基序列。

【0058】在一實施型態中，本發明之反義寡核苷酸係與包含標的區域中之至少 15 個連續鹼基的核酸互補，該標的區域係選自由序列編號 471 之鹼基序列之第 400 至 425 位、第 1581 至 1624 位、第 1878 至 1898 位、第 2094 至 2113 位、第 2629 至 2656 位、第 2700 至 2741 位、第 2839 至 2863 位、第 2962 至 2981 位、第 3302 至 3325 位、第 3631 至 3658 位、第 3687 至 3714 位、第 3745 至 3764 位、第 3980 至 4007 位、第 4177 至 4199 位、及第 4204 至 4223 位所構成之群組。

【0059】在一實施型態中，本發明之反義寡核苷酸係與包含標的區域中之至少 15 個連續鹼基的核酸互補，該標的區域係選自由序列編號 471 之鹼基序列之第 400 至 419 位、第 403 至 422 位、第 406 至 425 位、第 1581 至 1600 位、第 1582 至 1601 位、第 1583 至 1602 位、第 1584 至 1603 位、第 1585 至 1604 位、第 1587 至 1606 位、第 1588 至 1607 位、第 1590 至 1609 位、第 1591 至 1610 位、第 1592 至 1611 位、第 1593 至 1612 位、第 1594 至 1613 位、第 1596 至 1615 位、第 1597 至 1616 位、第 1599 至 1618 位、第 1600 至 1619 位、第 1602 至 1621 位、第 1603 至 1622 位、第 1605 至 1624 位、第 1878 至 1897 位、第 1879 至 1898 位、第 2094 至

2113 位、第 2629 至 2648 位、第 2637 至 2656 位、第 2700 至 2719 位、第 2701 至 2720 位、第 2703 至 2722 位、第 2704 至 2723 位、第 2706 至 2725 位、第 2707 至 2726 位、第 2709 至 2728 位、第 2710 至 2729 位、第 2712 至 2731 位、第 2713 至 2732 位、第 2715 至 2734 位、第 2716 至 2735 位、第 2718 至 2737 位、第 2719 至 2738 位、第 2721 至 2740 位、第 2722 至 2741 位、第 2839 至 2858 位、第 2840 至 2859 位、第 2842 至 2861 位、第 2843 至 2862 位、第 2844 至 2863 位、第 2962 至 2981 位、第 3302 至 3321 位、第 3306 至 3325 位、第 3631 至 3650 位、第 3632 至 3651 位、第 3633 至 3652 位、第 3634 至 3653 位、第 3636 至 3655 位、第 3637 至 3656 位、第 3638 至 3657 位、第 3639 至 3658 位、第 3687 至 3706 位、第 3695 至 3714 位、第 3745 至 3764 位、第 3980 至 3999 位、第 3988 至 4007 位、第 4177 至 4196 位、第 4178 至 4197 位、第 4180 至 4199 位、及第 4204 至 4223 位所構成之群組。

【0060】上述與包含標的序列中之至少 15 個連續鹼基之核酸互補的反義寡核苷酸之例可列舉包含下列(i)、(ii)或(iii)之鹼基序列，例如(i)之鹼基序列，或由其構成的反義寡核苷酸：

(i) 選自由序列編號 21、164 至 222、233、234、及 350 至 355 構成之群組的鹼基序列，

(ii) 在選自由序列編號 21、164 至 222、233、234、及 350 至 355 構成之群組的鹼基序列中，1 個或複數個鹼基經附加、缺失、或置換而成之鹼基序列，或

(iii) 相對於選自由序列編號 21、164 至 222、233、234、及 350 至 355 構成之群組的鹼基序列，具有 90%以上之序列一致性的鹼基序列。

【0061】在一實施型態中，本發明之反義寡核苷酸依照本案說明書之實施例記載之方法測定時，投予至 A204 細胞時之 ATN-1 基因表現量相對於投予屬於陽性對照反義寡核苷酸之 OMe-6 或 NRH-71 時之 ATN-1 基因表現量的比(平均值)，在任一實施例中，皆為選自 1.0 以下者。如此之反義寡核苷酸之例由 15 至 22 個核苷酸構成之反義寡核苷酸，其係與包含標的區域中之至少 15 個連續鹼基之核酸互補者，該標的區域係選自由序列編號 471 之鹼基序列之第 400 至 425 位、第 1581 至 1624 位、第 1878 至 1898 位、第 2637 至 2656 位、第 2700 至 2741 位、第 2839 至 2863 位、第 2962 至 2981 位、第 3302 至 3325 位、第 3631 至 3658 位、第 3687 至 3706 位、第 3745 至 3764 位、第 4177 至 4199 位、及第 4204 至 4223 位所構成之群組。又，可列舉由 15 至 22 個核苷酸構成之反義寡核苷酸，其係與包含標的區域中之至少 15 個連續鹼基之核酸互補者，該標的區域係選自由序列編號 471 之鹼基序列之第 400 至 419 位、第 403 至 422 位、第 406 至 425 位、第 1581 至 1600 位、第 1582 至 1601 位、第 1583 至 1602 位、第 1584 至 1603 位、第 1585 至 1604 位、第 1587 至 1606 位、第 1588 至 1607 位、第 1591 至 1610 位、第 1592 至 1611 位、第 1593 至 1612 位、第 1594 至 1613 位、第 1596 至 1615 位、第 1597 至 1616 位、第 1600 至 1619 位、第 1602 至 1621 位、第 1603 至 1622 位、第 1605 至 1624 位、第 1878 至 1897 位、第 1879 至 1898 位、第 2637 至 2656 位、第 2700 至 2719 位、第 2701 至 2720 位、第 2703 至 2722 位、第 2704 至 2723 位、第 2706 至

2725 位、第 2707 至 2726 位、第 2709 至 2728 位、第 2710 至 2729 位、第 2712 至 2731 位、第 2713 至 2732 位、第 2715 至 2734 位、第 2716 至 2735 位、第 2718 至 2737 位、第 2719 至 2738 位、第 2721 至 2740 位、第 2722 至 2741 位、第 2839 至 2858 位、第 2840 至 2859 位、第 2842 至 2861 位、第 2843 至 2862 位、第 2844 至 2863 位、第 2962 至 2981 位、第 3302 至 3321 位、第 3306 至 3325 位、第 3631 至 3650 位、第 3632 至 3651 位、第 3633 至 3652 位、第 3634 至 3653 位、第 3636 至 3655 位、第 3637 至 3656 位、第 3638 至 3657 位、第 3639 至 3658 位、第 3687 至 3706 位、第 3745 至 3764 位、第 4177 至 4196 位、第 4178 至 4197 位、第 4180 至 4199 位、及第 4204 至 4223 位所構成之群組。

【0062】上述與包含標的序列中之至少 15 個連續鹼基之核酸互補的反義寡核苷酸之例可列舉包含下列(i)、(ii)或(iii)之鹼基序列，例如(i)之鹼基序列，或由其構成的反義寡核苷酸：

(i) 選自由序列編號 21、164 至 171、173 至 177、179 至 184、187 至 214、216、219 至 222、233 至 234、及 350 至 355 構成之群組的鹼基序列，

(ii) 在選自由序列編號 21、164 至 171、173 至 177、179 至 184、187 至 214、216、219 至 222、233 至 234、及 350 至 355 構成之群組的鹼基序列中，1 個或複數個鹼基經附加、缺失、或置換而成之鹼基序列，或

(iii) 相對於選自由序列編號 21、164 至 171、173 至 177、179 至 184、187 至 214、216、219 至 222、233 至 234、及 350 至 355 構成之群組的鹼基序列，具有 90%以上之序列一致性的鹼基序列。

【0063】在一實施型態中，本發明之反義寡核苷酸依照本案說明書之實施例記載之方法測定時，投予至 A204 細胞時之 ATN-1 基因表現量相對於投予屬於陽性對照反義寡核苷酸之 OMe-6 或 NRH-71 時之 ATN-1 基因表現量的比(平均值)，在任一實施例中，皆為選自 0.75 以下者。如此之反義寡核苷酸之例可列舉由 15 至 22 個核苷酸構成之反義寡核苷酸，其係與包含標的區域中之至少 15 個連續鹼基之核酸互補者，該標的區域係選自由序列編號 471 之鹼基序列之第 1581 至 1624 位、第 2703 至 2740 位、第 3633 至 3655 位、及第 4177 至 4199 位所構成之群組。又，可列舉由 15 至 22 個核苷酸構成之反義寡核苷酸，其係與包含標的區域中之至少 15 個連續鹼基之核酸互補者，該標的區域係選自由序列編號 471 之鹼基序列之第 1581 至 1600 位、第 1582 至 1601 位、第 1584 至 1603 位、第 1585 至 1604 位、第 1587 至 1606 位、第 1588 至 1607 位、第 1594 至 1613 位、第 1596 至 1615 位、第 1597 至 1616 位、第 1602 至 1621 位、第 1603 至 1622 位、第 1605 至 1624 位、第 2703 至 2722 位、第 2707 至 2726 位、第 2709 至 2728 位、第 2710 至 2729 位、第 2712 至 2731 位、第 2713 至 2732 位、第 2715 至 2734 位、第 2716 至 2735 位、第 2718 至 2737 位、第 2719 至 2738 位、第 2721 至 2740 位、第 3633 至 3652 位、第 3634 至 3653 位、第 3636 至 3655 位、第 4177 至 4196 位、第 4178 至 4197 位、及第 4180 至 4199 位所構成之群組。

【0064】上述與包含標的序列中之至少 15 個連續鹼基之核酸互補的反義寡核苷酸之例可列舉包含下列(i)、(ii)或(iii)之鹼基序列，例如(i)之鹼基序列，或由其構成的反義寡核苷酸：

(i) 選自由序列編號 167 至 171、175 至 177、180 至 182、190、193 至 202、219 至 221、233、及 351 至 353 構成之群組的鹼基序列，

(ii) 在選自由序列編號 167 至 171、175 至 177、180 至 182、190、193 至 202、219 至 221、233、及 351 至 353 構成之群組的鹼基序列中，1 個或複數個鹼基經附加、缺失、或置換而成之鹼基序列，或

(iii) 相對於選自由序列編號 167 至 171、175 至 177、180 至 182、190、193 至 202、219 至 221、233、及 351 至 353 所構成之群組中的鹼基序列，具有 90%以上之序列一致性的鹼基序列。

【0065】在一實施型態中，本發明之反義寡核苷酸依照本案說明書之實施例記載之方法測定時，投予至 A204 細胞時之 ATN-1 基因表現量相對於投予屬於陽性對照反義寡核苷酸之 OMe-6 或 NRH-71 時之 ATN-1 基因表現量的比(平均值)，在任一實施例中，皆為選自 0.5 以下者。如此之反義寡核苷酸之例可列舉由 15 至 22 個核苷酸構成之反義寡核苷酸，其係與包含標的區域中之至少 15 個連續鹼基之核酸互補者，該標的區域係選自由序列編號 471 之鹼基序列之第 1587 至 1616 位、第 2712 至 2735 位、及第 4180 至 4199 位所構成之群組。又，可列舉由 15 至 22 個核苷酸構成之反義寡核苷酸，其係與包含標的區域中之至少 15 個連續鹼基之核酸互補者，該標的區域係選自由序列編號 471 之鹼基序列之第 1587 至 1606 位、第 1597 至 1616 位、第 2712 至 2731 位、第 2716 至 2735 位、及第 4180 至 4199 位所構成之群組。

【0066】上述與包含標的序列中之至少 15 個連續鹼基之核酸互補的反義寡核苷酸之例可列舉包含下列(i)、(ii)或(iii)之鹼基序列，例如(i)之鹼基序列，或由其構成的反義寡核苷酸：

(i) 選自由序列編號 170、177、196、199、及 221 構成之群組的鹼基序列，

(ii) 在選自由序列編號 170、177、196、199、及 221 構成之群組的鹼基序列中，1 個或複數個鹼基經附加、缺失、或置換而成之鹼基序列，或

(iii) 相對於選自由序列編號 170、177、196、199、及 221 構成之群組的鹼基序列，具有 90%以上之序列一致性的鹼基序列。

【0067】在一實施型態中，本發明係關於由 15 至 22 個核苷酸構成之反義寡核苷酸或其醫藥上可容許之鹽或彼等的水合物，其係與包含標的區域中之至少 15 個連續鹼基之核酸互補者，該標的區域係選自由序列編號 471 之鹼基序列之第 468 至 487 位、第 474 至 493 位、第 583 至 602 位、第 586 至 605 位、第 619 至 638 位、第 770 至 789 位、第 774 至 793 位、第 775 至 794 位、第 778 至 797 位、第 804 至 823 位、第 851 至 870 位、第 1160 至 1179 位、第 1162 至 1181 位、第 1170 至 1189 位、第 1173 至 1192 位、第 1205 至 1224 位、第 1210 至 1229 位、第 1216 至 1235 位、第 1217 至 1236 位、第 1219 至 1238 位、第 1385 至 1404 位、第 1441 至 1460 位、第 1818 至 1837 位、第 1902 至 1921 位、第 1905 至 1924 位、第 1908 至 1927 位、第 1914 至 1933 位、第 1931 至 1950 位、第 2117 至 2136 位、第 2749 至 2768 位、第 3100 至 3119 位、及第 4125 至 4144 位所構成之群組。

【0068】上述與包含標的序列中之至少 15 個連續鹼基之核酸互補的反義寡核苷酸之例可列舉包含下列(i)、(ii)或(iii)之鹼基序列，例如(i)之鹼基序列，或由其構成的反義寡核苷酸：

(i) 選自由序列編號 7、10、12、13、25、27、28、30、61 至 65、68 至 72、76 至 78、83 至 85、90、91、112 至 114、137、146、及 159 所構成之群組中的鹼基序列，

(ii) 在選自由序列編號 7、10、12、13、25、27、28、30、61 至 65、68 至 72、76 至 78、83 至 85、90、91、112 至 114、137、146、及 159 所構成之群組中的鹼基序列中，1 個或複數個鹼基經附加、缺失、或置換而成之鹼基序列，或

(iii) 相對於選自由序列編號 7、10、12、13、25、27、28、30、61 至 65、68 至 72、76 至 78、83 至 85、90、91、112 至 114、137、146、及 159 所構成之群組中的鹼基序列，具有 90%以上之序列一致性的鹼基序列。

【0069】在一實施型態中，本發明之反義寡核苷酸抑制標的區域之功能。在本說明書中，所謂「抑制標的區域之功能」意指包含下列一個以上：與標的區域結合後，與反義寡核苷酸形成雙股之包含標的區域的基因體 RNA 藉由 RNaseH 切斷；抑制包含標的區域之基因體 RNA 的複製；在標的區域被轉譯時抑制其轉譯；及抑制包含標的區域之基因體 RNA 的轉錄。在本說明書中，所謂「次基因體 RNA (subgenomic RNA)」意指以(+)鏈之基因體 RNA 作為模板藉由 RNA-依存性 RNA 聚合物酶(RNA-dependent RNA polymerase)合成出(-)鏈 RNA，以(-)鏈 RNA 之一部分作為模板藉由 RNA-依存性 RNA 聚合物酶(RNA-dependent RNA polymerase)合成的較

基因體 RNA 短的 RNA，並且作為用以合成病毒蛋白質(轉譯)之 mRNA 的 RNA。

【0070】本發明之反義寡核苷酸，係可使用各種自動合成裝置(例如，AKTA oligopilot plus 10 / 100(GE Healthcare))容易地合成，或是，亦可委託為第三方機關(例如，Promega 公司或 Takara 公司)等製作。

【0071】在一實施型態中，本發明係關於包含反義寡核苷酸或其醫藥上可容許之鹽或此等的水合物之醫藥組成物。在向對象投予本發明之反義核苷酸投予時，本發明之醫藥組成物亦可包含促進反義核苷酸送達的載體。如此之載體只要為醫藥上可容許者，則無特別限制，其例可列舉陽離子性脂質體、陽離子性聚合物等陽離子性載體；或利用病毒套膜(envelope)的載體。陽離子性脂質體可列舉例如：以 2-O-(2-二乙基胺基乙基)胺甲醯基-1,3-O-二酸甘油酯及磷脂質作為必須構成成分而形成的脂質體(以下，稱為「脂質體 A」)、Oligofectamine(註冊商標) (Invitrogen 公司製)、Lipofectin (註冊商標)(Invitrogen 公司製)、Lipofectamine (註冊商標)(Invitrogen 公司製)、Lipofectamine 2000(註冊商標)(Invitrogen 公司製)、DMRIE-C(註冊商標)(Invitrogen 公司製)、GeneSilencer(註冊商標)(Gene Therapy Systems 公司製)、TransMessenger (註冊商標)(QIAGEN 公司製)、TransIT TKO(註冊商標)(Mirus 公司製)、Nucleofector II (Lonza)。陽離子性聚合物可列舉例如：JetSI(註冊商標)(Qbiogene 公司製)、Jet-PEI(註冊商標)(聚伸乙基亞胺，Qbiogene 公司製)。利用病毒套膜之載體可列舉例如：GenomeOne(註冊商標)(HVJ-E 脂質體，石原產業公司製)。或者是，亦可使用日本特許

2924179 號記載之醫藥裝置、日本再公表專利公報第 2006/129594 號及日本再公表專利公報第 2008/096690 號記載之陽離子性載體。

【0072】在一實施型態中，本發明之反義寡核苷酸係為了促進反義寡核苷酸之送達，於醫藥組成物中可作成與脂質等之複合體(共軛(conjugate))。例如，如 Bijsterbosch, M.K. et al. (2000) Nucleic Acid Res., 28, 2717-2725 記載，可形成與膽固醇之共軛。

【0073】本發明之醫藥組成物，除了反義寡核苷酸或其醫藥上可容許之鹽或此等的水合物及任何上述載體之外，亦可包含醫藥上可容許的添加劑。該添加劑可列舉例如：乳化輔助劑(例如，碳數 6 至 22 之脂肪酸或其醫藥上可容許之鹽、白蛋白、葡萄聚糖)、安定化劑(例如，膽固醇、磷脂酸、甘露醇、山梨糖醇)、等張化劑(例如，氯化鈉、葡萄糖、麥芽糖、乳糖、蔗糖、海藻糖)、pH 調整劑(例如，鹽酸、硫酸、磷酸、乙酸、氫氧化鈉、氫氧化鉀、三乙醇胺)。可將此等使用一種或二種以上。本發明之組成物中之該添加劑的含量適當為 90 重量%以下，較佳為 70 重量%以下，更佳為 50 重量%以下。

【0074】本發明之醫藥組成物的調製法無限定，例如可藉由在載體之分散液中添加本發明之反義寡核苷酸，並進行適當攪拌而調製。又，添加劑可在本發明之反義寡核苷酸的添加前，亦可於添加後，以適當步驟添加。添加本發明之反義寡核苷酸時可使用的水性溶劑只要為醫藥上可容許者，則無特別限制，可列舉例如：注射用水、注射用蒸餾水、生理食鹽水等電解質液；葡萄糖液、麥芽糖液等糖液。又，所屬技術領域具有通常知識者可適當地選擇該情況之 pH 及溫度等條件。

【0075】本發明之醫藥組成物可作成例如液劑或其凍結乾燥製劑。該凍結乾燥製劑可依照常法，藉由將具有液劑之型態的本發明之組成物進行凍結乾燥處理而調製。例如，將具有液劑之型態的本發明之組成物進行適當滅菌後，將預定量分注於微量(vial)瓶中，以約-40℃至-20℃之範圍內的條件進行約 2 小時之預備凍結，再於約 0℃至 10℃之範圍內，減壓下進行一次乾燥，接著，於約 15℃至 25℃之範圍內，減壓下進行二次乾燥，而可實施凍結乾燥。接著，通常將小瓶內部以氮氣置換，密栓，而可得到本發明之組成物的凍結乾燥製劑。

【0076】本發明之醫藥組成物的凍結乾燥製劑通常可藉由添加任意之適當溶液(再溶解液)，再溶解後使用。如此之再溶解液可列舉：注射用水、生理食鹽水、其他一般輸液。該再溶解液之液量依用途等而異，無特別限制，較佳為凍結乾燥前之液量的 0.5 倍量至 2 倍量或 500mL 以下。

【0077】投予本發明之醫藥組成物時的用量，係期望考慮所含有之本發明之反義寡核苷酸的種類、劑型、年齡或體重等患者狀態、投予途徑、疾病之性質及程度下加以調節，然而對於成人，本發明的反義寡核苷酸之 1 次投予量為：每 1kg 體重投予 0.01mg 至 20mg，較佳為每 1kg 體重投予 0.03mg 至 10mg，更佳為每 1kg 體重投予 0.05mg 至 4mg，進一步更佳為每 1kg 體重投予 0.1mg 至 2mg。投予頻率可為每 1 至 3 日 1 次、每 1 週 1 次、或每 2 至 3 週 1 次。此數值係有依據作為標的疾病的種類、投予型態、標的分子而異之情況。因此，根據情況有投予此以下之用量或投予頻率即充分之情況，相反地，也有需要此以上之用量或投予頻率。

【0078】本發明之醫藥組成物之投予型態只要為醫藥上可容許投予型態，則無特別限制，可因應治療方法而選擇，可列舉例如：靜脈內投予、動脈內投予、肌內投予、皮下投予、經口投予、組織內投予、經皮投予、經肺投予、經鼻投予、對中樞神經之投予等。對中樞神經投予之例可列舉：髓鞘內投予、顱內投予(例如腦室內投予或側腦室投予)、腦實質內投予、及柔腦膜(軟腦膜)(Leptomeninx)下投予。又，本發明之組成物可採取的劑型無特別限制，可列舉例如：各種注射劑、口服劑、點滴劑、吸入劑、軟膏劑、洗滌劑、糊劑等。

【0079】本發明之反義寡核苷酸或醫藥組成物的投予對象可列舉例如哺乳動物，例如人類等靈長類；大鼠、小鼠、及褐鼠等實驗動物；豬、牛、馬、及綿羊等家畜動物等，較佳為人類。

【0080】在一實施型態中，本發明係關於一種齒狀紅核蒼白球路易氏體萎縮症(DRPLA)之治療及/或預防方法，其係包含向對象投予本發明之反義寡核苷酸或其醫藥上可容許之鹽或此等的水合物、或醫藥組成物的步驟。本實施型態中之醫藥組成物、及醫藥組成物的投予量及投予途徑等係如本說明書記載。

【0081】在本說明書中，所謂齒狀紅核蒼白球路易氏體萎縮症(DRPLA)之治療，意指包含齒狀紅核蒼白球路易氏體萎縮症或其症狀(例如，小兒方面為運動失調、肌躍症、癲癇、及進行性之智力退化，成人方面為運動失調、舞蹈指痙病(choreoathetosis)、失智症、或性格之變化的一種以上)之緩和、改善、及緩解之一種以上。在本說明書中，所謂 DRPLA 之預防係包含 DRPLA 或其症狀發生的風險之減低。

[實施例]

【0082】以下，列舉實施例及試驗例，進一步詳細地說明本發明，然而本發明並非限定於實施例所示的範圍者。

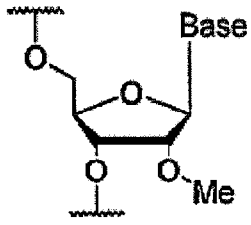
【0083】「間隔子(gapmer)」係具有被 2 個鄰接之非去氧寡核苷酸片段挾持的 2'-去氧寡核苷酸之中央區域的寡聚物化合物，一般定義為寡核苷酸。中央區域稱為「間隔(gap)」，鄰接之片段稱為「翼部(wing)」。本實施例中所用的間隔子，具有被 2 個鄰接之 5 個核苷酸之翼部挾持的 10 個核苷酸之間隔(gap)。將此稱為 5-10-5 間隔子。

【0084】＜實施例 1：間隔子(寡核苷酸)之合成＞

本實施例中所用之間隔子(寡核苷酸)係可依據一般 W. Brad Wan 氏等，Nucleic Acid Research, Vol. 42, No.22 13456(2014)等記載的方法製造。

【0085】在本實施例所用之間隔子中，在翼部之核苷具有式(a)所示之 2'-甲氧基(2'-OMe)基的具體寡核苷酸之一部分，係參照如上述之 W. Brad Wan 氏等，Nucleic Acid Research, Vol. 42, No. 22 13456(2014)記載的方法合成。又，其餘係委託 Gene Design 股份有限公司合成而入手。

【0086】

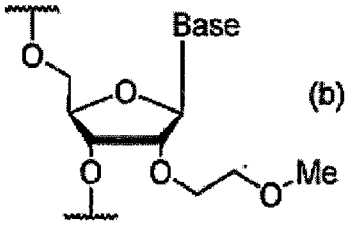


(a)

(式中，Base 為胞嘧啶(C)、脲嘧啶(U)、腺嘌呤(A)、或鳥糞嘌呤(G)，Me 為甲基)

本實施例中所用的間隔子之中，翼部之核苷具有式(b)所示之 2'-甲氧基乙基(2'-O-MOE)基的具體寡核苷酸，係參照如上述之 W. Brad Wan 氏等，Nucleic Acid Research, Vol.42, No. 22 13456 (2014)記載的方法合成。

【0087】



(式中，Base 為 5-甲基胞嘧啶(C)、胸腺嘧啶(T)、腺嘌呤(A)、或鳥糞嘌呤(G)，Me 為甲基)

【0088】翼部之核苷中具有式(a)所示之 2'-OMe 基或式(b)所示之 2'-O-MOE 基的 20mer 之受驗對象的間隔子(寡核苷酸)，係使用核酸自動合成機 NTS M-8-MX DNA/RNA(日本 Techno Service 股份有限公司)，以 1μmol 規模合成出。鏈長之伸長係依照標準的亞磷醯胺操作指南(phosphoramidite protocol)(固相載體：Glen UnySupport，硫化係使用 DDTT([(N,N-二甲基胺基亞甲基)胺基]-3H-1,2,4-二噻唑-3-硫酮)等，氧化係使用 0.02M 之碘/四氫呋喃：吡啶：水=7：1：2 等)實施，得到末端之 5'位的羥基經二甲氧基三苯甲基(DMTr)保護，且 3'位承載於固相的寡核苷酸。接著，藉由從富士 Film 和光股份有限公司入手之去封阻溶液-1(deblocking solution 1)處理，除去 DMTr 基後，藉由氨處理，將目標物從固相載體切出。餾除溶劑，將所得到之粗生成物藉由逆相 HPLC 精製，而得到目標物。

【0089】＜實施例 2：受驗對象之間隔子(寡核苷酸)的設計＞

受驗對象之間隔子(寡核苷酸)，係被設計成以人類 atrophin-1(ATN1)(Gen Bank：NM_001007026，序列編號 471)作為標的之反義寡核苷酸(ASO)。將以 DNA 之鹼基表記之寡核苷酸的序列示於表 1、表 2、表 3、表 4。

【0090】表 1 及表 2 中，寡核苷酸全部為 5-10-5 之間隔子，核苷間之鍵結全部為硫代磷酸酯鍵(phosphorothioate)(P=S)。又，關於表 1 之具有 2'-OMe 基的間隔子，翼部部分之 T(胸腺嘧啶)，實際上為 U(脲嘧啶)。又，關於表 2 之具有 2'-O-MOE 基的間隔子，間隔(gap)部分及翼部部分之 C(胞嘧啶)，實際上為甲基 C，翼部部分之 T 實際上為 T。

【0091】[表 1]

表 1　翼部之核苷具有 2'-OMe 基之受驗對象的間隔子(寡核苷酸)

ASO之鹼基序列(DNA表記) 5'至3'	ASO編號	序列編號471之開始部位	序列編號471之終止部位	標的外顯子	ASO名稱	序列編號
TCCTCCCACTTGGCGTCCAG	1	14	33	1	OMe-24	1
AGAAGCAGAGCGGGAGGCCC	2	54	73	1	OMe-25	2
TTCCCCACAGCTGTGGTCTG	3	148	167	2	OMe-97	3
GTGGAGGCTTCCTCTACTCG	4	413	432	4	OMe-112	4
AGGAGGAAAGAGTGGAGGTG	5	723	742	5	OMe-37	5
GGTGCTGTCTGGCGGTTGAG	6	747	766	5	OMe-98	6
TTCAAAGCTAGCCTCTGGCT	7	774	793	5	OMe-38	7
TTAGGGCCCCCCACTGATGA	8	965	984	5	OMe-129	8
GGCAGGTTCGGTGTCACATG	9	1127	1146	5	OMe-43	9
AGAGGCTGATGCATTGTTGA	10	1170	1189	5	OMe-44	10
TGGTTGGGCCCCCAGGCCAG	11	1194	1213	5	OMe-105	11
GCAGATGACCAGGTAGTGGT	12	1210	1229	5	OMe-45	12
GGAGAGGGCAGATGACCAGG	13	1217	1236	5	OMe-106	13
GGTGAAGGAGCCAGAGTTGG	14	1289	1308	5	OMe-47	14
GAGACAGAGAGGCTTGTTGG	15	1484	1503	5	OMe-23	15
ATTGGAGACAGAGAGGCTTG	16	1488	1507	5	OMe-22	16
CTGATTGGAGACAGAGAGGC	17	1491	1510	5	OMe-14	17
GGCTGATTGGAGACAGAGAG	18	1493	1512	5	OMe-21	18
AGAGAAGGCTGAGTATACTT	19	1517	1536	5	OMe-5	19
ACCCTGGCTCCACACAGCCT	20	1545	1564	5	OMe-15	20
GCATTGCTGTTGGCTAAGAG	21	1592	1611	5	OMe-50	21
CTGTTGCTGTTGCTGGTGGT	22	1686	1705	5	OMe-131	22
GGCCCAGAGTTTCCGTGATG	23	1748	1767	5	OMe-52	23
GGAGCTACCGCCCTCCAGTG	24	1794	1813	5	OMe-53	24
CATGGCGTAAGGGTGTGCGT	25	1818	1837	5	OMe-107	25
AGGACACCTGGCTGTGAGGT	26	1894	1913	5	OMe-110	26
GCCTGCTTGGCTGTAGGACA	27	1908	1927	5	OMe-55	27
GAAGAGACTGGAGGGCCATT	28	1931	1950	5	OMe-111	28
CCACGGTGGCAATGACCGTG	29	2086	2105	5	OMe-116	29
GAGGCCGTTTTGTAGCCTGC	30	2117	2136	5	OMe-117	30
GGCTCTCTTTCCGTACGGTG	31	2151	2170	5	OMe-60	31
GCGACCCGGGTTTGTATCCG	32	2206	2225	5	OMe-118	32
CGAGGTTCCTCGATAGCCCG	33	2253	2272	5	OMe-62	33
TCCCACGGTGGGCGAGCCCG	34	2301	2320	5	OMe-63	34
GGTGGTGGCAGCGATGGCAG	35	2354	2373	5	OMe-64	35
CAGCTTGGAGCCCTCCAGTG	36	2598	2617	6	OMe-68	36
CTGCTCGGCCTCGCGCCGCA	37	2649	2668	6	OMe-69	37
TCTTCGCGCGCGCGCTGCTC	38	2663	2682	6	OMe-96	38
TCTTTCTCGCGTTCCCGCTC	39	2699	2718	6	OMe-70	39
TCAAGCTCGCGCTCCTTCTC	40	2729	2748	6	OMe-132	40
ACGCTGCGTTCAAGCTCGCG	41	2738	2757	6	OMe-71	41
GCATTCCACCGGAGCACGGC	42	2775	2794	7	OMe-133	42
CGCACTGCCCGGTTCAAATG	43	2826	2845	7	OMe-73	43
GCTTCCCGTTCCCTCTCCCG	44	3032	3051	7	OMe-77	44
CACGGAGGTCTCGTTCACGG	45	3052	3071	7	OMe-135	45
GAAAGGGATCCAAGCCCGGC	46	3136	3155	7	OMe-79	46
GCCAGGCTGCAGAGCCAGGC	47	3168	3187	7	OMe-80	47
CTAGACGTTCTCGCTCCAGG	48	3232	3251	7	OMe-136	48
GCTGGCCCAGCTGCCAGCGC	49	3251	3270	7	OMe-82	49
GTGCAGGTGCGAGTGGATGT	50	3408	3427	7	OMe-83	50
AGAACTTCGTTCTCGTGCAG	51	3563	3582	8	OMe-86	51
GAGGCCGGCAGGTCCCGGTA	52	3608	3627	9	OMe-87	52
GCAGAAAGGGAGGCCGGCAG	53	3617	3636	9	OMe-123	53
GTGCATGGCCTGCAGCTGAT	54	3654	3673	9	OMe-88	54
CATGCAGCCACTGCTGCTGT	55	3709	3728	9	OMe-89	55
GCAGCGGCACACTGTGCAGC	56	3739	3758	9	OMe-90	56
CCCTCCCTCCCCCACTCTCT	57	3949	3968	10	OMe-9	57
GCCACCTCCCCACCTCTGCA	58	3999	4018	10	OMe-10	58

[表 2-1]

表 2 在翼部之核苷具有 2'-O-MOE 基之受驗對象的間隔子(寡核苷酸)

ASO之鹼基序列(DNA表記) 5'至3'	ASO編號	序列編號471之開始部位	序列編號471之終止部位	標的外顯子	ASO名稱	序列編號
GCAGGGGACAGCCTTGAAGT	59	34	53	1	DRA-3	59
CTCGGGCCTTCTTGGCTGTC	60	397	416	3	DRA-29	60
CTCACTTTCACTCTCTGAGA	61	468	487	4	DRA-9	61
GGTCTCCTCACTTTCACTCT	62	474	493	4	DRA-96	62
GGTCGCTGCTGCCATCATCA	63	583	602	5	DRA-105	63
TAGGGTCGCTGCTGCCATCA	64	586	605	5	DRA-13	64
GGGACGTGCTTCGGTTGTCC	65	619	638	5	DRA-14	65
CTGTCGAGGGGTGCTGTCTG	66	756	775	5	DRA-108	66
TGGCTGTCGAGGGGTGCTGT	67	759	778	5	DRA-109	67
AAGCTAGCCTCTGGCTGTCG	68	770	789	5	DRA-112	68
GTTCAAAGCTAGCCTCTGGC	69	775	794	5	NRH-156	69
GGGGTTCAAAGCTAGCCTCT	70	778	797	5	DRA-113	70
ATATCCAGTGGGTGTCACAG	71	804	823	5	DRA-16	71
GGAGGAGCCTGGAACATTCG	72	851	870	5	DRA-17	72
GGTCTCAGGGCAGGTGGGGG	73	1148	1167	5	DRA-128	73
AGGGGTCTCAGGGCAGGTGG	74	1151	1170	5	DRA-129	74
TTGAGGGGTCTCAGGGCAGG	75	1154	1173	5	DRA-130	75
GCATTGTTGAGGGGTCTCAG	76	1160	1179	5	NRH-177	76
ATGCATTGTTGAGGGGTCTC	77	1162	1181	5	NRH-171	77
AGAGGCTGATGCATTGTTGA	78	1170	1189	5	NRH-178	10
GGGAGAGGCTGATGCATTGT	79	1173	1192	5	NRH-174	78
CAGGCCAGGGGGAGAGGCTG	80	1182	1201	5	NRH-175	79
CCCCAGGCCAGGGGGAGAGG	81	1185	1204	5	NRH-176	80
GGCCCCCAGGCCAGGGGGAG	82	1188	1207	5	NRH-181	81
TTGGGCCCCCAGGCCAGGGG	83	1191	1210	5	NRH-182	82
TGGTTGGGCCCCCAGGCCAG	84	1194	1213	5	NRH-179	11
TGACCAGGTAGTGGTTGGGC	85	1205	1224	5	NRH-168	83
GCAGATGACCAGGTAGTGGT	86	1210	1229	5	NRH-180	12
GAGAGGGCAGATGACCAGGT	88	1216	1235	5	NRH-162	84
GGAGAGGGCAGATGACCAGG	89	1217	1236	5	NRH-150	13
GGGGAGAGGGCAGATGACCA	90	1219	1238	5	NRH-158	85
CCATGGCGTGGGGAGAGGGC	91	1228	1247	5	DRA-133	86
GTCCCATGGCGTGGGGAGAG	92	1231	1250	5	DRA-134	87
CCCTGTCCCATGGCGTGGGG	93	1235	1254	5	DRA-21	88
GGCCCTTCTCTGGGCCAGGA	94	1270	1289	5	DRA-31	89
GAAGAGGAGGCTGCTGCAGA	95	1385	1404	5	DRA-24	90
TGGGCAATGCCTGGGAAGCT	96	1441	1460	5	DRA-25	91
AGTATACTTGGGGGGCTGAT	97	1506	1525	5	DRA-26	92
CAGCCTGGGATGGGAGAGAA	98	1531	1550	5	DRA-32	93
TAAGAGGCGGCCATAGGGAG	99	1578	1597	5	DRA-33	94
CTGTTGGCTAAGAGGCGGCC	100	1586	1605	5	DRA-115	95
TTGCTGTTGGCTAAGAGGCG	101	1589	1608	5	DRA-116	96
TGGGCATTGCTGTTGGCTAA	102	1595	1614	5	DRA-117	97
GGATGGGCATTGCTGTTGGC	103	1598	1617	5	DRA-118	98
CCTGGATGGGCATTGCTGTT	104	1601	1620	5	DRA-119	99
GGGCCTGGATGGGCATTGCT	105	1604	1623	5	DRA-34	100
AAGGGGCCTGGATGGGCATT	106	1607	1626	5	DRA-120	101
GGGAAGGGGCCTGGATGGGC	107	1610	1629	5	DRA-121	102
GAAATGCTCCAGGAGGAGGG	108	1768	1787	5	DRA-36	103
GCAGGTGTGCTGGCCCTGGT	109	1870	1889	5	NRH-154	104
GGCAGGTGTGCTGGCCCTGG	110	1871	1890	5	NRH-160	105
GGGGGCAGGTGTGCTGGCCC	111	1874	1893	5	DRA-140	106
GGTGGGGGCAGGTGTGCTGG	112	1877	1896	5	DRA-141	107
TGAGGTGGGGGCAGGTGTGC	113	1880	1899	5	DRA-142	108
CTGTGAGGTGGGGGCAGGTG	114	1883	1902	5	DRA-143	109
TGGCTGTGAGGTGGGGGCAG	115	1886	1905	5	DRA-144	110
ACCTGGCTGTGAGGTGGGGG	116	1889	1908	5	DRA-145	111

[表 2-2]

ASO之鹼基序列(DNA表記) 5'至3'	ASO編號	序列編號471之開始部位	序列編號471之終止部位	標的外顯子	ASO名稱	序列編號
TTGGCTGTAGGACACCTGGC	117	1902	1921	5	DRA-148	112
TGCTTGGCTGTAGGACACCT	118	1905	1924	5	DRA-149	113
ATTGGGGCCTGCTTGGCTGT	119	1914	1933	5	DRA-152	114
GGCGCCCCTTGAGGGCCCTG	120	2015	2034	5	DRA-42	115
TGGCGAGGAAGCCACGGTGG	121	2097	2116	5	DRA-43	116
GCTGGCGAGGAAGCCACGGT	122	2099	2118	5	DRA-185	117
GAGGCCGTTTTGTAGCCTGC	124	2117	2136	5	DRA-191	30
GGCCCAGGTGGGGAGGCCGT	125	2129	2148	5	DRA-195	118
GCCCCCGGGGACGGGGCTCT	126	2165	2184	5	DRA-44	119
AGCCCGGTGGGGTCCCCGTT	127	2239	2258	5	DRA-46	120
AGCCCGGCTTGAAGGTCCCT	128	2287	2306	5	DRA-47	121
GTGGCAGGGGCCCAGGTCCC	129	2317	2336	5	DRA-48	122
CAGGCCTGAGGGCCCCGCAG	130	2337	2356	5	DRA-49	123
CTCAGGGGCGGCCCTGAGGC	131	2387	2406	5	DRA-53	124
GGCCCGCTTCTTGGCCAGCT	132	2613	2632	6	DRA-56	125
CGCACCTTCTCCACCAGGTC	133	2633	2652	6	DRA-57	126
CGCTCCTTTTCTTCGCGCGC	134	2672	2691	6	DRA-58	127
CGCTCTTTCTCGCGTTCCCG	135	2702	2721	6	DRA-156	128
TCGCGCTCTTTCTCGCGTTC	136	2705	2724	6	DRA-157	129
CGCTCGCGCTCTTTCTCGCG	137	2708	2727	6	DRA-158	130
TCGCGCTCGCGCTCTTTCTC	138	2711	2730	6	DRA-159	131
TTCTCGCGCTCGCGCTCTTT	139	2714	2733	6	DRA-59	132
TCCTTCTCGCGCTCGCGCTC	140	2717	2736	6	DRA-160	133
CGCTCCTTCTCGCGCTCGCG	141	2720	2739	6	DRA-161	134
TCGCGCTCCTTCTCGCGCTC	142	2723	2742	6	DRA-162	135
AGCTCGCGCTCCTTCTCGCG	143	2726	2745	6	DRA-163	136
GAGCCAACTTCACGCTGCGT	144	2749	2768	6	DRA-60	137
TGGGCCCAGAGATGGGCATT	145	2790	2809	7	DRA-61	138
CACCGCACTGCCCGGTTCAA	146	2829	2848	7	DRA-122	139
AGCCACCGCACTGCCCGGTT	147	2832	2851	7	DRA-123	140
TGTAGCCACCGCACTGCCCG	148	2835	2854	7	DRA-124	141
CACTGTAGCCACCGCACTGC	149	2838	2857	7	DRA-125	142
GGGCACTGTAGCCACCGCAC	150	2841	2860	7	DRA-62	143
GTAGGGGGGCACTGTAGCCA	151	2847	2866	7	DRA-126	144
GGTCCACTGCCCCCAGGGGC	152	2959	2978	7	DRA-64	145
GGGGTTCCAGCTCACTAGGC	153	3100	3119	7	DRA-66	146
AAAGGGTGCAGGCCAGGTGG	154	3188	3207	7	DRA-68	147
GCCTCTCAGCTGCCAGCCGC	155	3298	3317	7	DRA-69	148
CCAGGGCCGCCACCCTTTCT	156	3325	3344	7	DRA-70	149
TAAGGGGCAGCAAAGAGCTG	157	3590	3609	8	DRA-74	150
TGAGCTGCTGACATCGGGGC	158	3635	3654	9	DRA-75	151
AGCTCAGCTGACTGTGCGTG	159	3671	3690	9	DRA-76	152
GTTCCAGCGCCAAGCGCTGC	160	3691	3710	9	DRA-77	153
CTCCTGGGCAGGCAGCGGCA	161	3750	3769	9	DRA-78	154
CAGGCCAAGGGCACGGTGGG	162	3877	3896	10	DRA-81	155
TGGCCTTCTGTCTGTCCCTC	163	3964	3983	10	DRA-84	156
CTGCACACCACATCGGGCCT	164	3984	4003	10	DRA-85	157
GTCCCCATCCTCGCCACCTC	165	4011	4030	10	DRA-86	158
AATCACACCAACGGGGCAGG	166	4125	4144	10	DRA-87	159
TGGCACACGATGCTACGCAA	167	4170	4189	10	DRA-172	160
GGGTGGCACACGATGCTACG	168	4173	4192	10	DRA-89	161
CAGGGGTGGCACACGATGCT	169	4176	4195	10	DRA-173	162
GGGCAGGGGTGGCACACGAT	170	4179	4198	10	DRA-174	163

[表 2-3]

ASO之鹼基序列(DNA表記) 5'至3'	ASO編號	序列編號471之開始部位	序列編號471之終止部位	標的外顯子	ASO名稱	序列編號
CTACTCGGGCCTTCTTGGCT	171	400	419	3		164
CCTCTACTCGGGCCTTCTTG	172	403	422	3		165
CTTCCTCTACTCGGGCCTTC	173	406	425	3		166
GGCTAAGAGGCGGCCATAGG	174	1581	1600	5		167
GTTGGCTAAGAGGCGGCCAT	175	1584	1603	5		168
TGTTGGCTAAGAGGCGGCCA	176	1585	1604	5		169
GCTGTTGGCTAAGAGGCGGC	177	1587	1606	5		170
TGCTGTTGGCTAAGAGGCGG	178	1588	1607	5		171
ATTGCTGTTGGCTAAGAGGC	179	1590	1609	5		172
CATTGCTGTTGGCTAAGAGG	180	1591	1610	5		173
GCATTGCTGTTGGCTAAGAG	181	1592	1611	5		21
GGCATTGCTGTTGGCTAAGA	182	1593	1612	5		174
GGGCATTGCTGTTGGCTAAG	183	1594	1613	5		175
ATGGGCATTGCTGTTGGCTA	184	1596	1615	5		176
GATGGGCATTGCTGTTGGCT	185	1597	1616	5		177
TGGATGGGCATTGCTGTTGG	186	1599	1618	5		178
CTGGATGGGCATTGCTGTTG	187	1600	1619	5		179
GCCTGGATGGGCATTGCTGT	188	1602	1621	5		180
GGCCTGGATGGGCATTGCTG	189	1603	1622	5		181
GGGGCCTGGATGGGCATTGC	190	1605	1624	5		182
AGGTGGGGGCAGGTGTGCTG	191	1878	1897	5		183
GAGGTGGGGGCAGGTGTGCT	192	1879	1898	5		184
CGAGGAAGCCACGGTGGCAA	193	2094	2113	5		185
CCTTCTCCACCAGGTCGGCC	194	2629	2648	6		186
GCGCCGCACCTTCTCCACCA	195	2637	2656	6		187
CTCTTTCTCGCGTTCCCGCT	196	2700	2719	6		188
GCTCTTTCTCGCGTTCCCGC	197	2701	2720	6		189
GCGCTCTTTCTCGCGTTCCC	198	2703	2722	6		190
CGCGCTCTTTCTCGCGTTCC	199	2704	2723	6		191
CTCGCGCTCTTTCTCGCGTT	200	2706	2725	6		192
GCTCGCGCTCTTTCTCGCGT	201	2707	2726	6		193
GCGCTCGCGCTCTTTCTCGC	202	2709	2728	6		194
CGCGCTCGCGCTCTTTCTCG	203	2710	2729	6		195
CTCGCGCTCGCGCTCTTTCT	204	2712	2731	6		196
TCTCGCGCTCGCGCTCTTTC	205	2713	2732	6		197
CTTCTCGCGCTCGCGCTCTT	206	2715	2734	6		198
CCTTCTCGCGCTCGCGCTCT	207	2716	2735	6		199
CTCCTTCTCGCGCTCGCGCT	208	2718	2737	6		200
GCTCCTTCTCGCGCTCGCGC	209	2719	2738	6		201
GCGCTCCTTCTCGCGCTCGC	210	2721	2740	6		202
CGCGCTCCTTCTCGCGCTCG	211	2722	2741	6		203
GCACTGTAGCCACCGCACTG	212	2839	2858	7		204
GGCACTGTAGCCACCGCACT	213	2840	2859	7		205
GGGGCACTGTAGCCACCGCA	214	2842	2861	7		206
GGGGGCACTGTAGCCACCGC	215	2843	2862	7		207
GGGGGGCACTGTAGCCACCG	216	2844	2863	7		208
CCGGGTCCACTGCCCCCAGG	217	2962	2981	7		209
TGCTGCCTCTCAGCTGCCAG	218	3302	3321	7		210
TGCGTGCTGCCTCTCAGCTG	219	3306	3325	7		211
CTGCTGACATCGGGGCAGAA	220	3631	3650	9		212
CTGATGAGCTGCTGACATCG	221	3639	3658	9		213
CAGCGCCAAGCGCTGCAGCT	222	3687	3706	9		214
TGCTGTTCCAGCGCCAAGCG	223	3695	3714	9		215
GGGCAGGCAGCGGCACACTG	224	3745	3764	9		216
ACACCACATCGGGCCTTGGC	225	3980	3999	10		217
ACCTCTGCACACCACATCGG	226	3988	4007	10		218
GCAGGGGTGGCACACGATGC	227	4177	4196	10		219
GGCAGGGGTGGCACACGATG	228	4178	4197	10		220
GGGGCAGGGGTGGCACACGA	229	4180	4199	10		221
GGGCGCGCACACAGGGATCG	230	4204	4223	10		222

[表 2-4]

ASO之鹼基序列(DNA表記) 5' 至 3'	ASO編號	序列編號471之開始部位	序列編號471之終止部位	標的外顯子	ASO名稱	序列編號
ACTCGGGCCTTCTTGGCTGT	231	398	417	3		223
TACTCGGGCCTTCTTGGCTG	232	399	418	3		224
TCTACTCGGGCCTTCTTGGC	233	401	420	3		225
CTCTACTCGGGCCTTCTTGG	234	402	421	3		226
TCCTCTACTCGGGCCTTCTT	235	404	423	3		227
TTCCTCTACTCGGGCCTTCT	236	405	424	3		228
GCTTCCTCTACTCGGGCCTT	237	407	426	4		229
GGCTTCCTCTACTCGGGCCT	238	408	427	4		230
CTAAGAGGCGGCCATAGGGA	239	1579	1598	5		231
GCTAAGAGGCGGCCATAGGG	240	1580	1599	5		232
TGGCTAAGAGGCGGCCATAG	241	1582	1601	5		233
TTGGCTAAGAGGCGGCCATA	242	1583	1602	5		234
GTGAGGTGGGGGCAGGTGTG	243	1881	1900	5		235
TGTGAGGTGGGGGCAGGTGT	244	1882	1901	5		236
GCTGTGAGGTGGGGGCAGGT	245	1884	1903	5		237
GGCTGTGAGGTGGGGGCAGG	246	1885	1904	5		238
CTGGCTGTGAGGTGGGGGCA	247	1887	1906	5		239
GAGGAAGCCACGGTGGCAAT	248	2093	2112	5		240
CGGCCCGCTTCTTGGCCAGC	249	2614	2633	6		241
TCGGCCCGCTTCTTGGCCAG	250	2615	2634	6		242
GTCGGCCCGCTTCTTGGCCA	251	2616	2635	6		243
GGTCGGCCCGCTTCTTGGCC	252	2617	2636	6		244
AGGTCGGCCCGCTTCTTGGC	253	2618	2637	6		245
CAGGTCGGCCCGCTTCTTGG	254	2619	2638	6		246
CCAGGTCGGCCCGCTTCTTG	255	2620	2639	6		247
ACCAGGTCGGCCCGCTTCTT	256	2621	2640	6		248
CACCAGGTCGGCCCGCTTCT	257	2622	2641	6		249
CCACCAGGTCGGCCCGCTTC	258	2623	2642	6		250
TCCACCAGGTCGGCCCGCTT	259	2624	2643	6		251
CTCCACCAGGTCGGCCCGCT	260	2625	2644	6		252
TCTCCACCAGGTCGGCCCGC	261	2626	2645	6		253
TTCTCCACCAGGTCGGCCCG	262	2627	2646	6		254
CTTCTCCACCAGGTCGGCCC	263	2628	2647	6		255
ACCTTCTCCACCAGGTCGGC	264	2630	2649	6		256
CACCTTCTCCACCAGGTCGG	265	2631	2650	6		257
GCACCTTCTCCACCAGGTCG	266	2632	2651	6		258
CCGCACCTTCTCCACCAGGT	267	2634	2653	6		259
GCCGCACCTTCTCCACCAGG	268	2635	2654	6		260
CGCCGCACCTTCTCCACCAG	269	2636	2655	6		261
CGCGCCGCACCTTCTCCACC	270	2638	2657	6		262
TCGCGCCGCACCTTCTCCAC	271	2639	2658	6		263
CTCGCGCCGCACCTTCTCCA	272	2640	2659	6		264
CCTCGCGCCGCACCTTCTCC	273	2641	2660	6		265
GCCTCGCGCCGCACCTTCTC	274	2642	2661	6		266
GGCCTCGCGCCGCACCTTCT	275	2643	2662	6		267
CGGCCTCGCGCCGCACCTTC	276	2644	2663	6		268
TCGGCCTCGCGCCGCACCTT	277	2645	2664	6		269
CTCGGCCTCGCGCCGCACCT	278	2646	2665	6		270
GCTCGGCCTCGCGCCGCACC	279	2647	2666	6		271
TGCTCGGCCTCGCGCCGCAC	280	2648	2667	6		272
GCGCTCCTTTTCTTCGCGCG	281	2673	2692	6		273
CGCGCTCCTTTTCTTCGCGC	282	2674	2693	6		274
TCGCGCTCCTTTTCTTCGCG	283	2675	2694	6		275
CTCGCGCTCCTTTTCTTCGC	284	2676	2695	6		276
GCTCGCGCTCCTTTTCTTCG	285	2677	2696	6		277
CGCTCGCGCTCCTTTTCTTC	286	2678	2697	6		278
GCGCTCGCGCTCCTTTTCTT	287	2679	2698	6		279
CGCGCTCGCGCTCCTTTTCT	288	2680	2699	6		280
TCGCGCTCGCGCTCCTTTTC	289	2681	2700	6		281
CTCGCGCTCGCGCTCCTTTT	290	2682	2701	6		282

[表 2-5]

ASO之鹼基序列(DNA表記) 5'至3'	ASO編號	序列編號471之開始部位	序列編號471之終止部位	標的外顯子	ASO名稱	序列編號
GCTCGCGCTCGCGCTCCTTT	291	2683	2702	6		283
CGCTCGCGCTCGCGCTCCTT	292	2684	2703	6		284
CCGCTCGCGCTCGCGCTCCT	293	2685	2704	6		285
CCCGCTCGCGCTCGCGCTCC	294	2686	2705	6		286
TCCCGCTCGCGCTCGCGCTC	295	2687	2706	6		287
TTCCCGCTCGCGCTCGCGCT	296	2688	2707	6		288
GTTCCCGCTCGCGCTCGCGC	297	2689	2708	6		289
CGTTCCCGCTCGCGCTCGCG	298	2690	2709	6		290
GCGTTCCCGCTCGCGCTCGC	299	2691	2710	6		291
CGCGTTCCCGCTCGCGCTCG	300	2692	2711	6		292
TCGCGTTCCCGCTCGCGCTC	301	2693	2712	6		293
CTCGCGTTCCCGCTCGCGCT	302	2694	2713	6		294
TCTCGCGTTCCCGCTCGCGC	303	2695	2714	6		295
TTCTCGCGTTCCCGCTCGCG	304	2696	2715	6		296
TTTCTCGCGTTCCCGCTCGC	305	2697	2716	6		297
CTTTCTCGCGTTCCCGCTCG	306	2698	2717	6		298
CTCGCGCTCCTTCTCGCGCT	307	2724	2743	6		299
GCTCGCGCTCCTTCTCGCGC	308	2725	2744	6		300
AAGCTCGCGCTCCTTCTCGC	309	2727	2746	6		301
CAAGCTCGCGCTCCTTCTCG	310	2728	2747	6		302
TTCAAGCTCGCGCTCCTTCT	311	2730	2749	6		303
GTTCAAGCTCGCGCTCCTTC	312	2731	2750	6		304
CGTTCAAGCTCGCGCTCCTT	313	2732	2751	6		305
GCGTTCAAGCTCGCGCTCCT	314	2733	2752	6		306
CCGCACTGCCCGGTTCAAAT	315	2827	2846	7		307
ACCGCACTGCCCGGTTCAAA	316	2828	2847	7		308
CCACCGCACTGCCCGGTTCA	317	2830	2849	7		309
GCCACCGCACTGCCCGGTTC	318	2831	2850	7		310
TAGCCACCGCACTGCCCGGT	319	2833	2852	7		311
GTAGCCACCGCACTGCCCGG	320	2834	2853	7		312
CTGTAGCCACCGCACTGCCC	321	2836	2855	7		313
ACTGTAGCCACCGCACTGCC	322	2837	2856	7		314
CCCGGGTCCACTGCCCCCAG	323	2963	2982	7		315
GTGCTGCCTCTCAGCTGCCA	324	3303	3322	7		316
CGTGCTGCCTCTCAGCTGCC	325	3304	3323	7		317
GCGTGCTGCCTCTCAGCTGC	326	3305	3324	7		318
CTGCGTGCTGCCTCTCAGCT	327	3307	3326	7		319
TCTGCGTGCTGCCTCTCAGC	328	3308	3327	7		320
TTCTGCGTGCTGCCTCTCAG	329	3309	3328	7		321
TTTCTGCGTGCTGCCTCTCA	330	3310	3329	7		322
CTTTCTGCGTGCTGCCTCTC	331	3311	3330	7		323
CCTTTCTGCGTGCTGCCTCT	332	3312	3331	7		324
CCCTTTCTGCGTGCTGCCTC	333	3313	3332	7		325
ACCCTTTCTGCGTGCTGCCT	334	3314	3333	7		326
CACCCTTTCTGCGTGCTGCC	335	3315	3334	7		327
CCACCCTTTCTGCGTGCTGC	336	3316	3335	7		328
GCCACCCTTTCTGCGTGCTG	337	3317	3336	7		329
CGCCACCCTTTCTGCGTGCT	338	3318	3337	7		330
CCGCCACCCTTTCTGCGTGC	339	3319	3338	7		331
GCCGCCACCCTTTCTGCGTG	340	3320	3339	7		332
GGCCGCCACCCTTTCTGCGT	341	3321	3340	7		333
GGGCCGCCACCCTTTCTGCG	342	3322	3341	7		334
AGGGCCGCCACCCTTTCTGC	343	3323	3342	7		335
CAGGGCCGCCACCCTTTCTG	344	3324	3343	7		336
GGCAGAAAGGGAGGCCGGCA	345	3618	3637	9		337
GGGCAGAAAGGGAGGCCGGC	346	3619	3638	9		338
GGGGCAGAAAGGGAGGCCGG	347	3620	3639	9		339
CGGGGCAGAAAGGGAGGCCG	348	3621	3640	9		340
TCGGGGCAGAAAGGGAGGCC	349	3622	3641	9		341
ATCGGGGCAGAAAGGGAGGC	350	3623	3642	9		342

[表 2-6]

ASO之鹼基序列(DNA表記) 5' 至 3'	ASO編號	序列編號471之開始部位	序列編號471之終止部位	標的外顯子	ASO名稱	序列編號
CATCGGGGCAGAAAGGGAGG	351	3624	3643	9		343
ACATCGGGGCAGAAAGGGAG	352	3625	3644	9		344
GACATCGGGGCAGAAAGGGA	353	3626	3645	9		345
TGACATCGGGGCAGAAAGGG	354	3627	3646	9		346
CTGACATCGGGGCAGAAAGG	355	3628	3647	9		347
GCTGACATCGGGGCAGAAAG	356	3629	3648	9		348
TGCTGACATCGGGGCAGAAA	357	3630	3649	9		349
GCTGCTGACATCGGGGCAGA	358	3632	3651	9		350
AGCTGCTGACATCGGGGCAG	359	3633	3652	9		351
GAGCTGCTGACATCGGGGCA	360	3634	3653	9		352
ATGAGCTGCTGACATCGGGG	361	3636	3655	9		353
GATGAGCTGCTGACATCGGG	362	3637	3656	9		354
TGATGAGCTGCTGACATCGG	363	3638	3657	9		355
GCTGATGAGCTGCTGACATC	364	3640	3659	9		356
AGCTGATGAGCTGCTGACAT	365	3641	3660	9		357
CAGCTGATGAGCTGCTGACA	366	3642	3661	9		358
GCAGCTGATGAGCTGCTGAC	367	3643	3662	9		359
TGCAGCTGATGAGCTGCTGA	368	3644	3663	9		360
CTGCAGCTGATGAGCTGCTG	369	3645	3664	9		361
CCTGCAGCTGATGAGCTGCT	370	3646	3665	9		362
GCCTGCAGCTGATGAGCTGC	371	3647	3666	9		363
GGCCTGCAGCTGATGAGCTG	372	3648	3667	9		364
TGGCCTGCAGCTGATGAGCT	373	3649	3668	9		365
ATGGCCTGCAGCTGATGAGC	374	3650	3669	9		366
CATGGCCTGCAGCTGATGAG	375	3651	3670	9		367
GCATGGCCTGCAGCTGATGA	376	3652	3671	9		368
TGCATGGCCTGCAGCTGATG	377	3653	3672	9		369
CAGCTCAGCTGACTGTGCGT	378	3672	3691	9		370
GCAGCTCAGCTGACTGTGCG	379	3673	3692	9		371
TGCAGCTCAGCTGACTGTGC	380	3674	3693	9		372
CTGCAGCTCAGCTGACTGTG	381	3675	3694	9		373
GCTGCAGCTCAGCTGACTGT	382	3676	3695	9		374
CGCTGCAGCTCAGCTGACTG	383	3677	3696	9		375
GCGCTGCAGCTCAGCTGACT	384	3678	3697	9		376
AGCGCTGCAGCTCAGCTGAC	385	3679	3698	9		377
AAGCGCTGCAGCTCAGCTGA	386	3680	3699	9		378
CAAGCGCTGCAGCTCAGCTG	387	3681	3700	9		379
CCAAGCGCTGCAGCTCAGCT	388	3682	3701	9		380
GCCAAGCGCTGCAGCTCAGC	389	3683	3702	9		381
CGCCAAGCGCTGCAGCTCAG	390	3684	3703	9		382
GCGCCAAGCGCTGCAGCTCA	391	3685	3704	9		383
AGCGCCAAGCGCTGCAGCTC	392	3686	3705	9		384
CCAGCGCCAAGCGCTGCAGC	393	3688	3707	9		385
TCCAGCGCCAAGCGCTGCAG	394	3689	3708	9		386
TTCCAGCGCCAAGCGCTGCA	395	3690	3709	9		387
TGTTCCAGCGCCAAGCGCTG	396	3692	3711	9		388
CTGTTCCAGCGCCAAGCGCT	397	3693	3712	9		389
GCTGTTCCAGCGCCAAGCGC	398	3694	3713	9		390
CTGCTGTTCCAGCGCCAAGC	399	3696	3715	9		391
GCTGCTGTTCCAGCGCCAAG	400	3697	3716	9		392
TGCTGCTGTTCCAGCGCCAA	401	3698	3717	9		393
CTGCTGCTGTTCCAGCGCCA	402	3699	3718	9		394
ACTGCTGCTGTTCCAGCGCC	403	3700	3719	9		395
CACTGCTGCTGTTCCAGCGC	404	3701	3720	9		396
CCACTGCTGCTGTTCCAGCG	405	3702	3721	9		397
GCCACTGCTGCTGTTCCAGC	406	3703	3722	9		398
AGCCACTGCTGCTGTTCCAG	407	3704	3723	9		399
CAGCCACTGCTGCTGTTCCA	408	3705	3724	9		400
GCAGCCACTGCTGCTGTTCC	409	3706	3725	9		401
TGCAGCCACTGCTGCTGTTC	410	3707	3726	9		402

[表 2-7]

ASO之鹼基序列(DNA表記) 5'至3'	ASO編號	序列編號471之開始部位	序列編號471之終止部位	標的外擴子	ASO名稱	序列編號
ATGCAGCCACTGCTGCTGTT	411	3708	3727	9		403
GGCAGCGGCACACTGTGCAG	412	3740	3759	9		404
AGGCAGCGGCACACTGTGCA	413	3741	3760	9		405
CAGGCAGCGGCACACTGTGC	414	3742	3761	9		406
GCAGGCAGCGGCACACTGTG	415	3743	3762	9		407
GGCAGGCAGCGGCACACTGT	416	3744	3763	9		408
TTGGCCTTCTGTCTGTCCCT	417	3965	3984	10		409
CTTGGCCTTCTGTCTGTCCC	418	3966	3985	10		410
CCTTGGCCTTCTGTCTGTCC	419	3967	3986	10		411
GCCTTGGCCTTCTGTCTGTC	420	3968	3987	10		412
GGCCTTGGCCTTCTGTCTGT	421	3969	3988	10		413
GGGCCTTGGCCTTCTGTCTG	422	3970	3989	10		414
CGGGCCTTGGCCTTCTGTCT	423	3971	3990	10		415
TCGGGCCTTGGCCTTCTGTC	424	3972	3991	10		416
ATCGGGCCTTGGCCTTCTGT	425	3973	3992	10		417
CATCGGGCCTTGGCCTTCTG	426	3974	3993	10		418
ACATCGGGCCTTGGCCTTCT	427	3975	3994	10		419
CACATCGGGCCTTGGCCTTC	428	3976	3995	10		420
CCACATCGGGCCTTGGCCTT	429	3977	3996	10		421
ACCACATCGGGCCTTGGCCT	430	3978	3997	10		422
CACCACATCGGGCCTTGGCC	431	3979	3998	10		423
CACACCACATCGGGCCTTGG	432	3981	4000	10		424
GCACACCACATCGGGCCTTG	433	3982	4001	10		425
TGCACACCACATCGGGCCTT	434	3983	4002	10		426
TCTGCACACCACATCGGGCC	435	3985	4004	10		427
CTCTGCACACCACATCGGGC	436	3986	4005	10		428
CCTCTGCACACCACATCGGG	437	3987	4006	10		429
CACCTCTGCACACCACATCG	438	3989	4008	10		430
CCACCTCTGCACACCACATC	439	3990	4009	10		431
CCCACCTCTGCACACCACAT	440	3991	4010	10		432
CCCCACCTCTGCACACCACA	441	3992	4011	10		433
TCCCCACCTCTGCACACCAC	442	3993	4012	10		434
CTCCCCACCTCTGCACACCA	443	3994	4013	10		435
CCTCCCCACCTCTGCACACC	444	3995	4014	10		436
ACCTCCCCACCTCTGCACAC	445	3996	4015	10		437
CACCTCCCCACCTCTGCACA	446	3997	4016	10		438
CCACCTCCCCACCTCTGCAC	447	3998	4017	10		439
AGGGGCAGGGGTGGCACACG	448	4181	4200	10		440
GAGGGGCAGGGGTGGCACAC	449	4182	4201	10		441
GGAGGGGCAGGGGTGGCACA	450	4183	4202	10		442
GGGAGGGGCAGGGGTGGCAC	451	4184	4203	10		443
GGGGAGGGGCAGGGGTGGCA	452	4185	4204	10		444
CGGGGAGGGGCAGGGGTGGC	453	4186	4205	10		445
TCGGGGAGGGGCAGGGGTGG	454	4187	4206	10		446
ATCGGGGAGGGGCAGGGGTG	455	4188	4207	10		447
GATCGGGGAGGGGCAGGGGT	456	4189	4208	10		448
GGATCGGGGAGGGGCAGGGG	457	4190	4209	10		449
GGGATCGGGGAGGGGCAGGG	458	4191	4210	10		450
AGGGATCGGGGAGGGGCAGG	459	4192	4211	10		451
CAGGGATCGGGGAGGGGCAG	460	4193	4212	10		452
ACAGGGATCGGGGAGGGGCA	461	4194	4213	10		453
CACAGGGATCGGGGAGGGGC	462	4195	4214	10		454
ACACAGGGATCGGGGAGGGG	463	4196	4215	10		455
CACACAGGGATCGGGGAGGG	464	4197	4216	10		456
GCACACAGGGATCGGGGAGG	465	4198	4217	10		457
CGCACACAGGGATCGGGGAG	466	4199	4218	10		458
GCGCACACAGGGATCGGGGA	467	4200	4219	10		459
CGCGCACACAGGGATCGGGG	468	4201	4220	10		460
GCGCGCACACAGGGATCGGG	469	4202	4221	10		461
GGCGCGCACACAGGGATCGG	470	4203	4222	10		462
GGGGCGCGCACACAGGGATC	471	4205	4224	10		463
GGGGGCGCGCACACAGGGAT	472	4206	4225	10		464

表 3 中，寡核苷酸全部為具有 2'-O-MOE 基之 5-10-5 的間隔子，5'翼部部分及 3'翼部部分之核苷間的鍵結為硫代磷酸酯鍵(phosphorothioate)(P=S)或磷酸二酯鍵(P=O)，間隔(gap)部分之核苷間的鍵結，全部為硫代磷酸酯鍵(phosphorothioate)(P=S)。表 3 中，將為磷酸二酯(P=O)之鍵結以^表示。又，間隔部分及翼部部分之 C 實際上為甲基 C，翼部部分之 T 實際上為 T。

[表 3]

表 3　包含翼部之核苷間之鍵結為磷酸二酯鍵之受驗對象的間隔子(寡核苷酸)

ASO 之鹼基序列(DNA 表記) 5' 至 3'	ASO 編號	序列編號 471 之開始部位	序列編號 471 之終止部位	標的外顯子	ASO 名稱	序列編號
AG^A^G^ACCTGGTCCAAG^A^T^TC	473	4043	4062	10	DRA-274	472
AG^A^GACCTGGTCCAAGA^T^TC	474	4043	4062	10	DRA-275	472
AG^AG^ACCTGGTCCAAG^AT^TC	475	4043	4062	10	DRA-276	472
AGA^G^ACCTGGTCCAAG^A^TTC	476	4043	4062	10	DRA-277	472
AG^AGACCTGGTCCAAGAT^TC	477	4043	4062	10	DRA-278	472
AGA^GACCTGGTCCAAGA^TTC	478	4043	4062	10	DRA-279	472
AGAG^ACCTGGTCCAAG^ATTC	479	4043	4062	10	DRA-280	472
GA^T^G^GGCATTGCTGTT^G^G^CT	480	1597	1616	5	DRA-281	177
GA^T^GGGCATTGCTGTTG^G^CT	481	1597	1616	5	DRA-282	177
GA^TG^GGCATTGCTGTT^GG^CT	482	1597	1616	5	DRA-283	177
GAT^G^GGCATTGCTGTT^G^GCT	483	1597	1616	5	DRA-284	177
GA^TGGGCATTGCTGTTGG^CT	484	1597	1616	5	DRA-285	177
GAT^GGGCATTGCTGTTG^GCT	485	1597	1616	5	DRA-286	177
GATG^GGCATTGCTGTT^GGCT	486	1597	1616	5	DRA-287	177
TC^C^T^TCTCGCGCTCGC^G^C^TC	487	2717	2736	6	DRA-298	133
TC^C^TTCTCGCGCTCGCG^C^TC	488	2717	2736	6	DRA-308	133
TC^CT^TCTCGCGCTCGC^GC^TC	489	2717	2736	6	DRA-299	133
TCC^T^TCTCGCGCTCGC^G^CTC	490	2717	2736	6	DRA-309	133
TC^CTTCTCGCGCTCGCGC^TC	491	2717	2736	6	DRA-310	133
TCC^TTCTCGCGCTCGCG^CTC	492	2717	2736	6	DRA-311	133
TCCT^TCTCGCGCTCGC^GCTC	493	2717	2736	6	DRA-312	133
CT^C^G^CGCTCGCGCTCT^T^T^CT	494	2712	2731	6	DRA-300	196
CT^CG^CGCTCGCGCTCT^TT^CT	495	2712	2731	6	DRA-301	196
GC^T^G^TTGGCTAAGAGG^C^G^GC	496	1587	1606	5	DRA-302	170

^, 磷酸二酯鍵

表 4 中，寡核苷酸全部為具有 2'-O-MOE 基之 5-10-5 的間隔子，5'翼部部分及 3'翼部部分之核苷間的鍵結為硫代磷酸酯鍵(phosphorothioate)(P=S)或磷酸二酯鍵(P=O)，間隔(gap)部分之核苷間的鍵結全部為硫代磷酸酯鍵(phosphorothioate)(P=S)。表 4 中，將磷酸二酯(P=O)之鍵結以^表示。又，間隔(gap)部分及翼部部分之 C 實際上為甲基 C，翼部部分之 T 實際上為 T，3'翼部部分之畫底線的鹼基為與序列編號 196 相異之鹼基。

[表 4]

表 4　在 3'翼部與序列編號 196 具有 1 鹼基差異之受驗對象的間隔子(寡核苷酸)

ASO 之鹼基序列(DNA 表記) 5'至 3'	ASO 編號	序列編號 471 之開始部位	序列編號 471 之終止部位	標的外顯子	ASO 名稱	序列編號
CTCGCGCTCGCGCTCCTTCT	497	2712	2731	10	DRA-303	473
CT^C^G^CGCTCGCGCTCC^T^T^CT	498	2712	2731	10	DRA-304	473
CT^CG^CGCTCGCGCTCC^TT^CT	499	2712	2731	10	DRA-305	473

^, 磷酸二酯鍵

畫底線, 與序列編號 196 相異之鹼基

【0092】[試驗例 1]　使用了 A204 人類橫紋肌肉瘤細胞株之間隔子的 ATN-1 基因敲落(knock down)活性(抑制活性)測定

使用 SF Cell Line 4D-Nucleofector(TM) X KitS，依照套組隨附的操作指南(protocol)，藉由 4D-Nucleofector(TM)，將表 1 或表 2 的受驗對象之間隔子或陽性對照之間隔子以 1μM 或 2μM 之濃度，導入至 3.0×10^5 個 A204 細胞(自 ATCC 入手)中。程式係使用 DS-130。導入後，將細胞在包含 10%牛胎兒血清(FBS)(NICHIREI)及 1mM L-麩醯胺酸(Gibco)之 McCoy's 5A Medium(SIGMA)中，在 37℃、5% CO_2 條件下培養一晚。陽

性對照之間隔子係使用進行預備試驗(未示數據)，確認活性的翼部之核苷中具有 2'-OMe 基的 OMe-6(5'-AGAGACCTGGTCCAAGATTC-3'，序列編號 472)或翼部之核苷中具有 2'-O-MOE 基的 NRH-71(5'-AGAGACCTGGTCCAAGATTC-3'，序列編號 472)。兩寡核苷酸皆為 5-10-5 之間隔子，核苷間之鍵結全部為硫代磷酸酯鍵(phosphorothioate)(P=S)。又，關於 OMe-6，翼部部分之 T(胸腺嘧啶)實際上為 U(脲嘧啶)。又，關於 NRH-71，間隔(gap)部分及翼部部分之 C(胞嘧啶)實際上為甲基 C，翼部部分之 T 實際上為 T。此等陽性對照之間隔子，係與受驗對象之間隔子同樣地合成。次日，將細胞用 PBS(Nacalai Tesque)洗淨後，添加包含 1%之 2-巯基乙醇(Nacalai Tesque)的 RA1(Takara Bio)，使細胞溶解，在 NucleoSpin(R) Filter(Takara Bio)上回收。藉由離心除去不溶部分後，依照附加於 NucleoSpin(R) RNA(Takara Bio)之操作指南(protocol)，萃取全 RNA。萃取之全 RNA 的濃度，使用 NanoDrop(Thermo Fisher)測定。對於萃取之全 RNA 200 ng，使用 High Capacity cDNA Reverse Transcription Kit(Applied Biosystems)及 Kit 附屬之隨機引子，進行逆轉錄(RT)反應。具體而言，依照上述套組所附加之操作指南(protocol)，調製反應液。熱循環儀(thermal cycler)係使用 TaKaRa PCR Thermal Cycler Dice Touch (Takara Bio)。使用的 RT 反應之程式，如以下所述。

【0093】

25℃、10 分鐘：引子之黏合(annealing)

37℃、120 分鐘：逆轉錄反應

85℃、5 分鐘：逆轉錄酵素不活性化

然後，使用 Fast SYBR Green Master Mix(Thermo Fisher Scientific)，以 RT 反應液為模板進行 qPCR，測定在 A204 細胞中內在表現的 ATN1 之 RNA 表現量。qPCR 反應中，使用 ATN1 內之 2 處序列(外顯子 4 至外顯子 5，外顯子 6 至外顯子 7)作為模板。具體而言，依照上述套組隨附之操作指南(protocol)調製反應液。qPCR 係使用 QuantStudio6Flex Real-Time PCR System(applied biosystems)。使用的 qPCR 之程式，如以下所述。

【0094】

50℃、2 分鐘；95℃、10 分鐘；聚合酶活化、cDNA 熱變性

[95℃、15 秒；60℃、1 分鐘]x40 循環；PCR 增幅

95℃、15 秒；60℃、1 分鐘→95℃、15 秒(Melting Curve 0.05℃/s)：熔解曲線解析

將使用於 ATN1 RNA 之檢測的引子示於表 4。ATN1 RNA 表現量係以管家基因(housekeeping gene)之 β-肌動蛋白 RNA 表現量補正。將使用於 β-肌動蛋白 RNA 之檢測的引子示於表 4。將不添加間隔子只藉由 4D-Nucleofector(TM)進行導入操作之細胞之 ATN1 RNA 表現量的抑制比率，從受驗物質之間隔子導入時之 ATN1 RNA 表現量的比率算出，解析受驗物質之間隔子的抑制活性。將結果示於表 5 至 9。

【0095】[表 5-1]

表 5-1 使用於內源性 ATN1 RNA 之檢測的引子及識別外顯子部位

識別外顯子	檢測用引子組			
	正義(Sense)引子 5'至 3'	序列編號	反義(Reverse)引子 5'至 3'	序列編號
外顯子 4-5	TCAACAAGCAGGGTCGGAGT	465	CTTCGGTTGTCCTGGTCGATA	467
外顯子 6-7	TTGAACGCAGCGTGAAGTTG	466	TTGCGATTGCCAGGAGACAT	468

[表 5-2]

表 5-2 使用於屬於補正用基因之 β-肌動蛋白 RNA 之檢測的引子

補正用基因	檢測用引子組			
	正義引子 5'至 3'	序列編號	反義引子 5'至 3'	序列編號
β-肌動蛋白	GAAGATCAAGATCATTGCTCCT	469	TACTCCTGCTTGCTGATCCA	470

[表 6]

表 6 投予了在翼部之核苷具有 2'-OMe 基之間隔子(2.0μM)的 A204 細胞中之 ATN-1 基因表現量比

ASO 編號	mRNA 表現量 (外顯子-5)	mRNA 表現量比/OMe-6 (外顯子 4-5)	mRNA 表現量 (外顯子 6-7)	mRNA 表現量比/OMe-6 (外顯子 6-7)	mRNA 表現量比之平均值	序列編號
1	0.94	2.09	1.00	2.29	2.19	1
2	0.97	2.15	1.00	2.30	2.23	2
3	0.75	1.64	0.76	1.61	1.62	3
4	0.44	1.27	0.47	1.28	1.27	4
6	0.61	1.56	0.69	1.60	1.58	6
7	0.11	0.26	0.14	0.30	0.28	7
8	0.66	1.90	0.67	1.80	1.85	8

9	0.33	0.73	0.40	0.80	0.76	9
10	0.20	0.47	0.24	0.52	0.49	10
11	0.30	0.77	0.34	0.78	0.77	11
12	0.15	0.35	0.18	0.39	0.37	12
13	0.18	0.46	0.17	0.39	0.42	13
14	0.75	1.59	0.83	1.69	1.64	14
15	0.62	1.37	0.53	1.23	1.30	15
16	0.47	1.03	0.40	0.93	0.98	16
17	0.39	0.71	0.40	0.80	0.76	17
18	0.72	1.61	0.67	1.54	1.57	18
19	0.74	1.33	0.77	1.37	1.35	19
20	0.70	1.01	0.72	1.27	1.14	20
21	0.71	1.50	0.84	1.71	1.60	21
22	0.29	0.82	0.29	0.77	0.80	22
23	0.78	1.65	0.85	1.73	1.69	23
24	0.52	1.09	0.62	1.26	1.17	24
25	0.16	0.41	0.17	0.38	0.40	25
26	0.59	1.50	0.63	1.44	1.47	26
27	0.18	0.42	0.18	0.39	0.41	27
28	0.19	0.49	0.21	0.48	0.49	28
29	0.39	1.10	0.47	1.27	1.19	29
30	0.11	0.32	0.13	0.34	0.33	30
31	0.43	0.94	0.49	1.02	0.98	31
32	0.79	2.28	0.76	2.05	2.16	32
33	0.69	1.51	0.71	1.49	1.50	33
34	0.79	1.72	0.92	1.93	1.82	34
35	0.79	1.72	0.89	1.87	1.80	35
36	0.84	1.82	0.80	1.68	1.75	36
37	0.74	1.62	0.77	1.62	1.62	37
39	0.75	1.63	0.84	1.76	1.69	39
40	0.82	2.35	0.80	2.15	2.25	40
41	0.64	1.39	0.55	1.15	1.27	41

42	0.58	1.66	0.53	1.43	1.54	42
43	0.80	1.75	0.90	1.90	1.82	43
44	0.61	1.33	0.63	1.47	1.40	44
45	0.38	1.09	0.36	0.96	1.03	45
46	0.92	2.00	0.92	2.14	2.07	46
47	0.86	1.87	0.86	2.00	1.94	47
48	0.38	1.09	0.44	1.18	1.13	48
49	0.56	1.21	0.53	1.23	1.22	49
50	0.72	1.56	0.69	1.60	1.58	50
52	0.44	1.03	0.47	1.08	1.06	52
53	0.80	2.03	0.83	1.90	1.97	53
54	0.75	1.63	0.78	1.81	1.72	54
55	0.77	1.67	0.76	1.78	1.72	55
56	0.62	1.34	0.63	1.46	1.40	56
57	0.98	2.14	1.00	2.47	2.30	57
58	0.68	1.26	0.70	1.21	1.23	58

[表 7]

表 7　投予了在翼部之核苷具有 2'-OMe 基之間隔子(1.0μM)的 A204 細胞中之 ATN-1 基因表現量比

ASO 編號	mRNA 表現量 (外顯子 4-5)	mRNA 表現量/OMe-6 (外顯子 4-5)	mRNA 表現量 (外顯子 6-7)	mRNA 表現量比/OMe-6 (外顯子 6-7)	mRNA 表現量比之平均值	序列編號
1	0.91	1.25	1.00	1.21	1.23	1
2	0.88	1.21	1.00	1.22	1.21	2
7	0.15	0.30	0.15	0.29	0.30	7
10	0.23	0.46	0.25	0.49	0.47	10
12	0.21	0.42	0.21	0.40	0.41	12
27	0.25	0.48	0.25	0.48	0.48	27

[表 8]

投予了在翼部之核苷具有 2'-O-MOE 基之間隔子(2.0μM)的 A204 細胞中之 ATN-1 基因表現量比

ASO 編號	mRNA 表現量 (外顯子 4-5)	mRNA 表現量比/NRH-71 (外顯子 4-5)	mRNA 表現量 (外顯子 6-7)	mRNA 表現量比/NRH-71 (外顯子 6-7)	mRNA 表現量比之平均值	序列編號
59	1.00	3.18	0.88	2.44	2.81	59
60	0.23	0.46	0.23	0.58	0.52	60
61	0.04	0.11	0.07	0.20	0.15	61
64	0.04	0.12	0.13	0.35	0.23	64
65	0.11	0.34	0.22	0.62	0.48	65
69	0.05	0.18	0.04	0.24	0.21	69
71	0.11	0.32	0.12	0.34	0.33	71
72	0.15	0.32	0.13	0.31	0.31	72
88	0.03	0.09	0.03	0.16	0.12	84
89	0.06	0.19	0.06	0.33	0.26	13
93	0.63	1.33	0.64	1.50	1.42	88
94	0.87	1.77	0.89	2.27	2.02	89
95	0.12	0.26	0.14	0.33	0.30	90
96	0.16	0.33	0.14	0.32	0.32	91
97	0.35	0.75	0.23	0.55	0.65	92
98	0.67	1.36	0.71	1.82	1.59	93
99	0.65	1.31	0.63	1.62	1.46	94
105	0.09	0.19	0.09	0.23	0.21	100
108	0.45	0.92	0.43	1.09	1.00	103
109	0.07	0.24	0.06	0.35	0.29	104
110	0.10	0.34	0.09	0.51	0.43	105
120	1.00	2.05	0.89	2.26	2.16	115

121	0.22	0.45	0.21	0.53	0.49	116
127	0.44	0.89	0.41	1.06	0.97	120
128	0.35	0.83	0.39	0.93	0.88	121
129	0.30	0.71	0.34	0.80	0.75	122
130	0.53	1.28	0.56	1.33	1.31	123
131	0.89	2.14	0.76	1.81	1.98	124
132	0.42	1.00	0.48	1.13	1.07	125
133	0.23	0.56	0.24	0.57	0.56	126
134	0.43	1.04	0.43	1.02	1.03	127
139	0.13	0.31	0.10	0.24	0.27	132
144	0.23	0.56	0.06	0.14	0.35	137
145	0.65	1.55	0.56	1.34	1.44	138
150	0.14	0.35	0.05	0.12	0.24	143
152	0.23	0.56	0.23	0.53	0.55	145
153	0.17	0.41	0.23	0.54	0.48	146
154	0.51	1.35	0.51	1.35	1.35	147
155	0.24	0.65	0.22	0.59	0.62	148
156	0.36	0.96	0.41	1.09	1.03	149
157	0.58	1.55	0.51	1.35	1.45	150
158	0.22	0.59	0.20	0.52	0.56	151
159	0.32	0.86	0.27	0.72	0.79	152
160	0.23	0.61	0.21	0.54	0.58	153
161	0.20	0.53	0.20	0.53	0.53	154
162	0.45	1.19	0.44	1.17	1.18	155
163	0.38	1.00	0.33	0.87	0.93	156
164	0.24	0.63	0.21	0.55	0.59	157
165	0.58	1.53	0.59	1.57	1.55	158
166	0.12	0.31	0.11	0.28	0.29	159
168	0.15	0.39	0.14	0.37	0.38	161

[表 9]

投予了在翼部之核苷具有 2'-O-MOE 基之間隔子(1.0μM)的 A204 細胞中之 ATN-1 基因表現量比

ASO 編號	mRNA 表現量 (外顯子 4-5)	mRNA 表現量比/NRH-71 (外顯子 4-5)	mRNA 表現量 (外顯子 6-7)	mRNA 表現量比/NRH-71 (外顯子 6-7)	mRNA 表現量比之平均值	序列編號
69	0.16	0.23	0.16	0.24	0.23	69
76	0.27	0.39	0.25	0.37	0.38	76
77	0.23	0.34	0.18	0.27	0.31	77
78	0.26	0.39	0.24	0.36	0.37	10
79	0.26	0.39	0.27	0.40	0.39	78
80	0.64	0.92	0.70	1.01	0.97	79
81	0.66	0.95	0.48	0.69	0.82	80
82	0.93	1.35	1.00	1.54	1.44	81
83	0.82	1.19	0.79	1.15	1.17	82
84	0.44	0.64	0.46	0.67	0.66	11
85	0.26	0.38	0.27	0.40	0.39	83
86	0.16	0.23	0.17	0.25	0.24	12
88	0.07	0.10	0.08	0.11	0.11	84
89	0.21	0.32	0.21	0.33	0.33	13
90	0.27	0.39	0.28	0.42	0.41	85
109	0.31	0.44	0.28	0.43	0.44	104
110	0.33	0.48	0.35	0.54	0.51	105
121	0.44	0.65	0.39	0.63	0.64	116
139	0.31	0.46	0.26	0.41	0.43	132
144	0.41	0.61	0.09	0.14	0.38	137
166	0.20	0.31	0.19	0.33	0.32	159
168	0.30	0.46	0.26	0.45	0.45	161

[表 10]

投予了在翼部之核苷具有 2'-O-MOE 基之間隔子(0.5μM)的 A204 細胞中之 ATN-1 基因表現量比

ASO 編號	mRNA 表現量 (外顯子 4-5)	mRNA 表現量比/NRH-71 (外顯子 4-5)	mRNA 表現量 (外顯子 6-7)	mRNA 表現量比/NRH-71 (外顯子 6-7)	mRNA 表現量比之平均值	序列編號
62	0.24	0.31	0.39	0.52	0.41	62
63	0.30	0.38	0.42	0.56	0.47	63
66	0.88	1.12	0.72	0.94	1.03	66
67	0.79	1.00	0.72	0.96	0.98	67
68	0.16	0.19	0.20	0.23	0.21	68
70	0.26	0.31	0.29	0.33	0.32	70
73	0.72	0.87	0.77	0.89	0.88	73
74	0.83	1.00	0.87	1.00	1.00	74
75	0.82	0.99	0.87	0.99	0.99	75
91	0.93	1.18	0.96	1.34	1.26	86
92	0.79	1.01	0.84	1.16	1.09	87
100	0.50	0.60	0.58	0.67	0.63	95
101	0.72	0.87	0.69	0.79	0.83	96
102	0.55	0.66	0.55	0.63	0.64	97
103	0.41	0.50	0.42	0.48	0.49	98
104	0.73	0.88	0.80	0.92	0.90	99
106	0.28	0.33	0.33	0.37	0.35	101
107	0.72	0.87	0.72	0.82	0.85	102
111	0.52	0.66	0.51	0.72	0.69	106
112	0.46	0.58	0.47	0.66	0.62	107
113	0.89	1.10	0.84	0.95	1.03	108
114	0.94	1.16	0.86	0.97	1.07	109

115	0.73	0.91	0.73	0.83	0.87	110
116	0.76	0.94	0.68	0.77	0.86	111
117	0.11	0.14	0.11	0.13	0.13	112
118	0.18	0.22	0.20	0.23	0.22	113
119	0.35	0.43	0.37	0.42	0.43	114
122	0.67	0.80	0.66	0.90	0.85	117
124	0.31	0.37	0.29	0.39	0.38	30
125	0.97	1.17	0.80	1.09	1.13	118
135	0.56	0.69	0.51	0.58	0.64	128
136	0.79	0.98	0.74	0.83	0.91	129
137	0.47	0.58	0.47	0.53	0.56	130
138	0.38	0.46	0.38	0.43	0.45	131
140	0.25	0.30	0.22	0.25	0.28	133
141	0.45	0.56	0.47	0.54	0.55	134
142	0.92	1.14	0.86	0.97	1.05	135
143	0.65	0.84	0.67	0.79	0.82	136
146	0.96	1.16	0.95	1.09	1.12	139
147	0.64	0.77	0.72	0.83	0.80	140
148	0.85	1.02	0.85	0.98	1.00	141
149	0.90	1.13	0.91	1.12	1.13	142
151	0.80	0.97	0.82	0.95	0.96	144
161	0.50	0.72	0.59	0.73	0.73	154
167	0.25	0.32	0.25	0.30	0.31	160
169	0.49	0.63	0.51	0.60	0.61	162
170	0.39	0.50	0.42	0.50	0.50	163

[表 11]

投予了在翼部之核苷具有 2'-O-MOE 基之間隔子(0.5μM)的 A204 細胞中之 ATN-1 基因表現量比

ASO 編號	mRNA 表現量 (外顯子 4-5)	mRNA 表現量比/NRH-71 (外顯子 4-5)	mRNA 表現量 (外顯子 6-7)	mRNA 表現量比/NRH-71 (外顯子 6-7)	mRNA 表現量比之平均值	序列編號
171	0.63	0.89	0.68	0.83	0.86	164
172	0.73	1.03	0.73	0.89	0.96	165
173	0.68	0.96	0.64	0.78	0.87	166
174	0.61	0.72	0.65	0.79	0.75	167
175	0.50	0.59	0.48	0.58	0.58	168
176	0.52	0.58	0.57	0.64	0.61	169
177	0.32	0.39	0.35	0.39	0.39	170
178	0.57	0.78	0.61	0.71	0.74	171
179	1.01	1.42	1.10	1.35	1.39	172
180	0.57	0.81	0.68	0.83	0.82	173
181	0.86	0.87	0.85	1.00	0.93	21
182	0.73	0.74	0.67	0.78	0.76	174
183	0.60	0.62	0.57	0.63	0.63	175
184	0.50	0.52	0.53	0.59	0.56	176
185	0.31	0.35	0.33	0.38	0.37	177
186	0.93	0.95	0.92	1.07	1.01	178
187	0.82	0.83	0.75	0.88	0.86	179
188	0.63	0.64	0.59	0.69	0.67	180
189	0.52	0.54	0.58	0.64	0.59	181
190	0.48	0.46	0.57	0.55	0.51	182
191	0.96	0.97	0.88	1.03	1.00	183
192	0.79	0.80	0.76	0.89	0.84	184

193	0.77	1.09	0.84	1.03	1.06	185
194	0.81	0.96	0.88	1.05	1.01	186
195	0.73	0.87	0.81	0.97	0.92	187
196	0.79	0.76	0.81	0.79	0.78	188
197	0.86	0.86	0.84	0.87	0.87	189
198	0.60	0.59	0.71	0.69	0.64	190
199	1.03	1.03	0.92	0.95	0.99	191
200	0.82	0.83	0.80	0.94	0.88	192
201	0.55	0.56	0.56	0.66	0.61	193
202	0.60	0.62	0.63	0.69	0.66	194
203	0.62	0.60	0.69	0.67	0.64	195
204	0.31	0.34	0.32	0.34	0.34	196
205	0.45	0.51	0.46	0.52	0.52	197
206	0.65	0.74	0.67	0.76	0.75	198
207	0.36	0.41	0.41	0.42	0.41	199
208	0.55	0.57	0.62	0.68	0.63	200
209	0.53	0.55	0.63	0.69	0.62	201
210	0.67	0.65	0.75	0.73	0.69	202
211	0.91	0.88	0.91	0.88	0.88	203
212	1.00	0.97	0.92	0.90	0.93	204
213	0.80	0.90	0.74	0.77	0.83	205
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215	0.81	0.78	0.81	0.79	0.79	207
216	0.90	0.87	0.77	0.75	0.81	208
217	0.67	0.95	0.78	0.96	0.95	209
218	0.65	0.92	0.79	0.96	0.94	210
219	0.62	0.87	0.68	0.83	0.85	211
220	0.69	0.86	0.70	0.80	0.83	212
221	0.75	0.89	0.85	1.02	0.95	213

222	0.79	0.93	0.81	0.97	0.95	214
223	0.82	0.97	0.88	1.06	1.02	215
224	0.67	0.95	0.74	0.90	0.93	216
225	0.80	1.13	0.88	1.08	1.11	217
226	0.86	1.21	0.96	1.18	1.19	218
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228	0.51	0.63	0.53	0.61	0.62	220
229	0.39	0.47	0.39	0.45	0.46	221
230	0.81	0.96	0.85	1.02	0.99	222
241	0.69	0.67	0.69	0.67	0.67	233
242	0.80	0.77	0.90	0.87	0.82	234
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360	0.75	0.72	0.71	0.69	0.71	352
361	0.73	0.71	0.69	0.67	0.69	353
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363	0.88	0.85	0.90	0.88	0.86	355
473	0.45	0.58	0.45	0.58	0.58	472
474	0.48	0.62	0.41	0.54	0.58	472
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476	0.43	0.56	0.47	0.61	0.59	472
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478	0.58	0.74	0.51	0.66	0.70	472
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482	0.13	0.17	0.13	0.17	0.17	177
483	0.07	0.09	0.07	0.09	0.09	177
484	0.19	0.25	0.17	0.23	0.24	177

485	0.16	0.20	0.13	0.16	0.18	177
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490	0.32	0.32	0.24	0.24	0.28	133
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493	0.37	0.37	0.36	0.37	0.37	133
494	0.13	0.14	0.10	0.11	0.13	196
495	0.14	0.16	0.11	0.12	0.14	196
497	0.29	0.31	0.30	0.32	0.31	473
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【發明申請專利範圍】

【請求項1】一種反義寡核苷酸或其醫藥上可容許之鹽或此等的水合物，其係由 15 至 22 個核苷酸構成，並且與包含標的區域中之至少 15 個連續鹼基之核酸互補，該標的區域係選自由序列編號 471 之鹼基序列之第 1 至 84 位、第 142 至 168 位、第 197 至 224 位、第 286 至 317 位、第 324 至 370 位、第 391 至 434 位、第 519 至 540 位、第 623 至 643 位、第 690 至 780 位、第 824 至 855 位、第 860 至 897 位、第 948 至 987 位、第 1044 至 1072 位、第 1125 至 1174 位、第 1181 至 1213 位、第 1228 至 1255 位、第 1265 至 1327 位、第 1334 至 1356 位、第 1416 至 1440 位、第 1447 至 1631 位、第 1638 至 1667 位、第 1675 至 1705 位、第 1748 至 1823 位、第 1838 至 1861 位、第 1870 至 1913 位、第 1920 至 1941 位、第 2000 至 2040 位、第 2047 至 2075 位、第 2086 至 2120 位、第 2129 至 2187 位、第 2194 至 2415 位、第 2451 至 2497 位、第 2592 至 2759 位、第 2766 至 2870 位、第 2928 至 2948 位、第 2955 至 2989 位、第 3021 至 3086 位、第 3133 至 3209 位、第 3217 至 3284 位、第 3295 至 3350 位、第 3384 至 3436 位、第 3562 至 3771 位、第 3858 至 3905 位、第 3931 至 4039 位、第 4067 至 4134 位、第 4170 至 4232 位、第 4241 至 4283 位、及第 4286 至 4355 位所構成之群組。

【請求項2】如請求項 1 所述之反義寡核苷酸或其醫藥上可容許之鹽或此等的水合物，其係與包含標的區域中之至少 15 個連續鹼基的核酸互補，該標的區域係選自由序列編號 471 之鹼基序列之第 1 至 69 位、第 331 至 363 位、第 398 至 427 位、第 697 至 773 位、第 867 至 890 位、第 955

至 980 位、第 1132 至 1167 位、第 1272 至 1320 位、第 1454 至 1624 位、第 1682 至 1705 位、第 1748 至 1816 位、第 1877 至 1906 位、第 2007 至 2033 位、第 2093 至 2113 位、第 2136 至 2180 位、第 2201 至 2408 位、第 2458 至 2490 位、第 2599 至 2752 位、第 2773 至 2863 位、第 2962 至 2982 位、第 3028 至 3079 位、第 3140 至 3202 位、第 3224 至 3277 位、第 3302 至 3343 位、第 3391 至 3429 位、第 3569 至 3764 位、第 3865 至 3898 位、第 3938 至 4032 位、第 4074 至 4127 位、第 4177 至 4225 位、第 4248 至 4276 位、及第 4293 至 4355 位所構成之群組。

【請求項3】如請求項 1 所述之反義寡核苷酸或其醫藥上可容許之鹽或此等的水合物，其係與包含標的區域中之至少 15 個連續鹼基的核酸互補，該標的區域係選自由序列編號 471 之鹼基序列之第 14 至 33 位、第 34 至 53 位、第 54 至 73 位、第 148 至 167 位、第 397 至 432 位、第 723 至 742 位、第 747 至 778 位、第 965 至 984 位、第 1127 至 1146 位、第 1148 至 1173 位、第 1182 至 1213 位、第 1228 至 1254 位、第 1270 至 1308 位、第 1484 至 1564 位、第 1578 至 1629 位、第 1686 至 1705 位、第 1748 至 1767 位、第 1768 至 1787 位、第 1794 至 1813 位、第 1870 至 1913 位、第 2015 至 2034 位、第 2086 至 2118 位、第 2129 至 2148 位、第 2151 至 2184 位、第 2206 至 2225 位、第 2239 至 2272 位、第 2287 至 2336 位、第 2337 至 2373 位、第 2387 至 2406 位、第 2598 至 2757 位、第 2775 至 2809 位、第 2826 至 2866 位、第 2959 至 2982 位、第 3032 至 3051 位、第 3052 至 3071 位、第 3136 至 3155 位、第 3168 至 3187 位、第 3188 至 3207 位、第 3232 至 3270 位、第 3298 至 3344 位、第 3408 至 3427 位、

第 3563 至 3582 位、第 3590 至 3728 位、第 3739 至 3769 位、第 3877 至 3896 位、第 3949 至 4030 位、及第 4170 至 4225 位所構成之群組。

【請求項4】如請求項 3 所述之反義寡核苷酸或其醫藥上可容許之鹽或此等的水合物，其係與包含標的區域中之至少 15 個連續鹼基的核酸互補，該標的區域係與選自由序列編號 471 之鹼基序列之第 14 至 33 位、第 34 至 53 位、第 54 至 73 位、第 148 至 167 位、第 397 至 416 位、第 398 至 417 位、第 399 至 418 位、第 400 至 419 位、第 401 至 420 位、第 402 至 421 位、第 403 至 422 位、第 404 至 423 位、第 405 至 424 位、第 406 至 425 位、第 407 至 426 位、第 408 至 427 位、第 413 至 432 位、第 723 至 742 位、第 747 至 766 位、第 756 至 775 位、第 759 至 778 位、第 965 至 984 位、第 1127 至 1146 位、第 1148 至 1167 位、第 1151 至 1170 位、第 1154 至 1173 位、第 1182 至 1201 位、第 1185 至 1204 位、第 1188 至 1207 位、第 1191 至 1210 位、第 1194 至 1213 位、第 1228 至 1247 位、第 1231 至 1250 位、第 1235 至 1254 位、第 1270 至 1289 位、第 1289 至 1308 位、第 1484 至 1503 位、第 1488 至 1507 位、第 1491 至 1510 位、第 1493 至 1512 位、第 1506 至 1525 位、第 1517 至 1536 位、第 1531 至 1550 位、第 1545 至 1564 位、第 1578 至 1597 位、第 1579 至 1598 位、第 1580 至 1599 位、第 1581 至 1600 位、第 1582 至 1601 位、第 1583 至 1602 位、第 1584 至 1603 位、第 1585 至 1604 位、第 1586 至 1605 位、第 1587 至 1606 位、第 1588 至 1607 位、第 1589 至 1608 位、第 1590 至 1609 位、第 1591 至 1610 位、第 1592 至 1611 位、第 1593 至 1612 位、第 1594 至 1613 位、第 1595 至 1614 位、第 1596 至 1615 位、第 1597 至

1616位、第1598至1617位、第1599至1618位、第1600至1619位、第1601至1620位、第1602至1621位、第1603至1622位、第1604至1623位、第1605至1624位、第1607至1626位、第1610至1629位、第1686至1705位、第1748至1767位、第1768至1787位、第1794至1813位、第1870至1889位、第1871至1890位、第1874至1893位、第1877至1896位、第1878至1897位、第1879至1898位、第1880至1899位、第1881至1900位、第1882至1901位、第1883至1902位、第1884至1903位、第1885至1904位、第1886至1905位、第1887至1906位、第1889至1908位、第1894至1913位、第2015至2034位、第2086至2105位、第2093至2112位、第2094至2113位、第2097至2116位、第2099至2118位、第2129至2148位、第2151至2170位、第2165至2184位、第2206至2225位、第2239至2258位、第2253至2272位、第2287至2306位、第2301至2320位、第2317至2336位、第2337至2356位、第2354至2373位、第2387至2406位、第2598至2617位、第2613至2632位、第2614至2633位、第2615至2634位、第2616至2635位、第2617至2636位、第2618至2637位、第2619至2638位、第2620至2639位、第2621至2640位、第2622至2641位、第2623至2642位、第2624至2643位、第2625至2644位、第2626至2645位、第2627至2646位、第2628至2647位、第2629至2648位、第2630至2649位、第2631至2650位、第2632至2651位、第2633至2652位、第2634至2653位、第2635至2654位、第2636至2655位、第2637至2656位、第2638至2657位、第2639至2658位、第2640至

2659位、第2641至2660位、第2642至2661位、第2643至2662位、第2644至2663位、第2645至2664位、第2646至2665位、第2647至2666位、第2648至2667位、第2649至2668位、第2663至2682位、第2672至2691位、第2673至2692位、第2674至2693位、第2675至2694位、第2676至2695位、第2677至2696位、第2678至2697位、第2679至2698位、第2680至2699位、第2681至2700位、第2682至2701位、第2683至2702位、第2684至2703位、第2685至2704位、第2686至2705位、第2687至2706位、第2688至2707位、第2689至2708位、第2690至2709位、第2691至2710位、第2692至2711位、第2693至2712位、第2694至2713位、第2695至2714位、第2696至2715位、第2697至2716位、第2698至2717位、第2699至2718位、第2700至2719位、第2701至2720位、第2702至2721位、第2703至2722位、第2704至2723位、第2705至2724位、第2706至2725位、第2707至2726位、第2708至2727位、第2709至2728位、第2710至2729位、第2711至2730位、第2712至2731位、第2713至2732位、第2714至2733位、第2715至2734位、第2716至2735位、第2717至2736位、第2718至2737位、第2719至2738位、第2720至2739位、第2721至2740位、第2722至2741位、第2723至2742位、第2724至2743位、第2725至2744位、第2726至2745位、第2727至2746位、第2728至2747位、第2729至2748位、第2730至2749位、第2731至2750位、第2732至2751位、第2733至2752位、第2738至2757位、第2775至2794位、第2790至2809位、第2826至2845位、第2827至

2846位、第2828至2847位、第2829至2848位、第2830至2849位、第2831至2850位、第2832至2851位、第2833至2852位、第2834至2853位、第2835至2854位、第2836至2855位、第2837至2856位、第2838至2857位、第2839至2858位、第2840至2859位、第2841至2860位、第2842至2861位、第2843至2862位、第2844至2863位、第2847至2866位、第2959至2978位、第2962至2981位、第2963至2982位、第3032至3051位、第3052至3071位、第3136至3155位、第3168至3187位、第3188至3207位、第3232至3251位、第3251至3270位、第3298至3317位、第3302至3321位、第3303至3322位、第3304至3323位、第3305至3324位、第3306至3325位、第3307至3326位、第3308至3327位、第3309至3328位、第3310至3329位、第3311至3330位、第3312至3331位、第3313至3332位、第3314至3333位、第3315至3334位、第3316至3335位、第3317至3336位、第3318至3337位、第3319至3338位、第3320至3339位、第3321至3340位、第3322至3341位、第3323至3342位、第3324至3343位、第3325至3344位、第3408至3427位、第3563至3582位、第3590至3609位、第3608至3627位、第3617至3636位、第3618至3637位、第3619至3638位、第3620至3639位、第3621至3640位、第3622至3641位、第3623至3642位、第3624至3643位、第3625至3644位、第3626至3645位、第3627至3646位、第3628至3647位、第3629至3648位、第3630至3649位、第3631至3650位、第3632至3651位、第3633至3652位、第3634至3653位、第3635至3654位、第3636至

3655位、第3637至3656位、第3638至3657位、第3639至3658位、第3640至3659位、第3641至3660位、第3642至3661位、第3643至3662位、第3644至3663位、第3645至3664位、第3646至3665位、第3647至3666位、第3648至3667位、第3649至3668位、第3650至3669位、第3651至3670位、第3652至3671位、第3653至3672位、第3654至3673位、第3671至3690位、第3672至3691位、第3673至3692位、第3674至3693位、第3675至3694位、第3676至3695位、第3677至3696位、第3678至3697位、第3679至3698位、第3680至3699位、第3681至3700位、第3682至3701位、第3683至3702位、第3684至3703位、第3685至3704位、第3686至3705位、第3687至3706位、第3688至3707位、第3689至3708位、第3690至3709位、第3691至3710位、第3692至3711位、第3693至3712位、第3694至3713位、第3695至3714位、第3696至3715位、第3697至3716位、第3698至3717位、第3699至3718位、第3700至3719位、第3701至3720位、第3702至3721位、第3703至3722位、第3704至3723位、第3705至3724位、第3706至3725位、第3707至3726位、第3708至3727位、第3709至3728位、第3739至3758位、第3740至3759位、第3741至3760位、第3742至3761位、第3743至3762位、第3744至3763位、第3745至3764位、第3750至3769位、第3877至3896位、第3949至3968位、第3964至3983位、第3965至3984位、第3966至3985位、第3967至3986位、第3968至3987位、第3969至3988位、第3970至3989位、第3971至3990位、第3972至3991位、第3973至

3992位、第3974至3993位、第3975至3994位、第3976至3995位、第3977至3996位、第3978至3997位、第3979至3998位、第3980至3999位、第3981至4000位、第3982至4001位、第3983至4002位、第3984至4003位、第3985至4004位、第3986至4005位、第3987至4006位、第3988至4007位、第3989至4008位、第3990至4009位、第3991至4010位、第3992至4011位、第3993至4012位、第3994至4013位、第3995至4014位、第3996至4015位、第3997至4016位、第3998至4017位、第3999至4018位、第4011至4030位、第4170至4189位、第4173至4192位、第4176至4195位、第4177至4196位、第4178至4197位、第4179至4198位、第4180至4199位、第4181至4200位、第4182至4201位、第4183至4202位、第4184至4203位、第4185至4204位、第4186至4205位、第4187至4206位、第4188至4207位、第4189至4208位、第4190至4209位、第4191至4210位、第4192至4211位、第4193至4212位、第4194至4213位、第4195至4214位、第4196至4215位、第4197至4216位、第4198至4217位、第4199至4218位、第4200至4219位、第4201至4220位、第4202至4221位、第4203至4222位、第4204至4223位、第4205至4224位、及第4206至4225位所構成之群組。

【請求項5】如請求項2或3所述之反義寡核苷酸或其醫藥上可容許之鹽或此等的水合物，其係與包含標的區域中之至少15個連續鹼基的核酸互補，該標的區域係選自由序列編號471之鹼基序列之第14至33位、第34至53位、第398至427位、第723至742位、第747至766位、第

1148 至 1167 位、第 1289 至 1308 位、第 1484 至 1564 位、第 1578 至 1624 位、第 1686 至 1705 位、第 1748 至 1767 位、第 1768 至 1787 位、第 1794 至 1813 位、第 1877 至 1906 位、第 2093 至 2113 位、第 2151 至 2170 位、第 2206 至 2225 位、第 2239 至 2272 位、第 2287 至 2336 位、第 2337 至 2373 位、第 2387 至 2406 位、第 2613 至 2752 位、第 2775 至 2809 位、第 2826 至 2863 位、第 2962 至 2982 位、第 3032 至 3051 位、第 3052 至 3071 位、第 3168 至 3187 位、第 3232 至 3270 位、第 3302 至 3343 位、第 3408 至 3427 位、第 3590 至 3728 位、第 3739 至 3764 位、第 3877 至 3896 位、第 3949 至 4030 位、及第 4177 至 4225 位所構成之群組。

【請求項6】如請求項 5 所述之反義寡核苷酸或其醫藥上可容許之鹽或此等的水合物，其係與包含標的區域中之至少 15 個連續鹼基的核酸互補，該標的區域係選自由序列編號 471 之鹼基序列之第 14 至 33 位、第 34 至 53 位、第 398 至 417 位、第 399 至 418 位、第 400 至 419 位、第 401 至 420 位、第 402 至 421 位、第 403 至 422 位、第 404 至 423 位、第 405 至 424 位、第 406 至 425 位、第 407 至 426 位、第 408 至 427 位、第 723 至 742 位、第 747 至 766 位、第 1148 至 1167 位、第 1289 至 1308 位、第 1484 至 1503 位、第 1488 至 1507 位、第 1491 至 1510 位、第 1493 至 1512 位、第 1506 至 1525 位、第 1517 至 1536 位、第 1531 至 1550 位、第 1545 至 1564 位、第 1578 至 1597 位、第 1579 至 1598 位、第 1580 至 1599 位、第 1581 至 1600 位、第 1582 至 1601 位、第 1583 至 1602 位、第 1584 至 1603 位、第 1585 至 1604 位、第 1586 至 1605 位、第 1587 至 1606 位、第 1588 至 1607 位、第 1589 至 1608 位、第 1590 至 1609 位、第 1591 至

1610位、第1592至1611位、第1593至1612位、第1594至1613位、第1595至1614位、第1596至1615位、第1597至1616位、第1598至1617位、第1599至1618位、第1600至1619位、第1601至1620位、第1602至1621位、第1603至1622位、第1604至1623位、第1605至1624位、第1686至1705位、第1748至1767位、第1768至1787位、第1794至1813位、第1877至1896位、第1878至1897位、第1879至1898位、第1880至1899位、第1881至1900位、第1882至1901位、第1883至1902位、第1884至1903位、第1885至1904位、第1886至1905位、第1887至1906位、第2093至2112位、第2094至2113位、第2151至2170位、第2206至2225位、第2239至2258位、第2253至2272位、第2287至2306位、第2301至2320位、第2317至2336位、第2337至2356位、第2354至2373位、第2387至2406位、第2613至2632位、第2614至2633位、第2615至2634位、第2616至2635位、第2617至2636位、第2618至2637位、第2619至2638位、第2620至2639位、第2621至2640位、第2622至2641位、第2623至2642位、第2624至2643位、第2625至2644位、第2626至2645位、第2627至2646位、第2628至2647位、第2629至2648位、第2630至2649位、第2631至2650位、第2632至2651位、第2633至2652位、第2634至2653位、第2635至2654位、第2636至2655位、第2637至2656位、第2638至2657位、第2639至2658位、第2640至2659位、第2641至2660位、第2642至2661位、第2643至2662位、第2644至2663位、第2645至2664位、第2646至2665位、第2647至2666位、第2648至

2667位、第2649至2668位、第2663至2682位、第2672至2691位、第2673至2692位、第2674至2693位、第2675至2694位、第2676至2695位、第2677至2696位、第2678至2697位、第2679至2698位、第2680至2699位、第2681至2700位、第2682至2701位、第2683至2702位、第2684至2703位、第2685至2704位、第2686至2705位、第2687至2706位、第2688至2707位、第2689至2708位、第2690至2709位、第2691至2710位、第2692至2711位、第2693至2712位、第2694至2713位、第2695至2714位、第2696至2715位、第2697至2716位、第2698至2717位、第2699至2718位、第2700至2719位、第2701至2720位、第2702至2721位、第2703至2722位、第2704至2723位、第2705至2724位、第2706至2725位、第2707至2726位、第2708至2727位、第2709至2728位、第2710至2729位、第2711至2730位、第2712至2731位、第2713至2732位、第2714至2733位、第2715至2734位、第2716至2735位、第2717至2736位、第2718至2737位、第2719至2738位、第2720至2739位、第2721至2740位、第2722至2741位、第2723至2742位、第2724至2743位、第2725至2744位、第2726至2745位、第2727至2746位、第2728至2747位、第2729至2748位、第2730至2749位、第2731至2750位、第2732至2751位、第2733至2752位、第2775至2794位、第2790至2809位、第2826至2845位、第2827至2846位、第2828至2847位、第2829至2848位、第2830至2849位、第2831至2850位、第2832至2851位、第2833至2852位、第2834至2853位、第2835至2854位、第2836至

2855位、第2837至2856位、第2838至2857位、第2839至2858位、第2840至2859位、第2841至2860位、第2842至2861位、第2843至2862位、第2844至2863位、第2962至2981位、第2963至2982位、第3032至3051位、第3052至3071位、第3168至3187位、第3232至3251位、第3251至3270位、第3302至3321位、第3303至3322位、第3304至3323位、第3305至3324位、第3306至3325位、第3307至3326位、第3308至3327位、第3309至3328位、第3310至3329位、第3311至3330位、第3312至3331位、第3313至3332位、第3314至3333位、第3315至3334位、第3316至3335位、第3317至3336位、第3318至3337位、第3319至3338位、第3320至3339位、第3321至3340位、第3322至3341位、第3323至3342位、第3324至3343位、第3408至3427位、第3590至3609位、第3608至3627位、第3617至3636位、第3618至3637位、第3619至3638位、第3620至3639位、第3621至3640位、第3622至3641位、第3623至3642位、第3624至3643位、第3625至3644位、第3626至3645位、第3627至3646位、第3628至3647位、第3629至3648位、第3630至3649位、第3631至3650位、第3632至3651位、第3633至3652位、第3634至3653位、第3635至3654位、第3636至3655位、第3637至3656位、第3638至3657位、第3639至3658位、第3640至3659位、第3641至3660位、第3642至3661位、第3643至3662位、第3644至3663位、第3645至3664位、第3646至3665位、第3647至3666位、第3648至3667位、第3649至3668位、第3650至3669位、第3651至3670位、第3652至

3671 位、第 3653 至 3672 位、第 3654 至 3673 位、第 3671 至 3690 位、第 3672 至 3691 位、第 3673 至 3692 位、第 3674 至 3693 位、第 3675 至 3694 位、第 3676 至 3695 位、第 3677 至 3696 位、第 3678 至 3697 位、第 3679 至 3698 位、第 3680 至 3699 位、第 3681 至 3700 位、第 3682 至 3701 位、第 3683 至 3702 位、第 3684 至 3703 位、第 3685 至 3704 位、第 3686 至 3705 位、第 3687 至 3706 位、第 3688 至 3707 位、第 3689 至 3708 位、第 3690 至 3709 位、第 3691 至 3710 位、第 3692 至 3711 位、第 3693 至 3712 位、第 3694 至 3713 位、第 3695 至 3714 位、第 3696 至 3715 位、第 3697 至 3716 位、第 3698 至 3717 位、第 3699 至 3718 位、第 3700 至 3719 位、第 3701 至 3720 位、第 3702 至 3721 位、第 3703 至 3722 位、第 3704 至 3723 位、第 3705 至 3724 位、第 3706 至 3725 位、第 3707 至 3726 位、第 3708 至 3727 位、第 3709 至 3728 位、第 3739 至 3758 位、第 3740 至 3759 位、第 3741 至 3760 位、第 3742 至 3761 位、第 3743 至 3762 位、第 3744 至 3763 位、第 3745 至 3764 位、第 3877 至 3896 位、第 3949 至 3968 位、第 3964 至 3983 位、第 3965 至 3984 位、第 3966 至 3985 位、第 3967 至 3986 位、第 3968 至 3987 位、第 3969 至 3988 位、第 3970 至 3989 位、第 3971 至 3990 位、第 3972 至 3991 位、第 3973 至 3992 位、第 3974 至 3993 位、第 3975 至 3994 位、第 3976 至 3995 位、第 3977 至 3996 位、第 3978 至 3997 位、第 3979 至 3998 位、第 3980 至 3999 位、第 3981 至 4000 位、第 3982 至 4001 位、第 3983 至 4002 位、第 3984 至 4003 位、第 3985 至 4004 位、第 3986 至 4005 位、第 3987 至 4006 位、第 3988 至 4007 位、第 3989 至 4008 位、第 3990 至

4009 位、第 3991 至 4010 位、第 3992 至 4011 位、第 3993 至 4012 位、第 3994 至 4013 位、第 3995 至 4014 位、第 3996 至 4015 位、第 3997 至 4016 位、第 3998 至 4017 位、第 3999 至 4018 位、第 4011 至 4030 位、第 4177 至 4196 位、第 4178 至 4197 位、第 4179 至 4198 位、第 4180 至 4199 位、第 4181 至 4200 位、第 4182 至 4201 位、第 4183 至 4202 位、第 4184 至 4203 位、第 4185 至 4204 位、第 4186 至 4205 位、第 4187 至 4206 位、第 4188 至 4207 位、第 4189 至 4208 位、第 4190 至 4209 位、第 4191 至 4210 位、第 4192 至 4211 位、第 4193 至 4212 位、第 4194 至 4213 位、第 4195 至 4214 位、第 4196 至 4215 位、第 4197 至 4216 位、第 4198 至 4217 位、第 4199 至 4218 位、第 4200 至 4219 位、第 4201 至 4220 位、第 4202 至 4221 位、第 4203 至 4222 位、第 4204 至 4223 位、第 4205 至 4224 位、及第 4206 至 4225 位所構成之群組。

【請求項7】如請求項 3 所述之反義寡核苷酸或其醫藥上可容許之鹽或此等的水合物，其係與包含標的區域中之至少 15 個連續鹼基的核酸互補，該標的區域係選自由序列編號 471 之鹼基序列之第 14 至 33 位、第 34 至 53 位、第 54 至 73 位、第 148 至 167 位、第 397 至 432 位、第 747 至 778 位、第 965 至 984 位、第 1127 至 1146 位、第 1148 至 1173 位、第 1182 至 1213 位、第 1228 至 1254 位、第 1270 至 1308 位、第 1484 至 1564 位、第 1578 至 1629 位、第 1686 至 1705 位、第 1748 至 1767 位、第 1768 至 1787 位、第 1794 至 1813 位、第 1870 至 1913 位、第 2015 至 2034 位、第 2086 至 2118 位、第 2129 至 2148 位、第 2151 至 2170 位、第 2206 至 2225 位、第 2239 至 2272 位、第 2287 至 2336 位、第 2337 至 2373 位、

第 2387 至 2406 位、第 2598 至 2632 位、第 2633 至 2668 位、第 2672 至 2691 位、第 2699 至 2757 位、第 2775 至 2809 位、第 2826 至 2866 位、第 2959 至 2978 位、第 3032 至 3051 位、第 3052 至 3071 位、第 3136 至 3155 位、第 3168 至 3187 位、第 3188 至 3207 位、第 3232 至 3270 位、第 3298 至 3317 位、第 3325 至 3344 位、第 3408 至 3427 位、第 3590 至 3690 位、第 3691 至 3728 位、第 3739 至 3769 位、第 3877 至 3896 位、第 3949 至 3983 位、第 3984 至 4030 位、及第 4170 至 4198 位所構成之群組。

【請求項8】如請求項 7 所述之反義寡核苷酸或其醫藥上可容許之鹽或此等的水合物，其係與包含標的區域中之至少 15 個連續鹼基的核酸互補，該標的區域係選自由序列編號 471 之鹼基序列之第 14 至 33 位、第 34 至 53 位、第 54 至 73 位、第 148 至 167 位、第 397 至 416 位、第 413 至 432 位、第 747 至 766 位、第 756 至 775 位、第 759 至 778 位、第 965 至 984 位、第 1127 至 1146 位、第 1148 至 1167 位、第 1151 至 1170 位、第 1154 至 1173 位、第 1182 至 1201 位、第 1185 至 1204 位、第 1188 至 1207 位、第 1191 至 1210 位、第 1194 至 1213 位、第 1228 至 1247 位、第 1231 至 1250 位、第 1235 至 1254 位、第 1270 至 1289 位、第 1289 至 1308 位、第 1484 至 1503 位、第 1488 至 1507 位、第 1491 至 1510 位、第 1493 至 1512 位、第 1506 至 1525 位、第 1517 至 1536 位、第 1531 至 1550 位、第 1545 至 1564 位、第 1578 至 1597 位、第 1586 至 1605 位、第 1589 至 1608 位、第 1592 至 1611 位、第 1595 至 1614 位、第 1598 至 1617 位、第 1601 至 1620 位、第 1604 至 1623 位、第 1607 至 1626 位、第 1610 至

1629位、第1686至1705位、第1748至1767位、第1768至1787位、第1794至1813位、第1870至1889位、第1871至1890位、第1874至1893位、第1877至1896位、第1880至1899位、第1883至1902位、第1886至1905位、第1889至1908位、第1894至1913位、第2015至2034位、第2086至2105位、第2097至2116位、第2099至2118位、第2129至2148位、第2151至2170位、第2206至2225位、第2239至2258位、第2253至2272位、第2287至2306位、第2301至2320位、第2317至2336位、第2337至2356位、第2354至2373位、第2387至2406位、第2598至2617位、第2613至2632位、第2633至2652位、第2649至2668位、第2672至2691位、第2699至2718位、第2702至2721位、第2705至2724位、第2708至2727位、第2711至2730位、第2714至2733位、第2717至2736位、第2720至2739位、第2723至2742位、第2726至2745位、第2729至2748位、第2738至2757位、第2775至2794位、第2790至2809位、第2826至2845位、第2829至2848位、第2832至2851位、第2835至2854位、第2838至2857位、第2841至2860位、第2847至2866位、第2959至2978位、第3032至3051位、第3052至3071位、第3136至3155位、第3168至3187位、第3188至3207位、第3232至3251位、第3251至3270位、第3298至3317位、第3325至3344位、第3408至3427位、第3590至3609位、第3608至3627位、第3617至3636位、第3635至3654位、第3654至3673位、第3671至3690位、第3691至3710位、第3709至3728位、第3739至3758位、第3750至3769位、第3877至3896位、第3949至

3968 位、第 3964 至 3983 位、第 3984 至 4003 位、第 3999 至 4018 位、第 4011 至 4030 位、第 4170 至 4189 位、第 4173 至 4192 位、第 4176 至 4195 位、及第 4179 至 4198 位所構成之群組。

【請求項9】如請求項 5 或 7 所述之反義寡核苷酸或其醫藥上可容許之鹽或此等的水合物，其係與包含標的區域中之至少 15 個連續鹼基的核酸互補，該標的區域係選自由序列編號 471 之鹼基序列之第 14 至 33 位、第 34 至 53 位、第 747 至 766 位、第 1148 至 1167 位、第 1289 至 1308 位、第 1484 至 1564 位、第 1578 至 1623 位、第 1686 至 1705 位、第 1748 至 1767 位、第 1768 至 1787 位、第 1794 至 1813 位、第 1877 至 1905 位、第 2151 至 2170 位、第 2206 至 2225 位、第 2239 至 2272 位、第 2287 至 2336 位、第 2337 至 2373 位、第 2387 至 2406 位、第 2613 至 2632 位、第 2633 至 2668 位、第 2672 至 2691 位、第 2699 至 2748 位、第 2775 至 2809 位、第 2826 至 2860 位、第 3032 至 3051 位、第 3052 至 3071 位、第 3168 至 3187 位、第 3232 至 3270 位、第 3408 至 3427 位、第 3590 至 3690 位、第 3691 至 3728 位、第 3739 至 3758 位、第 3877 至 3896 位、第 3949 至 3983 位、第 3984 至 4030 位、及第 4179 至 4198 位所構成之群組。

【請求項10】如請求項 9 所述之反義寡核苷酸或其醫藥上可容許之鹽或此等的水合物，其係與包含標的區域中之至少 15 個連續鹼基的核酸互補，該標的區域係選自由序列編號 471 之鹼基序列之第 14 至 33 位、第 34 至 53 位、第 747 至 766 位、第 1148 至 1167 位、第 1289 至 1308 位、第 1484 至 1503 位、第 1488 至 1507 位、第 1491 至 1510 位、第 1493 至 1512

位、第 1506 至 1525 位、第 1517 至 1536 位、第 1531 至 1550 位、第 1545 至 1564 位、第 1578 至 1597 位、第 1586 至 1605 位、第 1589 至 1608 位、第 1592 至 1611 位、第 1595 至 1614 位、第 1598 至 1617 位、第 1601 至 1620 位、第 1604 至 1623 位、第 1686 至 1705 位、第 1748 至 1767 位、第 1768 至 1787 位、第 1794 至 1813 位、第 1877 至 1896 位、第 1880 至 1899 位、第 1883 至 1902 位、第 1886 至 1905 位、第 2151 至 2170 位、第 2206 至 2225 位、第 2239 至 2258 位、第 2253 至 2272 位、第 2287 至 2306 位、第 2301 至 2320 位、第 2317 至 2336 位、第 2337 至 2356 位、第 2354 至 2373 位、第 2387 至 2406 位、第 2613 至 2632 位、第 2633 至 2652 位、第 2649 至 2668 位、第 2672 至 2691 位、第 2699 至 2718 位、第 2702 至 2721 位、第 2705 至 2724 位、第 2708 至 2727 位、第 2711 至 2730 位、第 2714 至 2733 位、第 2717 至 2736 位、第 2720 至 2739 位、第 2723 至 2742 位、第 2726 至 2745 位、第 2729 至 2748 位、第 2775 至 2794 位、第 2790 至 2809 位、第 2826 至 2845 位、第 2829 至 2848 位、第 2832 至 2851 位、第 2835 至 2854 位、第 2838 至 2857 位、第 2841 至 2860 位、第 3032 至 3051 位、第 3052 至 3071 位、第 3168 至 3187 位、第 3232 至 3251 位、第 3251 至 3270 位、第 3408 至 3427 位、第 3590 至 3609 位、第 3608 至 3627 位、第 3617 至 3636 位、第 3635 至 3654 位、第 3654 至 3673 位、第 3671 至 3690 位、第 3691 至 3710 位、第 3709 至 3728 位、第 3739 至 3758 位、第 3877 至 3896 位、第 3949 至 3968 位、第 3964 至 3983 位、第 3984 至 4003 位、第 3999 至 4018 位、第 4011 至 4030 位、及第 4179 至 4198 位所構成之群組。

【請求項11】如請求項 7 所述之反義寡核苷酸或其醫藥上可容許之鹽或此等的水合物，其係與包含標的區域中之至少 15 個連續鹼基的核酸互補，該標的區域係選自由序列編號 471 之鹼基序列之第 1598 至 1626 位、第 1870 至 1890 位、第 2097 至 2116 位、第 2711 至 2736 位、第 2841 至 2860 位、及第 4170 至 4198 位所構成之群組。

【請求項12】如請求項 7 或 8 所述之反義寡核苷酸或其醫藥上可容許之鹽或此等的水合物，其係與包含標的區域中之至少 15 個連續鹼基的核酸互補，該標的區域係選自由序列編號 471 之鹼基序列之第 1598 至 1617 位、第 1604 至 1623 位、第 1607 至 1626 位、第 1870 至 1889 位、第 1871 至 1890 位、第 2097 至 2116 位、第 2711 至 2730 位、第 2714 至 2733 位、第 2717 至 2736 位、第 2841 至 2860 位、第 4170 至 4189 位、第 4173 至 4192 位、及第 4179 至 4198 位所構成之群組。

【請求項13】如請求項 1 至 12 中任一項所述之反義寡核苷酸或其醫藥上可容許之鹽或此等的水合物，其中，該反義寡核苷酸係與包含該標的區域之至少 20 個連續鹼基的核酸互補。

【請求項14】如請求項 3 或 4 所述之反義寡核苷酸或其醫藥上可容許之鹽或此等的水合物，其係包含下列(i)、(ii)或(iii)之鹼基序列：

(i) 選自由序列編號 1 至 6、8、9、11、14 至 24、26、29、31 至 60、66 至 67、73 至 75、79 至 82、86 至 89、92 至 111、115 至 136、138 至 145、147 至 158、及 160 至 464 所構成之群組中的鹼基序列，

(ii) 在選自由序列編號 1 至 6、8、9、11、14 至 24、26、29、31 至 60、66 至 67、73 至 75、79 至 82、86 至 89、92 至 111、115 至 136、138

至 145、147 至 158、及 160 至 464 所構成之群組中的鹼基序列中，1 個或複數個鹼基經附加、缺失、或置換而成之鹼基序列，或

(iii) 相對於選自由序列編號 1 至 6、8、9、11、14 至 24、26、29、31 至 60、66 至 67、73 至 75、79 至 82、86 至 89、92 至 111、115 至 136、138 至 145、147 至 158、及 160 至 464 所構成之群組中的鹼基序列，具有 90%以上之序列一致性的鹼基序列。

【請求項15】如請求項 5 或 6 所述之反義寡核苷酸或其醫藥上可容許之鹽或此等的水合物，其係包含下列(i)、(ii)或(iii)之鹼基序列：

(i) 選自由序列編號 1、5、6、14 至 24、31 至 35、37 至 40、42 至 45、47 至 50、52 至 59、73、92 至 100、103、107 至 110、120 至 136、138 至 143、150 至 153、155 至 158、及 163 至 464 所構成之群組中的鹼基序列，

(ii) 在選自由序列編號 1、5、6、14 至 24、31 至 35、37 至 40、42 至 45、47 至 50、52 至 59、73、92 至 100、103、107 至 110、120 至 136、138 至 143、150 至 153、155 至 158、及 163 至 464 構成之群組的鹼基序列中，1 個或複數個鹼基經附加、缺失、或置換而成之鹼基序列，或

(iii) 相對於選自由序列編號 1、5、6、14 至 24、31 至 35、37 至 40、42 至 45、47 至 50、52 至 59、73、92 至 100、103、107 至 110、120 至 136、138 至 143、150 至 153、155 至 158、及 163 至 464 構成之群組的鹼基序列，具有 90%以上之序列一致性的鹼基序列。

【請求項16】如請求項 7 或 8 所述之反義寡核苷酸或其醫藥上可容許之鹽或此等的水合物，其係包含下列(i)、(ii)或(iii)之鹼基序列：

(i) 選自由序列編號 1 至 4、6、8、9、11、14 至 24、26、29、31 至 37、39 至 50、52 至 60、66 至 67、73 至 75、79 至 82、86 至 89、92 至 111、115 至 118、120 至 136、138 至 145、147 至 158、及 160 至 163 所構成之群組中的鹼基序列，

(ii) 在選自由序列編號 1 至 4、6、8、9、11、14 至 24、26、29、31 至 37、39 至 50、52 至 60、66 至 67、73 至 75、79 至 82、86 至 89、92 至 111、115 至 118、120 至 136、138 至 145、147 至 158、及 160 至 163 所構成之群組中的鹼基序列中，1 個或複數個鹼基經附加、缺失、或置換而成之鹼基序列，或

(iii) 相對於選自由序列編號 1 至 4、6、8、9、11、14 至 24、26、29、31 至 37、39 至 50、52 至 60、66 至 67、73 至 75、79 至 82、86 至 89、92 至 111、115 至 118、120 至 136、138 至 145、147 至 158、及 160 至 163 所構成之群組中的鹼基序列，具有 90%以上之序列一致性的鹼基序列。

【請求項17】如請求項 9 或 10 所述之反義寡核苷酸或其醫藥上可容許之鹽或此等的水合物，其係包含下列(i)、(ii)或(iii)之鹼基序列：

(i) 選自由序列編號 1、6、14 至 24、31 至 35、37、39、40、42 至 45、47 至 50、52 至 59、73、92 至 100、103、107 至 110、120 至 136、138 至 143、150 至 153、155 至 158、及 163 所構成之群組中的鹼基序列，

(ii) 在選自由序列編號 1、6、14 至 24、31 至 35、37、39、40、42 至 45、47 至 50、52 至 59、73、92 至 100、103、107 至 110、120 至 136、138 至 143、150 至 153、155 至 158、及 163 所構成之群組中的鹼基序列中，1 個或複數個鹼基經附加、缺失、或置換而成之鹼基序列，或

(iii) 相對於選自由序列編號 1、6、14 至 24、31 至 35、37、39、40、42 至 45、47 至 50、52 至 59、73、92 至 100、103、107 至 110、120 至 136、138 至 143、150 至 153、155 至 158、及 163 所構成之群組中的鹼基序列，具有 90%以上之序列一致性的鹼基序列。

【請求項18】如請求項 11 或 12 所述之反義寡核苷酸或其醫藥上可容許之鹽或此等的水合物，其係包含下列(i)、(ii)或(iii)之鹼基序列：

(i) 選自由序列編號 98、100、101、104、105、116、131 至 133、143、160、161、及 163 所構成之群組中的鹼基序列，

(ii) 在選自由序列編號 98、100、101、104、105、116、131 至 133、143、160、161、及 163 所構成之群組中的鹼基序列中，1 個或複數個鹼基經附加、缺失、或置換而成之鹼基序列，或

(iii) 相對於選自由序列編號 98、100、101、104、105、116、131 至 133、143、160、161、及 163 所構成之群組中的鹼基序列，具有 90%以上之序列一致性的鹼基序列。

【請求項19】如請求項 11 或 12 所述之反義寡核苷酸或其醫藥上可容許之鹽或此等的水合物，其係包含下列(i)、(ii)或(iii)之鹼基序列：

(i) 選自由序列編號 21、164 至 222、233、234、及 350 至 355 所構成之群組中的鹼基序列，

(ii) 在選自由序列編號 21、164 至 222、233、234、及 350 至 355 所構成之群組中的鹼基序列中，1 個或複數個鹼基經附加、缺失、或置換而成之鹼基序列，或

(iii) 相對於選自由序列編號 21、164 至 222、233、234、及 350 至 355 所構成之群組中的鹼基序列，具有 90%以上之序列一致性的鹼基序列。

【請求項20】 如請求項 11 或 12 所述之反義寡核苷酸或其醫藥上可容許之鹽或此等的水合物，其係包含下列(i)、(ii)或(iii)之鹼基序列：

(i) 選自由序列編號 170、177、196、199、及 221 所構成之群組中的鹼基序列，

(ii) 在選自由序列編號 170、177、196、199、及 221 所構成之群組中的鹼基序列中，1 個或複數個鹼基經附加、缺失、或置換而成之鹼基序列，或

(iii) 相對於選自由序列編號 170、177、196、199、及 221 所構成之群組中的鹼基序列，具有 90%以上之序列一致性的鹼基序列。

【請求項21】 如請求項 14 至 20 中任一項所述之反義寡核苷酸或其醫藥上可容許之鹽或此等的水合物，其係包含(i)之鹼基序列。

【請求項22】 一種反義寡核苷酸或其醫藥上可容許之鹽或此等的水合物，其係由 15 至 22 個核苷酸構成，並且與包含標的區域中之至少 15 個連續鹼基之核酸互補，該標的區域係選自由序列編號 471 之鹼基序列之第 468 至 487 位、第 474 至 493 位、第 583 至 602 位、第 586 至 605 位、第 619 至 638 位、第 770 至 789 位、第 774 至 793 位、第 775 至 794 位、第 778 至 797 位、第 804 至 823 位、第 851 至 870 位、第 1160 至 1179 位、第 1162 至 1181 位、第 1170 至 1189 位、第 1173 至 1192 位、第 1205 至 1224 位、第 1210 至 1229 位、第 1216 至 1235 位、第 1217 至 1236 位、第 1219 至 1238 位、第 1385 至 1404 位、第 1441 至 1460 位、第 1818 至 1837 位、

第 1902 至 1921 位、第 1905 至 1924 位、第 1908 至 1927 位、第 1914 至 1933 位、第 1931 至 1950 位、第 2117 至 2136 位、第 2749 至 2768 位、第 3100 至 3119 位、及第 4125 至 4144 位所構成之群組。

【請求項23】如請求項 22 所述之反義寡核苷酸或其醫藥上可容許之鹽或此等的水合物，其係包含下列(i)、(ii)或(iii)之鹼基序列：

(i) 選自由序列編號 7、10、12、13、25、27、28、30、61 至 65、68 至 72、76 至 78、83 至 85、90、91、112 至 114、137、146、及 159 所構成之群組中的鹼基序列，

(ii) 在選自由序列編號 7、10、12、13、25、27、28、30、61 至 65、68 至 72、76 至 78、83 至 85、90、91、112 至 114、137、146、及 159 所構成之群組中的鹼基序列中，1 個或複數個鹼基經附加、缺失、或置換而成之鹼基序列，或

(iii) 相對於選自由序列編號 7、10、12、13、25、27、28、30、61 至 65、68 至 72、76 至 78、83 至 85、90、91、112 至 114、137、146、及 159 所構成之群組中的鹼基序列，具有 90%以上之序列一致性的鹼基序列。

【請求項24】如請求項 23 所述之反義寡核苷酸或其醫藥上可容許之鹽或此等的水合物，其係包含(i)之鹼基序列。

【請求項25】如請求項 1 至 24 中任一項所述之反義寡核苷酸或其醫藥上可容許之鹽或此等的水合物，其中，反義寡核苷酸係由 20 個核苷酸構成。

【請求項26】如請求項1至25中任一項所述之反義寡核苷酸或其醫藥上可容許之鹽或此等的水合物，其中，構成前述寡核苷酸之至少1個核苷酸的糖部分及/或磷酸鍵結部分經修飾。

【請求項27】如請求項26所述之反義寡核苷酸或其醫藥上可容許之鹽或此等的水合物，其中，該反義寡核苷酸為包含中央之間隔(gap)區域、及與間隔區域之5'末端側及3'末端側鄰接之2個翼部區域(5'翼部區域及3'翼部區域)的間隔子(gapmer)。

【請求項28】如請求項27所述之反義寡核苷酸或其醫藥上可容許之鹽或此等的水合物，其中，核苷間之鍵結全部為硫代磷酸酯(phosphorothioate)鍵。

【請求項29】如請求項27所述之反義寡核苷酸或其醫藥上可容許之鹽或此等的水合物，其中，從5'翼部區域之5'側算起第2與第3核苷間之鍵結、第3與第4核苷間之鍵結、及第4與第5核苷間之鍵結的一個以上為磷酸二酯(phosphodiester)鍵，及/或從3'翼部區域之5'側算起第1與第2核苷間之鍵結、第2與第3核苷間之鍵結、及第3與第4核苷間之鍵結的一個以上為磷酸二酯鍵，且其他核苷間之鍵結全部為硫代磷酸酯鍵。

【請求項30】如請求項29所述之反義寡核苷酸或其醫藥上可容許之鹽或此等的水合物，其中，從5'翼部區域之5'側算起第2與第3核苷間之鍵結及第4與第5核苷間之鍵結為磷酸二酯鍵，及/或從3'翼部區域之5'側算起第1與第2核苷間之鍵結及第3與第4核苷間之鍵結為磷酸二酯鍵，且其他核苷間之鍵結全部為硫代磷酸酯鍵。

【請求項31】如請求項 29 所述之反義寡核苷酸或其醫藥上可容許之鹽或此等的水合物，其中，從 5'翼部區域之 5'側算起第 2 與第 3 核苷間之鍵結、第 3 與第 4 核苷間之鍵結、及第 4 與第 5 核苷間之鍵結為磷酸二酯鍵，及/或從 3'翼部區域之 5'側算起第 1 與第 2 核苷間之鍵結、第 2 與第 3 核苷間之鍵結、及第 3 與第 4 核苷間之鍵結為磷酸二酯鍵，且其他核苷間之鍵結全部為硫代磷酸酯鍵。

【請求項32】如請求項 27 至 31 中任一項所述之反義寡核苷酸或其醫藥上可容許之鹽或此等的水合物，其中翼部區域包含 2'-OMe(2'-O-CH_3)基及/或 2'-O-MOE(2'-O-$CH_2CH_2OCH_3$)基。

【請求項33】一種醫藥組成物，其包含如請求項 1 至 32 中任一項所述之反義寡核苷酸或其醫藥上可容許之鹽或此等的水合物。

【請求項34】如請求項 1 至 32 中任一項所述之反義寡核苷酸或其醫藥上可容許之鹽或此等的水合物、或如請求項 33 所述之醫藥組成物，其係用以治療及/或預防齒狀紅核蒼白球路易氏體萎縮症(Dentatorubral–pallidoluysian atrophy，DRPLA)。

【請求項35】一種齒狀紅核蒼白球路易氏體萎縮症(DRPLA)之治療及/或預防方法，其係包含向對象投予請求項 1 至 32 中任一項所述之反義寡核苷酸或其醫藥上可容許之鹽或此等的水合物、或請求項 33 或 34 所述之醫藥組成物之步驟。