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

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(57) **ABSTRACT**

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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 form of α -galactosidase A. The invention also provides a method for diagnosing Fabry disease in patients suspected of having Fabry disease.

Related U.S. Application Data

(63) Continuation of application No. PCT/US2009/033963, filed on Feb. 12, 2009.

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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	V390fx6
M11	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	<i>del20-24aa</i>
M1L	H46Y	M76R	F113S	Y152C	M187T	D231G	P266R	A288D	V316E	E356A	T410I	<i>del13-Baa</i>
M1R	W47G	M76T	I117S	D155H	M187V	D231N	D266E	A288P	I317N	E358G	T410K	<i>del15aa</i>
M1T	W47L	W81C	R118C	A156T	L191Q	D231V	D266H	I289F	I317T	E358K	T410P	<i>del205-7aa</i>
M1V	E48D	W81S	L120P	A156V	L191Q	D234E	D266N	I289S	N320I	I359T	G411D	<i>del254aa</i>
A13P	E48K	G85D	L120S	A156Y	T194I	D234Y	D266V	M280I	N320K	G360C	L414S	<i>del358aa</i>
L14P	R49C	G85M	A121P	W162C	V198M	S235C	D266Y	A291T	N320Y	G360D	L415P	<i>ins247-8aa</i>
L16H	R49G	Y86C	A121T	W162G	S201F	S235F	M267I	A292P	Q321E	G360S	L33Y	
L16P	R49L	Y86D	V124D	W162R	S201Y	W238C	M267R	A292T	Q321L	G361R	L166G	
F18S	R49P	Y88D	H126P	G163V	C202W	W236L	L268S	P293A	Q321R	P362L	H46S	
L19P	R49S	L89P	S126G	D165H	C202Y	W236R	V269A	P283H	G325D	R363C	I124F	
A20P	F50C	L89R	G128E	D165V	P205L	S238N	V269M	P293S	G325S	R363H		
A31V	M51I	C90R	L129P	D165Y	P205P	I239T	I270T	P293T	Q327E	R363P		
L32P	M51K	B1T	L131P	D156Y	P205S	I242F	G271C	F295C	Q327K	L372P	Com plex	
D33Y	C52G	D92G	G132E	L166V	P205T	I242N	G271S	M298I	G328A	L372R	D55V/Q57L	
											L120P/A121	
N34K	C52R	D92H	G132R	L167P	L206P	L243F	G271V	M296V	G328E	G373D	I	
N34S	C52S	D92N	Y134H	K168N	Y207C	L243W	N272K	S297C	G328R	G373R		
											Small	
G35R	C52Y	D92Y	Y134S	K168R	Y207H	D244N	N272S	S297F	G328V	G373S	Ins/Del	
L36F	L54P	D83G	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	
											120del2aa/L	
P40L	C56G	C94S	G138E	G171C	Y216C	Q250P	S276N	D299G	E341D	C382W	12DH	
											152ins1aa/Y	
P40S	C56Y	C94Y	G138R	G171D	Y216D	I253T	Q279E	L300F	E341K	C382Y	152D	
T41I	Q57L	W95L	N139T	G171R	I219N	A257P	Q279H	L300H	R342L	I384N	153del1aa	
M42L	E59K	W95S	T141I	C172F	C223G	G268R	Q279K	L300P	R342Q	T385P	205del3aa	
M42R	P60L	A97P	C142R	C172G	C223R	G258V	Q279R	R301G	L344P	Q386P	205del7aa	
M42T	C63Y	A97V	C142W	C172R	C223Y	P269L	Q280H	R301P	S345P	P389R	254del1aa	
											281del1aa/V	
M42V	S65T	R100K	C142Y	C172S	N224D	P259R	Q280K	R301Q	A348P	F396Y	281A	
G43D	E66G	R100T	A143P	C172W	N224S	G260A	T282A	B03N	W349R	E398K	358del1aa	
G43R	E66K	E103Q	A143T	C172Y	H225D	G261D	T282N	K308N	A350P	L403S	382del1aa	
G43S	E66Q	L106R	G144V	C174G	H225R	W262C	Q283P	A309P	A352D	J407K	403del1aa	
G43V	L88F	Q107L	P148S	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	<u>P146S</u>	<u>G202Y</u>	A257P	M284T	N320Y	<u>C378Y</u>
<i>M1T</i>	<i>R49P</i>	C94Y	G147R	<u>C202W</u>	G258R	<u>A285P</u>	Q321E	<u>C378R</u>
<i>M1R</i>	R49S	<u>C94S</u>	S148N	P205R	P259R	<u>A285D</u>	Q321R	<u>C382Y</u>
<u>M1I</u>	<u>F50C</u>	W85S	<u>S148R</u>	P205L	P259L	<u>W287G</u>	G325D	C382W
L14P	M51K	A97V	Y152C	P205T	G260A	W287C	<u>Q327K</u>	I384N
L16P	M51I	A97P	<u>D155H</u>	Y207C	G261D	A288D	Q327E	<u>T385P</u>
L16H	<u>C52G</u>	<u>R100K</u>	A156V	Y207S	<u>W262C</u>	A288P	<u>G328R</u>	Q386P
L19P	C52R	<u>R100T</u>	A156T	N215S	N263S	I289F	G328A	P389R
A20P	<u>C52S</u>	<u>E103Q</u>	<u>W162R</u>	Y216D	<u>D264V</u>	<u>M290I</u>	G328E	<u>F396Y</u>
<u>A31V</u>	C56F	R112H	<u>W162C</u>	I219N	D264Y	A292P	G328V	E398K
L32P	C56G	R112S	G163V	<u>C223R</u>	P265R	P293A	E338K	L403S
D33Y	C56Y	R112C	<u>D165V</u>	C223G	P265L	P293S	V339E	<u>I407K</u>
N34K	E59K	F113L	<u>L166G</u>	<u>C223Y</u>	D266N	<u>P293T</u>	W340R	P409T
<u>N34S</u>	C63Y	<u>F113S</u>	L166V	N224S	D266H	F295C	E341D	P409A
G35R	S65T	R118C	<u>L167P</u>	N224D	<u>D266V</u>	M296I	<u>E341K</u>	P409S
A37V	E66G	L120P	K168N	H225R	<u>D266E</u>	M296V	R342Q	<u>T410K</u>
P40L	E66K	<u>L120S</u>	<u>K168R</u>	<u>W226R</u>	<u>M267R</u>	S297C	<u>L344P</u>	T410A
P40S	E66Q	<u>A121P</u>	F169S	W226C	M267I	S297F	S345P	G411D
T41I	L68F	A121T	<u>D170V</u>	<u>R227Q</u>	L268S	N296S	A348P	L414S
M42T	M72R	<u>Y124D</u>	D170H	A230T	V269A	N298K	<u>A350P</u>	<u>L415P</u>
M42L	M72I	<u>G128E</u>	<u>G171D</u>	D231N	V269M	N298H	A352D	
M42V	M72V	<u>L129P</u>	G171R	D231G	I270T	D299G	I354K	
<u>G43D</u>	A73V	<u>L131P</u>	<u>C172Y</u>	D234E	<u>G271C</u>	L300F	<u>N356K</u>	
<u>G43S</u>	M76R	G132E	<u>C172F</u>	D234Y	G271S	L300H	R356W	
<u>G43V</u>	W81C	G132R	<u>C172W</u>	S235G	<u>G271V</u>	L300P	E358G	
<u>G43R</u>	W81S	<u>Y134S</u>	<u>C172R</u>	W236R	N272K	R301G	E358K	

Fig. 1B (Cont.)

<u>W44C</u>	G85D	A136V	<u>C172G</u>	W236L	N272S	R301Q	E358A	
L45R	Y86C	D136H	G183D	W236C	S276N	R301P	I359T	
<u>H46R</u>	Y88D	<u>G138E</u>	G183S	I239T	S276G	I303N	G360S	Small Ins/Del
H46S	<u>L89P</u>	G138R	M187T	I242F	Q279R	L310F	G361R	<u>del20-24aa</u>
<u>H46L</u>	<u>L89R</u>	T141I	M187V	I242N	Q279H	Q312H	P362L	<u>del13-8aa</u>
<u>H46Y</u>	I91T	<u>C142R</u>	L191Q	L243F	Q279E	<u>D313Y</u>	R363H	<u>del153aa</u>
<u>W47G</u>	<u>D92N</u>	C142W	L191P	D244N	<u>Q279K</u>	V316E	R363C	<u>del205-7aa</u>
W47L	<u>D92H</u>	C142Y	T194I	D244H	Q280H	I317N	G373D	<u>del254aa</u>
E48D	<u>D92Y</u>	A143T	V199M	S247P	Q280K	I317T	G373R	<u>del358aa</u>
E48K	D93G	A143P	S201F	S247C	<u>T282N</u>	N320I	G373S	<u>ins247-8aa</u>
R49G	D93N	G144V	S201Y	Q250P	<u>Q283P</u>	<u>N320K</u>	A377D	

Fig. 1C**Fabry Mutations Generated by Site-Directed Mutagenesis**

Missense	R49L	D93V	P146S	C202Y	A257P	M284T	N320Y	C378Y
<i>M1T</i>	R49P	C94Y	G147R	C202W	G258R	A285P	Q321E	C378R
<i>M1R</i>	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
<i>L16P</i>	<i>M51I</i>	<i>A97P</i>	<i>D155H</i>	<i>Y207C</i>	<i>G261D</i>	<i>A288D</i>	<i>Q327E</i>	<i>T385P</i>
<i>L16H</i>	C52G	R100K	A156V	Y207S	W262C	A288P	G328R	Q386P
<i>L19P</i>	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	L416P
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.)

<i>W44C</i>	<i>G85D</i>	<i>A135V</i>	<u>C172G</u>	<i>W236L</i>	<i>N272S</i>	<i>R301Q</i>	<i>E358A</i>	
<i>L45R</i>	<i>Y86C</i>	<i>D136H</i>	<i>G183D</i>	<i>W236C</i>	<i>S276N</i>	<i>R301P</i>	<i>I359T</i>	
<u>H46R</u>	<i>Y88D</i>	<u>G138E</u>	<i>G183S</i>	<i>I239T</i>	<i>S276G</i>	<i>I303N</i>	<i>G360S</i>	Small Ins/Del
<i>H46S</i>	<i>L89P</i>	<i>G138R</i>	<i>M187T</i>	<i>I124F</i>	<i>Q279R</i>	<i>L310F</i>	<i>G361R</i>	<i>del20-24aa</i>
<u>H46L</u>	<u>L89R</u>	<i>T141I</i>	<i>M187V</i>	<i>I242N</i>	<i>Q279H</i>	<i>Q312H</i>	<i>P362L</i>	<i>del13-8aa</i>
<u>H46Y</u>	<i>I91T</i>	<u>C142R</u>	<i>L191Q</i>	<i>L243F</i>	<i>Q279E</i>	<u>D313Y</u>	<i>R363H</i>	<i>del153aa</i>
<i>W47G</i>	<u>D92N</u>	<i>C142W</i>	<i>L191P</i>	<i>D244N</i>	<u>Q279K</u>	<i>V316E</i>	<i>R363C</i>	<i>del205-7aa</i>
<i>W47L</i>	<i>D92H</i>	<i>C142Y</i>	<i>T194I</i>	<i>D244H</i>	<i>Q280H</i>	<i>I317N</i>	<i>G373D</i>	<i>del254aa</i>
<i>E48D</i>	<u>D92Y</u>	<i>A143T</i>	<i>V199M</i>	<i>S247P</i>	<i>Q280K</i>	<i>I317T</i>	<i>G373R</i>	<i>del358aa</i>
<i>E48K</i>	<i>D93G</i>	<i>A143P</i>	<i>S201F</i>	<i>S247C</i>	<i>T282N</i>	<i>N320I</i>	<i>G373S</i>	<i>ins247-8aa</i>
<i>R49G</i>	<i>D93N</i>	<i>G144V</i>	<i>S201Y</i>	<i>Q250P</i>	<i>Q283P</i>	<i>N320K</i>	<i>A377D</i>	

Mutation	Relative Increase (fold)	$\text{EC}_{50}(\mu\text{M})$	Mutation	Relative Increase (fold)	$\text{EC}_{50}(\mu\text{M})$
L14P	3.0±0.4	2.6±0.8	D244H	3.0±1.0	1.2±0.4
A20P	1.5±0.1	0.3±0.1	P259R	3.0±0.4	2.1±0.5
L32P	7.0±1.0	2.1±0.3	P259L	8.4±3.0	9.0±0.5
D33Y	2.9±0.5	5.4±1.4	G260A	8.5±2.6	1.2±1
N34K	1.8±2	100±31	N263S	4.8±1.2	2.3±0.4
G35R	5.0±1.6	7.0±1.5	D264Y	1.3±3	1.8±4
P40L	4.0±0.2	39±16	P265R	1.3±1	96±27
P40S	3.0±0.6	2.6±0.8	P265L	2.7±0.2	1.1±0.1
T41I	1.0±0.1	0.3±0.1	P265R	1.3±1	97±27
M42T	1.8±1	4.2±1.6	M267I	1.6±0.2	5.6±2.5
M42V	1.4±2	1.2±2.3	L268S	1.5±0.1	0.7±0.3
L45R	1.7±4	39±5	V269A	1.3±2	2.2±9
W47L	5.0±1.0	1.1±3	V269M	3.8±0.9	2.6±0.6
E48D	6.7±1.8	105±37	I270T	1.1±2	10.0±0.3
E48K	6.0±1.0	4.4±2.0	G271S	2.2±8	2.4±2
R48G	3.0±0.5	3.6±1.4	N272K	3.3±0.7	1.7±7
R49L	1.1±2	7.6±19	N272S	4.6±0.8	22.8±86
R49S	4.0±1.0	5.3±2.6	S276N	9.0±3.3	2.2±7
M51I	1.5±0.1	2.9±0.8	S276G	2.2±1	9.0±1.0
M51K	3.0±0.3	1.8±0.6	Q279E	4.5±0.6	2.2±5
C52R	3.6±0.6	5.3±2.3	Q279H	4.7±0.7	61±26
C56F	1.6±1	2.8±6	Q279R	3.5±0.3	11.9±5.6
C56G	6.5±1.0	400±77	Q280H	4.7±1.0	5.4±0.8
E59K	3.4±0.5	3.5±1.4	Q280K	1.7±0.1	1.1±0.3
S65T	3.0±0.5	2.2±0.6	M284T	20±4	2.8±8
E66G	1.6±0.2	3.9±1.5	W287C	20±4	968±74
E66K	3.7±1.0	10.8±1.5	A288D	5.7±0.6	159±36
E66Q	2.3±0.7	5.0±2.0	A288P	20±1	2.5±1
L68F	10.9±1.7	11.2±28	I289F	1.8±1	308±48
M72R	6.8±1.4	685±255	A292P	3.0±0.5	159±42
M72V	2.0±0.2	0.6±0.1	P293A	20±2	47.9±96
A73V	1.4±0.1	0.9±0.3	P293S	1.9±2	563±218
M76R	3.0±0.7	6.0±2.0	F295C	1.5±2	18±5
W81S	3.8±1.4	2.5±12	M296I	2.6±0.1	0.7±0.2
Y88D	3.1±0.4	5.2±17	M296V	1.9±0.1	0.7±0.3
I91T	1.2±2	5.9±2.8	S297C	3.0±0.7	61.6±230
C94Y	2.0±0.4	0.8±0.3	N298S	2.8±0.0	1.1±0.2
W95S	4.0±0.8	31.2±5.2	N298K	5.2±2.2	38±18
A97V	3.0±0.5	0.8±0.3	L300F	5.8±1.3	3.4±0.8
A97P	7.7±1.4	43±14	L300P	1.2±1	6.0±1.6
R112H	5.0±0.5	2.5±0.5	R301Q	6.5±0.3	3.8±0.4
R112C	1.5±2	297±59	R301P	4.2±4	118±14
R112S	8.0±1.8	9.1±28	I303N	1.3±1	68.1±22
F113L	2.3±0.2	2.4±1.0	L310F	1.7±0	71±11
R118C	1.4±0.1	6.0±2.0	Q312H	1.2±2	1.5±2
L120P	5.7±2.3	20±9	V316E	5.0±0.7	627±143
A121T	2.6±0.5	0.3±0.1	I317T	5.0±1.4	10±2
D136H	5.0±1.0	23±5	I317N	9.4±1.0	83±24
A143T	1.3±0.1	4.3±1.3	N320I	23.3	39±12
G144V	21±6	3.8±14	N320Y	1.8±1	29.5±7.6
G147R	2.4±0.4	4.2±1.6	Q321E	21±3	90±35
S148N	1.8±2	1391±442	Q321R	3.4±1.1	7.0±0.8
A156T	1.3±1	47±10	G325D	12±2	323±102
A156V	1.9±2	44±9	Q327E	2.4±0.2	11±3
L166V	5.0±0.5	1.3±4	G328A	1.8±5	1.4±2
K168N	22±3	6.8±32	E338K	4.4±0.2	16±4
G183S	6.8±1.0	7.1±1.9	W340R	10.0±1.5	103±38
G183D	1.5±3	42±13	E341D	2.9±0.1	17±4
M187T	8.4±2.0	2.3±8	R342Q	4.0±1.4	16±7
M187V	4.9±1.2	16±1	S346P	8.2±0.6	75±5
L191P	20±0	6.5±2.5	A348P	1.6±0.0	4.8±2.3
L191Q	1.6±4	148±61	A352D	5.0±0.5	16.3±23
T194I	1.2±2	19±1	I354K	1.9±4	17±3
V199M	1.2±0.0	3.5±1.6	R356W	2.8±0.6	0.9±0.1
S201F	8±2	2.1±0.6	E358A	21±3	9.4±2.0
S201Y	6.0±0.3	1.3±3	E358G	7.3±0.6	20±9
P205L	8.5±0.8	260±54	E358K	2.8±0.6	400±117
P205R	4.0±0.7	70±30	G361R	9.7±0.3	7.2±2.2
P205T	7.7±2.0	2.4±0.4	P362L	7.2±1.5	2.7±0.7
Y207S	3.2±0.4	6.7±5	R363H	1.7±0.1	1.0±0.4
N215S	2.6±0.3	4.3±0.9	R363C	2.3±0.3	2.1±0.9
I219N	1.3±1	167±67	G373D	3.2±0.4	5.4±2.6
N224D	1.5±3	186±39	G373S	2.6±0.4	2.2±0.7
N224S	2.6±0.1	6.3±1.8	E398K	1.3±0.0	6.9±2.4
H225R	27±2	860±135	P409S	14±2	2.7±0.6
D234E	14±3	341±47	T410A	1.9±3	2.3±0.9
I242N	1.2±1	9.3±1.0	G411D	1.5±0	5.3±2.0
L243F	8±1	9.9±1.5	L414S	5.8±0.6	1.8±3
D244N	4.0±1.0	3.5±1.3	Ins247-S	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	C280K	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±0.56	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	2.29±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±2.54	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	3.84±0.35
A121T	2.62±0.48	0.32±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	23.24±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	69.73±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±45.11	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	859.82±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	1.05±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

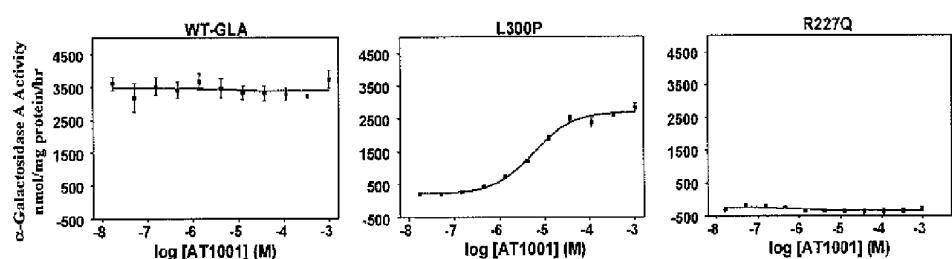


FIG. 4

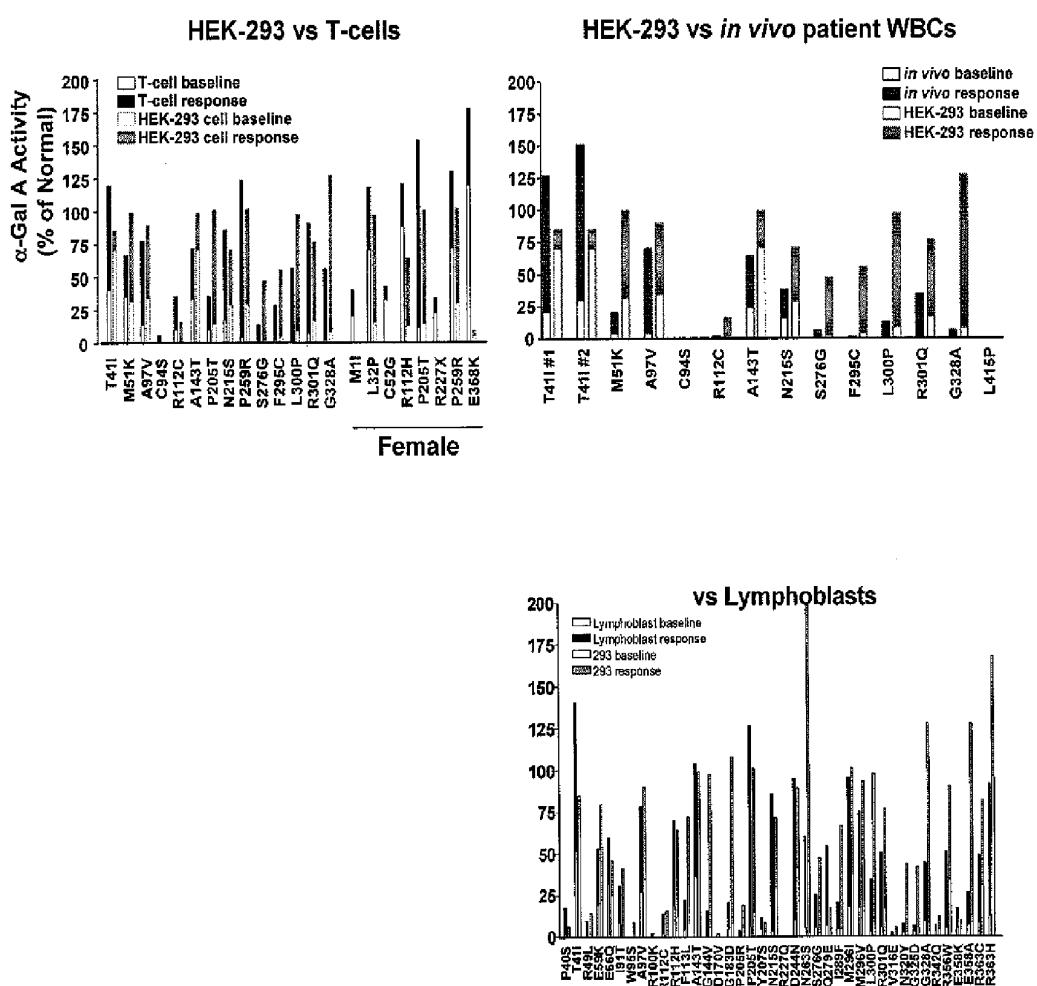


FIG. 5

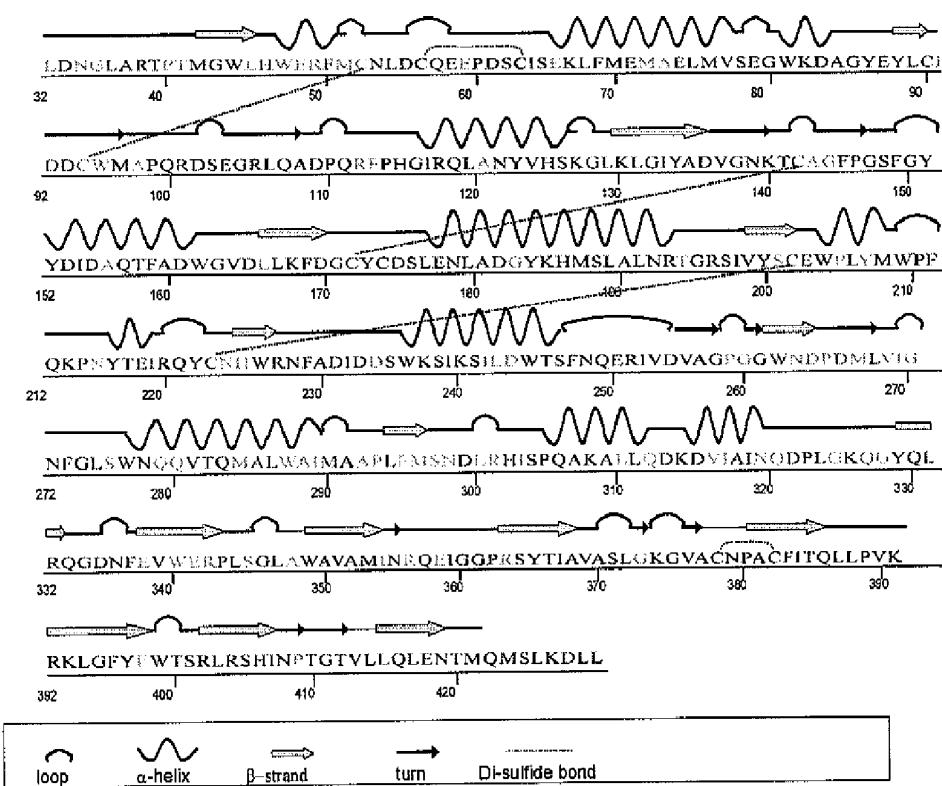


Fig. 6

α -Gal A mutation	Primer	α -Gal A mutation	Primer
GLA-MII-5'	CGTGACAATACAGCTGAG	GLA-R227Q-3'	GTCAGCAAAATTGCCAG TGATTGC
GLA-MII-3'	CTCAGCTGTATTGTCACG	GLA-A230T-5'	gcgaaatttt actgacattgtatg
GLA-MIT-5	CACCGTGACA ACG CAGCTGAGG	GLA-A230T-3'	CAT CAA TGT CAG TAA AAT TTC GC
GLA-MIT-3	CCT CAG CTG CGT TGT CAC GGT G	GLA-D231N-5	GGCGAAAATTGCT aAC ATTGATGATTCTG
GLA-L14P-5'	GGCTGCGCGCCTGCGCTTCG	GLA-D231N-3	CAG GAA TCA TCA ATG TTA GCA AAA TTT CGC C
GLA-L14P-3'	CGAACGCGCAGGCAGCAGCC	GLA-D231G-5'	CGAAATTGCT GgC ATTGATGATATTG
GLA-L16P/H-5'	GCGCTTGCAGCMTCGCTTCTGG	GLA-D231G-3'	GAA TAT CAT CAA TGC CAG CAA AAT TTC G
GLA-L16P/H-3'	CCAGGAAGCGAKGCGCAAGCGC	GLA-D234E-5'	tgcatttgat gag tcctggaaaag
GLA-L19P-5'	GCTTCGCTTCCCGGCCCTCGTTTC	GLA-D234E-3'	CTT TTC CAG GAC TCA TCA ATG TCA
GLA-L19P-3'	GAAACGAGGGCCGGGAAGCGAAGC	GLA-D234Y-5	GCTGACATTGAT tAT TCCTGGAAAAG
GLA-A31V-5'	GGGGCTAGAGTACTGGACAATGG	GLA-D234Y-3	CTT TTC CAG GAA TAA TCA ATG TCA GC
GLA-A31V-3'	CCATTGTCCAGTACTCTAGCCCC	GLA-S235C-5	CTGACATTGATGAT TgC TGGAAAAGTATAAAGAG
GLA-L32P-5'	GCTAGAGCACCGGACAATGGA	GLA-S235C-3	CTC TTT ATA CTT TTC CAG CAA TCA TCA ATG TCA G
GLA-L32P-3'	TCCATTGTCCGGTGCTCTAGC	GLA-W236R-5	GCTGACATTGATGATTCC cGG AAAAGTATAAAGAGTATC
GLA-L32P-5'	GCTAGAGCACCGGACAATGGA	GLA-W236R-3	GAT ACT CTT TAT ACT TTT CCG GGA ATC ATC AAT GTC AGC
GLA-L32P-3'	TCCATTGTCCGGTGCTCTAGC	GLA-W236L-5'	TGATGATTCC TTG AAAAGTATAA
GLA-D33Y-5'	CTAGAGCACTGTACAATGGATTG	GLA-W236L-3'	TTA TAC TTT TCA AGG AAT CAT CA
GLA-D33Y-3'	CAATCCATTGTACAGTGCTCTAG	GLA-W236L-5	cGACAT TGTGATGATTCC TgG AAAAGTATAAAGAG
GLA-N34K-5'	GCACTGGACAAAGGATTGGC	GLA-W236L-3	CTC TTT ATA CTT TTC AAG GAA TCA TCA ATG TCA G
GLA-N34K-3'	GCCAATCCTTGTCCAGTGC	GLA-W236C-5	GCTGACATTGATGATTCC TgG AAAAGTATAAAGAGTATCT TGG
GLA-N34S-5'	GCACTGGACAGTGGATTGGC	GLA-W236C-3	CCA AGA TAC TCT TTA TAC TTT TAC AGG AAT CAT CAA TGT CAG C
GLA-N34S-3'	GCCAATCCACTGTCCAGTGC	GLA-I239T-5'	TGGAAAAGT ACA AAGAGTATC

Fig. 6 (Cont.)

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

Fig. 6 (Cont.)

GLA-G35R-3'	CCTTCCAATCTATTGTCCAG	GLA-I239T-5	GATTCTGGAAAAGT AcA AAGAGTATCTTGGACTG
GLA-A37V-5'	AATGGATTGGTAAGGACGCC	GLA-I239T-3	CAG TCC AAG ATA CTC TTT GTA CTT TTC CAG GAA TC
GLA-A37V-3'	GGCGTCCTTACCAATCCATT	GLA-I242F-5'	AGTATAAAAGAGT TTC TTGGACTGGAC
GLA-P40L-5'	GCAAGGACGCTTACCATGGG	GLA-I242F-3'	GTC CAG TCC AAG AAA CTC TTT ATA CT
GLA-P40L-3'	CCCATGGTAAGCGTCCITGC	GLA-I242N-5'	GTATAAAAGAGT AAC TTGGACTGG
GLA-P40S-5'	GCAAGGACGCTTACCATGGG	GLA-I242N-3'	CCA GTC CAA GTT ACT CTT TAT AC
GLA-P40S-3'	CCCATGGTAGACGTCCTTGC	GLA-L243F-5'	AGAGTATCTTCGACTGGACATC
GLA-M42T-5	AGGACGCCCTACC AcG GGCTGGCTGCAC	GLA-L243F-3'	GAT GTC CAG TCG AAG ATA CTC T
GLA-M42I-3	GTG CAG CCA GCC CGT GGT AGG CGT CCT	GLA-D244H-5'	GAGTATCTTG CACTGGACATC
GLA-M42L-5	AGGACGCCCTACC TTG GGCTGGCTGCAC	GLA-D244H-3'	GAT GTC CAG TCG AAG ATA CTC T
GLA-M42L-3	GTG CAG CCA GCC CAA GGT AGG CGT CCT	GLA-S247C-5'	CTTGGACTGGACATGTTTAACCAGG AGAG
GLA-M42V-5	AGGACGCCCTACC GTG GGCTGGCTGC	GLA-S247C-3'	CTC TCC TGG TTA AAA CAT GTC CAG TCC AAG
GLA-M42V-3	GCA GCC AGC CCA CGG TAG GCG TCC T	GLA-S247P-5'	GGACTGGACA CCTTTAACCA
GLA-G43D/V-5'	CTACCATGGWCIGGCTGCAC	GLA-S247P-3'	TGG TTA AAA GGT GTC CAG TCC
GLA-G43D/V-3'	GTGCAGCCAGWCCATGGTAG	GLA-A257P-5'	GTTGATGTT CCTGGACCAAG
GLA-G43R-5'	CTACCATGCCTGGCTGCAC	GLA-A257P-3'	CTG GTC CAG GAA CAT CAA C
GLA-G43R-3'	GTGCAGCCAGCGCATGGTAG	GLA-G258R-5'	GATGTTGCT CGACCAAGGGG
GLA-W44C-5'	CATGGGCTCTGCAGTGG	GLA-G258R-3'	CCC CTG GTC GAG CAA CAT C
GLA-W44C-3'	CCAGTGCAGACAGCCCCATG	GLA-P259R-5'	GATGTTGCTGGACGAGGGGTTGGA
GLA-L45R-5'	ATGGGCTGGCGGCACTGGAG	GLA-P259R-3'	TCCAACCCCTCGTCCAGCAACATC
GLA-L45R-3'	CTCCCCAGTGCCTGGGAGC	GLA-P259L-5'	GTTGCTGGACTAGGGGTTGG
GLA-H46R-5'	CTGGCTGCCTGGGAGC	GLA-P259L-3'	CCA ACC CCC TAG TCC AGC AAC
GLA-H46R-3'	GCTCCCAGCGCAGCCAG	GLA-G260A-5'	GCTGGACCA GCG GGTTGGAATG
GLA-H46Y-5'	CTGGCTGTACTGGGAGC	GLA-G260A-3'	CAT TCC AAC CCG CTG GTC CAG C
GLA-H46Y-3'	GCTCCCAGTACAGCCAG	GLA-G261D-5'	GGACCAGGG GAT TGGAATGAC

Fig. 6 (Cont.)

GLA-W47G-5'	CTGGCTGCACGGGGAGCGCTTC	GLA-G261D-3'	GTC ATT CCA ATC CCC TGG TCC
GLA-W47G-3'	GAAGCGCTCCCGTGCAGCCAG	GLA-W262C-3'	CAGGGGGT'GC AATGACCCAG
GLA-W47L-5'	CTGGCTGCACITGGAGCGCTTC	GLA-W262C-3'	CTG GGT CAT' TGC AAC CCC CTG
GLA-W47L-3'	GAAGCGCTCCAAGTGCAGCCAG	GLA-N263S-3'	GGGGITGG AGT GACCCAGA
GLA-E48K-5'	GCTGCACTGGAAGCGCTTCATG	GLA-N263S-3'	TCT GGG TCA CTC CAA CCC C
GLA-E48K-3'	CATGAAGCGCTTCCAGTGCAGC	GLA-D264V-5'	GGTTGGAAT GTC CCAGATATG
GLA-R49P/L-5'	ACTGGGAGCYCTTCATGTGC	GLA-D264V-3'	CAT ATC TGG GAC ATT CCA ACC
GLA-R49P/L-3'	GCACATGAAGRGCCTCCAGT	GLA-D264Y-5'	GGGTTGGAAT TAC CCAGATATG
GLA-R49S/G-5'	CACTGGGAGRGCCTCATGT	GLA-D264Y-3'	CAT ATC TGG GTA ATT CCA ACC C
GLA-R49S/G-3'	ACATGAAGCYCTCCAGTG	GLA-P265R-5'	TGGAATGAC CGA GATATGTTA
GLA-F50C-5'	CTGGGAAGCGCTGCATGTGCAAC	GLA-P265R-3'	TAA CAT ATC TCG GTC ATT CCA
GLA-F50C-3'	GTTGCACATGCAGCGCTCCAG	GLA-P265L-5'	TTGGAATGAC CTA GATATGTTAG
GLA-M51K-3'	GAGCGCTTCAAGTGCAACCTTG	GLA-P265L-3'	CTA ACA TAT CTA GGT CAT TCC AA
GLA-M51K-5'	CAAGGTTGCACTTGAAGCGCTC	GLA-D266N/11-5'	GGAATGACCCA mAT ATGTTAGTG
GLA-M51I-5'	GCGCTTCATATGCAACC	GLA-D266N/H-3'	CAC TAA CAT ATT GGG TCA TTC C
GLA-M51I-3'	GGTTGCATATGAAGCGC	GLA-D266H-5	GGTTGGAAATGACCCA cAT ATGTTAGTGATGG
GLA-C52S-5'	GAGCGCTTCATGTCCAACCTTGACTG	GLA-D266H-3	CCA ATC ACT AAC ATA TGT GGG TCA TTC CAA CC
GLA-C52S-3'	CAGTCAAGGTTGGACATGAAGCGCTC	GLA-D266V-5'	GAATGACCCA GTT ATGTTAGTG
GLA-C52G/R-5'	CGCTTCATGSGCAACCTTGAC	GLA-D266V-3'	CAC TAA CAT AAC TGG GTC ATT C
GLA-C52G/R-3'	GTCAAGGTTGCSATGAAGCG	GLA-D266E-5'	ATGACCCA GAA ATGTTAGTG
GLA-C56G-5'	CAACCTTGACGCCAGGAAG	GLA-D266E-3'	TCA CTA ACA TTT CTG GGT CAT
GLA-C56G-3'	CTTCCTGGCCGTCAAGGTTG	GLA-M267R-5'	GACCCAGAT AGG TTAGTGATTG
GLA-C56Y/F-5'	CAACCTTGACTWCCAGGAAGAG	GLA-M267R-3'	CAA TCA CTA ACC TAT CTG GGT C
GLA-C56Y/F-3'	CTCTTCCCTGGWAGTCAGGTTG	GLA-M267I-5'	GACCCAGAT ATA TTAGTGATTGG
GLA-C56Y-5	GTGCAACCTTGACTACCAGGAAGAGCCAG	GLA-M267I-3'	CCA ATC ACT AAT ATA TCT GGG TC

Fig. 6 (Cont.)

GLA-C56Y-3	CTG GCT CTT CCT GGT AGT CAA GGT TGC AC	GLA-L268S-5'	CCA GAT ATG TCA GTG ATT GGC
GLA-C63Y-5	gaGCCAGATTCC TAC ATCAGTGAG\agc	GLA-L268S-3'	GCC AAT CAC TGA CAT ATC TGG
GLA-C63Y-3	GCT TCT CAC TGA TGT AGG AAT CTG GCT C	GLA-V269A-5'	gatatglia gcg attgcaac
GLA-S65T-5'	TCCTGCATCACTGAGAAGCTC	GLA-V269A-3'	GTT GCC AAT CGC TAA CAT ATC
GLA-S65T-3'	GAGCTCTCAGTGATGCAAGGA	GLA-V269M-5'	CAG ATA TGT TAA TGA TTG GCA AC
GLA-E66K-5'	CTGCATCAGTAAGAACGCTCTTC	GLA-V269M-3'	GTT GCC AAT CAT TAA CAT ATC TG
GLA-E66K-3'	GAAGAGCTCTTACTGATGCAG	GLA-I270T-5'	TATGTTAGTGA C TGGCAACTTG
GLA-E66G-5'	CTGCATCAGTGGGAAGCTCTTC	GLA-I270T-3'	CAA AGT TGC CAG TCA CTA ACA TA
GLA-E66G-3'	GAAGAGCTCTTACTGATGCAG	GLA-G271V-5'	TTAGTGATTGTCAACTTG
GLA-L68F-5'	CAGTGAGAAGTTCTCATGG	GLA-G271V-3'	CAAAGTTGACAATCACTAA
GLA-L68F-3'	CCAGGAAGAACCTCTCACTG	GLA-G271C-5'	TTAGTGATT T GCAACTTG
GLA-L68F-5	GCACTAGTGAGAAGTTCATGGAGATG	GLA-G271C-3'	CCA AAG TTG CAA ATC ACT AAC
GLA-L68F-3	CAT CTC CAT GAA GAA CTT CTC ACT GAT GC	GLA-G271S-5'	TGTTAGTGATT A GCAACTTG
GLA-M72R-5'	CTTCATGGAGAGGGCAGAGCTC	GLA-G271S-3'	GCC AAA GTT GCT AAT CAC TAA CA
GLA-M72R-3'	GAGCTCTGCCCTCTCATGAAG	GLA-N272K-5'	GTGATTGGC AAA TTTGGCCTCAG
GLA-M72I-5'	CTTCATGGAGATAGCAGAGCIC	GLA-N272K-3'	CTG AGG CCA AAT TTG CCA ATC AC
GLA-M72I-3'	GAGCTCTGCTATCTCATGAAG	GLA-N272S-5'	GTGATTGGC AGC TTTGGCCTC
GLA-A73V-5'	CATGGAGATGGTAGAGCTCATG	GLA-N272S-3'	GAG GCC AAA GCT GCC AAT CAC
GLA-A73V-3'	CATGAGCTTACCATCTCCATG	GLA-S276G-5'	CAACTTGGCCTCGGCTGGAATCAG
GLA-M76R-5'	GCAGAGCTCAGGGCTCAGAAG	GLA-S276G-3'	CTGATTCCAGCCGAGGCCAAAGTTG
GLA-M76R-3'	CTTCTGAGACCCTGAGCTCTGC	GLA-S276N-5'	CTTTGGCCTC AAC TGGAAATCAGC
GLA-W81C-5'	CTCAGAAGGC TGT AAGGATGCAGGT	GLA-S276N-3'	GCT GAT TCC AGT TGA GGC CAA AG
GLA-W81C-3'	ACC TGC ATC CTT ACA GCC TTC TGA G	GLA-Q279R-5'	AGCTGGAAT CGG CAAGTAAC
GLA-W81S-5'	CTCAGAAGGCCTCGAAGGATGCA	GLA-Q279R-3'	GAG TTA CTT GCC GAT TCC AGC T
GLA-W81S-3'	TGCATCCTCGAGCCTCTGAG	GLA-Q279H-5'	CAGCTGGAAT CAC CAAGTAAC

Fig. 6 (Cont.)

GLA-G85D-5'	GAAGGGATGCAGATTATGAGTAC	GLA-Q279H-3'	GAG TTA CTT GGT GAT TCC AGC TG
GLA-G85D-3'	GTACTCATATACTGCATCCTTC	GLA-Q279K-5'	CAGCTGGAAT AAG CAAGTAAC
GLA-Y86C-5'	GGATGCAGGT TGT GAGTACCTCTGc	GLA-Q279K-3'	GTT ACT TGC TTA TTC CAG CTG
GLA-Y86C-3'	GCA GAG GTA CTC ACA ACC TGC ATC C	GLA-Q280H-5'	GGAATCAGCAT GTAACTCAGA
GLA-Y88D-5'	GGTTATGAGGGACCTCTGCATTG	GLA-Q280H-3'	TCT GAG TTA CAT GCT GAT TCC
GLA-Y88D-3'	CAATGCAGAGGTCTCTATAACC	GLA-Q280K-5'	CTGGAATCAG AAA GTAACTCAG
GLA-L89P/R-5'	GTATGAGTACCSCTGCATTGATG	GLA-Q280K-3'	CTG AGT TAC TTT CTG ATT CCA
GLA-L89P/R-3'	CATCAATGCAGSGGTACTCATAAC	GLA-T282N-5'	CAGCAAGTAAATCAGATGGCC
GLA-D92N/H/Y-5'	CCTCTGCATTHATGACTGTTG	GLA-T282N-3'	GGC CAT CTG ATT TAC TTG CTG
GLA-D92N/H/Y-3'	CAACAGTCATDAATGCAGAGG	GLA-Q283P-5'	CAAGTAACT CCG ATGGCCCTC
GLA-D92N-5'	TACCTCTGCATT AAT GACTGTTGGATG	GLA-Q283P-3'	GAG GGC CAT CGG AGT TAC TTG
GLA-D92N-3'	CAT CCA ACA GTC ATT AAT GCA GAG GTA	GLA-M284T-5'	GTAACTCAG ACG GCCCTCTG
GLA-D92H-5'	TACCTCTGCATT CAT GACTGTTGGATG	GLA-M284T-3'	CAG AGG GCC GTC TGA GTT AC
GLA-D92H-3'	CAT CCA ACA GTC ATG AAT GCA GAG GTA	GLA-A285P-5'	TAACTCAGATG C CCCCTGGGCT
GLA-D92Y-5'	GAGTACCTCTGCATT tAT GACTGTTGGATG	GLA-A285P-3'	AGC CCA GAG GGG CAT CTG AGT TA
GLA-D92Y-3'	GAG CCA TCC AAC AGT CAT AAA TGC AGA GGT ACT C	GLA-A285D-5'	AACTCAGATGG A CCTCTGGGCT
GLA-D93G-5'	CTGCATTGATGGCTGTTGGATG	GLA-A285D-3'	AGC CCA GAG GTC CAT CTG AGT T
GLA-D93G-3'	CATCCAACAGCCATCAATGCAG	GLA-W287G-5'	GATGGCCCTC GGG GCTATCAT
GLA-D93V-5'	CTGCATTGATGTCGTTGGATG	GLA-W287G-3'	ATG ATA GCC CCG AGG GCC ATC
GLA-D93V-3'	CATCCAACAGACATCAATGCAG	GLA-W287C-5'	ATGGCCCTC TGT GCTATCATG
GLA-D93N-5'	CTGCATTGATAACTGTTGGATG	GLA-W287C-3'	CAT GAT AGC ACA GAG GGC CAT
GLA-D93N-3'	CATCCAACAGTTATCAATGCAG	GLA-A288D-5'	GCCCCCTGG GAT ATCATGGCTG
GLA-C94S-5'	GCATTGATGACTCTGGATGGCTC	GLA-A288D-3'	CAG CCA TGA TAT CCC AGA GGG C
GLA-C94S-3'	GAGCCATCCAAGAGTCATCAATGC	GLA-A288P-5'	GCCCCCTGG CCT ATCATGG

Fig. 6 (Cont.)

GLA-C94Y-5'	GCATTGATGACTATTGGATGGCTC	GLA-A288P-3'	CCA TGA TAG GCC AGA GGG C
GLA-C94Y-3'	GAGCCATCCAATAGTCATCAATGC	GLA-I289F-5'	CTCTGGGCT TTC ATGGCTGCTCCTT
GLA-W95S-5'	GATGACTGTTGATGGCTCCC	GLA-I289F-3'	AAG GAG CAG CCA TGA AAG CCC AGA G
GLA-W95S-3'	GGGAGCCATCGAACAGTCATC	GLA-M290I-5'	GGGCTATC ATC GCTGCTCCTT
GLA-A97P-5'	CTGTTGGATGCCTCCCCAAAGAG	GLA-M290I-3'	AAG GAG CAG CGA TGA TAG CCC
GLA-A97P-3'	CTCTTGGGGAGGCATCCAACAG	GLA-A292P-5'	CTATCATGGCT CCT CCTTATTTC
GLA-R100K/T-5'	GCTCCCCAAAMAGATTAGAAG	GLA-A292P-3'	GAA TAA AGG AGG AGC CAT GAT AG
GLA-R100K/T-3'	CTTCTGAATCTKTTGGGGAGC	GLA-P293A-5'	CATGGCTGCT GCT TTATTTCATG
GLA-R100T-5'	GGCT CCC CAA ACA GAT TCA GAA GG	GLA-P293A-3'	CAT GAA TAA AGC AGC AGC CAT G
GLA-R100I-3'	CCT TCT GAA TCT GTT TGG GGA GCC	GLA-P293S/T-5'	CATGGCTGCT WCT TTATTTCATG
GLA-E103Q-5'	CAAAGAGATTACAAGGCAGACTTC	GLA-P293S/T-3'	CAT GAA TAA AGW AGC AGC CAT G
GLA-L103Q-3'	GAAGTCTGCCCTGTGAATCTCTTG	GLA-F295C-5'	GCTGCTCCCTTA TGC ATGTCTAATGACC
GLA-R112S-5'	GCAGACCCCTCAGAGCTTCCTCATG	GLA-F295C-3'	GGT CAT TAG ACA TGC ATA AAG GAG CAG C
GLA-R112S-3'	CATGAGGAAAGCTCTGAGGGCTGC	GLA-S297C/F-5'	CTTTATTTCATG TKT AATGACCTCCG
GLA-R112C-5'	CAGACCCCTCAGTGCTTCCTCATG	GLA-S297C/F-3'	CGG AGG TCA TTA MAC ATG AAT AAA G
GLA-R112C-3'	CATGAGGAAAGCACTGAGGGCTG	GLA-N298S-5'	ATTCATGTCT AGT GACCTCCGAC
GLA-F113S-5'	CCCTCAGCGCTCTCCTCATG	GLA-N298S-3'	GTC GGA GGT CAC TAG ACA TGA AT
GLA-F113S-3'	CATGAGGAGAGCGCTGAGGG	GLA-N298K-5'	TATTCTATG TCTAAGGACCTCCGAC
GLA-R118C-5'	CTCATGGGATTGCCAGCTAGC	GLA-N298K-3'	GTCGGAGGTCCCTAGACATGAATA
GLA-R118C-3'	GCTAGCTGGCAAATCCCAGAG	GLA-N298H-5'	TATTCTATGTCT cAT GACCTCCGAC
GLA-1120P-5'	GATTCGCCAGCCAGCTAATTATG	GLA-N298I-3'	GTC GGA GGT CAT GAG ACA TGA ATA
GLA-L120P-3'	CATAATTAGCTGGCTGGCGAATC	GLA-D299G-5'	TCATGTCTAAAT GGC CTCCGACACATC
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
GLA-A121P/T-3'	GCT GTG AAC ATA ATT AGK TAG CTG GCG A	GLA-L300P-5'	GTCTAAATGACCCCCGACACATCAG
GLA-V124D-5'	GCTAGCTAATTAT GaT CACAGCAAAGGAC	GLA-L300P-3'	CTGATGTGTCGGGGTCATTAGAC

Fig. 6 (Cont.)

GLA-V124D-3'	GTC CTT TGC TGT GAT CAT AAT TAG CTA GC	GLA-L300F-5'	GTCTAAATGACTTCCGACACATC
GLA-G128E-5'	CACAGCAAAGaACTGAAGCTAG	GLA-L300F-3'	GATGTGTCGGAAGTCATTAGAC
GLA-G128E-3'	CTA GCT TCA GTT CTT TGC TGT G	GLA-L300H-5'	GTCTAAATGACCACCGACACATC
GLA-L129P-5'	CAG CAA AGG ACC GAA GCT AGG	GLA-L300H-3'	GATGTGTCGGTGGTCATTAGAC
GLA-L129P-3'	ATC CCT AGC TTC GGT CCT TTG CTG	GLA-R301G-5'	CTAAATGACCTCGGACACATCAGC
GLA-L131P-5'	AGGACTGAAGC C AGGGATTATGC	GLA-R301G-3'	GCTGATGTGTCGGAGGTCAATTAG
GLA-L131P-3'	GCA TAA ATC CCT GGC TTC AGT CCT	GLA-R301P-5'	CTAAATGACCTCCCACACATCAGC
GLA-G132E-5'	GGACTGAAGCTA GaG ATTATGCAGATG	GLA-R301P-3'	GCTGATGTGTCGGAGGTCAATTAG
GLA-G132E-3'	CAT CTG CAT AAA TCT CTA GCT TCA GTC C	GLA-I303N-5'	CTCCGACACAACAGCCCTCAAGC
GLA-G132R-5'	GAC TGA AGC TAA GGA TTT ATG CAG ATG	GLA-I303N-3'	GCTTGAGGGCTGTGTGTCGGAG
GLA-G132R-3'	CAT CTG CAT AAA TCC TTA GCT TCA GTC	GLA-L310F-5'	GCCAAAGCTTCCTTCAGGA
GLA-Y134S-5'	GCT AGG GAT TTC TGC AGA TGT TGG	GLA-L310F-3'	TCCTGAAGGAAAGCTTGGC
GLA-Y134S-3'	CCA ACA TCT GCA GAA ATC CCT AGC	GLA-Q312H-5'	GCTCTCCTTCACGATAAGGACG
GLA-A135V-5'	GCT AGG GAT TTA TGT AGA TGT TGG A	GLA-Q312H-3'	CGTCCTTATCGTGAAGGAGAGC
GLA-A135V-3'	TCC AAC ATC TAC ATA AAT CCC TAG C	GLA-D313Y-5'	CTCTCCTTCAGTATAAGGACG
GLA-D136H-5'	GGA TTT ATG CAC ATG TTG GAA	GLA-D313Y-3'	CGTCCTTATACTGAAGGAGAG
GLA-D136H-3'	TTC CAA CAT GTG CAT AAA TCC	GLA-V316E-5'	GATAAGGACGAAATTGCCATC
GLA-D136H-5	GGGATTATGCACAT GTTGGAAATAA AACC	GLA-V316E-3'	GATGGCAATTCTCGTCCTIATC
GLA-D136H-3	GGT TTT ATT TCC AAC ATG TGC ATA AAT CCC	GLA-I317N/T-5'	AAGGACGTAAMTGCCATCAATC
GLA-G138E-5'	TGC AGA TGT TGA AAA TAA AAC CTG	GLA-I317N/T-3'	GATTGATGGCAKTTACGTCTT
GLA-G138E-3'	CAG GTT TTA TTT TCA ACA TCT GCA	GLA-N320I-5'	AATTGCCATCATTCAGGACCC
GLA-G138R-5'	TGC AGA TGT TAG AAA TAA AAC CTG	GLA-N320I-3'	GGGGTCCTGAATGATGGCAATT
GLA-G138R-3'	CAG GTT TTA TTT CTA ACA TCT GCA	GLA-N320K-5'	AATTGCCATCAAGCAGGACCC
GLA-G138E-5	GGATTTATGCAGATGTT GaA AATAAAACCTGCGCAGC	GLA-N320K-3'	GGGGTCCTGCTTGTGGCAATT
GLA-G138E-3	GCT GCG CAG GTT TTA TTT TCA ACA TCT GCA TAA ATC C	GLA-N320Y-5'	AATTGCCATCTATCAGGACCC

Fig. 6 (Cont.)

GLA-G138R-5	GGATTTATGCAGATGTT cGA ΔΔΔΔΔΔΔCTGCGCAGC	GLA-N320Y-3'	GGGGTCCTGATAGATGGCAATT
GLA-G138R-3	GGA TTT ATG CAG ATG TTC GAA ATA AAA CCT GCG CAG C	GLA-Q321E-5'	TGCCATCAATGAGGACCCCTTG
GLA-T141I-5'	GGA AAT AAA ATC TGC GCA GGC T	GLA-Q321E-3'	CAAGGGGTCCCTATTGATGGCA
GLA-T141I-3'	AGC CTG CGC AGA TTT TAT TTC C	GLA-Q321R-5'	TGCCATCAATCGGGACCCCTTG
GLA-C142R-5'	GGA AAT AAA ACC CGC GCA GGC TTC	GLA-Q321R-3'	CAAGGGGTCCCATTGATGGCA
GLA-C142R-3'	GAA GCC TGC GCG GGT TTT ATT TCC	GLA-G325D-5'	GGACCCCTTGGACAAGCAAG
GLA-C142Y/W-5'	GA AAT AAA ACC TRC GCA GGC TTCC	GLA-G325D-3'	CTTGCTTGTCCAAGGGTCC
GLA-C142Y/W-3'	GGA AGC CTG CGY AGG TTT TAT TTC	GLA-Q327K/E-5'	CTTGGCAAGRAAGGGTACCAAG
GLA-C142W-5	GGAAATAAAACCTGGGCAGGCCTTCCCTG	GLA-Q327K/E-3'	CTGGTACCCCTTYCTTCCCCAAG
GLA-C142W-3	CAG GGA AGC CTG CCC AGG TTT TAT TTC	GLA-G328R-5'	GGCAAGCAAAGGTACCAGC
GLA-A143T-5'	GGAAATAAAACCTGCACAGGCTTCCC	GLA-G328R-3'	GCTGGTACCTTTGCTTGCC
GLA-A143T-3'	GGGAAGCCTGTGCAGGTTTATTC	GLA-G328A/V-5'	GGCAAGCAAGYGTACCAAGC
GLA-A143P-5'	ATAAAACCTGC cCA GGCTTCCC	GLA-G328A/V-3'	GCTGGTACRCTTGCTTGCC
GLA-A143P-3'	GGG AAG CCT GgG CAG GTT TTA T	GLA-G328E-5'	TGGGCAAGCAA GAG TACCAAGCTTAG
GLA-G144V-5'	CCT GCG CAG TCT TCC CTG G	GLA-G328E-3'	CTA AGC TGG TAC TCT TGC TTG CCC A
GLA-G144V-3'	CCA GGG AAG ACT GCG CAG G	GLA-E338K-5'	GAGACAACTTAAAGTGTGGG
GLA-G147R-5'	GGC TTC CCT AGG AGT TTT Gg	GLA-E338K-3'	CCCACACTTAAAGTTGTCTC
GLA-G147R-3'	cCAA AAC TCC TAG GGA AGC C	GLA-W340R-5'	CTTGAAAGTGCAGGAAACGAC
GLA-S148N-5'	TTC CCT GGG AAT TTT GGA TAC	GLA-W340R-3'	GTCGTTCCCGCACTCAAAG
GLA-S148N-3'	GTA TCC ΔΔΔ ATT CCC AGG GAA	GLA-E341D-5'	GAAGTGTGGGACCGACCTCTCTC
GLA-S148R-5'	C CCT GGG AGG TTT GGA TACT	GLA-E341D-3'	GAGAGAGGTGGTCCACACTTC
GLA-S148R-3'	AGT ATC CAA ACC TCC CAG GG	GLA-E341K-5'	GAAGTGTGGAAACGACCTCTCTC
GLA-Y152C-5'	GTITGGATACTGCGACATGATG	GLA-E341K-3'	GAGAGAGGTGTTCCACACTTC
GLA-Y152C-3'	CATCAATGTCGCACTATCCAAAAC	GLA-R342Q-5'	GTGTGGGAACAACCTCTCTCAG

Fig. 6 (Cont.)

GLA-D155H-5'	CTACGACATT C ATGCCAGAC	GLA-R342Q-3'	CTGAGAGAGGTGTTCCACAC
GLA-D155H-3'	GTC TGG GCA TGA ATG TCG TAG	GLA-L344P-5'	GAACGACCTCCCTCAGGCTTAG
GLA-A156T-5'	GACATTGAT ACC CAGACCTtg	GLA-L344P-3'	CTAACGCCTGAGGGAGGTCGTT
GLA-A156T-3'	CAA AGG TCT GGG TAT CAA TGT C	GLA-S345P-5'	CGACCTCTCCCAGGCTTAGCC
GLA-W162R-5'	CTTGCTGACCGGGAGTAGATC	GLA-S345P-3'	GGCTAAGCCTGGGAGAGGTCG
GLA-W162R-3'	GATCTACTCCCCGGTCAGCAAAG	GLA-A348P-5'	CTCAGGCTTACCCCTGGGCTGTAG
GLA-W162C-5'	CTTGCTGACTCGGGAGTAGATC	GLA-A348P-3'	CTACAGCCCAGGGTAAGCCTGAG
GLA-W162C-3'	GATCTACTCCCGCAGTCAGCAAAG	GLA-A350P-5'	CTTAGCCTGGCCTGTAGCTATG
GLA-G163V-5'	GCTGACTGGGTAGTAGATCTG	GLA-A350P-3'	CATACTACAGGCCAGGCTAAG
GLA-G163V-3'	CAGATCTACTACCCAGTCAGC	GLA-A352D-5'	CTGGGCTGTAGATATGATAAAC
GLA-D165V-5'	CTGGGGAGTAGTTCTGCTAAAATTG	GLA-A352D-3'	GTTTATCATATCTACAGCCCAG
GLA-D165V-3'	CAAAITTTAGCAGAACTACTCCCCAG	GLA-I354K-5'	GTAGCTATGAAAAACCGGCAGG
GLA-L167P-5'	GAGTAGATCTGC C AAAATTGATGG	GLA-I354K-3'	CCTGCCGGTTTCATAGCTAC
GLA-L167P-3'	CCA TCA AAT TTT GGC AGA TCT ACT C	GLA-N355K-5'	GCTATGATAAAACGGCAGGAG
GLA-K168R-5'	GTAGATCTGCTA AGA TTTGATGGTTG	GLA-N355K-3'	CTCCTGCCGTTTATCATAGC
GLA-K168R-3'	CAA ACC ATC AAA TCT TAG CAG ATC TAC	GLA-R356W-5'	GCTATGATAAACTGGCAGGAGATT
GLA-F169S-5	gtAGATCTGCTAAA TCT GATGGTTGTTACg	GLA-R356W-3'	AATCTCTGCCAGTTATCATAGC
GLA-F169S-3	CAG TAA CAA CCA TCA GAT TTT AGC AGA TCT AC	GLA-E358G/A-5'	ACCGGCAGGSGATTGGTGGAC
GLA-D170V-5'	GCTAAAATTG T TGTTGTTACTG	GLA-E358G/A-3'	GTCCACCAATCSCCTGCCGGT
GLA-D170V-3'	CAG TAA CAA CCA ACA AAT TTT AGC	GLA-E358K-5'	GATAAACCGGCAGAAGATTGGTGG
GLA-D170H-5'	GCTAAAATTTC AT GGTTGTTACTG	GLA-E358K-3'	CCACCAATCTCTGCCGGTTATC
GLA-D170H-3'	CAG TAA CAA CCA TGA AAT TTT AGC	GLA-E358A-5	GATAAACCGGCAG GcG ATTGGTGGACCTC
GLA-G171D-5'	CTAAAATTGAT GAT TGTTACTGTGAC	GLA-E358A-3	GAG GTC CAC CAA TCG CCT GCC GGT TTA TC
GLA-G171D-3'	GTC ACA GTA ACA ATC ATC AAA TTT TAG	GLA-I359T-5'	CCGGCAGGAGACTGGTGGACCTC
GLA-G171R-5'	CTAAAATTGAT CGT TGTTACTGTGAC	GLA-I359T-3'	GAGGTCCACCAGTCTCCTGCCGG

Fig. 6 (Cont.)

GLA-G171R-3'	GTC ACA GTA ACA ACG ATC AAA TTT TAG	GLA-G360S-5'	CAGGAGATTAGTGGACCTCGC
GLA-C172Y/F-5'	CTAAAATTTGATGGT TWT tactgtgacagT	GLA-G360S-3'	GCGAGGTCCACTAATCTCCTG
GLA-C172Y/F-3'	ACT GTC ACA GTA AWA ACC ATC AAA TTT TAG	GLA-G361R-5'	GGAGATTGGTAGACCTCGCTC
GLA-C172W-5'	CTAAAATTTGATGGT TGG tactgtgacagT	GLA-G361R-3'	GAGCGAGGTCTACCAATCTCC
GLA-C172W-3'	ACT GTC ACA GTA CCA ACC ATC AAA TTT TAG	GLA-P362L-5'	GATTGGTGGACTTCGCTCTTATAC
GLA-C172R-5'	CTAAAATTTGATGGT CGT tactgtgacagT	GLA-P362L-3'	GTATAAGAGCGAAGTCCACCAATC
GLA-C172R-3'	ACT GTC ACA GTA ACG ACC ATC AAA TTT TAG	GLA-R363H-5'	GGTGGACCTCACCTTATAC
GLA-C172G-5'	CTAAAATTTGATGGT GGT tactgtgacagT	GLA-R363H-3'	GTATAAGAGTGAGGTCCACC
GLA-C172G-3'	ACT GTC ACA GTA ACC ACC ATC AAA TTT TAG	GLA-R363C-5'	GGTGGACCTTGCTCTTATAC
GLA-G183D-5'	TTGGCAGATG A TTATAAGCAC	GLA-R363C-3'	GTATAAGAGCAAGGICCACC
GLA-G183D-3'	GTG CTT ATA ATC ATC TGC CAA	GLA-G373R-5'	TGCTTUCCTG CGT AAAGGAGTGG
GLA-G183S-5'	TTGGCAGAT A GTTATAAGCAC	GLA-G373R-3'	CCA CTC CTT TAC GCA GGG AAG CA
GLA-G183S-3'	GTG CTT ATA ACT ATC TGC CAA	GLA-A377D-5'	GTAAAGGAGTGGACTGTAATCCCTG
GLA-M187T-5'	GTTATAAGCAC A GTCCTGGCCCT	GLA-A377D-3'	CAGGATTACAGTCCACTCCTTAC
GLA-M187T-3'	AGG GCC AAG GAC GTG TGC TTA TAA C	GLA-C378Y-5'	AAAGGAGTGGCCATAATCCTGCC
GLA-M187V-5'	GTTATAAGCAC G TGTCTGGCC	GLA-C378Y-3'	GGCAGGATTATAGGCCACTCCTT
GLA-M187V-3'	GGC CAA GGA CAC GTG CTT ATA AC	GLA-C378R-5'	AAAGGAGTGGCCCTAATCCTGCC
GLA-L191Q-5'	GTCCTTGGCCCAGAACATAGGACTG	GLA-C378R-3'	GGCAGGATTACGGGCCACTCCTT
GLA-L191Q-3'	CAG TCC TAT TCT GGG CCA AGG AC	GLA-C382Y-5'	GTAATCCTGCCTACTTCATCACAC
GLA-L191P-5'	GTCCTTGGCCC C GAATAGGACTG	GLA-C382Y-3'	GTGTGATGAAGTAGGCAGGATTAC
GLA-L191P-3'	CAG TCC TAT TCG GGG CCA AGG AC	GLA-I384N-5	CTGCCCTGCTTC AaC ACACAGCTCCTC
GLA-T194I-5'	CTGAATAGGATTGGCAGAAGC	GLA-I384N-3	GAG GAG CTG TGT GTT GAA GCA GGC AG
GLA-T194I-3'	GCT TCT GCC AAT CCT ATT CAG	GLA-T385P-5'	CCTGCTTCATCCACAGCTCCTCC
GLA-V199M-5'	CAGAACATTATGTACTCCTG	GLA-T385P-3'	GGAGGAGCTGTGGGATGAAGCAGG
GLA-V199M-3'	CAG GAG TAC ATA ATG CTT CTG	GLA-Q386P-5'	CTTCATCACAC CCG CTCCCTCCIGT

Fig. 6 (Cont.)

GLA-S201F-5'	CATTGTGTACTCTGTGAGTGG	GLA-Q386P-3'	ACA GGG AGG AGC GGT GTG ATG AAG
GLA-S201F-3'	CCACTCACAGAAGTACACAATG	GLA-P389R-5'	CACAGCTCCTC CGT GTGAAAAGGAAGCT
GLA-S201Y-5'	CATTGTGTACTACTGTGAGTGGC	GLA-P389R-3'	AGC TTC CTT TTC ACA CGG AGG AGC TGT G
GLA-S201Y-3'	GCC ACT CAC AGT AGT ACA CAA TG	GLA-F396Y-5'	GGAAGCTAGGGTACTATGAATGG
GLA-C202Y-5'	GTG TAC TCC TAT GAG TGG CCT C	GLA-F396Y-3'	CCATTCAAGTACCCTAGCTTCC
GLA-C202Y-3'	GAG GCC ACT CAT AGG AGT ACA C	GLA-E398K-5'	AGGGTTCTATAAATGGACTTCA
GLA-C202W-5'	GTGTACTCCTGG GAGTGGCCTCT	GLA-F398K-3'	TGAAGTCATTTATAGAACCT
GLA-C202W-3'	AGA GGC CAC TCC CAG GAG TAC AC	GLA-L403S-5'	GACTTCAAGGTCAAGAAGTCAC
GLA-P205T-5'	CTGTGAGTGGACTCTTATATG	GLA-L403S-3'	GTGACTTCTTGACCTTGAAGTC
GLA-P205T-3'	CATATAAAGAGTCCACTCACAG	GLA-I407K-5'	GAAGTCACAAAAATCCACAG
GLA-P205R/L-5'	CTGTGAGTGG CKT CTTTATATG	GLA-I407K-3'	CTGTGGGATTTTGTGACTTC
GLA-P205R/L-3'	CAT ATA AAG AMG CCA CTC ACAG	GLA-P409T/A/S-5'	GTCACATAAATDCCACAGGCACTG
GLA-Y207S-5'	TGGCCTCTT TCT ATGTGGCCC	GLA-P409T/A/S-3'	CAGTGCCTGTGGHATTATGTGAC
GLA-Y207S-3'	GGG CCA CAT AGA AAG AGG CCA	GLA-T410K-5'	CACATAAATCCCAAAGGCACTG
GLA-Y207C-5'	AGTGGCCTCTT TgT ATGTGGCCCTT	GLA-T410K-3'	CAGTGCCTTGGGATTATGTG
GLA-Y207C-3'	AAG GGC CAC ATA CAA AGA GGC CACT	GLA-T410A-5'	CACATAAATCCCGCAGGCACTG
GLA-Y216D-5	CCTTTCAAAAGGCCAAT gAT ACAGAAATCCGACAG	GLA-T410A-3'	CAGTGCCTGCGGGATTATGTG
GLA-Y216D-3	CTG TCG GAT TTC TGT ATC ATT GGG CTT TTG AAA GG	GLA-G411D-5'	ATCCCACAGACACTGTTTGC
GLA-I219N-5'	CAATTATAACAGAA AAC CGACAGTACTGC	GLA-G411D-3'	GCAAAACAGTGTCTGTGGGAT
GLA-I219N-3'	GCA GTA CTG TCG GTT TTC TGT ATA ATT G	GLA-L414S-5'	GGCACTGTTCGCTTCAGCTAG
GLA-C223R/G-5'	CGACAGTAC SGC AATCACTGG	GLA-L414S-3'	CTAGCTGAAGCGAAACAGTGCC
GLA-C223R/G-3'	CCA GTG ATT GCS GTA CTG TCG	GLA-del20-24aa-5'	GCGCTTCGCTTCTGGACATCCCTGG GC
GLA-C223Y-5'	CGACAGTACTAC AATCACTGG	GLA-del20-24aa-3'	GCCCCAGGGATGTCCAGGAAGCGAAG CGC

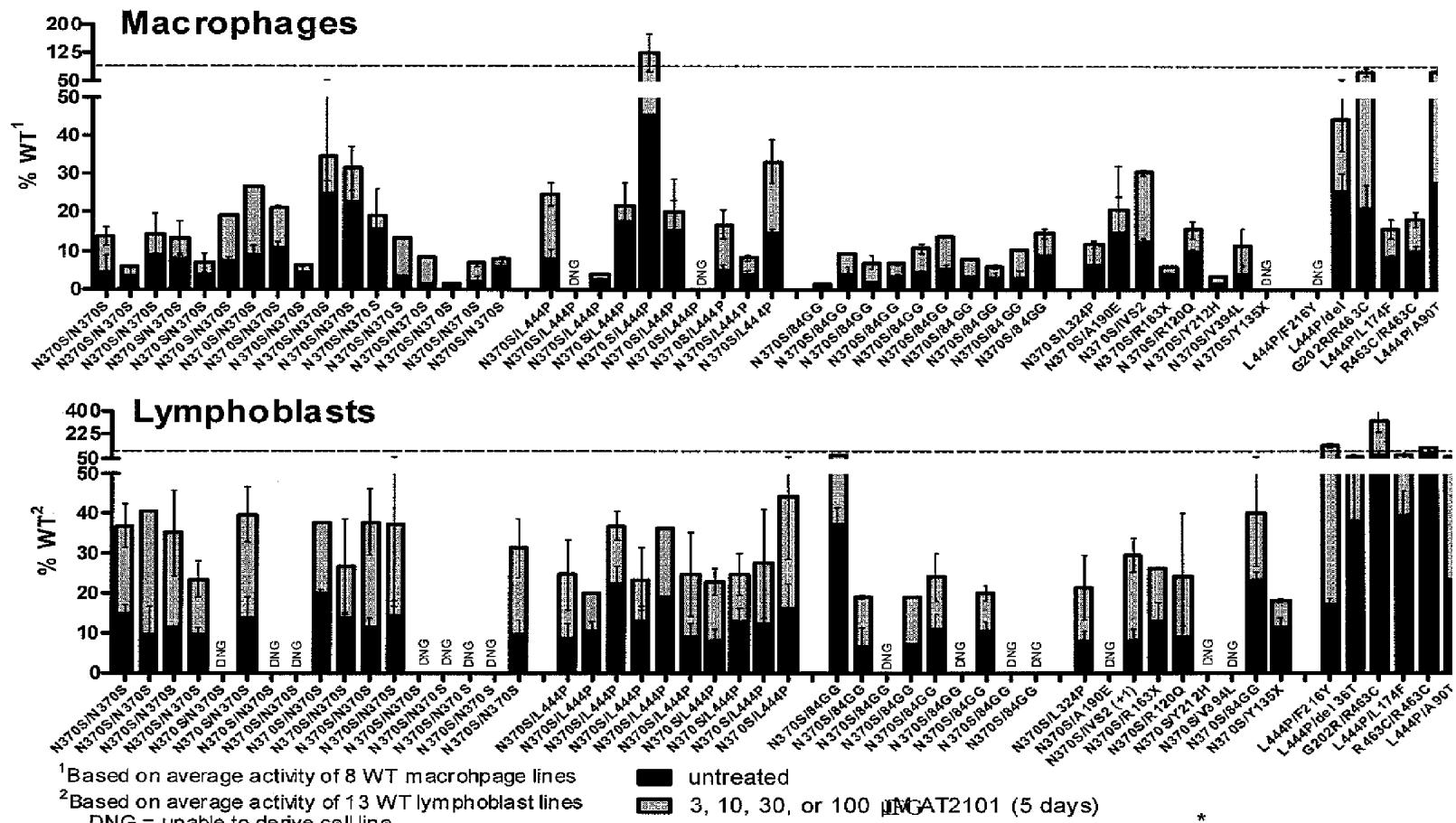
Fig. 6 (Cont.)

GLA-C223Y-3'	CCA GTG ATT GTA GTA CTG TCG	GLA-del113-8aa-5'	GCAGACCCCTCAGGCCAGCTAGCTAA TTATG
GLA-N224S-5'	CAGTACTGCAGTCAGTGGCGA	GLA-del113-8aa-5'	CATAATTAGCTAGCTGGCGCTGAGGG TCTGC
GLA-N224S-3'	TCG CCA GTG ACT GCA GTA CTG	GLA-del153aa-5'	GTTTTGGATACTACATTGATGCCAG
GLA-N224D-5'	CAGTACTGCGATCACTGGC	GLA-del153aa-3'	CTGGGCATCAATGTAGTATCCAAAAC
GLA-N224D-3'	GCC AGT GAT CGC AGT ACT G	GLA-del205-7aa-5'	CTCCTGTGAGTGGATGTGGCCCTT
GLA-H225R-5'	tactgcaat cgc tggcgaaat	GLA-del205-7aa-3'	AAGGGCCACATCCACTCACAGGAG
GLA-H225R-3'	ATT TCG CCA GCG ATT GCA GTA	GLA-del254aa-5'	CAGGAGAGAATTGATGTTGCTGG
GLA-W226R-5'	gcaatcac cgg cgaaat	GLA-del254aa-3'	CCAGCAACATCAATTCTCTCCCTG
GLA-W226R-3'	ATT TCG CCG GTG ATT GC	GLA-del358aa-5'	GATAAACCGGCAGATTGGTGGACCT
GLA-W226C-5'	gcaatcacgtcgaaattttgc	GLA-del358aa-3'	AGGTCCACCAATCTGCCGGTTATC
GLA-W226C-3'	GCA AAA TTT CGA CAG TGA TTG C	GLA-Ins247-8aa-5'	GACTGGACATCTTGGACATCTTTAAC CAGGAGAG
GLA-R227Q-5'	GCAATCACTGGCAAATTTGCTGAC	GLA-Ins247-8aa-3'	CTCTCTGGTTAAAGATGTCCAAGAT GTCCAGTC

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;

Fig. 7

GAATTCTCCGGTCACCGTGACAATGCAGCTGAGGAACCCAGAACTACATCTGGC
5 TCGCGCCTTGCCTCGCTCCTGGCCCTCGTTCTGGACATCCCTGGGCTAG
AGCACTGGACAATGGAITGGCAAGGACGCCAACCATGGGCTGGCTGCAGCTGGGA
GCGCTTCATGTGCAACCTTGACTGCCAGGAAGAGCCAGATTCCTGCATCAGTGAG
AAGCTCTCATGGAGATGGCAGAGCTCATGGCTCAGAAGGCTGGAAGGATGCA
GGTTATGAGTACCTCTGCATTGATGACTGTTGGATGGCTCCCCAAAGAGATTAG
10 AAGGCAGACTTCAGGCAGACCCCTCAGCGCTTCCTCATGGGATTCCCGAGCTAGC
TAATTATGTTCACAGCAAAGGACTGAAGCTAGGGATTATGCAGATGTTGAAAT
AAAACCTGCGCAGGCTTCCTGGGAGTTTGGATACTACGACATTGATGCCAGA
CCTTGCTGACTGGGAGTAGATCTGCTAAAATTGATGTTGTTACTGTGACAG
TTTGGAAAAATTGGCAGATGGTTATAAGCACATGTCCTGGCCCTGAATAGGACT
15 GGCAGAAGCATTGTGTACTCCGTGAGTGGCCTCTTATATGTTGCCCCTTCAA
AGCCCAATTATACAGAAATCCGACAGTACTGCAATCACTGGCGAAATTGCTGA
CATTGATGATTCTGGAAAAGTATAAGAGTATCTTGGACTGGACATCTTTAAC
CAGGAGAGAATTGTTGATGTTGCTGGACCAGGGGGTIGGAATGACCCAGATATG
TTAGTGATTGGCAACTTGGCCTCAGCTGGAAATCAGCAAGTAACTCAGATGGCC
20 TCTGGCTATCATGGCTGCTCTTATTCATGTCATAATGACCTCCGACACATCAGC
CCTCAAGCCAAAGCTCCCTCAGGATAAGGACGTAATTGCCATCAATCAGGACC
CCTTGGCAAGCAAGGTACAGCTAGACACGGAGACAACTTGAAGTGTGGG
AACGACCTCTCAGGCTAGCCTGGCTGTAGCTATGATAAAACCGGCAGGAGAT
TGGTGGACCTCGCTCTATACCATCGCAGTGTGCTCCCTGGTAAAGGAGTGGCC
25 TGTAATCCTGCCTGCTTCATCACACAGCTCCTCCGTGAAAAGGAAGCTAGGGT
TCTATGAATGGACCTCAAGGTTAAGAAGTCACATAAAATCCACAGGCAGTGT
GCTTCAGCTAGAAAATACAATGCAGATGTCATAAAAGACTTACTTAA

Fig. 8

*

Fig. 9

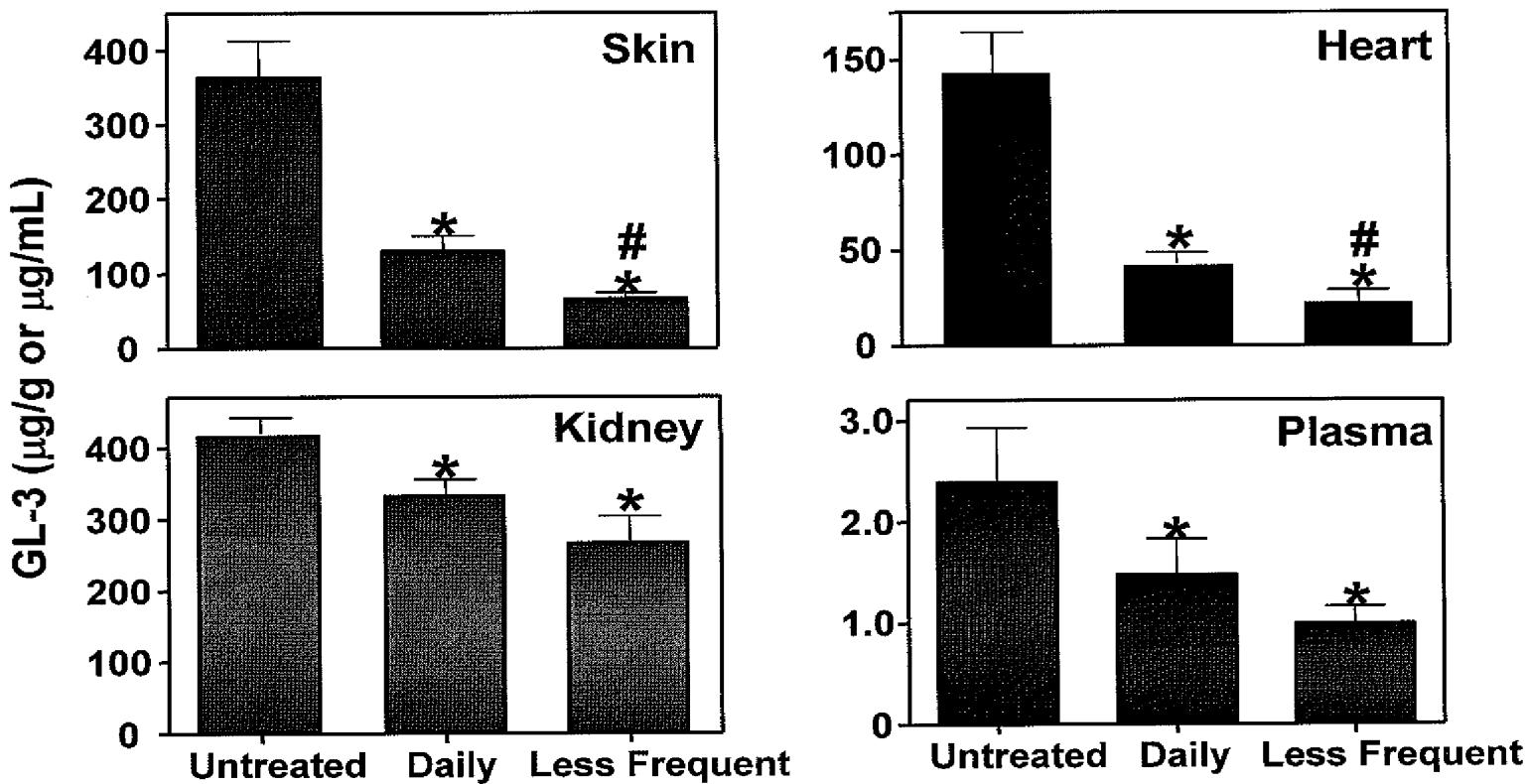


Fig. 10

Responsive GAA missense

GAA mutation	n	% wild-type GAA activity	
		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

Fig. 11

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

cagttggaa agctgagggtt gtcgccgggg ccegggggg aggteggggta tgaggcagca	60
ggtaggacac tgacctcggt gacgcgaagg accccggcca cctctaggtt ctctcgccc	120
gccccgttgtt cagcgaggga ggctctggc ctgcgcgcgc tgacggggaa actgaggcac	180
ggagcggggcc tggtaggatgt gtccaggcca tctccaacca tggagttag gcacccgccc	240
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gggcacatcc tactccatga ttccctgtgt gttcccgag agctgagtgg ctccctccca	360
gtccctggagg agactcaccac agctcaccag caggagccca gcagaccagg gccccgggat	420
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ggcccggtgc tgctgaacac gacgggtggcg cccctgtct ttccggacca gttcccttcag	960
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cccgacttca ccaacccac agccctggcc tgggtggagg acatgggtgc tgagttccat	1740
gaccagggtgc cttcgacgg catgtggatt gacatgaacg agccttccaa ttccatcaga	1800
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cccaacgcga ccgttcccg gtcgtccaga gggctggatg cctgcggc cccgagcaag 3540
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Fig. 12.

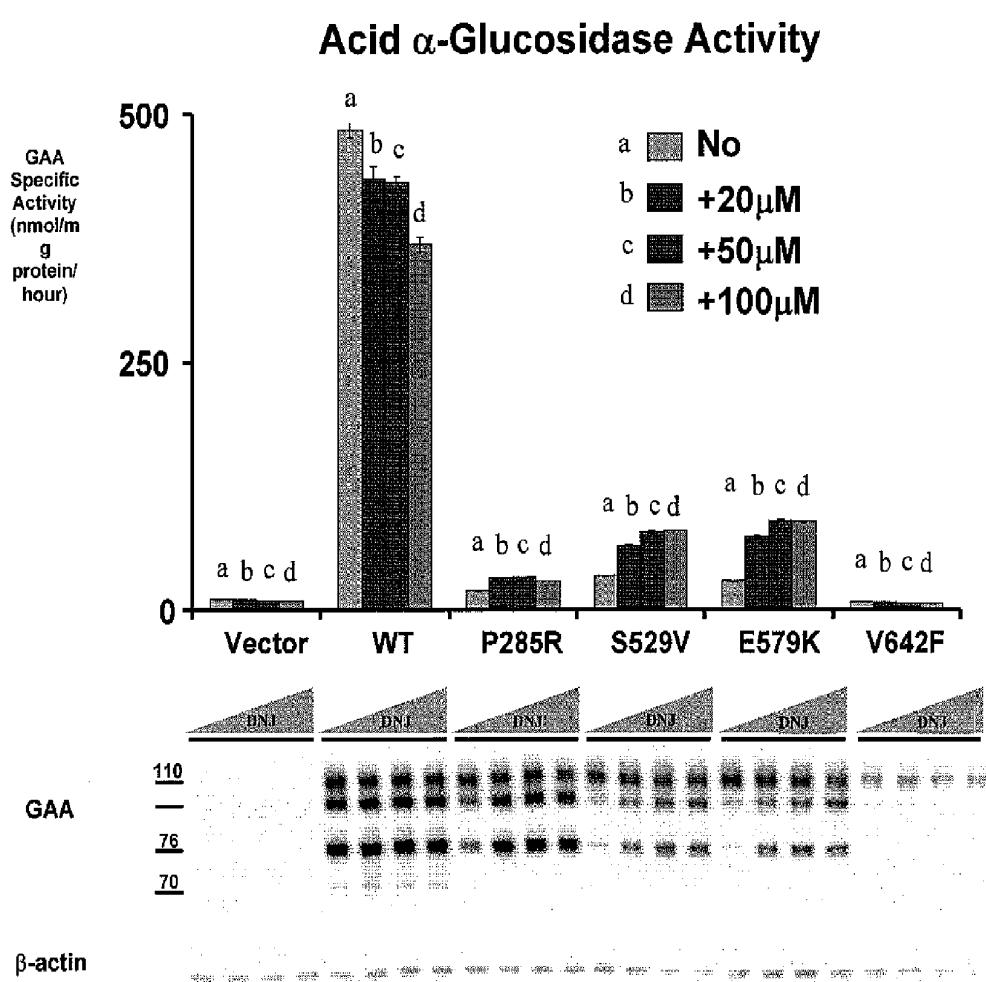


Fig. 13

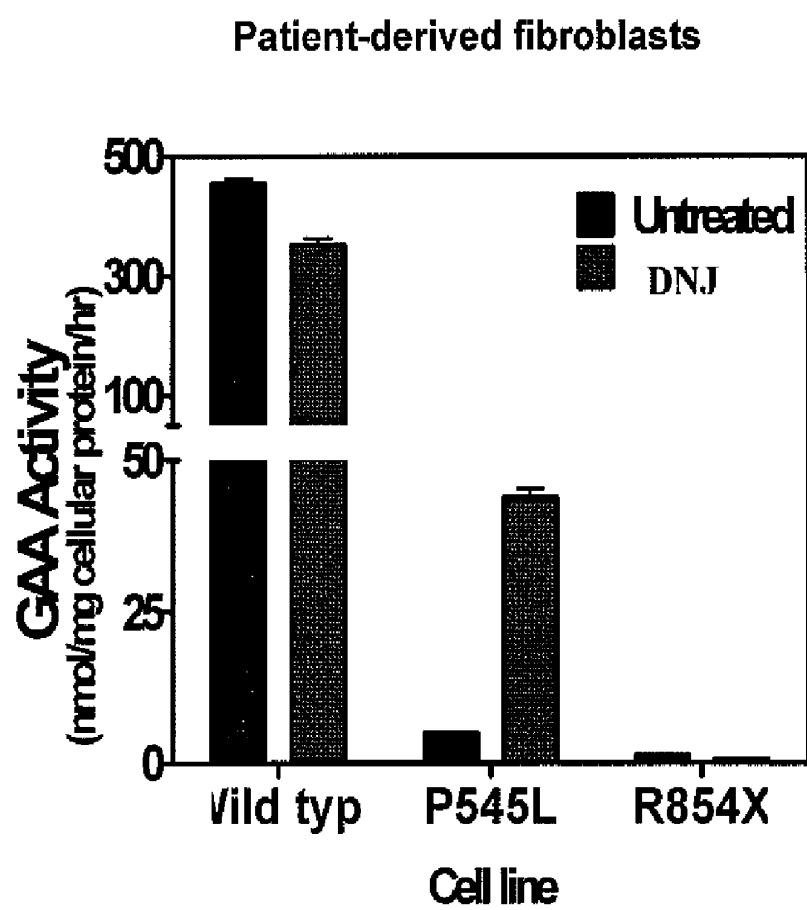


Fig. 14

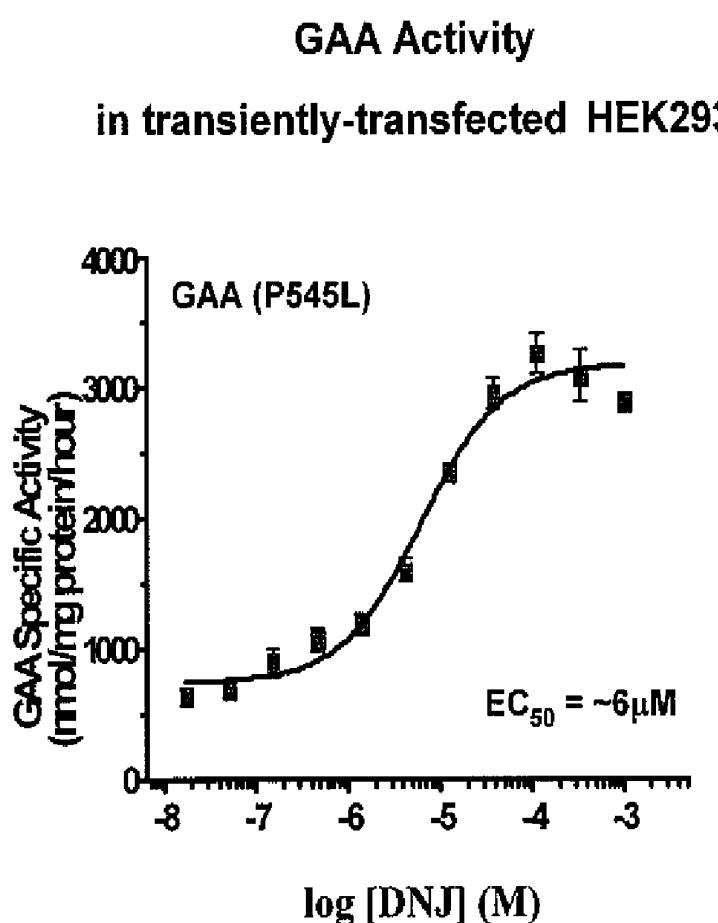


Fig. 15

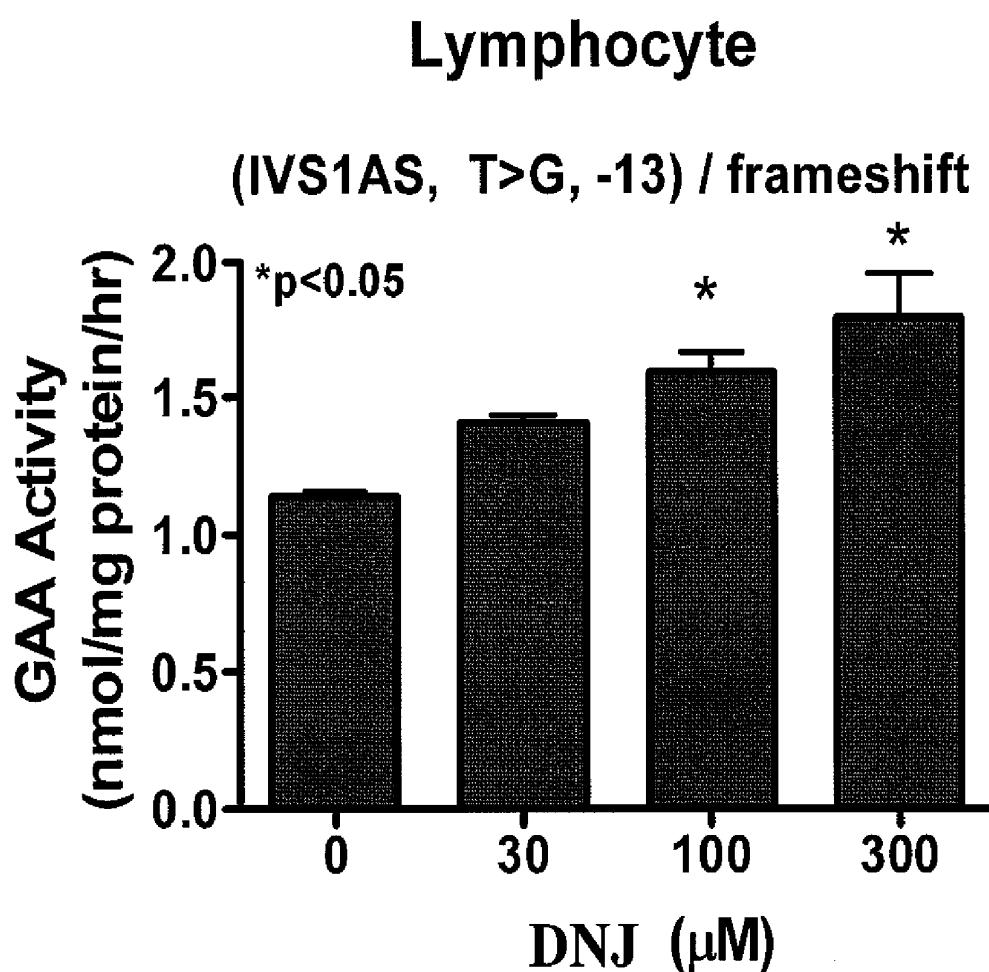


Fig. 16

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 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

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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
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 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 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 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
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	

METHOD TO PREDICT RESPONSE TO PHARMACOLOGICAL CHAPERONE TREATMENT OF DISEASES

CROSS-REFERENCE TO RELATED APPLICATION

[0001] The present application 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, the disclosures of which are herein incorporated by reference in their entireties.

FIELD OF THE INVENTION

[0002] 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-deoxyojojirimycin 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

[0003] 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.

[0004] 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.

[0005] 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 mis-

folded proteins in the ER may lead to various types of stress on cells, which may also contribute to cellular dysfunction and disease.

[0006] 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.

[0007] 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

[0008] 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

[0009] 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.

[0010] 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.

[0011] 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.

[0012] 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.

[0013] 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 ($ER \rightarrow Golgi$ apparatus \rightarrow endosomes \rightarrow 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.

[0014] 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.

[0015] 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

[0016] 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.

[0017] 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).

[0018] 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.

[0019] 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.

[0020] 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.

[0021] In one embodiment, the treatment reference table describes mutant forms of enzyme, such as a lysosomal 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).

[0022] 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.

[0023] 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).

[0024] The present invention also provides for diagnostic kits containing the components required to perform the assay.

BRIEF DESCRIPTION OF THE DRAWINGS

[0025] FIG. 1A-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 underlined=no response to DGJ; plain text (not italicized, bold, or underlined)=response to DGJ.

[0026] FIG. 2A-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. 1A-D that responded to DGJ treatment. The increase in enzyme activity is shown as a percentage of wild type α -Gal A activity.

[0027] 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.

[0028] 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.

[0029] 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.

[0030] FIG. 6 Shows the oligonucleotide primer pairs used to generate the point mutations in the α -Gal A gene through site-directed mutagenesis.

[0031] FIG. 7 Shows the α -Gal A cDNA sequence that was mutated through the site-directed mutagenesis.

[0032] 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.

[0033] 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).

[0034] 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.

[0035] FIG. 11 Shows the nucleic acid sequence of human lysosomal alpha-glucosidase (GAA) (GenBank Accession No.: Y00839).

[0036] FIG. 12 Shows the responsiveness of four different GAA mutations to DNJ treatment at concentrations of 0 μ M, 20 μ M, 50 μ M and 100 μ M. 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.

[0037] 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.

[0038] FIG. 14 Shows the EC₅₀ for DNJ induced GAA activity in HEK-293 cells transiently transfected with the P545L GAA mutation.

[0039] FIG. 15 Shows the responsiveness of Pompe patient-derived lymphocytes to DNJ treatment. The lymphocytes were heterozygous for the (IVSIAS, T>G, -13) GAA splicing defect and a GAA frameshift mutation.

[0040] FIG. 16 Shows the amino acid sequence encoded by a human lysosomal alpha-glucosidase (GAA) nucleic acid (GenBank Accession No.: Y00839).

DETAILED DESCRIPTION

[0041] The present invention provides an in vitro assay to provide accurate determination of whether an SPC enhances activity of a mutant protein.

[0042] 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.

[0043] 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.

[0044] 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.

[0045] 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.

[0046] 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.

[0047] 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.

[0048] 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.

[0049] 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.

[0050] 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.

[0051] 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.

[0052] 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.

[0053] 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.

[0054] 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

[0055] 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.

[0056] 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 trihexose side) and related glycosphingolipids in vascular endothelial lysosomes of the heart, kidneys, skin, and other tissues.

[0057] 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.

[0058] 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.

[0059] “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, Glycogenesis 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).

[0060] 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).

[0061] In Pompe, it has been shown that α-glucosidase is extensively modified post-translationally by glycosylation, phosphorylation, and proteolytic processing.

[0062] 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.

[0063] 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.

[0064] 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.

[0065] 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.

[0066] 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.

[0067] 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.

[0068] 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.

[0069] 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.

[0070] 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.

[0071] The term “human Gba gene” refers to the gene encoding acid β -glucosidase, also referred to as glucocerbrosidase 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).

[0072] 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.

[0073] 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.

[0074] 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.

[0075] 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.

[0076] 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.

[0077] 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.

[0078] 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)

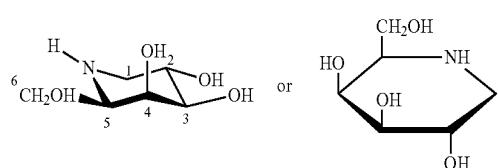
restores or enhances at least partial wild-type function and/or activity to the protein. A compound that specifically binds to e.g., α -Gal A, GAA or Gba, means that it binds to and exerts a chaperone effect on the enzyme and not a generic group of related or unrelated enzymes. More specifically, this 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. No. 5,900,360; U.S. Pat. No. 6,270,954; and U.S. Pat. No. 6,541,195). In the present invention, the SPC may be a reversible competitive inhibitor.

[0079] 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.

[0080] Thus, the inhibitor competes for the same active site as the substrate molecule, thus increasing the K_m . 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.

[0081] Following is a description of some specific pharmacological chaperones (SPCs) contemplated by this invention:

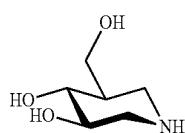
[0082] In one particular non-limiting embodiment, the SPC is 1-deoxygalactonorjirimycin which refers to a compound having the following structures:



[0083] or a pharmaceutically acceptable salt, ester or prodrug of 1-deoxygalactonorjirimycin. The hydrochloride salt of DGJ is known as migalastat hydrochloride (Migalastat).

[0084] 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-deoxygalactonorjirimycin, β -1-C-butyl-deoxygalactonorjirimycin, α -galacto-homonojirimycin, calystegine A₃, calystegine B₂, calystegine B₃, N-methyl-calystegine A₃, N-methyl-calystegine B₂ and N-methyl-calystegine B₃.

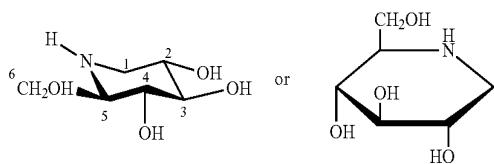
[0085] In one particular non-limiting embodiment, the SPC is isofagomine (IFG; (3R,4R,5R)-5-(hydroxymethyl)-3,4-piperidinediol) which is represented by the following formula:



[0086] or a pharmaceutically acceptable salt, ester or pro-drug of isofagomine, such as, for example, IFG tartrate (see, e.g., U.S. Patent Application Publication 20070281975.) IFG has a molecular formula of C₆H₁₃NO₃ 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.

[0087] 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 A₃, B₁, B₂ and C₁

[0088] In one particular non-limiting embodiment, the SPC is 1-deoxynorjirimycin (1-DNJ), which is represented by the following formula:



[0089] or a pharmaceutically acceptable salt, ester or pro-drug of 1-deoxynorjirimycin. In one embodiment, the salt is hydrochloride salt (i.e. 1-deoxynorjirimycin-HCl).

[0090] 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.

[0091] 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.

[0092] “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).

[0093] “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.

[0094] “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.

[0095] 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.

[0096] 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.

[0097] 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.

[0098] 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.

[0099] 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.

[0100] 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 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).

[0101] The dose that achieves one or more of the aforementioned responses is a “therapeutically effective dose.”

[0102] 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.

[0103] 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.

[0104] 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

[0105] 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

[0106] 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 Lysosomal Enzyme

[0107] 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.

[0108] 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.

[0109] 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.

[0110] 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.).

[0111] 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.

[0112] 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.

[0113] 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.

[0114] 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% CO₂ 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% CO₂ 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.

[0115] 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 deion-

ized 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.

[0116] 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-methylumbelliferon per hour. For each patient sample at least three normal samples may be tested concurrently.

[0117] 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.

[0118] 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 μ L fresh media at 37° C., 5% CO₂ for two hours followed by 2 additional PBS washes. After, cells can be lysed in 60 μ L Lysis Buffer (27 mM sodium citrate/46 mM sodium phosphate dibasic, 0.5% Triton X-100, pH 4.6). Ten μ L lysate can then be added to 50 μ L 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 μ L 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 μ L of cell lysate. A 4-methylumbelliferon (4-MU) standard curve ranging from 30 μ M 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

[0119] 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.

[0120] 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.

[0121] 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

[0122] 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

[0123] 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.

[0124] 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

[0125] 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.

[0126] As one non-limiting example, a kit for evaluating α -Gal A activity may contain, at a minimum:

[0127] a. a panel of host cells, each expressing 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;

[0128] b. a specific pharmacological chaperone;

[0129] c. a chromogenic or fluorogenic substrate for the enzyme assay (including an appropriate standard); and

[0130] 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.

[0131] In one embodiment, the SPC is supplied in dry form, and will be re-constituted prior to addition.

[0132] 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

[0133] 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

[0134] The present Example provides the in vitro diagnostic assay to determine a Fabry patient’s responsiveness to a specific pharmacological chaperone.

Introduction

[0135] 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

[0136] 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 μ L with the following: 41.6 μ L dH₂O, 5.0 μ L 10xPfuUltra HF reaction buffer, 0.5 μ L Forward-5'-primer (50 μ M), 0.5 μ L Reverse-3'-primer, 1.0 μ L dNTP mix (containing 25 mM each dA, dT, dC, dG), 0.9 μ L human GLA in pcDNA3 (2 ng/ μ L DNA), 0.5 μ L 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 μ L Dpn 1 (New England Biolabs) was added to each reaction and incubated at 37° C. for 2 hours. A volume of 7.5 μ L for each mutagenesis reaction was used to transform DH5a cells (New England Biolabs). Cells were then plated on LB-agar plates with 75 μ g/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% CO₂ for 24 hours before transfection. Cells were transfected with 0.1 μ g DNA and 0.35 μ L 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% CO₂ 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 μ L fresh media at 37° C., 5% CO₂ for two hours followed by 2 additional PBS washes. After, cells were lysed in 60 μ L Lysis Buffer (27 mM sodium citrate/46 mM sodium phosphate dibasic, 0.5% Triton X-100, pH 4.6). Ten μ L lysate were added to 50 μ L 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 μ L 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 μ L of cell lysate. A 4-methylumbelliflerone (4-MU) standard curve ranging from 30 μ M 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.

[0137] 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

[0138] 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).

[0139] 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).

[0140] 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

[0141] 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

[0142] Blank bars indicate basal level (without DGJ treatment) and filled bars indicate the elevated level after DGJ treatment (FIG. 4).

[0143] 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

[0144] 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.

[0145] 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.

[0146] 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 EC₅₀ values between 200 nM and >100 mM.

[0147] 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

[0148] 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, thrombocytopenia, 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.

[0149] 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.

[0150] 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).

[0151] 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 μ M) 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.

[0152] 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

[0153] 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.

[0154] 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 μ L lysate were mixed with 50 μ L 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.

[0155] 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.

[0156] 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

[0157] 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.

[0158] 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).

[0159] 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 (Invitrogen). 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.

[0160] COS-7 cells (derived from green monkey embryonic kidney cells) were aseptically seeded in 12-well tissue culture plates at a cell density of ~1.4×10⁵ cells per well in 3 ml of Dulbecco's Modified Essential Medium (DMEM) con-

taining 10% (v/v) fetal bovine serum and grown overnight at 37° C. in a humidified 5% CO₂ 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 to 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% CO₂ atmosphere.

[0161] 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% CO₂ 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.

[0162] Residual GAA enzyme activity was determined for each transiently-expressed GAA using a fluorogenic 4-methylumbelliferyl-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 Na₂CO₃ (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).

[0163] 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.

[0164] 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.

[0165] For a single HEK-293 cell line transfected with the GAA mutation, P545L, the DNJ EC₅₀ was also determined (FIG. 14).

[0166] 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.

[0167] 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).

[0168] 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).

[0169] 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.

[0170] 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.

[0171] 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).

[0172] 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.

[0173] 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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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	
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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
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
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
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
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

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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 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

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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	
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ctcagctgta ttgtcacg	18
<210> SEQ ID NO 7	
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<212> TYPE: DNA	
<213> ORGANISM: Artificial Sequence	
<220> FEATURE:	
<223> OTHER INFORMATION: Synthetic oligonucleotide	
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caccgtgaca acgcagctga gg	22
<210> SEQ ID NO 8	
<211> LENGTH: 22	
<212> TYPE: DNA	
<213> ORGANISM: Artificial Sequence	
<220> FEATURE:	
<223> OTHER INFORMATION: Synthetic oligonucleotide	
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cctcagctgc gttgtcacgg tg	22
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<211> LENGTH: 20	
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<220> FEATURE:	
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ggctgcgcgc ctgcgttcg	20
<210> SEQ ID NO 10	
<211> LENGTH: 20	
<212> TYPE: DNA	
<213> ORGANISM: Artificial Sequence	
<220> FEATURE:	
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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	
gcgcgttgcgc mtcgcttcct gg	22

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<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

<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

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

<400> SEQUENCE: 18

tccattgtcc ggtgctctag c

21

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

<400> SEQUENCE: 19

gcttagagcac cggtacaatgg a

21

<210> SEQ ID NO 20
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<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

<400> SEQUENCE: 21

ctagagcact gtacaatgg a 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

caatccattt tacagtgttc 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

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gccaatccctt 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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<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
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<212> TYPE: DNA
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<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 agtaaaaattt cgc 23

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<211> LENGTH: 31
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 31
ggcgaaattt tgctaaccatt 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 tcatatcc 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
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
tgacattgtat gactcccttggaa 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
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<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

ctttccagg 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

ctcttatac tttccagca atcatcaatg tcag

34

<210> SEQ ID NO 41
<211> LENGTH: 39
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 41

gctgacattg atgattcccg gaaaagtata aagagtatac

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

gatactctt atactttcc 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

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

<400> SEQUENCE: 46

ctctttatac tttcaagga atcatcaatg tcag 34

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

<400> SEQUENCE: 47

gctgacattg atgattcctg taaaagtata aagagtatct tgg 43

<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

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

<400> SEQUENCE: 50
gataactcttt gtactttcc 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:
<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
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<212> TYPE: DNA
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<220> FEATURE:  
<223> OTHER INFORMATION: Synthetic oligonucleotide  
  
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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  
  
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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 cttgggctg gctgcac 27  
  
<210> SEQ ID NO 61  
<211> LENGTH: 27  
<212> TYPE: DNA  
<213> ORGANISM: Artificial Sequence  
<220> FEATURE:  
<223> OTHER INFORMATION: Synthetic oligonucleotide  
  
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gtgcagccag cccaaaggtag gcgtcct 27  
  
<210> SEQ ID NO 62  
<211> LENGTH: 25  
<212> TYPE: DNA  
<213> ORGANISM: Artificial Sequence  
<220> FEATURE:  
<223> OTHER INFORMATION: Synthetic oligonucleotide  
  
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aggacgccta ccgtgggctg gctgc	25
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gcageccagcc cacggtaggc gtctct	25
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ctaccatggw ctggctgcac	20
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gtgcagccag wccatggtag	20
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ctaccatgcg ctggctgcac	20
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gtgcagccag cgcattggtag	20
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catgggctgt ctgcactgg	19

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

<400> SEQUENCE: 69
ccagtgcaga cagccccatg                                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
ctccccagtgc cgccagccccca t                                21

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

<400> SEQUENCE: 72
ctggctgcgc tggggagc                                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
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 74
ctggctgtac tggggagc                                17

<210> SEQ ID NO 75
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<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
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<220> FEATURE:  
<223> OTHER INFORMATION: Synthetic oligonucleotide  
  
<400> SEQUENCE: 75  
gctcccagta cagccag 17  
  
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<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  
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cagtccaaga tactctttgt acttttccag gaatc 35  
  
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agtataaaaga gtttcttgga ctggac 26  
  
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<211> LENGTH: 26  
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<220> FEATURE:  
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gtccagtcca agaaaactctt tatact 26  
  
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<212> TYPE: DNA  
<213> ORGANISM: Artificial Sequence  
<220> FEATURE:  
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gtataaagag taacttggac tgg 23  
  
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<210> SEQ ID NO 89
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<400> SEQUENCE: 89
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<400> SEQUENCE: 92
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<212> TYPE: DNA
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<400> SEQUENCE: 93
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<220> FEATURE:
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<400> SEQUENCE: 94

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25

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<400> SEQUENCE: 95

tccaaacccccc tcgtccagca acatc

25

<210> SEQ ID NO 96
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<212> TYPE: DNA
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<220> FEATURE:
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<400> SEQUENCE: 96

gttgctggac tagggggttg g

21

<210> SEQ ID NO 97
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<212> TYPE: DNA
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<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 97

ccaacccccc agtccagcaa c

21

<210> SEQ ID NO 98
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<400> SEQUENCE: 98

gctggaccag cggggttgaa tg

22

<210> SEQ ID NO 99
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cattccaacc cgctggtcca gc

22

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<400> SEQUENCE: 100

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ggaccagggg attggaatga c 21

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<400> SEQUENCE: 101

ctggctgcac ggggagcgct tc 22

<210> SEQ ID NO 102
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<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 102

gaagcgctcc ccgtgcagcc ag 22

<210> SEQ ID NO 103
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<212> TYPE: DNA
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<220> FEATURE:
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<400> SEQUENCE: 103

ctggctgcac ttggagcgct tc 22

<210> SEQ ID NO 104
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<212> TYPE: DNA
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<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 104

gaagcgctcc aagtgcagcc ag 22

<210> SEQ ID NO 105
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<212> TYPE: DNA
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<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 105

gctgcactgg aagcgcttca tg 22

<210> SEQ ID NO 106
<211> LENGTH: 22
<212> TYPE: DNA
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<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 106

catgaagcgc ttccagtgca gc 22

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<212> TYPE: DNA
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<400> SEQUENCE: 107
actgggagcy cttcatgtgc                                20

<210> SEQ ID NO 108
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<212> TYPE: DNA
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<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 108
gcacatgaag rgctcccaagt                                20

<210> SEQ ID NO 109
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<212> TYPE: DNA
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<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 109
cactgggaggr gcttcatgt                                19

<210> SEQ ID NO 110
<211> LENGTH: 19
<212> TYPE: DNA
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<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 110
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<212> TYPE: DNA
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<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 111
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<210> SEQ ID NO 112
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<212> TYPE: DNA
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<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 112
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<210> SEQ ID NO 113
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<212> TYPE: DNA
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<220> FEATURE:
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<400> SEQUENCE: 113

gagcgcttca agtgcaaacct tg

22

<210> SEQ ID NO 114
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<212> TYPE: DNA
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<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 114

caagggtgca cttaaggcgc tc

22

<210> SEQ ID NO 115
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<212> TYPE: DNA
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<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 115

gcgcattttata tgcaacc

17

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

<400> SEQUENCE: 116

ggttgcataat gaagcgc

17

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

<400> SEQUENCE: 117

gagcgcttca tgtccaaacct 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

cagtcaagggt tggacatgaa gcgcgc

26

<210> SEQ ID NO 119
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<212> TYPE: DNA
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<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 119

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cgcttcatgs gcaaccttga c 21

<210> SEQ ID NO 120
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<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 120

gtcaaggttg cscatgaagc g 21

<210> SEQ ID NO 121
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<212> TYPE: DNA
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<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
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<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 wagtcaagg t 22

<210> SEQ ID NO 125
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<212> TYPE: DNA
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<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 125

gtgcaacctt gactaccagg aagagccag 29

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<210> SEQ ID NO 126
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<212> TYPE: DNA
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<400> SEQUENCE: 126

gtcattccaa tccccctggtc c 21

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

<400> SEQUENCE: 127

cagggggttg 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 tccaaacccc 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

ggtttgaatg tcccgatata g 21

<210> SEQ ID NO 132
<211> LENGTH: 21
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence

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

<400> SEQUENCE: 132

cataatctggg acatttccaac c

21

<210> SEQ ID NO 133
<211> LENGTH: 22
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 133

gggttggaat tacccagata tg

22

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

<400> SEQUENCE: 134

cataatctggg taatttccaac cc

22

<210> SEQ ID NO 135
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<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

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

<400> SEQUENCE: 138

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gaatgaccca gttatgttag tg	22
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<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 145

atgaccgcaga aatgtttagtg a

21

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

<400> SEQUENCE: 146

tcaactaacat 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 ggtttagtgat 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 tatttagtgat 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

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

<400> SEQUENCE: 151

ctggcttcc ctggtagtca aggttgac

29

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

<400> SEQUENCE: 153

gcttctcaact gatgttagaa 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

tcctgcataca 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

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gaagagcttc ttactgatgc ag 22

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

<400> SEQUENCE: 158

ctgcatcagt gggaaagctct 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

gaagagcttc ccactgatgc ag 22

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

<400> SEQUENCE: 163

catctccatg aagaacttct cactgatgc 29

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<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
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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
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<220> FEATURE:
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<400> SEQUENCE: 170

gcagagctca gggtctcaga ag

22

<210> SEQ ID NO 171
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<212> TYPE: DNA
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<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 171

cttctgagac cctgagctct gc

22

<210> SEQ ID NO 172
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<212> TYPE: DNA
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<220> FEATURE:
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<400> SEQUENCE: 172

ctcagaaggc tgtaaggatg caggt

25

<210> SEQ ID NO 173
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<212> TYPE: DNA
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<220> FEATURE:
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<400> SEQUENCE: 173

acctgcattcc ttacagcctt ctgag

25

<210> SEQ ID NO 174
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<212> TYPE: DNA
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<220> FEATURE:
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<400> SEQUENCE: 174

ctcagaaggc tcgaaggatg ca

22

<210> SEQ ID NO 175
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<400> SEQUENCE: 175

tgcatttc gaggctctg ag

22

<210> SEQ ID NO 176
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ccagatatgt cagtgattgg c 21

<210> SEQ ID NO 177
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<400> SEQUENCE: 177

gccaatcact gacatatctg g 21

<210> SEQ ID NO 178
<211> LENGTH: 21
<212> TYPE: DNA
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gatatgttag cgattggcaa c 21

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gttgccaaatc gctaacatata c 21

<210> SEQ ID NO 180
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<212> TYPE: DNA
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<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 180

cagatatgtt aatgattggc aac 23

<210> SEQ ID NO 181
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<212> TYPE: DNA
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<220> FEATURE:
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<400> SEQUENCE: 181

gttgccaaatc attaacatata ctg 23

<210> SEQ ID NO 182
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<212> TYPE: DNA
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<400> SEQUENCE: 182

tatgttagtg actggcaact ttg 23

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<210> SEQ ID NO 183
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<400> SEQUENCE: 183

caaagttgcc agtcactaac ata

23

<210> SEQ ID NO 184
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ttagtgattg tcaacttg

19

<210> SEQ ID NO 185
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caaagttgac aatcactaa

19

<210> SEQ ID NO 186
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<400> SEQUENCE: 186

gttagtgatt tgcaacttg g

21

<210> SEQ ID NO 187
<211> LENGTH: 21
<212> TYPE: DNA
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<220> FEATURE:
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<400> SEQUENCE: 187

ccaaagttgc aaatcactaa c

21

<210> SEQ ID NO 188
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<212> TYPE: DNA
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<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 188

tgttagtgat tagcaacttt ggc

23

<210> SEQ ID NO 189
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<220> FEATURE:
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<400> SEQUENCE: 189

gccaaagttt ctaatcaacta aca

23

<210> SEQ ID NO 190
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<400> SEQUENCE: 190

gtgattggca aatttggcct cag

23

<210> SEQ ID NO 191
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<220> FEATURE:
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<400> SEQUENCE: 191

ctgaggccaa atttgccat cac

23

<210> SEQ ID NO 192
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<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 192

gtgattggca gctttggcct c

21

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

<400> SEQUENCE: 193

gaggccaaag ctgccatatca c

21

<210> SEQ ID NO 194
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<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
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<400> SEQUENCE: 194

caactttggc ctcggctgga atcag

25

<210> SEQ ID NO 195
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<212> TYPE: DNA
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<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 195

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gctgattcca gttgaggcca aag	23
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agctggaatc ggcaagtaac tc	22
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gaaggatgca gattatgagt ac	22

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<210> SEQ ID NO 202
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<212> TYPE: DNA
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<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 202

gtactcataa tctgcatacc tc 22

<210> SEQ ID NO 203
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<212> TYPE: DNA
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<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 203

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

<400> SEQUENCE: 205

ggttatgagg acctctgcatt tg 22

<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
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<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

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

<400> SEQUENCE: 214

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catccaacag tcatgaatgc agaggtta	27
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ctgcattgtat ggctgttggta tg	22
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catccaacag acatcaatgc ag	22

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

<400> SEQUENCE: 221
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<210> SEQ ID NO 222
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<212> TYPE: DNA
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<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 222
catccaacag ttatcaatgc ag                                22

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

<400> SEQUENCE: 223
gcattgtatga 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 agagtcatac atgc                                24

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

<400> SEQUENCE: 225
gagttaacttg gtgattccag ctg                                23

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

<400> SEQUENCE: 226
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<210> SEQ ID NO 227
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<212> TYPE: DNA
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<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 227

gttacttgct tattccagct g

21

<210> SEQ ID NO 228
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<212> TYPE: DNA
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<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
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<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 230

ctggaatcag aaagtaactc ag

22

<210> SEQ ID NO 231
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<212> TYPE: DNA
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<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 231

ctgagttact ttctgattcc a

21

<210> SEQ ID NO 232
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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
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<212> TYPE: DNA
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<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 233

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ggccatctga tttacttgct g 21

<210> SEQ ID NO 234
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<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
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<212> TYPE: DNA
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<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 236

gttaactcaga 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

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

agccccagagg ggcattctgag tta 23

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

<400> SEQUENCE: 241

agcccagaggg tccatctgag tt

22

<210> SEQ ID NO 242
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<212> TYPE: DNA
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<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 gtgcttatcat g

21

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

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<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

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

<400> SEQUENCE: 249

gcatttgatga 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 atagtcataca 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

<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

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gggagccatc gaacagtcat c	21
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<223> OTHER INFORMATION: Synthetic oligonucleotide	
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ctgttggatg cctcccccgg gag	23
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<212> TYPE: DNA	
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<220> FEATURE:	
<223> OTHER INFORMATION: Synthetic oligonucleotide	
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<210> SEQ ID NO 255	
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<212> TYPE: DNA	
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<400> SEQUENCE: 255	
gctccccaaa magattcaga ag	22
<210> SEQ ID NO 256	
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<212> TYPE: DNA	
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<223> OTHER INFORMATION: Synthetic oligonucleotide	
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cttctgaatc tktttgggg gc	22
<210> SEQ ID NO 257	
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<212> TYPE: DNA	
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<220> FEATURE:	
<223> OTHER INFORMATION: Synthetic oligonucleotide	
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<210> SEQ ID NO 258	
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<212> TYPE: DNA	
<213> ORGANISM: Artificial Sequence	
<220> FEATURE:	
<223> OTHER INFORMATION: Synthetic oligonucleotide	
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<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 agagcttcc tcata

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

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cagaccctca gtgctttcct catg

24

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<400> SEQUENCE: 264

catgaggaaa gcactgaggg tctg

24

<210> SEQ ID NO 265
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ccctcagcgc ttcctcatg

20

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<400> SEQUENCE: 266

cataggaga ggcgtgggg

20

<210> SEQ ID NO 267
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<400> SEQUENCE: 267

ctcatggat ttgccagcta gc

22

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gctagctggc aaatccatg ag

22

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<400> SEQUENCE: 269

gattcgccag ccagctaatt atg

23

<210> SEQ ID NO 270
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<400> SEQUENCE: 270

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23

<210> SEQ ID NO 271
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gctgtgaaca taatttagkta gctggcga	28
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gctagctaat tatgatcaca gcaaaggac	29
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<400> SEQUENCE: 278

aaggagcago gatgatagcc c

21

<210> SEQ ID NO 279
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23

<210> SEQ ID NO 280
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<400> SEQUENCE: 280

gaataaaagga ggagccatga tag

23

<210> SEQ ID NO 281
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<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 281

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22

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catgaataaaa gcagcagcca tg

22

<210> SEQ ID NO 283
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catggctgct wcttttattca tg

22

<210> SEQ ID NO 284
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<220> FEATURE:
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<400> SEQUENCE: 284

catgaataaaa gwagcagccca tg

22

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

gctgctccctt tatgcgtgtc taatgacc

28

<210> SEQ ID NO 286
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<220> FEATURE:
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<400> SEQUENCE: 286

ggtcatttaga catgcataaaa ggagcagc

28

<210> SEQ ID NO 287
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<220> FEATURE:
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<400> SEQUENCE: 287

ctttatttcat gtktaatgac ctccg

25

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<400> SEQUENCE: 288

cggaggatcat tamacatgaa taaag

25

<210> SEQ ID NO 289
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<400> SEQUENCE: 289

attcatgtct agtgacacctcc gac

23

<210> SEQ ID NO 290
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gtcgaggagtc actagacatg aat	23
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gtcgaggagtc cttagacatg aata	24
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<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 297
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<210> SEQ ID NO 298
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<212> TYPE: DNA
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<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
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<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 299
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<210> SEQ ID NO 300
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<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 300
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<210> SEQ ID NO 301
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<212> TYPE: DNA
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<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 301
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<210> SEQ ID NO 302
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<212> TYPE: DNA
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<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 302
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<210> SEQ ID NO 303
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<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 303

atccctagct tcggtccttt gctg

24

<210> SEQ ID NO 304
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<220> FEATURE:
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<400> SEQUENCE: 304

aggactgaag ccagggattt atgc

24

<210> SEQ ID NO 305
<211> LENGTH: 24
<212> TYPE: DNA
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<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 305

gcataaatcc ctggcttcag tcct

24

<210> SEQ ID NO 306
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<212> TYPE: DNA
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<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 306

ggactgaagc tagagattta tgcagatg

28

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

<400> SEQUENCE: 307

catctgcata aatctcttagc ttcaagtcc

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

<400> SEQUENCE: 309

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ccaacatctg cagaaatccc tagc	24
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<211> LENGTH: 30
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 316
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<210> SEQ ID NO 317
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<212> TYPE: DNA
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<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 317
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<210> SEQ ID NO 318
<211> LENGTH: 24
<212> TYPE: DNA
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<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 318
tgcatgtt 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
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<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
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<210> SEQ ID NO 321
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<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 321
caggtttat ttcttaacatc tgca                                         24

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

<400> SEQUENCE: 322

ggatttatgc agatgttgaa aataaaaacct ggcgcagc

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 ttttatttc aacatctgca taaatcc

37

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

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ctaatgacct cggacacatc agc	23
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gctgatgtgt gggaggtcat tag	23
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ctccgacaca acagccctca agc	23
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<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

gctctcccttc acgataagga cg

22

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

<400> SEQUENCE: 337

cgtccttatac 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

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

<400> SEQUENCE: 347

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ggggtcctgc ttgatggcaa tt 22

<210> SEQ ID NO 348
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<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 348

aattgccatc tatcaggacc cc 22

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

<400> SEQUENCE: 349

ggatttatgc agatgttcga aataaaacct ggcgac 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

ggatttatgc agatgttcga aataaaacct ggcgac 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

ggaaaataaaa 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 gattttatcc 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

ggaaaataaaa cccgcgcagg ctcc 24

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<211> LENGTH: 24
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 354
gaagcctgcg cgggtttat 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
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<210> SEQ ID NO 357
<211> LENGTH: 28
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 357
ggaaaataaaa cctgggcagg ctcccctg                           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
cagggaaagcc tgcccaagg ttatttcc                            28

<210> SEQ ID NO 359
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<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
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<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 360

gggaaggctg 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

gggaaggctg 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

<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

ccagggaga ctgcgcagg

19

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

<400> SEQUENCE: 365

ggctcccta ggagtttgg

20

<210> SEQ ID NO 366
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<212> TYPE: DNA
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<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 366

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ccaaaactcc tagggaagcc 20

<210> SEQ ID NO 367
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<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 367

ttccctggga atttggata c 21

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

<400> SEQUENCE: 368

gtatccaaa ttcccaggga a 21

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

<400> SEQUENCE: 369

ccctggagg tttggatact 20

<210> SEQ ID NO 370
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<212> TYPE: DNA
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<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 370

agtatccaaa cctcccaggg 20

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

<400> SEQUENCE: 371

gttttggata ctgcgcacatt gatg 24

<210> SEQ ID NO 372
<211> LENGTH: 24
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
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<400> SEQUENCE: 372

catcaatgtc gcagtgatcca aaac 24

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<220> FEATURE:
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<400> SEQUENCE: 373
gggttcctga tagatggcaa tt                                22

<210> SEQ ID NO 374
<211> LENGTH: 22
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
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<400> SEQUENCE: 374
tgccatcaat gaggaccct tg                                22

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<212> TYPE: DNA
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<400> SEQUENCE: 375
caaggggtcc tcattgtgg ca                                22

<210> SEQ ID NO 376
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<212> TYPE: DNA
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<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 376
tgccatcaat cgggaccct tg                                22

<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 cgattgtgg 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
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<210> SEQ ID NO 379
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<212> TYPE: DNA
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<220> FEATURE:
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<400> SEQUENCE: 379

cttgcttgtc caaggggtcc

20

<210> SEQ ID NO 380
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<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 380

cttggcaag raagggtacc ag

22

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

<400> SEQUENCE: 381

ctggtaacct 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

<400> SEQUENCE: 383

gctggtaacct ttgcttgcc

19

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

<400> SEQUENCE: 385

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gctggtacrc ttgcttgcc 19

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

<400> SEQUENCE: 386

tggcaagca 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

ctaagcttgtt 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 taaaagtgtgg g 21

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

<400> SEQUENCE: 389

cccacactt aaagttgtct c 21

<210> SEQ ID NO 390
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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
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<212> TYPE: DNA
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<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 391

gtcgttcccc cacttcaaag 20

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<210> SEQ ID NO 392
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<212> TYPE: DNA
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<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 392

gaagtgtggg accgacacctc ctc

23

<210> SEQ ID NO 393
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<212> TYPE: DNA
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<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 393

gagagaggc ggtcccacac ttc

23

<210> SEQ ID NO 394
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<212> TYPE: DNA
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<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 394

gaagtgtgga aacgacacctc ctc

23

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

<400> SEQUENCE: 395

gagagaggc gttcccacac ttc

23

<210> SEQ ID NO 396
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<212> TYPE: DNA
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<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 396

gtgtgggaac aacctctctc ag

22

<210> SEQ ID NO 397
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<212> TYPE: DNA
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<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 397

ctacgacatt catgccaga c

21

<210> SEQ ID NO 398
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<212> TYPE: DNA
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<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 cccagacatt tg

22

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

<400> SEQUENCE: 400

caaaggctcg ggtatcaatg tc

22

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

<400> SEQUENCE: 401

cttgctgac cggggagtag atc

23

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

<400> SEQUENCE: 403

cttgctgac 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

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gatctactcc gcagtcagca aag	23
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ctggggagta gttctgctaa aatttg	26
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<212> TYPE: DNA
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<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
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<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
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<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 415

gctaaaattt gttgggtt actg

24

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

<400> SEQUENCE: 416

cagtaacaac caacaaattt tagc

24

<210> SEQ ID NO 417
<211> LENGTH: 24
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence

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<220> FEATURE:  
<223> OTHER INFORMATION: Synthetic oligonucleotide  
  
<400> SEQUENCE: 417  
  
gctaaaattt catggttgtt actg 24  
  
<210> SEQ ID NO 418  
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<212> TYPE: DNA  
<213> ORGANISM: Artificial Sequence  
<220> FEATURE:  
<223> OTHER INFORMATION: Synthetic oligonucleotide  
  
<400> SEQUENCE: 418  
  
cagtaacaac catgaaaattt tagc 24  
  
<210> SEQ ID NO 419  
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<212> TYPE: DNA  
<213> ORGANISM: Artificial Sequence  
<220> FEATURE:  
<223> OTHER INFORMATION: Synthetic oligonucleotide  
  
<400> SEQUENCE: 419  
  
ctaaaaattt atgatttgtt 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 atttttag 27  
  
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<212> TYPE: DNA  
<213> ORGANISM: Artificial Sequence  
<220> FEATURE:  
<223> OTHER INFORMATION: Synthetic oligonucleotide  
  
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<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  
<211> LENGTH: 22  
<212> TYPE: DNA  
<213> ORGANISM: Artificial Sequence  
<220> FEATURE:  
<223> OTHER INFORMATION: Synthetic oligonucleotide  
  
<400> SEQUENCE: 423
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gaacgacctc cctcaggctt ag 22

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

<400> SEQUENCE: 424

ctaaggctga gggaggtcgt tc 22

<210> SEQ ID NO 425
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<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

ggctaaggctt 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 gggtaaggcct gag 23

<210> SEQ ID NO 429
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cttagcctgg cctgttagcta tg 22

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<400> SEQUENCE: 430
catagctaca ggccaggcta ag                                22

<210> SEQ ID NO 431
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<212> TYPE: DNA
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<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 431
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<210> SEQ ID NO 432
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<212> TYPE: DNA
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<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 432
gtttatcata tctacagccc ag                                22

<210> SEQ ID NO 433
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<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
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<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
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<212> TYPE: DNA
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<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 435
gctatgataa aacggcagga g                                21

<210> SEQ ID NO 436
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<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 436

ctcctgccgt tttatcatag c

21

<210> SEQ ID NO 437
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<212> TYPE: DNA
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<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 437

gctatgataaa actggcagga gatt

24

<210> SEQ ID NO 438
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<212> TYPE: DNA
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<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 438

aatctcctgc cagtttatca tagc

24

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

<400> SEQUENCE: 441

gataaacccgg cagaagattg gtgg

24

<210> SEQ ID NO 442
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<212> TYPE: DNA
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<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 442

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<212> TYPE: DNA	
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gaggtccacc agtctccctgc cgg	23
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<212> TYPE: DNA	
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<220> FEATURE:	
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<212> TYPE: DNA	
<213> ORGANISM: Artificial Sequence	
<220> FEATURE:	
<223> OTHER INFORMATION: Synthetic oligonucleotide	
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<210> SEQ ID NO 450
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<212> TYPE: DNA
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<400> SEQUENCE: 450
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<210> SEQ ID NO 451
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<220> FEATURE:
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<400> SEQUENCE: 451
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<212> TYPE: DNA
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<400> SEQUENCE: 452
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<400> SEQUENCE: 453
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<212> TYPE: DNA
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<400> SEQUENCE: 454
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<210> SEQ ID NO 455
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<220> FEATURE:
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<400> SEQUENCE: 455

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<400> SEQUENCE: 456

ttggcagatg attataagca c

21

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<400> SEQUENCE: 457

tggttataaa tcatactgccca a

21

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<400> SEQUENCE: 458

ttggcagata gttataagca c

21

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21

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25

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aggccaagg acgtgtgctt ataac 25

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<400> SEQUENCE: 462

gttataagca cgtgtccttg gcc 23

<210> SEQ ID NO 463
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ggccaaggac acgtgcttat aac 23

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cagtcttatt ctgggccaag gac 23

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<400> SEQUENCE: 466

gtccttggcc ccgaatagga ctg 23

<210> SEQ ID NO 467
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<400> SEQUENCE: 467

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<400> SEQUENCE: 469
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<212> TYPE: DNA
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<400> SEQUENCE: 470
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<400> SEQUENCE: 471
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<212> TYPE: DNA
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<400> SEQUENCE: 472
caggaggttca gtggacacctcg c 21

<210> SEQ ID NO 473
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<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 473
gcgagggttcca ctaatctcct g 21

<210> SEQ ID NO 474
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<220> FEATURE:
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<400> SEQUENCE: 474

ggagatttgtt agacctcgct c

21

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<400> SEQUENCE: 475

gagcagggtc taccaatctc c

21

<210> SEQ ID NO 476
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<212> TYPE: DNA
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<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 476

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

<400> SEQUENCE: 478

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20

<210> SEQ ID NO 479
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<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
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<212> TYPE: DNA
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<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 480

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ggtggaccctt gctcttataac	20
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tgcttccctg cgtaaaggag tgg	23
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ccactccctt acgcaggaa gca	23
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<210> SEQ ID NO 487
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<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
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<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 488

aaaggagtgg cccgtaatcc tgcc

24

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

<400> SEQUENCE: 489

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24

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<211> LENGTH: 24
<212> TYPE: DNA
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<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 490

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24

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

<400> SEQUENCE: 491

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24

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

<400> SEQUENCE: 492

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<210> SEQ ID NO 493
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<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence

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

<400> SEQUENCE: 493

gaggagctgt gtgttgaagc aggcag

26

<210> SEQ ID NO 494
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<212> TYPE: DNA
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<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 494

cctgcttcat cccacagctc ctcc

24

<210> SEQ ID NO 495
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<400> SEQUENCE: 495

ggaggagctg tgggatgaag cagg

24

<210> SEQ ID NO 496
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<212> TYPE: DNA
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<400> SEQUENCE: 496

cttcatcaca ccgctcctcc ctgt

24

<210> SEQ ID NO 497
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<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
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<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
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<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 499

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<210> SEQ ID NO 500
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<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 500

gccactcaca gtagtacaca atg 23

<210> SEQ ID NO 501
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<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 501

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<210> SEQ ID NO 502
<211> LENGTH: 22
<212> TYPE: DNA
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<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 502

gaggccactc ataggagta ac 22

<210> SEQ ID NO 503
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<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 503

gtgtactcct gggagtgccc tct 23

<210> SEQ ID NO 504
<211> LENGTH: 23
<212> TYPE: DNA
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<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 504

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<212> TYPE: DNA
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<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 505

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

<400> SEQUENCE: 506

catataaaaga 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

ctgtgagtggtgg cktctttata tg

22

<210> SEQ ID NO 508
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<212> TYPE: DNA
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<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 508

catataaaaga 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

tggccctctt ctagtggtgc 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

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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

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<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

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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
<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 cggtttctg 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
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<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 518

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ccagtgattg csgtactgtc g 21

<210> SEQ ID NO 519
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<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 519

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<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

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<210> SEQ ID NO 521
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<212> TYPE: DNA
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<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 521

cacagctcct ccgtgtgaaa aggaagct 28

<210> SEQ ID NO 522
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<212> TYPE: DNA
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<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 522

agttccctt tcacacggag gagctgtg 28

<210> SEQ ID NO 523
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<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

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<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
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<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<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 aaatccccaca 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 ttttgtgactt c

21

<210> SEQ ID NO 531
<211> LENGTH: 24
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence

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<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

cacataaaatc 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

cacataaaatc 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
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<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 537

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atccccacaga cactgttttg c 21

<210> SEQ ID NO 538
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<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 538

gcaaaaacagt gtctgtggga t 21

<210> SEQ ID NO 539
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<212> TYPE: DNA
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<220> FEATURE:
<223> OTHER INFORMATION: Synthetic oligonucleotide

<400> SEQUENCE: 539

ggcactgttt cgtttcagct 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 cgaaaacagtcc 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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22

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<400> SEQUENCE: 554

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<400> SEQUENCE: 555

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<400> SEQUENCE: 564

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25

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35

<210> SEQ ID NO 566
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35

1. A method for determining whether a patient expressing a mutant form of a protein will respond to treatment with a specific pharmacological chaperone for the protein, which method comprises

a. contacting a first host cell with a pharmacological chaperone specific for the protein, wherein the first host cell expresses the mutant form of the protein; and

b. comparing protein activity in a second host cell not contacted with the specific pharmacological chaperone, with protein activity in the first host cell contacted with the specific pharmacological chaperone,

wherein an increase in protein activity in the first host cell contacted with the specific pharmacological chaperone compared to the activity of the protein expressed by the second

host cell not contacted with the specific pharmacological chaperone indicates that the patient will respond to treatment with the specific pharmacological chaperone.

2. The method of claim 1, wherein the mutant form of the protein is caused by a missense mutation in a gene encoding the protein.

3. The method of claim 1, wherein the protein is an enzyme.

4. The method of claim 3, wherein the enzyme is a lysosomal enzyme.

5. The method of claim 4, wherein the patient has been diagnosed with a lysosomal storage disorder.

6. The method of claim 5, wherein the lysosomal enzyme is α -galactosidase A and the lysosomal storage disorder is Fabry disease.

7. The method of claim 6, wherein the α -galactosidase A is a mutant α -galactosidase A selected from the group consisting of the α -galactosidase A mutations 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.

8. The method of claim 7, wherein the mutant α -galactosidase A is selected from the group consisting of the α -galactosidase A mutations G144V, H225R, S276G, R301P, and N320I.

9. The method of claim 1, wherein the specific pharmacological chaperone is 1-deoxygalactonojirimycin.

10. (canceled)

11. (canceled)

12. (canceled)

13. (canceled)

14. (canceled)

15. The method of claim 1, wherein the host cell is selected from the group consisting of CHO cells, HeLa cells, HEK-293 cells, GripTite 293 MSR cells, 293T cells, COS cells, COS-7 cells, mouse primary myoblasts, and NIH 3T3 cells.

16. The method of claim 15, wherein the host cell is a HEK-293 cell.

17. The method of claim 15, wherein the host cell is a COS-7 cell.

18. The method of claim 15, wherein protein activity is determined using a fluorometric assay that quantifies hydrolysis of substrate in lysates from the host cell.

19. A method for producing a treatment therapy table, wherein the treatment therapy table indicates if a specific pharmacological chaperone is an effective compound for increasing the activity of a mutant protein, which method comprises:

a. contacting a first host cell with a pharmacological chaperone specific for the protein, wherein the first host cell expresses the mutant protein;

b. comparing protein activity in the first host cell contacted with the specific pharmacological chaperone with protein activity in a second host cell, wherein the second host cell expresses the mutant protein and is not contacted with the specific pharmacological chaperone; and

c. recording the result of step (b) in the treatment therapy table,

wherein a specific pharmacological chaperone recorded in the treatment therapy table that increases the activity of the mutant protein in the first host cell compared to the activity of the mutant protein in the second cell is a specific pharmacological chaperone that can be used as a therapy for a patient who expresses the mutant protein.

20. The method of claim 19, wherein the protein is an α -galactosidase A enzyme.

21. The method of claim 20, wherein the specific pharmacological chaperone is 1-deoxygalactonojirimycin.

22. (canceled)

23. (canceled)

24. (canceled)

25. (canceled)

26. A method of selecting a specific pharmacological chaperone for treating a patient expressing a mutant form of a protein,

wherein the Specific Pharmacological Chaperone is selected from a treatment reference table which comprises a list of mutations in the protein and the effect of the specific pharmacological chaperone on the activity of the protein mutations, and

wherein the Specific Pharmacological Chaperone selected for treating the patient increases the activity of the mutant protein expressed by the patient.

27. The method of claim 26, wherein the patient has been diagnosed with a lysosomal storage disorder.

28. The method of claim 27, wherein the protein is an α -galactosidase A enzyme.

29. The method of any one of claims 28, wherein the specific pharmacological chaperone is 1-deoxygalactonojirimycin.

30. (canceled)

31. (canceled)

32. (canceled)

33. (canceled)

34. 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 expresses a mutant α -galactosidase A selected from the group consisting of the α -galactosidase A mutations A121T, A156V, A20P, A288D, A288P, A292P, A348P, A73V, C52R, C94Y, D234E, D244H, D264Y, E338K, E341D, E398K, E48K, F113L, G144V, G260A, G271S, G328A, G35R, G373D, G373S, H225R, I219N, I242N, I270T, I303N, I317T, I354K, L14P, L166V, L243F, L300F, L310F, L32P, M267I, M284T, M296I, M72V, M76R, N224S, N298K, N298S, N320I, N34K, P259L, P265L, P265R, P293A, P293S, P409S, P40L, Q279H, Q279R, Q280H, Q280K, Q312H, Q321E, Q321R, Q327E, R301P, R363H, R49G, R49S, S201Y, S276N, S297C, S345P, T194I, V269M, W340R, W47L, and W95S.

35. (canceled)

36. A method for treating a patient who expresses a mutant protein comprising identifying the mutant protein, determining if the patient should respond to a specific pharmacological chaperone using a treatment therapy table, and if it is determined that the patient should respond to said specific pharmacological chaperone, administering said specific pharmacological chaperone to the patient.

37. The method of claim 36, wherein the mutant protein is a mutant lysosomal enzyme and the patient has been diagnosed with a lysosomal storage disorder.

38. The method of claim 37, wherein the lysosomal enzyme is α -galactosidase A and the lysosomal storage disorder is Fabry disease.

39. The method of claim 37, wherein the specific pharmacological chaperone is 1-deoxygalactonojirimycin.

40. (canceled)

41. (canceled)

42. (canceled)

43. (canceled)

44. A method of treating a patient diagnosed with Fabry disease which comprises administering to the patient a therapeutically effective dose of 1-deoxygalactonolactonejirimycin, wherein the patient expresses a mutant α -galactosidase A selected from the group consisting of the α -galactosidase A mutations A121T, A156V, A20P, A288D, A288P, A292P A348P, A73V, C52R, C94Y, D234E, D244H, D264Y, E338K, E341D, E398K, E48K, F113L, G144V, G260A, G271S, G328A, G35R, G373D, G373S, H225R, I219N, I242N, I270T, I303N, I317T, I354K, L14P, L166V, L243F, L300F,

L310F, L32P, M267I, M284T, M296I, M72V, M76R, N224S, N298K, N298S, N320I, N34K, P259L, P265L, P265R, P293A, P293S, P409S, P40L, Q279H, Q279R, Q280H, Q280K, Q312H, Q321E, Q321R, Q327E, R301P, R363H, R49G, R49S, S201Y, S276N, S297C, S345P, T194I, V269M, W340R, W47L, and W95S, and further wherein a treatment therapy table is produced according to the method of claim 19.

* * * * *