Table 2. 80 ASO screen data.

[Transcript Name] and Seq Name	Sequence	Position	cGAS-100nM	TLR9-500nM	TLR7 - 100nM	TLR8 - 500nM
†[CDKN2B-AS1]132	mU*mU*mA*mA*mA*T*A*A*T*C*T*A*G*T*T*mU*mG*mA*mA*mG	B5	52.20	98.18	25.66	6.43
†[CDKN2B-AS1]1415	mG*mU*mG*mU*mC*C*T*T*C*A*T*G*C*T*T*mU*mG*mG*mA*mU	F3	58.18	98.99	18.05	1.60
[CDKN2B-AS1]1519	mA*mG*mA*mA*mA*G*A*A*G*C*A*A*A*G*A*mU*mU*mC*mA*mA	F5	49.09	68.12	42.99	2.78
#[CDKN2B-AS1]1522	mC*mC*mU*mA*mG*A*A*A*G*A*A*G*C*A*A*mA*mG*mA*mU*mU	C5	60.90	42.44	57.20	4.94
[CDKN2B-AS1]1528	mG*mU*mC*mA*mA*A*C*C*T*A*G*A*A*A*G*mA*mA*mG*mC*mA	E4	68.94	68.13	23.64	1.85
#[CDKN2B-AS1]1773	mG*mA*mU*mU*mA*A*A*A*C*A*G*A*T*T*A*mA*mU*mA*mC*mA	A6	89.36	44.97	21.92	1.48
#[CDKN2B-AS1]1774	mG*mG*mA*mU*mU*A*A*A*A*C*A*G*A*T*T*mA*mA*mU*mA*mC	C6	50.11	27.79	27.16	1.67
[CDKN2B-AS1]1775	mA*mG*mG*mA*mU*T*A*A*A*A*C*A*G*A*T*mU*mA*mA*mU*mA	G4	88.54	63.48	36.28	2.63
[CDKN2B-AS1]2130	mA*mG*mA*mU*mU*A*T*C*T*T*C*T*T*T*T*mA*mA*mU*mU*mU	F6	55.80	78.72	37.10	6.26
[CDKN2B-AS1]2131	mA*mA*mG*mA*mU*T*A*T*C*T*T*C*T*T*T*mU*mA*mA*mU*mU	G5	73.50	59.77	42.09	5.62
[CDKN2B-AS1]2132	mA*mA*mA*mG*mA*T*T*A*T*C*T*T*C*T*T*mU*mU*mA*mA*mU	E5	74.59	63.14	49.28	5.04
[CDKN2B-AS1]2133	mA*mA*mA*mA*mG*A*T*T*A*T*C*T*T*T*C*T*T*mU*mU*mU*mA*mA	B6	57.68	80.95	47.41	4.68
[CDKN2B-AS1]2134	mG*mA*mA*mA*mA*G*A*T*T*A*T*C*T*T*T*C*mU*mU*mU*mU*mA	H5	51.49	61.11	34.44	1.87
[CDKN2B-AS1]2137	**mU*mG*mU*mG*mA*A*A*A*G*A*T*T*A*T*C*mU*mU*mC*mU*mU**	**G6**	**40.72**	**62.16**	**34.51**	**4.97**
[CDKN2B-AS1]2138	mU*mU*mG*mU*mG*A*A*A*A*G*A*T*T*A*T*mC*mU*mU*mC*mU	H6	69.36	61.15	35.02	1.94
#[CDKN2B-AS1]2139	**mC*mU*mU*mG*mU*G*A*A*A*A*G*A*T*T*A*mU*mC*mU*mU*mC**	**E6**	**33.75**	**34.91**	**85.33**	**6.02**
†[CDKN2B-AS1]2196	mG*mG*mU*mG*mG*C*C*A*C*A*G*G*C*A*A*mC*mG*mU*mC*mA	D4	48.58	97.04	39.07	0.98

[CDKN2B-AS1]2198	mA*mA*mG*mG*mU*G*G*C*C*A*C*A*G*G*C*mA*mA*mC*mG*mU	H3	60.48	84.28	57.85	0.78
[CDKN2B-AS1]2218	mA*mG*mG*mC*mC*T*C*C*A*G*T*G*T*C*T*mU*mC*mU*mC*mC	B3	62.85	81.24	44.73	4.66
[CDKN2B-AS1]2219	*mC*mA*mG*mG*mC*C*T*C*C*A*G*T*G*T*C*mU*mU*mC*mU*mC*	*H2*	*99.38*	*66.99*	*54.11*	*3.89*
[CDKN2B-AS1]2223	mG*mU*mC*mC*mC*A*G*G*C*C*T*C*C*A*G*mU*mG*mU*mC*mU	G3	74.22	67.61	19.01	2.17
#[CDKN2B-AS1]2227	**mC*mC*mA*mU*mG*T*C*C*C*A*G*G*C*C*T*mC*mC*mA*mG*mU**	**C4**	**36.34**	**48.79**	**41.39**	**1.46**
†*[CDKN2B-AS1]2230*	*mU*mC*mU*mC*mC*A*T*G*T*C*C*C*A*G*G*mC*mC*mU*mC*mC*	*C3*	*94.78*	*118.93*	*43.45*	*9.17*
[CDKN2B-AS1]2231	mG*mU*mC*mU*mC*C*A*T*G*T*C*C*C*A*G*mG*mC*mC*mU*mC	D2	84.16	77.80	23.75	1.25
†[CDKN2B-AS1]2232	mA*mG*mU*mC*mU*C*C*A*T*G*T*C*C*C*A*mG*mG*mC*mC*mU	B2	88.13	122.20	35.77	2.28
#[CDKN2B-AS1]2233	mC*mA*mG*mU*mC*T*C*C*A*T*G*T*C*C*C*mA*mG*mG*mC*mC	A2	75.92	55.13	47.75	3.81
[CDKN2B-AS1]2234	**mG*mC*mA*mG*mU*C*T*C*C*A*T*G*T*C*C*mC*mA*mG*mG*mC**	**C2**	**10.02**	**90.04**	**20.30**	**2.25**
[CDKN2B-AS1]2235	**mA*mG*mC*mA*mG*T*C*T*C*C*A*T*G*T*C*mC*mC*mA*mG*mG**	**F2**	**28.75**	**73.18**	**25.50**	**4.93**
[CDKN2B-AS1]2236	*mA*mA*mG*mC*mA*G*T*C*T*C*C*A*T*G*T*mC*mC*mC*mA*mG*	*G2*	*107.34*	*69.71*	*35.69*	*2.62*
[CDKN2B-AS1]2237	mA*mA*mA*mG*mC*A*G*T*C*T*C*C*A*T*G*mU*mC*mC*mC*mA	E2	70.95	87.17	27.16	3.38
[CDKN2B-AS1]495	mA*mG*mU*mG*mG*C*A*C*A*T*A*C*C*A*C*mA*mC*mC*mC*mU	B4	59.69	86.07	41.95	4.48
†[CDKN2B-AS1]611	mG*mU*mG*mU*mU*T*T*T*A*A*T*T*T*T*G*mU*mA*mG*mA*mG	H4	66.24	98.50	23.63	1.88
[CDKN2B-AS1]613	mC*mA*mG*mU*mG*T*T*T*T*T*A*A*T*T*T*mU*mG*mU*mA*mG	F4	60.94	92.59	62.68	6.73
[CDKN2B-AS1]626	mA*mU*mU*mU*mC*C*A*C*A*T*G*C*C*C*A*mG*mU*mG*mU*mU	A4	52.58	63.65	32.05	4.09
[CDKN2B-AS1]627	mU*mA*mU*mU*mU*C*C*A*C*A*T*G*C*C*C*mA*mG*mU*mG*mU	E3	80.99	71.20	30.54	3.87

#[CDKN2B-AS1]645	mA*mA*mU*mU*mU*A*A*A*G*C*A*T*G*A*A*mU*mA*mU*mU*mA	D6	67.63	53.26	46.75	5.02
[CDKN2B-AS1]79	*mA*mA*mA*mA*mU*A*A*G*G*G*G*A*A*T*A*mG*mG*mG*mG*mA*	*D5*	*94.10*	*67.44*	*68.45*	*0.71*
[CDKN2B-AS1]80	*mU*mA*mA*mA*mA*T*A*A*G*G*G*G*A*A*T*mA*mG*mG*mG*mG*	*A5*	*110.58*	*64.58*	*40.95*	*1.30*
[CDKN2B-AS1]831	*mA*mU*mA*mU*mC*T*G*C*T*G*C*C*C*A*C*mC*mU*mU*mC*mU*	*A3*	*108.01*	*73.46*	*47.52*	*5.89*
[CDKN2B-AS1]832	mA*mA*mU*mA*mU*C*T*G*C*T*G*C*C*C*A*mC*mC*mU*mU*mC	D3	83.17	70.72	43.66	4.45
[LINC-PINT]101	mU*mC*mC*mC*mA*T*C*C*C*T*T*C*T*G*C*mU*mG*mC*mC*mA	D9	86.62	59.80	43.08	10.88
†*[LINC-PINT]102*	*mG*mU*mC*mC*mC*A*T*C*C*C*T*T*C*T*G*mC*mU*mG*mC*mC*	*H9*	*113.87*	*101.22*	*22.47*	*5.07*
[LINC-PINT]103	**mG*mG*mU*mC*mC*C*A*T*C*C*C*T*T*C*T*mG*mC*mU*mG*mC**	**F9**	**45.23**	**88.75**	**20.75**	**1.87**
#[LINC-PINT]106	mU*mC*mU*mG*mG*T*C*C*C*A*T*C*C*C*T*mU*mC*mU*mG*mC	B10	48.75	56.60	29.42	5.25
†§*[LINC-PINT]108*	*mU*mC*mU*mC*mU*G*G*T*C*C*C*A*T*C*C*mC*mU*mU*mC*mU*	*A9*	*104.65*	*100.51*	*78.25*	*11.42*
§[LINC-PINT]109	mC*mU*mC*mU*mC*T*G*G*T*C*C*C*A*T*C*mC*mC*mU*mU*mC	B9	80.22	89.85	84.97	10.10
[LINC-PINT]110	*mU*mC*mU*mC*mU*C*T*G*G*T*C*C*C*A*T*mC*mC*mC*mU*mU*	*G9*	*92.39*	*74.25*	*43.82*	*11.27*
†[LINC-PINT]111	mU*mU*mC*mU*mC*T*C*T*G*G*T*C*C*C*A*mU*mC*mC*mC*mU	E9	77.41	98.01	26.22	9.51
[LINC-PINT]112	mC*mU*mU*mC*mU*C*T*C*T*G*G*T*C*C*C*mA*mU*mC*mC*mC	B8	82.64	64.35	56.20	9.21
#*[LINC-PINT]113*	*mC*mC*mU*mU*mC*T*C*T*C*T*G*G*T*C*C*mC*mA*mU*mC*mC*	*A8*	*103.79*	*55.47*	*60.90*	*3.51*
[LINC-PINT]114	mC*mC*mC*mU*mU*C*T*C*T*C*T*G*G*T*C*mC*mC*mA*mU*mC	C8	84.38	62.09	49.59	8.12
#[LINC-PINT]115	mA*mC*mC*mC*mU*T*C*T*C*T*C*T*G*G*T*mC*mC*mC*mA*mU	G8	89.81	32.00	43.37	7.57
§*[LINC-PINT]116*	*mC*mA*mC*mC*mC*T*T*C*T*C*T*C*T*G*G*mU*mC*mC*mC*mA*	*D10*	*97.19*	*102.85*	*73.30*	*5.97*

[LINC-PINT]1222	mU*mU*mA*mG*mC*T*C*C*T*T*G*C*C*T*C*mG*mU*mU*mC*mC	C9	63.80	78.17	31.67	8.41
[LINC-PINT]1126	*mG*mU*mC*mU*mC*C*T*C*C*A*C*A*C*C*C*mU*mU*mC*mU*mC*	*H8*	*114.36*	*77.09*	*25.01*	*7.17*
[LINC-PINT]127	mG*mG*mU*mC*mU*C*C*T*C*C*A*C*A*C*C*mC*mU*mU*mC*mU	D8	76.95	77.91	23.66	3.72
†[LINC-PINT]128	**mG*mG*mG*mU*mC*T*C*C*T*C*C*A*C*A*C*mC*mC*mU*mU*mC**	**E8**	**37.83**	**94.51**	**21.47**	**1.23**
[LINC-PINT]1284 KL	*mU*mC*mC*mC*mA*A*C*T*C*T*T*C*T*A*A*mC*mU*mC*mG*mU*	*G7*	*99.64*	*86.73*	*40.79*	*13.35*
#[LINC-PINT]1315 KL	**mG*mC*mA*mA*mG*G*C*A*G*A*G*A*A*A*C*mU*mC*mC*mA*mG**	**H7**	**30.64**	**53.46**	**19.99**	**2.69**
#[LINC-PINT]148 .1	mA*mA*mA*mU*mG*T*C*C*T*G*G*C*C*C*T*mC*mA*mC*mU*mG	A11	66.46	46.72	46.45	1.56
[LINC-PINT]1497 .1	**mG*mA*mU*mG*mG*T*T*C*C*A*G*T*C*C*C*mU*mC*mU*mU*mC**	**E10**	**26.05**	**80.47**	**22.32**	**1.01**
#[LINC-PINT]2673 .1	mU*mU*mG*mG*mC*C*T*G*T*G*G*A*T*G*C*mU*mU*mU*mG*mU	C11	68.35	40.71	21.43	0.94
#[LINC-PINT]2690	mU*mU*mU*mG*mA*A*A*T*T*C*A*G*A*A*G*mA*mU*mU*mU*mG	H11	84.15	54.33	35.07	4.93
[LINC-PINT]2755	*mC*mU*mU*mU*mA*T*A*T*T*A*C*A*A*A*G*mC*mU*mA*mC*mU*	*F11*	*92.54*	*84.43*	*54.83*	*6.37*
[LINC-PINT]283 .1	mU*mG*mA*mU*mG*A*T*G*C*T*T*G*C*A*G*mG*mA*mG*mG*mC	G10	85.85	65.76	25.50	1.57
†[LINC-PINT]2990	mC*mA*mC*mU*mG*T*A*T*T*T*T*A*T*T*A*mC*mA*mG*mA*mA	E11	69.47	117.42	58.13	4.86
#[LINC-PINT]384	mU*mG*mA*mC*mA*A*A*A*C*A*A*T*A*A*T*mA*mA*mC*mA*mG	G11	88.79	53.61	36.68	2.57
[LINC-PINT]412 KL	*mG*mU*mU*mC*mA*G*T*C*A*G*A*T*C*G*C*mU*mG*mG*mG*mA*	*A7*	*93.74*	*77.50*	*17.46*	*1.70*
[LINC-PINT]501 KL	mU*mG*mU*mU*mU*C*C*C*C*G*G*A*G*A*G*mC*mA*mA*mU*mG	B7	57.81	71.47	30.90	2.04
†[LINC-PINT]523 KL	mU*mG*mA*mC*mA*T*T*T*C*G*T*G*G*C*T*mC*mC*mU*mA*mC	C7	79.34	118.29	33.56	4.34
†[LINC-PINT]524 .1	*mA*mU*mG*mA*mC*A*T*T*T*C*G*T*G*G*C*mU*mC*mC*mU*mA*	*H10*	*99.38*	*107.12*	*32.53*	*1.20*

[LINC-PINT]587 KL	**mA*mG*mC*mC*mG*A*A*C*A*G*A*A*G*G*A*mG*mC*mG*mU*mC**	**D7**	**39.92**	**57.46**	**27.70**	**3.73**
[LINC-PINT]727 .1	mG*mU*mC*mC*mG*T*A*C*C*T*C*C*A*C*C*mC*mA*mC*mC*mG	B11	86.09	58.15	22.79	3.70
†[LINC-PINT]83 .1	mC*mA*mA*mG*mC*C*C*C*A*G*C*G*T*T*C*mC*mU*mC*mC*mG	F10	77.10	93.79	45.20	4.44
[LINC-PINT]877 KL	mC*mC*mC*mU*mA*A*T*G*C*T*T*T*C*C*T*mC*mU*mC*mC*mA	E7	89.09	86.47	58.39	8.39
#[LINC-PINT]935 KL	mG*mC*mG*mU*mA*G*T*T*T*C*T*C*T*T*C*mC*mU*mC*mC*mC	F7	50.62	52.04	27.23	4.12
[LINC-PINT]937 .1	mU*mG*mG*mC*mG*T*A*G*T*T*T*C*T*C*T*mU*mC*mC*mU*mC	D11	70.97	79.89	32.81	4.25
†§*[LINC-PINT]94*	*mC*mC*mU*mU*mC*T*G*C*T*G*C*C*A*A*G*mC*mC*mC*mC*mA*	*A10*	*104.33*	*96.69*	*85.57*	*3.71*
[LINC-PINT]98	mC*mA*mU*mC*mC*C*T*T*C*T*G*C*T*G*C*mC*mA*mA*mG*mC	F8	70.60	65.09	54.34	8.23
[LINC-PINT]99	mC*mC*mA*mU*mC*C*C*T*T*C*T*G*C*T*G*mC*mC*mA*mA*mG	C10	85.43	92.72	52.57	5.67

The targeted gene names are provided in brackets (e.g. [CDKN2B-AS1]), followed by the reference position in the target RNA. ASOs were synthesised with the following modifications: UPPERCASE alone for DNA, 'm' indicates 2'OMe base modifications, and * denotes the phosphorothioate backbone. The "Position" column denotes the position of the ASOs in the 96 well plate used in the screen. The concentration of the ASOs used in each screen is indicated. Averaged NF-κB-Luciferase or IP-10 levels from each screen are given relative to ISD70 (cGAS), ODN2006 (TLR9), R848 (TLR7/8 – Alharbi et al., 2020) conditions, as percentages (TLR7/9/cGAS) or fold increases (TLR8). **Bold** denotes the 10 strongest cGAS inhibitors used for motif discovery in Figure 6B. *Italic* denotes the 17 ASOs with less than 10% inhibition of "ISD70 only" condition used for motif discovery in Figure 6E. Underlined denotes the 10 most potent TLR9 inhibitors used for motif discovery in Figure 6C and 6D. The symbol "#" denotes the 16 most potent TLR9 inhibitors and the symbol "†" the 16 weakest inhibitors of TLR9 used in Figure 4G. The symbol "§" denotes the 4 ASOs inhibiting TLR7/9 and cGAS by less than 30%.

Table 2A. Unmodified ASOs described in Table 2.

[Transcript Name] and Seq Name	**Sequence**
Unmodified †[CDKN2B-AS1]132	UUAAATAATCTAGTTUGAAG (SEQ ID NO: 20)
Unmodified †[CDKN2B-AS1]1415	GUGUCCTTCATGCTTUGGAU (SEQ ID NO: 21)

Unmodified [CDKN2B-AS1]1519	AGAAAGAAGCAAAGAUUCAA (SEQ ID NO: 22)
Unmodified #[CDKN2B-AS1]1522	CCUAGAAAGAAGCAAAGAUU (SEQ ID NO: 164)
Unmodified [CDKN2B-AS1]1528	GUCAAACCTAGAAAGAAGCA (SEQ ID NO: 221)
Unmodified #[CDKN2B-AS1]1773	GAUUAAAACAGATTAAUACA (SEQ ID NO: 165)
Unmodified #[CDKN2B-AS1]1774	GGAUUAAAACAGATTAAUAC (SEQ ID NO: 55)
Unmodified [CDKN2B-AS1]1775	AGGAUTAAAACAGATUAAUA (SEQ ID NO: 232)
Unmodified [CDKN2B-AS1]2130	AGAUUATCTTCTTTTAAUUU (SEQ ID NO: 23)
Unmodified [CDKN2B-AS1]2131	AAGAUTATCTTCTTTUAAUU (SEQ ID NO: 234)
Unmodified [CDKN2B-AS1]2132	AAAGATTATCTTCTTUUAAU (SEQ ID NO: 241)
Unmodified [CDKN2B-AS1]2133	AAAAGATTATCTTCTUUUAA (SEQ ID NO: 24)
Unmodified [CDKN2B-AS1]2134	GAAAAGATTATCTTCUUUUA (SEQ ID NO: 25)
Unmodified [CDKN2B-AS1]2137	UGUGAAAAGATTATCUUCUU (SEQ ID NO: 26)
Unmodified [CDKN2B-AS1]2138	UUGUGAAAAGATTATCUUCU (SEQ ID NO: 229)
Unmodified #[CDKN2B-AS1]2139	CUUGUGAAAAGATTAUCUUC (SEQ ID NO: 27)
Unmodified †[CDKN2B-AS1]2196	GGUGGCCACAGGCAACGUCA (SEQ ID NO: 28)
Unmodified [CDKN2B-AS1]2198	AAGGUGGCCACAGGCAACGU (SEQ ID NO: 464)
Unmodified [CDKN2B-AS1]2218	AGGCCTCCAGTGTCTUCUCC (SEQ ID NO: 238)
Unmodified [CDKN2B-AS1]2219	CAGGCCTCCAGTGTCUUCUC (SEQ ID NO: 147)
Unmodified [CDKN2B-AS1]2223	GUCCCAGGCCTCCAGUGUCU (SEQ ID NO: 218)
Unmodified #[CDKN2B-AS1]2227	CCAUGTCCCAGGCCTCCAGU (SEQ ID NO: 29)
Unmodified †[CDKN2B-AS1]2230	UCUCCATGTCCCAGGCCUCC (SEQ ID NO: 216)
Unmodified [CDKN2B-AS1]2231	GUCUCCATGTCCCAGGCCUC (SEQ ID NO: 465)
Unmodified †[CDKN2B-AS1]2232	AGUCUCCATGTCCCAGGCCU (SEQ ID NO: 217)
Unmodified #[CDKN2B-AS1]2233	CAGUCTCCATGTCCCAGGCC (SEQ ID NO: 240)
Unmodified [CDKN2B-AS1]2234	GCAGUCTCCATGTCCCAGGC (SEQ ID NO: 30)
Unmodified [CDKN2B-AS1]2235	AGCAGTCTCCATGTCCCAGG (SEQ ID NO: 31)
Unmodified [CDKN2B-AS1]2236	AAGCAGTCTCCATGTCCCAG (SEQ ID NO: 231)

Unmodified [CDKN2B-AS1]2237	AAAGCAGTCTCCATGUCCCA (SEQ ID NO: 224)
Unmodified [CDKN2B-AS1]495	AGUGGCACATACCACACCCU (SEQ ID NO: 32)
Unmodified †[CDKN2B-AS1]611	GUGUUTTTAATTTTGUAGAG (SEQ ID NO: 220)
Unmodified [CDKN2B-AS1]613	CAGUGTTTTTAATTTUGUAG (SEQ ID NO: 466)
Unmodified [CDKN2B-AS1]626	AUUUCCACATGCCCAGUGUU (SEQ ID NO: 33)
Unmodified [CDKN2B-AS1]627	UAUUUCCACATGCCCAGUGU (SEQ ID NO: 225)
Unmodified #[CDKN2B-AS1]645	AAUUUAAAGCATGAAUAUUA (SEQ ID NO: 166)
Unmodified [CDKN2B-AS1]79	AAAAUAAGGGGAATAGGGGA (SEQ ID NO: 467)
Unmodified [CDKN2B-AS1]80	UAAAATAAGGGGAATAGGGG (SEQ ID NO: 233)
Unmodified [CDKN2B-AS1]831	AUAUCTGCTGCCCACCUUCU (SEQ ID NO: 144)
Unmodified [CDKN2B-AS1]832	AAUAUCTGCTGCCCACCUUC (SEQ ID NO: 236)
Unmodified [LINC-PINT]101	UCCCATCCCTTCTGCUGCCA (SEQ ID NO: 235)
Unmodified †[LINC-PINT]102	GUCCCATCCCTTCTGCUGCC (SEQ ID NO: 145)
Unmodified [LINC-PINT]103	GGUCCCATCCCTTCTGCUGC (SEQ ID NO: 34)
Unmodified #[LINC-PINT]106	UCUGGTCCCATCCCTUCUGC (SEQ ID NO: 35)
Unmodified †§[LINC-PINT]108	UCUCUGGTCCCATCCCUUCU (SEQ ID NO: 143)
Unmodified §[LINC-PINT]109	CUCUCTGGTCCCATCCCUUC (SEQ ID NO: 468)
Unmodified [LINC-PINT]110	UCUCUCTGGTCCCATCCCUU (SEQ ID NO: 237)
Unmodified †[LINC-PINT]111	UUCUCTCTGGTCCCAUCCCU (SEQ ID NO: 213)
Unmodified [LINC-PINT]112	CUUCUCTCTGGTCCCAUCCC (SEQ ID NO: 154)
Unmodified #[LINC-PINT]113	CCUUCTCTCTGGTCCCAUCC (SEQ ID NO: 142)
Unmodified [LINC-PINT]114	CCCUUCTCTCTGGTCCCAUC (SEQ ID NO: 155)
Unmodified #[LINC-PINT]115	ACCCUTCTCTCTGGTCCCAU (SEQ ID NO: 156)
Unmodified §[LINC-PINT]116	CACCCTTCTCTCTGGUCCCA (SEQ ID NO: 141)
Unmodified [LINC-PINT]1222	UUAGCTCCTTGCCTCGUUCC (SEQ ID NO: 226)
Unmodified [LINC-PINT]126	GUCUCCTCCACACCCUUCUC (SEQ ID NO: 146)
Unmodified [LINC-PINT]127	GGUCUCCTCCACACCCUUCU (SEQ ID NO: 222)
Unmodified †[LINC-PINT]128	GGGUCTCCTCCACACCCUUC (SEQ ID NO: 36)
Unmodified [LINC-PINT]1284 KL	UCCCAACTCTTCTAACUCGU (SEQ ID NO: 148)
Unmodified #[LINC-PINT]1315 KL	GCAAGGCAGAGAAACUCCAG (SEQ ID NO: 37)
Unmodified #[LINC-PINT]148 .1	AAAUGTCCTGGCCCTCACUG (SEQ ID NO: 162)
Unmodified [LINC-PINT]1497 .1	GAUGGTTCCAGTCCCUCUUC (SEQ ID NO: 38)
Unmodified #[LINC-PINT]2673 .1	UUGGCCTGTGGATGCUUUGU (SEQ ID NO: 161)
Unmodified #[LINC-PINT]2690	UUUGAAATTCAGAAGAUUUG (SEQ ID NO: 230)
Unmodified [LINC-PINT]2755	CUUUATATTACAAAGCUACU (SEQ ID NO: 469)

Unmodified [LINC-PINT]283 .1	UGAUGATGCTTGCAGGAGGC (SEQ ID NO: 223)
Unmodified †[LINC-PINT]2990	CACUGTATTTTATTACAGAA (SEQ ID NO: 470)
Unmodified #[LINC-PINT]384	UGACAAAACAATAATAACAG (SEQ ID NO: 167)
Unmodified [LINC-PINT]412 KL	GUUCAGTCAGATCGCUGGGA (SEQ ID NO: 214)
Unmodified [LINC-PINT]501 KL	UGUUUCCCCGGAGAGCAAUG (SEQ ID NO: 39)
Unmodified †[LINC-PINT]523 KL	UGACATTTCGTGGCTCCUAC (SEQ ID NO: 228)
Unmodified †[LINC-PINT]524 .1	AUGACATTTCGTGGCUCCUA (SEQ ID NO: 215)
Unmodified [LINC-PINT]587 KL	AGCCGAACAGAAGGAGCGUC (SEQ ID NO: 40)
Unmodified [LINC-PINT]727 .1	GUCCGTACCTCCACCCACCG (SEQ ID NO: 219)
Unmodified †[LINC-PINT]83 .1	CAAGCCCCAGCGTTCCUCCG (SEQ ID NO: 239)
Unmodified [LINC-PINT]877 KL	CCCUAATGCTTTCCTCUCCA (SEQ ID NO: 471)
Unmodified #[LINC-PINT]935 KL	GCGUAGTTTCTCTTCCUCCC (SEQ ID NO: 41)
Unmodified [LINC-PINT]937 .1	UGGCGTAGTTTCTCTUCCUC (SEQ ID NO: 227)
Unmodified †§[LINC-PINT]94	CCUUCTGCTGCCAAGCCCCA (SEQ ID NO: 472)
Unmodified [LINC-PINT]98	CAUCCCTTCTGCTGCCAAGC (SEQ ID NO: 473)
Unmodified [LINC-PINT]99	CCAUCCCTTCTGCTGCCAAG (SEQ ID NO: 474)

Table 3 – Additional oligonucleotide sequences

F5-EGFR-1014-MOE-Mut	/52MOErT/*/i2MOErG/*/i2MOErT/*/i2MOErC/*/i2MOErC/*T*T*G*C*A*C*G*T*G*C*/i2MOErC/*/i2MOErT/*/i2MOErA/*/i2MOErA/*/32MOErG/
B3-CTNN2B-916-MOE-Mut	/52MOErG/*/i2MOErG/*/i2MOErG/*/i2MOErA/*/i2MOErA/*A*C*G*C*T*A*T*G*C*A*/i2MOErA/*/i2MOErG/*/i2MOErG/*/i2MOErT/*/32MOErC/
F10-MB21D1-616-MOE-Mut	/52MOErG/*/i2MOErG/*/i2MOErA/*/i2MOErC/*/i2MOErC/*C*T*C*G*A*G*G*C*C*C*/i2MOErC/*/i2MOErA/*/i2MOErG/*/i2MOErG/*/32MOErC/
A1-CTNN2B-311-LNA-Mut	+C*+G*+C*T*T*T*T*C*T*C*T*C*C*+G*+G*+T
D2-CTNN2B-1642-LNA-Mut	+G*+C*+C*C*G*C*T*C*A*G*T*G*A*+T*+G*+T
ShortMut1:	mG*mG*mU*mA*mU
ShortMut1v3:	mC*mG*mU*mU*mU
Short660v1:	mC*mU*mU*mC*mG

HPRT-2OMe-847	mA*mU*mA* mG*mG*A* C*T*C* C*A*G* A*T*G* mU*mU*mU* mC*mC
HPRT-2OMe-847-Mut1	mG*mG*mU* mA*mU*mA* mG*mG*A* C*T*C* C*A*G* A*T*G* mU*mU*mU* mC*mC

Table 3A – Unmodified oligonucleotide sequences described in Table 3.

Unmodified F5-EGFR-1014-MOE-Mut	TGTCCTTGCACGTGCCTAAG (SEQ ID NO: 475)
Unmodified B3-CTNN2B-916-MOE-Mut	GGGAAACGCTATGCAAGGTC (SEQ ID NO: 476)
Unmodified F10-MB21D1-616-MOE-Mut	GGACCCTCGAGGCCCCAGGC (SEQ ID NO: 477)
Unmodified A1-CTNN2B-311-LNA-Mut	CGCTTTTCTCTCCGGT (SEQ ID NO: 117)
Unmodified D2-CTNN2B-1642-LNA-Mut	GCCCGCTCAGTGATGT (SEQ ID NO: 478)
Unmodified ShortMut1:	GGUAU (SEQ ID NO: 56)
Unmodified ShortMut1v3:	CGUUU (SEQ ID NO: 349)
Unmodified Short660v1:	CUUCG (SEQ ID NO: 479)
Unmodified HPRT-2OMe-847	AUAGGACTCCAGATGUUUCC (SEQ ID NO: 480)
Unmodified HPRT-2OMe-847-Mut1	GGUAUAGGACTCCAGATGUUUCC (SEQ ID NO: 118)

5

Table 4 – LNA modified oligonucleotide data

Well	Name	Sequence	TLR8 500nM	TLR8 100nM	TLR7 500nM	TLR7 100nM	TLR9 500nM	TLR9 100nM	cGAS 100nM
A1	CTNN2B-311 LNA KL	+C*+G*+C*T*T*T*T*C*T*G*T*C*T*+G*+G*+T	2.896	0.920	0.142	0.393	0.178	0.827	0.475
A10	HPRT LNA-665 V1	+A*+C*+A*C*T*T*C*G*T*G*G*G*G*+T*+C*+C	1.029	0.422	0.086	0.548	0.000	0.240	0.516
A11	HPRT LNA-332 V1	+T*+G*+A*T*G*G*C*C*T*C*C*C*A*+T*+C*+T	0.263	0.374	0.153	0.657	0.153	0.770	0.650
A12	HPRT LNA-330 V1	+A*+T*+G*G*C*C*T*C*C*C*A*T*C*+T*+C*+C	1.356	0.369	0.117	0.550	0.244	0.511	0.475
A2	CTNN2B-1575 LNA V1	+C*+C*+A*C*T*T*G*G*C*A*G*A*C*+C*+A*+T	1.213	0.684	0.470	0.765	0.111	1.112	0.532
A3	EGFR-2790 LNA KL	+G*+T*+G*A*T*C*T*T*G*A*C*A*T*+G*+C*+T	1.806	0.583	0.060	0.438	0.181	1.001	0.661
A4	EGFR-1225 LNA V1	+A*+G*+G*C*C*C*T*T*C*G*C*A*C*+T*+T*+C	0.967	0.507	0.164	0.737	0.211	0.576	0.629
A5	CAMSAP1-1635 LNA KL	+A*+C*+C*A*C*G*T*C*T*G*C*T*C*+T*+A*+A	4.259	0.933	0.532	1.078	0.162	0.842	0.638
A6	CAMSAP1-4915 LNA V1	+G*+C*+A*C*A*C*T*T*C*G*T*A*C*+C*+C*+A	1.091	0.319	0.221	0.657	0.147	0.683	0.383
A7	MB21D1-689 LNA KL	+A*+A*+C*C*C*C*T*T*T*C*A*C*C*+A*+T*+C	8.654	1.871	0.426	0.771	0.076	0.586	0.621
A8	MB21D1-525 LNA V1	+G*+A*+G*G*T*C*T*T*G*G*C*T*T*+C*+G*+T	0.642	0.574	0.067	0.793	0.224	0.897	0.508
A9	HPRT LNA-388 KL	+C*+C*+A*G*C*A*G*G*T*C*A*G*C*+A*+A*+A	1.499	0.412	0.942	1.101	0.149	0.736	0.552
B1	CTNN2B-916 LNA KL	+G*+A*+A*A*G*G*T*T*A*T*G*C*A*+A*+G*+G	4.110	1.156	0.101	0.166	0.606	0.748	0.473
B10	HPRT LNA-333 V1	+G*+T*+G*A*T*G*G*C*C*T*C*C*C*+A*+T*+C	1.112	0.517	0.139	0.665	0.694	0.890	0.724
B11	HPRT LNA-335 V1	+A*+T*+G*T*G*A*T*G*G*C*C*T*C*+C*+C*+A	1.840	0.637	0.128	0.499	0.451	0.776	0.606
B12	HPRT LNA-660 V1	+T*+C*+G*T*G*G*G*G*T*C*C*T*T*+T*+T*+C	2.966	0.778	0.318	0.540	0.462	0.461	0.729

B2	CTNN2B-808 LNA V1	+T*+G*+T*C*T*G*G*A*A*G*C*T*T*+C*+C*+T	0.871	0.600	0.278	0.495	0.648	1.320	0.617
B3	EGFR-3652 LNA KL	+A*+G*+T*G*T*T*G*A*G*A*T*A*C*+T*+C*+G	0.599	0.427	0.115	0.559	0.540	0.982	0.692
B4	EGFR-1015 LNA V1	+G*+T*+C*C*T*T*G*C*A*C*G*T*G*+G*+C*+T	0.936	0.570	0.251	0.471	0.722	1.310	0.645
B5	CAMSAP1-1739 LNA KL	+T*+A*+C*T*T*T*C*C*G*A*G*G*T*+G*+T*+C	1.585	0.417	0.451	0.738	0.356	0.915	0.638
B6	CAMSAP1-5594 LNA V1	+G*+G*+C*T*C*G*G*C*T*T*G*C*C*+T*+A*+C	0.706	0.374	0.186	0.569	0.350	0.714	0.761
B7	MB21D1-719 LNA KL	+G*+C*+A*C*T*T*C*A*G*T*C*T*G*+A*+G*+C	0.864	0.495	0.168	0.713	0.144	0.673	0.797
B8	MB21D1-523 LNA V1	+G*+G*+T*C*T*T*G*G*C*T*T*C*G*+T*+G*+G	1.386	0.616	0.042	0.481	0.417	0.658	0.648
B9	HPRT LNA-475 KL	+G*+G*+T*C*A*T*T*A*C*A*A*T*A*+G*+C*+T	1.381	0.500	0.049	0.580	0.604	0.438	0.751
C1	CTNN2B-1294 LNA KL	+G*+A*+T*A*G*C*A*C*C*T*T*C*A*+G*+C*+A	2.863	0.821	0.049	0.434	0.560	0.804	0.436
C10	HPRT LNA-667 V1	+C*+A*+A*C*A*C*T*T*C*G*T*G*G*+G*+G*+T	0.690	0.591	0.476	0.663	0.395	0.733	0.675
C11	HPRT LNA-334 V1	+T*+G*+T*G*A*T*G*G*C*C*T*C*C*+C*+A*+T	1.596	0.582	0.090	0.315	0.431	0.818	0.557
C12	HPRT LNA-669 V1	+T*+C*+C*A*A*C*A*C*T*T*C*G*T*+G*+G*+G	0.491	0.413	0.249	0.318	0.473	0.623	0.539
C2	CTNN2B-2545 LNA V1	+C*+C*+A*T*C*C*A*T*G*A*G*G*T*+C*+C*+T	1.169	0.675	0.644	0.992	0.476	1.383	0.533
C3	EGFR-3908 LNA KL	+G*+T*+A*T*C*G*A*A*A*G*A*G*T*+C*+T*+G	1.781	0.637	0.113	0.562	0.647	1.429	0.609
C4	EGFR-2874 LNA V1	+G*+C*+C*A*T*C*C*A*C*T*T*G*A*+T*+A*+G	0.681	0.440	0.123	0.671	0.589	0.772	0.688
C5	CAMSAP1-4295 LNA KL	+G*+G*+T*T*A*C*G*G*C*T*C*A*G*+T*+A*+T	1.848	0.804	0.140	0.438	0.400	0.943	0.661
C6	CAMSAP1-4916 LNA V1	+T*+G*+C*A*C*A*C*T*T*C*G*T*A*+C*+C*+C	0.370	0.411	0.299	0.806	0.244	0.283	0.572
C7	MB21D1-1181 LNA KL	+T*+C*+G*T*A*G*T*T*G*C*T*T*C*+C*+T*+A	1.583	0.557	0.198	0.380	0.224	0.987	0.610

C8	MB21D1-522 LNA V1	+G*+T*+C*T*T*G*G*C*T*T*C*G*T*+G*+G*+A	2.137	0.678	0.056	0.652	0.392	0.745	0.620
C9	HPRT LNA-489 KL	+G*+T*+C*C*C*C*T*G*T*T*G*A*C*+T*+G*+G	0.304	0.335	0.123	0.557	0.326	0.387	0.606
D1	CTNN2B-2341 LNA KL	+C*+C*+A*A*G*A*T*C*A*G*C*A*G*+T*+C*+T	2.920	1.015	0.697	0.882	0.669	1.424	0.356
D10	HPRT LNA-329 V1	+T*+G*+G*C*C*T*C*C*C*A*T*C*T*+C*+C*+T	1.127	0.495	0.217	0.877	0.277	0.743	0.494
D11	HPRT LNA-661 V1	+T*+T*+C*G*T*G*G*G*G*T*C*C*T*+T*+T*+T	3.144	0.621	0.178	0.487	0.523	0.963	0.520
D12	HPRT LNA-292 V1	+G*+T*+T*C*A*G*T*C*C*T*G*T*C*+C*+A*+T	4.129	1.069	0.114	0.456	0.382	1.081	0.563
D2	CTNN2B-1642 LNA V1	+G*+C*+A*G*G*C*T*C*A*G*T*G*A*+T*+G*+T	1.440	0.638	0.189	0.676	0.228	1.036	0.458
D3	EGFR-4705 LNA KL	+G*+G*+C*T*G*G*A*A*T*C*C*G*A*+G*+T*+T	0.577	0.562	0.041	0.417	0.492	1.051	0.592
D4	EGFR-3267 LNA V1	+G*+C*+A*T*C*C*A*C*C*A*C*G*T*+C*+G*+T	0.738	0.607	0.085	0.555	0.375	0.556	0.602
D5	CAMSAP1-4697 LNA KL	+T*+T*+T*T*G*G*C*T*G*G*G*A*T*+C*+A*+A	1.412	0.542	0.305	0.564	0.169	0.985	0.590
D6	CAMSAP1-2584 LNA V1	+G*+C*+C*A*T*G*C*T*G*G*C*T*C*+G*+G*+A	0.363	0.446	0.175	0.638	0.147	0.879	0.599
D7	MB21D1-1248 LNA KL	+G*+C*+C*A*T*G*T*T*T*C*T*T*C*+T*+T*+G	0.431	0.430	0.021	0.816	0.070	0.163	0.639
D8	MB21D1-168 LNA V1	+C*+G*+G*C*C*T*C*G*G*A*A*G*C*+T*+C*+T	0.219	0.402	0.139	0.594	0.116	0.218	0.617
D9	HPRT LNA-551 KL	+T*+C*+C*A*C*A*A*T*C*A*A*G*A*+C*+A*+T	0.893	0.474	0.533	0.863	0.308	0.851	0.601
E1	CTNN2B-3648 LNA KL	+C*+T*+T*G*A*A*G*C*A*T*C*G*T*+A*+T*+C	3.889	0.960	0.044	0.363	0.483	0.899	0.373
E10	HPRT LNA-666 V1	+A*+A*+C*A*C*T*T*C*G*T*G*G*G*+G*+T*+C	0.882	0.496	0.445	0.899	0.475	1.104	0.598
E11	HPRT LNA-662 V1	+C*+T*+T*C*G*T*G*G*G*G*T*C*C*+T*+T*+T	4.366	1.097	0.233	0.685	0.240	0.557	0.556
E12	HPRT LNA pos cont	+A*+G*+G*A*C*T*C*C*A*G*A*T*G*+T*+T*+T	1.034	0.278	0.293	0.437	0.511	0.816	0.632

E2	CTNN2B-2516 LNA V1	+A*+T*+C*T*G*G*C*A*G*C*C*C*A*+T*+C*+A	2.628	0.808	0.279	0.663	0.603	1.248	0.502
E3	EGFR-4885 LNA KL	+A*+G*+A*T*T*T*C*A*G*A*G*C*A*+G*+C*+T	0.770	0.401	0.021	0.438	0.438	0.848	0.625
E4	EGFR-1013 LNA V1	+C*+C*+T*T*G*C*A*C*G*T*G*G*C*+T*+T*+C	2.414	1.315	0.281	0.617	0.519	0.814	0.559
E5	CAMSAP1-6273 LNA KL	+A*+A*+A*G*G*A*C*T*G*A*G*G*A*+A*+A*+G	2.663	0.882	0.267	0.513	0.185	0.780	0.675
E6	CAMSAP1-2709 LNA V1	+T*+T*+C*A*G*G*C*G*C*T*G*C*C*+T*+T*+G	0.764	0.479	0.181	0.642	0.494	1.202	0.709
E7	MB21D1-1483 LNA KL	+T*+G*+A*C*T*G*T*C*T*T*G*A*G*+G*+G*+T	3.210	0.973	0.150	0.802	0.290	1.245	0.747
E8	MB21D1-520 LNA V1	+C*+T*+T*G*G*C*T*T*C*G*T*G*G*+A*+G*+C	0.594	0.458	0.098	0.806	0.371	0.596	0.666
E9	HPRT LNA-692 KL	+A*+A*+T*C*C*A*A*C*A*A*A*G*T*+C*+T*+G	1.900	0.591	0.433	0.727	0.529	1.050	0.649
F1	CTNN2B-809 LNA V1	+G*+T*+G*T*C*T*G*G*A*A*G*C*T*+T*+C*+C	2.057	0.923	0.067	0.355	0.613	0.493	0.482
F10	HPRT LNA-664 V1	+C*+A*+C*T*T*C*G*T*G*G*G*G*T*+C*+C*+T	1.446	0.425	0.240	0.868	0.074	0.215	0.562
F11	HPRT LNA-331 V1	+G*+A*+T*G*G*C*C*T*C*C*C*A*T*+C*+T*+C	0.186	0.278	0.119	0.558	0.476	1.033	0.632
F12	NC1 LNA PS 3-10-3	+C*+G*+T*A*T*T*A*T*A*G*C*C*G*+A*+T*+T	0.716	0.396	0.226	0.754	0.558	0.933	0.443
F2	CTNN2B-2136 LNA V1	+C*+T*+G*C*A*G*C*T*T*C*C*T*T*+G*+T*+C	0.936	0.478	0.053	0.467	0.263	0.358	0.613
F3	EGFR-1014 LNA V1	+T*+C*+C*T*T*G*C*A*C*G*T*G*G*+C*+T*+T	0.601	0.491	0.482	0.812	1.027	1.152	0.591
F4	EGFR-1016 LNA V1	+T*+G*+T*C*C*T*T*G*C*A*C*G*T*+G*+G*+C	1.158	0.636	0.199	0.502	0.853	1.020	0.678
F5	CAMSAP1-2112 LNA V1	+T*+C*+T*T*C*A*T*C*G*G*C*C*C*+T*+G*+C	1.393	0.595	0.511	0.820	0.445	0.921	0.548
F6	CAMSAP1-2456 LNA V1	+G*+T*+C*T*C*T*G*G*A*G*C*T*T*+C*+C*+T	2.402	0.764	0.084	0.477	0.272	0.935	0.627
F7	MB21D1-521 LNA V1	+T*+C*+T*T*G*G*C*T*T*C*G*T*G*+G*+A*+G	0.197	0.541	0.288	1.033	0.595	1.251	0.693

F8	MB21D1-616 LNA V1	+A*+G*+C*T*T*C*G*A*G*G*C*C*C*+C*+A*+G	0.865	0.331	0.111	0.554	0.085	0.114	0.648
F9	HPRT LNA-732 KL	+G*+T*+C*A*A*G*G*G*C*A*T*A*T*+C*+C*+T	2.301	0.543	0.142	0.650	0.387	0.844	0.636
G1	CTNN2B-2446 LNA V1	+T*+C*+C*A*T*A*C*C*C*A*A*G*G*+C*+A*+T	1.334	0.595	0.494	1.056	0.951	1.075	0.589
G10	HPRT LNA-668 V1	+C*+C*+A*A*C*A*C*T*T*C*G*T*G*+G*+G*+G	0.835	0.535	0.446	0.808	0.610	1.065	0.842
G11	HPRT LNA-294 V1	+A*+C*+G*T*T*C*A*G*T*C*C*T*G*+T*+C*+C	0.493	0.356	0.136	0.601	0.198	0.427	0.880
G12	NC5 LNA PS 3-10-3	+G*+A*+C*T*A*T*A*C*G*C*G*C*A*+A*+T*+A	3.376	0.777	0.098	0.282	0.403	0.784	0.991
G2	CTNN2B-2479 LNA V1	+T*+G*+G*T*G*G*C*C*A*C*C*C*A*+T*+C*+T	0.604	0.464	0.393	0.957	1.117	1.136	0.830
G3	EGFR-3266 LNA V1	+C*+A*+T*C*C*A*C*C*A*C*G*T*C*+G*+T*+C	2.417	0.778	0.353	0.741	0.620	0.722	0.902
G4	EGFR-727 LNA V1	+G*+T*+C*C*C*G*C*C*A*C*T*G*G*+A*+T*+G	0.745	0.585	0.311	0.843	1.172	0.871	0.908
G5	CAMSAP1-2113 LNA V1	+G*+T*+C*T*T*C*A*T*C*G*G*C*C*+C*+T*+G	2.086	0.664	0.119	0.641	0.617	0.797	0.809
G6	CAMSAP1-2906 LNA V1	+C*+C*+A*C*A*T*C*C*T*G*T*G*G*+C*+T*+C	0.232	0.291	0.363	0.789	0.337	0.338	0.999
G7	MB21D1-524 LNA V1	+A*+G*+G*T*C*T*T*G*G*C*T*T*C*+G*+T*+G	1.953	0.596	0.050	0.457	0.383	0.975	0.947
G8	MB21D1-697 LNA V1	+T*+G*+G*T*C*C*A*C*A*A*C*C*C*+C*+T*+T	1.454	0.559	0.545	1.008	0.587	1.018	0.935
G9	HPRT LNA-1027 KL	+T*+C*+C*G*C*C*C*A*A*A*G*G*G*+A*+A*+C	0.725	0.541	0.543	0.860	0.599	0.876	0.860
H1	CTNN2B-1576 LNA V1	+C*+C*+C*A*C*T*T*G*G*C*A*G*A*+C*+C*+A	1.865	0.899	0.639	1.024	0.656	0.381	
H10	HPRT LNA-663 V1	+A*+C*+T*T*C*G*T*G*G*G*G*T*C*+C*+T*+T	3.672	0.820	0.736	0.804	0.377	0.377	0.937
H11	HPRT LNA-326 V1	+C*+C*+T*C*C*C*A*T*C*T*C*C*T*+T*+C*+A	6.759	1.469	0.843	0.758	0.727	1.010	
H3	EGFR-2859 LNA V1	+G*+G*+C*A*C*T*T*T*G*C*C*T*C*+C*+T*+T	0.862	0.652	0.668	0.774	0.788	1.092	

H5	CAMSAP1-1850 LNA V1	+T*+G*+C*T*C*C*T*C*G*G*T*C*T*+C*+C*+C	4.771	1.097	0.595	0.751	0.535	0.548	
H7	MB21D1-526 LNA V1	+G*+G*+A*G*G*T*C*T*T*G*G*C*T*+T*+C*+G	0.882	0.575	0.119	0.503	0.674	0.912	1.061
H9	HPRT LNA-1353 KL	+T*+G*+A*C*A*A*A*G*A*T*T*C*A*+C*+T*+G	1.756	0.633	0.430	1.040	0.574	0.819	0.887

Table 4A. Unmodified oligonucleotide sequences described in Table 4.

Name	Sequence
Unmodified CTNN2B-311 LNA KL	CGCTTTTCTGTCTGGT (SEQ ID NO: 105)
Unmodified HPRT LNA-665 V1	ACACTTCGTGGGGTCC (SEQ ID NO: 110)
Unmodified HPRT LNA-332 V1	TGATGGCCTCCCATCT (SEQ ID NO: 481)
Unmodified HPRT LNA-330 V1	ATGGCCTCCCATCTCC (SEQ ID NO: 104)
Unmodified CTNN2B-1575 LNA V1	CCACTTGGCAGACCAT (SEQ ID NO: 112)
Unmodified EGFR-2790 LNA KL	GTGATCTTGACATGCT (SEQ ID NO: 312)
Unmodified EGFR-1225 LNA V1	AGGCCCTTCGCACTTC (SEQ ID NO: 201)
Unmodified CAMSAP1-1635 LNA KL	ACCACGTCTGCTCTAA (SEQ ID NO: 482)
Unmodified CAMSAP1-4915 LNA V1	GCACACTTCGTACCCA (SEQ ID NO: 99)
Unmodified MB21D1-689 LNA KL	AACCCCTTTCACCATC (SEQ ID NO: 483)
Unmodified MB21D1-525 LNA V1	GAGGTCTTGGCTTCGT (SEQ ID NO: 109)
Unmodified HPRT LNA-388 KL	CCAGCAGGTCAGCAAA (SEQ ID NO: 116)
Unmodified CTNN2B-916 LNA KL	GAAAGGTTATGCAAGG (SEQ ID NO: 103)
Unmodified HPRT LNA-333 V1	GTGATGGCCTCCCATC (SEQ ID NO: 484)
Unmodified HPRT LNA-335 V1	ATGTGATGGCCTCCCA (SEQ ID NO: 485)
Unmodified HPRT LNA-660 V1	TCGTGGGGTCCTTTTC (SEQ ID NO: 197)
Unmodified CTNN2B-808 LNA V1	TGTCTGGAAGCTTCCT (SEQ ID NO: 486)
Unmodified EGFR-3652 LNA KL	AGTGTTGAGATACTCG (SEQ ID NO: 487)
Unmodified EGFR-1015 LNA V1	GTCCTTGCACGTGGCT (SEQ ID NO: 317)
Unmodified CAMSAP1-1739 LNA KL	TACTTTCCGAGGTGTC (SEQ ID NO: 488)
Unmodified CAMSAP1-5594 LNA V1	GGCTCGGCTTGCCTAC (SEQ ID NO: 489)
Unmodified MB21D1-719 LNA KL	GCACTTCAGTCTGAGC (SEQ ID NO: 490)
Unmodified MB21D1-523 LNA V1	GGTCTTGGCTTCGTGG (SEQ ID NO: 319)
Unmodified HPRT LNA-475 KL	GGTCATTACAATAGCT (SEQ ID NO: 196)
Unmodified CTNN2B-1294 LNA KL	GATAGCACCTTCAGCA (SEQ ID NO: 100)
Unmodified HPRT LNA-667 V1	CAACACTTCGTGGGGT (SEQ ID NO: 491)
Unmodified HPRT LNA-334 V1	TGTGATGGCCTCCCAT (SEQ ID NO: 308)
Unmodified HPRT LNA-669 V1	TCCAACACTTCGTGGG (SEQ ID NO: 114)

Unmodified CTNN2B-2545 LNA V1	CCATCCATGAGGTCCT (SEQ ID NO: 113)
Unmodified EGFR-3908 LNA KL	GTATCGAAAGAGTCTG (SEQ ID NO: 492)
Unmodified EGFR-2874 LNA V1	GCCATCCACTTGATAG (SEQ ID NO: 493)
Unmodified CAMSAP1-4295 LNA KL	GGTTACGGCTCAGTAT (SEQ ID NO: 314)
Unmodified CAMSAP1-4916 LNA V1	TGCACACTTCGTACCC (SEQ ID NO: 189)
Unmodified MB21D1-1181 LNA KL	TCGTAGTTGCTTCCTA (SEQ ID NO: 309)
Unmodified MB21D1-522 LNA V1	GTCTTGGCTTCGTGGA (SEQ ID NO: 494)
Unmodified HPRT LNA-489 KL	GTCCCCTGTTGACTGG (SEQ ID NO: 194)
Unmodified CTNN2B-2341 LNA KL	CCAAGATCAGCAGTCT (SEQ ID NO: 97)
Unmodified HPRT LNA-329 V1	TGGCCTCCCATCTCCT (SEQ ID NO: 107)
Unmodified HPRT LNA-661 V1	TTCGTGGGGTCCTTTT (SEQ ID NO: 111)
Unmodified HPRT LNA-292 V1	GTTCAGTCCTGTCCAT (SEQ ID NO: 315)
Unmodified CTNN2B-1642 LNA V1	GCAGGCTCAGTGATGT (SEQ ID NO: 102)
Unmodified EGFR-4705 LNA KL	GGCTGGAATCCGAGTT (SEQ ID NO: 310)
Unmodified EGFR-3267 LNA V1	GCATCCACCACGTCGT (SEQ ID NO: 199)
Unmodified CAMSAP1-4697 LNA KL	TTTTGGCTGGGATCAA (SEQ ID NO: 495)
Unmodified CAMSAP1-2584 LNA V1	GCCATGCTGGCTCGGA (SEQ ID NO: 496)
Unmodified MB21D1-1248 LNA KL	GCCATGTTTCTTCTTG (SEQ ID NO: 186)
Unmodified MB21D1-168 LNA V1	CGGCCTCGGAAGCTCT (SEQ ID NO: 188)
Unmodified HPRT LNA-551 KL	TCCACAATCAAGACAT (SEQ ID NO: 497)
Unmodified CTNN2B-3648 LNA KL	CTTGAAGCATCGTATC (SEQ ID NO: 98)
Unmodified HPRT LNA-666 V1	AACACTTCGTGGGGTC (SEQ ID NO: 498)
Unmodified HPRT LNA-662 V1	CTTCGTGGGGTCCTTT (SEQ ID NO: 200)
Unmodified HPRT LNA pos cont	AGGACTCCAGATGTTT (SEQ ID NO: 311)
Unmodified CTNN2B-2516 LNA V1	ATCTGGCAGCCCATCA (SEQ ID NO: 108)
Unmodified EGFR-4885 LNA KL	AGATTTCAGAGCAGCT (SEQ ID NO: 313)
Unmodified EGFR-1013 LNA V1	CCTTGCACGTGGCTTC (SEQ ID NO: 499)
Unmodified CAMSAP1-6273 LNA KL	AAAGGACTGAGGAAAG (SEQ ID NO: 500)
Unmodified CAMSAP1-2709 LNA V1	TTCAGGCGCTGCCTTG (SEQ ID NO: 501)
Unmodified MB21D1-1483 LNA KL	TGACTGTCTTGAGGGT (SEQ ID NO: 502)
Unmodified MB21D1-520 LNA V1	CTTGGCTTCGTGGAGC (SEQ ID NO: 503)
Unmodified HPRT LNA-692 KL	AATCCAACAAAGTCTG (SEQ ID NO: 504)
Unmodified CTNN2B-809 LNA V1	GTGTCTGGAAGCTTCC (SEQ ID NO: 106)
Unmodified HPRT LNA-664 V1	CACTTCGTGGGGTCCT (SEQ ID NO: 187)
Unmodified HPRT LNA-331 V1	GATGGCCTCCCATCTC (SEQ ID NO: 505)
Unmodified NC1 LNA PS 3-10-3	CGTATTATAGCCGATT (SEQ ID NO: 101)
Unmodified CTNN2B-2136 LNA V1	CTGCAGCTTCCTTGTC (SEQ ID NO: 191)

Unmodified EGFR-1014 LNA V1	TCCTTGCACGTGGCTT (SEQ ID NO: 506)
Unmodified EGFR-1016 LNA V1	TGTCCTTGCACGTGGC (SEQ ID NO: 507)
Unmodified CAMSAP1-2112 LNA V1	TCTTCATCGGCCCTGC (SEQ ID NO: 115)
Unmodified CAMSAP1-2456 LNA V1	GTCTCTGGAGCTTCCT (SEQ ID NO: 318)
Unmodified MB21D1-521 LNA V1	TCTTGGCTTCGTGGAG (SEQ ID NO: 508)
Unmodified MB21D1-616 LNA V1	AGCTTCGAGGCCCCAG (SEQ ID NO: 185)
Unmodified HPRT LNA-732 KL	GTCAAGGGCATATCCT (SEQ ID NO: 509)
Unmodified CTNN2B-2446 LNA V1	TCCATACCCAAGGCAT (SEQ ID NO: 510)
Unmodified HPRT LNA-668 V1	CCAACACTTCGTGGGG (SEQ ID NO: 511)
Unmodified HPRT LNA-294 V1	ACGTTCAGTCCTGTCC (SEQ ID NO: 195)
Unmodified NC5 LNA PS 3-10-3	GACTATACGCGCAATA (SEQ ID NO: 307)
Unmodified CTNN2B-2479 LNA V1	TGGTGGCCACCCATCT (SEQ ID NO: 512)
Unmodified EGFR-3266 LNA V1	CATCCACCACGTCGTC (SEQ ID NO: 513)
Unmodified EGFR-727 LNA V1	GTCCCGCCACTGGATG (SEQ ID NO: 514)
Unmodified CAMSAP1-2113 LNA V1	GTCTTCATCGGCCCTG (SEQ ID NO: 515)
Unmodified CAMSAP1-2906 LNA V1	CCACATCCTGTGGCTC (SEQ ID NO: 190)
Unmodified MB21D1-524 LNA V1	AGGTCTTGGCTTCGTG (SEQ ID NO: 316)
Unmodified MB21D1-697 LNA V1	TGGTCCACAACCCCTT (SEQ ID NO: 516)
Unmodified HPRT LNA-1027 KL	TCCGCCCAAAGGGAAC (SEQ ID NO: 517)
Unmodified CTNN2B-1576 LNA V1	CCCACTTGGCAGACCA (SEQ ID NO: 193)
Unmodified HPRT LNA-663 V1	ACTTCGTGGGGTCCTT (SEQ ID NO: 192)
Unmodified HPRT LNA-326 V1	CCTCCCATCTCCTTCA (SEQ ID NO: 518)
Unmodified EGFR-2859 LNA V1	GGCACTTTGCCTCCTT (SEQ ID NO: 519)
Unmodified CAMSAP1-1850 LNA V1	TGCTCCTCGGTCTCCC (SEQ ID NO: 198)
Unmodified MB21D1-526 LNA V1	GGAGGTCTTGGCTTCG (SEQ ID NO: 520)
Unmodified HPRT LNA-1353 KL	TGACAAAGATTCACTG (SEQ ID NO: 521)

Table 5 – MOE modified oligonucleotide data

Well	ASO	Sequence	TLR8 500nM	TLR8 100nM	TLR7 500nM	TLR7 100nM	TLR9 500nM	TLR9 100nM	cGAS 100nM
A1	HPRT-489 MOE	/52MOErA/*/i2MOErT/*/i2MOErG/*/i2MOErT/*/i2MOErC/*C*C*C*T*G*T*T*G*A*C*/i2MOErT/*/i2MOErG/*/i2MOErG/*/i2MOErT/*/32MOErC/	2.118	1.752	0.224	0.426	0.953	0.968	0.574
A10	MB21D1-525 MOE	/52MOErC/*/i2MOErG/*/i2MOErG/*/i2MOErA/*/i2MOErG/*G*T*C*T*T*G*G*C*T*T*/i2MOErC/*/i2MOErG/*/i2MOErT/*/i2MOErG/*/32MOErG/	3.257	2.197	0.138	0.505	0.556	0.938	0.111
A2	HPRT-666 MOE	/52MOErC/*/i2MOErC/*/i2MOErA/*/i2MOErA/*/i2MOErC/*A*C*T*T*C*G*T*G*G*G*/i2MOErG/*/i2MOErT/*/i2MOErC/*/i2MOErC/*/32MOErT/	1.185	1.223	0.334	0.856	0.600	0.612	0.557
A3	CTNN2B-311 MOE	/52MOErG/*/i2MOErC/*/i2MOErC/*/i2MOErG/*/i2MOErC/*T*T*T*T*C*T*G*T*C*T*/i2MOErG/*/i2MOErG/*/i2MOErT/*/i2MOErT/*/32MOErC/	0.369	0.968	0.268	0.567	1.018	0.684	0.401
A4	CTNN2B-1575 MOE	/52MOErA/*/i2MOErC/*/i2MOErC/*/i2MOErC/*/i2MOErA/*C*T*T*G*G*C*A*G*A*C*/i2MOErC/*/i2MOErA/*/i2MOErT/*/i2MOErC/*/32MOErA/	3.985	2.822	0.336	0.473	0.556	0.725	0.571
A5	EGFR-2790 MOE	/52MOErC/*/i2MOErT/*/i2MOErG/*/i2MOErT/*/i2MOErG/*A*T*C*T*T*G*A*C*A*T*/i2MOErG/*/i2MOErC/*/i2MOErT/*/i2MOErG/*/32MOErC/	1.387	1.308	0.206	0.449	0.298	0.506	0.180
A6	EGFR-1225 MOE	/52MOErC/*/i2MOErA/*/i2MOErA/*/i2MOErG/*/i2MOErG/*C*C*C*T*T*C*G*C*A*C*/i2MOErT/*/i2MOErT/*/i2MOErC/*/i2MOErT/*/32MOErT/	1.236	1.115	0.336	0.587	0.712	0.624	0.490
A7	CAMSAP1-1635 MOE	/52MOErG/*/i2MOErA/*/i2MOErA/*/i2MOErC/*/i2MOErC/*A*C*G*T*C*T*G*C*T*C*/i2MOErT/*/i2MOErA/*/i2MOErA/*/i2MOErC/*/32MOErA/	3.827	2.787	0.291	0.597	0.466	0.588	0.518
A8	CAMSAP1-4915 MOE	/52MOErT/*/i2MOErT/*/i2MOErG/*/i2MOErC/*/i2MOErA/*C*A*C*T*T*C*G*T*A*C*/i2MOErC/*/i2MOErC/*/i2MOErA/*/i2MOErA/*/32MOErA/	1.972	1.555	0.233	0.418	0.524	0.894	0.392
A9	MB21D1-689 MOE	/52MOErA/*/i2MOErC/*/i2MOErA/*/i2MOErA/*/i2MOErC/*C*C*C*T*T*T*C*A*C*C*/i2MOErA/*/i2MOErT/*/i2MOErC/*/i2MOErC/*/32MOErC/	14.808	8.841	0.533	0.593	0.499	0.785	0.658
B1	HPRT-732 MOE	/52MOErT/*/i2MOErA/*/i2MOErG/*/i2MOErT/*/i2MOErC/*A*A*G*G*G*C*A*T*A*T*/i2MOErC/*/i2MOErC/*/i2MOErT/*/i2MOErA/*/32MOErC/	2.087	1.457	0.191	0.423	0.462	0.787	0.848
B10	MB21D1-	/52MOErG/*/i2MOErA/*/i2MOErG/*/i2MOErG/*/i2MOErT/*C*T*T*G*G*C	2.164	1.822	0.095	0.419	0.650	0.888	0.380

	523 MOE	*T*T*C*G*/i2MOErT/*/i2MOErG/*/i2MOErG/*/i2MOErA/*/32MOErG/							
B2	HPRT-664 MOE	/52MOErA/*/i2MOErA/*/i2MOErC/*/i2MOErA/*/i2MOErC/*T*T*C*G*T*G*G*G*G*T*/i2MOErC/*/i2MOErC/*/i2MOErT/*/i2MOErT/*/32MOErT/	3.167	2.725	0.226	0.406	0.402	0.426	0.615
B3	CTNN2B-916 MOE	/52MOErG/*/i2MOErG/*/i2MOErG/*/i2MOErA/*/i2MOErA/*A*G*G*T*T*A*T*G*C*A*/i2MOErA/*/i2MOErG/*/i2MOErG/*/i2MOErT/*/32MOErC/	3.500	3.117	0.163	0.599	0.505	0.521	0.156
B4	CTNN2B-808 MOE	/52MOErC/*/i2MOErG/*/i2MOErT/*/i2MOErG/*/i2MOErT/*C*T*G*G*A*A*G*C*T*T*/i2MOErC/*/i2MOErC/*/i2MOErT/*/i2MOErT/*/32MOErT/	1.222	1.476	0.350	0.541	0.259	0.568	0.426
B5	EGFR-3652 MOE	/52MOErA/*/i2MOErC/*/i2MOErA/*/i2MOErG/*/i2MOErT/*G*T*T*T*G*A*G*A*T*A*C*/i2MOErT/*/i2MOErC/*/i2MOErG/*/i2MOErG/*/32MOErG/	8.261	5.681	0.129	0.420	0.194	0.436	0.297
B6	EGFR-1015 MOE	/52MOErG/*/i2MOErT/*/i2MOErG/*/i2MOErT/*/i2MOErC/*C*T*T*G*C*A*C*G*T*G*/i2MOErG/*/i2MOErC/*/i2MOErT/*/i2MOErT/*/32MOErC/	1.274	1.383	0.212	0.377	0.641	0.784	0.384
B7	CAMSAP1-1739 MOE	/52MOErC/*/i2MOErT/*/i2MOErT/*/i2MOErA/*/i2MOErC/*T*T*T*C*C*G*A*G*G*T*/i2MOErG/*/i2MOErT/*/i2MOErC/*/i2MOErC/*/32MOErA/	4.827	3.892	0.336	0.588	0.531	0.647	0.473
B8	CAMSAP1-5594 MOE	/52MOErT/*/i2MOErT/*/i2MOErG/*/i2MOErG/*/i2MOErC/*T*C*G*G*C*T*T*G*C*C*/i2MOErT/*/i2MOErA/*/i2MOErC/*/i2MOErT/*/32MOErT/	0.813	1.096	0.204	0.523	0.445	0.705	0.295
B9	MB21D1-719 MOE	/52MOErT/*/i2MOErC/*/i2MOErG/*/i2MOErC/*/i2MOErA/*C*T*T*C*A*G*T*C*T*G*/i2MOErA/*/i2MOErG/*/i2MOErC/*/i2MOErA/*/32MOErG/	2.158	1.697	0.241	0.574	0.266	0.521	0.305
C1	HPRT-1027 MOE	/52MOErA/*/i2MOErA/*/i2MOErT/*/i2MOErC/*/i2MOErC/*G*C*C*C*A*A*A*G*G*G*/i2MOErA/*/i2MOErA/*/i2MOErC/*/i2MOErT/*/32MOErG/	4.659	2.685	0.521	0.691	0.591	0.591	0.494
C10	MB21D1-522 MOE	/52MOErA/*/i2MOErG/*/i2MOErG/*/i2MOErT/*/i2MOErC/*T*T*G*G*C*T*T*C*G*T*/i2MOErG/*/i2MOErG/*/i2MOErA/*/i2MOErG/*/32MOErC/	5.064	3.657	0.150	0.547	0.280	0.568	0.118
C2	HPRT-668 MOE	/52MOErA/*/i2MOErT/*/i2MOErC/*/i2MOErC/*/i2MOErA/*A*C*A*C*T*T*C*G*T*G*/i2MOErG/*/i2MOErG/*/i2MOErG/*/i2MOErT/*/32MOErC/	1.519	1.437	0.611	0.758	0.618	0.287	0.744
C3	CTNN2B-1294 MOE	/52MOErC/*/i2MOErA/*/i2MOErG/*/i2MOErA/*/i2MOErT/*A*G*C*A*C*C*T*T*C*A*/i2MOErG/*/i2MOErC/*/i2MOErA/*/i2MOErC/*/32MOErT/	2.356	1.773	0.254	0.497	0.484	0.583	0.388
C4	CTNN2B-2545 MOE	/52MOErG/*/i2MOErC/*/i2MOErC/*/i2MOErC/*/i2MOErA/*T*C*C*A*T*G*A*G*G*T*/i2MOErC/*/i2MOErC/*/i2MOErT/*/i2MOErG/*/32MOErG/	0.541	0.899	0.124	0.340	0.175	0.324	0.592

C5	EGFR-3908 MOE	/52MOErG/*/i2MOErG/*/i2MOErG/*/i2MOErT/*/i2MOErA/*T*C*G*A*A*A*G*A*G*T*/i2MOErC/*/i2MOErT/*/i2MOErG/*/i2MOErG/*/32MOErA/	4.073	3.138	0.079	0.350	0.203	0.349	0.427
C6	EGFR-2874 MOE	/52MOErA/*/i2MOErT/*/i2MOErG/*/i2MOErC/*/i2MOErC/*A*T*C*C*A*C*T*T*G*A*/i2MOErT/*/i2MOErA/*/i2MOErG/*/i2MOErG/*/32MOErC/	2.025	2.028	0.390	0.668	0.589	0.712	0.639
C7	CAMSAP1-4295 MOE	/52MOErT/*/i2MOErG/*/i2MOErG/*/i2MOErG/*/i2MOErT/*T*A*C*G*G*C*T*C*A*G*/i2MOErT/*/i2MOErA/*/i2MOErT/*/i2MOErG/*/32MOErG/	1.538	1.610	0.167	0.427	0.228	0.478	0.432
C8	CAMSAP1-4916 MOE	/52MOErT/*/i2MOErT/*/i2MOErT/*/i2MOErG/*/i2MOErC/*A*C*A*C*T*T*C*G*T*A*/i2MOErC/*/i2MOErC/*/i2MOErC/*/i2MOErA/*/32MOErA/	2.199	1.877	0.118	0.296	0.514	0.735	0.335
C9	MB21D1-1181 MOE	/52MOErA/*/i2MOErG/*/i2MOErT/*/i2MOErC/*/i2MOErG/*T*A*G*T*T*G*C*T*T*C*/i2MOErC/*/i2MOErT/*/i2MOErA/*/i2MOErA/*/32MOErC/	5.889	3.091	0.228	0.494	0.341	0.527	0.261
D1	HPRT-1353 MOE	/52MOErG/*/i2MOErC/*/i2MOErT/*/i2MOErG/*/i2MOErA/*C*A*A*A*G*A*T*T*C*A*/i2MOErC/*/i2MOErT/*/i2MOErG/*/i2MOErG/*/32MOErT/	3.067	1.475	0.190	0.375	0.654	0.653	0.335
D10	MB21D1-168 MOE	/52MOErT/*/i2MOErC/*/i2MOErC/*/i2MOErG/*/i2MOErG/*C*C*T*C*G*G*A*A*G*C*/i2MOErT/*/i2MOErC/*/i2MOErT/*/i2MOErC/*/32MOErT/	0.781	0.816	0.166	0.440	0.000	0.242	0.250
D2	HPRT-663 MOE	/52MOErA/*/i2MOErC/*/i2MOErA/*/i2MOErC/*/i2MOErT/*T*C*G*T*G*G*G*G*T*C*/i2MOErC/*/i2MOErT/*/i2MOErT/*/i2MOErT/*/32MOErT/	6.320	4.778	0.235	0.403	0.226	0.114	0.623
D3	CTNN2B-2341 MOE	/52MOErG/*/i2MOErT/*/i2MOErC/*/i2MOErC/*/i2MOErA/*A*G*A*T*C*A*G*C*A*G*/i2MOErT/*/i2MOErC/*/i2MOErT/*/i2MOErC/*/32MOErA/	3.364	3.021	0.120	0.298	0.535	0.430	0.705
D4	CTNN2B-1642 MOE	/52MOErT/*/i2MOErG/*/i2MOErG/*/i2MOErC/*/i2MOErA/*G*G*C*T*C*A*G*T*G*A*/i2MOErT/*/i2MOErG/*/i2MOErT/*/i2MOErC/*/32MOErT/	0.973	1.074	0.167	0.415	0.479	0.722	0.605
D5	EGFR-4705 MOE	/52MOErT/*/i2MOErG/*/i2MOErG/*/i2MOErG/*/i2MOErC/*T*G*G*A*A*T*C*C*G*A*/i2MOErG/*/i2MOErT/*/i2MOErT/*/i2MOErA/*/32MOErT/	2.058	1.452	0.095	0.270	0.241	0.443	0.433
D6	EGFR-3267 MOE	/52MOErC/*/i2MOErG/*/i2MOErG/*/i2MOErC/*/i2MOErA/*T*C*C*A*C*C*A*C*G*T*/i2MOErC/*/i2MOErG/*/i2MOErT/*/i2MOErC/*/32MOErC/	0.903	1.249	0.202	0.485	0.373	0.449	0.378
D7	CAMSAP1-4697 MOE	/52MOErG/*/i2MOErG/*/i2MOErT/*/i2MOErT/*/i2MOErT/*T*G*G*C*T*G*G*G*A*T*/i2MOErC/*/i2MOErA/*/i2MOErA/*/i2MOErG/*/32MOErT/	6.332	5.496	0.191	0.346	0.200	0.381	0.375
D8	CAMSAP1-2584 MOE	/52MOErT/*/i2MOErT/*/i2MOErG/*/i2MOErC/*/i2MOErC/*A*T*G*C*T*G*G*C*T*C*/i2MOErG/*/i2MOErG/*/i2MOErA/*/i2MOErC/*/32MOErT/	0.572	0.881	0.138	0.445	0.534	0.516	0.518

D9	MB21D1-1248 MOE	/52MOErC/*/i2MOErC/*/i2MOErG/*/i2MOErC/*/i2MOErC/*A*T*G*T*T*T*C*T*T*C*/i2MOErT/*/i2MOErT/*/i2MOErG/*/i2MOErG/*/32MOErA/	2.713	1.909	0.139	0.402	0.251	0.481	0.361
E1	HPRT-665 MOE	/52MOErC/*/i2MOErA/*/i2MOErA/*/i2MOErC/*/i2MOErA/*C*T*T*T*C*G*T*G*G*G*G*/i2MOErT/*/i2MOErC/*/i2MOErC/*/i2MOErT/*/32MOErT/	1.639	1.320	0.285	0.487	0.619	0.858	0.686
E10	MB21D1-520 MOE	/52MOErG/*/i2MOErT/*/i2MOErC/*/i2MOErT/*/i2MOErT/*G*G*C*T*T*C*G*T*G*G*/i2MOErA/*/i2MOErG/*/i2MOErC/*/i2MOErA/*/32MOErG/	3.536	2.383	0.095	0.372	0.599	0.709	0.291
E2	HPRT-332 MOE	/52MOErT/*/i2MOErG/*/i2MOErT/*/i2MOErG/*/i2MOErA/*T*G*G*C*C*T*C*C*C*A*/i2MOErT/*/i2MOErC/*/i2MOErT/*/i2MOErC/*/32MOErC/	0.938	0.940	0.238	0.312	0.782	0.674	0.438
E3	CTNN2B-3648 MOE	/52MOErC/*/i2MOErT/*/i2MOErC/*/i2MOErT/*/i2MOErT/*G*A*A*G*C*A*T*C*G*T*/i2MOErA/*/i2MOErT/*/i2MOErC/*/i2MOErA/*/32MOErC/	2.200	1.650	0.341	0.609	0.472	0.721	0.791
E4	CTNN2B-2516 MOE	/52MOErA/*/i2MOErG/*/i2MOErA/*/i2MOErT/*/i2MOErC/*T*G*G*C*A*G*C*C*C*A*/i2MOErT/*/i2MOErC/*/i2MOErA/*/i2MOErA/*/32MOErC/	4.465	3.069	0.201	0.500	0.268	0.607	0.677
E5	EGFR-4885 MOE	/52MOErG/*/i2MOErG/*/i2MOErA/*/i2MOErG/*/i2MOErA/*T*T*T*T*C*A*G*A*G*C*A*/i2MOErG/*/i2MOErC/*/i2MOErT/*/i2MOErT/*/32MOErC/	4.308	3.122	0.088	0.330	0.381	0.541	0.466
E6	EGFR-1013 MOE	/52MOErG/*/i2MOErT/*/i2MOErC/*/i2MOErC/*/i2MOErT/*T*G*C*A*C*G*T*G*G*C*/i2MOErT/*/i2MOErT/*/i2MOErC/*/i2MOErG/*/32MOErT/	1.593	1.900	0.088	0.216	0.602	0.682	0.374
E7	CAMSAP1-6273 MOE	/52MOErT/*/i2MOErC/*/i2MOErA/*/i2MOErA/*/i2MOErA/*G*G*A*C*T*G*A*G*G*A*/i2MOErA/*/i2MOErA/*/i2MOErG/*/i2MOErG/*/32MOErG/	3.406	3.896	0.189	0.397	0.040	0.265	0.634
E8	CAMSAP1-2709 MOE	/52MOErG/*/i2MOErC/*/i2MOErT/*/i2MOErT/*/i2MOErC/*A*G*G*C*G*C*T*G*C*C*/i2MOErT/*/i2MOErT/*/i2MOErG/*/i2MOErC/*/32MOErC/	0.620	0.985	0.196	0.527	0.824	0.833	0.510
E9	MB21D1-1483 MOE	/52MOErA/*/i2MOErC/*/i2MOErT/*/i2MOErG/*/i2MOErA/*C*T*G*T*C*T*T*G*A*G*/i2MOErG/*/i2MOErG/*/i2MOErT/*/i2MOErT/*/32MOErC/	3.185	2.454	0.299	0.627	0.291	0.424	0.221
F1	HPRT-333 MOE	/52MOErA/*/i2MOErT/*/i2MOErG/*/i2MOErT/*/i2MOErG/*A*T*G*G*C*C*T*C*C*C*/i2MOErA/*/i2MOErT/*/i2MOErC/*/i2MOErT/*/32MOErC/	1.429	0.939	0.345	0.643	0.918	0.900	0.439
F10	MB21D1-616 MOE	/52MOErG/*/i2MOErG/*/i2MOErA/*/i2MOErG/*/i2MOErC/*T*T*C*G*A*G*G*C*C*C*/i2MOErC/*/i2MOErA/*/i2MOErG/*/i2MOErG/*/32MOErC/	0.380	0.760	0.179	0.392	0.168	0.588	0.117
F2	HPRT-335 MOE	/52MOErC/*/i2MOErA/*/i2MOErA/*/i2MOErT/*/i2MOErG/*T*G*A*T*G*G*C*C*T*C*/i2MOErC/*/i2MOErC/*/i2MOErA/*/i2MOErT/*/32MOErC/	1.677	1.518	0.279	0.451	0.412	0.614	0.362

F3	CTN N2B-809 MOE	/52MOErG/*/i2MOErC/*/i2MOErG/*/i2MOErT/*/i2MOErG/*T*C*T*G*G*A*A*G*C*T*/i2MOErT/*/i2MOErC/*/i2MOErC/*/i2MOErT/*/32MOErT/	0.494	1.179	0.134	0.415	0.229	0.263	0.241
F4	CTN N2B-2136 MOE	/52MOErT/*/i2MOErT/*/i2MOErC/*/i2MOErT/*/i2MOErG/*C*A*G*C*T*T*C*C*T*T*/i2MOErG/*/i2MOErT/*/i2MOErC/*/i2MOErC/*/32MOErT/	2.408	2.049	0.059	0.183	0.467	0.746	0.821
F5	EGFR -1014 MOE	/52MOErT/*/i2MOErG/*/i2MOErT/*/i2MOErC/*/i2MOErC/*T*T*G*C*A*C*G*T*G*G*/i2MOErC/*/i2MOErT/*/i2MOErT/*/i2MOErC/*/32MOErG/	1.433	1.187	0.057	0.029	0.623	0.764	0.515
F6	EGFR -1016 MOE	/52MOErG/*/i2MOErG/*/i2MOErT/*/i2MOErG/*/i2MOErT/*C*C*T*T*G*C*A*C*G*T*/i2MOErG/*/i2MOErG/*/i2MOErC/*/i2MOErT/*/32MOErT/	1.019	1.532	0.131	0.358	0.714	1.064	0.315
F7	CAM SAP1 -2112 MOE	/52MOErT/*/i2MOErG/*/i2MOErT/*/i2MOErC/*/i2MOErT/*T*C*A*T*C*G*G*C*C*C*/i2MOErT/*/i2MOErG/*/i2MOErC/*/i2MOErC/*/32MOErT/	1.178	1.331	0.185	0.396	0.480	0.697	0.557
F8	CAM SAP1 -2456 MOE	/52MOErG/*/i2MOErA/*/i2MOErG/*/i2MOErT/*/i2MOErC/*T*C*T*G*G*A*G*C*T*T*/i2MOErC/*/i2MOErC/*/i2MOErT/*/i2MOErC/*/32MOErT/	0.683	0.849	0.170	0.469	0.127	0.594	0.250
F9	MB21 D1-521 MOE	/52MOErG/*/i2MOErG/*/i2MOErT/*/i2MOErC/*/i2MOErT/*T*G*G*C*T*T*C*G*T*G*/i2MOErG/*/i2MOErA/*/i2MOErG/*/i2MOErC/*/32MOErA/	4.596	3.386	0.171	0.460	0.243	0.518	0.256
G1	HPRT -667 MOE	/52MOErT/*/i2MOErC/*/i2MOErC/*/i2MOErA/*/i2MOErA/*C*A*C*T*T*C*G*T*G*G*/i2MOErG/*/i2MOErG/*/i2MOErT/*/i2MOErC/*/32MOErC/	1.432	1.142	0.578	0.929	0.616	0.792	0.799
G10	MB21 D1-697 MOE	/52MOErG/*/i2MOErG/*/i2MOErT/*/i2MOErG/*/i2MOErG/*T*C*C*A*C*A*A*C*C*C*/i2MOErC/*/i2MOErT/*/i2MOErT/*/i2MOErT/*/32MOErC/	3.700	2.121	0.097	0.620	0.071	0.456	0.292
G3	CTN N2B-2446 MOE	/52MOErG/*/i2MOErG/*/i2MOErT/*/i2MOErC/*/i2MOErC/*A*T*A*C*C*C*A*A*G*G*/i2MOErC/*/i2MOErA/*/i2MOErT/*/i2MOErC/*/32MOErC/	2.107	1.901	0.096	0.364	0.453	0.687	0.531
G4	CTN N2B-2479 MOE	/52MOErG/*/i2MOErG/*/i2MOErT/*/i2MOErG/*/i2MOErG/*T*G*G*C*C*A*C*C*C*C*A*/i2MOErT/*/i2MOErC/*/i2MOErT/*/i2MOErC/*/32MOErA/	0.874	1.491	0.192	0.480	0.317	0.761	0.456
G5	EGFR -3266 MOE	/52MOErG/*/i2MOErG/*/i2MOErC/*/i2MOErA/*/i2MOErT/*C*C*A*C*C*C*A*C*G*T*C*/i2MOErG/*/i2MOErT/*/i2MOErC/*/i2MOErC/*/32MOErA/	1.566	1.619	0.097	0.216	0.481	0.742	0.478
G6	EGFR -727 MOE	/52MOErA/*/i2MOErT/*/i2MOErG/*/i2MOErT/*/i2MOErC/*C*C*G*C*C*A*C*T*G*G*/i2MOErA/*/i2MOErT/*/i2MOErG/*/i2MOErC/*/32MOErT/	1.708	2.029	0.171	0.397	0.423	0.801	0.549
G7	CAM SAP1 -2113 MOE	/52MOErG/*/i2MOErT/*/i2MOErG/*/i2MOErT/*/i2MOErC/*T*T*C*A*T*C*G*G*C*C*/i2MOErC/*/i2MOErT/*/i2MOErG/*/i2MOErC/*/32MOErC/	1.093	1.247	0.132	0.371	0.201	0.611	0.606

G8	CAMSAP1-2906 MOE	/52MOErG/*/i2MOErT/*/i2MOErC/*/i2MOErC/*/i2MOErA/*C*A*T*C*C*T*G*T*G*G*/i2MOErC/*/i2MOErT/*/i2MOErC/*/i2MOErG/*/32MOErT/	0.493	0.919	0.119	0.299	0.254	0.559	0.455
G9	MB21D1-524 MOE	/52MOErG/*/i2MOErG/*/i2MOErA/*/i2MOErG/*/i2MOErG/*T*C*T*T*G*G*C*T*T*C*/i2MOErG/*/i2MOErT/*/i2MOErG/*/i2MOErG/*/32MOErA/	5.288	3.976	0.091	0.434	0.342	0.466	0.450
H1	HPRT-329 MOE	/52MOErG/*/i2MOErA/*/i2MOErT/*/i2MOErG/*/i2MOErG/*C*C*T*C*C*C*A*T*C*T*/i2MOErC/*/i2MOErC/*/i2MOErT/*/i2MOErT/*/32MOErC/	1.698	0.979	0.336	0.678	1.268	0.662	0.687
H10	NC52'MOE	/52MOErG/*/i2MOErC/*/i2MOErG/*/i2MOErA/*/i2MOErC/*T*A*T*A*C*G*C*G*C*A*/i2MOErA/*/i2MOErT/*/i2MOErA/*/i2MOErT/*/32MOErG/	0.883	1.067	0.294	0.948	0.035	0.395	0.720
H3	CTNN2B-1576 MOE	/52MOErC/*/i2MOErA/*/i2MOErC/*/i2MOErC/*/i2MOErC/*A*C*T*T*G*G*C*A*G*A*/i2MOErC/*/i2MOErC/*/i2MOErA/*/i2MOErT/*/32MOErC/	1.502	1.440	0.227	0.600	0.677	0.665	0.658
H5	EGFR-2859 MOE	/52MOErT/*/i2MOErA/*/i2MOErG/*/i2MOErG/*/i2MOErC/*A*C*T*T*T*G*C*C*T*C*/i2MOErC/*/i2MOErT/*/i2MOErT/*/i2MOErC/*/32MOErT/	0.884	0.773	0.205	0.455	0.914	0.808	0.378
H7	CAMSAP1-1850 MOE	/52MOErG/*/i2MOErA/*/i2MOErT/*/i2MOErG/*/i2MOErC/*T*C*C*T*C*G*G*T*C*T*/i2MOErC/*/i2MOErC/*/i2MOErC/*/i2MOErT/*/32MOErT/	1.954	1.392	0.199	0.453	0.196	0.792	0.413
H8	NC12'MOE	/52MOErG/*/i2MOErC/*/i2MOErG/*/i2MOErT/*/i2MOErA/*T*T*A*T*A*G*C*C*G*A*/i2MOErT/*/i2MOErT/*/i2MOErA/*/i2MOErA/*/32MOErC/	2.777	1.883	0.265	0.565	0.064	0.460	0.504
H9	MB21D1-526 MOE	/52MOErG/*/i2MOErC/*/i2MOErG/*/i2MOErG/*/i2MOErA/*G*G*T*C*T*T*G*G*C*T*/i2MOErT/*/i2MOErC/*/i2MOErG/*/i2MOErT/*/32MOErG/	2.226	1.598	0.154	0.453	0.246	0.682	0.346

Table 5A. Unmodified oliogonucleotide sequences described in Table 5.

Name	Sequence
Unmodified HPRT-489 MOE	ATGTCCCCTGTTGACTGGTC (SEQ ID NO: 522)
Unmodified MB21D1-525 MOE	CGGAGGTCTTGGCTTCGTGG (SEQ ID NO: 81)
Unmodified HPRT-666 MOE	CCAACACTTCGTGGGGTCCT (SEQ ID NO: 209)
Unmodified CTNN2B-311 MOE	GCCGCTTTTCTGTCTGGTTC (SEQ ID NO: 523)
Unmodified CTNN2B-1575 MOE	ACCCACTTGGCAGACCATCA (SEQ ID NO: 524)
Unmodified EGFR-2790 MOE	CTGTGATCTTGACATGCTGC (SEQ ID NO: 84)
Unmodified EGFR-1225 MOE	CAAGGCCCTTCGCACTTCTT (SEQ ID NO: 525)
Unmodified CAMSAP1-1635 MOE	GAACCACGTCTGCTCTAACA (SEQ ID NO: 526)
Unmodified CAMSAP1-4915 MOE	TTGCACACTTCGTACCCAAA (SEQ ID NO: 527)

Unmodified MB21D1-689 MOE	ACAACCCCTTTCACCATCCC (SEQ ID NO: 528)
Unmodified HPRT-732 MOE	TAGTCAAGGGCATATCCTAC (SEQ ID NO: 529)
Unmodified MB21D1-523 MOE	GAGGTCTTGGCTTCGTGGAG (SEQ ID NO: 530)
Unmodified HPRT-664 MOE	AACACTTCGTGGGGTCCTTT (SEQ ID NO: 177)
Unmodified CTNN2B-916 MOE	GGGAAAGGTTATGCAAGGTC (SEQ ID NO: 83)
Unmodified CTNN2B-808 MOE	CGTGTCTGGAAGCTTCCTTT (SEQ ID NO: 531)
Unmodified EGFR-3652 MOE	ACAGTGTTGAGATACTCGGG (SEQ ID NO: 91)
Unmodified EGFR-1015 MOE	GTGTCCTTGCACGTGGCTTC (SEQ ID NO: 532)
Unmodified CAMSAP1-1739 MOE	CTTACTTTCCGAGGTGTCCA (SEQ ID NO: 533)
Unmodified CAMSAP1-5594 MOE	TTGGCTCGGCTTGCCTACTT (SEQ ID NO: 90)
Unmodified MB21D1-719 MOE	TCGCACTTCAGTCTGAGCAG (SEQ ID NO: 92)
Unmodified HPRT-1027 MOE	AATCCGCCCAAAGGGAACTG (SEQ ID NO: 534)
Unmodified MB21D1-522 MOE	AGGTCTTGGCTTCGTGGAGC (SEQ ID NO: 82)
Unmodified HPRT-668 MOE	ATCCAACACTTCGTGGGGTC (SEQ ID NO: 172)
Unmodified CTNN2B-1294 MOE	CAGATAGCACCTTCAGCACT (SEQ ID NO: 535)
Unmodified CTNN2B-2545 MOE	GCCCATCCATGAGGTCCTGG (SEQ ID NO: 173)
Unmodified EGFR-3908 MOE	GGGTATCGAAAGAGTCTGGA (SEQ ID NO: 174)
Unmodified EGFR-2874 MOE	ATGCCATCCACTTGATAGGC (SEQ ID NO: 536)
Unmodified CAMSAP1-4295 MOE	TGGGTTACGGCTCAGTATGG (SEQ ID NO: 183)
Unmodified CAMSAP1-4916 MOE	TTTGCACACTTCGTACCCAA (SEQ ID NO: 94)
Unmodified MB21D1-1181 MOE	AGTCGTAGTTGCTTCCTAAC (SEQ ID NO: 88)
Unmodified HPRT-1353 MOE	GCTGACAAAGATTCACTGGT (SEQ ID NO: 95)
Unmodified MB21D1-168 MOE	TCCGGCCTCGGAAGCTCTCT (SEQ ID NO: 138)
Unmodified HPRT-663 MOE	ACACTTCGTGGGGTCCTTTT (SEQ ID NO: 170)
Unmodified CTNN2B-2341 MOE	GTCCAAGATCAGCAGTCTCA (SEQ ID NO: 178)
Unmodified CTNN2B-1642 MOE	TGGCAGGCTCAGTGATGTCT (SEQ ID NO: 537)
Unmodified EGFR-4705 MOE	TGGGCTGGAATCCGAGTTAT (SEQ ID NO: 179)
Unmodified EGFR-3267 MOE	CGGCATCCACCACGTCGTCC (SEQ ID NO: 180)
Unmodified CAMSAP1-4697 MOE	GGTTTTGGCTGGGATCAAGT (SEQ ID NO: 175)
Unmodified CAMSAP1-2584 MOE	TTGCCATGCTGGCTCGGACT (SEQ ID NO: 538)
Unmodified MB21D1-1248 MOE	CCGCCATGTTTCTTCTTGGA (SEQ ID NO: 184)
Unmodified HPRT-665 MOE	CAACACTTCGTGGGGTCCTT (SEQ ID NO: 208)
Unmodified MB21D1-520 MOE	GTCTTGGCTTCGTGGAGCAG (SEQ ID NO: 89)
Unmodified HPRT-332 MOE	TGTGATGGCCTCCCATCTCC (SEQ ID NO: 304)
Unmodified CTNN2B-3648 MOE	CTCTTGAAGCATCGTATCAC (SEQ ID NO: 539)
Unmodified CTNN2B-2516 MOE	AGATCTGGCAGCCCATCAAC (SEQ ID NO: 540)
Unmodified EGFR-4885 MOE	GGAGATTTCAGAGCAGCTTC (SEQ ID NO: 322)

Unmodified EGFR-1013 MOE	GTCCTTGCACGTGGCTTCGT (SEQ ID NO: 321)
Unmodified CAMSAP1-6273 MOE	TCAAAGGACTGAGGAAAGGG (SEQ ID NO: 171)
Unmodified CAMSAP1-2709 MOE	GCTTCAGGCGCTGCCTTGCC (SEQ ID NO: 541)
Unmodified MB21D1-1483 MOE	ACTGACTGTCTTGAGGGTTC (SEQ ID NO: 85)
Unmodified HPRT-333 MOE	ATGTGATGGCCTCCCATCTC (SEQ ID NO: 542)
Unmodified MB21D1-616 MOE	GGAGCTTCGAGGCCCCAGGC (SEQ ID NO: 14)
Unmodified HPRT-335 MOE	CAATGTGATGGCCTCCCATC (SEQ ID NO: 543)
Unmodified CTNN2B-809 MOE	GCGTGTCTGGAAGCTTCCTT (SEQ ID NO: 86)
Unmodified CTNN2B-2136 MOE	TTCTGCAGCTTCCTTGTCCT (SEQ ID NO: 323)
Unmodified EGFR-1014 MOE	TGTCCTTGCACGTGGCTTCG (SEQ ID NO: 302)
Unmodified EGFR-1016 MOE	GGTGTCCTTGCACGTGGCTT (SEQ ID NO: 93)
Unmodified CAMSAP1-2112 MOE	TGTCTTCATCGGCCCTGCCT (SEQ ID NO: 544)
Unmodified CAMSAP1-2456 MOE	GAGTCTCTGGAGCTTCCTCT (SEQ ID NO: 87)
Unmodified MB21D1-521 MOE	GGTCTTGGCTTCGTGGAGCA (SEQ ID NO: 139)
Unmodified HPRT-667 MOE	TCCAACACTTCGTGGGGTCC (SEQ ID NO: 545)
Unmodified MB21D1-697 MOE	GGTGGTCCACAACCCCTTTC (SEQ ID NO: 210)
Unmodified CTNN2B-2446 MOE	GGTCCATACCCAAGGCATCC (SEQ ID NO: 305)
Unmodified CTNN2B-2479 MOE	GGTGGTGGCCACCCATCTCA (SEQ ID NO: 546)
Unmodified EGFR-3266 MOE	GGCATCCACCACGTCGTCCA (SEQ ID NO: 320)
Unmodified EGFR-727 MOE	ATGTCCCGCCACTGGATGCT (SEQ ID NO: 547)
Unmodified CAMSAP1-2113 MOE	GTGTCTTCATCGGCCCTGCC (SEQ ID NO: 306)
Unmodified CAMSAP1-2906 MOE	GTCCACATCCTGTGGCTCGT (SEQ ID NO: 303)
Unmodified MB21D1-524 MOE	GGAGGTCTTGGCTTCGTGGA (SEQ ID NO: 182)
Unmodified HPRT-329 MOE	GATGGCCTCCCATCTCCTTC (SEQ ID NO: 548)
Unmodified NC5 2'MOE	GCGACTATACGCGCAATATG (SEQ ID NO: 176)
Unmodified CTNN2B-1576 MOE	CACCCACTTGGCAGACCATC (SEQ ID NO: 549)
Unmodified EGFR-2859 MOE	TAGGCACTTTGCCTCCTTCT (SEQ ID NO: 550)
Unmodified CAMSAP1-1850 MOE	GATGCTCCTCGGTCTCCCTT (SEQ ID NO: 551)
Unmodified NC1 2'MOE	GCGTATTATAGCCGATTAAC (SEQ ID NO: 181)
Unmodified MB21D1-526 MOE	GCGGAGGTCTTGGCTTCGTG (SEQ ID NO: 96)

Table 6 – 3mer 2'OMe ASOs

3mer	SEQ ID NO	Ref	Seq	Well	TLR7 400nM	TLR7 2uM	TLR8 1uM	TLR8 HEK 5uM	TLR9 2uM	TLR3 2uM
AAA	365	1	mA*mA*mA	A1	1.352	0.867	225.029	0.859	0.845	1.026
AGC	374	10	mA*mG*mC	A10	1.401	0.726	267.225	1.411	0.749	1.019
AAC	373	2	mA*mA*mC	A2	1.019	0.770	218.889	0.696	0.931	0.901
AAG	380	3	mA*mA*mG	A3	1.247	0.876	179.302	0.858	0.870	0.616
AAU	426	4	mA*mA*mU	A4	1.340	0.888	202.802	0.807	0.884	0.888
ACA	168	5	mA*mC*mA	A5	1.234	0.831	262.630	0.841	1.042	1.053
ACC	403	6	mA*mC*mC	A6	1.290	0.795	262.122	0.939	0.604	0.850
ACG	411	7	mA*mC*mG	A7	1.212	0.825	185.962	1.328	0.512	0.993
ACU	427	8	mA*mC*mU	A8	1.322	0.916	250.907	0.896	0.996	1.062
AGA	366	9	mA*mG*mA	A9	1.219	0.795	214.450	1.520	0.848	0.829
AGG	381	11	mA*mG*mG	B1	1.335	0.866	193.033	2.596	1.005	0.855
CAU	428	20	mC*mA*mU	B10	1.288	0.995	388.191	0.752	0.921	0.866
AGU	429	12	mA*mG*mU	B2	1.025	0.952	270.256	1.329	0.840	0.829
AUA	430	13	mA*mU*mA	B3	1.171	0.905	157.293	0.812	0.944	0.570
AUC	431	14	mA*mU*mC	B4	0.950	0.430	181.793	0.674	0.884	0.768

AUG	432	15	mA*m U*mG	B4	0.987	0.602	151.847	0.828	0.878	0.859
AUU	433	16	mA*m U*mU	B6	1.221	0.700	274.683	0.762	0.864	0.809
CAA	367	17	mC*m A*mA	B7	1.175	0.787	373.157	0.811	0.917	0.771
CAC	169	18	mC*m A*mC	B8	1.330	0.932	344.415	0.809	0.830	0.841
CAG	382	19	mC*m A*mG	B9	1.271	1.057	362.782	0.960	0.898	0.743
CCA	397	21	mC*m C*mA	C1	1.270	0.780	181.239	0.946	1.014	0.917
CUC	434	30	mC*m U*mC	C10	1.288	0.984	245.566	0.685	0.966	0.874
CCC	405	22	mC*m C*mC	C2	1.196	0.993	181.399	0.756	1.069	0.933
CCG	413	23	mC*m C*mG	C3	1.227	1.006	437.264	0.899	0.936	0.770
CCU	435	24	mC*m C*mU	C4	1.210	0.880	332.524	0.613	1.180	0.870
CGA	368	25	mC*m G*mA	C5	1.112	0.907	504.099	1.512	1.061	0.780
CGC	375	26	mC*m G*mC	C6	1.282	0.947	806.706	1.834	0.648	0.749
CGG	383	27	mC*m G*mG	C7	1.412	0.791	2548.596	2.877	1.078	0.847
CGU	436	28	mC*m G*mU	C8	1.372	0.963	346.350	1.327	1.237	0.833
CUA	437	29	mC*m U*mA	C9	1.388	0.953	243.564	0.642	1.182	0.851
CUG	438	31	mC*m U*mG	D1	1.405	0.804	264.072	1.074	0.948	0.870
GCU	439	40	mG*m C*mU	D10	1.339	0.852	193.279	0.810	1.429	0.808

CUU	153	32	**mC*mU*mU**	D2	1.277	0.913	167.148	0.712	1.108	0.846
GAA	369	33	mG*mA*mA	D3	1.233	0.433	138.047	0.647	0.863	0.786
GAC	376	34	mG*mA*mC	D4	1.138	0.505	141.925	0.494	1.213	0.832
GAG	384	35	mG*mA*mG	D5	0.958	0.465	130.205	0.471	1.047	0.844
GAU	440	36	mG*mA*mU	D6	1.406	0.580	147.162	0.528	0.700	0.771
GCA	399	37	mG*mC*mA	D7	1.240	0.717	218.474	0.786	1.047	0.798
GCC	407	38	mG*mC*mC	D8	1.360	0.645	209.536	0.701	1.305	0.884
GCG	415	39	mG*mC*mG	D9	1.185	0.627	290.409	1.191	1.299	0.830
GGA	370	41	mG*mG*mA	E1	1.053	0.474	195.033	1.919	0.853	0.979
UAC	441	50	mU*mA*mC	E10	1.161	1.003	254.486	0.813	0.997	0.813
GGC	377	42	mG*mG*mC	E2	0.659	0.259	151.618	1.697	1.009	0.792
GGG	385	43	mG*mG*mG	E3	1.141	0.680	214.414	1.147	0.734	0.849
GGU	59	44	**mG*mG*mU**	E4	0.938	0.847	274.989	1.380	1.177	0.829
GUA	60	45	**mG*mU*mA**	E5	0.702	0.239	133.537	0.792	1.042	0.839
GUC	442	46	mG*mU*mC	E6	0.140	0.017	131.948	0.763	0.856	0.752
GUG	443	47	mG*mU*mG	E7	0.449	0.072	158.982	0.882	1.374	0.786

GUU	444	48	mG*mU*mU	E8	0.781	0.119	166.278	0.668	1.159	0.825
UAA	445	49	mU*mA*mA	E9	1.126	1.029	224.188	0.907	1.176	0.790
UAG	446	51	mU*mA*mG	F1	1.158	0.918	226.441	1.443	0.977	0.940
UGU	447	60	mU*mG*mU	F10	1.108	0.984	331.923	1.120	1.085	0.967
UAU	448	52	mU*mA*mU	F2	1.086	0.935	213.758	0.887	1.145	0.915
UCA	449	53	mU*mC*mA	F3	1.122	0.819	1049.345	1.115	0.872	0.765
UCC	450	54	mU*mC*mC	F4	1.166	0.958	346.575	1.292	1.106	0.761
UCG	451	55	**mU*mC*mG**	F5	0.979	0.982	746.272	2.839	0.514	0.850
UCU	452	56	mU*mC*mU	F6	1.196	0.956	371.961	1.414	0.876	0.804
UGA	453	57	mU*mG*mA	F7	1.126	0.831	267.234	1.331	1.034	0.806
UGC	454	58	mU*mG*mC	F8	1.057	0.782	278.054	1.032	1.198	0.903
UGG	455	59	mU*mG*mG	F9	1.029	0.989	527.575	1.860	1.137	0.764
UUA	456	61	mU*mU*mA	G1	0.997	1.042	350.207	1.060	0.912	1.081
NT			NT	G10	0.000	0.000		0.020	0.005	0.000
UUC	457	62	mU*mU*mC	G2	0.536	0.642	213.878	0.968	0.770	1.023
UUG	458	63	mU*mU*mG	G3	0.945	1.074	347.573	1.071	0.816	1.030
UUU	459	64	mU*mU*mU	G4	0.861	1.084	307.213	0.870	0.936	0.970
Ligand			Ligand		1.000	1.000	355.752	1.000	1.000	1.000

NT			NT		0.000	0.000	134.831	0.000	0.000	0.000

Table 7 – 3mer DNA ASOs

3mer	SEQ ID NO	Ref	Seq	Position	TLR3 2uM
AAA	365	1	dA*dA*dA	A1	1.065
AGA	366	9	dA*dG*dA	A2	0.849
CAA	367	17	dC*dA*dA	A3	0.909
CGA	368	25	dC*dG*dA	A4	0.823
GAA	369	33	dG*dA*dA	A5	1.059
GGA	370	41	dG*dG*dA	A6	1.033
TAA	371	49	dT*dA*dA	A7	0.968
TGA	372	57	dT*dG*dA	A8	0.743
AAC	373	2	dA*dA*dC	B1	0.861
AGC	374	10	dA*dG*dC	B2	0.854
CAC	169	18	dC*dA*dC	B3	0.796
CGC	375	26	dC*dG*dC	B4	0.775
GAC	376	34	dG*dA*dC	B5	0.757
GGC	377	42	dG*dG*dC	B6	0.936
TAC	378	50	dT*dA*dC	B7	0.704
TGC	379	58	dT*dG*dC	B8	0.795
AAG	380	3	dA*dA*dG	C1	0.825
AGG	381	11	dA*dG*dG	C2	0.848
CAG	382	19	dC*dA*dG	C3	0.767
CGG	383	27	dC*dG*dG	C4	0.804
GAG	384	35	dG*dA*dG	C5	0.856
GGG	385	43	dG*dG*dG	C6	0.846
TAG	386	51	dT*dA*dG	C7	0.769
TGG	387	59	dT*dG*dG	C8	0.773
AAT	388	4	dA*dA*dT	D1	0.877
AGT	389	12	dA*dG*dT	D2	0.865
CAT	390	20	dC*dA*dT	D3	0.828
CGT	391	28	dC*dG*dT	D4	0.755
GAT	392	36	dG*dA*dT	D5	0.864
GGT	393	44	dG*dG*dT	D6	0.959
TAT	394	52	dT*dA*dT	D7	0.877

TGT	395	60	dT*dG*dT	D8	0.884
ACA	168	5	dA*dC*dA	E1	0.832
ATA	396	13	dA*dT*dA	E2	0.827
CCA	397	21	dC*dC*dA	E3	0.763
CTA	398	29	dC*dT*dA	E4	0.864
GCA	399	37	dG*dC*dA	E5	0.730
GTA	400	45	dG*dT*dA	E6	0.818
TCA	401	53	dT*dC*dA	E7	0.792
TTA	402	61	dT*dT*dA	E8	0.855
ACC	403	6	dA*dC*dC	F1	1.015
ATC	404	14	dA*dT*dC	F2	0.834
CCC	405	22	dC*dC*dC	F3	0.811
CTC	406	30	dC*dT*dC	F4	0.911
GCC	407	38	dG*dC*dC	F5	0.895
GTC	408	46	dG*dT*dC	F6	0.914
TCC	409	54	dT*dC*dC	F7	0.868
TTC	410	62	dT*dT*dC	F8	0.928
ACG	411	7	dA*dC*dG	G1	0.831
ATG	412	15	dA*dT*dG	G2	0.849
CCG	413	23	dC*dC*dG	G3	0.867
CTG	414	31	dC*dT*dG	G4	0.843
GCG	415	39	dG*dC*dG	G5	0.867
GTG	416	47	dG*dT*dG	G6	0.929
TCG	417	55	dT*dC*dG	G7	0.931
TTG	418	63	dT*dT*dG	G8	0.990
ACT	419	8	dA*dC*dT	H1	0.818
ATT	420	16	dA*dT*dT	H2	1.012
CCT	421	24	dC*dC*dT	H3	0.914
CTT	203	32	dC*dT*dT	H4	0.901
GCT	422	40	dG*dC*dT	H5	0.998
GTT	423	48	dG*dT*dT	H6	1.009
TCT	424	56	dT*dC*dT	H7	1.230
TTT	425	64	dT*dT*dT	H8	1.139
Ligand					1.000
NT					0.000

EXAMPLES

EXAMPLE 1: Methods

Cell isolation, Culture and Stimulation

Human Primary bone marrow-derived mesenchymal stem cell (MSCs) from 2 healthy adult donors (#1129 and #1980) were purchased from Lonza (#PT-2501) and were cultured in Dulbecco's modified Eagle's medium plus L-glutamine supplemented with 1× antibiotic/antimycotic (Thermo Fisher Scientific) and 10% heat-inactivated foetal bovine serum (referred to as complete DMEM). Culture media was replaced twice a week and cells were passaged at 80% confluency and seeded at a density of 2.5 x 10^3 cells/cm^2. These cells were confirmed free from pathogens and certified to meet MSC criteria as defined by the International Society of Cell and Gene Therapy. MSCs used herein were plated at passage 6-7. Rheumatoid arthritis (RA) patients fulfilled the American College of Rheumatology (ACR) criteria for the classification of RA (Arnett et al., 1987). RA and control primary fibroblast-like synoviocytes (FLS) were obtained from surgical specimens of synovial tissue and cultured as previously described (Leech et al., 1999). FLS were grown in RPMI 1640 plus L-glutamine medium (Life Technologies) complemented with 1x antibiotic/antimycotic and 10% heat inactivated foetal bovine serum (referred to as complete RPMI).

Trex1-mutant mice (used under animal ethics ref. A2018/38) have a single-based mutation in Trex1 leading to a premature stop codon (Q169X) and aberrant accumulation of cytoplasmic DNA, resulting in basal engagement of the cGAS-STING pathway (Ellyard J.I. and Vinuesa C.G., manuscript in preparation), similar to that reported in *Trex1*-deficient mice (Gray et al., 2015). Primary bone marrow derived macrophages (BMDMs) from wild-type, *Trex1*-mutant or $Tlr7^{Y264H}$ mutant mice were extracted and differentiated for 6 days in complete DMEM supplemented with L929 conditioned medium as previously reported (Ferrand and Gantier, 2016). 293XL-hTLR7-HA, 293XL-hTLR9-HA and HEK-Blue™ hTLR3 stably expressing human TLR7, TLR9 or TLR3 were purchased from Invivogen, and were maintained in complete DMEM supplemented with 10 μg/ml and 30 μg/ml Blasticidin (Invivogen), for TLR7/9 and TLR3 cells, respectively. HeLa cells, human colorectal cancer HT-29 (kind gift from R. Firestein), human fibroblasts expressing SV40 (large and small T antigens) with HRASG12V (kind gift from E. Sanij (Quin et al., 2016); referred to as BJ hTERT SV40T herein), LL171 cells (mouse L929 cells expressing an IFN stimulated response element (ISRE)-Luciferase - kind gift from V. Hornung (Ablasser et al., 2013), and immortalized wild-type mouse bone marrow macrophages (BMDMs) (Ferrand et al., 2018) were grown in complete DMEM. Human osteosarcoma MG-63 cells were purchased from

ATCC (#CRL-1427) and grown in ATCC-formulated Eagle's Minimum Essential Medium, supplemented with 10% heat-inactivated foetal bovine serum (Thermo Fisher Scientific) and 1× antibiotic/antimycotic (Thermo Fisher Scientific). Human acute myeloid leukemia THP-1 and their CRISPR-Cas9 derivatives (*cGAS-/-* (Mankan et al., 2014), *UNC93B1-/-* and *UNC93B1-/-* reconstituted with UNC93B1 (Pelka et al., 2014)) cells were grown in complete RPMI. THP-1 cells were not differentiated with PMA in any experiments, and rather used in suspension. All the cells were cultured at 37°C with 5% CO_2. Cell lines were passaged 2-3 times a week and tested for mycoplasma contamination on routine basis by PCR.

For cGAS stimulations, cells were treated for indicated duration with ASOs, prior to transfection with ISD70 (human cells) or ISD45 (mouse cells) (the ASOs were not washed off prior to ISD transfection unless otherwise indicated). The cGAS ligands ISD45 (Stetson and Medzhitov, 2006) and ISD70 (also known as VACV-70 (Unterholzner et al., 2010)) (Table 1) were resuspended as follows: 5 µl of sense and 5 µl of antisense strands at 10 µg/µl were added to 90 µl PBS under sterile conditions, heated at 75°C for 30 min, prior to letting cool down at room temperature and aliquoting (stock at 1 µg/1 µl). The ISDs were transfected at a concentration of 2.5 µg/ml at a ratio of 1 µg:1 µl with Lipofectamine 2000 in Opti-MEM (Thermo Fisher Scientific). HEK-TLR3, HEK-TLR7 and HEK-TLR9 were treated with indicated concentration of ASOs for 20-50 min, prior to stimulation with poly(I:C) (Invivogen), R848 (Invivogen), Motolimod (MedChemExpress) and the Class B CpG oligonucleotides ODN 2006 (synthesised by IDT and resuspended in RNase-free TE buffer [Table 1]), respectively. The TLR2/1 agonist PAM3CSK4 (Invivogen), the TLR4 agonist lipopolysaccharide (Invivogen), the Class B CpG oligonucleotides ODN 1826 (synthesised by IDT and resuspended in RNase-free TE buffer), the mouse Sting agonist DMXAA (Cayman) and the human STING agonist (compound #3 from (Raanjulu et al., 2018), referred to as GSK herein – kind gift from Cancer Therapeutics CRC, Australia) were used at indicated concentrations. Aspirin (Sigma - A2093) was resuspended in pure medium to 10 mM, filter sterilised and added to the cells at 2 mM final. All ASOs were synthesised by Integrated DNA Technologies (IDT), and resuspended in RNase-free TE buffer, pH 8.0 (Thermo Fisher Scientific). ASO sequences and modifications are provided in Tables 1 and 2. Cell viability was assessed by adding 1X fresh resazurin solution to the wells (10X solution made up with 7 mg resazurin [Sigma - R7017] dissolved in 3.5 ml PBS, sterile filtered at 0.2 µM) for 4 h, prior to reading at with a Fluostar OPTIMA (BMG LABTECH) plate-reader (fluorescence: Excitation 535 nm, Emission 590); wells with medium only and 1X resazurin were used as blanks.

Luciferase Assays

HEK293 cells stably expressing TLR3, 7 or 9 were reverse-transfected with pNF-κB-Luc4 reporter (Clontech), with Lipofectamine 2000 (Thermo Fisher Scientific), according to the manufacturer's protocol. Briefly, 500,000-700,000 cells were reverse-transfected with 400 ng of reporter with 1.2 µl of Lipofectamine 2000 per well of a 6-well plate, and incubated for 3-24 h at 37°C with 5% CO_2. Following transfection, the cells were collected from the 6-wells and aliquoted into 96-wells, just before ASO and overnight TLR stimulation (as above described). Similarly, the LL171 cells expressing and ISRE-Luc reporter were treated overnight. The next day, the cells were lysed in 40 µl (for a 96-well plate) of 1X Glo Lysis buffer (Promega) for 10 min at room temperature. 15 µl of the lysate was then subjected to firefly luciferase assay using 40 µl of Luciferase Assay Reagent (Promega). Luminescence was quantified with a Fluostar OPTIMA (BMG LABTECH) luminometer.

Beta-Galactosidase Staining

A β-Galactosidase staining assay was performed on FLS and MSCs treated with ASOs using the Senescence β-Galactosidase Staining kit (New England Biolabs). Briefly, FLS and MSCs were washed with PBS, fixed and stained over 24-48 h with X-Gal solution at 37°C according to the manufacturer's protocol. The cells were imaged using inverted phase microscopy. Three to 6 images were taken per condition and analysed with image J, counting the number of β-Galactosidase positive cells (blue) per image (totalling >100 cells for each condition). The relative proportion of blue cells per field was calculated for each image.

ASO Reverse-Transfections

For Figure 1A, 3F and 3G, ASOs were reverse-transfected with Lipofectamine 2000. Briefly, a solution of 1.125 µl Lipofectamine 2000 in 25 µl Opti-MEM was mixed to a solution of 1 µl of 10 µM ASO in 25 µL Opti-MEM. Following 20-25 min incubation at room temperature, the resulting 50 µl solution was dispensed into a 24-well, and 50-80,000 cells in 450 µl antibiotics-free medium were added, giving a final ASO concentration of 20 nM per well. For conditions with 50 and 100 nM ASOs (Figure 3F), the amount of Lipofectamine was kept constant. Cells were lysed in 150 µl RNA lysis Buffer (ISOLATE II RNA Mini Kit) after 24 h incubation.

RNA Reverse Transcription Quantitative Real-Time PCR (RT-qPCR)

Total RNA was purified from cells using the ISOLATE II RNA Mini Kit (Bioline). Random hexamer cDNA was synthesized from isolated RNA using the High-Capacity cDNA Archive kit (Thermo Fisher Scientific) according to the manufacturer's instructions. RT-qPCR was carried out with the Power SYBR Green Master Mix (Thermo Fisher Scientific) on the HT7900 and QuantStudio 6 RT-PCR system (Thermo Fisher Scientific). Each PCR was carried out in technical duplicate and human or mouse *18S* was used as reference gene. Each amplicon was gel-purified and used to generate a standard curve for the quantification of gene expression (used in each run). Melting curves were used in each run to confirm specificity of amplification. The primers used were the following: Human hIFIT1: hIFIT1-FWD TCACCAGATAGGGCTTTGCT (SEQ ID NO: 324); hIFIT1-REV CACCTCAAATGTGGGCTTTT (SEQ ID NO: 325); h18S: h18S-FWD CGGCTACCACATCCAAGGAA (SEQ ID NO: 326); h18S-REV GCTGGAATTACCGCGGCT (SEQ ID NO: 327); hIFI44: hIFI44-FWD ATGGCAGTGACAACTCGTTTG (SEQ ID NO: 328); hIFI44: TCCTGGTAACTCTCTTCTGCATA (SEQ ID NO: 329); Human IFIT2: hIFIT2-RT-FWD TTATTGGTGGCAGAAGAGGAAG (SEQ ID NO: 330); hIFIT2-RT-REV CCTCCATCAAGTTCCAGGTG (SEQ ID NO: 331); Human cGAS: hcGAS-FWD CACGTATGTACCCAGAACCC (SEQ ID NO: 332); hcGAS-REV GTCCTGAGGCACTGAAGAAAG (SEQ ID NO: 333); Mouse Rsad2: mRsad2-FWD CTGTGCGCTGGAAGGTTT (SEQ ID NO: 334); mRsad2-REV ATTCAGGCACCAAACAGGAC (SEQ ID NO: 335); Mouse 18S: mRnl8s- FWD GTAACCCGTTGAACCCCATT (SEQ ID NO: 336); mRn18s-REV CCATCCAATCGGTAGTAGCG (SEQ ID NO: 337); Mouse Ifih1: mIfih1-FWD TCTTGGACACTTGCTTCGAG (SEQ ID NO: 338); mIfih1-REV TCCTTCTGCACAATCCTTCTC (SEQ ID NO: 339); Mouse Ifit1: mIfit1-RT-FWD GAGAGTCAAGGCAGGTTTCT (SEQ ID NO: 340); mIfit1-RT-REV TCTCACTTCCAAATCAGGTATGT (SEQ ID NO: 341). Mouse OAS3: mOAS3-FWD GTACCACCAGGTGCAGACAC (SEQ ID NO: 342); mOAS3-REV GCCATAGTTTTCCGTCCAGA (SEQ ID NO: 343);

Detection of Cytokines

Human IP-10 and IFN-β levels were measured using supernatants from the different cultures and were quantified using IP-10 (BD Biosciences, #550926) or IFN-β (PBL assay science, #41415-1) ELISA kits respectively, according to the manufacturers' protocol. Tetramethylbenzidine substrate (Thermo Fisher Scientific) was used for quantification of the cytokines on a Fluostar OPTIMA (BMG LABTECH) plate-reader.

cGAS *in vitro* Assay and cGAMP ELISA

0.8 μg of Recombinant full-length human cGAS (Cayman, #22810) was used per single reaction in a 200 μl volume with 80 mM Tris-HCl (pH 7.5), 200 mM NaCl, 20 μM $ZnCl_2$, 20 mM $MgCl_2$, 0.25 mM GTP (Thermofisher #R0441) and 0.25 mM ATP (Thermofisher #R0461), with 20 μg of ISD70 (freshly annealed at 1 μg/μl in PBS), and 2 μl C2-Mut1/A151 diluted in TE buffer (to get 0.5, 2 or 10 μM ODN concentration in 200 μl). After 40 min at 37°C, 2.5 mM EDTA was added to each tube to stop the enzymatic reaction and the samples were either snap frozen and stored at -80°C or directly processed for cGAMP ELISA. cGAMP levels were measured with the DetectX Direct 2',3'-Cyclic GAMP Enzyme Immunoassay Kit (Arbor Assays), according to the manufacturer's protocol. Briefly, 50 μL of *in vitro* reaction were added per well of the kit microplate with 50 μL Assay buffer, 25 μL conjugate, and 25 μL Antibody per well, prior to a minimum of 2 h incubation. The standards were prepared with serial-dilution in Assay buffer. Quantification of cGAMP levels was performed on a Fluostar OPTIMA (BMG LABTECH) plate-reader at 450 nm.

Statistical Analyses

Statistical analyses were carried out using Prism 8 (GraphPad Software Inc.). Every experiment was repeated a minimum of two independent times (except the ASO screens – Figures 1D and 4D, for which key ASOs were validated in independent experiments). One-way and two-way analyses of variance (ANOVA) were used when comparing groups of conditions, while two-tailed unpaired non-parametric Mann-Whitney U tests or unpaired two-tailed *t*-tests were used when comparing pairs of conditions. Symbols used: * $P \leq 0.05$, ** $P \leq 0.01$, *** $P \leq 0.001$, **** $P \leq 0.0001$ and "ns" is non-significant.

EXAMPLE 2: Sequence-dependent effects of 2'OMe gapmer ASOs on cGAS sensing

cGAS has recently emerged as an essential sensor of cytosolic DNA deriving from pathogens and damaged endogenous nucleic acids (McWhirter and Jefferies, 2020). Upon activation by DNA, cGAS drives the formation of cyclic GMP-AMP (cGAMP), which binds to stimulator of interferon genes (STING) and promotes transcriptional induction of IRF3 responsive genes, including *CXCL10* (IP-10) and *IFNB1*. Since it instigates deleterious immune responses linked to a wide range of diseases, various approaches are being investigated currently to therapeutically target cGAS (An et al.,

2018; Laa et al., 2019; Padilla-Salinas et al., 2020; Vincent et al., 2017; Zhao et al., 2020). The present inventors originally hypothesised that strategies relying on the down-regulation of cGAS mRNA could provide other therapeutic avenues to those presented by chemical inhibitors of cGAS, which have been pursued in many other studies (An et al., 2018; Laa et al., 2019; Padilla-Salinas et al., 2020; Vincent et al., 2017; Zhao et al., 2020). To study this possibility, the present inventors designed a panel of 11 2'OMe gapmer ASOs (ASO1 to ASO11) that targeted the mRNA of human cGAS and tested their effects in HeLa cells and HT-29 cells which endogenously express cGAS (Figure 1A and Table 1). Transfection of the ASOs led to a sequence-dependent decrease of cGAS mRNA, although variable between the two cell lines, with ASO2 having a 30-50% impact, while ASO3/ASO4 robustly failed to decrease cGAS expression (Figure 1A).

The present inventors next tested the functional effect of there panel of ASOs on undifferentiated monocytic THP-1 cells, upon overnight uptake of the naked ASOs (Figure 1B). In contrast to the down-regulation signature seen in HeLa and HT-29 cells, ASO2 was the most potent oligonucleotide blocking IP-10 production after transfection of synthetic 70-bp interferon stimulating DNA (ISD70) acting as cGAS ligand (Unterholzner et al., 2010). This observation was reproduced in cGAS/STING-competent epithelial HT-29 cells (Xia et al., 2016) where overnight incubation with 125 nM of ASO2 (but not ASO4, ASO10 or ASO11) blunted ISD70-induced IP-10 production (Figure 1C). Critically, however, increased doses of ASO4, ASO10 and ASO11 also blocked ISD70-induced IP-10 production, when used at 250 or 500 nM in HT-29 (Figure 1C). Taking into account their differing effects on cGAS mRNA targeting (Figure 1A), the dose-dependent inhibitory effect of ASO4/ASO10/ASO11 on ISD70-sensing strongly suggests it was independent of cGAS mRNA targeting, but rather related to a competitive effect on cGAS sensing of ISD70; this aligns with the effect observed for PS-ODN A151 on cGAS sensing (Steinhagen et al., 2018). The hypothesis that ASOs have a direct effect on cGAS function was also consistent with the observation that ASO11 increased ISD70-sensing at low doses, but was also inhibitory at higher doses, which may relate to the binding of the ASO to the third DNA binding domain of cGAS, increasing its enzymatic activity at low dose (Xie et al., 2019) (Figure 1C).

Since ASO2 inhibited ISD70-sensing at a lower concentration than the other ASOs, it was posited that select motifs may increase the inhibitory effect of 2'OMe gapmer ASOs on ISD70-sensing of cGAS. To define this further, the present inventors screened a library of 80 2'OMe ASOs, designed to target the *CDKN2B-AS1* and *LINC-PINT* transcripts (Table 2 and (Alharbi et al., 2020)), in THP-1 transfected with ISD70 (Figure 1D). While none of these ASOs targeted the *cGAS* mRNA, 23 out of 80 decreased

ISD70-driven IP-10 production by more than 40% (Figure 1D and Table 2). A few highly inhibitory ASOs were selected from the screen for validation in THP-1 (C2, E10 and F2 ASOs) and HT-29 cells (C2 and E10 ASOs) transfected with ISD70 (Figure 1E, 1F). Overnight pre-treatment with C2 robustly inhibited ISD70-dependent IP-10 production in both cell models, while a significant effect of E10 was seen only in THP-1 cells (noting a reduction of 25% with this sequence in HT-29 cells). Importantly, C2 was a more potent inhibitor than ASO2 (Figure 1E) and A151 (Figure 1E, 1F).

The present inventors have recently shown that 2'OMe gapmer ASOs are spontaneously taken up by undifferentiated THP-1 and can modulate endosomal TLR7/8 sensing (Alharbi et al., 2020). To exclude a putative contribution of endosomal TLRs upon ISD70 transfection, the present inventors next tested the effect of C2 and ASO11 in THP-1 cells lacking *cGAS* (Mankan et al., 2014) or *UNC93B1* (Pelka et al., 2014), the latter being devoid of TLR7/8 and 9 sensing. While *cGAS*-deficient and *UNC93B1*-deficient cells similarly produced IP-10 upon stimulation with a synthetic human STING agonist (Raanjulu et al., 2018), *cGAS*-deficient THP-1 cells also lacked responsiveness to ISD70 transfection (Figure 1G). Conversely, the present inventors observed a dose-dependent inhibitory effect of C2 on ISD70 sensing in *UNC93B1*-deficient and matched wild-type cells, not seen with ASO11 (Figure 1G), ruling out a contribution of endosomal TLRs in the effects of C2 on ISD70 sensing. Collectively these results demonstrate a capacity for 2'OMe gapmer ASOs to inhibit cGAS sensing of transfected DNA, in a sequence-dependent manner.

EXAMPLE 3: Identification of a 2'OMe motif controlling cGAS inhibition

Having shown that ASO2, C2 and E10 were potent inhibitors of ISD70 sensing in THP-1, the present inventors next sought to define whether select motifs in these ASOs were involved in their inhibitory activities. MEME motif discovery analysis (Bailey and Elkan, 1994) performed on the three sequences identified a putative enriched motif in the 5' half of C2 and 3' half of both ASO2 and E10, with four highly conserved bases (Figure 2A and Figure 6A). To test the importance of these four bases, the present inventors first designed two variants of C2, substituting two (C2-Mut1) or four (C2-Mut2) of these bases (Figure 2A) – noting that the bases used to replace those in the motif were arbitrarily chosen, and could equally decrease or increase the inhibitory activity. In accord with a direct contribution of these specific bases, dose-response analyses of the C2 mutants on ISD70-driven IP-10 production in HT-29 cells showed increased inhibitory activity for both ASOs at 250 and 125 nM compared to the parent C2 ASO (this decrease being significant for C2-Mut1 at 125 nM; Figure 2B). Similarly, C2-Mut1

was significantly more inhibitory on ISD45-driven interferon stimulated response element (ISRE)-luciferase than C2 and ASO2 in mouse LL171 cells (Figure 2C). Conversely in LL171 cells, the 20-mer PS oligonucleotide (dT20) did not inhibit ISD45 sensing even at 600 nM – confirming the sequence-specific nature of the ASO inhibition in mouse cells (Figure 2C). In parallel, having shown that C2 was a more potent inhibitor than ASO2 (Figure 1E), the present inventors designed mutants of ASO2 harbouring the 5' region of C2 (ASO2up), or a mutant of the four conserved bases (ASO2down – Figure 2A). While not significant in HT-29 cells, the trend was that ASO2up was a more potent inhibitor of ISD70-driven IP-10 production than ASO2 (at 125 nM); conversely, ASO2down significantly increased IP-10 production at 62.5 and 125 nM, aligning with what was seen with ASO11 in HT-29 cells (Figure 2D).

Since two base mutations of C2 in C2-Mut1 significantly increased ISD70-driven IP-10 inhibition, the present inventors next designed a series of four C2-Mut1 mutants (C2-Mut1v1 to C2-Mut1v4) with base permutations to define whether the inhibition seen with C2-Mut1 could be improved further (Figure 2E). The present inventors also designed hybrid ASOs fusing the 5' half of C2-Mut1 to the 3' half of ASO2up (C2-ASO2-A) or ASO2down (C2-ASO2-B). Analyses of these sequences in HT-29 (Figure 2F) and THP-1 (Figure 2G) revealed that C2-Mut1 was robustly the most inhibitory sequence of ISD70 sensing, and was significantly more potent than its mutant C2-Mut1v3. Interestingly, C2-ASO2-A, which contains two fused inhibitory motifs (that of C2-Mut1 in the 5' half, and that of ASO2up/C2 in the 3' half), had a similar potency to that of C2-Mut1, indicating that duplicating the inhibitory motif in the 3' end region of the ASO did not significantly improve the inhibition (Figures 2F, 2G). Nonetheless, in THP-1 cells, C2-ASO2-B was significantly less inhibitory than C2-ASO2-A and ASO2down was significantly less inhibitory than ASO2up, confirming that 3' end regions could also play a role in the inhibition of ISD70 sensing (Figure 2G).

EXAMPLE 4: cGAS inhibition by a minimal mGmGmUATC motif

The present inventors next asked whether the 2'OMe chemical modification of gapmer ASOs was at play in their effect on cGAS. The inhibitory effect of C2-Mut1 was significantly decreased in a C2-Mut1 analogue where the 2'OMe ends were replaced by DNA bases on a PS-backbone (referred to as C2-Mut1-PS), in both mouse LL171 and human THP-1 cells (Figures 2H, 2I and Table 1). In addition, MEME motif discovery on the 10 most inhibitory ASOs from the screen (Figure 1D and Table 2) revealed that 5 ASOs harboured a conserved [A/G]GUC[U/C]C (SEQ ID NO: 344) motif aligned with that of C2 and C2-Mut1, which was predominantly overlapping with their 2'OMe 5' end

(Figure 6B). Interestingly, one of these sequences, '[LINC-PINT]103' (referred to as ASO103), was part of a family of sequences with single base increments (Table 2 and Figure 2J). Within this series, ASO103 was the only sequence significantly inhibiting ISD70-driven IP-10 production in THP-1 cells, further supporting that the 5'-end location and 2'OMe modifications were likely essential to the ASO inhibitory function (Figure 2K).

The data collected so far demonstrated that long (i.e. 6 h – 16 h) pre-incubation with 2'OMe gapmer led to inhibition of ISD sensing by cGAS. To tease out the role of the pre-incubation on the inhibitory activity of the ASOs, the present inventors compared the effect of C2-Mut1 pre-incubated for 6 h in LL171 cells, with or without a wash prior to the transfection of ISD45. Also tested was the effect of ASOs added a short time prior to the transfection of ISD45 (~20 min). While pre-incubation of the ASOs for a shorter duration did not impact their inhibitory effect on ISD45-driven ISRE-Luc expression, the addition of a washing step significantly blunted inhibition (Figure 2L). These findings suggested that the ASOs were somewhat co-transfected with the liposome containing ISD. Accordingly, increased intracellular fluorescent punctua of ASO2-Cy3 were observed following ISD70 transfection of HT-29 cells (Figure 7), altogether suggesting that the ASOs competed with ISD for cGAS sensing intracellularly.

Relying on this shorter ASO pre-incubation, the present inventors next sought to confirm the core motif modulating cGAS inhibition in C2-Mut1, starting from a 20-mer homopolymeric sequence of dCs on a PS backbone (dC20), to which the minimal 2'OMe containing terminal 5' mGmGmUATC motif of C2-Mut1 was added (referred to Mut1-dC) (Figure 2E). Mut1-dC was significantly more inhibitory than its precursor dC20 on ISD sensing in LL171 and THP-1 cells (Figures 2M, 2N). In addition, the two base-mutations (m**C**mGm**U**T**T**C) in Mut1v3-dC lacked significant inhibitory activity in both cell models (Figures 2M, 2N). Collectively with previous observations, these results establish that the minimal mGmGmUATC motif is sufficient to confer cGAS inhibition to a PS-modified homopolymeric sequence, with a predominant role for the two bases previously identified.

The present inventors further found that Mut-1dC, which harbours the cGAS inhibitory motif also demonstrates significantly higher TLR7 inhibition than dC20 (Figure 12). This establishes that the minimal motif presently defined for cGAS is also capable of conferring TLR7 inhibition to oligonucleotides.

EXAMPLE 5: Sequence-specific inhibition of cGAS activity by C2-mut1

Having identified C2-Mut1 as the most potent 2'OMe ASO inhibitor of cGAS, the present inventors performed dose-response analyses to determine its IC50 in the THP-1 model and to compare it to that of A151 (Steinhagen et al., 2018). Based on IP-10 driven production after ISD70 transfection, it was determined that the IC50 of C2-Mut1 was 56 nM compared to 165 nM for A151 (Figure 3A). This greater inhibitory activity of C2-Mut1 over that of A151 on DNA sensing was confirmed looking at the production of IFN-β, which was blocked with C2-Mut1 at 125 nM, while only reduced by ~50% for A151 (Figure 3B). It is also noteworthy that treatment of the cells with C2-Mut1 did not significantly impact cell viability in the assays in THP-1 and HT-29 cells (Figure 8).

Critically, 6 h pre-incubation with high dose C2-Mut1 (500 nM) did not significantly affect IP-10 production driven by lipopolysaccharide (LPS – TLR4 ligand) or STING synthetic agonists, in human MG-63 and immortalised mouse bone marrow derived macrophages (BMDMs), although significantly impacting ISD sensing (Figures 3C, 3D). Similarly, C2-Mut1 did not impact production of TNF-α upon LPS, PAM3CSK4 (TLR2/1 ligand) or DMXAA (mouse Sting agonist) treatment (Figure 3D). Nonetheless, C2-Mut1 pre-incubation significantly decreased sensing of the CpG ODN 1826 which activates mouse Tlr9, as revealed by dampened TNF-α production in immortalised BMDMs (Figure 3D). This is consistent with the previous report that PS-2'OMe ASO can impact endosomal sensing by TLRs such as TLR7/8 in phagocytes (Alharbi et al., 2020), but indicates that C2-Mut1 is not broadly inhibiting non-nucleic acid sensing pathways such as TLR1/2/4, nor acting at the level of downstream signalling cascades.

In vitro, cGAS has previously been shown to be bound and weakly activated by single stranded ISD45 (Kranzusch et al., 2013), leading us to posit that single stranded PS-ASOs could act as "inactive" competitors of double stranded ISD. To directly assess this, recombinant cGAS was incubated *in vitro* with 2.3 μM (0.1 μg/μl) of ISD70 in the presence of increasing amount of C2-Mut1 or A151 (0.5, 2 and 10 μM). Critically, while both PS-ODNs similarly reduced cGAMP production driven by ISD70 at 0.5 μM, the inhibitory activity of C2-Mut1 was significantly greater than that of A151 (about 2 fold more) at 2 μM (Figure 3E). Under these specific conditions *in vitro*, C2-Mut1 was therefore able to displace more molecules of ISD70 than A151, suggesting its stronger affinity for cGAS than A151. Collectively with the cell based assays, these observations support that C2-Mut1 acts as an inactive competitor of ISD70 binding to cGAS.

The present inventors further demonstrated that a fully 2'Ome modified version of C2Mut1 was also strongly blunting of cGAS activation by ISD70 (Figure 13).

EXAMPLE 6: C2-mut1 inhibits constitutively active cGAS signalling

Since the experiments to this point strictly relied on cGAS sensing of exogenously transfected ISD, the present inventors next investigated the effects of the ASOs on cell models with constitutive cGAS activation. They first compared the dose-dependent effect of C2-Mut1 and C2-Mut1v3 transfected In human BJ hTERT fibroblasts stably expressing SV40T and RASG12V (Quin et al., 2016), which display a basal level of constitutive cGAS activation (Pepin et al., 2017). Transfected C2-Mut1 was significantly more potent than its two nucleotide variant C2-Mut1v3 in inhibiting expression of several interferon stimulated genes (ISGs) (*IFIT1*, *IFIT2* and *IFI44*) constitutively expressed in these cells (Uhlen et al., 2017), while being comparable to aspirin treatment that blocks cGAS activity (Dai et al., 2019) (Figure 3F). Secondly, overnight transfection of C2-Mut1 and C2-Mut1-v3 significantly decreased the basal expression of two ISGs (*Rsad2* and *Ifit1*) in primary mouse bone marrow derived macrophages (BMDMs) from *Trex1*-mutant mice (Q169X – see Material and Methods) – which exhibit accumulated cytoplasmic DNA and constitutive cGAS-STING signalling (Figure 3G) (McWhirter and Jefferies, 2020). Conversely, transfection of a similar dose of A151 failed to inhibit these ISGs (Figure 3G).

cGAS activation has recently been shown to play an important role in the paracrine propagation of senescence between cells (Gluck et al., 2017; Dou et al., 2017). As such, senescence-associated β-galactosidase (SAB) was strongly decreased during the expansion of primary mouse fibroblasts from *cGas*-deficient mice (Gluck et al., 2017). the present inventors therefore decided to investigate the capacity of C2-Mut1 to inhibit spontaneous engagement of cGAS-STING signalling, in pre-senescent primary fibroblasts-like synoviocytes (FLS) and primary bone marrow-derived mesenchymal stem cells (MSCs). For this purpose they grew the primary cells in the presence of 1 to 5 μM C2-Mut1 ASO (passively taken up by the cells by gymnosis) for one to two weeks. While a large proportion of cells were senescent in non-ASO treated cells after this period (based on β-galactosidase positive staining – seen in up to ~40-50% of the cells), senescence was strongly reduced in C2-Mut1-treated FLS cells and MSCs (Figure 9A, 9B). Further experiments in another set of FLS cells showed that C2-Mut1 was more potent in inhibiting SAB than its PS only variant C2-Mut1-PS, or its mutant C2-Mut1v3. Similarly, C2-Mut1 was a more potent inhibitor of SAB than A151 (Figure 9C), aligning with the concept that this activity pertained to its increased inhibition of cGAS.

Collectively, these results demonstrate that C2-Mut1 significantly inhibits constitutive cGAS sensing of endogenous cytoplasmic DNA, in a sequence-dependent manner.

EXAMPLE 7: Sequence-dependent TLR9 inhibition by 2'OMe gapmer ASOs

Having demonstrated the sequence-dependent modulation of cGAS sensing of DNA by 2'OMe gapmer ASOs, the present inventors next turned to their effect on DNA sensing by TLR9, with the aim of providing a broad picture of their impact on DNA sensing in human cells. As such, while there is ample evidence for sequence-dependent TLR9 modulation with select PS-ASOs (Krieg et al., 1995; Barrat et al., 2005), including A151 (Gursel et al., 2003), the impact of 2'OMe moieties in the context of PS-gapmer ASOs, is not defined. They recently demonstrated that 2'OMe gapmer ASOs did not frequently activate TLR9, with the exception of "T" rich sequences (Alharbi et al., 2020). To characterise whether 2'OMe gapmer ASOs instead led to inhibition of DNA sensing by TLR9, as indicated with the results in BMDMs with C2-Mut1 (Figure 3D), the present inventors tested the panel of 11 cGAS ASOs on TLR9 sensing of CpG ODN2006 in HEK cells expressing human TLR9 (HEK-TLR9 hereafter) and a NF-κB luciferase reporter. They included PS-ODN A151 and IRS957, which have been reported to inhibit TLR9, along with their respective controls, C151 and IRS661 (Gursel et al., 2003; Barrat et al., 2005)). Several ASOs significantly inhibited TLR9 sensing of ODN2006, including ASO2, 4, 5, 6, 7, 8, 9, 10 (Figure 4A). However, ASO2, IRS957 and A151 were the only oligonucleotides reducing NF-κB luciferase induction by more than 80%. The previous observation that ASO11, which lacked the capacity to inhibit TLR9 but strongly potentiated TLR8 in HEK cells (Alharbi et al., 2020), indicated that the sequence-specific effects seen here were not related to uptake of the ASOs, but rather due a competitive effect of specific motifs on ODN2006 sensing by TLR9.

To investigate further the sequence determinants of TLR9 inhibition by 2'OMe gapmer ASOs, the present inventors initially assessed the effect of ASO2 3'-end mutants (ASO2up and ASO2down) and ASO11 mutants where the 5' or 3' 2'OMe regions had been swapped with those of ASO2 (ASO11Mut1 and ASO11Mut2) in HEK-TLR9 cells (Figures 4B, 4C). The four-base substitutions in the 3'-end of ASO2down significantly reduced TLR9 inhibition, unlike those in ASO2up, indicating the inhibitory effect was partially dependent on the sequence of the 3' half of ASO2. Critically, substitution of ASO11 5'-end 2'OMe region with that of ASO2 (ASO11Mut2), but not its 3'-end (ASO11Mut1), conferred significant TLR9 inhibition to ASO11, suggesting that the 5'-end of ASO2 is also at play in its regulatory effect on TLR9 (Figure 4C).

To gain further insights into the sequence-dependent inhibition of TLR9 sensing of DNA by 2'OMe gapmer ASOs, the present inventors next tested the panel of 80 2'OMe ASOs in HEK-TLR9 cells, (Figure 4D and Table 2). They observed that only 8 out of the 80 ASOs inhibited TLR9 by more than 50% (Table 2), and ASO2 remained the most potent ASO tested. MEME motif discovery on the top 10 ASOs from this screen revealed significant enrichment in 3 ASOs of a "GGCCTC" (SEQ ID NO: 204) motif also present in ASO2, and a "A"-rich central region in 5 out of the 10 ASOs (Figures 4E, 4F and Figures 6C, 6D). Accordingly, comparison of the central DNA regions of the 16 most and least inhibitory ASOs in the TLR9 screen showed a significantly higher proportion of central "As" in more potent TLR9 inhibitory sequences (Figure 4G and Table 2).

Closer analyses of two ASOs families from the screen with single base increments also pointed to an important role for 5' 2'OMe "CUU" (SEQ ID NO: 153) motifs in TLR9 inhibition (Table 2). Validation of the first family, referred to as the "CDKN2B-AS1" series (ASO2133-2139), suggested that addition of a 5'-end terminal "CUU" motif in ASO2139 significantly increased TLR9 inhibition (Figure 4H, 4I). Aligning with this observation, analyses of the "LINC-PINT" series of ASOs (ASO8-ASO116), also harbouring 5' or 3' "CUU" (SEQ ID NO: 153) motifs, demonstrated that "CUU/CUT" motifs (CUU - SEQ ID NO: 153; CUT - SEQ ID NO: 202) present in the 2'OMe region of the ASOs (ASO112-115) were associated with a significant increase in TLR9 inhibition compared to ASO108-110 containing such 2'OMe "CUU" (SEQ ID NO: 153) motifs in their 5' end (Figures 4I, 4J).

To define further the role of 2'OMe "CUU" (SEQ ID NO: 153) motifs on the modulation of TLR9 sensing, the present inventors next used an additional panel of 2'OMe ASOs targeting the mRNA of HPRT (Figure 4K and (Alharbi et al., 2020)). While 5'-end terminal "CUU" (SEQ ID NO: 153) motifs in ASO [HPRT]551 and 660 were associated with >60% inhibition of TLR9, addition of a single 5'-end terminal base to the "CUU" (SEQ ID NO: 153) motif ("ACUU", SEQ ID NO: 346) in ASO661 significantly limited inhibition (Figure 4K, 4L). Conversely, ASO662, with its "CACUUU" (SEQ ID NO: 347) 5'-end 2'OMe region displayed the strongest inhibition of this series of ASOs, although this may also be related to a contribution of its "UUUUC" (SEQ ID NO: 348) 3'-end (uniquely present in this sequence in this series). Interestingly, ASO666 also strongly inhibited TLR9, while not displaying any "CUU" (SEQ ID NO: 153) motif and only differing by two bases from ASO665, which was only poorly inhibitory (Figure 4K, 4L). Nonetheless these results are only suggestive of a role for selected motifs in the modulation of TLR9 inhibition, and need to be taken with

caution given the putative impact of base increments on 2'OMe regions, which could confound results interpretation. Taken together, these results demonstrate a complex regulation of TLR9 inhibition by 2'OMe gapmer ASOs, including preferential contributions from central (preferentially "A" rich) and 5'-end 2'OMe regions.

In contrast with these findings, the present inventors have recently reported that 2'OMe "CUU" ("CUU", SEQ ID NO: 153) motifs could help mitigate TLR7 inhibition by 2'OMe gapmer ASOs (Alharbi et al., 2020), suggesting an inverse relationship between the modulation of these two sensors. They therefore analysed the correlation of the effect of the 80 ASOs on TLR9 and TLR7 inhibition (Alharbi et al., 2020), presented in Figure 4M. There was no correlation between the activities of the ASOs on TLR7 and TLR9, exemplified with ASO[LINC-PINT]108, ASO109, ASO116 and A10 which had limited effect on TLR9, and TLR7, unlike ASO[CDKN2B-AS1]2139, which did not inhibit TLR7 but strongly inhibited TLR9.

EXAMPLE 8: C2-Mut1 is a potent inhibitor of human cGAS, TLR7 and TLR3 but not TLR9

Having generated immunomodulatory profiles for the panel of 80 2'OMe ASOs on TLR7/TLR8 (Alharbi et al., 2020), TLR9 and cGAS, the present inventors generated a bubble chart to visualise the correlation of inhibition of DNA sensing by cGAS and TLR9, while also incorporating data on TLR7 inhibition and TLR8 potentiation (Figure 5A and Table 2). There was no significant correlation between TLR9 and cGAS inhibition, illustrated by the example that C2, the most potent cGAS inhibitor in the screen did not inhibit TLR9 (Figure 5A). This observation was validated in HEK-TLR9 cells with C2 and its mutants C2-Mut1 and C2-ASO2-A. While the C2 mutants were significantly better inhibitors of TLR9 than their parent ASO, their inhibitory effect on TLR9 sensing was limited compared to that of ASO2 or A151 (Figure 5B).

As shown in Figure 5A, the patterns of immunomodulation on these sensors was highly variable with only a few ASOs inhibiting TLR7, TLR9 and cGAS (e.g. C4, C6 and H7) (Table 2). Nonetheless, there was a significant correlation between cGAS and TLR7 inhibition (Figure 5C), with the strongest inhibitors of cGAS also displaying strong TLR7 repression (e.g. C2, E10, F2, H7; Figure 5C). Consistent with this, the most potent cGAS inhibitor, C2-Mut1, was also a strong inhibitor of R848 sensing by TLR7, with an IC50 of 44 nM, against 132 nM for A151 (Figure 5D). Critically, only 4 ASOs in the screen (i.e. 5%) did not inhibit any of TLR7, TLR9 or cGAS by more than 30% (highlighted in red in Figure 5A, and in yellow in Table 2), demonstrating that most 2'OMe ASOs have immunosuppressive effects.

Unlike their inhibitory effect on TLR7, the present inventors recently discovered that select 2'OMe gapmer ASOs could potentiate TLR8 sensing of R848, presenting potential therapeutic opportunities in immune-oncology (Alharbi et al., 2020). Interestingly, TLR8 potentiation was also inversely correlated with cGAS inhibition, with the best TLR8 potentiators lacking cGAS inhibition (e.g. G7, A9, D9, G9) (Figure 5E). Accordingly C2 was a weak potentiator of TLR8, but select ASOs may be able to inhibit cGAS while potentiating TLR8 sensing, as seen with the example of ASO2 (Figure 1 and (Alharbi et al., 2020)).

Finally, the present inventors tested the effect of the panel of 11 cGAS ASOs on the sensing of untransfected double stranded RNA (polyI:C) by human TLR3 sensing (including IRS661, IRS957, A151 and its mutant C151) in HEK 293 cells stably expressing human TLR3 (HEK-TLR3) and a NF-κB luciferase reporter (noting that these cells are not responsive to the amount of untransfected polyI:C they used, through RIG-I or MDA5). While all 2'OMe gapmer ASOs used at 500 nM along with IRS661 and IRS957 blocked polyI:C sensing, A151 and C151 only partially reduced polyI:C-dependent TLR3 activation in these cells (Figure 10A). Sequence-specific inhibition of TLR3 was more visible with 100 nM ASOs, where only ASO5 retained significant inhibition of polyI:C sensing (Figure 10B). Direct comparison of the inhibitory effect of C2-Mut1 and A151 on TLR3 sensing in HEK-TLR3 cells confirmed the stronger inhibition of C2-Mut1, with an IC50 of 62 nM for C2-Mut1 and an IC50 greater than 750 nM for A151 (Figure 5F). Collectively these results demonstrate that C2-Mut1 is a potent inhibitor of human cGAS, TLR7 and TLR3, but a weaker inhibitor of TLR9.

EXAMPLE 9: Motif-specific inhibition of TLR7 by 2'O-methyl ASOs.

Previous Examples have shown that addition of the **mG*mG*mU*A*T** motif to a stretch of dCs on a phosphorothioate backbone was sufficient to promote inhibition of R848 sensing by TLR7 (see Figure 11, Mut1-dC compared to dC20 ASO), directly implicating the 2'O-methyl (2'OMe) motif in this inhibitory effect.

Critically, it is now found that substitution of two bases in this motif significantly altered TLR7 inhibition (compare Mut1-dC and Mut1-v3-dC), demonstrating the motif-specific effect of **mG*mG*mU*A*T** on TLR7 inhibition in HEK TLR7 cells (Figure 14A).

Further, it is hypothesized that similar to TLR8 sensing of RNA (Greulich et al., 2019), the ASOs may be cleaved at selective positions by a yet-to-be-defined enzyme, to release the TLR7 inhibitory motif. To test this, 5-nt short 2'OMe oligonucleotides were synthesized with a full PS-backbone containing the Mut1 motif and its variant Mut1-v3

(Mut1-short and Mut1-v3-short, respectively). The present inventors also included a short oligonucleotide which was not expected to inhibit TLR7 (based on ASO 660). Accordingly, it has been demonstrated that Mut1-short was sufficient to inhibit R848 sensing in HEK-TLR7 cells, while its variant and unrelated sequence failed to do so (Figure 14B). It is noteworthy that pre-incubation of 6 h was necessary to obtain inhibition with Mut1-short and no inhibition was observed with ~30 min pre-treatment. Collectively, these observations clearly demonstrate that TLR7 inhibition can be achieved by the specific "**mGmGmUmAmU**" motif.

EXAMPLE 10: Motif specific inhibition of Guanosine sensing by 2'O-methyl ASOs.

To broaden the present observations, the present inventors next tested whether the 2'OMe ASOs could inhibit TLR7 activation by Guanosine which acts as an endogenous TLR7 ligand (Shibata et al., 2016). For this purpose, the effect of the ASOs was tested on primary bone marrow derived macrophages (BMDMs) from wild-type mice, stimulated overnight with 500 μM Guanosine and pre-treated or not with 200 nM ASOs. Similar to what was seen with inhibition of R848 sensing by TLR7 in HEK TLR7 cells, the ASOs inhibited TNFα production induced by guanosine, in a sequence specific manner – with C2-Mut1 and Mut1-dC significantly inhibiting TNFα levels while Mut1-v3-dC or dC20 did not (Figure 14C).

In accordance with this, Mut1-dC but not its mutant Mut1-v3-dC significantly reduced constitutive TLR7 activation in primary BMDMs from *Tlr7* mutant mice (*Tlr7* Y264H – Brown and Vinuesa, et al. Nature, 2022, in press), as measured with reduced *TNFα* and *Oas3* mRNA levels. Importantly, the effect of Mut1-dC was specific to TLR7 since the ASOs did not reduce *TNFα* and *Oas3* mRNA levels in wild-type primary BMDMs (Figure 15).

Collectively, these results provided direct evidence that while most 2'OMe ASOs are strong TLR7 inhibitors (excluding those with a "CUU" motif that limits inhibition), selected motifs conferred a stronger inhibition of TLR7 sensing than others. The observation that the **mG*mG*mU*mA*mU** (SEQ ID NO: 56) of Mut1-dC and Mut1-short inhibits TLR7 sensing of guanosine but not its **mC*mG*mU*mU*mU** (SEQ ID NO: 349) variant, establishes a very specific activity of selected residues in the motif conferring inhibition.

Beyond the widespread inhibitory effect on TLR7 by ASOs, the present work establishes the capacity of selective short oligonucleotide motifs to act as strong TLR7 antagonists. This challenges the previous report that TLR7 inhibition could be achieved by any 2′OMe-U, 2′OMe-G, or 2′OMe-A modified RNAs with no sequence-dependent

effect (Robbins et al., 2007). The use of short 5-mer oligos such as Mut1-short could therefore present novel opportunities to limit TLR7 engagement when combined to unmodified T7-synthesised RNA used in mRNA vaccines, as an alternative to the use of uridine modifications (such as pseudo-uridine) of the mRNA itself.

EXAMPLE 11: Motif-specific inhibition of TLR7 is not restricted to 2'OMe ASOs.

Previous Examples have screened 91 LNA and 76 2'MOE modified ASOs for TLR7 inhibition in HEK TLR7 cells (see PCT 2020901606). While searching for motifs that may underpin TLR7 inhibition, the present inventors identified a selective GGCTTC (SEQ ID NO: 295) motif enriched in the top 10 2'MOE TLR7 inhibitors from this screen (Figure 16). More specifically, positions 2, 5 and 6 of this motif (i.e. xGxxTC) were very enriched. To confirm the involvement of this motif in TLR7 inhibition the present inventors chose one of these sequences, F5 (EGFR-1014 MOE), and mutated its predicted motif at positions 2, 5 and 6 (Figure 16). While F5 was strongly inhibiting TLR7, its mutant F5-Mut was significantly less inhibitory directly demonstrating the role of this motif in TLR7 inhibition. These results demonstrate that the 2'MOE GGCTCC (SEQ ID NO: 295) motif in F5 is directly implicated in TLR7 inhibition, establishing that motif specific TLR7 inhibition is not limited to 2'OMe ASOs and can also be observed with other chemical modifications.

EXAMPLE 12: Inhibition of cGAS by 2'O-methyl modified ASOs

Previous Examples have demonstrated that 2'OMe ASOs with a 5' end **mG*mG*mU*A*T** motif are potent inhibitors of cGAS (Valentin et al., 2021). Critically, this motif was sufficient to confer inhibition of cGAS to the 5'enf of a stretch of 15 dCs (effect which was ablated when the motif was mutated to **mC*mG*mU*T*T** directly implicating these two bases in the effect). To determine whether this approach could be used to turn any 2'OMe ASO into a cGAS inhibitor, the present inventors next assessed whether adding bases to the 5'end of an ASO targeted to the mRNA of HPRT [ASO 847] (with very potent gene targeting efficacy – see (Alharbi et al., 2020)) could increase its cGAS inhibitory activity. Critically, the 5'end of ASO847 is **mA*mU**, meaning that only **mG*mG*mU** was appended to its 5'end to reconstitute the **mG*mG*mU*mA*mU** motif (giving a 23 nt ASO – 847-Mut).

Accordingly, the present inventors tested the inhibitory effect of ASO847 and ASO847-Mut in THP-1 and MG-63 cells transfected with the cGAS ligand ISD70 (Figure 17). In both models it was demonstrated that ASO847-Mut was a much better inhibitor of cGAS – directly demonstrating proof-of- principle that adding a few 5'end

nucleotides to reconstitute the inhibitory motif of C2-Mut1 (Valentin et al., 2021) was sufficient to increase cGAS inhibition of an otherwise poorly inhibitory sequence. Similarly, ASO847-Mut was a better inhibitor against mouse cGAS activation by ISD45 in LL171 cells.

To further these observations it was tested whether ASO847-Mut retained its inhibitory activity against HPRT targeting, while inhibiting constitutive ISG expression in BJ7 cells (human fibroblasts expressing SV40T) (Valentin et al., 2021). These experiments confirmed that ASO847-Mut was still able to reduce HPRT levels, to the level seen with ASO847 (Figure 18). Critically however, ASO847-Mut was as potent as C2-Mut1 to decrease expressing of the ISG IFIT2 in these studies, while ASO847 was significantly less potent – aligning with the experiments conducted in MG-63 cells (Figure 17).

Collectively, these experiments established proof of principle that a pre-existing ASO could be modified through 5' end base additions to reconstitute the 5' **mG*mG*mU*mA/A*mU/T** cGAS inhibitor motif, to confer increased cGAS inhibition.

The present inventors have previously shown that the **mG*mG*mU*A*T** cGAS inhibitor motif, appended to the 5' end of a 15 bases dC oligonucleotide (Mut1-dC), significantly increased cGAS inhibition in a motif-dependent manner – since the 2 base mutant Mut1-v3-dC did not (4). Mut1-v3-dC contains mutations at position 1 and 4 of the motif **(mC*mG*mU*T*T)** establishing that at least one of these bases is essential for cGAS inhibition.

In order to define whether the **mG*mG*mU*A*T** cGAS inhibitor motif could be truncated further, the present inventors generated two shorter variants of Mut1-dC, referred to as Mut1-dC-v2 **(mG*mG*mU*A)** and Mut1-dC-v3 **(mG*mG*mU)** the latter lacking base #4 of the motif. Analyses in THP-1 cells stimulated with the cGAS ligand ISD70 demonstrated that both shorter forms significantly inhibited cGAS sensing, but that the 4-mer was more potent than the 3-mer motif (Figure 19). These results suggest that 5' additions to an ASO reconstituting a 5' **mG*mG*mU** or **mG*mG*mU*A/ mG*mG*mU*mA** motif are sufficient to increase its capacity to inhibit cGAS.

EXAMPLE 13: Inhibition of cGAS by 2'MOE and LNA modified ASOs

To define whether cGAS inhibition could be promoted by other ASO chemical modifications, 87 LNA and 76 2'MOE modified ASOs were screened for reduction of IP-10 production upon ISD70 transfection of THP-1 cells. While selected ASOs that

repressed cGAS sensing with either chemistry, the overall repression appeared stronger with 2MOE ASOs than LNA ASOs. As such, 32/87 (i.e. 36.7%) ASOs repressed cGAS signal by more than 40% with LNA, versus 59/76 (i.e. 77.6%) for 2MOE at the dose used (Figure 20).

The present inventors next selected the top 9 inhibiting ASOs for the LNA screen. In agreement with a lower inhibitory effect of LNA ASOs, several of the ASOs failed to significantly inhibit cGAS in validations experiments (Figure 21 – e.g. A6 and E1) – noting that 300 nM ASOs was used here, compared to 200 nM for MOE ASOs after. Nonetheless, select ASOs potently inhibited signalling, with A1, D2 and F1 being the most potent (Figure 21).

For the MOE screen, the present inventors selected the top 11 inhibiting ASOs. Aligning with their better inhibitory activity than LNA ASOs, all the MOE ASOs tested in these validation experiments significantly inhibited cGAS, with B3 and E9 being the most potent (Figure 21).

The present inventors also wanted to test whether the ASOs could inhibit murine cGAS – since it was found that some 2'OMe ASOs such as C2-Mut1 could be active in both species. The present inventors therefore tested the 9 LNA ASOs and 11 MOE ASOs from the screen and assessed them for inhibition of ISD sensing in LL171 reporter cells. For MOE ASOs, half the sequences significantly inhibited cGAS in this system, with B3, F3, F10 being the most potent (Figure 22).

Conversely, at the dose used, little to no inhibition was observed with the LNA ASOs, with two ASOs strongly potentiating the ISRE-Luciferase signal in response to transfected ISD – D2 and F1 (Figure 22). While surprising, the present inventors have previously observed a significant potentiation of cGAS with selected ASOs (Valentin et al., 2021), and it has recently been reported that selected CpG oligonucleotides could directly engage with cGAS to activate it (Bode et al., 2021). It was particularly noteworthy that D2 would potentiate cGAS signalling in mouse while being one of the few significant inhibitors of cGAS in human cells – highlighting key differences of ASO effects on cGAS between species.

EXAMPLE 14: Motif-specific inhibition of cGAS by 2'MOE and LNA modified ASOs

Motif discovery analyses was then performed with the MEME sequence analysis tool on the best cGAS inhibitors confirmed in human cells. For LNA ASOs, the present inventors first focused on a **G*T*C*T** (SEQ ID NO: 62) motif conserved between A1 and F1, which were both significant inhibitors of cGAS in THP-1 cells. The present

inventors mutated this 1st motif into a **C*T*C*C** (SEQ ID NO: 64) motif in A1-Mut (Figure 23). In addition, the present inventors were interested to confirm the sequence-specific and species-specific effect of D2 (which inhibited in human cells but potentiated in mouse cells). Alignment of the 5 best ASOs in THP-1 assays identified a 2nd motif conserved between B1, F1 and D2 which was mutated in D2 at position 3 and 4 – the most conserved bases. This resulted in D2-Mut (Figure 23).

Similarly, the present inventors looked for enriched motifs in the 11 MOE ASOs which strongly inhibited cGAS in THP-1 cells. The first MOE motif investigated was very conserved between B3 (the most potent ASO in THP-1 also inhibiting in mouse LL171 cells) and E9. Importantly, this **G*G*T*T** (SEQ ID NO: 72) motif was very similar to the **G*G*T*A** (SEQ ID NO: 350) motif from the 2'OMe C2-Mut1 ASO. This motif was mutated in B3 to obtain **C*G*C*T** (SEQ ID NO: 351) in B3-Mut. The second MOE motif selected was highly enriched in 8/11 ASOs. The conserved **G*C*T*T** (SEQ ID NO: 80) was mutated into **C*C*C*T** (SEQ ID NO: 352) within F10 (resulting in F10-Mut) (Figure 23).

These ASOs and their mutants were tested in THP-1 cells at a single dose (using 200 nM for MOE ASOs, and 300 nM for the LNA, which were less potent), and also tested them in LL171 cells.

In THP-1 cells, the mutants of B3-MOE, F10-MOE and D2-LNA all lost the capacity to inhibit cGAS signalling, establishing the importance of these specific motifs in cGAS inhibition. Surprisingly, the 2-base modifications of A1-LNA rather significantly increased cGAS inhibition in human cells (similar to what the present inventors obtained when they discovered C2-mut1 was more potent than the parent 2'OMe C2 ASO (Valentin et al., 2021)) (Figure 23). This suggests that bases substitutions rather improved cGAS inhibition for this motif.

In mouse LL171 cells, the mutations of B3-MOE and F10-MOE also significantly altered cGAS inhibition (Figure 23). Contrarily to human cells where it was a more potent inhibitor of cGAS, the mutant of A1-LNA lost inhibitory activity in mouse cells and rather potentiated signalling. In addition, the mutation of D2-LNA significantly thwarted its potentiating effect in mouse cells (Figure 23).

These observation for the LNA ASOs on mouse LL171 cells were confirmed in dose-response studies – where increasing amount of D2-LNA increased potentiation of ISD sensing (Figure 24).

The present inventors also tested the inhibitory effects of their ASOs and their mutants in human MG-63 osteosarcoma cells – which are responsive to cGAS ligands (Valentin et al., 2021) – to broaden their findings beyond the case of human monocytic

cells. Interestingly, in MG-63 cells, the ASOs were not as potent inhibitors of cGAS and only B3 and A1-Mut significantly reduced IP-10 levels at the doses tested. Critically, B3-Mut and A1 did not inhibit IP-10 production, confirming the sequence-specific effects of MOE and LNA ASOs in these cells (Figure 24).

Next, specificity of inhibition was assessed in MG-63 cells using a higher dose of ASOs (1 mM) for F10, A1-Mut and D2. In one preliminary experiment, all the ASOs only reduced IP-10 driven by ISD, and not that driven by direct stimulation of STING with the GSK synthetic agonist, or by TLR3 engagement with polyI:C (Figure 25).

Finally, the present inventors wanted to test whether the observations made in mouse LL171 cells could also be replicated in mouse macrophages. The best ASOs and associated mutants were tested in immortalised mouse bone marrow derived macrophages (iBMDMs), stimulated with ISD, looking at IP-10 production as a read-out. While B3 and F10 significantly reduced ISD-induced IP-10, none of the other ASOs were inhibitory in this context. Surprisingly, A1-Mut and D2 did not significantly potentiate IP-10 production, in opposition to what was seen in fibroblast LL171 cells. While cGAS sensing may be differentially regulated between the macrophages and LL171 cells, it is also possible that kinetics of potentiation may be different and mask early potentiation using an overnight time point.

Nonetheless, the A1-Mut induced low level IP-10 when transfected alone in the absence of ISD. Whether this is due to cGAS activation remains to be confirmed, but this aligns with the lack of inhibitory activity of this sequence on ISD sensing (Figure 26).

Collectively these results establish the motif-specific inhibitory effects of 2MOE and LNA ASOs on human and mouse cGAS sensing of DNA. Critically, the LNA motifs modulating cGAS activity in mouse fibroblasts had opposite effects in human cells – suggesting that at least for LNA modified ASOs there are critical inter-species differences to consider regarding their modulation of cGAS activity.

EXAMPLE 15: Analyses of 2'MOE and LNA modified ASOs potency compared to C2-Mut1

The present inventors have previously reported that the IC50 of C2-Mut1 was ~56 nM in THP-1 cells. The present inventors next assessed the inhibitory effect of the LNA and MOE ASOs and their sequence mutants, using dose-responses studies in THP-1 cells. First, for 2MOE ASOs, the present inventors determined that the IC50 of B3 and F10 were 133 and 147 nM, respectively (Figure 27). Motif mutation of B3 and F10 strongly impacted their inhibitory activities, with F10-Mut performing the worst.

Second, the present inventors independently determined that the IC50 of A1-Mut and D2 were 75 and 212 nM, respectively. Motif mutants were also strongly impacted (Figure 27). Collectively, these analyses indicated that 2'MOE B3 and LNA A1-Mut were the most potent inhibitors of cGAS in THP-1 cells (aligning with what had found previously in MG-63 cells).

Whether A1-Mut is more potent than B3 however remains to be confirmed in head-to-head comparisons, in the same experiments. Nonetheless the present inventors note that B3 was a much more potent cGAS inhibitor in MG-63 cells suggesting that it is a more robust inhibitor than A1-Mut overall between cells lines (Figures 27 and 24).

Interestingly, there is a discrepancy of activity between THP-1 and MG-63 cells regarding the activity of the F10 MOE ASO (Figures 27 and 24). While very potent in THP-1, this ASO failed to inhibit cGAS under 500 nM in MG-63 cells (although it was inhibitory when used at 1 mM – Figure 25).

Finally, a preliminary experiment was performed to assess the capacity of the MOE and LNA ASOs to inhibit human cGAS enzymatic activity in vitro. In this system, recombinant cGAS is incubated with ISD70 in the presence or absence of the ASOs and cGAMP formation is subsequently assessed using a specific cGAMP ELISA (Valentin et al., 2021). The present inventors tested the ASOs at 2 μM as per their previous studies (Valentin et al., 2021). Surprisingly, while all the ASOs and their respective mutants strongly inhibited cGAMP production at this dose, F10 and F10-Mutant had a much weaker inhibitory activity (Figure 28). These observations confirm that these ASOs directly compete with ISD for cGAS binding, thereby decreasing cGAMP activation. Nonetheless, at the dose used the mutants did not display significant differences to their parental sequences – which may be seen at different ASO doses. Critically, the observation that F10 and its mutant were less potent inhibitors indicates that their modality of action in vitro and in vivo differs. This aligns with the different activity of this ASO between MG-63 and THP-1 and argues for a different mechanism of action from the other ASOs which strongly impact cGAS activation in vitro.

Without being bound by any theory, it is proposed that F10 may be cleaved by a cellular nuclease, prior to being able to optimally engage cGAS and inhibit it (explaining the lower inhibitory activity in the in vitro assay). Alternatively, F10 may only bind cGAS in complex with a co-partner protein such as G3BP1 (Liu et al., 2019)– which is not possible in this vitro setup. Discrepancies seen between MG-63 and THP-1 would therefore rely on different expression of such a nuclease or co-partner protein. Further studies will be required to investigate how F10 impacts cGAS sensing of DNA.

EXAMPLE 16: Analyses of 2'MOE and LNA modified ASOs potency for TLR9 inhibition

Previous Examples have shown that 2'OMe ASOs could also inhibit human TLR9, although this effect was moderate with only 8/80 ASOs significantly inhibiting TLR9 by more than 50% at 500 nM. To define whether TLR9 inhibition could be promoted by other ASO chemical modifications, the present inventors screened 91 LNA and 76 2'MOE modified ASOs for reduction of NF-kB-Luciferase upon ODN2006 treatment of HEK-TLR9 cells.

The overall repression appeared similar with 2MOE and LNA ASOs, and significantly greater than that seen with 2'OMe ASOs. As such, 57/91 (i.e. 62.6%) LNA ASOs repressed TLR9 signal by more than 50% at 500 nM, versus 46/76 (i.e. 60.5%) for 2MOE ASOs (Figure 29).

The present inventors next looked to validate the top targets from each screen. For 2MOE, it is noted that one of the best inhibitors, HPRT-663 (D2) was closely related to 3 other sequences with base pair increments which were also included in the validations. Collectively, all the ASOs tested here at 100 nM significantly inhibited TLR9, with D2 and D10 (ASO2) being the most potent (Figure 30). Critically, HPRT-663 was a stronger inhibitor than 664/665 and 666 ASOs indicating an important contribution from its 5' or 3' ends.

For LNA ASOs, the effect on TLR9 was also clearly sequence-dependent with a strong impact of incremental bases in the HPRT series (660-669). As such, while 660 was not inhibitory, there was a progressive increase in inhibition peaking with 664 and 665 LNA ASOs, and decreasing again with 666 and further ASOs in the series. This suggests that the 5' and 3' end termini are likely at play here. D8 (ASO2) was also significantly inhibiting in LNA chemistry.

It should be noted that the LNA chemistry relies on 3-mer wings in the gapmer, instead of 5-mers for 2'OMe and 2'MOE; hence the sequences differ slightly for LNA and the two other chemistries. Interestingly, ASO663 in 2MOE is quite inhibitory and ASO665 in LNA is also inhibitory. When looking at the 5'end of these sequences, the present inventors note that ASO663 MOE is composed of a 5'end "ACA" motif, which is also seen in ASO665 LNA. Similarly, the 5'end of ASO662 2'OMe is "CAC" which is also seen in ASO664 LNA and is also inhibitory. These specific 5'end "ACA" and "CAC" motifs may therefore be related to the TLR9 inhibitory effect of the ASOs, independent of the chemistries used.

While the ends of the ASOs are impacting TLR9 sensing with the 3 chemistries, it is noted that the ASOs targeting 168-MB21D1, which is referred to as ASO2 (Valentin

et al., 2021), were consistently a very strong inhibitor of TLR9 – rather suggesting a key role for the central 16 nt in common between all chemistries. The present inventors therefore tested a panel of 2'OMe ASO2 variants including: ASO2 on a phosphodiester backbone (PO), lacking the 2'OMe moieties (PS), or containing a 3'-end Cy3 moiety, compared to ASO2 in 2'OMe, LNA and MOE chemistries (as per Figure 1G in (Alharbi et al., 2020)). These experiments confirmed the need for 5' and 3'-end modifications for TLR9 inhibition since the PS ASO2 entirely lacked its inhibitory activity on TLR9. Interestingly, the PO variant rather significantly potentiated TLR9 sensing – indicating that the sequence of ASO2 is likely directly facilitating interaction with TLR9 (Figure 31). This induction with the PO ASO2 also indicated that its lack of inhibitory activity was not related to its lack of uptake by the HEKs. Nonetheless, as suggested from their independent experiments, ASO2 significantly inhibited TLR9 when designed with the 2'OMe, LNA and MOE backbone with comparable efficacy (Figure 31).

EXAMPLE 17: Inhibition of RNA sensing by TLR7

Having shown C2-Mut1 and Mut1-dC inhibited TLR7 engagement with Guanosine, the present inventors also tested its effect on an immunostimulatory short single stranded RNA. For this experiment, a synthetic ssRNA (i.e., B-406-AS ssRNA (UAAUUGGCGUCUGGCCUUCUU, SEQ ID NO: 345)) was utilised, which the inventors have previously found to activate TLR7 (Gantier et al., 2010). This ssRNA was transfected with DOTAP (Roche) and pure DMEM in biological triplicate, as previously described (Gantier et al., 2010), to a final concentration of 250 nM. The ratio of DOTAP to RNA (at 80 uM) was 3.52 ug/ul of ssRNA.

As shown in Figure 32, pre-treatment of the primary BMDMs with C2-Mut1 and Mut1-dC, but not Mut1-v3-dC, significantly reduced TNFa production induced by ssRNA sensing compared to the dC20 control co-treatment, further confirming the sequence specific inhibition by the oligonucleotides described herein (and in particular the 5'-GGUAU-3' (SEQ ID NO: 56) motif) of TLR7 signalling driven by RNA.

EXAMPLE 18: TLR8 potentiation by 2'O-methyl ASOs is dependent on 3-base motifs

Previous work has shown the sequence specific potentiation of TLR8 with the example of ASO2 (2'OMe), but not its LNA variant ASO2-LNA, which lacks the terminal 5'mUmC motif (see below). When adding back this 5'mUmC motif to ASO2-LNA (giving ASO2-LNA-Mut1) there was no impact on TLR8 potentiation, suggesting that the +C+G (where "+" denotes an LNA base) bases somehow antagonised the effect

of the 5' UCCGG motif, otherwise found to directly potentiate TLR8 (as seen in ASO11-Mut2, see below).

ASO2: mU*mC*mC*mG*mG*C*C*T*C*G*G*A*A*G*C*mU*mC*mU*mC*mU

ASO2-LNA : +C*+G*+G*C*C*T*C*G*G*A*A*G*C*+T*+C*+T

ASO2-LNA Mut1: mU*mC*+C*+G*+G*C*C*T*C*G*G*A*A*G*C*+T*+C*+T

ASO2-LNA Mut2: mC*mU*mU*+C*+G*+G*C*C*T*C*G*G*A*A*G*C*+T*+C*+T*mU*mU*mC

2'Ome ASO660 is also a strong potentiator of TLR8 sensing. Such potentiation was directly dependent on a 5' mCmUmU[mCmG] motif, where "m" denotes a 2'OMethyl base, but was not seen in the context of a 5' mCmUmU[+C+G], in ASO2-LNA Mut2 (see above). This suggested again that the +C+G motif in the ASO2-LNA Mut2 was somehow antagonising the effect of the CUU (SEQ ID NO: 153) motif [PCT2021/050469].

To extend these results, here the present inventors synthesised ASO 660-Mut2 with the 5' mCmUmU[mCmG] motif changed into 5' mCmUmU[+C+G] motif, but otherwise keeping the entire sequence unaltered (Figure 33). These experiments demonstrated that changing these two bases strongly reduced TLR8 potentiation of R848 sensing for 660-Mut2 (Figure 33).

Collectively these results directly supported a key role for the "mCmG" residues of 660 and ASO2 in TLR8 potentiation – which was strongly decreased when these bases were replaced into LNA bases.

Speculating that these two bases would condition the processing of ASO 660 by endo/exonucleases to release 5' end products, the present inventors next synthesised a series of short 2'OMe ASOs of different lengths reproducing the 5'end of ASO 660 (referred to as Short-660 oligos). Overnight incubation of these short oligonucleotides prior to R848 stimulation demonstrated a length-dependent induction of IP-10 production by THP-1 cells, which was strongest with the last five 5'end bases (noting that the terminal CUU alone did not potentiate TLR8 – Figure 34).

The capacity to potentiate TLR8 with 5 bases lead the present inventors to speculate that, similar to TLR7, the effector motif on TLR8 might actually be shorter. Since mCmUmU (660-3) did not work, the present inventors also tested whether another 3 base-long oligo encompassing the important "mCmG" bases of ASO 660 could modulate TLR8 function (mUmCmG, referred to as 660-3b). Surprisingly, 660-3b significantly potentiated TLR8 sensing compared to 660-3 and R848 alone, with increasing activity with increasing levels of R848 (Figure 35).

Based on these previous findings, the present inventors next performed a screen of the 64 possible combinations of 3 bases on R848 sensing in HEK-TLR8 cells. The present inventors tested 3-mers made of 2'OMe bases on a phosphorothioate (PS) backbone, using 5 μM of naked oligos (i.e. non transfected) and 600 ng/ml of the TLR8 selective agonist Motolimod, in biological triplicate.

As shown in Figure 36, only a few 3-mers potentiated the sensing of R848, with "CGG" (SEQ ID NO: 383) being the most potent sequence, followed by "UCG" (i.e. 660-3b), "UGG", and "CGC" (SEQ ID NOs 451, 455, 375) in decreasing order of potency (also noting the potentiating effect of "AGG" and "GGA" (SEQ ID NOs: 381 and 370) in this screen). The first 3 potentiators ("CGG", "UCG", "UGG"; SEQ ID Nos: 383, 451, 455) were independently validated in repeat experiments, confirming that CGC and UCG significantly potentiated TLR8 sensing of Motolimod. Critically, the 4 sequences listed above were also found to be among the top potentiator of IP-10 production in the repeat screen of our 64 3-mers in THP-1 cells stimulated with R848 – confirming that the observation is robustly seen in different TLR8 cell models (Figure 36).

The very strong effect of "CGG" (SEQ ID NO 383) on R848/Motolimod sensing observed here is directly consistent with its presence in the 5'end of ASO2, and overlaps with the mCmG motif which, when mutated to +C+G with LNA bases lost a lot of activity.

Importantly, several 3-mer 2'OMe oligos appeared to inhibit Motolimod and R848 sensing (displaying IP-10 levels similar to those obtained without R848 in THP-1, and ~50% decreased NF-κB luciferase activity in HEK-TLR8). In this inhibiting category, the "GAX" (SEQ ID NO: 591) molecules (i.e. "GAG", "GAC", "GAU" and "GAA") were robustly the most potent in both HEK-TLR8 and THP-1 screens. "GUX" (SEQ ID NO 592) molecules (i.e. "GUC", "GUU", "GUA" and "GUG") were also robustly inhibitory in both models, although not as potent as GAX molecules. These trends were independently confirmed in a repeat experiment in HEK-TLR8 cells, collectively demonstrating that a few 3-mers can inhibit TLR8 sensing (Figure 36).

EXAMPLE 19: Inhibition of TLR7 by 2'O-methyl ASOs

Previous Examples have shown that the Short Mut1 "**mGmGmUmAmU**" 5-mer was sufficient to inhibit R848 sensing by TLR7 (Figure 14). However, this inhibition was reliant upon a 6 h incubation of the oligo which suggested it may be processed further

into shorter fragments. To address this possibility, the present inventors next investigated the effect of "mGmGmU" (shortMut1-3) and "mGmUmA" (shortMut1-3b) on TLR7 sensing, decreasing the incubation time of the oligos from 6 h to 30 min prior to R848 stimulation. The present inventors also included two other 3-mer sequences, 660-3 and 660-3b, as controls. These experiments confirmed that the effector motif in the Mut1 5-mer was in fact based on the "GAU" (SEQ ID NO: 440) 3-mer, which selectively inhibited TLR7 sensing (Figure 37). Dose-response analyses demonstrated an IC50 of 300 nM with this 3-mer oligo, and inhibition was robustly seen with increasing amounts of R848 (Figure 37).

Based on these results, the present inventors performed a screen of the 64 possible combinations of 3 2'OMe bases on R848 sensing by TLR7. The present inventors performed two independent screens, at 400 nm and 2 uM, in biological triplicate (Figure 38).

These screens demonstrated that the most potent 3-mer inhibiting TLR7 was "GUC", followed by "GUG", "GUA" and "GUU", then "GGC", "AUC", "GAG" and "GGA" (SEQ ID NOs: 442, 443, 60, 444, 377, 431, 384, 370). The clear over-representation of "**GUX**" (SEQ ID NO:"592) suggested a specific activity of these bases on TLR7 binding to site 2. Importantly, the GUX motifs also inhibited TLR8, and the same was true for "GAG" (SEQ ID NO: 384). Given the proximity of structures between TLR7 and TLR8, these results strongly support a preferential binding of these specific motifs to site 2 of these receptors, leading to the blocking of both TLR7/8 activation by R848.

Since these ASOs contained 10 internal DNA bases, the present inventors posited that 3-mer DNA fragments may also impact TLR7 sensing and conducted a screen of the 64 possible 3-mer DNA bases on a PS backbone, at 2 μM in biological triplicate. These analyses demonstrated that the most potent 3-mer DNA inhibited TLR7 by ~50%. Critically, the present inventors found that the two most potent DNA 3-mers inhibiting TLR7 were "TTT" and "TCT" (SEQ ID NOs: 425 and 424).

Collectively these analyses support a working model where the 20-mer gapmer ASOs used are rapidly degraded prior to be able to impact TLR7/8 sensing of R848 in the endolysosome. Since the present inventors can clearly replicate some of the inhibitory/potentiating activity with as few as 3-mer PS 2'OMe oligos, they believe that these degradation products are the effectors of the activity of longer 2'OMe ASOs on TLR7/8.

Since the 20-mers and the 3-mers do not need prolonged pre-treatment to act on TLR7/8 in HEK cells, but the 5-mer Mut1 sequence did not inhibit without a 6 h

incubation, the present inventors propose that endonuclease cleavage of the long 20-mer gapmers, probably through their middle DNA region, releases 2'OMe fragments that are further trimmed through exonuclease activity into 3-mers. Endo and exonucleases are probably coupled together which explains why 5-mers are less efficiently processed (length dependent uptake is unlikely the problem here since 3-mers are clearly efficiently taken up).

EXAMPLE 20: Length dependent inhibition of cGAS by 2'O-methyl modified ASOs

The previous Examples have shown that 20-mer long oligonucleotides containing a stretch of 17 dCs with as few as 3 2'OMe bases (Mut-1-dC-3) could inhibit cGAS sensing. Having shown that 5-mer oligos could inhibit TLR7 and potentiate TLR8, the present inventors investigated whether the 5-mer 2'OMe oligo with the Mut-1 motif (**mG*mG*mU*mA*mU**) could inhibit cGAS sensing. Independent of the dose used (125, 250 or 500 nM), none of the 5-mer tested significantly inhibited cGAS sensing of transfected ISD70 in THP-1 cells (Figure 39). To determine further the minimal length of an oligo required to inhibit cGAS, we generated two variants of C2-Mut1-dC, with 10 and 5 dC stretches at their 3'end (giving C2-Mut1-dC-15 and Mut1-dC-10). These shorter ASOs, albeit displaying the 5' end **mG*mG*mU*A*T** motif of C2-Mut1-dC, did not inhibit cGAS (Figure 39). Collectively, these results suggest that unlike that of TLR7/8, inhibition of cGAS sensing by 2'OMe ASOs is constrained by the length of the oligos used. In accord with this, LNA ASOs, which are only 16 bases, were overall less potent inhibitors of cGAS sensing compared to 2'OMe and 2'MOE 20-mer ASOs (Figure 20).

These results indicate that unlike that of TLR7/8, inhibition of cGAS sensing is not mediated by degradation products of the 20-mer ASOs such as C2-Mut1 and is rather conditioned by a minimum length >15-mer.

EXAMPLE 21: TLR9 inhibition

The previous Examples have shown that 2'OMe, 2'MOE and 2'LNA PS ASOs could inhibit human TLR9 in a sequence-specific manner. Interestingly, the present inventors have also found that C2-Mut1 was a very potent inhibitor of mouse TLR9 (while being much less potent on human TLR9). To define whether TLR9 inhibition could be narrowed down to a specific motif, which has not been shown to that stage, the inventors tested their panel of C2-Mut1 variants on mouse TLR9 inhibition (Figure 40). These analyses demonstrated that single base substitutions withing C2-Mut1 had a

drastic effect on the inhibition of mouse TLR9 sensing, with the example of C2-Mut1v1 and C2-Mut1v3 which only differ by one base (from UGUTT (SEQ ID NO: 596) to CGUTT (SEQ ID NO 597)), and strongly impairs inhibition. Critically, the present inventors also found that ASO 660v1, which inhibited human and mouse TLR9, retained inhibitory activity when cropped to the 9 bases from its 5' end (Figure 40).

Albeit clear differences existed between human and mouse TLR9 sensing, these findings demonstrated that mouse TLR9 inhibition was also directly dependent selective 2'OMe motifs – suggesting the same for human TLR9 (based on our prior analyses of ASO2) – and that molecules shorter than 20-mer could be inhibitory.

Previous studies have shown that TLR9 sensing of selected CpG ASO motifs was dependent on cleavage of longer ASOs by DNase II. Having demonstrated that 3-mer 2'OMe oligonucleotides could modulate TLR7/8, the present inventors hypothesised that 3-mer degradation products from longer ASOs may also control TLR9 sensing and tested their 2'OMe panel of 64 3-mers on human TLR9 sensing.

The 2'OMe panel revealed that TLR9 sensing was marginally inhibited (less than 50%) by select 2'OMe 3-mers: "ACC", "CGC", "GAU", "GGG", and the most potent, "UCG" and "ACG" (SEQ ID Nos: 403, 375, 440, 385, 451, 411) (Figure 41). Nonetheless the inhibitory effect of these few sequences was mild compared to that seen on TLR7 at this high dose of 3-mer, although this could be due to a saturation of TLR9 sensing with the agonist. Interestingly, a few of these inhibitors also modulated the function of TLR8 with GAU (SEQ ID NO: 440) (TLR8 inhibition), and UCG/CGC (SEQ ID NO: 451/375) (TLR8 potentiation).

Collectively, these findings suggest that TLR9 can be inhibited by 2'OMe PS oligos of at least 9 bases, and that select 2'OMe 3-mer oligos can also have an effect on sensing.

EXAMPLE 22: TLR3 inhibition

Having shown that 3-mer PS oligonucleotides could control TLR7/8 and 9 sensing, the present inventors speculated that selected motifs may also control TLR3 sensing – the concept being that endosomal sensing by TLR3/7/8/9 could be broadly impacting by short degradation products of longer PS oligonucleotides.

The present inventors therefore tested their 2'OMe and DNA panels of 64 3-mers on human TLR3 sensing (Figure 42 and Figure 43). For both panels, the inhibitory effect was between ~25-30%, with the strongest DNA 3-mer "TAC" (SEQ ID NO: 378) and the strongest 2'OMe 3-mer "CGC" (SEQ ID NO: 375). The present inventors further observed that "GCA", "UGA", "CAG", "UGG", "CGC" and "UCA" (where U can be a

T) (SEQ ID Nos: 399, 453, 382, 455, 375, 449) were inhibiting >20% with both DNA and 2'OMe.

These experiments collectively demonstrate that the 3-mers only have an inhibitory effect on RNA sensing by TLR3, when used at a high dose (2 μM).

It will be appreciated by persons skilled in the art that numerous variations and/or modifications may be made to the invention as shown in the specific embodiments without departing from the spirit or scope of the invention as broadly described. The present embodiments are, therefore, to be considered in all respects as illustrative and not restrictive.

All publications discussed and/or referenced herein are incorporated herein in their entirety.

Any discussion of documents, acts, materials, devices, articles or the like which has been included in the present specification is solely for the purpose of providing a context for the present invention. It is not to be taken as an admission that any or all of these matters for part of the prior art base or were coon general knowledge in the field relevant to the present invention as it existed before the priority date of each claim of this application.

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CLAIMS

1. A method for selecting or designing an oligonucleotide which inhibits cGAS activity, the method comprising

i) scanning a polynucleotide, or complement thereof, for a region having a motif including a sequence selected from the group consisting of:

(1) 5'-[A/G]GU[A/C][U/C]C-3';

(2) 5'-A[G/A][U/G]C[U/C]C-3';

(3) 5'-A[G/A][U/G]C[U/C]C[U/C][C/A]U-3';

(4) 5'-GGUAUA-3';

(5) 5'-UGUUUC-3';

(6) 5'-UGUGUC-3';

(7) 5'-CGUUUC-3';

(8) 5'-CGUGUC-3';

(9) 5'-AUGGCCTTTCCGTGCCAAGG-3';

(10) 5'-UCCGGCCTCGGAAGCUCUCU-3';

(11) 5'-GCAUUCCGTGCGGAAGCCUU-3';

(12) 5'-GGCCGAACTTTCCCGCCUUA-3';

(13) 5'-GGUCUTGGCTTCGTGGAGCA-3';

(14) 5'-GGAGCTTCGAGGCCCCAGGC-3';

(15) 5'-GGUGGTCCACAACCCCUUUC-3';

(16) 5'-CAUUAGGTGCAGAAAUCUUC-3';

(17) 5'-UUCUGGGGACTTCCAGUUUA-3';

(18) 5'-UGAUUCCAAAGCCAGGGUUA-3';

(19) 5'-CUUUAGTCGTAGTTGCUUCC-3';

(20) 5'-UUAAATAATCTAGTTUGAAG-3';

(21) 5'-GUGUCCTTCATGCTTUGGAU-3';

(22) 5'-AGAAAGAAGCAAAGAUUCAA-3';

(23) 5'-AGAUUATCTTCTTTTAAUUU-3';

(24) 5'-AAAAGATTATCTTCTUUUAA-3';

(25) 5'-GAAAAGATTATCTTCUUUUA-3';

(26) 5'-UGUGAAAAGATTATCUUCUU-3';

(27) 5’-CUUGUGAAAAGATTAUCUUC-3’;
(28) 5’-GGUGGCCACAGGCAACGUCA-3’;
(29) 5’-CCAUGTCCCAGGCCTCCAGU-3’;
(30) 5’-GCAGUCTCCATGTCCCAGGC-3’;
(31) 5’-AGCAGTCTCCATGTCCCAGG-3’;
(32) 5’-AGUGGCACATACCACACCCU-3’;
(33) 5’-AUUUCCACATGCCCAGUGUU-3’;
(34) 5’-GGUCCCATCCCTTCTGCUGC-3’;
(35) 5’-UCUGGTCCCATCCCTUCUGC-3’;
(36) 5’-GGGUCTCCTCCACACCCUUC-3’;
(37) 5’-GCAAGGCAGAGAAACUCCAG-3’;
(38) 5’-GAUGGTTCCAGTCCCUCUUC-3’;
(39) 5’-UGUUUCCCCGGAGAGCAAUG-3’;
(40) 5’-AGCCGAACAGAAGGAGCGUC-3’;
(41) 5’-GCGUAGTTTCTCTTCCUCCC-3’;
(42) 5’-GCGGUATCCATGTCCCAGGC-3’;
(43) 5’-GCGGUATACAGGTCCCAGGC-3’;
(44) 5’-GCUGUTTCCATGTCCCAGGC-3’;
(45) 5’-GCUGUGTCCATGTCCCAGGC-3’;
(46) 5’-GCCGUTTCCATGTCCCAGGC-3’;
(47) 5’-GCCGUGTCCATGTCCCAGGC-3’;
(48) 5’-GCGGUATCCATAGTCUCCAU-3’;
(49) 5’-GCGGUATCCATCAGAUAUCG-3’;
(50) 5’-CUUUAGTCGTAGTTGUCUCU-3’;
(51) 5’-UCCGGGTCGTAGTTGCUUCC-3’;
(52) 5’-UCCGGCCTCGGAGTCUCCAU-3’;
(53) 5’-UCCGGCCTCGGGAGAUCUCU-3’;
(54) 5’-GGUATCCCCCCCCCCCCCC-3’;
(55) 5’-GGAUUAAAACAGATTAAUAC-3’;
(56) 5’-GGUAU-3’;
(57) 5’-GGUA-3’;

(58) 5’-GUAU-3’;

(59) 5’-GGU-3’;

(60) 5’-GUA-3’;

(61) 5’-TGTCTG-3’;

(62) 5’-GTCT-3’;

(63) 5’-TCTCCG-3’;

(64) 5’-CTCC-3’;

(65) 5’-[G/A][A/C]AG[G/C][T/C]T[C/A];

(66) 5’-AAAGGTTA-3’;

(67) 5’-GAAGCTTC-3’;

(68) 5’-GCAGGCTC-3’;

(69) 5’-A[G/A]GGTT-3’;

(70) 5’-AGGGTT-3’;

(71) 5’-AAGGTT-3’;

(72) 5’-GGTT-3’;

(73) 5’-[A/G]GCT[T/C][T/C][G/C][T/A]-3’;

(74) 5’-AGCTTCCT-3’;

(75) 5’-AGCTTCGA-3’;

(76) 5’-GGCTTCGT-3’;

(77) 5’-TGCTTCCT-3’;

(78) 5’-AGCTCTCT-3’;

(79) 5’-G[G/C]TT-3’;

(80) 5’-GCTT-3’;

(81) 5’-CGGAGGTCTTGGCTTCGTGG-3’;

(82) 5’-AGGTCTTGGCTTCGTGGAGC-3’;

(83) 5’-GGGAAAGGTTATGCAAGGTC-3’;

(84) 5’-CTGTGATCTTGACATGCTGC-3’;

(85) 5’-ACTGACTGTCTTGAGGGTTC-3’;

(86) 5’-GCGTGTCTGGAAGCTTCCTT-3’;

(87) 5’-GAGTCTCTGGAGCTTCCTCT-3’;

(88) 5’-AGTCGTAGTTGCTTCCTAAC-3’;

(89) 5’-GTCTTGGCTTCGTGGAGCAG-3’;
(90) 5’-TTGGCTCGGCTTGCCTACTT-3’;
(91) 5’-ACAGTGTTGAGATACTCGGG-3’;
(92) 5’-TCGCACTTCAGTCTGAGCAG-3’;
(93) 5’-GGTGTCCTTGCACGTGGCTT-3’;
(94) 5’-TTTGCACACTTCGTACCCAA-3’;
(95) 5’-GCTGACAAAGATTCACTGGT-3’;
(96) 5’-GCGGAGGTCTTGGCTTCGTG-3’;
(97) 5’-CCAAGATCAGCAGTCT-3’;
(98) 5’-CTTGAAGCATCGTATC-3’;
(99) 5’-GCACACTTCGTACCCA-3’;
(100) 5’-GATAGCACCTTCAGCA-3’;
(101) 5’-CGTATTATAGCCGATT-3’;
(102) 5’-GCAGGCTCAGTGATGT-3’;
(103) 5’-GAAAGGTTATGCAAGG-3’;
(104) 5’-ATGGCCTCCCATCTCC-3’;
(105) 5’-CGCTTTTCTGTCTGGT-3’;
(106) 5’-GTGTCTGGAAGCTTCC-3’;
(107) 5’-TGGCCTCCCATCTCCT-3’;
(108) 5’-ATCTGGCAGCCCATCA-3’;
(109) 5’-GAGGTCTTGGCTTCGT-3’;
(110) 5’-ACACTTCGTGGGGTCC-3’;
(111) 5’-TTCGTGGGGTCCTTTT-3’;
(112) 5’-CCACTTGGCAGACCAT-3’;
(113) 5’-CCATCCATGAGGTCCT-3’;
(114) 5’-TCCAACACTTCGTGGG-3’;
(115) 5’-TCTTCATCGGCCCTGC-3’;
(116) 5’-CCAGCAGGTCAGCAAA-3’;
(117) 5’-CGCTTTTCTCTCCGGT-3’;
(118) 5’-GGUAUAGGACTCCAGATGUUUCC-3’; and

(119) a variant of the motifs or sequences of (1) to (118) having at least about 75% sequence identity thereto;

wherein the U may be a T and/or the T may be a U;

ii) producing one or more candidate oligonucleotides comprising the motif;

iii) testing the ability of the one or more candidate oligonucleotides to inhibit cGAS activity, and

iv) selecting an oligonucleotide which inhibits cGAS activity.

2. A method for increasing the cGAS inhibitory activity of an oligonucleotide, the method comprising modifying the oligonucleotide such that the modified oligonucleotide comprises a motif including a sequence selected from the group consisting of:

(1) 5'-[A/G]GU[A/C][U/C]C-3';

(2) 5'-A[G/A][U/G]C[U/C]C-3';

(3) 5'-A[G/A][U/G]C[U/C]C[U/C][C/A]U-3';

(4) 5'-GGUAUA-3';

(5) 5'-UGUUUC-3';

(6) 5'-UGUGUC-3';

(7) 5'-CGUUUC-3';

(8) 5'-CGUGUC-3';

(9) 5'-AUGGCCTTTCCGTGCCAAGG-3';

(10) 5'-UCCGGCCTCGGAAGCUCUCU-3';

(11) 5'-GCAUUCCGTGCGGAAGCCUU-3';

(12) 5'-GGCCGAACTTTCCCGCCUUA-3';

(13) 5'-GGUCUTGGCTTCGTGGAGCA-3';

(14) 5'-GGAGCTTCGAGGCCCCAGGC-3';

(15) 5'-GGUGGTCCACAACCCCUUUC-3';

(16) 5'-CAUUAGGTGCAGAAAUCUUC-3';

(17) 5'-UUCUGGGGACTTCCAGUUUA-3';

(18) 5'-UGAUUCCAAAGCCAGGGUUA-3';

(19) 5'-CUUUAGTCGTAGTTGCUUCC-3';

(20) 5'-UUAAATAATCTAGTTUGAAG-3';

(21) 5’-GUGUCCTTCATGCTTUGGAU-3’;
(22) 5’-AGAAAGAAGCAAAGAUUCAA-3’;
(23) 5’-AGAUUATCTTCTTTTAAUUU-3’;
(24) 5’-AAAAGATTATCTTCTUUUAA-3’;
(25) 5’-GAAAAGATTATCTTCUUUUA-3’;
(26) 5’-UGUGAAAAGATTATCUUCUU-3’;
(27) 5’-CUUGUGAAAAGATTAUCUUC-3’;
(28) 5’-GGUGGCCACAGGCAACGUCA-3’;
(29) 5’-CCAUGTCCCAGGCCTCCAGU-3’;
(30) 5’-GCAGUCTCCATGTCCCAGGC-3’;
(31) 5’-AGCAGTCTCCATGTCCCAGG-3’;
(32) 5’-AGUGGCACATACCACACCCU-3’;
(33) 5’-AUUUCCACATGCCCAGUGUU-3’;
(34) 5’-GGUCCCATCCCTTCTGCUGC-3’;
(35) 5’-UCUGGTCCCATCCCTUCUGC-3’;
(36) 5’-GGGUCTCCTCCACACCCUUC-3’;
(37) 5’-GCAAGGCAGAGAAACUCCAG-3’;
(38) 5’-GAUGGTTCCAGTCCCUCUUC-3’;
(39) 5’-UGUUUCCCCGGAGAGCAAUG-3’;
(40) 5’-AGCCGAACAGAAGGAGCGUC-3’;
(41) 5’-GCGUAGTTTCTCTTCCUCCC-3’;
(42) 5’-GCGGUATCCATGTCCCAGGC-3’;
(43) 5’-GCGGUATACAGGTCCCAGGC-3’;
(44) 5’-GCUGUTTCCATGTCCCAGGC-3’;
(45) 5’-GCUGUGTCCATGTCCCAGGC-3’;
(46) 5’-GCCGUTTCCATGTCCCAGGC-3’;
(47) 5’-GCCGUGTCCATGTCCCAGGC-3’;
(48) 5’-GCGGUATCCATAGTCUCCAU-3’;
(49) 5’-GCGGUATCCATCAGAUAUCG-3’;
(50) 5’-CUUUAGTCGTAGTTGUCUCU-3’;
(51) 5’-UCCGGGTCGTAGTTGCUUCC-3’;

(52) 5'-UCCGGCCTCGGAGTCUCCAU-3';

(53) 5'-UCCGGCCTCGGGAGAUCUCU-3';

(54) 5'-GGUATCCCCCCCCCCCCCC-3';

(55) 5'-GGAUUAAAACAGATTAAUAC-3';

(56) 5'-GGUAU-3';

(57) 5'-GGUA-3';

(58) 5'-GUAU-3';

(59) 5'-GGU-3';

(60) 5'-GUA-3';

(61) 5'-TGTCTG-3';

(62) 5'-GTCT-3';

(63) 5'-TCTCCG-3';

(64) 5'-CTCC-3';

(65) 5'-[G/A][A/C]AG[G/C][T/C]T[C/A];

(66) 5'-AAAGGTTA-3';

(67) 5'-GAAGCTTC-3';

(68) 5'-GCAGGCTC-3';

(69) 5'-A[G/A]GGTT-3';

(70) 5'-AGGGTT-3';

(71) 5'-AAGGTT-3';

(72) 5'-GGTT-3';

(73) 5'-[A/G]GCT[T/C][T/C][G/C][T/A]-3';

(74) 5'-AGCTTCCT-3';

(75) 5'-AGCTTCGA-3';

(76) 5'-GGCTTCGT-3';

(77) 5'-TGCTTCCT-3';

(78) 5'-AGCTCTCT-3';

(79) 5'-G[G/C]TT-3';

(80) 5'-GCTT-3';

(81) 5'-CGGAGGTCTTGGCTTCGTGG-3';

(82) 5'-AGGTCTTGGCTTCGTGGAGC-3';

(83) 5’-GGGAAAGGTTATGCAAGGTC-3’;
(84) 5’-CTGTGATCTTGACATGCTGC-3’;
(85) 5’-ACTGACTGTCTTGAGGGTTC-3’;
(86) 5’-GCGTGTCTGGAAGCTTCCTT-3’;
(87) 5’-GAGTCTCTGGAGCTTCCTCT-3’;
(88) 5’-AGTCGTAGTTGCTTCCTAAC-3’;
(89) 5’-GTCTTGGCTTCGTGGAGCAG-3’;
(90) 5’-TTGGCTCGGCTTGCCTACTT-3’;
(91) 5’-ACAGTGTTGAGATACTCGGG-3’;
(92) 5’-TCGCACTTCAGTCTGAGCAG-3’;
(93) 5’-GGTGTCCTTGCACGTGGCTT-3’;
(94) 5’-TTTGCACACTTCGTACCCAA-3’;
(95) 5’-GCTGACAAAGATTCACTGGT-3’;
(96) 5’-GCGGAGGTCTTGGCTTCGTG-3’;
(97) 5’-CCAAGATCAGCAGTCT-3’;
(98) 5’-CTTGAAGCATCGTATC-3’;
(99) 5’-GCACACTTCGTACCCA-3’;
(100) 5’-GATAGCACCTTCAGCA-3’;
(101) 5’-CGTATTATAGCCGATT-3’;
(102) 5’-GCAGGCTCAGTGATGT-3’;
(103) 5’-GAAAGGTTATGCAAGG-3’;
(104) 5’-ATGGCCTCCCATCTCC-3’;
(105) 5’-CGCTTTTCTGTCTGGT-3’;
(106) 5’-GTGTCTGGAAGCTTCC-3’;
(107) 5’-TGGCCTCCCATCTCCT-3’;
(108) 5’-ATCTGGCAGCCCATCA-3’;
(109) 5’-GAGGTCTTGGCTTCGT-3’;
(110) 5’-ACACTTCGTGGGGTCC-3’;
(111) 5’-TTCGTGGGGTCCTTTT-3’;
(112) 5’-CCACTTGGCAGACCAT-3’;
(113) 5’-CCATCCATGAGGTCCT-3’;

(114) 5'-TCCAACACTTCGTGGG-3';

(115) 5'-TCTTCATCGGCCCTGC-3';

(116) 5'-CCAGCAGGTCAGCAAA-3';

(117) 5'-CGCTTTTCTCTCCGGT-3';

(118) 5'-GGUAUAGGACTCCAGATGUUUCC-3'; and

(119) a variant of the motifs or sequences of (1) to (118) having at least about 75% sequence identity thereto;

wherein the U may be a T and/or the T may be a U.

3. The method of claim 2, wherein the step of modifying the oligonucleotide includes adding a sequence of nucleotides to the 5' and/or 3' end of the oligonucleotide such that the modified oligonucleotide comprises the motif.

4. The method of claim 2 or 3, which further comprises testing the ability of the modified oligonucleotide to inhibit cGAS activity, and selecting an oligonucleotide which inhibits cGAS activity to a greater extent than the unmodified oligonucleotide.

5. The method according to any one of the preceding claims, wherein the oligonucleotide does not bind or is not designed to bind a transcript that encodes cGAS or a complement thereof.

6. The method according to any one of the preceding claims, wherein the oligonucleotide binds or is designed to bind a target transcript that does not encode cGAS or a complement thereof.

7. The method according to any one of the preceding claims, wherein the motif is within eleven bases of the 5' and/or 3' end of the oligonucleotide.

8. The method of according to any one of the preceding claims, wherein the motif is within eight bases of the 5' and/or 3' end of the oligonucleotide.

9. The method according to any one of the preceding claims, wherein the motif is at or towards the 5’ and/or 3’ end of the oligonucleotide.

10. The method according to any one of the preceding claims, wherein the motif has the sequence 5’-GGUAUC-3’, 5’-AGUCUC-3’, 5’-GGUCCC-3’, 5’-GGUCUC-3’, 5’-AAGCUC-3’, 5’-AGUCCC-3’, 5’-GGUAUA-3’, 5’-UGUUUC-3’, 5’-UGUGUC-3’, 5’-CGUUUC-3’, 5’-CGUGUC-3’, 5’-GGUAU-3’, 5’-GGUA-3’, 5’-GGU-3’, 5’-TGTCTG-3’, 5’-GTCT-3’, 5’-CTCC-3’, 5’-AAAGGTTA-3’, 5’-GAAGCTTC-3’, 5’-GCAGGCTC-3’, 5’-AGGGTT-3’, 5’-AAGGTT-3’, 5’-GGTT-3’, 5’-AGCTTCCT-3’, 5’-AGCTTCGA-3’, 5’-GGCTTCGT-3’, 5’-TGCTTCCT-3’, 5’-AGCTCTCT-3’ or 5’-GCTT-3’, wherein the U may be a T.

11. The method according to any one of the preceding claims, wherein the motif has the sequence of 5’-GGUAUC-3’, 5’-GGUATC-3’, 5’-AGUCTC-3’, 5’-AGTCTC-3’, 5’-GGUCCC-3’, 5’-GGUCTC-3’, 5’-AAGCUC-3’, 5’-AGTCCC-3’, 5’-GGUATA-3’, 5’-UGUTTC-3’, 5’-UGUGTC-3’, 5’-CGUTTC-3’, 5’-CGUGTC-3’, 5’-GGUAU-3’, 5’-GGUAT-3’, 5’-GGUA-3’, 5’-GGU-3’, 5’-TGTCTG-3’, 5’-GTCT-3’, 5’-TCTCCG-3’, 5’-CTCC-3’, 5’-AAAGGTTA-3’, 5’-GAAGCTTC-3’, 5’-GCAGGCTC-3’, 5’-AGGGTT-3’, 5’-AAGGTT-3’, 5’-GGTT-3’, 5’-AGCTTCCT-3’, 5’-AGCTTCGA-3’, 5’-GGCTTCGT-3’, 5’-TGCTTCCT-3’, 5’-AGCTCTCT-3’ or 5’-GCTT-3’.

12. The method according to any one of the preceding claims, wherein one or more of the bases of the motif are a modified base and/or have a modified backbone.

13. The method according to any one of the preceding claims, wherein the motif has the sequence of 5’-mGmGmUATC-3’, 5’-mAmGmUCTC-3’, 5’-mAmGTCTC-3’, 5’-mGmGmUmCmCC-3’, 5’-mGmGmUmCTC-3’, 5’-AAGCmUmC-3’, 5’-AGTCCC-3’, 5’-mGmGmUATA-3’, 5’-mUmGmUTTC-3’, 5’-mUmGmUGTC-3’, 5’-mCmGmUTTC-3’, 5’-mCmGmUGTC-3’, 5’-mGmGmUAU-3’, 5’-mGmGmUAT-3’, 5’-mGmGmUmAU-3’, 5’-mGmGmUmAT-3’, 5’-mGmGmUmAmU-3’, 5’-mGmGmUA-3’, 5’-mGmGmUmA-3’, 5’-mGmGmU-3’, 5’-mTmGTCTG-3’, 5’-TGTCTmG-3’, 5’-mGTCT-3’, 5’-GTCT-3’, 5’-TCTCCG-3’, 5’-CTCC-3’, 5’-mAmAAGGTTA-3’, 5’-GAAGCTmTmC-3’, 5’-mGmCmAGGCTC-3’, 5’-

mAAGGTT-3', 5'-AGmGmGmTmT-3', 5'-AGCTmTmCmCmT-3', 5'-AGCTTmCmCmT-3', 5'-mAmGmCTTCGA-3', 5'-GGCTTmCmGmT-3', 5'-GGCTTCGT-3', 5'-TGCTTCmCmT-3' or 5'-AGCmTmCmTmCmT-3', wherein m is a modified base and/or has a modified backbone.

14. A method for selecting or designing an oligonucleotide which does not inhibit cGAS activity, the method comprising

i) scanning a polynucleotide, or complement thereof, for a region having a motif including a sequence selected from the group consisting of:

(1) 5'-[C/U]CUUCU-3';

(2) 5'-CACCCTTCTCTCTGGUCCCA-3';

(3) 5'-CCUUCTCTCTGGTCCCAUCC-3';

(4) 5'-UCUCUGGTCCCATCCCUUCU-3';

(5) 5'-AUAUCTGCTGCCCACCUUCU-3';

(6) 5'-GUCCCATCCCTTCTGCUGCC-3';

(7) 5'-GUCUCCTCCACACCCUUCUC-3';

(8) 5'-CAGGCCTCCAGTGTCUUCUC-3';

(9) 5'-UCCCAACTCTTCTAACUCGU-3'; and

(10) a variant of the motifs or sequences of (1) to (9) having at least about 75% sequence identity thereto;

wherein the U may be a T and/or the T may be a U;

ii) producing one or more candidate oligonucleotides comprising the motif;

iii) testing the ability of the one or more candidate oligonucleotides to inhibit cGAS activity, and

iv) selecting an oligonucleotide which does not inhibit cGAS activity.

15. A method for reducing the cGAS inhibitory activity of an oligonucleotide, the method comprising modifying the oligonucleotide such that the modified oligonucleotide comprises a motif including a sequence selected from the group consisting of:

(1) 5'-[C/U]CUUCU-3';

(2) 5'-CACCCTTCTCTCTGGUCCCA-3';

(3) 5'-CCUUCTCTCTGGTCCCAUCC-3';
(4) 5'-UCUCUGGTCCCATCCCUUCU-3';
(5) 5'-AUAUCTGCTGCCCACCUUCU-3';
(6) 5'-GUCCCATCCCTTCTGCUGCC-3';
(7) 5'-GUCUCCTCCACACCCUUCUC-3';
(8) 5'-CAGGCCTCCAGTGTCUUCUC-3';
(9) 5'-UCCCAACTCTTCTAACUCGU-3'; and
(10) a variant of the motifs or sequences of (1) to (9) having at least about 75% sequence identity thereto;

wherein the U may be a T and/or the T may be a U.

16. The method of claim 15, wherein the step of modifying the oligonucleotide includes adding a sequence of nucleotides to the 5' and/or 3' end of the oligonucleotide such that the modified oligonucleotide comprises the motif.

17. The method of claim 15 or 16, which further comprises testing the ability of the modified oligonucleotide to inhibit cGAS activity, and selecting an oligonucleotide which inhibits cGAS activity to a lesser extent than the unmodified oligonucleotide.

18. The method according to any one of claims 14 to 17, wherein the motif is within thirteen bases of the 5' and/or 3' end of the oligonucleotide.

19. The method according to any one of claims 14 to 18, wherein the motif is within nine bases of the 5' and/or 3' end of the oligonucleotide.

20. The method according to any one of claims 14 to 19, wherein the motif is at or towards the 5' and/or 3' end of the oligonucleotide.

21. The method according to any one of claims 14 to 20, wherein the motif has the sequence 5'-CCUUCU-3' or 5'-UCUUCU-3', wherein the U may be a T.

22. The method according to any one of claims 14 to 21, wherein one or more of the bases of the motif are a modified base and/or have a modified backbone.

23. The method according to any one of claims 14 to 22, wherein the motif has the sequence 5'-mCmCUUCU-3', 5'-mCmCmUmUmCU-3', 5'-CmCmUmUmCmU-3', 5'-CCUUCU-3', 5'-CCmUmUmCmU-3', 5'-UCmUmUmCmU-3' or 5'-UCUUCU-3', wherein the U may be a T and wherein m is a modified base and/or has a modified backbone.

24. A method for selecting or designing an oligonucleotide which inhibits TLR9 activity, the method comprising

i) scanning a polynucleotide, or complement thereof, for a region having a motif including a sequence selected from the group consisting of:

(1) 5'-G[G/C]CCT[C/G]-3';

(2) 5'-CUU-3', wherein the motif is within 10 bases of the 5' and/or 3' end of the oligonucleotide;

(3) 5'-CUUGUGAAAAGATTAUCUUC-3';

(4) 5'-CUUCUCTCTGGTCCCAUCCC-3';

(5) 5'-CCUUCTCTCTGGTCCCAUCC-3';

(6) 5'-CCCUUCTCTCTGGTCCCAUC-3';

(7) 5'-ACCCUTCTCTCTGGTCCCAU-3';

(8) 5'-CUUCCACAATCAAGACAUUC-3';

(9) 5'-CUUCGTGGGGTCCTTUUCAC-3';

(10) 5'-CACUUCGTGGGGTCCUUUUC-3';

(11) 5'-CCAACACTTCGTGGGGUCCU-3';

(12) 5'-UCCGGCCTCGGAAGCUCUCU-3';

(13) 5'-CCAUGTCCCAGGCCTCCAGU-3';

(14) 5'-UUGGCCTGTGGATGCUUUGU-3';

(15) 5'-AAAUGTCCTGGCCCTCACUG-3';

(16) 5'-UCCGGCCTCGGAGTCUCCAU-3';

(17) 5'-UCCGGCCTCGGCAGAUAUCG-3';

(18) 5’-GGCCGAACTTTCCCGCCUUA-3’;

(19) 5’-GGUCUTGGCTTCGTGGAGCA-3’;

(20) 5’-GGAGCTTCGAGGCCCCAGGC-3’;

(21) 5’-GGUGGTCCACAACCCCUUUC-3’;

(22) 5’-CAUUAGGTGCAGAAAUCUUC-3’;

(23) 5’-UUCUGGGGACTTCCAGUUUA-3’;

(24) 5’-UGAUUCCAAAGCCAGGGUUA-3’;

(25) 5’-UCCGGGTCGTAGTTGCUUCC-3’;

(26) 5’-CCUAGAAAGAAGCAAAGAUU-3’;

(27) 5’-GAUUAAAACAGATTAAUACA-3’;

(28) 5’-GGAUUAAAACAGATTAAUAC-3’;

(29) 5’-AAUUUAAAGCATGAAUAUUA-3’;

(30) 5’-GCGUAGTTTCTCTTCCUCCC-3’

(31) 5’-UGACAAAACAATAATAACAG-3’;

(32) 5’-ACA-3’, wherein the motif is at or towards the 5’ end of the oligonucleotide;

(33) 5’-CAC-3’, wherein the motif is at or towards the 5’ end of the oligonucleotide;

(34) 5’-ACACTTCGTGGGGTCCTTTT-3’;

(35) 5’-GCGTGTCTGGAAGCTTCCTT-3’;

(36) 5’-TCAAAGGACTGAGGAAAGGG-3’;

(37) 5’-ATCCAACACTTCGTGGGGTC-3’;

(38) 5’-GCCCATCCATGAGGTCCTGG-3’;

(39) 5’-GGGTATCGAAAGAGTCTGGA-3’;

(40) 5’-GGTTTTGGCTGGGATCAAGT-3’;

(41) 5’-GCGACTATACGCGCAATATG-3’;

(42) 5’-ACTGACTGTCTTGAGGGTTC-3’;

(43) 5’-AACACTTCGTGGGGTCCTTT-3’;

(44) 5’-GTCCAAGATCAGCAGTCTCA-3’;

(45) 5’-ACAGTGTTGAGATACTCGGG-3’;

(46) 5’-TGGGCTGGAATCCGAGTTAT-3’;

(47) 5’-CGGCATCCACCACGTCGTCC-3’;
(48) 5’-GCGTATTATAGCCGATTAAC-3’;
(49) 5’-GGAGGTCTTGGCTTCGTGGA-3’;
(50) 5’-TGGGTTACGGCTCAGTATGG-3’;
(51) 5’-CCGCCATGTTTCTTCTTGGA-3’;
(52) 5’-AGCTTCGAGGCCCCAG-3’;
(53) 5’-GCCATGTTTCTTCTTG-3’;
(54) 5’-CACTTCGTGGGGTCCT-3’;
(55) 5’-CGGCCTCGGAAGCTCT-3’;
(56) 5’-ACACTTCGTGGGGTCC-3’;
(57) 5’-TGCACACTTCGTACCC-3’;
(58) 5’-CCACATCCTGTGGCTC-3’;
(59) 5’-CTGCAGCTTCCTTGTC-3’;
(60) 5’-ACTTCGTGGGGTCCTT-3’;
(61) 5’-CCCACTTGGCAGACCA-3’;
(62) 5’-GTCCCCTGTTGACTGG-3’;
(63) 5’-ACGTTCAGTCCTGTCC-3’;
(64) 5’-GGTCATTACAATAGCT-3’;
(65) 5’-TCGTGGGGTCCTTTTC-3’;
(66) 5’-GTGTCTGGAAGCTTCC-3’;
(67) 5’-ATGGCCTCCCATCTCC-3’;
(68) 5’-TGCTCCTCGGTCTCCC-3’;
(69) 5’-GCATCCACCACGTCGT-3’;
(70) 5’-CTTCGTGGGGTCCTTT-3’;
(71) 5’-AGGCCCTTCGCACTTC-3’;
(72) 5’-GCGGUATCCATGTCCCAGGC-3’;
(73) 5’-GCUGUTTCCATGTCCCAGGC-3’;
(74) 5’-GCUGUGTCCATGTCCCAGGC-3’
(75) 5’-GCCGUTTCCATGTCCCAGGC-3’;
(76) 5’-GCGGUATCC-3’;
(77) 5’-GCUGUTTCC-3’;
(78) 5’-GCUGUGTCC-3’;

(79) 5'-GCCGUTTCC-3';
(80) 5'-CUUCGTGGGGTCCTTUUCAC;
(81) 5'-CUUCGTGGG-3';
(82) 5'-UCG-3';
(83) 5'-ACG-3';
(84) 5'-ACC-3';
(85) 5'-CGC-3';
(86) 5'-GAU-3';
(87) 5'-GGG-3';
(88) 5'-AGC-3';
(89) 5'-UUC-3';
(90) 5'-UUG-3';
(91) 5'-CAC-3';
and
and

(92) a variant of the motifs or sequences of (1) to (91) having at least about 75% sequence identity thereto;

wherein the U may be a T and/or the T may be a U;

ii) producing one or more candidate oligonucleotides comprising the motif;

iii) testing the ability of the one or more candidate oligonucleotides to inhibit TLR9 activity, and

iv) selecting an oligonucleotide which inhibits TLR9 activity.

25. A method for increasing the TLR9 inhibitory activity of an oligonucleotide, the method comprising modifying the oligonucleotide such that the modified oligonucleotide comprises a motif including a sequence selected from the group consisting of:

(1) 5'-G[G/C]CCT[C/G]-3';

(2) 5'-CUU-3', wherein the motif is within 10 bases of the 5' and/or 3' end of the oligonucleotide;

(3) 5'-CUUGUGAAAAGATTAUCUUC-3';
(4) 5'-CUUCUCTCTGGTCCCAUCCC-3';
(5) 5'-CCUUCTCTCTGGTCCCAUCC-3';
(6) 5'-CCCUUCTCTCTGGTCCCAUC-3';

(7) 5’-ACCCUTCTCTCTGGTCCCAU-3’;

(8) 5’-CUUCCACAATCAAGACAUUC-3’;

(9) 5’-CUUCGTGGGGTCCTTUUCAC-3’;

(10) 5’-CACUUCGTGGGGTCCUUUUC-3’;

(11) 5’-CCAACACTTCGTGGGGUCCU-3’;

(12) 5’-UCCGGCCTCGGAAGCUCUCU-3’;

(13) 5’-CCAUGTCCCAGGCCTCCAGU-3’;

(14) 5’-UUGGCCTGTGGATGCUUUGU-3’;

(15) 5’-AAAUGTCCTGGCCCTCACUG-3’;

(16) 5’-UCCGGCCTCGGAGTCUCCAU-3’;

(17) 5’-UCCGGCCTCGGCAGAUAUCG-3’;

(18) 5’-GGCCGAACTTTCCCGCCUUA-3’;

(19) 5’-GGUCUTGGCTTCGTGGAGCA-3’;

(20) 5’-GGAGCTTCGAGGCCCCAGGC-3’;

(21) 5’-GGUGGTCCACAACCCCUUUC-3’;

(22) 5’-CAUUAGGTGCAGAAAUCUUC-3’;

(23) 5’-UUCUGGGGACTTCCAGUUUA-3’;

(24) 5’-UGAUUCCAAAGCCAGGGUUA-3’;

(25) 5’-UCCGGGTCGTAGTTGCUUCC-3’;

(26) 5’-CCUAGAAAGAAGCAAAGAUU-3’;

(27) 5’-GAUUAAAACAGATTAAUACA-3’;

(28) 5’-GGAUUAAAACAGATTAAUAC-3’;

(29) 5’-AAUUUAAAGCATGAAUAUUA-3’;

(30) 5’-GCGUAGTTTCTCTTCCUCCC-3’;

(31) 5’-UGACAAAACAATAATAACAG-3’;

(32) 5’-ACA-3’, wherein the motif is at or towards the 5’ end of the oligonucleotide;

(33) 5’-CAC-3’, wherein the motif is at or towards the 5’ end of the oligonucleotide;

(34) 5’-ACACTTCGTGGGGTCCTTTT-3’;

(35) 5’-GCGTGTCTGGAAGCTTCCTT-3’;

(36) 5’-TCAAAGGACTGAGGAAAGGG-3’;
(37) 5’-ATCCAACACTTCGTGGGGTC-3’;
(38) 5’-GCCCATCCATGAGGTCCTGG-3’;
(39) 5’-GGGTATCGAAAGAGTCTGGA-3’;
(40) 5’-GGTTTTGGCTGGGATCAAGT-3’;
(41) 5’-GCGACTATACGCGCAATATG-3’;
(42) 5’-ACTGACTGTCTTGAGGGTTC-3’;
(43) 5’-AACACTTCGTGGGGTCCTTT-3’;
(44) 5’-GTCCAAGATCAGCAGTCTCA-3’;
(45) 5’-ACAGTGTTGAGATACTCGGG-3’;
(46) 5’-TGGGCTGGAATCCGAGTTAT-3’;
(47) 5’-CGGCATCCACCACGTCGTCC-3’;
(48) 5’-GCGTATTATAGCCGATTAAC-3’;
(49) 5’-GGAGGTCTTGGCTTCGTGGA-3’;
(50) 5’-TGGGTTACGGCTCAGTATGG-3’;
(51) 5’-CCGCCATGTTTCTTCTTGGA-3’;
(52) 5’-AGCTTCGAGGCCCCAG-3’;
(53) 5’-GCCATGTTTCTTCTTG-3’;
(54) 5’-CACTTCGTGGGGTCCT-3’;
(55) 5’-CGGCCTCGGAAGCTCT-3’;
(56) 5’-ACACTTCGTGGGGTCC-3’;
(57) 5’-TGCACACTTCGTACCC-3’;
(58) 5’-CCACATCCTGTGGCTC-3’;
(59) 5’-CTGCAGCTTCCTTGTC-3’;
(60) 5’-ACTTCGTGGGGTCCTT-3’;
(61) 5’-CCCACTTGGCAGACCA-3’;
(62) 5’-GTCCCCTGTTGACTGG-3’;
(63) 5’-ACGTTCAGTCCTGTCC-3’;
(64) 5’-GGTCATTACAATAGCT-3’;
(65) 5’-TCGTGGGGTCCTTTTC-3’;
(66) 5’-GTGTCTGGAAGCTTCC-3’;

(67) 5’-ATGGCCTCCCATCTCC-3’;
(68) 5’-TGCTCCTCGGTCTCCC-3’;
(69) 5’-GCATCCACCACGTCGT-3’;
(70) 5’-CTTCGTGGGGTCCTTT-3’;
(71) 5’-AGGCCCTTCGCACTTC-3’;
(72) 5’-GCGGUATCCATGTCCCAGGC-3’;
(73) 5’-GCUGUTTCCATGTCCCAGGC-3’;
(74) 5’-GCUGUGTCCATGTCCCAGGC-3’
(75) 5’-GCCGUTTCCATGTCCCAGGC-3’;
(76) 5’-GCGGUATCC-3’;
(77) 5’-GCUGUTTCC-3’;
(78) 5’-GCUGUGTCC-3’;
(79) 5’-GCCGUTTCC-3’;
(80) 5’-CUUCGTGGGGTCCTTUUCAC;
(81) 5’-CUUCGTGGG-3’;
(82) 5’-UCG-3’;
(83) 5’-ACG-3’;
(84) 5’-ACC-3’;
(85) 5’-CGC-3’;
(86) 5’-GAU-3’;
(87) 5’-GGG-3’;
(88) 5’-AGC-3’;
(89) 5’-UUC-3’;
(90) 5’-UUG-3’;
(91) 5’-CAC-3’;
and
and

(92) a variant of the motifs or sequences of (1) to (91) having at least about 75% sequence identity thereto;

wherein the U may be a T and/or the T may be a U.

26. The method of claim 25, which further comprises testing the ability of the modified oligonucleotide to inhibit TLR9 activity, and selecting an oligonucleotide which inhibits TLR9 activity to a greater extent than the unmodified oligonucleotide.

27. The method of claim 25 or claim 26, wherein the step of modifying the oligonucleotide includes adding a sequence of nucleotides to the 5' and/or 3' end of the oligonucleotide such that the modified oligonucleotide comprises the motif.

28. The method according to any one of claims 24 to 27, wherein the oligonucleotide does not bind or is not designed to bind a transcript that encodes TLR9 or a complement thereof.

29. The method according to any one of claims 24 to 28, wherein the oligonucleotide binds or is designed to bind a target transcript that does not encode TLR9 or a complement thereof.

30. The method according to any one of claims 24 to 29, wherein the motif is within 10 bases of the 5' and/or 3' end of the oligonucleotide.

31. The method according to any one of claims 24 to 30, wherein the motif is within 5 bases of the 5' and/or 3' end of the oligonucleotide.

32. The method according to any one of claims 24 to 31, wherein the motif is at or towards the 5' and/or 3' end of the oligonucleotide.

33. The method according to any one of claims 24 to 32, wherein the motif is at or towards the 5' end of the oligonucleotide.

34. The method according to any one of claims 24 to 33, wherein the motif has the sequence 5'-CUU-3', 5'-CUT-3', or 5'-CTT-3'.

35. The method according to any one of claims 24 to 33, wherein the motif has the sequence 5'-GGCCTC-3', 5'-GGCCTG-3', or 5'-GCCCTC-3', wherein the T may be a U.

36. The method according to any one of claims 24 to 35, wherein one or more of the bases of the motif are a modified base and/or have a modified backbone.

37. The method according to any one of claims 24 to 34 or 36, wherein the motif has the sequence 5'-mCmUmU-3' or 5'-mCmUT-3', wherein m is a modified base and/or has a modified backbone.

38. The method according to any one of claims 24 to 33, 35 or 36, wherein the motif has the sequence 5'-mGmGCCTC-3', 5'-GGCCTmC-3', 5'-mGmGmCCTG-3' or 5'-GCCCTmC-3', wherein the T may be a U and wherein m is a modified base and/or has a modified backbone.

39. The method according to any one of the preceding claims, wherein the oligonucleotide comprises

a) a 5' region comprising bases which are modified and/or which have a modified backbone,

b) a middle region comprising ribonucleic acid, deoxyribonucleic acid, or combination thereof, bases, which optionally have a modified backbone, and

c) a 3' region comprising bases which are modified and/or which have a modified backbone.

40. The method of claim 39, wherein the middle region is about 10 bases in length.

41. The method of claim 39 or claim 40, wherein the 5' region and/or the 3' region are: (a) about 3 bases in length; or (b) about 5 bases in length.

42. A method for selecting or designing an oligonucleotide which inhibits TLR9 activity, the method comprising

i) scanning a polynucleotide, or complement thereof, for regions having at least about 50% adenine bases;

ii) producing one or more candidate oligonucleotides comprising a 5' region, a 3' region and a middle region comprising ribonucleic acid, deoxyribonucleic acid, or combination thereof, bases, which optionally have a modified backbone, wherein one or both of the 5' region and the 3' region comprise bases which are modified and/or which have a modified backbone, and wherein at least about 50% of the bases of the middle region are adenine bases;

iii) testing the ability of the one or more candidate oligonucleotides to inhibit TLR9 activity, and

iv) selecting an oligonucleotide which inhibits TLR9 activity.

43. The method of claim 42, wherein the oligonucleotide comprises a motif having a sequence of 5'-[T/G][A/T][G/A/T]AA[A/C][A/G][G/C/A]A[T/G][T/G/C]A[A/T]-3', wherein the T may be a U.

44. The method according to claim 42 or claim 43, wherein the 5' region and/or the 3' region are about 5 bases in length and the middle region is about 10 bases in length, wherein the middle region comprises at least five adenine bases.

45. The method of claim 44, wherein two, three and/or four of the at least five adenine bases are in a continuous sequence.

46. The method according to any one of claims 42 to 45, wherein the oligonucleotide does not bind or is not designed to bind a transcript that encodes TLR9 or a complement thereof.

47. The method according to any one of claims 42 to 46, wherein the oligonucleotide binds or is designed to bind a target transcript that does not encode TLR9 or a complement thereof.

48. A method for selecting or designing an oligonucleotide which inhibits TLR7 activity, the method comprising

i) scanning a polynucleotide, or complement thereof, for a region having a motif including a sequence selected from the group consisting of:

(1) 5'-[A/G]GU[A/C][U/C]C-3';
(2) 5'-A[G/A][U/G]C[U/C]C-3';
(3) 5'-A[G/A][U/G]C[U/C]C[U/C][C/A]U-3';
(4) 5'-GGUAUA-3';
(5) 5'-UGUUUC-3';
(6) 5'-UGUGUC-3';
(7) 5'-CGUGUC-3';
(8) 5'-GCAGUCTCCATGTCCCAGGC-3';
(9) 5'-GAUGGTTCCAGTCCCUCUUC-3';
(10) 5'-AGCAGTCTCCATGTCCCAGG-3';
(11) 5'-GGGUCTCCTCCACACCCUUC-3';
(12) 5'-GGUGGCCACAGGCAACGUCA-3';
(13) 5'-GCCGUTTCCATGTCCCAGGC-3';
(14) 5'-GCGGUATCCATGTCCCAGGC-3';
(15) 5'-GCGGUATACAGGTCCCAGGC-3';
(16) 5'-GCUGUTTCCATGTCCCAGGC-3';
(17) 5'-GCUGUGTCCATGTCCCAGGC-3';
(18) 5'-GCCGUGTCCATGTCCCAGGC-3';
(19) 5'-GCGGUAUCCAUGUCCCAGGC-3';
(20) 5'-GGUATCCCCCCCCCCCCCC-3';
(21) 5'-GUCCCATCCCTTCTGCUGCC-3';
(22) 5'-UUCUCTCTGGTCCCAUCCCU-3';
(23) 5'-GUUCAGTCAGATCGCUGGGA-3';
(24) 5'-AUGACATTTCGTGGCUCCUA-3';
(25) 5'-UCUCCATGTCCCAGGCCUCC-3';
(26) 5'-AGUCUCCATGTCCCAGGCCU-3';
(27) 5'-CCAUGTCCCAGGCCTCCAGU-3';
(28) 5'-GCAAGGCAGAGAAACUCCAG-3';
(29) 5'-GGAUUAAAACAGATTAAUAC-3';

(30) 5’-AGCCGAACAGAAGGAGCGUC-3’;
(31) 5’-UCCGGCCTCGGAAGCUCUCU-3’;
(32) 5’-UCCGGCCTCGGAGTCUCCAU-3’;
(33) 5’-GCGGUATCCATAGTCUCCAU-3’;
(34) 5’-GAUUAAAACAGATTAAUACA-3’;
(35) 5’-UGACAAAACAATAATAACAG-3’;
(36) 5’-CCAACACTTCGTGGGGUCCU-3’;
(37) 5’-GUGUCCTTCATGCTTUGGAU-3’;
(38) 5’-GUCCCAGGCCTCCAGUGUCU-3’;
(39) 5’-UUGGCCTGTGGATGCUUUGU-3’;
(40) 5’-GUCCGTACCTCCACCCACCG-3’;
(41) 5’-GUGUUTTTAATTTTGUAGAG-3’;
(42) 5’-GUCAAACCTAGAAAGAAGCA-3’;
(43) 5’-GGUCUCCTCCACACCCUUCU-3’;
(44) 5’-GUCUCCTCCACACCCUUCUC-3’;
(45) 5’-UGAUGATGCTTGCAGGAGGC-3’;
(46) 5’-UUAAATAATCTAGTTUGAAG-3’;
(47) 5’-AAAGCAGTCTCCATGUCCCA-3’;
(48) 5’-GCGUAGTTTCTCTTCCUCCC-3’;
(49) 5’-UCUGGTCCCATCCCTUCUGC-3’;
(50) 5’-UAUUUCCACATGCCCAGUGU-3’;
(51) 5’-UGUUUCCCCGGAGAGCAAUG-3’;
(52) 5’-UUAGCTCCTTGCCTCGUUCC-3’;
(53) 5’-AUUUCCACATGCCCAGUGUU-3’;
(54) 5’-UGGCGTAGTTTCTCTUCCUC-3’;
(55) 5’-UGACATTTCGTGGCTCCUAC-3’;
(56) 5’-GAAAAGATTATCTTCUUUUA-3’;
(57) 5’-UGUGAAAAGATTATCUUCUU-3’;
(58) 5’-UUGUGAAAAGATTATCUUCU-3’;
(59) 5’-UUUGAAATTCAGAAGAUUUG-3’;
(60) 5’-AAGCAGTCTCCATGTCCCAG-3’;

(61) 5’-AGGAUTAAAACAGATUAAUA-3’;
(62) 5’-AGAUUATCTTCTTTTAAUUU-3’;
(63) 5’-UCCCAACTCTTCTAACUCGU-3’;
(64) 5’-UAAAATAAGGGGAATAGGGG-3’;
(65) 5’-AGUGGCACATACCACACCCU-3’;
(66) 5’-AAGAUTATCTTCTTTUAAUU-3’;
(67) 5’-AGAAAGAAGCAAAGAUUCAA-3’;
(68) 5’-UCCCATCCCTTCTGCUGCCA-3’;
(69) 5’-ACCCUTCTCTCTGGTCCCAU-3’;
(70) 5’-AAUAUCTGCTGCCCACCUUC-3’;
(71) 5’-UCUCUCTGGTCCCATCCCUU-3’;
(72) 5’-AGGCCTCCAGTGTCTUCUCC-3’;
(73) 5’-CAAGCCCCAGCGTTCCUCCG-3’;
(74) 5’-AAAUGTCCTGGCCCTCACUG-3’;
(75) 5’-AAUUUAAAGCATGAAUAUUA-3’;
(76) 5’-AAAAGATTATCTTCTUUUAA-3’;
(77) 5’-AUAUCTGCTGCCCACCUUCU-3’;
(78) 5’-CAGUCTCCATGTCCCAGGCC-3’;
(79) 5’-AAAGATTATCTTCTTUUAAU-3’;
(80) 5’-CCCUUCTCTCTGGTCCCAUC-3’;
(81) 5’-AUGGCCTTTCCGTGCCAAGG-3’;
(82) 5’-GCAUUCCGTGCGGAAGCCUU-3’;
(83) 5’-GGCCGAACTTTCCCGCCUUA-3’;
(84) 5’-GGUCUTGGCTTCGTGGAGCA-3’;
(85) 5’-GGAGCTTCGAGGCCCCAGGC-3’;
(86) 5’-GGUGGTCCACAACCCCUUUC-3’;
(87) 5’-UUCUGGGGACTTCCAGUUUA-3’;
(88) 5’-UGAUUCCAAAGCCAGGGUUA-3’;
(89) 5’-GGGUATCGAAAGAGTCUGGA-3’;
(90) 5’-CUUGCACGTGGCTTCGUCUC-3’;
(91) 5’-GUGUCCTTGCACGTGGCUUC-3’;

(92) 5’-GUAAAAAGCTTTTGAAGUGA-3’;
(93) 5’-AUGCCATCCACTTGAUAGGC-3’;
(94) 5’-UGAAGTAAAAATCAAUAGCG-3’;
(95) 5’-AAGGCCCTTCGCACTUCUUA-3’;
(96) 5’-GUACUCGTCGGCATCCACCA-3’;
(97) 5’-GUCCUTGCACGTGGCUUCGU-3’;
(98) 5’-GCCCATCCATGAGGTCCUGG-3’;
(99) 5’-GUAAAAGGAGAAAACUAUCU-3’;
(100) 5’-UUGAAGTGAAGTAAAAGGAG-3’;
(101) 5’-GUUACTCGTGCCTTGGCAAA-3’;
(102) 5’-GUCCAAGATCAGCAGUCUCA-3’;
(103) 5’-UUCAATGGGAGAATAAAGCA-3’;
(104) 5’-GCAAGGCCCTTCGCACUUCU-3’;
(105) 5’-GGGUCCACCACTAGCCAGUA-3’;
(106) 5’-GUAGAGAAATTATTTUAGGA-3’;
(107) 5’-AUCCACCACGTCGTCCAUGU-3’;
(108) 5’-GGCAUCCACCACGTCGUCCA-3’;
(109) 5’-UUACUTTAAAAGCAAAAGGA-3’;
(110) 5’-UUUGAAGTGAAGTAAAAGGA-3’;
(111) 5’-GAAGUGAAGTAAAAGGAGAA-3’;
(112) 5’-GGCCATCTCTGCTTCUUGGU-3’;
(113) 5’-UGGGCTGGAATCCGAGUUAU-3’;
(114) 5’-GGAGATTTCAGAGCAGCUUC-3’;
(115) 5’-UUUACGGTTTTCAGAAUAUC-3’;
(116) 5’-GCGUGTCTGGAAGCTUCCUU-3’;
(117) 5’-GCUUATTTTAAGCATAUUAA-3’;
(118) 5’-UUAUUTTAAGCATATUAAAA-3’;
(119) 5’-UUCUGCAGCTTCCTTGUCCU-3’;
(120) 5’-AUUACTTTAAAAGCAAAAGG-3’;
(121) 5’-AUUUUAAGCATATTAAAAAG-3’;
(122) 5’-UGUGGCTTGTCCTCAGACAU-3’;

(123) 5’-AAAAGGAGAAAACTAUCUUC-3’;
(124) 5’-GGGUCCATACCCAAGGCAUC-3’;
(125) 5’-ACAGUGTTGAGATACUCGGG-3’;
(126) 5’-GGAUCTGCATGCCCTCAUCU-3’;
(127) 5’-AGUAAAAAGCTTTTGAAGUG-3’;
(128) 5’-GUCGUGGCAAATAGTCCUAG-3’;
(129) 5’-GGAGATCAGATGAGAGGAGC-3’;
(130) 5’-GUGGUTAAGTACATGAGCUC-3’;
(131) 5’-GGACACTTAGCTGTTCCUCG-3’;
(132) 5’-GUCUCTACTGTTACCUCUGA-3’;
(133) 5’-GAGUUCTTCGTAGGCUUCUG-3’;
(134) 5’-AAAGUCAAAAAGAAAAACUG-3’;
(135) 5’-AAAAGTGGGAAATAAAGGUU-3’;
(136) 5’-AGUUUATAGATTTCAAGUAG-3’;
(137) 5’-AAAAAGTGGGAAATAAAGGU-3’;
(138) 5’-UUUAUATTACAAAGCUACUU-3’;
(139) 5’-UGCUATTCATATTTTUAUUU-3’;
(140) 5’-GGUAU-3’;
(141) 5’-[G/A/C][G/A][G/A/C][T/A/C]TC-3’;
(142) 5’-[G/A/C]G[G/A/C][T/A/C]TC-3’;
(143) 5’-GGCTTC-3’;
(144) 5’-GGCATC-3’;
(145) 5’-AGCTTC-3’;
(146) 5’-GGAATC-3’;
(147) 5’-CACATC-3’;
(148) 5’-GGCCTC-3’;
(149) 5’-CACTTC-3’;
(150) 5’-AAGATC-3’;
(151) 5’-TGTCCTTGCACGTGGCTTCG-3’;
(152) 5’-TTTGCACACTTCGTACCCAA-3’;
(153) 5’-GTCCACATCCTGTGGCTCGT-3’;

(154) 5’-TGTGATGGCCTCCCATCTCC-3’;
(155) 5’-GGTTTTGGCTGGGATCAAGT-3’;
(156) 5’-GGTGTCCTTGCACGTGGCTT-3’;
(157) 5’-GGTCCATACCCAAGGCATCC-3’;
(158) 5’-GTGTCTTCATCGGCCCTGCC-3’;
(159) 5’-GTCTTGGCTTCGTGGAGCAG-3’;
(160) 5’-GCTGACAAAGATTCACTGGT-3’;
(161) 5’-GAAAGGTTATGCAAGG-3’;
(162) 5’-GACTATACGCGCAATA-3’;
(163) 5’-TGTGATGGCCTCCCAT-3’;
(164) 5’-TCCAACACTTCGTGGG-3’;
(165) 5’-GTGTCTGGAAGCTTCC-3’;
(166) 5’-CTTGAAGCATCGTATC-3’;
(167) 5’-TCGTAGTTGCTTCCTA-3’;
(168) 5’-CGCTTTTCTGTCTGGT-3’;
(169) 5’-GGCTGGAATCCGAGTT-3’;
(170) 5’-GATAGCACCTTCAGCA-3’;
(171) 5’-AGGACTCCAGATGTTT-3’;
(172) 5’-GTGATCTTGACATGCT-3’;
(173) 5’-AGATTTCAGAGCAGCT-3’;
(174) 5’-GGTTACGGCTCAGTAT-3’;
(175) 5’-GTTCAGTCCTGTCCAT-3’;
(176) 5’-AGGTCTTGGCTTCGTG-3’;
(177) 5’-CTGCAGCTTCCTTGTC-3’;
(178) 5’-GTCCTTGCACGTGGCT-3’;
(179) 5’-GTCTCTGGAGCTTCCT-3’;
(180) 5’-GGTCTTGGCTTCGTGG-3’;
(181) 5’-GGUA-3’;
(182) 5’-GUAU-3’;
(183) 5’-GGU-3’;
(184) 5’-GUA-3’;

(185) 5'-GUC-3';
(186) 5'-GUG-3';
(187) 5'-GUU-3';
(188) 5'-GUA-3';
(189) 5'-GGC-3';
(190) 5'-AUC-3';
(191) 5'-GAA-3';
(192) 5'-GAG-3';
(193) 5'-GGA-3';
(194) 5'-GAC-3';
(195) 5'-GAU-3';
(196) 5'-AUG-3';
(197) 5'-GCG-3';
(198) 5'-UUC-3';
(199) 5'-GCC-3';
(200) 5'-GGG-3';
(201) 5'-AUU-3';
(202) 5'-GCA-3';
(203) 5'-AGC-3';
(204) 5'-AAC-3';
(205) 5'-CCA-3';
(206) 5'-UGC-3';
(207) 5'-CAA-3';
(208) 5'-CGG-3';
(209) 5'-ACC-3';
(210) 5'-AGA-3';
(211) 5'-TTT-3';
(212) 5'-TCT-3'and
and
(213) a variant of the motifs or sequences of (1) to (212) having at least about 75% sequence identity thereto;

wherein the U may be a T and/or the T may be a U;

ii) producing one or more candidate oligonucleotides comprising the motif;

iii) testing the ability of the one or more candidate oligonucleotides to inhibit TLR7 activity, and

iv) selecting an oligonucleotide which inhibits TLR7 activity.

49. A method for increasing the TLR7 inhibitory activity of an oligonucleotide, the method comprising modifying the oligonucleotide such that the modified oligonucleotide comprises a motif including a sequence selected from the group consisting of:

(1) 5'-[A/G]GU[A/C][U/C]C-3';
(2) 5'-A[G/A][U/G]C[U/C]C-3';
(3) 5'-A[G/A][U/G]C[U/C]C[U/C][C/A]U-3';
(4) 5'-GGUAUA-3';
(5) 5'-UGUUUC-3';
(6) 5'-UGUGUC-3';
(7) 5'-CGUGUC-3';
(8) 5'-GCAGUCTCCATGTCCCAGGC-3';
(9) 5'-GAUGGTTCCAGTCCCUCUUC-3';
(10) 5'-AGCAGTCTCCATGTCCCAGG-3';
(11) 5'-GGGUCTCCTCCACACCCUUC-3';
(12) 5'-GGUGGCCACAGGCAACGUCA-3';
(13) 5'-GCCGUTTCCATGTCCCAGGC-3';
(14) 5'-GCGGUATCCATGTCCCAGGC-3';
(15) 5'-GCGGUATACAGGTCCCAGGC-3';
(16) 5'-GCUGUTTCCATGTCCCAGGC-3';
(17) 5'-GCUGUGTCCATGTCCCAGGC-3';
(18) 5'-GCCGUGTCCATGTCCCAGGC-3';
(19) 5'-GCGGUAUCCAUGUCCCAGGC-3';
(20) 5'-GGUATCCCCCCCCCCCCCCC-3';
(21) 5'-GUCCCATCCCTTCTGCUGCC-3';
(22) 5'-UUCUCTCTGGTCCCAUCCCU-3';
(23) 5'-GUUCAGTCAGATCGCUGGGA-3';
(24) 5'-AUGACATTTCGTGGCUCCUA-3';
(25) 5'-UCUCCATGTCCCAGGCCUCC-3';
(26) 5'-AGUCUCCATGTCCCAGGCCU-3';

(27) 5’-CCAUGTCCCAGGCCTCCAGU-3’;
(28) 5’-GCAAGGCAGAGAAACUCCAG-3’;
(29) 5’-GGAUUAAAACAGATTAAUAC-3’;
(30) 5’-AGCCGAACAGAAGGAGCGUC-3’;
(31) 5’-UCCGGCCTCGGAAGCUCUCU-3’;
(32) 5’-UCCGGCCTCGGAGTCUCCAU-3’;
(33) 5’-GCGGUATCCATAGTCUCCAU-3’;
(34) 5’-GAUUAAAACAGATTAAUACA-3’;
(35) 5’-UGACAAAACAATAATAACAG-3’;
(36) 5’-CCAACACTTCGTGGGGUCCU-3’;
(37) 5’-GUGUCCTTCATGCTTUGGAU-3’;
(38) 5’-GUCCCAGGCCTCCAGUGUCU-3’;
(39) 5’-UUGGCCTGTGGATGCUUUGU-3’;
(40) 5’-GUCCGTACCTCCACCCACCG-3’;
(41) 5’-GUGUUTTTAATTTTGUAGAG-3’;
(42) 5’-GUCAAACCTAGAAAGAAGCA-3’;
(43) 5’-GGUCUCCTCCACACCCUUCU-3’;
(44) 5’-GUCUCCTCCACACCCUUCUC-3’;
(45) 5’-UGAUGATGCTTGCAGGAGGC-3’;
(46) 5’-UUAAATAATCTAGTTUGAAG-3’;
(47) 5’-AAAGCAGTCTCCATGUCCCA-3’;
(48) 5’-GCGUAGTTTCTCTTCCUCCC-3’;
(49) 5’-UCUGGTCCCATCCCTUCUGC-3’;
(50) 5’-UAUUUCCACATGCCCAGUGU-3’;
(51) 5’-UGUUUCCCCGGAGAGCAAUG-3’;
(52) 5’-UUAGCTCCTTGCCTCGUUCC-3’;
(53) 5’-AUUUCCACATGCCCAGUGUU-3’;
(54) 5’-UGGCGTAGTTTCTCTUCCUC-3’;
(55) 5’-UGACATTTCGTGGCTCCUAC-3’;
(56) 5’-GAAAAGATTATCTTCUUUUA-3’;
(57) 5’-UGUGAAAAGATTATCUUCUU-3’;

(58) 5’-UUGUGAAAAGATTATCUUCU-3’;
(59) 5’-UUUGAAATTCAGAAGAUUUG-3’;
(60) 5’-AAGCAGTCTCCATGTCCCAG-3’;
(61) 5’-AGGAUTAAAACAGATUAAUA-3’;
(62) 5’-AGAUUATCTTCTTTTAAUUU-3’;
(63) 5’-UCCCAACTCTTCTAACUCGU-3’;
(64) 5’-UAAAATAAGGGGAATAGGGG-3’;
(65) 5’-AGUGGCACATACCACACCCU-3’;
(66) 5’-AAGAUTATCTTCTTTUAAUU-3’;
(67) 5’-AGAAAGAAGCAAAGAUUCAA-3’;
(68) 5’-UCCCATCCCTTCTGCUGCCA-3’;
(69) 5’-ACCCUTCTCTCTGGTCCCAU-3’;
(70) 5’-AAUAUCTGCTGCCCACCUUC-3’;
(71) 5’-UCUCUCTGGTCCCATCCCUU-3’;
(72) 5’-AGGCCTCCAGTGTCTUCUCC-3’;
(73) 5’-CAAGCCCCAGCGTTCCUCCG-3’;
(74) 5’-AAAUGTCCTGGCCCTCACUG-3’;
(75) 5’-AAUUUAAAGCATGAAUAUUA-3’;
(76) 5’-AAAAGATTATCTTCTUUUAA-3’;
(77) 5’-AUAUCTGCTGCCCACCUUCU-3’;
(78) 5’-CAGUCTCCATGTCCCAGGCC-3’;
(79) 5’-AAAGATTATCTTCTTUUAAU-3’;
(80) 5’-CCCUUCTCTCTGGTCCCAUC-3’;
(81) 5’-AUGGCCTTTCCGTGCCAAGG-3’;
(82) 5’-GCAUUCCGTGCGGAAGCCUU-3’;
(83) 5’-GGCCGAACTTTCCCGCCUUA-3’;
(84) 5’-GGUCUTGGCTTCGTGGAGCA-3’;
(85) 5’-GGAGCTTCGAGGCCCCAGGC-3’;
(86) 5’-GGUGGTCCACAACCCCUUUC-3’;
(87) 5’-UUCUGGGGACTTCCAGUUUA-3’;
(88) 5’-UGAUUCCAAAGCCAGGGUUA-3’;

(89) 5’-GGGUATCGAAAGAGTCUGGA-3’;
(90) 5’-CUUGCACGTGGCTTCGUCUC-3’;
(91) 5’-GUGUCCTTGCACGTGGCUUC-3’;
(92) 5’-GUAAAAAGCTTTTGAAGUGA-3’;
(93) 5’-AUGCCATCCACTTGAUAGGC-3’;
(94) 5’-UGAAGTAAAAATCAAUAGCG-3’;
(95) 5’-AAGGCCCTTCGCACTUCUUA-3’;
(96) 5’-GUACUCGTCGGCATCCACCA-3’;
(97) 5’-GUCCUTGCACGTGGCUUCGU-3’;
(98) 5’-GCCCATCCATGAGGTCCUGG-3’;
(99) 5’-GUAAAAGGAGAAAACUAUCU-3’;
(100) 5’-UUGAAGTGAAGTAAAAGGAG-3’;
(101) 5’-GUUACTCGTGCCTTGGCAAA-3’;
(102) 5’-GUCCAAGATCAGCAGUCUCA-3’;
(103) 5’-UUCAATGGGAGAATAAAGCA-3’;
(104) 5’-GCAAGGCCCTTCGCACUUCU-3’;
(105) 5’-GGGUCCACCACTAGCCAGUA-3’;
(106) 5’-GUAGAGAAATTATTTUAGGA-3’;
(107) 5’-AUCCACCACGTCGTCCAUGU-3’;
(108) 5’-GGCAUCCACCACGTCGUCCA-3’;
(109) 5’-UUACUTTAAAAGCAAAAGGA-3’;
(110) 5’-UUUGAAGTGAAGTAAAAGGA-3’;
(111) 5’-GAAGUGAAGTAAAAGGAGAA-3’;
(112) 5’-GGCCATCTCTGCTTCUUGGU-3’;
(113) 5’-UGGGCTGGAATCCGAGUUAU-3’;
(114) 5’-GGAGATTTCAGAGCAGCUUC-3’;
(115) 5’-UUUACGGTTTTCAGAAUAUC-3’;
(116) 5’-GCGUGTCTGGAAGCTUCCUU-3’;
(117) 5’-GCUUATTTTAAGCATAUUAA-3’;
(118) 5’-UUAUUTTAAGCATATUAAAA-3’;
(119) 5’-UUCUGCAGCTTCCTTGUCCU-3’;

(120) 5’-AUUACTTTAAAAGCAAAAGG-3’;
(121) 5’-AUUUUAAGCATATTAAAAAG-3’;
(122) 5’-UGUGGCTTGTCCTCAGACAU-3’;
(123) 5’-AAAAGGAGAAAACTAUCUUC-3’;
(124) 5’-GGGUCCATACCCAAGGCAUC-3’;
(125) 5’-ACAGUGTTGAGATACUCGGG-3’;
(126) 5’-GGAUCTGCATGCCCTCAUCU-3’;
(127) 5’-AGUAAAAAGCTTTTGAAGUG-3’;
(128) 5’-GUCGUGGCAAATAGTCCUAG-3’;
(129) 5’-GGAGATCAGATGAGAGGAGC-3’;
(130) 5’-GUGGUTAAGTACATGAGCUC-3’;
(131) 5’-GGACACTTAGCTGTTCCUCG-3’;
(132) 5’-GUCUCTACTGTTACCUCUGA-3’;
(133) 5’-GAGUUCTTCGTAGGCUUCUG-3’;
(134) 5’-AAAGUCAAAAAGAAAAACUG-3’;
(135) 5’-AAAAGTGGGAAATAAAGGUU-3’;
(136) 5’-AGUUUATAGATTTCAAGUAG-3’;
(137) 5’-AAAAAGTGGGAAATAAAGGU-3’;
(138) 5’-UUUAUATTACAAAGCUACUU-3’;
(139) 5’-UGCUATTCATATTTTUAUUU-3’;
(140) 5’-GGUAU-3’;
(141) 5’-[G/A/C][G/A][G/A/C][T/A/C]TC-3’;
(142) 5’-[G/A/C]G[G/A/C][T/A/C]TC-3’;
(143) 5’-GGCTTC-3’;
(144) 5’-GGCATC-3’;
(145) 5’-AGCTTC-3’;
(146) 5’-GGAATC-3’;
(147) 5’-CACATC-3’;
(148) 5’-GGCCTC-3’;
(149) 5’-CACTTC-3’;
(150) 5’-AAGATC-3’;

(151) 5’-TGTCCTTGCACGTGGCTTCG-3’;
(152) 5’-TTTGCACACTTCGTACCCAA-3’;
(153) 5’-GTCCACATCCTGTGGCTCGT-3’;
(154) 5’-TGTGATGGCCTCCCATCTCC-3’;
(155) 5’-GGTTTTGGCTGGGATCAAGT-3’;
(156) 5’-GGTGTCCTTGCACGTGGCTT-3’;
(157) 5’-GGTCCATACCCAAGGCATCC-3’;
(158) 5’-GTGTCTTCATCGGCCCTGCC-3’;
(159) 5’-GTCTTGGCTTCGTGGAGCAG-3’;
(160) 5’-GCTGACAAAGATTCACTGGT-3’;
(161) 5’-GAAAGGTTATGCAAGG-3’;
(162) 5’-GACTATACGCGCAATA-3’;
(163) 5’-TGTGATGGCCTCCCAT-3’;
(164) 5’-TCCAACACTTCGTGGG-3’;
(165) 5’-GTGTCTGGAAGCTTCC-3’;
(166) 5’-CTTGAAGCATCGTATC-3’;
(167) 5’-TCGTAGTTGCTTCCTA-3’;
(168) 5’-CGCTTTTCTGTCTGGT-3’;
(169) 5’-GGCTGGAATCCGAGTT-3’;
(170) 5’-GATAGCACCTTCAGCA-3’;
(171) 5’-AGGACTCCAGATGTTT-3’;
(172) 5’-GTGATCTTGACATGCT-3’;
(173) 5’-AGATTTCAGAGCAGCT-3’;
(174) 5’-GGTTACGGCTCAGTAT-3’;
(175) 5’-GTTCAGTCCTGTCCAT-3’;
(176) 5’-AGGTCTTGGCTTCGTG-3’;
(177) 5’-CTGCAGCTTCCTTGTC-3’;
(178) 5’-GTCCTTGCACGTGGCT-3’;
(179) 5’-GTCTCTGGAGCTTCCT-3’;
(180) 5’-GGTCTTGGCTTCGTGG-3’;
(181) 5’-GGUA-3’;

(182) 5’-GUAU-3’;

(183) 5’-GGU-3’;

(184) 5’-GUA-3’;

(185) 5’-GUC-3’;

(186) 5’-GUG-3’;

(187) 5’-GUU-3’;

(188) 5’-GUA-3’;

(189) 5’-GGC-3’;

(190) 5’-AUC-3’;

(191) 5’-GAA-3’;

(192) 5’-GAG-3’;

(193) 5’-GGA-3’;

(194) 5’-GAC-3’;

(195) 5’-GAU-3’;

(196) 5’-AUG-3’;

(197) 5’-GCG-3’;

(198) 5’-UUC-3’;

(199) 5’-GCC-3’;

(200) 5’-GGG-3’;

(201) 5’-AUU-3’;

(202) 5’-GCA-3’;

(203) 5’-AGC-3’;

(204) 5’-AAC-3’;

(205) 5’-CCA-3’;

(206) 5’-UGC-3’;

(207) 5’-CAA-3’;

(208) 5’-CGG-3’;

(209) 5’-ACC-3’;

(210) 5’-AGA-3’;

(211) 5’-TTT-3’;

(212) 5’-TCT-3’and

and

(213) a variant of the motifs or sequences of (1) to (212) having at least about 75% sequence identity thereto;

wherein the U may be a T and/or the T may be a U.

50. The method of claim 49, wherein the step of modifying the oligonucleotide includes adding a sequence of nucleotides to the 5' and/or 3' end of the oligonucleotide such that the modified oligonucleotide comprises the motif.

51. The method of claim 49 or 50, which further comprises testing the ability of the modified oligonucleotide to inhibit TLR7 activity, and selecting an oligonucleotide which inhibits TLR7 activity to a greater extent than the unmodified oligonucleotide.

52. The method according to any one of claims 48 to 51, wherein the oligonucleotide does not bind or is not designed to bind a transcript that encodes TLR7 or a complement thereof.

53. The method according to any one of claims 48 to 52, wherein the oligonucleotide binds or is designed to bind a target transcript that does not encode TLR7 or a complement thereof.

54. The method according to any one of claims 48 to 53, wherein the motif is: (a) within eleven bases of the 5' and/or 3' end of the oligonucleotide; (b) within eight bases of the 5' and/or 3' end of the oligonucleotide; and/or (c) at or towards the 5' and/or 3' end of the oligonucleotide.

55. The method according to any one of claims 48 to 54, wherein the oligonucleotide comprises

a) a 5' region comprising bases which are modified and/or which have a modified backbone,

b) a middle region comprising ribonucleic acid, deoxyribonucleic acid, or combination thereof, bases, which optionally have a modified backbone, and

c) a 3' region comprising bases which are modified and/or which have a modified backbone.

56. The method of claim 55, wherein the middle region is about 10 bases in length and/or the 5' region and/or the 3' region are: (a) about 3 bases in length; or (b) about 5 bases in length.

57. The method according to any one of claims 48 to 56, wherein the motif has the sequence 5'-GGUAUC-3', 5'-AGUCUC-3', 5'-GGUCCC-3', 5'-GGUCUC-3', 5'-AAGCUC-3', 5'-AGUCCC-3', 5'-GGUAUA-3', 5'-UGUUUC-3', 5'-UGUGUC-3', 5'-CGUUUC-3', 5'-CGUGUC-3', 5'-GGUAU-3', 5'-GGUA-3', 5'-GUAU-3', 5'-GGU-3', 5'-GUA-3', (185) 5'-GUC-3'; 5'-GUG-3'; 5'-GUU-3'; 5'-GUA-3'; 5'-GGC-3'; 5'-AUC-3'; 5'-GAA-3'; 5'-GAG-3'; 5'-GGA-3'; 5'-GAC-3'; 5'-GAU-3'; 5'-AUG-3'; 5'-GCG-3'; 5'-UUC-3'; 5'-GCC-3'; 5'-GGG-3'; 5'-AUU-3'; 5'-GCA-3'; 5'-AGC-3'; 5'-AAC-3'; 5'-CCA-3'; 5'-UGC-3'; 5'-CAA-3'; 5'-CGG-3'; 5'-ACC-3'; 5'-AGA-3', wherein the U may be a T.

58. The method according to any one of claims 48 to 57, wherein the motif has the sequence of 5'-GGUAUC-3', 5'-GGUATC-3', 5'-AGUCTC-3', 5'-AGTCTC-3', 5'-GGUCCC-3', 5'-GGUCTC-3', 5'-AAGCUC-3', 5'-AGTCCC-3', 5'-GGUATA-3', 5'-UGUTTC-3', 5'-UGUGTC-3', 5'-CGUTTC-3', 5'-CGUGTC-3', 5'-GGUAU-3', 5'-GGUAT-3', 5'-GGUA-3', 5'-GUAU-3', 5'-GUAT-3', 5'-GGU-3' or 5'-GUA-3'.

59. The method according to any one of claims 48 to 58, wherein one or more of the bases of the motif are a modified base and/or have a modified backbone.

60. The method according to any one of claims 48 to 59, wherein the motif has the sequence of 5'-mGmGmUATC-3', 5'-mAmGmUCTC-3', 5'-mAmGTCTC-3', 5'-mGmGmUmCmCC-3', 5'-mGmGmUmCTC-3', 5'-AAGCmUmC-3', 5'-AGTCCC-3', 5'-mGmGmUATA-3', 5'-mUmGmUTTC-3', 5'-mUmGmUGTC-3', 5'-mCmGmUTTC-3', 5'-mCmGmUGTC-3', 5'-mGmGmUAU-3', 5'-mGmGmUAT-3', 5'-mGmGmUmAU-3', 5'-mGmGmUmAT-3', 5'-mGmGmUmAmU-3', 5'-mGmGmUmA-3', 5'-mGmUmAmU-3', 5'-mGmGmU-3' or 5'-mGmUmA-3', wherein m is a modified base and/or has a modified backbone.

61. A method for selecting or designing an oligonucleotide which increases or potentiates TLR8 activity, the method comprising

i) scanning a polynucleotide, or complement thereof, for a region having a motif including a sequence selected from the group consisting of:

5'-CUUCG-3';
5'-CUUCGTG-3';
5'-CUUCGTGGG-3';
5'-UCG-3';
5'-UCA-3';
5'-CGG-3';
5'-UGG-3';
5'-CGC-3';
5'-AGG-3';
5'-GGA-3';
5'-GGC-3';
5'-AGA-3';
5'-CGA-3';
5'-UAG-3';
5'-UCU-3';
5'-AGC-3';
5'-GGU-3';
5'-UGA-3';
5'-AGU-3';
5'-ACG-3';
5'-CGU-3';
5'-UCC-3';
5'-GCG-3';
5'-GGG-3';
5'-UGU-3';
5'-UCA-3';
5'-CUG-3';
5'-UUG-3';
5'-UUA-3';
5'-UGC-3';

and

a variant of the motifs or sequences thereof having at least about 75% sequence identity thereto;

wherein the U may be a T and/or the T may be a U;

ii) producing one or more candidate oligonucleotides comprising the motif;

iii) testing the ability of the one or more candidate oligonucleotides to increase or potentiate TLR8 activity, and

iv) selecting an oligonucleotide which increases or potentiate TLR8 activity.

62. A method for increasing or potentiating the TLR8 activity of an oligonucleotide, or increasing the potentiating activity of an oligonucleotide, the method comprising modifying the oligonucleotide such that the modified oligonucleotide comprises a motif including a sequence selected from the group consisting of:

5'-CUUCG-3';
5'-CUUCGTG-3';
5'-CUUCGTGGG-3';
5'-UCG-3';
5'-UCA-3';
5'-CGG-3';
5'-UGG-3';
5'-CGC-3';
5'-AGG-3';
5'-GGA-3';
5'-GGC-3';
5'-AGA-3';
5'-CGA-3';
5'-UAG-3';
5'-UCU-3';
5'-AGC-3';
5'-GGU-3';
5'-UGA-3';
5'-AGU-3';
5'-ACG-3';
5'-CGU-3';
5'-UCC-3';
5'-GCG-3';
5'-GGG-3';
5'-UGU-3';
5'-UCA-3';
5'-CUG-3';

5’-UUG-3’;
5’-UUA-3’;
5’-UGC-3’;
and
a variant of the motifs or sequences thereof having at least about 75% sequence identity thereto;
wherein the U may be a T and/or the T may be a U.

63. A method for selecting or designing an oligonucleotide which inhibits TLR8 activity, the method comprising
i) scanning a polynucleotide, or complement thereof, for a region having a motif including a sequence selected from the group consisting of:
5’-GAG-3’;
5’-GAC-3’;
5’-GAU-3’;
5’-GAA-3’;
5’-GUC-3’;
5’-GUU-3’;
5’-GUA-3’;
5’-GUG-3’;
5’-AUA-3’;
5’-AUG-3’;
5’-CUU-3’;
5’-AAG-3’;
5’-AUC-3’;
5’-CCC-3’;
5-GCU-3’;
5’-CCU-3’;
5’-CUA-3’;
5’-CUC-3’;
5’-AAC-3’;
and
a variant of the motifs or sequences thereof having at least about 75% sequence identity thereto;
wherein the U may be a T and/or the T may be a U;
ii) producing one or more candidate oligonucleotides comprising the motif;

iii) testing the ability of the one or more candidate oligonucleotides to inhibit TLR8 activity, and

iv) selecting an oligonucleotide which inhibits TLR8 activity.

64. A method for increasing the TLR8 inhibitory activity of an oligonucleotide, the method comprising modifying the oligonucleotide such that the modified oligonucleotide comprises a motif including a sequence selected from the group consisting of:

5'-GAG-3';
5'-GAC-3';
5'-GAU-3';
5'-GAA-3';
5'-GUC-3';
5'-GUU-3';
5'-GUA-3';
5'-GUG-3';
5'-AUA-3';
5'-AUG-3';
5'-CUU-3';
5'-AAG-3';
5'-AUC-3';
5'-CCC-3';
5-GCU-3';
5'-CCU-3';
5'-CUA-3';
5'-CUC-3';
5'-AAC-3';

and

a variant of the motifs or sequences thereof having at least about 75% sequence identity thereto;

wherein the U may be a T and/or the T may be a U.

65. A method for selecting or designing an oligonucleotide which inhibits TLR3 activity, the method comprising

i) scanning a polynucleotide, or complement thereof, for a region having a motif including a sequence selected from the group consisting of:

5'-TAC-3';

5’-CGC-3’;
5’-GCA-3’;
5’-UGA-3’;
5’-CAG-3’;
5’-UGG-3’;
5’-UCA-3’;
5’-TGA-3’;
5’-CGT-3’;
5’-GAC-3’;
5’-CCA-3’;
5’-TAG-3’;
5’-TGG-3’;
5’-TCA-3’;
5’-TGC-3’;
5’-CAC-3’;
5’-CGG-3’;
5’-CCC-3’;
5’-ACT-3’;
5’-GTA-3’;
5’-GGA-3’;
5’-AAG-3’;
5’-ATA-3’;
5’-GUC-3’;
5’-UCC-3’;
5’-AUC-3’;
5’-CCG-3’;
5’-CAA-3’;
5’-GAU-3’;
5’-CGA-3’;and

a variant of the motifs or sequences thereof having at least about 75% sequence identity thereto;

wherein the U may be a T and/or the T may be a U;

ii) producing one or more candidate oligonucleotides comprising the motif;

iii) testing the ability of the one or more candidate oligonucleotides to inhibit TLR3 activity, and

iv) selecting an oligonucleotide which inhibits TLR3 activity.

66. A method for increasing the TLR3 inhibitory activity of an oligonucleotide, the method comprising modifying the oligonucleotide such that the modified oligonucleotide comprises a motif including a sequence selected from the group consisting of:

5'-TAC-3';
5'-CGC-3';
5'-GCA-3';
5'-UGA-3';
5'-CAG-3';
5'-UGG-3';
5'-UCA-3';
5'-TGA-3';
5'-CGT-3';
5'-GAC-3';
5'-CCA-3';
5'-TAG-3';
5'-TGG-3';
5'-TCA-3';
5'-TGC-3';
5'-CAC-3';
5'-CGG-3';
5'-CCC-3';
5'-ACT-3';
5'-GTA-3';
5'-GGA-3';
5'-AAG-3';
5'-ATA-3';
5'-GUC-3';
5'-UCC-3';
5'-AUC-3';
5'-CCG-3';
5'-CAA-3';
5'-GAU-3';
5'-CGA-3';
and

a variant of the motifs or sequences thereof having at least about 75% sequence identity thereto;

wherein the U may be a T and/or the T may be a U.

67. The method according to any one of claims 12, 13, 22, 23, 36 to 47, 59 or 60, wherein the modified base comprises a 2'-O-methyl, 2'-O-methoxyethoxy, 2'-fluoro, 2'-allyl, 2'-O-[2-(methylamino)-2-oxoethyl], 4'-thio, 4'-CH2-O-2'-bridge, 4'-(CH2)2-O-2'-bridge, 2'-LNA, 2'-amino, fluoroarabinonucleotide, threose nucleic acid or 2'-O--(N-methlycarbamate).

68. The method according to any one of claims 12, 13, 22, 23, 36 to 47, 59 or 60, wherein the modified backbone comprises a phosphorothioate, a non-bridging oxygen atom substituting a sulfur atom, a phosphonate such as a methylphosphonate, a phosphodiester, a phosphoromorpholidate, a phosphoropiperazidate, amides, methylene(methylamino), fromacetal, thioformacetal, a peptide nucleic acid or a phosphoroamidate such as a morpholino phosphorodiamidate (PMO), N3'-P5' phosphoramidite or thiophosphoroamidite.

69. The method according to any one of the preceding claims, wherein at least a portion of the oligonucleotide has/is a ribonucleic acid, deoxyribonucleic acid, DNA phosphorothioate, RNA phosphorothioate, 2'-O-methyl-oligonucleotide, 2'-O-methyl-oligodeoxyribonucleotide, 2'-O-hydrocarbyl ribonucleic acid, 2'-O-hydrocarbyl DNA, 2'-O-hydrocarbyl RNA phosphorothioate, 2'-O-hydrocarbyl DNA phosphorothioate, 2'-F-phosphorothioate, 2'-F-phosphodiester, 2'-methoxyethyl phosphorothioate, 2-methoxyethyl phosphodiester, deoxy methylene(methylimino) (deoxy MMI), 2'-O-hydrocarby MMI, deoxy-methylphos-phonate, 2'-O-hydrocarbyl methylphosphonate, morpholino, 4'-thio DNA, 4'-thio RNA, peptide nucleic acid, 3'-amidate, deoxy 3'-amidate, 2'-O-hydrocarbyl 3'-amidate, locked nucleic acid, cyclohexane nucleic acid, tricycle-DNA, 2'fluoro-arabino nucleic acid, N3'-P5' phosphoroamidate, carbamate linked, phosphotriester linked, a nylon backbone modification and any combination thereof.

70. The method according to any one of claims 12, 13, 22, 23, 36 to 47, 59 or 60, wherein the modified base comprises:

(a) a 2'O-methyl and a phosphorothioate backbone;

(b) a 2'-LNA and a phosphorothioate backbone; or

(c) a 2'-O-methoxyethoxy and a phosphorothioate backbone.

71. The method according to any one of the preceding claims, wherein at least one of the bases of the oligonucleotide does not hybridize to a target polynucleotide.

72. The method according to any one of the preceding claims, wherein the oligonucleotide is an antisense oligonucleotide or a double stranded oligonucleotide for gene silencing.

73. The method of claim 72, wherein the oligonucleotide is a gapmer antisense oligonucleotide.

74. The method of claim 72 or claim 73, wherein one or more bases of the motif or the oligonucleotide are removed by an endonuclease *in vivo*.

75. The method of claim 72, wherein the double stranded oligonucleotide for gene silencing is an siRNA or an shRNA.

76. An oligonucleotide selected or designed using the method according to any one of claims 1, 5 to 14, 18 to 24, 28 to 48, or 52 to 75 or modified using the method according to any one of claims 2 to 13, 15 to 23, 25 to 41 or 49 to 75.

77. An oligonucleotide comprising a motif or sequence selected from the group consisting of:

(1) 5'-[A/G]GU[A/C][U/C]C-3';

(2) 5'-A[G/A][U/G]C[U/C]C-3';

(3) 5'-A[G/A][U/G]C[U/C]C[U/C][C/A]U-3';

(4) 5’-GGUAUA-3’;

(5) 5’-UGUUUC-3’;

(6) 5’-UGUGUC-3’;

(7) 5’-CGUUUC-3’;

(8) 5’-CGUGUC-3’;

(9) 5’-AUGGCCTTTCCGTGCCAAGG-3’;

(10) 5’-UCCGGCCTCGGAAGCUCUCU-3’;

(11) 5’-GCAUUCCGTGCGGAAGCCUU-3’;

(12) 5’-GGCCGAACTTTCCCGCCUUA-3’;

(13) 5’-GGUCUTGGCTTCGTGGAGCA-3’;

(14) 5’-GGAGCTTCGAGGCCCCAGGC-3’;

(15) 5’-GGUGGTCCACAACCCCUUUC-3’;

(16) 5’-CAUUAGGTGCAGAAAUCUUC-3’;

(17) 5’-UUCUGGGGACTTCCAGUUUA-3’;

(18) 5’-UGAUUCCAAAGCCAGGGUUA-3’;

(19) 5’-CUUUAGTCGTAGTTGCUUCC-3’;

(20) 5’-UUAAATAATCTAGTTUGAAG-3’;

(21) 5’-GUGUCCTTCATGCTTUGGAU-3’;

(22) 5’-AGAAAGAAGCAAAGAUUCAA-3’;

(23) 5’-AGAUUATCTTCTTTTAAUUU-3’;

(24) 5’-AAAAGATTATCTTCTUUUAA-3’;

(25) 5’-GAAAAGATTATCTTCUUUUA-3’;

(26) 5’-UGUGAAAAGATTATCUUCUU-3’;

(27) 5’-CUUGUGAAAAGATTAUCUUC-3’;

(28) 5’-GGUGGCCACAGGCAACGUCA-3’;

(29) 5’-CCAUGTCCCAGGCCTCCAGU-3’;

(30) 5’-GCAGUCTCCATGTCCCAGGC-3’;

(31) 5’-AGCAGTCTCCATGTCCCAGG-3’;

(32) 5’-AGUGGCACATACCACACCCU-3’;

(33) 5’-AUUUCCACATGCCCAGUGUU-3’;

(34) 5’-GGUCCCATCCCTTCTGCUGC-3’;

(35) 5’-UCUGGTCCCATCCCTUCUGC-3’;
(36) 5’-GGGUCTCCTCCACACCCUUC-3’;
(37) 5’-GCAAGGCAGAGAAACUCCAG-3’;
(38) 5’-GAUGGTTCCAGTCCCUCUUC-3’;
(39) 5’-UGUUUCCCCGGAGAGCAAUG-3’;
(40) 5’-AGCCGAACAGAAGGAGCGUC-3’;
(41) 5’-GCGUAGTTTCTCTTCCUCCC-3’;
(42) 5’-GCGGUATCCATGTCCCAGGC-3’;
(43) 5’-GCGGUATACAGGTCCCAGGC-3’;
(44) 5’-GCUGUTTCCATGTCCCAGGC-3’;
(45) 5’-GCUGUGTCCATGTCCCAGGC-3’;
(46) 5’-GCCGUTTCCATGTCCCAGGC-3’;
(47) 5’-GCCGUGTCCATGTCCCAGGC-3’;
(48) 5’-GCGGUATCCATAGTCUCCAU-3’;
(49) 5’-GCGGUATCCATCAGAUAUCG-3’;
(50) 5’-CUUUAGTCGTAGTTGUCUCU-3’;
(51) 5’-UCCGGGTCGTAGTTGCUUCC-3’;
(52) 5’-UCCGGCCTCGGAGTCUCCAU-3’;
(53) 5’-UCCGGCCTCGGGAGAUCUCU-3’;
(54) 5’-GGUATCCCCCCCCCCCCCC-3’;
(55) 5’-GGAUUAAAACAGATTAAUAC-3’;
(56) 5’-GGUAU-3’;
(57) 5’-GGUA-3’;
(58) 5’-GUAU-3’;
(59) 5’-GGU-3’;
(60) 5’-GUA-3’;
(61) 5’-TGTCTG-3’;
(62) 5’-GTCT-3’;
(63) 5’-TCTCCG-3’;
(64) 5’-CTCC-3’;
(65) 5’-[G/A][A/C]AG[G/C][T/C]T[C/A];

(66) 5’-AAAGGTTA-3’;

(67) 5’-GAAGCTTC-3’;

(68) 5’-GCAGGCTC-3’;

(69) 5’-A[G/A]GGTT-3’;

(70) 5’-AGGGTT-3’;

(71) 5’-AAGGTT-3’;

(72) 5’-GGTT-3’;

(73) 5’-[A/G]GCT[T/C][T/C][G/C][T/A]-3’;

(74) 5’-AGCTTCCT-3’;

(75) 5’-AGCTTCGA-3’;

(76) 5’-GGCTTCGT-3’;

(77) 5’-TGCTTCCT-3’;

(78) 5’-AGCTCTCT-3’;

(79) 5’-G[G/C]TT-3’;

(80) 5’-GCTT-3’;

(81) 5’-CGGAGGTCTTGGCTTCGTGG-3’;

(82) 5’-AGGTCTTGGCTTCGTGGAGC-3’;

(83) 5’-GGGAAAGGTTATGCAAGGTC-3’;

(84) 5’-CTGTGATCTTGACATGCTGC-3’;

(85) 5’-ACTGACTGTCTTGAGGGTTC-3’;

(86) 5’-GCGTGTCTGGAAGCTTCCTT-3’;

(87) 5’-GAGTCTCTGGAGCTTCCTCT-3’;

(88) 5’-AGTCGTAGTTGCTTCCTAAC-3’;

(89) 5’-GTCTTGGCTTCGTGGAGCAG-3’;

(90) 5’-TTGGCTCGGCTTGCCTACTT-3’;

(91) 5’-ACAGTGTTGAGATACTCGGG-3’;

(92) 5’-TCGCACTTCAGTCTGAGCAG-3’;

(93) 5’-GGTGTCCTTGCACGTGGCTT-3’;

(94) 5’-TTTGCACACTTCGTACCCAA-3’;

(95) 5’-GCTGACAAAGATTCACTGGT-3’;

(96) 5’-GCGGAGGTCTTGGCTTCGTG-3’;

(97) 5’-CCAAGATCAGCAGTCT-3’;
(98) 5’-CTTGAAGCATCGTATC-3’;
(99) 5’-GCACACTTCGTACCCA-3’;
(100) 5’-GATAGCACCTTCAGCA-3’;
(101) 5’-CGTATTATAGCCGATT-3’;
(102) 5’-GCAGGCTCAGTGATGT-3’;
(103) 5’-GAAAGGTTATGCAAGG-3’;
(104) 5’-ATGGCCTCCCATCTCC-3’;
(105) 5’-CGCTTTTCTGTCTGGT-3’;
(106) 5’-GTGTCTGGAAGCTTCC-3’;
(107) 5’-TGGCCTCCCATCTCCT-3’;
(108) 5’-ATCTGGCAGCCCATCA-3’;
(109) 5’-GAGGTCTTGGCTTCGT-3’;
(110) 5’-ACACTTCGTGGGGTCC-3’;
(111) 5’-TTCGTGGGGTCCTTTT-3’;
(112) 5’-CCACTTGGCAGACCAT-3’;
(113) 5’-CCATCCATGAGGTCCT-3’;
(114) 5’-TCCAACACTTCGTGGG-3’;
(115) 5’-TCTTCATCGGCCCTGC-3’;
(116) 5’-CCAGCAGGTCAGCAAA-3’;
(117) 5’-CGCTTTTCTCTCCGGT-3’;
(118) 5’-GGUAUAGGACTCCAGATGUUUCC-3’; and
(119) a variant of the motifs or sequences of (1) to (118) having at least about 75% sequence identity thereto;

wherein the U may be a T and/or the T may be a U and wherein the oligonucleotide inhibits cGAS activity when administered to a subject.

78. An oligonucleotide comprising a motif or sequence selected from the group consisting of:

(1) 5’[C/U]CUUCU-3’;
(2) 5’-CACCCTTCTCTCTGGUCCCA-3’;

(3) 5’-CCUUCTCTCTGGTCCCAUCC-3’;

(4) 5’-UCUCUGGTCCCATCCCUUCU-3’;

(5) 5’-AUAUCTGCTGCCCACCUUCU-3’;

(6) 5’-GUCCCATCCCTTCTGCUGCC-3’;

(7) 5’-GUCUCCTCCACACCCUUCUC-3’;

(8) 5’-CAGGCCTCCAGTGTCUUCUC-3’;

(9) 5’-UCCCAACTCTTCTAACUCGU-3’; and

(10) a variant of the motifs or sequences of (1) to (9) having at least about 75% sequence identity thereto;

wherein the U may be a T and/or the T may be a U and wherein the oligonucleotide does not inhibit or exhibits reduced inhibition of cyclic-GMP-AMP synthase (cGAS) activity when administered to a subject.

79. An oligonucleotide comprising, consisting essentially of or consisting of a motif or sequence selected from the group consisting of:

(1) 5’-G[G/C]CCT[C/G]-3’;

(2) 5’-CUU-3’, wherein the motif is within 10 bases of the 5’ and/or 3’ end of the oligonucleotide;

(3) 5’-CUUGUGAAAAGATTAUCUUC-3’;

(4) 5’-CUUCUCTCTGGTCCCAUCCC-3’;

(5) 5’-CCUUCTCTCTGGTCCCAUCC-3’;

(6) 5’-CCCUUCTCTCTGGTCCCAUC-3’;

(7) 5’-ACCCUTCTCTCTGGTCCCAU-3’;

(8) 5’-CUUCCACAATCAAGACAUUC-3’;

(9) 5’-CUUCGTGGGGTCCTTUUCAC-3’;

(10) 5’-CACUUCGTGGGGTCCUUUUC-3’;

(11) 5’-CCAACACTTCGTGGGGUCCU-3’;

(12) 5’-UCCGGCCTCGGAAGCUCUCU-3’;

(13) 5’-CCAUGTCCCAGGCCTCCAGU-3’;

(14) 5’-UUGGCCTGTGGATGCUUUGU-3’;

(15) 5’-AAAUGTCCTGGCCCTCACUG-3’;

(16) 5’-UCCGGCCTCGGAGTCUCCAU-3’;

(17) 5’-UCCGGCCTCGGCAGAUAUCG-3’;

(18) 5’-GGCCGAACTTTCCCGCCUUA-3’;

(19) 5’-GGUCUTGGCTTCGTGGAGCA-3’;

(20) 5’-GGAGCTTCGAGGCCCCAGGC-3’;

(21) 5’-GGUGGTCCACAACCCCUUUC-3’;

(22) 5’-CAUUAGGTGCAGAAAUCUUC-3’;

(23) 5’-UUCUGGGGACTTCCAGUUUA-3’;

(24) 5’-UGAUUCCAAAGCCAGGGUUA-3’;

(25) 5’-UCCGGGTCGTAGTTGCUUCC-3’;

(26) 5’-CCUAGAAAGAAGCAAAGAUU-3’;

(27) 5’-GAUUAAAACAGATTAAUACA-3’;

(28) 5’-GGAUUAAAACAGATTAAUAC-3’;

(29) 5’-AAUUUAAAGCATGAAUAUUA-3’;

(30) 5’-GCGUAGTTTCTCTTCCUCCC-3’;

(31) 5’-UGACAAAACAATAATAACAG-3’;

(32) 5’-ACA-3’, wherein the motif is at or towards the 5’ end of the oligonucleotide;

(33) 5’-CAC-3’, wherein the motif is at or towards the 5’ end of the oligonucleotide;

(34) 5’-ACACTTCGTGGGGTCCTTTT-3’;

(35) 5’-GCGTGTCTGGAAGCTTCCTT-3’;

(36) 5’-TCAAAGGACTGAGGAAAGGG-3’;

(37) 5’-ATCCAACACTTCGTGGGGTC-3’;

(38) 5’-GCCCATCCATGAGGTCCTGG-3’;

(39) 5’-GGGTATCGAAAGAGTCTGGA-3’;

(40) 5’-GGTTTTGGCTGGGATCAAGT-3’;

(41) 5’-GCGACTATACGCGCAATATG-3’;

(42) 5’-ACTGACTGTCTTGAGGGTTC-3’;

(43) 5’-AACACTTCGTGGGGTCCTTT-3’;

(44) 5’-GTCCAAGATCAGCAGTCTCA-3’;

(45) 5’-ACAGTGTTGAGATACTCGGG-3’;
(46) 5’-TGGGCTGGAATCCGAGTTAT-3’;
(47) 5’-CGGCATCCACCACGTCGTCC-3’;
(48) 5’-GCGTATTATAGCCGATTAAC-3’;
(49) 5’-GGAGGTCTTGGCTTCGTGGA-3’;
(50) 5’-TGGGTTACGGCTCAGTATGG-3’;
(51) 5’-CCGCCATGTTTCTTCTTGGA-3’;
(52) 5’-AGCTTCGAGGCCCCAG-3’;
(53) 5’-GCCATGTTTCTTCTTG-3’;
(54) 5’-CACTTCGTGGGGTCCT-3’;
(55) 5’-CGGCCTCGGAAGCTCT-3’;
(56) 5’-ACACTTCGTGGGGTCC-3’;
(57) 5’-TGCACACTTCGTACCC-3’;
(58) 5’-CCACATCCTGTGGCTC-3’;
(59) 5’-CTGCAGCTTCCTTGTC-3’;
(60) 5’-ACTTCGTGGGGTCCTT-3’;
(61) 5’-CCCACTTGGCAGACCA-3’;
(62) 5’-GTCCCCTGTTGACTGG-3’;
(63) 5’-ACGTTCAGTCCTGTCC-3’;
(64) 5’-GGTCATTACAATAGCT-3’;
(65) 5’-TCGTGGGGTCCTTTTC-3’;
(66) 5’-GTGTCTGGAAGCTTCC-3’;
(67) 5’-ATGGCCTCCCATCTCC-3’;
(68) 5’-TGCTCCTCGGTCTCCC-3’;
(69) 5’-GCATCCACCACGTCGT-3’;
(70) 5’-CTTCGTGGGGTCCTTT-3’;
(71) 5’-AGGCCCTTCGCACTTC-3’;
(72) 5’-GCGGUATCCATGTCCCAGGC-3’;
(73) 5’-GCUGUTTCCATGTCCCAGGC-3’;
(74) 5’-GCUGUGTCCATGTCCCAGGC-3’
(75) 5’-GCCGUTTCCATGTCCCAGGC-3’;
(76) 5’-GCGGUATCC-3’;

(77) 5’-GCUGUTTCC-3’;
(78) 5’-GCUGUGTCC-3’;
(79) 5’-GCCGUTTCC-3’;
(80) 5’-CUUCGTGGGGTCCTTUUCAC;
(81) 5’-CUUCGTGGG-3’;
(82) 5’-UCG-3’;
(83) 5’-ACG-3’;
(84) 5’-ACC-3’;
(85) 5’-CGC-3’;
(86) 5’-GAU-3’;
(87) 5’-GGG-3’;
(88) 5’-AGC-3’;
(89) 5’-UUC-3’;
(90) 5’-UUG-3’;
(91) 5’-CAC-3’;
and
(92) a variant of the motifs or sequences of (1) to (91) having at least about 75% sequence identity thereto;

wherein the U may be a T and/or the T may be a U and wherein the oligonucleotide inhibits TLR9 activity when administered to a subject.

80. An oligonucleotide which comprises:

a) a 5’ region comprising bases which are modified and/or which have a modified backbone,

b) a middle region comprising ribonucleic acid, deoxyribonucleic acid, or combination thereof, bases, which optionally have a modified backbone, wherein at least about 50% of the bases of the middle region are adenine bases; and

c) a 3’ region comprising bases which are modified and/or which have a modified backbone;

wherein the oligonucleotide inhibits TLR9 activity when administered to a subject.

81. The oligonucleotide of claim 80, comprising a motif or sequence selected from the group consisting of:

(1) 5’-GAUUAAAACAGATTAAUACA-3’;

(2) 5’-GGAUUAAAACAGATTAAUAC-3’;

(3) 5’-CUUGUGAAAAGATTAUCUUC-3’;

(4) 5’-CCUAGAAAGAAGCAAAGAUU-3’;

(5) 5’-AAUUUAAAGCATGAAUAUUA-3’; and

(6) a variant of the motifs or sequences of (1) to (5) having at least about 75% sequence identity thereto;

wherein the U may be a T and/or the T may be a U.

82. An oligonucleotide comprising a motif or sequence selected from the group consisting of:

(1) 5’-[A/G]GU[A/C][U/C]C-3’;

(2) 5’-A[G/A][U/G]C[U/C]C-3’;

(3) 5’-A[G/A][U/G]C[U/C]C[U/C][C/A]U-3’;

(4) 5’-GGUAUA-3’;

(5) 5’-UGUUUC-3’;

(6) 5’-UGUGUC-3’;

(7) 5’-CGUGUC-3’;

(8) 5’-GCAGUCTCCATGTCCCAGGC-3’;

(9) 5’-GAUGGTTCCAGTCCCUCUUC-3’;

(10) 5’-AGCAGTCTCCATGTCCCAGG-3’;

(11) 5’-GGGUCTCCTCCACACCCUUC-3’;

(12) 5’-GGUGGCCACAGGCAACGUCA-3’;

(13) 5’-GCCGUTTCCATGTCCCAGGC-3’;

(14) 5’-GCGGUATCCATGTCCCAGGC-3’;

(15) 5’-GCGGUATACAGGTCCCAGGC-3’;

(16) 5’-GCUGUTTCCATGTCCCAGGC-3’;

(17) 5’-GCUGUGTCCATGTCCCAGGC-3’;

(18) 5’-GCCGUGTCCATGTCCCAGGC-3’;

(19) 5’-GCGGUAUCCAUGUCCCAGGC-3’;

(20) 5’-GGUATCCCCCCCCCCCCCC-3’;

(21) 5’-GUCCCATCCCTTCTGCUGCC-3’;

(22) 5’-UUCUCTCTGGTCCCAUCCCU-3’;
(23) 5’-GUUCAGTCAGATCGCUGGGA-3’;
(24) 5’-AUGACATTTCGTGGCUCCUA-3’;
(25) 5’-UCUCCATGTCCCAGGCCUCC-3’;
(26) 5’-AGUCUCCATGTCCCAGGCCU-3’;
(27) 5’-CCAUGTCCCAGGCCTCCAGU-3’;
(28) 5’-GCAAGGCAGAGAAACUCCAG-3’;
(29) 5’-GGAUUAAAACAGATTAAUAC-3’;
(30) 5’-AGCCGAACAGAAGGAGCGUC-3’;
(31) 5’-UCCGGCCTCGGAAGCUCUCU-3’;
(32) 5’-UCCGGCCTCGGAGTCUCCAU-3’;
(33) 5’-GCGGUATCCATAGTCUCCAU-3’;
(34) 5’-GAUUAAAACAGATTAAUACA-3’;
(35) 5’-UGACAAAACAATAATAACAG-3’;
(36) 5’-CCAACACTTCGTGGGGUCCU-3’;
(37) 5’-GUGUCCTTCATGCTTUGGAU-3’;
(38) 5’-GUCCCAGGCCTCCAGUGUCU-3’;
(39) 5’-UUGGCCTGTGGATGCUUUGU-3’;
(40) 5’-GUCCGTACCTCCACCCACCG-3’;
(41) 5’-GUGUUTTTAATTTTGUAGAG-3’;
(42) 5’-GUCAAACCTAGAAAGAAGCA-3’;
(43) 5’-GGUCUCCTCCACACCCUUCU-3’;
(44) 5’-GUCUCCTCCACACCCUUCUC-3’;
(45) 5’-UGAUGATGCTTGCAGGAGGC-3’;
(46) 5’-UUAAATAATCTAGTTUGAAG-3’;
(47) 5’-AAAGCAGTCTCCATGUCCCA-3’;
(48) 5’-GCGUAGTTTCTCTTCCUCCC-3’;
(49) 5’-UCUGGTCCCATCCCTUCUGC-3’;
(50) 5’-UAUUUCCACATGCCCAGUGU-3’;
(51) 5’-UGUUUCCCCGGAGAGCAAUG-3’;
(52) 5’-UUAGCTCCTTGCCTCGUUCC-3’;

(53) 5’-AUUUCCACATGCCCAGUGUU-3’;
(54) 5’-UGGCGTAGTTTCTCTUCCUC-3’;
(55) 5’-UGACATTTCGTGGCTCCUAC-3’;
(56) 5’-GAAAAGATTATCTTCUUUUA-3’;
(57) 5’-UGUGAAAAGATTATCUUCUU-3’;
(58) 5’-UUGUGAAAAGATTATCUUCU-3’;
(59) 5’-UUUGAAATTCAGAAGAUUUG-3’;
(60) 5’-AAGCAGTCTCCATGTCCCAG-3’;
(61) 5’-AGGAUTAAAACAGATUAAUA-3’;
(62) 5’-AGAUUATCTTCTTTTAAUUU-3’;
(63) 5’-UCCCAACTCTTCTAACUCGU-3’;
(64) 5’-UAAAATAAGGGGAATAGGGG-3’;
(65) 5’-AGUGGCACATACCACACCCU-3’;
(66) 5’-AAGAUTATCTTCTTTUAAUU-3’;
(67) 5’-AGAAAGAAGCAAAGAUUCAA-3’;
(68) 5’-UCCCATCCCTTCTGCUGCCA-3’;
(69) 5’-ACCCUTCTCTCTGGTCCCAU-3’;
(70) 5’-AAUAUCTGCTGCCCACCUUC-3’;
(71) 5’-UCUCUCTGGTCCCATCCCUU-3’;
(72) 5’-AGGCCTCCAGTGTCTUCUCC-3’;
(73) 5’-CAAGCCCCAGCGTTCCUCCG-3’;
(74) 5’-AAAUGTCCTGGCCCTCACUG-3’;
(75) 5’-AAUUUAAAGCATGAAUAUUA-3’;
(76) 5’-AAAAGATTATCTTCTUUUAA-3’;
(77) 5’-AUAUCTGCTGCCCACCUUCU-3’;
(78) 5’-CAGUCTCCATGTCCCAGGCC-3’;
(79) 5’-AAAGATTATCTTCTTUUAAU-3’;
(80) 5’-CCCUUCTCTCTGGTCCCAUC-3’;
(81) 5’-AUGGCCTTTCCGTGCCAAGG-3’;
(82) 5’-GCAUUCCGTGCGGAAGCCUU-3’;
(83) 5’-GGCCGAACTTTCCCGCCUUA-3’;

(84) 5’-GGUCUTGGCTTCGTGGAGCA-3’;
(85) 5’-GGAGCTTCGAGGCCCCAGGC-3’;
(86) 5’-GGUGGTCCACAACCCCUUUC-3’;
(87) 5’-UUCUGGGGACTTCCAGUUUA-3’;
(88) 5’-UGAUUCCAAAGCCAGGGUUA-3’;
(89) 5’-GGGUATCGAAAGAGTCUGGA-3’;
(90) 5’-CUUGCACGTGGCTTCGUCUC-3’;
(91) 5’-GUGUCCTTGCACGTGGCUUC-3’;
(92) 5’-GUAAAAAGCTTTTGAAGUGA-3’;
(93) 5’-AUGCCATCCACTTGAUAGGC-3’;
(94) 5’-UGAAGTAAAAATCAAUAGCG-3’;
(95) 5’-AAGGCCCTTCGCACTUCUUA-3’;
(96) 5’-GUACUCGTCGGCATCCACCA-3’;
(97) 5’-GUCCUTGCACGTGGCUUCGU-3’;
(98) 5’-GCCCATCCATGAGGTCCUGG-3’;
(99) 5’-GUAAAAGGAGAAAACUAUCU-3’;
(100) 5’-UUGAAGTGAAGTAAAAGGAG-3’;
(101) 5’-GUUACTCGTGCCTTGGCAAA-3’;
(102) 5’-GUCCAAGATCAGCAGUCUCA-3’;
(103) 5’-UUCAATGGGAGAATAAAGCA-3’;
(104) 5’-GCAAGGCCCTTCGCACUUCU-3’;
(105) 5’-GGGUCCACCACTAGCCAGUA-3’;
(106) 5’-GUAGAGAAATTATTTUAGGA-3’;
(107) 5’-AUCCACCACGTCGTCCAUGU-3’;
(108) 5’-GGCAUCCACCACGTCGUCCA-3’;
(109) 5’-UUACUTTAAAAGCAAAAGGA-3’;
(110) 5’-UUUGAAGTGAAGTAAAAGGA-3’;
(111) 5’-GAAGUGAAGTAAAAGGAGAA-3’;
(112) 5’-GGCCATCTCTGCTTCUUGGU-3’;
(113) 5’-UGGGCTGGAATCCGAGUUAU-3’;
(114) 5’-GGAGATTTCAGAGCAGCUUC-3’;

(115) 5’-UUUACGGTTTTCAGAAUAUC-3’;
(116) 5’-GCGUGTCTGGAAGCTUCCUU-3’;
(117) 5’-GCUUATTTTAAGCATAUUAA-3’;
(118) 5’-UUAUUTTAAGCATATUAAAA-3’;
(119) 5’-UUCUGCAGCTTCCTTGUCCU-3’;
(120) 5’-AUUACTTTAAAAGCAAAAGG-3’;
(121) 5’-AUUUUAAGCATATTAAAAAG-3’;
(122) 5’-UGUGGCTTGTCCTCAGACAU-3’;
(123) 5’-AAAAGGAGAAAACTAUCUUC-3’;
(124) 5’-GGGUCCATACCCAAGGCAUC-3’;
(125) 5’-ACAGUGTTGAGATACUCGGG-3’;
(126) 5’-GGAUCTGCATGCCCTCAUCU-3’;
(127) 5’-AGUAAAAAGCTTTTGAAGUG-3’;
(128) 5’-GUCGUGGCAAATAGTCCUAG-3’;
(129) 5’-GGAGATCAGATGAGAGGAGC-3’;
(130) 5’-GUGGUTAAGTACATGAGCUC-3’;
(131) 5’-GGACACTTAGCTGTTCCUCG-3’;
(132) 5’-GUCUCTACTGTTACCUCUGA-3’;
(133) 5’-GAGUUCTTCGTAGGCUUCUG-3’;
(134) 5’-AAAGUCAAAAAGAAAAACUG-3’;
(135) 5’-AAAAGTGGGAAATAAAGGUU-3’;
(136) 5’-AGUUUATAGATTTCAAGUAG-3’;
(137) 5’-AAAAAGTGGGAAATAAAGGU-3’;
(138) 5’-UUUAUATTACAAAGCUACUU-3’;
(139) 5’-UGCUATTCATATTTTUAUUU-3’;
(140) 5’-GGUAU-3’;
(141) 5’-[G/A/C][G/A][G/A/C][T/A/C]TC-3’;
(142) 5’-[G/A/C]G[G/A/C][T/A/C]TC-3’;
(143) 5’-GGCTTC-3’;
(144) 5’-GGCATC-3’;
(145) 5’-AGCTTC-3’;

(146) 5’-GGAATC-3’;
(147) 5’-CACATC-3’;
(148) 5’-GGCCTC-3’;
(149) 5’-CACTTC-3’;
(150) 5’-AAGATC-3’;
(151) 5’-TGTCCTTGCACGTGGCTTCG-3’;
(152) 5’-TTTGCACACTTCGTACCCAA-3’;
(153) 5’-GTCCACATCCTGTGGCTCGT-3’;
(154) 5’-TGTGATGGCCTCCCATCTCC-3’;
(155) 5’-GGTTTTGGCTGGGATCAAGT-3’;
(156) 5’-GGTGTCCTTGCACGTGGCTT-3’;
(157) 5’-GGTCCATACCCAAGGCATCC-3’;
(158) 5’-GTGTCTTCATCGGCCCTGCC-3’;
(159) 5’-GTCTTGGCTTCGTGGAGCAG-3’;
(160) 5’-GCTGACAAAGATTCACTGGT-3’;
(161) 5’-GAAAGGTTATGCAAGG-3’;
(162) 5’-GACTATACGCGCAATA-3’;
(163) 5’-TGTGATGGCCTCCCAT-3’;
(164) 5’-TCCAACACTTCGTGGG-3’;
(165) 5’-GTGTCTGGAAGCTTCC-3’;
(166) 5’-CTTGAAGCATCGTATC-3’;
(167) 5’-TCGTAGTTGCTTCCTA-3’;
(168) 5’-CGCTTTTCTGTCTGGT-3’;
(169) 5’-GGCTGGAATCCGAGTT-3’;
(170) 5’-GATAGCACCTTCAGCA-3’;
(171) 5’-AGGACTCCAGATGTTT-3’;
(172) 5’-GTGATCTTGACATGCT-3’;
(173) 5’-AGATTTCAGAGCAGCT-3’;
(174) 5’-GGTTACGGCTCAGTAT-3’;
(175) 5’-GTTCAGTCCTGTCCAT-3’;
(176) 5’-AGGTCTTGGCTTCGTG-3’;

(177) 5’-CTGCAGCTTCCTTGTC-3’;
(178) 5’-GTCCTTGCACGTGGCT-3’;
(179) 5’-GTCTCTGGAGCTTCCT-3’;
(180) 5’-GGTCTTGGCTTCGTGG-3’;
(181) 5’-GGUA-3’;
(182) 5’-GUAU-3’;
(183) 5’-GGU-3’;
(184) 5’-GUA-3’;
(185) 5’-GUC-3’;
(186) 5’-GUG-3’;
(187) 5’-GUU-3’;
(188) 5’-GUA-3’;
(189) 5’-GGC-3’;
(190) 5’-AUC-3’;
(191) 5’-GAA-3’;
(192) 5’-GAG-3’;
(193) 5’-GGA-3’;
(194) 5’-GAC-3’;
(195) 5’-GAU-3’;
(196) 5’-AUG-3’;
(197) 5’-GCG-3’;
(198) 5’-UUC-3’;
(199) 5’-GCC-3’;
(200) 5’-GGG-3’;
(201) 5’-AUU-3’;
(202) 5’-GCA-3’;
(203) 5’-AGC-3’;
(204) 5’-AAC-3’;
(205) 5’-CCA-3’;
(206) 5’-UGC-3’;
(207) 5’-CAA-3’;
(208) 5’-CGG-3’;
(209) 5’-ACC-3’;
(210) 5’-AGA-3’;
(211) 5’-TTT-3’;

(212) 5’-TCT-3’and

(213) a variant of the motifs or sequences of (1) to (212) having at least about 75% sequence identity thereto;

wherein the U may be a T and/or the T may be a U and wherein the oligonucleotide inhibits TLR7 activity when administered to a subject.

83. An oligonucleotide comprising a motif or sequence selected from the group consisting of:

5’-CUUCG-3’;
5’-CUUCGTG-3’;
5’-CUUCGTGGG-3’;
5’-UCG-3’;
5’-UCA-3’;
5’-CGG-3’;
5’-UGG-3’;
5’-CGC-3’;
5’-AGG-3’;
5’-GGA-3’;
5’-GGC-3’;
5’-AGA-3’;
5’-CGA-3’;
5’-UAG-3’;
5’-UCU-3’;
5’-AGC-3’;
5’-GGU-3’;
5’-UGA-3’;
5’-AGU-3’;
5’-ACG-3’;
5’-CGU-3’;
5’-UCC-3’;
5’-GCG-3’;
5’-GGG-3’;
5’-UGU-3’;
5’-UCA-3’;
5’-CUG-3’;
5’-UUG-3’;

5’-UUA-3’;
5’-UGC-3’;
and
a variant of the motifs or sequences thereof having at least about 75% sequence identity thereto;
wherein the U may be a T and/or the T may be a U and wherein the oligonucleotide potentiates TLR8 activity when administered to a subject.

84. An oligonucleotide comprising a motif or sequence selected from the group consisting of:
5’-GAG-3’;
5’-GAC-3’;
5’-GAU-3’;
5’-GAA-3’;
5’-GUC-3’;
5’-GUU-3’;
5’-GUA-3’;
5’-GUG-3’;
5’-AUA-3’;
5’-AUG-3’;
5’-CUU-3’;
5’-AAG-3’;
5’-AUC-3’;
5’-CCC-3’;
5-GCU-3’;
5’-CCU-3’;
5’-CUA-3’;
5’-CUC-3’;
5’-AAC-3’;
and
wherein the U may be a T and/or the T may be a U and wherein the oligonucleotide inhibits TLR8 activity when administered to a subject.

85. An oligonucleotide comprising a motif or sequence selected from the group consisting of:
5’-TAC-3’;

5’-CGC-3’;
5’-GCA-3’;
5’-UGA-3’;
5’-CAG-3’;
5’-UGG-3’;
5’-UCA-3’;
5’-TGA-3’;
5’-CGT-3’;
5’-GAC-3’;
5’-CCA-3’;
5’-TAG-3’;
5’-TGG-3’;
5’-TCA-3’;
5’-TGC-3’;
5’-CAC-3’;
5’-CGG-3’;
5’-CCC-3’;
5’-ACT-3’;
5’-GTA-3’;
5’-GGA-3’;
5’-AAG-3’;
5’-ATA-3’;
5’-GUC-3’;
5’-UCC-3’;
5’-AUC-3’;
5’-CCG-3’;
5’-CAA-3’;
5’-GAU-3’;
5’-CGA-3’;
and

wherein the U may be a T and/or the T may be a U and wherein the oligonucleotide inhibits TLR3 activity when administered to a subject.

86. A composition comprising an oligonucleotide according to any one of claims 76 to 85.

87. The composition of claim 86, which further comprises a pharmaceutically acceptable carrier.

88. A composition consisting essentially of an oligonucleotide according to any one of claims 76 to 85 and a pharmaceutically acceptable carrier.

89. The composition of any one of claims 86 to 88, wherein at least about 10%, at least about 15%, at least about 20%, at least about 25%, at least about 30%, at least about 35%, at least about 40%, at least about 45%, at least about 50%, at least about 55%, at least about 60%, at least about 65%, at least about 70%, at least about 75%, at least about 80%, at least about 85%, at least about 90%, at least about 95% or at least about 100% of the oligonucleotide content of the composition is an oligonucleotide according to any one of claims 76 to 85.

90. The composition of any one of claims 86 to 88, wherein at least 10%, at least 15%, at least 20%, at least 25%, at least 30%, at least 35%, at least 40%, at least 45%, at least 50%, at least 55%, at least 60%, at least 65%, at least 70%, at least 75%, at least 80%, at least 85%, at least 90%, at least 95% or at least 100% of the oligonucleotide content of the composition is an oligonucleotide according to any one of claims 76 to 85.

91. The composition of any one of claims 86 to 91, wherein at least about 10%, at least about 15%, at least about 20%, at least about 25%, at least about 30%, at least about 35%, at least about 40%, at least about 45%, at least about 50%, at least about 55%, at least about 60%, at least about 65%, at least about 70%, at least about 75%, at least about 80%, at least about 85%, at least about 90%, at least about 95% or at least about 100% of the active pharmaceutical ingrediment in the composition is an oligonucleotide according to any one of claims 76 to 85.

92. A method of reducing expression of a target gene in a cell, the method comprising contacting the cell with an oligonucleotide according to any one of claims 76 to 85 or composition according to any one of claims 86 to 92.

93. A method of treating or preventing a disease, disorder or condition in a subject, the method comprising administering to the subject a therapeutically effective amount of an oligonucleotide according to any one of claims 76 to 85 or composition according to any one of claims 86 to 92 to thereby treat or prevent the disease, disorder or condition in the subject.

94. Use of an oligonucleotide according to any one of claims 76 to 85 or composition according to any one of claims 86 to 92 in the manufacture of a medicament for treating or preventing a disease, disorder or condition in a subject.

95. An oligonucleotide according to any one of claims 76 to 85 or composition according to any one of claims 86 to 92 for use in treating or preventing a disease, disorder or condition in a subject.

96. The method of claim 93, the use of claim 94 or the oligonucleotide of claim 95, wherein the oligonucleotide reduces the expression of a target gene involved in the disease, disorder or condition.

97. The method, use or oligonucleotide of any one of claims 93 to 96, wherein the disease, disorder or condition demonstrates increased, excessive or abnormal cGAS expression, activity and/or signalling.

98. The method, use or oligonucleotide of claim 97, wherein the disease, disorder or condition is selected from the group consisting of Huntington's disease, Parkinson's diseases, motor-neurone disease (MND), amyotrophic lateral sclerosis (ALS), prion disease, frontotemporal dementia, Traumatic brain injury, Alzheimer's disease, Acute pancreatitis, Silica- induced fibrosis, Age dependent macular degeneration, Aicardi–Goutières syndrome, myocardial infarction, heart failure, Polyarthritis/foetal and neonatal anaemia, Systemic lupus erythematosus, Acute Kidney Injury, Alcohol-related liver disease, Non-Alcohol-fatty liver disease, silica driven lung inflammation, chronic

obstructive pulmonary disease, brain injury after ischemic stroke, sepsis, Non-alcoholic steatohepatitis (NASH), cancer, sickle cell disease, Inflammatory bowel disease, type 2 diabetes mellitus, over-nutrition-induced obesity, COVID-19, hematopoietic disorders, aging-associated inflammation, Cutibacterium acnes Infection, Hepatitis B, posterior-segment eye diseases, arthritis, rheumatoid arthritis, emphysema, colorectal cancer, skin cancer, metastases, and breast cancer.

99. The method, use or oligonucleotide of any one of claims 93 to 96, wherein the disease, disorder or condition demonstrates increased, excessive or abnormal TLR9 expression, activity and/or signalling.

100. The method, use or oligonucleotide of claim 99, wherein the disease, disorder or condition is selected from the group consisting of psoriasis, rheumatoid arthritis, alopecia universalis, acute disseminated encephalomyelitis, Addison's disease, allergy, ankylosing spondylitis, antiphospholipid antibody syndrome, arteriosclerosis, atherosclerosis, autoimmune haemolytic anaemia, autoimmune hepatitis, Bullous pemphigoid, Chagas' disease, chronic obstructive pulmonary disease, coeliac disease, cutaneous lupus erythematosus (CLE), dermatomyositis, diabetes, dilated cardiomyopathy (DC), endometriosis, Goodpasture's syndrome, Graves' disease, Guillain-Barre syndrome, Hashimoto's disease, hidradenitis suppurativa, idiopathic thrombocytopenic purpura, inflammatory bowel disease, interstitial cystitis, morphea, multiple sclerosis (MS), myasthenia gravis, myocarditis, narcolepsy, neuromyotonia, pemphigus, pernicious anaemia, polymyositis, primary biliary cirrhosis, rheumatoid arthritis (RA), schizophrenia, Sjogren's syndrome, systemic lupus erythematosus (SLE), systemic sclerosis, temporal arteritis, vasculitis, vitiligo, vulvodynia, Wegener's granulomatosis, traumatic pain, neuropathic pain and acetaminophen toxicity, breast cancer, cervical squamous cell carcinoma, gastric carcinoma, glioma, hepatocellular carcinoma, lung cancer, melanoma, prostate cancer, recurrent glioblastoma, recurrent non-Hodgkin lymphoma and colorectal cancer.

101. The method, use or oligonucleotide of any one of claims 93 to 96, wherein the disease, disorder or condition demonstrates increased, excessive or abnormal TLR7 expression, activity and/or signalling.

102. The method, use or oligonucleotide of any one of claims 93 to 96, wherein the disease, disorder or condition of the three aforementioned aspects demonstrates increased, excessive or abnormal TLR8 expression, activity and/or signalling.

103. The method, use or oligonucleotide of any one of claims 93 to 96, wherein the disease, disorder or condition of the three aforementioned aspects demonstrates increased, excessive or abnormal TLR3 expression, activity and/or signalling.

104. The method, use or oligonucleotide of any one of claims 93 to 97, wherein the disease, disorder or condition is a senescence-associated disease, disorder or condition, such as aging and/or an aging-related disease, disorder or condition.

105. The method, use or oligonucleotide of any one of claims 93 to 97, 99, or 101 to 103, wherein the disease, disorder or condition is an inflammatory disease, disorder or condition associated with administration of a therapeutic oligonucleotide to the subject.

106. The method, use or oligonucleotide of claim 105, wherein the inflammatory disease, disorder or condition comprises hepatic inflammation.

107. A method of inhibiting cGAS in a subject, including the step of administering to the subject an effective amount of an oligonucleotide according to any one of claims 76 to 78, or a composition according to any one of claims 86 to 91.

108. A method of inhibiting cGAS in a cell, including the step of contacting the cell with an effective amount of an oligonucleotide of any one of claims 76 to 78 or a composition of any one of claims 86 to 91.

109. The method of claim 108, wherein the oligonucleotide inhibits or prevents senescence in the cell.

110. The method of claim 108 or 109, wherein the cell is an immune cell.

111. A method of inhibiting TLR9 in a subject, including the step of administering to the subject an effective amount of an oligonucleotide according to any one of claims 76 or 79 to 81, or a composition according to any one of claims 86 to 91.

112. A method of inhibiting TLR9 in a cell, including the step of contacting the cell with an effective amount of an oligonucleotide according to any one of claims 76 or 79 to 81, or a composition according to any one of claims 86 to 91.

113. A method of inhibiting TLR7 in a subject, including the step of administering to the subject an effective amount of an oligonucleotide according to any one of claims 76 or 82, or a composition according to any one of claims 86 to 91.

114. A method of inhibiting TLR7 in a cell, including the step of contacting the cell with an effective amount of an oligonucleotide according to any one of claims 76 or 82, or a composition according to any one of claims 86 to 91.

115. The method of claim 113 or claim 114, wherein the oligonucleotide at least partly inhibits TLR7 activation in the cell or the subject in response to an RNA molecule.

116. A method of inhibiting TLR7 activation by an RNA molecule in a cell, said method including the step of contacting the cell with an effective amount of an oligonucleotide according to any one of claims 76 or 82, or a composition according to any one of claims 86 to 91.

117. A method of inhibiting TLR7 activation by an RNA molecule in a subject, said method including the step of administering to the subject an effective amount of an

oligonucleotide according to any one of claims 76 or 82, or a composition according to any one of claims 86 to 91.

118. A method of inhibiting TLR8 in a subject, including the step of administering to the subject an effective amount of an oligonucleotide according to claim 76 or 84, or a composition according to any one of claims 86 to 91.

119. A method of inhibiting TLR8 in a cell, including the step of contacting the cell with an effective amount of an oligonucleotide according to claim 76 or 84, or a composition according to any one of claims 86 to 91.

120. A method of preventing or inhibiting TLR8 activation by an RNA molecule in a cell, said method including the step of contacting the cell with an effective amount of an oligonucleotide according to claim 76 or 84, or a composition according to any one of claims 86 to 91.

121. A method of preventing inhibiting TLR8 activation by an RNA molecule in a subject, said method including the step of administering to the subject an effective amount of an oligonucleotide according to claim 76 or 84, or a composition according to any one of claims 86 to 91.

122. A method of inhibiting TLR3 in a subject, including the step of administering to the subject an effective amount of an oligonucleotide according to claim 76 or 85, or a composition according to any one of claims 86 to 91.

123. A method of inhibiting TLR3 in a cell, including the step of contacting the cell with an effective amount of an oligonucleotide according to claim 76 or 85, or a composition according to any one of claims 86 to 91.

124. A method of preventing or inhibiting TLR3 activation by an RNA molecule in a cell, said method including the step of contacting the cell with an effective amount of an

oligonucleotide according to claim 76 or 85, or a composition according to any one of claims 86 to 91.

125. A method of preventing inhibiting TLR3 activation by an RNA molecule in a subject, said method including the step of administering to the subject an effective amount of an oligonucleotide according to claim 76 or 85, or a composition according to any one of claims 86 to 91.

126. A method of increasing the activity of, or potentiating, TLR8 in a subject, including the step of administering to the subject an effective amount of an oligonucleotide according to claim 76 or 83, or a composition according to any one of claims 86 to 91.

127. A method of increasing the activity of, or potentiating, TLR8 in a cell, including the step of contacting the cell with an effective amount of an oligonucleotide according to claim 76 or 83, or a composition according to any one of claims 86 to 91.

128. A method of increasing or potentiating TLR8 activation by an RNA molecule in a cell, said method including the step of contacting the cell with an effective amount of oligonucleotide according to claim 76 or 83, or a composition according to any one of claims 86 to 91.

129. A method of increasing or potentiating TLR8 activation by an RNA molecule in a subject, said method including the step of administering to the subject an effective amount of an oligonucleotide according to claim 76 or 83, or a composition according to any one of claims 86 to 91..

130. The method of any one of claims 116, 117, 120, 121, 124, 125, 128 or 129, wherein the RNA molecule is an mRNA molecule.

131. The method of claim 130, wherein the mRNA molecule is a component of or included within an immunogenic composition.

132. An immunogenic composition comprising an RNA molecule and an oligonucleotide according to any one of claims 76 to 85.

133. The method of claim 131 or the immunogenic composition of claim 132, wherein the immunogenic composition is an mRNA vaccine composition.

134. The method of any one of claims 107 to 110, 113 to 131 or 133 or the immunogenic composition of claim 132 or claim 133, wherein the oligonucleotide comprises, consists essentially of or consists of a sequence of 5'-GGUAUA-3', 5'-GGUAU-3', 5'-GGUA-3', 5'-GUAU-3', 5'-GGU-3' or 5'-GUA-3', wherein the U may be a T.

135. The steps, features, integers, compositions and/or compounds disclosed herein or indicated in the specification of this application individually or collectively, and any and all combinations of two or more of said steps or features.