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(54) **METHOD TO PREDICT RESPONSE TO PHARMACOLOGICAL CHAPERONE TREATMENT OF DISEASES**

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See application file for complete search history.

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(57) **ABSTRACT**

The present invention provides methods to determine whether a patient with a lysosomal storage disorder will benefit from treatment with a specific pharmacological chaperone. The present invention exemplifies an in vitro method for determining α-galactosidase A responsiveness to a pharmacological chaperone such as 1-deoxygalactonojirimycin in a cell line expressing a mutant from of α-galactosidase A. The invention also provides a method for diagnosing Fabry disease in patients suspected of having Fabry disease.

44 Claims, 37 Drawing Sheets

Specification includes a Sequence Listing.

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Fig. 1A

Fabry Mutations Generated by Site-Directed Mutagenesis

Missense	L45R	M72R	R112H	G147R	G183S	R227P	D264V	A285P	Q312R	R356G	P409S	V390fsX8
M1I	H46L	M72V	R112S	S148N	G183V	R227Q	D264Y	W287C	D313G	R356W	P409T	401ins1aa/T 401S
M1K	H46R	A73V	F113L	S148R	Y184C	A230T	P265L	W287G	D313Y	Q357X	T410A	del20-24aa
M1L	H46Y	M76R	F113S	Y152C	M187T	D231G	P265R	A288D	V316E	E358A	T410I	del13-8aa
M1R	W47G	M76T	R117S	D155H	M187V	D231N	D266E	A288P	I317N	E358G	T410K	del153aa
M1T	W47L	W81C	R118C	A156T	L191P	D231V	D266H	I289F	I317T	E358K	T410P	del205-7aa
M1V	E48D	W81S	L120P	A156V	L191Q	D234E	D266N	I289S	N320I	I359T	G411D	del254aa
A13P	E48K	G85D	L120S	A156Y	T194I	D234Y	D266V	M290I	N320K	G360C	L414S	del356aa
L14P	R49C	G85M	A121P	W162C	V199M	S235C	D266Y	A291T	N320Y	G360D	L416P	ins247-8aa
L16H	R49G	Y86C	A121T	W162G	S201F	S235F	M267I	A292P	Q321E	G360S	L33Y	
L16P	R49L	Y86D	V124D	W162R	S201Y	W236C	M267R	A292T	Q321L	G361R	L166G	
F16S	R49P	Y86D	H125P	G163V	C202W	W236L	L268S	P293A	Q321R	P362L	H46S	
L19P	R49S	L89P	S126G	D165H	C202Y	W236R	V269A	P293H	G325D	R363C	I124F	
A20P	F50C	L89R	G126E	D165V	P205L	S238N	V269M	P293S	G325S	R363H		
A31V	M51I	C90R	L129P	D165Y	P205R	I239T	I270T	P293T	Q327E	R363P		
L32P	M51K	I91T	L131P	D166Y	P205S	I242F	G271C	F295C	Q327K	L372P	Complex	
D33Y	C52G	D92G	G132E	L166V	P205T	I242N	G271S	M296I	G328A	L372R	D55V/Q57L	
N34K	C52R	D92H	G132R	L167P	L206P	L243F	G271V	M296V	G328E	G373D	L120P/A121T	
N34S	C52S	D92N	Y134H	K168N	Y207C	L243W	N272K	S297C	G328R	G373R		
G35R	C52Y	D92Y	Y134S	K168R	Y207H	D244N	N272S	S297F	G328V	G373S	Small Ins/Del	
L36F	L54P	D93G	A135V	F169S	Y207S	D244H	F273L	N298H	E338K	A377D	19del5aa	
L36S	D55V	D93N	D136H	D170H	N215D	S247C	L275F	N298K	V339E	C378R	86del6aa	
A37V	C56F	D93V	D136Y	D170V	N215S	S247P	S276G	N298S	W340R	C378Y	113del8aa	
P40L	C56G	C94S	G138E	G171C	Y216C	Q250P	S276N	D299G	E341D	C382W	120del2aa/L120H	
P40S	C56Y	C94Y	G138R	G171D	Y216D	Q253T	Q279E	L300F	E341K	C382Y	152ins1aa/Y152D	
T41I	Q57L	W95L	N139T	G171R	I219N	A257P	Q279H	L300H	R342L	I384N	153del1aa	
M42L	E59K	W95S	T141I	C172F	C223G	G258R	Q279K	L300P	R342Q	T385P	205del3aa	
M42R	P60L	A97P	C142R	C172G	C223R	G258V	Q279R	R301G	L344P	Q386P	205del7aa	
M42T	C63Y	A97V	C142W	C172R	C223Y	P259L	Q280H	R301P	S345P	P389R	254del1aa	
M42V	S65T	R100K	C142Y	C172S	N224D	P259R	Q280K	R301Q	A348P	F396Y	281del1aa/V281A	
G43D	E66G	R100T	A143P	C172W	N224S	G260A	T282A	S303N	W349R	E398K	368del1aa	
G43R	E66K	S103Q	A143T	C172Y	H225D	G261D	T282N	K308N	A350P	L403S	382del1aa	
G43S	E66Q	L106R	G144V	C174G	H225R	W262C	Q283P	A309P	A352D	I407K	403del1aa	
G43V	L68F	Q107L	P146S	G183A	W226C	N263S	M284T	L310F	I354K	I407R	247ins3aa	
W44C	M72I	R112C	G147E	G183D	W226R	D264A	A285D	Q312H	N355K	P409A	247ins8aa	

Fig. 1B

Fabry Mutations Generated by Site-Directed Mutagenesis

Missense	R49L	D93V	P146S	C202Y	A257P	M284T	N320Y	C378Y
M1T	R49P	C94Y	G147R	C202W	G258R	A285P	Q321E	C378R
M1R	R49S	C94S	S148N	P205R	P259R	A285D	Q321R	C382Y
M1I	F50C	W95S	S148R	P205L	P259L	W287G	G325D	C382W
L14P	M51K	A97V	Y152C	P205T	G260A	W287C	Q327K	I384N
L16P	M51I	A97P	D155H	Y207C	G261D	A288D	Q327E	T385P
L16H	C52G	R100K	A156V	Y207S	W262C	A288P	G328R	Q386P
L19P	C52R	R100T	A156T	N215S	N263S	I289F	G328A	P389R
A20P	C52S	E103Q	W162R	Y216D	D264V	M290I	G328E	F396Y
A31V	C56F	R112H	W162C	I219N	D264Y	A292P	G328V	E398K
L32P	C56G	R112S	G163V	C223R	P265R	P293A	E338K	L403S
D33Y	C56Y	R112C	D165V	C223G	P265L	P293S	V339E	I407K
N34K	E59K	F113L	L166G	C223Y	D266N	P293T	W340R	P409T
N34S	C63Y	F113S	L166V	N224S	D266H	F295C	E341D	P409A
G35R	S65T	R118C	L167P	N224D	D266V	M296I	E341K	P409S
A37V	E66G	L120P	K168N	H225R	D266E	M296V	R342Q	T410K
P40L	E66K	L120S	K168R	W226R	M267R	S297C	L344P	T410A
P40S	E66Q	A121P	F169S	W226C	M267I	S297F	S346P	G411D
T41I	L68F	A121T	D170V	R227Q	L268S	N298S	A348P	L414S
M42T	M72R	V124D	D170H	A230T	V269A	N298K	A350P	L415P
M42L	M72I	G128E	G171D	D231N	V269M	N298H	A352D	
M42V	M72V	L129P	G171R	D231G	I270T	D299G	I354K	
G43D	A73V	L131P	C172Y	D234E	G271C	L300F	N355K	
G43S	M76R	G132E	C172F	D234Y	G271S	L300H	R356W	
G43V	W81C	G132R	C172W	S235C	G271V	L300P	E358G	
G43R	W81S	Y134S	C172R	W236R	N272K	R301G	E358K	

Fig. 1B (Cont.)

W44C	*G85D*	A135V	C172G	*W236L*	N272S	R301Q	E358A	
L45R	*Y86C*	D136H	G183D	*W236C*	S276N	R301P	*I359T*	
H46R	Y88D	G138E	G183S	*I239T*	S276G	I303N	*G360S*	Small Ins/Del
H46S	L89P	*G138R*	M187T	I242F	Q279R	L310F	G361R	*del20-24aa*
H46L	L89R	*T141I*	M187V	I242N	Q279H	Q312H	P362L	del13-8aa
H46Y	I91T	C142R	L191Q	L243F	Q279E	D313Y	R363H	*del153aa*
W47G	D92N	*C142W*	L191P	D244N	Q279K	V316E	R363C	del205-7aa
W47L	D92H	*C142Y*	T194I	D244H	Q280H	I317N	G373D	*del254aa*
E48D	D92Y	A143T	V199M	*S247P*	Q280K	I317T	*G373R*	*del358aa*
E48K	*D93G*	*A143P*	S201F	*S247C*	T282N	N320I	G373S	Ins247-8aa
R49G	*D93N*	G144V	S201Y	*Q250P*	Q283P	N320K	*A377D*	

Fig. 1C

Fabry Mutations Generated by Site-Directed Mutagenesis

Missense	R49L	D93V	P146S	C202Y	A257P	M284T	N320Y	C378Y
M1T	R49P	C94Y	G147R	C202W	G258R	A285P	Q321E	C378R
M1R	R49S	C94S	S148N	P205R	P259R	A285D	Q321R	C382Y
M1I	F50C	W95S	S148R	P205L	P259L	W287G	G325D	C382W
L14P	M51K	A97V	Y152C	P205T	G260A	W287C	Q327K	I384N
L16P	M51I	A97P	D155H	Y207C	G261D	A288D	Q327E	T385P
L16H	C62G	R100K	A156V	Y207S	W262C	A288P	G328R	Q386P
L19P	C52R	R100T	A156T	N215S	N263S	I289F	G328A	P389R
A20P	C52S	E103Q	W162R	Y216D	D264V	M290I	G328E	F396Y
A31V	C56F	R112H	W162C	I219N	D264Y	A292P	G328V	E398K
L32P	C56G	R112S	G163V	C223R	P265R	P293A	E338K	L403S
L33Y	C56Y	R112C	D165V	C223G	P265L	P293S	V339E	I407K
N34K	E59K	F113L	L166G	C223Y	D266N	P293T	W340R	P409T
N34S	C63Y	F113S	L166V	N224S	D266H	F295C	E341D	P409A
G35R	S65T	R118C	L167P	N224D	D266V	M296I	E341K	P409S
A37V	E66G	L120P	K168N	H225R	D266E	M296V	R342Q	T410K
P40L	E66K	L120S	K168R	W226R	M267R	S297C	L344P	T410A
P40S	E66Q	A121P	F169S	W226C	M267I	S297F	S345P	G411D
T41I	L68F	A121T	D170V	R227Q	L268S	N298S	A348P	L414S
M42T	M72R	V124D	D170H	A230T	V269A	N298K	A350P	L415P
M42L	M72I	G128E	G171D	D231N	V269M	N298H	A352D	
M42V	M72V	L129P	G171R	D231G	I270T	D299G	I354K	
G43D	A73V	L131P	C172Y	D234E	G271C	L300F	N355K	
G43S	M76R	G132E	C172F	D234Y	G271S	L300H	R356W	
G43V	W81C	G132R	C172W	S235C	G271V	L300P	E358G	
G43R	W81S	Y134S	C172R	W236R	N272K	R301G	E358K	

Fig. 1C (Cont.)

W44C	*G85D*	*A135V*	**C172G**	*W236L*	*N272S*	R301Q	*E358A*	
L45R	*Y86C*	*D136H*	G183D	*W236C*	S276N	R301P	*I359T*	
H46R	*Y86D*	**G138E**	*G183S*	*I239T*	S276G	I303N	*G360S*	**Small Ins/Del**
H46S	*L89P*	*G138R*	*M187T*	*I124F*	Q279R	L310F	*G361R*	*del20-24aa*
H46L	**L89R**	*T141I*	*M187V*	I242N	Q279H	Q312H	*P362L*	*del13-8aa*
H46Y	I91T	**C142R**	*L191Q*	L243F	Q279E	**D313Y**	R363H	*del153aa*
W47G	**D92N**	*C142W*	*L191P*	D244N	**Q279K**	V316E	R363C	*del205-7aa*
W47L	*D92H*	*C142Y*	T194I	D244H	Q280H	*I317N*	G373D	*del254aa*
E48D	**D92Y**	A143T	*V199M*	*S247P*	Q280K	I317T	*G373R*	*del358aa*
E48K	*D93G*	*A143P*	S201F	*S247C*	*T282N*	N320I	G373S	*ins247-8aa*
R49G	*D93N*	G144V	S201Y	*Q250P*	*Q283P*	*N320K*	*A377D*	

Mutation	Relative Increase	EC_{50} (μM)
M1R	2.6±0.4	3±1
L14P	2.6±0.4	3±1
L16K	5±1	0.3±0.1
L16P	5±1	0.8±0.3
L19P	2.3±0.3	1.3±0.5
A20P	1.5±0.1	0.3±0.1
L32P	7±1	2.2±0.3
D33Y	3±1	5±1
N34K	19±2	100±30
G35R	5±2	7±2
L36F	10±1	13±1
A37V	1.6±0.1	33±9
P40L	3.8±0.2	39±18
P40S	3±1	3±1
T41I	1.3±0.1	0.3±0.1
M42L	1.5±0.1	7±2
M42R	5±1	12±5
M42T	18±1	42±16
M42V	14±2	120±20
L45R	17±4	40±5
W42L	5±1	11±3
E48D	7±2	160±37
E48K	6±1	4±2
R49G	3±1	4±1
R49L	11±2	60±20
R49P	3±1	3±1
R49S	4±1	5±2
M51I	1.5±0.1	3±1
M51K	2.9±0.3	2±0
C56R	4±1	53±23
L58F	10±2	8±2
D59V	15±2	3±1
C56S	10±1	28±8
C56G	7±1	400±100
C56Y	14±3	50±16
E59K	3±1	35±14
P63L	5±2	1.7±0.7
S65T	3±1	2.2±0.8
E66G	2±1	4±1
E66K	4±2	11±4
E66Q	2±1	5±2
L68F	11±2	100±30
M72R	7±1	700±250
M72V	2.2±0.2	0.8±0.1
A73V	1.4±0.1	0.9±0.3
M76R	3±1	8±2
N76T	8±1	11±3
W81C	19±1	70±20
W81S	4±1	25±12
G85D	7±1	12±2
G85M	2.3±0.2	2.6±0.8
Y86D	3.4±0.4	52±17
P1T	12±1	6±2
C94Y	2.1±0.4	0.8±0.4
W95S	4±1	300±50
A97P	8±1	43±14
A97V	3±1	0.8±0.2
R112C	15±2	300±80
R112H	5±1	2.5±0.5
R112S	8±2	90±36
F113C	2.3±0.2	2±1
D175S	3±1	2±1
R119C	1.4±0.1	5±2
L120P	6±2	20±9
A121T	3±1	0.3±0.1
A135V	14±2	350±120
D136H	5±1	23±6
A143T	1.3±0.1	4±1
G144V	21±6	38±14
G147R	2.4±0.4	4±2
S148N	18±3	1400±400
Y152C	4±1	26±11
A126T	12±1	50±10
A156V	19±2	44±9
A156Y	5±1	50±10
W162G	9±1	13±4
G163V	3.5±0.4	27±9
L166V	4.6±0.5	12±4
K168N	22±3	70±30
F169S	2.7±0.4	1±0
G171C	9±2	190±60
G171R	4±1	4±1
G172S	7±2	680±300
G183A	2.3±0.3	7±3
G183D	15±3	80±10
G183S	7±1	7±2
Y184C	16±1	74±1
M187T	6±2	23±6
M187V	5±1	16±1
L191P	3.0±0.3	7±2
L191Q	18±3	150±60
T194I	12±2	18±1
V199M	1.2±0.1	4±2
S201R	8±2	2±1
S201Y	6.3±0.3	15±3
P205L	9±1	260±50
P205R	4±1	70±30
P205S	5±2	4±1
P205T	8±2	2±0
Y207C	7±2	800±200
Y207S	3.2±0.4	67±6
N215D	1.2±0.1	9±4
N215S	3±0	4±1
Y216C	13±1	36±8
Y216D	16±1	350±150
H219N	13±1	167±87
H224D	12±3	190±40
H224S	2.0±0.1	0±2
H225R	27±2	900±100
A230T	4±1	27±12
D234E	14±3	340±50
S235C	4.0±0.1	120±40
W236L	9±2	900±150
S238N	2.8±0.4	1.6±0.3
I239T	1.7±0.1	3±1
I242N	12±1	9±1
L243P	8±1	10±2
L243W	37±2	21±4
D244N	4±2	4±1
D244H	3±1	1.2±0.4
S247C	2.0±0.3	8±1
S247P	16±3	350±120
Q250P	2.1±0.1	6±2
I253T	1.7±0.1	1.4±0.3
A257P	3.3±0.4	5±1
G258V	18±4	16±4
P259L	8±3	9±1
P259R	3.3±0.4	2±1
G260A	9±3	12±1
G261D	10±3	150±50
N263S	5±1	2.0±0.4
D264Y	13±3	18±4
P265I	2.7±0.2	1.1±0.1
P265R	13±1	97±27
M267I	1.6±0.1	6±2
L268S	1.5±0.1	0.7±0.3
V269A	13±2	32±9
V269M	4±1	2.0±0.6
I270T	11±2	10±0
Q271S	22±6	24±2
N272K	3±1	17±7
N272S	5±1	226±66
S276G	22±1	9±1
S276N	9±2	22±7
Q279E	5±1	23±6
Q279H	5±1	61±26
Q279R	4±2	12±6
Q280H	5±1	8±1
Q280K	1.7±0.1	1.1±0.3
T282A	15±5	24±3
M284T	20±5	28±8
W287C	20±4	1000±100
A288D	6±1	200±40
A288P	20±1	25±1
P289F	19±4	300±50
A292P	3±1	160±40
P293A	21±3	475±100
P293S	18±2	550±210
P293T	12±2	36±6
P295C	15±2	20±3
M296I	2.6±0.1	0.7±0.2
M296V	1.9±0.1	0.7±0.3
S297C	3±1	620±20
N298H	9.4±0.4	700±100
N298R	5±2	38±18
N298S	2.6±0.1	1.4±0.2
D299G	15±2	1500±140
L300R	8±1	3±1
L300P	12±1	8±2
R301G	1.8±0.2	2.5±0.4
R301P	42±4	120±14
R301Q	5.2±0.3	3.8±0.2
I303N	14±1	70±20
K308N	7±1	24±8
A309P	26±5	83±10
L310F	17±0	70±10
Q312H	12±2	15±2
Q312R	2±0	10±1
D313G	1.4±0.1	8±2
V316E	5±1	600±100
E317G	9±1	80±10
E317T	5±1	10±2
N320I	23±3	40±10
N320Y	18±2	300±80
Q321E	21±3	90±30
Q321L	12±1	18±3
Q321R	3±1	7±1
G325D	14±4	360±120
G325S	3±1	1.7±0.1
Q327E	2.4±0.2	11±2
G328A	19±5	14±2
E335K	8±0	18±4
V339E	2±0	7±2
W340R	10±2	100±40
E341D	3±0	17±4
R342Q	4±2	16±7
S345P	8±1	75±5
A348P	2±0	5±2
A352D	5±1	150±30
I356K	19±4	17±3
R358W	3±1	1.0±0.1
R358A	21±2	9±2
R358G	7±1	20±10
I358K	3±1	400±100
I359T	1.5±0.1	4±2
G360D	12±0	15±3
G360S	1.8±0.2	9±3
G361R	10±1	7±2
P362L	7±2	3±1
R363C	2.3±0.3	2±1
R363H	1.7±0.1	1.0±0.4
R363P	21±5	120±40
G373D	3.2±0.4	5±2
G373S	2.8±0.4	2±1
E388K	1.3±0.1	7±2
L403S	1.6±0.1	16±5
P409A	10±2	5±1
P409S	15±2	3±1
P409T	5±1	1.3±0.5
T410A	19±3	2±1
T410I	14±4	3.8±0.2
T410P	20±6	1200±580
G411D	15±0	5±2
L414S	8±1	19±3
234del3	1.8±0.1	3±1
247insS	21±1	400±180
D55V/Q57L	24±5	8±4
401ins/P401S	4±1	11±3

Fig. 2A: DGJ-Responsive Mutations described in Figure 1A: Potency and Response Magnitude

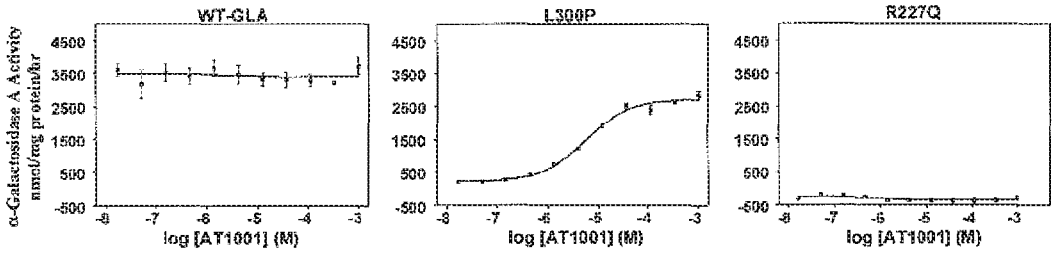
Mutation	Relative Increase (fold)	EC_{50}(μM)
L14P	3.0±0.4	2.6±0.8
A20P	1.5±0.1	0.3±0.1
L32P	7.0±1.0	2.2±0.3
D33Y	2.9±0.5	5.4±1.4
N34K	18±2	100±31
G35R	5.0±1.6	7.0±1.5
P40L	4.0±0.2	39±16
P40S	3.0±0.6	2.6±0.8
T41I	1.0±0.1	0.3±0.1
M42T	18±1	4.2±1.0
M42V	14±2	123±23
L45R	17±4	39±5
W47L	5.0±1.0	11±3
E48D	6.7±1.8	105±37
E48K	6.0±1.0	4.4±2.0
R49G	3.0±0.5	3.6±1.4
R49L	11±2	76±19
R49S	4.0±1.0	5.3±2.6
M51I	1.8±0.1	2.9±0.8
M51K	3.0±0.3	1.8±0.6
C52R	3.6±0.6	53±23
C56F	16±1	28±6
C56G	9.5±1.0	400±77
E59K	3.4±0.5	35±14
S65T	3.0±0.5	2.2±0.6
E66G	1.6±0.2	3.9±1.5
E66K	3.7±1.0	10.8±4.5
E66Q	2.3±0.7	5.0±2.0
L68F	10.9±1.7	112±28
M72R	6.6±1.4	685±155
M72V	2.0±0.2	0.6±0.1
A73V	1.4±0.1	0.9±0.3
M76R	3.0±0.7	6.0±2.0
W81S	3.8±1.4	25±12
Y88D	3.4±0.4	52±17
I91T	14±2	5.9±2.5
C94Y	2.0±0.4	0.8±0.3
W95S	4.0±0.8	312±52
A97V	3.0±0.5	0.8±0.3
A97P	7.7±1.4	43±14
R112H	5.0±0.5	2.5±0.3
R112C	15±2	297±59
R112S	8.0±1.8	91±28
F113L	2.3±0.2	2.4±1.0
R118C	1.4±0.1	6.0±2.6
L120P	5.7±2.3	20±9
A121T	2.6±0.5	0.3±0.1
D136H	5.0±1.0	2.3±5
A143T	1.3±0.1	4.3±1.3
G144V	21±6	38±14
Q147R	2.4±0.4	4.2±1.6
S148N	18±2	1391±442
A156T	1.3±1	47±10
A156V	19±2	44±9
L166V	5.0±0.5	13±4
K168N	22±3	68±32
G183S	6.8±1.0	7.1±1.9
G183D	15±3	42±13
M187T	8.4±2.0	23±8
M187V	4.9±1.2	16±1
L191P	20±0	6.5±2.5
L191Q	16±4	118±61
T194I	12±2	19±1
V195M	1.2±0.0	3.5±1.6
S201F	8±2	2.1±0.6
S201Y	6.0±0.3	15±3
P205L	8.5±0.8	260±54
P205R	4.0±0.7	70±30
P205T	7.7±2.0	2.4±0.4
Y207S	3.3±0.4	67±5
N215S	2.6±0.3	4.3±0.9
I219N	13±1	167±67
N224D	13±3	186±39
N224S	2.0±0.1	6.3±1.8
H225R	27±2	860±135
D234E	14±3	341±47
I242N	1.2±1	9.3±1.0
L243F	8±1	9.9±1.7
D244N	4.0±1.0	3.5±1.3
D244H	3.0±1.0	1.2±0.4
P259R	3.0±0.4	2.1±0.5
P259L	8.4±3.0	9.0±0.5
G260A	8.5±2.6	12±1
N263S	4.8±1.2	2.5±0.4
D264Y	13±3	18±4
P265R	13±1	96±27
P265L	2.7±0.2	1.1±0.1
P265R	13±1	97±27
M267I	1.6±0.2	5.6±2.5
L268S	1.5±0.1	0.7±0.3
V269A	13±2	22±9
V269M	3.8±0.9	2.0±0.6
I270T	11±2	10.0±0.3
G271S	22±3	24±2
N272K	5.3±0.7	17±7
N272S	4.6±0.8	228±86
S276N	8.0±2.3	22±7
S276S	22±1	8.0±1.0
Q279E	4.5±0.6	22±5
Q279H	4.7±0.7	81±26
Q279R	5.5±0.3	11.9±5.6
Q280H	4.7±1.0	5.4±0.8
Q280K	1.7±0.1	1.1±0.3
M284T	20±4	28±8
W287C	20±4	968±74
A288D	5.7±0.6	159±36
A288P	20±1	25±1
I289F	16±4	306±18
A292P	3.0±0.5	159±42
P293A	20±2	478±96
P293S	19±2	563±218
F295C	15±2	18±5
M296I	2.6±0.1	0.7±0.2
M296V	1.9±0.1	0.7±0.3
S297C	3.0±0.7	616±230
N298S	2.8±0.0	1.4±0.2
N298K	5.2±2.2	38±18
L300F	5.5±1.3	3.4±0.8
L300P	12±1	6.0±1.6
R301Q	6.5±0.3	3.8±0.4
R301P	42±4	118±14
I303N	13±1	68±22
L310F	17±0	71±11
Q312H	13±2	15±2
V316E	5.0±0.7	647±143
I317T	5.0±1.4	10±2
I317N	9.4±1.0	83±24
N320I	23±3	39±12
N320Y	18±1	295±76
Q321E	21±3	90±35
Q321R	3.4±1.1	7.0±0.8
G325D	12±2	323±102
Q327E	2.4±0.2	11±3
G328A	18±5	14±2
E332K	4.4±0.2	16±4
W340R	10.0±1.5	103±38
E341D	2.9±0.1	17±4
R342Q	4.0±1.4	16±7
S346P	8.2±0.6	76±5
A348P	1.6±0.0	4.8±2.3
A352D	5.0±0.5	165±28
I354K	19±4	17±3
R356W	2.8±0.6	0.9±0.1
E358A	21±2	9.4±2.0
E358G	7.3±0.6	20±9
E358K	2.8±0.6	400±117
G361R	0.7±0.8	7.2±2.2
P362L	7.2±1.5	2.7±0.7
R363H	1.7±0.1	1.0±0.4
R363C	2.3±0.3	2.1±0.9
G373D	3.2±0.4	5.4±2.6
G373S	2.6±0.4	2.2±0.7
E398K	1.3±0.0	6.9±2.4
P409S	14±2	2.7±0.6
T410A	19±3	2.3±0.9
G411D	1.5±0	5.8±3.0
L414S	5.8±0.6	18±3
Ins247-8	21±1	405±176

Fig. 2B: DGJ-Responsive Mutations described in Figure 1B: Potency and Response Magnitude

Mutation	Fold of Increase	EC_{50}(uM)	Mutation	Fold of Increase	EC_{50}(uM)
L14P	2.50±0.44	2.59±0.75	M267I	1.59±0.08	5.66±2.38
A20P	1.47±0.10	0.34±0.16	V269M	3.81±0.90	2.60±0.62
L32P	6.85±1.04	2.24±0.34	I270T	10.99±1.62	10.02±0.31
N34K	18.53±2.32	100.89±30.83	G271S	22.10±8.22	24.17±1.96
G35R	5.40±1.59	6.98±1.51	S276N	9.04±2.33	21.54±7.07
P40L	3.75±0.24	39.03±15.93	S276G	22.16±0.61	8.99±0.97
P40S	3.10±0.61	2.57±0.75	Q279E	4.52±0.63	22.46±4.98
T41I	1.29±0.09	0.32±0.10	Q279H	4.69±0.70	61.31±26.33
L45R	17.04±3.88	38.70±5.30	Q279R	3.47±0.34	11.93±5.58
W47L	4.73±1.22	10.83±3.20	Q280H	4.69±1.05	5.45±0.85
E48K	6.00±1.12	4.44±2.08	Q280K	1.70±0.10	1.09±0.26
R49G	3.44±0.54	3.64±1.36	M284T	19.92±4.56	28.31±7.83
R49L	10.93±1.71	75.71±18.70	W287C	20.11±3.61	968.45±74.22
R49S	3.56±0.81	5.26±2.62	A288D	5.67±0.61	198.63±36.31
M51K	287±0.26	1.82±0.36	A288P	19.52±0.70	25.33±1.44
C52R	3.62±0.57	53.08±22.95	I289F	18.53±4.44	308.39±48.52
E59K	3.41±0.49	34.77±13.52	A292P	3.07±0.51	158.87±41.66
E66Q	3.29±0.68	5.33±2.26	P293A	20.56±2.58	474.88±96.29
M72V	2.19±0.15	0.59±0.14	P293S	18.73±2.32	562.60±218.18
A73V	1.39±0.14	0.94±0.34	F295C	14.85±2.59	18.44±4.69
M76R	2.98±0.71	6.18±2.02	M296I	2.56±0.07	0.69±0.17
I91T	12.15±1.20	5.93±2.36	M296V	1.94±0.05	0.70±0.32
C94Y	2.12±0.36	0.79±0.35	S297C	2.99±0.74	616.10±230.41
W95S	4.02±0.79	312.17±52.17	N298S	2.79±0.02	1.42±0.21
A97V	2.70±0.50	0.78±0.26	N298K	5.20±2.22	38.12±18.48
R112H	4.85±0.48	2.54±0.47	L300F	5.53±1.31	3.35±0.80
R112C	15.34±1.94	296.59±59.28	L300P	12.38±1.39	6.04±1.56
F113L	2.33±0.19	2.39±0.90	R301Q	6.54±0.33	3.86±0.35
A121T	2.62±0.48	0.33±0.05	R301P	41.85±4.24	118.30±13.89
A143T	1.34±0.06	4.26±1.30	I303N	13.46±1.24	68.23±22.49
G144V	38.32±13.72	2.5±0.76	L310F	17.39±0.15	71.46±10.68
A156V	19.06±2.33	44.42±8.94	Q312H	12.39±2.11	15.38±2.49
L166V	4.77±0.51	12.94±4.03	V316E	4.99±0.74	627.13±142.62
G183D	14.71±3.41	41.60±12.82	I317T	5.06±1.37	10.14±2.48
T194I	12.39±2.05	18.93±0.89	N320I	23.34±2.77	38.92±11.74
S201F	8.43±2.18	2.08±0.63	N320Y	18.34±1.47	295.33±76.01
S201Y	5.97±0.34	15.31±3.24	Q321E	20.65±2.84	89.80±34.91
P205R	4.09±0.66	69.75±30.16	Q321R	3.35±1.12	7.01±0.80
P205T	7.69±2.03	2.42±0.42	G325D	12.23±1.99	323.52±102.44
Y207S	3.24±0.44	66.62±5.11	Q327E	2.43±0.23	11.30±2.06
N215S	2.55±0.34	4.25±0.87	G328A	18.54±5.39	13.56±1.82
I219N	13.22±0.64	167.06±66.53	E338K	4.37±0.15	16.27±4.34
N224S	2.57±0.14	6.34±1.84	W340R	10.13±1.50	103.46±37.51
H225R	27.40±1.84	859.83±134.62	E341D	2.86±0.11	16.83±3.83
D234E	13.64±3.01	341.35±47.17	R342Q	4.03±1.45	15.70±6.79
I242N	12.02±0.70	9.29±1.05	S345P	8.15±0.61	76.21±4.89
L243F	8.36±0.67	9.86±1.51	A348P	1.60±0.03	4.75±2.29
D244N	4.05±1.47	3.50±1.26	I354K	18.89±3.89	17.20±2.91
D244H	3.17±0.97	1.24±0.42	R356W	2.78±0.57	0.95±0.09
P259R	3.31±0.42	2.10±0.49	E358K	2.81±0.57	400.63±117.46
P259L	8.40±2.98	9.04±0.51	R363H	1.71±0.13	0.98±0.39
G260A	8.47±2.58	12.29±1.04	R363C	2.33±0.28	2.08±0.92
N263S	4.77±1.19	2.49±0.35	G373D	3.22±0.42	5.43±2.58
D264Y	13.15±3.23	18.24±3.73	G373S	2.64±0.42	2.24±0.69
P265R	12.61±1.21	96.58±26.62	E398K	1.28±0.03	6.94±2.43
P265L	2.74±0.20	1.10±0.07	P409S	14.45±1.75	2.67±0.61

Fig. 2C: DGJ-Responsive Mutations described in Figure 1C: Potency and Response Magnitude

FIG. 3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R227Q
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-6
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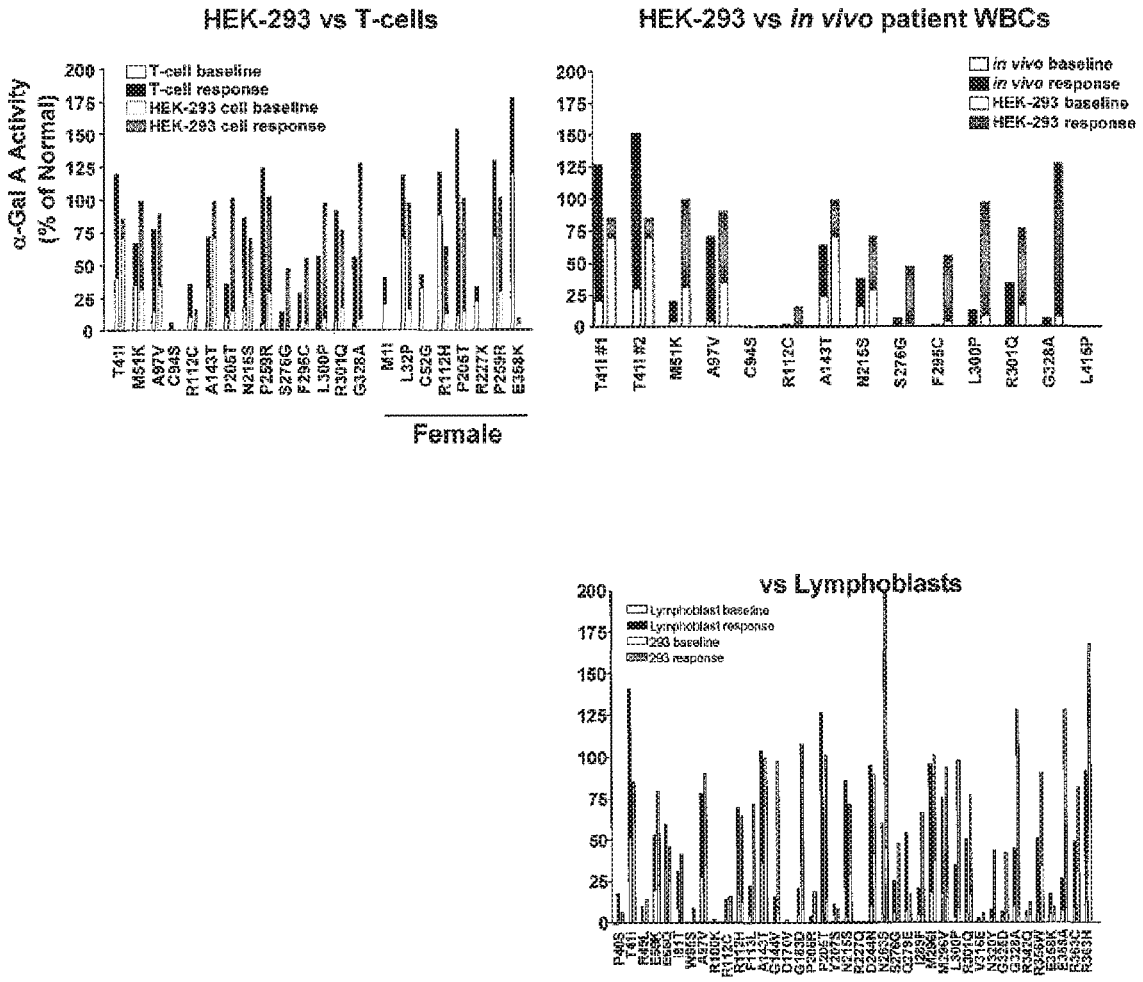
-3
log [AT1001] (M)

FIG. 4


HEK-293 vs T-cells
α-Gal A Activity (% of Normal)
T-cell baseline
T-cell response
HEK-293 cell baseline
HEK-293 cell response
Female
HEK-293 vs in vivo patient WBCs
in vivo baseline
in vivo response
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HEK-293 response
vs Lymphoblasts
Lymphoblast baseline
Lymphoblast response
293 baseline
293 response

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Fig. 5

Seq ID # 1

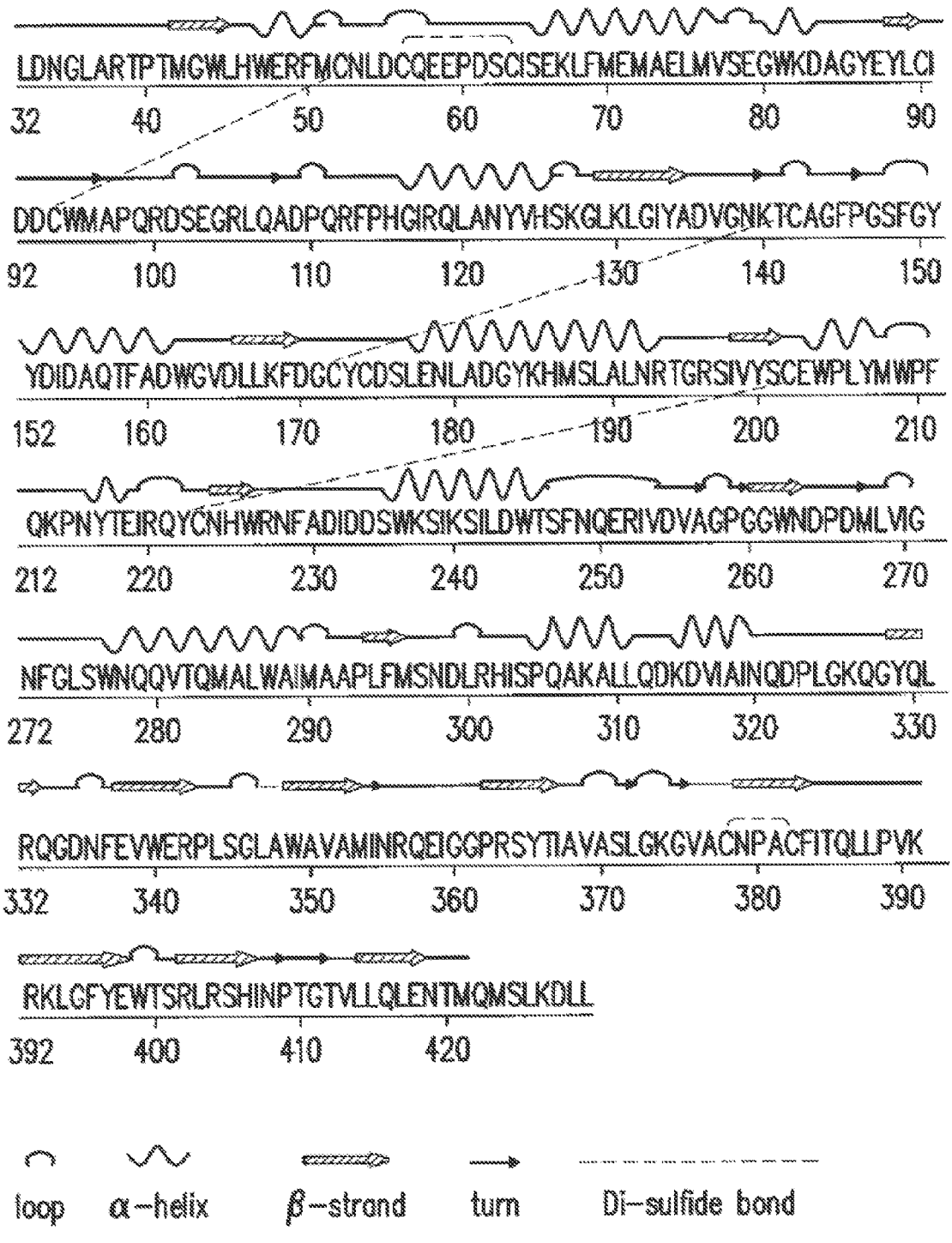

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Fig. 6

Seq ID	α-Gal A mutation	Primer	α-Gal A mutation	Primer	Seq ID
5	GLA-M1I-5'	CGTGACAATACAGCTGAG	GLA-R227Q-3'	GTCAGCAAAATTTTGCCAG TGATTGC	28
6	GLA-M1I-3'	CTCAGCTGTATTGTCACG	GLA-A230T-5'	gcggaaattt actgacattgatg	29
7	GLA-M1T-5	CACCGTGACA ACG CAGCTGAGG	GLA-A230T-3'	CAT CAA TGT CAG TAA AAT TTC GC	30
8	GLA-M1T-3	CCT CAG CTG CGT TGT CAC GGT G	GLA-D231N-5	GCCGAAATTTTGCT aAC ATTGATGATTCCTG	31
9	GLA-L14P-5'	GGCTGCGCGCCTGCGCTTCG	GLA-D231N-3	CAG GAA TCA TCA ATG TTA GCA AAA TTT CGC C	32
10	GLA-L14P-3'	CGAAGCGCAGGCGCGCAGCC	GLA-D231G-5'	CGAAATTTTGCT GgC ATTGATGATATTC	33
11	GLA-L16P/H-5'	GCGCTTGCGCMTCGCTTCCTGG	GLA-D231G-3'	GAA TAT CAT CAA TGC CAG CAA AAT TTC G	34
12	GLA-L16P/H-3'	CCAGGAAGCGAKGCGCAAGCGC	GLA-D234E-5'	tgacattgat gag tccaggaaaag	35
13	GLA-L19P-5'	GCTTCGCTTCCCGGCCCTCGTTTC	GLA-D234E-3'	CTT TTC CAG GAC TCA TCA ATG TCA	36
14	GLA-L19P-3'	GAAACGAGGGCCGGGAAGCGAAGC	GLA-D234Y-5	GCTGACATTGAT tAT TCCTGGAAAAG	37
15	GLA-A31V-5'	GGGGCTAGAGTACTGGACAATGG	GLA-D234Y-3	CTT TTC CAG GAA TAA TCA ATG TCA GC	38
16	GLA-A31V-3'	CCATTGTCCAGTACTCTAGCCCC	GLA-S235C-5	CTGACATTGATGAT TgC TGGAAAAGTATAAAGAG	39
17	GLA-L32P-5'	GCTAGAGCACCGGACAATGGA	GLA-S235C-3	CTC TTT ATA CTT TTC CAG CAA TCA TCA ATG TCA G	40
18	GLA-L32P-3'	TCCATTGTCCGGTGCTCTAGC	GLA-W236R-5	GCTGACATTGATGATTCC cGG AAAAGTATAAAGAGTATC	41
19	GLA-L32P-5'	GCTAGAGCACCGGACAATGGA	GLA-W236R-3	GAT ACT CTT TAT ACT TTT CCG GGA ATC ATC AAT GTC AGC	42
20	GLA-L32P-3'	TCCATTGTCCGGTGCTCTAGC	GLA-W236L-5'	TGATGATTCC TTG AAAAGTATAA	43
21	GLA-D33Y-5'	CTAGAGCACTGTACAATGGATTG	GLA-W236L-3'	TTA TAC TTT TCA AGG AAT CAT CA	44
22	GLA-D33Y-3'	CAATCCATTGTACAGTGCTCTAG	GLA-W236L-5	ctGACATTGATGATTCC TtG AAAAGTATAAAGAG	45
23	GLA-N34K-5'	GCACTGGACAAAGGATTGGC	GLA-W236L-3	CTC TTT ATA CTT TTC AAG GAA TCA TCA ATG TCA G	46
24	GLA-N34K-3'	GCCAATCCTTTGTCCAGTGC	GLA-W236C-5	GCTGACATTGATGATTCC TGt AAAAGTATAAAGAGTATCT TGG	47
25	GLA-N34S-5'	GCACTGGACAGTGGATTGGC	GLA-W236C-3	CCA AGA TAC TCT TTA TAC TTT TAC AGG AAT CAT CAA TGT CAG C	48
26	GLA-N34S-3'	GCCAATCCACTGTCCAGTGC	GLA-I239T-5'	TGGAAAAGT ACA AAGAGTATC	49

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Fig. 6 (Cont.)

27	GLA-G35R-5'	CTGGACAATAGATTGGCAAGG	GLA-I239T-3'	GAT ACT CTT TGT ACT TTT CCA	50

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Fig. 6 (Cont.)

51	GLA-G35R-3'	CCTTGCCAATCTATTGTCCAG	GLA-I239T-5	GATTCCTGGAAAAGT AcA AAGAGTATCTTGGACTG	76
52	GLA-A37V-5'	AATGGATTGGTAAGGACGCC	GLA-I239T-3	CAG TCC AAG ATA CTC TTT GTA CTT TTC CAG GAA TC	77
53	GLA-A37V-3'	GGCGTCCTTACCAATCCATT	GLA-I242F-5'	AGTATAAAGAGT TTC TTGGACTGGAC	78
54	GLA-P40L-5'	GCAAGGACGCTTACCATGGG	GLA-I242F-3'	GTC CAG TCC AAG AAA CTC TTT ATA CT	79
55	GLA-P40L-3'	CCCATGGTAAGCGTCCTTGC	GLA-I242N-5'	GTATAAAGAGT AAC TTGGACTGG	80
56	GLA-P40S-5'	GCAAGGACGTCTACCATGGG	GLA-I242N-3'	CCA GTC CAA GTT ACT CTT TAT AC	81
57	GLA-P40S-3'	CCCATGGTAGACGTCCTTGC	GLA-L243F-5'	AGAGTATCTTCGACTGGACATC	82
58	GLA-M42T-5	AGGACGCCTACC AcG GGCTGGCTGCAC	GLA-L243F-3'	GAT GTC CAG TCG AAG ATA CTC T	83
59	GLA-M42T-3	GTG CAG CCA GCC CGT GGT AGG CGT CCT	GLA-D244H-5'	GAGTATCTTG CACTGGACATC	84
60	GLA-M42L-5	AGGACGCCTACC TTG GGCTGGCTGCAC	GLA-D244H-3'	GAT GTC CAG TCG AAG ATA CTC T	85
61	GLA-M42L-3	GTG CAG CCA GCC CAA GGT AGG CGT CCT	GLA-S247C-5'	CTTGGACTGGACATGTTTTAACCAGG AGAG	86
62	GLA-M42V-5	AGGACGCCTACC GTG GGCTGGCTGC	GLA-S247C-3'	CTC TCC TGG TTA AAA CAT GTC CAG TCC AAG	87
63	GLA-M42V-3	GCA GCC AGC CCA CGG TAG GCG TCC T	GLA-S247P-5'	GGACTGGACA CCTTTTAACCA	88
64	GLA-G43D/V-5'	CTACCATGGWCTGGCTGCAC	GLA-S247P-3'	TGG TTA AAA GGT GTC CAG TCC	89
65	GLA-G43D/V-3'	GTGCAGCCAGWCCATGGTAG	GLA-A257P-5'	GTTGATGTT CCTGGACCAG	90
66	GLA-G43R-5'	CTACCATGCGCTGGCTGCAC	GLA-A257P-3'	CTG GTC CAG GAA CAT CAA C	91
67	GLA-G43R-3'	GTGCAGCCAGCGCATGGTAG	GLA-G258R-5'	GATGTTGCT CGACCAGGGG	92
68	GLA-W44C-5'	CATGGGCTGTCTGCACTGG	GLA-G258R-3'	CCC CTG GTC GAG CAA CAT C	93
69	GLA-W44C-3'	CCAGTGCAGACAGCCCATG	GLA-P259R-5'	GATGTTGCTGGACGAGGGGGTTGGA	94
70	GLA-L45R-5'	ATGGGCTGGCGGCACTGCGAG	GLA-P259R-3'	TCCAACCCCCTCGTCCAGCAACATC	95
71	GLA-L45R-3'	CTCGCAGTGCCGCCAGCCCAT	GLA-P259L-5'	GTTGCTGGACTAGGGGGTTGG	96
72	GLA-H46R-5'	CTGGCTGCGCTGGGAGC	GLA-P259L-3'	CCA ACC CCC TAG TCC AGC AAC	97
73	GLA-H46R-3'	GCTCCCAGCGCAGCCAG	GLA-G260A-5'	GCTGGACCA GCG GGTTGGAATG	98
74	GLA-H46Y-5'	CTGGCTGTACTGGGAGC	GLA-G260A-3'	CAT TCC AAC CCG CTG GTC CAG C	99
75	GLA-H46Y-3'	GCTCCCAGTACAGCCAG	GLA-G261D-5'	GGACCAGGG GAT TGGAATGAC	100

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Fig. 6 (Cont.)

101	GLA-W47G-5'	CTGGCTGCACGGGGAGCGCTTC	GLA-G261D-3'	GTC ATT CCA ATC CCC TGG TCC	126
102	GLA-W47G-3'	GAAGCGCTCCCCGTGCAGCCAG	GLA-W262C-5'	CAGGGGGT TGC AATGACCCAG	127
103	GLA-W47L-5'	CTGGCTGCACTTGGAGCGCTTC	GLA-W262C-3'	CTG GGT CAT TGC AAC CCC CTG	128
104	GLA-W47L-3'	GAAGCGCTCCAAGTGCAGCCAG	GLA-N263S-5'	GGGGTTGG AGT GACCCAGA	129
105	GLA-E48K-5'	GCTGCACTGGAAGCGCTTCATG	GLA-N263S-3'	TCT GGG TCA CTC CAA CCC C	130
106	GLA-E48K-3'	CATGAAGCGCTTCCAGTGCAGC	GLA-D264V-5'	GGTTGGAAT GTC CCAGATATG	131
107	GLA-R49P/L-5'	ACTGGGAGCYCTTCATGTGC	GLA-D264V-3'	CAT ATC TGG GAC ATT CCA ACC	132
108	GLA-R49P/L-3'	GCACATGAAGRGCTCCCAGT	GLA-D264Y-5'	GGGTTGGAAT TAC CCAGATATG	133
109	GLA-R49S/G-5'	CACTGGGAGRGCTTCATGT	GLA-D264Y-3'	CAT ATC TGG GTA ATT CCA ACC C	134
110	GLA-R49S/G-3'	ACATGAAGCYCTCCCAGTG	GLA-P265R-5'	TGGAATGAC CGA GATATGTTA	135
111	GLA-F50C-5'	CTGGGAGCGCTGCATGTGCAAC	GLA-P265R-3'	TAA CAT ATC TCG GTC ATT CCA	136
112	GLA-F50C-3'	GTTGCACATGCAGCGCTCCCAG	GLA-P265L-5'	TTGGAATGAC CTA GATATGTTAG	137
113	GLA-M51K-3'	GAGCGCTTCAAGTGCAACCTTG	GLA-P265L-3'	CTA ACA TAT CTA GGT CAT TCC AA	138
114	GLA-M51K-5'	CAAGGTTGCACTTGAAGCGCTC	GLA-D266N/H-5'	GGAATGACCCA nAT ATGTTAGTG	139
115	GLA-M51I-5'	GCGCTTCATATGCAACC	GLA-D266N/H-3'	CAC TAA CAT ATT GGG TCA TTC C	140
116	GLA-M51I-3'	GGTTGCATATGAAGCGC	GLA-D266H-5	GGTTGGAATGACCCA cAT ATGTTAGTGATTGG	141
117	GLA-C52S-5'	GAGCGCTTCATGTCCAACCTTGACTG	GLA-D266H-3	CCA ATC ACT AAC ATA TGT GGG TCA TTC CAA CC	142
118	GLA-C52S-3'	CAGTCAAGGTTGGACATGAAGCGCTC	GLA-D266V-5'	GAATGACCCA GTT ATGTTAGTG	143
119	GLA-C52G/R-5'	CGCTTCATGSGCAACCTTGAC	GLA-D266V-3'	CAC TAA CAT AAC TGG GTC ATT C	144
120	GLA-C52G/R-3'	GTCAAGGTTGCSCATGAAGCG	GLA-D266R-5'	ATGACCCA GAA ATGTTAGTGA	145
121	GLA-C56G-5'	CAACCTTGACGGCCAGGAAG	GLA-D266R-3'	TCA CTA ACA TTT CTG GGT CAT	146
122	GLA-C56G-3'	CTTCCTGGCCGTCAAGGTTG	GLA-M267R-5'	GACCCAGAT AGG TTAGTGATTG	147
123	GLA-C56Y/F-5'	CAACCTTGACTWCCAGGAAGAG	GLA-M267R-3'	CAA TCA CTA ACC TAT CTG GGT C	148
124	GLA-C56Y/F-3'	CTCTTCCTGGWAGTCAAGGTTG	GLA-M267I-5'	GACCCAGAT ATA TTAGTGATTGG	149
125	GLA-C56Y-5	GTGCAACCTTGACTACCAGGAAGAGCCAG	GLA-M267I-3'	CCA ATC ACT AAT ATA TCT GGG TC	150

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Fig. 6 (Cont.)

151	GLA-C66Y-3	CTG GCT CTT CCT GGT AGT CAA GGT TGC AC	GLA-L268S-5'	CCA GAT ATG TCA GTG ATT GGC	176
152	GLA-C63Y-5	ggGCCAGATTCC TAC ATCAGTGAGAagc	GLA-L268S-3'	GCC AAT CAC TGA CAT ATC TGG	177
153	GLA-C63Y-3	GCT TCT CAC TGA TGT AGG AAT CTG GCT C	GLA-V269A-5'	gatatgta gcg attggcaac	178
154	GLA-S65T-5'	TCCTGCATCACTGAGAAGCTC	GLA-V269A-3'	GTT GCC AAT CGC TAA CAT ATC	179
155	GLA-S65T-3'	GAGCTTCTCAGTGATGCAGGA	GLA-V269M-5'	CAG ATA TGT TAA TGA TTG GCA AC	180
156	GLA-E66K-5'	CTGCATCAGTAAGAAGCTCTTC	GLA-V269M-3'	GTT GCC AAT CAT TAA CAT ATC TG	181
157	GLA-E66K-3'	GAAGAGCTTCTTACTGATGCAG	GLA-I270T-5'	TATGTTAGTGA C TGGCAACTTTG	182
158	GLA-E66G-5'	CTGCATCAGTGGGAAGCTCTTC	GLA-I270T-3'	CAA AGT TGC CAG TCA CTA ACA TA	183
159	GLA-E66G-3'	GAAGAGCTTCCCACTGATGCAG	GLA-G271V-5'	TTAGTGATTGTCAACTTTG	184
160	GLA-L68F-5'	CAGTGAGAAGTTCTTCATGG	GLA-G271V-3'	CAAAGTTGACAATCACTAA	185
161	GLA-L68F-3'	CCAGGAAGAACTTCTCACTG	GLA-G271C-5'	GTTAGTGATT T GCAACTTTGG	186
162	GLA-L68F-5	GCATCAGTGAGAAG tTC TTCATGGAGATG	GLA-G271C-3'	CCA AAG TTG CAA ATC ACT AAC	187
163	GLA-L68F-3	CAT CTC CAT GAA GAA CTT CTC ACT GAT GC	GLA-G271S-5'	TGTTAGTGATT A GCAACTTTGGC	188
164	GLA-M72R-5'	CTTCATGGAGAGGGCAGAGCTC	GLA-G271S-3'	GCC AAA GTT GCT AAT CAC TAA CA	189
165	GLA-M72R-3'	GAGCTCTGCCCTCTCCATGAAG	GLA-N272K-5'	GTGATTGGC AAA TTTGGCCTCAG	190
166	GLA-M72I-5'	CTTCATGGAGATAGCAGAGCTC	GLA-N272K-3'	CTG AGG CCA AAT TTG CCA ATC AC	191
167	GLA-M72I-3'	GAGCTCTGCTATCTCCATGAAG	GLA-N272S-5'	GTGATTGGC AGC TTTGGCCTC	192
168	GLA-A73V-5'	CATGGAGATGGTAGAGCTCATG	GLA-N272S-3'	GAG GCC AAA GCT GCC AAT CAC	193
169	GLA-A73V-3'	CATGAGCTCTACCATCTCCATG	GLA-S276G-5'	CAACTTTGGCCTCGGCTGGAATCAG	194
170	GLA-M76R-5'	GCAGAGCTCAGGGTCTCAGAAG	GLA-S276G-3'	CTGATTCCAGCCGAGGCCAAAGTTG	195
171	GLA-M76R-3'	CTTCTGAGACCCTGAGCTCTGC	GLA-S276N-5'	CTTTGGCCTC AAC TGGAATCAGC	196
172	GLA-W81C-5'	CTCAGAAGGC TGC AAGGATGCAGGT	GLA-S276N-3'	GCT GAT TCC AGT TGA GGC CAA AG	197
173	GLA-W81C-3'	ACC TGC ATC CTT ACA GCC TTC TGA G	GLA-Q279R-5'	AGCTGGAAT GGG CAAGTAACTC	198
174	GLA-W81S-5'	CTCAGAAGGCTGGAAGGATGCA	GLA-Q279R-3'	GAG TTA CTT GCC GAT TCC AGC T	199
175	GLA-W81S-3'	TGCATCCTTCCAGCCTTCTGAG	GLA-Q279H-5'	CAGCTGGAAT CAC CAAGTAACTC	200

AMENDED

Fig. 6 (Cont.)

201	GLA-Q85D-5'	GAAGGATGCAGATTATGAGTAC	GLA-Q279H-3'	GAG TTA CTT GGT GAT TCC AGC TG	225
202	GLA-Q85D-3'	GTACTCATAATCTGCATCCTTC	GLA-Q279K-5'	CAGCTGGAAT AAG CAAGTAAC	226
203	GLA-Y86C-5	GGATGCAGGT TGT GAGTACCTCTG	GLA-Q279K-3'	GTT ACT TGC TTA TTC CAG CTG	227
204	GLA-Y86C-3	GCA GAG GTA CTC ACA ACC TGC ATC C	GLA-Q280H-5'	GGAATCAGCAT GTAACTCAGA	228
205	GLA-Y88D-5'	GGTTATGAGGACCTCTGCATTG	GLA-Q280H-3'	TCT GAG TTA CAT GCT GAT TCC	229
206	GLA-Y88D-3'	CAATGCAGAGGTCCTCATAACC	GLA-Q280K-5'	CTGGAATCAG AAA GTAACTCAG	230
207	GLA-L89P/R-5'	GTTATGAGTACCSCTGCATTGATG	GLA-Q280K-3'	CTG AGT TAC TTT CTG ATT CCA	231
208	GLA-L89P/R-3'	CATCAATGCAGSGGTACTCATAAC	GLA-T282N-5'	CAGCAAGTAAATCAGATGGCC	231
209	GLA-D92N/H/Y-5'	CCTCTGCATTHATGACTGTTG	GLA-T282N-3'	GGC CAT CTG ATT TAC TTG CTG	233
210	GLA-D92N/H/Y-3'	CAACAGTCATDAATGCAGAGG	GLA-Q283P-5'	CAAGTAACT CCG ATGCCCTC	234
211	GLA-D92N-5'	TACCTCTGCATT AAT GACTGTTGGATG	GLA-Q283P-3'	GAG GGC CAT CGG AGT TAC TTG	235
212	GLA-D92N-3'	CAT CCA ACA GTC ATT AAT GCA GAG GTA	GLA-M284T-5'	GTAACTCAG ACG GCCCTCTG	236
213	GLA-D92H-5'	TACCTCTGCATT CAT GACTGTTGGATG	GLA-M284T-3'	CAG AGG GCC GTC TGA GTT AC	237
214	GLA-D92H-3'	CAT CCa ACA GTC ATG AAT GCA GAG GTA	GLA-A285P-5'	TAACTCAGATG C CCCTCTGGGCT	238
215	GLA-D92Y-5	GAGTACCTCTGCATTTAT GACTGTTGGATGGCTC	GLA-A285P-3'	AGC CCA GAG GGG CAT CTG AGT TA	239
216	GLA-D92Y-3	GAG CCA TCC AAC AGT CAT AAA TGC AGA GGT ACT C	GLA-A285D-5'	AACTCAGATGG A CCTCTGGGCT	240
217	GLA-D93G-5'	CTGCATTGATGGCTGTTGGATG	GLA-A285D-3'	AGC CCA GAG GTC CAT CTG AGT T	241
218	GLA-D93G-3'	CATCCAACAGCCATCAATGCAG	GLA-W287G-5'	GATGGCCCTC GGG GCTATCAT	242
219	GLA-D93V-5'	CTGCATTGATGHCTGTTGGATG	GLA-W287G-3'	ATG ATA GCC CCG AGG GCC ATC	243
220	GLA-D93V-3'	CATCCAACAGACATCAATGCAG	GLA-W287C-5'	ATGGCCCTC TGT GCTATCATG	244
221	GLA-D93N-5'	CTGCATTGATAACTGTTGGATG	GLA-W287C-3'	CAT GAT AGC ACA GAG GGC CAT	245
222	GLA-D93N-3'	CATCCAACAGTTATCAATGCAG	GLA-A288D-5'	GCCCTCTGG GAT ATCATGGCTG	246
223	GLA-C94S-5'	GCATTGATGACTCTTGGATGGCTC	GLA-A288D-3'	CAG CCA TGA TAT CCC AGA GGG C	247
224	GLA-C94S-3'	GAGCCATCCAAGAGTCATCAATGC	GLA-A288P-5'	GCCCTCTGG CCT ATCATGG	248

AMENDED

Fig. 6 (Cont.)

249	GLA-C94Y-5'	GCATTGATGACTATTGGATGGCTC	GLA-A288P-3'	CCA TGA TAG GCC AGA GGC C	274
250	GLA-C94Y-3'	GAGCCATCCAATAGTCATCAATGC	GLA-I289F-5'	CTCTGGGCT TTC ATGGCTGCTCCTT	275
251	GLA-W95S-5'	GATGACTGTTCGATGGCTCCC	GLA-I289F-3'	AAG GAG CAG CCA TGA AAG CCC AGA G	276
252	GLA-W95S-3'	GGGAGCCATCGAACAGTCATC	GLA-M290I-5'	GGGCTATC ATC GCTGCTCCTT	277
253	GLA-A97P-5'	CTGTTGGATGCCTCCCCAAAGAG	GLA-M290I-3'	AAG GAG CAG CGA TGA TAG CCC	278
254	GLA-A97P-3'	CTCTTTGGGGAGGCATCCAACAG	GLA-A292P-5'	CTATCATGGCT CCT CCTTTATTC	279
255	GLA-R100K/T-5'	GCTCCCCAAAMAGATTCAGAAG	GLA-A292P-3'	GAA TAA AGG AGG AGC CAT GAT AG	280
256	GLA-R100K/T-3'	CTTCTGAATCTKTTTGGGGAGC	GLA-P293A-5'	CATGGCTGCT GCT TTATTCATG	281
257	GLA-R100T-5'	GGCT CCC CAA ACA GAT TCA GAA GG	GLA-P293A-3'	CAT GAA TAA AGC AGC AGC CAT G	282
258	GLA-R100T-3'	CCT TCT GAA TGT GTT TGG GGA GCC	GLA-P293S/T-5'	CATGGCTGCT WCT TTATTCATG	283
259	GLA-E103Q-5'	CAAAGAGATTCACAAGGCAGACTTC	GLA-P293S/T-3'	CAT GAA TAA AGW AGC AGC CAT G	284
260	GLA-E103Q-3'	GAAGTCTGCCTTGTGAATCTCTTTG	GLA-F295C-5'	GCTGCTCCTTTA TGC ATGTCTAATGACC	285
261	GLA-R112S-5'	GCAGACCCTCAGAGCTTTCCTCATG	GLA-F295C-3'	GGT CAT TAG ACA TGC ATA AAG GAG CAG C	286
262	GLA-R112S-3'	CATGAGGAAAGCTCTGAGGGTCTGC	GLA-S297C/F-5'	CTTTATTCATG TKT AATGAGCTCCG	287
263	GLA-R112C-5'	CAGACCCTCAGTGCTTTCCTCATG	GLA-S297C/F-3'	CGG AGG TCA TTA MAC ATG AAT AAA G	288
264	GLA-R112C-3'	CATGAGGAAAGCACTGAGGGTCTG	GLA-N298S-5'	ATTCATGTCT AGT GACCTCCGAC	289
265	GLA-F113S-5'	CCCTCAGCGCTCTCCTCATG	GLA-N298S-3'	GTC GGA GGT CAC TAG ACA TGA AT	290
266	GLA-F113S-3'	CATGAGGAGAGCGCTGAGGG	GLA-N298K-5'	TATTCATGTCTAAGGACCTCCGAC	291
267	GLA-R118C-5'	CTCATGGGATTTGCCAGCTAGC	GLA-N298K-3'	GTCGGAGGTCCTTAGACATGAATA	292
268	GLA-R118C-3'	GCTAGCTGGCAAATCCCATGAG	GLA-N298H-5'	TATTCATGTCT oAT GACCTCCGAC	293
269	GLA-L120P-5'	GATTCGCCAGCCAGCTAATTATG	GLA-N298H-3'	GTC GGA GGT CAT GAG ACA TGA ATA	294
270	GLA-L120P-3'	CATAATTAGCTGGCTGGCGAATC	GLA-D299G-5'	TCATGTCTAAT GGC CTCCGACACATC	295
271	GLA-A121P/T-5'	TC GCC AGC TAM CTA ATT ATG TTC ACA GC	GLA-D299G-3'	GAT GTG TCG GAG GCC ATT AGA CAT GA	296
272	GLA-A121P/T-3'	GCT GTG AAC ATA ATT AGK TAG CTG GCG A	GLA-L306P-5'	GTCTAATGACCCCCGACACATCAG	297
273	GLA-V124D-5'	GCTAGCTAATTAT GaT CACAGCAAAGGAC	GLA-L306P-3'	CTGATGTGTCGGGGGTCATTAGAC	298

AMENDED

Fig. 6 (Cont.)

299	GLA-V124D-3'	GTC CTT TGC TGT GAT CAT AAT TAG CTA GC	GLA-L306F-5'	GTCTAATGACTTCCGACACATC	324
300	GLA-G128E-5'	CACAGCAAAGaaCTGAAGCTAG	GLA-L306F-3'	GATGTGTCGGAAGTCATTAGAC	325
301	GLA-G128E-3'	CTA GCT TCA GTT CTT TGC TGT G	GLA-L306H-5'	GTCTAATGACCACCGACACATC	326
302	GLA-L129P-5'	CAG CAA AGG ACC GAA GCT AGG	GLA-L306H-3'	GATGTGTCGGTGGTCATTAGAC	327
303	GLA-L129P-3'	ATC CCT AGC TTC GGT CCT TTG CTG	GLA-R301G-5'	CTAATGACCTCGGACACATCAGC	328
304	GLA-L131P-5'	AGGACTGAAGC C AGGGATTTATGC	GLA-R301G-3'	GCTGATGTGTCCGAGGTCATTAG	329
305	GLA-L131P-3'	GCA TAA ATC CCT GGC TTC AGT CCT	GLA-R301P-5'	CTAATGACCTCCCACACATCAGC	330
306	GLA-G132E-5'	GCACTGAAGCTA GaG ATTTATGCAGATG	GLA-R301P-3'	GCTGATGTGTGGGAGGTCATTAG	331
307	GLA-G132E-3'	CAT CTG CAT AAA TCT CTA GCT TCA GTC C	GLA-I303N-5'	CTCCGACACAACAGCCCTCAAGC	332
308	GLA-G132R-5'	GAC TGA AGC TAA GGA TTT ATG CAG ATG	GLA-I303N-3'	GCTTGAGGGCTGTTGTGTCGGAG	333
309	GLA-G132R-3'	CAT CTG CAT AAA TCC TTA GCT TCA GTC	GLA-L310F-5'	GCCAAAGCTTTCCTTCAGGA	334
310	GLA-Y134S-5'	GCT AGG GAT TTC TGC AGA TGT TGG	GLA-L310F-3'	TCCTGAAGGAAAGCTTTGGC	335
311	GLA-Y134S-3'	CCA ACA TCT GCA GAA ATC CCT AGC	GLA-Q312H-5'	GCTCTCCTTCACGATAAGGACG	336
312	GLA-A135V-5'	GCT AGG GAT TTA TGT AGA TGT TGG A	GLA-Q312H-3'	CGTCCTTATCGTGAAGGAGAGC	337
313	GLA-A135V-3'	TCC AAC ATC TAC ATA AAT CCC TAG C	GLA-D313Y-5'	CTCTCCTTCAGTATAAGGACG	338
314	GLA-D136H-5'	GGA TTT ATG CAC ATG TTG GAA	GLA-D313Y-3'	CGTCCTTATACTGAAGGAGAG	339
315	GLA-D136H-3'	TTC CAA CAT GTG CAT AAA TCC	GLA-V316E-5'	GATAAGGACGAAATTGCCATC	340
316	GLA-D136H-5	GGGATTTATGCA cAT GTTGGAAATAA AACC	GLA-V316E-3'	GATGGCAATTTCGTCCTTATC	341
317	GLA-D136H-3	GGT TTT ATT TCC AAC ATG TGC ATA AAT CCC	GLA-I317N/T-5'	AAGGACGTAAMTGCCATCAATC	342
318	GLA-G138E-5'	TGC AGA TGT TGA AAA TAA AAC CTG	GLA-I317N/T-3'	GATTGATGGCAKTTACGTCCTT	343
319	GLA-G138E-3'	CAG GTT TTa TTT TCA ACA TCT GCA	GLA-N320I-5'	AATTGCCATCATTCAGGaCCCC	344
320	GLA-G138R-5'	TGC AGA TGT TAG AAA TAA AAC CTG	GLA-N320I-3'	GGGGTCCTGAATGATGGCAATT	345
321	GLA-G138R-3'	CAG GTT TTA TTT CTA ACA TCT GCA	GLA-N320K-5'	AATTGCCATCAAGCAGGACCCC	346
322	GLA-G138E-5	GGATTTATGCAGATGTT GaA AATAAAACCTGCGCAGC	GLA-N320K-3'	GGGGTCCTGCTTGATGGCAATT	347
323	GLA-G138E-3	GCT GCG CAG GTT TTA TTT TCA ACA TCT GCA TAA ATC C	GLA-N320Y-5'	AATTGCCATCTATCAGGACCCC	348

AMENDED

Fig. 6 (Cont.)

349	GLA-G138R-5	GGATTTATGCAGATGTT eGA AATAAAAACCTGCGCAGC	GLA-N320Y-3'	GGGGTCCTGATAGATGGCAATT	373
350	GLA-G138R-3	GGA TTT ATG CAG ATG TTC GAA ATA AAA CCT GCG CAG C	GLA-Q321E-5'	TGCCATCAATGAGGACCCCTTG	374
351	GLA-T141I-5'	GGA AAT AAA ATC TGC GCA GGC T	GLA-Q321E-3'	CAAGGGGTCCTCATTGATGGCA	375
352	GLA-T141I-3'	AGC CTG CGC AGA TTT TAT TTC C	GLA-Q321R-5'	TGCCATCAATCGGGACCCCTTG	376
353	GLA-C142R-5'	GGA AAT AAA ACC CGC GCA GGC TTC	GLA-Q321R-3'	CAAGGGGTCCCGATTGATGGCA	377
354	GLA-C142R-3'	GAA GCC TGC GCG GGT TTT ATT TCC	GLA-G325D-5'	GGACCCCTTGGACAAGCAAG	378
355	GLA-C142Y/W-5'	GA AAT AAA ACC TRC GCA GGC TTCC	GLA-G325D-3'	CTTGCTTGTCCAAGGGGTCC	379
356	GLA-C142Y/W-3'	GGA AGC CTG CGY AGG TTT TAT TTC	GLA-Q327K/E-5'	CTTGGGCAAGRAAGGGTACCAG	380
357	GLA-C142W-5	GGAAATAAAACCTGGGCAGGCTTCCCTG	GLA-Q327K/E-3'	CTGGTACCCTTYCTTGCCCAAG	381
358	GLA-C142W-3	CAG GGA AGC CTG CCC AGG TTT TAT TTC C	GLA-G328R-5'	GGCAAGCAAAGGTACCAGC	382
359	GLA-A143T-5'	GAAATAAAACCTGCACAGGCTTCCC	GLA-G328R-3'	GCTGGTACCTTTGCTTGCC	383
360	GLA-A143T-3'	GGGAAGCCTGTGCAGGTTTTATTTC	GLA-G328A/V-5'	GGCAAGCAAGYGTACCAGC	384
361	GLA-A143P-5'	ATAAAACCTGC eCA GGCTTCCC	GLA-G328A/V-3'	GCTGGTACRCTTGCTTGCC	385
362	GLA-A143P-3'	GGG AAG CCT GgG CAG GTT TTA T	GLA-G328E-5'	TGGGCAAGCAA GAG TACCAGCTTAG	386
363	GLA-G144V-5'	CCT GCG CAG TCT TCC CTG G	GLA-G328E-3'	CTA AGC TGG TAC TCT TGC TTG CCC A	387
364	GLA-G144V-3'	CCA GGG AAG ACT GCG CAG G	GLA-E338K-5'	GAGACAACTTTAAAGTGTGGG	388
365	GLA-G147R-5'	GGC TTC GCT AGG AGT TTT Gg	GLA-E338K-3'	CCCACACTTTAAACTTGTCTC	389
366	GLA-G147R-3'	eCAA AAC TCC TAG GGA AGC C	GLA-W340R-5'	CTTTGAAGTGCGGGAACGAC	390
367	GLA-S148N-5'	TTC CCT GGG AAT TTT GGA TAC	GLA-W340R-3'	GTCGTTCCCGCACTTCAAAG	391
368	GLA-S148N-3'	GTA TCC AAA ATT CCC AGG GAA	GLA-E341D-5'	GAAGTGTGGGACCGACCTCTCTC	392
369	GLA-S148R-5'	C CCT GGG AGG TTT GGA TACT	GLA-E341D-3'	GAGAGAGGTCGGTCCCACACTTC	393
370	GLA-S148R-3'	AGT ATC CAA ACC TCC CAG GG	GLA-E341K-5'	GAAGTGTGGAAACGACCTCTCTC	394
371	GLA-Y152C-5'	GTTTTGGATACTGCGACATTGATG	GLA-E341K-3'	GAGAGAGGTCGTTTCCACACTTC	395
372	GLA-Y152C-3'	CATCAATGTCGCAGTATCCAAAAC	GLA-R342Q-5'	GTGTGGGAACAACCTCTCTCAG	396

AMENDED

Fig. 6 (Cont.)

397	GLA-D155H-5'	CTACGACATT C ATGCCCAGAC	GLA-R342Q-3'	CTGAGAGAGGTTGTTCCCACAC	422
398	GLA-D155H-3'	GTC TGG GCA TGA ATG TCG TAG	GLA-L344P-5'	GAACGACCTCCCTCAGGCTTAG	423
399	GLA-A156T-5'	GACATTGAT ACC CAGACCTTg	GLA-L344P-3'	CTAAGCCTGAGGGAGGTCGTTC	424
400	GLA-A156T-3'	CAA AGG TCT GGG TAT CAA TGT C	GLA-S345P-5'	CGACCTCTCCCAGGCTTAGCC	425
401	GLA-W162R-5'	CTTTGCTGACCGGGGAGTAGATC	GLA-S345P-3'	GGCTAAGCCTGGGAGAGGTCG	426
402	GLA-W162R-3'	GATCTACTCCCCGGTCAGCAAAG	GLA-A348P-5'	CTCAGGCTTACCCTGGGCTGTAG	427
403	GLA-W162C-5'	CTTTGCTGACTGCGGAGTAGATC	GLA-A348P-3'	CTACAGCCCAGGGTAAGCCTGAG	428
404	GLA-W162C-3'	GATCTACTCCGCAGTCAGCAAAG	GLA-A350P-5'	CTTAGCCTGGCCTGTAGCTATG	429
405	GLA-G163V-5'	GCTGACTGGGTAGTAGATCTG	GLA-A350P-3'	CATAGCTACAGGCCAGGCTAAG	430
406	GLA-G163V-3'	CAGATCTACTACCCAGTCAGC	GLA-A352D-5'	CTGGGCTGTAGATATGATAAAC	431
407	GLA-D165V-5'	CTGGGGAGTAGTTCTGCTAAAATTTG	GLA-A352D-3'	GTTTATCATATCTACAGCCCAG	432
408	GLA-D165V-3'	CAAATTTTAGCAGAACTACTCCCCAG	GLA-I354K-5'	GTAGCTATGAAAAACCGGCAGG	433
409	GLA-L167P-5'	GAGTAGATCTGC C AAAATTTGATGG	GLA-I354K-3'	CCTGCCGGTTTTTCATAGCTAC	434
410	GLA-L167P-3'	CCA TCA AAT TTT GGC AGA TCT ACT C	GLA-N355K-5'	GCTATGATAAAACCGGCAGGAG	435
411	GLA-K168R-5'	GTAGATCTGCTA AGA TTTGATGGTTTG	GLA-N355K-3'	CTCCTGCCGTTTTATCATAGC	436
412	GLA-K168R-3'	CAA ACC ATC AAA TCT TAG CAG ATC TAC	GLA-R356W-5'	GCTATGATAAACTGGCAGGAGATT	437
413	GLA-F169S-5	gtcGATCTGCTAAAA TCT GATGGTTGTTACg	GLA-R356W-3'	AATCTCCTGCCAGTTTATCATAGC	438
414	GLA-F169S-3	CAG TAA CAA CCA TCA GAT TTT AGC AGA TCT AC	GLA-E358G/A-5'	ACCGGCAGGSGATTGGTGGAC	439
415	GLA-D170V-5'	GCTAAAATTTG T TGGTTGTTACTG	GLA-E358G/A-3'	GTCCACCAATCSCCTGCCGGT	440
416	GLA-D170V-3'	CAG TAA CAA CCA ACA AAT TTT AGC	GLA-E358K-5'	GATAAACCGGCAGAAGATTGGTGG	441
417	GLA-D170H-5'	GCTAAAATTTC AT GGTTGTTACTG	GLA-E358K-3'	CCACCAATCTTCTGCCGGTTTATC	442
418	GLA-D170H-3'	CAG TAA CAA CCA TGA AAT TTT AGC	GLA-E358A-5	GATAAACCGGCAG GcG ATTGGTGGACCTC	443
419	GLA-G171D-5'	CTAAAATTTGAT GAT TGTTACTGTGAC	GLA-E358A-3	GAG GTC CAC CAA TCG CCT GCC GGT TTA TC	444
420	GLA-G171D-3'	GTC ACA GTA ACA ATC ATC AAA TTT TAG	GLA-I359T-5'	CCGGCAGGAGACTGGTGGACCTC	445
421	GLA-G171R-5'	CTAAAATTTGAT CGT TGTTACTGTGAC	GLA-I359T-3'	GAGGTCCACCAGTCTCCTGCCGG	446

AMENDED

Fig. 6 (Cont.)

447	GLA-Q171R-3'	GTC ACA GTA ACA ACG ATC AAA TTT TAG	GLA-G360S-5'	CAGGAGATTAGTGGACCTCGC	472
448	GLA-C172Y/F-5'	CTAAAATTTGATGGT TWT tactgtgacagT	GLA-G360S-3'	GCGAGGTCCACTAATCTCCTG	473
449	GLA-C172Y/F-3'	ACT GTC ACA GTA AWA ACC ATC AAA TTT TAG	GLA-G361R-5'	GGAGATTGGTAGACCTCGCTC	474
450	GLA-C172W-5'	CTAAAATTTGATGGT TGG tactgtgacagT	GLA-G361R-3'	GAGCGAGGTCTACCAATCTCC	475
451	GLA-C172W-3'	ACT GTC ACA GTA CCA ACC ATC AAA TTT TAG	GLA-P362L-5'	GATTGGTGGACTTCGCTCTTATAC	476
452	GLA-C172R-5'	CTAAAATTTGATGGT CGT tactgtgacagT	GLA-P362L-3'	GTATAAGAGCGAAGTCCACCAATC	477
453	GLA-C172R-3'	ACT GTC ACA GTA ACG ACC ATC AAA TTT TAG	GLA-R363H-5'	GGTGGACCTCACTCTTATAC	478
454	GLA-C172G-5'	CTAAAATTTGATGGT GGT tactgtgacagT	GLA-R363H-3'	GTATAAGAGTGAGGTCCACC	479
455	GLA-C172G-3'	ACT GTC ACA GTA ACC ACC ATC AAA TTT TAG	GLA-R363C-5'	GGTGGACCTTGCTCTTATAC	480
456	GLA-G183D-5'	TTGGCAGATG A TTATAAGCAC	GLA-R363C-3'	GTATAAGAGCAAGGTCCACC	481
457	GLA-G183D-3'	GTG CTT ATA ATC ATC TGC CAA	GLA-G373R-5'	TGCTTCCCTG CGT AAAGGAGTGG	482
458	GLA-G183S-5'	TTGGCAGAT A GTTATAAGCAC	GLA-G373R-3'	CCA CTC CTT TAC GCA GGG AAG CA	483
459	GLA-G183S-3'	GTG CTT ATA ACT ATC TGC CAA	GLA-A377D-5'	GTAAAGGAGTGGACTGTAATCCTG	484
460	GLA-M187T-5'	GTTATAAGCACA C GTCCTTGGCCCT	GLA-A377D-3'	CAGGATTACAGTCCACTCCTTTAC	485
461	GLA-M187T-3'	AGG GCC AAG GAC GTG TGC TTA TAA C	GLA-C378Y-5'	AAAGGAGTGGCCTATAATCCTGCC	486
462	GLA-M187V-5'	GTTATAAGCAC G TGTCCTTGGCC	GLA-C378Y-3'	GGCAGGATTATAGGCCACTCCTTT	487
463	GLA-M187V-3'	GGC CAA GGA CAC GTG CTT ATA AC	GLA-C378R-5'	AAAGGAGTGGCCCGTAATCCTGCC	488
464	GLA-L191Q-5'	GTCCTTGGCCCAGAATAGGACTG	GLA-C378R-3'	GGCAGGATTACGGGCCACTCCTTT	489
465	GLA-L191Q-3'	CAG TCC TAT TCT GGG CCA AGG AC	GLA-C382Y-5'	GTAATCCTGCCTACTTCATCACAC	490
466	GLA-L191P-5'	GTCCTTGGCCC C GAATAGGACTG	GLA-C382Y-3'	GTGTGATGAAGTAGGCAGGATTAC	491
467	GLA-L191P-3'	CAG TCC TAT TCG GGG CCA AGG AC	GLA-I384N-5	CTGCCTGCTTC AsC ACACAGCTCCTC	492
468	GLA-T194I-5'	CTGAATAGGATTGGCAGAAGC	GLA-I384N-3	GAG GAG CTG TGT GTT GAA GCA GGC AG	493
469	GLA-T194I-3'	GCT TCT GCC AAT CCT ATT CAG	GLA-T385P-5'	CCTGCTTCATCCCACAGCTCCTCC	494
470	GLA-V199M-5'	CAGAAGCATTATGTACTCCTG	GLA-T385P-3'	GGAGGAGCTGTGGGATGAAGCAGG	495
471	GLA-V199M-3'	CAG GAG TAC ATA ATG CTT CTG	GLA-Q386P-5'	CTTCATCACA CCG CTCCTCCCTGT	496

AMENDED

Fig. 6 (Cont.)

497	GLA-S201F-5'	CATTGTGTACTTCTGTGAGTGG	GLA-Q386P-3'	ACA GGG AGG AGC GGT GTG ATG AAG	520
498	GLA-S201F-3'	CCACTCACAGAAGTACACAATG	GLA-P389R-5'	CACAGCTCCTC CGT GTGAAAAGGAAGCT	521
499	GLA-S201Y-5'	CATTGTGTACTACTGTGAGTGGC	GLA-P389R-3'	AGC TTC CTT TTC ACA CGG AGG AGC TGT G	522
500	GLA-S201Y-3'	GCC ACT CAC AGT AGT ACA CAA TG	GLA-F396Y-5'	GGAAGCTAGGGTACTATGAATGG	523
501	GLA-C202Y-5'	GTG TAC TCC TAT GAG TGG CCT C	GLA-F396Y-3'	CCATTCATAGTACCCTAGCTTCC	524
502	GLA-C202Y-3'	GAG GCC ACT CAT AGG AGT ACA C	GLA-P398K-5'	AGGGTTCTATAAATGGACTTCA	525
503	GLA-C202W-5'	GTGTACTCCTGG GAGTGGCCTCT	GLA-P398K-3'	TGAAGTCCATTTATAGAACCCT	526
504	GLA-C202W-3'	AGA GGC CAC TCC CAG GAG TAC AC	GLA-L403S-5'	GACTTCAAGGTCAAGAAGTCAC	527
505	GLA-P205T-5'	CTGTGAGTGGACTCTTTATATG	GLA-L403S-3'	GTGACTTCTTGACCTTGAAGTC	528
506	GLA-P205T-3'	CATATAAAGAGTCCACTCACAG	GLA-I407K-5'	GAAGTCACAAAAATCCCACAG	529
507	GLA-P205R/L-5'	CTGTGAGTGG CKT CTTTATATG	GLA-I407K-3'	CTGTGGGATTTTTGTGACTTC	530
508	GLA-P205R/L-3'	CAT ATA AAG AMG CCA CTC ACAG	GLA-P409T/A/S-5'	GTCACATAAATDCCACAGGCACTG	531
509	GLA-Y207S-5'	TGGCCTCTT TCT ATGTGGCCC	GLA-P409T/A/S-3'	CAGTGCCTGTGGHATTTATGTGAC	532
510	GLA-Y207S-3'	GGG CCA CAT AGA AAG AGG CCA	GLA-T410K-5'	CACATAAATCCCAAAGGCACTG	533
511	GLA-Y207C-5'	AGTGCCCTCTT TgT ATGTGGCCCTT	GLA-T410K-3'	CAGTGCCTTTGGGATTTATGTG	534
512	GLA-Y207C-3'	AAG GGC CAC ATA CAA AGA GGC CAC T	GLA-T410A-5'	CACATAAATCCCCCAGGCACTG	535
513	GLA-Y216D-5	CCTTTCAAAAGCCCAAT gAT ACAGAAATCCGACAG	GLA-T410A-3'	CAGTGCCTGCGGGATTTATGTG	536
514	GLA-Y216D-3	CTG TCG GAT TTC TGT ATC ATT GGG CTT TTG AAA GG	GLA-G411D-5'	ATCCCACAGACACTGTTTTGC	537
515	GLA-I219N-5'	CAATTATACAGAA AAC CGACAGTACTGC	GLA-G411D-3'	GCAAAACAGTGTCTGTGGGAT	538
516	GLA-I219N-3'	GCA GTA CTG TCG GTT TTC TGT ATA ATT G	GLA-L414S-5'	GGCACTGTTTCGCTTCAGCTAG	539
517	GLA-C223R/G-5'	CGACAGTAC SGC AATCACTGG	GLA-L414S-3'	CTAGCTGAAGCGAAACAGTGCC	540
518	GLA-C223R/G-3'	CCA GTG ATT GCS GTA CTG TCG	GLA-del20-24aa-5'	GCGCTTCGCTTCCTGGACATCCCTGGG GC	541
519	GLA-C223Y-5'	CGACAGTACTAC AATCACTGG	GLA-del20-24aa-3'	GCCCCAGGGATGTCCAGGAAGCGAAG CGC	542

AMENDED

Fig. 6 (Cont.)

543	GLA-C223Y-3'	CCA GTG ATT GTA GTA CTG TCG	GLA-del113-8aa-5'	GCAGACCCTCAGCGCCAGCTAGCTAATTATG	555
544	GLA-N224S-5'	CAGTACTGCAGTCACTGGCGA	GLA-del113-8aa-3'	CATAATTAGCTAGCTGGCGCTGAGGGTCTGC	556
545	GLA-N224S-3'	TCG CCA GTG ACT GCA GTA CTG	GLA-del153aa-5'	GTTTTGGATACTACATTGATGCCCAG	557
546	GLA-N224D-5'	CAGTACTGCGATCACTGGC	GLA-del153aa-3'	CTGGGCATCAATGTAGTATCCAAAAC	558
547	GLA-N224D-3'	GCC AGT GAT CGC AGT ACT G	GLA-del205-7aa-5'	CTCCTGTGAGTGGATGTGGCCCTT	559
548	GLA-H225R-5'	actgcaat cgc tggcgaaat	GLA-del205-7aa-3'	AAGGGCCACATCCACTCACAGGAG	560
549	GLA-H225R-3'	ATT TCG CCA GCG ATT GCA GTA	GLA-del254aa-5'	CAGGAGAGAATTGATGTTGCTGG	561
550	GLA-W226R-5'	gcaatcac cgg cgaaat	GLA-del254aa-3'	CCAGCAACATCAATTCTCTCCTG	562
551	GLA-W226R-3'	ATT TCG CCG GTG ATT GC	GLA-del358aa-5'	GATAAACCGGCAGATTGGTGGACCT	563
552	GLA-W226C-5'	gcaatcactgtgcaatttgc	GLA-del358aa-3'	AGGTCCACCAATCTGCCGGTTTATC	564
553	GLA-W226C-3'	GCA AAA TTT CGA CAG TGA TTG C	GLA-Ins247-8aa-5'	GACTGGACATCTTGGACATCTTTTAACCAGGAGAG	565
554	GLA-R227Q-5'	GCAATCACTGGCAAAATTTTGCTGAC	GLA-Ins247-8aa-3'	CTCTCCTGGTTAAAAGATGTCCAAGATGTCCAGTC	566

S=G+C; W=A+T; H=A+C+T; D=T+G+A; M=A+C; K=T+G; R=A+G; Y=T+C;

AMENDED

Fig. 7

SEQ ID No. 2

GAATTCTCCGGTCACCGTGACAATGCAGCTGAGGAACCCAGAACTACATCTGGGC
TGCGCGCTTGCGCTTCGCTTCCTGGCCCTCGTTTCCTGGGACATCCCTGGGGCTAG
AGCACTGGACAATGGATTGGCAAGGACGCCTACCATGGGCTGGCTGCACTGGGA
GCGCTTCATGTGCAACCTTGACTGCCAGGAAGAGCCAGATTCCTGCATCAGTGAG
AAGCTCTTCATGGAGATGGCAGAGCTCATGGTCTCAGAAGGCTGGAAGGATGCA
GGTTATGAGTACCTCTGCATTGATGACTGTTGGATGGCTCCCCAAAGAGATTCAG
AAGGCAGACTTCAGGCAGACCCTCAGCGCTTTCCTCATGGGATTCGCCAGCTAGC
TAATTATGTTCACAGCAAAGGACTGAAGCTAGGGATTTATGCAGATGTTGGAAAT
AAAACCTGCGCAGGCTTCCCTGGGAGTTTTGGATACTACGACATTGATGCCCAGA
CCTTTGCTGACTGGGGAGTAGATCTGCTAAAATTTGATGGTTGTTACTGTGACAG
TTTGGAAAATTTGGCAGATGGTTATAAGCACATGTCCTTGGCCCTGAATAGGACT
GGCAGAAGCATTGTGTACTCCTGTGAGTGGCCTCTTTATATGTGGCCCTTTCAAA
AGCCCAATTATACAGAAATCCGACAGTACTGCAATCACTGGCGAAATTTTGCTGA
CATTGATGATTCCTGGAAAAGTATAAAGAGTATCTTGGACTGGACATCTTTTAAC
CAGGAGAGAATTGTTGATGTTGCTGGACCAGGGGGTTGGAATGACCCAGATATG
TTAGTGATTGGCAACTTTGGCCTCAGCTGGAATCAGCAAGTAACTCAGATGGCCC
TCTGGGCTATCATGGCTGCTCCTTTATTCATGTCTAATGACCTCCGACACATCAGC
CCTCAAGCCAAAGCTCTCCTTCAGGATAAGGACGTAATTGCCATCAATCAGGACC
CCTTGGGCAAGCAAGGGTACCAGCTTAGACAGGGAGACAACTTTGAAGTGTGGG
AACGACCTCTCTCAGGCTTAGCCTGGGCTGTAGCTATGATAAACCGGCAGGAGAT
TGGTGGACCTCGCTCTTATACCATCGCAGTTGCTTCCCTGGGTAAAGGAGTGGCC
TGTAATCCTGCCTGCTTCATCACACAGCTCCTCCCTGTGAAAAGGAAGCTAGGGT
TCTATGAATGGACTTCAAGGTTAAGAAGTCACATAAATCCCACAGGCACTGTTTT
GCTTCAGCTAGAAAATACAATGCAGATGTCATTAAAAGACTTACTTTAA

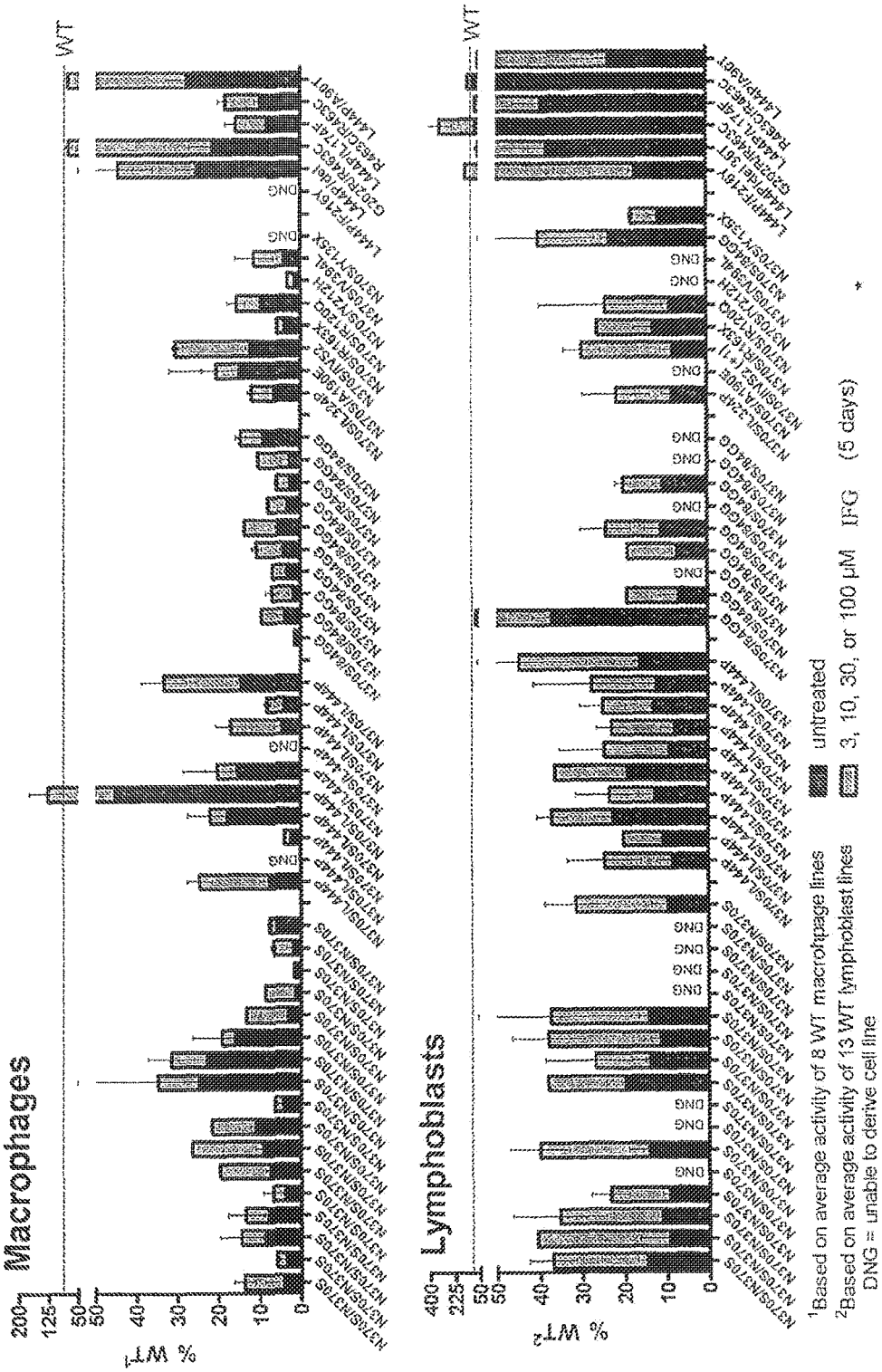

Macrophages
% WT¹
WT
Lymphoblasts
% WT²
untreated
3, 10, 30, or 100 μM IFG (5 days)
¹Based on average activity of 8 WT macrophage lines
²Based on average activity of 13 WT lymphoblast lines
DNG = unable to derive cell line

Fig. 8

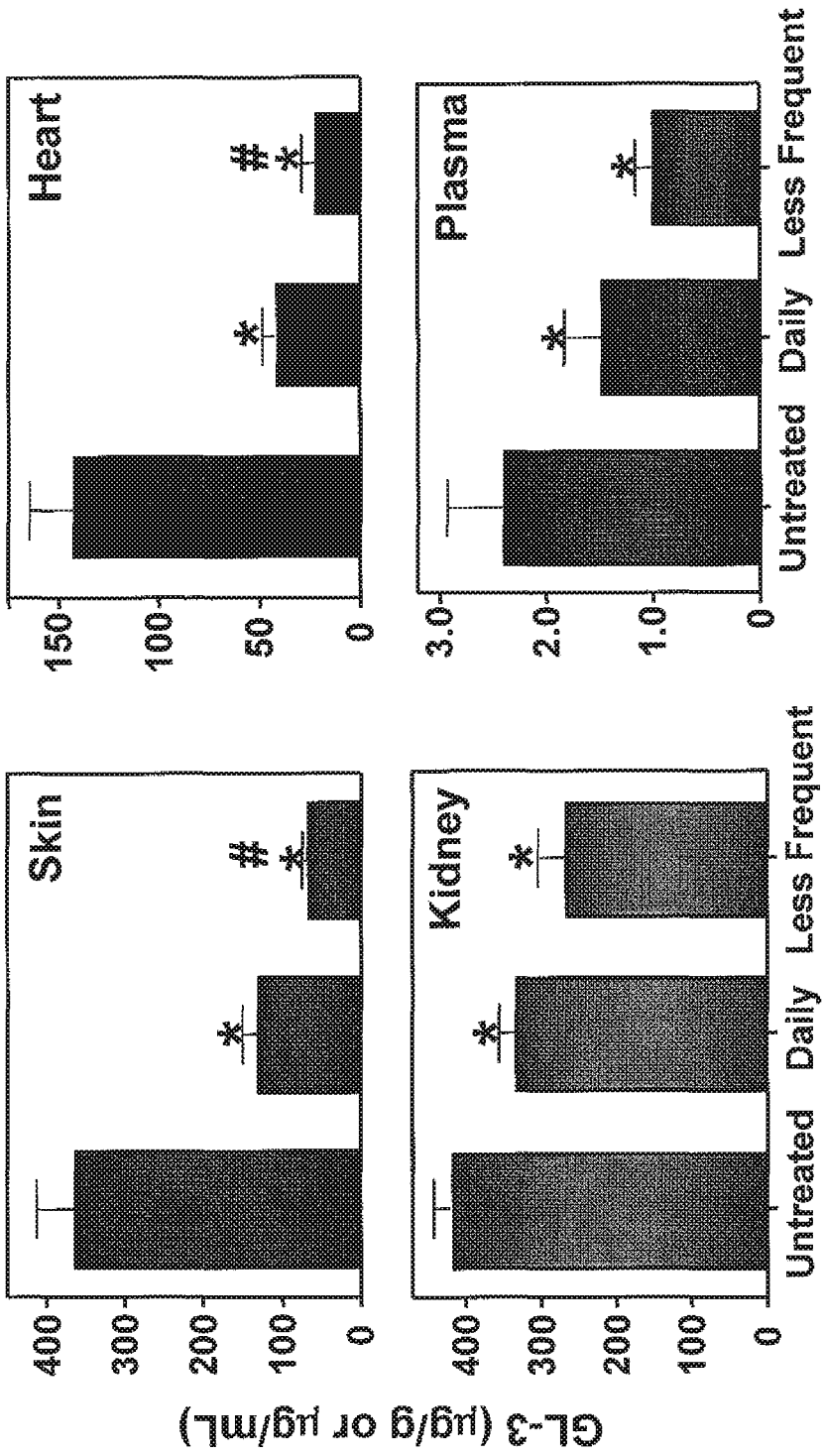

Heart
Plasma
Skin
Kidney
GL-3 (μg/g or μg/mL)
0
50
100
150
1.0
2.0
3.0
200
300
400
*
#
Untreated
Daily
Less Frequent

Fig. 9

Fig. 10

Responsive GAA missense

		% wild-type GAA activity	
GAA mutation	n	No DNJ	With 100nM DNJ
E262K	3	0.5 ± 0.3	1.8 ± 0.6
P266S	3	14.2 ± 0.3	22.4 ± 1.0
P285R	3	2.2 ± 0.4	4.8 ± 0.8
P285S	3	7.0 ± 0.9	11.8 ± 0.9
L291F	2	3.4 ± 0.9	4.4 ± 0.2
L291H	3	4.3 ± 0.7	6.0 ± 0.8
L291P	3	3.0 ± 0.5	6.8 ± 1.5
M318K	3	3.2 ± 0.9	11.2 ± 2.6
G377R	6	0.3 ± 0.1	0.7 ± 0.1
A445P	6	1.0 ± 0.2	1.9 ± 0.3
Y455C	1	3.1	8.6
Y455F	3	4.6 ± 0.5	11.0 ± 2.2
P457L	4	6.4 ± 0.8	13.5 ± 1.7
G483R	2	1.7 ± 0.6	8.6 ± 0.9
G483V	2	0.8 ± 0.3	6.5 ± 1.9
M519V	4	3.1 ± 0.3	5.1 ± 0.1
S529V	4	6.4 ± 0.7	14.6 ± 0.4
P545L	20	3.0 ± 0.2	13.0 ± 0.9
G549R	3	7.5 ± 1.1	13.5 ± 1.9
L552P	3	2.5 ± 0.8	9.6 ± 1.2
Y575S	7	0.4 ± 0.1	3.2 ± 0.4
E579K	7	3.8 ± 0.3	13.4 ± 1.1
A610V	3	0.5 ± 0.0	2.7 ± 0.3
H612Q	3	0.2 ± 0.1	0.9 ± 0.4
A644P	2	0.8 ± 0.1	2.1 ± 0.3
ΔN470	4	1.4 ± 0.2	3.8 ± 0.4

AMENDED

FIG. 11A

SEQ ID No. 3

Nucleic acid sequence of human lysosomal alpha-glucosidase (GAA) (GenBank Accession No.: Y00839).

cagttgggaa agctgaggtt gtcgccgggg ccgcgggtgg aggtcgggga tgaggcagca 60
ggtaggacag tgacctcggt gacgcgaagg acccccggcca cctctaggtt ctcctgtcc 120
gcccgttgtt cagcgaggga ggctctgggc ctgccgcagc tgacgggggaa actgaggcac 180
ggagcgggcc tgtaggagct gtccaggcca tctccaacca tgggagtgag gcacccgccc 240
tgctcccacc ggctcctggc cgtctgcgcc ctcgtgtcct tggcaacccgc tgcactcctg 300
gggcacatcc tactccatga tttcctgctg gttccccgag agctgagtgg ctcctccccca 360
gtcctggagg agactcaccc agctcaccag cagggagcca gcagaccagg gccccgggat 420
gcccaggcac acccccggccg tcccagagca gtgcccacac agtgcgacgt cccccccaac 480
agccgctteg attgcgcccc tgacaaggcc atcacccagg aacagtgcga ggcccgcggc 540
tgctgctaca tccctgcaaa gcaggggctg cagggagccc agatggggca gccctggtgc 600
ttctttccac ccagctaccc cagctacaag ctggagaacc tgagctcctc tgaaatgggc 660
tacacggcca ccctgacccg taccacccccc acattcttcc ccaaggacat cctgaccctg 720
cggctggacg tgatgatgga gactgagaac cgcctccact tcacgatcaa agatccagct 780
aacaggcgct acgaggtgcc cttggagacc ccgcgtgtcc acagccgggc accgtcccca 840
ctctacagcg tggagttctc cgaggagccc ttcggggtga tcgtgcaccg gcagctggac 900
ggccgcgtgc tgctgaacac gacggtggcg ccccctgttct ttgcggacca gttcctcag 960
ctgtccacct cgctgccctc gcagtatatc acaggcctcg ccgagcacct cagtcccctg 1020
atgctcagca ccagctggac caggatcacc ctgtggaacc gggaccttgc gcccacgccc 1080
ggtgcgaacc tctacgggtc tcaccctttc tacctggcgc tggaggacgg cgggtcggca 1140
cacggggtgt tcctgctaaa cagcaatgcc atggatgtgg tcctgcagcc gagccctgcc 1200
cttagctgga ggtcgacagg tgggatcctg gatgtctaca tcttcctggg ccccagagccc 1260
aagagcgtgg tgcagcagta cctggacgtt gtgggatacc cgttcatgcc gccatactgg 1320
ggcctgggct tccacctgtg ccgctggggc tactcctcca ccgctatcac ccgccaggtg 1380
gtggagaaca tgaccaggge ccacttcccc ctggacgtcc aatggaacga cctggactac 1440
atggactccc ggagggactt cacgttcaac aaggatggct tccgggactt cccggccatg 1500
gtgcaggagc tgcaccaggg cggccggcgc tacatgatga tcgtggatcc tgccatcagc 1560
agctcgggcc ctgccgggag ctacaggccc tacgacgagg gtctgcggag ggggggtttc 1620
atcaccaacg agaccggcca gccgctgatt gggaaggtat ggccccgggtc cactgccttc 1680
ccgacttca ccaaccccac agccctggcc tggtgggagg acatggtggc tgagttccat 1740
gaccaggtgc ccttcgacgg catgtggatt gacatgaacg agccttccaa cttcatcaga 1800
ggctctgagg acggctgccc caacaatgag ctggagaacc cacctacgt gcctgggggtg 1860
gttgggggga ccctccaggc ggccaccatc tgtgcctcca gccaccagtt tctctccaca 1920
cactacaacc tgcacaacct ctacggcctg acgaagccca tcgcctccca cagggcgctg 1980
gtgaaggctc gggggacacg ccccatttgtg atctccgct cgaccttttgc tggccacggc 2040
cgatacgccg gccactggac gggggacgtg tggagctcct gggagcagct cgcctcctcc 2100
gtgccagaaa tcctgcagtt taacctgctg ggggtgcctc tggtcgggggc cgacgtctgc 2160

AMENDED

FIG. 11B

SEQ ID No. 3 (cont.)

ggcttcctgg gcaacaccctc agaggagctg tgtgtgcgct ggacccagct gggggccttc 2220
tacccccttca tgcggaacca caacagcctg ctcagtctgc cccaggagcc gtacagcttc 2280
agcgagccgg cccagcaggc catgaggaag gccctcaccc tgcgctacgc actcctcccc 2340
cacctctaca cactgttcca ccaggcccac gtcgcggggg agaccgtggc ccggccccctc 2400
ttcctggagt tccccaagga ctctagcacc tggactgtgg accaccagct cctgtggggg 2460
gaggccctgc tcatcacccc agtgctccag gccgggaagg ccgaagtgac tggctacttc 2520
cccttgggca catggtacga cctgcagacg gtgccaatag aggccctlgg cagcctcccca 2580
ccccacctg cagctccccg tgagccagcc atccacagcg aggggcagtg ggtgacgctg 2640
ccggcccccc tggacaccat caacgtccac ctccgggctg ggtacatcat ccccctgcag 2700
ggccctggcc tcacaaccac agagtccccgc cagcagccca tggccctggc tgtggccctg 2760
accaagggtg gagaggcccg aggggagctg ttctgggacg atggagagag cctggaagtg 2820
ctggagcgag gggcctacac acaggtcatc ttcctggcca ggaataacac gatcgtgaat 2880
gagctggtac gtgtgaccag tgagggagct ggcctgcagc tgcagaaggt gactgtcctg 2940
ggcgtggcca cggcgccccca gcaggtcctc tccaacggtg tccctgtctc caacttcacc 3000
tacagccccg acaccaaggt cctggacatc tgtgtctcgc tgttgatggg agagcagttt 3060
ctcgtcagct ggtgttagcc gggcggagtg tgttagtctc tccagaggga ggctggttcc 3120
ccagggaagc agagcctgtg tgcgggcagc agctgtgtgc gggcctgggg gttgcatgtg 3180
tcacctggag ctgggcacta accattccaa gccgccgcat cgcttgtttc cacctcctgg 3240
gccggggctc tggccccccaa cgtgtctagg agagctttct ccctagatcg cactgtgggc 3300
cggggcctgg agggctgctc tgtgttaata agattgtaag gtttgccctc ctcaccigtt 3360
gccggcatgc gggtagtatt agccaccccc ctccatctgt tcccagcacc ggagaagggg 3420
gtgctcaggt ggaggtgtgg ggtatgcacc tgagctcctg cttcgcgcct gctgctctgc 3480
cccaacgcga ccgcttcccg gctgcccaga gggctggatg cctgccggtc ccgagcaag 3540
cctgggaact caggaaaatt cacaggactt gggagattct aaatcttaag tgcaattatt 3600
ttaataaaag gggcatttgg aatc 3624

Fig. 12.

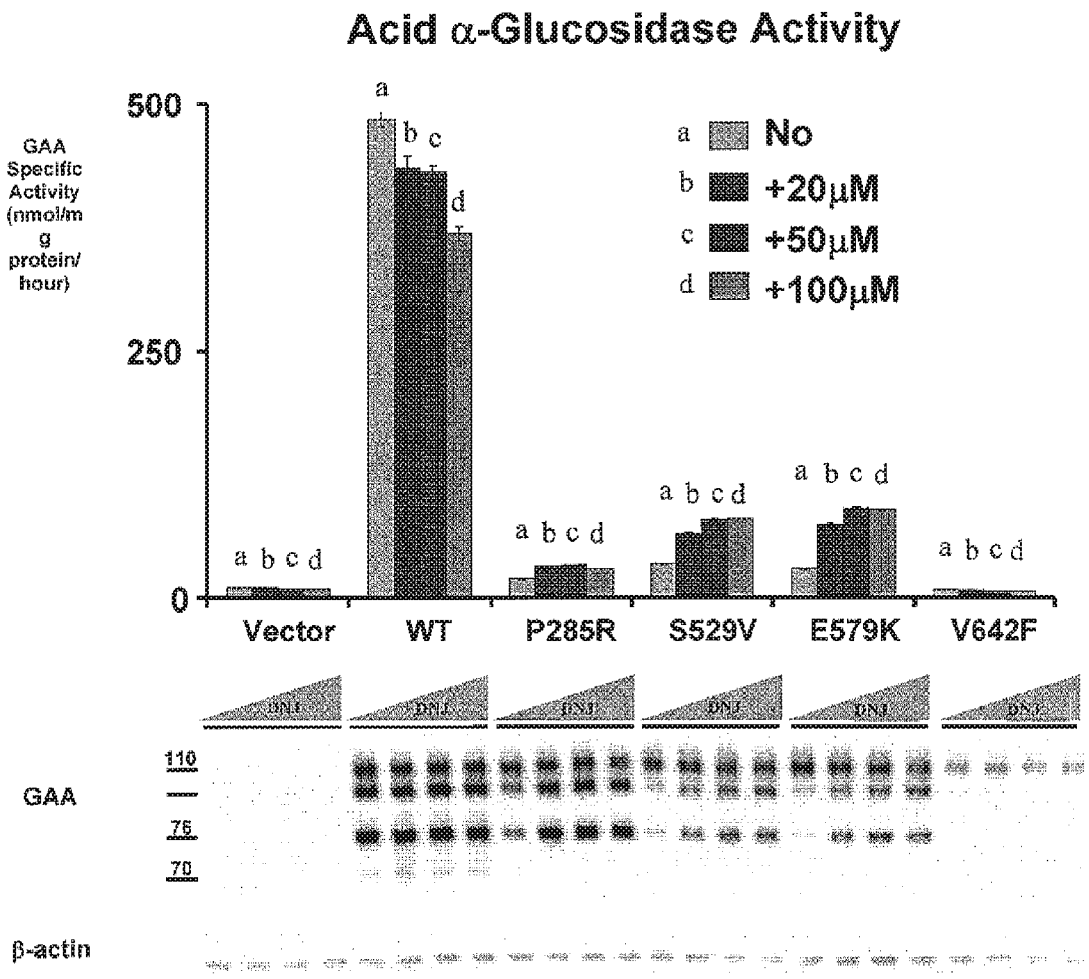

Acid α-Glucosidase Activity
GAA Specific Activity (nmol/mg protein/hour)
500
250
0
a
b c
d
a No
b +20μM
c +50μM
d +100μM
a b c d
Vector
WT
P285R
S529V
E579K
V642F
GAA
110
76
70
β-actin

Fig. 13

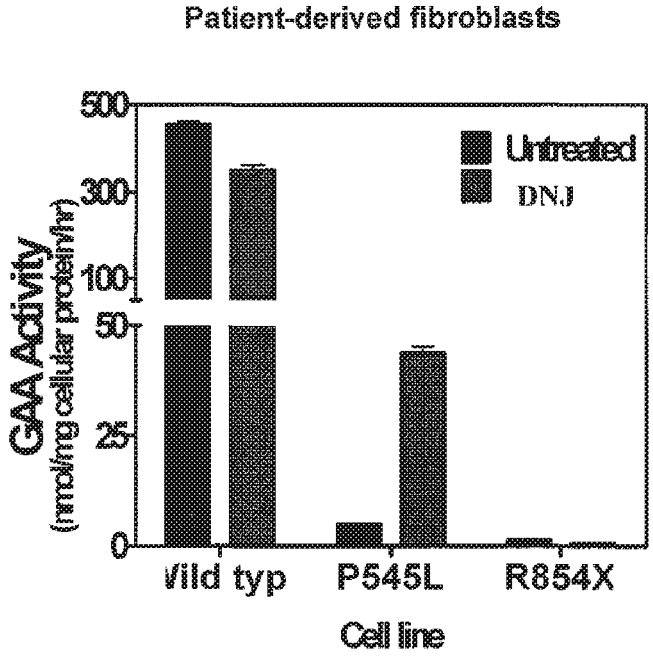

Patient-derived fibroblasts
GAA Activity
(nmol/mg cellular protein/hr)
500
300
100
50
25
0
Untreated
DNJ
Wild typ
P545L
R854X
Cell line

Fig. 14

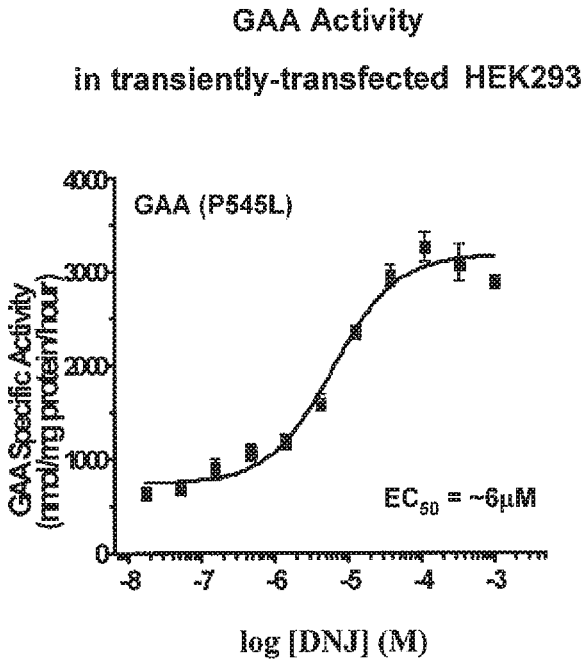
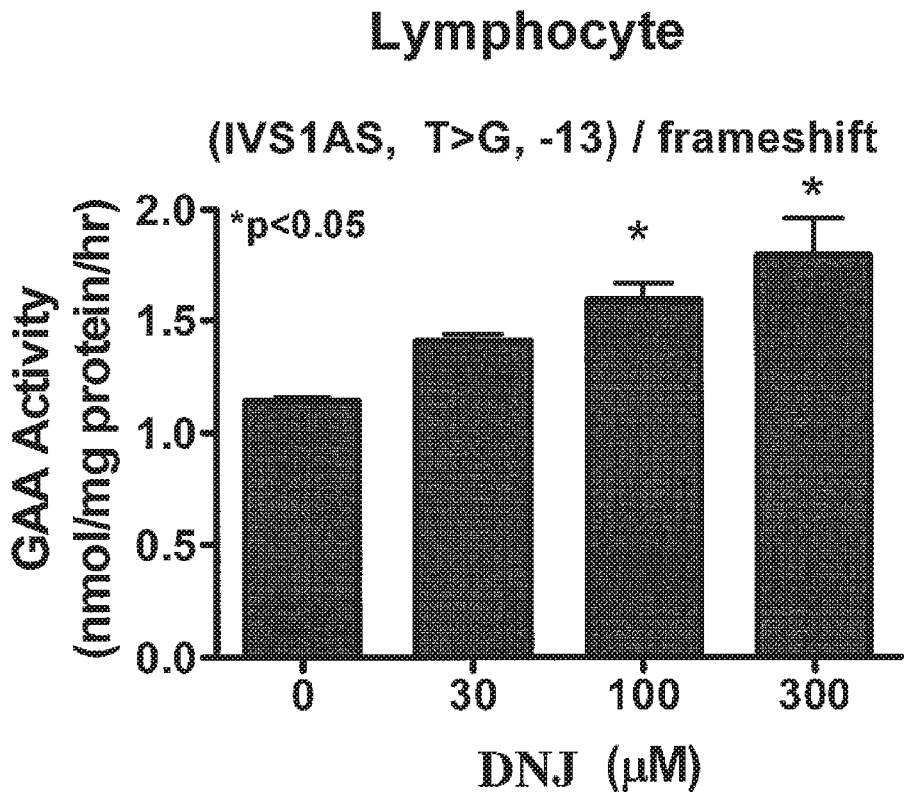

GAA Activity
in transiently-transfected HEK293
GAA (P545L)
GAA Specific Activity (nmol/mg protein/hour)
4000
3000
2000
1000
0
EC50 = ~6μM
-8
-7
-6
-5
-4
-3
log [DNJ] (M)

Fig. 15


Lymphocyte
(IVS1AS, T>G, -13) / frameshift
GAA Activity
(nmol/mg protein/hr)
*p<0.05
2.0
1.5
1.0
0.5
0.0
*
*
0
30
100
300
DNJ (μM)

AMENDED

FIG. 16A

SEQ ID No. 4

Amino acid sequence encoded by a human lysosomal alpha-glucosidase nucleic acid (GAA) (GenBank Accession No.: Y00839).

```
Met Gly Val Arg His Pro Pro Cys Ser His Arg Leu Leu Ala Val Cys
1               5                  10                  15
Ala Leu Val Ser Leu Ala Thr Ala Ala Leu Leu Gly His Ile Leu Leu
            20                  25                  30
His Asp Phe Leu Leu Val Pro Arg Glu Leu Ser Gly Ser Ser Pro Val
        35                  40                  45
Leu Glu Glu Thr His Pro Ala His Gln Gln Gly Ala Ser Arg Pro Gly
    50                  55                  60
Pro Arg Asp Ala Gln Ala His Pro Gly Arg Pro Arg Ala Val Pro Thr
65                  70                  75                  80
Gln Cys Asp Val Pro Pro Asn Ser Arg Phe Asp Cys Ala Pro Asp Lys
                85                  90                  95
Ala Ile Thr Gln Glu Gln Cys Glu Ala Arg Gly Cys Cys Tyr Ile Pro
            100                 105                 110
Ala Lys Gln Gly Leu Gln Gly Ala Gln Met Gly Gln Pro Trp Cys Phe
        115                 120                 125
Phe Pro Pro Ser Tyr Pro Ser Tyr Lys Leu Glu Asn Leu Ser Ser Ser
    130                 135                 140
Glu Met Gly Tyr Thr Ala Thr Leu Thr Arg Thr Thr Pro Thr Phe Phe
145                 150                 155                 160
Pro Lys Asp Ile Leu Thr Leu Arg Leu Asp Val Met Met Glu Thr Glu
                165                 170                 175
Asn Arg Leu His Phe Thr Ile Lys Asp Pro Ala Asn Arg Arg Tyr Glu
            180                 185                 190
Val Pro Leu Glu Thr Pro Arg Val His Ser Arg Ala Pro Ser Pro Leu
        195                 200                 205
Tyr Ser Val Glu Phe Ser Glu Glu Pro Phe Gly Val Ile Val His Arg
    210                 215                 220
Gln Leu Asp Gly Arg Val Leu Leu Asn Thr Thr Val Ala Pro Leu Phe
225                 230                 235                 240
Phe Ala Asp Gln Phe Leu Gln Leu Ser Thr Ser Leu Pro Ser Gln Tyr
                245                 250                 255
Ile Thr Gly Leu Ala Glu His Leu Ser Pro Leu Met Leu Ser Thr Ser
            260                 265                 270
Trp Thr Arg Ile Thr Leu Trp Asn Arg Asp Leu Ala Pro Thr Pro Gly
        275                 280                 285
Ala Asn Leu Tyr Gly Ser His Pro Phe Tyr Leu Ala Leu Glu Asp Gly
    290                 295                 300
Gly Ser Ala His Gly Val Phe Leu Leu Asn Ser Asn Ala Met Asp Val
305                 310                 315                 320
Val Leu Gln Pro Ser Pro Ala Leu Ser Trp Arg Ser Thr Gly Gly Ile
                325                 330                 335
Leu Asp Val Tyr Ile Phe Leu Gly Pro Glu Pro Lys Ser Val Val Gln
            340                 345                 350
Gln Tyr Leu Asp Val Val Gly Tyr Pro Phe Met Pro Pro Tyr Trp Gly
        355                 360                 365
```

AMENDED

FIG. 16B

SEQ ID No. 4 (cont.)

Leu Gly Phe His Leu Cys Arg Trp Gly Tyr Ser Ser Thr Ala Ile Thr
370 375 380
Arg Gln Val Val Glu Asn Met Thr Arg Ala His Phe Pro Leu Asp Val
385 390 395 400
Gln Trp Asn Asp Leu Asp Tyr Met Asp Ser Arg Arg Asp Phe Thr Phe
405 410 415
Asn Lys Asp Gly Phe Arg Asp Phe Pro Ala Met Val Gln Glu Leu His
420 425 430
Gln Gly Gly Arg Arg Tyr Met Met Ile Val Asp Pro Ala Ile Ser Ser
435 440 445
Ser Gly Pro Ala Gly Ser Tyr Arg Pro Tyr Asp Glu Gly Leu Arg Arg
450 455 460
Gly Val Phe Ile Thr Asn Glu Thr Gly Gln Pro Leu Ile Gly Lys Val
465 470 475 480
Trp Pro Gly Ser Thr Ala Phe Pro Asp Phe Thr Asn Pro Thr Ala Leu
485 490 495
Ala Trp Trp Glu Asp Met Val Ala Glu Phe His Asp Gln Val Pro Phe
500 505 510
Asp Gly Met Trp Ile Asp Met Asn Glu Pro Ser Asn Phe Ile Arg Gly
515 520 525
Ser Glu Asp Gly Cys Pro Asn Asn Glu Leu Glu Asn Pro Pro Tyr Val
530 535 540
Pro Gly Val Val Gly Gly Thr Leu Gln Ala Ala Thr Ile Cys Ala Ser
545 550 555 560
Ser His Gln Phe Leu Ser Thr His Tyr Asn Leu His Asn Leu Tyr Gly
565 570 575
Leu Thr Glu Ala Ile Ala Ser His Arg Ala Leu Val Lys Ala Arg Gly
580 585 590
Thr Arg Pro Phe Val Ile Ser Arg Ser Thr Phe Ala Gly His Gly Arg
595 600 605
Tyr Ala Gly His Trp Thr Gly Asp Val Trp Ser Ser Trp Glu Gln Leu
610 615 620
Ala Ser Ser Val Pro Glu Ile Leu Gln Phe Asn Leu Leu Gly Val Pro
625 630 635 640
Leu Val Gly Ala Asp Val Cys Gly Phe Leu Gly Asn Thr Ser Glu Glu
645 650 655
Leu Cys Val Arg Trp Thr Gln Leu Gly Ala Phe Tyr Pro Phe Met Arg
660 665 670
Asn His Asn Ser Leu Leu Ser Leu Pro Gln Glu Pro Tyr Ser Phe Ser
675 680 685
Glu Pro Ala Gln Gln Ala Met Arg Lys Ala Leu Thr Leu Arg Tyr Ala
690 695 700
Leu Leu Pro His Leu Tyr Thr Leu Phe His Gln Ala His Val Ala Gly
705 710 715 720
Glu Thr Val Ala Arg Pro Leu Phe Leu Glu Phe Pro Lys Asp Ser Ser
725 730 735
Thr Trp Thr Val Asp His Gln Leu Leu Trp Gly Glu Ala Leu Leu Ile
740 745 750
Thr Pro Val Leu Gln Ala Gly Lys Ala Glu Val Thr Gly Tyr Phe Pro
755 760 765
Leu Gly Thr Trp Tyr Asp Leu Gln Thr Val Pro Ile Glu Ala Leu Gly
770 775 780
Ser Leu Pro Pro Pro Pro Ala Ala Pro Arg Glu Pro Ala Ile His Ser
785 790 795 800
Glu Gly Gln Trp Val Thr Leu Pro Ala Pro Leu Asp Thr Ile Asn Val

AMENDED

FIG. 16C

SEQ ID No. 4 (cont.)

```
                    805                 810                 815
His Leu Arg Ala Gly Tyr Ile Ile Pro Leu Gln Gly Pro Gly Leu Thr
            820                 825                 830
Thr Thr Glu Ser Arg Gln Gln Pro Met Ala Leu Ala Val Ala Leu Thr
        835                 840                 845
Lys Gly Gly Glu Ala Arg Gly Glu Leu Phe Trp Asp Asp Gly Glu Ser
    850                 855                 860
Leu Glu Val Leu Glu Arg Gly Ala Tyr Thr Gln Val Ile Phe Leu Ala
865                 870                 875                 880
Arg Asn Asn Thr Ile Val Asn Glu Leu Val Arg Val Thr Ser Glu Gly
                885                 890                 895
Ala Gly Leu Gln Leu Gln Lys Val Thr Val Leu Gly Val Ala Thr Ala
            900                 905                 910
Pro Gln Gln Val Leu Ser Asn Gly Val Pro Val Ser Asn Phe Thr Tyr
        915                 920                 925
Ser Pro Asp Thr Lys Val Leu Asp Ile Cys Val Ser Leu Leu Met Gly
    930                 935                 940
Glu Gln Phe Leu Val Ser Trp Cys
945                 950
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METHOD TO PREDICT RESPONSE TO PHARMACOLOGICAL CHAPERONE TREATMENT OF DISEASES

CROSS-REFERENCE TO RELATED APPLICATION

The present application is a continuation of International Application No. PCT/US09/033963, filed Feb. 12, 2009 and claims the benefit of U.S. Provisional Application No. 61/028,141, filed Feb. 12, 2008, U.S. Provisional Application No. 61/035,684, filed Mar. 11, 2008, U.S. Provisional Application No. 61/093,631, filed Sep. 2, 2008, and U.S. Provisional Application No. 61/113,496, filed Nov. 11, 2008, Each of these applications are hereby incorporated by reference in their entireties.

FIELD OF THE INVENTION

The present invention provides methods to determine whether a patient with a lysosomal storage disorder will benefit from treatment with a specific pharmacological chaperone. The present invention also provides an in vitro method for determining enzyme (e.g., α-galactosidase A, α-glucosidase or glucocerebrosidase) responsiveness to a pharmacological chaperone (e.g., 1-deoxygalactonojirimycin, 1-deoxynojirimycin or isofagomine) in a cell line expressing a mutant form of the enzyme. The invention also provides a method for diagnosing a lysosomal storage disorder (e.g., Fabry disease, Pompe disease or Gaucher disease) in patients suspected of having a lysosomal storage disorder, and implementing the proper treatment based on the diagnosis (e.g., choosing a particular therapeutic agent to administer to the patient).

BACKGROUND

In the human body, proteins are involved in almost every aspect of cellular function. Proteins are linear strings of amino acids that fold and twist into specific three-dimensional shapes in order to function properly. Certain human diseases result from mutations that cause changes in the amino acid sequence of a protein which reduce its stability and may prevent it from folding properly. The majority of genetic mutations that lead to the production of less stable or misfolded proteins are called missense mutations. These mutations result in the substitution of a single amino acid for another in the protein. Because of this error, missense mutations often result in proteins that have a reduced level of biological activity. In addition to missense mutations, there are also other types of mutations that can result in proteins with reduced biological activity.

Proteins generally fold in a specific region of the cell known as the endoplasmic reticulum, or ER. The cell has quality control mechanisms that ensure that proteins are folded into their correct three-dimensional shape before they can move from the ER to the appropriate destination in the cell, a process generally referred to as protein trafficking. Misfolded proteins are often eliminated by the quality

control mechanisms after initially being retained in the ER. In certain instances, misfolded proteins can accumulate in the ER before being eliminated.

The retention of misfolded proteins in the ER interrupts their proper trafficking, and the resulting reduced biological activity can lead to impaired cellular function and ultimately to disease. In addition, the accumulation of misfolded proteins in the ER may lead to various types of stress on cells, which may also contribute to cellular dysfunction and disease.

Lysosomal storage diseases (LSDs) are characterized by deficiencies of lysosomal enzymes due to mutations in the genes encoding the lysosomal enzymes. This results in the pathologic accumulation of substrates of those enzymes, which include lipids, carbohydrates, and polysaccharides. There are about fifty known LSDs to date, which include Gaucher disease, Fabry disease, Pompe disease, Tay Sachs disease and the mucopolysaccharidoses (MPS). Most LSDs are inherited as an autosomal recessive trait, although males with Fabry disease and MPS II are hemizygotes because the disease genes are encoded on the X chromosome. For most LSDs, there is no available treatment beyond symptomatic management. For several LSDs, including Gaucher, Fabry, Pompe, and MPS I and VI, enzyme replacement therapy (ERT) using recombinant enzymes is available. For Gaucher disease, substrate reduction therapy (SRT) also is available in limited situations. SRT employs a small molecule inhibitor of an enzyme required for the synthesis of glucosylceramide (the GD substrate). The goal of SRT is to reduce production of the substrate and reduce pathologic accumulation.

Although there are many different mutant genotypes associated with each LSD, some of the mutations, including some of the most prevalent mutations, are missense mutations which can lead to the production of a less stable enzyme. These less stable enzymes are sometimes prematurely degraded by the ER-associated degradation pathway. This results in the enzyme deficiency in the lysosome, and the pathologic accumulation of substrate. Such mutant enzymes are sometimes referred to in the pertinent art as "folding mutants" or "conformational mutants."

Diagnosis of Fabry Disease

Because Fabry disease is rare, involves multiple organs, has a wide age range of onset, and is heterogeneous, proper diagnosis is a challenge. Awareness is low among health care professionals and misdiagnoses are frequent. Some examples of diagnoses seriously considered in patients who were eventually diagnosed with Fabry's disease include: mitral valve prolapse, glomerulonephritis, idiopathic proteinuria, systemic lupus erythematosus, Whipple's disease, acute abdomen, ulcerative colitis, acute intermittent porphyrias, and occult malignancies. Thus, even for classically affected males, diagnosis typically takes from about 5-7 years or even longer. This is a concern because the longer a person has Fabry disease, the more damage is likely to occur in the affected organs and tissues and the more serious the person's condition may become. Diagnosis of Fabry disease is most often confirmed on the basis of decreased α-Gal A activity in plasma or peripheral leukocytes (WBCs) once a patient is symptomatic, coupled with mutational analysis. In females, diagnosis is even more challenging since the enzymatic identification of carrier females is less reliable due to random X-chromosomal inactivation in some cells of carriers. For example, some obligate carriers (daughters of classically affected males) have α-Gal A enzyme activities

ranging from normal to very low activities. Since carriers can have normal α-Gal A enzyme activity in leukocytes, only the identification of an α-Gal A mutation by genetic testing provides precise carrier identification and/or diagnosis.

Treatment of Fabry Disease

One approved therapy for treating Fabry disease diseases is enzyme replacement therapy, which typically involves intravenous, infusion of a purified form of the corresponding wild-type protein (Fabrazyme®, Genzyme Corp.). One of the main complications with protein replacement therapy is attainment and maintenance of therapeutically effective amounts of protein in vivo due to rapid degradation of the infused protein. The current approach to overcome this problem is to perform numerous costly high dose infusions.

Protein replacement therapy has several additional caveats, such as difficulties with large-scale generation, purification, and storage of properly folded protein; obtaining glycosylated native protein; generation of an anti-protein immune response; and inability of protein to cross the blood-brain barrier to mitigate central nervous system pathologies (i.e., low bioavailability). In addition, replacement enzyme cannot penetrate the heart or kidney in sufficient amounts to reduce substrate accumulation in the renal podocytes or cardiac myocytes, which figure prominently in Fabry pathology.

Gene therapy using recombinant vectors containing nucleic acid sequences that encode a functional protein, or using genetically modified human cells that express a functional protein, is also being developed to treat protein deficiencies and other disorders that benefit from protein replacement.

A third, relatively recent approach to treating some enzyme deficiencies involves the use of small molecule inhibitors to reduce production of the natural substrate of deficient enzyme proteins, thereby ameliorating the pathology. This "substrate reduction" approach has been specifically described for a class of about 40 related enzyme disorders called lysosomal storage disorders that include glycosphingolipid storage disorders. The small molecule inhibitors proposed for use as therapy are specific for inhibiting the enzymes involved in synthesis of glycolipids, reducing the amount of cellular glycolipid that needs to be broken down by the deficient enzyme.

It has previously been shown that the binding of small molecule inhibitors of enzymes associated with LSDs can increase the stability of both mutant enzyme and the corresponding wild-type enzyme (see U.S. Pat. Nos. 6,274,597; 6,583,158; 6,589,964; 6,599,919; 6,916,829, and 7,141,582 all incorporated herein by reference). In particular, it was discovered that administration of small molecule derivatives of glucose and galactose, which are specific, selective competitive inhibitors for several target lysosomal enzymes, effectively increased the stability of the enzymes in cells in vitro and, thus, increased trafficking of the enzymes to the lysosome. Thus, by increasing the amount of enzyme in the lysosome, hydrolysis of the enzyme substrates is expected to increase. The original theory behind this strategy was as follows: since the mutant enzyme protein is unstable in the ER (Ishii et al., Biochem. Biophys. Res. Comm. 1996; 220: 812-815), the enzyme protein is retarded in the normal transport pathway (ER→Golgi apparatus→endosomes→lysosome) and prematurely degraded. Therefore, a compound which binds to and increases the stability of a mutant enzyme, may serve as a "chaperone" for the enzyme and increase the amount that can exit the ER and move to the lysosomes. In addition, because the folding and trafficking of some wild-type proteins is incomplete, with up to 70% of some wild-type proteins being degraded in some instances prior to reaching their final cellular location, the chaperones can be used to stabilize wild-type enzymes and increase the amount of enzyme which can exit the ER and be trafficked to lysosomes. This strategy has been shown to increase several lysosomal enzymes in vitro and in vivo, including β-glucocerebrosidase and α-glucosidase, deficiencies of which are associated with Gaucher and Pompe disease, respectively.

However, as indicated above, successful candidates for SPC therapy should have a mutation which results in the production of an enzyme that has the potential to be stabilized and folded into a conformation that permits trafficking out of the ER. Mutations which severely truncate the enzyme, such as nonsense mutations, or mutations in the catalytic domain which prevent binding of the chaperone, will not be as likely to be "rescuable" or "enhanceable" using SPC therapy, i.e., to respond to SPC therapy. While missense mutations outside the catalytic site are more likely to be rescuable using SPCs, there is no guarantee, necessitating screening for responsive mutations. This means that, even when Fabry disease is diagnosed by detecting deficient α-Gal A activity in WBCs, it is very difficult, if not impossible, to predict whether a particular Fabry patient will respond to treatment with an SPC without benefit of the present invention. Moreover, since WBCs only survive for a short period of time in culture (in vitro), screening for SPC enhancement of α-Gal A is difficult and not optimal for the patient.

In order to apply SPC therapy effectively, a broadly applicable, fast and efficient method for screening patients for responsiveness to SPC therapy needs to be adopted prior to initiation of treatment. Treatment can then be implemented based on the results of the screening Thus, there remains in the art a need for relatively non-invasive methods to rapidly assess enzyme enhancement with potential therapies prior to making treatment decisions, for both cost and emotional benefits to the patient.

SUMMARY OF THE INVENTION

One embodiment of the present invention provides a method for determining whether a patient will be a candidate for SPC therapy. Specifically, the present invention provides an in vitro assay to evaluate protein activity in the presence or absence of an SPC, wherein an SPC that increases the activity of the protein in the in vitro assay is an SPC that can be used for SPC therapy. In one embodiment, the in vitro assay comprises expressing a mutant protein in a host cell, contacting the mutant protein with a candidate SPC, and determining if the mutant protein contacted with the SPC exhibits an increased level of activity (preferably a statistically significant increase) when compared to a mutant protein expressed in a host cell that is not contacted with the candidate SPC. When a candidate SPC increases the activity of a mutant protein according to the assay of the invention, such a candidate SPC can be used for SPC therapy to treat a patient expressing the same mutant protein tested in the in vitro assay.

In one embodiment, the protein is an enzyme. In another embodiment, the protein is a lysosomal enzyme. In yet another embodiment, the protein is α-galactosidase A (α-GAL; α-GAL A). In other embodiments, the protein is alpha-glucosidase (Acid α-glucosidase ; α-glucosidase;

GAA). In other embodiments, the protein is glucocerebrosidase (β-glucosidase; Gba; GCase).

The present invention also includes the basis for evaluation of SPC as a treatment option for any number of other protein abnormalities and/or enzyme deficiencies and/or a protein folding disorders.

The present invention further provides a written record (e.g., a "treatment reference table") listing protein mutations and the responsiveness of each of the mutations to SPC therapy. Such a list can be used in determining treatment options for a patient, whereby the patient, or the patient's physician or doctor, can select the proper therapeutic approach, for example, an SPC for treatment by identifying the patient's protein mutation, and cross-referencing the mutation with the list to identify whether an SPC will increase the activity of the patients particular mutant enzyme.

In another embodiment, the "treatment reference table" lists mutations for a lysosomal enzyme, and the treatment reference table is employed to determine the best therapeutic approach to treat a lysosomal storage disorder. In a further embodiment of the invention, the protein is α-Gal A, and the disease is Fabry disease. In other embodiments of the invention, the protein is GAA, and the disease is Pompe disease, In other embodiments of the invention, the protein is Gba, and the disease is Gaucher disease.

In one embodiment, the treatment reference table describes mutant forms of enzyme, such as a lysomal enzyme (e.g., α-Gal A, Gcase, and GAA) and treatment options are ascertained for lysosomal storage disorders (e.g., Fabry, Gacher and Pompe Disease).

In one embodiment, the invention also provides for methods of creating a treatment reference table, wherein the treatment reference table can be for any protein folding disorder or disorder treatable with an SPC. This class of disease includes the other lysosomal storage disorders, Cystic Fibrosis (CFTR) (respiratory or sweat gland epithelial cells), familial hypercholesterolemia (LDL receptor; LPL-adipocytes or vascular endothelial cells), cancer (p53; PTEN-tumor cells), and amyloidoses (transthyretin) among others.

In another embodiment, the present invention provides for methods of treating a patient diagnosed as expressing certain mutant proteins (e.g., lysosomal enzymes such as α-GAL A), wherein activity of the mutant protein (e.g., α-Gal A), when expressed in a host cell, can be increased upon administration of an SPC for that protein (for example, 1-deoxygalactonojirimycin, DGJ, as an SPC for mutant α-GAL A).

The present invention also provides for diagnostic kits containing the components required to perform the assay.

BRIEF DESCRIPTION OF THE DRAWINGS

FIG. **1**A-C. Shows a listing of Fabry mutations generated by site-directed mutagenesis. The text indicates whether HEK-293 cells expressing each of the listed mutations responds to DGJ treatment in the transient transfection assay: italics=not yet tested; bold and underscored=no response to DGJ; plain text (not italicized, bold, or underscored)=response to DGJ.

FIG. **2**A-C Shows the responsiveness of different α-Gal A mutations to DGJ treatment. The magnitude of increase in α-Gal A activity levels after DGJ treatment and EC50 values are listed for every tested mutation in FIG. **1**A-D that responded to DGJ treatment. The increase in enzyme activity is shown as a percentage of wild type α-Gal A activity.

FIG. **3** Shows representative examples of wild type and mutant α-Gal A responses to DGJ treatment. α-Gal A activity (expressed as nmol/mg protein/hr of 4-MU released) was measured in lysates prepared from transfected HEK 293 cells incubated with increasing concentrations of DGJ. A typical concentration-dependent response is shown for L300P and a typical negative response to DGJ is shown for R227Q. Wild type exhibits high baseline activity and thus does not respond to DGJ in this assay.

FIG. **4** Shows that the mutation response in HEK 293 cells are comparable to patient-derived T-cells, lymphoblasts or white blood cells in vivo. α-Gal A levels measured in three different assays, reported as percentage of wild type, are compared for each mutation examined. α-Gal A levels were measured in T-Cells, lymphoblasts, white blood cells and HEK 293 cells expressing mutant α-Gal A before and after exposure to DGJ. Blank bars indicate basal level (without DGJ treatment) and filled bars indicate the elevated level after DGJ treatment.

FIG. **5** Shows that DGJ-responsive α-Gal A mutations are widely distributed on the α-Gal A protein sequence. Tested Fabry mutations are illustrated on the α-Gal A secondary structure. No significant correlation between response and location on the protein sequence of a mutation was observed, suggesting that responsive as well as non-responsive mutations are distributed widely across the entire protein. Text color indicates DGJ response: green=response; red=no response; brown indicates that of the multiple mutations on that same site some responded to DGJ treatment, while others did not.

FIG. **6** Shows the oligonucleotide primer pairs used to generate the point mutations in the α-Gal A gene through site-directed mutagenesis.

FIG. **7** Shows the α-Gal A cDNA sequence that was mutated through the site-directed mutagenesis.

FIG. **8** Shows the effect of isofagomine tartrate on patient-derived macrophages and lymphoblasts isolated from Gaucher disease patients with different mutations in their glucocerebrosidase (Gba; GCase) enzyme.

FIG. **9** Shows the effect on GL-3 levels of eight-week old male hR301Q α-Gal A Tg/KO mice which were treated for 4 weeks with 300 mg/kg DGJ in drinking water either daily or less frequently (4 days ON/3 days OFF).

FIG. **10** Shows a listing of Pompe mutations generated by site-directed mutagenesis. The text indicates whether COS-7 cells expressing each of the listed mutations responds to DNJ treatment in the transient transfection assay.

FIG. **11**A-B Shows the nucleic acid sequence of human lysosomal alpha-glucosidase (GAA) (GenBank Accession No.: Y00839).

FIG. **12** Shows the responsiveness of four different GAA mutations to DNJ treatment at concentrations of 0 μM, 20 μM, 50 μM and 100 μM. The increase in enzyme activity is shown as specific activity (nmol/mg protein/hour). FIG. **12** also shows that DNJ promoted processing of GAA to the 95/76/70 kDa forms.

FIG. **13** Shows the responsiveness of Pompe patient-derived fibroblasts to DNJ treatment. The fibroblasts were homozygous for either the P545L or R854X GAA mutation.

FIG. **14** Shows the EC_{50} for DNJ induced GAA activity in HEK-293 cells transiently transfected with the P545L GAA mutation.

FIG. **15** Shows the responsiveness of Pompe patient-derived lymphocytes to DNJ treatment. The lymphocyes were heterozygous for the (IVSIAS, T>G, −13) GAA splicing defect and a GAA frameshift mutation.

FIG. **16**A-C Shows the amino acid sequence encoded by a human lysosomal alpha-glucosidase (GAA) nucleic acid (GenBank Accession No.: Y00839).

DETAILED DESCRIPTION

The present invention provides an in vitro assay to provide accurate determination of whether an SPC enhances activity of a mutant protein.

In one embodiment, the protein is a lysosomal enzyme, wherein the lysosomal enzyme, when mutated, causes a lysosomal storage disorder. The concepts of the present invention, however, can be globally applied to any disease or condition characterized by mutant proteins amenable to SPC-therapy, in which the proteins have one or more specific mutations that can be generated in vitro, for example, by site-directed mutagenesis.

In one specific embodiment, the invention provides methods for determining whether an SPC enhances enzyme activity of a mutant α-Gal A enzyme, and can therefore be utilized as an effective therapeutic treatment for a Fabry disease patient expressing the same α-Gal A mutation.

In another specific embodiment, the invention provides methods for determining whether an SPC enhances enzyme activity of a mutant GAA enzyme, and can therefore be utilized as an effective therapeutic treatment for a Pompe disease patient expressing the same GAA mutation.

In another specific embodiment, the invention provides methods for determining whether an SPC enhances enzyme activity of a mutant Gba enzyme, and can therefore be utilized as an effective therapeutic treatment for a Gaucher disease patient expressing the same Gba mutation.

According to the methods of the present invention, assays are provided that allow for the determination of whether a patient expressing a mutant lysosomal enzyme will be a candidate for SPC therapy. The new in vitro assay is extremely sensitive and can be performed on a host cell transfected with a nucleic acid construct encoding a mutant lysosomal enzyme. Specific candidate SPCs can then be assayed to determine if the candidate SPC is capable of increasing the activity of the mutant enzyme expressed by the host cell. Thus, unlike assays which utilize cells derived from a patient with a lysosomal storage disorder, the assay of the invention avoids time consuming steps such as collection of a sample from a patient, purification of cells from the sample, and culturing the cells from the sample in vitro.

The present invention also provides for a method of determining whether a patient expressing a mutant protein (e.g. a lysosomal enzyme) will be a candidate for SPC therapy, wherein a person, for example, a patient's physician or doctor, can look up the mutant protein (e.g. a lysosomal enzyme mutation) in a treatment reference table to determine if the patient's mutation will respond to SPC therapy. The reference table is generated from the results of in vitro analysis of SPC response in a cell line that has been transformed with a nucleic acid vector which encodes the mutant protein.

Furthermore, the invention also provides a "Treatment Reference Table" that provides information describing if a particular SPC will be a successful therapy for enhancing the activity of a specific lysosomal enzyme mutation. According to the present invention, the treatment reference table provides information indicating if a candidate SPC can increase the activity of a mutant lysosomal enzyme expressed by a host cell. Based on the response of different mutations to different SPC therapies, the present invention can provide SPC therapy tailored to the patient's specific mutation.

In one non-limiting embodiment, the mutant protein is a mutant lysosomal enzyme, such as, for example, a mutant α-Gal A, GAA or Gba, and the cell line is transfected with a nucleic acid vector which encodes the mutant lysosomal enzyme.

In another non-limiting embodiment, the present invention provides a method of treating a Fabry patient that includes the step of administering to the Fabry patient a therapeutically effective dose of 1-deoxygalactonojirimycin (DGJ), wherein the patient expresses a mutant α-Gal A, the activity of which, when expressed in a host cell, can be increased when contacted with an SPC (e.g. DGJ). Such α-Gal A mutations treatable according to this method include, but are not limited to A121T, A156V, A20P, A288D, A288P, A292P A348P, A73V, C52R, C94Y, D234E, D244H, D244N, D264Y, E338K, E341D, E358K, E398K, E48K, E59K, E66Q, F113L, G144V, G183D, G260A, G271S, G325D, G328A, G35R, G373D, G373S, H225R, I219N, I242N, I270T, I289F, I303N, I317T, I354K, I91T, L14P, L166V, L243F, L300F, L310F, L32P, L45R, M267I, M284T, M296I, M296V, M72V, M76R, N224S, N263S, N298K, N298S, N320I, N320Y, N34K, P205R, P259L, P265L, P265R, P293A, P293S, P409S, P40L, P40S, Q279E, Q279H, Q279R, Q280H, Q280K, Q312H, Q321E, Q321R, Q327E, R301P, R342Q, R363C, R363H, R49G, R49L, R49S, S201Y, S276N, S297C, S345P, T194I, V269M, V316E, W340R, W47L, and W95S mutations.

In one embodiment, the following α-Gal A mutations are excluded from the methods of treating a Fabry patient with a therapeutically effective dose of DGJ: D244N, E358K, E59K, E66Q, G183D, G325D, I289F, I91T, L45R, M296V, N263S, N320Y, P205R, P40S, Q279E, R342Q, R363C, R49L, V316E.

One advantage of the assay described by the present invention is its applicability to female patients with an X-linked lysosomal storage disorder, such as Fabry disease. Because of X-chromosome inactivation, a sample taken from a female patient will comprise both normal healthy cells and enzyme deficient mutant cells. An assay for an SPC's effect on such a sample will show an enhancement in enzyme activity due to the normal wild type enzyme expression of the healthy cells even though the diseased cells with the mutant enzyme may not be responsive to the SPC. The present invention overcomes this obstacle because a cell line transfected with a vector encoding a mutant protein will only express the mutant form of the protein, and thus, there will be no wild type protein expressed by the cell line to cause such pseudo enhancement observed in assays with patient derived cells.

In another non-limiting embodiment, the present invention provides a method of treating a Pompe patient that includes the step of administering to the Pompe patient a therapeutically effective dose of 1-deoxynojirimycin (DNJ), wherein the patient expresses a mutant GAA, the activity of which, when expressed in a host cell, can be increased when contacted with an SPC (e.g. DNJ). Such GAA mutations treatable according to this method include, but are not limited to, E262K, P266S, P285R, P285S, L291F, L291H, L291P, M318K, G377R, A445P, Y455C, Y455F, P457L, G483R, G483V, M519V, S529V, P545L, G549R, L552P, Y575S, E579K, A610V, H612Q, A644P, and ΔN470 mutations.

In another non-limiting embodiment, the present invention provides a method of treating a Gaucher patient with a therapeutically effective dose of isofagomine (IFG), wherein

the patient expresses a mutant Gba, the activity of which, when expressed in a host cell, can be increased when contacted with an SPC (e.g. IFG).

Definitions

The terms used in this specification generally have their ordinary meanings in the art, within the context of this invention and in the specific context where each term is used. Certain terms are discussed below, or elsewhere in the specification, to provide additional guidance to the practitioner in describing the compositions and methods of the invention and how to make and use them.

The term "Fabry disease" refers to an X-linked inborn error of glycosphingolipid catabolism due to deficient lysosomal α-galactosidase A activity. This defect causes accumulation of globotriaosylceramide (ceramide trihexoside) and related glycosphingolipids in vascular endothelial lysosomes of the heart, kidneys, skin, and other tissues.

The term "atypical Fabry disease" refers to patients with primarily cardiac manifestations of the α-Gal A deficiency, namely progressive globotriaosylceramide (GL-3) accumulation in myocardial cells that leads to significant enlargement of the heart, particularly the left ventricle.

A "carrier" is a female who has one X chromosome with a defective α-Gal A gene and one X chromosome with the normal gene and in whom X chromosome inactivation of the normal allele is present in one or more cell types. A carrier is often diagnosed with Fabry disease.

"Pompe disease" refers to an autosomal recessive LSD characterized by deficient acid alpha glucosidase (GAA) activity which impairs lysosomal glycogen metabolism. The enzyme deficiency leads to lysosomal glycogen accumulation and results in progressive skeletal muscle weakness, reduced cardiac function, respiratory insufficiency, and/or CNS impairment at late stages of disease. Genetic mutations in the GAA gene result in either lower expression or produce mutant forms of the enzyme with altered stability, and/or biological activity ultimately leading to disease. (see generally Hirschhorn R, 1995, Glycogen Storage Disease Type II: Acid α-Glucosidase (Acid Maltase) Deficiency, The Metabolic and Molecular Bases of Inherited Disease, Scriver et al., eds., McGraw-Hill, New York, 7th ed., pages 2443-2464). The three recognized clinical forms of Pompe disease (infantile, juvenile and adult) are correlated with the level of residual α-glucosidase activity (Reuser A J et al., 1995, Glycogenosis Type II (Acid Maltase Deficiency), Muscle & Nerve Supplement 3, S61-S69). ASSC (also referred to elsewhere as "pharmacological chaperones") represent a promising new therapeutic approach for the treatment of genetic diseases, such as lysosomal storage disorders (e.g. Pompe Disease).

Infantile Pompe disease (type I or A) is most common and most severe, characterized by failure to thrive, generalized hypotonia, cardiac hypertrophy, and cardiorespiratory failure within the second year of life. Juvenile Pompe disease (type II or B) is intermediate in severity and is characterized by a predominance of muscular symptoms without cardiomegaly. Juvenile Pompe individuals usually die before reaching 20 years of age due to respiratory failure. Adult Pompe disease (type III or C) often presents as a slowly progressive myopathy in the teenage years or as late as the sixth decade (Felice K J et al., 1995, Clinical Variability in Adult-Onset Acid Maltase Deficiency: Report of Affected Sibs and Review of the Literature, Medicine 74, 131-135).

In Pompe, it has been shown that α-glucosidase is extensively modified post-translationally by glycosylation, phosphorylation, and proteolytic processing.

Conversion of the 110 kilodalton (kDa) precursor to 76 and 70 kDa mature forms by proteolysis in the lysosome is required for optimum glycogen catalysis.

As used herein, the term "Pompe Disease" refers to all types of Pompe Disease. The formulations and dosing regimens disclosed in this application may be used to treat, for example, Type I, Type II or Type III Pompe Disease.

The term "Gaucher disease" refers to a deficiency of the lysosomal enzyme β-glucocerebrosidase (Gba) that breaks down fatty glucocerebrosides. The fat then accumulates, mostly in the liver, spleen and bone marrow. Gaucher disease can result in pain, fatigue, jaundice, bone damage, anemia and even death. There are three clinical phenotypes of Gaucher disease. Patients with, Type 1 manifest either early in life or in young adulthood, bruise easily and experience fatigue due to anemia, low blood platelets, enlargement of the liver and spleen, weakening of the skeleton, and in some instances have lung and kidney impairment. There are no signs of brain involvement. In Type II, early-onset, liver and spleen enlargement occurs by 3 months of age and there is extensive brain involvement. There is a high mortality rate by age 2. Type III is characterized by liver and spleen enlargement and brain seizures. The β-glucocerebrosidase gene is located on the human 1q21 chromosome. Its protein precursor contains 536 amino acids and its mature protein is 497 amino acids long.

A "patient" refers to a subject who has been diagnosed with or is suspected of having a particular disease. The patient may be human or animal.

A "Fabry disease patient" refers to an individual who has been diagnosed with or suspected of having Fabry disease and has a mutated α-Gal A as defined further below. Characteristic markers of Fabry disease can occur in male hemizygotes and female carriers with the same prevalence, although females typically are less severely affected.

A "Pompe disease patient" refers to an individual who has been diagnosed with or suspected of having Pompe disease and has a mutated GAA as defined further below.

A "Gaucher disease patient" refers to an individual who has been diagnosed with or suspected of having Gaucher disease and has a mutated Gba as defined further below.

Human α-galactosidase A (α-Gal A) refers to an enzyme encoded by the human GLA gene. The human α-Gal A enzyme consists of 429 amino acids and is in GenBank Accession No. U78027.

In one non-limiting embodiment, human lysosomal alpha-glucosidase (Acid α-glucosidase; GAA) is a lysosomal enzyme which hydrolyzes alpha-1,4- and alpha-1,6-linked-D-glucose polymers present in glycogen, maltose, and isomaltose. Alternative names are as follows: glucoamylase; 1,4-α-D-glucan glucohydrolase; amyloglucosidase; gamma-amylase; and exo-1,4-α-glucosidase. The human GAA gene has been mapped to chromosome 17q25.2-25.3 and has nucleotide and amino acid sequences depicted in GenBank Accession No. Y00839.

The term "human Gba gene" refers to the gene encoding acid β-glucosidase, also referred to as glucocerebrosidase or Gba. The Gba gene is on chromosome 1q21 and involves 11 exons (GenBank Accession No. J03059). There is also a homologous pseudogene for Gba located about 16 kb downstream of the Gba gene (GenBank Accession No. M16328).

The "human Gba" protein refers to the wild-type human Gba protein. The Gba protein consists of 536 amino acids and is in GenBank Accession No. J03059.

The term "mutant protein" includes a protein which has a mutation in the gene encoding the protein which results in the inability of the protein to achieve a stable conformation under the conditions normally present in the ER. The failure to achieve a stable conformation results in a substantial amount of the enzyme being degraded, rather than being transported to the lysosome. Such a mutation is sometimes called a "conformational mutant." Such mutations include, but are not limited to, missense mutations, and in-frame small deletions and insertions.

As used herein in one embodiment, the term "mutant α-Gal A" includes an α-Gal A which has a mutation in the gene encoding α-Gal A which results in the inability of the enzyme to achieve a stable conformation under the conditions normally present in the ER. The failure to achieve a stable conformation results in a substantial amount of the enzyme being degraded, rather than being transported to the lysosome.

Non-limiting, exemplary α-Gal A mutations associated with Fabry disease which result in unstable α-Gal A include L32P; N34S; T41I; M51K; E59K; E66Q; I91T; A97V; R100K; R112C; R112H; F113L; T141L; A143T; G144V; S148N; A156V; L166V; D170V; C172Y; G183D; P205T; Y207C; Y207S; N215S; A228P; S235C; D244N; P259R; N263S; N264A; G272S; S276G; Q279E; Q279K; Q279H; M284T; W287C; I289F; M296I; M296V; L300P; R301Q; V316E; N320Y; G325D; G328A; R342Q; E358A; E358K; R363C; R363H; G370S; and P409A.

As used herein in one embodiment, the term "mutant GAA" includes a GAA which has a mutation in the gene encoding GAA which results in the inability of the enzyme to achieve a stable conformation under the conditions normally present in the ER. The failure to achieve a stable conformation results in a substantial amount of the enzyme being degraded, rather than being transported to the lysosome.

As used herein in one embodiment, the term "mutant Gba" includes a Gba which has a mutation in the gene encoding Gba which results in the inability of the enzyme to achieve a stable conformation under the conditions normally present in the ER. The failure to achieve a stable conformation results in a substantial amount of the enzyme being degraded, rather than being transported to the lysosome.

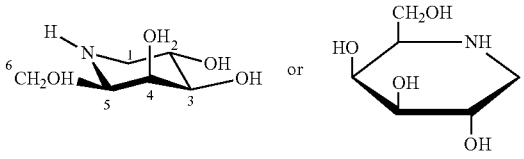
As used herein, the term "specific pharmacological chaperone" ("SPC") or "pharmacological chaperone" refers to any molecule including a small molecule, protein, peptide, nucleic acid, carbohydrate, etc. that specifically binds to a protein and has one or more of the following effects: (i) enhances the formation of a stable molecular conformation of the protein; (ii) induces trafficking of the protein from the ER to another cellular location, preferably a native cellular location, i.e., prevents ER-associated degradation of the protein; (iii) prevents aggregation of misfolded proteins; and/or (iv) restores or enhances at least partial wild-type function and/or activity to the protein. A compound that specifically binds to e.g., α-Gal A, GAA or Gba, means that it binds to and exerts a chaperone effect on the enzyme and not a generic group of related or unrelated enzymes. More specifically, this term does not refer to endogenous chaperones, such as BiP, or to non-specific agents which have demonstrated non-specific chaperone activity against various proteins, such as glycerol, DMSO or deuterated water, i.e., chemical chaperones (see Welch et al., Cell Stress and Chaperones 1996; 1(2):109-115; Welch et al., Journal of Bioenergetics and Biomembranes 1997; 29(5):491-502; U.S. Pat. Nos. 5,900,360; 6,270,954; and 6,541,195). In the present invention, the SPC may be a reversible competitive inhibitor.

A "competitive inhibitor" of an enzyme can refer to a compound which structurally resembles the chemical structure and molecular geometry of the enzyme substrate to bind the enzyme in approximately the same location as the substrate.

Thus, the inhibitor competes for the same active site as the substrate molecule, thus increasing the Km. Competitive inhibition is usually reversible if sufficient substrate molecules are available to displace the inhibitor, i.e., competitive inhibitors can bind reversibly. Therefore, the amount of enzyme inhibition depends upon the inhibitor concentration, substrate concentration, and the relative affinities of the inhibitor and substrate for the active site.

Following is a description of some specific pharmacological chaperones (SPCs) contemplated by this invention:

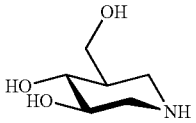
In one particular non-limiting embodiment, the SPC is 1-deoxygalactonorjirimycin which refers to a compound having the following structures:



or a pharmaceutically acceptable salt, ester or prodrug of 1-deoxygalactonorjirimycin. The hydrochloride salt of DGJ is known as migalastat hydrochloride (Migalastat).

Still other SPCs for α-Gal A are described in U.S. Pat. Nos. 6,274,597, 6,774,135, and 6,599,919 to Fan et al., and include α-3,4-di-epi-homonojirimycin, 4-epi-fagomine, α-allo-homonojirimycin, N-methyl-deoxygalactonojirimycin, β-1-C-butyl-deoxygalactonojirimycin, α-galacto-homonojirimycin, calystegine A_3, calystegine B_2, calystegine B_3, N-methyl-calystegine A_3, N-methyl-calystegine B_2 and N-methyl-calystegine B_3.

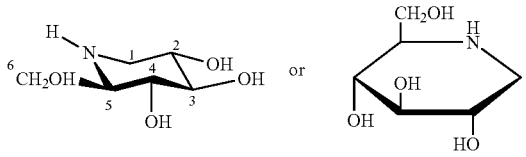
In one particular non-limiting embodiment, the SPC is isofagomine (IFG; (3R,4R,5R)-5-(hydroxymethyl)-3,4-piperidinediol) which is represented by the following formula:



or a pharmaceutically acceptable salt, ester or prodrug of isofagomine, such as, for example, IFG tartrate (see, e.g., U.S. Patent Application Publication 20070281975.) IFG has a molecular formula of $C_6H_{13}NO3$ and a molecular weight of 147.17. This compound is further described in U.S. Pat. No. 5,844,102 to Sierks et al., and U.S. Pat. No. 5,863,903, to Lundgren et al.

Still other SPCs for Gba are described in U.S. Pat. No. 6,916,829 to Fan et al., and include C-benzyl isofagomine and derivatives, N-alkyl (C9-12)-DNJ, Glucoimidazole (and derivatives), C-alkyl-IFG (and derivatives), N-alkyl-β-valeinamines, Fluphenozine, N-dodecyl-DNJ, calystegines A_3, B_1, B_2 and C_1

In one particular non-limiting embodiment, the SPC is 1-deoxynorjirimycin (1-DNJ), which is represented by the following formula:



or a pharmaceutically acceptable salt, ester or prodrug of 1-deoxynorjirimycin. In one embodiment, the salt is hydrochloride salt (i.e. 1-deoxynojirimycin-HCl).

Still other SPCs for GAA are described in U.S. Pat. Nos. 6,274,597; 6,583,158; 6,599,919 and 6,916,829 to Fan et al., and U.S. Published Application No. 2006/0264467, and include N-methyl-DNJ, N-ethyl-DNJ, N-propyl-DNJ, N-butyl-DNJ, N-pentyl-DNJ, N-hexyl-DNJ, N-heptyl-DNJ, N-octyl-DNJ, N-nonyl-DNJ, N-methylcyclopropyl-DNJ, N-methylcyclopentyl-DNJ, N-2-hydroxyethyl-DNJ, 5-N-carboxypentyl DNJ, α-homonojirimycin, and castanospermine.

As used herein, the term "specifically binds" refers to the interaction of a pharmacological chaperone with a protein such as α-Gal A, Gba or GAA, specifically, an interaction with amino acid residues of the protein that directly participate in contacting the pharmacological chaperone. A pharmacological chaperone specifically binds a target protein, e.g., α-Gal A, Gba or GAA, to exert a chaperone effect on the protein and not a generic group of related or unrelated proteins. The amino acid residues of a protein that interact with any given pharmacological chaperone may or may not be within the protein's "active site." Specific binding can be evaluated through routine binding assays or through structural studies, e.g., co-crystallization, NMR, and the like. The active site for α-Gal A, Gba or GAA is the substrate binding site.

"Deficient α-Gal A activity" refers to α-Gal A activity in cells from a patient which is below the normal range as compared (using the same methods) to the activity in normal individuals not having or suspected of having Fabry or any other disease (especially a blood disease).

"Deficient Gba activity" refers to Gba activity in cells from a patient which is below the normal range as compared (using the same methods) to the activity in normal individuals not having or suspected of having Gaucher or any other disease.

"Deficient GAA activity" refers to GAA activity in cells from a patient which is below the normal range as compared (using the same methods) to the activity in normal individuals not having or suspected of having Pompe or any other disease.

As used herein, the terms "enhance α-Gal A activity," "enhance Gba activity," and "enhance GAA activity" or "increase α-Gal A activity," "increase Gba activity," and "increase GAA activity" refer to increasing the amount of α-Gal A, Gba or GAA, respectively, that adopts a stable conformation in a cell contacted with a pharmacological chaperone specific for the α-Gal A, Gba or GAA, relative to the amount in a cell (preferably of the same cell-type or the same cell, e.g., at an earlier time) not contacted with the pharmacological chaperone specific for the α-Gal A, Gba or GAA. This term also refers to increasing the trafficking of α-Gal A, Gba or GAA to the lysosome in a cell contacted with a pharmacological chaperone specific for the α-Gal A, Gba or GAA, relative to the trafficking of α-Gal A, Gba or GAA not contacted with the pharmacological chaperone specific for the protein. These terms refer to both wild-type and mutant α-Gal A, Gba or GAA. In one embodiment, the increase in the amount of α-Gal A, Gba or GAA in the cell is measured by measuring the hydrolysis of an artificial substrate in lysates from cells that have been treated with the SPC. An increase in hydrolysis is indicative of increased α-Gal A, Gba or GAA activity.

The term "α-Gal A activity" refers to the normal physiological function of a wild-type α-Gal A in a cell. For example, α-Gal A activity includes hydrolysis of GL-3.

The term "Gba activity" refers to the normal physiological function of a wild-type αGba in a cell. For example, Gba activity includes metabolism of fatty glucocerebrosides.

The term "GAA activity" refers to the normal physiological function of a wild-type Gaa in a cell. For example, GAA activity includes lysosomal glycogen metabolism.

A "responder" is an individual diagnosed with or suspected of having a lysosomal storage disorder, such, for example, but not limited to, Fabry disease, Pompe disease or Gaucher disease, whose cells exhibit sufficiently increased α-Gal A, GAA or Gba activity, respectively, and/or amelioration of symptoms or improvement in surrogate markers, in response to contact with an SPC. Non-limiting examples of improvements in surrogate markers for Fabry and Pompe disease are disclosed in U.S. Ser. Nos. 60/909,185 and 61/035,869, respectively.

Non-limiting examples of improvements in surrogate markers for Fabry disease disclosed in U.S. Ser. No. 60/909,185 include increases in α-Gal A levels or activity in cells (e.g., fibroblasts) and tissue; reductions in of GL-3 accumulation; decreased plasma concentrations of homocysteine and vascular cell adhesion molecule-1 (VCAM-1); decreased GL-3 accumulation within myocardial cells and valvular fibrocytes; reduction in cardiac hypertrophy (especially of the left ventricle), amelioration of valvular insufficiency, and arrhythmias; amelioration of proteinuria; decreased urinary concentrations of lipids such as CTH, lactosylceramide, ceramide, and increased urinary concentrations of glucosylceramide and sphingomyelin (Fuller et al., Clinical Chemistry. 2005; 51: 688-694); the absence of laminated inclusion bodies (Zebra bodies) in glomerular epithelial cells; improvements in renal function; mitigation of hypohidrosis; the absence of angiokeratomas; and improvements hearing abnormalities such as high frequency sensorineural hearing loss progressive hearing loss, sudden deafness, or tinnitus. Improvements in neurological symptoms include prevention of transient ischemic attack (TIA) or stroke; and amelioration of neuropathic pain manifesting itself as acroparaesthesia (burning or tingling in extremities).

The dose that achieves one or more of the aforementioned responses is a "therapeutically effective dose."

The phrase "pharmaceutically acceptable" refers to molecular entities and compositions that are physiologically tolerable and do not typically produce untoward reactions when administered to a human. Preferably, as used herein, the term "pharmaceutically acceptable" means approved by a regulatory agency of the Federal or a state government or listed in the U.S. Pharmacopoeia or other generally recognized pharmacopoeia for use in animals, and more particularly in humans. The term "carrier" refers to a diluent, adjuvant, excipient, or vehicle with which the compound is administered. Such pharmaceutical carriers can be sterile liquids, such as water and oils. Water or aqueous solution

saline solutions and aqueous dextrose and glycerol solutions are preferably employed as carriers, particularly for injectable solutions. Suitable pharmaceutical carriers are described in "Remington's Pharmaceutical Sciences" by E. W. Martin, 18th Edition, or other editions.

As used herein, the term "isolated" means that the referenced material is removed from the environment in which it is normally found. Thus, an isolated biological material can be free of cellular components, i.e., components of the cells in which the material is found or produced. In the case of nucleic acid molecules, an isolated nucleic acid includes a PCR product, an mRNA band on a gel, a cDNA, or a restriction fragment. In another embodiment, an isolated nucleic acid is preferably excised from the chromosome in which it may be found, and more preferably is no longer joined to non-regulatory, non-coding regions, or to other genes, located upstream or downstream of the gene contained by the isolated nucleic acid molecule when found in the chromosome. In yet another embodiment, the isolated nucleic acid lacks one or more introns. Isolated nucleic acids include sequences inserted into plasmids, cosmids, artificial chromosomes, and the like. Thus, in a specific embodiment, a recombinant nucleic acid is an isolated nucleic acid. An isolated protein may be associated with other proteins or nucleic acids, or both, with which it associates in the cell, or with cellular membranes if it is a membrane-associated protein. An isolated organelle, cell, or tissue is removed from the anatomical site in which it is found in an organism. An isolated material may be, but need not be, purified.

The terms "about" and "approximately" shall generally mean an acceptable degree of error for the quantity measured given the nature or precision of the measurements. Typical, exemplary degrees of error are within 20 percent (%), preferably within 10%, and more preferably within 5% of a given value or range of values. Alternatively, and particularly in biological systems, the terms "about" and "approximately" may mean values that are within an order of magnitude, preferably within 10- or 5-fold, and more preferably within 2-fold of a given value. Numerical quantities given herein are approximate unless stated otherwise, meaning that the term "about" or "approximately" can be inferred when not expressly stated.

Method of Determining Treatment Options

To easily determine whether SPC therapy will be a viable treatment for patients, for example, Fabry, Pompe or Gaucher patients, and including female carriers of X-linked lysosomal storage disorders such as Fabry disease, a simple, non-invasive SPC rescue assay of protein activity in a cell line expressing a mutant form of the protein was developed.

In vitro Assay

In one embodiment, the diagnostic method of the present invention involves transforming a cell line with a nucleic acid vector which encodes a mutant lysosomal enzyme, for example, α-Gal A, GAA or Gba. The cell line is then treated with or without an SPC, e.g., DGJ, DNJ or IFG, for a sufficient time period to demonstrate enhancement (i.e., increase) of α-Gal A, GAA or Gba activity. The transformed cells are then lysed, and the lysate is used in an assay to determine enzyme activity. A sufficient increase in α-Gal A, GAA or Gba activity in the lysates from cells treated with the SPC over the activity in the lysates from untreated cells indicates that a patient who expresses α-Gal A, GAA or Gba with the same mutation as the cell line will likely respond to SPC therapy (i.e., the patient will be a "responder").

Transient Transfection of a Cell Line and Expression of a Mutant Lysosmal Enzyme

In one embodiment, to identify SPC-responsive mutations, all known lysosomal enzyme (e.g., α-Gal A, GAA or Gba) mutations, for example, missense mutations and in-frame small deletions and insertions, can be generated according to techniques known in the art, for example, by site-directed mutagenesis. Mutant enzyme constructs can then be transiently expressed in a cell line, for example, mammalian COS-7, HEK-293 or GripTite 293 MSR (Invitrogen Corp., Carlsbad, Calif., U.S.A.) cells. Transformed cells can then be incubated with increasing concentrations of SPC and enzymatic activity can be measured in cell lysates.

Mutagenesis: Nucleic acid vectors encoding a mutant protein (e.g. mutant α-Gal A, GAA or Gba) can be generated by conventional molecular biology, microbiology, and recombinant DNA techniques within the skill of the art. Such techniques are explained fully in the literature. (See, e.g., Sambrook, Fritsch & Maniatis, 2001, Molecular Cloning: A Laboratory Manual, Third Edition, Cold Spring Harbor Laboratory Press, Cold Spring Harbor, N.Y.; Glover, ed., 1985, DNA Cloning: A Practical Approach, Volumes I and II, Second Edition; Gait, M. J., ed., 1984, Oligonucleotide Synthesis: A practical approach; Hames, B. D. & Higgins, S. J. eds., 1985, Nucleic Acid Hybridization; Hames, B. D. & Higgins, S. J., eds., 1984, Transcription And Translation; Freshney, R. I., 2000, Culture of Animal Cells: A Manual of Basic Technique; Woodward, J., 1986, Immobilized Cells And Enzymes: A practical approach, IRL Press; Perbal, B. E., 1984, A Practical Guide To Molecular Cloning). For example, a single α-Gal A, GAA or Gba mutation can be introduced into a nucleic acid encoding a wild type α-Gal A, GAA or Gba gene through site directed mutagenesis of a nucleic acid encoding the wild type enzyme.

Transient transfection and expression: The coding sequences of the gene to be delivered, for example, a mutant α-Gal A, GAA or Gba, are operably linked to expression control sequences, e.g., a promoter that directs expression of the gene. As used herein, the phrase "operatively linked" refers to the functional relationship of a polynucleotide/gene with regulatory and effector sequences of nucleotides, such as promoters, enhancers, transcriptional and translational stop sites, and other signal sequences. For example, operative linkage of a nucleic acid to a promoter refers to the physical and functional relationship between the polynucleotide and the promoter such that transcription of DNA is initiated from the promoter by an RNA polymerase that specifically recognizes and binds to the promoter. The promoter directs the transcription of RNA from the polynucleotide. Expression of a mutant protein (e.g. mutant α-Gal A, GAA or Gba) may be controlled by any promoter/enhancer element known in the art, but these regulatory elements must be functional in the host selected for expression.

In one specific embodiment, a vector is used in which the coding sequences and any other desired sequences are flanked by regions that promote homologous recombination at a desired site in the genome, thus providing for expression of the construct from a nucleic acid molecule that has integrated into the genome (See Koller and Smithies, 1989, Proc. Natl. Acad. Sci. USA, 86:8932-8935; Zijlstra et al., 1989, Nature 342:435-438; U.S. Pat. No. 6,244,113 to Zarling et al.; and U.S. Pat. No. 6,200,812 to Pati et al.).

The term "host cell" means any cell of any organism that is selected, modified, transformed, grown, or used or manipulated in any way, for the production of a substance by the cell, for example the expression by the cell of a gene, a DNA or RNA sequence, a protein or an enzyme. In one embodiment, a host cells that is transfected with a vector encoding a mutant α-Gal A, GAA or Gba can be used for screening a candidate SPC, for example, DGJ, DNJ or IFG, to determine if the candidate SPC is an effective compound for increasing the activity of the mutant α-Gal A, GAA or Gba expressed by the host cell.

The term "expression system" means a host cell and compatible vector under suitable conditions, e.g., for the expression of a protein coded for by foreign DNA carried by the vector and introduced to the host cell. Expression systems include mammalian host cells and vectors. Suitable cells include PC12 cells, CHO cells, HeLa cells, GripTite 293 MSR cells (Invitrogen Corp., Carlsbad, Calif., U.S.A.), HEK-293 (also known as 293 cells) and 293T cells (derived from human embryonic kidney cells), COS cells (e.g. COS-7 cells), mouse primary myoblasts, NIH 3T3 cells.

Suitable vectors include viruses, such as adenoviruses, adeno-associated virus (AAV), vaccinia, herpesviruses, baculoviruses and retroviruses, parvovirus, lentivirus, bacteriophages, cosmids, plasmids, fungal vectors, naked DNA, DNA lipid complexes, and other recombination vehicles typically used in the art which have been described for expression in a variety of eukaryotic and prokaryotic hosts, and may be used for gene therapy as well as for simple protein expression.

In one non-limiting example, transient transfection can be carried out in GripTite 293 MSR cells (Invitrogen Corp., Carlsbad, Calif., U.S.A.) using the reagent Fugene HD (Roche). The cells can be seeded in a suitable assay container, such as a 96-well plate (Costar) at a density of, for example, 7.5-10k cells/well, and incubated under suitable conditions, such as, for example, 37° C., 5% CO_2 for 24 hours before transfection. After transfection with expression constructs containing a specific α-Gal A mutant, cells can be incubated again in, for example, 37° C., 5% CO_2 for one hour before adding DGJ at 50 nM to 1 mM. Cells can then be incubated for 4-5 days before lysis and assay.

Enzyme Activity/Enhancement Assay: Typically, following incubation with an SPC (e.g. DGJ, DNJ or IFG), host cells are lysed by the addition of lysis buffer (or deionized water) and physical disruption (pipetting, vortexing and/or agitation, and/or sonication) at room temperature or on ice, followed by pooling of the lysates on ice, then splitting the pooled lysate into small aliquots and freezing.

The lysates can be thawed immediately prior to the assay and should be suspended by use of a vortex mixer and sonicated prior to addition to appropriate wells e.g., in a microplate. In the context of Fabry disease, N-acetylgalactosamine (GalNAc) is then added to each well (to inhibit α-galactosidase B), followed by a short incubation. 4-methylumbelliferyl-α-D-galactopyranoside (4-MU Gal), or other appropriate labeled DGJ substrate, is then added and the plate is gently mixed for a brief period of time, covered, and incubated at 37° C. for a sufficient time for substrate hydrolysis, usually about 1 hour. To stop the reaction, NaOH-glycine buffer, pH 10.7, is added to each well and the plate is read on a fluorescent plate reader (e.g. Wallac 1420 Victor3™ or similar instrument). Excitation and emission wavelengths were customarily set at 355 nm and 460 nm, respectively. One unit of enzyme activity is defined as the amount of enzyme that catalyzes the hydrolysis of 1 nmole of 4-methylumbelliferone per hour. For each patient sample at least three normal samples may be tested concurrently.

Various modifications of this assay will be readily ascertainable to one of ordinary skill in the art. Examples of artificial substrates that can be used to detect α-Gal A activity include but are not limited to p-nitrophenyl-α-D-galactopyranoside and 4-MU GAL. Obviously, only substrates that can be cleaved by human α-Gal A are suitable for use. It is noted that while use of a fluorogenic substrate is preferred, other methods of determining enzymatic activity are contemplated for use in the method, including using chromogenic substrates or immunoquantification techniques.

In one specific example, following incubation with an SPC, for example, DGJ, the host cells can be washed two times with PBS then incubated in 200 μl fresh media at 37° C., 5% CO_2 for two hours followed by 2 additional PBS washes. After, cells can be lysed in 60 μL Lysis Buffer (27 mM sodium citrate/46 mM sodium phosphate dibasic, 0.5% Triton X-100, pH 4.6). Ten μL lysate can then be added to 50 μL assay buffer (Lysis Buffer without Triton X-100, but containing 6 mM 4-MU-α-D-galactopyranoside (4-MUG) and 117 mM N-acetyl-D-galactosamine (GalNac)), and incubated at 37° C. for 1 hr. Seventy μL Stop Solution (0.4 M glycine, pH 10.8) can then be added and fluorescence read on a Victor plate reader (Perkin Elmer) at 355 nm excitation and 460 nm emission. Raw fluorescence counts can be background subtracted as defined by counts from substrate solution only. A MicroBCA Protein Assay Kit (Pierce) was used according to manufacturer's instructions to determine protein concentration from 40 μL of cell lysate. A 4-methylumbelliferone (4-MU) standard curve ranging from 30 μM to 1.3 nM was run in parallel for calculation of absolute α-Gal A activity expressed as nmoles/mg protein/hr or further normalized to % of untreated wild type enzyme activity.

Treatment Reference Table

In another embodiment, the methods described supra can be used to generate a "treatment reference table" or "treatment therapy table," wherein the treatment reference table comprises a list of protein mutations, and further wherein the table indicates the responsiveness of each mutation to an SPC, such as DGJ, DNJ or IFG. The treatment reference table can then be used to determine if a particular SPC, for example, DGJ, DNJ or IFG, would be an effective SPC for treating a patient with a particular α-Gal A, GAA or Gba mutation, respectively.

As used herein "treatment therapy table" or "treatment reference table" refers to any written record that conveys whether a particular mutation is responsive to SPC therapy, and is not necessarily limited to written records presented in tabular form.

In one embodiment, the treatment reference table can be used by a treating physician or clinical professional to select an SPC for treating a patient, for example, a Fabry, Pompe or Gaucher patient who expresses a specific mutant α-Gal A, GAA or Gba, respectively, wherein the SPC is selected because the treatment reference table identifies the SPC as a compound that can increase the activity of the patient's mutant α-Gal A, GAA or Gba when the mutant α-Gal A, GAA or Gba is expressed in a host cell.

Treatable Disorders

While the present application has been discussed largely in the context of Fabry, Pompe and Gaucher diseases, and

the SPCs DGJ, DNJ and IFG, respectively, it should be understood that it is applicable to any SPC and disease. In one non-limiting embodiment, a treatment reference table can be generated for any candidate SPC and any lysosomal storage disorder, or any disorder involving protein misfolding. These diseases include other lysosomal storage disorders, for example, Cystic Fibrosis (CFTR) (respiratory or sweat gland epithelial cells), familial hypercholesterolemia (LDL receptor; LPL-adipocytes or vascular endothelial cells), cancer (p53; PTEN-tumor cells), Alzheimer's disease (α-secretase), Parkinson's disease (glucocerebrosidase), obesity (MC4R), and amyloidoses (transthyretin) among others.

Eligibility Determination Criteria

The criteria for determining eligibility for SPC therapy depends on the type of mutant GLA, GAA or Gba a patient expresses. In one embodiment, patients with Fabry, Pompe, or Gaucher disease could be categorized as eligible for SPC therapy if α-Gal A, GAA or Gba activity, respectively, in a host cell expressing the same mutation as the patient, in the presence of an SPC such as DGJ, DNJ or IFG, is at least about 1.5- to 20-fold (2% to 100%) activity of a host cell expressing a wild type α-Gal A, GAA or Gba.

This discovery provides a method for improving the diagnosis of and facilitating clinical treatment decisions for Fabry, Pompe and Gaucher diseases in particular, and lysosomal storage disease in general. Moreover, this method can be extended to a wide range of genetically defined diseases in appropriate cell types. This class of disease includes the other lysosomal storage disorders, Cystic Fibrosis (CFTR) (respiratory or sweat gland epithelial cells), familial hypercholesterolemia (LDL receptor; LPL-adipocytes or vascular endothelial cells), cancer (p53; PTEN-tumor cells), Alzheimer's disease (α-secretase), Parkinson's disease (glucocerebrosidase), obesity (MC4R), and amyloidoses (transthyretin) among others.

Kits

The present invention also provides for a commercial diagnostic test kit in order to make therapeutic treatment decisions. The kit provides all materials discussed above and more particularly in the Examples below, for preparing and running each assay in one convenient package, optionally including instructions and an analytic guide.

As one non-limiting example, a kit for evaluating α-Gal A activity may contain, at a minimum:

a. a panel of host cells, each expressign a mutant α-Gal A, or alternatively, a host cell, a vector encoding a mutant α-Gal A, and a means of transfecting the host cell such that the host cell expresses the mutant α-Gal A;
b. a specific pharmacological chaperone;
c. a chromogenic or fluorogenic substrate for the enzyme assay (including an appropriate standard); and
d. GalNAc.

The kit may also contain instructions for optimally performing the protein enhancement assay. In another embodiment, the kit will contain the appropriate tubes, buffers (e.g., lysis buffer), and microplates.

In one embodiment, the SPC is supplied in dry form, and will be re-constituted prior to addition.

Patients who express a mutant α-Gal A, GAA or Gba that previously tested positive for enzyme enhancement with a candidate SPC in assays of the present Mention can then be treated with that candidate SPC agent, whereas patients who express a mutant α-Gal A, GAA or Gba that does not display enzyme enhancement with a candidate SPC can avoid treatment which will save money and prevent the emotional toll of not responding to a treatment modality.

EXAMPLES

The present invention is further described by means of the examples, presented below. The use of such examples is illustrative only and in no way limits the scope and meaning of the invention or of any exemplified term. Likewise, the invention is not limited to any particular preferred embodiments described herein. Indeed, many modifications and variations of the invention will be apparent to those skilled in the art upon reading this specification. The invention is therefore to be limited only by the terms of the appended claims along with the full scope of equivalents to which the claims are entitled.

Example 1

Identification of Fabry Disease-Causing Mutations that are Responsive to the Pharmacological Chaperone DGJ

The present Example provides the in vitro diagnostic assay to determine a Fabry patient's responsiveness to a specific pharmacological chaperone.

Introduction

Fabry disease is a lysosomal storage disorder caused by mutations in the gene that encodes α-galactosidase A (α-GAL A). Over 600 Fabry mutations have been reported, and about 60% are missense. The iminosugar DGJ is currently being studied in Phase 2 clinical trials as a pharmacological chaperone for the treatment of Fabry disease. Previously, it has been shown that DGJ mediates selective and dose-dependent increases in α-Gal A levels in many Fabry patient-derived lymphoid cell lines. To identify additional DGJ-responsive mutations, GripTite 293 MSR, (Invitrogen Corp., Carlsbad, Calif., U.S.A.) cells were transiently transfected with expression vectors containing all known α-Gal A missense mutations and several in-frame small deletions and insertions generated by site-directed mutagenesis. Mutant α-Gal A constructs were transiently expressed in HEK-293 cells. Cells were incubated with increasing concentrations of DGJ and α-Gal A activity was measured in cell lysates. Assay validation has been carried out on more than 35 missense mutations and the results obtained in HEK-293 cells were similar to those obtained from both Fabry patient-derived lymphoid cells and primary T-cell cultures (see U.S. Ser. No. 11/749,512), as well as to the α-Gal A enzyme responses observed in the white blood cells of Fabry patients after oral administration of DGJ in Phase 2 clinical trials.

Methods and Materials

Mutagenesis: All mutations were generated by site-directed mutagenesis following standard molecular biology protocols. To generate point mutations, site-directed mutagenesis was used on the expression vector pcDNA3.1 (Invitrogen) containing human α-GAL A cDNA in-frame. Specific primer pairs were designed containing the desired mutation (FIG. **6**). The mutagenesis was performed through the polymerase chain reaction using PfuUltra high-fidelity DNA polymerase (Stratagene) in a thermocycler. Each reaction mixture contained a total volume of 50 μl with the following: 41.6 ul dH_2O, 5.0 ul 10×PfuUltra HF reaction buffer, 0.5 uL Forward-5'-primer

(50 uM), 0.5 ul Reverse-3'-primer, 1.0 ul dNTP mix (containing 25 mM each dA, dT, dC, dG), 0.9 ul human GLA in pcDNA3 (2 ng/ul DNA), 0.5 ul PfuUltra HD DNA polymerase. Thermocycler parameter used was the following: i) 94° C. for 30 seconds, ii) 94° C. for 30 seconds, 55-60° C. for 30 seconds, 68° C. for 6 minutes, iii) Repeat (ii) 16 times. Afterwards, 0.5 ul Dpn 1 (New England Biolabs) was added to each reaction and incubated at 37° C. for 2 hours. A volume of 7.5 ul for each mutagenesis reaction was used to transform DH5a cells (New England Biolabs). Cells were then plated on LB-agar plates with 75 ug/ml ampicillin, and incubated at 37° C. overnight. Bacterial colonies were picked, grown in liquid LB with ampicillin overnight, shaking, at 37° C., and plasmid DNA extracted using QuickLyse Miniprep Kit (Qiagen). Mutants were confirmed by sequencing the full-length human GLA gene. For some of the mutants, human GLA cDNA was contained in the vector plasmid pCXN. Mutagenesis was performed in this vector with the NEB Fusion DNA polymerase. After confirming the mutation through sequencing, the plasmid was digested with EcoRI and subcloned into expression vector pcDNA3.1. Correct orientation was confirmed by digestion with Xho I.

Transient transfection and expression: Transient transfection was carried out in GripTite 293 MSR cells (Invitrogen Corp., Carlsbad, Calif., U.S.A.) using the reagent Fugene HD (Roche). Briefly, cells were seeded in 96-well plates (Costar) at a density of 7.5-10k cells/well and incubated at 37° C., 5% CO_2 for 24 hours before transfection. Cells were transfected with 0.1 μg DNA and 0.35 μL of Fugene HD reagent per well (DNA: Reagent ratio of 2:7). After transfection with expression constructs containing the specific α-Gal A mutants, cells were incubated again in 37° C., 5% CO_2 for one hour before adding DGJ at 20 nM to 1 mM. Cells were then incubated for 4-5 days before lysis and assay.

α-GAL A activity measurement: Cells were washed two times with PBS then incubated in 200 μl fresh media at 37° C., 5% CO_2 for two hours followed by 2 additional PBS washes. After, cells were lysed in 60 μL Lysis Buffer (27 mM sodium citrate/46 mM sodium phosphate dibasic, 0.5% Triton X-100, pH 4.6). Ten μL lysate were added to 50 μL assay buffer (Lysis Buffer without Triton X-100, but containing 6 mM 4-MU-α-D-galactopyranoside (4-MUG) and 117 mM N-acetyl-D-galactosamine (GalNac)), and incubated at 37° C. for 1 hr. Seventy μL Stop Solution (0.4 M glycine, pH 10.8) were then added and fluorescence read on a Victor plate reader (Perkin Elmer) at 355 nm excitation and 460 nm emission. Raw fluorescence counts were background subtracted as defined by counts from substrate solution only. A MicroBCA Protein Assay Kit (Pierce) was used according to manufacturer's instructions to determine protein concentration from 40 μL of cell lysate. A 4-methylumbelliferone (4-MU) standard curve ranging from 30 μM to 1.3 nM was run in parallel for calculation of absolute α-Gal A activity expressed as nmoles/mg protein/hr or further normalized to % of untreated wild type enzyme activity.

Transient transfection and α-Gal A activity measurements were performed in quadruplicates and repeated at least 3 times for each mutation to calculate the average α-Gal A activity at each DGJ concentration. Significant response to DGJ was determined by a two-tailed, paired Student's T-test ($p<0.05$).

Results

All listed Fabry mutations were generated by site-directed mutagenesis (FIG. **1**). Mutations identified in italicized text were not tested, while those identified in plain text were α-Gal A mutants that were responsive to DGJ treatment in the transient transfection assay, and those identified in bold and underscored text were not responsive to DGJ treatment in the transient transfection assay. The magnitude of increase in α-Gal A levels after DGJ treatment and EC50 values are listed for every tested mutation that responded to DGJ treatment (FIG. **2**).

α-Gal A activity (expressed as nmol/mg protein/hr of 4-MU released) was measured in lysates prepared from transfected GripTite 293 cells incubated with increasing concentrations of DGJ. A typical concentration-dependent response is shown for L300P and a typical negative response to DGJ is shown for R227Q. Wild type exhibits high baseline activity and does not respond to DGJ in this assay (FIG. **3**).

α-Gal A levels were measured in three different assays, reported as percentage of wild type, are compared for each mutation by plotting side by side. The three different assays examined α-Gal A levels in T-cells and lymphoblasts isolated from

Fabry patients (for example, see U.S. Ser. No. 11/749,512), as well as in white blood cell (WBC) from DGJ Phase 2 studies

Blank bars indicate basal level (without DGJ treatment) and filled bars indicate the elevated level after DGJ treatment (FIG. **4**).

Tested Fabry mutations were illustrated on the α-Gal A secondary structure (FIG. **5**). No significant correlation between response and location on the protein sequence of a mutation was observed, suggesting that responsive as well as non-responsive mutations are distributed widely across the entire protein. Text color indicates DGJ response: green=response; red=no response; brown indicates that of the multiple mutations on that same site some responded to DGJ treatment, while others did not.

Conclusion

These described results are comparable to those obtained from Fabry patient-derived lymphoid or T cells, as well as to the α-Gal A enzyme responses observed in the white blood cells of Fabry patients after oral administration of DGJ in Phase 2 clinical trials.

Thus, the GripTite 293 MSR transient transfection assay is a reliable method for identifying DGJ-responsive mutations and characterizing the magnitude and potency of this response.

Among the responsive mutations identified, the increases in α-Gal A levels by DGJ treatment ranged from 1.3- to 40-fold (2% to 100% wild type), with EC_{50} values between 200 nM and >100 mM.

DGJ-responsive and non-responsive mutant forms did not appear to be located to particular regions or domains on the α-Gal A protein structure.

Example 2

Ex vivo Method for Evaluating Effects of an SPC on Glucocerebrosidase Activity—Prophetic Example

Gaucher disease (GD) is caused by a deficiency of lysosomal glucocerebrosidase (GCase). Deficient GCase activity leads to an accumulation of glucosylceramide (GlcCer) and the development of symptoms such as anemia, thrombocy-

topenia, hepatosplenomegaly, bone necrosis, infarcts and osteoporosis, and in some cases, neuropathic disease. The specific pharmacological chaperone isofagomine tartrate (IFG) selectively binds and stabilizes mutant (N370S/N370S) GCase in the ER and increases its trafficking to the lysosome.

To evaluate the effects of IFG on different GCase variants, an ex vivo diagnostic assay will be prepared using Cos7 cells in order to ascertain IFG-responsive mutations.

Using the techniques described in Examples 1 and 4, COS-7 cell lines will be prepared that express missense mutations and several in-frame small deletions and insertions by site-directed mutagenesis. Assays will be prepared for all of the mutations listed in the x-axis of FIG. **8**. IFG-activity response will be ascertained for each assay according to methods known in the art (see, e.g., U.S. Pat. No. 6,916,829, which is hereby incorporated by reference).

To determine the correlation of the IFG-response measured in the COS-7 cells to patient-derived cells, IFG-activity response was also measured in Patient-Derived Macrophages and Lymphoblasts. Macrophages were successfully derived from 46 of 63 patients and incubation with IFG (3, 10, 30 or 100 μM) for 5 days increased GCase levels in macrophages from 42 of 46 patients (mean=2.3-fold; range: 1.1- to 6.5-fold). Residual activity levels and response to IFG was more consistent for the same genotypes when measured in lymphoblasts compared to macrophages, potentially due to the variability in macrophage viability between different patients. The results are shown in FIG. **8**.

The response to IFG for the patient-derived cells will be compared to the results obtained in the Cos7 cell line.

Example 3

In vivo Effect of an SPC on α-GAL A Activity in Skin, Heart, Kidney and Plasma

To determine if increased mutant α-Gal A levels translate to increased α-Gal A activity in situ, the effect of DGJ administration on tissue GL-3 levels was investigated in vivo in hR301Q α-Gal A Tg/KO mice.

Eight-week old male hR301Q α-Gal A Tg/KO mice were treated for 4 weeks with 300 mg/kg DGJ in drinking water either daily or less frequently (4 days ON/3 days OFF). After dosing, lysates were prepared from skin, heart, kidney, and plasma by homogenizing ~50 mg tissue in Lysis Buffer (see above). 20 μL lysate were mixed with 50 μL of substrate (as detailed above). Reaction mixtures were incubated at 37° C. for 1 hr. After, 70 Stop Solution were added and fluorescence was read on a Victor plate reader as described above. Enzyme activity in the lysates was background subtracted, and normalized for protein concentration. A 4-MU standard curve was run for conversion of fluorescence data to absolute α-Gal A activity expressed as nmol/mg protein/hr.

Tissue samples were washed free of blood, weighed and homogenized with a solvent system in a FastPrep® system. Homogenate was then extracted using Solid Phase Extraction on a C18 cartridge. The eluent was evaporated and reconstituted prior to injection onto a LC-MS/MS system. Twelve GL-3 isoforms were measured using positive ESI-MS/MS. LC separation was achieved on 00839a Zorbax C18 column.

Significant decreases in GL-3 levels were seen with daily and less frequent DGJ dosing in skin, heart, kidney, and plasma (FIG. **9**). A trend of greater reduction in GL-3 levels was seen in multiple tissues and plasma with less frequent DGJ dosing. Collectively, these results indicate that DGJ merits further evaluation for the treatment of patients with Fabry disease.

Example 4

Identification of Pompe Disease-Causing Mutations that are Responsive to the Pharmacological Chaperone DNJ

Pompe disease is caused by deficient acid alpha glucosidase (GAA) activity which impairs lysosomal glycogen metabolism. The enzyme deficiency leads to lysosomal glycogen accumulation and results in progressive skeletal muscle weakness, reduced cardiac function, respiratory insufficiency, and CNS impairment at late stages of disease. Genetic mutations in the GAA gene result in either lower expression or produce mutant forms of the enzyme with altered stability, and/or biological activity ultimately leading to disease. Pharmacological chaperones represent a promising new therapeutic approach for the treatment of genetic diseases.

To evaluate the effects of DNJ on different GAA variants, an in vitro diagnostic assay was prepared using COS-7 and HEK-293 cells in order to ascertain DNJ-responsive mutations (FIGS. **10**, **12** and **14**)

A site-directed mutagenesis approach was employed to introduce specific mutations into the complementary DNA (cDNA) encoding wild-type human acid α-glucosidase (GAA). The initial wild-type GAA DNA construct was generated by subcloning the GAA coding region from cDNA clone 5739991 (Invitrogen) into the pcDNA6/V5-HisA mammalian expression vector (Initrogen). The resultant DNA construct (designated as wild-type GAA cDNA) was used as the DNA template for subsequent mutagenesis. These missense, small insertion or deletion mutations are cited in the Erasmus database and known to be associated with type 2 glycogen storage disorder (GSD II), also known as Pompe disease. Briefly, wild-type GAA cDNA was PCR-amplified using mutagenic primers to obtain plasmid DNA with the desired mutation These mutations were confirmed by DNA sequencing prior to protein expression in cells.

COS-7 cells (derived from green monkey embryonic kidney cells) were aseptically seeded in 12-well tissue culture plates at a cell density of ~1.4×10^5 cells per well in 3 ml of Dulbecco's Modified Essential Medium (DMEM) containing 10% (v/v) fetal bovine serum and grown overnight at 37° C. in a humidified 5% CO_2 atmosphere. On the following day, the cells (typically 60-80% confluent) were transfected with 0.75 μg of the individual DNA construct via a lipid transfection reagent such as FUGENE HD (Roche) according the manufacturer's instructions. Two wells were transfected with each DNA construct such that one well was incubated with DNJ (typically 0 μM, 20 μM, 50 μM or 100 μM) while an equivalent volume of PBS was added to the other well. Two additional wells were transfected with the empty vector (no GAA cDNA) and incubated with or without DNJ to serve as the background control for endogenous monkey GAA expression. Similarly, 2 additional wells were transfected with the wild-type human GAA cDNA and incubated with or without DNJ to serve as the positive control. All samples were incubated for ~48 hrs at 37° C. in a humidified 5% CO_2 atmosphere.

After the 48-hour incubation period, the spent media was removed and the cells were washed with PBS and then incubated with fresh 1-2 ml DMEM medium for 3 hours at 37° C. in a humidified 5% CO_2 atmosphere. The medium

was subsequently removed and cells were immediately washed with PBS and lysed with 200 μl of Lysis Buffer (25 mM Bis-Tris (pH 6.5), 150 mM NaCl, 1% (v/v) Triton X-100) containing a cocktail of protease inhibitors. The cell culture plate were then gently swirled on a rotating orbital shaker apparatus for 10 min at room temperature for complete cell lysis. The resultant cell lysates were transferred to clean 1.5 ml microcentrifuge tubes and spun at 20,000×g for 10 min to pellet cellular debris. Approximately 175 μl of each supernatant sample was then transferred to a 1.5 ml fresh microcentrifuge tube. This cell lysate was used for all subsequent assays including GAA enzyme activity, total protein concentration determination, and Western blotting.

Residual GAA enzyme activity was determined for each transiently-expressed GAA using a fluorogenic 4-methylumbeliferyl-α-glucopyranoside (4-MU-α-glucose) substrate (Sigma). Briefly, 10 μl of each cell lysate was assayed (in triplicate) in a 100 μl reaction in 96-well clear bottom black plates using 3 mM 4-MU-α-glucose and 50 mM KOAc (pH 4.0). The transiently-expressed wild-type GAA sample was diluted 20-fold with Lysis Buffer to ensure that the enzymatic reaction is maintained within the linear range of the instrument. The enzyme reactions were performed at 37° C. for 1 hour and terminated by the addition of 50 μl of 500 mM Na_2CO_3 (pH 10.5). The assay was then read in a fluorescence plate reader (using 355 nm excitation/460 nm emission) to quantitate the amount of GAA-dependent 4-MU fluorescence liberated. The GAA enzyme activity was then extrapolated from a free 4-MU standard curve after subtracting the background fluorescence (i.e., empty vector control).

Twenty five microliters of each cell lysate was used in a parallel assay to determine the total cellular protein concentration using the bicinchoninic acid (BCA) protein assay (Pierce) according to the manufacturer's protocol. The total cellular protein concentration was extrapolated from a bovine serum albumin (BSA) standard curve.

The GAA enzyme activity for each sample was normalized to the total cellular protein concentration and expressed as the nmoles of 4-MU released/mg total protein/hr to define the GAA specific activity. The resultant GAA specific activity after DNJ treatment was compared to GAA enzyme activity of the corresponding untreated sample to determine whether a specific GAA mutant responds to DNJ.

For a single HEK-293 cell line transfected with the GAA mutation, P545L, the DNJ EC_{50} was also determined (FIG. **14**).

To determine the correlation of the DNJ-response measured in the COS-7 cells to patient-derived cells, DNJ-activity response was also measured ex vivo in Patient-Derived Macrophages and Lymphoblasts.

Fibroblast and lymphocyte cell lines derived from Pompe patients were also generated as previously described (see U.S. Ser. No. 11/749,512). Fibroblast cell lines were derived from patients homozygous for the P545L or R854X GAA mutations (FIG. **13**). Lymphocyte cell lines were derived from patients heterozygous for the (IVS1AS, T>G, -13) GAA splicing defect and GAA frameshift mutation (FIG. **15**).

GAA activity was measured in the lymphocyte cell lines following incubation in 0 μM, 30 μM, 100 μM, or 300 μM DNJ (FIG. **15**). GAA activity was also measured in the fibroblast cell lines following DNJ incubation (FIG. **13**).

In this study, the pharmacological chaperone 1-deoxynojirimycin-HCl (DNJ) is shown to bind mutant GAA and increase its activity. In Pompe patient-derived fibroblasts (FIG. **13**) and lymphocytes (FIG. **15**), as well as in transiently transfected COS-7 (FIGS. **10** and **12**) or HEK-293 (FIG. **14**) cells expressing certain GAA missense mutations, DNJ significantly increases GAA levels.

DNJ increased GAA activity for 26 mutations (FIG. **10**) out of 131 mutants tested (data not shown). In addition to increasing the activity of these mutant GAA's, DNJ also promoted processing of GAA to the 95/76/70 kDa forms.

Furthermore, dose-dependent increases in GAA activity was observed in patient-derived lymphocytes containing the common IVS1AS, T>G, −13 splicing defect in one allele and a frameshift mutation in the second allele (FIG. **15**).

The present invention is not to be limited in scope by the specific embodiments described herein. Indeed, various modifications of the invention in addition to those described herein will become apparent to those skilled in the art from the foregoing description and the accompanying figures. Such modifications are intended to fall within the scope of the appended claims.

Patents, patent applications, publications, product descriptions, GenBank Accession Numbers, and protocols are cited throughout this application, the disclosures of which are incorporated herein by reference in their entireties for all purpose.

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accaagggtg gagaggcccg aggggagctg ttctgggacg atggagagag cctggaagtg   2820

ctggagcgag gggcctacac acaggtcatc ttcctggcca ggaataacac gatcgtgaat   2880

gagctggtac gtgtgaccag tgagggagct ggcctgcagc tgcagaaggt gactgtcctg   2940

ggcgtggcca cggcgcccca gcaggtcctc tccaacggtg tccctgtctc caacttcacc   3000

tacagccccg acaccaaggt cctggacatc tgtgtctcgc tgttgatggg agagcagttt   3060

ctcgtcagct ggtgttagcc gggcggagtg tgttagtctc tccagaggga ggctggttcc   3120

ccagggaagc agagcctgtg tgcgggcagc agctgtgtgc gggcctgggg gttgcatgtg   3180

tcacctggag ctgggcacta accattccaa gccgccgcat cgcttgtttc cacctcctgg   3240

gccggggctc tggcccccaa cgtgtctagg agagctttct ccctagatcg cactgtgggc   3300

cggggcctgg agggctgctc tgtgttaata agattgtaag gtttgccctc ctcacctgtt   3360

gccggcatgc gggtagtatt agccaccccc ctccatctgt tcccagcacc ggagaagggg   3420
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gtgctcaggt ggaggtgtgg ggtatgcacc tgagctcctg cttcgcgcct gctgctctgc 3480

cccaacgcga ccgcttcccg gctgcccaga gggctggatg cctgccggtc cccgagcaag 3540

cctgggaact caggaaaatt cacaggactt gggagattct aaatcttaag tgcaattatt 3600

ttaataaaag gggcatttgg aatc 3624

<210> SEQ ID NO 4
<211> LENGTH: 952
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 4

Met Gly Val Arg His Pro Pro Cys Ser His Arg Leu Leu Ala Val Cys
1 5 10 15

Ala Leu Val Ser Leu Ala Thr Ala Ala Leu Leu Gly His Ile Leu Leu
20 25 30

His Asp Phe Leu Leu Val Pro Arg Glu Leu Ser Gly Ser Ser Pro Val
35 40 45

Leu Glu Glu Thr His Pro Ala His Gln Gln Gly Ala Ser Arg Pro Gly
50 55 60

Pro Arg Asp Ala Gln Ala His Pro Gly Arg Pro Arg Ala Val Pro Thr
65 70 75 80

Gln Cys Asp Val Pro Pro Asn Ser Arg Phe Asp Cys Ala Pro Asp Lys
85 90 95

Ala Ile Thr Gln Glu Gln Cys Glu Ala Arg Gly Cys Cys Tyr Ile Pro
100 105 110

Ala Lys Gln Gly Leu Gln Gly Ala Gln Met Gly Gln Pro Trp Cys Phe
115 120 125

Phe Pro Pro Ser Tyr Pro Ser Tyr Lys Leu Glu Asn Leu Ser Ser Ser
130 135 140

Glu Met Gly Tyr Thr Ala Thr Leu Thr Arg Thr Thr Pro Thr Phe Phe
145 150 155 160

Pro Lys Asp Ile Leu Thr Leu Arg Leu Asp Val Met Met Glu Thr Glu
165 170 175

Asn Arg Leu His Phe Thr Ile Lys Asp Pro Ala Asn Arg Arg Tyr Glu
180 185 190

Val Pro Leu Glu Thr Pro Arg Val His Ser Arg Ala Pro Ser Pro Leu
195 200 205

Tyr Ser Val Glu Phe Ser Glu Glu Pro Phe Gly Val Ile Val His Arg
210 215 220

Gln Leu Asp Gly Arg Val Leu Leu Asn Thr Thr Val Ala Pro Leu Phe
225 230 235 240

Phe Ala Asp Gln Phe Leu Gln Leu Ser Thr Ser Leu Pro Ser Gln Tyr
245 250 255

Ile Thr Gly Leu Ala Glu His Leu Ser Pro Leu Met Leu Ser Thr Ser
260 265 270

Trp Thr Arg Ile Thr Leu Trp Asn Arg Asp Leu Ala Pro Thr Pro Gly
275 280 285

Ala Asn Leu Tyr Gly Ser His Pro Phe Tyr Leu Ala Leu Glu Asp Gly
290 295 300

Gly Ser Ala His Gly Val Phe Leu Leu Asn Ser Asn Ala Met Asp Val
305 310 315 320

Val Leu Gln Pro Ser Pro Ala Leu Ser Trp Arg Ser Thr Gly Gly Ile
325 330 335

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Leu Asp Val Tyr Ile Phe Leu Gly Pro Glu Pro Lys Ser Val Val Gln
            340                 345                 350

Gln Tyr Leu Asp Val Val Gly Tyr Pro Phe Met Pro Pro Tyr Trp Gly
        355                 360                 365

Leu Gly Phe His Leu Cys Arg Trp Gly Tyr Ser Ser Thr Ala Ile Thr
    370                 375                 380

Arg Gln Val Val Glu Asn Met Thr Arg Ala His Phe Pro Leu Asp Val
385                 390                 395                 400

Gln Trp Asn Asp Leu Asp Tyr Met Asp Ser Arg Arg Asp Phe Thr Phe
                405                 410                 415

Asn Lys Asp Gly Phe Arg Asp Phe Pro Ala Met Val Gln Glu Leu His
            420                 425                 430

Gln Gly Gly Arg Arg Tyr Met Met Ile Val Asp Pro Ala Ile Ser Ser
        435                 440                 445

Ser Gly Pro Ala Gly Ser Tyr Arg Pro Tyr Asp Glu Gly Leu Arg Arg
    450                 455                 460

Gly Val Phe Ile Thr Asn Glu Thr Gly Gln Pro Leu Ile Gly Lys Val
465                 470                 475                 480

Trp Pro Gly Ser Thr Ala Phe Pro Asp Phe Thr Asn Pro Thr Ala Leu
                485                 490                 495

Ala Trp Trp Glu Asp Met Val Ala Glu Phe His Asp Gln Val Pro Phe
            500                 505                 510

Asp Gly Met Trp Ile Asp Met Asn Glu Pro Ser Asn Phe Ile Arg Gly
        515                 520                 525

Ser Glu Asp Gly Cys Pro Asn Asn Glu Leu Glu Asn Pro Pro Tyr Val
    530                 535                 540

Pro Gly Val Val Gly Gly Thr Leu Gln Ala Ala Thr Ile Cys Ala Ser
545                 550                 555                 560

Ser His Gln Phe Leu Ser Thr His Tyr Asn Leu His Asn Leu Tyr Gly
                565                 570                 575

Leu Thr Glu Ala Ile Ala Ser His Arg Ala Leu Val Lys Ala Arg Gly
            580                 585                 590

Thr Arg Pro Phe Val Ile Ser Arg Ser Thr Phe Ala Gly His Gly Arg
        595                 600                 605

Tyr Ala Gly His Trp Thr Gly Asp Val Trp Ser Ser Trp Glu Gln Leu
    610                 615                 620

Ala Ser Ser Val Pro Glu Ile Leu Gln Phe Asn Leu Leu Gly Val Pro
625                 630                 635                 640

Leu Val Gly Ala Asp Val Cys Gly Phe Leu Gly Asn Thr Ser Glu Glu
                645                 650                 655

Leu Cys Val Arg Trp Thr Gln Leu Gly Ala Phe Tyr Pro Phe Met Arg
            660                 665                 670

Asn His Asn Ser Leu Leu Ser Leu Pro Gln Glu Pro Tyr Ser Phe Ser
        675                 680                 685

Glu Pro Ala Gln Gln Ala Met Arg Lys Ala Leu Thr Leu Arg Tyr Ala
    690                 695                 700

Leu Leu Pro His Leu Tyr Thr Leu Phe His Gln Ala His Val Ala Gly
705                 710                 715                 720

Glu Thr Val Ala Arg Pro Leu Phe Leu Glu Phe Pro Lys Asp Ser Ser
                725                 730                 735

Thr Trp Thr Val Asp His Gln Leu Leu Trp Gly Glu Ala Leu Leu Ile
            740                 745                 750

Thr Pro Val Leu Gln Ala Gly Lys Ala Glu Val Thr Gly Tyr Phe Pro
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        755                 760                 765

Leu Gly Thr Trp Tyr Asp Leu Gln Thr Val Pro Ile Glu Ala Leu Gly
    770                 775                 780

Ser Leu Pro Pro Pro Pro Ala Ala Pro Arg Glu Pro Ala Ile His Ser
785                 790                 795                 800

Glu Gly Gln Trp Val Thr Leu Pro Ala Pro Leu Asp Thr Ile Asn Val
                805                 810                 815

His Leu Arg Ala Gly Tyr Ile Ile Pro Leu Gln Gly Pro Gly Leu Thr
            820                 825                 830

Thr Thr Glu Ser Arg Gln Gln Pro Met Ala Leu Ala Val Ala Leu Thr
        835                 840                 845

Lys Gly Gly Glu Ala Arg Gly Glu Leu Phe Trp Asp Asp Gly Glu Ser
    850                 855                 860

Leu Glu Val Leu Glu Arg Gly Ala Tyr Thr Gln Val Ile Phe Leu Ala
865                 870                 875                 880

Arg Asn Asn Thr Ile Val Asn Glu Leu Val Arg Val Thr Ser Glu Gly
                885                 890                 895

Ala Gly Leu Gln Leu Gln Lys Val Thr Val Leu Gly Val Ala Thr Ala
            900                 905                 910

Pro Gln Gln Val Leu Ser Asn Gly Val Pro Val Ser Asn Phe Thr Tyr
        915                 920                 925

Ser Pro Asp Thr Lys Val Leu Asp Ile Cys Val Ser Leu Leu Met Gly
    930                 935                 940

Glu Gln Phe Leu Val Ser Trp Cys
945                 950


<210> SEQ ID NO 5
<211> LENGTH: 18
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 5

cgtgacaata cagctgag                                                  18


<210> SEQ ID NO 6
<211> LENGTH: 18
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 6

ctcagctgta ttgtcacg                                                  18


<210> SEQ ID NO 7
<211> LENGTH: 22
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 7

caccgtgaca acgcagctga gg                                             22


<210> SEQ ID NO 8
<211> LENGTH: 22
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
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<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 8

cctcagctgc gttgtcacgg tg 22

<210> SEQ ID NO 9
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 9

ggctgcgcgc ctgcgcttcg 20

<210> SEQ ID NO 10
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 10

cgaagcgcag gcgcgcagcc 20

<210> SEQ ID NO 11
<211> LENGTH: 22
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 11

gcgcttgcgc mtcgcttcct gg 22

<210> SEQ ID NO 12
<211> LENGTH: 22
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 12

ccaggaagcg akgcgcaagc gc 22

<210> SEQ ID NO 13
<211> LENGTH: 24
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 13

gcttcgcttc ccggccctcg tttc 24

<210> SEQ ID NO 14
<211> LENGTH: 24
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 14

gaaacgaggg ccgggaagcg aagc 24

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<210> SEQ ID NO 15
<211> LENGTH: 23
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 15

ggggctagag tactggacaa tgg 23

<210> SEQ ID NO 16
<211> LENGTH: 23
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 16

ccattgtcca gtactctagc ccc 23

<210> SEQ ID NO 17
<211> LENGTH: 21
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 17

gctagagcac cggacaatgg a 21

<210> SEQ ID NO 18
<211> LENGTH: 21
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 18

tccattgtcc ggtgctctag c 21

<210> SEQ ID NO 19
<211> LENGTH: 21
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 19

gctagagcac cggacaatgg a 21

<210> SEQ ID NO 20
<211> LENGTH: 21
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 20

tccattgtcc ggtgctctag c 21

<210> SEQ ID NO 21
<211> LENGTH: 23
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

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<400> SEQUENCE: 21

ctagagcact gtacaatgga ttg 23

<210> SEQ ID NO 22
<211> LENGTH: 23
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 22

caatccattg tacagtgctc tag 23

<210> SEQ ID NO 23
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 23

gcactggaca aaggattggc 20

<210> SEQ ID NO 24
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 24

gccaatcctt tgtccagtgc 20

<210> SEQ ID NO 25
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 25

gcactggaca gtggattggc 20

<210> SEQ ID NO 26
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 26

gccaatccac tgtccagtgc 20

<210> SEQ ID NO 27
<211> LENGTH: 21
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 27

ctggacaata gattggcaag g 21

<210> SEQ ID NO 28

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<211> LENGTH: 26
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 28

gtcagcaaaa ttttgccagt gattgc 26

<210> SEQ ID NO 29
<211> LENGTH: 23
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 29

gcgaaatttt actgacattg atg 23

<210> SEQ ID NO 30
<211> LENGTH: 23
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 30

catcaatgtc agtaaaattt cgc 23

<210> SEQ ID NO 31
<211> LENGTH: 31
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 31

ggcgaaattt tgctaacatt gatgattcct g 31

<210> SEQ ID NO 32
<211> LENGTH: 31
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 32

caggaatcat caatgttagc aaaatttcgc c 31

<210> SEQ ID NO 33
<211> LENGTH: 28
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 33

cgaaattttg ctggcattga tgatattc 28

<210> SEQ ID NO 34
<211> LENGTH: 28
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 34

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gaatatcatc aatgccagca aaatttcg 28

<210> SEQ ID NO 35
<211> LENGTH: 24
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 35

tgacattgat gagtcctgga aaag 24

<210> SEQ ID NO 36
<211> LENGTH: 24
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 36

cttttccagg actcatcaat gtca 24

<210> SEQ ID NO 37
<211> LENGTH: 26
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 37

gctgacattg attattcctg gaaaag 26

<210> SEQ ID NO 38
<211> LENGTH: 26
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 38

cttttccagg aataatcaat gtcagc 26

<210> SEQ ID NO 39
<211> LENGTH: 34
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 39

ctgacattga tgattgctgg aaaagtataa agag 34

<210> SEQ ID NO 40
<211> LENGTH: 34
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 40

ctctttatac ttttccagca atcatcaatg tcag 34

<210> SEQ ID NO 41
<211> LENGTH: 39
<212> TYPE: DNA

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<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 41

gctgacattg atgattcccg gaaaagtata aagagtatc 39

<210> SEQ ID NO 42
<211> LENGTH: 39
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 42

gatactcttt atacttttcc gggaatcatc aatgtcagc 39

<210> SEQ ID NO 43
<211> LENGTH: 23
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 43

tgatgattcc ttgaaaagta taa 23

<210> SEQ ID NO 44
<211> LENGTH: 23
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 44

ttatactttt caaggaatca tca 23

<210> SEQ ID NO 45
<211> LENGTH: 34
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 45

ctgacattga tgattccttg aaaagtataa agag 34

<210> SEQ ID NO 46
<211> LENGTH: 34
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 46

ctctttatac ttttcaagga atcatcaatg tcag 34

<210> SEQ ID NO 47
<211> LENGTH: 43
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 47

gctgacattg atgattcctg taaaagtata aagagtatct tgg 43

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<210> SEQ ID NO 48
<211> LENGTH: 43
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 48

ccaagatact ctttatactt ttacaggaat catcaatgtc agc 43

<210> SEQ ID NO 49
<211> LENGTH: 21
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 49

tggaaaagta caaagagtat c 21

<210> SEQ ID NO 50
<211> LENGTH: 21
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 50

gatactcttt gtacttttcc a 21

<210> SEQ ID NO 51
<211> LENGTH: 21
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 51

ccttgccaat ctattgtcca g 21

<210> SEQ ID NO 52
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 52

aatggattgg taaggacgcc 20

<210> SEQ ID NO 53
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 53

ggcgtcctta ccaatccatt 20

<210> SEQ ID NO 54
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:

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<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 54

gcaaggacgc ttaccatggg 20

<210> SEQ ID NO 55
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 55

cccatggtaa gcgtccttgc 20

<210> SEQ ID NO 56
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 56

gcaaggacgt ctaccatggg 20

<210> SEQ ID NO 57
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 57

cccatggtag acgtccttgc 20

<210> SEQ ID NO 58
<211> LENGTH: 27
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 58

aggacgccta ccacgggctg gctgcac 27

<210> SEQ ID NO 59
<211> LENGTH: 27
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 59

gtgcagccag cccgtggtag gcgtcct 27

<210> SEQ ID NO 60
<211> LENGTH: 27
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 60

aggacgccta ccttgggctg gctgcac 27

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<210> SEQ ID NO 61
<211> LENGTH: 27
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 61

gtgcagccag cccaaggtag gcgtcct 27

<210> SEQ ID NO 62
<211> LENGTH: 25
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 62

aggacgccta ccgtgggctg gctgc 25

<210> SEQ ID NO 63
<211> LENGTH: 25
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 63

gcagccagcc cacggtaggc gtcct 25

<210> SEQ ID NO 64
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 64

ctaccatggw ctggctgcac 20

<210> SEQ ID NO 65
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 65

gtgcagccag wccatggtag 20

<210> SEQ ID NO 66
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 66

ctaccatgcg ctggctgcac 20

<210> SEQ ID NO 67
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

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<400> SEQUENCE: 67

gtgcagccag cgcatggtag 20

<210> SEQ ID NO 68
<211> LENGTH: 19
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 68

catgggctgt ctgcactgg 19

<210> SEQ ID NO 69
<211> LENGTH: 19
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 69

ccagtgcaga cagcccatg 19

<210> SEQ ID NO 70
<211> LENGTH: 21
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 70

atgggctggc ggcactggga g 21

<210> SEQ ID NO 71
<211> LENGTH: 21
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 71

ctcccagtgc cgccagccca t 21

<210> SEQ ID NO 72
<211> LENGTH: 17
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 72

ctggctgcgc tgggagc 17

<210> SEQ ID NO 73
<211> LENGTH: 17
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 73

gctcccagcg cagccag 17

<210> SEQ ID NO 74
<211> LENGTH: 17

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<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 74

ctggctgtac tgggagc 17

<210> SEQ ID NO 75
<211> LENGTH: 17
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 75

gctcccagta cagccag 17

<210> SEQ ID NO 76
<211> LENGTH: 35
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 76

gattcctgga aaagtacaaa gagtatcttg gactg 35

<210> SEQ ID NO 77
<211> LENGTH: 35
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 77

cagtccaaga tactctttgt acttttccag gaatc 35

<210> SEQ ID NO 78
<211> LENGTH: 26
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 78

agtataaaga gtttcttgga ctggac 26

<210> SEQ ID NO 79
<211> LENGTH: 26
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 79

gtccagtcca agaaactctt tatact 26

<210> SEQ ID NO 80
<211> LENGTH: 23
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
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<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 80

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gtataaagag taacttggac tgg 23

<210> SEQ ID NO 81
<211> LENGTH: 23
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 81

ccagtccaag ttactcttta tac 23

<210> SEQ ID NO 82
<211> LENGTH: 22
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 82

agagtatctt cgactggaca tc 22

<210> SEQ ID NO 83
<211> LENGTH: 22
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 83

gatgtccagt cgaagatact ct 22

<210> SEQ ID NO 84
<211> LENGTH: 21
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 84

gagtatcttg cactggacat c 21

<210> SEQ ID NO 85
<211> LENGTH: 22
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 85

gatgtccagt cgaagatact ct 22

<210> SEQ ID NO 86
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<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 86

cttggactgg acatgtttta accaggagag 30

<210> SEQ ID NO 87
<211> LENGTH: 30
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence

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<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 87

ctctcctggt taaaacatgt ccagtccaag 30

<210> SEQ ID NO 88
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<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 88

ggactggaca ccttttaacc a 21

<210> SEQ ID NO 89
<211> LENGTH: 21
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 89

tggttaaaag gtgtccagtc c 21

<210> SEQ ID NO 90
<211> LENGTH: 19
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 90

gttgatgttc ctggaccag 19

<210> SEQ ID NO 91
<211> LENGTH: 19
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 91

ctggtccagg aacatcaac 19

<210> SEQ ID NO 92
<211> LENGTH: 19
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 92

gatgttgctc gaccagggg 19

<210> SEQ ID NO 93
<211> LENGTH: 19
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 93

cccctggtcg agcaacatc 19

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<210> SEQ ID NO 94
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<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 94

gatgttgctg gacgaggggg ttgga 25

<210> SEQ ID NO 95
<211> LENGTH: 25
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 95

tccaaccccc tcgtccagca acatc 25

<210> SEQ ID NO 96
<211> LENGTH: 21
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 96

gttgctggac taggggttg g 21

<210> SEQ ID NO 97
<211> LENGTH: 21
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 97

ccaacccct agtccagcaa c 21

<210> SEQ ID NO 98
<211> LENGTH: 22
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 98

gctggaccag cgggttggaa tg 22

<210> SEQ ID NO 99
<211> LENGTH: 22
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 99

cattccaacc cgctggtcca gc 22

<210> SEQ ID NO 100
<211> LENGTH: 21
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

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<400> SEQUENCE: 100

ggaccagggg attggaatga c 21

<210> SEQ ID NO 101
<211> LENGTH: 22
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 101

ctggctgcac ggggagcgct tc 22

<210> SEQ ID NO 102
<211> LENGTH: 22
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 102

gaagcgctcc ccgtgcagcc ag 22

<210> SEQ ID NO 103
<211> LENGTH: 22
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 103

ctggctgcac ttggagcgct tc 22

<210> SEQ ID NO 104
<211> LENGTH: 22
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 104

gaagcgctcc aagtgcagcc ag 22

<210> SEQ ID NO 105
<211> LENGTH: 22
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 105

gctgcactgg aagcgcttca tg 22

<210> SEQ ID NO 106
<211> LENGTH: 22
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 106

catgaagcgc ttccagtgca gc 22

<210> SEQ ID NO 107

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<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 107

actgggagcy cttcatgtgc 20

<210> SEQ ID NO 108
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 108

gcacatgaag rgctcccagt 20

<210> SEQ ID NO 109
<211> LENGTH: 19
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 109

cactgggagr gcttcatgt 19

<210> SEQ ID NO 110
<211> LENGTH: 19
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 110

acatgaagcy ctcccagtg 19

<210> SEQ ID NO 111
<211> LENGTH: 22
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 111

ctgggagcgc tgcatgtgca ac 22

<210> SEQ ID NO 112
<211> LENGTH: 22
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 112

gttgcacatg cagcgctccc ag 22

<210> SEQ ID NO 113
<211> LENGTH: 22
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 113

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gagcgcttca agtgcaacct tg 22

<210> SEQ ID NO 114
<211> LENGTH: 22
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 114

caaggttgca cttgaagcgc tc 22

<210> SEQ ID NO 115
<211> LENGTH: 17
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 115

gcgcttcata tgcaacc 17

<210> SEQ ID NO 116
<211> LENGTH: 17
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 116

ggttgcatat gaagcgc 17

<210> SEQ ID NO 117
<211> LENGTH: 26
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 117

gagcgcttca tgtccaacct tgactg 26

<210> SEQ ID NO 118
<211> LENGTH: 26
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 118

cagtcaaggt tggacatgaa gcgctc 26

<210> SEQ ID NO 119
<211> LENGTH: 21
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 119

cgcttcatgs gcaaccttga c 21

<210> SEQ ID NO 120
<211> LENGTH: 21
<212> TYPE: DNA

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<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 120

gtcaaggttg cscatgaagc g 21

<210> SEQ ID NO 121
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 121

caaccttgac ggccaggaag 20

<210> SEQ ID NO 122
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 122

cttcctggcc gtcaaggttg 20

<210> SEQ ID NO 123
<211> LENGTH: 22
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 123

caaccttgac twccaggaag ag 22

<210> SEQ ID NO 124
<211> LENGTH: 22
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 124

ctcttcctgg wagtcaaggt tg 22

<210> SEQ ID NO 125
<211> LENGTH: 29
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 125

gtgcaacctt gactaccagg aagagccag 29

<210> SEQ ID NO 126
<211> LENGTH: 21
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 126

gtcattccaa tcccctggtc c 21

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<210> SEQ ID NO 127
<211> LENGTH: 21
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 127

caggggttg caatgaccca g 21

<210> SEQ ID NO 128
<211> LENGTH: 21
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 128

ctgggtcatt gcaacccct g 21

<210> SEQ ID NO 129
<211> LENGTH: 19
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 129

ggggttggag tgacccaga 19

<210> SEQ ID NO 130
<211> LENGTH: 19
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 130

tctgggtcac tccaacccc 19

<210> SEQ ID NO 131
<211> LENGTH: 21
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 131

ggttggaatg tcccagatat g 21

<210> SEQ ID NO 132
<211> LENGTH: 21
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 132

catatctggg acattccaac c 21

<210> SEQ ID NO 133
<211> LENGTH: 22
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:

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<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 133

gggttggaat tacccagata tg 22

<210> SEQ ID NO 134
<211> LENGTH: 22
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 134

catatctggg taattccaac cc 22

<210> SEQ ID NO 135
<211> LENGTH: 21
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 135

tggaatgacc gagatatgtt a 21

<210> SEQ ID NO 136
<211> LENGTH: 21
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 136

taacatatct cggtcattcc a 21

<210> SEQ ID NO 137
<211> LENGTH: 23
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 137

ttggaatgac ctagatatgt tag 23

<210> SEQ ID NO 138
<211> LENGTH: 23
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 138

ctaacatatc taggtcattc caa 23

<210> SEQ ID NO 139
<211> LENGTH: 23
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 139

ggaatgaccc amatatgtta gtg 23

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<210> SEQ ID NO 140
<211> LENGTH: 22
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 140

cactaacata ttgggtcatt cc 22

<210> SEQ ID NO 141
<211> LENGTH: 32
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 141

ggttggaatg acccacatat gttagtgatt gg 32

<210> SEQ ID NO 142
<211> LENGTH: 32
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 142

ccaatcacta acatatgtgg gtcattccaa cc 32

<210> SEQ ID NO 143
<211> LENGTH: 22
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 143

gaatgaccca gttatgttag tg 22

<210> SEQ ID NO 144
<211> LENGTH: 22
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 144

cactaacata actgggtcat tc 22

<210> SEQ ID NO 145
<211> LENGTH: 21
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 145

atgacccaga aatgttagtg a 21

<210> SEQ ID NO 146
<211> LENGTH: 21
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

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<400> SEQUENCE: 146

tcactaacat ttctgggtca t 21

<210> SEQ ID NO 147
<211> LENGTH: 22
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 147

gacccagata ggttagtgat tg 22

<210> SEQ ID NO 148
<211> LENGTH: 22
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 148

caatcactaa cctatctggg tc 22

<210> SEQ ID NO 149
<211> LENGTH: 23
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 149

gacccagata tattagtgat tgg 23

<210> SEQ ID NO 150
<211> LENGTH: 23
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 150

ccaatcacta atatatctgg gtc 23

<210> SEQ ID NO 151
<211> LENGTH: 29
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 151

ctggctcttc ctggtagtca aggttgcac 29

<210> SEQ ID NO 152
<211> LENGTH: 28
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 152

gagccagatt cctacatcag tgagaagc 28

<210> SEQ ID NO 153
<211> LENGTH: 28

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<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 153

gcttctcact gatgtaggaa tctggctc 28

<210> SEQ ID NO 154
<211> LENGTH: 21
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 154

tcctgcatca ctgagaagct c 21

<210> SEQ ID NO 155
<211> LENGTH: 21
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 155

gagcttctca gtgatgcagg a 21

<210> SEQ ID NO 156
<211> LENGTH: 22
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 156

ctgcatcagt aagaagctct tc 22

<210> SEQ ID NO 157
<211> LENGTH: 22
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 157

gaagagcttc ttactgatgc ag 22

<210> SEQ ID NO 158
<211> LENGTH: 22
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 158

ctgcatcagt gggaagctct tc 22

<210> SEQ ID NO 159
<211> LENGTH: 22
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 159

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gaagagcttc ccactgatgc ag 22

<210> SEQ ID NO 160
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 160

cagtgagaag ttcttcatgg 20

<210> SEQ ID NO 161
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 161

ccaggaagaa cttctcactg 20

<210> SEQ ID NO 162
<211> LENGTH: 29
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 162

gcatcagtga gaagttcttc atggagatg 29

<210> SEQ ID NO 163
<211> LENGTH: 29
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 163

catctccatg aagaacttct cactgatgc 29

<210> SEQ ID NO 164
<211> LENGTH: 22
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 164

cttcatggag agggcagagc tc 22

<210> SEQ ID NO 165
<211> LENGTH: 22
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 165

gagctctgcc ctctccatga ag 22

<210> SEQ ID NO 166
<211> LENGTH: 22
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence

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<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 166

cttcatggag atagcagagc tc 22

<210> SEQ ID NO 167
<211> LENGTH: 22
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 167

gagctctgct atctccatga ag 22

<210> SEQ ID NO 168
<211> LENGTH: 22
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 168

catggagatg gtagagctca tg 22

<210> SEQ ID NO 169
<211> LENGTH: 22
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 169

catgagctct accatctcca tg 22

<210> SEQ ID NO 170
<211> LENGTH: 22
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 170

gcagagctca gggtctcaga ag 22

<210> SEQ ID NO 171
<211> LENGTH: 22
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 171

cttctgagac cctgagctct gc 22

<210> SEQ ID NO 172
<211> LENGTH: 25
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 172

ctcagaaggc tgtaaggatg caggt 25

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<210> SEQ ID NO 173
<211> LENGTH: 25
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 173

acctgcatcc ttacagcctt ctgag 25

<210> SEQ ID NO 174
<211> LENGTH: 22
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 174

ctcagaaggc tcgaaggatg ca 22

<210> SEQ ID NO 175
<211> LENGTH: 22
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 175

tgcatccttc gagccttctg ag 22

<210> SEQ ID NO 176
<211> LENGTH: 21
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 176

ccagatatgt cagtgattgg c 21

<210> SEQ ID NO 177
<211> LENGTH: 21
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 177

gccaatcact gacatatctg g 21

<210> SEQ ID NO 178
<211> LENGTH: 21
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 178

gatatgttag cgattggcaa c 21

<210> SEQ ID NO 179
<211> LENGTH: 21
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

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<400> SEQUENCE: 179

gttgccaatc gctaacatat c 21

<210> SEQ ID NO 180
<211> LENGTH: 23
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 180

cagatatgtt aatgattggc aac 23

<210> SEQ ID NO 181
<211> LENGTH: 23
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 181

gttgccaatc attaacatat ctg 23

<210> SEQ ID NO 182
<211> LENGTH: 23
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 182

tatgttagtg actggcaact ttg 23

<210> SEQ ID NO 183
<211> LENGTH: 23
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 183

caaagttgcc agtcactaac ata 23

<210> SEQ ID NO 184
<211> LENGTH: 19
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 184

ttagtgattg tcaactttg 19

<210> SEQ ID NO 185
<211> LENGTH: 19
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 185

caaagttgac aatcactaa 19

<210> SEQ ID NO 186

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<211> LENGTH: 21
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 186

gttagtgatt tgcaactttg g 21

<210> SEQ ID NO 187
<211> LENGTH: 21
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 187

ccaaagttgc aaatcactaa c 21

<210> SEQ ID NO 188
<211> LENGTH: 23
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 188

tgttagtgat tagcaacttt ggc 23

<210> SEQ ID NO 189
<211> LENGTH: 23
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 189

gccaaagttg ctaatcacta aca 23

<210> SEQ ID NO 190
<211> LENGTH: 23
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 190

gtgattggca aatttggcct cag 23

<210> SEQ ID NO 191
<211> LENGTH: 23
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 191

ctgaggccaa atttgccaat cac 23

<210> SEQ ID NO 192
<211> LENGTH: 21
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 192

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gtgattggca gctttggcct c 21

<210> SEQ ID NO 193
<211> LENGTH: 21
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 193

gaggccaaag ctgccaatca c 21

<210> SEQ ID NO 194
<211> LENGTH: 25
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 194

caactttggc ctcggctgga atcag 25

<210> SEQ ID NO 195
<211> LENGTH: 25
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 195

ctgattccag ccgaggccaa agttg 25

<210> SEQ ID NO 196
<211> LENGTH: 23
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 196

ctttggcctc aactggaatc agc 23

<210> SEQ ID NO 197
<211> LENGTH: 23
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 197

gctgattcca gttgaggcca aag 23

<210> SEQ ID NO 198
<211> LENGTH: 22
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 198

agctggaatc ggcaagtaac tc 22

<210> SEQ ID NO 199
<211> LENGTH: 22
<212> TYPE: DNA

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<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 199

gagttacttg ccgattccag ct 22

<210> SEQ ID NO 200
<211> LENGTH: 23
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 200

cagctggaat caccaagtaa ctc 23

<210> SEQ ID NO 201
<211> LENGTH: 22
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 201

gaaggatgca gattatgagt ac 22

<210> SEQ ID NO 202
<211> LENGTH: 22
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 202

gtactcataa tctgcatcct tc 22

<210> SEQ ID NO 203
<211> LENGTH: 25
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 203

ggatgcaggt tgtgagtacc tctgc 25

<210> SEQ ID NO 204
<211> LENGTH: 25
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 204

gcagaggtac tcacaacctg catcc 25

<210> SEQ ID NO 205
<211> LENGTH: 22
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 205

ggttatgagg acctctgcat tg 22

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<210> SEQ ID NO 206
<211> LENGTH: 22
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 206

caatgcagag gtcctcataa cc 22

<210> SEQ ID NO 207
<211> LENGTH: 24
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 207

gttatgagta ccsctgcatt gatg 24

<210> SEQ ID NO 208
<211> LENGTH: 24
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 208

catcaatgca gsggtactca taac 24

<210> SEQ ID NO 209
<211> LENGTH: 21
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 209

cctctgcatt hatgactgtt g 21

<210> SEQ ID NO 210
<211> LENGTH: 21
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 210

caacagtcat daatgcagag g 21

<210> SEQ ID NO 211
<211> LENGTH: 27
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 211

tacctctgca ttaatgactg ttggatg 27

<210> SEQ ID NO 212
<211> LENGTH: 27
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:

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<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 212

catccaacag tcattaatgc agaggta 27

<210> SEQ ID NO 213
<211> LENGTH: 27
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 213

tacctctgca ttcatgactg ttggatg 27

<210> SEQ ID NO 214
<211> LENGTH: 27
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 214

catccaacag tcatgaatgc agaggta 27

<210> SEQ ID NO 215
<211> LENGTH: 34
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 215

gagtacctct gcatttatga ctgttggatg gctc 34

<210> SEQ ID NO 216
<211> LENGTH: 34
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 216

gagccatcca acagtcataa atgcagaggt actc 34

<210> SEQ ID NO 217
<211> LENGTH: 22
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 217

ctgcattgat ggctgttgga tg 22

<210> SEQ ID NO 218
<211> LENGTH: 22
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 218

catccaacag ccatcaatgc ag 22

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<210> SEQ ID NO 219
<211> LENGTH: 22
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 219

ctgcattgat gtctgttgga tg 22

<210> SEQ ID NO 220
<211> LENGTH: 22
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 220

catccaacag acatcaatgc ag 22

<210> SEQ ID NO 221
<211> LENGTH: 22
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 221

ctgcattgat aactgttgga tg 22

<210> SEQ ID NO 222
<211> LENGTH: 22
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 222

catccaacag ttatcaatgc ag 22

<210> SEQ ID NO 223
<211> LENGTH: 24
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 223

gcattgatga ctcttggatg gctc 24

<210> SEQ ID NO 224
<211> LENGTH: 24
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 224

gagccatcca agagtcatca atgc 24

<210> SEQ ID NO 225
<211> LENGTH: 23
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

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<400> SEQUENCE: 225

gagttacttg gtgattccag ctg 23

<210> SEQ ID NO 226
<211> LENGTH: 21
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 226

cagctggaat aagcaagtaa c 21

<210> SEQ ID NO 227
<211> LENGTH: 21
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 227

gttacttgct tattccagct g 21

<210> SEQ ID NO 228
<211> LENGTH: 21
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 228

ggaatcagca tgtaactcag a 21

<210> SEQ ID NO 229
<211> LENGTH: 21
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 229

tctgagttac atgctgattc c 21

<210> SEQ ID NO 230
<211> LENGTH: 22
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 230

ctggaatcag aaagtaactc ag 22

<210> SEQ ID NO 231
<211> LENGTH: 21
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 231

ctgagttact ttctgattcc a 21

<210> SEQ ID NO 232
<211> LENGTH: 21

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<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 232

cagcaagtaa atcagatggc c 21

<210> SEQ ID NO 233
<211> LENGTH: 21
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 233

ggccatctga tttacttgct g 21

<210> SEQ ID NO 234
<211> LENGTH: 21
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 234

caagtaactc cgatggccct c 21

<210> SEQ ID NO 235
<211> LENGTH: 21
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 235

gagggccatc ggagttactt g 21

<210> SEQ ID NO 236
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 236

gtaactcaga cggccctctg 20

<210> SEQ ID NO 237
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 237

cagagggccg tctgagttac 20

<210> SEQ ID NO 238
<211> LENGTH: 23
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 238

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taactcagat gcccctctgg gct 23

<210> SEQ ID NO 239
<211> LENGTH: 23
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 239

agcccagagg ggcatctgag tta 23

<210> SEQ ID NO 240
<211> LENGTH: 22
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 240

aactcagatg gacctctggg ct 22

<210> SEQ ID NO 241
<211> LENGTH: 22
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 241

agcccagagg tccatctgag tt 22

<210> SEQ ID NO 242
<211> LENGTH: 21
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 242

gatggccctc ggggctatca t 21

<210> SEQ ID NO 243
<211> LENGTH: 21
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 243

atgatagccc cgagggccat c 21

<210> SEQ ID NO 244
<211> LENGTH: 21
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 244

atggccctct gtgctatcat g 21

<210> SEQ ID NO 245
<211> LENGTH: 21
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence

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<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 245

catgatagca cagagggcca t 21

<210> SEQ ID NO 246
<211> LENGTH: 22
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 246

gccctctggg atatcatggc tg 22

<210> SEQ ID NO 247
<211> LENGTH: 22
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 247

cagccatgat atcccagagg gc 22

<210> SEQ ID NO 248
<211> LENGTH: 19
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 248

gccctctggc ctatcatgg 19

<210> SEQ ID NO 249
<211> LENGTH: 24
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 249

gcattgatga ctattggatg gctc 24

<210> SEQ ID NO 250
<211> LENGTH: 24
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 250

gagccatcca atagtcatca atgc 24

<210> SEQ ID NO 251
<211> LENGTH: 21
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 251

gatgactgtt cgatggctcc c 21

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<210> SEQ ID NO 252
<211> LENGTH: 21
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 252

gggagccatc gaacagtcat c 21

<210> SEQ ID NO 253
<211> LENGTH: 23
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 253

ctgttggatg cctccccaaa gag 23

<210> SEQ ID NO 254
<211> LENGTH: 23
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 254

ctctttgggg aggcatccaa cag 23

<210> SEQ ID NO 255
<211> LENGTH: 22
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 255

gctccccaaa magattcaga ag 22

<210> SEQ ID NO 256
<211> LENGTH: 22
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 256

cttctgaatc tktttgggga gc 22

<210> SEQ ID NO 257
<211> LENGTH: 24
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 257

ggctccccaa acagattcag aagg 24

<210> SEQ ID NO 258
<211> LENGTH: 24
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

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<400> SEQUENCE: 258

ccttctgaat ctgtttgggg agcc 24

<210> SEQ ID NO 259
<211> LENGTH: 25
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 259

caaagagatt cacaaggcag acttc 25

<210> SEQ ID NO 260
<211> LENGTH: 25
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 260

gaagtctgcc ttgtgaatct ctttg 25

<210> SEQ ID NO 261
<211> LENGTH: 25
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 261

gcagaccctc agagctttcc tcatg 25

<210> SEQ ID NO 262
<211> LENGTH: 25
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 262

catgaggaaa gctctgaggg tctgc 25

<210> SEQ ID NO 263
<211> LENGTH: 24
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 263

cagaccctca gtgctttcct catg 24

<210> SEQ ID NO 264
<211> LENGTH: 24
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 264

catgaggaaa gcactgaggg tctg 24

<210> SEQ ID NO 265

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<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
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<400> SEQUENCE: 265

ccctcagcgc tctcctcatg 20

<210> SEQ ID NO 266
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 266

catgaggaga gcgctgaggg 20

<210> SEQ ID NO 267
<211> LENGTH: 22
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 267

ctcatgggat ttgccagcta gc 22

<210> SEQ ID NO 268
<211> LENGTH: 22
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 268

gctagctggc aaatcccatg ag 22

<210> SEQ ID NO 269
<211> LENGTH: 23
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 269

gattcgccag ccagctaatt atg 23

<210> SEQ ID NO 270
<211> LENGTH: 23
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 270

cataattagc tggctggcga atc 23

<210> SEQ ID NO 271
<211> LENGTH: 28
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 271

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tcgccagcta mctaattatg ttcacagc 28

<210> SEQ ID NO 272
<211> LENGTH: 28
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<220> FEATURE:
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<400> SEQUENCE: 272

gctgtgaaca taattagkta gctggcga 28

<210> SEQ ID NO 273
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<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
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<400> SEQUENCE: 273

gctagctaat tatgatcaca gcaaaggac 29

<210> SEQ ID NO 274
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<212> TYPE: DNA
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<220> FEATURE:
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<400> SEQUENCE: 274

ccatgatagg ccagagggc 19

<210> SEQ ID NO 275
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<212> TYPE: DNA
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<400> SEQUENCE: 275

ctctgggctt tcatggctgc tccttt 25

<210> SEQ ID NO 276
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<212> TYPE: DNA
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<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 276

aaggagcagc catgaaagcc cagag 25

<210> SEQ ID NO 277
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<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 277

gggctatcat cgctgctcct t 21

<210> SEQ ID NO 278
<211> LENGTH: 21
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<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 278

aaggagcagc gatgatagcc c 21

<210> SEQ ID NO 279
<211> LENGTH: 23
<212> TYPE: DNA
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<220> FEATURE:
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<400> SEQUENCE: 279

ctatcatggc tcctccttta ttc 23

<210> SEQ ID NO 280
<211> LENGTH: 23
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
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<400> SEQUENCE: 280

gaataaagga ggagccatga tag 23

<210> SEQ ID NO 281
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<212> TYPE: DNA
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<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 281

catggctgct gctttattca tg 22

<210> SEQ ID NO 282
<211> LENGTH: 22
<212> TYPE: DNA
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<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 282

catgaataaa gcagcagcca tg 22

<210> SEQ ID NO 283
<211> LENGTH: 22
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

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catggctgct wctttattca tg 22

<210> SEQ ID NO 284
<211> LENGTH: 22
<212> TYPE: DNA
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<220> FEATURE:
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<400> SEQUENCE: 284

catgaataaa gwagcagcca tg 22

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<210> SEQ ID NO 285
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<212> TYPE: DNA
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<220> FEATURE:
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<400> SEQUENCE: 285

gctgctcctt tatgcatgtc taatgacc 28

<210> SEQ ID NO 286
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<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
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<400> SEQUENCE: 286

ggtcattaga catgcataaa ggagcagc 28

<210> SEQ ID NO 287
<211> LENGTH: 25
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 287

ctttattcat gtktaatgac ctccg 25

<210> SEQ ID NO 288
<211> LENGTH: 25
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 288

cggaggtcat tamacatgaa taaag 25

<210> SEQ ID NO 289
<211> LENGTH: 23
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 289

attcatgtct agtgacctcc gac 23

<210> SEQ ID NO 290
<211> LENGTH: 23
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 290

gtcggaggtc actagacatg aat 23

<210> SEQ ID NO 291
<211> LENGTH: 24
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:

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<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 291

tattcatgtc taaggacctc cgac 24

<210> SEQ ID NO 292
<211> LENGTH: 24
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 292

gtcggaggtc cttagacatg aata 24

<210> SEQ ID NO 293
<211> LENGTH: 24
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 293

tattcatgtc tcatgacctc cgac 24

<210> SEQ ID NO 294
<211> LENGTH: 24
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 294

gtcggaggtc atgagacatg aata 24

<210> SEQ ID NO 295
<211> LENGTH: 26
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 295

tcatgtctaa tggcctccga cacatc 26

<210> SEQ ID NO 296
<211> LENGTH: 26
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 296

gatgtgtcgg aggccattag acatga 26

<210> SEQ ID NO 297
<211> LENGTH: 24
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 297

gtctaatgac ccccgacaca tcag 24

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<210> SEQ ID NO 298
<211> LENGTH: 24
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 298

ctgatgtgtc gggggtcatt agac 24

<210> SEQ ID NO 299
<211> LENGTH: 29
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 299

gtcctttgct gtgatcataa ttagctagc 29

<210> SEQ ID NO 300
<211> LENGTH: 22
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 300

cacagcaaag aactgaagct ag 22

<210> SEQ ID NO 301
<211> LENGTH: 22
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 301

ctagcttcag ttctttgctg tg 22

<210> SEQ ID NO 302
<211> LENGTH: 21
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 302

cagcaaagga ccgaagctag g 21

<210> SEQ ID NO 303
<211> LENGTH: 24
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 303

atccctagct tcggtccttt gctg 24

<210> SEQ ID NO 304
<211> LENGTH: 24
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

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<400> SEQUENCE: 304

aggactgaag ccagggattt atgc 24

<210> SEQ ID NO 305
<211> LENGTH: 24
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 305

gcataaatcc ctggcttcag tcct 24

<210> SEQ ID NO 306
<211> LENGTH: 28
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 306

ggactgaagc tagagattta tgcagatg 28

<210> SEQ ID NO 307
<211> LENGTH: 28
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 307

catctgcata aatctctagc ttcagtcc 28

<210> SEQ ID NO 308
<211> LENGTH: 27
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 308

gactgaagct aaggatttat gcagatg 27

<210> SEQ ID NO 309
<211> LENGTH: 27
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 309

catctgcata aatccttagc ttcagtc 27

<210> SEQ ID NO 310
<211> LENGTH: 24
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 310

gctagggatt tctgcagatg ttgg 24

<210> SEQ ID NO 311
<211> LENGTH: 24

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<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 311

ccaacatctg cagaaatccc tagc 24

<210> SEQ ID NO 312
<211> LENGTH: 25
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 312

gctagggatt tatgtagatg ttgga 25

<210> SEQ ID NO 313
<211> LENGTH: 25
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 313

tccaacatct acataaatcc ctagc 25

<210> SEQ ID NO 314
<211> LENGTH: 21
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 314

ggatttatgc acatgttgga a 21

<210> SEQ ID NO 315
<211> LENGTH: 21
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 315

ttccaacatg tgcataaatc c 21

<210> SEQ ID NO 316
<211> LENGTH: 30
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 316

gggatttatg cacatgttgg aaataaaacc 30

<210> SEQ ID NO 317
<211> LENGTH: 30
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 317

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ggttttattt ccaacatgtg cataaatccc 30

<210> SEQ ID NO 318
<211> LENGTH: 24
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 318

tgcagatgtt gaaaataaaa cctg 24

<210> SEQ ID NO 319
<211> LENGTH: 24
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 319

caggttttat tttcaacatc tgca 24

<210> SEQ ID NO 320
<211> LENGTH: 24
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 320

tgcagatgtt agaaataaaa cctg 24

<210> SEQ ID NO 321
<211> LENGTH: 24
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 321

caggttttat ttctaacatc tgca 24

<210> SEQ ID NO 322
<211> LENGTH: 37
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 322

ggatttatgc agatgttgaa aataaaacct gcgcagc 37

<210> SEQ ID NO 323
<211> LENGTH: 37
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 323

gctgcgcagg ttttattttc aacatctgca taaatcc 37

<210> SEQ ID NO 324
<211> LENGTH: 22
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence

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<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 324

gtctaatgac ttccgacaca tc 22

<210> SEQ ID NO 325
<211> LENGTH: 22
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 325

gatgtgtcgg aagtcattag ac 22

<210> SEQ ID NO 326
<211> LENGTH: 22
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 326

gtctaatgac caccgacaca tc 22

<210> SEQ ID NO 327
<211> LENGTH: 22
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 327

gatgtgtcgg tggtcattag ac 22

<210> SEQ ID NO 328
<211> LENGTH: 23
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 328

ctaatgacct cggacacatc agc 23

<210> SEQ ID NO 329
<211> LENGTH: 23
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 329

gctgatgtgt ccgaggtcat tag 23

<210> SEQ ID NO 330
<211> LENGTH: 23
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 330

ctaatgacct cccacacatc agc 23

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<210> SEQ ID NO 331
<211> LENGTH: 23
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 331

gctgatgtgt gggaggtcat tag 23

<210> SEQ ID NO 332
<211> LENGTH: 23
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 332

ctccgacaca acagccctca agc 23

<210> SEQ ID NO 333
<211> LENGTH: 23
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 333

gcttgagggc tgttgtgtcg gag 23

<210> SEQ ID NO 334
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 334

gccaaagctt tccttcagga 20

<210> SEQ ID NO 335
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 335

tcctgaagga aagctttggc 20

<210> SEQ ID NO 336
<211> LENGTH: 22
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 336

gctctccttc acgataagga cg 22

<210> SEQ ID NO 337
<211> LENGTH: 22
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

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<400> SEQUENCE: 337

cgtccttatc gtgaaggaga gc 22

<210> SEQ ID NO 338
<211> LENGTH: 21
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 338

ctctccttca gtataaggac g 21

<210> SEQ ID NO 339
<211> LENGTH: 21
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 339

cgtccttata ctgaaggaga g 21

<210> SEQ ID NO 340
<211> LENGTH: 21
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 340

gataaggacg aaattgccat c 21

<210> SEQ ID NO 341
<211> LENGTH: 21
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 341

gatggcaatt tcgtccttat c 21

<210> SEQ ID NO 342
<211> LENGTH: 22
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 342

aaggacgtaa mtgccatcaa tc 22

<210> SEQ ID NO 343
<211> LENGTH: 22
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 343

gattgatggc akttacgtcc tt 22

<210> SEQ ID NO 344

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<211> LENGTH: 22
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 344

aattgccatc attcaggacc cc 22

<210> SEQ ID NO 345
<211> LENGTH: 22
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 345

ggggtcctga atgatggcaa tt 22

<210> SEQ ID NO 346
<211> LENGTH: 22
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 346

aattgccatc aagcaggacc cc 22

<210> SEQ ID NO 347
<211> LENGTH: 22
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 347

ggggtcctgc ttgatggcaa tt 22

<210> SEQ ID NO 348
<211> LENGTH: 22
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 348

aattgccatc tatcaggacc cc 22

<210> SEQ ID NO 349
<211> LENGTH: 37
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 349

ggatttatgc agatgttcga aataaaacct gcgcagc 37

<210> SEQ ID NO 350
<211> LENGTH: 37
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 350

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ggatttatgc agatgttcga aataaaacct gcgcagc 37

<210> SEQ ID NO 351
<211> LENGTH: 22
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 351

ggaaataaaa tctgcgcagg ct 22

<210> SEQ ID NO 352
<211> LENGTH: 22
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 352

agcctgcgca gattttattt cc 22

<210> SEQ ID NO 353
<211> LENGTH: 24
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 353

ggaaataaaa cccgcgcagg cttc 24

<210> SEQ ID NO 354
<211> LENGTH: 24
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 354

gaagcctgcg cgggttttat ttcc 24

<210> SEQ ID NO 355
<211> LENGTH: 24
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 355

gaaataaaac ctrcgcaggc ttcc 24

<210> SEQ ID NO 356
<211> LENGTH: 24
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 356

ggaagcctgc gyaggtttta tttc 24

<210> SEQ ID NO 357
<211> LENGTH: 28
<212> TYPE: DNA

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<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 357

ggaaataaaa cctgggcagg cttccctg 28

<210> SEQ ID NO 358
<211> LENGTH: 28
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 358

cagggaagcc tgcccaggtt ttatttcc 28

<210> SEQ ID NO 359
<211> LENGTH: 25
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 359

gaaataaaac ctgcacaggc ttccc 25

<210> SEQ ID NO 360
<211> LENGTH: 25
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 360

gggaagcctg tgcaggtttt atttc 25

<210> SEQ ID NO 361
<211> LENGTH: 22
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 361

ataaaacctg cccaggcttc cc 22

<210> SEQ ID NO 362
<211> LENGTH: 22
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 362

gggaagcctg ggcaggtttt at 22

<210> SEQ ID NO 363
<211> LENGTH: 19
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 363

cctgcgcagt cttccctgg 19

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<210> SEQ ID NO 364
<211> LENGTH: 19
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 364

ccagggaaga ctgcgcagg 19

<210> SEQ ID NO 365
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 365

ggcttcccta ggagttttgg 20

<210> SEQ ID NO 366
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 366

ccaaaactcc tagggaagcc 20

<210> SEQ ID NO 367
<211> LENGTH: 21
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 367

ttccctggga attttggata c 21

<210> SEQ ID NO 368
<211> LENGTH: 21
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 368

gtatccaaaa ttcccaggga a 21

<210> SEQ ID NO 369
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 369

ccctgggagg tttggatact 20

<210> SEQ ID NO 370
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:

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<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 370

agtatccaaa cctcccaggg 20

<210> SEQ ID NO 371
<211> LENGTH: 24
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 371

gttttggata ctgcgacatt gatg 24

<210> SEQ ID NO 372
<211> LENGTH: 24
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 372

catcaatgtc gcagtatcca aaac 24

<210> SEQ ID NO 373
<211> LENGTH: 22
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 373

ggggtcctga tagatggcaa tt 22

<210> SEQ ID NO 374
<211> LENGTH: 22
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 374

tgccatcaat gaggacccct tg 22

<210> SEQ ID NO 375
<211> LENGTH: 22
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 375

caaggggtcc tcattgatgg ca 22

<210> SEQ ID NO 376
<211> LENGTH: 22
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 376

tgccatcaat cgggacccct tg 22

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<210> SEQ ID NO 377
<211> LENGTH: 22
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 377

caaggggtcc cgattgatgg ca 22

<210> SEQ ID NO 378
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 378

ggacccccttg gacaagcaag 20

<210> SEQ ID NO 379
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 379

cttgcttgtc caaggggtcc 20

<210> SEQ ID NO 380
<211> LENGTH: 22
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 380

cttgggcaag raagggtacc ag 22

<210> SEQ ID NO 381
<211> LENGTH: 22
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 381

ctggtaccct tycttgccca ag 22

<210> SEQ ID NO 382
<211> LENGTH: 19
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 382

ggcaagcaaa ggtaccagc 19

<210> SEQ ID NO 383
<211> LENGTH: 19
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

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<400> SEQUENCE: 383

gctggtacct ttgcttgcc 19

<210> SEQ ID NO 384
<211> LENGTH: 19
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 384

ggcaagcaag ygtaccagc 19

<210> SEQ ID NO 385
<211> LENGTH: 19
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 385

gctggtacrc ttgcttgcc 19

<210> SEQ ID NO 386
<211> LENGTH: 25
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 386

tgggcaagca agagtaccag cttag 25

<210> SEQ ID NO 387
<211> LENGTH: 25
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 387

ctaagctggt actcttgctt gccca 25

<210> SEQ ID NO 388
<211> LENGTH: 21
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 388

gagacaactt taaagtgtgg g 21

<210> SEQ ID NO 389
<211> LENGTH: 21
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 389

cccacacttt aaagttgtct c 21

<210> SEQ ID NO 390
<211> LENGTH: 20

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<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 390

ctttgaagtg cgggaacgac 20

<210> SEQ ID NO 391
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 391

gtcgttcccg cacttcaaag 20

<210> SEQ ID NO 392
<211> LENGTH: 23
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 392

gaagtgtggg accgacctct ctc 23

<210> SEQ ID NO 393
<211> LENGTH: 23
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 393

gagagaggtc ggtcccacac ttc 23

<210> SEQ ID NO 394
<211> LENGTH: 23
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 394

gaagtgtgga aacgacctct ctc 23

<210> SEQ ID NO 395
<211> LENGTH: 23
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 395

gagagaggtc gtttccacac ttc 23

<210> SEQ ID NO 396
<211> LENGTH: 22
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 396

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gtgtgggaac aacctctctc ag 22

<210> SEQ ID NO 397
<211> LENGTH: 21
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 397

ctacgacatt catgcccaga c 21

<210> SEQ ID NO 398
<211> LENGTH: 21
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 398

gtctgggcat gaatgtcgta g 21

<210> SEQ ID NO 399
<211> LENGTH: 22
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 399

gacattgata cccagacctt tg 22

<210> SEQ ID NO 400
<211> LENGTH: 22
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 400

caaaggtctg ggtatcaatg tc 22

<210> SEQ ID NO 401
<211> LENGTH: 23
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 401

ctttgctgac cggggagtag atc 23

<210> SEQ ID NO 402
<211> LENGTH: 23
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 402

gatctactcc ccggtcagca aag 23

<210> SEQ ID NO 403
<211> LENGTH: 23
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence

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<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 403

ctttgctgac tgcggagtag atc 23

<210> SEQ ID NO 404
<211> LENGTH: 23
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 404

gatctactcc gcagtcagca aag 23

<210> SEQ ID NO 405
<211> LENGTH: 21
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 405

gctgactggg tagtagatct g 21

<210> SEQ ID NO 406
<211> LENGTH: 21
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 406

cagatctact acccagtcag c 21

<210> SEQ ID NO 407
<211> LENGTH: 26
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 407

ctggggagta gttctgctaa aatttg 26

<210> SEQ ID NO 408
<211> LENGTH: 26
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 408

caaattttag cagaactact ccccag 26

<210> SEQ ID NO 409
<211> LENGTH: 25
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 409

gagtagatct gccaaaattt gatgg 25

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<210> SEQ ID NO 410
<211> LENGTH: 25
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 410

ccatcaaatt ttggcagatc tactc 25

<210> SEQ ID NO 411
<211> LENGTH: 27
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 411

gtagatctgc taagatttga tggtttg 27

<210> SEQ ID NO 412
<211> LENGTH: 27
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 412

caaaccatca aatcttagca gatctac 27

<210> SEQ ID NO 413
<211> LENGTH: 32
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 413

gtagatctgc taaaatctga tggttgttac tg 32

<210> SEQ ID NO 414
<211> LENGTH: 32
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 414

cagtaacaac catcagattt tagcagatct ac 32

<210> SEQ ID NO 415
<211> LENGTH: 24
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 415

gctaaaattt gttggttgtt actg 24

<210> SEQ ID NO 416
<211> LENGTH: 24
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

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<400> SEQUENCE: 416

cagtaacaac caacaaattt tagc 24

<210> SEQ ID NO 417
<211> LENGTH: 24
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 417

gctaaaattt catggttgtt actg 24

<210> SEQ ID NO 418
<211> LENGTH: 24
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 418

cagtaacaac catgaaattt tagc 24

<210> SEQ ID NO 419
<211> LENGTH: 27
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 419

ctaaaatttg atgattgtta ctgtgac 27

<210> SEQ ID NO 420
<211> LENGTH: 27
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 420

gtcacagtaa caatcatcaa attttag 27

<210> SEQ ID NO 421
<211> LENGTH: 27
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 421

ctaaaatttg atcgttgtta ctgtgac 27

<210> SEQ ID NO 422
<211> LENGTH: 22
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 422

ctgagagagg ttgttcccac ac 22

<210> SEQ ID NO 423

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<211> LENGTH: 22
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 423

gaacgacctc cctcaggctt ag 22

<210> SEQ ID NO 424
<211> LENGTH: 22
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 424

ctaagcctga gggaggtcgt tc 22

<210> SEQ ID NO 425
<211> LENGTH: 21
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 425

cgacctctcc caggcttagc c 21

<210> SEQ ID NO 426
<211> LENGTH: 21
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 426

ggctaagcct gggagaggtc g 21

<210> SEQ ID NO 427
<211> LENGTH: 23
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 427

ctcaggctta ccctgggctg tag 23

<210> SEQ ID NO 428
<211> LENGTH: 23
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 428

ctacagccca gggtaagcct gag 23

<210> SEQ ID NO 429
<211> LENGTH: 22
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 429

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cttagcctgg cctgtagcta tg 22

<210> SEQ ID NO 430
<211> LENGTH: 22
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 430

catagctaca ggccaggcta ag 22

<210> SEQ ID NO 431
<211> LENGTH: 22
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 431

ctgggctgta gatatgataa ac 22

<210> SEQ ID NO 432
<211> LENGTH: 22
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 432

gtttatcata tctacagccc ag 22

<210> SEQ ID NO 433
<211> LENGTH: 22
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 433

gtagctatga aaaaccggca gg 22

<210> SEQ ID NO 434
<211> LENGTH: 22
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 434

cctgccggtt tttcatagct ac 22

<210> SEQ ID NO 435
<211> LENGTH: 21
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 435

gctatgataa aacggcagga g 21

<210> SEQ ID NO 436
<211> LENGTH: 21
<212> TYPE: DNA

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<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 436

ctcctgccgt tttatcatag c 21

<210> SEQ ID NO 437
<211> LENGTH: 24
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 437

gctatgataa actggcagga gatt 24

<210> SEQ ID NO 438
<211> LENGTH: 24
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 438

aatctcctgc cagtttatca tagc 24

<210> SEQ ID NO 439
<211> LENGTH: 21
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 439

accggcaggs gattggtgga c 21

<210> SEQ ID NO 440
<211> LENGTH: 21
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 440

gtccaccaat cscctgccgg t 21

<210> SEQ ID NO 441
<211> LENGTH: 24
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 441

gataaaccgg cagaagattg gtgg 24

<210> SEQ ID NO 442
<211> LENGTH: 24
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 442

ccaccaatct tctgccggtt tatc 24

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<210> SEQ ID NO 443
<211> LENGTH: 29
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 443

gataaaccgg caggcgattg gtggacctc 29

<210> SEQ ID NO 444
<211> LENGTH: 29
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 444

gaggtccacc aatcgcctgc cggtttatc 29

<210> SEQ ID NO 445
<211> LENGTH: 23
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 445

ccggcaggag actggtggac ctc 23

<210> SEQ ID NO 446
<211> LENGTH: 23
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 446

gaggtccacc agtctcctgc cgg 23

<210> SEQ ID NO 447
<211> LENGTH: 27
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 447

gtcacagtaa caacgatcaa attttag 27

<210> SEQ ID NO 448
<211> LENGTH: 30
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 448

ctaaaatttg atggttwtta ctgtgacagt 30

<210> SEQ ID NO 449
<211> LENGTH: 30
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:

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<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 449

actgtcacag taawaaccat caaattttag 30

<210> SEQ ID NO 450
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<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 450

ctaaaatttg atggttggta ctgtgacagt 30

<210> SEQ ID NO 451
<211> LENGTH: 30
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 451

actgtcacag taccaaccat caaattttag 30

<210> SEQ ID NO 452
<211> LENGTH: 30
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 452

ctaaaatttg atggtcgtta ctgtgacagt 30

<210> SEQ ID NO 453
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<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 453

actgtcacag taacgaccat caaattttag 30

<210> SEQ ID NO 454
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<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
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<400> SEQUENCE: 454

ctaaaatttg atggtggtta ctgtgacagt 30

<210> SEQ ID NO 455
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<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

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actgtcacag taaccaccat caaattttag 30

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<210> SEQ ID NO 456
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<212> TYPE: DNA
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<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 456

ttggcagatg attataagca c 21

<210> SEQ ID NO 457
<211> LENGTH: 21
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 457

gtgcttataa tcatctgcca a 21

<210> SEQ ID NO 458
<211> LENGTH: 21
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 458

ttggcagata gttataagca c 21

<210> SEQ ID NO 459
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<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 459

gtgcttataa ctatctgcca a 21

<210> SEQ ID NO 460
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<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 460

gttataagca cacgtccttg gccct 25

<210> SEQ ID NO 461
<211> LENGTH: 25
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 461

agggccaagg acgtgtgctt ataac 25

<210> SEQ ID NO 462
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<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

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<400> SEQUENCE: 462

gttataagca cgtgtccttg gcc 23

<210> SEQ ID NO 463
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<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 463

ggccaaggac acgtgcttat aac 23

<210> SEQ ID NO 464
<211> LENGTH: 23
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
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<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 464

gtccttggcc cagaatagga ctg 23

<210> SEQ ID NO 465
<211> LENGTH: 23
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 465

cagtcctatt ctgggccaag gac 23

<210> SEQ ID NO 466
<211> LENGTH: 23
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 466

gtccttggcc ccgaatagga ctg 23

<210> SEQ ID NO 467
<211> LENGTH: 23
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 467

cagtcctatt cggggccaag gac 23

<210> SEQ ID NO 468
<211> LENGTH: 21
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 468

ctgaatagga ttggcagaag c 21

<210> SEQ ID NO 469
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<212> TYPE: DNA
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<400> SEQUENCE: 469

gcttctgcca atcctattca g 21

<210> SEQ ID NO 470
<211> LENGTH: 21
<212> TYPE: DNA
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<220> FEATURE:
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<400> SEQUENCE: 470

cagaagcatt atgtactcct g 21

<210> SEQ ID NO 471
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<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 471

caggagtaca taatgcttct g 21

<210> SEQ ID NO 472
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<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 472

caggagatta gtggacctcg c 21

<210> SEQ ID NO 473
<211> LENGTH: 21
<212> TYPE: DNA
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<400> SEQUENCE: 473

gcgaggtcca ctaatctcct g 21

<210> SEQ ID NO 474
<211> LENGTH: 21
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 474

ggagattggt agacctcgct c 21

<210> SEQ ID NO 475
<211> LENGTH: 21
<212> TYPE: DNA
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<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 475

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gagcgaggtc taccaatctc c 21

<210> SEQ ID NO 476
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<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 476

gattggtgga cttcgctctt atac 24

<210> SEQ ID NO 477
<211> LENGTH: 24
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 477

gtataagagc gaagtccacc aatc 24

<210> SEQ ID NO 478
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 478

ggtggacctc actcttatac 20

<210> SEQ ID NO 479
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 479

gtataagagt gaggtccacc 20

<210> SEQ ID NO 480
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 480

ggtggacctt gctcttatac 20

<210> SEQ ID NO 481
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 481

gtataagagc aaggtccacc 20

<210> SEQ ID NO 482
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<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence

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<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 482

tgcttccctg cgtaaaggag tgg 23

<210> SEQ ID NO 483
<211> LENGTH: 23
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 483

ccactccttt acgcagggaa gca 23

<210> SEQ ID NO 484
<211> LENGTH: 24
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 484

gtaaaggagt ggactgtaat cctg 24

<210> SEQ ID NO 485
<211> LENGTH: 24
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 485

caggattaca gtccactcct ttac 24

<210> SEQ ID NO 486
<211> LENGTH: 24
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 486

aaaggagtgg cctataatcc tgcc 24

<210> SEQ ID NO 487
<211> LENGTH: 24
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 487

ggcaggatta taggccactc cttt 24

<210> SEQ ID NO 488
<211> LENGTH: 24
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 488

aaaggagtgg cccgtaatcc tgcc 24

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<210> SEQ ID NO 489
<211> LENGTH: 24
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 489

ggcaggatta cgggccactc cttt 24

<210> SEQ ID NO 490
<211> LENGTH: 24
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 490

gtaatcctgc ctacttcatc acac 24

<210> SEQ ID NO 491
<211> LENGTH: 24
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 491

gtgtgatgaa gtaggcagga ttac 24

<210> SEQ ID NO 492
<211> LENGTH: 26
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 492

ctgcctgctt caacacacag ctcctc 26

<210> SEQ ID NO 493
<211> LENGTH: 26
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 493

gaggagctgt gtgttgaagc aggcag 26

<210> SEQ ID NO 494
<211> LENGTH: 24
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 494

cctgcttcat cccacagctc ctcc 24

<210> SEQ ID NO 495
<211> LENGTH: 24
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

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<400> SEQUENCE: 495

ggaggagctg tgggatgaag cagg 24

<210> SEQ ID NO 496
<211> LENGTH: 24
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 496

cttcatcaca ccgctcctcc ctgt 24

<210> SEQ ID NO 497
<211> LENGTH: 22
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 497

cattgtgtac ttctgtgagt gg 22

<210> SEQ ID NO 498
<211> LENGTH: 22
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 498

ccactcacag aagtacacaa tg 22

<210> SEQ ID NO 499
<211> LENGTH: 23
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 499

cattgtgtac tactgtgagt ggc 23

<210> SEQ ID NO 500
<211> LENGTH: 23
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 500

gccactcaca gtagtacaca atg 23

<210> SEQ ID NO 501
<211> LENGTH: 22
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 501

gtgtactcct atgagtggcc tc 22

<210> SEQ ID NO 502

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<211> LENGTH: 22
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 502

gaggccactc ataggagtac ac 22

<210> SEQ ID NO 503
<211> LENGTH: 23
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 503

gtgtactcct gggagtggcc tct 23

<210> SEQ ID NO 504
<211> LENGTH: 23
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 504

agaggccact cccaggagta cac 23

<210> SEQ ID NO 505
<211> LENGTH: 22
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 505

ctgtgagtgg actctttata tg 22

<210> SEQ ID NO 506
<211> LENGTH: 22
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 506

catataaaga gtccactcac ag 22

<210> SEQ ID NO 507
<211> LENGTH: 22
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 507

ctgtgagtgg cktctttata tg 22

<210> SEQ ID NO 508
<211> LENGTH: 22
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 508

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catataaaga mgccactcac ag 22

<210> SEQ ID NO 509
<211> LENGTH: 21
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 509

tggcctcttt ctatgtggcc c 21

<210> SEQ ID NO 510
<211> LENGTH: 21
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 510

gggccacata gaaagaggcc a 21

<210> SEQ ID NO 511
<211> LENGTH: 25
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 511

agtggcctct ttgtatgtgg ccctt 25

<210> SEQ ID NO 512
<211> LENGTH: 25
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 512

aagggccaca tacaaagagg ccact 25

<210> SEQ ID NO 513
<211> LENGTH: 35
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 513

cctttcaaaa gcccaatgat acagaaatcc gacag 35

<210> SEQ ID NO 514
<211> LENGTH: 35
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 514

ctgtcggatt tctgtatcat tgggcttttg aaagg 35

<210> SEQ ID NO 515
<211> LENGTH: 28
<212> TYPE: DNA

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<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 515

caattataca gaaaaccgac agtactgc 28

<210> SEQ ID NO 516
<211> LENGTH: 28
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 516

gcagtactgt cggttttctg tataattg 28

<210> SEQ ID NO 517
<211> LENGTH: 21
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 517

cgacagtacs gcaatcactg g 21

<210> SEQ ID NO 518
<211> LENGTH: 21
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 518

ccagtgattg csgtactgtc g 21

<210> SEQ ID NO 519
<211> LENGTH: 21
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 519

cgacagtact acaatcactg g 21

<210> SEQ ID NO 520
<211> LENGTH: 24
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 520

acagggagga gcggtgtgat gaag 24

<210> SEQ ID NO 521
<211> LENGTH: 28
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 521

cacagctcct ccgtgtgaaa aggaagct 28

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<210> SEQ ID NO 522
<211> LENGTH: 28
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 522

agcttccttt tcacacggag gagctgtg 28

<210> SEQ ID NO 523
<211> LENGTH: 23
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 523

ggaagctagg gtactatgaa tgg 23

<210> SEQ ID NO 524
<211> LENGTH: 23
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 524

ccattcatag taccctagct tcc 23

<210> SEQ ID NO 525
<211> LENGTH: 22
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 525

agggttctat aaatggactt ca 22

<210> SEQ ID NO 526
<211> LENGTH: 22
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 526

tgaagtccat ttatagaacc ct 22

<210> SEQ ID NO 527
<211> LENGTH: 22
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 527

gacttcaagg tcaagaagtc ac 22

<210> SEQ ID NO 528
<211> LENGTH: 22
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:

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<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 528

gtgacttctt gaccttgaag tc 22

<210> SEQ ID NO 529
<211> LENGTH: 21
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 529

gaagtcacaa aaatcccaca g 21

<210> SEQ ID NO 530
<211> LENGTH: 21
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 530

ctgtgggatt tttgtgactt c 21

<210> SEQ ID NO 531
<211> LENGTH: 24
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 531

gtcacataaa tdccacaggc actg 24

<210> SEQ ID NO 532
<211> LENGTH: 24
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 532

cagtgcctgt gghatttatg tgac 24

<210> SEQ ID NO 533
<211> LENGTH: 22
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 533

cacataaatc ccaaaggcac tg 22

<210> SEQ ID NO 534
<211> LENGTH: 22
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 534

cagtgccttt gggatttatg tg 22

<210> SEQ ID NO 535
<211> LENGTH: 22
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 535

cacataaatc ccgcaggcac tg 22

<210> SEQ ID NO 536
<211> LENGTH: 22
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 536

cagtgcctgc gggatttatg tg 22

<210> SEQ ID NO 537
<211> LENGTH: 21
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 537

atcccacaga cactgttttg c 21

<210> SEQ ID NO 538
<211> LENGTH: 21
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 538

gcaaaacagt gtctgtggga t 21

<210> SEQ ID NO 539
<211> LENGTH: 22
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 539

ggcactgttt cgcttcagct ag 22

<210> SEQ ID NO 540
<211> LENGTH: 22
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 540

ctagctgaag cgaaacagtg cc 22

<210> SEQ ID NO 541
<211> LENGTH: 29
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

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<400> SEQUENCE: 541

gcgcttcgct tcctggacat ccctggggc 29

<210> SEQ ID NO 542
<211> LENGTH: 29
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 542

gccccaggga tgtccaggaa gcgaagcgc 29

<210> SEQ ID NO 543
<211> LENGTH: 21
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 543

ccagtgattg tagtactgtc g 21

<210> SEQ ID NO 544
<211> LENGTH: 21
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 544

cagtactgca gtcactggcg a 21

<210> SEQ ID NO 545
<211> LENGTH: 21
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 545

tcgccagtga ctgcagtact g 21

<210> SEQ ID NO 546
<211> LENGTH: 19
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 546

cagtactgcg atcactggc 19

<210> SEQ ID NO 547
<211> LENGTH: 19
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 547

gccagtgatc gcagtactg 19

<210> SEQ ID NO 548
<211> LENGTH: 21

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<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 548

tactgcaatc gctggcgaaa t 21

<210> SEQ ID NO 549
<211> LENGTH: 21
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 549

atttcgccag cgattgcagt a 21

<210> SEQ ID NO 550
<211> LENGTH: 17
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 550

gcaatcaccg gcgaaat 17

<210> SEQ ID NO 551
<211> LENGTH: 17
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 551

atttcgccgg tgattgc 17

<210> SEQ ID NO 552
<211> LENGTH: 22
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
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<400> SEQUENCE: 552

gcaatcactg tcgaaatttt gc 22

<210> SEQ ID NO 553
<211> LENGTH: 22
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 553

gcaaaatttc gacagtgatt gc 22

<210> SEQ ID NO 554
<211> LENGTH: 26
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 554

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gcaatcactg gcaaaatttt gctgac 26

<210> SEQ ID NO 555
<211> LENGTH: 31
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 555

gcagaccctc agcgccagct agctaattat g 31

<210> SEQ ID NO 556
<211> LENGTH: 31
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 556

cataattagc tagctggcgc tgagggtctg c 31

<210> SEQ ID NO 557
<211> LENGTH: 26
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 557

gttttggata ctacattgat gcccag 26

<210> SEQ ID NO 558
<211> LENGTH: 26
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 558

ctgggcatca atgtagtatc caaaac 26

<210> SEQ ID NO 559
<211> LENGTH: 24
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 559

ctcctgtgag tggatgtggc cctt 24

<210> SEQ ID NO 560
<211> LENGTH: 24
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 560

aagggccaca tccactcaca ggag 24

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<210> SEQ ID NO 561
<211> LENGTH: 23
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 561

caggagagaa ttgatgttgc tgg 23

<210> SEQ ID NO 562
<211> LENGTH: 23
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 562

ccagcaacat caattctctc ctg 23

<210> SEQ ID NO 563
<211> LENGTH: 25
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 563

gataaaccgg cagattggtg gacct 25

<210> SEQ ID NO 564
<211> LENGTH: 25
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 564

aggtccacca atctgccggt ttatc 25

<210> SEQ ID NO 565
<211> LENGTH: 35
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 565

gactggacat cttggacatc ttttaaccag gagag 35

<210> SEQ ID NO 566
<211> LENGTH: 35
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 566

ctctcctggt taaaagatgt ccaagatgtc cagtc 35

What is claimed is:

1. A method of treating a patient diagnosed with Fabry disease which comprises administering to the patient a therapeutically effective dose of **[**1-deoxygalactonorjirimycin**]** *1-deoxygalactonojirimycin*, wherein the patient is identified as having a **[**mutant**]** *mutation in* α-galactosidase A, relative to a human α-galactosidase A encoded by a nucleic acid sequence set forth in SEQ ID NO:2, said mutation selected from the group consisting of the α-galactosidase A mutations A121T, A288D, A288P, A292P A348P, A73V,

C52R, C94Y, D234E, D244H, D264Y, E338K, E341D, E398K, E48K, G271S, G35R, H225R, I219N, I242N, I270T, I303N, I317T, I354K, L14P, L243F, L300F, L310F, L45R, M267I, M76R, N224S, N298K, N298S, N320I, N34K, P205R, P259L, P265L, P265R, P293A, P293S, P409S, P40L, P40S, Q279R, Q280H, Q280K, Q321E, Q321R, Q327E, R301P, R49G, R49L, R49S, S201Y, S276N, S297C, S345P, V269M, W340R, W47L, and W95S.

2. The method of claim **1** wherein the patient is female.

3. The method of claim **1**, wherein 1-deoxygalactonojirimycin is in a pharmaceutically acceptable salt form.

4. The method of claim **3**, wherein the pharmaceutically acceptable salt form is 1-deoxygalactonojirimycin hydrochloride.

5. The method of claim 1, wherein the patient is male.

6. A method of treating a patient diagnosed with Fabry disease which comprises administering to the patient a therapeutically effective dose of 1-deoxygalactonojirimycin, wherein the patient is identified as having a mutation in α-galactosidase A, relative to a human α-galactosidase A encoded by a nucleic acid sequence set forth in SEQ ID NO:2, said mutation selected from the group consisting of the α-galactosidase A mutations A121T, A288P, A73V, D244H, D264Y, E338K, E398K, G271S, G35R, I219N, I242N, I270T, I303N, I317T, I354K, L243F, L300F, L310F, N224S, N298S, N320I, N34K, P259L, P265L, P409S, Q280H, Q280K, Q321R, Q327E, R301P, S201Y, S276N, S345P and V269M.

7. The method of claim 6, wherein the patient is female.

8. The method of claim 6, wherein 1-deoxygalactonojirimycin is in a pharmaceutically acceptable salt form.

9. The method of claim 8, wherein the pharmaceutically acceptable salt form is 1-deoxygalactonojirimycin hydrochloride.

10. The method of claim 6, wherein the patient is male.

11. The method of claim 6, wherein the mutation is A121T.

12. The method of claim 6, wherein the mutation is A288P.

13. The method of claim 6, wherein the mutation is A73V.

14. The method of claim 6, wherein the mutation is D244H.

15. The method of claim 6, wherein the mutation is D264Y.

16. The method of claim 6, wherein the mutation is E338K.

17. The method of claim 6, wherein the mutation is E398K.

18. The method of claim 6, wherein the mutation is G271S.

19. The method of claim 6, wherein the mutation is G35R.

20. The method of claim 6, wherein the mutation is I219N.

21. The method of claim 6, wherein the mutation is I242N.

22. The method of claim 6, wherein the mutation is I270T.

23. The method of claim 6, wherein the mutation is I303N.

24. The method of claim 6, wherein the mutation is I317T.

25. The method of claim 6, wherein the mutation is I354K.

26. The method of claim 6, wherein the mutation is L243F.

27. The method of claim 6, wherein the mutation is L300F.

28. The method of claim 6, wherein the mutation is L310F.

29. The method of claim 6, wherein the mutation is N224S.

30. The method of claim 6, wherein the mutation is N298S.

31. The method of claim 6, wherein the mutation is N320I.

32. The method of claim 6, wherein the mutation is N34K.

33. The method of claim 6, wherein the mutation is P259L.

34. The method of claim 6, wherein the mutation is P265L.

35. The method of claim 6, wherein the mutation is P409S.

36. The method of claim 6, wherein the mutation is Q280H.

37. The method of claim 6, wherein the mutation is Q280K.

38. The method of claim 6, wherein the mutation is Q321R.

39. The method of claim 6, wherein the mutation is Q327E.

40. The method of claim 6, wherein the mutation is R301P.

41. The method of claim 6, wherein the mutation is S201Y.

42. The method of claim 6, wherein the mutation is S276N.

43. The method of claim 6, wherein the mutation is S345P.

44. The method of claim 6, wherein the mutation is V269M.

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