



(86) Date de dépôt PCT/PCT Filing Date: 2000/09/18
(87) Date publication PCT/PCT Publication Date: 2001/03/22
(45) Date de délivrance/Issue Date: 2012/01/24
(85) Entrée phase nationale/National Entry: 2002/03/07
(86) N° demande PCT/PCT Application No.: US 2000/025510
(87) N° publication PCT/PCT Publication No.: 2001/019380
(30) Priorité/Priority: 1999/09/17 (US09/397,873)

(51) Cl.Int./Int.Cl. *A61K 35/76* (2006.01),
A61K 38/21 (2006.01), *A61P 35/00* (2006.01),
C07K 14/145 (2006.01), *C12N 15/47* (2006.01),
C12N 7/00 (2006.01), *C12N 7/02* (2006.01),
A61K 38/00 (2006.01)

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(54) Title: ONCOLYTIC VIRUS

(57) **Abrégé/Abstract:**

The present invention is directed to a method of reducing the viability of a tumor cell involving administering a virus that is not a common human pathogen to the tumor cell. Preferably, the virus exhibits differential susceptibility, in that normal cells are not affected by the virus. This differential susceptibility is more pronounced in the presence of interferon. The tumor cell is characterized by having low levels, or no, PKR activity, or as being PKR^{-/-}, STAT1^{-/-} or both PKR^{-/-} and STAT1^{-/-}. The virus is selected from the group consisting of Rhabdovirus and picornavirus, and preferably is vesicular stomatitis virus (VSV) or a derivative thereof.

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(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau



(43) International Publication Date
22 March 2001 (22.03.2001)

PCT

(10) International Publication Number
WO 01/19380 A3

(51) International Patent Classification⁷: **A61K 35/76**,
A61P 35/00, C12N 7/00, 7/02, 15/47 // (A61K 35/76,
38:21)

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(22) International Filing Date:
18 September 2000 (18.09.2000)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
09/397,873 17 September 1999 (17.09.1999) US

(81) Designated States (*national*): AE, AG, AL, AM, AT, AU,
AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ,
DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR,
HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR,
LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ,
NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM,
TR, TT, TZ, UA, UG, UZ, VN, YU, ZA, ZW.

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(84) Designated States (*regional*): ARIPO patent (GH, GM,
KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW), Eurasian
patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European
patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE,
IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG,
CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).

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Published:

— with international search report

(88) Date of publication of the international search report:
22 November 2001

*For two-letter codes and other abbreviations, refer to the "Guid-
ance Notes on Codes and Abbreviations" appearing at the begin-
ning of each regular issue of the PCT Gazette.*

(54) Title: ONCOLYTIC VIRUS

(57) Abstract: The present invention is directed to a method of reducing the viability of a tumor cell involving administering a virus that is not a common human pathogen to the tumor cell. Preferably, the virus exhibits differential susceptibility, in that normal cells are not affected by the virus. This differential susceptibility is more pronounced in the presence of interferon. The tumor cell is characterized by having low levels, or no. PKR activity, or as being PKR^{-/-}, STAT1^{-/-} or both PKR^{-/-} and STAT1^{-/-}. The virus is selected from the group consisting of Rhabdovirus and picornavirus, and preferably is vesicular stomatitis virus (VSV) or a derivative thereof.



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ONCOLYTIC VIRUS

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10 **FIELD OF THE INVENTION**

The present invention relates to a novel cancer therapeutic. More specifically, this invention relates to viruses that selectively infect and inhibit tumour cell growth.

15

BACKGROUND OF THE INVENTION

The use of oncolytic bacteria, or compositions of oncolytic bacterias, for combatting neoplasms in humans and animals is known. For example EP 564 121, GB
20 1,587,244 and U.S. 3,192,116 disclose the use of non-pathogenic bacteria that result in the liquification and lysis of tumours in vertebrates. However in many instances, for example with the use of *Clostridium*, the tumours are only partially destroyed, and tumour regrowth may still occur. To ensure control of tumour growth the administration of bacteria, followed by chemotherapeutic drugs, for example 5-
25 fluorodeoxyuridine or alkylating agents, has been suggested (e.g. GB 1,069,144).

Several viruses have also been shown to exhibit tumoricidal properties, for example parvovirus H-1 (Dupressoir et al., 1996. Cancer Res, 49:3203-3208), Newcastle disease virus (Reichand et al., 1992. J. Surg. Res, 52:448-453) or retroviral
30 vectors containing drug susceptibility genes (Takamiya et al., 1993. J. Neurosurg, 79:104-110). WO97/26904 and WO96/03997 disclose a mutant herpes simplex virus (HSV-1761) that inhibits tumour cell growth. Administration of HSV-1716 comprising a 759 base pair deletion in each copy of γ 34.5 of the long repeat region

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(R_L) to tumour cells kills these cells. However, this virus is specific for neuronal cells as HSV is known to selectively inhabit the neuronal system. Furthermore, the use of common human pathogens as an oncolytic virus is limited as it is likely that the general population has been infected and acquired an immune response to such viruses. A preexisting immune response to a viral strain similar to the one used as a therapeutic agent in the treatment of a cancer may attenuate the effectiveness of the virus as therapeutic agent.

Other virus strains have reported oncolytic activity. The ONYX-015 human adenovirus (produced by ONYX pharmaceuticals) is believed to replicate preferentially in p53 negative tumour cells. This virus shows promise in clinical trials with head and neck cancer patients (Kim, D., T. et al., Nat Med, 1998. 4:1341-1342). Reovirus type 3 is being developed by Oncolytic Biotech as a cancer therapeutic, which preferentially grows in PKR -/- cells (Yin, H.S., J Virol Methods, 1997. 67:93-101; Strong, J.E. and P.W. Lee., J Virol, 1996. 70:612-616; Strong, J.E., et al., Virology, 1993. 197:405-411; Minuk, G.Y., et al., J Hepatol, 1987. 5:8-13; Rozee, K.R., et al., Appl Environ Microbiol, 1978. 35:297-300). Reovirus, type III exhibited enhanced replication properties in cells which expressed the mutated ras oncogene (Coffey, M.C., et al., Science, 1998. 282:1332-1334; Strong, J.E., et al., Embo J, 1998. 17:3351-1362). Mundschau and Faller (Mundschau, L.J. and D.V. Faller, J Biol Chem, 1992. 267:23092-23098) have shown that the ras oncogene product activated an inhibitor of PKR, and this coupled with the observation that the PKR chemical inhibitor 2-aminopurine increased the growth of Reo type III in normal cells implicates PKR is a critical regulator of the growth of reovirus.

25

WO 99/04026 teaches the use of VSV as a vector in gene therapy for the expression of a wide range of products including antibodies, immunogens, toxins, etc. for the treatment of a variety of disease disorders.

30

Interferons are circulating factors which bind to cell surface receptors activating a signalling cascade ultimately leading to a number of biological responses.

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Two of the outcomes of interferon signalling are tightly linked: (1) an antiviral response and (2) induction of growth inhibitory and/or apoptotic signals.

U.S. 4,806,347 discloses the use of γ Interferon and a fragment of INF- γ
5 (known as $\Delta 4\alpha 2$) against human tumour cells.

WO 99/18799 reports the cytotoxic activity of Newcastle Disease Virus (NDV) and Sindbis virus towards several human cancer cells. However, both viruses demonstrated selectivity in their cytotoxic activity towards tumor cells.

10

WO 99/18799 discloses that interferon addition to normal cells renders these cells resistant to NDV, yet, this effect was not observed with interferon-treated tumor cells which continued to exhibit NDV-induced sensitivity. WO 99/18799 also discloses the cytotoxic activity of VSV cells against KB cells (head and neck
15 carcinoma) and HT 1080 (Fibrosarcoma), and alleviation of cytotoxicity in normal and tumor cells, by VSV, in the presence of interferon. No other cell types were tested against VSV cytotoxic activity.

Certain mutant strains of VSV have been reported. Stanners, et al., Virology
20 (1987) 160(1):255-8. Francoeur, et al., Virology (1987) 160(1):236-45. Stanners, et al., J. Gen. Virol. (1975) 29(3):281-96. Stanners, et al., Cell (1977) 11(2):273-81.

The present invention relates to viral formulations that are useful in the treatment of diseases and cancers, preferably leukaemia. Such formulations may also
25 comprise an oncolytic VSV strain and a chemical agent, for example a cytokine which confers to normal cells, resistance to viral infection, but leaves diseased or cancerous cells susceptible to viral infection and lysis.

It is an object of the invention to overcome disadvantages of the prior art.

30

The above object is met by the combinations of features of the main claims, the sub-claims disclose further advantageous embodiments of the invention.

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SUMMARY OF THE INVENTION

The present invention relates to a novel cancer therapeutic. More specifically, this invention relates to viruses that selectively infect and inhibit tumour cell growth.

5

According to the present invention there is provided a method of reducing the viability of a tumour cell comprising administering a virus to the tumour cell, wherein the virus is characterized as not being a common human pathogen. Preferably the tumour cell lacks PKR activity, and the virus is selected from the group consisting of rhabdovirus. More preferably the virus is VSV.

10

This invention is also directed to a method of reducing the viability of a tumour cell comprising administering a virus to the tumour cell, wherein the virus is characterized as being unable to inactivate PKR activity within a host cell. Preferably the virus is selected from the group consisting of vesicular stomatitis virus, picornavirus, influenza virus, and adenovirus.

15

The present invention also pertains to a method of reducing the viability a tumour cell within a population of cells comprising administering a virus to the population of cells, wherein the virus is characterized as being able to selectively infect and kill the tumour cell. Preferably the virus is further characterized by being unable to inactivate PKR activity in a host cell.

20

This invention also relates to the method as defined above, wherein the population of cells is treated with interferon prior to administering the virus.

25

This invention provides a method for identifying a tumor susceptible to treatment with a virus, comprising: (a) dividing a sample containing cells of the tumor into a first portion and a second portion; (b) treating the first portion with the virus; and (c) determining whether the percentage of dead cells in the first portion is higher than in the second portion, wherein the tumor is susceptible to treatment with the virus if the percentage of dead cells in the first portion is higher than in the second portion.

30

- 5 -

This invention provides a method for identifying a tumor susceptible to treatment with a virus, comprising: (a) dividing a sample containing cells of the tumor into a first portion and a second portion; (b) treating the first portion with the virus and an amount of interferon sufficient to improve survival of interferon-responsive cells in the presence of the virus, and treating the second portion with the virus in the absence of interferon; and (c) determining whether the percentage of dead cells in the first portion is higher than in the second portion, wherein the tumor is susceptible to treatment with the virus if the percentage of dead cells in the first portion is higher than in the second portion.

The present invention is directed to a mutant VSV, characterized in that the mutant VSV grows poorly in interferon-responsive cells. Such strains are also referred to herein as attenuated strains of VSV, or VSV strains that grow poorly in interferon-responsive cells. They can be identified by their producing smaller plaques in monolayers of interferon-responsive cells than in interferon-nonresponsive cells, as described below. Attenuated VSV strains can also be identified by their having a higher LD50 when administered intranasally to PKR+/- mice as compared to WT Indiana, in the assay described below.

The present invention also pertains to a method for isolating VSV using an affinity matrix, comprising adding the VSV to the affinity matrix to produce bound VSV, washing the bound VSV, and eluting the VSV from the affinity matrix. Also included in the present invention is a modified VSV that comprises a non-native fusion protein on the outer surface of the virus. The non-native protein may be fusion protein comprising an affinity tag and a viral envelope protein, or it may be derived from a producer cell.

The present invention is also directed to isolated nucleic acid molecules (DNA or RNA) having a sequence coding for mutant VSV proteins and sequences

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complementary thereto. Such nucleic acid molecules can be used in the preparation of a recombinant VSV or as a DNA vaccine.

There are several advantages for the use of a virus as described herein as a
5 therapeutic virus over other viruses:

- 10 • Rhabdoviruses are not common human pathogens. For example, VSV is found mostly in insects, rodents and domestic farm animals, and therefore a large proportion of individuals will not have been infected or immunized to VSV infection. On the other hand, Adenovirus or Reovirus are human pathogens and most of the general population have been infected and acquired an immune response to both of these viruses. A preexisting immune response to a viral strain similar to the one used as a therapeutic agent in the treatment of a cancer may attenuate the effectiveness of the virus as therapeutic agent;
15
- VSV replicates much more quickly than either Adenovirus or Reovirus, and can be readily concentrated to high titres. Production of high titre virus preparations is a significant limitation of other potential viral therapeutic strains;
20
- VSV is simple virus comprising only five genes, easily amenable to genetic manipulation. No such system is currently available for Reovirus;
25
- Cellular infection by VSV is highly responsive to additional chemical agents such as interferon, a feature which enhances its therapeutic value.
30
- VSV has a broad host range and is capable of infecting most types of human cells, whereas other viruses are more limited in regard to the types of cells they may infect.
- VSV is a RNA virus and spends its entire lifecycle in the cytoplasm. Therefore it involves less danger of unwanted integration into the genome of a patient.

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Collectively, these VSV attributes provide significant advantages over the use of the other viruses known to exhibit oncolytic activity.

- 5 This summary of the invention does not necessarily describe all necessary features of the invention but that the invention may also reside in a sub-combination of the described features.

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BRIEF DESCRIPTION OF THE DRAWINGS

These and other features of the invention will become more apparent from the following description in which reference is made to the appended drawings wherein:

5

FIGURE 1 shows a general schematic of the interferon cascade.

FIGURE 2 shows the effect of VSV on normal human fibroblasts, human melanoma cell line SK-MEL3, LNCaP a prostate cancer cell line, and the ovarian carcinoma cell
10 A2780 in the presence and absence of interferon as determined by a modified cpe assay. Monolayers of cells were infected at an moi of 0.1 pfu in a 12 well plate. At time 0 and every 12 hours subsequent up to 48 hours, one well of infected cells was fixed with 0.5 ml Leukostat fixative for 2 minutes. At the end of the experiment monolayers were stained with Leukostat stains.

15

FIGURE 3 shows the cytopathic effect of VSV in normal fibroblasts cells (Figure 3 (a)), and tumour cell lines, including ovarian tumour cells (Figure 3 (b)) and KB tumour cells (Figure 3 (c)).

20 **FIGURE 4** shows the effect of VSV on normal human fibroblasts co-cultured with 293T tumour cells over a period of 24 hours. Co-cultures were infected at an moi of 0.1 pfu/cell and the infection allowed to proceed in the presence (IFN+) or absence (IFN-) of interferon. Cultures were stained with antibodies to large T antigen (red nuclei) to detect the 293T cells and with DAPI (blue nuclei) which stains all cell
25 types.

FIGURE 5 shows the effect of VSV *in vivo* on tumors implanted within nude mice. Human melanoma cells were implanted within nude mice and either mock injected (VSV(-)), injected with wild type VSV (data not presented), or injected with
30 additional melanoma cells infected in vitro with VSV for one hour prior to injection into the tumour site VSV(+)). Size of the tumors were determined over a 7 day period.

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FIGURE 6 shows ulcers formed on a tumor produced within a nude mouse as described in Figure 5.

5 **FIGURE 7:** VSV and VSV infected cells inhibit growth of human melanoma xenografts in nude mice.

FIGURES 8A and 8B: PKR $-/-$ mice are acutely sensitive to intranasal VSV infection and demonstrate a deficiency in IFN mediated resistance.

10

FIGURE 9: Interferon can protect xenograft bearing nude mice during VSV treatment.

15 **FIGURES 10A and 10B:** Virus production from tumour cells and normal cells infected with wild type Indiana and various mutant VSV strains.

FIGURE 11: Malignant cells are rapidly killed following VSV (WT Indiana) infection and are not protected by IFN- α .

20 **FIGURE 12:** VSV induced cytopathic effect visible in human melanoma cells but not in primary human cells with or without IFN- α .

FIGURE 13: Efficacy of a single intravenous dose of mutant VSV in treating human melanoma xenografts in nude mice.

25

FIGURE 14: N Protein cDNA sequence of wild type and mutant VSVs.

FIGURE 15: N Protein amino acid sequence of wild type and mutant VSVs.

30 **FIGURE 16:** P Protein cDNA sequence of wild type and mutant VSVs.

FIGURE 17: P Protein amino acid sequence of wild type and mutant VSVs.

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FIGURE 18: M Protein cDNA sequence of wild type and mutant VSVs.

FIGURE 19: M Protein amino acid sequence of wild type and mutant VSVs.

5

FIGURE 20: G Protein cDNA sequence of wild type and mutant VSVs.

FIGURE 21: G Protein amino acid sequence of wild type and mutant VSVs.

10

FIGURE 22: L Protein cDNA sequence of wild type and mutant VSVs.

FIGURE 23: L Protein amino acid sequence of wild type and mutant VSVs.

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DESCRIPTION OF PREFERRED EMBODIMENTS

The present invention relates to a novel cancer therapeutic. More specifically, this invention relates to viruses that selectively infect and inhibit tumour cell growth.

5

The following description is of a preferred embodiment by way of example only and without limitation to the combination of features necessary for carrying the invention into effect.

10

Cancer cells gain a survival advantage over their normal counterparts by acquiring mutations in growth inhibitory or apoptotic pathways and, in the case of interferons, would do so at the expense of critical antiviral defence mechanisms. As tumour cells gain a significant growth advantage by mutating interferon response genes, they will be more susceptible to virus infection.

15

By “reducing the viability” of a tumour cell it is meant either killing the tumour cell or limiting its growth for a period of time.

20

By “not a common human pathogen” it is meant a virus that is found mostly in non-human hosts, for example, but not limited to insects, rodents, and farm animals. Such viruses are not typically found within the general human population.

25

As used herein Mutant I, Mutant 1, Mut 1 and M1 refer to attenuated mutant strain T1026. Mutants II, III, IV and V (and variant nomenclature analogous to Mutant I) refer to attenuated mutants T1026R, TP3, TP6 and G31, respectively.

30

The novel cancer therapeutic of the present invention incorporates the use of at least one oncolytic virus that selectively targets tumour cells and leads to their destruction. Preferably the oncolytic virus is a Vesicular stomatitis virus (VSV), for example the Indiana strain, or other strains, or a derivative thereof. By a derivative of VSV, it is meant a VSV virus obtained by either selecting the virus under different growth conditions, or one that has been subjected to a range of selection pressures, or

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one that has been genetically modified using recombinant techniques known within the art. For example, which are not to be considered limiting in any manner, a derivative of VSV may include a mutant VSV selected following infection on a human cell that has been treated with interferon as described herein, or a VSV that displays an affinity tag useful for affinity purification.

The effectiveness of oncolytic virus suppression of tumour cell growth in part resides in the differential susceptibility of tumour cells, compared to normal cells, to viral infection. Without wishing to be bound by theory, the differential susceptibility may in part be due to the down regulation or inactivation of factors within a cell that otherwise function to protect the cell from tumorous growth and virus infection. Examples of factors that when inactivated result in tumorous cell growth, and that are also involved in mediating virus infection include but are not limited to PKR (double stranded RNA dependent kinase) and PML (Promyelocytic Leukemia gene), however, it is to be understood that other factors may also play a role.

The down regulation or inactivation of PKR, through a variety of mechanisms including but not limited to PKR-related mediators, is known to be associated with tumour cell growth, while normal cells exhibit active PKR. Furthermore, wild type cells exposed to viral infection exhibit elevated PKR expression which results in the suppression of viral replication, while cells that exhibit reduced, or no, PKR activity are susceptible to viral attack and exhibit cancerous growth. Similarly, the PML gene product functions as a tumour suppressor and it is also known to suppress viral replication.

By "differential susceptibility", it is meant a property associated with a cell that results in both tumour cell growth and the inability of the cell to suppress viral replication. Cells exhibiting differential susceptibility are preferred candidates for treatment of tumorous cell growth using the cancer therapeutic of the present invention. This differential susceptibility may be accentuated through the addition of one or more chemical agents prior to or during treatment of the tumour cell. Preferably, this chemical agent increases the resistance of a wild-type cell to viral

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infection, but has little or no effect on the response of a tumour cell to viral infection. An example, which is not to be considered limiting in any manner, of such a chemical agent is interferon.

5 By "PKR" it is meant a serine/threonine kinase that exhibits multiple functions including roles in the control of mRNA translation and gene transcription (1,2). The kinase harbors two double-stranded RNA dsRNA binding motifs in its amino terminal regulatory half and catalytic kinase domain in its carboxyl tail. Binding of dsRNA to the amino terminus induces a conformational change in the enzyme revealing and
10 activating the catalytic kinase domain. The expression of PKR is induced by several PKR-mediators, including but not limited to, interferon.

By "PKR-mediator" it is meant proteins or compounds that directly, or indirectly affect PKR activity either at the gene or protein level and include both PKR-
15 activators and PKR-inhibitors. Examples of PKR-activators include, but are not limited to STAT1 (see Figure 1), Interferon regulatory factor (IRF-1), and interferon. Examples of PKR-inhibitors, include, but are not limited to, VA RNAs, p58(IPK), factors associated with the Ras pathway, the ribosomal protein L18, or proteases that degrade PKR protein. PKR activity may also be mediated through mutations to the
20 gene encoding PKR, or to the regulatory region that drives the expression of *PKR*. These mutations may either increase or decrease PKR activity. Mutations to PKR that reduce PKR activity include, but are not limited to, the loss of dsRNA binding ability of PKR, or mutations that result in negative catalytic mutants. Mutations that increase PKR activity include, but are not limited to over-expression of PKR, or mutations that
25 resulted in a more active PKR protein.

PKR regulates translation through the phosphorylation of eIF-2 α , a factor involved in the initiation of protein translation. Once phosphorylated, eIF-2 α -GDP, forms an inactive complex with eIF-2B resulting in a rapid inhibition of protein
30 synthesis. PKR impinges on gene transcription indirectly via activation of NF κ B. This activation appears to be carried out by PKR phosphorylation of an I κ B kinase (3) which in turn phosphorylates I κ B leading to its targeted destruction.

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PKR Antiviral activity

5

Infection of a cell by many distinct virus types leads to the formation of dsRNA (e.g. as replicative intermediates) resulting in the activation of PKR and its subsequent downstream effectors (see Figure 1). In particular, protein synthesis is rapidly terminated and an apoptotic cascade is initiated (4,5). As a result of the
10 activation of PKR, the production of new virions is curtailed and the spread of virus through the organism is limited. Der et al (12) report a requirement for PKR in the induction of cellular apoptosis in response to a variety of stress inducers.

Without being bound by theory, it is possible that malignancies arise as a
15 result of multiple mutations in genes that control cell proliferation and apoptosis. PKR's role in regulating protein synthesis coupled with its antiproliferative and pro-apoptotic properties make it a target for oncogenic mutations, which directly or indirectly affect its activity.

20 As described in more detail in the examples an initial screen of several viruses using PKR -/- animals indicated that PKR null animals are susceptible to infection by Vesicular stomatitis virus (VSV). Similar results were obtained *in vitro*, where VSV infection proceeded more rapidly in PKR-/- fibroblasts, when compared to infection in PKR +/+ fibroblasts. These results demonstrate that PKR is required by mammalian
25 cells to resist infections by VSV. Furthermore, certain cell lines, for example, but not limited to primary human bone marrow, were resistant to VSV infection, while leukemia cell lines were susceptible to VSV infection.

It is contemplated that viruses related to VSV, or other viruses that exhibit
30 similar mechanisms of viral infection can be identified that exhibit the property of selectively infecting cells with reduced or no PKR activity. One of skill in the art can readily screen other viruses using the methods as described herein, for their ability to

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reduce the viability of cells, or kill cells lacking PKR activity, or PKR^{-/-} cells, PKR^{-/-} animals, or both PKR^{-/-} cells and animals.

As indicated in the examples below, pretreatment of cells with interferon
5 reduces virus infectivity by several orders of magnitude. Without wishing to be bound by theory, the addition of interferon may upregulate PKR expression resulting in this increased resistance to viral infection.

Because of its potent antiviral activity, viruses have evolved strategies to
10 circumvent PKR. For example, HIV and Hepatitis C encode proteins dedicated to the binding and inactivation of PKR (6,7). Adenovirus encodes small RNA molecules (VA RNAs) which bind to but do not activate PKR (8). Influenza virus usurps a cellular protein p58(IPK) to inhibit PKR while polio virus initiates the proteolytic degradation of PKR (9,10). Large T antigen of SV-40 appears to function downstream
15 of eIF-2 α to promote protein translation even in the presence of activated PKR (10).

PKR and Tumour Suppression

Expression of dominant negative PKR catalytic mutants in NIH 3T3 cells
20 leads to their malignant transformation and facilitates their growth as tumours in nude mouse models (13,14). A similar phenomena has been observed using PKR mutants which have lost dsRNA binding activity. Induced expression of PKR in *S. cerevisiae* leads to growth arrest in the yeast—a phenomena that can be reversed by co-expression of a non-phosphorylatable version of eIF-2 α . Therefore, PKR has anti-proliferative
25 activity and functions as a tumour suppressor.

There are several lines of evidence that PKR is inactivated, absent or reduced in expression in a broad spectrum of human malignancies:

- 30 • Oncogenic Ras mutations occur in about 30% of all human tumours while mutations in upstream Ras activators (ie EGF receptor, Neu receptor, PDGF receptor) are even more common. Mundschau and Faller (15,16) have

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described an oncogenic Ras induced PKR inhibitor. Furthermore, Strong et al (17) demonstrated that activation of the Ras pathway results in down regulation of PKR activity.

- 5 • The ribosomal protein L18 is overexpressed in primary colorectal cancer tissues and has recently been shown to bind to and inactivate PKR (18).
- Patients with 5q translocations exhibit diminished PKR expression (19-21). Interferon regulatory factor 1 (IRF-1) is a transcription factor with tumour
10 suppressor activity, which maps to the human chromosomal region 5q. PKR gene transcription is regulated in part by IRF-1.
- Human PKR maps to 2p21-22 and has been recently identified as the site of translocation in a case of acute myelogenous leukemia .
- 15 • In biopsies from poorly differentiated, highly malignant tumours, PKR protein was present at very low levels or was undetectable (23-25).

STAT1

20

STAT1 is an essential mediator of the interferon pathway and its activation results in an upregulation of PKR mRNA and protein (see figure 1).

25

There is marked deficiency in the level/activity of STAT1 protein in interferon resistant melanoma cell lines and primary melanoma biopsy material (26), in a variety of human tumour cell lines including a myeloid leukemia, cervical carcinomas, ovarian cancer, and a lung carcinoma (27), and in a gastric adenocarcinoma (28,29). Furthermore, cutaneous T cell lymphoma (CTCL) is a malignancy which in general is responsive to interferon (however frequently clinical resistance arises in a substantial
30 portion of cases). Sun et al (30) have reported that STAT1 protein is absent in a CTCL cell line suggesting that development of clinical resistance to interferon may arise due to STAT1 mutations.

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PML: Promyelocytic Leukemia Gene

PML is an interferon induced gene that normally functions as a tumour suppressor and a key regulator of Fas, TNF α and interferon induced apoptosis. Recently, Chelbi-Alix et al have shown that another normal function of the PML gene product is to suppress virus replication. The PML-RAR fusion protein functions as a dominant negative inhibitor of interferon induced apoptosis and we would predict will also make APL cells preferentially susceptible to virus infection.

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Down regulation of PKR protein or activity occurs in a broad spectrum of human malignancies. While cancer cells have attained a growth advantage and unbridled protein translation capacity by eliminating PKR or PKR-mediators, these cells have simultaneously eliminated one of the cell's primary and potent antiviral defence mechanisms. Therefore, tumour cells with reduced PKR activity will be more susceptible to infection than their normal counterparts. As indicated above, other components (e.g. STAT1 and PML) of the interferon pathway are frequently mutated in human malignancies, and loss of their activity will render tumour cells sensitive to virus infection. This differential susceptibility forms the basis for the use of viral-based cancer therapeutics of the present invention for the treatment of tumorous cell growth.

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Screening of PKR null mouse strains with several different viruses indicated that PKR null animals are capable of suppressing a number of virus infections including vaccinia, influenza and EMCV. However, Vesicular Stomatitis Virus (VSV) exhibited an ability to infect PKR $-/-$ animals. VSV, a member of the Rhabdovirus family, was observed to kill 100% of PKR null animals following intranasal infection by as little as 50 infectious virus particles (or plaque forming units, pfu). In contrast, over 20,000 times as many VSV particles were required to kill half of infected wild type littermates.

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VSV is an enveloped, negative sense RNA virus with a simple five gene genome. This is a very well characterized virus family with several serologically distinct laboratory strains and a multitude of characterized mutants. The natural hosts of VSV include insects, rodents and domestic farm animals. In general, very few North Americans have come in contact with the virus – most human infections occurring in laboratory personnel and farmers. In humans infections are either asymptomatic or manifested as mild “flu”. There are no reported cases of severe illness or death amongst infected humans.

The ability of VSV to selectively infect tumour cells over wild-type cells was also observed. Tumour cell lines, following an overnight infection exhibited a 100 to 1000 times higher rate of infection than that detected in normal primary fibroblasts. Furthermore, the cytopathic effect (cpe) was accelerated in the tumour cell cultures.

Since PKR is an interferon inducible gene product, pretreatment of cells with interferon prior to exposure to VSV was tested to determine the effect of viral infection. Wild-type cell cultures, that were pretreated with interferon, were resistant to VSV infection, while tumour cell lines, for example, but not limited to, fibrosarcoma, melanoma, prostate carcinoma, leukaemia and ovarian sarcoma, were susceptible to virus infection (see Table 1, Example 2; Figure 2). Lung carcinoma cells (LC80) were also susceptible to VSV infection in the presence and absence of interferon (data not presented). However, several tumour cell lines were resistant to VSV infection in the presence of interferon.

Ovarian carcinoma cells, fibrosarcoma, lung carcinoma, melanoma, prostate carcinoma, lung carcinoma, and leukaemia cells are VSV sensitive, and this sensitivity was maintained in the presence of interferon, therefore, such tumor cells and cancers derived therefrom may be particularly amenable to VSV treatment. However, other cancers may also be amenable to viral treatment as described herein. Studies with respect to VSV sensitivity using primary tumour material is readily available in ascites fluid. Further, since the tumour is contained within the peritoneal cavity it may prove particularly suited to localized administration of a virally based

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therapeutic. In this regard, live tissue from patient's ascitic fluid can be tested for the ability of the tumour cells to support VSV infection in the presence and absence of interferon.

5 It is expected that VSV will have therapeutic activity *in vivo*, and will have the ability to kill distant (metastatic) tumour growths. To date no significant organ pathology in treated mice have been observed, however, the kinetics of VSV viremia need to be further studied. Nude mice, implanted with human melanoma cells received VSV, or additional melanoma cells infected *in vitro* with VSV (see Example
10 5), to ensure the continuous production of infective particles to the tumour over a several hour period, via injection (Figure 5). In mock-injected animals (VSV(-); injection with vehicle alone) tumours grew continuously over the course of the experiment. Animals which received only pure virus showed initially continuous growth of tumours over the first four day period, after this time the tumours began to
15 reduce in size and continued to do so over the course of this experiment. Tumours that were injected with infected cells stopped growing and regressed to small hard nodules resembling scar tissue. In some of the larger injected tumours, ulcers formed on the tumour within 1-2 days, (see Figure 6). While both injection of purified virus and infected melanoma cells caused significant regressions, infected producer cells were
20 more effective.

 Studies with an immunocompetent mouse tumour model (i.e. as described by Strong et al; 17) will examine the affects of antibody response to therapeutic VSV infection, and determine if VSV infection of tumour cells increases their
25 immunogenicity and promotes recognition of tumour antigens by the host organism.

 Primary human bone marrow was also found to be resistant to VSV infection in the absence of interferon pretreatment (see Table 1, Example 2), indicating that these cells have an innate resistance to VSV infection. In contrast two leukemia cell
30 lines (M07E and L1210) were also tested and found to be susceptible to VSV infection as evidenced by cytopathic effect, virus growth and loss of cell viability.

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While the results disclosed herein relate to VSV, it is to be understood that one of skill in the art, by following the methods outlined in this document, will be readily able to screen other VSV strains, derivatives of VSV including mutants of VSV, or related viruses for the ability to selectively kill tumour cells. There are several other serologically and biologically distinct strains of VSV, which can be tested for this property. Such VSV strains include, but are not limited to New Jersey, Piry, Coccal, and Chandipura. Identification of other suitable serologically unrelated strains may be useful if sequential VSV injections are required to completely eradicate tumours. Furthermore, picornaviruses (eg rhinoviruses) are known to be relatively innocuous to normal human tissues yet grow extremely well in transformed cells in tissue culture, and these viruses may also be used. Furthermore, combinations of viruses may be used to enhance the cytopathic effect observed with VSV.

In order to determine whether the presence of either a normal or tumor cell could affect the other cell type (either normal and tumor cell) and alter the resistance or susceptibility of either of these cells to VSV infection, normal cells and fibroblasts were co-cultured in the presence of VSV. The culture was infected at an moi of 0.1 pfu/cell and the infection allowed to proceed in the presence or absence of interferon. At 0, 12 and 24 hours (Figure 4) the cultures were fixed and stained with antibodies to large T antigen (red nuclei) to detect the 293T cells and with DAPI (blue nuclei) which stains all cell types (Figure 4). The number of 293T cells (red nuclei) steadily declined during the time course and displayed severely condensed or fragmented nuclei characteristic of a cell dying from virally induced apoptosis. This selective destruction of the transformed cells was seen both in the presence and absence of interferon. The normal fibroblasts did not develop nuclear changes nor were their numbers reduced in response to VSV infection even though 293T cells were producing copious amounts of virus within the co-culture. This indicates that mixtures of cell populations may be treated with VSV while still maintaining tumor cell sensitivity, and normal cell resistance to VSV.

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In addition there are a number of mutants of VSV, for example, but not limited to mutants which are impaired in the shut down of host protein synthesis or are more

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or less sensitive to interferon, which may exhibit differential infection between normal and tumour cells. For example, which is not intended to be limiting in any manner, other viral mutants are known which show tropism for STAT1 or PKR negative cells include an influenza virus strain which is unable to inactivate PKR has been described
5 (36) Adenovirus mutants which lack the PKR inactivating VA gene are known to grow better in the absence of PKR.

As described herein, VSV mutants were isolated that grew poorly on interferon responsive cells. These mutants were selected based upon their ability to
10 form small plaques in monolayers of interferon-responsive cells. On interferon non-responsive cells (i.e. tumor cells) these mutants form large plaques. The selection of mutants by size of plaque in interferon-responsive cells allows for the isolation of virus that grows poorly in normal cells. However, other VSV mutants may be obtained under different selection criteria. Mutants isolated using interferon-
15 responsive cells were amplified and tested for their ability to kill tumour and normal cells. The rationale here is that VSV mutants, which can induce interferon in target cells, would limit their own replication in an interferon responsive cell population. These same viruses would however have unrestricted growth in tumour cells that lack interferon responsiveness. These mutants are of value, as they have even less
20 cytopathic effect on normal tissues while maintaining oncolytic activity than wild type VSV.

Four mutants (Mut 1-4) were obtained based on their ability to form plaques in monolayers of interferon-responsive cells. These mutants, and wild type virus (moi of
25 1.0 pfu/cell) were used to infect melanoma cells and normal human foreskin fibroblasts. All of the mutants were able to kill tumour cells efficiently but normal cells infected with the mutants even after long periods of infection appeared completely uninfected. At this same moi wild type VSV demonstrated a cytopathic effect on the normal cells. These results indicate that the mutant virus have a greater
30 therapeutic effect in that they kill tumour cells efficiently while sparing normal cells, and that they also have the ability to produce more virus particles and increase virus spread throughout the tumour (see Example 4). Surprisingly these mutants grew more

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rapidly than wild type VSV (Indiana) in HCT 116 colon carcinoma cells but not in OSF7 cells (See Example 21 and Figures 10A and 10B). VSV mutants that display rapid growth in the tumour cell of interest but not in normal cells are preferred.

5 Earlier experiments indicated that PKR $-/-$ mice were killed with VSV by several routes of infection, however, these mice were not affected by intravenous injections of the virus. In order to determine whether plasma components were inactivating the virus upon contact, VSV produced from several sources including within mouse L cells was incubated with human serum (from normal uninfected
10 donor) and the virus titer after incubation determined (Example 6). The viral titer of L cell-produced VSV dropped four hundred fold, while VSV produced in human melanoma cells was unaffected by incubation in plasma. These results indicate that the choice of cell line for the production of VSV is critical. Based on this observation it is possible to screen human cell lines for those that produce optimum amounts of
15 virus that is not sensitive to human serum.

Without wishing to be bound by theory, it may be that the difference in these two virus preparations reflects the nature of the cohort of proteins found on the surface of the virus producing cells. As part of its replicative cycle, VSV buds through
20 the plasma membrane and acquires cellular protein on its envelope. Certain proteins found on L cells when expressed in the context of the virus particle could activate complement. Indeed, it has been shown earlier that retrovirus particles produced in certain mouse cells are inactivated by serum while the same virus produced in a subset of human cell lines was unaffected by plasma. (Pensiero, M.N., et al. Hum Gene
25 Ther, 1996. 7:1095-1101).

Conventional techniques for VSV production are difficult to scale up for industrial production. Therefore, the purification of VSV, using an affinity matrix, for example affinity chromatography was explored. (See Example 7). However, other
30 protocols for affinity purification may also be used as known within the art, for example, but not limited to, batch processing a solution of virus and affinity matrix, pelleting the VSV-bound matrix by centrifugation, and isolating the virus. In order to

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provide the virus with an affinity tag to be used for the purification of the virus, the virus may be genetically modified, using techniques well known in the art, to express one or more affinity tags on its surface, preferably as a fusion viral envelope protein, or producer cell lines may be engineered to express one or more affinity tags on their plasma membranes which would be acquired by the virus as it buds through membrane, however, endogenous viral envelope proteins may also be used. One well characterized affinity tag involve the use of Histidine residues which binds to immobilized nickel columns, however, it is to be understood that other affinity tags may also be employed.

Cell lines can be prepared that act as a universal producer of VSV, or other virus, that expresses a chimeric VSV protein with nickel binding, or other affinity tag properties. This universal producer cell may be used for the production of a chimeric protein (affinity tag) for any enveloped virus (including all enveloped RNA and DNA viruses). For the purification of virus which bud through the nuclear membrane (such as Herpes virus), a tag to be expressed on the viral envelope protein expressed in the nuclear membrane is engineered.

Other affinity tags include antibodies, preferably an antibody which recognizes a particular peptide under conditions of low salt, low temperature or in the presence of a critical cation/anion. Physiological salt concentrations, thermal elution or chelation could effect elution. Antibodies generated against di or tripeptides may also be used for purification. In this manner, two or more of these tags on the surface of a single virus particle would allow for the sequential affinity purification of the virus.

VSV may be genetically modified in order alter its properties for use *in vivo*. Methods for the genetic modification of VSV are well established within the art. For example a reverse genetic system has been established for VSV (Roberts A. and J.K. Rose, Virology, 1998. 247:1-6) making it possible to alter the genetic properties of the virus. Furthermore, standard techniques well known to one of skill in the art may be used to genetically modify VSV and introduce desired genes within the VSV

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genome to produce recombinant VSVs (e.g. Sambrook *et al.*, 1989, A Laboratory Manual. New York: Cold Spring Harbor Laboratory Press).

VSV may be targeted to a desired site *in vivo* to increase viral efficacy. For example, modification of VSV G protein to produce fusions that target specific sites may be used to enhance VSV efficiency *in vivo*. However, it is to be understood that other protein targets in addition to the VSV G protein may also be modified to produce such fusion proteins. Such fusion proteins may comprise, for example, but not limited to, Single chain Fv fragments (Lorimer, I.A., et al. Proc. Natl. Acad. Sci. U.S.A., 1996. 93:14815-20) that have specificity for tumour antigens. An example of such a single chain Fv fragment that may be used to prepared a VSV G fusion protein, is an Fv fragment that targets a mutant EGF receptor found on about 80% of human breast tumour cells.

VSV may also be modified to express one or more suicide genes capable of metabolizing a pro-drug into a toxic metabolite thereby permitting VSV infected cells to be killed by administration of a pro-drug. For example, VSV comprising the herpes virus thymidine kinase gene or the cytosine deaminase gene encodes an enzyme that can convert ganciclovir or 5-FC, respectively, into a toxic compound. However, it is to be understood that other suicide genes may also be employed. As it is well established that ganciclovir metabolites kill not only cell expressing HSV TK but also cells in the immediate vicinity, rVSV comprising these suicide genes exhibit several advantages. For example, the effective killing by the virus is increased since one infected cell kills ten or more surrounding tumour cells, furthermore rVSV comprising a suicide gene permits the elimination of virus if desired from an individual infected with the virus. This may be important in situations where it is unclear how VSV may affect an individual. For instance, an immune comprised individual may be unexpectedly susceptible to VSV. Thus the addition of a suicide gene would be an improvement on the safety of the viral therapeutic.

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VSV may also be modified by the introduction of a mammalian gene product. Such a mammalian gene product would limit VSV growth in normal cells, but not the

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growth of VSV in tumour or diseased cells. For example, rVSV capable of expressing one or more transactivators of p53, activates apoptotic pathways in normal cells but not tumor cells. Such rVSVs therefore selectively limit virus spread in normal tissues. However, it is to be understood that other mammalian gene products may also be expressed within VSV for this purpose. Another example, which is not to be considered limiting in any manner is the PKR gene. A rVSV expressing the PKR gene limits virus replication in all normal cells, however, in cells that express PKR inhibitors, the virally encoded PKR is inactivated. An example of a cell that expresses one or more PKR inhibitors is a chronically Hepatitis C infected cell. Since Hepatitis C encodes and expresses two known inhibitors of PKR (i.e. NS5A and E2), a VSV encoded PKR gene product is be neutralized, and VSV allowed to replicate freely.

The above description is not intended to limit the claimed invention in any manner, furthermore, the discussed combination of features might not be absolutely necessary for the inventive solution.

The present invention will be further illustrated in the following examples. However it is to be understood that these examples are for illustrative purposes only, and should not be used to limit the scope of the present invention in any manner.

Example 1: PKR negative cells are susceptible to VSV infection

***In vivo* experiments**

Initial studies were directed to identifying viruses that are capable of infecting PKR^{-/-} animals and cells. Using homologous recombination strategies, PKR null mouse strains were generated (35) and tested for their ability to fight virus infections. Since these mice are PKR^{-/-}, they should be susceptible to virus infection. Several species of virus were administered to PKR null animals over a range of concentrations.

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Infection of PKR null mice:

A PKR null mouse line was generated using conventional knockout technology (Abraham, N., et al., J Biol Chem, 1999. 274:5953-5962.). Groups of five female mice, 3 months of age or greater, were infected intranasally with varying amounts of vesicular stomatitis virus (Indiana strain). Age matched wild type animals were infected in parallel and both sets of animals were monitored on a daily basis for signs of infection. These include, hydration, piloerection, activity level, appetite, hind limb paralysis, respiratory rate, body weight and any other symptoms indicating that the animal was in distress.

Wild type animals showed few and only transient symptoms at multiplicities of infection up to 10^5 pfu with VSV. In contrast, PKR null animals very rapidly developed dehydration, piloerection, loss of appetite, rapid respiratory rate, decreased activity and squinting crusty eyes. At high doses of VSV infection (10^5 pfu) the animals showed symptoms in less than 24 hours and usually succumbed to the infection within 48 hours. At doses of infection as low as 25 pfu, 100 percent of the PKR null animals died of VSV infection within 5 days. In separate experiments groups of five wild type and PKR null animals were sacrificed at 48 hours post infection with VSV and organs were removed to assess viral titres. In the PKR animals titres in excess of one million PFU / ml of lung homogenate were found at this time while in wild type animals virus titres ranged from 0 to 100 pfu per ml of lung homogenate. In the wild type and PKR null animals similar amounts of virus were found in the brain. The remainder of the tissues in both mouse strains had undetectable virus at this time post infection.

Vesicular stomatitis virus, a member of the Rhabdovirus family was able to kill 100% of PKR null animals following intranasal infection by as little as 50 infectious virus particles (or plaque forming units, pfu). In contrast, over 20,000 times as many VSV particles were required to kill half of infected normal littermates. These results indicate that PKR null animals are capable of suppressing a number of virus infections including vaccinia, influenza and EMCV. However, VSV exhibited

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an ability to infect PKR-/- animals. These results also indicate that PKR is required by mammalian cells to resist infections by VSV (Indiana laboratory strain).

Example 2: Selective killing of tumour cells with VSV

5 *In vitro* experiments

Several tumour cell lines were chosen at random from the Ottawa Regional Cancer Center and tested for their susceptibility to VSV infection. Primary fibroblast cultures from healthy adult volunteers or primary bone marrow samples from healthy
10 donors were used as control cells.

Infection of tumour cells with VSV:

As a first test of the oncolytic properties of VSV, virus production and
15 cytopathic effect following an overnight incubation with VSV was assessed. Monolayers of cells were incubated with the Indiana strain of VSV at a multiplicity of infection (moi) of 0.1 plaque forming units (pfu). After allowing virus to adsorb for 30 minutes at 37 C, the cultures were rinsed thoroughly with phosphate buffered saline (PBS) and then cultured an additional 18 hours at 37 C. At this time, the
20 cultures were examined microscopically for cytopathic effect (cpe) and photographed. The 18 hour supernatant was removed and virus titres per ml of medium determined. In some experiments, cultures were preincubated for 12 hours with human alpha interferon (100 units/ml) prior to infection.

25 To examine the kinetics of infection of the assorted cell types a modified cpe assay (Heise, C., et al., Nat Med, 1997. 3:639-645) was used. Essentially, monolayers of cells were infected at an moi of 0.1 pfu in a 12 well plate. At time 0 and every 12 hours subsequent up to 48 hours, one well of infected cells was fixed with 0.5 ml Leukostat fixative (Fisher Diagnostics) for 2 minutes. At the end of the experiment
30 monolayers were stained with Leukostat stains 1 and 2 following manufacturers instructions. Since PKR is an interferon inducible gene product, the pretreatment with interferon, 100 units/ml of human alpha interferon 12 hours prior to infection, was

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tested to determine if interferon could enhance protection within the assorted cell cultures. The data are presented in Table 1 and Figures 2-3.

TABLE 1: Cell lines tested for VSV sensitivity

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Cell line	cell type	Reference	Untreated Overnight Virus Yield	Interferon Overnight Virus Yield
OSF 16	human normal fibroblast	ORCC ¹	1 X 10 ⁵ pfu	0 pfu
AG1522	human foreskin fibroblast	[20]		0 pfu
OSF 7	human normal fibroblast	ORCC	1 X 10 ⁶	0 pfu
OSF 12	human normal fibroblast	ORCC	2 X 10 ⁵ pfu	0 pfu
MN11	mouse fibrosarcoma	[21]	1 X 10 ⁸	1 X 10 ⁴
A2780	human ovarian carcinoma	[22]	2 X 10 ⁸	1 X 10 ⁷
H-1078	normal human bone marrow	ORCC	0 pfu (moi 10 pfu)	Not determined
M07E	human leukemic cell line	[23]	2 X 10 ⁶ (moi 1.0 pfu)	Not determined
L1210	mouse leukemic cell line	[24]	4 X 10 ⁶	2 X 10 ⁴
SK-MEL3	human melanoma	[25]	Not determined: cpe assay positive	Not determined: cpe assay positive
LNCAP	human prostate carcinoma	[26]	Not determined: cpe assay positive	Not determined; cpe assay positive
293T	fibrosarcoma transformed with SV-40 Large T and Adeno E1A	[27]	1 X 10 ⁸	8 X 10 ⁷
OVCA 432		[28]	1 X 10 ⁷	0 pfu
C13	ovarian carcinoma	[29]	1 X 10 ⁸	1 X 10 ⁵
OVCA 3		[30]	5 X 10 ⁷	Not determined
COS	Large T transformed simian kidney cell line	[31]	2 X 10 ⁸	Not determined
HCT 116	colon carcinoma	[32]	Not determined: cpe assay positive	Not determined cpe assay positive

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OVCA 420		[28]	1×10^8	3×10^6
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1 established at the ORCC from forearm biopsy.

From the data in Table 1 it can be seen that although normal human fibroblasts
5 can support viral replication, the amount of virus produced and the progression to cell
lysis was substantially delayed when compared to tumour cells. An even more
substantial difference in virus production was observed following pretreatment with
interferon. While normal human fibroblast monolayers were completely protected
from the cytolytic affect of VSV by interferon, tumour cells remained sensitive,
10 producing copious amounts of viral particles and rapidly undergoing cytolysis.

Other cells lines, including a lung carcinoma cell line (LC80) and a leukaemia
cell line, AML5 (acute myelogenous leukemia 5) cells were also found to be
effectively killed by VSV. In the case of AML5, at a moi of 1.0 pfu/ml cells were
15 completely killed within 24 hours, while at 0.0001 pfu/ml the cells were killed within
72 hours, further indicating the sensitivity of leukaemia cells to VSV.

As can be seen in Figure 2, monolayers of tumour cells were much more
rapidly destroyed by VSV infection as compared to normal human fibroblasts. The
20 human melanoma cell line SK-MEL3, the LNCaP prostate cancer cell line and the
ovarian carcinoma cell A2780 all showed substantial cpe as early as 12 hours post
infection. Although the normal human fibroblast cultures were infected and capable
of producing virus (see Table 1), the kinetics of infection was substantially slower
than in the three tumour cell lines tested in this experiment. In addition, as with the
25 overnight virus growth assay (Table 1, Figure 2), interferon alpha treatment
completely protected the normal human fibroblasts, but was ineffective at protecting
the three tumor cell lines from the cytopathic effect of VSV.

The results obtained for Table 1 demonstrate that a screening strategy for
30 determining the types of tumours which are susceptible to killing by VSV may be
employed using for example, but not limited to, the NIH/NCI standard panel of

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tumour cell lines available from ATCC. These cell lines are screened in order to determine the time to complete cpe and/or virus growth using various initial multiplicities of infection. These experiments are done in the presence and absence of interferon so that the number of and types of tumours that are VSV sensitive and are
5 resistant to interferon's antiviral activity are determined.

VSV Treatment of Leukemia

VSV does not productively infect bone marrow stem cells , even at high moi
10 of 10 pfu/cell (H-1078; Table 1). The treated cultures retained all of their stem cell characteristics. Two leukemia cell lines (MO7E and L1210; Table 1) were killed following an overnight infection and produced large amounts of virus.

To determine whether VSV could kill primary leukemia cells from a cancer
15 patient, a peripheral blood sample was obtained from an AML patient and white blood cells collected and plated in RPMI media plus 10% FBS (10^7 /well in 6 well plate, each infection in duplicate). Cells were mock infected or infected at an moi of 10.0/cell. VSV selectively killed myeloid leukemic cells as indicated by the decrease in the percentage of blast cells (leukemic blasts), while the overall cell number was
20 minimally affected (i.e. neutrophils flourished). The leukemic sample produced titres of VSV exceeding 10^7 pfu/ml at 16 hours post infection. The number of blast cells in the sample was dramatically reduced at 21 hours post infection while the proportion of normal neutrophils increased. Mock infected cells (-VSV) contained almost 70% blast cells in a monolayer, while in cells infected with VSV (+VSV) normal cells
25 predominated. These results demonstrate VSV is able to preferentially kill primary leukemic blast cells while sparing normal blood cells.

Example 3: Killing of tumour cells in mixed cultures:

30 Normal human fibroblasts and 293T tumour cells were co-cultured in a 50:50 mixture. Since 293T cells express the large T antigen which is not found in normal cells, the two cell types can be distinguished by immunofluoresence.

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In this experiment cultures were infected at an moi of 0.1 pfu/cell and the infection allowed to proceed in the presence or absence of interferon. At 0, 18 and 24 hours (Figure 4) the cultures were fixed and stained with antibodies to large T antigen (red nuclei) to detect the 293T cells and with DAPI (blue nuclei) which stains all cell types (Figure 4). Initially both cell types displayed a spindle-like morphology with large oval nuclei. After 18 hours the number of 293T cells (red nuclei) were reduced and many of the remaining 293T cells displayed altered nuclear morphology. By 24 hours post-infection very few 293T cells were detected and those few that remained displayed severely condensed or fragmented nuclei characteristic of a cell dying from virally induced apoptosis.

This selective destruction of the transformed cells was seen both in the presence and absence of interferon. The normal fibroblasts did not develop nuclear changes nor were their numbers reduced in response to VSV infection even though 293T cells were producing copious amounts of virus within the co-culture.

Example 4: VSV Mutants as Oncolytic Agents:

VSV mutants were isolated based upon their ability to form small plaques in monolayers of interferon-responsive cells, as compared to the size of plaques in monolayers of interferon-nonresponsive cells. Viral isolates, which form small plaques in interferon-responsive cells were picked, amplified and re-cloned. Mutants isolated in this way were amplified and tested for their ability to kill tumour and normal cells. The rationale here is that VSV mutants, which can induce interferon in target cells, would limit their own replication in an interferon responsive cell population. These same viruses would however have unrestricted growth in tumour cells that lack interferon responsiveness. These mutants would be of value, as they should have even less cytopathic effect on normal tissues while maintaining oncolytic activity.

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Four mutants (Mut 1-4) were obtained based on their ability to form small plaques in monolayers of interferon-responsive cells. These mutants were initially identified by Dr. Lauren Poliquin (University of Quebec at Montreal) and provided by him. After five rounds of plaque purification, these mutants and wild type virus (moi of 1.0 pfu/cell) were used to infect melanoma cells and normal human foreskin fibroblasts and titres of released virus determined 12 and 24 hours post infection.

All of the mutants were able to kill tumour cells efficiently but normal cells infected with the mutants even after long time points appeared completely uninfected. At this same moi wild type VSV demonstrated a cytopathic effect on the normal cells. It was also observed that all of the VSV mutants produced approximately ten times more virus than the wild type VSV following an overnight infection of melanoma cells. On normal cells, while the Mutants 1-4 had significantly less cytopathic effect than wild type VSV, similar amounts of virus were produced from the infected cultures. These results indicate that the mutant virus have a greater therapeutic effect in that they kill tumour cells efficiently while sparing normal cells, and that they also have the ability to produce more virus particles and increase virus spread throughout the tumour.

Example 5: Infection of Nude Mice Bearing Human Tumour Xenografts:

Nude mice were implanted with human melanoma cells and divided into groups. One group received a mock injection (VSV(-)), and the other were injected with wild type VSV or injected with additional melanoma cells infected *in vitro* with VSV for one hour prior to injection into the tumour site in order to deliver cells that would continuously produce infective particles to the tumour over a several hour period (VSV(+)). The results of these experiments are seen in Figure 5 which shows the average of the tumour area with time in treated and mock injected animals.

In the case of mock-injected animals (VSV(-); injection with vehicle alone) tumours grew continuously over the course of the experiment. Animals which

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received only pure virus showed initially continuous growth of tumours although at day 4 post infection the tumours began to shrink and continued to do so over the course of this experiment. Tumours that were injected with infected cells demonstrated the most dramatic regressions. Essentially most tumours stopped
5 growing and regressed to small hard nodules resembling scar tissue.

In some of the larger injected tumours, ulcers formed on the tumour within 1-2 days, (see Figure 6), followed by continuous shrinkage of the once rapidly growing malignancy. While both injection of purified virus and infected melanoma cells
10 caused significant regressions, infected producer cells were more effective.

Example 6: The choice of cell line for producing VSV affects sensitivity of the virus to plasma:

15 Earlier experiments indicated that PKR $-/-$ mice were killed with VSV by several routes of infection, however, these mice were not affected by intravenous injections of the virus. Without wishing to be bound by theory, this could be because the PKR $-/-$ vascular endothelial cells provide a barrier to tissue infection or because plasma components were inactivating the virus upon contact. To test this latter idea
20 VSV produced from several sources including within mouse L cells was incubated with human serum (from normal uninfected donor) and the virus titer after incubation determined.

Following incubation of VSV in human serum, the viral titer of L cell-
25 produced VSV dropped four hundred fold. On the on the other hand VSV produced in human melanoma cells was unaffected by incubation in plasma.

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These results indicate that the choice of cell line for the production of VSV is critical. Based on this observation it is possible to screen human cell lines for those that produce optimum amounts of virus that is not sensitive to human serum.

5 **Example 7: Strategy for VSV concentration and purification**

Conventional techniques for VSV production include centrifugation steps and gradient purification - both of these approaches difficult to scale up for industrial production. Therefore, alternate protocols for the purification of VSV, for example
10 affinity columns for the simultaneous concentration and purification of virus particles has been explored.

In order to provide the virus with an affinity tag to be used for the purification of the virus, endogenous proteins may be used or, the virus may be engineered to
15 express one or more affinity tags on its surface, or producer cell lines may be engineered to express one or more affinity tags on their plasma membranes which would be acquired by the virus as it buds through membrane. The unique viral envelope proteins can be purified using affinity chromatography.

20 One such affinity tag may involve the use of Histidine residues which binds to immobilized nickel columns, however, it is to be understood that other affinity tags may also be employed. This approach has been tested using the bacterial virus M13. Using a phage peptide display system (Koivunen, E., et al., J. Nucl Med, 1999. 40:883-888), viral particles expressing Histidine containing peptides which bind to
25 nickel columns, but that can be eluted with imidazole, were selected including:

CTTHRHHSTNC (SEQ ID NO:1); CLNAHRTTHHHC (SEQ ID NO:2);
CHGLHSNMRHC (SEQ ID NO:3); CHHHHRLNC (SEQ ID NO:4); CHSHHHRGC
(SEQ ID NO:5); CWDHHNHHC (SEQ ID NO:6); CDNNHHHHC (SEQ ID NO:7);
CHHHRISSHC (SEQ ID NO:8). The expression of these peptides on the surface of

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M13 phage resulted in the purification concentration of the virus on nickel resins and their elution using low concentrations of imidazole.

One or more of these sequences can be integrated into the VSV G protein to result in an increased concentration of the viral particles bearing these peptides on nickel residues. The eluted virus is expected to retain its infectivity.

In this manner a cell line that can be a universal producer of VSV, or other virus, that expresses a chimeric VSV protein with nickel binding properties is produced. This universal producer cell may be used for the production of such a chimeric protein (affinity tag) for any enveloped virus (including all enveloped RNA and DNA viruses). For the purification of virus which bud through the nuclear membrane (such as Herpes virus), a tag to be expressed on the viral envelope protein expressed in the nuclear membrane is engineered.

15

Other affinity tags include antibodies, preferably an antibody which recognizes a particular peptide under conditions of low salt, low temperature or in the presence of a critical cation/anion. Physiological salt concentrations, thermal elution or chelation could effect elution. Antibodies generated against di or tripeptides may also be used for for purification. In this manner, two or more of these tags on the surface of a single virus particle would allow for the sequential affinity purification of the virus.

20

Example 8: Use of VSV to treat chronic infections

Some human disorders arise as a result of chronic viral infections including latent herpes infection, hepatitis, AIDS and cervical cancer. In each of these cases, the causative viral agent has evolved mechanisms to inactivate components of the interferon response pathway including PKR (e.g. Chelbi-Alix, M.K. and H. de The, Oncogene, 1999. 18:935-941;. Gale, M.J., Jr., et al., Virology, 1997. 230: 217-227;

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Gale, M.J., et al., Clin Diagn Virol, 1998. 10:157-162; Gale, M., Jr. and M.G. Katze, Methods, 1997. 11:383-401; Barnard, P. and N.A. McMillan, Virology, 1999. 259:305-313). Therefore, the administration of VSV, or interferon inducing VSV mutants, or a combination thereof, to individuals suffering from these disorders, selectively ablates the chronically infected cells. Further therapeutic efficacy could be found by targeting through cell or viral receptors only the chronically infected cells.

Example 9: Genetic modification of VSV

A reverse genetic system has been established for VSV (Roberts A. and J.K. Rose, Virology, 1998. 247:1-6) making it possible to alter the genetic properties of the virus.

Targeting VSV to desired sites *in vivo*

Presently VSV can bind to most mammalian cell types although its replication once inside the cell can be restricted (i.e. by interferon responsive gene products including PKR). Thus the effective dose of virus that can actually find target cells (i.e. tumour cells) for productive infection can be greatly limited simply by the "sink" that other normal tissues provide. Therefore, VSV may be genetically modified in order to bind and infect only tumour cells.

Recombinant DNA techniques well known in the art (e.g. Sambrook *et al.*, 1989, A Laboratory Manual. New York: Cold Spring Harbor Laboratory Press) are used to modify VSV G protein. Single chain Fv fragments (Lorimer, I.A., et al. Proc. Natl. Acad. Sci. U.S.A., 1996. 93:14815-20) that have specificity for tumour antigens are fused to VSV G protein. An example of such a single chain Fv fragment is one that targets the mutant EGF receptor that is found on about 80% of human breast tumour cells.

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Expression of suicide genes within VSV

The VSV genome is modified so that it comprises the herpes virus thymidine kinase gene or the cytosine deaminase gene. Both of these genes encode enzymes which can convert pro-drugs into toxic compounds (e.g. ganciclovir or 5-FC). Viruses modified in this way express these suicide genes, thereby permitting VSV infected cells to be killed by administration of the pro-drug. This provides two advantages since (1) it is well established that ganciclovir metabolites kill not only cell expressing HSV TK but also can cells in the immediate vicinity. This "by-stander effect" can increase the effective killing by the virus (i.e. one infected cell could result in the killing of ten or more surrounding tumour cells); and (2) having a VSV with a suicide gene could allow the elimination of virus if desired from an individual infected with the virus.

Controlling VSV growth *in vivo*

15

A mammalian gene product is introduced within VSV to limit VSV growth in normal cells, but this gene product does not affect VSV growth in tumour or diseased cells.

20

Recombinant VSVs (rVSV) comprising one or more transactivators of p53, activate apoptotic pathways in normal cells but not tumour cells. Such rVSVs limit virus spread in normal tissues but allow virus growth in tumour cells.

25

rVSV comprising the PKR gene limits virus replication in all normal cells, however, in cells that express PKR inhibitors, the virally encoded PKR is inactivated. An example of a cell that expresses one or more PKR inhibitors is a chronically Hepatitis C infected cell. Since Hepatitis C encodes and expresses two known inhibitors of PKR (i.e. NS5A and E2), a VSV encoded PKR gene product is be neutralized, and VSV allowed to replicate freely.

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Example 10. Progressive loss of interferon responsiveness with oncogenic transformation

5 Murine fibroblasts at various stages of transformation, either pretreated with 100 units of interferon alpha or left untreated, were infected with WT Indiana VSV at an MOI of 0.1 pfu/cell. Viral production was measured 18 hours pi by standard plaque assay. MEF: mouse fibroblast primary cultures isolated from Balb/C mouse embryos. NIH 3T3 cells: immortalized mouse embryo fibroblasts. PVSrc: NIH 3T3
10 cells transformed with the viral src gene. MOP 8: NIH 3T3 cells transformed with the polyoma virus Large T antigen. Results are shown in Table 2.

In this example, loss of interferon responsiveness correlates with susceptibility to VSV infection and progression of the malignant phenotype. The MEF cells are mortal (ie have a limited lifespan in culture) and completely interferon responsive.
15 NIH 3T3 cells although not tumourigenic are immortalized and are about ten thousand fold less responsive to interferon than MEFs. The PVSrc and MOP 8 cells are fully tumourigenic, support robust VSV replication and are minimally protected by interferon treatment.

20 **TABLE 2**

Cell Line	Viral Titre (pfu/ml)	
	Untreated	IFN- α
25 MEF (Mouse Embryonic Fibroblast)	4×10^6	<10
NIH3T3	8×10^7	1×10^4
PVSrc	3×10^9	2×10^7
MOP 8	1×10^8	5×10^6

30

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Example 11. Virus yield after overnight infection of various cell lines either untreated or treated with IFN

A variety of normal and transformed cell lines were either untreated or pre-
 5 treated with 100 units of IFN- α , infected at an MOI of 0.1 pfu/ml with WT Indiana VSV and incubated for 18 hours at 37 °C. Culture media from each sample was titred for VSV production. Results are shown in Table 3.

This example demonstrates that viral production is ten to ten thousand times more efficient in a range of tumour cell types as compared to normal primary tissues.
 10 In the presence of interferon alpha, virus production in normal primary cells is almost completely blocked while in tumour cells interferon has little or no effect on VSV replication.

TABLE 3

15	Cell Line	Viral Titre (pfu/ml)	
		Untreated	IFN- α
	OSF7 (primary normal human fibroblast)	1×10^6	<10
	OSF12 (primary normal human fibroblast)	2×10^5	<10
20	OSF16 (primary normal human fibroblast)	1×10^5	<10
	PrEC (primary normal human prostate epithelium)	8×10^6	<10
	HOSE (primary normal human ovarian surface epithelium)	1×10^7	<1000
	A2780 (human ovarian carcinoma)	2×10^8	1×10^7
	OVCA 420 (human ovarian carcinoma)	1×10^8	3×10^6
25	C13 (human ovarian carcinoma)	1×10^8	1×10^5
	LC80 (human lung carcinoma)	2×10^9	6×10^7
	SK-MEL3 (human melanoma)	1×10^9	1×10^9
	LNCAP (human prostate carcinoma)	4×10^9	5×10^9
	HCT116 (human colon carcinoma)	1×10^9	2×10^9
30	293T (HEK cells transformed with T antigen and Ad virus E1A)	1×10^8	8×10^7

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Example 12. LD₅₀ for WT and mutant VSV delivered intranasally to PKR^{+/-} (129xBalb/c) mice.

5 8-10 week old female mice were anaesthetised and infected intranasally with virus diluted in 50 µl of phosphate buffered saline (PBS) into the nares of each animal (PKR^{+/-} ; 129 x Balb/c strain). Lethal dose 50 values were calculated using the Korler-Spearman method. Results are shown in Table 4.

10 This example demonstrates that mutants I, II and III in particular, are attenuated as compared to the wild type Indiana strain of virus when tested for toxicity in 129 X Balb/c mice.

TABLE 4

15

Virus	Intranasal LD ₅₀ (pfu)
WT Indiana	1 x10 ⁴
Mutant I	1 x10 ¹⁰
20 Mutant II	>1 x10 ¹⁰
Mutant III	3 x10 ⁸
Mutant IV	<1 x10 ⁵

25

Example 13. PKR^{-/-} mice are exquisitely sensitive to VSV compared to various PKR^{+/+} mouse strains.

30 PKR^{-/-} and PKR^{+/+} mice were infected intranasally at various doses and their survival monitored over time. All PKR^{-/-} mice succumbed to the infection between days 2 and 5 depending on the dose, while control mice remained alive beyond this point. Results are shown in Table 5.

 This example demonstrates the importance of the PKR gene product in the

resistance of mice to VSV infection.

TABLE 5

5	Genetic Background		IN Dose (pfu)	Survival at day 5
	PKR ^{+/+}	Balb/c	5x10 ⁴	5/5
		CD-1	5x10 ⁴	5/5
		Balb/c x 129	5x10 ⁴	5/5
10	PKR ^{-/-}	Balb/c x 129	5x10 ⁴	0/5
			5x10 ³	0/4
			5x10 ²	0/3
			5x10 ¹	0/3

15

Example 14. AML3 cells die by apoptosis following infection with VSV

20 OCI/AML3 (acute myelogenous leukemia) cells were infected with VSV at an
MOI of 3.0 pfu/cell . Fourteen and twenty hours post-infection unfixed samples were
analyzed. Apoptotic cells with phosphatidylserine membrane translocation were
detected by flow cytometry using Annexin-V-Biotin-X/NeutrAvidin-PE red
fluorescent protein (Molecular Probes). Mitochondrial membrane depolarization in
25 early apoptotic cells were analyzed by flow cytometry using JC-1 potential-sensitive
dye (Molecular Probes). JC-1 is accumulated by polarized mitochondria shifting
fluorescence emission from green to red spectra. Non-viable AML3 cells were
identified using Ethidium (EthD-1) homodimer-1 red fluorescent vital dye (Molecular
probes). Assays were performed following the manufacturers specifications. Results
30 are shown in Table 6.

 This example demonstrates that VSV kills AML cells at least in part through a
virally induced apoptotic pathway.

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TABLE 6

	Tests		MOI 0.0	MOI 3.0	Net ⁵ Positive (Dead)
			Percent Positive	Percent Positive	
14 hrs					
p.i.	EthD-1		6.6	32.3	¹⁰ 25.7
	Annexin V		14.3	52.7	38.4
	JC-1		7.5	21.4	13.4
					15
20 hrs					
p.i.	EthD-1 positive		6.4	58.5	52.1
	Annexin-V positive		10.8	79.6	^{68.8} 20
	JC-1		3.9	43.2	39.3

Example 15: Mutant VSV strains infect and kill AML cells

25

OCI/AML3 (acute myelogenous leukemia) cells were infected at an MOI of 1.0 and incubated for 23 hours. Unfixed cells were stained with Eth-D1 (ethidium dimer, Molecular Probes) to detect non-viable cells following manufacturers specifications. Number of stained cells per 10,000 counted used to calculate percent dead. Results are shown in Table 7.

30

This example demonstrates that the mutant VSV strains used are as effective as the wild type Indiana strain in killing AML cells.

TABLE 7

	Mock	WT IND	Mut I	Mut II	Mut III	Mut IV	Mut V
Percent Dead	30.0	64.7	60.7	86.7	72.1	74.4	82.8

5

Example 16. VSV and VSV infected cells exhibit antitumor activity against human melanoma xenografts in nude mice.

10 SK-MEL 3 (melanoma) derived tumours were developed in 8-10 week old female Balb/c athymic mice. On day 0, tumours were either left untreated or were infected with 10^8 pfu WT Indiana VSV in culture media or 2.5×10^6 WT Indiana VSV infected SK-MEL 3 cells (VSV producing cells). Statistical differences were calculated between treated and untreated groups at each data point with the following
 15 confidence values (b: $p < 0.01$; c: $p < 0.001$; d: $p = 0.007$). Results are shown in Figure 7. On day 3, only tumours treated with VSV producing cells were significantly smaller than untreated tumours (a: $p < 0.001$). No statistically significant differences in tumour volumes between groups were apparent from day 0 to day 2. Data points represent means $\pm$ SEM from multiple tumours (untreated $n=8$; VSV producing cells
 20 $n=8$; VSV alone $n=4$).

This example demonstrates that a single injection of VSV, directly into solid tumours profoundly affects tumour growth resulting in partial to complete regression. The use of infected tumour cells as a vehicle to deliver virus is also efficacious.

25

Example 17: PKR^{-/-} mice are acutely sensitive to intranasal VSV infection and demonstrate a deficiency in IFN mediated resistance.

(A & B) PKR^{-/-} and control mice (Balb/c X129) were infected intranasally with 5×10^4 pfu of VSV and monitored for morbidity and survival over the course of
 30 14 days, after which remaining animals were deemed to have survived the infection.

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Results are shown in Figures 8A and 8B. $\text{PKR}^{-/-}$ mice showed a severe decrease in survival compared to control mice (WT), succumbing by day 3 or 4, while all control mice survived the infection. $\text{IFN-}\alpha/\beta$ pretreatment (18 h prior to infection) with either 2×10^4 IU (Fig. 8A) or 2×10^5 IU (Fig. 8B) had no protective effect in $\text{PKR}^{-/-}$ animals.

5 This example demonstrates that a single defect in the interferon pathway (absence of PKR gene product) is sufficient to render mice unable to resist VSV infections. This defect cannot be rescued by interferon.

10 **Example 18. Interferon can protect xenograft bearing nude mice during VSV treatment**

SK-MEL 3 melanoma cells were injected intradermally into CD-1 athymic nude mice. On day 0, tumours were injected with either live WT Indiana VSV (1×10^9 pfu) or an equivalent amount of UV inactivated VSV, and measured daily.

15 Results are shown in Figure 9. Interferon was administered to a subset of animals (VSV IFN) at the times indicated (black arrows). (UV-VSV n=4; VSV IFN n=6; VSV n=6). In these experiments a single intratumoural injection of VSV is tumour-inhibiting in all cases. All tumours had at least a partial regression and in three of twelve mice treated a complete tumour regression. Tumours receiving UV inactivated virus continued to grow unabated until these animals were sacrificed at day 11. Nude mice not receiving interferon and injected with live virus began to die at day 10 and only two of six remained viable by day 15. In contrast, all interferon treated, infected, nude mice were protected from VSV toxicity and remained symptom free for more than 45 days.

25 This example demonstrates that a single intratumoural injection of live VSV is efficacious against tumours. Furthermore infected, tumour bearing, nude mice can be rescued from VSV toxicity by interferon injection.

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Example 19. VSV infects and kills leukemia and myeloma cells.

The indicated cell lines were infected with VSV Indiana HR strain at a multiplicity of infection of one plaque forming unit per cell. At 24, 48 and 72 hours post infection (p.i.) samples were taken from the infected cultures and stained directly with propidium iodide following manufacturers instructions (Molecular Probes). Samples were then analysed by flow cytometry using the FACSort WinMDI Version 2.7 program. In Table 8 the percentage of cells dead for each leukemic cell type is shown for the indicated times post infection.

This example shows that VSV is able to infect and kill a diverse set of leukemia types. The K-562 cell is isolated from a chronic myelogenous leukemia (CML) patient while MOLT-4 is a T cell leukemia and SR and H929 are myelomas.

TABLE 8

<i>Cell Line</i>	<u>24 hr. p.i.</u>	<u>48 hr. p.i.</u>	<u>72 hr. p.i.</u>
K-562 (CML)	15.38 %	52.36 %	N/D
MOLT-4 (T cell Leukemia)	53.94 %	48.80 %	N/D
SR (Myeloma)	32.10 %	46.38 %	N/D
H929(Myeloma)	10.73 %	17.35 %	64.41 %

Example 20: Vesicular stomatitis virus (VSV) strains including wild type Indiana and five attenuated VSV mutants demonstrate selective cytotoxicity toward human prostate carcinoma cells compared to normal human fibroblasts.

Vesicular stomatitis virus strains including wild type Indiana and attenuated mutant strains I (TR1026), II (TR1026R), III (TP3), IV (TP6) and V (G31) were obtained from Dr. Lauren Poliquin, University of Quebec at Montreal. Each of these

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virus strains was plaque purified five times prior to use in this experiment.

Human prostate carcinoma cells (LNCAP) and normal human cells (OSF 7 forearm fibroblast) were grown in 96-well tissue culture plates to a density of approximately 5×10^4 cells per well. Virus was added in 10-fold dilutions ranging from 5×10^5 pfu to 5 pfu. Control wells with no virus were included on each plate. The plates were incubated for 48 hours at 37 °C in 5% CO₂. Cytotoxicity was quantified using a colorimetric MTS ((3-[4,5-dimethylthiazol-2-yl]-5-[3-carboxymethoxyphenyl]-2-[4-sulfophenyl]-2H-tetrazolium, inner salt) assay (CellTiter 96 Aqueous, catalog #G1112, Promega Corporation, Madison WI 53711-5399), monitored at 490 nm, that detects mitochondrial enzyme activity. The amount of cell killing in the virus treated wells was determined by the loss in viability in the virus treated wells relative to the untreated wells. The data was plotted graphically as pfu/cell vs. percentage cell killing relative to control. The TC₅₀ for these cells was calculated as the amount of virus in pfu/cell causing a 50% reduction in the amount of viable cells. Lower TC₅₀ values reflect increased sensitivity of the cells to the lytic effects of the virus. The *in vitro* therapeutic index for each VSV strain was calculated as the ratio of TC₅₀ for the OSF7 cells compared to the TC₅₀ for the LNCAP cells.

The results are shown in Table 9. Wild type VSV-Indiana and each of the five mutants demonstrated a high degree of cytotoxicity toward the human prostate carcinoma cells as reflected in the low TC₅₀ values, all less than 0.01 pfu/cell. The normal human fibroblasts cells were one to more than 3 orders of magnitude more resistant to the cytotoxic effects of all six VSV strains. All five mutants had less toxicity on the normal OSF7 fibroblasts cells and had a higher *in vitro* therapeutic index than the wild-type Indiana VSV.

TABLE 9. Cytotoxicity Assay Results for VSV Strains (Wild type Indiana and Mutants I through V) Against Prostate Carcinoma Cells and Normal Fibroblasts.

	Mutant I	Mutant II	Mutant III	Mutant IV	Mutant V	WT Indiana

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LNCAP Prostate Carcinoma TC50 (pfu/cell)	0.0064	0.0048	0.0014	0.0006	0.0012	0.0017
OSF7 Normal Fibroblasts TC50 (pfu/cell)	>42	22	4.3	0.031	9.8	0.022
Therapeutic Index (TC50 OSF7/ TC50 LNCAPP)	>6562	4583	3071	52	8167	13

**Example 21: Virus Production from Tumour Cells and Normal Cells Infected
with Wild Type Indiana and Various Mutant VSV Strains**

HCT 116 colon carcinoma cells and OSF 7 forearm fibroblasts were grown to confluence in 35 mm tissue culture dishes. Media was removed and virus was added in a volume of 30 μ l with a multiplicity of infection of 0.1 pfu/cell for the HCT 116 cells and 1.5 pfu/cell for the OSF 7 cells. After a 1 hour incubation period at 37°C, 5% CO₂, 1 ml of tissue culture media was added to the dishes. Results are shown in Figures 10A and B. At the indicated time points, 10 μ l samples of media were removed from the dishes. The virus titre of these samples was determined by a plaque assay.

This example demonstrates the rapid replication kinetics of wild type and mutant VSV strains in HCT 116 colon carcinoma cells. All four mutant VSV strains had more rapid growth in HCT116 tumor cells than the wild type VSV. Note that in the normal OSF-7 cell cultures a ten fold higher input of virus is required to attain similar replication kinetics.

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Example 22. Malignant cells are rapidly killed following VSV (WT Indiana) infection and are not protected by IFN- α .

Monolayers of normal primary human fibroblasts (AG 1522) and several
5 tumour cell lines were either untreated or pretreated with IFN- α (100 units) and then
infected with VSV at an MOI of 0.1 pfu/ml. At 12 hours increments the infections
were terminated by cell fixation and staining to determine the kinetics of cell killing.
Control (CNTL) monolayers were left to grow, uninfected, over the course of the
experiment and therefore stain more intensely. Results are shown in Figure 11.
10 LNCAP is a human prostate carcinoma; A2780 is an human ovarian epithelial
carcinoma, and Sk MEL3 is a human melanoma.

This example demonstrates the rapid kinetics of tumour cell killing by VSV
Indiana even in the presence of interferon alpha. While normal cells are also killed by
VSV, the kinetics are slower and normal cells can be completely protected by
15 interferon alpha.

Example 23: VSV induced cytopathic effect visible in human melanoma cells but not in primary human cells with or without IFN- α .

20 Gelatin-coated coverslips with normal human cells and SK-MEL3 cells
untreated or pretreated with IFN- α (100 U/ml) were infected with WT Indiana VSV at
an MOI of 0.1 pfu/ml. Results are shown in Figure 12. The human melanoma cells
(SK-MEL3) displayed cpe at 12 hours post-infection even in the presence of
interferon. At 24 hours post-infection these malignant cells had died and lifted from
25 the coverslip. Human primary cells including foreskin fibroblasts (AG1522), ovarian
surface epithelial cells (HOSE) and prostate epithelial cells (PrEC) did not show CPE
(cytopathic effect) until 36 hours in the absence of interferon and were completely
protected in the presence of interferon beyond 72 hours post-infection.

This example demonstrates that VSV Indiana is able to rapidly destroy
30 melanoma cells even in the presence of interferon alpha whereas normal fibroblasts
and epithelial cells are slower to be killed and can be completely protected by
interferon alpha.

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Example 24. VSV selectively kills transformed cells co-cultured with normal fibroblasts.

5 Equal numbers of 293T cells (human embryo kidney cells transformed with adenovirus E1A and Large T antigen) and normal human foreskin fibroblasts were plated on gelatin-coated coverslips and infected (WT Indiana VSV) at an MOI of 0.1 both in the presence and absence of interferon. Cells were fixed at 12 (not shown), 24 and 36 hours post-infection. Fixed cells were stained with an anti-TAg antibody and
10 DAPI. The red staining 293T cells were quickly killed as early as 12 hours post-infection, regardless of interferon treatment, with those few remaining cells displaying condensed or fragmented nuclei. The normal fibroblasts displayed altered nuclei by 36 hours post-infection in the absence of interferon but were protected from the virus in the presence of interferon beyond this time point.

15 This example demonstrates that in a mixed culture of normal and tumour cells, VSV Indiana preferentially replicates and kills tumour cells. Normal cells in the infected co-cultures are slower to die and can be completely rescued by interferon treatment.

20

Example 25. Efficacy of a single intravenous dose of mutant VSV in treating human melanoma xenografts in nude mice.

 SK-Mel3 human melanoma xenografts were established in 5-6 week old CD-1 athymic mice. On day 0, tumours were either left untreated or were treated
25 intravenously with 5×10^9 pfu of mutant VSV as indicated. Results are shown in Figure 13.

 This example demonstrates that mutants II and III are able to inhibit tumour growth following a single intravenous injection. Thus virus need not be administered at the tumour site to be effective in inhibiting tumour growth. Furthermore, the
30 mutants while being attenuated for growth in normal mouse tissues, are still able to target tumour cells *in vivo*.

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Example 26. Selective killing of AML Cells Co-cultured with normal bone marrow.

The growth factor independent cell line OCI/AML3 was mixed 1:9 with
 5 normal bone marrow and infected for 24 hours with WT Indiana VSV. Various
 dilutions of cells were then plated in methylcellulose plus and minus growth factors
 and colony counts were performed 14 days later. Table 10 shows data for dishes
 receiving 10^4 cells. The asterisk (*) signifies that no leukemic colonies were detected
 on the growth factor minus dishes even when 10^5 cells were plated per dish.

10 This example demonstrates the rapid and selective killing of leukemia cells in
 the presence of normal bone stem cells. Furthermore it demonstrates that bone
 marrow is not a dose-limiting target of VSV oncolytic therapy as it is with most other
 conventional cancer therapies.

15

TABLE 10

Colony Type	Multiplicity of Infection		
	0.0	1.0	5.0
20 Leukemic	172	0*	0*
Neutrophil	12	7	5
Mixed	6	3	4
Monocyte	10	7	5

25

Example 27. VSV Sequences

The genome of VSV contains genes that encode viral proteins N, P, M, G and
 30 L. The cDNA sequences of the open reading frames (ORF) for these proteins from
 wild type heat resistant VSV (HR) and three mutant VSVs were determined (based on
 sequencing five times each) and compared with the sequences of GenBank Accession
 No. NC 001560 (derived from Colorado and San Juan strains of VSV). The mutants

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are M2 (TR1026R), M3 (TP3) and M4 (TP6). The nucleic acid sequences are shown in Figures 14, 16, 18, 20 and 22. The corresponding deduced amino acid sequences are shown in Figures 15, 17, 19, 21 and 23, respectively. Differences are indicated by highlighted letters. Dotted lines represent incomplete sequencing.

5 Some of the differences between the amino acid sequences are shown in Table 11 using notation based on column heading (i.e. for column heading "Differences Between GenBank and HR" notation K155R means that the amino acid at position 155 is K in GenBank and R in HR). In those cases where HR sequence is not yet available comparisons can only be made between GenBank and a particular mutant.

10 M3* denotes a difference between mutant 3 and HR but in this case the amino acid matches the GenBank deposit at that position (i.e. mutant 3 and the Genbank sequence agree at that position while HR is different).

 This data demonstrates the many differences in sequence between the HR strain and the GenBank deposit (which is primarily derived from the San Juan strain).

15 It also demonstrates some of the differences between the mutants and the HR strain from which they were derived. These genetic differences correlate with phenotypic differences.

TABLE 11

Gene	Differences Between GenBank and HR	Differences Between HR and Mutants	Differences Between Genbank and Mutant #2	Differences Between GenBank and Mutant #4
N	D10A, K155R, N353S	A10D (M3*) None (M4)		
P	K50R, A76V, Q77P, E99D P110Q, S126L, S140L Y151H, M168I, E170K D237N	None (M2, M3 and M4)		
M	S32N, Y54H, N57H, T133A, I171V, I226V	M51R (M3) None (M4)		
G	H24Y, I57L, Q96H, V141A, Y172D, G132D H242R, S438T, L453F H487Y	Q26R, R242H, S431A (all M3) E254G (M4)	A331V	
L	T367A, T689S, T2026I	None (M4)		I202L, K296R

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5 The present invention has been described with regard to preferred embodiments. However, it will be obvious to persons skilled in the art that a number of variations and modifications can be made without departing from the scope of the invention as described herein.

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57/ 6

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Gly Arg Thr Gln Met Pro Glu Tyr Arg Lys Arg Leu Met Asp Gly Leu
 145 150 155 160

Thr Asn Gln Cys Lys Met Ile Asn Glu Gln Phe Glu Pro Leu Val Pro
 165 170 175

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Glu Gly Arg Asp Ile Phe Asp Val Trp Gly Asn Asp Ser Asn Tyr Thr
 180 185 190
 Lys Ile Val Ala Ala Val Asp Met Phe Phe His Met Phe Lys Lys His
 195 200 205
 Glu Cys Ala Ser Phe Arg Tyr Gly Thr Ile Val Ser Arg Phe Lys Asp
 210 215 220
 Cys Ala Ala Leu Ala Thr Phe Gly His Leu Cys Lys Ile Thr Gly Met
 225 230 235 240
 Ser Thr Glu Asp Val Thr Thr Trp Ile Leu Asn Arg Glu Val Ala Asp
 245 250 255
 Glu Met Val Gln Met Met Leu Pro Gly Gln Glu Ile Asp Lys Ala Asp
 260 265 270
 Ser Tyr Met Pro Tyr Leu Ile Asp Phe Gly Leu Ser Ser Lys Ser Pro
 275 280 285
 Tyr Ser Ser Val Lys Asn Pro Ala Phe His Phe Trp Gly Gln Leu Thr
 290 295 300
 Ala Leu Leu Leu Arg Ser Thr Arg Ala Arg Asn Ala Arg Gln Pro Asp
 305 310 315 320
 Asp Ile Glu Tyr Thr Ser Leu Thr Thr Ala Gly Leu Leu Tyr Ala Tyr
 325 330 335
 Ala Val Gly Ser Ser Ala Asp Leu Ala Gln Gln Phe Cys Val Gly Asp
 340 345 350
 Ser Lys Tyr Thr Pro Asp Asp Ser Thr Gly Gly Leu Thr Thr Asn Ala
 355 360 365
 Pro Pro Gln Gly Arg Asp Val Val Glu Trp Leu Gly Trp Phe Glu Asp
 370 375 380
 Gln Asn Arg Lys Pro Thr Pro Asp Met Met Gln Tyr Ala Lys Arg Ala
 385 390 395 400
 Val Met Ser Leu Gln Gly Leu Arg Glu Lys Thr Ile Gly Lys Tyr Ala
 405 410 415
 Lys Ser Glu Phe Asp Lys
 420

<210> 17

<211> 342

<212> PRT

<213> Vesicular stomatitis virus

<220>

57/11

<221> MOD_RES

<222> (1)..(342)

<223> "Xaa" represents any, other or unknown amino acid

<400> 17

Ser	Ile	Ile	His	Val	Asn	Ser	Tyr	Leu	Tyr	Gly	Ala	Leu	Lys	Asp	Ile	1	5	10	15
Arg	Gly	Lys	Leu	Asp	Lys	Asp	Trp	Ser	Ser	Phe	Gly	Ile	Asn	Ile	Gly	20	25	30	
Lys	Ala	Gly	Asp	Thr	Ile	Gly	Ile	Phe	Asp	Leu	Val	Ser	Leu	Lys	Ala	35	40	45	
Leu	Asp	Gly	Val	Leu	Pro	Asp	Gly	Val	Ser	Asp	Ala	Ser	Arg	Thr	Ser	50	55	60	
Ala	Asp	Asp	Lys	Trp	Leu	Pro	Leu	Tyr	Leu	Leu	Gly	Leu	Tyr	Arg	Val	65	70	75	80
Gly	Arg	Thr	Gln	Met	Pro	Glu	Tyr	Arg	Lys	Arg	Leu	Met	Asp	Gly	Leu	85	90	95	
Thr	Asn	Gln	Cys	Lys	Met	Ile	Asn	Glu	Gln	Phe	Glu	Pro	Leu	Val	Pro	100	105	110	
Glu	Gly	Arg	Asp	Ile	Phe	Asp	Val	Trp	Gly	Asn	Asp	Ser	Asn	Tyr	Thr	115	120	125	
Lys	Ile	Val	Ala	Ala	Val	Asp	Met	Phe	Phe	His	Met	Phe	Lys	Lys	His	130	135	140	
Glu	Cys	Ala	Ser	Phe	Arg	Tyr	Gly	Thr	Ile	Val	Ser	Arg	Phe	Lys	Asp	145	150	155	160
Cys	Ala	Ala	Leu	Ala	Thr	Phe	Gly	His	Leu	Cys	Lys	Ile	Thr	Gly	Met	165	170	175	
Ser	Thr	Glu	Asp	Val	Thr	Thr	Trp	Ile	Leu	Asn	Arg	Glu	Val	Ala	Asp	180	185	190	
Glu	Met	Val	Gln	Met	Met	Leu	Pro	Gly	Gln	Glu	Ile	Asp	Lys	Ala	Asp	195	200	205	
Ser	Tyr	Met	Pro	Tyr	Leu	Ile	Asp	Phe	Gly	Leu	Ser	Ser	Lys	Ser	Pro	210	215	220	
Tyr	Ser	Ser	Val	Lys	Asn	Pro	Ala	Phe	His	Phe	Trp	Gly	Gln	Leu	Thr	225	230	235	240
Asp	Ile	Glu	Tyr	Thr	Ser	Xaa	Thr	Thr	Ala	Gly	Leu	Leu	Tyr	Ala	Tyr	245	250	255	
Ala	Val	Gly	Ser	Ser	Ala	Asp	Leu	Ala	Xaa	Gln	Phe	Cys	Val	Gly	Asp	260	265	270	

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Ser Lys Tyr Thr Pro Asp Asp Ser Thr Gly Gly Leu Thr Thr Asn Ala
 275 280 285

Pro Pro Gln Gly Arg Asp Val Val Glu Trp Leu Gly Trp Phe Glu Asp
 290 295 300

Gln Asn Arg Lys Pro Thr Pro Asp Met Met Gln Tyr Ala Lys Arg Ala
 305 310 315 320

Val Met Ser Leu Gln Gly Leu Arg Glu Lys Thr Ile Gly Lys Tyr Ala
 325 330 335

Lys Ser Glu Phe Asp Lys
 340

<210> 18

<211> 798

<212> DNA

<213> Vesicular stomatitis virus

<400> 18

```

atggataatc tcacaaaagt tcgtgagtat ctcaagtcct attctcgtct ggatcaggcg 60
gtaggagaga tagatgagat cgaagcacaa cgagctgaaa agtccaatta tgagttgttc 120
caagaggatg gagtggaaga gcatactaag ccctcttatt ttcaggcagc agatgattct 180
gacacagaat ctgaaccaga aattgaagac aatcaagggt tgtatgcaca ggatccagaa 240
gctgagcaag ttgaaggctt tatacagggg cctttagatg actatgcaga tgaggaagtg 300
gatgttgtat ttacttcgga ctggaaacca cctgagcttg aatctgacga gcatggaaag 360
accttacggg tgacatcgcc agagggttta agtggagagc agaaatccca gtggctttcg 420
acgattaaag cagtcgtgca aagtgccaaa tactggaatc tggcagagtg cacatttgaa 480
gcatcgggag aaggggtcat tatgaaggag cgccagataa ctccggatgt atataaggtc 540
actccagtga tgaacacaca tccgtcccaa tcagaagcag tatcagatgt ttggtctctc 600
tcaaagacat ccatgacttt ccaacccaag aaagcaagtc ttcagcctct caccatatcc 660
ttggatgaat tgttctcatc tagaggagag ttcattctctg tcggaggtga cggacgaatg 720
tctcataaag aggccatcct gctcggcctg agatacaaaa agttgtacaa tcaggcgaga 780
gtcaaatatt ctctgtag                                     798

```

<210> 19

<211> 798

<212> DNA

<213> Vesicular stomatitis virus

<400> 19

```

atggataatc tcacaaaagt tcgtgagtat ctcaagtcct attctcgtct agatcaggcg 60
gtaggagaga tagatgagat cgaagcacaa cgagctgaaa agtccaatta tgagttgttc 120
caagaggacg gagtggaaga gcatactagg ccctcttatt ttcaggcagc agatgattct 180
gacacagaat ctgaaccaga aattgaagac aatcaaggct tgtatgtacc agatccggaa 240
gctgagcaag ttgaaggctt tatacagggg cctttagatg actatgcgga tgaggacgtg 300
gatgttgtat tcacttcgga ctggaaacag cctgagcttg aatccgacga gcatggaaag 360
accttacggg tgacattgcc agagggttta agtggagagc agaaatccca gtggcttttg 420
acgattaaag cagtcgttca aagtgccaaa cactggaatc tggcagagtg cacatttgaa 480
gcatcgggag aaggggtcat cataaaaaag cgccagataa ctccggatgt atataaggtc 540
actccagtga tgaacacaca tccgtcccaa tcagaagccg tatcagatgt ttggtctctc 600
tcaaagacat ccatgacttt ccaacccaag aaagcaagtc ttcagcctct caccatatcc 660

```

57/13

```

ttggatgaat tgttctcatc tagaggagaa ttcattctctg tcggaggtaa cggacgaatg 720
tctcataaag aggccatcct gctcggctctg aggtacaaaa agttgtacaa tcaggcgaga 780
gtcaaatatt ctctgtag 798

```

<210> 20

<211> 570

<212> DNA

<213> Vesicular stomatitis virus

<400> 20

```

atggataatc tcacaaaagt tcgtgagtat ctcaagtcct attctcgtct agatcaggcg 60
gtaggagaga tagatgagat cgaagcacaa cgagctgaaa agtccaatta tgagttgttc 120
caagaggacg gagtggaaga gcatactagg ccctcttatt ttcaggcagc agatgattct 180
gacacagaat ctgaaccaga aattgaagac aatcaaggct tgtatgtacc agatccggaa 240
gctgagcaag ttgaaggctt tatacagggg ccttttagatg actatgcgga tgaggacgtg 300
gatgttgtat tcacttcgga ctggaaacag cctgagcttg aatccgacga gcatggaaag 360
accttacggg tgacattgcc agagggttta agtggagagc agaaatccca gtggcttttg 420
acgattaaag cagtcgttca aagtgccaaa cactggaatc tggcagagtg cacatttgaa 480
gcatcgggag aaggggtcat cataaaaaag cgccagataa ctccggatgt atataaggtc 540
actccagtga tgaacacaca tccgtcccaa 570

```

<210> 21

<211> 798

<212> DNA

<213> Vesicular stomatitis virus

<400> 21

```

atggataatc tcacaaaagt tcgtgagtat ctcaagtcct attctcgtct agatcaggcg 60
gtaggagaga tagatgagat cgaagcacaa cgagctgaaa agtccaatta tgagttgttc 120
caagaggacg gagtggaaga gcatactagg ccctcttatt ttcaggcagc agatgattct 180
gacacagaat ctgaaccaga aattgaagac aatcaaggct tgtatgtacc agatccggaa 240
gctgagcaag ttgaaggctt tatacagggg ccttttagatg actatgcgga tgaggacgtg 300
gatgttgtat tcacttcgga ctggaaacag cctgagcttg aatccgacga gcatggaaag 360
accttacggg tgacattgcc agagggttta agtggagagc agaaatccca gtggcttttg 420
acgattaaag cagtcgttca aagtgccaaa cactggaatc tggcagagtg cacatttgaa 480
gcatcgggag aaggggtcat cataaaaaag cgccagataa ctccggatgt atataaggtc 540
actccagtga tgaacacaca tccgtcccaa tcggaagccg tatcagatgt ttggtctctc 600
tcaaagacat ccatgacttt ccaaccgaag aaagcaagtc ttcagcctct caccatatcc 660
ttggatgaat tgttctcatc tagaggagaa ttcattctctg tcggaggtaa cggacgaatg 720
tctcataaag aggccatcct gctcggctctg aggtacaaaa agttgtacaa tcaggcgaga 780
gtcaaatatt ctctgtag 798

```

<210> 22

<211> 798

<212> DNA

<213> Vesicular stomatitis virus

<400> 22

```

atggataatc tcacaaaagt tcgtgagtat ctcaagtcct attctcgtct agatcaggcg 60
gtaggagaga tagatgagat cgaagcacaa cgagctgaaa agtccaatta tgagttgttc 120
caagaggacg gagtggaaga gcatactagg ccctcttatt ttcaggcagc agatgattct 180
gacacagaat ctgaaccaga aattgaagac aatcaaggct tgtatgtacc agatccggaa 240

```

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```

gctgagcaag ttgaaggctt tatacagggg ccttttagatg actatgcgga tgaggacgtg 300
gatgttgtat tcacttcgga ctggaaacag cctgagcttg aatccgacga gcatggaaag 360
accttacggt tgacattgcc agagggttta agtggagagc agaaatccca gtggcttttg 420
acgattaaag cagtcgttca aagtgcctaa cactggaatc tggcagagtg cacatttgaa 480
gcatcgggag aaggggtcat cataaaaaag cgccagataa ctccggatgt atataaggtc 540
actccagtga tgaacacaca tccgtcccaa tcagaagccg tatcagatgt ttgggtctctc 600
tcaaagacat ccatgacttt ccaacccaag aaagcaagtc ttcagcctct caccatatcc 660
ttggatgaat tgttctcatc tagaggagaa ttcattctctg tcggaggtaa cggacgaatg 720
tctcataaag aggccatcct gctcgggtctg aggtacaaaa agttgtacaa tcaggcgaga 780
gtcaaatatt ctctgtag 798

```

<210> 23

<211> 265

<212> PRT

<213> Vesicular stomatitis virus

<400> 23

```

Met Asp Asn Leu Thr Lys Val Arg Glu Tyr Leu Lys Ser Tyr Ser Arg
  1                      5                      10                      15

```

```

Leu Asp Gln Ala Val Gly Glu Ile Asp Glu Ile Glu Ala Gln Arg Ala
          20                      25                      30

```

```

Glu Lys Ser Asn Tyr Glu Leu Phe Gln Glu Asp Gly Val Glu Glu His
          35                      40                      45

```

```

Thr Lys Pro Ser Tyr Phe Gln Ala Ala Asp Asp Ser Asp Thr Glu Ser
          50                      55                      60

```

```

Glu Pro Glu Ile Glu Asp Asn Gln Gly Leu Tyr Ala Gln Asp Pro Glu
          65                      70                      75                      80

```

```

Ala Glu Gln Val Glu Gly Phe Ile Gln Gly Pro Leu Asp Asp Tyr Ala
          85                      90                      95

```

```

Asp Glu Glu Val Asp Val Val Phe Thr Ser Asp Trp Lys Pro Pro Glu
          100                      105                      110

```

```

Leu Glu Ser Asp Glu His Gly Lys Thr Leu Arg Leu Thr Ser Pro Glu
          115                      120                      125

```

```

Gly Leu Ser Gly Glu Gln Lys Ser Gln Trp Leu Ser Thr Ile Lys Ala
          130                      135                      140

```

```

Val Val Gln Ser Ala Lys Tyr Trp Asn Leu Ala Glu Cys Thr Phe Glu
          145                      150                      155                      160

```

```

Ala Ser Gly Glu Gly Val Ile Met Lys Glu Arg Gln Ile Thr Pro Asp
          165                      170                      175

```

```

Val Tyr Lys Val Thr Pro Val Met Asn Thr His Pro Ser Gln Ser Glu
          180                      185                      190

```

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Ala Val Ser Asp Val Trp Ser Leu Ser Lys Thr Ser Met Thr Phe Gln
 195 200 205

Pro Lys Lys Ala Ser Leu Gln Pro Leu Thr Ile Ser Leu Asp Glu Leu
 210 215 220

Phe Ser Ser Arg Gly Glu Phe Ile Ser Val Gly Gly Asp Gly Arg Met
 225 230 235 240

Ser His Lys Glu Ala Ile Leu Leu Gly Leu Arg Tyr Lys Lys Leu Tyr
 245 250 255

Asn Gln Ala Arg Val Lys Tyr Ser Leu
 260 265

<210> 24

<211> 265

<212> PRT

<213> Vesicular stomatitis virus

<400> 24

Met Asp Asn Leu Thr Lys Val Arg Glu Tyr Leu Lys Ser Tyr Ser Arg
 1 5 10 15

Leu Asp Gln Ala Val Gly Glu Ile Asp Glu Ile Glu Ala Gln Arg Ala
 20 25 30

Glu Lys Ser Asn Tyr Glu Leu Phe Gln Glu Asp Gly Val Glu Glu His
 35 40 45

Thr Arg Pro Ser Tyr Phe Gln Ala Ala Asp Asp Ser Asp Thr Glu Ser
 50 55 60

Glu Pro Glu Ile Glu Asp Asn Gln Gly Leu Tyr Val Pro Asp Pro Glu
 65 70 75 80

Ala Glu Gln Val Glu Gly Phe Ile Gln Gly Pro Leu Asp Asp Tyr Ala
 85 90 95

Asp Glu Asp Val Asp Val Val Phe Thr Ser Asp Trp Lys Gln Pro Glu
 100 105 110

Leu Glu Ser Asp Glu His Gly Lys Thr Leu Arg Leu Thr Leu Pro Glu
 115 120 125

Gly Leu Ser Gly Glu Gln Lys Ser Gln Trp Leu Leu Thr Ile Lys Ala
 130 135 140

Val Val Gln Ser Ala Lys His Trp Asn Leu Ala Glu Cys Thr Phe Glu
 145 150 155 160

Ala Ser Gly Glu Gly Val Ile Ile Lys Lys Arg Gln Ile Thr Pro Asp
 165 170 175

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Val Tyr Lys Val Thr Pro Val Met Asn Thr His Pro Ser Gln Ser Glu
 180 185 190

Ala Val Ser Asp Val Trp Ser Leu Ser Lys Thr Ser Met Thr Phe Gln
 195 200 205

Pro Lys Lys Ala Ser Leu Gln Pro Leu Thr Ile Ser Leu Asp Glu Leu
 210 215 220

Phe Ser Ser Arg Gly Glu Phe Ile Ser Val Gly Gly Asn Gly Arg Met
 225 230 235 240

Ser His Lys Glu Ala Ile Leu Leu Gly Leu Arg Tyr Lys Lys Leu Tyr
 245 250 255

Asn Gln Ala Arg Val Lys Tyr Ser Leu
 260 265

<210> 25
 <211> 190
 <212> PRT
 <213> Vesicular stomatitis virus

<400> 25
 Met Asp Asn Leu Thr Lys Val Arg Glu Tyr Leu Lys Ser Tyr Ser Arg
 1 5 10 15

Leu Asp Gln Ala Val Gly Glu Ile Asp Glu Ile Glu Ala Gln Arg Ala
 20 25 30

Glu Lys Ser Asn Tyr Glu Leu Phe Gln Glu Asp Gly Val Glu Glu His
 35 40 45

Thr Arg Pro Ser Tyr Phe Gln Ala Ala Asp Asp Ser Asp Thr Glu Ser
 50 55 60

Glu Pro Glu Ile Glu Asp Asn Gln Gly Leu Tyr Val Pro Asp Pro Glu
 65 70 75 80

Ala Glu Gln Val Glu Gly Phe Ile Gln Gly Pro Leu Asp Asp Tyr Ala
 85 90 95

Asp Glu Asp Val Asp Val Val Phe Thr Ser Asp Trp Lys Gln Pro Glu
 100 105 110

Leu Glu Ser Asp Glu His Gly Lys Thr Leu Arg Leu Thr Leu Pro Glu
 115 120 125

Gly Leu Ser Gly Glu Gln Lys Ser Gln Trp Leu Leu Thr Ile Lys Ala
 130 135 140

Val Val Gln Ser Ala Lys His Trp Asn Leu Ala Glu Cys Thr Phe Glu
 145 150 155 160

Pro Lys Lys Ala Ser Leu Gln Pro Leu Thr Ile Ser Leu Asp Glu Leu
210 215 220

57/18

Phe Ser Ser Arg Gly Glu Phe Ile Ser Val Gly Gly Asn Gly Arg Met
 225 230 235 240

Ser His Lys Glu Ala Ile Leu Leu Gly Leu Arg Tyr Lys Lys Leu Tyr
 245 250 255

Asn Gln Ala Arg Val Lys Tyr Ser Leu
 260 265

<210> 27

<211> 265

<212> PRT

<213> Vesicular stomatitis virus

<400> 27

Met Asp Asn Leu Thr Lys Val Arg Glu Tyr Leu Lys Ser Tyr Ser Arg
 1 5 10 15

Leu Asp Gln Ala Val Gly Glu Ile Asp Glu Ile Glu Ala Gln Arg Ala
 20 25 30

Glu Lys Ser Asn Tyr Glu Leu Phe Gln Glu Asp Gly Val Glu Glu His
 35 40 45

Thr Arg Pro Ser Tyr Phe Gln Ala Ala Asp Asp Ser Asp Thr Glu Ser
 50 55 60

Glu Pro Glu Ile Glu Asp Asn Gln Gly Leu Tyr Val Pro Asp Pro Glu
 65 70 75 80

Ala Glu Gln Val Glu Gly Phe Ile Gln Gly Pro Leu Asp Asp Tyr Ala
 85 90 95

Asp Glu Asp Val Asp Val Val Phe Thr Ser Asp Trp Lys Gln Pro Glu
 100 105 110

Leu Glu Ser Asp Glu His Gly Lys Thr Leu Arg Leu Thr Leu Pro Glu
 115 120 125

Gly Leu Ser Gly Glu Gln Lys Ser Gln Trp Leu Leu Thr Ile Lys Ala
 130 135 140

Val Val Gln Ser Ala Lys His Trp Asn Leu Ala Glu Cys Thr Phe Glu
 145 150 155 160

Ala Ser Gly Glu Gly Val Ile Ile Lys Lys Arg Gln Ile Thr Pro Asp
 165 170 175

Val Tyr Lys Val Thr Pro Val Met Asn Thr His Pro Ser Gln Ser Glu
 180 185 190

Ala Val Ser Asp Val Trp Ser Leu Ser Lys Thr Ser Met Thr Phe Gln
 195 200 205

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Pro Lys Lys Ala Ser Leu Gln Pro Leu Thr Ile Ser Leu Asp Glu Leu
 210 215 220

Phe Ser Ser Arg Gly Glu Phe Ile Ser Val Gly Gly Asn Gly Arg Met
 225 230 235 240

Ser His Lys Glu Ala Ile Leu Leu Gly Leu Arg Tyr Lys Lys Leu Tyr
 245 250 255

Asn Gln Ala Arg Val Lys Tyr Ser Leu
 260 265

<210> 28

<211> 690

<212> DNA

<213> Vesicular stomatitis virus

<400> 28

```

atgagttcct taaagaagat tctcgggtctg aaggggaaag gtaagaaatc taagaaatta 60
gggatcgcac cacccttcta tgaagaggac actagcatgg agtatgctcc gagcgctcca 120
attgacaaat cctattttgg agttgacgag atggacacct atgatccgaa tcaattaaga 180
tatgagaaat tcttctttac agtgaaaatg acggtttagat ctaatcgtcc gttcagaaca 240
tactcagatg tggcagccgc tgtatcccat tgggatcaca tgtacatcgg aatggcaggg 300
aaacgtccct tctacaaaat cttgggtttt ttgggttctt ctaatctaaa ggccactcca 360
gcggtattgg cagatcaagg tcaaccagag tatcacactc actgcgaagg cagggttat 420
ttgccacata ggatggggaa gaccctccc atgctcaatg taccagagca cttcagaaga 480
ccattcaata taggtcttta caaggaacg attgagctca caatgaccat ctacgatgat 540
gagtcactgg aagcagctcc tatgatctgg gatcatttca attcttcaa attttctgat 600
ttcagagaga aggccttaat gtttggcctg attgtcgaga aaaaggcatc tggagcgtgg 660
gtcctggatt ctatcagcca cttcaaata 690

```

<210> 29

<211> 690

<212> DNA

<213> Vesicular stomatitis virus

<400> 29

```

atgagttcct taaagaagat tctcgggtctg aaggggaaag gtaagaaatc taagaaatta 60
gggatcgcac cacccttcta tgaagaggac actaacatgg agtatgctcc gagcgctcca 120
attgacaaat cctattttgg agttgacgag atggacactc atgatccgca tcaattaaga 180
tatgagaaat tcttctttac agtgaaaatg acggtttagat ctaatcgtcc gttcagaaca 240
tactcagatg tggcagccgc tgtatcccat tgggatcaca tgtacatcgg aatggcaggg 300
aaacgtccct tctacaagat cttgggtttt ttgggttctt ctaatctaaa ggccactcca 360
gcggtattgg cagatcaagg tcaaccagag tatcacgctc actgtgaagg cagggttat 420
ttgccacaca gaatggggaa gaccctccc atgctcaatg taccagagca cttcagaaga 480
ccattcaata taggtcttta caaggaacg gttgagctca caatgaccat ctacgatgat 540
gagtcactgg aagcagctcc tatgatctgg gatcatttca attcttcaa attttctgat 600
ttcagagaga aggccttaat gtttggcctg attgtcgaga aaaaggcatc tggagcgtgg 660
gtcctggatt ctgtcagcca cttcaaata 690

```

<210> 30

<211> 690

57/20

<212> DNA

<213> Vesicular stomatitis virus

<400> 30

```

atgagttcct taaagaagat tctcgggtctg aaggggaaag gtaagaaatc taagaaatta 60
gggatcgcac caccacctta tgaagaggac actaacatgg agtatgctcc gagcgctcca 120
attgacaaat cctatctttgg agttgacgag agggacactc atgatccgca tcaattaaga 180
tatgagaaat tcttctttac agtgaaaatg acggtttagat ctaatcgctc gttcagaaca 240
tactcagatg tggcagccgc tgtatcccat tgggatcaca tgtacatcgg aatggcaggg 300
aaacgtccct tctacaagat cttgggtttt ttgggwtctt ctaatctaaa ggccactcca 360
gcggtattgg cagatcaagg tcaaccagag tatcacgctc actgtgaagg cagggcttat 420
ttgccacaca gaatggggaa gaccctccc atgctcaatg taccagagca cttcagaaga 480
ccattcaata taggtcttta caaggaacg gttgagctca caatgaccat ctacgatgat 540
gagtcactgg aagcagctcc tatgatctgg gatcatttca attcttccaa attttctgat 600
ttcagagaga aggccttaat gtttggcctg attgtcgaga aaaaggcatc tggagcttgg 660
gtcctggatt ctgtcagcca cttcaaata 690

```

<210> 31

<211> 690

<212> DNA

<213> Vesicular stomatitis virus

<400> 31

```

atgagttcct taaagaagat tctcgggtctg aaggggaaag gtaagaaatc taagaaatta 60
gggatcgcac caccacctta tgaagaggac actaacatgg agtatgctcc gagcgctcca 120
attgacaaat cctatctttgg agttgacgag atggacactc atgatccgca tcaattaaga 180
tatgagaaat tcttctttac agtgaaaatg acggtttagat ctaatcgctc gttcagaaca 240
tactcagatg tggcagccgc tgtatcccat tgggatcaca tgtacatcgg aatggcaggg 300
aaacgtccct tctacaagat cttgggtttt ttggggttctt ctaatctaaa ggccactcca 360
gcggtattgg cagatcaagg tcaaccagag tatcacgctc actgtgaagg cagggcttat 420
ttgccacaca gaatggggaa gaccctccc atgctcaatg taccagagca cttcagaaga 480
ccattcaata taggtcttta caaggaacg gttgagctca caatgaccat ctacgatgat 540
gagtcactgg aagcagctcc tatgatctgg gatcatttca attcttccaa attttctgat 600
ttcagagaga aggccttaat gtttggcctg attgtcgaga aaaaggcatc tggagcttgg 660
gtcctggatt ctgtcagcca cttcaaata 690

```

<210> 32

<211> 229

<212> PRT

<213> Vesicular stomatitis virus

<400> 32

```

Met Ser Ser Leu Lys Lys Ile Leu Gly Leu Lys Gly Lys Gly Lys Lys
 1                      5                      10                      15

Ser Lys Lys Leu Gly Ile Ala Pro Pro Pro Tyr Glu Glu Asp Thr Ser
      20                      25                      30

Met Glu Tyr Ala Pro Ser Ala Pro Ile Asp Lys Ser Tyr Phe Gly Val
      35                      40                      45

Asp Glu Met Asp Thr Tyr Asp Pro Asn Gln Leu Arg Tyr Glu Lys Phe
      50                      55                      60

```

57/21

Phe Phe Thr Val Lys Met Thr Val Arg Ser Asn Arg Pro Phe Arg Thr
 65 70 75 80
 Tyr Ser Asp Val Ala Ala Ala Val Ser His Trp Asp His Met Tyr Ile
 85 90 95
 Gly Met Ala Gly Lys Arg Pro Phe Tyr Lys Ile Leu Ala Phe Leu Gly
 100 105 110
 Ser Ser Asn Leu Lys Ala Thr Pro Ala Val Leu Ala Asp Gln Gly Gln
 115 120 125
 Pro Glu Tyr His Thr His Cys Glu Gly Arg Ala Tyr Leu Pro His Arg
 130 135 140
 Met Gly Lys Thr Pro Pro Met Leu Asn Val Pro Glu His Phe Arg Arg
 145 150 155 160
 Pro Phe Asn Ile Gly Leu Tyr Lys Gly Thr Ile Glu Leu Thr Met Thr
 165 170 175
 Ile Tyr Asp Asp Glu Ser Leu Glu Ala Ala Pro Met Ile Trp Asp His
 180 185 190
 Phe Asn Ser Ser Lys Phe Ser Asp Phe Arg Glu Lys Ala Leu Met Phe
 195 200 205
 Gly Leu Ile Val Glu Lys Lys Ala Ser Gly Ala Trp Val Leu Asp Ser
 210 215 220
 Ile Ser His Phe Lys
 225

<210> 33

<211> 229

<212> PRT

<213> Vesicular stomatitis virus

<400> 33

Met Ser Ser Leu Lys Lys Ile Leu Gly Leu Lys Gly Lys Gly Lys Lys
 1 5 10 15
 Ser Lys Lys Leu Gly Ile Ala Pro Pro Pro Tyr Glu Glu Asp Thr Asn
 20 25 30
 Met Glu Tyr Ala Pro Ser Ala Pro Ile Asp Lys Ser Tyr Phe Gly Val
 35 40 45
 Asp Glu Met Asp Thr His Asp Pro His Gln Leu Arg Tyr Glu Lys Phe
 50 55 60
 Phe Phe Thr Val Lys Met Thr Val Arg Ser Asn Arg Pro Phe Arg Thr
 65 70 75 80

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Tyr Ser Asp Val Ala Ala Ala Val Ser His Trp Asp His Met Tyr Ile
85 90 95

Gly Met Ala Gly Lys Arg Pro Phe Tyr Lys Ile Leu Ala Phe Leu Gly
100 105 110

Ser Ser Asn Leu Lys Ala Thr Pro Ala Val Leu Ala Asp Gln Gly Gln
115 120 125

Pro Glu Tyr His Ala His Cys Glu Gly Arg Ala Tyr Leu Pro His Arg
130 135 140

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

Pro Phe Asn Ile Gly Leu Tyr Lys Gly Thr Val Glu Leu Thr Met Thr
165 170 175

Ile Tyr Asp Asp Glu Ser Leu Glu Ala Ala Pro Met Ile Trp Asp His
180 185 190

Phe Asn Ser Ser Lys Phe Ser Asp Phe Arg Glu Lys Ala Leu Met Phe
195 200 205

Gly Leu Ile Val Glu Lys Lys Ala Ser Gly Ala Trp Val Leu Asp Ser
210 215 220

Val Ser His Phe Lys
225

<210> 34

<211> 229

<212> PRT

<213> Vesicular stomatitis virus

<400> 34

Met Ser Ser Leu Lys Lys Ile Leu Gly Leu Lys Gly Lys Gly Lys Lys
1 5 10 15

Ser Lys Lys Leu Gly Ile Ala Pro Pro Pro Tyr Glu Glu Asp Thr Asn
20 25 30

Met Glu Tyr Ala Pro Ser Ala Pro Ile Asp Lys Ser Tyr Phe Gly Val
35 40 45

Asp Glu Met Asp Thr His Asp Pro His Gln Leu Arg Tyr Glu Lys Phe
50 55 60

Phe Phe Thr Val Lys Met Thr Val Arg Ser Asn Arg Pro Phe Arg Thr
65 70 75 80

Tyr Ser Asp Val Ala Ala Ala Val Ser His Trp Asp His Met Tyr Ile
85 90 95

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Gly Met Ala Gly Lys Arg Pro Phe Tyr Lys Ile Leu Ala Phe Leu Gly
 100 105 110
 Ser Ser Asn Leu Lys Ala Thr Pro Ala Val Leu Ala Asp Gln Gly Gln
 115 120 125
 Pro Glu Tyr His Ala His Cys Glu Gly Arg Ala Tyr Leu Pro His Arg
 130 135 140
 Met Gly Lys Thr Pro Pro Met Leu Asn Val Pro Glu His Phe Arg Arg
 145 150 155 160
 Pro Phe Asn Ile Gly Leu Tyr Lys Gly Thr Val Glu Leu Thr Met Thr
 165 170 175
 Ile Tyr Asp Asp Glu Ser Leu Glu Ala Ala Pro Met Ile Trp Asp His
 180 185 190
 Phe Asn Ser Ser Lys Phe Ser Asp Phe Arg Glu Lys Ala Leu Met Phe
 195 200 205
 Gly Leu Ile Val Glu Lys Lys Ala Ser Gly Ala Trp Val Leu Asp Ser
 210 215 220
 Val Ser His Phe Lys
 225

<210> 35

<211> 229

<212> PRT

<213> Vesicular stomatitis virus

<400> 35

Met Ser Ser Leu Lys Lys Ile Leu Gly Leu Lys Gly Lys Gly Lys Lys
 1 5 10 15
 Ser Lys Lys Leu Gly Ile Ala Pro Pro Pro Tyr Glu Glu Asp Thr Asn
 20 25 30
 Met Glu Tyr Ala Pro Ser Ala Pro Ile Asp Lys Ser Tyr Phe Gly Val
 35 40 45
 Asp Glu Arg Asp Thr His Asp Pro His Gln Leu Arg Tyr Glu Lys Phe
 50 55 60
 Phe Phe Thr Val Lys Met Thr Val Arg Ser Asn Arg Pro Phe Arg Thr
 65 70 75 80
 Tyr Ser Asp Val Ala Ala Ala Val Ser His Trp Asp His Met Tyr Ile
 85 90 95
 Gly Met Ala Gly Lys Arg Pro Phe Tyr Lys Ile Leu Ala Phe Leu Gly
 100 105 110

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Ser Ser Asn Leu Lys Ala Thr Pro Ala Val Leu Ala Asp Gln Gly Gln
 115 120 125

Pro Glu Tyr His Ala His Cys Glu Gly Arg Ala Tyr Leu Pro His Arg
 130 135 140

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

Pro Phe Asn Ile Gly Leu Tyr Lys Gly Thr Val Glu Leu Thr Met Thr
 165 170 175

Ile Tyr Asp Asp Glu Ser Leu Glu Ala Ala Pro Met Ile Trp Asp His
 180 185 190

Phe Asn Ser Ser Lys Phe Ser Asp Phe Arg Glu Lys Ala Leu Met Phe
 195 200 205

Gly Leu Ile Val Glu Lys Lys Ala Ser Gly Ala Trp Val Leu Asp Ser
 210 215 220

Val Ser His Phe Lys
 225

<210> 36

<211> 1536

<212> DNA

<213> Vesicular stomatitis virus

<400> 36

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atgaagtgcc ttttgtactt agccttttta ttcattgggg tgaattgcaa gttcaccata 60
gtttttccac acaacccaaa aggaaactgg aaaaatgttc cttctaatta ccattattgc 120
ccgtcaagct cagattttaa ttggcataat gacttaatag gcacagccat acaagtcaaa 180
atgcccaaga gtcacaaggc tattcaagca gacggttgga tgtgtcatgc ttccaaatgg 240
gtcactactt gtgatttccg ctggtatgga ccgaagtata taacacagtc catccgatcc 300
ttcactccat ctgtagaaca atgcaaggaa agcattgaac aaacgaaaca aggaacttgg 360
ctgaatccag gcttccctcc tcaaagttgt ggatatgcaa ctgtgacgga tgccgaagca 420
gtgattgtcc aggtgactcc tcaccatgtg ctgggtgatg aatacacagg agaatggggt 480
gattcacagt tcatcaacgg aaaatgcagc aattacatat gccccactgt ccataactct 540
acaacctggc attctgacta taaggtcaaa gggctatgtg attctaacct catttccatg 600
gacatcacct tcttctcaga ggacggagag ctatcatccc tgggaaagga gggcacaggg 660
ttcagaagta actactttgc ttatgaaact ggaggcaagg cctgcaaaat gcaatactgc 720
aagcattggg gagtcagact cccatcaggt gtctgggtcg agatggctga taaggatctc 780
tttgctgcag ccagattccc tgaatgccca gaaggggtcaa gtatctctgc tccatctcag 840
acctcagtgg atgtaagtct aattcaggac gttgagagga tcttggatta ttccctctgc 900
caagaaacct ggagcaaaat cagagcgggt cttccaatct ctccagtgga tctcagctat 960
cttgctccta aaaacccagg aaccggtcct gctttcacca taatcaatgg taccctaaaa 1020
tactttgaga ccagatacat cagagtcgat attgctgctc caatcctctc aagaatgggtc 1080
ggaatgatca gtggaactac cacagaaagg gaactgtggg atgactgggc accatatgaa 1140
gacgtggaaa ttggacccaa tggagttctg aggaccagtt caggatataa gtttccttta 1200
tacatgattg gacatggtat gttggactcc gatcttcac ttagctcaaa ggctcagggtg 1260
ttcgaacatc ctcacattca agacgctgct tcgcaacttc ctgatgatga gagtttattt 1320
tttggtgata ctgggctatc caaaaatcca atcgagcttg tagaagggtg gttcagtagt 1380
tggaagagct ctattgcctc ttttttcttt atcatagggt taatcattgg actattcttg 1440

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gttctccgag ttggtatcca tctttgcatt aaattaaagc acaccaagaa aagacagatt 1500
 tatacagaca tagagatgaa ccgacttgga aagtaa 1536

<210> 37
 <211> 885
 <212> DNA
 <213> Vesicular stomatitis virus

<220>
 <221> modified_base
 <222> (1)..(885)
 <223> "n" represents a, t, c, g, other or unknown

<400> 37
 atgaagtgcc ttttgkactt agcttttttta ttcacogggg tgaattgcaa gttcaccata 60
 gttttttccat acaacccaaa aggaaactgg aaaaatgttc cttccaatta ccattattgc 120
 ccgtcaagct cagattttaa ttgncataat gacttaatag gcacagcctt acaagtcaaa 180
 atgcccaga gtcacaaggc tattcaagca gacgggttga tgtgtcatgc ttccaaatgg 240
 gtcactactt gtgatttccg ctggtacgga ccgaagtata taacacattc catccgatcc 300
 ttcactccat ctgtagaaca atgcaaggaa agcattgaac aaacgaaaca aggaacttgg 360
 ctgaatccag gcttccctcc tcaaagttgt ggatatgcaa ctgtgacgga tgctgaagca 420
 gcgattgtcc aggtgactcc tcaccatgtg cttgttgatg aatacacagg agaatgggtt 480
 gattcacagt tcatcaacgg aaaatgcagc aatgacatat gcccactgt ccataactcc 540
 acaacctggc attccgacta taagggtcaa gggctatgtg attctaacct catttccatg 600
 gacatcacct tcttctcaga ggacggagag ctatcatccc taggaaagga gggcacaggg 660
 ttcagaagta actactttgc ttatgaaact ggagacaagg cctgcaaaat gcagtactgc 720
 aagcgttggg gagtcagact cccatcaggt gtctgggtcg agatggctga taaggatctc 780
 tttgctgcag ccagattccc tgaatgccc gaaggggtcaa gtatctctgc tccatctcag 840
 acctcagtgg atgtaagtct cattcaggac gttgagagga tcttg 885

<210> 38
 <211> 705
 <212> DNA
 <213> Vesicular stomatitis virus

<400> 38
 ccatctcaga cctcagtgga tgtaagtctc attcaggacg ttgagaggat cttggattat 60
 tccctctgcc aagaaacctg gagcaaaatc agagcgggtc ttcccatctc tcagtggat 120
 ctcagctatc ttgctcctaa aaaccagga accggtcctg tctttaccat aatcaatgg 180
 accctaaaat actttgagac cagatacatc agagtcgata ttgctgctcc aatcctctca 240
 agaatggctg gaatgatcag tggaaactacc acagaaaggg aactgtggga tgactgggct 300
 ccatatgaag acgtggaaat tggacccaat ggagttctga ggaccagttc aggatataag 360
 tttcctttat atatgattgg acatgggtatg ttggactccg atcttcatct tagctcaaag 420
 gctcaggtgt ttgaacatcc tcacattcaa gacgctgctt cgcagcttcc tgatgatgag 480
 actttatttt ttggtgatac tgggctatcc aaaaatccaa tcgagtttgt agaagggttg 540
 ttcagtagtt ggaagagctc tattgcctct tttttcttta tcatagggtt aatcattgga 600
 ctattcttgg ttctccgagt tggatattat ctttgcatta aattaaagca caccaagaaa 660
 agacagattt atacagacat agagatgaac cgacttggga agtaa 705

<210> 39
 <211> 1536
 <212> DNA

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<213> Vesicular stomatitis virus

<400> 39

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atgaagtgcc ttttgtactt agcttttttta ttcacgcgggg tgaattgcaa gttcaccata 60
gttttttccat acaaccgaaa aggaaactgg aaaaatgttc cttccaatta ccattattgc 120
ccgtcaagct cagattttaa ttggcataat gacttaatag gcacagcctt acaagtcaaa 180
atgcccaga gtcacaaggc tattcaagca gacggttgga tgtgtcatgc ttccaaatgg 240
gtcactactt gtgatttccg ctggtacgga ccgaagtata taacacattc catccgatcc 300
ttcactccat ctgtagaaca atgcaaggaa agcattgaac aaacgaaaca aggaacttgg 360
ctgaatccag gcttccctcc tcaaagttgt ggatatgcaa ctgtgacgga tgctgaagca 420
gcgattgtcc aggtgactcc tcaccatgtg cttgttgatg aatacacagg agaatggggt 480
gattcacagt tcatcaacgg aaaatgcagc aatgacatat gcccactgt ccataactcc 540
acaacctggc attccgacta taagggtcaa gggctatgtg attctaacct catttccatg 600
gacatcacct tcttctcaga ggacggagag ctatcatccc taggaaagga gggcacaggg 660
ttcagaagta actactttgc ttatgaaact ggagacaagg cctgcaaaat gcagtactgc 720
aagcattggg gagtcagact cccatcaggt gtctgggtcg agatggctga taaggatctc 780
tttgctgcag ccagattccc tgaatgccc gaaggggtcaa gtatctctgc tccatctcag 840
acctcagtgg atgtaagtct cattcaggac gttgagagga tcttggatta ttccctctgc 900
caagaaacct ggagcaaaat cagagcgggt cttcccatct ctccagtgga tctcagctat 960
cttgctccta aaaaccagg aaccggtcct gctttcacca taatcaatgg taccctaaaa 1020
tactttgaga ccagatacat cagagtcgat attgctgctc caatcctctc aagaatgggtc 1080
ggaatgatca gtggaactac cacagaaagg gaactgtggg atgactgggc tccatatgaa 1140
gacgtggaaa ttggacccaa tggagttctg aggaccagtt caggatataa gtttccttta 1200
tatatgattg gacatggtat gttggactcc gatcttcatc ttagctcaaa ggctcaggtg 1260
tttgaacatc ctcacattca agacgctght gcgcagcttc ctgatgatga gactttattt 1320
tttggtgata ctgggctatc caaaaatcca atcgagtttg tagaagggtg gttcagtagt 1380
tggaagagct ctattgcctc ttttttcttt atcatagggt taatcattgg actattcttg 1440
gttctccgag ttggtattta tctttgcatt aaattaaagc acaccaagaa aagacagatt 1500
tatacagaca tagagatgaa ccgacttggg aagtaa 1536

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<210> 40

<211> 1399

<212> DNA

<213> Vesicular stomatitis virus

<400> 40

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atgaagtgcc ttttgtactt agcttttttta ttcacgcgggg tgaattgcaa gttcaccata 60
gttttttccat acaaccaaaa aggaaactgg aaaaatgttc cttccaatta ccattattgc 120
ccgtcaagct cagattttaa ttggcataat gacttaatag gcacagcctt acaggtcaaa 180
atgcccaga gtcacaaggc tattcaagca gacggttgga tgtgtcatgc ttccaaatgg 240
gtcactactt gtgatttccg ctggtacgga ccgaagtata taacacattc catccgatcc 300
ttcactccat ctgtagaaca atgcaaggaa agcattgaac aaacgaaaca aggaacttgg 360
ctgaatccag gcttccctcc tcaaagttgt ggatatgcaa ctgtgacgga tgctgaagca 420
gcgattgtcc aggtgactcc tcaccatgtg cttgttgatg aatacacagg agaatggggt 480
gattcacagt tcatcaacgg aaaatgcagc aatgacatat gcccactgt ccataactcc 540
acaacctggc attccgacta taagggtcaa gggctatgtg attctaacct catttccatg 600
gacatcacct tcttctcaga ggacggagag ctatcatccc taggaaagga gggcacaggg 660
ttcagaagta actactttgc ttatgaaact ggagacaagg cctgcaaaat gcagtactgc 720
aagcgttggg gagtcagact cccatcaggt gtctgggtcg ggatggctga taaggatctc 780
tttgctgcag ccagattccc tgaatgccc gaaggggtcaa gtatctctgc tccatctcag 840
acctcagtgg atgtaagtct cattcaggac gttgagagga tcttactttg agaccagata 900
catcagagtc gatattgctg ctccaatcct ctcaagaatg gtccgaatga tcagtggaac 960
taccacagaa agggaaactgt gggatgactg ggctccatat gaagacgtgg aaattggacc 1020
caatggagtt ctgaggacca gttcaggata taagtttctt ttatatatga ttggacatgg 1080

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tatgttggac tccgatcttc atcttagctc aaaggctcag gtgtttgaac atcctcacat 1140
 tcaagacgct gcttcgcagc ttcctgatga tgagacttta ttttttggtg atactgggct 1200
 atccaaaaat ccaatcgagt ttgtagaagg ttggttcagt agttggaaga gctctattgc 1260
 ctcttttttc tttatcatag gggttaatcat tggactattc ttggttctcc gagttggtat 1320
 ttatctttgc attaaattaa agcacaccaa gaaaagacag atttatacag acatagagat 1380
 gaaccgactt gggaagtaa 1399

<210> 41

<211> 511

<212> PRT

<213> Vesicular stomatitis virus

<400> 41

Met Lys Cys Leu Leu Tyr Leu Ala Phe Leu Phe Ile Gly Val Asn Cys
 1 5 10 15

Lys Phe Thr Ile Val Phe Pro His Asn Gln Lys Gly Asn Trp Lys Asn
 20 25 30

Val Pro Ser Asn Tyr His Tyr Cys Pro Ser Ser Ser Asp Leu Asn Trp
 35 40 45

His Asn Asp Leu Ile Gly Thr Ala Ile Gln Val Lys Met Pro Lys Ser
 50 55 60

His Lys Ala Ile Gln Ala Asp Gly Trp Met Cys His Ala Ser Lys Trp
 65 70 75 80

Val Thr Thr Cys Asp Phe Arg Trp Tyr Gly Pro Lys Tyr Ile Thr Gln
 85 90 95

Ser Ile Arg Ser Phe Thr Pro Ser Val Glu Gln Cys Lys Glu Ser Ile
 100 105 110

Glu Gln Thr Lys Gln Gly Thr Trp Leu Asn Pro Gly Phe Pro Pro Gln
 115 120 125

Ser Cys Gly Tyr Ala Thr Val Thr Asp Ala Glu Ala Val Ile Val Gln
 130 135 140

Val Thr Pro His His Val Leu Val Asp Glu Tyr Thr Gly Glu Trp Val
 145 150 155 160

Asp Ser Gln Phe Ile Asn Gly Lys Cys Ser Asn Tyr Ile Cys Pro Thr
 165 170 175

Val His Asn Ser Thr Thr Trp His Ser Asp Tyr Lys Val Lys Gly Leu
 180 185 190

Cys Asp Ser Asn Leu Ile Ser Met Asp Ile Thr Phe Phe Ser Glu Asp
 195 200 205

Gly Glu Leu Ser Ser Leu Gly Lys Glu Gly Thr Gly Phe Arg Ser Asn
 210 215 220

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Tyr	Phe	Ala	Tyr	Glu	Thr	Gly	Gly	Lys	Ala	Cys	Lys	Met	Gln	Tyr	Cys
225					230					235					240
Lys	His	Trp	Gly	Val	Arg	Leu	Pro	Ser	Gly	Val	Trp	Phe	Glu	Met	Ala
				245					250					255	
Asp	Lys	Asp	Leu	Phe	Ala	Ala	Ala	Arg	Phe	Pro	Glu	Cys	Pro	Glu	Gly
			260					265					270		
Ser	Ser	Ile	Ser	Ala	Pro	Ser	Gln	Thr	Ser	Val	Asp	Val	Ser	Leu	Ile
		275					280					285			
Gln	Asp	Val	Glu	Arg	Ile	Leu	Asp	Tyr	Ser	Leu	Cys	Gln	Glu	Thr	Trp
	290					295					300				
Ser	Lys	Ile	Arg	Ala	Gly	Leu	Pro	Ile	Ser	Pro	Val	Asp	Leu	Ser	Tyr
305					310					315					320
Leu	Ala	Pro	Lys	Asn	Pro	Gly	Thr	Gly	Pro	Ala	Phe	Thr	Ile	Ile	Asn
				325					330					335	
Gly	Thr	Leu	Lys	Tyr	Phe	Glu	Thr	Arg	Tyr	Ile	Arg	Val	Asp	Ile	Ala
			340					345					350		
Ala	Pro	Ile	Leu	Ser	Arg	Met	Val	Gly	Met	Ile	Ser	Gly	Thr	Thr	Thr
		355					360					365			
Glu	Arg	Glu	Leu	Trp	Asp	Asp	Trp	Ala	Pro	Tyr	Glu	Asp	Val	Glu	Ile
	370					375					380				
Gly	Pro	Asn	Gly	Val	Leu	Arg	Thr	Ser	Ser	Gly	Tyr	Lys	Phe	Pro	Leu
385					390					395					400
Tyr	Met	Ile	Gly	His	Gly	Met	Leu	Asp	Ser	Asp	Leu	His	Leu	Ser	Ser
				405					410					415	
Lys	Ala	Gln	Val	Phe	Glu	His	Pro	His	Ile	Gln	Asp	Ala	Ala	Ser	Gln
			420					425					430		
Leu	Pro	Asp	Asp	Glu	Ser	Leu	Phe	Phe	Gly	Asp	Thr	Gly	Leu	Ser	Lys
		435					440					445			
Asn	Pro	Ile	Glu	Leu	Val	Glu	Gly	Trp	Phe	Ser	Ser	Trp	Lys	Ser	Ser
	450					455					460				
Ile	Ala	Ser	Phe	Phe	Phe	Ile	Ile	Gly	Leu	Ile	Ile	Gly	Leu	Phe	Leu
465					470					475					480
Val	Leu	Arg	Val	Gly	Ile	His	Leu	Cys	Ile	Lys	Leu	Lys	His	Thr	Lys
				485					490					495	
Lys	Arg	Gln	Ile	Tyr	Thr	Asp	Ile	Glu	Met	Asn	Arg	Leu	Gly	Lys	
		500						505					510		

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<220>
<221> MOD_RES
<222> (1)..(295)
<223> "Xaa" represents any, other or unknown amino acid
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<400> 42
Met  Lys  Cys  Leu  Leu  Xaa  Leu  Ala  Phe  Leu  Phe  Ile  Gly  Val  Asn  Cys
  1              5              10              15

Lys  Phe  Thr  Ile  Val  Phe  Pro  Tyr  Asn  Gln  Lys  Gly  Asn  Trp  Lys  Asn
              20              25              30

Val  Pro  Ser  Asn  Tyr  His  Tyr  Cys  Pro  Ser  Ser  Ser  Asp  Leu  Asn  Xaa
              35              40              45

His  Asn  Asp  Leu  Ile  Gly  Thr  Ala  Leu  Gln  Val  Lys  Met  Pro  Lys  Ser
  50              55              60

His  Lys  Ala  Ile  Gln  Ala  Asp  Gly  Trp  Met  Cys  His  Ala  Ser  Lys  Trp
  65              70              75              80

Val  Thr  Thr  Cys  Asp  Phe  Arg  Trp  Tyr  Gly  Pro  Lys  Tyr  Ile  Thr  His
              85              90              95

Ser  Ile  Arg  Ser  Phe  Thr  Pro  Ser  Val  Glu  Gln  Cys  Lys  Glu  Ser  Ile
              100              105              110

Glu  Gln  Thr  Lys  Gln  Gly  Thr  Trp  Leu  Asn  Pro  Gly  Phe  Pro  Pro  Gln
              115              120              125

Ser  Cys  Gly  Tyr  Ala  Thr  Val  Thr  Asp  Ala  Glu  Ala  Ala  Ile  Val  Gln
  130              135              140

Val  Thr  Pro  His  His  Val  Leu  Val  Asp  Glu  Tyr  Thr  Gly  Glu  Trp  Val
  145              150              155              160

Asp  Ser  Gln  Phe  Ile  Asn  Gly  Lys  Cys  Ser  Asn  Asp  Ile  Cys  Pro  Thr
              165              170              175

Val  His  Asn  Ser  Thr  Thr  Trp  His  Ser  Asp  Tyr  Lys  Val  Lys  Gly  Leu
              180              185              190

Cys  Asp  Ser  Asn  Leu  Ile  Ser  Met  Asp  Ile  Thr  Phe  Phe  Ser  Glu  Asp
              195              200              205

Gly  Glu  Leu  Ser  Ser  Leu  Gly  Lys  Glu  Gly  Thr  Gly  Phe  Arg  Ser  Asn
  210              215              220

Tyr  Phe  Ala  Tyr  Glu  Thr  Gly  Asp  Lys  Ala  Cys  Lys  Met  Gln  Tyr  Cys
  225              230              235              240

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Val Glu Gly Trp Phe Ser Ser Trp Lys Ser Ser Ile Ala Ser Phe Phe
180 185 190

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Phe Ile Ile Gly Leu Ile Ile Gly Leu Phe Leu Val Leu Arg Val Gly
 195 200 205

Ile Tyr Leu Cys Ile Lys Leu Lys His Thr Lys Lys Arg Gln Ile Tyr
 210 215 220

Thr Asp Ile Glu Met Asn Arg Leu Gly Lys
 225 230

<210> 44

<211> 511

<212> PRT

<213> Vesicular stomatitis virus

<220>

<221> MOD_RES

<222> (1)..(511)

<223> "Xaa" represents any, other or unknown amino acid

<400> 44

Met Lys Cys Leu Leu Tyr Leu Ala Phe Leu Phe Ile Gly Val Asn Cys
 1 5 10 15

Lys Phe Thr Ile Val Phe Pro Tyr Asn Arg Lys Gly Asn Trp Lys Asn
 20 25 30

Val Pro Ser Asn Tyr His Tyr Cys Pro Ser Ser Ser Asp Leu Asn Trp
 35 40 45

His Asn Asp Leu Ile Gly Thr Ala Leu Gln Val Lys Met Pro Lys Ser
 50 55 60

His Lys Ala Ile Gln Ala Asp Gly Trp Met Cys His Ala Ser Lys Trp
 65 70 75 80

Val Thr Thr Cys Asp Phe Arg Trp Tyr Gly Pro Lys Tyr Ile Thr His
 85 90 95

Ser Ile Arg Ser Phe Thr Pro Ser Val Glu Gln Cys Lys Glu Ser Ile
 100 105 110

Glu Gln Thr Lys Gln Gly Thr Trp Leu Asn Pro Gly Phe Pro Pro Gln
 115 120 125

Ser Cys Gly Tyr Ala Thr Val Thr Asp Ala Glu Ala Ala Ile Val Gln
 130 135 140

Val Thr Pro His His Val Leu Val Asp Glu Tyr Thr Gly Glu Trp Val
 145 150 155 160

Asp Ser Gln Phe Ile Asn Gly Lys Cys Ser Asn Asp Ile Cys Pro Thr
 165 170 175

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Val	His	Asn	Ser	Thr	Thr	Trp	His	Ser	Asp	Tyr	Lys	Val	Lys	Gly	Leu
			180					185					190		
Cys	Asp	Ser	Asn	Leu	Ile	Ser	Met	Asp	Ile	Thr	Phe	Phe	Ser	Glu	Asp
		195					200					205			
Gly	Glu	Leu	Ser	Ser	Leu	Gly	Lys	Glu	Gly	Thr	Gly	Phe	Arg	Ser	Asn
	210					215					220				
Tyr	Phe	Ala	Tyr	Glu	Thr	Gly	Asp	Lys	Ala	Cys	Lys	Met	Gln	Tyr	Cys
225					230					235					240
Lys	His	Trp	Gly	Val	Arg	Leu	Pro	Ser	Gly	Val	Trp	Phe	Glu	Met	Ala
				245					250					255	
Asp	Lys	Asp	Leu	Phe	Ala	Ala	Ala	Arg	Phe	Pro	Glu	Cys	Pro	Glu	Gly
			260					265					270		
Ser	Ser	Ile	Ser	Ala	Pro	Ser	Gln	Thr	Ser	Val	Asp	Val	Ser	Leu	Ile
		275					280					285			
Gln	Asp	Val	Glu	Arg	Ile	Leu	Asp	Tyr	Ser	Leu	Cys	Gln	Glu	Thr	Trp
	290					295					300				
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His Lys Ala Ile Gln Ala Asp Gly Trp Met Cys His Ala Ser Lys Trp
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Val His Asn Ser Thr Thr Trp His Ser Asp Tyr Lys Val Lys Gly Leu
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Lys
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<213> Vesicular stomatitis virus

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<210> 48

<211> 348

<212> DNA

<213> Vesicular stomatitis virus

<400> 48

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tctgataatc atgatgccag tcaagggtat agttttttac atgaagtg 348

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<210> 49
 <211> 6330
 <212> DNA
 <213> Vesicular stomatitis virus

<220>
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<400> 49
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<210> 50

<211> 2109

<212> PRT

<213> Vesicular stomatitis virus

<400> 50

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Asp Asp Tyr Ala Thr Arg Glu Phe Leu Asn Pro Asp Glu Arg Met Thr
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Tyr Leu Asn His Ala Asp Tyr Asn Leu Asn Ser Pro Leu Ile Ser Asp
                35                      40                      45

Asp Ile Asp Asn Leu Ile Arg Lys Phe Asn Ser Leu Pro Ile Pro Ser
                50                      55                      60

Met Trp Asp Ser Lys Asn Trp Asp Gly Val Leu Glu Met Leu Thr Ser
  65                      70                      75                      80

Cys Gln Ala Asn Pro Ile Ser Thr Ser Gln Met His Lys Trp Met Gly
                85                      90                      95

Ser Trp Leu Met Ser Asp Asn His Asp Ala Ser Gln Gly Tyr Ser Phe
                100                     105                     110

Leu His Glu Val Asp Lys Glu Ala Glu Ile Thr Phe Asp Val Val Glu
                115                     120                     125

Thr Phe Ile Arg Gly Trp Gly Asn Lys Pro Ile Glu Tyr Ile Lys Lys
                130                     135                     140

Glu Arg Trp Thr Asp Ser Phe Lys Ile Leu Ala Tyr Leu Cys Gln Lys
  145                     150                     155                     160

Phe Leu Asp Leu His Lys Leu Thr Leu Ile Leu Asn Ala Val Ser Glu
                165                     170                     175

Val Glu Leu Leu Asn Leu Ala Arg Thr Phe Lys Gly Lys Val Arg Arg
                180                     185                     190

Ser Ser His Gly Thr Asn Ile Cys Arg Ile Arg Val Pro Ser Leu Gly
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Leu	Met	Asp	Arg	Asn	Phe	Leu	Leu	Met	Val	Lys	Asp	Val	Ile	Ile	Gly	225	230	235	240
Arg	Met	Gln	Thr	Val	Leu	Ser	Met	Val	Cys	Arg	Ile	Asp	Asn	Leu	Phe	245	250	255	
Ser	Glu	Gln	Asp	Ile	Phe	Ser	Leu	Leu	Asn	Ile	Tyr	Arg	Ile	Gly	Asp	260	265	270	
Lys	Ile	Val	Glu	Arg	Gln	Gly	Asn	Phe	Ser	Tyr	Asp	Leu	Ile	Lys	Met	275	280	285	
Val	Glu	Pro	Ile	Cys	Asn	Leu	Lys	Leu	Met	Lys	Leu	Ala	Arg	Glu	Ser	290	295	300	
Arg	Pro	Leu	Val	Pro	Gln	Phe	Pro	His	Phe	Glu	Asn	His	Ile	Lys	Thr	305	310	315	320
Ser	Val	Asp	Glu	Gly	Ala	Lys	Ile	Asp	Arg	Gly	Ile	Arg	Phe	Leu	His	325	330	335	
Asp	Gln	Ile	Met	Ser	Val	Lys	Thr	Val	Asp	Leu	Thr	Leu	Val	Ile	Tyr	340	345	350	
Gly	Ser	Phe	Arg	His	Trp	Gly	His	Pro	Phe	Ile	Asp	Tyr	Tyr	Thr	Gly	355	360	365	
Leu	Glu	Lys	Leu	His	Ser	Gln	Val	Thr	Met	Lys	Lys	Asp	Ile	Asp	Val	370	375	380	
Ser	Tyr	Ala	Lys	Ala	Leu	Ala	Ser	Asp	Leu	Ala	Arg	Ile	Val	Leu	Phe	385	390	395	400
Gln	Gln	Phe	Asn	Asp	His	Lys	Lys	Trp	Phe	Val	Asn	Gly	Asp	Leu	Leu	405	410	415	
Pro	His	Asp	His	Pro	Phe	Lys	Ser	His	Val	Lys	Glu	Asn	Thr	Trp	Pro	420	425	430	
Thr	Ala	Ala	Gln	Val	Gln	Asp	Phe	Gly	Asp	Lys	Trp	His	Glu	Leu	Pro	435	440	445	
Leu	Ile	Lys	Cys	Phe	Glu	Ile	Pro	Asp	Leu	Leu	Asp	Pro	Ser	Ile	Ile	450	455	460	
Tyr	Ser	Asp	Lys	Ser	His	Ser	Met	Asn	Arg	Ser	Glu	Val	Leu	Lys	His	465	470	475	480
Val	Arg	Met	Asn	Pro	Asn	Thr	Pro	Ile	Pro	Ser	Lys	Lys	Val	Leu	Gln	485	490	495	

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Thr	Met	Leu	Asp	Thr	Lys	Ala	Thr	Asn	Trp	Lys	Glu	Phe	Leu	Lys	Glu			
			500					505					510					
Ile	Asp	Glu	Lys	Gly	Leu	Asp	Asp	Asp	Asp	Leu	Ile	Ile	Gly	Leu	Lys			
		515					520					525						
Gly	Lys	Glu	Arg	Glu	Leu	Lys	Leu	Ala	Gly	Arg	Phe	Phe	Ser	Leu	Met			
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Ser	Trp	Lys	Leu	Arg	Glu	Tyr	Phe	Val	Ile	Thr	Glu	Tyr	Leu	Ile	Lys			
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Thr	His	Phe	Val	Pro	Met	Phe	Lys	Gly	Leu	Thr	Met	Ala	Asp	Asp	Leu			
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Thr	Ala	Val	Ile	Lys	Lys	Met	Leu	Asp	Ser	Ser	Ser	Gly	Gln	Gly	Leu			
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Lys	Ser	Tyr	Glu	Ala	Ile	Cys	Ile	Ala	Asn	His	Ile	Asp	Tyr	Glu	Lys			
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Trp	Asn	Asn	His	Gln	Arg	Lys	Leu	Ser	Asn	Gly	Pro	Val	Phe	Arg	Val			
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Arg	Val	His	Asn	Asn	Thr	Leu	Ile	Asn	Ser	Thr	Ser	Gln	Arg	Val	Cys			
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Trp	Gln	Gly	Gln	Glu	Gly	Gly	Leu	Glu	Gly	Leu	Arg	Gln	Lys	Gly	Trp			
		675					680					685						
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Thr	Ala	Val	Lys	Val	Leu	Ala	Gln	Gly	Asp	Asn	Gln	Val	Ile	Cys	Thr			
705					710					715					720			
Gln	Tyr	Lys	Thr	Lys	Lys	Ser	Arg	Asn	Val	Val	Glu	Leu	Gln	Gly	Ala			
				725				730					735					
Leu	Asn	Gln	Met	Val	Ser	Asn	Asn	Glu	Lys	Ile	Met	Thr	Ala	Ile	Lys			
			740					745					750					
Ile	Gly	Thr	Gly	Lys	Leu	Gly	Leu	Leu	Ile	Asn	Asp	Asp	Glu	Thr	Met			
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Gln	Ser	Ala	Asp	Tyr	Leu	Asn	Tyr	Gly	Lys	Ile	Pro	Ile	Phe	Arg	Gly			
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Val	Ile	Arg	Gly	Leu	Glu	Thr	Lys	Arg	Trp	Ser	Arg	Val	Thr	Cys	Val	785	790	795	800
Thr	Asn	Asp	Gln	Ile	Pro	Thr	Cys	Ala	Asn	Ile	Met	Ser	Ser	Val	Ser	805	810	815	
Thr	Asn	Ala	Leu	Thr	Val	Ala	His	Phe	Ala	Glu	Asn	Pro	Ile	Asn	Ala	820	825	830	
Met	Ile	Gln	Tyr	Asn	Tyr	Phe	Gly	Thr	Phe	Ala	Arg	Leu	Leu	Leu	Met	835	840	845	
Met	His	Asp	Pro	Ala	Leu	Arg	Gln	Ser	Leu	Tyr	Glu	Val	Gln	Asp	Lys	850	855	860	
Ile	Pro	Gly	Leu	His	Ser	Ser	Thr	Phe	Lys	Tyr	Ala	Met	Leu	Tyr	Leu	865	870	875	880
Asp	Pro	Ser	Ile	Gly	Gly	Val	Ser	Gly	Met	Ser	Leu	Ser	Arg	Phe	Leu	885	890	895	
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Phe	Ile	His	Val	His	Ala	Arg	Ser	Glu	His	Leu	Lys	Glu	Met	Ser	Ala	915	920	925	
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Tyr	His	Glu	Glu	Asp	Arg	Leu	Arg	Ser	Phe	Leu	Trp	Ser	Ile	Asn	Pro	995	1000	1005	
Leu	Phe	Pro	Arg	Phe	Leu	Ser	Glu	Phe	Lys	Ser	Gly	Thr	Phe	Leu	Gly	1010	1015	1020	
Val	Ala	Asp	Gly	Leu	Ile	Ser	Leu	Phe	Gln	Asn	Ser	Arg	Thr	Ile	Arg	1025	1030	1035	1040
Asn	Ser	Phe	Lys	Lys	Lys	Tyr	His	Arg	Glu	Leu	Asp	Asp	Leu	Ile	Val	1045	1050	1055	
Arg	Ser	Glu	Val	Ser	Ser	Leu	Thr	His	Leu	Gly	Lys	Leu	His	Leu	Arg	1060	1065	1070	

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Leu Arg Tyr Lys Ser Trp Gly Arg Thr Val Ile Gly Thr Thr Val Pro		
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His Pro Leu Glu Met Leu Gly Pro Gln His Arg Lys Glu Thr Pro Cys		
1105	1110	1115 1120
Ala Pro Cys Asn Thr Ser Gly Phe Asn Tyr Val Ser Val His Cys Pro		
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Asp Gly Ile His Asp Val Phe Ser Ser Arg Gly Pro Leu Pro Ala Tyr		
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Leu Gly Ser Lys Thr Ser Glu Ser Thr Ser Ile Leu Gln Pro Trp Glu		
	1155	1160 1165
Arg Glu Ser Lys Val Pro Leu Ile Lys Arg Ala Thr Arg Leu Arg Asp		
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Ala Ile Ser Trp Phe Val Glu Pro Asp Ser Lys Leu Ala Met Thr Ile		
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Leu Ser Asn Ile His Ser Leu Thr Gly Glu Glu Trp Thr Lys Arg Gln		
	1205	1210 1215
His Gly Phe Lys Arg Thr Gly Ser Ala Leu His Arg Phe Ser Thr Ser		
	1220	1225 1230
Arg Met Ser His Gly Gly Phe Ala Ser Gln Ser Thr Ala Ala Leu Thr		
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Arg Leu Met Ala Thr Thr Asp Thr Met Arg Asp Leu Gly Asp Gln Asn		
	1250	1255 1260
Phe Asp Phe Leu Phe Gln Ala Thr Leu Leu Tyr Ala Gln Ile Thr Thr		
1265	1270	1275 1280
Thr Val Ala Arg Asp Gly Trp Ile Thr Ser Cys Thr Asp His Tyr His		
	1285	1290 1295
Ile Ala Cys Lys Ser Cys Leu Arg Pro Ile Glu Glu Ile Thr Leu Asp		
	1300	1305 1310
Ser Ser Met Asp Tyr Thr Pro Pro Asp Val Ser His Val Leu Lys Thr		
	1315	1320 1325
Trp Arg Asn Gly Glu Gly Ser Trp Gly Gln Glu Ile Lys Gln Ile Tyr		
	1330	1335 1340
Pro Leu Glu Gly Asn Trp Lys Asn Leu Ala Pro Ala Glu Gln Ser Tyr		
1345	1350	1355 1360

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Gln Val Gly Arg Cys Ile Gly Phe Leu Tyr Gly Asp Leu Ala Tyr Arg
 1365 1370 1375

Lys Ser Thr His Ala Glu Asp Ser Ser Leu Phe Pro Leu Ser Ile Gln
 1380 1385 1390

Gly Arg Ile Arg Gly Arg Gly Phe Leu Lys Gly Leu Leu Asp Gly Leu
 1395 1400 1405

Met Arg Ala Ser Cys Cys Gln Val Ile His Arg Arg Ser Leu Ala His
 1410 1415 1420

Leu Lys Arg Pro Ala Asn Ala Val Tyr Gly Gly Leu Ile Tyr Leu Ile
 1425 1430 1435 1440

Asp Lys Leu Ser Val Ser Pro Pro Phe Leu Ser Leu Thr Arg Ser Gly
 1445 1450 1455

Pro Ile Arg Asp Glu Leu Glu Thr Ile Pro His Lys Ile Pro Thr Ser
 1460 1465 1470

Tyr Pro Thr Ser Asn Arg Asp Met Gly Val Ile Val Arg Asn Tyr Phe
 1475 1480 1485

Lys Tyr Gln Cys Arg Leu Ile Glu Lys Gly Lys Tyr Arg Ser His Tyr
 1490 1495 1500

Ser Gln Leu Trp Leu Phe Ser Asp Val Leu Ser Ile Asp Phe Ile Gly
 1505 1510 1515 1520

Pro Phe Ser Ile Ser Thr Thr Leu Leu Gln Ile Leu Tyr Lys Pro Phe
 1525 1530 1535

Leu Ser Gly Lys Asp Lys Asn Glu Leu Arg Glu Leu Ala Asn Leu Ser
 1540 1545 1550

Ser Leu Leu Arg Ser Gly Glu Gly Trp Glu Asp Ile His Val Lys Phe
 1555 1560 1565

Phe Thr Lys Asp Ile Leu Leu Cys Pro Glu Glu Ile Arg His Ala Cys
 1570 1575 1580

Lys Phe Gly Ile Ala Lys Asp Asn Asn Lys Asp Met Ser Tyr Pro Pro
 1585 1590 1595 1600

Trp Gly Arg Glu Ser Arg Gly Thr Ile Thr Thr Ile Pro Val Tyr Tyr
 1605 1610 1615

Thr Thr Thr Pro Tyr Pro Lys Met Leu Glu Met Pro Pro Arg Ile Gln
 1620 1625 1630

Asn Pro Leu Leu Ser Gly Ile Arg Leu Gly Gln Leu Pro Thr Gly Ala
 1635 1640 1645

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His Tyr Lys Ile Arg Ser Ile Leu His Gly Met Gly Ile His Tyr Arg		
1650	1655	1660
Asp Phe Leu Ser Cys Gly Asp Gly Ser Gly Gly Met Thr Ala Ala Leu		
1665	1670	1675 1680
Leu Arg Glu Asn Val His Ser Arg Gly Ile Phe Asn Ser Leu Leu Glu		
	1685	1690 1695
Leu Ser Gly Ser Val Met Arg Gly Ala Ser Pro Glu Pro Pro Ser Ala		
	1700	1705 1710
Leu Glu Thr Leu Gly Gly Asp Lys Ser Arg Cys Val Asn Gly Glu Thr		
	1715	1720 1725
Cys Trp Glu Tyr Pro Ser Asp Leu Cys Asp Pro Arg Thr Trp Asp Tyr		
	1730	1735 1740
Phe Leu Arg Leu Lys Ala Gly Leu Gly Leu Gln Ile Asp Leu Ile Val		
	1745	1750 1755 1760
Met Asp Met Glu Val Arg Asp Ser Ser Thr Ser Leu Lys Ile Glu Thr		
	1765	1770 1775
Asn Val Arg Asn Tyr Val His Arg Ile Leu Asp Glu Gln Gly Val Leu		
	1780	1785 1790
Ile Tyr Lys Thr Tyr Gly Thr Tyr Ile Cys Glu Ser Glu Lys Asn Ala		
	1795	1800 1805
Val Thr Ile Leu Gly Pro Met Phe Lys Thr Val Asp Leu Val Gln Thr		
	1810	1815 1820
Glu Phe Ser Ser Ser Gln Thr Ser Glu Val Tyr Met Val Cys Lys Gly		
	1825	1830 1835 1840
Leu Lys Lys Leu Ile Asp Glu Pro Asn Pro Asp Trp Ser Ser Ile Asn		
	1845	1850 1855
Glu Ser Trp Lys Asn Leu Tyr Ala Phe Gln Ser Ser Glu Gln Glu Phe		
	1860	1865 1870
Ala Arg Ala Lys Lys Val Ser Thr Tyr Phe Thr Leu Thr Gly Ile Pro		
	1875	1880 1885
Ser Gln Phe Ile Pro Asp Pro Phe Val Asn Ile Glu Thr Met Leu Gln		
	1890	1895 1900
Ile Phe Gly Val Pro Thr Gly Val Ser His Ala Ala Ala Leu Lys Ser		
	1905	1910 1915 1920
Ser Asp Arg Pro Ala Asp Leu Leu Thr Ile Ser Leu Phe Tyr Met Ala		
	1925	1930 1935

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Ile Ile Ser Tyr Tyr Asn Ile Asn His Ile Arg Val Gly Pro Ile Pro
 1940 1945 1950
 Pro Asn Pro Pro Ser Asp Gly Ile Ala Gln Asn Val Gly Ile Ala Ile
 1955 1960 1965
 Thr Gly Ile Ser Phe Trp Leu Ser Leu Met Glu Lys Asp Ile Pro Leu
 1970 1975 1980
 Tyr Gln Gln Cys Leu Ala Val Ile Gln Gln Ser Phe Pro Ile Arg Trp
 1985 1990 1995 2000
 Glu Ala Val Ser Val Lys Gly Gly Tyr Lys Gln Lys Trp Ser Thr Arg
 2005 2010 2015
 Gly Asp Gly Leu Pro Lys Asp Thr Arg Thr Ser Asp Ser Leu Ala Pro
 2020 2025 2030
 Ile Gly Asn Trp Ile Arg Ser Leu Glu Leu Val Arg Asn Gln Val Arg
 2035 2040 2045
 Leu Asn Pro Phe Asn Glu Ile Leu Phe Asn Gln Leu Cys Arg Thr Val
 2050 2055 2060
 Asp Asn His Leu Lys Trp Ser Asn Leu Arg Arg Asn Thr Gly Met Ile
 2065 2070 2075 2080
 Glu Trp Ile Asn Arg Arg Ile Ser Lys Glu Asp Arg Ser Ile Leu Met
 2085 2090 2095
 Leu Lys Ser Asp Leu His Glu Glu Asn Ser Trp Arg Asp
 2100 2105

<210> 51

<211> 1753

<212> PRT

<213> Vesicular stomatitis virus

<220>

<221> MOD_RES

<222> (1)..(1753)

<223> "Xaa" represents any, other or unknown amino acid

<400> 51

His Trp Gly His Pro Phe Ile Asp Tyr Tyr Ala Gly Leu Glu Lys Leu
 1 5 10 15

His Ser Gln Val Thr Xaa Lys Lys Asp Ile Asp Val Ser Tyr Ala Lys
 20 25 30

Ala Leu Ala Ser Asp Leu Ala Arg Ile Val Leu Phe Gln Gln Phe Asn
 35 40 45

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Asp	His	Xaa	Lys	Trp	Phe	Val	Asn	Gly	Asp	Leu	Leu	Pro	His	Asp	His	50	55	60	
Pro	Phe	Lys	Ser	His	Val	Lys	Glu	Asn	Thr	Trp	Pro	Thr	Ala	Ala	Gln	65	70	75	80
Val	Gln	Asp	Phe	Gly	Asp	Lys	Trp	His	Glu	Leu	Pro	Leu	Ile	Lys	Cys	85	90	95	
Phe	Glu	Ile	Pro	Asp	Leu	Leu	Asp	Pro	Ser	Ile	Ile	Tyr	Ser	Asp	Lys	100	105	110	
Ser	His	Ser	Met	Asn	Arg	Ser	Glu	Val	Leu	Lys	His	Val	Arg	Met	Asn	115	120	125	
Pro	Asn	Thr	Pro	Ile	Pro	Ser	Lys	Lys	Val	Leu	Gln	Thr	Met	Leu	Asp	130	135	140	
Thr	Lys	Ala	Thr	Asn	Trp	Lys	Glu	Phe	Leu	Lys	Glu	Ile	Asp	Glu	Lys	145	150	155	160
Gly	Leu	Asp	Asp	Asp	Asp	Leu	Ile	Ile	Gly	Leu	Lys	Gly	Lys	Glu	Arg	165	170	175	
Glu	Leu	Lys	Leu	Ala	Gly	Arg	Phe	Phe	Ser	Leu	Met	Ser	Trp	Lys	Leu	180	185	190	
Arg	Glu	Tyr	Phe	Val	Ile	Thr	Glu	Tyr	Leu	Ile	Lys	Thr	His	Phe	Val	195	200	205	
Pro	Met	Phe	Lys	Gly	Leu	Thr	Met	Ala	Asp	Asp	Leu	Thr	Ala	Val	Ile	210	215	220	
Lys	Lys	Met	Leu	Asp	Ser	Ser	Ser	Gly	Gln	Gly	Leu	Lys	Ser	Tyr	Glu	225	230	235	240
Ala	Ile	Cys	Ile	Ala	Asn	His	Ile	Asp	Tyr	Glu	Lys	Trp	Asn	Asn	His	245	250	255	
Gln	Arg	Lys	Leu	Ser	Asn	Gly	Pro	Val	Phe	Arg	Val	Met	Gly	Gln	Phe	260	265	270	
Leu	Gly	Tyr	Pro	Ser	Leu	Ile	Glu	Arg	Thr	His	Glu	Phe	Phe	Glu	Lys	275	280	285	
Ser	Leu	Ile	Tyr	Tyr	Asn	Gly	Arg	Pro	Asp	Leu	Met	Arg	Val	His	Asn	290	295	300	
Asn	Thr	Leu	Ile	Asn	Ser	Thr	Ser	Gln	Arg	Val	Cys	Trp	Gln	Gly	Gln	305	310	315	320
Glu	Gly	Gly	Leu	Glu	Gly	Leu	Arg	Gln	Lys	Gly	Trp	Ser	Ile	Leu	Asn	325	330	335	

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Leu	Leu	Val	Ile	Gln	Arg	Glu	Ala	Lys	Ile	Arg	Asn	Thr	Ala	Val	Lys	340	345	350	
Val	Leu	Ala	Gln	Gly	Asp	Asn	Gln	Val	Ile	Cys	Thr	Gln	Tyr	Lys	Thr	355	360	365	
Lys	Lys	Ser	Arg	Asn	Val	Val	Glu	Leu	Gln	Gly	Ala	Leu	Asn	Gln	Met	370	375	380	
Val	Ser	Asn	Asn	Glu	Lys	Ile	Met	Thr	Ala	Ile	Lys	Ile	Gly	Thr	Gly	385	390	395	400
Lys	Leu	Gly	Leu	Leu	Ile	Asn	Asp	Asp	Glu	Thr	Met	Gln	Ser	Ala	Asp	405	410	415	
Tyr	Leu	Asn	Tyr	Gly	Lys	Ile	Pro	Ile	Phe	Arg	Gly	Val	Ile	Arg	Gly	420	425	430	
Leu	Glu	Thr	Lys	Arg	Trp	Ser	Arg	Val	Thr	Cys	Val	Thr	Asn	Asp	Gln	435	440	445	
Ile	Pro	Thr	Cys	Ala	Asn	Ile	Met	Ser	Ser	Val	Ser	Thr	Asn	Ala	Leu	450	455	460	
Thr	Val	Ala	His	Phe	Ala	Glu	Asn	Pro	Ile	Asn	Ala	Met	Ile	Gln	Tyr	465	470	475	480
Asn	Tyr	Phe	Gly	Thr	Phe	Ala	Arg	Leu	Leu	Leu	Met	Met	His	Asp	Pro	485	490	495	
Ala	Leu	Arg	Gln	Ser	Leu	Tyr	Glu	Val	Gln	Asp	Lys	Ile	Pro	Gly	Leu	500	505	510	
His	Ser	Ser	Thr	Phe	Lys	Tyr	Ala	Met	Leu	Tyr	Leu	Asp	Pro	Ser	Ile	515	520	525	
Gly	Gly	Val	Ser	Gly	Met	Ser	Leu	Ser	Arg	Phe	Leu	Ile	Arg	Ala	Phe	530	535	540	
Pro	Asp	Pro	Val	Thr	Glu	Ser	Leu	Ser	Phe	Trp	Arg	Phe	Ile	His	Val	545	550	555	560
His	Ala	Arg	Ser	Glu	His	Leu	Lys	Glu	Met	Ser	Ala	Val	Phe	Gly	Asn	565	570	575	
Pro	Glu	Ile	Ala	Lys	Phe	Arg	Ile	Thr	His	Ile	Asp	Lys	Leu	Val	Glu	580	585	590	
Asp	Pro	Thr	Ser	Leu	Asn	Ile	Ala	Met	Gly	Met	Ser	Pro	Ala	Asn	Leu	595	600	605	
Leu	Lys	Thr	Glu	Val	Lys	Lys	Cys	Leu	Ile	Glu	Ser	Arg	Gln	Thr	Ile	610	615	620	

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Arg	Asn	Gln	Val	Ile	Lys	Asp	Ala	Thr	Ile	Tyr	Leu	Tyr	His	Glu	Glu
625					630					635					640
Asp	Arg	Leu	Arg	Ser	Phe	Leu	Trp	Ser	Ile	Asn	Pro	Leu	Phe	Pro	Arg
				645					650					655	
Phe	Leu	Ser	Glu	Phe	Lys	Ser	Gly	Thr	Phe	Leu	Gly	Val	Ala	Asp	Gly
			660					665					670		
Leu	Ile	Ser	Leu	Phe	Gln	Asn	Ser	Arg	Thr	Ile	Arg	Asn	Ser	Phe	Lys
		675					680					685			
Lys	Lys	Tyr	His	Arg	Glu	Leu	Asp	Asp	Leu	Ile	Val	Arg	Ser	Glu	Val
	690					695					700				
Ser	Ser	Leu	Thr	His	Leu	Gly	Lys	Leu	His	Leu	Arg	Arg	Gly	Ser	Cys
705					710					715					720
Lys	Met	Trp	Thr	Cys	Ser	Ala	Thr	His	Ala	Asp	Thr	Leu	Arg	Tyr	Lys
				725					730					735	
Ser	Trp	Gly	Arg	Thr	Val	Ile	Gly	Thr	Thr	Val	Pro	His	Pro	Leu	Glu
			740					745					750		
Met	Leu	Gly	Pro	Gln	His	Arg	Lys	Glu	Thr	Pro	Cys	Ala	Pro	Cys	Asn
		755					760					765			
Thr	Ser	Gly	Phe	Asn	Tyr	Val	Ser	Val	His	Cys	Pro	Asp	Gly	Ile	His
	770					775					780				
Asp	Val	Phe	Ser	Ser	Arg	Gly	Pro	Leu	Pro	Ala	Tyr	Leu	Gly	Ser	Lys
785					790					795					800
Thr	Ser	Glu	Ser	Thr	Ser	Ile	Leu	Gln	Pro	Trp	Glu	Arg	Glu	Ser	Lys
				805					810					815	
Val	Pro	Leu	Ile	Lys	Arg	Ala	Thr	Arg	Leu	Arg	Asp	Ala	Ile	Ser	Trp
			820					825					830		
Phe	Val	Glu	Pro	Asp	Ser	Lys	Leu	Ala	Met	Thr	Ile	Leu	Ser	Asn	Ile
		835					840					845			
His	Ser	Leu	Thr	Gly	Glu	Glu	Trp	Thr	Lys	Arg	Gln	His	Gly	Phe	Lys
	850					855					860				
Arg	Thr	Gly	Ser	Ala	Leu	His	Arg	Phe	Ser	Thr	Ser	Arg	Met	Ser	His
865					870					875					880
Gly	Gly	Phe	Ala	Ser	Gln	Ser	Thr	Ala	Ala	Leu	Thr	Arg	Leu	Met	Ala
				885					890					895	
Thr	Thr	Asp	Thr	Met	Arg	Asp	Leu	Gly	Asp	Gln	Asn	Phe	Asp	Phe	Leu
			900					905					910		

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Phe	Gln	Ala	Thr	Leu	Leu	Tyr	Ala	Gln	Ile	Thr	Thr	Thr	Val	Ala	Arg	915	920	925	
Asp	Gly	Trp	Ile	Thr	Ser	Cys	Thr	Asp	His	Tyr	His	Ile	Ala	Cys	Lys	930	935	940	
Ser	Cys	Leu	Arg	Pro	Ile	Glu	Glu	Ile	Thr	Leu	Asp	Ser	Ser	Met	Asp	945	950	955	960
Tyr	Thr	Pro	Pro	Asp	Val	Ser	His	Val	Leu	Lys	Thr	Trp	Arg	Asn	Gly	965	970	975	
Glu	Gly	Ser	Trp	Gly	Gln	Glu	Ile	Lys	Gln	Ile	Tyr	Pro	Leu	Glu	Gly	980	985	990	
Asn	Trp	Lys	Asn	Leu	Ala	Pro	Ala	Glu	Gln	Ser	Tyr	Gln	Val	Gly	Arg	995	1000	1005	
Cys	Ile	Gly	Phe	Leu	Tyr	Gly	Asp	Leu	Ala	Tyr	Arg	Lys	Ser	Thr	His	1010	1015	1020	
Ala	Glu	Asp	Ser	Ser	Leu	Phe	Pro	Leu	Ser	Ile	Gln	Gly	Arg	Ile	Arg	1025	1030	1035	1040
Gly	Arg	Gly	Phe	Leu	Lys	Gly	Leu	Leu	Asp	Gly	Leu	Met	Arg	Ala	Ser	1045	1050	1055	
Cys	Cys	Gln	Val	Ile	His	Arg	Arg	Ser	Leu	Ala	His	Leu	Lys	Arg	Pro	1060	1065	1070	
Ala	Asn	Ala	Val	Tyr	Gly	Gly	Leu	Ile	Tyr	Leu	Ile	Asp	Lys	Leu	Ser	1075	1080	1085	
Val	Ser	Pro	Pro	Phe	Leu	Ser	Leu	Thr	Arg	Ser	Gly	Pro	Ile	Arg	Asp	1090	1095	1100	
Glu	Leu	Glu	Thr	Ile	Pro	His	Lys	Ile	Pro	Thr	Ser	Tyr	Pro	Thr	Ser	1105	1110	1115	1120
Asn	Arg	Asp	Met	Gly	Val	Ile	Val	Arg	Asn	Tyr	Phe	Lys	Tyr	Gln	Cys	1125	1130	1135	
Arg	Leu	Ile	Glu	Lys	Gly	Lys	Tyr	Arg	Ser	His	Tyr	Ser	Gln	Leu	Trp	1140	1145	1150	
Leu	Phe	Ser	Asp	Val	Leu	Ser	Ile	Asp	Phe	Ile	Gly	Pro	Phe	Ser	Ile	1155	1160	1165	
Ser	Thr	Thr	Leu	Leu	Gln	Ile	Leu	Tyr	Lys	Pro	Phe	Leu	Ser	Gly	Lys	1170	1175	1180	
Asp	Lys	Asn	Glu	Leu	Arg	Glu	Leu	Ala	Asn	Leu	Ser	Ser	Leu	Leu	Arg	1185	1190	1195	1200

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Ser Gly Glu Gly Trp Glu Asp Ile His Val Lys Phe Phe Thr Lys Asp
 1205 1210 1215
 Ile Leu Leu Cys Pro Glu Glu Ile Arg His Ala Cys Lys Phe Gly Ile
 1220 1225 1230
 Ala Lys Asp Asn Asn Lys Asp Met Ser Tyr Pro Pro Trp Gly Arg Glu
 1235 1240 1245
 Ser Arg Gly Thr Ile Thr Thr Ile Pro Val Tyr Tyr Thr Thr Thr Pro
 1250 1255 1260
 Tyr Pro Lys Met Leu Glu Met Pro Pro Arg Ile Gln Asn Pro Leu Leu
 1265 1270 1275 1280
 Ser Gly Ile Arg Leu Gly Gln Leu Pro Thr Gly Ala His Tyr Lys Ile
 1285 1290 1295
 Arg Ser Ile Leu His Gly Met Gly Ile His Tyr Arg Asp Phe Leu Ser
 1300 1305 1310
 Cys Gly Asp Gly Ser Gly Gly Met Thr Ala Ala Leu Leu Arg Glu Asn
 1315 1320 1325
 Val His Ser Arg Gly Ile Phe Asn Ser Leu Leu Glu Leu Ser Gly Ser
 1330 1335 1340
 Val Met Arg Gly Ala Ser Pro Glu Pro Pro Ser Ala Leu Glu Thr Leu
 1345 1350 1355 1360
 Gly Gly Asp Lys Ser Arg Cys Val Asn Gly Glu Thr Cys Trp Glu Tyr
 1365 1370 1375
 Pro Ser Asp Leu Cys Asp Pro Arg Thr Trp Asp Tyr Phe Leu Arg Leu
 1380 1385 1390
 Lys Ala Gly Leu Gly Leu Gln Ile Asp Leu Ile Val Met Asp Met Glu
 1395 1400 1405
 Val Arg Asp Ser Ser Thr Ser Leu Lys Ile Glu Thr Asn Val Arg Asn
 1410 1415 1420
 Tyr Val His Arg Ile Leu Asp Glu Gln Gly Val Leu Ile Tyr Lys Thr
 1425 1430 1435 1440
 Tyr Gly Thr Tyr Ile Cys Glu Ser Glu Lys Asn Ala Val Thr Ile Leu
 1445 1450 1455
 Gly Pro Met Phe Lys Thr Val Asp Leu Val Gln Thr Glu Phe Ser Ser
 1460 1465 1470
 Ser Gln Thr Ser Glu Val Tyr Met Val Cys Lys Gly Leu Lys Lys Leu
 1475 1480 1485

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Ile Asp Glu Pro Asn Pro Asp Trp Ser Ser Ile Asn Glu Ser Trp Lys
 1490 1495 1500
 Asn Leu Tyr Ala Phe Gln Ser Ser Glu Gln Glu Phe Ala Arg Ala Lys
 1505 1510 1515 1520
 Lys Val Ser Thr Tyr Phe Thr Leu Thr Gly Ile Pro Ser Gln Phe Ile
 1525 1530 1535
 Pro Asp Pro Phe Val Asn Ile Glu Thr Met Leu Gln Ile Phe Gly Val
 1540 1545 1550
 Pro Thr Gly Val Ser His Ala Ala Ala Leu Lys Ser Ser Asp Arg Pro
 1555 1560 1565
 Ala Asp Leu Leu Thr Ile Ser Leu Phe Tyr Met Ala Ile Ile Ser Tyr
 1570 1575 1580
 Tyr Asn Ile Asn His Ile Arg Val Gly Pro Ile Pro Pro Asn Pro Pro
 1585 1590 1595 1600
 Ser Asp Gly Ile Ala Gln Asn Val Gly Ile Ala Ile Thr Gly Ile Ser
 1605 1610 1615
 Phe Trp Leu Ser Leu Met Glu Lys Asp Ile Pro Leu Tyr Gln Gln Cys
 1620 1625 1630
 Leu Ala Val Ile Gln Gln Ser Phe Pro Ile Arg Trp Glu Ala Val Ser
 1635 1640 1645
 Val Lys Gly Gly Tyr Lys Gln Lys Trp Ser Thr Arg Gly Asp Gly Leu
 1650 1655 1660
 Pro Lys Asp Thr Arg Ile Ser Asp Ser Leu Ala Pro Ile Gly Asn Trp
 1665 1670 1675 1680
 Ile Arg Ser Leu Glu Leu Val Arg Asn Gln Val Arg Leu Asn Pro Phe
 1685 1690 1695
 Asn Glu Ile Leu Phe Asn Gln Leu Cys Arg Thr Val Asp Asn His Leu
 1700 1705 1710
 Lys Trp Ser Asn Leu Arg Lys Asn Thr Gly Met Ile Glu Trp Ile Asn
 1715 1720 1725
 Arg Arg Ile Ser Lys Glu Asp Arg Ser Ile Leu Met Leu Lys Ser Asp
 1730 1735 1740
 Leu His Glu Glu Asn Ser Trp Arg Asp
 1745 1750

<210> 52

<211> 2109

<212> PRT

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<213> Vesicular stomatitis virus

<220>

<221> MOD_RES

<222> (1)..(2109)

<223> "Xaa" represents any, other or unknown amino acid

<400> 52

Met	Glu	Val	His	Asp	Phe	Glu	Thr	Asp	Glu	Phe	Asn	Asp	Phe	Asn	Glu
1				5					10					15	

Asp	Asp	Tyr	Ala	Thr	Arg	Glu	Phe	Leu	Asn	Pro	Asp	Glu	Arg	Met	Thr
			20					25					30		

Tyr	Leu	Asn	His	Ala	Asp	Tyr	Asn	Leu	Asn	Ser	Pro	Leu	Ile	Ser	Asp
		35					40					45			

Asp	Ile	Asp	Asn	Leu	Ile	Arg	Lys	Phe	Asn	Ser	Leu	Pro	Ile	Pro	Ser
	50					55					60				

Met	Trp	Asp	Ser	Lys	Asn	Trp	Asp	Gly	Val	Leu	Glu	Met	Leu	Thr	Ser
65					70					75					80

Cys	Gln	Ala	Asn	Pro	Ile	Ser	Thr	Ser	Gln	Met	His	Lys	Trp	Met	Gly
				85					90					95	

Ser	Trp	Leu	Met	Ser	Asp	Asn	His	Asp	Ala	Ser	Gln	Gly	Tyr	Ser	Phe
		100						105					110		

Leu	His	Glu	Val	Asp	Lys	Glu	Ala	Glu	Ile	Thr	Phe	Asp	Val	Val	Glu
		115					120					125			

Thr	Phe	Ile	Arg	Gly	Trp	Gly	Asn	Lys	Pro	Ile	Glu	Tyr	Ile	Lys	Lys
	130					135					140				

Glu	Arg	Trp	Thr	Asp	Ser	Phe	Lys	Ile	Leu	Ala	Tyr	Leu	Cys	Gln	Lys
145					150					155					160

Phe	Leu	Asp	Leu	His	Lys	Leu	Thr	Leu	Ile	Leu	Asn	Ala	Val	Ser	Glu
				165					170					175	

Val	Glu	Leu	Leu	Asn	Leu	Ala	Arg	Thr	Phe	Lys	Gly	Lys	Val	Arg	Arg
			180					185					190		

Ser	Ser	His	Gly	Thr	Asn	Ile	Cys	Arg	Leu	Arg	Val	Pro	Ser	Leu	Gly
		195					200					205			

Pro	Thr	Phe	Ile	Ser	Glu	Gly	Trp	Ala	Tyr	Phe	Lys	Lys	Leu	Asp	Ile
	210					215					220				

Leu	Met	Asp	Arg	Asn	Phe	Leu	Leu	Met	Val	Lys	Asp	Val	Ile	Ile	Gly
225					230					235					240

Arg	Met	Gln	Thr	Val	Leu	Ser	Met	Val	Cys	Arg	Ile	Asp	Asn	Leu	Phe
				245					250					255	

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Ser	Glu	Gln	Asp	Ile	Phe	Ser	Leu	Leu	Asn	Ile	Tyr	Arg	Ile	Gly	Asp		
			260						265					270			
Lys	Ile	Val	Glu	Arg	Gln	Gly	Asn	Phe	Ser	Tyr	Asp	Leu	Ile	Lys	Met		
		275					280					285					
Val	Glu	Pro	Ile	Cys	Asn	Leu	Arg	Leu	Met	Lys	Leu	Ala	Arg	Glu	Ser		
	290					295					300						
Arg	Pro	Leu	Val	Pro	Gln	Phe	Pro	His	Phe	Glu	Asn	His	Ile	Lys	Thr		
305					310					315					320		
Ser	Val	Asp	Glu	Gly	Ala	Lys	Ile	Asp	Arg	Gly	Ile	Arg	Phe	Leu	His		
				325					330					335			
Asp	Gln	Ile	Met	Ser	Val	Lys	Thr	Val	Asp	Leu	Thr	Leu	Val	Ile	Tyr		
			340					345					350				
Gly	Ser	Phe	Arg	His	Trp	Gly	His	Pro	Phe	Ile	Asp	Tyr	Tyr	Ala	Gly		
		355					360					365					
Leu	Glu	Lys	Leu	His	Ser	Gln	Val	Thr	Met	Lys	Lys	Asp	Ile	Asp	Val		
	370					375					380						
Ser	Tyr	Ala	Lys	Ala	Leu	Ala	Ser	Asp	Leu	Ala	Arg	Ile	Val	Leu	Phe		
385					390					395					400		
Gln	Gln	Phe	Asn	Asp	His	Lys	Lys	Trp	Phe	Val	Asn	Gly	Asp	Leu	Leu		
				405					410					415			
Pro	His	Asp	His	Pro	Phe	Lys	Ser	His	Val	Lys	Glu	Asn	Thr	Trp	Pro		
			420					425					430				
Thr	Ala	Ala	Gln	Val	Gln	Asp	Phe	Gly	Asp	Lys	Trp	His	Glu	Leu	Pro		
		435					440					445					
Leu	Ile	Lys	Cys	Phe	Glu	Ile	Pro	Asp	Leu	Leu	Asp	Pro	Ser	Ile	Ile		
	450					455					460						
Tyr	Ser	Asp	Lys	Ser	His	Ser	Met	Asn	Arg	Ser	Glu	Val	Leu	Lys	His		
465					470					475					480		
Val	Arg	Met	Asn	Pro	Asn	Thr	Pro	Ile	Pro	Ser	Lys	Lys	Val	Leu	Gln		
				485					490					495			
Thr	Met	Leu	Asp	Thr	Lys	Ala	Thr	Asn	Trp	Lys	Glu	Phe	Leu	Lys	Glu		
			500					505					510				
Ile	Asp	Glu	Lys	Gly	Leu	Asp	Asp	Asp	Asp	Leu	Ile	Ile	Gly	Leu	Lys		
		515					520					525					
Gly	Lys	Glu	Arg	Glu	Leu	Lys	Leu	Ala	Gly	Arg	Phe	Phe	Ser	Leu	Met		
						535					540						

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Ser	Trp	Lys	Leu	Arg	Glu	Tyr	Phe	Val	Ile	Thr	Glu	Tyr	Leu	Ile	Lys	545	550	555	560
Thr	His	Phe	Val	Pro	Met	Phe	Lys	Gly	Leu	Thr	Met	Ala	Asp	Asp	Leu	565	570	575	
Thr	Ala	Val	Ile	Lys	Lys	Met	Leu	Asp	Ser	Ser	Ser	Gly	Gln	Gly	Leu	580	585	590	
Lys	Ser	Tyr	Glu	Ala	Ile	Cys	Ile	Ala	Asn	His	Ile	Asp	Tyr	Glu	Lys	595	600	605	
Trp	Asn	Asn	His	Gln	Arg	Lys	Leu	Ser	Asn	Gly	Pro	Val	Phe	Arg	Val	610	615	620	
Met	Gly	Gln	Phe	Leu	Gly	Tyr	Pro	Ser	Leu	Ile	Glu	Arg	Thr	His	Glu	625	630	635	640
Phe	Phe	Glu	Lys	Ser	Leu	Ile	Tyr	Tyr	Asn	Gly	Arg	Pro	Asp	Leu	Met	645	650	655	
Arg	Val	His	Asn	Asn	Thr	Leu	Ile	Asn	Ser	Thr	Ser	Gln	Arg	Val	Cys	660	665	670	
Trp	Gln	Gly	Gln	Glu	Gly	Gly	Leu	Glu	Gly	Leu	Arg	Gln	Lys	Gly	Trp	675	680	685	
Ser	Ile	Leu	Asn	Leu	Leu	Val	Ile	Gln	Arg	Glu	Ala	Lys	Ile	Arg	Asn	690	695	700	
Thr	Ala	Val	Lys	Val	Leu	Ala	Gln	Gly	Asp	Asn	Gln	Val	Ile	Cys	Thr	705	710	715	720
Gln	Tyr	Lys	Thr	Lys	Lys	Ser	Arg	Asn	Val	Val	Glu	Leu	Gln	Gly	Ala	725	730	735	
Leu	Asn	Gln	Met	Val	Ser	Asn	Asn	Glu	Lys	Ile	Met	Thr	Ala	Ile	Lys	740	745	750	
Ile	Gly	Thr	Gly	Lys	Leu	Gly	Leu	Leu	Ile	Asn	Asp	Asp	Glu	Thr	Met	755	760	765	
Gln	Ser	Ala	Asp	Tyr	Leu	Asn	Tyr	Gly	Lys	Ile	Pro	Ile	Phe	Arg	Gly	770	775	780	
Val	Ile	Arg	Gly	Leu	Glu	Thr	Lys	Arg	Trp	Ser	Arg	Val	Thr	Cys	Val	785	790	795	800
Thr	Asn	Asp	Gln	Ile	Pro	Thr	Cys	Ala	Asn	Ile	Met	Ser	Ser	Val	Ser	805	810	815	
Thr	Asn	Ala	Leu	Thr	Val	Ala	His	Phe	Ala	Glu	Asn	Pro	Ile	Asn	Ala	820	825	830	

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Met	Ile	Gln	Tyr	Asn	Tyr	Phe	Gly	Thr	Phe	Ala	Arg	Leu	Leu	Leu	Met	835	840	845
Met	His	Asp	Pro	Ala	Leu	Arg	Gln	Ser	Leu	Tyr	Glu	Val	Gln	Asp	Lys	850	855	860
Ile	Pro	Gly	Leu	His	Ser	Ser	Thr	Phe	Lys	Tyr	Ala	Met	Leu	Tyr	Leu	865	870	875
Asp	Pro	Ser	Ile	Gly	Gly	Val	Ser	Gly	Met	Ser	Leu	Ser	Arg	Phe	Leu	885	890	895
Ile	Arg	Ala	Phe	Pro	Asp	Pro	Val	Thr	Glu	Ser	Leu	Ser	Phe	Trp	Arg	900	905	910
Phe	Ile	His	Val	His	Ala	Arg	Ser	Glu	His	Leu	Lys	Glu	Met	Ser	Ala	915	920	925
Val	Phe	Gly	Asn	Pro	Glu	Ile	Ala	Lys	Phe	Arg	Ile	Thr	His	Ile	Asp	930	935	940
Lys	Leu	Val	Glu	Asp	Pro	Thr	Ser	Leu	Asn	Ile	Ala	Met	Gly	Met	Ser	945	950	955
Pro	Ala	Asn	Leu	Leu	Lys	Thr	Glu	Val	Lys	Lys	Cys	Leu	Ile	Glu	Ser	965	970	975
Arg	Gln	Thr	Ile	Arg	Asn	Gln	Val	Ile	Lys	Asp	Ala	Thr	Ile	Tyr	Leu	980	985	990
Tyr	His	Glu	Glu	Asp	Arg	Leu	Arg	Ser	Phe	Leu	Trp	Ser	Ile	Asn	Pro	995	1000	1005
Leu	Phe	Pro	Arg	Phe	Leu	Ser	Glu	Phe	Lys	Ser	Gly	Thr	Phe	Leu	Gly	1010	1015	1020
Val	Ala	Asp	Gly	Leu	Ile	Ser	Leu	Phe	Gln	Asn	Ser	Arg	Thr	Ile	Arg	1025	1030	1035
Asn	Ser	Phe	Lys	Lys	Lys	Tyr	His	Arg	Glu	Leu	Asp	Asp	Leu	Ile	Val	1045	1050	1055
Arg	Ser	Glu	Val	Ser	Ser	Leu	Thr	His	Leu	Gly	Lys	Leu	His	Leu	Arg	1060	1065	1070
Arg	Gly	Ser	Cys	Lys	Met	Trp	Thr	Cys	Ser	Ala	Thr	His	Ala	Asp	Thr	1075	1080	1085
Leu	Arg	Tyr	Lys	Ser	Trp	Gly	Arg	Thr	Val	Ile	Gly	Thr	Thr	Val	Pro	1090	1095	1100
His	Pro	Leu	Glu	Met	Leu	Gly	Pro	Gln	His	Arg	Lys	Glu	Thr	Pro	Cys	1105	1110	1115

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Ala Pro Cys Asn Thr Ser Gly Phe Asn Tyr Val Ser Val His Cys Pro		
1125	1130	1135
Asp Gly Ile His Asp Val Phe Ser Ser Arg Gly Pro Leu Pro Ala Tyr		
1140	1145	1150
Leu Gly Ser Lys Thr Ser Glu Ser Thr Ser Ile Leu Gln Pro Trp Glu		
1155	1160	1165
Arg Glu Ser Lys Val Pro Leu Ile Lys Arg Ala Thr Arg Leu Arg Asp		
1170	1175	1180
Ala Ile Ser Trp Phe Val Glu Pro Asp Ser Lys Leu Ala Met Thr Ile		
1185	1190	1195 1200
Leu Ser Asn Ile His Ser Leu Thr Gly Glu Glu Trp Thr Lys Arg Gln		
1205	1210	1215
His Gly Phe Lys Arg Thr Gly Ser Ala Leu His Arg Phe Ser Thr Ser		
1220	1225	1230
Arg Met Ser His Gly Gly Phe Ala Ser Gln Ser Thr Ala Ala Leu Thr		
1235	1240	1245
Arg Leu Met Ala Thr Thr Asp Thr Met Arg Asp Leu Gly Asp Gln Asn		
1250	1255	1260
Phe Asp Phe Leu Phe Xaa Ala Thr Leu Leu Tyr Ala Xaa Ile Thr Thr		
1265	1270	1275 1280
Thr Val Ala Arg Asp Gly Trp Ile Thr Ser Cys Thr Asp His Tyr His		
1285	1290	1295
Ile Ala Cys Lys Ser Cys Leu Arg Pro Ile Glu Glu Ile Thr Leu Asp		
1300	1305	1310
Ser Ser Met Asp Tyr Thr Pro Pro Asp Val Ser His Val Leu Lys Thr		
1315	1320	1325
Trp Arg Asn Gly Glu Gly Ser Trp Gly Gln Glu Ile Lys Gln Ile Tyr		
1330	1335	1340
Pro Leu Glu Gly Asn Trp Lys Asn Leu Ala Pro Ala Glu Gln Ser Tyr		
1345	1350	1355 1360
Gln Val Gly Arg Cys Ile Gly Phe Leu Tyr Gly Asp Leu Ala Tyr Arg		
1365	1370	1375
Lys Ser Thr His Ala Glu Asp Ser Ser Leu Phe Pro Leu Ser Ile Gln		
1380	1385	1390
Gly Arg Ile Arg Gly Arg Gly Phe Leu Lys Gly Leu Leu Asp Gly Leu		
1395	1400	1405

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Met Arg Ala Ser Cys Cys Gln Val Ile His Arg Arg Ser Leu Ala His
 1410 1415 1420

Leu Lys Arg Pro Ala Asn Ala Val Tyr Gly Gly Leu Ile Tyr Leu Ile
 1425 1430 1435 1440

Asp Lys Leu Ser Val Ser Pro Pro Phe Leu Ser Leu Thr Arg Ser Gly
 1445 1450 1455

Pro Ile Arg Asp Glu Leu Glu Thr Ile Pro His Lys Ile Pro Thr Ser
 1460 1465 1470

Tyr Pro Thr Ser Asn Arg Asp Met Gly Val Ile Val Arg Asn Tyr Phe
 1475 1480 1485

Lys Tyr Gln Cys Arg Leu Ile Glu Lys Gly Lys Tyr Arg Ser His Tyr
 1490 1495 1500

Ser Gln Leu Trp Leu Phe Ser Asp Val Leu Ser Ile Asp Phe Ile Gly
 1505 1510 1515 1520

Pro Phe Ser Ile Ser Thr Thr Leu Leu Gln Ile Leu Tyr Lys Pro Phe
 1525 1530 1535

Leu Ser Gly Lys Asp Lys Asn Glu Leu Arg Glu Leu Ala Asn Leu Ser
 1540 1545 1550

Ser Leu Leu Arg Ser Gly Glu Gly Trp Glu Asp Ile His Val Lys Phe
 1555 1560 1565

Phe Thr Lys Asp Ile Leu Leu Cys Pro Glu Glu Ile Arg His Ala Cys
 1570 1575 1580

Lys Phe Gly Ile Ala Lys Asp Asn Asn Lys Asp Met Ser Tyr Pro Pro
 1585 1590 1595 1600

Trp Gly Arg Glu Ser Arg Gly Thr Ile Thr Thr Ile Pro Val Tyr Tyr
 1605 1610 1615

Thr Thr Thr Pro Tyr Pro Lys Met Leu Glu Met Pro Pro Arg Ile Gln
 1620 1625 1630

Asn Pro Leu Leu Ser Gly Ile Arg Leu Gly Gln Leu Pro Thr Gly Ala
 1635 1640 1645

His Tyr Lys Ile Arg Ser Ile Leu His Gly Met Gly Ile His Tyr Arg
 1650 1655 1660

Asp Phe Leu Ser Cys Gly Asp Gly Ser Gly Gly Met Thr Ala Ala Leu
 1665 1670 1675 1680

Leu Arg Glu Asn Val His Ser Arg Gly Ile Phe Asn Ser Leu Leu Glu
 1685 1690 1695

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Leu Ser Gly Ser Val Met Arg Gly Ala Ser Pro Glu Pro Pro Ser Ala
 1700 1705 1710

Leu Glu Thr Leu Gly Gly Asp Lys Ser Arg Cys Val Asn Gly Glu Thr
 1715 1720 1725

Cys Trp Glu Tyr Pro Ser Asp Leu Cys Asp Pro Arg Thr Trp Asp Tyr
 1730 1735 1740

Phe Leu Arg Leu Lys Ala Gly Leu Gly Leu Gln Ile Asp Leu Ile Val
 1745 1750 1755 1760

Met Asp Met Glu Val Arg Asp Ser Ser Thr Ser Leu Lys Ile Glu Thr
 1765 1770 1775

Asn Val Arg Asn Tyr Val His Arg Ile Leu Asp Glu Gln Gly Val Leu
 1780 1785 1790

Ile Tyr Lys Thr Tyr Gly Thr Tyr Ile Cys Glu Ser Glu Lys Asn Ala
 1795 1800 1805

Val Thr Ile Leu Gly Pro Met Phe Lys Thr Val Asp Leu Val Gln Thr
 1810 1815 1820

Glu Phe Ser Ser Ser Gln Thr Ser Glu Val Tyr Met Val Cys Lys Gly
 1825 1830 1835 1840

Leu Lys Lys Leu Ile Asp Glu Pro Asn Pro Asp Trp Ser Ser Ile Asn
 1845 1850 1855

Glu Ser Trp Lys Asn Leu Tyr Ala Phe Gln Ser Ser Glu Gln Glu Phe
 1860 1865 1870

Ala Arg Ala Lys Lys Val Ser Thr Tyr Phe Thr Leu Thr Gly Ile Pro
 1875 1880 1885

Ser Gln Phe Ile Pro Asp Pro Phe Val Asn Ile Glu Thr Met Leu Gln
 1890 1895 1900

Ile Phe Gly Val Pro Thr Gly Val Ser His Ala Ala Ala Leu Lys Ser
 1905 1910 1915 1920

Ser Asp Arg Pro Ala Asp Leu Leu Thr Ile Ser Leu Phe Tyr Met Ala
 1925 1930 1935

Ile Ile Ser Tyr Tyr Asn Ile Asn His Ile Arg Val Gly Pro Ile Pro
 1940 1945 1950

Pro Asn Pro Pro Ser Asp Gly Ile Ala Gln Asn Val Gly Ile Ala Ile
 1955 1960 1965

Thr Gly Ile Ser Phe Trp Leu Ser Leu Met Glu Lys Asp Ile Pro Leu
 1970 1975 1980

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Tyr	Gln	Gln	Cys	Leu	Ala	Val	Ile	Gln	Gln	Ser	Phe	Pro	Ile	Arg	Trp
1985						1990				1995					2000
Glu	Ala	Val	Ser	Val	Lys	Gly	Gly	Tyr	Lys	Gln	Lys	Trp	Ser	Thr	Arg
				2005					2010					2015	
Gly	Asp	Gly	Leu	Pro	Lys	Asp	Thr	Arg	Ile	Ser	Asp	Ser	Leu	Ala	Pro
			2020					2025					2030		
Ile	Gly	Asn	Trp	Ile	Arg	Ser	Leu	Glu	Leu	Val	Arg	Asn	Gln	Val	Arg
	2035						2040					2045			
Leu	Asn	Pro	Phe	Asn	Glu	Ile	Leu	Phe	Asn	Gln	Leu	Cys	Arg	Thr	Val
	2050					2055					2060				
Asp	Asn	His	Leu	Lys	Trp	Ser	Asn	Leu	Arg	Lys	Asn	Thr	Gly	Met	Ile
2065				2070					2075					2080	
Glu	Trp	Ile	Asn	Arg	Arg	Ile	Ser	Lys	Glu	Asp	Arg	Ser	Ile	Leu	Met
			2085						2090					2095	
Leu	Lys	Ser	Asp	Leu	His	Glu	Glu	Asn	Ser	Trp	Arg	Asp			
			2100					2105							

CLAIMS:

1. Use of an oncolytic attenuated vesicular stomatitis virus for the manufacture of a medicament for reducing the viability of a tumor cell in a mammalian subject and wherein the oncolytic attenuated vesicular stomatitis virus is contained in a cell infected with said virus, and wherein the tumor cell is a hematopoietic tumor cell, a melanoma, a sarcoma, a neuroendocrine tumor, a lung carcinoma, a colon carcinoma, a prostate carcinoma or an ovarian carcinoma.

2. Use of an oncolytic attenuated vesicular stomatitis virus for the manufacture of a medicament for reducing the viability of a tumor cell within a population of cells, wherein the oncolytic attenuated vesicular stomatitis virus is contained in a cell infected with said virus, and wherein the tumor cell is a hematopoietic tumor cell, a melanoma, a sarcoma, a neuroendocrine tumor, a lung carcinoma, a colon carcinoma, a prostate carcinoma or an ovarian carcinoma.

3. The use of claim 1 or 2, wherein the hematopoietic tumor cell is a leukemia.

4. The use of claim 3, wherein the leukemia is acute myelogenous leukemia.

5. The use of claim 3, wherein the leukemia is chronic myelogenous leukemia.

6. The use of claim 3, wherein the leukemia is promyelocytic leukemia.

7. The use of claim 3, wherein the leukemia is T cell leukemia.

8. The use of claim 1 or 2, wherein the hematopoietic tumor cell is a lymphoma.

9. The use of claim 1 or 2 wherein the hematopoietic tumor cell is a myeloma.

10. The use according to any one of claims 1 to 9, wherein the tumor cell is **PKR^{-/-}**; **STAT1^{-/-}**; or both **PKR^{-/-}** and **STAT1^{-/-}**.

11. The use of claim 1, wherein the mammalian subject is a human.

12. The use of claim 1, wherein the mammalian subject is a non-human mammal.

13. The use of claim 1 or 2, wherein the medicament is formulated for intratumoral, intravenous or intraperitoneal administration.

14. The use according to any one of claims 1 to 13, wherein the tumor cell has been previously treated with interferon.

15. The use of claim 2, wherein the medicament is formulated for administration to the population of cells *in vitro*.

16. The use according to any one of claims 1-15, wherein the virus is incapable of inactivating PKR activity within the tumor cell.

17. The use according to any one of claims 1-15, wherein the virus is vesicular stomatitis virus strain M1.

18. The use according to any one of claims 1-15, wherein the virus is vesicular stomatitis virus strain M2.

19. The use according to any one of claims 1-15, wherein the virus is vesicular stomatitis virus strain M3.

20. The use according to any one of claims 1-15, wherein the virus is vesicular stomatitis virus strain M4.

21. The use according to any one of claims 1-15, wherein the virus is vesicular stomatitis virus strain M5.

22. The use according to any one of claims 1-15, wherein the virus has an N gene nucleic acid sequence that codes for the same N protein amino acid sequence as the N gene cDNA sequence for vesicular stomatitis virus strain M2, M3 or M4, depicted in SEQ ID NOs: 11, 12 and 13.

23. The use according to any one of claims 1-15, wherein the virus has a P gene nucleic acid sequence that codes for the same P protein amino acid sequence as the P gene cDNA sequence for vesicular stomatitis virus strain M2, M3 or M4, as depicted in SEQ ID NOs: 20, 21 and 22.

24. The use according to any one of claims 1-15, wherein the virus has a M gene nucleic acid sequence that codes for the same M protein amino acid sequence as the M gene cDNA sequence for vesicular stomatitis virus strain M3 or M4, as depicted in SEQ ID NOs: 30 and 31.

25. The use according to any one of claims 1-15 wherein the virus has a G gene nucleic acid sequence that codes for the same G protein amino acid sequence as the G gene cDNA sequence for vesicular stomatitis virus strain M2, M3 or M4, as depicted in SEQ ID NOs: 38, 39 and 40.

26. The use according to any one of claims 1-15, wherein the virus has a L gene nucleic acid sequence that codes for the same L protein amino acid sequence as the L gene cDNA sequence for vesicular stomatitis virus strain M2 or M4, as depicted in SEQ ID NOs: 48 and 49.

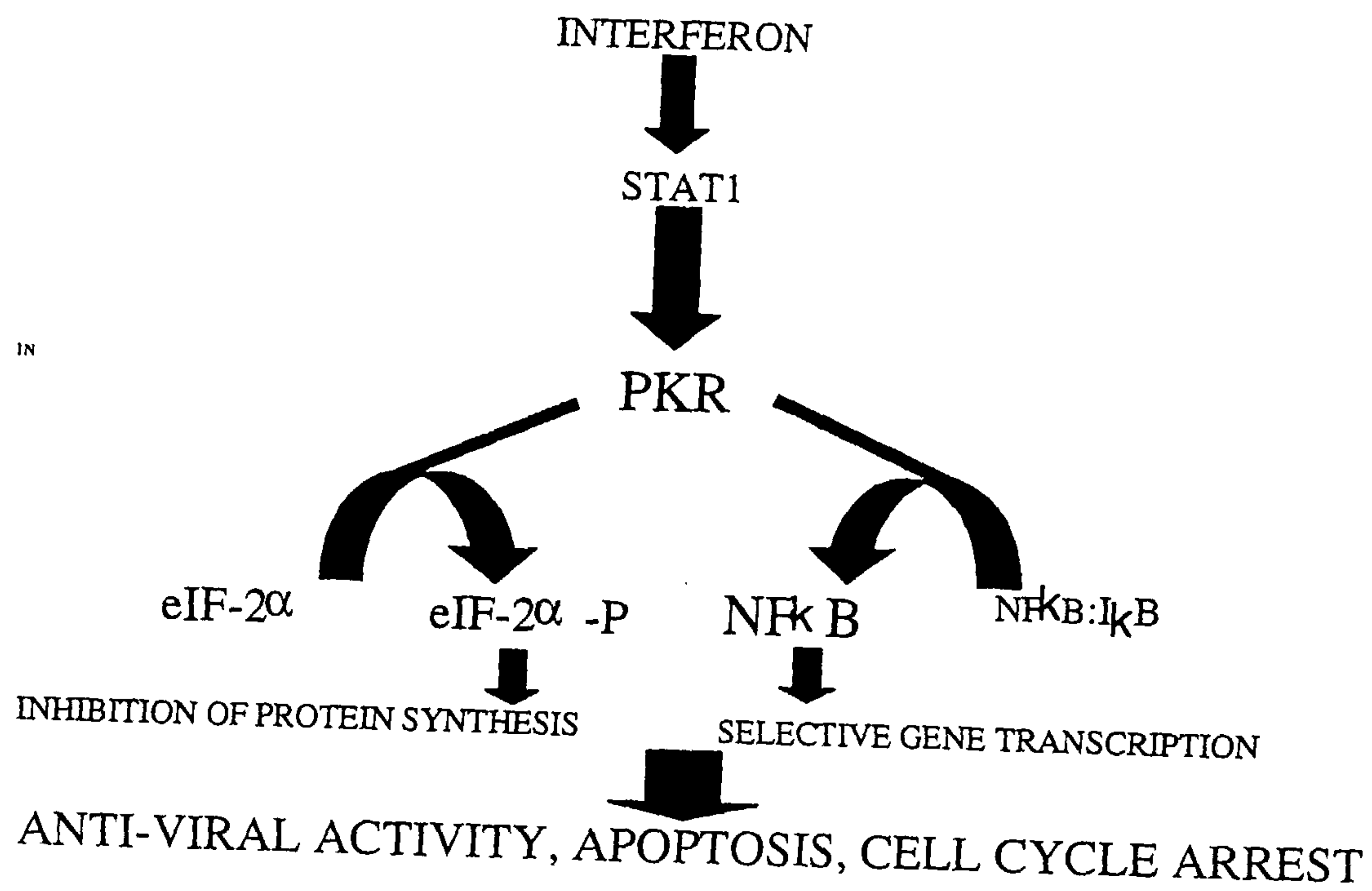


FIGURE 1

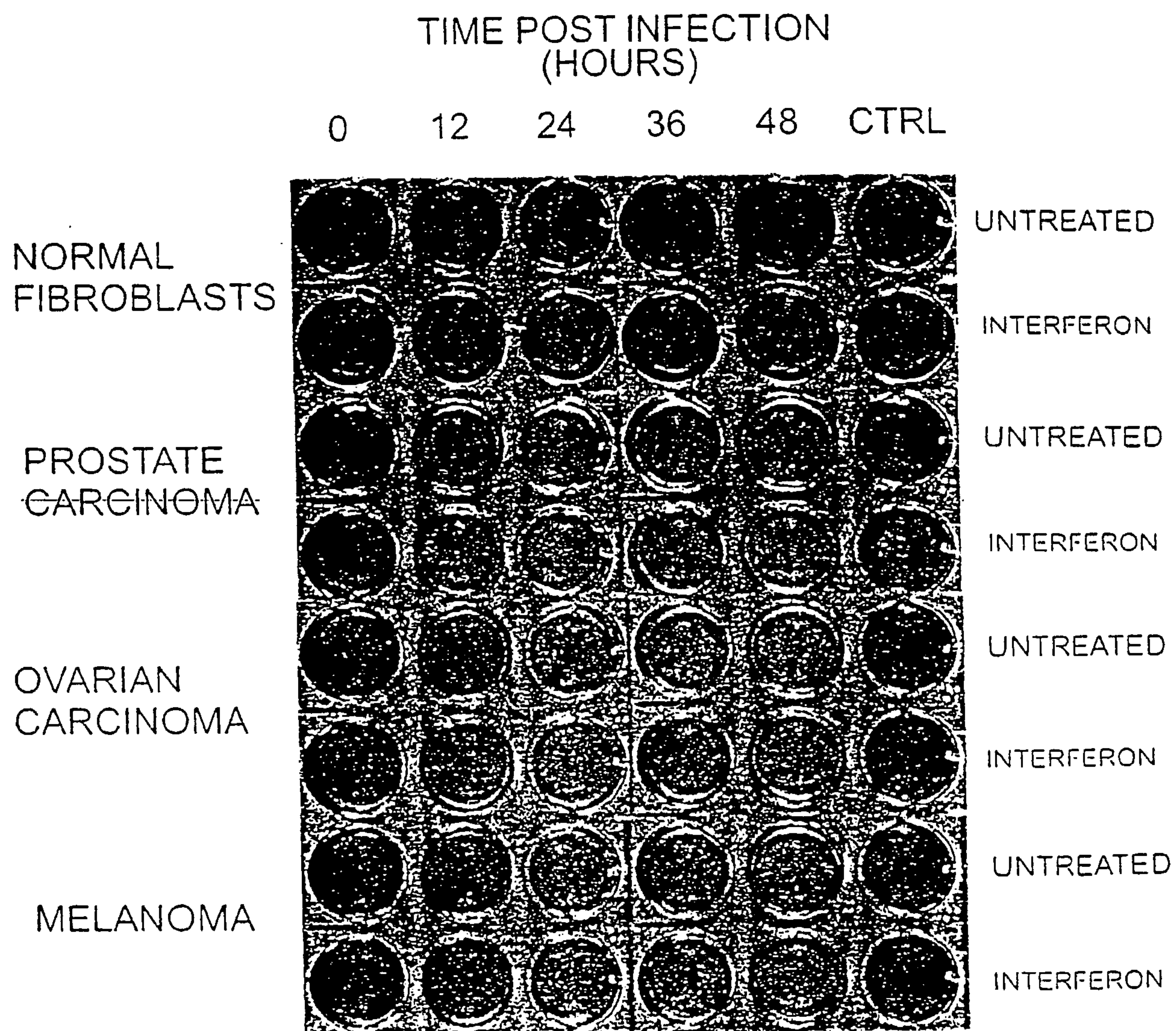
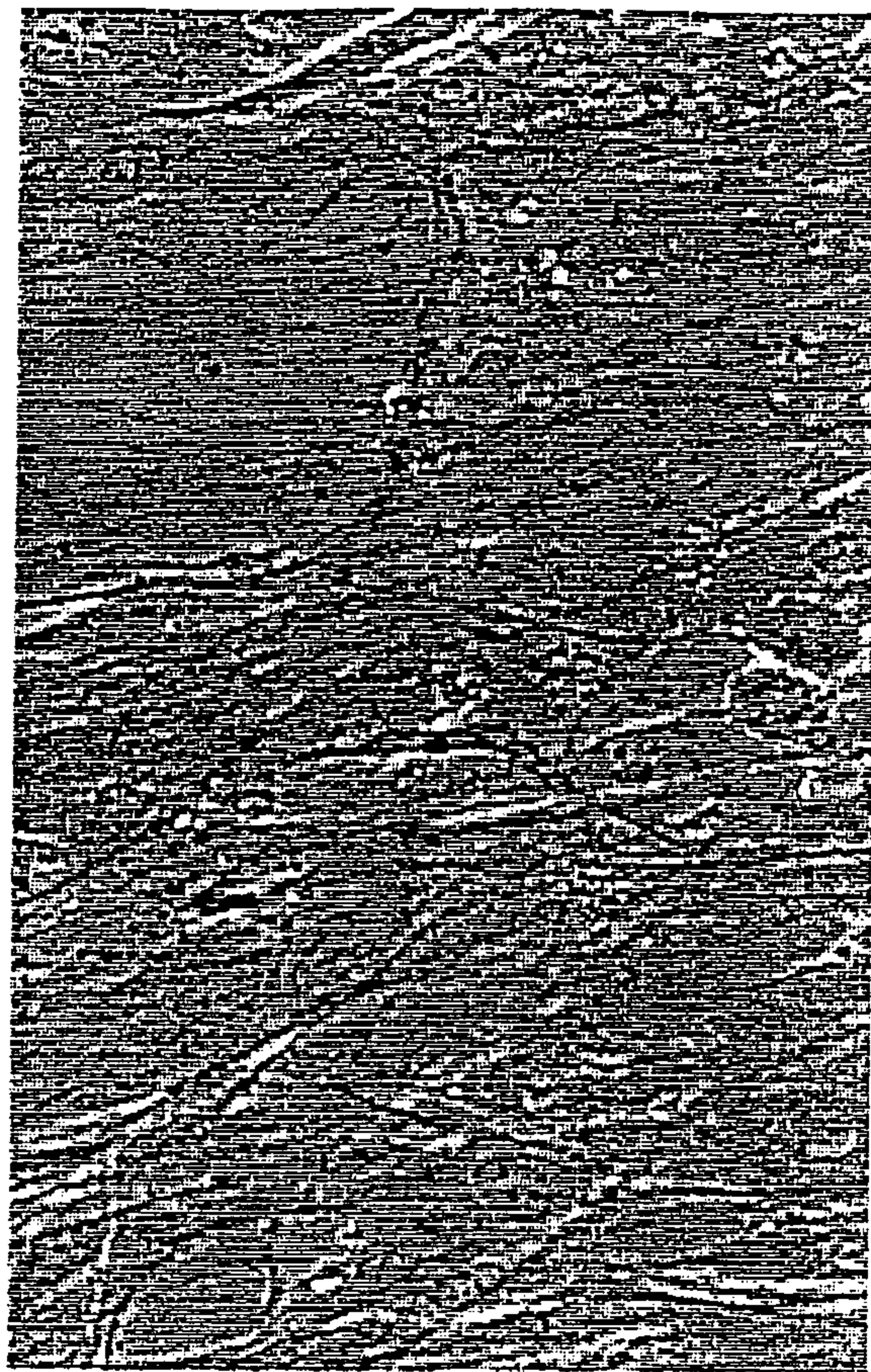
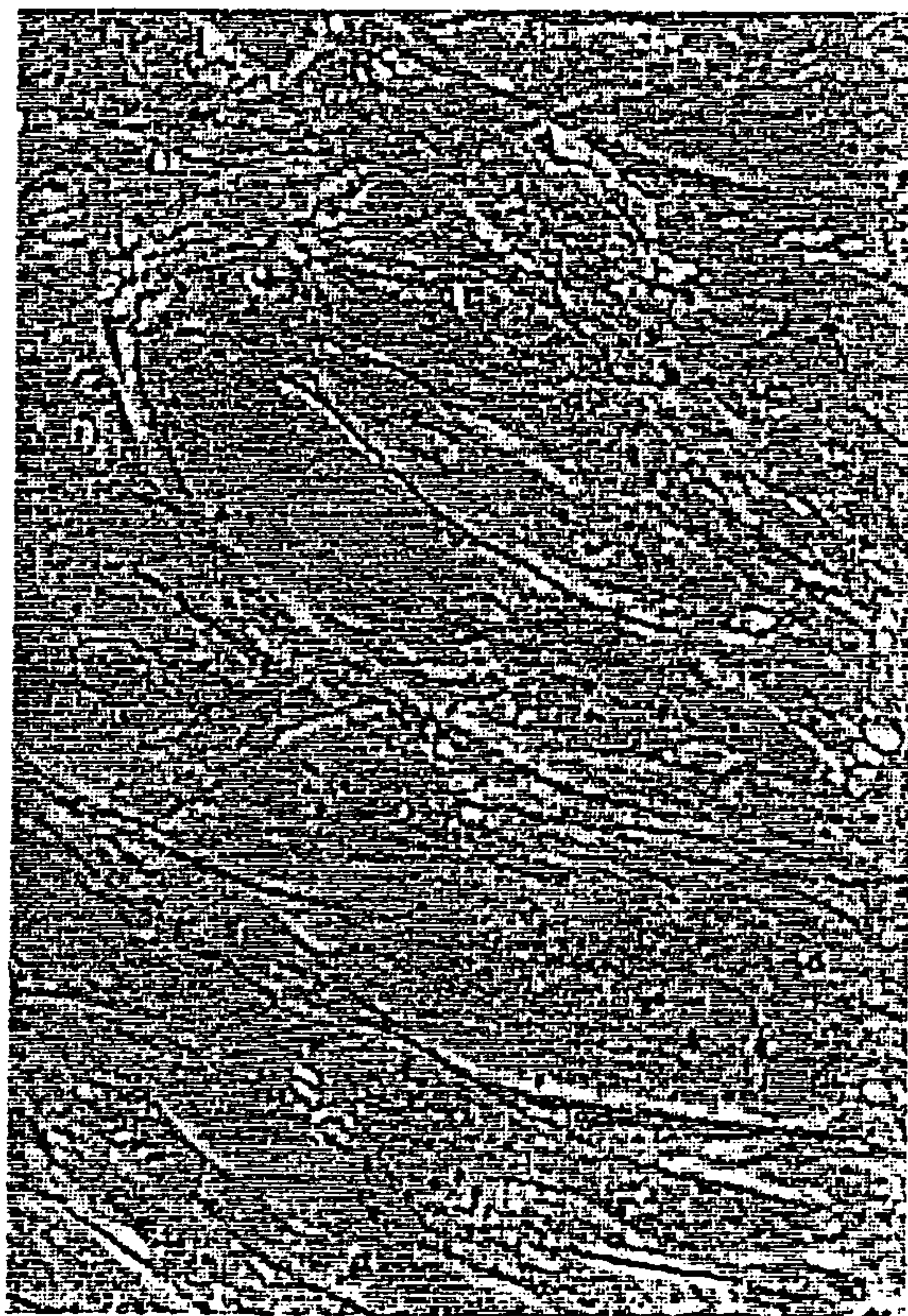


FIGURE 2

VSV INFECTION OF NORMAL HUMAN FIBROBLASTS

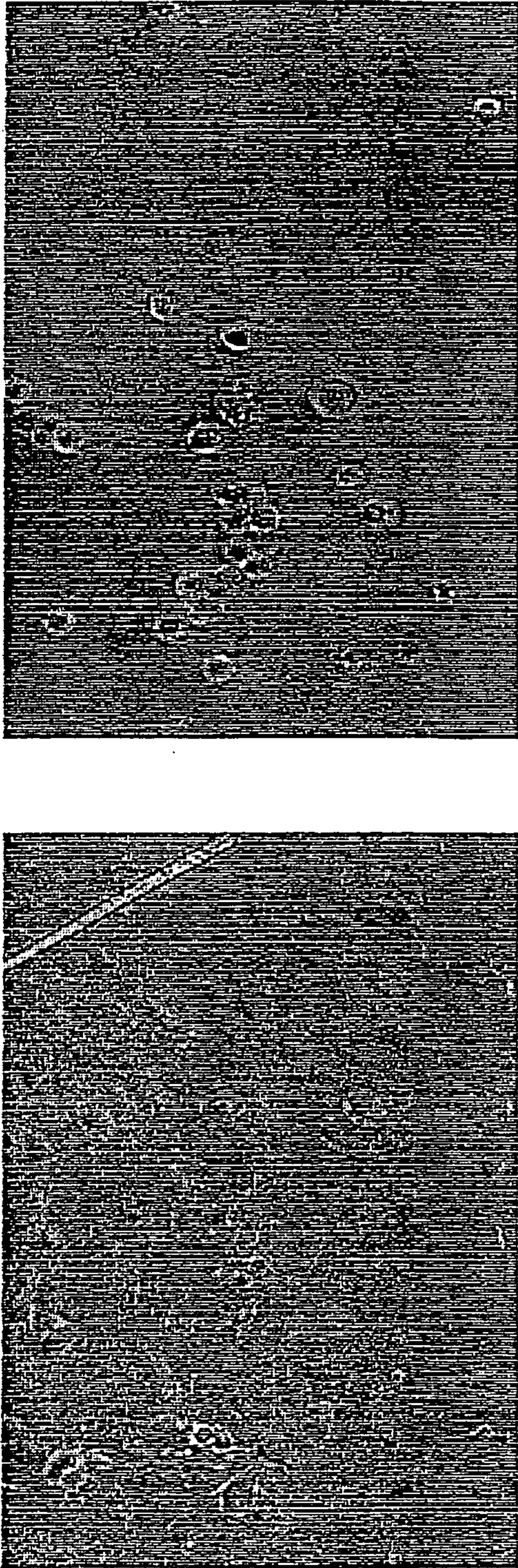


MOCK INFECTED

VSV MOI 1 PFU/18
HOURS

FIGURE 3A

VSV INFECTION OF
OVCAR433

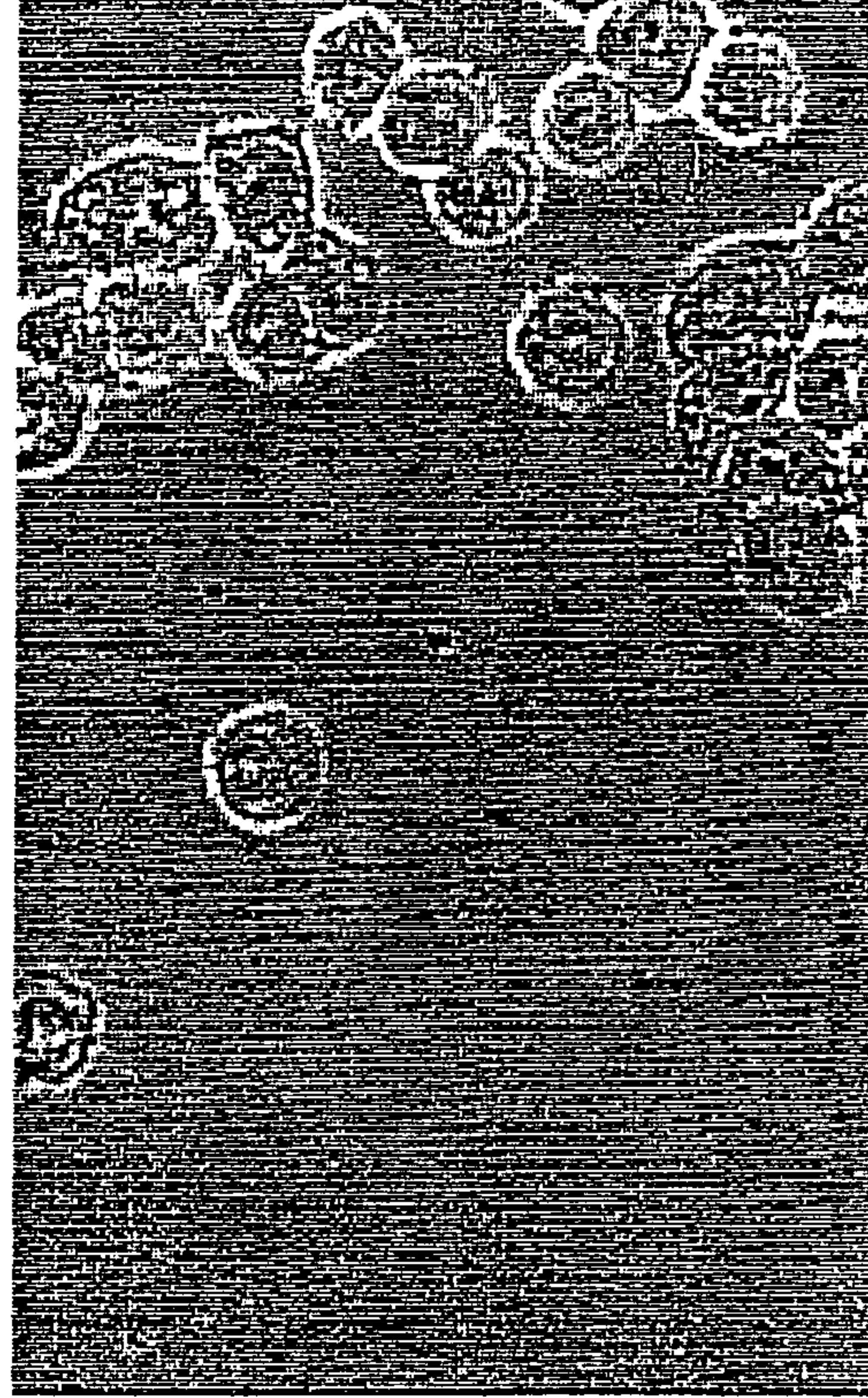
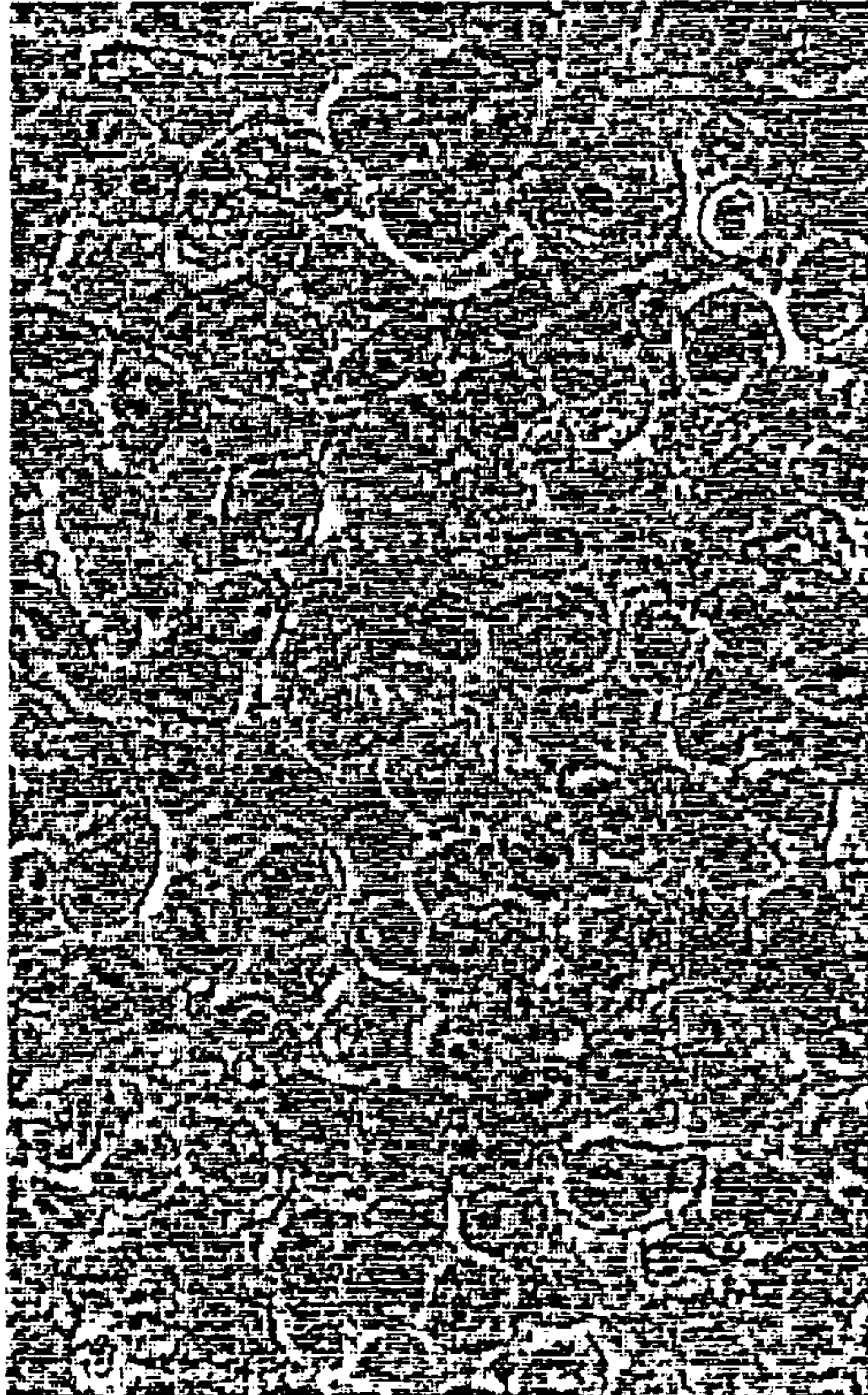


MOCK INFECTED

VSV 0.1PFU/18 HRS

FIGURE 3B

VSV INFECTION OF KB CELLS



MOCK INFECTED

VSV moi 1 PFU/18HRS

FIGURE 3C

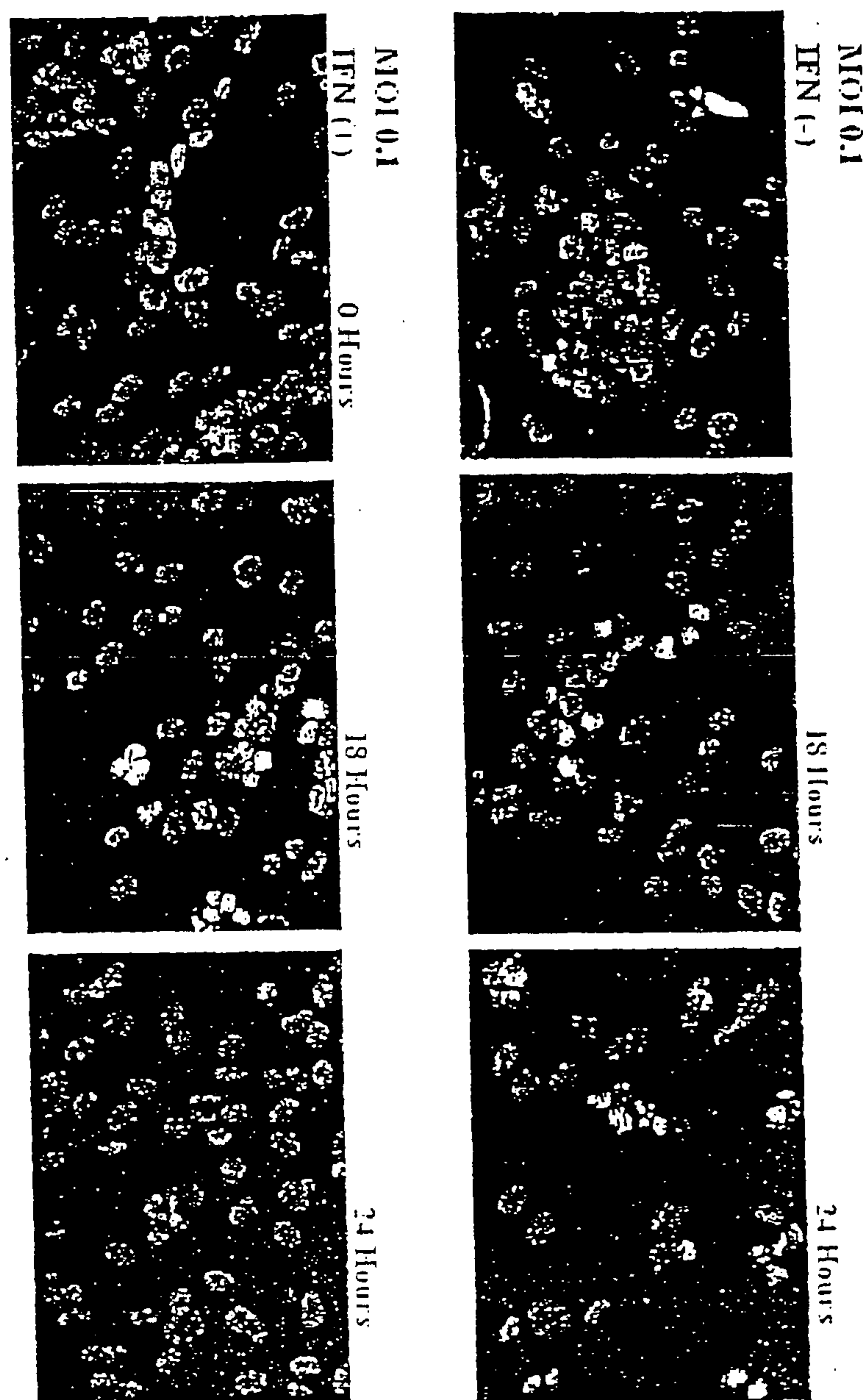


FIGURE 4

Nude Mouse Tumours

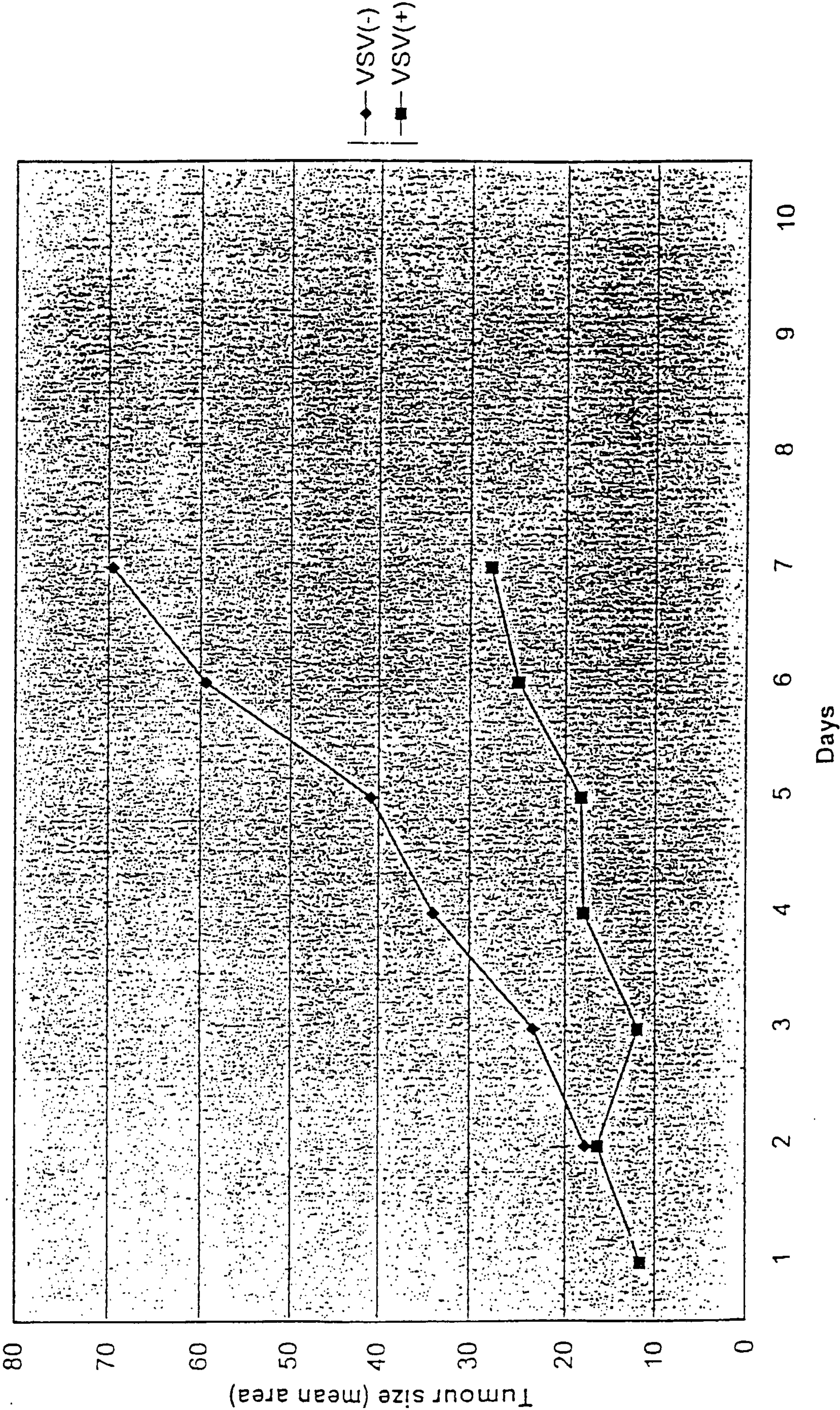
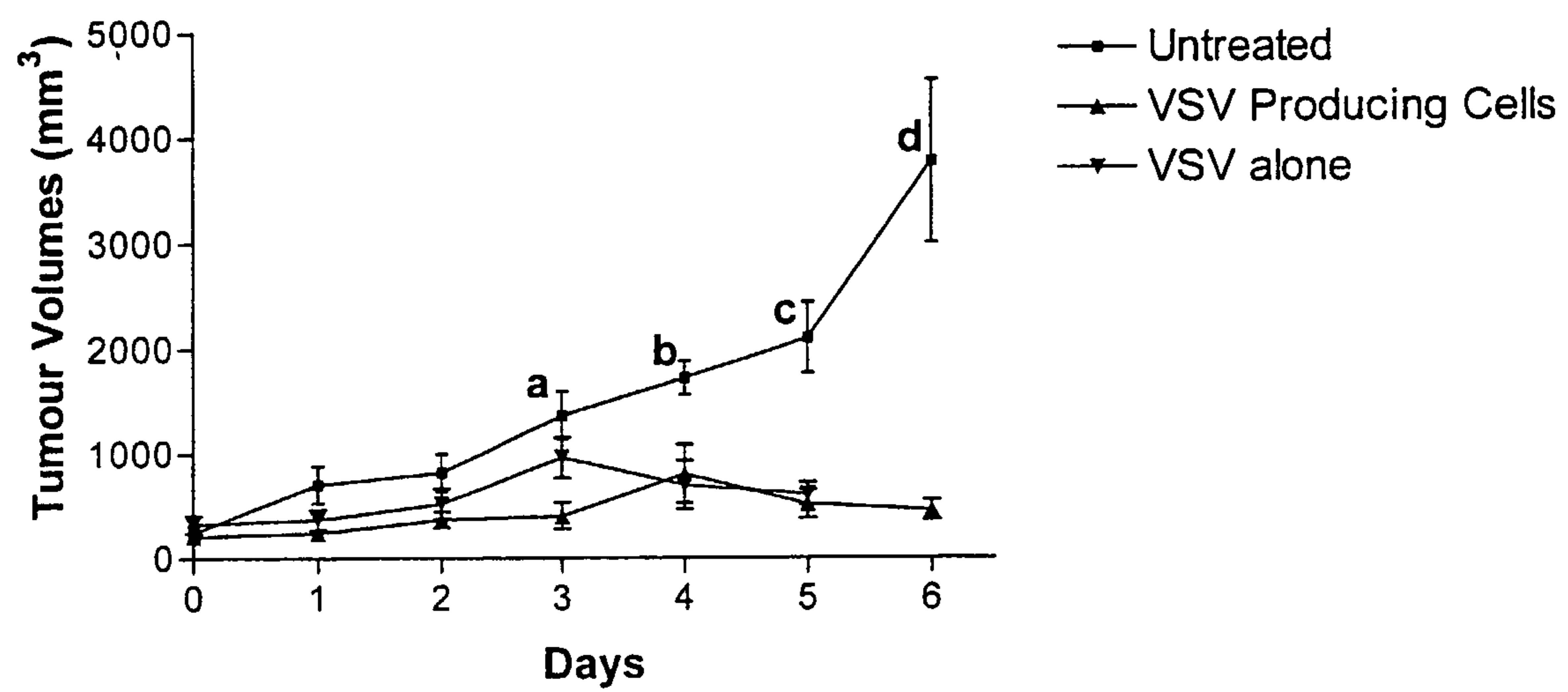
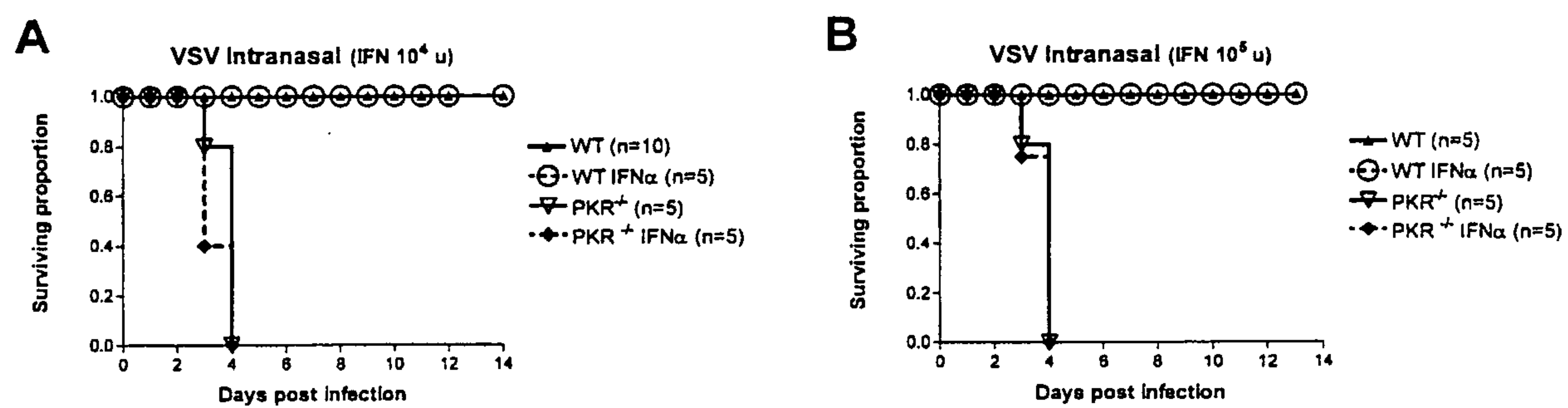


FIGURE 5



FIGURE 6

**FIGURE 7**



FIGURES 8A AND 8B

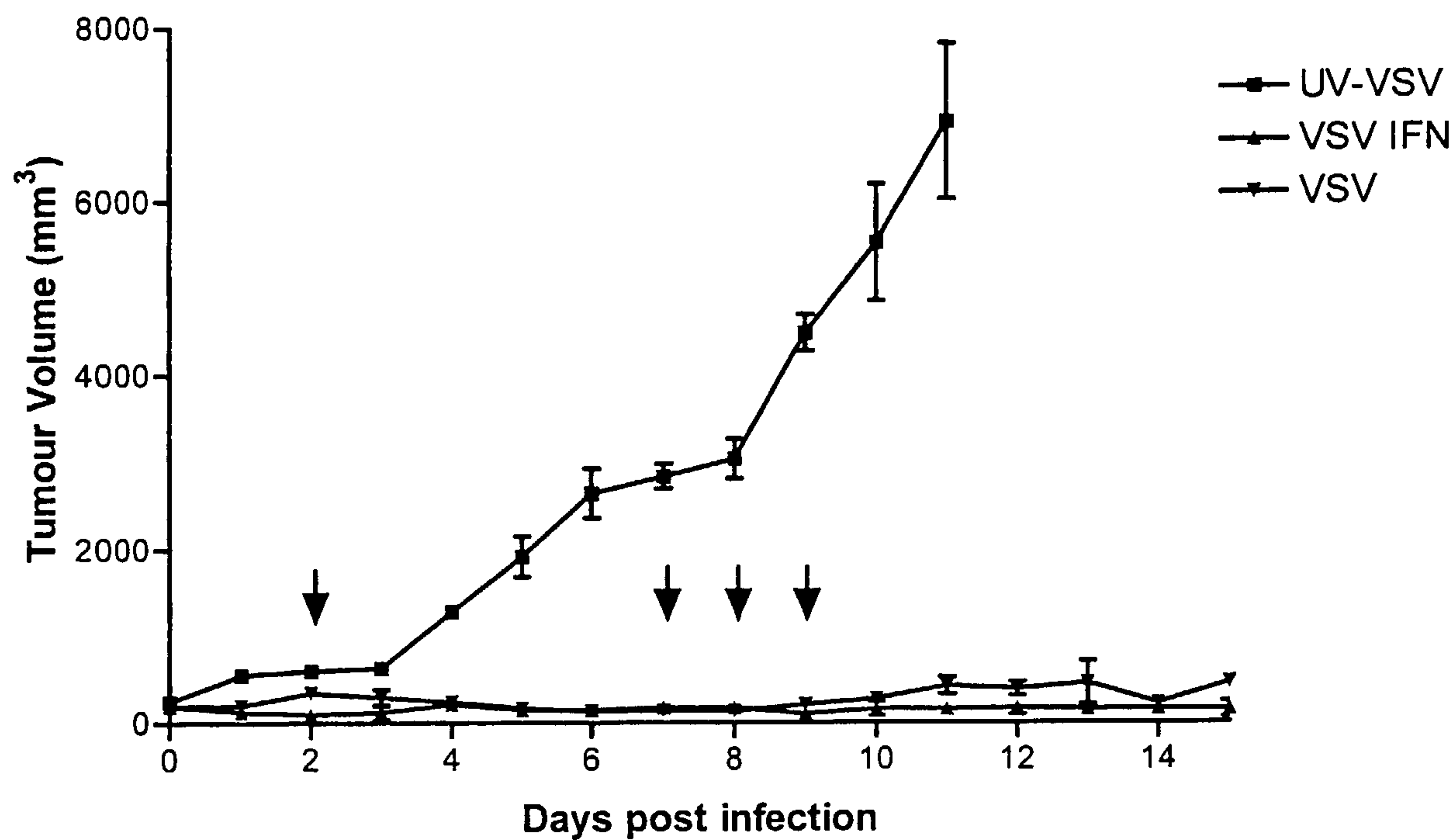
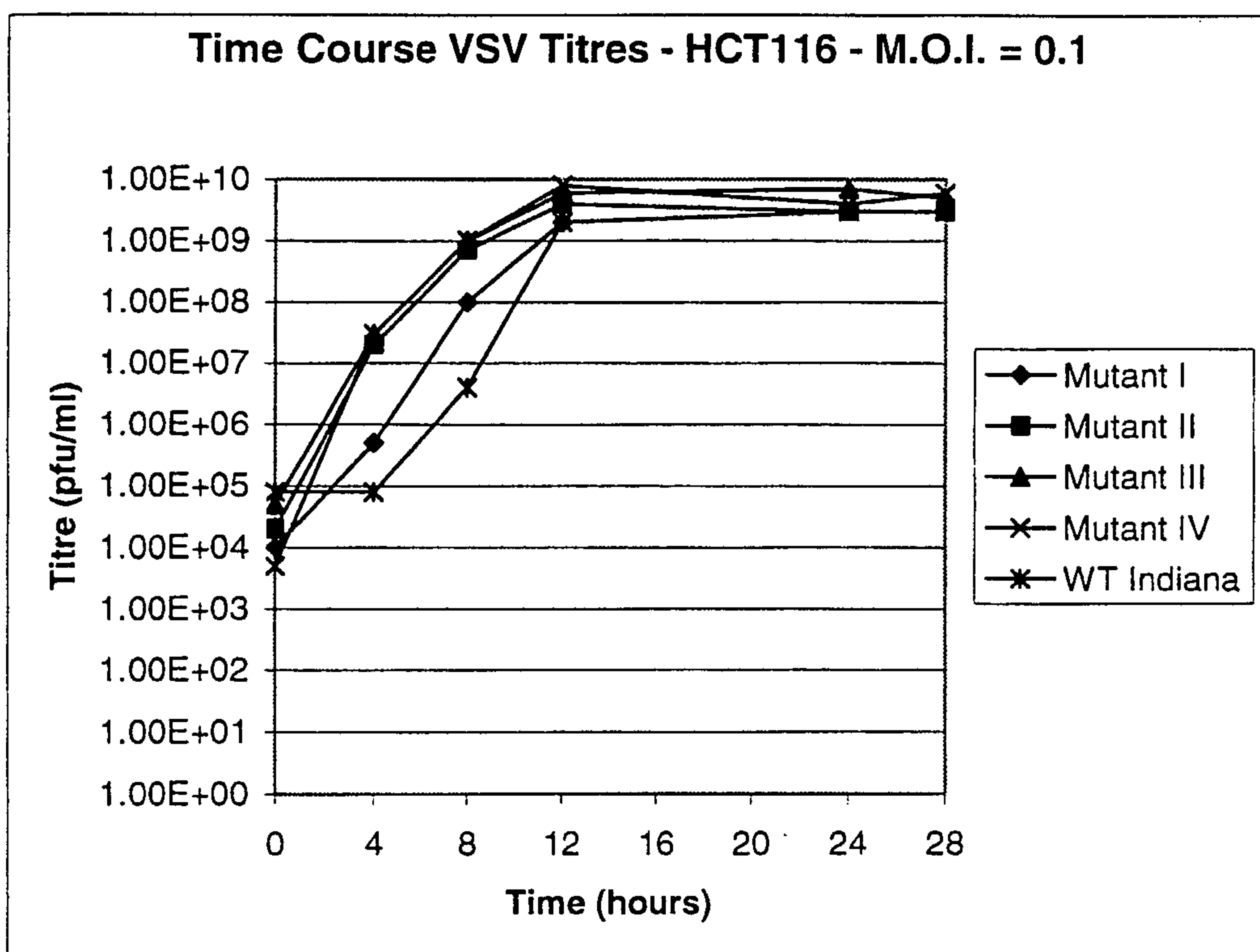
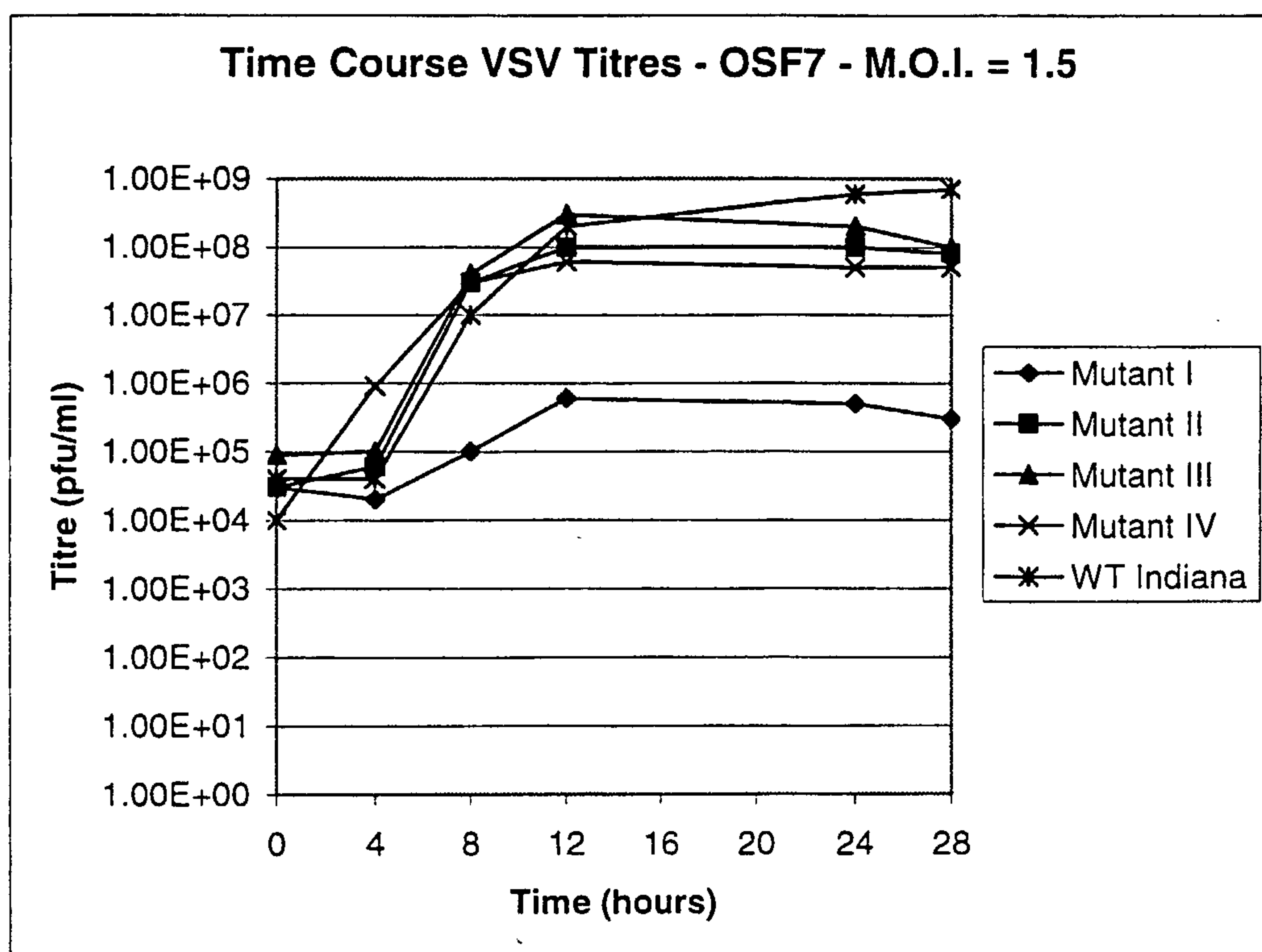


FIGURE 9

**FIGURE 10A**

**FIGURE 10B**

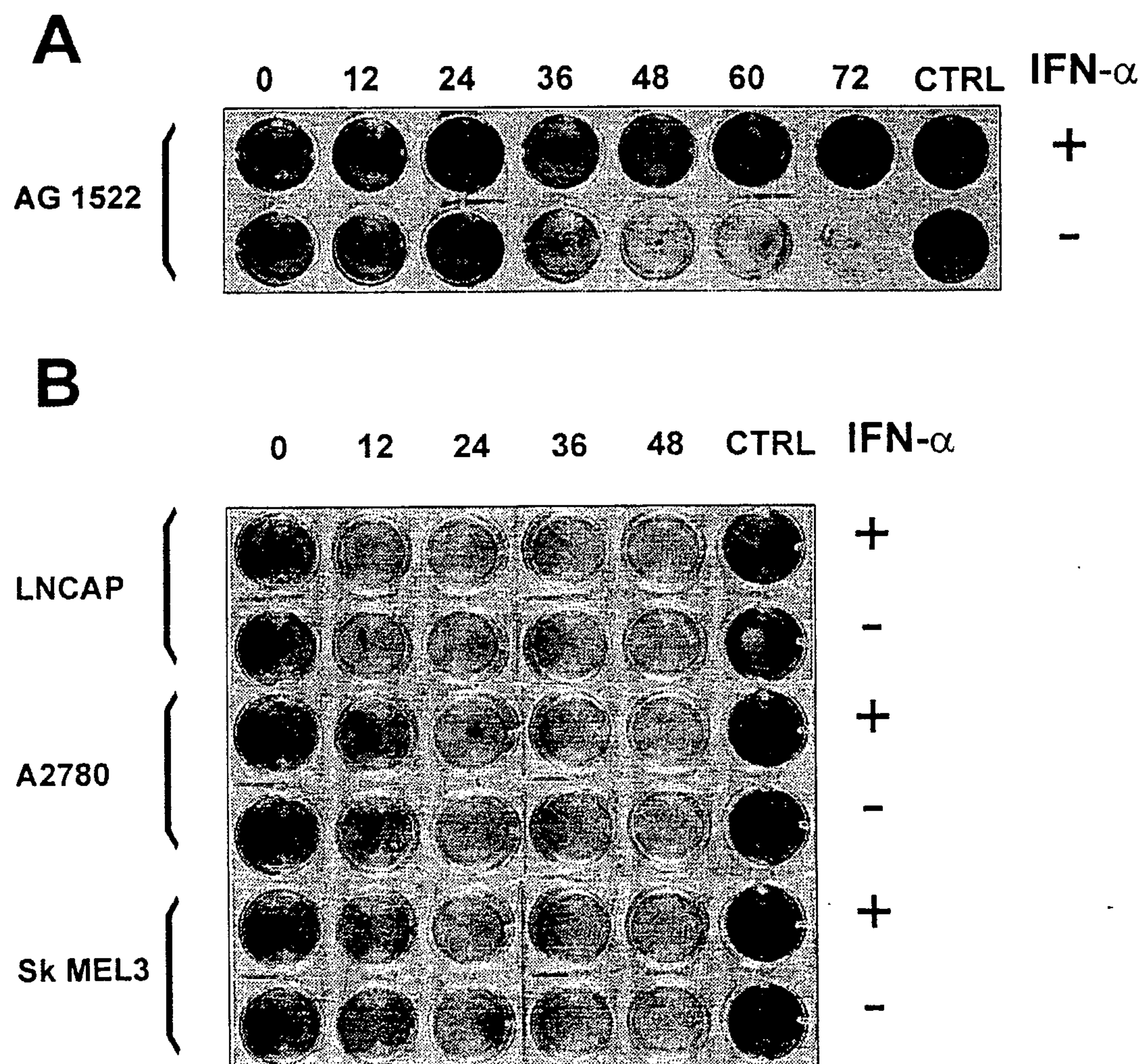


FIGURE 11

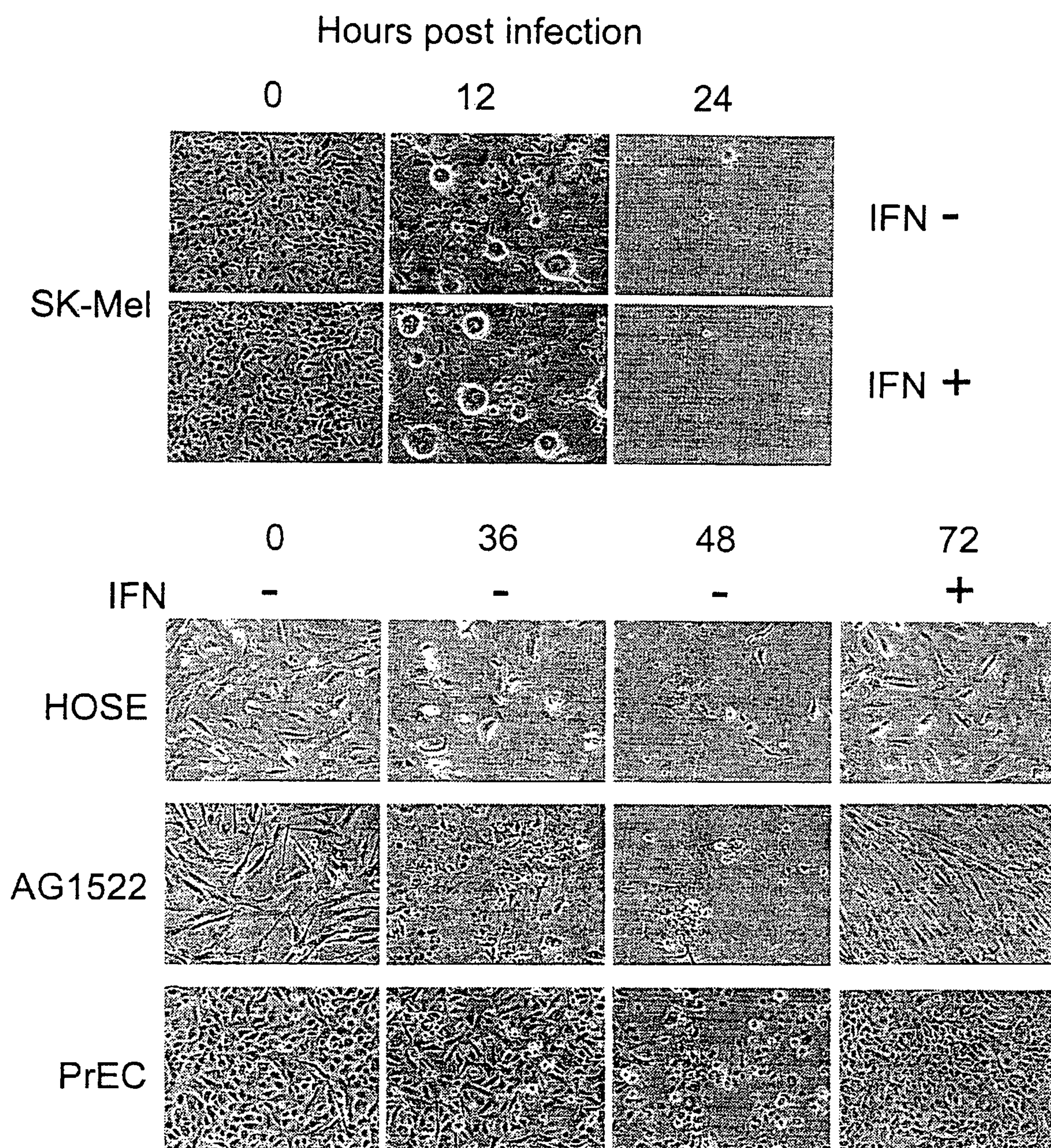


FIGURE 12

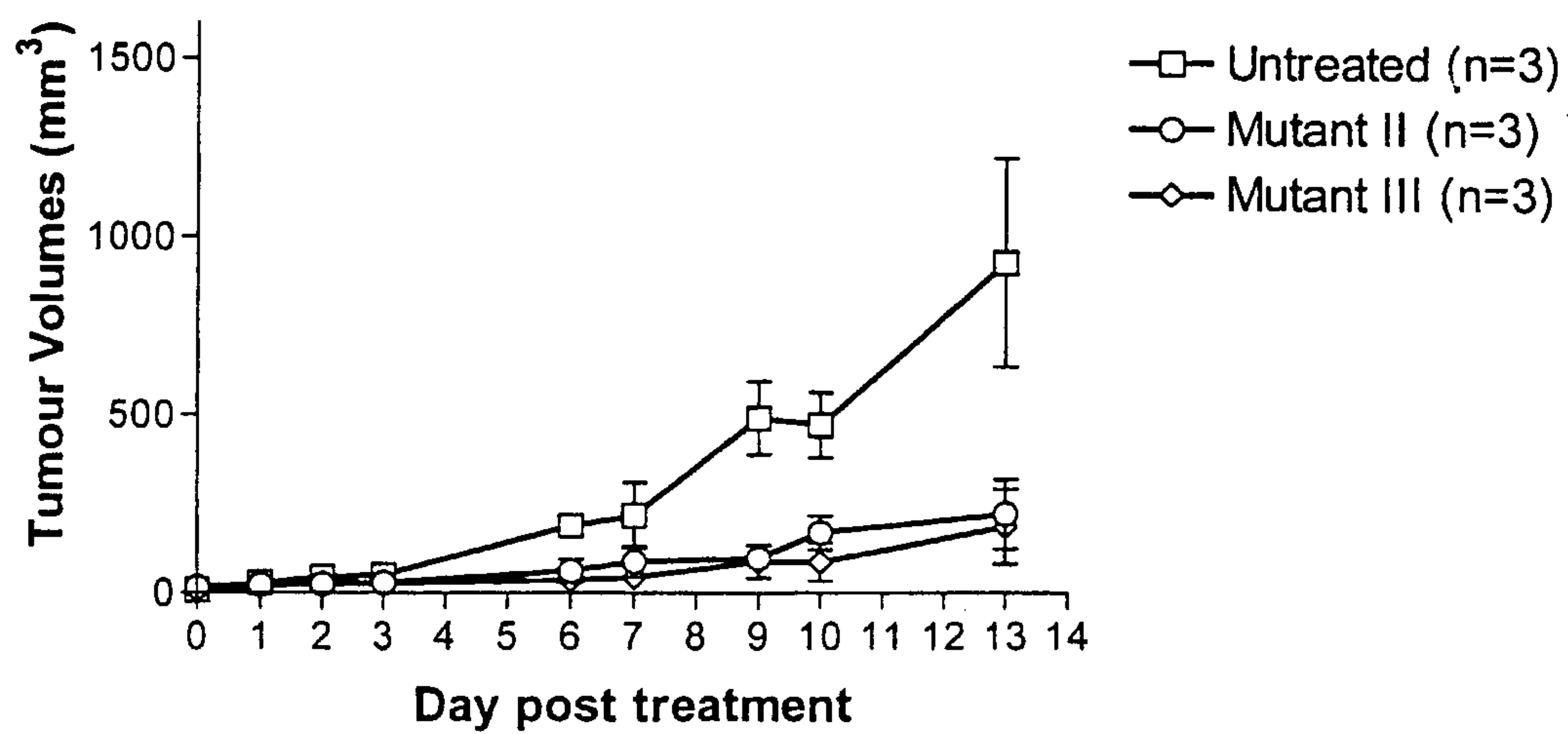


FIGURE 13

```

1                                     60
GenBank N nucl. ATGTCTGTTACAGTCAAGAGAATCATTGACAACACAGTCATAGTTCCAAAACCTTCCTGCA
HR N nucl. ATGTCTGTTACAGTCAAGAGAATCATTGCAACACAGTCATAGTTCCAAAACCTTCCTGCA
M2 N nucl. ATGTCTGTTACAGTCAAGAGAATCATTGACAACACAGTCATAGTTCCAAAACCTTCCTGCA
M3 N nucl. ATGTCTGTTACAGTCAAGAGAATCATTGACAACACAGTCATAGTTCCAAAACCTTCCTGCA
M4 N nucl. ....

61                                     120
GenBank N nucl. AATGAGGATCCAGTGAATACCCGGCAGATTACTTCAGAAAATCAAAGGAGATTCCTCTT
HR N nucl. AATGAGGATCCAGTGAATACCCGGCAGATTACTTCAGAAAATCAAAGGAGATTCCTCTT
M2 N nucl. AATGAGGATCCAGTGAATACCCGGCAGATTACTTCAGAAAATCAAAGGAGATTCCTCTT
M3 N nucl. AATGAGGATCCAGTGAATACCCGGCAGATTACTTCAGAAAATCAAAGGAGATTCCTCTT
M4 N nucl. ....

121                                    180
GenBank N nucl. TACATCAATACTACAAAAAGTTTGTCTAGATCTAAGAGGATATGTCTACCAAGGCCTCAAA
HR N nucl. TACATCAATACTACAAAAAGTTTGTCTAGATCTAAGAGGATATGTCTACCAAGGCCTCAAA
M2 N nucl. TACATCAATACTACAAAAAGTTTGTCTAGATCTAAGAGGATATGTCTACCAAGGCCTCAAA
M3 N nucl. TACATCAATACTACAAAAAGTTTGTCTAGATCTAAGAGGATATGTCTACCAAGGCCTCAAA
M4 N nucl. ....

181                                    240
GenBank N nucl. TCCGGAAATGTATCAATCATAACATGTCAACAGCTACTTGTATGGAGCATTGAAGGACATC
HR N nucl. TCCGGAAATGTATCAATCATAACATGTCAACAGCTACTTGTATGGAGCATTGAAGGACATC
M2 N nucl. TCCGGAAATGTATCAATCATAACATGTCAACAGCTACTTGTATGGAGCATTGAAGGACATC
M3 N nucl. TCCGGAAATGTATCAATCATAACATGTCAACAGCTACTTGTATGGAGCATTGAAGGACATC
M4 N nucl. ....TCAATCATAACATGTCAACAGCTACTTGTATGGAGCATTGAAGGACATC

241                                    300
GenBank N nucl. CGGGGTAAGTTGGATAAAGATTGGTCAAGTTTCGGAATAAACATCGGGAAAGCAGGGGAT
HR N nucl. CGGGGTAAGTTGGATAAAGATTGGTCAAGTTTCGGAATAAACATCGGGAAAGGCAGGGGAT
M2 N nucl. CGGGGTAAGTTGGATAAAGATTGGTCAAGTTTCGGAATAAACATCGGGAAAGGCAGGGGAT
M3 N nucl. CGGGGTAAGTTGGATAAAGATTGGTCAAGTTTCGGAATAAACATCGGGAAAGGCAGGGGAT
M4 N nucl. CGGGGTAAGTTGGATAAAGATTGGTCAAGTTTCGGAATAAACATCGGGAAAGGCAGGGGAT

301                                    360
GenBank N nucl. ACAATCGGAATATTTGACCTTGTATCCTTGAAAGCCCTGGACGGGTACTTCCAGATGGA
HR N nucl. ACAATCGGAATATTTGACCTTGTATCCTTGAAAGCCCTGGACGGGTACTTCCAGATGGA
M2 N nucl. ACAATCGGAATATTTGACCTTGTATCCTTGAAAGCCCTGGACGGGTACTTCCAGATGGA
M3 N nucl. ACAATCGGAATATTTGACCTTGTATCCTTGAAAGCCCTGGACGGGTACTTCCAGATGGA
M4 N nucl. ACAATCGGAATATTTGACCTTGTATCCTTGAAAGCCCTGGACGGGTACTTCCAGATGGA

361                                    420
GenBank N nucl. GTATCGGATGCTTCCAGAACCAGCGCAGATGACAAATGGTTGCCTTTGTATCTACTTGGC
HR N nucl. GTATCGGATGCTTCCAGAACCAGCGCAGATGACAAATGGTTGCCTTTGTATCTACTTGGC
M2 N nucl. GTATCGGATGCTTCCAGAACCAGCGCAGATGACAAATGGTTGCCTTTGTATCTACTTGGC
M3 N nucl. GTATCGGATGCTTCCAGAACCAGCGCAGATGACAAATGGTTGCCTTTGTATCTACTTGGC
M4 N nucl. GTATCGGATGCTTCCAGAACCAGCGCAGATGACAAATGGTTGCCTTTGTATCTACTTGGC

421                                    480
GenBank N nucl. TTATACAGAGTGGGCAGAACACAAATGCCTGAATACAGAAAAAGCTCATGGATGGGCTG
HR N nucl. TTATACAGAGTGGGCAGAACACAAATGCCTGAATACAGAAAAAGGCTCATGGATGGGCTG
M2 N nucl. TTATACAGAGTGGGCAGAACACAAATGCCTGAATACAGAAAAAGGCTCATGGATGGGCTG
M3 N nucl. TTATACAGAGTGGGCAGAACACAAATGCCTGAATACAGAAAAAGGCTCATGGATGGGCTG
M4 N nucl. TTATACAGAGTGGGCAGAACACAAATGCCTGAATACAGAAAAAGGCTCATGGATGGGCTG

```

FIGURE 14-1

		481	540
GenBank	N nucl.	ACAAATCAATGCAAAATGATCAATGAACAGTTTGAACCTCTTGTGCCAGAAGGTCGTGAC	
HR	N nucl.	ACAAATCAATGCAAAATGATCAATGAACAGTTTGAACCTCTTGTGCCAGAAGGTCGTGAC	
M2	N nucl.	ACAAATCAATGCAAAATGATCAATGAACAGTTTGAACCTCTTGTGCCAGAAGGTCGTGAC	
M3	N nucl.	ACAAATCAATGCAAAATGATCAATGAACAGTTTGAACCTCTTGTGCCAGAAGGTCGTGAC	
M4	N nucl.	ACAAATCAATGCAAAATGATCAATGAACAGTTTGAACCTCTTGTGCCAGAAGGTCGTGAC	
		541	600
GenBank	N nucl.	ATTTTGTGATGTGTGGGGAAATGACAGTAATTACACAAAAATTGTCGCTGCAGTGGACATG	
HR	N nucl.	ATTTTGTGATGTGTGGGGAAATGACAGTAATTACACAAAAATTGTCGCTGCAGTGGACATG	
M2	N nucl.	ATTTTGTGATGTGTGGGGAAATGACAGTAATTACACAAAAATTGTCGCTGCAGTGGACATG	
M3	N nucl.	ATTTTGTGATGTGTGGGGAAATGACAGTAATTACACAAAAATTGTCGCTGCAGTGGACATG	
M4	N nucl.	ATTTTGTGATGTGTGGGGAAATGACAGTAATTACACAAAAATTGTCGCTGCAGTGGACATG	
		601	660
GenBank	N nucl.	TTCTTCCACATGTTCAAAAAACATGAATGTGCCTCGTTCAGATACGGAACCTATTGTTTCC	
HR	N nucl.	TTCTTCCACATGTTCAAAAAACATGAATGTGCCTCGTTCAGATACGGAACCTATTGTTTCC	
M2	N nucl.	TTCTTCCACATGTTCAAAAAACATGAATGTGCCTCGTTCAGATACGGAACCTATTGTTTCC	
M3	N nucl.	TTCTTCCACATGTTCAAAAAACATGAATGTGCCTCGTTCAGATACGGAACCTATTGTTTCC	
M4	N nucl.	TTCTTCCACATGTTCAAAAAACATGAATGTGCCTCGTTCAGATACGGAACCTATTGTTTCC	
		661	720
GenBank	N nucl.	AGATTCAAAGATTGTGCTGCATTGGCAACATTTGGACACCTCTGCAAAATAACCGGAATG	
HR	N nucl.	AGATTCAAAGATTGTGCTGCATTGGCAACATTTGGACACCTCTGCAAAATAACCGGAATG	
M2	N nucl.	AGATTCAAAGATTGTGCTGCATTGGCAACATTTGGACACCTCTGCAAAATAACCGGAATG	
M3	N nucl.	AGATTCAAAGATTGTGCTGCATTGGCAACATTTGGACACCTCTGCAAAATAACCGGAATG	
M4	N nucl.	AGATTCAAAGATTGTGCTGCATTGGCAACATTTGGACACCTCTGCAAAATAACCGGAATG	
		721	780
GenBank	N nucl.	TCTACAGAAGATGTAACGACCTGGATCTTGAACCGAGAAGTTGCAGATGAGATGGTCCAA	
HR	N nucl.	TCTACAGAAGATGTAACGACCTGGATCTTGAACCGAGAAGTTGCAGATGAGATGGTCCAA	
M2	N nucl.	TCTACAGAAGATGTAACGACCTGGATCTTGAACCGAGAAGTTGCAGATGAGATGGTCCAA	
M3	N nucl.	TCTACAGAAGATGTAACGACCTGGATCTTGAACCGAGAAGTTGCAGATGAGATGGTCCAA	
M4	N nucl.	TCTACAGAAGATGTAACGACCTGGATCTTGAACCGAGAAGTTGCAGATGAGATGGTCCAA	
		781	840
GenBank	N nucl.	ATGATGCTTCCAGGCCAAGAAATTGACAAGGCCGATTCATACATGCCTTATTTGATCGAC	
HR	N nucl.	ATGATGCTTCCAGGCCAAGAAATTGACAAGGCCGATTCATACATGCCTTATTTGATCGAC	
M2	N nucl.	ATGATGCTTCCAGGCCAAGAAATTGACAAGGCCGATTCATACATGCCTTATTTGATCGAC	
M3	N nucl.	ATGATGCTTCCAGGCCAAGAAATTGACAAGGCCGATTCATACATGCCTTATTTGATCGAC	
M4	N nucl.	ATGATGCTTCCAGGCCAAGAAATTGACAAGGCCGATTCATACATGCCTTATTTGATCGAC	
		841	900
GenBank	N nucl.	TTTGGATTGTCTTCTAAGTCTCCATATTCTTCCGTCAAAAACCCTGCCTTCCACTTCTGG	
HR	N nucl.	TTTGGATTGTCTTCTAAGTCTCCATATTCTTCCGTCAAAAACCCTGCCTTCCACTTCTGG	
M2	N nucl.	TTTGGATTGTCTTCTAAGTCTCCATATTCTTCCGTCAAAAACCCTGCCTTCCACTTCTGG	
M3	N nucl.	TTTGGATTGTCTTCTAAGTCTCCATATTCTTCCGTCAAAAACCCTGCCTTCCACTTCTGG	
M4	N nucl.	TTTGGATTGTCTTCTAAGTCTCCATATTCTTCCGTCAAAAACCCTGCCTTCCACTTCTGG	

FIGURE 14-2

		901	960
GenBank	N nucl.	GGGCAATTGACAGCTCTTCTGCTCAGATCCACCAGAGCAAGGAATGCCCCGACAGCCTGAT	
	HR N nucl.	GGGCAATTGACAGCTCTTCTGCTCAGATCCACCAGAGCAAGGAATGCCCCGACAGCCTGAT	
	M2 N nucl.	GGGCAATTGACAGCTCTTCTGCTCAGATCACCAGAGCAAGGAATGCCCCGACAGCCTGAT	
	M3 N nucl.	GGGCAATTGACAGCTCTTCTGCTCAGATCCACCAGAGCAAGGAATGCCCCGACAGCCTGAT	
	M4 N nucl.	GGGCAATTGAC.....T	
		961	1020
GenBank	N nucl.	GACATTGAGTATACATCTCTTACTACAGCAGGTTTGTGTGACGCTTATGCAGTAGGATCC	
	HR N nucl.	GACATTGAGTATACATCTCTTACTACAGCAGGTTTGTGTGACGCTTATGCAGTAGGATCC	
	M2 N nucl.	GACATTGAGTATACATCTCTTACTACAGCAGGTTTGTGTGACGCTTATGCAGTAGGATCC	
	M3 N nucl.	GACATTGAGTATACATCTCTTACTACAGCAGGTTTGTGTGACGCTTATGCAGTAGGATCC	
	M4 N nucl.	GACATTGAGTATACATCTCTTACTACAGCAGGTTTGTGTGACGCTTATGCAGTAGGATCC	
		1021	1080
GenBank	N nucl.	TCTGCTGACTTGGCACAACAGTTTTGTGTGTTGGAGATAACAAATACACTCCAGATGATAGT	
	HR N nucl.	TCTGCTGACTTGGCACAACAGTTTTGTGTGTTGGAGATAGCAAATACACTCCAGATGATAGT	
	M2 N nucl.	TCTGCTGACTTGGCACAACAGTTTTGTGTGTTGGAGATAGCAAATACACTCCAGATGATAGT	
	M3 N nucl.	TCTGCTGACTTGGCACAACAGTTTTGTGTGTTGGAGATAGCAAATACACTCCAGATGATAGT	
	M4 N nucl.	TCTGCTGACTTGGCACAACAGTTTTGTGTGTTGGAGATAGCAAATACACTCCAGATGATAGT	
		1081	1140
GenBank	N nucl.	ACCGGAGGATTGACGACTAATGCACCGCCACAAGGCAGAGATGTGGTTCGAATGGCTCGGA	
	HR N nucl.	ACCGGAGGATTGACGACTAATGCACCGCCACAAGGCAGAGATGTGGTTCGAATGGCTCGGA	
	M2 N nucl.	ACCGGAGGATTGACGACTAATGCACCGCCACAAGGCAGAGATGTGGTTCGAATGGCTCGGA	
	M3 N nucl.	ACCGGAGGATTGACGACTAATGCACCGCCACAAGGCAGAGATGTGGTTCGAATGGCTCGGA	
	M4 N nucl.	ACCGGAGGATTGACGACTAATGCACCGCCACAAGGCAGAGATGTGGTTCGAATGGCTCGGA	
		1141	1200
GenBank	N nucl.	TGGTTTGAAGATCAAAACAGAAAACCGACTCCTGATATGATGCAGTATGCGAAAAGAGCA	
	HR N nucl.	TGGTTTGAAGATCAAAACAGAAAACCGACTCCTGATATGATGCAGTATGCGAAAACGAGCA	
	M2 N nucl.	TGGTTTGAAGATCAAAACAGAAAACCGACTCCTGATATGATGCAGTATGCGAAAACGAGCA	
	M3 N nucl.	TGGTTTGAAGATCAAAACAGAAAACCGACTCCTGATATGATGCAGTATGCGAAAACGAGCA	
	M4 N nucl.	TGGTTTGAAGATCAAAACAGAAAACCGACTCCTGATATGATGCAGTATGCGAAAACGAGCA	
		1201	1260
GenBank	N nucl.	GTCATGTCACTGCAAGGCCTAAGAGAGAAGACAATTGGCAAGTATGCTAAGTCAGAATTT	
	HR N nucl.	GTCATGTCACTGCAAGGCCTAAGAGAGAAGACAATTGGCAAGTATGCTAAGTCAGAATTT	
	M2 N nucl.	GTCATGTCACTGCAAGGCCTAAGAGAGAAGACAATTGGCAAGTATGCTAAGTCAGAATTT	
	M3 N nucl.	GTCATGTCACTGCAAGGCCTAAGAGAGAAGACAATTGGCAAGTATGCTAAGTCAGAATTT	
	M4 N nucl.	GTCATGTCACTGCAAGGCCTAAGAGAGAAGACAATTGGCAAGTATGCTAAGTCAGAATTT	
		1261	1269
GenBank	N nucl.	GACAAATGA	
	HR N nucl.	GACAAATGA	
	M2 N nucl.	GACAAATGA	
	M3 N nucl.	GACAAATGA	
	M4 N nucl.	GACAAATGA	

FIGURE 14-3

	1	60
GenBank N a.a.	MSVTVKRIIDNTVIVPKLPANEDPVEYPADYFRKSKEIPLYINTTKSLSDLRGYVYQGLK	
HR N a.a.	MSVTVKRIIDNTVIVPKLPANEDPVEYPADYFRKSKEIPLYINTTKSLSDLRGYVYQGLK	
M3 N a.a.	MSVTVKRIIDNTVIVPKLPANEDPVEYPADYFRKSKEIPLYINTTKSLSDLRGYVYQGLK	
M4 N a.a.		
	61	120
GenBank N a.a.	SGNVSIHVN SYLYGALKDIRGKLDKDWSSFGINIGKAGDTIGIFDLVSLKALDGVLPDG	
HR N a.a.	SGNVSIHVN SYLYGALKDIRGKLDKDWSSFGINIGKAGDTIGIFDLVSLKALDGVLPDG	
M3 N a.a.	SGNVSIHVN SYLYGALKDIRGKLDKDWSSFGINIGKAGDTIGIFDLVSLKALDGVLPDG	
M4 N a.a.	SIIHVN SYLYGALKDIRGKLDKDWSSFGINIGKAGDTIGIFDLVSLKALDGVLPDG	
	121	180
GenBank N a.a.	VSDASRTSADDKWLPLYLLGLYRVGRTQMPEYRKRLMDGLTNQCKMINEQFEPLVPEGRD	
HR N a.a.	VSDASRTSADDKWLPLYLLGLYRVGRTQMPEYRKRLMDGLTNQCKMINEQFEPLVPEGRD	
M3 N a.a.	VSDASRTSADDKWLPLYLLGLYRVGRTQMPEYRKRLMDGLTNQCKMINEQFEPLVPEGRD	
M4 N a.a.	VSDASRTSADDKWLPLYLLGLYRVGRTQMPEYRKRLMDGLTNQCKMINEQFEPLVPEGRD	
	181	240
GenBank N a.a.	IFDVWGNDSNYTKIVA AVDMFFHMFKKHECASFRYGTIVSRFKDCAALATFGHLCKITGM	
HR N a.a.	IFDVWGNDSNYTKIVA AVDMFFHMFKKHECASFRYGTIVSRFKDCAALATFGHLCKITGM	
M3 N a.a.	IFDVWGNDSNYTKIVA AVDMFFHMFKKHECASFRYGTIVSRFKDCAALATFGHLCKITGM	
M4 N a.a.	IFDVWGNDSNYTKIVA AVDMFFHMFKKHECASFRYGTIVSRFKDCAALATFGHLCKITGM	
	241	300
GenBank N a.a.	STEDVTTWILNREVADEMVMMLPGQEIDKADSYMPYLIDFGLSSKSPYSSVKNPAFHFW	
HR N a.a.	STEDVTTWILNREVADEMVMMLPGQEIDKADSYMPYLIDFGLSSKSPYSSVKNPAFHFW	
M3 N a.a.	STEDVTTWILNREVADEMVMMLPGQEIDKADSYMPYLIDFGLSSKSPYSSVKNPAFHFW	
M4 N a.a.	STEDVTTWILNREVADEMVMMLPGQEIDKADSYMPYLIDFGLSSKSPYSSVKNPAFHFW	
	301	360
GenBank N a.a.	GQLTALLRSTRARNARQPDDIEYTSLT TAGLLYAYAVGSSADLAQQFCVGDN KYTPDDS	
HR N a.a.	GQLTALLRSTRARNARQPDDIEYTSLT TAGLLYAYAVGSSADLAQQFCVGD SKYTPDDS	
M3 N a.a.	GQLTALLRSTRARNARQPDDIEYTSLT TAGLLYAYAVGSSADLAQQFCVGD SKYTPDDS	
M4 N a.a.	GQLT.....DIEYTSX TAGLLYAYAVGSSADLAQFCVGD SKYTPDDS	
	361	420
GenBank N a.a.	TGGLTTNAPPQGRDVVEWLGW FEDQNRKPTPDMMQYAKRAVMSLQGLREKTIGKYAKSEF	
HR N a.a.	TGGLTTNAPPQGRDVVEWLGW FEDQNRKPTPDMMQYAKRAVMSLQGLREKTIGKYAKSEF	
M3 N a.a.	TGGLTTNAPPQGRDVVEWLGW FEDQNRKPTPDMMQYAKRAVMSLQGLREKTIGKYAKSEF	
M4 N a.a.	TGGLTTNAPPQGRDVVEWLGW FEDQNRKPTPDMMQYAKRAVMSLQGLREKTIGKYAKSEF	
	421 423	
GenBank N a.a.	DK.	
HR N a.a.	DK.	
M3 N a.a.	DK.	
M4 N a.a.	DK.	

FIGURE 15

1 60
GenBank P nucl. ATGGATAATCTCACAAAAGTTTCGTGAGTATCTCAAGTCCTATTCTCGTCTGATCAGGCG
HR P nucl. ATGGATAATCTCACAAAAGTTTCGTGAGTATCTCAAGTCCTATTCTCGTCTAGATCAGGCG
M2 P nucl. ATGGATAATCTCACAAAAGTTTCGTGAGTATCTCAAGTCCTATTCTCGTCTAGATCAGGCG
M3 P nucl. ATGGATAATCTCACAAAAGTTTCGTGAGTATCTCAAGTCCTATTCTCGTCTAGATCAGGCG
M4 P nucl. ATGGATAATCTCACAAAAGTTTCGTGAGTATCTCAAGTCCTATTCTCGTCTAGATCAGGCG

61 120
GenBank P nucl. GTAGGAGAGATAGATGAGATCGAAGCACAACGAGCTGAAAAGTCCAATTATGAGTTGTTC
HR P nucl. GTAGGAGAGATAGATGAGATCGAAGCACAACGAGCTGAAAAGTCCAATTATGAGTTGTTC
M2 P nucl. GTAGGAGAGATAGATGAGATCGAAGCACAACGAGCTGAAAAGTCCAATTATGAGTTGTTC
M3 P nucl. GTAGGAGAGATAGATGAGATCGAAGCACAACGAGCTGAAAAGTCCAATTATGAGTTGTTC
M4 P nucl. GTAGGAGAGATAGATGAGATCGAAGCACAACGAGCTGAAAAGTCCAATTATGAGTTGTTC

121 180
GenBank P nucl. CAAGAGGATGGAGTGGAAAGAGCATACTAGGCCCTCTTATTTTCAGGCAGCAGATGATTCT
HR P nucl. CAAGAGGACGGAGTGGAAAGAGCATACTAGGCCCTCTTATTTTCAGGCAGCAGATGATTCT
M2 P nucl. CAAGAGGACGGAGTGGAAAGAGCATACTAGGCCCTCTTATTTTCAGGCAGCAGATGATTCT
M3 P nucl. CAAGAGGACGGAGTGGAAAGAGCATACTAGGCCCTCTTATTTTCAGGCAGCAGATGATTCT
M4 P nucl. CAAGAGGACGGAGTGGAAAGAGCATACTAGGCCCTCTTATTTTCAGGCAGCAGATGATTCT

181 240
GenBank P nucl. GACACAGAATCTGAACCAGAAATTGAAGACAATCAAGGCTTGTATGACAGGATCCAGAA
HR P nucl. GACACAGAATCTGAACCAGAAATTGAAGACAATCAAGGCTTGTATGTACCAGATCCGGAA
M2 P nucl. GACACAGAATCTGAACCAGAAATTGAAGACAATCAAGGCTTGTATGTACCAGATCCGGAA
M3 P nucl. GACACAGAATCTGAACCAGAAATTGAAGACAATCAAGGCTTGTATGTACCAGATCCGGAA
M4 P nucl. GACACAGAATCTGAACCAGAAATTGAAGACAATCAAGGCTTGTATGTACCAGATCCGGAA

241 300
GenBank P nucl. GCTGAGCAAGTTGAAGGCTTTATACAGGGGCCTTTAGATGACTATGCGAGATGAGGAAGTG
HR P nucl. GCTGAGCAAGTTGAAGGCTTTATACAGGGGCCTTTAGATGACTATGCGGATGAGGACGTG
M2 P nucl. GCTGAGCAAGTTGAAGGCTTTATACAGGGGCCTTTAGATGACTATGCGGATGAGGACGTG
M3 P nucl. GCTGAGCAAGTTGAAGGCTTTATACAGGGGCCTTTAGATGACTATGCGGATGAGGACGTG
M4 P nucl. GCTGAGCAAGTTGAAGGCTTTATACAGGGGCCTTTAGATGACTATGCGGATGAGGACGTG

301 360
GenBank P nucl. GATGTTGTATTACTTCGGACTGGAAACACCTGAGCTTGAATCTGACGAGCATGGAAAG
HR P nucl. GATGTTGTATTCACTTCGGACTGGAAACAGCCTGAGCTTGAATCCGACGAGCATGGAAAG
M2 P nucl. GATGTTGTATTCACTTCGGACTGGAAACAGCCTGAGCTTGAATCCGACGAGCATGGAAAG
M3 P nucl. GATGTTGTATTCACTTCGGACTGGAAACAGCCTGAGCTTGAATCCGACGAGCATGGAAAG
M4 P nucl. GATGTTGTATTCACTTCGGACTGGAAACAGCCTGAGCTTGAATCCGACGAGCATGGAAAG

361 420
GenBank P nucl. ACCTTACGGTTGACATTGCCAGAGGGTTTAAGTGGAGAGCAGAAATCCCAGTGGCTTTTG
HR P nucl. ACCTTACGGTTGACATTGCCAGAGGGTTTAAGTGGAGAGCAGAAATCCCAGTGGCTTTTG
M2 P nucl. ACCTTACGGTTGACATTGCCAGAGGGTTTAAGTGGAGAGCAGAAATCCCAGTGGCTTTTG
M3 P nucl. ACCTTACGGTTGACATTGCCAGAGGGTTTAAGTGGAGAGCAGAAATCCCAGTGGCTTTTG
M4 P nucl. ACCTTACGGTTGACATTGCCAGAGGGTTTAAGTGGAGAGCAGAAATCCCAGTGGCTTTTG

FIGURE 16-1

		421		480
GenBank	P nucl.	ACGATTAAAGCAGTCGT	CAAAGTGCCAAA	ACTGGAATCTGGCAGAGTGCACATTTGAA
HR	P nucl.	ACGATTAAAGCAGTCGTTCAAAGTGCCAAACACTGGAATCTGGCAGAGTGCACATTTGAA		
M2	P nucl.	ACGATTAAAGCAGTCGTTCAAAGTGCCAAACACTGGAATCTGGCAGAGTGCACATTTGAA		
M3	P nucl.	ACGATTAAAGCAGTCGTTCAAAGTGCCAAACACTGGAATCTGGCAGAGTGCACATTTGAA		
M4	P nucl.	ACGATTAAAGCAGTCGTTCAAAGTGCCAAACACTGGAATCTGGCAGAGTGCACATTTGAA		
		481		540
GenBank	P nucl.	GCATCGGGAGAAGGGGTCAT	TATGAAAGGAGCGCCAGATAACTCCGGATGTATATAAGGTC	
HR	P nucl.	GCATCGGGAGAAGGGGTCATCATAAAAAAGCGCCAGATAACTCCGGATGTATATAAGGTC		
M2	P nucl.	GCATCGGGAGAAGGGGTCATCATAAAAAAGCGCCAGATAACTCCGGATGTATATAAGGTC		
M3	P nucl.	GCATCGGGAGAAGGGGTCATCATAAAAAAGCGCCAGATAACTCCGGATGTATATAAGGTC		
M4	P nucl.	GCATCGGGAGAAGGGGTCATCATAAAAAAGCGCCAGATAACTCCGGATGTATATAAGGTC		
		541		600
GenBank	P nucl.	ACTCCAGTGATGAACACACATCCGTCCCAATCAGAAGC	AGTATCAGATGTTTGGTCTCTC	
HR	P nucl.	ACTCCAGTGATGAACACACATCCGTCCCAATCAGAAGCCGTATCAGATGTTTGGTCTCTC		
M2	P nucl.	ACTCCAGTGATGAACACACATCCGTCCCAA		
M3	P nucl.	ACTCCAGTGATGAACACACATCCGTCCCAATC	GGAAGCCGTATCAGATGTTTGGTCTCTC	
M4	P nucl.	ACTCCAGTGATGAACACACATCCGTCCCAATCAGAAGCCGTATCAGATGTTTGGTCTCTC		
		601		660
GenBank	P nucl.	TCAAAGACATCCATGACTTTCCAACCCAAGAAAGCAAGTCTTCAGCCTCTCACCATATCC		
HR	P nucl.	TCAAAGACATCCATGACTTTCCAACCCAAGAAAGCAAGTCTTCAGCCTCTCACCATATCC		
M2	P nucl.			
M3	P nucl.	TCAAAGACATCCATGACTTTCCAACCCAAGAAAGCAAGTCTTCAGCCTCTCACCATATCC		
M4	P nucl.	TCAAAGACATCCATGACTTTCCAACCCAAGAAAGCAAGTCTTCAGCCTCTCACCATATCC		
		661		720
GenBank	P nucl.	TTGGATGAATTGTTCTCATCTAGAGGAGA	TTTCATCTCTGTCTCGGAGGTACGGACGAATG	
HR	P nucl.	TTGGATGAATTGTTCTCATCTAGAGGAGAATTCATCTCTGTCTCGGAGGTAACGGACGAATG		
M2	P nucl.			
M3	P nucl.	TTGGATGAATTGTTCTCATCTAGAGGAGAATTCATCTCTGTCTCGGAGGTAACGGACGAATG		
M4	P nucl.	TTGGATGAATTGTTCTCATCTAGAGGAGAATTCATCTCTGTCTCGGAGGTAACGGACGAATG		
		721		780
GenBank	P nucl.	TCTCATAAAGAGGCCATCCTGCTCGG	CTGAGATACAAAAAGTTGTACAATCAGGCGAGA	
HR	P nucl.	TCTCATAAAGAGGCCATCCTGCTCGGTCTGAGGTACAAAAAGTTGTACAATCAGGCGAGA		
M2	P nucl.			
M3	P nucl.	TCTCATAAAGAGGCCATCCTGCTCGGTCTGAGGTACAAAAAGTTGTACAATCAGGCGAGA		
M4	P nucl.	TCTCATAAAGAGGCCATCCTGCTCGGTCTGAGGTACAAAAAGTTGTACAATCAGGCGAGA		
		781	798	
GenBank	P nucl.	GTCAAATATTCTCTGTAG		
HR	P nucl.	GTCAAATATTCTCTGTAG		
M2	P nucl.			
M3	P nucl.	GTCAAATATTCTCTGTAG		
M4	P nucl.	GTCAAATATTCTCTGTAG		

FIGURE 16-2

		1		60
GenBank	P a . a .	MDNLT	TKVREYLKSYSRLDQAVGEIDEIEAQRAEKS	SNYELFQEDGVEEHTKPSYFQAADDS
HR	P a . a .	MDNLT	TKVREYLKSYSRLDQAVGEIDEIEAQRAEKS	SNYELFQEDGVEEHTRPSYFQAADDS
M2	P a . a .	MDNLT	TKVREYLKSYSRLDQAVGEIDEIEAQRAEKS	SNYELFQEDGVEEHTRPSYFQAADDS
M3	P a . a .	MDNLT	TKVREYLKSYSRLDQAVGEIDEIEAQRAEKS	SNYELFQEDGVEEHTRPSYFQAADDS
M4	P a . a .	MDNLT	TKVREYLKSYSRLDQAVGEIDEIEAQRAEKS	SNYELFQEDGVEEHTRPSYFQAADDS
		61		120
GenBank	P a . a .	DTESEPEIEDNQGLY	ADPEAEQVEGFIQG	PLDDYADEEVDVVF
HR	P a . a .	DTESEPEIEDNQGLY	VPDPEAEQVEGFIQG	PLDDYADEEDVDVVF
M2	P a . a .	DTESEPEIEDNQGLY	VPDPEAEQVEGFIQG	PLDDYADEEDVDVVF
M3	P a . a .	DTESEPEIEDNQGLY	VPDPEAEQVEGFIQG	PLDDYADEEDVDVVF
M4	P a . a .	DTESEPEIEDNQGLY	VPDPEAEQVEGFIQG	PLDDYADEEDVDVVF
		121		180
GenBank	P a . a .	TLRLT	SPGLSGEQKSQWL	STIKAVVQSAKYWNLAECTFEASGEGVI
HR	P a . a .	TLRLT	SPGLSGEQKSQWLL	TIKAVVQSAKHWNLAECTFEASGEGV
M2	P a . a .	TLRLT	SPGLSGEQKSQWLL	TIKAVVQSAKHWNLAECTFEASGEGV
M3	P a . a .	TLRLT	SPGLSGEQKSQWLL	TIKAVVQSAKHWNLAECTFEASGEGV
M4	P a . a .	TLRLT	SPGLSGEQKSQWLL	TIKAVVQSAKHWNLAECTFEASGEGV
		181		240
GenBank	P a . a .	TPVMNTHPSQSEAVSDVWSLSKTSMTFQPKKASLQPLTISLDEL	FSSRGEFISVGG	DGRM
HR	P a . a .	TPVMNTHPSQSEAVSDVWSLSKTSMTFQPKKASLQPLTISLDEL	FSSRGEFISVGG	NGRM
M2	P a . a .	TPVMNTHPSQ		
M3	P a . a .	TPVMNTHPSQSEAVSDVWSLSKTSMTFQPKKASLQPLTISLDEL	FSSRGEFISVGG	NGRM
M4	P a . a .	TPVMNTHPSQSEAVSDVWSLSKTSMTFQPKKASLQPLTISLDEL	FSSRGEFISVGG	NGRM
		241		266
GenBank	P a . a .	SHKEA	ILLGLRYKKLYNQARVKYSL	
HR	P a . a .	SHKEA	ILLGLRYKKLYNQARVKYSL	
M2	P a . a .			
M3	P a . a .	SHKEA	ILLGLRYKKLYNQARVKYSL	
M4	P a . a .	SHKEA	ILLGLRYKKLYNQARVKYSL	

FIGURE 17

	1	60
GenBank M nucl.	ATGAGTTCCTTAAAGAAGATTCTCGGTCTGAAGGGGAAAGGTAAGAAATCTAAGAAATTA	
HR M nucl.	ATGAGTTCCTTAAAGAAGATTCTCGGTCTGAAGGGGAAAGGTAAGAAATCTAAGAAATTA	
M3 M nucl.	ATGAGTTCCTTAAAGAAGATTCTCGGTCTGAAGGGGAAAGGTAAGAAATCTAAGAAATTA	
M4 M nucl.	ATGAGTTCCTTAAAGAAGATTCTCGGTCTGAAGGGGAAAGGTAAGAAATCTAAGAAATTA	
	61	120
GenBank M nucl.	GGGATCGCACCACCCCTTATGAAGAGGACACTA ~~C~~ CATGGAGTATGCTCCGAGCGCTCCA	
HR M nucl.	GGGATCGCACCACCCCTTATGAAGAGGACACTAACATGGAGTATGCTCCGAGCGCTCCA	
M3 M nucl.	GGGATCGCACCACCCCTTATGAAGAGGACACTAACATGGAGTATGCTCCGAGCGCTCCA	
M4 M nucl.	GGGATCGCACCACCCCTTATGAAGAGGACACTAACATGGAGTATGCTCCGAGCGCTCCA	
	121	180
GenBank M nucl.	ATTGACAAATCCTATTTTGGAGTTGACGAGATGGACAC ~~C~~ ATGATCCG ~~A~~ ATCAATTAAGA	
HR M nucl.	ATTGACAAATCCTATTTTGGAGTTGACGAGATGGACACTCATGATCCGCATCAATTAAGA	
M3 M nucl.	ATTGACAAATCCTATTTTGGAGTTGACGAGA ~~C~~ GGACACTCATGATCCGCATCAATTAAGA	
M4 M nucl.	ATTGACAAATCCTATTTTGGAGTTGACGAGATGGACACTCATGATCCGCATCAATTAAGA	
	181	240
GenBank M nucl.	TATGAGAAATTCTTCTTTACAGTGAAAATGACGGTTAGATCTAATCGTCCGTTTCAGAACA	
HR M nucl.	TATGAGAAATTCTTCTTTACAGTGAAAATGACGGTTAGATCTAATCGTCCGTTTCAGAACA	
M3 M nucl.	TATGAGAAATTCTTCTTTACAGTGAAAATGACGGTTAGATCTAATCGTCCGTTTCAGAACA	
M4 M nucl.	TATGAGAAATTCTTCTTTACAGTGAAAATGACGGTTAGATCTAATCGTCCGTTTCAGAACA	
	241	300
GenBank M nucl.	TACTCAGATGTGGCAGCCGCTGTATCCCATTGGGATCACATGTACATCGGAATGGCAGGG	
HR M nucl.	TACTCAGATGTGGCAGCCGCTGTATCCCATTGGGATCACATGTACATCGGAATGGCAGGG	
M3 M nucl.	TACTCAGATGTGGCAGCCGCTGTATCCCATTGGGATCACATGTACATCGGAATGGCAGGG	
M4 M nucl.	TACTCAGATGTGGCAGCCGCTGTATCCCATTGGGATCACATGTACATCGGAATGGCAGGG	
	301	360
GenBank M nucl.	AAACGTCCCTTCTACAA ~~A~~ ATCTTGGCTTTTTTGGGTTCTTCTAATCTAAAGGCCACTCCA	
HR M nucl.	AAACGTCCCTTCTACAAGATCTTGGCTTTTTTGGGTTCTTCTAATCTAAAGGCCACTCCA	
M3 M nucl.	AAACGTCCCTTCTACAAGATCTTGGCTTTTTTGGG ~~T~~ CTTCTAATCTAAAGGCCACTCCA	
M4 M nucl.	AAACGTCCCTTCTACAAGATCTTGGCTTTTTTGGGTTCTTCTAATCTAAAGGCCACTCCA	
	361	420
GenBank M nucl.	GCGGTATTGGCAGATCAAGGTCAACCAGAGTATCAC ~~A~~ CTCACTG ~~C~~ GAAGGCAGGGCTTAT	
HR M nucl.	GCGGTATTGGCAGATCAAGGTCAACCAGAGTATCACGCTCACTGTGAAGGCAGGGCTTAT	
M3 M nucl.	GCGGTATTGGCAGATCAAGGTCAACCAGAGTATCACGCTCACTGTGAAGGCAGGGCTTAT	
M4 M nucl.	GCGGTATTGGCAGATCAAGGTCAACCAGAGTATCACGCTCACTGTGAAGGCAGGGCTTAT	
	421	480
GenBank M nucl.	TTGCCACAT ~~A~~ AG ~~C~~ ATGGGGAAGACCCCTCCCATGCTCAATGTACCAGAGCACTTCAGAAGA	
HR M nucl.	TTGCCACACAGAATGGGGAAGACCCCTCCCATGCTCAATGTACCAGAGCACTTCAGAAGA	
M3 M nucl.	TTGCCACACAGAATGGGGAAGACCCCTCCCATGCTCAATGTACCAGAGCACTTCAGAAGA	
M4 M nucl.	TTGCCACACAGAATGGGGAAGACCCCTCCCATGCTCAATGTACCAGAGCACTTCAGAAGA	
	481	540
GenBank M nucl.	CCATTCAATATAGGTCTTTACAAGGGAACG ~~A~~ TTGAGCTCACAATGACCATCTACGATGAT	
HR M nucl.	CCATTCAATATAGGTCTTTACAAGGGAACGGTTGAGCTCACAATGACCATCTACGATGAT	
M3 M nucl.	CCATTCAATATAGGTCTTTACAAGGGAACGGTTGAGCTCACAATGACCATCTACGATGAT	
M4 M nucl.	CCATTCAATATAGGTCTTTACAAGGGAACGGTTGAGCTCACAATGACCATCTACGATGAT	

FIGURE 18-1

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541                                     600
GenBank M nucl. GAGTCACTGGAAGCAGCTCCTATGATCTGGGATCATTTCAATTCTTCCAAATTTTCTGAT
HR M nucl. GAGTCACTGGAAGCAGCTCCTATGATCTGGGATCATTTCAATTCTTCCAAATTTTCTGAT
M3 M nucl. GAGTCACTGGAAGCAGCTCCTATGATCTGGGATCATTTCAATTCTTCCAAATTTTCTGAT
M4 M nucl. GAGTCACTGGAAGCAGCTCCTATGATCTGGGATCATTTCAATTCTTCCAAATTTTCTGAT

601                                     660
GenBank M nucl. TTCAGAGAGAAGGCCTTAATGTTTGGCCTGATTGTCGAGAAAAAGGCATCTGGAGCCTGG
HR M nucl. TTCAGAGAGAAGGCCTTAATGTTTGGCCTGATTGTCGAGAAAAAGGCATCTGGAGCTTGG
M3 M nucl. TTCAGAGAGAAGGCCTTAATGTTTGGCCTGATTGTCGAGAAAAAGGCATCTGGAGCTTGG
M4 M nucl. TTCAGAGAGAAGGCCTTAATGTTTGGCCTGATTGTCGAGAAAAAGGCATCTGGAGCTTGG

661                                     690
GenBank M nucl. GTCCTGGATTCTATCAGCCACTTCAAATGA
HR M nucl. GTCCTGGATTCTGTCAGCCACTTCAAATGA
M3 M nucl. GTCCTGGATTCTGTCAGCCACTTCAAATGA
M4 M nucl. GTCCTGGATTCTGTCAGCCACTTCAAATGA
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FIGURE 18-2

	1	60
GenBank M a . a .	MSSLKKILGLKGKGKKSKKLGIAPPPYEEDTSM EYAPSAPIDKSYFGVDEMDT YDPNQLR	
HR M a . a .	MSSLKKILGLKGKGKKSKKLGIAPPPYEEDTNMEYAPSAPIDKSYFGVDEMDTHDPHQLR	
M4 M a . a .	MSSLKKILGLKGKGKKSKKLGIAPPPYEEDTNMEYAPSAPIDKSYFGVDEMDTHDPHQLR	
M3 M a . a .	MSSLKKILGLKGKGKKSKKLGIAPPPYEEDTNMEYAPSAPIDKSYFGVDE R DTHDPHQLR	
	61	120
GenBank M a . a .	YEKFFFTVKMTVRSNRPFRTYSDVAAAVSHWDHMYIGMAGKRPFYKILAF LGSSNLKATP	
HR M a . a .	YEKFFFTVKMTVRSNRPFRTYSDVAAAVSHWDHMYIGMAGKRPFYKILAF LGSSNLKATP	
M4 M a . a .	YEKFFFTVKMTVRSNRPFRTYSDVAAAVSHWDHMYIGMAGKRPFYKILAF LGSSNLKATP	
M3 M a . a .	YEKFFFTVKMTVRSNRPFRTYSDVAAAVSHWDHMYIGMAGKRPFYKILAF LGSSNLKATP	
	121	180
GenBank M a . a .	AVLADQGGQPEYH HCEGRAYLPHRMGKTPPMLNVPEHFRRPFNIGLYKGT IELTMTIYDD	
HR M a . a .	AVLADQGGQPEYHAHCEGRAYLPHRMGKTPPMLNVPEHFRRPFNIGLYKGTVELTMTIYDD	
M4 M a . a .	AVLADQGGQPEYHAHCEGRAYLPHRMGKTPPMLNVPEHFRRPFNIGLYKGTVELTMTIYDD	
M3 M a . a .	AVLADQGGQPEYHAHCEGRAYLPHRMGKTPPMLNVPEHFRRPFNIGLYKGTVELTMTIYDD	
	181	230
GenBank M a . a .	ESLEAAPMIWDHFNSSKFSDFREKALMFGLIVEKKASGAWVLDS I SHFK .	
HR M a . a .	ESLEAAPMIWDHFNSSKFSDFREKALMFGLIVEKKASGAWVLDSVSHFK .	
M4 M a . a .	ESLEAAPMIWDHFNSSKFSDFREKALMFGLIVEKKASGAWVLDSVSHFK .	
M3 M a . a .	ESLEAAPMIWDHFNSSKFSDFREKALMFGLIVEKKASGAWVLDSVSHFK .	

FIGURE 19

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1                                     60
GenBank G nucl. ATGAAGTGCCTTTTGTACTTAGCCTTTTTATTCATGGGGTGAATTGCAAGTTCACCATA
HR G nucl. ATGAAGTGCCTTTTGTACTTAGCTTTTTATTCATCGGGGTGAATTGCAAGTTCACCATA
M2 G nucl. .....
M3 G nucl. ATGAAGTGCCTTTTGTACTTAGCTTTTTATTCATCGGGGTGAATTGCAAGTTCACCATA
M4 G nucl. ATGAAGTGCCTTTTGTACTTAGCTTTTTATTCATCGGGGTGAATTGCAAGTTCACCATA

61                                     120
GenBank G nucl. GTTTTTCACACAACCAAAAAGGAAACTGGAAAAATGTTTCCTTCAATTACCATTATTGC
HR G nucl. GTTTTTCATACAACCAAAAAGGAAACTGGAAAAATGTTTCCTTCCAATTACCATTATTGC
M2 G nucl. .....
M3 G nucl. GTTTTTCATACAACCAAAAAGGAAACTGGAAAAATGTTTCCTTCCAATTACCATTATTGC
M4 G nucl. GTTTTTCATACAACCAAAAAGGAAACTGGAAAAATGTTTCCTTCCAATTACCATTATTGC

121                                    180
GenBank G nucl. CCGTCAAGCTCAGATTTAAATTGGCATAATGACTTAATAGGCACAGCCATACAAGTCAAA
HR G nucl. CCGTCAAGCTCAGATTTAAATTGNCATAATGACTTAATAGGCACAGCCTTACAAGTCAAA
M2 G nucl. .....
M3 G nucl. CCGTCAAGCTCAGATTTAAATTGGCATAATGACTTAATAGGCACAGCCTTACAAGTCAAA
M4 G nucl. CCGTCAAGCTCAGATTTAAATTGGCATAATGACTTAATAGGCACAGCCTTACAGGTCAAA

181                                    240
GenBank G nucl. ATGCCCAAGAGTCACAAGGCTATTCAAGCAGACGGTTGGATGTGTCATGCTTCCAAATGG
HR G nucl. ATGCCCAAGAGTCACAAGGCTATTCAAGCAGACGGTTGGATGTGTCATGCTTCCAAATGG
M2 G nucl. .....
M3 G nucl. ATGCCCAAGAGTCACAAGGCTATTCAAGCAGACGGTTGGATGTGTCATGCTTCCAAATGG
M4 G nucl. ATGCCCAAGAGTCACAAGGCTATTCAAGCAGACGGTTGGATGTGTCATGCTTCCAAATGG

241                                    300
GenBank G nucl. GTCACTACTTGTGATTTCCGCTGGTAAGGACCGAAGTATATAACACAGTCCATCCGATCC
HR G nucl. GTCACTACTTGTGATTTCCGCTGGTACGGACCGAAGTATATAACACATTCCATCCGATCC
M2 G nucl. .....
M3 G nucl. GTCACTACTTGTGATTTCCGCTGGTACGGACCGAAGTATATAACACATTCCATCCGATCC
M4 G nucl. GTCACTACTTGTGATTTCCGCTGGTACGGACCGAAGTATATAACACATTCCATCCGATCC

301                                    360
GenBank G nucl. TTCACTCCATCTGTAGAACAATGCAAGGAAAGCATTGAACAAACGAAACAAGGAAGTGG
HR G nucl. TTCACTCCATCTGTAGAACAATGCAAGGAAAGCATTGAACAAACGAAACAAGGAAGTGG
M2 G nucl. .....
M3 G nucl. TTCACTCCATCTGTAGAACAATGCAAGGAAAGCATTGAACAAACGAAACAAGGAAGTGG
M4 G nucl. TTCACTCCATCTGTAGAACAATGCAAGGAAAGCATTGAACAAACGAAACAAGGAAGTGG

361                                    420
GenBank G nucl. CTGAATCCAGGCTTCCCTCCTCAAAGTTGTGGATATGCAACTGTGACGGATGCTGAAGCA
HR G nucl. CTGAATCCAGGCTTCCCTCCTCAAAGTTGTGGATATGCAACTGTGACGGATGCTGAAGCA
M2 G nucl. .....
M3 G nucl. CTGAATCCAGGCTTCCCTCCTCAAAGTTGTGGATATGCAACTGTGACGGATGCTGAAGCA
M4 G nucl. CTGAATCCAGGCTTCCCTCCTCAAAGTTGTGGATATGCAACTGTGACGGATGCTGAAGCA

421                                    480
GenBank G nucl. GTGATTGTCCAGGTGACTCCTCACCATGTGCTGTTGATGAATACACAGGAGAATGGGTT
HR G nucl. GCGATTGTCCAGGTGACTCCTCACCATGTGCTTGTGATGAATACACAGGAGAATGGGTT
M2 G nucl. .....
M3 G nucl. GCGATTGTCCAGGTGACTCCTCACCATGTGCTTGTGATGAATACACAGGAGAATGGGTT
M4 G nucl. GCGATTGTCCAGGTGACTCCTCACCATGTGCTTGTGATGAATACACAGGAGAATGGGTT

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FIGURE 20-1

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481
GenBank G nucl. GATTCACAGTTCATCAACGGAAAATGCAGCAATACATATGCCCCACTGTCCATAACTCC
HR G nucl. GATTCACAGTTCATCAACGGAAAATGCAGCAATGACATATGCCCCACTGTCCATAACTCC
M2 G nucl.
M3 G nucl. GATTCACAGTTCATCAACGGAAAATGCAGCAATGACATATGCCCCACTGTCCATAACTCC
M4 G nucl. GATTCACAGTTCATCAACGGAAAATGCAGCAATGACATATGCCCCACTGTCCATAACTCC

541
GenBank G nucl. ACAACCTGGCATTCTGACTATAAGGTCAAAGGGCTATGTGATTCTAACCTCATTTCCATG
HR G nucl. ACAACCTGGCATTCCGACTATAAGGTCAAAGGGCTATGTGATTCTAACCTCATTTCCATG
M2 G nucl.
M3 G nucl. ACAACCTGGCATTCCGACTATAAGGTCAAAGGGCTATGTGATTCTAACCTCATTTCCATG
M4 G nucl. ACAACCTGGCATTCCGACTATAAGGTCAAAGGGCTATGTGATTCTAACCTCATTTCCATG

601
GenBank G nucl. GACATCACCTTCTTCTCAGAGGACGGAGAGCTATCATCCCTGGAAAGGAGGGGCACAGGG
HR G nucl. GACATCACCTTCTTCTCAGAGGACGGAGAGCTATCATCCCTAGGAAAGGAGGGGCACAGGG
M2 G nucl.
M3 G nucl. GACATCACCTTCTTCTCAGAGGACGGAGAGCTATCATCCCTAGGAAAGGAGGGGCACAGGG
M4 G nucl. GACATCACCTTCTTCTCAGAGGACGGAGAGCTATCATCCCTAGGAAAGGAGGGGCACAGGG

661
GenBank G nucl. TTCAGAAGTAACTACTTTTGCTTATGAAACTGGAGCAAGGCCTGCAAAATGCAATACTGC
HR G nucl. TTCAGAAGTAACTACTTTTGCTTATGAAACTGGAGACAAGGCCTGCAAAATGCAGTACTGC
M2 G nucl.
M3 G nucl. TTCAGAAGTAACTACTTTTGCTTATGAAACTGGAGACAAGGCCTGCAAAATGCAGTACTGC
M4 G nucl. TTCAGAAGTAACTACTTTTGCTTATGAAACTGGAGACAAGGCCTGCAAAATGCAGTACTGC

721
GenBank G nucl. AAGCAATTGGGGAGTCAGACTCCCATCAGGTGTCTGGTTCGAGATGGCTGATAAGGATCTC
HR G nucl. AAGCGTTGGGGAGTCAGACTCCCATCAGGTGTCTGGTTCGAGATGGCTGATAAGGATCTC
M2 G nucl.
M3 G nucl. AAGCAATTGGGGAGTCAGACTCCCATCAGGTGTCTGGTTCGAGATGGCTGATAAGGATCTC
M4 G nucl. AAGCGTTGGGGAGTCAGACTCCCATCAGGTGTCTGGTTCGGATGGCTGATAAGGATCTC

781
GenBank G nucl. TTTGCTGCAGCCAGATTCCCTGAATGCCCAGAAGGGTCAAGTATCTCTGCTCCATCTCAG
HR G nucl. TTTGCTGCAGCCAGATTCCCTGAATGCCCAGAAGGGTCAAGTATCTCTGCTCCATCTCAG
M2 G nucl.
M3 G nucl. TTTGCTGCAGCCAGATTCCCTGAATGCCCAGAAGGGTCAAGTATCTCTGCTCCATCTCAG
M4 G nucl. TTTGCTGCAGCCAGATTCCCTGAATGCCCAGAAGGGTCAAGTATCTCTGCTCCATCTCAG

841
GenBank G nucl. ACCTCAGTGGATGTAAGTCTATTCAGGACGTTGAGAGGATCTTGATTATTCCCTCTGC
HR G nucl. ACCTCAGTGGATGTAAGTCTCATTTCAGGACGTTGAGAGGATCTTG.....
M2 G nucl. ACCTCAGTGGATGTAAGTCTCATTTCAGGACGTTGAGAGGATCTTGATTATTCCCTCTGC
M3 G nucl. ACCTCAGTGGATGTAAGTCTCATTTCAGGACGTTGAGAGGATCTTGATTATTCCCTCTGC
M4 G nucl. ACCTCAGTGGATGTAAGTCTCATTTCAGGACGTTGAGAGGATCT.....

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FIGURE 20-2

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          901                                     960
GenBank G nucl. CAAGAAACCTGGAGCAAAATCAGAGCGGGTCTTCCATCTCTCCAGTGGATCTCAGCTAT
HR G nucl. ....
M2 G nucl. CAAGAAACCTGGAGCAAAATCAGAGCGGGTCTTCCCATCTCTCCAGTGGATCTCAGCTAT
M3 G nucl. CAAGAAACCTGGAGCAAAATCAGAGCGGGTCTTCCCATCTCTCCAGTGGATCTCAGCTAT
M4 G nucl. ....

          961                                     1020
GenBank G nucl. CTTGCTCCTAAAAACCCAGGAACCGGTCCTGCTTTCACCATAATCAATGGTACCCTAAAA
HR G nucl. ....
M2 G nucl. CTTGCTCCTAAAAACCCAGGAACCGGTCCTGCTTTCACCATAATCAATGGTACCCTAAAA
M3 G nucl. CTTGCTCCTAAAAACCCAGGAACCGGTCCTGCTTTCACCATAATCAATGGTACCCTAAAA
M4 G nucl. ....

          1021                                     1080
GenBank G nucl. TACTTTGAGACCAGATACATCAGAGTCGATATTGCTGCTCCAATCCTCTCAAGAATGGTC
HR G nucl. ....
M2 G nucl. TACTTTGAGACCAGATACATCAGAGTCGATATTGCTGCTCCAATCCTCTCAAGAATGGTC
M3 G nucl. TACTTTGAGACCAGATACATCAGAGTCGATATTGCTGCTCCAATCCTCTCAAGAATGGTC
M4 G nucl. TACTTTGAGACCAGATACATCAGAGTCGATATTGCTGCTCCAATCCTCTCAAGAATGGTC

          1081                                     1140
GenBank G nucl. GGAATGATCAGTGGAACCTACCACAGAAAGGGAACCTGTGGGATGACTGGGCACCATATGAA
HR G nucl. ....
M2 G nucl. GGAATGATCAGTGGAACCTACCACAGAAAGGGAACCTGTGGGATGACTGGGCTCCATATGAA
M3 G nucl. GGAATGATCAGTGGAACCTACCACAGAAAGGGAACCTGTGGGATGACTGGGCTCCATATGAA
M4 G nucl. GGAATGATCAGTGGAACCTACCACAGAAAGGGAACCTGTGGGATGACTGGGCTCCATATGAA

          1141                                     1200
GenBank G nucl. GACGTGGAAATTGGACCCAATGGAGTTCTGAGGACCAGTTCAGGATATAAGTTTCCTTTA
HR G nucl. ....
M2 G nucl. GACGTGGAAATTGGACCCAATGGAGTTCTGAGGACCAGTTCAGGATATAAGTTTCCTTTA
M3 G nucl. GACGTGGAAATTGGACCCAATGGAGTTCTGAGGACCAGTTCAGGATATAAGTTTCCTTTA
M4 G nucl. GACGTGGAAATTGGACCCAATGGAGTTCTGAGGACCAGTTCAGGATATAAGTTTCCTTTA

          1201                                     1260
GenBank G nucl. TACATGATTGGACATGGTATGTTGGACTCCGATCTTCATCTTAGCTCAAAGGCTCAGGTG
HR G nucl. ....
M2 G nucl. TATATGATTGGACATGGTATGTTGGACTCCGATCTTCATCTTAGCTCAAAGGCTCAGGTG
M3 G nucl. TATATGATTGGACATGGTATGTTGGACTCCGATCTTCATCTTAGCTCAAAGGCTCAGGTG
M4 G nucl. TATATGATTGGACATGGTATGTTGGACTCCGATCTTCATCTTAGCTCAAAGGCTCAGGTG

          1261                                     1320
GenBank G nucl. TTTGAACATCCTCACATTCAAGACGCTGCTTCGCACTTCCTGATGATGAGACTTTATTT
HR G nucl. ....
M2 G nucl. TTTGAACATCCTCACATTCAAGACGCTGCTTCGCACTTCCTGATGATGAGACTTTATTT
M3 G nucl. TTTGAACATCCTCACATTCAAGACGCTGCTTCGCACTTCCTGATGATGAGACTTTATTT
M4 G nucl. TTTGAACATCCTCACATTCAAGACGCTGCTTCGCACTTCCTGATGATGAGACTTTATTT

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FIGURE 20-3

		1321		1380
GenBank	G	nucl.	TTTGGTGATACTGGGCTATCCAAAAATCCAATCGAGCTTGTAGAAGGTTGGTTCAGTAGT	
	HR	G	nucl.	
	M2	G	nucl.	TTTGGTGATACTGGGCTATCCAAAAATCCAATCGAGTTTGTAGAAGGTTGGTTCAGTAGT
	M3	G	nucl.	TTTGGTGATACTGGGCTATCCAAAAATCCAATCGAGTTTGTAGAAGGTTGGTTCAGTAGT
	M4	G	nucl.	TTTGGTGATACTGGGCTATCCAAAAATCCAATCGAGTTTGTAGAAGGTTGGTTCAGTAGT
		1381		1440
GenBank	G	nucl.	TGGAAAGCTCTATTGCCTCTTTTTTCTTTATCATAGGGTTAATCATTTGGACTATTCTTG	
	HR	G	nucl.	
	M2	G	nucl.	TGGAAGAGCTCTATTGCCTCTTTTTTCTTTATCATAGGGTTAATCATTTGGACTATTCTTG
	M3	G	nucl.	TGGAAGAGCTCTATTGCCTCTTTTTTCTTTATCATAGGGTTAATCATTTGGACTATTCTTG
	M4	G	nucl.	TGGAAGAGCTCTATTGCCTCTTTTTTCTTTATCATAGGGTTAATCATTTGGACTATTCTTG
		1441		1500
GenBank	G	nucl.	GTTCTCCGAGTTGGTATCCATCTTTGCATTAAATTAAAGCACACCAAGAAAAGACAGATT	
	HR	G	nucl.	
	M2	G	nucl.	GTTCTCCGAGTTGGTATTTATCTTTGCATTAAATTAAAGCACACCAAGAAAAGACAGATT
	M3	G	nucl.	GTTCTCCGAGTTGGTATTTATCTTTGCATTAAATTAAAGCACACCAAGAAAAGACAGATT
	M4	G	nucl.	GTTCTCCGAGTTGGTATTTATCTTTGCATTAAATTAAAGCACACCAAGAAAAGACAGATT
		1501		1536
GenBank	G	nucl.	TATACAGACATAGAGATGAACCGACTTGGGAAGTAA	
	HR	G	nucl.	
	M2	G	nucl.	TATACAGACATAGAGATGAACCGACTTGGGAAGTAA
	M3	G	nucl.	TATACAGACATAGAGATGAACCGACTTGGGAAGTAA
	M4	G	nucl.	TATACAGACATAGAGATGAACCGACTTGGGAAGTAA

FIGURE 20-4

	1	60
GenBank G a.a.	MKCLLYLAFLFIGVNCKFTIVFPINQKGNWKNVPSNYHYCPSSSDLNWHNDLIGTAIQVK	
HR G a.a.	MKCLLYLAFLFIGVNCKFTIVFPYNQKGNWKNVPSNYHYCPSSSDLNWHNDLIGTALQVK	
M2 G a.a.		
M3 G a.a.	MKCLLYLAFLFIGVNCKFTIVFPYNQKGNWKNVPSNYHYCPSSSDLNWHNDLIGTALQVK	
M4 G a.a.	MKCLLYLAFLFIGVNCKFTIVFPYNQKGNWKNVPSNYHYCPSSSDLNWHNDLIGTALQVK	
	61	120
GenBank G a.a.	MPKSHKAIQADGWMCHASKWVTTCDFRWYGPKYITQSIRSFTPSVEQCKESIEQTKQGTW	
HR G a.a.	MPKSHKAIQADGWMCHASKWVTTCDFRWYGPKYITHSIRSFTPSVEQCKESIEQTKQGTW	
M2 G a.a.		
M3 G a.a.	MPKSHKAIQADGWMCHASKWVTTCDFRWYGPKYITHSIRSFTPSVEQCKESIEQTKQGTW	
M4 G a.a.	MPKSHKAIQADGWMCHASKWVTTCDFRWYGPKYITHSIRSFTPSVEQCKESIEQTKQGTW	
	121	180
GenBank G a.a.	LNPGFPPQSCGYATVTDAAEIVQVTPHHVLVDEYTGEWVDSQFINGKCSNYICPTVHNS	
HR G a.a.	LNPGFPPQSCGYATVTDAAEIVQVTPHHVLVDEYTGEWVDSQFINGKCSNDICPTVHNS	
M2 G a.a.		
M3 G a.a.	LNPGFPPQSCGYATVTDAAEIVQVTPHHVLVDEYTGEWVDSQFINGKCSNDICPTVHNS	
M4 G a.a.	LNPGFPPQSCGYATVTDAAEIVQVTPHHVLVDEYTGEWVDSQFINGKCSNDICPTVHNS	
	181	240
GenBank G a.a.	TTWHSDYKVKGLCDSNLISMDITFFSEDGELSSLGKEGTGFRSNYFAYETGCKACKMQYC	
HR G a.a.	TTWHSDYKVKGLCDSNLISMDITFFSEDGELSSLGKEGTGFRSNYFAYETGDKACKMQYC	
M2 G a.a.		
M3 G a.a.	TTWHSDYKVKGLCDSNLISMDITFFSEDGELSSLGKEGTGFRSNYFAYETGDKACKMQYC	
M4 G a.a.	TTWHSDYKVKGLCDSNLISMDITFFSEDGELSSLGKEGTGFRSNYFAYETGDKACKMQYC	
	241	300
GenBank G a.a.	KHWGVRLPSGVWFEMADKDLFAAARFPECPEGSSISAPSQTSVDVSLIQDVERILDYSLC	
HR G a.a.	KRWGVRLPSGVWFEMADKDLFAAARFPECPEGSSISAPSQTSVDVSLIQDVERIL.....	
M2 G a.a.	PSQTSVDVSLIQDVERILDYSLC	
M3 G a.a.	KHWGVRLPSGVWFEMADKDLFAAARFPECPEGSSISAPSQTSVDVSLIQDVERILDYSLC	
M4 G a.a.	KRWGVRLPSGVWFEMADKDLFAAARFPECPEGSSISAPSQTSVDVSLIQDVERI.....	
	301	360
GenBank G a.a.	QETWSKIRAGLPISPVDLSYLAPKNPGTGPAFTIINGTLKYFETRYIRVDIAAPILSRMV	
HR G a.a.		
M2 G a.a.	QETWSKIRAGLPISPVDLSYLAPKNPGTGPAFTIINGTLKYFETRYIRVDIAAPILSRMV	
M3 G a.a.	QETWSKIRAGLPISPVDLSYLAPKNPGTGPAFTIINGTLKYFETRYIRVDIAAPILSRMV	
M4 G a.a.	YFETRYIRVDIAAPILSRMV	
	361	420
GenBank G a.a.	GMISGTTTERELWDDWAPYEDVEIGPNGVLRRTSSGYKFPLYMIGHGMLDSDLHLSSKAQV	
HR G a.a.		
M2 G a.a.	GMISGTTTERELWDDWAPYEDVEIGPNGVLRRTSSGYKFPLYMIGHGMLDSDLHLSSKAQV	
M3 G a.a.	GMISGTTTERELWDDWAPYEDVEIGPNGVLRRTSSGYKFPLYMIGHGMLDSDLHLSSKAQV	
M4 G a.a.	GMISGTTTERELWDDWAPYEDVEIGPNGVLRRTSSGYKFPLYMIGHGMLDSDLHLSSKAQV	

FIGURE 21-1

		421		480
GenBank	G a.a.	FEHPHIQDAASQLPDDE	SLFFGDTGLSKNPIEL	VEGWFSSWKSSIASFFFIIGLIIGLFL
HR	G a.a.			
M2	G a.a.	FEHPHIQDAASQLPDDE	TLFFGDTGLSKNPIEF	VEGWFSSWKSSIASFFFIIGLIIGLFL
M3	G a.a.	FEHPHIQDA	XAQLPDDETLFFGDTGLSKNPIEF	VEGWFSSWKSSIASFFFIIGLIIGLFL
M4	G a.a.	FEHPHIQDAASQLPDDE	TLFFGDTGLSKNPIEF	VEGWFSSWKSSIASFFFIIGLIIGLFL
		481		512
GenBank	G a.a.	VLRVGI	HL	LCIKLKHTKKRQIYTDIEMNRLGK
HR	G a.a.			
M2	G a.a.	VLRVGIYLCIKLKHTKKRQIYTDIEMNRLGK		
M3	G a.a.	VLRVGIYLCIKLKHTKKRQIYTDIEMNRLGK		
M4	G a.a.	VLRVGIYLCIKLKHTKKRQIYTDIEMNRLGK		

FIGURE 21-2

GenBank L nucl.	1	60
HR L nucl.	ATGGAAGTCCACGATTTTGAGACCGACGAGTTCAATGATTTCAATGAAGATGACTATGCC	
M2 L nucl.		
M4 L nucl.	ATGGAAGTCCACGATTTTGAGACCGACGAGTTCAATGATTTCAATGAAGATGACTATGCC	
GenBank L nucl.	61	120
HR L nucl.	ACAAGAGAATTCCTGAATCCCGATGAGCGCATGACGTACTTGAATCATGCTGATTACAAT	
M2 L nucl.		
M4 L nucl.	ACAAGAGAATTCCTGAATCCCGATGAGCGCATGACGTACTTGAATCATGCTGATTACAAT	
GenBank L nucl.	121	180
HR L nucl.	TTGAATTCTCCTCTAATTAGTGATGATATTGACAATTTGATCAGGAAATTCAATTCTCTT	
M2 L nucl.		
M4 L nucl.	TTGAATTCTCCTCTAATTAGTGATGATATTGACAATTTGATCAGGAAATTCAATTCTCTT	
GenBank L nucl.	181	240
HR L nucl.	CCGATTCCCTCGATGTGGGATAGTAAGAACTGGGATGGAGTTCTTGAGATGTTAACATCA	
M2 L nucl.		
M4 L nucl.	CCGATTCCCTCGATGTGGGATAGTAAGAACTGGGATGGAGTTCTTGAGATGTTAACATCA	
GenBank L nucl.	241	300
HR L nucl.	TGTCAAGCCAATCCCATCTCAACATCTCAGATGCATAAATGGATGGGAAGTTGGTTAATG	
M2 L nucl.		
M4 L nucl.	TGTCAAGCCAATCCCATCTCAACATCTCAGATGCATAAATGGATGGGAAGTTGGTTAATG	
GenBank L nucl.	301	360
HR L nucl.	TCTGATAATCATGATGCCAGTCAAGGGTATAGTTTTTTTACATGAAGTGGACAAAGAGGCA	
M2 L nucl.		
M4 L nucl.	TCTGATAATCATGATGCCAGTCAAGGGTATAGTTTTTTTACATGAAGTGGACAAAGAGGCA	
GenBank L nucl.	361	420
HR L nucl.	GAAATAACATTTGACGTGGTGGAGACCTTCATCCGCGGCTGGGGCAACAAACCAATTGAA	
M2 L nucl.		
M4 L nucl.	GAAATAACATTTGACGTGGTGGAGACCTTCATCCGCGGCTGGGGCAACAAACCAATTGAA	
GenBank L nucl.	421	480
HR L nucl.	TACATCAAAAAGGAAAGATGGACTGACTCATTCAAAATTCTCGCTTATTTGTGTCAAAAG	
M2 L nucl.		
M4 L nucl.	TACATCAAAAAGGAAAGATGGACTGACTCATTCAAAATTCTCGCTTATTTGTGTCAAAAG	
GenBank L nucl.	481	540
HR L nucl.	TTTTTGGACTTACACAAGTTGACATTAATCTTAAATGCTGTCTCTGAGGTGGAATTGCTC	
M2 L nucl.		
M4 L nucl.	TTTTTGGACTTACACAAGTTGACATTAATCTTAAATGCTGTCTCTGAGGTGGAATTGCTC	

FIGURE 22-1

GenBank L nucl.	541	600
HR L nucl.	AACTTGGCGAGGACTTTCAAAGGCAAAGTCAGAAGAAGTTCTCATGGAACGAACATATGC	
M2 L nucl.		
M4 L nucl.	AACTTGGCGAGGACTTTCAAAGGCAAAGTCAGAAGAAGTTCTCATGGAACGAACATATGC	
GenBank L nucl.	601	660
HR L nucl.	AGGATTAGGGTTCCCAGCTTGGGTCCTACTTTTATTTTCAGAAGGATGGGCTTACTTCAAG	
M2 L nucl.		
M4 L nucl.	AGGCTTAGGGTTCCCAGCTTGGGTCCTACTTTTATTTTCAGAAGGATGGGCTTACTTCAAG	
GenBank L nucl.	661	720
HR L nucl.	AAACTTGATATTCTAATGGACCGAACTTTCTGTTAATGGTCAAAGATGTGATTATAGGG	
M2 L nucl.		
M4 L nucl.	AAACTTGATATTCTAATGGACCGAACTTTCTGTTAATGGTCAAAGATGTGATTATAGGG	
GenBank L nucl.	721	780
HR L nucl.	AGGATGCAAACGGTGCTATCCATGGTATGTAGAATAGACAACCTGTTCTCAGAGCAAGAC	
M2 L nucl.		
M4 L nucl.	AGGATGCAAACGGTGCTATCCATGGTATGTAGAATAGACAACCTGTTCTCAGAGCAAGAC	
GenBank L nucl.	781	840
HR L nucl.	ATCTTCTCCCTTCTAAATATCTACAGAATTGGAGATAAAATTGTGGAGAGGCAGGGAAAT	
M2 L nucl.		
M4 L nucl.	ATCTTCTCCCTTCTAAATATCTACAGAATTGGAGATAAAATTGTGGAGAGGCAGGGAAAT	
GenBank L nucl.	841	900
HR L nucl.	TTTTCTTATGACTTGATTAAAATGGTGGAACCGATATGCAACTTGAGCTGATGAAATTA	
M2 L nucl.		
M4 L nucl.	TTTTCTTATGACTTGATTAAAATGGTGGAACCGATATGCAACTTGAGCTGATGAAATTA	
GenBank L nucl.	901	960
HR L nucl.	GCAAGAGAATCAAGGCCTTTAGTCCCACAATTCCCTCATTTTGAAAATCATATCAAGACT	
M2 L nucl.		
M4 L nucl.	GCAAGAGAATCAAGGCCTTTAGTCCCACAATTCCCTCATTTTGAAAATCATATCAAGACT	
GenBank L nucl.	961	1020
HR L nucl.	TCTGTTGATGAAGGGGCAAAAATTGACCGAGGTATAAGATTCCTCCATGATCAGATAATG	
M2 L nucl.		
M4 L nucl.	TCTGTTGATGAAGGGGCAAAAATTGACCGAGGTATAAGATTCCTCCATGATCAGATAATG	

FIGURE 22-2

GenBank L nucl.	1021	1080
HR L nucl.	AGTGTGAAAACAGTGGATCTCACACTGGTGATTTATGGATCGTTCAGACATTGGGGGTCAT	
M2 L nucl.	CATTGGGGGTCAT	
M4 L nucl.	AGTGTGAAAACAGTGGATCTCACACTGGTGATTTATGGATCGTTCAGACATTGGGGGTCAT	
GenBank L nucl.	1081	1140
HR L nucl.	CCTTTTATAGATTATTACACTGGACTAGAAAAATTACATTCCCAAGTAACCATGAAGAAA	
M2 L nucl.	CCTTTTATAGATTATTACGCTGGCTAGAAAAATTACATTCCCAAGTACCATGAAGAAA	
M4 L nucl.	CCTTTTATAGATTATTACGCTGGACTAGAAAAATTACATTCCCAAGTAACCATGAAGAAA	
GenBank L nucl.	1141	1200
HR L nucl.	GATATTGATGTGTCATATGCAAAAGCACTTGCAAGTGATTTAGCTCGGATTGTTCTATTT	
M2 L nucl.	GATATTGATGTGTCATATGCRAAAAGCACTTGCAAGTGATTTAGCTCGGATTGTTCTATTT	
M4 L nucl.	GATATTGATGTGTCATATGCAAAAGCACTTGCAAGTGATTTAGCTCGGATTGTTCTATTT	
GenBank L nucl.	1201	1260
HR L nucl.	CAACAGTTCAATGATCATAAAAAGTGGTTCGTGAATGGAGACTTGCTCCCTCATGATCAT	
M2 L nucl.	CAACAGTTCAATGATCATAAAAAGTGGTTCGTGAATGGAGACTTGCTCCCTCATGATCAT	
M4 L nucl.	CAACAGTTCAATGATCATAAAAAGTGGTTCGTGAATGGAGACTTGCTCCCTCATGATCAT	
GenBank L nucl.	1261	1320
HR L nucl.	CCCTTTAAAAGTCATGTTAAAGAAAATACATGGCCACAGCTGCTCAAGTTCAAGATTTT	
M2 L nucl.	CCCTTTAAAAGTCATGTTAAAGAAAATACATGGCCACAGCTGCTCAAGTTCAAGATTTT	
M4 L nucl.	CCCTTTAAAAGTCATGTTAAAGAAAATACATGGCCACAGCTGCTCAAGTTCAAGATTTT	
GenBank L nucl.	1321	1380
HR L nucl.	GGAGATAAATGGCATGAACTTCCGCTGATTAAATGTTTTGAAATACCCGACTTACTAGAC	
M2 L nucl.	GGAGATAAATGGCATGAACTTCCGCTGATTAAATGTTTTGAAATACCCGACTTACTAGAC	
M4 L nucl.	GGAGATAAATGGCATGAACTTCCGCTGATTAAATGTTTTGAAATACCCGACTTACTAGAC	
GenBank L nucl.	1381	1440
HR L nucl.	CCATCGATAATATACTCTGACAAAAGTCATTCAATGAATAGGTCAGAGGTGTTGAAACAT	
M2 L nucl.	CCATCGATAATATACTCTGACAAAAGTCATTCAATGAATAGGTCAGAGGTGTTGAAACAT	
M4 L nucl.	CCATCGATAATATACTCTGACAAAAGTCATTCAATGAATAGGTCAGAGGTGTTGAAACAT	
GenBank L nucl.	1441	1500
HR L nucl.	GTCCGAATGAATCCGAACACTCCTATCCCTAGTAAAAAGGTGTTGCAGACTATGTTGGAC	
M2 L nucl.	GTCCGAATGAATCCGAACACTCCTATCCCTAGTAAAAAGGTGTTGCAGACTATGTTGGAC	
M4 L nucl.	GTCCGAATGAATCCGAACACTCCTATCCCTAGTAAAAAGGTGTTGCAGACTATGTTGGAC	

FIGURE 22-3

GenBank L nucl.	1501	1560
HR L nucl.	ACAAAGGCTACCAATTGGAAAGAATTTCTTAAAGAGATTGATGAGAAGGGCTTAGATGAT	
M2 L nucl.	ACAAAGGCTACCAATTGGAAAGAATTTCTTAAAGAGATTGATGAGAAGGGCTTAGATGAT	
M4 L nucl.		
	ACAAAGGCTACCAATTGGAAAGAATTTCTTAAAGAGATTGATGAGAAGGGCTTAGATGAT	
GenBank L nucl.	1561	1620
HR L nucl.	GATGATCTAATTATTGGTCTTAAAGGAAAGGAGAGGGAACTGAAGTTGGCAGGTAGATTT	
M2 L nucl.	GATGATCTAATTATTGGTCTTAAAGGAAAGGAGAGGGAACTGAAGTTGGCAGGTAGATTT	
M4 L nucl.		
	GATGATCTAATTATTGGTCTTAAAGGAAAGGAGAGGGAACTGAAGTTGGCAGGTAGATTT	
GenBank L nucl.	1621	1680
HR L nucl.	TTCTCCCTAATGTCTTGGAAATTGCGAGAATACTTTGTAATTACCGAATATTTGATAAAG	
M2 L nucl.	TTCTCCCTAATGTCTTGGAAATTGCGAGAATACTTTGTAATTACCGAATATTTGATAAAG	
M4 L nucl.		
	TTCTCCCTAATGTCTTGGAAATTGCGAGAATACTTTGTAATTACCGAATATTTGATAAAG	
GenBank L nucl.	1681	1740
HR L nucl.	ACTCATTTTCGTCCCTATGTTTAAAGGCCTGACAATGGCGGACGATCTAACTGCAGTCATT	
M2 L nucl.	ACTCATTTTCGTCCCTATGTTTAAAGGCCTGACAATGGCGGACGATCTAACTGCAGTCATT	
M4 L nucl.		
	ACTCATTTTCGTCCCTATGTTTAAAGGCCTGACAATGGCGGACGATCTAACTGCAGTCATT	
GenBank L nucl.	1741	1800
HR L nucl.	AAAAAGATGTTAGATTCCTCATCCGGCCAAGGATTGAAGTCATATGAGGCAATTTGCATA	
M2 L nucl.	AAAAAGATGTTAGATTCCTCATCCGGCCAAGGATTGAAGTCATATGAGGCAATTTGCATA	
M4 L nucl.		
	AAAAAGATGTTAGATTCCTCATCCGGCCAAGGATTGAAGTCATATGAGGCAATTTGCATA	
GenBank L nucl.	1801	1860
HR L nucl.	GCCAATCACATTGATTACGAAAAATGGAATAACCACCAAAGGAAGTTATCAAACGGCCCA	
M2 L nucl.	GCCAATCACATTGATTACGAAAAATGGAATAACCACCAAAGGAAGTTATCAAACGGCCCA	
M4 L nucl.		
	GCCAATCACATTGATTACGAAAAATGGAATAACCACCAAAGGAAGTTATCAAACGGCCCA	
GenBank L nucl.	1861	1920
HR L nucl.	GTGTTCCGAGTTATGGGCCAGTTCTTAGGTTATCCATCCTTAATCGAGAGAACTCATGAA	
M2 L nucl.	GTGTTCCGAGTTATGGGCCAGTTCTTAGGTTATCCATCCTTAATCGAGAGAACTCATGAA	
M4 L nucl.		
	GTGTTCCGAGTTATGGGCCAGTTCTTAGGTTATCCATCCTTAATCGAGAGAACTCATGAA	
GenBank L nucl.	1921	1980
HR L nucl.	TTTTTTGAGAAAAGTCTTATATACTACAATGGAAGACCAGACTTGATGCGTGTTTCAAC	
M2 L nucl.	TTTTTTGAGAAAAGTCTTATATACTACAATGGAAGACCAGACTTGATGCGTGTTTCAAC	
M4 L nucl.		
	TTTTTTGAGAAAAGTCTTATATACTACAATGGAAGACCAGACTTGATGCGTGTTTCAAC	
GenBank L nucl.	1981	2040
HR L nucl.	AACACACTGATCAATTCAACCTCCCAACGAGTTTGTGTTGGCAAGGACAAGAGGGTGGACTG	
M2 L nucl.	AACACACTGATCAATTCAACCTCCCAACGAGTTTGTGTTGGCAAGGACAAGAGGGTGGACTG	
M4 L nucl.		
	AACACACTGATCAATTCAACCTCCCAACGAGTTTGTGTTGGCAAGGACAAGAGGGTGGACTG	

FIGURE 22-4

GenBank L nucl.	2041	2100
HR L nucl.	GAAGGTCTACGGCAAAAAGGATGGAGCTATCCTCAATCTACTGGTTATTCAAAGAGAGGCT	
M2 L nucl.	GAAGGTCTACGGCAAAAAGGATGGAGTATCCTCAATCTACTGGTTATTCAAAGAGAGGCT	
M4 L nucl.		
	GAAGGTCTACGGCAAAAAGGATGGAGTATCCTCAATCTACTGGTTATTCAAAGAGAGGCT	
GenBank L nucl.	2101	2160
HR L nucl.	AAAATCAGAAACACTGCTGTCAAAGTCTTGGCACAAGGTGATAATCAAGTTATTTGCACA	
M2 L nucl.	AAAATCAGAAACACTGCTGTCAAAGTCTTGGCACAAGGTGATAATCAAGTTATTTGCACA	
M4 L nucl.		
	AAAATCAGAAACACTGCTGTCAAAGTCTTGGCACAAGGTGATAATCAAGTTATTTGCACA	
GenBank L nucl.	2161	2220
HR L nucl.	CAGTATAAAACGAAGAAATCGAGAAACGTTGTAGAATTACAGGGTGCTCTCAATCAAATG	
M2 L nucl.	CAGTATAAAACGAAGAAATCGAGAAACGTTGTAGAATTACAGGGTGCTCTCAATCAAATG	
M4 L nucl.		
	CAGTATAAAACGAAGAAATCGAGAAACGTTGTAGAATTACAGGGTGCTCTCAATCAAATG	
GenBank L nucl.	2221	2280
HR L nucl.	GTTTCTAATAATGAGAAAATTATGACTGCAATCAAAATAGGGACAGGGAAGTTAGGACTT	
M2 L nucl.	GTTTCTAATAATGAGAAAATTATGACTGCAATCAAAATAGGGACAGGGAAGTTAGGACTT	
M4 L nucl.		
	GTTTCTAATAATGAGAAAATTATGACTGCAATCAAAATAGGGACAGGGAAGTTAGGACTT	
GenBank L nucl.	2281	2340
HR L nucl.	TTGATAAATGACGATGAGACTATGCAATCTGCAGATTACTTGAATTATGGAAAAATACCG	
M2 L nucl.	TTGATAAATGACGATGAGACTATGCAATCTGCAGATTACTTGAATTATGGAAAAATACCG	
M4 L nucl.		
	TTGATAAATGACGATGAGACTATGCAATCTGCAGATTACTTGAATTATGGAAAAATACCA	
GenBank L nucl.	2341	2400
HR L nucl.	ATTTTCCGTGGAGTGATTAGAGGGTTAGAGACCAAGAGATGGTCACGAGTGACTTGTGTC	
M2 L nucl.	ATTTTCCGTGGAGTGATTAGAGGGTTAGAGACCAAGAGATGGTCACGAGTGACTTGTGTC	
M4 L nucl.		
	ATTTTCCGTGGAGTGATTAGAGGGTTAGAGACCAAGAGATGGTCACGAGTGACTTGTGTC	
GenBank L nucl.	2401	2460
HR L nucl.	ACCAATGACCAAATACCCACTTGTGCTAATATAATGAGCTCAGTTTCCACAAATGCTCTC	
M2 L nucl.	ACCAATGACCAAATACCCACTTGTGCTAATATAATGAGCTCAGTTTCCACAAATGCTCTC	
M4 L nucl.		
	ACCAATGACCAAATACCCACTTGTGCTAATATAATGAGCTCAGTTTCCACAAATGCTCTC	
GenBank L nucl.	2461	2520
HR L nucl.	ACCGTAGCTCATTTTGCTGAGAACCCAATCAATGCCATGATACAGTACAATTATTTTGGG	
M2 L nucl.	ACCGTAGCTCATTTTGCTGAGAACCCAATCAATGCCATGATACAGTACAATTATTTTGGG	
M4 L nucl.		
	ACCGTAGCTCATTTTGCTGAGAACCCAATCAATGCCATGATACAGTACAATTATTTTGGG	
GenBank L nucl.	2521	2580
HR L nucl.	ACATTTGCTAGACTCTTGTTGATGATGCATGATCCTGCTCTTCGTCAATCATTTGTATGAA	
M2 L nucl.	ACATTTGCTAGACTCTTGTTGATGATGCATGATCCTGCTCTTCGTCAATCATTTGTATGAA	
M4 L nucl.		
	ACATTTGCTAGACTCTTGTTGATGATGCATGATCCTGCTCTTCGTCAATCATTTGTATGAA	

FIGURE 22-5

GenBank L nucl.	2581	2640
HR L nucl.	GTTCAAGATAAGATAACCGGGCTTGACACAGTTCTACTTTCAAATACGCCATGTTGTATTTG	
M2 L nucl.	GTTCAAGATAAGATAACCGGGCTTGACACAGTTCTACTTTCAAATACGCCATGTTGTATTTG	
M4 L nucl.		
	GTTCAAGATAAGATAACCGGGCTTGACACAGTTCTACTTTCAAATACGCCATGTTGTATTTG	
GenBank L nucl.	2641	2700
HR L nucl.	GACCCTTCCATTGGAGGAGTGTCTGGGCATGTCTTTGTCCAGGTTTTTGATTAGAGCCTTC	
M2 L nucl.	GACCCTTCCATTGGAGGAGTGTCTGGGCATGTCTTTGTCCAGGTTTTTGATTAGAGCCTTC	
M4 L nucl.		
	GACCCTTCCATTGGAGGAGTGTCTGGGCATGTCTTTGTCCAGGTTTTTGATTAGAGCCTTC	
GenBank L nucl.	2701	2760
HR L nucl.	CCAGATCCCGTAACAGAAAGTCTCTCATTTCTGGAGATTCATCCATGTACATGCTCGAAGT	
M2 L nucl.	CCAGATCCCGTAACAGAAAGTCTCTCATTTCTGGAGATTCATCCATGTACATGCTCGAAGT	
M4 L nucl.		
	CCAGATCCCGTAACAGAAAGTCTCTCATTTCTGGAGATTCATCCATGTACATGCTCGAAGT	
GenBank L nucl.	2761	2820
HR L nucl.	GAGCATCTGAAGGAGATGAGTGCAGTATTTGGAAACCCCGAGATAGCCAAGTTTCGAATA	
M2 L nucl.	GAGCATCTGAAGGAGATGAGTGCAGTATTTGGAAACCCCGAGATAGCCAAGTTTCGAATA	
M4 L nucl.		
	GAGCATCTGAAGGAGATGAGTGCAGTATTTGGAAACCCCGAGATAGCCAAGTTTCGAATA	
GenBank L nucl.	2821	2880
HR L nucl.	ACTCACATAGACAAGCTAGTAGAAGATCCAACCTCTCTGAACATCGCTATGGGAATGAGT	
M2 L nucl.	ACTCACATAGACAAGCTAGTAGAAGATCCAACCTCTCTGAACATCGCTATGGGAATGAGT	
M4 L nucl.		
	ACTCACATAGACAAGCTAGTAGAAGATCCAACCTCTCTGAACATCGCTATGGGAATGAGT	
GenBank L nucl.	2881	2940
HR L nucl.	CCAGCGAACTTGTTAAAGACTGAGGTAAAAAATGCTTAATCGAATCAAGACAAACCATC	
M2 L nucl.	CCAGCGAACTTGTTAAAGACTGAGGTAAAAAATGCTTAATCGAATCAAGACAAACCATC	
M4 L nucl.		
	CCAGCGAACTTGTTAAAGACTGAGGTAAAAAATGCTTAATCGAATCAAGACAAACCATC	
GenBank L nucl.	2941	3000
HR L nucl.	AGGAACCAGGTGATTAAGGATGCAACCATATATTTGTATCATGAAGAGGATCGGCTCAGA	
M2 L nucl.	AGGAACCAGGTGATTAAGGATGCAACCATATATTTGTATCATGAAGAGGATCGGCTCAGA	
M4 L nucl.		
	AGGAACCAGGTGATTAAGGATGCAACCATATATTTGTATCATGAAGAGGATCGGCTCAGA	
GenBank L nucl.	3001	3060
HR L nucl.	AGTTTCTTATGGTCAATAAATCCTCTGTTCCCTAGATTTTTTAAGTGAATTCAAATCAGGC	
M2 L nucl.	AGTTTCTTATGGTCAATAAATCCTCTGTTCCCTAGATTTTTTAAGTGAATTCAAATCAGGC	
M4 L nucl.		
	AGTTTCTTATGGTCAATAAATCCTCTGTTCCCTAGATTTTTTAAGTGAATTCAAATCAGGC	
GenBank L nucl.	3061	3120
HR L nucl.	ACTTTTTTGGGAGTCGCAGACGGGCTCATCAGTCTATTTCAAATTTCTCGTACTATTTCGG	
M2 L nucl.	ACTTTTTTGGGAGTCGCAGACGGGCTCATCAGTCTATTTCAAATTTCTCGTACTATTTCGG	
M4 L nucl.		
	ACTTTTTTGGGAGTCGCAGACGGGCTCATCAGTCTATTTCAAATTTCTCGTACTATTTCGG	

FIGURE 22-6

GenBank L nucl.	3121	3180
HR L nucl.	AACTCCTTTAAGAAAAAGTATCATAGGGAATTGGATGATTTGATTGTGAGGAGTGAGGTA	
M2 L nucl.	AACTCCTTTAAGAAAAAGTATCATAGGGAATTGGATGATTTGATTGTGAGGAGTGAGGTA	
M4 L nucl.		
	AACTCCTTTAAGAAAAAGTATCATAGGGAATTGGATGATTTGATTGTGAGGAGTGAGGTA	
GenBank L nucl.	3181	3240
HR L nucl.	TCCTCTTTGACACATTTAGGGAACTTCATTTGAGAAGGGGATCATGTAAAATGTGGACA	
M2 L nucl.	TCCTCTTTGACACATTTAGGGAACTTCATTTGAGAAGGGGATCATGTAAAATGTGGACA	
M4 L nucl.		
	TCCTCTTTGACACATTTAGGGAACTTCATTTGAGAAGGGGATCATGTAAAATGTGGACA	
GenBank L nucl.	3241	3300
HR L nucl.	TGTTTCAGCTACTCATGCTGACACATTAAGATACAAATCCTGGGGCCGTACAGTTATTGGG	
M2 L nucl.	TGTTTCAGCTACTCATGCTGACACATTAAGATACAAATCCTGGGGCCGTACAGTTATTGGG	
M4 L nucl.		
	TGTTTCAGCTACTCATGCTGACACATTAAGATACAAATCCTGGGGCCGTACAGTTATTGGG	
GenBank L nucl.	3301	3360
HR L nucl.	ACAACGTACCCCATCCATTAGAAATGTTGGGTCCACAACATCGAAAAGAGACTCCTTGT	
M2 L nucl.	ACAACGTACCCCATCCATTAGAAATGTTGGGTCCACAACATCGAAAAGAGACTCCTTGT	
M4 L nucl.		
	ACAACGTACCCCATCCATTAGAAATGTTGGGTCCACAACATCGAAAAGAGACTCCTTGT	
GenBank L nucl.	3361	3420
HR L nucl.	GCACCATGTAACACATCAGGGTTCAATTATGTTTCTGTGCATTGTCCAGACGGGATCCAT	
M2 L nucl.	GCACCATGTAACACATCAGGGTTCAATTATGTTTCTGTGCATTGTCCAGACGGGATCCAT	
M4 L nucl.		
	GCACCATGTAACACATCAGGGTTCAATTATGTTTCTGTGCATTGTCCAGACGGGATCCAT	
GenBank L nucl.	3421	3480
HR L nucl.	GACGTCTTTAGTTCACGGGGACCATTGCCTGCTTATCTAGGGTCTAAAACATCTGAATCT	
M2 L nucl.	GACGTCTTTAGTTCACGGGGACCATTGCCTGCTTATCTAGGGTCTAAAACATCTGAATCT	
M4 L nucl.		
	GACGTCTTTAGTTCACGGGGACCATTGCCTGCTTATCTAGGGTCTAAAACATCTGAATCT	
GenBank L nucl.	3481	3540
HR L nucl.	ACATCTATTTTGCAGCCTTGGGAAAGGGAAAGCAAAGTCCCACTGATTAAAAGAGCTACA	
M2 L nucl.	ACATCTATTTTGCAGCCTTGGGAAAGGGAAAGCAAAGTCCCACTGATTAAAAGAGCTACA	
M4 L nucl.		
	ACATCTATTTTGCAGCCTTGGGAAAGGGAAAGCAAAGTCCCACTGATTAAAAGAGCTACA	
GenBank L nucl.	3541	3600
HR L nucl.	CGTCTTAGAGATGCTATCTCTTGGTTTGTTGAACCCGACTCTAAACTAGCAATGACTATA	
M2 L nucl.	CGTCTTAGAGATGCTATCTCTTGGTTTGTTGAACCCGACTCTAAACTAGCAATGACTATA	
M4 L nucl.		
	CGTCTTAGAGATGCTATCTCTTGGTTTGTTGAACCCGACTCTAAACTAGCAATGACTATA	
GenBank L nucl.	3601	3660
HR L nucl.	CTTTCTAACATCCACTCTTTAACAGGCGAAGAATGGACCAAAGGCAGCATGGGTTCAAA	
M2 L nucl.	CTTTCTAACATCCACTCTTTAACAGGCGAAGAATGGACCAAAGGCAGCATGGGTTCAAA	
M4 L nucl.		
	CTTTCTAACATCCACTCTTTAACAGGCGAAGAATGGACCAAAGGCAGCATGGGTTCAAA	

FIGURE 22-7

GenBank L nucl.	3661	3720
HR L nucl.	AGAACAGGGTCTGCCCTTCATAGGTTTTTCGACATCTCGGATGAGCCATGGTGGGTTCGCA	
M2 L nucl.	AGAACAGGGTCTGCCCTTCATAGGTTTTTCGACATCTCGGATGAGCCATGGTGGGTTCGCA	
M4 L nucl.	AGAACAGGGTCTGCCCTTCATAGGTTTTTCGACATCTCGGATGAGCCATGGTGGGTTCGCA	
GenBank L nucl.	3721	3780
HR L nucl.	TCTCAGAGCACTGCAGCATTGACCAGGTTGATGGCAACTACAGACACCATGAGGGATCTG	
M2 L nucl.	TCTCAGAGCACTGCAGCATTGACCAGGTTGATGGCAACTACAGACACCATGAGGGATCTG	
M4 L nucl.	TCTCAGAGCACTGCAGCATTGACCAGGTTGATGGCAACTACAGACACCATGAGGGATCTG	
GenBank L nucl.	3781	3840
HR L nucl.	GGAGATCAGAATTTTCGACTTTTTATTCCAAGCAACGTTGCTCTATGCTCAATTACCACC	
M2 L nucl.	GGAGATCAGAATTTTCGACTTTTTATTCCAAGCAACGTTGCTCTATGCTCAATTACCACC	
M4 L nucl.	GGAGATCAGAATTTTCGACTTTTTATTCCAAGCAACGTTGCTCTATGCTCAATTACCACC	
GenBank L nucl.	3841	3900
HR L nucl.	ACTGTTGCAAGAGACGGATGGATCACCAGTTGTACAGATCATTATCATATTGCCTGTAAG	
M2 L nucl.	ACTGTTGCAAGAGACGGATGGATCACCAGTTGTACAGATCATTATCATATTGCCTGTAAG	
M4 L nucl.	ACTGTTGCAAGAGACGGATGGATCACCAGTTGTACAGATCATTATCATATTGCCTGTAAG	
GenBank L nucl.	3901	3960
HR L nucl.	TCCTGTTTGAGACCCATAGAAGAGATCACCTGGACTCAAGTATGGACTACACGCCCCCA	
M2 L nucl.	TCCTGTTTGAGACCCATAGAAGAGATCACCTGGACTCAAGTATGGACTACACGCCCCCA	
M4 L nucl.	TCCTGTTTGAGACCCATAGAAGAGATCACCTGGACTCAAGTATGGACTACACGCCCCCA	
GenBank L nucl.	3961	4020
HR L nucl.	GATGTATCCCATGTGCTGAAGACATGGAGGAATGGGGAAGGTTTCGTGGGGACAAGAGATA	
M2 L nucl.	GATGTATCCCATGTGCTGAAGACATGGAGGAATGGGGAAGGTTTCGTGGGGACAAGAGATA	
M4 L nucl.	GATGTATCCCATGTGCTGAAGACATGGAGGAATGGGGAAGGTTTCGTGGGGACAAGAGATA	
GenBank L nucl.	4021	4080
HR L nucl.	AAACAGATCTATCCTTTAGAGGGAATTGGAAGAATTTAGCACCTGCTGAGCAATCCTAT	
M2 L nucl.	AAACAGATCTATCCTTTAGAGGGAATTGGAAGAATTTAGCACCTGCTGAGCAATCCTAT	
M4 L nucl.	AAACAGATCTATCCTTTAGAGGGAATTGGAAGAATTTAGCACCTGCTGAGCAATCCTAT	
GenBank L nucl.	4081	4140
HR L nucl.	CAAGTCGGCAGATGTATAGGTTTTCTATATGGAGACTTGGCGTATAGAAAATCTACTCAT	
M2 L nucl.	CAAGTCGGCAGATGTATAGGTTTTCTATATGGAGACTTGGCGTATAGAAAATCTACTCAT	
M4 L nucl.	CAAGTCGGCAGATGTATAGGTTTTCTATATGGAGACTTGGCGTATAGAAAATCTACTCAT	
GenBank L nucl.	4141	4200
HR L nucl.	GCCGAGGACAGTTCTCTATTTTCCTCTATCTATAACAAGGTCGTATTAGAGGTCGAGGTTTC	
M2 L nucl.	GCCGAGGACAGTTCTCTATTTTCCTCTATCTATAACAAGGTCGTATTAGAGGTCGAGGTTTC	
M4 L nucl.	GCCGAGGACAGTTCTCTATTTTCCTCTATCTATAACAAGGTCGTATTAGAGGTCGAGGTTTC	

FIGURE 22-8

	4201	4260
GenBank L nucl.	TTAAAAGGGTTGCTAGACGGATTAATGAGAGCAAGTTGCTGCCAAGTAATACACCGGAGA	
HR L nucl.	TTAAAAGGGTTGCTAGACGGATTAATGAGAGCAAGTTGCTGCCAAGTAATACACCGGAGA	
M2 L nucl.		
M4 L nucl.	TTAAAAGGGTTGCTAGACGGATTAATGAGAGCAAGTTGCTGCCAAGTAATACACCGGAGA	
	4261	4320
GenBank L nucl.	AGTCTGGCTCATTTGAAGAGGCCGGCCAACGCAGTGTACGGAGGTTTGATTTACTTGATT	
HR L nucl.	AGTCTGGCTCATTTGAAGAGGCCGGCCAACGCAGTGTACGGAGGTTTGATTTACTTGATT	
M2 L nucl.		
M4 L nucl.	AGTCTGGCTCATTTGAAGAGGCCGGCCAACGCAGTGTACGGAGGTTTGATTTACTTGATT	
	4321	4380
GenBank L nucl.	GATAAATTGAGTGTATCACCTCCATTCCTTTCTCTTACTAGATCAGGACCTATTAGAGAC	
HR L nucl.	GATAAATTGAGTGTATCACCTCCATTCCTTTCTCTTACTAGATCAGGACCTATTAGAGAC	
M2 L nucl.		
M4 L nucl.	GATAAATTGAGTGTATCACCTCCATTCCTTTCTCTTACTAGATCAGGACCTATTAGAGAC	
	4381	4440
GenBank L nucl.	GAATTAGAAACGATTCCCCACAAGATCCCAACCTCCTATCCGACAAGCAACCGTGATATG	
HR L nucl.	GAATTAGAAACGATTCCCCACAAGATCCCAACCTCCTATCCGACAAGCAACCGTGATATG	
M2 L nucl.		
M4 L nucl.	GAATTAGAAACGATTCCCCACAAGATCCCAACCTCCTATCCGACAAGCAACCGTGATATG	
	4441	4500
GenBank L nucl.	GGGGTGATTGTCAGAAATTACTTCAAATACCAATGCCGTCTAATTGAAAAGGGAAAATAC	
HR L nucl.	GGGGTGATTGTCAGAAATTACTTCAAATACCAATGCCGTCTAATTGAAAAGGGAAAATAC	
M2 L nucl.		
M4 L nucl.	GGGGTGATTGTCAGAAATTACTTCAAATACCAATGCCGTCTAATTGAAAAGGGAAAATAC	
	4501	4560
GenBank L nucl.	AGATCACATTATTCACAATTATGGTTATTCTCAGATGTCTTATCCATAGACTTCATTGGA	
HR L nucl.	AGATCACATTATTCACAATTATGGTTATTCTCAGATGTCTTATCCATAGACTTCATTGGA	
M2 L nucl.		
M4 L nucl.	AGATCACATTATTCACAATTATGGTTATTCTCAGATGTCTTATCCATAGACTTCATTGGA	
	4561	4620
GenBank L nucl.	CCATTCTCTATTTCCACCACCCTCTTGCAAATCCTATACAAGCCATTTTATCTGGGAAA	
HR L nucl.	CCATTCTCTATTTCCACCACCCTCTTGCAAATCCTATACAAGCCATTTTATCTGGGAAA	
M2 L nucl.		
M4 L nucl.	CCATTCTCTATTTCCACCACCCTCTTGCAAATCCTATACAAGCCATTTTATCTGGGAAA	
	4621	4680
GenBank L nucl.	GATAAGAATGAGTTGAGAGAGCTGGCAAATCTTTCTTCATTGCTAAGATCAGGAGAGGGG	
HR L nucl.	GATAAGAATGAGTTGAGAGAGCTGGCAAATCTTTCTTCATTGCTAAGATCAGGAGAGGGG	
M2 L nucl.		
M4 L nucl.	GATAAGAATGAGTTGAGAGAGCTGGCAAATCTTTCTTCATTGCTAAGATCAGGAGAGGGG	
	4681	4740
GenBank L nucl.	TGGGAAGACATACATGTGAAATTCTTCACCAAGGACATATTATTGTGTCCAGAGGAAATC	
HR L nucl.	TGGGAAGACATACATGTGAAATTCTTCACCAAGGACATATTATTGTGTCCAGAGGAAATC	
M2 L nucl.		
M4 L nucl.	TGGGAAGACATACATGTGAAATTCTTCACCAAGGACATATTATTGTGTCCAGAGGAAATC	

FIGURE 22-9

	4741	4800
GenBank L nucl.	AGACATGCTTGCAAGTTCGGGATTGCTAAGGATAATAATAAAGACATGAGCTATCCCCCT	
HR L nucl.	AGACATGCTTGCAAGTTCGGGATTGCTAAGGATAATAATAAAGACATGAGCTATCCCCCT	
M2 L nucl.		
M4 L nucl.	AGACATGCTTGCAAGTTCGGGATTGCTAAGGATAATAATAAAGACATGAGCTATCCCCCT	
	4801	4860
GenBank L nucl.	TGGGGAAGGGAATCCAGAGGGACAATTACAACAATCCCTGTTTATTATACGACCACCCCT	
HR L nucl.	TGGGGAAGGGAATCCAGAGGGACAATTACAACAATCCCTGTTTATTATACGACCACCCCT	
M2 L nucl.		
M4 L nucl.	TGGGGAAGGGAATCCAGAGGGACAATTACAACAATCCCTGTTTATTATACGACCACCCCT	
	4861	4920
GenBank L nucl.	TACCCAAAGATGCTAGAGATGCCTCCAAGAATCCAAAATCCCCTGCTGTCCGGAATCAGG	
HR L nucl.	TACCCAAAGATGCTAGAGATGCCTCCAAGAATCCAAAATCCCCTGCTGTCCGGAATCAGG	
M2 L nucl.		
M4 L nucl.	TACCCAAAGATGCTAGAGATGCCTCCAAGAATCCAAAATCCCCTGCTGTCCGGAATCAGG	
	4921	4980
GenBank L nucl.	TTGGGCCAATTACCAACTGGCGCTCATTATAAAATTCGGAGTATATTACATGGAATGGGA	
HR L nucl.	TTGGGCCAGTTACCAACTGGCGCTCATTATAAAATTCGGAGTATATTACATGGAATGGGA	
M2 L nucl.		
M4 L nucl.	TTGGGCCAGTTACCAACTGGCGCTCATTATAAAATTCGGAGTATATTACATGGAATGGGA	
	4981	5040
GenBank L nucl.	ATCCATTACAGGGACTTCTTGAGTTGTGGAGACGGCTCCGGAGGGATGACTGCTGCATTA	
HR L nucl.	ATCCATTACAGGGACTTCTTGAGTTGTGGAGACGGCTCCGGAGGGATGACTGCTGCATTA	
M2 L nucl.		
M4 L nucl.	ATCCATTACAGGGACTTCTTGAGTTGTGGAGACGGCTCCGGAGGGATGACTGCTGCATTA	
	5041	5100
GenBank L nucl.	CTACGAGAAAATGTGCATAGCAGAGGAATATTCAATAGTCTGTTAGAATTATCAGGGTCA	
HR L nucl.	CTACGAGAAAATGTGCATAGCAGAGGAATATTCAATAGTCTGTTAGAATTATCAGGGTCA	
M2 L nucl.		
M4 L nucl.	CTACGAGAAAATGTGCATAGCAGAGGAATATTCAATAGTCTGTTAGAATTATCAGGGTCA	
	5101	5160
GenBank L nucl.	GTCATGCGAGGCGCCTCTCCTGAGCCCCCAGTGCCCTAGAACTTTAGGAGGAGATAAA	
HR L nucl.	GTCATGCGAGGCGCCTCTCCTGAGCCCCCAGTGCCCTAGAACTTTAGGAGGAGATAAA	
M2 L nucl.		
M4 L nucl.	GTCATGCGAGGCGCCTCTCCTGAGCCCCCAGTGCCCTAGAACTTTAGGAGGAGATAAA	
	5161	5220
GenBank L nucl.	TCGAGATGTGTAAATGGTGAAACATGTTGGGAATATCCATCTGACTTATGTGACCCAAGG	
HR L nucl.	TCGAGATGTGTAAATGGTGAAACATGTTGGGAATATCCATCTGACTTATGTGACCCAAGG	
M2 L nucl.		
M4 L nucl.	TCGAGATGTGTAAATGGTGAAACATGTTGGGAATATCCATCTGACTTATGTGACCCAAGG	
	5221	5280
GenBank L nucl.	ACTTGGGACTATTTCCCTCCGACTCAAAGCAGGCTTGGGGCTTCAAATTGATTTAATTGTA	
HR L nucl.	ACTTGGGACTATTTCCCTCCGACTCAAAGCAGGCTTGGGGCTTCAAATTGATTTAATTGTA	
M2 L nucl.		
M4 L nucl.	ACTTGGGACTATTTCCCTCCGACTCAAAGCAGGCTTGGGGCTTCAAATTGATTTAATTGTA	

FIGURE 22-10

GenBank L nucl.	5281	5340
HR L nucl.	ATGGATATGGAAGTTCGGGATTCTTCTACTAGCCTGAAAATTGAGACGAATGTTAGAAAT	
M2 L nucl.	ATGGATATGGAAGTTCGGGATTCTTCTACTAGCCTGAAAATTGAGACGAATGTTAGAAAT	
M4 L nucl.		
	ATGGATATGGAAGTTCGGGATTCTTCTACTAGCCTGAAAATTGAGACGAATGTTAGAAAT	
GenBank L nucl.	5341	5400
HR L nucl.	TATGTGCACCGGATTTTGGATGAGCAAGGAGTTTAAATCTACAAGACTTATGGAACATAT	
M2 L nucl.	TATGTGCACCGGATTTTGGATGAGCAAGGAGTTTAAATCTACAAGACTTATGGAACATAT	
M4 L nucl.		
	TATGTGCACCGGATTTTGGATGAGCAAGGAGTTTAAATCTACAAGACTTATGGAACATAT	
GenBank L nucl.	5401	5460
HR L nucl.	ATTTGTGAGAGCGAAAAGAATGCAGTAACAATCCTTGGTCCCATGTTCAAGACGGTCGAC	
M2 L nucl.	ATTTGTGAGAGCGAAAAGAATGCAGTAACAATCCTTGGTCCCATGTTCAAGACGGTCGAC	
M4 L nucl.		
	ATTTGTGAGAGCGAAAAGAATGCAGTAACAATCCTTGGTCCCATGTTCAAGACGGTCGAC	
GenBank L nucl.	5461	5520
HR L nucl.	TTAGTTCAAACAGAATTTAGTAGTTCTCAAACGTCTGAAGTATATATGGTATGTAAAGGT	
M2 L nucl.	TTAGTTCAAACAGAATTTAGTAGTTCTCAAACGTCTGAAGTATATATGGTATGTAAAGGT	
M4 L nucl.		
	TTAGTTCAAACAGAATTTAGTAGTTCTCAAACGTCTGAAGTATATATGGTATGTAAAGGT	
GenBank L nucl.	5521	5580
HR L nucl.	TTGAAGAAATTAATCGATGAACCCAATCCCGATTGGTCTTCCATCAATGAATCCTGGAAA	
M2 L nucl.	TTGAAGAAATTAATCGATGAACCCAATCCCGATTGGTCTTCCATCAATGAATCCTGGAAA	
M4 L nucl.		
	TTGAAGAAATTAATCGATGAACCCAATCCCGATTGGTCTTCCATCAATGAATCCTGGAAA	
GenBank L nucl.	5581	5640
HR L nucl.	AACCTGTACGCATTCCAGTCATCAGAACAGGAATTTGCCAGAGCAAAGAAGGTTAGTACA	
M2 L nucl.	AACCTGTACGCATTCCAGTCATCAGAACAGGAATTTGCCAGAGCAAAGAAGGTTAGTACA	
M4 L nucl.		
	AACCTGTACGCATTCCAGTCATCAGAACAGGAATTTGCCAGAGCAAAGAAGGTTAGTACA	
GenBank L nucl.	5641	5700
HR L nucl.	TACTTTACCTTGACAGGTATTCCCTCCCAATTCATTCCTGATCCTTTTGTGAACATTGAG	
M2 L nucl.	TACTTTACCTTGACAGGTATTCCCTCCCAATTCATTCCTGATCCTTTTGTGAACATTGAG	
M4 L nucl.		
	TACTTTACCTTGACAGGTATTCCCTCCCAATTCATTCCTGATCCTTTTGTGAACATTGAG	
GenBank L nucl.	5701	5760
HR L nucl.	ACTATGCTACAAATATTCGGAGTACCCACGGGTGTGTCTCATGCGGCTGCCTTAAATCA	
M2 L nucl.	ACTATGCTACAAATATTCGGAGTACCCACGGGTGTGTCTCATGCGGCTGCCTTAAATCA	
M4 L nucl.		
	ACTATGCTACAAATATTCGGAGTACCCACGGGTGTGTCTCATGCGGCTGCCTTAAATCA	
GenBank L nucl.	5761	5820
HR L nucl.	TCTGATAGACCTGCAGATTTATTGACCATTAGCCTTTTTTATATGGCGATTATATCGTAT	
M2 L nucl.	TCTGATAGACCTGCAGATTTATTGACCATTAGCCTTTTTTATATGGCGATTATATCGTAT	
M4 L nucl.		
	TCTGATAGACCTGCAGATTTATTGACCATTAGCCTTTTTTATATGGCGATTATATCGTAT	

FIGURE 22-11

GenBank L nucl.	5821	5880
HR L nucl.	TATAACATCAATCATATCAGAGTAGGACCGATACCTCCGAACCCCCCATCAGATGGAATT	
M2 L nucl.	TATAACATCAATCATATCAGAGTAGGACCGATACCTCCGAACCCCCCATCAGATGGAATT	
M4 L nucl.		
	TATAACATCAATCATATCAGAGTAGGACCGATACCTCCGAACCCCCCATCAGATGGAATT	
GenBank L nucl.	5881	5940
HR L nucl.	GCACAAAATGTGGGGATCGCTATAACTGGTATAAGCTTTTGGCTGAGTTTGATGGAGAAA	
M2 L nucl.	GCACAAAATGTGGGGATCGCTATAACTGGTATAAGCTTTTGGCTGAGTTTGATGGAGAAA	
M4 L nucl.		
	GCACAAAATGTGGGGATCGCTATAACTGGTATAAGCTTTTGGCTGAGTTTGATGGAGAAA	
GenBank L nucl.	5941	6000
HR L nucl.	GACATTCCACTATATCAACAGTGTTTAGCAGTTATCCAGCAATCATTCCCGATTAGGTGG	
M2 L nucl.	GACATTCCACTATATCAACAGTGTTTAGCAGTTATCCAGCAATCATTCCCGATTAGGTGG	
M4 L nucl.		
	GACATTCCACTATATCAACAGTGTTTAGCAGTTATCCAGCAATCATTCCCGATTAGGTGG	
GenBank L nucl.	6001	6060
HR L nucl.	GAGGCTGTTTCAGTAAAAGGAGGATACAAGCAGAAGTGGAGTACTAGAGGTGATGGGCTC	
M2 L nucl.	GAGGCTGTTTCAGTAAAAGGAGGATACAAGCAGAAGTGGAGTACTAGAGGTGATGGGCTC	
M4 L nucl.		
	GAGGCTGTTTCAGTAAAAGGAGGATACAAGCAGAAGTGGAGTACTAGAGGTGATGGGCTC	
GenBank L nucl.	6061	6120
HR L nucl.	CCAAAAGATACCCGAATTCAGACTCCTTGGCCCCAATCGGGAAGTGGATCAGATCTCTG	
M2 L nucl.	CCAAAAGATACCCGAATTCAGACTCCTTGGCCCCAATCGGGAAGTGGATCAGATCTCTG	
M4 L nucl.		
	CCAAAAGATACCCGAATTCAGACTCCTTGGCCCCAATCGGGAAGTGGATCAGATCTCTG	
GenBank L nucl.	6121	6180
HR L nucl.	GAATTGGTCCGAAACCAAGTTCGTCTAAATCCATTCAATGAGATCTTGTTCAATCAGCTA	
M2 L nucl.	GAATTGGTCCGAAACCAAGTTCGTCTAAATCCATTCAATGAGATCTTGTTCAATCAGCTA	
M4 L nucl.		
	GAATTGGTCCGAAACCAAGTTCGTCTAAATCCATTCAATGAGATCTTGTTCAATCAGCTA	
GenBank L nucl.	6181	6240
HR L nucl.	TGTCGTACAGTGGATAATCATTTGAAATGGTCAAATTTGCGAAAGAAACACAGGAATGATT	
M2 L nucl.	TGTCGTACAGTGGATAATCATTTGAAATGGTCAAATTTGCGAAAAAACACAGGAATGATT	
M4 L nucl.		
	TGTCGTACAGTGGATAATCATTTGAAATGGTCAAATTTGCGAAAAAACACAGGAATGATT	
GenBank L nucl.	6241	6300
HR L nucl.	GAATGGATCAATAGACGAATTTCAAAGAAGACCGGTCTATACTGATGTTGAAGAGTGAC	
M2 L nucl.	GAATGGATCAATAGACGAATTTCAAAGAAGACCGGTCTATACTGATGTTGAAGAGTGAC	
M4 L nucl.		
	GAATGGATCAATAGACGAATTTCAAAGAAGACCGGTCTATACTGATGTTGAAGAGTGAC	

FIGURE 22-12

	6301	6360
GenBank L nucl.	CTACA	GGAGGAAA
HR L nucl.	CTACAT	GGAGGAAA
M2 L nucl.		
M4 L nucl.	CTACAT	GGAGGAAA
	6361	6395
GenBank L nucl.		
HR L nucl.	ATGAAAAA	AACTTTGATCCTTAAGACCCTCTTGTG
M2 L nucl.		
M4 L nucl.		

FIGURE 22-13

GenBank L	a.a.	1	60
HR L	a.a.	MEVHDFETDEFNDFNEDDYATREFLNPDERMTYLNHADYNLNSPLISDDIDNLIRKFNSL	
M4 L	a.a.		
		1	60
GenBank L	a.a.	61	120
HR L	a.a.	PIPSMWDSKNWDGVLEMLTSCQANPISTSQMHKWMGSWLMSDNHDASQGYNFLHEVDKEA	
M4 L	a.a.		
		61	120
GenBank L	a.a.	121	180
HR L	a.a.	EITFDVVETFIRGWGNKPIEYIKKERWTDSFKILAYLCQKFLDLHKLTILNAVSEVELL	
M4 L	a.a.		
		121	180
GenBank L	a.a.	181	240
HR L	a.a.	NLARTFKGKVRSSSHGTNICRIRVPSLGPTFISEGWAYFKKLDILMDRNFLLMVKDVIIG	
M4 L	a.a.		
		181	240
GenBank L	a.a.	241	300
HR L	a.a.	RMQTVLSMVCRIDNLFSEQDIFSLNLIYRIGDKIVERQGNFSYDLIKMVEPICNLRLMKL	
M4 L	a.a.		
		241	300
GenBank L	a.a.	301	360
HR L	a.a.	ARESRLVPQFPFHFNHIKTSVDEGAKIDRGIRFLHDQIMSVKTVDLTLVIYGSFRHWGH	
M4 L	a.a.	HWGH	
		301	360
GenBank L	a.a.	361	420
HR L	a.a.	PFIDYYTGLEKLHSQVTMKKDIDVSYAKALASDLARIVLFQQFNDHKKWVFVNGDLLPHDH	
M4_L.pro		PFIDYYAGLEKLHSQVTMKKDIDVSYAKALASDLARIVLFQQFNDHKKWVFVNGDLLPHDH	
		361	420
GenBank L	a.a.	421	480
HR L	a.a.	PFSKSHVKENTWPTAAQVQDFGDKWHELPLIKCFEIPDLLDPSIIYSDKSHSMNRSEVLKH	
M4 L	a.a.	PFSKSHVKENTWPTAAQVQDFGDKWHELPLIKCFEIPDLLDPSIIYSDKSHSMNRSEVLKH	
		421	480
GenBank L	a.a.	481	540
HR L	a.a.	VRMNPNTPIPSKKVLQTMMLDTKATNWKEFLKEIDEKGLDDDDLIIGLKGKERELKLAGRF	
M4 L	a.a.	VRMNPNTPIPSKKVLQTMMLDTKATNWKEFLKEIDEKGLDDDDLIIGLKGKERELKLAGRF	
		481	540
GenBank L	a.a.	541	600
HR L	a.a.	FSLMSWKLREYFVITEYLIKTHFVPMFKGLTMADDLTAVIKKMLDSSSGQGLKSYEAICI	
M4 L	a.a.	FSLMSWKLREYFVITEYLIKTHFVPMFKGLTMADDLTAVIKKMLDSSSGQGLKSYEAICI	
		541	600

FIGURE 23-1

GenBank L	a.a.	601	660
HR L a.a.		ANHIDYEKWNHQRKLSNGPVFRVMGQFLGYPSLIERTHEFFEKSIIYYNGRPDLMRVHN	
M4 L a.a.		ANHIDYEKWNHQRKLSNGPVFRVMGQFLGYPSLIERTHEFFEKSIIYYNGRPDLMRVHN	
GenBank L	a.a.	661	720
HR L a.a.		NTLINSTSQRVCWQGGQEGGLEGLRQKGWILNLLVIQREAKIRNTAVKVLAQGDNQVICT	
M4 L a.a.		NTLINSTSQRVCWQGGQEGGLEGLRQKGWSILNLLVIQREAKIRNTAVKVLAQGDNQVICT	
GenBank L	a.a.	721	780
HR L a.a.		QYKTKKSRNVVELQGALNQMVSNNEKIMTAIKIGTGKLGLLINDDETMSADYLNYGKIP	
M4 L a.a.		QYKTKKSRNVVELQGALNQMVSNNEKIMTAIKIGTGKLGLLINDDETMSADYLNYGKIP	
GenBank L	a.a.	781	840
HR L a.a.		IFRGVIRGLETKRWSRVTCVTNDQIPTCANIMSSVSTNALTVAHFAENPINAMIQYNYFG	
M4 L a.a.		IFRGVIRGLETKRWSRVTCVTNDQIPTCANIMSSVSTNALTVAHFAENPINAMIQYNYFG	
GenBank L	a.a.	841	900
HR L a.a.		TFARLLLMMHDPALRQSLYEVDKIPGLHSSTFKYAMLYLDPSIGGVSGMSLSRFLIRAF	
M4 L a.a.		TFARLLLMMHDPALRQSLYEVDKIPGLHSSTFKYAMLYLDPSIGGVSGMSLSRFLIRAF	
GenBank L	a.a.	901	960
HR L a.a.		PDPVTESLSFWRFIHVHARSEHLKEMSAVFGNPEIAKFRITHIDKLVEDPTSLNIAMGMS	
M4 L a.a.		PDPVTESLSFWRFIHVHARSEHLKEMSAVFGNPEIAKFRITHIDKLVEDPTSLNIAMGMS	
GenBank L	a.a.	961	1020
HR L a.a.		PANLLKTEVKKCLIESRQTIRNQVIKDATTIYLYHEEDRLRSFLWSINPLFPRFLSEFKSG	
M4 L a.a.		PANLLKTEVKKCLIESRQTIRNQVIKDATTIYLYHEEDRLRSFLWSINPLFPRFLSEFKSG	
GenBank L	a.a.	1021	1080
HR L a.a.		TFLGVADGLISLQNSRTIRNSFKKKYHRELDDLIVRSEVSSLTHLGKLHLRRGCKMWT	
M4 L a.a.		TFLGVADGLISLQNSRTIRNSFKKKYHRELDDLIVRSEVSSLTHLGKLHLRRGCKMWT	
GenBank L	a.a.	1081	1140
HR L a.a.		CSATHADTLRYKSWGRTVIGTTVPHPLEMLGPQHRKETPCAPCNTSGFNYVSVHCPDGIH	
M4 L a.a.		CSATHADTLRYKSWGRTVIGTTVPHPLEMLGPQHRKETPCAPCNTSGFNYVSVHCPDGIH	
GenBank L	a.a.	1141	1200
HR L a.a.		DVFSSRGPLPAYLGSKTSESTSILOPWERESKVPLIKRATRLRDAISWFVEPDSKLAMTI	
M4 L a.a.		DVFSSRGPLPAYLGSKTSESTSILOPWERESKVPLIKRATRLRDAISWFVEPDSKLAMTI	

FIGURE 23-2

GenBank L	a.a.	1201	1260
HR L a.a.		LSNIHSLTGE EWTKRQHGFKRTGSALHFRFSTSRMSHGGFASQSTAALTRLMATTTDTMRDL	
M4 L a.a.		LSNIHSLTGE EWTKRQHGFKRTGSALHFRFSTSRMSHGGFASQSTAALTRLMATTTDTMRDL	
GenBank L	a.a.	1261	1320
HR L a.a.		GDQNFDFLFQATLLYAQITTTVARDGWITSCTDHYHIACKSCLRPIEEITLDSSMDYTPP	
M4 L a.a.		GDQNFDFLFQATLLYAQITTTVARDGWITSCTDHYHIACKSCLRPIEEITLDSSMDYTPP	
GenBank L	a.a.	1321	1380
HR L a.a.		DVSHVLKTRWNGEGSWGQEIKQIYPLEGNWKNLAPAEQSYQVGRGIGFLYGDLAYRKSTH	
M4 L a.a.		DVSHVLKTRWNGEGSWGQEIKQIYPLEGNWKNLAPAEQSYQVGRGIGFLYGDLAYRKSTH	
GenBank L	a.a.	1381	1440
HR L a.a.		AEDSSLFPLSIQGRIRGRGFLKGLLDGLMRASCCQVIHRRSLAHLKR PANAVYGG LIYLI	
M4 L a.a.		AEDSSLFPLSIQGRIRGRGFLKGLLDGLMRASCCQVIHRRSLAHLKR PANAVYGG LIYLI	
GenBank L	a.a.	1441	1500
HR L a.a.		DKLSVSPFPLSLTRSGPIRDELETIPHKIPTSYPTSNRDMGVIVRNYFKYQCRLIEKGKY	
M4 L a.a.		DKLSVSPFPLSLTRSGPIRDELETIPHKIPTSYPTSNRDMGVIVRNYFKYQCRLIEKGKY	
GenBank L	a.a.	1501	1560
HR L a.a.		RSHYSQLWLFSVDLSIDFIGPFSISTTLLQILYKPFLSGKDKNELRELANLSSLLRS GEG	
M4 L a.a.		RSHYSQLWLFSVDLSIDFIGPFSISTTLLQILYKPFLSGKDKNELRELANLSSLLRS GEG	
GenBank L	a.a.	1561	1620
HR L a.a.		WEDIHVKFFTKDILLCP E EIRHACKFGIAKDNNKDMSYPPWGRESRGTITTIPVYYTTTP	
M4 L a.a.		WEDIHVKFFTKDILLCP E EIRHACKFGIAKDNNKDMSYPPWGRESRGTITTIPVYYTTTP	
GenBank L	a.a.	1621	1680
HR L a.a.		YPKMLEMPPRIQNPLLSGIRLGQLPTGAHYKIRSILHGMGIHYRDFLSCGDGSGGMTAAL	
M4 L a.a.		YPKMLEMPPRIQNPLLSGIRLGQLPTGAHYKIRSILHGMGIHYRDFLSCGDGSGGMTAAL	
GenBank L	a.a.	1681	1740
HR L a.a.		LRENVHSRGIFNSLLELSGSVMRGASPEPPSALETLG GDKSRCVNGETCWEYPSDLC DPR	
M4 L a.a.		LRENVHSRGIFNSLLELSGSVMRGASPEPPSALETLG GDKSRCVNGETCWEYPSDLC DPR	
GenBank L	a.a.	1741	1800
HR L a.a.		TWDYFLRLKAGLGLQIDLIVMDMEVRDSSTSLKIETNVRNYVHRILDEQGVLIYKTYGTY	
M4 L a.a.		TWDYFLRLKAGLGLQIDLIVMDMEVRDSSTSLKIETNVRNYVHRILDEQGVLIYKTYGTY	
GenBank L	a.a.	1801	1860
HR L a.a.		ICESEKNAV TILGPMFKTVDLVQTEFSSSQ TSEVYMVCKGLKKLIDEPNPDWSSINESWK	
M4 L a.a.		ICESEKNAV TILGPMFKTVDLVQTEFSSSQ TSEVYMVCKGLKKLIDEPNPDWSSINESWK	

FIGURE 23-3

GenBank L	a.a.	1861	1920
HR L	a.a.	NLYAFQSSEQEFARAKKVSTYFTLTGIPSQFIPDPFVNIETMLQIFGVPTGVSHAAALKS	
M4 L	a.a.	NLYAFQSSEQEFARAKKVSTYFTLTGIPSQFIPDPFVNIETMLQIFGVPTGVSHAAALKS	
GenBank L	a.a.	1921	1980
HR L	a.a.	SDRPADLLTISLFYMAIISYYNINHIRVGPIPPNPPSDGIAQNVGIAITGISFWLSLMEK	
M4 L	a.a.	SDRPADLLTISLFYMAIISYYNINHIRVGPIPPNPPSDGIAQNVGIAITGISFWLSLMEK	
GenBank L	a.a.	1981	2040
HR L	a.a.	DIPLYQQCLAVIQQSFPPIRWEAVSVKGGYKQKWSTRGDGLPKDTRISDSLAPIGNWIRSL	
M4 L	a.a.	DIPLYQQCLAVIQQSFPPIRWEAVSVKGGYKQKWSTRGDGLPKDTRISDSLAPIGNWIRSL	
GenBank L	a.a.	2041	2100
HR L	a.a.	ELVRNQVRLNPFNEILFNQLCRTVDNHLKWSNLRKNTGMIEWINRRISKEDRSILMLKSD	
M4 L	a.a.	ELVRNQVRLNPFNEILFNQLCRTVDNHLKWSNLRKNTGMIEWINRRISKEDRSILMLKSD	
GenBank L	a.a.	2101	2110
HR L	a.a.	LHEENSWRD	
M4 L	a.a.	LHEENSWRD	

FIGURE 23-4