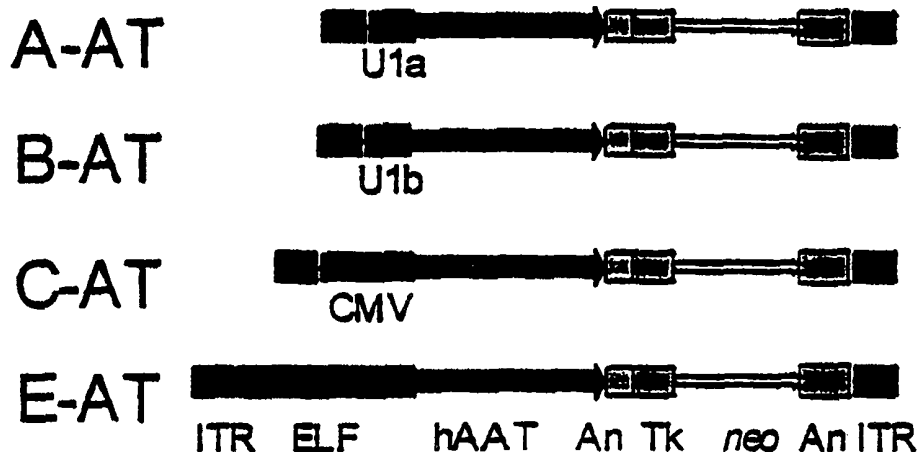




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(54) Title: MATERIALS AND METHODS FOR GENE THERAPY



(57) Abstract

The subject invention concerns materials and methods for gene therapy. One aspect of the invention pertains to vectors which can be used to effect genetic therapy in animals or humans having genetic disorders where expression of high levels of a protein of interest are required to treat or correct the disorder. The subject invention also pertains to methods for treating animals or humans in need of gene therapy to treat or correct a genetic disorder. The materials and methods of the invention can be used to provide therapeutically effective levels of a protein that is non-functional, or that is absent or deficient in the animal or human to be treated. In one embodiment, the materials and methods can be used to treat alpha-1-antitrypsin deficiency.

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DESCRIPTIONMATERIALS AND METHODS FOR GENE THERAPY

5 The subject invention was made with government support under a research project supported by National Institute of Health NHLBI Grant No. HL 59412. The government has certain rights in this invention.

Cross-Reference to a Related Application

10 This application claims priority from provisional application U.S. Serial No. 60/083,025, filed April 24, 1998.

Background of the Invention

15 Alpha-1-antitrypsin (AAT) deficiency is the second most common monogenic lung disease in man, accounting for approximately 3% of all early deaths due to obstructive pulmonary disease. AAT protein is normally produced in the liver, secreted into the serum and circulated to the lung where it protects the fine supporting network of elastin fibers from degradation by neutrophil elastase. Current therapy for AAT deficiency includes avoidance of cigarette smoke exposure and weekly intravenous
20 infusions of recombinant human AAT (hAAT) protein. Attempts to devise gene therapy strategies to replace AAT either in the lung itself or within any of a number of other tissues which are capable of AAT secretion have been limited by the short duration of expression from some vectors and by the relatively high circulating levels of AAT which is required for therapeutic effect. Methods of gene therapy have been described in U.S.
25 Patent No. 5,399,346.

 It has recently been demonstrated that adeno-associated virus (AAV) vectors are capable of stable *in vivo* expression and may be less immunogenic than other viral vectors (Flotte *et al.*, 1996; Xiao *et al.*, 1996; Kessler *et al.*, 1996; Jooss *et al.*, 1998). AAV is a non-pathogenic human parvovirus whose life cycle naturally includes a
30 mechanism for long-term latency. In the case of wild-type AAV (wtAAV), this persistence is due to site-specific integration into a site on human chromosome 19 (the AAVSI site) in the majority of cells (Kotin *et al.*, 1990), whereas with recombinant

AAV (rAAV) vectors, persistence appears to be due to a combination of episomal persistence and integration into non-chromosome 19 locations (Afione *et al.*, 1996; Kearns *et al.*, 1996). Recombinant AAV latency also differs from that of wtAAV in that wtAAV is rapidly converted to double-stranded DNA in the absence of helper virus (*e.g.*, adenovirus) infection, while with rAAV leading strand synthesis is delayed in the absence of helper virus (Fisher *et al.*, 1996; Ferrari *et al.*, 1996). U.S. Patent No. 5,658,785 describes adeno-associated virus vectors and methods for gene transfer to cells.

Kessler *et al.* (1996) demonstrated that murine skeletal myofibers transduced by an rAAV vector were capable of sustained secretion of biologically active human erythropoietin (hEpo), apparently without eliciting a significant immune response against the secreted hEpo. See also U.S. Patent No. 5,858,351 issued to Podsakoff *et al.* Likewise, Murphy *et al.* (1997) have observed the expression and secretion of sustained levels of leptin in *ob/ob* mice after AAV muscle transduction. Brantly *et al.* (U.S. Patent No. 5,439,824) disclose methods for increasing expression of AAT using vectors comprising intron II of the human AAT gene. However, the level of leptin expression observed was only in the range of 2 to 5 ng/ml. Therapy for AAT deficiency requires serum levels of at least about 800 μ g/ml. Thus, there remains a need in the art for a means of providing therapeutically beneficial levels of a protein to a person in need of such treatment.

Brief Summary of the Invention

The subject invention concerns materials and methods for gene therapy. One aspect of the invention pertains to vectors which can be used to provide genetic therapy in animals or humans having a genetic disorder where relatively high levels of expression of a protein is required to treat the disorder. The vectors of the invention are based on adeno-associated virus (AAV). The vectors are designed to provide high levels of expression of heterologous DNA contained in the vector. In one embodiment, the vectors comprise AAV inverted terminal repeat sequences and constitutive or regulatable promoters for driving high levels of gene expression. The subject invention also pertains to methods for treating animals or humans in need of gene therapy, *e.g.*, to correct a genetic deficiency disorder.

Brief Description of the Drawings

Figure 1 shows rAAV-AAT vector cassettes used according to the subject invention. The A-AT and B-AT constructs contain the promoters from the small nuclear RNA genes, U1a and U1b, respectively. The C-AT construct contains the CMV promoter, whereas the E-AT vector uses the human elongation factor 1- α (ELF in the figure) promoter. ITR refers to AAV inverted terminal repeat; An refers to polyA signal; Tk refers to the HSV thymidine kinase promoter; *neo* refers to the Tn5 neomycin phosphotransferase gene.

Figure 2 shows hAAT secretion rates *in vitro* from transiently transfected murine C2C12 myoblast cell line using expression vectors according to the subject invention. C-AT does not differ significantly from E-AT, but both differ from A-AT and B-AT ($p < 0.05$) AAT expression was detected using an ELISA assay specific for human AAT.

Figure 3 shows hAAT secretion rates *in vitro* from stably transduced murine C2C12 myoblast cell line using viral particles comprising expression vectors according to the subject invention. The mean rates of secretion from G418-resistant cultures 1 mo after transduction with either packaged E-AT vector or packaged C-AT vector are shown. In each instance, a "low" multiplicity transduction (4×10^5 particles/cell) and a high multiplicity transduction (4×10^6 particles/cell) were performed. E-AT "low" and "high" are greater than "high" multiplicity C-AT ($P = 0.02$) but are not significantly different from each other ($n = 3$). AAT expression was detected using an ELISA assay specific for human AAT.

Figure 4 shows additional constructs tested for hAAT expression. The murine myoblast C2C12 cells were grown in 35-mm wells with approximately 4×10^5 cell per well and were transfected with 5 μ g of the appropriate plasmid DNA using Superfect transfection (Qiagen Inc., CA). Secretion of hAAT into the medium was assessed at 2 days after transfection using an antigen-capture ELISA. Each bar represents the mean of results from three experiments (triplicate in each experiment).

Data from transfection experiments indicate that the expression from p43CB-AT was at least three times higher than that from C-AT *in vitro*.

Figures 5A and 5B show sustained secretion of therapeutic levels of hAAT using either the C-AT vector or the E-AT vector in either SCID or C57BL mice. Figure 5A shows the mean total serum levels of hAAT observed in groups of either SCID (squares)

or C57BL (circles) mice receiving either low dose (5×10^{11} particles) (open symbols) or high dose (1.4×10^{13} particles) (filled symbols) single injections into muscle of the C-AT vector measured at time points ranging from 1 to 16 wk after injection. For each strain, the high-dose curve is significantly different from the low-dose curve ($P=0.009$ for SCID, $P=0.02$ for C57BL), but the strains do not differ from each other. Figure 5B shows analogous data with the E-AT vector. None of these differences were significant.

Figure 5C shows long term secretion of hAAT from murine muscle transduced with C-AT. C57B1/6 or C57B1/6-SCID mice received 3.5×10^{10} IU, 1.4×10^{13} particles/mouse. One year after injection, serum hAAT levels were still $400 \mu\text{g/ml}$ in C57B1/6-SCID and $200 \mu\text{g/ml}$ in C57B1/6. This level are comparable with the peak levels observed (800 or $400 \mu\text{g/ml}$, respectively).

Figure 6 shows an immunoblot of sera taken from several of the C-AT vector-treated mice at 11 weeks after vector administration. Ten microliters of a 1:100 dilution of serum was electrophoresed by 10% SDS/PAGE, blotted, and incubated with 1:1,500 dilution of goat anti-hAAT-horseradish peroxidase conjugate (Cappel/ICN). Samples from three high-dose SCID (h1-h3), one high-dose C57BL (h3), and three low-dose C57BL (lo1-lo3) were included, along with one negative control (saline-injected = sal) serum to indicate the level of reactivity with endogenous mAAT. As a standard, hAAT was added either to negative-control C57BL serum (first hAAT lane) or to PBS (second hAAT) lane to final equivalent serum concentration of $100 \mu\text{g/ml}$.

Figures 7A and 7B show that some BALB/c mice mount humoral immune responses to hAAT, which correlate with lower serum levels but no observable toxicity. Figure 7A shows serum hAAT levels and Figure 7B shows serum anti-hAAT antibody levels as determined by ELISA performed on serum taken from mice injected with 1×10^{11} particles of the C-AT vector. Each set of symbols represents an individual animal ($\square$, no. 1; Δ , no. 2; $\circ$, no. 3). Note the inverse correlation between the presence of antibody and the presence of circulating hAAT.

Figure 8 shows the persistence of rAAV-AAT vector DNA in high molecular weight form. PCR products were amplified from DNA prepared by Hirt extraction from three SCID mice injected 16 wk earlier with 5×10^{11} resistant-particles of C-AT and analyzed by Southern blot. The high molecular weight Hirt pellet (genomic DNA lanes) and the low molecular weight supernatant (episomal DNA lanes) were analyzed

separately. Control lanes include a sample in which an hAAT cDNA plasmid was the template DNA (+) and a control in which water was the template (-). In this internal PCR reaction, a 500-bp product is expected regardless of whether or not the vector genome is integrated.

5 **Figure 9** shows serum hAAT in C57B1/6 mice transduced with C-AT and p43CB-AT. C57B1/6 mice were injected in muscle with C-AT (3.5×10^{10} IU/mouse, 1×10^{12} particles/mouse) or p43CB-AT (6×10^9 IU, 1×10^{12} particles/mouse). The level of hAAT from p43CB-AT were projected based on an estimation of the equivalent dosage (infectious unit) of C-AT.

10 **Figure 10** shows enhancement of CMV promoter activity by a synthetic enhancer in C2C12 cells. The murine myoblast C2C12 cells were grown in 35-mm wells with approximately 4×10^5 cell per well and were transfected with $5 \mu\text{g}$ of p.43rmsENC-AT vector DNA using SUPERFECT transfection (Qiagen Inc, CA). Secretion of hAAT into the medium was assessed at 2 days after transfection using an antigen-capture ELISA.
15 Each bar represents the mean of results from one experiment (triplicate).

Figure 11 shows secretion of hAAT from mouse liver cells (HO15) transfected with different constructs. The murine liver cells (HO15) were grown in 35-mm wells with approximately 4×10^5 cell per well and were transfected with $5 \mu\text{g}$ of the plasmid DNA using LIPOFECTAMINE reagents (Life Technologies Inc, MD). Secretion of
20 hAAT into the medium was assessed at 2 days after transfection using an antigen-capture ELISA. Each bar represents the mean of results from two experiments (triplicate).

Figure 12 shows secretion of hAAT from mouse liver cells (HO15) transfected using different methods. The murine liver cells (HO15) were grown in 35-mm wells with approximately 4×10^5 cell per well and were transfected with $5 \mu\text{g}$ of the p43CB-AT vector
25 using Superfect (Qiagen Inc., CA), FuGENE (Boehringer Mannheim Co, IN), Lipofectin, LipofectAMINE (Life Technologies Inc, MD) reagents and Calcium phosphate (CA-PO₄) transfection. Secretion of hAAT into the medium was assessed at 2 days after transfection using an antigen-capture ELISA. Each bar represents the mean of results from one experiment (triplicate).

30 **Figure 13** shows hAAT secretion from mouse liver transduced with rAAV. C57B1/6 mice were injected with either p43CB-AT, C-AT or E-AT vector either by portal vein or tail vein injection. PV=portal vein injection. TV=tail vein injection.

Figure 14 shows serum hAAT levels in C57Bl/6 mice after intratracheal (IT) injection of C-AT or p43CB-AT vector. Mice received either 10^9 IU of C-AT (open circles), 10^9 IU of p43CB-AT (open triangles) or 10^{10} IU of p43CB-AT (open squares).

Figure 15 shows a map and nucleotide sequence for the vector of the present invention designated as C-AT.

Figure 16 shows a map and nucleotide sequence for the vector of the present invention designated as E-AT.

Figure 17 shows a map and nucleotide sequence for the vector of the present invention designated as dE-AT.

Figure 18 shows a map and nucleotide sequence for the vector of the present invention designated as p43C-AT.

Figure 19 shows a map and nucleotide sequence for the vector of the present invention designated as p43C-AT-IN. This vector includes intron II from human AAT gene to enhance transcription.

Figure 20 shows a map and nucleotide sequence for the vector of the present invention designated as p43CB-AT.

Figure 21 shows a map and nucleotide sequence for the vector of the present invention designated as C-AT2.

Figure 22 shows a map and nucleotide sequence for the vector of the present invention designated as p43msENC-AT. This vector is similar to p43C-AT but also comprises an enhancer sequence upstream of the CMV promoter.

Figure 23 shows a map and nucleotide sequence for the vector of the present invention designated as p43rmsENC-AT. This vector is the same as the p43msENC-AT vector except that the enhancer sequence is in an opposite orientation.

Figure 24 shows a map and nucleotide sequence for the vector of the present invention designated as p43msENCB-AT. This vector is similar to p43CB-AT but also comprises an enhancer sequence upstream of the CMV promoter.

Figure 25 shows a map and nucleotide sequence for the vector of the present invention designated as p43rmsENCB-AT. This vector is the same as p43msENCB-AT except that the enhancer sequence is in an opposite orientation.

Detailed Disclosure of the Invention

The subject invention pertains to novel materials and methods for providing gene therapy to a mammal or human having a condition or disorder, such as genetic deficiency disorders, where high levels of expression of a protein are required to treat the disorder or condition. In one method of the subject invention, a viral vector is introduced into cells of an animal wherein a therapeutic protein is produced, thereby providing genetic therapy for the animal. In one embodiment, a method of the invention comprises introducing into an animal cell or tissue an effective amount of viral particles or vector comprising a recombinant genome which includes heterologous polynucleotide encoding a protein useful in genetic therapy and that can be expressed by the cell or tissue. Expression of the heterologous polynucleotide results in production of the protein. Preferably, the therapeutic protein encoded by the heterologous polynucleotide is a serum protein. In a preferred embodiment, vector material comprising the heterologous polynucleotide is integrated into a chromosome of the cell of the host animal.

In one embodiment, a recombinant polynucleotide vector of the present invention is derived from adeno-associated virus (AAV) and comprises a constitutive or regulatable promoter capable of driving sufficient levels of expression of the heterologous DNA in the viral vector. Preferably, a recombinant vector of the invention comprises inverted terminal repeat sequences of AAV, such as those described in WO 93/24641. In a preferred embodiment, a vector of the present invention comprises polynucleotide sequences of the pTR-UF5 plasmid. The pTR-UF5 plasmid is a modified version of the pTR_{BS}-UF/UF1/UF2/UFB series of plasmids (Zolotukhin *et al.*, 1996). The pTR-UF5 plasmid contains modifications to the sequence encoding the green fluorescent protein (GFP).

Promoters useful with the subject invention include, for example, the cytomegalovirus immediate early promoter (CMV), the human elongation factor 1-alpha promoter (EF1), the small nuclear RNA promoters (Ula and Ulb), α -myosin heavy chain promoter, Simian virus 40 promoter (SV40), Rous sarcoma virus promoter (RSV), adenovirus major late promoter, β -actin promoter and hybrid regulatory element comprising a CMV enhancer/ β -actin promoter. These promoters have been shown to be active in a wide range of mammalian cells. In addition to the natural promoters described above, synthetic promoters can be used in the present invention. For example, a synthetic

enhancer randomly assembled from Spc5-12-derived elements including muscle-specific elements, serum response factor binding element (SRE), myocyte-specific enhancer factor-1 (MEF-1), myocyte-specific enhancer factor -2 (MEF-2), transcription enhancer factor-1 (TEF-1) and SP-1 (Li et al., 1999; Deshpande *et al.*, 1997; Stewart *et al.*, 1996; Mitchell *et al.*, 1989; Briggs et al., 1986; Pitluk *et al.*, 1991) can be used in vectors of the invention.

The promoters are operably linked with heterologous DNA encoding the protein of interest. By "operably linked," it is intended that the promoter element is positioned relative to the coding sequence to be capable of effecting expression of the coding sequence.

Promoters particularly useful for expression of a protein in muscle cells include, for example, hybrid CMV/ β -actin promoters, CMV promoters, synthetic promoters and EF1 promoter. Promoters particularly useful for expression of a protein in liver cells include, for example, hybrid CMV/ β -actin promoters and EF1 promoters.

Also contemplated for use with the vectors of the present invention are inducible and cell type specific promoters. For example, Tet-inducible promoters (Clontech, Palo Alto, CA) and VP16-LexA promoters (Nettelbeck *et al.*, 1998) can be used in the present invention.

The vectors can also include introns inserted into the polynucleotide sequence of the vector as a means for increasing expression of heterologous DNA encoding a protein of interest. For example, an intron can be inserted between a promoter sequence and the region coding for the protein of interest on the vector. Introns can also be inserted in the coding regions. Transcriptional enhancer elements which can function to increase levels of transcription from a given promoter can also be included in the vectors of the invention. Enhancers can generally be placed in either orientation, 3' or 5', with respect to promoter sequences.

Heterologous polynucleotide in the recombinant vector can include, for example, polynucleotides encoding normal, functional proteins which provide therapeutic replacement for normal biological function in animals afflicted with genetic disorders which cause the animal to produce a defective protein, or abnormal or deficient levels of that protein. Proteins, and the polynucleotide sequences that encode them, which can be provided by gene therapy using the subject invention include, but are not limited to, anti-

proteases, enzymes, structural proteins, coagulase factors, interleukins, cytokines, growth factors, interferons, and lymphokines. In an exemplified embodiment, heterologous DNA in a recombinant AAV vector encodes human alpha-1-antitrypsin protein.

5 The gene therapy methods of the invention can be performed by *ex vivo* or *in vivo* treatment of the patient's cells or tissues. Cells and tissues contemplated within the scope of the invention include, for example, muscle, liver, lung, skin and other cells and tissues that are capable of producing and secreting serum proteins. The vectors of the invention can be introduced into suitable cells, cell lines or tissue using methods known in the art. The viral particles and vectors can be introduced into cells or tissue *in vitro* 10 or *in vivo*. Methods contemplated include transfection, transduction, injection and inhalation. For example, vectors can be introduced into cells using liposomes containing the subject vectors, by direct transfection with vectors alone, electroporation or by particle bombardment. In an exemplified embodiment, muscle cells are infected *in vivo* by injection of viral particles comprising recombinant vector into muscle tissue of an 15 animal. In another embodiment, liver cells are infected *in vivo* by injection of recombinant virus into either the portal vein or peripheral veins.

The methods and materials of the subject invention can be used to provide genetic therapy for any conditions or diseases treatable by protein or cytokine infusion such as, for example, alpha-1-antitrypsin deficiency, hemophilia, adenosine deaminase deficiency, 20 and diabetes. The methods and materials of the subject invention can also be used to provide genetic therapy for treating conditions such as, for example, cancer, autoimmune diseases, neurological disorders, immunodeficiency diseases, and bacterial and viral infections. For example, the present invention can be used to provide genetic therapy to a patient wherein cells from the patient are transformed to express and produce 25 interleukins such as interleukin-2.

Animals that can be treated with the materials and methods of the invention include mammals such as bovine, porcine, equine, ovine, feline and canine mammals. Preferably, the mammals are primates such as chimpanzees and humans.

30 The subject invention also concerns cells containing recombinant vectors of the present invention. The cells can be, for example, animal cells such as mammalian cells. Preferably, the cells are human cells. More preferably, the cells are human myofibers or myoblasts, hepatocytes or lung cells. In a preferred embodiment, a recombinant vector

of the present invention is stably integrated into the host cell genome. Cell lines containing the recombinant vectors are also within the scope of the invention.

In an exemplified embodiment, recombinant AAV vectors comprising the human AAT gene (hAAT) using either the CMV promoter (AAV-C-AT) or the human elongation factor 1-alpha (EF1) promoter (AAV-E-AT) to drive expression were constructed and packaged using standard techniques. A murine myoblast cell line, C2C12, was transduced with each vector and expression of hAAT into the medium was measured by ELISA. *In vitro*, the EF1 promoter construct resulted in 10-fold higher hAAT expression than the CMV promoter construct. *In vivo* transduction was performed by injecting doses of up to 1.4×10^{13} Dnase-resistant particles of each vector into skeletal muscles of a number of different strains of mice (including C57B1/6, Balb/c, and SCID). *In vivo*, the CMV promoter construct resulted in higher levels of expression, with sustained serum levels up to 800 $\mu\text{g/ml}$ in SCID mice, approximately 10,000-fold higher than those previously observed with proteins secreted from AAV vectors in muscle. At lower doses in both C57B1/6 and SCID mice, expression was delayed for several weeks, but was sustained for over 10 weeks without declining. Thus, increasing dosage AAV vector via transduction of skeletal muscle provides a means for replacing AAT or other serum proteins.

Transduction of muscle using the vectors of the subject invention presents several advantages in that it is stable, non-toxic, and relatively nonimmunogenic. Furthermore, certain transcription promoters, such as the CMV promoter, which appear to be markedly down-regulated in other contexts have been found to remain active over time as used in the subject invention. Using the materials and methods of the subject invention, microgram/ml serum levels of a therapeutic protein can be achieved. In an exemplified embodiment, the levels of *in vivo* protein expression achieved represent a 10,000-fold or more increase over previously published results. In addition, a dose-effect relationship was demonstrable within the range of doses used, providing for further increases in expression levels as vector dose is increased.

In another embodiment of the invention, recombinant AAV vectors *i.e.*, C-AT, p43C-AT, P43CB-AT, E-AT and dE-AT comprising the human AAT gene (hAAT) using were constructed and packaged using standard techniques. A murine liver cell line, HO15, was transfected with each vector and expression of hAAT into the medium was

measured by ELISA. *In vitro*, transduction with the p43CB-AT vector exhibited the highest level of hAAT expression. *In vivo*, the p43CB-AT vector also gave higher levels of expression. Portal vein administration appeared to be the more efficient route of administration as mice injected in this manner exhibited higher levels of expression than those receiving peripheral vein injections. Transduction of liver offers the same advantages as for muscle, but hepatocytes may be more efficient at secretion of protein.

The dosage of recombinant vector or the virus to be administered to an animal in need of such treatment can be determined by the ordinarily skilled clinician based on various parameters such as mode of administration, duration of treatment, the disease state or condition involved, and the like. Typically, recombinant virus of the invention is administered in doses between 10^5 and 10^{14} infectious units. The recombinant vectors and virus of the present invention can be prepared in formulations using methods and materials known in the art. Numerous formulations can be found in Remington's Pharmaceutical Sciences, 15th Edition (1975).

All publications and patents cited herein are expressly incorporated by reference.

Materials and Methods

Construction of rAAV plasmids. The rAAV-AAT vector plasmids used for these experiments are depicted diagrammatically (Figure 1). Briefly, the plasmid pN2FAT (Garver *et al.* (1987) plasmid was digested with *Xho*I to release 1.8-kb fragment containing the human AAT cDNA along with the SV40 promoter and a polyadenylation signal. This fragment was subcloned into a plasmid, pBlueScript (Stratagene) and, after the removal of the SV40 promoter by *Hind* III digestion and religation, the hAAT cDNA with its polyA signal was released by *Xba*I and *Xho*I digestion. This 1.4-kb *Xba*I-*Xho*I fragment was then cloned in to the pTR-UF5 (an AAV-inverted terminal repeat-containing vector) plasmid (Zolotukhin *et al.*, 1996) between the *Xba*I site 3' to the CMV promoter and the *Xho*I site 5' to the polyoma virus enhancer/HSVthymidine kinase promoter cassette, which drives *neo* in that construct. This yielded the pAAV-CMV-AAT construct (C-AT). Analogous constructs using the promoter from the small nuclear RNA proteins, Ula and Ulb, (to give the A-AT and B-AT constructs, respectively) and

human elongation factor 1-alpha (EF1) promoter (to give the E-AT construct) were constructed by substituting each of these promoter cassettes in place of the CMV promoter, between the KpnI and XbaI sites.

The construct, dE-AT derived from E-AT by deletion of the silencer (352 bp) by SAC II-cut (Wakabayashi-Ito *et al.*, 1994). C-AT2 is similar with C-AT except there are SV40 intron and poly (A) sequences flanking the cDNA of hAAT. The p43C-AT was constructed by insertion of hAAT cDNA to an AAV-vector plasmid (p43), which has CMV promoter, intron and poly (A) sequences. The p43CB-AT is derived by replacement of CMV promoter with CMV enhancer and chicken β -actin promoter sequences. The p43C-AT-IN is derived from p43C-AT by insertion of intron II sequences of hAAT gene to hAAT cDNA (Brantly *et al.*, 1995).

Packaging of rAAV vectors. Vectors were packaged using a modification of the method described by Ferrari *et al.* (1997). Briefly, plasmids containing the AAV *rep* and *cap* genes (Li *et al.*, 1997) and the Ad genes (E2a, E4 and VA-RNA) were co-transfected along with the appropriate AAV-AAT vector plasmid into 293 cells grown in Cell Factories (Nunc). Cells were harvested by trypsinization and disrupted by freeze-thaw lysis to release vector virions which were then purified by iodixanol gradient ultracentrifugation followed by heparin sepharose affinity column purification. Alternatively, recombinant virus can be prepared according to methods described in Zolotukhin *et al.* (1999).

Vector preparations had their physical titer assessed by quantitative competitive PCR and their biological titer assessed by infectious center assay. The presence of wild-type AAV was also assessed using these same assays with appropriate internal AAV probes. The high-dose C-AT stock had a particle-titer of 2.0×10^{14} particles/ml and an infectious titer of 5.0×10^{11} infectious units (i.u.)/ml (particle to i.u. ratio = 400:1). The low-dose C-AT measured 8×10^{12} particles/ml and 1.2×10^{10} i.u./ml (particle to i.u. = 667:1). For the E-AT experiments, the titers were 1×10^{13} particles/ml and 2.5×10^{10} i.u./ml (particle to i.u. = 400:1). The low-dose C-AT stock had a wt-like AAV particle titer (*i.e.*, positive AAV genome PCR) equal to 0.1 times the recombinant titer but no detectable infectious wtAAV. The other two preparations had wt-like AAV particle titers $< 10^{-5}$ times the recombinant titer and no detectable infectious wtAAV.

In vitro transfection and transduction experiments. The C2C12 murine myoblast line was used for *in vitro* transfection and transduction experiments. Cells were grown in 35-mm wells with approximately 4×10^5 cells per well and transfected with $5 \mu\text{g}$ of each plasmid DNA using Superfect (Qiagen Corp.). Secretion of hAAT into the medium was assessed at 2 days after transfection using an antigen-capture ELISA assay with standards (Brantly *et al.*, 1991). An SV40 promoter luciferase-expression plasmid, pGL2 (Promega), was used as an internal control. For transduction experiments, cells were grown under similar conditions and were transduced with vector at multiplicities of infection ranging from 4×10^5 to 4×10^6 particles per cell. Cells were then passaged in the presence of geneticin sulfate ($350 \mu\text{g/ml}$) and geneticin-resistant clones were isolated for hAAT secretion studies.

In vivo injection of AAV-C-AT and AAV-E-AT vectors into murine muscle. Mice strains (C57B1/6, SCID, and Balb/c) were obtained from Jackson Laboratories (Bar Harbor, ME) and were handled under specific pathogen-free conditions under a protocol approved by the University of Florida Institutional Animal Care and Use Committee. Animals were anesthetized by metaphane inhalation and aliquots of vector were injected percutaneously into the quadriceps femoris muscles of both hind limbs. The volume of vector ranged from 50 to $100 \mu\text{l}$ per injection site and the total amount of virus injected per animal ranged from 5×10^{10} to 1.4×10^{13} Dnase-resistant particles.

Antigen capture ELISA assay for hAAT expression. Microtiter plates (Immulon 4, Dynex Technologies, Chantilly, VA) were coated with $100 \mu\text{l}$ of a 1:200 dilution of goat anti-human AAT (CAPPEL/ICN) in Vollers buffer ($\text{Na}_2\text{CO}_3=2.76\text{g}$, $\text{NaHCO}_3=1.916\text{g}$, $\text{NaN}_3=0.2\text{g}$, $\text{d.H}_2\text{O}=1$ liter, Adjust $\text{PH}=9.6$) overnight at 4°C . After washing, standards and unknown samples containing hAAT were incubated in the plates at 37°C for 1 hour. After blocking in 3% BSA in PBS-Tween 20 at 37°C for 1 hour, a second antibody (1:1000 dilution of rabbit anti-human AAT, Boehringer Mannheim) was reacted with the captured antigen at 37°C for 1 hour. Detection was performed using a third antibody incubation (1:800 dilution of goat anti-rabbit IgG-peroxidase conjugate, 37°C) followed by *o*-phenylenediamine (OPD, Sigma) detection and measurement of the absorbance at 490nm.

ELISA assay for anti-hAAT and anti-AAV VP3 antibodies. Wells were coated with antigen ($1 \mu\text{g}$ of hAAT or 100ng of VP3) at 4°C overnight, blocked with 3% BSA

and then reacted with dilutions of either test serum or with positive control antibodies at 37°C for 1 hour. After washing, a goat-anti-mouse IgG-peroxidase conjugate was used as a secondary antibody (1:1500 dilution) to detect bound anti-AAT antibody, using a standard OPD reaction, as described above. Antibody levels were quantitated by comparison with a standard curve generated by reacting dilutions of known positive monoclonal antibodies against VP3 and hAAT.

Lymphocyte proliferation assays to detect cell-mediated immune responses.

Lymphocyte proliferation assays were performed in order to detect T cell responses to the hAAT and VP3 antigens. Freshly isolated splenocytes were grown in primary culture in 96 well plates coated with 0, 0.1, 1, and 10 µg of either hAAT or VP3 in RPMI-C+ medium. On day three, a pulse of ³H-thymidine was added, and the cells were harvested on day 4 for lysis and scintillation counting. Phytohemagglutinin (PHA) was used as a mitogen for positive control wells. A stimulation index was calculated for each antigen dosage level by dividing the counts per minute (cpm) of ³H-thymidine incorporated in the antigen-stimulated cells by the cpm in a control (unstimulated) well.

Following are examples which illustrate procedures for practicing the invention. These examples should not be construed as limiting. All percentages are by weight and all solvent mixture proportions are by volume unless otherwise noted.

Example 1 – *In vitro* studies in murine C2C12 myoblasts

In order to determine the relative strength of a number of constitutively active promoters in the context of AAV-AAT vectors, packageable AAV-AAT expression vectors containing one of the CMV, EF1, Ula or Ulb promoters (Figure 1) were constructed. Each of these constructs were transfected in to the murine C2C12 myoblast cell line. Both the EF1 and the CMV promoter were active for AAT expression, with EF1 construct (AAV-E-AT) expressing 850 ng/10⁵ cells/day and the CMV construct (AAV-C-AT) expressing approximately 670 ng/10⁵ cells/day, as measured by a human-specific ELISA assay for AAT (Figure 2). This difference was not statistically significant. The levels of expression from the Ula and Ulb constructs were undetectable.

In order to better characterize the level and duration of expression in the setting of vector transduction, cultures of C2C12 cells were transduced with either AAV-E-AT

or AAV-C-AT at multiplicities of infection ranging from 4×10^5 to 4×10^6 Dnase-resistant particles per cell. Cells were then selected for expression of the *neo* gene (present in each of the AAV constructs) by growth in G418-containing medium. Several cell clones and pooled cell populations were independently analyzed for AAT expression at four weeks post-transduction (Figure 3). There was a clear trend toward higher levels of expression at higher multiplicities of infection, and the E-AT construct expressed at least 10-fold greater quantities under all conditions in these long-term cultures. The most active E-AT clone expressed hAAT at a rate of over 1400 ng/ 10^5 cells/day.

Example 2—*In vivo* expression of hAAT from murine skeletal muscle

In order to determine whether the AAV-AAT constructs would be active *in vivo* in skeletal muscle, doses of vector were injected into the quadriceps femoris muscle of mice. Circulating serum levels of hAAT were then measured for 11 to 15 weeks after the initial injection. Four saline-injected animals from each mouse strain served as controls. In the case of the C-AT vector (Figure 5A), levels of expression were sufficient to achieve serum levels in excess of 800 $\mu\text{g/ml}$ in SCID mice after a single injection of 1.4×10^{13} particles. A dose-effect relationship was observed, with expression levels in SCID being at least 20-fold lower at the 5×10^{11} particle dose. The levels of expression increased over the first several weeks after injection and were stable thereafter until the time of sacrifice. Since hAAT has a half-life of less than 1 week, this indicated continuous expression. Levels from C57B1/6 mice were comparable, and also achieved values close to the therapeutic range. In similar studies, two of three Balb/c mice injected with 1×10^{11} particles of the C-AT vector did not express hAAT at detectable levels. Both of these were found to have developed high levels of anti-hAAT antibodies.

Surprisingly, expression levels from the AAV-E-AT vector after *in vivo* injection were modestly lower than those seen with the C-AT vector (Figure 5B), with maximal levels of approximately 250 ng/ml at the 5×10^{11} dose at and beyond 7 weeks in SCID mice. When the dose was further increased to 1×10^{12} particles, levels of approximately 1200 ng/ml were observed. These levels were stable for one year post-injection (Figure 5C). Levels observed in SCID and immune competent C57B1/6 mice were similar.

Example 3 — Immunologic Studies

In studies in Balb/c mice, antibody levels against hAAT were high in 2 of 3 animals injected. The one which did not have circulating anti-hAAT was the only animal with levels of hAAT expression similar to those in the C57B1/6 and SCID groups. The high-dose C57-C-AT injection group had detectable levels of antibody directed against VP3, but not hAAT.

In order to determine whether any cell-mediated immune responses were mounted, lymphocyte proliferation assays were performed using either hAAT or AAV-VP3 for antigenic stimulation of primary splenic lymphocytes harvested at the time of animal sacrifice, 16 weeks post-vector injection. Using this method, no immune responses were detectable in any of the mice.

Example 4 — Lack of toxicity from direct vector injection

In order to determine whether there was any direct toxicity, inflammation, or neoplastic change associated with vector injection, animals underwent complete necropsies. Histopathologic examination was performed on 5 μ m sections taken from the site of vector injection and from a panel of other organs, including the brain, heart, lungs, trachea, pancreas, spleen, liver, kidney, and jejunum. No histologic abnormalities were observed in any of these sites, even among those mice which developed humanol immune responses against hAAT.

Example 5 — Molecular evidence of AAV-AAT vector persistence

To confirm the presence of vector DNA, a vector-specific PCR (*neo* primers 5'-TATGGGATCGGCCATTGAAC-3', and 5'-CCTGATGCTCTTC-GTCCAGA-3'), was performed on DNA extracted from 3 SCID mice 16 weeks after injection with the C-AT vector, and PCR products were analyzed by Southern blot analysis with a ³²P-labeled vector-specific probe (Figure 8). The state of vector DNA was analyzed using the Hirt procedure (Carter *et al*, 1983) to separate the low molecular weight episomal DNA from the high molecular weight fraction, which would contain integrated forms and large concatemers. In each case, vector DNA was present in the high molecular weight DNA fraction, whereas in only one of the animals was there a signal in the episomal fraction. This result indicates that by 16 weeks most of the vector DNA in our animals was either integrated or in large concatemers.

Example 6 — *In vivo* expression of hAAT from murine liver

Portal vein or tail vein injections were performed on 18 female C57BL/6 mice 8-10 weeks of age. The injection volume was 100 μ l per mouse.

Each group had the following parameters:

- 5 1. Group 1: 100 μ l of PBS n=4.
2. Group 2: 100 μ l of p43CB-AT (3×10^{10} IU/animal) n=3.
3. Group 3: 100 μ l of p43CB-AT (4×10^9 IU/animal) n=4.
4. Group 4: 100 μ l of C-AT (4×10^9 IU/animal) n=2.
5. Group 5: 100 μ l of E-AT (4×10^9 IU/animal) n=4.
- 10 6. Group 6: EATM TV=100 μ l by tail vein injection of E-AT (4×10^9 IU/animal) n=3.
7. Group 0: 100 μ l of PBS by tail vein injection n=2.

A total of 22 animals were used in this study.

15 All animals were anesthetized with 2-2-2 tribromoethanol (Avertin) using a working solution of 20 mg/ml at a dosage of 0.5 mg/g IP. A 2 cm ventral midline abdominal incision was made from the pubic symphysis extending cranially to the xyphoid process through skin and muscle layers. The portal vein was exposed by retracting the intestines and associated mesentery to the left side of the animal. Additionally, the quadrate and right medial lobes of the liver were retracted cranially.

20 Intestines and peritoneal cavity were continuously lavaged with 0.9% NaCl.

25 Virus or PBS was delivered into the portal vein using a 30 g needle attached to a 100 μ l capillary pipette using mouth delivery via rubber tubing and a Drummond self-locking double layer 0.8 μ m filter. A small piece of Gel-Foam (.5x.5cm) was applied to the injection site before the needle was removed from the portal vein. The needle was retracted from beneath the Gel-Foam and the piece was held in place with forceps while the intestines were replaced into the peritoneal cavity.

30 The muscle and skin were closed in one layer using 2 simple interrupted 3-0 nylon sutures on an FS-1 cutting needle. Surgeries were performed on a thermoregulated operating board designed to maintain a temperature of 37 degrees. For recovery from anesthesia, the animals were placed under a heat lamp adjusted to maintain an ambient temperature of approximately 37 degrees and given subcutaneous fluid if there was a significant amount of blood loss during surgery.

Serum levels of hAAT in the mice were measured two weeks after injection. Serum levels of about 200-150 $\mu\text{g/ml}$ hAAT were detected in mice receiving the p43CB-AT vector (Figure 13). Studies using the E-AT vector show that injection of vector by portal vein led to greater levels of hAAT secretion as compared to E-AT administered by tail vein injection.

Example 7— *In vivo* expression of hAAT from murine lung

Mice were injected intratracheally with either C-AT or p43CB-AT vector. Serum levels of hAAT in the mice were measured at day 3, 14 and 31 after injection (Figure 14). The p43CB-AT vector mediated high levels of expression of hAAT in lung.

It should be understood that the examples and embodiments described herein are for illustrative purposes only and that various modifications or changes in light thereof will be suggested to persons skilled in the art and are to be included within the spirit and purview of this application and the scope of the appended claims.

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We claim:

Claims

1 1. A method for providing an animal with a therapeutically effective amount of
2 a serum protein, said method comprising introducing into cells of said animal an effective
3 amount of viral particles or vector, wherein said viral particles or viral vector comprises
4 a polynucleotide encoding said protein.

1 2. The method according to claim 1, wherein said animal is a mammal.

1 3. The method according to claim 2, wherein said mammal is a human.

1 4. The method according to claim 1, wherein said vector is an adeno-associated
2 virus vector.

1 5. The method according to claim 1, wherein said vector comprises a promoter
2 sequence capable of driving expression of said polynucleotide encoding said protein.

1 6. The method according to claim 5, wherein said promoter sequence is selected
2 from the group consisting of CMV promoter sequences, hybrid CMV enhancer/ β -actin
3 promoter sequences, EF1 promoter sequences, Ula promoter sequences and U1b
4 promoter sequences.

1 7. The method according to claim 5, wherein said promoter sequence is an
2 inducible promoter selected from the group consisting of Tet-inducible promoters and
3 VP16-LexA promoters.

1 8. The method according to claim 5, wherein said vector further comprises an
2 enhancer sequence.

1 9. The method according to claim 8, wherein said enhancer is a synthetic
2 enhancer.

1 10. The method according to claim 1, wherein said animal has a condition that
2 results in a defective protein or a deficiency of said protein encoded by said
3 polynucleotide.

1 11. The method according to claim 1, wherein said animal has a condition that
2 can be ameliorated or treated by said protein encoded by said polynucleotide.

1 12. The method according to claim 1, wherein said protein encoded by said
2 polynucleotide is selected from the group consisting of anti-proteases, enzymes,
3 structural proteins, coagulase factors, interleukins, cytokines, growth factors, interferons,
4 and lymphokines.

1 13. The method according to claim 1, wherein said cells are myofibers,
2 myoblasts, hepatocytes, or lung cells.

1 14. The method according to claim 1, wherein said polynucleotide encodes
2 human alpha-1-antitrypsin protein, or a biologically active fragment or variant thereof.

1 15. The method according to claim 4, wherein said polynucleotide encodes
2 human alpha-1-antitrypsin protein, or a biologically active fragment or variant thereof.

1 16. The method according to claim 1, wherein said viral particles are introduced
2 into said cells or tissue by infection or injection.

1 17. The method according to claim 1, wherein said vector is introduced into said
2 cells by transfection or injection.

1 18. The method according to claim 1, wherein said viral particles or vector is
2 introduced into said cells *in vitro* and said treated cells are introduced into said animal.

1 19. The method according to claim 1, wherein said viral particles or vector is
2 introduced into said cells *in vivo*.

1 20. The method according to claim 19, wherein said viral particles or vector is
2 injected into muscle.

1 21. The method according to claim 19, wherein said viral particles or vector is
2 injected into portal or peripheral vein.

1 22. The method according to claim 19, wherein said viral particles or vector is
2 injected intratracheally or inhaled into the lungs.

1 23. The method according to claim 15, wherein said vector is selected from the
2 group consisting of dE-AT, E-AT, C-AT, C-AT2, p43C-AT, p43CB-AT, p43C-AT-IN,
3 p43msENC-AT, p43rmsENC-AT, p43msENCB-AT and p43rmsENCB-AT.

1 24. A recombinant viral vector comprising a polynucleotide encoding a protein
2 capable of providing a therapeutic effect to an animal when expressed in said animal.

1 25. The vector according to claim 24, wherein said animal is a mammal.

1 26. The vector according to claim 25, wherein said mammal is a human.

1 27. The vector according to claim 26, wherein said vector is an adeno-associated
2 virus vector.

1 28. The vector according to claim 24, wherein said vector comprises a promoter
2 sequence capable of driving expression of said polynucleotide encoding said protein.

1 29. The vector according to claim 24, wherein said promoter sequence is selected
2 from the group consisting of CMV promoter sequences, hybrid CMV enhancer/ β -actin

3 promoter sequences, EF1 promoter sequences, Ula promoter sequences and U1b
4 promoter sequences.

1 30. The vector according to claim 24, wherein said polynucleotide encodes
2 human alpha-1-antitrypsin protein, of a biologically active fragment or variant thereof.

1 31. The vector according to claim 27, wherein said polynucleotide encodes
2 human alpha-1-antitrypsin protein, of a biologically active fragment or variant thereof.

1 32. The vector according to claim 31, wherein said vector is selected from the
2 group consisting of dE-AT, E-AT, C-AT, C-AT2, p43C-AT, p43CB-AT, p43C-AT-IN,
3 p43msENC-AT, p43rmsENC-AT, p43msENCB-AT and p43rmsENCB-AT.

1 33. A viral particle comprising the vector of claim 24.

1 34. A cell comprising the vector of claim 24.

1 35. The cell according to claim 34, wherein said cell is a myofiber, myoblast,
2 hepatocyte, or lung cell.

1 36. A method for treating alpha-1-antitrypsin deficiency in an animal, said
2 method comprising introducing into cells of said animal a vector according to claim 24,
3 wherein said polynucleotide of said vector encodes alpha-1-antitrypsin protein, or a
4 biologically active fragment or variant thereof.

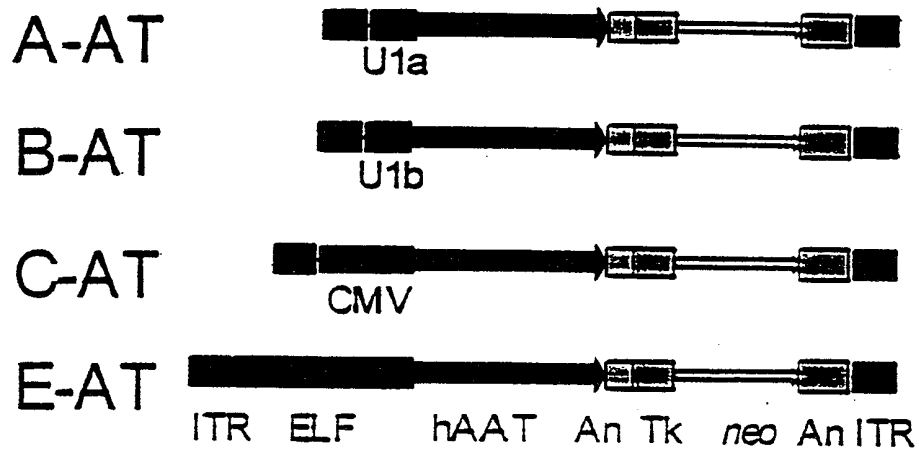


FIGURE 1

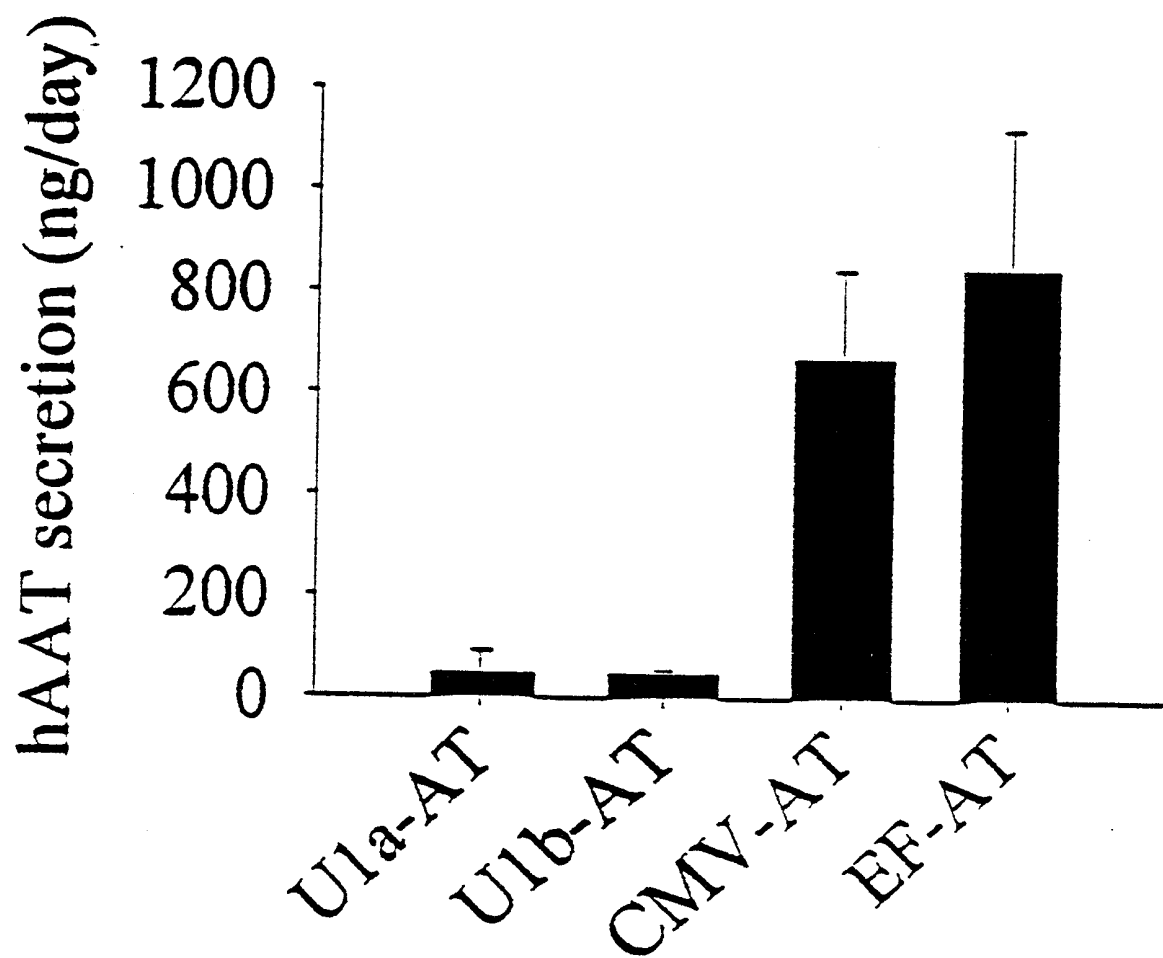


FIGURE 2

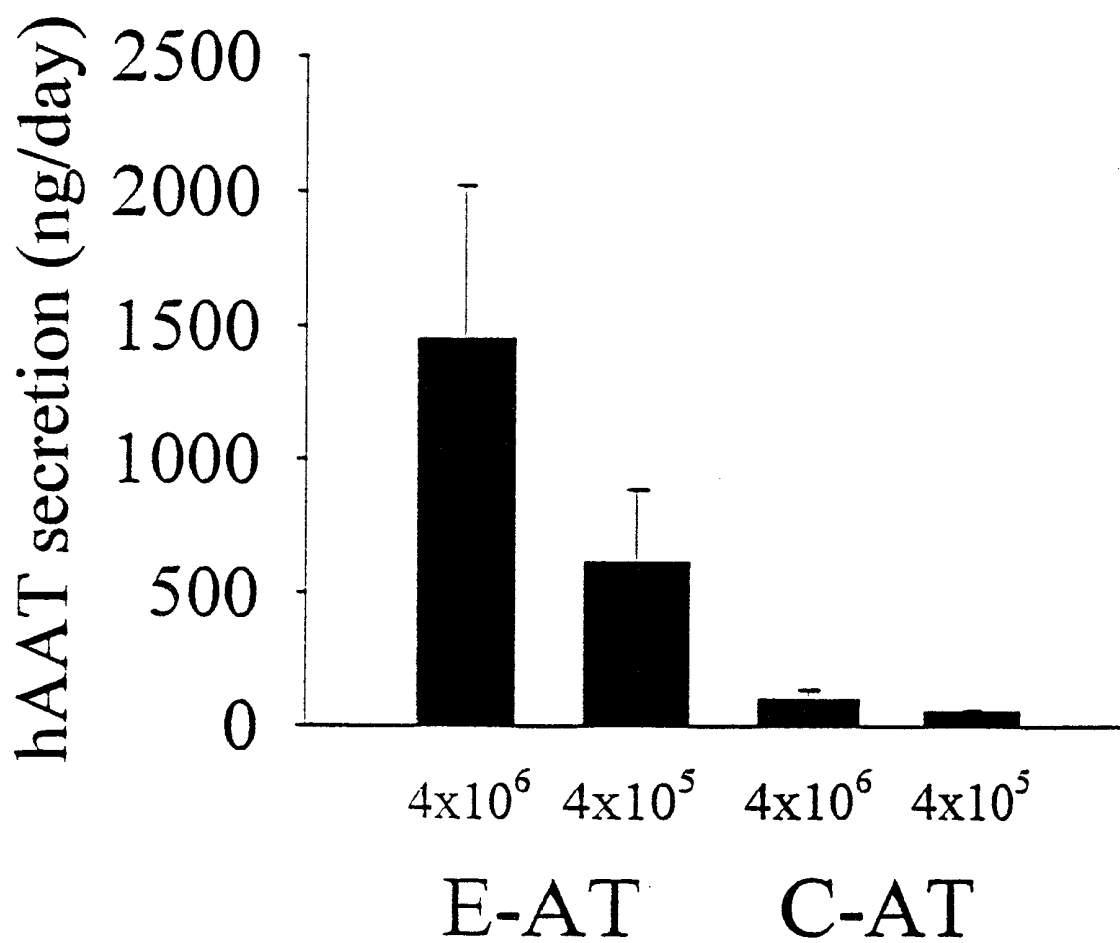


FIGURE 3

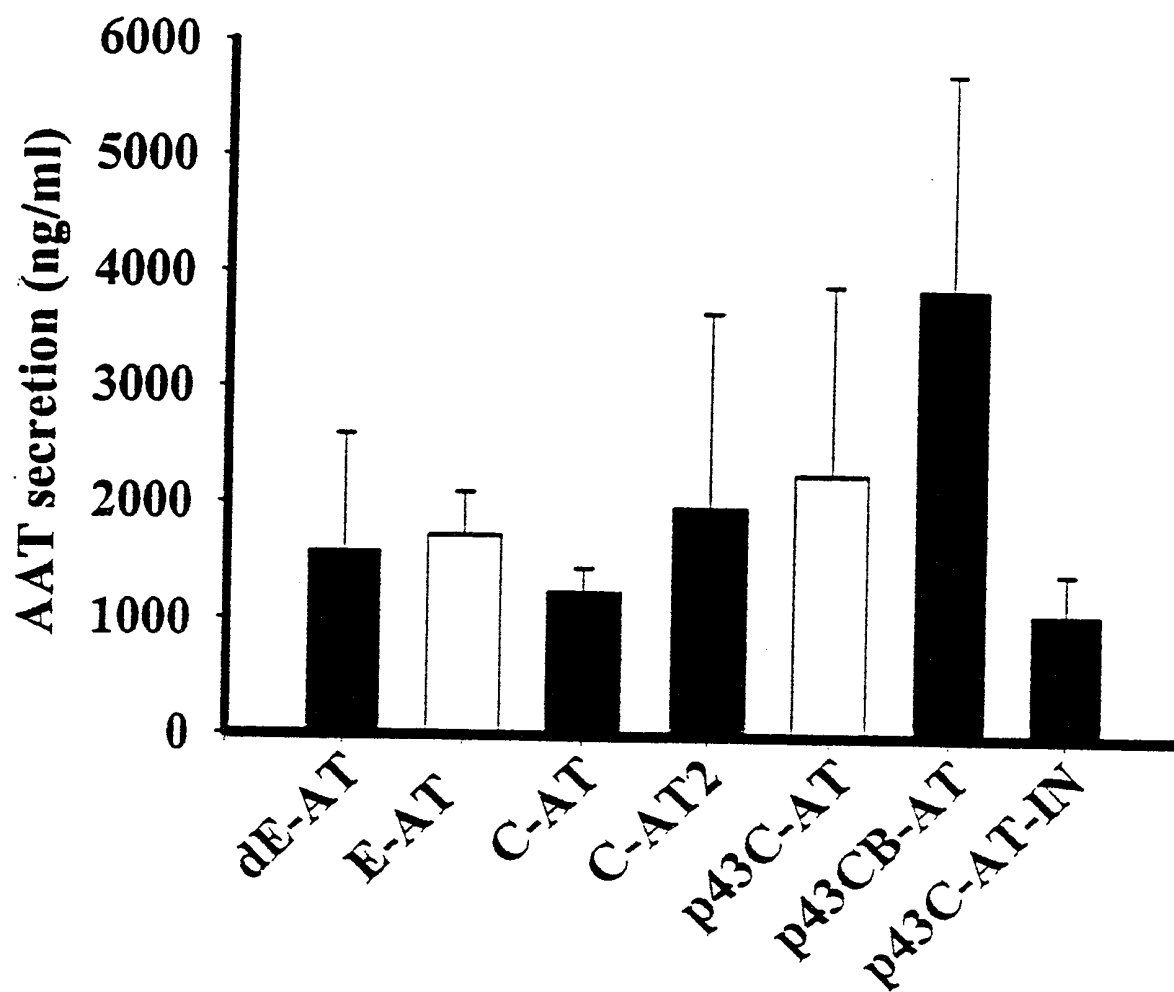


FIGURE 4

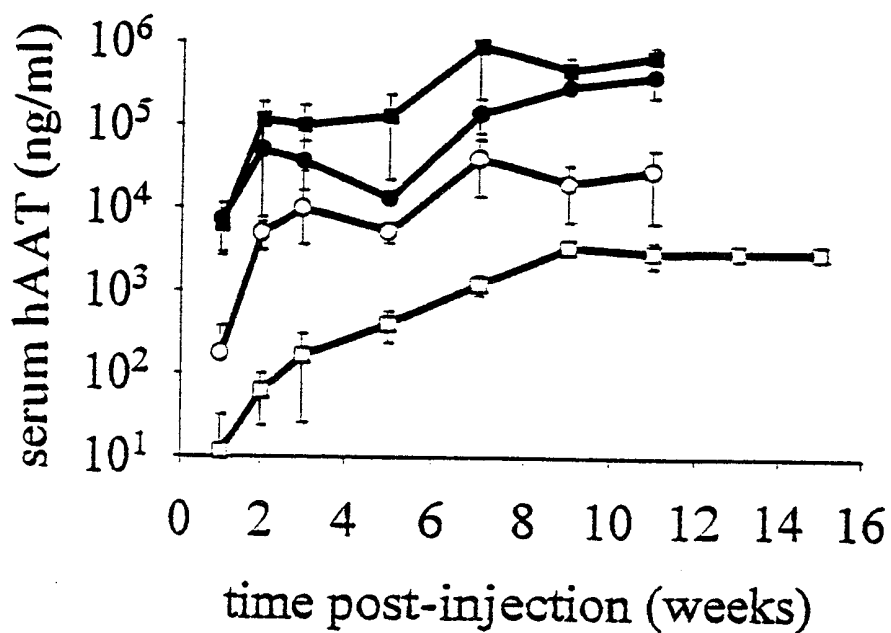


FIGURE 5A

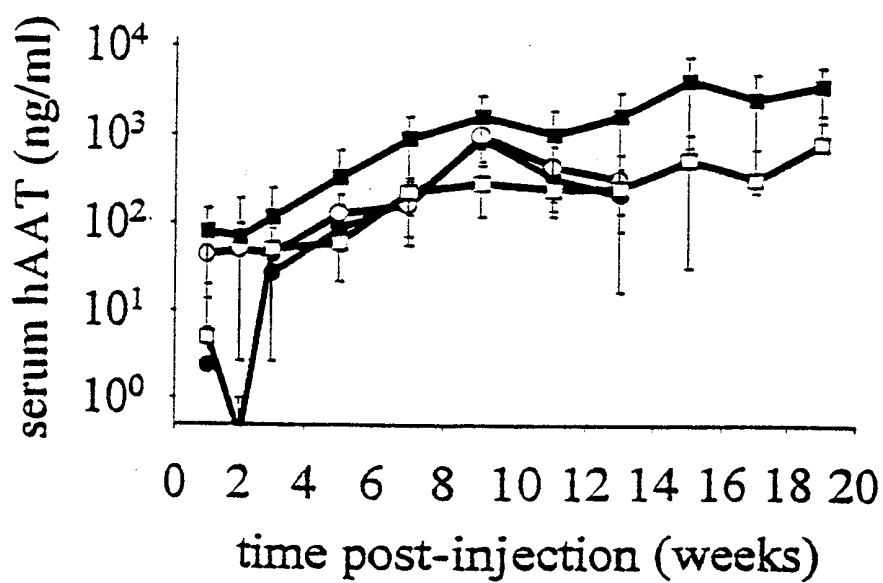


FIGURE 5B

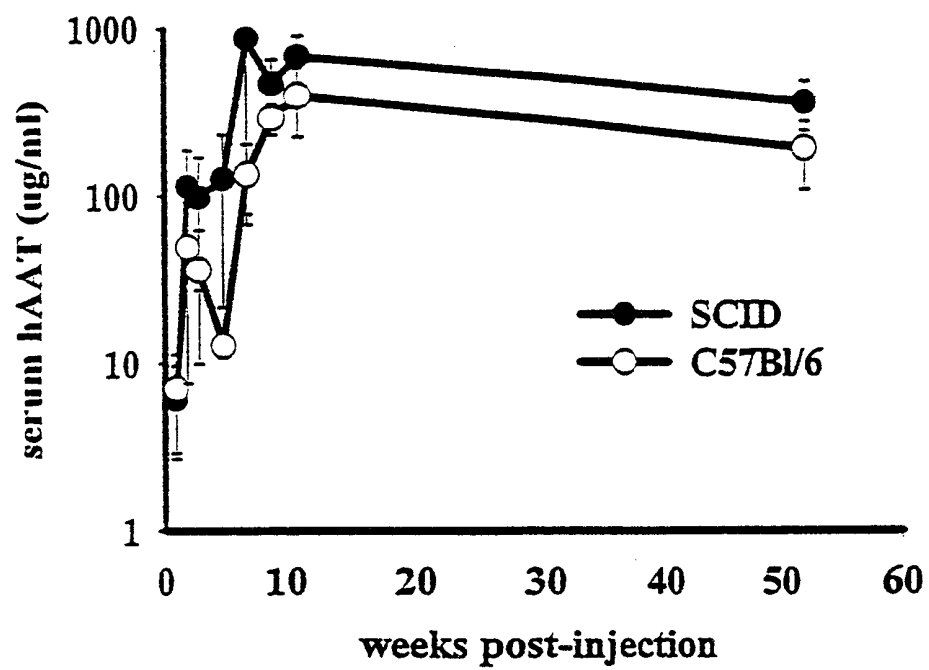


FIGURE 5C

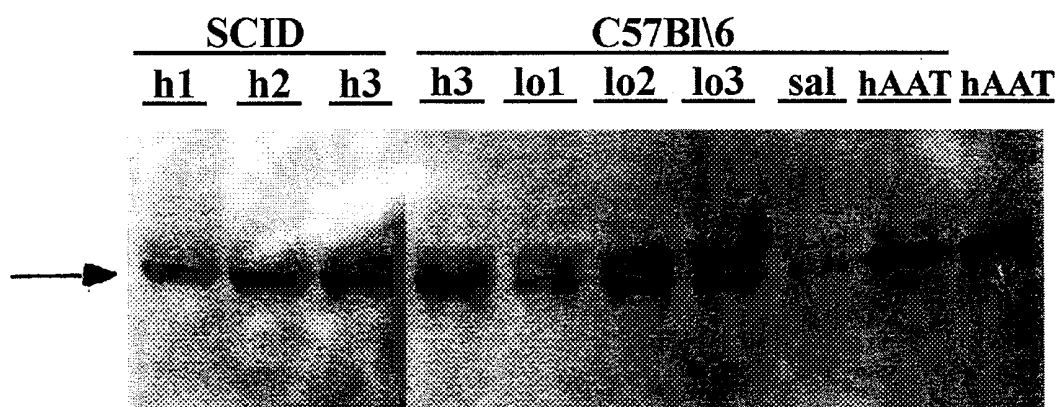


FIGURE 6

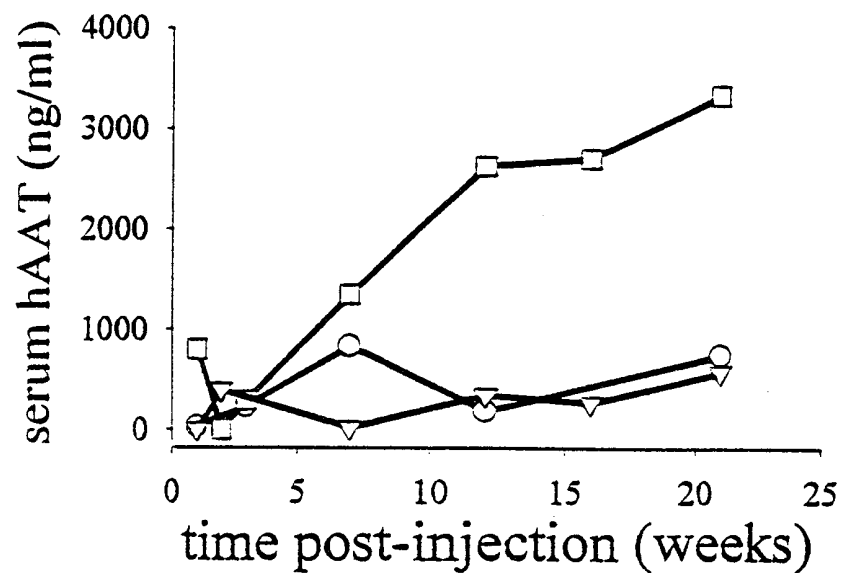


FIGURE 7A

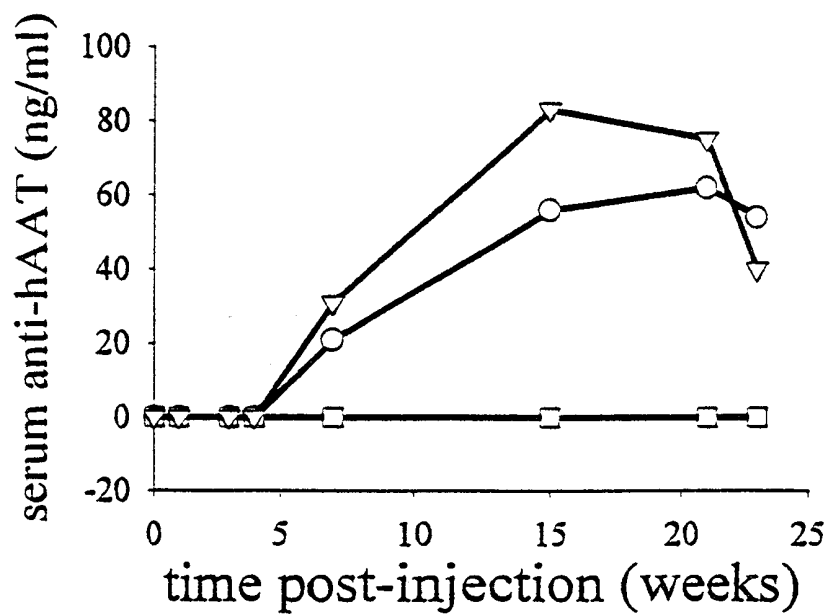


FIGURE 7B

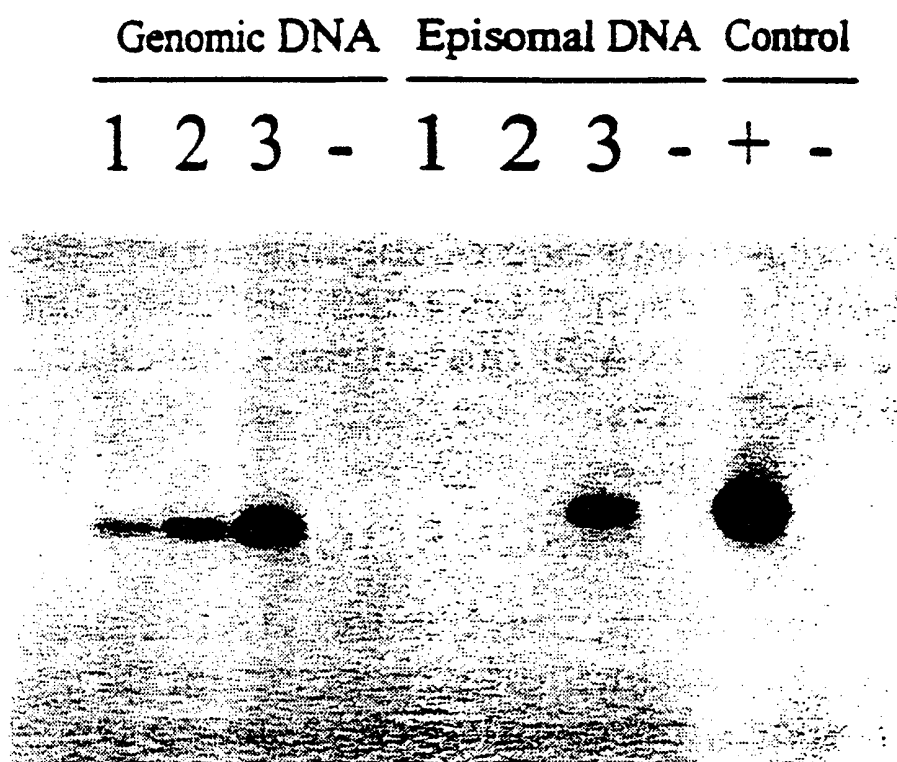


FIGURE 8

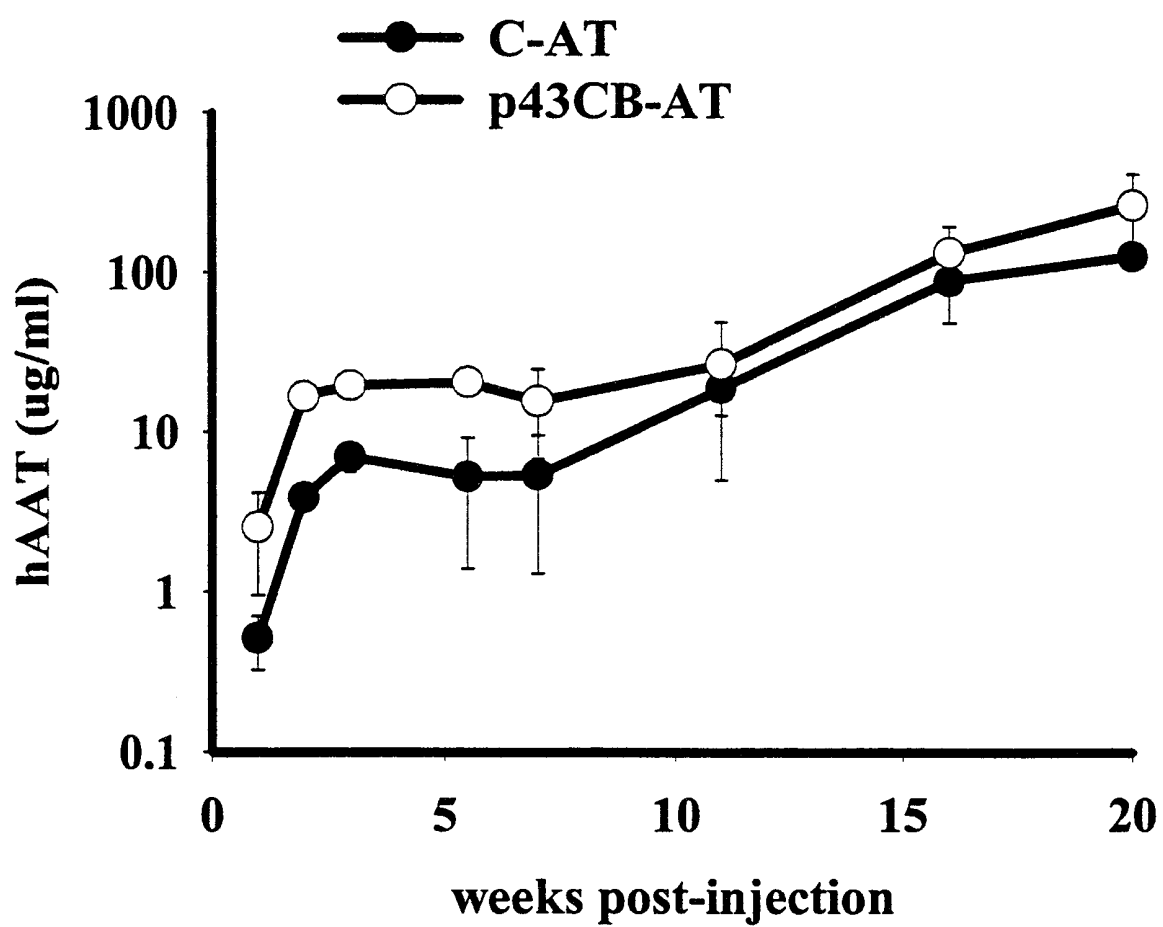


FIGURE 9

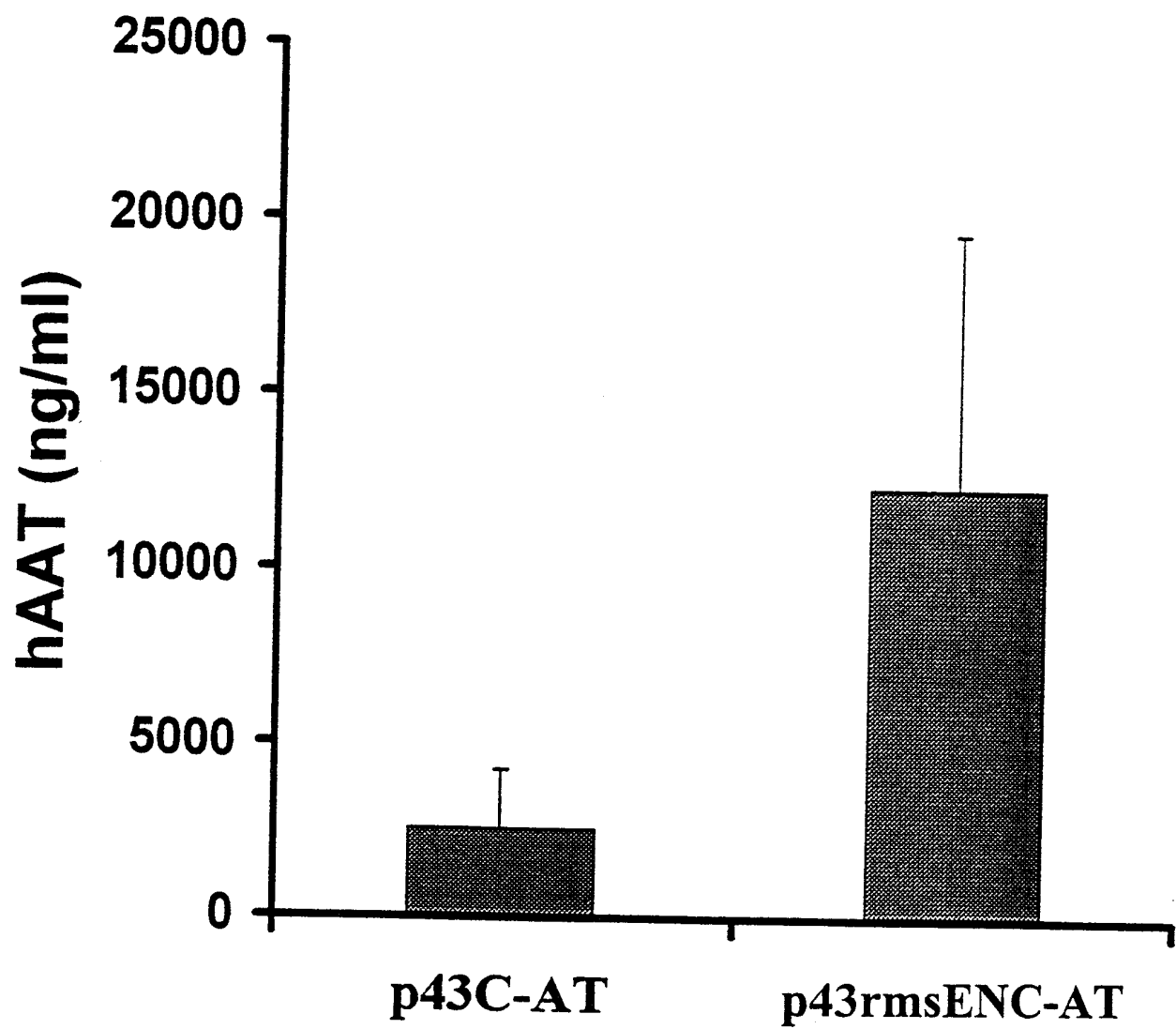


FIGURE 10

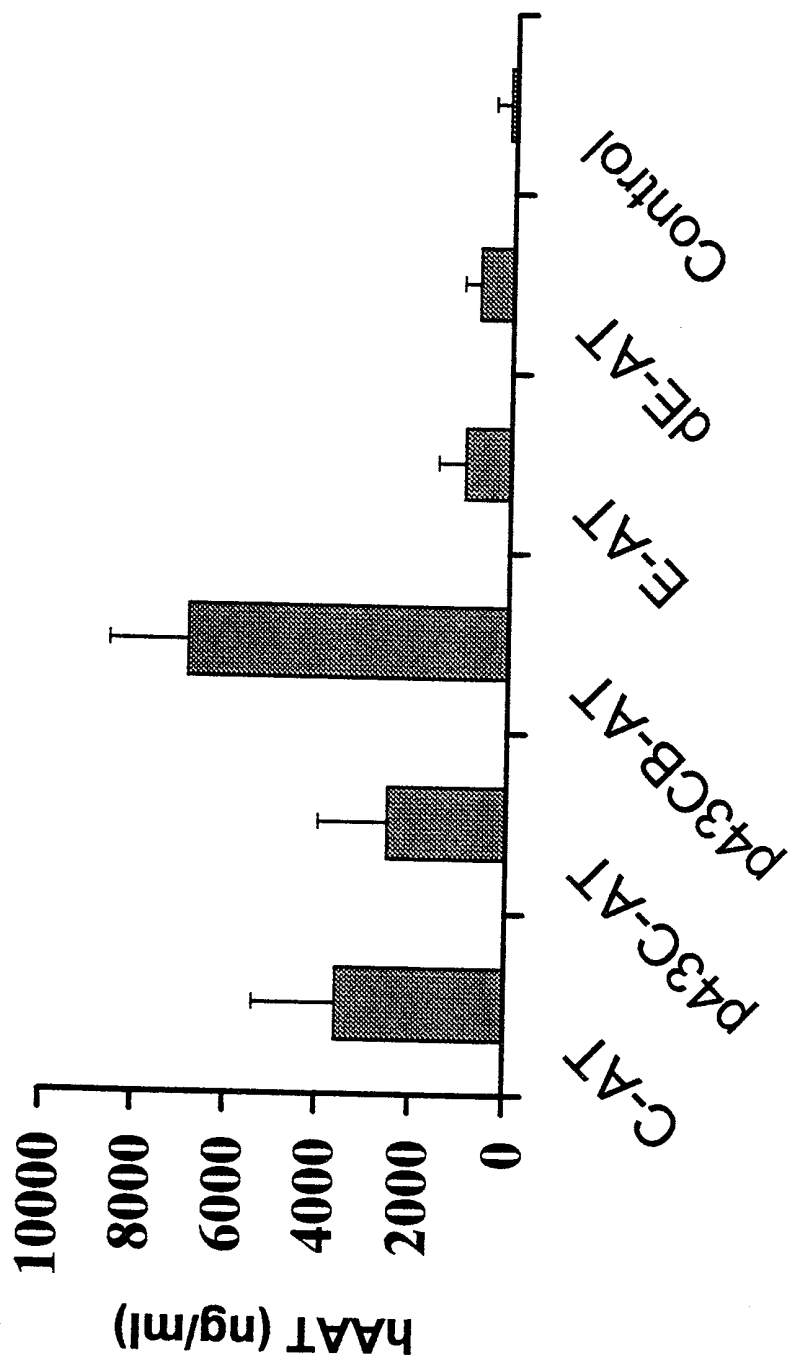


FIGURE 11

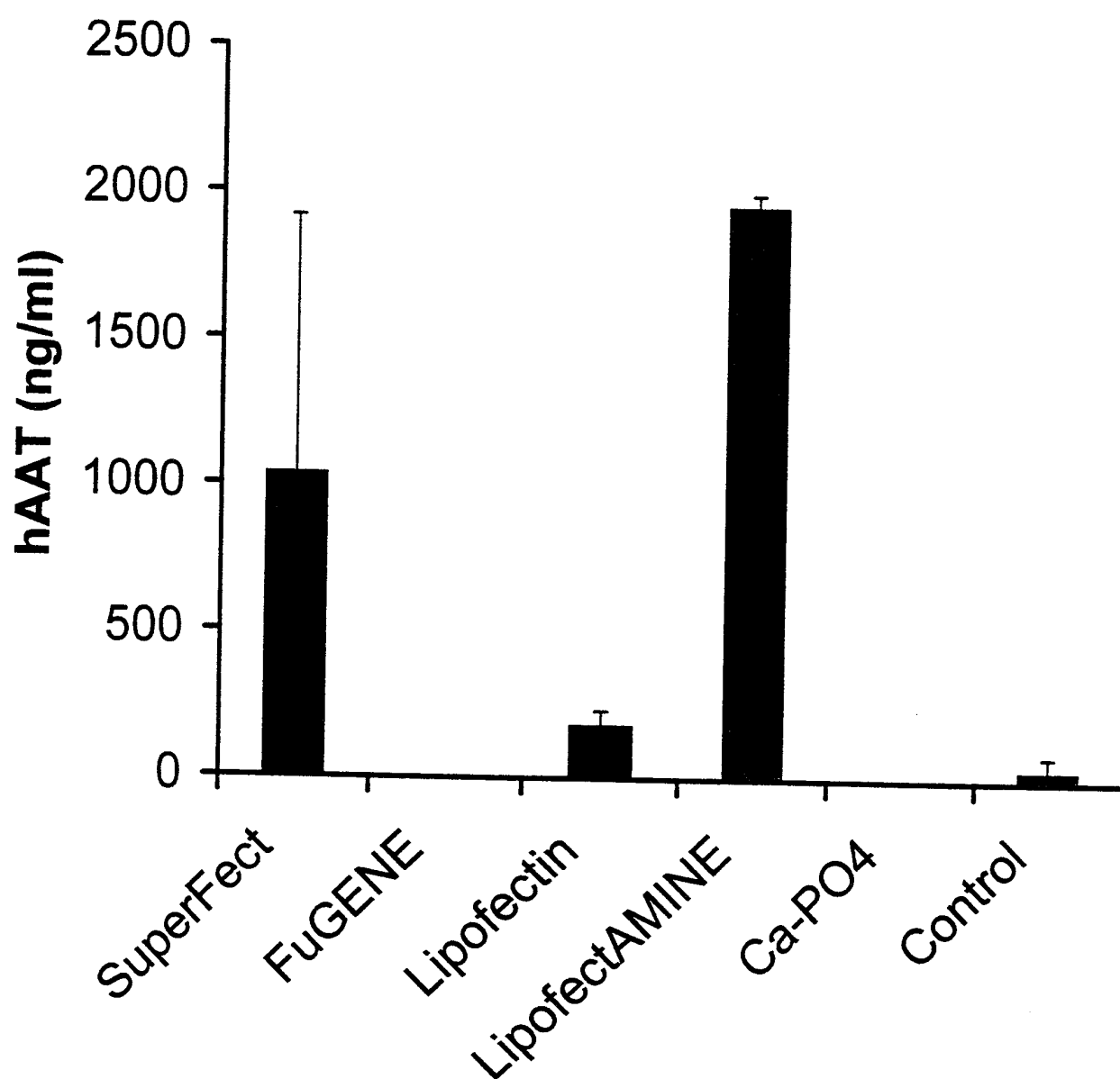


FIGURE 12

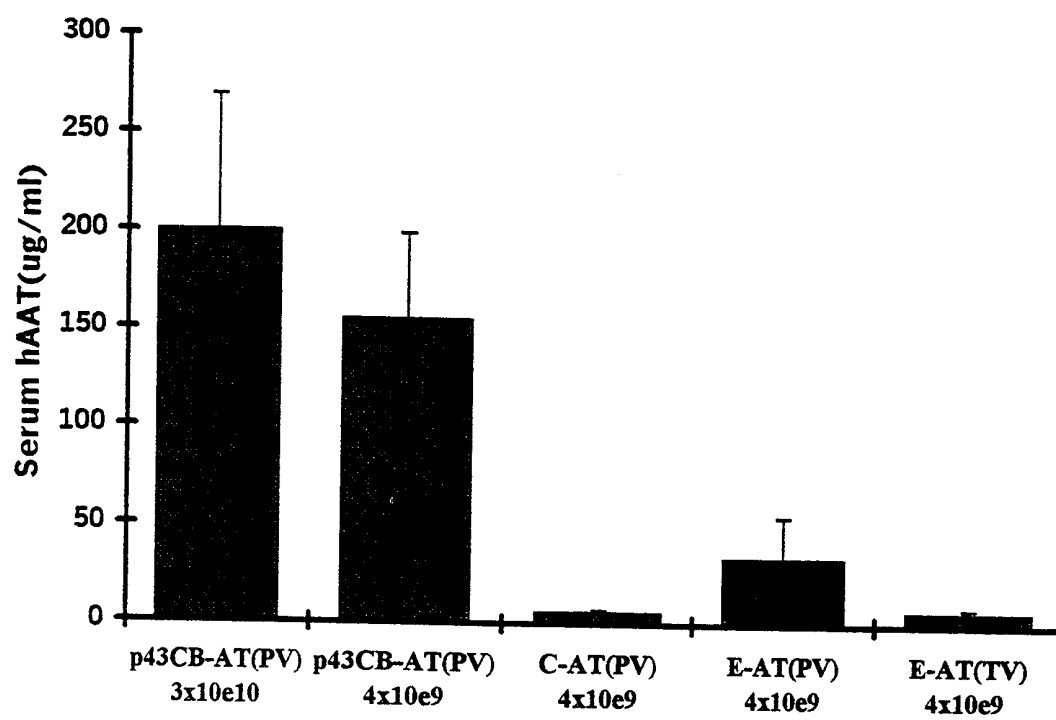


FIGURE 13

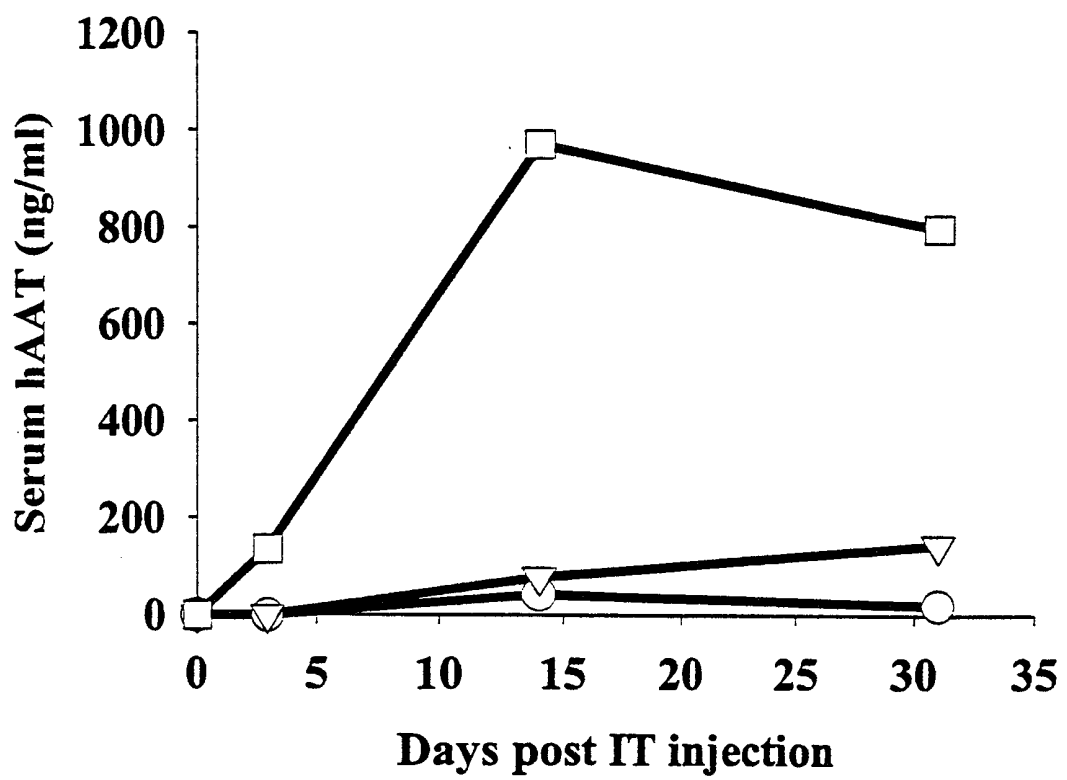


FIGURE 14

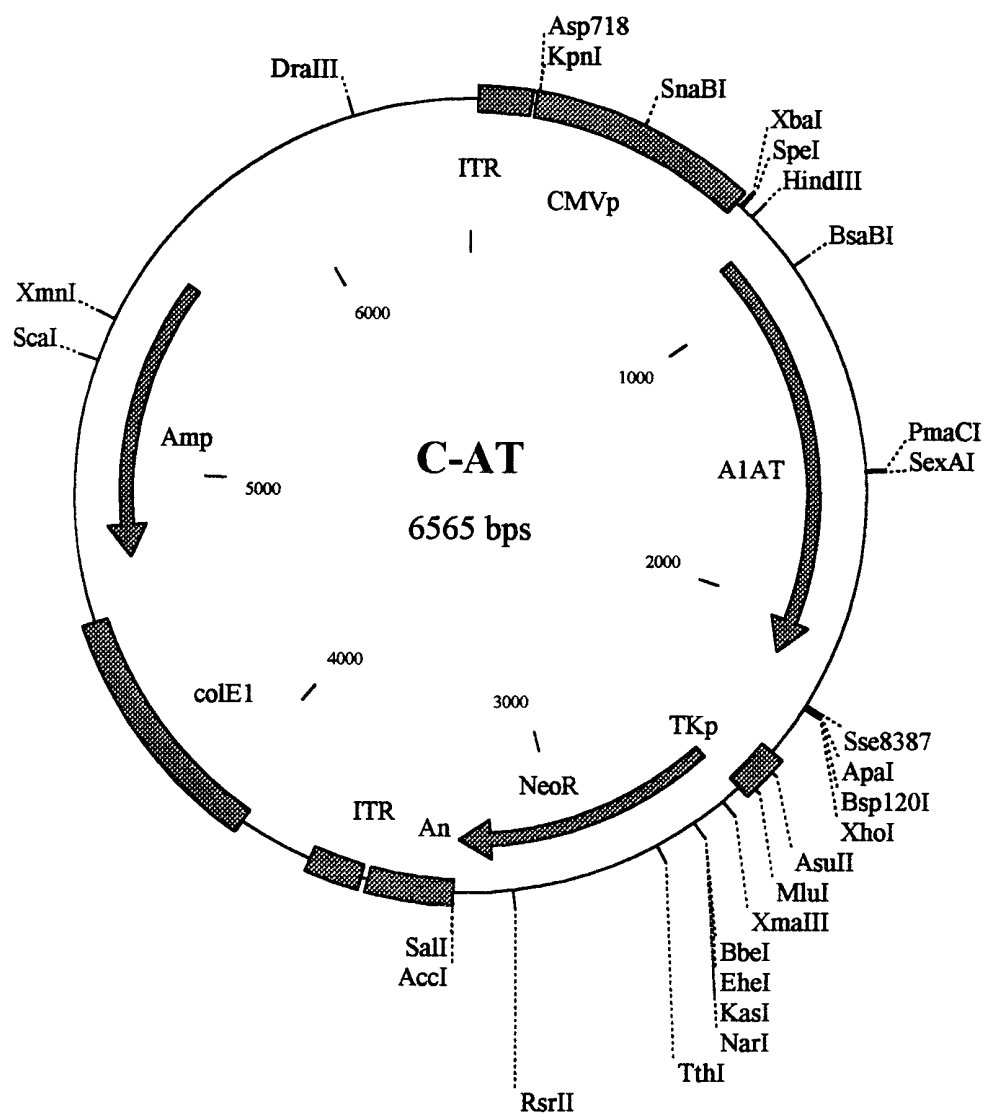


FIGURE 15

Molecule Name: C-AT 6565 bps DNA Circular
 Sequence Printed: 1-6565 (Full) Date Printed 16 Apr 1999
 Description: Ligation of pTR and aat

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1  gggggggggg gggggggggt ggccactccc tctctgcgcg ctgcgtcgtc
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151 actagggggt cctagatctg aattcgggtac ccgttacata acttacggta
201 aatggcccgc ctggctgacc gcccacgac ccccgcccat tgacgtcaat
251 aatgacgtat gttcccatag taacgccaat agggactttc cattgacgtc
301 aatgggtgga gtatttacgg taaactgccc acttggcagt acatcaagtg
351 tatcatatgc caagtacgcc ccctattgac gtcaatgacg gtaaattggc
401 cgctggcat tatgcccagt acatgacctt atgggacttt cctacttggc
451 agtacatcta cgtattagtc atcgctatta ccattggtgat gcggttttgg
501 cagtacatca atgggcgtgg atagcggttt gactcacggg gatttccaag
551 tctccacccc attgacgtca atgggagttt gttttggcac caaatcaac
601 gggactttcc aaaatgtcgt aacaactccg cccattgac gcaaatgggc
651 ggtaggcgtg tacggtggga ggtctatata agcagagctc gtttagtgaa
701 ccgtcagatc gcctggagac gccatccacg ctgttttgac ctccatagaa
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801 ggctgcagga attcgatatc aagcttgggg attttcaggc accaccactg
851 acctgggaca gtgaatcgac aatgccgtct tctgtctcgt ggggcatcct
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951 cccaggggaga tgctgcccag aagacagata catcccacca tgatcaggat
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1151 gctgacactc acgatgaaat cctggagggc ctgaatttca acctcacgga
1201 gattccggag gctcagatcc atgaaggctt ccaggaactc ctccgtaccc
1251 tcaaccagcc agacagccag ctccagctga ccaccggcaa tggcctgttc
1301 ctcagcggag gcctgaagct agtggataag tttttggagg atgttaaaaa
1351 gttgtaccac tcagaagcct tcactgtcaa ctccggggac accgaagagg
1401 ccaagaaaca gatcaacgat tcactggaga aggtactca agggaaaatt
1451 gtggatttgg tcaaggagct tgacagagac acagtttttg ctctggtgaa
1501 ttacatcttc tttaaaggca aatgggagag accctttgaa gtcaaggaca
1551 ccgaggaaga ggacttccac gtggaccagg tgaccaccgt gaaggtgcct
1601 atgatgaagc gtttaggcac gtttaacatc cagcactgta agaagctgtc
1651 cagctgggtg ctgctgatga aatacctggg caatgccacc gccatcttct
1701 tcctgcctga tgaggggaaa ctacagcacc tggaaaatga actcaccac
1751 gatatcatca ccaagtccct ggaaaatgaa gacagaaggt ctgccagctt
1801 acatttacct aaactgtcca ttactggaac ctatgatctg aagagcgtcc
1851 tgggtcaact gggcatcact aaggtcttca gcaatggggc tgacctctcc
1901 ggggtcacag aggaggcacc cctgaagctc tccaaggccg tgcataaggc
1951 tgtgctgacc atcgacgaga aagggactga agctgctggg gccatgtttt
2001 tagaggccat acccatgtct atcccccccg aggtcaagtt caacaaaccc
2051 tttgtcttct taatgattga acaaaatacc aagtctcccc tcttcatggg
2101 aaaagtgggt aatcccaccc aaaaataact gcctctcgct cctcaacccc
2151 tcccctccat ccttggcccc ctccctggat gacattaaag aagggttgag
2201 ctggtaaccc ccccccccc tgcaggggccc ctcgagcagt gtggttttgc
2251 aagaggaagc aaaaagcctc tccaccagg cctggaatgt ttccacccaa
2301 gtcgaaggca gtgtggtttt gcaagaggaa gcaaaaagcc tctccaccca
2351 ggcctggaat gtttccaccc aatgtcgagc aaccccgcgc agcgtcttgt
2401 cattggcgaa ttcgaacacg cagatgcagt cggggcgggc cgggtcccagg
2451 tccacttcgc atattaaggt gacgcgtgtg gcctcgaaca ccgagcgacc
2501 ctgcagccaa tatgggatcg gccattgaac aagatggatt gcacgcaggt
2551 tctccggccg cttgggtgga gaggttatte ggctatgact gggcacaaca
2601 gacaatcggc tgctctgatg ccgctgtgtt ccggtgttca gcgcaggggc
2651 gcccggttct ttttgtcaag accgacctgt ccggtgccct gaatgaactg
2701 caggacgagg cagcgcggct atcgtggctg gccacgacgg gcgttccttg

```

FIGURE 15A

```

2751 cgcagctgtg ctcgacgttg tcactgaagc ggggaagggac tggctgctat
2801 tgggcgaagt gccggggcag gatctcctgt catctcacct tgctcctgcc
2851 gagaaagtat ccatcatggc tgatgcaatg cggcggctgc atacgcttga
2901 tccggctacc tgcccattcg accaccaagc gaaacatcgc atcgagcgag
2951 cacgtactcg gatggaagcc ggtcttgctg atcaggatga tctggacgaa
3001 gagcatcagg ggctcgcgcc agccgaactg ttcgccagge tcaaggcgcg
3051 catgcccagc ggcgaggatc tcgtcgtgac ccatggcgat gcctgcttgc
3101 cgaatatcat ggtggaaaat ggccgctttt ctggattcat cgactgtggc
3151 cggctgggtg tggcggaccg ctatcaggac atagcgttgg ctaccctgga
3201 tattgctgaa gagcttgggc gcgaatgggc tgaccgcttc ctctgctttt
3251 acggtatcgc cgtccccgat tcgcagcgca tcgccttcta tcgccttctt
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3401 cttccttgac cctggaaggt gccactccca ctgtcctttc ctaataaaat
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3751 tcggccaacg cgcggggaga ggcggtttgc gtattgggag ctcttccgct
3801 tcctcgctca ctgactcgct gcgctcggtc gttcggctgc ggcgagcggt
3851 atcagctcac tcaaaggcgg taatacgggt atccacagaa tcaggggata
3901 acgcaggaaa gaacatgtga gcaaaaggcc agcaaaaggc caggaaccgt
3951 aaaaaggccg cgttgctggc gtttttccat aggctccgcc cccctgacga
4001 gcatcacaaa aatcgacgct caagttagag gtggcgaaac ccgacaggac
4051 tataaagata ccaggcgttt cccctggaa gctccctcgt gcgctctcct
4101 gttccgacct tgccgcttac cggatacctg tccgccttcc tcccttcggg
4151 aagcgtggcg ctttctcaat gctcacgctg taggtatctc agttcgggtg
4201 aggtcgcttc ctccaagctg ggctgtgtgc acgaacccc cgttcagccc
4251 gaccgctgcg ctttatccgg taactatcgt cttgagtcca acccggtaa
4301 acacgactta tcgccactgg cagcagccac tggtaacagg attagcagag
4351 cgaggatatg aggcggtgct acagagttct tgaagtgggt gcctaactac
4401 ggctacacta gaaggacagt atttggatc tgcgctctgc tgaagccagt
4451 taccttcgga aaaagagttg gtagctcttg atccggcaaa caaaccaccg
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4851 cccagtgcgt caatgatacc gcgagaccca cgctcaccgg ctccagattt
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5001 gtaagtagtt cgccagttaa cagtcttgcg aacgttggtg ccattgctac
5051 aggcacgtg gtgtcacgct cgtcgtttgg tatggcttca ttcagctccg
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5251 tgccatccgt aagatgcttt tctgtgactg gtgagtactc aaccaagtca
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5501 tactttcacc agcgtttctg ggtgagcaaa aacaggaagg caaaatgccg
5551 caaaaaaggg aataaggcgc acacggaaat gttgaatact catactcttc
5601 ctttttcaat attattgaag catttatcag ggttattgtc tcatgagcgg
5651 atacatattt gaatgtattt agaaaaataa acaaataggg gttccgcgca
5701 catttccccg aaaagtgcc cctgacgtct aagaaaccat tattatcatg

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FIGURE 15B

```
5751 acattaacct ataaaaaatag gcgtatcacg aggccctttc gtctcgcgcg
5801 tttcggatgat gacgggtgaaa acctctgaca catgcagctc ccggagacgg
5851 tcacagcttg tctgtaagcg gatgccggga gcagacaagc ccgtcagggc
5901 gcgtcagcgg gtgttggcgg gtgtcggggc tggcttaact atgcggcatc
5951 agagcagatt gtactgagag tgcaccatat gcggtgtgaa ataccgcaca
6001 gatgcgtaag gagaaaatac cgcatacagga aattgtaaac gttaatatatt
6051 tgttaaaaatt cgcgttaaat ttttgttaaa tcagctcatt ttttaaccaa
6101 taggccgaaa tcggcaaaat cccttataaa tcaaaagaat agaccgagat
6151 aggggttgagt gttgttccag tttggaacaa gagtccacta ttaaagaacg
6201 tggactccaa cgtcaaaggc cgaaaaaccg tctatcaggg cgatggccca
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6301 agcactaaat cggaacccta aaggagagccc ccgatttaga gcttgacggg
6351 gaaagccggc gaacgtggcg agaaaggaag ggaagaaagc gaaaggagcg
6401 ggcgctaggg cgctggcaag tgtagcggtc acgctgcgcg taaccaccac
6451 acccgccgcg cttaatgcgc cgctacaggg cgcgtcgcgc cattcgccat
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6551 ttacgccagg ctgca
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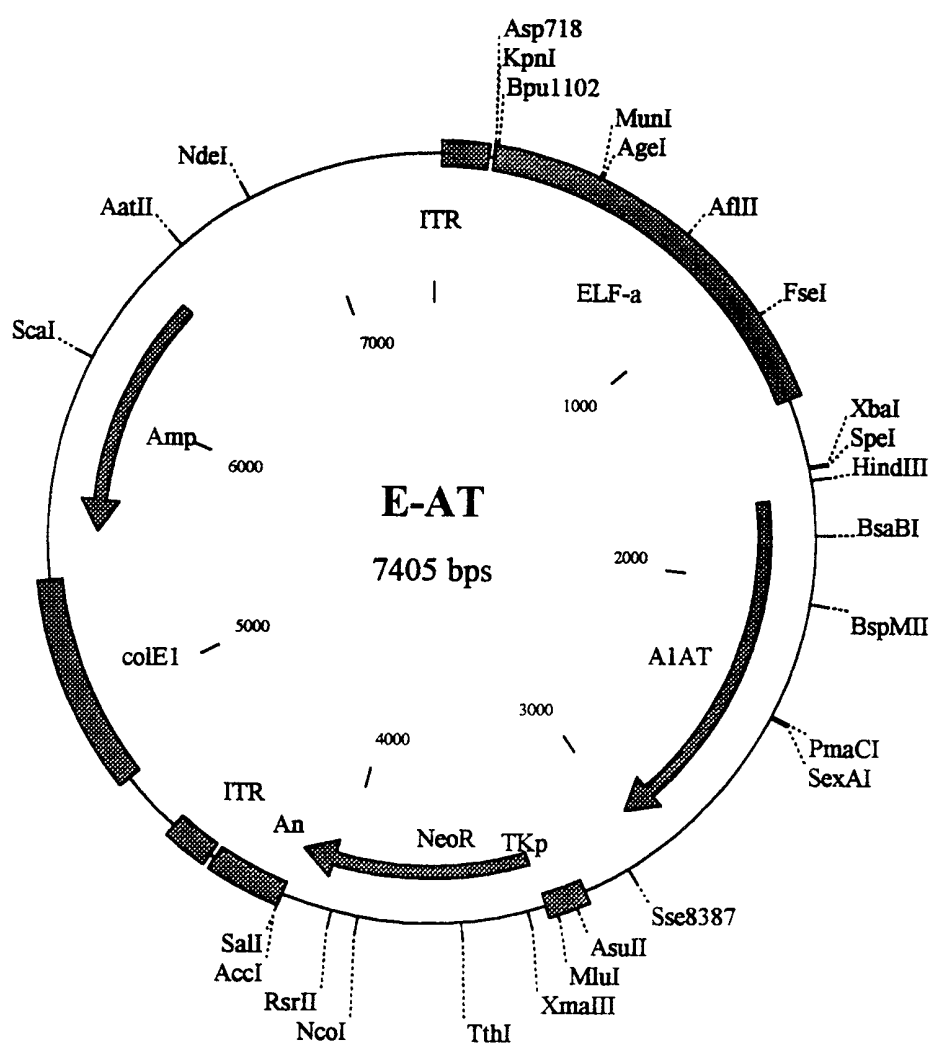


FIGURE 16

Molecule Name: E-A¹ 7405 bps DNA Circular
 Sequence Printed: 1-7405 (Full) Date Printed 16 Apr 1999
 Description: Ligation of AAT and elf

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1  gggggggggg gggggggggt ggccactccc tctctgcgcg ctcgctcgct
51  cactgaggcc gggcgaccaa aggtcgcccc acgcccgggc tttggccggg
101 cggcctcagt gagcgagcga gcgcgcagag agggagtggc caactccatc
151 actaggggtt cctagatctg aattcgggtac cttggagcta agccagcaat
201 ggtagaggga agattctgca cgtcccttcc aggcggcctc cccgtcacca
251 ccccccccaa cccgccccga ccggagctga gagtaattca tacaaaagga
301 ctgcgccctg ccttggggaa tcccagggac cgtcgttaaa ctcccactaa
351 cgtagaacct agagatcgct gcgttcccgc cccctcaccc gccgcctctc
401 gtcatcactg aggtggagaa gagcatcgct gaggtccggg tgcccgtcag
451 tgggcagagc gcacatcgcc cacagtcctc gagaagtggg ggggaggggt
501 cggcaattga accggtgcct agagaagggt gcgcggggta aactgggaaa
551 gtgatgtcgt gtactggctc cgcttttttc ccgaggggtg gggagaaccg
601 tatataagtg cagtagtcgc cgtgaacgtt ctttttcgca acgggtttgc
651 cgccagaaca caggaagtgc ccgtgtgtgg tcccgcggg cctggcctct
701 ttacgggtta tggcccttgc gtgccttgaa ttacttcac gccctggct
751 gcagtacgtg attcttgatc ccgagcttcg gggttgaagt ggggtggaga
801 gttcgaggcc ttgcgcttaa ggagcccctt cgctcgtgc ttgagttgag
851 gcctggcctg ggcgctgggg ccgcgcgctg cgaatctggg ggcaccttcg
901 cgctgtctc gctgcttttc ataagtctct agccatttaa aatttttgat
951 gacctgctgc gacgtttttt ttctggcaag atagtcttgt aaatgcgggc
1001 caagatctgc acactggtat ttcggttttt ggggcccggg gcggcgacgg
1051 ggcccggtgc tccagcgca catgttcggc gaggcggggc ctgcgagcgc
1101 ggccaccgag aatcggacgg gggtagtctc aagctggccg gcctgctctg
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1201 ggcccggtcg gcaccagttg cgtgagcgga aagatggccg cttcccggcc
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1301 ggtgagtcac ccacacaaag gaaaagggcc tttccgtcct cagccgtcgc
1351 ttcatgtgac tccacggagt accgggcgcc gtccaggcac ctcgattagt
1401 tctcgagctt ttggagtacg tcgtctttag gttgggggga ggggttttat
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1501 ttggcacttg atgtaattct ccttgggaat tgcccttttt gagtttggat
1551 cttgggttcat tctcaagcct cagacagtgg ttcaaagtgt ttttcttcca
1601 tttcaggtgt cgtgaaaatc tagaactagt ggatcccccg ggctgcagga
1651 attcgatata aagcttgggg attttcaggc accaccactg acctgggaca
1701 gtgaatcgac aatgccgtct tctgtctcgt ggggcatcct cctgctggca
1751 ggctgtgct gcctggtccc tgtctccctg gctgaggatc cccagggaga
1801 tgctgcccag aagacagata catcccacca tgatcaggat caccacacct
1851 tcaacaagat ccccccaac ctggctgagt tcgccttcag cctataccgc
1901 cagctggcac accagtccaa cagcaccaat atcttcttct cccagttag
1951 catcgctaca gcctttgcaa tgctctccct ggggaccaag gctgacactc
2001 acgatgaaat cctggagggc ctgaatttca acctcacgga gattccggag
2051 gctcagatcc atgaaggctt ccagggaact ctcctgacct tcaaccagcc
2101 agacagccag ctccagctga ccaccggcaa tggcctgttc ctcagcgagg
2151 gcctgaagct agtggataag tttttggagg atgttaaaaa gttgtaccac
2201 tcagaagcct tactgtcaa cttcggggac accgaagagg ccaagaaaca
2251 gatcaacgat tacgtggaga agggtactca agggaaaatt gtggatttgg
2301 tcaaggagct tgacagagac acagtttttg ctctggtgaa ttacatcttc
2351 tttaaaaggca aatgggagag accctttgaa gtcaaggaca ccgaggaaga
2401 ggacttccac gtggaccagg tgaccaccgt gaaggtgcct atgatgaagc
2451 gtttaggcat gtttaacatc cagcactgta agaagctgtc cagctgggtg
2501 ctgctgatga aatacctggg caatgccacc gccatcttct tctgcctga
2551 tgaggggaaa ctacagcacc tggaaaatga actcaccac gatatcatca
2601 ccaagtccct ggaaaatgaa gacagaaggt ctgccagctt acatttacc
2651 aaactgtcca ttactggaac ctatgatctg aagagcgctc tgggtcaact
2701 gggcatcact aaggctctca gcaatggggc tgacctctcc ggggtcacag

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FIGURE 16A

```

2751  aggaggcacc ccaaagctc tccaaggccg tgcataaggc tgcgctgacc
2801  atcgacgaga aagggactga agctgctggg gccatgtttt tagaggccat
2851  acccatgtct atcccccccg aggtcaagtt caacaaaccc tttgtcttct
2901  taatgattga acaaaataacc aagtctcccc tcttcatggg aaaagtggg
2951  aatcccaccc aaaaataact gcctctcgct cctcaacccc tccccctcat
3001  cccctggccc ctccctggat gacattaaag aagggttgag ctggtaaccc
3051  cccccccccc tgcaggggcc ctcgagcagt gtggttttgc aagaggagac
3101  aaaaagcctc tccaccagg cctggaatgt tccacccaa gtcgaaggca
3151  gtgtgggtttt gcaagaggaa gcaaaaagcc tctccaccca ggcctggaat
3201  gtttccaccc aatgtcgagc aaccccgcgc agcgtcttgt cattggcgaa
3251  ttcgaacacg cagatgcagt cggggcgggc cgggtcccagg tccacttcgc
3301  atattaaggt gacgcgtgtg gcctcgaaca ccgagcgacc ctgcagccaa
3351  tatgggatcg gccattgaac aagatggatt gcacgcaggt tctccggccg
3401  cttgggtgga gaggtatctt ggctatgact gggcacaaca gacaatcggc
3451  tgctctgatg ccgcctgtgt ccggctgtca gcgcaggggc gcccggttct
3501  ttttgtcaag accgacctgt ccgggtgccct gaatgaactg caggacgagg
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3601  ctcgacgttg tcaactgaagc gggaaggagc tggctgctat tgggcgaagt
3651  gccggggcag gatctcctgt catctcacct tgctcctgcc gagaaagtat
3701  ccatcatggc tgatgcaatg cggcggctgc atacgttga tccggctacc
3751  tgcccattcg accaccaagc gaaacatcgc atcgagcgag cacgtactcg
3801  tgagggaagc ggtcttgtcg atcaggatga tctggacgaa gagcatcagg
3851  ggctcgcgcc agccgaactg ttcgccaggc tcaaggcgcg catgcccagc
3901  ggcgaggatc tcgtcgtgac ccatggcgat gcctgcttgc cgaatatcat
3951  ggtggaaaat ggccgctttt ctggattcat cgactgtggc cggctgggtg
4001  tggcggaccg ctatcaggac atagcgttgg ctaccctga tattgtgaa
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4251  cctggaaggt gccactccca ctgtcctttc ctaataaaaat gaggaattg
4301  catcgcatcg tctgagtagg tgtcattcta ttctgggggg tggggtgggg
4351  caggacagca agggggagga ttgggaagac aatagcaggc atgctgggga
4401  tgcatctagg aacccctagt gatggagtgt gccactccct ctctgcgcgc
4451  tcgctcgctc actgaggccg cccgggcaaa gcccgggcgt cgggcgacct
4501  ttggtcgccc ggccctcagt agcgagcgag cgcgcagaga gggagtggcc
4551  aacccccccc cccccccccc tgcagccctg cattaatgaa tcggccaacg
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4851  aatcgacgct caagtcaag gtggcgaaac ccgacaggac tataaagata
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5201  aggcggtgct acagagttct tgaagtgggt gcctaactac ggctacacta
5251  gaaggacagt atttggtatc tgcgctctgc tgaagccagt taccttcgga
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5351  tggttttttt gtttgcaagc agcagattac gcgcagaaaa aaaggatctc
5401  aagaagatcc tttgatcttt tctacggggt ctgacgctca gtggaacgaa
5451  aactcacgtt aagggttttt ggtcatgaga ttatcaaaaa ggatcttcac
5501  ctagatcctt ttaaattaaa aatgaagttt taaatcaatc taaagtatat
5551  atgagtaaac ttggtctgac agttaccaat gcttaatcag tgaggcacct
5601  atctcagcga tctgtctatt tcgttcatcc atagttgcct gactccccgt
5651  cgtgtagata actacgatac gggagggtt accatctggc ccagtgctg
5701  caatgatacc gcgagaccca cgctcaccgg ctccagattt atcagcaata

```

FIGURE 16B

```

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5801 cgctccatc cagtctatta attggtgccg ggaagctaga gtaagtagtt
5851 cgccagttaa tagtttgccg aacgttggtg ccattgctac aggcacgtg
5901 gtgtcacgct cgtcgtttgg tatggcttca ttcagctccg gttcccaacg
5951 atcaaggcga gttacatgat ccccatgtt gtgcaaaaaa gcggttagct
6001 ccttcgggtcc tccgatcggt gtcagaagta agttggccgc agtggtatca
6051 ctcatggtta tggcagcact gcataattct cttactgtca tgccatccgt
6101 aagatgcttt tctgtgactg gtgagtactc aaccaagtca ttctgagaat
6151 agtgtatgcg gcgaccgagt tgctcttgcc cggcgtcaat acgggataat
6201 accgcgccac atagcagaac tttaaaagtg ctcattcattg gaaaacgttc
6251 ttcggggcga aaactctcaa ggatcttacc gctgttgaga tccagttcga
6301 tgtaaccacac tcgtgcaccc aactgatctt cagcatcttt tactttcacc
6351 agcgtttctg ggtgagcaaa aacaggaagg caaaatgccg caaaaaaggg
6401 aataagggcg acacggaaat gttgaatact catactcttc ctttttcaat
6451 attattgaag catttatcag gtttattgtc tcatgagcgg atacatat
6501 gaatgtattt agaaaaataa acaaataagg gttccgcgca catttccccg
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6601 ataaaaatag gcgtatcacg aggccctttc gtctcgcgcg ttccggtgat
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6801 gtactgagag tgcaccatat gcggtgtgaa ataccgcaca gatgcgtaag
6851 gagaaaatac cgcatacagga aattgtaaac gttaatat
6901 cgcggttaaat ttttggttaa tcagctcatt ttttaaccaa taggccgaaa
6951 tcggcaaaat cccttataaa tcaaaagaat agaccgagat aggggtgagt
7001 gttgttccag tttggaacaa gagtccacta ttaaagaacg tggactccaa
7051 cgtcaaaggg cgaaaaaccg tctatcaggg cgatggccca ctacgtgaac
7101 catcacccta atcaagtttt ttggggtcga ggtgccgtaa agcactaaat
7151 cggaacccta aaggagccc ccgatttaga gcttgacggg gaaagccggc
7201 gaacgtggcg agaaaggaag ggaagaaagc gaaaggagcg ggcgctaggg
7251 cgctggcaag tgtagcggtc acgctgcgcg taaccaccac acccgccgcg
7301 cttaatgcgc cgctacaggg cgcgtcgcgc cattcgccat tcaggctacg
7351 caactgttgg gaagggcgat cgggtgcgggc ctcttcgcta ttacgccagg
7401 ctgca

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FIGURE 16C

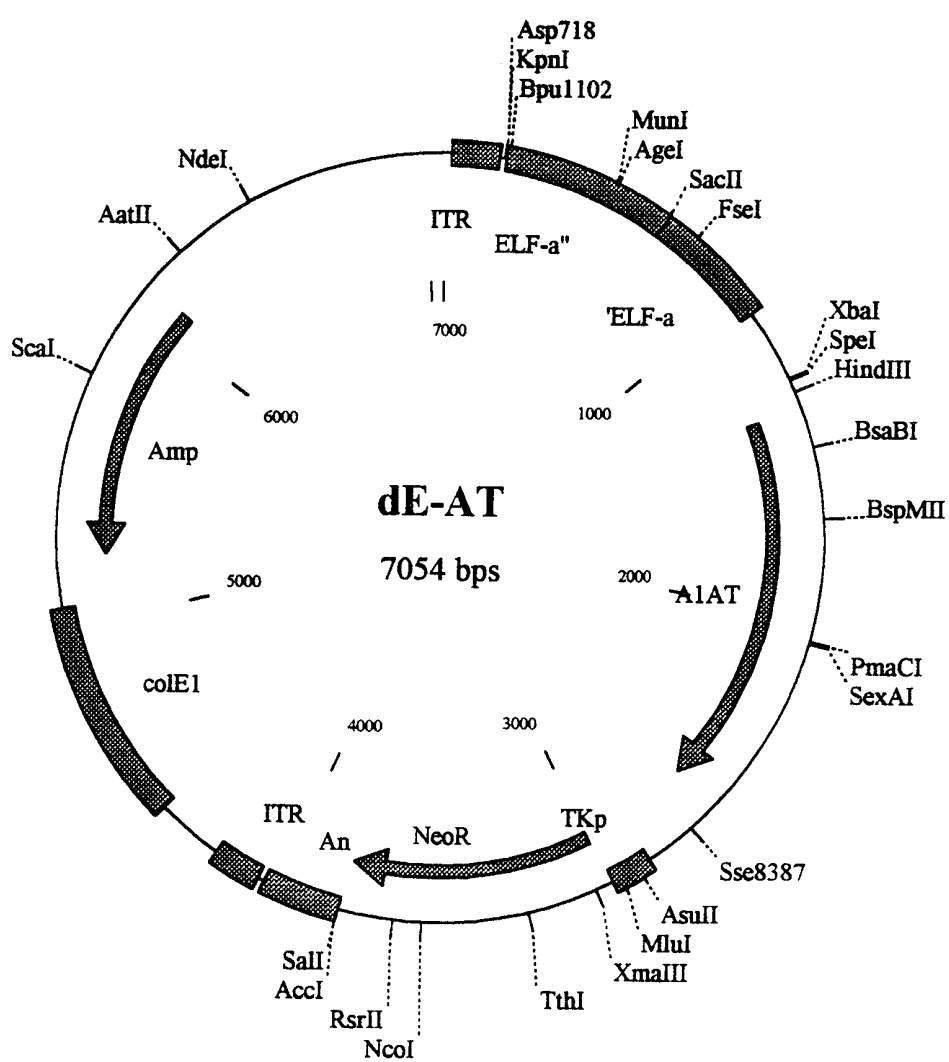


FIGURE 17

Molecule Name: dE-AT

7054 bps DNA Circular

Sequence Printed: 1-7054 (Full)

Date Printed 16 Apr 1999

Description: Fragment 2 Circularized

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1  gggggggggg gggggggggtt ggccactccc tctctgcgcg ctgcctcgcg
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101 cggcctcagt gagcgagcga gcgcgcagag agggagtggc caactccatc
151 actaggggtt cctagatctg aattcggtac cttggagcta agccagcaat
201 ggtagaggga agattctgca cgtcccttcc aggcggcctc cccgtcacca
251 ccccccccaa cccgccccga cggagactga gagtaattca tacaaaagga
301 ctgcgccctg ccttggggaa tcccagggaac cgtcgttaaa ctcccactaa
351 cgtagaaccc agagatcgct gcgttcccgc cccctcaccg gcccgctctc
401 gtcatcactg aggtggagaa gagcatgcgt gaggctccgg tgcccgtcag
451 tgggcagagc gcacatcgcc cacagtcccc gagaagttgg ggggaggggt
501 cggcaattga accggtgcct agagaagggt gcgcggggta aactgggaaa
551 gtgatgtcgt gtactggctc cgcctttttc ccgagggtgg gggagaaccg
601 tatataagtg cagtagtcgc cgtgaacgtt ctttttcgca acgggtttgc
651 cgccagaaca caggtaagtg ccgtgtgtgg tcccgcgggg cggcgacggg
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751 gccaccgaga atcggacggg ggtagtctca agctggccgg cctgctctgg
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901 tgctgcaggg agctcaaaat ggaggacgcg gcgctcggga gagcgggcgg
951 gtgagtcacc cacacaaagg aaaagggcct ttccgtcctc agccgtcgcg
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1051 ctcgagcttt tggagtacgt cgtcttttagg ttgggggggag gggttttatg
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1251 ttcaggtgtc gtgaaaatct agaactagtg gatcccccg gctgcaggaa
1301 ttcgatatac agcttgggga ttttcaggca ccaccactga cctgggacag
1351 tgaatcgaca atgccgtctt ctgtctcgtg gggcatcctc ctgctggcag
1401 gcctgtgctg cctggtccct gtctccctgg ctgaggatcc ccagggagat
1451 gctgcccaga agacagatac atcccaccat gatcaggatc acccaacctt
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1601 atcgctacag cctttgcaat gctctccctg gggaccaagg ctgacactca
1651 cgatgaaatc ctggagggcc tgaatttcaa cctcacggag attccggagg
1701 ctcagatcca tgaaggcttc caggaaactc tccgtaccct caaccagcca
1751 gacagccagc tccagctgac caccggcaat ggcctgttcc tcagcagggg
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1851 cagaagcctt cactgtcaac ttcggggaca ccgaagaggc caagaaacag
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1951 caaggagctt gacagagaca cagtttttgc tctgggtgaat tacatcttct
2001 tttaaaggca atgggagaga ccctttgaag tcaaggacac cgaggaagag
2051 gacttccacg tggaccaggt gaccaccgtg aaggtgccta tgatgaagcg
2101 tttaggcatg tttaacatcc agcactgtaa gaagctgtcc agctgggtgc
2151 tgctgatgaa atacctgggc aatgccaccg ccattcttct cctgcctgat
2201 gaggggaaac tacagcacct ggaaaatgaa ctcaccacag atatcatcac
2251 caagttcctg gaaaatgaag acagaaggtc tgccagctta catttaccac
2301 aactgtccat tactggaacc tatgatctga agagcgctct ggggtcaactg
2351 ggcataccta aggtcttcag caatggggct gacctctccg ggggtcacaga
2401 ggaggcacc cagaagctct ccaaggccgt gcataaggct gtgctgacca
2451 tcgacgagaa agggactgaa gctgctgggg ccattgtttt agaggccata
2501 cccatgtcta tccccccga ggtcaagttc aacaaaccct ttgtcttctt
2551 aatgattgaa caaaataacca agtctccctt cttcatggga aaagtgggtga
2601 atcccacca aaaataactg cctctcgtct ctcaaccctt cccctccatc
2651 cctggccccc tccctggatg acattaaaga agggttgagc tggtaacccc
2701 cccccccct gcaggggccc tcgagcagtg tggttttgca agaggaagca

```

FIGURE 17A

2751	aaaagcctct	ccacccaggc	ctggaatggt	tccacccaag	tcgaaggcag
2801	tgtggttttg	caagaggaag	caaaaagcct	ctccacccag	gcctggaatg
2851	tttccaccca	atgtcgagca	accccgccca	gcgtcttgct	attggcgaat
2901	tcgaacacgc	agatgcagtc	ggggcggcgc	ggtcccaggt	ccacttcgca
2951	tattaagggtg	acgcgtgtgg	cctcgaacac	cgagcgaccc	tgcagccaat
3001	atgggatcgg	ccattgaaca	agatggattg	cacgcaggtt	ctccggccgc
3051	ttgggtggag	aggctattcg	gctatgactg	ggcacaacag	acaatcggct
3101	gctctgatgc	cgccgtgttc	cggctgtcag	cgagggggcg	cccggttctt
3151	tttgtcaaga	ccgacctgtc	cgggtgccctg	aatgaactgc	aggacgaggc
3201	agcgcggcta	tcgtggctgg	ccacgacggg	cgttccttgc	gcagctgtgc
3251	tcgacgttgt	cactgaagcg	ggaagggact	ggctgctatt	ggcggaagtg
3301	ccggggcagg	atctcctgtc	atctcacctt	gctcctgccg	agaaagtatc
3351	catcatggct	gatgcaatgc	ggcggctgca	tacgcttgat	ccggctacct
3401	gccatttcga	ccaccaagcg	aaacatcgca	tcgagcgagc	acgtactcgg
3451	atggaagccg	gtcttgctga	tcaggatgat	ctggacgaag	agcatcaggg
3501	gctcgcgcca	gccgaactgt	tcgccaggct	caaggcgcg	atgcccgacg
3551	gcgaggatct	cgtcgtgacc	catggcgatg	cctgcttgcc	gaatatcatg
3601	gtggaaaatg	gccgcttttc	tggattcatc	gactgtggcc	ggctgggtgt
3651	ggcggaccgc	tatcaggaca	tagcgttggc	tacccgtgat	attgctgaag
3701	agcttggcgg	cgaatgggct	gaccgcttcc	tcgtgcttta	cggtatcgcc
3751	gctcccagatt	cgcagcgcat	cgccttctat	cgccttcttg	acgagttctt
3801	ctgaggggat	ccgtcgacta	gagctcgctg	atcagcctcg	actgtgcctt
3851	ctagttgccca	gccatctgtt	gtttgccccct	cccccgctgcc	ttccttgacc
3901	ctggaagggtg	ccactcccac	tgtcctttcc	taataaaaatg	aggaaaattgc
3951	atcgcatgtg	ctgagtaggt	gtcattctat	tctgggggggt	gggggtggggc
4001	aggacagcaa	gggggaggat	tgggaagaca	atagcaggca	tgctggggag
4051	agatctagga	acccttagtg	atggagttgg	ccactccctc	tctgcgcgct
4101	cgctcgctca	ctgaggccgc	ccgggcaaag	cccgggcgtc	gggcgacctt
4151	tggctgccccg	gcctcagtga	gcgagcgagc	gcgcagagag	ggagtggcca
4201	accccccccc	ccccccccct	gcagccctgc	attaatgaat	cggccaacgc
4251	gcgggggagag	gcggttttg	tattgggcgc	tcttcgcgtt	ctcgcctcac
4301	tgactcgctg	cgctcggtcg	ttcggtcgcg	gcgagcggtg	ttagctcact
4351	caaaggcgggt	aatacggtta	tccacagaat	caggggataa	cgcaggaaag
4401	aacatgtgag	caaaaggcca	gcaaaaggcc	aggaaccgta	aaaaggccgc
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4551	caggcgtttc	cccctggaag	ctccctcgctg	cgctctcctg	ttccgacctt
4601	gccgcttacc	ggataacctgt	ccgcctttct	cccttcggga	agcgtggcgc
4651	tttctcaatg	ctcacgctgt	aggtatctca	gttcggtgta	ggctggtcgc
4701	tccaagctgg	gctgtgtgca	cgaaccccc	gttcagccc	accgctgcgc
4751	cttatccgggt	aactatcgct	ttgagtccta	cccggtaaga	cacgacttat
4801	cgccactggc	agcagccact	ggtaacagga	ttagcagagc	gaggtatgta
4851	ggcgggtgcta	cagagttctt	gaagtgggtg	cctaactacg	gctacactag
4901	aaggacagta	tttggtatct	gcgctctgct	gaagccagtt	accttcggaa
4951	aaagagttgg	tagctcttga	tccggcaaac	aaaccaccgc	tggtagcggt
5001	ggtttttttg	tttgcaagca	gcagattacg	cgcagaaaaa	aaggatctca
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5151	tagatccctt	taaattaaaa	atgaagtttt	aatcaatct	aaagtatata
5201	tgagtaaact	tgggtctgaca	gttaccaatg	cttaatcagt	gaggcaccta
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5301	gtgtagataa	ctacgatacg	ggagggttta	ccatctggcc	ccagtgtgc
5351	aatgataccg	cgagacccac	gctcaccggc	tccagattta	tcagcaataa
5401	accagccagc	cgggaaggcc	gagcgcagaa	gtggctcctgc	aactttatcc
5451	gcctccatcc	agtctattaa	ttgttgccgg	gaagctagag	taagtagttc
5501	gccagttaat	agtttgcgca	acgttggtgc	cattgctaca	ggcatcggtg
5551	tgtcacgctc	gtcgtttgggt	atggcttcat	tcagctccgg	ttcccaacga
5601	tcaaggcgag	ttacatgatc	ccccatgttg	tgcaaaaaag	cggttagctc
5651	cttcgggtcct	ccgatcgttg	tcagaagtaa	gttggccgca	gtgttatcac
5701	tcatggttat	ggcagcactg	cataattctc	ttactgtcat	gccatccgta

FIGURE 17B

```

5751 agatgctttt ctgtgactgg tgagtactca accaagtcac tctgagaata
5801 gtgtatgcgg cgaccgagtt gctcttgccc ggcgtcaata cgggataata
5851 ccgcgccaca tagcagaact ttaaaagtgc tcatcattgg aaaacgttct
5901 tcggggcgaa aactctcaag gatcttaccg ctgttgagat ccagttcgat
5951 gtaaccctact cgtgcaccca actgatcttc agcatctttt actttcacca
6001 gcgtttctgg gtgagcaaaa acaggaaggc aaaatgccgc aaaaaaggga
6051 ataagggcga cacggaaatg ttgaatactc atactcttcc tttttcaata
6101 ttattgaagc atttatcagg gttattgtct catgagcgga tacatatttg
6151 aatgtattta gaaaaataaa caaatagggg ttccgcgcac atttccccga
6201 aaagtgccac ctgacgtcta agaaaccatt attatcatga cattaaccta
6251 taaaaatagg cgtatcacga ggccttttcg tctcgcgcgt ttcggtgatg
6301 acggtgaaaa cctctgacac atgcagctcc cggagacggt cacagcttgt
6351 ctgtaagcgg atgccgggag cagacaagcc cgtcagggcg cgtcagcggg
6401 tggtggcggg tgtcggggct ggcttaacta tgcggcatca gagcagattg
6451 tactgagagt gcaccatatg cgggtgtgaaa taccgcacag atgcgtaagg
6501 agaaaaatacc gcatcaggaa attgtaaacg ttaatatattt gttaaaattc
6551 gcgttaaatt tttgttaaatt cagctcattt ttttaaccaat aggccgaaat
6601 cggcaaaatc cttataaat caaaagaata gaccgagata gggttgagtg
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6851 aacgtggcga gaaaggaagg gaagaaagcg aaaggagcgg gcgctagggc
6901 gctggcaagt gtagcgggtc cgctgcgcgt aaccaccaca cccgccgcgc
6951 ttaatgcgcc gctacagggc gcgtcgcgcc attcgccatt caggctacgc
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7051 tgca

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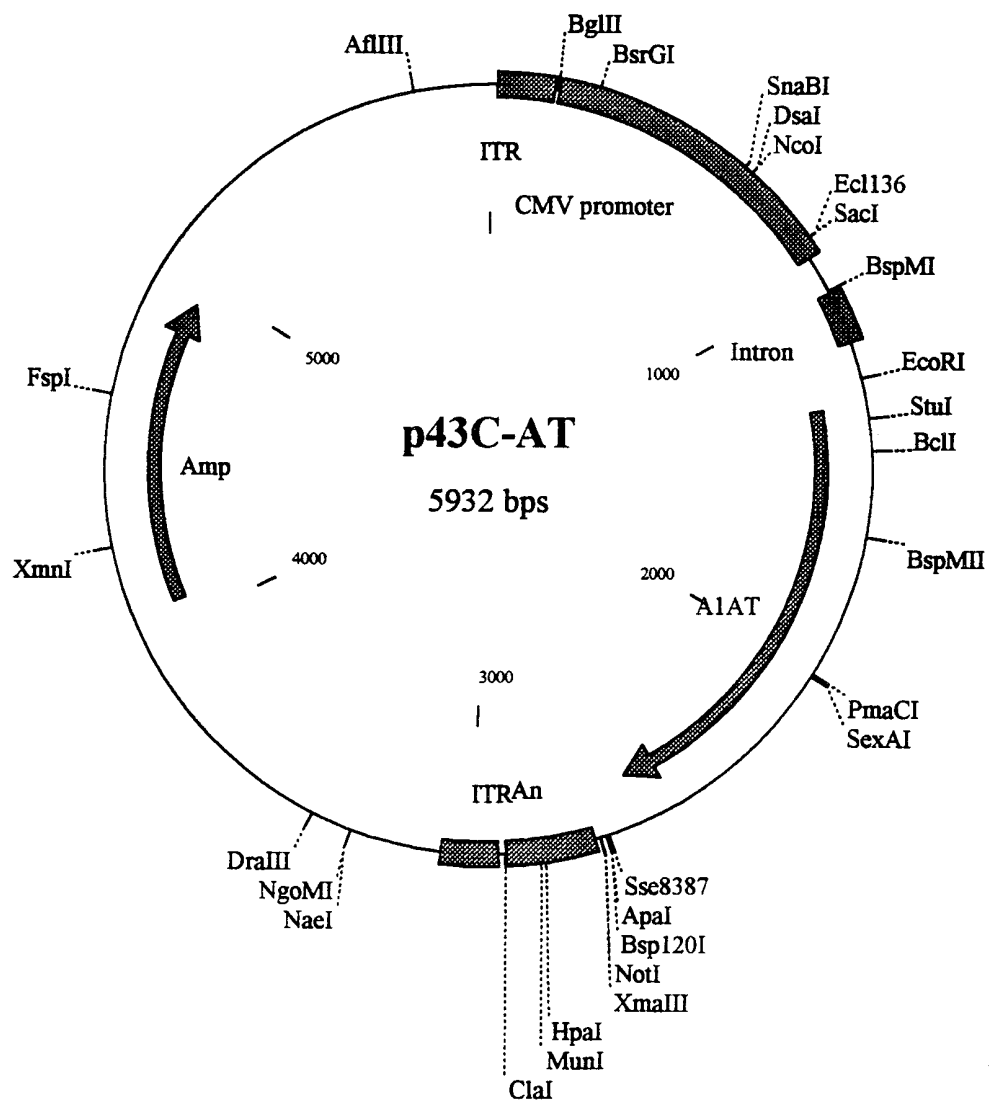


FIGURE 18

Molecule Name: p43C-AT
 Sequence Printed: 1-5932 (Full)
 Description: Ligation of TR and aat

5932 bps DNA Circular
 Date Printed 16 Apr 1999

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51 actgaggccg ggcgaccaa ggtcgcccg cgcccgggct ttgcccgggc
101 ggcctcagtg agcgagcgag cgcgcgagaga gggagtggcc aactccatca
151 ctaggggttc ctagatcttc aatattggcc attagccata ttattcattg
201 gttatatagc ataaatcaat attggctatt ggccattgca tacgttgat
251 ctatatcata atatgtacat ttatatgggc tcatgtccaa tatgaccgcc
301 atgttggcat tgattattga ctagtattata atagtaatca attacggggg
351 cattagttca tagcccatat atggagttcc gcgttacata acttacggta
401 aatggcccg ctaggtgacc gcccaacgac ccccgcccat tgacgtcaat
451 aatgacgtat gttcccatag taacgccaat agggactttc cattgacgtc
501 aatgggtgga gtatttacgg taaactgccc acttggcagt acatcaagt
551 tatcatatgc caagtccgcc ccctattgac gtcaatgacg gtaaattggc
601 cgcttggtat tatgccagt acatgacctt acgggacttt cctacttggc
651 agtacatcta cgtattagtc atcgctatta ccatgggtgat gcggttttgg
701 cagtacacca atgggcgtgg atagcggttt gactcacggg gatttccaa
751 tctccacccc attgacgtca atgggagttt gttttggcac caaaatcaac
801 gggactttcc aaaatgtcgt aataaccccg ccccggtgac gcaaatgggc
851 ggtaggcgtg tacgggtgga ggtctatata agcagagctc gtttagtgaa
901 ccgtcagatc actagaagct ttattgcggt agtttatcac agttaaattg
951 ctaacgcagt cagtgttct gacacaacag tctcgaactt aagctgcaga
1001 agttggctcg gaggcactgg gcaggtaagt atcaaggtta caagacaggt
1051 ttaaggagac caatagaaac tgggcttgct gagacagaga agactcttgc
1101 gtttctgata ggcacctatt ggtcttactg acatccactt tgcccttctc
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1201 ttaatacgac tcaactatagg ctagaactag tggatcccc gggctgcagg
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1401 atgctgccc gaagacagat acatcccacc atgatcagga tcaccaacc
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1801 ctcaagacc ttcactgtca acttcgggga caccgaagag gccagaaac
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2001 aggacttcca cgtggaccag gtgaccaccg tgaagggtgc tatgatgaag
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2151 atgaggggaa actacagcac ctggaaaatg aactcaccca cgatatcatc
2201 accaagttcc tggaaaatga agacagaagg tctgccagct tacatttacc
2251 caaactgtcc attactggaa cctatgatct gaagagcgct ctgggtcaac
2301 tgggcatcac taaggctctc agcaatgggg ctgacctctc cggggtcaca
2351 gaggagcac ccctgaagct ctccaaggcc gtgcataagg ctgtgctgac
2401 catcgacgag aaagggactg aagctgctgg ggccatgttt ttagaggcca
2451 taccatgtc tatccccccc gaggtcaagt tcaacaacc ctttgtcttc
2501 ttaatgattg aacaaaatac caagtctccc ctcttcatgg gaaaagtgg
2551 gaatcccacc caaaaataac tgcctctcgc tcctcaacc ctccctcca
2601 tccctggccc cctccctgga tgacattaaa gaagggttga gctggtaac
2651 ccccccccc ctgcaggggc cctcgaccgg ggcggccgct tcgagcagac
2701 atgataagat acattgatga gtttggacaa accacaacta gaatgcagt

```

FIGURE 18A

2751	aaaaaaatgc	tttattttgtg	aaattttgtga	tgctatttget	ttattttgtaa
2801	ccattataag	ctgcaataaaa	caagttaaca	acaacaattg	cattcattttt
2851	atgtttcagg	ttcaggggga	gatgtgggag	gtttttttaa	gcaagtaaaa
2901	cctctacaaa	tgtggtaaaa	tcgataagga	tctaggaacc	cctagtgatg
2951	gagttggcca	ctccctctct	gcgcgctcgc	tcgctcactg	aggccgcccg
3001	ggcaaagccc	gggcgtcggg	cgaccttttg	tcgcccggcc	tcagtgagcg
3051	agcgagcgcg	cagagagggg	gtggccaacc	ccccccccc	ccccctgca
3101	gcctggcgta	atagcgaaga	ggcccgcacc	gatcgccctt	cccaacagtt
3151	gcgtagcctg	aatggcgaat	ggcgcgacgc	gccctgtagc	ggcgcattaa
3201	gcgcggcggg	tgtggtgggt	acgcgcagcg	tgaccgctac	acttgccagc
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3501	cactcaaccc	tatctcggtc	tattcttttg	atttataagg	gattttgccc
3551	atttcggcct	attgggttaa	aatgagctg	atttaacaaa	aatttaacgc
3601	gaattttaac	aaaatattaa	cgtttacaat	ttcctgatgc	ggtattttct
3651	ccttacgcac	ctgtgcggta	tttcacaccg	catatggtgc	actctcagta
3701	caatctgctc	tgatgccgca	tagttaagcc	agccccgaca	cccgcacaa
3751	cccgtgacg	cgccctgacg	ggcttgtctg	ctcccggcat	ccgcttacag
3801	acaagctgtg	accgtctccg	ggagctgcat	gtgtcagagg	ttttaccggt
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3901	taggttaatg	tcattgataat	aatggtttct	tagacgtcag	gtggcacttt
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4401	tacggatggc	atgacagtaa	gagaattatg	cagtgtctgc	ataaccatga
4451	gtgataaac	tgccggccaac	ttacttctga	caacgatcgg	aggaccgaag
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5451	gcgaacgacc	tacaccgaac	tgagatacct	acagcgtgag	cattgagaaa
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FIGURE 18B

```
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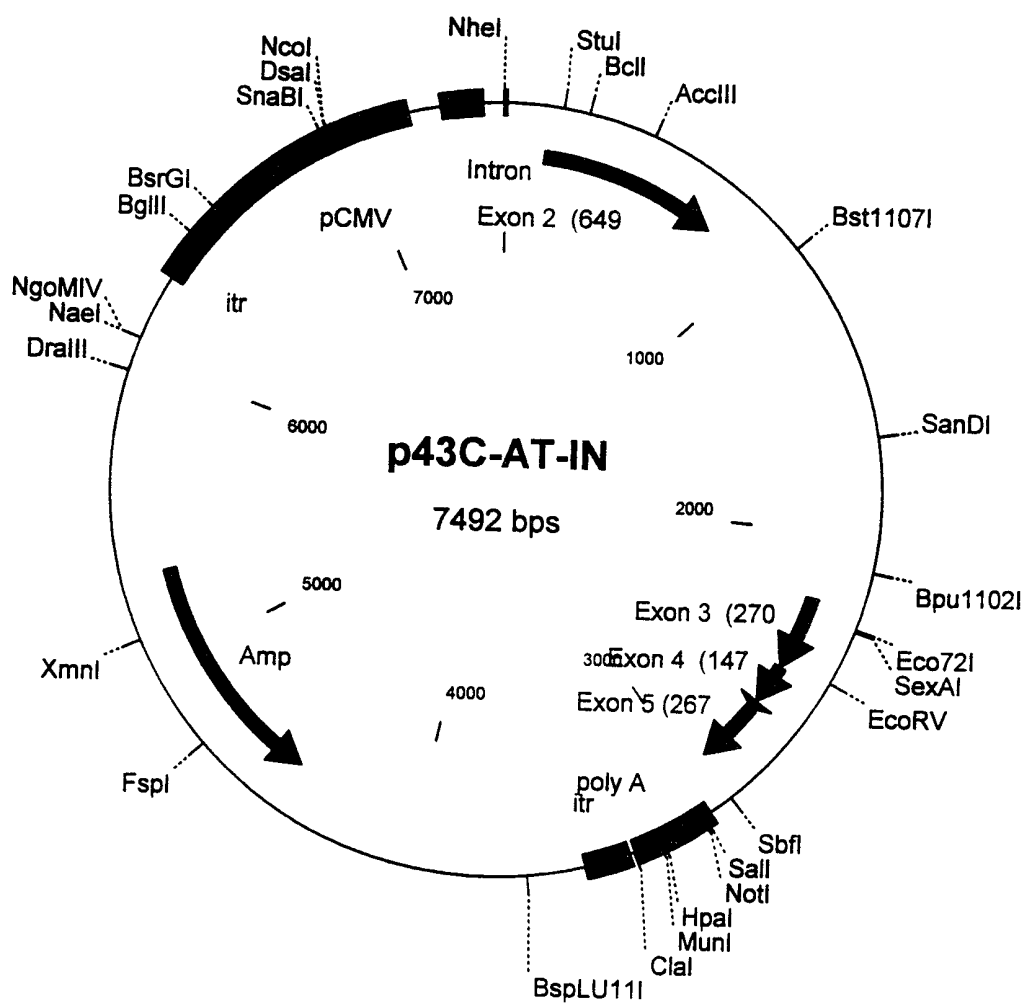


FIGURE 19

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 Sequence Printed: 1-7492 (Full) Date Printed 16 Apr 1999
 Description: Ligation of p43-C into IN

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101 ttgactgcct ggccccccca tctctgtctt gcaggacaat gccgtcttct
151 gtctcgtggg gcatcctcct gctggcaggg ctgtgctgcc tggtcctgtt
201 ctccctgggt gaggatcccc agggagatgc tgcccagaag acagatacat
251 cccaccatga tcaggatcac ccaaccttca acaagatcac cccaacctg
301 gctgagttcg ccttcagcct ataccgccag ctggcacacc agtccaacag
351 caccaatata ttcttctccc cagtgaagcat cgctacagcc tttgcaatgc
401 tctccctggg gaccaaggct gacactcacg atgaaatcct ggagggcctg
451 aatttcaacc tcacggagat tccggagggt cagatccatg aaggcttcca
501 ggaactcctc cgtacctca accagccaga cagccagctc cagctgacca
551 ccggcaatgg cctgttcctc agcgagggcc tgaagctagt ggataagttt
601 ttggaggatg ttaaaaagtt gtaccactca gaagccttca ctgtcaactt
651 cggggacacc gaagaggcca agaaacagat caacgattac gtggagaagg
701 gtactcaagg gaaaattgtg gatttggtca aggagcttga cagagacaca
751 gtttttgctc tgggtgaatta catcttcttt aaaggtaagg ttgctcaacc
801 agcctgagct gtttcccata gaaacaagca aaaatatttc tcaaaccatc
851 agttcttgaa ctctccttgg caatgcatta tgggccatag caatgctttt
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951 cattgagtaa tttgaggaaa taatagatta aactgtcaaa actactgacg
1001 ctctgcagaa cttttcagag cctttaatgt ccttggtgat actgtatatg
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2601 atggggctga cctctccggg gtcacagagg aggcaccctt gaagctctcc
2651 aaggccgtgc ataaggctgt gctgaccatc gacgagaaag ggactgaagc
2701 tgctggggcc atgttttttag aggccatacc catgtctatc cccccgagg

```

FIGURE 19A

```

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2801 tctccccctt tcatgggaaa agtgggtgaat cccacccaaa aataactgcc
2851 tctcgcctct caaacccctcc cctccatccc tggccccctc cctggatgac
2901 attaaagaag ggttgagctg gtaaccccc cccccctgc aggccctcga
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3001 cgccagtgtg ctggaattca cgcggtgtac ctctagagtc gaccggggcg
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3151 attgctttat ttgtaaccat tataagctgc aataaacaag ttaacaacaa
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3251 tttaaagcaa gtaaaacctc tacaatgtg gtaaaatcga taaggatcta
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5651 actatgcggc atcagagcag attgtactga gagtgcacca tatgcgggtg
5701 gaaataccgc acagatgcgt aaggagaaaa taccgcatca ggaaattgta

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FIGURE 19B

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FIGURE 19C

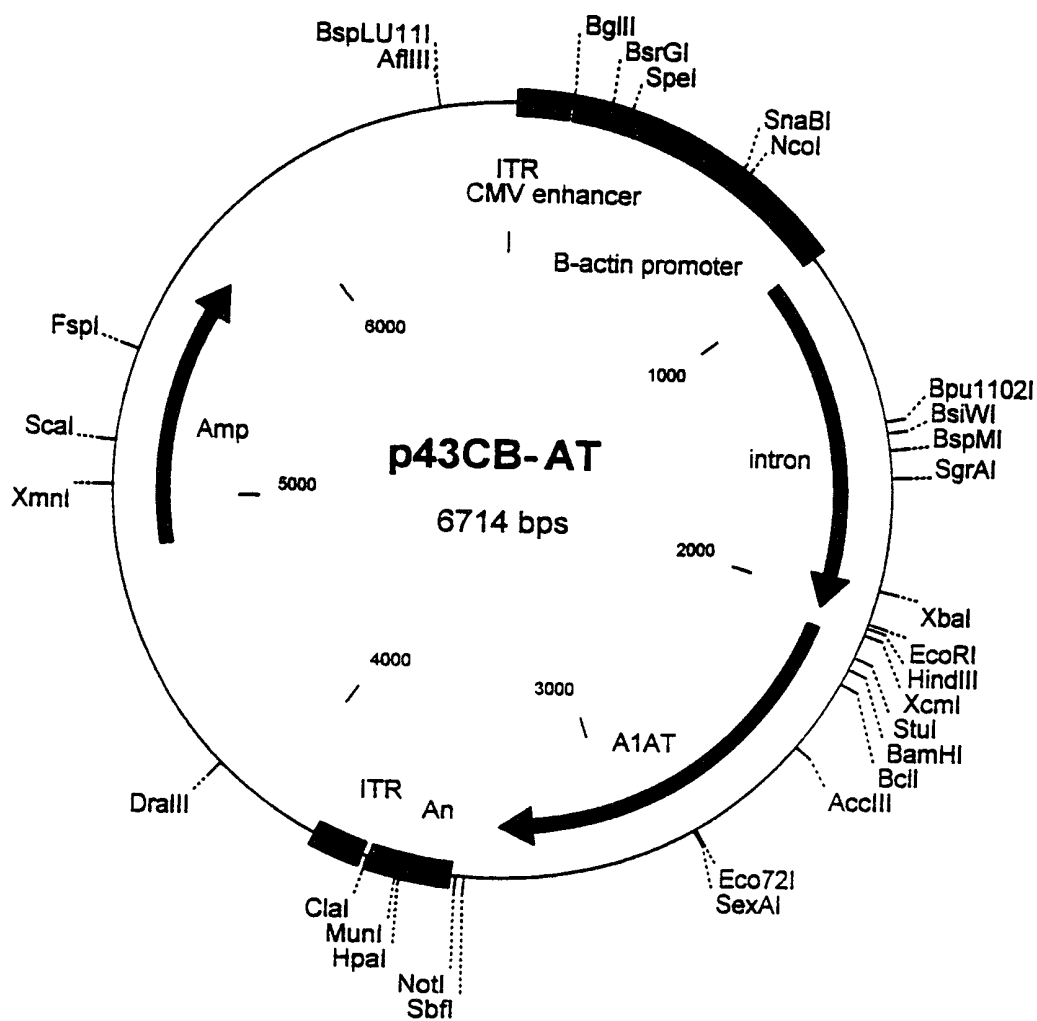


FIGURE 20

16 Apr 1999

Sequence Data

Page 1

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File Name: CB-AAT.cm5, dated 17 Nov 1998
Printed: 1-6714 bps (Full), format Single Strand

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201 gttatatagc ataaatcaat attggctatt ggccattgca tacgttgtat
251 ctatatcata atatgtacat ttatatggc tcatgtccaa tatgaccgcc
301 atgttggcat tgattattga ctagtattta atagtaatca attacggggt
351 cattagttca tagcccatat atggagtacc gcgttacata acttacggta
401 aatggcccg ctaggtgacc gcccaacgac ccccgcccat tgacgtcaat
451 aatgacgtat gttcccatag taacgccaat agggactttc cattgacgtc
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601 cgcctggcat tatgcccagt acatgacctt acgggacttt cctacttggc
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FIGURE 20A

p43CB-AT

Page 2

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2551	aagtttttgg	aggatgttaa	aaagttgtac	cactcagaag	ccttcactgt
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2651	agaagggtac	tcaagggaaa	attgtggatt	tggtcaagga	gcttgacaga
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2801	aggtgaccac	cgtgaagggtg	cctatgatga	agcgttttagg	catgtttaac
2851	atccagcact	gtaagaagct	gtccagctgg	gtgctgctga	tgaaatacct
2901	gggcaatgcc	accgccatct	tcttcctgcc	tgatgagggg	aaactacagc
2951	acctggaaaa	tgaactcacc	cacgatataca	tcaccaagtt	cctggaaaaat
3001	gaagacagaa	ggctctgccag	cttacattta	cccaaactgt	ccattactgg
3051	aacctatgat	ctgaagagcg	tcctgggtca	actgggcctc	actaagggtct
3101	tcagcaatgg	ggctgacctc	tcgggggtca	cagaggaggc	acccctgaag
3151	ctctccaagg	ccgtgcataa	ggctgtgctg	accatcgacg	agaaagggac
3201	tgaagctgct	ggggccatgt	ttttagaggc	catacccatg	tctatcccc
3251	ccgaggtcaa	gttcaacaaa	ccctttgtct	tcttaatgat	tgaacaaaat
3301	accaagtctc	ccctcttcat	gggaaaagtg	gtgaatccca	cccaaaaata
3351	actgcctctc	gctcctcaac	ccctcccctc	catccctggc	cccctccctg
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3451	gccctcgacc	cgggcggccg	cttcgagcag	acatgataag	atacattgat
3501	gagtttgagc	aaaccacaac	tagaatgcag	tgaaaaaaat	gctttatttg
3551	tgaattttgt	gatgctattg	ctttatttgt	aaccattata	agctgcaata
3601	aacaagttaa	caacaacaat	tgcattcatt	ttatgtttca	ggttcagggg
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3701	aatcgataag	gatctaggaa	cccctagtga	tggagttggc	cactccctct
3751	ctgcgcgctc	gctcgcctac	tgaggccgcc	cgggcaaagc	ccgggcgtcg
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3901	gaggcccga	ccgatcgccc	ttcccaacag	ttgcgtagcc	tgaatggcga
3951	atggcgcgac	gcgcctgtga	gcggcgcat	aagcgcggcg	ggtgtggtgg
4001	ttacgcgcag	cgtgaccgct	acacttgcca	gcgccctagc	gcccgcctct
4051	ttcgctttct	tcccttcctt	tctcgccacg	ttcgccgct	ttcccgtca
4101	agctctaaat	cgggggctcc	ctttagggtt	ccgatttagt	gctttacggc
4151	acctcgaccc	caaaaaactt	gattaggggtg	atggttcacg	tagtgggcca
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4251	taatagtgga	ctcttggtcc	aaactggaac	aacactcaac	cctatctcgg
4301	tctattcttt	tgatttataa	gggattttgc	cgatttcggc	ctattgggta
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4401	aacgtttaca	atttcctgat	gcggtatttt	ctccttacgc	atctgtgcgg
4451	tatttcacac	cgcatatggt	gcactctcag	tacaatctgc	tctgatgccg
4501	catagttaag	ccagccccga	caccgcgcaa	caccgcgtga	cgcgccttga
4551	cgggcttgct	tgctcccggc	atccgcttac	agacaagctg	tgaccgtctc
4601	cgggagctgc	atgtgtcaga	ggttttcacc	gtcatcaccg	aaacgcgcga
4651	gacgaaaggg	cctcgtgata	cgcctatttt	tataggttaa	tgatcatgata
4701	ataatggttt	cttagacgtc	agggtggcact	tttcggggaa	atgtgcgcgg
4751	aacccttatt	tgttttatttt	tctaaataca	ttcaaatatg	tatccgctca
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4851	atgagtattc	aacatttcctg	tgctgccttt	attccctttt	ttgcggcatt
4901	ttgccttcct	gtttttgtct	accagaaaac	gctggtgaaa	gtaaaagatg
4951	ctgaagatca	gttggggtgca	cgagtgggtt	acatcgaact	ggatctcaac
5001	agcggtaaga	tccttgagag	ttttcgcccc	gaagaacgtt	ttccaatgat
5051	gagcactttt	aaagttctgc	tatgtggcgc	ggtatttatcc	cgtattgacg
5101	ccgggcaaga	gcaactcggg	cgccgcatac	actattctca	gaatgacttg
5151	gttgagtact	caccagtcac	agaaaagcat	cttacggatg	gcatgacagt

FIGURE 20B

p43CB-AT

Page 3

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5201 aagagaatta tgcagtgctg ccataaccat gagtgataac actgcggcca
5251 acttacttct gacaacgatc ggaggaccga aggagctaac cgcttttttg
5301 cacaacatgg gggatcatgt aactcgcctt gatcggtggg aaccggagct
5351 gaatgaagcc ataccaaacg acgagcgtga caccacgatg cctgtagcaa
5401 tggcaacaac gttgcgcaaa ctattaactg gcgaactact tactctagct
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5601 ggtaagccct cccgtatcgt agttatctac acgacgggga gtcaggcaac
5651 tatggatgaa cgaaatagac agatcgctga gatagggtgc tactgatta
5701 agcattggta actgtcagac caagtttact catatatact ttagattgat
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5801 taatctcatg accaaaatcc cttaacgtga gttttcgttc cactgagcgt
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5951 ttgtttgccg gatcaagagc taccaactct tttccgaag gtaactggct
6001 tcagcagagc gcagatacca aatactgtcc ttctagtgtg gccgtagtta
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6101 aatcctgtta ccagtggctg ctgccagtgg cgataagtcg tgtcttaccg
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6701 atgcagggct gcag

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FIGURE 20C

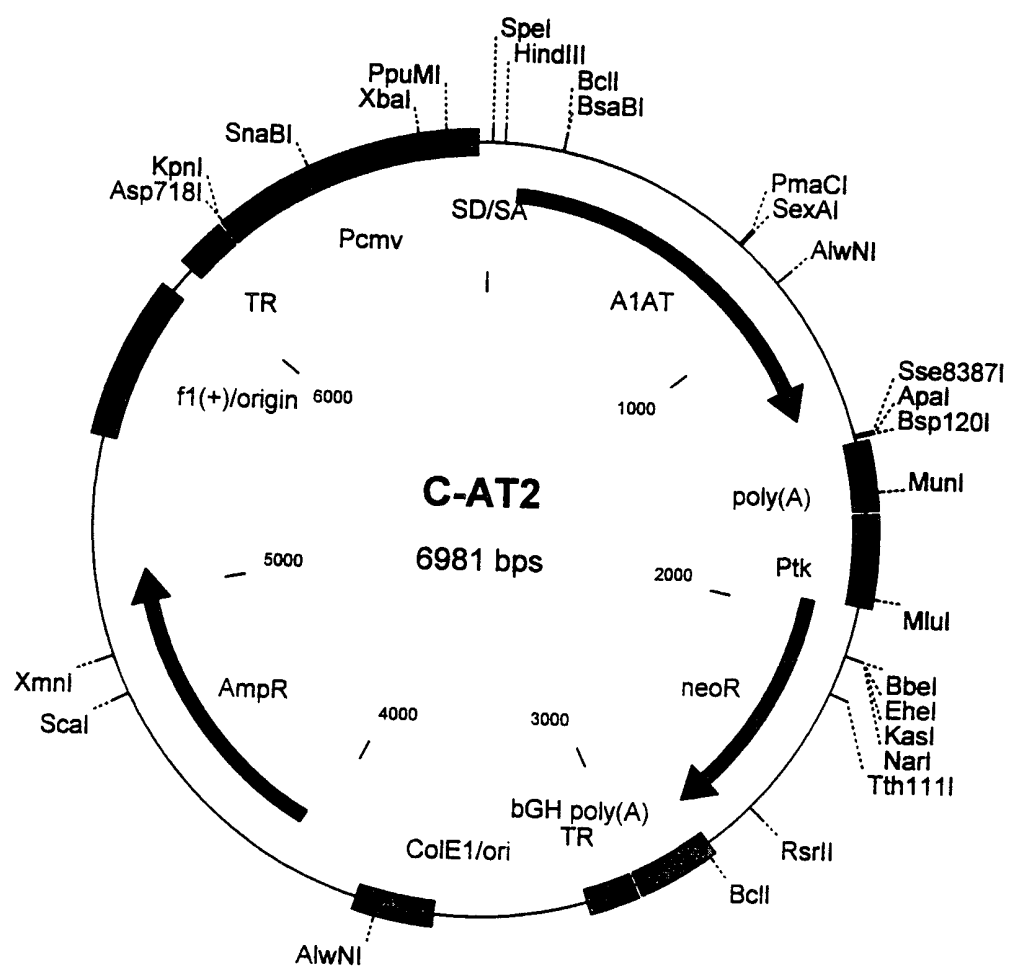


FIGURE 21

Molecule Name: C-AT2 6981 bps DNA Circular
 Sequence Printed: 1-6981 (Full) Date Printed 16 Apr 1999
 Description: Ligation of Fragment 1 and Fragment 2

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51  gatttttcagg caccaccact gacctgggac agtgaatcga caatgccgtc
101 ttctgtctcg tggggcatcc tctgtctggc aggcctgtgc tgectgggtc
151 ctgtctccct ggctgaggat ccccagggag atgctgcccc gaagacagat
201 acatcccacc atgatcagga tcacccaacc ttcaacaaga tcacccccaa
251 cctggctgag ttgccttca gcctataccg ccagctggca caccagtcca
301 acagcaccaa tatcttcttc tccccagtga gcatcgctac agcctttgca
351 atgctctccc tggggaccaa ggctgacact cacgatgaaa tcttggaggg
401 cctgaatttc aacctcacgg agattccgga ggctcagatc catgaaggct
451 tccaggaact cctccgtacc ctcaaccagc cagacagcca gctccagctg
501 accaccggca atggcctgtt cctcagcgag ggcctgaagc tagtggataa
551 gtttttggag gatgttaaaa agttgtacca ctcaagaagc ttcactgtca
601 acttcgggga caccgaagag gccaaagaaac agatcaacga ttacgtggag
651 aagggtactc aagggaatat tgtggatttg gtcaaggagc ttgacagaga
701 cacagttttt gctctggtga attacatctt ctttaaaggc aaatgggaga
751 gaccctttga agtcaaggac accgaggaag aggacttcca cgtggaccag
801 gtgaccaccg tgaagggtgc tatgatgaag cgtttaggca tgtttaacat
851 ccagcactgt aagaagctgt ccagctgggt gctgctgatg aaatacctgg
901 gcaatgccac cgccatcttc ttcctgcctg atgaggggaa actacagcac
951 ctggaaaatg aactcaccca cgatatcatc accaagttcc tggaaaatga
1001 agacagaagg tctgccagct tacatttacc caaactgtcc attactggaa
1051 cctatgatct gaagagcgct ctgggtcaac tgggcatcac taaggcttct
1101 agcaatgggg ctgacctctc cggggtcaca gaggaggcac ccctgaagct
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1201 aagctgctgg ggccatgttt ttagaggcca taccatgtc tatccccccc
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1451 cctcgaggcc gcggggatcc agacatgata agatacattg atgagtttgg
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1651 ggaggttttt tagtcgacct cgagcagtggt ggttttgcaa gaggaagcaa
1701 aaagcctctc caccagggcc tggaatgttt ccacccaagt cgaaggcagt
1751 gtggttttgc aagaggaagc aaaaagcctc tccaccaggg cctggaatgt
1801 tccacccaa tgtcgagcaa ccccgcccag cgtcttgctc ttggcgaatt
1851 cgaacacgca gatgcagtcg gggcggcgcg gtcccaggtc cacttcgcat
1901 attaagtgga cgcgtgtggc ctogaacacc gagcgaccct gcagccaata
1951 tgggatcggc cattgaacaa ctatgatttg acgcaggttc tccggccgct
2001 tgggtggaga ggctattcgg ctatgactgg gcacaacaga caatcggctg
2051 ctctgatgcc gccgtgttcc ggctgtcagc gcaggggcgc ccggttcttt
2101 ttgtcaagac cgacctgtcc ggtgccctga atgaactgca ggacgaggca
2151 gcgcggttat cgtggctggc cagcaggggc gttccttgcg cagctgtgct
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2301 atcatggctg atgcaatgcg gcggctgcat acgcttgatc cggctacctg
2351 cccattcgac caccaagcga aacatcgcat cgagcgagca cgtactcgga
2401 tgggaagccg tcttgctgat caggatgatc tggacgaaga gcatcagggg
2451 ctgcgcgccg ccgaactgtt cgccaggctc aaggcgcgca tgcccagcgg
2501 cgaggatctc gtcgtgaccc atggcgatgc ctgcttgccg aatatcatgg
2551 tggaaaatgg ccgcttttct ggattcatcg actgtggccg gctgggtgtg
2601 gcggaccgct atcaggacat agcgttggct acccgtgata ttgctgaaga
2651 gcttggcggc gaatgggctg accgcttcct cgtgctttac ggtatcgccg
2701 ctcccgatcc gcagcgcata gccttctatc gccttcttga cgagttcttc

```

FIGURE 21A

42 / 59

2751	tgagggggtac	cgtcgactag	agctcgtga	tcagcctcga	ctgtgccttc
2801	tagttgccag	ccatctgttg	tttggccctc	ccccgtgcct	tccttgacct
2851	tggaagggtgc	cactcccaact	gtccttttct	aataaaatga	ggaaattgca
2901	tcgcattgtc	tgagtaggtg	tcattctatt	ctgggggggtg	gggtggggca
2951	ggacagcaag	ggggaggatt	gggaagacaa	tagcaggcat	gctggggaga
3001	gatctaggaa	cccctagtga	tggagttggc	cactccctct	ctgcgcgtc
3051	gctcgcctac	tgaggccgcc	cgggcaaagc	cggggcgtcg	ggcgaccttt
3101	ggtcgcccgg	cctcagtgag	cgagcgagcg	cgcagagagg	gagtggccaa
3151	ccccccccc	ccccccctg	cagccctgca	ttaatgaatc	ggccaacgcg
3201	cggggagagg	cggtttgctg	attgggcgt	cttccgcttc	ctcgtcact
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3351	acatgtgagc	aaaaggccag	caaaaggcca	ggaaccgtaa	aaaggccgcg
3401	ttgctggcgt	ttttccatag	gctccgcccc	cctgacgagc	atcacaaaaa
3451	tcgacgtca	agtcagaggt	ggcgaaaccc	gacaggacta	taaagatacc
3501	aggcgtttcc	ccctggaagc	tcctcgtgc	gctctcctgt	tcggacctg
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4951	cgtttctggg	tgagcaaaaa	caggaaggca	aaatgccgca	aaaaagggaa
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5101	atgtatttag	aaaaataaac	aaataggggt	tcgcgcgaca	tttccccgaa
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5201	aaaaataggc	gtatcacgag	gccctttcgt	ctcgcgcgtt	tcgggtgatga
5251	cggtgaaaac	ctctgacaca	tgcagctccc	ggagacggtc	acagcttgct
5301	tgtaaagcga	tgccggggagc	agacaagccc	gtcagggcgc	gtcagcgggt
5351	gttggcgggt	gtcgggggctg	gcttaactat	gcggcatcag	agcagattgt
5401	actgagagt	caccatatgc	ggtgtgaaat	accgcacaga	tgcgtaagga
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5601	tgttccagtt	tgtgaacaaga	gtccactatt	aaagaacgtg	gactccaacg
5651	tcaaagggcg	aaaaaccgtc	tatcagggcg	atggccact	acgtgaacca
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FIGURE 21B

```

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5851  ctggcaagtg  tagcggtcac  gctgcgcgta  accaccacac  ccgccgcgct
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6851  tttatttcag  gtcccggatc  cggtggtgg  gcaaatacaa  gaactgctcc
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FIGURE 21C

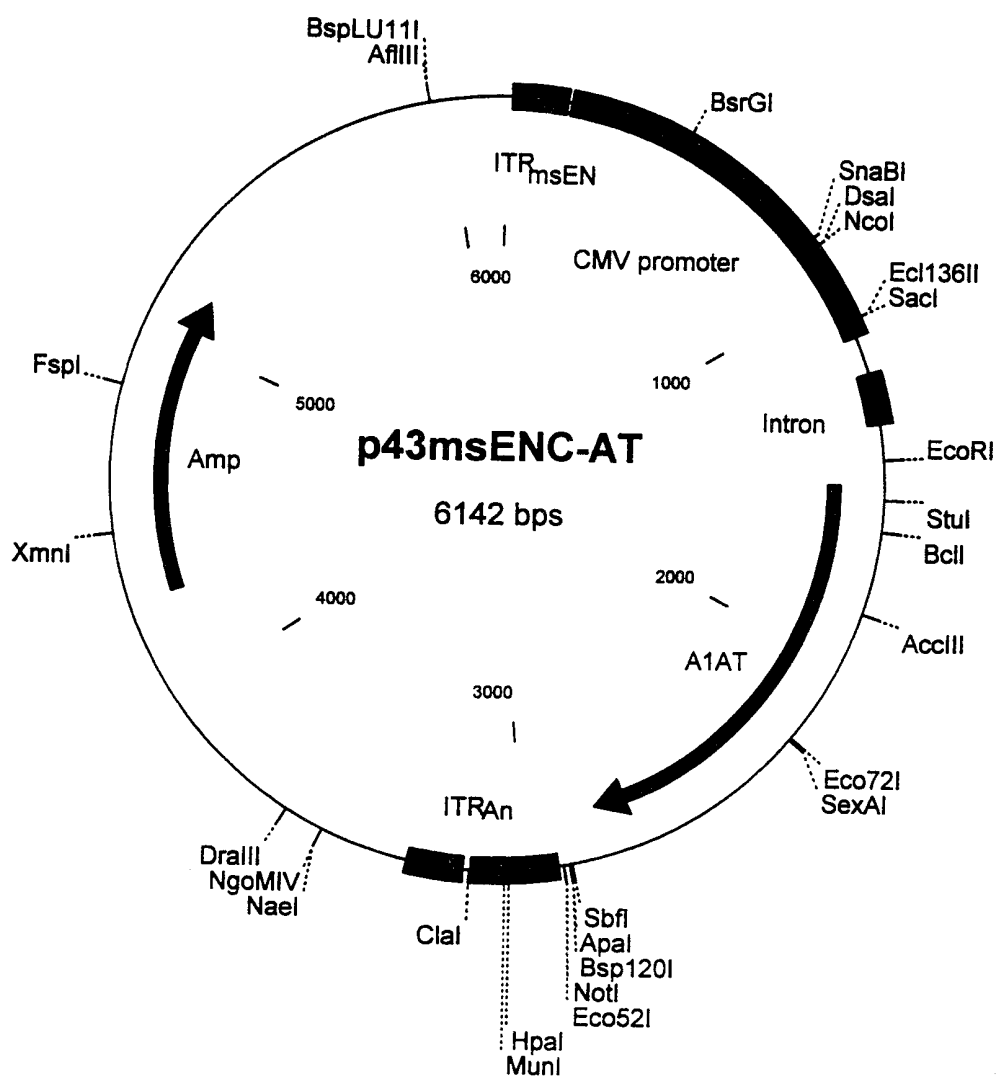


FIGURE 22

19 Apr 1999

Sequence Data

Page 1

Molecule: p43msENC-AT, 6142 bps DNA Circular
 Description: Ligation of inverted msEnhancer into p43-AAT*
 File Name: p43smENC-AT.cm5, dated 19 Apr 1999
 Printed: 1-6142 bps (Full), format Single Strand

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101 ggcctcagtg agcgagcgag cgcgcagaga gggagtggcc aactccatca
151 ctaggggttc ctagatctga cacccaaata tggcctgggg tgaggaatgg
201 tgccgtcgcc atatttgggt gtccaccatt cctcaccgct ctaaaaataa
251 ctcccgggag ttatttttag agcgccaaca cctgctgcct gccaccatt
301 cctcaccgct ctaaaaataa ctccccacca ttctcaccg gtcgccatat
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451 tacgttgtat ctatatcata atatgtacat ttatattggc tcatgtccaa
501 tatgaccgcc atgttggcat tgattattga ctagttatta atagtaatca
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901 gcggttttgg cagtacacca atgggcgttg atagcggttt gactcacggg
951 gatttccaag tctccacccc attgacgtca atgggagttt gttttggcac
1001 caaatcaaac gggactttcc aaaatgtcgt aataaccccg ccccgttgac
1051 gcaaatgggc ggtaggcggtg tacggtggga ggtctatata agcagagctc
1101 gttagtgaa ccgtcagatc actagaagct ttattgcggt agtttatcac
1151 agttaaatg ctaacgcagt cagtgtctct gacacaacag tctcgaactt
1201 aagctgcaga agttggctgt gaggcactgg gcaggtaagt atcaaggtta
1251 caagacaggt ttaaggagac caatagaaac tgggcttgct gagacagaga
1301 agactcttgc gtttctgata ggcacctatt ggtcttactg acatccactt
1351 tgctttctc tccacaggtg tccactccca gttcaattac agctcttaag
1401 gctagagtac ttaatacgac tcaactatag ctagaactag tggctcccc
1451 gggctgcagg aattcgatat caagcttggg gattttcagg caccaccact
1501 gacctgggac agtgaatcga caatgccgtc ttctgtctcg tggggcatcc
1551 tctgctggc aggcctgtgc tgctgtgctc ctgtctccct ggctgaggat
1601 ccccagggag atgctgcccc gaagacagat acatcccacc atgatcagga
1651 tcaccaaac ttcaacaaga tcaccccca cctggctgag ttgccttca
1701 gcctataacc ccagctggca caccagtcca acagcaccaa tatcttcttc
1751 tcccagtgat gcatcgctac agcctttgca atgctctccc tggggacca
1801 ggctgacact cagatgaaa tcctggaggg cctgaatttc aacctcacgg
1851 agattccgga ggctcagatc catgaaggct tccaggaact cctccgtacc
1901 ctcaaccagc cagacagcca gctccagctg accaccggca atggcctgtt
1951 cctcagcgag ggctgaagc tagtgataaa gtttttgagg gatgttaaaa
2001 agttgtacca ctcagaagcc ttcactgtca acttcgggga caccgaagag
2051 gccaaagaa agatcaacga ttacgtggag aagggtactc aagggaat
2101 tgtggatttg gtcaaggagc ttgacagaga cacagttttt gctctggtga
2151 attacatctt ctttaaaggc aaatgggaga gaccctttga agtcaaggac
2201 accgaggaag aggacttcca cgtggaccag gtgaccaccg tgaagggtgc
2251 tatgatgaag cgttttaggc gtgttaacat ccagcactgt aagaagctgt
2301 ccagctgggt gctgctgatg aaatacctgg gcaatgccac cgccatcttc
2351 ttctgcctg atgaggggaa actacagcac ctggaaaatg aactcaccca
2401 cgatatcatc accaagttcc tggaaaatga agacagaagg tctgccagct

```

FIGURE 22A

p43msENC-AT

Page 2

```

2451  tacattttacc caaactgtcc attactggaa cctatgatct gaagagcgtc
2501  ctgggtcaac tgggcatcac taaggctctc agcaatgggg ctgacctctc
2551  cggggtcaca gaggaggcac ccctgaagct ctccaaggcc gtgcataagg
2601  ctgtgctgac catcgacgag aaagggaactg aagctgctgg ggccatgttt
2651  ttagaggcca taccatgtc tatccccccc gaggtcaagt tcaacaacc
2701  ctttgtcttc ttaatgattg aacaaaatac caagtctccc ctcttcatgg
2751  gaaaagtggg gaatcccacc caaaaataac tgcctctcgc tcctcaaccc
2801  ctccccctca tccctggccc cctccctgga tgacattaaa gaagggttga
2851  gctggtaacc cccccccccc ctgcaggggc cctcgaccgc ggcgccgct
2901  tcgagcagac atgataagat acattgatga gtttggacaa accacaacta
2951  gaatgcagtg aaaaaaatgc tttatttgtg aaatttgtga tgctattgct
3001  ttatttgtaa ccattataag ctgcaataaa caagttaaca acaacaattg
3051  cattcatttt atgtttcagg ttcaggggga gatgtgggag gttttttaa
3101  gcaagtaaaa cctctacaaa tgtggtaaaa tcgataagga tctaggaacc
3151  cctagtgatg gagttggcca ctccctctct gcgcgctcgc tcgctcactg
3201  aggcgcgccg ggcaaagccc gggcgctcgg cgacctttgg tcgcccggcc
3251  tcagtgagcg agcgagcgcg cagagaggga gtggccaacc cccccccccc
3301  cccccctgca gcctggcgta atagcgaaga ggcccgacc gatcgccctt
3351  cccaacagtt gcgtagcctg aatggcgaaat ggcgcgacgc gccctgtagc
3401  ggcgcattaa gcgcggcggg tgtgggtggt acgcgcagcg tgaccgctac
3451  acttgccagc gccctagcgc ccgctccttt cgctttcttc ccttcccttc
3501  tcgccacggt cgccggcctt ccccgctcaag ctctaaatcg ggggctccct
3551  ttagggttcc gatttagtgc tttacggcac ctcgacccca aaaaacttga
3601  ttagggtgat ggttcacgta gtgggcccac gccctgatag acggtttttc
3651  gccctttgac gttggagtc acgttcttta atagtggact cttgttccaa
3701  actggaacaa cactcaacc tatctcggtc tattcttttg atttataagg
3751  gattttgccg atttcggcct attggttaaa aaatgagctg atttaacaaa
3801  aatttaacgc gaattttaac aaaatattaa cgtttacaat ttccctgatgc
3851  ggtattttct ccttacgcat ctgtgcggta tttcacaccg catatggtgc
3901  actctcagta caatctgctc tgatgccgca tagttaagcc agccccgaca
3951  cccgccaaaca cccgctgacg cgccctgacg ggcttgtctg ctcccggcat
4001  ccgcttacag acaagctgtg accgtctccg ggagctgcat gtgtcagagg
4051  ttttcaccgt catcaccgaa acgcgcgaga cgaaagggcc tcgtgatcag
4101  cctattttta taggttaatg tcatgataat aatggtttct tagagctcag
4151  gtggcacttt tcggggaaat gtgcgcggaa cccctatttg tttatttttc
4201  taaatacatt caaatatgta tccgctcatg agacaataac cctgataaat
4251  gtttcaataa tattgaaaaa ggaagagtat gagtattcaa catttccgtg
4301  tcgcccttat tccctttttt gcggcatttt gccttctctg ttttgcctac
4351  ccagaaacgc tgggtgaaagt aaaagatgct gaagatcagt tgggtgcacg
4401  agtgggttac atcgaaactg atctcaacag cggttaagatc cttgagagtt
4451  ttcgccccga agaacgtttt ccaatgatga gcacttttaa agttctgcta
4501  tgtggcgcgg tattatcccg tattgacgcc gggcaagagc aactcggtcg
4551  ccgcatacac tattctcaga atgacttggt tgagtactca ccagtcacag
4601  aaaagcatct tacggatggc atgacagtaa gagaattatg cagtgtctgcc
4651  ataaccatga gtgataaacac tgcggccaac ttacttctga caacgatcgg
4701  aggaccgaag gagctaaccg ctttttttga caacatgggg gatcatgtaa
4751  ctgcgcttga tcgttgggaa ccggagctga atgaagccat accaaacgac
4801  gagcgtgaca ccacgatgcc tgtagcaatg gcaacaacgt tgcgcaaact
4851  attaaactggc gaactactta ctctagcttc ccggcaacaa ttaatagact
4901  ggatggaggc ggataaagtt gcaggaccac ttctgcgctc ggcccttccg
4951  gctggctggg ttattgctga taaatctgga gccggtgagc gtgggtctcg
5001  cggtatcatt gcagcactgg ggccagatgg taagccctcc cgtatcgtag
5051  ttatctacac gacggggagt caggcaacta tggatgaacg aaatagacag
5101  atcgctgaga taggtgcctc actgattaag cattggtaac tgtcagacca
5151  agtttactca tatatacttt agattgattt aaaacttcat ttttaattta

```

FIGURE 22B

p43msENC-AT

Page 3

5201	aaaggatcta	ggtgaagatc	cttttttgata	atctcatgac	caaaatccct
5251	taacgtgagt	tttcgttcca	ctgagcgtca	gaccccgtag	aaaagatcaa
5301	aggatcttct	tgagatcctt	tttttctgcg	cgtaatctgc	tgcttgcaaa
5351	caaaaaaacc	accgctacca	gcggtggttt	gtttgccgga	tcaagagcta
5401	ccaactcttt	ttccgaaggt	aactggcttc	agcagagcgc	agataccaaa
5451	tactgtcctt	ctagtgtagc	cgtagttagg	ccaccacttc	aagaactctg
5501	tagcacgcc	tacatacctc	gctctgctaa	tcctggtacc	agtggctgct
5551	gccagtggcg	ataagtcgtg	tcttaccggg	ttggactcaa	gacgatagtt
5601	accggataag	gcgcagcggg	cgggctgaac	ggggggttcg	tgcacacagc
5651	ccagcttgga	gcgaacgacc	tacaccgaac	tgagatacct	acagcgtgag
5701	cattgagaaa	gcgccacgct	tcccgaagg	agaaaggcgg	acaggtatcc
5751	ggtaagcggc	agggtcggaa	caggagagcg	cacgaggag	cttccagggg
5801	gaaacgcctg	gtatctttat	agtcctgtcg	ggtttcgcca	cctctgactt
5851	gagcgtcgat	ttttgtgatg	ctcgtcaggg	gggcggagcc	tatggaaaaa
5901	cgccagcaac	gcggcctttt	tacggttcct	ggccttttgc	tggccttttg
5951	ctcacatggt	ctttcctgcg	ttatcccctg	attctgtgga	taaccgtatt
6001	accgcctttg	agtgagctga	taccgctcgc	cgcagccgaa	cgaccgagcg
6051	cagcgagtca	gtgagcgagg	aagcggaaga	gcgcccaata	cgcaaaccgc
6101	ctctccccgc	gcgttggccg	attcattaat	gcagggctgc	ag

FIGURE 22C

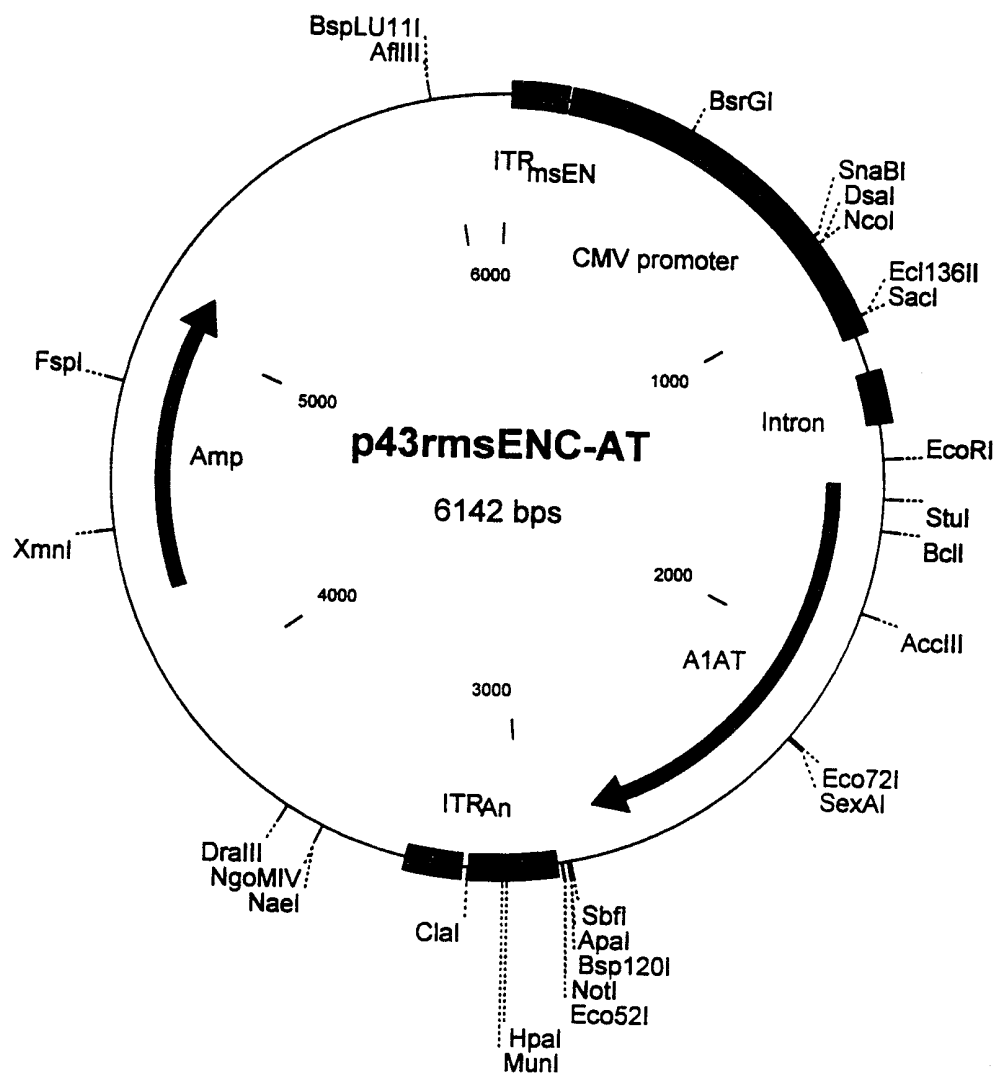


FIGURE 23

19 Apr 1999

Sequence Data

Page 1

Molecule: p43rmsENC-AT, 6142 bps DNA Circular
Description: Ligation of inverted msEnhancer into p43-AAT*
File Name: p43rmsENC-AT.cm5, dated 19 Apr 1999
Printed: 1-6142 bps (Full), format Single Strand

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1  gggggggggg ggggggggttg gccactccct ctctgcgcgcg tcgctcgctc
51  actgaggccg ggcgaccaa ggtcgcccga cgcccgggct ttgcccgggc
101 ggcctcagtg agcgagcgag cgcgcagaga gggagtggcc aactccatca
151 ctaggggttc ctagatctga cacccaaata tggcctgggg tgaggaatgg
201 tgccgtcgcc atatttgggt gtccaccatt cctcaccgct ctaaaaataa
251 ctcccgggag ttatttttag agcgccaaca cctgctgcct gccaccatt
301 cctcaccgct ctaaaaataa ctcccacca ttcctcaccg gtcgccatat
351 ttgggtgtcg tgaggaatgg tgagatcttc aatattggcc attagccata
401 ttattcattg gttatatagc ataatcaat attggctatt ggccattgca
451 tacgttgtat ctatatcata atatgtacat ttatattggc tcatgtccaa
501 tatgaccgcc atgttggcat tgattattga ctagttatta atagtaatca
551 attacggggt cattagtcca tagcccatat atggagtccc gcgttacata
601 acttacggta aatggcccgc ctggctgacc gcccaacgac ccccgcccat
651 tgacgtcaat aatgacgtat gttcccatag taacgccaat agggactttc
701 cattgacgtc aatgggtgga gtatttacgg taaactgccc acttggcagt
751 acatcaagtg tatcatatgc caagtccgcc ccctattgac gtcaatgacg
801 gtaaatggcc cgcttggcat tatgccagc acatgacctt acgggacttt
851 cctacttggc agtacatcta cgtattagtc atcgctatta ccatggtgat
901 gcggttttgg cagtacacca atgggcgtgg atagcggttt gactcacggg
951 gatttccaag tctccacccc attgacgtca atgggagttt gttttggcac
1001 caaatcaac gggactttcc aaaatgtcgt aataaccccg ccccgttgac
1051 gcaaatgggc ggtaggcggt tacggtggga ggtctatata agcagagctc
1101 gttagtgaa ccgtcagatc actagaagct ttattgcggt agtttatcac
1151 agttaaatg ctaacgcagt cagtgtctct gacacaacag tctcgaactt
1201 aagctgcaga agttggtcgt gaggcactgg gcaggtaagt atcaaggtta
1251 caagacaggt ttaaggagac caatagaaac tgggcttgct gagacagaga
1301 agactcttgc gtttctgata ggcacctatt ggtcttactg acatccactt
1351 tgcctttctc tccacaggtg tccactccca gttcaattac agctcttaag
1401 gctagagtac ttaatacgac tcaactatagg ctagaactag tggatcccc
1451 gggctgcagg aattcgatat caagcttggg gattttcagg caccaccact
1501 gacctgggac agtgaatcga caatgccgtc ttctgtctcg tggggcatcc
1551 tctgctggc aggcctgtgc tgcttggctc ctgtctccct ggctgaggat
1601 ccccagggag atgctgcccc gaagacagat acatcccacc atgatcagga
1651 tcacccaacc ttcaacaaga tcacccccaa cctggctgag ttcgccttca
1701 gcctataacc ccagctggca caccagtcca acagcaccaa tatcttcttc
1751 tccccagtga gcatcgctac agcctttgca atgctctccc tggggaccaa
1801 ggctgacact cacgatgaaa tcctggaggg cctgaatttc aacctcacgg
1851 agattccgga ggctcagatc catgaaggct tccaggaact cctccgtacc
1901 ctcaaccagc cagacagcca gctccagctg accaccggca atggcctgtt
1951 cctcagcgag ggctgaagc tagtgataaa gtttttgagg gatgttaaaa
2001 agttgtacca ctcagaagcc ttcactgtca acttcgggga caccgaagag
2051 gccaaagaac agatcaacga ttacgtggag aagggtactc aagggaat
2101 tgtggatttg gtcaaggagc ttgacagaga cacagttttt gctctggtga
2151 attacatctt ctttaaaggc aaatgggaga gaccttttga agtcaaggac
2201 accgaggaag aggacttcca cgtggaccag gtgaccaccg tgaagggtgc
2251 tatgatgaag cgttttaggca tgtttaacat ccagcactgt aagaagctgt
2301 ccagctgggt gctgctgatg aaatacctgg gcaatgccac cgccatcttc
2351 ttctgcctg atgaggggaa actacagcac ctggaaaatg aactcaccca
2401 cgatatcatc accaagttcc tggaaaatga agacagaagg tctgccagct
```

FIGURE 23A

p43rmsENC-AT

Page 2

```

2451   tacatttacc caaactgtcc attactggaa cctatgatct gaagagcgtc
2501   ctgggtcaac tgggcatcac taaggtcttc agcaatgggg ctgacctctc
2551   cggggtcaca gaggaggcac ccctgaagct ctccaaggcc gtgcataagg
2601   ctgtgctgac catcgacgag aaagggactg aagctgctgg ggccatgttt
2651   ttagaggcca taccatgtc tatccccccc gaggtcaagt tcaacaaacc
2701   ctttgtcttc ttaatgattg aacaaaatac caagtctccc ctcttcattg
2751   gaaaagtggg gaatcccacc caaaaataac tgcctctcgc tcctcaaccc
2801   cccccctcca tccctggccc cctccctgga tgacattaaa gaagggttga
2851   gctggtaacc cccccccccc ctgcaggggc cctcgaccgg ggcgccgct
2901   tcgagcagac atgataagat acattgatga gtttggaaca accacaacta
2951   gaatgcagtg aaaaaaatgc tttattttgt aaatttgtga tgctattgct
3001   ttattttgtaa ccattataag ctgcaataaa caagttaaca acaacaattg
3051   cattcatttt atgtttcagg ttcaggggga gatgtgggag gttttttaaa
3101   gcaagtaaaa cctctacaaa tgtggtaaaa tcgataagga tctaggaacc
3151   cctagtgatg gagttggcca ctccctctct gcgcgctcgc tcgctcactg
3201   aggccgcccg ggcaaagccc gggcgctcgg cgacctttgg tcgcccggcc
3251   tcagtgagcg agcgagcgcg cagagaggga gtggccaacc cccccccccc
3301   cccccctgca gcctggcgta atagcgaaga ggcccgccac gatcgccctt
3351   cccaacagtt gcgtagcctg aatggcgaat ggcgcgacgc gccctgtagc
3401   ggcgcattaa gcgcggcggg tgtggtggtt acgcgcagcg tgaccgctac
3451   acttgccagc gccctagcgc ccgctccttt cgctttcttc ccttcctttc
3501   tcgccacgtt cgccggcttt ccccgtaacg ctctaaatcg ggggctccct
3551   ttagggttcc gatttagtgc tttacggcac ctcgacccca aaaaacttga
3601   ttagggtgat ggttcacgta gtgggccatc gccctgatag acggtttttc
3651   gccctttgac gttggagtcc acgttcttta atagtggact cttgttccaa
3701   actggaacaa cactcaaccc tatctcggtc tattcttttg atttataagg
3751   gatttttgcg atttcggcct attggttaaa aaatgagctg atttaacaaa
3801   aatttaacgc gaatttttaac aaaatattaa cgtttacaat ttcctgatgc
3851   ggtattttct ccttacgcac ctgtgcggtt tttcacaccg catatggtgc
3901   actctcagta caatctgctc tgatgccgca tagttaagcc agccccgaca
3951   cccgccaaac cccgctgacg cgccctgacg ggcttgtctg ctcccggcat
4001   ccgcttacag acaagctgtg accgtctccg ggagctgcac gtgtcagagg
4051   ttttcaccgt catcaccgaa acgcgcgaga cgaaagggcc tcgtgatcag
4101   cctattttta taggttaatg tcatgataat aatggtttct tagagctcag
4151   gtggcacttt tcggggaaat gtgcgcggaa cccctatttg tttatttttc
4201   taaatacatt caaatatgta tccgctcatg agacaataac cctgataaat
4251   gcttcaataa tattgaaaaa ggaagagtat gagtattcaa catttccgtg
4301   tcgcccttat tccctttttt gcggcatttt gccttcctgt ttttgctcac
4351   ccagaaacgc tggtgaaagt aaaagatgct gaagatcagt tgggtgcacg
4401   agtgggttac atcgaaactgg atctcaacag cggtaagatc cttgagagtt
4451   ttcgccccga agaacgtttt ccaatgatga gcacttttaa agttctgcta
4501   tgtggcgcgg tattatcccg tattgacgcc gggcaagagc aactcggtcg
4551   ccgcatacac tattctcaga atgacttggg tgagtactca ccagtcacag
4601   aaaagcatct tacggatggc atgacagtaa gagaattatg cagtgtcgcc
4651   ataaccatga gtgataacac tgcggccaac ttacttctga caacgatcgg
4701   aggaccgaag gagctaaccg ctttttttgca caacatgggg gatcatgtaa
4751   ctgccttga tcgttgggaa ccggagctga atgaagccat accaaacgac
4801   gagcgtgaca ccacgatgcc tgtagcaatg gcaacaacgt tgcgcaaaact
4851   attaactggc gaactactta ctctagcttc ccggcaacaa ttaatagact
4901   ggatggaggc ggataaagtt gcaggaccac ttctgcgctc ggcccttccg
4951   gctggctggt ttattgctga taaatctgga gccggtgagc gtgggtctcg
5001   cggtatcatt gcagcactgg ggccagatgg taagccctcc cgtatcgtag
5051   ttatctacac gacggggagt caggcaacta tggatgaacg aaatagacag
5101   atcgctgaga taggtgcctc actgattaag cattggtaac tgtcagacca
5151   agtttactca tatatacttt agattgattt aaaacttcat ttttaattta

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FIGURE 23B

p43rmsENC-AT

Page 3

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5201 aaaggatcta ggtgaagatc ctttttgata atctcatgac caaaatccct
5251 taacgtgagt ttctgttcca ctgagcgtca gaccccgtag aaaagatcaa
5301 aggatcttct tgagatcctt tttttctgcg cgtaatctgc tgcttgcaaa
5351 caaaaaaacc accgctacca gcggtggttt gtttgccgga tcaagagcta
5401 ccaactcttt ttccgaaggt aactggcttc agcagagcgc agataccaaa
5451 tactgtcctt ctagtgtagc cgtagttagg ccaccacttc aagaactctg
5501 tagcaccgcc tacatacctc gctctgctaa tcctgttacc agtggtctgct
5551 gccagtggcg ataagtcgtg tcttaccggg ttggactcaa gacgatagtt
5601 accggataag gcgcagcggg cgggctgaac ggggggttcg tgcacacagc
5651 ccagcttgga gcgaacgacc tacaccgaac tgagatacct acagcgtgag
5701 cattgagaaa gcgccacgct tcccgaaggg agaaaggcgg acaggtatcc
5751 ggtaagcggc agggtcggaa caggagagcg cacgagggag cttccagggg
5801 gaaacgcctg gtatctttat agtcctgtcg ggttcgcca cctctgactt
5851 gagcgtcgat ttttgtgatg ctctgcaggg gggcggagcc tatggaaaaa
5901 cgccagcaac gcggcctttt tacggttcct ggccttttgc tggccttttg
5951 ctacatggtt ctttcctgcg ttatcccctg attctgtgga taaccgtatt
6001 accgcctttg agtgagctga taccgctcgc cgcagccgaa cgaccgagcg
6051 cagcgagtca gtgagcgagg aagcggaaga gcgccaata cgcaaaccgc
6101 ctctccccgc gcgttggccg attcattaat gcagggtctg ag

```

FIGURE 23C

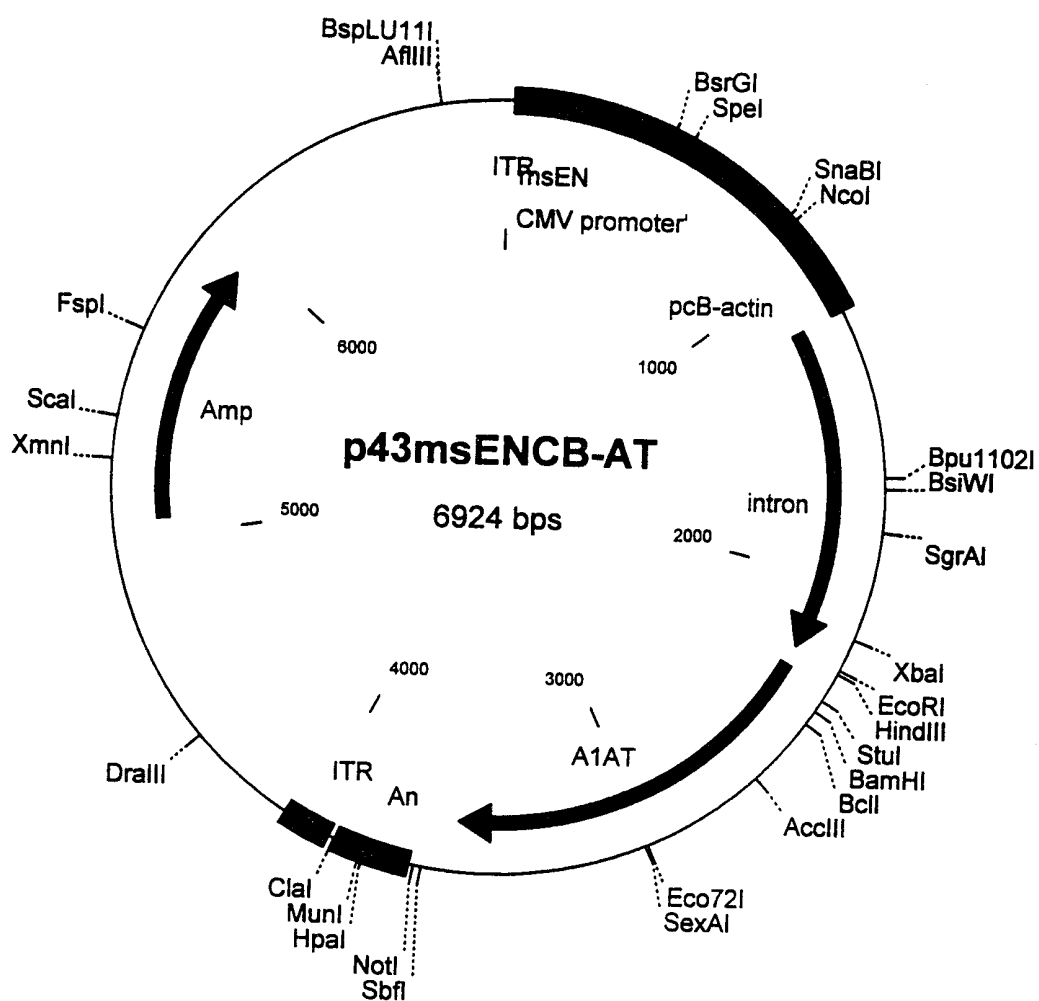


FIGURE 24

19 Apr 1999

Sequence Data

Page 1

Molecule: p43msENCB-AT, 6924 bps DNA Circular
Description: Ligation of msEnhacer into p43CB-AT*
File Name: p43msENCB-AT.cm5, dated 19 Apr 1999
Printed: 1-6924 bps (Full), format Single Strand

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51  actgaggccg ggcgaccaa ggtcgcccg cgcccgggct ttgcccgggc
101 ggcctcagtg agcgagcgag cgcgcgagaga gggagtggcc aactccatca
151 ctaggggttc ctagatctca ccattcctca cgacacccaa atatggcgac
201 gggtaggaa tggtagggag ttatttttag agcggtagag aatggtagggc
251 aggcagcagg tgttgccgct ctaaaaataa ctcccgggag ttatttttag
301 agcggtagag aatggtaggac acccaaatat ggcgacggca ccattcctca
351 cccagggcca tatttggtg tcagatcttc aatattggcc attagccata
401 ttattcattg gttatatagc ataaatcaat attggctatt ggccattgca
451 tacgttgat ctatatcata atagtacat ttatattggc tcatgtccaa
501 tatgaccgcc atgttgcat tgattattga ctagttatta atagtaatca
551 attacgggt cattagttca tagcccatat atggagtacc gcgttacata
601 acttacggta aatggccgc ctggctgacc gcccaacgac cccgccccat
651 tgacgtcaat aatgacgtat gttcccatag taacgccaat agggactttc
701 cattgacgtc aatgggtgga gtatttacgg taaactgccc acttggcagt
751 acatcaagt tatcatatgc caagtccgcc ccctattgac gtcaatgacg
801 gtaaattggc cgctggcat tatgccagc acatgacctt acgggacttt
851 cctacttggc agtacatcta cgtattagtc atcgctatta ccatggtcga
901 ggtgagcccc acgttctgct tcaactctcc catctcccc cctccccac
951 ccccaatttt gtatttattt attttttaat tattttgtgc agcgatgggg
1001 gcgggggggg ggggggggag cgcgccaggc ggggaggggc ggggagagg
1051 gcggggaggg gcgagggcga gaggtgcggc ggcagccaat cagagcggcg
1101 cgctccgaaa gtttcctttt atggcgaggc ggcggcgggc gcggccctat
1151 aaaaagcgaa gcgcgcggcg ggcgggagtc gctgcgacgc tgccttcgcc
1201 ccgtgccccg ctccgcgcgc gcctcgcgc gcccgccccg gctctgactg
1251 accgcgttac tcccacaggt gagcggcgcg gacggccctt ctctccggg
1301 ctgtaattag cgcttggttt aatgacggct tgtttctttt ctgtggctgc
1351 gtgaaagcct tgaggggctc cgggaggggc ctttgtgcgg ggggagcgg
1401 ctcggggggt gcgtgcgtgt gtgtgtgcgt ggggagcgcc gcgtgcggcc
1451 cgcgctgccc ggcggctgtg agcgtgcgg gcgcggcgcg ggcctttgtg
1501 cgctccgcag tgtgcgcgag gggagcgcg ccggggggcg tgcccgcgg
1551 tgcggggggg gctgcgaggg gaacaaaggc tgcgtgcggg taagtgtcgt
1601 ggggggggtg gcaggggggt tgggcgcggc ggtcgggctg taaccccccc
1651 ctgcaccccc ctccccgagt tgctgagcac ggcccggctt cgggtgcggg
1701 gctccgtacg gggcgtggcg cggggtcgc cgtgcggggc ggggggtggc
1751 ggcaggtggg ggtgccgggc ggggcggggc cgcctcgggc cggggagggc
1801 tcgggggagg ggcgcggcg ccccgggagc gccggcggtg gtcgagcgcg
1851 ggcgagccgc agccattgcc ttttatggta atcgtgcgag agggcgagg
1901 gacttccttt gtcccaaata tgtgcggagc cgaaatctgg gaggcggcg
1951 cgcaccccc ctgaggggag cggggcgaa cgggtgcggc ccggcaggaa
2001 ggaaatgggc ggggaggggc ttctgtgcgt gccgcggcg cgtccccctt
2051 tccctctcca gcctcggggc tgtccgcggg gggacggctg ccttcggggg
2101 ggacggggca gggcgggggt cggttcttgg cgtgtgaccg gcggctctag
2151 agcctctgct aaccatgttc atgccttctt ctttttcta cagctcctgg
2201 gcaacgtgct ggttattgtg ctgtctcctc attttgcaa agaattcgat
2251 atcaagcttg gggattttca ggcaccacca ctgacctggg acagtgaatc
2301 gacaatgccg tcttctgtct cgtggggcat cctcctgctg gcaggcctgt
2351 gctgcctggt cctgtctctc ctggctgagg atccccagg agatgctgcc
2401 cagaagacag atacatccca ccatgatcag gatcacccaa ctttcaacaa
```

FIGURE 24A

p43msENCB-AT

Page 2

```

2451 gatcaccccc aacctggctg agttcgcctt cagcctatac cgccagctgg
2501 cacaccagtc caacagcacc aatatcttct tctccccagt gagcatcgct
2551 acagcctttg caatgctctc cctggggacc aaggctgaca ctcacgatga
2601 aatcctggag ggcctgaatt tcaacctcac ggagattccg gaggctcaga
2651 tccatgaagg cttccaggaa ctccctcgta ccctcaacca gccagacagc
2701 cagctccagc tgaccaccgg caatggcctg ttccctcagcg agggcctgaa
2751 gctagtggat aagtttttgg aggatgttaa aaagtgttac cactcagaag
2801 ctttactgt caacttcggg gacaccgaag aggccaagaa acagatcaac
2851 gattacgtgg agaaggggtac tcaagggaaa attgtggatt tgggtcaagga
2901 gcttgacaga gacacagttt ttgctctggt gaattacatc ttctttaaag
2951 gcaaattggga gagacccttt gaagtcaagg acaccgagga agaggacttc
3001 cacgtggacc aggtgaccac cgtgaagggt cctatgatga agcgtttagg
3051 catgtttaac atccagcact gtaagaagct gtccagctgg gtgctgctga
3101 tgaaatacct gggcaatgcc accgccatct tcttcctgcc tgatgagggg
3151 aaactacagc acctggaaaa tgaactcacc cacgatatca tcaccaagtt
3201 cctggaaaat gaagacagaa ggtctgccag cttacattta cccaaactgt
3251 ccattactgg aacctatgat ctgaagagcg tccctgggtca actgggcatc
3301 actaaggctc tcagcaatgg ggtgacctc tccgggggtca cagaggaggc
3351 acccctgaag ctctccaagg ccgtgcataa ggctgtgctg accatcgacg
3401 agaaagggac tgaagctgct ggggccatgt ttttagaggc catacccatg
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3501 tgaacaaaaat accaagtctc cctcttcat gggaaaagtg gtgaatccca
3551 cccaaaaata actgcctctc gctcctcaac ccctcccctc catccctggc
3601 cccctccctg gatgacatta aagaagggtt gagctggtaa ccccccccc
3651 ccctgcaggg gccctcgacc cgggcggccg cttcgagcag acatgataag
3701 atacattgat gagtttggac aaaccacaac tagaatgcag tgaaaaaaat
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3801 agctgcaata aacaagttaa caacaacaat tgcattcatt ttatgtttca
3851 ggttcagggg gagatgtggg aggtttttta aagcaagtaa aacctctaca
3901 aatgtggtaa aatcgataag gatctaggaa cccctagtga tggagttggc
3951 cactccctct ctgcgcgctc gctcgctcac tgaggccgcc cgggcaaagc
4001 ccgggcgctg ggcgaccttt ggtcgcccg cctcagtga cagcctggcg
4051 cgcagagagg gagtggccaa ccccccccc cctcagtga cgcgcgagcg
4101 taatagcgaa gagggccgca ccgatcgccc ttcccaacag ttgcgtagcc
4151 tgaatggcga atggcgcgac gcgcctgta gcggcgcat aagcgcggcg
4201 ggtgtggtgg ttacgcgcag cgtgaccgt acacttgcca gcgcctagc
4251 gcccgctcct ttcgctttct tcccttctt tctcgccacg ttcgcccgt
4301 ttccccgtca agctctaaat cgggggctcc ctttaggggt ccgacttagt
4351 gctttacggc acctcgaccc caaaaaactt gattaggggt atggttcacg
4401 tagtgggcca tcgccctgat agacggtttt tcgccctttg acgttggagt
4451 ccacgttctt taatagtga ctcttgctcc aaactggaac aacactcaac
4501 cctatctcgg tctattcttt tgatttataa gggattttgc cgatttcggc
4551 ctattgggta aaaaatgagc tgattttaaca aaaatttaac gcgaatttta
4601 acaaaatatt aacgtttaca atttcctgat gcggtatttt ctccttacgc
4651 atctgtgcgg tatttcacac cgcatatggt gcaactctcag tacaatctgc
4701 tctgatgccg catagttaag ccagccccga caccgcgcaa caccgctga
4751 cgcgccctga cgggcttgct tgctcccgcc atccgcttac agacaagctg
4801 tgaccgtctc cgggagctgc atgtgtcaga ggttttcacc gtcatacccg
4851 aaacgcgcga gacgaaagg cctcgtgata cgcctatttt tatagggtta
4901 tgtcatgata ataatgggtt cttagacgtc aggtggcact ttcgggggaa
4951 atgtgcgcgg aacccttatt tgtttatttt tctaaataca ttcaaatacg
5001 tatccgctca tgagacaata accctgataa atgcttcaat aatattgaaa
5051 aaggaagagt atgagtattc aacatttccg tgcgcctt attccctttt
5101 ttgcggcatt ttgccttctt gtttttgctc acccagaaac gctggtgaaa
5151 gtaaaagatg ctgaagatca gttgggtgca cgagtgggtt acatcgaact

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FIGURE 24B

p43msENCB-AT

Page 3

```

5201  ggatctcaac agcggtaaga tccttgagag ttttcgcccc gaagaacgtt
5251  ttccaatgat gagcactttt aaagtctctgc tatgtggcgc ggtattatcc
5301  cgtattgacg ccgggcaaga gcaactcggc cgccgcatac actattctca
5351  gaatgacttg gttgagtact caccagtcac agaaaagcat cttacggatg
5401  gcatgacagt aagagaatta tgcagtgctg ccataaccat gagtataaac
5451  actgcggcca acttacttct gacaacgatc ggaggaccga aggagctaac
5501  cgcttttttg cacaacatgg gggatcatgt aactcgcctt gatcgttggg
5551  aaccggagct gaatgaagcc ataccaaacg acgagcgtga caccagatg
5601  cctgtagcaa tggcaacaac gttgcgcaaa ctattaactg gcgaactact
5651  tactctagct tcccggcaac aattaataga ctggatggag gcgataaaag
5701  ttgcaggacc acttctgcgc tcggcccttc cggctggctg gtttattgct
5751  gataaatctg gagccggtga gcgtgggtct cgcggtatca ttgcagcact
5801  ggggcccagat ggtaagccct cccgtatcgt agttatctac acgacgggga
5851  gtcaggcaac tatggatgaa cgaaatagac agatcgctga gatagggtcc
5901  tcaactgatta agcattggtg actgtcagac caagtttact catatatact
5951  ttagattgat ttaaaacttc atttttaatt taaaaggatc taggtgaaga
6001  tcctttttga taatctcatg accaaaatcc cttaacgtga gttttcgttc
6051  cactgagcgt cagaccccgt agaaaagatc aaaggatctt cttgagatcc
6101  tttttttctg cgcgtaatct gctgcttgca aacaaaaaaa ccaccgctac
6151  cagcggtggt ttgtttgccg gatcaagagc taccaactct ttttccgaag
6201  gtaactggct tcagcagagc gcagatacca aatactgtcc ttctagtgtg
6251  gccgtagtta ggccaccact tcaagaactc tgtagcaccg cctacatacc
6301  tcgctctgct aatcctgtta ccagtggctg ctgccagtgg cgataagtcg
6351  tgtcttaccg ggttggaactc aagacgatag ttaccggata aggcgagcg
6401  gtcgggctga acggggggtt cgtgcacaca gcccagcttg gagcgaacga
6451  cctacaccga actgagatac ctacagcgtg agcattgaga aagcgccacg
6501  cttcccgaag ggagaaaggc ggacaggtat ccggtaaagc gcagggtcgg
6551  aacaggagag cgcacgaggg agcttccagg gggaaacgcc tggatatctt
6601  atagtcctgt cgggtttcgc cacctctgac ttgagcgtcg atttttgtga
6651  tgctcgtcag gggggcggag cctatggaaa aacgccagca acgcggcctt
6701  ttacgggttc ctggcctttt gctggccttt tgctcacatg ttctttcctg
6751  cgttatcccc tgattctgtg gataaccgta ttaccgcctt tgagttagct
6801  gataccgctc gccgcagccg aacgaccgag cgcagcgagt cagttagcga
6851  ggaagcggaa gagcgcccaa tacgcaaacc gcctctcccc gcgcgttggc
6901  cgattcatta atgcagggtc gcag

```

FIGURE 24C

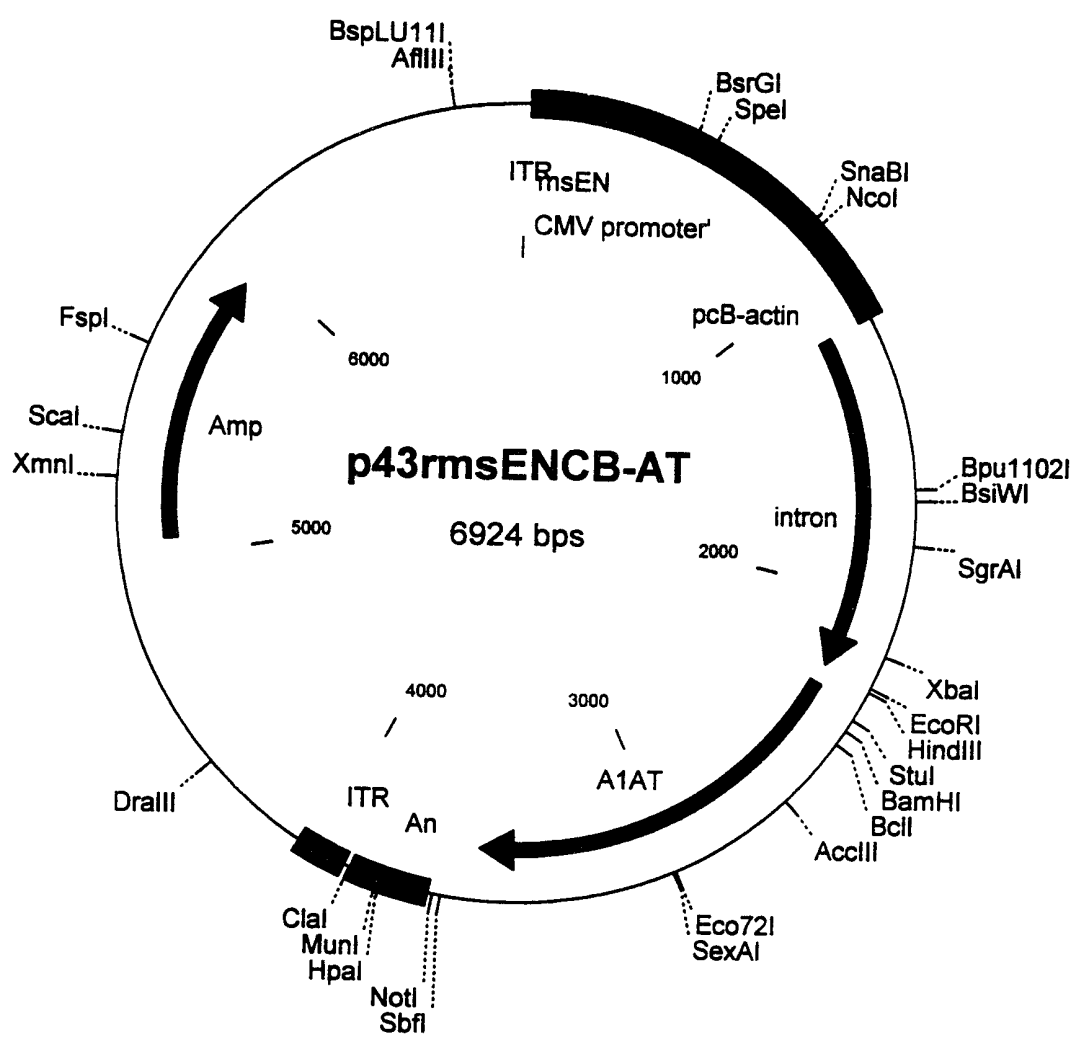


FIGURE 25

19 Apr 1999

Sequence Data

Page 1

Molecule: p43rmsENCB-AT, 6924 bps DNA Circular
Description: Ligation of inverted msEnhacer into p43CB-AT*
File Name: p43rmsCB-AT.cm5, dated 19 Apr 1999
Printed: 1-6924 bps (Full), format Single Strand

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51  actgaggccg ggcgaccaa ggtcgcccga cgcccgggct ttgcccgggc
101 ggcctcagtg agcgagcgag cgcgcagaga gggagtggcc aactccatca
151 ctaggggttc ctatgcttga caccacaata tggcctgggg tgaggaatgg
201 tgccgtcgcc atatttgggt gtccaccatt cctcaccgct ctaaaaataa
251 ctcccgggag ttattttttag agcgccaaca cctgctgcct gccaccatt
301 cctcaccgct ctaaaaataa ctcccaccca ttctcaccg gtcgccatat
351 ttgggtgtcg tgaggaatgg tgagatcttc aatattggcc attagccata
401 ttattcattg gttatatagc ataatcaat attggctatt ggccattgca
451 tacgttgat ctatatcata atatgtacat ttatattggc tcatgtccaa
501 tatgaccgcc atgttggcat tgattattga ctagtatta atagtaatca
551 attacggggt cattagttca tagcccatat atggagtacc gcgttacata
601 acttacggt aatggccgc ctggctgacc gcccaacgac ccccgcccat
651 tgacgtcaat aatgacgtat gttcccatag taacgccaat agggactttc
701 cattgacgtc aatgggtgga gtatttacgg taaactgcc acttggcagt
751 acatcaagt tatcatatgc caagtccgcc ccctattgac gtcaatgacg
801 gtaaatggc cgcctggcat tatgccagc acatgacctt acgggacttt
851 cctacttggc agtacatcta cgtattagtc atcgctatta ccatggtcga
901 ggtgagcccc acgttctgct tcaactctcc catctcccc ccctccccac
951 cccaatttt gtattttatt attttttaat tattttgtgc agcgatgggg
1001 gcgggggggg ggggggggag cgcgccaggc ggggcggggc ggggcgaggg
1051 gcggggcggg gcgagggcga gaggtgcggc ggcagccaat cagagcgggc
1101 cgctccgaaa gtttcctttt atggcgaggc ggcgggcgcg gcggccctat
1151 aaaaagcgaa gcgcgcggcg ggcgggagtc gctgcgacgc tgccttcgcc
1201 ccgtgccccg ctccgcgcgc gcctcgcgcc gcccgccccg gctctgactg
1251 accgcgttac tcccacaggt gagcgggcgg gacggccctt ctctccggg
1301 ctgtaattag cgcttggttt aatgacggct tgtttcttt ctgtggctgc
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1401 ctcggggggt gcgtgcgtgt gtgtgtgcgt ggggagcgcc gcgtgcggcc
1451 cgcgctgccc ggcggtgtgt agcgtgcgg gcgcggcgcg gggctttgtg
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1601 ggggggggtg gcagggggtg tgggcgcggc ggtcgggctg taaccccccc
1651 ctgcaccccc ctccccgagt tgctgagcac ggcccggtt cgggtgcggg
1701 gctccgtacg gggcgtggcg cggggctcgc cgtgccgggc ggggggtggc
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1801 tcgggggagg ggcgcggcg ccccgaggc gccggcggt gtcgaggcg
1851 ggcgagccgc agccattgcc ttttatggt atcgtgcgag agggcgagc
1901 gacttccttt gtcccaaata tgtgcggagc cgaatctgg gaggcggcg
1951 cgcaccccc ctacggggcg cggggcgaag cgtgcggcg ccggcaggaa
2001 ggaaatgggc ggggagggcc ttcgtgcgt gccgcggcg cgtccccttc
2051 tccctctcca gcctcggggc tgtccgcgg gggacggctg ccttcggggg
2101 ggacggggca gggcggggtt cggcttctg cgtgtgacc gcggtctag
2151 agcctctgct aacctgttc atgccttct ctttttcta cagctcctgg
2201 gcaacgtgct ggttattgtg ctgtctcat attttggca agaattcgat
2251 atcaagcttg gggattttca ggcaccacca ctgacctgg acagtgaatc
2301 gacaatgccg tcttctgtct cgtggggcat cctcctgct gcaggcctgt
2351 gctgcctggt ccctgtctcc ctggctgagg atccccagg agatgctgcc
2401 cagaagacag atacatccca ccatgatcag gatcaccaa ccttcaacaa
```

FIGURE 25A

p43rmsENCB-AT

Page 2

2451	gatcaccccc	aacctggctg	agttcgcctt	cagcctatac	cgccagctgg
2501	cacaccagtc	caacagcacc	aatatcttct	tctccccagt	gagcatcgct
2551	acagcctttg	caatgctctc	cctggggacc	aaggctgaca	ctcacgatga
2601	aatcctggag	ggcctgaatt	tcaacctcac	ggagattccg	gaggctcaga
2651	tccatgaagg	cttccaggaa	ctcctccgta	ccctcaacca	gccagacagc
2701	cagctccagc	tgaccaccgg	caatggcctg	ttcctcagcg	agggcctgaa
2751	gctagtggat	aagtttttgg	aggatgttaa	aaagttgtac	cactcagaag
2801	ccttcactgt	caacttcggg	gacaccgaag	aggccaagaa	acagatcaac
2851	gattacgtgg	agaagggtag	tcaagggaaa	attgtggatt	tggtcaaggaa
2901	gcttgacaga	gacacagttt	ttgctctggg	gaattacatc	ttctttaaag
2951	gcaaattggga	gagacccttt	gaagtcaagg	acaccgagga	agaggacttc
3001	cacgtggacc	aggtgaccac	cgtgaagggt	cctatgatga	agcgtttagg
3051	catgtttaac	atccagcact	gtaagaagct	gtccagctgg	gtgctgctga
3101	tgaaatacct	gggcaatgcc	accgccatct	tcttcctgcc	tgatgagggg
3151	aaactacagc	acctggaaaa	tgaactcacc	cacgatatca	tcaccaagtt
3201	cctggaaaat	gaagacagaa	ggtctgccag	cttacattta	cccaaactgt
3251	ccattactgg	aacctatgat	ctgaagagcg	tcctgggtca	actgggcatac
3301	actaagggtc	tcagcaatgg	ggctgacctc	tcgggggtca	cagaggaggc
3351	acccctgaag	ctctccaagg	ccgtgcataa	ggctgtgctg	accatcgacg
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3551	cccaaaaata	actgcctctc	gctcctcaac	ccctcccctc	catccctggc
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3801	agctgcaata	aacaagttaa	caacaacaat	tgcattcatt	ttatgtttca
3851	ggttcagggg	gagatgtggg	aggtttttta	aagcaagtaa	aacctctaca
3901	aatgtggtaa	aatcgataag	gatctaggaa	cccctagtga	tgaggttggc
3951	cactccctct	ctgcgcgctc	gctcgcctac	tgaggccgcc	cgggcaaagc
4001	ccgggcgctc	ggcgaccttt	ggtcgcccgg	cctcagttag	cgagcgagcg
4051	cgagagagag	gagtgggcaa	ccccccccc	ccccccctg	cagcctggcg
4101	taatagcgaa	gaggcccgca	ccgatcgccc	ttccaacag	ttgcgtagcc
4151	tgaatggcga	atggcgcgac	cgccctgtga	gcggcgcat	aagcgcgcg
4201	ggtgtgggtg	ttacgcgcag	cgtgaccgct	acacttgcca	gcgccctagc
4251	gcccgctcct	ttcgctttct	tcccttcctt	tctcgccacg	ttcgccggct
4301	ttccccgtca	agctctaaat	cgggggctcc	ctttagggtt	ccgatttagt
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4551	ctattggtta	aaaaatgagc	tgattttaaca	aaaatttaac	gcgaatttta
4601	acaaaatatt	aacgtttaca	atcttcctgat	gcgggtattt	ctccttacgc
4651	atctgtgcgg	tatttcacac	cgcataatgg	gcactctcag	tacaatctgc
4701	tctgatgccg	catagttaag	ccagccccga	caccgcgcaa	caccgcgtga
4751	cgcgccctga	cgggcttgct	tgctcccggc	atccgcttac	agacaagctg
4801	tgaccgtctc	cgggagctgc	atgtgtcaga	ggttttcacc	gtcatcaccg
4851	aaacgcgcga	gacgaaaggg	cctcgtgata	cgcctatttt	tataggttaa
4901	tgtcatgata	ataatggttt	cttagacgtc	aggtggcact	tttcggggaa
4951	atgtgcgcgg	aacccttatt	tgttttattt	tctaaataca	ttcaaatatg
5001	tatccgctca	tgagacaata	accctgataa	atgcttcaat	aatattgaaa
5051	aaggaagagt	atgagtattc	aacatttcgg	tgctgcctct	attccctttt
5101	ttgcggcatt	ttgccttcct	gtttttgctc	accagaaaac	gctggtgaaa
5151	gtaaaagatg	ctgaagatca	gttgggtgca	cgagtgggtt	acatcgaact

FIGURE 25B

p43rmsENCB-AT

Page 3

5201	ggatctcaac	agcggtaaga	tccttgagag	ttttcgcccc	gaagaacggt
5251	ttccaatgat	gagcactttt	aaagtctctgc	tatgtggcgc	ggtattatcc
5301	cgtattgacg	ccgggcaaga	gcaactcggg	cgccgcatac	actattctca
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5401	gcatgacagt	aagagaatta	tgcagtgctg	ccataaccat	gagtataaac
5451	actgcggcca	acttactttc	gacaacgatc	ggaggaccga	aggagctaac
5501	cgcttttttg	cacaacatgg	gggatcatgt	aactcgcctt	gacggttggg
5551	aaccggagct	gaatgaagcc	ataccaaacg	acgagcgtga	caccacgatg
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5651	tactctagct	tcccggcaac	aattaataga	ctggatggag	gcgataaag
5701	ttgcaggacc	acttctgcgc	tcggcccttc	cggttgctg	gtttattgct
5751	gataaatctg	gagccggtga	gcgtgggtct	cgcggtatca	ttgcagcact
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5851	gtcaggcaac	tatggatgaa	cgaaatagac	agatcgctga	gatagggtgcc
5901	tactgatta	agcattggta	actgtcagac	caagtttact	catatatact
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6001	tcctttttga	taatctcatg	acaaaaatcc	cttaacgtga	gttttcgttc
6051	cactgagcgt	cagaccccg	agaaaagatc	aaaggatctt	cttgagatcc
6101	tttttttctg	cgcgtaatat	gctgcttgca	aacaaaaaaa	ccaccgctac
6151	cagcggtggt	ttgtttgccg	gatcaagagc	taccaactct	ttttccgaag
6201	gtaactggct	tcagcagagc	gcagatacca	aatactgtcc	ttctagtgtg
6251	gccgtagtta	ggccaccact	tcaagaactc	tgtagcaccg	cctacatacc
6301	tcgctctgct	aatcctgtta	ccagtggctg	ctgccagtgg	cgataagtgc
6351	tgtcttaccg	ggttggactc	aagacgatag	ttaccggata	aggcgcagcg
6401	gtcgggctga	acgggggggt	cgtgcacaca	gcccagcttg	gagcgaacga
6451	cctacaccga	actgagatac	ctacagcgtg	agcattgaga	aagcgccacg
6501	cttcccgaag	ggagaaaggc	ggacaggtat	ccggtaaagc	gcagggtcgg
6551	aacaggagag	cgcacgaggg	agcttccagg	gggaaacgcc	tggtatcttt
6601	atagtcctgt	cgggtttcgc	cacctctgac	ttgagcgtcg	atttttgtga
6651	tgctcgtcag	gggggcggag	cctatggaaa	aacgccagca	acgcggcctt
6701	tttacggttc	ctggcctttt	gctggccttt	tgctcacatg	ttctttcctg
6751	cgttatcccc	tgattctgtg	gataaccgta	ttaccgcctt	tgagtgaagt
6801	gataccgctc	gccgcagccg	aacgaccgag	cgcagcgagt	cagtgaagca
6851	ggaagcgga	gagcgcccaa	tacgcaaacc	gcctctcccc	gcgcggtggc
6901	cgattcatta	atgcagggct	gcag		

FIGURE 25C