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(72) Inventeurs/Inventors:
GAIGER, ALEXANDER, AT;
ALGATE, PAUL A., US;
MANNION, JANE, US;
CLAPPER, JONATHAN DAVID, US;
WANG, AIJUN, US;
ORDONEZ, NADIA, US;

...

(73) Propriétaire/Owner:

(54) Titre : COMPOSITIONS ET METHODES DE DETECTION, DE DIAGNOSTIC ET DE TRAITEMENT DES
MALIGNITES HEMATOLOGIQUES
(54) Title: COMPOSITIONS AND METHODS FOR THE DETECTION, DIAGNOSIS AND THERAPY OF
HEMATOLOGICAL MALIGNANCIES

(57) **Abrégé/Abstract:**

Disclosed are methods and compositions for the detection, diagnosis, prognosis, and therapy of hematological malignancies, and in particular, B cell leukemias, lymphomas and multiple myelomas. Disclosed are compositions, methods and kits for eliciting immune and T cell responses to specific malignancy-related antigenic polypeptides and antigenic polypeptide fragments thereof in an animal. Also disclosed are compositions and methods for use in the identification of cells and biological samples containing one or more hematological malignancy-related compositions, and methods for the detection and diagnosis of such diseases and affected cell types. Also disclosed are diagnostic and therapeutic kits, as well as methods for the diagnosis, therapy and/or prevention of a variety of leukemias and lymphomas.

(72) Inventeurs(suite)/Inventors(continued): CARTER, LAUREN, US; MCNEILL, PATRICIA DIANNE, US

(73) Propriétaires(suite)/Owners(continued):CORIXA CORPORATION, US

(74) Agent: GOWLING WLG (CANADA) LLP

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Declarations under Rule 4.17:

- *as to applicant's entitlement to apply for and be granted a patent (Rule 4.17(ii)) for the following designations AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, UZ, VC, VN, YU, ZA, ZM, ZW, ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, SI, SK, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG)*
- *as to the applicant's entitlement to claim the priority of the earlier application (Rule 4.17(iii)) for all designations*
- *of inventorship (Rule 4.17(iv)) for US only*

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(71) Applicant (*for all designated States except US*): **CORIXA CORPORATION** [US/US]; 1124 Columbia Street, Suite 200, Seattle, WA 98104 (US).

(72) Inventors; and

(75) Inventors/Applicants (*for US only*): **GAIGER, Alexander** [AT/AT]; Doeblinger Hauptstrasse 62/14, A-1190 Vienna (AT). **ALGATE, Paul, A.** [GB/US]; 580 Kalmia Place, NW, Issaquah, WA 98027 (US). **MANNION, Jane** [US/US]; 8904 192nd Street, SW, Edmonds, WA 98026 (US). **CLAPPER, Jonathan, David** [US/US]; 2149 Dexter Avenue, North, #4, Seattle, WA 98109 (US). **WANG, Aijun** [CN/US]; 3106 - 213th Place, SE, Issaquah, WA 98029 (US). **ORDONEZ, Nadia** [US/US]; 2011 No. 154 Court, Seattle, WA 98133 (US). **CARTER, Lauren** [US/US]; 7143 Beach Drive, SW, Seattle, WA 98136 (US). **MCNEILL, Patricia, Dianne** [US/US]; 1333 South - 290th Place, Federal Way, WA 98003 (US).

(74) Agents: **FANG, Carol, A.** et al.; Townsend and Townsend and Crew LLP, Two Embarcadero Center, Eighth Floor, San Francisco, CA 94111 (US).

(81) Designated States (*national*): AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH,

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

(54) Title: COMPOSITIONS AND METHODS FOR THE DETECTION, DIAGNOSIS AND THERAPY OF HEMATOLOGICAL MALIGNANCIES

(57) Abstract: Disclosed are methods and compositions for the detection, diagnosis, prognosis, and therapy of hematological malignancies, and in particular, B cell leukemias, lymphomas and multiple myelomas. Disclosed are compositions, methods and kits for eliciting immune and T cell responses to specific malignancy-related antigenic polypeptides and antigenic polypeptide fragments thereof in an animal. Also disclosed are compositions and methods for use in the identification of cells and biological samples containing one or more hematological malignancy-related compositions, and methods for the detection and diagnosis of such diseases and affected cell types. Also disclosed are diagnostic and therapeutic kits, as well as methods for the diagnosis, therapy and/or prevention of a variety of leukemias and lymphomas.

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WHAT IS CLAIMED IS:

1. Use of an isolated monoclonal antibody that specifically binds to a polypeptide comprising the sequence set forth in SEQ ID NO: 4 in the manufacture of a medicament for treatment of a hematological malignancy in a mammalian subject, wherein the hematological malignancy is chronic lymphocytic leukemia or multiple myeloma.
2. Use of an isolated monoclonal antibody that specifically binds to a polypeptide comprising the sequence set forth in SEQ ID NO: 4 for treatment of a hematological malignancy in a mammalian subject, wherein the hematological malignancy is chronic lymphocytic leukemia or multiple myeloma.
3. The use according to claim 1 or 2, wherein the hematological malignancy is associated with overexpression of the polypeptide comprising in the sequence set forth in SEQ ID NO: 4.
4. The use of any one of claims 1 to 3, wherein said antibody is a humanized antibody.
5. The use of any one of claims 1 to 3, wherein said antibody is a chimeric antibody.
6. The use of any one of claims 1 to 3, wherein said antibody is a Fab fragment.
7. The use of any one of claims 1 to 3, wherein said antibody is a Fv fragment.
8. The use of any one of claims 1 to 3, wherein said antibody is a scFv.
9. The use of any one of claims 1 to 8, wherein said antibody further comprises a therapeutic moiety.
10. The use of claim 9, wherein the therapeutic moiety is radionuclide.
11. The use of claim 10, wherein the radionuclide is a member selected from the group consisting of: ^{90}Y , ^{123}I , ^{125}I , ^{131}I , ^{186}Re , ^{111}At , and ^{212}Bi .
12. The use of any one of claims 1 to 11, wherein the mammalian subject is a human.
13. The use of any one of claims 1 to 11, wherein the antibody is for intravenous use.

Outline of Microarray Chip Technology approach

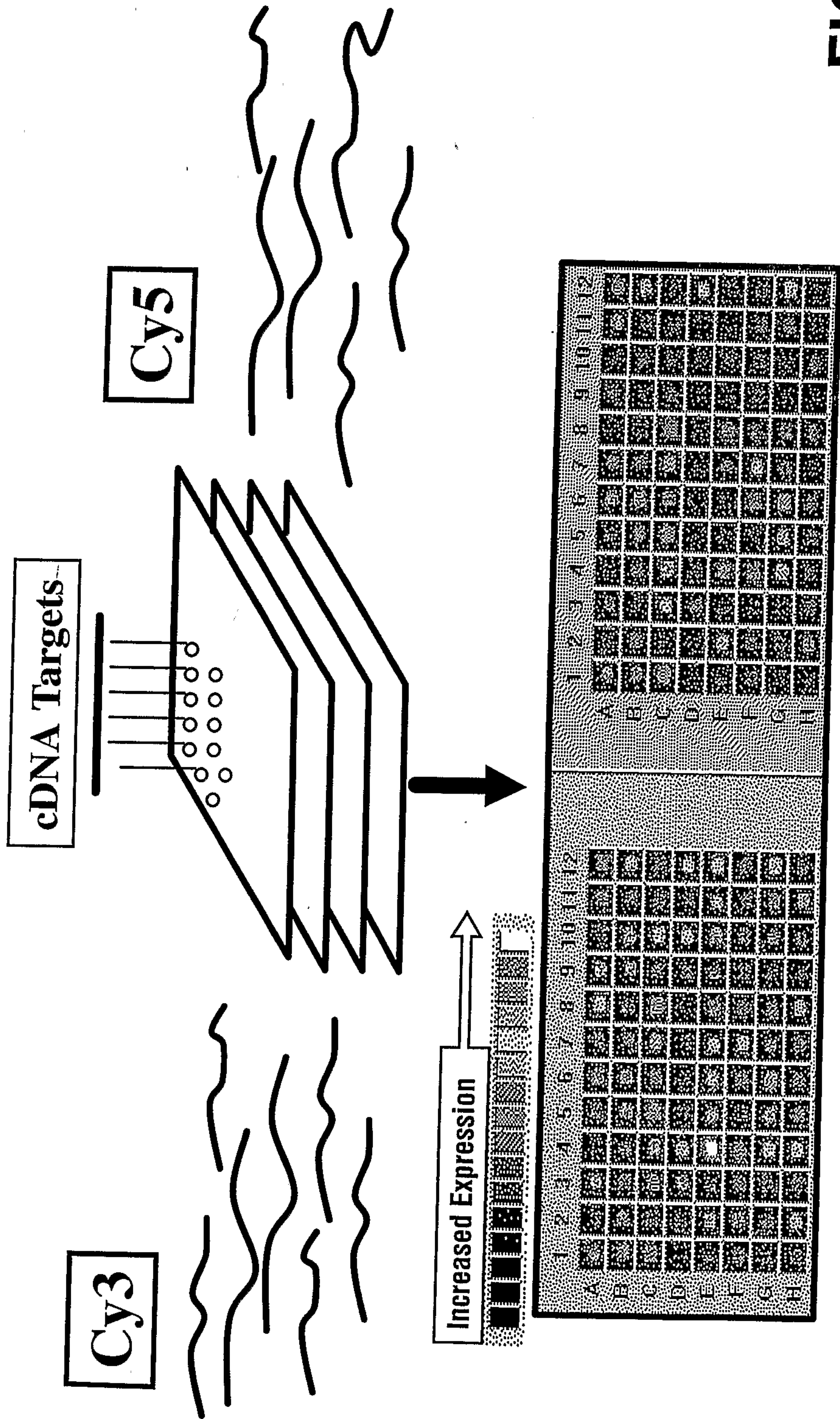


FIG. 1

General protocol for *in-vitro* whole gene CD8 T cell priming

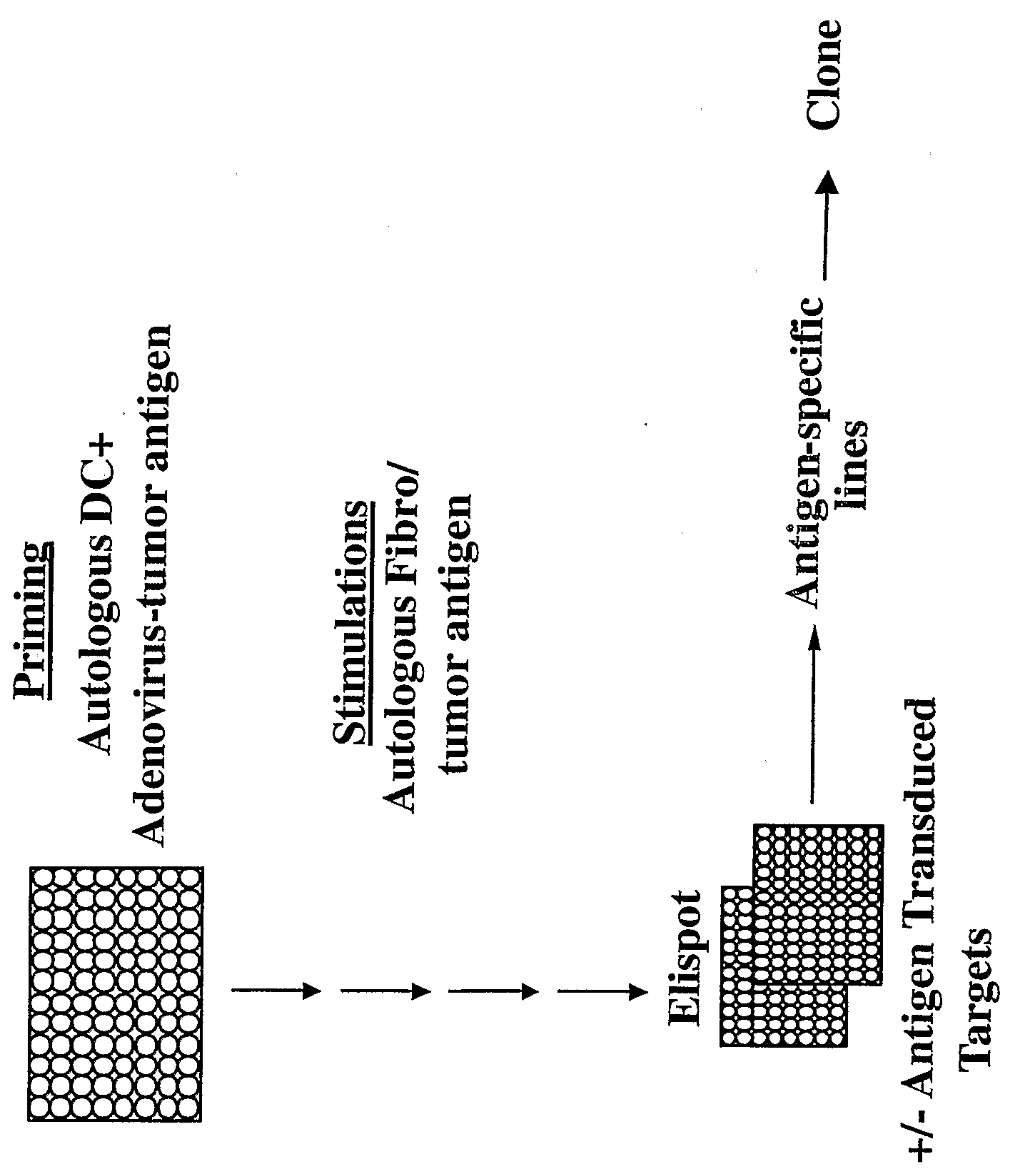


FIG. 2

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General protocol for *in-vitro* whole gene CD4 T cell priming

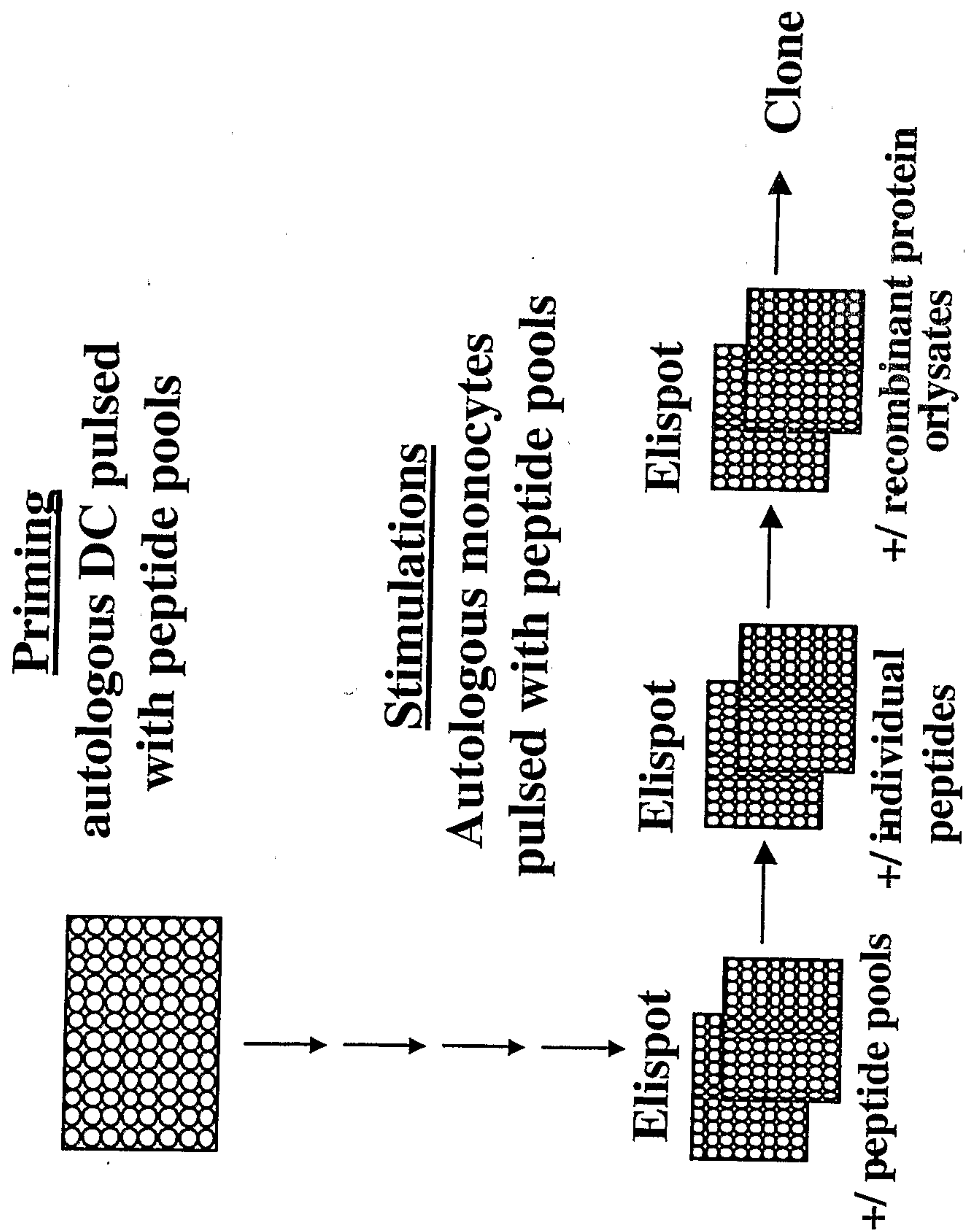


FIG. 3

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LEUKEMIA/LYMPHOMA CHIP #3: PROBES USED IN ANALYSIS

Cy3 Probe		Cy5 Probe	
Tissue	RNA#	RNA#	Tissue
Lymphoma, T cell	952	SPACT74	Kidney N
Lymphoma, B cell	955	SPACT81	Liver N
Lymphoma, B cell	953	SPACT78	Lung N
Lymphoma	916	SPACT42	Brain N
Lymphoma, Hodgkins	950	138598B	Skin N
Lymphoma, Hodgkins	950	SPACT49	Bone Marrow N
Lymphoma, B cell	CL151	888	PBMC resting
Lymphoma, T cell	904B	SPACT55	Stomach N
Lymphoma, Hodgkins see RNA 959	CL153	SPACT70	Thymus N
Lymphoma, B cell	CL152	SPACT75	Skeletal Muscle N
Lymphoma, B cell see RNA 958	CL155	SPACT73	Heart N
Lymphoma, B cell	944	243502B	Esophagus N
Lymphoma, B cell	958	1006	Colon N
Lymphoma, B cell	954	SPACT65	Small Intestine N
Lymphoma	960	779B	Trachea N
Lymphoma, T cell	957	S9327328	Bladder N
Lymphoma, B cell	914B		
Lymphoma, B cell	913		
Lymphoma, B cell	944B		
Lymphoma, B cell/failed	903		

GREEN: Tumor probes where gene expression would be desired.
RED: Normal essential tissue probes where gene expression is to be avoided.
BLACK: Normal tissue probes where gene expression is acceptable.

FIG. 4**AMENDED SHEET**

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Hematology Therapeutic Ab Candidates

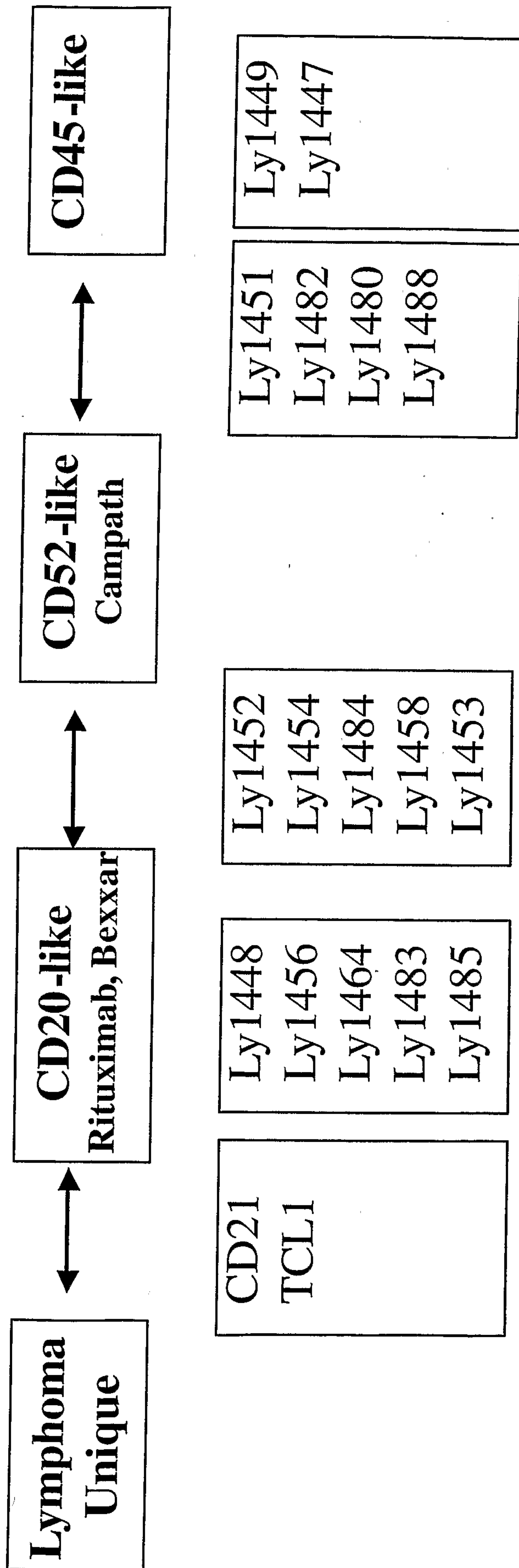


FIG. 5

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a. TMpred Report for Ly1484 Long

RDFQSEVLLSAMELFHMTSGGDAAMFRDGKEPQPSAEAAAAPSLANISCF
 TQKLVEKLYSGMFSADPRHILLFILEHIMVVIE TASSQORDTVLSTLYSSL
 NKVILYCLSKPQOSLSECLGLLSILGFLQEHWDVVFAT YNSNISFLLCLM
 HCLLLLNERSYPEGFGLEPKPRMSTYHQVFLSPNEDVKEKREDLP SLSDV
 QHNIQKTVQTLWQQLVAQRQQTLEDAFKIDLSVKPGEREVKIEEVTPLWE
 ETMLKAWQHYLASEKKSLASRSNVAHHSKVTLWSGSLSSAMKLMGRQAK
 DPECKTEDFVSCIENYRRRGQELYASLYKDHVQRRKCGNIKAANAWARIQ
 EQLFGELGLWSQGEETKPCSPWELDWREGPARMRKRIKRLSPLEALSSGR
 HKESQDKNDHISQTNAENQDELTLREAEGEREDEVGVDC TQLTFFPALHES
 LHSEDFLELCRERQVILQELL DKEKVTQKFSLVIVQGHVSEGVLLFGHQ
 HFYICENFELSPTGDIVYCTRHCLSNISDPFIFNLCSKDRSTDHYSQCHS
 YADMRELROARFLLQDIALEIFFHNGYSKFLV FYNNDRSKAFKSFCFQF
 SLKGKATSEDTLNLRRYPGSDRIMLQKWQKRD ISNFEYLMYLN TAAGRTC
 NDYMQYPVFPWVLADYTSETLNLANPKIFRDLSKPMGAQTKERKLKFIQR
 FKEVEKTEGDMTVQCHYYTHYSSAIIVASYLVRMPPTQAF CALQ GGSFD
 VADRMFHSVKSTWESASRENMSDVRELTP EFFYLPEFLTNCNGVEFGCMQ
 DQTVLGDVQLPPWADGDPRKFTSLHRKALESDFVSANLHHWIDLIFGYKQ
 QCPAAVDVNIHFHPYFYCDRMDLSSITDPLIKSTILGFVS NFGQV PKOLF
 TKPHPARTAAACKPLPGKDVSTPVSLPGHPQPFYSLQSLRPSQVTVKDMY
 LFSLCSESPKCAIGHIVSTEKTILAVERNKVLLPPLWNRTFSWGFDDFSC
 CLGSYGSDKVLMEFENLAANGRC LCAVCPSPTTIVTSCTSTVVCVWELSM
 TKGRPRGLRLRQALYCHTQAVTCLAASVTFSLLVSGSODCTCILWDL DHL
 THVTRLPAHREGISAITISDVSGTIVSCAGAHLSLWNVNGOPLASITTAW
 GPEGAITCCCLMECPAWDTSQIITIGSODGMVRVWKTEDVKMSVPGRPAG
 EEPLAQPPSPRGHKWEKNLALSREL DVSIALTGKPSKTS PAVTALAVSRN
 HTEKLLVGDERGRIFCWSADG (SEQ ID NO: 120)

Black = INTRACELLULAR, Red = TRANSMEMBRANE,
 Blue = EXTRACELLULAR

Ly1484 Long has 1269 amino acids and 5
 Transmembrane Domains

Transmembrane Domain 1:	63 - 84	Score: 1.36675
Transmembrane Domain 2:	118 - 139	Score: 1.38695
Transmembrane Domain 3:	480 - 501	Score: 1.36185
Transmembrane Domain 4:	562 - 583	Score: 1.31785
Transmembrane Domain 5:	725 - 746	Score: 1.3521

FIG. 6

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b. TMpred Report for Ly1484 (short)

MLQKWQKRDI SNFEYLMYLNTAAGRTCNDYMQYPVFPWVLADYTSETLNL
ANPKIFRDLSKPMGAQTKERKLKFI QRFKEVEKTEGDMTVQCHYYTHYSS
AIIVASYLVRMP PFTQAF CALQ GGSFDVADRMFHSVKSTWESASRENMSD
VRELTP EFFYLPEFLNCNCEVEFCMODGTVLGDVQLPPWADGDPRKFIS
LHRKALESDFVSANLHHWIDLIFCYKQOGPAAVDAVNIFHPYFYGDRMDL
SSITDPLIKSTILGFVSNFCQVPKOLF TKPHPARTAAGKPLPGKDVSTPV
SLPCHPOPFYSLQSLRPSQVTVKDMYLFSLGSESPKGAIGHIVSTEKTI
LAVERNKVLLPPLWNRTFSWGFDDFSCCLGSYGSDKVLMEFFENLAAWGRC
LCAVCPSPFTTIVTSGTSTVVCWELSMTEKGRPRGLRLROALYCHTQAVTC
LAASVTFSLLVSGSODCTCILWDLDHLLHVTRLPAHREGISAITISDVSG
TIVSCAGAHLSLWNVNGOPLASITTAWGPEGAITCCCLMEGPAWDTSQII
ITGSQDCMVRVWKTEDVKMSVPCRPAGEEPLAQPPSPRGHKWEKNLALSR
ELDVSTIALTGKPSKTS PAVTALAVSRNHKLLVGDERGRIFCWSADG

(SEQ ID NO: 121)

Black = INTRACELLULAR, Red = TRANSMEMBRANE,
Blue = EXTRACELLULAR

Ly1484 has 646 amino acids and 1 Transmembrane
Domains

Transmembrane Domain 1: 102 - 123 Score: 1.3521

FIG. 6 (cont.)

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ANALYSIS RESULTS OF THE PROGRAM TSITES.

These are the results of the analysis of the file--> LY1484~1.TXT
Beginning with residue: 1 and ending with residue: 1270
AMPHI Window size: 11

A-AMPHI mid points of blocks.
R-Residues matching the Rothbard/Taylor motif.
D-Residues matching the IAd motif.
d-Residues matching the IEd motif.

(SEQ ID NO: 120)

5	10	15	20	25	30	35	40	45	50	55	60	65	70	75
RDFQSEVLLS	AMELFHMT	SGGDAAM	FRDGE	QPSAE	AAAP	SLANIS	CF	TQKL	VEKLY	SGMFS	ADPR	HILL	FIL	
.....	AAAAA					AAAA	AAA		AAAA	AAAA	AAAA	AAAA	AAAA	
RRRRR	RRRRRR							RRRRR	RRRRRR	RRRR	RRRR	RRRR	RRRR	
.....						DDDDDD								
.....														
80	85	90	95	100	105	110	115	120	125	130	135	140	145	150
EHIMVVI	TASSQ	RD	TVL	STLY	SSLN	KVIL	YCL	SKP	QQL	SECL	GLLS	ILG	FLQ	EHWD
.....			AAAA	AAAA	AAAA	AAAA	AAAA	AAAA	AAAA	AAAA	AAAA	AAAA	AAAA	AAAA
RRRR	RRRR	RRRR	RRRR	RRRR	RRRR	RRRR	RRRR	RRRR	RRRR	RRRR	RRRR	RRRR	RRRR	RRRR
DDDDDD	DDDDDD	DDDDDD	DDDDDD	DDDDDD	DDDDDD	DDDDDD	DDDDDD	DDDDDD	DDDDDD	DDDDDD	DDDDDD	DDDDDD	DDDDDD	DDDDDD
.....														

FIG. 7

PEANUS

AMENDED SHEET

```

155 160 165 170 175 180 185 190 195 200 205 210 215 220 225
HCLLLNERSYPEGFGLEPKPRMSTYHQVFLSPNEDVKEKREDLPSLDVQHNIQKTVQTLWQQLVAQRQQTLED
.....AAAAA.AAAAAA.AAAAAA.....
.....RRRR.....R
.....
230 235 240 245 250 255 260 265 270 275 280 285 290 295 300
AFKIDL SVKPGEREVKIEEVTPLWEETMLKAWQHYLASEKKSLASRSNVAAHHSKVTLWSGSLSSAMKILMPGRQAK
.....AAAAA.AAAAAA.....AAAAA
RRR.....RRRRRRRRRR.....RRRR
.....
.....ddd
305 310 315 320 325 330 335 340 345 350 355 360 365 370 375
DPECKTEDFVSCIENYRRRGQELYASLYKDHVQRRKCGNIKAANAWARIQEQLFGELGLWSQGEETKPCSPWELD
AAAAAA.....AAAAA
.....RRRR.....RRRR
.....
.....
380 385 390 395 400 405 410 415 420 425 430 435 440 445 450
WREGPARMRKRIKRLSPLEALSSGRHKESQDKNDHISQTNQDELTLREAEGEPDEVGVDCTQLTFFPALHES
AAAAAA.AAAAAA.AAAAAA.....RRRR
.....RRRR
.....DDDDDD
.....ddd

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FIG. 7 (cont.)

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[illegible]

FIG. 7 (cont.)

AMENDED SHEET

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..... DDDDDDDDDDD
..... ddd
755 760 765 770 775 780 785 790 795 800 805 810 815 820 825
VADRMFHSVKSTWESASRENMSDVRELTPEFFYLPEFLTNCNGVEFGCMQDGTVLGDVQLPPWADGDPKRFISLH
AAAAAAAAAAAA.AA.AAAA.AAAAAA
RRRRRRR.....RRRRR.....RRRRR.....RRRRR.....RRRRR.....RRRRR.....
.....
.....
830 835 840 845 850 855 860 865 870 875 880 885 890 895 900
RKALESDFVSANLHHWIDLIFGYKQQGPAAVDVNIHFPYFYGDRMDLSSITDPLIKSTILGFVSNFGQVPKQLF
.....AAAAAAAAA.....AAAAAAAAAAAA
RRRRR.RRRR.....RRRRR.....RRRRR.....RRRRR.....RRRRR.....RRRRR.....
.....
.....
.....
905 910 915 920 925 930 935 940 945 950 955 960 965 970 975
TKPHPARTAAGKPLPGKDVSTPVSILPGHPQFFYSLQSLRPSQVTVKDMYLFSLGSESPKGAIGHIVSTEKTILA
.....AAAAAAAAA
RRRRR.....RRRRR.....RRRRR.....RRRRR.....RRRRR.....RRRRR.....
DDDDDD.....DDDDDD.....DDDDDD.....DDDDDD.....DDDDDD.....DDDDDD.....
.....

FIG. 7 (cont.)

IPEANUS

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980 985 990 995 1000 1000 1010 1015 1020 1025 1030 1030 1040 1045 1050  
VERNKVLLPPLWNRTFSWGFDFFSCCLGSYGSDKVLMTTFENLAAWGRCCLCAVCPSPTTIVTSGTSTVVCVWELSM  
. . . . .AAAAA  
. . . . .RRRR.  
. . . . .  
. . . . .DDDDDDDDDD.  
. . . . .DDD  
  
1055 1060 1065 1070 1075 1080 1085 1090 1095 1100 1105 1110 1115 1120 1125  
TKGRPRGLRLRQALYGHTQAVTCLAASVTFSLLVSGSQDCTCILWDHLTHVTRLPAHREGISAITISDVSGTI  
. . . . .AAAAA  
. . . . .RRRRRR.  
DDD. . . . .DDDDDDDDDD.  
. dddddd  
. . . . .DDDDDD. . DDDDD  
  
1130 1135 1140 1145 1150 1155 1160 1165 1170 1175 1180 1185 1190 1195 1200  
VSCAGAHLSLWNVNGQPLASITTAWGPBGAITCCCLMEGPAWDTSQIIITGSQDGMVRVWKTEDVKMSVPGRPAG  
A. . . . .AAA.  
RR. . . . .RRRR.  
D. . . . .DDDDDD  
. . . . .DDDDDD. . DDDDD  
  
1205 1210 1215 1220 1225 1230 1235 1240 1245 1250 1255 1260 1265 1270 1275  
EEPLAQPPSPRGHKWEKNLALSRELDVSIALTGKPSKTSPAVTALAVSRNHTKLLVGDERGRIFCWSADG  
. . . . .  
. . . . .RRRR.  
. . . . .DDDDDD. . DDDDD  
. . . . .
```

FIG. 7 (cont.)

8. G. F.

These are the results of the analysis of the file--> LY1484~2.TXT
Beginning with residue: 1 and ending with residue: 647
AMPHI Window size: 11

A-AMPHI mid points of blocks.
 R-Residues matching the Rothbard/Taylor motif.
 D-Residues matching the IAd motif.
 d-Residues matching the IEd motif.

(SEQ ID NO: 121)

[illegible]

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FIG. 8 (cont.)

PCT/US03/02353.14082003

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530 535 540 545 550 555 560 565 570 575 580 585 590 595 600
AWGPEGAITCCCLMEGPAWDTSQIIITGSQDGMVRVWKTEDVKMSVPGRPAGEEPLAQPPSPRGHKWEKNLALSR
.....AAAAAAA
RRRRR.....RRRRR.....
D.....DDDDDD.....DDDDDD.....
.....
605 610 615 620 625 630 635 640 645 650 655 660 665 670 675
ELDVSIALTGKPSKTSPAVALAVSRNHTKLLVGDERGRIFCWSADG
.....RRRRR.....
DDDDDDDDDD.....ddddd.....
.....

FIG. 8 (cont.)