

(19) AUSTRALIAN PATENT OFFICE

- (54) Title
Novel nucleotide and amino acid sequences, and assays and methods of use thereof for diagnosis of lung cancer
- (51)⁶ International Patent Classification(s)
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- (21) Application No: **2005320352** (22) Application Date: **2005 .01 .27**
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- | (31) Number | (32) Date | (33) Country |
|-------------|--------------|--------------|
| 60/620,924 | 2004 .10 .22 | US |
| 60/620,918 | 2004 .10 .22 | US |
| 60/539,129 | 2004 .01 .27 | US |
| 60/621,053 | 2004 .10 .25 | US |
| 60/628,178 | 2004 .11 .17 | US |
| 60/628,111 | 2004 .11 .17 | US |
| 60/620975 | 2004 .10 .22 | US |
| 60/539,128 | 2004 .01 .27 | US |
| 60/620,874 | 2004 .10 .22 | US |
| 60/628,101 | 2004 .11 .17 | US |
| 60/589,815 | 2004 .07 .22 | US |
| 60/620,868 | 2004 .10 .22 | US |
| 60/628112 | 2004 .11 .17 | US |
| 60/621,004 | 2004 .10 .22 | US |
| 60/620,656 | 2004 .10 .22 | US |
| 60/620,974 | 2004 .10 .22 | US |
| 60/634,075 | 2004 .12 .08 | US |
| 60/607,307 | 2004 .09 .07 | US |
| 60/621,131 | 2004 .10 .25 | US |
| 11/051,720 | 2005 .01 .27 | US |
| 60/628,145 | 2004 .11 .17 | US |
| 60/589,815 | 2004 .07 .22 | US |
| 60/628,189 | 2004 .11 .17 | US |
| 60/628,123 | 2004 .11 .17 | US |
| 60/607,307 | 2004 .09 .07 | US |
| 60/620,853 | 2004 .10 .22 | US |
| 60/628,251 | 2004 .11 .17 | US |
| 60/620,677 | 2004 .10 .22 | US |
| 60/628,134 | 2004 .11 .17 | US |
| 60/620,917 | 2004 .10 .22 | US |
| 60/628,167 | 2004 .11 .17 | US |
| 60/628,156 | 2004 .11 .17 | US |
| 60/620,906 | 2004 .10 .22 | US |
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ABSTRACT OF THE DISCLOSURE

Novel markers for lung cancer that are both sensitive and accurate. These markers are overexpressed in lung cancer specifically, as opposed to normal lung tissue. The measurement of these markers, alone or in combination, in patient samples provides information that the diagnostician can correlate with a probable diagnosis of lung cancer. The markers of the present invention, alone or in combination, show a high degree of differential detection between lung cancer and non-cancerous states.

File reference: 2005320352

Subject: Editorial Note

The description for this application was filed on CD and can be viewed by contacting IP Australia

10 August 2006

WHAT IS CLAIMED IS:

1. An isolated polynucleotide comprising a polynucleotide having a sequence of R11723_PEA_1_T5.
2. The isolated polynucleotide of claim 1, comprising a node having a sequence of : R11723_PEA_1_node_13.
3. An isolated polypeptide comprising a polypeptide having a sequence of : R11723_PEA_1_P13.
4. The isolated of claim 3, comprising a chimeric polypeptide encoding for R11723_PEA_1_P13, comprising a first amino acid sequence being at least 95 % homologous to
MWVLGIAATFCGLFLLPGFALQIQCYQCEEFQLNNDCSSPEFIVNCTVNVQDMCQKEV
MEQSA corresponding to amino acids 1 - 63 of Q96AC2, which also corresponds to amino acids 1 - 63 of R11723_PEA_1_P13, and a second amino acid sequence being at least about 95% homologous to a polypeptide having the sequence DTKRTNTLLFEMRHFAKQLTT corresponding to amino acids 64 - 84 of R11723_PEA_1_P13, wherein said first and second amino acid sequences are contiguous and in a sequential order.
4. The isolated polypeptide of claim 4, comprising a tail of R11723_PEA_1_P13, comprising a polypeptide being at least about 95% homologous to the sequence DTKRTNTLLFEMRHFAKQLTT in R11723_PEA_1_P13.
5. The isolated oligonucleotide of claim 1, comprising an amplicon according to SEQ ID NO: 1684.
6. A primer pair, comprising a pair of isolated oligonucleotides capable of amplifying said amplicon of claim 5.

7. The primer pair of claim 6, comprising a pair of isolated oligonucleotides: SEQ NOs 1682 and 1683.
8. An antibody capable of specifically binding to an epitope of an amino acid sequence of claim 3.
9. The antibody of claim 8, wherein said amino acid sequence comprises said tail of claim 4.
10. The antibody of claim 8, wherein said antibody is capable of differentiating between a splice variant having said epitope and a corresponding known protein PSEC.
11. A kit for detecting lung cancer, comprising a kit detecting overexpression of a splice variant according to claim 1.
12. The kit of claim 11, wherein said kit comprises a NAT-based technology.
13. The kit of claim 11, wherein said kit further comprises at least one primer pair capable of selectively hybridizing to a nucleic acid sequence according to claim 1.
14. The kit of claim 11, wherein said kit further comprises at least one oligonucleotide capable of selectively hybridizing to a nucleic acid sequence according to claim 1.
12. A kit for detecting lung cancer, comprising a kit detecting overexpression of a splice variant according to claim 3, said kit comprising an antibody according claim 8.
13. The kit of claim 12, wherein said kit further comprises at least one reagent for performing an ELISA or a Western blot.

14. A method for detecting lung cancer, comprising detecting overexpression of a splice variant according to claim 1.

15. The method of claim 14, wherein said detecting overexpression is performed with a NAT-based technology.

16. A method for detecting lung cancer, comprising detecting overexpression of a splice variant according to claim 3, wherein said detecting overexpression is performed with an immunoassay.

17. The method of claim 16, wherein said immunoassay comprises an antibody according to claim 8.

18. A biomarker capable of detecting lung cancer, comprising a nucleic acid sequence according to claim 1 or a fragment thereof, or an amino acid sequence according to claim 3 or a fragment thereof.

19. A method for screening for lung cancer, comprising detecting lung cancer cells with a biomarker according to claim 18.

20. A method for diagnosing lung cancer, comprising detecting lung cancer cells with a biomarker according to claim 18.

21. A method for monitoring disease progression and/or treatment efficacy and/or relapse of lung cancer, comprising detecting lung cancer cells with a biomarker according to claim 18.

22. A method of selecting a therapy for lung cancer, comprising detecting lung cancer cells with a biomarker according to claim 18 and selecting a therapy according to said detection.

Figure 1: Schematic description of the cancer biomarker selection engine.

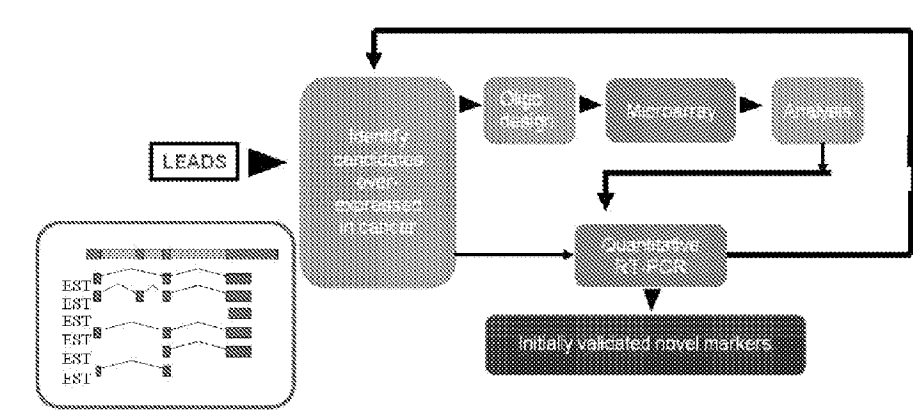
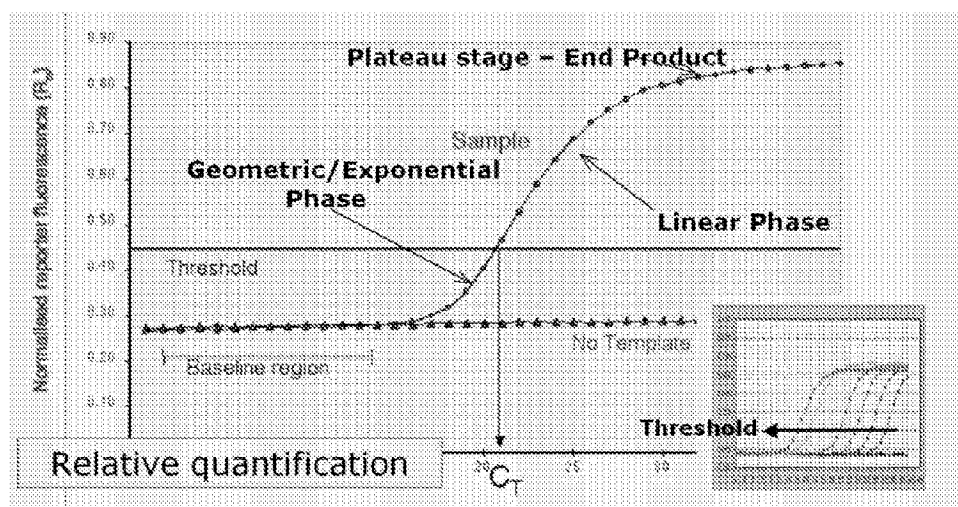


Figure 2: Schematic illustration, depicting grouping of transcripts of a given cluster based on presence or absence of unique sequence regions.

Transcript 1	<u>1</u>	<u>2</u>		<u>5</u>	<u>6</u>
Transcript 2	<u>1</u>		<u>3</u>	<u>5</u>	
Transcript 3	<u>1</u>		<u>3</u>	<u>4</u>	

Figure 3: Schematic summary of quantitative real-time PCR analysis.



C_T = Threshold Cycle point – A calculated cycle number in which PCR products signal is above the background level (passive dye ROX) and still in the Geometric/Expo phase.

Figure 4: Schematic presentation of the oligonucleotide based microarray fabrication.

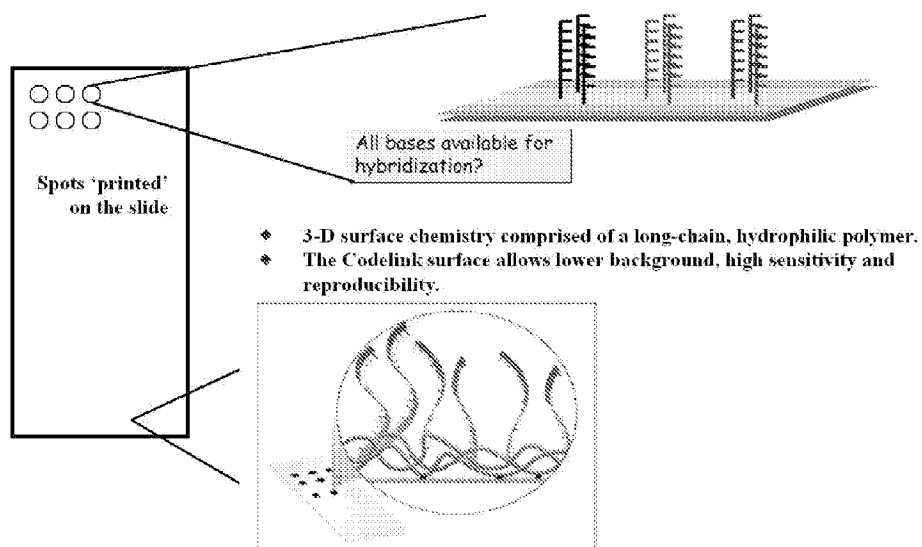


Figure 5: Schematic summary of the oligonucleotide based microarray experimental flow.

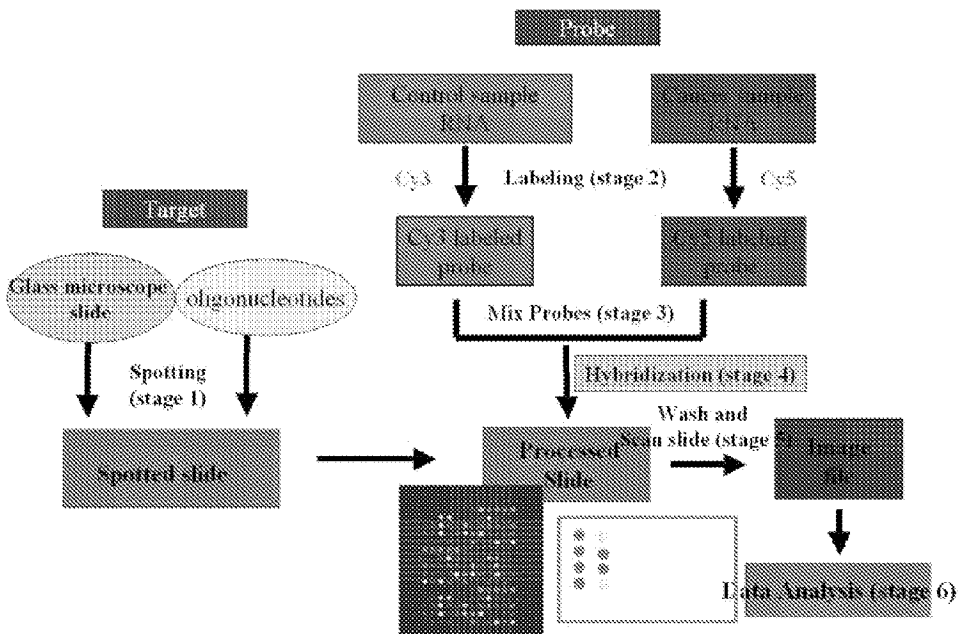


Figure 6:

Figure 6 - Cancer and cell-line vs. normal tissue expression

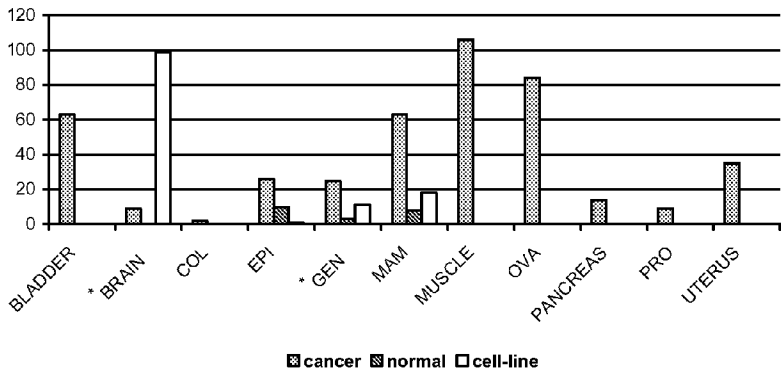


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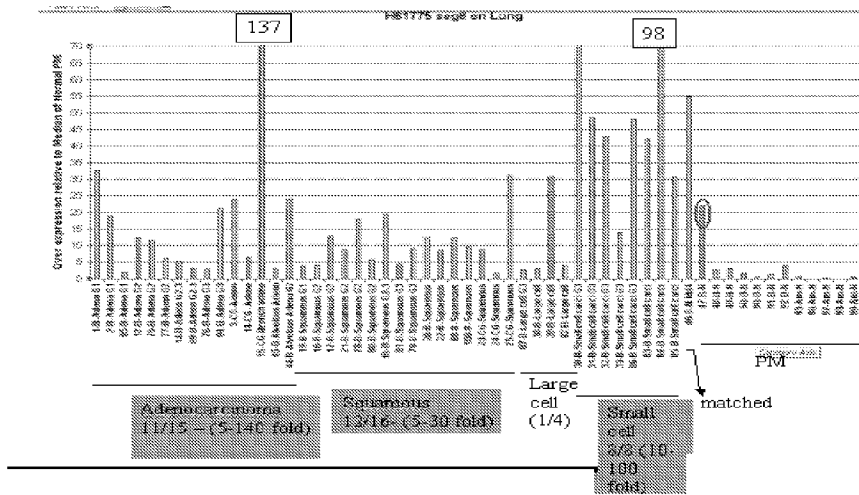


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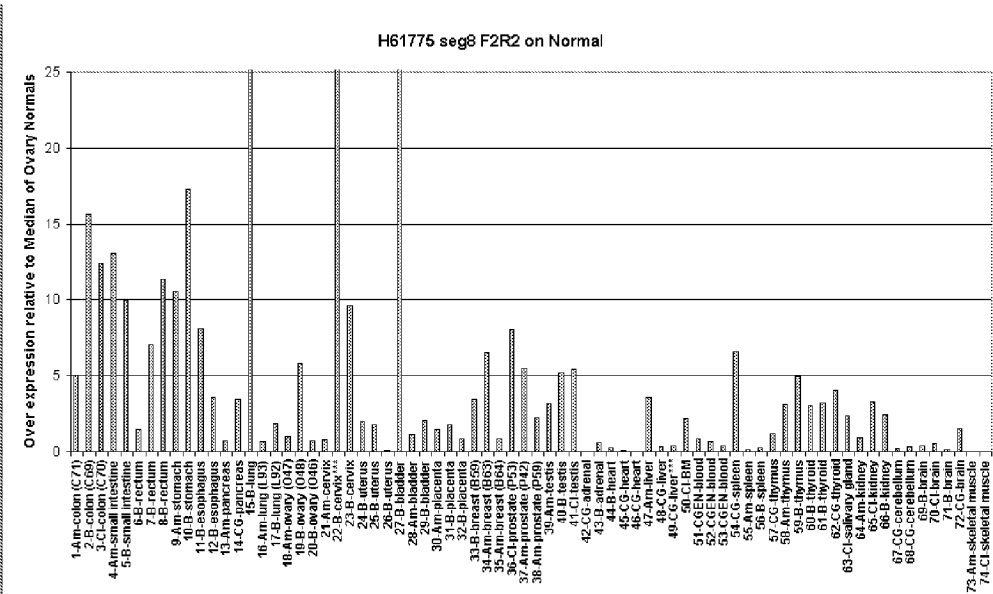


Figure 9:

Figure 9 - Cancer and cell-line vs. normal tissue expression

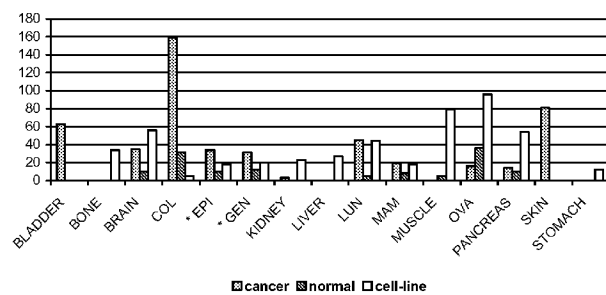


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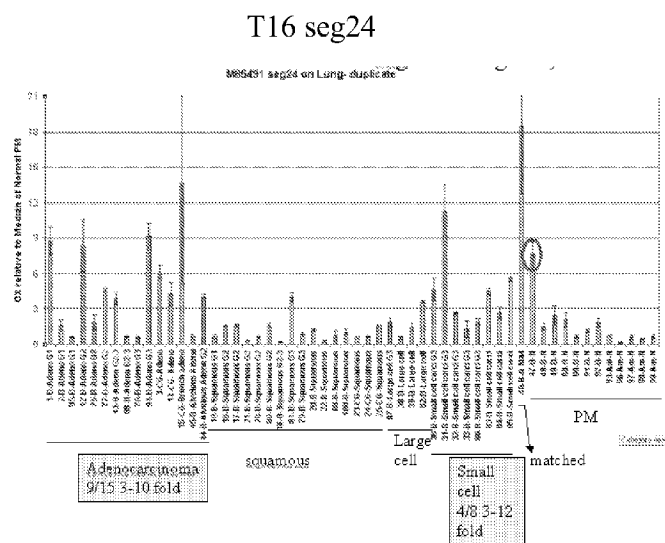


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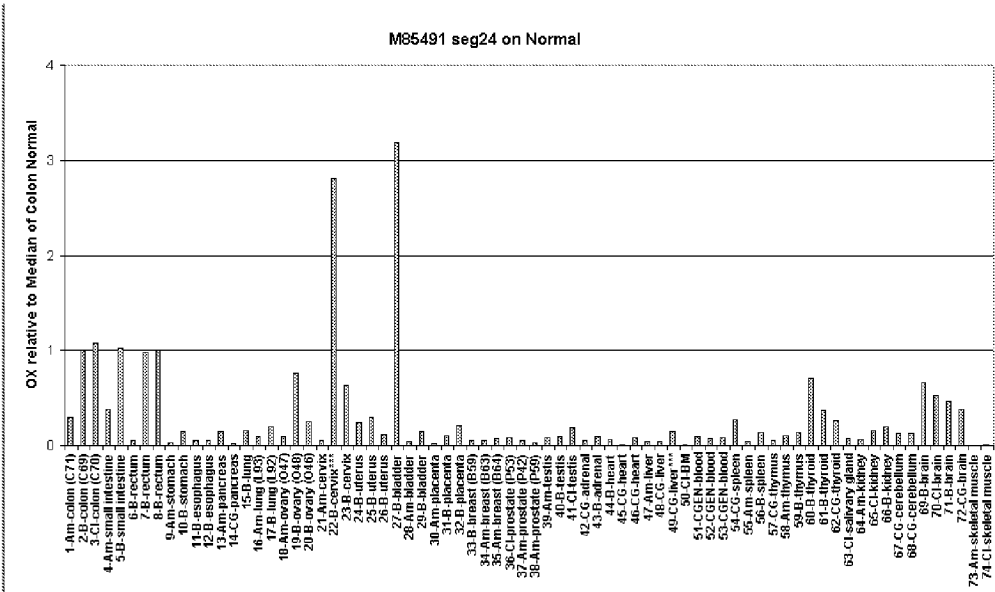


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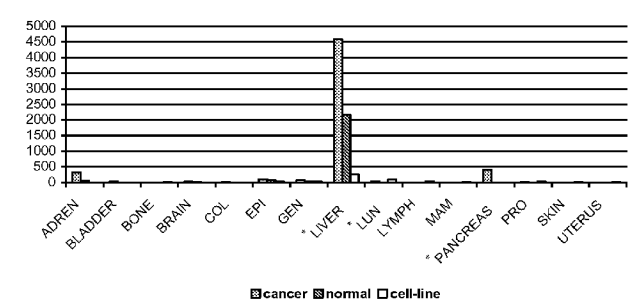


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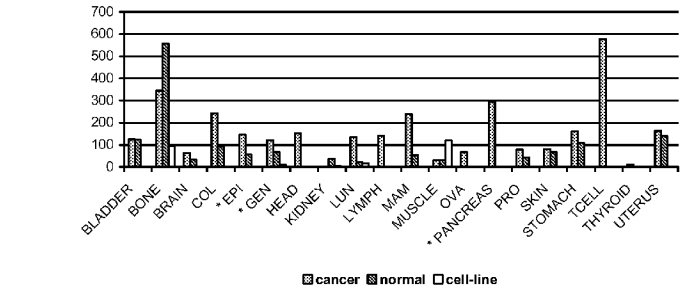


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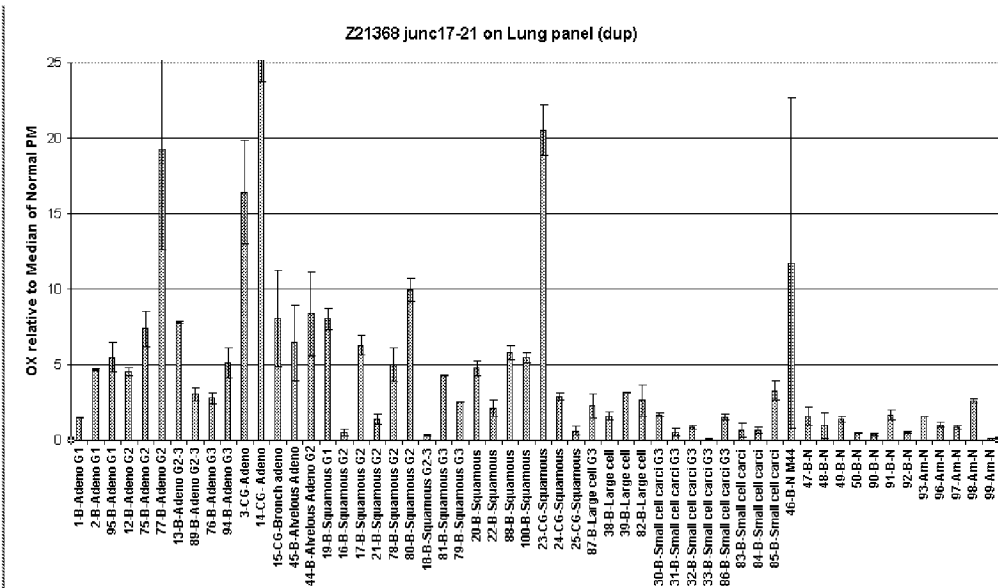


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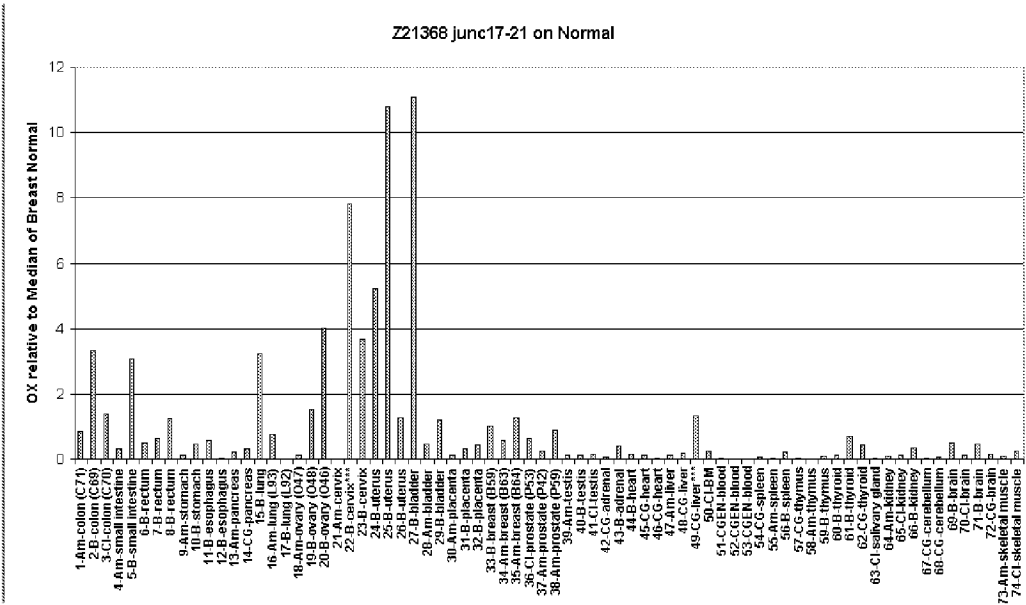


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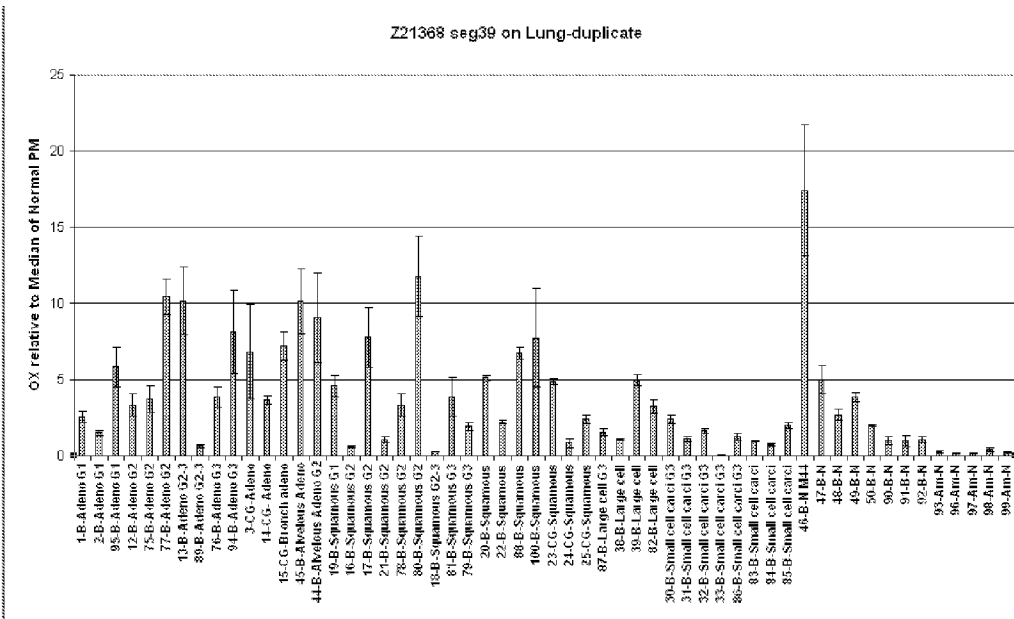


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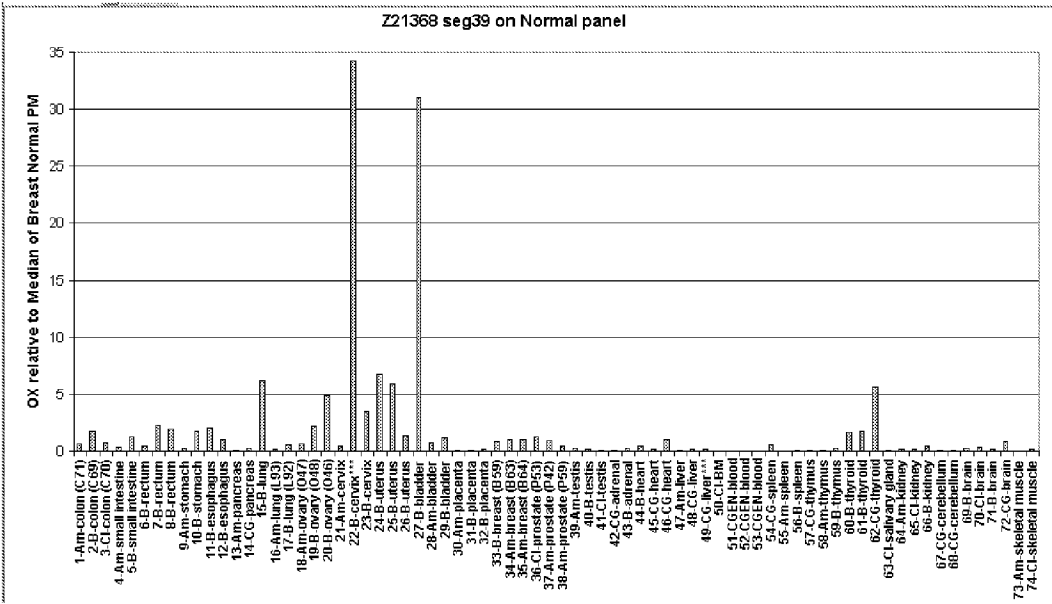


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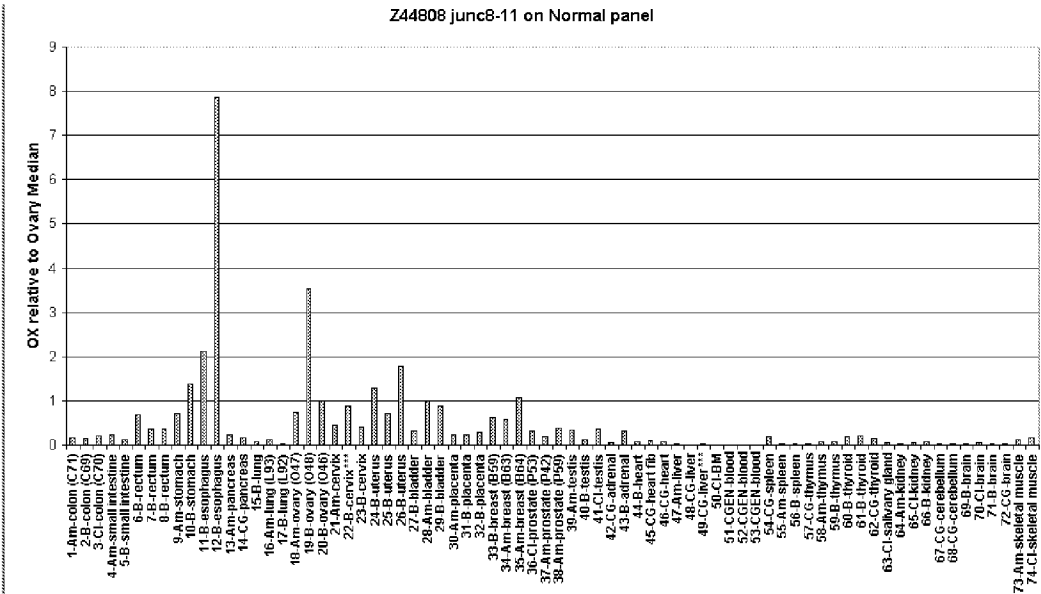


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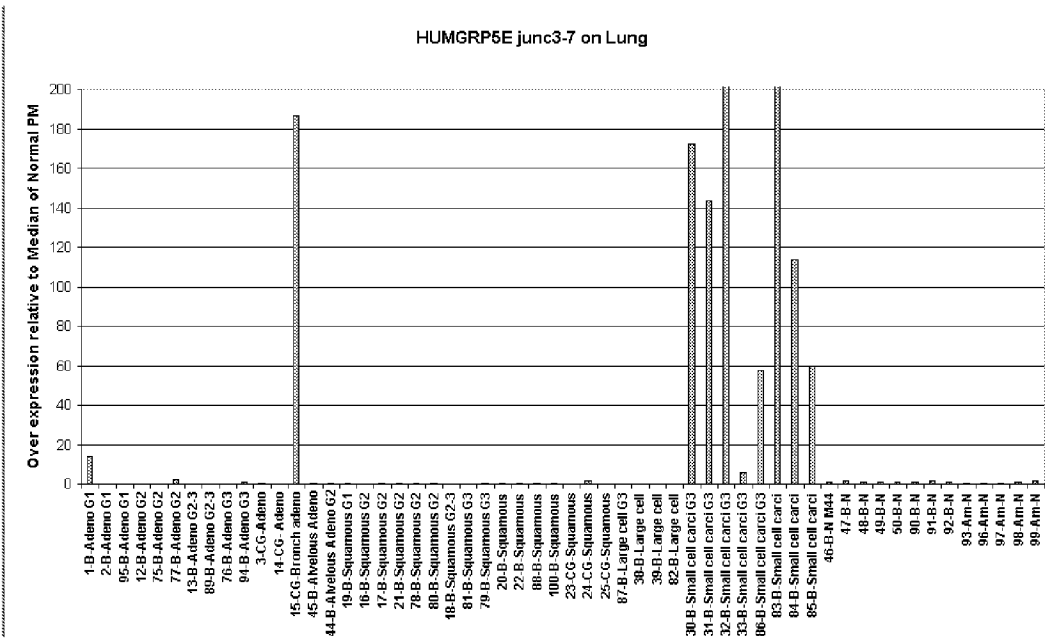


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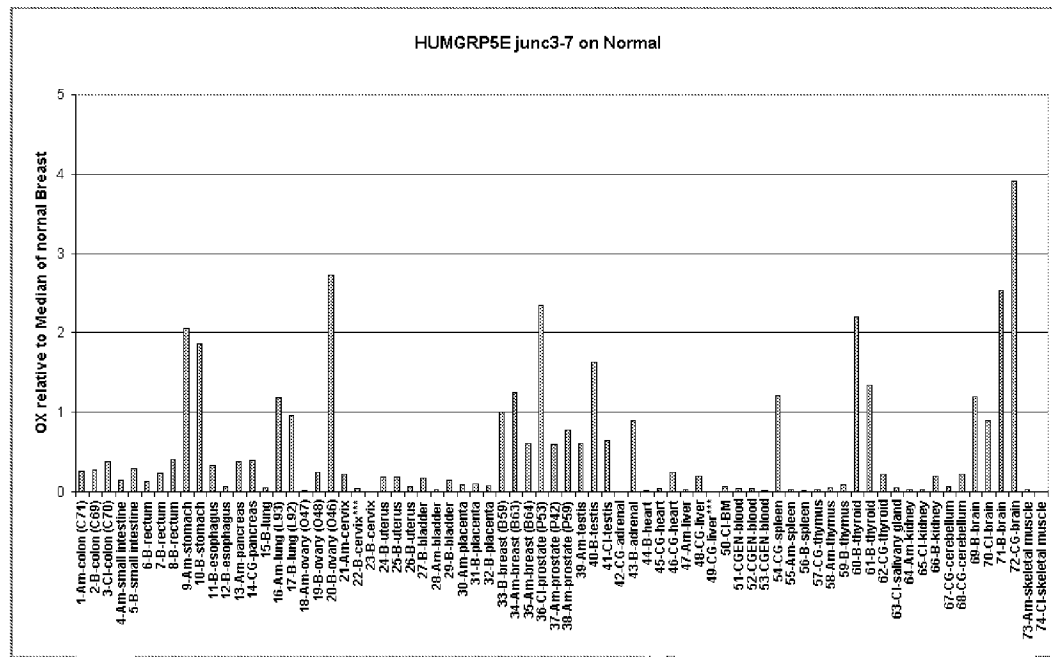


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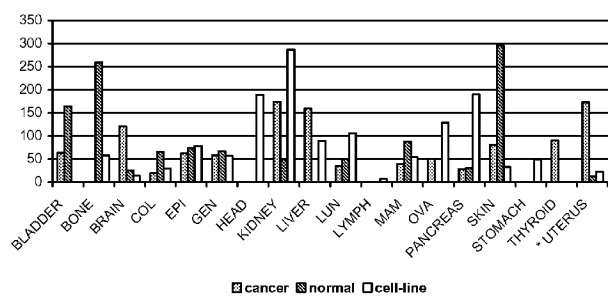


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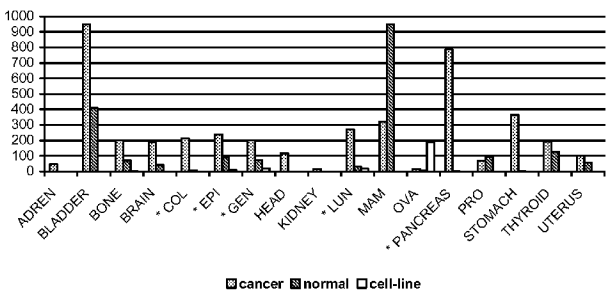


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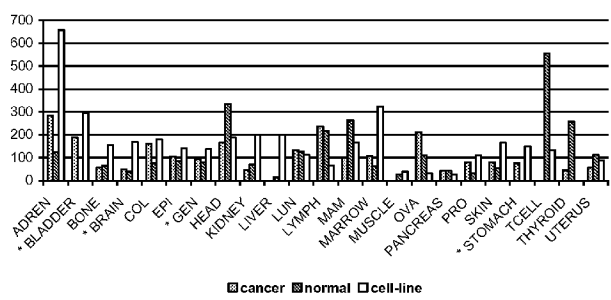


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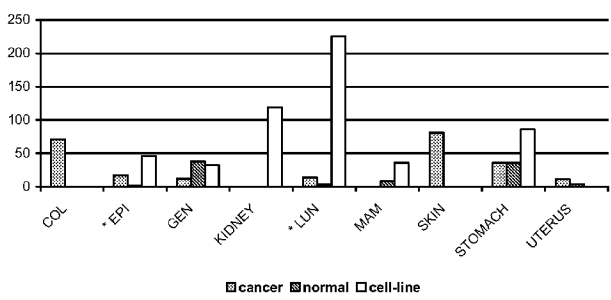


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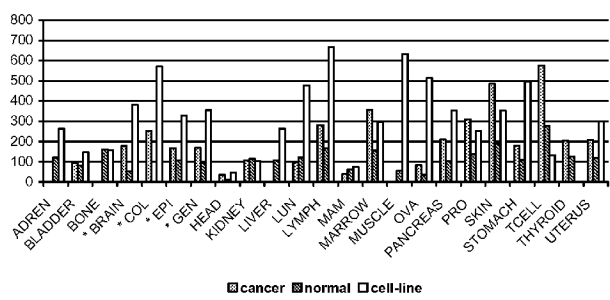


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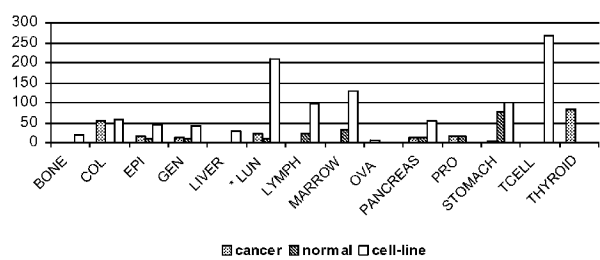


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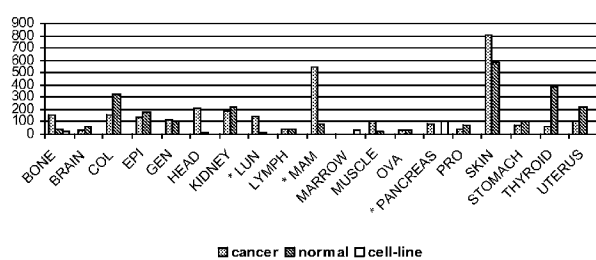


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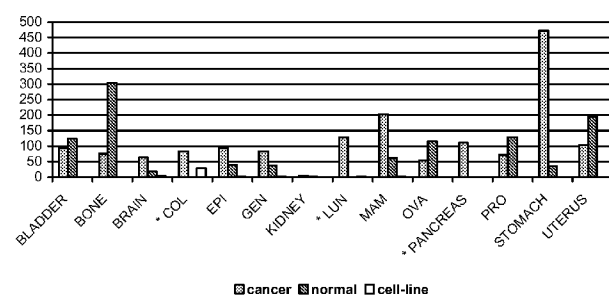


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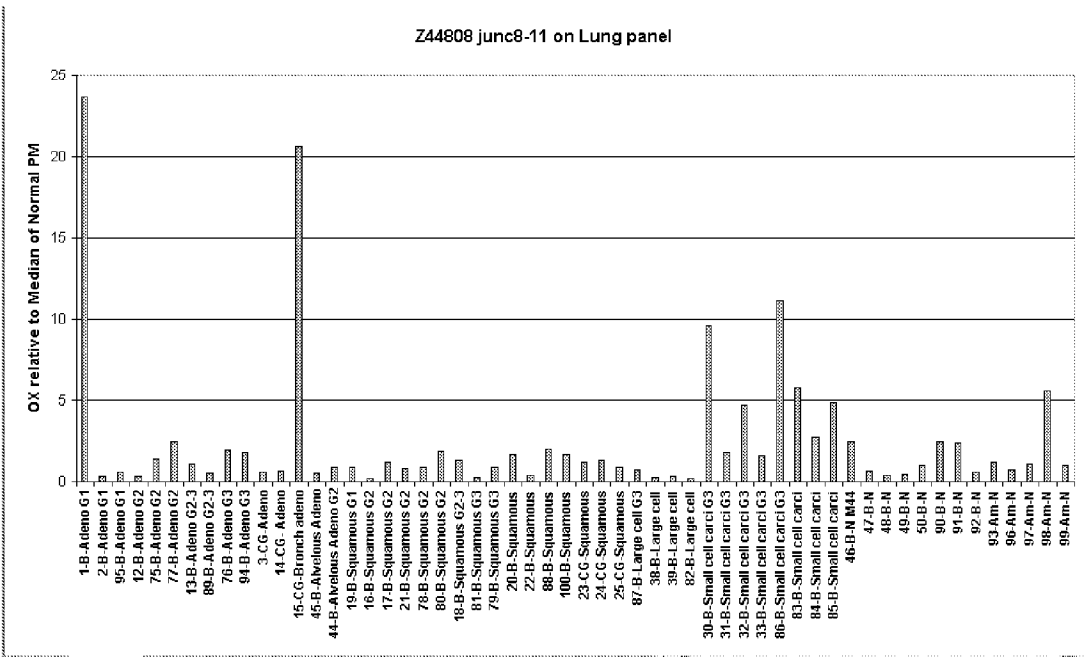


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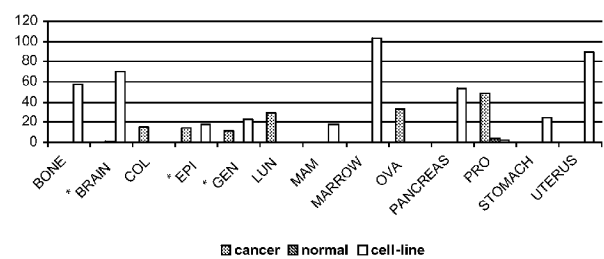


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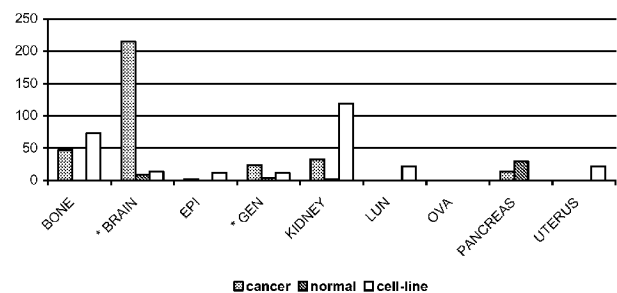


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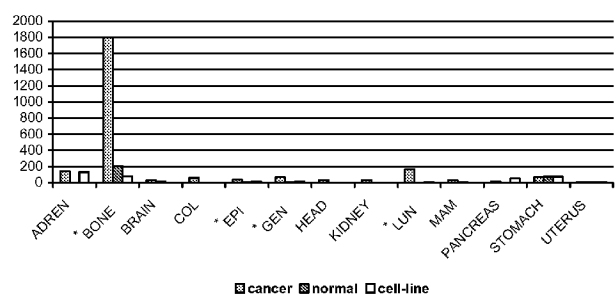


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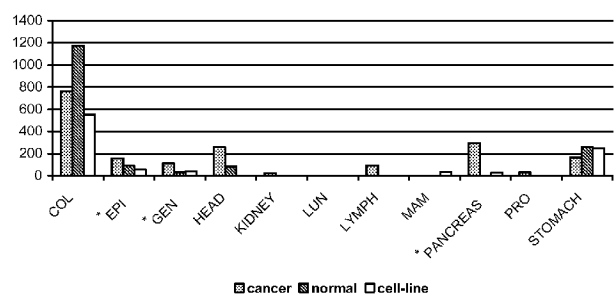


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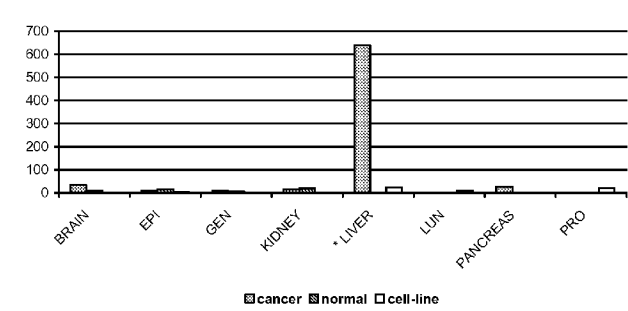


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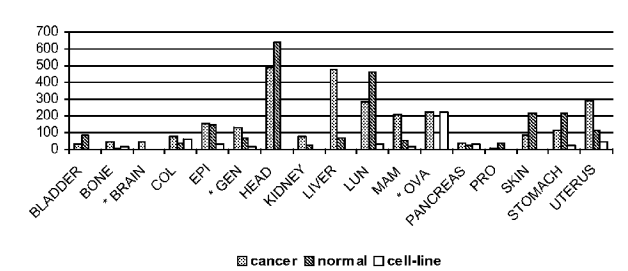


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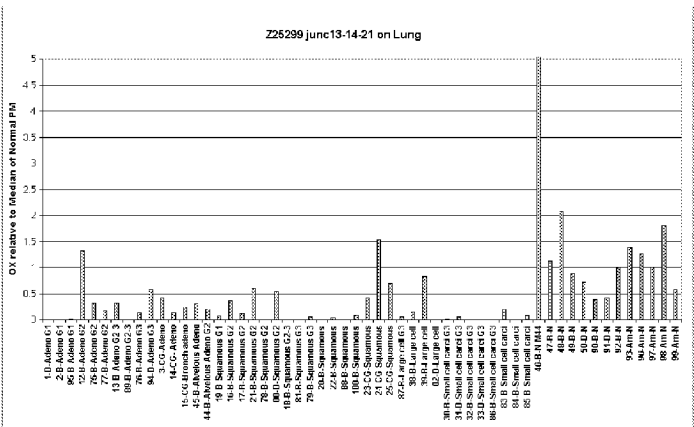


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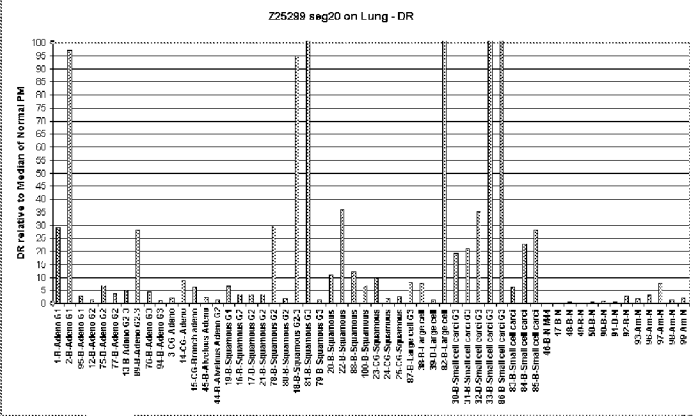


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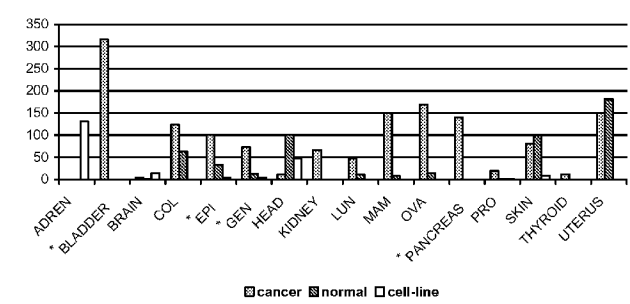


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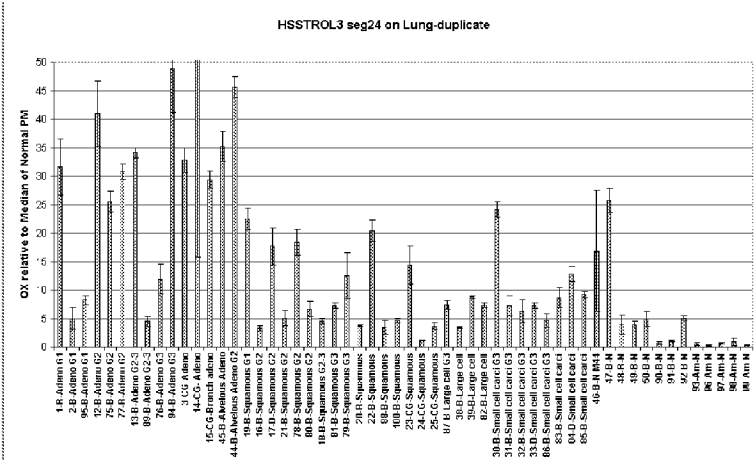


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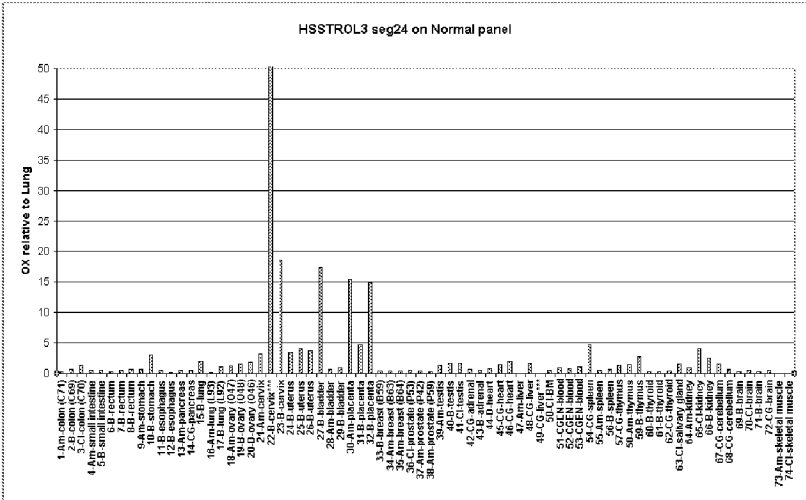


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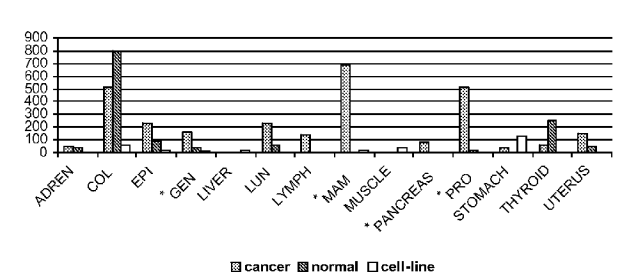


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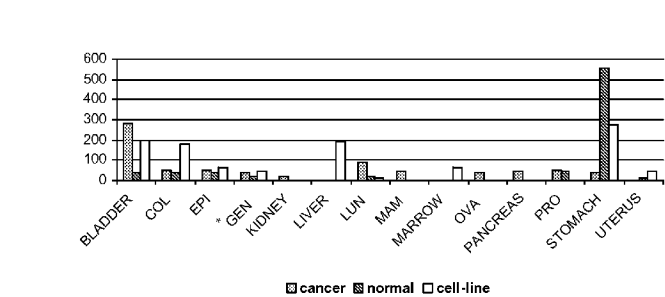


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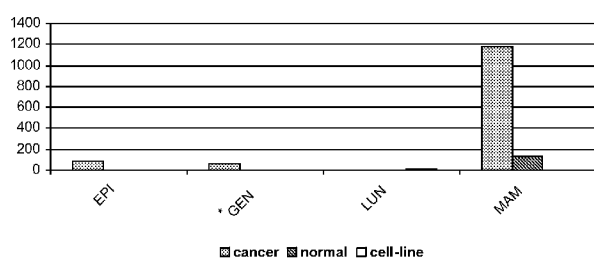


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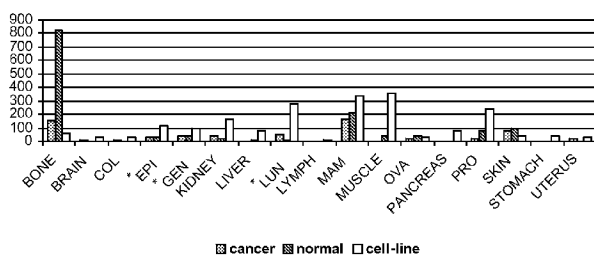


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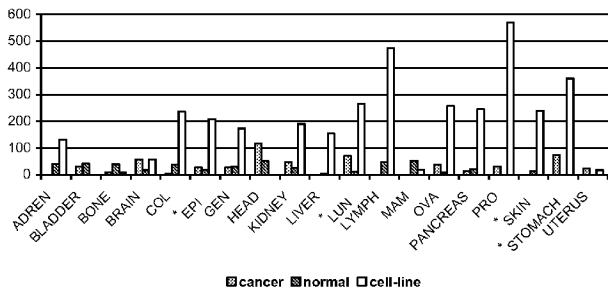


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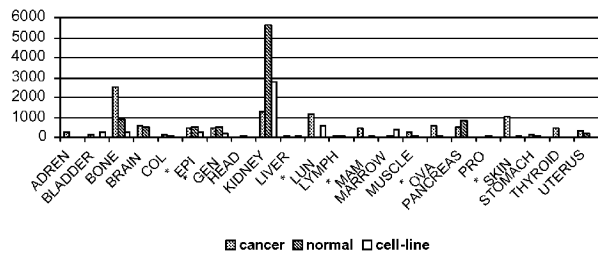


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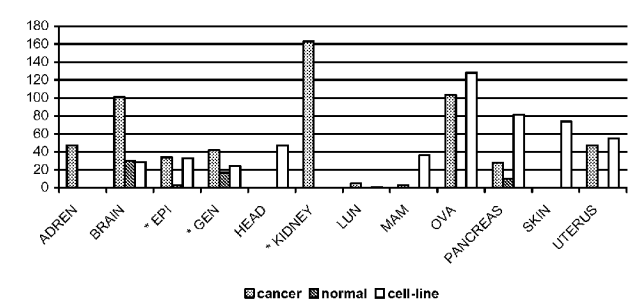


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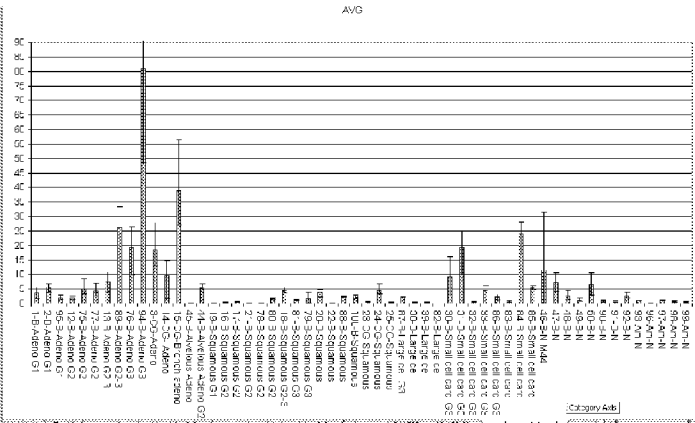


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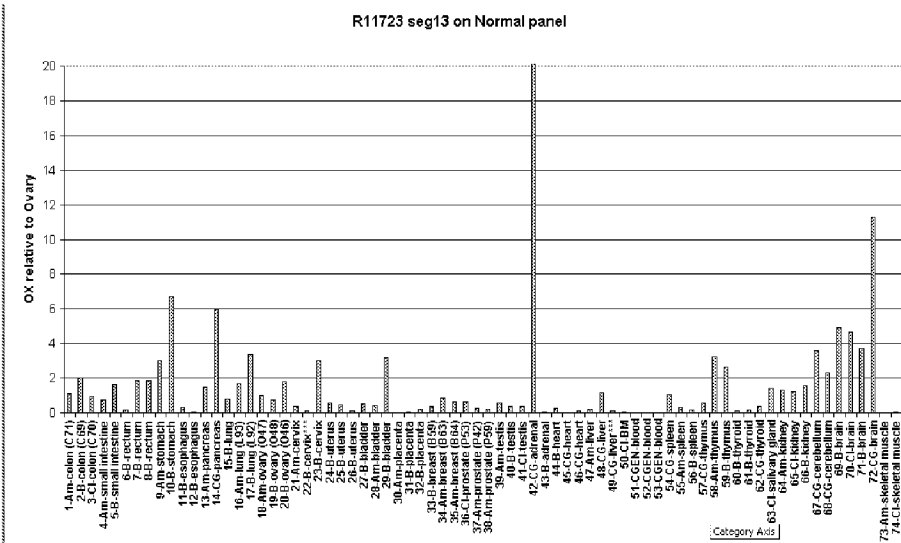


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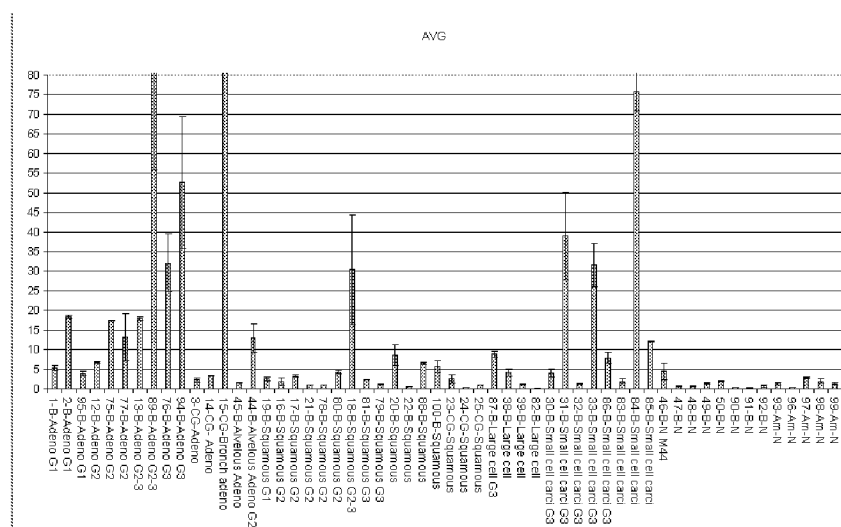


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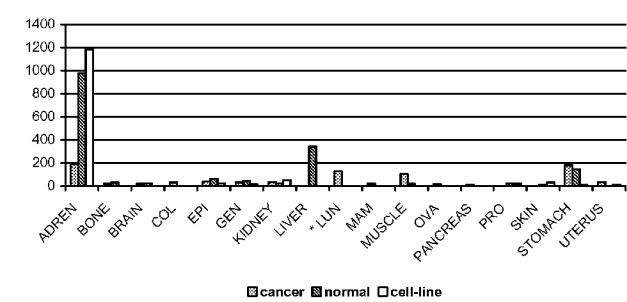


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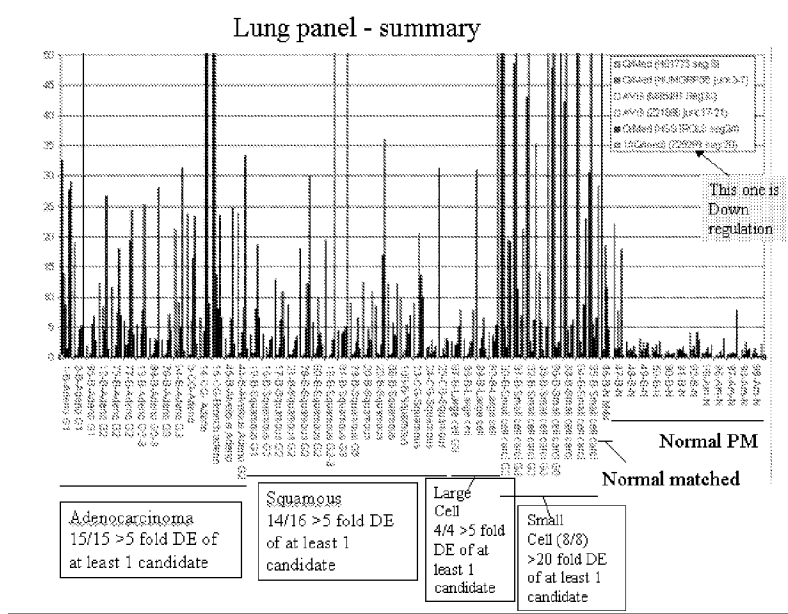


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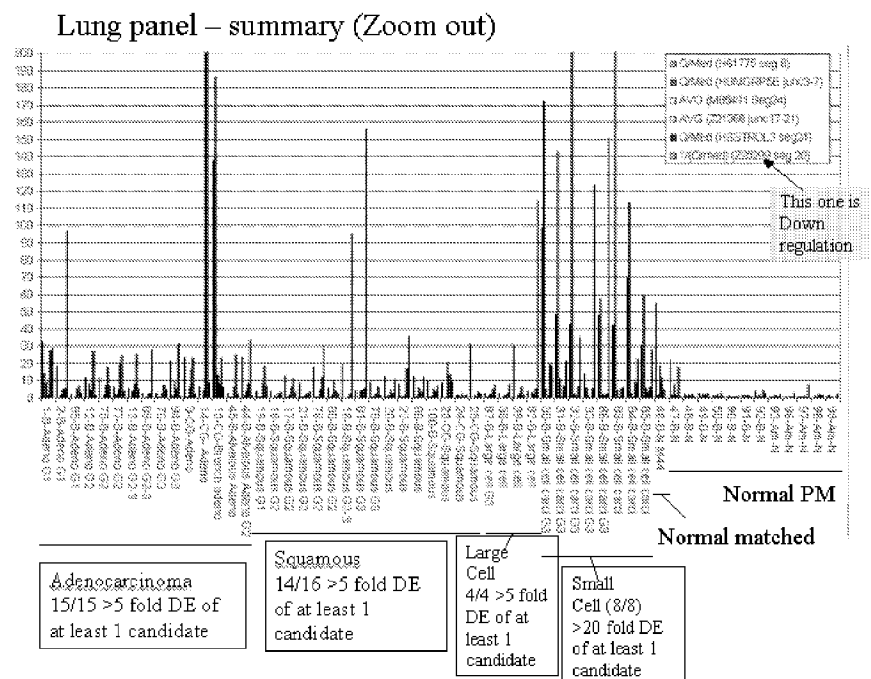


Figure 54a

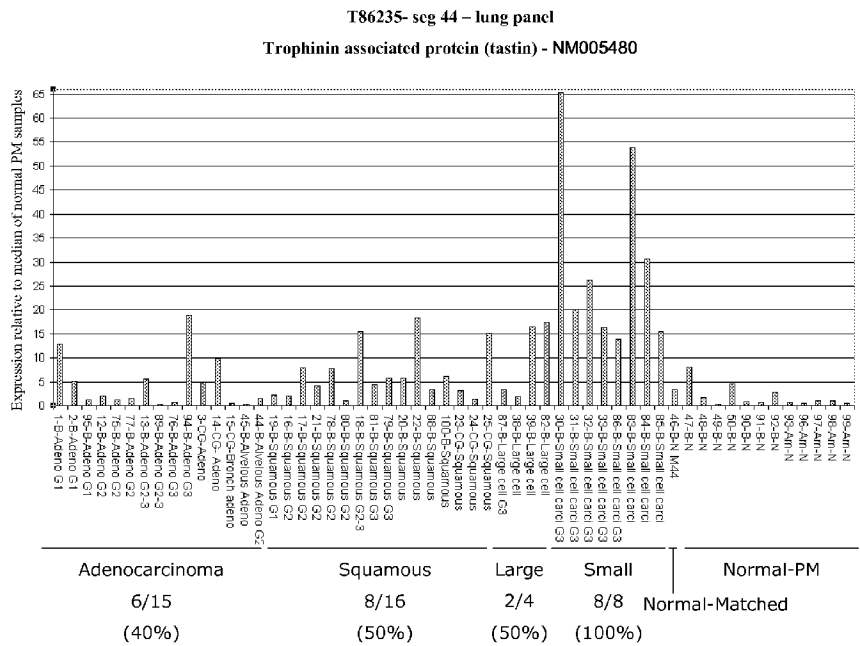


Figure 54b

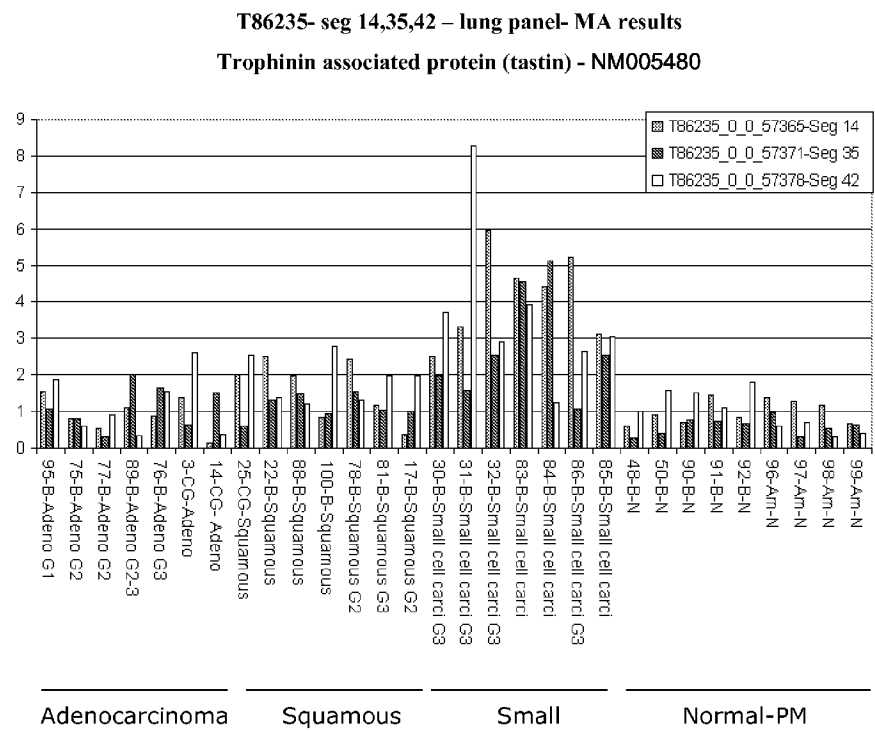
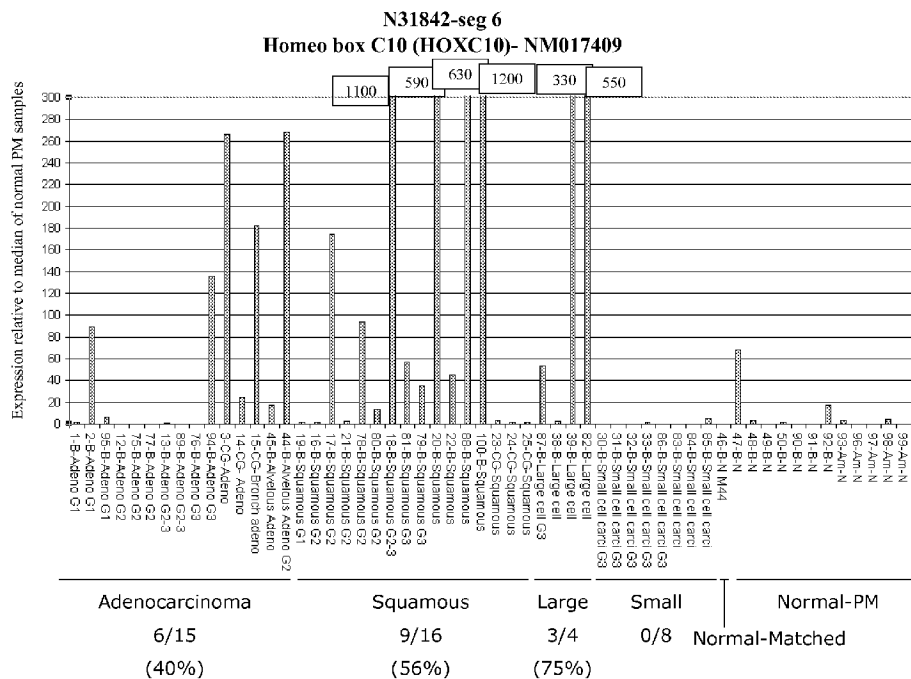


Figure 55



T06014-seg 1
Nucleolar protein 4 (NOL4)-NM003787



Figure 56b

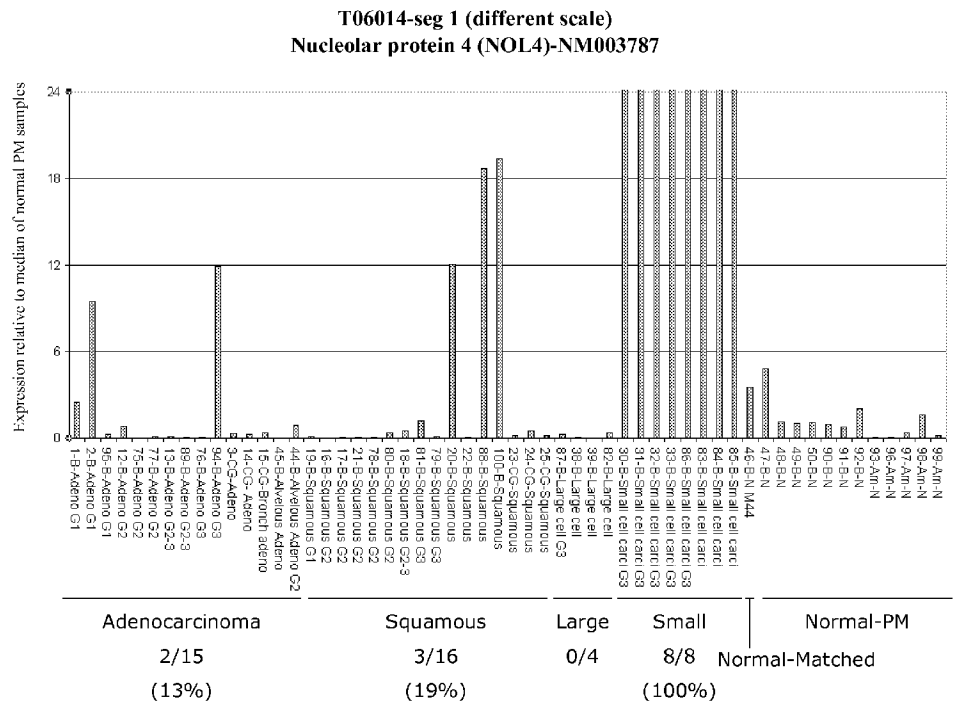


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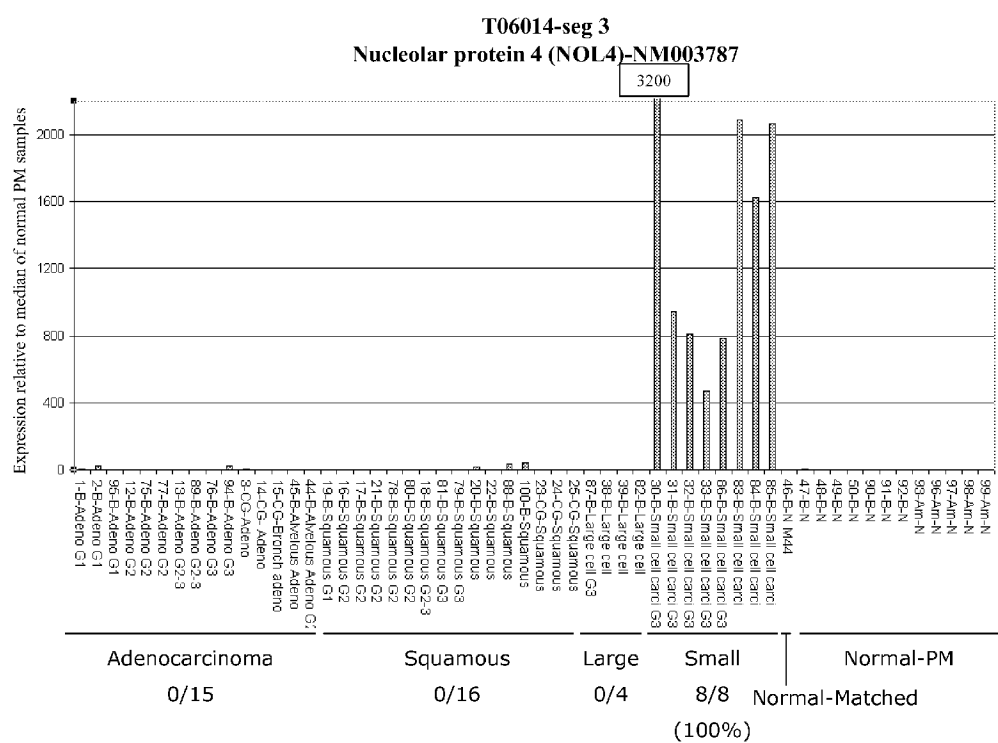


Figure 57b

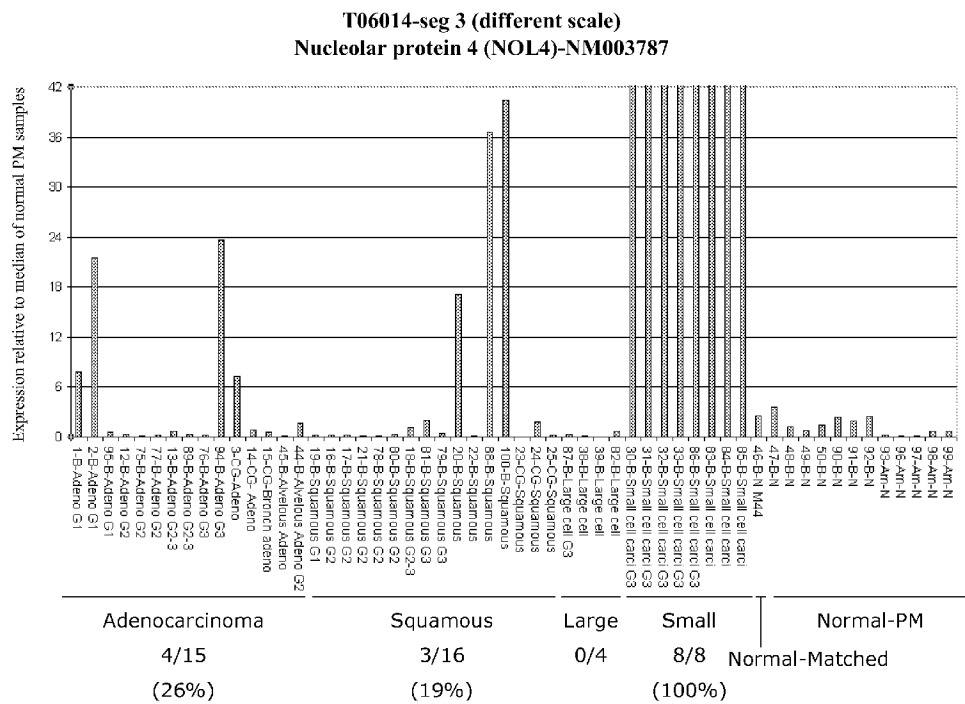


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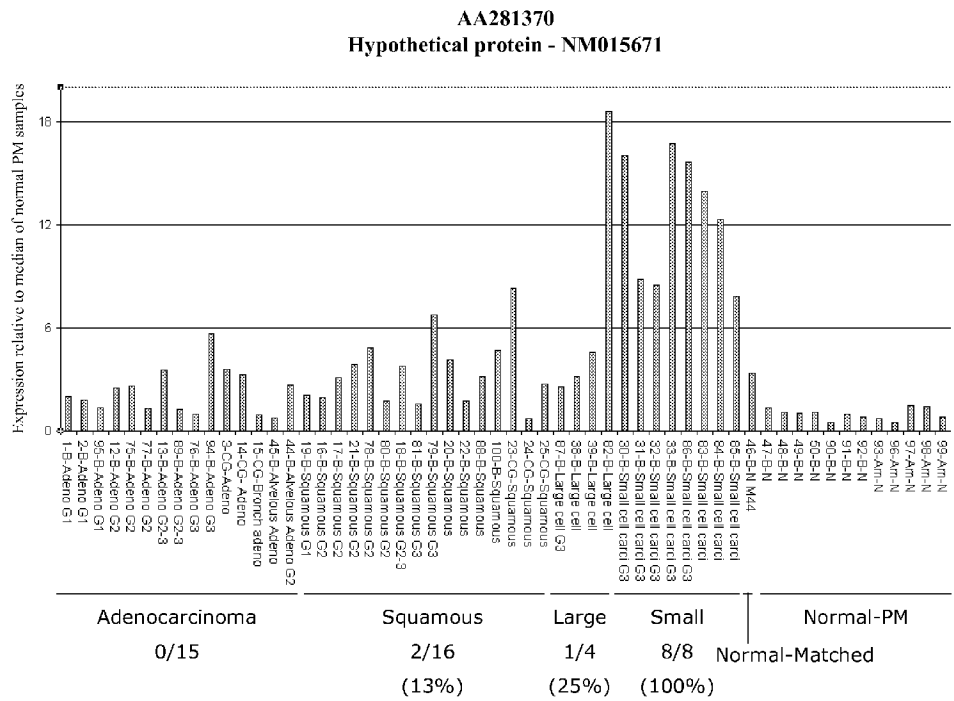


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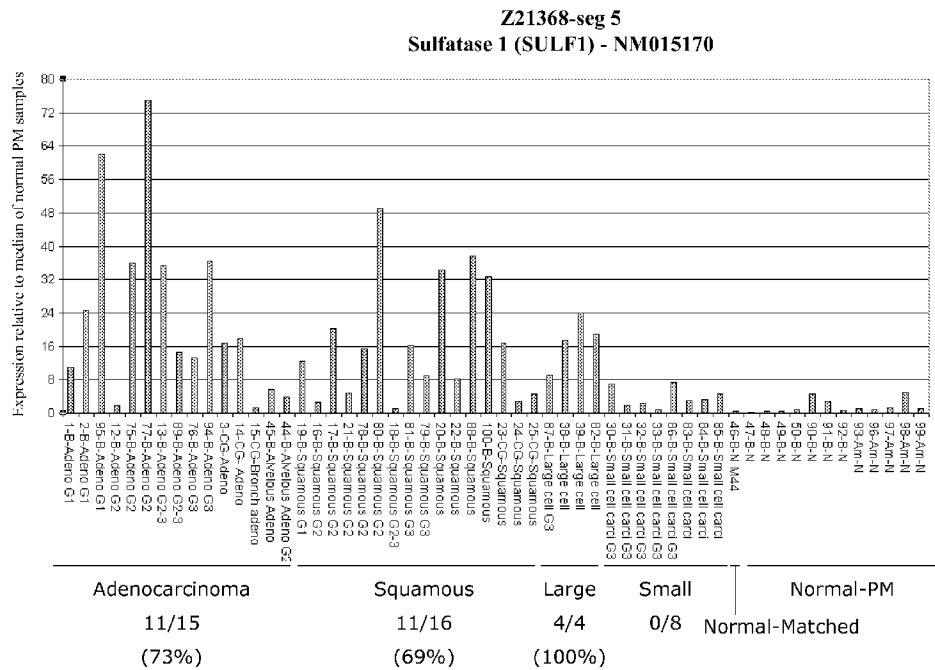


Figure 60

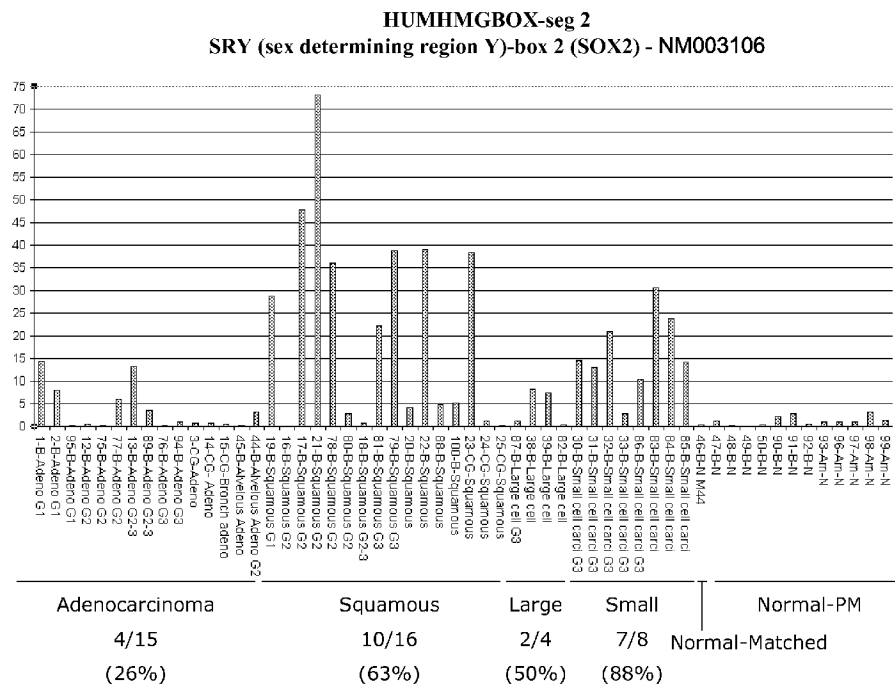


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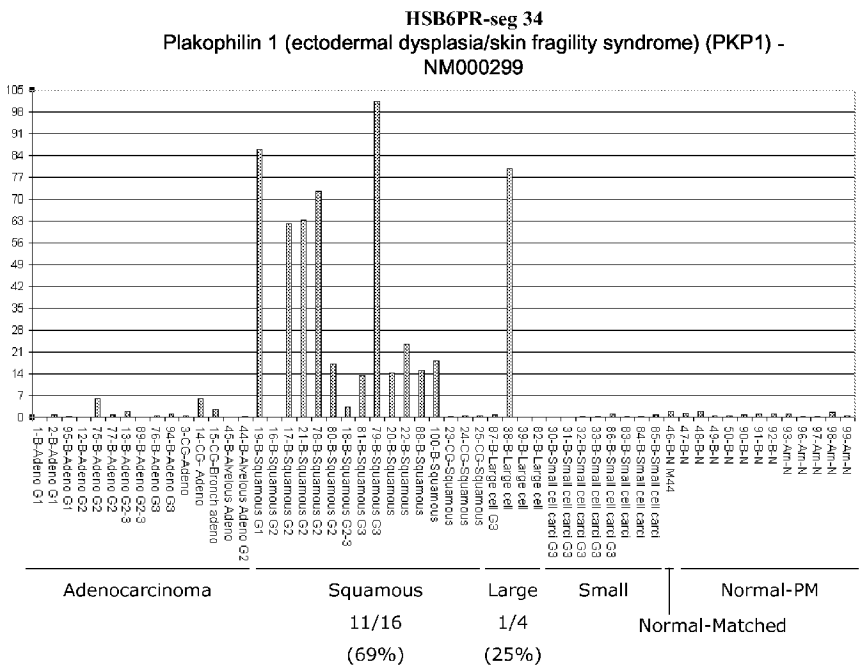


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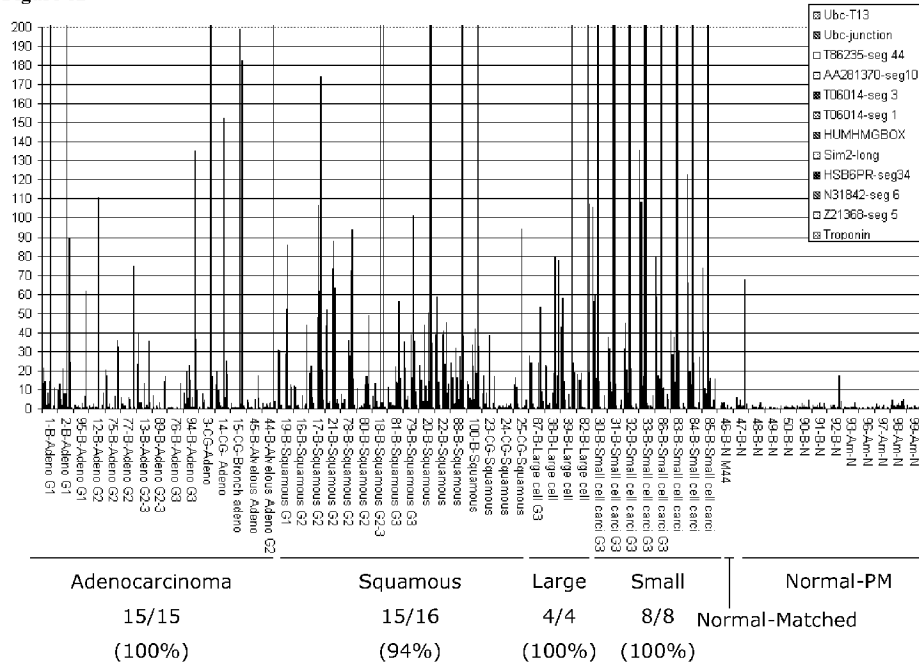


Figure 63a

>gi|47124623|gb|AAH70449.1|  Mapkbp1 protein [Mus musculus]

Length = 1503

Score = 311 bits (2354), Expect = 0.0
Identities = 447/759 (58%), Positives = 576/759 (75%), Gaps = 11/759 (1%)

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IP L LRR Δ IIVILKVLGIT GL CDP G VAY AGCVVVI
Sbjct: 19 STGCKLRRTX--AGNRSDLSKVTLEKVLGVTVSGRGLACDPRSGDVAYSAGCVVVLE 76

Query: 100 DPKRNKQQTPTNARKSTSAAPSPDGKYVTGTVNGRPAVRITWDVFPKQVARMGKYY 159
+P---+KQ HT N++RK++A"APSPDGKY+VTGP+GF PAVR+WDV P++QVARE+ HKY
Sbjct: 77 NPAKHKQGHLLNLSRKLI LALAKSPDGKYLVICSSGHEAVAYWDVAERSQVAELQEHKZ 136

Query: 160 GVACVAFSPENMKHIVSKGYCHDEVLNVMDNRKDIIVASNKVSGVIALGFSEDSSTYFVIV 219
GVACVAFSPFI R IVSIGYQHDIINVM NRKIIIVASNRVS RV AISPSTD SYFVT
Sbjct: 137 GVACVAFSPGAKYLVSGVGTQIDKLVNVWNRKNLVVASNKVSGVIAVSPGLDSTYFVIA 196

Query: 220 GAKHIVKFWPLXXXXXXXXXXXXXPLVGRSCLCELLAAFGCVAGGRNRKAGSHGVSEYCG 279
GVNHH+FW+ PL+GSGHISPTLN+P VACGRG A SPCH+ SG
Sbjct: 197 GYRIHKFWYLDGSKTSYVA"VPLTAGSG"ISPLANN"PTVACGRGPKAGSHCTTSSG 256

Query: 280 TLGGNTPKRYTAKWNLXXXXXXXXXXGNTIPCGGTDGTVRTQANSHIVIANPKPTV 339
LLG+T++R+C-KH+ L+ CE IFCGG DG VR+P +LH+L- LF+PH
Sbjct: 207 LLCEFSRRLLEDKVELDGVVHGLSVQGEYIFCGGADGTVRLFNCSNLHPLSLIDRHA 316

Query: 340 TGVGVAGQSTPDSPIPHKARAVYPTVA"TFDDTHQWTSCVYKDESTYKDYKDTNRVGR 399
LG DTA Δ S LP A YPDT-ALPDP +QWLSGVY DESLY+WDV-D +VCA
Sbjct: 317 LGTDIASLILASRLFGGVARYPDTALPDPDIAQWLSGVYADESLYWDVADPKKVCQ 376

Query: 400 VMSGLFHSFYVMNVVYPTSEED-QRACLESSEFLTCSSENTIISFWNLDSRP--DSHWQXX 456
V S +HSG VM VTYVPT D IACTP SPITCSSENTIRWN LSS S IY
Sbjct: 377 VIGALYHSGVMSVETYPALKDSHQACLPSPSPITCSSENTILALWNLCSGVLGTLHRA 436

Query: 457 ITGNILLKVVYVENDIQLLQDSHPDAGSLNCTPHDVKACVVMQVSEDDQLLASCDAS 516
T SN I+K++YV- + Q T D + P +G+ MG + G+R - +SP+GGTASGTR
Sbjct: 437 TLGNRIKTIIVVDNTQALD-TPLPGGKACGSTMGRVGTAGVCTSPNGQT"ASGTRM 495

Query: 517 GYTRTHPTITPMDIYKVVAIDAPVICTLYSKPPTG"ITASAGRER"TIIVLNVRKNYNTA 576
G LRIHEL - E++KVAED+E+LQLEYSKP+TCLLAFASRDLIHVL- +Y+L+
Sbjct: 496 GCLRIHILQGLSDMLKVZAEDEILQLEYSKPDTGLCLLAFASRDLIHVLDAGRDYSLQ 555

Query: 577 QTTDFHSSSTIAKPAEVR-DTQNTSGGAKSTYPRSAQQSEDGTHVRTTFFVARKTTTY 636
QLD+HSSSILA-KFA + ++ELSGGAKSLYPR-AQ+ +G- : RLHNV KILLZ
Sbjct: 566 QTTDFHSSSTIAVKPAAIDGGVRRITSGGAKSTYPR"AGKSGVGQTTRT"FFVARKTTTY 616

Query: 636 DMDIDITQYVAVACQDRVVRVYNTVXGKQKKCYKSGQDECSLKVHVDPSCITLATRC 696

```

DMD I I A A CQDA RIIN GKQKK IGGSGIISIL KY DRSG IATSC
Sbjct: 616 DMDVFRSKYTAAGQDRVTRFNTSSGKQKKLFRGSGQFQSTLRVQTDPSTYTATSC 675

Query: 636 SDASISYIDITYSGELIAAMLGSELTLSMKETLDC...LITVSGDSQVPLWLGELIIMK 755
SDK ISI DP SGRGIA MFGHSPTLP MKFI DG FTTVSGDSQIFIK I RIT M
Sbjct: 676 SDKNSIFDFSSGECVATHGHSRTLVGSKFSNDCKELISVSGDSQIFVWLGSEMILSR 735

Query: 756 QG...ELDHLQ---QQQ...NKKRGG...RQ...VVS 790
+Q I E+ RQ QQ D- ++ SG + V DS
Sbjct: 736 RQRATMRQQRGTKQGGPSSQGRASGAKGHHAPVWPS 774

```

Figure 63b

>gi|34856717|ref|XP_342499.1|  similar to JNK-binding protein JNKBP1 [Rattus norvegicus]
Length = 1530

Score = 910 bits (2353), Expect = 0.0

Identities = 467/868 (53%), Positives = 611/868 (70%), Gaps = 29/868 (3%)

```

Query: 40 APPCLRRRTLSFAS...TVQNRVSLKYL...CITAQASSGLI...DPG...GHVAYLAGGVVIL 99
+P - IRR - S - ++V+KKVSGH GH DDP -S VAY AGGVVV+
Sbjct: 18 GPGTKTRRKY--AGNRKSDSSKVTLKKVSGTVSGGRGLACDPRSGTNAVYPAGGVVVL 75

Query: 100 DPKRNKQGHFNTPARKSLSATAFSPDGKYLVTGTVGFRPAVRLTMDVFFKNQVAKMCHXY 159
+D---KQ III N+RK++-ALAFSPDGKY+VTGZ+GL DAVR+WDV E+NOYAE+ PKY
Sbjct: 76 NPKRHKQHHLNDSRKTICALAFSPDGKYLVTGSGGEMPAVRXWVDVAERNQVAEIQEHXY 135

Query: 160 GVACVAFSPNMRHTVSMGYCHDFVLNVWAKKKTIVVASNKVSGRVATLSPFSRDSYFVT 219
GVACVAFSP+ K-LVS+GYCHDE++VW WKK+LVVASNKVS RV A+SPGLD SYFVL
Sbjct: 136 GVACVAFSPGARYTVSGVGYCHDFTVNVWAKKNTIVVASNKVSGRVAVSPFSRDSYFVTA 195

Query: 220 GNRHIVRFWFLXXXXXXXXXXXXDLVGRGGILLGELNNIFGSAVACGRGRKAGSDTCVSYSG 279
GNRHIFWIL ELGGGILGEL NK F VACGEGI A GSECIIG
Sbjct: 196 GNRHIKFWYLDSDSKTCKVNAIVPLLGSGILLGELNNIFTDVACGRGRKAGSDTCITSG 255

Query: 280 LDCQ...NKR...LKKWLNK-----XXXXXXXXXXQ...LCCCTDGLVRIPQAL...HYLAN 333
LTC-+++++--KW+ L+ QF FCGC DG VR+P --H+L+
Sbjct: 256 LDCQSSDRALLEKAVELALDSFTTVAHCLRVQQLVLCGGADGLVRLEAPSNLHPLRT 315

Query: 334 LPKPHYLGVDAQGLEFGFLFHRKASAVYEDTVALCTDPIHQWLSCVYKDSGYIWDVXD 393
LP-DH LG D-A E S LF A A YDCT+ALCTDP +QWLSCVY DSGY+WDV+D
Sbjct: 318 LPKPHALGIDALITLHAGALSGGANAAYEDTIALDPDEANQWLSCVYNDSLYVWDVAD 375

Query: 394 TCRVGRKVS...FSSVWVWVVPFFED-GRAC...PSGSF...SSNTTFRFW...SSP--D 450
-VCKV+R L-HSS VW-VLYPE -D +ALP SP+LSSSNTTFR WA -SS
Sbjct: 376 PKVVGKVSATVHSSCVWGVVPFFTKDSNACTPSSFTTSSSNTTFRWYTRSSGVHG 435

```

Query: 431 SPWQKNIFEVYVKKVYVFNKDIQHIQDMSHFPTGSRNGTMDVYKAGVRYVMQVSQSGHT 570
 6 +NT SY -K++VV- - Q T D - P -G+ MD - G+R + -S+SQHT
 Subject: 436 SAJIRNILEADLKILYVDGNTQALLD-LLPCCDAAGSLMDPRVGLRVC-SFNCQL 494

Query: 511 ASGDRSGMLA-EHLHFKDS-KVEAE-DAEVLCLFYSKPEISLTLASASRDALHVLNV 570
 ASGER G LA-EEL + EL-KVEAE-D-E+LQLEYERD+TGL LLAASARDALHVL+
 Subject: 495 ASGDRMGLELHVELEQLSAL-KVEAE-DGELICLFYSKPEISLTLASASRDALHVLJAG 554

Query: 571 KXVNTQTTIDFSSSTTA-KFAGNR-DQMTSCGADKSTYPRSAQGSSTFVRTHHVA 629
 + Y-L+QILLD-LSSSLIA-KJA + --MLSCADKSTYPR+AQ- +G+ L RTHHV
 Subject: 555 KYSYQTTIDFSSSTTAVKFAAGGQVRNTSCGADKSTYPRTAGKSGPVGQTRTHHV 674

Query: 630 KXVNTQTTIDFSSSTTA-KFAGNR-DQMTSCGADKSTYPRSAQGSSTFVRTHHVA 689
 KXVNTQTTIDFSSSTTA-KFAGNR-DQMTSCGADKSTYPRSAQGSSTFVRTHHVA
 Subject: 615 KXVNTQTTIDFSSSTTAVKFAAGGQVRNTSCGADKSTYPRTAGKSGPVGQTRTHHV 674

Query: 690 FIADSGSTKSTSVTDFYSGRGTAKYRGPSTITTSMTFVYQHTFVSGRSCVFTWHIGP 749
 I ADGSGSTKSTSVTDFYSGRGTAKYRGPSTITTSMTFVYQHTFVSGRSCVFTWHIGP
 Subject: 675 FIADSGSTKSTSVTDFYSGRGTAKYRGPSTITTSMTFVYQHTFVSGRSCVFTWHIGP 734

Query: 700 EIDNCKQQLLELCHIQ---QQQHTNDKRRSCHPQDITYVSTPSEIHSLSPOXXXXXX 800
 E-D M+Q L E- RQ QQ T- -K SG - V PS P
 Subject: 735 EIDNCKQQLLELCHIQ---QQQHTNDKRRSCHPQDITYVSTPSEIHSLSPOXXXXXX 789

Query: 806 XXXXXXXXKLA-FSKJSLDFFPRLDLENGKLEL-----WAKLLGJJVADGSAFPAK 858
 - 2+ L + L-G P W ++ G A A
 Subject: 790 EIDNCKQQLLELCHIQ---QQQHTNDKRRSCHPQDITYVSTPSEIHSLSPOXXXXXX 789

Query: 859 KSYQPHGRWARRAGQPFITKTTTDAQDLD 886
 SHWA I I L L
 Subject: 800 KSYQPHGRWARRAGQPFITKTTTDAQDLD 886

Figure 64

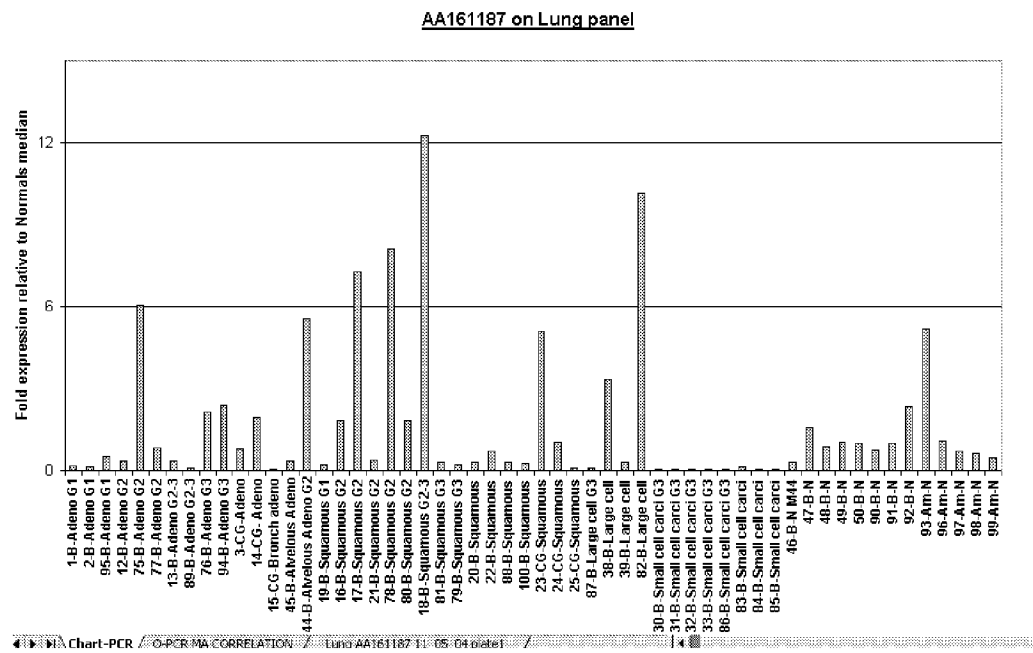
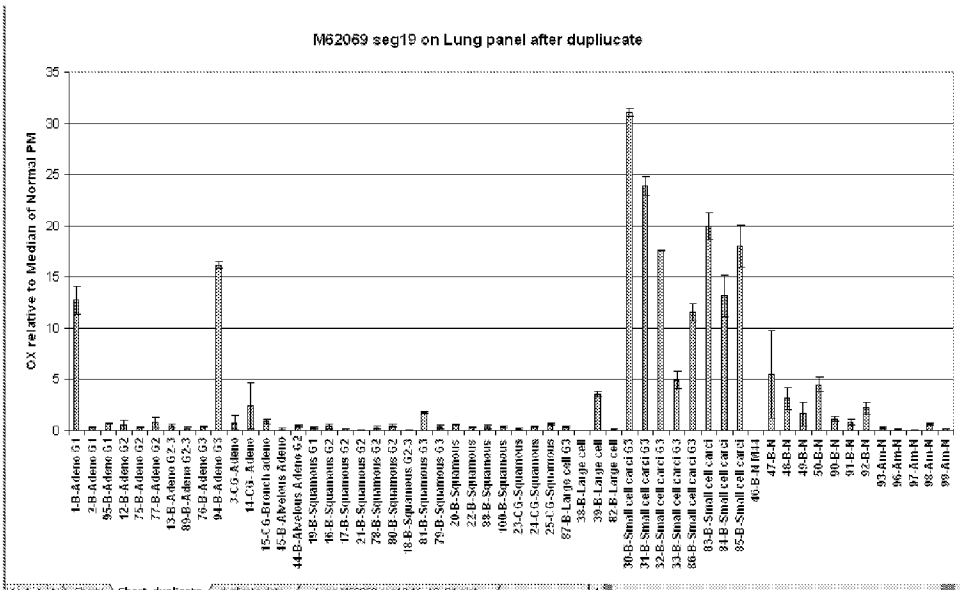


Figure 65



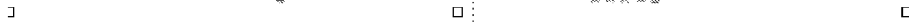
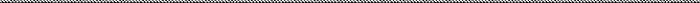


Figure 67

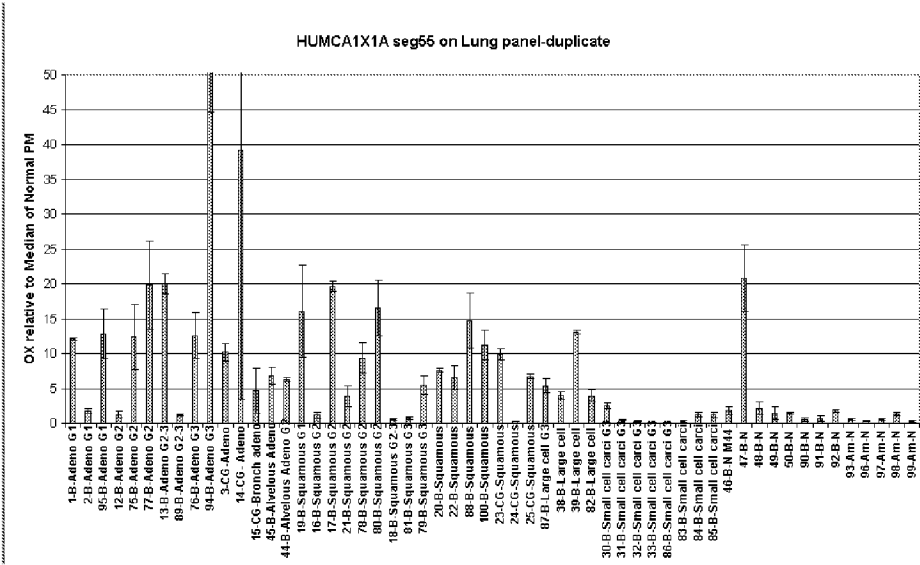


Figure 68

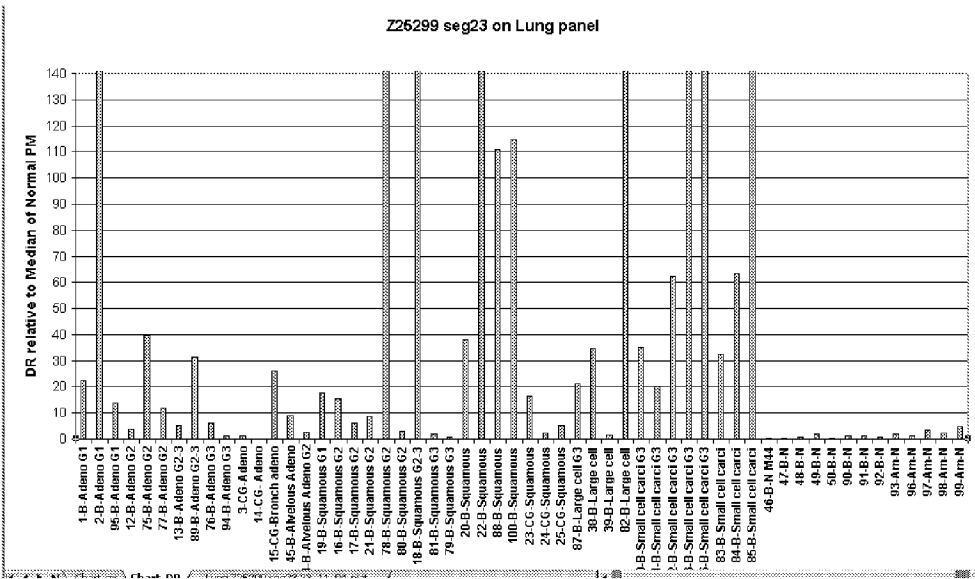


Figure 69

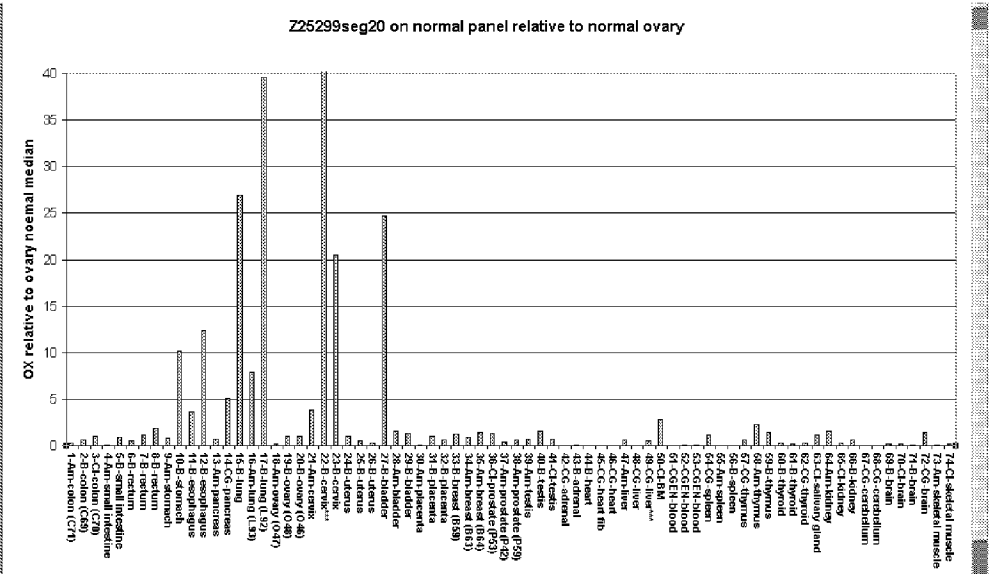


Figure 70

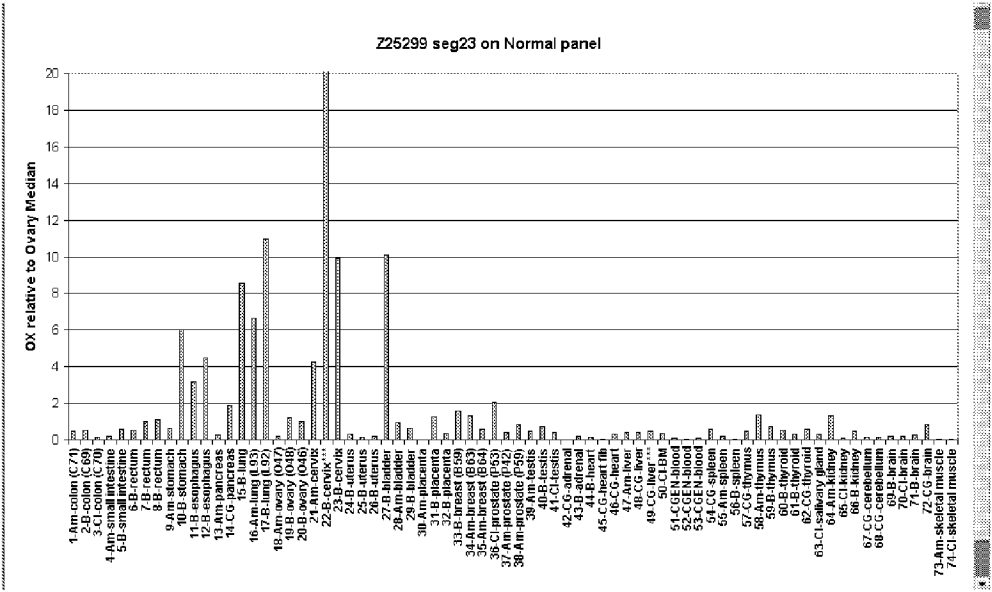


Figure 71

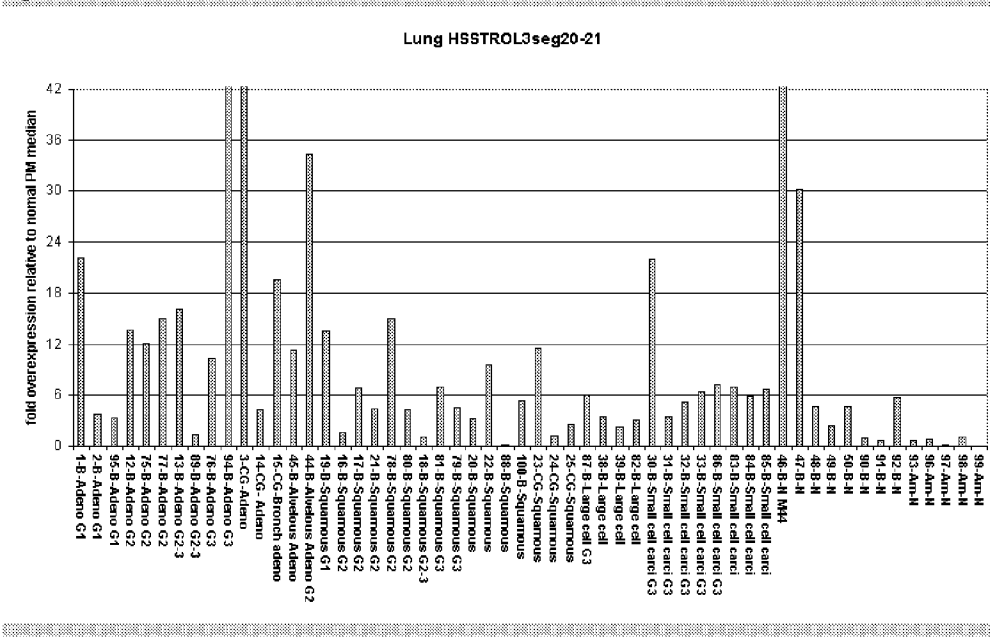


Figure 72

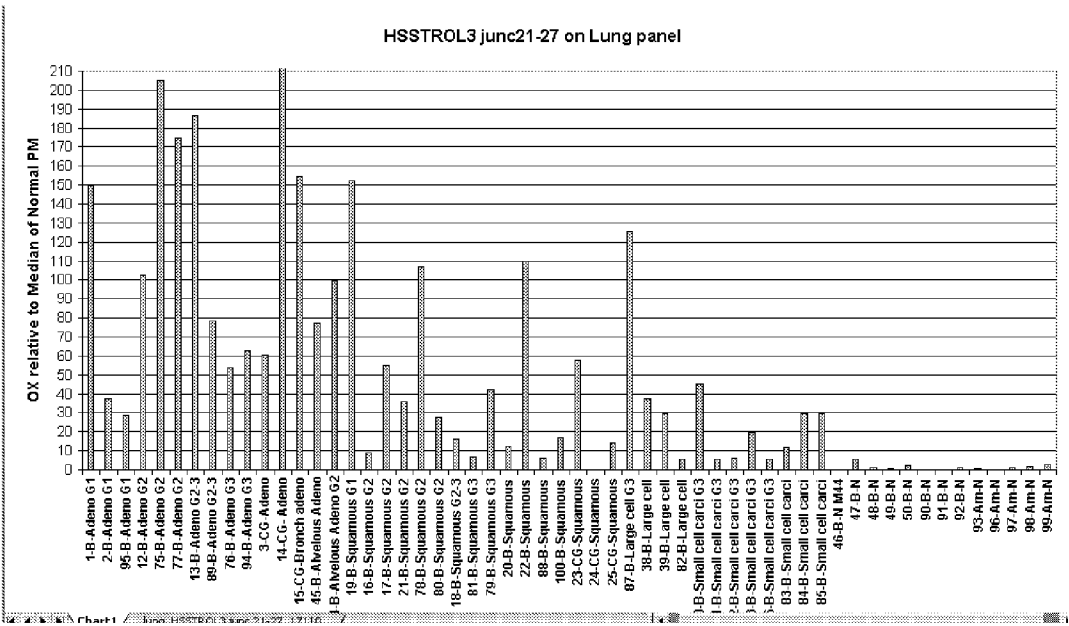


Figure 73

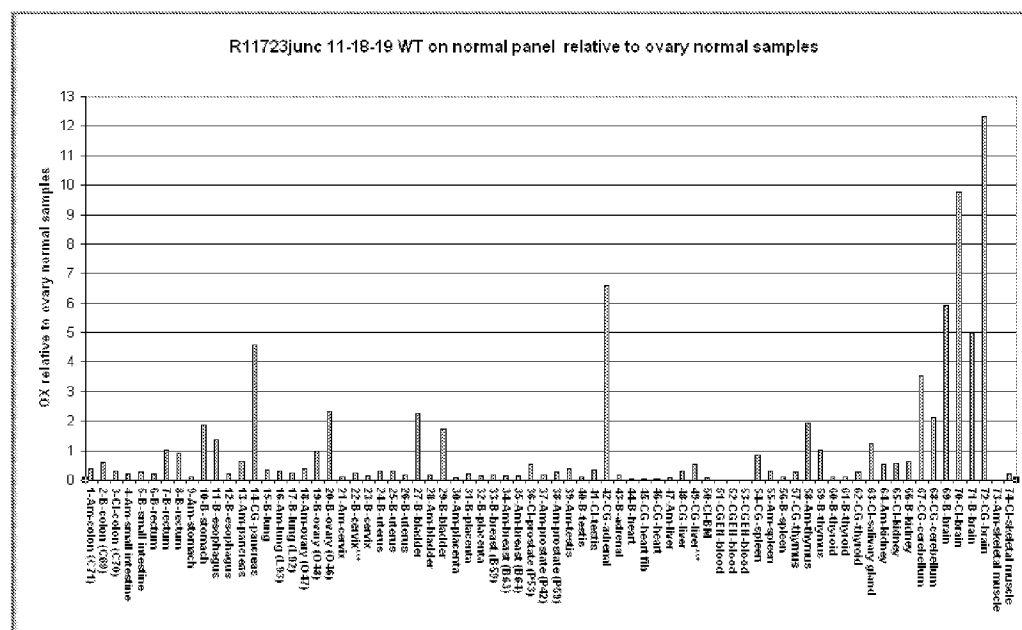


Figure 74

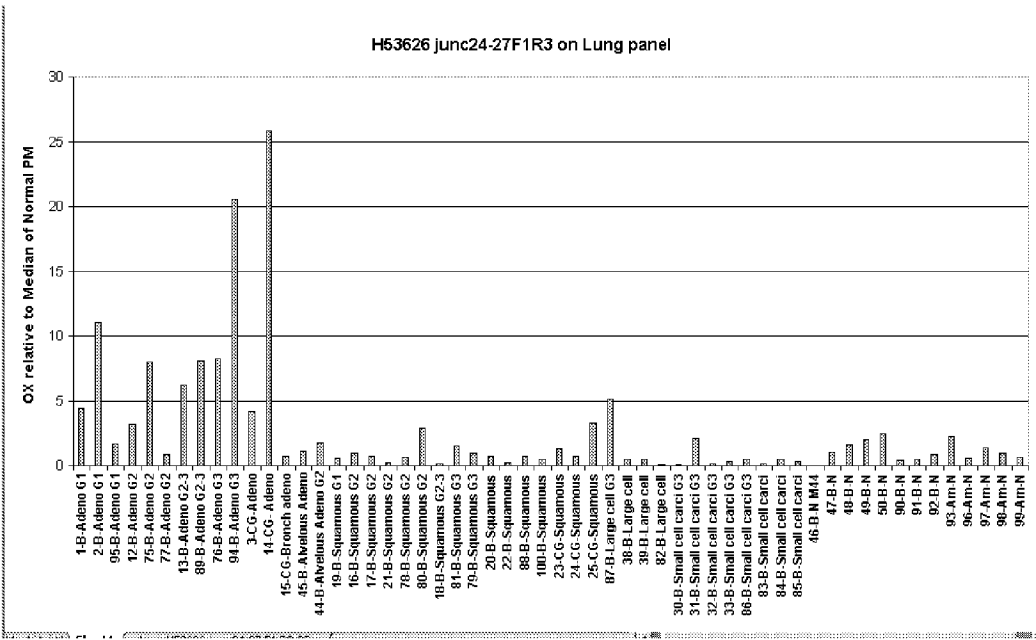


Figure 75

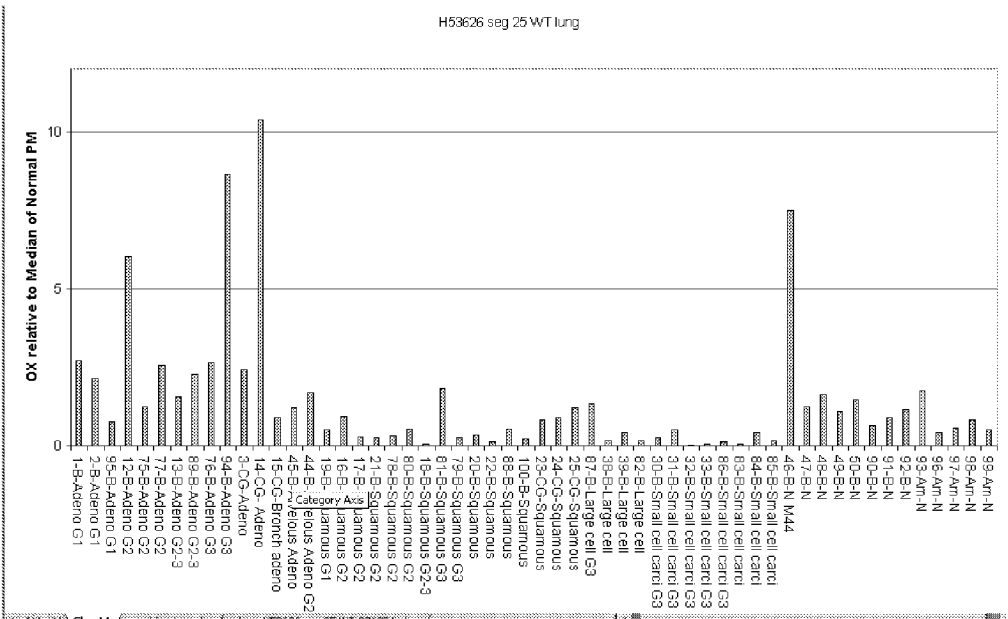


Figure 76

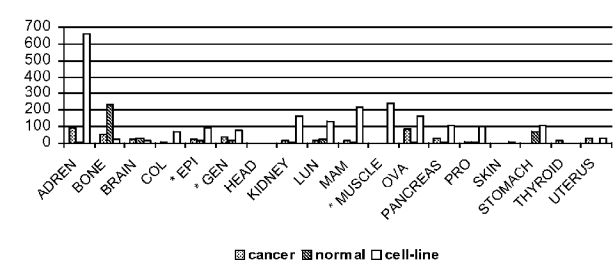


Figure 77

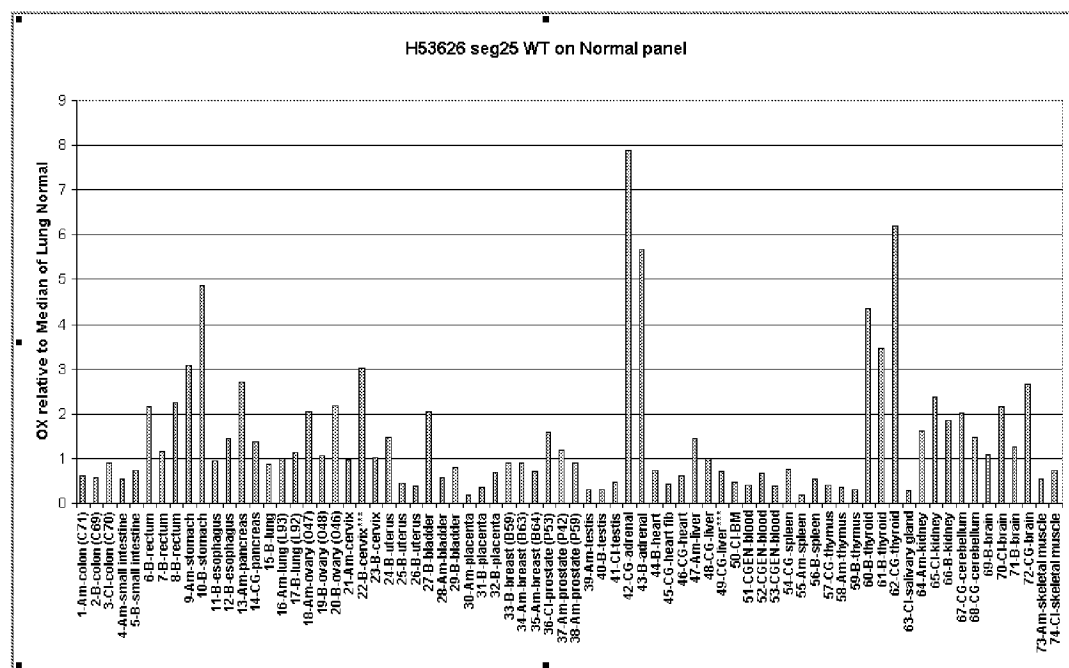


Figure 79

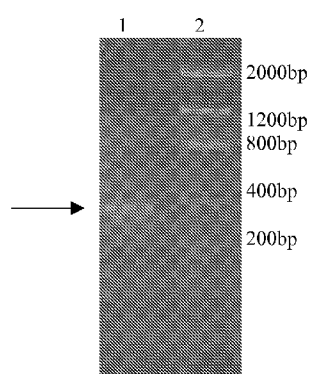


Figure 80

TGCTGTCGCCCTCCTGTGATGCGCTTGCCCTCTCCGGCCCCGGGACTCCGGGAGAAATGTGGGTCCTAGGCATCGCG
GCAACTTTTIGCGGATTGTTCTTGCTTCCAGGCTTTGCGCTGCAAAATCCAGTGCTACCAGTGTGAAGAATTCCAGCT
GAACAACGACTGCTCCTCCCCGAGTTCATTGTGAATTGCACGGTGAACGTTCAAGACATGTGTCAGAAAGAAGTG
ATGGAGCAAAGTGCCGACACTAAAAGAACAACACCTTGCTCTTCGAGATGAGACATTTTGCCAAGCAGTTGACCA
CTTAGTTCTCAAGAAGCAACTATCTCTTTCATGTGCCTTCTGAGG

Figure 81

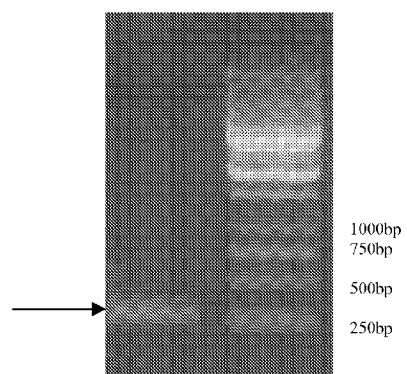


Figure 82

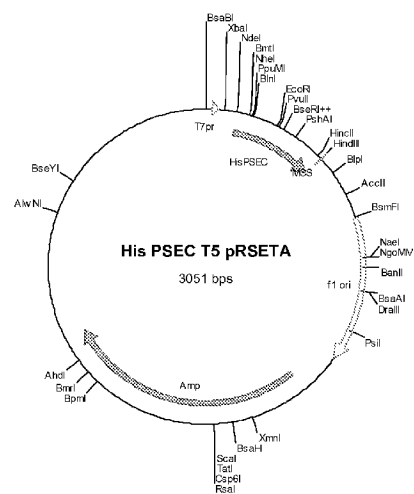


Figure 83

MRGSHHHHHHGMASMWVLGIAATFCGLFLLPGFALQICYQCEEFQLNNDCSSPEFIVNCTVNVQDMCQKEVMEQSADTKRT
NTLLFEMRHFALQLTT

Figure 84

GATCTCGATCCCGCGAAATTAATACGACTCACTATAGGGAGACCACAACGGTTTCCCTCTAGAAATAATTTTGTTAACTTTAAG
AAGGAGATATACATATGCGGGGTTCTCATCATCATCATCATGGTATGGCTAGCATGTGGGTCTTAGGCATCGCGG
CAACTTTTGGCGGATTGTTCTTGCTTCCAGGCTTTGCGCTGCAAATCCAGTGCTACCAGTGGAAGAATTCCAGCTG
AACAACGACTGCTCCTCCCCGAGTTTCATTGTGAATTGCACGGTGAAACGTTCAAGACATGTGTGAGAAAGAAGTGA
TGGAGCAAAGTGCCGACACTAAAAGAACAACACCTTGCTCTTCGAGATGAGACATTTTGCCAAGCAGTTGACCAC
TTAGAAAGCTTGATCCGGCTGCTAACAAAGCCCCGAAAGGAAGCTGAGTTGGCTGCTGCCACCGCTGAGCAATAACTAGCATAACCC
CTTGGGGCCTCTAAACGGGTCTTGAGGGGTTTTTGTCTGAAAGGAGGAACTATATCCGGATCTGGCGTAATAGCGAAGAGGCCCCG
CACCGATCGCCCTTCCCAACAGTTGCGCAGCCTGAATGGCGAATGGGACGCGCCCTGTAGCGGCGCATTAAAGCGGGCGGGTGT
GGTGGTTACGCGCAGCGTGACCGCTACACTTGCCAGCGCCCTAGCGCCCGCTCCTTTTCGCTTTCTTCCCTTCCTTTCTCGCCAC
GTTTCGCCGGCTTTCCCCGTCAAGCTCTAAATCGGGGGCTCCCTTTAAGGTTCCGATTTAGTGCTTTACGGCACCTCGACCCC
AAAAAACTTGATTAGGGTGATGGTTCACGTAGTGGGCCATCGCCCTGATAGACGGTTTTTCGCCCTTTGACGTTGGAGTCC
ACGTTCTTTAATAGTGGACTCTTGTTCCAAACTGGAACAACACTCAACCCTATCTCGGTCTATTCTTTGATTATAAGGGA
TTTTGCCGATTTGGCCCTATTGGTTAAAAAATGAGCTGATTTAACAAAAATTTAACGCGAATTTTAACAAAATATTAACGC
TTACAATTTAGGTGGCACTTTTCGGGGAAATGTGCGCGGAACCCCTATTTGTTTATTTTCTAAATACATTCAAATATGTAT
CCGCTCATGAGACAATAACCTGATAAATGCTTCAATAATATTGAAAAAGGAAGAGTATGAGTATTCAACATTTCCGTGTC
GCCCTTATTCCCTTTTTTTCGGGCATTTTGCCCTTCCTGTTTTTGTCTACCCAGAAACGCTGGTGAAAGTAAAAGATGCTGAAG
ATCAGTTGGGTGCACGAGTGGGTTACATCGAACTGGATCTCAACAGCGGTAAGATCCTTGAGAGTTTTTCGCCCCGAAGAA
CGTTTTCCAATGATGAGCACTTTTAAAGTTCTGCTATGTGGCGCGGTATTATCCCGTATTGACGCCGGGCAAGAGCAACTC
GGTCGCCGCATACACTATTCTCAGAATGACTTGTTGAGTACTACCAGTACACAGAAAAGCATCTTACGGATGGCATGACA
GTAAGAGAATTATGCAGTGCTGCCATAACCATGAGTGATAACACTGCGGCCAACTTACTTCTGACAACGATCGGAGGACC
GAAGGAGCTAACCGCTTTTTTGCACAACATGGGGGATCATGTAACCTCGCCTTGATCGTTGGGAACCGGAGCTGAATGAAG
CCATACCAAACGACGAGCGTGACACCACGATGCCTGTAGCAATGGCAACAACGTTGCGCAAACTATTAAGTGGCGAACTA

CTTACTCTAGCTTCCCGCAACAATTAATAGACTGGATGGAGGCGGATAAAAGTTGCAGGACCACCTTCTGCGCTCGGCCCTT
CCGGCTGGCTGGTTTATTGCTGATAAATCTGGAGCCGGTGAGCGTGGGTCTCGCGGTATCATTGCAGCACTGGGGCCAGAT
GGTAAGCCCTCCCGTATCGTAGTTATCTACACGACGGGGAGTCAGGCAACTATGGATGAACGAAATAGACAGATCGCTGA
GATAGGTGCCTCACTGATTAAGCATTGGTAACTGTCAGACCAAGTTTACTCATATATACTTTAGATTGATTAAAACTTCAT
TTTTAATTTAAAAGGATCTAGGTGAAGATCCTTTTTGATAATCTCATGACCAAAATCCCTTAACGTGAGTTTTCGTTCCACT
GAGCGTCAGACCCCGTAGAAAAGATCAAAGGATCTTCTTGAGATCCTTTTTTCTGCGCGTAATCTGCTGCTTGCAAACAA
AAAAACCACCGCTACCAGCGGTGGTTTGTGTTGCCGGATCAAGAGCTACCAACTCTTTTTCCGAAGGTAAGTGGCTTCAGCA
GAGCGCAGATACCAAATACTGTTCTTCTAGTGTAGCCGTAGTTAGGCCACCACTTCAAGAACTCTGTAGCACCGCCTACAT
ACCTCGCTCTGCTAATCCTGTTACCAGTGGCTGCTGCCAGTGGCGATAAGTCGTGTCTTACCGGGTTGGACTCAAGACGAT
AGTTACCGGATAAGGCGCAGCGGTGCGGCTGAACGGGGGGTTCTGTGCACACAGCCCAGCTTGGAGCGAACGACCTACACC
GAACTGAGATACCTACAGCGTGAGCTATGAGAAAGCGCCACGCTTCCCGAAGGGAGAAAGGCGGACAGGTATCCGGTAA
GCGGCAGGGTCGGAACAGGAGAGCGCACGAGGGAGCTTCCAGGGGGAAACGCCTGGTATCTTTATAGTCCTGTGCGGGTTT
CGCCACCTCTGACTTGAGCGTCGATTTTTGTGATGCTGCTCAGGGGGGCGGAGCCTATGGAAAAACGC
CAGCAACGCGGCCTTTTTACGGTTCCTGGCCTTTTGCTGGCCTTTTGCTCACATGTTCTTTCCTGCGTTATCCCCTGATTCTG
TGGATAACCGTATTACCGCCTTTGAGTGAGCTGATACCGCTCGCCGAGCCGAACGACCGAGCGCAGCGAGTCAGTGAGC
GAGGAAGCGGAAGAGCGCCAATACGCAAACCGCCTCTCCCGCGCGTTGGCCGATTCATTAATGCAG

Figure 85

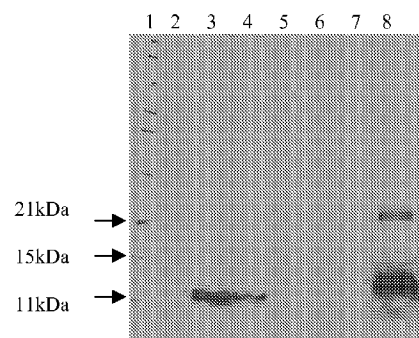


Figure 78

