DNA sequences at immunoglobulin switch region recombination sites

Wesley Dunnick, Gerald Z.Hertz¹, Lori Scappino² and Christine Gritzmacher^{2,3}

Department of Microbiology and Immunology, University of Michigan Medical School, Ann Arbor, MI 48109-0620, ¹Department of Molecular, Cellular, and Developmental Biology, University of Colorado, Boulder, CO, ²Medical Biology Institute, La Jolla, CA and ³Scripps Clinic and Research Foundation, La Jolla, CA, USA

Received October 22, 1992; Revised and Accepted December 28, 1992

ABSTRACT

The immunoglobulin heavy chain switch from synthesis of IgM to IgG, IgA or IgE is mediated by a DNA recombination event. Recombination occurs within switch regions, 2 - 10 kb segments of DNA that lie upstream of heavy chain constant region genes. A compilation of DNA sequences at more than 150 recombination sites within heavy chain switch regions is presented. Switch recombination does not appear to occur by homologous recombination. An extensive search for a recognition motif failed to find such a sequence, implying that switch recombination is not a site-specific event. A model for switch recombination that involves illegitimate priming of one switch region on another, followed by error-prone DNA synthesis, is proposed.

INTRODUCTION

Single immunoglobulin-producing lymphocytes (B cells) have the capability to produce one type of immunoglobulin (usually IgM) early in their development and another type (IgG, IgE, or IgA) after antigen-induced differentiation. All the types of immunoglobulin produced by the progeny of a single B cell have the same light chain and variable (VH) region of the heavy chain (excepting somatic mutations-ref. 1), but differ in the constant (C) region of the heavy chain. The switch in heavy chain C region is brought about by a DNA deletion that moves the VH gene from its position about 8 kb 5' of the C μ gene to a similar location 5' of C α , C ϵ , or C γ genes. (There are four C γ genes in mice, called $\gamma 1$, $\gamma 2a$, $\gamma 2b$, and $\gamma 3$.) The DNA deletion begins and ends in switch (S) regions, 2-10 kb segments that are found 5' of each CH gene except Cô. S regions are composed of simple sequences repeated in tandem. Murine $S\mu$, $S\epsilon$, and $S\alpha$ are composed of variations of pentamers such as GGGGT, GAGCT, and GGGCT; the S γ regions are composed of repeats of a 49 or 52 bp sequence (2-7). Human S regions include similar sequences, but with a more irregular repetition pattern (8).

The switch deletion can also be thought of as a recombination event between the donor S region (usually $S\mu$) and the acceptor switch region (usually $S\gamma$, $S\epsilon$, or $S\alpha$). Switch recombination is a reciprocal event, at least to a first approximation. Not only is a breakpoint in the donor S region joined to a breakpoint in the acceptor S region, but also the ends of the deleted DNA are ligated together (9-11). The mechanism of switch recombination at the level of the chromosome and the heavy chain locus has been reviewed extensively, as has the regulation of switch recombination (12-14). We will discuss what has been learned about the mechanism of switch recombination from evaluation of DNA sequences at recombination sites.

DEFINING SWITCH RECOMBINATION SITES VERSUS SECONDARY, NON-SWITCH, DNA REARRANGEMENTS

More than 150 recombination sites in switch regions have been sequenced (Table 1). A continuing controversy has been the validity of subsets of switch recombination data. S regions might undergo secondary rearrangements, which are not related to switch recombination. These secondary rearrangements would delete the true switch recombination site and create a new site, obscuring the nature of true switch recombination sites. As discussed below, it is difficult to define characteristics that differentiate switch recombination sites from other illegitimate recombination events which are not B cell specific. Hence, it is not possible to distinguish switch recombination from secondary recombination by sequence evaluation.

Rearrangements of S regions during growth of bacteriophage clones is one type of secondary rearrangement that is known to occur (2, 49). In a few studies, the sequenced fragment has been shown to be the same size as the corresponding fragment in genomic DNA. However, for the majority of the switch region recombination sites, secondary rearrangement during recombinant clone growth or during PCR amplification is a formal possibility.

Available data suggest that secondary recombination within lymphoid cells is relatively rare. The $S\mu S\gamma 2b$, $S\mu - 3'c$ -myc, and $S\mu - 5'$ c-myc sites from MOPC21 have been cloned and sequenced by two or three laboratories (29, 35, 56). The three cell lines from which these recombination sites were cloned had been separated from one another by hundreds of generations. Nevertheless, the independent determination of each of the above recombination sites are identical in sequence, demonstrating that secondary rearrangments did not occur in cell lines derived from

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	Т٤	ıble	1.	Com	plilation	of	DNA	Sequence	s in	Switch	Regions
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DONO	R SEQUENCE	2 S :					Myel	omas:					
Bce	lls:						92.	MPC11	GACTCAGATGTGCTAGACTG	AGCTGTACTGGATGATCTGG.	μ-μΙ		28
No.	Name	Sequence		Mut	tations?	Ref.	93.	McPC603	AACAAGGTTGAGAGCCCTAG	TAAGCGAGGCTCTAAAAAGC	μ-μ		4
1.	RH20	GCGTGTATACAATTGTCTGG	AATTATTTCAGTTAAGTGTA	μ-μ		15	94.	TPC1033	GTAAGCCAGAGGCGCCACAG	CTGTGGCTGCTGCTCTTAAA	μ-δ		24
2.	GAM3-2	GGCTGAGCTGGACTCAGATG	TGCTAGACTGAGCTGTACTG	μ-γ3	7 ins.	15	95.	TPC1017	ACAGAGAAGGCCAGACTCAT	AAAGCTTGCTGAGCAAAATT	μ-δ		24
3.	GAM3-8	AGTAAGCGAGGCTCTAAAAA	OCATGGCTGAGCTGAGATGG	μ-γ3		15	90.	MOPC21	AGCTOGGGTGAGCTGAGCTG CGTGAGCTGAGCTGAGCTGA	G	μ-γ3		26
4. c	T2-26 K	GCTGGGGTGAGCTGGGCTGA	arte secrecere secrete	μ-γ3		16	98.	MOPC21	TGGGGTGAGCTGAGCTGGGG	Т	μ-12b		29
6.	DCS29 R	GATCGAGCTGAGCTGAGCTG	GOTGAGCTGAGCTGAGCTGA	μ-γ3		17	99.	MOPC141	ACTTCCTGGTTGTTAAAGAA	TGGTATCAAAGGACAGTGCT	μ-γ2b		2
7.	pCS35 R	TGTGTGAGCTGAGCTGGGGT	CAOCTGAGCAAGAGTGAGTA	μ-γ3		17	100.	MPC11	TTAATCTAGGTTGAATAGAG	CTAAACTCTACTGCCTACAC	μ-γ2Ъ		30
8.	pCS28 R	CTGAGCTGAGCTGAGCTGGG	GTGAGCTGGGCTGAGCTGAG	μ-γ3		17	101.	TEPC15	TGTTAAAGAATGGTATCAAA	GGACAGTGCTTAGATCCAAG	μ-α		4
9.	pCS23 R		GAGTTGGGGTGAGCTGAGCT	μ-γ3		17	102.	MCPC603	GCTGGGCTGAGCTGGGCTGA		μ-α		4
10.	RH4	CCACCCAGACCTGGGAATGT	ATGGTTGTGGCTTCTGCCAC	μ-γ1		15	103.	.1558	TCACCTCATCTCA A ATCACC	ACTOTGAGGTAAGCAAAGCT	μ-α	4/86	31
11.	RH20	GAGCIGAGCIGAGCIGOGGI	GAG	μ-γ1		15	105.	MOPC167	AACAAGGTTGAGAGCCCTAG	TAAGCGAGGCTCTAAAAAGC	μ-α 1-α		33
12.	pCS7 R	IGAGGIACIGAIGCIGICIC	ACTICAGITATACATOLOG ACCTGAGCTGAGCTGAGCT	μ-γι μ-γ1		10	106.	ABPC45	AAGAAAAGATGTTTTTAGTT	TTTATAGAAAACACTACTAC	μ-αΙ		34
14.	pCS6 R		OCTGAGCTGAGCTGGGGTGA	μ-γ1		10	107.	J558	GGCACCGCAAATGGTAAGCC	AGAGGCAGCCACAGCTGTGG	µ-с-тус		35
15.	pCS5 R		TGGGGTGAGCTGAGCTGGGG	μ-γ1		10	108.	MOPC21	TGGGGTGAGCTGAGCTGGGG	TG	µ-c-myc		29
16.	pC\$8 R		GCTGGGGTGAGCTGAGCTGA	μ-γ1		10	109.	MOPC21		AGAGCTGAGGTGAGCTGAGC	µ-с-тус		29
17.	pCS3 R		AGCTGAGCTGGGGGTGAGCTG	μ-γ1		10	110.	MC101	GAGCACCTACAGTAGAGCTG	GGGCAGCTCTGGGGGGATCTG	γ3-γ2b		5
18.	pCS9 R		CTGAGCTGAGCTGAGCTGAG	μ-γ1	1 ins.	10	112	MOPC167	GCTGIGIGIGIGCIGCIGG	ACCTGAGCTGAGCTGGAGTGA	a-91	1/33	20
20	N5-2 R	TACTTCGTTATACATGTGGG	TTTGAATTTTGAATCTATTC	μ-γ1 μ-γ1		16						1/00	
21.	N5-4 R	TACTICOTTATACATOLOGO	GTGGGGTGAGCTGGGCTGAG	μ-γ1		16	Hybr	idomas (i	n vitro); T cells:				
22.	148-3 R		TGAGATCTGAGCTGGGCTGA	μ-γ1		16							
23.	148-21 R		CTGGGCTGAGCTGGGGTGAG	μ-γ1		16	129.	9.9.2.1	GTCAAGGGAGAAAGGCATCT	AGCCTCGGTCTCAAAAGGGT	μ-γ2а		37
24.	N52-1 R	GAGCTGAGTGAGCTGAGCTG		μ-γ1		16	130.	9.7.1	CAACCCCTGTCCTCCATGCA	AGGAGTGTCACAAATGCCCA	12b-12a		37
25.	p3 R		OGGCTGAGCTGGGGGTGAGCT	μ-γ2ъ		9	131.	ICD137	AGCTGAGCTGAGCTGGGGTG	TO ACCTOR ACCTOCOCCTO	µ-эн µ-ли		38
26.	pCS24 R	GAGCTGGGGTGAGCTGAGCT	GAGCTGAGCTGAGCTGGGGT	μ-γ25	1 inc	17	132.	ICD110	AGCTGAGCTGAGCTGGGGTG	IGAGE IGAGE IGGGGT CAGE	µ-38		38
27.	N52-1 R	GAGE I GAGE I GAGE I GGGGI	CTGAGCTGAGCTGAGCTGGG	µ-120 u-£	I Ins.	16	134.	ICD162	CTCAGCTATGCTACGCTGTG	TTGGGGTGAGCTGATCTGAA	μ-ЈН		38
29.	T2-11 R		AGCTGGGGTGAGCTGAGCTG	μ-α		11	135.	ICD171	GCTGAGCTGAGCTGGGGTGA		μ-JH		38
30.	T2-26 R		CTGAGCTGAGCTGAGCTGGC	μ-α		16	136.	ICD172	GAGCTGAGCTGGGGGGGGGTC		μ-ЈН		38
31.	pCS18 R		TGGGCTGAGCTGGGTGAGCT	μ-α		17	137.	ICD165	GCTGAGCTGAGCTGTGCAGG		μ-јн		38
32.	L32-52 R	CCAGGCTGGACGGCTCTGGG	GGTAGCTAGGGTAAGTGAGG	y3-y2b		11	theme	11					
33.	T2-7 R	AGGCTGAGCAGCTCTCAGGG	AGCTGGGGGGGGGGGGGGGGGGGGGGGGGGGGGGGGGGG	γ3-α ν2 ~		11	Ruma	n cells:					
34.	T2-2 R	GTAGTTGGGGGGTGTGGGGGAC	TAGGCTGGGCAGCTCTGGGG	γ3-α γ3-α		11	138.	SKS251	TGGGCTGAGCTAACCTGGGC	AGGCTGAGCTGGGCTGAGC	и-и		39
35.	N5-7 R	TGTGGGGACCCTGTAGGGTA	GCTGTAGGGAAATCAGGACA	γ1-ε		16	139.	2C10	GAGCTGGGCTGGGCTGGGCT	GGGCTGAGCGGTCTAGCGGG	μ-γι	4/50	40
37.	1412-3	Toroboacceroradoorn	AGGGAGCCAGGACAGGTAGA	γ1-ε		16	140.	U266	TTGAGCTTAGCTGGGCTGAG	TAACCTGGGCAGGGCTGAGC	μ-ε	33 ins.	39
38.	1412-4		AGGGAGGACAGGTAGAAGTG	γ1-ε		16	141.	2C4	GCTAGGCTGGGCTGAGCTGG	GCTGAGCTAGGCTGGGCTGG	μ-ε	1/55	40
39.	T2-4 R	CAGCTAGGAGGGAGCTGGGG	CAGGTGGGAGTGTGAGGGAC	γ2b-α		11	142.	SKS251	AGCTGGGCTGAGCTAACCTG	GGCTGGGCTGAGCTAACCTG	μ-ε		39
40.	pCS43 R	ATGTGGAGGACCAGACCTAA	CAGCTAGGAGGGAGCTGGGG	γ2b-α		17	143.	SKS252	AAGCTGGGCTGAGCTGGGCA	GOGCTGGGCTGAGCTGAGCT	μ-ε		39
41.	pCS44 R		GGGACCTGACAGTACATCTG	γ2b-α	1 4	17	144.	SKS2/1 SKS274	CAGGCTGGGCTGAGCTGAGCTGAG	CTOCCTCCCCTCAGCT	μ-ε	3/43	39
42.	pCS20 R	AGGGACCAGTCTCAGCAGC	CACCTATACCCCCCCCCCCCCCCCCCCCCCCCCCCCCC	120-0	1/23	17	146	SKS275	CTTTCAGAAATGGACTCAGA	TOGCTAAACTGAGCCTAAGC	μ-ε		39
43.	DCS32 R	CTAGCAGCAGTGGGTGACTT	AGGAATGTTGGAAATGTGAG	γ2b-α	1,00	17	147.	SKS278	GCTGGGCTTGGCTGCACTAA	GCTGGGCTGAGCTGGGCAGG	μ-ε		39
45.	pCS31 R	GCCCTGGCCTAAGTAGACTG	GGCTAGGCTGAGCAAATCTA	α-α		17	148.	SKS281	GGCTGAGCTGGGCAGGGCTG	GGCTGAGCTGAGCTGGGCTG	μ-ε		41
	•						149.	SKS282	AGTTGAACTGGGTTGAGCTG	AGCTGAGCTGAGCTGGGCTA	μ-ε		41
Lymp	homas/leu	kemias:					150.	SKS283	GCTGAGTTGAACTGGGTTGA	GCTGAGCTGAGCTGG	μ-ε		41
						• •	151.	SK5285	ACTOCCTTC ACCTCACATC	GCTGAGCTGGGCCTAAGCTG	μ-ε μ_ε		41
46.	18.81A2	GATTACTCTGAGGTAAGCAA	AGCTOGGCTTGAGCCAAAAT	μ-μ		18	152.	SKS280	GAGACAAAAGATGGAAGCCA	GCCTGGCTGTGCAGGAACCC	и-е 11-е		41
4/.	1.29	CACTGAGCTGGGGTGAGCT	GAGE / GGGG	µ-12b		18	154.	SKS288	GCTGAACTGGGCTGAGTTGA	ACTGGGTTGAGCTGAGCTGA	u-e		41
40.	18.81 R	GCTAAGAATAGACTACCTGA	ATTGTGCCAAACTGGGCTGG	μ-γ2b	1/22	20	155.	2C10	GGAAGCTCCTGGAGCTCAGA	GA	γ-ε		40
50.	300-18	ACTTAAGTTTATCGACTTCT	AAAATGTATTTAGAATTCAT	μ-γ2Ы		21							
51.	1.29(40)	GGGGTGAGCTGAGCTGGGCT	OGGCTGAGCTGGGCTGAGCT	μ-α		22	ACCE	PTOR SEQU	ENCES :				
52.	BFO.3	TGAGCTGAGCTAGGGTGAGC	TGAGCTOGGGTGAGCTGAGC	μ-α	1/32	22							
53.	I.29 (Joc)	TGAGCTGGGGTGA <u>AT</u> TG <u>G</u> G <u>G</u>	TGGGGTGAGCTGAGCTGAGC	μ-α 20-1-20-	6/300	22	все	115:					
54. 55	300-18	CTC ACCT ACC ACTTCT ACC A	CTGAAGATGGTAGGAATGT	1201-12L	, 0, 5, 8	21	2.	GAM3 - 2	AGGCTGGGCAGCCTGGGGAG	CTAGGGTAGGTGGGATGTGG	ц- ү 3	1/46	15
56.	300-18	ATATGAGGGACCAGTCTCAG	CAGCTATGGAGGAGCTGGGG	Y2b-Y2b		21	з.	GAM3-8	AGCTCTCAGGGAGCTGGGGT	OGGTGGGGTTGTGAGGACCA	μ-γ3	2/274	15
				•			4.	T2-26 R	GGGAACCAGGCTGGACAGCT	CTGGGGAAACTGGGGTACAT	μ-γ3		16
Leuk	emias (on	retroviral vectors):					5.	L32-21 R	CAGGCTGGACGGCTCTGGGG	GTAGCTAGGGTAAGTGAGGA	μ-γ3		11
						22	ь. 7	pCS29 R	TGAGCACCTACAGTAGAGCT	GOOGCAGCTCTGGGGGGATCT	μ-γ3	1/20	17
57.	NB32	ATTACTCTGAGGTAAGCAAA	GCTGGGCTTGAGCCAAAATG	μ-μ μ-γ2b		23	7. 8	pCS35 R	GGTAGGTGGGGATGTGGGGGAC	CAGGE I GGGGAGCAGE I CIG	µ-73		17
58. 59	NB27	AGATTGCCTACACTGGACTG AGATTGCCCCTGGGATCACCT	GTACTCAGATGAGCTGGGAT	μ-120 μ-12b		23	9.	pCS23 R	GAGATATGTGGGGGTTGTGGG	GAACAGGTTGGACAGCTCTG	μ-γ3		17
60.	NB7	CTCAGCTATGCTACGCGTGT	TGGGGTGAGCTGATCTGAAA	μ-γ2b		23	10.	RH4	AGCTATAGGGGAGCCAGGAC	AGGTGGAAGTGTGGTGACCC	μ-γ1		15
61.	NB1	GGGCTGAGCTGGACTGAGCT	G	μ-γ2Ъ		23	11.	RH20	TTCCAAACAGAAGAGCTACA	GAGGAGCCAAGACAACTAGA	μ-γ1	2/78	15
62.	NB29	TGGGGTAAGATGGGATGAGC	TGTGGTGAGGGGAGCTGGAT	μ-γ2Ъ		23	12.	RH21		GAGCCAGGACAGGTGGAAGT	μ-γ1		15
63.	NB32	ATGAGCTGAACTGGGGTAAG	ATGGGATGAGCTGTGGTGAG	μ-γ2b		23	13.	pCS7 R	AGGAAAGGTGGAAGTGTGGG	GUTCCAGGCAGAGCAGTTAT	μ-γ1		15
64.	NB32	CAGTCCTAGAAGCTATGGGG	GATCTGGAATAGGTAGTAGA	120-42D		23	14.	pCS5 P	CCAGGCAGAGCAGCAGTGTGGT	TTAGCCAGGCAGAGCAGCTAT	μ-γ1 μ-γ1	1/24	10
Hyb-	idomaer						16.	pCS8 R	TGTGGTGACCCAGGCAGAGC	AGCTATAGGGGAGCCAGGAC	μ-γ1	-/ 47	10
							17.	pCS3 R	GGAAGTGTGGGGGAGCCAGGC	AGAGCAGCTCCAGGGCAGCC	μ-γ1		10
65.	180.2B2	AACTCTCCAGCCACAGTAAT	GACCCAGACAGAGAAGGCCA	μ-μ		25	18.	pCS9 R	CCAGGCAGAGCAGCTCCAGG	GCAGCCAGGACAGGTGGAAA	μ-γ1		10
66.	KWD1	GAAAAACTAGTAAAAGAAAA	ATGTTGCCTGTTAACCAACC	μ-δ		24	20.	N5-2 R	GCAGCCAGGACAGGTGGAAG		μ-γ1		16
67.	KWD2	GGGCCAAAGGTCTGAGACCA	GGCTGCTGCTGGGTAGGCCT	μ-δ μ-8		24	21.	N5-4 R	GATCCAGGCTGAGCAGCTCC	AGCTTAGCTGGGTAGGTGGA	μ-γ1		16
ь8. 69	KWD4 KWD5	GUTGAGUTGAGCTGAGCTGG CTAAACTCTACTCCCTACAC	TORACTORECTORE CACCEGE	μ-υ μ-δ		24	22.	148-3 R 148-21 P	TGGAAGTCCAGGGCAGCCAGGA	CAGGIGGAAGIGIGGGGACC	µ-11 µ-11		16
70	KWD6	CAACTCAATGTGGTTTTAATG	AATTTGAAGTTGCCAGTAAA	μ-δ		24	24.	N52-1 R	CAGGCAGAGTAGCTATACCC	AGCCAGGACAGGTGGAAGTG	μ-γ1		16
71.	KWD8	GCTGGGGTGAGCTGAGCTGG	OGTGAGCTGGACTGAGCTGA	μ-δ		24	25.	p3 R	AAGGACCAGAACTAGCAGCT	GTGGGAGAGCTGGGGATGGT	μ-γ2ь		9
72.	KWD9	ттссттдааааастастааа	AGAAAAATGTTGCCTGTTAA	μ-δ		24	26.	pCS24 R	GGCAGCTGGGGATGGTAG	GAATGTGGAGGACCAGACCT	μ-γ2ь		17
73.	180.2B2	GCTGAGCTGGGGTGAGCTGA	GCTGGG	μ-γ3		26	27.	pCS22 R	GATAGGAATGTGGAGGACCA	GTCCTAACAGCTAGGAGGGA	μ-γ2b	1 ins.	17
/4. 75	59.6C5	AAACTGAGGTGATTACTCTG	AGGTAAGCAAAGCTGGGCTT	μ-γ3		25	32. 28	152-52 R	GATGATAGGAATGTGGAGGA	CUAGTUCTAACAGCTAGGAG	γ3-γ2b Π-₽		11
76	470	GCAGCTGGGGGTAAGCTGGAT		μ-γ3		26	36.	N5-7 R	AAGTTAGGAGGGACTTGGCT	TGGCTTAGCTGGGCCAAGCT	γ1-ε		16
77.	137.5G6	AGCTGAGCGAGCTGGGGTGA		μ-γ1		26	37.	1412-3	GCTGTATGAGCTGTCTATCC		γ1-e		16
78.	3B12	ACTCAGTCAGTCAGTGGCGT	GAAGGGCTTCTAAGCCAGTC	μ-γ1	Th	nis pub.	38.	1412-4	TGGTATGAGCTGGTCTAATC		γ1-ε		16
79.	HB137	AACTTCATTAATCTAGGTTG	AATAGAGCTAAACTCTACTG	μ-γ1 3,	/341 Th	nis pub.	29.	T2-11 R	GGCTAGGCTGAGCTGAGCTG	GGAATGAGCTGGGAT	μ-α		11
80. o•	8-1 TTD141	GGCTGAGCTGAGATGGGTGG	GUTTUTUTGAGCGCTTUTAA	μ-γ∠D μ-γ2⊃ €	/1313 11-	/ vie nub	۵۵. ۱۲	T2-26 R	ACTTOGGTGAGCTAACTAGT	CTGATGGAGTACTGA	μ-α μ-α		16
82	284	TATGGATACGCAGAAGGAAGGC	OCCACAGCTGTACAGAATTG	μ-γ2a	3/96	27	33.	T2-7 R	TGAGCTGAGCTAGGCTGAGC	LOUC LOAAC LAGUTOGAA	μ-α. γ3-α:		11
83.	198.508	TGAGCACCTACAGTAGAGCT	GGGGCAGCTCTGGGGGATCT	7 3 I - 7 3		19	34.	T2-2 R	ATGAGCTGGGATGGGCTGAA	CTAGGCTGGAATAGGCTGGG	γ3-α	1/30	11
84.	470	GGGGACCAGGCTGGACAGCT	CTCGGGGGGGGGCTAGGGTAGG	y 3 - y 1		26	35.	pCS19 R	ACTGGGCTAGGGTTGGATGG	OCTCAATAACTGGGCTAATC	γ3-α		17
85.	470	GGGGAGCCAGGACAGGTGGA		γ1-γ1		19	39.	T2-4 R	CTGAGCTGGAATGAGCTGGG	ATGGGCTGAGCTAGGCTGGA	γ2b-α		17
86.	HB137	GGAGCCAGGACAGGTGGAAA	TGTGGTGACCCAGGCAGAGT	γ1-γ1 3/ γ1-ε	עוצי Th עוצי די-	is pub.	40.	pCS43 R	ACTGGCTGGGCTGGAATTTG	CTUGGCTGTGCTGAGCTGGG	γ210-01 γ210-01		17
88.	HB137	AGTGCAGAGAGATCCAAGCTGA	OCAGCTCCAGCTTAGCTGTA	γ1-e 4/	632 Th	is pub.	42.	pCS20 R	CTACTCTGGCATGGTCTGGG	CTAGGCTAGAATGGACTGAG	γ2b-α	l ins.	17
89.	26.82	TGGGATAGCTATGTGGGGAG	ACCAGGTTAAGCAAACAGTG	γ1-ε 13/	148 Th	is pub.	43.	pCS41 R	AGCTGGAATGAGCTGGGATG	GCTGAACTAGGCTGGAATA	γ2b-α		17
90.	ε-1	GCAGCTAGGAGGGAGCTGGG	GCAGGTGGGAGTGTGAGGGA	γ 2b-ε		7	44.	pCS32 R	AGCTGGGTTAGGCTGAGCTG	AGCTGAGCTGAGCTGAGCTG	γ2b-α		17
91.	TIB141	AGGGGCACATGGGGTCCACA	GAAACTCTAGAAACTTAGGG	Y2a-e 7/	'547 Th	is pub.	45.	pCS31 R	TGAGCTGGGTTAGGCTGAGC	TGAGCTGAGCTGGAATGAGC	α-α	2/21	17

Lymp	homas/leu	kemias:					98.	MOPC21	CTCAGCAGCTAGGAGGGAGC	TGGGGCAGGTGGGAGTGTGA	ц- γ2Ъ		29
							99.	MOPC141	AGTCCTGGGGGCCAGGAGAG	TTGTCCGATTGAGCAGGAAC	u-1/2b		2
46.	18.81A2		AGCTGAGCTGAGCTGCGGTT	μ-μ		18	100.	MPC11	GTGACTTGCAGATGTTGGAA	ATGTGAGGTACCAGTCCTAG	u-1/2b	4/69	30
47.	1.29	CTGCCTGAAGGGCCACAGGG	GAGCTGGGGCTATCAGATCA	μ-γ3		19	110	MPC11	ANGETAGGGGGAGCGGGAT	ACCTCCCACTATTACCCACT	v3-v2b	2/813	Š
48.	18.81A2	CAGTCCCAGCAGCCGTGAAG	GAGCTGGGGATGGTAGGAAT	μ-γ2b		18	111	MC101	CACCACCOCACCTCCACCTCCA	TOCOTATAAAAACGTACCAG	N-V1	2,010	36
49.	18.81 R	GAAAATCTGTGGTGCAACTG	TAACAGGTGGGGTGTGAGGA	μ-γ2b		20	113	MORC21	ANCTOTOCOCOCOCOCOCOC	ACCACCTATACACCOCCACCAC			42
50.	300-18	ACTACTCCTAGCAGCAGTGA		μ-γ2bI		21	114	452_1	COTOCOCOCOCOCOCOCOC	COTION ACTOTOCOCO	v1-000		43
54.	300-18		GAAGCTATGGGGGGGGGCTGGG	12bI-12b	4/294	21	114.	MORC21	CACACCTICANANACCACCA	ACCERCACCACACCE	11-0DC		43
55.	300-18	AGAGACCAGTCCCAGCAGCC	CTGAAGGAGCTGGGGATGGT	12b-12b		21	115.	MOPC21	CHOCOCOLANCEAGGAI	AACCCTGAGCAGACGTGAGT	12a-5.11		43
56.	300-18	ATGTGGAGGACCAGACCTAA	CAGCTAGGAGGGAGCTGGGG	12b-12b		21	117	MDC11	CIGOGGCAMAGAGAGAIGCC	CECECCOCCENTCIC	120-0-1		15
51.	T.29(40)	GAGCTGGGCTAGGCTGAGCT	GAGCTGGAATGAGCTGGGAT	μ-α		22	110	MPC11		CICIOGGIGGGIAACIAGGC	124-0-11		45
52.	BFO.3	TAGGCTGGGCTCGGCTGGTG	TGAGCTGAGCTAGGCTGAGC	u-a	1/45	22	110.	MPC11	GIAGACAGATAAGCICIGGI		12a-C-III	,c	45
53	1 29(.10)	TACCCTCCAATACCCTCCCC	TCCCTCCTCACCTCACC	µ-0	6/360	22	101.	TEPC15	TGGGCTGAGCTGGAATGAGC	TGGGTTGAGCTGAACTAGAT	μ-α		4
	1.29(00)	INDUCTODATIADUCTODUC	10000100101040010400	μ u	0/000	~~	102.	MCPC603	GCTAGGCTGGAATAGGTTGG	OCTGGGCTGGTGCGAGCTGG	μ-α	3.055.6	4
Louk	omian (on	retrovival vesters).					103.	MC101	CTGAGCTGAGCTGAGCTGGA	ATGAGCTGGGATGAGCTGAG	μ-α	1/556	31
Dear		rectovitar vectors):					104.	J558	AGCACTGTCTGGCTAGGCTG	TACTGGAATGAGCTGAGCTG	μ-α		32
57	MB20					22	105.	MOPC167	CTGGAATGAGCTGGGATTGG	CTAGAATAGGCTGGGCTGGA	μ-α	3 ins.	33
57.	ND32		SCI GGGC IGAGC IGGACIGA	μ-μ μ κΩΈ		23	106.	ABPC45	GGGTGAGCTGGAATGAGCTG	GGATGAACTGAGCGAGGCTG	μ-αι		34
50.	ND3	GTATOGTTTGAATAGGGGAC	TATATCTAGCAGCTATGGGG	μ-120		23	112.	MOPC167	CTAGGTTGAGTCTAGCGGA	AGCTOGAATGAGCTGGGATG	α-α		34
59.	NB7	ATGGTAGCAATGTGGGGAAC	CAGICCTAGAAGCTATGGGG	μ-γ26		23	119.	MOPC167	AGCTGGGATGGACTAGGATA	AACTAAGCTGGGATGAGACA	α-c-myc	1/193	46
60.	NB27	GAAATTTTGCACATCCAGTTC	TAGA	μ-γ25		23	120.	McPC603	GGCTGAGCTGGAATGAGCTG	GGTTGAGCTGAACTAGTATA	α-c-myc		46
61.	NB1	GAAGATGGTAGGAATGTGGA	GGACCAGACCTAACAGCTAG	μ-γ26	1/28	23	121.	J558	TCGCTAGGCTGTACTGGAAT	GAGCTGAGCTGAGCTGGGAT	α-c-myc		47
62.	NB29	GACCAGATCTCGCAGCTATG	GAGGAGCAGGGATAGGTG <u>G</u> A	μ-γ2ь		23	122.	ABPC45	GCCTAGACTGGTCTGACGCG	GGCTAATCTGGGATGAGTGG	α-c-myc		34
63.	NB32	GGGACTATATCTAGCAGCTA	TGGGGAAGCAAGGATAGGTG	μ-γ2ь		23	123.	W267	GCTGGGCTGGGCTGGTGTGA	GCTGGGCTAGGCTGAGCTGA	α-c-myc		35
64.	NB32	ATGGAGCTGGAGAAGGTGGG	AATATGAGGGAGAAGTCCTA	ү2b-ү2b	22 ins.	23	124.	W267	GCTAGGCTGAGCTGAGCTGG	AATGAGCTGGGATTGGCTAG	α-c-myc		35
							125.	HOPC1	GAGATTGAACCATAATGAGC	TGGGATGAGCTGGGATGAGC	α-c-myc		35
Hybr	idomas:						126.	HOPC1	GCTAGGCTGGAATAGGTTGG	GCTGGGCTGGTGTGACAGCT	α-c-myc		35
							127	MOPC315	CTCCAATGAGCTCCCATTCC	CTAGAATAGGCTGGGCTGGA	a-c-mvc	6 ins	40
								1101 0313	CIOCHAICACCICCOAIICO	CINGHAIN00010000100001		• • • • • • •	
65.	180.2B2		CTGAGCTGGGTGAGCTGAGC	μ-μ		25	128.	MOPC104E	TGCAGGTCGACTCTAGAGGA		02?-c-mv	c 1	48
65. 73.	180.2B2 180.2B2	GTTAGGAGTGTAGGGACCAG	CTGAGCTGGGTGAGCTGAGC GCTGGGCAGCTCTGGGGGAG	μ-μ μ-γ3		25 25	128.	MOPC104E	TGCAGGTCGACTCTAGAGGA		α?-c-my	c	48
65. 73. 74.	180.2B2 180.2B2 59.6C5	GTTAGGAGTGTAGGGACCAG GACCAGGCTGAGCAGCTCTC	CTGAGCTGGGTGAGCTGAGC GCTGGGCAGCTCTGGGGGAG AGGGAGCTGGGGGAGGTGGAG	μ-μ μ-γ3 μ-γ3		25 25 25	128. Hybri	MOPC104E	TGCAGGTCGACTCTAGAGGA		α?-c-my	c	48
65. 73. 74. 75.	180.2B2 180.2B2 59.6C5 198.5C8	GTTAGGAGTGTAGGGACCAG GACCAGGCTGAGCAGCTCTC GCTGGACAGCTCTGGAGGGA	CTGAGCTGGGTGAGCTGAGC GCTGGGCAGCTCTGGGGGAG AGGGAGCTGGGGAGGTGGAG GCTAGGATAAGTGAGGATGT	μ-μ μ-γ3 μ-γ3 μ-γ3		25 25 25 19	128. Hybri	MOPC104E	TGCAGGTCGACTCTAGAGGA		α?-c-my	c	48
65. 73. 74. 75. 76.	180.2B2 180.2B2 59.6C5 198.5C8 470	GTTAGGAGTGTAGGGACCAG GACCAGGCTGAGCAGCTCTC GCTGGACAGCTCTGGAGGGA GGAGTGTAGGGAGCAGCTG	CTGAGCTGGGTGAGCTGAGC GCTGGGCAGCTCTGGGGGAG AGGGAGCTGGGGAGGTGGAG GCTAGGATAAGTGAGGATGT GACAGCTCTGAGGGGAAGCT	μ-μ μ-γ3 μ-γ3 μ-γ3 μ-γ3		25 25 25 19 26	128. Hybri	MOPC104E	TGCAGGTCGACTCTAGAGGA	AGCAAACACCTAAAACAGGA	02?-c-my	c	48
65. 73. 74. 75. 76. 83.	180.2B2 180.2B2 59.6C5 198.5C8 470 198.5C8	GTTAGGAGTGTAGGGACCAG GACCAGGCTGAGCAGCACTCTC GCTGGACAGCTCTGGAGGAG GGAGTGTAGGGAGCAGCAGGCGG CTCTCAGGGAGCTGGGGAG	CTGAGCTGGGTGAGCTGAGC GCTGGGCAGCTCTGGGGAG AGGAGCTGGGGAGCTGGAG GCTAGGATAAGTGAGGATGT GACAGCTCTGAGGGAAGCT TGGACCTCTGGGGAACCAGC	μ-μ μ-үз μ-үз μ-үз μ-үз үз1-үз		25 25 19 26 19	128. Hybri 129.	MOPC104E .domas (ir 9.9.2.1	TGCAGGTCGACTCTAGAGGA vitro): GTACACATCTAAGGCCTCTA	АGСАЛАСАССТАЛААСАGGA	α?-c-my μ-γ2a γ2b-γ2a	c	48 37 37
65. 73. 74. 75. 76. 83. 77.	180.2B2 180.2B2 59.6C5 198.5C8 470 198.5C8 137.5G6	GTTAGGAGTGTAGGGACCAG GACCAGGCTGAGCAGCTCTC GCTGGACAGCTCTGGAGGGA GGAGTGTAGGGAGCAGGCTG CTCTCAGGGAGCTGGGGAGG CAGGCAGAGCAGCTGTATAGGG	CTGAGCTGGGTGAGCTGAGC GCTGGGCAGCTGTGGGGAG GCTAGGATAAGTGAGGAGGG GCTAGGATAAGTGAGGAAGCT GAGCAGCTGGAGGACCAGGC GAGCCAGGACAGGTGGAAGT	μ-μ μ-γ3 μ-γ3 μ-γ3 μ-γ3 γ3Ι-γ3 μ-γ1		25 25 19 26 19 26	128. Hybri 129. 130.	MOPC104E .domas (ir 9.9.2.1 9.7.1	TGCAGGTCGACTCTAGAGGA 1 vitro): GTACACATCTAAGGCCTCTA GAAAGAGAGTAAATGCTCCC	АGCAAACACCTAAAACAGGA АGCAGCTGTGGGACAGATGG	α?-c-my μ-γ2a γ2b-γ2a	c	48 37 37
65. 73. 74. 75. 76. 83. 77. 78.	180.282 180.282 59.6C5 198.5C8 470 198.5C8 137.5G6 3B12	GTTAGGAGTGTAGGGACCAG GACCAGGCTGAGCAGCTCTC GCTGGACAGCTCTCGGAGGA GGAGTGTAGGGAGCAGCTG CTCTCAGGGAGCAGCAGCAG AGCAGCTCCAGGGAGCGAG AGCAGCTCCAGGGAGCCAG	CTGAGCTGGGTGAGCTGAGC GCTGGGCAGCTGGGGAGGTGGAG AGGJAGCTGGGGAGGTGGAG GCTAGGATAAGTGAGGAGATGT GACAGCTGTGGGGAACCAGGC GAGCGTGGGAAGTGGGAGG GAGCGTGGAACTGGGAGG	μ-μ μ-γ3 μ-γ3 μ-γ3 μ-γ3 γ3Ι-γ3 μ-γ1 μ-γ1 2,	/311 Th	25 25 25 19 26 19 26 26 19 26	128. Hybri 129. 130.	MOPC104E .domas (ir 9.9.2.1 9.7.1	TGCAGGTCGACTCTAGAGGA vitro): GTACACATCTAAGGCCTCTA GAAAGAGAGTAAATGCTCCC	AGCAAACACCTAAAAACAGGA	α?-c-my μ-γ2a γ2b-γ2a	c	48 37 37
65. 73. 74. 75. 76. 83. 77. 78. 79.	180.282 180.282 59.6C5 198.5C8 470 198.5C8 137.5G6 3B12 HB137	GTTAGGAGTGTAGGGACCAG GACCAGGCTGAGCAGCTCTC GCTGGACAGCTCTGGAGGGA GGATGTAGGGAGCAGCAGC CTCTCAGGGAGCTGGGAGG CAGGCAGAGCAGCTATAGGG AGCACCTCCAGGGAGCCAG GTGGAAGCTGCTGCTGCCACCCAG	CTGAGCTGGGTGAGCTGAGC GCTGGCAGCTCTGGGGAG AGGACCTGGGGAGGTGGAG GCTAGGATAAGTGAGGATGT GACAGCTGGGGGACCAGG GAGCCAGGACAGGTGGAAGT GACAGGCAGCACGGCAG GCCAGGCAGCTCCAGGCAG	μ-μ μ-γ3 μ-γ3 μ-γ3 μ-γ3 γ3Ι-γ3 μ-γ1 μ-γ1 μ-γ1 2,	/311 Th Th	25 25 25 19 26 19 26 is pub. is pub.	128. Hybri 129. 130. Humar	MOPC104E .domas (ir 9.9.2.1 9.7.1 switches	TGCAGTCTCGACTCTAGAGA vitro): GTACACATCTAAGGCCTCTA GAAAGAGAGTAAATGCTCCC s:	AGCAAACACCTAAAACAGGA AGCACCTGTGGGACAGATGG	α?-c-my μ-γ2a γ2b-γ2a	c	48 37 37
65. 73. 74. 75. 76. 83. 77. 78. 79. 80.	180.2B2 180.2B2 59.6C5 198.5C8 470 198.5C8 137.5G6 3B12 HB137 ε-1	GTTAGGAGTGTAGGGACCAG GACCAGCCTGAGCAGCTCTC GCTGGACAGCTCTGGAGGGA GAGTGTAGGAGCCAGGGGG CTCTCAGGGAGCCAGGGAGC CAGCCAGAGCAGCATTAGG AGCAGCTCCAGGGAGCCAG GTGGAACTGTGGTGACCAG GATCTAGCAGCTGTAGGGA	CTGAGCTGGGTAGCTGAGC GCTGGGCAGCTGGGGAGCTGGAG GCTAGGATAGGTGGGGAGCTGGAG GCTAGGATAAGTGAGGATGT GAGCAGCTGTGGGGAGCCAGGC GAGCCAGGACAGCTGGAAGT GACAGGTGGAAGTGGGAAGT GCAGGATAGGTGGGAGTGT	μ-μ μ-γ3 μ-γ3 μ-γ3 μ-γ3 γ3Ι-γ3 μ-γ1 μ-γ1 μ-γ2 μ-γ2 μ-γ2 μ-γ2	/311 Th Th 6/395	25 25 25 19 26 19 26 is pub. is pub. 7	128. Hybri 129. 130. Humar	MOPC104E domas (ir 9.9.2.1 9.7.1 switches	TGCAGGTCGACTCTAGAGGA 1 vitro): GTACACATCTAAGGCCTCTA GAAAGAGAGTAAATGCTCCC 5: TCCCCTCACCTAACCTCAGCCCCC	AGCAAACACCTAAAACAGGA AGCAGCTGTGGGACAGATGG	α?-c-my μ-γ2a γ2b-γ2a	c	48 37 37
65. 73. 74. 75. 76. 83. 77. 78. 79. 80. 81.	180.2B2 180.2B2 59.6C5 198.5C8 470 198.5C8 137.5G6 3B12 HB137 ε-1 TIB141	GTTAGGAGTGTAGGGACCAG GACCAGCCTGAGCAGCTCTC GCTGGACAGCTGTGAGGAG GGAGTGTAGGGAGCAGGCAG CTCTCAGGAGCTGCAGGAG AGCAGTCCAAGGGAGCAA AGCAGCTCCAAGGGAGCAG GTGGAAGTGTGGTGACCCAG GATCTAGCAGCTGTAGGGG AGCAGCACAAGGACGAGTGG	CTGACTGGGTGAGCGAGC GCTGGCAGCTGGGGAGCGGGAG GCTAGGCTGGGGAGCGGAG GCTAGGATAAGTGAGGGAAGCT TGGACGTCGTGGGGACAGG GACAGCCAGGACAGCTGGAGA GCAGGAGCAGCTCCAGGGAGTG GCAGGAGCAGCACCAAG	μ-μ μ-γ3 μ-γ3 μ-γ3 μ-γ3 γ3Ι-γ3 μ-γ1 μ-γ1 μ-γ2 μ-γ2a	/311 Th Th 6/395 Th	25 25 25 19 26 19 26 19 26 is pub. 7 7 is pub.	128. Hybri 129. 130. Humar 138.	MOPC104E domas (ir 9.9.2.1 9.7.1 a switches SKS251 2010	TGCAGTCGACTCTAGAGA vitro): GTACACATCTAAGGCCTCTA GAAAGAAGAGTAAATGCTCCC s: TGGGCTGAGCTAACCTGGGC GCCLCALCCTACCTGGGC	AGCANACACCTANAACAGGA AGCAGCTGTGGGACAGATGG AGAGCTGAGCT	α?-c-my μ-γ2a γ2b-γ2a μ-μ	c	48 37 37 39
65. 73. 74. 75. 76. 83. 77. 78. 79. 80. 81. 82.	180.2B2 180.2B2 59.6C5 198.5C8 470 198.5C8 137.5G6 3B12 HB137 ε-1 TIB141 2B4	GTTAGGAGTGTAGGGACCAG GACCAGGCTGAGCAGCTGTG GGTGGACAGCTCTGGAGGGA GGAGTGTAGGGAGCAGCAGG CTCTCAGGGAGCTGGGGAG CAGGCAGAGCAGCTATAGGG AGCAGCTCCAGGGGACCCAG GTGGAAGTGTGGTGGTCACCCAG GACCTGTGGAGCGGA CAGAGACCAGGGGACCATGGA	CTGACTGGGTGAGCTGAGC GCTGGCAGCTGGGGAGCTGGAG AGGACCTGGGGAGGTGGAG GCTAGGATAAGTGAGGATGT GACAGTGGGGACCAGG GAGCCAGGACAGGTGGAAGT GACAGGCAGCTCCAGGCAG GCCAGGCAGCTCCAGGCAG GCAGAGCAGCTCCAGGCAGTGT TGTATGGGCGAAGTGA	μ-μ μ-γ3 μ-γ3 μ-γ3 μ-γ3 γ3Ι-γ3 μ-γ1 μ-γ1 μ-γ2 μ-γ2a μ-γ2a	/311 Th Th 6/395 Th	25 25 25 19 26 19 26 is pub. 7 is pub. 27	128. Hybri 129. 130. Humar 138. 139.	MOPC104E .domas (ir 9.9.2.1 9.7.1 5 switches 5KS251 2C10 2016	TGCAGTCGACTCTAGAGA vitro): GTACACATCTAAGGCCTCTA GAAAGAGAGTAAATGCTCCC s: TGGGCTGAGCTAACCTGGGC GGCAGGAGGATCAGCTAGCT	AGCAAACACCTAAAAACAGGA AGCAGCTGTGGGACAGATGG AGAGCTGAGCT	α?-c-my μ-γ2a γ2b-γ2a μ-μ	c	48 37 37 39 40
65. 73. 75. 75. 76. 83. 77. 78. 79. 80. 81. 82. 84	180.2B2 180.2B2 59.6C5 198.5C8 470 198.5C8 137.5G6 3B12 HB137 ε-1 TIB141 2B4 470	GTTAGGAGTGTAGGGACCAG GACCAGGCTGAGCAGCTGTC GCTGGACAGCTGTGGAGGA GGATGTAGGGACCAGGTG CTCTCAGGGAGCTGGGGAG AGCAGTCCAGGGAGCTATAGGG AGCAGTCCAGGGAGCCAG GTGGAAGTGTGGTGACCCAG GATCTAGCAGCTGTAGGAC GGAACGTAGGACGAGTGG GGAACGTAGGTGATCATGGA	CTGRACTGGGTGAGCGAGC GCTGGGCAGCTCGGGGAG AGGCAGCTGGGGAGCGGGGA GCTGGGAGAAGTGGAGAAGCT GGAGCTGTGGGGACCAGGC GAGCGTGGGGACCAGGC GAGAGTGGGAGCAGCTCGAGG GCAGGGAGCAGCTCCAGGGCGG GAAGCTGGAGCAAGTCCAAG GAAAATCTATGGTGGCACTG GGAATGGGGCCGCCCAGG	μ-μ μ-γ3 μ-γ3 μ-γ3 μ-γ3 η-γ1 μ-γ1 μ-γ1 μ-γ2 μ-γ2a μ-γ2a μ-γ2a μ-γ2a	/311 Th Th 6/395 Th	25 25 25 19 26 19 26 is pub. is pub. 7 7 is pub. 27	128. Hybri 129. 130. Humar 138. 139. 140.	MOPC104E domas (ir 9.9.2.1 9.7.1 switches SKS251 2C10 U266	TGCAGGTCGACTCTAGAGA vitro): GTACACATCTAAGGCCTCTA GAAAGAGAGATAAATGCTCCC : TGGGCTGAGCTAACCTGGGC GGCAGAGGAGCAGAGCTAGCTAGCT TGGGCCGAGCGGGGCTGGAT	Адсаласассталалсадда адсастотодасадатод адастотодастодостодостодос аспользититодостодостодос	α?-c-my μ-γ2a γ2b-γ2a μ-μ μ-γΙ μ-ε	c and	48 37 37 39 40 39
65. 73. 75. 76. 83. 77. 78. 79. 80. 81. 82. 84.	180.2B2 180.2B2 59.6C5 198.5C8 137.5G6 3B12 HB137 E-1 TIB141 2B4 470 470	GTTAGGAGTGTAGGGACCAG GACCAGGCTGAGCAGCTGTC GCTGGACAGCTGTGGAGGAG GGAGTGTAGGGAGCAGGCAG CTCTCAGGAGCAGCAGCTATAGGG AGCAGCCAGAGGAGCAG GTGGAAGTGTGGTGACCAG GTTGAAGCTGTGGAGCAGTGG GGAACGTAGGAGCAGTGG GGAACGTAGGTGGTGATCATGGA	CTGACTGGGTGAGCGAGC GCTGGCAGCTGGGGAGCTGGGGAG GCTAGGCTGGGGAGCGGAGC	μ-μ μ-γ3 μ-γ3 μ-γ3 μ-γ3 μ-γ1 μ-γ1 μ-γ1 μ-γ2 μ-γ2 μ-γ2a μ-γ2a μ-γ2a γ3-γ1	/311 Th Th 6/395 Th 4/1092	25 25 25 19 26 19 26 15 pub. 27 27 26 19	128. Hybri 129. 130. Humar 138. 139. 140. 141.	MOPC104E domas (ir 9.9.2.1 9.7.1 switches SKS251 2C10 U266 2C4	TGCAGTCGACTCTAGAGA vitro): GTACACATCTAAGGCCTCTA GAAAGAGAGTAAATGCTCCC s: TGGGCTGAGCTAACCTGGGC GGCAGGAGGATCAGCTAGCT ACTGAGTTCTGCTGGGATAA	AGCAAACACCTAAAACAGGA AGCAGCTGTGGGACAGATGG AGAGCTGAGCT	α?-c-my μ-γ2a γ2b-γ2a μ-μ μ-γΙ μ-ε μ-ε	2/71	48 37 37 39 40 39 40
65. 73. 74. 75. 76. 83. 77. 78. 79. 80. 81. 82. 84. 85.	180.2B2 180.2B2 59.6C5 198.5C8 470 198.5C8 137.5G6 3B12 HB137 ε-1 TIB141 2B4 470 470 470 470	GTTAGGAGTGTAGGGACCAG GACCAGGCTGAGCAGCTCTC GCTGGACAGCTCTGGAGGGA GGACTGTGGGGAGCCAGGCAG CTCTCAGGGAGCTGGGGAGCCAG AGCAGCTCCAGGGAGCCAG GTGGAAGTGTGGTGGTACCCAG GATCTAGCAGCTGTAGGGA CAGAGACCAGGGAGCAGGG GGAACGTACGTGATCATGGA	CTGACTGGGTGAGCTGAGC GCTGGCAGCTGGGGAGCTGGAG GCTAGGATAAGTGAGGATGGAG GCTAGGATAAGTGAGGATGGA GCAGGCTGGGGACCAGGC GAGCCAGGACAGCTGGAAGT GAGAGCGAGCCCAGGCAG GCAGAGCAGCTCCAGGCAG GCAGAGCAGCTCCAGGCAG GAAAATCTATGGTGCAACTG GAAAATCTATGGTGCAACTG GGAATGTGGTGCACCAGGAAG CTTATGGGCCAGCAGGAGG	$\begin{array}{c} \mu - \mu \\ \mu - \gamma_3 \\ \mu - \gamma_3 \\ \mu - \gamma_3 \\ \mu - \gamma_3 \\ \gamma_3 I - \gamma_3 \\ \mu - \gamma_1 \\ \mu - \gamma_1 \\ \mu - \gamma_1 \\ \mu - \gamma_2 \\ \mu - \gamma_2 \\ \eta - \gamma_2 \\ \gamma_3 - \gamma_1 \\ \gamma_1 - \gamma_1$	/311 Th Th 6/395 Th 4/1092 Th	25 25 25 19 26 19 26 is pub. 7 is pub. 27 26 19 19	128. Hybri 129. 130. Humar 138. 139. 140. 141. 142.	MOPC104E domas (ir 9.9.2.1 9.7.1 switches SKS251 2C10 U266 2C4 SKS251	TGGAGTCGACTCTAGAGA vitro): GTACACATCTAAGGCCTCTA GAAAGAGAGTAAATGCTCCC s: TGGGCTGAGCTAACCTGGGC GGCAGGAGGATCAGCTAGCT TGGGCCGAGGATCAGCTAGCT GGCACGAGGGATCAGCTGGGT	AGCAAACACCTAAAACAGGA AGCAGCTGAGCTGGGACAGATGG AGAGCTGAGCT	α?-c-my μ-γ2a γ2b-γ2a μ-μ μ-γΙ μ-ε μ-ε μ-ε	2/71	48 37 37 37 39 40 39 40 39
65. 73. 74. 75. 76. 83. 77. 78. 79. 80. 81. 82. 84. 85. 86. 85.	180.2B2 180.2B2 59.6C5 198.5C8 470 198.5C8 137.5G6 3B12 HB137 E-1 TIB141 2B4 470 HB137 3B12	GTTAGGAGTGTAGGGACCAG GACCAGCCTGAGCAGCTGTC GCTGGACAGCTGTGGGGAG GCATGTAGGGACAGCTG CTCTCAGGGAGCTGGGGAG CAGGCAGGCAGGCAGCTATAGGG AGCAGTCCAGGGAGCCAG GTGGAAGTGTGGTGACCCAG GAACGTACGTGATGAGGATCGAG GGAACGTACGTGGGGATCCAG	CTGACTGGGTGAGCGAGC GCTGGCAGCTGGGGAGCGGGGG GCTAGGCTGGGGAGCGGGGG GCTAGGATAAGTGAGGAAGC GCAGCTGTGGGGACCAGG GACACTGTGGGGAACGGGAAGC GCAGGGAAGCTCCAGGGAGC GCAGGGATGGTGGACCAG GAAATCTATGGTGCACCG GGAAATCTATGGTGCACCG GTATAGGCGGCCCGGAAG GTAAAGCTGGACTGGGAAGC	$\begin{array}{c} \mu - \mu \\ \mu - \gamma_3 \\ \mu - \gamma_3 \\ \mu - \gamma_3 \\ \gamma_3 1 - \gamma_3 \\ \mu - \gamma_1 \\ \mu - \gamma_1 \\ \mu - \gamma_1 \\ \mu - \gamma_1 \\ \mu - \gamma_2 \\ \mu - \gamma_2 \\ \mu - \gamma_2 \\ \mu - \gamma_2 \\ \eta - \gamma_1 \\ \gamma_1 - \gamma_1 \\ \gamma$	/311 Th Th 6/395 Th 4/1092 Th Th	25 25 25 19 26 19 26 is pub. 7 is pub. 27 26 19 19 26 19 19 is pub.	128. Hybri 129. 130. Humar 138. 139. 140. 141. 142. 143.	MOPC104E domas (ir 9.9.2.1 9.7.1 switches SKS251 2C10 U266 2C4 SKS251 SKS251 SKS252	TGCAGTTCGACTCTAGAGA vitro): GTACACTCTAAGGCCTCTA GAAAGAAGAGTAAATGCTCCC s: TGGGCTGAGCTAACCTGGG GGCAGGAGGATCAGCTAGCT TGGGCAGAGGCTGGGCTGGGT ACTGAGTTCTGCTGGGATA ACTGAGTTCTGCTGGGC CGGCTGGGCTGGGTCAGCT	AGCAAACACCTAAAAACAGGA AGCAGCTGTGGGACAGATGG AGAGCTGAGCT	α?-c-my μ-γ2a γ2b-γ2a μ-γ μ-γ μ-ε μ-ε μ-ε μ-ε	2/71 1/27	48 37 37 37 39 40 39 40 39
65. 73. 74. 75. 76. 83. 77. 78. 79. 80. 81. 82. 84. 85. 86. 87. 89.	180.2B2 180.2B2 198.5C3 470 198.5C8 470 198.5C8 137.5G6 3B12 HB137 ε-1 TIB141 2B4 470 HB137 3B12 HB137	GTTAGGAGTGTAGGGACCAG GACCAGGCTGAGCAGCTGTC GCTGGACAGCTGTGGGGAGCAGCTGTC GCTGGACAGCAGCAGCAGCAGCTG CTCTCAGGAGCAGCAGCTATAGGG AGCAGCCCAGGGGAGCCAG GTGGAAGTGTGGGGAGCCAG GTGGAGTGTGGGGAGCAGGG GGAACGTAGGGGGTATCATGGG GTGGGAGTGTGGGGATCCAG TGGGGGGTATACTCAGCTGA	CTGAGCTGGGTGAGCTGAGC GCTGGCAGCTGGGGAGCTGGGGAG GCTGGCTGGGGAGGTGGAG GCTGGGCTGG	μ-μ μ-γ3 μ-γ3 μ-γ3 μ-γ3 μ-γ1 μ-γ1 μ-γ1 μ-γ1 μ-γ2b μ-γ2b μ-γ2a μ-γ2a μ-γ2a γ1-γ1 γ1-γ1 γ1-γ1 γ1-γ1 γ1-γ1	/311 Th Th 6/395 Th 4/1092 Th Th Th	25 25 25 19 26 19 26 15 9 26 15 9 15 9 19 15 9 15 9 15 9 15 9 15 9	128. Hybri 129. 130. Humar 138. 139. 140. 141. 142. 143. 144.	MOPC104E domas (ir 9.9.2.1 9.7.1 switches SKS251 2C10 U266 2C4 SKS251 SKS251 SKS251 SKS251 SKS251	TGCAGTCGACTCTAGAGA vitro): GTACACATCTAAGGCCTCTA GAAAGAAGAGTAAATGCTCCC S: TGGGCTGAGCTAACCTGGGC GGCAGGAGGATCAGCTAGCT ACTGAGTTCTGCTGGGATAA GCAACTGGTATTCAGCTGGGT GGGCTGGGCTGAGCTGAGT GGGCTGGGTGAGCTGAGTGGGT	AGCAAACACCTAAAACAGGA AGCACCTGTGGGACAGATGG AGAGCTGAGCT	α?-c-my μ-γ2a γ2b-γ2a μ-μ μ-γΙ μ-ε μ-ε μ-ε μ-ε μ-ε μ-ε μ-ε	2/71 1/27 1/22	48 48 37 37 37 39 40 39 40 39 39 39
65. 73. 74. 75. 76. 83. 77. 78. 79. 80. 81. 82. 84. 85. 86. 87. 88.	180.2B2 180.2B2 59.6C5 198.5C8 470 198.5C8 137.5G6 3B12 HB137 ε-1 TIB141 2B4 470 470 HB137 3B12 HB137 26.92	GTTAGGAGTGTAGGGACCAG GACCAGGCTGAGCAGCTGTC GCTGGACAGCTGTGGGGAG GGACGTAGGGAGCAGGTG CTCTCAGGGAGCAGGTG CAGGCAGAGCAGCTATAGGG AGCAGTCCAGGGAGCCAG GTGGAACTGTGGTGACCCAG GATCTAGCAGCTGTAGGAG GGACGTAGGTGTGGGGATCCAG GGAGGGATGTGGGGGATCCAG GGAGCGAGCTGAGCT	CTGACTGGGTGAGCGAGC GCTGGGCAGCTCGGGGGAG AGGDACTGGGGAGCGGGGAG GCTGGGAGAAGTGGAGGAGCGGG GCACGCTGGGGGACCAGGC GACACTGGGGACCAGGC GACAGTGGAACTGTGGAG CCAGGATAGGTGGCAGGTG GACAGTGGACCAGGCCAGG	μ-μ μ-γ3 μ-γ3 μ-γ3 μ-γ3 μ-γ1 μ-γ1 μ-γ1 μ-γ2a μ-γ2a μ-γ2a μ-γ2a γ3-γ1 γ1-γ1 γ1-γ2 γ1-γ1 γ1-ε	/311 Th Th 6/395 Th 4/1092 Th Th Th Th	25 25 25 19 26 19 26 is pub. is pub. 27 27 26 19 is pub. is pub. is pub.	128. Hybri 129. 130. Humar 138. 139. 140. 141. 142. 143. 144. 145.	MOPC104E domas (ir 9.9.2.1 9.7.1 a switches SK5251 2C10 U266 2C4 SK5251 SK5251 SK5271 SK5274	TGGAGTTGGACTAGAGAA vitro): GTACACATCTAAGGCCTCTA GAAAGAGAGATAAATGCTCCC s: TGGGCTGAGCTAACCTGGGC GGCAGGAGATCAGCTAGCT TGGGCCGAGCTGGGCTGGGTTCAGCT GGGCTGGACTGGGTTGGGTC GGGCTGAGCTGGGCTGGGCTGGGCT	Адсаласассталалсадата Адсастотодостодостолог Адастотодостодостолос Астотостотостодостолос сстолостосостодостолос содостодостолосостолосто сполосостодостолосто сполосостодостолосто сполосостодостолосто сполосостодостолосто сполосостодостолосто сполосостодостолососто сполосостодостолососто сполосостодостолососто сполосостодостолососто сполосостодостолососто сполосостодостолососто сполосостодостолососто сполосостодостолососто сполосостодостолососто сполосостодостолососто сполосостодостолососто сполосостодостодостолососто сполосостодостодостолососто сполосостодостодостолососто сполосостодостодостолососто сполосостодостодостолососто сполосостодостодостодосто сполосостодостодостодосто сполосостодостодостодосто сполосостодостодостодосто сполосостодостодостодосто сполосостодостодостодостодосто сполосостодостодостодосто сполосостодостодостодосто сполосостодостодостодостодостодосто сполосостодостодостодостодосто сполосостодостодостодостодосто сполосостодостодостодостодосто сполосостодостодостодостодостодосто сполосостодостодостодостодостодостодостодо	α?-c-my μ-γ2a γ2b-γ2a μ-μ μ-ε μ-ε μ-ε μ-ε μ-ε μ-ε μ-ε	2/71 1/27 1/22	48 37 37 37 39 40 39 40 39 39 39 39
65. 73. 74. 75. 76. 83. 77. 78. 80. 81. 82. 84. 85. 86. 87. 88. 89.	180.2B2 180.2B2 59.6C5 198.5C8 470 198.5C8 137.5G6 3B12 HB137 <i>z</i> -1 TIB141 2B4 470 HB137 3B12 HB137 26.82	GTTAGGAGTGTAGGGACCAG GACCAGCCTGAGCAGCCTCTC GCTGGACAGCTGTGAGGAG GGAGTGTAGGGAGCAGGCG CTCTCAGGAGCAGCAGCTG CCTCCAGGAGCAGCATATAGGG AGCAGTCCAGGGAGCAGCAG GTGGAAGTGTGGGGACCAG GTGGAGTGTGGGGATCAGGA GGACGACCAAGGACGAGTGG GGAACGCTAGCTGGGATCCAG TGGGGGGTGTGGGGATCCAG TGGGGCGGACTGGGGATCCAG TGGGGCGGACTGGGGATCCAG TGGGGCTGGCTGGGCATCCAG	CTGAGCTGGGTGAGCTGAGC GCTGGCAGCTGGGGAGCTGGAG GCTAGGCTGGGGGAGCTGGAG GCTAGGCTGGGGGAAGCT GGAGCTGGGGGAAGCGTGGAG GCAGGACAGCAGAACGTGGAG GCAGGAGCAGCTCCAGGGAGC GCAGGAGCAGCTCCAGGGAGC GCAGGAGCAGCTCCAGGGAGC GCAGGAGCAGCAGCAGCAG GAAATCTATGGTGCAACTG TGGTATGGGGACCAGGAAAG GTATAGGCTGGACCAGGAAAG GTATAGGCTGGACAAGTTAAGTT	μ-μ μ-γ3 μ-γ3 μ-γ3 μ-γ3 μ-γ1 μ-γ1 μ-γ1 μ-γ2 μ-γ2 μ-γ2 γ3-γ1 γ1-γ1 γ1-γ1 γ1-γ2 γ1-γ2 γ1-γ2 γ1-γ2 γ1-γ2 γ1-ε γ1-ε	/311 Th Th 6/395 Th 4/1092 Th Th Th Th Th	25 25 25 19 26 15 26 15 26 15 27 26 19 15 pub. 15 pub. 15 pub. 15 pub. 27 26 19 15 20 27 26 19 26 19 26 27 27 26 25 25 25 25 25 25 25 25 25 25 25 25 25	128. Hybri 129. 130. Humar 138. 139. 140. 141. 142. 143. 144. 145. 146.	MOPC104E MOPC104E domas (ir 9.9.2.1 9.7.1 witches SKS251 2C10 U266 SKS252 SKS271 SKS274 SKS275	TGCAGTCGACTCTAGAGA vitro): GTAACATCTAAGGCCTCTA GAAAGAGAGTAAATGCTCCC 5: TGGGCTGAGCTAACCTGGGC GGCAGGAGCGGGGTAGGTA ACTGAGTCTGCTGGGGTAGAT ACTGAGTCTGCTGGGTTGGGT AGCTGGCTGAGCTGGGTTGGGT AGCTGGGCTGACTGGGTTGGCT GGCTGGGCTGACTGGGTTGGCT GGCTGGGCTGACTGGGTTGGCT	AGCANACACCTANAACAGGA AGAGCTGAGCTGGGACAGATGG AGAGCTGAGCT	α?-c-my μ-γ2a γ2b-γ2a μ-μ μ-ε μ-ε μ-ε μ-ε μ-ε μ-ε μ-ε μ-ε μ-ε	2/71 1/27 1/22 3/34	48 37 37 37 37 39 40 39 39 39 39 39 39 39 39
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65. 73. 75. 75. 75. 76. 83. 77. 80. 81. 82. 84. 84. 84. 85. 86. 87. 90. 91. 91. 92. 93.	180.282 180.282 59.6C5 198.5C8 470 198.5C8 137.5G6 3B12 HB137 2E-1 TIB141 2B4 470 HB137 26.82 E-1 TIB141 Lomas: MPC11 MCPC603	GTTAGGAGTGTAGGGACCAG GACCAGGCTGAGCAGCTGTC GCTGGACAGCTGTGGGGACGGCTG GCACGTAGGGACCAGGCTG CTCTCAGGGAGCTGGGGAG AGCAGCTCCAGGGAGCTAGGG GATCTAGCAGCTGTAGGGAGCCAG GTGGAACTGTGGTGACCAGG GAACGTAGGACTGTAGGGATCCAG GTGGGAGTGTGGGGGATCCAG GGACGTAGGCTAGGC	СТОЛОСТОСОТСАОСТОЛОСТОВОСА ССТОЗОСЛОСТСТОВОСАСА АСОЗЛОСТТОВОСАСТОВОС САСАСТСТОВОСАЛОСТОВОС САСАСТСТОВОСАЛОСТОВОС САСАСТСТОВОСАЛОСТОВОЛ САСАСТСТОВОСАЛОСТОВОЛОС САСАСТСТОВОСАЛОСТОВОЛОС САСАСТСАСАЛОСТОВОСТОВОСТОВОСТОВОСТОВОСТОВОСТОВОСТО	µ-µ µ-үз µ-үз µ-үз µ-үз үзI-үз µ-ү1 µ-ү2а үз-ү1 үз-ү1 үз-үз үз-үг үз-е ү2а-е µ-µ µ-µ	/311 Th Th 6/395 Th 4/1092 Th Th Th Th Th Th	25 25 25 19 26 19 26 is pub. 7 is pub. is pub. is pub. is pub. is pub. is pub. 4	128. Hybri 129. 130. Humar 138. 139. 140. 141. 144. 143. 144. 145. 144. 145. 146. 147. 148. 146. 150. 151. 152. 153.	MOPC104E domas (ir 9.9.2.1 9.7.1 a switches SK5251 2C10 U266 2C4 SK5251 SK5252 SK5271 SK5275 SK5275 SK5278 SK5281 SK5281 SK5283 SK5283 SK5285 SK5285 SK5285 SK5285 SK5287 SK57 SK57 SK57 SK57 SK57 SK57 SK57 SK57 SK57	TGGAGTGAGCTGAGCTGAGAGA vitro): GTACACATCTAAGGGCTCTA GAAAGAGAGATAAATGCTCCC 3: TGGGCTGAGGTAAATGCTCCC 3: TGGGCTGAGGATCAGCTAGCT GGCAGGAGGATCAGCTAGCT GGCAGGAGCGGGGCTGGGTCAGCT GGCACTGATTCAGCTGGGTCAGCT GGCTGAGCTGGGTTCAGCT GTTCTGCTGGATAAACTGGGTTG GTTCTGCTGGATAAACTGGGTTG GTTCTGCTGGATAAACTGGGT GGGCTAAACTGGGTGGACT TGGGCTAAACTGGGTGGACT CTGAGTCACAACCGGTGGGCGAC TGGGCTAAACTGGGTGAGCT	AGCAAACACCTAAAAACAGGA AGCAGCTGAGCTGGGACAGATGG AGAGCTGAGCT	α?-c-my μ-γ2a γ2b-γ2a μ-μ μ-γ μ-γ μ-ε μ-ε μ-ε μ-ε μ-ε μ-ε μ-ε μ-ε	2/71 1/27 1/22 3/34 1/23 1/23	48 48 37 37 37 37 39 40 39 39 39 39 39 39 39 39 39 39 39 39 39
65. 73. 75. 75. 76. 83. 77. 78. 79. 80. 81. 82. 84. 85. 84. 85. 84. 89. 90. 91. 92. 93. 93. 96.	180.282 180.282 59.6C5 198.5C8 470 198.5C8 137.5G6 3812 HB137 2-1 284 470 HB137 26.82 2-1 TIB141 Iomas: MPC11 McPC603 3606	GTTAGGAGTGTAGGGACCAG GACCAGCCTGAGCAGCTGTC GCTGGACAGCTGTGGGGAGCAGCTG GCTGTAGGGAGCAGGAGCAGGGG CCTCTCAGGGAGCAGCAGCAG GTGGAAGTGTGGGGACCAG GTGGAAGTGTGGGGACCAG GTGGAAGTGTGGGGATCAGG GGACGACAAGGACGAGGGG GGACGACCAAGGACGAGCTGG GGACGAGCTGGGCTGAGCTAGC TGGGGGTGTAGGGTGAGCTGGC TGGAAGTGGGTCTAAGCTAGC TGGAATGGGTTGAGCTGGC	CTGAGCTGGGTGAGCTGAGC GCTGGCAGCTGGGGAGCTGGAG GCTAGGCTGGGGAGCTGGAG GCTAGGCTGGGGGAGCGAGC GCAGCCTGGGGGGAAGCT GGAGCTGGGGGAACGTGGAG GCAGGACAGCTCCAGGGAG GCAGGACAGCTCCAGGGAGC GCAGGACAGCTCCAGGGAGC GCAGGCAGACAGCTCCAGGGAGC GCAGGCAGACAGCTGGGACCAG GAAATCTATGGTGCAACTG GGAAATCTGGGACAGAAAG GTATAGGCGGACCAGGAAG GTATAGGCGGACCAGAAAG GTATAGGCTGGACCAGCAGAAG GTCTGAGCTAACTAAGTT TTTGTATATTCGGTGCAAC GAACTGGGCTGAACTGAGCT GAACTGGGCTGAACTGAGCT GGGGTGAGCTGAGC	μ-μ μ-γ3 μ-γ3 μ-γ3 γ31-γ3 μ-γ3 μ-γ1 μ-γ2α μ-γ2α μ-γ2α μ-γ2α μ-γ2α γ2-γ γ1-ε γ2b-ε γ2a-ε μ-μ μ-γ3	/311 Th 6/395 Th 4/1092 Th Th Th Th Th 7/97	25 25 25 19 26 15 26 15 pub. 27 26 19 15 pub. 15 pub. 15 pub. 15 pub. 15 pub. 27 26 19 15 s pub. 15 pub. 27 26 19 26 19 26 30 27 27 26 19 26 30 26 30 27 30 26 30 26 30 26 30 30 26 30 30 30 30 30 30 30 30 30 30 30 30 30	128. Hybri 129. 130. Humar 138. 139. 140. 141. 142. 143. 144. 145. 146. 147. 148. 149. 150. 151. 152. 153. 154.	domas (ir 9.9.2.1 9.7.1 a switches SKS251 2C10 SKS252 SKS271 SKS275 SKS278 SKS278 SKS283 SKS283 SKS283 SKS283 SKS286 SKS288	TGCAGTTCGACTCTAGAGA TCGAGTTCGACTCTAGAGAGA TVILTO): GTAACAACATCTAAGGCCTCTA GAAAGAGAGTAAATGCTCCC S: TGGGCTGAGCTAACCTGGGC GGCAGGAGCGGGGCTGGGAT ACTGAGTCAGCTGGGCTGGGT ACTGAGTCGACTGAGTTGGGT GGCTGAGCTGAGCTGGGTTAGCTG GTTCTGCTGGGATAACTGGGTTAGCTA GACTAGCTGGTTTGGGCTA GACTAAGCTGGTTTGGGCTA GACTAAGCTGGTTTGGGCTA GACTAACTGGGTTAGCTGA GACTAACTGGGTTAGCGGAC CGGACTGACTGGACTGAGCTGG ACCTAACTGGGCTGAGCTGG CCGACTGGACTGAGCTGG	AGCANACACCTANANACAGGA AGCAGCTGAGCTGGGACAGATGG AGAGCTGAGCT	α?-c-my μ-γ2a γ2b-γ2a μ-μ μ-ε μ-ε μ-ε μ-ε μ-ε μ-ε μ-ε	2/71 1/27 1/22 3/34 1/23 1/23	42 48 37 37 37 39 40 39 40 39 39 39 39 39 39 39 39 39 39 39 41 41 41 41 41 41
65. 73. 75. 75. 75. 76. 83. 77. 77. 79. 80. 81. 82. 84. 85. 84. 85. 84. 87. 89. 91. 91. 92. 93. 97.	180.282 180.282 59.6C5 198.5C8 470 198.5C8 137.5G6 3B12 HB137 ε-1 TIB141 284 470 HB137 26.82 ε-1 TIB141 lomas: MPC11 MOPC21	GTTAGGAGTGTAGGGACCAG GACCAGGCTGAGCAGCTGTC GCTGGACAGCTGTGGGAGG CAGGCAGAGCAGCTGCGGGAGG CAGGCAGAGCAGCTATAGGG GACCGTCAGGGAGCAGCTAG GACGTAGCAGCTGTAGGGA GATCTAGCAGCTGTAGGGAG GAACGTAGGAGTGTGAGGAGATCCAG GGACGTAGGTGTAGGGATCCAG GGACGTAGGTGTAGCTAGC CAGGGAGTGTGGGGGATCCAG GGACGACTAAGCTGAGCTAGC CAGGGAGTGTGGGGTATACTCAGCTAGC CAGGGCTGAACTAGCTAGC GGACGACTGAGCTGAG	СТОКАСТОСОТСАВСТОЛОССАОС ССТОЗОСЛОСТСТОСОСОАС АСОЗАССТОЗОСЛАСТОВОСАКА ССТОЗОСЛАСТОВОСАКАСТ САСАССТСТОВОСАКАССТ ТОСАССТОВОСАКАСТОВОСАКАССТ ТОСАСТОВОСАКАСТОВОСАКАССТ САСАССТОСАСАСАСАСТОСАСОССАС САСССАСАСАСАСАСТОСАСОССАС САСССАССАСАСАСАССАССАСССАССС САСССАСС	$\begin{array}{c} \mu - \mu \\ \mu - \gamma_3 \\ \mu - \gamma_3 \\ \mu - \gamma_3 \\ \gamma_3 1 - \gamma_3 \\ \mu - \gamma_1 \\ \gamma_1 - \gamma_1 \\ \mu - \gamma_1 \\ \mu - \gamma_2 \\ \mu - \gamma_1 \\ \mu - \gamma_2 \\ \mu - \gamma_2 \\ \gamma_1 - \gamma_1 \\ \gamma_1 - \varepsilon \\ \gamma_2 \\ \gamma_2 \\ \gamma_2 \\ \gamma_2 \\ \gamma_2 \\ \gamma_2 \\ - \varepsilon \end{array}$	/311 Th Th 6/395 Th 4/1092 Th Th Th Th Th Th 7/97	25 25 19 26 19 26 15 pub. 15 pub. 15 pub. 15 pub. 15 pub. 15 pub. 15 pub. 15 pub. 15 pub. 27 26 19 15 pub. 15 pub. 28 4 7 26	128. Hybri 129. 130. Humar 138. 139. 140. 141. 142. 144. 145. 144. 145. 144. 145. 144. 145. 150. 151. 152. 153. 154. 155.	MoPc104E domas (ir 9.9.2.1 9.7.1) switches SKS251 2C10 2C4 SKS252 SKS271 SKS274 SKS274 SKS274 SKS275 SKS278 SKS282 SKS285 SKS285 SKS286 SKS288 SKS288	TGCAGTCGACTCTAGAGA TGCAGTCGACTCTAGAGAGA TGCAGTCGACTCTAAGGCCTCTA GAAAGAAGAAGTAAATGCTCCC GACAGGCGAGCTAACCTGGGC GGCAGGGCGAGCTAACCTGGGC GGCAGGGCGGGGTCAGCTGGGT ACTGAGTTCTGCTGGGATGAGT ACTGAGTTCTGCTGGGTGGAT ACTGAGTCTGCTGGGTCAGCT GGCCTGACCTGGGTCAGCTGG GTATTACCTGCTGGGTTAGGCTA TGGGCGAACTGGTCAGCTGG GCCTAACCGGGTCAGCTGG ACCTAGCTAACCGGGTCAGCTG ACCTAACCTGGGTCAGCTGG CCCAACCGGCTCAGCTGGGTCAGCTG GGCCAACCGGACTGAGCTGG	AGCAAACACCTAAAACAGGA AGCAGCTGAGCTGGGACAGATGG AGAGCTGAGCT	α?-c-my μ-γ2a γ2b-γ2a μ-μ μ-γ μ-γ μ-ε μ-ε μ-ε μ-ε μ-ε μ-ε μ-ε μ-ε	2/71 1/27 1/22 3/34 1/23 1/25 1/23 3/61	42 48 37 37 39 40 39 40 39 39 39 39 39 39 39 39 39 39 39 39 39

Each sequence is assigned a number (left most column) for purposes of reference; the numbers of the acceptor and donor sequence are the same for the same recombination site. Each sequence is named by the cell line from which it was obtained or by the name of the corresponding molecular clone. 'R' indicates the reciprocal product of recombination (*i. e.*, a deletion circle). Germline sequences are presented; bp which are changed in the actual recombination site are underlined. Sequences that do not fill up the space are those for which the germline sequence is not available. The breakpoint in the sequence represents the 5'-most recombination site; bp which could be assigned to either the acceptor or donor sequences are italicized. The nature of the recombinations' column indicate the number of discrepancies as compared to the germline sequence/number of bp examined. For most recombination events, this data is not available. The sequence of the inserted bp, which are designated by 'ins.', are not shown. References for germline sequences: $S\mu$ (2, 52); $S\gamma3$ (6, 25); $S\gamma1$ (49); $S\gamma2b$ (5); $S\gamma2a$ (7); $S\epsilon$ (50, 51) and $S\alpha$ (4, 17, 31, 34). Sequences 78, 79, 81, 86, 87, 88, 89, and 91 are presented for the first time in this publication. DNA clones containing rearranged Se sequences were isolated from IgE-producing hybridomas 71–3B 12.1 (called 3B12, ref. 50, a gift from Ann Feeney), IGEL b4 (ref. 53, ATCC # TIB141), SE 1.3 (ATCC # HB137), and DNP- ϵ -26.82 (called 26.82, ref. 54, a gift from Fu-Tong Lui). Size selected *Eco*RI fragments were isolated and cloned into the vector gZAP (Stratagene). Subclones in Bluescript were sequenced by the dideoxy method (55). Germline $S\gamma2a$ sequences were obtained from the plasmid pS $\gamma2a$ -1, a gift of Ken Marcu.

MOPC21. The MOPC21 $S\mu S\gamma 1$ recombination site has been cloned from various cell lines three times with no change in sequence at the recombination site (3, 26, 57). Similarly, identical S α -c-myc sites from the J558 myeloma have been sequenced twice (35, 47). Finally, there are many examples of independently derived hybridomas from a single mouse that share somatic mutations in the VH or VL regions. These hybridomas must have been derived from sister B cells which arose from antigen driven expansion of a single B cell. These hybridomas almost always share one or more recombined switch regions of identical size, as determined by a Southern blot (58-62). Thus, secondary rearrangements of these switch regions did not occur during the expansion of the B cell clone in vivo, nor during the expansion of the hybridoma in vitro. Therefore, we see no compelling reason to suspect that either myeloma or hybridoma recombination sites are more likely to be derived from secondary rearrangements than are sites derived from other sources.

CHARACTERISTICS OF SWITCH RECOMBINATION SITES

Switch recombination occurs within the tandemly repeated sequences; $S\mu$ is a noteworthy exception

With a few exceptions, all of the recombination sites within S_{γ} , S_{ϵ} , and S_{α} regions occur within the tandemly repeated elements (Table 2). Recombination sites are found throughout the tandemly repeated elements, at the 5'end, middle, and 3' end of the switch region.

Recombination sites within $S\mu$ do not always fall within the tandemly repeated elements. About 40% of $S\mu$ recombinations fall outside of the tandemly repeated sequences; most of those are 5' of $S\mu$. $S\mu$ recombination sites from different sources are similar in this regard. For example, 15 of 25 B cell and hybridoma recombination sites are outside of the tandem repeats and 9 of 14 myeloma sites are outside of the $S\mu$ tandem repeats.

Table 2. Murine switch recombination sites within or outside of tandemly repeated sequences

	Within $S\mu$ repeats	Outside $S\mu$ repeats	Within Sγ,Sα,Sε repeats	Outside $S\gamma$, $S\alpha$, $S\epsilon$ repeats
All murine sequences	57*	35	119	14**
Deleted circles	30	2	46	3

*Number of recombination sites in the indicated sequences.

**Of these 14, seven are recombinations to the $\gamma 2a$ gene. Three of the 119 recombinations within the $S\gamma$, $S\alpha$, or $S\epsilon$ repeats are to the $\gamma 2a$ gene.



Figure 1. Location of murine recombination sites within the switch region consensus tandem repeat. Murine switch region recombination sites, with numbers corresponding to those in Table 1, are located on the various consensus sequences (determined from all the available sequence information) for the tandemly repeated elements found in Sy3 (25), Sy1 (49), Sy2b (5), Sy2a (7), and S α (31). The 5' end of each tandem repeat is arbitrarily defined; any bp position could have been designated the 5' end. For sites with uncertainty in the point of recombination due to sharing of bp between the donor and acceptor switch regions, the 5' most site is indicated. Nineteen sites could not be placed due to poor similarity with the consensus sequence. Eleven were S α recombinations that occurred within the common pentamer elements associated with S α , but the arrangement of these pentamers does not fit the reported consensus sequence. Six of the sites that could not be placed were recombinations to the S γ 2a gene.

Switch recombination sites from deleted circles show a more skewed distribution; almost all $S\mu$ recombination sites fall within the tandemly repeated sequences (Table 2). This might mean that switch recombination naturally favors the tandemly repeated sequences of $S\mu$ and that the deleted circles reflect the natural event better than do hybridoma, lymphoma, or myeloma data. However, the skewed distribution might also reflect the choice of restriction fragments and bacteriophage vectors used to clone these recombination sites. Phage λ has a very strong preference for optimum size of its DNA (63). There might be strong selection against inserts with recombination sites 5' of $S\mu$; these inserts would be as much as 6 kb larger than those with recombination sites in the tandemly repeated sequences. This problem is illustrated by the more unusual results obtained by cloning of $S\mu S\alpha$ switches via XbaI sites into gZapII (17). These cloned inserts have recombination sites, not in the tandemly repeated sequences, but 3' of S μ (and in the 5' end of S α). It is not clear

Table 3. Sharing of base pairs between donor and acceptor sequences at switch region recombination sites

none:41(59)*	1 bp:27(29)	2 bp:15(11)	
3 bp:5(3.6)	>3 bp:16(1.6)	• • •	

*Number of recombination sites for which the indicated number of bp are shared by the donor and acceptor sequences at the site of recombination. This is also the number of italicized bp in Table 1. Shown in parentheses is the number of sequences that would share, by chance, the indicated number of bp. This was estimated by multiplying the probability of sharing the indicated number of bp (and not more or less) by the total number of sequences (104) by the number of ways to share the indicated number of bp given a defined recombination site. For sharing of 2 bp, the estimate is $3/4 \times 1/4 \times 1/4 \times 3/4 \times 104 \times 3$. That is, there are 3 ways to share 2 bp (1/4 chance of sharing one bp), but not share the adjacent bp (3/4 chance of two bp being different). The 3 ways are: the two bp 5' to the recombination site, the two bp on either side of the recombination site, and the two bp 3' of the recombination site.

whether these small inserts arose because switch recombination in B cells favored these parts of the S regions or because this vector is designed to accomodate relatively small inserts (64).

One must consider the possibility that switch recombination in $S\mu$ might be different than switch recombination in other switch regions. The important role of chromatin configuration and accessibility in the regulation of switch recombination has been established by several different results (reviewed in 12-14). Among the heavy chain genes, μ is unique in that it has a very strong enhancer at its 5' end. Perhaps the intronic immunoglobulin enhancer plays a role in directing switch recombinase to the 5' end of $S\mu$.

Switch recombination occurs throughout the unit tandem repeat

By locating recombination sites on a consensus tandem repeat, one can pose a second question: Is any part of the consensus tandem repeat used preferentially in recombination? There are more sites found in one half of the tandemly repeated element compared to the other half. (Figure 1—In this Figure more recombination sites are found in the left half than in the right half of the tandemly repeated elements. The start and end of the repeated unit are defined arbitrarily; more sites could be found in the middle or right end, depending on where one chose to 'begin' the element. It is important to note that the four S_γ elements are aligned, by allowing one bp gaps, to one another.) However, sites in the right-hand end of the consensus element are used, and it is possible that recombination is random with respect to position within the tandemly repeated elements.

Switch recombination sites frequently lack donor-acceptor homology

At those recombination sites for which both donor and acceptor sequences are known, 39% share no bp, and an additional 25% have a single bp shared between donor and acceptor sequences at the recombination site (Table 3). Furthermore, if homologous pairing were important in switch recombination, recombination would have occurred with the tandemly repeated elements from the donor and acceptor S regions lined up 'in register' so that the homology between the elements would be maximized. Recombination would then occur between (for example) bp 23 of the donor tandem repeat and bp 24 of the acceptor tandem repeat. In most S_{γ} - S_{γ} recombination sites studied (sequences 32, 54, 64, 83, 84, 85, 110 in Table 1), recombination occurred between disparate bp of the donor and acceptor tandemly repeated between disparate bp of the donor and acceptor tandemly repeated between disparate bp of the donor and acceptor tandemly repeated between disparate bp of the donor and acceptor tandemly repeated between disparate bp of the donor and acceptor tandemly repeated between disparate bp of the donor and acceptor tandemly repeated between tandemly repeated between disparate bp of the donor and acceptor tandemly repeated between disparate bp of the donor and acceptor tandemly repeated between disparate bp of the donor and acceptor tandemly repeated between tandeml



Figure 2. Computer assisted search for a switch recombination site consensus sequence. **A.** Information content of each residue 1–75 for aligned donor sequences from B cells and hybridomas. The sequence data used in this analysis extended beyond that shown in Table 1. **B.** Information content for the same sequences as in Part A., but after allowing up to 5 bp slippage. **C.** Information content for myeloma and lymphoma acceptor sequences, allowing up to 5 bp slippage. **D.** The sequences in B were randomized and then aligned as in B to optimize information content. **E.** The distribution of bp at positions 30-53 for the alignment graphed in B. The formula for information content is $\Sigma_{i=AGCT} f_i \log_2 f_i / p_i$, in which f_i is the observed frequency for base *i* at the indicated postion and p_i is the prior probability for base *i*. We used the bp composition of the subset of sequences being analyzed as the 'prior distribution'. In addition, we adjusted the information content for sample size by subtracting the average information expected from random sequences having the data using different subsets, S_{μ} and non- S_{μ} . We also aligned subject the recombination of the recombination content, but the motifs identified were once again those that are prevalent in S regions. The motifs in the latter analysis were also placed randomly relative to switch recombination sites.

elements. Recombination occurred at homologous positions in the donor and acceptor tandem repeats in only two $S\gamma S\gamma$ sites (sequences 55 and 56—Figure 1).

Switch recombination sites are often associated with mutations

Mutations are found in some recombined switch regions. This was recognized when two products of a single switch recombination event were isolated (22). The two products differed by several single bp changes, even though the $S\mu S\alpha$ recombination sites were identical for both products. Subsequent analysis revealed that, in the $S\mu$ sequences, one product had all the mutations, the other had none (63). In the compilation of switch recombination sites (Table 1), there are many recombined S sequences with mutations relative to the germline. Importantly, in a series of $S\gamma S\epsilon$ recombination sites (sequences 87, 88, 89, 91), the $S\gamma$ sequences are always mutated, whereas the $S\epsilon$ sequences are not. Other switch recombination sites demonstrate this characteristic of mutations on one side of the recombination site, but not the other.

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Table 4. Putative recognition sequences at switch recombination sites

Sites with GAGCT or	
GGGGT	60
Sites with YAGGTTG	39
Neither	67

Switch region recombination sites were scored as having a GAGCT or GGGGT pentamer if there was a 4 out of 5 match to either pentamer in the recombination site or immediately next to it. Sites were scored as having a YAGGTTG motif if there was a 5 out of 7 match within 3 bp of the site. This is a different criteria than originally proposed (32). Using the original criteria (4 out of 7 match, 7-14 bp 5' of the recombination site), 126 sites score as having a YAGGTTG motif. The two motifs suggested by Wuerffel and colleagues (66) for switch recombination to c3 were also evaluated. For 13 Sc3 sites, the best fit was to the motif CAGC-TCTGGGGAGC; the mean identity was 9 bp, with a range of 5 to 11 bp. For the other 9 Sc3 sites, the best fit was to the motif GGGGACTAACC; the mean identity was 5 bp, with a range of 3 to 9 bp.

Switch recombination sites sometimes include bp that cannot be derived directly from either germline S region. Insertions of one to 33 bp have been observed (Table 1). The larger insertions usually have some similarity to S region sequences. For example, the NB32 recombination site (sequence 64) includes 22 bp which are very similar to $S\gamma 2b$ sequences, but are not identical to any cloned $S\gamma 2b$ sequences inserted into this switch recombination retrovirus.

Switch recombination does not necessarily follow transcriptional polarity

There are several examples of S-S recombination in which one of the S regions is inverted. For example, in the recombined switch region in 300-18 cells, $S\mu$ is joined to a segment of $S\gamma 2b$ which is inverted. A second recombination site is found a few hundred bp downstream, where the inverted $S\gamma 2b$ is joined to $S\gamma 2b$ which is in the same orientation as the $C\gamma 2b$ gene (sequences 50 and 54).

Switch recombination may involve multiple sites within a single switch region

Recombined S regions often have internal deletions in either the donor or acceptor S regions. This implies an internal switch recombination event between two sites in a single S region. Similarly, a few S regions include duplications, which must also result from the use of at least two recombination sites.

Switch recombination sites lack a consensus sequence

After the first few switch recombination sites had been sequenced, it was apparent that switch recombination was not a site specific recombination event akin to V-D-J joining (12-13). The wellconserved sequences used in V-D-J joining are not found at switch recombination sites. This is not surprising, as the two recombination events occur at different developmental stages and at different DNA locations. The lack of V-D-J recombination signals at switch recombination sites does not rule out a role of some of the enzymes involved in V-D-J joining; it does argue against those involved in sequence recognition.

Various short motifs have been suggested as recognition sequences in switch recombination (7, 26, 32, 66). Some of the proposed motifs are prevalent in S regions. Nevertheless, about 25% of switch recombination sites lack stringent similarity to any of the proposed motifs (Table 4). To determine if switch recombination is mediated by a more subtle recognition sequence, we aligned germline sequences, using the switch recombination



Figure 3. An illegitimate priming model for switch recombination. A. S_D and S_A designate the donor and acceptor S regions, respectively. Newly synthesized DNA, including mutations, is noted by a dotted line. Base pairing at sites of priming for DNA synthesis are noted by bold vertical lines. The region with 'Xs' symbolizes repair of the mismatched region at the recombination site. Formation of deletion circles would be accomplished by the symetrical reaction using the remaining two 3' ends. **B.** The template switching model for switch recombination. Symbols used are the same. The vertical line indicates the recombination site. Note that this model predicts that recombined sequences with mutations will have mutations on both side of the recombination site. See text for further explanation.

sites shown in Table 1, for those B cell and hybridoma sequences for which the germline sequence was known. The information content, a measure of the divergence from a prior (random) distribution of bp, of each position in the alignment was determined (67). A high information content at a particular position means that the bp composition at that position is nonrandom. No significant information was detected in the sequence alignments for either the donor or the acceptor sequences from B cells and hybridomas (Figure 2A—the recombination site is between residues 32 and 33). The information content was consistent with what would be observed with random sequences being arbitrarily aligned (68).

We next tested whether small shifts in the alignments might identify a peak of information. We aligned the sequences for optimal information, allowing up to 5 bp of sliding (67). The resulting alignments (Figure 2B) had significantly more information than the alignments that did not allow sliding. There appeared to be a clustering of information in the region just 3' of the recombination sites (which vary from residue 28 to 39), particularly in the donor sequences. A notable feature of the cluster of information is that it is based on the motif G/A A/G G C T, the common pentamer found frequently in S μ , S α , and Se and less often in the four Sys. Since GAGCT, or variants of it, are found so often in switch regions, one might expect that this motif would arise in this analysis, even if it had little to do with sequence recognition in the switch recombination. Also arguing against a role for this cluster of information in switch recombinase recognition is the fact that clusters of information that arose from the analysis of other data subsets (for example,

the acceptor sequences for myelomas and lymphomas, Figure 2C) were less dramatic and located differently relative to the recombination site. To summarize, we were able to derive some interesting sequence motifs by information content analysis (including other analyses described in the Legend to Figure 2), but the characteristics of those motifs prevented a strong conclusion concerning their role in switch recombination.

AN ILLEGITIMATE PRIMING MODEL FOR SWITCH RECOMBINATION

To account for the duplications and mutations found in some recombined switch regions, it has been proposed that DNA synthesis plays a role in switch recombination (22). At least two mechanisms have been considered-template switching and illegitimate priming (65). If the switch were accomplished by template switching from donor to acceptor S region, this would imply that either both S regions or neither S region would harbor mutations (Fig. 3B). On the other hand, illegitimate priming by one S region for error-prone DNA synthesis on the other S region would predict mutations on only one side of the recombination site, the S region that was synthesized (Fig. 3A). The other side (the primer S region) would lack mutations, since it is formed from pre-existing DNA. The available data favor an illegitimate priming mechanism (see above).

To accomplish switch recombination for both strands of DNA, a reciprocal reaction must also occur (Figure 3). Since there is no a priori reason to suspect that the two priming reactions would occur exactly opposite one another, a bubble of two single strands, with many mismatches, would be found at the recombination site (Fig. 3A). This bubble might be repaired using one strand or the other as a template, resulting in an apparent recombination site with bp shared between the donor and acceptor switch regions. These shared bp represent the short sequence identity needed for the priming reaction. Alternatively, repair might occur from both ends of the bubble, which could lead to a apparent recombination site with no shared bp. Finally, repair could be more or less random, leading to a recombination site with several 'inserted' or mutated bp. The fact that the number of inserted bp is usually small suggests that the bubble region must be likewise small.

The compilation of sequences at switch region recombination sites is available from W.A.D. in printed form (Table 1) or on diskette. Investigators are encouraged to send corrections or additions to the compilation to W.A.D.

ACKNOWLEDGEMENTS

The authors thank Dr Michael Savageau for careful reading of the manuscript and the many workers in switch recombination for their helpful discussions. Work in the authors laboratories was supported by grants from the National Institutes of Health (CA34068 to W.A.D., HG00249 to Gary Stormo, and AI25086 to C.G.)

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