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Krasnoperov et al.

(54) **POLYPEPTIDE COMPOUNDS FOR INHIBITING ANGIOGENESIS AND TUMOR GROWTH**

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Related U.S. Application Data

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(52) **U.S. Cl.** **424/156.1**

(57) **ABSTRACT**

In certain embodiments, this present invention provides polypeptide compositions, and methods for inhibiting Ephrin B2 or EphB4 activity. In other embodiments, the present invention provides methods and compositions for treating cancer or for treating angiogenesis-associated diseases.

Amino acid sequence of the B4ECv3 protein

MELRVLLCWASLAAALEETLLNTKLETADLKWVTFPQVDGQWEELSG
LDEEQHSVRTYEVCEVQRAPGQAHWLRTGWVPRRGAVHVYATLRFTM
LECLSLPRAGRSCKETFTVFYYESDADTATALTPAWMENPYIKVDTV
AAEHLTRKRPGAEATGKVNVKTLRLGPLSKAGFYLAFQDQGACMALL
SLHLFYKKCAQLTVNLTRFPETVPRELVVPVAGSCVVDAVPAPGPSP
SLYCREDGQWAEQPVTGCSCAPGFEAAEGNTKCRACAQGTFKPLSGE
GSCQPCPANSHSNTIGSAVCQCRVGYFRARTDPRGAPCTTPPSAPRS
VVSRLNGSSLHLEWSAPLESGGREDLTYALRCRECRPGGSCAPCGGD
LTFDPGPRDLVEPWVVVRGLRPDFTYTFEVTALNGVSSLATGPVPFE
PVNVTTDREVPPAVSDIRVTRSSPSSLSLAWAVPRAPSGAWLDYEVK
YHEKGAEGPSSVRFLKTSENRAELRGLKRGASYLVQVRARSEAGYGP
FGQEHHSQTQLDESEGWREQGSKRAILQIEGKPIPNPLLGLDSTRTG
HHHHHH

Amino acid sequence of the B4ECv3 protein

MELRVLLCWASLAAALEETLLNTKLETADLKWVTFPQVDGQWEELSG
LDEEQHSVRTYEVCEVQRAPGQAHWLRTGWVPRRGAVHVYATLRFTM
LECLSLPRAGRSCKETFTVFYYESDADTATALTPAWMENPYIKVDTV
AAEHLTRKRPGAEATGKVNVKTLRLGPLSKAGFYLAFQDQGACMALL
SLHLFYKKCAQLTVNLTRFPETVPRELVVPVAGSCVVDAVPAPGPSP
SLYCREDGQWAEQPVTGCSCAPGFEAAEGNTKCRACAQGTFKPLSGE
GSCQPCPANSHSNTIGSAVCQCRVGYFRARTDPRGAPCTTPPSAPRS
VVSRLNGSSLHLEWSAPLESGGREDLTYALRCRECRPGGSCAPCGGD
LTFDPGPRDLVEPWVVVRGLRPDFTYTFEVTALNGVSSLATGPVPFE
PVNVTTDREVPPAVSDIRVTRSSPSSLSLAWAVPRAPSGAWLDYEVK
YHEKGAEGPSSVRFLKTSENRAELRGLKRGASYLVQVRARSEAGYGP
FGQEHHSQTQLDESEGWREQGSKRAILQIEGKPIPNPLLGLDSTRTG
HHHHHH

Fig. 1

Amino acid sequence of the B4ECv3NT protein

MELRVLLCWASLAAALEETLLNTKLETADLKWVTFPQVDGQWEELSGL
DEEQHSVRTYEVCEVQRAPGQAHWLRTGWVPRRGAVHVYATLRFTMLE
CLSLPRAGRSCKETFTVFYYESDADTATALTPAWMENPYIKVDTVAAE
HLTRKRPGAEATGKVNVKTLRLGPLSKAGFYLAFQDQGACMALLSLHL
FYKKCAQLTVNLTRFPETVPRELVVPVAGSCVVDAVPAPGPSPSLYCR
EDGQWAEQPVTGCSCAPGFEAAEGNTKCRACAQGTFKPLSGEGSCQPC
PANSHSNTIGSAVCQCRVGYFRARTDPRGAPCTTPPSAPRSVVSRLNG
SSLHLEWSAPLESGGREDLTYALRCRECRPGGSCAPCGGDLTFDPGPR
DLVEPWVVVRGLRPDFTYTFEVTALNGVSSLATGPVPFEPVNVTTDRE
VPPAVSDIRVTRSSPSSLSLAWAVPRAPSGAWLDYEVKYHEKGAEGPS
SVRFLKTSENRAELRGLKRGASYLVQVRARSEAGYGPFGQEHHSQTQL
DESEGWREQGSKRAILQISSTVAAARV

Fig. 2

Amino acid sequence of the B2EC protein

MAVRRDSVWKYCWGVLMVLCRTAISKSIVLEPIYWNSSNSKFLPGQGL
VLYPQIGDKLDIICPKVDSKTVGQYEYYKVYMVDKDQADRCTIKKENT
PLLNCAKPDQDIKFTIKFQEFSPNLWGLEFQKNKDYYIISTSNGSLEG
LDNQEGGVCQTRAMKILMKVGQDASSAGSTRNKDPTRRPELEAGTNGR
SSTTSPFVKPNPGSSTDGNSAGHSGNNILGSEVGSHHHHHH

Fig. 3

Amino acid sequence of the B4ECv3-FC protein

MELRVLLCWASLAAALEETLLNTKLETADLKWVTFPQVDGQWEEL
SGLDEEQHSVRTYEVCEVQRAPGQAHWLRTGWVPRRGAVHVYATL
RFTMLECLSLPRAGRSCKETFTVFYYESDADTATALTPAWMENPY
IKVDTVAAEHLTRKRPGAEATGKVNVKTLRLGPLSKAGFYLAFQD
QGACMALLSLHLFYKKCAQLTVNLTRFPETVPRELVVPVAGSCVV
DAVPAPGPSPSLYCREDGQWAEQPVTGCSCAPGFEAAEGNTKCRA
CAQGTFKPLSGEGSCQPCPANSHSNTIGSAVCQCRVGYFRARTDP
RGAPCTTPPSAPRSVVSRLNGSSLHLEWSAPLESGGREDLTYALR
CRECRPGGSCAPCGGDLTFDPGPRDLVEPWVVVRGLRPDFTYTFE
VTALNGVSSLATGPVPFEPVNVTTDREVPPAVSDIRVTRSSPSSL
SLAWAVPRAPSGAWLDYEVKYHEKGAEGPSSVRFLKTSENRAELR
GLKRGASYLVQVRARSEAGYGPFGQEHHSQTQLDESEGWREQDPE
PKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTC
VVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVL
TVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTL
PPSRDELTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPP
VLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSL
SLSPGK

Fig. 4

Amino acid sequence of the B2EC-FC protein

MAVRRDSVWKYCWGVLMVLCRTAISKSIVLEPIYWNSSNSKFLPGQ
GLVLYPQIGDKLDIICPKVDSKTVGQYEYYKVYMVDKDQADRCTIK
KENTPLLNCAKPDQDIKFTIKFQEFSPNLWGLEFQKNKDYYIISTS
NGSLEGLDNQEGGVCQTRAMKILMKVGQDASSAGSTRNKDPTRRPE
LEAGTNGRSSTTSPFVKPNPGSSTDGNSAGHSGNNILGSEVDPEPK
SCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVV
DVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLH
QDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRD
ELTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDG
SFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK

Fig. 5

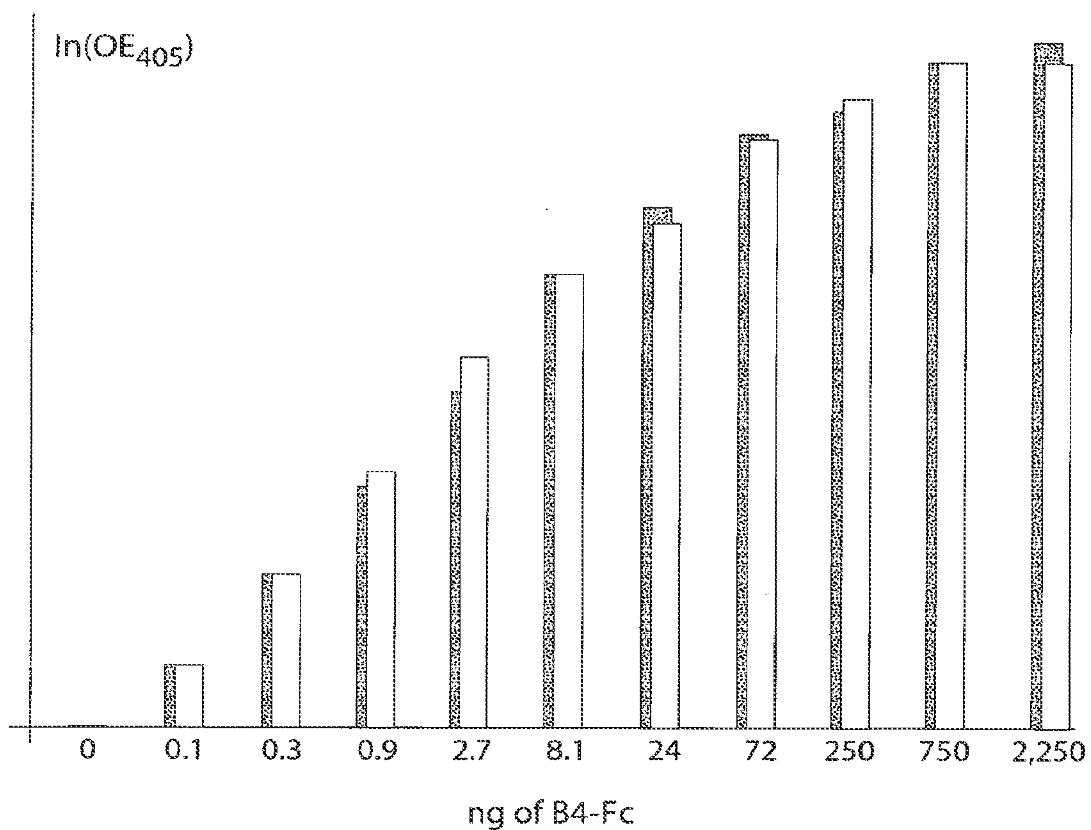


Fig. 6

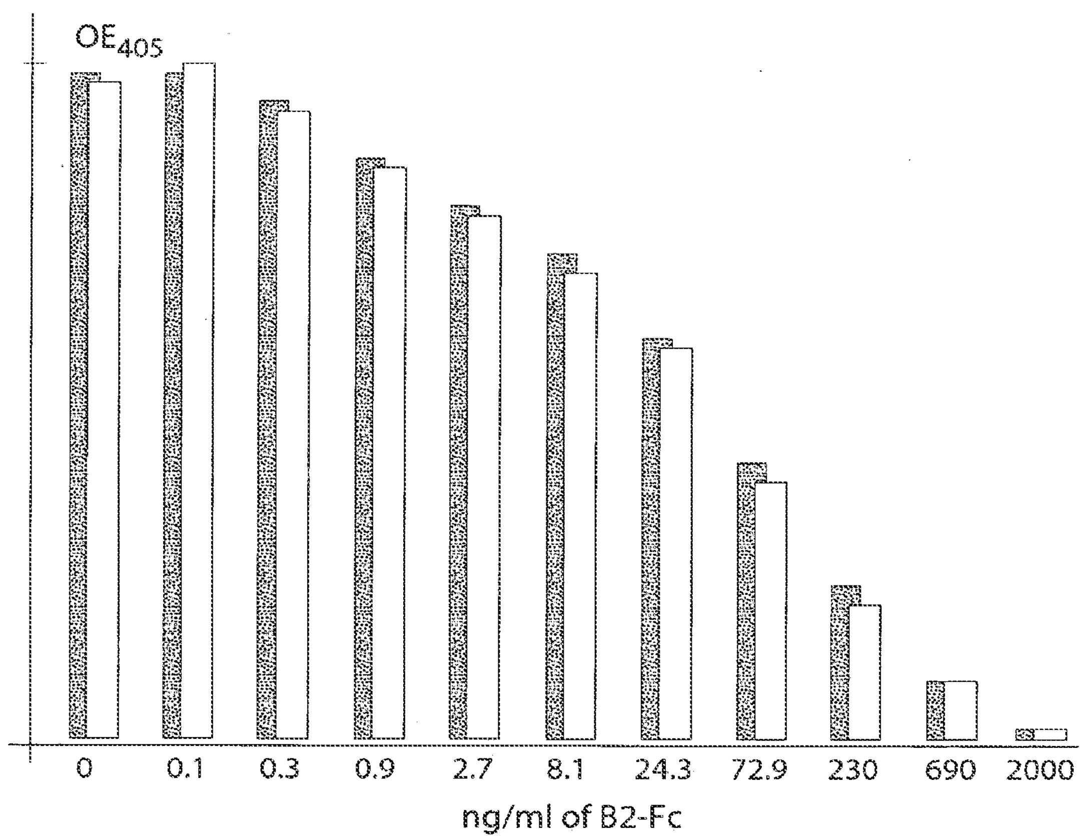


Fig. 7

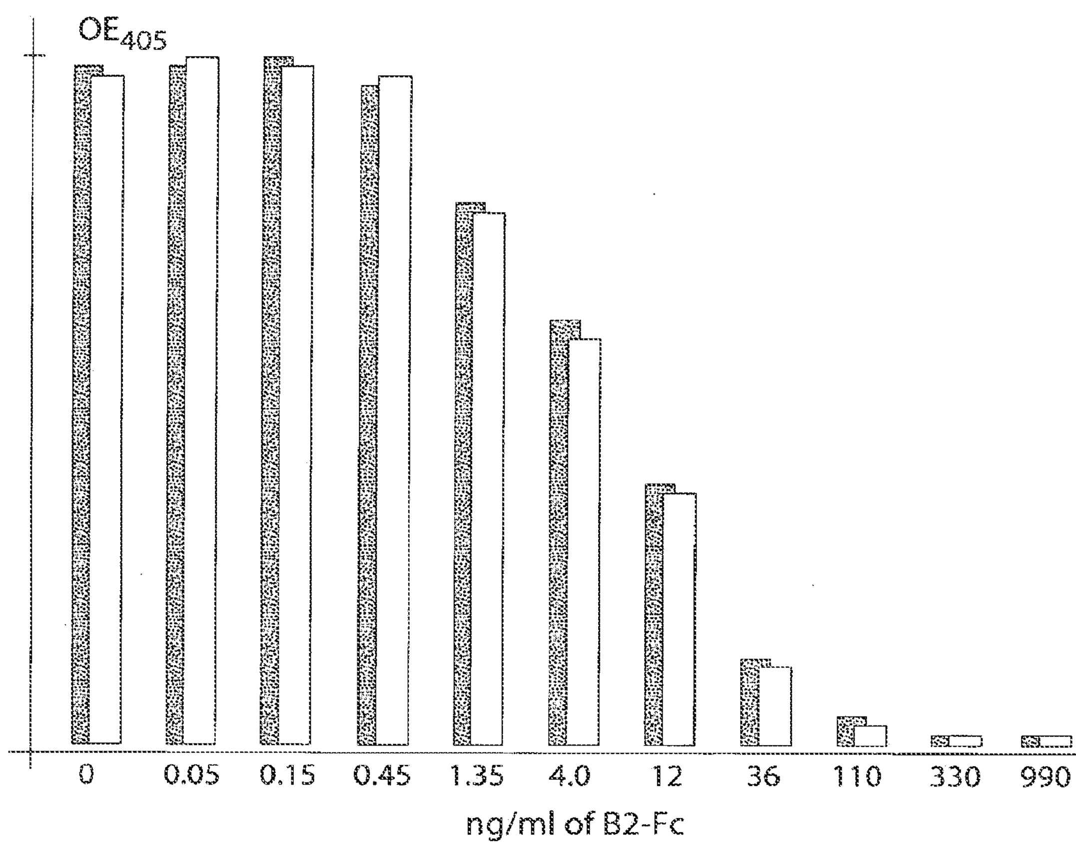


Fig. 8

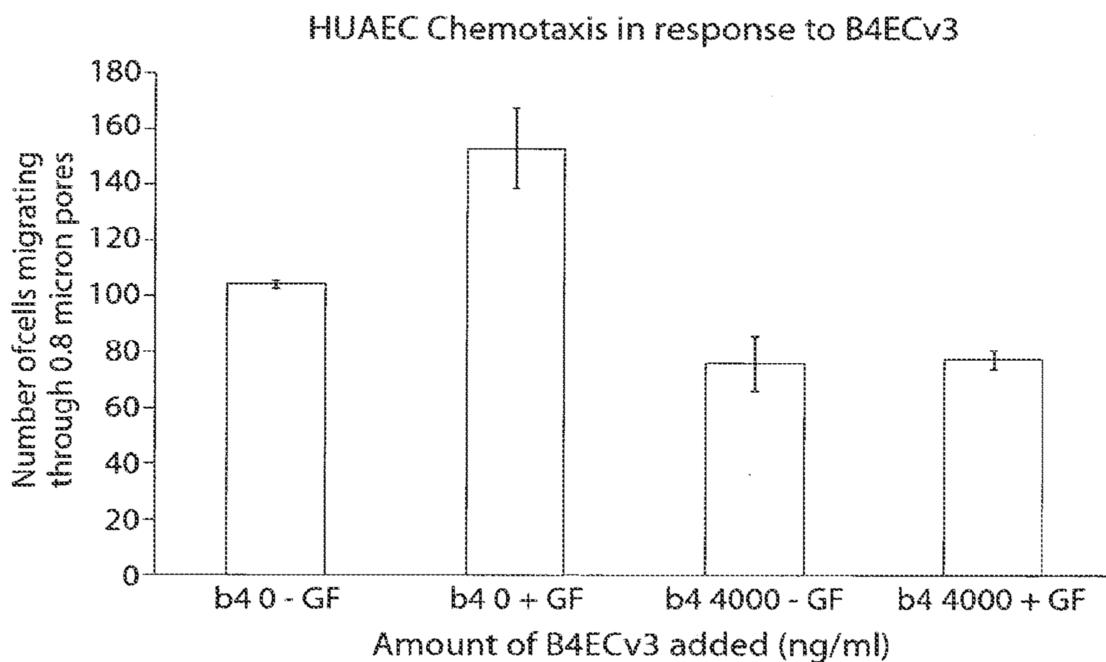


Fig. 9

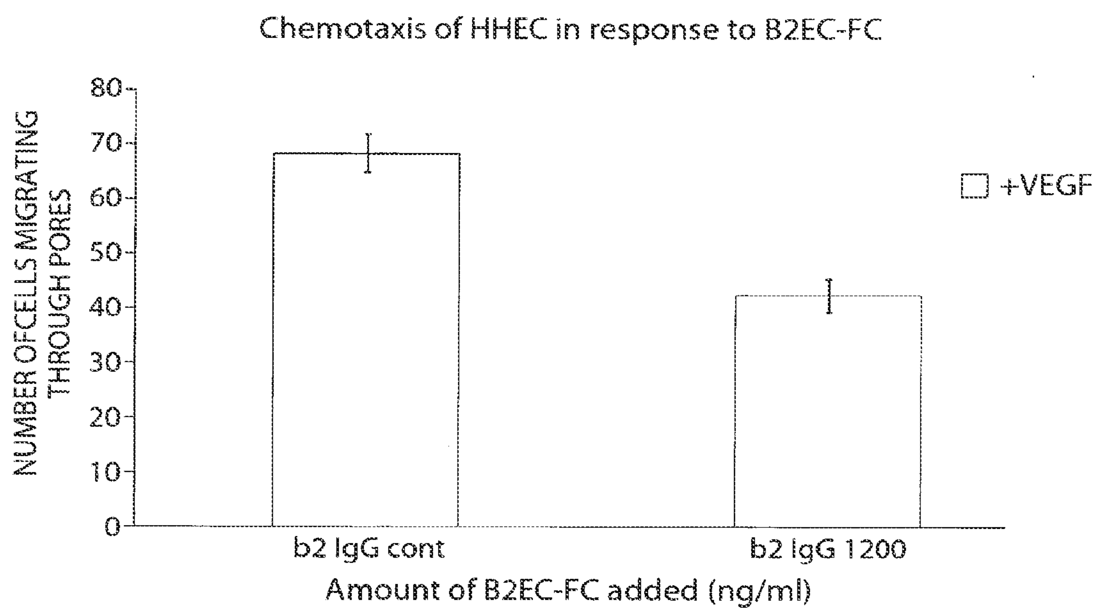


Fig. 10

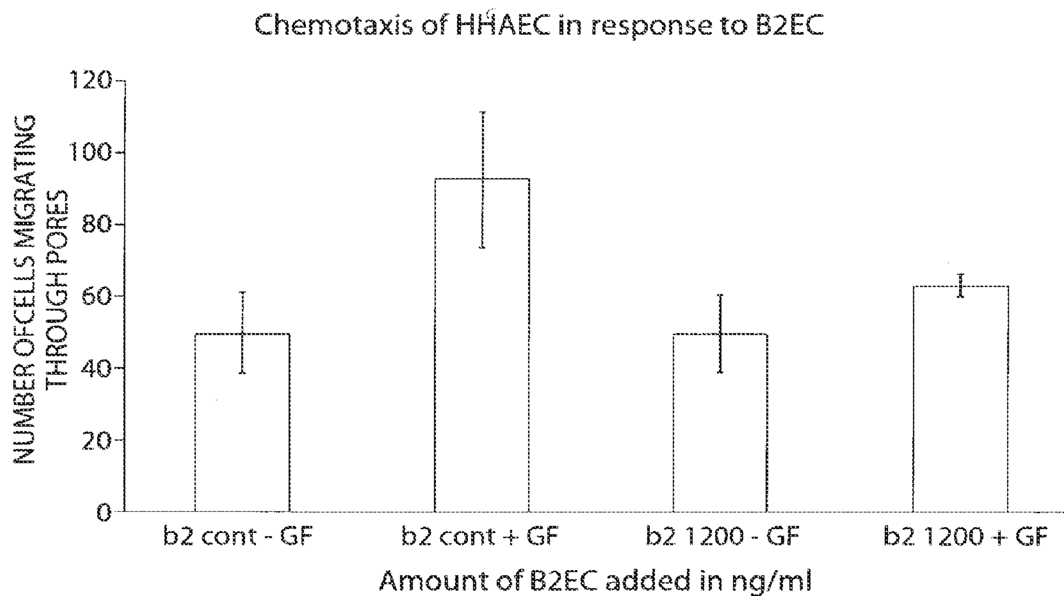


Fig. 11

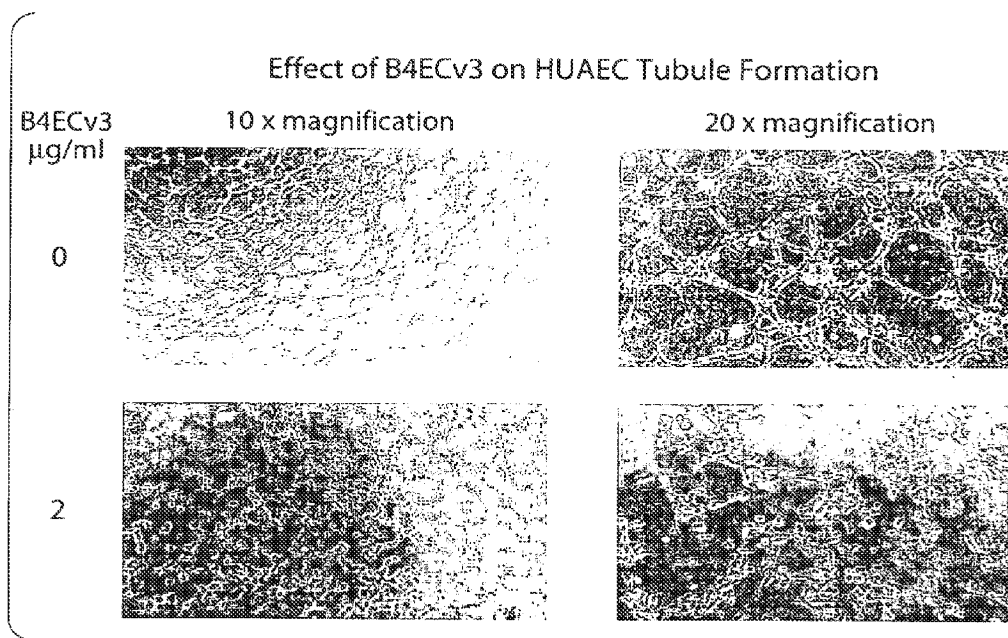


Fig. 12

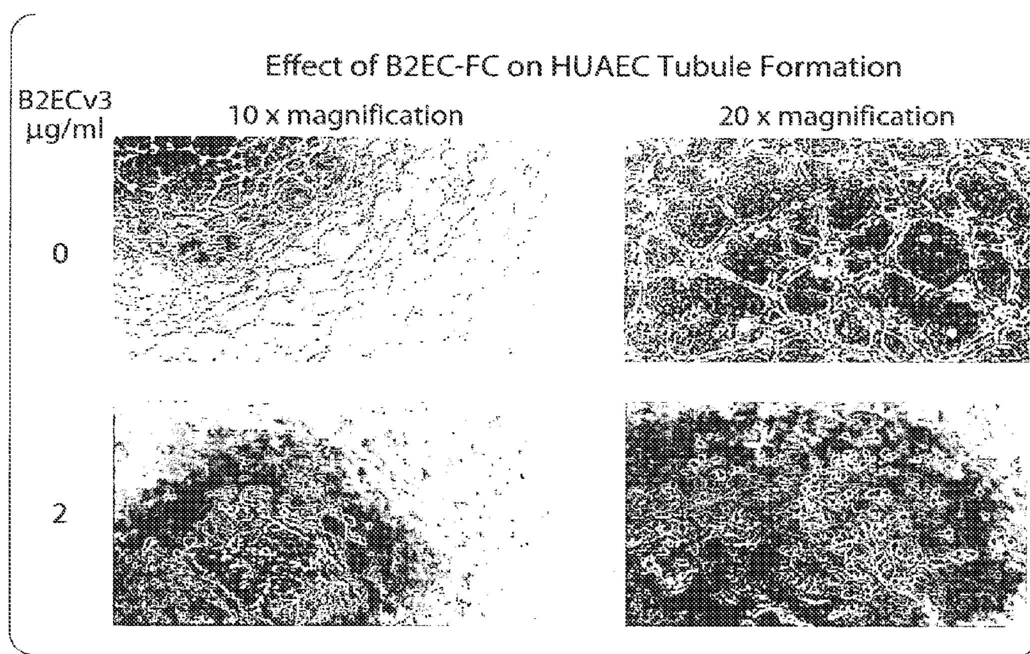


Fig. 13

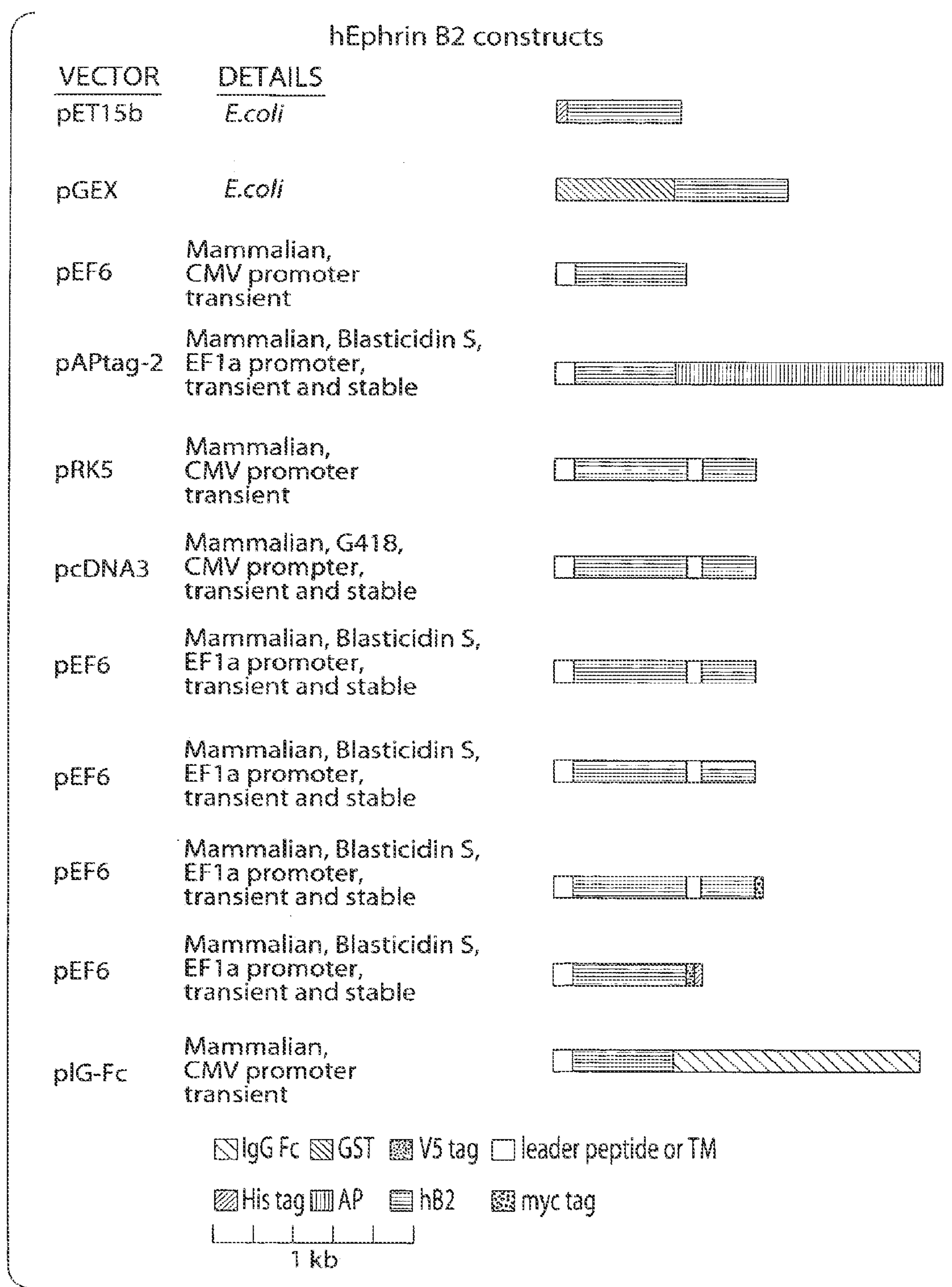


Fig. 14

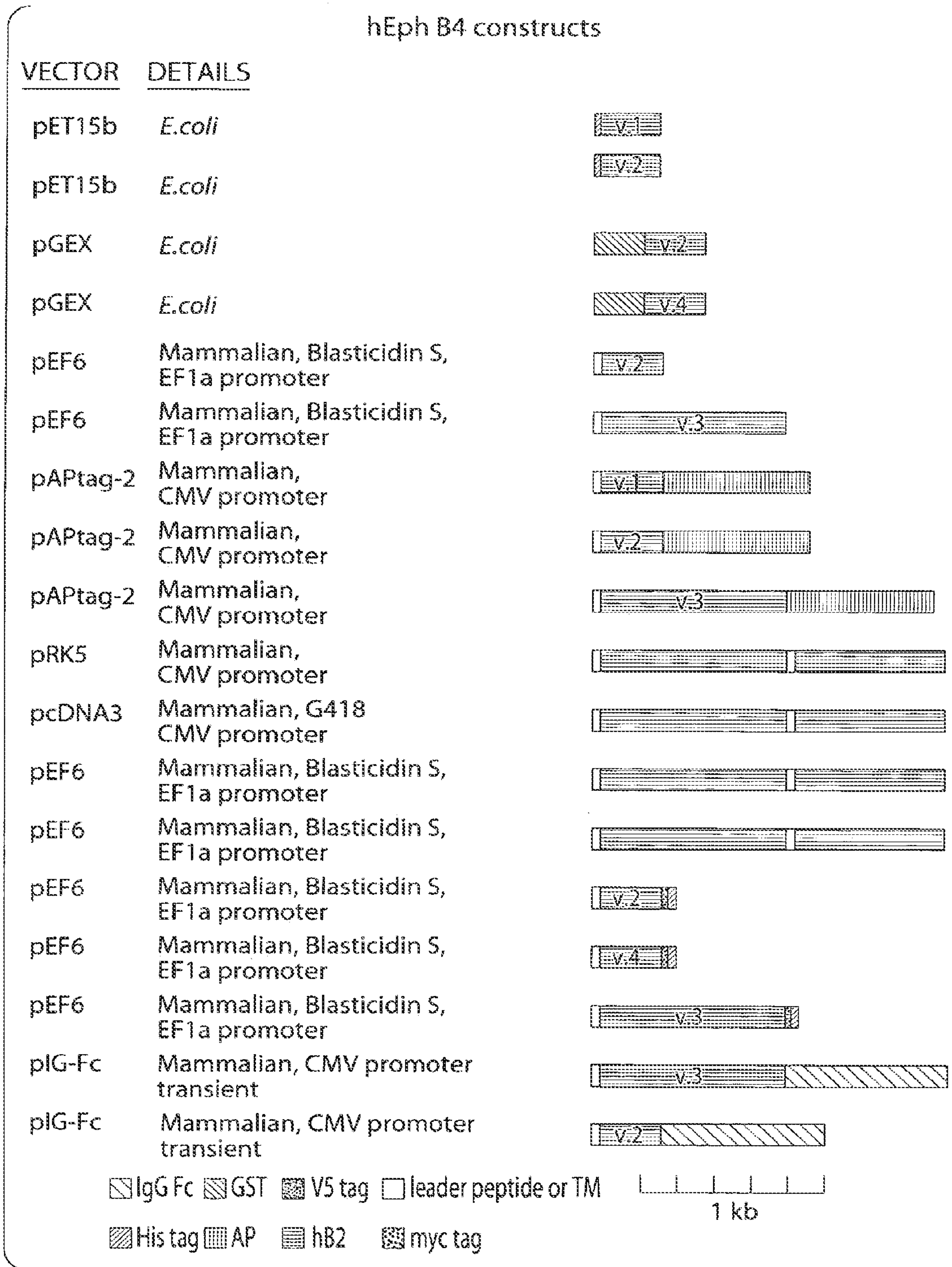


Fig. 15

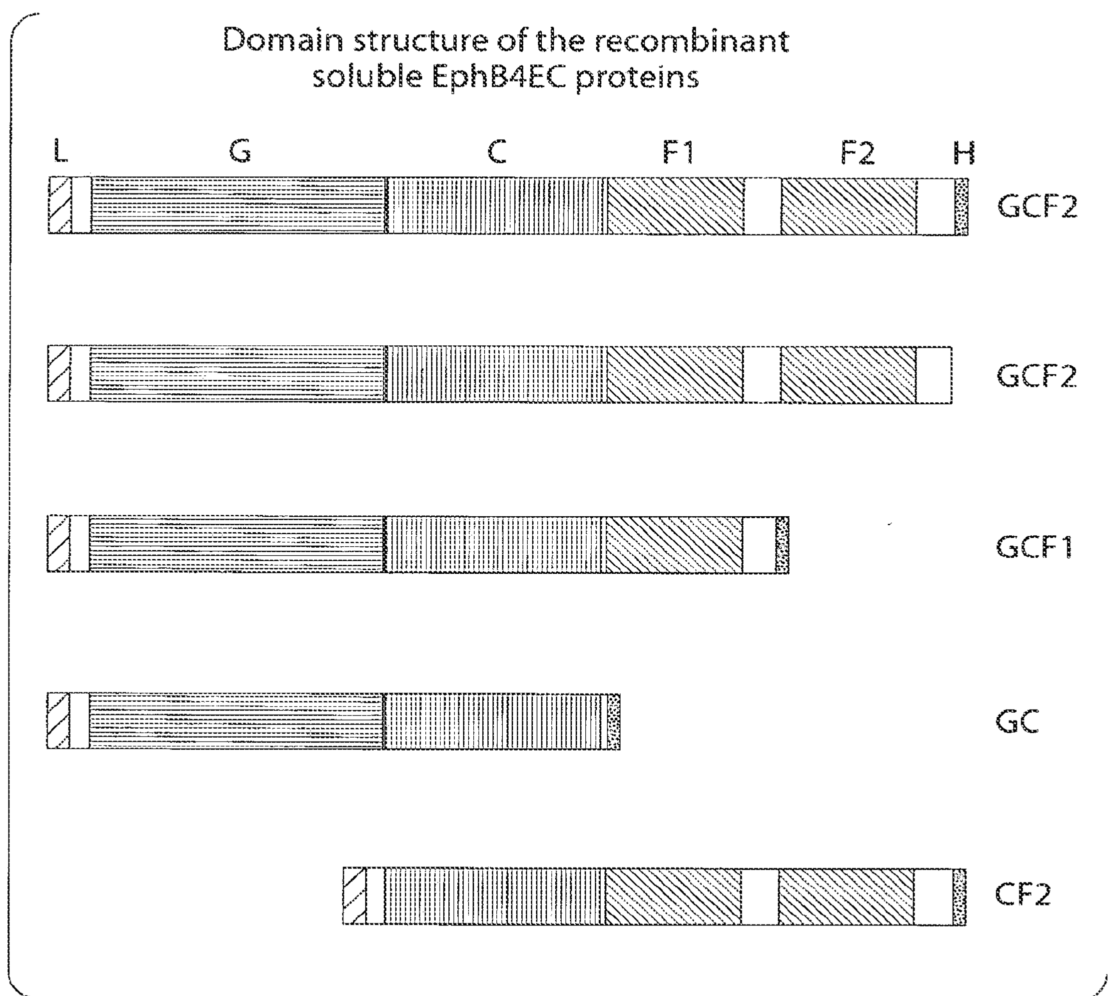


Fig. 16

Purification and ligand binding properties of the EphB4EC proteins

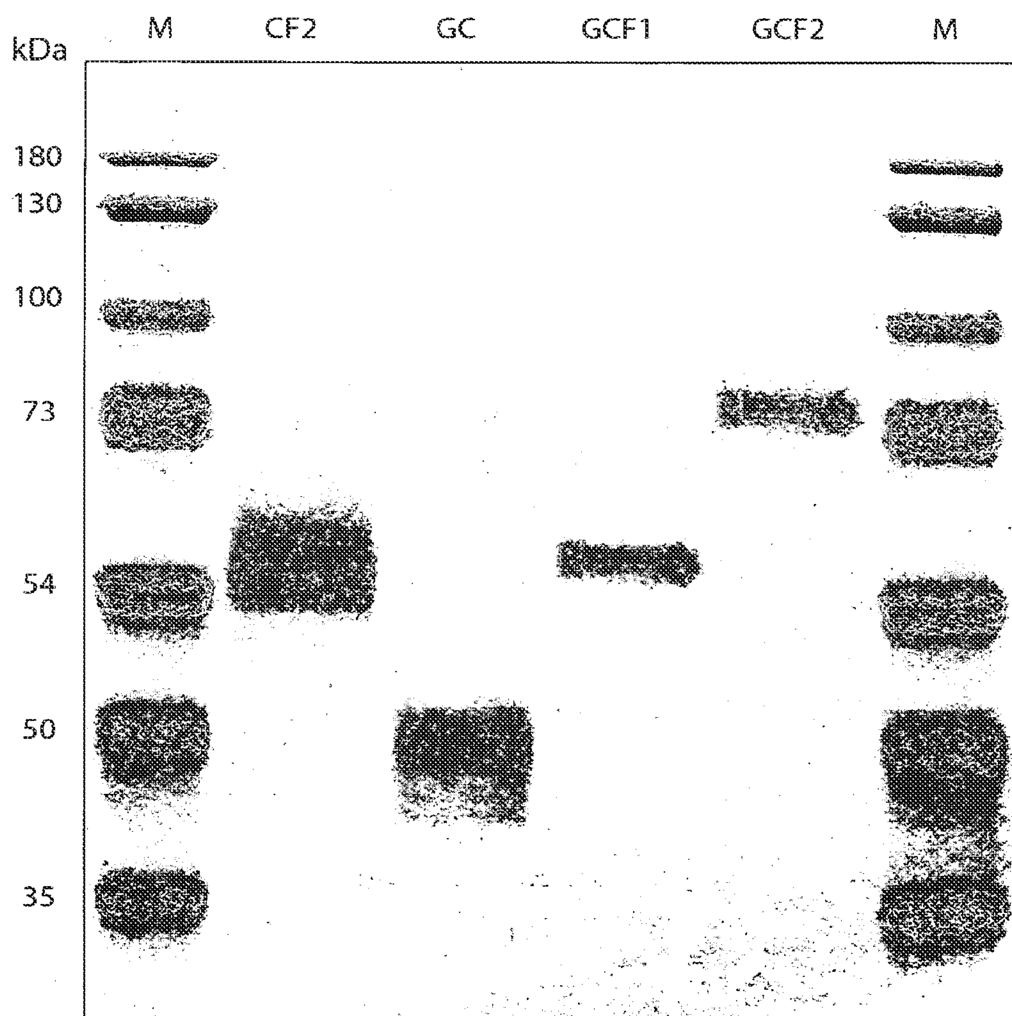


Fig. 17A

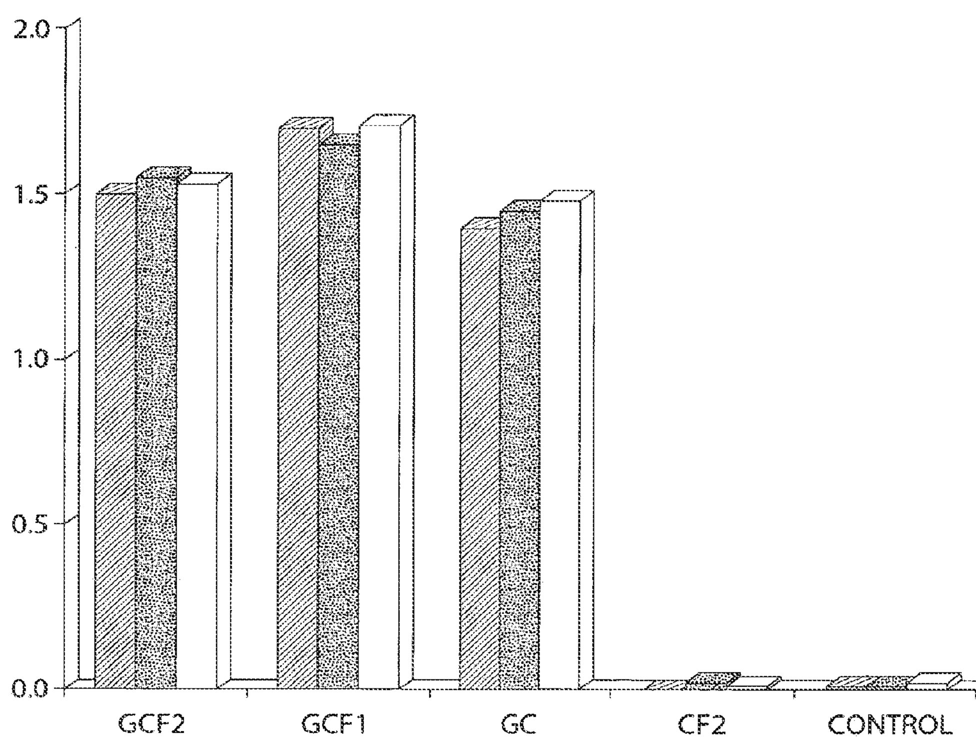


Fig. 17B

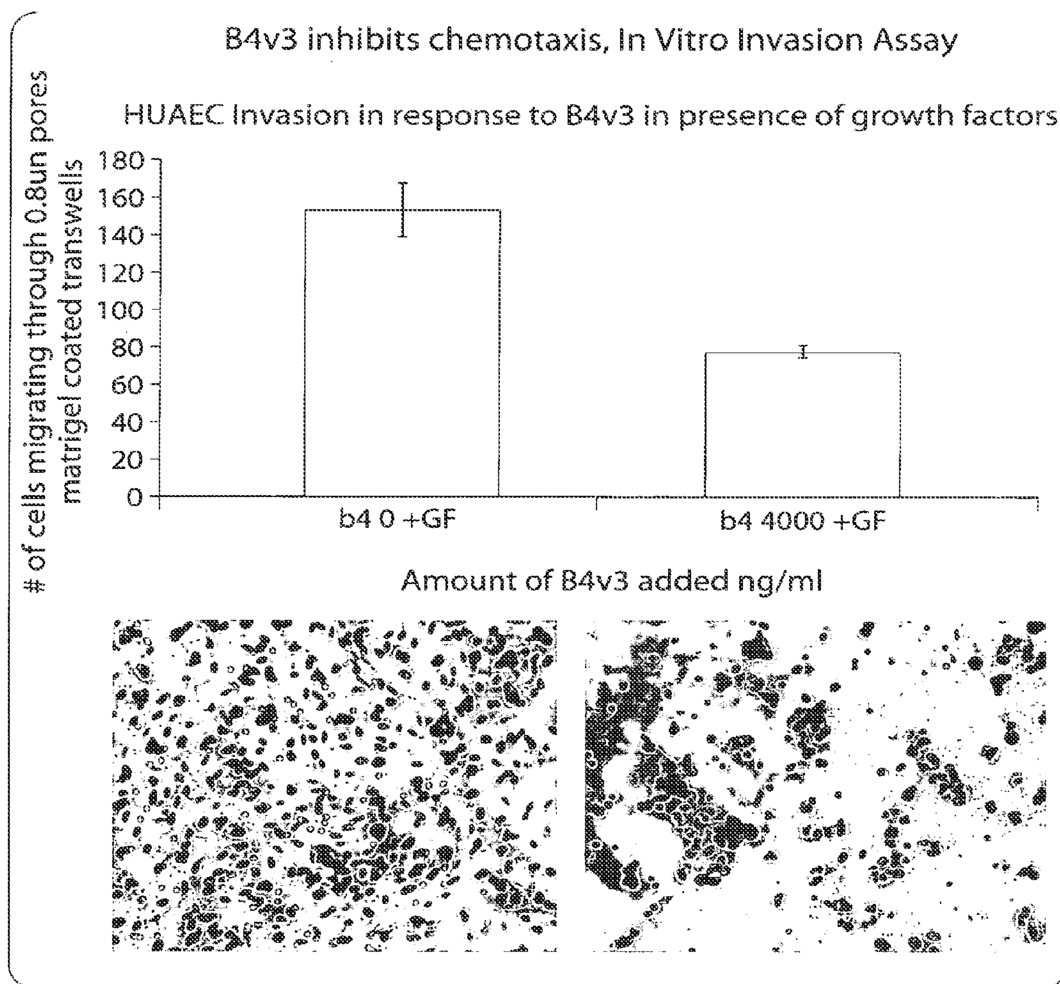


Fig. 18

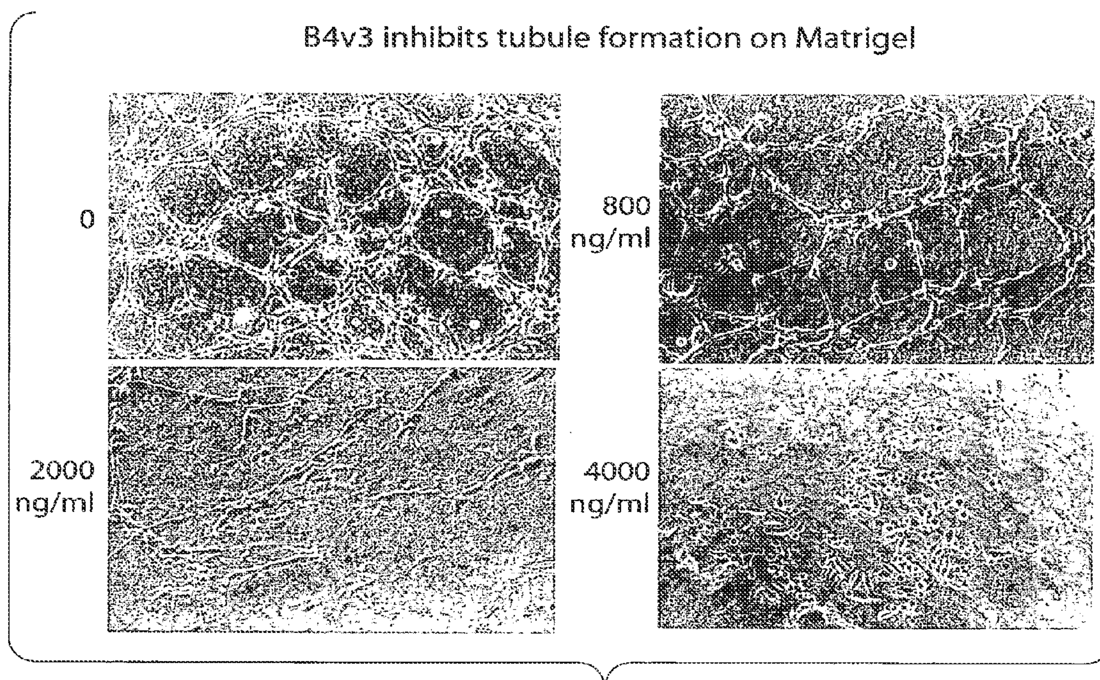


Fig. 19A

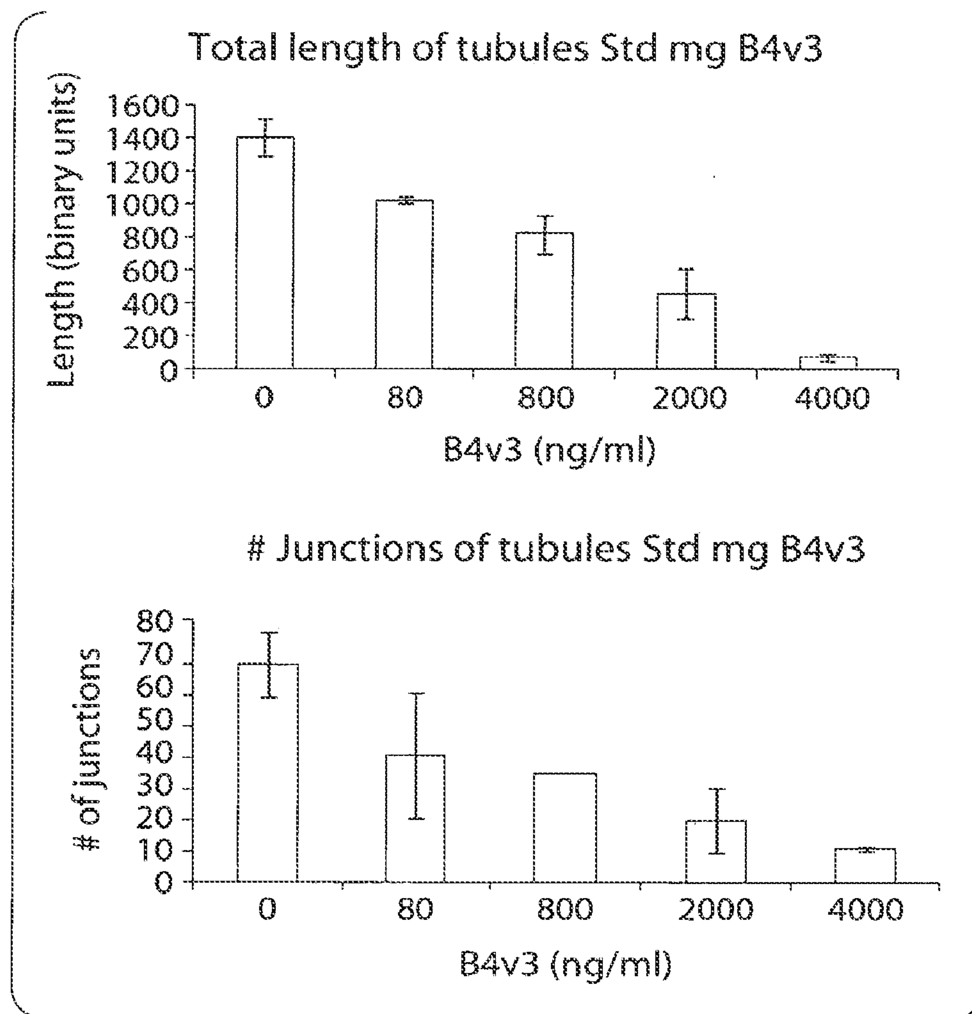


Fig. 19B

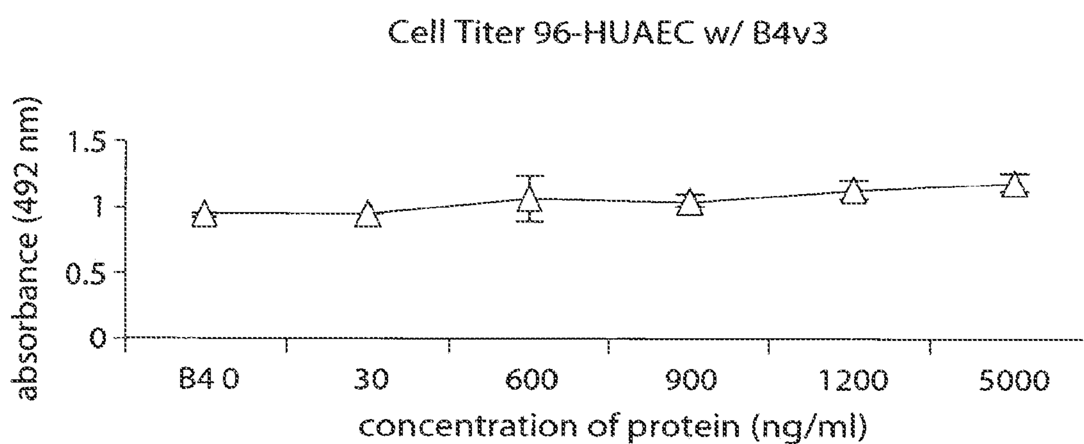


Fig. 20

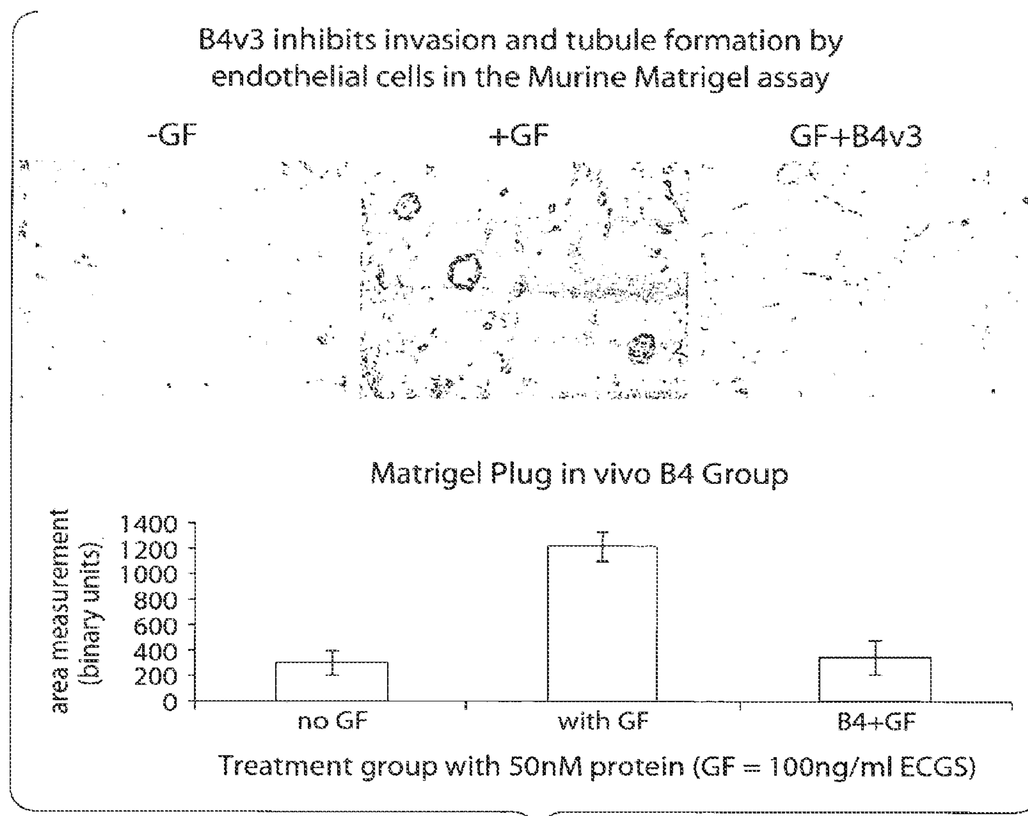


Fig. 21

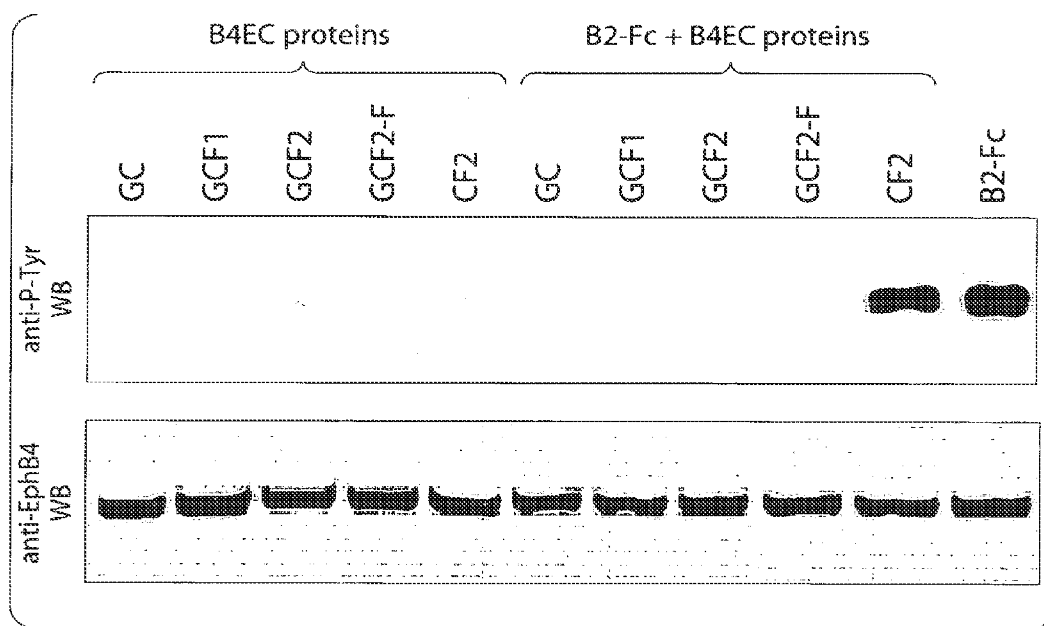


Fig. 22

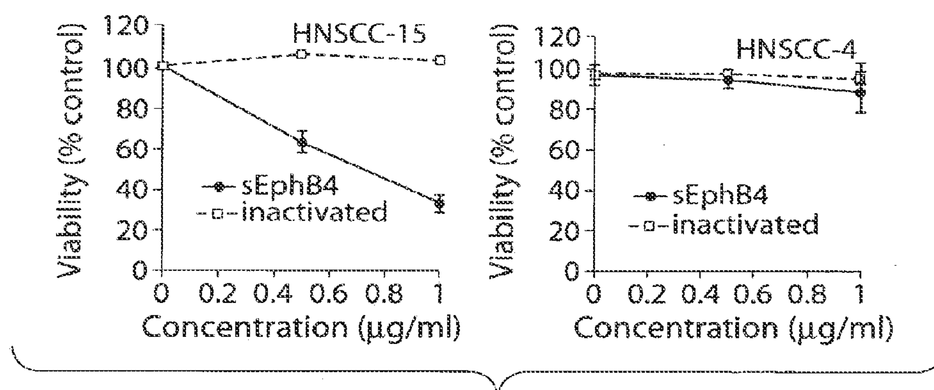


Fig. 23A

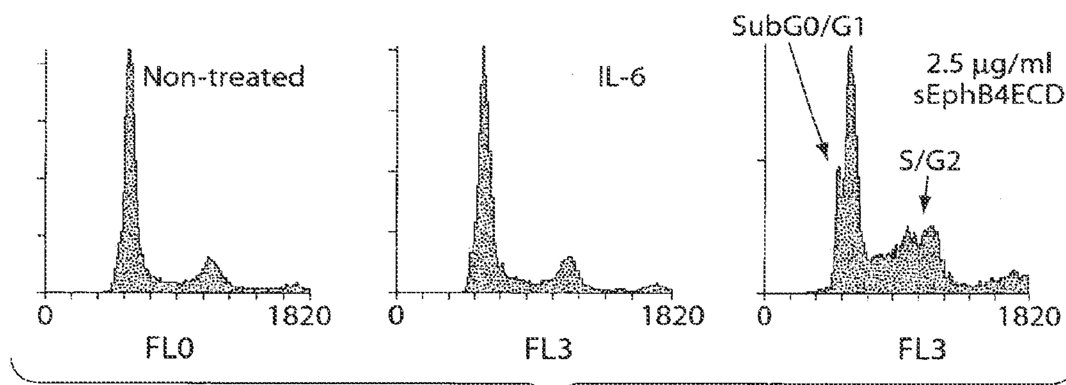


Fig. 23B

B4v3 inhibitis neovascular response in a murine corneal hydron micropocket assay

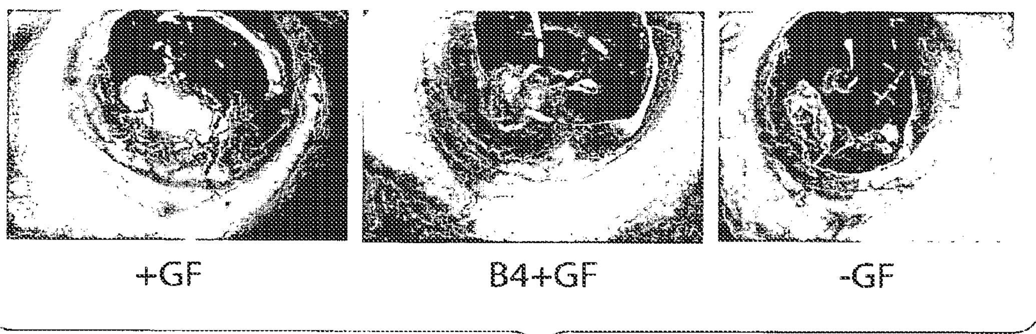


Fig. 24

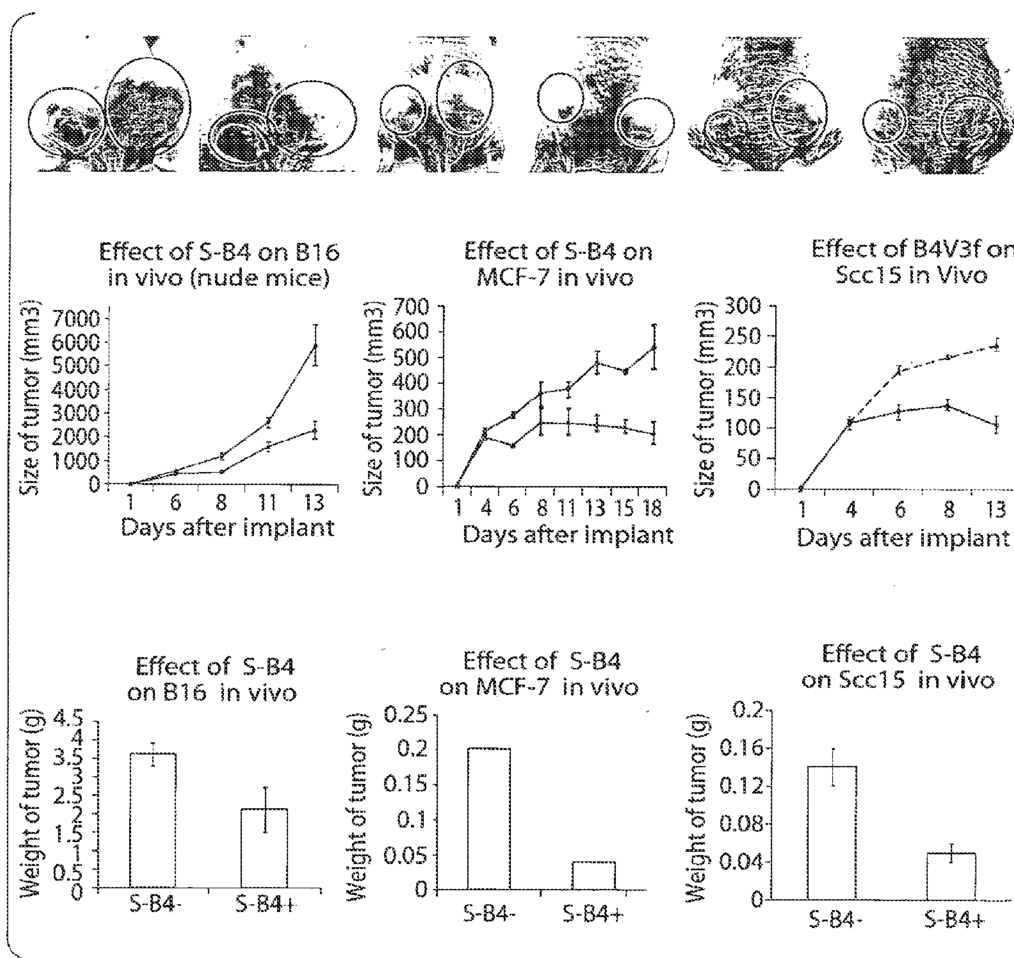


Fig. 25

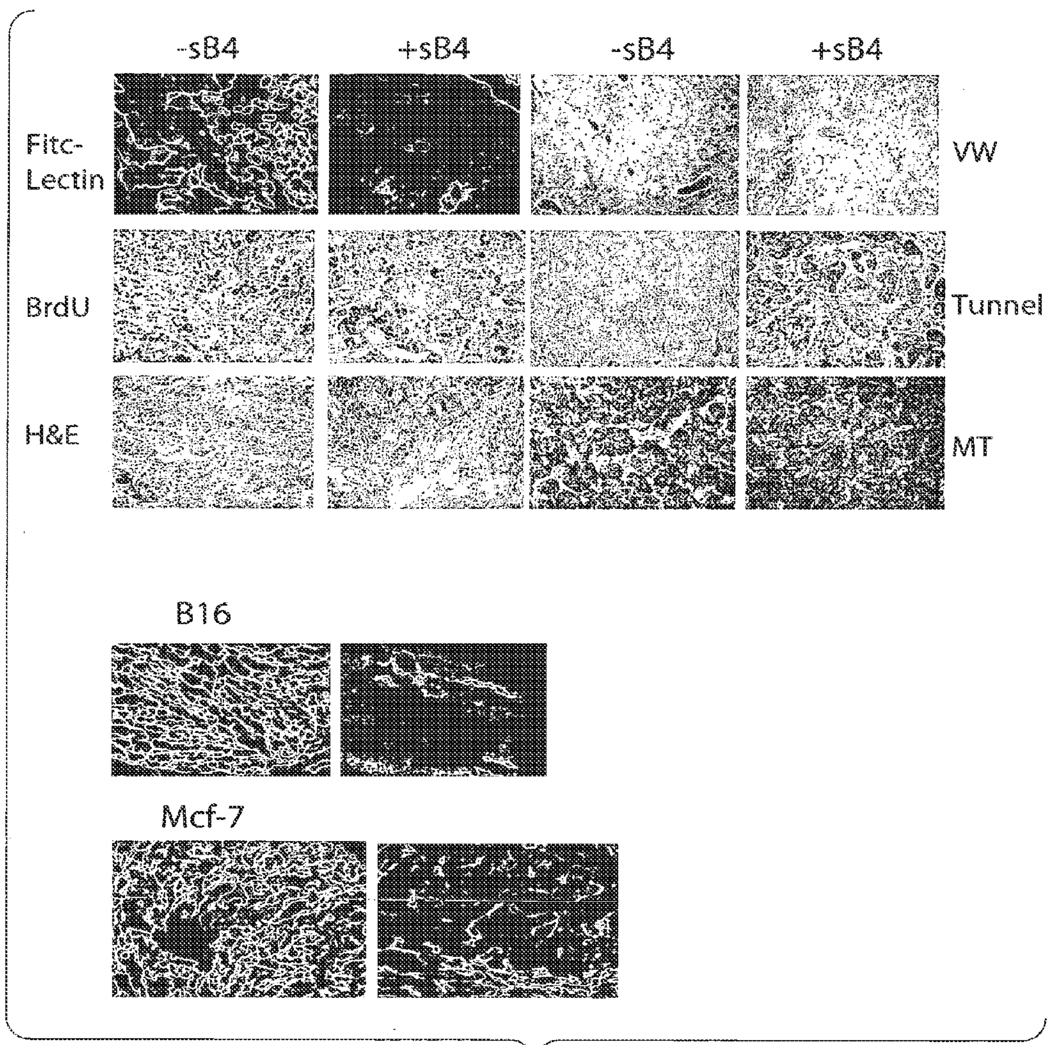


Fig. 26

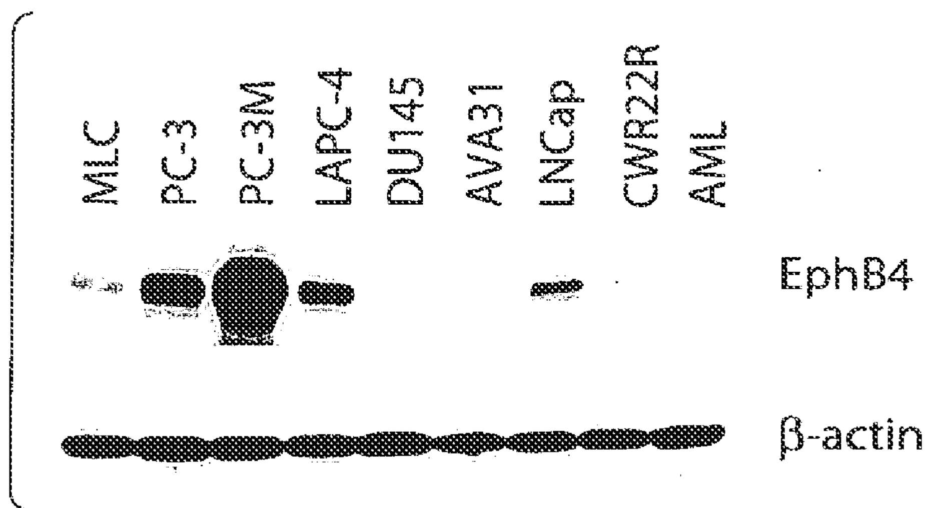


Fig. 27A

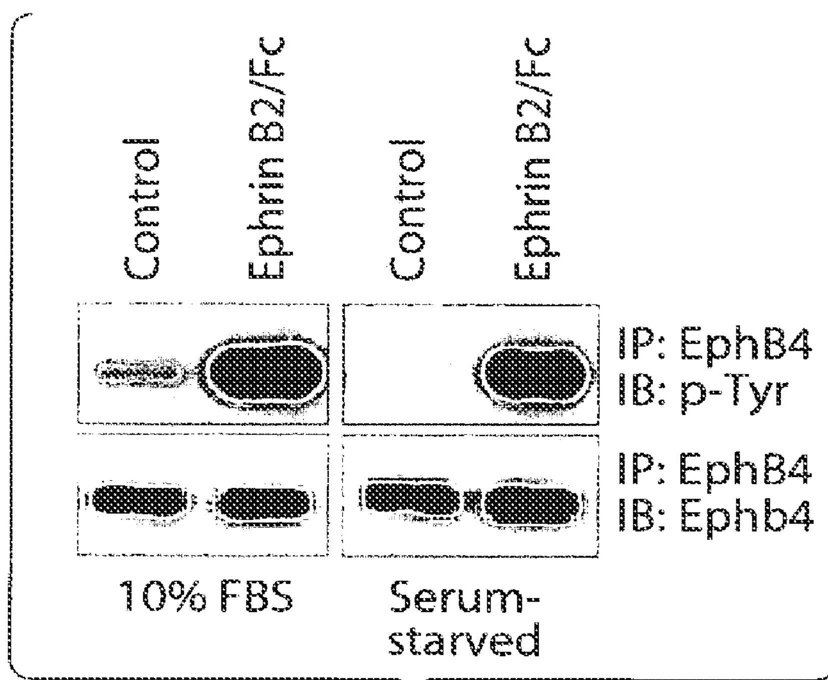
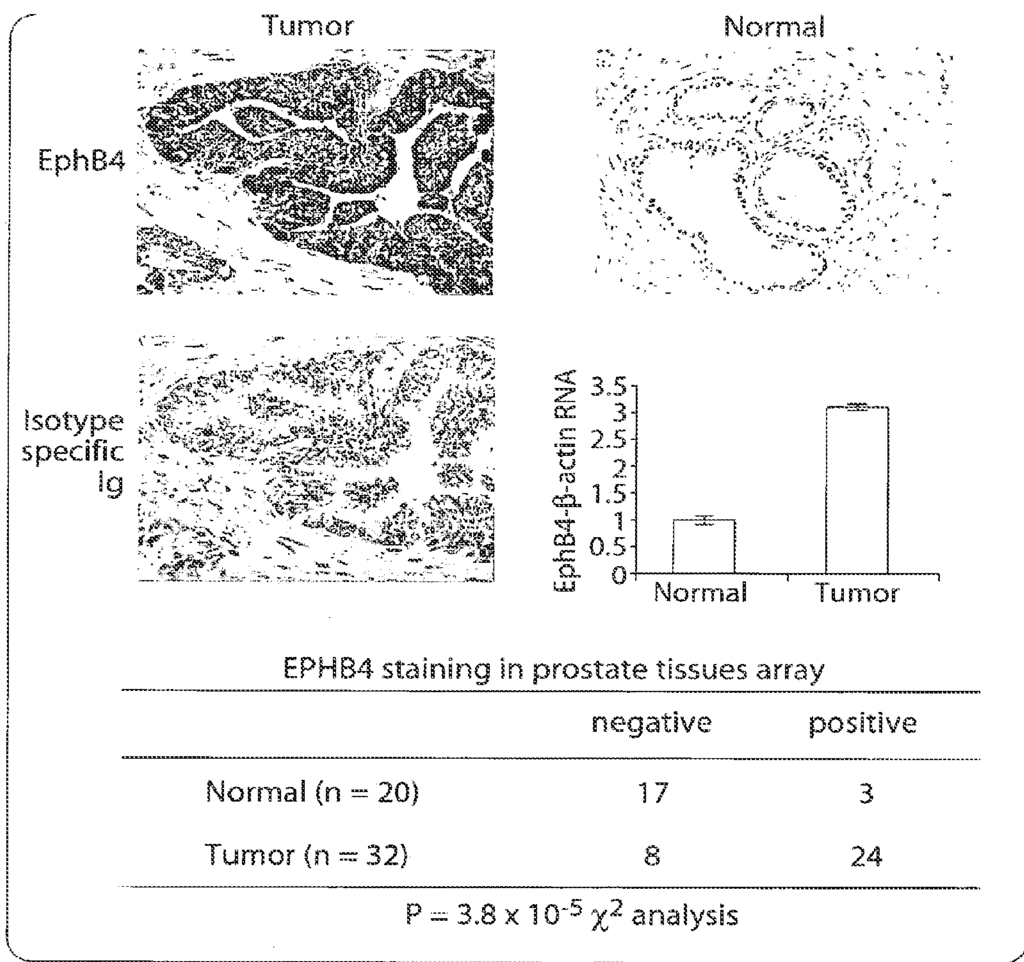


Fig. 27B



EPHB4 staining in prostate tissues array

	negative	positive
Normal (n = 20)	17	3
Tumor (n = 32)	8	24

$P = 3.8 \times 10^{-5}$ χ^2 analysis

Fig. 28

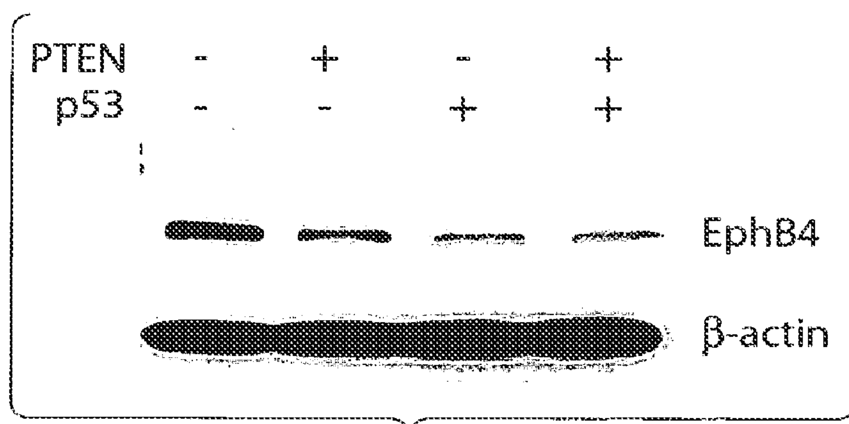


Fig. 29A

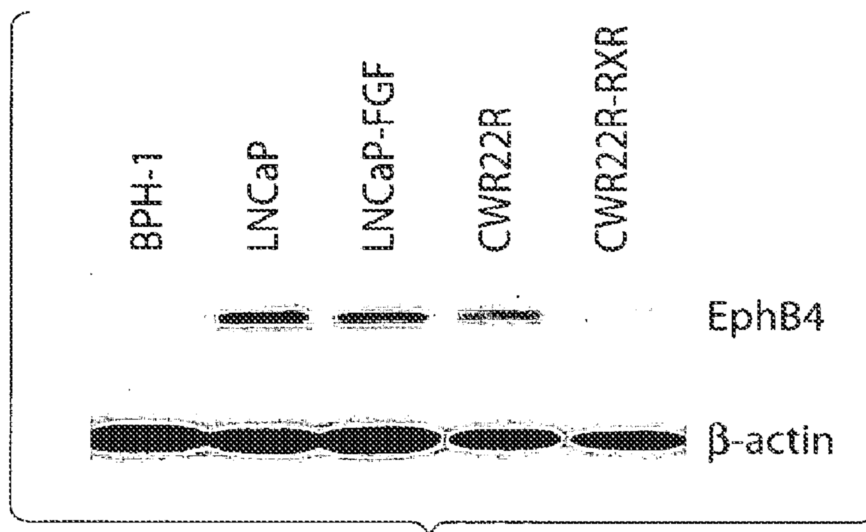


Fig. 29B

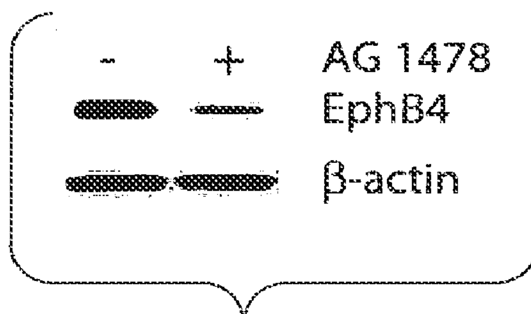


Fig. 30A

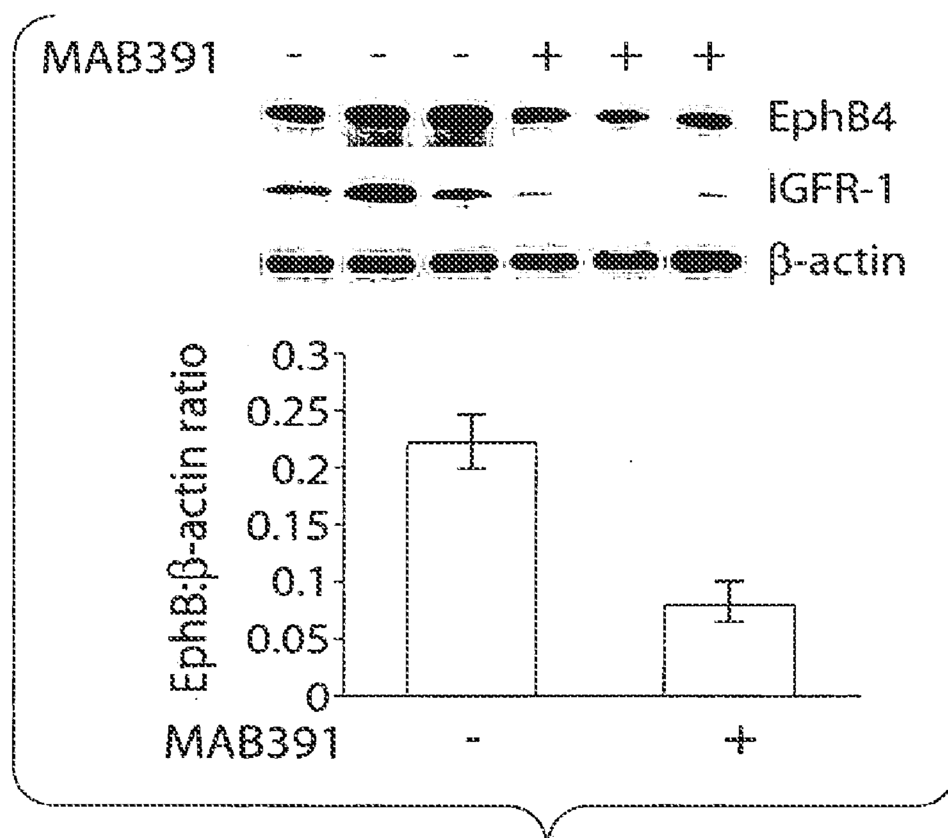


Fig. 30B

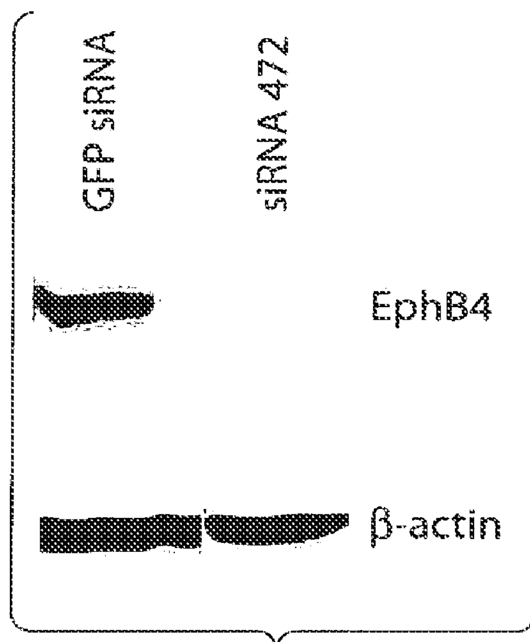


Fig. 31A

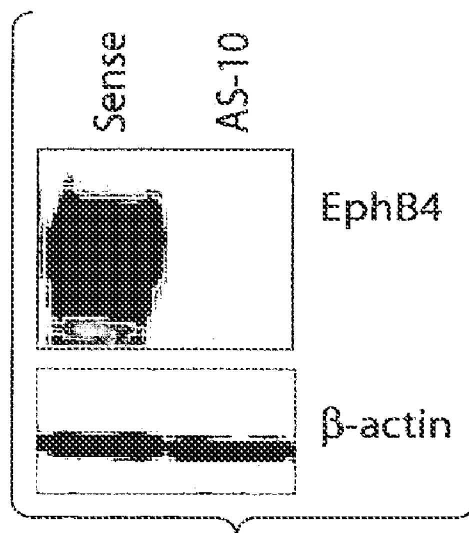


Fig. 31B

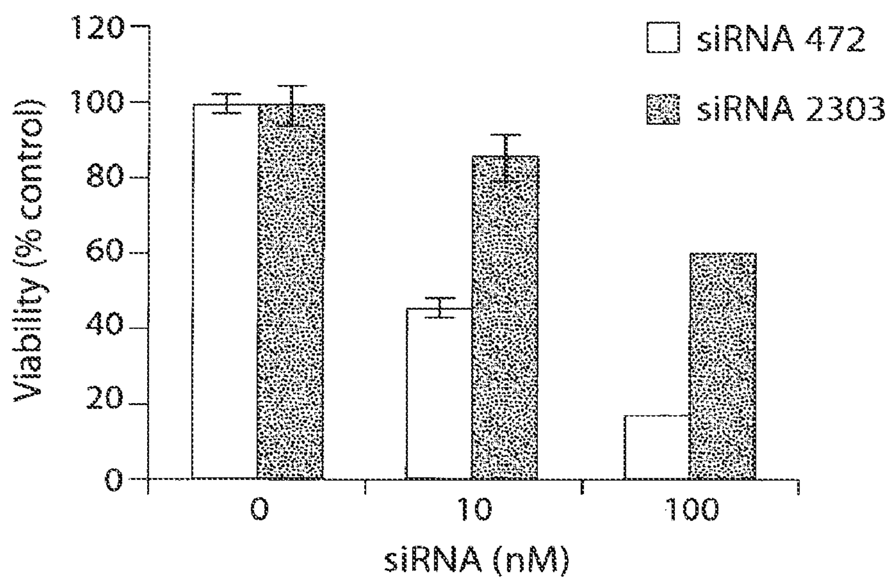


Fig. 31C

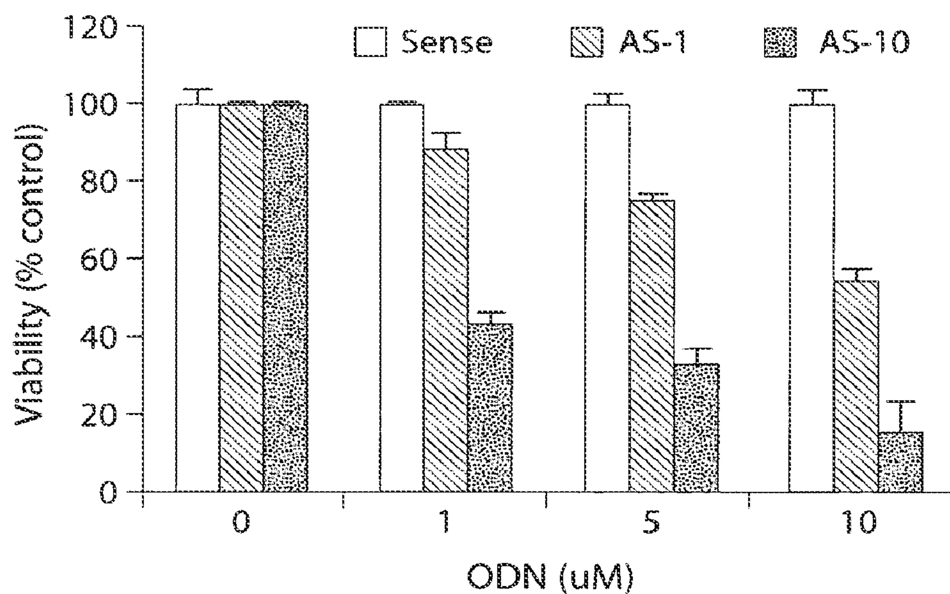


Fig. 31D

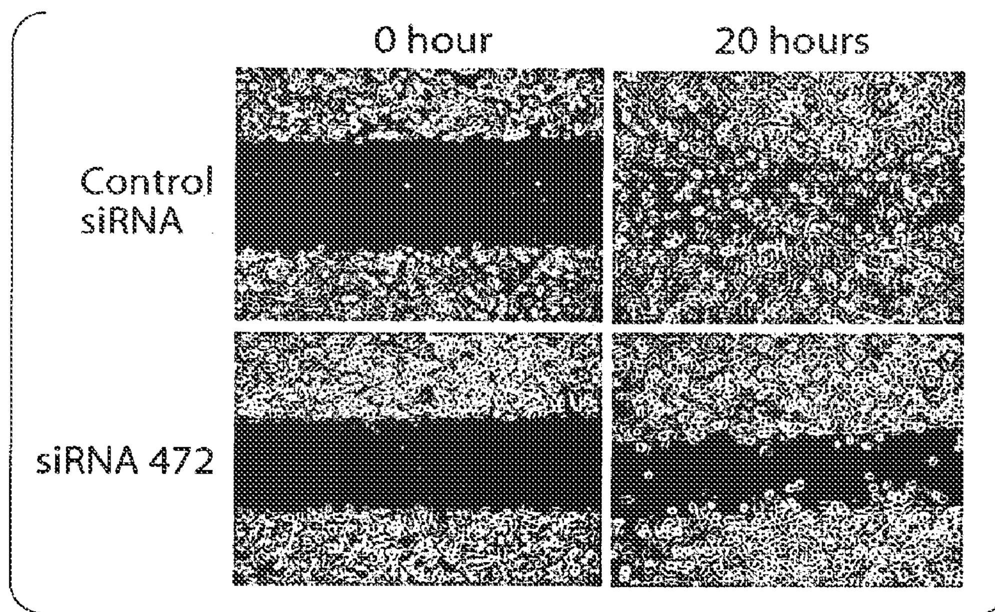


Fig. 31E

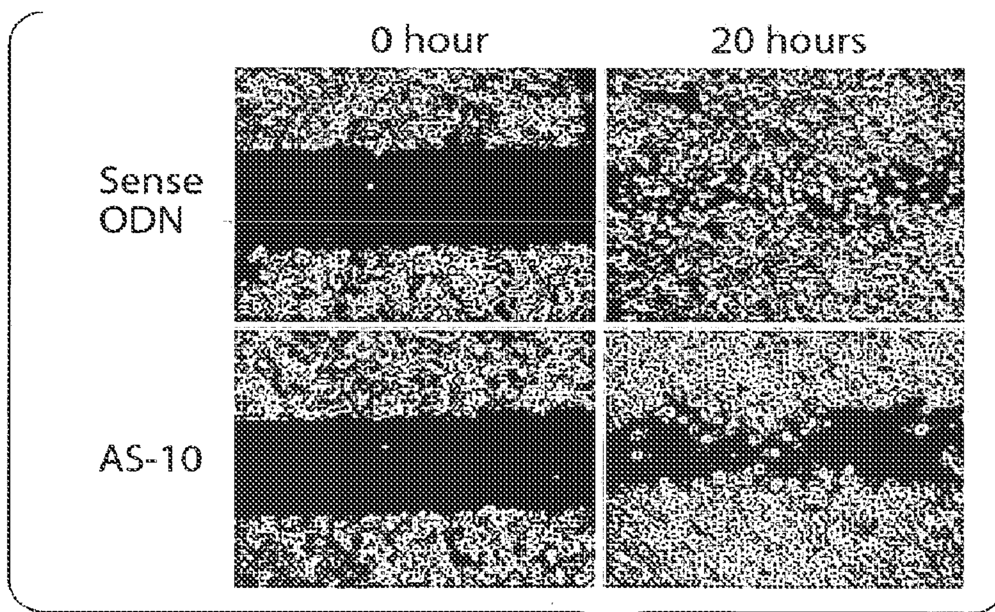


Fig. 31F

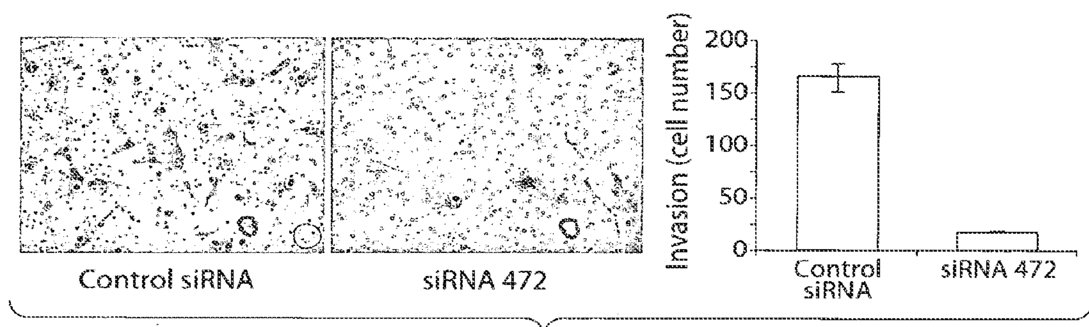


Fig. 31G

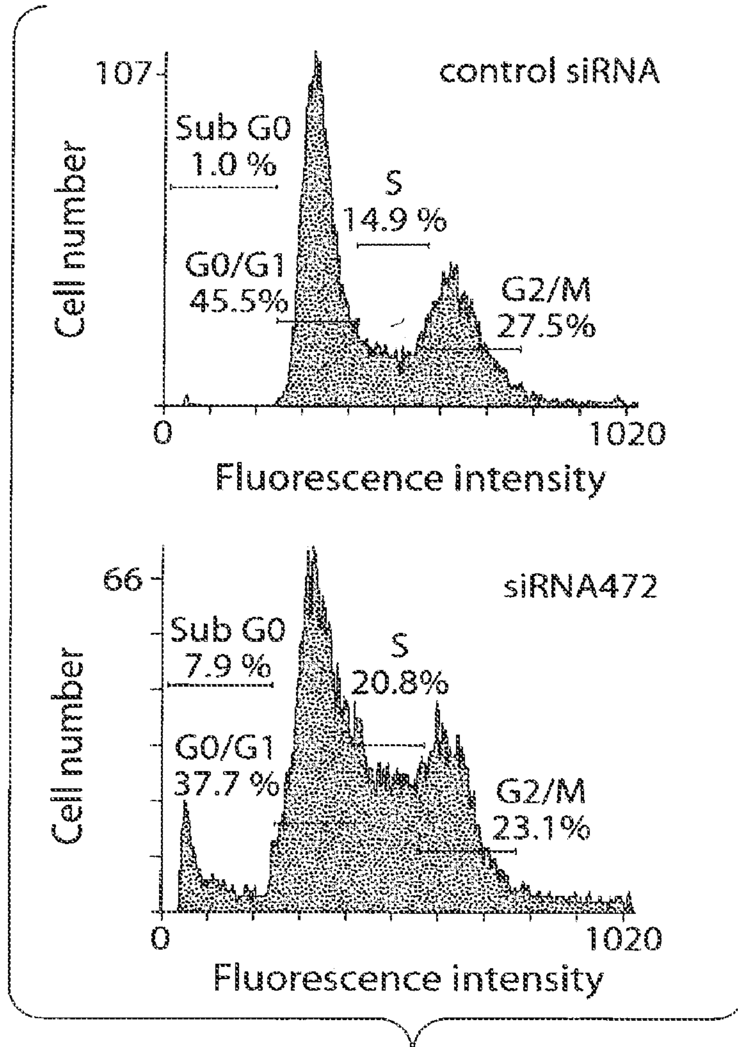


Fig. 32A

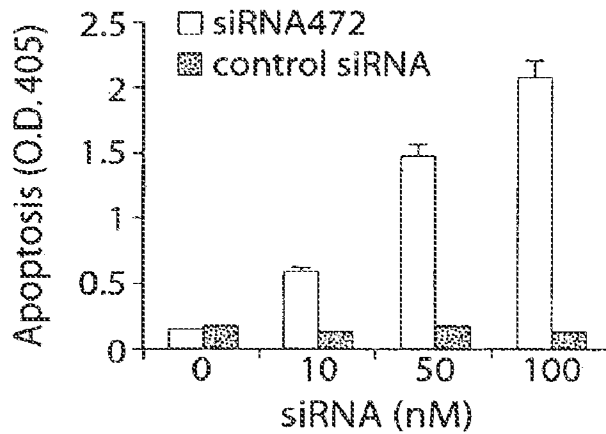


Fig. 32B

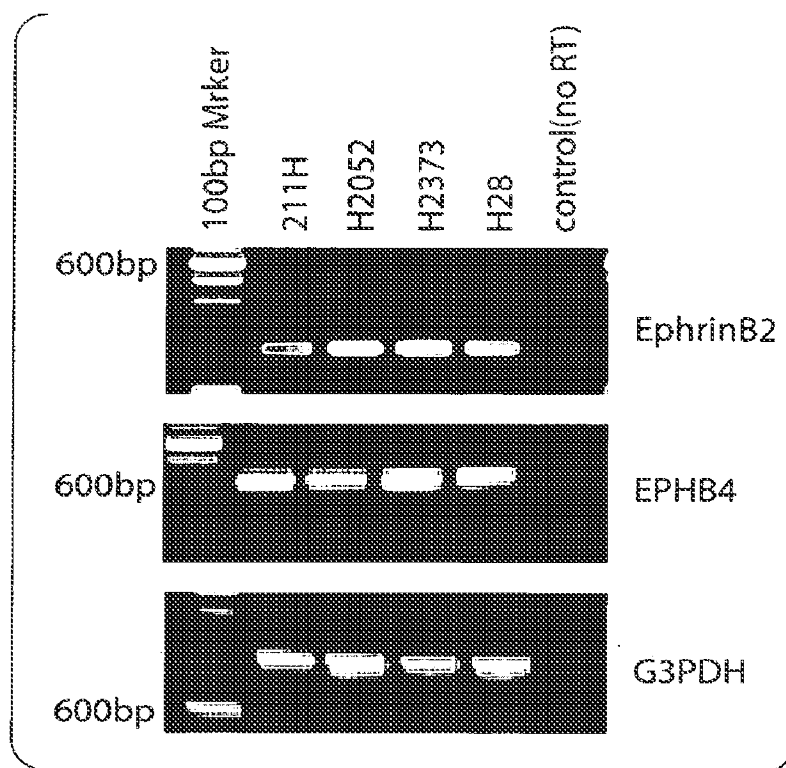


Fig. 33A

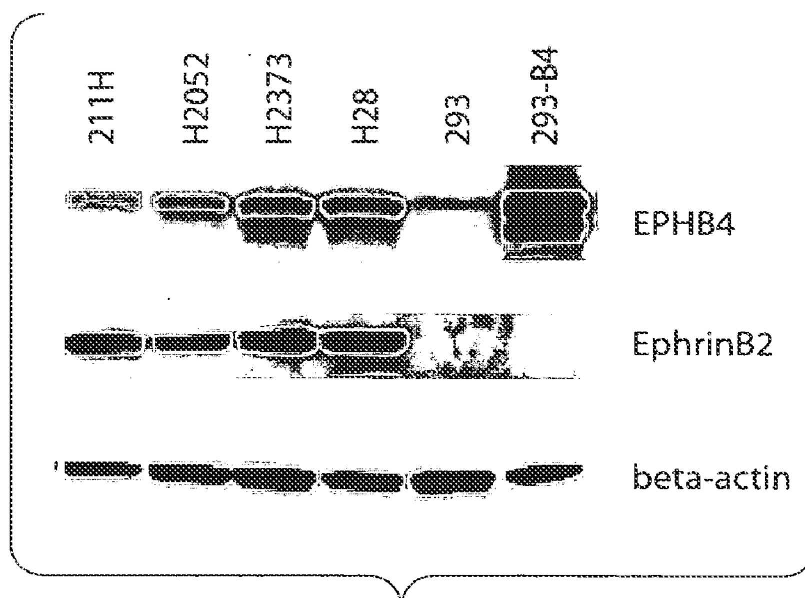


Fig. 33B

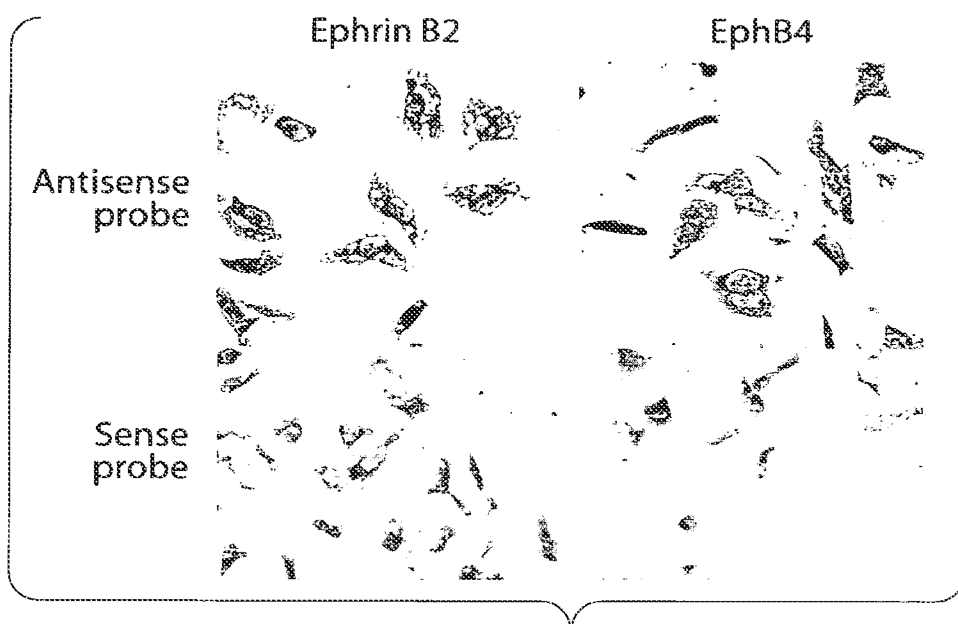


Fig. 34

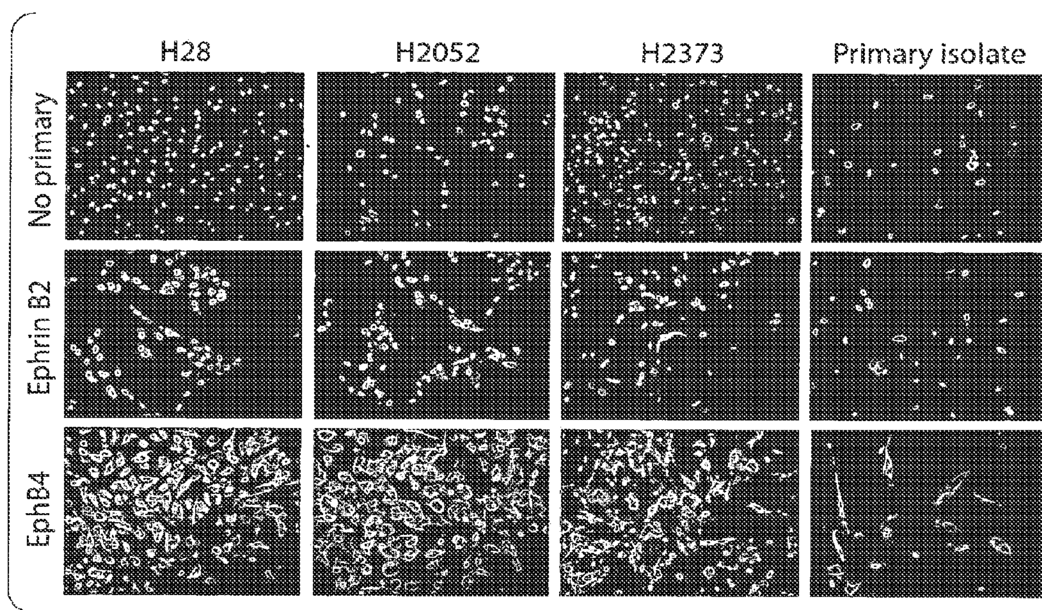


Fig. 35

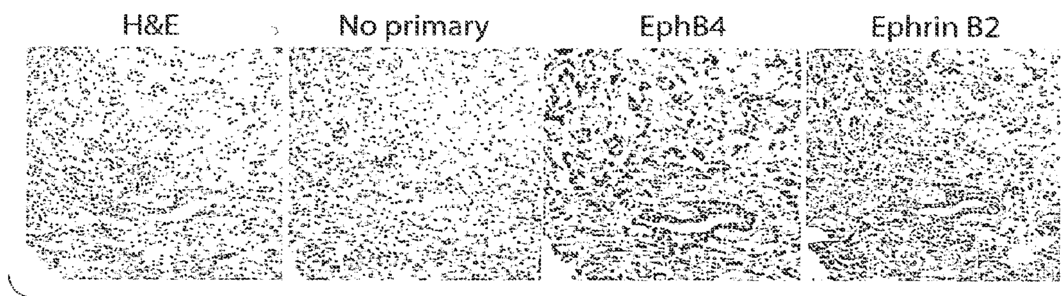


Fig. 36

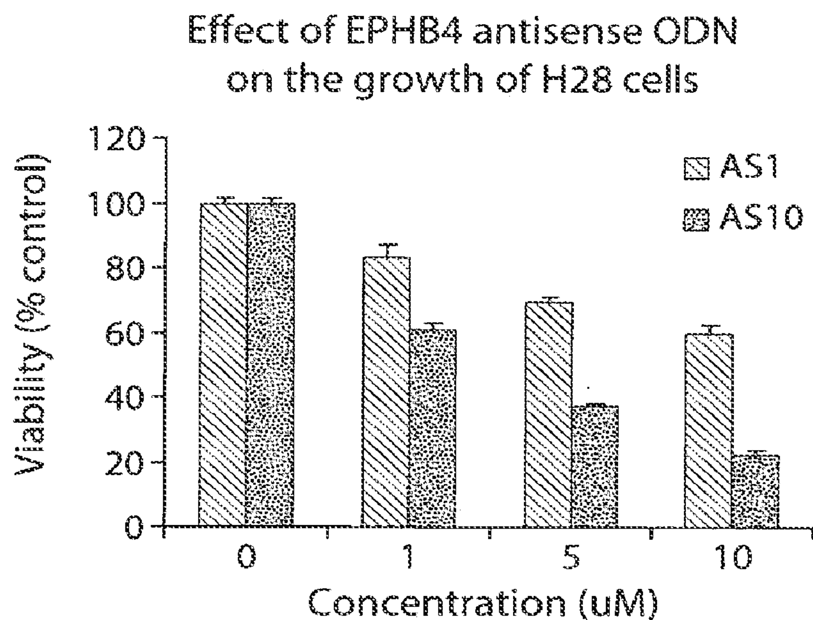


Fig. 37A

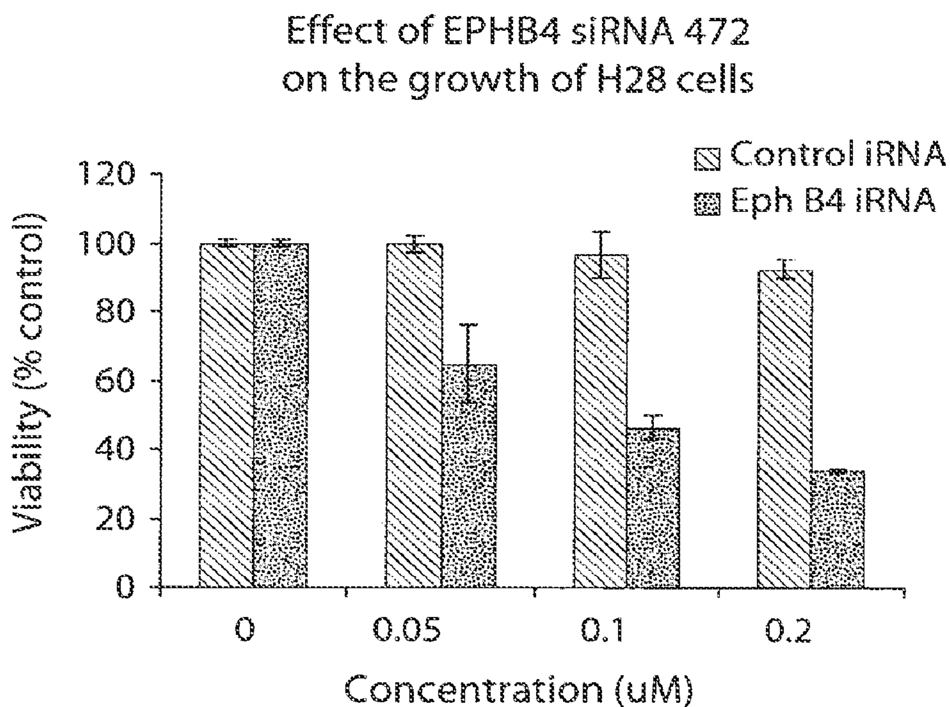


Fig. 37B

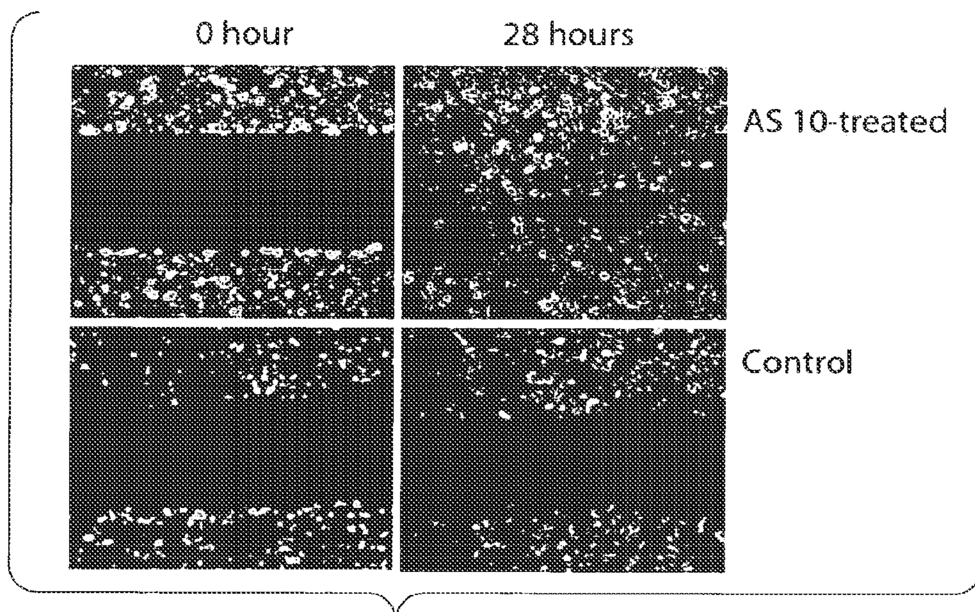


Fig. 38A

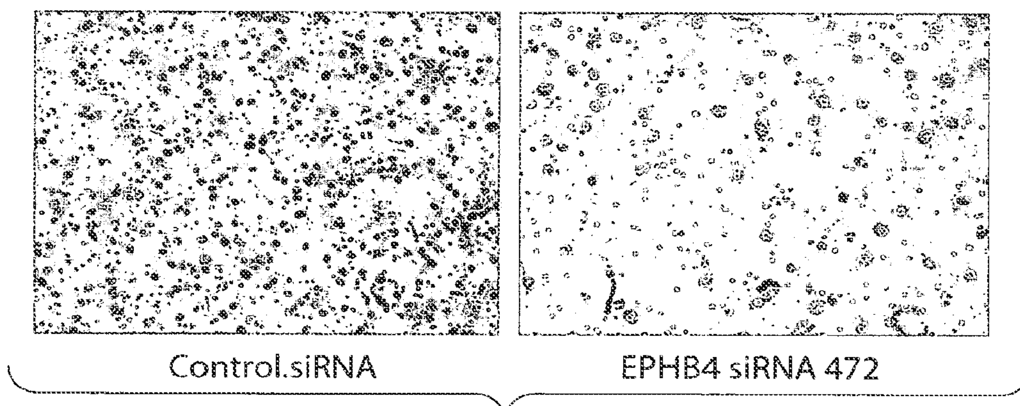


Fig. 38B

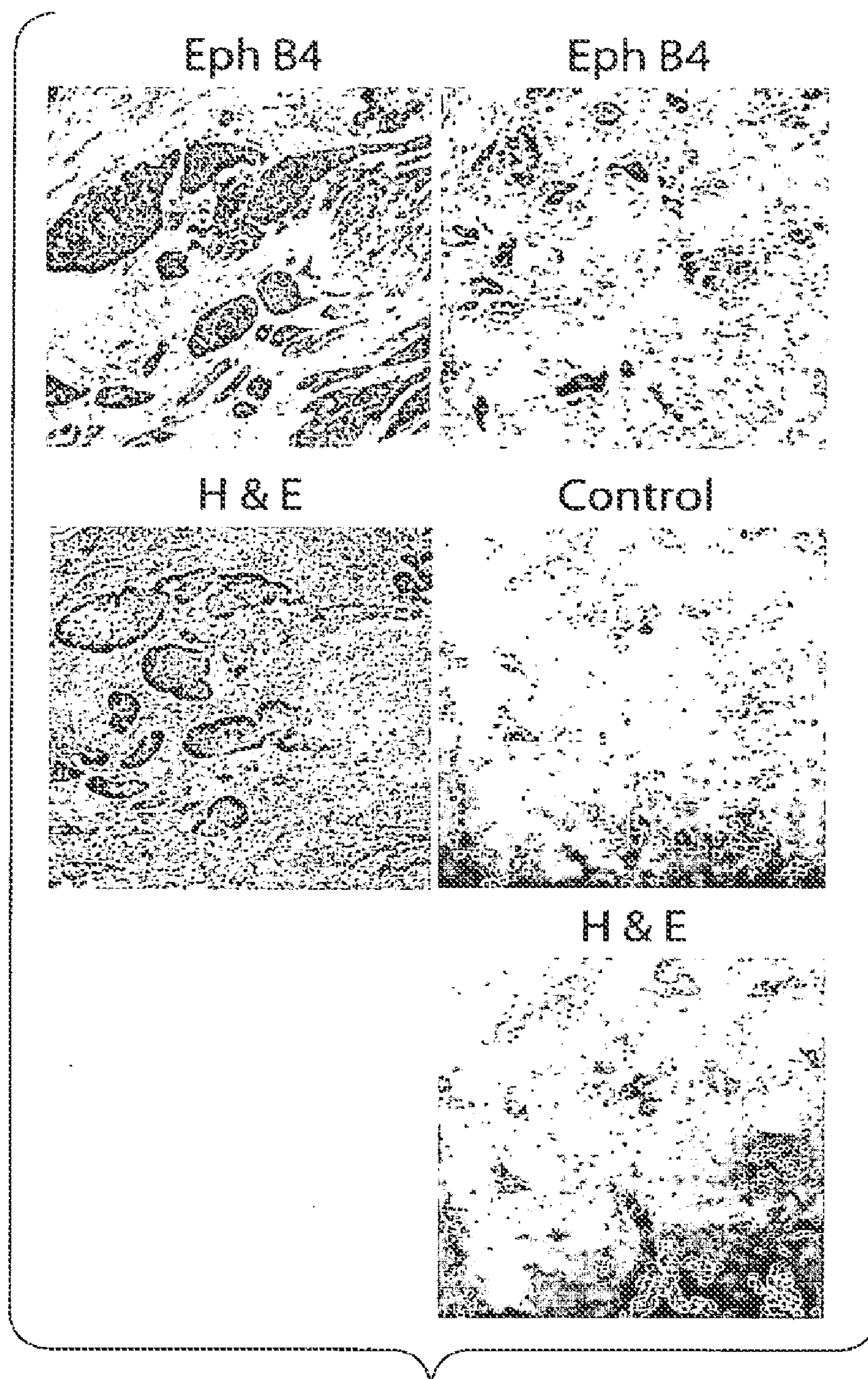


Fig. 39A

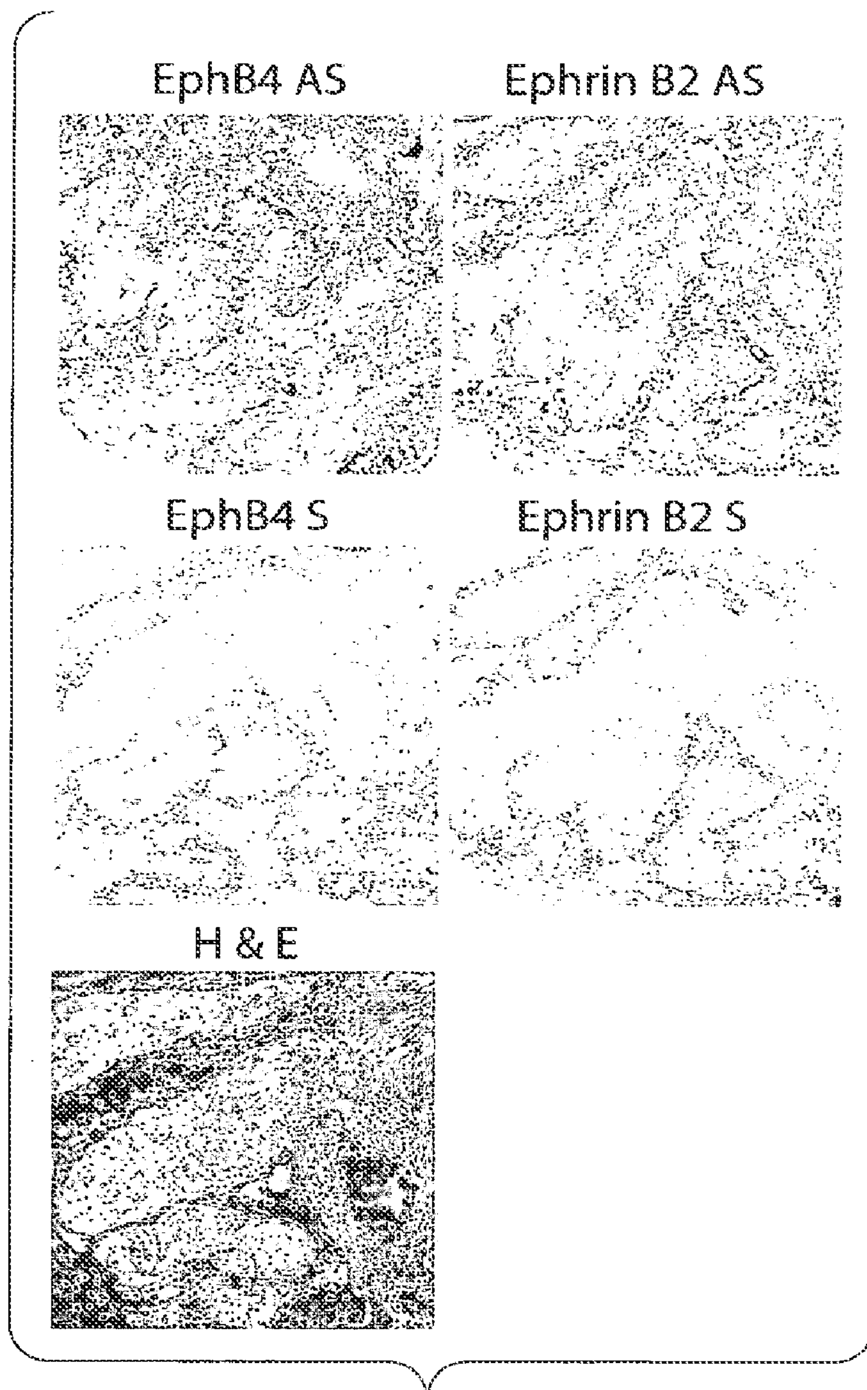


Fig. 39B

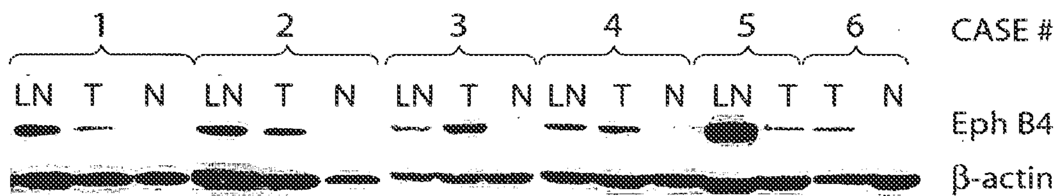


Fig. 39C

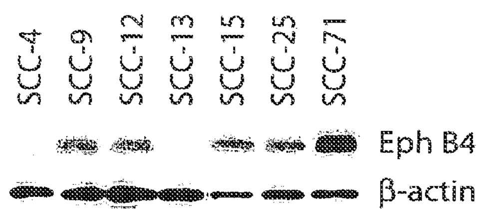


Fig. 40A

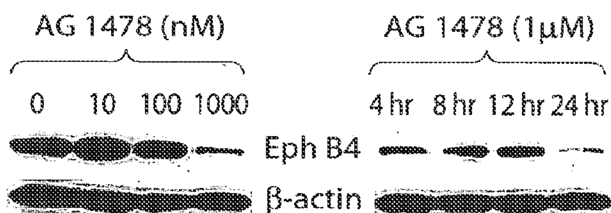


Fig. 40B

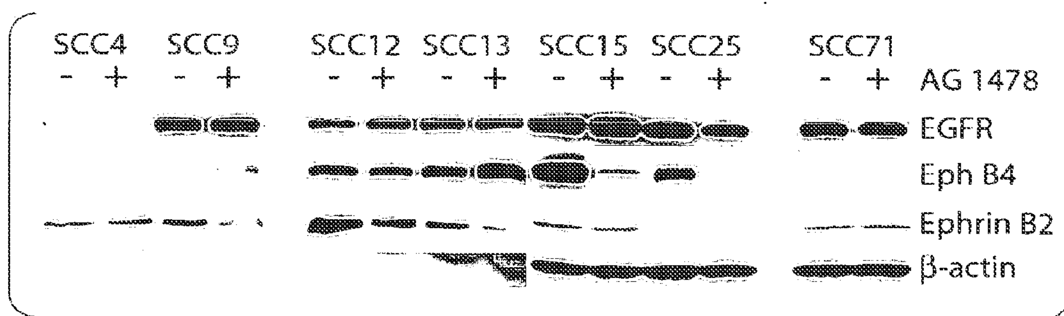


Fig. 40C

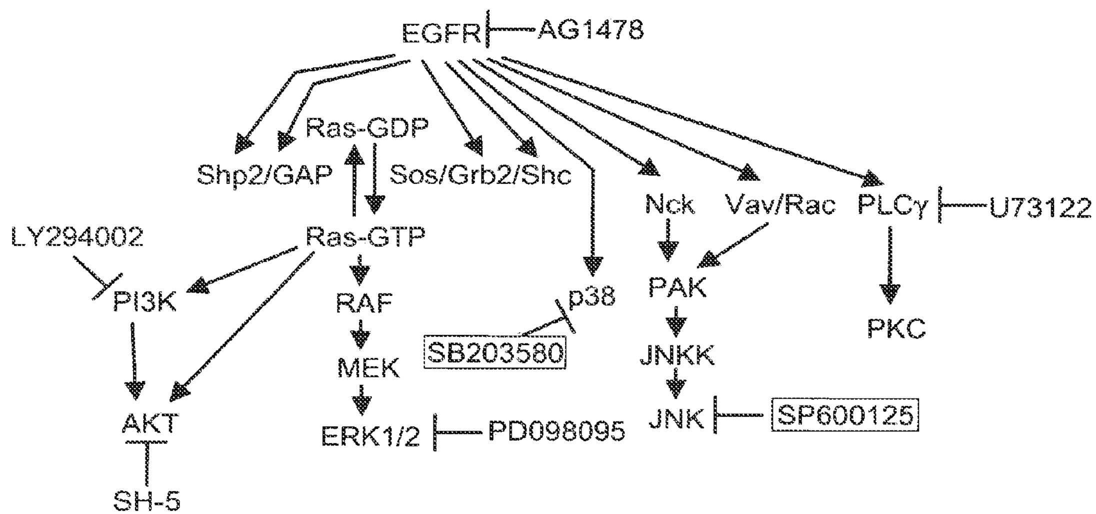


Fig. 41A

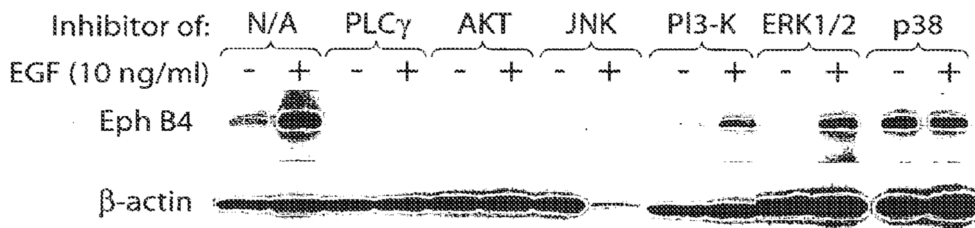


Fig. 41B

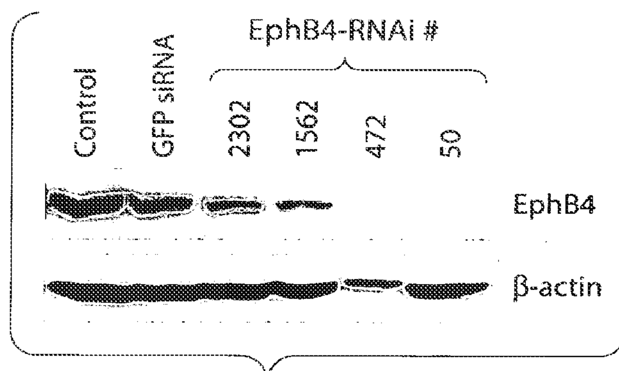


Fig. 42A

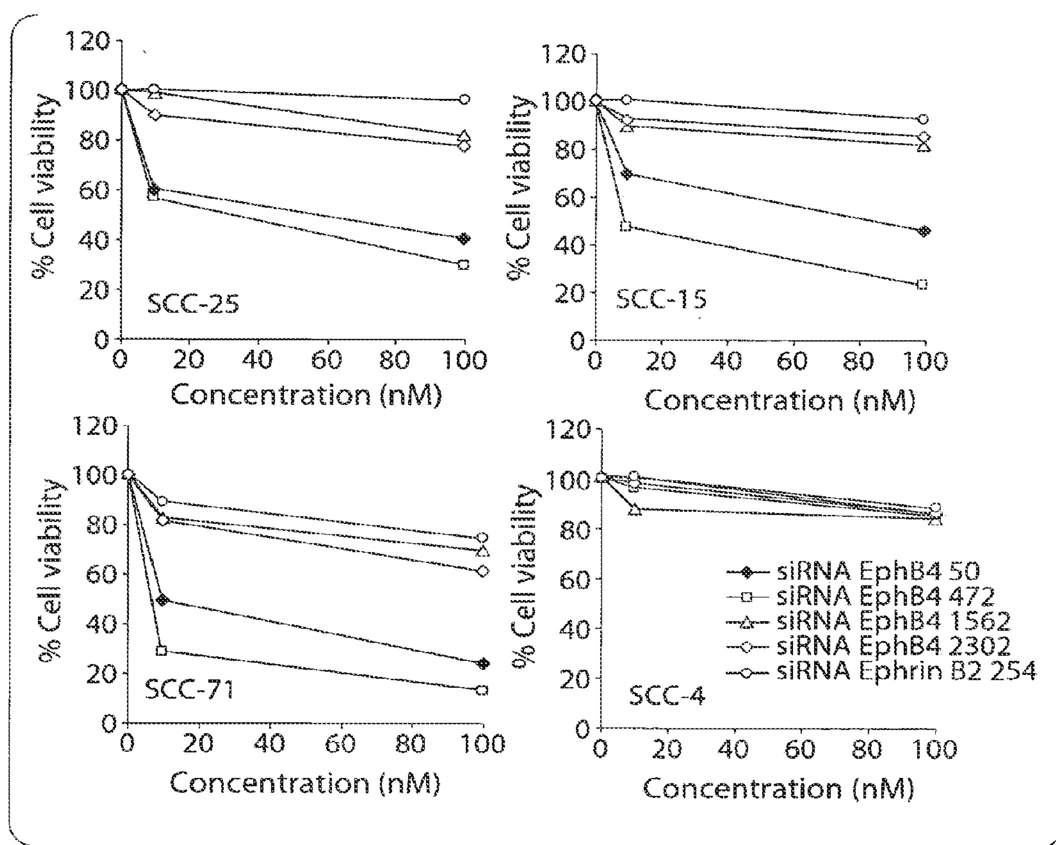


Fig. 42B

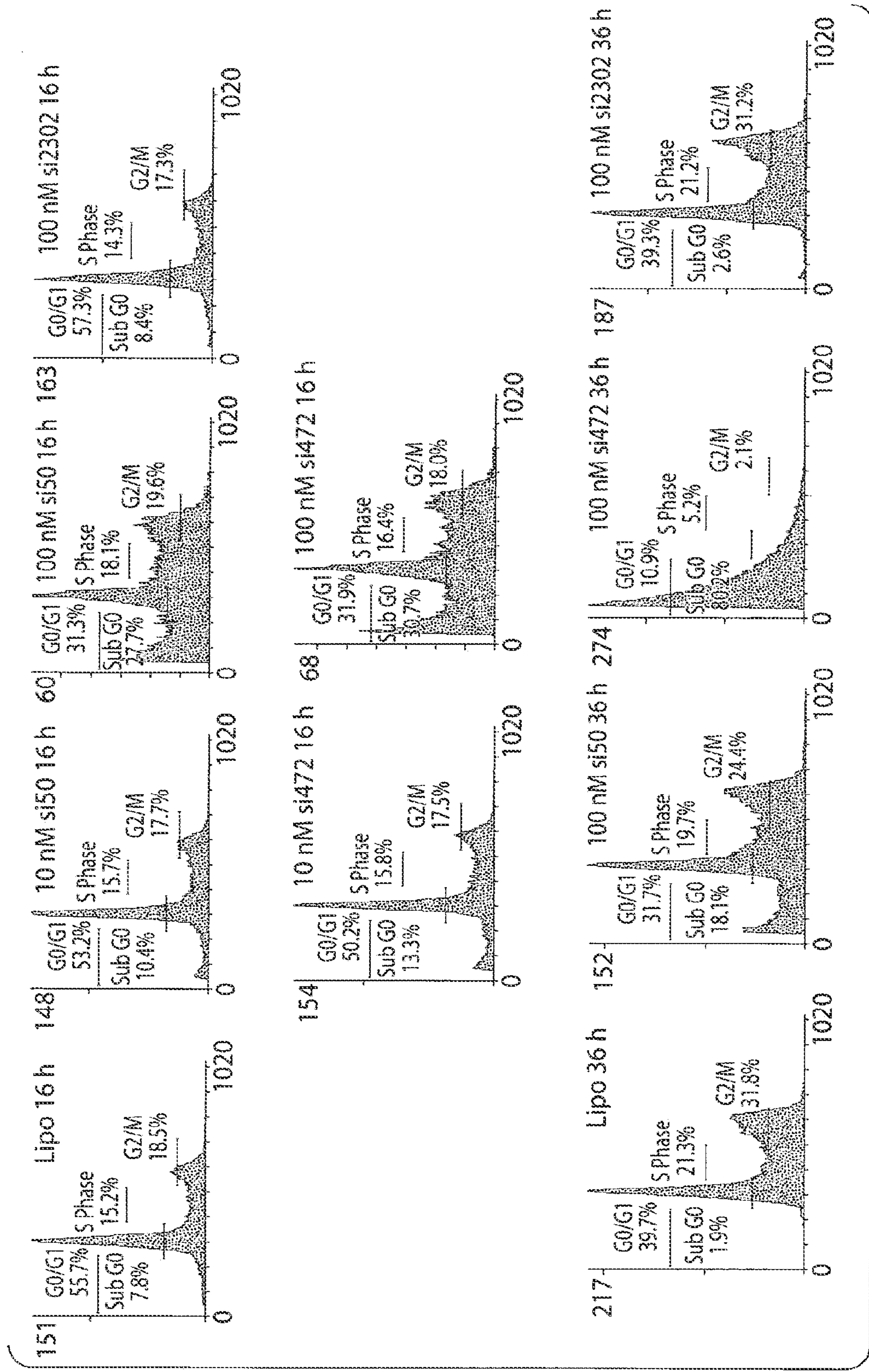


Fig. 42C

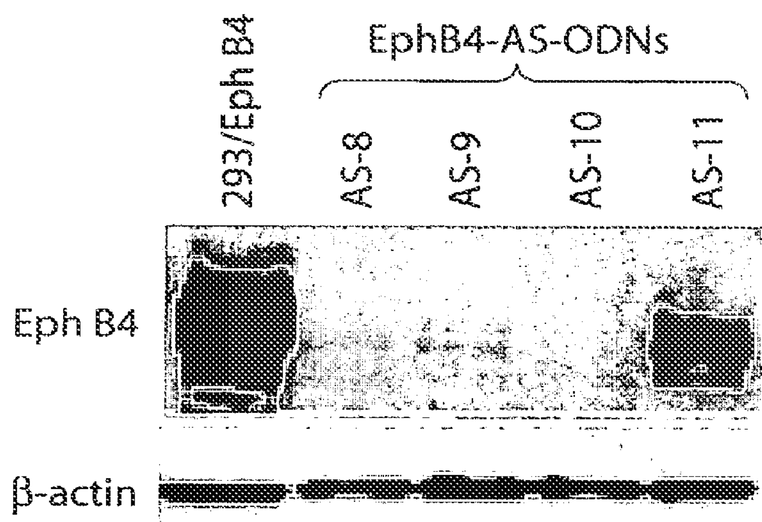


Fig. 43A

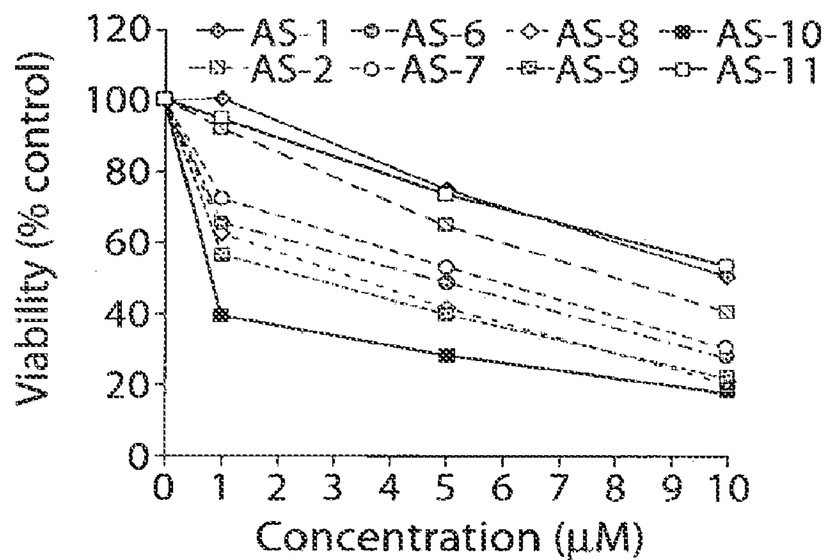


Fig. 43B

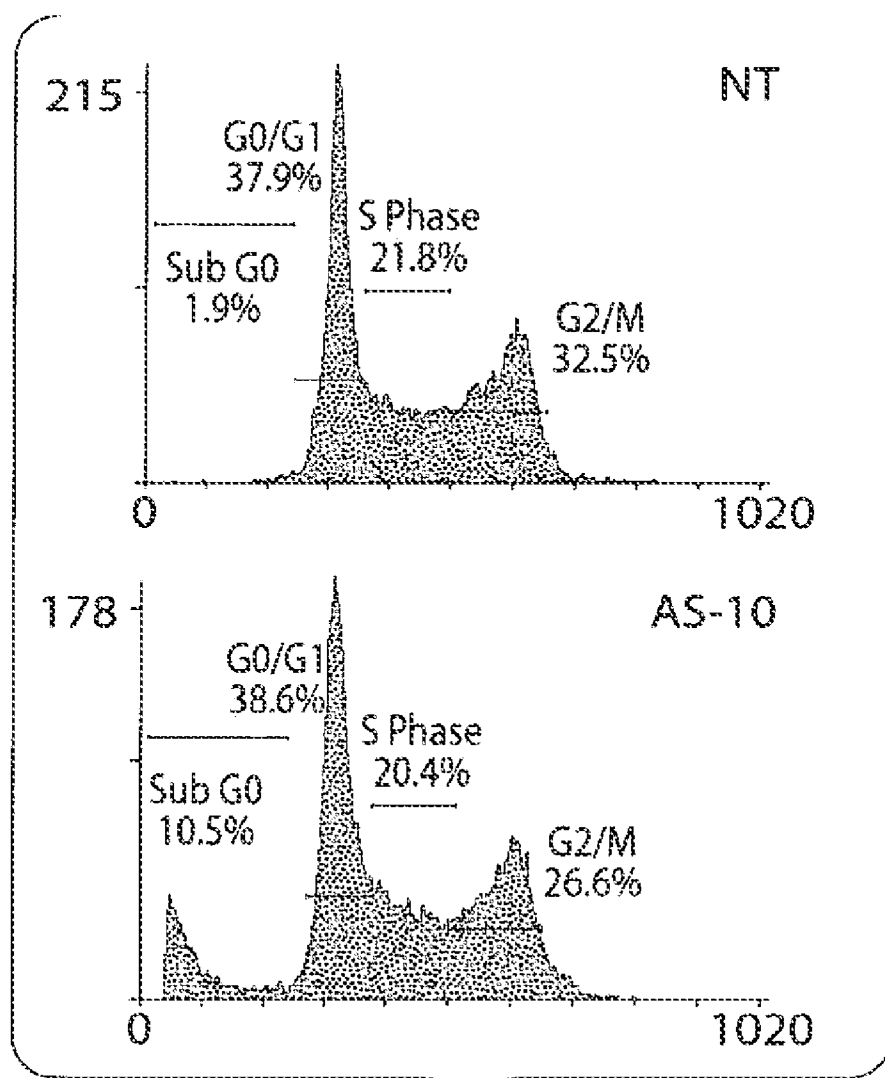


Fig. 43C

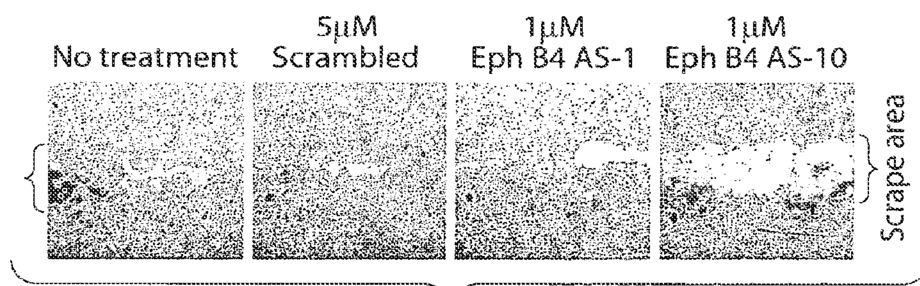


Fig. 43D

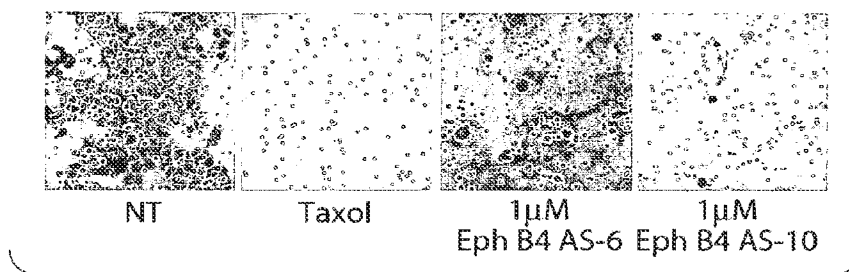


Fig. 43E

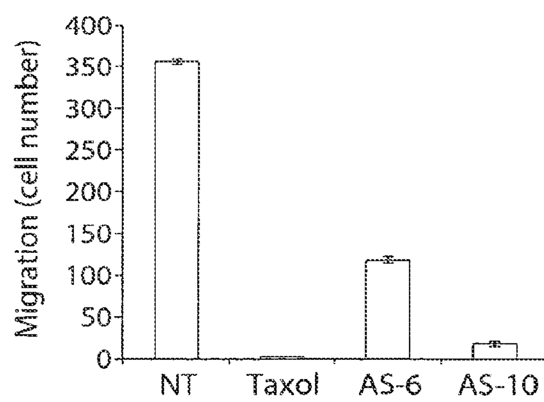


Fig. 43F

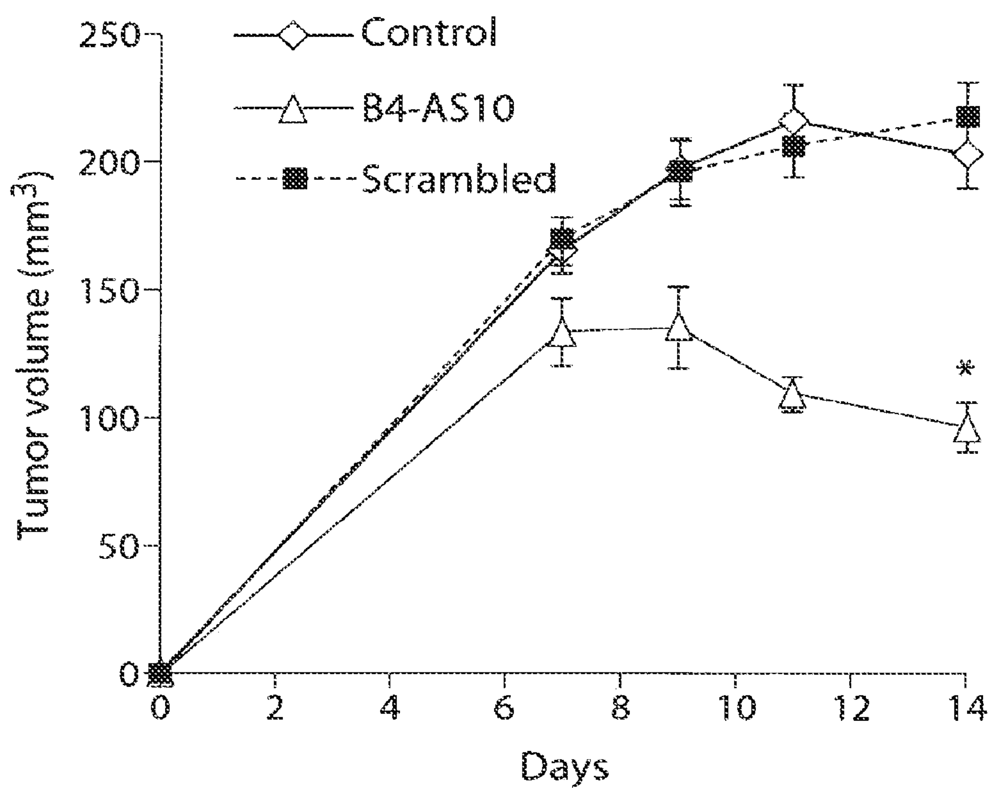


Fig. 44

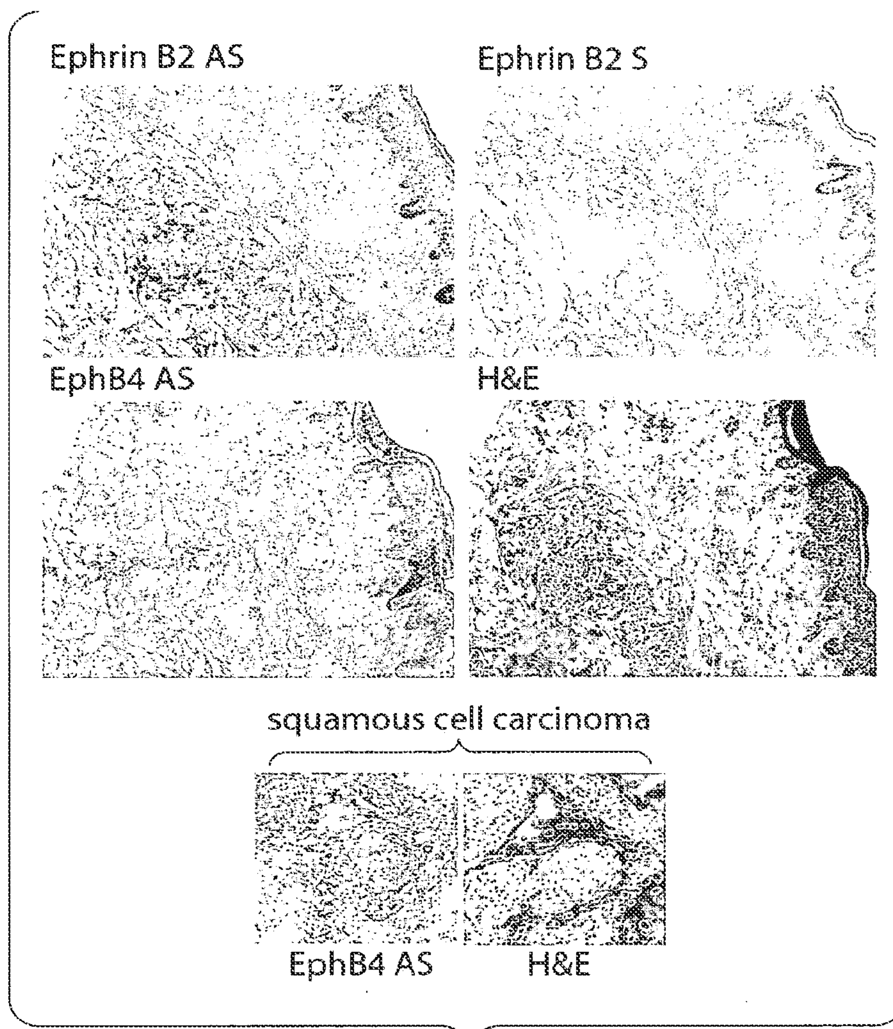


Fig. 45A

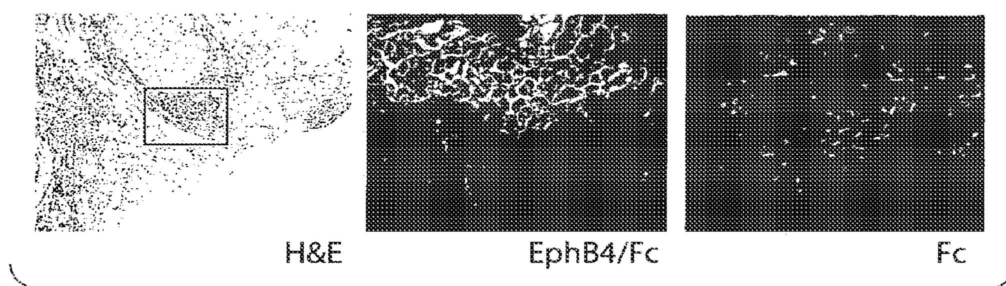


Fig. 45B

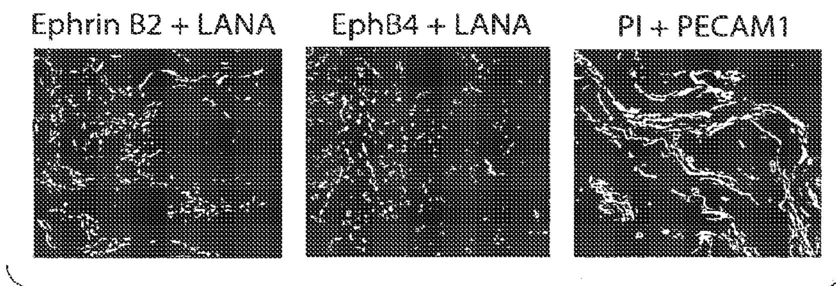


Fig. 45C

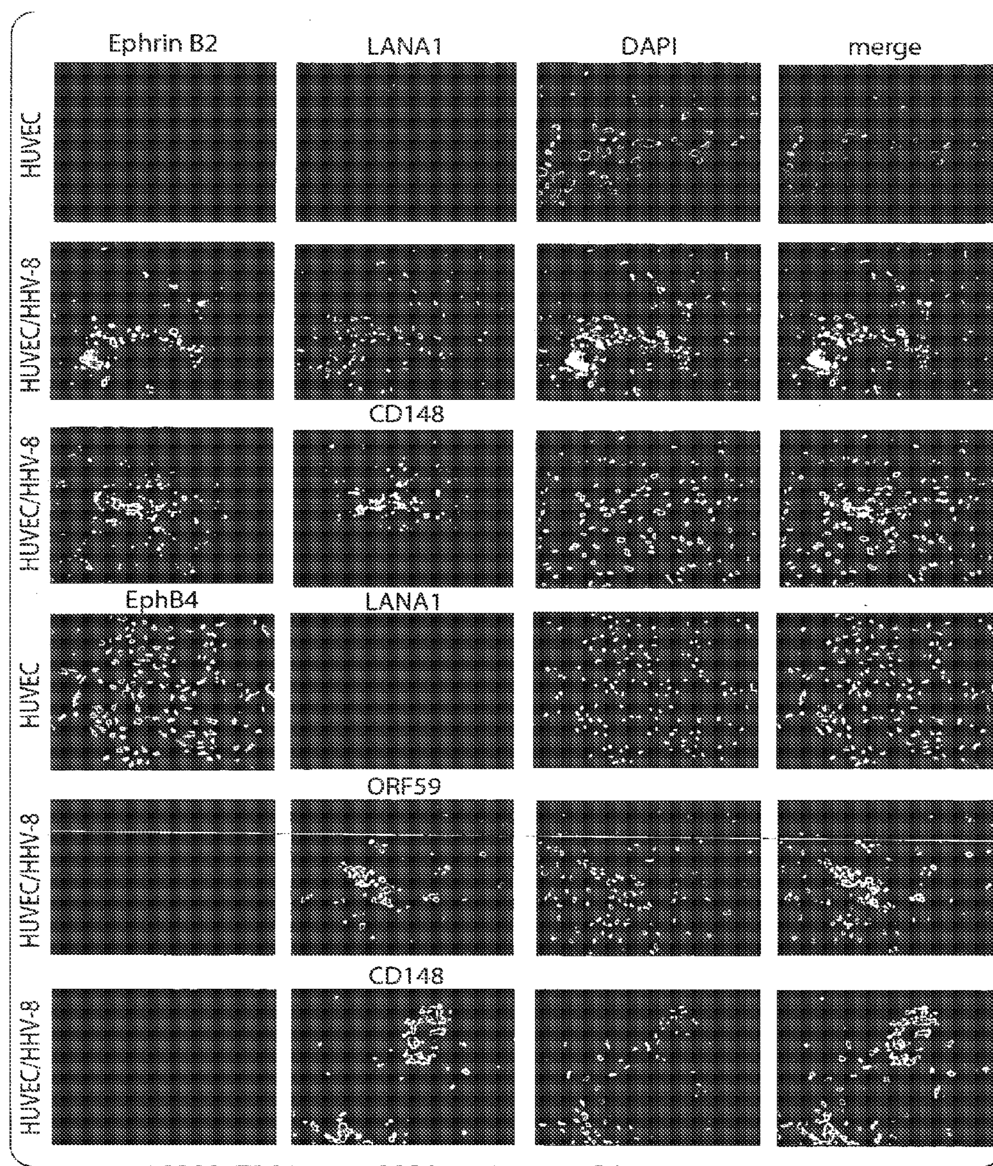


Fig. 46A

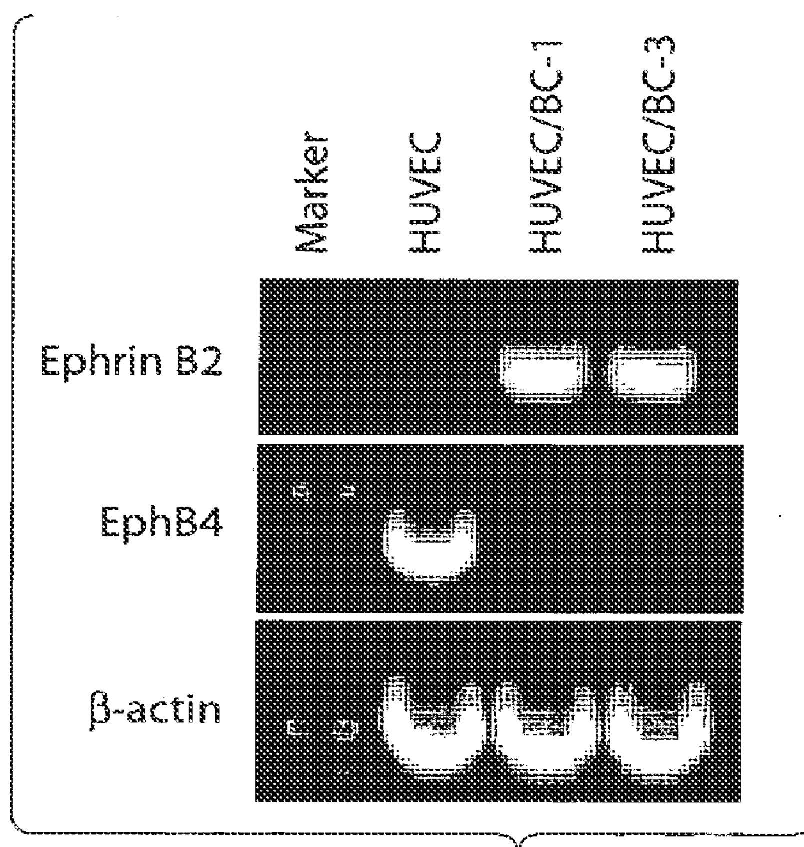


Fig. 46B

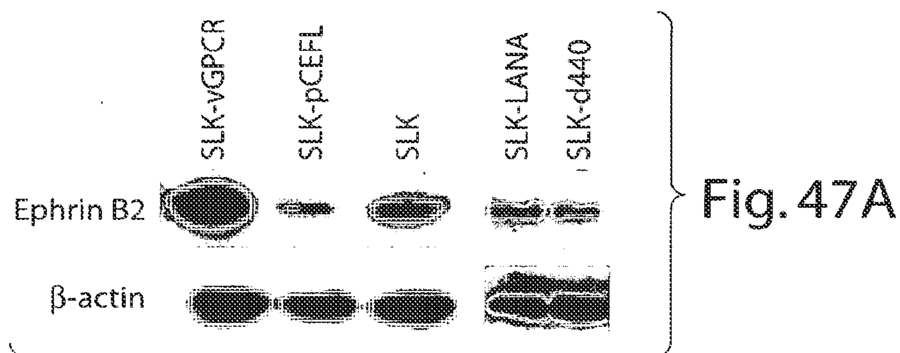


Fig. 47A

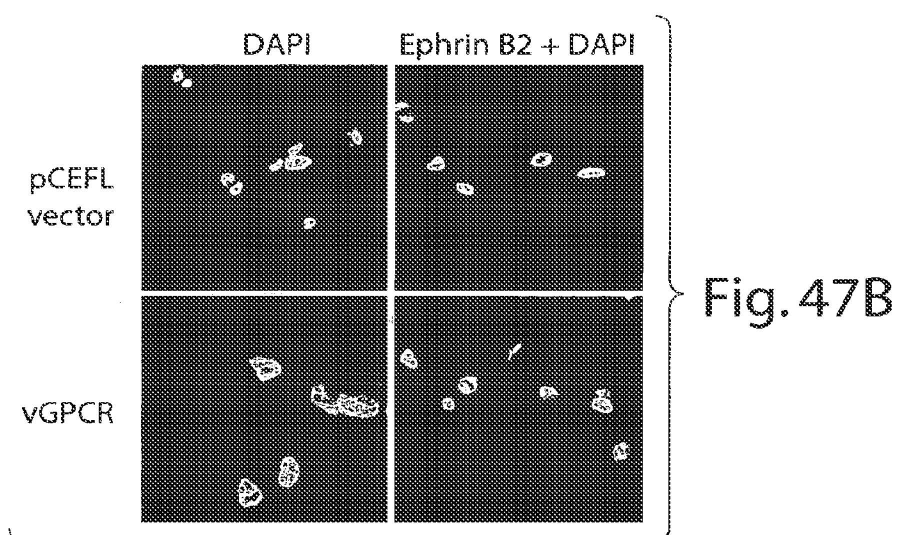


Fig. 47B

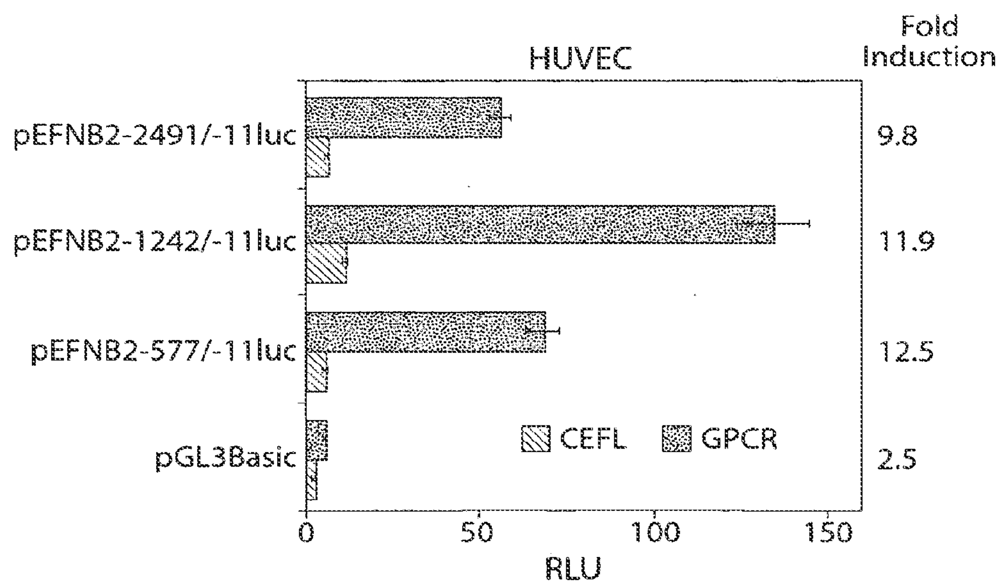


Fig. 47C

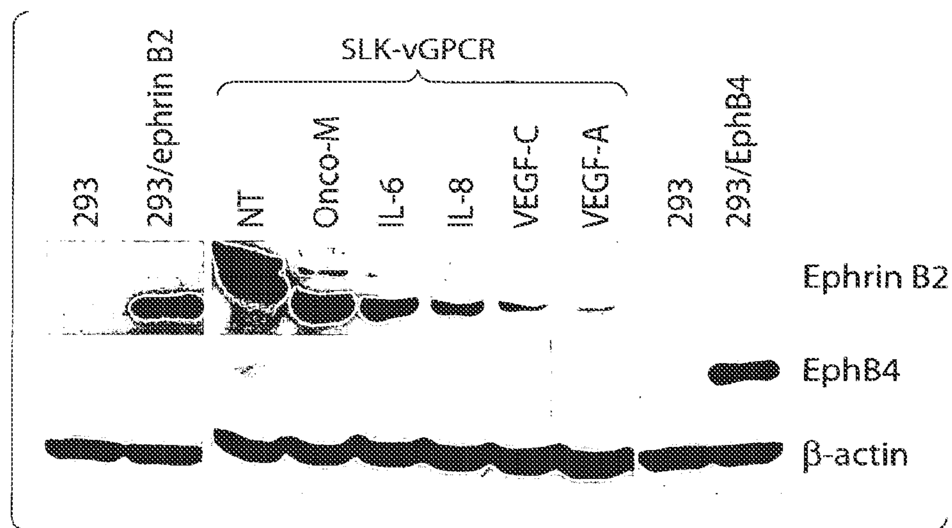


Fig. 48A

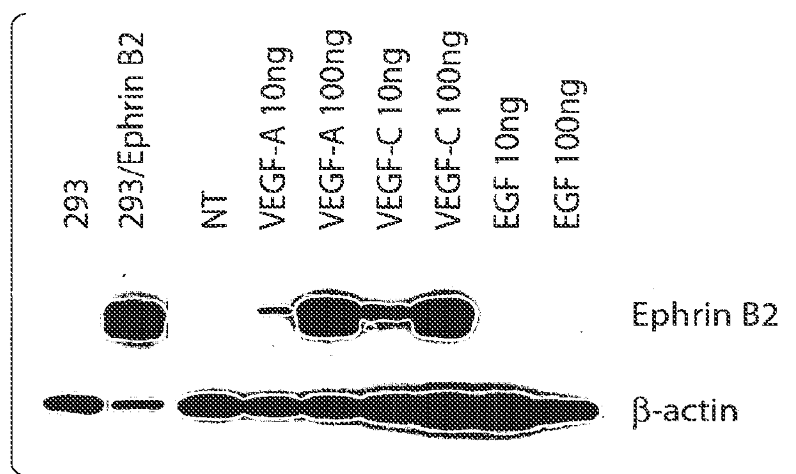


Fig. 48B

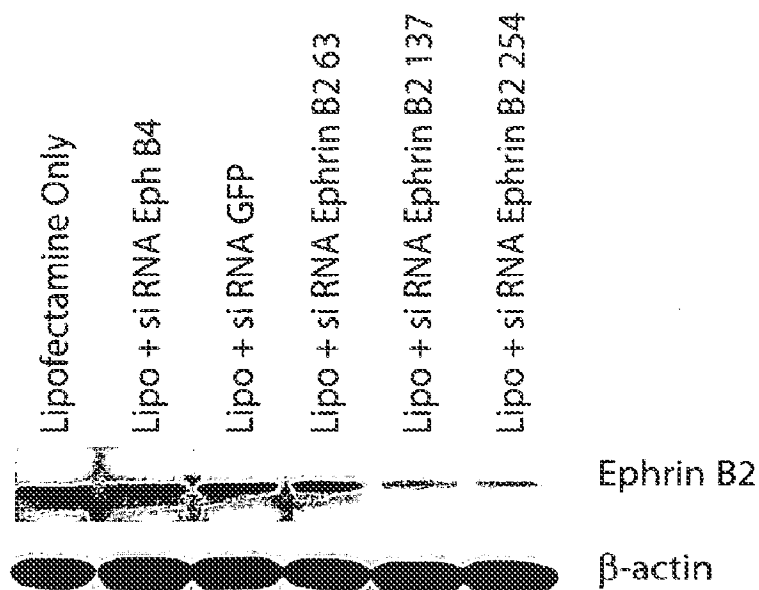


Fig. 49A

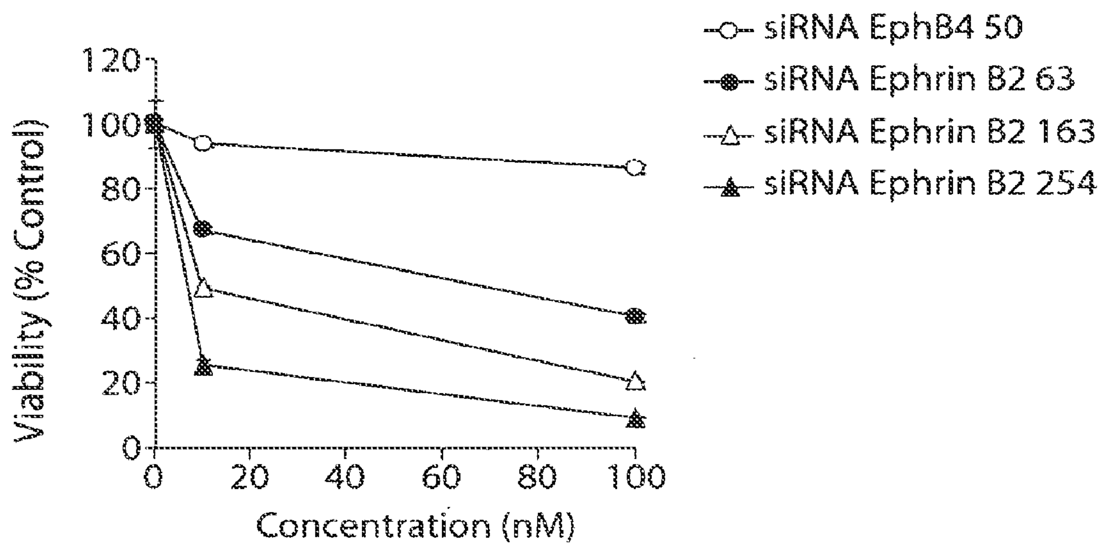


Fig. 49B

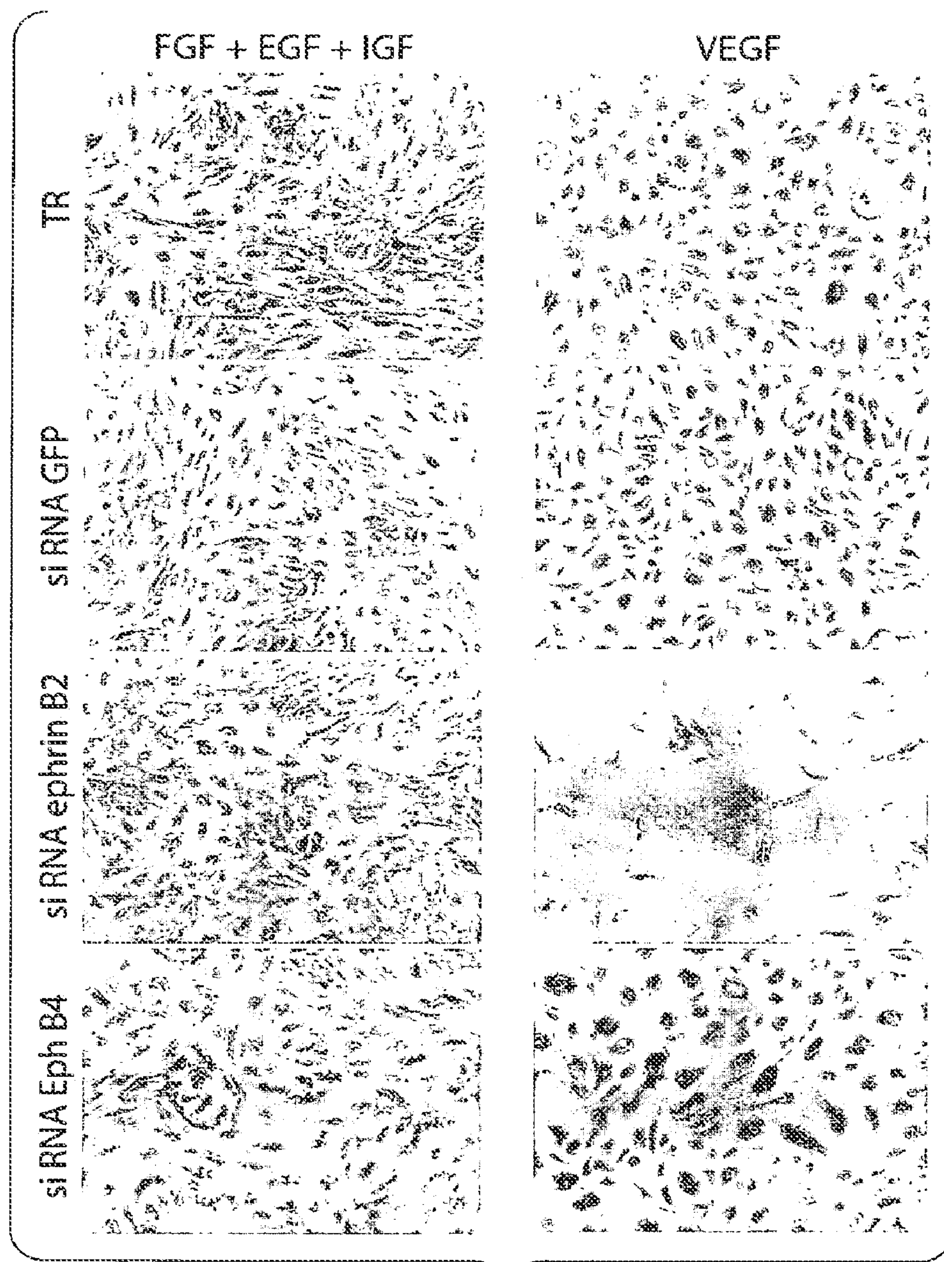


Fig. 49C

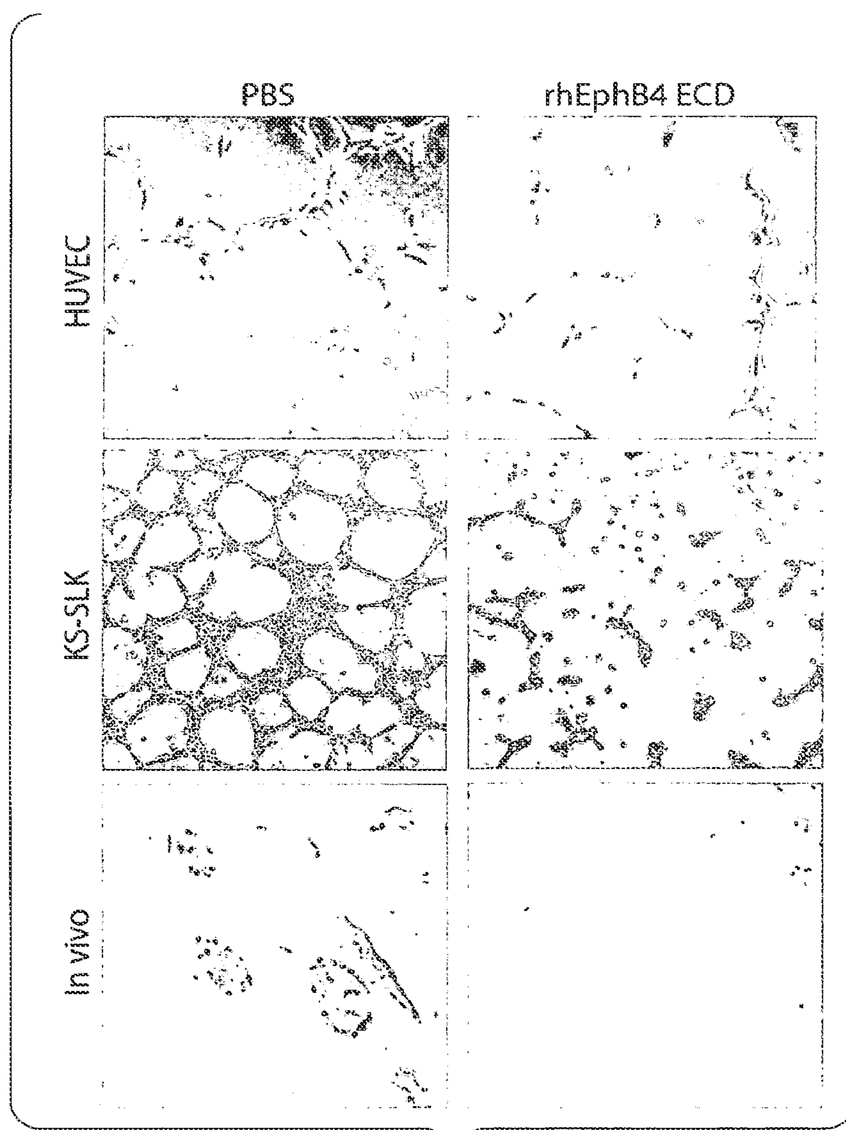


Fig. 50

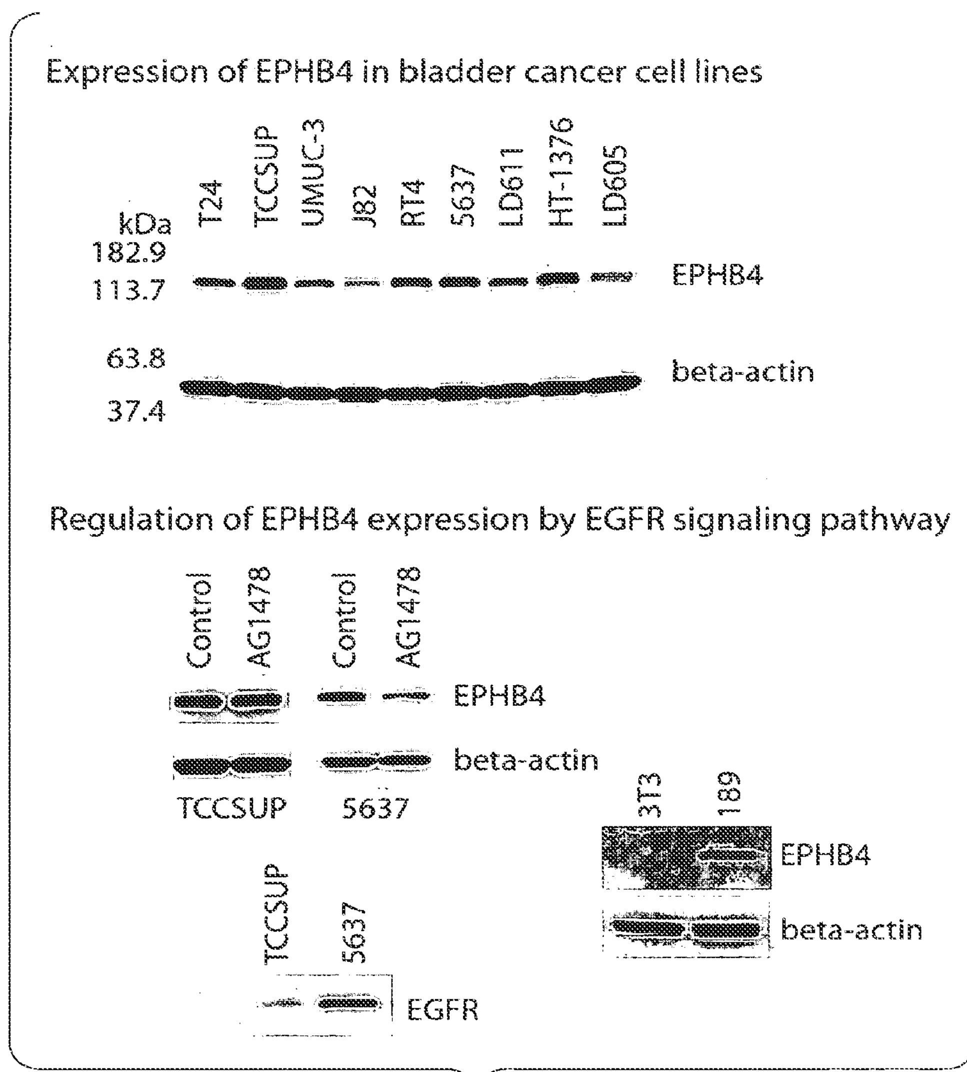


Fig. 51

Transfection of p53 inhibit the expression of EPHB4 in 5637 cell

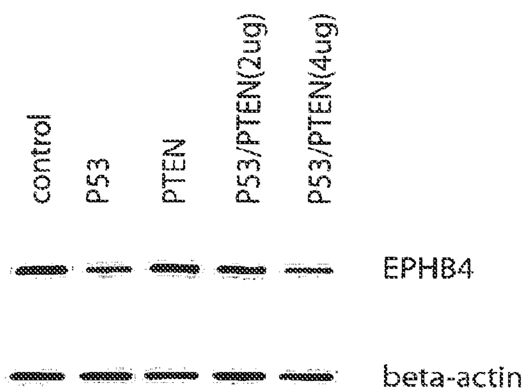


Fig. 52

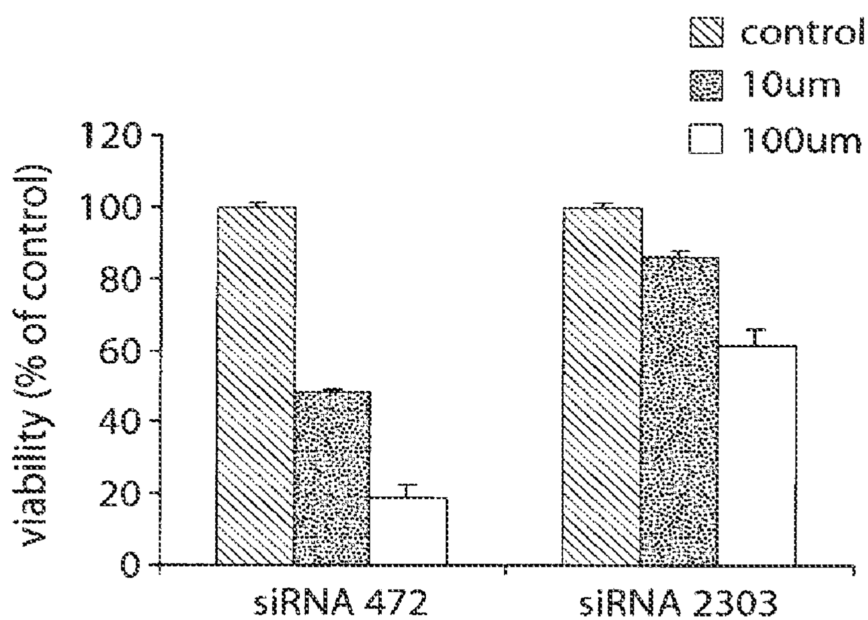


Fig. 53

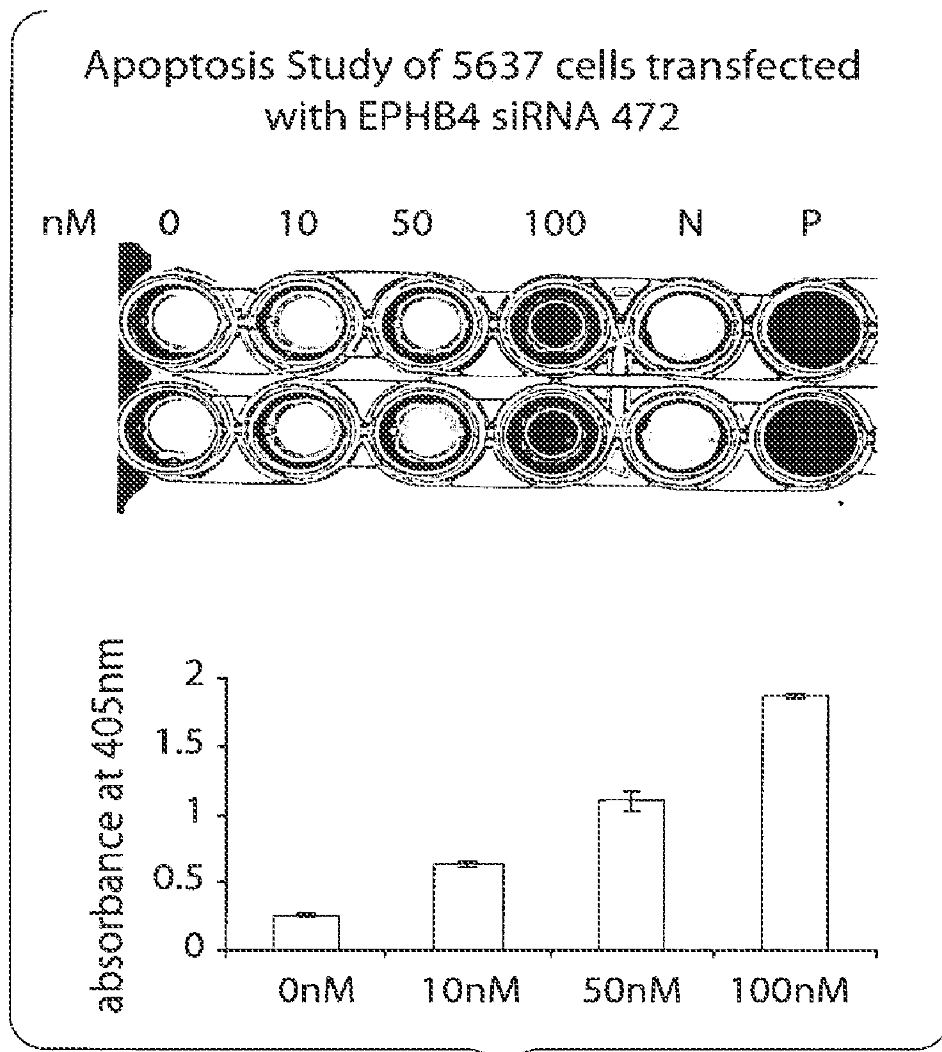


Fig. 54

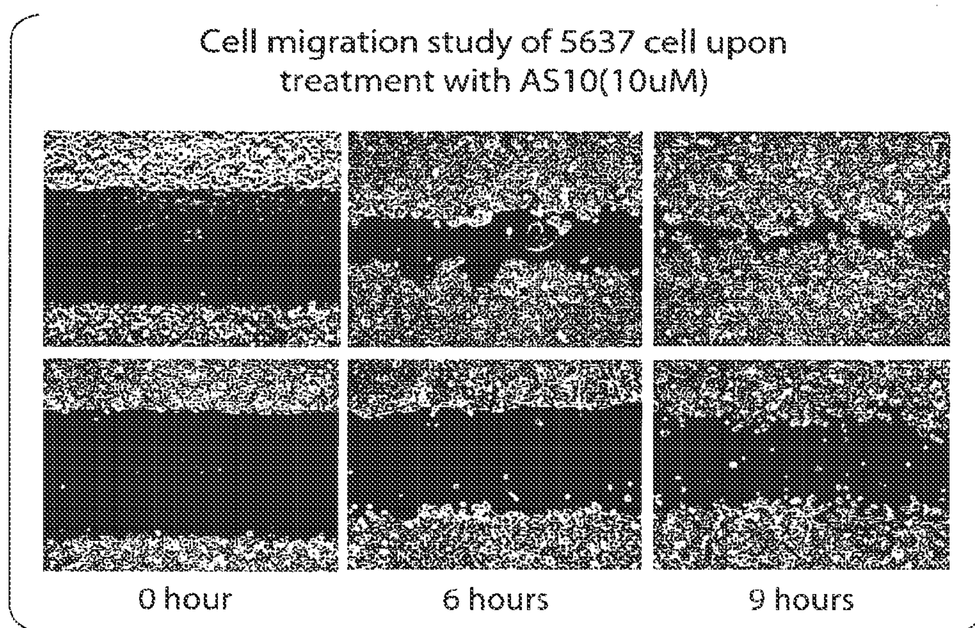
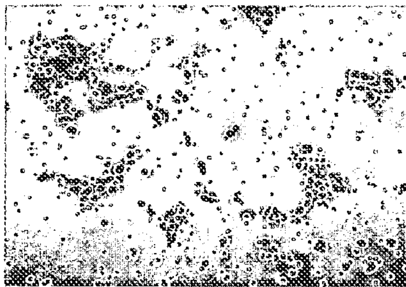
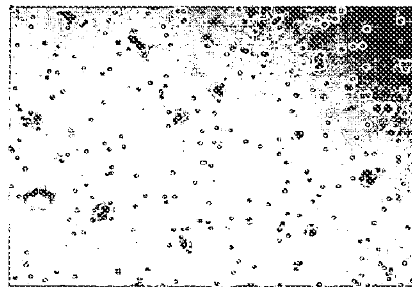


Fig. 55

Invasion study of 5637 cell transfected with siRNA 472 or control siRNA



Control



siRNA472

Fig. 56

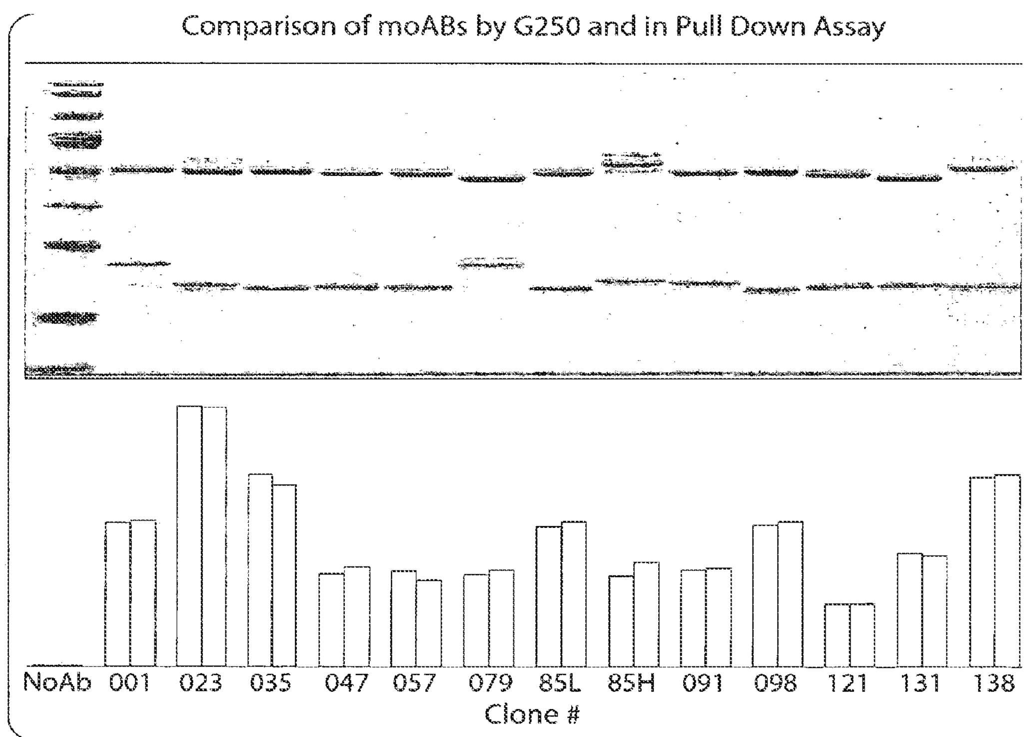


Fig. 57

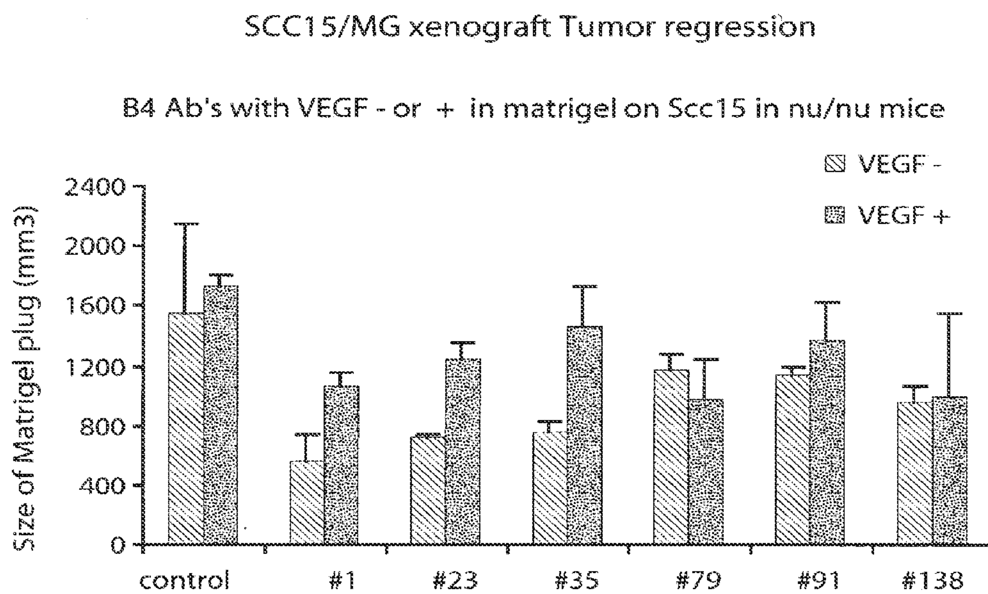


Fig. 58

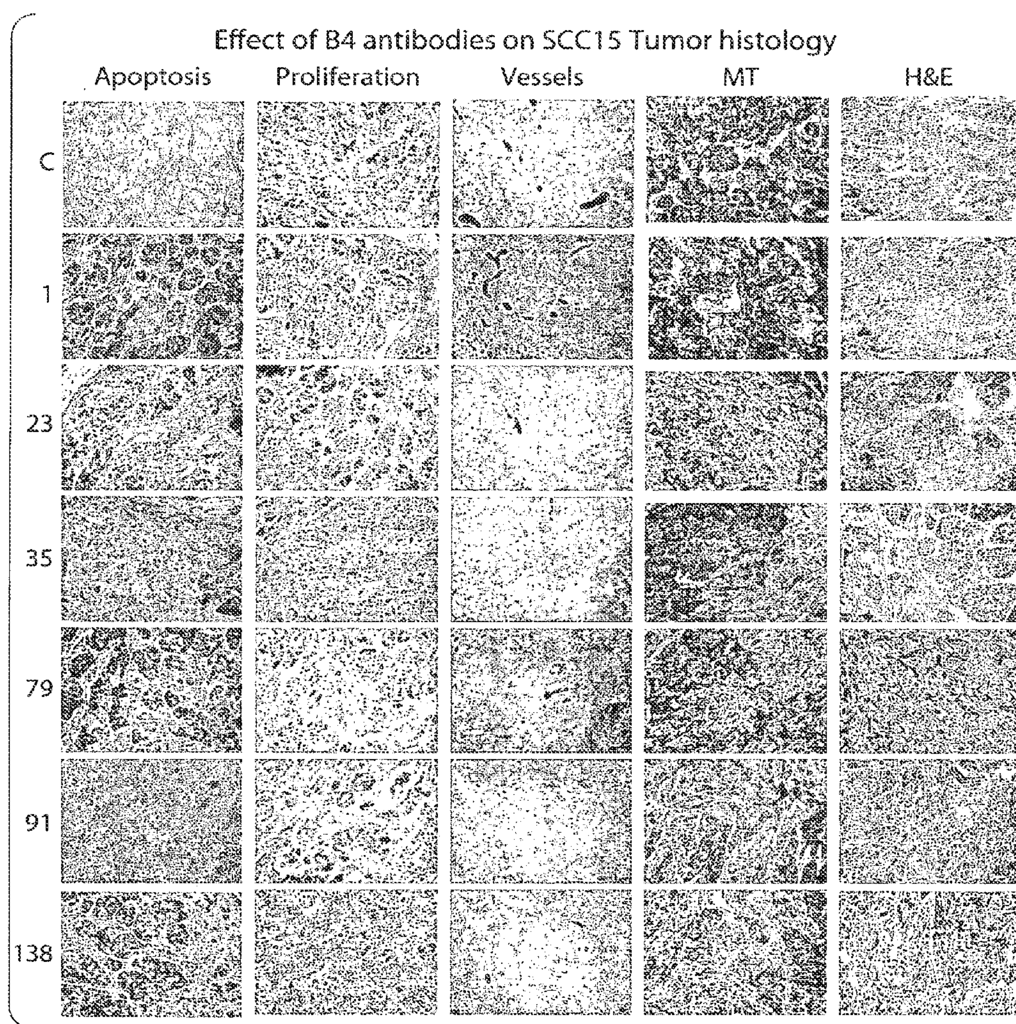


Fig. 59

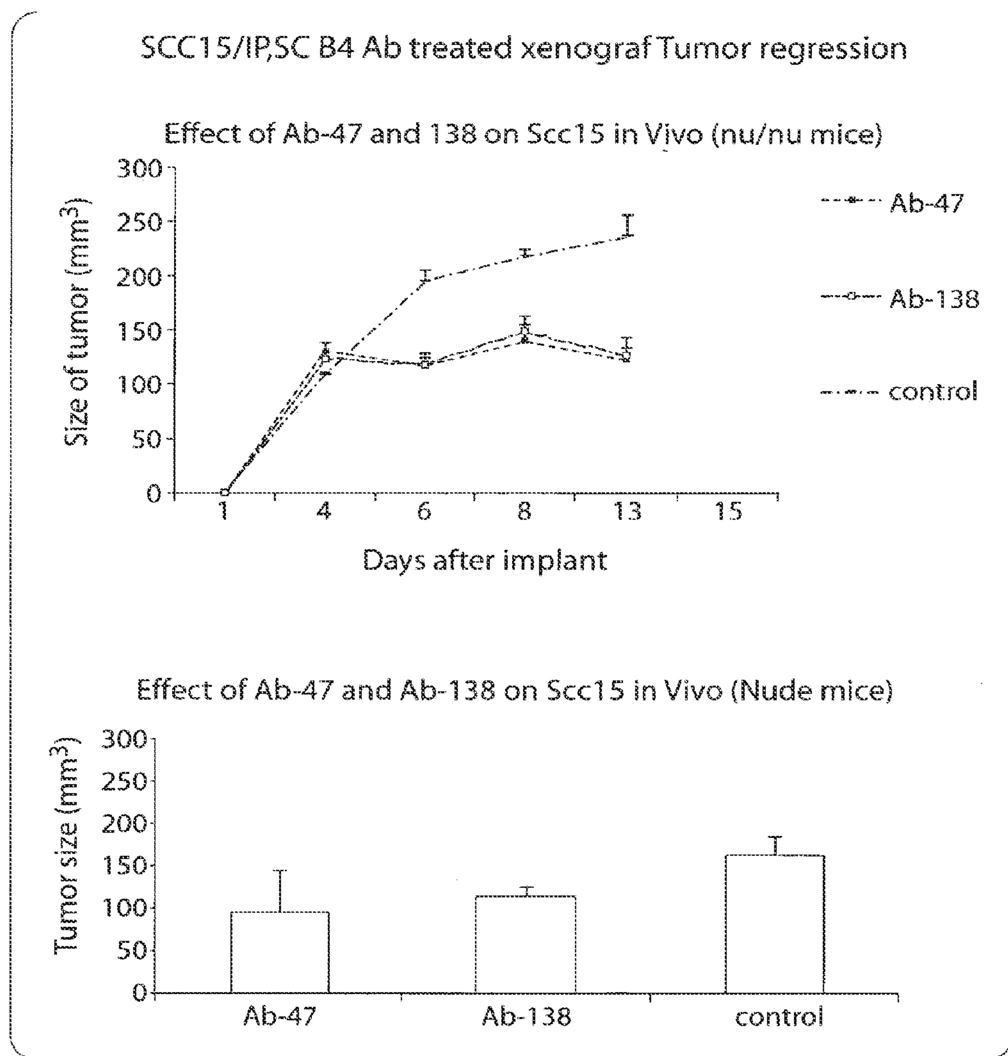


Fig. 60

EphB4 gene

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Fig. 61A

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Fig. 61B

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5401 cgctgtctcc ttgactctga ggtcaaggcc tggcatggcg tcagtgtcag taaatgtttg
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5521 ctttgcaagg ctgaatggac agtgtggggg cctgcagaaa gtgtgccctg gggaaggtgg
5581 agggaagatt ctggaacggg aaccaaggag gtccgggagg gtgagctggg aagaacacaa
5641 cagtccgctg ggtcctcagg gagtggggac agcagcggtg tgcctccccc ccgccggcag
5701 gtggacacgg tggccgcgga gcatctcacc cggaagcgcc ctggggccga ggccaccggg
5761 aaggtgaatg tcaagacgct gcgtctggga ccgctcagca aggctggctt ctacctggcc
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5881 gcccagctga ctgtgaacct gactcgattc ccggagactg tgcctcggga gctggttgtg
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6001 tactgccgtg aggatggcca gtgggccgaa cagccggtca cgggctgcag ctgtgctccg
6061 gggttcgagg cagctgaggg gaacaccaag tgccgaggtg agagctggag cttcccctgc
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6181 cattttgtat agttagatgt tgaaatggag gcttgctctg tcacccaggc tggagtgcag
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6361 ttgtatttta gtagagacgg ggtttcgcca tgttggccag gctggtctcg aactcctgac
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6481 cacccagctg gaaaaaaaaa agactttatt ttcacctgaa attcattaat ttccacttga
6541 aattccacct gcagttgtag caggacctga cacttgggcc ccatggaaat cacaggtatt
6601 gcctgacaca gtggttcatg cccatagtgc cagcactttg agatgccaag gtgggaggat
6661 cacttgagcc caggagttcg agatcagcct gggtgacaga gcaagacccc gtctctaaaa
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6781 ggtgcgatct cggctcactg caagctccgc ctcccaagtt aacaccattc tcctgcctca
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6901 ttagtagaga tggagtttca ccgtgttagc caggatggtc tcgatctcct gacctcatga
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7501 aggtatttac aggccattcc aagtgccaaa agattgtttt tgctcatggt gacttcagta
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7741 tcaccagact gccgagatca gggtcgaaac aggtgaggac cccttctctg gagagagtct
7801 cctttctcct ctaagaggaa aggttttgag atcttttgtc cattttccca ccttagcact
7861 tcatcagcct taaaagaagc tggaattttt tttttttttt ttggagatgg gatctcgata
```

Fig. 61C

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7921  tgttgcccag gctggtcttg aacccottgg ctcaagcgat cctccagcct cagcctccca
7981  aagtgctggg attcgaggca tgagccaccg agcccaccgt gcagatggat gtttttgtgc
8041  atgcttttga tgaatgcttt ctctctctca gcctgtgccc agggcacctt caagcccctg
8101  tcaggagaag ggtcctgcca gccatgccca gccaatagcc actctaacac cattggatca
8161  gccgtctgcc agtgccgcgt cgggtacttc cgggcacgca cagacccccg gggtgcaccc
8221  tgcaccagta agtgaccagc acccaggtgc agttcactgg ggaggggtca cagacctctg
8281  aggtggaccc tcacatggcc cccatcctcc ctgggcttct tccctttgtc cctggcatgc
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8401  gctgctggtg cctccattgc cctctcccca ccaccgcaga gcaggtcggc ctctgcctga
8461  ctccctggtc tcctgcagcc cctccttcgg ctccgcggag cgtggtttcc cgcctgaacg
8521  gctcctccct gcacctggaa tggagtgccc ccctggagtc tggtggccga gaggacctca
8581  cctacgccct ccgctgccgg gagtgccgac ccggaggctc ctgtgcgccc tgcgggggag
8641  acctgacttt tgaccccggc ccccgggacc tggtggagcc ctgggtggtg gttcgagggc
8701  tacgtcctga cttcacctat acctttgagg tcactgcatt gaacggggta tcctccttag
8761  ccacggggcc cgtcccattt gagcctgtca atgtcaccac tgaccgagag ggtgagactt
8821  gggggctggg gcggctggtg gtctggcggg agagatgtca ctgagggcct gaaggggaga
8881  ggcaggggct gtgaagttgg gtaccccgga agtgtgaggg gctaaggctt tgggggcaag
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9001  gaggctgaga caggcggatc acttgagccc tggagttcaa gaccagcctg ggtaacatag
9061  gaagatctct ctacaaaaaa taaaaatatt agccaggcga ggtggtgcat gcctgtggtc
9121  ccagctactc aagaggctga ggcaggagga ttgcttgagc ccaggagtcg gaggctgcag
9181  tgagctatga tcgcaccgct gcatgccagc ctgggtgaca gagcagtgtg agatcctctc
9241  tcaaaataaa tgaataagaa agagagggtg aggagctcgt aaagctgggc tggagagtta
9301  agtacaggaa ggcccccagt gggactgggg ccagagagaa tcagaaggaa ttctcgaaac
9361  agccaggggg aaattgagac aagtgtagcc agcagaggaa gtgttggaaa agataaggga
9421  catggccagg ctgatcacaa ggtcaggagt tcaagactag cctggccaac gtggtgaaac
9481  cccatgtcta ctaaaaataa aaaaattagc caggcatggt ggtgggcacc tgtaatccac
9541  ttgggaagca accagaagaa ttgcttgaac ccaggaggcg gaggttgcag taagctgaga
9601  ctgcgccact gcactccagc ctgggtgata gagcacgact ccgtctcgaa aaaaaaaatt
9661  tttttaagt taagggacag agctaccatg cacaagggtt ccctgtgtct ctgcctctca
9721  cagtacctcc tgcagtgtct gacatccggg tgacgcggtc ctcacccagc agcttgagcc
9781  tggcctgggc tgttccccgg gcacccagtg ggctgtgct ggactacgag gtcaaatacc
9841  atgagaaggt aaggccatcc cccagccctg gggtgggtgg gcaatgggtt gtgctctcct
9901  ggctgggaca cctgggttgc aggcacctgg caggcatttg aattccagct ctgccatgga
9961  ttccctgggc agccttgggt aagccccttg gcctgtctga gcctcagact cttcatctat
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10261 atcacaaggt caggagtatc gagaccatcc tggctaacac ggtgaaaccc catctctact
10321 aaaaatacaa aaaattagcc aggcgcggtg gcaggcgcct gtagtcccag ctactcggga
10381 ggctgaggca ggagaatggc gtgaacccag gaggcggagc ttgcagtgag ccgagatagc
10441 gccactgcag tccggcctgg gcgaaagaac aagactctgt ctccaaaaaa aaaaaaaaaa
10501 aaaaaaaacg caaaaaatac ttaaaatgaa aaaaattaga ctgggcacag tggctcatgc
```

Fig. 61D

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10561 ctgtaatccc ggcactttgg gaggccgagg tgggtagaac acctggggtg aagagttcga
10621 gaccagcctg gccaacaagg tgaaatcccc gtctctacta caaatagcaa aatcagctga
10681 gtgtgttggc gggcccctgt aatcccagct actcaggagg ctgagacagg agaatcactg
10741 gaacccaagt gattctcgac ttgaggtcga ggctgcagtg agtcgtgttt gcaccattgc
10801 attccagcct gagaaagtga gaccttgtct taaaaaaaag gaatgatatt atgaatacag
10861 cacatggctt gcatgcgtaa gttctcccaa aggcctcacc agttgcaagg caggctagtg
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11101 gtgcaggtac gggcgcgctc tgaggccggc tacgggccct tcggccagga acatcacagc
11161 cagacccaac tggatggtga gcctggggaa gggggtgagg gtgggggttg gaaagacccc
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11281 tttttgagat ggagtcttgc tctgtccctc aggctggagt gcagtggcac catctccgct
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11641 aaaccaaaac caacagctga gttttgtgaa gtctggcctg cttcactctg taccccccagg
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12601 caatcctccc gcatcggcct cccaaagtgc tgggattaca ggcatgagcc gccacaccca
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12721 gttcccctgc catacaattt gcctgttcaa agtgtacaat cgatgacttt tgatacattc
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12961 cgagcagaat gttttcaagg tttatgtatg ttgtagtata tatccgtggg ttttttttggt
13021 tgtggtttgt tttttgtttg ttttggaaac agggtctcgc tctgtcaccc aggctggagt
13081 gcagtggttc aattacagct cactgcagcc tcaacctccc aggctcaagt gatcctccca
13141 cctcagcctc ccaagcagct gggactgtag gcatgagcca ccatgcccag ctaatttttt
```

Fig. 61E

13201 ttggtatttt ttgtaaagac agggtttcac catgtttccc aggctggtct cgaactcctg
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13321 tggacctggc ctgttttttg tttttgtttt gaacacacga ttttgctttg tcacccaggc
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13861 aggctggttt gagactagcc tgtccaacct ggtgaaagcc catctctact aaaaatacac
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15541 gagggcgtgg tcaccaacag catgcccgtc atgattctca cagagttcat ggagaacggc
15601 gccctggact ccttcctgcg ggtgagcacc ctccctggct tctgcggcca cccggagttc
15661 ccacttacac ccagaggcca cttgggttaa gaagccagga cagacagtgg gtcccaggtc
15721 acctcctcca gcctttccct cttgggctaa gccctggtcc tctgcctttt cttttttta
15781 agacagagcc tcgctctgtc gcccaggctg gagtgcagtg gcgcgatctc ggctcattgc

Fig. 61F

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15841 tgtctccacc tccagggttc aagcgattct cctgcctcag tctcccaagt agctggtact
15901 ataggcatgc accaccatgc tgactaattt ttgtattttt agtagacaca gggtttcacc
15961 atgtaggcca ggctggtatc aaactcctga cctcaagtga tctccccacc tcagcctccc
16021 aaagtgctgg tattacaggt gtgaggcacc acgcctggcc agccctctgc ctttaatttt
16081 ccctctggga aaggctgggc tcctgggacc ttcctttccc actgccccat acagctgaag
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16861 tacacacggc aaactggatt tctcctcttg gggagcagag ggtctaatgg ggcaggggga
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16981 tgaaaaaaag caaacggggt ccttcatgca gatgtggcta gagaggaaag agaactgctt
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17101 gcttttcttt tttcttgaga tggagtttcc atctgtcacc caggctggag tgcagtggtg
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17701 tggctcaggt gatcctcctg cctcagcctc ctgggtagct ggaactacag gtgcacacca
17761 ccacacctgg ctaattttta aatttttttac ggagatgggg gtctcgctat gttgcccagg
17821 ctggtctcaa actcctggac tcaagcgatc ctccctcctt aacctctcaa agtgctggga
17881 ttacaggcgt gagccaccac gcctgctgat tattatattt tcgagcctct ctaaatcttg
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18001 tcttgatttc tggatttatg aaattcttct tatgggatca tttagcttgt ctctctgtat
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18121 gagatggagt cctgctgtcg cccaggctgg agtgcagtgg cacaatctcg gctcactgca
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18241 caggcgagtg ccaccatgcc cagctaattt ttgtattttt agtagagaca gggtttcacc
18301 atattggcca ggatggtctc gaacttctga cctcgtgatc tgcccaccac ctcagcctcc
18361 cacagtgctg ggattacagg catgagccac tatgcccggc taatttttgt atttttagta
```

Fig. 61G

```
18421 gagacagggc ttcgccatgt tggccaggct gatctgaaac ccctggcctc aagccatcca
18481 ccctccttgg cctcccaaag tgctgggatt aaacgcgtga gccaccgtgc ctggtcgaag
18541 agacagaaag ggtcttaaag gttcagtgac acacacctgt aatcccagca ctttgggaag
18601 ctgaggctgg tggatcactc gaggccagga gttagagatc accctgggca acatggtgaa
18661 accccgtctc tacacaaaat acaaaaatgg gcagagcatg atggtgcata tctgtagtcc
18721 cagctactcg ggaggctgag gcgggaggat cacttaagcc tgggagatcg aggctgtagt
18781 gagccatcat tgcactactg cattccagcc tgggcgatcc catctcttaa aaagagagag
18841 agatgggaag accagcacag gtgaaactgg tgaacagagg agagatggta gatgctgcat
18901 tgggcagtgt gacgggaacc cgctggaggg ctttggcagg agagtagttt aagaggatcc
18961 cagctgggca cagtggctca cacttgtgat cccagcactt ggggaggccg gggcaggtgg
19021 atcacttgag gtcaggagtt cgagaccagc ctggccaaca tggtgaaacc ctgtctgtac
19081 taaaaataca aaaaccagcc aggcatggtg gtgcacccct gtaatcccag ctactcagga
19141 gactaagaca ggagaatcgc ttgaactcag gaggcagagg ttgcagtgag ccaagatcac
19201 gccactttac tccagcctgg gcagtagagc gagactccat ctcaaaaaaa taaataaata
19261 aaaagacctc tttgctgggt gctagggagc aagagcagga gctgggagag gcctgcagca
19321 gaagcctgtt gccagcatcc aggccgtggg gtgaagggaa gggtttggat ttgggacatg
19381 tcttggaagc atcaccagca gaacttgctg atggattgga agtggctggt gagggagaaa
19441 aggggtcaa aggaaactct gaggtctata ccctgaccat ctggcaagtg gtggtgttgc
19501 cacaaactga gcggggagta gggcaggtgc aggtctggag gatggattca aaattcagtt
19561 tttggagtct atgtccctgg ttctgtaggg ctgcagatgg tctgccaaat cttagcggaa
19621 cccagaatac gggatttgtt tactgtctgt gacttgttgg tttccctggt gagagcaaac
19681 tctttaaagg tcaaggttgg gcttcagacc ttggtttttg caccgatcat tggtcatact
19741 gcagttcctc actcttctct tgcaaatcca tacacagcta gtccaagaga gctgaacagc
19801 tttgtggttg gatcagcacc aatgtatctc cacctgtaga cgggttgctc aggtgactca
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20521 agaccagcct gggcaacata gtgggaacct atctctacta aaaattaaaa aattatccag
20581 gcataatggc acatgcctat tgttccagct actcaggagg cttgcctgag cccaggaggt
20641 tgaggctgca gtgagctatg atggcaccac tgcactccag cctgggcgac agaacaagac
20701 cctgtctcta aaaaaaaaag atgtggatgg gaggggaac ggtgggtggg ctgtcctcac
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20881 caccgagacc tggctgctcg caacatccta gtcaacagca acctcgtctg caaagtgtct
20941 gactttggcc tttcccgatt cctggaggag aactcttccg atcccaccta cacgagctcc
21001 ctggtaatgc tgggggtaat actgggtgtg agcttcttag ggccaggtgg gcagggcagg
```

Fig. 61H

```
21061 ttggaaaggt gggaggctga gggtttggca gccctgctcc agggagagga tacaggagca
21121 ggctgtgggt gggggacag tcagctccag gaagccgact tccagatgtc taggaaaata
21181 acagttggat aacctgggca acatagcaag accccatctc tacaaaaaaa ttaaaagatt
21241 agccaggcgc agtggcatgc acctgtagtc ccagctactt gggaggttga ggcaggagga
21301 ttgcttaagc ccaggagttg gaggctgcag tgagctatga atgtgccact gtactgcaga
21361 ctgggcgaca gagcaagacc ctgtctcaaa agaacagtgg ccaggtgtgg tggctcacgc
21421 ctgtaaatcc agcactttgg gaggctgagg caggaggatc gcctgaggtc aggagttcga
21481 gaccagcctg gccaacatgg gaaaaccctg tcgctactaa aaatacaaaa ttagctgagg
21541 gtggtggtac acgcctgtaa tccgagctac tcaggaggct gaggtaggag aaccagttga
21601 acccgggagg cggagtttca gtgagccaag atcgcaccac tgcactccaa cctgggcaaa
21661 cagagttgga gagtaggagg cttggggcct gagctagggg gaaaaagcag aggcaggtgg
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21841 gccttccgga agttcacttc cgccagtgat gcctggagtt acgggattgt gatgtgggag
21901 gtgatgtcat ttggggagag gccgtactgg gacatgagca atcaggacgt aagtgtcccg
21961 tggtcctacc aagctttcct cgagtgttct ctcacctggg atttggggtg aagggtgggt
22021 tcccagagag tcatcactgc tgggttcttg agaccatgga gatgacaaaa aggagaattg
22081 atctttgtat caaagagttg agatacaggg ccaggcctag tggctcaagc ctgtaatccc
22141 agcactttgg gaggccaagg tgggcagatc acctaaggtt aggagttcaa gaccagcctg
22201 gccaacatgg tgaaaccccg tctctaaaaa aatacaaaaa attagcccag catgatgggc
22261 gggtgcctgt aatcccagct actcaggagg ctgagacagg ataatcgctt gaacccagga
22321 acagaggttg cagtgagctg agatcacgcc attgctttcc agcctgggca actgagcgag
22381 actctgtctt aataaataaa taaaagagtt gggtacagca tatttgggtc gcagaaggat
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22501 gggccttcag ccacagagag cttcaactcc ggctaggagg attcctggat ctgttatttt
22561 ttgggggct gtggctccta tcctaccatc ttccaagtca ccatttcctg ggcctgttag
22621 catctttgct tttcctggac agcctcaccc agagcttctt cccctctttc caggtgatca
22681 atgccattga acaggactac cggctgcccc cgcccccaga ctgtcccacc tccctccacc
22741 agctcatgct ggactgttgg cagaaagacc ggaatgcccg gccccgcttc ccccaggtgg
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23521 tgtgtcaact cgggttctct ttttccaacc ataaaaggag aagattgggc taggttttgg
23581 agatcctctt cagcttttat gtgaaatggt tttatgattc cttgcctccc aaaggctgcg
23641 tatccccact tggcctttgt ctgctactcc ccctttctgc cttcccgttc ctctcccaag
23701 atctcctctc accccaggtt gaataacaga aatagaagga atagaaatct gaaggccggg
23761 catggtggct catgcctgta atgccagcac tttgggaggc cgaggtgggc agatcacttg
```

Fig. 61I

```
23821 aggttaggag ttcgagacca ttgtggacaa cttggtgaaa ccttatgtct actaaaaata
23881 caaaaattag ctgggcatgg tggtgcgtgc ctgtaatacc agctactgag gaggctgagg
23941 caggagaatc gcttgaaccc gggaggtgga ggttgcagtg agccgagatc gcaccactgc
24001 actccagcct ggatgacaga gtgaaattcc atctcaaaaa aaaaaaaaaa aaaaaaaaag
24061 aaatgtgaag gccaggtggt ggctcacgcc tgtaatctca gcactttggg aggctcaggt
24121 ggaccgattg cttgagccca ggagtttgag agcagcctgg ccaaaatagc aaaacccccat
24181 ctctacaaaa caaaaacaaa aaaattagct gggcatggtg gtgcgtgcct gtggtcccag
24241 ctactcagga ggctagagcc agagggtctc aggccagtct gcccctgccc cacggggcct
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24361 tttttcccct tatctcagcc tccagccatc agcaacctcc tcttcctctc cacccagctc
24421 ttcctctccc acttcggcct tttctttctc acactccatt tccctctacg gcaatctgtg
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24541 cccaagccaa aggccctgcc tctggcctcc agccctaccc ccttctgcgg ttgcacagaa
24601 ggatggctgc ccagctctta aaaaaactgc ccgggaactg ttgacatctg ttctccctcc
24661 cccgctggct tttctgattg gcttacaatc ctgaggctag gaccgtctca ggagccaaga
24721 gaggagagcg gccacaggga acctagggtc tcaccaagct ctcctttcct tctgcaggga
24781 cctgctccga atcggagtca ctctggcggg acaccagaag aaaatcttgg ccagtgtcca
24841 gcacatgaag tcccaggcca agccgggaac cccgggtggg acaggaggac cggcccccgca
24901 gtactgacct gcaggaactc ccccaccccag ggacaccgcc tccccatttt ccggggcaga
24961 gtggggactc acagaggccc ccagccctgt gccccgctgg attgcacttt gagcccgtgg
25021 ggtgaggagt tggcaatttg gagagacagg atttgggggt tctgccataa taggagggga
25081 aaatcacccc ccagccacct cggggaactc cagaccaagg gtgagggcgc ctttccctca
25141 ggactgggtg tgaccagagg aaaaggaagt gcccaacatc tcccagcctc cccaggtgcc
25201 cccctcacct tgatgggtgc gttcccgcag accaaagaga gtgtgactcc cttgccagct
25261 ccagagtggg ggggctgtcc cagggggcaa gaagggggtgt cagggcccag tgacaaaatc
25321 attggggttt gtagtcccaa cttgctgctg tcaccaccaa actcaatcat tttttttccct
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25561 aggggcccat catcatgtct gtttccagaa cagtgccttg gtcatcccac atccccggac
25621 cccgcctggg acccccaagc tgtgtcctat gaagggggtgt ggggtgaggt agtgaaaagg
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25741 tatttaaaaa agtaactttt tgtataaata aaagaaaatg ggacgtgtcc cagctccagg
25801 ggtgatgggg gtgatggact agatttctaa ggagagtggg gctgggtagg gagggctttg
25861 tggctgaccg agaggtgtca gaggtctgga ggctgcaggg ctgtaggggc tggaacttgg
25921 ttatcagccc cagggtatgt ttgaggtggt ggggtggggg ccgagcgaga tgaatcattc
25981 gcagctgctt ctaacgtctc
```

Fig. 61J

EphB4, mRNA

```
   1 ctcggcccgg cggcgcgagc agagccactc cagggagggg gggagaccgc gagcggccgg
  61 ctcagccccc gccacccggg gcgggacccc gaggccccgg agggacccca actccagcca
 121 cgtcttgctg cgcgcccgcc cggcgcggcc actgccagca cgctccgggc ccgccgcccg
 181 cgcgcgcggc acagacgcgg ggccacactt ggcgccgccg cccggtgccc cgcacgctcg
 241 catgggcccg cgctgagggc cccgacgagg agtcccgcgc ggagtatcgg cgtccacccg
 301 cccagggaga gtcagacctg ggggggcgag ggcccccaa actcagttcg gatcctaccc
 361 gagtgaggcg gcgccatgga gctccgggtg ctgctctgct gggcttcgtt ggccgcagct
 421 ttggaagaga ccctgctgaa cacaaaattg gaaactgctg atctgaagtg ggtgacattc
 481 cctcaggtgg acgggcagtg ggaggaactg agcggcctgg atgaggaaca gcacagcgtg
 541 cgcacctacg aagtgtgtga cgtgcagcgt gccccgggcc aggcccactg gcttcgcaca
 601 ggttgggtcc cacggcgggg cgccgtccac gtgtacgcca cgctgcgctt caccatgctc
 661 gagtgcctgt ccctgcctcg ggctgggcgc tcctgcaagg agaccttcac cgtcttctac
 721 tatgagagcg atgcggacac ggccacggcc ctcacgccag cctggatgga gaacccctac
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1621 gccacggggc ccgtcccatt tgagcctgtc aatgtcacca ctgaccgaga ggtacctcct
1681 gcagtgtctg acatccgggt gacgcggtcc tcacccagca gcttgagcct ggcctgggct
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1921 gggcccttcg gccaggaaca tcacagccag acccaactgg atgagagcga gggctggcgg
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2101 gacaaacacg gacagtatct catcggacat ggtactaagg tctacatcga cccсttcact
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2281 gccccaggga agaaggagag ctgtgtggca atcaagaccc tgaagggtgg ctacacggag
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2461 atggagaacg gcgccctgga ctccttcctg cggctaaacg acggacagtt cacagtcatc
2521 cagctcgtgg gcatgctgcg gggcatcgcc tcgggcatgc ggtacccttgc cgagatgagc
2581 tacgtccacc gagacctggc tgctcgcaac atcctagtca acagcaacct cgtctgcaaa
```

Fig. 62A

```
2641 gtgtctgact ttggcctttc ccgattcctg gaggagaact cttccgatcc cacctacacg
2701 agctccctgg gaggaaagat tcccatccga tggactgccc cggaggccat tgccttccgg
2761 aagttcactt ccgccagtga tgcctggagt tacgggattg tgatgtggga ggtgatgtca
2821 tttggggaga ggccgtactg ggacatgagc aatcaggacg tgatcaatgc cattgaacag
2881 gactaccggc tgccccogcc cccagactgt cccacctccc tccaccagct catgctggac
2941 tgttggcaga aagaccggaa tgcccggccc cgcttccccc aggtggtcag cgccctggac
3001 aagatgatcc ggaaccccgc cagcctcaaa atcgtggccc gggagaatgg cggggcctca
3061 caccctctcc tggaccagcg gcagcctcac tactcagctt ttggctctgt gggcgagtgg
3121 cttcgggcca tcaaaatggg aagatacgaa gaaagtttcg cagccgctgg ctttggctcc
3181 ttcgagctgg tcagccagat ctctgctgag gacctgctcc gaatcggagt cactctggcg
3241 ggacaccaga agaaaatctt ggccagtgtc cagcacatga agtcccaggc caagccggga
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3721 aagaaggggt gtcagggccc agtgacaaaa tcattggggt ttgtagtccc aacttgctgc
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3841 ttcatattga aggtttttga gttttgtttt tggtcttaat ttttctcccc gttccctttt
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4021 aacagtgcct tggtcatccc acatccccgg accccgcctg ggacccccaa gctgtgtcct
4081 atgaaggggt gtggggtgag gtagtgaaaa gggcggtagt tggtggtgga acccagaaac
4141 ggacgccggt gcttggaggg gttcttaaat tatatttaaa aaagtaactt tttgtataaa
4201 taaaagaaaa tgggacgtgt cccagctcca ggggt
```

Fig. 62B

EphrinB2 Gene

```
   1 gcgcctcgga gctgcctgcg ggcgcacgcc gtcttccccg ccagtctgcc ccggaggatt
  61 gggggtccca gcctgcgtcc cgtcagtccc ttcttggccc ggagtgcgcg gagctgggag
 121 tggcttggcc atggctgtga gaagggactc cgtgtggaag tactgctggg gtgttttgat
 181 ggttttatgc agaactgcga tttccaaatc gatagtttta gagcctatct attggaattc
 241 ctcgaactcc aagtaagtgg cgtccgcgat ccccctatgt ccccgccccg gggtccgccg
 301 cgccgtccgg gcgggaggag gggtcagtcc gcggggcctc ggagcctgtt tctggaacct
 361 cggttccccg tcccccaccc ccaacccccg ccccatttca ctaggtggag actcctcgct
 421 cggctttcca acccgagccc cgctggaacg gacggtctct ccgcctttcc tccccgaac
 481 gctcccaggc gctaaaagct actatcggct cgggtgtcaa gtccgggaag gtgtccgatg
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 661 cgggcggcgt ggtccggggc ccgcgggcgg gcgaccgggg tggcaggacg ctggcagcga
 721 agcgcgttct ggagagggga gcctggagtc gctacgctgc ccgcagagcc ctggagccgg
 781 ggcgccttgg caccgcgccg ccagcccgag ggtgcgcggg gagctcgcct gcttcgcagg
 841 agaactcggg cgtcgagccc tttcctccgc gccggggaga cgggccttag gcttctccct
 901 gagggcccgc cgcacctcgg cctcccgctt cgttcataag ccggtagccc cggagtatgc
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1081 cagatttgct cttaccggac tctacagccg ggagcgagcc aggccttgtg gagagtaact
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1261 cacagccaaa acatatttta cagaatcttg gaattgtagt ctcgggaaac ttggagaaga
1321 agtatgcaga cattagctgg tttctggaga aaacgtttga gatcagaagc aaaatcaatg
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1741 aggcgccagg tggtgccgga aggagccggg ctaggacctc gcgcagcagc gggtcccgga
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1861 gcccggtgcc tccagaggtc actcttccat gcggaatcgc gcagcgccag gcctcgcccc
1921 tcccccaggc cgcctgctcc agccactctg cactttcact gaccggttct ctttgaggct
1981 gttttttttt ttcttatgag gatttaatat ttctgtttaa atctagttga aagcaattcc
2041 gttagcctct tcagcgttta gttcggtgtg tgtatcttta tctttgcgct atattaacta
2101 ttagtttgtg tgtatccggt aggagaatta gaaataccta gttgggagaa aaagaaaagt
2161 agaacaatag ttatttcaac ctaaggttta gacgttaata acttcttttt gtaatgtgtc
2221 gagatggggg gtcctggggg gaggtgacag gtactcacca ctcccccccc ccattctgat
2281 gatgaagatg agtctgtctt tccagctatg tccagacctg cgagggccct gcgtttctgg
2341 aagcctgccg tttgcgcggt tgaggttgct gctgctgtct tgtcctccac agcagcattt
2401 cttttaaaat tctcctgata acggcctgcc tggatgactg gataatgtgt gcctggaaaa
2461 ggtctccctt gcagctgaat gctagctcca gagatcagaa agatttcttc ctgtaggagc
2521 cataggaaag agtcctctct aagtttttga gaatgcatac aacccccctga tgacaggggg
2581 tcgctttcct tggggaagtt ttatatttat ttccagagga aagtttgaat cggtaaatat
```

Fig. 63A

2641 gatgtggcag gaaggtaatc aaatgcattg aagtttcaca tcagttccta tgaactgtgg
2701 aacaattcat ttgtaatgaa gccgccatca gtaattagat ttgtttcatt cagaggtcag
2761 ctttttagc aggtggtcga cacagggagc atgcagcagc tgtttggata cagggtccag
2821 aaaacccttt gtaaattcag cgtctccgta actactttaa tcacattgtc ggctctcccg
2881 tccctgactg tatgtaataa tggaaagatg tcctgcgtgc tgaaacagta gctgccctgt
2941 taggttattc acattgcttt gatacgttct ggtagagttg ggtccgttgt agccattttg
3001 gttgtttaaa gttttggttt ttttttgtt ttttttttaa ttcagcagag aacagtaatg
3061 cctagcttcc gtttttaact taacacttca gtagaacatt ttcttccaag agggagattt
3121 tggcctaagt aaagtagtgg gctcttttt aaaaaaaaat taattttact ttaatgtgag
3181 caaatctgta ttggtatggt gttctgcaat gcattacact gactttgaaa atttcgagta
3241 ctaatgcctt atgtctgggg ttaccattcc ctgtgcatca catactagtt agttaacata
3301 gcatttgct tttcccatgt aatttttcc ctatataata ctggattcct gatactaatt
3361 gacttgatac aaaagaatgg ctggatgata tccagataac gtataataca tgggcttcac
3421 cacaatcagg ctctgaataa atacagacct gtcagagatt gataaaataa actacaatgg
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3601 ttgaactatg ctccacagtt tgcgtttggg ttaatcttgt cggttttaat atagagagaa
3661 aaaagctcaa agcaccaggg gtggaattgt tagtgctttc acatccacat tcctcacatt
3721 ttgtcaggat gataaactgt aggtaatgga ctgtcgttgt tctgcaggac aactgagcca
3781 ggcagagcac aaagactaag ctaaagcgat acctcacaac atgcttggta gccttctttt
3841 cagatgagaa tttatttgag aatcatgtgt ctagggactg cacatcttaa cctcaacagt
3901 tacagcttca agccccagaa acaggagctg gaggttaaga tgatttgcta agcacctggt
3961 tctaaatctt ttacaaagca taagctgttg acgctggttc tgccgacgca aagacatgca
4021 gatgactcca acatttccag aggcttctga cttaagctaa agtgtgtgga caggtgaatt
4081 cgccatgggc ctggagacca gcttgctaaa aactatgtgt ttgaatggtt cctccagaca
4141 gagtcagctg aagaacaatt ggtggattta tattaaaacc tcttgtctgt aaacttactg
4201 aggtgcatcc ttcggttggt ggatcagtga gataattgcc ttcagatgga cattgcaact
4261 ggagcaacta aatccttgct gtctttcctt cctctgaaat cttccaggta gctcccgaga
4321 gcttcagtat gacaccaaac ttcgggcgac gttttagagt gcgttcacct aatgggaaac
4381 tattcgagat cccagcgtga ctgcagtaat gcgtcatagg aatgggagtg gcaggggaaa
4441 aggaaataca gattgtagac cctaataaaa aaatttttag gaaagatatt tctttaacgt
4501 tttatgagaa cttcattctt aaaatactta attgcaaatt agacaaatag aagtgctctt
4561 ctaaggaagg tgattaaact ggtcctccta tcagcctaat ctctgcctgc ctttgctgct
4621 gacataaaga acctgttttt caggtcactt aatatacatc tacatagatt tgcttatgag
4681 ctcacccttt gtgtagcgga gtagagcctt aaagaggagt gctcaactgt ttaaaatatt
4741 ttgattaaaa tatgcagaac ccatagaact ataagcttct agtcaggaat tagctctttc
4801 agggaacagc tccccccttc tttttaaggg gggaattaga aggaggctgg gggaggaata
4861 taagaacagc aaagaaggaa ggatagcaaa tgggacatgt tccgaacagc ttggaaaaac
4921 tcctgtggct tcattgtctc tataaagcca aagaatacaa agacataagc aattcagccc
4981 ttctcccatg atggaagatg taaaccgttg acatgcctcc cctgtttaac ttgtttaatt
5041 ctcattttaa attcagcacg atactagccg tgtgaactct gaagatttct ttagtaatcc
5101 attttgtagt tccgaatcaa aaacaaagtg aaagggtctg acacaatttg cttttatttt
5161 taggcaaatc aaccctggtc atagttaata aggggattac aactcagact aggtctttac
5221 agatgtgatg taaatcaagg gcagagtata aagaaactga tccctttga ttgaagtata

Fig. 63B

5281 gtaaaaaggc atagagaaac tagcagcagt aatctgattg tatggcaata aaaccaccat
5341 tttctgtctt tcagataaaa ataatgtggt aaatccatgc agttcataag atgtaaaggc
5401 agataaaggg tgaagccatg gcaacatata gattagcttg atgttagaaa tgacacgtct
5461 ctgaaaaggg cgcgggacga aggcccttgc ctccaggctg ttgggcatta tgtgagaacc
5521 acacagactt ggaaactggg attaggaagt atgaaagctc tacttgtggt ctgggatggc
5581 tgaggcagta aagaaaagct gctcagttct tgctcattgg tggtggataa tatggcaaag
5641 gtagatttca ttgactgcct tttttataga ttgagattgg ggctgattaa aacttcagat
5701 cactgcagtt gttagggcct gggagatttt cctttttaac tcctggccta acagcagcag
5761 ccgttctgta ggattaactg cacttcgcgg tcgttgcctt aatctatttg ggcttcaggc
5821 agggacatgc tgggaaggaa cagagaccag aggggatagg tagggctggg gttatctgaa
5881 aagaaaacag agaccttttg atttcagcca tcttttcaga cccagctccc tctcccgctg
5941 catgggagaa gcaaaggtaa acaggacaca ttgtccctct ccctcagcca cagagctctt
6001 ctgtgagttt tgtctttccc accctggaaa aaaagataaa atacaatttt taaaagggga
6061 gggaggaatt tagttttaat tcaaatgagt agtaatccaa tatgccaaaa gcagtgggct
6121 ctacctagat gtaattttac tcgtaaatgt gagtcttaaa ctttgagttg aatggggcag
6181 gctgttagag gtggtgtaaa ttacaggatt ataaaaatgt tagtgctgcc cagccttaaa
6241 gtcaaaaaca gaaaaatctc tgtgctgttg agtcttcccg ccctctctcc tgaacaacct
6301 tgtaagtaag ctagactttt gtttttgcct tccatacttt ccatttcagc cattaaacaa
6361 aataagccat tgaaaccacg attgggttcc atgcagagtg acatccgcaa tcgggtcaag
6421 ccagaaggaa atacttgctc gattgccccc tatttggcat tacaggaaag tctccacact
6481 ttggaagagt ctgaactctc aagacattga aaatgccaaa ggctgcaaac accctgtgtc
6541 tttcttgatg gagtgcatct tggtgtgttt tacaaagggg aattcagtgc tgtttttttg
6601 ttgttgttgt tgtttttttt ttttaaagag cagcataggg cccttctaga ctcttggatt
6661 ctgtgtctga caaaaatggt cattaaatga gcaatattat aatttagacc catttcactg
6721 attttgttcc aaattctcaa ctgacttgag catctgtttg ggctgtaga tacattgccc
6781 ttgttgactg tttttctcgt ttctatggga attactgtag ccattactat gtagctttca
6841 tagactcaaa acattttaa agtattgcat ataggctggc catatccagt gcctgttact
6901 ttaccttctt tttctaactt aatgcagcag tctgtattaa cagatccatt tcatttgtct
6961 agcttcatca gagagaggct acccccctgat ttacaggctg ctcacatcca agcaccttgc
7021 attctacact tgacagtgat tgctaatggc ccattcaact aaagtatttg cttgttaaca
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7321 cagaagtatt agagataagg aaggaggatc tagcaaacca gtgaaaagag taggtgacca
7381 gttataaaat gctttccatg cacattgaat gccaggcgaa cctatttctg ttattccagc
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7561 agaaaacata gcaagggaaa gctccattaa acaagttgtt tctgccctta gtaattctct
7621 aaacaagata ggaagaaaaa gtggacagta gtggagtatt aatagtgtgc tcttttcatt
7681 ctctaaagca cgagtaagta agcgttcaaa ctactctgtg gtgggcatac atttagagcg
7741 ctgtgaatga accactgctg ttctgccata cttaatttat ttatattatt atttttattt
7801 tattgttgtt tttatgtatt attataatta tttatttata ttactaattt attttctcaa
7861 tttaaatcct gttgcatcca atttaatta cagtttttgt atctgccttc ccatacttgc

Fig. 63C

```
7921  taccccacgtc cccattgcca ctgcggcctt atccatgttt tctgtgtaca ccactctcgt
7981  atcaccccag aataattatg agtgctaccc agacttttga aaccactaga gtcaacatgt
8041  ttgtctttga ggaaagccaa tgatgcttta gcatttttgg caggggtgga tgtgtgttta
8101  agtggggtgg gtgcagctcc ttattgtctg cctattctac tgttgttccc aatccacatt
8161  ccctgcgggg cacctaacct gtgtgcatag caaagaattt ccgaccttca gagccagaag
8221  tgtttctcaa ttgatctctt ccagcctagg gttatagctg atgaattata atccttgctc
8281  tttccacacc tttacctggg cttaccatgg ccctaaaaca tttgcccaga atcagaattg
8341  tctcatgagt gagtggggca aggcaaatcc tgttccagac cagctgagaa tgtacctagc
8401  tgcagaagaa gttagaaagt gtcatctttt acttatctac cagaactata ttcgaggtac
8461  atttagatt taaaaaaaaa gcaagttctc gtaggccttg aatccccccc ttgctatggg
8521  aaaatggatc attattataa tggactgtcc agtaaagttc atgatttctc ctagacatgt
8581  tctctctctt tatgacctag atcaagagtg atctctttaa gtcttttctt cataatccca
8641  cagcactttg tacttagatg tacttagaaa gaaccatata cacggtacgt catgattgat
8701  atgcaagcct tcaccactct acctgtccta aaagtcaggg acacaccttc ttcatttcat
8761  cagtccctac ttctatccag cattggcatc cagtaagtat tagtggaatg gacagacaac
8821  ccgaatttgt gctgatggca gtttaccctg ttttaactgt catccttctg ctactagaca
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9061  cgctggcaac tgctgcctca gggccatgct gagaaccctc gccctacaca aacctttctg
9121  ggaaaacaac tcaacattaa agctgtttgg ggatctctga agaaatctgt agtccttgcc
9181  ttgttggggg agcatcaggg atctaaccat tgatggtgga gtatttgttg ttaattcagc
9241  aagcaactat taagtgttag gcctgttact cggctctaac aatacaaggc agagtgacct
9301  gtaccctcga gatttaaagt ctaagtcctg tagagagaag cccaggtggg agcaagcaca
9361  tttagagtta ggtgcttggt gcaaggtggg gacacagaag aagggaatgg catttgcctc
9421  tggaggggtc cggaaacagc ctagggagga ggagcttgag tcttgaaata ctgtgggcat
9481  ctctaagcaa agtcacagta gacagctgaa ataaagaaaa tagtaagcaa gccaaagaaa
9541  cagtatttca gccaagggca gcgtgtgtct atcacgtcca cctgtgaaca cgtcccagga
9601  ttctctgcat ccggccattg ctcaagacag atccctcaca ggaacagcta agccactgat
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9781  agttaagggc acatgcttta gagtttggct atgtgagtcc aatcccagtt tagccattta
9841  ttagctgggt agctttagga gcagtagcct tagtgtctct cagttgtccc atctctataa
9901  tagggacaat aacataatag tgctgaataa aagagtaaca aaattttggt caacatttaa
9961  tgtatttaaa gagctaagct ccgtgattgg cacaatgaac caatcaatca aacaccagtt
10021 gttattaata aaagtcagtt gaatatgtac tgtgtgcctg gccgtggttc aatttgcctt
10081 tgcatacaag gaaaaaatta aaatactctg ttaataaaga ctatagcata atactttcac
10141 cttaaacttc ttgatgttaa tttattttgt ttacctgcca aacttctact cattccttat
10201 gactttctgc tacatgaaac accctttgta attcttttgt cctattaaat taagttctct
10261 ctcctctgct ttcctgcttt tggtgctttc taataacact tttaaccctg gactttctca
10321 ttcagctgtg caactgtgga ctgagaggag gctctttgaa ttcattttgt atattctagt
10381 agagagtact gtgagcagtt gggttgttga atgaatacat taattcaacc tggagggatg
10441 ggcagtattg catttttttac attgatatta catgatattt agaaaactgc ttaactggtg
10501 gacgttgttt tattaacagc attttgtgta tagcactcac tatgtgccag ctgctattct
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Fig. 63D

```
10561 aactgcctga caaatactcc tgaaaccttc atggtaacca tatgagggaa gcacttttaa
10621 tatatccata ataccaacgg ggagactgtg gccaaattgg ttaattaact tagccaaagt
10681 catattgaac taataagtgg atttaaaccc agctagtctg gggccagggt ccctctttta
10741 atcttctgcc tcctgcttat gctgttgcat ggagtagtct ttatcatata actaaattaa
10801 gcatgcattt gcttaaagca gtgcatacat gatggatcaa aaagtttgtg gtataattgg
10861 tttaattctg tcattatcca ttttgattta tagtcacttt cttatgatgg tcgtgtagtt
10921 ttaaatggaa cctttgaatc tttgatataa taaggttatg tcaaatcttg ggtataataa
10981 ggttataccc aatggaaaca gaataatgat cagcccattt aaaggatgac tggagagtta
11041 ttacaataca taatagtcat gcatatattg agtagtattc ctttggtaac attttccttt
11101 taaaaattgt aacatttgat tgttccttgt tgggagaaaa ggaggtcaga ttttgaggg
11161 gagatccatt tggtgagatg ctgagtgtgt gtcaagctaa ggagatagta tgacatcttt
11221 tttagagtct agtcacaatt aaatgccatt ttattttgga ttttgggatc cgtgccagct
11281 tccagcttgt cagagctgag aagactcaaa tcaagtccag gcttatttct acagcaaact
11341 gggattctgg cttcttgccg gtggattcat tcagtacagc ccatctggct tttgatgttc
11401 tgcaagtttg gagccatttg ttgaaggaag ccaggcggtg aatattggtg gtcctggggt
11461 tctcttgact ccaagtggtg ccccttggtt tgcattttca ccatgcttag catctgctta
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11581 gaactcagag tccccagcac atcctccttc ctcctccttg tccaattact ttcatgcagt
11641 tctcagtagc tgcttgtttg aatcacttat agtatttaac ttctagggtg tttttgggtt
11701 ttggtcaagg taattccagg ctgaatgtgg tgactaagca ggaaataaat gggtcgtcct
11761 caaagttaca gtggagcgct gtttctattt tcctaaggta cacagttgtg ggggcgatcc
11821 gtatggaagt caggaaccca gtctgatttt gcttcctttt gatggtagca gtacagacct
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11941 caaagccctg agacgtgcag gaaaatgtct cctgtcatac gcccacagca gacctagccc
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12061 tgcacacagc cttgtaaact gtgttactgg gctgattata cttgattggc aaggtgaatc
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12541 aggcattccc tgtatgactt acgtgagcct ttcatctccg cgatttttcc cattcaggta
12601 aatgagcaaa tggatttgaa cactcatatc taaaacaaga gagaaccagc tggaaatgcc
12661 ctttgaattt ctttctctat gtaaaccatt tttctttctg gtgcctcacc tataaataac
12721 aggagttcca ccttccttta tagactcttg ctgaaagcat ggtttggaac aagaccgtac
12781 aggtgcacac aaattacagt tgggaaagaa gcctgcagtg catcttgtct ctgaaggtta
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12961 caaatctcca cattttttct tatctagcta caaaattcat aggctgattt ttttggggtg
13021 cgtgtgtggt ttttttttttg tttttttggt aaataaagac ctgcattttt attttgatat
13081 aggtggttga gttttgtctt taatttcatg acagagattt aactagtctc aactttttgaa
13141 aagacaacaa tgatatttgg ggatcacaca cttaaagtta gatttctaga tgattaatac
```

Fig. 63E

```
13201 caaagtagat gatttttag cctcagccat ttataggtat gcccttctgt gaatttttta
13261 tgacagtgaa aatcatggca cagataaaaa ttaaataaat acttctgtta ttttcctgaa
13321 gaaaaaaaaa aaaagcttaa actatgagaa tactgtcttt gagcacttta aaataaaatt
13381 gacttcagcc agcaggattt tgagcattac atcacaaata aaaaacaaga ttaacatcaa
13441 aaggagtcag ttttcattca attgtgcagc actgtgggct gtgaaattta atattatttt
13501 gactcatatg ctaattgtag actgacagag gaaaatggat tgtgtttaaa taaaaggata
13561 cacagcatca cacgcagctg tatcaaatac aagttgaggt ctttgggcca ggaactgggg
13621 gccctctagc tctgttattg cagattcaag tttgacaaat aaaactttcc tttagactgt
13681 agtttaatta cttttttca aaggtatgcg tgatgaagag gcacaaatac acctcacctt
13741 gaagagttgc taaactggtt tgtgtgccga tcagttcacc gtgtgtttga atttctgtgc
13801 ttctcatctt tccttttctt gaaaagattt tgcttgtcat tggtgtgaat tgtacccccc
13861 acccccaccc atctagtctt tgctctcaga tttataacac tttaatggtt ccaaattgta
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13981 tatttgtttt aggaaagtgt gaaagaaggg gcacctgtga aaacacgcaa ttgttccaac
14041 acacatatac atccaaatta aagcagaaaa tgtcaaagcc tccaatcact accttatttc
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14281 ttaaagtgca aaagggggca gtaaagtgct atccacaaaa aaggaaaaac attttccaag
14341 tatttcttat tactgcctgt gtctttcgta ggccctgcct ttatttattc attttataac
14401 aaaactctta tgtttggggc attcagagaa taccttatta agctgttgca gcaatctagc
14461 attaaatgga agacatgcaa gactgaagat cctgcctgtt tatgaagtgt gccatcaaat
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14761 ctcatctgca ttcggaattg cagatgaacc agtttgtact cgacttctct tcttcactgt
14821 aggctttgac atttaattaa aaattaaagc cttttatgga aaaagtacat gttttccaaa
14881 atggggtaaa ttcgaagtat acttgataca gaacactggc ttgggaataa acctgtgata
14941 ttacatgact tttggtttgc aactgctagg ctgagcctct ttgtaaagct gggatttaga
15001 atctttgaaa tgtttgtaca gttcaatgat taagcataaa ttgtatatat tccctttttt
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15121 ttaaataggc cacaacttca actaggataa ttttatttat ctgcttgtta gggaattgca
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15241 gaaagatagc acaaagtttt tctgaaacta cattaaaaaa ataatgtttt aatcttatca
15301 caaaagcatt gactatttat tgcaaagaaa acacagaaag ctaaaaatca ttctaagtcc
15361 accattcagt agcccaaagt ggtctcaggt aaaggcggtg tgtgtgacca tttgtttatg
15421 gttgtctccg tgcagtcagc aaaataaaca gaacaacatg ccatatatta ttgatgtgta
15481 tattttcaac tgaaattagc catctgctta caatgatcat atacactaat ggtataattt
15541 tgaaatgaaa agaaaaataa aataattctt tgtggagagt aatgcgaatt gacttatgaa
15601 tctcgccctg cttggcagtt tgctctagag gtagaagagc tttatgtgtg ggcctcctcc
15661 cccccacac atttattctg ctcacacttg caccagcatc catgtcagga ctcaccttgt
15721 cctgttacat gagtaacatg gccctgattc tcaagtgcat gataactgcc ataattacac
15781 ataaatatta aatatttaaa tagatcttta cgtgtgtaat attaggtaga agtggctctg
```

Fig. 63F

15841 gatcgaatct gatgcttttt aaatagaagc tttcccacaa catttccaag cactgtcatc
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15961 agttcctgtt tgtatctttt ttgttctgat ctctttattc tgtgtcagct aaatattctt
16021 gcagtcagtt actaacatat taactcatcc ttgtttggaa actttggcat atccttccat
16081 ggtttccttc cgtggacctg tcgcgtctct caggagagcc accaggtata ttgtcacaca
16141 tttcgcatgt attttcagag actacagcag catcaagtgg ccccccagcg atttgggttt
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16261 atgtttgtgc taaggtgcgt gtagtatggt cagaggaaga aagaagcagg gaaaatggag
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16501 caatacaggt cagcagaaaa gtccagactt gacatcccaa cgtgccatgg tctggtctgt
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18181 tcatatatat tctgctattt gcataattgt ctggagtcca tatgtaatat taaatgtaaa
18241 acacaaatgc catgtagctg gtctgtttct tcctcacctt ttggttcctg gcctcctggg
18301 gaagggttgc acatctgagc cgtggtctca gatgactgcc tcggaagaag cctcttccct
18361 tcaggcacca ctgatgtgtg cttggtgtgg agctagactt tccctggctc tccatgtgac
18421 gctcacatgt gcgtgtcttg atttccctta acttcatggc ttatctatga acagcttgat

Fig. 63G

18481 ttgggggaaa aaaatgtgtt tcccaatgct ggagttataa ttgaatgtgc tgcagtcaaa
18541 actgaaatgt gtgcagagaa agggggcttt tcctgtcatg ctcattgggc accagtgtgt
18601 cttcacctgt tttgtgtgtt aggtccatgc gtcatgctga aatgaagaac atgggatgta
18661 tggggctttg gacagtgctg agccaaaagc aagtgctcaa aagcagctgt gtttgtatta
18721 ttagtggttc tggaggtggc tgattgcctt gcattttaag tagagaggga ttgtagaaga
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19081 ccttgggtgt ttaatactga attagtcaca tgtgggactt gcctgccctc agggagctag
19141 actataaatt cctaatgatc agtggtctcc acttttctgt cactcataat gtctggcaca
19201 acataggtta cttgagttgt tacactcaca gtactgttgt ttgctgccat ggtgctttag
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20941 ctcttttggg ggttgtacag taacacattc ccaagaaaga ggtaacagcc acatacattt
21001 ttcttcccaa taaagagtgt gggtttttaa tatgaatcca tagtatgatt tctgttatgt
21061 tttgtgctgc ttcataacca cactcatgca cttttcagaa aattaatacc attcattagc

Fig. 63H

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21181 ctttatctct tagtgaatta tgaccctgta gtcatcatgg ctggtgggcg tctctggtta
21241 aagaaagggt tggattggaa ggattcagag gcgattcttt gttcttaggc tttaatattt
21301 taatgagcct gcaggcttgg ctgcttacga acgagctgag atttctaagt gtgttgttag
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23641 ggctggcgtg cagtggcatg atcacagctc actgtagcct tgaactccag ggctcaagtg
23701 atcctcccac ctcagcctcc aagtagctcg gactacaggc atgtgccact gcacccagct
23761 caagagctac acttcaaagc acagaatgaa aacctatttt taaagccaac ttgatacata
```

Fig. 63I

23821 gagtagctta ccaagaatta gtaacaacaa caacaagaaa aaaaagagag aatgtggtag
23881 agtatatact tagtaaggag taattattat aaaataaaag cattctgaaa tgaaacaggt
23941 agatggggtg gccaagtatg cagcatagta gggaaatctt tgaaaatgta aaatagttac
24001 caggtaaaat aaatggaaac tttaagcttt tggaagccta acaatgtatt tatattagta
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Fig. 63J

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28921 gcgttgtttc tgttatttct gaacatcatg tgaactcctt ttctgggtgt attaaaggtt
28981 ttcccagtgt gtgtcagtga gactcctgat tgaatttaat atgaataaag ataaattctt
29041 tacatttaag gattaaagtc tcagcttctg cttaacttga gattgcactg agaaactcct
```

Fig. 63K

29101 ggctctcggg tatagcggag tcacgacctg gggatgtctg tcccatatgg ctctgtgtgt
29161 aagaagaaaa agctgctgtg gacggagact ctgttcacat taaatgacat cacctaagcc
29221 atcatgacag caagaattat ttaggaattg ctcagaataa aactgccttc attatttcat
29281 aaaatgtatc ttggtatctt tagcacctta tttatggctt tttaaaggtt cactgggatt
29341 tataaataat tggacaatgc tagagaccta gtacaagaat gaaagaggac aggcttcttt
29401 cttaataacc tttaaacatt catcaggaag ataaaacttt aaagcaaaat aaaacacatg
29461 aaaatagcca agatgcacag accagacaag caaatactac tttaacttat ttgtatagtt
29521 cttaagagtc acatttgttc ctgaagtttc aaaatctcgg gctgagtgtt tgatcactta
29581 gggaagtgtt gtggccttca catactcttg tctcactttg aagtctagaa acacaggtct
29641 tagagcaatt tttatcactg tgagaaagct gaaacttagt gtgagtagct tagtacaatt
29701 cagttggcca tcaaatgtca gaaacaaaac tcagtccagg gccgctggac ccttaggccg
29761 gcgttgttag tttacaacag tgcctcctgg gtccaaacat ctaagtgcac atgtagcaat
29821 agtaaagata gtatgtatgc atacataaca catatgtaga gacagcagag tatacgtaca
29881 cacatgttgc atacatagca acagcagaga agctcatgaa ctataaagga tggactgtat
29941 gcttgtatca gacattttgg tactgacgct ttgtcatata ttgtgtaaca tataaccagc
30001 ttgcaatcat ctgcccccaa agttgaacta agaaaatcct acagggtact aggaaaggaa
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30181 gttagcaagt actttaagcc cctcaataga aagttgctac atcatatagt gattaaaaat
30241 aaaaatctct caaacataca agtagaggtg gtatgagact tcaaattccc ttagccaagt
30301 acaagtgcag cagttttgtt ggctggctgg ctgcatagaa ggactgatgg attggcagac
30361 cctcaagctg gagtgtaatt gatctcatta cagaggagcc aggctgggtg acagttgtgc
30421 tttgcaagtg gtttttttgca ttggtgaagt agcccatttt gttgttcctg atgttaaaca
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30661 tgtgatgtcc atctaagctg tgtgtgtcca tgagagtgac gcattttctc ctctgcagtg
30721 ttgttatatt ctaaactgtc agcagacatt aattcggtcg ctggtgaagt cccaccgcct
30781 agagatgaac tctgcctccg atggatgttt tccacttcag tgccactcgt ctcgcaatta
30841 ctgggtcatt aatatcattg catgcaatta gtgacagtag aaagagctag agggttgtgg
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31261 aaaacacaat tcctctatct tagtagattt tggcccatat taagcatatc aagaatgact
31321 tttttttttt caagacatgg ggttttattg gggcttata tacaaggaaa gagagagtcc
31381 agtggcagtg ggctggacaa gatatccaca tggccctgtg gcagtgagct gggcaggaaa
31441 actgcaactg cttgcaaaca gcatgtagtt catctatagc attttcactt aacaccaccc
31501 agctaatgac ttccacctgg caaccttcat ttaatccaga acttaggacc tcgagtccct
31561 gtacggccca tgttccacag gatgggccga gggctcagct gttcctcata gacaaggaat
31621 gactctccac attggccact cccggattcc ctagctcagg acacatattc aggtgtgtct
31681 aaggctggct cttctatgtg aagttactta ttcttttacc attgactctc atgttcccac
31741 tatattaagt tttctgaat tactgtggca ataagaaacg gtcccttaaa ttatactaga

Fig. 63L

31801 agaaaagctt tttttttgtt ttgtttttta ttttgaaatt atgttaaatt tttttttctta
31861 actgagagat tccacctgca taaatcgtca taacttttaa cagtaagatc ttagacttag
31921 aaagtgatgt ttttcctcaa cagaatttat taaaaatcaa gacaccaagc tgttccaaac
31981 aatagtttga ggggaaataa aataaacaac tccataaata atcttatgtt gttaaacatg
32041 tctctagcaa aacaaacaaa caaaaaagtc gggggttggg ggaggtgcag tttattgcca
32101 gtactgtctg gtctttctca gaaaagcgtc agtgtacatc actgagcctg gacggtatgt
32161 tttcttgatc tatacccccct atgtgtacat gtgcttgcac gcacacacat gtagacacgc
32221 acacatgtgc acctgccatc actttctgct cttccgtctt ttcactcttg agtgtctgta
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32341 attgctattt gacattcata cggtttttaa tggttaaaag gctttatgcg aaagctgtga
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32461 tagattgacc ttctccctca gtgtccaagc ctcgcatagc atgatggcac ctgtaaactc
32521 agttctgtat cctggtatcc tttctcttcc caagtagaag caattaagta atatatgtca
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32641 tccatgttta acactcttct ttctgagctc tgggtagaat gtcctattat tgttcatcat
32701 gaatatttga aattaaagaa ataaaactgt accattttct ttaagagcat ccatttgtac
32761 ttgataacat cttcagtcat atttcaatgc tggcaaagag gaggggagtt ctaaactgtg
32821 actcaatttt agaatctact ttttccaaat tattctgttt agtgcagaaa actaattaat
32881 agtgttgcat agaaaagtca ctgaagctaa gccagttatt acttcttaat gcatgattta
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33061 ttatacagtg ttttagctgt ggctccctgc atgcaaaata agagttaatc aaatgtcagt
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33361 tgtagtccca gctactcggg aggctgaggc aggagaatgg cgtgaacctg ggaggcagag
33421 cttgtggtga gccaagatca caccactgca ctccagcctg ggtgacagag cgagactccg
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34261 caagataaca gtcttccgat cttcagaagt ctgtatcaag cttaaggaaa ctgatgtgta
34321 ggaagactcg cctaagaagt ccaaattagc aaggctagca tgtgaggaca tgctggaaaa
34381 gaatagttcc catagatatt gacagagaat gttcataaaa tgctacttgt tttgtggtta
34441 catgagagta acttgtgtcc agtgcagctg tatgtaaggg caacgttttt attctgacga

Fig. 63M

34501 ctctgtggtt ttcatgaccc tggatgctta tcatgtctct ctgttggact tcttcaacgg
34561 agttgataca aatacttgct tccaagtgtc catctgccct ctcctccatc ctggccccat
34621 acaaatacgc tacattttta aataatttga aataccctca atagtattta tatttcctgg
34681 tgcttcattc tttccataag aactgtgata ccattattct gtaggatttt tttgtgcttc
34741 cccgtttcac atctctgtgc cagtgagacc catatatcgg tgcaaatcca gaagtttgat
34801 tgtccatctg attagcacac tgttagcaat gtggtggact aaacacagcc aagatgtggg
34861 gctggagctt agcctcctgg gagcagagcg gtgaacatca gatgaagaca tgtgaaaatg
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35281 acaggctgta aaatgcccat gtatctttat taagcctatt ttccaactgg atagagaaat
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35581 taaaaattcc cagtacattc aaatgaacaa tgaaaataat tgcagaattg tctcctgaaa
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35701 ctaagccttt cagagcttct tggtgactat tgcaggagaa atcagaatat taatcttgtg
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36121 ccctttataa gcaaccaagt atttgggatg ttatttgat attagtagtg aatttttcag
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36781 ctctactgtg cctgtttttc tcttgctgat actcatttaa ttgtttttct tttggatctg
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36961 tttagcaaca aaaagtcagt tacttacttt gagtaagtaa ctcaaagtaa gttaactttg
37021 agtttgagtg cacttttgcg tgtaggttca tttatgtgct tgtgaattta aaaacattgg
37081 gattccacct gaatgaagta aaccaaacat tttaaactat cagccagata gagacatcag
37141 cctttcactt ctttctatat gcagacatat cctaattttt tagaaaaatc aaataggaaa

Fig. 63N

37201 attctcaaca attaattgaa gattatagct ctgctctgaa atggtccaga aataggatct
37261 gctcatagaa actcatagtt tgaagcctct gggaggaaag gatactttaa aatttagtca
37321 catatttgga ggagggaaaa gggaaagagc agaatgaaga actgaaaaaa atcacacacc
37381 ggggcctgtc gtgaggtggg ggactggggg agggatagca ttaggagata tacctaatgt
37441 aaatgacgag ttaacaggcg cagcccacca acatggcaca cgtatacata tgtaacaaac
37501 ctgcacgttg tgcacatgta ccctagaact taaagtataa taaaaaaaaa ttttaatagc
37561 cccattaaat aattaaaaag attttttta gattcacaga agtgtacaaa atttttaggt
37621 tttttttttt ttaagctgtc tgctgaatag tttcttaatg gtctacaatg tttgtatcta
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37861 gtctttgttt tgaggaaaac agtgaaagta aagttaattc aagaccacaa agacaagtaa
37921 ataagtgcct tatttttgta gttaatataa tttcagtgga atgcatattt ctaccataaa
37981 tgcatataga acttgtttgc tgacctactg tttggaaaac aaacaatccc attagaagaa
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39601 atagatagat agatagatag atatttcttt ttaaaaagca aaacactttg gttcaaaatc
39661 aaaatatcca gaatgaaaac taaaagcttg tgcagttttg ctcatttctg aatcttgact
39721 acagaagagt tttgttcatt gtgacttttc caatatagat aacctattgt gcagaaagaa
39781 ataattattc ttctaattaa aaattggtat agtagtcaat caacttgctc agttaaattg
39841 aaatgtcatc tgcaatgctt tgcctgccaa atgcaagaat ccctatagtt tccacagatg

Fig. 63O

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39901 gcctcacgtt ctaaacctct gaaataacta gtataaccat tttgttttaa aagaaaaatt
39961 atattcttgt atttcacagt actttgcata aagactctta tgttcattgc tattcatgcc
40021 tgttgaaata tatatgcagc tcctaaagct agatattgtc agatgtctgt gccgtaatta
40081 atcatttgtt tttcatatag atgcaagttc tgctggatca accaggaata aagatccaac
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40201 aaaaccaaat ccaggtataa cagcatgatc tgtgtgtatg gaggtctgtg ggtaccacat
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42361 gaagccaagg gaagacagtg gtttgtggac gagagggctg tgagcatcct ggcaggtgcc
42421 ccaggatgcc acgcctggaa gggccggctt ctgcctgggg tgcatttccc ccgcagtgca
42481 taccggactt gtcacacgga cctcgggcta gttaaggtgt gcaaagatct ctagagttta
42541 gtccttactg tctcactcgt tctgttaccc agggctctgc agcacctcac ctgagacctc
```

Fig. 63P

```
42601 cactccacat ctgcatcact catggaacac tcatgtctgg agtcccctcc tccagccgct
42661 ggcaacaaca gcttcagtcc atgggtaatc cgttcataga aattgtgttt gctaacaagg
42721 tgccctttag ccagatgcta ggctgtctgc gaagaaggct aggagttcat agaagggagt
42781 ggggctgggg aaagggctgg ctgcaattgc agctcactgc tgctgcctct gaaacagaaa
42841 gttggaaagg aaaaaagaaa aaagcaatta ggtagcacag cactttggtt ttgctgagat
42901 cgaagaggcc agtaggagac acgacagcac acacagtgga ttccagtgca tggggaggca
42961 ctcgctgtta tcaaatagcg atgtgcagga agaaaagccc ctcttcattc cggggaacaa
43021 agacgggtat tgttgggaaa ggaacaggct tggagggaag ggagaaagta ggccgctgat
43081 gatatattcg ggcaggactg ttgtggtact ggcaataaga tacacagctc cgagctgtag
43141 gagagtcggt ctgctttgga tgatttttta agcagactca gctgctatac ttatcacatt
43201 ttattaaaca cagggaaagc atttaggaga atagcagaga gccaaatctg acctaaaagt
43261 tgaaaagcca aaggtcaaac aggctgtaat tccatcatca tcgttgttat taaagaatcc
43321 ttatctataa aaggtaggtc agatccccct ccccccaggt tcctccttcc cctcccgatt
43381 gagccttacg acactttggt ttatgcggtg ctgtccgggt gccagggctg cagggtcggt
43441 actgatggag gctgcagcgc ccggtgctct gtgtcaaggt gaagcacata cggcagacct
43501 cttagagtcc ttaagacgga agtaaattat gatgtccagg gggagaagga agataggacg
43561 tatttataat aggtatatag aacacaaggg atataaaatg aaagattttt actaatatat
43621 attttaaggt tgcacacagt acacaccaga agatgtgaaa ttcatttgtg gcaattaagt
43681 ggtcccaatg ctcagcgctt aaaaaaacaa attggacagc tacttctggg aaaaacaaca
43741 tcattccaaa aagaacaata atgagagcaa atgcaaaaat aaccaagtcc tccgaaggca
43801 tctcacggaa ccgtagacta ggaagtacga gccccacaga gcaggaagcc gatgtgactg
43861 catcatatat ttaacaatga caagatgttc cggcgtttat ttctgcgttg ggtttccct
43921 tgccttatgg gctgaagtgt tctctaga
```

Fig. 63Q

EphrinB2, mRNA

```
   1 gcgcggagct gggagtggct tcgccatggc tgtgagaagg gactccgtgt ggaagtactg
  61 ctggggtgtt ttgatggttt tatgcagaac tgcgatttcc aaatcgatag ttttagagcc
 121 tatctattgg aattcctcga actccaaatt tctacctgga caaggactgg tactataccc
 181 acagatagga gacaaattgg atattatttg ccccaaagtg gactctaaaa ctgttggcca
 241 gtatgaatat tataaagttt atatggttga taaagaccaa gcagacagat gcactattaa
 301 gaaggaaaat acccctctcc tcaactgtgc caaaccagac caagatatca aattcaccat
 361 caagtttcaa gaattcagcc ctaacctctg gggtctagaa tttcagaaga acaaagatta
 421 ttacattata tctacatcaa atgggtcttt ggagggcctg gataaccagg agggaggggt
 481 gtgccagaca agagccatga agatcctcat gaaagttgga caagatgcaa gttctgctgg
 541 atcaaccagg aataaagatc caacaagacg tccagaacta gaagctggta caaatggaag
 601 aagttcgaca acaagtccct ttgtaaaacc aaatccaggt tctagcacag acggcaacag
 661 cgccggacat tcggggaaca acatcctcgg ttccgaagtg gccttatttg cagggattgc
 721 ttcaggatgc atcatcttca tcgtcatcat catcacgctg gtggtcctct tgctgaagta
 781 ccggaggaga cacaggaagc actcgccgca gcacacgacc acgctgtcgc tcagcacact
 841 ggccacaccc aagcgcagcg gcaacaacaa cggctcagag cccagtgaca ttatcatccc
 901 gctaaggact gcggacagcg tcttctgccc tcactacgag aaggtcagcg gggactacgg
 961 gcacccggtg tacatcgtcc aggagatgcc cccgcagagc ccggcgaaca tttactacaa
1021 ggtctgagag ggaccctggt ggtacctgtg ctttcccaga ggacacctaa tgtcccgatg
1081 cctcccttga gggtttgaga gcccgcgtgc tggagaattg actgaagcac agcaccgggg
1141 gagagggaca ctcctcctcg gaagagcccg tcgcgctgga cagcttacct agtcttgtag
1201 cattcggcct tggtgaacac acacgctccc tggaagctgg aagactgtgc agaagacgcc
1261 cattcggact gctgtgccgc gtcccacgtc tcctcctcga agccatgtgc tgcggtcact
1321 caggcctctg cagaagccaa gggaagacag tggtttgtgg acgagagggc tgtgagcatc
1381 ctggcaggtg ccccaggatg ccacgcctgg aagggccggc ttctgcctgg ggtgcatttc
1441 ccccgcagtg cataccggac ttgtcacacg gacctcgggc tagttaaggt gtgcaaagat
1501 ctctagagtt tagtccttac tgtctcactc gttctgttac ccagggctct gcagcacctc
1561 acctgagacc tccactccac atctgcatca ctcatggaac actcatgtct ggagtcccct
1621 cctccagccg ctggcaacaa cagcttcagt ccatgggtaa tccgttcata gaaattgtgt
1681 ttgctaacaa ggtgcccttt agccagatgc taggctgtct gcgaagaagg ctaggagttc
1741 atagaaggga gtggggctgg ggaaagggct ggctgcaatt gcagctcact gctgctgcct
1801 ctgaaacaga aagttggaaa ggaaaaaaga aaaaagcaat taggtagcac agcactttgg
1861 ttttgctgag atcgaagagg ccagtaggag acacgacagc acacacagtg gattccagtg
1921 catggggagg cactcgctgt tatcaaatag cgatgtgcag gaagaaaagc ccctcttcat
1981 tccggggaac aaagacgggt attgttggga aaggaacagg cttggaggga agggagaaag
2041 taggccgctg atgatatatt cgggcaggac tgttgtggta ctggcaataa gatacacagc
2101 tccgagctgt aggagagtcg gtctgctttg gatgattttt taagcagact cagctgctat
2161 acttatcaca ttttattaaa cacagggaaa gcatttagga gaatagcaga gagccaaatc
2221 tgacctaaaa gttgaaaagc caaaggtcaa acaggctgta attccatcat catcgttgtt
2281 attaaagaat ccttatctat aaaaggtagg tcagatcccc ctccccccag gttcctcctt
2341 cccctcccga ttgagcctta cgacactttg gtttatgcgg tgctgtccgg gtgccagggc
2401 tgcagggtcg gtactgatgg aggctgcagc gcccggtgct ctgtgtcaag gtgaagcaca
2461 tacggcagac ctcttagagt ccttaagacg gaagtaaatt atgatgtcca gggggagaag
2521 gaagatagga cgtatttata ataggtatat agaacacaag ggatataaaa tgaaagattt
2581 ttactaatat atattttaag gttgcacaca gtacacacca gaagatgtga aattcatttg
```

Fig. 64A

```
2641 tggcaattaa gtggtcccaa tgctcagcgc ttaaaaaaac aaattggaca gctacttctg
2701 ggaaaaacaa catcattcca aaaagaacaa taatgagagc aaatgcaaaa ataaccaagt
2761 cctccgaagg catctcacgg aaccgtagac taggaagtac gagccccaca gagcaggaag
2821 ccgatgtgac tgcatcatat atttaacaat gacaagatgt tccggcgttt atttctgcgt
2881 tgggttttcc cttgccttat gggctgaagt gttctctaga atccagcagg tcacactggg
2941 ggcttcaggt gacgatttag ctgtggctcc ctcctcctgt cctcccccgc acccccctccc
3001 ttctgggaaa caagaagagt aaacaggaaa cctacttttt atgtgctatg caaaatagac
3061 atctttaaca tagtcctgtt actatggtaa cactttgctt tctgaattgg aagggaaaaa
3121 aaatgtagcg acagcatttt aaggttctca gacctccagt gagtacctgc aaaaatgagt
3181 tgtcacagaa attatgatcc tctatttcct gaacctggaa atgatgttgg tccaaagtgc
3241 gtgtgtgtat gtgtgagtgg gtgcgtggta tacatgtgta catatatgta taatatatat
3301 ctacaatata tattatatat atctatatca tatttctgtg gagggttgcc atggtaacca
3361 gccacagtac atatgtaatt ctttccatca ccccaacctc tcctttctgt gcattcatgc
3421 aagagtttct tgtaagccat cagaagttac ttttaggatg gggagagggg gcgagaaggg
3481 gaaaaatggg aaatagtctg atttaatga aatcaaatgt atgtatcatc agttggctac
3541 gttttggttc tatgctaaac tgtgaaaaat cagatgaatt gataaaagag ttccctgcaa
3601 ccaattgaaa agtgttctgt gcgtctgttt tgtgtctggt gcagaatatg acaatctacc
3661 aactgtccct ttgtttgaag ttggtttagc tttggaaagt tactgtaaat gccttgcttg
3721 tatgatcgtc cctggtcacc cgactttgga atttgcacca tcatgtttca gtgaagatgc
3781 tgtaaatagg ttcagatttt actgtctatg gatttggggt gttacagtag ccttattcac
3841 ctttttaata aaaatacaca tgaaaacaag aaagaaatgg cttttcttac ccagattgtg
3901 tacatagagc aatgttggtt ttttataaag tctaagcaag atgttttgta taaaatctga
3961 attttgcaat gtatttagct acagcttgtt taacggcagt gtcattcccc tttgcactgt
4021 aatgaggaaa aaatggtata aaaggttgcc aaattgctgc atatttgtgc cgtaattatg
4081 taccatgaat atttatttaa aatttcgttg tccaatttgt aagtaacaca gtattatgcc
4141 tgagttataa atattttttt ctttctttgt tttattttaa tagcctgtca taggttttaa
4201 atctgcttta gtttcacatt gcagttagcc ccagaaaatg aaatccgtga agtcacattc
4261 cacatctgtt tcaaactgaa tttgttctta aaaaaataaa atattttttt cctatggaaa
4321 aaaaaaaaaa aaaaa
```

Fig. 64B

EphB4 Precursor Protein

```
  1 melrvllcwa slaaaleetl lntkletadl kwvtfpqvdg qweelsglde eqhsvrtyev
 61 cdvqrapgqa hwlrtgwvpr rgavhvyatl rftmleclsl pragrscket ftvfyyesda
121 dtataltpaw menpyikvdt vaaehltrkr pgaeatgkvn vktlrlgpls kagfylafqd
181 qgacmallsl hlfykkcaql tvnltrfpet vprelvvpva gscvvdavpa pgpspslycr
241 edgqwaeqpv tgcscapgfe aaegntkcra caqgtfkpls gegscqpcpa nshsntigsa
301 vcqcrvgyfr artdprgapc ttppsaprsv vsrlngsslh lewsaplesg gredltyalr
361 crecrpggsc apcggdltfd pgprdlvepw vvvrglrpdf tytfevtaln gvsslatgpv
421 pfepvnvttd revppavsdi rvtrsspssl slawavprap sgavldyevk yhekgaegps
481 svrflktsen raelrglkrg asylvqvrar seagygpfgq ehhsqtqlde segwreqlal
541 iagtavvgvv lvlvvivvav lclrkqsngr eaeysdkhgq ylighgtkvy idpftyedpn
601 eavrefakei dvsyvkieev igagefgevc rgrlkapgkk escvaiktlk ggyterqrre
661 flseasimgq fehpniirle gvvtnsmpvm iltefmenga ldsflrlndg qftviqlvgm
721 lrgiasgmry laemsyvhrd laarnilvns nlvckvsdfg lsrfleenss dptytsslgg
781 kipirwtape aiafrkftsa sdawsygivm wevmsfgerp ywdmsnqdvi naieqdyrlp
841 pppdcptslh qlmldcwqkd rnarprfpqv vsaldkmirn paslkivare nggashplld
901 qrqphysafg svgewlraik mgryeesfaa agfgsfelvs qisaedllri gvtlaghqkk
961 ilasvqhmks qakpgtpggt ggpapqy
```

Fig. 65

EphrinB2

```
  1 mavrrdsvwk ycwgvlmvlc rtaisksivl epiywnssns kflpgqglvl ypqigdkldi
 61 icpkvdsktv gqyeyykvym vdkdqadrct ikkentplln cakpdqdikf tikfqefspn
121 lwglefqknk dyyiistsng slegldnqeg gvcqtramki lmkvgqdass agstrnkdpt
181 rrpeleagtn grssttspfv kpnpgsstdg nsaghsgnni lgsevalfag iasgciifiv
241 iiitlvvlll kyrrrhrkhs pqhtttlsls tlatpkrsgn nngsepsdii iplrtadsvf
301 cphyekvsgd yghpvyivqe mppqspaniy ykv
```

Fig. 66

POLYPEPTIDE COMPOUNDS FOR INHIBITING ANGIOGENESIS AND TUMOR GROWTH

RELATED APPLICATIONS

[0001] This application claims the benefit of priority of U.S. Provisional Application No. 60/454,300 filed Mar. 12, 2003 and U.S. Provisional Application No. 60/454,432 filed Mar. 12, 2003. The entire teachings of the referenced Provisional Applications are incorporated herein by reference in their entirety.

BACKGROUND OF THE INVENTION

[0002] Angiogenesis, the development of new blood vessels from the endothelium of a preexisting vasculature, is a critical process in the growth, progression, and metastasis of solid tumors within the host. During physiologically normal angiogenesis, the autocrine, paracrine, and amphicrine interactions of the vascular endothelium with its surrounding stromal components are tightly regulated both spatially and temporally. Additionally, the levels and activities of proangiogenic and angiostatic cytokines and growth factors are maintained in balance. In contrast, the pathological angiogenesis necessary for active tumor growth is sustained and persistent, representing a dysregulation of the normal angiogenic system. Solid and hematopoietic tumor types are particularly associated with a high level of abnormal angiogenesis.

[0003] It is generally thought that the development of tumor consists of sequential, and interrelated steps that lead to the generation of an autonomous clone with aggressive growth potential. These steps include sustained growth and unlimited self-renewal. Cell populations in a tumor are generally characterized by growth signal self-sufficiency, decreased sensitivity to growth suppressive signals, and resistance to apoptosis. Genetic or cytogenetic events that initiate aberrant growth sustain cells in a prolonged "ready" state by preventing apoptosis.

[0004] It is a goal of the present disclosure to provide agents and therapeutic treatments for inhibiting angiogenesis and tumor growth.

SUMMARY OF THE INVENTION

[0005] In certain aspects, the disclosure provides polypeptide agents that inhibit EphB4 or EphrinB2 mediated functions, including monomeric ligand binding portions of the EphB4 and EphrinB2 proteins and antibodies that bind to and affect EphB4 or EphrinB2 in particular ways. As demonstrated herein, EphB4 and EphrinB2 participate in various disease states, including cancers and diseases related to unwanted or excessive angiogenesis. Accordingly, certain polypeptide agents disclosed herein may be used to treat such diseases. In further aspects, the disclosure relates to the discovery that EphB4 and/or EphrinB2 are expressed, often at high levels, in a variety of tumors. Therefore, polypeptide agents that downregulate EphB4 or EphrinB2 function may affect tumors by a direct effect on the tumor cells as well as an indirect effect on the angiogenic processes recruited by the tumor. In certain embodiments, the disclosure provides the identity of tumor types particularly suited to treatment with an agent that downregulates EphB4 or EphrinB2 function.

[0006] In certain aspects, the disclosure provides soluble EphB4 polypeptides comprising an amino acid sequence of an extracellular domain of an EphB4 protein. The soluble EphB4 polypeptides bind specifically to an EphrinB2 polypeptide. The term "soluble" is used merely to indicate that these polypeptides do not contain a transmembrane domain or a portion of a transmembrane domain sufficient to compromise the solubility of the polypeptide in a physiological salt solution. Soluble polypeptides are preferably prepared as monomers that compete with EphB4 for binding to ligand such as EphrinB2 and inhibit the signaling that results from EphB4 activation. Optionally, a soluble polypeptide may be prepared in a multimeric form, by, for example, expressing as an Fc fusion protein or fusion with another multimerization domain. Such multimeric forms may have complex activities, having agonistic or antagonistic effects depending on the context. In certain embodiments the soluble EphB4 polypeptide comprises a globular domain of an EphB4 protein. A soluble EphB4 polypeptide may comprise a sequence at least 90% identical to residues 1-522 of the amino acid sequence defined by FIG. **65**. A soluble EphB4 polypeptide may comprise a sequence at least 90% identical to residues 1-412 of the amino acid sequence defined by FIG. **65**. A soluble EphB4 polypeptide may comprise a sequence at least 90% identical to residues 1-312 of the amino acid sequence defined by FIG. **65**. A soluble EphB4 polypeptide may comprise a sequence as set forth in FIG. **1** or **2**. In certain embodiments, the soluble EphB4 polypeptide may inhibit the interaction between Ephrin B2 and EphB4. The soluble EphB4 polypeptide may inhibit clustering of or phosphorylation of Ephrin B2 or EphB4. Phosphorylation of EphrinB2 or EphB4 is generally considered to be one of the initial events in triggering intracellular signaling pathways regulated by these proteins. As noted above, the soluble EphB4 polypeptide may be prepared as a monomeric or multimeric fusion protein. The soluble polypeptide may include one or more modified amino acids. Such amino acids may contribute to desirable properties, such as increased resistance to protease digestion.

[0007] In certain aspects, the disclosure provides soluble EphrinB2 polypeptides comprising an amino acid sequence of an extracellular domain of an EphrinB2 protein. The soluble EphrinB2 polypeptides bind specifically to an EphB4 polypeptide. The term "soluble" is used merely to indicate that these polypeptides do not contain a transmembrane domain or a portion of a transmembrane domain sufficient to compromise the solubility of the polypeptide in a physiological salt solution. Soluble polypeptides are preferably prepared as monomers that compete with EphrinB2 for binding to ligand such as EphB4 and inhibit the signaling that results from EphrinB2 activation. Optionally, a soluble polypeptide may be prepared in a multimeric form, by, for example, expressing as an Fc fusion protein or fusion with another multimerization domain. Such multimeric forms may have complex activities, having agonistic or antagonistic effects depending on the context. A soluble EphrinB2 polypeptide may comprise residues 1-225 of the amino acid sequence defined by FIG. **66**. A soluble EphrinB2 polypeptide may comprise a sequence defined by FIG. **3**. In certain embodiments, the soluble EphrinB2 polypeptide may inhibit the interaction between Ephrin B2 and EphB4. The soluble EphrinB2 polypeptide may inhibit clustering of or phosphorylation of EphrinB2 or EphB4. As noted above, the soluble EphrinB2 polypeptide may be prepared as a monomeric or

multimeric fusion protein. The soluble polypeptide may include one or more modified amino acids. Such amino acids may contribute to desirable properties, such as increased resistance to protease digestion.

[0008] In certain aspects, the disclosure provides antagonist antibodies for EphB4 and EphrinB2. An antibody may be designed to bind to an extracellular domain of an EphB4 protein and inhibit an activity of the EphB4. An antibody may be designed to bind to an extracellular domain of an Ephrin B2 protein and inhibit an activity of the Ephrin B2. An antibody may be designed to inhibit the interaction between Ephrin B2 and EphB4. An antagonist antibody will generally affect Eph and/or Ephrin signaling. For example, an antibody may inhibit clustering or phosphorylation of Ephrin B2 or EphB4. An antagonist antibody may be essentially any polypeptide comprising a variable portion of an antibody, including, for example, monoclonal and polyclonal antibodies, single chain antibodies, diabodies, minibodies, etc.

[0009] In certain aspects, the disclosure provides pharmaceutical formulations comprising a polypeptide reagent and a pharmaceutically acceptable carrier. The polypeptide reagent may be any disclosed herein, including, for example, soluble EphB4 or EphrinB2 polypeptides and antagonist antibodies. Additional formulations include cosmetic compositions and diagnostic kits.

[0010] In certain aspects the disclosure provides methods of inhibiting signaling through Ephrin B2/EphB4 pathway in a cell. A method may comprise contacting the cell with an effective amount of a polypeptide agent, such as (a) a soluble polypeptide comprising an amino acid sequence of an extracellular domain of an EphB4 protein, wherein the EphB4 polypeptide is a monomer and binds specifically to an Ephrin B2 polypeptide; (b) a soluble polypeptide comprising an amino acid sequence of an extracellular domain of an Ephrin B2 protein, wherein the soluble Ephrin B2 polypeptide is a monomer and binds with high affinity to an EphB4 polypeptide; (c) an antibody which binds to an extracellular domain of an EphB4 protein and inhibits an activity of the EphB4; or (d) an antibody which binds to an extracellular domain of an Ephrin B2 protein and inhibits an activity of the Ephrin B2.

[0011] In certain aspects the disclosure provides methods for reducing the growth rate of a tumor, comprising administering an amount of a polypeptide agent sufficient to reduce the growth rate of the tumor, wherein the polypeptide agent is selected from the group consisting of: (a) a soluble polypeptide comprising an amino acid sequence of an extracellular domain of an EphB4 protein, wherein the EphB4 polypeptide is a monomer and binds specifically to an Ephrin B2 polypeptide; (b) a soluble polypeptide comprising an amino acid sequence of an extracellular domain of an Ephrin B2 protein, wherein the soluble Ephrin B2 polypeptide is a monomer and binds with high affinity to an EphB4 polypeptide; (c) an antibody which binds to an extracellular domain of an EphB4 protein and inhibits an activity of the EphB4; and (d) an antibody which binds to an extracellular domain of an Ephrin B2 protein and inhibits an activity of the Ephrin B2. Optionally, the tumor comprises cells expressing a higher level of EphB4 and/or EphrinB2 than noncancerous cells of a comparable tissue.

[0012] In certain aspects, the disclosure provides methods for treating a patient suffering from a cancer. A method may comprise administering to the patient a polypeptide agent selected from the group consisting of: (a) a soluble polypeptide comprising an amino acid sequence of an extracellular domain of an EphB4 protein, wherein the EphB4 polypeptide is a monomer and binds specifically to an Ephrin B2 polypeptide; (b) a soluble polypeptide comprising an amino acid sequence of an extracellular domain of an Ephrin B2 protein, wherein the soluble Ephrin B2 polypeptide is a monomer and binds with high affinity to an EphB4 polypeptide; (c) an antibody which binds to an extracellular domain of an EphB4 protein and inhibits an activity of the EphB4; and (d) an antibody which binds to an extracellular domain of an Ephrin B2 protein and inhibits an activity of the Ephrin B2. Optionally, the cancer comprises cancer cells expressing EphrinB2 and/or EphB4 at a higher level than noncancerous cells of a comparable tissue. The cancer may be a metastatic cancer. The cancer may be selected from the group consisting of colon carcinoma, breast tumor, mesothelioma, prostate tumor, squamous cell carcinoma, Kaposi sarcoma, and leukemia. Optionally, the cancer is an angiogenesis-dependent cancer or an angiogenesis independent cancer. The polypeptide agent employed may inhibit clustering or phosphorylation of Ephrin B2 or EphB4. A polypeptide agent may be co-administered with one or more additional anti-cancer chemotherapeutic agents that inhibit cancer cells in an additive or synergistic manner with the polypeptide agent.

[0013] In certain aspects, the disclosure provides methods of inhibiting angiogenesis. A method may comprise contacting a cell with an amount of a polypeptide agent sufficient to inhibit angiogenesis, wherein the polypeptide agent is selected from the group consisting of: (a) a soluble polypeptide comprising an amino acid sequence of an extracellular domain of an EphB4 protein, wherein the EphB4 polypeptide is a monomer and binds specifically to an Ephrin B2 polypeptide; (b) a soluble polypeptide comprising an amino acid sequence of an extracellular domain of an Ephrin B2 protein, wherein the soluble Ephrin B2 polypeptide is a monomer and binds with high affinity to an EphB4 polypeptide; (c) an antibody which binds to an extracellular domain of an EphB4 protein and inhibits an activity of the EphB4; and (d) an antibody which binds to an extracellular domain of an Ephrin B2 protein and inhibits an activity of the Ephrin B2.

[0014] In certain aspects, the disclosure provides methods for treating a patient suffering from an angiogenesis-associated disease, comprising administering to the patient a polypeptide agent selected from the group consisting of: (a) a soluble polypeptide comprising an amino acid sequence of an extracellular domain of an EphB4 protein, wherein the EphB4 polypeptide is a monomer and binds specifically to an Ephrin B2 polypeptide; (b) a soluble polypeptide comprising an amino acid sequence of an extracellular domain of an Ephrin B2 protein, wherein the soluble Ephrin B2 polypeptide is a monomer and binds with high affinity to an EphB4 polypeptide; (c) an antibody which binds to an extracellular domain of an EphB4 protein and inhibits an activity of the EphB4; and (d) an antibody which binds to an extracellular domain of an Ephrin B2 protein and inhibits an activity of the Ephrin B2. The soluble polypeptide may be formulated with a pharmaceutically acceptable carrier. An angiogenesis related disease or unwanted angiogenesis related process may be selected from the group consisting of angiogenesis-dependent cancer, benign tumors, inflammatory disorders, chronic articular rheumatism and psoriasis, ocular angiogenic diseases, Osler-Webber Syndrome, myocardial angiogenesis, plaque neovascularization, telangiectasia, hemophiliac joints, angiofibroma, wound granulation, wound healing, telangiectasia psoriasis scleroderma, pyogenic granuloma,

coronary collaterals, ischemic limb angiogenesis, rubeosis, arthritis, diabetic neovascularization, fractures, vasculogenesis, and hematopoiesis. An polypeptide agent may be co-administered with at least one additional anti-angiogenesis agent that inhibits angiogenesis in an additive or synergistic manner with the soluble polypeptide.

[0015] In certain aspects, the disclosure provides for the use of a polypeptide agent in the manufacture of medicament for the treatment of cancer or an angiogenesis related disorder, wherein the polypeptide agent is selected from the group consisting of: (a) a soluble polypeptide comprising an amino acid sequence of an extracellular domain of an EphB4 protein, wherein the EphB4 polypeptide is a monomer and binds specifically to an Ephrin B2 polypeptide; (b) a soluble polypeptide comprising an amino acid sequence of an extracellular domain of an Ephrin B2 protein, wherein the soluble Ephrin B2 polypeptide is a monomer and binds with high affinity to an EphB4 polypeptide; (c) an antibody which binds to an extracellular domain of an EphB4 protein and inhibits an activity of the EphB4; and (d) an antibody which binds to an extracellular domain of an Ephrin B2 protein and inhibits an activity of the Ephrin B2.

[0016] In certain aspects, the disclosure provides methods for treating a patient suffering from a cancer, comprising: (a) identifying in the patient a tumor having a plurality of cancer cells that express EphB4 and/or EphrinB2; and (b) administering to the patient a polypeptide agent selected from the group consisting of: (i) a soluble polypeptide comprising an amino acid sequence of an extracellular domain of an EphB4 protein, wherein the EphB4 polypeptide is a monomer and binds specifically to an Ephrin B2 polypeptide; (ii) a soluble polypeptide comprising an amino acid sequence of an extracellular domain of an Ephrin B2 protein, wherein the soluble Ephrin B2 polypeptide is a monomer and binds with high affinity to an EphB4 polypeptide; (iii) an antibody which binds to an extracellular domain of an EphB4 protein and inhibits an activity of the EphB4; and (iv) an antibody which binds to an extracellular domain of an Ephrin B2 protein and inhibits an activity of the Ephrin B2. Optionally, a method may comprise identifying in the patient a tumor having a plurality of cancer cells having a gene amplification of the EphB4 and/or EphrinB2 gene.

[0017] In certain aspects, the disclosure provides methods for identifying a tumor that is suitable for treatment with an EphrinB2 or EphB4 antagonist. A method may comprise detecting in the tumor cell one or more of the following characteristics: (a) expression of EphB4 protein and/or mRNA; (b) expression of EphrinB2 protein and/or mRNA; (c) gene amplification of the EphB4 gene; or (d) gene amplification of the EphrinB2 gene. A tumor cell having one or more of characteristics (a)-(d) may be suitable for treatment with an EphrinB2 or EphB4 antagonist, such as a polypeptide agent described herein.

BRIEF DESCRIPTION OF THE DRAWINGS

[0018] FIG. **1** shows amino acid sequence of the B4ECv3 protein (predicted sequence of the precursor including uncleaved Eph 134 leader peptide is shown).

[0019] FIG. **2** shows amino acid sequence of the B4ECv3NT protein (predicted sequence of the precursor including uncleaved Eph B4 leader peptide is shown).

[0020] FIG. **3** shows amino acid sequence of the B2EC protein (predicted sequence of the precursor including uncleaved Ephrin B2 leader peptide is shown).

[0021] FIG. **4** shows amino acid sequence of the B4ECv3-FC protein (predicted sequence of the precursor including uncleaved Eph B4 leader peptide is shown).

[0022] FIG. **5** shows amino acid sequence of the B2EC-FC protein (predicted sequence of the precursor including uncleaved Ephrin B2 leader peptide is shown).

[0023] FIG. **6** shows B4EC-FC binding assay (Protein A-agarose based).

[0024] FIG. **7** shows B4EC-FC inhibition assay (Inhibition in solution).

[0025] FIG. **8** shows B2EC-FC binding assay (Protein-A-agarose based assay).

[0026] FIG. **9** shows chemotaxis of HUAEC in response to B4Ecv3.

[0027] FIG. **10** shows chemotaxis of HHEC in response to B2EC-FC.

[0028] FIG. **11** shows chemotaxis of HUAEC in response to B2EC.

[0029] FIG. **12** shows effect of B4Ecv3 on HUAEC tubule formation.

[0030] FIG. **13** shows effect of B2EC-FC on HUAEC tubule formation.

[0031] FIG. **14** is a schematic representation of human Ephrin B2 constructs.

[0032] FIG. **15** is a schematic representation of human EphB4 constructs.

[0033] FIG. **16** shows the domain structure of the recombinant soluble EphB4EC proteins. Designation of the domains are as follows: L—leader peptide, G—globular (ligand-binding domain), C—Cys-rich domain, F1, F2—fibronectin type III repeats, H—6×His-tag.

[0034] FIG. **17** shows purification and ligand binding properties of the EphB4EC proteins. A. SDS-PAAG gel electrophoresis of purified EphB4-derived recombinant soluble proteins (Coomassie-stained). B. Binding of Ephrin B2-AP fusion to EphB4-derived recombinant proteins immobilized on Ni-NTA-agarose beads. Results of three independent experiments are shown for each protein. Vertical axis—optical density at 420 nm.

[0035] FIG. **18** shows that EphB4v3 inhibits chemotaxis.

[0036] FIG. **19** shows that EphB4v3 inhibits tubule formation on Matrigel. A displays the strong inhibition of tubule formation by B4v3 in a representative experiment. B shows a quantitation of the reduction of tube-length obtained with B4v3 at increasing concentrations as well as a reduction in the number of junctions, in comparison to cells with no protein. Results are displayed as mean values_S.D. obtained from three independent experiments performed with duplicate wells.

[0037] FIG. **20** shows that soluble EphB4 has no detectable cytotoxic effect as assessed by MTS assay.

[0038] FIG. **21** shows that B4v3 inhibits invasion and tubule formation by endothelial cells in the Matrigel assay. (A) to detect total invading cells, photographed at 20× magnification or with Masson's Trichrome Top left of A B displays section of a Matrigel plug with no GF, top right of A displays section with B4IgG containing GF and lower left section contains OF, and lower right shows GF in the presence of B4v3. Significant invasion of endothelial cells is only seen in GF containing Matrigel. Top right displays an area with a high number of invaded cells induced by B4IgG, which signifies the dimeric form of B4v3. The left upper parts of the pictures correspond to the cell layers formed around the Matrigel plug from which cells invade toward the center of the

plug located in the direction of the right lower corner. Total cells in sections of the Matrigel plugs were quantitated with Scion Image software. Results obtained from two experiments with duplicate plugs are displayed as mean values_S. D.

[0039] FIG. **22** shows tyrosine phosphorylation of EphB4 receptor in PC3 cells in response to stimulation with EphrinB2-Fc fusion in presence or absence of EphB4-derived recombinant soluble proteins.

[0040] FIG. **23** shows effects of soluble EphB4ECD on viability and cell cycle. A) 3-day cell viability assay of two HNSCC cell lines. B) FACS analysis of cell cycle in HNSCC-15 cells treated as in A. Treatment of these cells resulted in accumulation in subG0/G1 and S/G2 phases as indicated by the arrows.

[0041] FIG. **24** shows that B4v3 inhibits neovascular response in a murine corneal hydron micropocket assay.

[0042] FIG. **25** shows that that SCC15, B16, and MCF-7 co-injected with sB4v3 in the presence of matrigel and growth factors, inhibits the in vivo tumor growth of these cells.

[0043] FIG. **26** shows that soluble EphB4 causes apoptosis, necrosis and decreased angiogenesis in three tumor types, B16 melanoma, SCC15, head and neck carcinoma, and MCF-7 Breast carcinoma. Tumors were injected premixed with Matrigel plus growth factors and soluble EphB4 subcutaneously. After 10 to 14 days, the mice were injected intravenously with fitc-lectin (green) to assess blood vessel perfusion. Tumors treated with control PBS displayed abundant tumor density and a robust angiogenic response Tumors treated with sEphB4 displayed a decrease in tumor cell density and a marked inhibition of tumor angiogenesis in regions with viable tumor cells, as well as tumor necrosis and apoptosis.

[0044] FIG. **27** shows expression of EphB4 in prostate cell lines. A) Western blot of total cell lysates of various prostate cancer cell lines, normal prostate gland derived cell line (MLC) and acute myeloblastic lymphoma cells (AML) probed with EphB4 monoclonal antibody. B) Phosphorylation of EphB4 in PC-3 cells determined by Western blot.

[0045] FIG. **28** shows expression of EphB4 in prostate cancer tissue. Representative prostate cancer frozen section stained with EphB4 monoclonal antibody (top left) or isotype specific control (bottom left). Adjacent BPH tissue stained with EphB4 monoclonal antibody (top right). Positive signal is brown color in the tumor cells. Stroma and the normal epithelia are negative. Note membrane localization of stain in the tumor tissue, consistent with trans-membrane localization of EphB4. Representative QRT-PCR of RNA extracted from cancer specimens and adjacent BPH tissues (lower right).

[0046] FIG. **29** shows downregulation of EphB4 in prostate cancer cells by tumor suppressors and RXR expression. A) PC3 cells were co-transfected with truncated CD4 and p53 or PTEN or vector only 24 h later CD4-sorted cells were collected, lysed and analyzed sequentially by Western blot for the expression of EphB4 and β-actin, as a normalizer protein. B) Western blot as in (A) of various stable cell lines. LNCaP-FGF is a stable transfection clone of FGF-8, while CWR22R-RXR stably expresses the RXR receptor. BPH-1 was established from benign hypertrophic prostatic epithelium.

[0047] FIG. **30** shows downregulation of EphB4 in prostate cancer cells by EGFR and IGFR-1. A) Western blot of PC3 cells treated with or without EGFR specific inhibitor AG1478 (1 nM) for 36 hours. Decreased EphB4 signal is observed after AG 1478 treatment. The membrane was stripped and reprobed with β-actin, which was unaffected. B) Western Blot of triplicate samples of PC3 cells treated with or without IGFR-1 specific neutralizing antibody MAB391 (2 μg/ml; overnight). The membrane was sequentially probed with EphB4, IGFR-1 and β-actin antibodies. IGFR-1 signal shows the expected repression of signal with MAB391 treatment.

[0048] FIG. **31** shows effect of specific EphB4 AS-ODNs and siRNA on expression and prostate cell functions. A) 293 cells stably expressing full-length construct of EphB4 was used to evaluate the ability of siRNA 472 to inhibit EphB4 expression. Cells were transfected with 50 nM RNAi using Lipofectamine 2000. Western blot of cell lysates 40 h post transfection with control siRNA (green fluorescence protein; GFP siRNA) or EphB4 siRNA 472, probed with EphB4 monoclonal antibody, stripped and reprobed with β-actin monoclonal antibody. B) Effect of EphB4 AS-10 on expression in 293 transiently expressing full-length EphB4. Cells were exposed to AS-10 or sense ODN for 6 hours and analyzed by Western blot as in (A). C) 48 h viability assay of PC3 cells treated with siRNA as described in the Methods section. Shown is mean±s.e.m. of triplicate samples. D) 5-day viability assay of PC3 cells treated with ODNs as described in the Methods. Shown is mean±s.e.m. of triplicate samples. E) Scrape assay of migration of PC3 cells in the presence of 50 nM siRNAs transfected as in (A). Shown are photomicrographs of representative 20× fields taken immediately after the scrape was made in the monolayer (0 h) and after 20 h continued culture. A large number of cells have filled in the scrape after 20 h with control siRNA, but not with EphB4 siRNA 472. F) Shown is a similar assay for cells treated with AS-10 or sense ODN (both 10 μM). G) Matrigel invasion assay of PC3 cells transfected with siRNA or control siRNA as described in the methods. Cells migrating to the underside of the Matrigel coated insert in response to 5 mg/ml fibronectin in the lower chamber were fixed and stained with Giemsa. Shown are representative photomicrographs of control siRNA and siRNA 472 treated cells. Cell numbers were counted in 5 individual high-powered fields and the average±s.e.m. is shown in the graph (bottom right).

[0049] FIG. **32** shows effect of EphB4 siRNA 472 on cell cycle and apoptosis. A) PC3 cells transfected with siRNAs as indicated were analyzed 24 h post transfection for cell cycle status by flow cytometry as described in the Methods. Shown are the plots of cell number vs. propidium iodide fluorescence intensity. 7.9% of the cell population is apoptotic (in the Sub G0 peak) when treated with siRNA 472 compared to 1% with control siRNA. B) Apoptosis of PC3 cells detected by Cell Death Detection ELISA^{plus} kit as described in the Methods. Absorbance at 405 nm increases in proportion to the amount of histone and DNA-POD in the nuclei-free cell fraction. Shown is the mean±s.e.m. of triplicate samples at the indicated concentrations of siRNA 472 and GFP siRNA (control).

[0050] FIG. **33** shows that EphB4 and EphrinB2 are expressed in mesothelioma cell lines as shown by RT-PCR (A) and Western Blot (B).

[0051] FIG. **34** shows expression of ephrin B2 and EphB4 by in situ hybridization in mesothelioma cells. NCI H28 mesothelioma cell lines cultured in chamber slides hybridized with antisense probe to ephrin 132 or EphB4 (top row). Control for each hybridization was sense (bottom row). Positive reaction is dark blue cytoplasmic stain.

[0052] FIG. **35** shows cellular expression of EphB4 and ephrin B2 in mesothelioma cultures. Immunofluorescence staining of primary cell isolate derived from pleural effusion of a patient with malignant mesothelioma and cell lines NCI H28, NCI H2373, and NCI H2052 for ephrin B2 and EphB4. Green color is positive signal for FITC labeled secondary antibody. Specificity of immunofluorescence staining was demonstrated by lack of signal with no primary antibody (first row). Cell nuclei were counterstained with DAPI (blue color) to reveal location of all cells. Shown are merged images of DAPI and FITC fluorescence. Original magnification 200×.

[0053] FIG. **36** shows expression of ephrin B2 and EphB4 in mesothelioma tumor. Immunohistochemistry of malignant mesothelioma biopsy. H&E stained section to reveals tumor architecture; bottom left panel is background control with no primary antibody. EphB4 and ephrin B2 specific staining is brown color. Original magnification 200×.

[0054] FIG. **37** shows effects of EPHB4 antisense probes (A) and EPHB4 siRNAs (B) on the growth of H28 cells.

[0055] FIG. **38** shows effects of EPHB4 antisense probes (A) and EPHB4 siRNAs (B) on cell migration.

[0056] FIG. **39** shows that EphB4 is expressed in HNSCC primary tissues and metastases. A) Top: Immunohistochemistry of a representative archival section stained with EphB4 monoclonal antibody as described in the methods and visualized with DAB (brown color) localized to tumor cells. Bottom: Hematoxylin and Eosin (H&E) stain of an adjacent section. Dense purple staining indicates the presence of tumor cells. The right hand column are frozen sections of lymph node metastasis stained with EphB4 polyclonal antibody (top right) and visualized with DAB. Control (middle) was incubation with goat serum and H&E (bottom) reveals the location of the metastatic foci surrounded by stroma which does not stain. B) In situ hybridization of serial frozen sections of a HNSCC case probed with EphB4 (left column) and ephrin B2 (right column) DIG labeled antisense or sense probes generated by run-off transcription. Hybridization signal (dark blue) was detected using alkaline-phosphatase-conjugated anti-DIG antibodies and sections were counterstained with Nuclear Fast Red. A serial section stained with H&E is shown (bottom left) to illustrate tumor architecture. C) Western blot of protein extract of patient samples consisting of tumor (T), uninvolved normal tissue (N) and lymph node biopsies (LN). Samples were fractionated by polyacrylamide gel electrophoresis in 4-20% Tris-glycine gels and subsequently electroblotted onto nylon membranes. Membranes were sequentially probed with EphB4 monoclonal antibody and β-actin MoAb. Chemiluminescent signal was detected on autoradiography film. Shown is the EphB4 specific band which migrated at 120 kD and β-actin which migrated at 40 kD. The β-actin signal was used to control for loading and transfer of each sample.

[0057] FIG. **40** shows that EphB4 is expressed in HNSCC cell lines and is regulated by EGF: A) Survey of EphB4 expression in SCC cell lines. Western blot of total cell lysates sequentially probed with EphB4 monoclonal antibody, stripped and reprobed with β-actin monoclonal antibody as described for FIG. **39**C. B) Effect of the specific EGFR inhibitor AG1478 on EphB4 expression: Western blot of crude cell lysates of SCC15 treated with 0-1000 nM AG 1478 for 24 h in media supplemented with 10% FCS (left) or with 1 mM AG 1478 for 4, 8, 12 or 24 h (right). Shown are membranes sequentially probed for EphB4 and β-actin. C) Effect of inhibition of EGFR signaling on EphB4 expression in SCC cell lines: Cells maintained in growth media containing 10% FCS were treated for 24 hr with 1 μM AG 1478, after which crude cell lysates were analyzed by Western blots of cell lysates sequentially probed with for EGFR, EphB4, ephrin B2 and β-actin antibodies. Specific signal for EGFR was detected at 170 kD and ephrin B2 at 37 kD in addition to EphB4 and β-actin as described in FIG. **1**C. β-actin serves as loading and transfer control.

[0058] FIG. **41** shows mechanism of regulation of EphB4 by EGF: A) Schematic of the EGFR signaling pathways, showing in red the sites of action and names of specific kinase inhibitors used. B) SCC15 cells were serum-starved for 24 h prior to an additional 24 incubation as indicated with or without EGF (10 ng/ml), 3 μM U73122, or 5 μM SH-5, 5 μM SP600125, 25 nM LY294002, —μM PD098095 or 5 μM SB203580. N/A indicates cultures that received equal volume of diluent (DMSO) only. Cell lysates were subjected to Western Blot with EphB4 monoclonal antibody. β-actin signal serves as control of protein loading and transfer.

[0059] FIG. **42** shows that specific EphB4 siRNAs inhibit EphB4 expression, cell viability and cause cell cycle arrest. A) 293 cells stably expressing full length EphB4 were transfected with 50 nM RNAi using Lipofectamine™2000. 40 h post-transfection cells were harvested, lysed and processed for Western blot. Membranes were probed with EphB4 monoclonal antibody, stripped and reprobed with β-actin monoclonal antibody as control for protein loading and transfer. Negative reagent control was RNAi to scrambled green fluorescence protein (GFP) sequence and control is transfection with Lipofectamine™2000 alone. B) MTT cell viability assays of SCC cell lines treated with siRNAs for 48 h as described in the Methods section. Shown is mean±s.e.m. of triplicate samples. C) SCC15 cells transfected with siRNAs as indicated were analyzed 24 h post transfection for cell cycle status by flow cytometry as described in the Methods. Shown are the plots of cell number vs. propidium iodide fluorescence intensity. Top and middle row show plots for cells 16 h after siRNA transfection, bottom row shows plots for cells 36 h post transfection. Specific siRNA and concentration are indicated for each plot. Lipo=Lipofectamine™200 mock transfection.

[0060] FIG. **43** shows in vitro effects of specific EphB4 AS-ODNs on SCC cells. A) 293 cells transiently transfected with EphB4 full-length expression plasmid were treated 6 h post transfection with antisense ODNs as indicated. Cell lysates were collected 24 h after AS-ODN treatment and subjected to Western Blot. B) SCC25 cells were seeded on 48 well plates at equal densities and treated with EphB4 AS-ODNs at 1, 5, and 10 μM on days 2 and 4. Cell viability was measured by MTT assay on day 5. Shown is the mean±s.e.m. of triplicate samples. Note that AS-ODNs that were active in inhibiting EphB4 protein levels were also effective inhibitors of SCC15 cell viability. C) Cell cycle analysis of SCC15 cells treated for 36 h with AS-10 (bottom) compared to cells that were not treated (top). D) Confluent cultures of SCC15 cells scraped with a plastic Pasteur pipette to produce 3 mm wide breaks in the monolayer. The ability of the cells to migrate and close the wound in the presence of inhibiting EphB4 AS-ODN (AS-10) and non-inhibiting AS-ODN (AS-1) was assessed after 48 h. Scrambled ODN is included as a negative control ODN. Culture labeled no treatment was not exposed to ODN. At initiation of the experiment, all cultures showed scrapes of equal width and similar to that seen in 1 μM EphB4 AS-10 after 48 h. The red brackets indicate the width of the

original scrape. E) Migration of SCC15 cells in response to 20 mg/ml EGF in two-chamber assay as described in the Methods. Shown are representative photomicrographs of non-treated (NT), AS-6 and AS-10 treated cells and 10 ng/ml Taxol as positive control of migration inhibition. F) Cell numbers were counted in 5 individual high-powered fields and the average+s.e.m. is shown in the graph.

[0061] FIG. **44** shows that EphB4 AS-ODN inhibits tumor growth in vivo. Growth curves for SCC15 subcutaneous tumor xenografts in Balb/C nude mice treated with EphB4 AS-10 or scrambled ODN at 20 mg/kg/day starting the day following implantation of 5×106 cells. Control mice received and equal volume of diluent (PBS). Shown are the mean±s.e.m. of 6 mice/group. * P=0.0001 by Student's t-test compared to scrambled ODN treated group.

[0062] FIG. **45** shows that Ephrin B2, but not EphB4 is expressed in KS biopsy tissue. (A) In situ hybridization with antisense probes for ephrin B2 and EphB4 with corresponding H&E stained section to show tumor architecture. Dark blue color in the ISH indicates positive reaction for ephrin B2. No signal for EphB4 was detected in the Kaposi's sarcoma biopsy. For contrast, ISH signal for EphB4 is strong in squamous cell carcinoma tumor cells. Ephrin B2 was also detected in KS using EphB4-AP fusion protein (bottom left). (B) Detection of ephrin B2 with EphB4/Fc fusion protein. Adjacent sections were stained with H&E (left) to show tumor architecture, black rectangle indicates the area shown in the EphB4/Fc treated section (middle) detected with FITC-labeled anti-human Fc antibody as described in the methods section. As a control an adjacent section was treated with human Fc fragment (right). Specific signal arising from EphB4/Fc binding to the section is seen only in areas of tumor cells. (C) Co-expression of ephrin B2 and the HHV8 latency protein LANA1. Double-label confocal immunofluorescence microscopy with antibodies to ephrin B2 (red) LANA1 (green), or EphB4 (red) of frozen KS biopsy material directly demonstrates co-expression of LANA1 and ephrin B2 in KS biopsy. Coexpression is seen as yellow color. Double label confocal image of biopsy with antibodies to PECAM-1 (green) in cells with nuclear propidium iodide stain (red), demonstrating the vascular nature of the tumor.

[0063] FIG. **46** shows that HHV-8 induces arterial marker expression in venous endothelial cells. (A) Immunofluorescence of cultures of HUVEC and HUVEC/BC-1 for artery/vein markers and viral proteins. Cultures were grown on chamber slides and processed for immunofluorescence detection of ephrin B2 (a, e, i), EphB4 (m, q, u), CD148 (j, v), and the HHV-8 proteins LANA1 (b, f, m) or ORF59 (r) as described in the Materials and Methods. Yellow color in the merged images of the same field demonstrate co-expression of ephrin B2 and LANA or ephrin B2 and CD148. The positions of viable cells were revealed by nuclear staining with DAPI (blue) in the third column (c, g, k, o, s, w). Photomicrographs are of representative fields. (B) RT-PCR of HUVEC and two HHV-8 infected cultures (HUVEC/BC-1 and HUVEC/BC-3) for ephrin B2 and EphB4. Ephrin 82 product (200 bp) is seen in HUVEC/BC-1, HUVEC/BC-3 and EphB4 product (400 bp) is seen in HUVEC. Shown also is β-actin RT-PCR as a control for amount and integrity of input RNA.

[0064] FIG. **47** shows that HHV-8 induces arterial marker expression in Kaposi's sarcoma cells. (A) Western blot for ephrin B2 on various cell lysates. SLK-vGPCR is a stable clone of SLK expressing the HHV-8 vGPCR, and SLK-pCEFL is control stable clone transfected with empty expression vector. SLK cells transfected with LANA or LANAΔ440 are SLK-LANA and SLK-Δ440 respectively. Quantity of protein loading and transfer was determined by reprobing the membranes with β-actin monoclonal antibody. (B) Transient transfection of KS-SLK cells with expression vector pvG-PCR-CEFL resulted in the expression of ephrin B2 as shown by immunofluorescence staining with FITC (green), whereas the control vector pCEFL had no effect. KS-SLK cells (0.8×105/well) were transfected with 0.8 μg DNA using Lipofectamine 2000. 24 hr later cells were fixed and stained with ephrin B2 polyclonal antibody and FITC conjugated secondary antibody as described in the methods. (C) Transient transfection of HUVEC with vGPCR induces transcription from ephrin B2 luciferase constructs. 8×103 HUVEC in 24 well plates were transfected using Superfect with 0.8 μg/well ephrin B2 promoter constructs containing sequences from -2941 to -11 with respect to the translation start site, or two 5'-deletions as indicated, together with 80 ng/well pCEFL or pvG-PCR-CEFL. Luciferase was determined 48 h post transfection and induction ratios are shown to the right of the graph. pGL3Basic is promoterless luciferase control vector. Luciferase was normalized to protein since GPCR induced expression of the cotransfected β-galactosidase. Graphed is mean±SEM of 6 replicates. Shown is one of three similar experiments.

[0065] FIG. **48** shows that VEGF and VEGF-C regulate ephrin B2 expression. A) Inhibition of ephrin B2 by neutralizing antibodies. Cells were cultured in full growth medium and exposed to antibody (100 ng/ml) for 36 hr before collection and lysis for Western blot. B) For induction of ephrin B2 expression cells were cultured in EBM growth medium containing 5% serum lacking growth factors. Individual growth factors were added as indicated and the cells harvested after 36 h. Quantity of protein loading and transfer was determined by reprobing the membranes β-actin monoclonal antibody.

[0066] FIG. **49** shows that Ephrin B2 knock-down with specific siRNA inhibits viability in KS cells and HUVEC grown in the presence of VEGF but not IGF, EGF or bFGF. A) KS-SLK cells were transfected with various siRNA to ephrin B2 and controls. After 48 hr the cells were harvested and crude cell lysates fractionated on 4-20% SDS-PAGE. Western blot was performed with monoclonal antibody to ephrin B2 generated in-house. The membrane was stripped and reprobed with β-actin monoclonal antibody (Sigma) to illustrate equivalent loading and transfer. B) 3 day cell viability assay of KS-SLK cultures in the presence of ephrin B2 and EphB4 siRNAs. 1×10^5 cells/well in 24-well plates were treated with 0, 10 and 100 ng/ml siRNAs as indicated on the graph. Viability of cultures was determined by MIT assay as described in the methods section. Shown are the mean±standard deviation of duplicate samples. C) HUVE cells were seeded on eight wells chamber slides coated with fibronectin. The HUVE cells were grown overnight in EGM-2 media, which contains all growth supplements. On the following day, the media was replaced with media containing VEGF (10 ng/ml) or EGF, FGF and IGF as indicated. After 2 hrs of incubation at 37° C., the cells were transfected using Lipofectamine 2000 (Invitrogen) in Opti-MEM medium containing 10 nM of siRNA to ephrin B2, Eph B4 or green fluorescence protein (GFP) as control. The cells were incubated for 2 hr and then the fresh media containing growth factors or VEGF alone was added to their respective wells. After 48 hrs, the cells were stained with crystal violet and the pictures were taken immediately by digital camera at 10× magnification.

[0067] FIG. **50** shows that soluble EphB4 inhibits KS and EC cord formation and in vivo angiogenesis. Cord formation assay of HUVEC in Matrigel™ (upper row). Cells in exponential growth phase were treated overnight with the indicated concentrations of EphB4 extracellular domain (ECD) prior to plating on Matrigel™. Cells were trypsinized and plated (1×10^5 cells/well) in a 24-well plate containing 0.5 ml Matrigel™. Shown are representative 20× phase contrast fields of cord formation after 8 hr plating on Matrigel™ in the continued presence of the test compounds as shown. Original magnification 200×. KS-SLK cells treated in a similar manner (middle row) in a cord formation assay on Matrigel™. Bottom row shows in vivo Matrigel™ assay: Matrigel™ plugs containing growth factors and EphB4 ECD or PBS were implanted subcutaneously in the mid-ventral region of mice. After 7 days the plugs were removed, sectioned and stained with H&E to visualize cells migrating into the matrix. Intact vessels with large lumens are observed in the control, whereas EphB4 ECD almost completely inhibited migration of cells into the Matrigel.

[0068] FIG. **51** shows expression of EPHB4 in bladder cancer cell lines (A), and regulation of EPHB4 expression by EGFR signaling pathway (B).

[0069] FIG. **52** shows that transfection of p53 inhibit the expression of EPHB4 in 5637 cell.

[0070] FIG. **53** shows growth inhibition of bladder cancer cell line (5637) upon treatment with EPHB4 siRNA 472.

[0071] FIG. **54** shows results on apoptosis study of 5637 cells transfected with EPHB4 siRNA 472.

[0072] FIG. **55** shows effects of EPHB4 antisense probes on cell migration. 5637 cells were treated with EPHB4AS10 (10 μM).

[0073] FIG. **56** shows effects of EPHB4 siRNA on cell invasion. 5637 cells were transfected with siRNA 472 or control siRNA.

[0074] FIG. **57** shows comparison of EphB4 monoclonal antibodies by 6250 and in pull-down assay.

[0075] FIG. **58** shows that EphB4 antibodies inhibit the growth of SCC15 xenograft tumors.

[0076] FIG. **59** shows that EphB4 antibodies cause apoptosis, necrosis and decreased angiogenesis in SCC15, head and neck carcinoma tumor type.

[0077] FIG. **60** shows that systemic administration of EphB4 antibodies leads to tumor regression.

[0078] FIG. **61** shows a genomic nucleotide sequence of human EphB4.

[0079] FIG. **62** shows a cDNA nucleotide sequence of human EphB4.

[0080] FIG. **63** shows a genomic nucleotide sequence of human Ephrin B2.

[0081] FIG. **64** shows a cDNA nucleotide sequence of human Ephrin B2.

[0082] FIG. **65** shows an amino acid sequence of human EphB4.

[0083] FIG. **66** shows an amino acid sequence of human Ephrin B2.

DETAILED DESCRIPTION OF THE INVENTION

I. Overview

[0084] The current invention is based in part on the discovery that signaling through the ephrin/ephrin receptor pathway contributes to tumorigenesis. Applicants detected expression of ephrin B2 and EphB4 in tumor tissues and developed anti-tumor therapeutic agents for blocking signaling through the ephrin/ephrin receptor. In addition, the disclosure provides polypeptide therapeutic agents and methods for polypeptide-based inhibition of the function of EphB4 and/or Ephrin B2. Accordingly, in certain aspects, the disclosure provides numerous polypeptide compounds (agents) that may be used to treat cancer as well as angiogenesis related disorders and unwanted angiogenesis related processes.

[0085] As used herein, the terms Ephrin and Eph are used to refer, respectively, to ligands and receptors. They can be from any of a variety of animals (e.g., mammals/non-mammals, vertebrates/non-vertebrates, including humans). The nomenclature in this area has changed rapidly and the terminology used herein is that proposed as a result of work by the Eph Nomenclature Committee, which can be accessed, along with previously-used names at web site http://www.eph-nomenclature.com.

[0086] The work described herein, particularly in the examples, refers to Ephrin B2 and EphB4. However, the present invention contemplates any ephrin ligand and/or Eph receptor within their respective family, which is expressed in a tumor. The ephrins (ligands) are of two structural types, which can be further subdivided on the basis of sequence relationships and, functionally, on the basis of the preferential binding they exhibit for two corresponding receptor subgroups. Structurally, there are two types of ephrins: those which are membrane-anchored by a glycerophosphatidylinositol (GPI) linkage and those anchored through a transmembrane domain. Conventionally, the ligands are divided into the Ephrin-A subclass, which are GPI-linked proteins which bind preferentially to EphA receptors, and the Ephrin-B subclass, which are transmembrane proteins which generally bind preferentially to EphB receptors.

[0087] The Eph family receptors are a family of receptor protein-tyrosine kinases which are related to Eph, a receptor named for its expression in an erythropoietin-producing human hepatocellular carcinoma cell line. They are divided into two subgroups on the basis of the relatedness of their extracellular domain sequences and their ability to bind preferentially to Ephrin-A proteins or Ephrin-B proteins. Receptors which interact preferentially with Ephrin-A proteins are EphA receptors and those which interact preferentially with Ephrin-B proteins are EphB receptors.

[0088] Eph receptors have an extracellular domain composed of the ligand-binding globular domain, a cysteine rich region followed by a pair of fibronectin type III repeats (e.g., see FIG. **16**). The cytoplasmic domain consists of a juxtamembrane region containing two conserved tyrosine residues; a protein tyrosine kinase domain; a sterile α-motif (SAM) and a PDZ-domain binding motif. EphB4 is specific for the membrane-bound ligand Ephrin B2 (Sakano, S. et al 1996; Brambilla R. et al 1995). Ephrin B2 belongs to the class of Eph ligands that have a transmembrane domain and cytoplasmic region with five conserved tyrosine residues and PDZ domain. Eph receptors are activated by binding of clustered, membrane attached ephrins (Davis S et al, 1994), indicating that contact between cells expressing the receptors and cells expressing the ligands is required for Eph activation.

[0089] Upon ligand binding, an Eph receptor dimerizes and autophosphorylate the juxtamembrane tyrosine residues to acquire full activation (Kalo M S et al, 1999, Binns K S, 2000). In addition to forward signaling through the Eph receptor, reverse signaling can occur through the ephrin Bs. Eph engagement of ephrins results in rapid phosphorylation

of the conserved intracellular tyrosines (Bruckner K, 1997) and somewhat slower recruitment of PDZ binding proteins (Palmer A 2002). Recently, several studies have shown that high expression of Eph/ephrins may be associated with increased potentials for tumor growth, tumorigenicity, and metastasis (Easty D J, 1999; Kiyokawa E, 1994; Tang X X, 1999; Vogt T, 1998; Liu W, 2002; Stephenson S A, 2001; Steube K G 1999; Berclaz G, 1996).

[0090] In certain embodiments, the present invention provides polypeptide therapeutic agents that inhibit activity of Ephrin B2, EphB4, or both. As used herein, the term "polypeptide therapeutic agent" or "polypeptide agent" is a generic term which includes any polypeptide that blocks signaling through the Ephrin B2/EphB4 pathway. A preferred polypeptide therapeutic agent of the invention is a soluble polypeptide of Ephrin B2 or EphB4. Another preferred polypeptide therapeutic agent of the invention is an antagonist antibody that binds to Ephrin B2 or EphB4. For example, such polypeptide therapeutic agent can inhibit function of Ephrin B2 or EphB4, inhibit the interaction between Ephrin B2 and EphB4, inhibit the phosphorylation of Ephrin B2 or EphB4, or inhibit any of the downstream signaling events upon binding of Ephrin B2 to EphB4.

II. Soluble Polypeptides

[0091] In certain aspects, the invention relates to a soluble polypeptide comprising an extracellular domain of an Ephrin B2 protein (referred to herein as an Ephrin B2 soluble polypeptide) or comprising an extracellular domain of an EphB4 protein (referred to herein as an EphB4 soluble polypeptide). Preferably, the subject soluble polypeptide is a monomer and is capable of binding with high affinity to Ephrin B2 or EphB4. In a specific embodiment, the EphB4 soluble polypeptide of the invention comprises a globular domain of an EphB4 protein. Specific examples EphB4 soluble polypeptides are provided in FIGS. **1**, **2**, and **15**. Specific examples of Ephrin B2 soluble polypeptides are provided in FIGS. **3** and **14**.

[0092] As used herein, the subject soluble polypeptides include fragments, functional variants, and modified forms of EphB4 soluble polypeptide or an Ephrin B2 soluble polypeptide. These fragments, functional variants, and modified forms of the subject soluble polypeptides antagonize function of EphB4, Ephrin B2 or both.

[0093] In certain embodiments, isolated fragments of the subject soluble polypeptides can be obtained by screening polypeptides recombinantly produced from the corresponding fragment of the nucleic acid encoding an EphB4 or Ephrin B2 soluble polypeptides. In addition, fragments can be chemically synthesized using techniques known in the art such as conventional Merrifield solid phase f-Moc or t-Boc chemistry. The fragments can be produced (recombinantly or by chemical synthesis) and tested to identify those peptidyl fragments that can function to inhibit function of EphB4 or Ephrin B2, for example, by testing the ability of the fragments to inhibit angiogenesis or tumor growth.

[0094] In certain embodiments, a functional variant of an EphB4 soluble polypeptide has an amino acid sequence that is at least 90%, 95%, 97%, 99% or 100% identical to residues 1-522, residues 1-412, or residues 1-312 of the amino acid sequence defined by FIG. **65**. In other embodiments, a functional variant of an Ephrin 82 soluble polypeptide has a sequence at least 90%, 95%, 97%, 99% or 100% identical to residues 1-225 of the amino acid sequence defined by FIG. **66**.

[0095] In certain embodiments, the present invention contemplates making functional variants by modifying the structure of the subject soluble polypeptide for such purposes as enhancing therapeutic or prophylactic efficacy, or stability (e.g., ex vivo shelf life and resistance to proteolytic degradation in vivo). Such modified soluble polypeptide are considered functional equivalents of the naturally-occurring EphB4 or Ephrin B2 soluble polypeptide. Modified soluble polypeptides can be produced, for instance, by amino acid substitution, deletion, or addition. For instance, it is reasonable to expect, for example, that an isolated replacement of a leucine with an isoleucine or valine, an aspartate with a glutamate, a threonine with a serine, or a similar replacement of an amino acid with a structurally related amino acid (e.g., conservative mutations) will not have a major effect on the biological activity of the resulting molecule. Conservative replacements are those that take place within a family of amino acids that are related in their side chains.

[0096] This invention further contemplates a method of generating sets of combinatorial mutants of the EphB4 or Ephrin B2 soluble polypeptides, as well as truncation mutants, and is especially useful for identifying functional variant sequences. The purpose of screening such combinatorial libraries may be to generate, for example, soluble polypeptide variants which can act as antagonists of EphB4, EphB2, or both. Combinatorially-derived variants can be generated which have a selective potency relative to a naturally occurring soluble polypeptide. Such variant proteins, when expressed from recombinant DNA constructs, can be used in gene therapy protocols. Likewise, mutagenesis can give rise to variants which have intracellular half-lives dramatically different than the corresponding wild-type soluble polypeptide. For example, the altered protein can be rendered either more stable or less stable to proteolytic degradation or other cellular process which result in destruction of, or otherwise inactivation of the protein of interest (e.g., a soluble polypeptide). Such variants, and the genes which encode them, can be utilized to alter the subject soluble polypeptide levels by modulating their half-life. For instance, a short half-life can give rise to more transient biological effects and, when part of an inducible expression system, can allow tighter control of recombinant soluble polypeptide levels within the cell. As above, such proteins, and particularly their recombinant nucleic acid constructs, can be used in gene therapy protocols.

[0097] There are many ways by which the library of potential homologs can be generated from a degenerate oligonucleotide sequence. Chemical synthesis of a degenerate gene sequence can be carried out in an automatic DNA synthesizer, and the synthetic genes then be ligated into an appropriate gene for expression. The purpose of a degenerate set of genes is to provide, in one mixture, all of the sequences encoding the desired set of potential soluble polypeptide sequences. The synthesis of degenerate oligonucleotides is well known in the art (see for example, Narang, S A (1983) Tetrahedron 39:3; Itakura et al., (1981) Recombinant DNA, Proc. 3rd Cleveland Sympos. Macromolecules, ed. AG Walton, Amsterdam: Elsevier pp 273-289; Itakura et al., (1984) Annu. Rev. Biochem. 53:323; Itakura et al., (1984) Science 198:1056; Ike et al., (1983) Nucleic Acid Res. 11:477). Such techniques have been employed in the directed evolution of other proteins

(see, for example, Scott et al., (1990) Science 249:386-390; Roberts et al., (1992) PNAS USA 89:2429-2433; Devlin et al., (1990) Science 249: 404-406; Cwirla et al., (1990) PNAS USA 87: 6378-6382; as well as U.S. Pat. Nos. 5,223,409, 5,198,346, and 5,096,815).

[0098] Alternatively, other forms of mutagenesis can be utilized to generate a combinatorial library. For example, soluble polypeptide variants (e.g., the antagonist forms) can be generated and isolated from a library by screening using, for example, alanine scanning mutagenesis and the like (Ruf et al., (1994) Biochemistry 33:1565-1572; Wang et al., (1994) J. Biol. Chem. 269:3095-3099; Balint et al., (1993) Gene 137:109-118; Grodberg et al., (1993) Eur. J. Biochem. 218: 597-601; Nagashima et al., (1993) J. Biol. Chem. 268:2888-2892; Lowman et al., (1991) Biochemistry 30:10832-10838; and Cunningham et al., (1989) Science 244:1081-1085), by linker scanning mutagenesis (Gustin et al., (1993) Virology 193:653-660; Brown et al., (1992) Mol. Cell. Biol. 12:2644-2652; McKnight et al., (1982) Science 232:316); by saturation mutagenesis (Meyers et al., (1986) Science 232:613); by PCR mutagenesis (Leung et al., (1989) Method Cell Mol Biol 1:11-19); or by random mutagenesis, including chemical mutagenesis, etc. (Miller et al., (1992) A Short Course in Bacterial Genetics, CSHL Press, Cold Spring Harbor, N.Y.; and Greener et al., (1994) Strategies in Mol Biol 7:32-34). Linker scanning mutagenesis, particularly in a combinatorial setting, is an attractive method for identifying truncated (bioactive) forms of the subject soluble polypeptide.

[0099] A wide range of techniques are known in the art for screening gene products of combinatorial libraries made by point mutations and truncations, and, for that matter, for screening cDNA libraries for gene products having a certain property. Such techniques will be generally adaptable for rapid screening of the gene libraries generated by the combinatorial mutagenesis of the subject soluble polypeptides. The most widely used techniques for screening large gene libraries typically comprises cloning the gene library into replicable expression vectors, transforming appropriate cells with the resulting library of vectors, and expressing the combinatorial genes under conditions in which detection of a desired activity facilitates relatively easy isolation of the vector encoding the gene whose product was detected. Each of the illustrative assays described below are amenable to high through-put analysis as necessary to screen large numbers of degenerate sequences created by combinatorial mutagenesis techniques.

[0100] In certain embodiments, the subject soluble polypeptides of the invention include a small molecule such as a peptide and a peptidomimetic. As used herein, the term "peptidomimetic" includes chemically modified peptides and peptide-like molecules that contain non-naturally occurring amino acids, peptoids, and the like. Peptidomimetics provide various advantages over a peptide, including enhanced stability when administered to a subject. Methods for identifying a peptidomimetic are well known in the art and include the screening of databases that contain libraries of potential peptidomimetics. For example, the Cambridge Structural Database contains a collection of greater than 300,000 compounds that have known crystal structures (Allen et al., Acta Crystallogr. Section B, 35:2331 (1979)). Where no crystal structure of a target molecule is available, a structure can be generated using, for example, the program CONCORD (Rusinko et al., J. Chem. Inf. Comput. Sci. 29:251 (1989)). Another database, the Available Chemicals Directory (Molecular Design Limited, Informations Systems; San Leandro Calif.), contains about 100,000 compounds that are commercially available and also can be searched to identify potential peptidomimetics of the EphB4 or Ephrin B2 soluble polypeptides.

[0101] To illustrate, by employing scanning mutagenesis to map the amino acid residues of a soluble polypeptide which are involved in binding to another protein, peptidomimetic compounds can be generated which mimic those residues involved in binding. For instance, non-hydrolyzable peptide analogs of such residues can be generated using benzodiazepine (e.g., see Freidinger et al., in Peptides: Chemistry and Biology, G. R. Marshall ed., ESCOM Publisher: Leiden, Netherlands, 1988), azepine (e.g., see Huffman et al., in Peptides: Chemistry and Biology, G. R. Marshall ed., ESCOM Publisher: Leiden, Netherlands, 1988), substituted gamma lactam rings (Garvey et al., in Peptides: Chemistry and Biology, G. R. Marshall ed., ESCOM Publisher: Leiden, Netherlands, 1988), keto-methylene pseudopeptides (Ewenson et al., (1986) J. Med. Chem. 29:295; and Ewenson et al., in Peptides: Structure and Function (Proceedings of the 9th American Peptide Symposium) Pierce Chemical Co. Rockland, Ill., 1985), b-turn dipeptide cores (Nagai et al., (1985) Tetrahedron Lett 26:647; and Sato et al., (1986) J Chem Soc Perkin Trans 1:1231), and b-aminoalcohols (Gordon et al., (1985) Biochem Biophys Res Commun 126:419; and Dann et al., (1986) Biochem Biophys Res Commun 134:71).

[0102] In certain embodiments, the soluble polypeptides of the invention may further comprise post-translational modifications. Such modifications include, but are not limited to, acetylation, carboxylation, glycosylation, phosphorylation, lipidation, and acylation. As a result, the modified soluble polypeptides may contain non-amino acid elements, such as polyethylene glycols, lipids, poly- or mono-saccharide, and phosphates. Effects of such non-amino acid elements on the functionality of a soluble polypeptide may be tested for its antagonizing role in EphB4 or Ephrin B2 function, e.g, it inhibitory effect on angiogenesis or on tumor growth.

[0103] In certain aspects, functional variants or modified forms of the subject soluble polypeptides include fusion proteins having at least a portion of the soluble polypeptide and one or more fusion domains. Well known examples of such fusion domains include, but are not limited to, polyhistidine, Glu-Glu, glutathione S transferase (GST), thioredoxin, protein A, protein G, and an immunoglobulin heavy chain constant region (Fc), maltose binding protein (MBP), which are particularly useful for isolation of the fusion proteins by affinity chromatography. For the purpose of affinity purification, relevant matrices for affinity chromatography, such as glutathione-, amylase-, and nickel- or cobalt-conjugated resins are used. Another fusion domain well known in the art is green fluorescent protein (GFP). Fusion domains also include "epitope tags," which are usually short peptide sequences for which a specific antibody is available. Well known epitope tags for which specific monoclonal antibodies are readily available include FLAG, influenza virus haemagglutinin (HA), and c-myc tags. In some cases, the fusion domains have a protease cleavage site, such as for Factor Xa or Thrombin, which allows the relevant protease to partially digest the fusion proteins and thereby liberate the recombinant proteins therefrom. The liberated proteins can then be isolated from the fusion domain by subsequent chromatographic separation. In certain embodiments, the soluble polypeptides of the present invention contain one or more modifications that are capable of stabilizing the soluble polypeptides. For example,

such modifications enhance the in vitro half life of the soluble polypeptides, enhance circulatory half life of the soluble polypeptides or reducing proteolytic degradation of the soluble polypeptides.

[0104] In certain embodiments, soluble polypeptides (unmodified or modified) of the invention can be produced by a variety of art-known techniques. For example, such soluble polypeptides can be synthesized using standard protein chemistry techniques such as those described in Bodansky, M. Principles of Peptide Synthesis, Springer Verlag, Berlin (1993) and Grant G. A. (ed.), Synthetic Peptides: A User's Guide, W. H. Freeman and Company, New York (1992). In addition, automated peptide synthesizers are commercially available (e.g., Advanced ChemTech Model 396; Milligen/Biosearch 9600). Alternatively, the soluble polypeptides, fragments or variants thereof may be recombinantly produced using various expression systems as is well known in the art (also see below).

III. Nucleic Acids Encoding Soluble Polypeptides

[0105] In certain aspects, the invention relates to isolated and/or recombinant nucleic acids encoding an EphB4 or Ephrin B2 soluble polypeptide. The subject nucleic acids may be single-stranded or double-stranded, DNA or RNA molecules. These nucleic acids are useful as therapeutic agents. For example, these nucleic acids are useful in making recombinant soluble polypeptides which are administered to a cell or an individual as therapeutics. Alternative, these nucleic acids can be directly administered to a cell or an individual as therapeutics such as in gene therapy.

[0106] In certain embodiments, the invention provides isolated or recombinant nucleic acid sequences that are at least 80%, 85%, 90%, 95%, 97%, 98%, 99% or 100% identical to a region of the nucleotide sequence depicted in FIG. **62** or **63**. One of ordinary skill in the art will appreciate that nucleic acid sequences complementary to the subject nucleic acids, and variants of the subject nucleic acids are also within the scope of this invention. In further embodiments, the nucleic acid sequences of the invention can be isolated, recombinant, and/or fused with a heterologous nucleotide sequence, or in a DNA library.

[0107] In other embodiments, nucleic acids of the invention also include nucleotide sequences that hybridize under highly stringent conditions to the nucleotide sequence depicted in FIG. **62** or **63**, or complement sequences thereof. As discussed above, one of ordinary skill in the art will understand readily that appropriate stringency conditions which promote DNA hybridization can be varied. One of ordinary skill in the art will understand readily that appropriate stringency conditions which promote DNA hybridization can be varied. For example, one could perform the hybridization at 6.0× sodium chloride/sodium citrate (SSC) at about 45° C., followed by a wash of 2.0×SSC at 50° C. For example, the salt concentration in the wash step can be selected from a low stringency of about 2.0×SSC at 50° C. to a high stringency of about 0.2×SSC at 50° C. In addition, the temperature in the wash step can be increased from low stringency conditions at room temperature, about 22° C., to high stringency conditions at about 65° C. Both temperature and salt may be varied, or temperature or salt concentration may be held constant while the other variable is changed. In one embodiment, the invention provides nucleic acids which hybridize under low stringency conditions of 6×SSC at room temperature followed by a wash at 2×SSC at room temperature.

[0108] Isolated nucleic acids which differ from the subject nucleic acids due to degeneracy in the genetic code are also within the scope of the invention. For example, a number of amino acids are designated by more than one triplet. Codons that specify the same amino acid, or synonyms (for example, CAU and CAC are synonyms for histidine) may result in "silent" mutations which do not affect the amino acid sequence of the protein. However, it is expected that DNA sequence polymorphisms that do lead to changes in the amino acid sequences of the subject proteins will exist among mammalian cells. One skilled in the art will appreciate that these variations in one or more nucleotides (up to about 3-5% of the nucleotides) of the nucleic acids encoding a particular protein may exist among individuals of a given species due to natural allelic variation. Any and all such nucleotide variations and resulting amino acid polymorphisms are within the scope of this invention.

[0109] In certain embodiments, the recombinant nucleic acids of the invention may be operably linked to one or more regulatory nucleotide sequences in an expression construct. Regulatory nucleotide sequences will generally be appropriate for a host cell used for expression. Numerous types of appropriate expression vectors and suitable regulatory sequences are known in the art for a variety of host cells. Typically, said one or more regulatory nucleotide sequences may include, but are not limited to, promoter sequences, leader or signal sequences, ribosomal binding sites, transcriptional start and termination sequences, translational start and termination sequences, and enhancer or activator sequences. Constitutive or inducible promoters as known in the art are contemplated by the invention. The promoters may be either naturally occurring promoters, or hybrid promoters that combine elements of more than one promoter. An expression construct may be present in a cell on an episome, such as a plasmid, or the expression construct may be inserted in a chromosome. In a preferred embodiment, the expression vector contains a selectable marker gene to allow the selection of transformed host cells. Selectable marker genes are well known in the art and will vary with the host cell used.

[0110] In certain aspect of the invention, the subject nucleic acid is provided in an expression vector comprising a nucleotide sequence encoding an EphB4 or Ephrin B2 soluble polypeptide and operably linked to at least one regulatory sequence. Regulatory sequences are art-recognized and are selected to direct expression of the soluble polypeptide. Accordingly, the term regulatory sequence includes promoters, enhancers, and other expression control elements. Exemplary regulatory sequences are described in Goeddel; *Gene Expression Technology: Methods in Enzymology*, Academic Press, San Diego, Calif. (1990). For instance, any of a wide variety of expression control sequences that control the expression of a DNA sequence when operatively linked to it may be used in these vectors to express DNA sequences encoding a soluble polypeptide. Such useful expression control sequences, include, for example, the early and late promoters of SV40, tet promoter, adenovirus or cytomegalovirus immediate early promoter, the lac system, the trp system, the TAC or TRC system, T7 promoter whose expression is directed by T7 RNA polymerase, the major operator and promoter regions of phage lambda, the control regions for fd coat protein, the promoter for 3-phosphoglycerate kinase or other glycolytic enzymes, the promoters of acid phosphatase, e.g., Pho5, the promoters of the yeast α-mating factors, the polyhedron promoter of the baculovirus system and other

sequences known to control the expression of genes of prokaryotic or eukaryotic cells or their viruses, and various combinations thereof. It should be understood that the design of the expression vector may depend on such factors as the choice of the host cell to be transformed and/or the type of protein desired to be expressed. Moreover, the vector's copy number, the ability to control that copy number and the expression of any other protein encoded by the vector, such as antibiotic markers, should also be considered.

[0111] This invention also pertains to a host cell transfected with a recombinant gene including a coding sequence for one or more of the subject soluble polypeptide. The host cell may be any prokaryotic or eukaryotic cell. For example, a soluble polypeptide of the invention may be expressed in bacterial cells such as *E. coli*, insect cells (e.g., using a baculovirus expression system), yeast, or mammalian cells. Other suitable host cells are known to those skilled in the art.

[0112] Accordingly, the present invention further pertains to methods of producing the subject soluble polypeptides. For example, a host cell transfected with an expression vector encoding an EphB4 soluble polypeptide can be cultured under appropriate conditions to allow expression of the EphB4 soluble polypeptide to occur. The EphB4 soluble polypeptide may be secreted and isolated from a mixture of cells and medium containing the soluble polypeptides. Alternatively, the soluble polypeptides may be retained cytoplasmically or in a membrane fraction and the cells harvested, lysed and the protein isolated. A cell culture includes host cells, media and other byproducts. Suitable media for cell culture are well known in the art. The soluble polypeptides can be isolated from cell culture medium, host cells, or both using techniques known in the art for purifying proteins, including ion-exchange chromatography, gel filtration chromatography, ultrafiltration, electrophoresis, and immunoaffinity purification with antibodies specific for particular epitopes of the soluble polypeptides. In a preferred embodiment, the soluble polypeptide is a fusion protein containing a domain which facilitates its purification.

[0113] A recombinant nucleic acid of the invention can be produced by ligating the cloned gene, or a portion thereof, into a vector suitable for expression in either prokaryotic cells, eukaryotic cells (yeast, avian, insect or mammalian), or both. Expression vehicles for production of a recombinant soluble polypeptide include plasmids and other vectors. For instance, suitable vectors include plasmids of the types: pBR322-derived plasmids, pEMBL-derived plasmids, pEX-derived plasmids, pBTac-derived plasmids and pUC-derived plasmids for expression in prokaryotic cells, such as *E. coli*.

[0114] The preferred mammalian expression vectors contain both prokaryotic sequences to facilitate the propagation of the vector in bacteria, and one or more eukaryotic transcription units that are expressed in eukaryotic cells. The pcDNAI/amp, pcDNAI/neo, pRc/CMV, pSV2gpt, pSV2neo, pSV2-dhfr, pTk2, pRSVneo, pMSG, pSVT7, pko-neo and pHyg derived vectors are examples of mammalian expression vectors suitable for transfection of eukaryotic cells. Some of these vectors are modified with sequences from bacterial plasmids, such as pBR322, to facilitate replication and drug resistance selection in both prokaryotic and eukaryotic cells. Alternatively, derivatives of viruses such as the bovine papilloma virus (BPV-1), or Epstein-Barr virus (pHEBo, pREP-derived and p205) can be used for transient expression of proteins in eukaryotic cells. Examples of other viral (including retroviral) expression systems can be found below in the description of gene therapy delivery systems. The various methods employed in the preparation of the plasmids and transformation of host organisms are well known in the art. For other suitable expression systems for both prokaryotic and eukaryotic cells, as well as general recombinant procedures, see *Molecular Cloning A Laboratory Manual,* 2nd Ed., ed. by Sambrook, Fritsch and Maniatis (Cold Spring Harbor Laboratory Press, 1989) Chapters 16 and 17. In some instances, it may be desirable to express the recombinant SLC5A8 polypeptide by the use of a baculovirus expression system. Examples of such baculovirus expression systems include pVL-derived vectors (such as pVL1392, pVL1393 and pVL941), pAcUW-derived vectors (such as pAcUW1), and pBlueBac-derived vectors (such as the β-gal containing pBlueBac III).

[0115] Techniques for making fusion genes are well known. Essentially, the joining of various DNA fragments coding for different polypeptide sequences is performed in accordance with conventional techniques, employing blunt-ended or stagger-ended termini for ligation, restriction enzyme digestion to provide for appropriate termini, filling-in of cohesive ends as appropriate, alkaline phosphatase treatment to avoid undesirable joining, and enzymatic ligation. In another embodiment, the fusion gene can be synthesized by conventional techniques including automated DNA synthesizers. Alternatively, PCR amplification of gene fragments can be carried out using anchor primers which give rise to complementary overhangs between two consecutive gene fragments which can subsequently be annealed to generate a chimeric gene sequence (see, for example, *Current Protocols in Molecular Biology*, eds. Ausubel et al., John Wiley & Sons: 1992).

IV. Antibodies

[0116] In certain aspects, the present invention provides antagonist antibodies against Ephrin B2 or EphB4. As described herein, the term "antagonist antibody" refers to an antibody that inhibits function of Ephrin B2 or EphB4. Preferably, the antagonist antibody binds to an extracellular domain of Ephrin B2 or EphB4. It is understood that antibodies of the invention may be polyclonal or monoclonal; intact or truncated, e.g., F(ab')2, Fab, Fv; xenogeneic, allogeneic, syngeneic, or modified forms thereof, e.g., humanized, chimeric, etc.

[0117] For example, by using immunogens derived from an Ephrin B2 or EphB4 polypeptide, anti-protein/anti-peptide antisera or monoclonal antibodies can be made by standard protocols (see, for example, Antibodies: A Laboratory Manual ed. by Harlow and Lane (Cold Spring Harbor Press: 1988)). A mammal, such as a mouse, a hamster or rabbit can be immunized with an immunogenic form of the peptide. (e.g., a polypeptide or an antigenic fragment which is capable of eliciting an antibody response, or a fusion protein). Techniques for conferring immunogenicity on a protein or peptide include conjugation to carriers or other techniques well known in the art. An immunogenic portion of an Ephrin B2 or EphB4 polypeptide can be administered in the presence of adjuvant. The progress of immunization can be monitored by detection of antibody titers in plasma or serum. Standard ELISA or other immunoassays can be used with the immunogen as antigen to assess the levels of antibodies. In one embodiment, antibodies of the invention are specific for the extracellular portion of the Ephrin B2 or EphB4 protein. In another embodiment, antibodies of the invention are specific

for the intracellular portion or the transmembrane portion of the Ephrin B2 or EphB4 protein. In a further embodiment, antibodies of the invention are specific for the extracellular portion of the Ephrin B2 or EphB4 protein.

[0118] Following immunization of an animal with an antigenic preparation of an Ephrin 82 or EphB4 polypeptide, antisera can be obtained and, if desired, polyclonal antibodies can be isolated from the serum. To produce monoclonal antibodies, antibody-producing cells (lymphocytes) can be harvested from an immunized animal and fused by standard somatic cell fusion procedures with immortalizing cells such as myeloma cells to yield hybridoma cells. Such techniques are well known in the art, and include, for example, the hybridoma technique (originally developed by Kohler and Milstein, (1975) Nature, 256: 495-497), the human B cell hybridoma technique (Kozbar et al., (1983) Immunology Today, 4: 72), and the EBV-hybridoma technique to produce human monoclonal antibodies (Cole et al., (1985) Monoclonal Antibodies and Cancer Therapy, Alan R. Liss, Inc. pp. 77-96). Hybridoma cells can be screened immunochemically for production of antibodies specifically reactive with an Ephrin 82 or EphB4 polypeptide and monoclonal antibodies isolated from a culture comprising such hybridoma cells.

[0119] The term antibody as used herein is intended to include fragments thereof which are also specifically reactive with an Ephrin B2 or EphB4 polypeptides. Antibodies can be fragmented using conventional techniques and the fragments screened for utility in the same manner as described above for whole antibodies. For example, $F(ab)_2$ fragments can be generated by treating antibody with pepsin. The resulting $F(ab)_2$ fragment can be treated to reduce disulfide bridges to produce Fab fragments. The antibody of the present invention is further intended to include bispecific, single-chain, and chimeric and humanized molecules having affinity for an Ephrin B2 or EphB4 polypeptide conferred by at least one CDR region of the antibody. Techniques for the production of single chain antibodies (U.S. Pat. No. 4,946,778) can also be adapted to produce single chain antibodies. Also, transgenic mice or other organisms including other mammals, may be used to express humanized antibodies. In preferred embodiments, the antibodies further comprise a label attached thereto and able to be detected (e.g., the label can be a radioisotope, fluorescent compound, enzyme or enzyme co-factor).

[0120] In certain preferred embodiments, an antibody of the invention is a monoclonal antibody, and in certain embodiments the invention makes available methods for generating novel antibodies. For example, a method for generating a monoclonal antibody that binds specifically to an Ephrin B2 or EphB4 polypeptide may comprise administering to a mouse an amount of an immunogenic composition comprising the Ephrin B2 or EphB4 polypeptide effective to stimulate a detectable immune response, obtaining antibody-producing cells (e.g., cells from the spleen) from the mouse and fusing the antibody-producing cells with myeloma cells to obtain antibody-producing hybridomas, and testing the antibody-producing hybridomas to identify a hybridoma that produces a monoclonal antibody that binds specifically to the Ephrin B2 or EphB4 polypeptide. Once obtained, a hybridoma can be propagated in a cell culture, optionally in culture conditions where the hybridoma-derived cells produce the monoclonal antibody that binds specifically to the Ephrin B2 or EphB4 polypeptide. The monoclonal antibody may be purified from the cell culture.

[0121] In addition, the techniques used to screen antibodies in order to identify a desirable antibody may influence the properties of the antibody obtained. For example, an antibody to be used for certain therapeutic purposes will preferably be able to target a particular cell type. Accordingly, to obtain antibodies of this type, it may be desirable to screen for antibodies that bind to cells that express the antigen of interest (e.g., by fluorescence activated cell sorting). Likewise, if an antibody is to be used for binding an antigen in solution, it may be desirable to test solution binding. A variety of different techniques are available for testing antibody:antigen interactions to identify particularly desirable antibodies. Such techniques include ELISAs, surface plasmon resonance binding assays (e.g. the Biacore binding assay, Bia-core AB, Uppsala, Sweden), sandwich assays (e.g. the paramagnetic bead system of IGEN International, Inc., Gaithersburg, Md.), western blots, immunoprecipitation assays and immunohistochemistry.

V. Drug Screening Assays

[0122] There are numerous approaches to screening for polypeptide therapeutic agents as antagonists of EphB4, Ephrin B2 or both. For example, high-throughput screening of compounds or molecules can be carried out to identify agents or drugs which inhibit angiogenesis or inhibit tumor growth. Test agents can be any chemical (element, molecule, compound, drug), made synthetically, made by recombinant techniques or isolated from a natural source. For example, test agents can be peptides, polypeptides, peptoids, sugars, hormones, or nucleic acid molecules. In addition, test agents can be small molecules or molecules of greater complexity made by combinatorial chemistry, for example, and compiled into libraries. These libraries can comprise, for example, alcohols, alkyl halides, amines, amides, esters, aldehydes, ethers and other classes of organic compounds. Test agents can also be natural or genetically engineered products isolated from lysates or growth media of cells—bacterial, animal or plant—or can be the cell lysates or growth media themselves. Presentation of test compounds to the test system can be in either an isolated form or as mixtures of compounds, especially in initial screening steps.

[0123] For example, an assay can be carried out to screen for compounds that specifically inhibit binding of Ephrin B2 (ligand) to EphB4 (receptor), or vice-versa, e.g., by inhibition of binding of labeled ligand- or receptor-Fc fusion proteins to immortalized cells. Compounds identified through this screening can then be tested in animals to assess their anti-angiogenesis or anti-tumor activity in vivo.

[0124] In one embodiment of an assay to identify a substance that interferes with interaction of two cell surface molecules (e.g., Ephrin B2 and EphB4), samples of cells expressing one type of cell surface molecule (e.g., EphB4) are contacted with either labeled ligand (e.g., Ephrin B2, or a soluble portion thereof, or a fusion protein such as a fusion of the extracellular domain and the Fc domain of IgG) or labeled ligand plus a test compound (or group of test compounds). The amount of labeled ligand which has bound to the cells is determined. A lesser amount of label (where the label can be, for example, a radioactive isotope, a fluorescent or colormetric label) in the sample contacted with the test compound(s) is an indication that the test compound(s) interferes with binding. The reciprocal assay using cells expressing a ligand (e.g., an Ephrin B2 ligand or a soluble form thereof) can be used to test for a substance that interferes with the binding of an Eph receptor or soluble portion thereof.

[0125] An assay to identify a substance which interferes with interaction between an Eph receptor and an ephrin can be performed with the component (e.g., cells, purified protein, including fusion proteins and portions having binding activity) which is not to be in competition with a test compound, linked to a solid support. The solid support can be any suitable solid phase or matrix, such as a bead, the wall of a plate or other suitable surface (e.g., a well of a microtiter plate), column pore glass (CPG) or a pin that can be submerged into a solution, such as in a well. Linkage of cells or purified protein to the solid support can be either direct or through one or more linker molecules.

[0126] In one embodiment, an isolated or purified protein (e.g., an Eph receptor or an ephrin) can be immobilized on a suitable affinity matrix by standard techniques, such as chemical cross-linking, or via an antibody raised against the isolated or purified protein, and bound to a solid support. The matrix can be packed in a column or other suitable container and is contacted with one or more compounds (e.g., a mixture) to be tested under conditions suitable for binding of the compound to the protein. For example, a solution containing compounds can be made to flow through the matrix. The matrix can be washed with a suitable wash buffer to remove unbound compounds and non-specifically bound compounds. Compounds which remain bound can be released by a suitable elution buffer. For example, a change in the ionic Strength or pH of the elution buffer can lead to a release of compounds. Alternatively, the elution buffer can comprise a release component or components designed to disrupt binding of compounds (e.g., one or more ligands or receptors, as appropriate, or analogs thereof which can disrupt binding or competitively inhibit binding of test compound to the protein).

[0127] Fusion proteins comprising all, or a portion of, a protein (e.g., an Eph receptor or an ephrin) linked to a second moiety not occurring in that protein as found in nature can be prepared for use in another embodiment of the method. Suitable fusion proteins for this purpose include those in which the second moiety comprises an affinity ligand (e.g., an enzyme, antigen, epitope). The fusion proteins can be produced by inserting the protein (e.g., an Eph receptor or an ephrin) or a portion thereof into a suitable expression vector which encodes an affinity ligand. The expression vector can be introduced into a suitable host cell for expression. Host cells are disrupted and the cell material, containing fusion protein, can be bound to a suitable affinity matrix by contacting the cell material with an affinity matrix under conditions sufficient for binding of the affinity ligand portion of the fusion protein to the affinity matrix.

[0128] In one aspect of this embodiment, a fusion protein can be immobilized on a suitable affinity matrix under conditions sufficient to bind the affinity ligand portion of the fusion protein to the matrix, and is contacted with one or more compounds (e.g., a mixture) to be tested, under conditions suitable for binding of compounds to the receptor or ligand protein portion of the bound fusion protein. Next, the affinity matrix with bound fusion protein can be washed with a suitable wash buffer to remove unbound compounds and non-specifically bound compounds without significantly disrupting binding of specifically bound compounds. Compounds'which remain bound can be released by contacting the affinity matrix having fusion protein bound thereto with a suitable elution buffer (a compound elution buffer). In this aspect, compound elution buffer can be formulated to permit retention of the fusion protein by the affinity matrix, but can be formulated to interfere with binding of the compound(s) tested to the receptor or ligand protein portion of the fusion protein. For example, a change in the ionic strength or pH of the elution buffer can lead to release of compounds, or the elution buffer can comprise a release component or components designed to disrupt binding of compounds to the receptor or ligand protein portion of the fusion protein (e.g., one or more ligands or receptors or analogs thereof which can disrupt binding of compounds to the receptor or ligand protein portion of the fusion protein). Immobilization can be performed prior to, simultaneous with, or after contacting the fusion protein with compound, as appropriate. Various permutations of the method are possible, depending upon factors such as the compounds tested, the affinity matrix selected, and elution buffer formulation. For example, after the wash step, fusion protein with compound bound thereto can be eluted from the affinity matrix with a suitable elution buffer (a matrix elution buffer). Where the fusion protein comprises a cleavable linker, such as a thrombin cleavage site, cleavage from the affinity ligand can release a portion of the fusion with compound bound thereto. Bound compound can then be released from the fusion protein or its cleavage product by an appropriate method, such as extraction.

VI. Methods of Treatment

[0129] In certain embodiments, the present invention provides methods of inhibiting angiogenesis and methods of treating angiogenesis-associated diseases. In other embodiments, the present invention provides methods of inhibiting or reducing tumor growth and methods of treating an individual suffering from cancer. These methods involve administering to the individual a therapeutically effective amount of one or more polypeptide therapeutic agents as described above. These methods are particularly aimed at therapeutic and prophylactic treatments of animals, and more particularly, humans.

[0130] As described herein, angiogenesis-associated diseases include, but are not limited to, angiogenesis-dependent cancer, including, for example, solid tumors, blood born tumors such as leukemias, and tumor metastases; benign tumors, for example hemangiomas, acoustic neuromas, neurofibromas, trachomas, and pyogenic granulomas; inflammatory disorders such as immune and non-immune inflammation; chronic articular rheumatism and psoriasis; ocular angiogenic diseases, for example, diabetic retinopathy, retinopathy of prematurity, macular degeneration, corneal graft rejection, neovascular glaucoma, retrolental fibroplasia, rubeosis; Osler-Webber Syndrome; myocardial angiogenesis; plaque neovascularization; telangiectasia; hemophiliac joints; angiofibroma; and wound granulation and wound healing; telangiectasia psoriasis scleroderma, pyogenic granuloma, coronary collaterals, ischemic limb angiogenesis, corneal diseases, rubeosis, arthritis, diabetic neovascularization, fractures, vasculogenesis, hematopoiesis.

[0131] It is understood that methods and compositions of the invention are also useful for treating any angiogenesis-independent cancers (tumors). As used herein, the term "angiogenesis-independent cancer" refers to a cancer (tumor) where there is no or little neovascularization in the tumor tissue.

[0132] In particular, polypeptide therapeutic agents of the present invention are useful for treating or preventing a cancer (tumor), including, but not limited to, colon carcinoma, breast

cancer, mesothelioma, prostate cancer, bladder cancer, squamous cell carcinoma of the head and neck (HNSCC), Kaposi sarcoma, and leukemia.

[0133] In certain embodiments of such methods, one or more polypeptide therapeutic agents can be administered, together (simultaneously) or at different times (sequentially). In addition, polypeptide therapeutic agents can be administered with another type of compounds for treating cancer or for inhibiting angiogenesis.

[0134] In certain embodiments, the subject methods of the invention can be used alone. Alternatively, the subject methods may be used in combination with other conventional anti-cancer therapeutic approaches directed to treatment or prevention of proliferative disorders (e.g., tumor). For example, such methods can be used in prophylactic cancer prevention, prevention of cancer recurrence and metastases after surgery, and as an adjuvant of other conventional cancer therapy. The present invention recognizes that the effectiveness of conventional cancer therapies (e.g., chemotherapy, radiation therapy, phototherapy, immunotherapy, and surgery) can be enhanced through the use of a subject polypeptide therapeutic agent.

[0135] A wide array of conventional compounds have been shown to have anti-neoplastic activities. These compounds have been used as pharmaceutical agents in chemotherapy to shrink solid tumors, prevent metastases and further growth, or decrease the number of malignant cells in leukemic or bone marrow malignancies. Although chemotherapy has been effective in treating various types of malignancies, many anti-neoplastic compounds induce undesirable side effects. It has been shown that when two or more different treatments are combined, the treatments may work synergistically and allow reduction of dosage of each of the treatments, thereby reducing the detrimental side effects exerted by each compound at higher dosages. In other instances, malignancies that are refractory to a treatment may respond to a combination therapy of two or more different treatments.

[0136] When a polypeptide therapeutic agent of the present invention is administered in combination with another conventional anti-neoplastic agent, either concomitantly or sequentially, such therapeutic agent is shown to enhance the therapeutic effect of the anti-neoplastic agent or overcome cellular resistance to such anti-neoplastic agent. This allows decrease of dosage of an anti-neoplastic agent, thereby reducing the undesirable side effects, or restores the effectiveness of an anti-neoplastic agent in resistant cells.

[0137] Pharmaceutical compounds that may be used for combinatory anti-tumor therapy include, merely to illustrate: aminoglutethimide, amsacrine, anastrozole, asparaginase, bcg, bicalutamide, bleomycin, buserelin, busulfan, campothecin, capecitabine, carboplatin, carmustine, chlorambucil, cisplatin, cladribine, clodronate, colchicine, cyclophosphamide, cyproterone, cytarabine, dacarbazine, dactinomycin, daunorubicin, dienestrol, diethylstilbestrol, docetaxel, doxorubicin, epirubicin, estradiol, estramustine, etoposide, exemestane, filgrastim, fludarabine, fludrocortisone, fluorouracil, fluoxymesterone, flutamide, gemcitabine, genistein, goserelin, hydroxyurea, idarubicin, ifosfamide, imatinib, interferon, irinotecan, ironotecan, letrozole, leucovorin, leuprolide, levamisole, lomustine, mechlorethamine, medroxyprogesterone, megestrol, melphalan, mercaptopurine, mesna, methotrexate, mitomycin, mitotane, mitoxantrone, nilutamide, nocodazole, octreotide, oxaliplatin, paclitaxel, pamidronate, pentostatin, plicamycin, porfimer, procarbazine, raltitrexed, rituximab, streptozocin, suramin, tamoxifen, temozolomide, teniposide, testosterone, thioguanine, thiotepa, titanocene dichloride, topotecan, trastuzumab, tretinoin, vinblastine, vincristine, vindesine, and vinorelbine.

[0138] These chemotherapeutic anti-tumor compounds may be categorized by their mechanism of action into, for example, following groups: anti-metabolites/anti-cancer agents, such as pyrimidine analogs (5-fluorouracil, floxuridine, capecitabine, gemcitabine and cytarabine) and purine analogs, folate antagonists and related inhibitors (mercaptopurine, thioguanine, pentostatin and 2-chlorodeoxyadenosine (cladribine)); antiproliferative/antimitotic agents including natural products such as vinca alkaloids (vinblastine, vincristine, and vinorelbine), microtubule disruptors such as taxane (paclitaxel, docetaxel), vincristin, vinblastin, nocodazole, epothilones and navelbine, epidipodophyllotoxins (etoposide, teniposide), DNA damaging agents (actinomycin, amsacrine, anthracyclines, bleomycin, busulfan, camptothecin, carboplatin, chlorambucil, cisplatin, cyclophosphamide, cytoxan, dactinomycin, daunorubicin, doxorubicin, epirubicin, hexamethylmelamineoxaliplatin, iphosphamide, melphalan, merchlorehtamine, mitomycin, mitoxantrone, nitrosourea, plicamycin, procarbazine, taxol, taxotere, teniposide, triethylenethiophosphoramide and etoposide (VP16)); antibiotics such as dactinomycin (actinomycin D), daunorubicin, doxorubicin (adriamycin), idarubicin, anthracyclines, mitoxantrone, bleomycins, plicamycin (mithramycin) and mitomycin; enzymes (L-asparaginase which systemically metabolizes L-asparagine and deprives cells which do not have the capacity to synthesize their own asparagine); antiplatelet agents; antiproliferative/antimitotic alkylating agents such as nitrogen mustards (mechlorethamine, cyclophosphamide and analogs, melphalan, chlorambucil), ethylenimines and methylmelamines (hexamethylmelamine and thiotepa), alkyl sulfonates-busulfan, nitrosoureas (carmustine (BCNU) and analogs, streptozocin), trazenes—dacarbazinine (DTIC); antiproliferative/antimitotic antimetabolites such as folic acid analogs (methotrexate); platinum coordination complexes (cisplatin, carboplatin), procarbazine, hydroxyurea, mitotane, aminoglutethimide; hormones, hormone analogs (estrogen, tamoxifen, goserelin, bicalutamide, nilutamide) and aromatase inhibitors (letrozole, anastrozole); anticoagulants (heparin, synthetic heparin salts and other inhibitors of thrombin); fibrinolytic agents (such as tissue plasminogen activator, streptokinase and urokinase), aspirin, dipyridamole, ticlopidine, clopidogrel, abciximab; antimigratory agents; antisecretory agents (breveldin); immunosuppressives (cyclosporine, tacrolimus (FK-506), sirolimus (rapamycin), azathioprine, mycophenolate mofetil); anti-angiogenic compounds (TNP-470, genistein) and growth factor inhibitors (vascular endothelial growth factor (VEGF) inhibitors, fibroblast growth factor (FGF) inhibitors); angiotensin receptor blocker; nitric oxide donors; anti-sense oligonucleotides; antibodies (trastuzumab); cell cycle inhibitors and differentiation inducers (tretinoin); mTOR inhibitors, topoisomerase inhibitors (doxorubicin (adriamycin), amsacrine, camptothecin, daunorubicin, dactinomycin, eniposide, epirubicin, etoposide, idarubicin and mitoxantrone, topotecan, irinotecan), corticosteroids (cortisone, dexamethasone, hydrocortisone, methylprednisolone, prednisone, and prednisolone); growth factor signal transduction kinase inhibitors; mitochondrial dysfunction inducers and caspase activators; and chromatin disruptors.

[0139] In certain embodiments, pharmaceutical compounds that may be used for combinatory anti-angiogenesis therapy include: (1) inhibitors of release of "angiogenic molecules," such as bFGF (basic fibroblast growth factor); (2) neutralizers of angiogenic molecules, such as an anti-βbFGF antibodies; and (3) inhibitors of endothelial cell response to angiogenic stimuli, including collagenase inhibitor, basement membrane turnover inhibitors, angiostatic steroids, fungal-derived angiogenesis inhibitors, platelet factor 4, thrombospondin, arthritis drugs such as D-penicillamine and gold thiomalate, vitamin D_3 analogs, alpha-interferon, and the like. For additional proposed inhibitors of angiogenesis, see Blood et al., Bioch. Biophys. Acta., 1032:89-118 (1990), Moses et al., Science, 248:1408-1410 (1990), Ingber et al., Lab. Invest., 59:44-51 (1988), and U.S. Pat. Nos. 5,092,885, 5,112,946, 5,192,744, 5,202,352, and 6573256. In addition, there are a wide variety of compounds that can be used to inhibit angiogenesis, for example, peptides or agents that block the VEGF-mediated angiogenesis pathway, endostatin protein or derivatives, lysine binding fragments of angiostatin, melanin or melanin-promoting compounds, plasminogen fragments (e.g., Kringles 1-3 of plasminogen), troponin subunits, antagonists of vitronectin $\alpha_v\beta_3$, peptides derived from Saposin B, antibiotics or analogs (e.g., tetracycline, or neomycin), dienogest-containing compositions, compounds comprising a MetAP-2 inhibitory core coupled to a peptide, the compound EM-138, chalcone and its analogs, and naaladase inhibitors. See, for example, U.S. Pat. Nos. 6,395,718, 6,462,075, 6,465,431, 6,475,784, 6,482,802, 6,482,810, 6,500,431, 6,500,924, 6,518,298, 6,521,439, 6,525,019, 6,538,103, 6,544,758, 6,544,947, 6,548,477, 6,559,126, and 6,569,845.

[0140] Depending on the nature of the combinatory therapy, administration of the polypeptide therapeutic agents of the invention may be continued while the other therapy is being administered and/or thereafter. Administration of the polypeptide therapeutic agents may be made in a single dose, or in multiple doses. In some instances, administration of the polypeptide therapeutic agents is commenced at least several days prior to the conventional therapy, while in other instances, administration is begun either immediately before or at the time of the administration of the conventional therapy.

VII. Methods of Administration and Pharmaceutical Compositions

[0141] In certain embodiments, the subject polypeptide therapeutic agents (e.g., soluble polypeptides or antibodies) of the present invention are formulated with a pharmaceutically acceptable carrier. Such therapeutic agents can be administered alone or as a component of a pharmaceutical formulation (composition). The compounds may be formulated for administration in any convenient way for use in human or veterinary medicine. Wetting agents, emulsifiers and lubricants, such as sodium lauryl sulfate and magnesium stearate, as well as coloring agents, release agents, coating agents, sweetening, flavoring and perfuming agents, preservatives and antioxidants can also be present in the compositions.

[0142] Formulations of the subject polypeptide therapeutic agents include those suitable for oral/nasal, topical, parenteral, rectal, and/or intravaginal administration. The formulations may conveniently be presented in unit dosage form and may be prepared by any methods well known in the art of pharmacy. The amount of active ingredient which can be combined with a carrier material to produce a single dosage form will vary depending upon the host being treated, the particular mode of administration. The amount of active ingredient which can be combined with a carrier material to produce a single dosage form will generally be that amount of the compound which produces a therapeutic effect.

[0143] In certain embodiments, methods of preparing these formulations or compositions include combining another type of anti-tumor or anti-angiogenesis therapeutic agent and a carrier and, optionally, one or more accessory ingredients. In general, the formulations can be prepared with a liquid carrier, or a finely divided solid carrier, or both, and then, if necessary, shaping the product.

[0144] Formulations for oral administration may be in the form of capsules, cachets, pills, tablets, lozenges (using a flavored basis, usually sucrose and acacia or tragacanth), powders, granules, or as a solution or a suspension in an aqueous or non-aqueous liquid, or as an oil-in-water or water-in-oil liquid emulsion, or as an elixir or syrup, or as pastilles (using an inert base, such as gelatin and glycerin, or sucrose and acacia) and/or as mouth washes and the like, each containing a predetermined amount of a subject polypeptide therapeutic agent as an active ingredient.

[0145] In solid dosage forms for oral administration (capsules, tablets, pills, dragees, powders, granules, and the like), one or more polypeptide therapeutic agents of the present invention may be mixed with one or more pharmaceutically acceptable carriers, such as sodium citrate or dicalcium phosphate, and/or any of the following: (1) fillers or extenders, such as starches, lactose, sucrose, glucose, mannitol, and/or silicic acid; (2) binders, such as, for example, carboxymethylcellulose, alginates, gelatin, polyvinyl pyrrolidone, sucrose, and/or acacia; (3) humectants, such as glycerol; (4) disintegrating agents, such as agar-agar, calcium carbonate, potato or tapioca starch, alginic acid, certain silicates, and sodium carbonate; (5) solution retarding agents, such as paraffin; (6) absorption accelerators, such as quaternary ammonium compounds; (7) wetting agents, such as, for example, cetyl alcohol and glycerol monostearate; (8) absorbents, such as kaolin and bentonite clay; (9) lubricants, such a talc, calcium stearate, magnesium stearate, solid polyethylene glycols, sodium lauryl sulfate, and mixtures thereof; and (10) coloring agents. In the case of capsules, tablets and pills, the pharmaceutical compositions may also comprise buffering agents. Solid compositions of a similar type may also be employed as fillers in soft and hard-filled gelatin capsules using such excipients as lactose or milk sugars, as well as high molecular weight polyethylene glycols and the like.

[0146] Liquid dosage forms for oral administration include pharmaceutically acceptable emulsions, microemulsions, solutions, suspensions, syrups, and elixirs. In addition to the active ingredient, the liquid dosage forms may contain inert diluents commonly used in the art, such as water or other solvents, solubilizing agents and emulsifiers, such as ethyl alcohol, isopropyl alcohol, ethyl carbonate, ethyl acetate, benzyl alcohol, benzyl benzoate, propylene glycol, 1,3-butylene glycol, oils (in particular, cottonseed, groundnut, corn, germ, olive, castor, and sesame oils), glycerol, tetrahydrofuryl alcohol, polyethylene glycols and fatty acid esters of sorbitan, and mixtures thereof. Besides inert diluents, the oral compositions can also include adjuvants such as wetting agents, emulsifying and suspending agents, sweetening, flavoring, coloring, perfuming, and preservative agents.

[0147] Suspensions, in addition to the active compounds, may contain suspending agents such as ethoxylated isostearyl alcohols, polyoxyethylene sorbitol, and sorbitan esters, microcrystalline cellulose, aluminum metahydroxide, bentonite, agar-agar and tragacanth, and mixtures thereof.

[0148] In particular, methods of the invention can be administered topically, either to skin or to mucosal membranes such as those on the cervix and vagina. This offers the greatest opportunity for direct delivery to tumor with the lowest chance of inducing side effects. The topical formulations may further include one or more of the wide variety of agents known to be effective as skin or stratum corneum penetration enhancers. Examples of these are 2-pyrrolidone, N-methyl-2-pyrrolidone, dimethylacetamide, dimethylformamide, propylene glycol, methyl or isopropyl alcohol, dimethyl sulfoxide, and azone. Additional agents may further be included to make the formulation cosmetically acceptable. Examples of these are fats, waxes, oils, dyes, fragrances, preservatives, stabilizers, and surface active agents. Keratolytic agents such as those known in the art may also be included. Examples are salicylic acid and sulfur.

[0149] Dosage forms for the topical or transdermal administration include powders, sprays, ointments, pastes, creams, lotions, gels, solutions, patches, and inhalants. The subject polypeptide therapeutic agents may be mixed under sterile conditions with a pharmaceutically acceptable carrier, and with any preservatives, buffers, or propellants which may be required. The ointments, pastes, creams and gels may contain, in addition to a subject polypeptide agent, excipients, such as animal and vegetable fats, oils, waxes, paraffins, starch, tragacanth, cellulose derivatives, polyethylene glycols, silicones, bentonites, silicic acid, talc and zinc oxide, or mixtures thereof.

[0150] Powders and sprays can contain, in addition to a subject polypeptide therapeutic agent, excipients such as lactose, talc, silicic acid, aluminum hydroxide, calcium silicates, and polyamide powder, or mixtures of these substances. Sprays can additionally contain customary propellants, such as chlorofluorohydrocarbons and volatile unsubstituted hydrocarbons, such as butane and propane.

[0151] Pharmaceutical compositions suitable for parenteral administration may comprise one or more polypeptide therapeutic agents in combination with one or more pharmaceutically acceptable sterile isotonic aqueous or nonaqueous solutions, dispersions, suspensions or emulsions, or sterile powders which may be reconstituted into sterile injectable solutions or dispersions just prior to use, which may contain antioxidants, buffers, bacteriostats, solutes which render the formulation isotonic with the blood of the intended recipient or suspending or thickening agents. Examples of suitable aqueous and nonaqueous carriers which may be employed in the pharmaceutical compositions of the invention include water, ethanol, polyols (such as glycerol, propylene glycol, polyethylene glycol, and the like), and suitable mixtures thereof, vegetable oils, such as olive oil, and injectable organic esters, such as ethyl oleate. Proper fluidity can be maintained, for example, by the use of coating materials, such as lecithin, by the maintenance of the required particle size in the case of dispersions, and by the use of surfactants.

[0152] These compositions may also contain adjuvants, such as preservatives, wetting agents, emulsifying agents and dispersing agents. Prevention of the action of microorganisms may be ensured by the inclusion of various antibacterial and antifungal agents, for example, paraben, chlorobutanol, phenol sorbic acid, and the like. It may also be desirable to include isotonic agents, such as sugars, sodium chloride, and the like into the compositions. In addition, prolonged absorption of the injectable pharmaceutical form may be brought about by the inclusion of agents which delay absorption, such as aluminum monostearate and gelatin.

[0153] Injectable depot forms are made by forming microencapsule matrices of one or more polypeptide therapeutic agents in biodegradable polymers such as polylactide-polyglycolide. Depending on the ratio of drug to polymer, and the nature of the particular polymer employed, the rate of drug release can be controlled. Examples of other biodegradable polymers include poly(orthoesters) and poly(anhydrides). Depot injectable formulations are also prepared by entrapping the drug in liposomes or microemulsions which are compatible with body tissue.

[0154] Formulations for intravaginal or rectally administration may be presented as a suppository, which may be prepared by mixing one or more compounds of the invention with one or more suitable nonirritating excipients or carriers comprising, for example, cocoa butter, polyethylene glycol, a suppository wax or a salicylate, and which is solid at room temperature, but liquid at body temperature and, therefore, will melt in the rectum or vaginal cavity and release the active compound.

[0155] In other embodiments, the polypeptide therapeutic agents of the instant invention can be expressed within cells from eukaryotic promoters. For example, a soluble polypeptide of EphB4 or Ephrin B2 can be expressed in eukaryotic cells from an appropriate vector. The vectors are preferably DNA plasmids or viral vectors. Viral vectors can be constructed based on, but not limited to, adeno-associated virus, retrovirus, adenovirus, or alphavirus. Preferably, the vectors stably introduced in and persist in target cells. Alternatively, viral vectors can be used that provide for transient expression. Such vectors can be repeatedly administered as necessary. Delivery of vectors encoding the subject polypeptide therapeutic agent can be systemic, such as by intravenous or intramuscular administration, by administration to target cells ex-planted from the patient followed by reintroduction into the patient, or by any other means that would allow for introduction into the desired target cell (for a review see Couture et al., 1996, TIG., 12, 510).

EXEMPLIFICATION

[0156] The invention now being generally described, it will be more readily understood by reference to the following examples, which are included merely for purposes of illustration of certain aspects and embodiments of the present invention, and are not intended to limit the invention.

Example 1

Soluble Derivatives of the Extracellular Domains of Human Ephrin B2 and EphB4 Proteins

[0157] Soluble derivatives of the extracellular domains of human Ephrin B2 and EphB4 proteins represent either truncated full-length predicted extracellular domains of Ephrin B2 (B4ECv3, B2EC) or translational fusions of the domains with constant region of human immunoglobulins (IgG1 Fc fragment), such as B2EC-FC, B4ECv2-FC and B4ECv3-FC. Representative human Ephrin B2 constructs and human EphB4 constructs are shown FIGS. **14** and **15**.

[0158] The cDNA fragments encoding these recombinant proteins were subcloned into mammalian expression vectors, expressed in transiently or stably transfected mammalian cell lines and purified to homogeneity as described in detail in Materials and Methods section (see below). Predicted amino acid sequences of the proteins are shown in FIGS. **1-5**. High purity of the isolated proteins and their recognition by the corresponding anti-Ephrin B2 and anti-EphB4 monoclonal or polyclonal antibodies were confirmed. The recombinant proteins exhibit the expected high-affinity binding, binding competition and specificity properties with their corresponding binding partners as corroborated by the biochemical assays (see e.g., FIGS. **6-8**).

[0159] Such soluble derivative proteins human Ephrin B2 and EphB4 exhibit potent biological activity in several cell-based assays and in vivo assays which measure angiogenesis or anti-cancer activities, and are therefore perspective drug candidates for anti-angiogenic and anti-cancer therapy. B4ECv3 as well as B2EC and B2EC-FC proteins blocked chemotaxis of human endothelial cells (as tested with umbilical cord and hepatic AECs or VECs), with a decrease in degradation of the extracellular matrix, Matrigel, and a decrease in migration in response to growth factor stimuli (FIGS. **9-11**). B4ECv3 and B2EC-FC proteins have potent anti-angiogenic effect as demonstrated by their inhibition of endothelial cell tube formation (FIGS. **12-13**).

Materials and Methods

[0160] 1) Mammalian Expression Vectors for Producing Recombinant Soluble Derivatives of Ephrin B2 and Eph B4

[0161] Plasmids vectors for expressing recombinant soluble derivatives of Ephrin B2 and EphB4 were based on pEF6/V5-His-TOPO vector (Invitrogen), pIG (Novagen) or pRK5. pEF6/V5-His-TOPO contains human elongation factor 1a enhancer/promoter and blasticidin resistance marker. pIG vector is designed for high-level expression of protein fusions with Fc portion of human IgG1 under CMV promoter control and pRK5 is a general purpose CMV promoter-containing mammalian expression vector. To generate plasmid construct pEF6-B4EC-NT, cDNA fragment of human EphB4 was amplified by PCR using oligo primers 5'-GGATCCGCC ATGGAGCTC CGGGTGCTGCT-3' and 5'-TGGATCCCT GCTCCCGC CAGCCCTCG CTCTCATCCA-3', and TOPO-cloned into pEF6/V5-His-TOPO vector. pEF6-hB4ECv3 was derived from pEF6-B4ECNT by digesting the plasmid DNA with EcoRV and BstBI, filling-in the ends with Klenow enzyme and religating the vector. Recombinant EphB4 derivative encoded by pEF6-B4EC-NT does not contain epitope- or purification tags, while the similar B4ECv3 protein encoded by pEF6-hB4ECv3 contains V5 epitope tag and 6×His tag on its C-terminus to facilitate purification from conditioned media. Plasmid construct pEF6-hB2EC was created by PCR amplification of Ephrin B2 cDNA using oligo primers 5'-TGGATCCAC CATGGCTGT GAGAAGGGAC-3' plus 5'-ATTAATGGTGATGGT GAT GATGACTAC CCACTTCGG AACCGAGGATGTTGTTC-3' and TOPO-cloning into pEF6/V5-His-TOPO vector. Plasmid construct pIG-hB2EC-FC was created by PCR amplification of Ephrin B2 cDNA with oligo primers 5'-TAAAGCTTCCGCCATGG CTGTGAGAAGGGAC-3' and 5'-TAGGATCCACT-TCGGA ACCGAGGATGTTGTT CCC-3', followed by TOPO-cloning and sequencing the resulting PCR fragment with consecutive subcloning in pIG hIgG1 Fc fusion expression vector cut with Bam HI and Hind III. Similarly, pIG-hB2EC and pIG-hB4ECv3 were generated by PCR amplifying portions of EphB4 ECD cDNA using oligo primers 5'-ATAAGCTTCC GCCATGGAGC TCCGGGTGCTG-3' plus 5'-TTGGATCCTGCTCCCG CCAGCCCTCGC TCT-CATC-3' with consecutive subcloning into pIG hIgG1 Fc fusion expression vector cut with Bam HI and Hind III. Predicted sequences of the proteins encoded by the vectors described above are shown in FIGS. **1-5**.

[0162] 2) Mammalian Cell Culture and Transfections

[0163] HEK293T (human embryonic kidney line) cells were maintained in DMEM with 10% dialyzed fetal calf serum and 1% penicillin/streptomycin/neomycin antibiotics. Cells were maintained at 37° C. in a humidified atmosphere of 5% CO_2/95% air. Transfections were performed using Lipofectamine 2000 reagent (Invitrogen) according to the manufacturer's protocol. One day before transfections, 293T cells were seeded at a high density to reach 80% confluence at the time of transfection. Plasmid DNA and Lipofectamine reagent at 1:3 ratio were diluted in Opti-MEM I reduced serum medium (Invitrogen) for 5 min and mixed together to form DNA:Lipofectamine complex. For each 10 cm culture dish, 10 μg of plasmid DNA was used. After 20 min, above complex was added directly to cells in culture medium. After 16 hours of transfection, medium was aspirated, washed once with serum free DMEM and replaced with serum free DMEM. Secreted proteins were harvested after 48 hours by collecting conditional medium. Conditional medium was clarified by centrifugation at 10,000 g for 20 min, filtered through 0.2 μm filter and used for purification.

[0164] 3) Generating Stable Cell Lines

[0165] To create stable cell lines producing EphB4ECv3 and EphB4ECnt HEK293 or HEK293T cells were transfected with either pEF6-B4ECv3 or pEF6-B4EC-NT plasmid constructs as described above and selected using antibiotic Blasticidin. After 24 hours of transfection, cells were seeded at low density. Next day, cells were treated with 10 μg/ml of Blasticidin. After two weeks of drug selection, surviving cells were pooled and selected further for single cell clone expansion. After establishing stable cells, they were maintained at 4 μg/ml Blasticidin. Conditioned media were tested to confirm expression and secretion of the respective recombinant proteins. Specificity of expression was confirmed by Western blot with anti-B4 mono- or polyclonal ABs and B2EC-AP reagent binding and competition assays.

[0166] 4) Protein Purification

[0167] HEK293 cells were transiently transfected with a plasmid encoding secreted form of EphB4ectodomain (B4ECv3). Conditional media was harvested and supplemented with 10 mM imidazole, 0.3 M NaCl and centrifuged at 20,000 g for 30 min to remove cell debris and insoluble particles. 80 ml of obtained supernatant were applied onto the pre-equilibrated column with 1 ml of Ni-NTA-agarose (Qiagen) at the flow rate of 10 ml/h. After washing the column with 10 ml of 50 mM Tris-HCl, 0.3 M NaCl and 10 mM imidazole, pH 8, remaining proteins were eluted with 3 ml of 0.25 M imidazole. Eluted proteins were dialyzed against 20 mM Tris-HCl, 0.15 M NaCl, pH 8 overnight. Purity and identity of B4ECv3 was verified by PAGE/Coomassie G-250 and Western blot with anti-Eph.B4 antibody. Finally, the concentration of B4ECv3 was measured, and the protein was aliquoted and stored at −70° C.

[0168] B4EC-FC protein and B2EC-FC protein were similarly purified.

[0169] 5) Biochemical Assays

[0170] A. Binding Assay

[0171] 10 μl of Ni-NTA-Agarose were incubated in microcentrifuge tubes with 50 μl of indicated amount of B4ECv3 diluted in binding buffer BB (20 mM Tris-HCl, 0.15 M NaCl, 0.1% bovine serum albumin pH 8) After incubation for 30 min on shaking platform, Ni-NTA beads were washed twice with 1.4 ml of BB, followed by application of 50 μl of B2-AP in the final concentration of 50 nM. Binding was performed for 30 min on shaking platform, and then tubes were centrifuged and washed one time with 1.4 ml of BB. Amount of precipitated AP was measured colorimetrically after application of PNPP.

[0172] B. Inhibition Assay

[0173] Inhibition in solution. Different amounts of B4ECv3 diluted in 50 μl of BB were pre-incubated with 50 μl of 5 nM B2EC-AP reagent (protein fusion of Ephrin B2 ectodomain with placental alkaline phosphatase). After incubation for 1 h, unbound B2EC-AP was precipitated with 5,000 HEK293 cells expressing membrane-associated full-length EphB4 for 20 min. Binding reaction was stopped by dilution with 1.2 ml of BB, followed by centrifugation for 10 min. Supernatants were discarded and alkaline phosphatase activities associated with collected cells were measured by adding para-nitrophenyl phosphate (PNPP) substrate.

[0174] Cell based inhibition. B4ECv3 was serially diluted in 20 mM Tris-HCl, 0.15 M NaCl, 0.1% BSA, pH 8 and mixed with 5,000 HEK293 cells expressing membrane-associated full-length Ephrin B2. After incubation for 1 h, 50 μl of 5 nM B4EC-AP reagent (protein fusion of EphB4 ectodomain with placental alkaline phosphatase were added into each tube for 30 min to detect unoccupied Ephrin B2 binding sites. Binding reactions were stopped by dilution with 1.2 ml of BB and centrifugation. Colorimetric reaction of cell-precipitated AP was developed with PNPP substrate.

[0175] C. B4EC-FC Binding Assay

[0176] Protein A-agarose based assay. 10 μl of Protein A-agarose were incubated in Eppendorf tubes with 50 μl of indicated amount of B4EC-FC diluted in binding buffer BB (20 mM Tris-HCl, 0.15 M NaCl, 0.1% BSA pH 8). After incubation for 30 min on shaking platform, Protein AAagarose beads were washed twice with 1.4 ml of BB, followed by application of 50 μl of B2ECAP reagent at the final concentration of 50 nM. Binding was performed for 30 min on shaking platform, and then tubes were centrifuged and washed once with 1.4 ml of BB. Colorimetric reaction of precipitated AP was measured after application of PNPP (FIG. **6**).

[0177] Nitrocellulose based assay. B4EC-FC was serially diluted in 20 mM Tris-HCl, 0.15 M NaCl, 50 μg/ml BSA, pH 8. 2 μl of each fraction were applied onto nitrocellulose strip and spots were dried out for 3 min. Nitrocellulose strip was blocked with 5% non-fat milk for 30 min, followed by incubation with 5 nM B2EC-AP reagent. After 45 min incubation for binding, nitrocellulose was washed twice with 20 mM Tris-HCl, 0.15 M NaCl, 50 μg/ml BSA, pH 8 and color was developed by application of alkaline phosphatase substrate Sigma Fast (Sigma).

[0178] D. B4EC-FC Inhibition Assay

[0179] Inhibition in solution. See above, for B4ECv3. The results were shown in FIG. **7**.

[0180] Cell based inhibition. See above, for B4ECv3.

[0181] E. B2EC-FC Binding Assay

[0182] Protein-A-agarose based assay. See above, for B4EC-FC. The results were shown in FIG. **8**.

[0183] Nitrocellulose based assay. See above, for B4EC-FC.

[0184] 6) Cell-Based Assays

[0185] A. Growth Inhibition Assay

[0186] Human umbilical cord vein endothelial cells (HUVEC) (1.5×103) are plated in a 96-well plate in 100 μl of EBM-2 (Clonetic # CC3162). After 24 hours (day 0), the test recombinant protein (100 μl) is added to each well at 2× the desired concentration (5-7 concentration levels) in EBM-2 medium. On day 0, one plate is stained with 0.5% crystal violet in 20% methanol for 10 minutes, rinsed with water, and air-dried. The remaining plates are incubated for 72 h at 37° C. After 72 h, plates are stained with 0.5% crystal violet in 20% methanol, rinsed with water and airdried. The stain is eluted with 1:1 solution of ethanol: 0.1 M sodium citrate (including day 0 plate), and absorbance is measured at 540 nm with an ELISA reader (Dynatech Laboratories). Day 0 absorbance is subtracted from the 72 h plates and data is plotted as percentage of control proliferation (vehicle treated cells). IC50 (drug concentration causing 50% inhibition) is calculated from the plotted data.

[0187] B. Cord Formation Assay (Endothelial Cell Tube Formation Assay)

[0188] Matrigel (60 μl of 10 mg/ml; Collaborative Lab #35423) is placed in each well of an ice-cold 96-well plate. The plate is allowed to sit at room temperature for 15 minutes then incubated at 37° C. for 30 minutes to permit the matrigel to polymerize. In the mean time, HUVECs are prepared in EGM-2 (Clonetic # CC3162) at a concentration of 2×10^5 cells/ml. The test compound is prepared at 2× the desired concentration (5 concentration levels) in the same medium. Cells (500 μl) and 2× drug (500 μl) is mixed and 200 μl of this suspension are placed in duplicate on the polymerized matrigel. After 24 h incubation, triplicate pictures are taken for each concentration using a Bioquant Image Analysis system. Drug effect (IC50) is assessed compared to untreated controls by measuring the length of cords formed and number of junctions.

[0189] C. Cell Migration Assay

[0190] Migration is assessed using the 48-well Boyden chamber and 8 μm pore size collagen-coated (10 μg/ml rat tail collagen; Collaborative Laboratories) polycarbonate filters (Osmonics, Inc.). The bottom chamber wells receive 27-29 μl of DMEM medium alone (baseline) or medium containing chemo-attractant (bFGF, VEGF or Swiss 3T3 cell conditioned medium). The top chambers receive 45 μl of HUVEC cell suspension (1×10^6 cells/ml) prepared in DMEM+1% BSA with or without test compound. After 5 h incubation at 37° C., the membrane is rinsed in PBS, fixed and stained in Diff-Quick solutions. The filter is placed on a glass slide with the migrated cells facing down and cells on top are removed using a Kimwipe. The testing is performed in 4-6 replicates and five fields are counted from each well. Negative unstimulated control values are subtracted from stimulated control and drug treated values and data is plotted as mean migrated cell ±S.D. IC50 is calculated from the plotted data.

Example 2

Extracellular Domain Fragments of EphB4 Receptor Inhibit Angiogenesis and Tumor Growth

A. Globular Domain of EphB4 is Required for EphrinB2 Binding and for the Activity of EphB4-Derived Soluble Proteins in Endothelial Tube Formation Assay.

[0191] To identify subdomain(s) of the ectopic part of EphB4 necessary and sufficient for the anti-angiogenic activity of the soluble recombinant derivatives of the receptor, four recombinant deletion variants of EphB4EC were produced and tested (FIG. **16**). Extracellular part of EphB4, similarly to the other members of EphB and EphA receptor family, contains N-terminal ligand-binding globular domain followed by cysteine-rich domain and two fibronectin type III repeats (FNIII). In addition to the recombinant B4-GCF2 protein containing the complete ectopic part of EphB4, we constructed three deletion variants of EphB4EC containing globular domain and Cys-rich domain (B4-GC); globular, Cys-rich and the first FNIII domain (GCF1) as well as the ECD version with deleted globular domain (CF2), Our attempts to produce several versions of truncated EphB4EC protein containing the globular domain alone were not successful due to the lack of secretion of proteins expressed from all these constructs and absence of ligand binding by the intracellularly expressed recombinant proteins. In addition, a non-tagged version of B4-GCF2, called GCF2-F, containing complete extracellular domain of EphB4 with no additional fused amino acids was expressed, purified and used in some of the experiments described here.

[0192] All four C-terminally 6×His tagged recombinant proteins were preparatively expressed in transiently transfected cultured mammalian cells and affinity purified to homogeneity from the conditioned growth media using chromatography on Ni^{2+}-chelate resin (FIG. **17**). Apparently due to their glycosylation, the proteins migrate on SDS-PAAG somewhat higher than suggested by their predicted molecular weights of 34.7 kDa (GC), 41.5 (CF2), 45.6 kDa (GCF1) and 57.8 kDa (GCF2). Sequence of the extracellular domain of human EphB4 contains three predicted N-glycosylation sites (NXS/T) which are located in the Cys-rich domain, within the first fibronectin type III repeat and between the first and the second fibronectin repeats.

[0193] To confirm ability of the purified recombinant proteins to bind Ephrin B2, they were tested in an in vitro binding assay. As expected, GC, GCF1 and GCF2, but not CF2 are binding the cognate ligand Ephrin B2 as confirmed by interaction between Ephrin B2-alkaline phosphatase (Ephrin B2-AP) fusion protein with the B4 proteins immobilized on Ni^{2+} resin or on nitrocellulose membrane (FIG. **17**).

[0194] All four proteins were also tested for their ability to block ligand-dependent dimerization and activation of Eph B4 receptor kinase in PC3 cells. The PC3 human prostate cancer cell line is known to express elevated levels of human Eph B4. Stimulation of PC3 cells with Ephrin B2

[0195] IgG Fc fusion protein leads to a rapid induction of tyrosine phosphorylation of the receptor. However, preincubation of the ligand with GCF2, GCF1 or GC, but not CF2 proteins suppresses subsequent EphB4 autophosphorylation. Addition of the proteins alone to the PC3 cells or preincubation of the cells with the proteins followed by changing media and adding the ligand does not affect EphB4 phosphorylation status.

[0196] Further, we found that globular domain of EphB4 is required for the activity of EphB4-derived soluble proteins in endothelial tube formation assay.

B. Effects of Soluble EphB4 on HUV/AEC In Vitro.

[0197] Initial experiments were performed to determine whether soluble EphB4 affected the three main stages in the angiogenesis pathway. These were carried out by establishing the effects of soluble EphB4 on migration/invasion, proliferation and tubule formation by HUV/AEC in vitro. Exposure to soluble EphB4 significantly inhibited both bFGF and VEGF-induced migration in the Boyden chamber assay in a dose-dependent manner, achieving significance at nM (FIG. **18**). Tubule formation by HUV/AECS on wells coated with Matrigel was significantly inhibited by soluble EphB4 in a dose-dependent manner in both the absence and presence of bFGF and VEGF (FIG. **19**). We also assessed in vitro, whether nM of soluble EphB4 was cytotoxic for HUVECS. Soluble EphB4 was found to have no detectable cytotoxic effect at these doses, as assessed by MTS assay (FIG. **20**).

C. Soluble EphB4 Receptor Inhibits Vascularization of Matrigel Plugs, In Vivo

[0198] To demonstrate that soluble EphB4 can directly inhibit angiogenesis in vivo, we performed a murine matrigel plug experiment. Matrigel supplemented with bFGF and VEGF with and without soluble EphB4 was injected s.c. into Balb/C nu/nu mice, forming semi-solid plugs, for six days. Plugs without growth factors had virtually no vascularization or vessel structures after 6 days (FIG. **21**). In contrast, plugs supplemented with bFGF and VEGF had extensive vascularization and vessels throughout the plug. Plugs taken from mice treated with μg of soluble EphB4 had markedly reduced vascularization of plugs, comparable to plugs without growth factor (FIG. **21**). Furthermore, histological examination of plugs showed decreased vessel staining (FIG. **21**). Treatment at 0 μg/dose significantly inhibited the amount of infiltration in Matrigel plugs compared to control (FIG. **21**).

[0199] We examined EphB4 receptor phosphorylation in HUVECs by performing Western blot analyses with lysates from soluble EphB4-treated cells and antibodies against phosphor-tyrosine. We found that soluble EphB4 treatment of serum-starved HUVECs stimulated a rapid and transient decrease in the level of phosphorylated EphB4, in the presence of EphrinB2Fc, EphB4 ligand dimer. Ephrin B2Fc without the soluble EphB4 protein induced phosphorylation of EphB4 receptor (FIG. **22**).

D. Effects of Soluble EphB4 on Tumor Growth, In Vitro.

[0200] We found that soluble EphB4 inhibits the growth of SCC15 tumors grown in Balb/C Nu/Nu mice (FIG. **23**).

E. Soluble EphB4 Inhibited Corneal Neovascularization

[0201] To further investigate the antiangiogenic activity of soluble EphB4 in vivo, we studied the inhibitory effect of administration of soluble EphB4 on neovascularization in the mouse cornea induced by bFGF. Hydron Pellets implanted into corneal micropocket could induce angiogenesis, in the presence of growth factors, in a typically avascular area. The angiogenesis response in mice cornea was moderate, the appearance of vascular buds was delayed and the new capillaries were sparse and grew slowly. Compared with the control group, on day 7 of implantation, the neovascularization induced by bFGF in mice cornea was markedly inhibited in soluble EphB4-treated group (FIG. **24**).

F. Effects of Soluble EphB4 on Tumor Growth, In Vivo.

[0202] The same model was used to determine the effects of soluble EphB4 in vivo. SCC15 tumors implanted subcutaneously, pre-incubated with matrigel and with or w/o growth factors, as well as implanted sc alone, and mice treated sc or ip daily with 1-5 ug of soluble EphB4 were carried out.

[0203] Tumors in the control group continued to grow steadily over the treatment period, reaching a final tumor volume of mm3. However, animals injected with soluble EphB4 exhibited a significantly (p<0.0/) reduced growth rate, reaching a final tumor volume of only mm3 (FIG. **25**). Similar results were obtained in two further cohorts of such tumor-bearing mice. Soluble EphB4 administration appeared to be well tolerated in vivo, with no significant effect on body weight or the general well-being of the animals (as determined by the absence of lethargy, intermittent hunching, tremors or disturbed breathing patterns).

G. Effects of Soluble EphB4 on Tumor Histology.

[0204] Histological analysis revealed the presence of a central area of necrosis in all SCC15 tumors, which was usually surrounded by a viable rim of tumor cells um in width. The central necrotic areas were frequently large and confluent and showed loss of cellular detail. Necrosis, assessed as a percentage of tumor section area, was significantly (p<0.02) more extensive in the soluble EphB4-treated group (% necrosis in treated vs. control). To determine whether the reduced volume of soluble EphB4 treated tumors was due to an effect of this protein on the tumor vascular supply, endothelial cells in blood vessels were identified in tumor sections using immunostaining with an anti-platelet cell adhesion molecule (PECAM-1; CD31) antibody (FIG. **26**) and the density of microvessels was assessed. Microvessel density was similar in the outer viable rim of tumor cells (the uniform layer of cells adjacent to the tumor periphery with well defined nuclei) in control and soluble EphB4-treated tumors. Microvessel density was significantly in the inner, less viable region of tumor cells abutting the necrotic central areas in soluble EphB4-treated than control tumors. Fibrin deposition, as identified by Masson's Trichrome staining, was increased in and around blood vessels in the inner viable rim and the central necrotic core of soluble EphB4 treated than control tumors. In the outer viable rim of soluble EphB4 treated tumors, although the vessel lumen remained patent and contained red blood cells, fibrin deposition was evident around many vessels. Soluble EphB4 was found to have no such effects on the endothelium in the normal tissues examined (lungs, liver and kidneys).

H. Materials and Methods

[0205] 1) Expression Constructs

[0206] To construct expression vectors for producing soluble, 6×His-tagged EphB4-ECD variants, cloned full-length human EphB4 cDNA was amplified by PCR using the following oligo primers: TACTAGTCCGCCATGGAGCTCCGGGTGCTGCT (common EphB4 N-terminal primer) and GCGGCCGCTTAATGGTGATGGTGA TGATGAGCCGAAGGA GGGGTGGTGCA (B4-GC), AGCGGCCGCTTAATGGTGATGGTGAT GATGGACATTGA CAGGCTCAAATGGGA (B4-GCF1) or TGCGGCCGCTTAATGGTGATGGTGATGAT GCTGCTCCCGCCAGCCCTCGCTCTCAT (B4-GCF2). The resulting PCR fragments were TA-cloned into mammalian expression vector pEF6/V5-His-TOPO (Invitrogen) under EF-1α promoter control. The expressed recombinant proteins encode the following fragments of the Mature extracellular part of human EphB4: amino acid positions 1-522 (GCF2), 1-412 (GCF1) and 1-312 (GC). To generate the B4-CF2 deletion (8 amino acids 13-183) PCR fragment for pEF6 cloning, EphB4 cDNA was amplified by two-step overlap PCR using oligo primers TACTAGTCCGCCATGGAGCTCCGGGTGCTGCT, CAGCTGAGTTTCCAATTTTGTGTTC, GAACACAAAATTGGAAACTCAGCTGACTGTGAACCTGAC and GCGGCCGCCCTGCTCCCGCCAGCCCTCGCT.

[0207] Vector for producing secreted human EphrinB2-alkaline phosphatase (B2-AP) reagent was constructed by PCR amplification of human Ephrin B2 cDNA using primers TAAAGCTTCCGCCATGGCTGTGAGAAGGGAC and TAGGATCCTTCGGAACCG AGGATGTTGTTCCC and cloning the resulting fragment, digested with Hind III and Bam HI, into Hind III-Bgl II digested pAPTag2 vector (GenHunter, Inc.). In each case, inserts in expression vectors were verified by complete sequencing.

[0208] 2) Antibodies and Other Reagents

[0209] Anti-Eph B4 monoclonal antibodies mAB79 and mAB23 were raised in mice against the GCF2 protein containing amino acids 1-522 of mature human EphB4 and purified from hybridoma supernatants by Protein A chromatography. The anti-phosphotyrosine antibody 4G10 was from UBI (Lake Placid, N.Y.). Protein G-HRP conjugate was purchased from Bio-Rad.

[0210] 3) Expression and Purification of EphB4-Derived Recombinant Proteins

[0211] To produce the EphB4-ECD soluble proteins, cultured human embryonic kidney cells HEK293T were transfected with the corresponding plasmid constructs using standard calcium phosphate or Lipofectamin 2000 reagent (Invitrogen) protocols. Twelve to sixteen hours post-transfection, the growth medium (DMEM+10% fetal bovine serum) was aspirated, cells washed once with serum free DMEM and replaced with serum free DMEM. Conditioned media containing the secreted proteins were harvested 72-96 hours later, clarified by centrifugation and used for purification of His-tagged proteins using Ni-NTA Agarose (Qiagen). The purity and quantity of the recombinant proteins was tested by SDS-PAAG electrophoresis with Coomassie Blue or silver staining, Western blotting and UV spectroscopy. Purified proteins were dialyzed against 20 mM Tris-HCl, 0.15 M NaCl, pH 8 and stored at −70° C.

[0212] To test ligand binding properties of the proteins, 10 μl of Ni-NTA-Agarose (Qiagen) were incubated in microcentrifuge tubes with 10-500 ng sample of a B4-ECD protein diluted in 0.5 ml of binding buffer BB (20 mM Tris-HCl, 0.15 M NaCl, 0.1% bovine serum albumin, pH 8). After incubation for 30 min on shaking platform, Ni-NTA beads were washed twice with 1.4 ml of BB, followed by addition of B2-AP fusion protein at concentration of 50 nM. Binding was performed for 30 min on a shaking platform. Tubes were centrifuged and washed once with 1.4 ml of BB. Amount of precipitated AP was measured colorimetrically at 420 nm after application of p-nitrophenyl phosphate (PNPP) and incubation for 5-30 min.

[0213] 4) Immunoprecipitation

[0214] All lysates were processed at 4° C. Cells were lysed in 1 ml of buffer containing 20 mM Hepes at pH 7.4, 100 mM sodium chloride, 50 mM sodium fluoride, 2 mM EDTA, 2

mM EGTA, 1 mM sodium orthovanadate, 1% (v/v) NP-40, 0.5% (w/v) sodium deoxycholate, 1 mM phenyl methylsulphonyl fluoride (added freshly) and 1000 Trasylol. Lysates were scraped into Eppendorf tubes and 50 μl of boiled, formalin-fixed *Staphylococcus aureus* was added (Calbiochem, San Diego). After 30 min of mixing, the lysates were centrifuged for 5 min at 25,000 g in a minifuge and the supernatants transferred to new tubes containing the appropriate antibody. Lysates were mixed with antibodies for 1 h, after which time 50 μl of protein A-Sepharose beads were added and the contents of the tubes mixed for 1 h to collect the immunoprecipitates. Protein A beads were collected by centrifugation at 25,000 g for 30 s. The supernatants were discarded and the beads washed three times with 1 ml lysis buffer minus deoxycholate.

[0215] 5) Cell-Based EphB4 Tyrosine Kinase Assay

[0216] The human prostate carcinoma cell line PC3 cells were maintained in RPMI medium with 10% dialyzed fetal calf serum and 1% penicillin/streptomycin/neomycin antibiotics mix. Cells were maintained at 37° C. in a humidified atmosphere of 5% CO_2/95% air. Typically, cells were grown in 60 mm dishes until confluency and were either treated with mouse Ephrin B2-Fc fusion at 1 μg/ml in RPMI for 10 min to activate EphB4 receptor or plain medium as a control. To study the effect of different derivatives of soluble EphB4 ECD proteins on EphB4 receptor activation, three sets of cells were used. In the first set, cells were treated with various proteins (5 proteins; GC, GCF1, GCF2, GCF2-F, CF2) at 5 μg/ml for 20 min. In the second set of cells, prior to application, proteins were premixed with ephrinB2-Fc at 1:5 (EphB4 protein: B2-Fc) molar ratio, incubated for 20 min and applied on cells for 10 min. In the third set of cells, cells were first treated with the proteins for 20 min at 5 μg/ml, media was replaced with fresh media containing 1 μg/ml of EphrinB2-Fc and incubated for another 10 min.

[0217] After the stimulation, cells were immediately harvested with protein extraction buffer containing 20 mM Tris-HCl, pH 7.4, 150 mM NaCl, 1% (v/v) Triton X100, 1 mM EDTA, 1 mM PMSF, 1 mM Sodium vanadate. Protein extracts were clarified by centrifugation at 14,000 rpm for 20 min at 4° C. Clarified protein samples were incubated overnight with protein A/G coupled agarose beads pre-coated with anti-EphB4 monoclonal antibodies. The IP complexes were washed twice with the same extraction buffer containing 0.1% Triton X100. The immunoprecipitated proteins were solubilized in 1×SDS-PAGE sample loading buffer and separated on 10% SDS-PAGE. For EphB4 receptor activation studies, electroblotted membrane was probed with anti-pTyr specific antibody 4G10 at 1:1000 dilution followed by Protein G-HRP conjugate at 1:5000 dilutions.

[0218] 6) Cell Culture

[0219] Normal HUVECs were obtained from Cambrex (BioWhittaker) and maintained in EBM2 medium supplemented with 0.1 mg/ml endothelial growth supplement (crude extract from bovine brain), penicillin (50 U/ml), streptomycin (50 U/ml), 2 mmol/l glutamine and 0.1 mg/ml sodium heparin. Aliquots of cells were preserved frozen between passages 1 and 3. For all experiments, HUVECs were used at passages 4 or below and collected from a confluent dish.

[0220] 7) Endothelial Cell Tube Formation Assay

[0221] Matrigel (60 μl of 10 mg/ml; Collaborative Lab, Cat. No. 35423) was placed in each well of an ice-cold 96-well plate. The plate was allowed to sit at room temperature for 15 minutes then incubated at 37° C. for 30 minutes to permit Matrigel to polymerize. In the mean time, human umbilical vein endothelial cells were prepared in EGM-2 (Clonetic, Cat. No. CC3162) at a concentration of 2×10^5 cells/ml. The test protein was prepared at 2× the desired concentration (5 concentration levels) in the same medium. Cells (500 μl) and 2× protein (500 μl) were mixed and 200 μl of this suspension were placed in duplicate on the polymerized Matrigel. After 24 h incubation, triplicate pictures were taken for each concentration using a Bioquant Image Analysis system. Protein addition effect (IC_{50}) was assessed compared to untreated controls by measuring the length of cords formed and number of junctions.

[0222] 8) Cell Migration Assay

[0223] Chemotaxis of HUVECs to VEGF was assessed using a modified Boyden chamber, transwell membrane filter inserts in 24 well plates, 6.5 mm diam, 8 μm pore size, 10 μm thick matrigel coated, polycarbonate membranes (BD Biosciences). The cell suspensions of HUVECs (2×10^5 cells/ml) in 200 μl of EBM were seeded in the upper chamber and the soluble EphB4 protein were added simultaneously with stimulant (VEGF or bFGF) to the lower compartment of the chamber and their migration across a polycarbonate filter in response to 10-20 ng/ml of VEGF with or without 100 nM-1 μM test compound was investigated. After incubation for 4-24 h at 37° C., the upper surface of the filter was scraped with swab and filters were fixed and stained with Diff Quick. Ten random fields at 200× mag were counted and the results expressed as mean # per field. Negative unstimulated control values were subtracted from stimulated control and protein treated sample values and the data was plotted as mean migrated cell ±S.D. IC_{50} was calculated from the plotted data.

[0224] 9) Growth Inhibition Assay

[0225] HUVEC (1.5×10^3 cells) were plated in a 96-well plate in 100 μl of EBM-2 (Clonetic, Cat. No. CC3162). After 24 hours (day 0), the test recombinant protein (100 μl) is added to each well at 2× the desired concentration (5-7 concentration levels) in EBM-2 medium. On day 0, one plate was stained with 0.5% crystal violet in 20% methanol for 10 minutes, rinsed with water, and air-dried. The remaining plates were incubated for 72 h at 37° C. After 72 h, plates were stained with 0.5% crystal violet in 20% methanol, rinsed with water and air-dried. The stain was eluted with 1:1 solution of ethanol: 0.1 M sodium citrate (including day 0 plate), and absorbance measured at 540 nm with an ELISA reader (Dynatech Laboratories). Day 0 absorbance was subtracted from the 72 h plates and data is plotted as percentage of control proliferation (vehicle treated cells). IC_{50} value was calculated from the plotted data.

[0226] 10) Murine Matrigel Plug Angiogenesis Assay

[0227] In vivo angiogenesis was assayed in mice as growth of blood vessels from subcutaneous tissue into a Matrigel plug containing the test sample. Matrigel rapidly forms a solid gel at body temperature, trapping the factors to allow slow release and prolonged exposure to surrounding tissues. Matrigel (8.13 mg/ml, 0.5 ml) in liquid form at 4° C. was mixed with Endothelial Cell Growth Supplement (ECGS), test proteins plus ECGS or Matrigel plus vehicle alone (PBS containing 0.25% BSA). Matrigel (0.5 ml) was injected into the abdominal subcutaneous tissue of female nu/nu mice (6 wks old) along the peritoneal mid line. There were 3 mice in each group. The animals were cared for in accordance with institutional and NIH guidelines. At day 6, mice were sacrificed and plugs were recovered and processed for histology.

Typically the overlying skin was removed, and gels were cut out by retaining the peritoneal lining for support, fixed in 10% buffered formalin in PBS and embedded in paraffin. Sections of 3 μm were cut and stained with H&E or Masson's trichrome stain and examined under light microscope

[0228] 11) Mouse Corneal Micropocket assay

[0229] Mouse corneal micropocket assay was performed according to that detailed by Kenyon et al., 1996. Briefly, hydron pellets (polyhydroxyethylmethacrylate [poly-HEMA], Interferon Sciences, New Brunswick, N.J., U.S.A.) containing either 90 ng of bFGF (R&D) or 180 ng of VEGF (R&D Systems, Minneapolis, Minn., U.S.A.) and 40 μg of sucrose aluminium sulfate (Sigma) were prepared. Using an operating microscope, a stromal linear keratotomy was made with a surgical blade (Bard-Parker no. 15) parallel to the insertion of the lateral rectus muscle in an anesthetized animal. An intrastromal micropocket was dissected using a modified von Graefe knife (2"30 mm). A single pellet was implanted and advanced toward the temporal corneal limbus (within 0±7±1±0 mm for bFGF pellets and 0±5 mm for VEGF pellets). The difference in pellet location for each growth factor was determined to be necessary given the relatively weaker angiogenic stimulation of VEGF in this model. Antibiotic ointment (erythromycin.) was then applied to the operated eye to prevent infection and to decrease surface irregularities. The subsequent vascular response was measured extending from the limbal vasculature toward the pellet and the contiguous circumferential zone of neovascularization Data and clinical photos presented here were obtained on day 6 after pellet implantation, which was found to be the day of maximal angiogenic response.

[0230] 12) In Vitro Invasion Assay

[0231] "Matrigel" matrix-coated 9-mm cell culture inserts (pore size, 8 μm; Becton Dickinson, Franklin Lakes, N.J.) were set in a 24-well plate. The HUVEC cells were seeded at a density of 5×10^3 cells per well into the upper layer of the culture insert and cultured with serum-free EBM in the presence of EphB4 ECD for 24 h. The control group was cultured in the same media without EphB4. Then 0.5 ml of the human SCC15 cell line, conditioned medium was filled into the lower layer of the culture insert as a chemo-attractant. The cells were incubated for 24 h, then the remaining cells in the upper layer were swabbed with cotton and penetrating cells in the lower layer were fixed with 5% glutaraldehyde and stained with Diff Quick. The total number of cells passing through the Matrigel matrix and each 8 μm pore of the culture insert was counted using optical microscopy and designated as an invasion index (cell number/area).

[0232] 13) SCC15 Tumor Growth in Mice

[0233] Subcutaneously inject logarithmically growing SCC15, head and neck squamous cell carcinoma cell line, at 5×10^6 cell density; with or without EphB4 ECD in the presence or absence of human bFGF, into athymic Balb/c nude mice, along with Matrigel (BD Bioscience) synthetic basement membrane (1:1 v/v), and examine tumors within 2 weeks. Tumor volumes in the EphB4 ECD group, in the presence and absence of growth factor after implantation were three-fold smaller than those in the vehicle groups. There was no difference in body weight between the groups. Immunohistochemical examination of cross-sections of resected tumors and TUNEL-positive apoptosis or necrosis, CD34 immunostaining, and BrdU proliferation rate will be performed, after deparaffinized, rehydrated, and quenched for endogenous peroxidase activity, and after 10 min permeabilization with proteinase K. Quantitative assessment of vascular densities will also be performed. Local intratumoral delivery or IV delivery of EphB4 ECD will also be performed twice a week.

[0234] 30 athymic nude mice, BALB/c (nu/nu), were each injected with 1×10^6 B16 melanoma cells with 0.1 ml PBS mixed with 0.1 ml matrigel or 1.5×10^6SCC15 cells resuspended in 200 μl of DMEM serum-free medium and injected subcutaneously on day 0 on the right shoulder region of mice. Proteins were injected intravenously or subcutaneously, around the tumor beginning on day 1 at a loading dose of 4 μg/mg, with weekly injections of 2 ug/mg. (10 μg/g, 50 μg/kg/day), and at 2 weeks post-inoculation. Mice are sacrificed on Day 14. Control mice received PBS 50 μl each day.

[0235] 14) Tumor Formation in Nude Mice

[0236] All animals were treated under protocols approved by the institutional animal care committees. Cancer cells (5×10^6) were subcutaneously inoculated into the dorsal skin of nude mice. When the tumor had grown to a size of about 100 mm^3 (usually it took 12 days), sEphB4 was either intraperitoneally or subcutaneously injected once/day, and tumorigenesis was monitored for 2 weeks. Tumor volume was calculated according to the formula $a^2\times b$, where a and b are the smallest and largest diameters, respectively. A Student's t test was used to compare tumor volumes, with $P<0.05$ being considered significant.

[0237] 15) Quantification of Microvessel Density

[0238] Tumors were fixed in 4% formaldehyde, embedded in paraffin, sectioned by 5 μm, and stained with hematoxylineosin. Vessel density was semi-quantitated using a computer-based image analyzer (five fields per section from three mice in each group).

Example 3

EphB4 is Upregulated and Imparts Growth Advantage in Prostate Cancer

A. Expression of EphB4 in Prostate Cancer Cell Lines

[0239] We first examined the expression of EphB4 protein in a variety of prostate cancer cell lines by Western blot. We found that prostate cancer cell lines show marked variation in the abundance of the 120 kD EphB4. The levels were relatively high in PC3 and even higher in PC3M, a metastatic clone of PC3, while normal prostate gland derived cell lines (MLC) showed low or no expression of EphB4 (FIG. **27**A). We next checked the activation status of EphB4 in PC3 cells by phosphorylation study. We found that even under normal culture conditions, EphB4 is phosphorylated though it can be further induced by its ligand, ephrin B2 (FIG. **27**B).

B. Expression of EphB4 in Clinical Prostate Cancer Samples

[0240] To determine whether EphB4 is expressed in clinical prostate samples, tumor tissues and adjacent normal tissue from prostate cancer surgical specimens were examined. The histological distribution of EphB4 in the prostate specimens was determined by immunohistochemistry. Clearly, EphB4 expression is confined to the neoplastic epithelium (FIG. **28**, top left), and is absent in stromal and normal prostate epithelium (FIG. **28**, top right). In prostate tissue array, 24 of the 32 prostate cancers examined were positive. We found EphB4 mRNA is expressed both in the normal and tumor tissues of clinical samples by quantitative RT-PCR. However, tumor EphB4 mRNA levels were at least 3 times higher than in the normal in this case (FIG. **28**, lower right).

C. p53 and PTEN Inhibited the Expression of EphB4 in PC3 Cells

[0241] PC3 cells are known to lack PTEN expression (Davis, et al., 1994, Science. 266:816-819) and wild-type p53 function (Gale, et al., 1997, Cell Tissue Res. 290:227-241). We investigated whether the relatively high expression of EphB4 is related to p53 and/or PTEN by re-introducing wild-type p53 and/or PTEN into PC3 cells. To compensate for the transfection efficiency and the dilution effect, transfected cells were sorted for the cotransfected truncated CD4 marker. We found that the expression of EphB4 in PC3 cells was reduced by the re-introduction of either wild-type p53 or PTEN. The co-transfection of p53 and PTEN did not further inhibit the expression of EphB4 (FIG. **29**A).

D. Retinoid X Receptor (RXRα) Regulates the Expression of EphB4

[0242] We previously found that RXRα was down-regulated in prostate cancer cell lines (Zhong, et al., 2003, Cancer Biol Ther. 2:179-184) and here we found EphB4 expression has the reverse expression pattern when we looked at "normal" prostate (MLC), Prostate cancer (PC3), and metastatic prostate cancer (PC3M) (FIG. **27**A), we considered whether RXRα regulates the expression of EphB4. To confirm the relationship, the expression of EphB4 was compared between CWR22R and CWR22R-RXRα, which constitutively expresses RXRα. We found a modest decrease in EphB4 expression in the RXRα overexpressing cell line, while FGF8 has no effect on EphB4 expression. Consistent with initial results, EphB4 was not found in "normal" benign prostate hypertrophic cell line BPH-1 (FIG. **29**B).

E. Growth Factor Signaling Pathway of EGFR and IGF-1R Regulates EphB4 Expression

[0243] EGFR and IGF-1R have both been shown to have autocrine and paracrine action on PC3 cell growth. Because we found that EphB4 expression is higher in the more aggressive cell lines, we postulated that EphB4 expression might correlate with these pro-survival growth factors. We tested the relationship by independently blocking EGFR and IGF-1R signaling. EphB4 was down-regulated after blocking the EGFR signaling using EGFR kinase inhibitor AG 1478 (FIG. **30**A) or upon blockade of the IGF-1R signaling pathway using IGF-1R neutralizing antibody (FIG. **30**B).

F. EphB4 siRNA and Antisense ODNs Inhibit PC3 Cell Viability

[0244] To define the significance of this EphB4 overexpression in our prostate cancer model, we concentrated our study on PC3 cells, which have a relatively high expression of EphB4. The two approaches to decreasing EphB4 expression were siRNA and AS-ODNs. A number of different phosphorothioate-modified AS-ODNs complementary to different segments of the EphB4 coding region were tested for specificity and efficacy of EphB4 inhibition. Using 293 cells transiently transfected with full-length EphB4 expression vector AS-10 was found to be the most effective (FIG. **31**B). A Similar approach was applied to the selection of specific siRNA. EphB4 siRNA 472 effectively knocks down EphB4 protein expression (FIG. **31**A). Both siRNA 472 and antisense AS-10 ODN reduced the viability of PC3 cells in a dose dependent manner (FIG. **31**C, D). Unrelated siRNA or sense oligonucleotide had no effect on viability.

G. EphB4 siRNA and Antisense ODNs Inhibit the Mobility of PC3 Cells

[0245] PC3 cells can grow aggressively locally and can form lymph node metastases when injected orthotopically into mice. In an effort to study the role of EphB4 on migration of PC3 cells in vitro, we performed a wound-healing assay. When a wound was introduced into a monolayer of PC3 cells, over the course of the next 20 hours cells progressively migrated into the cleared area. However, when cells were transfected with siRNA 472 and the wound was introduced, this migration was significantly inhibited (FIG. **31**E). Pretreatment of PC3 cells with 10 μM EphB4 AS-10 for 12 hours generated the same effect (FIG. **31**F). In addition, knock-down of EphB4 expression in PC3 cells with siRNA 472 severely reduced the ability of these cells to invade Matrigel as assessed by a double-chamber invasion assay (FIG. **31**G), compared to the control siRNA.

H. EphB4 siRNA Induces Cell Cycle Arrest and Apoptosis in PC3 Cells

[0246] Since knock-down of EphB4 resulted in decreased cell viability (FIG. **31**C) we sought to determine whether this was due to effects on the cell cycle. In comparison to control siRNA transfected cells, siRNA 472 resulted in an accumulation of cells in the sub G0 and S phase fractions compared to cells treated with control siRNA. The sub G0 fraction increased from 1% to 7.9%, and the S phase fraction from 14.9% to 20.8% in siRNA 472 treated cells compared to control siRNA treated cells (FIG. **32**A). Cell cycle arrest at sub G0 and G2 is indicative of apoptosis. Apoptosis as a result of EphB4 knock-down was confirmed by ELISA assay. A dose-dependent increase in apoptosis was observed when PC3 cells were transfected with siRNA 472, but not with control siRNA (FIG. **32**B). At 100 nM there was 15 times more apoptosis in siRNA 472 transfected than control siRNA transfected PC3 cells.

I. Materials and Methods

[0247] 1) Reagents

[0248] Neutralizing IGF-1R antibody was from R&D Systems (Minneapolis Minn.). Anti-IGF-1R(β), -EGFR, -EphB4 (C-16) were from Santa Cruz Biotech (Santa Cruz, Calif.). β-actin monoclonal antibody was purchased from Sigma Chemical Co. (St Louis, Mo.): Media and fetal bovine serum (FBS) were from Invitrogen (Carlsbad, Calif.). AG 1478(4-(3'-Chloroanilino)-6,7-dimethoxy-quinazoline) was from Calbiochem (San Diego, Calif.).

[0249] 2) Antisense Oligodeoxynucleotides and EphB4 siRNAs

[0250] EphB4 specific antisense phosphorothioate-modified oligodeoxynucleotide (ODN) and sense ODN were synthesized and purified by Qiagen (Alameda Calif.). The sequences are: Sense, 5'-TCC-TGC-AAG-GAG-ACC-TTC-AC-3'; AS1: 5'-GTG-CAG-GGA-TAG-CAG-GGC-CAT-3'; AS10: 5'-ATG-GAG-GCC-TCG-CTC-AGA-AA-3'. siRNAs were synthesized at the USC/Norris Comprehensive Cancer Center Microchemical Core laboratory. Sequences of EphB4 siRNAs are siRNA 472 5'-GGU-GAA-UGU-CAA-GAC-GCU-GUU-3' and siRNA 2303 5'-cuc-uuc-cga-ucc-cac-cua-cuu-3'. Negative control siRNA to scrambled GAPDH was from Ambion (Austin, Tex.)

[0251] 3) Cell Lines and Culture

[0252] The prostate cancer cell lines, PC3, PC3M, DU145, ALVA31, LAPC-4, LNCaP, CWR22R and adult human normal prostate epithelial cell line MLC SV40, and BPH-1 were

obtained and cultured as described previously (7). Stable cell line CWR22R-RXR, LNCaP-FGF8 were established and cultured as described before (7, 33).

[0253] 4) Generation of EphB4 Monoclonal Antibody

[0254] The extracellular domain (ECD) of EphB4 was cloned into pGEX-4T-1 to generate GST-fused ECD (GST-ECD). EphB4ECD expressed as a GST fusion protein in BL21 *E. coli* was purified by affinity chromatography and the GST domain was cleaved by thrombin. Monoclonal antibody was generated and the sensitivity and specificity of the antibody was reconfirmed by Western blot with whole cell lysate of 293 cells stably transfected with EphB4.

[0255] 5) One-Step RT-PCR and Quantitative RT-PCR

[0256] Total RNA was extracted using RNA STAT-60 (Tel-Test, Inc. Friendswood Tex.) from prostate cancer specimens and adjacent normal specimens. For quantitative RT-PCR first strand cDNA was synthesized from 5 μg of total RNA using SuperScript III (Invitrogen, Carlsbad Calif.). Quantitative RT-PCR was performed on the Stratagene MX3000P system (Stratagene, La Jolla Calif.) using SYBR Green I Brilliant Mastermix (Stragene) according to the manufacture's instructions. Optimized reactions for EphB4 and β-actin (used as the normalizer gene) were 150 nM each of the forward primer 63-actin, 5'-GGA-CCT-GAC-TGA-CTA-CCT-A-3'; EphB4,5'-AAG-GAG-ACC-TTC-ACC-GTC-TT-3') and reverse primer (β-actin 5'-TTG-AAG-GTA-GTT-TCG-TGG-AT-3'; EphB4,5'-TCG-AGT-CAG-GTT-CAC-AGT-CA-3') with DNA denaturation/activation of polymerase at 95° C. for 10 min followed by 40 cycles of 95° C. for 30 s, 60° C. for 1 min, 72° C. for 1 min. The specificity of the gene-specific amplification was confirmed by the presence of a single dissociation peak. All reactions were performed in triplicate with RT and no template negative controls.

[0257] 6) Immunohistochemistry

[0258] OCT-embedded tissues were sectioned at 5 μm and fixed in phosphate-buffered 4% paraformaldehyde. Sections were washed for 3×5 min in PBS and endogenous peroxidase was blocked by incubation in 0.3% H_2O_2 in PBS for 10 min at room temperature. Sections were incubated with Eph4 (C-16) antibody (1:50) for 1 h at room temperature followed by three washes in PBS and incubation with donkey anti-goat secondary antibody (Santa Cruz Biotech.) for 1 h at room temperature. After three washes in PBS, peroxidase activity was localized by incubation in DAB substrate solution (Vector Laboratories, Inc. Burlingame Calif.) for 10 min at room temperature. Sections were counterstained with Hematoxylin for 20 s, dehydrated and mounted. Negative control for staining was substitution of normal goat serum for primary antibody. Immunohistochemical staining on prostate array (BioMeda, Foster City, Calif.) was done using goat ABC Staining System (Santa Cruz Biotech.) according to the manufacturer's instructions.

[0259] 7) Western Blot

[0260] Whole cell lysates were prepared using Cell Lysis Buffer (GeneHunter, Basgvukke Tenn.) supplemented with protease inhibitor cocktail (Pierce, Rockford Ill.), unless otherwise noted. Total protein was determined using the DC reagent system (Bio-Rad, Hercules Calif.). Typically, 20 μg whole cell lysate was run on 4-20% Tris-Glycine gradient gel. The samples were electro-transferred to PVDF membrane and the non-specific binding was blocked in TBST buffer (0.5 mM Tris-HCl, 45 mM NaCl, 0.05% Tween-20, pH 7.4) containing 5% non-fat milk. Membranes were first probed with primary antibody overnight, stripped with Restore™ Western Blot stripping buffer (Pierce, Rockford Ill.) and reprobed with β-actin to confirm equivalent loading and transfer of protein. Signal was detected using SuperSignal West Femto Maximum Sensitivity Substrate (Pierce).

[0261] 8) Phosphorylation Analysis

[0262] Cells growing in 60 mm dishes were either serum starved (1% FBS supplemented RPMI 1640, 24 hours) or cultured in normal conditions (10% FBS) and then treated with or without 1 μg/ml mouse ephrin $B2/F_c$ for 10 min to activate EphB4 receptor Cleared cell lysates were incubated with EphB4 monoclonal antibody overnight at 4° C. Antigen-antibody complex was immunoprecipitated by the addition of 100 μl of Protein G-Sepharose in 20 mM sodium phosphate, pH 7.0 with incubation overnight at 4° C. Immunoprecipitates were analyzed by Western blot with pTyr specific antibody (Upstate, clone 4G10) at 1:1000 dilution followed by incubation with protein G-HRP (Bio-Rad) at 1:5000 dilution. To monitor immunoprecipitation efficiency, a duplicate membrane was probed with EphB4 specific monoclonal antibody.

[0263] 9) Transient Transfection and Sorting of Transfected Cells

[0264] PC3 cells were cotransfected with pMACS 4.1 coding for CD4 and wild type p53 (pC53-SN3) or PTEN vector or both using Lipofectamine 2000 (Invitrogen) according to the manufacturer's instructions. The molar ratio of CD4 to p53 or PTEN or vector was 1:3 and total plasmid was 24 μg for a 10 cm^2 dish of 90% confluent cells using 60 μl of Lipofectamine 2000. 24 hours after transfection, a single cell suspension was made and sorted using truncated CD4 as a surface marker according to the manufacturer's protocol (Miltenyi Biotec, Germany). Sorted cells were lysed in 1×SDS sampling buffer and analyzed by Western blot.

[0265] 10) Study of IGF and EGF Signaling Pathway on the Expression of EphB4

[0266] PC3 cells were seeded into 6-well plates and cultured until 80% confluent and treated with 2 μg/ml neutralizing IGF-1R monoclonal antibody, MAB391 (Hailey, et al., 2002, Mol Cancer Ther. 1:1349-1353), or with 1 nM AG 1478, a strong EGFR inhibitor (Liu, et al., 1999, J Cell Sci. 112 (Pt 14):2409-2417) for 24 h. Crude cell lysates were analyzed by Western blot. Band density was quantified with the Bio-Rad QuantityOne System software.

[0267] 11) Cell Viability Assay

[0268] PC3 cells were seeded on 48-well plates at a density of approximately 1×10^4 cells/well in a total volume of 200 ml. Media was changed after the cells were attached and the cells were treated with various concentrations (1-10 μM) of EphB4 antisense ODN or sense ODN as control. After three days media was changed and fresh ODNs added. Following a further 48 h incubation, cell viability was assessed by MIT as described previously (36). EphB4 siRNAs (10-100 nM) were introduced into 2×10^4 PC3 cells/well of a 48-well plate using 2 μl of Lipofectamine™ 2000 according to the manufacturer's instructions. 4 h post-transfection the cells were returned to growth media (RPMI 1640 supplemented with 10% FBS). Viability was assayed by MTT 48 h following transfection.

[0269] 12) Wound Healing Migration Assay

[0270] PC3 cells were seeded into 6-well plates and cultured until confluent. 10 μM AS-10 or sense ODN as control were introduced to the wells as described for the viability assay 12 hours before wounding the monolayer by scraping it with a sterile pipette tip. Medium was changed to RPMI 1640

supplemented with 5% FBS and fresh ODNs. Confluent cultures transfected with 50 nM siRNA 472 or GAPDH negative control siRNA 12 hours prior to wounding were also examined. The healing process was examined dynamically and recorded with a Nikon Coolpix 5000 digital camera with microscope adapter.

[0271] 13) Invasion Assay

[0272] PC3 cells were transfected with siRNA 472 or control siRNA using Lipofectamine™ 2000 and 6 hours later 0.5×105 cells were transferred into 8 μm Matrigel-precoated inserts (BD Bioscience, Palo Alto, Calif.). The inserts were placed in companion wells containing RPMI supplemented with 5 FBS and 5 μg/ml fibronectin as a chemoattractant. Following 22 h incubation the inserts were removed and the noninvading cells on the upper surface were removed by with a cotton swab. The cells on the lower surface of the membrane were fixed in 100% methanol for 15 min, air dried and stained with Giemsa stain for 2 min. The cells were counted in five individual high-powered fields for each membrane under a light microscope. Assays were performed in triplicate for each treatment group.

[0273] 14) Cell Cycle Analysis

[0274] 80% confluent cultures of PC3 cells in 6-well plates were transfected with siRNA472 (100 nM) using Lipofectamine™ 2000. 24 hours after transfection, cells were trypsinized, washed in PBS and incubated for 1 h at 4° C. in 1 ml of hypotonic solution containing 50 μg/ml propidium iodide, 0.1% sodium citrate, 0.1 Triton X-100 and 20 μg/ml Dnase-free RnaseA. Cells were analyzed in linear mode at the USC Flow cytometry facility. Results were expressed as percentages of elements detected in the different phases of the cell cycle, namely Sub G0 peak (apoptosis), G0/G1 (no DNA synthesis), S (active DNA synthesis), G2 (premitosis) and M (mitosis).

[0275] 15) Apoptosis ELISA

[0276] Apoptosis was studied using the Cell Death Detection ELISAplus Kit (Roche, Piscataway, N.J.) according to the manufacturer's instructions. Briefly, PC3 80% confluent cultures in 24-well plates were transfected using Lipofectamine™ 2000 with various concentrations (0-100 nM) of siRNA 472 or 100 nM control siRNA. 16 hours later, cells were detached and 1×10^4 cells were incubated in 200 μl lysis buffer. Nuclei were pelleted by centrifugation and 20 μl of supernatant containing the mono- or oligonucleosomes was taken for ELISA analysis. Briefly, the supernatant was incubated with anti-histone-biotin and anti-DNA-POD in streptavidin-coated 96-well plate for 2 hours at room temperature. The color was developed with ABST and absorbance at 405 nm was read in a microplate reader (Molecular Devices, Sunnyvale, Calif.).

Example 4

Expression of EPHB4 in Mesothelioma: a Candidate Target for Therapy

[0277] Malignant mesothelioma (MM) is a rare neoplasm that most often arises from the pleural and peritoneal cavity serous surface. The pleural cavity is by far the most frequent site affected (>90%), followed by the peritoneum (6-10%) (Carbone et al., 2002, Semin Oncol. 29:2-17). There is a strong association with asbestos exposure, about 80% of malignant mesothelioma cases occur in individuals who have ingested or inhaled asbestos. This tumor is particularly resistant to the current therapies and, up to now, the prognosis of these patients is dramatically poor (Lee et al., 2000, Curr Opin Pulm Med. 6:267-74).

[0278] Several clinical problems regarding the diagnosis and treatment of malignant mesothelioma remain unsolved. Making a diagnosis of mesothelioma from pleural or abdominal fluid is notoriously difficult and often requires a thoracoscopic or laparoscopic or open biopsy and Immunohistochemical staining for certain markers such as meosthelin expressed preferentially in this tumor. Until now, no intervention has proven to be curative, despite aggressive chemotherapeutic regimens and prolonged radiotherapy. The median survival in most cases is only 12-18 months after diagnosis.

[0279] In order to identify new diagnostic markers and targets to be used for novel diagnostic and therapeutic approaches, we assessed the expression of EPHB4 and its ligand EphrinB2 in mesothelioma cell lines and clinical samples.

A. EPHB4 and EphrinB2 is Expressed in Mesothelioma Cell Lines

[0280] The expression of Ephrin B2 and EphB4 in malignant mesothelioma cell lines was determined at the RNA and protein level by a variety of methods. RT-PCR showed that all of the four cell lines express EphrinB2 and EPHB4 (FIG. **33**A). Protein expression was determined by Western blot in these cell lines. Specific bands for EphB4 were seen at 120 kD. In addition, Ephrin B2 was detected in all cell lines tested as a 37 kD band on Western blot (FIG. **33**B). No specific band for Ephrin B2 was observed in 293 human embryonic kidney cells, which were included as a negative control.

[0281] To confirm the presence of EphB4 transcription in mesothelioma cells, in situ hybridization was carried out on NCI H28 cell lines cultured on chamber slides. Specific signal for EphB4 was detected using antisense probe Ephrin B2 transcripts were also detected in the same cell line. Sense probes for both EphB4 and Ephrin 132 served as negative controls and did not hybridize to the cells (FIG. **34**). Expression of EphB4 and Ephrin B2 proteins was confirmed in the cell lines by immunofluorescence analysis (FIG. **35**). Three cell lines showed strong expression of EphB4, whereas expression of Ephrin 132 was present in 1-128 and 1-12052, and weakly detectable in H2373.

B. Evidence of Expression of EPHB4 and EphrinB2 in Clinical Samples

[0282] Tumor cells cultured from the pleural effusion of a patient diagnosed with pleural malignant mesothelioma were isolated and showed positive staining for both EphB4 and Ephrin B2 at passage 1 (FIG. **35**, bottom row). These results confirm co-expression of EphB4 and Ephrin B2 in mesothelioma cell lines. To determine whether these results seen in tumor cell lines were a real reflection of expression in the disease state, tumor biopsy samples were subjected to immunohistochemical staining for EphB4 and Ephrin 132. Antibodies to both proteins revealed positive stain in the tumor cells. Representative data is shown in FIG. **36**.

C. EPHB4 is Involved in the Cell Growth and Migration of Mesothelioma

[0283] The role of EphB4 in cell proliferation was tested using EPHB4 specific antisepses oligonucleotides and siRNA. The treatment of cultured H28 with EPHB4 antisense

reduced cell viability. One of the most active inhibitor of EphB4 expression is EPHB4AS-10 (FIG. 37A). Transfection of EPHB4 siRNA 472 generated the same effect (FIG. 37B).

[0284] MM is a locally advancing disease with frequent extension and growth into adjacent vital structures such as the chest wall, heart, and esophagus. In an effort to study this process in vitro, we perform wound healing assay using previously described techniques (3:36). When a wound was introduced into sub confluent H28 cells, over the course of the next 28 hours cells would progressively migrate into the area of the wound. However, when cells were pretreated with EPHB4AS-10 for 24 hours, and the wound was introduced, this migration was virtually completely prevented (FIG. 38A). The migration study with Boyden Chamber assay with EPHB4 siRNA showed that cell migration was greatly inhibited with the inhibition of EPHB4 expression (FIG. 38B).

D. Materials and Methods

[0285] 1) Cell Lines and Reagents

[0286] NCI H28, NCI 112052, NCI H2373, MSTO 211H mesothelioma cell lines and 293 human embryonic kidney cells were obtained from the ATCC (Manassas, Va.). Cells were maintained in RPMI 1640 media supplemented with 10% heat-inactivated fetal bovine serum (FBS; Life Technologies, Gaithersburg, Md.) and antibiotics. Primary cells were obtained from pleural effusion of patients with mesothelioma. A large number of EPHB4 phosphorothioate modified antisense oligonucleotides were synthesized. Similarly a number of EphB4 specific siRNAs were generated. Monoclonal antibody produced against EPHB4 was used for western blot. Polyclonal antibody against EphrinB2 and EPHB4 (C-16) (for immunohistochemical staining) was from Santa Cruz.

[0287] 2) RT-PCR

[0288] Total RNA was reversed transcribed by use of random hexamers (Invitrogen). Primers for EphB4 and EphrinB2 were designed with Primer 3 software. The sequences for all primers are as follows: EPHB4 forward primer and EPHB4 reverse primer (see, e.g., in Example 2); EphrinB2 forward primer and EphrinB2 reverse primer (see, e.g., in Example 6); G3PDH forward primer, 5'-GGAGCCAAAAGGGTCATCAT-3'; G3PDH reverse primer, 5'-GGCATTGCTGCAAAGAAAGAG-3'; Clonetics kit was used for PCR. PCRs were performed with the ABI PCR System 2700 (Applied Biosystem). The PCR conditions were 95° C. for 5 min, followed by 35 cycles of 95° C. for 30 seconds, 60° C. for 30 seconds and 72° C. for 1 min.

[0289] 3) Preparation of Digoxigenin-Labeled RNA Probes

[0290] Ephrin-B2 and EphB4 PCR products were cloned using the pGEM-T Easy System (Promega, Madison Wis.) according to the manufacturer's description. The primers and PCR products were 5'-tccgtgtggaagtactgctg-3' (forward), 5'-tctggtttggcacagttgag-3' (reverse), for ephrin-B2 that yielded a 296-bp product and 5'-ctttggaagagaccctgctg-3' (forward), 5% agacggtgaaggtctccttg-3', for EphB4 that yielded a 297-bp product. The authenticity and insert orientation were confirmed by DNA sequencing.

[0291] The pGEM-T Easy plasmids containing the PCR product of the human ephrin-B2 or EphB4 gene were linearized with Spe I or Nco I. Antisense or sense digoxigenin (DIG)-labeled RNA probes were transcribed from T7 or SP6 promoters by run-off transcription using a DIG RNA labeling kit (Roche, Indianapolis Ind.). RNA probes were quantitated by spot assay as described in the DIG RNA labeling kit instructions.

[0292] 4) In Situ Hybridization

[0293] Cells were cultured in Labtech II 4-well chamber slides (Nalge Nunc International, Naperville, Ill.). Cells were washed in PBS (37° C.), then fixed for 30 min at 25° C. in a solution of 4% (w/v) formaldehyde, 5% (v/v) acetic acid, and 0.9% (w/v) NaCl. After fixation, slides were rinsed with PBS and stored in 70% ethanol at 4° C. until further use. Before in situ hybridization, cells were dehydrated, washed in 100% xylene to remove residual lipid and then rehydrated, finally in PBS. Cells were permeabilized by incubating at 37° C. with 0.1% (w/v) pepsin in 0.1 N HCl for 20 min and post-fixed in 1% formaldehyde for 10 min. Prehybridization was performed for 30 min at 37° C. in a solution of 4×SSC containing 50% (v/v) deionized formamide. Slides were hybridized overnight at 42° C. with 25 ng antisense or sense RNA probes in 40% deionized formamide, 10% dextran sulfate, 1×Denhardt's solution, 4×SSC, 10 mM DTT, 1 mg/ml yeast t-RNA and 1 mg/ml denatured and sheared salmon sperm DNA in a total volume of 40 Slides were then washed at 37° C. as follows: 2×15 min with 2×SSC, 2×15 min with 1×SSC, 2×15 min with 0.5×SSC and 2×30 min with 0.2×SSC. Hybridization signal was detected using alkaline-phosphatase-conjugated anti-DIG antibodies (Roche) according to the manufacturer's instructions. Color development was stopped by two washes in 0.1 M Tris-HCl, 1 mM EDTA, pH 8.0 for 10 min. Cells were visualized by counterstaining of nucleic acids with Nuclear Fast Red (Vector Laboratories, Burlingame, Calif.) and the slides were mounted with IMMU-MOUNT (Shandon, Astmoor UK).

[0294] 5) Western Blot

[0295] Crude cell lysates were prepared by incubation in cell lysis buffer (10 mM Tris, pH 7.5, 1 mM EDTA, 150 mM NaCl, 1% Triton X-100, 1 mM DTT, 10% glycerol). Lysates were cleared by centrifugation at 10,000×g for 10 min. Total protein was determined by Bradford assay (Bio-Rad). Samples (20 μg protein) were fractionated on a 4-20% Tris-glycine polyacrylamide gel and transferred to polyvinylidene difluoride (PVDT) membrane (Bio-Rad) by electroblotting. Membranes were blocked with 5% non-fat milk prior to incubation with antibody to EphB4 (1:5000 dilution) at C, for 16 h. Secondary antibody (1:100,000 dilution) conjugated with horseradish peroxidase was applied for 1 h at 25° C. The membranes were developed using the SuperSignal West Femto Maximum sensitivity chemiluminescent substrate (Pierce, Rockford, Ill.) according to the manufacturer's instructions.

[0296] 6) Immunohistochemistry

[0297] Formalin-fixed tissue sections were deparaffinized and incubated with 10% goat serum at −70° C. for 10 minutes and incubated with the primary rabbit antibodies against either Ephrin B2 or EphB4 (Santa Cruz Biotechnologies; 1:100) at 4° C. overnight. Isotype-specific rabbit IgG was used as control. The immunoreactivity for these receptors was revealed using an avidin-biotin kit from Vector Laboratories. Peroxidase activity was revealed by the diaminobenzidine (Sigma) cytochemical reaction. The slides were then counterstained with H&E.

[0298] 7) Immunofluorescence Studies

[0299] Cells were cultured on Labtech II 4-well chamber slides and fixed in 4% paraformaldehyde in Dulbecco's phosphate buffered saline pH 7.4 (PBS) for 30 min. The slides

were rinsed twice in PBS and preincubated with blocking buffer (0.2% Triton-X100, 1% BSA in PBS) for 20 min. The slides were then incubated with antibodies to EphB4 or ephrin B2 (1:100 dilution in PBS) in blocking buffer at 4° C. for 16 hr. After washing three times, the slides were incubated with the appropriate fluorescein-conjugated secondary antibodies (Sigma-Aldrich, St. Louis, Mo.). Nuclei were counterstained with 4',6-diamidino-2-phenylindole dihydrochloride hydrate (DAPI), washed extensively with PBS and mounted with Vectasheild antifade mounting solution (Vector Laboratories). Images were obtained using an Olympus AX70 fluorescence microscope and Spot v2.2.2 (Diagnostic Instruments Inc., Sterling Heights, Mich.) digital imaging system.

[0300] 8) Cell Viability Assay

[0301] Cells were seeded at a density of 5×10^3 per well in 48-well plates on day 0 in appropriate growth media containing 2% fetal calf serum (FCS). On the following day, the media was changed and cells were treated with various concentrations (1-10 μM) of EphB4 Antisense. On day 4, viability was assessed using 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT) at a final concentration of 0.5 mg/ml. Cells were incubated for 2 hr, medium was aspirated, and the cells were dissolved in acidic isopropanol (90% isopropanol, 0.5% SDS and 40 mM HCl). Optical density was read in an ELISA reader at 490 nm using isopropanol as blank (Molecular Devices, CA).

[0302] 9) Cell Migration

[0303] In vitro wound healing assay was adopted. Briefly, cells were seeded onto 6-cm plates in full culture media for 24 hours, and then switched to medium containing 5% FBS. EPHB4 antisense 10 (10 μM) was also added to treated well. 24 hours later, wounds were made using the tip of a p-200 pipette man; a line was drawn through the middle of the plates. The plate was photographed at 0, 12, 24 hours. The experiment was repeated three times.

Example 5

EphB4 is Expressed in Squamous Cell Carcinoma of the Head and Neck: Regulation by Epidermal Growth Factor Signaling Pathway and Growth Advantage

[0304] Squamous cell carcinoma of the head and neck (HNSCC) is the sixth most frequent cancer worldwide, with estimated 900,000 cases diagnosed each year. It comprises almost 50% of all malignancies in some developing nations. In the United States, 50,000 new cases and 8,000 deaths are reported each year. Tobacco carcinogens are believed to be the primary etiologic agents of the disease, with alcohol consumption, age, gender, and ethnic background as contributing factors.

[0305] The differences between normal epithelium of the upper aerodigestive tract and cancer cells arising from that tissue are the result of mutations in specific genes and alteration of their expression. These genes control DNA repair, proliferation, immortalization, apoptosis, invasion, and angiogenesis. For head and neck cancer, alterations of three signaling pathways occur with sufficient frequency and produce such dramatic phenotypic changes as to be considered the critical transforming events of the disease. These changes include mutation of the p53 tumor suppressor, overexpression of epidermal growth factor receptor (EGFR), and inactivation of the cyclin dependent kinase inhibitor p16. Other changes such as Rb mutation, ras activation, cyclin D amplification, and myc overexpression are less frequent in HNSCC.

[0306] Although high expression of EphB4 has been reported in hematologic malignancies, breast carcinoma, endometrial carcinoma, and colon carcinoma, there is limited data on the protein levels of EphB4, and complete lack of data on the biological significance of this protein in tumor biology such as HNSCC.

A. HNSCC Tumors Express EphB4

[0307] We studied the expression of EphB4 in human tumor tissues by immunohistochemistry, in situ hybridization, and Western blot. Twenty prospectively collected tumor tissues following IRB approval have been evaluated with specific EphB4 monoclonal antibody that does not react with other members of the EphB and EphA family. EphB4 expression is observed in all cases, with varying intensity of staining. FIG. **39**A (top left) illustrates a representative case, showing that EphB4 is expressed in the tumor regions only, as revealed by the HE tumor architecture (FIG. **39**A bottom left). Note the absence of staining for EphB4 in the stroma. Secondly, a metastatic tumor site in the lymph node shows positive staining while the remainder of the lymph node is negative (FIG. **39**A, top right).

[0308] In situ hybridization was carried out to determine the presence and location of EphB4 transcripts in the tumor tissue. Strong signal for EphB4 specific antisense probe was detected indicating the presence of transcripts (FIG. **39** B, top left). Comparison with the H&E stain (FIG. **39**B, bottom left) to illustrate tumor architecture reveals that the signal was localized to the tumor cells, and was absent from the stromal areas. Ephrin B2 transcripts were also detected in tumor sample, and as with EphB4, the signal was localized to the tumor cells (FIG. **39**B, top right). Neither EphB4 nor ephrin B2 sense probes hybridized to the sections, proving specificity of the signals.

B. High Expression of EphB4 in Primary and Metastatic Sites of HNSCC

[0309] Western blots of tissue from primary tumor, lymph node metastases and uninvolved tissue were carried out to determine the relative levels of EphB4 expression in these sites. Tumor and normal adjacent tissues were collected on 20 cases, while lymph nodes positive for tumor were harvested in 9 of these 20 cases. Representative cases are shown in FIG. **39**C. EphB4 expression is observed in each of the tumor samples. Similarly, all tumor positive lymph nodes show EphB4 expression that was equal to or greater than the primary tumor. No or minimal expression is observed in the normal adjacent tissue.

C. EphB4 Expression and Regulation by EGFR Activity in HNSCC Cell Lines

[0310] Having demonstrated the expression of EphB4 limited to tumor cells, we next sought to determine whether there was an in vitro model of EphB4 expression in HNSCC. Six HN SCC cell lines were surveyed for EphB4 protein expression by Western Blot (FIG. **40**A). A majority of these showed strong EphB4 expression and thus established the basis for subsequent studies. Since EGFR is strongly implicated in HNSCC we asked whether EphB4 expression is associated with the activation of EGFR. Pilot experiments in SCC-15, which is an EGFR positive cell line, established an optimal time of 24 h and concentration of 1 mM of the specific EGFR kinase inhibitor AG 1478 (FIG. **40**B) to inhibit expression of

EphB4. When all the cell lines were studied, we noted robust EGFR expression in all but SCC-4, where it is detectable but not strong (FIG. **40**C, top row). In response to EGFR inhibitor AG1478 marked loss in the total amount of EphB4 was observed in certain cell lines (SCC-15, and SCC-25) while no effect was observed in others (SCC-9, -12, -13 and -71). Thus SCC-15 and -25 serve as models for EphB4 being regulated by EGFR activity, while SCC-9, -12, -13 and -71 are models for regulation of EphB4 in HNSCC independent of EGFR activity, where there may be input from other factors such as p53, PTEN, IL-6 etc. We also noted expression of the ligand of EphB4, namely ephrin B2, in all of the cell lines tested. As with EphB4 in some lines ephrin B2 expression appears regulated by EGFR activity, while it is independent in other cell lines.

[0311] Clearly, inhibition of constitutive EGFR signaling repressed EphB4 levels in SCC15 cells. We next studied whether EGF could induce EphB4. We found that EphB4 levels were induced in SCC15 cells that had been serum starved for 24 h prior to 24 h treatment with 10 ng/ml EGF as shown in FIG. **41**B (lanes 1 and 2). The downstream signaling pathways known for EGFR activation shown in FIG. **41**A, (for review see Yarden & Slikowski 2001) were then investigated for their input into EGF mediated induction of EphB4. Blocking PLCg, AKT and JNK phosphorylation with the specific kinase inhibitors U73122, SH-5 and SP600125 respectively reduced basal levels and blocked EGF stimulated induction of EphB4 (FIG. **41**B, lanes 3-8). In contrast, inhibition of ERK1/2 with PD098095 and PI3-K with LY294002 or Wortmannin had no discernible effect on EGF induction of EphB4 levels. However, basal levels of EphB4 were reduced when ERK1/2 phosphorylation was inhibited. Interestingly, inhibition of p38 MAPK activation with SB203580 increased basal, but not EGF induced EphB4 levels. Similar results were seen in the SCC25 cell line (data not shown).

D. Inhibition of EphB4 in High Expressing Cell Lines Results in Reduced Viability and Causes Cell-Cycle Arrest

[0312] We next turned to the role of EphB4 expression in HNSCC by investigating the effect of ablating expression using siRNA or AS-ODN methods. Several siRNAs to EphB4 sequence were developed (Table 1) which knocked-down EphB4 expression to varying degrees as seen in FIG. **42**A. Viability was reduced in SCC-15, -25 and -71 cell lines transfected with siRNAs 50 and 472, which were most effective in blocking EphB4 expression (FIG. **42**B). Little effect on viability was seen with EphB4 siRNA 1562 and 2302 or ephrin B2 siRNA 254. Note that in SCC-4, which does not express EphB4 (see FIG. **40**A) there was no reduction in cell viability. The decreased cell viability seen with siRNA 50 and 472 treatment was attributable to accumulation of cells in sub G0, indicative of apoptosis. This effect was both time and dose-dependant (FIG. **42**C and Table 2). In contrast, siRNA2302 that was not effective in reducing EphB4 levels and had only minor effects on viability did not produce any changes in the cell cycle when compared with the mock Lipofectamine™2000 transfection.

TABLE 1

EphB4 siRNAs

Name	siRNA sequence
Eph B4 50:	5'-GAGACCCUGCUGAACACAAUU-3' 3'-UUCUCUGGGACGACUUGUGUU-5'
Eph B4 472:	5'-GGUGAAUGUCAAGACGCUGUU-3' 3'-UUCCACUUACAGUUCUGCGAC-5'
Eph B4 1562:	5'-CAUCACAGCCAGACCCAACUU-3' 3'-UUGUAGUGUCGGUCUGGGUUG-5'
Eph B4 2302	5'-CUCUUCCGAUCCCACCUACUU-3' 3'-UUGAGAAGGCUAGGGUGGAUG-5'

TABLE 2

Effect of different EphB4 siRNA on Cell Cycle

Treatment	Sub G0	G1	S	G2
36 hr				
Lipo alone	1.9	39.7	21.3	31.8
100 nM 2302	2.0	39.3	21.2	31.2
100 nM 50	18.1	31.7	19.7	24.4
100 nM 472	80.2	10.9	5.2	2.1
16 hr				
Lipo alone	7.8	55.7	15.2	18.5
100 nM 2302	8.4	57.3	14.3	17.3
10 nM 50	10.4	53.2	15.7	17.7
100 nM 50	27.7	31.3	18.1	19.6
10 nM 472	13.3	50.2	15.8	17.5
100 nM 472	30.7	31.9	16.4	18.0

[0313] In addition, over 50 phosphorothioate AS-ODNs complementary to the human EphB4 coding sequences were synthesized and tested for their ability to inhibit EphB4 expression in 293 cells transiently transfected with full length EphB4 expression plasmid. FIG. **43**A shows a representative sample of the effect of some of these AS-ODNs on EphB4 expression. Note that expression is totally abrogated with AS-10, while AS-11 has only a minor effect. The effect on cell viability in SCC15 cells was most marked with AS-ODNs that are most effective in inhibiting EphB4 expression as shown in FIG. **43**B. The IC_{50} for AS-10 was approximately 1 μM, while even 10 μM AS-11 was not sufficient to attain 50% reduction of viability. When the effect that AS-10 had on the cell cycle was investigated, it was found that the sub G0 fraction increased from 1.9% to 10.5% compared to non-treated cells, indicative of apoptosis (FIG. **43**C).

E. EphB4 Regulates Cell Migration

[0314] We next wished to determine if EphB4 participates in the migration of HNSCC. Involvement in migration may have implications for growth and metastasis. Migration was assessed using the wound-healing/scrape assay. Confluent SCC15 and SCC25 cultures were wounded by a single scrape with a sterile plastic Pasteur pipette, which left a 3 mm band with clearly defined borders. Migration of cells into the cleared area in the presence of test compounds was evaluated and quantitated after 24, 48 and 72 hr. Cell migration was markedly diminished in response to AS-10 that block EphB4 expression while the inactive compounds, AS-1 and

scrambled ODN had little to no effect as shown in FIG. **43**D. Inhibition of migration with AS-10 was also shown using the Boyden double chamber assay (FIG. **43**E).

F. EphB4 AS-10 In Vivo Anti-Tumor Activity

[0315] The effect of EphB4 AS-10, which reduces cell viability and motility, was determined in SCC15 tumor xenografts in Balb/C nude mice. Daily treatment of mice with 20 mg/kg AS-10, sense ODN or equal volume of PBS by I.P. injection was started the day following tumor cell implantation. Growth of tumors in mice receiving AS-10 was significantly retarded compared to mice receiving either sense ODN or PBS diluent alone (FIG. **44**). Non-specific effects attributable to ODN were not observed, as there was no difference between the sense ODN treated and PBS treated groups.

G. Materials and Methods

[0316] 1) Cell Lines and Reagents

[0317] HNSCC-4, -9, 12, -13, -15, -25, and -71 were obtained from and 293 human embryonic kidney cells were obtained from the ATCC (Manassas, Va.). Cells were maintained in RPM' 1640 media supplemented with 10% heat-inactivated fetal bovine serum (FBS; Invitrogen, Carlsbad, Calif.) and antibiotics. EGFR, EphB4(C-16) polyclonal antibodies were from Santa Cruz Biotech (Santa Cruz, Calif.). β-actin monoclonal antibody was purchased from Sigma Chemical Co. (St Louis, Mo.). Ephrin B2 and EphB4 polyclonal antibodies and their corresponding blocking peptides were obtained from Santa Cruz Biotechnology (Santa Cruz, Calif.). AG 1478 (4-(3'-Chloroanilino)-6,7-dimethoxy-quinazoline) was from Calbiochem (San Diego, Calif.). Kinase inhibitors SH-5 and SP 600125 were from A.G. Scientific (San Diego, Calif.), PD98095, U73122, SB203580, LY294002, and Wortmannin were obtained from Sigma.

[0318] 2) Preparation of Digoxigenin-Labeled RNA Probes See above, e.g., Example 3.

[0319] 3) In Situ Hybridization

[0320] See above, e.g., Example 3.

[0321] 4) Immunohistochemistry

[0322] Formalin-fixed tissue sections were deparaffinized and incubated with 10% goat serum at −70° C. for 10 minutes and incubated with the EphB4 monoclonal antibody 4° C. overnight. Isotype specific rabbit IgG was used as control. The immunoreactivity for these receptors was revealed using an avidin-biotin kit from Vector Laboratories. Peroxidase activity was revealed by the diaminobenzidine (Sigma) cytochemical reaction. The slides were then counterstained with 0.12% methylene blue or H&E. For frozen sections, OCT-embedded tissues were sectioned at 5 μm and fixed in phosphate-buffered 4% paraformaldehyde. Sections were washed for 3×5 min in PBS and endogenous peroxidase was blocked by incubation in 0.3% H_2O_2 in PBS for 10 min at room temperature. Sections were incubated with Eph4 (C-16) antibody (1:50) for 1 h at room temperature followed by three washes in PBS and incubation with donkey anti-goat secondary antibody (Santa Cruz Biotech.) for 1 h at room temperature. After three washes in PBS, peroxidase activity was localized by incubation in DAB substrate solution (Vector Laboratories, Inc. Burlingame Calif.) for 10 min at room temperature. Sections were, counterstained with Hematoxylin for 20 s, dehydrated and mounted. Negative control for staining was substitution of normal goat serum for primary antibody. Immunohistochemical staining on prostate array (BioMeda, Foster City, Calif.) was done using goat ABC Staining System (Santa Cruz Biotech.) according to the manufacturer's instructions.

[0323] 5) Western Blot

[0324] See above, e.g., Example 3.

[0325] 6) Synthesis of EphB4 siRNA by In Vitro Transcription

[0326] The Silencer™ siRNA construction kit (Ambion, Austin Tex.) was used to synthesize siRNA to EphB4. Briefly, 21 bp target sequences containing 19 bp downstream of 5'-AA dinucleotides were identified that showed no significant homology to other sequences in the GenBank database. Sense and antisense siRNA 29-mer DNA oligonucleotide templates were synthesized at the USC Norris Microchemical Core Facility. Antisense template corresponded to the target sequence followed by 8 bp addition (5'-CCTGTCTC-3') at the 3' end complementary to the T7 promoter primer provided by the Silencer™ siRNA construction kit. Sense template comprised 5'-AA followed by the complement of the target 19 bp, then the T7 8 bp sequence as above.

[0327] In separate reactions, the two siRNA oligonucleotide templates were hybridized to a T7 promoter primer. The 3' ends of the hybridized oligonucleotides were extended by the Klenow fragment of DNA polymerase to create double-stranded siRNA transcription templates. The sense and antisense siRNA templates were transcribed by T7 RNA polymerase and the resulting RNA transcripts were hybridized to create dsRNA. The leader sequences were removed by digesting the dsRNA with a single-stranded specific ribonuclease leaving the overhanging UU dinucleotides. The DNA template was removed at the same time by treatment with RNase free deoxyribonuclease. The resulting siRNA was purified by glass fiber filter binding to remove excess nucleotides, short oligomers, proteins, and salts in the reaction. The end products (shown in Table 3) were double-stranded 21-mer siRNAs with 3' terminal uridine that can effectively reduce the expression of target mRNA when transfected into cells.

[0328] A number of phosphorothioate AS-ODNs were also synthesized (Operon, Valencia Calif.) to test for inhibition of EphB4 expression (Table 3).

TABLE 3

EphB4 Antisense ODNs

Name	Position	Sequence (5' → 3')
Eph B4 AS-1	(552-572)	GTG CAG GGA TAG CAG GGC CAT
Eph B4 AS-2	(952-972)	AAG GAG GGG TGG TGC ACG GTG
Eph B4 AS-3	(1007-1027)	TTC CAG GTG CAG GGA GGA GCC
Eph B4 AS-4	(1263-1285)	GTG GTG ACA TTG ACA GGC TCA
Eph B4 AS-5	(1555-1575)	TCT GGC TGT GAT GTT CCT GGC
Eph B4 AS-6	(123-140)	GCC GCT CAG TTC CTC CCA
Eph B4 AS-7	(316-333)	TGA AGG TCT CCT TGC AGG
Eph B4 AS-8	(408-428)	CGC GGC CAC CGT GTC CAC CTT

TABLE 3-continued

EphB4 Antisense ODNs		
Name	Position	Sequence (5' → 3')
Eph B4 AS-9	(1929-1949)	CTT CAG GGT CTT GAT TGC CAC
Eph B4 AS-10	(1980-1999)	ATG GAG GCC TCG CTC AGA AA
Eph b4 AS-11	(2138-2158)	CAT GCC CAC GAG CTG GAT GAC

[0329] 7) Cell Viability Assay

[0330] Cells were seeded at a density of 5×10^{3}' per well in 48-well plates on day 0 in appropriate growth media containing 2% fetal calf serum (FCS). Cells were treated with various concentrations (1-10 μg/ml) of ODNs on days 2 and 4. On day 5, viability was assessed using 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT) as previously described (Masood et al '03). For viability with siRNA, 2×10^{4} cells/well of SCC-4, -15, -25 or -71 in a 48-well plate were transfected with siRNAs (10-100 nM) using 2 μl of Lipofectamine™ 2000 according to the manufacturer's instructions. 4 h post-transfection the cells were returned to growth media (RPMI 1640 supplemented with 10% FBS). Viability was assayed by MTT 48 h following transfection.

[0331] 8) Cell Cycle Analysis

[0332] 80% confluent cultures of SCC15 cells in 6-well plates were transfected with siRNA472 (100 nM) using Lipofectamine™ 2000. Either 16 or 36 hours after transfection, cells were trypsinized, washed in PBS and incubated for 1 h at 4° C. in 1 ml of hypotonic solution containing 50 μg/ml propidium iodide, 0.1% sodium citrate, 0.1 Triton X-100 and 20 μg/ml DNase-free RNaseA. Cells were analyzed in linear mode at the USC Flow cytometry facility. Results were expressed as percentages of elements detected in the different phases of the cell cycle, namely Sub G0 peak (apoptosis), G0/G1 (no DNA synthesis), S (active DNA synthesis), G2 (premitosis) and M (mitosis). For AS-ODN experiment the cells were exposed to 5 μM ODN for 36 h prior to processing.

[0333] 9) Wound Healing Migration Assay

[0334] SCC15 cells were seeded into 6-well plates and cultured until confluent. 10 μM AS-1, AS-10, or sense ODN as control were introduced to the wells as described for the viability assay 12 hours before wounding the monolayer by scraping it with a sterile pipette tip. Medium was changed to RPMI 1640 supplemented with 5% FBS and fresh ODNs. The healing process was examined dynamically and recorded with a Nikon Coolpix 5000 digital camera with microscope adapter.

[0335] 10) Boyden Chamber Assay of Migration

[0336] Cell migration assays were performed as previously described (Masood ANUP paper '99) except that 1 μM AS-10 or AS-6 were added to the upper chamber. EGF (20 ng/ml) was used as chemoattractant in the lower chamber. Taxol at 10 ng/ml was used as a negative control.

[0337] 11) In Vivo Studies

[0338] SCC15 (5×10^{6} cells) were injected subcutaneously in the lower back of 5-week old male Balb/C Nu^{+}/nu^{+} athymic mice. Treatment consisted of daily intraperitoneal injection of ODN (20 mg/kg in a total volume of 100 μl) or diluent (PBS) begun the day following tumor cell implantation and continued for two weeks. Tumor growth in mice was measured as previously described (Masood CCR '01). Mice were sacrificed at the conclusion of the study. All mice were maintained in accord with the University of Southern California Animal Care and Use Committee guidelines governing the care of laboratory mice.

Example 6

Ephrin B2 Expression in Kaposi's Sarcoma is Induced by Human Herpesvirus Type 8: Phenotype Switch from Venous to Arterial Endothelium

[0339] Kaposi's Sarcoma (KS) manifests as a multifocal angioproliferative disease, most commonly of the skin and mucus membranes, with subsequent spread to visceral organs (1) Hallmarks of the disease are angiogenesis, edema, infiltration of lymphomononuclear cells and growth of spindle-shaped tumor cells. Pathologically, established lesions exhibit an extensive vascular network of slit-like spaces. The KS vascular network is distinct from normal vessels in the lack of basement membranes and the abnormal spindle shaped endothelial cell (tumor cell) lining these vessels. Defective vasculature results in an accumulation of the blood components including albumin, red and mononuclear cells in the lesions (1). The KS tumor is endothelial in origin; the tumor cells express many endothelial markers, including lectin binding sites for *Ulex europeaus* agglutinin-1 (UEA-1), CD34, EN-4, PAL-E (2) and the endothelial cell specific tyrosine kinase receptors, VEGFR-1 (Flt-1), VEGFR-2 (Flk-1/KDR), VEGFR-3 (Flt-4), Tie-1 and Tie-2 (3, RM & PSG unpublished data). KS cells co-express lymphatic endothelial cell related proteins including LYVE and podoplanin (4).

[0340] The herpesvirus HHV-8 is considered the etiologic agent for the disease. In 1994 sequences of this new herpes virus were identified in KS tumor tissue (5), and subsequent molecular-epidemiology studies have shown that nearly all KS tumors contain viral genome. Sero-epidemiology studies show that HIV infected patients with KS have the highest prevalence of HHV-8 and secondly that those with HIV infection but no KS have increased risk of development of KS over the ensuing years if they are also seropositive for HHV-8 (6). Direct evidence for the role of HHV-8 in KS is the transformation of bone marrow endothelial cells after infection with HHV-8 (7). A number of HHV-8 encoded genes could contribute to cellular transformation (reviewed in 8). However, the most evidence has accumulated for the G-protein coupled receptor (vGPCR) in this role (9).

[0341] We investigated whether KS tumor cells are derived from arterial or venous endothelium. In addition, we investigated whether HHV-8 has an effect on expression of arterial or venous markers in a model of KS. KS tumor cells were found to express the ephrin B2 arterial marker. Further, ephrin B2 expression was induced by HHV-8 vGPCR in KS and endothelial cell lines. Ephrin B2 is a potential target for treatment of KS because inhibition of ephrin B2 expression or signaling was detrimental to KS cell viability and function.

A. KS Tumors Express Ephrin B2, but not EphB4

[0342] The highly vascular nature of KS lesions and the probable endothelial cell origin of the tumor cells prompted investigation of expression of EphB4 and ephrin B2 which are markers for venous and arterial endothelial cells, respectively. Ephrin B2, but not EphB4 transcripts were detected in tumor cells of KS biopsies by in situ hybridization (FIG.

45A). Comparison of the positive signal with ephrin B2 antisense probe and tumor cells as shown by H&E staining shows that ephrin B2 expression is limited to the areas of the biopsy that contain tumor cells. The lack of signal in KS with EphB4 antisense probe is not due to a defect in the probe, as it detected transcripts in squamous cell carcinoma, which we have shown expresses this protein (18). Additional evidence for the expression of ephrin B2 in KS tumor tissue is afforded by the localization of EphB4/Fc signal to tumor cells, detected by FITC conjugated anti human Fc antibody. Because ephrin B2 is the only ligand for EphB4 this reagent is specific for the expression of ephrin B2 (FIG. **45**B, left). An adjacent section treated only with the secondary reagent shows no specific signal. Two-color confocal microscopy demonstrated the presence of the HHV-8 latency protein, LANA1 in the ephrin B2 positive cells (FIG. **45**C, left), indicating that it is the tumor cells, not tumor vessels, which are expressing this arterial marker. Staining of tumor biopsy with PECAM-1 antibody revealed the highly vascular nature of this tumor (FIG. **45**C, right). A pilot study of the prevalence of this pattern of ephrin B2 and EphB4 expression on KS biopsies was conducted by RT-PCR analysis. All six samples were positive for ephrin B2, while only 2 were weakly positive for EphB4 (data not shown).

B. Infection of Venous Endothelial Cells with HHV-8 Causes a Phenotype Switch to Arterial Markers

[0343] We next asked whether HHV-8, the presumed etiologic agent for KS, could itself induce expression of ephrin B2 and repress EphB4 expression in endothelial cells. Coculture of HUVEC and BC-1 lymphoma cells, which are productively infected with HHV-8, results in effective infection of the endothelial cells (16). The attached monolayers of endothelial cells remaining after extensive washing were examined for ephrin 132 and EphB4 by RT-PCR and immunofluorescence. HUVEC express EphB4 venous marker strongly at the RNA level, but not ephrin B2 (FIG. **46**B). In contrast, HHV-8 infected cultures (HUVEC/BC-1 and HUVEC/BC-3) express ephrin B2, while EphB4 transcripts are almost absent.

[0344] Immunofluorescence analysis of cultures of HUVEC and HUVEC/HHV-8 for artery/vein markers and viral proteins was undertaken to determine whether changes in protein expression mirrored that seen in the RNA. In addition, cellular localization of the proteins could be determined. Consistent with the RT-PCR data HUVEC are ephrin B2 negative and EphB4 positive (FIG. **46**A(a & m)). As expected they do not express any HHV-8 latency associated nuclear antigen (LANA1) (FIG. **46**A(b, n)). Co-culture of BC-1 cells, which are productively infected with HHV-8, resulted in infection of HUVEC as shown by presence of viral proteins LANA1 and ORF59 (FIG. **46**A(f, r)). HHV-8 infected HUVEC now express ephrin B2 but not EphB4 (FIG. **46**A(e, q, u), respectively). Expression of ephrin B2 and LANA1 co-cluster as shown by yellow signal in the merged image (FIG. **46**A(h)). HHV-8 infected HUVEC positive for ephrin B2 and negative for Eph B4 also express the arterial marker CD148 (19) (FIG. **46**A (j, v)). Expression of ephrin B2 and CD148 co-cluster as shown by yellow signal in the merged image (FIG. **46**A(l)). Uninfected HUVEC expressing Eph B4 were negative for CD148 (not shown).

[0345] C. HHV-8 vGPCR Induces Ephrin B2 Expression

[0346] To test whether individual viral proteins could induce the expression of ephrin B2 seen with the whole virus KS-SLK cells were stably transfected with HHV-8 LANA, or LANAΔ440 or vGPCR. Western Blot of stable clones revealed a five-fold induction of ephrin B2 in KS-SLK transfected with vGPCR compared to SLK-LANA or SLK-LANAΔ440 (FIG. **47**A). SLK transfected with vector alone (pCEFL) was used as a control. SLK-vGPCR and SLK-pCEFL cells were also examined for ephrin B2 and Eph B4 expression by immunofluorescence in transiently transfected KS-SLK cells. FIG. **478** shows higher expression of ephrin B2 in the SLK-vGPCR cells compared to SLK-pCEFL. No changes in Eph B4 were observed in SLK-vGPCR compared to SLK-pCEFL. This clearly demonstrates that SLK-vGPCR cells expressed high levels of ephrin 132 compared to SLK-pCEFL cells. This suggests that vGPCR of HHV-8 is directly involved in the induction of Ephrin B2 and the arterial phenotype switch in KS. Since we had shown that HHV-8 induced expression of ephrin B2 in HUVEC, we next asked if this could be mediated by a transcriptional effect. Ephrin B2 5'-flanking DNA-luciferase reporter plasmids were constructed as described in the Materials and Methods and transiently transfected into HUVECs. Ephrin B2 5'-flanking DNA sequences -2491/-11 have minimal activity in HUVEC cells (FIG. **47**C). This is consistent with ephrin B2 being an arterial, not venous marker. However, we have noted that HUVEC in culture do express some ephrin B2 at the RNA level. Cotransfection of HHV-8 vGPCR induces ephrin B2 transcription approximately 10-fold compared to the control expression vector pCEFL. Roughly equal induction was seen with ephrin B2 sequences -2491/-11, -1242/-11, or -577/-11, which indicates that elements between -577 and -11 are sufficient to mediate the response to vGPCR, although maximal activity is seen with the -1242/-11 luciferase construct.

D. Expression of Ephrin B2 is Regulated by VEGF and VEGF-C

[0347] We next asked whether known KS growth factors could be involved in the vGPCR-mediated induction of ephrin B2 expression. SLK-vGPCR cells were treated with neutralizing antibodies to oncostatin-M, IL-6, IL-8, VEGF or VEGF-C for 36 hr. FIG. **48**A shows that neutralization of VEGF completely blocked expression of ephrin B2 in SLK-vGPCR cells. A lesser, but significant decrease in ephrin B2 was seen neutralization of VEGF-C and IL-8. No appreciable effect was seen with neutralization of oncostatin-M or IL-6. To verify that VEGF and VEGF-C are integral to the induction of ephrin B2 expression we treated HUVEC with VEGF, VEGF-C or EGF. HUVECs were grown in EBM-2 media containing 5% FBS with two different concentration of individual growth factor (10 ng, 100 ng/ml) for 48 h. Only VEGF-A or VEGF-C induced ephrin B2 expression in a dose dependent manner (FIG. **48**B). In contrast, EGF had no effect on expression of ephrin B2.

E. Ephrin B2 siRNA Inhibits the Expression of Ephrin B2 in KS

[0348] Three ephrin B2 siRNA were synthesized as described in the methods section. KS-SLK cells were transfected with siRNA and 48 h later ephrin B2 expression was determined by Western Blot. Ephrin B2 siRNAs 137 or 254 inhibited about 70% of ephrin B2 expression compared to control siRNA such as siRNA Eph B4 50 or siRNA GFP. Ephrin B2 63 siRNA was less effective than the above two siRNA Ephrin B2 (FIG. **49**A).

F. Ephrin B2 is Necessary for Full KS and EC Viability, Cord Formation and In Vivo Angiogenesis Activities

[0349] The most effective ephrin B2 siRNA (254) was then used to determine whether inhibiting expression of ephrin B2 has any effect on the growth of KS-SLK or HUVEC cells. The

viability of KS-SLK cells was decreased by the same siRNAs that inhibited ephrin B2 protein levels (FIG. **49**B). KS-SLK express high levels of ephrin B2 and this result shows maintenance of ephrin B2 expression is integral to cell viability in this setting. HUVECs do not express ephrin B2, except when stimulated by VEGF as shown in FIG. **48**B. Ephrin B2 siRNA 264 dramatically reduced growth of HUVECs cultured with VEGF as the sole growth factor. In contrast, no significant effect was seen when HUVECs were cultured with IGF, EGF and bFGF. As a control, EphB4 siRNA 50 had no detrimental effect on HUVECs in either culture condition (FIG. **49**C). In addition to inhibition of viability of KS and primary endothelial cells, EphB4-ECD inhibits cord formation in HUVEC and KS-SLK and in vivo angiogenesis in the Matrigel™ plug assay (FIG. **50**).

G. Methods and Materials

[0350] 1) Cell Lines and Reagents

[0351] Human vascular endothelial cells (HUVEC) were from Clonetics (San Diego, Calif.) and were maintained in EGM-2 and EGM-2MV media respectively (Clonetics). TI human fibroblast line was from Dr. Peter Jones, USC. BC-1 and BC-3 human pleural effusion lymphoma cell lines and monoclonal antibodies to LANA1 and ORF59 were the kind gift of Dr. Dharam Ablashi (Advanced Biotechnologies Inc., Columbia, Md.). KS-SLK was isolated from a Classic Kaposi's sarcoma patient (15). Polyclonal antibodies to EphB4, ephrin B2, CD148, PECAM-1 were obtained from Santa Cruz Biotechnology (Santa Cruz, Calif.). Mouse EphB4/F_c' and monoclonal antibodies to human vascular endothelial growth factor (VEGF), VEGF-C, interleukin-$(IL)_6$, IL-8 and oncostatin-M were purchased from R & D Systems (Minneapolis, Minn.). Expression vectors pKSvGPCR-CEFL and pCEFL were the kind gill of Dr. Enrique Mesri (Cornell University, New York, N.Y.). Expression vectors for HHV-8 latency associated nuclear antigen (LANA) were kindly provided by Dr Matthew Rettig, Veteran's Administration Greater Los Angeles Healthcare System.

[0352] 2) Collection and Preparation of Human Tissue

[0353] Human cutaneous Kaposi's sarcoma biopsy material was obtained under local anesthesia with informed consent from patients at the LAC/USC Medical Center, using an IRB approved consent form. Biopsies were processed for either total RNA, paraffin blocks or frozen tissue blocks in OCT. Total RNA was extracted by homogenization in guanidine isothiocyanate, (RNAzol: Tel-Test, Inc., Friendswoods, Tex.). cDNAs were synthesized by reverse transcriptase using a random hexamer primer (Superscript II; Invitrogen, Carlsbad, Calif.).

[0354] 3) Preparation of Digoxigenin-Labeled RNA Probes

[0355] Ephrin B2 and EphB4 PCR products from the primers shown in Table 4 for in situ hybridization were cloned using the pGEM-T Easy system (Promega, Madison Wis.) according to the manufacturer's description using. The authenticity and insert orientation were confirmed by DNA sequencing. The pGEM-T Easy plasmids containing the PCR product of the human ephrin-B2 or EphB4 gene were linearized with Spe. I or Nco I. Antisense or sense digoxigenin (DIG)-labeled RNA probes were transcribed from T7 or SP6 promoters by run-off transcription using a DIG RNA labeling kit (Roche, Indianapolis Ind.). RNA probes were quantitated by spot assay as described in the DIG RNA labeling kit instructions.

TABLE 4

Primers for Ephrin B2 and EphB4.

Gene	Primer sequence	Product Size (bp)
ISH Probe Primers		
ephrin B2	5'-TCC GTG TGG AGT ACT GCT G-3' 5'-TCT GGT TTG GCA CAG TTG AG-3'	296
Eph B4	5'-CTT TGG AAG AGA CCC TGC TG-3' 5'-AGA CGG TGA AGG TCT CCT TG-3'	297
RT-PCR Primers		
ephrin B2	5'-AGA CAA GAG CCA TGA AGA TC-3' 5'-GGA TCC CAC TTC GGA CCC GAG-3'	200
Eph B4	5'-TCA GGT CAC TGC ATT GAA CGG G-3' 5'-AAC TCG CTC TCA TCC AGT T-3'	400
β-actin	5'-GTG GGG CGC CCC AGG CAC CA-3' 5'-CTC CTT AAT GTC ACG CAC GAT TTC-3'	546

[0356] 4) In Situ Hybridization

[0357] See above, e.g., Example 3.

[0358] 5) Co-Culture of HUVEC and BC-1

[0359] HUVEC cells were grown to 50-70% confluence in EGM-2 on gelatin-coated Labtech II 4-well chamber slides (Nalge Nunc International, Naperville, Ill.). Co-culture with BC-1 or BC-3 was essentially as described by Sakurada and coworkers (16). Briefly, BC-1 or BC-3 cells were pretreated with TPA (20 ng/ml) to induce virus for 48 hrs and then added to the HUVEC culture at a ratio of 10:1 for cocultivation for two days. The HUVECs were washed extensively with PBS to remove the attached BC-1 or BC-3 cells.

[0360] 6) Preparation of cDNA and RT-PCR

[0361] The TITANIUM™ One-Step RT-PCR kit (Clontech, Palo Alto, Calif.) was used for RT-PCR from 1×10^5 cells. Primer pairs for amplification of EphB4, ephrin B2 and β-actin are shown in Table 4. Each PCR cycle consisted of denaturation at 94° C. for 30 s, primer annealing at 60° C. for 30 s and extension at 72° C. for 30 s. The samples were amplified for 30 cycles. PCR products were separated on 1.5% agarose gels and stained with ethidium bromide.

[0362] 7) Cell Viability Assay

[0363] KS-SLK cells were seeded at a density of 1×10^4 per well in 48-well plates on day 0 in appropriate growth media containing 2% fetal calf serum (FCS). On the following day, the media was changed and cells were treated with 0, 10 or 100 nM siRNA. On day 3, viability was assessed using 3-(4, 5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT) as previously described (17).

[0364] 8) Immunofluorescence Studies

[0365] Cells cultured on Labtech II 4-well chamber slides or frozen sections of KS biopsy material were fixed in 4% paraformaldehyde in Dulbecco's phosphate buffered saline pH 7.4 (PBS) for 30 min. The slides were rinsed twice in PBS and preincubated with blocking buffer (0.2% Triton-X100, 1% BSA in PBS) for 20 min, followed by incubation with antibodies to EphB4, ephrin B2, CD148, LANA1 or ORF59 (1:100 dilution in PBS) in blocking buffer at 4° C. for 16 hr. After washing three times, the slides were incubated with the appropriate fluorescein or rhodamine-conjugated secondary

antibodies (Sigma-Aldrich, St. Louis, Mo.). Nuclei were counterstained with 4',6-diamidino-2-phenylindole dihydrochloride hydrate (DAPI), washed extensively with PBS and mounted with Vectasheild antifade mounting solution (Vector Laboratories, Burlingame, Calif.). Images were obtained using a Olympus AX70 fluorescence microscope and Spot v2.2.2 (Diagnostic Instruments Inc., Sterling Heights, Mich.) digital imaging system.

[0366] Immunofluorescence detection of EphrinB2 with EPHB4-Fc was done as follows. Frozen sections fixed in 4% paraformaldehyde and blocked with 20% FBS were incubated with 5 μg/ml EphB4/Fc (R&D Systems) for 1 h at RT. Sections were then incubated with 10 μg/ml rabbit anti-human IgG-FITC in PBS (Jackson ImmunoResearch Laboratories West Grove, Pa.) at RT for 1 hour. Nuclei were counterstained with DAPI and sections mounted as above. Human Fc (Jackson ImmunoResearch) was used as the negative control.

[0367] 9) Western Blot

[0368] Crude cell lysates were prepared, quantitated, fractionated and transferred to membranes as described previously (17). Membranes were blocked with 5% non-fat milk prior to incubation with antibody to ephrin B2 (1:5000 dilution) at 4° C., for 16 h. Secondary antibody (1:100,000 dilution) conjugated with horseradish peroxidase was applied for 1 h at 25° C. The membranes were developed using the SuperSignal West Femto Maximum sensitivity chemiluminescent substrate (Pierce, Rockford, Ill.) according to the manufacturer's instructions. Membranes were stripped using Restore™ Western Blot Stripping Buffer (Pierce) and reprobed with EphB4 or β-actin.

[0369] 10) Cord Formation Assay

[0370] Matrigel™ Basement Membrane Matrix (BD Biosciences Discovery Labware, Bedford, Mass.) was mixed with growth medium (3:1) on ice and 0.5 ml liquid placed in 24-well plates. Incubation of plates at 37° C. for 15 min caused Matrigel™ polymerization. HUVEC or KS-SLK in exponential phase growth were treated with 2 or 8 μg/ml EphB4-ECD or PBS as control for 16 h prior to trypsinizing and plating on the Matrigel™. Culture on Matrigel™ was continued in the presence of recombinant fusion proteins for 6 h. Cultures were fixed in 4% paraformaldehyde for 30 min and evaluated by inverted phase-contrast photomicroscopy.

[0371] 11) Synthesis of Ephrin B2 and EphB4 siRNA by In Vitro Transcription

[0372] The Silencer™ siRNA construction kit (Ambion, Austin Tex.) was used to synthesize siRNA to ephrin B2 and EphB4. Briefly, three 21 bp target sequences comprising 19 bp downstream of a 5'-AA dinucleotide were identified in the ephrin B2 cDNA (Accession number NM_004093) that showed no significant homology to other sequences in the GenBank database. Sense and antisense siRNA 29-mer DNA oligonucleotide templates were synthesized at the USC Norris Microchemical Core Facility. Antisense template corresponded to the target sequence followed by 8 bp addition (5'-CCTGTCTC-3') at the 3' end complementary to the T7 promoter primer provided with the Silencer SiRNA Construction Kit. Sense template comprised 5'-AA followed by the complement of the target 19 bp, then the T7 8 bp sequence as above. In separate reactions, the two siRNA oligonucleotide templates were hybridized to a T7 promoter primer. The 3' ends of the hybridized oligonucleotides were extended by the Klenow fragment of DNA polymerase to create double-stranded siRNA transcription templates. The sense and antisense siRNA templates were transcribed by T7 RNA polymerase and the resulting RNA transcripts were hybridized to create dsRNA. The dsRNA consisted of 5' terminal single-stranded leader sequences, a 19 nt target specific dsRNA, and 3' terminal UUs. The leader sequences were removed by digesting the dsRNA with a single-stranded specific ribonuclease. The DNA template was removed at the same time by treatment with RNAse free deoxyribonuclease.

[0373] The resulting siRNAs were purified by glass fiber filter binding to remove excess nucleotides, short oligomers, proteins, and salts in the reaction. End product double-stranded 21mer siRNAs are shown in Table 5. Similarly, an EphB4 and green fluorescence protein (GFP) siRNAs were synthesized.

TABLE 5

siRNAs of ephrin B2 and EphB4.	
ephrin B2 264	5'-GCAGACAGAUGCACUAUUAUU-3' 3'-UUCGUCUGUCUACGUGAUAAU-5'
ephrin B2 63:	5'-CUGCGAUUUCCAAAUCGAUUU-3' 3'-UUGACGCUAAAGGUUUAGCUA-5'
ephrin B2 137:	5'-GGACUGGUACUAUACCCACUU-3' 3'-UUCCUGACCAUGAUAUGGGUG-5'
Eph B4 50:	5'-GAGACCCUGCUGAACACAAUU-3' 3'-UUCUCUGGGACGACUUGUGUU-5'
GFP	5'-CGCUGACCCUGAAGUUCAUUU-3' 3'-UUGCGACUGGGACUUCAAGUA-5'

[0374] 12) Transfection of Ephrin 132 or EphB4 siRNA

[0375] HUVEC were seeded on eight-well chamber slides coated with fibronectin and grown overnight in EGM-2 (Cambrex, Walkersville, Md.). 16 h later media was replaced either with EBM-2 supplemented with 5% fetal calf serum (FCS) and EGM-2 BulletKit supplements bFGF, hEGF and R^3-IGF-I at the concentrations provided by the manufacturer, or EBM-2 supplemented with 5% FCS and 10 ng/ml rhVEGF (R&D Systems). After 2 h incubation at 37° C., the cells were transfected using Lipofectamine 2000 (1 μg/ml; Invitrogen) and 10 nM specific siRNAs in Opti-MEM-1 serum-free medium (Invitrogen). Following transfection for 1 hr in Opti-MEM-1, media supplemented as above was replaced in the appropriate wells. After 48 hrs, the cells were stained with crystal violet and immediately photographed at 10× magnification.

[0376] 13) Construction of Ephrin B2 Reporter Plasmids

[0377] Human ephrin B2 5'-flanking DNA from -2491 to -11 with respect to the translation start site was amplified from BACPAC clone RP11-29716 (BacPac Resources, Children's Hospital, Oakland, Calif.) using the Advantage GC Genomic PCR kit (Clontech Palo Alto, Calif.) to overcome the large tracts of CG-rich sequence in the target area. Primers were designed to contain MluI sites for cloning. Amplified product was digested with MluI, gel purified and ligated into the MluI site in the multiple cloning site of pGL3Basic (Promega, Madison, Wis.). Orientation of the resulting clones was confirmed by restriction digest analysis. The correct clone was designated pEFNB2.$_{2491/-11}$luc. Digestion of this clone with either KpnI or SacI followed by recircularization yielded pEFNB2.$_{2491/-11}$luc and pEFNB2.$_{577/-11}$luc, respectively. Plasmid DNAs used for transient transfections were purified using a Mega Prep kit (QIAGEN, Valencia, Calif.).

[0378] 14) Transient Transfection

[0379] HUVEC cells (0.8×10^4 cells/well in 24 well plates) maintained in EGM-2 media were transiently co-transfected with 0.5 μg/well ephrin B2 promoter-luciferase constructs together with 50 ng/well either pCEFL or pKSvGPCR-CEFL, using Superfect reagent (QIAGEN) according to the manufactures instructions. Cells were harvested 48 h post-transfection and lysed with Luciferase cell lysis buffer (Promega). Luciferase activity was assayed using the Luciferase Assay System (Promega) according to the manufacturer's instructions. Luciferase was normalized to protein, because pCEFL-vGPCR induced the expression of β-galactosidase from pCMV-Sport-β-gal (Invitrogen).

[0380] 15) Construction and Purification of EphB4 Extra Cellular Domain (ECD) Protein

[0381] See above, e.g., Example 1.

Example 7

Expression of EphB4 in Bladder Cancer: a Candidate Target for Therapy

[0382] FIG. **51** shows expression of EPHB4 in bladder cancer cell lines (A), and regulation of EPHB4 expression by EGFR signaling pathway (B).

[0383] FIG. **52** shows that transfection of p53 inhibit the expression of EPHB4 in 5637 cell.

[0384] FIG. **53** shows growth inhibition of bladder cancer cell line (5637) upon treatment with EPHB4 siRNA 472.

[0385] FIG. **54** shows results on apoptosis study of 5637 cells transfected with EPHB4 siRNA 472.

[0386] FIG. **55** shows effects of EPHB4 antisense probes on cell migration. 5637 cells were treated with EPHB4AS10 (10 μM).

[0387] FIG. **56** shows effects of EPHB4 siRNA on cell invasion. 5637 cells were transfected with siRNA 472 or control siRNA.

Example 8

Inhibition of EphB4 Gene Expression by EphB4 Antisense Probes and RNAi Probes

[0388] Cell lines expressing EphB4 were treated with the synthetic phosphorothioate modified oligonucleotides and harvested after 24 hr. Cell lysates were prepared and probed by western blot analysis for relative amounts of EphB4 compared to untreated control cells.

[0389] Studies on inhibition of cell proliferation were done in HNSCC cell lines characterized to express EphB4. Loss of cell viability was shown upon knock-down of EphB4 expression. Cells were treated in vitro and cultured in 48-Well plates, seeded with 10 thousand cells per well. Test compounds were added and the cell viability was tested on day 3. The results on EphB4 antisense probes were summarized below in Table 6. The results on EphB4 RNAi probes were summarized below in Table 7.

TABLE 6

Inhibition of EphB4 Gene Expression by EphB4 antisense probes

Name	Sequence 5' → 3'	position	Inhibition of Eph B4 Expression	Percent reduction in viability
Eph B4 169	TCA GTA CTG CGG GGC CGG TCC	(2944-2963)	++	36
Eph B4 168	TCC TGT CCC ACC CGG GGT TC	(2924-2943)	++	51
Eph B4 167	CCG GCT TGG CCT GGG ACT TC	(2904-2923)	+++	66
Eph B4 166	ATG TGC TGG ACA CTG GCC AA	(2884-2903)	++++	70
Eph B4 165	GAT TTT CTT CTG GTG TCC CG	(2864-2883)	++++	75
Eph B4 164	CCA GAG TGA CTC CGA TTC GG	(2844-2863)	++	40
Eph B4 163	AGC AGG TCC TCA GCA GAG AT	(2824-2843)	++++	66
Eph B4 162	CTG GCT GAC CAG CTC GAA GG	(2804-2823)		25
Eph B4 161	AGC CAA AGC CAG CGG CTG CG	(2784-2803)	+	33
Eph B4 160	AAA CTT TCT TCG TAT CTT CC	(2763-2783)	+	25
Eph B4 159	CAT TTT GAT GGC CCG AAG CC	(2743-2762)	++	40
Eph B4 158	ACT CGC CCA CAG AGC CAA AA	(2723-2742)		30
Eph B4 157	GCT GAG TAG TGA GGC TGC CG	(2703-2722)	+	25
Eph B4 156	CTG GTC CAG GAG AGG GTG TG	(2683-2702)	++	30
Eph B4 155	AGG CCC CGC CAT TCT CCC GG	(2663-2682)		25
Eph B4 154	GCC ACG ATT TTG AGG CTG GC	(2643-2662)	++	40
Eph B4 153	GGG GTT CCG GAT CAT CTT GT	(2623-2642)	++	35

TABLE 6-continued

Inhibition of EphB4 Gene Expression by EphB4 antisense probes

Name	Sequence 5' → 3'	position	Inhibition of Eph B4 Expression	Percent reduction in viability
Eph B4 152	CCA GGG CGC TGA CCA CCT GG	(2603-2622)	+	30
Eph B4 151	GGG AAG CGG GGC CGG GCA TT	(2583-2602)	+	25
Eph B4 150	CCG GTC TTT CTG CCA ACA GT	(2563-2582)	++	25
Eph B4 149	CCA GCA TGA GCT GGT GGA GG	(2543-2562)	++	20
Eph B4 148	GAG GTG GGA CAG TCT GGG GG	(2523-2542)	+	30
Eph B4 147	CGG GGG CAG CCG GTA GTC CT	(2503-2522)	++	40
Eph B4 146	GTT CAA TGG CAT TGA TCA CG	(2483-2502)	++++	70
Eph B4 145	TCC TGA TTG CTC ATG TCC CA	(2463-2482)	++++	80
Eph B4 144	GTA CGG CCT CTC CCC AAA TG	(2443-2462)	+++	60
Eph B4 143	ACA TCA CCT CCC ACA TCA CA	(2423-2442)	++++	80
Eph B4 142	ATC CCG TAA CTC CAG GCA TC	(2403-2422)	++	40
Eph B4 141	ACT GGC GGA AGT GAA CTT CC	(2383-2402)	+++	50
Eph B4 140	GGA AGG CAA TGG CCT CCG GG	(2363-2382)	++	45
Eph B4 139	GCA GTC CAT CGG ATG GGA AT	(2343-2362)	++++	70
Eph B4 138	CTT TCC TCC CAG GGA GCT CG	(2323-2342)	++++	70
Eph B4 137	TGT AGG TGG GAT CGG AAG AG	(2303-2322)	++	40
Eph B4 136	TTC TCC TCC AGG AAT CGG GA	(2283-2302)	++	35
Eph B4 135	AAG GCC AAA GTC AGA CAC TT	(2263-2282)	++++	60
Eph B4 134	GCA GAC GAG GTT GCT GTT GA	(2243-2262)	++	50
Eph B4 133	CTA GGA TGT TGC GAG CAG CC	(2223-2242)	++	40
Eph B4 132	AGG TCT CGG TGG ACG TAG CT	(2203-2222)	++	40
Eph B4 131	CAT CTC GGC AAG GTA CCG CA	(2183-2202)	+++	50
Eph B4 130	TGC CCG AGG CGA TGC CCC GC	(2163-2182)	++	50
Eph B4 129	AGC ATG CCC ACG AGC TGG AT	(2143-2162)	++	50
Eph B4 128	GAC TGT GAA CTG TCC GTC GT	(2123-2142)	++	50
Eph B4 127	TTA GCC GCA GGA AGG AGT CC	(2103-2122)	+++	60
Eph B4 126	AGG GCG CCG TTC TCC ATG AA	(2083-2102)	++	50
Eph B4 125	CTC TGT GAG AAT CAT GAC GG	(2063-2082)	++++	80
Eph B4 124	GCA TGC TGT TGG TGA CCA CG	(2043-2062)	++++	70
Eph B4 123	CCC TCC AGG CGG ATG ATA TT	(2023-2042)	++	50
Eph B4 122	GGG GTG CTC GAA CTG GCC CA	(2003-2022)	++++	80
Eph B4 121	TGA TGG AGG CCT CGC TCA GA	(1983-2002)	++	50
Eph B4 120	AAC TCA CGC CGC TGC CGC TC	(1963-1982)	++	40
Eph B4 119	CGT GTA GCC ACC CTT CAG GG	(1943-1962)	++++	75

TABLE 6-continued

Inhibition of EphB4 Gene Expression by EphB4 antisense probes

Name	Sequence 5' → 3'	position	Inhibition of Eph B4 Expression	Percent reduction in viability
Eph B4 118	TCT TGA TTG CCA CAC AGC TC	(1923-1942)	++++	80
Eph B4 117	TCC TTC TTC CCT GGG GCC TT	(1903-1922)	++++	70
Eph B4 116	GAG CCG CCC CCG GCA CAC CT	(1883-1902)	++	50
Eph B4 115	CGC CAA ACT CAC CTG CAC CA	(1863-1882)	++++	60
Eph B4 114	ATC ACC TCT TCA ATC TTG AC	(1843-1862)	++++	65
Eph B4 113	GTA GGA GAC ATC GAT CTC TT	(1823-1842)	++++	90
Eph B4 112	TTG CAA ATT CCC TCA CAG CC	(1803-1822)	++++	70
Eph B4 111	TCA TTA GGG TCT TCA TAA GT	(1783-1802)	++++	70
Eph B4 110	GAA GGG GTC GAT GTA GAC CT	(1763-1782)	++++	80
Eph B4 109	TAG TAC CAT GTC CGA TGA GA	(1743-1762)	++	50
Eph B4 108	TAC TGT CCG TGT TTG TCC GA	(1723-1742)	++	45
Eph B4 107	ATA TTC TGC TTC TCT CCC AT	(1703-1722)	++++	70
Eph B4 106	TGC TCT GCT TCC TGA GGC AG	(1683-1702)	++++	70
Eph B4 105	AGA ACT GCG ACC ACA ATG AC	(1663-1682)	++	40
Eph B4 104	CAC CAG GAC CAG GAC CAC AC	(1643-1662)	++++	70
Eph B4 103	CCA CGA CTG CCG TGC CCG CA	(1623-1642)	++	40
Eph B4 102	ATC AGG GCC AGC TGC TCC CG	(1603-1622)	+++	50
Eph B4 101	CCA GCC CTC GCT CTC ATC CA	(1583-1602)	++++	80
Eph B4 100	GTT GGG TCT GGC TGT GAT GT	(1563-1582)	++++	80
Eph B4 99	TCC TGG CCG AAG GGC CCG TA	(1543-1562)	++	35
Eph B4 98	GCC GGC CTC AGA GCG CGC CC	(1523-1542)	++	50
Eph B4 97	GTA CCT GCA CCA GGT AGC TG	(1503-1522)	++++	80
Eph B4 96	GCT CCC CGC TTC AGC CCC CG	(1483-1502)	++	50
Eph B4 95	CAG CTC TGC CCG GTT TTC TG	(1463-1482)	++	50
Eph B4 94	ACG TCT TCA GGA ACC GCA CG	(1443-1462)	++++	80
Eph B4 93	CTG CTG GGA CCC TCG GCG CC	(1423-1442)	++	40
Eph B4 92	CTT CTC ATG GTA TTT GAC CT	(1403-1422)	++++	80
Eph B4 91	CGT AGT CCA GCA CAG CCC CA	(1383-1402)	++++	85
Eph B4 90	CTG GGT GCC CGG GGA ACA GC	(1363-1382)	+++	50
Eph B4 89	CCA GGC CAG GCT CAA GCT GC	(1343-1462)	++++	70
Eph B4 88	TGG GTG AGG ACC GCG TCA CC	(1323-1342)	++	40
Eph B4 87	CGG ATG TCA GAC ACT GCA GG	(1303-1322)	++++	60
Eph B4 86	AGG TAC CTC TCG GTC AGT GG	(1283-1302)	++	50
Eph B4 85	TGA CAT TGA CAG GCT CAA AT	(1263-1282)	++++	80
Eph B4 84	GGG ACG GGC CCC GTG GCT AA	(1243-1262)	++	50

TABLE 6-continued

Inhibition of EphB4 Gene Expression by EphB4 antisense probes

Name	Sequence 5' → 3'	position	Inhibition of Eph B4 Expression	Percent reduction in viability
Eph B4 83	GGA GGA TAC CCC GTT CAA TG	(1223-1242)	+++	60
Eph B4 82	CAG TGA CCT CAA AGG TAT AG	(1203-1222)	++++	70
Eph B4 81	GTG AAG TCA GGA CGT AGC CC	(1183-1202)	+++	60
Eph B4 80	TCG AAC CAC CAC CCA GGG CT	(1163-1182)	+++	50
Eph B4 79	CCA CCA GGT CCC GGG GGC CG	(1143-1162)	++	40
Eph B4 78	GGG TCA AAA GTC AGG TCT CC	(1123-1142)	++++	70
Eph B4 77	CCC GCA GGG CGC ACA GGA GC	(1103-1122)	+++	60
Eph B4 76	CTC CGG GTC GGC ACT CCC GG	(1083-1102)	+++	60
Eph B4 75	CAG CGG AGG GCG TAG GTG AG	(1063-1082)	++	40
Eph B4 74	GTC CTC TCG GCC ACC AGA CT	(1043-1062)	++	50
Eph B4 73	CCA GGG GGG CAC TCC ATT CC	(1023-1042)	++	50
Eph B4 72	AGG TGC AGG GAG GAG CCG TT	(1003-1022)	++++	70
Eph B4 71	CAG GCG GGA AAC CAC GCT CC	(983-1002)	++	40
Eph B4 70	GCG GAG CCG AAG GAG GGG TG	(963-982)	+++	50
Eph B4 69	GTG CAG GGT GCA CCC CGG GG	(943-962)	+++	50
Eph B4 68	GTC TGT GCG TGC CCG GAA GT	(923-942)	++	40
Eph B4 67	ACC CGA CGC GGC ACT GGC AG	(903-922)	++	40
Eph B4 66	ACG GCT GAT CCA ATG GTG TT	(883-902)	++	50
Eph B4 65	AGA GTG GCT ATT GGC TGG GC	(863-882)	++++	60
Eph B4 64	ATG GCT GGC AGG ACC CTT CT	(843-862)	++++	80
Eph B4 63	CCT GAC AGG GGC TTG AAG GT	(823-842)	++++	80
Eph B4 62	GCC CTG GGC ACA GGC TCG GC	(803-822)	+++	70
Eph B4 61	ACT TGG TGT TCC CCT CAG CT	(783-802)	++++	80
Eph B4 60	GCC TCG AAC CCC GGA GCA CA	(763-782)	+++	50
Eph B4 59	GCT GCA GCC CGT GAC CGG CT	(743-762)	+++	50
Eph B4 58	GTT CGG CCC ACT GGC CAT CC	(723-742)	++	45
Eph B4 57	TCA CGG CAG TAG AGG CTG GG	(703-722)	+++	70
Eph B4 56	GCT GGG GCC AGG GGC GGG GA	(683-702)	++	50
Eph B4 55	CGG CAT CCA CCA CGC AGC TA	(663-682)	++	50
Eph B4 54	CCG GCC ACG GGC ACA ACC AG	(643-662)	++	50
Eph B4 53	CTC CCG AGG CAC AGT CTC CG	(623-642)	+++	50
Eph B4 52	GGA ATC GAG TCA GGT TCA CA	(603-622)	++++	90
Eph B4 51	GTC AGC TGG GCG CAC TTT TT	(583-602)	+++	70
Eph B4 50	GTA GAA GAG GTG CAG GGA TA	(563-582)	++++	80

TABLE 6-continued

Inhibition of EphB4 Gene Expression by EphB4 antisense probes

Name	Sequence 5' → 3'	position	Inhibition of Eph B4 Expression	Percent reduction in viability
Eph B4 49	GCA GGG CCA TGC AGG CAC CC	(543-562)	++++	80
Eph B4 48	TGG TCC TGG AAG GCC AGG TA	(523-542)	++++	90
Eph B4 47	GAA GCC AGC CTT GCT GAG CG	(503-522)	++++	80
Eph B4 46	GTC CCA GAC GCA GCG TCT TG	(483-502)	++	40
Eph B4 45	ACA TTC ACC TTC CCG GTG GC	(463-482)	+++	50
Eph B4 44	CTC GGC CCC AGG GCG CTT CC	(443-462)	++	50
Eph B4 43	GGG TCA GAT GCT CCG CGG CC	(423-442)	+++	60
Eph B4 42	ACC GTG TCC ACC TTG ATG TA	(403-422)	++++	80
Eph B4 41	GGG GTT CTC CAT CCA GGC TG	(383-402)	++++	80
Eph B4 40	GCG TGA GGG CCG TGG CCG TG	(363-382)	++	50
Eph B4 39	TCC GCA TCG CTC TCA TAG TA	(343-362)	+++	60
Eph B4 38	GAA GAC GGT GAA GGT CTC CT	(323-342)	++++	80
Eph B4 37	TGC AGG AGC GCC CAG CCC GA	(303-322)	+++	50
Eph B4 36	GGC AGG GAC AGG CAC TCG AG	(283-302)	+++	45
Eph B4 35	CAT GGT GAA GCG CAG CGT GG	(263-282)	++	50
Eph B4 34	CGT ACA CGT GGA CGG CGC CC	(243-262)	++	40
Eph B4 33	CGC CGT GGG ACC CAA CCT GT	(223-242)	+++	60
Eph B4 32	GCG AAG CCA GTG GGC CTG GC	(203-222)	++++	70
Eph B4 31	CCG GGG CAC GCT GCA CGT CA	(183-202)	+++	60
Eph B4 30	CAC ACT TCG TAG GTG CGC AC	(163-182)	+++	70
Eph B4 29	GCT GTG CTG TTC CTC ATC CA	(143-162)	++++	80
Eph B4 28	GGC CGC TCA GTT CCT CCC AC	(123-142)	++	40
Eph B4 27	TGC CCG TCC ACC TGA GGG AA	(103-122)	++	50
Eph B4 26	TGT CAC CCA CTT CAG ATC AG	(83-102)	++++	70
Eph B4 25	CAG TTT CCA ATT TTG TGT TC	(63-82)	++++	70
Eph B4 24	AGC AGG GTC TCT TCC AAA GC	(43-62)	++++	80
Eph B4 23	TGC GGC CAA CGA AGC CCA GC	(23-42)	++	50
Eph B4 22	AGA GCA GCA CCC GGA GCT CC	(3-22)	+++	50
Eph B4 21	AGC AGC ACC CGG AGC TCC AT	(1-20)	+++	50

Additional antisense probes described in the specification

Name	Sequence	position
EphB4 AS-1	GTG CAG GGA TAG CAG GGC CAT	(552-572)
EphB4 AS-2	AAG GAG GGG TGG TGC ACG GTG	(952-972)
EphB4 AS-3	TTC CAG GTG CAG GGA GGA GCC	(1007-1027)
EphB4 AS-4	GTG GTG ACA TTG ACA GGC TCA	(1263-1285)
EphB4 AS-5	TCT GGC TGT GAT GTT CCT GGC	(1555-1575)

TABLE 6-continued

Inhibition of EphB4 Gene Expression by EphB4 antisense probes

Name	Sequence 5' → 3'	position	Inhibition of Eph B4 Expression	Percent reduction in viability
EphB4 AS-6	GCC GCT CAG TTC CTC CCA	(123-140)		
EphB4 AS-7	TGA AGG TCT CCT TGC AGG	(316-333)		
EphB4 AS-8	CGC GGC CAC CGT GTC CAC CTT	(408-428)		
EphB4 AS-9	CTT CAG GGT CTT GAT TGC CAC	(1929-1949)		
EphB4 AS-10	ATG GAG GCC TCG CTC AGA AA	(1980-1999)		
Ephb4 AS-11	CAT GCC CAC GAG CTG GAT GAC	(2138-2158)		

TABLE 7

Inhibition of EphB4 Gene Expression by EphB4 RNAi probes

RNAi		EphB4 RNAi sequence		Inhibition of EphB4 Expression	Percent reductio-n in viability
1	446	aaattggaaactgctgatctg	466		
2	447	aattggaaactgctgatctga	467	+++	70
3	453	aaactgctgatctgaagtggg	473	++++	70
4	454	aactgctgatctgaagtgggt	474	+++	80
5	854	aatgtcaagacgctgcgtctg	874	+++	65
6	467	aagtgggtgacattccctcag	487	+	35
7	848	aaggtgaatgtcaagacgctg	868	++	50
8	698	aaggagaccttcaccgtcttc	718	+++	75
9	959	aaaaagtgcgcccagctgact	979	+	40
10	1247	aatagccactctaacaccatt	1267	++	50
11	1259	aacaccattggatcagccgtc	1279	++	50
12	1652	aatgtcaccactgaccgagag	1672	+	35
13	1784	aaataccatgagaagggcgcc	1804	+++	65
14	1832	aagacgtcagaaaaccgggca	1852	+	30
15	1938	aacatcacagccagacccaac	19	++	50
16	2069	aagcagagcaatgggagagaa	2089	++++	75
17	2078	aatgggagagaagcagaatat	2098	+++	65
18	2088	aagcagaatattcggacaaac	2108	+++	70
19	2094	aatattcggacaaacacggac	2114	++	40
20	2105	aaacacggacagcatctcatc	2125	++	50
21	2106	aacacggacagtacctcatcg	2126	+	35
22	2197	aaaagagatcgatgtctccta	2217	+++	65

TABLE 7-continued

Inhibition of EphB4 Gene Expression by EphB4 RNAi probes

RNAi	EphB4 RNAi sequence			Inhibition of EphB4 Expression	Percent reductio-n in viability
23	2174	aatgaggctgtgagggaacct	2194	++	50
24	2166	aagaccctaatgaggctgtga	2186	++	50
25	2199	aaagagatcgatgtctcctac	2216	+++	55
26	2199	aagagaccgacgcctcctacg	2219	+++	70
27	2229	aagaggtgactggtgcaggtg	2249	+	33
28	2222	aagactgaagaggtgattggt	2242	+	30
29	2429	aacagcatgcccgccatgact	2449	++	40
30	2291	aagaaggagagctgcgtggca	2311	+++	50
31	2294	aaggagagctgtgcggcaatc	2314	+++	60
32	2311	aatcaagaccctgaagggtgg	2331	+++	70
33	2497	aaacgacggacagttcacagt	2517	+	35
34	2498	aacgacggacagttcacagtc	2518	+	40
35	2609	aacatcccagtcaacagcaac	2629	++	50
36	2621	aacagcaacctcgtccgcaaa	2641	+	35
37	2678	aactcttccgaccccacctac	2698	++	50
38	2640	aagcgcctgacttcggcctct	2660	+++	70
39	2621	aacctcgtctgcaaagtgtcc	2647	++	50
40	2639	aaagtgtctgaccttggcctt	2659	+	25
41	2852	aatcaggacgtgatcaatgcc	2872	+++	75
42	2716	aaagattcccatccgatggac	2736	++	50
43	2717	aagatccccatccgatggact	2737	++	60
44	2762	aagttcacttccgccagtgat	2782	+++	70
45	3142	aagatacgaagaaagtttcgc	3162	++	50
46	3136	aatgggaagatacgaagaaag	3156	+++	66
47	2867	aatgccactgaacaggaccac	2887		
46	3029	aaaaccgcggcccgggagaat	3049	+	33
49	3254	aaaatcttggccagtgtccag	3274	++	50
50	3255	aaatctcggccagtgcccagc	3275	+++	75
51	3150	aagaaagtttcgcagccgctg	3170	+++	80
52	3251	aagaaaatcttggccagtgcc	3271	++	50
53	3256	aatcctggccagtgcccagca	3276	++	50

Additional RNAi probes described in the specification

Eph B4 50	gagacccugcugaacacaauu
Eph B4 472	ggugaaugucaagacgcuguu
Eph B4 1562	caucacagccagacccaacuu

TABLE 7-continued

Inhibition of EphB4 Gene Expression by EphB4 RNAi probes			
RNAi	EphB4 RNAi sequence	Inhibition of EphB4 Expression	Percent reductio-n in viability
siRNA 2303	cucuuccgaucccaccuacuu		
Eph B4 2302	cucuuccgaucccaccuacuu		

Example 9

Inhibition of Ephrin B2 Gene Expression by Ephrin B2 Antisense Probes and RNAi Probes

[0390] KS SLK, a cell line expressing endogenous high level of ephrin B2. Cell viability was tested using fixed dose of each oligonucleotide (5UM). Gene expression downregulation was done using cell line 293 engineered to stably express full-length ephrin B2. KS SLK expressing EphrinB2 were also used to test the viability in response to RNAi probes tested at the fixed dose of 50 nM. Protein expression levels were measured using 293 cells stably expressing full-length EphrinB2, in cell lysates after 24 hr treatment with fixed 50 nM of RNAi probes.

[0391] The results on Ephrin B2 antisense probes were summarized below in Table 8. The results on Ephrin B2 RNAi probes were summarized below in Table 9.

TABLE 8

Ephrin B2 antisense ODNs.				
	sequence	Coding region	Percent reduction in visability	Inhibition of Ephrin B2 Expression
Ephrin AS-51	TCA GAC CTT GTA GTA AAT GT	(983-1002)	35	++
Ephrin AS-50	TCG CCG GGC TCT GCG GGG GC	(963-982)	50	+++
Ephrin AS-49	ATC TCC TGG ACG ATG TAC AC	(943-962)	45	++
Ephrin AS-48	CGG GTG CCC GTA GTC CCC GC	(923-942)	35	++
Ephrin AS-47	TGA CCT TCT CGT AGT GAG GG	(903-922)	40	+++
Ephrin AS-46	CAG AAG ACG CTG TCC GCA GT	(883-902)	40	++
Ephrin AS-45	CCT TAG CGG GAT GAT AAT GT	(863-882)	35	++
Ephrin AS-44	CAC TGG GCT CTG AGC CGT TG	(843-862)	60	+++
Ephrin AS-43	TTG TTG CCG CTG CGC TTG GG	(823-842)	40	++
Ephrin AS-42	TGT GGC CAG TGT GCT GAG CG	(803-822)	40	++
Ephrin AS-41	ACA GCG TGG TCG TGT GCT GC	(783-802)	70	+++
Ephrin AS-40	GGC GAG TGC TTC CTG TGT CT	(763-782)	80	++++
Ephrin AS-39	CCT CCG GTA CTT CAG CAA GA	(743-762)	50	+++
Ephrin AS-38	GGA CCA CCA GCG TGA TGA TG	(723-742)	60	+++
Ephrin AS-37	ATG ACG ATG AAG ATG ATG CA	(703-722)	70	+++
Ephrin AS-36	TCC TGA AGC AAT CCC TGC AA	(683-702)	60	+++
Ephrin AS-35	ATA AGG CCA CTT CGG AAC CG	(663-682)	45	++
Ephrin AS-34	AGG ATG TTG TTC CCC GAA TG	(643-662)	50	+++
Ephrin AS-33	TCC GGC GCT GTT GCC GTC TG	(623-642)	75	+++
Ephrin AS-32	TGC TAG AAC CTG GAT TTG GT	(603-622)	60	+++
Ephrin AS-31	TTT ACA AAG GGA CTT GTT GT	(583-602)	66	+++

TABLE 8-continued

Ephrin B2 antisense ODNs.				
	sequence	Coding region	Percent reduction in visability	Inhibition of Ephrin B2 Expression
Ephrin AS-30	CGA ACT TCT TCC ATT TGT AC	(563-582)	50	++
Ephrin AS-29	CAG CTT CTA GTT CTG GAC GT	(543-562)	50	+++
Ephrin AS-28	CTT GTT GGA TCT TTA TTC CT	(523-542)	70	+++
Ephrin AS-27	GGT TGA TCC AGC AGA ACT TG	(503-522)	65	+++
Ephrin AS-26	CAT CTT GTC CAA CTT TCA TG	(483-502)	75	+++
Ephrin AS-25	AGG ATC TTC ATG GCT CTT GT	(463-482)	60	+++
Ephrin AS-24	CTG GCA CAC CCC TCC CTC CT	(443-462)	45	++
Ephrin AS-23	GGT TAT CCA GGC CCT CCA AA	(423-442)	50	+++
Ephrin AS-22	GAC CCA TTT GAT GTA GAT AT	(403-422)	50	+++
Ephrin AS-21	AAT GTA ATA ATC TTT GTT CT	(383-402)	60	+++
Ephrin AS-20	TCT GAA ATT CTA GAC CCC AG	(363-382)	60	+++
Ephrin AS-19	AGG TTA GGG CTG AAT TCT TG	(343-362)	75	+++
Ephrin AS-18	AAA CTT GAT GGT GAA TTT CA	(323-342)	60	+++
Ephrin AS-17	TAT CTT GGT CTG GTT TGG CA	(303-322)	50	++
Ephrin AS-16	CAG TTG AGG AGA GGG GTA TT	(283-302)	40	++
Ephrin AS-15	TTC CTT CTT AAT AGT GCA TC	(263-282)	66	+++
Ephrin AS-14	TGT CTG CTT GGT CTT TAT CA	(243-262)	70	++++
Ephrin AS-13	ACC ATA TAA ACT TTA TAA TA	(223-242)	50	+++
Ephrin AS-12	TTC ATA CTG GCC AAC AGT TT	(203-222)	50	+++
Ephrin AS-11	TAG AGT CCA CTT TGG GGC AA	(183-202)	70	++++
Ephrin AS-10	ATA ATA TCC AAT TTG TCT CC	(163-182)	70	++++
Ephrin AS-9	TAT CTG TGG GTA TAG TAC CA	(143-162)	80	++++
Ephrin AS-8	GTC CTT GTC CAG GTA GAA AT	(123-142)	60	+++
Ephrin AS-7	TTG GAG TTC GAG GAA TTC CA	(103-122)	80	+++
Ephrin AS-6	ATA GAT AGG CTC TAA AAC TA	(83-102)	70	+++
Ephrin AS-5	TCG ATT TGG AAA TCG CAG TT	(63-82)	50	++
Ephrin AS-4	CTG CAT AAA ACC ATC AAA AC	(43-62)	80	++++
Ephrin AS-3	ACC CCA GCA GTA CTT CCA CA	(23-42)	85	+++
Ephrin AS-2	CGG AGT CCC TTC TCA CAG CC	(3-22)	70	+++
Ephrin AS-1	GAG TCC CTT CTC ACA GCC AT	(1-20)	80	++++

TABLE 9

Ephrin B2 RNAi probes.

RNAi Sequence and homology with other human genes.			Percent reduction in viability	Inhibition of Ephrin B2 Expression	RNAi no.
89	aactgcgatttccaaatcgat	109	80	++++	1
141	aactccaaatttctacctgga	161	70	++++	2
148	aatttctacctggacaaggac	168	75	+++	3
147	aaatttctacctggacaagga	167	60	+++	4
163	aaggactggtactatacccac	183	40	++	5
217	aagtggactctaaaactgttg	237	80	++++	6
229	aaactgttggccagtatgaat	249	50	+++	7
228	aaaactgttggccagtatgaa	248	80	++++	8
274	aagaccaagcagacagatgca	294	80	++++	11
273	aaagaccaagcagacagatgc	293	60	+++	12
363	aagtttcaagaattcagccct	383	66	+++	13
370	aagaattcagccctaacctct	390	50	+++	14
373	aattcagccctaacctctggg	393	50	+++	15
324	aactgtgccaaaccagaccaa	344	90	++++	16
440	aaatgggtctttggagggcct	460	80	++++	17
501	aagatcctcatgaaagttgga	521	50	+++	18
513	aaagttggacaagatgcaagt	533	50	+++	19
491	aagagccatgaagatcctcat	511	50	+++	20
514	aagttggacaagatgcaagtt	534	66	+++	21
523	aagatgcaagttctgctggat	543	66	+++	22
530	aagttctgctggatcaaccag	550	50	+++	23
545	aaccaggaataaagatccaac	565	35	++	24
555	aaagatccaacaagacgtcca	575	40	++	25
556	aagatccaacaagacgtccag	576	60	+++	26
563	aacaagacgtccagaactaga	583	60	+++	27
566	aagacgtccagaactagaagc	586	70	+++	28
593	aaatggaagaagttcgacaac	613	75	++++	29
577	aactagaagctggtacaaatg	597	66	+++	30
594	aatggaagaagttcgacaaca	614	35	++	31
583	aagctggtacaaatggaagaa	603	50	+++	32
611	aacaagtccctttgtaaaacc	631	70	++++	33
599	aagaagttcgacaacaagtcc	619	70	++++	34
602	aagttcgacaacaagtccctt	622	80	++++	35
626	aaaaccaaatccaggttctag	646	50	+++	36
627	aaaccaaatccaggttctagc	647	25	+	37

TABLE 9-continued

Ephrin B2 RNAi probes.

RNAi Sequence and homology with other human genes.	Percent reduction in viability	Inhibition of Ephrin B2 Expression	RNAi no.
628 aaccaaatccaggttctagca 648	30	++	38
632 aaatccaggttctagcacaga 652	60	+++	39
633 aatccaggttctagcacagac 653	40	++	40
678 aacaacatcctcggttccgaa 698	30	++	41
681 aacatcctcggttccgaagtg 701	20	+	42
697 aagtggccttatttgcaggga 717	30	++	43
Additional Ephrin B2 RNAi probes described in the specification			
GCAGACAGAUGCACUAUUAUU			ephrin B2 264
CUGCGAUUUCCAAAUCGAUUU			ephrin B2 63
GGACUGGUACUAUACCCACUU			ephrin B2 137

Example 10

EphB4 Antibodies Inhibit Tumor Growth

[0392] FIG. **57** shows results on comparison of EphB4 monoclonal antibodies by 6250 and in Pull-down assay.

[0393] FIG. **58** shows that EphB4 antibodies, in the presence of matrigel and growth factors, inhibit the in vivo tumor growth of SCC15 cells.

[0394] BaIbC nude mice were injected subcutaneously with 2.5×10^6 viable tumor cells SCC15 is a head and neck squamous cell carcinoma line. Tumors were initiated in nu/nu mice by injecting $2.5-5\times10^6$ cells premixed with matrigel and Growth factors, and Ab's subcutaneously to initiate tumor xenografts. Mice were opened 14 days after injections. SCC15 is a head and neck squamous cell carcinoma line, B16 is a melanoma cell line, and MCF-7 is a breast carcinoma line. The responses of tumors to these treatments were compared to control treated mice, which receive PBS injections. Animals were observed daily for tumor growth and subcutaneous tumors were measured using a caliper every 2 days. Antibodies #1 and #23 showed significant regression of SCC15 tumor size compared to control, especially with no additional growth factor added.

[0395] FIG. **59** shows that EphB4 antibodies cause apoptosis, necrosis and decreased angiogenesis in SCC15, head and neck carcinoma tumor type.

[0396] Angiogenesis was assessed by CD-31 immunohistochemistry. Tumor tissue sections from treated and untreated mice were stained for CD31. Apoptosis was assessed by immunohistochemical TUNNEL, and proliferation by BrdU assay. Following surgical removal, tumors were immediately sliced into 2 mm serial sections and embedded in paraffin using standard procedures. Paraffin embedded tissue were sectioned at 5 μm, the wax removed and the tissue rehydrated. The rehydrated tissues were microwave irradiated in antigen retrieval solution. Slides were rinsed in PBS, and TUNNEL reaction mixture (Terminal deoxynucleotidyl transferase and flourescein labeled nucleotide solution), and BrdU were added in a humidity chamber completely shielded from light. The TUNNEL and BrdU reaction mixture were then removed, slides were rinsed and anti-flourescein antibody conjugated with horseradish peroxidase was added. After incubation and rinsing, 3,3' diaminobenzidine was added. Masson's Trichrome and Hematoxylin and Eosin were also used to stain the slides to visualize morphology. Masson's Trichrome allows to visualize necrosis and fibrosis. The tumor gets blood support from tumor/skin, muscle boundary. As tumor grows, inner regions get depleted of nutrients. This leads to necrosis (cell death), preferably at the tumor center. After cells die, (tumor) tissue gets replaced with fibroblastic tissue. Slides were visualized under 20-fold magnification with digital images acquired. A different morphology was obtained on SCC tumors with each antibody administered. Ab #1 showed an increase in necrosis and fibrosis but not apoptosis. Ab #23 showed an increase in apoptosis, necrosis and fibrosis and a decrease in vessel infiltration. Ab #35 showed an increase in necrosis and fibrosis, and a small increase in apoptosis and a decrease in vessel infiltration. Ab #79 showed a large increase in apoptosis, and necrosis and fibrosis. Ab #91 showed no change in apoptosis but an increase in proliferation. And Ab #138 showed an increase in apoptosis, necrosis, fibrosis and a decrease in proliferation and vessel infiltration. Tumors treated with control PBS displayed abundant tumor density and a robust angiogenic response. Tumors treated with EphB4 antibodies displayed a decrease in tumor cell density and a marked inhibition of tumor angiogenesis in regions with viable tumor cells, as well as tumor necrosis and apoptosis.

[0397] FIG. **60** shows that systemic administration of antibodies on xenografts leads to tumor regression in SCC15 tumor xenografts.

[0398] Alternate day treatment with EphB4 monoclonal antibody or an equal volume of PBS as control were initiated on day 4, after the tumors have established, and continued for 14 days. Systemic administration was administered either IP or SC with no significant difference. All the experiments were carried out in a double-blind manner to eliminate investigator bias. Mice were sacrificed at the conclusion of the two week treatment period. Tumors were harvested immediately post-mortem and fixed and processed for immunohistochemistry. EphB4 antibodies 40 mg per kg body weight were administered. Treatment with EphB4 antibody significantly inhibited human SCC tumor growth compared with control-treated mice ($p<0.05$). Treatment with EphB4 antibody significantly inhibited tumor weight compared with control-treated mice ($p<0.05$).

INCORPORATION BY REFERENCE

[0399] All publications and patents mentioned herein are hereby incorporated by reference in their entirety as if each individual publication or patent was specifically and individually indicated to be incorporated by reference.

[0400] While specific embodiments of the subject invention have been discussed, the above specification is illustrative and not restrictive. Many variations of the invention will become apparent to those skilled in the art upon review of this specification and the claims below. The full scope of the invention should be determined by reference to the claims, along with their full scope of equivalents, and the specification, along with such variations.

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<400> SEQUENCE: 21

atggaggcct cgctcagaaa 20

<210> SEQ ID NO 22
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ggugaauguc aagacgcugu u 21

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<212> TYPE: RNA
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cucuuccgau cccaccuacu u 21

<210> SEQ ID NO 24
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ggacctgact gactaccta 19

<210> SEQ ID NO 25
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<212> TYPE: DNA
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aaggagacct tcaccgtctt 20

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ttgaaggtag tttcgtggat 20

<210> SEQ ID NO 27
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tcgagtcagg ttcacagtca 20

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ggagccaaaa gggtcatcat 20

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ggcattgctg caaagaaaga g 21

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tccgtgtgga agtactgctg 20

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tctggtttgg cacagttgag 20

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ctttggaaga gaccctgctg 20

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agacggtgaa ggtctccttg 20

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gagacccugc ugaacacaau u 21

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uuguguucag cagggucucu u 21

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ggugaauguc aagacgcugu u 21

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cagcgucuug acauucaccu u 21

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caucacagcc agacccaacu u 21

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guugggucug gcugugaugu u 21

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cucuuccgau cccaccuacu u 21

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guaggugggа ucggaagagu u 21

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gtgcagggat agcagggcca t 21

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aaggaggggt ggtgcacggt g 21

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ttccaggtgc agggaggagc c 21

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gtggtgacat tgacaggctc a 21

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<212> TYPE: DNA
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<223> OTHER INFORMATION: Oligonucleotide

<400> SEQUENCE: 46

tctggctgtg atgttcctgg c 21

<210> SEQ ID NO 47
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<213> ORGANISM: Unknown
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<223> OTHER INFORMATION: Oligonucleotide

<400> SEQUENCE: 47

gccgctcagt tcctccca 18

<210> SEQ ID NO 48
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<212> TYPE: DNA
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tgaaggtctc cttgcagg 18

<210> SEQ ID NO 49
<211> LENGTH: 21
<212> TYPE: DNA
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<400> SEQUENCE: 49

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cgcggccacc gtgtccacct t 21

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<400> SEQUENCE: 50

cttcagggtc ttgattgcca c 21

<210> SEQ ID NO 51
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<212> TYPE: DNA
<213> ORGANISM: Unknown
<220> FEATURE:
<223> OTHER INFORMATION: Oligonucleotide

<400> SEQUENCE: 51

atggaggcct cgctcagaaa 20

<210> SEQ ID NO 52
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<212> TYPE: DNA
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<220> FEATURE:
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<400> SEQUENCE: 52

catgcccacg agctggatga c 21

<210> SEQ ID NO 53
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<212> TYPE: DNA
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<400> SEQUENCE: 53

tccgtgtgga gtactgctg 19

<210> SEQ ID NO 54
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<400> SEQUENCE: 54

tctggtttgg cacagttgag 20

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<212> TYPE: DNA
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<400> SEQUENCE: 55

ctttggaaga gaccctgctg 20

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<210> SEQ ID NO 56
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<400> SEQUENCE: 56

agacggtgaa ggtctccttg 20

<210> SEQ ID NO 57
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<212> TYPE: DNA
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<400> SEQUENCE: 57

agacaagagc catgaagatc 20

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<211> LENGTH: 21
<212> TYPE: DNA
<213> ORGANISM: Unknown
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<400> SEQUENCE: 58

ggatcccact tcggacccga g 21

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<212> TYPE: DNA
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<400> SEQUENCE: 59

tcaggtcact gcattgaacg gg 22

<210> SEQ ID NO 60
<211> LENGTH: 19
<212> TYPE: DNA
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<223> OTHER INFORMATION: Oligonucleotide

<400> SEQUENCE: 60

aactcgctct catccagtt 19

<210> SEQ ID NO 61
<211> LENGTH: 20
<212> TYPE: DNA
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<400> SEQUENCE: 61

gtggggcgcc ccaggcacca 20

<210> SEQ ID NO 62
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<212> TYPE: DNA
<213> ORGANISM: Unknown

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<220> FEATURE:
<223> OTHER INFORMATION: Oligonucleotide

<400> SEQUENCE: 62

ctccttaatg tcacgcacga tttc 24

<210> SEQ ID NO 63
<211> LENGTH: 21
<212> TYPE: RNA
<213> ORGANISM: Unknown
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<223> OTHER INFORMATION: Oligonucleotide

<400> SEQUENCE: 63

gcagacagau gcacuauuau u 21

<210> SEQ ID NO 64
<211> LENGTH: 21
<212> TYPE: RNA
<213> ORGANISM: Unknown
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<223> OTHER INFORMATION: Oligonucleotide

<400> SEQUENCE: 64

uaauagugca ucugucugcu u 21

<210> SEQ ID NO 65
<211> LENGTH: 21
<212> TYPE: RNA
<213> ORGANISM: Unknown
<220> FEATURE:
<223> OTHER INFORMATION: Oligonucleotide

<400> SEQUENCE: 65

cugcgauuuc caaaucgauu u 21

<210> SEQ ID NO 66
<211> LENGTH: 21
<212> TYPE: RNA
<213> ORGANISM: Unknown
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<223> OTHER INFORMATION: Oligonucleotide

<400> SEQUENCE: 66

aucgauuugg aaaucgcagu u 21

<210> SEQ ID NO 67
<211> LENGTH: 21
<212> TYPE: RNA
<213> ORGANISM: Unknown
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<223> OTHER INFORMATION: Oligonucleotide

<400> SEQUENCE: 67

ggacugguac uauacccacu u 21

<210> SEQ ID NO 68
<211> LENGTH: 21
<212> TYPE: RNA
<213> ORGANISM: Unknown
<220> FEATURE:
<223> OTHER INFORMATION: Oligonucleotide

<400> SEQUENCE: 68

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gugggguauag uaccaguccu u 21

<210> SEQ ID NO 69
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<212> TYPE: RNA
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<220> FEATURE:
<223> OTHER INFORMATION: Oligonucleotide

<400> SEQUENCE: 69

gagacccugc ugaacacaau u 21

<210> SEQ ID NO 70
<211> LENGTH: 21
<212> TYPE: RNA
<213> ORGANISM: Unknown
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<223> OTHER INFORMATION: Oligonucleotide

<400> SEQUENCE: 70

uuguguucag cagggucucu u 21

<210> SEQ ID NO 71
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<212> TYPE: RNA
<213> ORGANISM: Unknown
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<223> OTHER INFORMATION: Oligonucleotide

<400> SEQUENCE: 71

cgcugacccu gaaguucauu u 21

<210> SEQ ID NO 72
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<212> TYPE: RNA
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<400> SEQUENCE: 72

augaacuuca gggucagcgu u 21

<210> SEQ ID NO 73
<211> LENGTH: 21
<212> TYPE: DNA
<213> ORGANISM: Unknown
<220> FEATURE:
<223> OTHER INFORMATION: Oligonucleotide

<400> SEQUENCE: 73

tcagtactgc ggggccggtc c 21

<210> SEQ ID NO 74
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<212> TYPE: DNA
<213> ORGANISM: Unknown
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<223> OTHER INFORMATION: Oligonucleotide

<400> SEQUENCE: 74

tcctgtccca cccggggttc 20

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<210> SEQ ID NO 75
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Unknown
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<400> SEQUENCE: 75

ccggcttggc ctgggacttc 20

<210> SEQ ID NO 76
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Unknown
<220> FEATURE:
<223> OTHER INFORMATION: Oligonucleotide

<400> SEQUENCE: 76

atgtgctgga cactggccaa 20

<210> SEQ ID NO 77
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Unknown
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<400> SEQUENCE: 77

gattttcttc tggtgtcccg 20

<210> SEQ ID NO 78
<211> LENGTH: 20
<212> TYPE: DNA
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<220> FEATURE:
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<400> SEQUENCE: 78

ccagagtgac tccgattcgg 20

<210> SEQ ID NO 79
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Unknown
<220> FEATURE:
<223> OTHER INFORMATION: Oligonucleotide

<400> SEQUENCE: 79

agcaggtcct cagcagagat 20

<210> SEQ ID NO 80
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Unknown
<220> FEATURE:
<223> OTHER INFORMATION: Oligonucleotide

<400> SEQUENCE: 80

ctggctgacc agctcgaagg 20

<210> SEQ ID NO 81
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Unknown

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<220> FEATURE:
<223> OTHER INFORMATION: Oligonucleotide

<400> SEQUENCE: 81

agccaaagcc agcggctgcg 20

<210> SEQ ID NO 82
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Unknown
<220> FEATURE:
<223> OTHER INFORMATION: Oligonucleotide

<400> SEQUENCE: 82

aaactttctt cgtatcttcc 20

<210> SEQ ID NO 83
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<212> TYPE: DNA
<213> ORGANISM: Unknown
<220> FEATURE:
<223> OTHER INFORMATION: Oligonucleotide

<400> SEQUENCE: 83

cattttgatg gcccgaagcc 20

<210> SEQ ID NO 84
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Unknown
<220> FEATURE:
<223> OTHER INFORMATION: Oligonucleotide

<400> SEQUENCE: 84

actcgcccac agagccaaaa 20

<210> SEQ ID NO 85
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Unknown
<220> FEATURE:
<223> OTHER INFORMATION: Oligonucleotide

<400> SEQUENCE: 85

gctgagtagt gaggctgccg 20

<210> SEQ ID NO 86
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Unknown
<220> FEATURE:
<223> OTHER INFORMATION: Oligonucleotide

<400> SEQUENCE: 86

ctggtccagg agagggtgtg 20

<210> SEQ ID NO 87
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Unknown
<220> FEATURE:
<223> OTHER INFORMATION: Oligonucleotide

<400> SEQUENCE: 87

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aggccccgcc attctcccgg 20

<210> SEQ ID NO 88
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Unknown
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<223> OTHER INFORMATION: Oligonucleotide

<400> SEQUENCE: 88

gccacgattt tgaggctggc 20

<210> SEQ ID NO 89
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Unknown
<220> FEATURE:
<223> OTHER INFORMATION: Oligonucleotide

<400> SEQUENCE: 89

ggggttccgg atcatcttgt 20

<210> SEQ ID NO 90
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Unknown
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<223> OTHER INFORMATION: Oligonucleotide

<400> SEQUENCE: 90

ccagggcgct gaccacctgg 20

<210> SEQ ID NO 91
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Unknown
<220> FEATURE:
<223> OTHER INFORMATION: Oligonucleotide

<400> SEQUENCE: 91

gggaagcggg gccgggcatt 20

<210> SEQ ID NO 92
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Unknown
<220> FEATURE:
<223> OTHER INFORMATION: Oligonucleotide

<400> SEQUENCE: 92

ccggtctttc tgccaacagt 20

<210> SEQ ID NO 93
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Unknown
<220> FEATURE:
<223> OTHER INFORMATION: Oligonucleotide

<400> SEQUENCE: 93

ccagcatgag ctggtggagg 20

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<210> SEQ ID NO 94
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Unknown
<220> FEATURE:
<223> OTHER INFORMATION: Oligonucleotide

<400> SEQUENCE: 94

gaggtgggac agtctggggg 20

<210> SEQ ID NO 95
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Unknown
<220> FEATURE:
<223> OTHER INFORMATION: Oligonucleotide

<400> SEQUENCE: 95

cgggggcagc cggtagtcct 20

<210> SEQ ID NO 96
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Unknown
<220> FEATURE:
<223> OTHER INFORMATION: Oligonucleotide

<400> SEQUENCE: 96

gttcaatggc attgatcacg 20

<210> SEQ ID NO 97
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Unknown
<220> FEATURE:
<223> OTHER INFORMATION: Oligonucleotide

<400> SEQUENCE: 97

tcctgattgc tcatgtccca 20

<210> SEQ ID NO 98
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Unknown
<220> FEATURE:
<223> OTHER INFORMATION: Oligonucleotide

<400> SEQUENCE: 98

gtacggcctc tccccaaatg 20

<210> SEQ ID NO 99
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Unknown
<220> FEATURE:
<223> OTHER INFORMATION: Oligonucleotide

<400> SEQUENCE: 99

acatcacctc ccacatcaca 20

<210> SEQ ID NO 100
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Unknown

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<220> FEATURE:
<223> OTHER INFORMATION: Oligonucleotide

<400> SEQUENCE: 100

atcccgtaac tccaggcatc 20

<210> SEQ ID NO 101
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Unknown
<220> FEATURE:
<223> OTHER INFORMATION: Oligonucleotide

<400> SEQUENCE: 101

actggcggaa gtgaacttcc 20

<210> SEQ ID NO 102
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Unknown
<220> FEATURE:
<223> OTHER INFORMATION: Oligonucleotide

<400> SEQUENCE: 102

ggaaggcaat ggcctccggg 20

<210> SEQ ID NO 103
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Unknown
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<223> OTHER INFORMATION: Oligonucleotide

<400> SEQUENCE: 103

gcagtccatc ggatgggaat 20

<210> SEQ ID NO 104
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Unknown
<220> FEATURE:
<223> OTHER INFORMATION: Oligonucleotide

<400> SEQUENCE: 104

ctttcctccc agggagctcg 20

<210> SEQ ID NO 105
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Unknown
<220> FEATURE:
<223> OTHER INFORMATION: Oligonucleotide

<400> SEQUENCE: 105

tgtaggtggg atcggaagag 20

<210> SEQ ID NO 106
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Unknown
<220> FEATURE:
<223> OTHER INFORMATION: Oligonucleotide

<400> SEQUENCE: 106

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ttctcctcca ggaatcggga 20

<210> SEQ ID NO 107
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Unknown
<220> FEATURE:
<223> OTHER INFORMATION: Oligonucleotide

<400> SEQUENCE: 107

aaggccaaag tcagacactt 20

<210> SEQ ID NO 108
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Unknown
<220> FEATURE:
<223> OTHER INFORMATION: Oligonucleotide

<400> SEQUENCE: 108

gcagacgagg ttgctgttga 20

<210> SEQ ID NO 109
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Unknown
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<223> OTHER INFORMATION: Oligonucleotide

<400> SEQUENCE: 109

ctaggatgtt gcgagcagcc 20

<210> SEQ ID NO 110
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Unknown
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<400> SEQUENCE: 110

aggtctcggt ggacgtagct 20

<210> SEQ ID NO 111
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Unknown
<220> FEATURE:
<223> OTHER INFORMATION: Oligonucleotide

<400> SEQUENCE: 111

catctcggca aggtaccgca 20

<210> SEQ ID NO 112
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Unknown
<220> FEATURE:
<223> OTHER INFORMATION: Oligonucleotide

<400> SEQUENCE: 112

tgcccgaggc gatgccccgc 20

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<210> SEQ ID NO 113
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Unknown
<220> FEATURE:
<223> OTHER INFORMATION: Oligonucleotide

<400> SEQUENCE: 113

agcatgccca cgagctggat 20

<210> SEQ ID NO 114
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Unknown
<220> FEATURE:
<223> OTHER INFORMATION: Oligonucleotide

<400> SEQUENCE: 114

gactgtgaac tgtccgtcgt 20

<210> SEQ ID NO 115
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Unknown
<220> FEATURE:
<223> OTHER INFORMATION: Oligonucleotide

<400> SEQUENCE: 115

ttagccgcag gaaggagtcc 20

<210> SEQ ID NO 116
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Unknown
<220> FEATURE:
<223> OTHER INFORMATION: Oligonucleotide

<400> SEQUENCE: 116

agggcgccgt tctccatgaa 20

<210> SEQ ID NO 117
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Unknown
<220> FEATURE:
<223> OTHER INFORMATION: Oligonucleotide

<400> SEQUENCE: 117

ctctgtgaga atcatgacgg 20

<210> SEQ ID NO 118
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Unknown
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<223> OTHER INFORMATION: Oligonucleotide

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gcatgctgtt ggtgaccacg 20

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<220> FEATURE:
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ccctccaggc ggatgatatt 20

<210> SEQ ID NO 120
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<212> TYPE: DNA
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ggggtgctcg aactggccca 20

<210> SEQ ID NO 121
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<212> TYPE: DNA
<213> ORGANISM: Unknown
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tgatggaggc ctcgctcaga 20

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<213> ORGANISM: Unknown
<220> FEATURE:
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aactcacgcc gctgccgctc 20

<210> SEQ ID NO 123
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<212> TYPE: DNA
<213> ORGANISM: Unknown
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<400> SEQUENCE: 123

cgtgtagcca cccttcaggg 20

<210> SEQ ID NO 124
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tcttgattgc cacacagctc 20

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tccttcttcc ctggggcctt 20

<210> SEQ ID NO 126
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<213> ORGANISM: Unknown
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<400> SEQUENCE: 126

gagccgcccc cggcacacct 20

<210> SEQ ID NO 127
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cgccaaactc acctgcacca 20

<210> SEQ ID NO 128
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atcacctctt caatcttgac 20

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gtaggagaca tcgatctctt 20

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ttgcaaattc cctcacagcc 20

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tcattagggt cttcataagt 20

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gaaggggtcg atgtagacct 20

<210> SEQ ID NO 133
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tagtaccatg tccgatgaga 20

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atattctgct tctctcccat 20

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tgctctgctt cctgaggcag 20

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<223> OTHER INFORMATION: Oligonucleotide

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agaactgcga ccacaatgac 20

<210> SEQ ID NO 138
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<220> FEATURE:
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<400> SEQUENCE: 138

caccaggacc aggaccacac 20

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ccacgactgc cgtgcccgca 20

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<212> TYPE: DNA
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<400> SEQUENCE: 140

atcagggcca gctgctcccg 20

<210> SEQ ID NO 141
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ccagccctcg ctctcatcca 20

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<212> TYPE: DNA
<213> ORGANISM: Unknown
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<400> SEQUENCE: 142

gttgggtctg gctgtgatgt 20

<210> SEQ ID NO 143
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tcctggccga agggcccgta 20

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gccggcctca gagcgcgccc 20

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<400> SEQUENCE: 145

gtacctgcac caggtagctg 20

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<212> TYPE: DNA
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<220> FEATURE:
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<400> SEQUENCE: 146

gctccccgct tcagcccccg 20

<210> SEQ ID NO 147
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<212> TYPE: DNA
<213> ORGANISM: Unknown
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<223> OTHER INFORMATION: Oligonucleotide

<400> SEQUENCE: 147

cagctctgcc cggttttctg 20

<210> SEQ ID NO 148
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Unknown
<220> FEATURE:
<223> OTHER INFORMATION: Oligonucleotide

<400> SEQUENCE: 148

acgtcttcag gaaccgcacg 20

<210> SEQ ID NO 149
<211> LENGTH: 20
<212> TYPE: DNA
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<223> OTHER INFORMATION: Oligonucleotide

<400> SEQUENCE: 149

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<210> SEQ ID NO 150
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<212> TYPE: DNA
<213> ORGANISM: Unknown
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<400> SEQUENCE: 150

cttctcatgg tatttgacct 20

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<400> SEQUENCE: 151

cgtagtccag cacagcccca 20

<210> SEQ ID NO 152
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<212> TYPE: DNA
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<400> SEQUENCE: 152

ctgggtgccc ggggaacagc 20

<210> SEQ ID NO 153
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<212> TYPE: DNA
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<220> FEATURE:
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<400> SEQUENCE: 153

ccaggccagg ctcaagctgc 20

<210> SEQ ID NO 154
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<212> TYPE: DNA
<213> ORGANISM: Unknown
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<400> SEQUENCE: 154

tgggtgagga ccgcgtcacc 20

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<212> TYPE: DNA
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<400> SEQUENCE: 155

cggatgtcag acactgcagg 20

<210> SEQ ID NO 156
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<212> TYPE: DNA
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<223> OTHER INFORMATION: Oligonucleotide

<400> SEQUENCE: 156

aggtacctct cggtcagtgg 20

<210> SEQ ID NO 157
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<212> TYPE: DNA
<213> ORGANISM: Unknown

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<220> FEATURE:
<223> OTHER INFORMATION: Oligonucleotide

<400> SEQUENCE: 157

tgacattgac aggctcaaat 20

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<211> LENGTH: 20
<212> TYPE: DNA
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<223> OTHER INFORMATION: Oligonucleotide

<400> SEQUENCE: 158

gggacgggcc ccgtggctaa 20

<210> SEQ ID NO 159
<211> LENGTH: 20
<212> TYPE: DNA
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<223> OTHER INFORMATION: Oligonucleotide

<400> SEQUENCE: 159

ggaggatacc ccgttcaatg 20

<210> SEQ ID NO 160
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<212> TYPE: DNA
<213> ORGANISM: Unknown
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<223> OTHER INFORMATION: Oligonucleotide

<400> SEQUENCE: 160

cagtgacctc aaaggtatag 20

<210> SEQ ID NO 161
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Unknown
<220> FEATURE:
<223> OTHER INFORMATION: Oligonucleotide

<400> SEQUENCE: 161

gtgaagtcag gacgtagccc 20

<210> SEQ ID NO 162
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<212> TYPE: DNA
<213> ORGANISM: Unknown
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<223> OTHER INFORMATION: Oligonucleotide

<400> SEQUENCE: 162

tcgaaccacc acccagggct 20

<210> SEQ ID NO 163
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Unknown
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<223> OTHER INFORMATION: Oligonucleotide

<400> SEQUENCE: 163

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ccaccaggtc ccgggggccg 20

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<212> TYPE: DNA
<213> ORGANISM: Unknown
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<400> SEQUENCE: 164

gggtcaaaag tcaggtctcc 20

<210> SEQ ID NO 165
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Unknown
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<223> OTHER INFORMATION: Oligonucleotide

<400> SEQUENCE: 165

cccgcagggc gcacaggagc 20

<210> SEQ ID NO 166
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Unknown
<220> FEATURE:
<223> OTHER INFORMATION: Oligonucleotide

<400> SEQUENCE: 166

ctccgggtcg gcactcccgg 20

<210> SEQ ID NO 167
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Unknown
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<223> OTHER INFORMATION: Oligonucleotide

<400> SEQUENCE: 167

cagcggaggg cgtaggtgag 20

<210> SEQ ID NO 168
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Unknown
<220> FEATURE:
<223> OTHER INFORMATION: Oligonucleotide

<400> SEQUENCE: 168

gtcctctcgg ccaccagact 20

<210> SEQ ID NO 169
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<212> TYPE: DNA
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<223> OTHER INFORMATION: Oligonucleotide

<400> SEQUENCE: 169

ccagggggc actccattcc 20

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<210> SEQ ID NO 170
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<212> TYPE: DNA
<213> ORGANISM: Unknown
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<223> OTHER INFORMATION: Oligonucleotide

<400> SEQUENCE: 170

aggtgcaggg aggagccgtt 20

<210> SEQ ID NO 171
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<212> TYPE: DNA
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<220> FEATURE:
<223> OTHER INFORMATION: Oligonucleotide

<400> SEQUENCE: 171

caggcgggaa accacgctcc 20

<210> SEQ ID NO 172
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<212> TYPE: DNA
<213> ORGANISM: Unknown
<220> FEATURE:
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<400> SEQUENCE: 172

gcggagccga aggaggggtg 20

<210> SEQ ID NO 173
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<212> TYPE: DNA
<213> ORGANISM: Unknown
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<223> OTHER INFORMATION: Oligonucleotide

<400> SEQUENCE: 173

gtgcagggtg caccccgggg 20

<210> SEQ ID NO 174
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<212> TYPE: DNA
<213> ORGANISM: Unknown
<220> FEATURE:
<223> OTHER INFORMATION: Oligonucleotide

<400> SEQUENCE: 174

gtctgtgcgt gcccggaagt 20

<210> SEQ ID NO 175
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Unknown
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<223> OTHER INFORMATION: Oligonucleotide

<400> SEQUENCE: 175

acccgacgcg gcactggcag 20

<210> SEQ ID NO 176
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Unknown

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<220> FEATURE:
<223> OTHER INFORMATION: Oligonucleotide

<400> SEQUENCE: 176

acggctgatc caatggtgtt 20

<210> SEQ ID NO 177
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Unknown
<220> FEATURE:
<223> OTHER INFORMATION: Oligonucleotide

<400> SEQUENCE: 177

agagtggcta ttggctgggc 20

<210> SEQ ID NO 178
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Unknown
<220> FEATURE:
<223> OTHER INFORMATION: Oligonucleotide

<400> SEQUENCE: 178

atggctggca ggacccttct 20

<210> SEQ ID NO 179
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Unknown
<220> FEATURE:
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<400> SEQUENCE: 179

cctgacaggg gcttgaaggt 20

<210> SEQ ID NO 180
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Unknown
<220> FEATURE:
<223> OTHER INFORMATION: Oligonucleotide

<400> SEQUENCE: 180

gccctgggca caggctcggc 20

<210> SEQ ID NO 181
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Unknown
<220> FEATURE:
<223> OTHER INFORMATION: Oligonucleotide

<400> SEQUENCE: 181

acttggtgtt cccctcagct 20

<210> SEQ ID NO 182
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Unknown
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<400> SEQUENCE: 182

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gcctcgaacc ccggagcaca 20

<210> SEQ ID NO 183
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Unknown
<220> FEATURE:
<223> OTHER INFORMATION: Oligonucleotide

<400> SEQUENCE: 183

gctgcagccc gtgaccggct 20

<210> SEQ ID NO 184
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Unknown
<220> FEATURE:
<223> OTHER INFORMATION: Oligonucleotide

<400> SEQUENCE: 184

gttcggccca ctggccatcc 20

<210> SEQ ID NO 185
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Unknown
<220> FEATURE:
<223> OTHER INFORMATION: Oligonucleotide

<400> SEQUENCE: 185

tcacggcagt agaggctggg 20

<210> SEQ ID NO 186
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<212> TYPE: DNA
<213> ORGANISM: Unknown
<220> FEATURE:
<223> OTHER INFORMATION: Oligonucleotide

<400> SEQUENCE: 186

gctggggcca ggggcgggga 20

<210> SEQ ID NO 187
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Unknown
<220> FEATURE:
<223> OTHER INFORMATION: Oligonucleotide

<400> SEQUENCE: 187

cggcatccac cacgcagcta 20

<210> SEQ ID NO 188
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Unknown
<220> FEATURE:
<223> OTHER INFORMATION: Oligonucleotide

<400> SEQUENCE: 188

ccggccacgg gcacaaccag 20

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<210> SEQ ID NO 189
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Unknown
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<223> OTHER INFORMATION: Oligonucleotide

<400> SEQUENCE: 189

ctcccgaggc acagtctccg 20

<210> SEQ ID NO 190
<211> LENGTH: 20
<212> TYPE: DNA
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<220> FEATURE:
<223> OTHER INFORMATION: Oligonucleotide

<400> SEQUENCE: 190

ggaatcgagt caggttcaca 20

<210> SEQ ID NO 191
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<212> TYPE: DNA
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<400> SEQUENCE: 191

gtcagctggg cgcacttttt 20

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<212> TYPE: DNA
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<220> FEATURE:
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<400> SEQUENCE: 192

gtagaagagg tgcagggata 20

<210> SEQ ID NO 193
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<212> TYPE: DNA
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<223> OTHER INFORMATION: Oligonucleotide

<400> SEQUENCE: 193

gcagggccat gcaggcaccc 20

<210> SEQ ID NO 194
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<212> TYPE: DNA
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<220> FEATURE:
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<400> SEQUENCE: 194

tggtcctgga aggccaggta 20

<210> SEQ ID NO 195
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<212> TYPE: DNA
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<220> FEATURE:
<223> OTHER INFORMATION: Oligonucleotide

<400> SEQUENCE: 195

gaagccagcc ttgctgagcg 20

<210> SEQ ID NO 196
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Unknown
<220> FEATURE:
<223> OTHER INFORMATION: Oligonucleotide

<400> SEQUENCE: 196

gtcccagacg cagcgtcttg 20

<210> SEQ ID NO 197
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Unknown
<220> FEATURE:
<223> OTHER INFORMATION: Oligonucleotide

<400> SEQUENCE: 197

acattcacct tcccggtggc 20

<210> SEQ ID NO 198
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Unknown
<220> FEATURE:
<223> OTHER INFORMATION: Oligonucleotide

<400> SEQUENCE: 198

ctcggcccca gggcgcttcc 20

<210> SEQ ID NO 199
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Unknown
<220> FEATURE:
<223> OTHER INFORMATION: Oligonucleotide

<400> SEQUENCE: 199

gggtgagatg ctccgcggcc 20

<210> SEQ ID NO 200
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Unknown
<220> FEATURE:
<223> OTHER INFORMATION: Oligonucleotide

<400> SEQUENCE: 200

accgtgtcca ccttgatgta 20

<210> SEQ ID NO 201
<211> LENGTH: 20
<212> TYPE: DNA
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<220> FEATURE:
<223> OTHER INFORMATION: Oligonucleotide

<400> SEQUENCE: 201

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ggggttctcc atccaggctg 20

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<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Unknown
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<223> OTHER INFORMATION: Oligonucleotide

<400> SEQUENCE: 202

gcgtgagggc cgtggccgtg 20

<210> SEQ ID NO 203
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Unknown
<220> FEATURE:
<223> OTHER INFORMATION: Oligonucleotide

<400> SEQUENCE: 203

tccgcatcgc tctcatagta 20

<210> SEQ ID NO 204
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Unknown
<220> FEATURE:
<223> OTHER INFORMATION: Oligonucleotide

<400> SEQUENCE: 204

gaagacggtg aaggtctcct 20

<210> SEQ ID NO 205
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Unknown
<220> FEATURE:
<223> OTHER INFORMATION: Oligonucleotide

<400> SEQUENCE: 205

tgcaggagcg cccagcccga 20

<210> SEQ ID NO 206
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Unknown
<220> FEATURE:
<223> OTHER INFORMATION: Oligonucleotide

<400> SEQUENCE: 206

ggcagggaca ggcactcgag 20

<210> SEQ ID NO 207
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Unknown
<220> FEATURE:
<223> OTHER INFORMATION: Oligonucleotide

<400> SEQUENCE: 207

catggtgaag cgcagcgtgg 20

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<210> SEQ ID NO 208
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<212> TYPE: DNA
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<400> SEQUENCE: 208

cgtacacgtg gacggcgccc 20

<210> SEQ ID NO 209
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<212> TYPE: DNA
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<220> FEATURE:
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<400> SEQUENCE: 209

cgccgtggga cccaacctgt 20

<210> SEQ ID NO 210
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<212> TYPE: DNA
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<220> FEATURE:
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<400> SEQUENCE: 210

gcgaagccag tgggcctggc 20

<210> SEQ ID NO 211
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<212> TYPE: DNA
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<220> FEATURE:
<223> OTHER INFORMATION: Oligonucleotide

<400> SEQUENCE: 211

ccggggcacg ctgcacgtca 20

<210> SEQ ID NO 212
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<212> TYPE: DNA
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<220> FEATURE:
<223> OTHER INFORMATION: Oligonucleotide

<400> SEQUENCE: 212

cacacttcgt aggtgcgcac 20

<210> SEQ ID NO 213
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<212> TYPE: DNA
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<400> SEQUENCE: 213

gctgtgctgt tcctcatcca 20

<210> SEQ ID NO 214
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<212> TYPE: DNA
<213> ORGANISM: Unknown

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<220> FEATURE:
<223> OTHER INFORMATION: Oligonucleotide

<400> SEQUENCE: 214

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<210> SEQ ID NO 215
<211> LENGTH: 20
<212> TYPE: DNA
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<220> FEATURE:
<223> OTHER INFORMATION: Oligonucleotide

<400> SEQUENCE: 215

tgcccgtcca cctgagggaa 20

<210> SEQ ID NO 216
<211> LENGTH: 20
<212> TYPE: DNA
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tgtcacccac ttcagatcag 20

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<212> TYPE: DNA
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cagtttccaa ttttgtgttc 20

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agcagggtct cttccaaagc 20

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tgcggccaac gaagcccagc 20

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agagcagcac ccggagctcc 20

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agcagcaccc ggagctccat 20

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gtgcagggat agcagggcca t 21

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aaggaggggt ggtgcacggt g 21

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ttccaggtgc agggaggagc c 21

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gtggtgacat tgacaggctc a 21

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tctggctgtg atgttcctgg c 21

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gccgctcagt tcctccca 18

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tgaaggtctc cttgcagg 18

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cgcggccacc gtgtccacct t 21

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cttcagggtc ttgattgcca c 21

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atggaggcct cgctcagaaa 20

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catgcccacg agctggatga c 21

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aaactgctga tctgaagtgg g 21

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aagtgggtga cattccctca g 21

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aaggtgaatg tcaagacgct g 21

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aaggagacct tcaccgtctt c 21

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aaaaagtgcg cccagctgac t 21

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aatagccact ctaacaccat t 21

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aacaccattg gatcagccgt c 21

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<400> SEQUENCE: 245

aaataccatg agaagggcgc c 21

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aagacgtcag aaaaccgggc a 21

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<212> TYPE: DNA
<213> ORGANISM: Unknown
<220> FEATURE:
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<400> SEQUENCE: 247

aacatcacag ccagacccaa c 21

<210> SEQ ID NO 248
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<400> SEQUENCE: 248

aagcagagca atgggagaga a 21

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<400> SEQUENCE: 249

aatgggagag aagcagaata t 21

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<400> SEQUENCE: 250

aagcagaata ttcggacaaa c 21

<210> SEQ ID NO 251
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<400> SEQUENCE: 251

aatattcgga caaacacgga c 21

<210> SEQ ID NO 252
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<220> FEATURE:
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aaacacggac agtatctcat c 21

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<212> TYPE: DNA
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<400> SEQUENCE: 253

aacacggaca gtatctcatc g 21

<210> SEQ ID NO 254
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<400> SEQUENCE: 254

aaaagagatc gatgtctcct a 21

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<223> OTHER INFORMATION: Oligonucleotide

<400> SEQUENCE: 255

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<210> SEQ ID NO 256
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<212> TYPE: DNA
<213> ORGANISM: Unknown
<220> FEATURE:
<223> OTHER INFORMATION: Oligonucleotide

<400> SEQUENCE: 256

aagaccctaa tgaggctgtg a 21

<210> SEQ ID NO 257
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<212> TYPE: DNA
<213> ORGANISM: Unknown
<220> FEATURE:
<223> OTHER INFORMATION: Oligonucleotide

<400> SEQUENCE: 257

aaagagatcg atgtctccta c 21

<210> SEQ ID NO 258
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<212> TYPE: DNA
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<400> SEQUENCE: 258

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aagagatcga tgtctcctac g 21

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<400> SEQUENCE: 259

aagaggtgat tggtgcaggt g 21

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<212> TYPE: DNA
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<220> FEATURE:
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aagattgaag aggtgattgg t 21

<210> SEQ ID NO 261
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<400> SEQUENCE: 261

aacagcatgc ccgtcatgat t 21

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<212> TYPE: DNA
<213> ORGANISM: Unknown
<220> FEATURE:
<223> OTHER INFORMATION: Oligonucleotide

<400> SEQUENCE: 262

aagaaggaga gctgtgtggc a 21

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<223> OTHER INFORMATION: Oligonucleotide

<400> SEQUENCE: 263

aaggagagct gtgtggcaat c 21

<210> SEQ ID NO 264
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<213> ORGANISM: Unknown
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<223> OTHER INFORMATION: Oligonucleotide

<400> SEQUENCE: 264

aatcaagacc ctgaagggtg g 21

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<210> SEQ ID NO 265
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<212> TYPE: DNA
<213> ORGANISM: Unknown
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<223> OTHER INFORMATION: Oligonucleotide

<400> SEQUENCE: 265

aaacgacgga cagttcacag t 21

<210> SEQ ID NO 266
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<212> TYPE: DNA
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<223> OTHER INFORMATION: Oligonucleotide

<400> SEQUENCE: 266

aacgacggac agttcacagt c 21

<210> SEQ ID NO 267
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<212> TYPE: DNA
<213> ORGANISM: Unknown
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<223> OTHER INFORMATION: Oligonucleotide

<400> SEQUENCE: 267

aacatcctag tcaacagcaa c 21

<210> SEQ ID NO 268
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<213> ORGANISM: Unknown
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<400> SEQUENCE: 268

aacagcaacc tcgtctgcaa a 21

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<212> TYPE: DNA
<213> ORGANISM: Unknown
<220> FEATURE:
<223> OTHER INFORMATION: Oligonucleotide

<400> SEQUENCE: 269

aactcttccg atcccaccta c 21

<210> SEQ ID NO 270
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<212> TYPE: DNA
<213> ORGANISM: Unknown
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<400> SEQUENCE: 270

aagtgtctga ctttggcctt t 21

<210> SEQ ID NO 271
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<212> TYPE: DNA
<213> ORGANISM: Unknown

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<220> FEATURE:
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<400> SEQUENCE: 271

aacctcgtct gcaaagtgtc t 21

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<212> TYPE: DNA
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<220> FEATURE:
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<400> SEQUENCE: 272

aaagtgtctg actttggcct t 21

<210> SEQ ID NO 273
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<212> TYPE: DNA
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<400> SEQUENCE: 273

aatcaggacg tgatcaatgc c 21

<210> SEQ ID NO 274
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<212> TYPE: DNA
<213> ORGANISM: Unknown
<220> FEATURE:
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<400> SEQUENCE: 274

aaagattccc atccgatgga c 21

<210> SEQ ID NO 275
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<212> TYPE: DNA
<213> ORGANISM: Unknown
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<223> OTHER INFORMATION: Oligonucleotide

<400> SEQUENCE: 275

aagattccca tccgatggac t 21

<210> SEQ ID NO 276
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<212> TYPE: DNA
<213> ORGANISM: Unknown
<220> FEATURE:
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<400> SEQUENCE: 276

aagttcactt ccgccagtga t 21

<210> SEQ ID NO 277
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<212> TYPE: DNA
<213> ORGANISM: Unknown
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<223> OTHER INFORMATION: Oligonucleotide

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aagatacgaa gaaagtttcg c 21

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<212> TYPE: DNA
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<220> FEATURE:
<223> OTHER INFORMATION: Oligonucleotide

<400> SEQUENCE: 278

aatgggaaga tacgaagaaa g 21

<210> SEQ ID NO 279
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<212> TYPE: DNA
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<220> FEATURE:
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aatgccattg aacaggacta c 21

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<212> TYPE: DNA
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aaaatcgtgg cccgggagaa t 21

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<212> TYPE: DNA
<213> ORGANISM: Unknown
<220> FEATURE:
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<400> SEQUENCE: 281

aaaatcttgg ccagtgtcca g 21

<210> SEQ ID NO 282
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<212> TYPE: DNA
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<400> SEQUENCE: 282

aaatcttggc cagtgtccag c 21

<210> SEQ ID NO 283
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<212> TYPE: DNA
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<220> FEATURE:
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<400> SEQUENCE: 283

aagaaagttt cgcagccgct g 21

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<212> TYPE: DNA
<213> ORGANISM: Unknown
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<400> SEQUENCE: 284

aagaaaatct tggccagtgt c 21

<210> SEQ ID NO 285
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<212> TYPE: DNA
<213> ORGANISM: Unknown
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<223> OTHER INFORMATION: Oligonucleotide

<400> SEQUENCE: 285

aatcttggcc agtgtccagc a 21

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<212> TYPE: RNA
<213> ORGANISM: Unknown
<220> FEATURE:
<223> OTHER INFORMATION: Oligonucleotide

<400> SEQUENCE: 286

gagacccugc ugaacacaau u 21

<210> SEQ ID NO 287
<211> LENGTH: 21
<212> TYPE: RNA
<213> ORGANISM: Unknown
<220> FEATURE:
<223> OTHER INFORMATION: Oligonucleotide

<400> SEQUENCE: 287

ggugaauguc aagacgcugu u 21

<210> SEQ ID NO 288
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<212> TYPE: RNA
<213> ORGANISM: Unknown
<220> FEATURE:
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<400> SEQUENCE: 288

caucacagcc agacccaacu u 21

<210> SEQ ID NO 289
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<212> TYPE: RNA
<213> ORGANISM: Unknown
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cucuuccgau cccaccuacu u 21

<210> SEQ ID NO 290
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<212> TYPE: RNA
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<220> FEATURE:
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<400> SEQUENCE: 290

cucuuccgau cccaccuacu u 21

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<212> TYPE: DNA
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<220> FEATURE:
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<400> SEQUENCE: 291

tcagaccttg tagtaaatgt 20

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<212> TYPE: DNA
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<220> FEATURE:
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<400> SEQUENCE: 292

tcgccgggct ctgcgggggc 20

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<212> TYPE: DNA
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atctcctgga cgatgtacac 20

<210> SEQ ID NO 294
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<212> TYPE: DNA
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<220> FEATURE:
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<400> SEQUENCE: 294

cgggtgcccg tagtccccgc 20

<210> SEQ ID NO 295
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<212> TYPE: DNA
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<400> SEQUENCE: 295

tgaccttctc gtagtgaggg 20

<210> SEQ ID NO 296
<211> LENGTH: 20
<212> TYPE: DNA
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<400> SEQUENCE: 296

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cagaagacgc tgtccgcagt 20

<210> SEQ ID NO 297
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<212> TYPE: DNA
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<220> FEATURE:
<223> OTHER INFORMATION: Oligonucleotide

<400> SEQUENCE: 297

ccttagcggg atgataatgt 20

<210> SEQ ID NO 298
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Unknown
<220> FEATURE:
<223> OTHER INFORMATION: Oligonucleotide

<400> SEQUENCE: 298

cactgggctc tgagccgttg 20

<210> SEQ ID NO 299
<211> LENGTH: 20
<212> TYPE: DNA
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<400> SEQUENCE: 299

ttgttgccgc tgcgcttggg 20

<210> SEQ ID NO 300
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<212> TYPE: DNA
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<400> SEQUENCE: 300

tgtggccagt gtgctgagcg 20

<210> SEQ ID NO 301
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Unknown
<220> FEATURE:
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<400> SEQUENCE: 301

acagcgtggt cgtgtgctgc 20

<210> SEQ ID NO 302
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Unknown
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<400> SEQUENCE: 302

ggcgagtgct tcctgtgtct 20

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<210> SEQ ID NO 303
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Unknown
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<223> OTHER INFORMATION: Oligonucleotide

<400> SEQUENCE: 303

cctccggtac ttcagcaaga 20

<210> SEQ ID NO 304
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Unknown
<220> FEATURE:
<223> OTHER INFORMATION: Oligonucleotide

<400> SEQUENCE: 304

ggaccaccag cgtgatgatg 20

<210> SEQ ID NO 305
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Unknown
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<223> OTHER INFORMATION: Oligonucleotide

<400> SEQUENCE: 305

atgacgatga agatgatgca 20

<210> SEQ ID NO 306
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Unknown
<220> FEATURE:
<223> OTHER INFORMATION: Oligonucleotide

<400> SEQUENCE: 306

tcctgaagca atccctgcaa 20

<210> SEQ ID NO 307
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<212> TYPE: DNA
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<400> SEQUENCE: 307

ataaggccac ttcggaaccg 20

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aggatgttgt tccccgaatg 20

<210> SEQ ID NO 309
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<212> TYPE: DNA
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<220> FEATURE:
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<400> SEQUENCE: 309

tccggcgctg ttgccgtctg 20

<210> SEQ ID NO 310
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Unknown
<220> FEATURE:
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<400> SEQUENCE: 310

tgctagaacc tggatttggt 20

<210> SEQ ID NO 311
<211> LENGTH: 20
<212> TYPE: DNA
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<220> FEATURE:
<223> OTHER INFORMATION: Oligonucleotide

<400> SEQUENCE: 311

tttacaaagg gacttgttgt 20

<210> SEQ ID NO 312
<211> LENGTH: 20
<212> TYPE: DNA
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<220> FEATURE:
<223> OTHER INFORMATION: Oligonucleotide

<400> SEQUENCE: 312

cgaacttctt ccatttgtac 20

<210> SEQ ID NO 313
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Unknown
<220> FEATURE:
<223> OTHER INFORMATION: Oligonucleotide

<400> SEQUENCE: 313

cagcttctag ttctggacgt 20

<210> SEQ ID NO 314
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Unknown
<220> FEATURE:
<223> OTHER INFORMATION: Oligonucleotide

<400> SEQUENCE: 314

cttgttggat ctttattcct 20

<210> SEQ ID NO 315
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Unknown
<220> FEATURE:
<223> OTHER INFORMATION: Oligonucleotide

<400> SEQUENCE: 315

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ggttgatcca gcagaacttg 20

<210> SEQ ID NO 316
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Unknown
<220> FEATURE:
<223> OTHER INFORMATION: Oligonucleotide

<400> SEQUENCE: 316

catcttgtcc aactttcatg 20

<210> SEQ ID NO 317
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Unknown
<220> FEATURE:
<223> OTHER INFORMATION: Oligonucleotide

<400> SEQUENCE: 317

aggatcttca tggctcttgt 20

<210> SEQ ID NO 318
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Unknown
<220> FEATURE:
<223> OTHER INFORMATION: Oligonucleotide

<400> SEQUENCE: 318

ctggcacacc cctccctcct 20

<210> SEQ ID NO 319
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Unknown
<220> FEATURE:
<223> OTHER INFORMATION: Oligonucleotide

<400> SEQUENCE: 319

ggttatccag gccctccaaa 20

<210> SEQ ID NO 320
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Unknown
<220> FEATURE:
<223> OTHER INFORMATION: Oligonucleotide

<400> SEQUENCE: 320

gacccatttg atgtagatat 20

<210> SEQ ID NO 321
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Unknown
<220> FEATURE:
<223> OTHER INFORMATION: Oligonucleotide

<400> SEQUENCE: 321

aatgtaataa tctttgttct 20

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<210> SEQ ID NO 322
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Unknown
<220> FEATURE:
<223> OTHER INFORMATION: Oligonucleotide

<400> SEQUENCE: 322

tctgaaattc tagaccccag 20

<210> SEQ ID NO 323
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Unknown
<220> FEATURE:
<223> OTHER INFORMATION: Oligonucleotide

<400> SEQUENCE: 323

aggttagggc tgaattcttg 20

<210> SEQ ID NO 324
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Unknown
<220> FEATURE:
<223> OTHER INFORMATION: Oligonucleotide

<400> SEQUENCE: 324

aaacttgatg gtgaatttga 20

<210> SEQ ID NO 325
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Unknown
<220> FEATURE:
<223> OTHER INFORMATION: Oligonucleotide

<400> SEQUENCE: 325

tatcttggtc tggtttggca 20

<210> SEQ ID NO 326
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Unknown
<220> FEATURE:
<223> OTHER INFORMATION: Oligonucleotide

<400> SEQUENCE: 326

cagttgagga gaggggtatt 20

<210> SEQ ID NO 327
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Unknown
<220> FEATURE:
<223> OTHER INFORMATION: Oligonucleotide

<400> SEQUENCE: 327

ttccttctta atagtgcatc 20

<210> SEQ ID NO 328
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Unknown

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<220> FEATURE:
<223> OTHER INFORMATION: Oligonucleotide

<400> SEQUENCE: 328

tgtctgcttg gtctttatca 20

<210> SEQ ID NO 329
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Unknown
<220> FEATURE:
<223> OTHER INFORMATION: Oligonucleotide

<400> SEQUENCE: 329

accatataaa ctttataata 20

<210> SEQ ID NO 330
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Unknown
<220> FEATURE:
<223> OTHER INFORMATION: Oligonucleotide

<400> SEQUENCE: 330

ttcatactgg ccaacagttt 20

<210> SEQ ID NO 331
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Unknown
<220> FEATURE:
<223> OTHER INFORMATION: Oligonucleotide

<400> SEQUENCE: 331

tagagtccac tttggggcaa 20

<210> SEQ ID NO 332
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Unknown
<220> FEATURE:
<223> OTHER INFORMATION: Oligonucleotide

<400> SEQUENCE: 332

ataatatcca atttgtctcc 20

<210> SEQ ID NO 333
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Unknown
<220> FEATURE:
<223> OTHER INFORMATION: Oligonucleotide

<400> SEQUENCE: 333

tatctgtggg tatagtacca 20

<210> SEQ ID NO 334
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Unknown
<220> FEATURE:
<223> OTHER INFORMATION: Oligonucleotide

<400> SEQUENCE: 334

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gtccttgtcc aggtagaaat 20

<210> SEQ ID NO 335
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Unknown
<220> FEATURE:
<223> OTHER INFORMATION: Oligonucleotide

<400> SEQUENCE: 335

ttggagttcg aggaattcca 20

<210> SEQ ID NO 336
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Unknown
<220> FEATURE:
<223> OTHER INFORMATION: Oligonucleotide

<400> SEQUENCE: 336

atagataggc tctaaaacta 20

<210> SEQ ID NO 337
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Unknown
<220> FEATURE:
<223> OTHER INFORMATION: Oligonucleotide

<400> SEQUENCE: 337

tcgatttgga aatcgcagtt 20

<210> SEQ ID NO 338
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Unknown
<220> FEATURE:
<223> OTHER INFORMATION: Oligonucleotide

<400> SEQUENCE: 338

ctgcataaaa ccatcaaaac 20

<210> SEQ ID NO 339
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Unknown
<220> FEATURE:
<223> OTHER INFORMATION: Oligonucleotide

<400> SEQUENCE: 339

accccagcag tacttccaca 20

<210> SEQ ID NO 340
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Unknown
<220> FEATURE:
<223> OTHER INFORMATION: Oligonucleotide

<400> SEQUENCE: 340

cggagtccct tctcacagcc 20

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<210> SEQ ID NO 341
<211> LENGTH: 20
<212> TYPE: DNA
<213> ORGANISM: Unknown
<220> FEATURE:
<223> OTHER INFORMATION: Oligonucleotide

<400> SEQUENCE: 341

gagtcccttc tcacagccat 20

<210> SEQ ID NO 342
<211> LENGTH: 21
<212> TYPE: DNA
<213> ORGANISM: Unknown
<220> FEATURE:
<223> OTHER INFORMATION: Oligonucleotide

<400> SEQUENCE: 342

aactgcgatt tccaaatcga t 21

<210> SEQ ID NO 343
<211> LENGTH: 21
<212> TYPE: DNA
<213> ORGANISM: Unknown
<220> FEATURE:
<223> OTHER INFORMATION: Oligonucleotide

<400> SEQUENCE: 343

aactccaaat ttctacctgg a 21

<210> SEQ ID NO 344
<211> LENGTH: 21
<212> TYPE: DNA
<213> ORGANISM: Unknown
<220> FEATURE:
<223> OTHER INFORMATION: Oligonucleotide

<400> SEQUENCE: 344

aatttctacc tggacaagga c 21

<210> SEQ ID NO 345
<211> LENGTH: 21
<212> TYPE: DNA
<213> ORGANISM: Unknown
<220> FEATURE:
<223> OTHER INFORMATION: Oligonucleotide

<400> SEQUENCE: 345

aaatttctac ctggacaagg a 21

<210> SEQ ID NO 346
<211> LENGTH: 21
<212> TYPE: DNA
<213> ORGANISM: Unknown
<220> FEATURE:
<223> OTHER INFORMATION: Oligonucleotide

<400> SEQUENCE: 346

aaggactggt actataccca c 21

<210> SEQ ID NO 347
<211> LENGTH: 21
<212> TYPE: DNA
<213> ORGANISM: Unknown

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<220> FEATURE:
<223> OTHER INFORMATION: Oligonucleotide

<400> SEQUENCE: 347

aagtggactc taaaactgtt g 21

<210> SEQ ID NO 348
<211> LENGTH: 21
<212> TYPE: DNA
<213> ORGANISM: Unknown
<220> FEATURE:
<223> OTHER INFORMATION: Oligonucleotide

<400> SEQUENCE: 348

aaactgttgg ccagtatgaa t 21

<210> SEQ ID NO 349
<211> LENGTH: 21
<212> TYPE: DNA
<213> ORGANISM: Unknown
<220> FEATURE:
<223> OTHER INFORMATION: Oligonucleotide

<400> SEQUENCE: 349

aaaactgttg gccagtatga a 21

<210> SEQ ID NO 350
<211> LENGTH: 21
<212> TYPE: DNA
<213> ORGANISM: Unknown
<220> FEATURE:
<223> OTHER INFORMATION: Oligonucleotide

<400> SEQUENCE: 350

aagaccaagc agacagatgc a 21

<210> SEQ ID NO 351
<211> LENGTH: 21
<212> TYPE: DNA
<213> ORGANISM: Unknown
<220> FEATURE:
<223> OTHER INFORMATION: Oligonucleotide

<400> SEQUENCE: 351

aaagaccaag cagacagatg c 21

<210> SEQ ID NO 352
<211> LENGTH: 21
<212> TYPE: DNA
<213> ORGANISM: Unknown
<220> FEATURE:
<223> OTHER INFORMATION: Oligonucleotide

<400> SEQUENCE: 352

aagtttcaag aattcagccc t 21

<210> SEQ ID NO 353
<211> LENGTH: 21
<212> TYPE: DNA
<213> ORGANISM: Unknown
<220> FEATURE:
<223> OTHER INFORMATION: Oligonucleotide

<400> SEQUENCE: 353

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aagaattcag ccctaacctc t 21

<210> SEQ ID NO 354
<211> LENGTH: 21
<212> TYPE: DNA
<213> ORGANISM: Unknown
<220> FEATURE:
<223> OTHER INFORMATION: Oligonucleotide

<400> SEQUENCE: 354

aattcagccc taacctctgg g 21

<210> SEQ ID NO 355
<211> LENGTH: 21
<212> TYPE: DNA
<213> ORGANISM: Unknown
<220> FEATURE:
<223> OTHER INFORMATION: Oligonucleotide

<400> SEQUENCE: 355

aactgtgcca aaccagacca a 21

<210> SEQ ID NO 356
<211> LENGTH: 21
<212> TYPE: DNA
<213> ORGANISM: Unknown
<220> FEATURE:
<223> OTHER INFORMATION: Oligonucleotide

<400> SEQUENCE: 356

aaatgggtct ttggagggcc t 21

<210> SEQ ID NO 357
<211> LENGTH: 21
<212> TYPE: DNA
<213> ORGANISM: Unknown
<220> FEATURE:
<223> OTHER INFORMATION: Oligonucleotide

<400> SEQUENCE: 357

aagatcctca tgaaagttgg a 21

<210> SEQ ID NO 358
<211> LENGTH: 21
<212> TYPE: DNA
<213> ORGANISM: Unknown
<220> FEATURE:
<223> OTHER INFORMATION: Oligonucleotide

<400> SEQUENCE: 358

aaagttggac aagatgcaag t 21

<210> SEQ ID NO 359
<211> LENGTH: 21
<212> TYPE: DNA
<213> ORGANISM: Unknown
<220> FEATURE:
<223> OTHER INFORMATION: Oligonucleotide

<400> SEQUENCE: 359

aagagccatg aagatcctca t 21

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<210> SEQ ID NO 360
<211> LENGTH: 21
<212> TYPE: DNA
<213> ORGANISM: Unknown
<220> FEATURE:
<223> OTHER INFORMATION: Oligonucleotide

<400> SEQUENCE: 360

aagttggaca agatgcaagt t 21

<210> SEQ ID NO 361
<211> LENGTH: 21
<212> TYPE: DNA
<213> ORGANISM: Unknown
<220> FEATURE:
<223> OTHER INFORMATION: Oligonucleotide

<400> SEQUENCE: 361

aagatgcaag ttctgctgga t 21

<210> SEQ ID NO 362
<211> LENGTH: 21
<212> TYPE: DNA
<213> ORGANISM: Unknown
<220> FEATURE:
<223> OTHER INFORMATION: Oligonucleotide

<400> SEQUENCE: 362

aagttctgct ggatcaacca g 21

<210> SEQ ID NO 363
<211> LENGTH: 21
<212> TYPE: DNA
<213> ORGANISM: Unknown
<220> FEATURE:
<223> OTHER INFORMATION: Oligonucleotide

<400> SEQUENCE: 363

aaccaggaat aaagatccaa c 21

<210> SEQ ID NO 364
<211> LENGTH: 21
<212> TYPE: DNA
<213> ORGANISM: Unknown
<220> FEATURE:
<223> OTHER INFORMATION: Oligonucleotide

<400> SEQUENCE: 364

aaagatccaa caagacgtcc a 21

<210> SEQ ID NO 365
<211> LENGTH: 21
<212> TYPE: DNA
<213> ORGANISM: Unknown
<220> FEATURE:
<223> OTHER INFORMATION: Oligonucleotide

<400> SEQUENCE: 365

aagatccaac aagacgtcca g 21

<210> SEQ ID NO 366
<211> LENGTH: 21
<212> TYPE: DNA
<213> ORGANISM: Unknown

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<220> FEATURE:
<223> OTHER INFORMATION: Oligonucleotide

<400> SEQUENCE: 366

aacaagacgt ccagaactag a 21

<210> SEQ ID NO 367
<211> LENGTH: 21
<212> TYPE: DNA
<213> ORGANISM: Unknown
<220> FEATURE:
<223> OTHER INFORMATION: Oligonucleotide

<400> SEQUENCE: 367

aagacgtcca gaactagaag c 21

<210> SEQ ID NO 368
<211> LENGTH: 21
<212> TYPE: DNA
<213> ORGANISM: Unknown
<220> FEATURE:
<223> OTHER INFORMATION: Oligonucleotide

<400> SEQUENCE: 368

aaatggaaga agttcgacaa c 21

<210> SEQ ID NO 369
<211> LENGTH: 21
<212> TYPE: DNA
<213> ORGANISM: Unknown
<220> FEATURE:
<223> OTHER INFORMATION: Oligonucleotide

<400> SEQUENCE: 369

aactagaagc tggtacaaat g 21

<210> SEQ ID NO 370
<211> LENGTH: 21
<212> TYPE: DNA
<213> ORGANISM: Unknown
<220> FEATURE:
<223> OTHER INFORMATION: Oligonucleotide

<400> SEQUENCE: 370

aatggaagaa gttcgacaac a 21

<210> SEQ ID NO 371
<211> LENGTH: 21
<212> TYPE: DNA
<213> ORGANISM: Unknown
<220> FEATURE:
<223> OTHER INFORMATION: Oligonucleotide

<400> SEQUENCE: 371

aagctggtac aaatggaaga a 21

<210> SEQ ID NO 372
<211> LENGTH: 21
<212> TYPE: DNA
<213> ORGANISM: Unknown
<220> FEATURE:
<223> OTHER INFORMATION: Oligonucleotide

<400> SEQUENCE: 372

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aacaagtccc tttgtaaaac c 21

<210> SEQ ID NO 373
<211> LENGTH: 21
<212> TYPE: DNA
<213> ORGANISM: Unknown
<220> FEATURE:
<223> OTHER INFORMATION: Oligonucleotide

<400> SEQUENCE: 373

aagaagttcg acaacaagtc c 21

<210> SEQ ID NO 374
<211> LENGTH: 21
<212> TYPE: DNA
<213> ORGANISM: Unknown
<220> FEATURE:
<223> OTHER INFORMATION: Oligonucleotide

<400> SEQUENCE: 374

aagttcgaca acaagtccct t 21

<210> SEQ ID NO 375
<211> LENGTH: 21
<212> TYPE: DNA
<213> ORGANISM: Unknown
<220> FEATURE:
<223> OTHER INFORMATION: Oligonucleotide

<400> SEQUENCE: 375

aaaaccaaat ccaggttcta g 21

<210> SEQ ID NO 376
<211> LENGTH: 21
<212> TYPE: DNA
<213> ORGANISM: Unknown
<220> FEATURE:
<223> OTHER INFORMATION: Oligonucleotide

<400> SEQUENCE: 376

aaaccaaatc caggttctag c 21

<210> SEQ ID NO 377
<211> LENGTH: 21
<212> TYPE: DNA
<213> ORGANISM: Unknown
<220> FEATURE:
<223> OTHER INFORMATION: Oligonucleotide

<400> SEQUENCE: 377

aaccaaatcc aggttctagc a 21

<210> SEQ ID NO 378
<211> LENGTH: 21
<212> TYPE: DNA
<213> ORGANISM: Unknown
<220> FEATURE:
<223> OTHER INFORMATION: Oligonucleotide

<400> SEQUENCE: 378

aaatccaggt tctagcacag a 21

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<210> SEQ ID NO 379
<211> LENGTH: 21
<212> TYPE: DNA
<213> ORGANISM: Unknown
<220> FEATURE:
<223> OTHER INFORMATION: Oligonucleotide

<400> SEQUENCE: 379

aatccaggtt ctagcacaga c 21

<210> SEQ ID NO 380
<211> LENGTH: 21
<212> TYPE: DNA
<213> ORGANISM: Unknown
<220> FEATURE:
<223> OTHER INFORMATION: Oligonucleotide

<400> SEQUENCE: 380

aacaacatcc tcggttccga a 21

<210> SEQ ID NO 381
<211> LENGTH: 21
<212> TYPE: DNA
<213> ORGANISM: Unknown
<220> FEATURE:
<223> OTHER INFORMATION: Oligonucleotide

<400> SEQUENCE: 381

aacatcctcg gttccgaagt g 21

<210> SEQ ID NO 382
<211> LENGTH: 21
<212> TYPE: DNA
<213> ORGANISM: Unknown
<220> FEATURE:
<223> OTHER INFORMATION: Oligonucleotide

<400> SEQUENCE: 382

aagtggcctt atttgcaggg a 21

<210> SEQ ID NO 383
<211> LENGTH: 21
<212> TYPE: RNA
<213> ORGANISM: Unknown
<220> FEATURE:
<223> OTHER INFORMATION: Oligonucleotide

<400> SEQUENCE: 383

gcagacagau gcacuauuau u 21

<210> SEQ ID NO 384
<211> LENGTH: 21
<212> TYPE: RNA
<213> ORGANISM: Unknown
<220> FEATURE:
<223> OTHER INFORMATION: Oligonucleotide

<400> SEQUENCE: 384

cugcgauuuc caaaucgauu u 21

<210> SEQ ID NO 385
<211> LENGTH: 21
<212> TYPE: RNA
<213> ORGANISM: Unknown

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<220> FEATURE:
<223> OTHER INFORMATION: Oligonucleotide

<400> SEQUENCE: 385

ggacugguac uauacccacu u                                              21


<210> SEQ ID NO 386
<211> LENGTH: 570
<212> TYPE: PRT
<213> ORGANISM: Unknown
<220> FEATURE:
<223> OTHER INFORMATION: Recombinant B4ECv3 protein

<400> SEQUENCE: 386

Met Glu Leu Arg Val Leu Leu Cys Trp Ala Ser Leu Ala Ala Ala Leu
1               5                   10                  15

Glu Glu Thr Leu Leu Asn Thr Lys Leu Glu Thr Ala Asp Leu Lys Trp
            20                  25                  30

Val Thr Phe Pro Gln Val Asp Gly Gln Trp Glu Glu Leu Ser Gly Leu
        35                  40                  45

Asp Glu Glu Gln His Ser Val Arg Thr Tyr Glu Val Cys Glu Val Gln
    50                  55                  60

Arg Ala Pro Gly Gln Ala His Trp Leu Arg Thr Gly Trp Val Pro Arg
65                  70                  75                  80

Arg Gly Ala Val His Val Tyr Ala Thr Leu Arg Phe Thr Met Leu Glu
                85                  90                  95

Cys Leu Ser Leu Pro Arg Ala Gly Arg Ser Cys Lys Glu Thr Phe Thr
            100                 105                 110

Val Phe Tyr Tyr Glu Ser Asp Ala Asp Thr Ala Thr Ala Leu Thr Pro
        115                 120                 125

Ala Trp Met Glu Asn Pro Tyr Ile Lys Val Asp Thr Val Ala Ala Glu
    130                 135                 140

His Leu Thr Arg Lys Arg Pro Gly Ala Glu Ala Thr Gly Lys Val Asn
145                 150                 155                 160

Val Lys Thr Leu Arg Leu Gly Pro Leu Ser Lys Ala Gly Phe Tyr Leu
                165                 170                 175

Ala Phe Gln Asp Gln Gly Ala Cys Met Ala Leu Leu Ser Leu His Leu
            180                 185                 190

Phe Tyr Lys Lys Cys Ala Gln Leu Thr Val Asn Leu Thr Arg Phe Pro
        195                 200                 205

Glu Thr Val Pro Arg Glu Leu Val Val Pro Val Ala Gly Ser Cys Val
    210                 215                 220

Val Asp Ala Val Pro Ala Pro Gly Pro Ser Pro Ser Leu Tyr Cys Arg
225                 230                 235                 240

Glu Asp Gly Gln Trp Ala Glu Gln Pro Val Thr Gly Cys Ser Cys Ala
                245                 250                 255

Pro Gly Phe Glu Ala Ala Glu Gly Asn Thr Lys Cys Arg Ala Cys Ala
            260                 265                 270

Gln Gly Thr Phe Lys Pro Leu Ser Gly Glu Gly Ser Cys Gln Pro Cys
        275                 280                 285

Pro Ala Asn Ser His Ser Asn Thr Ile Gly Ser Ala Val Cys Gln Cys
    290                 295                 300

Arg Val Gly Tyr Phe Arg Ala Arg Thr Asp Pro Arg Gly Ala Pro Cys
305                 310                 315                 320
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Thr Thr Pro Pro Ser Ala Pro Arg Ser Val Val Ser Arg Leu Asn Gly
                325                 330                 335

Ser Ser Leu His Leu Glu Trp Ser Ala Pro Leu Glu Ser Gly Gly Arg
            340                 345                 350

Glu Asp Leu Thr Tyr Ala Leu Arg Cys Arg Glu Cys Arg Pro Gly Gly
        355                 360                 365

Ser Cys Ala Pro Cys Gly Gly Asp Leu Thr Phe Asp Pro Gly Pro Arg
    370                 375                 380

Asp Leu Val Glu Pro Trp Val Val Val Arg Gly Leu Arg Pro Asp Phe
385                 390                 395                 400

Thr Tyr Thr Phe Glu Val Thr Ala Leu Asn Gly Val Ser Ser Leu Ala
                405                 410                 415

Thr Gly Pro Val Pro Phe Glu Pro Val Asn Val Thr Thr Asp Arg Glu
            420                 425                 430

Val Pro Pro Ala Val Ser Asp Ile Arg Val Thr Arg Ser Ser Pro Ser
        435                 440                 445

Ser Leu Ser Leu Ala Trp Ala Val Pro Arg Ala Pro Ser Gly Ala Trp
    450                 455                 460

Leu Asp Tyr Glu Val Lys Tyr His Glu Lys Gly Ala Glu Gly Pro Ser
465                 470                 475                 480

Ser Val Arg Phe Leu Lys Thr Ser Glu Asn Arg Ala Glu Leu Arg Gly
                485                 490                 495

Leu Lys Arg Gly Ala Ser Tyr Leu Val Gln Val Arg Ala Arg Ser Glu
            500                 505                 510

Ala Gly Tyr Gly Pro Phe Gly Gln Glu His His Ser Gln Thr Gln Leu
        515                 520                 525

Asp Glu Ser Glu Gly Trp Arg Glu Gln Gly Ser Lys Arg Ala Ile Leu
    530                 535                 540

Gln Ile Glu Gly Lys Pro Ile Pro Asn Pro Leu Leu Gly Leu Asp Ser
545                 550                 555                 560

Thr Arg Thr Gly His His His His His His
                565                 570


<210> SEQ ID NO 387
<211> LENGTH: 555
<212> TYPE: PRT
<213> ORGANISM: Unknown
<220> FEATURE:
<223> OTHER INFORMATION: Recombinant B4ECv3NT protein

<400> SEQUENCE: 387

Met Glu Leu Arg Val Leu Leu Cys Trp Ala Ser Leu Ala Ala Ala Leu
1               5                   10                  15

Glu Glu Thr Leu Leu Asn Thr Lys Leu Glu Thr Ala Asp Leu Lys Trp
            20                  25                  30

Val Thr Phe Pro Gln Val Asp Gly Gln Trp Glu Glu Leu Ser Gly Leu
        35                  40                  45

Asp Glu Glu Gln His Ser Val Arg Thr Tyr Glu Val Cys Glu Val Gln
    50                  55                  60

Arg Ala Pro Gly Gln Ala His Trp Leu Arg Thr Gly Trp Val Pro Arg
65                  70                  75                  80

Arg Gly Ala Val His Val Tyr Ala Thr Leu Arg Phe Thr Met Leu Glu
                85                  90                  95
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Cys Leu Ser Leu Pro Arg Ala Gly Arg Ser Cys Lys Glu Thr Phe Thr
            100                 105                 110

Val Phe Tyr Tyr Glu Ser Asp Ala Asp Thr Ala Thr Ala Leu Thr Pro
        115                 120                 125

Ala Trp Met Glu Asn Pro Tyr Ile Lys Val Asp Thr Val Ala Ala Glu
    130                 135                 140

His Leu Thr Arg Lys Arg Pro Gly Ala Glu Ala Thr Gly Lys Val Asn
145                 150                 155                 160

Val Lys Thr Leu Arg Leu Gly Pro Leu Ser Lys Ala Gly Phe Tyr Leu
                165                 170                 175

Ala Phe Gln Asp Gln Gly Ala Cys Met Ala Leu Leu Ser Leu His Leu
            180                 185                 190

Phe Tyr Lys Lys Cys Ala Gln Leu Thr Val Asn Leu Thr Arg Phe Pro
        195                 200                 205

Glu Thr Val Pro Arg Glu Leu Val Val Pro Val Ala Gly Ser Cys Val
    210                 215                 220

Val Asp Ala Val Pro Ala Pro Gly Pro Ser Pro Ser Leu Tyr Cys Arg
225                 230                 235                 240

Glu Asp Gly Gln Trp Ala Glu Gln Pro Val Thr Gly Cys Ser Cys Ala
                245                 250                 255

Pro Gly Phe Glu Ala Ala Glu Gly Asn Thr Lys Cys Arg Ala Cys Ala
            260                 265                 270

Gln Gly Thr Phe Lys Pro Leu Ser Gly Glu Gly Ser Cys Gln Pro Cys
        275                 280                 285

Pro Ala Asn Ser His Ser Asn Thr Ile Gly Ser Ala Val Cys Gln Cys
    290                 295                 300

Arg Val Gly Tyr Phe Arg Ala Arg Thr Asp Pro Arg Gly Ala Pro Cys
305                 310                 315                 320

Thr Thr Pro Pro Ser Ala Pro Arg Ser Val Val Ser Arg Leu Asn Gly
                325                 330                 335

Ser Ser Leu His Leu Glu Trp Ser Ala Pro Leu Glu Ser Gly Gly Arg
            340                 345                 350

Glu Asp Leu Thr Tyr Ala Leu Arg Cys Arg Glu Cys Arg Pro Gly Gly
        355                 360                 365

Ser Cys Ala Pro Cys Gly Gly Asp Leu Thr Phe Asp Pro Gly Pro Arg
    370                 375                 380

Asp Leu Val Glu Pro Trp Val Val Val Arg Gly Leu Arg Pro Asp Phe
385                 390                 395                 400

Thr Tyr Thr Phe Glu Val Thr Ala Leu Asn Gly Val Ser Ser Leu Ala
                405                 410                 415

Thr Gly Pro Val Pro Phe Glu Pro Val Asn Val Thr Thr Asp Arg Glu
            420                 425                 430

Val Pro Pro Ala Val Ser Asp Ile Arg Val Thr Arg Ser Ser Pro Ser
        435                 440                 445

Ser Leu Ser Leu Ala Trp Ala Val Pro Arg Ala Pro Ser Gly Ala Trp
    450                 455                 460

Leu Asp Tyr Glu Val Lys Tyr His Glu Lys Gly Ala Glu Gly Pro Ser
465                 470                 475                 480

Ser Val Arg Phe Leu Lys Thr Ser Glu Asn Arg Ala Glu Leu Arg Gly
                485                 490                 495
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Leu Lys Arg Gly Ala Ser Tyr Leu Val Gln Val Arg Ala Arg Ser Glu
            500                 505                 510

Ala Gly Tyr Gly Pro Phe Gly Gln Glu His His Ser Gln Thr Gln Leu
        515                 520                 525

Asp Glu Ser Glu Gly Trp Arg Glu Gln Gly Ser Lys Arg Ala Ile Leu
    530                 535                 540

Gln Ile Ser Ser Thr Val Ala Ala Ala Arg Val
545                 550                 555


<210> SEQ ID NO 388
<211> LENGTH: 233
<212> TYPE: PRT
<213> ORGANISM: Unknown
<220> FEATURE:
<223> OTHER INFORMATION: Recombinant B2EC protein

<400> SEQUENCE: 388

Met Ala Val Arg Arg Asp Ser Val Trp Lys Tyr Cys Trp Gly Val Leu
1               5                   10                  15

Met Val Leu Cys Arg Thr Ala Ile Ser Lys Ser Ile Val Leu Glu Pro
            20                  25                  30

Ile Tyr Trp Asn Ser Ser Asn Ser Lys Phe Leu Pro Gly Gln Gly Leu
        35                  40                  45

Val Leu Tyr Pro Gln Ile Gly Asp Lys Leu Asp Ile Ile Cys Pro Lys
    50                  55                  60

Val Asp Ser Lys Thr Val Gly Gln Tyr Glu Tyr Tyr Lys Val Tyr Met
65                  70                  75                  80

Val Asp Lys Asp Gln Ala Asp Arg Cys Thr Ile Lys Lys Glu Asn Thr
                85                  90                  95

Pro Leu Leu Asn Cys Ala Lys Pro Asp Gln Asp Ile Lys Phe Thr Ile
            100                 105                 110

Lys Phe Gln Glu Phe Ser Pro Asn Leu Trp Gly Leu Glu Phe Gln Lys
        115                 120                 125

Asn Lys Asp Tyr Tyr Ile Ile Ser Thr Ser Asn Gly Ser Leu Glu Gly
    130                 135                 140

Leu Asp Asn Gln Glu Gly Gly Val Cys Gln Thr Arg Ala Met Lys Ile
145                 150                 155                 160

Leu Met Lys Val Gly Gln Asp Ala Ser Ser Ala Gly Ser Thr Arg Asn
                165                 170                 175

Lys Asp Pro Thr Arg Arg Pro Glu Leu Glu Ala Gly Thr Asn Gly Arg
            180                 185                 190

Ser Ser Thr Thr Ser Pro Phe Val Lys Pro Asn Pro Gly Ser Ser Thr
        195                 200                 205

Asp Gly Asn Ser Ala Gly His Ser Gly Asn Asn Ile Leu Gly Ser Glu
    210                 215                 220

Val Gly Ser His His His His His His
225                 230


<210> SEQ ID NO 389
<211> LENGTH: 771
<212> TYPE: PRT
<213> ORGANISM: Unknown
<220> FEATURE:
<223> OTHER INFORMATION: Recombinant B4ECv3-FC protein

<400> SEQUENCE: 389
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Met Glu Leu Arg Val Leu Leu Cys Trp Ala Ser Leu Ala Ala Ala Leu
1               5                   10                  15

Glu Glu Thr Leu Leu Asn Thr Lys Leu Glu Thr Ala Asp Leu Lys Trp
            20                  25                  30

Val Thr Phe Pro Gln Val Asp Gly Gln Trp Glu Glu Leu Ser Gly Leu
        35                  40                  45

Asp Glu Glu Gln His Ser Val Arg Thr Tyr Glu Val Cys Glu Val Gln
    50                  55                  60

Arg Ala Pro Gly Gln Ala His Trp Leu Arg Thr Gly Trp Val Pro Arg
65                  70                  75                  80

Arg Gly Ala Val His Val Tyr Ala Thr Leu Arg Phe Thr Met Leu Glu
                85                  90                  95

Cys Leu Ser Leu Pro Arg Ala Gly Arg Ser Cys Lys Glu Thr Phe Thr
            100                 105                 110

Val Phe Tyr Tyr Glu Ser Asp Ala Asp Thr Ala Thr Ala Leu Thr Pro
        115                 120                 125

Ala Trp Met Glu Asn Pro Tyr Ile Lys Val Asp Thr Val Ala Ala Glu
    130                 135                 140

His Leu Thr Arg Lys Arg Pro Gly Ala Glu Ala Thr Gly Lys Val Asn
145                 150                 155                 160

Val Lys Thr Leu Arg Leu Gly Pro Leu Ser Lys Ala Gly Phe Tyr Leu
                165                 170                 175

Ala Phe Gln Asp Gln Gly Ala Cys Met Ala Leu Leu Ser Leu His Leu
            180                 185                 190

Phe Tyr Lys Lys Cys Ala Gln Leu Thr Val Asn Leu Thr Arg Phe Pro
        195                 200                 205

Glu Thr Val Pro Arg Glu Leu Val Val Pro Val Ala Gly Ser Cys Val
    210                 215                 220

Val Asp Ala Val Pro Ala Pro Gly Pro Ser Pro Ser Leu Tyr Cys Arg
225                 230                 235                 240

Glu Asp Gly Gln Trp Ala Glu Gln Pro Val Thr Gly Cys Ser Cys Ala
                245                 250                 255

Pro Gly Phe Glu Ala Ala Glu Gly Asn Thr Lys Cys Arg Ala Cys Ala
            260                 265                 270

Gln Gly Thr Phe Lys Pro Leu Ser Gly Glu Gly Ser Cys Gln Pro Cys
        275                 280                 285

Pro Ala Asn Ser His Ser Asn Thr Ile Gly Ser Ala Val Cys Gln Cys
    290                 295                 300

Arg Val Gly Tyr Phe Arg Ala Arg Thr Asp Pro Arg Gly Ala Pro Cys
305                 310                 315                 320

Thr Thr Pro Pro Ser Ala Pro Arg Ser Val Val Ser Arg Leu Asn Gly
                325                 330                 335

Ser Ser Leu His Leu Glu Trp Ser Ala Pro Leu Glu Ser Gly Gly Arg
            340                 345                 350

Glu Asp Leu Thr Tyr Ala Leu Arg Cys Arg Glu Cys Arg Pro Gly Gly
        355                 360                 365

Ser Cys Ala Pro Cys Gly Gly Asp Leu Thr Phe Asp Pro Gly Pro Arg
    370                 375                 380

Asp Leu Val Glu Pro Trp Val Val Val Arg Gly Leu Arg Pro Asp Phe
385                 390                 395                 400
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Thr Tyr Thr Phe Glu Val Thr Ala Leu Asn Gly Val Ser Ser Leu Ala
                405                 410                 415

Thr Gly Pro Val Pro Phe Glu Pro Val Asn Val Thr Thr Asp Arg Glu
            420                 425                 430

Val Pro Pro Ala Val Ser Asp Ile Arg Val Thr Arg Ser Ser Pro Ser
        435                 440                 445

Ser Leu Ser Leu Ala Trp Ala Val Pro Arg Ala Pro Ser Gly Ala Trp
    450                 455                 460

Leu Asp Tyr Glu Val Lys Tyr His Glu Lys Gly Ala Glu Gly Pro Ser
465                 470                 475                 480

Ser Val Arg Phe Leu Lys Thr Ser Glu Asn Arg Ala Glu Leu Arg Gly
                485                 490                 495

Leu Lys Arg Gly Ala Ser Tyr Leu Val Gln Val Arg Ala Arg Ser Glu
            500                 505                 510

Ala Gly Tyr Gly Pro Phe Gly Gln Glu His His Ser Gln Thr Gln Leu
        515                 520                 525

Asp Glu Ser Glu Gly Trp Arg Glu Gln Asp Pro Glu Pro Lys Ser Cys
    530                 535                 540

Asp Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Leu Leu Gly
545                 550                 555                 560

Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met
                565                 570                 575

Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser His
            580                 585                 590

Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val
        595                 600                 605

His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr
    610                 615                 620

Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly
625                 630                 635                 640

Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile
                645                 650                 655

Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val
            660                 665                 670

Tyr Thr Leu Pro Pro Ser Arg Asp Glu Leu Thr Lys Asn Gln Val Ser
        675                 680                 685

Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu
    690                 695                 700

Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro
705                 710                 715                 720

Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val
                725                 730                 735

Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met
            740                 745                 750

His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser
        755                 760                 765

Pro Gly Lys
    770

<210> SEQ ID NO 390
<211> LENGTH: 459
<212> TYPE: PRT
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<213> ORGANISM: Unknown
<220> FEATURE:
<223> OTHER INFORMATION: Recombinant B2EC-FC protein

<400> SEQUENCE: 390

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Met Ala Val Arg Arg Asp Ser Val Trp Lys Tyr Cys Trp Gly Val Leu
1               5                   10                  15

Met Val Leu Cys Arg Thr Ala Ile Ser Lys Ser Ile Val Leu Glu Pro
            20                  25                  30

Ile Tyr Trp Asn Ser Ser Asn Ser Lys Phe Leu Pro Gly Gln Gly Leu
        35                  40                  45

Val Leu Tyr Pro Gln Ile Gly Asp Lys Leu Asp Ile Ile Cys Pro Lys
    50                  55                  60

Val Asp Ser Lys Thr Val Gly Gln Tyr Glu Tyr Tyr Lys Val Tyr Met
65                  70                  75                  80

Val Asp Lys Asp Gln Ala Asp Arg Cys Thr Ile Lys Lys Glu Asn Thr
                85                  90                  95

Pro Leu Leu Asn Cys Ala Lys Pro Asp Gln Asp Ile Lys Phe Thr Ile
            100                 105                 110

Lys Phe Gln Glu Phe Ser Pro Asn Leu Trp Gly Leu Glu Phe Gln Lys
        115                 120                 125

Asn Lys Asp Tyr Tyr Ile Ile Ser Thr Ser Asn Gly Ser Leu Glu Gly
    130                 135                 140

Leu Asp Asn Gln Glu Gly Gly Val Cys Gln Thr Arg Ala Met Lys Ile
145                 150                 155                 160

Leu Met Lys Val Gly Gln Asp Ala Ser Ser Ala Gly Ser Thr Arg Asn
                165                 170                 175

Lys Asp Pro Thr Arg Arg Pro Glu Leu Glu Ala Gly Thr Asn Gly Arg
            180                 185                 190

Ser Ser Thr Thr Ser Pro Phe Val Lys Pro Asn Pro Gly Ser Ser Thr
        195                 200                 205

Asp Gly Asn Ser Ala Gly His Ser Gly Asn Asn Ile Leu Gly Ser Glu
    210                 215                 220

Val Asp Pro Glu Pro Lys Ser Cys Asp Lys Thr His Thr Cys Pro Pro
225                 230                 235                 240

Cys Pro Ala Pro Glu Leu Leu Gly Gly Pro Ser Val Phe Leu Phe Pro
                245                 250                 255

Pro Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr
            260                 265                 270

Cys Val Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn
        275                 280                 285

Trp Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg
    290                 295                 300

Glu Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val
305                 310                 315                 320

Leu His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser
                325                 330                 335

Asn Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys
            340                 345                 350

Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Asp
        355                 360                 365

Glu Leu Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe
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    370                 375                 380

Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu
385                 390                 395                 400

Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe
                405                 410                 415

Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly
            420                 425                 430

Asn Val Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr
        435                 440                 445

Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly Lys
    450                 455


<210> SEQ ID NO 391
<211> LENGTH: 26000
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 391

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tttctttacc gttgtttcct cgatttttct ctactcccta gcgcagctta gtgcgcgcct    180

cctctggaca tttttcaggg cttggttgcg cgcacagtag gtccccaaca ctgaatgttt    240

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<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 392

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<211> LENGTH: 43948
<212> TYPE: DNA
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catcatatat ttaacaatga caagatgttc cggcgtttat ttctgcgttg ggttttccct 43920

tgccttatgg gctgaagtgt tctctaga 43948

<210> SEQ ID NO 394
<211> LENGTH: 4335
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 394

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ctggggtgtt ttgatggttt tatgcagaac tgcgatttcc aaatcgatag ttttagagcc 120

tatctattgg aattcctcga actccaaatt tctacctgga caaggactgg tactataccc 180

acagatagga gacaaattgg atattatttg ccccaaagtg gactctaaaa ctgttggcca 240

gtatgaatat tataaagttt atatggttga taaagaccaa gcagacagat gcactattaa 300

gaaggaaaat acccctctcc tcaactgtgc caaaccagac caagatatca aattcaccat 360

caagtttcaa gaattcagcc ctaacctctg ggtctagaa tttcagaaga acaaagatta 420

ttacattata tctacatcaa atgggtcttt ggagggcctg gataaccagg agggaggggt 480

gtgccagaca agagccatga agatcctcat gaaagttgga caagatgcaa gttctgctgg 540

atcaaccagg aataaagatc caacaagacg tccagaacta gaagctggta caaatggaag 600

aagttcgaca acaagtccct ttgtaaaacc aaatccaggt tctagcacag acggcaacag 660

cgccggacat tcggggaaca acatcctcgg ttccgaagtg gccttatttg cagggattgc 720

ttcaggatgc atcatcttca tcgtcatcat catcacgctg gtggtcctct tgctgaagta 780

ccggaggaga cacaggaagc actcgccgca gcacacgacc acgctgtcgc tcagcacact 840

ggccacaccc aagcgcagcg gcaacaacaa cggctcagag cccagtgaca ttatcatccc 900

gctaaggact gcggacagcg tcttctgccc tcactacgag aaggtcagcg gggactacgg 960

gcacccggtg tacatcgtcc aggagatgcc cccgcagagc ccggcgaaca tttactacaa 1020

ggtctgagag ggaccctggt ggtacctgtg ctttcccaga ggacacctaa tgtcccgatg 1080

cctcccttga gggtttgaga gcccgcgtgc tggagaattg actgaagcac agcaccgggg 1140

gagagggaca ctcctcctcg gaagagcccg tcgcgctgga cagcttacct agtcttgtag 1200

cattcggcct tggtgaacac acacgctccc tggaagctgg aagactgtgc agaagacgcc 1260

cattcggact gctgtgccgc gtcccacgtc tcctcctcga agccatgtgc tgcggtcact 1320

caggcctctg cagaagccaa gggaagacag tggtttgtgg acgagagggc tgtgagcatc 1380

ctggcaggtg ccccaggatg ccacgcctgg aagggccggc ttctgcctgg ggtgcatttc 1440

ccccgcagtg cataccggac ttgtcacacg gacctcgggc tagttaaggt gtgcaaagat 1500

ctctagagtt tagtccttac tgtctcactc gttctgttac ccagggctct gcagcacctc 1560

acctgagacc tccactccac atctgcatca ctcatggaac actcatgtct ggagtcccct 1620

cctccagccg ctggcaacaa cagcttcagt ccatgggtaa tccgttcata gaaattgtgt 1680

ttgctaacaa ggtgcccttt agccagatgc taggctgtct gcgaagaagg ctaggagttc 1740

atagaaggga gtggggctgg ggaaagggct ggctgcaatt gcagctcact gctgctgcct 1800

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ctgaaacaga aagttggaaa ggaaaaaaga aaaaagcaat taggtagcac agcactttgg   1860
ttttgctgag atcgaagagg ccagtaggag acacgacagc acacacagtg gattccagtg   1920
catggggagg cactcgctgt tatcaaatag cgatgtgcag gaagaaaagc ccctcttcat   1980
tccggggaac aaagacgggt attgttggga aaggaacagg cttggaggga agggagaaag   2040
taggccgctg atgatatatt cgggcaggac tgttgtggta ctggcaataa gatacacagc   2100
tccgagctgt aggagagtcg gtctgctttg gatgattttt taagcagact cagctgctat   2160
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cccctcccga ttgagcctta cgacactttg gtttatgcgg tgctgtccgg gtgccagggc   2400
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tgggttttcc cttgccttat gggctgaagt gttctctaga atccagcagg tcacactggg   2940
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aaatgtagcg acagcatttt aaggttctca gacctccagt gagtacctgc aaaaatgagt   3180
tgtcacagaa attatgatcc tctatttcct gaacctggaa atgatgttgg tccaaagtgc   3240
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gccacagtac atatgtaatt ctttccatca ccccaacctc tcctttctgt gcattcatgc   3420
aagagtttct tgtaagccat cagaagttac ttttaggatg ggggagaggg gcgagaaggg   3480
gaaaaatggg aaatagtctg attttaatga aatcaaatgt atgtatcatc agttggctac   3540
gttttggttc tatgctaaac tgtgaaaaat cagatgaatt gataaaagag ttccctgcaa   3600
ccaattgaaa agtgttctgt gcgtctgttt tgtgtctggt gcagaatatg acaatctacc   3660
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attttgcaat gtatttagct acagcttgtt taacggcagt gtcattcccc tttgcactgt   4020
aatgaggaaa aaatggtata aaaggttgcc aaattgctgc atatttgtgc cgtaattatg   4080
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taccatgaat atttatttaa aatttcgttg tccaatttgt aagtaacaca gtattatgcc   4140

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atctgcttta gtttcacatt gcagttagcc ccagaaaatg aaatccgtga agtcacattc   4260

cacatctgtt tcaaactgaa tttgttctta aaaaaataaa atattttttt cctatggaaa   4320

aaaaaaaaaa aaaaa                                                    4335
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<210> SEQ ID NO 395
<211> LENGTH: 987
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 395

```
Met Glu Leu Arg Val Leu Leu Cys Trp Ala Ser Leu Ala Ala Ala Leu
1               5                   10                  15

Glu Glu Thr Leu Leu Asn Thr Lys Leu Glu Thr Ala Asp Leu Lys Trp
            20                  25                  30

Val Thr Phe Pro Gln Val Asp Gly Gln Trp Glu Glu Leu Ser Gly Leu
        35                  40                  45

Asp Glu Glu Gln His Ser Val Arg Thr Tyr Glu Val Cys Asp Val Gln
    50                  55                  60

Arg Ala Pro Gly Gln Ala His Trp Leu Arg Thr Gly Trp Val Pro Arg
65                  70                  75                  80

Arg Gly Ala Val His Val Tyr Ala Thr Leu Arg Phe Thr Met Leu Glu
                85                  90                  95

Cys Leu Ser Leu Pro Arg Ala Gly Arg Ser Cys Lys Glu Thr Phe Thr
            100                 105                 110

Val Phe Tyr Tyr Glu Ser Asp Ala Asp Thr Ala Thr Ala Leu Thr Pro
        115                 120                 125

Ala Trp Met Glu Asn Pro Tyr Ile Lys Val Asp Thr Val Ala Ala Glu
    130                 135                 140

His Leu Thr Arg Lys Arg Pro Gly Ala Glu Ala Thr Gly Lys Val Asn
145                 150                 155                 160

Val Lys Thr Leu Arg Leu Gly Pro Leu Ser Lys Ala Gly Phe Tyr Leu
                165                 170                 175

Ala Phe Gln Asp Gln Gly Ala Cys Met Ala Leu Leu Ser Leu His Leu
            180                 185                 190

Phe Tyr Lys Lys Cys Ala Gln Leu Thr Val Asn Leu Thr Arg Phe Pro
        195                 200                 205

Glu Thr Val Pro Arg Glu Leu Val Val Pro Val Ala Gly Ser Cys Val
    210                 215                 220

Val Asp Ala Val Pro Ala Pro Gly Pro Ser Pro Ser Leu Tyr Cys Arg
225                 230                 235                 240

Glu Asp Gly Gln Trp Ala Glu Gln Pro Val Thr Gly Cys Ser Cys Ala
                245                 250                 255

Pro Gly Phe Glu Ala Ala Glu Gly Asn Thr Lys Cys Arg Ala Cys Ala
            260                 265                 270

Gln Gly Thr Phe Lys Pro Leu Ser Gly Glu Gly Ser Cys Gln Pro Cys
        275                 280                 285

Pro Ala Asn Ser His Ser Asn Thr Ile Gly Ser Ala Val Cys Gln Cys
    290                 295                 300
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Arg Val Gly Tyr Phe Arg Ala Arg Thr Asp Pro Arg Gly Ala Pro Cys
305                 310                 315                 320

Thr Thr Pro Pro Ser Ala Pro Arg Ser Val Val Ser Arg Leu Asn Gly
                325                 330                 335

Ser Ser Leu His Leu Glu Trp Ser Ala Pro Leu Glu Ser Gly Gly Arg
            340                 345                 350

Glu Asp Leu Thr Tyr Ala Leu Arg Cys Arg Glu Cys Arg Pro Gly Gly
        355                 360                 365

Ser Cys Ala Pro Cys Gly Gly Asp Leu Thr Phe Asp Pro Gly Pro Arg
    370                 375                 380

Asp Leu Val Glu Pro Trp Val Val Val Arg Gly Leu Arg Pro Asp Phe
385                 390                 395                 400

Thr Tyr Thr Phe Glu Val Thr Ala Leu Asn Gly Val Ser Ser Leu Ala
                405                 410                 415

Thr Gly Pro Val Pro Phe Glu Pro Val Asn Val Thr Thr Asp Arg Glu
            420                 425                 430

Val Pro Pro Ala Val Ser Asp Ile Arg Val Thr Arg Ser Ser Pro Ser
        435                 440                 445

Ser Leu Ser Leu Ala Trp Ala Val Pro Arg Ala Pro Ser Gly Ala Val
    450                 455                 460

Leu Asp Tyr Glu Val Lys Tyr His Glu Lys Gly Ala Glu Gly Pro Ser
465                 470                 475                 480

Ser Val Arg Phe Leu Lys Thr Ser Glu Asn Arg Ala Glu Leu Arg Gly
                485                 490                 495

Leu Lys Arg Gly Ala Ser Tyr Leu Val Gln Val Arg Ala Arg Ser Glu
            500                 505                 510

Ala Gly Tyr Gly Pro Phe Gly Gln Glu His His Ser Gln Thr Gln Leu
        515                 520                 525

Asp Glu Ser Glu Gly Trp Arg Glu Gln Leu Ala Leu Ile Ala Gly Thr
    530                 535                 540

Ala Val Val Gly Val Val Leu Val Leu Val Val Ile Val Val Ala Val
545                 550                 555                 560

Leu Cys Leu Arg Lys Gln Ser Asn Gly Arg Glu Ala Glu Tyr Ser Asp
                565                 570                 575

Lys His Gly Gln Tyr Leu Ile Gly His Gly Thr Lys Val Tyr Ile Asp
            580                 585                 590

Pro Phe Thr Tyr Glu Asp Pro Asn Glu Ala Val Arg Glu Phe Ala Lys
        595                 600                 605

Glu Ile Asp Val Ser Tyr Val Lys Ile Glu Glu Val Ile Gly Ala Gly
    610                 615                 620

Glu Phe Gly Glu Val Cys Arg Gly Arg Leu Lys Ala Pro Gly Lys Lys
625                 630                 635                 640

Glu Ser Cys Val Ala Ile Lys Thr Leu Lys Gly Gly Tyr Thr Glu Arg
                645                 650                 655

Gln Arg Arg Glu Phe Leu Ser Glu Ala Ser Ile Met Gly Gln Phe Glu
            660                 665                 670

His Pro Asn Ile Ile Arg Leu Glu Gly Val Val Thr Asn Ser Met Pro
        675                 680                 685

Val Met Ile Leu Thr Glu Phe Met Glu Asn Gly Ala Leu Asp Ser Phe
    690                 695                 700

Leu Arg Leu Asn Asp Gly Gln Phe Thr Val Ile Gln Leu Val Gly Met
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705                 710                 715                 720

Leu Arg Gly Ile Ala Ser Gly Met Arg Tyr Leu Ala Glu Met Ser Tyr
                725                 730                 735

Val His Arg Asp Leu Ala Ala Arg Asn Ile Leu Val Asn Ser Asn Leu
            740                 745                 750

Val Cys Lys Val Ser Asp Phe Gly Leu Ser Arg Phe Leu Glu Glu Asn
        755                 760                 765

Ser Ser Asp Pro Thr Tyr Thr Ser Ser Leu Gly Gly Lys Ile Pro Ile
    770                 775                 780

Arg Trp Thr Ala Pro Glu Ala Ile Ala Phe Arg Lys Phe Thr Ser Ala
785                 790                 795                 800

Ser Asp Ala Trp Ser Tyr Gly Ile Val Met Trp Glu Val Met Ser Phe
                805                 810                 815

Gly Glu Arg Pro Tyr Trp Asp Met Ser Asn Gln Asp Val Ile Asn Ala
            820                 825                 830

Ile Glu Gln Asp Tyr Arg Leu Pro Pro Pro Pro Asp Cys Pro Thr Ser
        835                 840                 845

Leu His Gln Leu Met Leu Asp Cys Trp Gln Lys Asp Arg Asn Ala Arg
    850                 855                 860

Pro Arg Phe Pro Gln Val Val Ser Ala Leu Asp Lys Met Ile Arg Asn
865                 870                 875                 880

Pro Ala Ser Leu Lys Ile Val Ala Arg Glu Asn Gly Gly Ala Ser His
                885                 890                 895

Pro Leu Leu Asp Gln Arg Gln Pro His Tyr Ser Ala Phe Gly Ser Val
            900                 905                 910

Gly Glu Trp Leu Arg Ala Ile Lys Met Gly Arg Tyr Glu Glu Ser Phe
        915                 920                 925

Ala Ala Ala Gly Phe Gly Ser Phe Glu Leu Val Ser Gln Ile Ser Ala
    930                 935                 940

Glu Asp Leu Leu Arg Ile Gly Val Thr Leu Ala Gly His Gln Lys Lys
945                 950                 955                 960

Ile Leu Ala Ser Val Gln His Met Lys Ser Gln Ala Lys Pro Gly Thr
                965                 970                 975

Pro Gly Gly Thr Gly Gly Pro Ala Pro Gln Tyr
            980                 985


<210> SEQ ID NO 396
<211> LENGTH: 333
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 396

Met Ala Val Arg Arg Asp Ser Val Trp Lys Tyr Cys Trp Gly Val Leu
1               5                   10                  15

Met Val Leu Cys Arg Thr Ala Ile Ser Lys Ser Ile Val Leu Glu Pro
            20                  25                  30

Ile Tyr Trp Asn Ser Ser Asn Ser Lys Phe Leu Pro Gly Gln Gly Leu
        35                  40                  45

Val Leu Tyr Pro Gln Ile Gly Asp Lys Leu Asp Ile Ile Cys Pro Lys
    50                  55                  60

Val Asp Ser Lys Thr Val Gly Gln Tyr Glu Tyr Tyr Lys Val Tyr Met
65                  70                  75                  80
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Val Asp Lys Asp Gln Ala Asp Arg Cys Thr Ile Lys Lys Glu Asn Thr
                85                  90                  95

Pro Leu Leu Asn Cys Ala Lys Pro Asp Gln Asp Ile Lys Phe Thr Ile
            100                 105                 110

Lys Phe Gln Glu Phe Ser Pro Asn Leu Trp Gly Leu Glu Phe Gln Lys
        115                 120                 125

Asn Lys Asp Tyr Tyr Ile Ile Ser Thr Ser Asn Gly Ser Leu Glu Gly
    130                 135                 140

Leu Asp Asn Gln Glu Gly Gly Val Cys Gln Thr Arg Ala Met Lys Ile
145                 150                 155                 160

Leu Met Lys Val Gly Gln Asp Ala Ser Ser Ala Gly Ser Thr Arg Asn
                165                 170                 175

Lys Asp Pro Thr Arg Arg Pro Glu Leu Glu Ala Gly Thr Asn Gly Arg
            180                 185                 190

Ser Ser Thr Thr Ser Pro Phe Val Lys Pro Asn Pro Gly Ser Ser Thr
        195                 200                 205

Asp Gly Asn Ser Ala Gly His Ser Gly Asn Asn Ile Leu Gly Ser Glu
    210                 215                 220

Val Ala Leu Phe Ala Gly Ile Ala Ser Gly Cys Ile Ile Phe Ile Val
225                 230                 235                 240

Ile Ile Ile Thr Leu Val Val Leu Leu Leu Lys Tyr Arg Arg Arg His
                245                 250                 255

Arg Lys His Ser Pro Gln His Thr Thr Thr Leu Ser Leu Ser Thr Leu
            260                 265                 270

Ala Thr Pro Lys Arg Ser Gly Asn Asn Asn Gly Ser Glu Pro Ser Asp
        275                 280                 285

Ile Ile Ile Pro Leu Arg Thr Ala Asp Ser Val Phe Cys Pro His Tyr
    290                 295                 300

Glu Lys Val Ser Gly Asp Tyr Gly His Pro Val Tyr Ile Val Gln Glu
305                 310                 315                 320

Met Pro Pro Gln Ser Pro Ala Asn Ile Tyr Tyr Lys Val
                325                 330
```

1-62. (canceled)

63. A method for reducing the growth rate of a tumor, comprising administering an amount of an isolated monoclonal antibody, or a fragment thereof, sufficient to reduce the growth rate of the tumor, wherein the antibody or fragment thereof binds to the extracellular domain of EphB4 and inhibits an activity of EphB4.

64. The method of claim **63**, wherein the tumor comprises cells expressing a higher level of EphB4 and/or EphrinB2 than noncancerous cells of a comparable tissue.

65. A method for treating a patient suffering from a cancer, comprising administering to the patient an isolated monoclonal antibody, or a fragment thereof, that binds to the extracellular domain of EphB4 and inhibits an activity of EphB4.

66. The method of claim **65**, wherein the cancer comprises cancer cells expressing EphrinB2 and/or EphB4 at a higher level than noncancerous cells of a comparable tissue.

67. The method of claim **65**, wherein the cancer is metastatic cancer.

68. The method of claim **65**, wherein the tumor is selected from colon carcinoma, breast tumor, mesothelioma, prostate tumor, squamous cell carcinoma, Kaposi sarcoma, and leukemia.

69. The method of claim **65**, wherein the cancer is an angiogenesis-dependent cancer.

70. The method of claim **65**, wherein the cancer is an angiogenesis-independent cancer.

71. The method of claim **65**, wherein the antibody inhibits the interaction between EphrinB2 and EphB4.

72. The method of claim **65**, wherein the antibody inhibits clustering of EphrinB2 or EphB4.

73. The method of claim **65**, wherein the antibody inhibits phosphorylation of EphrinB2 or EphB4.

74. The method of claim **65**, wherein the antibody is formulated with a pharmaceutically acceptable carrier.

75. The method of claim **65**, further including administering at least one additional anti-cancer chemotherapeutic agent that inhibits cancer cells in an additive or synergistic manner with the antibody.

76. A method for inhibiting angiogenesis, comprising contacting a cell with an amount of an isolated monoclonal antibody, or a fragment thereof, sufficient to inhibit angiogenesis, wherein the antibody or fragment thereof binds to the extracellular domain of EphB4 and inhibits an activity of EphB4.

77. The method of claim **76**, wherein the cell expresses EphB4 or EphrinB2.

78. A method for treating a patient suffering from an angiogenesis-associated disease, comprising administering to the patient an isolated monoclonal antibody, or a fragment thereof, that binds to the extracellular domain of EphB4 and inhibits an activity of EphB4.

79. The method of claim **78**, wherein the antibody is formulated with a pharmaceutically acceptable carrier.

80. The method of claim **78**, wherein the angiogenesis-associated disease is selected angiogenesis-dependent cancer, benign tumors, inflammatory disorders, chronic articular rheumatism, psoriasis, ocular angiogenic diseases, Osler-Webber Syndrome, myocardial angiogenesis, plaque neovascularization, telangiectasia, hemophiliac joints, angiofibroma, wound granulation, wound healing, scleroderma, pyogenic granuloma, coronary collaterals, ischemic limb angiogenesis, rubeosis, arthritis, diabetic neovascularization, fractures, vasculogenesis, and hematopoiesis.

81. The method of claim **78**, further including administering at least one additional anti-angiogenesis agent that inhibits angiogenesis in an additive or synergistic manner with the antibody.

* * * * *