

US 20080095776A1

(19) United States (12) Patent Application Publication (10) Pub. No.: US 2008/0095776 A1 **DEVRIES** et al.

Apr. 24, 2008 (43) **Pub. Date:**

(54) ERYTHROPOIETIN RECEPTOR BINDING ANTIBODIES

(75) Inventors: Peter J. DEVRIES, Des Plaines, IL (US); David H. OSTROW, Lake Zurich, IL (US); Edward B. REILLY, Libertyville, IL (US); Larry L. GREEN, San Francisco, CA (US); James WEILER, Beverly, MA (US)

> Correspondence Address: DYKEMA GOSSETT PLLC 10 S. WACKER DR., STE. 2300 CHICAGO, IL 60606 (US)

- (73) Assignee: ABBOTT LABORATORIES, Abbott Park, IL (US)
- (21) Appl. No.: 11/834,122
- (22) Filed: Aug. 6, 2007

Related U.S. Application Data

(63) Continuation of application No. 10/684,109, filed on Oct. 10, 2003.

(60) Provisional application No. 60/418,031, filed on Oct. 14, 2002.

Publication Classification

(51)	Int. Cl.	
	A61K 39/40	(2006.01)
	A61P 43/00	(2006.01)
	C07H 21/04	(2006.01)
	C07K 16/00	(2006.01)
(52)	U.S. Cl	424/137.1 ; 530/300; 530/387.9;
		536/22.1

(57)ABSTRACT

The present invention relates to antibodies and antibody fragments thereof that bind to and activate an erythropoietin receptor. The present invention also relates to methods of modulating the endogenous activity of an erythropoietin receptor in a mammal using said antibodies as well as pharmaceutical compositions containing said antibodies.

801	MetlysHisleuTrp ATGAAGCATCTGTG TACTTCGTAGACAC
851	·PhePheLeuLeuLeuValAlaAlaProArgTrpValLeuSerGlnValGln GTTCTTCCTTCTCCTAGTGGCAGCTCCCAGATGGGTCCTGTCCCAGGTGC CAAGAAGGAAGAGGATCACCGTCGAGGGTCTACCCAGGACAGGGTCCACG
901	••LeuGlnGluSerGlyProGlyLeuValLysProSerGluThrLeuSer AGCTGCAGGAGTCGGGCCCAGGACTGGTGAAGCCTTCGGAGACCCTGTCC TCGACGTCCTCAGCCCGGGTCCTGACCACTTCGGAAGCCTCTGGGACAGG
951	LeuThrCysThrValSerGlyAlaSerIleSerSerTyrTyrTrpSerTrp CTCACCTGCACTGTCTCTGGTGCCTCCATCAGTAGTTACTACTGGAGCTG GAGTGGACGTGACAGAGACCACGGAGGTAGTCATCAATGATGACCTCGAC
1001	·IleArgGlnProProGlyLysGlyLeuGluTrpIleGlyTyrIleTyrTyr GATCCGGCAGCCCCCAGGGAAGGGACTGGAGTGGATTGGGTATATCTATT CTAGGCCGTCGGGGGTCCCTTCCCT
1051	••SerGlySerThrAsnTyrAsnProSerLeuLysSerArgValThrIle ACAGTGGGAGCACCAACTACAACCCCTCCCTCAAGAGTCGAGTCACCATA TGTCACCCTCGTGGTTGATGTTGGGGAGGGAGTTCTCAGCTCAGTGGTAT
1101	SerValAspThrSerLysAsnGlnPheSerLeuLysLeuArgSerValThr TCAGTAGACACGTCCAAGAACCAGTTCTCCCTGAAGCTGAGGTCTGTGAC AGTCATCTGTGCAGGTTCTTGGTCAAGAGGGACTTCGACTCCAGACACTG
1151	•AlaAlaAspThrAlaValTyrTyrCysAlaArgGluArgLeuGlyIleGly CGCTGCGGACACGGCCGTGTATTACTGTGCGAGAGAGCGACTGGGGATCG GCGACGCCTGTGCCCGGCACATAATGACACGCTCTCTCGCTGACCCCTAGC
1201	••AspTyrTrpGlyGlnGlyThrLeuValThrValSerSerAlaSerThr GGGACTACTGGGGCCAAGGAACCCTGGTCACCGTCTCCTCAGCCTCCACC CCCTGATGACCCCGGTTCCTTGGGACCAGTGGCAGAGGAGTCGGAGGTGG
1251	LysG1yProSerVa1PheProLeuAlaProCysSerArgSerThrSerG1u AAGGGCCCATCGGTCTTCCCCCTGGCGCCCTGC <u>TCTAGA</u> AGCACCTCCGA TTCCCGGGTAGCCAGAAGGGGGACCGCGGACGAGATCTTCGTGGAGGCT
1301	 SerThrAlaAlaLeuGlyCysLeuValLysAspTyrPheProGluProVal GAGCACAGCCGCCCTGGGCTGCCTGGTCAAGGACTACTTCCCCGAACCGG CTCGTGTCGGCGGGGACCCGACCGACCAGTTCCTGATGAAGGGGCTTGGCC

801	MetLysHisLeuTrp ATGAAGCATCTGTG TACTTCGTAGACAC
851	 PhePheLeuLeuValAlaAlaProArgTrpValLeuSerGlnValGln GTTCTTCCTTCTCCTAGTGGCAGCTCCCAGATGGGTCCTGTCCCAGGTGC CAAGAAGGAAGAGGATCACCGTCGAGGGTCTACCCAGGACAGGGTCCACG
901	<pre>LeuGlnGluSerGlyProGlyLeuValLysProSerGluThrLeuSer AGCTGCAGGAGTCGGGGCCCAGGACTGGTGAAGCCTTCGGAGACCCTGTCC TCGACGTCCTCAGCCCGGGTCCTGACCACTTCGGAAGCCTCTGGGACAGG</pre>
951	LeuThrCysThrValSerGlyAlaSerIleSerSerTyrTyrTrpSerTrp CTCACCTGCACTGTCTCTGGTGCCTCCATCAGTAGTTACTACTGGAGCTG GAGTGGACGTGACAGAGACCACGGAGGTAGTCATCAATGATGACCTCGAC
1001	·IleArgGlnProProGlyLysGlyLeuGluTrpIleGlyTyrIleTyrTyr GATCCGGCAGCCCCCAGGGAAGGGACTGGAGTGGATTGGGTATATCTATT CTAGGCCGTCGGGGGTCCCTTCCCT
1051	••SerGlySerThrAsnTyrAsnProSerLeuLysSerArgValThrIle ACAGTGGGAGCACCAACTACAACCCCTCCCTCAAGAGTCGAGTCACCATA TGTCACCCTCGTGGTTGATGTTGGGGAGGGAGTTCTCAGCTCAGTGGTAT
1101	SerValAspThrSerLysAsnGlnPheSerLeuLysLeuArgSerValThr TCAGTAGACACGTCCAAGAACCAGTTCTCCCTGAAGCTGAGGTCTGTGAC AGTCATCTGTGCAGGTTCTTGGTCAAGAGGGACTTCGACTCCAGACACTG
1151	 AlaAlaAspThrAlaValTyrTyrCysAlaArgGluArgLeuGlyIleGly CGCTGCGGACACGGCCGTGTATTACTGTGCGAGAGAGCGACTGGGGATCG GCGACGCCTGTGCCGGCACATAATGACACGCTCTCTCGCTGACCCCTAGC
1201	••AspTyrTrpGlyGlnGlyThrLeuValThrValSerSerAlaSerThr GGGACTACTGGGGCCAAGGAACCCTGGTCACCGTCTCCTCAGCCTCCACC CCCTGATGACCCCGGTTCCTTGGGACCAGTGGCAGAGGAGTCGGAGGTGG
1251	LysGlyProSerValPheProLeuAlaProCysSerArgSerThrSerGlu AAGGGCCCATCGGTCTTCCCCCTGGCGCCCTGC <u>TCTAGA</u> AGCACCTCCGA TTCCCGGGTAGCCAGAAGGGGGGACCGCGGGACGAGATCTTCGTGGAGGCT
1301	 SerThrAlaAlaLeuGlyCysLeuValLysAspTyrPheProGluProVal GAGCACAGCCGCCCTGGGCTGCCTGGTCAAGGACTACTTCCCCGAACCGG CTCGTGTCGGCGGGGACCCGACGGACCAGTTCCTGATGAAGGGGCTTGGCC

1351	<pre>・・ThrValSerTrpAsnSerGlyAlaLeuThrSerGlyValHisThrPhe TGACGGTGTCGTGGAACTCAGGCGCTCTGACCAGCGGCGTGCACACCTTC ACTGCCACAGCACCTTGAGTCCGCGAGACTGGTCGCCGCACGTGTGGAAG</pre>
1401	ProAlaValLeuGlnSerSerGlyLeuTyrSerLeuSerSerValValThr CCAGCTGTCCTACAGTCCTCAGGACTCTACTCCCTCAGCAGCGTGGTGAC GGTCGACAGGATGTCAGGAGTCCTGAGATGAGGGAGTCGTCGCACCACTG
1451	•ValProSerSerAsnPheGlyThrGlnThrTyrThrCysAsnValAspHis CGTGCCCTCCAGCAACTTCGGCACCCAGACCTACACCTGCAACGTAGATC GCACGGGAGGTCGTTGAAGCCGTGGGTCTGGATGTGGACGTTGCATCTAG
1501	••LysProSerAsnThrLysValAspLysThrVal ACAAGCCCAGCAACACCAAGGTGGACAAGACAGTTGGTGAGAGGGCCAGCT TGTTCGGGTCGTTGTGGTTCCACCTGTTCTGTCAACCACTCTCCGGTCGA
1551	CAGGGAGGGAGGGTGTCTGCTGGAAGCCAGGCTCAGCCCTCCTGCCTG
1601	CGCACCCCGGCTGTGCAGCCCAGCCCAGGGCAGCAAGGCAGGC
1651	TGTCTCCTCACCCGGAGGCCTCTGCCCGCCCCACTCATGCTCAGGGAGAG ACAGAGGAGTGGGCCTCCGGAGACGGGCGGGGGTGAGTACGAGTCCCTCTC
17 01	GGTCTTCTGGCTTTTTCCACCAGGCTCCAGGCAGGCACAGGCTGGGTGCC CCAGAAGACCGAAAAAGGTGGTCCGAGGTCCGTCCGTGTCCGACCCACGG
1751	CCTACCCCAGGCCCTTCACACAGGGGGCAGGTGCTTGGCTCAGACCTGC GGATGGGGTCCGGGAAGTGTGTGTCCCCGTCCACGAACCGAGTCTGGACG
1801	CAAAAGCCATATCCGGGAGGACCCTGCCCCTGACCTAAGCCGACCCCAAA GTTTTCGGTATAGGCCCTCCTGGGACGGGGACTGGATTCGGCTGGGGTTT
1851	GGCCAAACTGTCCACTCCCTCAGCTCGGACACCTTCTCTCCCCCAGATC CCGGTTTGACAGGTGAGGGAGTCGAGCCTGTGGAAGAGAGGGGGGGTCTAG
1901	GluArgLysCysCysValGluCys CGAGTAACTCCCCAATCTTCTCTGCAGAGCGCAAATGTTGTGTCGAGTG GCTCATTGAGGGTTAGAAGAGAGAGACGTCTCGCGTTTACAACACAGCTCAC
1951	•ProProCysPro CCCACCGTGCCCAGGTAAGCCAGCCCAGGCCTCGCCCTCCAGCTCAAGGC GGGTGGCACGGGTCCATTCGGTCGGGTCCGGAGCGGGAGGTCGAGTTCCG
2001	GGGACAGGTGCCCTAGAGTAGCCTGCATCCAGGGACAGGCCCCAGCTGGG CCCTGTCCACGGGATCTCATCGGACGTAGGTCCCTGTCCGGGGTCGACCC

2051	AlaProProValAlaGlyPro TGCTGACACGTCCACCTCCATCTTCCTCAGCACCACCTGTGGCAGGAC ACGACTGTGCAGGTGGAGGTAGAGAAGGAGTCGTGGTGGACACCGTCCTG
2101	••SerValPheLeuPheProProLysProLysAspThrLeuMetIleSer CGTCAGTCTTCCTCTTCCCCCCAAAACCCAAGGACACCCTCATGATCTCC GCAGTCAGAAGGAGAAGGGGGGGTTTTGGGTTCCTGTGGGAGTACTAGAGG
2151	ArgThrProGluValThrCysValValValAspValSerHisGluAspPro CGGACCCCTGAGGTCACGTGCGTGGTGGTGGACGTGAGCCACGAAGACCC GCCTGGGGACTCCAGTGCACGCACCACCACCTGCACTCGGTGCTTCTGGG
2201	•GluValGlnPheAsnTrpTyrValAspGlyValGluValHisAsnAlaLys CGAGGTCCAGTTCAACTGGTACGTGGACGGCGTGGAGGTGCATAATGCCA GCTCCAGGTCAAGTTGACCATGCACCTGCCGCACCTCCACGTATTACGGT
2251	••ThrLysProArgGluGluGlnPheAsnSerThrPheArgValValSer AGACAAAGCCACGGGAGGAGCAGTTCAACAGCACGTTCCGTGTGGTCAGC TCTGTTTCGGTGCCCTCCTCGTCAAGTTGTCGTGCAAGGCACACCAGTCG
2301	ValLeuThrValValHisGlnAspTrpLeuAsnGlyLysGluTyrLysCys GTCCTCACCGTTGTGCACCAGGACTGGCTGAACGGCAAGGAGTACAAGTG CAGGAGTGGCAACACGTGGTCCTGACCGACTTGCCGTTCCTCATGTTCAC
2351	 LysValSerAsnLysGlyLeuProAlaProIleGluLysThrIleSerLys CAAGGTCTCCCAACAAAGGCCTCCCAGCCCCCATCGAGAAAACCATCTCCA GTTCCAGAGGTTGTTTCCGGAGGGTCGGGGGTAGCTCTTTTGGTAGAGGT
2401	••ThrLys AAACCAAAGGTGGGACCCGCGGGGTATGAGGGCCACATGGACAGAGGCCG TTTGGTTTCCACCCTGGGCGCCCCATACTCCCGGTGTACCTGTCTCCGGC
2451	GCTCGGCCCACCCTCTGCCCTGGGAGTGACCGCTGTGCCAACCTCTGTCC CGAGCCGGGTGGGAGACGGGACCCTCACTGGCGACACGGTTGGAGACAGG
2501	GlyGlnProArgGluProGlnValTyrThrLeuProProSerArg CTACAGGGCAGCCCCGAGAACCACAGGTGTACACCCTGCCCCCATCCCGG GATGTCCCGTCGGGGCTCTTGGTGTCCACATGTGGGACGGGGGTAGGGCC
2551	GluGluMetThrLysAsnGlnValSerLeuThrCysLeuValLysGlyPhe GAGGAGATGACCAAGAACCAGGTCAGCCTGACCTGCCTGGTCAAAGGCTT CTCCTCTACTGGTTCTTGGTCCAGTCGGACTGGACGGACCAGTTTCCGAA
2601	•TyrProSerAspIleAlaValGluTrpGluSerAsnGlyGlnProGluAsn CTACCCCAGCGACATCGCCGTGGAGTGGGAGAGCAATGGGCAGCCGGAGA GATGGGGTCGCTGTAGCGGCACCTCACCCTCTCGTTACCCGTCGGCCTCT

2651	··AsnTyrLysThrThrProProMetLeuAspSerAspGlySerPhePhe ACAACTACAAGACCACACCTCCCATGCTGGACTCCGACGGCTCCTTCTTC TGTTGATGTTCTGGTGTGGAGGGGTACGACCTGAGGCTGCCGAGGAAGAAG
2701	LeuTyrSerLysLeuThrValAspLysSerArgTrpGlnGlnGlyAsnVal CTCTACAGCAAGCTCACCGTGGACAAGAGCAGGTGGCAGCAGGGGAACGT GAGATGTCGTTCGAGTGGCACCTGTTCTCGTCCACCGTCGTCCCCTTGCA
2751	 PheSerCysSerValMetHisGluAlaLeuHisAsnHisTyrThrGlnLys CTTCTCATGCTCCGTGATGCATGAGGCTCTGCACAACCACTACACGCAGA GAAGAGTACGAGGCACTACGTACTCCGAGACGTGTTGGTGATGTGCGTCT
2801	··SerLeuSerLeuSerProGlyLys AGAGCCTCTCCCTGTCTCCGGGTAAA

TCTCGGAGAGGGGACAGAGGCCCATTT

.

FIGURE 2

901	MetArgValProAlaGlnLeuLeuGlyLeuLeuLeuLeuTrp ATGAGGGTCCCCGCTCAGCTCCTGGGGCTCCTGCTGCTCT TACTCCCAGGGGCGAGTCGAGGACCCCGAGGACGACGAGA
951	•••PheProGlyAlaArgCysLysLeuAspIleGlnLeuThrGlnSerPro GGTTCCCAGGTGCCAGGTGTAAGCTTGACATCCAGCTGACCCAATCTCCA CCAAGGGTCCACGGTCCACATTCGAACTGTAGGTCGACTGGGTTAGAGGT
1001	SerSerLeuSerAlaSerValGlyAspArgValThrIleThrCysArgAla TCCTCCCTGTCTGCATCTGTAGGAGACAGAGTCACCATCACTTGCCGGGC AGGAGGGACAGACGTAGACATCCTCTGTCTCAGTGGTAGTGAACGGCCCG
1051	 SerGlnGlyIleArgAsnAspLeuGlyTrpTyrGlnGlnLysProGlyLys AAGTCAGGGCATTAGAAATGATTTAGGCTGGTATCAGCAGAAACCAGGGA TTCAGTCCCGTAATCTTTACTAAATCCGACCATAGTCGTCTTTGGTCCCT
1101	··AlaProLysArgLeuIleTyrAlaAlaSerSerLeuGlnSerGlyVal AAGCCCCTAAGCGCCTGATCTATGCTGCATCCAGTTTGCAAAGTGGGGTC TTCGGGGATTCGCGGACTAGATACGACGTAGGTCAAACGTTTCACCCCAG
1151	ProSerArgPheSerGlySerGlySerGlyThrGluPheThrLeuThrIle CCATCAAGGTTCAGCGGCAGTGGATCTGGGACAGAATTCACTCTCACAAT GGTAGTTCCAAGTCGCCGTCACCTAGACCCTGTCTTAAGTGAGAGTGTTA
1201	•SerSerLeuGlnProGluAspPheAlaThrTyrTyrCysLeuGlnHisAsn CAGCAGCCTGCAGCCTGAAGATTTTGCAACTTATTACTGTCTACAGCATA GTCGTCGGACGTCGGACTTCTAAAACGTTGAATAATGACAGATGTCGTAT
1251	··ThrTyrProProThrPheGlyGlnGlyThrLysValGluIleLysArg ATACTTACCCTCCGACGTTCGGCCAAGGGACCAAGGTGGAAATCAAACGA TATGAATGGGAGGCTGCAAGCCGGTTCCCTGGTTCCACCTTTAGTTTGCT
1301	ThrValAlaAlaProSerValPheIlePheProProSerAspGluGlnLeu ACTGTGGCTGCACCATCTGTCTTCATCTTCCCGCCATCTGATGAGCAGTT TGACACCGACGTGGTAGACAGAAGTAGAAGGGCGGTAGACTACTCGTCAA
1351	 LysSerGlyThrAlaSerValValCysLeuLeuAsnAsnPheTyrProArg GAAATCTGGAACTGCTAGCGTTGTGTGCCTGCTGAATAACTTCTATCCCA CTTTAGACCTTGACGATCGCAACACACGGACGACTTATTGAAGATAGGGT
1401	··GluAlaLysValGlnTrpLysValAspAsnAlaLeuGlnSerGlyAsn GAGAGGCCAAAGTACAGTGGAAGGTGGATAACGCCCTCCAATCGGGTAAC CTCTCCGGTTTCATGTCACCTTCCACCTATTGCGGGAGGTTAGCCCATTG

SerGlnGluSer 1451 TCCCAGGAGAGT AGGGTCCTCTCA

801	MetGluLeuGlyLeu ATGGAATTGGGGCT TACCTTAACCCCGA
851	•ArgTrpValPheLeuValAlaLeuLeuArgGlyValGlnCysGlnValGln CCGCTGGGTTTTCCTCGTTGCTCTTTTAAGAGGTGTCCAGTGTCAGGTGC GGCGACCCAAAAGGAGCAACGAGAAAATTCTCCACAGGTCACAGTCCACG
901	··LeuValGluSerGlyGlyGlyValValGlnProGlyArgSerLeuArg AGCTGGTGGAGTCTGGGGGGAGGCGTGGTCCAGCCTGGGAGGTCCCTGAGA TCGACCACCTCAGACCCCCTCCGCACCAGGTCGGACCCTCCAGGGACTCT
951	LeuSerCysValAlaSerGlyPheThrPheSerSerTyrGlyMetHisTrp CTCTCCTGTGTAGCCTCTGGATTCACCTTCAGTAGCTATGGCATGCACTG GAGAGGACACATCGGAGACCTAAGTGGAAGTCATCGATACCGTACGTGAC
1001	 ValArgGlnAlaProGlyLysGlyLeuGluTrpValAlaValIleSerTyr GGTCCGCCAGGCTCCAGGCAAGGGGCTGGAGTGGGTGGCAGTTATATCAT CCAGGCGGTCCGAGGTCCGTTCCCCGACCTCACCCACCGTCAATATAGTA
1051	··AspGlySerAsnLysTyrTyrAlaAspSerValLysGlyArgPheThr ATGATGGAAGTAATAAATACTATGCAGACTCCGTGAAGGGCCGATTCACC TACTACCTTCATTATTATGATACGTCTGAGGCACTTCCCGGCTAAGTGG
1101	IleSerArgAspAsnSerLysAsnThrLeuTyrLeuGlnMetAsnSerLeu ATCTCCAGAGACAATTCCAAGAACACGCTGTATCTGCAAATGAACAGCCT TAGAGGTCTCTGTTAAGGTTCTTGTGCGACATAGACGTTTACTTGTCGGA
1151	•ArgValGluAspThrAlaValTyrTyrCysAlaArgAspHisGlyGlyArg GAGAGTTGAGGACACGGCTGTGTATTACTGTGCGAGAGATCACGGTGGGA CTCTCAACTCCTGTGCCGACACATAATGACACGCTCTCTAGTGCCACCCT
1201	••TyrValTyrAspTyrGlyMetAspValTrpGlyGlnGlyThrThrVal GGTACGTCTACGACTACGGTATGGACGTCTGGGGCCAAGGGACCACGGTC CCATGCAGATGCTGATGCCATACCTGCAGACCCCGGTTCCCTGGTGCCAG
1251	ThrValSerSerAlaSerThrLysGlyProSerValPheProLeuAlaPro ACCGTCTCCTCAGCCTCCACCAAGGGCCCATCGGTCTTCCCCCTGGCGCC TGGCAGAGGAGTCGGAGGTGGTTCCCCGGGTAGCCAGAAGGGGGACCGCGG
1301	•CysSerArgSerThrSerGluSerThrAlaAlaLeuGlyCysLeuValLys CTGC <u>TCTAGA</u> AGCACCTCCGAGAGCACAGCCGCCCTGGGCTGCCTGGTCA GACGAGATCTTCGTGGAGGCTCTCGTGTCGGCGGGACCCGACGGACCAGT

1351	··AspTyrPheProGluProValThrValSerTrpAsnSerGlyAlaLeu AGGACTACTTCCCCGAACCGGTGACGGTGTCGTGGAACTCAGGCGCTCTG TCCTGATGAAGGGGCTTGGCCACTGCCACAGCACCTTGAGTCCGCGAGAC
1401	ThrSerGlyValHisThrPheProAlaValLeuGlnSerSerGlyLeuTyr ACCAGCGGCGTGCACACCTTCCCAGCTGTCCTACAGTCCTCAGGACTCTA TGGTCGCCGCACGTGTGGAAGGGTCGACAGGATGTCAGGAGTCCTGAGAT
1451	•SerLeuSerSerValValThrValProSerSerAsnPheGlyThrGlnThr CTCCCTCAGCAGCGTGGTGACCGTGCCCTCCAGCAACTTCGGCACCCAGA GAGGGAGTCGTCGCACCACTGGCACGGGAGGTCGTTGAAGCCGTGGGTCT
1501	•••TyrThrCysAsnValAspHisLysProSerAsnThrLysValAspLys CCTACACCTGCAACGTAGATCACAAGCCCAGCAACACCAAGGTGGACAAG GGATGTGGACGTTGCATCTAGTGTTCGGGTCGTTGTGGTTCCACCTGTTC
1551	ThrVal ACAGTTGGTGAGAGGCCAGCTCAGGGAGGGAGGGTGTCTGCTGGAAGCCA TGTCAACCACTCTCCGGTCGAGTCCCTCCCTCCCACAGACGACCTTCGGT
1601	GGCTCAGCCCTCCTGCCTGGACGCACCCCGGCTGTGCAGCCCCAGCCCAG CCGAGTCGGGAGGACGGACCTGCGTGGGGCCGACACGTCGGGGTCGGGTC
1651	GGCAGCAAGGCAGGCCCCATCTGTCTCCTCACCCGGAGGCCTCTGCCCGC CCGTCGTTCCGTCCGGGGTAGACAGAGGAGTGGGCCTCCGGAGACGGGCG
1701	CCCACTCATGCTCAGGGAGAGGGGTCTTCTGGCTTTTTCCACCAGGCTCCA GGGTGAGTACGAGTCCCTCTCCCAGAAGACCGAAAAAGGTGGTCCGAGGT
1751	GGCAGGCACAGGCTGGGTGCCCCTACCCCAGGCCCTTCACACACA
1801	AGGTGCTTGGCTCAGACCTGCCAAAAGCCATATCCGGGAGGACCCTGCCC TCCACGAACCGAGTCTGGACGGTTTTCGGTATAGGCCCTCCTGGGACGGG
1851	CTGACCTAAGCCGACCCCAAAGGCCAAACTGTCCACTCCCTCAGCTCGGA GACTGGATTCGGCTGGGGTTTCCGGTTTGACAGGTGAGGGAGTCGAGCCT
1901	Glu CACCTTCTCTCCCCAGATCCGAGTAACTCCCAATCTTCTCTCTGCAGA GTGGAAGAGAGGGGGGTCTAGGCTCATTGAGGGTTAGAAGAGAGACGTCT
1951	•ArgLysCysCysValGluCysProProCysPro GCGCAAATGTTGTGTCGAGTGCCCACCGTGCCCAGGTAAGCCAGCC

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2001	CCTCGCCCTCCAGCTCAAGGCGGGACAGGTGCCCTAGAGTAGCCTGCATC GGAGCGGGAGGTCGAGTTCCGCCCTGTCCACGGGATCTCATCGGACGTAG
2051	CAGGGACAGGCCCCAGCTGGGTGCTGACACGTCCACCTCCATCTCTTCCT GTCCCTGTCCGGGGTCGACCCACGACTGTGCAGGTGGAGGTAGAGAAGGA
2101	AlaProProValAlaGlyProSerValPheLeuPheProProLysPro CAGCACCACCTGTGGCAGGACCGTCAGTCTTCCTCTTCCCCCCCAAAACCC GTCGTGGTGGACACCGTCCTGGCAGTCAGAAGGAGAAGGGGGGGTTTTGGG
2151	LysAspThrLeuMetIleSerArgThrProGluValThrCysValValVal AAGGACACCCTCATGATCTCCCGGACCCCTGAGGTCACGTGCGTG
2201	 AspValSerHisGluAspProGluValGlnPheAsnTrpTyrValAspGly GGACGTGAGCCACGAAGACCCCCGAGGTCCAGTTCAACTGGTACGTGGACG CCTGCACTCGGTGCTTCTGGGGCTCCAGGTCAAGTTGACCATGCACCTGC
2251	••ValGluValHisAsnAlaLysThrLysProArgGluGluGlnPheAsn GCGTGGAGGTGCATAATGCCAAGACAAAGCCACGGGAGGAGCAGTTCAAC CGCACCTCCACGTATTACGGTTCTGTTTCGGTGCCCTCCTCGTCAAGTTG
2301	SerThrPheArgValValSerValLeuThrValValHisGlnAspTrpLeu AGCACGTTCCGTGTGGTCAGCGTCCTCACCGTTGTGCACCAGGACTGGCT TCGTGCAAGGCACACCAGTCGCAGGAGTGGCAACACGTGGTCCTGACCGA
2351	 AsnGlyLysGluTyrLysCysLysValSerAsnLysGlyLeuProAlaPro GAACGGCAAGGAGTACAAGTGCAAGGTCTCCAACAAAGGCCTCCCAGCCC CTTGCCGTTCCTCATGTTCACGTTCCAGAGGTTGTTTCCGGAGGGTCGGG
2401	<pre> ••IleGluLysThrIleSerLysThrLys CCATCGAGAAAACCATCTCCAAAACCAAAGGTGGGACCCGCGGGGTATGA GGTAGCTCTTTTGGTAGAGGTTTTGGTTTCCACCCTGGGCGCCCCATACT</pre>
2451	GGGCCACATGGACAGAGGCCGGCTCGGCCCACCCTCTGCCCTGGGAGTGA CCCGGTGTACCTGTCTCCGGCCGAGCCGGGTGGGAGACGGGACCCTCACT
2501	GlyGlnProArgGluProGlnVal CCGCTGTGCCAACCTCTGTCCCTACAGGGCAGCCCCGAGAACCACAGGTG GGCGACACGGTTGGAGACAGGGATGTCCCGTCGGGGGCTCTTGGTGTCCAC
2551	TyrThrLeuProProSerArgGluGluMetThrLysAsnGlnValSerLeu TACACCCTGCCCCCATCCCGGGAGGAGATGACCAAGAACCAGGTCAGCCT ATGTGGGACGGGGGTAGGGCCCTCCTCTACTGGTTCTTGGTCCAGTCGGA

2601	•ThrCysLeuValLysGlyPheTyrProSerAspIleAlaValGluTrpGlu GACCTGCCTGGTCAAAGGCTTCTACCCCAGCGACATCGCCGTGGAGTGGG CTGGACGGACCAGTTTCCGAAGATGGGGTCGCTGTAGCGGCACCTCACCC
2651	••SerAsnGlyGlnProGluAsnAsnTyrLysThrThrProProMetLeu AGAGCAATGGGCAGCCGGAGAACAACTACAAGACCACACCTCCCATGCTG TCTCGTTACCCGTCGGCCTCTTGTTGATGTTCTGGTGTGGAGGGTACGAC
2701	AspSerAspGlySerPhePheLeuTyrSerLysLeuThrValAspLysSer GACTCCGACGGCTCCTTCTTCCTCTACAGCAAGCTCACCGTGGACAAGAG CTGAGGCTGCCGAGGAAGAAGGAGATGTCGTTCGAGTGGCACCTGTTCTC
2751	 ArgTrpGlnGlnGlyAsnValPheSerCysSerValMetHisGluAlaLeu CAGGTGGCAGCAGGGGAACGTCTTCTCATGCTCCGTGATGCATGAGGCTC GTCCACCGTCGTCCCCTTGCAGAAGAGTACGAGGCACTACGTACTCCGAG
2801	••HisAsnHisTyrThrGlnLysSerLeuSerLeuSerProGlyLys TGCACAACCACTACACGCAGAAGAGCCTCTCCCTGTCTCCGGGTAAA ACGTGTTGGTGATGTGCGTCTTCTCGGAGAGGGACAGAGGCCCATTT

901	MetArgValProAlaGlnLeuLeuGlyLeuLeuLeuLeuTrpPhePro ATGAGGGTCCCCGCTCAGCTCCTGGGGCTCCTGCTGCTCTGGTTCC TACTCCCAGGGGCGAGTCGAGGACCCCGAGGACGACGAGACCAAGG
951	••GlySerArgCysAspIleGlnMetThrGlnSerProSerSerValSer CAGGTTCCAGATGCGACATCCAGATGACCCAATCTCCATCTTCCGTGTCT GTCCAAGGTCTACGCTGTAGGTCTACTGGGTTAGAGGTAGAAGGCACAGA
1001	AlaSerIleGlyAspArgValSerIleThrCysArgAlaSerGlnGlyIle GCATCTATAGGAGACAGAGTCTCCATCACTTGTCGGGCGAGTCAGGGTAT CGTAGATATCCTCTGTCTCAGAGGTAGTGAACAGCCCGCTCAGTCCCATA
1051	•SerSerTrpLeuAlaTrpTyrGlnGlnLysProGlyLysAlaProThrLeu TAGCAGCTGGTTAGCCTGGTATCAGCAGAAACCAGGGAAAGCCCCTACGC ATCGTCGACCAATCGGACCATAGTCGTCTTTGGTCCCTTTCGGGGATGCG
1101	<pre>••LeuIleTyrAlaAlaSerThrLeuGlnArgGlyValProSerArgPhe TCCTTATCTATGCTGCATCCACTTTGCAACGTGGGGTCCCATCAAGGTTC AGGAATAGATACGACGTAGGTGGAAACGTTGCACCCCAGGGTAGTTCCAAG</pre>
1151	SerGlySerGlySerGlyThrAspPheThrLeuThrIleSerSerLeuGln AGCGGCAGTGGATCTGGGACAGATTTCACTCTCACCATCAGCAGCCTGCA TCGCCGTCACCTAGACCCTGTCTAAAGTGAGAGTGGTAGTCGTCGGACGT
1201	 ProGluAspPheAlaThrTyrPheCysGlnGlnAlaAsnSerPheProPhe GCCTGAAGATTTTGCAACTTACTTTTGTCAACAGGCTAACAGTTTCCCAT CGGACTTCTAAAACGTTGAATGAAAACAGTTGTCCGATTGTCAAAGGGTA
1251	••ThrPheGlyProGlyThrLysValAspIleLysArgThrValAlaAla TCACTTTCGGCCCTGGGACCAAAGTGGATATCAAACGAACTGTGGCTGCA AGTGAAAGCCGGGACCCTGGTTTCACCTATAGTTTGCTTGACACCGACGT
1301	ProSerValPheIlePheProProSerAspGluGlnLeuLysSerGlyThr CCATCTGTCTTCATCTTCCCGCCATCTGATGAGCAGTTGAAATCTGGAAC GGTAGACAGAAGTAGAAGGGCGGTAGACTACTCGTCAACTTTAGACCTTG
1351	•AlaSerValValCysLeuLeuAsnAsnPheTyrProArgGluAlaLysVal T <u>GCTAGC</u> GTTGTGTGCCTGCTGAATAACTTCTATCCCAGAGAGGGCCAAAG ACGATCGCAACACACGGACGACTTATTGAAGATAGGGTCTCTCCGGTTTC
1401	••GlnTrpLysValAspAsnAlaLeuGlnSerGlyAsnSerGlnGluSer TACAGTGGAAGGTGGATAACGCCCTCCAATCGGGTAACTCCCAGGAGAGT ATGTCACCTTCCACCTATTGCGGGAGGTTAGCCCATTGAGGGTCCTCTCA

ValThrGluGlnAspSerLysAspSerThrTyrSerLeuSerSerThrLeu 1451 GTCACAGAGCAGGACAGCAAGGACAGCACCTACAGCCTCAGCAGCACCCT CAGTGTCTCGTCCTGTCGTCGTGGGATGTCGGAGTCGTCGTGGGA

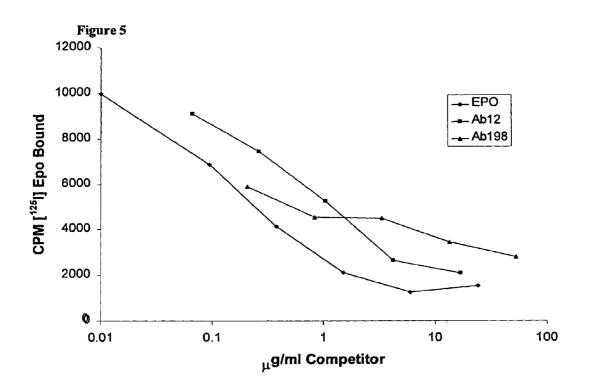
•ThrLeuSerLysAlaAspTyrGluLysHisLysValTyrAlaCysGluVal 1501 GACGCTGAGCAAAGCAGACTACGAGAAACACAAAGTCTACGCCTGCGAAG CTGCGACTCGTTTCGTCTGATGCTCTTTGTGTTTCAGATGCGGACGCTTC

··ThrHisGlnGlyLeuSerSerProValThrLysSerPheAsnArgGly

1551 TCACCCATCAGGGCCTGAGCTCGCCCGTCACAAAGAGCTTCAACAGGGGA AGTGGGTAGTCCCGGACTCGAGCGGGCAGTGTTTCTCGAAGTTGTCCCCCT

GluCys

1601 GAGTGT CTCACA



Erythropoietic Activity of Ab Candidates on F36e Human Erythroleukemic Cell Line

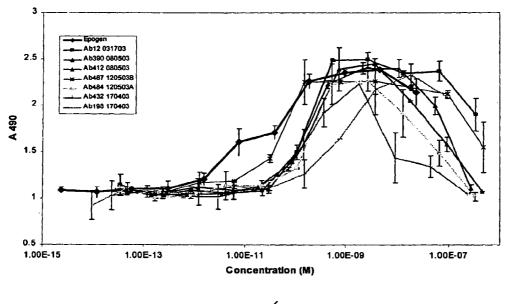
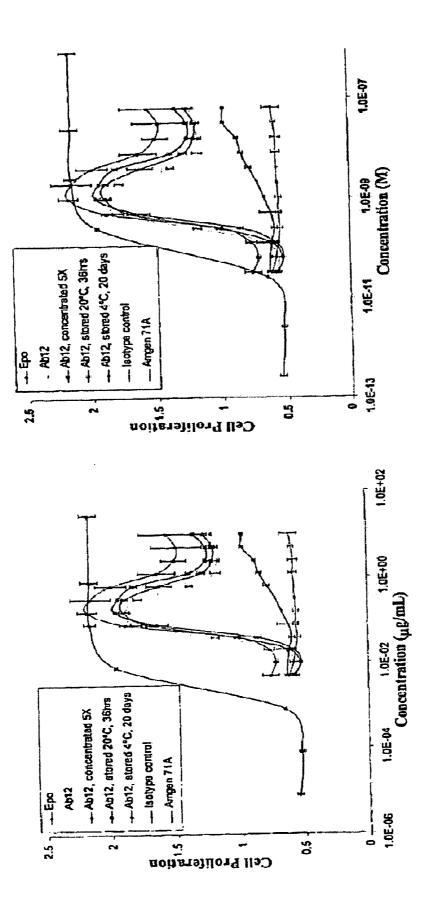


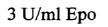
FIGURE 6





No Epo Control



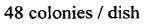


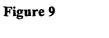


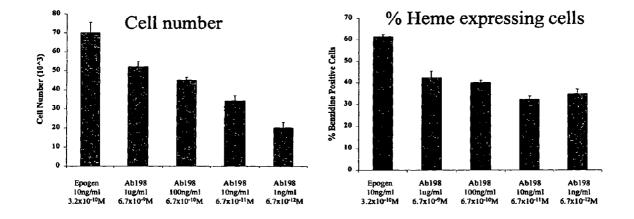
150 colonies / dish

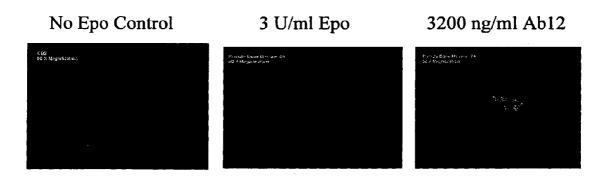
500 ng/ml Ab12











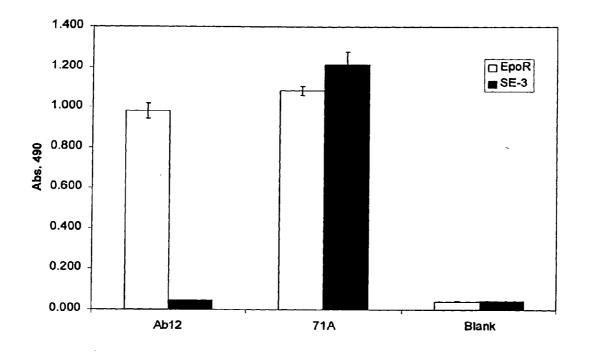


Figure 11

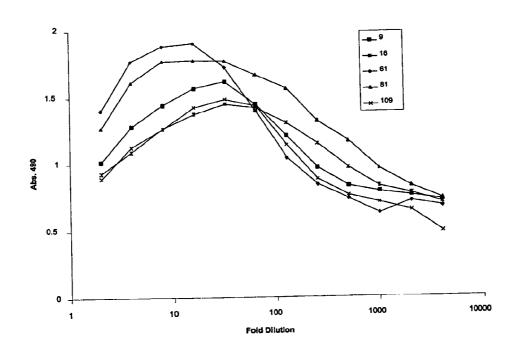
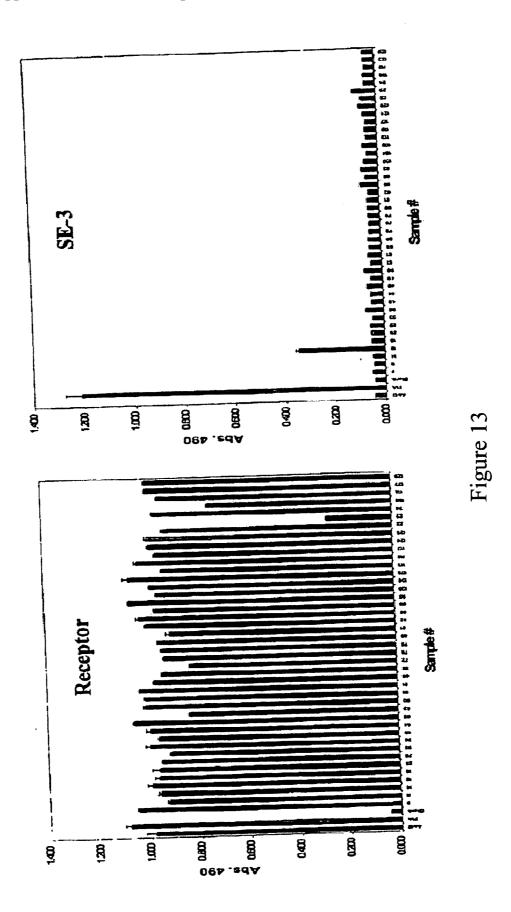
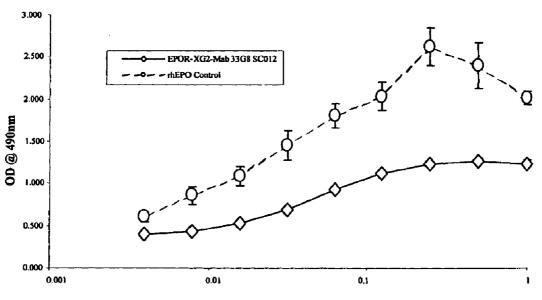


Figure 12





Effect of ABT2-SCX-012 on the proliferation of UT7/Epo cells

Concentration [ug/mL]

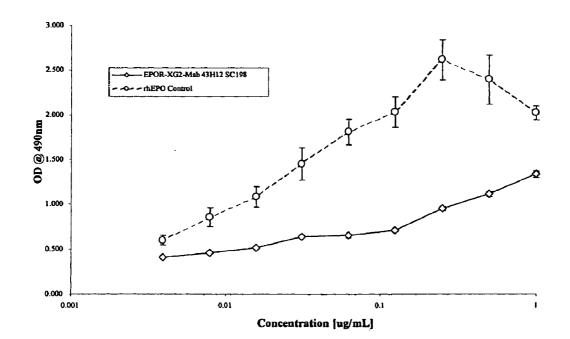
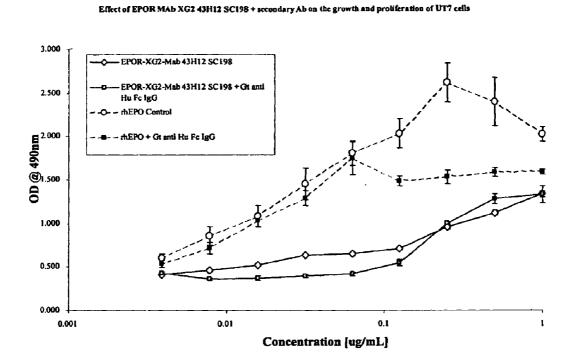
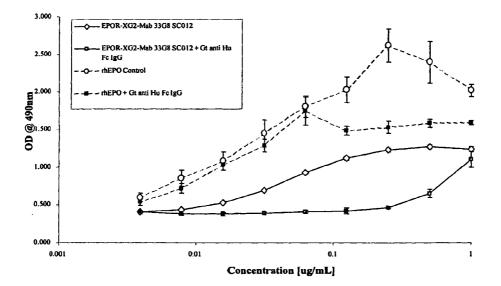


Figure 15

Effect of EPOR MAb XG2 43H12 SC198 on theproliferation of UT7/Epo cells







A-- ABT2-SCX-003 Nucleotide sequence of heavy chain variable region:

B-- ABT2-SCX-003 Amino acid sequence of heavy chain variable region: QVQLVESGGGVVQPGRSLRLSCAASGFTFSSYGMHWVRQAPGKGLEWVAVISY DGSNKYYADSVKGRFTISRDNSKNTLYLQMNSLRVEDTAVYYCARDHGGRYVY DYGMDVWGQGTTVTVSS

C-- ABT2-SCX-003 Nucleotide sequence of light chain variable region:

D-- ABT2-SCX-003 Amino acid sequence of light chain variable region:

DIQMTQSPSSVSASVGDRVSITCRASQGISSWLVWYQQKPGKAPALLIYAASSLQ RGVPSRFSGSGSGTDFTLTISSLQPEDFATYFCQQANSFPFTFGPGTKVDIK

A-- ABT2-SCX-012 Nucleotide sequence of heavy chain variable region:

B-- ABT2-SCX-012 Amino acid sequence of heavy chain variable region:

QVQLQESGPGLVKPSETLSLTCTVSGASISSYYWSWIRQPPGKGLEWIGYIYYSGS TNYNPSLKSRVTISVDTSKNQFSLKLRSVTAADTAVYYCARERLGIGDYWGQGT LVTVSS

C-- ABT2-SCX-012 Nucleotide sequence of light chain variable region:

5'GACATCCAGCTGACCCAATCTCCATCCTCCCTGTCTGCATCTGTAGGAGACA GAGTCACCATCACTTGCCGGGCAAGTCAGGGCATTAGAAATGATTTAGGCTG GTATCAGCAGAAACCAGGGGAAAGCCCCTAAGCGCCTGATCTATGCTGCATCC AGTTTGCAAAGTGGGGTCCCATCAAGGTTCAGCGGCAGTGGATCTGGGACAG AATTCACTCTCACAATCAGCAGCCTGCAGCCTGAAGATTTTGCAACTTATTAC TGTCTACAGCATAATACTTACCCTCCGACGTTCGGCCAAGGGACCAAGGTGG AAATCAAAC3'

D-- ABT2-SCX-012 Amino acid sequence of light chain variable region:

DIQLTQSPSSLSASVGDRVTITCRASQGIRNDLGWYQQKPGKAPKRLIYAASSLQS GVPSRFSGSGSGTEFTLTISSLQPEDFATYYCLQHNTYPPTFGQGTKVEIK

A-- ABT2-SCX-022 Nucleotide sequence of heavy chain variable region:

B-- ABT2-SCX-022 Amino acid sequence of heavy chain variable region:

QVQLVESGGGVVQPGRSLRLSCAASGFTFSSYGMHWVRQAPGKGLEWVVVISY DGSNKYYADSVKGRFTISRDNSKNTLYLQMNSLRVEDTAVYYCARDHGGRYVY DYGMDVWGQGTTVTVSS

C-- ABT2-SCX-022 Nucleotide sequence of light chain variable region:

D-- ABT2-SCX-022 Amino acid sequence of light chain variable region:

DIQMTQSPSSVSASVGDRVSITCRASQGISSWLAWYQQKPGKAPTLLIYAASSLQ RGVPSRFSGSGSGTDFTLTISSLQPEDFATYFCQQANSFPFTFGPGTKVDIK

A-- ABT2-SCX-054 Nucleotide sequence of heavy chain variable region:

CCTGAGACTCTCCTGTGCAGCGTCTGGATTCACCTTCAGTAAATATGGCATGC GTATGATGGAAGTAATAAATACTATGCAGACTCCGTGAAGGGCCGATTCACC ATCTCCAGAGACAATTCCAAGAACACGCTGTATCTGCAAATGAACAGCCTGA GAGCCGAGGACACGGCTGTGTATTACTGTGCGAGAGGTCCGTACTACTTTGA CTACTGGGGCCAGGGAACCCTGGTCACCGTCTCCTCAG3'

B-- ABT2-SCX-054 Amino acid sequence of heavy chain variable region:

OVOLVESGGGVVOPGRSLRLSCAASGFTFSKYGMHWVROAPGKGLEWVAVLW YDGSNKYYADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCARGPYYFDY WGQGTLVTVSS

C-- ABT2-SCX-054 Nucleotide sequence of light chain variable region:

5'GAAATTGTGTTGACGCAGTCTCCAGGCACCCTGTCTTTGTCTCCAGGGGAAA GAGCCACCCTCTCCTGCAGGGCCAGTCAGAGTGTTAGCAGCAGCTACTTAGC CTGGTACCAGCAGAAACCTGGCCAGGCTCCCAGGCTCCTCATCTATGGTGCA TCCAGCAGGGCCACTGGCATCCCAGACAGGTTCAGTGGCAGTGGGTCTGGGA CAGACTTCACTGTCACCATCAGCAGACTGGAACCTGAAGATTTTGCAGTGTAT TACTGTCAGCAGTATGGTAGTTCACCGTGGACGTTCGGCCAAGGGACCAAGG **TGGAAATCAAAC3'**

D-- ABT2-SCX-054 Amino acid sequence of light chain variable region:

EIVLTQSPGTLSLSPGERATLSCRASQSVSSSYLAWYQQKPGQAPRLLIYGASSRA TGIPDRFSGSGSGTDFTVTISRLEPEDFAVYYCQQYGSSPWTFGQGTKVEIK

A-- ABT2-SCX-060 Nucleotide sequence of heavy chain variable region:

5'CAGGTGCAGCTGGTGGAGTCTGGGGGGGGGGGGGGGTGGTCCAGCCTGGGAGGTCC CTGAGACTCTCCTGTGCAGCCTCTGGATTCACCTTCAGTAGCTATGGCATGCA CTGGGTCCGCCAGGCTCCAGGCAAGGGGCTGGAGTGGGGGGGCAGTTATATCA TATGATGGAAGTAATAAATACTATGCAGACTCCGTGAAGGGCCGATTCACCA TCTCCAGAGACAATTCCAAGAACACGCTGTATCTGCAAATGAACAGCCTGAG AGTTGAGGACACGGCTGTGTATTACTGTGCGAGAGATCACGGTGGGAAGGTAC GTCTACGACTACGGTATGGACGTCTGGGGCCAAGGGACCACGGTCACCGTCT CCTCAG3'

B-- ABT2-SCX-060 Amino acid sequence of heavy chain variable region: QVQLVESGGGVVQPGRSLRLSCAASGFTFSSYGMHWVRQAPGKGLEWVAVISY DGSNKYYADSVKGRFTISRDNSKNTLYLQMNSLRVEDTAVYYCARDHGGRYVY DYGMDVWGQGTTVTVSS

C-- ABT2-SCX-060 Nucleotide sequence of light chain variable region:

D-- ABT2-SCX-060 Amino acid sequence of light chain variable region: DIQMTQSPSSVSASVGDRVSITCRASQGISSWLAWYQQKPGKAPTLLIYAASSLQ RGVPSRFSGSGSGTDFTLTISSLQPEDFATYFCQQANSFPFTFGPGTKVDIK

A-- ABT2-SCX-102 Nucleotide sequence of heavy chain variable region:

B-- ABT2-SCX-102 Amino acid sequence of heavy chain variable region:

QVQLVESGGGVVQPGRSLRLSCAASGFTFSSYGMHWVRQAPGKGLEWVAVISY DGSNKYYADSVKGRFTISRDNSKNTLYLQMNSLRVEDTAVYYCARDHGGRYVY DYGMDVWGQGTTVTVSS

C-- ABT2-SCX-102 Nucleotide sequence of light chain variable region:

D-- ABT2-SCX-102 Amino acid sequence of light chain variable region:

DIQMTQSPSSVSASVGDRVSITCRASQGISSWLAWYQQKPGKAPKRLIYAASSLQ RGVPSRFSGSGSGTDFTLTISSLQPEDFATYFCQQANSFPFTFGPGTKVDIK

A-- ABT2-SCX-135 Nucleotide sequence of heavy chain variable region:

CTGAGACTCTCCTGTGCAGCCTCTGGATTCACCTTCAGTAGCTATGGCATGCA TATGATGGAAGTAATAAATACTATGCAGACTCCGTGAAGGGCCGATTCACCA TCTCCAGAGACAATTCCAAGAACACGCTGTATCTGCAAATGAACAGCCTGAG AGTTGAGGACACGGCTGTGTATTACTGTGCGAGAGATCACGGTGGGAGGTAC GTCTACGACTACGGTATGGACGTCTGGGGGCCAAGGGACCACGGTCACCGTCT CCTCAG 3'

B-- ABT2-SCX-135 Amino acid sequence of heavy chain variable region:

QVQLVESGGGVVQPGRSLRLSCAASGFTFSSYGMHWVRQAPGKGLEWVAVISY DGSNKYYADSVKGRFTISRDNSKNTLYLOMNSLRVEDTAVYYCARDHGGRYVY DYGMDVWGQGTTVTVSS

C-- ABT2-SCX-135 Nucleotide sequence of light chain variable region:

5'GACATCCAGATGACCCAGTCTCCATCTTCCGTGTCTACATCTGTAGGAGACA GAGTCTCCATCACTTGTCGGGCGAGTCAGGGTATTGGCAGCTGGTTAGCCTG GTATCAGCAGAAACCAGGGCAAGCCCCTACGCTCCTAATCTATGCTGCATCC AGTTTGCAACGTGGGGTCCCATCAAGATTCAGCGGCAGTGGATCTGGGACAG TGTCAACAGGCTAACAGTTTCCCATTCACTTTCGGCCCTGGGACCAAAGTGGA **TGTCAAAC3**

D-- ABT2-SCX-135 Amino acid sequence of light chain variable region: DIOMTOSPSSVSTSVGDRVSITCRASOGIGSWLAWYOOKPGOAPTLLIYAASSLO RGVPSRFSGSGSGTDFTLTINSLQPEDFATYFCQQANSFPFTFGPGTKVDVK

A-- ABT2-SCX-145 Nucleotide sequence of heavy chain variable region:

B-- ABT2-SCX-145 Amino acid sequence of heavy chain variable region:

QVQLVESGGGVVQPGRSLRLSCAASGFTFSSYGMHWVRQAPGKGLEWVAVISY DGSNKYYADSVKGRFTISRDNSKNTLYLQMNSLRVEDTAVYYCARDHGGRYVY DYGMDVWGQGTTVTVSS

C-- ABT2-SCX-145 Nucleotide sequence of light chain variable region:

D-- ABT2-SCX-145 Amino acid sequence of light chain variable region: DIQMTQSPSSVSASVGDRVSITCRASQGIGSWLAWYQQKPGQAPTLLIYAASSLQ RGVPSRFSGSGSGTDFTLTINSLQPEDFATYFCQQANSFPFTFGPGTKVDVK

A-- ABT2-SCX-198 Nucleotide sequence of heavy chain variable region:

B-- ABT2-SCX-198 Amino acid sequence of heavy chain variable region:

QVQLVESGGGVVQPGRSLRLSCVASGFTFSSYGMHWVRQAPGKGLEWVAVISY DGSNKYYADSVKGRFTISRDNSKNTLYLQMNSLRVEDTAVYYCARDHGGRYVY DYGMDVWGQGTTVTVSS

C-- ABT2-SCX-198 Nucleotide sequence of light chain variable region:

D-- ABT2-SCX-198 Amino acid sequence of light chain variable region:

DIQMTQSPSSVSASIGDRVSITCRASQGISSWLAWYQQKPGKAPTLLIYAASTLQR GVPSRFSGSGSGTDFTLTISSLQPEDFATYFCQQANSFPFTFGPGTKVDIK

A-- ABT2-SCX-254 Nucleotide sequence of heavy chain variable region:

B-- ABT2-SCX-254 Amino acid sequence of heavy chain variable region: QVQLVESGGGVVQPGRSLRLSCAASGFTFSSYGMHWVRQAPGKGLEWVAVIWF DGNNKFYADSVKGRFTISRDNSKNTLYLQMNSLRVEDTAVYYCARGGSYWDY WGQGTLVTVSS

C-- ABT2-SCX-254 Nucleotide sequence of light chain variable region:

D-- ABT2-SCX-254 Amino acid sequence of light chain variable region:

DIVMTQTPLFSFVMIGQPASISCRSRQSLVHSDGNTYLNWLQQRPGQPPRLLIYKT SNRFSGVPDRFSGSGAGTDFTLKISRVEAEDVGVYYCMQATQFPITFGQGTRLEI K

A-- ABT2-SCX-267 Nucleotide sequence of heavy chain variable region:

B-- ABT2-SCX-267 Amino acid sequence of heavy chain variable region:

QVQLVESGGGVVQPGRSLRLSCAASGFTFSSYGMHWVRQAPGKGLEWVAVISY DGSNKYYADSVKGRFTISRDNSKNTLYLQMNSLRVEDTAVYYCAKDHGGRYV YDYGMDVWGQGTTVTVSS

C-- ABT2-SCX-267 Nucleotide sequence of light chain variable region:

D-ABT2-SCX-267 Amino acid sequence of light chain variable region:

 $DIQMTQSPSSVSASVGDRVSITCRASQGIGSWLAWYQQKPGQAPTLLIYAASSLQ\\ RGVPSRFSGSGSGTDFTLTINSLQPEDFATYFCQQANSFPFTFGPGTKVDVK$

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CDR2	VISYDGSNKYYADSVKG							*************	VISYDGSNKYYADSVKG		VISYDGSNKYYADSVKG					XIYYSGNYNPSLKS			PR4	MGQGTTVTVSS								WGQGTTVTVSS	1
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FR2	WVRQAPGKGLEWVA		Λ				*****		WVRQAPGKGLEWVA		WVRQAPGKGLEWVA	-				WIRQPPGKGLEWIG	1		CDR3	DHGGRYVYDYĠMDV									
CDR1	GFTFSSYGMH								GFTFSSYGMH		GFTFSSYGMH	K				GGSISSYYWS								1				~	
θ	GFTFS				1				GPTFS	1	GFTFS					GGS18	A-			AVYYCAR								AVYYCAF	
FR1	QVQLVESGGGVVQPGRSLRLSCAAS							A	QVQLVESGGGVVQPGRSLRLSCAAS		QVQLVESGGGVVQPGRSLRLSCAAS					OVOLOESGPGLVKPSETLSLTCTVS			FR3	RFTI SRDNSKNTLYLQMNSLRAEDTAVYYCAR	Λ	A	AA	A	AA	AA	A	RFTISRDNSKNTLYLQMNSLRAEDTAVYYCAK	A
V Heavy/D/J	Germline		<u>L</u>		VH3 - 30 (V3 -	30)/D4-23/1H6D		- .	Germline	VH3-30.5 (DP- 49) /D4-23/JH6b	Germline	VH3-33 (DP- 50) /DIR3/JH4b	- du) EE - EHM	50) /D21 -	10rc/JH4b	Germline	VH4-59 (DP-	71)/DIR4rc/JM4a	V Heavy/D/J	Germline				VH3-30 (V3-	30)/D4-23/LH6b			Germline	VH3-30.5 (DP-
Single		e E	22	60	102	135	145	1 98	2	267		54	75.4	2		,	12		Single	1	m	22	60	201	135	145	198	1	267

FR4	MGQGTTVTVSS								MGQGTTVTVSS	1 1 1 1 1 1 1 1 1 1		MGQGTLVTVSS						MGQGTLVTVSS		
CDR3	DHGGRYVYDYĠMDV						_ = = = = = = = = = = = = = = = = = = =						GPYYFDY		GGSYWDY				ERLGIGDY	
FR3	RFTISRDNSKNTLYLQMNSLRAEDTAVYYCAR	ΛΛ	AA	AA		A	AA	AA	RFTISRDNSKNTLYLQMNSLRAEDTAVYYCAK	AA		RFTISRDNSKNTLYLQMNSLRAEDTAVYYCAR			AA			RVTISVDTSKNQFSLKLSSVTAADTAVYYCAR		
V Heavy/D/J	Germline				VH3-30 (V3-	30)/D4-23/DH6D		_	Germline	VH3-30.5 (DP-	49)/D4-23/JH6b	Germline	-40) EE-EHV	50)/DIR3/JH4b	VH3-33 (DP-	50)/D21-	10rc/JH4b	Germline	-40 -59 (DP-	71)/DIR4rc/JM4a
Single		m	22	60	102	135	145	198	,	267		1	54		254			-	12	

Patent Application Publication Apr. 24, 2008 Sheet 37 of 79 US 2008/0095776 A1

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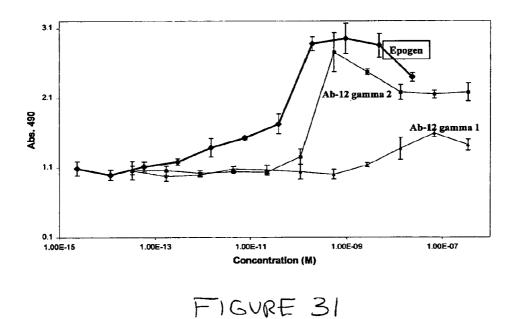
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Single Cell	V Kappa/J	FR1	CDR1	rr2	CDR2
-	Gernline	EIVLTQSPGTLSLSPGERATLSC	RASOSVSSSYLA	HYOOKPGOAFRLLIY	GASSRAT
54	VkIII (A27)/Jkl	~~~~~~~~~~~~~~~~~			*******
-	Germline	DIOMOSPSSVSASVGDRVTITC	RASOGISSWLA	NYQQKPGKAPKLLIY	AASSLOS
3		S	V	A	R
22	1 Γ	S	*****	T	R
60		S	*****	TT	R
102	VkI (L5)/Jk3	S	*******	R	R
135	AKT (72)1/0K2	S	G	QT	R
145	1	S	G	QT	R
198	1	S	********	T	TR
267	1	S	G	QT	R
-	Germline	DIOMOSPSSLSASVGDRVTITC	RASOGIRNDLG	HYQQKPGKAPKRLIY	AASSLOS
12	VkI (A30)/Jk1	L	****	*****	
-	Gernline	DIVMOTPLSSPVTLGOPASISC	RSSQSLVHSDGNTYLS	WLQQRPGQPPRLLIY	KISNRFS
254	VkII (A23)/Jk5	F-F-M	RN	******	-T

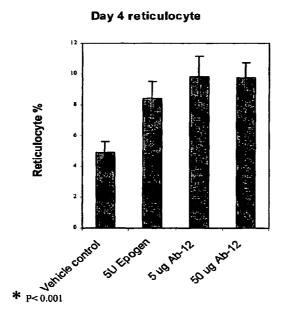
Figure 30

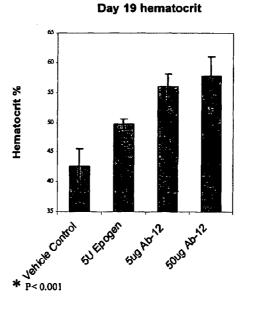
Single Cell	V Kappa/J	FR3	CDR3	J
-	Germline	GIPDRFSGSGSGTDFTLTISRLEPEDFAVYYC	<u>O</u> OYGSS FIFT	FGOGTKVEIK
54	VkIII (A27)/Jkl	VV	****	
-	Germline	GVPSRFSGSGSGTDFTLTISSLOPEDFATYYC	QQANSFPFT	FGPGTKVDIK
3 -		F-		*****
22		F-		
60		F-		
102	VkI (L5)/Jk3	F-		
135	ANT (TO)/ONO	F-		V-
145	1	F-		V-
198	1	F-		
267	1	F-		V-
-	- Germline	GVPSRFSGSGSGTEFTLTISSLOPEDFATYYC	LOHNSYPPT	FGQGTKVEIK
12	VkI (A30)/Jk1		T	
-		GVFDRFSGSGAGTD FTLK I SRVEAEDVGVYYC	MOATOFPIT	FGQGTRLEIK
254	VkII (A23)/Jk5			

Comparison of Erythropoietic Activity of Gamma 1 Ab-12 versus Gamma 2 Ab-12 on F36e Human Erythroleukemic Cell Line

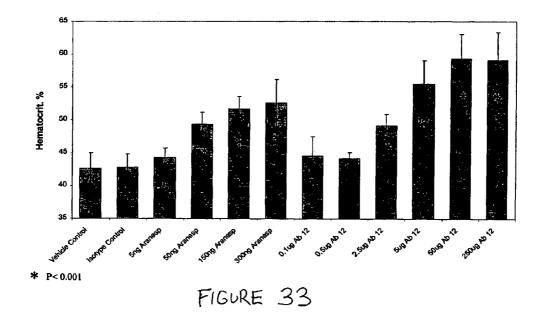


Ab-12 Increases Reticulocyte Count and Hematocrit in Transgenic Mice

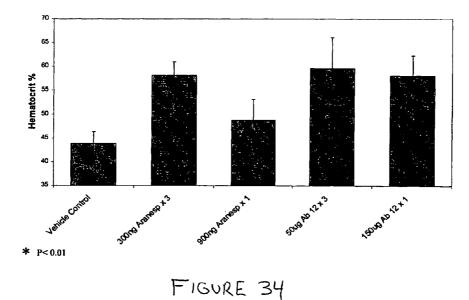




Day 19 Hematocrit in Transgenic Mice Following Weekly Dosing with Ab-12 or Aranesp



Day 19 Hematocrit in Transgenic Mice Comparing Single vs. Weekly Dosing with Ab-12 or Aranesp



A. Ab390 nucleotide sequence of heavy chain variable region:

5' CAGGTGCAGCTGCAGGAGTCGGGCCCAGGACTGGTGAAGCCTTCGGAGACC **CTGTCCCTCACCTGCACTGTCTCTGGTGCCTCCATCAGTAATTACTACTGG** AGCTGGATCCGGCAGCCCCCAGGGAAGGGACTGGAGTGGATTGGGTATGTC TCTTACAGTGGGAGTACGTACTACAACCCCTCCCTCAAGGGTCGAGTCACC ATGTCAGTAGACACGTCCAAGAACCAGTTCTCCCTGAAGCTGAGCTCTGTG ACCGCTGCGGACACGGCCGTGTATTACTGTGCGAGAGAAAAACTGGGGATT GGAGACTACTGGGGCCAGGGAACCCTGGTCACCGTCTCCTCA3'

B. Ab390 Amino acid sequence of heavy chain variable region:

QVQLQESGPGLVKPSETLSLTCTVSGASISNYYWSWIRQPPGKGLEWIGYVSYSGS TYYNPSLKGRVTMSVDTSKNQFSLKLSSVTAADTAVYYCAREKLGIGDYWGQGTLV TVSS

C. Ab390 nucleotide sequence of light chain variable region:

5' GACATCCAGATGACCCAGTCTCCATCCTCCCTGTCTGCATCTGTAGGAGACA GAGTCACCATCACTTGCCGGGCAAGTCAGGGCATTAAAAATGATTTAGGCTG GTATCAGCAGAAAACCAGGGAAAGCCCCTAAGCGCCTGATCTATGCTGCATCC AGTTTGCAAAGTGGGGTCCCATCAAGGTTCAGCGGCAGTGGATCTGGGACAG AATTCACTCTCACAATCAGCAGCCTGCAGCCTGAAGATTTTGCAACTTATTA CTGTCTACAGCATAATAGTTATCCGTGCAGTTTTGGCCAGGGGACCAAGCTG GAGATCAAAC3'

D. Ab390 Amino acid sequence of light chain variable region:

DIQMTQSPSSLSASVGDRVTITCRASQGIKNDLGWYQQKPGKAPKRLIYAASSLQS GVPSRFSGSGSGTEFTLTISSLQPEDFATYYCLQHNSYPCSFGQGTKLEIK

A. Ab412 nucleotide sequence of heavy chain variable region:

5' CAGGTGCAGCTGCAGGAGTCGGGGCCCAGGACTGGTGAAGCCTTCACAGACCC TGTCCCTCACCTGCACTGTCTCTGGTGCCTCCATCAGCAGTGGTGCTTACTA CTGGAGTTGGATCCGCCAGCACCCAGGGAAGGGCCTGGAGTGGATTGGGTAC ATCTATAAGAGTGAGACCTCCTACTACAACCCGTCCCTCAAGAGTCGACTTA CCCTATCAGTAGACACGTCTAAGAACCAGTTCTCCCTGAACCTGATCTCTGT GACTGCCGCGGACACGGCCGTGTATTATTGTGCGAGAGATAAACTGGGGATC GCGGACTACTGGGGCCAGGGAACCCTGGTCACCGTCTCCTCA3'

B. Ab412 Amino acid sequence of heavy chain variable region:

QVQLQESGPGLVKPSQTLSLTCTVSGASISSGAYYWSWIRQHPGKGLEWIGY IYKSETSYYNPSLKSRLTLSVDTSKNQFSLNLISVTAADTAVYYCARDKLGI ADYWGQGTLVTVSS

C. Ab412 nucleotide sequence of light chain variable region:

5' GACATCCAGATGACCCAGTCTCCATCCTCCCTGTCTGCATCTGTAGGAGACA GAGTCACCATCACTTGCCGGGCAAGTCAGGACATTAGAAATGATTTAGGCTG GTATCAGCAGAAACCAGGGAAAGCCCCTAAGCGCCTGATCTATGCTGCATCC AATTTGCAAAGTGGGGTCCCATCAAGGTTCAGCGGCAGTGGATCTGGGACAG AATTCACTCTCACAATCAGCAGCCTGCAGCCTGAAGATTTTGCAACTTATTA CTGTCTACAGCATAATAGCTACCCTCCCACTTTCGGCGGAGGGACCAAGGTG GAAATCAAAC3'

D. Ab412 Amino acid sequence of light chain variable region:

DIQMTQSPSSLSASVGDRVTITCRASQDIRNDLGWYQQKPGKAPKRLIYAAS NLQSGVPSRFSGSGSGTEFTLTISSLQPEDFATYYCLQHNSYPPTFGGGTKV EIK

A. Ab432 nucleotide sequence of heavy chain variable region:

B. Ab432 Amino acid sequence of heavy chain variable region:

QVQLQESGPGLVKPSETLSLTCTVSGVSISNYYWSWIRQSPGKGLEWIGYIY YSGSPYYNPSLKSRVTISADTSKNQFSLKLSSVTAADTAIYYCAREKLGIGD YWGQGTLVTVSS

C. Ab430 nucleotide sequence of light chain variable region:

5' GACATCCAGATGACCCAGTCTCCATCCTCCCTGTCTGCATCTGTCGGAGACA GAGTCACCATCACTTGCCGGGCAAGTCAGGGCATTAGAAATGATTTAGGCTG GTATCAGCAGAAACCAGGGAAAGCCCCTAAGCGCCTGATCTATGCTGCATCC AGTTTGCAAAGTGGGGTCCCATCAAGGTTCAGCGGCAGTGGATCTGGGACAG AATTCACTCTCACAATCAGCAGCCTGCAGCCTGAAGATTTTGCAACTTATTA CTGTCTACAGCATAATAGTTACCCTCCCACTTTCGGCCCTGGGACCAAGGTG GATATCAAAC3'

D. Ab430 Amino acid sequence of light chain variable region:

DIQMTQSPSSLSASVGDRVTITCRASQGIRNDLGWYQQKPGKAPKRLIYAAS SLQSGVPSRFSGSGSGTEFTLTISSLQPEDFATYYCLQHNSYPPTFGPGTKV DIK

A. Ab467 nucleotide sequence of heavy chain variable region:

B. Ab467 Amino acid sequence of heavy chain variable region:

QVQLQESGPGLVKPSETLSLTCTVSGGSISRYYWSWIRQPPGKGLEWIGYVS YSGSTYYNPSLKSRVTISVDTSKNQFSLKLSSVTAADTAVYYCARDKLGIGD YWGQGTLVTVSS

C. Ab467 nucleotide sequence of light chain variable region:

5' GACATCCAGATGACCCAGTCTCCATCCTCCCTGTCTGCATCTGTAGGAGACA GAGTCACCATCACTTGCCGGGCAAGTCAGGGCATTAGAAATGATTTAGGCTG GTATCAGCAGAAACCGGGGAAAGCCCCTAAGCGCCTGATCTATGCTGCATCC AGTTTGCAAAGTGGGGTCCCATCAAGGTTCAGCGGCAGTGGATCTGGGACAG AATTCACTCTCACAATCAGCAGCCTGCAGCCTGAAGATTTTGCAACTTATTA CTGTCTACAGCATAATAGTTACCCGTGCAGTTTTGGCCAGGGGACCAAGCTG GAGATCAAAC3'

D. Ab467 Amino acid sequence of light chain variable region:

DIQMTQSPSSLSASVGDRVTITCRASQGIRNDLGWYQQKPGKAPKRLIYAAS SLQSGVPSRFSGSGSGTEFTLTISSLQPEDFATYYCLQHNSYPCSFGQGTKL EIK

A. Ab484 nucleotide sequence of heavy chain variable region:

5' CAGGTGCAGCTGCAGGAGTCGGGGCCCAGGACTGGTGAAGCCTTTACAGACCC TGTCCCTCACCTGCACTGTCTCTGGTGGCTCCATCAGCAGTGGTGTTTACTA CTGGAGCTGGATCCGCCAGCACCCAGGGAAGGGCCTGGAGTGGATTGGGTAC **ATCTATAACAGTAAGACCTCCTATTATAATCCGTCCCTCAAGAGTCGACTTA** CCCTATCAGTAGACACGTCTAAGAACCAGTTCTCCCTGAACCTGATCTCTGT GACTGCCGCGGACACGGCCGTGTATTACTGTGCGAGAGATAAATTGGGGGATC GCGGACTACTGGGGCCAGGGAACCCTGGTCACCGTCTCCTCAG3'

B. Ab484 Amino acid sequence of heavy chain variable region:

QVQLQESGPGLVKPLQTLSLTCTVSGGSISSGVYYWSWIRQHPGKGLEWIGY IYNSKTSYYNPSLKSRLTLSVDTSKNQFSLNLISVTAADTAVYYCARDKLGI ADYWGQGTLVTVSS

C. Ab484 nucleotide sequence of light chain variable region:

5' GACATCCAGATGACCCAGTCTCCATCCTCCCTGTCTGCATCTGTAGGAGACA GAGTCACCATCACTTGCCGGACAAGTCAGGGCATTAGAAATGATTTAGGCTG GTATCAGCAGAAACCAGGGAAAGCCCCTAAGCGCCTGATCTATGCTGCATCC AGTTTGCAAAGTGGGGTCCCATCAAGGTTCAGCGGCAGTGGATCTGGGACAG AATTCACTCTCACAATCAGCAGCCTGCAGCCTGAAGATTTTGCAACTTATTA CTGTCTACAGCATAATAGCTACCCTCCCACTTTCGGCGGAGGGACCAAGGTG GAGATCAAAC3'

D. Ab484 Amino acid sequence of light chain variable region:

DIQMTQSPSSLSASVGDRVTITCRTSQGIRNDLGWYQQKPGKAPKRLIYAAS SLQSGVPSRFSGSGSGTEFTLTISSLQPEDFATYYCLQHNSYPPTFGGGTKV EIK

Single Cell	Chain ID	V Heavy/D/J	FRI	CDR1	FR2
	Att 2010 Germline	•	OVOLVESGGGVVOPGRSLRLSCAAS GFTFSSYGMH WVROAPGKGLEWVA	GFTFSSYGMH	WVROAPGKGLEWVA
198	14325.3	VH3-30/D4-23/JH6			
•	Germline		QVQLQESGPGLVKPSETLSLTCTVS	GGSISSYYWS	WIRQPPGKGLEWIG
12	13308.1	VH4-59/DIR4RC/JH4			
•			OVQLQESGPFLVKPSQTLSLTCTVS GGSISSGGYYWS WIRQHPGKGLEWIG	GGSISSGGYYWS	WIRQHPGKGLEWIG
412	54995.1	V4-31/DIR4rc/JH4	<u>0</u>		
•	Contraction of the Correline	•	OVQLQESGPGLVKPSQTLSLTCTVS GGSISSGGYYWS WIRQHPGKGLEWIG	GGSISSGGYYWS	WIROHPGKGLEWIG
484	57130.1	V4-30.1/DIR4rc/JH4			
-	Germline	•	QVQLQESGPGLVKPSETLSLTCTVS	GGSISSYYWS	WIRQPPGKGLEWIG
467	56977.2	V4-59/D7-27/JH4		R	
390	57141.2	VH4-59/D7-27/JH4b		NA-	
432	57354.11	VH4-59/D7-27/JH4b		N	S

FNE	WGQGTTVTVSS		MGQGTLVTVSS		MGQGTLVTVSS		WGQGTLVTVSS		MGQGTLVTVSS			
CDR3		DHGGRYVYDYGMDV		ERLGIGDY		DKLGIADY		DKLGIADY		DKLGIGDY	EKTGIGDY	EKLGIGDY
FK3	SVKG RFTISRDNSKNTLYLQMNSLRAEDTAVYYCAK	VR	RVTISVDTSKNQFSLKLSSVTAADTAVYYCAR	R	RVTISVDTSKNQFSLKLSSVTAADTAVYYCAR	-L-L ² N-I	RVTISVDTSKNQFSLKLSSVTAADTAVYYCAR	-L-LN-I	RVTISVDTSKNQFSLKLSSVTAADTAVYYCAR			·····A······I······
CDR2	VISYDGSNKYYADSVKG		YIYYSGSTNYNPSLKS		VIYYSGSTYYNPSLKS	K-ETS	YIYYSGSTYYNPSLKS	KTS	VIYYSGSTNYNPSLKS	-VSY	-vs6	PY

Figure 40

Well	Single Cell	Chain ID	V Kappa/J	FIR 1	CDRI	FR2
•	•	State of Germline	•	DIQMTQSPSSVSASVGDRVTITC RASQGISSWLA WYQQKPGKAPKLLIY	RASQGISSWLA	WYQQKPGKAPKLLIY
43H12	198	14325.3	LS/Jk3	SI		T
•	•	Contraction of Cermline Contraction of Contraction	-	DIQMTQSPSSLSASVGDRVTITC RASQGIRNDLG WYQQKPGKAPKRLIY	RASQGIRNDLG	WYQQKPGKAPKRLIY
33G8	12	13308.1	A30/Jk3			
223H2	430	54494.1	A30/Jk3			
•	-	Germline	-	DIQMTQSPSSLSASVGDRVTITC RASQGIRNDLG WYQQKPGKAPKRLIY	RASQGIRNDLG	WYQQKPGKAPKRLIY
230A4	412	54732.2	A30(Vk1)/Jk4		D	
•	•	Germline	-	DIQMTQSPSSLSASVGDRVTITC	RASQGIRNDLG	RASQGIRNDLG WYQQKPGKAPKRLIY
208A12	484	57094.1	A30(Vk1)/Jk4		- T	
ı	•	Germline Commence	•	DIQMTQSPSSLSASVGDRVTITC RASQGIRNDLG WYQQKPGKAPKRLIY	RASQGIRNDLG	WYQQKPGKAPKRLIY
259C12	467	56956.1	A30(Vk1)/Jk2			
236D12	390	56829.3	A30(Vk1)/Jk2		K	

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FXL	FGPGTKVDIK		FGQGTKVEIK		PD	FGGGTKVEIK		FGGGTKVEIK	*******	FGQGTKLEIK		
CDR3	QQANSFPFT		LAHNSYPFT	T	-d	LIAYSVHJ	P-	LIAYNNYPLT	P.	LQHNSYPLT	CS	CS
FR3	GVPSRFSGSGSGTDFTLTISSLQPEDFATYYC QQANSFPFT	F.	AASSLQS GVPSRFSGSGSGTEFTLTISSLQPEDFATYYC LQHNSYPF1			GVPSRFSGSGSGTEFTLTISSLQPEDFATYYC LQHNSYPLT		AASSLQS GVPSRFSGSGSGTEFTLTISSLQPEDFATYYC LQHNSYPLT		GVPSRFSGSGSGTEFTLTISSLQPEDFATYYC		
CDR2	AASSLQS	TR	AASSLQS			AASSLQS	N	AASSLQS		SOISSAA		
		198		12	430		412		484		464	390

Figure 41

1	MetLysHisLeuTrpPhePheLeuLeuLeuValAla ATGAAGCATCTGTGGTTCTTCCTTCTCCTGGTGG TACTTCGTAGACACCAAGAAGGAAGAGGACCACC
51	··AlaProArgTrpValLeuSerGlnValGlnLeuGlnGluSerGlyPro CAGCTCCCAGATGGGTCCTGTCCCAGGTGCAGCTGCAGGAGTCGGGCCCA GTCGAGGGTCTACCCAGGACAGGGTCCACGTCGACGTCCTCAGCCCGGGT
101	GlyLeuValLysProSerGluThrLeuSerLeuThrCysThrValSerGly GGACTGGTGAAGCCTTCGGAGACCCTGTCCCTCACCTGCACTGTCTCTGG CCTGACCACTTCGGAAGCCTCTGGGACAGGGAGTGGACGTGACAGAGACC
151	 AlaSerIleSerAsnTyrTyrTrpSerTrpIleArgGlnProProGlyLys TGCCTCCATCAGTAATTACTACTGGAGCTGGATCCGGCAGCCCCCAGGGA ACGGAGGTAGTCATTAATGATGACCTCGACCTAGGCCGTCGGGGGGTCCCT
201	••GlyLeuGluTrpIleGlyTyrValSerTyrSerGlySerThrTyrTyr AGGGACTGGAGTGGATTGGGTATGTCTCTTACAGTGGGAGTACGTAC
251	AsnProSerLeuLysGlyArgValThrMetSerValAspThrSerLysAsn AACCCCTCCCTCAAGGGTCGAGTCACCATGTCAGTAGACACGTCCAAGAA TTGGGGAGGGAGTTCCCAGCTCAGTGGTACAGTCATCTGTGCAGGTTCTT
301	•GlnPheSerLeuLysLeuSerSerValThrAlaAlaAspThrAlaValTyr CCAGTTCTCCCTGAAGCTGAGCTCTGTGACCGCTGCGGACACGGCCGTGT GGTCAAGAGGGACTTCGACTCGAGACACTGGCGACGCCTGTGCCGGCACA
351	••TyrCysAlaArgGluLysLeuGlyIleGlyAspTyrTrpGlyGlnGly ATTACTGTGCGAGAGAAAAACTGGGGGATTGGAGACTACTGGGGCCAGGGA TAATGACACGCTCTCTTTTTGACCCCCTAACCTCTGATGACCCCGGTCCCT
401	ThrLeuValThrValSerSerAlaSerThrLysGlyProSerValPhePro ACCCTGGTCACCGTCTCCTCAGCCTCCACCAAGGGCCCATCGGTCTTCCC TGGGACCAGTGGCAGAGGAGTCGGAGGTGGTTCCCCGGGTAGCCAGAAGGG
451	 LeuAlaProCysSerArgSerThrSerGluSerThrAlaAlaLeuGlyCys CCTGGCGCCCTGC<u>TCTAGA</u>AGCACCTCCGAGAGCACAGCCGCCCTGGGCT GGACCGCGGGACGAGATCTTCGTGGAGGCTCTCGTGTCGGCGGGACCCGA
501	··LeuValLysAspTyrPheProGluProValThrValSerTrpAsnSer GCCTGGTCAAGGACTACTTCCCCGAACCGGTGACGGTGTCGTGGAACTCA CGGACCAGTTCCTGATGAAGGGGGCTTGGCCACTGCCACAGCACCTTGAGT

551	GlyAlaLeuThrSerGlyValHisThrPheProAlaValLeuGlnSerSer GGCGCTCTGACCAGCGGCGTGCACACCTTCCCAGCTGTCCTACAGTCCTC CCGCGAGACTGGTCGCCGCACGTGTGGAAGGGTCGACAGGATGTCAGGAG
601	•GlyLeuTyrSerLeuSerSerValValThrValProSerSerAsnPheGly AGGACTCTACTCCCTCAGCAGCGTGGTGACCGTGCCCTCCAGCAACTTCG TCCTGAGATGAGGGAGTCGTCGCACCACTGGCACGGGAGGTCGTTGAAGC
651	••ThrGlnThrTyrThrCysAsnValAspHisLysProSerAsnThrLys GCACCCAGACCTACACCTGCAACGTAGATCACAAGCCCAGCAACACCAAG CGTGGGTCTGGATGTGGACGTTGCATCTAGTGTTCGGGTCGTTGTGGTTC
701	ValAspLysThrVal GTGGACAAGACAGTTGGTGAGAGGCCAGCTCAGGGAGGGA
751	TGGAAGCCAGGCTCAGCCCTCCTGCCTGGACGCACCCCGGCTGTGCAGCC ACCTTCGGTCCGAGTCGGGAGGACGGACCTGCGTGGGGCCGACACGTCGG
801	CCAGCCCAGGGCAGCAAGGCAGGCCCCATCTGTCTCCTCACCCGGAGGCC GGTCGGGTCCCGTCGTTCCGTCCGGGGTAGACAGAGGAGTGGGCCTCCGG
851	TCTGCCCGCCCCACTCATGCTCAGGGAGAGGGTCTTCTGGCTTTTTCCAC AGACGGGCGGGGTGAGTACGAGTCCCTCTCCCAGAAGACCGAAAAAGGTG
901	CAGGCTCCAGGCAGGCACAGGCTGGGTGCCCCTACCCCAGGCCCTTCACA GTCCGAGGTCCGTCCGTGTCCGACCCACGGGGATGGGGTCCGGGAAGTGT
951	CACAGGGGCAGGTGCTTGGCTCAGACCTGCCAAAAGCCATATCCGGGAGG GTGTCCCCGTCCACGAACCGAGTCTGGACGGTTTTCGGTATAGGCCCTCC
1001	ACCCTGCCCCTGACCTAAGCCGACCCCAAAGGCCAAACTGTCCACTCCCT TGGGACGGGGACTGGATTCGGCTGGGGTTTCCGGTTTGACAGGTGAGGGA
1051	CAGCTCGGACACCTTCTCTCCCCCAGATCCGAGTAACTCCCAATCTTCT GTCGAGCCTGTGGAAGAGAGGAGGGGTCTAGGCTCATTGAGGGTTAGAAGA
1101	GluArgLysCysCysValGluCysProProCysPro CTCTGCAGAGCGCAAATGTTGTGTCGAGTGCCCACCGTGCCCAGGTAAGC GAGACGTCTCGCGTTTACAACACAGCTCACGGGTGGCACGGGTCCATTCG
1151	CAGCCCAGGCCTCGCCCTCCAGCTCAAGGCGGGACAGGTGCCCTAGAGTA GTCGGGTCCGGAGCGGGGAGGTCGAGTTCCGCCCTGTCCACGGGATCTCAT
1201	GCCTGCATCCAGGGACAGGCCCCAGCTGGGTGCTGACACGTCCACCTCCA CGGACGTAGGTCCCTGTCCGGGGTCGACCCACGACTGTGCAGGTGGAGGT

1251	AlaProProValAlaGlyProSerValPheLeuPhePro TCTCTTCCTCAGCACCACCTGTGGCAGGACCGTCAGTCTTCCTCTTCCCC AGAGAAGGAGTCGTGGTGGACACCGTCCTGGCAGTCAGAAGGAGAAGGGG
1301	ProLysProLysAspThrLeuMetIleSerArgThrProGluValThrCys. CCAAAACCCAAGGACACCCTCATGATCTCCCGGACCCCTGAGGTCACGTG GGTTTTGGGTTCCTGTGGGAGTACTAGAGGGCCTGGGGACTCCAGTGCAC
1351	 ValValValAspValSerHisGluAspProGluValGlnPheAsnTrpTyr CGTGGTGGTGGACGTGAGCCACGAAGACCCCCGAGGTCCAGTTCAACTGGT GCACCACCACCTGCACTCGGTGCTTCTGGGGGCTCCAGGTCAAGTTGACCA
1401	···ValAspGlyValGluValHisAsnAlaLysThrLysProArgGluGlu ACGTGGACGGCGTGGAGGTGCATAATGCCAAGACAAAGCCACGGGAGGAG TGCACCTGCCGCACCTCCACGTATTACGGTTCTGTTTCGGTGCCCTCCTC
1451	GlnPheAsnSerThrPheArgValValSerValLeuThrValValHisGln· CAGTTCAACAGCACGTTCCGTGTGGTCAGCGTCCTCACCGTTGTGCACCA GTCAAGTTGTCGTGCAAGGCACACCAGTCGCAGGAGTGGCAACACGTGGT
1501	 AspTrpLeuAsnGlyLysGluTyrLysCysLysValSerAsnLysGlyLeu GGACTGGCTGAACGGCAAGGAGTACAAGTGCAAGGTCTCCAACAAAGGCC CCTGACCGACTTGCCGTTCCTCATGTTCACGTTCCAGAGGTTGTTTCCGG
1551	<pre> ••ProAlaProIleGluLysThrIleSerLysThrLys TCCCAGCCCCCATCGAGAAAACCATCTCCAAAACCAAAGGTGGGACCCGC AGGGTCGGGGGTAGCTCTTTGGTAGAGGTTTTGGTTTCCACCCTGGGCG</pre>
1601	GGGGTATGAGGGCCACATGGACAGAGGCCGGCTCGGCCCACCCTCTGCCC CCCCATACTCCCGGTGTACCTGTCTCCGGCCGAGCCGGGTGGGAGACGGG
1651	GlyGlnProArgGlu TGGGAGTGACCGCTGTGCCAACCTCTGTCCCTACAGGGCAGCCCCGAGAA ACCCTCACTGGCGACACGGTTGGAGACAGGGATGTCCCGTCGGGGCTCTT
1701	ProGlnValTyrThrLeuProProSerArgGluGluMetThrLysAsnGln. CCACAGGTGTACACCCTGCCCCCATCCCGGGAGGAGATGACCAAGAACCA GGTGTCCACATGTGGGACGGGGGGTAGGGCCCTCCTCTACTGGTTCTTGGT
1751	 ValSerLeuThrCysLeuValLysGlyPheTyrProSerAspIleAlaVal GGTCAGCCTGACCTGGCTGGTCAAAGGCTTCTACCCCAGCGACATCGCCG CCAGTCGGACTGGACGGACCAGTTTCCGAAGATGGGGTCGCTGTAGCGGC
1801	··GluTrpGluSerAsnGlyGlnProGluAsnAsnTyrLysThrThrPro TGGAGTGGGAGAGCAATGGGCAGCCGGAGAACAACTACAAGACCACACCT ACCTCACCCTCTCGTTACCCGTCGGCCTCTTGTTGATGTTCTGGTGTGGA

1851	ProMetLeuAspSerAspGlySerPhePheLeuTyrSerLysLeuThrVal· CCCATGCTGGACTCCGACGGCTCCTTCTTCCTCTACAGCAAGCTCACCGT GGGTACGACCTGAGGCTGCCGAGGAAGAAGGAGATGTCGTTCGAGTGGCA
1901	 AspLysSerArgTrpGlnGlnGlyAsnValPheSerCysSerValMetHis GGACAAGAGCAGGTGGCAGCAGGGGAACGTCTTCTCATGCTCCGTGATGC CCTGTTCTCGTCCACCGTCGTCCCCTTGCAGAAGAGTACGAGGCACTACG
1951	••GluAlaLeuHisAsnHisTyrThrGlnLysSerLeuSerLeuSerPro ATGAGGCTCTGCACAACCACTACACGCAGAAGAGCCTCTCCCTGTCTCCG TACTCCGAGACGTGTTGGTGATGTGCGTCTTCTCGGAGAGGGACAGAGGC
2001	GlyLys GGTAAA

CCATTT

1	MetArgLeuProAlaGlnLeuLeuGlyLeuLeuLeu ATGAGGCTCCCCGCTCAGCTCCTGGGGGCTCCTGC TACTCCGAGGGGCGAGTCGAGGACCCCGAGGACG
51	••LeuTrpPheProGlyAlaArgCysAspIleGlnMetThrGlnSerPro TGCTCTGGTTCCCAGGTGCCAGGTGTGACATCCAGATGACCCAGTCTCCA ACGAGACCAAGGGTCCACGGTCCACACTGTAGGTCTACTGGGTCAGAGGT
101	SerSerLeuSerAlaSerValGlyAspArgValThrIleThrCysArgAla TCCTCCCTGTCTGCATCTGTAGGAGACAGAGTCACCATCACTTGCCGGGC AGGAGGGACAGACGTAGACATCCTCTGTCTCAGTGGTAGTGAACGGCCCG
151	•SerGlnGlyIleLysAsnAspLeuGlyTrpTyrGlnGlnLysProGlyLys AAGTCAGGGCATTAAAAATGATTTAGGCTGGTATCAGCAGAAACCAGGGA TTCAGTCCCGTAATTTTTACTAAATCCGACCATAGTCGTCTTTGGTCCCT
201	··AlaProLysArgLeuIleTyrAlaAlaSerSerLeuGlnSerGlyVal AAGCCCCTAAGCGCCTGATCTATGCTGCATCCAGTTTGCAAAGTGGGGTC TTCGGGGATTCGCGGACTAGATACGACGTAGGTCAAACGTTTCACCCCAG
251	ProSerArgPheSerGlySerGlySerGlyThrGluPheThrLeuThrIle CCATCAAGGTTCAGCGGCAGTGGATCTGGGACAGAATTCACTCTCACAAT GGTAGTTCCAAGTCGCCGTCACCTAGACCCTGTCTTAAGTGAGAGTGTTA
301	•SerSerLeuGlnProGluAspPheAlaThrTyrTyrCysLeuGlnHisAsn CAGCAGCCTGCAGCCTGAAGATTTTGCAACTTATTACTGTCTACAGCATA GTCGTCGGACGTCGGACTTCTAAAACGTTGAATAATGACAGATGTCGTAT
351	··SerTyrProCysSerPheGlyGlnGlyThrLysLeuGluIleLysArg ATAGTTATCCGTGCAGTTTTGGCCAGGGGACCAAGCTGGAGATCAAACGA TATCAATAGGCACGTCAAAACCGGTCCCCTGGTTCGACCTCTAGTTTGCT
401	ThrValAlaAlaProSerValPheIlePheProProSerAspGluGlnLeu ACTGTGGCTGCACCATCTGTCTTCATCTTCCCGCCATCTGATGAGCAGTT TGACACCGACGTGGTAGACAGAAGTAGAAGGGCGGTAGACTACTCGTCAA
451	 LysSerGlyThrAlaSerValValCysLeuLeuAsnAsnPheTyrProArg GAAATCTGGAACTGCTAGCGTTGTGTGCCTGCTGAATAACTTCTATCCCA CTTTAGACCTTGACGATCGCAACACACGGACGACTTATTGAAGATAGGGT
501	··GluAlaLysValGlnTrpLysValAspAsnAlaLeuGlnSerGlyAsn GAGAGGCCAAAGTACAGTGGAAGGTGGATAACGCCCTCCAATCGGGTAAC CTCTCCGGTTTCATGTCACCTTCCACCTATTGCGGGAGGTTAGCCCATTG

551	SerGlnGluSerValThrGluGlnAspSerLysAspSerThrTyrSerLeu TCCCAGGAGAGTGTCACAGAGCAGGACAGGACAGGACAG
601	 SerSerThrLeuThrLeuSerLysAlaAspTyrGluLysHisLysValTyr CAGCAGCACCCTGACGCTGAGCAAAGCAGACTACGAGAAACACAAAGTCT GTCGTCGTGGGACTGCGACTCGTTTCGTCTGATGCTCTTTGTGTTTCAGA
651	··AlaCysGluValThrHisGlnGlyLeuSerSerProValThrLysSer ACGCCTGCGAAGTCACCCATCAGGGCCTGAGCTCGCCCGTCACAAAGAGC TGCGGACGCTTCAGTGGGTAGTCCCGGACTCGAGCGGGCAGTGTTTCTCG
701	PheAsnArgGlyGluCys TTCAACAGGGGAGAGTGT AAGTTGTCCCCTCTCACA

1	MetLysHisLeuTrpPhePheLeuLeuLeuValAla ATGAAACATCTGTGGTTCTTCCTCCTGCTGGTGG TACTTTGTAGACACCAAGAAGGAGGACGACCACC
51	··AlaProArgTrpValLeuSerGlnValGlnLeuGlnGluSerGlyPro CAGCTCCCAGATGGGTCCTGTCCCAGGTGCAGCTGCAGGAGTCGGGCCCA GTCGAGGGTCTACCCAGGACAGGGTCCACGTCGACGTCCTCAGCCCGGGT
101	GlyLeuValLysProSerGlnThrLeuSerLeuThrCysThrValSerGly GGACTGGTGAAGCCTTCACAGACCCTGTCCCTCACCTGCACTGTCTCTGG CCTGACCACTTCGGAAGTGTCTGGGACAGGGAGTGGACGTGACAGAGACC
151	 AlaSerIleSerSerGlyAlaTyrTyrTrpSerTrpIleArgGlnHisPro TGCCTCCATCAGCAGTGGTGCTTACTACTGGAGTTGGATCCGCCAGCACC ACGGAGGTAGTCGTCACCACGAATGATGACCTCAACCTAGGCGGTCGTGG
201	••GlyLysGlyLeuGluTrpIleGlyTyrIleTyrLysSerGluThrSer CAGGGAAGGGCCTGGAGTGGATTGGGTACATCTATAAGAGTGAGACCTCC GTCCCTTCCCGGACCTCACCTAACCCATGTAGATATTCTCACTCTGGAGG
251	TyrTyrAsnProSerLeuLysSerArgLeuThrLeuSerValAspThrSer TACTACAACCCGTCCCTCAAGAGTCGACTTACCCTATCAGTAGACACGTC ATGATGTTGGGCAGGGAGTTCTCAGCTGAATGGGATAGTCATCTGTGCAG
301	•LysAsnGlnPheSerLeuAsnLeuIleSerValThrAlaAlaAspThrAla TAAGAACCAGTTCTCCCTGAACCTGATCTCTGTGACTGCCGCGGACACGG ATTCTTGGTCAAGAGGGACTTGGACTAGAGACACTGACGGCGCCTGTGCC
351	••ValTyrTyrCysAlaArgAspLysLeuGlyIleAlaAspTyrTrpGly CCGTGTATTATTGTGCGAGAGATAAACTGGGGATCGCGGACTACTGGGGC GGCACATAATAACACGCTCTCTATTTGACCCCTAGCGCCTGATGACCCCG
401	GlnGlyThrLeuValThrValSerSerAlaSerThrLysGlyProSerVal CAGGGAACCCTGGTCACCGTCTCCTCAGCCTCCACCAAGGGCCCATCGGT GTCCCTTGGGACCAGTGGCAGAGGAGTCGGAGGTGGTTCCCGGGTAGCCA
451	 PheProLeuAlaProCysSerArgSerThrSerGluSerThrAlaAlaLeu CTTCCCCCTGGCGCCCTGC<u>TCTAGA</u>AGCACCTCCGAGAGCACAGCCGCCC GAAGGGGGACCGCGGGACGAGATCTTCGTGGAGGCTCTCGTGTCGGCGGG
501	···GlyCysLeuValLysAspTyrPheProGluProValThrValSerTrp TGGGCTGCCTGGTCAAGGACTACTTCCCCGAACCGGTGACGGTGTCGTGG ACCCGACGGACCAGTTCCTGATGAAGGGGCTTGGCCACTGCCACAGCACC

AsnSerGlyAlaLeuThrSerGlyValHisThrPheProAlaValLeuGln AACTCAGGCGCTCTGACCAGCGGCGTGCACACCTTCCCAGCTGTCCTACA 551 TTGAGTCCGCGAGACTGGTCGCCGCACGTGTGGAAGGGTCGACAGGATGT SerSerGlyLeuTyrSerLeuSerSerValValThrValProSerSerAsn 601 GTCCTCAGGACTCTACTCCCTCAGCAGCGTGGTGACCGTGCCCTCCAGCA CAGGAGTCCTGAGATGAGGGAGTCGTCGCACCACTGGCACGGGAGGTCGT • PheGlyThrGlnThrTyrThrCysAsnValAspHisLysProSerAsn ACTTCGGCACCCAGACCTACACCTGCAACGTAGATCACAAGCCCAGCAAC 651 TGAAGCCGTGGGTCTGGATGTGGACGTTGCATCTAGTGTTCGGGTCGTTG ThrLysValAspLysThrVal 701 751 GTCTGCTGGAAGCCAGGCTCAGCCCTCCTGCCTGGACGCACCCCGGCTGT CAGACGACCTTCGGTCCGAGTCGGGAGGACGGACCTGCGTGGGGCCGACA 801 GCAGCCCCAGCCCAGGGCAGCAAGGCAGGCCCCATCTGTCTCCTCACCCG CGTCGGGGTCGGGTCCCGTCGTTCCGTCCGGGGTAGACAGAGGAGTGGGC 851 GAGGCCTCTGCCCGCCCCACTCATGCTCAGGGAGAGGGTCTTCTGGCTTT TTCCACCAGGCTCCAGGCAGGCACAGGCTGGGTGCCCCTACCCCAGGCCC 901 AAGGTGGTCCGAGGTCCGTCCGTGTCCGACCCACGGGGATGGGGTCCGGG TTCACACACAGGGGCAGGTGCTTGGCTCAGACCTGCCAAAAGCCATATCC 951 AAGTGTGTGTCCCCGTCCACGAACCGAGTCTGGACGGTTTTCGGTATAGG GGGAGGACCCTGCCCCTGACCTAAGCCGACCCCAAAGGCCAAACTGTCCA 1001 CCCTCCTGGGACGGGGACTGGATTCGGCTGGGGTTTCCGGTTTGACAGGT CTCCCTCAGCTCGGACACCTTCTCTCCCCCAGATCCGAGTAACTCCCAA 1051 GAGGGAGTCGAGCCTGTGGAAGAGAGGAGGGGTCTAGGCTCATTGAGGGTT GluArgLysCysCysValGluCysProProCysPro TCTTCTCTCTGCAGAGCGCAAATGTTGTGTGTCGAGTGCCCACCGTGCCCAG 1101 AGAAGAGAGACGTCTCGCGTTTACAACACAGCTCACGGGTGGCACGGGTC GTAAGCCAGCCCAGGCCTCGCCCTCCAGCTCAAGGCGGGACAGGTGCCCT 1151 CATTCGGTCGGGTCCGGAGCGGGAGGTCGAGTTCCGCCCTGTCCACGGGA AGAGTAGCCTGCATCCAGGGACAGGCCCCAGCTGGGTGCTGACACGTCCA 1201 TCTCATCGGACGTAGGTCCCTGTCCGGGGTCGACCCACGACTGTGCAGGT

	AlaProProValAlaGlyProSerValPheLeu
1251	CCTCCATCTCTTCCTCAGCACCACCTGTGGCAGGACCGTCAGTCTTCCTC
	GGAGGTAGAGAAGGAGTCGTGGTGGACACCGTCCTGGCAGTCAGAAGGAG
	PheProProLysProLysAspThrLeuMetIleSerArgThrProGluVal
1301	TTCCCCCCAAAAACCCAAGGACACCCTCATGATCTCCCGGACCCCTGAGGT
	AAGGGGGGTTTTGGGTTCCTGTGGGAGTACTAGAGGGCCTGGGGACTCCA
	 ThrCysValValValAspValSerHisGluAspProGluValGlnPheAsn
1351	CACGTGCGTGGTGGTGGACGTGAGCCACGAAGACCCCCGAGGTCCAGTTCA
	GTGCACGCACCACCTGCACTCGGTGCTTCTGGGGGCTCCAGGTCAAGT
	$\cdot\cdot$ TrpTyrValAspGlyValGluValHisAsnAlaLysThrLysProArg
1401	ACTGGTACGTGGACGCGTGGAGGTGCATAATGCCAAGACAAAGCCACGG
	TGACCATGCACCTGCCGCACCTCCACGTATTACGGTTCTGTTTCGGTGCC
	${\tt GluGluGlnPheAsnSerThrPheArgValValSerValLeuThrValVal}$
1451	GAGGAGCAGTTCAACAGCACGTTCCGTGTGGTCAGCGTCCTCACCGTTGT
1.01	CTCCTCGTCAAGTTGTCGTGCAAGGCACACCAGTCGCAGGAGTGGCAACA
	·HisGlnAspTrpLeuAsnGlyLysGluTyrLysCysLysValSerAsnLys
1501	GCACCAGGACTGGCTGAACGGCAAGGAGTACAAGTGCAAGGTCTCCAACA
1001	CGTGGTCCTGACCGACTTGCCGTTCCTCATGTTCACGTTCCAGAGGTTGT
	$\cdot \cdot \texttt{GlyLeuProAlaProIleGluLysThrIleSerLysThrLys}$
1551	AAGGCCTCCCAGCCCCCATCGAGAAAACCATCTCCAAAACCAAAGGTGGG
1001	TTCCGGAGGGTCGGGGGTAGCTCTTTTGGTAGAGGTTTTGGTTTCCACCC
1601	ACCCGCGGGGTATGAGGGCCACATGGACAGAGGCCGGCTCGGCCCACCCT
	TGGGCGCCCCATACTCCCGGTGTACCTGTCTCCGGCCGAGCCGGGTGGGA
	GlyGlnPro
1651	CTGCCCTGGGAGTGACCGCTGTGCCAACCTCTGTCCCTACAGGGCAGCCC
1001	GACGGGACCCTCACTGGCGACACGGTTGGAGACAGGGATGTCCCGTCGGG
	ArgGluProGlnValTyrThrLeuProProSerArgGluGluMetThrLys
1701	CGAGAACCACAGGTGTACACCCTGCCCCCATCCCGGGAGGAGATGACCAA
	GCTCTTGGTGTCCACATGTGGGACGGGGGGTAGGGCCCTCCTCTACTGGTT
	·AsnGlnValSerLeuThrCysLeuValLysGlyPheTyrProSerAspIle
1751	GAACCAGGTCAGCCTGACCTGCCTGGTCAAAGGCTTCTACCCCAGCGACA
1751	CTTGGTCCAGTCGGACTGGACGGACCAGTTTCCGAAGATGGGGTCGCTGT
	··AlaValGluTrpGluSerAsnGlyGlnProGluAsnAsnTyrLysThr
1801	TCGCCGTGGAGTGGGAGAGCAATGGGCAGCCGGAGAACAACTACAAGACC
TOOT	AGCGGCACCTCACCCTCTCGTTACCCGTCGGCCTCTTGTTGATGTTCTGG
	NGCGGCNCCTCHCCCGTCGTCGGCCTCTTGTTGATGTTCTGG

1851	ThrProProMetLeuAspSerAspGlySerPhePheLeuTyrSerLysLeu ACACCTCCCATGCTGGACTCCGACGGCTCCTTCTTCCTCTACAGCAAGCT TGTGGAGGGTACGACCTGAGGCTGCCGAGGAAGAAGGAGATGTCGTTCGA
1901	•ThrValAspLysSerArgTrpGlnGlnGlyAsnValPheSerCysSerVal CACCGTGGACAAGAGCAGGTGGCAGCAGGGGAACGTCTTCTCATGCTCCG GTGGCACCTGTTCTCGTCCACCGTCGTCCCCTTGCAGAAGAGTACGAGGC
1951	••MetHisGluAlaLeuHisAsnHisTyrThrGlnLysSerLeuSerLeu TGATGCATGAGGCTCTGCACAACCACTACACGCAGAAGAGCCTCTCCCTG ACTACGTACTCCGAGACGTGTTGGTGATGTGCGTCTTCTCGGAGAGGGAC
2001	SerProGlyLys TCTCCGGGTAAA

AGAGGCCCATTT

1	MetArgValProAlaGlnLeuLeuGlyLeuLeuLeu ATGAGGGTCCCCGCTCAGCTCCTGGGGCTCCTGC TACTCCCAGGGGCGAGTCGAGGACCCCGAGGACG
51	··LeuTrpPheProGlyAlaArgCysAspIleGlnMetThrGlnSerPro TGCTCTGGTTCCCAGGCGCCAGGTGTGACATCCAGATGACCCAGTCTCCA ACGAGACCAAGGGTCCGCGGTCCACACTGTAGGTCTACTGGGTCAGAGGT
101	SerSerLeuSerAlaSerValGlyAspArgValThrIleThrCysArgAla TCCTCCCTGTCTGCATCTGTAGGAGACAGAGTCACCATCACTTGCCGGGC AGGAGGGACAGACGTAGACATCCTCTGTCTCAGTGGTAGTGAACGGCCCG
151	•SerGlnAspIleArgAsnAspLeuGlyTrpTyrGlnGlnLysProGlyLys AAGTCAGGACATTAGAAATGATTTAGGCTGGTATCAGCAGAAACCAGGGA TTCAGTCCTGTAATCTTTACTAAATCCGACCATAGTCGTCTTTGGTCCCT
201	··AlaProLysArgLeuIleTyrAlaAlaSerAsnLeuGlnSerGlyVal AAGCCCCTAAGCGCCTGATCTATGCTGCATCCAATTTGCAAAGTGGGGTC TTCGGGGATTCGCGGACTAGATACGACGTAGGTTAAACGTTTCACCCCAG
251	ProSerArgPheSerGlySerGlySerGlyThrGluPheThrLeuThrIle CCATCAAGGTTCAGCGGCAGTGGATCTGGGACAGAATTCACTCTCACAAT GGTAGTTCCAAGTCGCCGTCACCTAGACCCTGTCTTAAGTGAGAGTGTTA
301	•SerSerLeuGlnProGluAspPheAlaThrTyrTyrCysLeuGlnHisAsn CAGCAGCCTGCAGCCTGAAGATTTTGCAACTTATTACTGTCTACAGCATA GTCGTCGGACGTCGGACTTCTAAAACGTTGAATAATGACAGATGTCGTAT
351	••SerTyrProProThrPheGlyGlyGlyThrLysValGluIleLysArg ATAGCTACCCTCCCACTTTCGGCGGAGGGACCAAGGTGGAAATCAAACGA TATCGATGGGAGGGTGAAAGCCGCCTCCCTGGTTCCACCTTTAGTTTGCT
401	ThrValAlaAlaProSerValPheIlePheProProSerAspGluGlnLeu ACTGTGGCTGCACCATCTGTCTTCATCTTCCCGCCATCTGATGAGCAGTT TGACACCGACGTGGTAGACAGAAGTAGAAGGGCGGTAGACTACTCGTCAA
451	•LysSerGlyThrAlaSerValValCysLeuLeuAsnAsnPheTyrProArg GAAATCTGGAACT <u>GCTAGC</u> GTTGTGTGCCTGCTGAATAACTTCTATCCCA CTTTAGACCTTGACGATCGCAACACACGGACGACTTATTGAAGATAGGGT
501	••GluAlaLysValGlnTrpLysValAspAsnAlaLeuGlnSerGlyAsn GAGAGGCCAAAGTACAGTGGAAGGTGGATAACGCCCTCCAATCGGGTAAC CTCTCCGGTTTCATGTCACCTTCCACCTATTGCGGGAGGTTAGCCCATTG

551	SerGlnGluSerValThrGluGlnAspSerLysAspSerThrTyrSerLeu TCCCAGGAGAGTGTCACAGAGCAGGACAGCAAGGACAGCACCTACAGCCT AGGGTCCTCTCACAGTGTCTCGTCCTGTCGTTCCTGTCGTGGATGTCGGA
601	•SerSerThrLeuThrLeuSerLysAlaAspTyrGluLysHisLysValTyr CAGCAGCACCCTGACGCTGAGCAAAGCAGACTACGAGAAACACAAAGTCT GTCGTCGTGGGACTGCGACTCGTTTCGTCTGATGCTCTTTGTGTTTCAGA
651	••AlaCysGluValThrHisGlnGlyLeuSerSerProValThrLysSer ACGCCTGCGAAGTCACCCATCAGGGCCTGAGCTCGCCCGTCACAAAGAGC TGCGGACGCTTCAGTGGGTAGTCCCGGACTCGAGCGGGCAGTGTTTCTCG
701	PheAsnArgGlyGluCys TTCAACAGGGGAGAGTGT

AAGTTGTCCCCTCTCACA

1	MetLysHisLeuTrpPhePheLeuLeuLeuValAla ATGAAACACCTGTGGTTCTTCCTTCTCCTGGTGG TACTTTGTGGACACCAAGAAGGAAGAGGACCACC
51	••AlaProArgTrpValLeuSerGlnValGlnLeuGlnGluSerGlyPro CAGCTCCCAGATGGGTCCTGTCCCAGGTGCAGCTGCAGGAGTCGGGCCCA GTCGAGGGTCTACCCAGGACAGGGTCCACGTCGACGTCCTCAGCCCGGGT
101	GlyLeuValLysProSerGluThrLeuSerLeuThrCysThrValSerGly GGACTGGTGAAGCCTTCGGAGACCCTGTCCCTCACCTGCACTGTCTCTGG CCTGACCACTTCGGAAGCCTCTGGGACAGGGAGTGGACGTGACAGAGACC
151	 ValSerIleSerAsnTyrTyrTrpSerTrpIleArgGlnSerProGlyLys TGTCTCCATCAGTAATTACTACTGGAGCTGGATCCGGCAGTCCCCAGGGA ACAGAGGTAGTCATTAATGATGACCTCGACCTAGGCCGTCAGGGGTCCCT
201	··GlyLeuGluTrpIleGlyTyrIleTyrTyrSerGlySerProTyrTyr AGGGACTGGAGTGGATTGGATATATCTATTACAGTGGGAGTCCCTATTAC TCCCTGACCTCACCTAACCTA
251	AsnProSerLeuLysSerArgValThrIleSerAlaAspThrSerLysAsn AACCCCTCCCTCAAGAGTCGAGTCACTATATCTGCAGACACGTCCAAGAA TTGGGGAGGGAGTTCTCAGCTCAG
301	•GlnPheSerLeuLysLeuSerSerValThrAlaAlaAspThrAlaIleTyr CCAATTCTCCCTGAAGCTGAGCTCTGTGACCGCTGCGGACACGGCCATTT GGTTAAGAGGGACTTCGACTCGAGACACTGGCGACGCCTGTGCCGGTAAA
351	••TyrCysAlaArgGluLysLeuGlyIleGlyAspTyrTrpGlyGlnGly ATTACTGTGCGAGAGAAAAACTGGGGATTGGAGACTACTGGGGCCAGGGA TAATGACACGCTCTCTTTTTGACCCCCTAACCTCTGATGACCCCGGTCCCT
401	ThrLeuValThrValSerSerAlaSerThrLysGlyProSerValPhePro ACCCTGGTCACCGTCTCCTCAGCCTCCACCAAGGGCCCATCGGTCTTCCC TGGGACCAGTGGCAGAGGAGTCGGAGGTGGTTCCCGGGTAGCCAGAAGGG
451	•LeuAlaProCysSerArgSerThrSerGluSerThrAlaAlaLeuGlyCys CCTGGCGCCCTGC <u>TCTAGA</u> AGCACCTCCGAGAGCACAGCCGCCCTGGGCT GGACCGCGGGACGAGATCTTCGTGGAGGCTCTCGTGTCGGCGGGACCCGA
501	··LeuValLysAspTyrPheProGluProValThrValSerTrpAsnSer GCCTGGTCAAGGACTACTTCCCCGAACCGGTGACGGTGTCGTGGAACTCA CGGACCAGTTCCTGATGAAGGGGGCTTGGCCACTGCCACAGCACCTTGAGT

551	GlyAlaLeuThrSerGlyValHisThrPheProAlaValLeuGlnSerSer GGCGCTCTGACCAGCGGCGTGCACACCTTCCCAGCTGTCCTACAGTCCTC CCGCGAGACTGGTCGCCGCACGTGTGGAAGGGTCGACAGGATGTCAGGAG
601	•GlyLeuTyrSerLeuSerSerValValThrValProSerSerAsnPheGly AGGACTCTACTCCCTCAGCAGCGTGGTGACCGTGCCCTCCAGCAACTTCG TCCTGAGATGAGGGAGTCGTCGCACCACTGGCACGGGAGGTCGTTGAAGC
651	••ThrGlnThrTyrThrCysAsnValAspHisLysProSerAsnThrLys GCACCCAGACCTACACCTGCAACGTAGATCACAAGCCCAGCAACACCAAG CGTGGGTCTGGATGTGGACGTTGCATCTAGTGTTCGGGTCGTTGTGGTTC
701	ValAspLysThrVal GTGGACAAGACAGTTGGTGAGAGGCCAGCTCAGGGAGGGA
751	TGGAAGCCAGGCTCAGCCCTCCTGCCTGGACGCACCCCGGCTGTGCAGCC ACCTTCGGTCCGAGTCGGGAGGACGGACCTGCGTGGGGCCGACACGTCGG
801	CCAGCCCAGGGCAGCAAGGCAGGCCCCATCTGTCTCCTCACCCGGAGGCC GGTCGGGTCCCGTCGTTCCGTCCGGGGTAGACAGAGGAGTGGGCCTCCGG
851	TCTGCCCGCCCCACTCATGCTCAGGGAGAGGGTCTTCTGGCTTTTTCCAC AGACGGGCGGGGTGAGTACGAGTCCCTCTCCCAGAAGACCGAAAAAGGTG
901	CAGGCTCCAGGCAGGCACAGGCTGGGTGCCCCTACCCCAGGCCCTTCACA GTCCGAGGTCCGTCCGTGTCCGACCCACGGGGATGGGGTCCGGGAAGTGT
951	CACAGGGGCAGGTGCTTGGCTCAGACCTGCCAAAAGCCATATCCGGGAGG GTGTCCCCGTCCACGAACCGAGTCTGGACGGTTTTCGGTATAGGCCCTCC
1001	ACCCTGCCCCTGACCTAAGCCGACCCCAAAGGCCAAACTGTCCACTCCCT TGGGACGGGGACTGGATTCGGCTGGGGTTTCCGGTTTGACAGGTGAGGGA
1051	CAGCTCGGACACCTTCTCTCCCCCAGATCCGAGTAACTCCCAATCTTCT GTCGAGCCTGTGGAAGAGAGGAGGGGTCTAGGCTCATTGAGGGTTAGAAGA
1101	GluArgLysCysCysValGluCysProProCysPro CTCTGCAGAGCGCAAATGTTGTGTCGAGTGCCCACCGTGCCCAGGTAAGC GAGACGTCTCGCGTTTACAACACAGCTCACGGGTGGCACGGGTCCATTCG
1151	CAGCCCAGGCCTCGCCCTCCAGCTCAAGGCGGGACAGGTGCCCTAGAGTA GTCGGGTCCGGAGCGGGAGGTCGAGTTCCGCCCTGTCCACGGGATCTCAT
1201	GCCTGCATCCAGGGACAGGCCCCAGCTGGGTGCTGACACGTCCACCTCCA CGGACGTAGGTCCCTGTCCGGGGTCGACCCACGACTGTGCAGGTGGAGGT

	${\tt AlaProProValAlaGlyProSerValPheLeuPhePro}$
1251	TCTCTTCCTCAGCACCACCTGTGGCAGGACCGTCAGTCTTCCTCTTCCCC
	AGAGAAGGAGTCGTGGTGGACACCGTCCTGGCAGTCAGAAGGAGAAGGGG
	ProLysProLysAspThrLeuMetIleSerArgThrProGluValThrCys
1301	CCAAAACCCAAGGACACCCTCATGATCTCCCGGACCCCTGAGGTCACGTG
	GGTTTTGGGTTCCTGTGGGAGTACTAGAGGGCCTGGGGACTCCAGTGCAC
	\cdot ValValValAspValSerHisGluAspProGluValGlnPheAsnTrpTyr
1351	CGTGGTGGTGGACGTGAGCCACGAAGACCCCGAGGTCCAGTTCAACTGGT
	GCACCACCACCTGCACTCGGGTGCTTCTGGGGGCTCCAGGTCAAGTTGACCA
	$\cdot\cdot$ ValAspGlyValGluValHisAsnAlaLysThrLysProArgGluGlu
1401	ACGTGGACGGCGTGGAGGTGCATAATGCCAAGACAAAGCCACGGGAGGAG
	TGCACCTGCCGCACCTCCACGTATTACGGTTCTGTTTCGGTGCCCTCCTC
	GlnPheAsnSerThrPheArgValValSerValLeuThrValValHisGln
1451	CAGTTCAACAGCACGTTCCGTGTGGGTCAGCGTCCTCACCGTTGTGCACCA
	GTCAAGTTGTCGTGCAAGGCACACCAGTCGCAGGAGTGGCAACACGTGGT
	 AspTrpLeuAsnGlyLysGluTyrLysCysLysValSerAsnLysGlyLeu
1501	GGACTGGCTGAACGGCAAGGAGTACAAGTGCAAGGTCTCCAACAAAGGCC
	CCTGACCGACTTGCCGTTCCTCATGTTCACGTTCCAGAGGTTGTTTCCGG
	••ProAlaProIleGluLysThrIleSerLysThrLys
1551	TCCCAGCCCCCATCGAGAAAACCATCTCCAAAAACCAAAGGTGGGACCCGC
	AGGGTCGGGGGTAGCTCTTTTGGTAGAGGTTTTGGTTTCCACCCTGGGCG
1601	GGGGTATGAGGGCCACATGGACAGAGGCCGGCTCGGCCCACCCTCTGCCC
	CCCCATACTCCCGGTGTACCTGTCTCCGGCCGAGCCGGGTGGGAGACGGG
	GlyGlnProArgGlu
1651	TGGGAGTGACCGCTGTGCCAACCTCTGTCCCTACAGGGCAGCCCCGAGAA
	ACCCTCACTGGCGACACGGTTGGAGACAGGGATGTCCCGTCGGGGCTCTT
	ProGlnValTyrThrLeuProProSerArgGluGluMetThrLysAsnGln
1701	CCACAGGTGTACACCCTGCCCCCATCCCGGGAGGAGATGACCAAGAACCA
	GGTGTCCACATGTGGGACGGGGGGGGGGGGGCCCTCCTCTACTGGTTCTTGGT
	 ValSerLeuThrCysLeuValLysGlyPheTyrProSerAspIleAlaVal
1751	GGTCAGCCTGACCTGCCTGGTCAAAGGCTTCTACCCCAGCGACATCGCCG
	CCAGTCGGACTGGACGGACCAGTTTCCGAAGATGGGGTCGCTGTAGCGGC
	$\cdot\cdot \texttt{GluTrpGluSerAsnGlyGlnProGluAsnAsnTyrLysThrThrPro}$
1801	TGGAGTGGGAGAGCAATGGGCAGCCGGAGAACAACTACAAGACCACACCT
	ACCTCACCCTCTCGTTACCCGTCGGCCTCTTGTTGATGTTCTGGTGTGGA

1851	ProMetLeuAspSerAspGlySerPhePheLeuTyrSerLysLeuThrVal CCCATGCTGGACTCCGACGGCTCCTTCTTCCTCTACAGCAAGCTCACCGT GGGTACGACCTGAGGCTGCCGAGGAAGAAGGAGATGTCGTTCGAGTGGCA
1901	 AspLysSerArgTrpGlnGlnGlyAsnValPheSerCysSerValMetHis GGACAAGAGCAGGTGGCAGCAGGGGAACGTCTTCTCATGCTCCGTGATGC CCTGTTCTCGTCCACCGTCGTCCCCTTGCAGAAGAGTACGAGGCACTACG
1951	••GluAlaLeuHisAsnHisTyrThrGlnLysSerLeuSerLeuSerPro ATGAGGCTCTGCACAACCACTACACGCAGAAGAGCCTCTCCCTGTCTCCG TACTCCGAGACGTGTTGGTGATGTGCGTCTTCTCGGAGAGGGGACAGAGGC
2001	GlyLys GGTAAA CCATTT

1	MetArgValProAlaGlnLeuLeuGlyLeuLeuLeu ATGAGGGTCCCCGCTCAGCTCCTGGGGCTCCTGC TACTCCCAGGGGCGAGTCGAGGACCCCGAGGACG
51	<pre>・・LeuTrpPheProGlyAlaArgCysAspIleGlnMetThrGlnSerPro TGCTCTGGTTCCCAGGTGCCAGGTGTGACATCCAGATGACCCAGTCTCCA ACGAGACCAAGGGTCCACGGTCCACACTGTAGGTCTACTGGGTCAGAGGT</pre>
101	SerSerLeuSerAlaSerValGlyAspArgValThrIleThrCysArgAla TCCTCCCTGTCTGCATCTGTCGGAGACAGAGTCACCATCACTTGCCGGGC AGGAGGGACAGACGTAGACAGCCTCTGTCTCAGTGGTAGTGAACGGCCCG
151	•SerGlnGlyIleArgAsnAspLeuGlyTrpTyrGlnGlnLysProGlyLys AAGTCAGGGCATTAGAAATGATTTAGGCTGGTATCAGCAGAAACCAGGGA TTCAGTCCCGTAATCTTTACTAAATCCGACCATAGTCGTCTTTGGTCCCT
201	••AlaProLysArgLeuIleTyrAlaAlaSerSerLeuGlnSerGlyVal AAGCCCCTAAGCGCCTGATCTATGCTGCATCCAGTTTGCAAAGTGGGGTC TTCGGGGATTCGCGGACTAGATACGACGTAGGTCAAACGTTTCACCCCAG
251	ProSerArgPheSerGlySerGlySerGlyThrGluPheThrLeuThrIle CCATCAAGGTTCAGCGGCAGTGGATCTGGGACAGAATTCACTCTCACAAT GGTAGTTCCAAGTCGCCGTCACCTAGACCCTGTCTTAAGTGAGAGTGTTA
301	•SerSerLeuGlnProGluAspPheAlaThrTyrTyrCysLeuGlnHisAsn CAGCAGCCTGCAGCCTGAAGATTTTGCAACTTATTACTGTCTACAGCATA GTCGTCGGACGTCGGACTTCTAAAACGTTGAATAATGACAGATGTCGTAT
351	··SerTyrProProThrPheGlyProGlyThrLysValAspIleLysArg ATAGTTACCCTCCCACTTTCGGCCCTGGGACCAAGGTGGATATCAAACGA TATCAATGGGAGGGTGAAAGCCGGGACCCTGGTTCCACCTATAGTTTGCT
401	ThrValAlaAlaProSerValPheIlePheProProSerAspGluGlnLeu ACTGTGGCTGCACCATCTGTCTTCATCTTCCCGCCATCTGATGAGCAGTT TGACACCGACGTGGTAGACAGAAGTAGAAGGGCGGTAGACTACTCGTCAA
451	•LysSerGlyThrAlaSerValValCysLeuLeuAsnAsnPheTyrProArg GAAATCTGGAACTGCTAGCGTTGTGTGCCTGCTGAATAACTTCTATCCCA CTTTAGACCTTGACGATCGCAACACACGGACGACTTATTGAAGATAGGGT
501	··GluAlaLysValGlnTrpLysValAspAsnAlaLeuGlnSerGlyAsn GAGAGGCCAAAGTACAGTGGAAGGTGGATAACGCCCTCCAATCGGGTAAC CTCTCCGGTTTCATGTCACCTTCCACCTATTGCGGGAGGTTAGCCCATTG

551	SerGlnGluSerValThrGluGlnAspSerLysAspSerThrTyrSerLeu TCCCAGGAGAGTGTCACAGAGCAGGACAGCAAGGACAGCACCTACAGCCT AGGGTCCTCTCACAGTGTCTCGTCCTGTCGTTGCGTGGATGTCGGA
601	 SerSerThrLeuThrLeuSerLysAlaAspTyrGluLysHisLysValTyr CAGCAGCACCCTGACGCTGAGCAAAGCAGACTACGAGAAACACAAAGTCT GTCGTCGTGGGACTGCGACTCGTTTCGTCTGATGCTCTTTGTGTTTCAGA
651	••AlaCysGluValThrHisGlnGlyLeuSerSerProValThrLysSer ACGCCTGCGAAGTCACCCATCAGGGCCTGAGCTCGCCCGTCACAAAGAGC TGCGGACGCTTCAGTGGGTAGTCCCGGACTCGAGCGGGCAGTGTTTCTCG
701	PheAsnArgGlyGluCys TTCAACAGGGGAGAGTGT AAGTTGTCCCCTCTCACA

1	MetLysHisLeuTrpPhePheLeuLeuValAla ATGAAACATCTGTGGTTCTTCCTTCCTGGTGG TACTTTGTAGACACCAAGAAGGAAGAGGACCACC
51	••AlaProArgTrpValLeuSerGlnValGlnLeuGlnGluSerGlyPro CAGCTCCCAGATGGGTCCTGTCCCAGGTGCAGCTGCAGGAGTCGGGCCCA GTCGAGGGTCTACCCAGGACAGGGTCCACGTCGACGTCCTCAGCCCGGGT
101	GlyLeuValLysProSerGluThrLeuSerLeuThrCysThrValSerGly GGACTGGTGAAGCCTTCGGAGACCCTGTCCCTCACCTGCACTGTCTCTGG CCTGACCACTTCGGAAGCCTCTGGGACAGGGAGTGGACGTGACAGAGACC
151	•GlySerIleSerArgTyrTyrTrpSerTrpIleArgGlnProProGlyLys TGGCTCCATCAGTCGTTACTACTGGAGCTGGATCCGGCAGCCCCCAGGGA ACCGAGGTAGTCAGCAATGATGACCTCGACCTAGGCCGTCGGGGGTCCCT
201	<pre>••GlyLeuGluTrpIleGlyTyrValSerTyrSerGlySerThrTyrTyr AGGGACTGGAGTGGATTGGGTATGTCTCTTACAGTGGGAGCACCTACTAC TCCCTGACCTCACCTAACCCATACAGAGAATGTCACCCTCGTGGATGATG</pre>
251	AsnProSerLeuLysSerArgValThrIleSerValAspThrSerLysAsn AACCCCTCCCTCAAGAGTCGAGTCACCATATCAGTAGACACGTCCAAGAA TTGGGGAGGGAGTTCTCCAGCTCAGTGGTATAGTCATCTGTGCAGGTTCTT
301	•GlnPheSerLeuLysLeuSerSerValThrAlaAlaAspThrAlaValTyr CCAGTTCTCCCTGAAGCTGAGCTCTGTGACCGCTGCGGACACGGCCGTGT GGTCAAGAGGGACTTCGACTCGAGACACTGGCGACGCCTGTGCCGGCACA
351	••TyrCysAlaArgAspLysLeuGlyIleGlyAspTyrTrpGlyGlnGly ATTACTGTGCGAGAGATAAACTGGGGATTGGAGACTACTGGGGCCAGGGA TAATGACACGCTCTCTATTTGACCCCTAACCTCTGATGACCCCGGTCCCT
401	ThrLeuValThrValSerSerAlaSerThrLysGlyProSerValPhePro ACCCTGGTCACCGTCTCCTCAGCCTCCACCAAGGGCCCATCGGTCTTCCC TGGGACCAGTGGCAGAGGAGTCGGAGGTGGTTCCCCGGGTAGCCAGAAGGG
451	 LeuAlaProCysSerArgSerThrSerGluSerThrAlaAlaLeuGlyCys CCTGGCGCCCTGC<u>TCTAGA</u>AGCACCTCCGAGAGCACAGCCGCCCTGGGCT GGACCGCGGGACGAGATCTTCGTGGAGGCTCTCGTGTCGGCGGGACCCGA
501	··LeuValLysAspTyrPheProGluProValThrValSerTrpAsnSer GCCTGGTCAAGGACTACTTCCCCGAACCGGTGACGGTGTCGTGGAACTCA CGGACCAGTTCCTGATGAAGGGGGCTTGGCCACTGCCACAGCACCTTGAGT

551	GlyAlaLeuThrSerGlyValHisThrPheProAlaValLeuGlnSerSer GGCGCTCTGACCAGCGGCGTGCACACCTTCCCAGCTGTCCTACAGTCCTC
	CCGCGAGACTGGTCGCCGCACGTGTGGAAGGGTCGACAGGATGTCAGGAG
601	•GlyLeuTyrSerLeuSerSerValValThrValProSerSerAsnPheGly
001	AGGACTCTACTCCCTCAGCAGCGTGGTGACCGTGCCCTCCAGCAACTTCG TCCTGAGATGAGGGAGTCGTCGCACCACTGGCACGGGAGGTCGTTGAAGC
651	••ThrGlnThrTyrThrCysAsnValAspHisLysProSerAsnThrLys GCACCCAGACCTACACCTGCAACGTAGATCACAAGCCCAGCAACACCAAG
031	CGTGGGTCTGGATGTGGACGTTGCATCTAGTGTTCGGGTCGTTGTGGGTCC
701	ValAspLysThrVal GTGGACAAGACAGTTGGTGAGAGGCCAGCTCAGGGAGGGA
, , ,	CACCTGTTCTGTCAACCACTCTCCGGTCGAGTCCCCCCCC
753	
751	TGGAAGCCAGGCTCAGCCCTCCTGCCTGGACGCACCCCGGCTGTGCAGCC ACCTTCGGTCCGAGTCGGGAGGACGGACCTGCGTGGGGCCGACACGTCGG
801	CCAGCCCAGGGCAGCAAGGCAGGCCCCATCTGTCTCCTCACCCGGAGGCC
	GGTCGGGTCCCGTCGTTCCGTCCGGGGTAGACAGAGGAGTGGGCCTCCGG
851	TCTGCCCGCCCCACTCATGCTCAGGGAGAGGGTCTTCTGGCTTTTTCCAC
	AGACGGGCGGGGTGAGTACGAGTCCCTCTCCCAGAAGACCGAAAAAGGTG
901	CAGGCTCCAGGCAGGCACAGGCTGGGTGCCCCTACCCCAGGCCCTTCACA
	GTCCGAGGTCCGTCCGTGTCCGACCCACGGGGATGGGGTCCGGGAAGTGT
951	CACAGGGGCAGGTGCTTGGCTCAGACCTGCCAAAAGCCATATCCGGGAGG
	GTGTCCCCGTCCACGAACCGAGTCTGGACGGTTTTCGGTATAGGCCCTCC
1001	ACCCTGCCCTGACCTAAGCCGACCCCAAAGGCCAAACTGTCCACTCCCT
	TGGGACGGGGACTGGATTCGGCTGGGGTTTCCGGTTTGACAGGTGAGGGA
1051	CAGCTCGGACACCTTCTCTCCCCCAGATCCGAGTAACTCCCAATCTTCT
	GTCGAGCCTGTGGAAGAGAGGGGGGGTCTAGGCTCATTGAGGGGTTAGAAGA
	GluArgLysCysCysValGluCysProProCysPro
1101	CTCTGCAGAGCGCAAATGTTGTGTCGAGTGCCCACCGTGCCCAGGTAAGC
	GAGACGTCTCGCGTTTACAACACAGCTCACGGGTGGCACGGGTCCATTCG
1151	CAGCCCAGGCCTCGCCCTCCAGCTCAAGGCGGGACAGGTGCCCTAGAGTA
	GTCGGGTCCGGAGCGGGAGGTCGAGTTCCGCCCTGTCCACGGGATCTCAT
1201	GCCTGCATCCAGGGACAGGCCCCAGCTGGGTGCTGACACGTCCACCTCCA
	CGGACGTAGGTCCCTGTCCGGGGTCGACCACGACGACGACGTGGAGGTGGAGGT

1251	AlaProProValAlaGlyProSerValPheLeuPhePro TCTCTTCCTCAGCACCACCTGTGGCAGGACCGTCAGTCTTCCTCTTCCCC AGAGAAGGAGTCGTGGTGGACACCGTCCTGGCAGTCAGAAGGAGAAGGGG
1301	ProLysProLysAspThrLeuMetIleSerArgThrProGluValThrCys CCAAAACCCAAGGACACCCTCATGATCTCCCGGACCCCTGAGGTCACGTG GGTTTTGGGTTCCTGTGGGAGTACTAGAGGGCCTGGGGGACTCCAGTGCAC
1351	 ValValValAspValSerHisGluAspProGluValGlnPheAsnTrpTyr CGTGGTGGTGGACGTGAGCCACGAAGACCCCCGAGGTCCAGTTCAACTGGT GCACCACCACCTGCACTCGGTGCTTCTGGGGGCTCCAGGTCAAGTTGACCA
1401	••ValAspGlyValGluValHisAsnAlaLysThrLysProArgGluGlu ACGTGGACGGCGTGGAGGTGCATAATGCCAAGACAAAGCCACGGGAGGAG TGCACCTGCCGCACCTCCACGTATTACGGTTCTGTTTCGGTGCCCTCCTC
1451	GlnPheAsnSerThrPheArgValValSerValLeuThrValValHisGln CAGTTCAACAGCACGTTCCGTGTGGTCAGCGTCCTCACCGTTGTGCACCA GTCAAGTTGTCGTGCAAGGCACACCAGTCGCAGGAGTGGCAACACGTGGT
1501	•AspTrpLeuAsnGlyLysGluTyrLysCysLysValSerAsnLysGlyLeu GGACTGGCTGAACGGCAAGGAGTACAAGTGCAAGGTCTCCAACAAAGGCC CCTGACCGACTTGCCGTTCCTCATGTTCACGTTCCAGAGGTTGTTTCCGG
1551	••ProAlaProIleGluLysThrIleSerLysThrLys TCCCAGCCCCCATCGAGAAAACCATCTCCAAAACCAAAGGTGGGACCCGC AGGGTCGGGGGTAGCTCTTTTGGTAGAGGTTTTGGTTTCCACCCTGGGCG
1601	GGGGTATGAGGGCCACATGGACAGAGGCCGGCTCGGCCCACCCTCTGCCC CCCCATACTCCCGGTGTACCTGTCTCCGGCCGAGCCGGGTGGGAGACGGG
1651	GlyGlnProArgGlu TGGGAGTGACCGCTGTGCCAACCTCTGTCCCTACAGGGCAGCCCCGAGAA ACCCTCACTGGCGACACGGTTGGAGACAGGGATGTCCCGTCGGGGCTCTT
1701	ProGlnValTyrThrLeuProProSerArgGluGluMetThrLysAsnGln CCACAGGTGTACACCCTGCCCCCATCCCGGGAGGAGATGACCAAGAACCA GGTGTCCACATGTGGGACGGGGGGTAGGGCCCTCCTCTACTGGTTCTTGGT
1751	 ValSerLeuThrCysLeuValLysGlyPheTyrProSerAspIleAlaVal GGTCAGCCTGACCTGCCTGGTCAAAGGCTTCTACCCCAGCGACATCGCCG CCAGTCGGACTGGACGGACCAGTTTCCGAAGATGGGGTCGCTGTAGCGGC
	·

1851	ProMetLeuAspSerAspGlySerPhePheLeuTyrSerLysLeuThrVal CCCATGCTGGACTCCGACGGCTCCTTCTTCCTCTACAGCAAGCTCACCGT GGGTACGACCTGAGGCTGCCGAGGAAGAAGGAGATGTCGTTCGAGTGGCA
1901	 AspLysSerArgTrpGlnGlnGlyAsnValPheSerCysSerValMetHis GGACAAGAGCAGGTGGCAGCAGGGGGAACGTCTTCTCATGCTCCGTGATGC CCTGTTCTCGTCCACCGTCGTCCCCTTGCAGAAGAGTACGAGGCACTACG
1951	··GluAlaLeuHisAsnHisTyrThrGlnLysSerLeuSerLeuSerPro ATGAGGCTCTGCACAACCACTACACGCAGAAGAGCCTCTCCCTGTCTCCG TACTCCGAGACGTGTTGGTGATGTGCGTCTTCTCGGAGAGGGACAGAGGC
2001	GlyLys GGTAAA CCATTT

FIGURE 49

1	MetArgLeuProAlaGlnLeuLeuGlyLeuLeuLeu ATGAGGCTCCCTGCTCAGCTCCTGGGGCTCCTGC TACTCCGAGGGACGAGTCGAGGACCCCGAGGACG
51	••LeuTrpPheProGlyAlaArgCysAspIleGlnMetThrGlnSerPro TGCTCTGGTTCCCAGGTGCCAGGTGTGACATCCAGATGACCCAGTCTCCA ACGAGACCAAGGGTCCACGGTCCACACTGTAGGTCTACTGGGTCAGAGGT
101	SerSerLeuSerAlaSerValGlyAspArgValThrIleThrCysArgAla TCCTCCCTGTCTGCATCTGTAGGAGACAGAGTCACCATCACTTGCCGGGC AGGAGGGACAGACGTAGACATCCTCTGTCTCAGTGGTAGTGAACGGCCCG
151	 SerGlnGlyIleArgAsnAspLeuGlyTrpTyrGlnGlnLysProGlyLys AAGTCAGGGCATTAGAAATGATTTAGGCTGGTATCAGCAGAAACCGGGGA TTCAGTCCCGTAATCTTACTAAATCCGACCATAGTCGTCTTTGGCCCCT
201	••AlaProLysArgLeuIleTyrAlaAlaSerSerLeuGlnSerGlyVal AAGCCCCTAAGCGCCTGATCTATGCTGCATCCAGTTTGCAAAGTGGGGTC TTCGGGGATTCGCGGACTAGATACGACGTAGGTCAAACGTTTCACCCCAG
251	ProSerArgPheSerGlySerGlySerGlyThrGluPheThrLeuThrIle CCATCAAGGTTCAGCGGCAGTGGATCTGGGACAGAATTCACTCTCACAAT GGTAGTTCCAAGTCGCCGTCACCTAGACCCTGTCTTAAGTGAGAGTGTTA
301	•SerSerLeuGlnProGluAspPheAlaThrTyrTyrCysLeuGlnHisAsn CAGCAGCCTGCAGCCTGAAGATTTTGCAACTTATTACTGTCTACAGCATA GTCGTCGGACGTCGGACTTCTAAAACGTTGAATAATGACAGATGTCGTAT
351	•••SerTyrProCysSerPheGlyGlnGlyThrLysLeuGluIleLysArg ATAGTTACCCGTGCAGTTTTGGCCAGGGGACCAAGCTGGAGATCAAACGA TATCAATGGGCACGTCAAAACCGGTCCCCTGGTTCGACCTCTAGTTTGCT
401	ThrValAlaAlaProSerValPheIlePheProProSerAspGluGlnLeu ACTGTGGCTGCACCATCTGTCTTCATCTTCCCGCCATCTGATGAGCAGTT TGACACCGACGTGGTAGACAGAAGTAGAAGGGCGGTAGACTACTCGTCAA
451	 LysSerGlyThrAlaSerValValCysLeuLeuAsnAsnPheTyrProArg GAAATCTGGAACTGCTAGCGTTGTGTGTGCCTGCTGAATAACTTCTATCCCA CTTTAGACCTTGACGATCGCAACACACGGACGACTTATTGAAGATAGGGT
501	··GluAlaLysValGlnTrpLysValAspAsnAlaLeuGlnSerGlyAsn GAGAGGCCAAAGTACAGTGGAAGGTGGATAACGCCCTCCAATCGGGTAAC CTCTCCGGTTTCATGTCACCTTCCACCTATTGCGGGAGGTTAGCCCATTG

551	SerGlnGluSerValThrGluGlnAspSerLysAspSerThrTyrSerLeu TCCCAGGAGAGTGTCACAGAGCAGGACAGCAAGGACAGCACCTACAGCCT AGGGTCCTCTCACAGTGTCTCGTCCTGTCGTTCCTGTCGTGGATGTCGGA
601	•SerSerThrLeuThrLeuSerLysAlaAspTyrGluLysHisLysValTyr CAGCAGCACCCTGACGCTGAGCAAAGCAGACTACGAGAAACACAAAGTCT GTCGTCGTGGGACTGCGACTCGTTTCGTCTGATGCTCTTTGTGTTTCAGA
651	••AlaCysGluValThrHisGlnGlyLeuSerSerProValThrLysSer ACGCCTGCGAAGTCACCCATCAGGGCCTGAGCTCGCCCGTCACAAAGAGC TGCGGACGCTTCAGTGGGTAGTCCCGGACTCGAGCGGGCAGTGTTTCTCG
701	PheAsnArgGlyGluCys TTCAACAGGGGAGAGTGT AAGTTGTCCCCTCTCACA

FIGURE 50

1	MetLysHisLeuTrpPhePheLeuLeuLeuValAla ATGAAGCATCTGTGGTTCTTCCTCCTGCTGGTGG TACTTCGTAGACACCAAGAAGGAGGACGACCACC
51	··AlaProArgTrpValLeuSerGlnValGlnLeuGlnGluSerGlyPro CAGCTCCCAGATGGGTCCTGTCCCAGGTGCAGCTGCAGGAGTCGGGCCCA GTCGAGGGTCTACCCAGGACAGGGTCCACGTCGACGTCCTCAGCCCGGGT
101	GlyLeuValLysProLeuGlnThrLeuSerLeuThrCysThrValSerGly GGACTGGTGAAGCCTTTACAGACCCTGTCCCTCACCTGCACTGTCTCTGG CCTGACCACTTCGGAAATGTCTGGGACAGGGAGTGGACGTGACAGAGACC
151	•GlySerIleSerSerGlyValTyrTyrTrpSerTrpIleArgGlnHisPro TGGCTCCATCAGCAGTGGTGTTTACTACTGGAGCTGGATCCGCCAGCACC ACCGAGGTAGTCGTCACCACAAATGATGACCTCGACCTAGGCGGTCGTGG
201	··GlyLysGlyLeuGluTrpIleGlyTyrIleTyrAsnSerLysThrSer CAGGGAAGGGCCTGGAGTGGATTGGGTACATCTATAACAGTAAGACCTCC GTCCCTTCCCGGACCTCACCTAACCCATGTAGATATTGTCATTCTGGAGG
251	TyrTyrAsnProSerLeuLysSerArgLeuThrLeuSerValAspThrSer TATTATAATCCGTCCCTCAAGAGTCGACTTACCCTATCAGTAGACACGTC ATAATATTAGGCAGGGAGTTCTCAGCTGAATGGGATAGTCATCTGTGCAG
301	 LysAsnGlnPheSerLeuAsnLeuIleSerValThrAlaAlaAspThrAla TAAGAACCAGTTCTCCCTGAACCTGATCTCTGTGACTGCCGCGGACACGG ATTCTTGGTCAAGAGGGGACTTGGACTAGAGACACTGACGGCGCCTGTGCC
351	••ValTyrTyrCysAlaArgAspLysLeuGlyIleAlaAspTyrTrpGly CCGTGTATTACTGTGCGAGAGATAAATTGGGGATCGCGGACTACTGGGGC GGCACATAATGACACGCTCTCTATTTAACCCCCTAGCGCCTGATGACCCCG
401	GlnGlyThrLeuValThrValSerSerAlaSerThrLysGlyProSerVal CAGGGAACCCTGGTCACCGTCTCCTCAGCCTCCACCAAGGGCCCATCGGT GTCCCTTGGGACCAGTGGCAGAGGAGTCGGAGGTGGTTCCCCGGGTAGCCA
451	 PheProLeuAlaProCysSerArgSerThrSerGluSerThrAlaAlaLeu CTTCCCCCTGGCGCCCTGC<u>TCTAGA</u>AGCACCTCCGAGAGCACAGCCGCCC GAAGGGGGACCGCGGGACGAGATCTTCGTGGAGGCTCTCGTGTCGGCGGG
501	••GlyCysLeuValLysAspTyrPheProGluProValThrValSerTrp TGGGCTGCCTGGTCAAGGACTACTTCCCCGAACCGGTGACGGTGTCGTGG ACCCGACGGACCAGTTCCTGATGAAGGGGGCTTGGCCACTGCCACAGCACC

551	AsnSerGlyAlaLeuThrSerGlyValHisThrPheProAlaValLeuGln AACTCAGGCGCTCTGACCAGCGGCGTGCACACCTTCCCAGCTGTCCTACA TTGAGTCCGCGAGACTGGTCGCCGCACGTGTGGAAGGGTCGACAGGATGT
601	 SerSerGlyLeuTyrSerLeuSerSerValValThrValProSerSerAsn GTCCTCAGGACTCTACTCCCTCAGCAGCGTGGTGACCGTGCCCTCCAGCA CAGGAGTCCTGAGATGAGGGAGTCGTCGCACCACTGGCACGGGAGGTCGT
651	••PheGlyThrGlnThrTyrThrCysAsnValAspHisLysProSerAsn ACTTCGGCACCCAGACCTACACCTGCAACGTAGATCACAAGCCCAGCAAC TGAAGCCGTGGGTCTGGATGTGGACGTTGCATCTAGTGTTCGGGTCGTTG
701	ThrLysValAspLysThrVal ACCAAGGTGGACAAGACAGTTGGTGAGAGGCCAGCTCAGGGAGGG
751	GTCTGCTGGAAGCCAGGCTCAGCCCTCCTGCCTGGACGCACCCCGGCTGT CAGACGACCTTCGGTCCGAGTCGGGAGGACGGACCTGCGTGGGGGCCGACA
801	GCAGCCCCAGCCCAGGGCAGCAAGGCAGGCCCCATCTGTCTCCTCACCCG CGTCGGGGTCGGGTC
851	GAGGCCTCTGCCCGCCCCACTCATGCTCAGGGAGAGGGTCTTCTGGCTTT CTCCGGAGACGGGGGGGGGG
901	TTCCACCAGGCTCCAGGCAGGCACAGGCTGGGTGCCCCTACCCCAGGCCC AAGGTGGTCCGAGGTCCGTCCGTGTCCGACCCACGGGGATGGGGTCCGGG
951	TTCACACACAGGGGCAGGTGCTTGGCTCAGACCTGCCAAAAGCCATATCC AAGTGTGTGTCCCCGTCCACGAACCGAGTCTGGACGGTTTTCGGTATAGG
1001	GGGAGGACCCTGCCCCTGACCTAAGCCGACCCCAAAGGCCAAACTGTCCA CCCTCCTGGGACGGGGACTGGATTCGGCTGGGGTTTCCGGTTTGACAGGT
1051	CTCCCTCAGCTCGGACACCTTCTCTCCCCCAGATCCGAGTAACTCCCAA GAGGGAGTCGAGCCTGTGGAAGAGAGGGGGGGTCTAGGCTCATTGAGGGTT
	GluArgLysCysCysValGluCysProProCysPro
1101	TCTTCTCTCTGCAGAGCGCAAATGTTGTGTCGAGTGCCCACCGTGCCCAG AGAAGAGAGACGTCTCGCGTTTACAACACAGCTCACGGGTGGCACGGGTC
1151	GTAAGCCAGCCCAGGCCTCGCCCTCCAGCTCAAGGCGGGACAGGTGCCCT CATTCGGTCGGGTCCGGAGCGGGAGGTCGAGTTCCGCCCTGTCCACGGGA
1201	AGAGTAGCCTGCATCCAGGGACAGGCCCCAGCTGGGTGCTGACACGTCCA TCTCATCGGACGTAGGTCCCTGTCCGGGGTCGACCCACGACTGTGCAGGT

	AlaProProValAlaGlyProSerValPheLeu
1251	CCTCCATCTCTTCCTCAGCACCACCTGTGGCAGGACCGTCAGTCTTCCTC
	GGAGGTAGAGAAGGAGTCGTGGTGGACACCGTCCTGGCAGTCAGAAGGAG
	PheProProLysProLysAspThrLeuMetIleSerArgThrProGluVal
1301	TTCCCCCCAAAACCCAAGGACACCCTCATGATCTCCCGGACCCCTGAGGT
1001	AAGGGGGGTTTTGGGTTCCTGTGGGAGTACTAGAGGGCCTGGGGACCCCA
	ANGGGGGGTTTTGGGTTCTGTGGGAGTACTAGAGGGCCTGGGGACTCCA
1001	$\cdot \texttt{ThrCysValValAspValSerHisGluAspProGluValGlnPheAsn}$
1351	CACGTGCGTGGTGGTGGACGTGAGCCACGAAGACCCCGAGGTCCAGTTCA
	GTGCACGCACCACCTGCACTCGGTGCTTCTGGGGGCTCCAGGTCAAGT
	$\cdot\cdot$ TrpTyrValAspGlyValGluValHisAsnAlaLysThrLysProArg
1401	ACTGGTACGTGGACGGCGTGGAGGTGCATAATGCCAAGACAAAGCCACGG
	TGACCATGCACCTGCCGCACCTCCACGTATTACGGTTCTGTTTCGGTGCC
	GluGluGlnPheAsnSerThrPheArgValValSerValLeuThrValVal
1451	GAGGAGCAGTTCAACAGCACGTTCCGTGTGGTCAGCGTCCTCACCGTTGT
	CTCCTCGTCAAGTTGTCGTGCAAGGCACACCAGTCGCAGGAGTGGCAACA
	 HisGlnAspTrpLeuAsnGlyLysGluTyrLysCysLysValSerAsnLys
1501	GCACCAGGACTGGCTGAACGGCAAGGAGTACAAGTGCAAGGTCTCCAACA
	CGTGGTCCTGACCGACTTGCCGTTCCTCATGTTCACGTTCCAGAGGTTGT
	··GlyLeuProAlaProIleGluLysThrIleSerLysThrLys
1551	AAGGCCTCCCAGCCCCCATCGAGAAAACCATCTCCAAAACCAAAGGTGGG
1001	TTCCGGAGGGTCGGGGGGGGGGGGGGGCTCTTTTGGTAGAGGGGGGGG
	TICCGGAGGGICGGGGIAGCICITIIGGIAGAGGITTTGGTTTCCACCC
1601	
TOOT	
	TGGGCGCCCCATACTCCCGGTGTACCTGTCTCCGGCCGAGCCGGGTGGGA
	GlyGlnPro
1651	CTGCCCTGGGAGTGACCGCTGTGCCAACCTCTGTCCCTACAGGGCAGCCC
	GACGGGACCCTCACTGGCGACACGGTTGGAGACAGGGATGTCCCGTCGGG
	${\tt ArgGluProGlnValTyrThrLeuProProSerArgGluGluMetThrLys}$
1701	CGAGAACCACAGGTGTACACCCTGCCCCATCCCGGGAGGAGATGACCAA
	GCTCTTGGTGTCCACATGTGGGACGGGGGGTAGGGCCCTCCTCTACTGGTT
	 AsnGlnValSerLeuThrCysLeuValLysGlyPheTyrProSerAspIle
1751	GAACCAGGTCAGCCTGACCTGCCTGGTCAAAGGCTTCTACCCCAGCGACA
	CTTGGTCCAGTCGGACTGGACGGACCAGTTTCCGAAGATGGGGTCGCTGT
	$\cdot\cdot$ AlaValGluTrpGluSerAsnGlyGlnProGluAsnAsnTyrLysThr
1801	TCGCCGTGGAGTGGGAGAGCAATGGGCAGCCGGAGAACAACTACAAGACC
	AGCGGCACCTCACCCTCTCGTTACCCGTCGGCCTCTTGTTGATGTTCTGG
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1851	ThrProProMetLeuAspSerAspGlySerPhePheLeuTyrSerLysLeu ACACCTCCCATGCTGGACTCCGACGGCTCCTTCTTCCTCTACAGCAAGCT TGTGGAGGGTACGACCTGAGGCTGCCGAGGAAGAAGGAGATGTCGTTCGA
1901	 ThrValAspLysSerArgTrpGlnGlnGlyAsnValPheSerCysSerVal CACCGTGGACAAGAGCAGGTGGCAGCAGGGGAACGTCTTCTCATGCTCCG GTGGCACCTGTTCTCGTCCACCGTCGTCCCCTTGCAGAAGAGTACGAGGC
1951 .	••MetHisGluAlaLeuHisAsnHisTyrThrGlnLysSerLeuSerLeu TGATGCATGAGGCTCTGCACAACCACTACACGCAGAAGAGCCTCTCCCTG ACTACGTACTCCGAGACGTGTTGGTGATGTGCGTCTTCTCGGAGAGGGAC
2001	SerProGlyLys TCTCCGGGTAAA

AGAGGCCCATTT

FIGURE 51

1	MetArgValProAlaGlnLeuLeuGlyLeuLeu ATGAGGGTCCCTGCTCAGCTCCTGGGGGCTCCTGC TACTCCCAGGGACGAGTCGAGGACCCCGAGGACG
51	••LeuTrpPheProGlyAlaArgCysAspIleGlnMetThrGlnSerPro TGCTCTGGTTCCCAGGTGCCAGGTGTGACATCCAGATGACCCAGTCTCCA ACGAGACCAAGGGTCCACGGTCCACACTGTAGGTCTACTGGGTCAGAGGT
101	SerSerLeuSerAlaSerValGlyAspArgValThrIleThrCysArgThr TCCTCCCTGTCTGCATCTGTAGGAGACAGAGTCACCATCACTTGCCGGAC AGGAGGGACAGACGTAGACATCCTCTGTCTCAGTGGTAGTGAACGGCCTG
151	•SerGlnGlyIleArgAsnAspLeuGlyTrpTyrGlnGlnLysProGlyLys AAGTCAGGGCATTAGAAATGATTTAGGCTGGTATCAGCAGAAACCAGGGA TTCAGTCCCGTAATCTTTACTAAATCCGACCATAGTCGTCTTTGGTCCCT
201	••AlaProLysArgLeuIleTyrAlaAlaSerSerLeuGlnSerGlyVal AAGCCCCTAAGCGCCTGATCTATGCTGCATCCAGTTTGCAAAGTGGGGGTC TTCGGGGATTCGCGGACTAGATACGACGTAGGTCAAACGTTTCACCCCAG
251	ProSerArgPheSerGlySerGlySerGlyThrGluPheThrLeuThrIle CCATCAAGGTTCAGCGGCAGTGGATCTGGGACAGAATTCACTCTCACAAT GGTAGTTCCAAGTCGCCGTCACCTAGACCCTGTCTTAAGTGAGAGAGTGTTA
301	•SerSerLeuGlnProGluAspPheAlaThrTyrTyrCysLeuGlnHisAsn CAGCAGCCTGCAGCCTGAAGATTTTGCAACTTATTACTGTCTACAGCATA GTCGTCGGACGTCGGACTTCTAAAACGTTGAATAATGACAGATGTCGTAT
351	••SerTyrProProThrPheGlyGlyGlyThrLysValGlulleLysArg ATAGCTACCCTCCCACTTTCGGCGGAGGGACCAAGGTGGAGATCAAACGA TATCGATGGGAGGGTGAAAGCCGCCTCCCTGGTTCCACCTCTAGTTTGCT
401	ThrValAlaAlaProSerValPheIlePheProProSerAspGluGlnLeu ACTGTGGCTGCACCATCTGTCTTCATCTTCCCGCCATCTGATGAGCAGTT TGACACCGACGTGGTAGACAGAAGTAGAAGGGCGGTAGACTACTCGTCAA
451	 LysSerGlyThrAlaSerValValCysLeuLeuAsnAsnPheTyrProArg GAAATCTGGAACTGCTAGCGTTGTGTGTGCCTGCTGAATAACTTCTATCCCA CTTTAGACCTTGACGATCGCAACACACGGACGACTTATTGAAGATAGGGT
501	••GluAlaLysValGlnTrpLysValAspAsnAlaLeuGlnSerGlyAsn GAGAGGCCAAAGTACAGTGGAAGGTGGATAACGCCCTCCAATCGGGTAAC CTCTCCGGTTTCATGTCACCTTCCACCTATTGCGGGGAGGTTAGCCCATTG

SerGlnGluSerValThrGluGlnAspSerLysAspSerThrTyrSerLeu
TCCCAGGAGAGTGTCACAGAGCAGGACAGCAAGGACAGCACCTACAGCCT
AGGGTCCTCTCACAGTGTCTCGTCCTGTCGTCGTGGATGTCGGA
$\cdot \texttt{SerSerThrLeuThrLeuSerLysAlaAspTyrGluLysHisLysValTyr}$
CAGCAGCACCCTGACGCTGAGCAAAGCAGACTACGAGAAACACAAAGTCT
GTCGTCGTGGGACTGCGACTCGTTTCGTCTGATGCTCTTTGTGTTTCAGA
$\cdot\cdot$ AlaCysGluValThrHisGlnGlyLeuSerSerProValThrLysSer
ACGCCTGCGAAGTCACCCATCAGGGCCTGAGCTCGCCCGTCACAAAGAGC
TGCGGACGCTTCAGTGGGTAGTCCCGGACTCGAGCGGGCAGTGTTTCTCG
PheAsnArgGlyGluCys
TTCAACAGGGGAGAGTGT
AAGTTGTCCCCTCTCACA

ERYTHROPOIETIN RECEPTOR BINDING ANTIBODIES

APPLICATION HISTORY

[0001] This application claims priority to U.S. Provisional Application Ser. No. 60/418,031, filed Oct. 14, 2002, hereby incorporated by reference in its entirety.

TECHNICAL FIELD OF THE INVENTION

[0002] The present invention relates to antibodies that recognize, bind to and, preferably, activate the erythropoietin receptor.

BACKGROUND OF THE INVENTION

[0003] Erythropoietin ("EPO") is a glycoprotein that is the primary regulator of erythropoiesis. Specifically, EPO is responsible for promoting the growth, differentiation and survival of erythroid progenitors, which give rise to mature red blood cells. In response to changes in the level of oxygen in the blood and tissues, erythropoietin appears to stimulate both proliferation and differentiation of immature erythroblasts. It also functions as a growth factor, stimulating the mitotic activity of erythroid progenitor cells, such as erythrocyte burst forming and colony-forming units. It also acts as a differentiation factor, triggering transformation of an erythrocyte colony-forming-unit into a proerythroblast (See Erslev, A., *New Eng. J. Med.*, 316:101-103 (1987)).

[0004] EPO has a molecular weight of about 34,000 daltons and can occur in three forms—alpha, beta and asialo. During mid- to late gestation, EPO is synthesized in the fetal liver. Subsequently, EPO is synthesized in the kidney, circulates in the plasma and is excreted in the urine.

[0005] Human urinary EPO has been isolated and purified (See, Miyake et al., *J. Biol. Chem.*, 252:5558 (1977)). Moreover, methods for identifying, cloning and expressing genes encoding EPO (See U.S. Pat. No. 4,703,008) as well as purifying recombinant EPO from a cell medium (See U.S. Pat. No. 4,667,016) are known in the art.

[0006] The activity of EPO is mediated through the binding and activation of a cell surface receptor referred to as the erythropoietin receptor. The EPO receptor belongs to the cytokine receptor superfamily and is believed to contain at least two distinct polypeptides, a 55-72 kDa species and a 85-100 kDa species (See U.S. Pat. No. 6,319,499, Mayeux et al., *J. Biol. Chem.*, 266:23380 (1991), McCaffery et al., *J. Biol. Chem.*, 264:10507 (1991)). Other studies have revealed other polypeptide complexes of EPO receptor having molecular weights such as 110, 130 and 145 kDa (See U.S. Pat. No. 6,319,499).

[0007] Both the murine and human EPO receptors have been cloned and expressed (See D'Andrea et al., *Cell*, 57:277 (1989); Jones et al., *Blood*, 76:31 (1990); Winkelmann et al., *Blood*, 76:24 (1990); WO 90/08822/U.S. Pat. No. 5,278,065). The full length human EPO receptor is a 483 amino acid transmembrane protein with an approximately 25 amino acid signal peptide (See U.S. Pat. No. 6,319,499). The human receptor demonstrates about a 82% amino acid sequence homology with the murine receptor. Id.

[0008] In the absence of ligand the EPO receptor exists in a preformed dimer. The binding of EPO to its receptor

causes a conformational change such that the cytoplasmic domains are placed in close proximity. While not completely understood, it is believed that this "dimerization" plays a role in the activation of the receptor. The activation of the EPO receptor results in a number of biological effects. Some of these activities include stimulation of proliferation, stimulation of differentiation and inhibition of apoptosis (See U.S. Pat. No. 6,319,499, Liboi et al., *PNAS USA*, 90:11351 (1993), Koury, *Science*, 248:378 (1990)).

[0009] It is the relationship between the EPO receptor dimerization and activation that can be used to identify compounds (i.e. such as antibodies) other than EPO that are capable of: (1) dimerizing the EPO receptor; and (2) activating the receptor. These compounds would be useful in treating mammals suffering from anemia and in identifying mammals having a dysfunctional EPO receptor.

SUMMARY OF THE INVENTION

[0010] In one embodiment, the invention relates to antibodies that bind to the human erythropoietin receptor. In one embodiment, the antibodies comprise a heavy chain variable region that is selected from the group consisting of SEQ ID NOS: 3, 7, 11, 15, 19, 31, 35, 39, 43, 47, 51, 55 and fragments thereof. In another embodiment, the antibodies comprise a light chain variable region that is selected from the group consisting of SEQ ID NOS: 5, 9, 13, 17, 21, 23, 25, 27, 29, 33, 37, 41, 45, 49, 53, 57 and fragments thereof.

[0011] In another embodiment, the present invention relates to an isolated antibody that is capable of binding a human erythropoietin receptor in a mammal. Such an antibody comprises a heavy chain variable region or a light chain variable region that comprises a continuous sequence from CDR1 through CDR3. The amino acid sequence of the heavy chain variable region comprising the continuous sequence from CDR1 through CDR3 is selected from the group consisting of: SEQ ID NO:58, SEQ ID NO:59, SEQ ID NO:60, SEQ ID NO:61 and fragments thereof. The amino acid sequence of the light chain variable region comprising the continuous sequence from CDR1 through CDR3 is selected from the group consisting of: SEQ ID NO:62, SEQ ID NO:63, SEQ ID NO:64, SEQ ID NO:65, SEQ ID NO:66, SEQ ID NO:67, SEQ ID NO:68 and fragments thereof.

[0012] In another embodiment, the present invention relates to an antibody that activates an endogenous activity of a human erythropoietin receptor in a mammal but does not interact with a peptide having an amino acid sequence of PGNYSFSYQLEDEPWKLCRLHQAPTARGAV (SEQ ID NO:1).

[0013] In another embodiment, the present invention relates to an antibody that is capable of activating an endogenous activity of a human erythropoietin receptor in a mammal, wherein said antibody or antibody fragment thereof exhibits a binding affinity within one hundred fold of the binding affinity of endogenous human erythropoietin to the erythropoietin receptor.

[0014] In yet another embodiment, the present invention relates to an antibody or antibody fragment thereof that activates an endogenous activity of a human erythropoietin receptor in a mammal. The antibody or antibody fragment thereof comprises at least one human heavy chain variable

region having the amino acid sequence of SEQ ID NO:3 or antibody fragment thereof, and/or at least one human light chain variable region having the amino acid sequence of SEQ ID NO:5 or antibody fragment thereof, provided that said antibody or antibody fragment thereof does not interact with a peptide having an amino acid sequence of PGNYS-FSYQLEDEPWKLCRLHQAPTARGAV (SEQ ID NO:1).

[0015] In yet another embodiment, the present invention relates to an antibody or antibody fragment thereof that activates an endogenous activity of a human erythropoietin receptor in a mammal. The antibody or antibody fragment thereof comprises at least one heavy chain variable region having the amino acid sequence of SEQ ID NO:7 or antibody fragment thereof, and/or at least one light chain variable region having the amino acid sequence of SEQ ID NO:9 or antibody fragment thereof, provided that said antibody or antibody fragment thereof does not interact with a peptide having an amino acid sequence of PGNYSF-SYQLEDEPWKLCRLHQAPTARGAV (SEQ ID NO:1).

[0016] This embodiment also includes other heavy chain variable regions selected from the group consisting of SEQ ID NO: 11, 15, 19, 31, 35, 39, 43, 47, 51, and 55 or an antibody fragment of any of these aforementioned SEQ ID NOS, wherein said antibody or antibody fragment thereof does not interact with a peptide having an amino acid sequence of SEQ ID NO:1. Other light chain variable regions included in this embodiment may be selected from the group consisting of SEQ ID NO: 13, 17, 21, 23, 25, 27, 29, 33, 37, 41, 45, 49, 53 and 57 or an antibody fragment of any of these aforementioned SEQ ID NOS, wherein said antibody or antibody fragment thereof does not interact with a peptide having an amino acid sequence of SEQ ID NOS.

[0017] In yet another embodiment, the invention provides an antibody or antibody fragment thereof that activates an endogenous activity of a human erythropoietin receptor in a mammal, the antibody comprising the amino acid sequences of at least one heavy chain variable region and at least one light chain variable region selected from the group consisting of SEQ ID NO:11/SEQ ID NO:13, SEQ ID NO:15/SEQ ID NO:17, SEQ ID NO:19/SEQ ID NO:21, SEQ ID NO:11/ SEQ ID NO:23, SEQ ID NO:11/SEQ ID NO:25, SEQ ID NO:11/SEQ ID NO:27, SEQ ID NO:11/SEQ ID NO:29, SEQ ID NO:31/SEQ ID NO:33, SEQ ID NO:35/SEQ ID NO:37, SEQ ID NO:39/SEQ ID NO:41, SEQ ID NO:43/ SEQ ID NO:45, SEQ ID NO:47/SEQ ID NO:49, SEQ ID NO:51/SEQ ID NO:53 and SEQ ID NO:55/SEQ ID NO:57 or antibody fragment thereof, wherein said antibody or antibody fragment thereof does not interact with a peptide having an amino acid sequence of SEQ ID NO:1.

[0018] In yet another embodiment, the present invention relates to a method of activating an endogenous activity of a human erythropoietin receptor in a mammal. The method involves the step of administering to a mammal a therapeutically effective amount of an antibody or antibody fragment thereof to activate the EPO receptor. The antibody or antibody fragment thereof does not interact with a peptide having an amino acid sequence of PGNYSFSYQLEDEP-WKLCRLHQAPTARGAV (SEQ ID NO:1).

[0019] In yet a further embodiment, the present invention relates to a method of modulating an endogenous activity of a human erythropoietin receptor in a mammal. The method involves administering to a mammal a therapeutically effec-

tive amount of an antibody or antibody fragment thereof to modulate the endogenous activity of a human erythropoietin receptor in a mammal but does not interact with a peptide having an amino acid sequence of PGNYSFSYQLEDEP-WKLCRLHQAPTARGAV (SEQ ID NO:1).

[0020] In yet a further embodiment, the present invention relates to a method of treating a mammal suffering from pure red cell aplasia induced by neutralizing anti-erythropoietin antibodies. The method involves administering to a mammal in need of treatment a therapeutically effective amount of an antibody or antibody fragment thereof to activate said receptor, wherein said antibody or antibody fragment thereof does not interact with a peptide having an amino acid sequence of PGNYSFSYQLEDEPWKLCRLHQAPTARGAV (SEQ ID NO:1).

[0021] In yet a further embodiment, the present invention relates to pharmaceutical compositions. The pharmaceutical compositions of the present invention contain a therapeutically effective amount of an antibody or antibody fragment thereof and a pharmaceutically acceptable excipient. The antibody or antibody fragment contained in the pharmaceutical composition activates an endogenous activity of a human erythropoietin receptor in a mammal but does not interact with a peptide having an amino acid sequence of PGNYSFSYQLEDEPWKLCRLHQAPTARGAV (SEQ ID NO:1).

[0022] In yet a further embodiment, the present invention relates to an IgG2 antibody or antibody fragment that binds to and activates the erythropoietin receptor. The IgG2 antibodies or antibody fragments of this embodiment bind to and interact with any epitope that is involved in activating the EPO receptor. Such antibodies may be polyclonal or monoclonal antibodies or any antibody fragment thereof. The IgG2 antibodies may be chimeric, humanized or human antibodies.

[0023] In yet a further embodiment, the present invention provides a method of activating an endogenous activity of a human erythropoietin receptor in a mammal comprising the step of administering to a mammal a therapeutically effective amount of an IgG2 antibody or antibody fragment of the invention to activate the receptor.

[0024] In yet a further embodiment, the present invention provides a method of modulating an endogenous activity of a human erythropoietin receptor in a mammal comprising the step of administering to a mammal a therapeutically effective amount of an IgG2 antibody or antibody fragment of the invention to modulate the receptor.

[0025] In yet another embodiment, the present invention provides a method of treating a mammal suffering aplasia, the method comprising the step of administering to a mammal in need of treatment a therapeutically effective amount of an IgG2 antibody or antibody fragment of the invention to activate the receptor.

[0026] In yet another embodiment, the present invention provides a method of treating a mammal suffering aplasia, the method comprising the step of administering to a mammal in need of treatment a therapeutically effective amount of an IgG2 antibody or antibody fragment of the invention to modulate the receptor.

[0027] In yet another embodiment, the present invention provides a pharmaceutical composition comprising a thera-

peutically effective amount of an IgG2 antibody or antibody fragment of the invention and a pharmaceutically acceptable excipient.

[0028] Finally, the present invention relates to isolated and purified polynucleotide and amino acid sequences. The isolated and purified polynucleotide sequences can be selected from the group consisting of: SEQ ID NO:2, SEQ ID NO:4, SEQ ID NO:6, SEQ ID NO:8, SEQ ID NO:10, SEQ ID NO:12, SEQ ID NO:14, SEQ ID NO:16, SEQ ID NO:18, SEQ ID NO:20, SEQ ID NO:22, SEQ ID NO:24, SEQ ID NO:26, SEQ ID NO:34, SEQ ID NO:36, SEQ ID NO:38, SEQ ID NO:40, SEQ ID NO:42, SEQ ID NO:54, SEQ ID NO:55, SEQ ID NO:54, SEQ ID NO:56 and fragments, complements and degenerate codon equivalents thereof.

[0029] The present invention further relates to isolated and purified amino acid sequences selected from the group consisting of: SEQ ID NO:3, SEQ ID NO:5, SEQ ID NO:7, SEQ ID NO:9, SEQ ID NO:11, SEQ ID NO:13, SEQ ID NO:15, SEQ ID NO:17, SEQ ID NO:19, SEQ ID NO:21, SEQ ID NO:23, SEQ ID NO:25, SEQ ID NO:29, SEQ ID NO:31, SEQ ID NO:33, SEQ ID NO:35, SEQ ID NO:37, SEQ ID NO:39, SEQ ID NO:41, SEQ ID NO:43, SEQ ID NO:45, SEQ ID NO:47, SEQ ID NO:49, SEQ ID NO:51, SEQ ID NO:53, SEQ ID NO:55, SEQ ID NO:57, SEQ ID NO:58, SEQ ID NO:59, SEQ ID NO:60, SEQ ID NO:61, SEQ ID NO:62, SEQ ID NO:63, SEQ ID NO:64, SEQ ID NO:65, SEQ ID NO:66, SEQ ID NO:67, SEQ ID NO:68 and fragments and complements and thereof.

BRIEF DESCRIPTION OF THE FIGURES

[0030] FIG. **1** shows the isolated and purified polynucleotide (top strand and bottom strands, SEQ ID NO:69 and SEQ ID NO:70, respectively) and amino acid sequence of the heavy chain of human antibody Ab12. The amino acid sequence comprises SEQ ID NOS:71 through 74. The sequence of the constant region alone is shown as SEQ ID NO:75. The variable chain ends at nucleotide 1283. The variable/constant joining region (underlined) is at nucleotides 1284-1289. The constant region is from nucleotides 1290-2826.

[0031] FIG. **2** shows the isolated and purified polynucleotide (top strand and bottom strands, SEQ ID NO:76 and SEQ ID NO:77, respectively) and amino acid sequence of the light chain of human antibody Ab12. The amino acid sequence comprises SEQ ID NOS:78. The sequence of the constant region alone is shown as SEQ ID NO: 79. The variable chain ends at nucleotide 1363. The variable/constant joining region (underlined) is at nucleotides 1364-1369. The constant region is from nucleotides 1370-1618.

[0032] FIG. **3** shows the isolated and purified polynucleotide (top strand and bottom strands, SEQ ID NO:80 and SEQ ID NO:81, respectively) and amino acid sequence of the heavy chain of human antibody Ab198. The amino acid sequence comprises SEQ ID NOS:82 and SEQ ID NOS 72 through 74. The variable chain ends at nucleotide 1304. The variable/constant joining region (underlined) is at nucleotides 1305-1310. The constant region is from nucleotides 1311-2847.

[0033] FIG. **4** shows the isolated and purified polynucleotide (top strand and bottom strands, SEQ ID NO:83 and SEQ ID NO:84, respectively) and amino acid sequence of the light chain of human antibody Ab198. The amino acid sequence comprises SEQ ID NOS:78. The variable chain ends at nucleotide 1351. The variable/constant joining region (underlined) is at nucleotides 1352-1357. The constant region is from nucleotides 1358-1606.

[0034] FIG. **5** shows the competition of Ab12 with ¹²⁵I-labeled EPO for binding to Chinese Hamster Ovary cells expressing recombinant EPO receptor.

[0035] FIG. **6** shows the results of an EPO dependent human cell proliferation assay using Ab12 and Ab198.

[0036] FIG. 7 shows that Ab12 remains active in inducing the proliferation of F36E cells after storage at 4° C. for up to 20 days.

[0037] FIG. **8** shows that Ab 12 induces the formation of CFU-E (colony forming unit—erythroid) from human 36⁺ progenitor cells.

[0038] FIG. **9** shows the induction of proliferation of human erythroid producing cells with Ab198.

[0039] FIG. **10** shows that Ab198 induces the formation of CFU-E colonies from cynomologous bone marrow-derived erythroid progenitor cells.

[0040] FIG. **11** shows that Ab12 does not interact with the peptide SE-3. Ab71A interacts with the SE-3 peptide.

[0041] FIG. **12** shows that human Abs secreted by primary hybridomas induce the proliferation of F36E cells.

[0042] FIG. **13** shows that human Ab supernatants secreted by primary hybridomas interact with intact EPO receptor, but not with peptide SE-3.

[0043] FIG. 14 shows the activity of various concentrations of Ab 12 on the proliferation of UT7/EPO cells.

[0044] FIG. **15** shows the activity of various concentrations of Ab198 on the proliferation of UT7/EPO cells.

[0045] FIG. **16** shows the activity of various concentrations of Ab198 (with or without the addition of a secondary goat anti-human FC antibody) on the growth and proliferation of UT7/EPO cells.

[0046] FIG. **17** shows the activity of various concentrations of Ab12 (with or without the addition of a secondary goat anti-human FC antibody) on the growth and proliferation of UT7/EPO cells.

[0047] FIG. 18 is a series of representations of the heavy chain and light chain variable region nucleotide and amino acid sequences of the human anti-EPO-R antibody expressed by the cell line designated ABT2-SCX-003 of the invention, with FIG. 18A (SEQ ID NO:10) representing the nucleotide sequence encoding the variable region of the heavy chain, FIG. 18B (SEQ ID NO:11) representing the amino acid sequence encoded by the nucleotide sequence shown in FIG. 18A, FIG. 18C (SEQ ID NO:12) representing the nucleotide sequence encoding the variable region of the light chain, and FIG. 18D (SEQ ID NO:13) representing the amino acid sequence encoded by the nucleotide sequence shown in FIG. 18D (SEQ ID NO:13) representing the amino acid sequence encoded by the nucleotide sequence shown in FIG. 18C.

[0048] FIG. **19** is a series of representations of the heavy chain and light chain variable region nucleotide and amino acid sequences of the human anti-EPO-R antibody

expressed by the cell line designated ABT2-SCX-012 (also referred to herein as Ab 12) of the invention, with FIG. **19**A (SEQ ID NO:2) representing the nucleotide sequence encoding the variable region of the heavy chain, FIG. **19**B (SEQ ID NO:3) representing the amino acid sequence encoded by the nucleotide sequence shown in FIG. **19**A, FIG. **19**C (SEQ ID NO:4) representing the nucleotide sequence encoding the variable region of the light chain, and FIG. **19**D (SEQ ID NO:5) representing the amino acid sequence encoded by the nucleotide sequence shown in FIG. **19**C (SEQ ID NO:5) representing the amino acid sequence encoded by the nucleotide sequence shown in FIG. **19**C (SEQ ID NO:5) representing the amino acid sequence encoded by the nucleotide sequence shown in FIG. **19**C.

[0049] FIG. 20 is a series of representations of the heavy chain and light chain variable region nucleotide and amino acid sequences of the human anti-EPO-R antibody expressed by the cell line designated ABT2-SCX-022 of the invention, with FIG. 20A (SEQ ID NO:14) representing the nucleotide sequence encoding the variable region of the heavy chain, FIG. 20B (SEQ ID NO:15) representing the amino acid sequence encoded by the nucleotide sequence shown in FIG. 20A, FIG. 20C (SEQ ID NO:16) representing the nucleotide sequence encoding the variable region of the light chain, and FIG. 20D (SEQ ID NO:17) representing the amino acid sequence encoded by the nucleotide sequence shown in FIG. 20D (SEQ ID NO:17) representing the amino acid sequence encoded by the nucleotide sequence shown in FIG. 20C.

[0050] FIG. 21 is a series of representations of the heavy chain and light chain variable region nucleotide and amino acid sequences of the human anti-EPO-R antibody expressed by the cell line designated ABT2-SCX-054 of the invention, with FIG. 21A (SEQ ID NO:18) representing the nucleotide sequence encoding the variable region of the heavy chain, FIG. 21B (SEQ ID NO:19) representing the amino acid sequence encoded by the nucleotide sequence shown in FIG. 21A, FIG. 21C (SEQ ID NO:20) representing the nucleotide sequence encoding the variable region of the light chain, and FIG. 21D (SEQ ID NO:21) representing the amino acid sequence encoded by the nucleotide sequence shown in FIG. 21D (SEQ ID NO:21) representing the amino acid sequence encoded by the nucleotide sequence shown in FIG. 21C.

[0051] FIG. 22 is a series of representations of the heavy chain and light chain variable region nucleotide and amino acid sequences of the human anti-EPO-R antibody expressed by the cell line designated ABT2-SCX-060 of the invention, with FIG. 22A (SEQ ID NO:10) representing the nucleotide sequence encoding the variable region of the heavy chain, FIG. 22B (SEQ ID NO:11) representing the amino acid sequence encoded by the nucleotide sequence shown in FIG. 22A, FIG. 22C (SEQ ID NO:22) representing the nucleotide sequence encoding the variable region of the light chain, and FIG. 22D (SEQ ID NO:23) representing the amino acid sequence encoded by the nucleotide sequence shown in FIG. 22D (SEQ ID NO:23) representing the amino acid sequence encoded by the nucleotide sequence shown in FIG. 22C.

[0052] FIG. 23 is a series of representations of the heavy chain and light chain variable region nucleotide and amino acid sequences of the human anti-EPO-R antibody expressed by the cell line designated ABT2-SCX-102 of the invention, with FIG. 23A (SEQ ID NO:10) representing the nucleotide sequence encoding the variable region of the heavy chain, FIG. 23B (SEQ ID NO:11) representing the amino acid sequence encoded by the nucleotide sequence shown in FIG. 23A, FIG. 23C (SEQ ID NO:24) representing the nucleotide sequence encoding the variable region of the light chain, and FIG. 23D (SEQ ID NO:25) representing the amino acid sequence encoded by the nucleotide sequence shown in FIG. 23C.

[0053] FIG. 24 is a series of representations of the heavy chain and light chain variable region nucleotide and amino acid sequences of the human anti-EPO-R antibody expressed by the cell line designated ABT2-SCX-135 of the invention, with FIG. 24A (SEQ ID NO:10) representing the nucleotide sequence encoding the variable region of the heavy chain, FIG. 24B (SEQ ID NO:11) representing the amino acid sequence encoded by the nucleotide sequence shown in FIG. 24A, FIG. 24C (SEQ ID NO:26) representing the nucleotide sequence encoding the variable region of the light chain, and FIG. 24D (SEQ ID NO:27) representing the amino acid sequence encoded by the nucleotide sequence shown in FIG. 24C.

[0054] FIG. 25 is a series of representations of the heavy chain and light chain variable region nucleotide and amino acid sequences of the human anti-EPO-R antibody expressed by the cell line designated ABT2-SCX-145 of the invention, with FIG. 25A (SEQ ID NO:10) representing the nucleotide sequence encoding the variable region of the heavy chain, FIG. 25B (SEQ ID NO:11) representing the amino acid sequence encoded by the nucleotide sequence shown in FIG. 25A, FIG. 25C (SEQ ID NO:28) representing the nucleotide sequence encoding the variable region of the light chain, and FIG. 25D (SEQ ID NO:29) representing the amino acid sequence encoded by the nucleotide sequence shown in FIG. 25D (SEQ ID NO:29) representing the amino acid sequence encoded by the nucleotide sequence shown in FIG. 25C.

[0055] FIG. 26 is a series of representations of the heavy chain and light chain variable region nucleotide and amino acid sequences of the human anti-EPO-R antibody expressed by the cell line designated ABT2-SCX-198 (also referred to herein as Ab198) of the invention, with FIG. 26A (SEQ ID NO:6) representing the nucleotide sequence encoding the variable region of the heavy chain, FIG. 26B (SEQ ID NO:7) representing the amino acid sequence encoded by the nucleotide sequence shown in FIG. 26A, FIG. 26C (SEQ ID NO:8) representing the nucleotide sequence encoding the variable region of the light chain, and FIG. 26D (SEQ ID NO:9) representing the amino acid sequence encoded by the nucleotide sequence shown in FIG. 26C.

[0056] FIG. 27 is a series of representations of the heavy chain and light chain variable region nucleotide and amino acid sequences of the human anti-EPO-R antibody expressed by the cell line designated ABT2-SCX-254 of the invention, with FIG. 27A (SEQ ID NO:30) representing the nucleotide sequence encoding the variable region of the heavy chain, FIG. 27B (SEQ ID NO:31) representing the amino acid sequence encoded by the nucleotide sequence shown in FIG. 27A, FIG. 27C (SEQ ID NO:32) representing the nucleotide sequence encoding the variable region of the light chain, and FIG. 27D (SEQ ID NO:33) representing the amino acid sequence encoded by the nucleotide sequence shown in FIG. 27C.

[0057] FIG. 28 is a series of representations of the heavy chain and light chain variable region nucleotide and amino acid sequences of the human anti-EPO-R antibody expressed by the cell line designated ABT2-SCX-267 of the invention, with FIG. 28A (SEQ ID NO:34) representing the nucleotide sequence encoding the variable region of the heavy chain, FIG. 28B (SEQ ID NO:35) representing the amino acid sequence encoded by the nucleotide sequence shown in FIG. 28A, FIG. 28C (SEQ ID NO:36) representing the nucleotide sequence encoding the variable region of the heavy chain, FIG. 28A, FIG. 28C (SEQ ID NO:36) representing the nucleotide sequence encoding the variable region of the heavy chain, FIG. 28A, FIG. 28C (SEQ ID NO:36) representing the nucleotide sequence encoding the variable region of the heavy chain and sequence encoding the variable region of the heavy chain and sequence encoding the variable region of the heavy chain and sequence encoding the variable region of the heavy chain and sequence encoding the variable region of the heavy chain and sequence encoding the variable region of the heavy chain and sequence encoding the variable region of the heavy chain and sequence encoding the variable region of the heavy chain and sequence encoding the variable region of the heavy chain and sequence encoding the variable region of the heavy chain and sequence encoding the variable region of the heavy chain and sequence encoding the variable region of the heavy chain and sequence encoding the variable region of the heavy chain and the sequence encoding the variable region of the heavy chain and the sequence encoding the variable region of the heavy chain and the sequence encoding the variable region of the heavy chain and the sequence encoding the variable region of the heavy chain and the sequence encoding the variable region of the heavy chain and the sequence encoding the variable region of the heavy chain and the sequence encoding the variable region of the heavy chain and theavy chain and the sequence encoding th

light chain, and FIG. **28**D (SEQ ID NO:37) representing the amino acid sequence encoded by the nucleotide sequence shown in FIG. **28**C.

[0058] FIG. **29** is a table showing amino acid sequence alignments of heavy chain variable regions of anti-EPOr mAbs generated according to the invention with their associated germline variable region sequences and identifying framework regions and complementarity determining regions.

[0059] FIG. **30** is a table showing amino acid sequence alignments of light chain variable regions of anti-EPOr mAbs generated according to the invention with their associated germline variable region sequences and identifying framework regions and complementarity determining regions.

[0060] FIG. **31** is a graph comparing the erythropoietic activity, at various concentrations, of a gamma-1 Ab 12 monoclonal antibody (Mab) and a gamma-2 Ab 12 Mab on an F36e human erythroleukemic cell line.

[0061] FIG. 32 is a graph showing the increase in percent reticulocyte and percent hematocrit in transgenic mice subjected to a multiple dosing regimen of vehicle, Epogen (5U) or Ab 12 antibody (5 or 50 μ g).

[0062] FIG. 33 is a graph showing the increase in percent hematocrit in transgenic mice subjected to a weekly dosing regimen (over 3 weeks) of various concentrations of AranespTM or Ab 12.

[0063] FIG. 34 is a graph showing the increase in percent hematocrit in transgenic mice subjected to single versus weekly dosing regimens of various concentrations of AranespTM or Ab 12.

[0064] FIG. 35 is a series of representations of the heavy chain and light chain variable region nucleotide and amino acid sequences of the human anti-EPO-R antibody expressed by the cell line designated ABT2-SCX-390 of the invention, with FIG. 35A (SEQ ID NO:38) representing the nucleotide sequence encoding the variable region of the heavy chain, FIG. 35B (SEQ ID NO:39) representing the amino acid sequence encoded by the nucleotide sequence shown in FIG. 35A, FIG. 35C (SEQ ID NO:40) representing the nucleotide sequence encoding the variable region of the light chain, and FIG. 35D (SEQ ID NO:41) representing the amino acid sequence encoded by the nucleotide sequence shown in FIG. 35D (SEQ ID NO:41) representing the amino acid sequence encoded by the nucleotide sequence shown in FIG. 35C.

[0065] FIG. 36 is a series of representations of the heavy chain and light chain variable region nucleotide and amino acid sequences of the human anti-EPO-R antibody expressed by the cell line designated ABT2-SCX-412 of the invention, with FIG. 36A (SEQ ID NO:42) representing the nucleotide sequence encoding the variable region of the heavy chain, FIG. 36B (SEQ ID NO:43) representing the amino acid sequence encoded by the nucleotide sequence shown in FIG. 36A, FIG. 36C (SEQ ID NO:44) representing the nucleotide sequence encoding the variable region of the light chain, and FIG. 36D (SEQ ID NO:45) representing the amino acid sequence encoded by the nucleotide sequence shown in FIG. 36D (SEQ ID NO:45) representing the amino acid sequence encoded by the nucleotide sequence shown in FIG. 36C.

[0066] FIG. **37** is a series of representations of the heavy chain and light chain variable region nucleotide and amino acid sequences of the human anti-EPO-R antibody

expressed by the cell line designated ABT2-SCX-430/432 of the invention, with FIG. **37**A (SEQ ID NO:46) representing the nucleotide sequence encoding the variable region of the heavy chain, FIG. **37**B (SEQ ID NO:47) representing the amino acid sequence encoded by the nucleotide sequence shown in FIG. **37**A, FIG. **37**C (SEQ ID NO:48) representing the nucleotide sequence encoding the variable region of the light chain, and FIG. **37**D (SEQ ID NO:49) representing the amino acid sequence encoded by the nucleotide sequence shown in FIG. **37**C.

[0067] FIG. 38 is a series of representations of the heavy chain and light chain variable region nucleotide and amino acid sequences of the human anti-EPO-R antibody expressed by the cell line designated ABT2-SCX-467 of the invention, with FIG. 38A (SEQ ID NO:50) representing the nucleotide sequence encoding the variable region of the heavy chain, FIG. 38B (SEQ ID NO:51) representing the amino acid sequence encoded by the nucleotide sequence shown in FIG. 38A, FIG. 38C (SEQ ID NO:52) representing the nucleotide sequence encoding the variable region of the light chain, and FIG. 38D (SEQ ID NO:53) representing the amino acid sequence encoded by the nucleotide sequence shown in FIG. 38D (SEQ ID NO:53) representing the amino acid sequence encoded by the nucleotide sequence shown in FIG. 38C.

[0068] FIG. 39 is a series of representations of the heavy chain and light chain variable region nucleotide and amino acid sequences of the human anti-EPO-R antibody expressed by the cell line designated ABT2-SCX-484 of the invention, with FIG. 39A (SEQ ID NO:54) representing the nucleotide sequence encoding the variable region of the heavy chain, FIG. 39B (SEQ ID NO:55) representing the amino acid sequence encoded by the nucleotide sequence shown in FIG. 39A, FIG. 39C (SEQ ID NO:56) representing the nucleotide sequence encoding the variable region of the light chain, and FIG. 39D (SEQ ID NO:57) representing the amino acid sequence encoded by the nucleotide sequence shown in FIG. 39D (SEQ ID NO:57) representing the amino acid sequence encoded by the nucleotide sequence shown in FIG. 39C.

[0069] FIG. **40** is a table showing amino acid sequence alignments of heavy chain variable regions of anti-EPOr mAbs generated according to the invention with their associated germline variable region sequences and identifying framework regions and complementarity determining regions.

[0070] FIG. **41** is a table showing amino acid sequence alignments of light chain variable regions of anti-EPOr mAbs generated according to the invention with their associated germline variable region sequences and identifying framework regions and complementarity determining regions.

[0071] FIG. **42** shows the isolated and purified polynucleotide (top strand and bottom strands, SEQ ID NO:86 and SEQ ID NO:87, respectively) and amino acid sequence of the heavy chain of human antibody Ab390. The amino acid sequence comprises SEQ ID NOS:88 and SEQ ID NOS 72 through 74. The variable chain ends at nucleotide 463. The variable/constant joining region (underlined) is at nucleotides 464-469. The constant region is from nucleotides 470-2006.

[0072] FIG. **43** shows the isolated and purified polynucleotide (top strand and bottom strands, SEQ ID NO:89 and SEQ ID NO:90, respectively) and amino acid sequence of the light chain of human antibody Ab390. The amino acid sequence comprises SEQ ID NOS:91. The variable chain ends at nucleotide 463. The variable/constant joining region (underlined) is at nucleotides 464-469. The constant region is from nucleotides 470-718.

[0073] FIG. 44 shows the isolated and purified polynucleotide (top strand and bottom strands, SEQ ID NO:92 and SEQ ID NO:93, respectively) and amino acid sequence of the heavy chain of human antibody Ab412. The amino acid sequence comprises SEQ ID NOS:94 and SEQ ID NOS 72 through 74. The variable chain ends at nucleotide 469. The variable/constant joining region (underlined) is at nucleotides 470-475. The constant region is from nucleotides 476-2012.

[0074] FIG. **45** shows the isolated and purified polynucleotide (top strand and bottom strands, SEQ ID NO:95 and SEQ ID NO:96, respectively) and amino acid sequence of the light chain of human antibody Ab412. The amino acid sequence comprises SEQ ID NOS:97. The variable chain ends at nucleotide 463. The variable/constant joining region (underlined) is at nucleotides 464-469. The constant region is from nucleotides 470-718.

[0075] FIG. **46** shows the isolated and purified polynucleotide (top strand and bottom strands, SEQ ID NO:98 and SEQ ID NO:99, respectively) and amino acid sequence of the heavy chain of human antibody Ab432. The amino acid sequence comprises SEQ ID NOS:100 and SEQ ID NOS 72 through 74. The variable chain ends at nucleotide 463. The variable/constant joining region (underlined) is at nucleotides 464-469. The constant region is from nucleotides 470-2006.

[0076] FIG. **47** shows the isolated and purified polynucleotide (top strand and bottom strands, SEQ ID NO:101 and SEQ ID NO:102, respectively) and amino acid sequence of the light chain of human antibody Ab430. The amino acid sequence comprises SEQ ID NOS:103. The variable chain ends at nucleotide 463. The variable/constant joining region (underlined) is at nucleotides 464-469. The constant region is from nucleotides 470-718.

[0077] FIG. **48** shows the isolated and purified polynucleotide (top strand and bottom strands, SEQ ID NO:104 and SEQ ID NO:105, respectively) and amino acid sequence of the heavy chain of human antibody Ab467. The amino acid sequence comprises SEQ ID NOS:106 and SEQ ID NOS 72 through 74. The variable chain ends at nucleotide 463. The variable/constant joining region (underlined) is at nucleotides 464-469. The constant region is from nucleotides 470-2006.

[0078] FIG. **49** shows the isolated and purified polynucleotide (top strand and bottom strands, SEQ ID NO:107 and SEQ ID NO:108, respectively) and amino acid sequence of the light chain of human antibody Ab467. The amino acid sequence comprises SEQ ID NOS:109. The variable chain ends at nucleotide 463. The variable/constant joining region (underlined) is at nucleotides 464-469. The constant region is from nucleotides 470-718.

[0079] FIG. **50** shows the isolated and purified polynucleotide (top strand and bottom strands, SEQ ID NO:110 and SEQ ID NO:111, respectively) and amino acid sequence of the heavy chain of human antibody Ab484. The amino acid sequence comprises SEQ ID NOS:112 and SEQ ID NOS 72 through 74. The variable chain ends at nucleotide 469. The variable/constant joining region (underlined) is at nucleotides 470-475. The constant region is from nucleotides 470-2012.

[0080] FIG. **51** shows the isolated and purified polynucleotide (top strand and bottom strands, SEQ ID NO:113 and SEQ ID NO:114, respectively) and amino acid sequence of the light chain of human antibody Ab484. The amino acid sequence comprises SEQ ID NOS:115. The variable chain ends at nucleotide 463. The variable/constant joining region (underlined) is at nucleotides 464-469. The constant region is from nucleotides 470-718.

DETAILED DESCRIPTION OF THE INVENTION

Definitions

[0081] As used herein, the term "antibody" or "immunoglobulin" refers to single chain, two-chain, and multi-chain proteins and glycoproteins that belong to the classes of polyclonal, monoclonal, chimeric and human or humanized. The term "antibody" also includes synthetic and genetically engineered variants thereof.

[0082] As used herein, the term "antibody fragment" refers to Fab, Fab', $F(ab')_2$ and Fv fragments, as well as any portion of an antibody having specificity toward at least one desired epitope.

[0083] As used herein, the term "gamma-2", "gamma-2 isotype" or "IgG2" refers to subclass 2 of immunoglobulin G (IgG), as well as any antibody fragment thereof. The four subclasses of IgG molecules are well characterized and well known to those of ordinary skill in the art. (See for example, Molecular Biology of the Cell, 2^{nd} Edition by Bruce Alberts et al., 1989) Panels of monoclonal antibodies are available that recognize all human isotypes (IgA, IgG, IgD IgE, and IgM) and subisotypes (IgA1, IgA2, IgG1, IgG2, IgG3, and IgG4) of human immunoglobulins.

[0084] As used herein, the term "humanized antibody" refers to an antibody that is derived from a non-human antibody (i.e murine) that retains or substantially retains the antigen-binding properties of the parent antibody but is less immunogenic in humans.

[0085] As used herein, the term "human antibody" refers to an antibody that possesses a sequence that is derived from a human germ-line immunoglobulin sequence, such as antibodies derived from transgenic mice having human immunoglobulin genes (e.g., XenoMouse® mice), human phage display libraries, or human B cells.

[0086] As used herein, the term "epitope" refers to any protein determinate capable of specifically binding to an antibody or T-cell receptors. Epitopic determinants usually consist of chemically active surface groupings of molecules such as amino acids or sugar side chains and usually have specific three dimensional structural characteristics, as well as specific charge characteristics.

[0087] As used herein, the term "endogenous" refers to a product or activity arising in the body or cell as opposed to a product or activity coming from outside.

[0088] As used herein the phrase, a polynucleotide "derived from" or "specific for a designated sequence refers to a polynucleotide sequence that comprises a contiguous

sequence of approximately at least 6 nucleotides, preferably at least about 8 nucleotides, more preferably at least about 10-12 nucleotides, and even more preferably at least about 15-20 nucleotides corresponding, i.e., identical or complementary to, a region of the designated nucleotide sequence. The sequence may be complementary or identical to a sequence that is unique to a particular polynucleotide sequence as determined by techniques known in the art. Regions from which sequences may be derived, include but are not limited to, regions encoding specific epitopes, as well as non-translated and/or non-transcribed regions.

[0089] The derived polynucleotide will not necessarily be derived physically from the nucleotide sequence of interest under study, but may be generated in any manner, including, but not limited to, chemical synthesis, replication, reverse transcription or transcription, that is based on the information provided by the sequence of bases in the region(s) from which the polynucleotide is derived. As such, it may represent either a sense or an antisense orientation of the original polynucleotide. In addition, combinations of regions corresponding to that of the designated sequence may be modified in ways known in the art to be consistent with the intended use.

[0090] As used herein, the phrase "encoded by" refers to a nucleic acid sequence that codes for a polypeptide sequence, wherein the polypeptide sequence or a portion thereof contains an amino acid sequence of at least 3 to 5 amino acids, more preferably at least 8 to 10 amino acids, and even more preferably at least 15 to 20 amino acids from a polypeptide encoded by the nucleic acid sequence. Also encompassed are polypeptide sequences that are immunologically identifiable with a polypeptide encoded by the sequence. Thus, a "polypeptide," "protein" or "amino acid" sequence has at least about 50%, 60%, 70%, 75%, 80%, 85%, 90%, 95% or more identity to the antibodies of the present invention. Further, the antibodies of the present invention may have at least about 60%, 70%, 75%, 80%, 85%, 90% or 95% similarity to a polypeptide or amino sequences of the antibodies of the present invention. The amino acid sequences of the antibodies of the present invention can be selected from the group consisting of SEQUENCE ID NOS: 3, 5, 7, 9, 11, 13, 15, 17, 19, 21, 23, 25, 27, 29, 31, 33, 35, 37, 39, 41, 43, 45, 47, 49, 51, 53, 55 and 57. Preferred amino acid sequences of the antibodies of the present invention are selected from the group consisting of SEQ ID NOS: 3, 5, 7, 9, 51 and 53.

[0091] As used herein, the phrase "recombinant polypeptide,""recombinant protein," or "a polypeptide produced by recombinant techniques", which terms may be used interchangeably herein, describes a polypeptide that by virtue of its origin or manipulation is not associated with all or a portion of the polypeptide with which it is associated in nature and/or is linked to a polypeptide other than that to which it is lined in nature. A recombinant or encoded polypeptide or protein is not necessarily translated from a designated nucleic acid sequence. It also may be generated in any manner, including chemical synthesis or expression of a recombinant expression system.

[0092] As used herein, the phrase "synthetic peptide" refers to a polymeric form of amino acids of any length, which may be chemically synthesized by methods well known in the art (See U.S. Pat. Nos. 4,816,513, 5,854,389, 5,891,993 and 6,184,344).

[0093] As used herein, the term "polynucleotide" refers to a polymeric form of nucleotides of any length, either ribonucleotides or deoxyribonucleotides. This term refers only to the primary structure of the molecule. Thus, the term includes double and single-stranded DNA as well as doubleand single-stranded RNA. It also includes modifications, such as methylation or capping and unmodified forms of the polynucleotide. The terms "polynucleotide", "oligomer,""oligonucleotide," and "oligo," are used interchangeably herein.

[0094] As used herein the phrase "purified polynucleotide" refers to a polynucleotide of interest or fragment thereof that is essentially free, e.g. contains less than about 50%, 60%, 70%, 75%, 80%, 85%, 90%, 95% of the protein with which the polynucleotide is naturally associated. Techniques for purifying polynucleotides of interest are well known in the art and include, for example, disruption of the cell containing the polynucleotide with a chaotropic agent and separation of the polynucleotide(s) and proteins by ion-exchange chromatography, affinity chromatography and sedimentation according to density.

[0095] As used herein, the phrase "purified polypeptide" or "purified protein" means a polypeptide of interest or fragment thereof which is essentially free of, e.g., contains less than about 50%, 60%, 70%, 75%, 80%, 85%, 90%, 95%, cellular components with which the polypeptide of interest is naturally associated. Methods for purifying polypeptides of interest are known in the art.

[0096] As used herein, the term "isolated" refers to material that is removed from its original environment (e.g., the natural environment if it is naturally occurring). For example, a naturally occurring polynucleotide or polypeptide present in a living animal is not isolated, but the same polynucleotide or DNA or polypeptide, separated from some or all of the coexisting materials in the natural system, is isolated. Such polynucleotide could be part of a vector and/or such polynucleotide or polypeptide could be part of a composition, and still be isolated in that the vector or composition is not part of its natural environment.

[0097] As used herein, the term "polypeptide" and "protein" are used interchangeably and refer to at least one molecular chain of amino acids linked through covalent and/or non-covalent bonds. The terms do not refer to a specific length of the product. Thus, peptides, oligopeptides and proteins are included within the definition of polypeptide. The terms include post-translational modifications of the polypeptide, including, but not limited to, glycosylations, acetylations, phosphorylations and the like. In addition, protein fragments, analogs, mutated or variant proteins, fusion proteins and the like are included within the meaning of polypeptide.

[0098] As used herein, the phrase "recombinant host cells, "'host cells,""cells,""cell lines,""cell cultures," and other such terms denoting microorganisms or higher eukaryotic cell lines cultured as unicellular entities refer to cells that can be, or have been, used as recipients for recombinant vector or other transferred DNA, and include the original progeny of the original cell that has been transfected.

[0099] As used herein, the term "replicon" refers to any genetic element, such as a plasmid, a chromosome or a virus, that behaves as an autonomous unit of polynucleotide replication within a cell.

[0100] As used herein, the term "operably linked" refers to a situation wherein the components described are in a relationship permitting them to function in their intended manner. Thus, for example, a control sequence "operably linked" to a coding sequence is ligated in such a manner that expression of the coding sequence is achieved under conditions compatible with the control sequence.

[0101] As used herein, the term "vector" refers to a replicon in which another polynucleotide segment is attached, such as to bring about the replication and/or expression of the attached segment.

[0102] As used herein, the term "control sequence" refers to a polynucleotide sequence that is necessary to effect the expression of a coding sequence to which it is ligated. The nature of such control sequences differs depending upon the host organism. In prokaryotes, such control sequences generally include a promoter, a ribosomal binding site and terminators and, in some instances, enhancers. The term "control sequence" thus is intended to include at a minimum all components whose presence is necessary for expression, and also may include additional components whose presence is advantageous, for example, leader sequences.

[0103] The term "transfection" refers to the introduction of an exogenous polynucleotide into a prokaryotic or eucaryotic host cell, irrespective of the method used for the introduction. The term "transfection" refers to both stable and transient introduction of the polynucleotide, and encompasses direct uptake of polynucleotides, transformation, transduction and f-mating. Once introduced into the host cell, the exogenous polynucleotide may be maintained as a non-integrated replicon, for example, a plasmid, or alternatively, may be integrated into the host genome.

[0104] As used herein, the term "treatment" refers to prophylaxis and/or therapy.

[0105] As used herein, the term "purified product" refers to a preparation of the product which has been isolated from the cellular constituents with which the product is normally associated and from other types of cells that may be present in the sample of interest.

[0106] As used herein, the phrase "activation of an erythropoietin (EPO) receptor" refers to one or more molecular processes which an EPO receptor undergoes that result in the transduction of a signal to the interior of a receptor-bearing cell. Ultimately, this signal brings about one or more changes in cellular physiology. Activation of the EPO receptor typically results in the proliferation or differentiation of EPO receptor-bearing cells, such as, but not limited to, erythroid progenitor cells. A number of events are involved in the activation of the EPO receptor, such as, but not limited to, the dimerization of the receptor.

[0107] The structural unit of an antibody is a tetramer. Each tetramer is composed of two identical pairs of polypeptide chains, each pair having one "light" (25 kDa) and one "heavy" chain (about 50-70 kDa). The amino-terminal portion of each chain includes a variable region that is primarily responsible for antigen recognition. The carboxy-terminal portion of the chain defines a constant region that is responsible for the effector function of the antibody. Human light chains are classified as kappa and lambda light chains. Heavy chains are classified as mu, delta, gamma, alpha, or epsilon and define the antibody's isotype as IgM, IgD, IgG, IgA, and IgE. IgG immunoglobulins are classified further into four subclasses (IgG1, IgG2, IgG3 and IgG4) having gamma-1, gamma-2, gamma-3 and gamma-4 heavy chains, respectively. Most of the therapeutic human, chimeric or humanized antibodies available are of the IgG1 antibody type including Herceptin for breast cancer, Rituxan for Non-Hodgkins lymphoma and Humira and Remicade for rheumatoid arthritis (See Glennie, M. J. et al., *Drug Discovery Today*, 8:503 (2003).

[0108] Within the light and heavy chains, the variable and constant regions are joined by a "J" region with the heavy chain also include a "D" region. The variable regions of each light/heavy chain pair form the antigen binding site. Thereupon, an intact antibody has two binding sites, which, except in bifunctional or bispecific antibodies, are the same. Bifunctional or bispecific antibodies are artificial hybrid antibodies that have two different heavy/light chain pairs and two different binding sites. Bifunctional or bispecific antibodies are artificial number of the same and two different binding sites. Bifunctional or bispecific antibodies in the art.

[0109] The structure of the chains of an antibody exhibit the same general structure of relatively conserved framework regions (FR) joined by three hyper variable regions, also called complementarity determining regions or CDRs. The CDRs from the two chains of each pair are aligned by the framework regions, enabling binding to a specific epitope. From N-terminal to C-terminal, both the light and heavy chains comprise the domains FR1, CDR1, FR2, CDR2, FR3, CDR3 and FR4.

[0110] U.S. Pat. No. 6,319,499 describes antibodies that bind to and activate an erythropoietin receptor (EPO-R). The antibodies specifically identified in this patent are Mabs 71 and 73. Mab 71 binds to a peptide designated "SE-3" having the amino acid sequence of PGNYSFSYQLEDEPWKLCR-LHQAPTARGAV (SEQ ID NO:1) (See Example 3). SE-3 is located on the human EPO-R between amino acid residues 49-78. According to U.S. Pat. No. 6,319,499, when this region of the EPO-R (i.e. amino acid residues 49-79) is bound with a cross linker such as Mab 71, this results in the activation of the EPO receptor. Example 6 in U.S. Pat. No. 6,319,499 states that Mab 71 binds "significant amounts of peptide SE-3" compared to other peptides tested. This example further states that this "indicates that Mab 71 binds to a region of the human EPO-R containing or overlapping residues 49 to 78." Mabs 71 and 73 are murine antibodies. Although rodent and human antibodies may both provide precision for target specificity, human antibodies interact far more effectively with the natural defenses of the body and do not elicit anti-antibody responses to the same extent as rodent antibodies (Winter, G. and Milstein, C. Nature 349: 293 (1991). Additionally, the flexibility of human IgG subclasses differ (Roux, K. H. et al., J. Immunol. 159: 3372 (1997) and this difference also extends to rodent IgG isotypes since rodent IgG isotypes differ from their human counterparts. Since protein flexibility may affect antibodyantigen recognition (Jimenez, R., et al. Proc. Natl. Acad. Sci. USA, 100: 92 (2003), human IgG2 isotypes may result in antigen recognition mechanisms distinct from those of murine antibodies. Murine IgG isotypes generally differ from those of humans.

[0111] In one embodiment, the present invention relates to an antibody or antibody fragment that binds to the erythro-

poietin receptor. The antibody or antibody fragment that binds to the erythropoietin receptor comprises at least one heavy chain having an amino acid sequence selected from the group consisting of: SEQ ID NOS: 3, 7, 11, 15, 19, 31, 35, 39, 43, 47, 51, 55 and fragments thereof. In a second embodiment, the antibody or antibody fragment that binds to the erythropoietin receptor comprises at least one light chain having an amino acid sequence selected from the group consisting of: SEQ ID NOS: 5, 9, 13, 17, 21, 23, 25, 27, 29, 33, 37, 41, 45, 49, 53, 57 and fragments thereof.

[0112] In a third embodiment, the present invention relates to an isolated antibody that is capable of binding a human erythropoietin receptor in a mammal.

[0113] More specifically, the antibody comprises a heavy chain variable region or a light chain variable region which comprises a continuous sequence from CDR1 through CDR3. The amino acid sequence of the heavy chain variable region comprising the continuous sequence from CDR1 through CDR3 is selected from the group consisting of: SEQ ID NO:58, SEQ ID NO:59, SEQ ID NO:60 and SEQ ID NO:61, and fragments thereof. The amino acid sequence of the light chain variable region comprising the continuous sequence from CDR1 through CDR3 is selected from the group consisting of: SEQ ID NO:62, SEQ ID NO:63, SEQ ID NO:64, SEQ ID NO:65, SEQ ID NO:66, SEQ ID NO:67, and SEQ ID NO:68, and fragments thereof. In addition, the present invention relates to an isolated antibody which comprises a heavy chain variable region or a light chain variable region which comprises at least one CDR. More specifically, the antibody comprises a heavy chain variable region comprising at least one CDR selected from the group consisting of amino acid residues 99-112 of SEQ ID NO:1, 26-35 of SEQ ID NO:3, 50-65 of SEQ ID NO:3, 98-105 of SEQ ID NO:3, 26-35 of SEQ ID NO:19, 50-66 of SEQ ID NO:19, 99-105 of SEQ ID NO:19, 50-66 of SEQ ID NO:31, 99-105 of SEQ ID NO:31, 26-35 of SEQ ID NO:39, 50-65 of SEQ ID NO:39, 98-105 of SEQ ID NO:39, 26-37 of SEQ ID NO:43, 52-67 of SEQ ID NO:43, 100-107 of SEQ ID NO:43, 26-35 of SEQ ID NO:47, 50-65 of SEQ ID NO:47, 26-35 of SEQ ID NO:51, 50-65 of SEQ ID NO:51, 98-105 of SEQ ID NO:51, 26-37 of SEQ ID NO:55 and 52-67 of SEQ ID NO:55 or a light chain variable region comprising at least one CDR selected from the group consisting of amino acid residues 24-34 of SEQ ID NO:13, 50-56 of SEQ ID NO:13, 89-97 of SEQ ID NO:5, 24-34 of SEQ ID NO:27, 50-56 of SEQ ID NO:9, 24-39 of SEQ ID NO:33, 55-61 of SEQ ID NO:33, 24-34 of SEQ ID NO:41, 89-97 of SEQ ID NO:41, 24-34 of SEQ ID NO:45, 50-56 of SEQ ID NO:45, 89-97 of SEQ ID NO:45, 89-97 of SEQ ID NO:49 and 24-34 of SEQ ID NO:57.

[0114] In a fourth embodiment, the present invention relates to an antibody or antibody fragment that binds to and activates the erythropoietin receptor. The antibodies of the present invention bind to at least one epitope that is involved in activating the EPO receptor (Example 4). Unlike other antibodies or fragments known in the art that bind to and activate an erythropoietin receptor, such as the antibodies described in U.S. Pat. No. 6,319,499, the antibodies of the present invention do not interact with the peptide designated SE-3. Surprisingly, the antibodies of the present invention are erythropoietic even though the antibodies do not bind to the SE-3 peptide. Therefore, the human antibodies of the

present invention interact with at least one different epitope on the human EPO receptor than the antibodies described in U.S. Pat. No. 6,319,499.

[0115] In a fifth embodiment, the present invention relates to an IgG2 antibody or antibody fragment that binds to and activates the erythropoietin receptor. The IgG2 antibodies or antibody fragments of this embodiment bind to and interact with any epitope that is involved in activating the EPO receptor.

[0116] Additionally, as demonstrated by the BIAcore results shown in Example 1, the antibodies of the present invention exhibit a binding affinity to the erythropoietin receptor within one hundred fold of the binding affinity of endogenous human erythropoietin to the erythropoietin receptor. A high (~1 nM) and low (~1 μ M) affinity of the EPO receptor for EPO has been reported resulting from two nonequivalent receptor binding sites on EPO (See Philo, J. S. et al., *Biochemistry*, 35:1681 (1996)).

[0117] The antibodies of the present invention can be polyclonal antibodies, monoclonal antibodies, chimeric antibodies (See U.S. Pat. No. 6,020,153) or human or humanized antibodies or antibody fragments thereof. Synthetic and genetically engineered variants (See U.S. Pat. No. 6,331, 415) of any of the foregoing are also contemplated by the present invention. Preferably, however, the antibodies of the present invention are human or humanized antibodies. The advantage of human or humanized antibodies is that they potentially decrease or eliminate the immunogenicity of the antibody in a host recipient, thereby permitting an increase in the bioavailability and a reduction in the possibility of adverse immune reaction, thus potentially enabling multiple antibody administrations.

[0118] Humanized antibodies include chimeric or CDRgrafted antibodies. Also, human antibodies can be produced using genetically engineered strains of animals in which the antibody gene expression of the animal is suppressed and functionally replaced with human antibody gene expression.

[0119] Methods for making humanized and human antibodies are known in the art. One method for making human antibodies employs the use of transgenic animals, such as a transgenic mouse. These transgenic animals contain a substantial portion of the human antibody producing genome inserted into their own genome and the animal's own endogenous antibody production is rendered deficient in the production of antibodies. Methods for making such transgenic animals are known in the art. Such transgenic animals can be made using XenoMouse® technology or by using a "minilocus" approach. Methods for making Xenomice™ are described in U.S. Pat. Nos. 6,162,963, 6,150,584, 6,114,598 and 6,075,181. Methods for making transgenic animals using the "minilocus" approach are described in U.S. Pat. Nos. 5,545,807, 5,545,806 and 5,625,825. Also see International Publication No. WO93/12227.

[0120] Using the XenoMouse® technology, human antibodies can be obtained by immunizing a XenoMouse® mouse (Abgenix, Fremont, Calif.) with an antigen of interest. The lymphatic cells (such as B-cells) are recovered from the mice that express antibodies. These recovered cells can be fused with myeloid-type cell line to prepare immortal hybridoma cell lines. These hybridoma cell lines can be screened and selected to identify hybridoma cell lines that

produce antibodies specific to the antigen of interest. Alternatively, the antibodies can be expressed in cell lines other than hybridoma cell lines. More specifically, sequences encoding particular antibodies can be cloned from cells producing the antibodies and used for transformation of a suitable mammalian host cell.

[0121] Transformation can be by any known method for introducing polynucleotides into a host cell, including, for example, packaging the polynucleotide in a virus or into a viral vector and transducing a host cell with a virus or vector or by transfection procedures known in the art such as those described in U.S. Pat. Nos. 4,399,216, 4,912,040, 4,740,461 and 4,959,455. For example, one or more genes encoding the heavy chain can be expressed in a cell and one or more genes encoding the light chain can be expressed in a second cell. The resulting heavy and light chains can then be fused together to form the antibodies of the present invention using techniques known in the art. Alternatively, genes encoding for parts of the heavy and light chains can be ligated using restriction endonucleases to reconstruct the gene coding for each chain. Such a gene can then be expressed in a cell to produce the antibodies of the present invention.

[0122] The transformation procedure used will depend upon the host to be transformed. Methods for introducing heterologous polynucleotides into mammalian cells are well known in the art and include dextran-mediated transfection, calcium phosphate precipitation, polybrene mediated transfection, protoplast fusion, electroporation, encapsulation of the polynucleotide(s) into liposomes and direct microinjection of the DNA molecule.

[0123] Mammalian cell lines that can be used as hosts for expression are well known in the art and include, but are not limited to, Chinese hamster ovary (CHO) cells, HeLa cells, baby hamster kidney (BHK) cells, monkey kidney cells (COS), human hepatocellular carcinoma cells bacterial cells, such as *E. coli*, yeast cells, such as *Saccharomyces cerevisiae*, etc.

[0124] Humanized antibodies can also be made using a CDR-grafted approach. Such humanized antibodies are well known in the art. Generally, humanized antibodies are produced by obtaining nucleic acid sequences that encode the variable heavy and variable light sequences of an antibody that binds to the EPO receptor, identifying the complementary determining region or "CDR" in the variable heavy and variable light sequences and grafting the CDR nucleic acid sequences. (See, for example, U.S. Pat. Nos. 4,816,567 and 5,225,539).

[0125] The human framework that is selected is one that is suitable for in vivo administration, meaning that it does not exhibit immunogenicity. For example, such a determination can be made by prior experience with in vivo usage of such antibodies and studies of amino acid similarities.

[0126] Methods for cloning nucleic acids are known in the art. These methods involve amplification of the antibody sequences to be cloned using appropriate primers by polymerase chain reaction (PCR). Primers that are suitable for amplifying antibody nucleic acid sequences and specifically murine variable heavy and variable light sequences are known in the art.

[0127] Once the CDRs and FRs of the cloned antibody sequences that are to be humanized are identified, the amino acid sequences encoding the CDRs are identified and the corresponding nucleic acid sequences grafted on to selected human FRs. This can be done using known primers and linkers, the selection of which are known in the art.

[0128] After the CDRs are grafted onto selected human FRs, the resulting "humanized" variable heavy and variable light sequences are expressed to produce a humanized Fv or humanized antibody that binds to the EPO receptor. Typically, the humanized variable heavy and light sequences are expressed as a fusion protein with human constant domain sequences so an intact antibody that binds to the EPO receptor is obtained. However, a humanized Fv antibody can be produced that does not contain the constant sequences. Fusion of the human constant sequence to the humanized variable region is preferred.

[0129] The EPO receptor that is bound by and preferably activated using the antibodies of the present invention is preferably a mammalian EPO receptor, most preferably a human EPO receptor. The present invention also contemplates the use of analogs of the EPO receptor, such as those described in U.S. Pat. No. 5,292,654. Human EPO receptor can be purchased from R & D Systems (Minneapolis, Minn.).

[0130] An example of two (2) antibodies that (1) bind to and activate the EPO receptor; (2) do not interact with a peptide having an amino acid sequence of PGNYSF-SYQLEDEPWKLCRLHQAPTARGAV (SEQ ID NO: 1); and (3) exhibit a binding affinity within one hundred fold of the binding affinity of endogeous human EPO to the EPO receptor, are the human antibodies designated Ab12 and Ab198. Ab12 and Ab198 are human antibodies that were developed using the XenoMouse® XenoMax technology described herein (See Example 1).

[0131] In another embodiment, the present invention relates to polynucleotide and polypeptide sequences that encode for the antibodies described herein. Preferably, such polynucleotides encode for both the variable and constant regions of each of the heavy and light chains, although other combinations are also contemplated by the present invention.

[0132] The present invention also contemplates oligonucleotide fragments derived from the disclosed polynucleotides and nucleic acid sequences complementary to these polynucleotides. The polynucleotides can be in the form of RNA or DNA. Polynucleotides in the form of DNA, cDNA, genomic DNA, nucleic acid analogs and synthetic DNA are within the scope of the present invention. The DNA may be double-stranded or single-stranded, and if single stranded, may be the coding (sense) strand or non-coding (anti-sense) strand. The coding sequence that encodes the polypeptide may be identical to the coding sequence provided herein or may be a different coding sequence which coding sequence, as a result of the redundancy or degeneracy of the genetic code, encodes the same polypeptide as the DNA provided herein.

[0133] Preferably, the polynucleotides encode at least one heavy chain variable region and at least one light chain variable region of the present invention. Examples of such polynucleotides are shown in SEQ ID NOS: 2, 4, 6, 8, 10,

12, 14, 16, 18, 20, 22, 24, 26, 28, 30, 32, 34, 36, 38, 40, 42, 44, 46, 48, 50, 52, 54 and 56 as well as fragments, complements and degenerate codon equivalents thereof. For example, SEQ ID NO: 2 encodes for the heavy chain of Ab12 (variable region) and SEQ ID NO:4 encodes for the light chain of Ab12 (variable region). SEQ ID NO:6 encodes for the heavy chain of Ab 198 (variable region) and SEQ ID NO: 8 encodes for the light chain of Ab198 (variable region).

[0134] The present invention also includes variant polynucleotides containing modifications such as polynucleotide deletions, substitutions or additions, and any polypeptide modification resulting from the variant polynucleotide sequence. A polynucleotide of the present invention may also have a coding sequence that is a naturally occurring variant of the coding sequence provided herein.

[0135] It is contemplated that polynucleotides will be considered to hybridize to the sequences provided herein if there is at least 50%, 60%, 70%, 75%, 80%, 85%, 90%, 95% identity between the polynucleotide and the sequence.

[0136] The present invention further relates to polypeptides that encode for the antibodies of the present invention as well as fragments, analogs and derivatives of such polypeptides. The polypeptides of the present invention may be recombinant polypeptides, naturally purified polypeptides or synthetic polypeptides. The fragment, derivative or analogs of the polypeptides of the present invention may be one in which one or more of the amino acid residues is substituted with a conserved or non-conserved amino acid residue (preferably a conserved amino acid residue) and such substituted amino acid residue may or may not be one encoded by the genetic code; or it may be one in which one or more of the amino acid residues includes a substituent group; or it may be on in which the polypeptide is fused with another compound, such as a compound to increase the half-life of the polypeptide (for example, polyethylene glycol); or it may be one in which the additional amino acids are fused to the polypeptide, such as a leader or secretory sequence or a sequence that is employed for purification of the polypeptide or a proprotein sequence. Such fragments, derivatives and analogs are within the scope of the present invention.

[0137] A polypeptide of the present invention may have an amino acid sequence that is identical to that of the antibodies described herein or that is different by minor variations due to one or more amino acid substitutions. The variation may be a "conservative change" typically in the range of about 1 to 5 amino acids, wherein the substituted amino acid has similar structural or chemical properties, e.g., replacement of leucine with isoleucine or threonine with serine. In contrast, variations may include nonconservative changes, e.g., replacement of a glycine with a tryptophan. Similar minor variations may also include amino acid deletions or insertions or both. Guidance in determining which and how many amino acid residues may be substituted, inserted, or deleted without changing biological or immunological activity may be found using computer programs well known in the art, for example DNASTAR software (DNASTAR, Inc., Madison, Wis.).

[0138] Preferably, the polypeptides encode at least one heavy chain variable region or at least one light chain variable region of the antibodies of the present invention.

More preferably, the polypeptides encode at least one heavy chain variable region and one light chain variable region of the antibodies of the present invention. Examples of such polypeptides are those having the amino acid sequences shown in SEQ ID NOS: 3, 5, 7, 9, 11, 13, 15, 17, 19, 21, 23, 25, 27, 29, 31, 33, 35, 37, 39, 41, 43, 45, 46, 47, 49, 51, 53, 55, 57, 58, 59, 60, 61, 62, 63, 64, 65, 66, 67, 68, and fragments thereof. Specifically, the heavy chain of Ab 12 has the amino acid sequence shown in SEQ ID NO: 3 and the light chain has the amino acid sequence of the heavy chain of Ab198 is shown in SEQ ID NO:7 and the light chain has the amino acid sequence shown in SEQ ID NO:9.

[0139] The present invention also provides vectors that include the polynucleotides of the present invention, host cells which are genetically engineered with vectors of the present invention and the production of the antibodies of the present invention by recombinant techniques.

[0140] Host cells are genetically engineered (transfected, transduced or transformed) with vectors, such as, cloning vectors or expression vectors. The vector may be in the form of a plasmid, a viral particle, a phage, etc. The engineered host cells can be cultured in conventional nutrient media modified as appropriate for activating promoters, selecting transfected cells, etc. The culture conditions, such as temperature, pH and the like, are those previously used with the host cell selected for expression, and will be apparent to those of skilled in the art.

[0141] The polynucleotides of the present invention can be employed to produce the polypeptides and hence the antibodies of the present invention. The polynucleotide sequences of the present invention can be included in any one of a variety of expression vehicles, in particular, vectors or plasmids for expressing a polypeptide. Such vectors include chromosomal, nonchromosomal and synthetic DNA sequences, derivatives of SV40, bacterial plasmids, phage DNA, yeast plasmids, vectors derived from combinations of plasmids and phage DNA, viral DNA such as vaccinia, adenovirus, fowl pox virus and pseudorabies. However, any other plasmid or vector may be used so long as it is replicable and viable in the host.

[0142] The appropriate DNA sequence may be inserted into the vector by a variety of procedures. In general, the DNA sequence is inserted into appropriate restriction endonuclease sites by procedures known in the art. The polynucleotide sequence in the expression vector is operatively linked to an appropriate expression control sequence (i.e. promoter) to direct mRNA synthesis. Examples of such promoters include, but are not limited to, the LTR or the SV40 promoter, the *E. coli* lac or trp, the phage lambda P_L promoter and other promoters known to control expression of genes in prokaryotic or eukaryotic cells or their viruses. The expression vector also contains a ribosome binding site for translation initiation and a transcription terminator. The vector may also include appropriate sequences for amplifying expression. For example, the vector can contain enhancers, which are transcription-stimulating DNA sequences of viral origin, such as those derived form simian virus such as SV40, polyoma virus, bovine papilloma virus or Moloney sarcoma virus, or genomic, origin. The vector preferably also contains an origin of replication. The vector can be constructed to contain an exogenous origin of replication or,

such an origin of replication can be derived from SV40 or another viral source, or by the host cell chromosomal replication mechanism.

[0143] In addition, the vectors preferably contain a marker gene for selection of transfected host cells such as dihydro-folate reductase or antibiotics, such as G-418 (geneticin, a neomycin-derivative) or hygromycin, or genes which complement a genetic lesion of the host cells such as the absence of thymidine kinase, hypoxanthine phosphoribosyl transferase, dihydrofolate reductase, etc.

[0144] Suitable vectors for use in the present invention are known in the art. Any plasmid or vector can be used in the present invention as long as it is replicable and is viable in the host. Examples of vectors that can be used include those that are suitable for mammalian hosts and based on viral replication systems, such as simian virus 40 (SV40), Rous sarcoma virus (RSV), adenovirus 2, bovine papilloma virus (BPV), papovavirus BK mutant (BKV), or mouse and human cytomegalovirus (CVM).

[0145] In a further embodiment, the present invention relates to host cells containing the above-described constructs. The host cell can be a higher eukaryotic cell, such as a mammalian cell, or a lower eukaryotic cell, such as a yeast cell, or the host cell can be a prokaryotic cell, such as a bacterial cell. Preferably, the host cells provide a suitable environment for the production of active antibodies, since the biosynthesis of functional tetrameric antibody molecules requires correct nascent polypeptide chain folding, glycosylation, and assembly. Example of suitable host cells, include mammalian cells, such as COS-7 cells, Bowes melanoma cells, Chinese hamster ovary (CHO) cells, embryonic lung cells L-132, and mammalian cells of lymphoid origin, such as myeloma or lymphoma cells. The host cells can be transfected with a vector containing a polynucleotide sequence encoding the H-chain alone, with a second vector encoding the light chain alone (such as by using two different vectors as discussed previously). Preferably, the host cells are transfected with two different vectors.

[0146] Introduction of the vectors into the host cell can be effected by calcium phosphate transfection, DEAE-Dextran mediated transfection or electroporation (L. David et al., *Basic Methods in Molecular Biology* 2^{nd} Edition, Appleton and Lang, Paramount Publishing, East Norwalk, Conn. (1994)).

[0147] In order to obtain the antibodies of the present invention, one or more polynucleotide sequences that encode for the light and heavy chain variable regions and light and heavy chain constant regions of the antibodies of the present invention should be incorporated into a vector. Polynucleotide sequences encoding the light and heavy chains of the antibodies of the present invention can be incorporated into one or multiple vectors and then incorporated into the host cells.

[0148] Cell lines expressing Ab12 and Ab467 antibodies were deposited with the American Type Culture Collection (ATCC), 10801 University Boulevard, Manassas, Va. 20110, under the terms of the Budapest Treaty, on Sep. 30, 2003 and were accorded accession numbers PTA-5554 and PTA-5555. These deposits are provided for the convenience of those skilled in the art and are neither an admission that such

deposits are required to practice the invention nor that equivalent embodiments are not within the skill of the art in view of the present disclosure. The public availability of these deposits is not a grant of a license to make, use or sell the deposited materials under this or any other patents. The nucleic acid sequences of the deposited materials are incorporated in the present disclosure by reference and are controlling if in conflict with any sequence described herein.

[0149] The antibodies of the present invention have a number of uses. In general, the antibodies may be used to treat any condition treatable by erythropoietin or a biologically active variant or analog thereof. For example, antibodies of the invention are useful for treating disorders characterized by low red blood cell levels and/or decreased hemoglobin levels (e.g. anemia). In addition, the antibodies of the invention may be used for treating disorders characterized by decreased or subnormal levels of oxygen in the blood or tissue, such as, for example, hypoxemia or chronic tissue hypoxia and/or diseases characterized by inadequate blood circulation or reduced blood flow. Antibodies of the invention also may be useful in promoting wound healing or for protecting against neural cell and/or tissue damage, resulting from brain/spinal cord injury, stroke and the like. Non-limiting examples of conditions that may be treatable by the antibodies of the invention include anemia, such as chemotherapy-induced anemia, cancer associated anemia, anemia of chronic disease, HIV-associated anemia, bone marrow transplant-associated anemia and the like, heart failure, ischemic heart disease and renal failure. As such, the invention includes methods of treating any of the aforementioned diseases or conditions comprising the step of administering to a mammal a therapeutically effective amount of said antibody. Preferably, the mammal is a human.

[0150] The antibodies of the present invention also can be used to identify and diagnose mammals that have a dysfunctional EPO receptor. Mammals that have a dysfunctional EPO receptor are characterized by disorders such as anemia. Preferably, the mammal being identified and diagnosed is a human. Additionally, the antibodies of the present invention can be used in the treatment of anemia in mammals suffering from red blood cell aplasia. Red blood cell aplasia may result from the formation of neutralizing antierythropoietin antibodies in patients during treatment with recombinant erythropoietin (Casadevall, N. et al., n. Eng. J. Med. 346: 469 (2002)). The method involves the step of administering to a mammal suffering from said aplasia and in need of treatment a therapeutically effective amount of the antibodies of the present invention.

[0151] In another embodiment of the invention, the EPO receptor antibodies and antibody fragments of the invention also can be used to detect EPO receptor (e.g., in a biological sample, such as tissue specimens, intact cells, or extracts thereof), using a conventional immunoassay, such as an enzyme linked immunosorbent assay (ELISA), a radioimmunoassay (RIA) or tissue immunohistochemistry. The invention provides a method for detecting EPO receptor in a biological sample comprising contacting a biological sample with an antibody or antibody fragment of the invention and detecting either the antibody (or antibody portion), to thereby detect EPO receptor in the biological sample. The antibody or antibody fragment is directly or indirectly labeled with a detectable substance to facilitate detection of the bound or unbound antibody or antibody fragment. A

variety of immunoassay formats may be practiced (such as competitive assays, direct or indirect sandwich immunoassays and the like) and are well known to those of ordinary skill in the art.

[0152] Suitable detectable substances include various enzymes, prosthetic groups, fluorescent materials, luminescent materials and radioactive materials. Examples of suitable enzymes include horseradish peroxidase, alkaline phosphatase, B-galactosidase, or acetylcholinesterase; examples of suitable prosthetic group complexes include streptavidin/ biotin and avidin/biotin; examples of suitable fluorescent materials include umbelliferone, fluorescein, fluorescein isothiocyanate, rhodamine, dichlorotriazinylamine, dansyl chloride or phycoerythrin; and an example of a luminescent material include luminol; and examples of suitable radioactive material include location active material inc

[0153] In yet another embodiment, the present invention relates to a pharmaceutical composition containing a therapeutically effective amount of the antibody of the present invention along with a pharmaceutically acceptable carrier or excipient. As used herein, "pharmaceutically acceptable carrier" or "pharmaceutically acceptable excipient" includes any and all solvents, dispersion media, coating, antibacterial and antifungal agents, isotonic and absorption delaying agents, and the like that are physiologically compatible. Examples of pharmaceutically acceptable carriers or excipients include one or more of water, saline, phosphate buffered saline, dextrose, glycerol, ethanol and the like as well as combinations thereof. In many cases, it will be preferable to include isotonic agents, for example, sugars, polyalcohols such as mannitol, sorbitol, or sodium chloride in the composition. Pharmaceutically acceptable substances such as wetting or minor amounts of auxiliary substances such as wetting or emulsifying agents, preservatives or buffers, which enhance the shelf life or effectiveness of the of the antibody or antibody portion also may be included. Optionally, disintegrating agents can be included, such as crosslinked polyvinyl pyrrolidone, agar, alginic acid or a salt thereof, such as sodium alginate and the like. In addition to the excipients, the pharmaceutical composition can include one or more of the following, carrier proteins such as serum albumin, buffers, binding agents, sweeteners and other flavoring agents; coloring agents and polyethylene glycol.

[0154] The compositions of this invention may be in a variety of forms. They include, for example, liquid, semisolid and solid dosage forms, such as liquid solutions (e.g. injectable and infusible solutions), dispersions or suspensions, tablets, pills, powders, liposomes and suppositories. The preferred form depends on the intended mode of administration and therapeutic application. Typical preferred compositions are in the form of injectable or infusible solutions, such as compositions similar to those used for passive immunization of humans with other antibodies. The preferred mode of administration is parenteral (e.g., intravenous, subcutaneous, intraperitoneal, intramuscular). In a preferred embodiment, the antibody is administered by intravenous infusion or injection. In another preferred embodiment, the antibody or antibody fragment is administered by intramuscular or subcutaneous injection.

[0155] Other suitable routes of administration for the pharmaceutical composition include, but are not limited to, rectal, transdermal, vaginal, transmucosal or intestinal administration.

[0156] Therapeutic compositions typically must be sterile and stable under the conditions of manufacture and storage. The composition can be formulated as a solution, microemulsion, dispersion, liposome, or other ordered structure suitable to high drug concentration. Sterile injectable solutions can be prepared by incorporating the active compound (i.e. antibody or antibody fragment) in the required amount in an appropriate solvent with one or a combination of ingredients enumerated above, as required, followed by filtered sterilization. Generally, dispersions are prepared by incorporating the active compound into a sterile vehicle that contains a basic dispersion medium and the required other ingredients from those enumerated above. In the case of sterile powders for the preparation of sterile injectable solutions, the preferred methods of preparation are vacuum drying and freeze-drying that yields a powder of the active ingredient plus any additional desired ingredient from a previously sterile-filtered solution thereof. The proper fluidity of a solution can be maintained, for example, by the use of a coating such as lecithin, by the maintenance of the required particle size in the case of dispersion and by the use of surfactants. Prolonged absorption of injectable compositions can be brought about by including in the composition an agent that delays absorption, for example, monostearate salts and gelatin.

[0157] The antibodies and antibody fragments of the invention can be administered by a variety of methods known in the art, although for many therapeutic applications, the preferred route/mode of administration is intravenous injection or infusion. As will be appreciated by the skilled artisan, the route and/or mode of administration will vary depending upon the desired results. In certain embodiments, the active compound may be prepared with a carrier that will protect the compound against rapid release, such as a controlled release formulation, including implants, transdermal patches, and microencapsulated delivery systems. Biodegradable, biocompatible polymers can be used, such as ethylene vinyl acetate, polyanhydrides, polyglycolic acid, collagen, polyorthoesters, and polylactic acid. Many methods for the preparation of such formulations are patented or generally known to those skilled in the art. See, e.g. Sustained and Controlled Release Drug Delivery Systems, J. R. Robinson, ed., Marcel Dekker, Inc., New York, 1978).

[0158] In certain embodiments, an antibody or antibody portion of the invention may be orally administered, for example, with an inert diluent or an assimilable edible carrier. The compound (and other ingredients if desired) may also be enclosed in a hard or soft shell gelatin capsule, compressed into tablets, buccal tablets, troches, capsules, elixirs, suspensions, syrups, wafers, and the like. To administer an antibody or antibody fragment of the invention by other than parenteral administration, it may be necessary to coat the compound with, or co-administer the compound with, a material to prevent its inactivation.

[0159] Supplementary active compounds also can be incorporated into the compositions. In certain embodiments, an antibody or antibody fragment of the invention is coformulated with and/or coadministered with one or more additional therapeutic agents. For example, an EPO receptor antibody or antibody fragment of the invention may be coformulated and/or coadministered with one or more additional antibodies that bind other targets (e.g., antibodies that bind other cytokines or that bind cell surface molecules) or

one or more cytokines. Furthermore, one or more antibodies of the invention may be used in combination with two or more of the foregoing therapeutic agents. Such combination therapies may advantageously utilize lower dosages of the administered therapeutic agents, thus avoiding possible toxicities or complications associated with the various monotherapies.

[0160] As used herein, the term "therapeutically effective amount" means an amount of antibody or antibody fragment that produces the effects for which it is administered. The exact dose will be ascertainable by one skilled in the art. As known in the art, adjustments based on age, body weight, sex, diet, time of administration, drug interaction and severity of condition may be necessary and will be ascertainable with routine experimentation by those skilled in the art. A therapeutically effective amount is also one in which the therapeutically beneficial effects outweigh any toxic or detrimental effects of the antibody or antibody fragment. A "prophylactically effective amount" refers to an amount effective, at dosages and for periods of time necessary to achieve the desired prophylactic result. Typically, since a prophylactic dose is used in subjects prior to or at an earlier stage of disease, the prophylactically effective amount will be less than the therapeutically effective amount.

[0161] Dosage regimens may be adjusted to provide the optimum desired response (e.g., a therapeutic or prophylactic response). For example, a single bolus may be administered, several divided doses may be administered over time or the dose may be proportionally reduced or increased as indicated by the exigencies of the therapeutic situation. It is especially advantageous to formulate parenteral compositions in dosage unit form for ease of administration and uniformity of dosage. Dosage unit form as used herein refers to physically discrete units suited as unitary dosages for the mammalian subjects to be tested; each unit containing a predetermined quantity of active compound calculated to produce the desired therapeutic effect in association with the required pharmaceutical carrier. The specification for the dosage unit forms of the invention are dictated by and directly dependent on (a) the unique characteristics of the active compound and the particular therapeutic or prophylactic effect to be achieved and (b) the limitations inherent in the art of compounding such an active compound for the treatment of sensitivity in individuals.

[0162] An exemplary, non-limiting range for a therapeutically or prophylactically effective amount of an antibody or antibody portion of the invention is 0.1-20 mg/kg, more preferably 1-10 mg/kg. It is to be noted that dosage values may vary with the type and severity of the condition to be alleviated. It is to be further understood that for any particular subject, specific dosage regimens should be adjusted over time according to the individual need and the professional judgment of the person administering or supervising the administration of the compositions, and that dosage ranges set forth herein are exemplary only and are not intended to limit the scope or practice of the claimed composition.

[0163] By way of example, and not of limitation, examples of the present invention shall now be given.

EXAMPLE 1

Generation of human Erythropoietin Receptor Antibodies

[0164] Antigen Preparation. The antigen used for immunization of XenoMouse® animals was coupled to a universal T-cell epitope (TCE) (*J. Immunol.*, 148(5):1499 (1992)) using two different methods. A mixture containing an equal amount of each was used as the immunogen.

[0165] 1) 2.3 mg of Dithiothreitol (DTT), and 200 mcg of cysteine coupled TCE (*J. Immunol.*, 148(5):1499 (1992)) are mixed at room temperature for 30 minutes. DTT is removed by centrifugation through a Sephadex G10 (Pharmacia, Upsala, Sweden) chromatography column. The reduced cysteine coupled TCE is added to 200 mcg soluble extracellular domain of human EpoR (R&D Systems, Minneapolis, Minn.) re-suspended in Phosphate Buffered Saline (PBS) (8.1 mM Na₂HPO₄, 1.6 mM NaH₂PO₄, 136 mM NaCl, 2.6 mM KCl, pH 7.4) and 33 mcg of Sulfosuccinimidyl 4-(N-maleimidomethyl)-cyclohexane-1-carboxylate (sulfo SMCC), and mixed 4° C. over night. Un-reacted EpoR was removed by centrifugation through a 10 KDa cut off Centricon column (Millipore, Bedford, Mass.).

[0166] 2) The soluble extracellular domain (200 mcg) of human EpoR (R&D Systems, Minneapolis, Minn.) was re-suspended in PBS and mixed with 4 mcg of TCE-BPA (p-Benzoyl Phenylalanine) and incubated under UV light (362 nM) at room temperature for 45 minutes. The unreacted EpoR was removed by centrifugation through a 10 KDa cut off Centricon column (Millipore, Bedford, Mass.).

[0167] Immunization of animals. Monoclonal antibodies of the invention, including Ab12 and Ab198 (also referred to herein as AB-ABT2-XG2-012 and AB-ABT2-XG2-198, respectively) were developed by immunizing XenoMouse® mice (XenoMouse® XG2, Abgenix, Inc., Fremont, Calif. and Vancouver, BC) with soluble EpoR coupled to a TCE as described above. The initial immunization was with 20 mcg of antigen and mixed 1:1 v/v with Complete Freund's Adjuvant (CFA) (Sigma, St Louis, Mo.) per mouse. The subsequent immunizations were with 20 mcg of antigen mixed 1:1 v/v with incomplete Freund's (IFA). In particular, each animal was immunized at the base of tail and by intraperitoneal injection on days 0, 14, 28 and 42.

[0168] Biotinylation of EpoR. 300 mcg of EpoR (Abbott CHO cell derived ref.# RB69084:4) was re-suspended in 990 mcL of PBS pH 8.6 and added to 100 mcg of biotin-NHS (Pierce, Rockford, Ill.) dissolved in DMSO (Dimethyl Sulfoxide) incubated for forty minutes at room temperature (RT). Free biotin and buffer was removed by centrifugation through a 5 kDa Centricon column with several washes with PBS pH 7.4 and re-suspended in an appropriate volume to a final concentration was 600 mcg/mL.

[0169] Selection of animals for harvest. Anti-EpoR antibody titers were determined by ELISA. 0.7 mcg/ml biotin EpoR (described above) was coated onto streptavadin plates (Sigma, St Louis, Mo.) at room temperature for 1 hour. The solution containing unbound biotin EpoR was removed and all plates were washed five times with dH₂O. XenoMouse® sera from the EpoR immunized animals, or naïve Xen-Mouse® animals, were titrated in 2% milk/PBS at a 1:2 dilution in duplicate from a 1:100 initial dilution. The last

well was left blank, and plates were washed five times with dH_2O . A goat anti-human IgG Fc-specific horseradish peroxidase (HRP) (Pierce, Rockford, III.) conjugated antibody was added at a final concentration of 1 mcg/mL for 1 hour at room temperature. The plates were washed five times with dH_2O . The plates were developed with the addition of TMB chromogenic substrate (KPL, Gaithersburg, Md.) for 30 minutes and the ELISA was stopped by the addition of 1 M phosphoric acid. The specific titers obtained from XenoMouse® animals were determined from the optical density at 450 nm and are shown in Table 1. The titer represents the reciprocal dilution of the serum and therefore the higher the number the greater the humoral immune response to EpoR.

TABLE 1

Mouse I.D.	Titer	
11	1600	
12	12800	
13	51200	
14	102400	
15	102400	
16	0	
17	102400	
18	3200	
19	102400	
20	2560	

XenoMouse® animal 14 was selected for harvest based on the serology data in Table 1.

[0170] Culture and selection of B cells. B cells from the harvested animals were cultured and those secreting EpoR-specific antibodies were isolated essentially as described in Babcook et al., *Proc. Natl. Acad. Sci. USA*, 93:7843-7848 (1996). ELISA, performed as described above for sera titers, was used to identify EpoR-specific wells. Fifty plates cultured at 500 cells/well were screened on biotin EpoR to identify the antigen-specific wells. The data as shown in Table 2 demonstrated the presence of 701 wells with ODs significantly over background (0.05).

TABLE 2

		_
Optical Density	Number of Positives	
0.1	701	_
0.2	273	
0.3	163	
0.4	130	
0.5	102	
0.6	91	
0.7	76	
0.8	70	
0.9	67	
1.0	65	
2.0	25	
3.0	7	

[0171] These data indicated a very low frequency of hits and indicated that the wells were monoclonal for antigen-specificity. These 701 positive wells were re-screened on biotin EpoR and 137 wells (shown in bold in Table 3 below) were found to repeat as real antigen-specific wells with ODs significantly over background (0.05).

TABLE 3

Optical Density	Number of Positives
0.1	207
0.15	137
0.2	110
0.3	94
0.4	85
0.5	79
0.6	71
0.7	63
0.8	57
0.9	53
1.0	50
2.0	32
3.0	13

[0172] Agonist activity assay. Proliferation of an Epo responsive cell line was used as the basis for the agonist screen. These 137 wells were then screened for agonist activity using the human erythroleukemia cell line UT-7/Epo (Abbott ref#.RB29454-174). 12.5 mcL of supernatant were added to 1×105 cells per well in RPMI 1640 (10% FCS) to a final volume of 50 mcL in a half-area 96 well plate. The well size is half the area of a typical 96 well plate. Proliferation was identified visually and compared to cells in media containing a titration of human Epo or no Epo as a base line control. Eleven wells with proliferation activity were identified.

[0173] EpoR-specific Hemolytic Plaque Assay. A number of specialized reagents are needed to conduct the assay. These reagents were prepared as follows.

[0174] Biotinylation of Sheep red blood cells (SRBC): SRBC are stored in RPMI media as a 25% stock. A 250 ul SRBC packed-cell pellet was obtained by aliquoting 1.0 ml of the stock into a 15-ml falcon tube, spinning down the cells and removing the supernatant. The cell pellet was then re-suspended in 4.75 ml PBS at pH 8.6 in a 50 ml tube. In a separate 50 ml tube, 2.5 mg of Sulfo-NHS biotin was added to 45 ml of PBS at pH 8.6. Once the biotin had completely dissolved, 5 ml of SRBCs were added and the tube rotated at RT for 1 hour. The SRBCs were centrifuged at 3000 g for 5 min, the supernatant drawn off and 25 mls PBS at pH 7.4 as a wash. The wash cycle was repeated 3 times, then 4.75 ml immune cell media (RPMI 1640 with 10% FCS) was added to the 250 ul biotinylated-SRBC (B-SRBC) pellet to gently re-suspend the B-SRBC (5% B-SRBC stock). Stock was stored at 4° C. until needed.

[0175] Streptavidin (SA) coating of B-SRBC: One ml of the 5% B-SRBC stock was transferred into to a fresh eppendorf tube. The B-SRBC cells were pelleted with a pulse spin at 8000 rpm (6800 rcf) in a microfuge, the supernatant drawn off, the pellet re-suspended in 1.0 ml PBS at pH 7.4, and the centrifugation repeated. The wash cycle was repeated 2 times, then the B-SRBC pellet was resuspended in 1.0 ml of PBS at pH 7.4 to give a final concentration of 5% (v/v). 10 ul of a 10 mg/ml streptavidin (CalBiochem, San Diego, Calif.) stock solution was added and the tube mixed and rotated at RT for 20 min. The washing steps were repeated and the SA-SRBC were resuspended in 1 ml PBS pH 7.4 (5% (v/v)).

[0176] EpoR coating of SA-SRBC: The SA-SRBC were coated with biotinylated EpoR at 10 ug/ml, the mixed and

rotated at RT for 20 min. The SRBC were washed twice with 1.0 ml of PBS at pH 7.4 as above. The EpoR-coated SRBC were re-suspended in RPMI (+10% FCS) to a final concentration of 5% (v/v).

[0177] Determination of the quality of EpoR-SRBC by immunofluorescence (IF): 10 ul of 5% SA-SRBC and 10 ul of 5% PTH-coated SRBC were each added to separate fresh 1.5 ml eppendorf tube containing 40 ul of PBS. The murine anti-EpoR antibody (R&D Systems Cat.# MAB307) was added to each sample of SRBCs at 20 ug/ml. The tubes were rotated at RT for 25 min, and the cells were then washed three times with 100 ul of PBS. The cells were re-suspended in 50 ul of PBS and incubated with 40 mcg/mL Gt-anti mouse IgG Fc antibody conjugated to Alexa488 (Molecular Probes, Eugene, Oreg.). The tubes were rotated at RT for 25 min, and then washed with 100 ul PBS and the cells re-suspended in 10 ul PBS. 10 ul of the stained cells were spotted onto a clean glass microscope slide, covered with a glass coverslip, observed under fluorescent light, and scored on an arbitrary scale of 0-4.

[0178] Preparation of plasma cells: The contents of a single microculture well identified by the previous assays as containing a B cell clone secreting the immunoglobulin of interest were harvested. Using a 100-1000 ul pipettman, the contents of the well were recovered by adding 37C RPMI (+10% FCS). The cells were re-suspended by pipetting and then transferred to a fresh 1.5 ml eppendorf tube (final vol. approx 500-700 ul). The cells were centrifuged in a microfuge at 1500 rpm (240 rcf) for 2 minutes at room temperature, then the tube rotated 180 degrees and spun again for 2 minutes at 1500 rpm. The freeze media was drawn off and the immune cells resuspended in 100 ul RPMI (10% FCS), then centrifuged. This washing with RPMI (10% FCS) and stored on ice until ready to use.

[0179] Plague assay: Glass slides $(2\times3 \text{ inch})$ were prepared in advance with silicone edges and allowed to cure overnight at RT. Before use the slides were treated with approx. 5 ul of SigmaCoat (Sigma, Oakville, ON) wiped evenly over glass surface, allowed to dry and then wiped vigorously. To a 60 ul sample of cells was added 60 ul each of EpoR-coated SRBC (5% v/v stock), 4× guinea pig complement (Sigma, Oakville, ON) stock prepared in RPMI with 10% FCS, and 4× enhancing sera stock (1:900 in RPMI with 10% FCS). The mixture (3-5 ul) was spotted onto the prepared slides and the spots covered with undiluted paraffin oil. The slides were incubated at 37° C. for a minimum of 45 minutes.

[0180] Plague assay results: The coating was determined qualitatively by immunofluorescent microscopy to be very high (4/4) using MAB307 to detect coating compared to a secondary detection reagent alone (0/4). There was no signal detected using the MAB307 antibody on red blood cells that were only coated with streptavidin (0/4). These red blood cells were then used to identify antigen-specific plasma cells from the fourteen wells identified in Table 4. After micromanipulation to rescue the antigen-specific plasma cells, the genes encoding the variable region genes were rescued by RT-PCR on a single plasma cell.

TABLE 4

Plate ID	Single Cell numbers
11G10	ABT2-SCX-251-260
21D1	ABT2-SCX-54
25C3	ABT2-SCX-134-144
29G8	ABT2-SCX-1-11
33G8	ABT2-SCX-12-18
37A11	ABT2-SCX-19-44
43H12	ABT2-SCX-185-201, 233-239
16F7	ABT2-SCX-267-278
24C3	ABT2-SCX-55-77
24F8	ABT2-SCX-82-102
34D4	ABT2-SCX-145-168

[0181] Expression. After isolation of the single plasma cells, mRNA was extracted and reverse transcriptase PCR was conducted to generate cDNA. The cDNA encoding the variable heavy and light chains was specifically amplified using polymerase chain reaction. The variable heavy chain region was cloned into an IgG2 expression vector. This vector was generated by cloning the constant domain of human IgG2 into the multiple cloning site of pcDNA3.1+/ Hygro (Invitrogen, Burlington, ON). The variable light chain region was cloned into an IgK expression vector. This vector was generated by cloning the constant domain of human IgK into the multiple cloning site of pcDNA3.1+/ Neo (Invitrogen, Burlington, ON). The appropriate pairs of heavy chain and the light chain expression vectors were then co-lipofected into a 60 mm dish of 70% confluent human embryonal kidney 293 cells and the transfected cells were left to secrete a recombinant antibody for 24 hours. The supernatant (3 mL) was harvested from the HEK 293 cells and the secretion of an intact antibody (AB-ABT2-XG2-012 and AB-ABT2-XG2-198) was demonstrated with a sandwich ELISA to specifically detect human IgG (Table 5, fourth column). The specificity of AB-ABT2-XG2-012 and AB-ABT2-XG2-198 was assessed through binding of the recombinant antibody to biotinylated EpoR using ELISA (Table 5, fifth column).

TABLE 5

Well ID	Single cell number	Secretion	Binding
11G10 21D1 25C3 29G8 33G8 37A11 43H12 16F7 24C3 24F8 34D4	ABT2-SCX-254 ABT2-SCX-054 ABT2-SCX-054 ABT2-SCX-003 ABT2-SCX-012 ABT2-SCX-022 ABT2-SCX-198 ABT2-SCX-267 ABT2-SCX-267 ABT2-SCX-102 ABT2-SCX-102 ABT2-SCX-145	1:4 >1:64 1:4 >1:64 >1:64 >1:64 >1:64 >1:64 >1:64 >1:64	1:8 >1:64 1:4 >1:64 >1:64 >1:64 >1:64 >1:64 >1:64 >1:64

[0182] The ELISA for antigen specific antibody secretion was performed as follows. Control plates were coated with 2 mg/mL Goat anti-human IgG H+L O/N. For the binding plates, biotin-EpoR (0.7 mcg/mL) was coated onto strepta-vadin 96 well plates (Sigma, St Louis, Mo.) for one hour at room temperature. The plates were washed five times with dH₂O. Recombinant antibodies were titrated 1:2 for 7 wells from the undiluted minilipofection supernatant. The plates were washed five times with dH₂O. A goat anti-human IgG

Fc-specific HRP-conjugated antibody was added at a final concentration of 1 ug/mL for 1 hour at RT for the secretion and the binding ELISA. The plates were washed five times with dH_2O . The plates were developed with the addition of TMB chromogenic substrate (KPL, Gaithersburg, Md.) for 30 minutes and the ELISA was stopped by the addition of 1 M phosphoric acid. Each ELISA plate was analyzed to determine the optical density of each well at 450 nm.

[0183] Purification of AB-ABT2-XG2-012 and AB-ABT2-XG2-198. For larger scale production, the heavy and light chain expression vectors (2.5 ug of each chain/ dish) were lipofected into ten 100 mm dishes that were 70% confluent with HEK 293 cells. The transfected cells were incubated at 37° C. for 4 days, the supernatant (6 mL) was harvested and replaced with 6 mL of fresh media. At day 7, the supernatant was removed and pooled with the initial harvest (120 mL total from 10 plates). The ABT2-XG2-012 and ABT2-XG2-198 antibody were purified from the supernatant using a Protein-A Sepharose (Amersham Biosciences, Piscataway, N.J.) affinity chromatography (1 mL). The antibody was eluted from the Protein-A column with 500 mcL of 0.1 M Glycine pH 2.5. The eluate was dialysed in PBS pH 7.4 and filter sterilized. The antibody was analyzed by non-reducing SDS-PAGE to assess purity and yield.

[0184] Agonist activity of recombinant antibodies. The ability of these recombinant antibodies to stimulate the proliferation of Epo responsive cells was examined using the UT-7/Epo cells with proliferation quantitated by MTS reagent (Promega, Madison, Wis.) measured at 490 nm as described in the Agonist Activity Assay above. ABT2-SCX-012 and ABT2-SCX-198 induced proliferation in comparison to cells in media without antibody and are shown below (FIGS. **14** and **15** respectively).

[0185] Effect of anti-Human Fc. It is possible that the agonist activity of ABT2-SCX-012 and ABT2-SCX-198 are due to self-aggregation. In order to address this issue we induced aggregation by the addition of an anti-human Fc secondary antibody and the effect on the agonist activity of ABT2-SCX-012 and ABT2-SCX-198 was determined using the UT-7/Epo cells. As shown below the addition of a secondary antibody had no effect on the activity of ABT2-SCX-198 (FIG. **16**) and inhibited the activity of ABT2-SCX-012 (FIG. **417**).

[0186] Since the addition of secondary Ab inhibited the activity of ABT2-SCX-012 we concluded that aggregation of this antibody interferes with it's activity and thus it is unlikely that ABT2-SCX-012 has agonist activity due to aggregation. However, the results of ABT2-SCX-198 are more difficult to interpret. The lack of an effect could suggest that ABT2-SCX-198 is fully aggregated and thus the addition of secondary Ab has no further effects on its activity. Alternatively, the lack of effect suggests the activity of ABT2-SCX-198 is not perturbed by the conformational restrictions applied by a secondary antibody.

[0187] Sequence analysis of ABT2-SCX-012 and ABT2-SCX-198 The variable heavy chains and the variable light chains for antibodies ABT2-SCX-012 and ABT2-SCX-198 were sequenced to determine their DNA sequences. The complete sequence information for the anti-EpoR antibodies shown in FIGS. 1, 2, and 18-30 with nucleotide and amino acid sequences for each variable region of the heavy chain gamma and kappa light chains. FIGS. 1 and 2 provide full-length sequences, including the constant regions.

[0188] The variable heavy sequences were analyzed to determine the VH family, the D-region sequence and the J-region sequence. The sequences were then translated to determine the primary amino acid sequence (FIG. 29) and compared to the germline VH, D and J-region sequences to assess somatic hypermutations. The primary amino acid sequences of all the anti-EpoR antibody gamma chains are shown in FIG. 16. The germline sequences are shown above and the mutations are indicated with the new amino acid sequence. Unaltered amino acids are indicated with a dash (-). The light chain was analyzed similarly to determine the V and the J-regions and to identify any somatic mutations from germline kappa sequences (FIG. 30). The heavy chain of ABT2-SCX-012 was shown to utilize the VH 4-59 (DP-71), DIR4rc and the JH4a gene segments, while the light chain was shown to use the VkI (A30) and the Jk1 gene segments. The heavy chain of ABT2-SCX-198 was shown to utilize the VH 3-30 (V3-30), D4-23 and the JH6b gene segments, while the light chain was shown to use the VkI (L5) and the Jk3 gene segments.

EXAMPLE 2

Competition of Ab12 with ¹²⁵I-Labeled EPO for Binding CHO Cells Expressing Recombinant EPO Receptor

[0189] CHO cells expressing the full length recombinant human EPO receptor were plated at 5×10^5 cells/well in 24 well plates 72 hours prior to the assay. On the day of the assay, 95 ul of Ab12, Ab198, or EPO at indicated concentrations (shown in FIG. 5) diluted in RPMI 1640, 0.5% BSA, 1 mM Na N₃ and 5 ul (6 ng) of ¹²⁵I-EPO (Amersham Cat. #IM 178, Arlington Heights, Ill. 486 ci/mM) were added to the wells. After incubating at 37° C. for 1.5 hours, the wells were washed three times with cold HBSS and harvested using 0.5 ml 0.1N NaOH. Samples were counted in a Micromedic ME Plus gamma counter. The results are shown in FIG. 5. Specifically, the results show that Abs 12 and 198 competed with EPO for binding to the erythropoietin receptor.

EXAMPLE 3

Biacore Studies

[0190] The studies described below were performed on a Biacore 2000 utilizing the Biacontrol software version 3.1. (Biacore, Uppsala, Sweden). Binding analyses were performed with antibody immobilized directly to the chip surface and followed by injection of varying receptor concentrations.

Immobilization of Antibody

[0191] Immobilizations of antibody were performed using the default immobilization program in the Biacore software package. Antibodies were diluted to 10 ug/mL in the supplied acetate buffers to prescreen for the appropriate pH at which to conduct the immobilizations. For immobilizations, antibodies were diluted into the appropriate acetate buffer (10 mM acetate pH 4.0) and coupled directly to the chip surface using standard EDC chemistry at three different protein levels (500, 1000, and 1500 RU). The fourth flow cell was mock coupled with EDC to cap the carboxyl groups and provide a background surface as a negative control.

Binding Studies

[0192] Binding studies were performed by successive injections of varying concentrations of soluble human EPO receptor over the chip surface (500 RU immobilized protein). Binding analyses were performed in the supplied HBS-EP buffer [HBS buffer-10 mM HEPES pH=7.4, 150 mM NaCl, 3 mM EDTA, 0.005% Polysorbate 20 (v/v), Biacore] using receptor diluted to the desired concentrations (10-200 nM) using the running buffer (HBS-EP). Experiments were performed at a flow rate of 30 uL/min. The receptor was injected over a period of 3 minutes followed by a 15 minute dissociation period. Simultaneous injections over the flow cell created as a negative control were also performed. All injections were performed in triplicate.

Model Fitting

[0193] Data were fit to the models available in the BiaE-valuation 3.0.2 software package (Biacore). The data points from the experimental injections were corrected by subtraction of data points from simultaneous over the negative control surface. The corrected data were used to fit to the 1:1 (Langmuir) binding model as well as the bivalent analyte model available in the BiaEvaluation software package. Dissociation constants were calculated directly from fitting to the Langmuir binding model. For the bivalent analyte model, the dissociation constants were calculated indirectly using the calculated values for the kinetic dissociation and kinetic association constants, k_d and k_a .

TABLE 6

Antibody	kD	
Ab 12 Ab 198	17.5 nM 13.9 nM	

EXAMPLE 4

EPO Dependent Human Cell Proliferation Assay

[0194] Stock cultures of the human erythroleukemic cell line, F36E cells were maintained in RPMI 1640 media with 10% fetal bovine serum and 1 unit per mL of recombinant human erythropoietin. Prior to assays, cells were cultured overnight at a density of 4.0 to 5.0×10^5 cells per mL in growth medium without EPO. Cells were recovered, washed and resuspended at a density of 1.0×10^6 cells per mL in assay medium (RPMI 1640+10% FBS) and 50 uL of cells added to wells of a 96 well microtiter plate. 50 uL of each of Ab12, Ab 390, Ab 412, Ab 467, Ab 484, Ab 430/432 and Ab198 or EPO standards (recombinant human EPO (rHuEPO)) in assay medium were added to wells and the plates were incubated in a humidified incubator at 37° C. with a 5% CO₂ atmosphere. After 72 hours, 20 µL of Promega Cell Titer 96 Aqueous® reagent (as prepared per manufacturer's instructions, Madison, Wis.) was added to all wells. Plates were incubated at 37° C. with a 5% $\rm CO_2$ atmosphere for 4 hours and the optical density at 490 nm was determined using a microplate reader (Wallac Victor 1420 Multilabel Counter, Wallac Company, Boston, Mass.). The results are shown in FIG. 6. All Abs stimulated proliferation of the F36E cell line. Maximal proliferative activity was similar to that observed with the EPO control and shown by a bell shaped curve as concentration increased. The results in FIG. 7 demonstrate that Ab 12, after storage at 4° C. for up to 20 days, is active in inducing the proliferation of F36E cells. Proliferative activity was similar to that observed with the EPO control with the maximal response differing about ten-fold on a molar equivalent basis

EXAMPLE 5

Human CD36+ CFUe Assay

[0195] Frozen human CD36+ erythroid progenitor cells obtained from Poietics (Biowhittaker (Walkersville, Md.)) were thawed and 10⁴ cells/ml in IMDM-2% FBS. Cells (0.3 ml) were added to 0.3 ml tubes containing 2.4 ml Methocult (StemCell Technologies, Vancouver, Canada) Cat. #04230), 0.3 ml stem cell growth factor (Sigma, St. Louis, Mo. Cat. #S7901, 100 ug/ml), and 0.3 ml EPO(R&D Systems), Ab 12, or IMDM-2% FBS. After mixing, 1.1 ml of the Methocult suspension was added to a 35 mm non tissue culture treated sterile petri dish and incubated at 37° C., 5% CO₂ for 2 weeks. Colonies were identified microscopically. The results are shown in FIG. **8**. Specifically, Ab12 induced the formation of CFU-E colonies from human

[0196] CD 36+ progenitor cells. The colonies, identified microscopically, were red in color. The size and number of the colonies is reduced compared to those observed with the EPO control probably due to a reduced proliferative signal.

EXAMPLE 6

Demonstration of Erythropoietic Activity in Liquid Cultures

[0197] CD34+ cells were enriched from human peripheral blood using a Direct CD34+Progenitor Cell Isolation Kit (Miltenyi, Auburn, Calif.). Recovered cells were washed twice with alpha-medium and re-suspended in suspension culture media (alpha-media supplemented with 30% FCS, 1% deionized BSA, 10^{-5} M β -mercaptoethanol, 10^{-6} M dexamethasone, 0.3 mg/mL human hollo-transferrin and 10 ng/mL human recombinant stem cell factor). Cells were plated out at a density of 1×10^4 cells/mL in duplicates in 6-well microplates with test antibody at concentrations ranging from 0.1-100 ng/mL. Plates were incubated at 37° C. and 5% CO₂ for two weeks. Duplicate samples from each well were recovered for cell counts and staining with benzidine (Reference Fibach, E., 1998 *Hemoglobin*, 22:5-6, 445-458).

[0198] The results are shown in FIG. **9**. Specifically, Ab198 induced the proliferation of human erythroid producing cells derived from progenitor cells in a dose dependent manner. The number of proliferating cells and the percentage expressing hemoglobin, as indicated by staining with benzidine, was reduced compared to the EPO treated controls again probably due to a reduced proliferative signal.

EXAMPLE 7

Cynomolgus Bone Marrow CFUe Assay

[0199] Bone marrow was harvested from cynomolgus monkeys and diluted 1:2 with PBS. Three ml of the diluted bone marrow was layered over six ml of Lymphoprep (Gibco (Invitrogen), Carlsbad, Calif. Cat. #1001967), centrifuged at 2700 rpm for 20 minutes and the buffy coat recovered and diluted in 10 ml IMDM-2% FBS. Cells were

centrifuged and resuspended at 10^6 cells/ml in IMDM-2% FBS. Cells (0.3 ml) were added to tubes containing 2.4 ml Methocult (StemCell Technologies, Vancouver, Canada) Cat. #04230), 0.3 ml stem cell growth factor (Sigma, Cat. #S7901, 100 ug/ml), 0.3 ml EPO (R& D Systems, Minneapolis, Minn.), test antibody (Ab198), or IMDM-2% FBS. After mixing, 1.1 ml of the Methocult suspension was added to a 35 mm non tissue culture treated sterile petri dish and incubated at 37° C., 5% CO₂ for 2 weeks. Colonies were identified microscopically. The results of this assay are shown in FIG. **10** demonstrate that Ab198 induced the formation of CFU-E colonies (although the number of colonies was reduced compared to that observed with the EPO control).

EXAMPLE 8

ELISA to Measure Binding of SE-3 Peptide

[0200] 96 well polystyrene plates (Dynatec (Elk Grove Village, Ill.) Immunolon 4) were coated with 80 ul of 5 ug/ml soluble EPO receptor (sEPOR) (R&D Systems (Minneapolis, Minn.) Cat. #307-ER/LF), or peptide SE-3 (PGNYSFSYQLEDEPWKLCRLHWAPTARGAV) (described in U.S. Pat. No. 6,319,499) diluted in 0.015M Na₂CO₃, 0.035M NaHCO₃, pH 9.4 for 2 hours at room temperature and overnight at 4° C. Plates were blocked for 30 minutes at room temperature with 100 ul of 5% BSA in PBS (Gibco (Invitrogen (Carlsbad, Calif.)) Cat.#10010). After removal of blocking solution, 50 ul of Ab12 at 5 ug/ml in PBS with 1% BSA was added to wells and plates were incubated at room temperature for 2 hours. Plates were washed three times using a Skatron 400 Plate Washer with PBS/0.05% Tween 20 and 50 ul of secondary antibody diluted in PBS/0.25% BSA/0.05% Tween 20 added to the wells. For Ab12, goat anti-human IgG (Fc)-HRP (Caltag (Burlingame, Calif.) Cat.#H10507) diluted 1:1000 was used and for Ab 71A (available from the American Type Culture Collection HB11689, also described in U.S. Pat. No. 6,319, 499), goat anti mouse IgG (Fc)-HRP (Jackson Laboratories (West Grove, Pa.) Cat.#115-035-164) diluted 1:5000 was used. After a 1 hour incubation at room temperature, plates were washed three times as before and 50 ul of OPD Developing Reagent (Sigma #P9187) added to each well. Color development was stopped by addition of 50 ul of 1N HCl to the wells and optical density measured at 490 nm on a Victor 1420 Multi-Label Counter.

[0201] FIG. **11** shows that Ab12 does not interact (i.e. bind) with SE-3 peptide. Ab 71A does interact (i.e. binds) with the SE-3 peptide Both Abs 12, and 71A interacted with immobilized erythropoietin receptor.

EXAMPLE 9

EPO Dependent Proliferation Assay

[0202] Primary hybridoma supernatants were diluted in assay medium and tested for their ability to stimulate the proliferation of the F36E human erythroleukemic cells as described in EXAMPLE 5. Results with five primary supernatants are shown in FIG. **12**. These samples stimulated the proliferation of F36E cells.

EXAMPLE 10

ELISA to Measure Binding of Hybridoma Supernatants to SE-3 Peptide

[0203] Forty-two primary hybridoma supernatants were tested for their ability to bind to either immobilized EPO receptor or peptide SE-3 as described in EXAMPLE 10. FIG. **13** shows that whereas all the hybridoma supernatants tested interact with immobilized EPO receptor, only sample 16 interacted with SE-3 peptide at levels above background.

EXAMPLE 11

Comparison of Erythropoietic Activity of Gamma-1 Ab12 Versus Gamma-2 Ab12

[0204] Proliferation assays (as described in Example 4) were performed to compare the erythropoietic activity of gamma-1 Ab 12 and gamma-2 Ab 12 on F36e human erythroleukemic cells. The results are shown in FIG. **31**. As FIG. **31** shows, gamma-2 Ab 12 was more effective at stimulating proliferation of the F36E cell line than gamma-1 Ab 12.

EXAMPLE 12

Effect of Ab 12 on Erythropoiesis In Vivo

[0205] (a) Construction of mEpoR –/–, hEopR+ transgenic mice: Transgenic mice that produced only human EpoR (hEpoR+, single allele) and no endogenous mouse EpoR (mEpoR –/–, double allele mutation) were generated as described in Liu, C. et al., *Journal of Biological Chemistry*. 272:32395 (1997) and Yu, X., et al., *Blood*, 98(2):475 (2001). Breeding colonies were established to generate mice for in vivo studies of erythropoiesis.

[0206] (b) Multiple dosing regimen: In initial experiments, animals were subjected to a multiple dosing regimen of Ab 12 to determine whether the antibody would cause an increase in reticulocyte counts and/or % hematocrit. Five transgenic mice (mEpoR –/–, hEpoR+, were injected subcutaneously with either 5 μ g or 50 μ g of Ab 12 in 0.2 mL vehicle (phosphate buffered saline [PBS] containing 0.1% bovine serum albumin ([BSA]). Control animals also were injected in the same manner with equal volumes of the vehicle alone or vehicle containing 5U Epogen® (Amgen®, Thousand Oaks, Calif.). All animals were dosed over a three-week period in accordance with the following schedule:

Week 1	Week 2	Week 3
Monday, Tuesday, Wednesday,	Monday, Wednesday,	Monday,
Friday	Friday	Wednesday

Sample bleeds were taken on day 4 (Thursday of week 1) for determining reticulocyte counts and on day 19 (Friday of week 3) for determining hematocrits. Reticulocyte counts and hematocrit determinations were made using methods well known in the art. As FIG. **32** shows, Ab 12 caused a statistically significant increase (over controls) in reticulocyte count and % hematocrit in animals receiving either 5 or 50 μ g of Ab 12 antibody.

[0207] (c) Weekly dosing regimen: To assess whether the results seen under a multiple dosing regimen still would be observed in animals receiving fewer doses of Ab 12, transgenic mice were injected (as described in (b) above) with varying concentrations (0.5, 2.5, 5.0, 50 and 250 µg) of Ab 12 or a control, Aranesp[™] (Amgen[®], Thousand Oaks, Calif.), a more active variant of Epogen® on days 1, 8 and 15 and bled on days 4 and 19 for determination of reticulocyte count and hematocrit, respectively. Control animals received a single dose of vehicle only or a human IgG2 isotype control. FIG. 33 shows that Ab 12 caused a statistically significant increase (over vehicle and isotype controls) in percent hematocrit with all but the lowest concentrations tested.

[0208] (d) Single versus weekly dosing regimens: To determine whether a single dose of Ab-12 would have an effect on erythropoiesis after 3 weeks, transgenic mice were dosed with Ab 12 (50 µg), at one week intervals for 3 weeks or with a single dose of Ab 12 (150 µg) and bled on day 19 for determination of percent hematocrit. Control animals received vehicle alone, a single dose of AranespTM (900 ng) or 3 total doses of AranespTM injected at weekly intervals (300 ng×3). FIG. 34 shows that both dosing regimens of Ab 12 caused a statistically significant increase in percent hematocrit over the vehicle control. In contrast, the single dose regimen of AranespTM did not have this effect.

[0209] All abstracts, references, patents and published patent applications referred to herein are hereby incorporated by reference.

[0210] The present invention is illustrated by way of the foregoing description and examples. The foregoing description is intended as a non-limiting illustration, since many variations will become apparent to those skilled in the art in view thereof.

[0211] Changes can be made to the composition, operation and arrangement of the method of the present invention described herein without departing from the concept and scope of the invention.

60

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26

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Tyr Ala Ala Ser Ser Leu Gln Arg Gly Val Pro Ser Arg Phe Ser Gly 50 55 60	
Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro 65 70 75 80	
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28

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	20					25					30			
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ro Arg Leu	. Leu	Ile	Tyr	Lys	Thr	Ser	Asn	Arg	Phe	Ser	Gly	Val	Pro	
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Asp Arg Phe	Ser	Gly	Ser 70	Gly	Ala	Gly	Thr	Asp 75	Phe	Thr	Leu	Lys	Ile 80	
	a 1			7		a 1	**- 7		m	G	N	G]		
Ser Arg Val	GIu	A1a 85	GIu	Asp	Val	GIY	Val 90	Tyr	Tyr	Сүз	Met	GIn 95	Ala	
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Ser Leu Arg	j Leu	Ser	Cys	Ala	Ala	Ser	Gly	Phe	Thr	Phe	Ser	Ser	Tyr	
5	20		-			25	-				30		-	
Gly Met His	Trp					Pro	-	-	-		Glu	Trp	Val	
35													_	
Ala Val Ile 50	Ser	Tyr	Asp	G1y 55	Ser	Asn	ГЛЗ	Tyr	Tyr 60	Ala	Asp	Ser	Val	
Lys Gly Arg	Phe	Thr	Ile	Ser	Arq	Asp	Asn	Ser	Lys	Asn	Thr	Leu	Tyr	
65			70		5	-		75	1				80	
Leu Gln Met	Asn		Leu	Arg	Val	Glu	-	Thr	Ala	Val	Tyr	-	Cys	
_		85					90					95		
Ala Lys Asp) His 100	Gly	Gly	Arg	Tyr	Val 105		Asp	Tyr	Gly	Met 110	Asp	Val	
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Ser																			
H: 322 DNA	no sa <u>r</u>	piens	3																
ICE: 40																			
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Trp Ile Gly Tyr I 50	le Tyr Lys Ser G 55	lu Thr Ser Ty 60	yr Tyr Asn Pro Ser	
Leu Lys Ser Arg L 65	Leu Thr Leu Ser Va 70	al Asp Thr Se 75	er Lys Asn Gln Phe 80	
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Gln Gly Ile Arg Asn Asp Leu Gly Trp Tyr Gln Gln Lys Pro Gly Lys 50 55 60	
Ala Pro Lys Arg Leu Ile Tyr Ala Ala Ser Ser Leu Gln Ser Gly Val 65 70 75 80	
Pro Ser Arg Phe Ser Gly Ser Gly Ser Gly Thr Glu Phe Thr Leu Thr 85 90 95	

Ile Ser Ser Leu Gln Pro Glu Asp Phe Ala Thr Tyr Tyr Cys Leu Gln 105 100 110 His Asn Thr Tyr Pro Pro Thr Phe Gly Gln Gly Thr Lys Val Glu Ile 115 120 125 Lys Arg Thr Val Ala Ala Pro Ser Val Phe Ile Phe Pro Pro Ser Asp 130 135 140 Glu Gln Leu Lys Ser Gly Thr Ala Ser Val Val Cys Leu Leu Asn Asn 145 150 155 160 Phe Tyr Pro Arg Glu Ala Lys Val Gln Trp Lys Val Asp Asn Ala Leu 165 170 175 Gln Ser Gly Asn Ser Gln Glu Ser 180 <210> SEQ ID NO 79 <211> LENGTH: 31 <212> TYPE: PRT <213> ORGANISM: Homo sapiens <400> SEQUENCE: 79 Val Val Cys Leu Leu Asn Asn Phe Tyr Pro Arg Glu Ala Lys Val Gln 5 1 Trp Lys Val Asp Asn Ala Leu Gln Ser Gly Asn Ser Gln Glu Ser 20 25 30 <210> SEQ ID NO 80 <211> LENGTH: 2011 <212> TYPE: DNA <213> ORGANISM: Homo sapiens <400> SEQUENCE: 80 atqqaattqq qqctccqctq qqttttcctc qttqctcttt taaqaqqtqt ccaqtqtcaq 60 gtgcagctgg tggagtctgg gggaggcgtg gtccagcctg ggaggtccct gagactctcc 120 180 tqtqtaqcct ctqqattcac cttcaqtaqc tatqqcatqc actqqqtccq ccaqqctcca ggcaaggggc tggagtgggt ggcagttata tcatatgatg gaagtaataa atactatgca 240 gactccgtga agggccgatt caccatctcc agagacaatt ccaagaacac gctgtatctg 300 caaatgaaca gcctgagagt tgaggacacg gctgtgtatt actgtgcgag agatcacggt 360 gggaggtacg tctacgacta cggtatggac gtctggggcc aagggaccac ggtcaccgtc 420 teetcageet ccaccaaggg cccatcggte tteecectgg cgeeetgete tagaageaee 480 teegagagea cageegeeet gggetgeetg gteaaggaet actteeeega aceggtgaeg 540 gtgtcgtgga actcaggcgc tctgaccagc ggcgtgcaca ccttcccagc tgtcctacag 600 teetcaggae tetacteect cagcagegtg gtgacegtge ectecageaa etteggeace 660 cagacctaca cctgcaacgt agatcacaag cccagcaaca ccaaggtgga caagacagtt 720 ggtgagaggc cagctcaggg agggagggtg tctgctggaa gccaggctca gccctcctgc 780 ctggacgcac cccggctgtg cagccccagc ccagggcagc aaggcaggcc ccatctgtct 840 cctcacccgg aggcctctgc ccgccccact catgctcagg gagagggtct tctggctttt 900 tccaccagge tccaggeagg cacaggetgg gtgcccctae cccaggeeet tcacacacag 960 qqqcaqqtqc ttqqctcaqa cctqccaaaa qccatatecq qqaqqacect qcccctqace 1020 taaqccqacc ccaaaqqcca aactqtccac tccctcaqct cqqacacctt ctctcctccc 1080

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Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val Leu Gln 195 205 200 Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro Ser Ser 210 215 220 Asn Phe Gly Thr Gln Thr Tyr Thr Cys Asn Val Ala Ser Pro His Lys 225 230 235 240 Pro Ser Asn Thr Lys Val Ala Ser Pro Lys Thr Val 245 250 <210> SEQ ID NO 83 <211> LENGTH: 752 <212> TYPE: DNA <213> ORGANISM: Homo sapiens <400> SEQUENCE: 83 atgagggtcc ccgctcagct cctggggctc ctgctgctct ggttcccagg ttccagatgc 60 120 gacatecaga tgacecaate tecatettee gtgtetgeat etataggaga cagagtetee atcacttgtc gggcgagtca gggtattagc agctggttag cctggtatca gcagaaacca 180 gggaaageee etacgeteet tatetatget geateeactt tgeaaegtgg ggteeeatea 240 aggttcagcg gcagtggatc tgggacagat ttcactctca ccatcagcag cctgcagcct 300 gaagattttg caacttactt ttgtcaacag gctaacagtt tcccattcac tttcggccct 360 gggaccaaag tggatatcaa acgaactgtg gctgcaccat ctgtcttcat cttcccgcca 420 tetgatgage agttgaaate tggaactget agegttgtgt geetgetgaa taaettetat 480 cccagagagg ccaaagtaca gtggaaggtg gataacgccc tccaatcggg taactcccag 540 qaqaqtqtca caqaqcaqqa caqcaaqqac aqcacctaca qcctcaqcaq caccctqacq 600 ctgagcaaag cagactacga gaaacacaaa gtctacgcct gcgaagtcac ccatcagggc 660 ctgagctcgc ccgtcacaaa gagcttcaac aggggaagtg ggtagtcccg gactcgagcg 720 ggcagtgttt ctcgaagttg tcccctgagt gt 752 <210> SEQ ID NO 84 <211> LENGTH: 752 <212> TYPE: DNA <213> ORGANISM: Homo sapiens <400> SEOUENCE: 84 acactcaggg gacaacttcg agaaacactg cccgctcgag tccgggacta cccacttccc 60 ctgttgaagc tctttgtgac gggcgagctc aggccctgat gggtgacttc gcaggcgtag 120 actttgtgtt tctcgtagtc tgctttgctc agcgtcaggg tgctgctgag gctgtaggtg 180 ctgtccttgc tgtcctgctc tgtgacactc tcctgggagt tacccgattg gagggcgtta 240 tccaccttcc actgtacttt ggcctctctg ggatagaagt tattcagcag gcacacaacg 300 ctagcagttc cagatttcaa ctgctcatca gatggcggga agatgaagac agatggtgca 360 gccacagttc gtttgatatc cactttggtc ccagggccga aagtgaatgg gaaactgtta 420 gcctgttgac aaaagtaagt tgcaaaatct tcaggctgca ggctgctgat ggtgagagtg 480 aaatctgtcc cagatccact gccgctgaac cttgatggga ccccacgttg caaagtggat 540 gcagcataga taaggagcgt aggggctttc cctggtttct gctgatacca ggctaaccag 600 660 ctqctaatac cctqactcqc ccqacaaqtq atqqaqactc tqtctcctat aqatqcaqac

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Pro Arg Glu Ala Lys Val Gln Trp Lys Val Asp Asn Ala Leu Gln Ser 165 170 175
Gly Asn Ser Gln Glu Ser Val Thr Glu Gln Asp Ser Lys Asp Ser Thr 180 185 190
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cottgaggga cggattataa taggaggtot tactgttata gatgtaccca atccactoca 1800 ggccottooc tgggtgotgg cggatccago tocagtagta aacaccactg otgatggago 1860 saccagagac agtgcaggtg agggacaggg totgtaaagg ottoaccagt cotgggocog 1920 saccagaggt otgcacotgg gacaggacco atotgggago tgccaccago aggaggaaga 1980 saccacagatg ottoat 1996 scottagatg ottoatagatg	agteegegat eeccaattta tetetegeae agtaataeae ggeegtgtee geggeagtea	1680
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Actectgcag etgeaeetgg gacaggaeee atetgggage tgeeaeeage aggaggaaga 1980 Aceeaeagatg etteat 1996 Aceeaeagatg etteat 1996 Aceeaeaagatg etteatagatg etteatagatg etteatagatg etteatagatg ettea	ggcccttccc tgggtgctgg cggatccagc tccagtagta aacaccactg ctgatggagc	1860
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Met Lys His Leu Trp Phe Phe Leu Leu Leu Val Ala Ala Pro Arg Trp 1 /al Leu Ser Gln Val Gln Leu Gln Glu Ser Gly Pro Gly Leu Val Lys 20 25 30 20 25 30 20 20 20 20 20 20 20 20 20 20 20 20 20	<210> SEQ ID NO 112 <211> LENGTH: 235 <212> TYPE: PRT <213> ORGANISM: homo sapiens	
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	Val Leu Ser Gln Val Gln Leu Gln Glu Ser Gly Pro Gly Leu Val Lys 20 25 30	
	Pro Leu Gln Thr Leu Ser Leu Thr Cys Thr Val Ser Gly Gly Ser Ile 35 40 45	

Ser Ser Gly Val Tyr Tyr Trp Ser Trp Ile Arg Gln His Pro Gly Lys 50 55 60	
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Asn Gln Phe Ser Leu Asn Leu Ile Ser Val Thr Ala Ala Asp Thr Ala 100 105 110	
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Gln Gly Thr Leu Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser 130 135 140	
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Ala Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val 165 170 175	
Ser Trp Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala 180 185 190	
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Ile Arg Asn Asp Leu Gly Trp Tyr Gln Gln Lys Pro Gly Lys 50 55 60	Ala Pro
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Arg Phe Ser Gly Ser Gly Ser Gly Thr Glu Phe Thr Leu Thr 85 90	Ile Ser 95
Ser Leu Gln Pro Glu Asp Phe Ala Thr Tyr Tyr Cys Leu Gln 100 105 110	His Asn
Ser Tyr Pro Pro Thr Phe Gly Gly Gly Thr Lys Val Glu Ile 115 120 125	Lys Arg
Thr Val Ala Ala Pro Ser Val Phe Ile Phe Pro Pro Ser Asp130135140	Glu Gln
Leu Lys Ser Gly Thr Ala Ser Val Val Cys Leu Leu Asn Asn 145 150 155	Phe Tyr 160
Pro Arg Glu Ala Lys Val Gln Trp Lys Val Asp Asn Ala Leu 165 170	Gln Ser 175
Gly Asn Ser Gln Glu Ser Val Thr Glu Gln Asp Ser Lys Asp 180 185 190	Ser Thr
Tyr Ser Leu Ser Ser Thr Leu Thr Leu Ser Lys Ala Asp Tyr 195 200 205	Glu Lys

His	Lys 210	Val	Tyr	Ala	Сүз	Glu 215	Val	Thr	His	Gln	Gly 220	Leu	Ser	Ser	Pro
Val 225	Thr	Lys	Ser	Phe	Asn 230	Arg	Gly	Glu	Сүз						

^{1. (}canceled)

- 3. (canceled)
- 4. (canceled)

5. An antibody or antibody fragment thereof that activates an endogenous activity of a human erythropoietin receptor in a mammal, comprising:

- at least one heavy chain variable region having the amino acid sequence of SEQ ID NO: 3 or antibody fragment thereof; and
- at least one light chain variable region having the amino acid sequence of SEQ ID NO: 5 or antibody fragment thereof,
- wherein said antibody or antibody fragment thereof does not interact with a peptide having an amino acid sequence of SEQ ID NO:1.

6. An antibody or antibody fragment thereof that activates an endogenous activity of a human erythropoietin receptor in a mammal, comprising

at least one heavy chain variable region having the amino acid sequence of SEQ ID NO: 7 or antibody fragment thereof; wherein said antibody or antibody fragment thereof does not interact with a peptide having an amino acid sequence of SEQ ID NO:1.

7. An antibody or antibody fragment thereof that activates an endogenous activity of a human erythropoietin receptor in a mammal, comprising

at least one light chain variable region having the amino acid sequence of SEQ ID NO: 9 or antibody fragment thereof; wherein said antibody or antibody fragment thereof does not interact with a peptide having an amino acid sequence of SEQ ID NO:1.

8. An antibody or antibody fragment thereof that activates an endogenous activity of a human erythropoietin receptor in a mammal, said antibody comprising:

- at least one heavy chain variable region having the amino acid sequence of SEQ ID NO: 7 or antibody fragment thereof; and
- at least one light chain variable region having the amino acid sequence of SEQ ID NO: 9 or antibody fragment thereof,
- wherein said antibody or antibody fragment thereof does not interact with a peptide having an amino acid sequence of SEQ ID NO:1.
- 9. (canceled)
- 10. (canceled)

11. An antibody or antibody fragment thereof that activates an endogenous activity of a human erythropoietin receptor in a mammal, said antibody comprising:

the amino acid sequences of at least one heavy chain variable region and at least one light chain variable region selected from the group consisting of SEQ ID NO:11/SEQ ID NO:13, SEQ ID NO:15/SEQ ID NO:17, SEQ ID NO:19/SEQ ID NO:21, SEQ ID NO:11/SEQ ID NO:23, SEQ ID NO:11/SEQ ID NO:25, SEQ ID NO:11/SEQ ID NO:27, SEQ ID NO:31/SEQ ID NO:33, SEQ ID NO:35/SEQ ID NO:37, SEQ ID NO:39/SEQ ID NO:41, SEQ ID NO:43/SEQ ID NO:45, SEQ ID NO:47/SEQ ID NO:49, SEQ ID NO:51/SEQ ID NO:53 and SEQ ID NO:55/SEQ ID NO:57 or antibody fragment thereof, wherein said antibody or antibody fragment thereof does not interact with a peptide having an amino acid sequence of SEQ ID NO:1.

- (canceled)
 (canceled)
 (canceled)
 (canceled)
- 15. (canceled)
- 16. (canceled)
- 17. (canceled)
- 18. (canceled)
- 19. (canceled)
- 20. (canceled)
- 21. (canceled)
- 22. (canceled)
- 23. (canceled)
- 24. (canceled)
- 25. (canceled)
- **26**. (canceled) **27**. (canceled)
- **27**. (canceled) **28**. (canceled)
- **29**. (canceled)
- **30**. (canceled)
- **31**. (canceled)
- **32**. (canceled)
- **33**. (canceled)
- **34**. (canceled)
- **34**. (canceled) **35**. (canceled)
- 35. (canceled
- 36. (canceled)
- 37. (canceled)
- 38. (canceled)
- 39. (canceled)

40. An isolated antibody capable of binding a human erythropoietin receptor in a mammal, said antibody comprising a heavy chain variable region comprising a continuous sequence from CDR1 through CDR3 having the amino acid sequence selected from the group consisting of: SEQ ID NO:58, SEQ ID NO:59, SEQ ID NO:60, and SEQ ID NO:61 and fragments thereof.

41. An isolated antibody capable of binding a human erythropoietin receptor in a mammal, said antibody comprising a light chain variable region comprising a continuous sequence from CDR1 through CDR3 having the amino acid sequence selected from the group consisting of: SEQ ID NO:62, SEQ ID NO:63, SEQ ID NO:64, SEQ ID NO:65,

^{2. (}canceled)

SEQ ID NO:66, SEQ ID NO:67, SEQ ID NO:68, SEQ ID NO:74, SEQ ID NO:75, SEQ ID NO:76, SEQ ID NO:77, SEQ ID NO:78 and fragments thereof.

42. A method of activating an endogenous activity of a human erythropoietin receptor in a mammal, the method comprising the step of administering to said mammal a therapeutically effective amount of an antibody or antibody fragment thereof to activate said receptor, wherein said antibody or antibody fragment thereof does not interact with a peptide having an amino acid sequence of SEQ ID NO:1.

43. (canceled)

44. A method of treating a mammal suffering aplasia, the method comprising the step of administering to a mammal in need of treatment a therapeutically effective amount of an antibody or antibody fragment thereof to activate said receptor, wherein said antibody or antibody fragment thereof does not interact with a peptide having an amino acid sequence of SEQ ID NO:1.

45. (canceled)

46. A pharmaceutical composition comprising a therapeutically effective amount of an antibody or antibody fragment thereof and a pharmaceutically acceptable excipient, wherein said antibody or antibody fragment thereof does not interact with a peptide having an amino acid sequence of SEQ ID NO:1.

47. An isolated and purified polynucleotide sequence selected from the group consisting of: SEQ ID NO:2, SEQ ID NO:4, SEQ ID NO:6, SEQ ID NO:8, SEQ ID NO:10, SEQ ID NO:12, SEQ ID NO:14, SEQ ID NO:16, SEQ ID NO:18, SEQ ID NO:20, SEQ ID NO:22, SEQ ID NO:24, SEQ ID NO:26, SEQ ID NO:28, SEQ ID NO:30, SEQ ID NO:32, SEQ ID NO:34, SEQ ID NO:36, SEQ ID NO:38, SEQ ID NO:40, SEQ ID NO:42, SEQ ID NO:44, SEQ ID NO:46, SEQ ID NO:48, SEQ ID NO:50, SEQ ID NO:52, SEQ ID NO:54, SEQ ID NO:56, fragments, complements, and degenerate codon equivalents thereof.

48. An isolated and purified amino acid sequence selected from the group consisting of: SEQ ID NO:3, SEQ ID NO:5, SEQ ID NO:7, SEQ ID NO:9, SEQ ID NO:11, SEQ ID NO:13, SEQ ID NO:15, SEQ ID NO:17, SEQ ID NO:19, SEQ ID NO:21, SEQ ID NO:23, SEQ ID NO:25, SEQ ID NO:27, SEQ ID NO:29, SEQ ID NO:31, SEQ ID NO:33, SEQ ID NO:35, SEQ ID NO:37, SEQ ID NO:39, SEQ ID NO:41, SEQ ID NO:43, SEQ ID NO:45, SEQ ID NO:47, SEQ ID NO:55, SEQ ID NO:57, SEQ ID NO:58, SEQ ID NO:59, SEQ ID NO:60, SEQ ID NO:61, SEQ ID NO:62, SEQ ID NO:63, SEQ ID NO:64, SEQ ID NO:65, SEQ ID NO:66, SEQ ID NO:67, SEQ ID NO:68 and fragments thereof.

49. An antibody or antibody fragment thereof that activates an endogenous activity of a human erythropoietin

receptor in a mammal wherein said antibody or antibody fragment is a gamma-2 isotype.

50. The antibody or antibody fragment of claim 49 wherein said antibody or antibody fragment is a monoclonal antibody.

51. The antibody or antibody fragment of claim 50 wherein said antibody or antibody fragment is a humanized antibody.

52. The antibody or antibody fragment of claim 50 wherein said antibody or antibody fragment is a human antibody.

53. The antibody or antibody fragment of claim 50 wherein said antibody or antibody fragment does not interact with a peptide having an amino acid sequence of SEQ ID NO:1.

54. The antibody or antibody fragment of claim 50 wherein said antibody or antibody fragment is selected from the group consisting of Ab3, Ab12, Ab22, Ab54, Ab60, Ab102, Ab135, Ab145, Ab198, Ab254, Ab267, Ab390, Ab412, Ab430/432, Ab467 and Ab484.

55. A method of activating an endogenous activity of a human erythropoietin receptor in a mammal, the method comprising the step of administering to a mammal a therapeutically effective amount of the antibody or antibody fragment of claim 49 to activate said receptor.

56. A method of modulating an endogenous activity of a human erythropoietin receptor in a mammal, the method comprising the step of administering to a mammal a therapeutically effective amount of the antibody or antibody fragment of claim 49 to modulate the activity of the receptor.

57. A method of treating a mammal suffering aplasia, the method comprising the step of administering to a mammal in need of treatment a therapeutically effective amount of the antibody or antibody fragment of claim 49 to activate the receptor.

58. A method of treating a mammal suffering aplasia, the method comprising the step of administering to a mammal in need of treatment a therapeutically effective amount of the antibody or antibody fragment of claim 49 to modulate the activity of the receptor.

59. A method of treating a mammal suffering anemia, the method comprising the steps of administering to a mammal in need of treatment a therapeutically effective amount of the antibody or antibody fragment of claim 49 to modulate the activity of the receptor.

60. A pharmaceutical composition comprising a therapeutically effective amount of the antibody or antibody fragment of claim 49 and a pharmaceutically acceptable excipient.

* * * * *