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(54) **METHOD FOR REDUCING THE IMMUNOGENICITY OF ANTIBODY VARIABLE DOMAINS**

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(58) **Field of Search** **530/387.1, 387.3; 435/69.6, 70.21; 424/130.1, 133.1**

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(57) **ABSTRACT**

A unique method is disclosed for identifying and replacing immunoglobulin surface amino acid residues which converts the antigenicity of a first mammalian species to that of a second mammalian species. The method will simultaneously change immunogenicity and strictly preserve ligand binding properties. The judicious replacement of exterior amino acid residues has no effect on the ligand binding properties but greatly alters immunogenicity.

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Position	Fractional Accessibility				Residues In Subgroup		
		KOL	J539		I	II	III
	Residue	Exposure	Residue	Exposure			
1	E	1.00 Ex	E	1.00 Ex	Q	Q	E
2	V	0.23 mB	V	0.37 mB	V	V	V M
3	Q	0.82 Ex	K	0.82 Ex	Q	T Q	Q
4	L	0.00 Bu	L	0.10 Bu	L	L	L
5	V	0.87 Ex	L	1.00 Ex	V	RQKT	VL
6	Q	0.00 Bu	E	0.09 Bu	Q	E	E
7	S	0.94 Ex	S	0.94 Ex	S	S	S
8	G	1.00 Ex	G	1.00 Ex	G	G	G
9	G	0.00 Bu	G	0.00 Bu	A	P	G
10	G	1.00 Ex	G	1.00 Ex	E	AGT	GA
11	V	0.90 Ex	L	0.81 Ex	V	L	LF
12	V	0.25 mB	V	0.25 mB	K	V	V
13	Q	0.71 mE	Q	0.87 Ex	K	K	Q
14	P	0.59 PB	P	0.64 mE	P	P	P
15	G	1.00 Ex	G	1.00 Ex	G	TS	G
16	R	0.73 mE	G	1.00 Ex	S A	EQ	G
17	S	0.66 mE	S	0.75 mE	S	T	S
18	L	0.28 mB	L	0.26 mB	V	L	L
19	R	0.66 mE	K	0.75 mE	RK	TS	RK
20	L	0.00 Bu	C	0.00 Bu	V	L	L
21	S	0.71 mE	S	0.82 Ex	S	T	S
22	C	0.00 Bu	C	0.00 Bu	C	C	C
23	S	1.00 Ex	A	1.00 Ex	K	T	A
24	S	0.00 Bu	A	0.00 Bu	ATV	FV	A
25	S	0.87 Ex	S	1.00 Ex	S	S	S
26	G	1.00 Ex	G	1.00 Ex	G	G	G
27	F	0.10 Bu	F	0.10 Bu	GYD	FLG	F
28	I	0.85 Ex	D	0.72 mE	T	S	TN
29	F	0.00 Bu	F	0.00 Bu	F	LI	F
30	S	0.74 mE	S	0.83 Ex	SNVI	S	S
36	W	0.00 Bu	W	0.00 Bu	W	W	W
37	V	0.00 Bu	V	0.00 Bu	V	I	V
38	R	0.10 Bu	R	0.31 mB	R	R	R
39	Q	0.15 Bu	Q	0.28 mB	Q	Q	Q
40	A	0.95 Ex	A	0.75 mE	A	P	A
41	P	0.90 Ex	P	0.73 mE	P	P	PS
42	G	1.00 Ex	G	1.00 Ex	G	G	G
43	K	0.86 Ex	K	0.86 Ex	QRKH	KR	K
44	G	1.00 Ex	G	1.00 Ex	G	AG	GS
45	L	0.00 Bu	L	0.00 Bu	L	L	L

FIG. 1a

Position	Fractional Accessibility		Residues In Subgroup							
	KOL	J539	I	II	III					
	Residue	Exposure	Residue	Exposure						
46	E	0.75 mE	E	0.73 mE	E	E	E	E		
47	W	0.10 Bu	W	0.04 Bu	W	W	W	W		
48	V	0.00 Bu	I	0.00 Bu	MV	LI	V	V		
49	A	0.00 Bu	G	0.00 Bu	G	AG	GSA	GSA		
66	R	0.36 mB	K	0.51 pB	R	R	R	R		
67	F	0.00 Bu	F	0.00 Bu	V	LV	F	F		
68	T	0.87 Ex	I	0.88 Ex	T	T	T	T		
69	I	0.00 Bu	I	0.00 Bu	VMI	IV	I	I		
70	S	0.78 mE	S	0.79 mE	TS	ST	S	S		
71	R	0.11 Bu	R	0.00 Bu	RLA	KV	R	R		
72	N	0.61 mE	D	0.55 pB	DK	D	DN	DN		
73	D	0.44 pB	N	0.43 pB	PETAS	T	DN	DN		
74	S	0.85 Ex	A	0.97 Ex	S	S	S	S		
75	K	0.88 Ex	K	0.77 mE	TF	KR	K	K		
76	N	0.69 mE	N	0.68 mE	NST	N	N	N		
77	T	0.41 pB	S	0.33 mB	TQ	Q	T	T		
78	L	0.00 Bu	L	0.00 Bu	AV	VF	LA	LA		
79	F	0.45 pB	Y	0.35 mB	Y	VS	YF	YF		
80	L	0.00 Bu	L	0.00 Bu	M	L	L	L		
81	Q	0.53 pB	Q	0.69 mE	E	TKSIN	Q	Q		
82	M	0.00 Bu	M	0.00 Bu	L	ML	M	M		
82a	D	0.73 mE	S	0.58 pB	SVRT	TSNIR	ND	ND		
82b	S	0.98 Ex	K	0.96 Ex	S	NS	S	S		
82c	L	0.00 Bu	V	0.00 Bu	L	VM	L	L		
83	R	0.73 mE	R	0.83 Ex	RFI	DT	RE	RE		
84	P	0.75 mE	S	0.90 Ex	S	PA	PA	PA		
85	E	0.82 Ex	E	0.90 Ex	E	VA	ED	ED		
86	D	0.00 Bu	D	0.11 Bu	D	D	D	D		
87	T	0.54 pB	T	0.47 pB	T	T	T	T		
88	G	1.00 Ex	A	0.00 Bu	A	A	A	A		
89	V	0.58 PB	L	0.63 mE	V	TV	VL	VL		
90	Y	0.00 Bu	Y	0.00 Bu	Y	Y	Y	Y		
91	F	0.00 Bu	Y	0.08 Bu	Y	Y	Y	Y		
92	C	0.00 Bu	C	0.00 Bu	C	C	C	C		
93	A	0.00 Bu	A	0.00 Bu	A	A	AT	AT		
94	R	0.17 Bu	R	0.15 Bu	R	RH	RP	RP		
					JH1	JH2	JH3	JH4	JH5	JH6
103	W	0.09 Bu	W	0.07 Bu	W	W	W	W	W	W
104	G	0.00 Bu	G	1.00 Ex	G	G	G	G	G	G

FIG. 1b

Position	Fractional Accessibility		Residue	Exposure	I	Residues In Subgroup				
	KOL					II	III			
Residue	Exposure	Residue	Exposure		JH1	JH2	JH3	JH4	JH5	JH6
105	Q	0.93 Ex	Q	0.99 Ex	Q	R	Q	Q	Q	Q
106	G	0.00 Bu	G	0.00 Bu	G	G	G	G	G	G
107	T	0.22 mB	T	0.26 mB	T	T	T	T	T	T
108	P	0.99 Ex	L	0.67 mE	L	L	M	L	L	T
109	V	0.00 Bu	V	0.00 Bu	V	V	V	V	V	V
110	T	0.76 mE	T	0.69 mE	T	T	T	T	T	T
111	V	0.00 Bu	V	0.00 Bu	V	V	V	V	V	V
112	S	0.98 Ex	S	0.74 mE	S	S	S	S	S	S
113	S	0.94 Ex	A	0.84 Ex	S	S	S	S	S	S

FIG. 1c

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