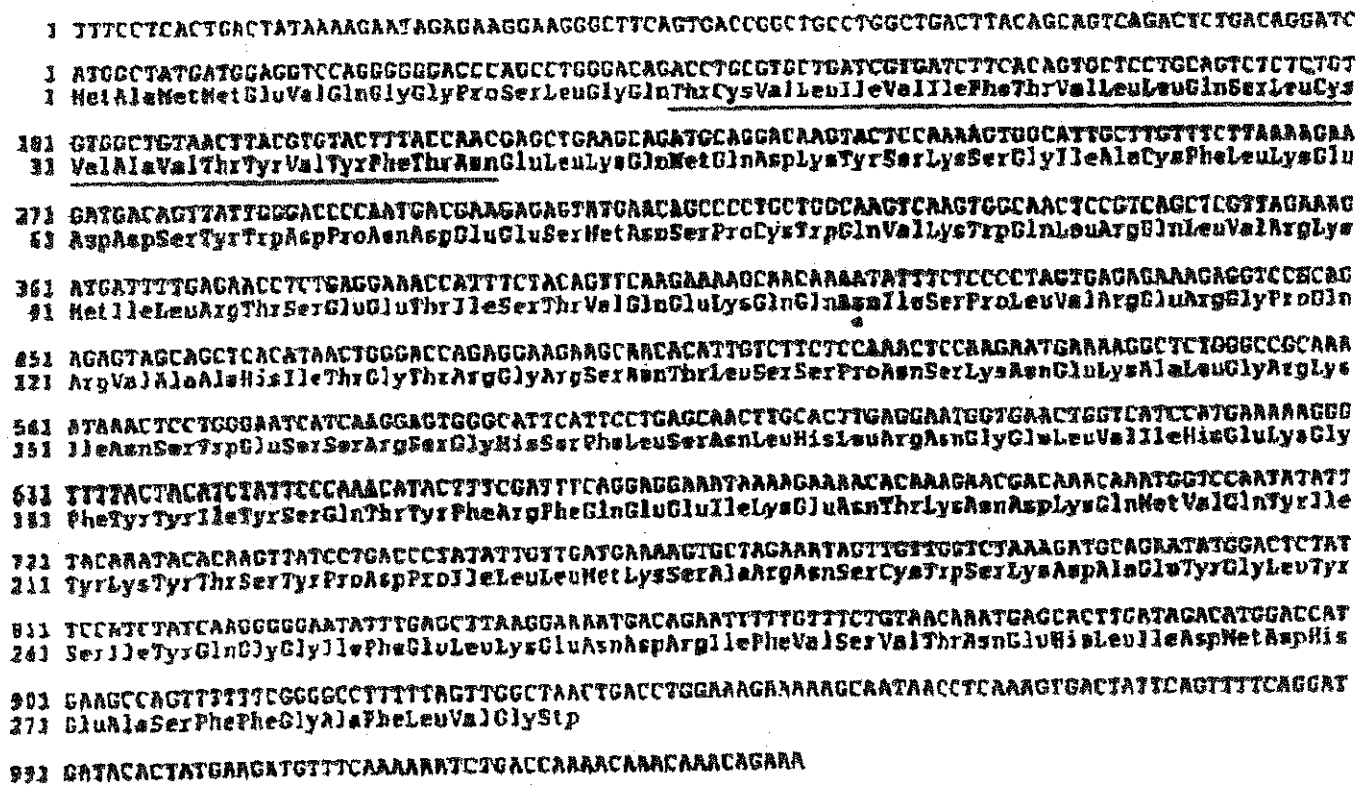

1 TTTCCTCACTGACTATAAAAGAATAGAGAAGGAAGGGCTTCAGTGACCGCCTGCCTGGCTGACTTACAGCAGTCAGACTCTGACAGGATC
1 ATGGCTATGATGGAGGTCCAGGGGGGACCCAGCCTGGGACAGACCTGCGTGCTGATCGTGATCTTCACAGTGCTCCTGCAGTCTCTCTGT
1 MetAlaMetMetGluValGlnGlyGlyProSerLeuGlyGlnThrCysValLeuIleValIlePheThrValLeuLeuGlnSerLeuCys
101 GTGGCTGTAACTTACGTGTACTTTACCAACGAGCTGAAGCAGATGCAGGACAAGTACTCCAAAAGTGGCATTGCTTGTTTCTTAAAAGAA
31 ValAlaValThrTyrValTyrPheThrAsnGluLeuLysGlnMetGlnAspLysTyrSerLysSerGlyIleAlaCysPheLeuLysGlu
271 GATGACAGTTATTGGGACCCCAATGACGAAGAGAGTATGAACAGCCCCTGCTGGCAAGTCAAGTGGCAACTCCGTCAGCTCGTTAGAAAG
61 AspAspSerTyrTrpAspProAsnAspGluGluSerMetAsnSerProCysTrpGlnValLysTrpGlnLeuArgGlnLeuValArgLys
361 ATGATTTTGAGAACCTCTGAGGAAACCATTTCTACAGTTCAAGAAAAGCAACAAAATATTTCTCCCCTAGTGACAGAAAGAGGTCCHCAG
91 MetIleLeuArgThrSerGluGluThrIleSerThrValGlnGluLysGlnGlnAsnIleSerProLeuValArgGluArgGlyProGln
451 AGAGTAGCAGCTCACATAACTGGGACCAGAGGAAGAAGCAACACATTGTCTTCTCCAAACTCCAAGAATGAAAAGGCTCTGGGCCGCAAA
121 ArgValAlaAlaHisIleThrGlyThrArgGlyArgSerAsnThrLeuSerSerProAsnSerLysAsnGluLysAlaLeuGlyArgLys
541 ATAAACTCCTGGGAATCATCAAGGAGTGGGCATTCATTCCTGAGCAACTTGCACTTGAGGAATGGTGAACTGGTCATCCATGAAAAAGGG
151 IleAsnSerTrpGluSerSerArgSerGlyHisSerPheLeuSerAsnLeuHisLeuArgAsnGlyGluLeuValIleHisGluLysGly
631 TTTTACTACATCTATTCCCAAACATACTTTCGATTTCAGGAGGAAATAAAAGAAAACACAAAGAACGACAAACAAATGGTCCAATATATT
181 PheTyrTyrIleTyrSerGlnThrTyrPheArgPheGlnGluGluIleLysGluAsnThrLysAsnAspLysGlnMetValGlnTyrIle
721 TACAAATACACAAGTTATCCTGACCCTATATTGTTGATGAAAAGTGCTAGAAATAGTTGTTGGTCTAAAGATGCAGAATATGGACTCTAT
211 TyrLysTyrThrSerTyrProAspProIleLeuLeuMetLysSerAlaArgAsnSerCysTrpSerLysAspAlaGluTyrGlyLeuTyr
811 TCCATCTATCAAGGGGGAATATTTGAGCTTAAGGAAAATGACAGAATTTTTGTTTCTGTAACAAATGAGCACTTGATAGACATGGACCAT
241 SerIleTyrGlnGlyGlyIlePheGluLeuLysGluAsnAspArgIlePheValSerValThrAsnGluHisLeuIleAspMetAspHis
901 GAAGCCAGTTTTTTCGGGGCCTTTTTAGTTGGCTAACTGACCTGGAAAGAAAAAGCAATAACCTCAAAGTGACTATTCAGTTTTCAGGAT
271 GluAlaSerPhePheGlyAlaPheLeuValGlyStp
991 GATACACTATGAAGATGTTTCAAAAAATCTGACCAAAACAAACAAACAGAAA

FIG._1

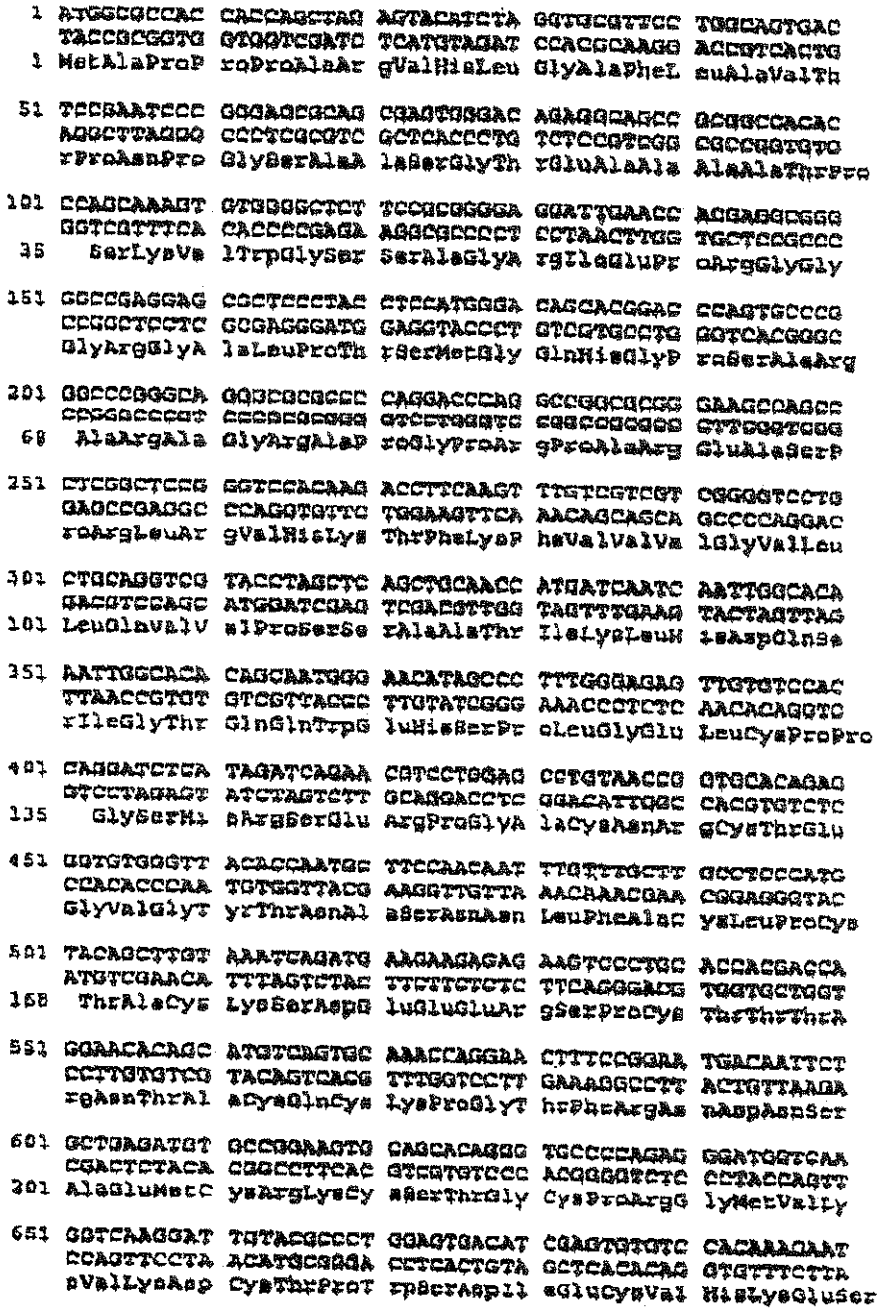


FIG. 2A

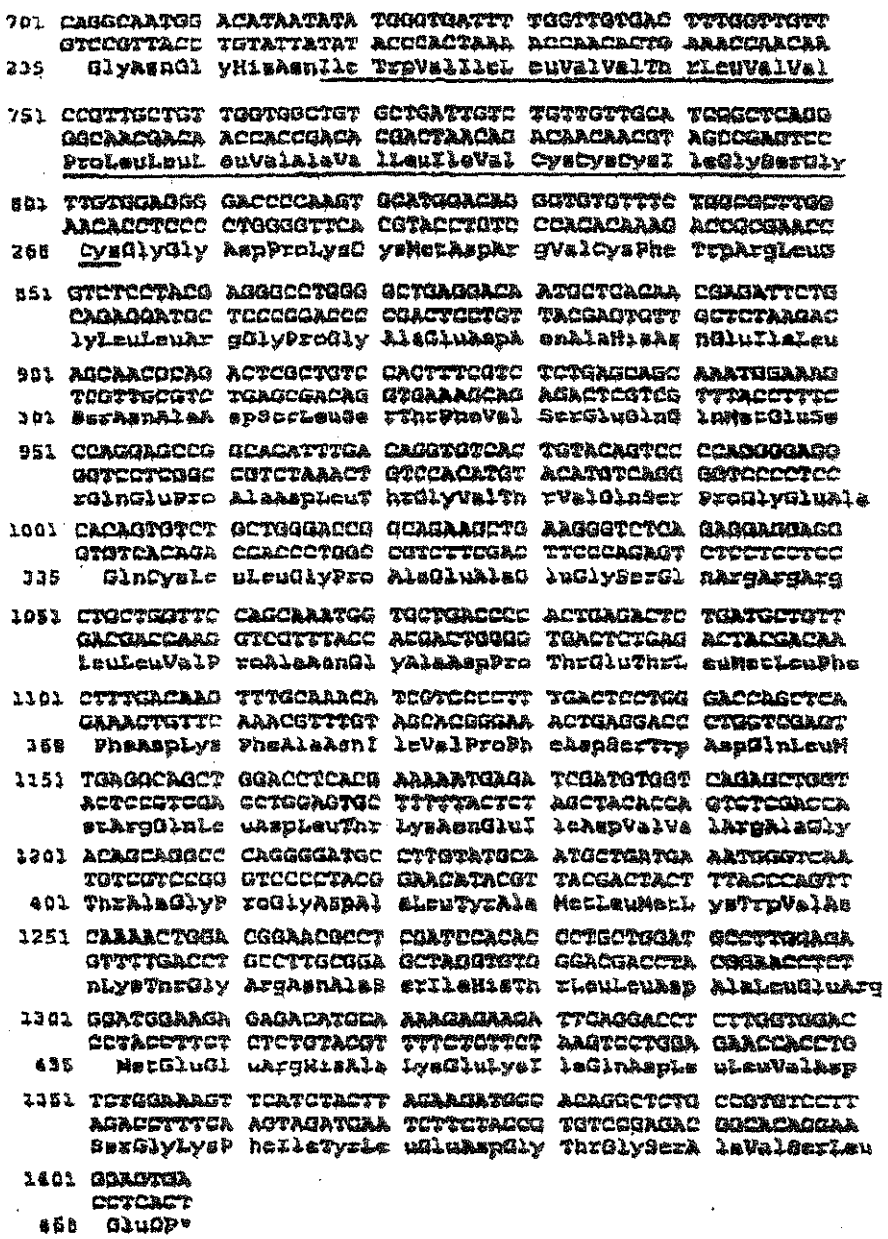


FIG. 2B

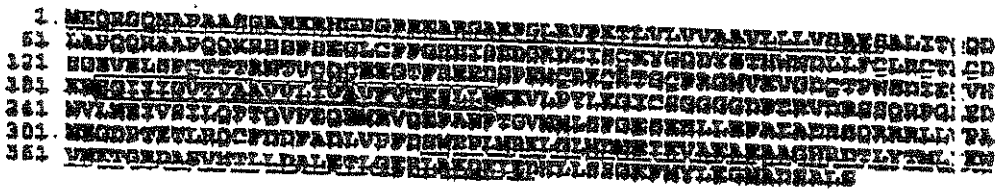


FIG._3A

Met Glu Gln Arg Gly Gln Asn Ala Pro Ala Ala Ser Gly Ala Arg Lys
1 5 10 15

Arg His Gly Pro Gly Pro Arg Glu Ala Arg Gly Ala Arg Pro Gly Pro
20 25 30

Arg Val Pro Lys Thr Leu Val Leu Val Val Ala Ala Val Leu Leu Leu
35 40 45

Val Ser Ala Glu Ser Ala Leu Ile Thr Gln Gln Asp Leu Ala Pro Gln
50 55 60

Gln Arg Ala Ala Pro Gln Gln Lys Arg Ser Ser Pro Ser Glu Gly Leu
65 70 75 80

Cys Pro Pro Gly His His Ile Ser Glu Asp Gly Arg Asp Cys Ile Ser
85 90 95

Cys Lys Tyr Gly Gln Asp Tyr Ser Thr His Trp Asn Asp Leu Leu Phe
100 105 110

Cys Leu Arg Cys Thr Arg Cys Asp Ser Gly Glu Val Glu Leu Ser Pro
115 120 125

Cys Thr Thr Thr Arg Asn Thr Val Cys Gln Cys Glu Glu Gly Thr Phe
130 135 140

Arg Glu Glu Asp Ser Pro Glu Met Cys Arg Lys Cys Arg Thr Gly Cys
145 150 155 160

Pro Arg Gly Met Val Lys Val Gly Asp Cys Thr Pro Trp Ser Asp Ile
165 170 175

Glu Cys Val His Lys Glu Ser Gly Thr Lys His Ser Gly Glu Ala Pro
180 185 190

Ala Val Glu Glu Thr Val Thr Ser Ser Pro Gly Thr Pro Ala Ser Pro
195 200 205

Cys Ser Leu Ser Gly Ile Ile Ile Gly Val Thr Val Ala Ala Val Val
210 215 220

Leu Ile Val Ala Val Phe Val Cys Lys Ser Leu Leu Trp Lys Lys Val
225 230 235 240

Leu Pro Tyr Leu Lys Gly Ile Cys Ser Gly Gly Gly Gly Asp Pro Glu
245 250 255

Arg Val Asp Arg Ser Ser Gln Arg Pro Gly Ala Glu Asp Asn Val Leu
260 265 270

Asn Glu Ile Val Ser Ile Leu Gln Pro Thr Gln Val Pro Glu Gln Glu
275 280 285

FIG._3B

Met Glu Val Gln Glu Pro Ala Glu Pro Thr Gly Val Asn Met Leu Ser
290 295 300

Pro Gly Glu Ser Glu His Leu Leu Glu Pro Ala Glu Ala Glu Arg Ser
305 310 315 320

Gln Arg Arg Arg Leu Leu Val Pro Ala Asn Glu Gly Asp Pro Thr Glu
325 330 335

Thr Leu Arg Gln Cys Phe Asp Asp Phe Ala Asp Leu Val Pro Phe Asp
340 345 350

Ser Trp Glu Pro Leu Met Arg Lys Leu Gly Leu Met Asp Asn Glu Ile
355 360 365

Lys Val Ala Lys Ala Glu Ala Ala Gly His Arg Asp Thr Leu Tyr Thr
370 375 380

Met Leu Ile Lys Trp Val Asn Lys Thr Gly Arg Asp Ala Ser Val His
385 390 395 400

Thr Leu Leu Asp Ala Leu Glu Thr Leu Gly Glu Arg Leu Ala Lys Gln
405 410 415

Lys Ile Glu Asp His Leu Leu Ser Ser Gly Lys Phe Met Tyr Leu Glu
420 425 430

Gly Asn Ala Asp Ser Ala Met Ser *
435 440

FIG._3C

```
   1 GCTGTGGGAA CCTCTCCACG CGCACGAACT CAGCCAACGA TTTCTGATAG ATTTTTGGGA GTTTGACCAG AGATGCAAGG GGTGAAGGAG CGCTTCCTAC
     CGACACCCTT GGAGAGGTGC GCGTGCTTGA GTCGGTTGCT AAAGACTATC TAAAAACCCT CAAACTGGTC TCTACGTTCC CCACTTCCTC GCGAAGGATG

 101 CGTTAGGGAA CTCTGGGGAC AGAGCGCCCC GGCCGCCTGA TGGCCGAGGC AGGGTGCGAC CCAGGACCCA GGACGGCGTC GGGAACCATA CCATGGCCCG
     GCAATCCCTT GAGACCCCTG TCTCGCGGGG CCGGCGGACT ACCGGCTCCG TCCCACGCTG GGTCCTGGGT CCTGCCGCAG CCCTTGGTAT GGTACCGGGC
   1                                                                                                   MetAlaArg

 201 GATCCCCAAG ACCCTAAAGT TCGTCGTCGT CATCGTCGCG GTCCTGCTGC CAGTCCTAGC TTACTCTCCC ACCACTGCCC GGCAGGAGGA AGTTCCCCAG
     CTAGGGGTTC TGGGATTTCA AGCAGCAGCA GTAGCAGCGC CAGGACGACG GTCAGGATCG AATGAGACGG TGGTGACGGG CCGTCCTCCT TCAAGGGGTC
   4  IleProLys ThrLeuLysP heValValVa lIleValAla ValLeuLeuP roValLeuAl aTyrSerAla ThrThrAlaA rgGlnGluGl uValProGln

 301 CAGACAGTGG CCCCACAGCA ACAGAGCCAC AGCTTCAAGG GGGAGGAGTG TCCAGCAGGA TCTCATAGAT CAGAACATAC TGGAGCCTGT AACCCGTGCA
     GTCTGTCACC GGGGTGTCGT TGTCTCCGTG TCGAAGTTCC CCCTCCTCAC AGGTCGTCCT AGAGTATCTA GTCTTGTATG ACCTCGGACA TTGGGCACGT
  37 GlnThrValA laProGlnGL nGlnArgHis SerPheLysG lyGluGluCy sProAlaGly SerHisArgS erGluHisTh rGlyAlaCys AsnProCysThr

 401 CAGAGGGTGT GGATTACACC AACGCTTCCA ACAATGAACC TTCTTGCTTC CCATGTACAG TTTGTAAATC AGATCAAAAA CATAAAAGTT CCTGCACCAT
     GTCTCCCACA CCTAATGTGG TTGCGAAGGT TGTTACTTGG AAGAACGAAG GGTACATGTC AAACATTTAG TCTAGTTTTT GTATTTTCAA GGACGTGGTA
  71   GluGlyVa lAspTyrThr AsnAlaSerA snAsnGluPr oSerCysPhe ProCysThrV alCysLysSe rAspGlnLys HisLysSerS erCysThrMet

 501 GACCAGAGAC ACAGTGTGTC AGTGTAAAGA AGGCACCTTC CGGAATGAAA ACTCCCCAGA GATGTGCCGG AAGTGTAGCA GGTGCCCTAG TGGGGAAGTC
     CTGGTCTCTG TGTCACACAG TCACATTTCT TCCGTGGAAG GCCTTACTTT TGAGGGGTCT CTACACGGCC TTCACATCGT CCACGGGATC ACCCCTTCAG
 104  ThrArgAsp ThrValCysG lnCysLysGl uGlyThrPhe ArgAsnGluA snSerProGl uMetCysArg LysCysSerA rgCysProSe rGlyGluVal

 601 CAAGTCAGTA ATTGTACGTC CTGGGATGAT ATCCAGTGTG TTGAAGAATT TGGTGCCAAT GCCACTGTGG AAACCCCAGC TGCTGAAGAG ACAATGAACA
     GTTCAGTCAT TAACATGCAG GACCCTACTA TAGGTCACAC AACTTCTTAA ACCACGGTTA CGGTGACACC TTTGGGGTCG ACGACTTCTC TGTTACTTGT
 137 GlnValSerA snCysThrSe rTrpAspAsp IleGlnCysV alGluGluPh eGlyAlaAsn AlaThrValG luThrProAl aAlaGluGlu ThrMetAsnThr

 701 CCAGCCCGGG GACTCCTGCC CCAGCTGCTG AAGAGACAAT GAACACCAGC CCAGGGACTC CTGCCCCAGC TGCTGAAGAG ACAATGACCA CCAGCCCGGG
     GGTCGGGCCC CTGAGGACGG GGTCGACGAC TTCTCTGTTA CTTGTGGTCG GGTCCCTGAG GACGGGGTCG ACGACTTCTC TGTTACTGGT GGTCGGGCCC
 171   SerProGl yThrProAla ProAlaAlaG luGluThrMe tAsnThrSer ProGlyThrP roAlaProAl aAlaGluGlu ThrMetThrT hrSerProGly
```

FIG. 3D-1

```
801 GACTCCTGCC CCAGCTGCTG AAGACACAAT GACCACCAGC CCGGCGACTC CTGCCCCAGC TGCTGAAGAG ACAATGACCA CCAGCCCGGG GACTCCTGCC
    CTGAGGACGG GGTCGACGAC TTCTCTGTTA CTGGTGGTCG GGCCCCTGAG GACGGGGTCG ACGACTTCTC TGTTACTGGT GGTCGGGCCC CTGAGGACGG
204  ThrProAla ProAlaAlaG luGluThrMe tThrThrSer ProGlyThrP roAlaProAl aAlaGluGlu ThrMetThrT hrSerProGl yThrProAla

901 TCTTCTCATT ACCTCTCATG CACCATCGTA GGCATCATAG TTCTAATTGT GCTTCTGATT GTGTTTGTTT GAAAGACTTC ACTGTGGAAG AAATTCCTTC
    AGAAGAGTAA TGGAGAGTAC GTGGTAGCAT CCGTAGTATC AAGATTAACA CGAAGACTAA CACAAACAAA CTTTCTGAAG TGACACCTTC TTTAAGGAAG
237 SerSerHisT yrLeuSerCy sThrIleVal GlyIleIleV alLeuIleVa lLeuLeuIle ValPheVal

1001 CTTACCTGAA AGGTTCAGGT AGGCGCTGGC TGAGGGCGGG GGGCGCTGGA CACTCTCTGC CCTGCCTCCC TCTGCTGTGT TCCCACAGAC AGAAACGCCT
     GAATGGACTT TCCAAGTCCA TCCGCGACCG ACTCCCGCCC CCCGCGACCT GTGAGAGACG GGACGGAGGG AGACGACACA AGGGTGTCTG TCTTTGCGGA

1101 GCCCCTGCCC CAAAAAAAAA AAAAAAAAAA AAAAAAAAAA AAAAAAAAAA AAAAAAAAAA AAAAAAAAAA AAAAAAAAAA
     CGGGGACGGG GTTTTTTTTT TTTTTTTTTT TTTTTTTTTT TTTTTTTTTT TTTTTTTTTT TTTTTTTTTT TTTTTTTTTT

  1 GCTGTGGGAA CCTCTCCACG CGCACGAACT CAGCCAACGA TTTCTGATAG ATTTTTCGGA GTTTGACCAG AGATGCAAGG GGTGAAGGAG CGCTTCCTAC
    CGACACCCTT GGAGAGGTGC GCGTGCTTGA GTCGGTTGCT AAACACTATC TAAAAACCCT CAAACTGGTC TCTACGTTCC CCACTTCCTC GCGAAGGATG
-40                                                                                  MetGlnGl yValLysGlu ArgPheLeuPro

101 CGTTAGCGAA CTCTGGGGAC AGAGCGCCCC GGCCGCCTGA TGCCCGAGGC AGGGTGCGAC CCAGGACCCA GGACGGCGTC GGCAACCATA CCATGGCCCG
    GCAATCCCTT GAGACCCCTG TCTCGCGGGG CCGGCGGACT ACCGGCTCCG TCCCACGCTG GGTCCTGGGT CCTGCCGCAG CCCTTCGTAT GGTACCGGGC
-30   LeuGlyAs nSerGlyAsp ArgAlaProA rgProProAs pGlyArgGly ArgValArgP roArgThrGl nAspGlyVal GlyAsnHisT hrMetAlaArg

201 GATCCCCAAG ACCCTAAAGT TCGTCGTCGT CATCGTCGCC GTCCTGCTGC CAGTCCTAGC TTACTCTGCC ACCACTGCCC GGCAGGAGGA AGTTCCCCAG
    CTAGGGGTTC TGGGATTTCA AGCAGCAGCA GTAGCAGCGG CAGGACGACG GTCAGGATCG AATGAGACGG TCGTGACGGG CCGTCCTCCT TCAAGGGGTC
  4  IleProLys ThrLeuLysP heValValVa lIleValAla ValLeuLeuP roValLeuAl aTyrSerAla ThrThrAlaA rgGlnGluGl uValProGln

301 CAGACAGTGG CCCCACAGCA ACAGAGGCAC AGCTTCAAGG GGGAGGAGTG TCCAGCAGGA TCTCATAGAT CAGAACATAC TGGAGCCTGT AACCCGTGCA
    GTCTGTCACC GGGGTGTCGT TGTCTCCGTG TCGAAGTTCC CCCTCCTCAC AGGTCGTCCT AGAGTATCTA GTCTTGTATG ACCTCGGACA TTGGGCACGT
37 GlnThrValA laProGlnGl nGlnArgHis SerPheLysG lyGluGluCy sProAlaGly SerHisArgS erGluHisTh rGlyAlaCys AsnProCysThr
```

FIG. 3D-2

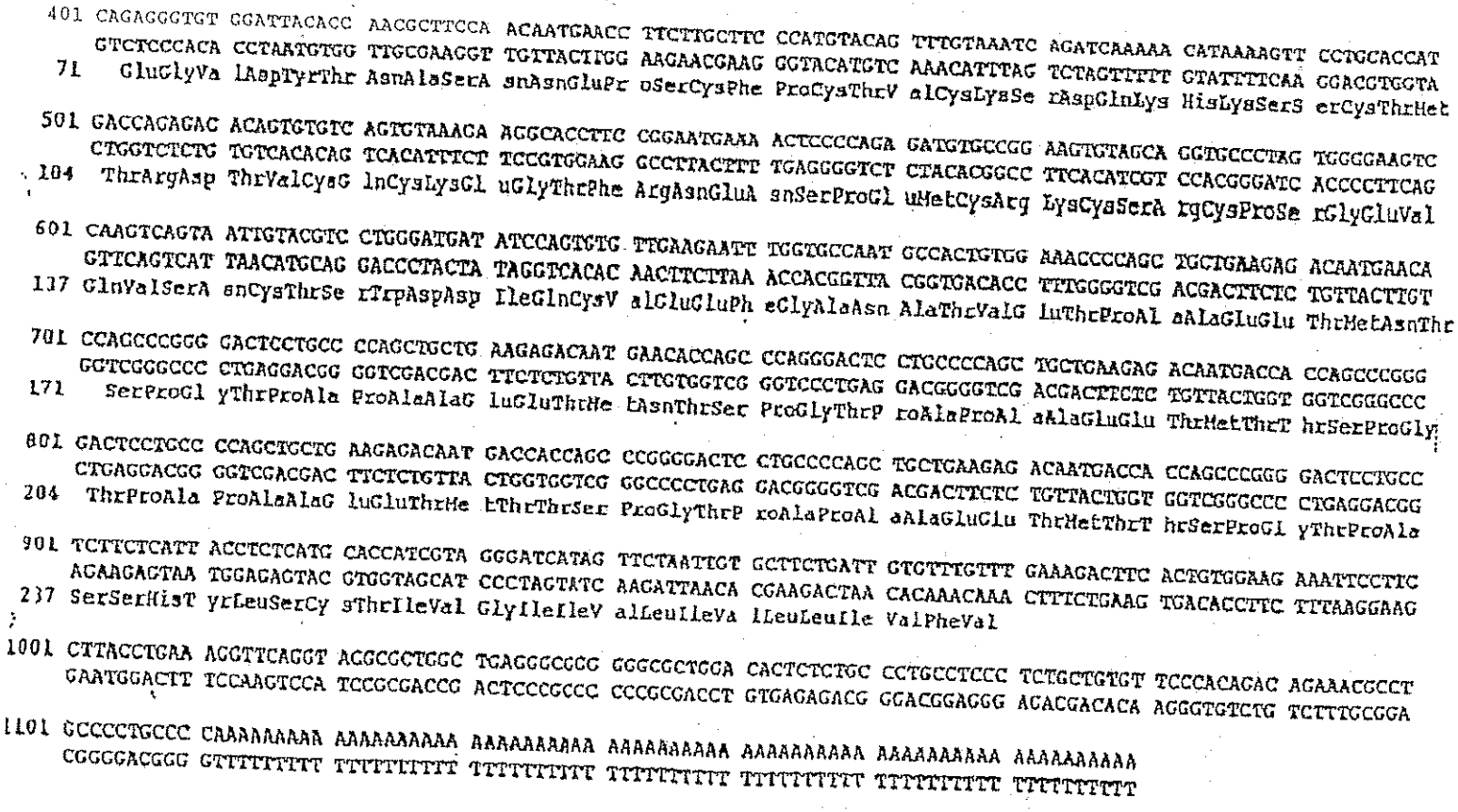

401 CAGAGGGTGT GGATTACACC AACGCTTCCA ACAATGAACC TTCTTGCTTC CCATGTACAG TTTGTAAATC AGATCAAAAA CATAAAAGTT CCTGCACCAT
GTCTCCCACA CCTAATGTGG TTGCGAAGGT TGTTACTTGG AAGAACGAAG GGTACATGTC AAACATTTAG TCTAGTTTTT GTATTTTCAA GGACGTGGTA
71 GluGlyVa lAspTyrThr AsnAlaSerA snAsnGluPr oSerCysPhe ProCysThrV alCysLysSe rAspGlnLys HisLysSerS erCysThrHet
501 GACCAGAGAC ACAGTGTGTC AGTGTAAAGA AGGCACCTTC CGGAATGAAA ACTCCCCAGA GATGTGCCGG AAGTGTAGCA GGTGCCCTAG TGGGGAAGTC
CTGGTCTCTG TGTCACACAG TCACATTTCT TCCGTGGAAG GCCTTACTTT TGAGGGGTCT CTACACGGCC TTCACATCGT CCACGGGATC ACCCCTTCAG
104 ThrArgAsp ThrValCysG lnCysLysGl uGlyThrPhe ArgAsnGluA snSerProGl uMetCysArg LysCysSerA rgCysProSe rGlyGluVal
601 CAAGTCAGTA ATTGTACGTC CTGGGATGAT ATCCAGTGTG TTGAAGAATT TGGTGCCAAT GCCACTGTGG AAACCCCAGC TGCTGAAGAG ACAATGAACA
GTTCAGTCAT TAACATGCAG GACCCTACTA TAGGTCACAC AACTTCTTAA ACCACGGTTA CGGTGACACC TTTGGGGTCG ACGACTTCTC TGTTACTTGT
137 GlnValSerA snCysThrSe rTrpAspAsp IleGlnCysV alGluGluPh eGlyAlaAsn AlaThrValG luThrProAl aAlaGluGlu ThrMetAsnThr
701 CCAGCCCGGG GACTCCTGCC CCAGCTGCTG AAGAGACAAT GAACACCAGC CCAGGGACTC CTGCCCCAGC TGCTGAAGAG ACAATGACCA CCAGCCCGGG
GGTCGGGCCC CTGAGGACGG GGTCGACGAC TTCTCTGTTA CTTGTGGTCG GGTCCCTGAG GACGGGGTCG ACGACTTCTC TGTTACTGGT GGTCGGGCCC
171 SerProGl yThrProAla ProAlaAlaG luGluThrHe tAsnThrSer ProGlyThrP roAlaProAl aAlaGluGlu ThrMetThrT hrSerProGly
801 GACTCCTGCC CCAGCTGCTG AAGAGACAAT GACCACCAGC CCGGGGACTC CTGCCCCAGC TGCTGAAGAG ACAATGACCA CCAGCCCGGG GACTCCTGCC
CTGAGGACGG GGTCGACGAC TTCTCTGTTA CTGGTGGTCG GGCCCCTGAG GACGGGGTCG ACGACTTCTC TGTTACTGGT GGTCGGGCCC CTGAGGACGG
204 ThrProAla ProAlaAlaG luGluThrHe tThrThrSer ProGlyThrP roAlaProAl aAlaGluGlu ThrMetThrT hrSerProGl yThrProAla
901 TCTTCTCATT ACCTCTCATG CACCATCGTA GGGATCATAG TTCTAATTGT GCTTCTGATT GTGTTTGTTT GAAAGACTTC ACTGTGGAAG AAATTCCTTC
AGAAGAGTAA TGGAGAGTAC GTGGTAGCAT CCCTAGTATC AAGATTAACA CGAAGACTAA CACAAACAAA CTTTCTGAAG TGACACCTTC TTTAAGGAAG
237 SerSerHisT yrLeuSerCy sThrIleVal GlyIleIleV alLeuIleVa lLeuLeuIle ValPheVal
1001 CTTACCTGAA AGGTTCAGGT AGGCGCTGGC TGAGGGCGCG GGGCGCTGGA CACTCTCTGC CCTGCCTCCC TCTGCTGTGT TCCCACACAC AGAAACGCCT
GAATGGACTT TCCAAGTCCA TCCGCGACCG ACTCCCGCCC CCCGCGACCT GTGAGAGACG GGACGGAGGG ACACGACACA AGGGTGTCTG TCTTTGCGGA
1101 GCCCCTGCCC CAAAAAAAAA AAAAAAAAAA AAAAAAAAAA AAAAAAAAAA AAAAAAAAAA AAAAAAAAAA AAAAAAAAAA
CGGGGACGGG GTTTTTTTTT TTTTTTTTTT TTTTTTTTTT TTTTTTTTTT TTTTTTTTTT TTTTTTTTTT TTTTTTTTTT

FIG. 3D-3

```
1 CCAACTGCAC CTCGGTTCTA TCGATTGAAT TCCCCGGGGA TCCTCTAGAG ATCCCTCGAC

61 CTCGACCCAC GCGTCCGGAA CCTTTGCACG CGCACAAACT ACGGGGACGA TTTCTGATTG

121 ATTTTTGGCG CTTTCGATCC ACCGTTCCTC CTTCTCATGG GACTTTGGGG ACAAAGCGTC
1                                   M  G  L  W  G  Q  S  F

181 CCGACCGCCT CGAGCGCTCG AGCAGGACGC TATCCAGGAG CCAGCACAGC GTCGGAACC
9   P  T  A  S  S  A  R  A  G  R  Y  P  G  A  R  T  A  S  G  T

241 AGACCATGGC TCCTGGACCC CAGATCCTT AGTTCGTCG TCTTCATCGT CGCGTTCTG
29  R  P  W  L  L  D  P  K  I  L  K  P  V  V  F  I  V  A  V  L

301 CTGCCCGGTCC GCGTTGACTC TGCCATCATC CCCCGGCAGG ACGAGTTCC CCAGCAGACA
49  L  P  V  R  V  D  S  A  T  I  P  R  Q  D  E  V  F  P  Q  Q  T

361 GTGGCCCCAC AGCAACAGAG GCGCAGCCTC AAGGAGGAGG AGTGTCCAGC AGCATCTCAT
69  V  A  P  Q  Q  Q  R  R  S  L  K  E  E  E  C  P  A  G  S  H

421 AGATTGAAAT ATACTGCAGC CTGTAACCCG TGCACAGAGG GTGTGGATTA CACCATTGCT
89  R  S  K  Y  T  G  A  C  M  P  C  T  E  G  V  D  Y  T  I  A

481 TCCAGCAATT TGCCTTCTTG CCTGCTATGT ACAGTTTGTA AATCAGGTCA AACAAATAAA
109 S  N  N  L  P  S  C  L  L  C  T  V  C  K  S  G  Q  T  K  K

541 AGTTCCCGTA CCACGACCAG AGACACCGTG TGTCAGTGTG AAAAGGAAG CTTCCAGGAT
129 S  S  C  T  T  T  R  D  T  V  C  Q  C  E  K  G  S  F  Q  D

601 AAAACTCCC CTGAGATGTG CCGGACGTGT ACAACAGGGT GTCCAGAGG GATGCTCAAG
149 K  M  S  P  E  M  C  R  T  C  R  T  G  C  P  R  G  M  V  K

661 GTCAGTAATT GTACGCCCCG GAGTGACATC AAGTGCAAAA ATGAATCAGC TGCCAGTTCC
169 V  S  M  C  T  P  R  S  D  I  K  C  K  N  E  S  A  S  S

721 ACTGCGAAAA CCCCAGCAGC GGAGGAGACA GTGACCACCA TCCTGGGGAT GCTTGCCTCT
189 T  G  K  T  P  A  A  E  E  T  V  T  T  I  L  G  M  L  A  S

781 CCCTATCACT ACCTTATCAT CATAGTGGTT TTAGTCATCA TTTTAGCTTG GGTTGTGTT
209 P  Y  H  Y  L  I  I  I  V  V  L  V  I  I  L  A  V  V  V  V

841 GGCTTTTCAT GTCGGAAGAA ATTCATTTCT TACCTCAAAG GCATCTGCTC AGGTGGTGGA
229 G  F  S  C  R  K  K  P  I  S  Y  L  K  G  I  C  S  G  G  G
```

FIG. 3E-1

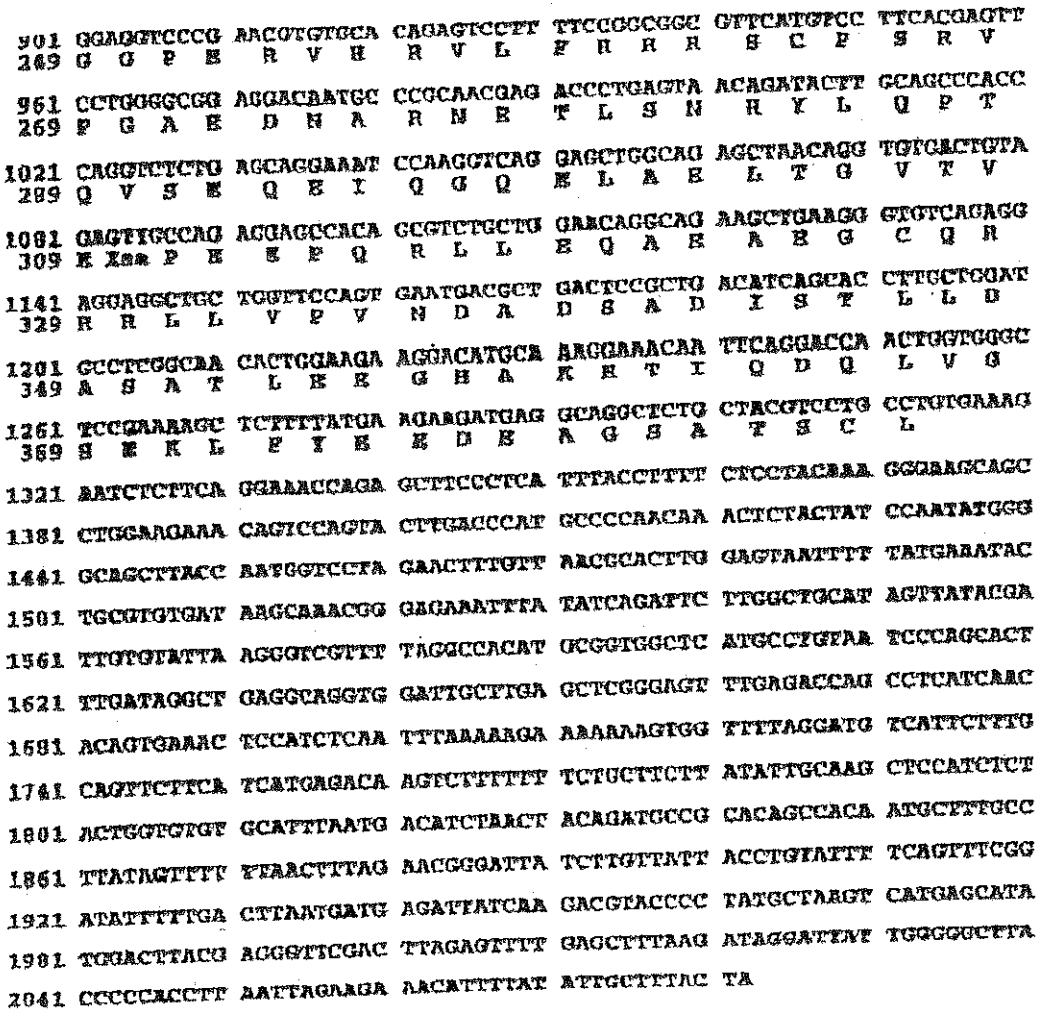
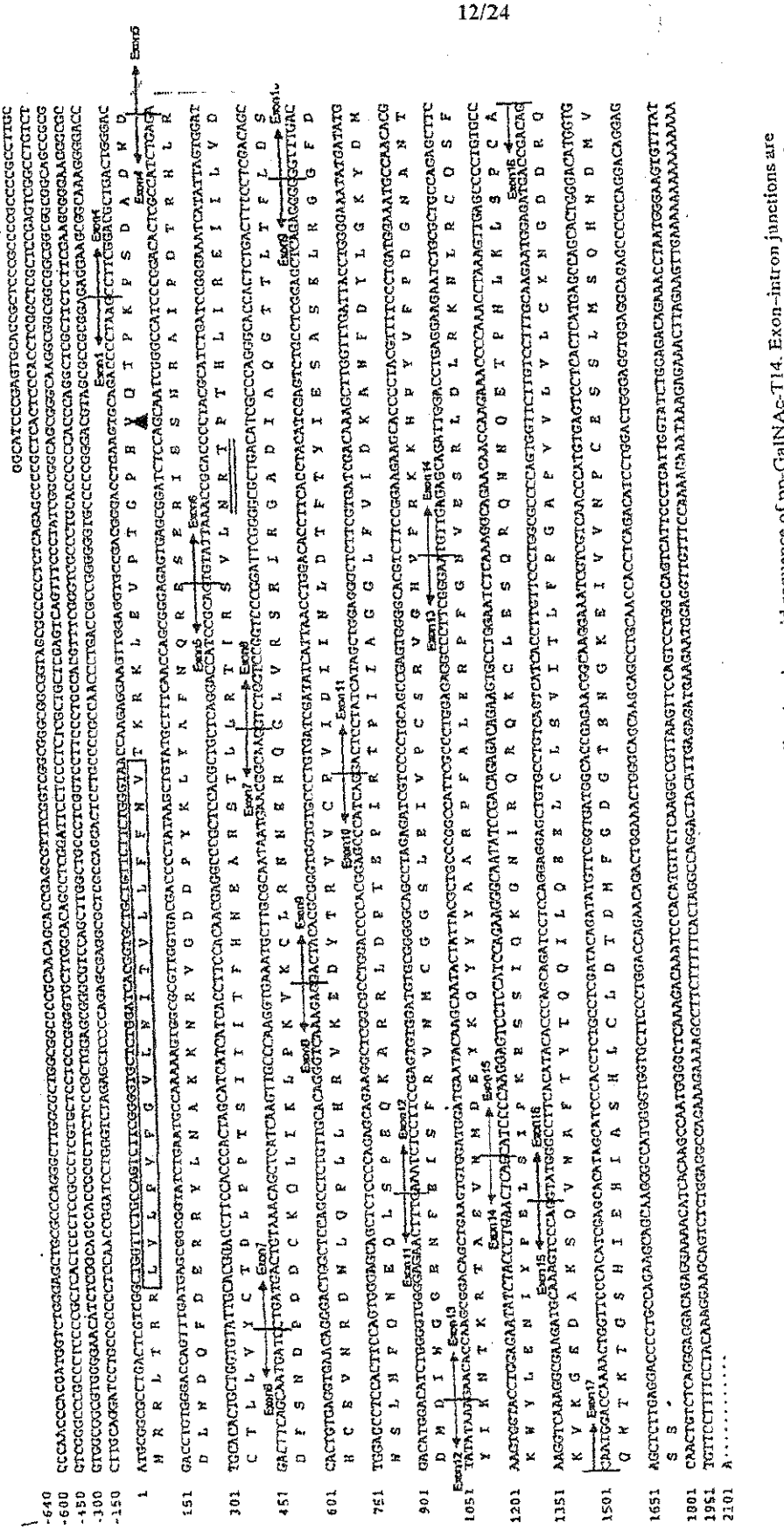

901 GGAGGTCCCG AACGTGTGCA CAGAGTCCTT TTCCGGCGGC GTTCATGTCC TTCACGAGTT
269 G G P E R V H R V L F R R R S C F S R V
961 CCTGGGCGGG AGGACAATGC CCGCAACGAG ACCCTGAGTA ACAGATACTT GCAGCCCACC
289 P G A E D N A R N E T L S N R Y L Q P T
1021 CAGGTCTCTG AGCAGGAAAT CCAAGGTCAG GAGCTGGCAG AGCTAACAGG TGTGACTGTA
289 Q V S E Q E I Q G Q E L A E L T G V T V
1081 GAGTTGCCAG AGGAGCCACA GCGTCTGCTG GAACAGGCAG AAGCTGAAGG GTGTCAGAGG
309 E Xaa P E E P Q R L L E Q A E A E G C Q R
1141 AGGAGGCTGC TGGTTCCAGT GAATGACGCT GACTCCGCTG ACATCAGCAC CTTGCTGGAT
329 R R L L V P V N D A D S A D I S T L L D
1201 GCCTCGGCAA CACTGGAAGA AGGACATGCA AAGGAAACAA TTCAGGACCA ACTGGTGGGC
349 A S A T L E K G H A K K T I Q D Q L V G
1261 TCCGAAAAGC TCTTTTATGA AGAAGATGAG GCAGGCTCTG CTACGTCCTG CCTGTGAAAG
369 S E K L F Y E E D E A G S A T S C L
1321 AATCTCTTCA GGAAACCAGA GCTTCCCTCA TTTACCTTTT CTCCTACAAA GGGAAGCAGC
1381 CTGGAAGAAA CAGTCCAGTA CTTGACCCAT GCCCCAACAA ACTCTACTAT CCAATATGGG
1441 GCAGCTTACC AATGGTCCTA GAACTTTGTT AACGCACTTG GAGTAATTTT TATGAAATAC
1501 TGCGTGTGAT AAGCAAACGG GAGAAATTTA TATCAGATTC TTGGCTGCAT AGTTATACGA
1561 TTGTGTATTA AGGGTCGTTT TAGGCCACAT GCGGTGGCTC ATGCCTGTAA TCCCAGCACT
1621 TTGATAGGCT GAGGCAGGTG GATTGCTTGA GCTCGGGAGT TTGAGACCAG CCTCATCAAC
1681 ACAGTGAAAC TCCATCTCAA TTTAAAAAGA AAAAAAGTGG TTTTAGGATG TCATTCTTTG
1741 CAGTTCTTCA TCATGAGACA AGTCTTTTTT TCTGCTTCTT ATATTGCAAG CTCCATCTCT
1801 ACTGGTGTGT GCATTTAATG ACATCTAACT ACAGATGCCG CACAGCCACA ATGCTTTGCC
1861 TTATAGTTTT TTAACTTTAG AACGGGATTA TCTTGTTATT ACCTGTATTT TCAGTTTCGG
1921 ATATTTTTGA CTTAATGATG AGATTATCAA GACGTACCCC TATGCTAAGT CATGAGCATA
1981 TGGACTTACG AGGGTCGAC TTAGAGTTTT GAGCTTTAAG ATAGGATTAT TGGGGGCTTA
2041 CCCCCACCTT AATTAGAAGA AACATTTTAT ATTGCTTTAC TA

FIG. 3E-2



j Nucleotide sequence of the pp-GalNAc-T14 cDNA and the predicted amino acid sequence of pp-GalNAc-T14. Exon–intron junctions are indicated. The putative N-terminal transmembrane domain was *boxed*. A putative N-glycosylation site was indicated by *double underline*. The starting position of the truncated form was indicated by *triangle*.

Fig. 4A

The amino acid sequence is shown in single-letter codes. The hydrophobic segment representing the putative transmembrane domain is *underlined* with a *double line* (Kyte & Doolittle, window of 8) (32), and adjacent charged amino acid *underlined* with a *dotted line*. Four potential *N*-linked glycosylation sites are indicated by *asterisks*.

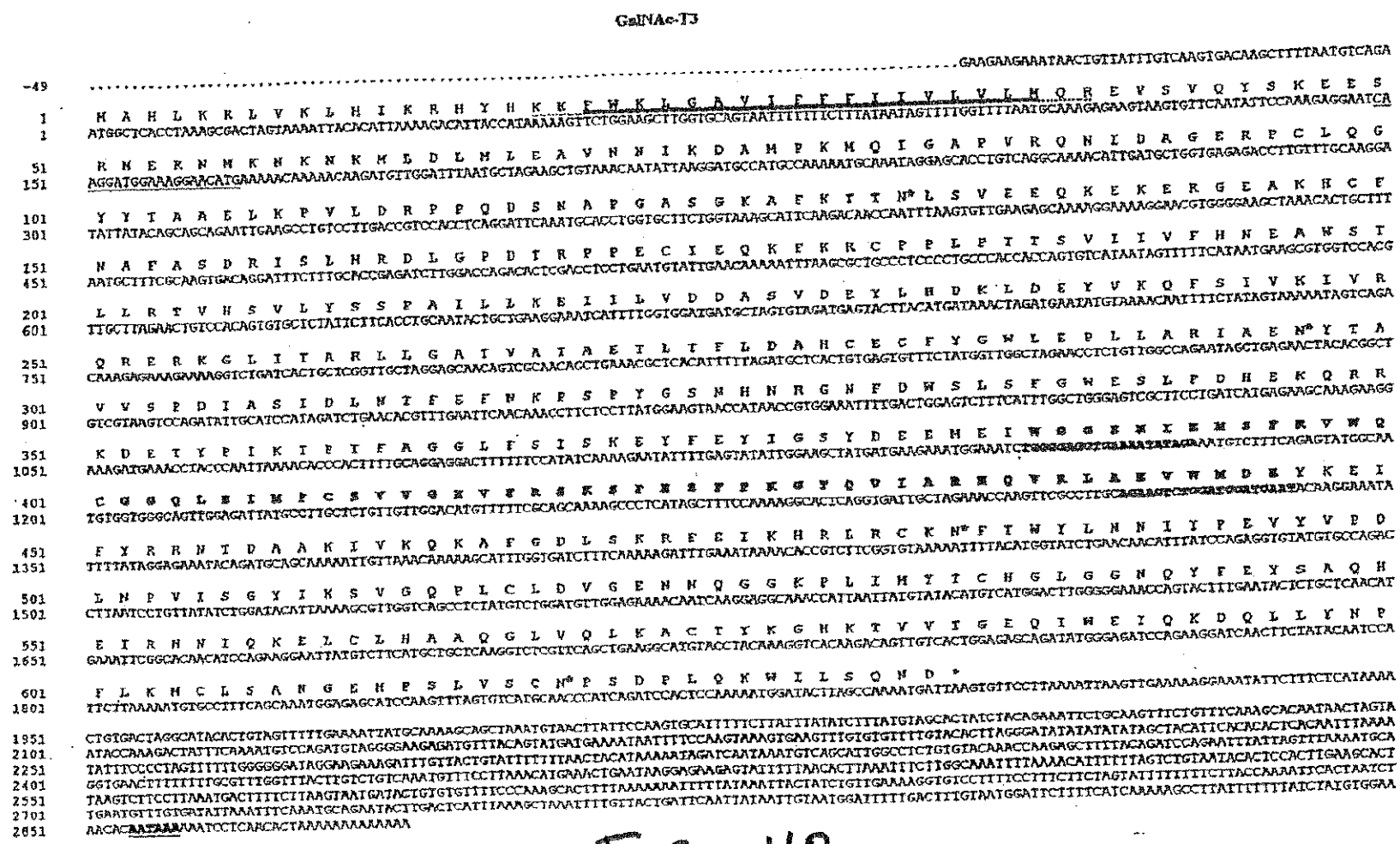


FIG. 4B

NSCLC IC50 Summary

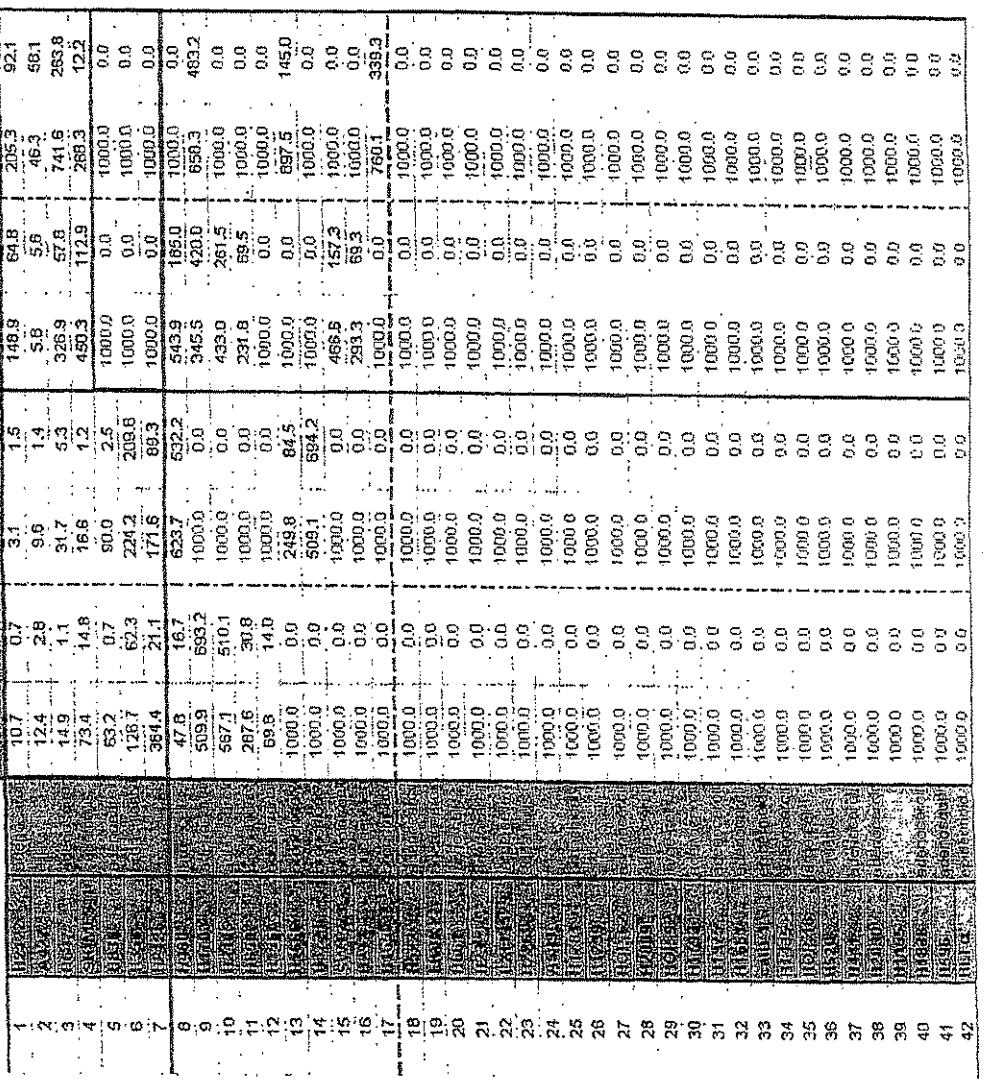
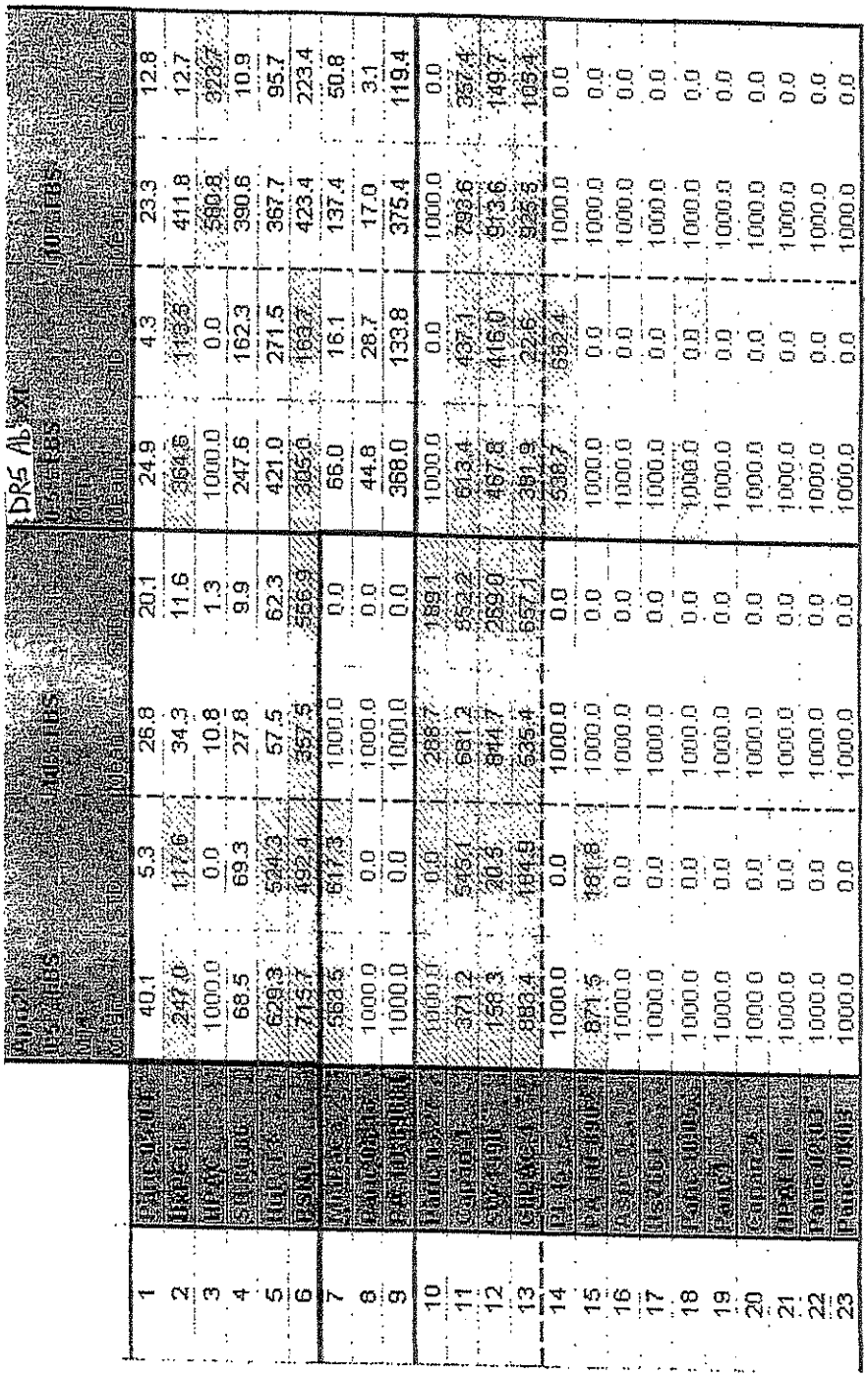


FIG. 5

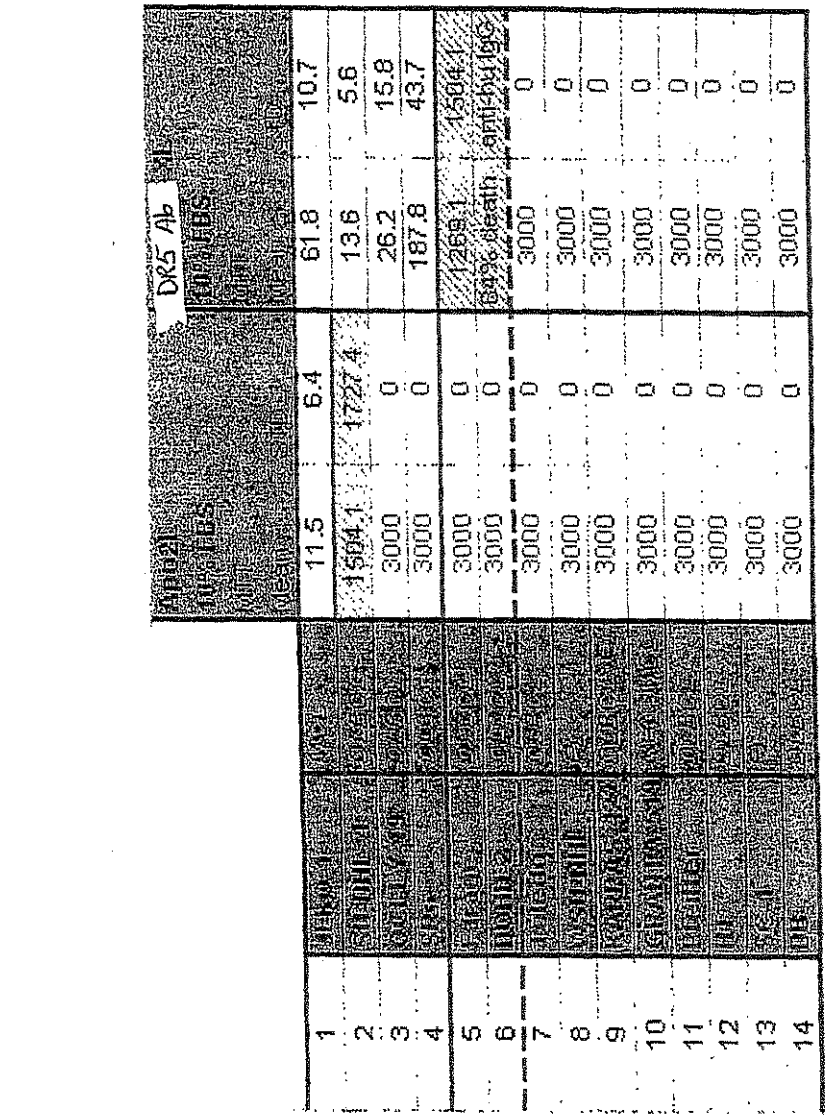
Pancreatic Cancer IC50 Summary



1	PANC 10.05	40.1	5.3	26.8	20.1	24.9	4.3	23.3	12.8														
2	HPAC	247.0	117.6	34.3	11.6	364.6	119.5	411.8	12.7														
3	HPAF	1000.0	0.0	10.8	1.3	1000.0	0.0	580.8	323.7														
4	SW1990	68.5	69.3	27.8	9.9	247.6	162.3	390.6	10.9														
5	HuP-T3	629.3	524.3	57.5	62.3	421.0	271.5	367.7	95.7														
6	PSN1	715.7	492.4	357.5	356.9	385.0	169.7	423.4	223.4														
7	MIA PaCa-2	563.5	617.3	1000.0	0.0	66.0	16.1	137.4	50.8														
8	PANC 08.13	1000.0	0.0	1000.0	0.0	44.8	28.7	17.0	3.1														
9	PANC 10.05	1000.0	0.0	1000.0	0.0	368.0	133.8	375.4	119.4														
10	Hs 766T	1000.0	0.0	288.7	189.1	1000.0	0.0	1000.0	0.0														
11	Capan-1	371.2	545.1	681.2	552.2	613.4	437.1	298.6	357.4														
12	SW 480	158.3	20.5	844.7	269.0	467.8	416.0	513.6	149.7														
13	CFPAC-1	883.4	104.9	535.4	657.1	381.9	22.6	935.5	108.4														
14	BxPC-3	1000.0	0.0	1000.0	0.0	538.7	532.4	1000.0	0.0														
15	AsPC-1	871.5	181.8	1000.0	0.0	1000.0	0.0	1000.0	0.0														
16	SU.86.86	1000.0	0.0	1000.0	0.0	1000.0	0.0	1000.0	0.0														
17	Hs 700T	1000.0	0.0	1000.0	0.0	1000.0	0.0	1000.0	0.0														
18	Panc 03.27	1000.0	0.0	1000.0	0.0	1000.0	0.0	1000.0	0.0														
19	Panc 05.04	1000.0	0.0	1000.0	0.0	1000.0	0.0	1000.0	0.0														
20	Capan-2	1000.0	0.0	1000.0	0.0	1000.0	0.0	1000.0	0.0														
21	HPAF-II	1000.0	0.0	1000.0	0.0	1000.0	0.0	1000.0	0.0														
22	Panc 02.03	1000.0	0.0	1000.0	0.0	1000.0	0.0	1000.0	0.0														
23	Panc 08.13	1000.0	0.0	1000.0	0.0	1000.0	0.0	1000.0	0.0														

Fig. 6

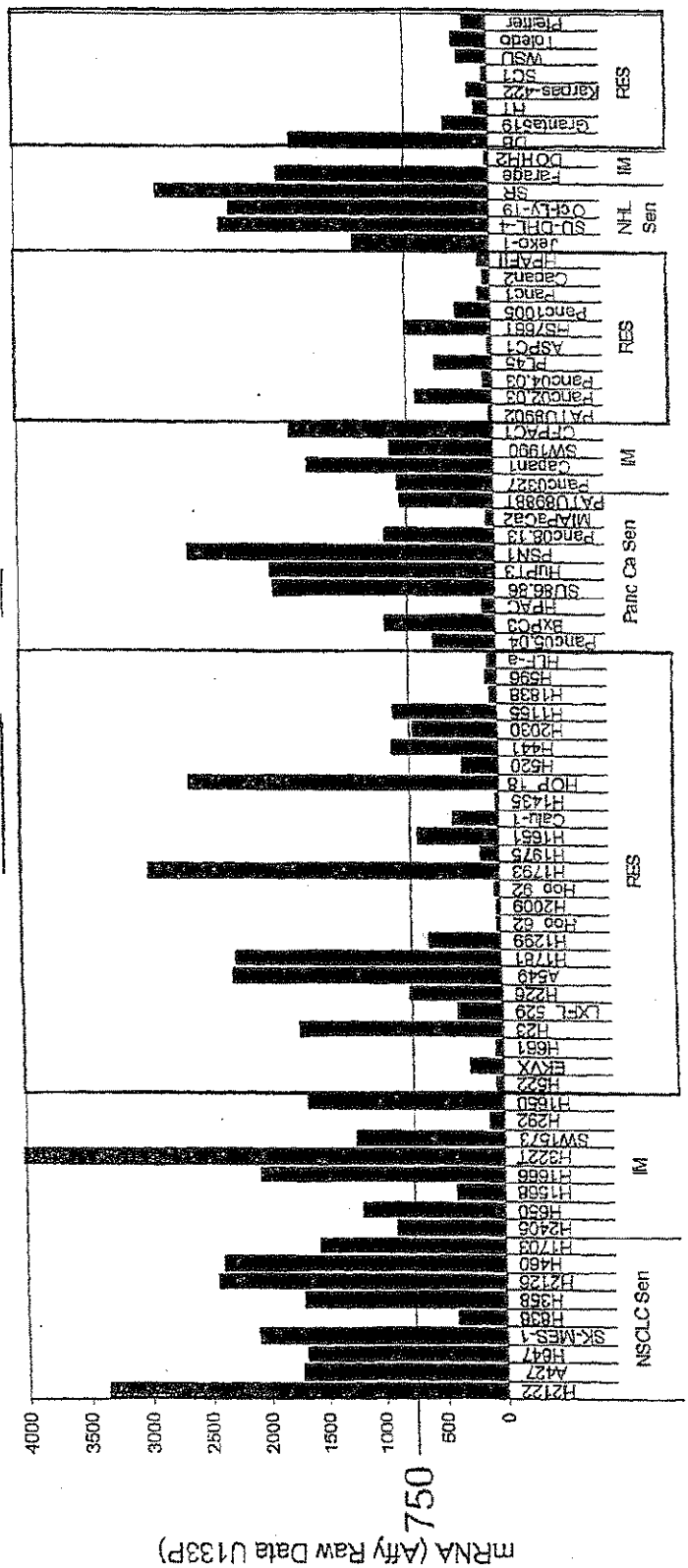
NHL IC50 Summary



					Apo2L	DR5 Ab	TRAIL							
					10% TBS	10% TBS	10% TBS							
					(ug/ml)	(ug/ml)	(ug/ml)							
1					11.5	6.4	61.8	10.7						
2					1504.1	1722.4	13.6	5.6						
3					3000	0	26.2	15.8						
4					3000	0	187.8	43.7						
5					3000	0	1269.1	1504						
6					3000	0	64% death	21% death						
7					3000	0	3000	0						
8					3000	0	3000	0						
9					3000	0	3000	0						
10					3000	0	3000	0						
11					3000	0	3000	0						
12					3000	0	3000	0						
13					3000	0	3000	0						
14					3000	0	3000	0						

Fig. 7

Fig. 8 DR5 Ab + Sensitivity Data and Correlation with GalNAc-T14 Expression: NSCLC, Panc Ca, NHL



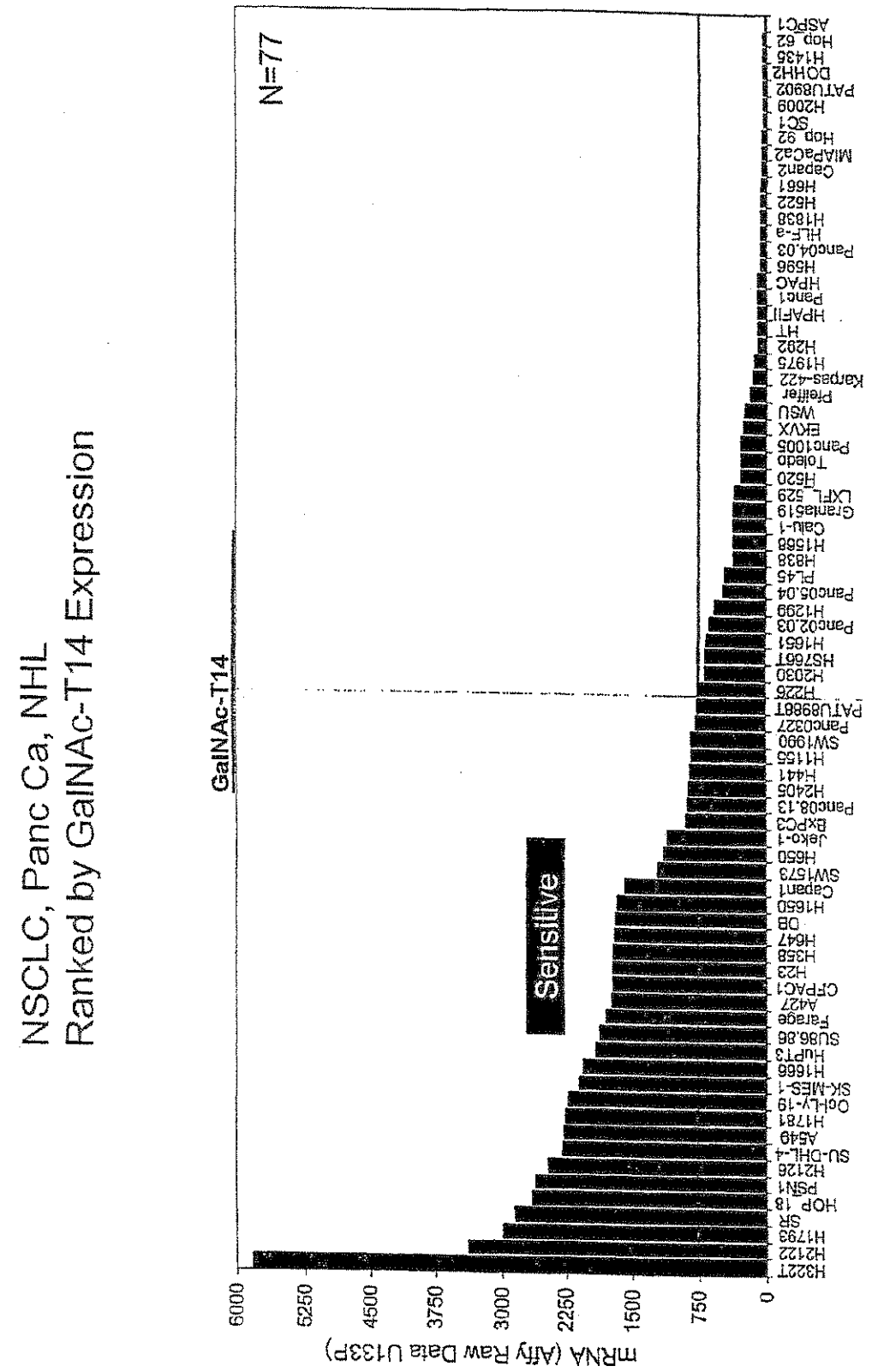

NSCLC, Panc Ca, NHL
Ranked by GalNAc-T14 Expression
N=77
GalNAc-T14
Sensitive
RESISTANT
mRNA (Affy Raw Data U133P)
6000
5250
4500
3750
3000
2250
1500
750
0
H322T
H2122
H1793
SR
HOP 18
PSN1
H2126
SU-DHL-4
A549
H1781
OciLy-19
SK-MES-1
H1666
HuPT3
SU86.86
Farage
A427
CFPAC1
H23
H358
H647
DB
H1650
Capan1
SW1573
H650
Jeko-1
BxPC3
Panc08.13
H2405
H441
H1155
SW1990
Panc0327
PATU8988T
H226
H2030
H5766T
H1651
Panc02.03
H1299
Panc05.04
PL45
H838
H1568
Calu-1
Granta519
LXFL_529
H520
Toledo
Panc1005
EKVX
WSU
Pfeiffer
Karpas-422
H1975
H292
HT
HPAFII
Panc1
HPAC
H596
Panc04.03
HLF-a
H1838
H522
H661
Capan2
MIAPaCa2
Hop_92
SC1
H2009
PATU8902
DOHH2
H1435
Hop_62
ASPC1

Fig. 9

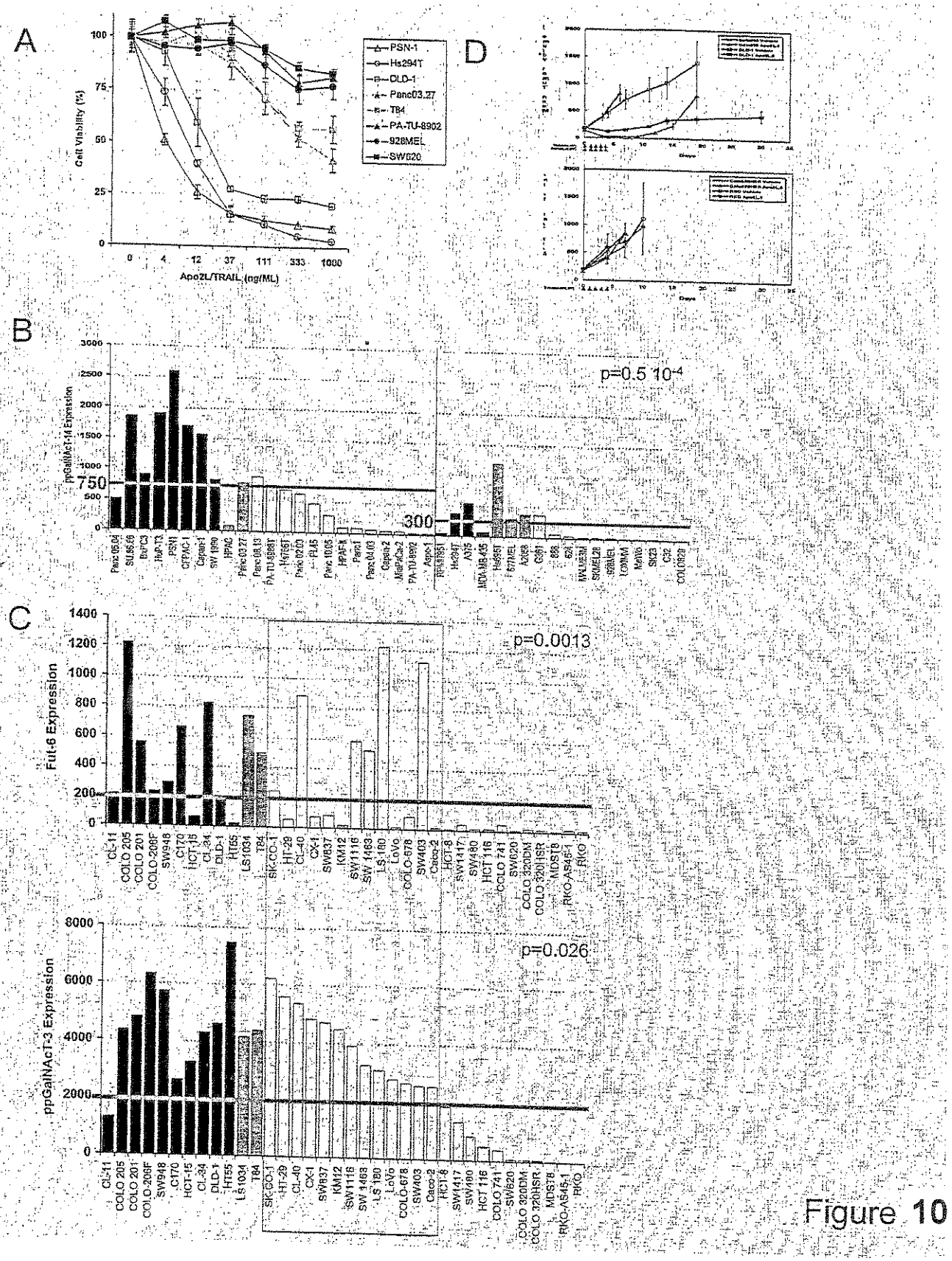

A
Cell Viability (%)
Apo2L/TRAIL (ng/ML)
PSN-1
Hs294T
DLD-1
Panc03.27
T84
PA-TU-8902
928MEL
SW620
D
B
ppGalNAcT-14 Expression
p=0.5 10-4
C
Fut-6 Expression
p=0.0013
ppGalNAcT-3 Expression
p=0.026

Figure 10

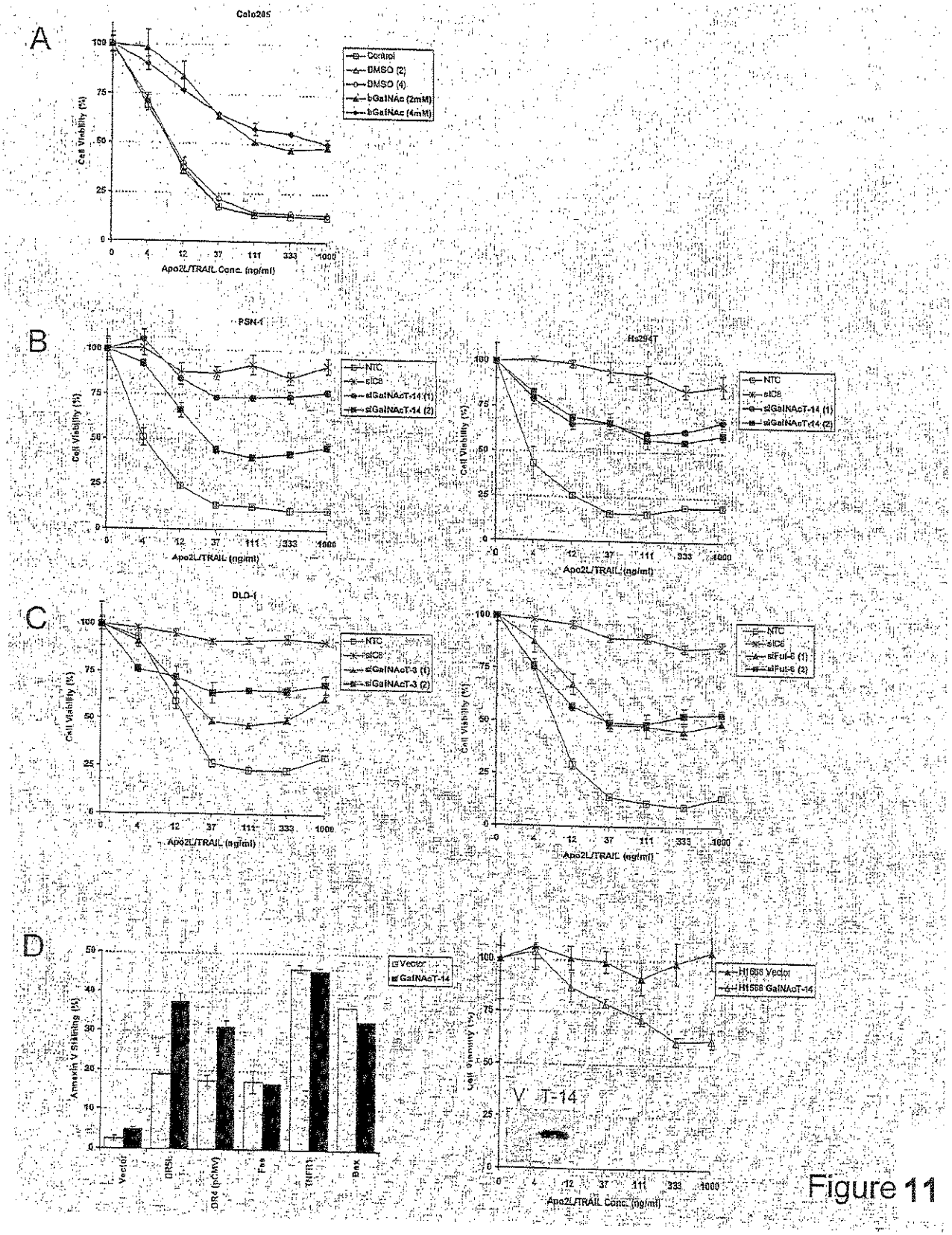

A
Colo205
Control
DMSO (2)
DMSO (4)
bGalNAc (2mM)
bGalNAc (4mM)
Cell Viability (%)
Apo2L/TRAIL Conc. (ng/ml)
B
PSN-1
NTC
siC8
siGalNAcT-14 (1)
siGalNAcT-14 (2)
Cell Viability (%)
Apo2L/TRAIL (ng/ml)
Hs294T
NTC
siC8
siGalNAcT-14 (1)
siGalNAcT-14 (2)
Cell Viability (%)
Apo2L/TRAIL (ng/ml)
C
DLD-1
NTC
siC8
siGalNAcT-3 (1)
siGalNAcT-3 (2)
Cell Viability (%)
Apo2L/TRAIL (ng/ml)
NTC
siC8
siFut-6 (1)
siFut-6 (2)
Cell Viability (%)
Apo2L/TRAIL (ng/ml)
D
Vector
GalNAcT-14
Annexin V Staining (%)
Vector
DR5
DR4 (pCMV)
Fas
TNFR1
Bax
H1688 Vector
H1688 GalNAcT-14
Cell Viability (%)
V T-14
Apo2L/TRAIL Conc. (ng/ml)

Figure 11

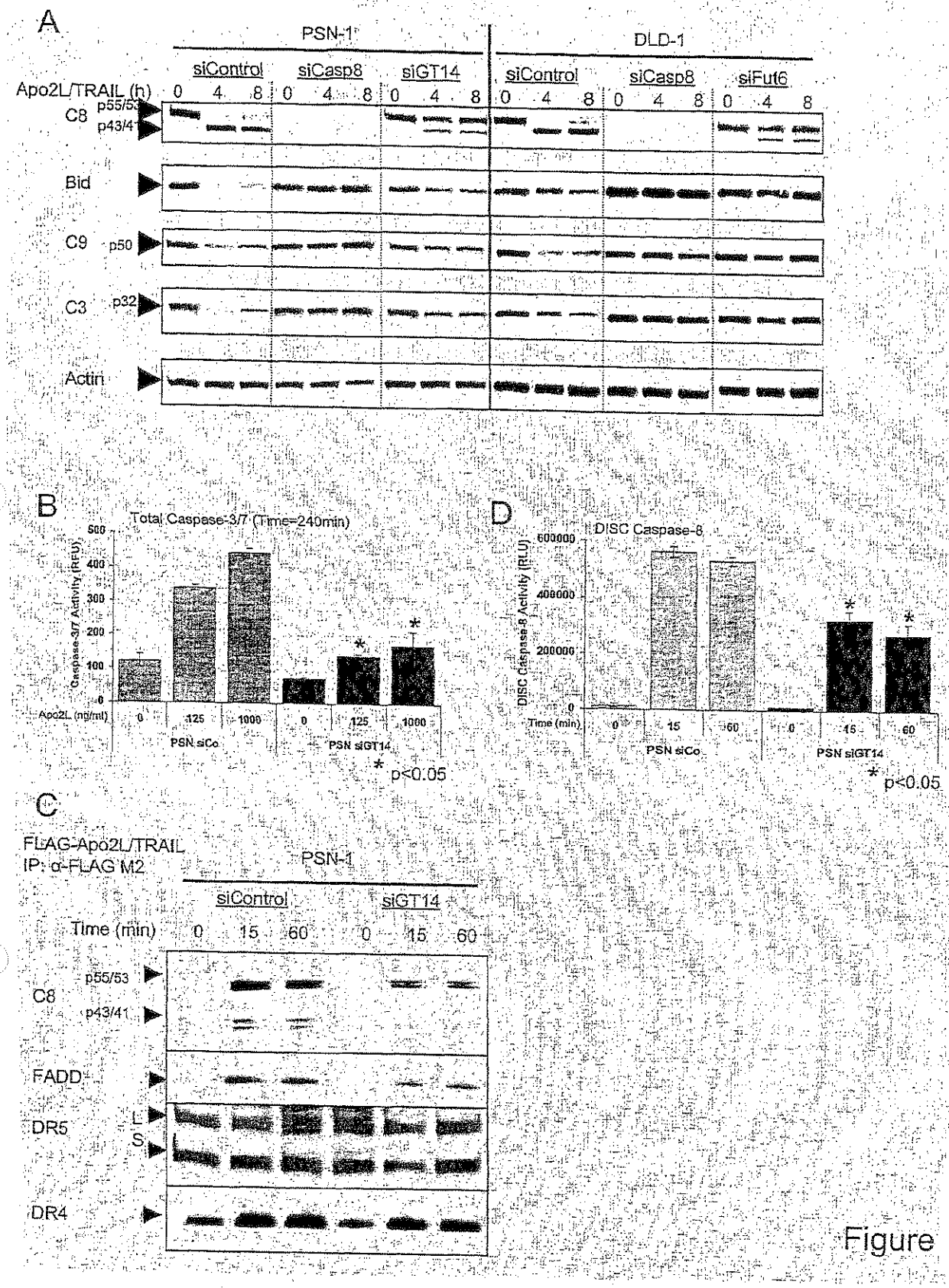

A
PSN-1
DLD-1
siControl
siCasp8
siGT14
siFut6
Apo2L/TRAIL (h)
0 4 8
C8
p55/53
p43/41
Bid
C9
p50
C3
p32
Actin
B
Total Caspase-3/7 (Time=240min)
Caspase-3/7 Activity (RFU)
Apo2L (ng/ml)
PSN siCo
PSN siGT14
* p<0.05
D
DISC Caspase-8
DISC Caspase-8 Activity (RLU)
Time (min)
PSN siCo
PSN siGT14
* p<0.05
C
FLAG-Apo2L/TRAIL
IP: α-FLAG M2
PSN-1
siControl
siGT14
Time (min)
0 15 60
C8
p55/53
p43/41
FADD
DR5
L
S
DR4

Figure 12

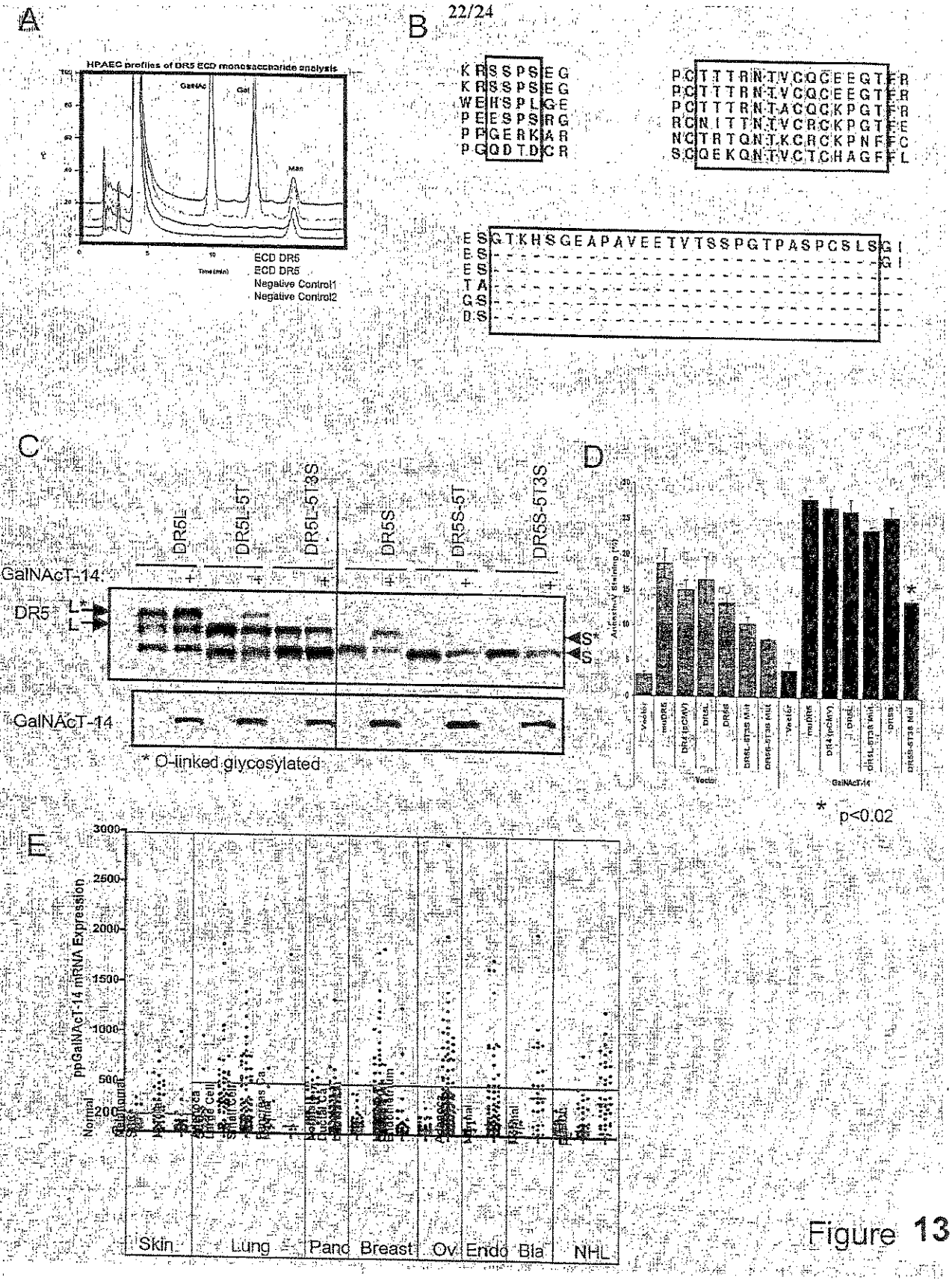
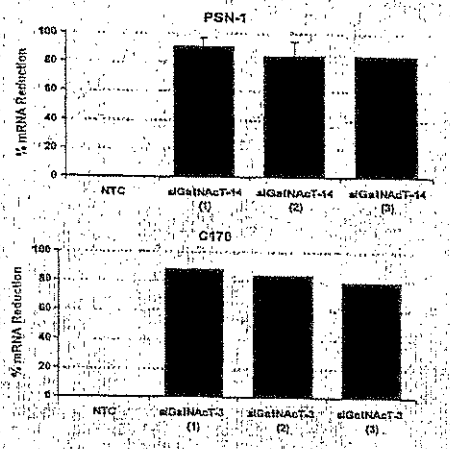
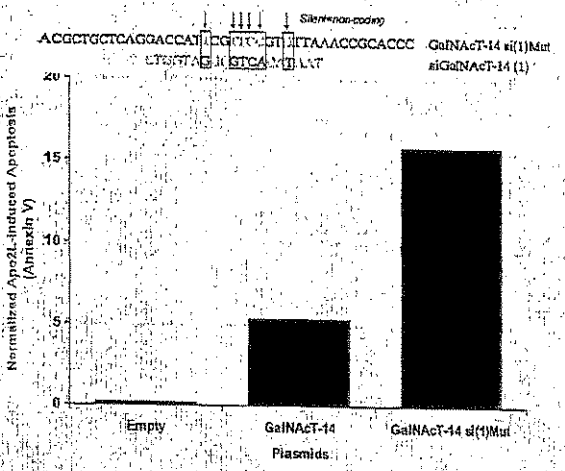

A
HPAEC profiles of DR5 ECD monosaccharide analysis
GalNAc
Gal
Man
ECD DR5
ECD DR5
Negative Control1
Negative Control2
B
C
DR5L
DR5L-5T
DR5L-5T3S
DR5S
DR5S-5T
DR5S-5T3S
GalNAcT-14
DR5
L*
L
S*
S
GalNAcT-14
* O-linked glycosylated
D
Antibody Binding (%)
GalNAcT-14
* p<0.02
E
ppGalNAcT-14 mRNA Expression
Normal
Skin
Lung
Panc
Breast
Ov
Endo
Bla
NHL

Figure 13

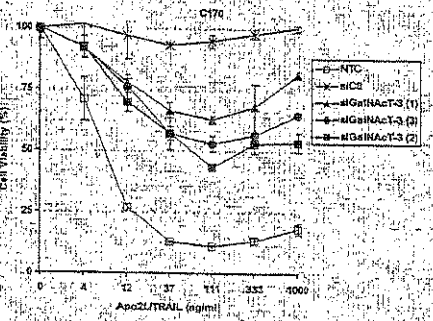
A

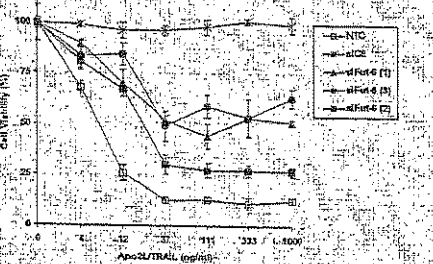


B



C

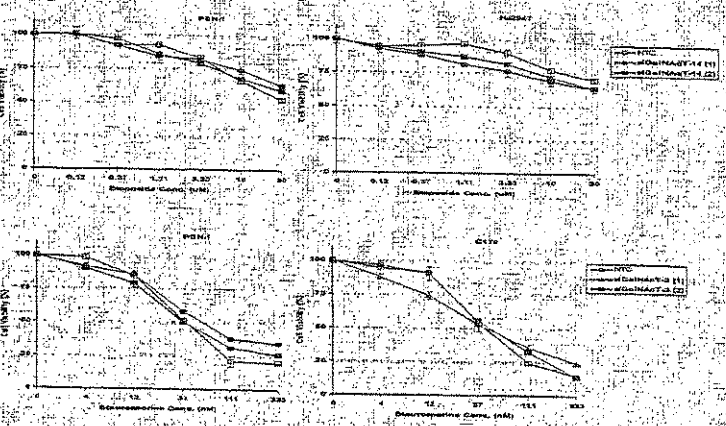




T1

Tumor Type	Cell Line	Transient RNAi	Retroviral shRNA	Apo2L/TRAIL Protection by Knock-down		
				pGalNAcT-14	pGalNAcT-3	Fut-6
Pancreatic Cancer	PSN-1	Yes		++		
	Panc 05.04	Yes		++		
	Panc 03.27	Yes		+		
	Su.86.86	No	Yes	+		
	Hup-T3	Yes		0		
				4/5		
Melanoma	A375	Yes		++		
	Hs294T	Yes		++		
				2/2		
Colorectal Cancer	C170	Yes			++	++
	DLD-1	Yes			++	++
	SW948	Yes			0	0
					2/3	2/3

D,E



F

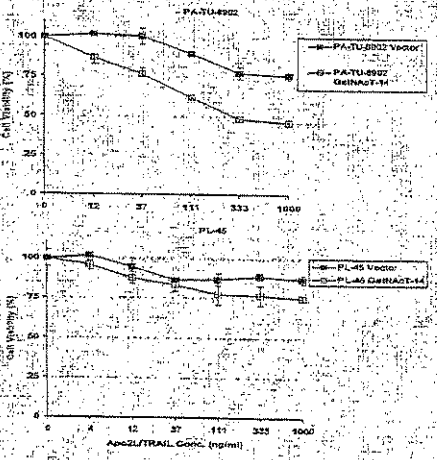


Figure 14

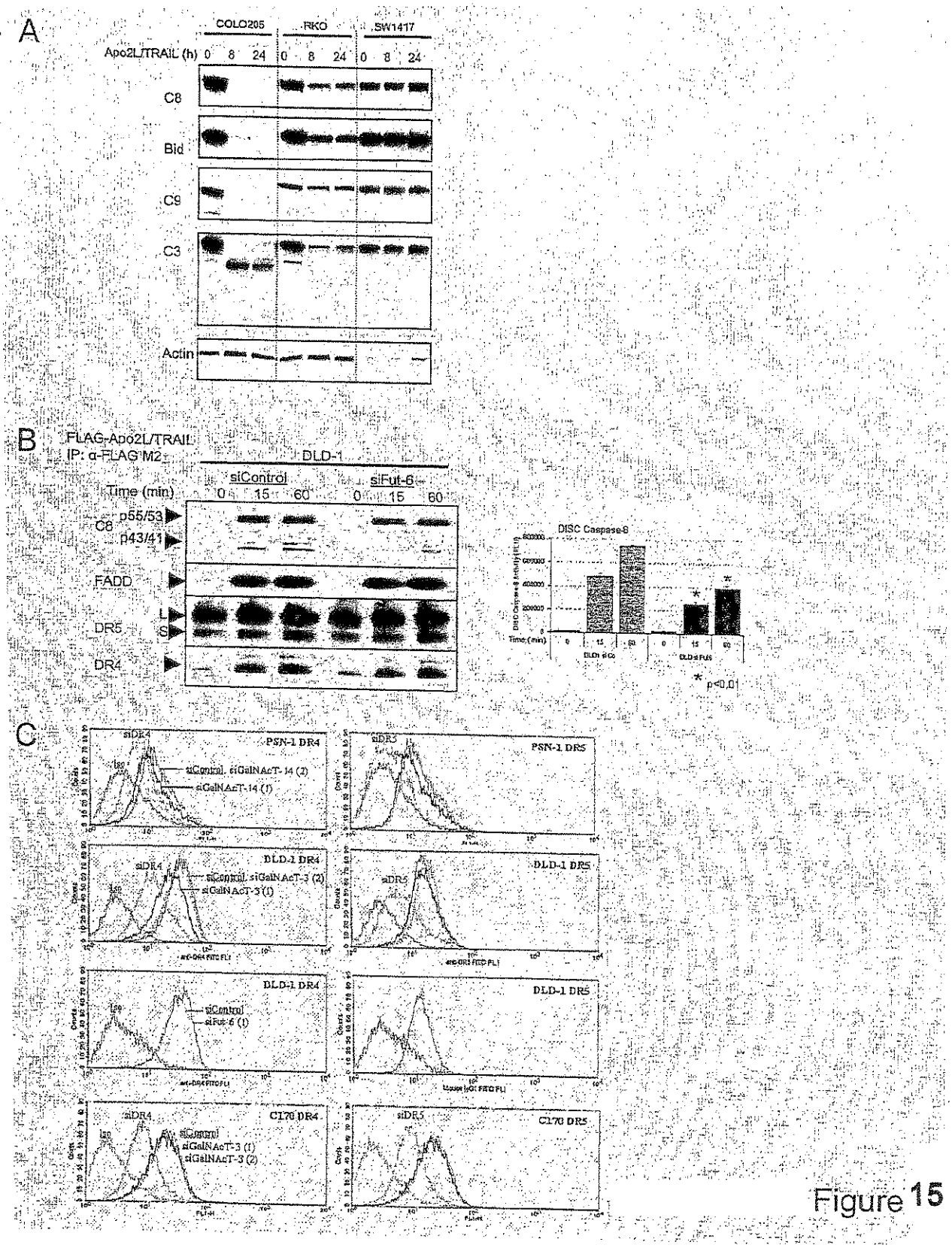

A
COLO205
RKO
SW1417
Apo2L/TRAIL (h) 0 8 24 0 8 24 0 8 24
C8
Bid
C9
C3
Actin
B
FLAG-Apo2L/TRAIL
IP: α-FLAG M2
DLD-1
siControl
siFut-6
Time (min) 0 15 60 0 15 60
C8 p55/53
p43/41
FADD
DR5
L
S
DR4
DISC Caspase-8
* p<0.01
C
PSN-1 DR4
PSN-1 DR5
DLD-1 DR4
DLD-1 DR5
C170 DR4
C170 DR5
siControl, siGalNAcT-14 (2)
siGalNAcT-14 (1)
siControl, siGalNAcT-3 (2)
siGalNAcT-3 (1)
siFut-6 (1)
siControl
siGalNAcT-3 (1)
siGalNAcT-3 (2)

Figure 15