US006797492B2

(12) **United States Patent**
Daugherty et al.

(10) **Patent No.: US 6,797,492 B2**
(45) **Date of Patent: Sep. 28, 2004**

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

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(*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 0 days.

(21) Appl. No.: **09/810,502**

(22) Filed: **Mar. 16, 2001**

(65) **Prior Publication Data**

US 2002/0034765 A1 Mar. 21, 2002

Related U.S. Application Data

(63) Continuation of application No. 08/905,280, filed on Aug. 1, 1997, now abandoned, which is a continuation of application No. 08/609,218, filed on Mar. 1, 1996, now abandoned, which is a continuation of application No. 08/109,187, filed on Aug. 19, 1993, now abandoned, which is a continuation-in-part of application No. 07/702,217, filed on May 17, 1991, now abandoned.

(51) **Int. Cl.**[7] **C12N 15/00**
(52) **U.S. Cl.** **435/69.6**; 530/387.1; 530/387.3
(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 ligind binding properties. The judicious replacement of exterior amino acid residues has no effect on the ligind binding properties but greatly alters immunogenicity.

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Position	Fractional Accessibility KOL Residue	Exposure	J539 Residue	Exposure	Residues In Subgroup I	II	III
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	R Q K T	V L
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	A G T	G A
11	V	0.90 Ex	L	0.81 Ex	V	L	L F
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	T S	G
16	R	0.73 mE	G	1.00 Ex	S A	E Q	G
17	S	0.66 mE	S	0.75 mE	S	T	S
18	L	0.28 mB	L	0.26mB	V	L	L
19	R	0.66 mE	K	0.75 mE	R K	T S	R K
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	A T V	F V	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	G Y D	F L G	F
28	I	0.85 Ex	D	0.72 mE	T	S	T N
29	F	0.00 Bu	F	0.00 Bu	F	L I	F
30	S	0.74 mE	S	0.83 Ex	S N V I	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	P S
42	G	1.00 Ex	G	1.00 Ex	G	G	G
43	K	0.86 Ex	K	0.86 Ex	Q R K H	K R	K
44	G	1.00 Ex	G	1.00 Ex	G	A G	G S
45	L	0.00 Bu	L	0.00 Bu	L	L	L

FIG. 1a

Position	Fractional Accessibility KOL Residue	Exposure	J539 Residue	Exposure	Residues In Subgroup I	II	III
46	E	0.75 mE	E	0.73 mE	E	E	E
47	W	0.10 Bu	W	0.04 Bu	W	W	W
48	V	0.00 Bu	I	0.00 Bu	M V	L I	V
49	A	0.00 Bu	G	0.00 Bu	G	A G	G S A
66	R	0.36 mB	K	0.51 pB	R	R	R
67	F	0.00 Bu	F	0.00 Bu	V	L V	F
68	T	0.87 Ex	I	0.88 Ex	T	T	T
69	I	0.00 Bu	I	0.00 Bu	VMI	I V	I
70	S	0.78 mE	S	0.79 mE	T S	S T	S
71	R	0.11 Bu	R	0.00 Bu	R L A	K V	R
72	N	0.61 mE	D	0.55 pB	D K	D	D N
73	D	0.44 pB	N	0.43 pB	P E T A S	T	D N
74	S	0.85 Ex	A	0.97 Ex	S	S	S
75	K	0.88 Ex	K	0.77 mE	T F	K R	K
76	N	0.69 mE	N	0.68 mE	N S T	N	N
77	T	0.41 pB	S	0.33 mB	T Q	Q	T
78	L	0.00 Bu	L	0.00 Bu	A V	V F	L A
79	F	0.45 pB	Y	0.35 mB	Y	V S	Y F
80	L	0.00 Bu	L	0.00 Bu	M	L	L
81	Q	0.53 pB	Q	0.69 mE	E	T K S I N	Q
82	M	0.00 Bu	M	0.00 Bu	L	M L	M
82a	D	0.73 mE	S	0.58 pB	S V R T	T S N I R	N D
82b	S	0.98 Ex	K	0.96 Ex	S	N S	S
82c	L	0.00 Bu	V	0.00 Bu	L	V M	L
83	R	0.73 mE	R	0.83 Ex	R F I	D T	R E
84	P	0.75 mE	S	0.90 Ex	S	P A	P A
85	E	0.82 Ex	E	0.90 Ex	E	V A	E D
86	D	0.00 Bu	D	0.11 Bu	D	D	D
87	T	0.54 pB	T	0.47 pB	T	T	T
88	G	1.00 Ex	A	0.00 Bu	A	A	A
89	V	0.58 PB	L	0.63 mE	V	T V	V L
90	Y	0.00 Bu	Y	0.00 Bu	Y	Y	Y
91	F	0.00 Bu	Y	0.08 Bu	Y	Y	Y
92	C	0.00 Bu	C	0.00 Bu	C	C	C
93	A	0.00 Bu	A	0.00 Bu	A	A	A T
94	R	0.17 Bu	R	0.15 Bu	R	R H	R P

					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 KOL Residue	KOL Exposure	J539 Residue	J539 Exposure	Residues In Subgroup I JH1	I JH2	II JH3	II JH4	III JH5	III 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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