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(56) Related Art
Bachmann et al., Arch. Virol., 1975, vol. 48, no. 2, pp. 107-120
Randall et al., J. Gen. Virol., 1987, vol. 68, no. 11, pp. 2769-2780
Lin & Lamb, J. Virol., 2000, vol. 74, no. 19, pp. 9152-9166
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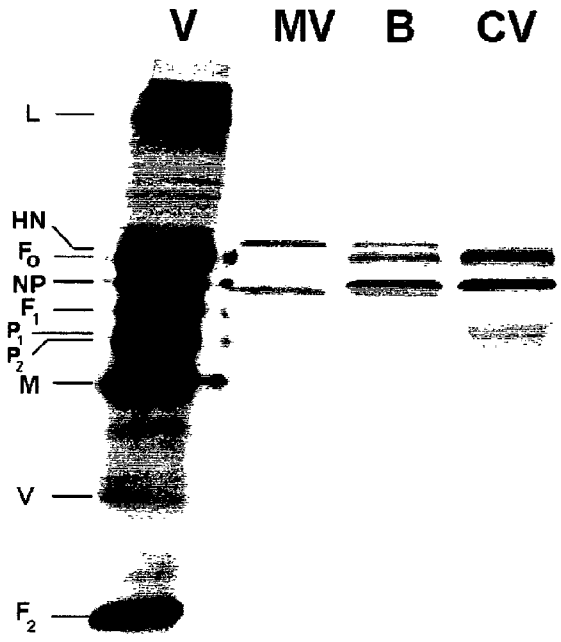
(54) Title: A NOVEL VIRUS (CRYPTOVIRUS) WITHIN THE RUBULAVIRUS GENUS AND USES THEREFOR



(57) Abstract: The present invention is based on the discovery of a novel human virus that has been designated as a *Cryptovirus*, which falls within the *Rubulavirus* genus of the Paramyxoviridae. Disclosed are isolated *Cryptovirus*-specific nucleic acids, nucleic acid constructs containing the *Cryptovirus*-specific nucleic acids, *Cryptovirus*-specific proteins, isolated*Cryptovirus* particles, isolated anti-*Cryptovirus* antibodies, and compositions containing them. Uses for manufacturing a vaccine or a medicament are also disclosed. Also disclosed are inventive vectors containing the *Cryptovirus*-specific nucleic acids and host cells containing the vectors. Methods if isolating and propagating *Cryptovirus* are disclosed, as are methods of producing a mammalian cell line acutely or non productively infected with *Cryptovirus*; such cells are disclosed. Disclosed also are methods of detecting *Cryptovirus* particles, proteins or anti-*Cryptovirus* antibodies in a sample of a biological material. *In vitro* and *in vivo* screening methods for identifying potential antiviral therapeutic or prophylactic agents are disclosed. Methods of detecting a *Cryptovirus* infection in a mammal are disclosed. Methods of detecting *Cryptovirus* infection in a mammal are disclosed. Also disclosed is an animal model for human diseases, such as neurological, neurodegenerative, and/or neuropsychiatric diseases, including epileptiform diseases (e.g., epilepsy, multiple sclerosis, chronic fatigue syndrome, and subacute sclerosing panencephalitis).

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NEUROVIRULENT VIRUS (*CRYPTOVIRUS*) WITHIN THE *RUBULAVIRUS* GENUS AND USES THEREFOR

Throughout the application various publications are referenced in parentheses. The disclosures of these publications in their entireties are hereby incorporated by reference in the application in order to more fully describe the state of the art to which this invention pertains.

BACKGROUND OF THE INVENTION

1. Field of the Invention

This invention relates to the medical arts and particularly to the field of virology, and, more particularly, to a novel human *Rubulavirus* which has been designated as a "*Cryptovirus*".

2. Discussion of the Related Art

The *Rubulavirus* genus of the Paramyxoviridae (see Fig. 1) are enveloped viruses characterized by a single minus-stranded RNA genome. There is substantial evidence that some rubulaviruses infect domestic animals and can cause neurological diseases in them. These neuropathic rubulaviruses include Canine Parainfluenza Virus Type 2, Porcine Rubulavirus (*aka* La Piedad-Michoacan-Mexico Virus), and Menangle Virus. The strong sequence homologies amongst these viruses imply that each of these viruses represent separate host-adapted species of a common ancestral Rubulavirus species.

Canine Parainfluenza Virus Type 2 (which is also known as CPIV) is associated with infectious tracheobronchitis in dogs. This is a non-lethal disease (usually) of the respiratory tract (Appel and Binn, Canine Infectious Tracheobronchitis. *In* Virus Infections of Carnivores. Elsevier Science Publishing Co., New York, N.Y., pp 201-211, 1987). However, the virus has also been found to be associated with posterior paresis (Evermann *et al. J.A.V.M.A.* 177:1132-1134, 1980), neurological dysfunction (Baumgartner *et al. Infect. Immun.* 31:1177-1183,1981), encephalitis (Evermann *et al. Arch. Virol.* 68:165-172, 1981) and hydrocephalus (Baumgartner *et al. Vet. Pathol.* 19:79-92, 1982) in dogs.

Porcine Rubulavirus (which is also known as La Piedad-Michoacan-Mexico Virus or LPMV) is associated with Blue-Eye Disease (BED) of pigs. The symptoms of the disease include corneal opacity, extreme "nervousness" in young pigs and infertility in sows and boars (Ramirez-Mendoza *et al., J. Comp. Pathol.* 117:237-252, 1997). The virus persists in the central nervous system of pigs after recovery from BED (Wiman *et al.* 1998; Hjertner *et al.* 1998). This virus also shares more than 95% of its nucleotide sequence with *Cryptovirus*.

Menangle virus is an emergent rubulavirus that was first identified in Australia in 1997 (Philbey *et al.*, *Emerging Infectious Diseases* 4:269-271, 1998). This virus is associated with severe degeneration of the brain and spinal cord of stillborn piglets (Philbey *et al.* 1998). Neurons of these animals contained Menangle virus inclusion bodies (nucleocapsids). Serological studies have also found neutralizing antibodies to the virus in pigs, fruit bats and at least two human piggery workers.

A number of human rubulaviruses are known to cause illness in humans. These include: (1) mumps virus (causes human mumps); (2) human parainfluenza virus type 2 (*aka* HPIV-2; associated with relatively mild upper respiratory, flu-like illness; (3) human parainfluenza virus types 4A and 4B (*aka* HPIV-4A, HPIV-4B; also associated with relatively mild upper respiratory, flu-like illnesses). With mumps there is also evidence of nervous system involvement in a significant number of patients, although this is virtually never life threatening.

In contrast, there are no published studies clearly demonstrating that another *Rubulavirus*, Simian Virus 5 (SV5), causes disease either in humans or in experimentally-infected animals, and there has been at least one published study demonstrating that SV5 does not cause disease in experimentally-infected mice, even mice with severe combined immunodeficiency (SCID mice) (Didcock *et al.*, *J. Virol.* 73:3125-3133, 1999).

In 1978, a report described the isolation of an "infectious agent" from the bone marrow of patients with multiple sclerosis (MS). (Mitchell, DN *et al.*, *Isolation of an infectious agent from bone marrow of patients with mutiple sclerosis*, Lancet ii:387-391 [1978]). Subsequent reports described five separate "human SV5 isolates" derived from different MS patients. (Goswami, KKA *et al.*, *Does simian virus 5 infect humans?* Journal of General Virology 65:1295-1303 [1984]; Goswami, KKA *et al.*, *Evidence for the persistence of paramyxoviruses in human bone marrows*, Journal of General Virology 65:1881-1888 [1985]; Randall, RE *et al.*, *Isolation and characterization of monoclonal antibodies to simian virus 5 and their use in revealing antigenic differences between human, canine and simian isolates*, Journal of General Virology 68:2769-2780 [1987]). Nevertheless, a causal link between SV5 and MS remained speculative.

In 1987, Goswami *et al.* reported that the cerebrospinal fluid (CSF) of some MS patients contained antibodies to SV5. (Goswami KKA *et al.*, *Antibodies against the paramyxovirus SV5 in the cerebrospinal fluids of some multiple sclerosis patients*, Nature 327:244-247 [1987]). However, this report was controversial, since the results subsequently failed to be reproducible by other well respected paramyxovirologists. (Vandvik, B. and Norrby, E., *Paramyxovirus SV5 and multiple sclerosis*, Nature 338:769-771 [1989]; but see, Russell, WC and Randall, RE, *Multiple sclerosis and*

paramyxovirus, Nature 340:104 [1989]). Therefore, a clear causal link between SV5 and MS was not established in the art.

Multiple Sclerosis is a chronic degenerative central nervous system disease that most commonly affects young and early middle-aged adults (between 18 and 40 years of age). It is less commonly diagnosed in adolescents and even less so in children. Affecting 350,000 Americans, MS is one of the most frequent causes of neurologic disability except for traumatic injuries. (S.L. Hauser, *Multiple Sclerosis and other demyelinating diseases* In: *Harrison's Principles of Internal Medicine*, 13th ed., K.J. Isselbacher *et al.* (eds.), McGraw-Hill, pp.2287-95 [1994]). The onset, progression and outcome of the disease are highly variable with patients manifesting one of several patterns of illness. For example, for reasons that are unclear, MS affects twice as many females as males. Although the individual components that comprise the diagnostic, clinical tableau of MS have long been delineated, their sequence and severity of presentation from case to case are subject to great variation. (Hallpike J.F., Adams C.W.M., and Tourtellotte W.W., Eds, 1983, *Multiple Sclerosis: Pathology, Diagnosis and Management*, Chapman & Hall, London; McAlpine E. *et al.*, 1972, *Multiple Sclerosis: A Reappraisal*, Churchill Livingstone, Edinburgh; Rose A.S., 1972, Multiple Sclerosis: A Clinical Interpretation. *In Multiple Sclerosis: Immunology, Virology and Ultrastructure* Wolfgram F., Ellison G.W., Stevens J.G., and Andrews J.M., Eds., Academic Press, New York). It is fair to say that no two patients with MS are alike, and, consequently, there is contention as to what constitutes the stereotypic clinical history.

Most commonly, MS first presents as a series of neurological attacks followed by complete or partial remissions where symptoms lessen only to return after some period of stability (relapsing-remitting MS). In other patients, the disease is characterized by a gradual decline with no clear remissions but sometimes with brief plateaus or minor relief of symptoms (primary-progressive MS). In still other patients, there can be a relapsing and remitting course of illness in the early stages followed by progressive decline (secondary-progressive MS).

In general, the primary manifestations of chronic progressive and chronic relapsing MS do not vary greatly. Evidence for an insidious disease (apathy, depression, fatigue, loss of weight, muscle pains) often can be uncovered from the patient's chart before the first neurological manifestations. Among the first signs in about 50% of all definite MS cases are limb weakness, numbness, or tingling (parathesias) in one or more limbs, the extremities, or around the trunk. There is often discordance between signs and symptoms. Adams and Victor (1997, Multiple sclerosis and allied demyelinative diseases. *In Principles of Neurology*. Adams R.D. and Victor M., Eds., McGraw Hill, New York) mention that "it is a common aphorism that the patient with MS presents

with symptoms in one leg and signs (bilateral Babinski) in both." Another common initial sign is a short-lived episode of retrobulbar neuritis affecting one or both eyes. Many MS patients will display papillitis (swelling of the optic nerve head), which depends on the proximity of the demyelinated plaque to the nerve head. There is considerable debate as to whether optic neuritis in a significant percentage of cases constitutes a separate disease or subclass of MS, but in about 50% of cases, the disease progresses to MS (Arnason *et al.*, *J. Neurol. Sci.* 22:419, 1974).

As diagnosis becomes established, a more regular group of clinical syndromes develops either progressively or in a remitting fashion. The majority of patients display a mixed or generalized type of disease involving optic nerves, brain stem, cerebellum, and spinal cord. About one third will exhibit a spinal form, and about 5% will display a cerebellar or pontobulbar-cerebellar form, and a similar percentage will have an amaurotic form. Adams and Victor (*supra*) estimate that at least 80% of their own clinical material comprised cerebrospinal and spinal forms of the disease.

Psychologic disturbances are frequently observed and can present as an inappropriate euphoric state, attributed by Adams and Victor (*supra*) probably to extensive white matter lesions in the frontal lobes. In a much higher percentage of MS patients depression and irritability are observed.

Until relatively recently, MS and epilepsy were considered discrete entities. The publication of numerous recent studies demonstrating an "overlap" between these disorders has corrected this misperception. Epidemiological and demographic studies conducted over the last decade have provided substantial evidence of concurrent epileptiform symptomology in a significant proportion of MS patients. While the concurrence of epileptiform symptoms is markedly higher in early onset MS (i.e. in children and adolescents), the overall prevalence of epilepsy in MS patients is many times higher than in the general population.

Human epilepsy is an enigmatic medical condition which, in fact, is not a specific disease – or even a single syndrome – but, rather a broad category of symptom complexes arising from any number of disordered brain functions that themselves can be secondary to a variety of pathologic processes. Today, a large number of clinical phenomena are recognized as epileptic seizures, some of which (*e.g.*, myoclonic and atonic seizures) are currently poorly understood and could, in fact, reflect neuronal mechanisms that are somewhat different from the pathophysiologic processes traditionally considered to be "epileptic." Perhaps the best reflection of the enigmatic and complex nature of these illnesses is the simple fact that the etiology of the disease, in the overwhelming majority of the cases (greater than 70%), is either "cryptogenic" (*i.e.*, of obscure, indeterminate origin) or "idiopathic" (*i.e.*, of unknown cause).

Epilepsy is more than seizures. Epileptics typically exhibit a spectrum of responses, from little or no seizure activity, through mild activity (*petit mal* or "absence" seizures), to recurrent and intractable *grand mal* seizures (the occurrence of which is often misunderstood by the lay public to be the defining symptom of all forms of epilepsy; *see Epilepsy: A Comprehensive Textbook*, Engel, Jr. J. and Pedley, T.A., Eds., Lippincott-Raven, 1997). The condition in its entirety is comprised of many facets, different for each individual, that contribute to disability and impaired quality of life. While the physical spectrum of symptoms ranges from extremely subtle *petit mal* or "absence" seizures to profoundly disabling *grand mal* seizures, many patients experience other co-morbid processes (*e.g.*, memory loss, confusion, lethargy, sleep disturbances, and clinical depression) which can be equally disabling. Treatment that focuses solely on seizures often does little to lessen disability. This is perhaps best illustrated by the patient who, having undergone successful surgical resection of epileptogenic brain tissue, becomes seizure-free but remains socially isolated and unemployed, with little evidence of an improved life. Therapeutic intervention can be optimal only when the multiple and interacting medical, psychological, and environmental factors that constitute epilepsy are addressed.

Another epileptiform disease is Subacute Sclerosing Panencephalitis (SSPE), a rare and fatal degenerative central nervous system disease of children and adolescents. (Sever and Zeman, editors, Measles Virus and Subacute Sclerosing Panencephalitis. *Neurology (Supplement 1)* 18:1-192, 1968; Payne and Baublis, *Perspectives in Virology* 7:179-195, 1971; Johannes and Sever, *Ann. Rev. Med.* 26:589-601, 1975; Meulen *et al., Comp. Virol.* 18:105-159, 1983; Dyken, *Neurol. Clin.* 3:179-196, 1985). In its early stages it commonly presents as an affective or other behavioral disorder and progresses over a period of months to profound epileptiform neurological disease. Its later stages are characterized by intractable seizures, decerebrate rigidity, coma and death. At some time, virtually all SSPE patients are "misdiagnosed" with epilepsy.

Cases of SSPE have been described in both industrialized and developing countries throughout the world (Canal and Torck, *J. Neurol. Sci.* 1:380-389, 1964; Pettay *et al., J. Infect. Dis.* 124:439-444, 1971; Haddad *et al., Lancet* 2:1025, 1974; Soffer *et al., Israeli J. Med. Sci.* 11:1-4, 1975; Naruszewicz-Lesiuk *et al., Przeg Epidemiologiczna* 23:1-8, 1979; Moodie *et al., South African Med. J.* 58:964-967, 1980). The frequency of the disease varies greatly, ranging from 0.06 and 0.10 cases per million total population per year (cpmpy) in Britain (Dick, *Brit. Med. J.* 3:359-360, 1973) and the United States (Jabbour *et al., J. A. M. A.* 220:959-962, 1972) to 3.40 and 7.70 cpmpy in Israel (Soffer, *et al., Israeli J. Med. Sci.* 11:1-4, 1975) and New Zealand (Baguley and Glasgow, *Lancet*

2:763-765, 1973). The factor(s) that are responsible for the ultimate etiopathogeneis of the disease are unclear.

Numerous studies have shown that the central nervous system tissues of SSPE patients are persistently-infected with measles virus. Substantial evidence indicates that the disease involves the recrudescence of a persistent measles virus infection acquired earlier in life. Specific findings in SSPE patients which support this hypothesis include: (1) a history of childhood measles, (2) markedly elevated titers of measles virus-specific antibodies in serum, (3) the presence of measles virus-specific antibodies in cerebrospinal fluid, (4) the presence of measles virus antigens in CNS tissues demonstrated by specific immunofluorescence, (5) intracellular inclusions of paramyxoviral nucleocapsids in oligodendroglial and neuronal cells, and (6) the isolation of infectious measles virus from brain and lymphatic tissues when co-cultivated with susceptible cells (Bouteille *et al., Revue Neurologie* 113:454-458, 1965; Connolly *et al., Lancet* 1:542-544, 1967; Legg, *Brit. Med. J.* 3:350-354, 1967; Payne *et al., New Eng. J. Med.* 281585-589, 1969; Horta-Barbosa *et al., Nature* 221:974, 1969). Finally, and perhaps most convincingly, epidemiological evidence suggests that vaccination against measles substantially reduces the risk of developing the disease (Modlin *et al., Pediatrics* 59:505-512, 1977; Halsey *et al., Am. J. Epidemiol.* 111:415-424, 1980; Dyken *et al., Morb. Mortal. Weekly Report* 31:585-588, 1982).

Despite these findings, there are a number of anomalies that have been observed which are inconsistent with measles virus alone being the sole cause of the illness. These include the following.

First, neurovirulence. Clinical isolates of measles virus from patients with rubeola have not been shown to cause an SSPE-like illness in experimentally infected animals. Cell-associated SSPE-derived strains, however, have been shown to cause such disease in ferrets, marmosets and monkeys (Katz *et al., J. Infect. Dis.* 121:188-195, 1970; Thormar *et al., J. Infect. Dis.* 127:678-685, 1973; Ueda *et al., Biken Journal* 18:179-181, 1975; Yamanouchi *et al., Japan. J. Med. Sci. Biol.* 29177-186, 1976; Thormar *et al., J. Infect. Dis.* 136:229-238, 1977; Albrecht *et al., Science* 195:64-66, 1977; Thormar *et al., J. Exp. Med.* 148:674-691, 1978; Ohuchi *et al., Microbiol. Immunol.* 25:887-893 [1981]).

Second, distribution and morphology of virus inclusion bodies. Measles virus antigens in infected cells form large coalescing intracytoplasmic inclusions when examined by fluorescent antibody techniques. When labeled with SSPE patient sera, virus antigens demonstrate distinctly different patterns in cell-associated SSPE-derived virus strains and in experimentally-infected animal CNS tissues. In such materials, intracellular inclusion bodies demonstrate a "peppery," particulate and/or "splattered" distribution (Doi *et al., Japan. J. Med. Sci. Biol.* 25:321-333, 1972; Kimoto and

Baba, *Biken Journal* 18:123-133, 1975; de Felici *et al., Annales Microbiologie* 126:523-538, 1975; Ohuchi *et al., Microbiol. Immunol.* 23:877-888, 1979).

Third, ultrastructural morphology of virus nucleocapsids. In measles virus infected cells, cytoplasmic nucleocapsids are predominantly of a "fuzzy" or "granular" morphology (Tawara, *Virus (Osaka)* 14:85-88, 1965; Matsumoto, *Bull. Yamaguchi Med. School* 13: 167-189, 1966; Nakai *et al., Virology* 38:50-67, 1969; Nakai and Imagawa, *J. Virol.* 3:187-197, 1969). In SSPE-derived CNS tissues, both fuzzy and smooth nucleocapsids have been consistently observed (Oyanagi *et al., J. Virol.* 7:176-182, 1971; Dubois-Dalcq *et al., Arch. Neurol.* 31:355-364, 1974). Smooth cytoplasmic nucleocapsids have also been observed in most cell-associated SSPE-derived cell lines (Doi *et al., Japan. J. Med. Sci. Biol.* 25:321-333, 1972; Makino *et al., Microbiol. Immunol.* 21:193-205, 1977; Ueda *et al., Biken Journal* 18:113-122, 1975; Burnstein *et al., Infect. Immun.* 10:1378-1382, 1974; Mirchamsy *et al., Intervirology* 9:106-118, 1978; Schott *et al., Revue Neurologie* 135:653-664, 1979) with some containing only such structures (Doi *et al., Japan. J. Med. Sci. Biol.* 25:321-333, 1972; Thormar *et al., J. Exp. Med.* 148:674-691, 1978).

Fourth, immunoreactivity of virus nucleocapsids. While fuzzy nucleocapsid aggregates are labeled with HRP-conjugated measles virus-specific antibody experimentally raised in animals, smooth virus nucleocapsids are not (Dubois-Dalcq *et al., Lab. Invest.* 30:241-250, 1974; Brown *et al., Acta Neuropathologica* 50:181-186, 1980). Most interestingly, both can readily be labeled with SSPE sera (Brown *et al., Acta Neuropathologica* 50:181-186, 1980).

And fifth, epidemiology. The least understood feature of the measles virus theory of SSPE aetiopathogenesis is the extremely low incidence of the disease. Despite numerous investigations into the role of socioeconomic, demographic and genetic factors (Canal and Torck, *J. Neurol. Sci.* 1:380-389, 1964; Pettay *et al., J. Infect. Dis.* 124:439-444, 1971; Haddad *et al., Lancet* 2:1025, 1974; Soffer *et al., Israeli J. Med. Sci.* 11:1-4, 1975; Naruszewicz-Lesiuk *et al., Przeg Epidemiologiczna* 23:1-8, 1979; Moodie *et al., South African Med. J.* 58:964-967, 1980; Dick, *Brit. Med. J.* 3:359-360, 1973; Jabbour *et al., J. A. M. A.* 220:959-962, 1972; Baguley and Glasgow, *Lancet* 2:763-765, 1973; Modlin *et al., Pediatrics* 59:505-512, 1977; Halsey *et al., Am. J. Epidemiol.* 111:415-424, 1980; Dyken *et al., Morb. Mortal. Weekly Report* 31:585-588, 1982), it has, until now, been completely unclear why SSPE is so rare when measles virus annually infects millions of children throughout the world.

A much more common idiopathic neurological and/or neuropsychiatric disease, which affects more than a half million Americans, is chronic fatigue syndrome (CFS), which frequently involves concurrent epileptiform symptomology. (P. H. Levine, *What we know about chronic fatigue*

syndrome and its relevance to the practicing physician, Am. J. Med. 105(3A):100S-03S [1998]). Chronic fatigue syndrome is characterized by a sudden onset of persistent, debilitating fatigue and energy loss that lasts at least six months and cannot be attributed to other medical or psychiatric conditions; symptoms include headache, cognitive and behavioral impairment (e.g., short-term memory loss), sore throat, pain in lymph nodes and joints, and low grade fever. (M. Terman *et al.*, *Chronic Fatigue Syndrome and Seasonal; Affective Disorder: Comorbidity, Diagnostic Overlap, and Implications for Treatment*, Am. J. Med. 105(3A):115S-24S [1998]). Depression and related symptoms are also common, including sleep disorders, anxiety, and worsening of premenstrual symptoms or other gynecological complications. (A.L. Komaroff and D. Buchwald, *Symptoms and signs of chronic fatigue syndrome*, Rev. Infect. Dis. 13:S8-S11 [1991]; B.L. Harlow *et al.*, *Reproductive correlates of chronic fatigue syndrome*, Am. J. Med. 105(3A):94S-99S [1998]). Other physiologic abnormalities are also associated with CFS in many patients, including neurally-mediated hypotension, hypocortisolism, and immunologic dysregulation. (P.H. Levine [1998]). A subgroup of CFS patients complain of exacerbated mood state, diminished ability to work and difficulty awakening during winter months, reminiscent of seasonal affective disorder. (M. Terman *et al.* [1998]).

The etiology of CFS has been unknown, and the heterogeneity of CFS symptoms has precluded the use of any particular diagnostic laboratory test. (P.H. Levine [1998]). Symptomatic parallels have been suggested between CFS and a number of other disease conditions, resulting from viral or bacterial infection, toxic exposure, orthostatic hypotension, and stress, but none of these has been shown to have a causal role in CFS. (E.g., I.R. Bell *et al.*, *Illness from low levels of environmental chemicals: relevance to chronic fatigue syndrome and fibromyalgia*, Am. J. Med. 105(3A):74S-82S [1998]; R.L. Bruno *et al.*, *Parallels between post-polio fatigue and chronic fatigue syndrome: a common pathophysiology?*, Am. J. Med. 105(3A):66S-73S [1998]; R. Glaser and J.K. Kiecolt-Glaser, *Stress-associated immune modulation: relevance to viral infections and chronic fatigue syndrome*, Am. J. Med. 105(3A):35S-42S [1998]; P.C. Rowe and H. Calkins, *Neurally mediated hypotension and chronic fatigue syndrome*, Am. J. Med. 105(3A):15S-21S [1998]; L.A. Jason *et al.*, *Estimating the prevalence of chronic fatigue syndrome among nurses*, Am. J. Med. 105(3A):91S-93S [1998]). Accordingly, there has been no known cause to which diagnosis and/or treatment of CSF could be directed. Consequently, the diagnosis and treatment of CFS have continued to be directed to symptoms, rather than to an underlying treatable cause. For example, the use of relaxin has been described for relaxing the involuntary muscles and thus relieve pain associated

with CFS. (S.K. Yue, *Method of treating myofascial pain syndrome with relaxin*, U.S. Patent No. 5,863,552).

There remains a need for an underlying causal factor for many idiopathic neurological, neurodegenerative, neuropsychological and neuropsychiatric disorders and primary tracheobronchial and/or lymphadenopathy-associated diseases, to which diagnostic testing, research and development, including screening of potential new antiviral drugs, and treatment can be directed. This and other benefits of the present invention are described herein.

SUMMARY OF THE INVENTION

The present invention is based on the discovery and isolation of a novel human virus that has been designated as a "*Cryptovirus*", which falls within the genus *Rubulavirus* of the family Paramyxoviridae. The genome of the isolated *Cryptovirus* of the present invention is a minus strand RNA having a nucleotide sequence entirely complementary to (SEQ ID NO:1).

The present invention relates to isolated nucleic acids that are *Cryptovirus*-specific. The inventive *Cryptovirus*-specific nucleic acids encompass: (A) nucleotide sequence of contiguous nucleotide positions 1-15246 of (SEQ ID NO:1), such as, but not limited, to plus strand RNAs (e.g., mRNAs) and cDNAs; or (B) a nucleotide sequence complementary to contiguous nucleotide positions 1-15246 of (SEQ ID NO:1), such as, but not limited to minus strand RNAs (e.g., genomic or cloned RNAs) and cDNAs; or (C) *Cryptovirus*-specific fragments of (A) or (B), such fragments being at least about five nucleotides long. The present invention encompasses both RNAs and DNAs, and thus it is understood by the skilled artisan that the present invention encompasses nucleic acids, i.e., RNAs, in which uracil residues ("U") replace the thymine residues ("T") in (SEQ ID NO:1). The inventive nucleic acids include useful *Cryptovirus*-specific probes and primers.

Inventive nucleic acid constructs, including cloning vectors and expression vectors, are provided that contain the inventive nucleic acid. Such inventive recombinant vectors are contained in a host cell of the present invention.

The present invention also relates to an isolated *Cryptovirus* protein encoded by a *Cryptovirus*-specific nucleic acid segment. The inventive *Cryptovirus* proteins include isolated *Cryptovirus* nucleocapsid and envelope proteins and chimeric proteins comprising a *Cryptovirus* protein moiety.

The invention relates to an isolated virion or other viral particle that contains the inventive *Cryptovirus* nucleic acid, such as a viral expression vector, or contains the inventive *Cryptovirus*

protein, such as an inventive pseudotyped virion or an inventive isolated *Cryptovirus* virion or other *Cryptovirus* particle.

Inventive compositions of matter that include the inventive *Cryptovirus* nucleic acid, *Cryptovirus* protein, or isolated virions and other viral particles, together with a carrier, are also included in the present invention.

Moreover, the present invention provides a method of isolating a *Cryptovirus* virion. The inventive method involves culturing a plurality of peripheral blood mononuclear cells (PBMNCs) that have been obtained from a human having a *Cryptovirus* infection. The PBMNCs are cultured in an artificial aqueous medium that includes an agent that increases cellular guanylyl cyclase activity, such as but not limited to cyclic GMP. The PBMNCs are then co-cultured in with a plurality of mammalian amnion cells in fresh aqueous medium including the agent, and the co-culture is passaged one or more times. Passaging is followed by co-cultivating a plurality of mammalian epithelial cells together with the PBMNCs and the mammalian amnion cells in fresh aqueous medium comprising the agent. This co-cultivation results in the production of *Cryptovirus* virions that are released into the aqueous medium. A supernatant of the aqueous medium is separated from the cells in the culture, to obtain the *Cryptovirus* virions, which are found in the supernatant. The inventive method facilitates the isolation from cellular material of *Cryptovirus* virions in great numbers. Virions isolated thereby can be further propagated by an inventive method of propagating a *Cryptovirus*, which the present invention provides.

The inventive method of propagating a *Cryptovirus* involves exposing a plurality of mammalian epithelial cells to a plurality of cell-free *Cryptovirus* virions, thus isolated, and further cultivating the *Cryptovirus* virion-exposed mammalian epithelial cells in an artificial aqueous medium comprising an agent that increases the activity of cellular guanylyl cyclase. Thus, a mammalian epithelial cell acutely infected with *Cryptovirus* is provided, which inventive cell is produced by the method.

The present invention also relates to a method of producing a mammalian cell line nonproductively infected with *Cryptovirus*. The method involves co-culturing PBMNCs that have been obtained from a human having a *Cryptovirus* infection, with mammalian amnion cells (e.g., rodent or primate amnion cells), in an artificial aqueous medium comprising an agent that increases cellular guanylyl cyclase activity, such that the mammalian amnion cells become nonproductively infected by *Cryptovirus*. After passaging the nonproductively infected mammalian amnion cells with the peripheral blood mononuclear cells, the co-culture becomes a monoculture of the nonproductively

infected mammalian amnion cells. The present invention also relates to a cell nonproductively infected with *Cryptovirus*, which cell is produced in accordance with the method.

Cryptovirus is associated with cryptogenic and idiopathic forms of human disease, e.g., epilepsy. *Cryptovirus* is also associated with other human neurological, neurodegenerative, and/or neuropsychiatric diseases where neural dysfunction and neuropathology are evident and where epileptiform symptomology is always concurrent (e.g. subacute sclerosing panencephalitis, SSPE) or is frequently concurrent (e.g., multiple sclerosis [MS] and chronic fatigue syndrome [CFS]). Thus, the inventive cell lines, viral particles and virions are particularly useful for screening potential antiviral agents to discover those that could be effective in treating mammals, including humans, infected with *Cryptovirus*.

In particular, useful in vitro methods of screening a potential antiviral therapeutic agent are provided. In accordance with the in vitro screening methods, the inventive *Cryptovirus*-infected cells are cultured, and then exposed to the potential antiviral therapeutic agent. If acutely infected mammalian epithelial cells are used, then the effect of the potential antiviral therapeutic agent on *Cryptovirus* replication and/or *Cryptovirus* virion assembly is measured (e.g., effect on *Cryptovirus* genomic replication, *Cryptovirus* transcription, and/or translation, i.e., protein synthesis, from *Cryptovirus* mRNAs, effect on numbers of *Cryptovirus* virions produced or completeness of *Cryptovirus* particles). Inhibition of *Cryptovirus* replication and/or *Cryptovirus* virion assembly, relative to a control not receiving the agent, indicates antiviral activity of the potential therapeutic agent. Alternatively, if nonproductively infected cells are used, measurement is made of the effect of the potential antiviral therapeutic agent on *Cryptovirus* replication, *Cryptovirus* genome replication, and/or *Cryptovirus*-specific transcription. Inhibition of *Cryptovirus* replication, *Cryptovirus* genome replication, and/or *Cryptovirus*-specific transcription, relative to a control not receiving the agent, indicates antiviral activity of the potential therapeutic agent. These inventive methods are useful for identifying, screening, or isolating promising new antiviral drugs. Once the potential of a chemical agent is identified by the inventive methods, then, further research can be done to ascertain its clinical usefulness. Thus, the inventive methods of screening a potential chemotherapeutic agent are of benefit in finding and developing pharmaceutical antiviral drugs aimed at treating *Cryptovirus*-related conditions and other conditions associated with other viruses of the Mononegavirales.

The present invention now also provides an animal model for the study of human diseases, for example a neurological, neurodegenerative, and/or neuropsychiatric disease (e.g., idiopathic epileptiform diseases, such as epilepsy, SSPE, MS, and CFS). The animal model involves a non-human mammal, which has been inoculated with an infectious cell-free *Cryptovirus* having a genome

comprising a single stranded RNA complementary to (SEQ ID NO:1), or has been inoculated with a cell nonproductively-infected with the *Cryptovirus*. The inoculated non-human mammal of the animal model exhibits at least one symptom characteristic of a human disease after being thus inoculated, which was not previously exhibited by the non-human mammal before inoculation.

The animal model is useful in an in vivo method of screening a potential antiviral therapeutic agent. The method involves administering the potential therapeutic agent to be screened, to the inventive animal model. Before administration of the potential therapeutic agent, the non-human mammal exhibits at least one symptom characteristic of a human disease. After administration of the potential therapeutic agent, the presence or absence of a beneficial antiviral effect is detected; the presence of a beneficial antiviral effect, in comparison to a control animal not receiving the agent, indicates activity of the potential therapeutic agent.

Employing an alternative embodiment of the inventive animal model, an in vivo method of screening a potential antiviral prophylactic agent is provided. The method involves administering a potential prophylactic agent to be screened to a non-human mammal, which does not have a symptom of a human disease, for example a neurological, neurodegenerative, and/or neuropsychiatric disease. Then the animal is inoculated, as previously described, with an infectious cell-free *Cryptovirus* having a genome comprising a single stranded RNA complementary to (SEQ ID NO:1), or with a mammalian cell nonproductively-infected with the *Cryptovirus*. Subsequently, the presence or absence in the non-human mammal of a beneficial antiviral effect is detected, compared to a control not receiving the potential prophylactic agent. The subsequent presence of a beneficial antiviral effect in the inoculated non-human mammal indicates activity of the potential prophylactic agent.

The inventive nucleic acid constructs, *Cryptovirus* proteins, and particles and virions are also particularly useful in producing *Cryptovirus*-specific antibodies, and in the production or manufacture of vaccines, which antibodies and vaccines are directed specifically against *Cryptovirus* proteins, such as the nucleocapsid or envelope proteins of *Cryptovirus*. These vaccines can include live attenuated virus; killed virus; recombinant chimeric viruses; proteins or other parts of virus; or one or more isolated or recombinantly expressed *Cryptovirus* proteins.

The present invention relates also to an isolated antibody that specifically binds a *Cryptovirus* protein and the use of the inventive antibody in manufacturing a medicament for the treatment of *Cryptovirus* infections. Also provided are compositions of matter comprising the antibody and a carrier.

In other aspects, the invention is usefully directed to methods and assays, e.g., for determining whether biological materials are contaminated with *Cryptovirus* or whether a mammal, including a human, is or has been infected with *Cryptovirus*.

In particular, the invention provides methods of detecting the presence or absence of a *Cryptovirus* protein, *Cryptovirus*-specific RNA, or *Cryptovirus*-specific antibody in a sample of a biological material, such as serum.

In the method of detecting *Cryptovirus* protein, the sample of the biological material is contacted with an inventive antibody that specifically binds a *Cryptovirus* protein; and if the presence of specific binding of the antibody to a constituent of the sample is detected, this indicates the presence of the *Cryptovirus* protein in the sample.

Similarly, in the method of detecting *Cryptovirus*-specific RNA in a sample of a biological material containing RNA, the sample is contacted with the inventive Cryptovirus-specific probe under at least moderately stringent hybridization conditions, and the formation of detectable hybridization products indicates the presence of the *Cryptovirus* RNA in the sample.

Alternatively, the sample containing RNA is subjected to an amplification of *Cryptovirus*-specific RNA in the sample, using at least one inventive *Cryptovirus*-specific primer in an amplification reaction mixture. By detecting the presence or absence of *Cryptovirus*-specific nucleic acid amplification products in the amplification reaction mixture, the presence or absence of *Cryptovirus*-specific RNA in the sample can be determined, with the presence of *Cryptovirus*-specific amplification products in the reaction mixture indicating the presence of the *Cryptovirus*-specific RNA in the sample.

The present invention also provides a method of detecting the presence or absence of a *Cryptovirus*-specific antibody in a sample of an antibody-containing biological material, such as serum. The method involves contacting the sample of biological material with the inventive protein, such as a *Cryptovirus* envelope protein, or alternatively, with the inventive virion or viral particle, under conditions allowing the formation of a specific protein-antibody complex, or antibody-bound virus complex, respectively. Detection of the presence of such specific protein-antibody complexes, or antibody-bound virus complexes, indicates the presence of the *Cryptovirus*–specific antibody in the sample. Inventive anti-*Cryptovirus* antibody detecting kits are also provided, which are useful for practicing the method.

Thus, by practicing any of the foregoing inventive methods of detecting the presence or absence of a *Cryptovirus* protein, *Cryptovirus*-specific RNA, or *Cryptovirus*-specific antibody, with a sample of biological materials from a mammal, including a human, an inventive method of detecting

or diagnosing a *Cryptovirus* infection in the mammal is provided, as indicated by the presence in the sample of *Cryptovirus* protein, *Cryptovirus*-specific RNA, or *Cryptovirus*-specific antibody. These diagnostic methods are valuable because, regardless of the therapeutic strategy, it is advantageous to begin therapy at the time of "primary" infection *(i.e.,* the first exposure to the virus) or as soon as possible thereafter *(i.e.,* during development of the primary infection).

In a first aspect the invention provides an isolated nucleic acid, comprising:

(A) contiguous nucleotide positions 1-15246 of (SEQ ID NO: 1);

(B) a nucleotide sequence complementary to (A); or

(C) *Cryptovirus*-specific fragment of (A) or (B), comprising a nucleic acid segment selected from the group consisting of:

(i) contiguous nucleotide positions 152-1678 of (SEQ ID NO:1), a complementary sequence, or a degenerate coding sequence;

(ii) contiguous nucleotide positions 1850-2515 of (SEQ ID NO:1), a complementary sequence, or a degenerate coding sequence;

(iii) contiguous nucleotide positions 1850-3023 of (SEQ ID NO:1), a complementary sequence, or a degenerate coding sequence;

(iv) contiguous nucleotide positions 1850-3023 of (SEQ ID NO:1) combined with a further insertion of two guanine residues between nucleotide position 2339 of (SEQ ID NO:1) and nucleotide position 2340 of (SEQ ID NO:1), a complementary sequence, or a degenerate coding sequence;

(v) contiguous nucleotide positions 3141-4271 of (SEQ ID NO:1), a complementary sequence, or a degenerate coding sequence;

(vi) contiguous nucleotide positions 4530-6182 of (SEQ ID NO:1), a complementary sequence, or a degenerate sequence;

(vii) contiguous nucleotide positions 4587-6182 of (SEQ ID NO:1), a complementary sequence, or a degenerate sequence;

(viii) contiguous nucleotide positions 4587-4835 of (SEQ ID NO:1), a complementary sequence, or a degenerate sequence;

(ix) contiguous nucleotide positions 4836-6182 of (SEQ ID NO:1), a complementary sequence, or a degenerate sequence;

(x) contiguous nucleotide positions 4272-6515 of (SEQ ID NO:1), a complementary sequence, or a degenerate coding sequence;

(xi) contiguous nucleotide positions 6303-6434 of (SEQ ID NO:1), a complementary sequence, or a degenerate coding sequence;

(xii) contiguous nucleotide positions 6584-8278 of (SEQ ID. NO:1), a complementary sequence, or a degenerate coding sequence; and

(xiii) contiguous nucleotide positions 8414-15178 of (SEQ ID NO:1), a complementary sequence, or a degenerate coding sequence; and

(xiv) contiguous nucleotide positions 1684-1701 (of SEQ ID NO:1), a complementary sequence, or a degenerate coding sequence; and

(xv) contiguous nucleotide positions 1700-1717 (of SEQ ID NO:1), a complementary sequence, or a degenerate coding sequence; and

(xvi) contiguous nucleotide positions 4283-4300 (of SEQ ID NO:1), a complementary sequence, or a degenerate coding sequence; and

(xvii) contiguous nucleotide positions 4299-4316 (of SEQ ID NO:1), a complementary sequence, or a degenerate coding sequence; and

(xviii) contiguous nucleotide positions 4285-4302 (of SEQ ID NO:1), a complementary sequence, or a degenerate coding sequence; and

(xix) contiguous nucleotide positions 4300-4317 (of SEQ ID NO:1), a complementary sequence, or a degenerate coding sequence; and

(xx) contiguous nucleotide positions 4518-4535 (of SEQ ID NO:1), a complementary sequence, or a degenerate coding sequence; and

(xxi) contiguous nucleotide positions 4533-4550 (of SEQ ID NO:1), a complementary sequence, or a degenerate coding sequence; and

(xxii) contiguous nucleotide positions 6191-6208 (of SEQ ID NO:1), a complementary sequence, or a degenerate coding sequence; and

(xxiii) contiguous nucleotide positions 6116-6133 (of SEQ ID NO:1), a complementary sequence, or a degenerate coding sequence; and

(xxiv) contiguous nucleotide positions 6192-6209 (of SEQ ID NO:1), a complementary sequence, or a degenerate coding sequence; and

(xxv) contiguous nucleotide positions 7501-7518 (of SEQ ID NO:1), a complementary sequence, or a degenerate coding sequence; and

(xxvi) contiguous nucleotide positions 7517-7534 (of SEQ ID NO:1), a complementary sequence, or a degenerate coding sequence; and

(xxvii) contiguous nucleotide positions 4292-4549 (of SEQ ID NO:1), a complementary sequence, or a degenerate coding sequence.

In a second aspect the invention provides a nucleic acid construct, comprising the nucleic acid of the first aspect.

In a third aspect the invention provides an expression vector, comprising the nucleic acid construct of the second aspect.

In a fourth aspect the invention provides a cloning vector, comprising the nucleic acid construct of the second aspect.

In a fifth aspect the invention provides a host cell, comprising the expression vector of the third aspect or the cloning vector of the fourth aspect.

In a sixth aspect the invention provides an isolated *Cryptovirus* protein encoded by a nucleic acid segment comprising:

(A) contiguous nucleotide positions 152-1678 of (SEQ ID NO: 1) or a degenerate sequence;

(B) contiguous nucleotide positions 1850-2515 of (SEQ ID NO: 1) or a degenerate sequence.

(C) contiguous nucleotide positions 1850-3023 of (SEQ ID NO: 1) combined with a further insertion of two guanine residues between nucleotide position 2339 of (SEQ ID NO: 1) and a nucleotide position 2340 of (SEQ ID NO: 1), or a degenerate sequence.

(D) contiguous nucleotide positions 3141-4271 of (SEQ ID NO: 1) or a degenerate sequence.

(E) contiguous nucleotide positions 4530-6182 of (SEQ ID NO: 1) or a degenerate sequence.

(F) contiguous nucleotide positions 4587-6182 of (SEQ ID NO: 1) or a degenerate sequence.

(G) contiguous nucleotide positions 4587-4835 (SEQ ID NO: 1) or a degenerate sequence.

(H) contiguous nucleotide positions 4836-6182 of (SEQ ID NO: 1) or a degenerate sequence.

(I) contiguous nucleotide positions 6303-6434 of (SEQ ID NO: 1) or a degenerate sequence.

(J) contiguous nucleotide positions 6584-8278 of (SEQ ID NO: 1) or a degenerate sequence.

(K) contiguous nucleotide positions 8414-15178 of (SEQ ID NO: 1) or a degenerate sequence.

In a seventh aspect embodiment the invention provides a chimeric protein, comprising a *Cryptovirus* protein encoded by a nucleic acid segment comprising:

(A) contiguous nucleotide positions 152-1678 of (SEQ ID NO: 1) or a degenerate sequence.

(B) contiguous nucleotide positions 1850-2515 of (SEQ ID NO: 1) or a degenerate sequence.

(C) contiguous nucleotide positions 1850-3023 of (SEQ ID NO: 1) combined with a further insertion of two guanine residues into the nucleotide sequence between nucleotide position 2339 of (SEQ ID NO: 1) and a nucleotide position 2340 of (SEQ ID NO: 1), or a degenerate sequence.

(D) contiguous nucleotide positions 3141-4271 of (SEQ ID NO: 1) or a degenerate sequence.

(E) contiguous nucleotide positions 4530-6182 of (SEQ ID NO: 1) or a degenerate sequence.

(F) contiguous nucleotide positions 4587-6182 of (SEQ ID NO: 1) or a degenerate sequence.

(G) contiguous nucleotide positions 4587-4835 (SEQ ID NO: 1) or a degenerate sequence.

(H) contiguous nucleotide positions 4836-6182 of (SEQ ID NO: 1) or a degenerate sequence.

(I) contiguous nucleotide positions 6303-6434 of (SEQ ID NO: 1) or a degenerate sequence.

(J) contiguous nucleotide positions 6584-8278 of (SEQ ID NO: 1) or a degenerate sequence.

(K) contiguous nucleotide positions 8414-15178 of (SEQ ID NO: 1) or a degenerate sequence.

In one embodiment of the chimeric protein the *Cryptovirus* protein is a *Cryptovirus* envelope protein encoded by a nucleic acid segment comprising (E), (F), (G), (H), (I) or (J).

In an eighth aspect the invention provides use of the protein of the sixth or seventh aspect in producing a *Cryptovirus*-specific antibody.

In a ninth aspect the invention provides an isolated antibody that specifically binds the protein of the sixth or seventh aspect.

In one embodiment of the ninth aspect of the invention the antibody is polyclonal.

In one embodiment of the ninth aspect of the invention the antibody is monoclonal.

In one embodiment of the ninth aspect of the invention the antibody is chimeric.

In a tenth aspect the invention provides use of the antibody of the ninth aspect in manufacturing a medicament for the treatment of *Cryptovirus* infections.

In an eleventh aspect the invention provides an isolated viral particle comprising the nucleic acid of the first aspect.

In a twelfth aspect the invention provides an isolated *Cryptovirus* particle, comprising a genome having a nucleotide sequence entirely complementary to (SEQ ID NO: 1).

In a thirteenth aspect the invention provides a composition of matter, comprising the nucleic acid of the first aspect, the protein of the sixth or seventh aspect, the antibody of the ninth aspect or the virion of the eleventh aspect, and a carrier.

In a fourteenth aspect the invention provides an isolated viral particle comprising the protein of the sixth or seventh aspect.

In a fifteenth aspect the invention provides use of the nucleic acid of the first aspect, the nucleic acid construct of the second aspect, the protein of the sixth or seventh aspect, the viral particle of the ninth or eleventh aspect or the isolated *Cryptovirus* particle of the twelfth or fourteenth aspect in manufacturing a vaccine.

In one embodiment of the fifteenth aspect the viral particle is an attenuated virion.

In one embodiment of the fifteenth aspect of the viral particle is a killed viron.

In a sixteenth aspect the invention provides an isolated *Cryptovirus* particle, wherein the *Cryptovirus* is Strain BBR.

In a seventeenth aspect the invention provides a probe or primer comprising the nucleic acid of the first aspect.

In an eighteenth aspect the invention provides a method of detecting the presence or absence of a *Cryptovirus* protein in a sample of a biological material, comprising:

contacting the sample of the biological material with the antibody of the invention; and

detecting specific binding of the antibody to a constituent of the sample, wherein the presence of specific binding indicates the presence of the *Cryptovirus* protein in the sample.

In a nineteenth aspect invention provides a method of detecting the presence or absence of a *Cryptovirus*-specific RNA in a sample of a biological material, comprising:

obtaining a sample of a biological material comprising RNA;

contacting the sample with the probe of the invention under at least moderately stringent hybridization conditions, wherein the formation of detectable hybridization products indicates the presence of the *Cryptovirus*-specific RNA in the sample.

In a twentieth aspect the invention provides a method of detecting the presence or absence of a *Cryptovirus*-specific RNA in a sample of a biological material, comprising:

obtaining a sample of a biological material comprising RNA;

amplifying *Cryptovirus*-specific RNA in the sample using at least one primer of the invention in an amplification reaction mixture;

then detecting the presence or absence of *Cryptovirus*-specific nucleic acid amplification products in the amplification reaction mixture, wherein the presence of the amplification products in the reaction mixture indicates the presence of *Cryptovirus* RNA in the sample.

In one embodiment of the eighteenth, nineteenth or twentieth aspect the biological material is a cellular material.

In one embodiment of the eighteenth, nineteenth or twentieth aspect the biological material is blood or serum.

In one embodiment of the eighteenth, nineteenth or twentieth aspect the biological material is cerebrospinal fluid.

In one embodiment of the eighteenth, nineteenth or twentieth aspect the biological material is lymphoid tissue.

In one embodiment of the eighteenth, nineteenth or twentieth aspect the biological material is nervous tissue. In one embodiment the nervous tissue is brain tissue.

In a twentyfirst aspect the invention provides a method of detecting the presence or absence of a *Cryptovirus*-specific antibody in a sample of a biological material, comprising:

contacting the sample with the protein according to the invention;

allowing the formation of a specific protein-antibody complex;

detecting the presence of the specific protein-antibody complex, wherein the presence of a specific protein-antibody complex indicates the presence of the *Cryptovirus*-specific antibody in the sample.

In a twentysecond aspect the invention provides a method of detecting the presence or absence of a *Cryptovirus*-specific antibody in a sample of a biological material, comprising:

contacting the sample with the protein of the invention;

allowing the formation of a specific protein-antibody complex;

detecting the presence of the specific protein-antibody complex, wherein the presence of a specific protein-antibody complex indicates the presence of the *Cryptovirus*-specific antibody in the sample.

In a twentythird aspect the invention provides an assay method for detecting the presence or absence of an antibody that selective binds *Cryptovirus* in a sample of an antibody-containing biological material originating from a human, comprising:

contacting the sample, the sample originating from an individual suspected of having a *Cryptovirus* infection, with the envelope protein of the invention such that if antibody selectively binding *Cryptovirus* is present, an antibody-bound envelope protein complex forms;

contacting any antibody-bound protein complexes thus formed with an anti-human-antibody binding antibody, and allowing the formation of complexes of the antibody, with the antibody-bound envelope protein complexes; and

detecting the presence or absence of any antibody-bound envelope protein complexes thus formed, the presence of such complexes indicating the presence in the sample of antibody selectively binding *Cryptovirus*.

In a twentyfourth aspect the invention provides an assay method for detecting the presence or absence of antibody that selectively binds *Cryptovirus* antigen in a sample of an antibody-containing biological material originating from a human, the method comprising:

contacting the sample, the sample originating from an individual suspected of having a *Cryptovirus* infection, with the viral particle of the invention, such that, if antibody selectively binding *Cryptovirus* antigen is present, an antibody-bound virus complex forms;

contacting any antibody-bound virus complexes thus formed with anti-human antibody-binding antibody, and allowing the formation of complexes of the anti-human antibody-binding antibody with the antibody-bound virus complexes; and

detecting the presence or absence of any complexes formed, the presence of such complexes indicating the presence in the sample of antibody selectively binding *Cryptovirus* antigen.

In a twentyfifth aspect the invention provides a method of detecting a *Cryptovirus* infection in a mammal, comprising:

obtaining a sample of a biological material from the mammal; and

performing the method of the eighteenth, nineteenth, twentieth, twentyfirst, twentysecond, twentythird or tentyfourth aspect using the sample, whereby detecting the presence of the *Cryptovirus* protein, *Cryptovirus*-specific RNA, and/or *Cryptovirus*-specific antibody in the sample indicates a *Cryptovirus* infection in the mammal.

In one embodiment of the twenty first, twentysecond, twentythird, twentyfourth or twentyfifth aspect the biological material is a cellular material.

In one embodiment of the twenty first, twentysecond, twentythird, twentyfourth or twentyfifth aspect the biological material is blood or serum.

In one embodiment of the twenty first, twentysecond, twentythird, twentyfourth or twentyfifth aspect the biological material is cerebrospinal fluid.

In one embodiment of the twenty first, twentysecond, twentythird, twentyfourth or twentyfifth aspect the biological material is lympohoid tissue.

In one embodiment of the twenty first, twentysecond, twentythird, twentyfourth or twentyfifth aspect the biological material is nervous tissue. In one embodiment the nervous tissue is brain tissue.

In one embodiment of the twentyfifth aspect the mammal is a human. In one embodiment the human has a neurological, neurodegenerative, and/or neuropsychiatric disease. In one embodiment the human has a primary tracheobronchial and/or lymphadenopathy-associated illness.

In a twentysixth aspect the invention provides a method of isolating a *Cryptovirus* virion, comprising:

(a) culturing a plurality of peripheral blood mononuclear cells that have been obtained from a human having a *Cryptovirus* infection, in an artificial aqueous medium comprising an agent that increases cellular guanylyl cyclase activity;

(b) co-culturing the plurality of peripheral blood mononuclear cells with a plurality of mammalian amnion cells in fresh artificial aqueous medium comprising an agent that increases cellular guanylyl cylase activity;

(c) passaging the peripheral blood mononuclear cells with the mammalian amnion cells in co-culture;

(d) co-cultivating a plurality of mammalian epithelial cells together with the peripheral blood mononuclear cells and the mammalian amnion cells in fresh artificial aqueous medium comprising an agent that increases cellular guanylyl cyclase activity; and

(e) separating a supernatant of the aqueous medium from the cells, to obtain a *Cryptovirus* virion in the supernatant.

In a twentyseventh aspect the invention provides a method of propagating a *Cryptovirus*, comprising:

(a) exposing a plurality of mammalian epithelial cells to a plurality of cell-free *Cryptovirus* virions, said *Cryptovirus* virions having been isolated by the method of the invention; and

(b) further cultivating the mammalian epithelial cells, thus virion-exposed, in an artificial aqueous medium comprising an agent that increases the activity of cellular guanylyl cyclase.

In a twentyeighth aspect the invention provides a method of producing a mammalian cell line non-productively infected with *Cryptovirus*, comprising:

(a) co-culturing peripheral blood mononuclear cells that have been obtained from a human having a *Cryptovirus* infection, with mammalian amnion cells, in an artificial aqueous medium comprising an agent that increases cellular guanylyl cyclase activity, such that the mammalian amnion cells become non-productively infected by *Cryptovirus*; and

(b) passaging the non-productively infected mammalian amnion cells with the peripheral blood mononuclear cells, whereby the co-culture becomes a monoculture of the non-productively infected mammalian amnion cells.

In one embodiment of the twentysixth, twentyseventh or twentyeighth aspect the mammalian amnion cells are human amnion cells. In one embodiment the human amnion cells are AV_3 cells.

In one embodiment of the twentysixth, twentyseventh or twentyeighth aspect the mammalian epithelial cells are simian epithelial cells selected from the group consisting of Vero or CV-1 cells. In one embodiment the CV-1 cells are subline CV-1 cells.

In one embodiment of the twentysixth, twentyseventh or twentyeighth aspect the agent that increases cellular guanylyl cyclase activity is cyclic GMP, insulin, zinc

dication, or a combination of any of these. In one embodiment the cyclic GMP is in a concentration of about 0.05 to about 5mM in the artificial aqueous medium.

In one embodiment of the twentyseventh, twentyeighth or twentyninth aspect the agent that increases cellular guanylyl cyclase activity is nitric oxide or a nitric oxide donor selected from the group consisting of organic nitrate compounds, iron nitrosyl compounds, S-nitrosothiol compounds, sydnonimine compounds, and nonoate compounds.

In one embodiment of the twentyseventh, twentyeighth or twentyninth aspect the aqueous medium further comprises glutamine.

In a thirtieth aspect the invention provides a method of producing a mammalian epithelial cell line acutely infected with *Cryptovirus*, comprising the method of the invention.

In a thirtyfirst aspect the invention provides a mammalian epithelial cell acutely infected with *Cryptovirus*, said cell being produced by the method of the invention.

In a thirtysecond aspect the invention provides a cell non-productively infected with *Cryptovirus,* wherein said cell is produced in accordance with a method of the invention.

In a thirtythird aspect the invention provides an *in vitro* method of screening a potential antiviral therapeutic agent, comprising:

(a) culturing a mammalian epithelial cell acutely infected with *Cryptovirus* of the invention;

(b) exposing the cells to the potential antiviral therapeutic agent; and

(c) measuring the effect of the agent on *Cryptovirus* replication and/or *Cryptovirus* virion assembly, wherein inhibition of *Cryptovirus* replication and/or *Cryptovirus* virion assembly relative to a control indicates antiviral activity of the potential therapeutic agent.

In a thirtyfourth aspect the invention provides an *in vitro* method of screening a potential antiviral therapeutic agent, comprising:

(a) culturing a cell non-productively infected with *Cryptovirus* of the invention;

(b) exposing the cells to the potential antiviral therapeutic agent; and

(c) measuring the effect of the agent on *Cryptovirus* replication, *Cryptovirus* genome replication, and/or *Cryptovirus*-specific wherein inhibition of *Cryptovirus* replication, *Cryptovirus* genome replication, and/or *Cryptovirus*-specific relative to a control, indicates antiviral activity of the potential therapeutic agent

In a thirtyfourth aspect the invention provides an animal model for the study of human diseases, comprising a non-human mammal, said non-human mammal having been artificially inoculated with an infectious cell-free *Cryptovirus* having a genome comprising a single stranded RNA complementary to (SEQ ID NO: 1), or having been inoculated with a cell non-productively-infected with the *Cryptovirus*, whereby the non-human mammal exhibits at least one symptom characteristic of a human disease after being thus inoculated, said symptom not being previously exhibited by the non-human mammal.

In one embodiment of the thirtyfourth aspect the non-human mammal is a rodent or lagomorph.

In one embodiment of the thirtyfourth aspect the non-human mammal is a non-human primate.

In one embodiment of the thirtyfourth aspect the human disease is a neurological, neurodegenerative, and/neuropsychiatric disease.

In a thirtyfifth aspect the invention provides an in vivo method of screening a potential therapeutic agent, comprising:

(a) administering the potential therapeutic agent to be screened to the animal model of the invention, wherein the non-human mammal exhibits, before administration of the potential therapeutic agent, at least one symptom characteristic of a human disease; and

(b) detecting the present or absence of a beneficial antiviral effect of the potential therapeutic agent, wherein the presence of a beneficial antiviral effect indicates activity of the potential therapeutic agent.

In a thirtysixth aspect the invention provides an in vivo method of screening a potential prophylactic agent, comprising:

(a) administering the potential prophylactic agent to be screened, to a non-human mammal not previously having a symptom of a human disease;

(b) inoculating the non-human mammal with an infectious cell-free *Cryptovirus* having a genome comprising a single stranded RNA complementary to (SEQ ID NO: 1), or with a mammalian cell non-productively-infected with the *Cryptovirus*; and

(c) detecting the subsequent presence or absence in the non-human mammal of a beneficial antiviral effect, whereby the presence of a beneficial antiviral effect in the inoculated non-human mammal indicates activity of the potential prophylactic agent.

In one embodiment of the thirtysixth aspect the potential prophylactic agent is an immunoprophylactic agent.

In one embodiment of the thirtyfifth or thirtysixth aspect the non-human mammal is a rodent or a lagomorph.

In one embodiment of the thirtyfifth or thirtysixth aspect the non-human mammal is a non-human primate.

In one embodiment of the thirtyfifth or thirtysixth aspect the human disease is a neurological, neurodegenerative, and/or neuropsychiatric disease.

In a thirtyseventh aspect the invention provides an anti-*Cryptovirus* antibody detecting kit, comprising:

the *Cryptovirus* particle of the invention; and

a labelled anti-human antibody-binding antibody.

In one embodiment of the thirtyseventh aspect the kit further comprises a solid matrix for supporting said *Cryptovirus* particle.

In thirtyeighth aspect the invention provides an anti-*Cryptovirus* antibody detecting kit, comprising:

the protein according to the invention; and

a labeled anti-human antibody- binding antibody.

In one embodiment of the thirtyeighth aspect the kit further comprises a solid matrix for supporting said protein.

Other features, objects, and advantages of the invention will be apparent from the accompanying drawings and the detailed description of the preferred embodiments hereinbelow.

BRIEF DESCRIPTION OF THE DRAWINGS

Fig. 1 is a chart showing the taxonomic assignment of the human *Cryptovirus* of the present invention to the genus Rubulavirus of the Paramyxoviridae.

Fig. 2 is a phylogenetic tree, modified from the version appearing in Collins *et al.* (Chapter 41, page 1206, *Parainfluenza Viruses*, in *Virology*, 3rd Ed., Fields, Knipe, and Howley, Eds., Lippincott-Raven, Philadelphia, 1996). The modified tree emphasizes the clustering of three Rubulavirus species (Porcine *Rubulavirus*; Canine Parainfluenza Virus Type 2; and the human *Cryptovirus* of the present invention) as distinct from the prototype Rubulavirus Simian Virus 5.

Fig. 3 is a representation of the genetic maps of typical members of each genus of the family Paramyxoviridae. The gene size is drawn to scale. Vertical lines demark

gene boundaries. The pneumovirus L gene transcription overlaps that of the 22K (M2) gene and is thus shown in a staggered format. This overlap configuration is seen in human and animal viruses, but not in other pneumoviruses (Lamb and Kolakofsky, Chapter 40, page 1181, *The Viruses and Their Replication,* in *Virology, supra*).

Fig. 4 is a representation of revised Rubulavirus genetic maps, which distinguish Simian Virus 5 from a cluster of related viruses that demonstrate neurotropism and encode an additional 22 amino acid "tail" at the carboxy terminus of their fusion proteins i. e., the "neurotropic species" of human *Cryptovirus*, Canine Parainfluenza Type 2, and Porcine *Rubulavirus)*. The fusion (F) proteins of each neurotropic virus species are more closely related to each other than they are to the fusion protein of Simian Virus 5 (see Fig. 10).

Fig. 5 shows a schematic and comparative autoradiograms of the [^{35}S]-methionine labeled proteins of gradient-purified human *Cryptovirus* (Strain BBR) and Simian Virus 5 (*NIH 21005-2WR* strain) following SDS-PAGE on 10% acrylamide Laemmli slab gels under reducing conditions.

Fig. 6 is a collage of matched sets of fluorescent photomicrographs taken of various SSPE-derived nonproductively infected cell cultures following direct double labeling with rhodamine isothiocyanate-labeled goat anti-measles virus serum (Panels A, C, E, G and I) and rabbit anti-*Cryptovirus* serum, then followed with fluorescein isothiocyanate-labeled goat anti-rabbit IgG (Panels B, D, F, H and J). Panels A and B represent AV_3/SSPE/MV cells persistently-infected with *Cryptovirus* and also infected with the Edmonston strain of measles virus before being passaged onto coverslips for these immunofluorescent studies; Panels C and D represent the nonproductive SSPE-derived cell line designated "Kitaken" (Ueda *et al., Biken Journal* 18:179-181, 1975); Panels E and F represent the nonproductive SSPE-derived cell line designated "Niigata" (Doi *et al., Japan. J. Med. Sci. Biol.* 25:321-333, 1972); Panels G and H and I and J, respectively, represent the nonproductive SSPE-derived cell line designated "Biken" (Yamanouchi *et al., Japan. J. Med. Sci. Biol.* 29:177-186, 1976; Ohuchi *et al., Microbiol. Immunol.* 25:887-983, 1981).

Fig. 7 shows photographs of two male Colored mice, born of the same litter, two months after neonatal (two days after birth) intracerebral inoculation with plaque-purified *Cryptovirus* (strain BBR; Fig. 7A) or with the NIH 21005-2WR strain of Simian Virus 5 (SV5; Fig. 7B).

Fig. 8 shows photographs of two female Colored mice, born of the same litter, three months after neonatal (two days after birth) intracerebral inoculation with plaque-purified Cryptovirus (strain BBR; Fig. 8A) and six months after neonatal (two days after birth) intracerebral inoculation with plaque-purified Cryptovirus (Fig. 8B).

Fig. 9 is a comparison of the FASTA formatted (i.e., mRNA sense: 5' to 3') sequence of human *Cryptovirus Strain BBR* (SEQ ID NO:1) and Simian Virus 5 *Strain W3A* (SEQ ID NO:2). The number of variations from (SEQ ID NO:1) in each line of (SEQ. ID.NO:2) is tallied in the right-hand margin. The *Cryptovirus*-specific nucleotide positions that differ from the sequence of SV5 are in bold underlined type; if the difference is in a coding region, the relevant amino acid encoded is printed above the codon of the *Cryptovirus* nucleotide sequence, and if the different *Cryptovirus* nucleotide results in a codon encoding a different amino acid than the SV5 codon in the analogous position, an arrow leads from the SV5 amino acid to the different amino acid in the analogous *Cryptovirus* protein. Boxed nucleotides indicate known SV5 and analogous *Cryptovirus* start or stop sites, as indicated.

Fig. 10 is a comparison of Rubulavirus F Protein nucleotide (Fig. 10A; comparison of the FASTA formatted, i.e., mRNA sense: 5' to 3' sequence) and encoded amino acid (Fig. 10B) sequences. The first line (uppermost) represents an embodiment of the sequence of an inventive

Cryptovirus F protein ("CV" [*Strain BBR*]); the second line represents Canine Parainfluenza Virus Type 2 ("CPV" [*Strain T1*]; see Ito *et al., J. Gen. Virol.* 81 719-727, 2000); the third line represents Porcine Rubulavirus ("PR"; Klenk and Klenk, *Direct Submission to EMBL / GenBank Databases,* September 2000, GenBank Accession AJ278916); the fourth line represents Simian Virus 5 ("W3A" [*Strain W3A*]; Paterson *et al., Proc. Natl. Acad. Sci. USA* 81:6706-6710, 1984); and the fifth (bottom) line represents Simian Virus 5 ("WR" [*Strain WR*]; Ito *et al., J. Virol.* 71:9855-9858, 1997). Amino acids that are bold and underlined denote amino acids that differ from those in the analogous sequence of the Cryptovirus F protein, and the tallies in the right margin are the number of differences for each sequence block.

Fig. 11 demonstrates expression of *Cryptovirus* proteins. Fig. 11 is a photograph of an autoradiogram of gradient-purified [^{35}S]-methionine-labeled *Cryptovirus* virions produced in acutely-infected Vero cells after SDS-PAGE under reducing conditions. The approximate molecular weights of the proteins indicated on the right side of Fig. 12A were calculated by comparing their migrations to marker proteins of known molecular weight (Sigma Biochemicals). L = the largest nucleocapsid associated protein, the major component of the virion-associated RNA dependent RNA polymerase; HN = the hemagglutinin protein, one of the envelope-associated glycoproteins; F_O = the uncleaved fusion protein, a second envelope-associated glycoprotein; NP = the nucleocapsid protein, the major structural protein associated with the nucleocapsid; F_1 = the larger fragment of the cleaved fusion protein; P = the nucleocapsid associated phosphoprotein; M = the virion-associated matrix or membrane protein; V = a minor RNA binding protein thought to be a component of the viral polymerase; F_2 = the smaller fragment of the cleaved fusion protein. Note: the SH protein (about 5 kD), a small envelope-associated protein, ran off the gel and is not shown. Fig. 12 shows photographs of autoradiograms of typical radioimmunoassay profiles (RIPs) obtained by the precipitation and SDS-PAGE separation of [^{35}S]-methionine-labeled virus-specific proteins using the cerebrospinal fluids (CSFs) of a patient diagnosed with subacute sclerosing panencephalitis (Fig. 12A) and the CSFs of six randomly-selected neurology/ neurosurgery patients who had CSF taken for microbiological screening (Fig. 12B). Fig. 12A shows the RIPs resulting from the precipitation of [^{35}S]-methionine-labeled CV-1_C cells acutely-infected with the Edmonston strain of measles virus (Lane MV), identically-labeled CV-1_C cells acutely-infected with the BBR strain of *Cryptovirus* (Lane CV) or a mixture of both (Lane B) by the CSF of an 11 year male SSPE patient. Lane V represents a SDS-PAGE profile of [^{35}S]-methionine-labeled gradient purified *Cryptovirus* virions (see also Fig. 11). Fig. 12B shows the RIPs resulting from the precipitation of proteins from [^{35}S]-methionine-labeled CV-1_C cells acutely-infected with the BBR strain of *Cryptovirus* by the CSFs of

six neurology/neurosurgery patients. The patient whose RIP profile appears in Lane 2 was an adult male who had presented with ataxia, confusion and memory loss and had not been given a specific diagnosis. The patient whose RIP profile appears in Lane 4 was an infant female who presented with hydrocephalus and intractable seizures and subsequently died in *status epilepticus*. None of the CSFs from the patients in Fig. 12B precipitated any of the envelope proteins of measles virus (data not shown). Fig. 12A is the same as Fig. 23 (described below), but is reduced to the same scale as Fig. 12B for the purpose of comparison.

Fig. 13 shows a higher resolution autoradiogram of the radioimmunoassay profiles (RIPs) of the *Cryptovirus*-specific proteins precipitated from [^{35}S]-methionine-labeled CV-1$_C$ cells acutely-infected with the BBR strain of *Cryptovirus* by two CSF specimens (Fig. 13A) and a schematic showing the migration of the major corresponding structural proteins of gradient-purified virions of the BBR strain of *Cryptovirus* (Fig. 13B Lane CV) and the NIH 21005-WR strain of SV5 (Fig. 13B Lane SV5). The RIPs in Fig. 13A represent CSF precipitates from patients assessed as *Cryptovirus*-negative (Lane "–"; i.e. not containing *Cryptovirus*-specific antibodies) and *Cryptovirus*-positive (Lane "+" ; i.e. containing *Cryptovirus*-specific antibodies). Fig. 13B is a schematic showing the near co-migration of the F_0 and HN proteins of *Cryptovirus* and their separate migration in Simian Virus 5 (see also SDS-PAGE profiles in Fig. 5).

Fig. 14 shows an ELISA of matched serum and CSF specimens from four seropositive neurology/neurosurgery patients using gradient-purified *Cryptovirus* virions as the target. Control sera were rabbit antisera generated against mock-infected CV-1$_C$ cells (column 1; "-") and hyperimmune rabbit antisera generated against gradient-purified *Cryptovirus* virions (column 2; "+"). FN = infant female diagnosed with hydrocephalus and intractable seizures; SG = adult female diagnosed with idiopathic intracranial hypertension; WK = male child diagnosed with acute viral meningitis; JK = adult male having an undetermined diagnosis. Serum dilutions began at 1:20 (in the top rows) and proceeded by 2-fold serial dilution to the bottom. CSF dilutions began at 1:2, at the top, before proceeding likewise. Serum specimens were aliquoted from left to right while CSF specimens were aliquoted from right to left. Note that although all of the patients had *Cryptovirus*-specific antibodies in their serum, only the patient with a seizure disorder (FN) had such antibodies in her CSF.

Fig. 15 is a photograph of RIP assays using three sets of matched serum (S) and CSF (C) samples from patients diagnosed with Alzheimer's disease.

Fig. 16 is a photograph of an autoradiogram following an RIP analysis using four CSF specimens from patients diagnosed with chronic fatigue syndrome (CFS). Lanes 1-3 were assessed as "*Cryptovirus* positive"; Lane 4 assessed as "*Cryptovirus* negative".

Fig. 17 is a photograph of an autoradiogram following an RIP analysis using CSF samples obtained as "Collection 1" (see hereinbelow). The positive CSF precipitate in Lane 2 was subsequently found to have been obtained from a 55 year-old adult male who presented with ataxia, memory loss, blackouts, seizures, diplopia, and headaches.

Fig. 18 is a photograph of an autoradiogram following a RIP analysis using CSF samples obtained as "Collection 2" (see hereinbelow).

Fig. 19 is a photograph of an autoradiogram following an RIP assay conducted with serum samples obtained from 5 MS patients (out of the 38 samples obtained).

Fig. 20 is a photograph of an autoradiogram following an RIP assay conducted with serum samples from an 25 additional MS patients (out of the 38 samples obtained).

Fig. 21 is a photograph of an autoradiogram following an RIP assay conducted with 16 CSF specimens obtained from 16 MS patients.

Fig. 22 is a photograph of an autoradiogram obtained following creation of RIP profiles of the *Cryptovirus* NP protein (p63) precipitated from [^{35}S]-methionine-labeled AV_3/SSPE cells by the sera of six Australian SSPE patients (Lanes 1-6) and six control sera (Lanes 7-12; sera from pediatric patients without antibodies to the *Cryptovirus* major envelope proteins (F_0 and HN).

Fig. 23 is a photograph of an autoradiogram of RIP profiles of measles virus-specific proteins or *Cryptovirus*-specific proteins precipitated from [^{35}S]-methionine-labeled measles virus-infected CV-1_C cells (Lane MV), *Cryptovirus*-infected CV-1_C cells (Lane CV) or a mixture of both (Lane B) by CSF from an 11 year old male diagnosed with SSPE. Lane V = gradient-purified *Cryptovirus* virions from [^{35}S]-methionine-labeled *Cryptovirus*-infected CV-1_C cells. L = the largest nucleocapsid associated protein, the major component of the virion-associated RNA dependent RNA polymerase; HN = the hemagglutinin protein, one of the envelope-associated glycoproteins; F_O = the uncleaved fusion protein, a second envelope-associated glycoprotein; NP = the nucleocapsid protein, the major structural protein associated with the nucleocapsid; F_1 = the larger fragment of the cleaved fusion protein; P = the nucleocapsid associated phosphoprotein; M = the virion-associated matrix or membrane protein; V = a minor RNA binding protein thought to be a component of the viral

polymerase; F_2 = the smaller fragment of the cleaved fusion protein. Note: the SH protein (about 5 kD), a small envelope-associated protein, ran off the gel and is not shown.

Fig. 24 shows photomicrographs of *Cryptovirus*-infected neurons. Fig. 24A demonstrates *Cryptovirus*-specific immunofluorescence in a single neuron in the brain of a Colored mouse inoculated when two days old with *Cryptovirus Strain BBR* (sacrificed 2 months post inoculation after presenting with seizures). Fig. 24B demonstrates cytoplasmic immunofluorescence in a single neuron from the brain of a guinea pig presenting with a subacute encephalopathy after inoculation with the Niigata-1 strain of SSPE-derived cell-associated virus (detected by an indirect fluorescent antibody technique using SSPE serum)(Doi *et al.*, *Japan. J. Med. Sci. Biol.* 25:321-333, 1972).

Fig. 25 shows photomicrographs of differential immunogold-labeling of the intracellular nucleocapsids of *Cryptovirus* and measles virus in persistently-infected AV_3/SSPE/MV cells. Fig. 25A shows labeling of the about 15-nm to about 17-nm "smooth" and narrow nucleocapsids of *Cryptovirus* with 10-nm gold beads. The etching technique used results in a loss of resolution of the fine structure of the smooth nucleocapsids making the herringbone pattern somewhat difficult to see. Fig. 25B shows labeling of the 25-nm "fuzzy" and wide nucleocapsids of measles virus with 15-nm gold beads. Magnification is approximately 500,000X.

DETAILED DESCRIPTION OF THE PREFERRED EMBODIMENTS

The novel virus described herein has been designated a *Cryptovirus* (CV) on the basis of its inapparent, or "cryptic," cytopathology in cultured human cells and its slow and "encrypted" pathogenesis in experimentally infected animals. Given the nucleotide sequence present in the virus, and its structural, biological, and pathogenetic characteristics, *Cryptovirus* fits best within the *Rubulavirus* genus of the family Paramyxoviridae (Fig. 1). More specifically, this virus most closely resembles the viruses known as Canine Parainfluenza Virus Type 2 (which is also known as Canine Parainfluenza Virus, CPI and CPIV) and Porcine Rubulavirus (which is also known as La-Piedad-Michoacan-Mexico Virus and LPMV). (see Fig. 2). The relationships between *Cryptovirus* and these two viruses can be seen in the relationships between their sequences and their structural, biological, and pathogenetic characteristics (see Fig. 3). CPIV shares more than 95% of its nucleotide sequence with *Cryptovirus*. The extent of Menangle virus nucleotide sequence homology with *Cryptovirus* is presently unknown as the sequence of the Menangle virus genome has not yet been published.

There is also an apparent relationship between *Cryptovirus* and: (1) simian parainfluenza virus type 5 (which is also known as simian virus 5 and SV5; see Fig. 4, Fig. 5, Fig. 9, and Fig. 10; here, there is a relationship between the sequences and structural and immunological properties of the

viruses but little or no biological or pathogenetic similarity); (2) human mumps virus (here, there are certain structural, biological, and pathogenetic relationships); and (3) human measles virus (here again, there are certain structural, biological and pathogenetic relationships). These relationships help to classify *Cryptovirus* and to establish its novelty.

In addition to having a role in idiopathic and cryptogenic forms of epilepsy or epileptiform disease, i.e., an illness, disorder, or condition having epileptiform symptomology (e.g., CFS, MS, SSPE), *Cryptovirus* is also implicated in a spectrum of idiopathic disorders of the central nervous system (CNS) that present with compulsive or iterative physical, behavioral, or psychological symptoms. The manifestation of symptoms of these disorders as a consequence of *Cryptovirus* infection is exclusively subacute or slow in nature taking weeks, months, or even years to develop. The spectrum of physical symptoms that have been presented by human patients that have been infected with *Cryptovirus* includes febrile response, opthalmological disorders (photosensitivity, blurred vision, nystagmus, loss of vision) parathesias, paralysis, tremor, myoclonus, and *grand mal* and *petit mal* (absence) seizures. The spectrum of behavioral or psychological symptoms that have been presented by patients includes repetitive movements and compulsive behaviors (characteristic of obsessive compulsive disorder), sleep disturbances, memory loss, and dysophoria, anorexia nervosa, autism, mental retardation, affective disorder, dysthymia (clinical depression), schizophrenia, and bipolar disorder.

While not essential features of the present invention, the portal of entry for *Cryptovirus* infection can be the oral mucosa of the throat (*i.e.*, the tracheo-bronchial epithelium), and the virus' incubation period can be of subacute duration (*i.e.*, many days to weeks). Newly infected individuals can develop a febrile pharyngitis and lymphadenopathy of prolonged duration, not unlike infectious mononucleosis. Alternatively, it is thought that the portal of entry for the virus can also be transplacental, so that a mother carrying the virus can transmit it to her child *in utero*, and the child can subsequently develop a neurological, neurodegenerative, and/or neuropsychiatric disease or other developmental disorder (e.g., autism, cerebral palsy, hydrocephalus, birth defect, partial paralysis). Such a child is frequently diagnosed or labelled as "retarded". Indeed, the incidence of epilepsy and seizures are dramatically higher in the severely "mentally-retarded" (as much as 50-fold higher than the general population).

The nucleotide sequence of the human *Cryptovirus* genome (15,246 contiguous nucleotides), in FASTA format (*i.e.*, mRNA sense; 5' to 3'), is shown in Fig. 9 (SEQ ID NO:1). The actual genome of the virus is negative-stranded (antisense to mRNA), having a nucleotide sequence entirely complementary to (SEQ ID NO:1).

Accordingly, the present invention encompasses an isolated human negative-stranded RNA virus that, in FASTA format (*i.e.* in positive-stranded, mRNA-sense, the reverse and complementary sequence to the actual genome), has the sequence of SEQ ID NO:1. In Fig. 9, nucleotides that vary from those of the W3A strain of Simian Virus 5 are highlighted and the number of variations in each line is tallied in the right margin. The FASTA formatted sequence of human Cryptovirus *Strain BBR* was compared to Simian Virus 5 *Strain W3A* (SEQ ID NO:2; see Fig. 9). Comparisons between various Rubulavirus F Protein amino acid sequences have also been made (Fig 10).

A *Cryptovirus* "particle" is an entire *Cryptovirus* virion, as well as encompassing particles which are intermediates in virion formation (e.g., nucleocapsids), or otherwise partial. *Cryptovirus* particles generally have one or more *Cryptovirus* proteins associated with the *Cryptovirus*-specific nucleic acid they contain. A preferred *Cryptovirus* particle or virion is *Cryptovirus* Strain BBR, which is deposited as ATCC Accession No. PTA-4745.

The present invention also relates to a composition of matter comprising the inventive Cryptovirus particle and a carrier.

As used herein a "carrier" can be an organic or an inorganic carrier or excipient, such as water or an aqueous solution, or an emulsion such as an oil/water or water/oil emulsion, and various types of wetting agents. The active ingredient, such as the inventive viral particle, nucleic acid construct, protein, or antibody, can optionally be compounded in a composition formulated, for example, with non-toxic, physiologically acceptable carriers for infusions, tablets, pellets, capsules, solutions, emulsions, suspensions, or in any other formulation suitable for its intended in vitro or in vivo use. Such carriers also include glucose, lactose, gum acacia, gelatin, mannitol, starch paste, magnesium trisilicate, talc, corn starch, keratin, colloidal silica, potato starch, urea, medium chain length triglycerides, dextrans, normal saline, phosphate buffered saline and other carriers suitable for use in manufacturing preparations, in solid, semisolid, or liquid form. In addition auxiliary, stabilizing, thickening and coloring agents and perfumes can be used as appropriate. Other examples of suitable carriers are described hereinbelow, but any suitable carrier known in the art is intended.

In the inventive method of isolating the *Cryptovirus* virion, as described hereinabove, the PBMNCs that have been obtained from a human having a *Cryptovirus* infection are cultured in an artificial aqueous medium that includes, importantly, an agent that increases cellular guanylyl cyclase activity.

For purposes of the present invention, the artificial aqueous medium is made by adding the agent that increases cellular guanylyl cyclase activity to a known minimal cell culture medium, such as IMEMZO, MEM, HYQPF Vero (Hyclone), or RPMI, buffered (e.g., with HEPES) to pH 6.8-7.8

and most preferably to pH 6.8-7.2. The agent operates to permit and facilitate the isolation and/or propagation of Cryptovirus in accordance with the invention.

Optionally, fetal calf serum (about 2% v/v to about 10% v/v) is added to the medium. Antibiotics, such as penicillin or streptomycin, in conventional amounts, can also be added to the medium.

It is not essential to the present invention that cellular guanylyl cyclase activity actually be measured. In addition, the present invention is dependent neither upon any particular mechanism by which the agent may actually operate to increase cellular guanylyl cyclase activity (or not), nor upon any mechanism by which the agent operates to permit and/or facilitate the isolation and/or propagation of Cryptovirus in accordance with the invention.

Useful examples of the agent that increases cellular guanylyl cyclase activity include most preferably guanosine 3',5'-cyclic monophosphate ("cyclic GMP") (free acid, or preferably, a pharmaceutically acceptable salt thereof, such as a sodium, potassium, magnesium, calcium, or ammonium salt, or the like), insulin (preferably human insulin), zinc dication (preferably provided in a chloride, sulfate, carbonate, bicarbonate, nitrate, acetate, or other pharmaceutically acceptable salt thereof), or a combination of any or all of these.

Preferably, the cyclic GMP is used in a concentration of about 0.05 to about 5 mM in the artificial aqueous medium. More preferably, the cyclic GMP concentration in the medium is about 0.5 to about 2.5 mM, and most preferably about 0.75 mM to about 1.25 mM. A concentration above about 5 mM cyclic GMP is not optimally conducive to cultivating, propagating, or isolating *Cryptovirus*.

A preferred concentration range for insulin in the artificial aqueous medium is about 1 to about 10 mg/L, more preferably about 2 to about 6 mg/L, and most preferably about 3 to about 5 mg/L.

A preferred concentration range for zinc dication in the artificial aqueous medium is equivalent to about 0.05 to about 0.25 mg/L of $ZnSO_4 \cdot 7H_2O$, more preferably equivalent to about 0.10 to about 0.20 mg/L of $ZnSO_4 \cdot 7H_2O$, or most preferably equivalent to about 0.13 to about 0.15 mg/L of $ZnSO_4 \cdot 7H_2O$.

Alternatively, in some embodiments, the agent that increases cellular guanylyl cyclase activity is nitric oxide or a nitric oxide donor. Nitric oxide gas is fully permeable across biological membranes. Inhalable nitric oxide gas can be administered to a mammalian subject by, for example, a mask in a controlled gas mixture as is known in the art. (E.g., Kieler-Jensen, N. *et al.*, *Inhaled nitric oxide in the evaluation of heart transplant candidates with elevated pulmonary vascular*

resistance, J Heart Lung Transplant. 13(3):366-75 [1994]; Rajek, A. *et al.*, *Inhaled nitric oxide reduces pulmonary vascular resistance more than prostaglandin E(1) during heart transplantation*, Anesth Analg. 90(3):523-30 [2000]; Solina, A. *et al.*, *A comparison of inhaled nitric oxide and milrinone for the treatment of pulmonary hypertension in adult cardiac surgery patients*, J Cardiothorac Vasc. Anesth.14(1):12-17 [2000]; Fullerton, D.A. *et al.*, *Effective control of pulmonary vascular resistance with inhaled nitric oxide after cardiac operation*, J Thorac Cardiovasc Surg 111(4):753-62, discussion 762-3 [1996]). The concentration in the gas mixture of nitric oxide (NO) is preferably about 1 to 100 ppm NO, more preferably about 4 to 80 ppm NO, and most preferably about 20 to 40 ppm NO. The gas mixture also contains appropriate concentrations of oxygen and nitrogen and/or other inert gases, such as carbon dioxide, helium or argon.

Nitric oxide donors are compounds that produce NO-related physiological activity when applied to biological systems. Thus, NO-donors can mimic an endogenous NO-related response or substitute for an endogenous NO deficiency. The skilled artisan is aware that in biological systems there are at least three redox states of NO that can be released by various NO donors (NO^+, NO^0, or NO^-), all of which are encompassed by the terms "nitric oxide" or "NO" for purposes of the present invention. The redox state of NO makes a substantial difference to the NO donors reactivity towards other biomolecules, the profile of by-products, and the bioresponse (Feelisch, M., *The use of nitric oxide donors in pharmacological studies*, Naunyn-Schmiedebergs Arch. Pharmacol.358:113-22 [1998]). Some classes of NO donors require enzymatic catalysis, while others produce NO non-enzymatically; some NO donors require reduction, for example by thiols, and some oxidation, in order to release NO.

Preferred examples of nitric oxide donors include organic nitrate compounds, which are nitric acid esters of mono- and polyhydric alcohols. Typically, these have low water solubility, and stock solutions are prepared in ethanol or dimethyl sulfoxide (DMSO). Examples are glyceryl trinitrate (GTN) or nitroglycerin (NTG), pentaerythrityl tetranitrate (PETN), isosorbide dinitrate (ISDN), and isosorbide 5-mononitrate (IS-5-N). Administration of organic nitrates can be done intravenously, intraperitoneally, intramuscularly, transdermally, or in the case of PETN, ISDN, NTG, and IS-5-N, orally.

Other preferred examples of nitric oxide donors are S-nitrosothiol compounds, including S-nitroso-N-acetyl-D,L-penicillamine (SNAP), S-nitrosoglutathione (SNOG), S-nitrosoalbumin, S-nitrosocysteine. S-nitrosothiol compounds are particularly light-sensitive, but stock solutions kept on ice and in the dark are stable for several hours, and chelators such as EDTA can be added to stock

solutions to enhance stability. Administration is preferably by an intravenous or intra-arterial delivery route.

Other preferred examples of nitric oxide donors include sydnonimine compounds, such as molsidomine (N-ethoxycarbonyl-3-morpholino-sydnonimine), linsidomine (SIN-1; 3-morpholino-sydnonimine or 3-morpholinylsydnoneimine or 5-amino-3morpholinyl-1,2,3-oxadiazolium, e.g., chloride salt), and pirsidomine (CAS 936). Stock solutions are typically prepared in DMSO or DMF, and are stable at 4°C to room temperature, if protected from light. Linsidomine is highly water soluble and stable in acidic solution in deoxygenated distilled water, adjusted to about pH 5, for an entire day. At physiological pH, SIN-1 undergoes rapid non-enzymatic hydrolysis to the open ring form SIN-1A, also a preferred nitric oxide donor, which is stable at pH 7.4 in the dark. Administration is preferably by an intravenous or intra-arterial delivery route.

Also useful as nitric oxide donors are iron nitrosyl compounds, such as sodium nitroprusside (SNP; sodium pentacyanonitrosyl ferrate(II)). Aqueous stock solutions are preferably made freshly in deoxygenated water before use and kept in the dark; stability of stock solutions is enhanced at pH 3-5. Inclusion in the delivery buffer of a physiologically compatible thiol, such as glutathione, can enhance release of NO. SNP is administered by intravenous infusion, and the skilled practitioner is aware that long-term use is precluded by the release of five equivalents of toxic CN-per mole SNP as NO is released.

A most preferred nitric oxide donor is chosen from among the so-called NONOate compounds. The NONOates are adducts of NO with nucleophilic residues (X^-), such as an amine or sulfite group, in which an NO dimer is bound to the nucleophilic residue via a nitrogen atom to form a functional group of the structure $X[-N(O)NO]^-$. The NONOates typically release NO at predictable rates largely unaffected by biological reactants, and NO release is thought to be by acid-catalyzed dissociation with the regeneration of X^- and NO.

NONOates include most preferably diethylamine-NONOate (DEA/NO; N-Ethylethanamine:1,1-Diethyl-2-hydroxy-2-nitrosohydrazine (1:1) or 1-[N,N-diethylamino]diazen-1-ium-1,2-diolate). Other preferred NONOates include diethylene triamine-NONOate(DETA/NO; 2,2'-Hydroxynitrosohydrazino]bis-ethanamine), spermine-NONOate (SPER/NO; N-(4-[-1-(3-Aminopropyl)-2-hydroxy-2-nitrosohydrazino] butyl)-1,3-propanediamine), propylamino-propylamine-NONOate (PAPA/NO; 3-(2-Hydroxy-2-nitroso-1-propylhydrazino)-1-propanamine or (Z)-1-[N-(3-aminopropyl)-N-

(n-propyl)amino]diazen-1-ium-1,2-diolate), MAHMA-NONOate (MAHMA/NO; 6-(2-Hydroxy-1-methyl-2- nitrosohydrazino)-N-methyl-1-hexanamine), dipropylenetriamine-NONOate (DPTA/NO; 3,3'- (Hydroxynitrosohydrazino)bis-1-propanamine), PIPERAZI/NO, proli-NONOate (PROLI/NO; 1-([2-carboxylato]pyrrolidin-1-yl)diazen-1-ium-1,2-diolate-methanol, e.g., disodium salt), SULFO-NONOate (SULFO/NO; hydroxydiazenesulfonic acid 1-oxide, e.g., diammonium salt), the sulfite NONOate (SULFI/NO), and Angelis salt (OXI/NO).

Almost all NONOate compounds are highly soluble in water, and aqueous stock solutions are prepared in cold deoxygenated 1 to 10 mM NaOH (preferably about pH 12) just prior to use. Alkaline stock solutions are stable for several hours if kept on ice in the dark. The characteristic UV absorbance of NONOates can be used for spectrophotometric quantification of NONOate in aqueous solutions. NONOates are preferably administered intravenously or intra-arterially.

Nitric oxide donors have different potencies (Ferraro, R. *et al.*, *Comparative effects of several nitric oxide donors on intracellular cyclic GMP levels in bovine chromaffin cells: correlation with nitric oxide production*, Br. J. Pharmacol. 127(3):779-87 [1999]). For example, DEA/NO is among the most potent nitric oxide donors, with a half-life of about 2 to 4 minutes; less potent are PAPA/NO ($t_{1/2}$ about 15 minutes),SPER/NO ($t_{1/2}$ about 34-40 minutes); even less potent are DETA/NO ($t_{1/2}$ about 20 hours) and SNAP ($t_{1/2}$ about 33 to 41 hours, although this can be shortened in the presence of a physiological reductant such as glutathione). SNP is also a potent NO donor. (See, Ferrero *et al.* [1999]; Salom, J.B. *et al.*, *Relaxant effects of sodium nitroprusside and NONOates in rabbit basilary artery*, Pharmacol. 57(2):79-87 [1998]; Salom, J.B. *et al.*, *Comparative relaxant effects of the NO donors sodium nitroprusside, DEA/NO and SPER/NO in rabbit carotid arteries*, Gen. Pharmacol. 32(1):75-79 [1999]; Salom, J.B. *et al.*, *Relaxant effects of sodium nitroprusside and NONOates in goat middle cerebral artery: delayed impairment by global ischemia-reperfusion*, Nitric Oxide 3(1):85-93 [1999]; Kimura, M. *et al.*, *Responses of human basilar and other isolated arteries to novel nitric oxide donors*, J. Cardiovac. Pharmacol. 32(5):695-701 [1998]). Consequently, effective concentrations or doses of NONOates or other NO donors will vary, but can be determined by routine screening.

Stock solutions of NO donors are preferably made up freshly before use (at the appropriate pH for each particular NO donor), chilled on ice, and protected from light (e.g., by the use of darkened glass vials wrapped in aluminum foil), although organic nitrates can be stored for months to years if the vial is properly sealed. Preferably, immediately before administration to the subject, final dilutions are prepared in pharmaceutically acceptable buffer and the final pH of the NO

donor-containing buffer is checked for physiological suitability, especially when strongly acidic (e.g., hydrochloride salts) or alkaline (e.g., NONOates) stock solutions are used.

The product of NO exposure time and NO concentration largely determines the quality and magnitude of the biological response to exogenously supplied NO. Short-lived NO donors, such as DEA/NO, are most preferably administered by continuous infusion rather than by bolus to avoid delivering only a short burst of NO.

In accordance with the invention, the artificial aqueous medium preferably, but not necessarily, further includes glutamine at a preferred concentration of about 0.5 to about 5 mM concentration. A more preferred concentration of glutamine in the medium is about 1 to about 3 mM.

In the inventive methods of isolating a *Cryptovirus* virion and of producing a mammalian cell line nonproductively infected with *Cryptovirus*, the PBMNCs are co-cultured with mammalian amnion cells in the artificial aqueous medium, as described above.

Examples of useful mammalian cells include, but are not limited to, rodent, lagomorph, primate, ovine, bovine, canine, feline or porcine cells.

In accordance with the present invention, one preferred embodiment is a primate cell, i.e., a cell originating from a primate source. A primate is a member of the mammalian order Primates, including lemurs, tarsiers, monkeys (e.g., African Green Monkeys, colobus monkeys, and baboons), apes (e.g., chimpanzees, gorillas, orangutans, and gibbons), and humans.

An amnion cell is a cultured cell originally derived from an amniotic membrane or amniotic sac.

A preferred primate amnion cell is a human amnion cell, e.g., AV_3.

An example of the inventive cell nonproductively infected by the method is AV_3/SSPE, which is deposited as ATCC Accession No. PTA4746.

In these inventive methods, passaging of a co-culture of PBMNCs and mammalian amnion cells is done one or more times. Passaging of cultured cells into fresh culture medium (culture medium as described above), is typically done about twice per week. Preferably, at least about two to about 12 passages are done in accordance with the methods. Typically after about eight to twelve passages of the co-culture, virtually all mammalian amnion cells are nonproductively infected with *Cryptovirus*. Generally, within about two to about three passages, the PBMNCs have disappeared from the culture, leaving the mammalian amnion cells.

In accordance with the present invention, a mammalian epithelial cell is a cultured cell originally derived from a mammalian epithelial tissue. In one preferred embodiment, the mammalian epithelial cell is a rodent epithelial cell, such as baby hamster kidney (BHK) cells. In another preferred embodiment, the mammalian epithelial cell is a simian epithelial cell, for example a Vero or a CV-1 cell. Most preferably the CV-1 cell is subline $CV\text{-}1_c$.

In addition to the sequence information provided herein to identify the inventive *Cryptovirus* particle, the inventive *Cryptovirus* and its viral subcomponents can be, and have been, characterized by numerous virological, biochemical, and molecular techniques, including the following, by way of example:

Plaque Titration Assay: Formation of macroscopically visible plaques on monolayers of mammalian epithelial cells (e.g., BHK, Vero or CV-1_C) can be used to quantitate preparations of infectious *Cryptovirus* (Robbins *et al., J. Infect. Disease* 143:396-403, 1981).

Neutralization Titration Assay: Plaque formation can be inhibited by serial dilutions of clinical serum specimens and *Cryptovirus*-specific antisera generated in rabbits (*see* e.g., Robbins *et al., J. Infect. Disease* 143:396-403, 1981). Neutralization titration assays are routinely used in medical virological research to demonstrate that a given patient has neutralizing antibodies to a particular virus. A neutralization assay can be used diagnostically for the presence or absence of neutralizing antibody to *Cryptovirus*. In a typical example of a neutralization assay, serial dilutions of a biological material, such as a sample of serum or CSF to be tested, are typically incubated for about one hour at 4°C with sufficient infectious virus to yield a net plating concentration of between about 100-200 plaque forming units of the virus per 0.2 mL of final diluent (including the diluted serum or CSF). After incubation, about 0.2 mL of the diluted virus-serum (or CSF) mixtures are then typically plated onto monolayers of susceptible cells (*e.g.* Vero or CV-1) and the cells are incubated at 37°C in a partial CO_2 atmosphere (e.g., 5% v/v) (typically, with redistribution of the inoculum every 15 minutes). At the end of the incubation period, inoculated monolayers are typically overlayed with sufficient volumes of a 2% (w/v) solution of carboxymethylcellulose in an artificial aqueous cell culture medium (e.g., IMEMZO medium, buffered at pH between about 6.8 and about 7.4, typically containing fetal calf serum, and a suitable quantity of antibiotic, such as about 200 Units penicillin / mL and/or 100 µg streptomycin / mL) to last 10-12 days (*i.e.*, enough volume so that the monolayers won't dry out). Optimally, the plates must not be moved during the incubation period. After 10-12 days, the overlay is aspirated and the cells are fixed with formalin fixative and stained with a protein stain (*e.g.*, Giemsa). The number of plaques formed on each plate is then enumerated and the PRD_{50} calculated (PRD_{50} = the Plaque Reduction Dilution; the dilution of serum or CSF at

which a 50% reduction in the number of plaques formed on controls [tubes containing virus and saline only] is observed).

Density Gradient Purification: Virions and intracellular nucleocapsids from productively- (e.g., Vero and CV-1_C) and nonproductively-infected (e.g., AV_3/SSPE) cells can be purified on sucrose-potassium tartrate gradients (virions) and CsCl gradients (nucleocapsids) (*see* Robbins *et al.*, *J. Infect. Disease* 143:396-403, 1981; Rapp and Robbins, *Intervirology* 16:160-167, 1981; Robbins and Rapp, *Arch. Virol.* 71:85-91, 1982; and Robbins and Abbott-Smith, *J. Virol. Meth.* 11:253-257, 1985).

Electron Microscopy: Electron microscopy, such as transmission or scanning electron microscopy are useful for examining the inventive *Cryptovirus* virion. When examined by electron microscopy, the *Cryptovirus* has been shown to have a morphology and ultrastructure consistent with other members of the Paramyxoviridae (*i.e.*, enveloped pleomorphic virions, about 100 nm to about 120 nm in diameter, containing helical nucleocapsids). Intracellular inclusions of the virus in thin sections of productively- (e.g., Vero and CV-1_C) and nonproductively-infected cells (e.g., AV_3/SSPE) have also been shown to be comprised of aggregates of filamentous structures with dimensions similar to the nucleocapsids of other members of the Paramyxoviridae (*i.e.*, helical herringbone-like structures, about 15 to about 17 nm in diameter) (*see* Robbins *et al.*, *J. Infect. Disease* 143:396-403, 1981 and Robbins and Rapp, *Arch. Virol.* 71:85-91, 1982).

Radioimmunoprecipitation (RIP) *Assay*: Extensive data has been generated by the comparative analysis of *Cryptovirus*-specific immunoprecipitates of [^{35}S]-methionine-labeled uninfected, nonproductively- and productively-infected mammalian cells by sodium dodecyl sulfate polyacrylamide gel electrophoresis (SDS-PAGE; see below).

SDS-PAGE: Purified virions and cytoplasmic nucleocapsids of the virus have been analyzed by SDS-PAGE under reducing and non-reducing conditions (see Fig. 11 and Fig. 12), an autoradiogram of gradient-purified [^{35}S]-methionine-labeled *Cryptovirus* virions produced in acutely-infected Vero cells after SDS-PAGE under reducing conditions. The approximate molecular weights of the proteins indicated on the right side of Fig. 11 were calculated by comparing their migrations to marker proteins of known molecular weights (Sigma Chemical Co., St. Louis, MO). The SH protein, a small envelope-associated protein having a MW of about 5 kD, is not shown in Fig. 11, because it has run off the gel.

Immuno-ultrastructural Analysis (Immunogold Analysis). The intracellular nucleocapsids of nonproductively and productively-infected mammalian cells are typically localized under the electron

microscope using *Cryptovirus*-specific or *Cryptovirus* nucleocapsid-specific antibodies, for example hyperimmune rabbit antibodies, and an indirect immunogold labeling technique (discussed hereinbelow).

The preceding are merely illustrative, and not an exhaustive list, of the known techniques typically useful for characterizing the isolated *Cryptovirus* virion of the present invention. Additional conventional techniques, or virological techniques yet to be discovered, can also be employed to further characterize the inventive *Cryptovirus* virion.

Additional characteristics of *Cryptovirus* include the following:

Latency and Persistence. *Cryptovirus* latently and persistently infects human peripheral blood mononuclear cells (PBMNCs). No other member of the Paramyxoviridae has been shown to do this. The evidence for infection includes: (1) detection of *Cryptovirus-specific* proteins by an indirect immunofluorescent antibody technique in PBMNCs following *in vitro* cultivation and induction with mitogens and/or cyclic GMP, (2) recovery of the virus from PBMNCs by serial cocultivation with mammalian cells (see Robbins *et al.*, *J. Infect. Dis.* 143:396-403, 1981) and (3) the ability to repeatedly recover the virus from PBMNCs drawn from an SSPE patient over a period of 18 months.

Defective Fusion Activity. Cell fusion, which is a hallmark of the Paramyxoviridae, is either defective or extremely limited in experimental *Cryptovirus* infections *in vitro* (*i.e.*, in dysgenic nonproductive infections of human amnion cells (AV_3) and productive infections of monkey kidney cells (e.g., Vero and CV-1_c; *see* Robbins *et al.*, *J. Infect. Dis.* 143:396-403, 1981, and Robbins and Rapp, *Arch. Virol.* 71:85-91, 1982).

Restricted Expression in Latently-Infected Cells. *Cryptovirus*-specific protein expression is dysgenic in experimental nonproductive latent infections of mammalian amnion cells (e.g., human AV_3 cells). This restriction involves severely decreased expression, or non-expression, of the virus-encoded envelope proteins (F, HN and SH) (*see* Robbins and Rapp, *Arch. Virol.* 71:85-91, 1982).

B Cell Lymphotropism. *Cryptovirus* demonstrates a tropism for B cells, and can be harbored by such cells *in situ*. This has been demonstrated by successfully infecting EBV-transformed B cell lines from human donors with the virus (*i.e.*, by detecting the progressive formation of *Cryptovirus*-specific inclusion bodies in the cytoplasm of experimentally-infected EBV-transformed B cell lines by *Cryptovirus*-specific immunofluorescence). In contrast, *Cryptovirus*-specific proteins could not be detected in an experimentally-infected human T cell line, CCRF-CEM. Accordingly, *Cryptovirus* can reside in B cells in infected individuals.

Neurotropism. Cryptovirus also demonstrates a clear tropism for neurons in mice following intracerebral inoculation of neonatal animals (as detected by *Cryptovirus*-specific immunofluorescence). It is less clear whether other nervous system tissues are infected. While neurotropism, itself, may not be unique to *Cryptovirus* when compared and contrasted to other human members of the Paramyxoviridae (*e.g.*, Measles Virus, Mumps Virus), some of the neuropathological consequences of *Cryptovirus* infection of CNS tissues (including neurons) appear to be (see below).

Hind Limb Atrophy and Paralysis. Hind limb paralysis and atrophy were seen in approximately 33% of Quackenbush mice intracerebrally-inoculated with *Cryptovirus* as newborns. In addition, hind limb atrophy and paralysis was observed in some of the offspring of adult female Quackenbush mice that had been inoculated with *Cryptovirus* as newborns but did not develop any overt symptomology. The frequency of the symptoms appearing in the latter situation was difficult to assess because the mothers tended to cannibalize the newborn animals that were born with, or subsequently developed, such characteristics.

Subacute/Slow Encephalopathic and Epileptigenic Potential. Approximately 30% of neonatal Colored mice that were inoculated with infectious *Cryptovirus* preparations went on to develop subacute/slow encephalopathic and/or epileptiform illness (the specific symptoms displayed by such animals are described below). The number of animals that actually developed encephalopathic and/or epileptiform illness was likely higher than 30%, because a number of previously asymptomatic animals were found dead in their cages in clonic postures (a symptom associated with death following or during intractable seizure). On at least two occasions, this occurred in animals after they had suffered from recurrent seizures the day before. The animals that developed such illnesses were predominantly male (approximately 2:1, male: female).

Slow Psychopathogenic Potential. Of the Colored mice that survived intracerebral inoculation with infectious *Cryptovirus* preparations as newborns and did not develop epileptiform illness as adolescent or young adult animals, approximately 30% went on to develop profound physical and behavioral abnormalities as adults. The abnormalities displayed by these animals are described hereinbelow. Sudden death was not seen in this group of animals. The animals which developed such symptoms were predominantly female (approximately 3:1, female: male).

The preceding are merely illustrative, and are not an exhaustive list, of some of the observable properties of the inventive *Cryptovirus* particle.

The present invention also relates to isolated nucleic acids and isolated proteins that are "*Cryptovirus*-specific," i.e., unique to *Cryptovirus*.

A *Cryptovirus*-specific nucleic acid segment or protein is determined by sequence similarity or homology to known sequences of bases or amino acids, respectively, for example other rubulavirus nucleic acid or protein sequences. Base and amino acid sequence homology is determined by conducting a sequence similarity search of a genomics/proteomics data base, such as the GenBank database of the National Center for Biotechnology Information (NCBI; www.ncbi.nlm.nih.gov/BLAST/), using a computerized algorithm, such as PowerBLAST, QBLAST, PSI-BLAST, PHI-BLAST, gapped or ungapped BLAST, or the "Align" program through the Baylor College of Medicine server (www.hgsc.bcm.tmc.edu/seq_data). (E.g., Altchul, S.F., *et al.*, *Gapped BLAST and PSI-BLAST: a new generation of protein database search programs*, Nucleic Acids Res. 25(17):3389-402 [1997]; Zhang, J., & Madden, T.L., *PowerBLAST: a new network BLAST application for interactive or automated sequence analysis and annotation*, Genome Res. 7(6):649-56 [1997]; Madden, T.L., *et al.*, *Applications of network BLAST server*, Methods Enzymol. 266:131-41 [1996]; Altschul, S.F., *et al.*, *Basic local alignment search tool*, J. Mol. Biol. 215(3):403-10 [1990]).

For purposes of the present invention the term "isolated" encompasses "purified". Thus, an isolated nucleic acid, protein, viral particle, or antibody that is further purified to a greater level of homogeneity, is also "isolated."

For purposes of the present invention the term "nucleic acid" includes a polynucleotide, of any length, either polymeric ribonucleotides (RNA) or polymeric deoxyribonucleotides (DNA), such as cDNA.

The term "isolated nucleic acid" refers to a *Cryptovirus* genomic RNA which is essentially free, i.e., contains less than about 50%, preferably less than about 70%, and even more preferably less than about 90% of the polypeptides with which the *Cryptovirus* genome is naturally associated. Alternatively, an "isolated" nucleic acid of the present invention is a *Cryptovirus*-specific "recombinant polynucleotide", which as used herein intends a polynucleotide of genomic RNA, sense RNA (i.e., mRNA sense), cDNA, semisynthetic, or synthetic origin, which, by virtue of its origin or manipulation: (1) is not associated with all or a portion of a polynucleotide with which it is associated in nature, (2) is linked to a polynucleotide other than that to which it is linked in nature, or (3) does not occur in nature. The inventive nucleic acid can be in a sense or antisense orientation.

As used herein, the "sense strand" of a nucleic acid contains the sequence that has sequence homology to that of mRNA. The "anti-sense strand" contains a sequence which is complementary to that of the "sense strand." Inventive nucleic acids also include double- and single-stranded DNA and RNA.

Techniques for purifying viral polynucleotides from viral particles are known in the art, and include for example, disruption of the particle with a chaotropic agent, differential extraction and separation of the polynucleotide(s) and polypeptides by ion-exchange chromatography, affinity chromatography, and sedimentation according to density.

Inventive nucleic acids also encompass polynucleotides with known types of modifications, for example, labels, methylation, "caps", substitution of one or more of the naturally occurring nucleotides with a nucleotide analog, internucleotide modifications such as, for example, polynucleotides with uncharged linkages (e.g., methyl phosphonates, phosphotriesters, phosphoamidates, carbamates, etc.) and with charged linkages (e.g., phosphorothioates, phosphorodithioates, etc.), those containing pendant moieties, such as, for example proteins (including for e.g., nucleases, toxins, antibodies, signal peptides, poly-L-lysine, etc.), those with intercalators (e.g., acridine, psoralen, etc.), those containing chelators (e.g., metals, radioactive metals, boron, oxidative metals, etc.), those containing alkylators, those with modified linkages (e.g., alpha anomeric nucleic acids, etc.), as well as unmodified forms of the polynucleotide.

A "nucleic acid segment" is a polynucleotide subportion of a larger nucleic acid.

A nucleotide sequence complementary to an inventive *Cryptovirus*-specific nucleotide sequence, as used herein, is one binding specifically or hybridizing with a *Cryptovirus*-specific nucleotide base sequence. The phrase "binding specifically" or "hybridizing" encompasses the ability of a polynucleotide sequence to recognize a complementary base sequence and to form double-helical segments therewith via the formation of hydrogen bonds between the complementary base pairs. Thus, a complementary sequence includes, for example, an antisense sequence with respect to a sense sequence or coding sequence. As known to those of skill in the art, the stability of hybrids is reflected in the melting temperature (T_m) of the hybrids. In general, the stability of a hybrid is a function of sodium ion concentration and temperature. Typically, the hybridization reaction is performed under conditions of relatively low stringency, followed by washes of varying, but higher, stringency. Reference to hybridization stringency relates to such washing conditions.

As used herein, the phrase "moderately stringent hybridization" refers to conditions that permit target-RNA or DNA to bind a complementary nucleic acid that has at least about 95%, about 96%, about 97%, about 98%, about 99%, or about 100% identity to the target RNA segment or DNA segment. Preferably, moderately stringent conditions are conditions approximately equivalent in stringency to hybridization in 50% formamide, 5 x Denhart's solution, 5 x SSPE, 0.2% SDS at 42°C, followed by washing in 0.2 x SSPE, 0.2% SDS, at 65°C.

The phrase "high stringency hybridization" refers to conditions that permit hybridization of only those nucleic acid sequences that form stable hybrids in 0.018 M NaCl at 65°C (i.e., if a hybrid is not stable in 0.018 M NaCl at 65°C, it will not be stable under high stringency conditions, as contemplated herein). High stringency conditions can be provided, for example, by hybridization in 50% formamide, 5X Denhart's solution, 5X SSPE, 0.2% SDS at 42°C, followed by washing in 0.1 x SSPE, and 0.1% SDS at 65°C.

The phrase "low stringency hybridization" typically refers to conditions equivalent to hybridization in 10% formamide, 5X Denhart's solution, 6 x SSPE, 0.2% SDS at 42°C, followed by washing in 1 x SSPE, 0.2% SDS, at 50°C. Denhart's solution and SSPE (see, e.g., Sambrook et al., Molecular Cloning, A Laboratory Manual, Cold Spring Harbor Laboratory Press [1989]) are well known to those of skill in the art, as are other suitable hybridization buffers.

The inventive nucleic acids include a *Cryptovirus*-specific nucleic acid fragment at least about five contiguous nucleotides long, and up to 15245 contiguous nucleotides long, of SEQ ID NO:1, or a complementary sequence.

Thus, useful fragments include nucleic acid segments consisting of an open reading frame of the Cryptovirus genome or a complementary sequence. An "open reading frame" (ORF) is a region of a polynucleotide sequence which encodes a polypeptide; this region may represent a portion of a coding sequence or an entire coding sequence.

A "coding sequence" is a polynucleotide sequence which is transcribed into mRNA and/or translated into a polypeptide when placed under the control of appropriate regulatory sequences. The boundaries of the coding sequence are determined by a translation start codon at the 5'-terminus and a translation stop codon at the 3'-terminus. A coding sequence can include, but is not limited to, mRNA, cDNA, and recombinant polynucleotide sequences.

Useful examples of the fragment include nucleic acid segments that encode *Cryptovirus* proteins, such as (i) contiguous nucleotide positions 152-1678 of (SEQ ID NO:1)(also designated [SEQ ID NO:3]); (ii) contiguous nucleotide positions 1850-2515 of (SEQ ID NO:1)(also designated [SEQ ID NO:5]); (iii) contiguous nucleotide positions 1850-3023 of (SEQ ID NO:1)(also designated [SEQ ID NO:33]); (iv) contiguous nucleotide positions 1850-3023 of (SEQ ID NO:1) combined with a further insertion of two guanine (G) residues between nucleotide position 2339 of (SEQ ID NO:1) and nucleotide position 2340 of (SEQ ID NO:1)(the combined sequence including the "GG" insertion being designated [SEQ ID NO:7]); (v) contiguous nucleotide positions 3141-4271 of (SEQ ID NO:1)(also designated [SEQ ID NO:9]); (vi) contiguous nucleotide positions 4530-6182 of (SEQ ID NO:1)(also designated [SEQ ID NO:11]); (vii) contiguous nucleotide positions 4587-6182 of (SEQ

ID NO:1)(also designated [SEQ ID NO:13]); (viii) contiguous nucleotide positions 4587-4835 of (SEQ ID NO:1)(also designated [SEQ ID NO:15]); (ix) contiguous nucleotide positions 4836-6182 of (SEQ ID NO:1)(also designated [SEQ ID NO:17]); (x) contiguous nucleotide positions 4272-6515 of (SEQ ID NO:1)(also designated [SEQ ID NO:34]); (xi) contiguous nucleotide positions 6303-6434 of (SEQ ID NO:1)(also designated [SEQ ID NO:19]); (xii) contiguous nucleotide positions 6584-8278 of (SEQ ID NO:1)(also designated [SEQ ID NO:21]); or (xiii) contiguous nucleotide positions 8414-15178 of (SEQ ID NO:1)(also designated [SEQ ID NO:23]). A nucleotide complementary to any of (SEQ ID NOS:3, 5, 7, 9, 11, 13, 15, 17, 19, 21, 23, 33, or 34), or a degenerate coding sequence of any of (SEQ ID NOS:3, 5, 7, 9, 11, 13, 15, 17, 19, 21, 23, 33, or 34) is also encompassed by the nucleic acid fragment.

As used herein, the term "degenerate coding sequence", or interchangeably, "degenerate sequence", refers to a protein-encoding nucleic acid sequence that has at least one codon that differs in at least one nucleotide position from any reference nucleic acid, e.g., any of SEQ ID NO:3, 5, 7, 9, 11, 13, 15, 17, 19, 21, or 23, but which encodes the same amino acids as the reference nucleic acid. For example, codons specified by the triplets "UCU", "UCC", "UCA", and "UCG" are degenerate with respect to each other since all four of these codons encode the amino acid serine.

In some embodiments, the *Cryptovirus*-specific fragment is up to about 500 nucleotides long. In other embodiments, the fragment is up to about 50 nucleotides long. Other embodiments of the inventive nucleic acid fragment are about fifteen nucleotides to about 35 nucleotides long; for example, this is a preferred length for a *Cryptovirus*-specific primer of the present invention, which is a *Cryptovirus*-specific oligonucleotide for use in nucleic acid amplification reactions. Most preferably, the inventive *Cryptovirus*-specific primer is about 17 to about 22 nucleotides long, but primers as short as 7 contiguous nucleotides may be useful for some gene-specific sequences. (E.g., Vincent, J., *et al.*, *Oligonucleonucleotides as short as 7-mers can be used for PCR amplification*, DNA Cell Biol. 13(1):75-82 [1994]).

The inventive probe is preferably about 7 to about 500 nucleotides long, most preferably about 15 to about 150 nucleotides long, and comprises, for at least part of its length, a *Cryptovirus*-specific nucleotide sequence at least 7 to 15 nucleotides long, such that the probe hybridizes to a *Cryptovirus*-specific single stranded nucleic acid under suitably stringent hybridization conditions. For example, probes comprising the inventive oligonucleotide primer sequences described herein can be labeled for use as probes for detecting or analyzing *Cryptovirus*-specific nucleic acid, including nucleic acid amplification products.

Non-limiting examples of the *Cryptovirus*-specific fragments useful as primers or probes include nucleic acids comprising: contiguous nucleotide positions 1684-1701 of SEQ ID NO:1 (designated SEQ ID NO:35); contiguous nucleotide positions 1700-1717 of SEQ ID NO:1 (designated SEQ ID NO:36); contiguous nucleotide positions 4283-4300 of SEQ ID NO:1 (designated SEQ ID NO:37); contiguous nucleotide positions 4299-4316 of SEQ ID NO:1 (designated SEQ ID NO:38); contiguous nucleotide positions 4285-4302 of SEQ ID NO:1 (designated SEQ ID NO:39); contiguous nucleotide positions 4300-4317 of SEQ ID NO:1 (designated SEQ ID NO:40); contiguous nucleotide positions 4518-4535 of SEQ ID NO:1 (designated SEQ ID NO:41); contiguous nucleotide positions 4533-4550 of SEQ ID NO:1 (designated SEQ ID NO:42); contiguous nucleotide positions 6116-6133 of SEQ ID NO:1 (designated SEQ ID NO:44); contiguous nucleotide positions 6192-6209 of SEQ ID NO:1 (designated SEQ ID NO:45); contiguous nucleotide positions 6191-6208 of SEQ ID NO:1 (designated SEQ ID NO:43); contiguous nucleotide positions 7501-7518 of SEQ ID NO:1 (designated SEQ ID NO:46); contiguous nucleotide positions 7517-7534 of SEQ ID NO:1 (designated SEQ ID NO:47); or a nucleotide sequence complementary to any of the preceding SEQ ID NOS:35-47. A polynucleotide particularly useful as a probe, especially for probing nucleic acids in samples of biological materials originating from a human or amplification products derived therefrom, is a nucleic acid comprising contiguous nucleotide positions 4292-4549 of SEQ ID NO:1 (designated SEQ ID NO:48) or a complementary sequence. For probing nucleic acids derived from a sample of biological material from a human, even a large nucleic acid segment of SEQ ID NO:1 can be used, for example a nucleic acid comprising contiguous nucleotide positions 4272-6515 of SEQ ID NO:1 (designated SEQ ID NO:34) or a complementary sequence.

The primer is capable of acting as a point of initiation of synthesis of a polynucleotide strand when placed under appropriate conditions. The primer will be completely or substantially complementary to a region of the polynucleotide strand to be copied. Thus, under conditions conducive to hybridization, the primer will anneal to the complementary region of the analyte strand. Upon addition of suitable reactants, (e.g., a polymerase, nucleotide triphosphates, and the like), the primer is extended by the polymerizing agent to form a copy of the analyte strand. The primer may be single-stranded, or alternatively maybe partially or fully double-stranded.

The terms "analyte polynucleotide" and "analyte strand" refer to a single- or double-stranded nucleic acid molecule which is suspected of containing a *Cryptovirus*-specific target sequence, and which may be present in a sample of biological material.

The inventive probe is a structure comprised of a polynucleotide which forms a hybrid structure with a *Cryptovirus*-specific target sequence, due to complementarity of at least one nucleotide sequence in the probe with a sequence in the target region. The polynucleotide regions of probes may be composed of DNA, and/or RNA, and/or synthetic nucleotide analogs. "Target region" refers to a region of the nucleic acid which is to be amplified and/or detected. The term "target sequence" refers to a *Cryptovirus*-specific sequence with which a probe or primer will form a stable hybrid under desired conditions.

Included within probes are "capture probes" and "label probes". Preferably the probe does not contain a sequence complementary to sequence(s) used to prime a nucleic acid amplification reaction.

The term "capture probe" as used herein refers to a polynucleotide comprised of a single-stranded polynucleotide coupled to a binding partner. The single-stranded polynucleotide is comprised of a targeting polynucleotide sequence, which is complementary to a target sequence in a target region to be detected in the analyte polynucleotide. This complementary region is of sufficient length and complementarity to the target sequence to afford a duplex of stability which is sufficient to immobilize the analyte polynucleotide to a solid surface (via the binding partners). The binding partner is specific for a second binding partner; the second binding partner can be bound to the surface of a solid support, or may be linked indirectly via other structures or binding partners to a solid support.

The term "binding partner" as used herein refers to a molecule capable of binding a ligand molecule with high specificity, as for example an antigen and an antibody specific therefor. In general, the specific binding partners must bind with sufficient affinity to immobilize the analyte copy/complementary strand duplex (in the case of capture probes) under the isolation conditions. Specific binding partners are known in the art, and include, for example, biotin and avidin or streptavidin, IgG and protein A, the numerous known receptor-ligand couples, and complementary polynucleotide strands. In the case of complementary polynucleotide binding partners, the partners are generally at least about 15 bases in length, and may be at least 40 bases in length; in addition, they have a content of Gs and Cs of at least about 25% and as much as about 75%. The polynucleotides may be composed of DNA, RNA, or synthetic nucleotide analogs.

"Coupled" as used herein refers to attachment by covalent bonds or by strong non-covalent interactions (e.g., hydrophobic interactions, hydrogen bonds, etc.). Covalent bonds may be, for example, ester, ether, phosphoester, amide, peptide, imide, carbon-sulfur bonds, carbon-phosphorus bonds, and the like.

A "support" refers to any solid or semi-solid surface to which a desired binding partner may be anchored. Suitable supports include glass, plastic, metal, polymer gels, and the like, and may take the form of beads, wells, dipsticks, membranes, and the like.

As used herein, the term "label probe" refers to an oligonucleotide which is comprised of a targeting polynucleotide sequence, which is complementary to a target sequence to be detected in the analyte polynucleotide. This complementary region is of sufficient length and complementarity to the target sequence to afford a duplex comprised of the "label probe" and the "target sequence" to be detected by the label. The oligonucleotide is coupled to a label either directly, or indirectly via a set of ligand molecules with high specificity for each other.

A "label" includes any atom or moiety which can be used to provide a detectable (preferably quantifiable) signal, and which can be attached by conventional means to a polynucleotide or to polypeptide, such as an antibody. The label can be used alone or in conjunction with additional reagents. Such labels are themselves well-known in the art. The label can be a radioisotope, such as ^{14}C, ^{32}P, ^{35}S, ^{3}H, or ^{15}O, which is detected with suitable radiation detection means. Alternatively, the label can be a fluorescent labeling agent that chemically binds to antibodies or antigens without denaturation to form a fluorochrome (dye) that is a useful immunofluorescent tracer. A description of immunofluorescent analytic techniques is found in DeLuca, "Immunofluorescence Analysis", in *Antibody As a Tool*, Marchalonis et al., eds., John Wiley & Sons, Ltd., pp. 189-231 (1982). As well, any of diverse fluorescent dyes can optionally be used to label probes or primers or amplification products for ease of detection and/or analysis. Useful fluorescent dyes include, but are not limited to, rhodamine, fluorescein, SYBR Green I, YIO-PRO-1, thiazole orange, Hex (i.e., 6-carboxy-2',4',7',4,7-hexachlorofluoroscein), pico green, edans, fluorescein, FAM (i.e., 6-carboxyfluorescein), or TET (i.e., 4,7,2',7'-tetrachloro-6-carboxyfluoroscein). (E.g., J. Skeidsvoll and P.M. Ueland, *Analysis of double-stranded DNA by capillary electrophoresis with laser-induced fluorescence detection using the monomeric dye SYBR green I*, Anal. Biochem. 231(20):359-65 [1995]; H. Iwahana *et al.*, *Multiple fluorescence-based PCR-SSCP analysis using internal fluorescent labeling of PCR products*, Biotechniques 21(30:510-14, 516-19 [1996]).

The inventive nucleic acid constructs include recombinant cloning and expression vectors (including plasmids and viral expression vectors, such as retroviral or adenoviral vectors), that contain the inventive nucleic acid. A "vector" is a replicon in which another polynucleotide segment is attached, so as to bring about the replication and/or expression of the attached segment. A "replicon" is any genetic element, e.g., a plasmid, a chromosome, a virus, a cosmid, etc., that behaves as an autonomous unit of polynucleotide replication within a cell, i.e., being capable of replication

under the replicon's own control. Inventive recombinant expression vectors contain one or more inventive nucleic acid segments and include at least a promoter region operatively linked to the inventive nucleic acid segment in a transcriptional unit. Preferred examples of inventive nucleic acid constructs are those that include one or more nucleic acid segments encoding a *Cryptovirus* protein, the *Cryptovirus* coding sequence(s) being thus suitably placed and operatively linked to suitable regulatory sequences within one or more transcriptional units within the construct.

"Control" or "regulatory" sequences, elements or regions refers to polynucleotide sequences which are necessary to effect the expression of coding sequences to which they are ligated. The nature of such control sequences differs depending upon the host organism; in prokaryotes, such control sequences generally include promoter, ribosomal binding site, and terminators; in eukaryotes, generally, such control sequences include promoters, terminators and, in some instances, enhancers. The term "control sequences" is intended to include, at a minimum, all components whose presence is necessary for expression, and may also include additional components whose presence is advantageous, for example, leader sequences.

As used herein, "expression" refers to the process by which genes are transcribed into mRNA, which is in turn translated into peptides, polypeptides, or proteins. With respect to a recombinant expression vector, a promoter region refers to a segment of nucleic acid that controls transcription of a coding sequence to which it is operatively linked. The promoter region includes specific sequences that are sufficient for RNA polymerase recognition, binding and transcription initiation. In addition, the promoter region includes sequences that modulate this recognition, binding and transcription initiation activity of RNA polymerase. These sequences may be *cis* acting or may be responsive to *trans* acting factors. Promoters, depending upon the nature of the regulation, may be constitutive or regulated developmentally or inducibly. Exemplary promoters contemplated for use in the practice of the present invention include the SV40 early promoter, the cytomegalovirus (CMV) promoter, the mouse mammary tumor virus (MMTV) steroid-inducible promoter, Moloney murine leukemia virus (MMLV) promoter, and the like.

For optimal expression of foreign genes in mammalian cells (e.g., the *Cryptovirus* genes of the present invention), the expression vector may also require terminator sequences and poly A addition sequences; enhancer sequences which increase expression may also be included, and sequences which cause amplification of the gene may also be desirable. Such sequences are known in the art.

As used herein, the term "operatively linked" refers to the functional relationship of nucleic acid with regulatory (control or effector) nucleotide sequences, such as promoters, enhancers,

transcriptional and translational stop sites, and other signal sequences. For example, operative linkage of DNA or RNA to a promoter refers to the physical and functional relationship between the DNA or RNA and the promoter such that the transcription of such DNA or RNA is initiated from the promoter by an RNA polymerase that specifically recognizes, binds to and transcribes the DNA or RNA, respectively. A regulatory sequence "operatively linked" to a coding sequence is ligated in such a way that expression of the coding sequence is achieved under conditions compatible with the regulatory sequences. Thus, for example, within a transcriptional unit, the promoter sequence, is located upstream (i.e., 5' in relation thereto) from the coding sequence and the coding sequence, is 3' to the promoter, or alternatively is in a sequence of genes or open reading frames 3' to the promoter and expression is coordinately regulated thereby. Both the promoter and coding sequences are oriented in a 5' to 3' manner, such that transcription can take place in vitro in the presence of all essential enzymes, transcription factors, co-factors, activators, and reactants, under favorable physical conditions, e.g., suitable pH and temperature. This does not mean that, in any particular cell, conditions will favor transcription. For example, transcription from a tissue-specific promoter is generally not favored in heterologous cell types from different tissues.

The inventive expression vector, comprising a *Cryptovirus*-specific nucleic acid, is used to transform a cell. "Transformation", as used herein, refers to the insertion of an exogenous polynucleotide into a host cell, irrespective of the method used for the insertion, for example, direct uptake, transfection, transduction, f-mating, microparticle bombardment, or electroporation. The exogenous polynucleotide may be maintained as a non-integrated vector, for example, a plasmid, or alternatively, may be integrated into the host genome. A "transformed" host cell refers to both the immediate cell that has undergone transformation and its progeny that maintain the originally exogenous polynucleotide.

Appropriate expression vectors are well known to those of skill in the art and include those that are replicable in eukaryotic cells and/or prokaryotic cells and those that remain episomal or those which integrate into the host cell genome.

Exemplary, eukaryotic expression vectors, include the cloned bovine papilloma virus genome, the cloned genomes of the murine retroviruses, and eukaryotic cassettes, such as the pSV-2 gpt system (described by Mulligan and Berg, 1979, Nature Vol. 277:108-114) the Okayama-Berg cloning system (Mol. Cell Biol. Vol. 2:161-170, 1982), pGAL4, pCI (e.g., pCI-neo), and the expression cloning vector described by Genetics Institute (Science Vol. 228:810-815, 1985), are available which provide substantial assurance of at least some expression of the protein of interest in the transformed mammalian cell.

Preferred are vectors which contain regulatory elements that can be linked to the inventive nucleic acids, for transfection or transduction of mammalian cells. Examples are cytomegalovirus (CMV) promoter-based vectors such as pcDNA1 (Invitrogen, San Diego, CA), MMTV promoter-based vectors such as pMAMNeo (Clontech, Palo Alto, CA) and pMSG (Pharmacia, Piscataway, NJ), and SV40 promoter-based vectors such as pSVβ (Clontech, Palo Alto, CA). In one embodiment of the present invention, adenovirus-transferrin/polylysine-DNA (TfAdpl-DNA) vector complexes (Wagner et al., 1992, PNAS, USA, 89:6099-6103; Curiel et al., 1992, Hum. Gene Therapy, 3:147-154; Gao et al., 1993, Hum. Gene Ther., 4:14-24) are employed to transduce mammalian cells with heterologous *Cryptovirus*-specific nucleic acid. Any of the plasmid expression vectors described herein may be employed in a TfAdpl-DNA complex.

In addition, expression vectors may contain appropriate packaging signals that enable the vector to be packaged by a number of viral virions, e.g., retroviruses, such as human immune-deficiency virus, lentiviruses, mumps virus, herpes viruses, adenoviruses, resulting in the formation of a "viral vector." (See, e.g., Anderson, W.F., *Gene therapy scores against cancer*, Nat. Med. 6(8):862-63 [2000]). These viral vectors include, for example, Herpes simplex virus vectors (e.g., Geller *et al.*, 1988, Science, 241:1667-1669), Vaccinia virus vectors (e.g., Piccini *et al.*, 1987, Meth. in Enzymology, 153:545-563); Cytomegalovirus vectors (Mocarski *et al.*, in *Viral Vectors*, Y. Gluzman and S.H. Hughes, Eds., Cold Spring Harbor Laboratory, Cold Spring Harbor, N.Y., 1988, pp. 78-84), Moloney murine leukemia virus vectors (Danos *et al.*, 1980, PNAS, USA, 85:6469), adenovirus vectors (e.g., Logan *et al.*, 1984, PNAS, USA, 81:3655-3659; Jones *et al.*, 1979, Cell, 17:683-689; Berkner, 1988, Biotechniques, 6:616-626; Cotten *et al.*, 1992, PNAS, USA, 89:6094-6098; Graham *et al.*, 1991, Meth. Mol. Biol., 7:109-127), adeno-associated virus vectors, retrovirus vectors (see, e.g., U.S. Patent 5,252,479, WIPO publications WO 92/07573, WO 90/06997, WO 89/05345, WO 92/05266 and WO 92/14829, U.S. Patent Nos. 4,405,712 and 4,650,764; Shackleford et al., 1988, PNAS, USA, 85:9655-9659), and the like.

A preferred viral vector is Moloney murine leukemia virus and the pseudotyped retroviral vector derived from Moloney virus called vesicular-stomatitis-virus-glycoprotein (VSV-G)-Moloney murine leukemia virus. A most preferred viral vector is a pseudotyped (VSV-G) lentiviral vector derived from the HIV virus, which is used to transduce mammalian cells. (Naldini, L., *et al.*, *In vivo gene delivery and stable transduction of nondividing cells by a lentiviral vector*, Science 272: 263-267 [1996]). This gene delivery system employs retroviral particles generated by a three-plasmid expression system. In this system a packaging construct contains the human cytomegalovirus (hCMV) immediate early promoter, driving the expression of all viral proteins. The construct's

design eliminates the cis-acting sequences crucial for viral packaging, reverse transcription and integration of these transcripts. The second plasmid encodes a heterologous envelope protein (*env*), namely the G glycoprotein of the vesicular stomatitis virus (VSV-G). The third plasmid, the transducing vector (pHR'), contains cis-acting sequences of human immunodeficiency virus (HIV) required for packaging, reverse transcription and integration, as well as unique restriction sites for cloning heterologous complementary DNAs (cDNAs). For example, a genetic selection marker, such as green fluorescent protein (GFP), enhanced green fluorescent protein (EGFP), blue fluorescent protein, yellow fluorescent protein, a fluorescent phycobiliprotein, β-galactosidase, and/or a gene encoding another preselected product is cloned downstream of the hCMV promoter in the HR'vector, and is operatively linked so as to form a transcriptional unit. A VSV-G pseudotyped retroviral vector system is capable of infecting a wide variety of cells including cells from different species and of integrating into the genome. Some retroviruses, i.e., lentiviruses, such as HIV, have the ability to infect non-dividing cells. Lentiviruses have a limited capacity for heterologous DNA sequences, the size limit for this vector being 7-7.5 kilobases (Verma, I.M. and Somia, N., *Gene Therapy – promises, problems and prospects*, Nature 389:239-242 [1997]). *In vivo* experiments with lentiviruses show that expression does not shut off like other retroviral vectors and that *in vivo* expression in brain, muscle, liver or pancreatic-islet cells, is sustained at least for over six months – the longest time tested so far (Verma and Somia [1997]; Anderson, WF., *Human Gene Therapy*, Nature (Suppl). 392:25-30 [1998]).

All of the above viruses may require modification to render them non-pathogenic or less antigenic. Other known viral vector systems, however, are also useful within the confines of the invention.

A particularly useful expression vector which is useful to express foreign cDNA and which may be used in vaccine preparation is *Vaccinia* virus. In this case, the heterologous cDNA is inserted into the *Vaccinia* genome. Techniques for the insertion of foreign cDNA into the vaccinia virus genome are known in the art, and utilize, for example, homologous recombination. The insertion of the heterologous cDNA is generally into a gene which is non-essential in nature, for example, the thymidine kinase gene (tk), which also provides a selectable marker. Plasmid vectors that greatly facilitate the construction of recombinant viruses have been described (see, for example, Mackett *et al.* (1984) in "*DNA Cloning*" Vol II IRL Press, p. 191, Chakrabarti *et al.* (1985), Mol. Cell Biol. 5:3403; Moss (1987) in "*Gene Transfer Vectors for Mammalian Cells*" (Miller and Calos, eds., p. 10). Expression of the desired polypeptides containing immunoreactive regions then occurs in cells and mammals that are infected and/or immunized with the live recombinant *Vaccinia* virus.

The inventive "nucleic acid construct" also encompasses a construct that is not contained in a vector, for example, a synthetic antisense oligonucleotide, such as a phosphorothioate oligodeoxynucleotide. Synthetic antisense oligonucleotides, or other antisense chemical structures designed to recognize and selectively bind to mRNA, are constructed to be complementary to portions of the *Cryptovirus* coding strand, for example, to coding sequences shown in SEQ ID NO:3, 5, 7, 9, 11, 13, 15, 17, 19, 21, or 23. When taken up by a mammalian cell, the antisense oligonucleotide prevents translational expression of at least part of the *Cryptovirus* coding region, the inventive antisense oligonucleotide is useful to prevent expression of a *Cryptovirus* protein. Antisense oligonucleotides inactivate target mRNA sequences by either binding thereto and inducing degradation of the mRNA by, for example, RNase I digestion, or inhibiting translation of mRNA target sequence by interfering with the binding of translation-regulating factors or ribosomes, or by inclusion of other chemical structures, such as ribozyme sequences or reactive chemical groups which either degrade or chemically modify the target mRNA. Gene-based therapy strategies employing antisense oligonucleotides are well known in the art. (E.g., Rait, A. et al., *3'-End conjugates of minimally phosphorothioate-protected oligonucleotides with 1-O-hexadecylglycerol: synthesis and anti-ras activity in radiation-resistant cells*, Bioconjug Chem., 11(2):153-60 [2000]; Stenton, G. R. et al., *Aerosolized syk antisense suppresses syk expression, mediator release from macrophages, and pulmonary inflammation*, J. Immunol., 164(7):3790-7 [2000]; Suzuki, J. et al., *Antisense Bcl-x oligonucleotide induces apoptosis and prevents arterial neointimal formation in murine cardiac allografts*, Cardiovas. Res., 45(3):783-7 [2000]; Kim, J. W. et al., *Antisense oligodeoxynucleotide of glyceraldehyde-3-phosphate dehydrogenase gene inhibits cell proliferation and induces apoptosis in human cervical carcinoma cell line*, Antisense Nucleic Acid Drug Dev., 9(6):507-13 [1999]; Han, D. C. *et al.*, *Therapy with antisense TGF-betal oligodeoxynucleotides reduces kidney weight and matrix mRNAs in diabetic mice*, Am. J. Physiol. Renal Physiol., 278(4):F628-F634 [2000]; Scala, S. et al., *Adenovirus-mediated suppression of HMGI (Y) protein synthesis as potential therapy of human malignant neoplasias*, Proc. Natl. Acad. Sci. USA., 97(8):4256-4261 [2000]; Arteaga, C. L., *et al.*, *Tissue-targeted antisense c-fos retroviral vector inhibits established breast cancer xenografts in nude mice*, Cancer Res., 56(5):1098-1103 [1996]; Muller, M. et al., *Antisense phosphorothioate oligodeoxynucleotide down-regulation of the insulin-like growth factor I receptor in ovarian cancer cells*, Int. J. Cancer, 77(4):567-71 [1998]; Engelhard, H. H., *Antisense Oligodeoxynucleotide Technology: Potential Use for the Treatment of Malignant Brain Tumors*, Cancer Control, 5(2):163-170 [1998]; Alvarez-Salas, L. M. et al., *Growth inhibition of cervical tumor cells by antisense oligodeoxynucleotides directed to the human papillomavirus type 16 E6 gene*, Antisense Nucleic Acid

Drug Dev., 9(5):441-50 [1999]; Im, S. A., et al., *Antiangiogenesis treatment for gliomas: transfer of antisense-vascular endothelial growth factor inhibits tumor growth in vivo*, Cancer Res., 59(4):895-900 [1999]; Maeshima, Y. et al., *Antisense oligonucleotides to proliferating cell nuclear antigen and Ki-67 inhibit human mesangial cell proliferation*, J. Am. Soc. Nephrol., 7(10):2219-29 [1996]; Chen, D. S. et al., *Retroviral Vector-mediated transfer of an antisense cyclin G1 construct inhibits osteosarcoma tumor growth in nude mice*, Hum. Gene Ther, 8(14):1667-74 [1997]; Hirao, T. et al., *Antisense epidermal growth factor receptor delivered by adenoviral vector blocks tumor growth in human gastric cancer*, Cancer Gene Ther. 6(5):423-7 [1999]; Wang, X. Y. et al., *Antisense inhibition of protein kinase Calpha reverses the transformed phenotype in human lung carcinoma cells*, Exp. Cell Res., 250(1):253-63 [1999]; Sacco, M.G. et al., *In vitro and in vivo antisense-mediated growth inhibition of a mammary adenocarcinoma from MMTV-neu transgenic mice*, Gene Ther., 5(3);388-93 [1998]; Leonetti, C. et al., *Antitumor effect of c-myc antisense phosphorothioate oligodeoxynucleotides on human melanoma cells in vitro and in mice*, J. Natl. Cancer Inst., 88(7):419-29 [1996]; Laird, A. D. et al., *Inhibition of tumor growth in liver epithelial cells transfected with a transforming growth factor alpha antisense gene*, Cancer Res. 54(15):4224-32 (Aug 1, 1994); Yazaki, T. et al., *Treatment of glioblastoma U-87 by systemic administration of an antisense protein kinase C-alpha phosphorothioate oligodeoxynucleotide*, Mol. Pharmacol., 50(2):236-42 [1996]; Ho, P. T. *et al., Antisense oligonucleotides as therapeutics for malignant diseases, Semin. Oncol., 24(2):187-202* [1997]; Muller, M. *et al., Antisense phosphorothioate oligodeoxynucleotide down-regulation of the insulin-like growth factor I receptor in ovarian cancer cells*, Int. J. Cancer, 77(4):567-71 [1998]; Elez, R. *et al., Polo-like kinasel, a new target for antisense tumor therapy*, Biochem. Biophys. Res. Commun., 269(2):352-6 [2000]; Monia, B. P. et al., *Antitumor activity of a phosphorothioate antisense oligodeoxynucleotide targeted against C-raf kinase*, Nat. Med., 2(6):668-75 [1996]).

The present invention relates to an isolated *Cryptovirus* protein. The term "protein" refers to a polymer of amino acids of any length, i.e., a polypeptide, and does not refer to a specific length of the product; thus, "polypeptides", "peptides", and "oligopeptides", are included within the definition of "protein", and such terms are used interchangeably herein with "protein". The term "protein" also includes post-expression modifications of the polypeptide, for example, glycosylations, acetylations, phosphorylations and the like. Included within the definition of "protein" are, for example, polypeptides containing one or more analogs of an amino acid (including, for example, unnatural amino acids, etc.), polypeptides with substituted linkages, as well as other modifications known in the

art, both naturally occurring and non-naturally occurring. Methods of inserting analogs of amino acids into a peptide sequence are known in the art.

The phrase "isolated *Cryptovirus* protein" refers to a cryptoviral protein which is substantially free, i.e., contains less than about 50%, preferably less than about 70%, and even more preferably less than about 90%, of the cellular components and/or contaminants normally associated with a native in vivo environment. An isolated *Cryptovirus* protein of the present invention can also be further isolated from one or more other components of a *Cryptovirus* particle, for example, other *Cryptovirus* protein species, phospholipid components of the viral envelope, or the viral genome. In some useful embodiments the inventive isolated *Cryptovirus* protein is purified to homogeneity by known virological and biochemical methods.

The inventive protein is encoded by a *Cryptovirus*-specific nucleic acid segment, which nucleic acid segment comprises:

(i) contiguous nucleotide positions 152-1678 of (SEQ ID NO:1)(also designated SEQ ID NO:3), or a degenerate coding sequence, which encodes the *Cryptovirus* nucleocapsid (NP) protein;

(ii) contiguous nucleotide positions 1850-2515 of (SEQ ID NO:1)(also designated SEQ ID NO:5), or a degenerate coding sequence, which encodes a *Cryptovirus* RNA binding (V) protein thought to be a component of the viral RNA-dependent RNA polymerase;

(iii) contiguous nucleotide positions 1850-3023 of (SEQ ID NO:1)(also designated SEQ ID NO:33) combined with a further insertion of two guanine (G) residues between nucleotide position 2339 of (SEQ ID NO:1) and nucleotide position 2340 of (SEQ ID NO:1)(the combined coding sequence including the "GG" insertion being designated [SEQ ID NO:7]), or a degenerate coding sequence thereof; this frameshift-causing insertion into the mRNA encoding the *Cryptovirus* nucleocapsid-associated phosphoprotein (P protein) occurs during processing of the mRNA and is not templated by the Cryptovirus minus stranded RNA genomic sequence;

(iv) contiguous nucleotide positions 3141-4271 of (SEQ ID NO:1)(also designated SEQ ID NO:9), or a degenerate coding sequence, which encodes the *Cryptovirus* virion-associated matrix or membrane (M) protein;

(v) contiguous nucleotide positions 4530-6182 of (SEQ ID NO:1)(also designated SEQ ID NO:11) or a degenerate coding sequence, which encodes the *Cryptovirus* (uncleaved) fusion (F) protein, which is a propeptide form of a major envelope-associated glycoprotein, and includes a 19-amino acid signal region at its amino terminus;

(vi) contiguous nucleotide positions 4587-6182 of (SEQ ID NO:1)(also designated SEQ ID NO:13), or a degenerate coding sequence, which encodes the *Cryptovirus* (uncleaved) fusion (F_0)

protein, which is a propeptide form of a major envelope-associated glycoprotein, minus the 19-amino acid signal region at its amino terminus;

(vii) contiguous nucleotide positions 4587-4835 of (SEQ ID NO:1)(also designated SEQ ID NO:15), or a degenerate coding sequence, which encodes the cleaved F_2 protein;

(viii) contiguous nucleotide positions 4836-6182 of (SEQ ID NO:1)(also designated SEQ ID NO:17), or a degenerate coding sequence, which encodes the cleaved F_1 protein, including a 22-amino acid carboxy terminal peptide segment that is thought to be important to *Cryptovirus* infectivity;

(ix) contiguous nucleotide positions 6303-6434 of (SEQ ID NO:1)(also designated SEQ ID NO:19), or a degenerate coding sequence, which encodes the *Cryptovirus* SH protein, a small envelope-associated protein;

(x) contiguous nucleotide positions 6584-8278 of (SEQ ID NO:1)(also designated SEQ ID NO:21), or a degenerate coding sequence, which encodes the *Cryptovirus* hemagglutinin (HN) protein, another major envelope protein; or

(xi) contiguous nucleotide positions 8414-15178 of (SEQ ID NO:1)(also designated SEQ ID NO:23), or a degenerate coding sequence, which encodes the *Cryptovirus* largest nucleocapsid associated protein (L protein).

These are the amino acid sequences corresponding to the preceding inventive proteins in the same order:

(i) NP has the following amino acid sequence (SEQ ID NO:4):

```
Met Ser Ser Val Leu Lys Ala Tyr Glu Arg Phe Thr Leu Thr Gln Glu
 1               5                  10                  15
Leu Gln Asp Gln Ser Glu Glu Gly Thr Ile Pro Pro Thr Thr Leu Lys
            20                  25                  30
Pro Val Ile Arg Val Phe Val Leu Thr Ser Asn Asn Pro Glu Leu Arg
        35                  40                  45
Ser Arg Leu Leu Leu Phe Cys Leu Arg Ile Val Leu Ser Asn Gly Ala
    50                  55                  60
Arg Asp Ser His Arg Phe Gly Ala Leu Leu Thr Met Phe Ser Leu Pro
65                  70                  75                  80
Ser Ala Thr Met Leu Asn His Val Lys Leu Ala Asp Gln Ser Pro Glu
                85                  90                  95
Ala Asp Ile Glu Arg Val Glu Ile Asp Gly Phe Glu Glu Gly Ser Phe
            100                 105                 110
Arg Leu Ile Pro Asn Ala Arg Ser Gly Met Ser Arg Gly Glu Ile Asn
        115                 120                 125
Ala Tyr Ala Ala Leu Ala Glu Asp Leu Pro Asp Thr Leu Asn His Ala
    130                 135                 140
Thr Pro Phe Val Asp Ser Glu Val Glu Gly Thr Ala Trp Asp Glu Ile
145                 150                 155                 160
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Glu Thr Phe Leu Asp Met Cys Tyr Ser Val Leu Met Gln Ala Trp Ile
                165                 170                 175
Val Thr Cys Lys Cys Met Thr Ala Pro Asp Gln Pro Ala Ala Ser Ile
            180                 185                 190
Glu Lys Arg Leu Gln Lys Tyr Arg Gln Gln Gly Arg Ile Asn Pro Arg
        195                 200                 205
Tyr Leu Leu Gln Pro Glu Ala Arg Arg Ile Ile Gln Asn Val Ile Arg
    210                 215                 220
Lys Gly Met Val Val Arg His Phe Leu Thr Phe Glu Leu Gln Leu Ala
225                 230                 235                 240
Arg Ala Gln Ser Leu Val Ser Asn Arg Tyr Tyr Ala Met Val Gly Asp
                245                 250                 255
Val Gly Lys Tyr Ile Glu Asn Cys Gly Met Gly Gly Phe Phe Leu Thr
            260                 265                 270
Leu Lys Tyr Ala Leu Gly Thr Arg Trp Pro Thr Leu Ala Leu Ala Ala
        275                 280                 285
Phe Ser Gly Glu Leu Thr Lys Leu Lys Ser Leu Met Ala Leu Tyr Gln
    290                 295                 300
Thr Leu Gly Glu Gln Ala Arg Tyr Leu Ala Leu Leu Glu Ser Pro His
305                 310                 315                 320
Leu Met Asp Phe Ala Ala Ala Asn Tyr Pro Leu Leu Tyr Ser Tyr Ala
                325                 330                 335
Met Gly Ile Gly Tyr Val Leu Asp Val Asn Met Arg Asn Tyr Ala Phe
            340                 345                 350
Ser Arg Ser Tyr Met Asn Lys Thr Tyr Phe Gln Leu Gly Met Glu Thr
        355                 360                 365
Ala Arg Lys Gln Gln Gly Ala Val Asp Met Arg Met Ala Glu Asp Leu
    370                 375                 380
Gly Leu Thr Gln Ala Glu Arg Thr Glu Met Ala Asn Thr Leu Ala Lys
385                 390                 395                 400
Leu Thr Thr Ala Asn Arg Gly Ala Asp Thr Arg Gly Gly Val Asn Pro
                405                 410                 415
Phe Ser Ser Val Thr Gly Thr Thr Gln Met Pro Ala Ala Ala Thr Gly
            420                 425                 430
Asp Thr Phe Glu Ser Tyr Met Ala Ala Asp Arg Leu Arg Gln Arg Tyr
        435                 440                 445
Ala Asp Ala Gly Thr His Asp Asp Glu Met Pro Pro Leu Glu Glu Glu
    450                 455                 460
Glu Glu Asp Asp Thr Ser Ala Gly Pro Arg Thr Glu Pro Thr Pro Glu
465                 470                 475                 480
Gln Val Ala Leu Asp Ile Gln Ser Ala Ala Val Gly Ala Pro Ile His
                485                 490                 495
Thr Asp Asp Leu Asn Ala Ala Leu Gly Asp Leu Asp Ile
            500                 505
```

//(SEQ ID NO:4);

(ii) V has the following amino acid sequence (SEQ ID NO:6):

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

//(SEQ ID NO:6);

(iii) P has the following amino acid sequence (SEQ ID NO:8):

```
Met Asp Pro Thr Asp Leu Ser Phe Ser Pro Asp Glu Ile Asn Lys Leu
 1               5                  10                  15
Ile Glu Thr Gly Leu Asn Thr Val Glu Tyr Phe Thr Ser Gln Gln Val
            20                  25                  30
Thr Gly Thr Ser Ser Leu Gly Lys Asn Thr Ile Pro Pro Gly Val Thr
        35                  40                  45
Gly Leu Leu Thr Asn Ala Ala Glu Ala Lys Ile Gln Glu Ser Ile Asn
    50                  55                  60
His Gln Lys Gly Ser Val Gly Gly Gly Thr Asn Pro Lys Lys Pro Arg
65                  70                  75                  80
Ser Lys Ile Ala Ile Val Pro Ala Asp Asp Lys Thr Val Pro Glu Lys
                85                  90                  95
Pro Ile Pro Asn Pro Leu Leu Gly Leu Asp Ser Thr Pro Ser Thr Gln
            100                 105                 110
Thr Val Leu Asp Leu Ser Gly Lys Thr Leu Pro Ser Gly Ser Tyr Lys
        115                 120                 125
Gly Val Lys Leu Ala Lys Phe Gly Lys Glu Asn Leu Met Thr Arg Phe
    130                 135                 140
Ile Glu Glu Pro Arg Glu Asn Pro Ile Ala Thr Ser Ser Pro Ile Asp
145                 150                 155                 160
Phe Lys Arg Gly Ala Glu Ile Pro Val Gly Ser Ile Glu Gly Ser Thr
                165                 170                 175
Gln Ser Asp Gly Trp Glu Met Lys Ser Arg Ser Leu Ser Gly Ala Ile
            180                 185                 190
```

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

//(SEQ ID NO:8);

(iv) M has the following amino acid sequence (SEQ ID NO:10):

```
Met Pro Ser Ile Ser Ile Pro Ala Asp Pro Thr Asn Pro Arg Gln Ser
 1                   5                  10                  15
Ile Lys Ala Phe Pro Ile Val Ile Asn Ser Asp Gly Gly Glu Lys Gly
            20                  25                  30
Arg Leu Val Lys Gln Leu Arg Thr Thr Tyr Leu Asn Asp Leu Asp Thr
        35                  40                  45
His Glu Pro Leu Val Thr Phe Val Asn Thr Tyr Gly Phe Ile Tyr Glu
    50                  55                  60
Gln Asn Arg Gly Asn Ala Ile Val Gly Glu Asp Gln Leu Gly Lys Lys
65                  70                  75                  80
Arg Glu Ala Val Thr Ala Ala Met Val Thr Leu Gly Cys Gly Pro Asn
                85                  90                  95
Leu Pro Ser Leu Gly Asn Val Leu Arg Gln Leu Ser Glu Phe Gln Val
            100                 105                 110
Ile Val Arg Lys Thr Ser Ser Lys Ala Glu Glu Met Val Phe Glu Ile
        115                 120                 125
Val Lys Tyr Pro Arg Ile Phe Arg Gly His Thr Leu Ile Gln Lys Gly
    130                 135                 140
Leu Val Cys Val Ser Ala Glu Lys Phe Val Lys Ser Pro Gly Lys Val
145                 150                 155                 160
Gln Ser Gly Met Asp Tyr Leu Phe Ile Pro Thr Phe Leu Ser Val Thr
                165                 170                 175
```

```
Tyr Cys Pro Ala Ala Ile Lys Phe Gln Val Pro Gly Pro Met Leu Lys
            180                 185                 190
Met Arg Ser Arg Tyr Thr Gln Ser Leu Gln Leu Glu Leu Met Ile Arg
        195                 200                 205
Ile Leu Cys Lys Pro Asp Ser Pro Leu Met Lys Val His Ile Pro Asp
    210                 215                 220
Lys Glu Gly Arg Gly Cys Leu Val Ser Val Trp Leu His Val Cys Asn
225                 230                 235                 240
Ile Phe Lys Ser Gly Asn Lys Asn Gly Ser Glu Trp Gln Glu Tyr Trp
                245                 250                 255
Met Arg Lys Cys Ala Asn Met Gln Leu Glu Val Ser Ile Ala Asp Met
            260                 265                 270
Trp Gly Pro Thr Ile Ile Ile His Ala Arg Gly His Ile Pro Lys Ser
        275                 280                 285
Ala Lys Leu Phe Phe Gly Lys Gly Gly Trp Ser Cys His Pro Leu His
    290                 295                 300
Glu Ile Val Pro Ser Val Thr Lys Thr Leu Trp Ser Val Gly Cys Glu
305                 310                 315                 320
Ile Thr Lys Ala Lys Ala Ile Ile Gln Glu Ser Ser Ile Ser Leu Leu
                325                 330                 335
Val Glu Thr Thr Asp Ile Ile Ser Pro Lys Val Lys Ile Ser Ser Lys
            340                 345                 350
His Arg Arg Phe Gly Lys Ser Asn Trp Gly Leu Phe Lys Lys Thr Lys
        355                 360                 365
Ser Leu Pro Asn Leu Thr Glu Leu Glu
    370                 375         //(SEQ ID NO:10);
```

(v) F has the following amino acid sequence (SEQ ID NO:12):

```
Met Ser Thr Ile Ile Gln Ser Leu Val Val Ser Cys Leu Leu Ala Gly
 1                   5                  10                  15
Ala Gly Ser Leu Asp Pro Ala Ala Leu Met Gln Ile Gly Val Ile Pro
            20                  25                  30
Thr Asn Val Arg Gln Leu Met Tyr Tyr Thr Glu Ala Ser Ser Ala Phe
        35                  40                  45
Ile Val Val Lys Leu Met Pro Thr Ile Asp Ser Pro Ile Ser Gly Cys
    50                  55                  60
Asn Ile Thr Ser Ile Ser Ser Tyr Asn Ala Thr Val Thr Lys Leu Leu
65                  70                  75                  80
Gln Pro Ile Gly Glu Asn Leu Glu Thr Ile Arg Asn Gln Leu Ile Pro
                85                  90                  95
Thr Arg Arg Arg Arg Arg Phe Ala Gly Val Val Ile Gly Leu Ala Ala
            100                 105                 110
Leu Gly Val Ala Thr Ala Ala Gln Val Thr Ala Ala Val Ala Leu Val
        115                 120                 125
Lys Ala Asn Glu Asn Thr Ala Ala Ile Leu Asn Leu Lys Asn Ala Ile
    130                 135                 140
Gln Lys Thr Asn Ala Ala Val Ala Asp Val Val Gln Ala Thr Gln Ser
145                 150                 155                 160
Leu Gly Thr Ala Val Gln Ala Val Gln Asp His Ile Asn Ser Val Ile
                165                 170                 175
```

```
Ser Pro Ala Ile Thr Ala Ala Asn Cys Lys Ala Gln Asp Ala Ile Ile
            180                 185                 190
Gly Ser Ile Leu Asn Leu Tyr Leu Thr Glu Leu Thr Thr Ile Phe His
        195                 200                 205
Asn Gln Ile Thr Asn Pro Ala Leu Ser Pro Ile Thr Ile Gln Ala Leu
    210                 215                 220
Arg Ile Leu Leu Gly Ser Thr Leu Pro Thr Val Val Glu Lys Ser Phe
225                 230                 235                 240
Asn Thr Gln Ile Ser Ala Ala Glu Leu Leu Ser Ser Gly Leu Leu Thr
                245                 250                 255
Gly Gln Ile Val Gly Leu Asp Leu Thr Tyr Met Gln Met Val Ile Lys
            260                 265                 270
Ile Glu Leu Pro Thr Leu Thr Val Gln Pro Ala Thr Gln Ile Ile Asp
        275                 280                 285
Leu Ala Thr Ile Ser Ala Phe Ile Asn Asn Gln Glu Val Met Ala Gln
    290                 295                 300
Leu Pro Thr Arg Val Ile Val Thr Gly Ser Leu Ile Gln Ala Tyr Pro
305                 310                 315                 320
Ala Ser Gln Cys Thr Ile Thr Pro Asn Thr Val Tyr Cys Arg Tyr Asn
                325                 330                 335
Asp Ala Gln Val Leu Ser Asp Asp Thr Met Ala Cys Leu Gln Gly Asn
            340                 345                 350
Leu Thr Arg Cys Thr Phe Ser Pro Val Val Gly Ser Phe Leu Thr Arg
        355                 360                 365
Phe Val Leu Phe Asp Gly Ile Val Tyr Ala Asn Cys Arg Ser Met Leu
    370                 375                 380
Cys Lys Cys Met Gln Pro Ala Ala Val Ile Leu Gln Pro Ser Ser Ser
385                 390                 395                 400
Pro Val Thr Val Ile Asp Met His Lys Cys Val Ser Leu Gln Leu Asp
                405                 410                 415
Asp Leu Arg Phe Thr Ile Thr Gln Leu Ala Asn Val Thr Tyr Asn Ser
            420                 425                 430
Thr Ile Lys Leu Glu Thr Ser Gln Ile Leu Pro Ile Asp Pro Leu Asp
        435                 440                 445
Ile Ser Gln Asn Leu Ala Ala Val Asn Lys Ser Leu Ser Asp Ala Leu
    450                 455                 460
Gln His Leu Ala Gln Ser Asp Thr Tyr Leu Ser Ala Ile Thr Ser Ala
465                 470                 475                 480
Thr Thr Thr Ser Val Leu Ser Ile Ile Ala Ile Cys Leu Gly Ser Leu
                485                 490                 495
Gly Leu Ile Leu Ile Ile Leu Leu Ser Val Val Val Trp Lys Leu Leu
            500                 505                 510
Thr Ile Val Ala Ala Asn Arg Asn Arg Met Glu Asn Phe Val Tyr His
        515                 520                 525
Asn Ser Ala Phe His His Pro Arg Ser Asp Leu Ser Glu Lys Asn Gln
    530                 535                 540
Pro Ala Thr Leu Gly Thr Arg
545                 550
```

//(SEQ ID NO:12);

(vi) F_0 has the following amino acid sequence (SEQ ID NO:14):

```
Leu Asp Pro Ala Ala Leu Met Gln Ile Gly Val Ile Pro Thr Asn Val
 1               5                  10                  15
Arg Gln Leu Met Tyr Tyr Thr Glu Ala Ser Ser Ala Phe Ile Val Val
            20                  25                  30
Lys Leu Met Pro Thr Ile Asp Ser Pro Ile Ser Gly Cys Asn Ile Thr
        35                  40                  45
Ser Ile Ser Ser Tyr Asn Ala Thr Val Thr Lys Leu Leu Gln Pro Ile
    50                  55                  60
Gly Glu Asn Leu Glu Thr Ile Arg Asn Gln Leu Ile Pro Thr Arg Arg
65                  70                  75                  80
Arg Arg Arg Phe Ala Gly Val Val Ile Gly Leu Ala Ala Leu Gly Val
                85                  90                  95
Ala Thr Ala Ala Gln Val Thr Ala Ala Val Ala Leu Val Lys Ala Asn
            100                 105                 110
Glu Asn Thr Ala Ala Ile Leu Asn Leu Lys Asn Ala Ile Gln Lys Thr
        115                 120                 125
Asn Ala Ala Val Ala Asp Val Val Gln Ala Thr Gln Ser Leu Gly Thr
    130                 135                 140
Ala Val Gln Ala Val Gln Asp His Ile Asn Ser Val Ile Ser Pro Ala
145                 150                 155                 160
Ile Thr Ala Ala Asn Cys Lys Ala Gln Asp Ala Ile Ile Gly Ser Ile
                165                 170                 175
Leu Asn Leu Tyr Leu Thr Glu Leu Thr Thr Ile Phe His Asn Gln Ile
            180                 185                 190
Thr Asn Pro Ala Leu Ser Pro Ile Thr Ile Gln Ala Leu Arg Ile Leu
        195                 200                 205
Leu Gly Ser Thr Leu Pro Thr Val Val Glu Lys Ser Phe Asn Thr Gln
    210                 215                 220
Ile Ser Ala Ala Glu Leu Leu Ser Ser Gly Leu Leu Thr Gly Gln Ile
225                 230                 235                 240
Val Gly Leu Asp Leu Thr Tyr Met Gln Met Val Ile Lys Ile Glu Leu
                245                 250                 255
Pro Thr Leu Thr Val Gln Pro Ala Thr Gln Ile Ile Asp Leu Ala Thr
            260                 265                 270
Ile Ser Ala Phe Ile Asn Asn Gln Glu Val Met Ala Gln Leu Pro Thr
        275                 280                 285
Arg Val Ile Val Thr Gly Ser Leu Ile Gln Ala Tyr Pro Ala Ser Gln
    290                 295                 300
Cys Thr Ile Thr Pro Asn Thr Val Tyr Cys Arg Tyr Asn Asp Ala Gln
305                 310                 315                 320
Val Leu Ser Asp Asp Thr Met Ala Cys Leu Gln Gly Asn Leu Thr Arg
                325                 330                 335
Cys Thr Phe Ser Pro Val Val Gly Ser Phe Leu Thr Arg Phe Val Leu
            340                 345                 350
Phe Asp Gly Ile Val Tyr Ala Asn Cys Arg Ser Met Leu Cys Lys Cys
        355                 360                 365
Met Gln Pro Ala Ala Val Ile Leu Gln Pro Ser Ser Ser Pro Val Thr
    370                 375                 380
Val Ile Asp Met His Lys Cys Val Ser Leu Gln Leu Asp Asp Leu Arg
```

385 390 395 400
Phe Thr Ile Thr Gln Leu Ala Asn Val Thr Tyr Asn Ser Thr Ile Lys
405 410 415
Leu Glu Thr Ser Gln Ile Leu Pro Ile Asp Pro Leu Asp Ile Ser Gln
420 425 430
Asn Leu Ala Ala Val Asn Lys Ser Leu Ser Asp Ala Leu Gln His Leu
435 440 445
Ala Gln Ser Asp Thr Tyr Leu Ser Ala Ile Thr Ser Ala Thr Thr Thr
450 455 460
Ser Val Leu Ser Ile Ile Ala Ile Cys Leu Gly Ser Leu Gly Leu Ile
465 470 475 480
Leu Ile Ile Leu Leu Ser Val Val Val Trp Lys Leu Leu Thr Ile Val
485 490 495
Ala Ala Asn Arg Asn Arg Met Glu Asn Phe Val Tyr His Asn Ser Ala
500 505 510
Phe His His Pro Arg Ser Asp Leu Ser Glu Lys Asn Gln Pro Ala Thr
515 520 525
Leu Gly Thr Arg
530 //(SEQ ID NO:14);

(vii) F_2 has the folowing amino acid sequence (SEQ ID NO:16):

Leu Asp Pro Ala Ala Leu Met Gln Ile Gly Val Ile Pro Thr Asn Val
1 5 10 15
Arg Gln Leu Met Tyr Tyr Thr Glu Ala Ser Ser Ala Phe Ile Val Val
20 25 30
Lys Leu Met Pro Thr Ile Asp Ser Pro Ile Ser Gly Cys Asn Ile Thr
35 40 45
Ser Ile Ser Ser Tyr Asn Ala Thr Val Thr Lys Leu Leu Gln Pro Ile
50 55 60
Gly Glu Asn Leu Glu Thr Ile Arg Asn Gln Leu Ile Pro Thr Arg Arg
65 70 75 80
Arg Arg Arg
//(SEQ ID NO:16);

(viii) F_1 has the amino acid sequence (SEQ ID NO:18);

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

```
                100                 105                 110
Ala Leu Ser Pro Ile Thr Ile Gln Ala Leu Arg Ile Leu Leu Gly Ser
            115                 120                 125
Thr Leu Pro Thr Val Val Glu Lys Ser Phe Asn Thr Gln Ile Ser Ala
    130                 135                 140
Ala Glu Leu Leu Ser Ser Gly Leu Leu Thr Gly Gln Ile Val Gly Leu
145                 150                 155                 160
Asp Leu Thr Tyr Met Gln Met Val Ile Lys Ile Glu Leu Pro Thr Leu
                165                 170                 175
Thr Val Gln Pro Ala Thr Gln Ile Ile Asp Leu Ala Thr Ile Ser Ala
            180                 185                 190
Phe Ile Asn Asn Gln Glu Val Met Ala Gln Leu Pro Thr Arg Val Ile
        195                 200                 205
Val Thr Gly Ser Leu Ile Gln Ala Tyr Pro Ala Ser Gln Cys Thr Ile
    210                 215                 220
Thr Pro Asn Thr Val Tyr Cys Arg Tyr Asn Asp Ala Gln Val Leu Ser
225                 230                 235                 240
Asp Asp Thr Met Ala Cys Leu Gln Gly Asn Leu Thr Arg Cys Thr Phe
                245                 250                 255
Ser Pro Val Val Gly Ser Phe Leu Thr Arg Phe Val Leu Phe Asp Gly
            260                 265                 270
Ile Val Tyr Ala Asn Cys Arg Ser Met Leu Cys Lys Cys Met Gln Pro
        275                 280                 285
Ala Ala Val Ile Leu Gln Pro Ser Ser Ser Pro Val Thr Val Ile Asp
    290                 295                 300
Met His Lys Cys Val Ser Leu Gln Leu Asp Asp Leu Arg Phe Thr Ile
305                 310                 315                 320
Thr Gln Leu Ala Asn Val Thr Tyr Asn Ser Thr Ile Lys Leu Glu Thr
                325                 330                 335
Ser Gln Ile Leu Pro Ile Asp Pro Leu Asp Ile Ser Gln Asn Leu Ala
            340                 345                 350
Ala Val Asn Lys Ser Leu Ser Asp Ala Leu Gln His Leu Ala Gln Ser
        355                 360                 365
Asp Thr Tyr Leu Ser Ala Ile Thr Ser Ala Thr Thr Thr Ser Val Leu
    370                 375                 380
Ser Ile Ile Ala Ile Cys Leu Gly Ser Leu Gly Leu Ile Leu Ile Ile
385                 390                 395                 400
Leu Leu Ser Val Val Val Trp Lys Leu Leu Thr Ile Val Ala Ala Asn
                405                 410                 415
Arg Asn Arg Met Glu Asn Phe Val Tyr His Asn Ser Ala Phe His His
            420                 425                 430
Pro Arg Ser Asp Leu Ser Glu Lys Asn Gln Pro Ala Thr Leu Gly Thr
        435                 440                 445
Arg
```

//(SEQ ID NO:18);

(ix) SH has the following amino acid sequence (SEQ ID NO:20):

```
Met Leu Pro Asp Pro Glu Asp Pro Glu Ser Lys Lys Ala Thr Arg Arg
 1               5                  10                  15
```

```
Thr Gly Asn Leu Ile Ile Cys Phe Leu Phe Ile Phe Phe Leu Phe Val
            20                  25                  30
Thr Leu Ile Val Pro Thr Leu Arg His Leu Leu Ser
        35                  40                  //(SEQ ID NO:20);
```

(x) HN has the following amino acid sequence (SEQ ID NO:22):

```
Met Ile Ala Glu Asp Ala Pro Val Lys Gly Thr Cys Arg Val Leu Phe
 1               5                  10                  15
Arg Thr Thr Thr Leu Ile Phe Leu Cys Thr Leu Leu Ala Leu Ser Ile
            20                  25                  30
Ser Ile Leu Tyr Glu Ser Leu Ile Thr Gln Lys Gln Ile Met Ser Gln
        35                  40                  45
Ala Gly Ser Thr Gly Ser Asn Ser Gly Leu Gly Gly Ile Thr Asp Leu
    50                  55                  60
Leu Asn Asn Ile Leu Ser Val Ala Asn Gln Ile Ile Tyr Asn Ser Ala
65                  70                  75                  80
Val Ala Leu Pro Leu Gln Leu Asp Thr Leu Glu Ser Thr Leu Leu Thr
                85                  90                  95
Ala Ile Lys Ser Leu Gln Thr Ser Asp Lys Leu Glu Gln Asn Cys Ser
            100                 105                 110
Trp Gly Ala Ala Leu Ile Asn Asp Asn Arg Tyr Ile Asn Gly Ile Asn
        115                 120                 125
Gln Phe Tyr Phe Ser Ile Ala Glu Gly Arg Asn Leu Thr Leu Gly Pro
    130                 135                 140
Leu Leu Asn Ile Pro Ser Phe Ile Pro Thr Ala Thr Thr Pro Glu Gly
145                 150                 155                 160
Cys Thr Arg Ile Pro Ser Phe Ser Leu Thr Lys Thr His Trp Cys Tyr
                165                 170                 175
Thr His Asn Val Ile Leu Asn Gly Cys Gln Asp His Val Ser Ser Asn
            180                 185                 190
Gln Phe Val Ser Met Gly Ile Ile Glu Pro Thr Ser Ala Gly Phe Pro
        195                 200                 205
Ser Phe Arg Thr Leu Lys Thr Leu Tyr Leu Ser Asp Gly Val Asn Arg
    210                 215                 220
Lys Ser Cys Ser Ile Ser Thr Val Pro Gly Gly Cys Met Met Tyr Cys
225                 230                 235                 240
Phe Val Ser Thr Gln Pro Glu Arg Asp Asp Tyr Phe Ser Thr Ala Pro
                245                 250                 255
Pro Glu Gln Arg Ile Ile Ile Met Tyr Tyr Asn Asp Thr Ile Val Glu
            260                 265                 270
Arg Ile Ile Asn Pro Pro Gly Val Leu Asp Val Trp Ala Thr Leu Asn
        275                 280                 285
Pro Gly Thr Gly Ser Gly Val Tyr Tyr Leu Gly Trp Val Leu Phe Pro
    290                 295                 300
Ile Tyr Gly Gly Val Ile Lys Asn Thr Ser Leu Trp Asn Asn Gln Ala
305                 310                 315                 320
Asn Lys Tyr Phe Ile Pro Gln Met Val Ala Ala Leu Cys Ser Gln Asn
                325                 330                 335
Gln Ala Thr Gln Val Gln Asn Ala Lys Ser Ser Tyr Tyr Ser Ser Trp
            340                 345                 350
```

```
Phe Gly Asn Arg Met Ile Gln Ser Gly Ile Leu Ala Cys Pro Leu Gln
        355                 360                 365
Gln Asp Leu Thr Asn Glu Cys Leu Val Leu Pro Phe Ser Asn Asp Gln
    370                 375                 380
Val Leu Met Gly Ala Glu Gly Arg Leu Tyr Met Tyr Gly Asp Ser Val
385                 390                 395                 400
Tyr Tyr Tyr Gln Arg Ser Asn Ser Trp Trp Pro Met Thr Met Leu Tyr
                405                 410                 415
Lys Val Thr Ile Thr Phe Thr Asn Gly Gln Pro Ser Ala Ile Ser Ala
            420                 425                 430
Gln Asn Val Pro Thr Gln Gln Val Pro Arg Pro Gly Thr Gly Asp Cys
        435                 440                 445
Phe Ala Thr Asn Arg Cys Pro Gly Phe Cys Leu Thr Gly Val Tyr Ala
    450                 455                 460
Asp Ala Trp Leu Leu Thr Asn Pro Ser Ser Thr Ser Thr Phe Gly Ser
465                 470                 475                 480
Glu Ala Thr Phe Thr Gly Ser Tyr Leu Asn Ala Ala Thr Gln Arg Ile
                485                 490                 495
Asn Pro Thr Met Tyr Ile Ala Asn Asn Thr Gln Ile Ile Ser Ser Gln
            500                 505                 510
Gln Phe Gly Ser Ser Gly Gln Glu Ala Ala Tyr Gly His Thr Thr Cys
        515                 520                 525
Phe Arg Asp Thr Gly Ser Val Met Val Tyr Cys Ile Tyr Ile Ile Glu
    530                 535                 540
Leu Ser Ser Ser Leu Leu Gly Gln Phe Gln Ile Val Pro Phe Ile Arg
545                 550                 555                 560
Gln Val Thr Leu Ser
                565 //(SEQ ID NO:22);
```

and

(xi) L has the following amino acid sequence (SEQ ID NO:24):

```
Met Ala Gly Ser Arg Glu Ile Leu Leu Pro Glu Val His Leu Asn Ser
 1                5                  10                  15
Pro Ile Val Lys His Lys Leu Tyr Tyr Tyr Ile Leu Leu Gly Asn Leu
            20                  25                  30
Pro Asn Glu Ile Asp Ile Asp Asp Leu Gly Pro Leu His Asn Gln Asn
        35                  40                  45
Trp Asn Gln Ile Ala His Glu Glu Ser Asn Leu Ala Gln Arg Leu Val
    50                  55                  60
Asn Val Arg Asn Phe Leu Ile Thr His Ile Pro Asp Leu Arg Lys Gly
65                  70                  75                  80
His Trp Gln Glu Tyr Val Asn Val Ile Leu Trp Pro Arg Ile Leu Pro
                85                  90                  95
Leu Ile Pro Asp Phe Lys Ile Asn Asp Gln Leu Pro Leu Leu Lys Asn
            100                 105                 110
Trp Asp Lys Leu Val Lys Glu Ser Cys Ser Val Ile Asn Ala Gly Thr
        115                 120                 125
Ser Gln Cys Ile Gln Asn Leu Ser Tyr Gly Leu Thr Gly Arg Gly Asn
    130                 135                 140
```

Leu Phe Thr Arg Ser Arg Glu Leu Ser Gly Asp Arg Arg Asp Ile Asp
145 150 155 160
Leu Lys Thr Val Val Ala Ala Trp His Asp Ser Asp Trp Lys Arg Ile
165 170 175
Ser Asp Phe Trp Ile Met Ile Lys Phe Gln Met Arg Gln Leu Ile Val
180 185 190
Arg Gln Thr Asp His Asn Asp Pro Asp Leu Ile Thr Tyr Ile Glu Asn
195 200 205
Arg Glu Gly Ile Ile Ile Ile Thr Pro Glu Leu Val Ala Leu Phe Asn
210 215 220
Thr Glu Asn His Thr Leu Thr Tyr Met Thr Phe Glu Ile Val Leu Met
225 230 235 240
Val Ser Asp Met Tyr Glu Gly Arg His Asn Ile Leu Ser Leu Cys Thr
245 250 255
Val Ser Thr Tyr Leu Asn Pro Leu Lys Lys Arg Ile Thr Tyr Leu Leu
260 265 270
Ser Leu Val Asp Asn Leu Ala Phe Gln Ile Gly Asp Ala Val Tyr Asn
275 280 285
Ile Ile Ala Leu Leu Glu Ser Phe Val Tyr Ala Gln Leu Gln Met Ser
290 295 300
Asp Pro Ile Pro Glu Leu Arg Gly Gln Phe His Ala Phe Val Cys Ser
305 310 315 320
Glu Ile Leu Asp Ala Leu Arg Gly Thr Asn Ser Phe Thr Gln Asp Glu
325 330 335
Leu Arg Thr Val Thr Thr Asn Leu Ile Ser Pro Phe Gln Asp Leu Thr
340 345 350
Pro Asp Leu Thr Ala Glu Leu Leu Cys Ile Met Arg Leu Trp Gly His
355 360 365
Pro Met Leu Thr Ala Ser Gln Ala Ala Gly Lys Val Arg Glu Ser Met
370 375 380
Cys Ala Gly Lys Val Leu Asp Phe Pro Thr Ile Met Lys Thr Leu Ala
385 390 395 400
Phe Phe His Thr Ile Leu Ile Asn Gly Tyr Arg Arg Lys His His Gly
405 410 415
Val Trp Pro Pro Leu Asn Leu Pro Gly Asn Ala Ser Lys Gly Leu Thr
420 425 430
Glu Leu Met Asn Asp Asn Thr Glu Ile Ser Tyr Glu Phe Thr Leu Lys
435 440 445
His Trp Lys Glu Ile Ser Leu Ile Lys Phe Lys Lys Cys Phe Asp Ala
450 455 460
Asp Ala Gly Glu Glu Leu Ser Ile Phe Met Lys Asp Lys Ala Ile Ser
465 470 475 480
Ala Pro Lys Gln Asp Trp Met Ser Val Phe Arg Arg Ser Leu Ile Lys
485 490 495
Gln Arg His Gln His His Gln Val Pro Leu Pro Asn Pro Phe Asn Arg
500 505 510
Arg Leu Leu Leu Asn Phe Leu Gly Asp Asp Lys Phe Asp Pro Asn Val
515 520 525
Glu Leu Gln Tyr Val Thr Ser Gly Glu Tyr Leu His Asp Asp Thr Phe
530 535 540
Cys Ala Ser Tyr Ser Leu Lys Glu Lys Glu Ile Lys Pro Asp Gly Arg

545 550 555 560
Ile Phe Ala Lys Leu Thr Lys Arg Met Arg Ser Cys Gln Val Ile Ala
565 570 575
Glu Ser Leu Leu Ala Asn His Ala Gly Lys Leu Met Lys Glu Asn Gly
580 585 590
Val Val Met Asn Gln Leu Ser Leu Thr Lys Ser Leu Leu Thr Met Ser
595 600 605
Gln Ile Gly Ile Ile Ser Glu Arg Ala Arg Lys Ser Thr Arg Asp Asn
610 615 620
Ile Asn Arg Pro Gly Phe Gln Asn Ile Gln Arg Asn Lys Ser His His
625 630 635 640
Ser Lys Gln Val Asn Gln Arg Asp Pro Ser Asp Asp Phe Glu Leu Ala
645 650 655
Ala Ser Phe Leu Thr Thr Asp Leu Lys Lys Tyr Cys Leu Gln Trp Arg
660 665 670
Tyr Gln Thr Ile Ile Pro Phe Ala Gln Ser Leu Asn Arg Met Tyr Gly
675 680 685
Tyr Pro His Leu Phe Glu Trp Ile His Leu Arg Leu Met Arg Ser Thr
690 695 700
Leu Tyr Val Gly Asp Pro Phe Asn Pro Pro Ala Asp Thr Ser Gln Phe
705 710 715 720
Asp Leu Asp Lys Val Ile Asn Gly Asp Ile Phe Ile Val Ser Pro Arg
725 730 735
Gly Gly Ile Glu Gly Leu Cys Gln Lys Ala Trp Thr Met Ile Ser Ile
740 745 750
Ser Val Ile Ile Leu Ser Ala Thr Glu Ser Gly Thr Arg Val Met Ser
755 760 765
Met Val Gln Gly Asp Asn Gln Ala Ile Ala Val Thr Thr Arg Val Pro
770 775 780
Arg Ser Leu Pro Thr Leu Glu Lys Lys Thr Ile Ala Phe Arg Ser Cys
785 790 795 800
Asn Leu Phe Phe Glu Arg Leu Lys Cys Asn Asn Phe Gly Leu Gly His
805 810 815
His Leu Lys Glu Gln Glu Thr Ile Ile Ser Ser His Phe Phe Val Tyr
820 825 830
Ser Lys Arg Ile Phe Tyr Gln Gly Arg Ile Leu Thr Gln Ala Leu Lys
835 840 845
Asn Ala Ser Lys Leu Cys Leu Thr Ala Asp Val Leu Gly Glu Cys Thr
850 855 860
Gln Ser Ser Cys Ser Asn Leu Ala Thr Thr Val Met Arg Leu Thr Glu
865 870 875 880
Asn Gly Val Glu Lys Asp Ile Cys Phe Tyr Leu Asn Ile Tyr Met Thr
885 890 895
Ile Lys Gln Leu Ser Tyr Asp Ile Ile Phe Pro Gln Val Ser Ile Pro
900 905 910
Gly Asp Gln Ile Thr Leu Glu Tyr Ile Asn Asn Pro His Leu Val Ser
915 920 925
Arg Leu Ala Leu Leu Pro Ser Gln Leu Gly Gly Leu Asn Tyr Leu Ser
930 935 940
Cys Ser Arg Leu Phe Asn Arg Asn Ile Gly Asp Pro Val Val Ser Ala
945 950 955 960

Val Ala Asp Leu Lys Arg Leu Ile Lys Ser Gly Cys Met Asp Tyr Trp
965 970 975
Ile Leu Tyr Asn Leu Leu Gly Arg Lys Pro Gly Asn Gly Ser Trp Ala
980 985 990
Thr Leu Ala Ala Asp Pro Tyr Ser Ile Asn Ile Glu Tyr Gln Tyr Pro
995 1000 1005
Pro Thr Thr Ala Leu Lys Arg His Thr Gln Gln Val Leu Met Glu Leu
1010 1015 1020
Ser Thr Asn Pro Met Leu Arg Gly Ile Phe Ser Asp Asn Ala Gln Ala
1025 1030 1035 1040
Glu Glu Asn Asn Leu Ala Arg Phe Leu Leu Asp Arg Glu Val Ile Phe
1045 1050 1055
Pro Arg Val Ala His Ile Ile Ile Glu Gln Thr Ser Val Gly Arg Arg
1060 1065 1070
Lys Gln Ile Gln Gly Tyr Leu Asp Ser Thr Arg Ser Ile Met Arg Lys
1075 1080 1085
Ser Leu Glu Ile Lys Pro Leu Ser Asn Arg Lys Leu Asn Glu Ile Leu
1090 1095 1100
Asp Tyr Asn Ile Asn Tyr Leu Ala Tyr Asn Leu Ala Leu Leu Lys Asn
1105 1110 1115 1120
Ala Ile Glu Pro Pro Thr Tyr Leu Lys Ala Met Thr Leu Glu Thr Cys
1125 1130 1135
Ser Ile Asp Ile Ala Arg Ser Leu Arg Lys Leu Ser Trp Ala Pro Leu
1140 1145 1150
Leu Gly Gly Arg Asn Leu Glu Gly Leu Glu Thr Pro Asp Pro Ile Glu
1155 1160 1165
Ile Thr Ala Gly Ala Leu Ile Val Gly Ser Gly Tyr Cys Glu Gln Cys
1170 1175 1180
Ala Ala Gly Asp Asn Arg Phe Thr Trp Phe Phe Leu Pro Ser Gly Ile
1185 1190 1195 1200
Glu Ile Gly Gly Asp Pro Arg Asp Asn Pro Pro Ile Arg Val Pro Tyr
1205 1210 1215
Ile Gly Ser Arg Thr Asp Glu Arg Arg Val Ala Ser Met Ala Tyr Ile
1220 1225 1230
Arg Gly Ala Ser Ser Ser Leu Lys Ala Val Leu Arg Leu Ala Gly Val
1235 1240 1245
Tyr Ile Trp Ala Phe Gly Asp Thr Leu Glu Asn Trp Ile Asp Ala Leu
1250 1255 1260
Asp Leu Ser His Thr Arg Val Asn Ile Thr Leu Glu Gln Leu Gln Ser
1265 1270 1275 1280
Leu Thr Pro Leu Pro Thr Ser Ala Asn Leu Thr His Arg Leu Asp Asp
1285 1290 1295
Gly Thr Thr Thr Leu Lys Phe Thr Pro Ala Ser Ser Tyr Thr Phe Ser
1300 1305 1310
Ser Phe Thr His Ile Ser Asn Asp Glu Gln Tyr Leu Thr Ile Asn Asp
1315 1320 1325
Lys Thr Ala Asp Ser Asn Ile Ile Tyr Gln Gln Leu Met Ile Thr Gly
1330 1335 1340
Leu Gly Ile Leu Glu Thr Trp Asn Asn Pro Pro Ile Asn Arg Thr Phe
1345 1350 1355 1360
Glu Glu Ser Thr Leu His Leu His Thr Gly Ala Ser Cys Cys Val Arg

1365 1370 1375
Pro Val Asp Ser Cys Ile Ile Ser Glu Ala Leu Thr Val Lys Pro His
1380 1385 1390
Ile Thr Val Pro Tyr Ser Asn Lys Phe Val Phe Asp Glu Asp Pro Leu
1395 1400 1405
Ser Glu Tyr Glu Thr Ala Lys Leu Glu Ser Leu Ser Phe Gln Ala Gln
1410 1415 1420
Leu Gly Asn Ile Asp Ala Val Asp Met Thr Gly Lys Leu Thr Leu Leu
1425 1430 1435 1440
Ser Gln Phe Thr Ala Arg Gln Ile Ile Asn Ala Ile Thr Gly Leu Asp
1445 1450 1455
Glu Ser Val Ser Leu Thr Asn Asp Ala Ile Val Ala Ser Asp Tyr Val
1460 1465 1470
Ser Asn Trp Ile Ser Glu Cys Met Tyr Thr Lys Leu Asp Glu Leu Phe
1475 1480 1485
Met Tyr Cys Gly Trp Glu Leu Leu Leu Glu Leu Ser Tyr Gln Met Tyr
1490 1495 1500
Tyr Leu Arg Val Val Gly Trp Ser Asn Ile Val Asp Tyr Ser Tyr Met
1505 1510 1515 1520
Ile Leu Arg Arg Ile Pro Gly Ala Ala Leu Asn Asn Leu Ala Ser Thr
1525 1530 1535
Leu Ser His Pro Lys Leu Phe Arg Arg Ala Ile Asn Leu Asp Ile Val
1540 1545 1550
Ala Pro Leu Asn Ala Pro His Phe Ala Ser Leu Asp Tyr Ile Lys Met
1555 1560 1565
Ser Met Asp Ala Ile Leu Trp Gly Cys Lys Arg Val Ile Asn Val Leu
1570 1575 1580
Ser Asn Gly Gly Asp Leu Glu Leu Val Val Thr Ser Glu Asp Ser Leu
1585 1590 1595 1600
Ile Leu Ser Asp Arg Ser Met Asn Leu Ile Ala Arg Lys Leu Thr Leu
1605 1610 1615
Leu Ser Leu Ile His His Asn Gly Leu Glu Leu Pro Lys Ile Lys Gly
1620 1625 1630
Phe Ser Pro Asp Glu Lys Cys Phe Ala Leu Thr Glu Phe Leu Arg Lys
1635 1640 1645
Val Val Asn Ser Gly Leu Ser Ser Ile Glu Asn Leu Ser Asn Phe Met
1650 1655 1660
Tyr Asn Val Glu Asn Pro Arg Leu Ala Ala Phe Ala Ser Asn Asn Tyr
1665 1670 1675 1680
Tyr Leu Thr Arg Lys Leu Leu Asn Ser Ile Arg Asp Thr Glu Ser Gly
1685 1690 1695
Gln Val Ala Val Thr Ser Tyr Tyr Glu Ser Leu Glu Tyr Ile Asp Ser
1700 1705 1710
Leu Lys Leu Thr Pro His Val Pro Gly Thr Ser Cys Ile Glu Asp Asp
1715 1720 1725
Ser Leu Cys Thr Asn Asp Tyr Ile Ile Trp Ile Ile Glu Ser Asn Ala
1730 1735 1740
Asn Leu Glu Lys Tyr Pro Ile Pro Asn Ser Pro Glu Asp Asp Ser Asn
1745 1750 1755 1760
Phe His Asn Phe Lys Leu Asn Ala Pro Ser His His Thr Leu Arg Pro
1765 1770 1775

Leu Gly Leu Ser Ser Thr Ala Trp Tyr Lys Gly Ile Ser Cys Cys Arg
1780 1785 1790
Tyr Leu Glu Arg Leu Lys Leu Pro Gln Gly Asp His Leu Tyr Ile Ala
1795 1800 1805
Glu Gly Ser Gly Ala Ser Met Thr Ile Ile Glu Tyr Leu Phe Pro Gly
1810 1815 1820
Arg Lys Ile Tyr Tyr Asn Ser Leu Phe Ser Ser Gly Asp Asn Pro Pro
1825 1830 1835 1840
Gln Arg Asn Tyr Ala Pro Met Pro Thr Gln Phe Ile Glu Ser Val Pro
1845 1850 1855
Tyr Lys Leu Trp Gln Ala His Thr Asp Gln Tyr Pro Glu Ile Phe Glu
1860 1865 1870
Asp Phe Ile Pro Leu Trp Asn Gly Asn Ala Ala Met Thr Asp Ile Gly
1875 1880 1885
Met Thr Ala Cys Val Glu Phe Ile Ile Asn Arg Val Gly Pro Arg Thr
1890 1895 1900
Cys Ser Leu Val His Val Asp Leu Glu Ser Ser Ala Ser Leu Asn Gln
1905 1910 1915 1920
Gln Cys Leu Ser Lys Pro Ile Ile Asn Ala Ile Ile Thr Ala Thr Thr
1925 1930 1935
Val Leu Cys Pro His Gly Val Leu Ile Leu Lys Tyr Ser Trp Leu Pro
1940 1945 1950
Phe Thr Arg Phe Ser Thr Leu Ile Thr Phe Leu Trp Cys Tyr Phe Glu
1955 1960 1965
Arg Ile Thr Val Leu Arg Ser Thr Tyr Ser Asp Pro Ala Asn His Glu
1970 1975 1980
Val Tyr Leu Ile Cys Ile Leu Ala Asn Asn Phe Ala Phe Gln Thr Val
1985 1990 1995 2000
Ser Gln Ala Thr Gly Met Ala Met Thr Leu Thr Asp Gln Gly Phe Thr
2005 2010 2015
Leu Ile Ser Pro Glu Arg Ile Asn Gln Tyr Trp Asp Gly His Leu Lys
2020 2025 2030
Gln Glu Arg Ile Val Ala Glu Ala Ile Asp Lys Val Val Leu Gly Glu
2035 2040 2045
Asn Ala Leu Phe Asn Ser Ser Asp Asn Glu Leu Ile Leu Lys Cys Gly
2050 2055 2060
Gly Thr Pro Asn Ala Arg Asn Leu Ile Asp Ile Glu Pro Val Ala Thr
2065 2070 2075 2080
Phe Ile Glu Phe Glu Gln Leu Ile Cys Thr Met Leu Thr Thr His Leu
2085 2090 2095
Lys Glu Ile Ile Asp Ile Thr Arg Ser Gly Thr Gln Asp Tyr Glu Ser
2100 2105 2110
Leu Leu Leu Thr Pro Tyr Asn Leu Gly Leu Leu Gly Lys Ile Ser Thr
2115 2120 2125
Ile Val Arg Leu Leu Thr Glu Arg Ile Leu Asn His Thr Ile Arg Asn
2130 2135 2140
Trp Leu Ile Leu Pro Pro Ser Leu Gln Met Ile Val Lys Gln Asp Leu
2145 2150 2155 2160
Glu Phe Gly Ile Phe Arg Ile Thr Ser Ile Leu Asn Ser Asp Arg Phe
2165 2170 2175
Leu Lys Leu Ser Pro Asn Arg Lys Tyr Leu Ile Thr Gln Leu Thr Ala

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            2180                2185                2190
Gly Tyr Ile Arg Lys Leu Ile Glu Gly Asp Cys Asn Ile Asp Leu Thr
        2195                2200                2205
Arg Pro Ile Gln Lys Gln Ile Trp Lys Ala Leu Gly Cys Val Val Tyr
    2210                2215                2220
Cys His Asp Pro Met Asp Gln Arg Glu Ser Thr Glu Phe Ile Asp Ile
2225                2230                2235                2240
Asn Ile Asn Glu Glu Ile Asp Arg Gly Ile Asp Gly Glu Glu Ile
                2245                2250                2255
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//(SEQ ID NO:24).

The inventive protein also encompasses a polypeptide having substantially the same amino acid sequence as (SEQ ID NO:4), (SEQ ID NO:6) (SEQ ID NO:8), (SEQ ID NO:10), (SEQ ID NO:12), (SEQ ID NO:14), (SEQ ID NO:16), (SEQ ID NO:18), (SEQ ID NO:20), (SEQ ID NO:22), or (SEQ ID NO:24). As employed herein, the term "substantially the same amino acid sequence" refers to amino acid sequences having at least about 80%, still more preferably about 90% amino acid identity with respect to a reference amino acid sequence; with greater than about 95% amino acid sequence identity being especially preferred. It is recognized, however, that polypeptide containing less than the described levels of sequence identity arising as splice variants or that are modified by conservative amino acid substitutions are also encompassed within the scope of the present invention. The degree of sequence homology is determined by conducting an amino acid sequence similarity search of a protein data base, such as the database of the National Center for Biotechnology Information (NCBI; www.ncbi.nlm.nih.gov/BLAST/), using a computerized algorithm, such as PowerBLAST, QBLAST, PSI-BLAST, PHI-BLAST, gapped or ungapped BLAST, or the "Align" program through the Baylor College of Medicine server (www.hgsc.bcm.tmc.edu/seq_data). (E.g., Altchul, S.F., *et al.*, *Gapped BLAST and PSI-BLAST: a new generation of protein database search programs*, Nucleic Acids Res. 25(17):3389-402 [1997]; Zhang, J., & Madden, T.L., *PowerBLAST: a new network BLAST application for interactive or automated sequence analysis and annotation*, Genome Res. 7(6):649-56 [1997]; Madden, T.L., *et al.*, *Applications of network BLAST server*, Methods Enzymol. 266:131-41 [1996]; Altschul, S.F., *et al.*, *Basic local alignment search tool*, J. Mol. Biol. 215(3):403-10 [1990]).

Also encompassed by the term *Cryptovirus* protein, are biologically functional or active peptide analogs thereof. The term peptide "analog" includes any polypeptide having an amino acid residue sequence substantially identical to a sequence specifically shown herein in which one or more residues have been conservatively substituted with a functionally similar residue and which displays the ability to mimic the biological activity of a native *Cryptovirus* protein.

Examples of conservative substitutions include the substitution of one non-polar (hydrophobic) residue such as isoleucine, valine, leucine or methionine for another, the substitution of one polar (hydrophilic) residue for another such as between arginine and lysine, between glutamine and asparagine, between glycine and serine, the substitution of one basic residue such as lysine, arginine or histidine for another, or the substitution of one acidic residue, such as aspartic acid or glutamic acid for another.

The phrase "conservative substitution" also includes the use of a chemically derivatized residue in place of a non-derivatized residue, provided that such polypeptide displays the requisite biological activity.

"Chemical derivative" refers to a subject polypeptide having one or more residues chemically derivatized by reaction of a functional side group. Such derivatized molecules include, for example, those molecules in which free amino groups have been derivatized to form amine hydrochlorides, p-toluene sulfonyl groups, carbobenzoxy groups, t-butyloxycarbonyl groups, chloroacetyl groups or formyl groups. Free carboxyl groups may be derivatized to form salts, methyl and ethyl esters or other types of esters or hydrazides. Free hydroxyl groups may be derivatized to form O-acyl or O-alkyl derivatives. The imidazole nitrogen of histidine may be derivatized to form N-im-benzylhistidine. Also included as chemical derivatives are those peptides which contain one or more naturally occurring amino acid derivatives of the twenty standard amino acids. For example, 4-hydroxyproline may be substituted for proline; 5-hydroxylysine may be substituted for lysine; 3-methylhistidine may be substituted for histidine; homoserine may be substituted for serine; and ornithine may be substituted for lysine. The inventive polypeptide also includes any polypeptide having one or more additions and/or deletions of residues, relative to the sequence of an inventive polypeptide whose sequence is shown herein, so long as the requisite biological activity is maintained.

The present invention also encompasses a variant of a *Cryptovirus* protein designated by (SEQ ID NO:4), (SEQ ID NO:6) (SEQ ID NO:8), (SEQ ID NO:10), (SEQ ID NO:12), (SEQ ID NO:14), (SEQ ID NO:16), (SEQ ID NO:18), (SEQ ID NO:20), (SEQ ID NO:22), or (SEQ ID NO:24); a "variant" refers to a polypeptide in which the amino acid sequence of the designated *Cryptovirus* protein has been altered by the deletion, substitution, addition or rearrangement of one or more amino acids in the sequence. Methods by which variants occur (for example, by recombination) or are made (for example, by site directed mutagenesis) are known in the art.

The *Cryptovirus* protein can also include one or more labels, which are known to those of skill in the art.

The inventive proteins are isolated or purified by a variety of known biochemical means, including, for example, by the recombinant expression systems described herein, precipitation, gel filtration, ion-exchange, reverse-phase and affinity chromatography, electrophoresis, and the like. Other well-known methods are described in Deutscher *et al.*, *Guide to Protein Purification: Methods in Enzymology* Vol. 182, (Academic Press, [1990]).

The isolated *Cryptovirus* protein of the present invention can also be chemically synthesized. For example, synthetic polypeptide can be produced using Applied Biosystems, Inc. Model 430A or 431A automatic peptide synthesizer (Foster City, CA) employing the chemistry provided by the manufacturer and the amino acid sequences provided herein. Alternatively, the *Cryptovirus* protein can be isolated or purified from native cellular sources. Alternatively, the *Cryptovirus* protein can be isolated from the inventive chimeric proteins by the use of suitable proteases.

Alternatively, the *Cryptovirus* proteins can be recombinantly derived, for example, produced by eukaryotic or prokaryotic cells genetically modified to express *Cryptovirus* protein-encoding polynucleotides in accordance with the inventive technology as described herein. Recombinant methods are well known, as described, for example, in Sambrook *et al.*, supra., 1989). An example of the means for preparing the inventive *Cryptovirus* protein is to express nucleic acids encoding the *Cryptovirus* protein of interest in a suitable host cell that contains the inventive expression vector, such as a bacterial cell, a yeast cell, an insect cell, an amphibian cell (i.e., oocyte), or a mammalian cell, using methods well known in the art, and recovering the expressed polypeptide, again using well-known methods.

"Recombinant host cells", "host cells", "cells", "cell lines", "cell cultures", and other such terms denoting prokaryotic or eukaryotic cell lines cultured as unicellular or monolayer entities, and refer to cells which can be, or have been, used as recipients for a recombinant expression vector or other foreign nucleic acids, such as DNA or RNA, and include the progeny of the original cell which has been transfected. It is understood that the progeny of a single parental cell may not necessarily be completely identical in morphology or in genomic or total DNA complement as the original parent, due to natural, accidental, or deliberate mutation.

The present invention includes chimeric proteins. The term "chimeric protein" generally refers to a polypeptide comprising an amino acid sequence drawn from two or more individual proteins that are not naturally so linked. In the present invention, "chimeric protein" is used to denote a polypeptide comprising a *Crytovirus* protein, or a truncate or polypeptide variant thereof having an altered amino acid sequence, fused to a non-*Cryptovirus* protein or polypeptide moiety.

Chimeric proteins are most conveniently produced by expression of a fused gene, which encodes a portion of one polypeptide at the 5' end and a portion of a different polypeptide at the 3' end, where the different portions are joined in one reading frame which may be expressed in a suitable host cell. In some embodiments, the *Cryptovirus* protein is positioned at the carboxy terminus of the chimeric protein. In other embodiments the *Cryptovirus* protein is positioned at the amino terminus of the chimeric protein.

The non-*Cryptovirus* protein moiety, or "chimeric partner", of the inventive chimeric protein can be a functional enzyme fragment. Suitable functional enzyme fragments are those polypeptides which exhibit a quantifiable activity when expressed fused to the *Cryptovirus* protein. Exemplary enzymes include, without limitation, ß-galactosidase (ß-gal), ß-lactamase, horseradish peroxidase (HRP), glucose oxidase (GO), human superoxide dismutase (hSOD), urease, and the like. These enzymes are convenient because the amount of chimeric protein produced can be quantified by means of simple colorimetric assays. Alternatively, one may employ antigenic proteins or fragments, e.g., human superoxide dismutase (hSOD), to permit simple detection and quantification of chimeric proteins using antibodies specific for the non-*Cryptovirus* protein chimeric partner. In chimeric proteins, useful chimeric partners include amino acid sequences that provide for secretion from a recombinant host, enhance the immunological reactivity of a *Cryptovirus* protein epitope(s), or facilitate the coupling of the *Cryptovirus* polypeptide to a support or a vaccine carrier. (See, e.g., EPO Pub. No. 116,201; U.S. Pat. No. 4,722,840; EPO Pub. No. 259,149; U.S. Pat. No. 4,629,783).

Embodiments of the inventive *Cryptovirus* protein are useful as immunoreactive polypeptides, including use for the production of a *Cryptovirus*-specific antibody. "Immunoreactive" refers to the ability of a polypeptide to bind immunologically to an antibody and/or to a lymphocyte antigen receptor due to antibody or receptor recognition of a specific epitope contained within the polypeptide; or the ability of a polypeptide to be immunogenic. An "immunogenic" protein is a polypeptide that elicits a cellular and/or humoral immune response, whether alone or linked to a carrier in the presence or absence of an adjuvant. The immunogenicity of various isolated *Cryptovirus* proteins, or *Cryptovirus* protein fragments, of interest is determined by routine screening. Immunological reactivity may be determined by antibody binding, more particularly by the kinetics of antibody binding, and/or by competition in binding using as competitor(s) a known polypeptide(s) containing an epitope against which the antibody is directed. The techniques for determining whether a polypeptide is immunologically reactive with an antibody are known in the art. Particularly useful examples of immunogenic *Cryptovirus* proteins are the envelope proteins, i.e., F, F_0, F_2, F_1, , HN, and SH proteins.

As used herein, "epitope" refers to an antigenic determinant of a polypeptide. An epitope can comprise 3 amino acids in a spatial conformation which is unique to the epitope. Epitopes typically are mapped to comprise at least about five amino acids, more usually at least about 8 amino acids to about 10 amino acids, or more. Methods of determining the spatial conformation of amino acids are known in the art, and include, for example, x-ray crystallography and two-dimensional nuclear magnetic resonance.

Immunogenic *Cryptovirus* proteins are useful for producing or manufacturing vaccines. As described above, *Cryptovirus* belongs to the Paramyxoviridae family of viruses. Numerous vaccines have been developed for humans and domestic animals against viruses in this virus family. For example, there are effective vaccines against measles virus, mumps virus, canine distemper virus, canine parainfluenza virus type 2, and Newcastle's disease virus (of fowl). These viruses were amenable to the development of effective vaccines because they have a narrow species tropism (*i.e.*, they infect only one, or only a few, species), they exist as only one, or only one predominant, serotype (making a vaccine universally protective against the virus), they cause significant morbidity in their host (*i.e.*, they are significant causes of human illness), and they are pandemic (*i.e.*, there is a worldwide concern).

Cryptovirus is amenable to vaccine development for the same reasons other family members have proven so. There is evidence for cross- neutralizability of hyper immune rabbit antiserum made against different sources of the virus, and very similar nucleotide sequences of the virus genome have been obtained from two sources of the virus (BBR strain and Niigata cell-associated strain).

In accordance with the invention, multivalent or monovalent vaccines can be prepared against one or more *Cryptovirus* proteins. In particular, vaccines are contemplated comprising one or more *Cryptovirus* proteins, such as, but not limited to, envelope proteins F, F_0, F_2, F_1, HN, and/or SH. Methods for manufacturing vaccines which contain an immunogenic polypeptide as an active ingredient, are known to one skilled in the art. Typically, such vaccines are prepared as injectable compositions comprising the *Cryptovirus* protein(s), either as liquid solutions or suspensions; solid forms suitable for solution in, or suspension in, liquid prior to injection may also be prepared. The preparation may also be emulsified, or the protein encapsulated in liposomes. The active immunogenic ingredients are typically mixed with excipients which are pharmaceutically acceptable and compatible with the active ingredient. Suitable excipients or carriers are, for example, water, saline, dextrose, glycerol, ethanol, or the like and combinations thereof. In addition, if desired, the vaccine may contain minor amounts of auxiliary substances such as wetting or emulsifying agents, pH buffering agents, and/or adjuvants which enhance the effectiveness of the vaccine.

Examples of adjuvants which may be effective include but are not limited to: aluminum hydroxide, N-acetyl-muramyl-L-theronyl-D-isoglutamine (thr-MDP), N-acetyl-nor-muramyl-L-alanyl-D-isoglutamine (CGP 11637, referred to as nor-MDP), N-acetylmuramyl-L-alanyl-D-isoglutaminyl-L-alanine-2-(1-2-dipalmitoyl-sn-glycero-3-hydroxyphosphoryloxy)-ethylamine (CGP 19835A, referred to as MTP-PE), and RIBI, which contains three components extracted from bacteria, monophosphoryl lipid A, trehalose dimycolate and cell wall skeleton (MPL+TDM+CWS) in a 2% squalene/Tween 80 emulsion. The effectiveness of a particular adjuvant can be determined by measuring the amount of antibodies directed against an immunogenic *Cryptovirus* protein resulting from administration of this protein in vaccines which are also comprised of the adjuvant.

The proteins can be formulated into the vaccine as neutral or salt forms. Pharmaceutically acceptable salts include the acid addition salts (formed with free amino groups of the peptide) and which are formed with inorganic acids such as, for example, hydrochloric or phosphoric acids, or organic acids such as acetic, oxalic, tartaric, maleic, and the like. Salts formed with the free carboxyl groups may also be derived from inorganic bases such as, for example, sodium, potassium, ammonium, calcium, or ferric hydroxides, and such organic bases as isopropylamine, trimethylamine, 2-ethylamino ethanol, histidine, procaine, and the like.

The vaccines are conventionally administered parenterally by injection, for example, either subcutaneously or intramuscularly, but they can also be delivered intranasally, enterically, or by any other delivery route. Administration can be with or without adjuvants. Additional formulations of the vaccine composition that are suitable for other non-injection modes of administration include suppositories and, in some cases, oral formulations. For suppositories, traditional binders and carriers can include, for example, polyalkylene glycols or triglycerides; such suppositories may be formed from mixtures containing the active ingredient in the range of 0.5% to 10%, preferably 1%-2%. Oral formulations include such normally employed excipients as, for example, pharmaceutical grades of mannitol, lactose, starch, magnesium stearate, sodium saccharine, cellulose, magnesium carbonate, and the like. These compositions can take the form of solutions, suspensions, emulsions, tablets, pills, capsules, caplets, sustained release formulations or powders and contain typically 10%-95% of active ingredient, preferably 25%-70%.

In addition to the above, it is also possible to manufacture live vaccines of attenuated microorganisms, e.g., weakened or avirulent virus particles, including mutated *Cryptovirus* particles, and other attenuated virus particles containing an inventive recombinant nucleic acid encoding one or more *Cryptovirus* proteins, or host cells that express recombinant *Cryptovirus* proteins encoded by

inventive expression vectors, as described herein. Suitable attenuated microorganisms are known in the art and include, for example, viruses (e.g., vaccinia virus) as well as bacteria.

Alternatively, killed *Cryptovirus* particles or virions, or killed pseudotyped viral particles or virions bearing *Cryptovirus* envelope proteins, are useful in the manufacture of a vaccine. Virions are killed for vaccine purposes by known methods.

The vaccines are administered in a manner compatible with the dosage formulation, and in such amount as will be prophylactically and/or therapeutically effective. The quantity to be administered, which is generally in the range of about 5 μg to about 250 μg of antigen per dose, depends on the subject to be vaccinated, capacity of the subject's immune system to synthesize antibodies, and the degree of protection desired. Precise amounts of active ingredient required to be administered depend on the judgment of the practitioner and can be particular to each vaccinated animal or human. Any suitable vertebrate animal can be vaccinated, particularly a member of a mammalian species, including rodents, lagomorphs, goats, pigs, cattle, sheep, and primates.

The vaccine may be given in a single dose schedule, or preferably in a multiple dose schedule. A multiple dose schedule is one in which a primary course of vaccination may be with 1-10 separate doses, followed by other doses given at subsequent time intervals required to maintain and/or reinforce the immune response, for example, at 1-4 months for a second dose, and if needed, a subsequent dose(s) after several months. The dosage regimen will also, at least in part, be determined by the immunological characteristics and needs of the individual animal or human to be vaccinated and must be dependent upon the judgment of the practitioner.

In addition, the vaccine containing the *Cryptovirus* proteins described above, can be administered in conjunction with other immunoregulatory agents, for example, immunoglobulins.

Compositions of the present invention can be administered to individual animals or humans to generate polyclonal antibodies (purified or isolated from serum using conventional techniques) which can then be used in a number of applications. For example, the polyclonal antibodies can be used to passively immunize an animal or human, or as immunochemical reagents, as described hereinbelow.

The present invention is also directed to an isolated antibody that specifically binds a *Cryptovirus* protein, such as the *Cryptovirus* NP, V, P, M, F, F_0, F_2, F_1, SH, HN, or L proteins. The term "antibody" refers to a polypeptide or group of polypeptides which are comprised of at least one antibody binding domain. A "binding domain" is formed from the folding of variable domains of an antibody molecule to form three-dimensional binding spaces with an internal surface shape and charge distribution complementary to the features of an epitope of an antigen, which allows an

immunological reaction with the antigen. An antibody binding domain can be formed from a heavy and/or a light chain domain (V_H and V_L, respectively), which form hypervariable loops which contribute to antigen binding. Typical vertebrate antibodies are tetramers or aggregates thereof, comprising light and heavy chains which are typically aggregated in a "Y" configuration and which may or may not have covalent linkages between the chains. In vertebrate antibodies, the amino acid sequences of all the chains of a particular antibody are homologous with the chains found in one antibody produced by the lymphocyte which produces that antibody in vivo, or in vitro (for example, in hybridomas).

An "isolated" antibody is an antibody, for instance polyclonal antibody, removed from the body of an animal or human that produced it. The inventive polyclonal antibody can be further purified from cellular material, e.g., in blood, lymph, or milk. A preferred embodiment is in the form of an antiserum directed against one or more *Cryptovirus* proteins. Alternatively, an "isolated" antibody of the present invention includes antibodies the production of which involves a manipulation or human intervention, for example, monoclonal antibody or chimeric antibody.

The inventive "antibody" includes any immunoglobulin, including IgG, IgM, IgA, IgD or IgE, or antibody fragment that binds a specific *Cryptovirus* epitope. Such antibodies can also be produced by hybridoma, chemical synthesis or recombinant methods known in the art. (E.g., Sambrook *et al.*, *Molecular Cloning: A Laboratory Manual* (2 ed.), Cold Spring Harbor Laboratory Press, Cold Spring Harbor, New York, USA [1989]); Harlow and Lane, *Antibodies: A Laboratory Manual* (Cold Spring Harbor Laboratory [1988]). Both anti-*Cryptovirus* protein and anti-chimeric protein antibodies can be useful within the scope of the present invention. (See, e.g., Bahouth *et al.*, Trends Pharmacol. Sci. 12:338 [1991]; Ausubel *et al.*, *Current Protocols in Molecular Biology* (John Wiley and Sons, NY [1989]). Examples of chimeric antibodies are discussed in U.S. Pat. Nos. 4,816,397 and 4,816,567. Flurorescent-labeled antibodies, enzyme-conjugated antibodies, or antibodies otherwise labeled for facility of detection, as known in the art, are also included within "antibody."

"Antibody" also includes "chimeric antibody." Chimeric antibodies are antibodies in which the heavy and/or light chains are chimeric proteins. Typically the constant domain of the chains is from one particular species and/or class, and the variable domains are from a different species and/or class. Also included is any antibody in which either or both of the heavy or light chains are composed of combinations of sequences mimicking the sequences in antibodies of different sources, whether these sources be differing classes, or different species of origin, and whether or not the fusion point is at the variable/constant boundary. Thus, it is possible to produce antibodies in which neither the

constant nor the variable region mimic known antibody sequences. It then becomes possible, for example, to construct antibodies whose variable region has a higher specific affinity for a particular antigen, or whose constant region can elicit enhanced complement fixation, or to make other improvements in properties possessed by a particular constant region.

Included also within the definition of "antibody" are Fab and $F(ab')_2$ fragments of antibodies. The "Fab" region refers to those portions of the heavy and light chains which are roughly equivalent, or analogous, to the sequences which comprise the branch portion of the heavy and light chains, and which have been shown to exhibit immunological binding to a specified antigen, but which lack the effector F_c portion. A "Fab" fragment is an aggregate of one heavy and one light chain. A $F(ab')_2$ fragment, which also lacks the effector F_c portion, is a tetramer containing the 2H and 2L chains, which are capable of selectively reacting with a designated antigen or antigen family. Methods of producing "Fab" and $F(ab')_2$ fragments of antibodies are known within the art and include, for example, proteolysis, and synthesis by recombinant techniques. Thus, the inventive anti-*Cryptovirus* antibodies can also be Fab or $F(ab')_2$ antibody fragments.

Also useful is a "single domain antibody" (dAb), which is an antibody which is comprised of a V_H domain, which reacts immunologically with a *Cryptovirus* antigen. A dAB does not contain a V_L domain, but may contain other antigen binding domains known to exist in antibodies, for example, the kappa and lambda domains. Methods for preparing dABs are known in the art. (See, e.g., Ward *et al.*, Nature 341: 544 [1989]).

Other preferred embodiments include altered antibodies such as humanized, CDR-grafted or bifunctional, i.e., divalent antibodies, all of which can also be produced by methods well known in the art. "Altered antibodies", which refers to antibodies in which the naturally occurring amino acid sequence in a vertebrate antibody has been varied. Utilizing recombinant DNA techniques, antibodies can be redesigned to obtain desired characteristics. The possible variations are many, and range from the changing of one or more amino acids to the complete redesign of a region, for example, the constant region. Changes in the constant region, in general, to attain desired cellular process characteristics, e.g., changes in complement fixation, interaction with membranes, and other effector functions. Changes in the variable region may be made to alter antigen binding characteristics. The antibody may also be engineered to aid the specific delivery of a molecule or substance to a specific cell or tissue site. The desired alterations may be made by known techniques in molecular biology, e.g., recombinant techniques, site directed mutagenesis, etc.

A preferred embodiment of the inventive antibody specifically binds a *Cryptovirus* envelope protein described hereinabove. Another preferred embodiment of the inventive antibody specifically

binds a *Cryptovirus* nucleocapsid protein, but antibodies that specificaally bind any other *Cryptovirus* protein are also useful and preferred.

The inventive antibody can be used, inter alia, in diagnostic or assay methods and systems to detect *Cryptovirus* proteins present in a sample of biological material. With respect to the detection of such polypeptide, the antibodies can be used for in vitro diagnostic or assay methods, or in vivo imaging methods. Such antibodies can also be used for the immunoaffinity or affinity chromatography purification of the inventive *Cryptovirus* proteins.

The present invention includes an in vitro method of detecting the presence or absence of a *Cryptovirus* protein in a sample of a biological material. The method is particularly, but not exclusively, useful for testing clinical or experimental biological materials for diagnostic or pathology purposes.

The sample is contacted with the inventive antibody described herein; and known immunological procedures are employed for detecting specific binding of the antibody to a constituent of the sample. The presence of specific binding indicates the presence of the *Cryptovirus* protein in the sample.

Immunological procedures, useful for in vitro detection of target *Cryptovirus* proteins in a sample, include immunoassay systems that employ the inventive *Cryptovirus* protein-specific antibody in a detectable form.

Known protocols for such immunoassay techniques and systems are based, for example, upon competition, or direct reaction, or sandwich type assays. Such immunoassay techniques and systems include, for example, ELISA, immunoblotting, immunofluorescence assay (IFA), Pandex microfluorimetric assay, agglutination assays, flow cytometry, serum diagnostic assays and immunohistochemical staining procedures which are well known in the art.

An antibody can be made detectable by various means well known in the art. Assay systems that amplify the signals from a primary antibody-antigen complex are also known; examples of which are assays which utilize biotin and avidin, and enzyme-labeled and mediated immunoassays, such as ELISA assays. A detectable marker can be directly or indirectly attached to a primary or secondary antibody in the assay protocol. Useful markers include, for example, radionuclides, enzymes, fluorogens, chromogens and chemiluminescent labels. Embodiments can employ solid support matrices, or can involve immunoprecipitation.

These same immunoassay techniques and systems can be employed in the inventive method of detecting the presence or absence of a *Cryptovirus*-specific antibody in an antibody-containing biological material. Antibody-containing biological materials include, but are not limited to, whole blood and blood components, plasma, serum, spinal fluid, lymph fluid, the external sections of the respiratory, intestinal, and genitourinary tracts, tears, saliva, milk, white blood cells, and myelomas. Processed antibody-containing fractions or dilutions of any of these are also considered antibody-containing biological materials.

One preferred embodiment of the method of detecting the presence or absence of a *Cryptovirus*-specific antibody involves contacting the sample originating from an individual suspected of having a *Cryptovirus* infection with a viral virion or other viral particle containing one or more Cryptovirus envelope proteins, as described herein, such that, if antibody selectively binding *Cryptovirus* antigen is present, an antibody-bound complex forms. Then any antibody-bound *Cryptovirus* antigen complexes thus formed are contacted with anti-human antibody-binding immunoglobulin or anti-human antibody-binding fragments thereof, for example, Fab and/or $F(ab')_2$, fragments, and complexes of the immunoglobulin or the fragments thereof, are allowed to form with the antibody-bound *Cryptovirus* complexes. The presence or absence of any complexes formed is detected, by any known immunodetection means as described herein. The presence of such complexes indicates the presence in the sample of antibody that selectively binds *Cryptovirus* antigen.

Another more preferred embodiment involves contacting the sample originating from an individual suspected of having a *Cryptovirus* infection with the inventive *Cryptovirus* envelope protein, such that, if antibody selectively binding *Cryptovirus* is present, an antibody-bound envelope protein complex forms. Any antibody-bound envelope protein complexes thus formed are then contacted with anti-human antibody-binding immunoglobulin or anti-human antibody-binding fragments, such as Fab and $F(ab')_2$ fragments. The formation of complexes of the immunoglobulin or the Fab and $F(ab')_2$ fragments thereof is allowed with the antibody-bound envelope protein complexes; and the presence or absence of any antibody-bound envelope protein complexes thus formed is detected. The presence of such complexes indicating the presence in the sample of antibody selectively binding *Cryptovirus*.

The terms "selective" or "specific" binding of antibody to *Cryptovirus* proteins or *Cryptovirus* antigens therein, includes asymmetric cross-reactive binding with closely related rubulaviruses, such as SV5, but does not include non-specific binding to unrelated antigens or surfaces. The skilled artisan is aware of important controls that are preferably included in any

immunoassay system for the determination of non-specific antibody binding. Typically, for example in ELISA, a background level of non-specific binding is determined and used as a baseline.

"Complexed" means that a protein, such as an antibody, is a constituent or member of a complex, i.e., a mixture or adduct resulting from chemical binding or bonding between and/or among the other constituents. Chemical binding or bonding can have the nature of a covalent bond, ionic bond, hydrogen bond, hydrophobic bond, or any combination of these bonding types linking the constituents of the complex at any of their parts or moieties, of which a constituent can have one or a multiplicity of moieties of various sorts. Antibody-antigen binding is typically non-covalent. Not every constituent of a complex need be bound to every other constituent, but each constituent has at least one chemical bond with at least one other constituent of the complex. For example, a secondary antibody in the assay system may not be directly bound with the *Cryptovirus* antigen, or the viral particle or virion, yet it is "complexed" with it.

By way of further non-limiting illustration of a clinical diagnostic embodiment for detecting *Cryptovirus* infection in a human patient, a serum specimen from the patient is screened for *Cryptovirus*-specific antibodies to the major envelope proteins of the virus (F_0 and HN) by ELISA, radio-immunoprecipitation, immunoblotting techniques or any other immunological technique (*e.g.*, direct or indirect fluorescent antibody techniques, immunobeads, *etc.*). Optionally, another blood sample is obtained from any seropositive individual. The virus can be detected in the PBMNCs of such samples by isolating the cells on a suitable gradient medium, culturing the cells in the presence of cyclic GMP and then either (1) screening the cells for intracellular *Cryptovirus*-specific inclusions with *Cryptovirus*-specific fluorescent antibodies or (2) PCR amplification of induced PBMNC with *Cryptovirus*-specific nucleotide primers.

While *Cryptovirus*-specific antibodies have been found in the serum of seropositive individuals, indicating current or former *Cryptovirus* infection, these antibodies are not necessarily indicative of epileptiform or encephalopathic disease. *Cryptovirus* appears to infect and be carried in the PBMNCs of a significant proportion of individuals without necessarily causing encephalopathic disease. These individuals can overtly appear to be asymptomatic. The neuropathological (e.g., epileptiform, encephalopathic, and other neurological, neurodegenerative, and/or neuropsychiatric disease) potential of the virus only appears to become manifest in individuals in whom the virus has infected nervous system tissues. Consequently, only *Cryptovirus*-specific antibodies (*i.e.* those directed against the major envelope proteins of the virus, F and HN) found in the cerebrospinal fluid (CSF) are fully indicative of neurological, neurodegenerative, and/or neuropsychiatric disease and then, they are virtually always indicative. By way of further example, ten human patients who were

previously diagnosed with chronic fatigue syndrome involving significant short-term memory loss, and for whom CSF samples could be obtained, were all found to have *Cryptovirus*-specific antibody in their CSF and electroencephalographic profiles consistent with a diagnosis of absence epilepsy (i.e., *petit mal* epilepsy).

The present invention also relates to an anti-*Cryptovirus* antibody detecting kit, useful for testing or assaying a biological sample, in particular an antibody-containing biological material. Thus, the inventive kits are beneficial for screening clinical supplies of human blood, serum, platelets, plasma, tissues and organs, to determine their safety for transfusion or transplantation purposes. Diagnostic applications of the inventive kits are also useful.

The inventive kit is particularly useful for practicing the inventive assay methods for detecting antibody that selectively binds *Cryptovirus* and its antigens and the inventive methods of detecting the presence or absence of a *Cryptovirus*-specific antibody. In some preferred embodiments, the kit contains an isolated *Cryptovirus* particle, comprising a genome having a nucleotide sequence entirely complementary to (SEQ ID NO:1). The kit also contains labeled anti-human antibody-binding antibody, preferably anti-human immunoglobulin or labeled anti-human antibody-binding antibody fragments, such as Fab and/or $F(ab')_2$. A preferred embodiment of the kit further contains a solid matrix for supporting the *Cryptovirus* particle(s). In a preferred embodiment, the Cryptovirus particles in the anti-*Cryptovirus* antibody detecting kit are *Cryptovirus* virions, and in a preferred embodiment the *Cryptovirus* virions are produced from an acutely *Cryptovirus*-infected cell line, such as an acutely infected baby hamster kidney (BHK) cell-derived cell line, a Vero-derived cell line, or a CV-1-derived cell line (e.g., a CV-1_c-derived cell line, described hereinbelow.).

Alternatively, in a most preferred embodiment of the inventive anti-*Cryptovirus* antibody detecting kit, which does not include *Cryptovirus* particles, the kit includes a plurality of one or more kinds of isolated *Cryptovirus* proteins and/or chimeric proteins comprising a *Cryptovirus* protein moiety, as described hereinabove. In some preferred embodiments, the Cryptovirus protein or protein moiety is an envelope protein, as described herein. Such embodiments also contain labeled anti-human antibody-binding antibody, such as anti-human immunoglobulin or labeled anti-human antibody-binding antibody fragments, such as Fab and/or $F(ab')_2$ fragments. A preferred embodiment of such a kit further contains a solid matrix for supporting the *Cryptovirus* proteins.

Solid matrices, or supports, and methods for attaching or adsorbing viral particles and proteins to a solid matrix, are well known in the art. In accordance with the inventive kits, the term "solid matrix" includes any solid or semi-solid support or surface to which the viral particle or protein

can be anchored or adhered. Suitable matrices are made of glass, plastic, metal, polymer gels, and the like, and may take the form of beads, wells (e.g., single- or multi-well serum plates) slides, dipsticks, membranes, and the like.

As is known to the skilled artisan in using such kits, e.g., for ELISA, RIA, or sandwich-type assays, the biological sample, optimally solubilized or suspended and in an optimized dilution, is contacted with the viral particles or proteins, typically supported on the surface of the solid matrix (e.g., well of a serum plate), and after appropriate washes and incubations, is further contacted with the labeled anti-human antibody-binding immunoglobulin or labeled anti-human antibody-binding fragments. After further washes, commercially available plate readers and/or other accessory detection equipment are typically employed in conjunction with the inventive kit, for detecting the formation of bound anti-human antibody complexes with human antibody that has bound to *Cryptovirus* particles or proteins.

Instructions for use are included in the kit. "Instructions for use" typically include a tangible expression describing the reagent concentration or at least one assay method parameter, such as the relative amounts of reagent and sample to be admixed, maintenance time periods for reagent/sample admixtures, temperature, buffer conditions, incubations, washes, and the like, typically for an intended purpose, in particular the inventive assay methods as described herein.

Optionally, the kit also contains other useful components, such as, diluents, buffers, or other acceptable carriers, specimen containers, syringes, pipetting or measuring tools, paraphernalia for concentrating, sedimenting, or fractionating samples, or the inventive antibodies for use in controls.

The materials or components assembled in the kit can be provided to the practitioner stored in any convenient and suitable ways that preserve their operability and utility. For example the components can be in dissolved, dehydrated, or lyophilized form; they can be provided at room, refrigerated or frozen temperatures.

The components are typically contained in suitable packaging material(s). As employed herein, the phrase "packaging material" refers to one or more physical structures used to house the contents of the kit. The packaging material is constructed by well known methods, preferably to provide a sterile, contaminant-free environment.

The packaging materials employed in the kit are those customarily utilized in virus- and peptide-based systems. As used herein, the term "package" refers to a suitable solid matrix or material such as glass, plastic, paper, foil, and the like, capable of holding the individual kit components. Thus, for example, a package can be a glass vial used to contain suitable quantities of

an inventive composition containing viral or peptide components. The packaging material generally has an external label which indicates the contents, quantities, and/or purpose of the kit and/or its components.

Thus the present invention provides immunoassay methods and kits, useful for research, clinical diagnostics, and screening of blood, blood components or products, and tissue and organs intended for transfusion or transplantation. These applications are of great value and utility, because strong evidence shows that peripheral blood mononuclear cells (PBMNCs) can harbor *Cryptovirus* and can subsequently infect and cause disease in a patient who receives such contaminated blood, blood products, tissues, or cells.

The inventive methods of detecting the presence or absence of a *Cryptovirus*-specific RNA in a sample of a biological material, described hereinabove, are also particularly useful for these and other purposes. In accordance with the most preferred embodiments of the method, *Cryptovirus* RNAs are amplified by any of numerous known methods of amplifying nucleic acid segments, in the form of RNA or cDNA. Before amplification, it is preferable, but not necessary, to extract or separate RNA from DNA in the sample and to amplify nucleic acids remaining in that fraction of the sample separated from the DNA. The amplifications products, if any, are then analyzed to detect the presence of *Cryptovirus*-specific amplification products. If *Cryptovirus*-specific amplification products are present, the findings are indicative of the presence of *Cryptovirus* RNA in the sample. For greater confidence in the interpretation of negatives (i.e., no detectable *Cryptovirus*-specific amplification products), analysis is optionally carried out following a control amplification of mRNAs specific for a cellular housekeeping gene, for example, a gene encoding β-actin, phosphofructokinase (PFK), glyceraldehyde 3-phosphate dehydrogenase, or phosphoglycerate kinase.

The RNAs in the sample, are amplified by a suitable amplification method. For example, in a preferred embodiment, a reverse transcriptase-mediated polymerase chain reaction (RT-PCR) is employed to amplify *Cryptovirus*-specific nucleic acids. Briefly, two enzymes are used in the amplification process, a reverse transcriptase to transcribe *Cryptovirus*-specific cDNA from a *Cryptovirus*-specific RNA template in the sample, a thermal resistant DNA polymerase (e.g., *Taq* polymerase), and *Cryptovirus*-specific primers to amplify the cDNA to produce *Cryptovirus*-specific amplification products. The use of limited cycle PCR yields semi-quantitative results. (E.g., Gelfand *et al., Reverse transcription with thermostable DNA polymerase-high temperature reverse transcription*, U.S. Patent Nos. 5,310,652; 5,322,770; Gelfand *et al., Unconventional nucleotide substitution in temperature selective RT-PCR*, U.S. Patent No. 5,618,703).

In another preferred embodiment of the inventive method, single enzyme RT-PCR is employed to amplify *Cryptovirus*-specific nucleic acids. Single enzymes now exist to perform both reverse transcription and polymerase functions, in a single reaction. For example, the Perkin Elmer recombinant *Thermus thermophilus* (rTth) enzyme (Roche Molecular), or other similar enzymes, are commercially available. Cycling instruments such as the Perkin Elmer ABI Prism 7700, the so-called Light Cycler (Roche Molecular), and/or other similar instruments are useful for carrying out RT-PCR. Optionally, single enzyme RT-PCR technology, for example, employing rTth enzyme, can be used in a PCR system.

By way of illustration only, RT-PCR-based testing is quite sensitive for detection of the virus. For example, a RT-PCR-priming technique has been used to confirm a detectable *Cryptovirus* carriage rate in PBMNCs nonproductively harboring the virus (without culturing, cyclic GMP induction, and passaging) on the order of $1:10^5$ PBMNC. In addition, numerous fragments of the *Cryptovirus* genome have been cloned from AV_3/SSPE cells using *Cryptovirus*-specific primers and a RT-PCR-based amplification technique.

Preferably, amplification and analysis are carried out in an automated fashion, with automated extraction of RNA from a sample, followed by PCR, and fluorescence detection of amplification products using probes, such as TaqMan or Molecular Beacon probes. Typically, the instrumentation includes software that provides quantitative analytical results during or directly following PCR without further amplification or analytical steps.

In another preferred embodiment, transcription-mediated amplification (TMA) is employed to amplify *Cryptovirus*-specific nucleic acids. (E.g., K. Kamisango *et al.*, *Quantitative detection of hepatitis B virus by transcription-mediated amplification and hybridization protection assay*, J. Clin. Microbiol. 37(2):310-14 [1999]; M. Hirose *et al.*, *New method to measure telomerase activity by transcription-mediated amplification and hybridization protection assay*, Clin. Chem. 44(12)2446-52 [1998]). Rather than employing RT-PCR for the amplification of a cDNA, TMA uses a probe that recognizes a *Cryptovirus*-specific (target sequence) RNA; in subsequent steps, from a promoter sequence built into the probe, an RNA polymerase repetitively transcribes a cDNA intermediate, in effect amplifying the original RNA transcripts and any new copies created, for a level of sensitivity approaching that of RT-PCR. The reaction takes place isothermally (one temperature), rather than cycling through different temperatures as in PCR.

Other useful amplification methods include a reverse transcriptase-mediated ligase chain reaction (RT-LCR), which has utility similar to RT-PCR. RT-LCR relies on reverse transcriptase to

generate cDNA from mRNA, then DNA ligase to join adjacent synthetic oligonucleotides after they have bound the target cDNA.

Most preferably, amplification of a *Cryptovirus*-specific nucleic acid segment in the sample can be achieved using *Cryptovirus*-specific oligonucleotide primers of the present invention, as described herein.

Optionally, high throughput analysis may be achieved by multiplexing techniques well known in the art, employing multiple primer sets, for example primers directed not only to *Cryptovirus*-specific nucleic acids, but to amplifying expression products of housekeeping genes (controls) or of other potential diagnostic markers, to yield additional diagnostic information. (E.g., Z. Lin *et al.*, *Multiplex genotype determination at a large number of gene loci*, Proc. Natl. Acad. Sci. USA 93(6):2582-87 [1996]; Demetriou *et al.*, *Method and probe for detection of gene associated with liver neoplastic disease*, U.S. Patent No. 5,866,329).

Hybridization analysis is a preferred method of analyzing the amplification products to detect the presence or absence of *Cryptovirus*-specific nucleic acid amplification products, employing one or more *Cryptovirus*-specific probe(s) that, under suitable conditions of stringency, hybridize(s) with single stranded *Cryptovirus*-specific nucleic acid amplification products comprising complementary nucleotide sequences. The amplification products are typically deposited on a substrate, such as a cellulose or nitrocellulose membrane, and then hybridized with labeled *Cryptovirus*-specific probe(s), optionally after an electrophoresis. Conventional dot blot, Southern, Northern, or fluorescence in situ (FISH) hybridization protocols, *in liquid* hybridization, hybridization protection assays, or other semi-quantitative or quantitative hybridization analysis methods are usefully employed along with the *Cryptovirus*-specific probes of the present invention. As is readily apparent to the skilled artisan, such analytical hybridization techniques and others (e.g., Northern blotting), are useful in accordance with other embodiments of the inventive method of detecting the presence or absence of a *Cryptovirus*-specific RNA in a sample of a biological material that do not involve any amplification step(s). In these embodiments, the inventive *Cryptovirus*-specific probes are contacted directly with RNA in the sample to perform hybridization analysis.

Alternatively, electrophoresis for analyzing or detecting amplification products is done rapidly and with high sensitivity by using any of various methods of conventional slab or capillary electrophoresis, with which the practitioner can optionally choose to employ any facilitating means of nucleic acid fragment detection, including, but not limited to, radionuclides, UV-absorbance or laser-induced fluorescence. (K. Keparnik *et al.*, *Fast detection of a (CA)18 microsatellite repeat in the IgE receptor gene by capillary electrophoresis with laser-induced fluorescence detection*, Electrophoresis

19(2);249-55 [1998]; H. Inoue *et al.*, *Enhanced separation of DNA sequencing products by capillary electrophoresis using a stepwise gradient of electric field strength*, J. Chromatogr. A. 802(1):179-84 [1998]; N.J. Dovichi, *DNA sequencing by capillary electrophoresis*, Electrophoresis 18(12-13):2393-99 [1997]; H. Arakawa *et al.*, *Analysis of single-strand conformation polymorphisms by capillary electrophoresis with laser induced fluorescence detection*, J. Pharm. Biomed. Anal. 15(9-10):1537-44 [1997]; Y. Baba, *Analysis of disease-causing genes and DNA-based drugs by capillary electrophoresis. Towards DNA diagnosis and gene therapy for human diseases*, J. Chromatgr B. Biomed. Appl. 687(2):271-302 [1996]; K.C. Chan *et al.*, *High-speed electrophoretic separation of DNA fragments using a short capillary*, J. Chromatogr B. Biomed. Sci. Appl. 695(1):13-15 [1997]).

Any biological material can be sampled for the purpose of practicing the inventive methods of detecting the presence or absence of a *Cryptovirus*-specific protein or *Cryptovirus*-specific RNA in a sample of a biological material. Preferred biological materials for sampling include blood or serum, lymphoid tissue, nervous tissue, including brain tissue. However, the biological material can be cerebrospinal fluid (CSF), lymph, plasma, feces, semen, prostatic fluid, tears, saliva, milk, gastric juice, mucus, synovial fluid, pleural effusion, peritoneal effusion, pericardial effusion, skin, vascular epithelium, oral epithelium, vaginal epithelium, cervical epithelium, uterine epithelium, intestinal epithelium, bronchial epithelium, esophageal epithelium, or mesothelium, or other biopsy sample of cellular material from any tissue. Cellular material includes any sample containing mammalian cells, including samples of tissues, expressed tissue fluids, tissue wash or tissue rinsate fluids, blood cells (e.g., peripheral blood mononuclear cells), tumors, organs, and also samples of in vitro cell culture constituents (including but not limited to conditioned medium resulting from the growth of cells in cell culture medium, putatively virally infected cells, recombinant cells, and cell components), or the like.

Tissue samples that can be collected include, but are not limited to, cell-containing material from the brain, blood, spleen, lymph node, vasculature, kidney, pituitary, ureter, bladder, urethra, thyroid, parotid gland, submaxillary gland, sublingual gland, bone, cartilage, lung, mediastinum, breast, uterus, ovary, testis, prostate, cervix uteri, endometrium, pancreas, liver, adrenal, esophagus, stomach, and/or intestine.

The sample is alternatively derived from cultured mammalian cells, cell-free extracts, or other specimens indirectly derived from a mammalian subject's body, as well as from substances taken directly from a subject's body. The samples can be stored before detection methods are applied (for example nucleic acid amplification and/or analysis, or immunochemical detection) by well known storage means that will preserve nucleic acids or proteins in a detectable and/or

analyzable condition, such as quick freezing, or a controlled freezing regime, in the presence of a cryoprotectant, for example, dimethyl sulfoxide (DMSO), glycerol, or propanediol-sucrose. Samples may also be pooled before or after storage for purposes of amplifying their *Cryptovirus*-specific nucleic acids for analysis and detection, or for purposes of detecting *Cryptovirus* protein.

The sample is optionally pre-treated by refrigerated or frozen storage overnight, by dilution, by phenol-chloroform extraction, or by other like means, to remove factors that may inhibit various amplification reactions that may be employed; such as heme-containing pigments or urinary factors. (E.g., J. Mahony *et al., Urine specimens from pregnant and non-pregnant women inhibitory to amplification of Chlamydia trachomatis nucleic acid by PCR, ligase chain reaction, and transcription-mediated amplification: identification of urinary substances associated with inhibition and removal of inhibitory activity*, J. Clin. Microbiol. 36(11):3122-26 [1998]).

The present invention is also directed to an animal model for the study of human diseases, preferably, but not limited to, neurological, neurodegenerative, and/or neuropsychiatric diseases. The term "neurological diseases" refers to diseases of the nervous system, including neuropathies manifested in the central nervous system and/or the peripheral nervous system. These include epileptiform diseases and non-epileptiform CNS diseases (e.g. Parkinsonism) and peripheral nervous system disease(s) (e.g. amyotrophic lateral sclerosis or "Lou Gehrig's Disease." "Neurodegenerative" diseases involve wasting or paralytic neurological diseases, which typically present with tremor, weakness and atrophy, for example Lou Gehrig's Disease or Alzheimer's disease. The terms "neuropsychiatric" and "neuropsychological" are used interchangeably herein. "Neuropsychiatric diseases" are neurological diseases that also include behavioral symptoms that derive from the underlying neurophysiological processes. The animal model is a non-human mammal, such as, but not limited to, a rodent, a lagomorph, or a non-human primate.

A rodent is any of the relatively small gnawing mammals of the order Rodentia , such as mice, rats, hamsters, guinea pigs, squirrels, marmots, beavers, gophers, voles, porcupines, and agoutis. A lagomorph is any of various herbivorous mammals belonging to the order Lagomorpha, which includes rabbits, hares, and pikas.

The animal is, or has been, inoculated with an infectious cell-free *Cryptovirus* virion of the present invention. Alternatively, the animal is, or has been, artificially inoculated with a cell nonproductively-infected with *Cryptovirus*, such as AV_3/SSPE.

Inoculation can be by a peripheral or an intracerebral delivery route. For the study of neurological, neurodegenerative, and/or neuropsychiatric diseases, intracerebral inoculation is

preferred, although for diseases presenting with involvement of the peripheral nervous system, peripheral inoculation can also be useful.

Intracerebral inoculation is by any suitable means, but preferably by direct injection into the brain, preferably into neural tissue, and most preferably by stereotactic injection means known in the art. Alternatively, intracerebral inoculation with *Cryptovirus* or nonproductitively infected cells can be by intraarterial (e.g., intracarotid) or intravenous injection or infusion, in conjunction with at least transient disruption of the blood brain barrier by physical or chemical means, delivered simultaneously with the *Cryptovirus* or nonproductively infected cells.

"Simultaneously" means that the physical or chemical means for disrupting the blood brain barrier are administered contemporaneously or concurrently with the *Cryptovirus* virions or nonproductively infected cells. "Simultaneously" also encompasses disrupting means being administered within about one hour after the *Cryptovirus* or nonproductively infected cells are last administered, preferably within about 30 minutes after, and most preferably, being administered simultaneously with the *Cryptovirus* or nonproductively infected cells. Alternatively, "simultaneously" means that the medicant is administered within about 30 minutes before, and preferably within about 15 minutes before the *Cryptovirus* or nonproductively infected cells are first administered.

Physical disruption of the blood brain barrier includes by means of "mechanical" injury or other physical trauma that breaches the blood brain barrier in at least one location of the brain's vasculature. Chemical disruption includes by an agent that transiently permeabilizes the blood-brain barrier and allows the *Cryptovirus* to enter the brain from the blood stream via the brain microvasculature. Such permeabilizing agents are known, for example, bradykinin and bradykinin analogs, and activators of calcium-dependent or ATP-dependent potassium channels. (e.g., B. Malfroy-Camine, *Method for increasing blood-brain barrier permeability by administering a bradykinin agonist of blood-brain barrier permeability*, U.S. Patent No. 5,112,596; J.W. Kozarich *et al.*, *Increasing blood brain barrier permeability with permeabilizer peptides*, U.S. Patent No. 5,268,164; Inamura, T. et *al.*, *Bradykinin selectively opens blood-tumor barrier in experimental brain tumors*, J. Cereb. Blood Flow Metab. 14(5):862-70 [1994]; K.L. Black, *Method for selective opening of abnormal brain tissue capillaries*, U.S. Patent Nos. 5,527,778 and 5,434,137; N.G. Rainov, *Selective uptake of viral and monocrystalline particles delivered intra-arterially to experimental brain neoplasms*, Hum. Gene. Ther. 6(12):1543-52 [1995]; N.G. Rainov *et al.*, *Long-term survival in a rodent brain tumor model by bradykinin-enhanced intra-arterial delivery of a therapeutic herpes simplex virus vector*, Cancer Gene Ther. 5(3):158-62 [1998]; F.H. Barnett *et al.*,

Selective delivery of herpes virus vectors to experimental brain tumors using RMP-7, Cancer Gene Ther. 6(1):14-20 [1999]; WO 01/54771 A2; and WO 01/54680 A2).

The inoculated non-human mammal exhibits at least one symptom characteristic of a human neurological, neurodegenerative, and/or neuropsychiatric disease after being thus inoculated, which was not previously exhibited by the non-human mammal before inoculation. Such symptoms include subacute symptoms and more slowly developing symptoms.

Generally, the subacute symptoms (developing from about 3 weeks to about 2 months post inoculation) associated with such experimental infections include: (1) cachexia/anorexia (*i.e.*, wasting or diminution of body mass and size); (2) degenerative neurologic wasting or paralysis; (3) atrophy of limb(s); (4) hindlimb paralysis; (5) photosensitivity or repetitive blinking; (6) hyperactivity or hyperesthesia (*e.g.*, nervousness, agitation, racing, jumpiness, extreme sensitivity to touch and sound); (7) ataxia (*i.e.*, loss of balance, wobbly gait); (8) hypesthesia; (9) withdrawal and isolation from other animals, closing of eyes, "hunched" posture; (10) stupor (*i.e.*, rigidity, semi-comatose, somnambulant motionlessness); (11) convulsions or seizures (*i.e.*, flaying of limbs, loss of consciousness, whirling, rolling and/or circling); (12) muscle spasms or myoclonus (*e.g.*, tremor, twitching of muscles, repetitive jerking of muscles); (13) corneal opacity (a clouding of the cornea) and (14) sudden death. Individual animals can present with one or more of the preceding subacute symptoms, but are generally observed displaying a complex of two or more symptoms. Subacute symptoms are more frequently observed in male animals compared to female animals.

More slowly developing symptoms (*i.e.*, those developing after about two months and sometimes not for about six months or more after inoculation) include: (1) obesity; (2) hypesthesia (i.e., decreased sensitivity to sensory stimuli); (3) extreme lethargy and prolonged sleeping; (4) hyperactivity or hyperesthesia (i.e., increased sensitivity to sensory stimuli); (5) aggressiveness (*e.g.*, jumping or biting); (6) obsessive compulsive behavior (*e.g.*, excessive and prolonged washing of the face or continual scratching); (7) self-mutilation (the extreme end of obsessive compulsive washing or scratching where the skin is damaged); (8) still-born fetuses and deformities in newborn animals (usually paralysis or limb atrophy) born to experimentally-infected females; and (9) infanticide (cannibalism of numerous newborns or entire litters). Individual animals can present with one or more of the preceding more slowly developing symptoms, but are generally observed displaying a complex of two or more symptoms. More slowly developing symptoms are more frequently observed in female animals compared to male animals.

The inventive animal model is an excellent model system for the study of neurodegenerative, wasting or paralytic neurological diseases which typically present with tremor, weakness and atrophy.

The inventive animal model is also, in particular, an excellent model system for the study of idiopathic epileptiform diseases because the infected animals present with virtually the entire spectrum of symptoms associated with epileptiform illnesses in humans. At present, most existing animal models of epilepsy (*e.g.*, induction of seizure by inoculation with the glutamate receptor agonist, kainite, or by partial suffocation) are contrived to produce seizures and the gross anatomical pathology associated with seizures without reference to the etiology of the actual symptomatic spectrum of the illnesses in humans. While these models are useful in developing therapeutics for seizure activity, there is little or no evidence that they are relevant to the ultimate aetiopathogenesis of epileptiform illnesses in humans or the actual spectrum of symptoms which occur.

In contrast, the animal model of the present invention is a truly homologous animal model; that is, one in which the actual factors/symptoms associated with the disease in humans are extant and can be specifically targeted by both therapeutic and prophylactic strategies. Thus, the inventive animal models disclosed herein can be used to screen antiviral medications or medicaments, including anti-epileptic and anti-psychotropic medicaments, as well as to test vaccines and other prophylactic remedies and to determine how to best coordinate and optimize any and all treatment strategies.

Cryptovirus is mildly cytopathic in cell culture but causes profound neuropathological disease in experimentally-infected animals. Any of the cytopathogenic and neuropathogenic traits of the virus can be used as markers in screens designed to identify and test potential antiviral therapeutic and/or prophylactic agents.

Accordingly, the present invention features *in vitro* and *in vivo* methods of screening potential antiviral therapeutic agents and/or antiviral prophylactic agents, including immunoprophylactic agents. A "potential" antiviral therapeutic or prophylactic agent is an agent that has not yet been clinically confirmed (i.e., in phase III clinical trials) to have antiviral properties effective against *Cryptovirus*. Agents that have not been tested clinically against *Cryptovirus* infections or have been tested clinically against *Cryptovirus* infections only with respect to phase I and phase II clinical trials are also encompassed by "potential" antiviral therapeutic and/or prophylactic agents for purposes of the present invention.

In accordance with the inventive *in vitro* methods of screening a potential therapeutic or prophylactic agent, either acutely- or productively-infected mammalian cell cultures (e.g., BHK, Vero, or CV-1_C cells) or nonproductively infected carrier cultures (e.g., AV_3/SSPE cells) can be used to evaluate the potential antiviral agent. While the acutely infected (productive) cellular system is preferentially useful for screening agents targeted at the processing and assembly of *Cryptovirus* envelope glycoproteins (*e.g.*, protease inhibition of F_0 cleavage activation), the nonproductively

infected cellular system (e.g., AV_3/SSPE cells) is preferred for screening for the efficacy of long-term treatment with transcriptional or other polymerase inhibitors (inhibiting the buildup of intracellular nucleocapsids and the eventual triggering of apoptotic cell death).

The inventive animal model is usefully employed in the *in vivo* method of screening a potential antiviral therapeutic agent. The method involves administering the potential therapeutic agent to be screened, to the inventive animal model after its inoculation with *Cryptovirus*, in accordance with the inventive animal model.

An alternative embodiment of the inventive animal model is employed in the *in vivo* method of screening a potential antiviral prophylactic agent. The method involves administering a potential prophylactic agent to be screened to a non-human mammal, which does not have a symptom of a human disease, such as but not limited to a neurological, neurodegenerative, and/or neuropsychiatric disease (e.g., an epileptiform disease). Then the animal is inoculated, as described herein, with the infectious cell-free *Cryptovirus* or with the mammalian cell nonproductively-infected with the *Cryptovirus*. The method is particularly, but not exclusively, useful for identifying potential anti-epileptic or anti-psychotropic antiviral prophylactic agents.

Administration of the potential prophylactic agent or therapeutic agent is by any suitable delivery route, enteral (e.g., orally or by suppository) or parenteral (e.g., by injection, infusion, transmembrane, transdermal, or inhalation delivery route).

Examples of agents that can be evaluated, in accordance with the invention, include compounds or substances with known antiviral properties against viruses other than *Cryptovirus*; novel compounds or mixtures of compounds, such as cell, plant or animal extracts, with potential antiviral activity; and vaccines, as described hereinabove; or any combination of these.

Using the inventive in vivo method of screening, potential immunoprophylactic agents (*i.e.*, vaccines which stimulate the immune system to respond to, attack or inhibit virus replication, assembly or any other process associated with virus reproduction and spread) are also amenable to testing because non-human mammals can be inoculated with a putative prophylactic agent or vaccine (as mentioned above) and then challenged with infectious *Cryptovirus* to assess its utility in preventing the development of *Cryptovirus*-associated diseases. The use of such agents discovered in accordance with the invention may ultimately be necessary to control and eradicate *Cryptovirus*-associated diseases in the human population much as measles and mumps vaccines have been used to bring these diseases under control in many countries.

In addition to those named above, one of ordinary skill in the art will recognize numerous potential antiviral chemo- and molecular-therapeutic agents that could be analyzed or evaluated using

the *in vitro* (cell culture) or *in vivo* methods of screening provided herein. These potential antiviral therapeutic and/or prophylactic agents can include existing antiviral agents known to affect viruses other than *Cryptovirus* (*e.g.*, Ribavirin™, which is also known as Virazole™) and new potential antiviral agents. For example, molecular therapeutic agents (*e.g.*, anti-sense nucleotides and ribozymes) or protease inhibitors can also be tested using the inventive in vitro and/or in vivo methods of screening. Agents that might inhibit the cleavage of the viral fusion protein (F_0) can be sought, and these could be particularly valuable, as there is evidence that cleavage of the fusion protein and its association with the viral hemagglutinin/neuraminidase protein (HN) are critical events in determining the pathogenicity of infections by other Paramyxovirdae (Yao *et al., J. Virol.* 71: 650-656, 1997). Further, these potential antiviral agents may be directed, for example, at *Cryptovirus* replication or assembly, or the expression or activity of *Cryptovirus* genes and proteins, such as, but not limited to, the *Cryptovirus*-encoded RNA-dependent RNA polymerase comprising the L protein and its companion P and V proteins. The inventive screening methods also can be employed to develop broad-spectrum antiviral agents, effective against viruses other than *Cryptovirus*.

Immunotherapeutic agents, such as those that attack, or stimulate the immune system to attack, infected cells or virus particles (by, *e.g.*, passive antibody administration or introduction of *Cryptovirus*-specific monoclonal antibodies) are also amenable to testing because they can block or inhibit the assembly, release or cell-to-cell transfer of virions. However, administration of these agents may be of only limited value in "curing" persistent and chronic *Cryptovirus* infections because the virus appears to survive *in situ* by shutting off production of its envelope proteins and going into a "latent" or inapparent state, in which it appears to be undetectable by the immune system.

Appropriate amounts of potential prophylactic or therapeutic agents vary and are determined by routine screening.

In accordance with the inventive *in vivo* methods of screening a potential therapeutic agent or prophylactic agent, the agent is evaluated for an ability to induce, create, bring about, or result in a beneficial antiviral effect in the inventive animal model. A "beneficial antiviral effect" includes the prevention of infection with *Cryptovirus* or a reduction in the duration or severity of at least one symptom associated with *Cryptovirus* infection, in the animal subjected to the assay, compared to tissues in control animals. A "beneficial antiviral effect" also includes a prevention or reduction of cytopathic effect (CPE) in tissues sampled from the animal subjected to assay by the screening method. Also encompassed by a "beneficial antiviral effect" is an inhibitory effect on *Cryptovirus* replication and/or *Cryptovirus* virion assembly (e.g., inhibitory effect on *Cryptovirus* genomic replication, *Cryptovirus* transcription, and/or translation, i.e., protein synthesis, from *Cryptovirus*

mRNAs, or a diminution in the numbers of *Cryptovirus* virions produced or a relative lack of completeness of *Cryptovirus* particles, compared to a suitable control), which effect is measured by known means in cells or tissues sampled from the animal subjected to the assay.

Appropriate controls for use in the screening methods will be self-evident to the skilled artisan. Such controls can include: (1) animals administered with the same potential prophylactic or therapeutic agent and challenged with sterile artificial aqueous culture medium alone or the culture medium containing a strain of SV5; (2) animals mock-treated with saline (or the same carriers used in delivering the potential prophylactic or therapeutic agent) and challenged with *Cryptovirus*; and (3) animals mock-treated with saline (or the same carriers used in delivering the potential prophylactic or therapeutic agent) and challenged with sterile artificial aqueous culture medium alone or the culture medium containing a strain of SV5.

The practice of the present invention will employ, unless otherwise indicated, conventional or other known techniques of biochemistry, molecular biology, microbiology, virology, recombinant nucleic acid technology, and immunology, which are within the skill of the art. Such techniques are explained fully in the literature. (e.g., Maniatis *et al.*, *Molecular Cloning: A Laboratory Manual*, Cold Spring Harbor Laboratory Press, Cold Spring Harbor, New York, USA (1982); *DNA Cloning*, Vols. I and II (D. N Glover ed. 1985); Sambrook et al., Molecular Cloning: A Laboratory Manual (2 ed.), Cold Spring Harbor Laboratory Press, Cold Spring Harbor, New York, USA (1989); Davis *et al.*, *Basic Methods in Molecular Biology*, Elsevier Science Publishing, Inc., New York, USA (1986); or *Methods in Enzymology: Guide to Molecular Cloning Techniques* Vol.152, S. L. Berger and A. R. Kimmerl Eds., Academic Press Inc., San Diego, USA (1987); *Oligonucleotide Synthesis* (M. J. Gait ed, 1984); *Nucleic Acid Hybridization* (B. D. Hames & S. J. Higgins eds. 1984); Transcription And Translation (B. D. Hames & S. J. Higgins eds. 1984); Animal Cell Culture (R. I. Freshney ed. 1986); Immobilized Cells And Enzymes (IRL Press, 1986); B. Perbal, A *Practical Guide To Molecular Cloning* (1984); the series, *Methods In Enzymology* (Academic Press, Inc.); *Gene Transfer Vectors For Mammalian Cells* (J. H. Miller and M. P. Calos eds. 1987, Cold Spring Harbor Laboratory), Methods in Enzymology Vol. 154 and Vol. 155 (Wu and Grossman, and Wu, eds., respectively), Mayer and Walker, eds. (1987), *Immunochemical Methods In Cell And Molecular Biology* (Academic Press, London), Scopes, (1987), *Protein Purification: Principles And Practice*, Second Edition (Springer-Verlag, N.Y.), and *Handbook Of Experimental Immunology*, Volumes I-IV (D. M. Weir and C. C. Blackwell eds 1986).

The invention will now be described in greater detail by reference to the following non-limiting examples.

EXAMPLES

Example 1. Detection of *Cryptovirus* in Infected Cells and Isolation and Purification of *Cryptovirus* Viral Particles.

In accordance with the present invention, cell-free *Cryptovirus* particles were recovered from cells of the buffy coat (peripheral blood mononuclear cells; PBMNC) obtained from the peripheral blood of patients with SSPE. The technique used was modified from that of Robbins *et al.* (*J. Infect. Dis.* 143:396-403, 1981). Modifications included the addition of cyclic GMP (to a final concentration of 1 mM) to the aqueous culture medium, in accordance with the present invention, which medium was added to the initial PBMNC cultures and the primary cocultivate with human amnion cells (AV_3). Results were further optimized by using as the mammalian epithelial cell line in a co-cultivation step with the PBMNCs and amnion cells, a clonal subline of CV-1 cells (CV-l_c).

Successful isolation of the virus requires viable PBMNCs. Such PBMNCs were separated from other blood components by standard procedures on Ficoll-Hypaque™ gradient media. After centrifugation, the buffy coat cells banded at the interface of the media and were removed with a sterile pipette. They were then gently washed by dilution in 50 volumes of RPMI cell culture media containing 1-2% fetal calf serum and centrifuged in a table-top refrigerated centrifuge (1000 rpm for 5 minutes). The pelleted PBMNCs were then diluted to 2 x 10^5 cells per ml in RPMI media containing 10% fetal calf serum and 1 mM cyclic GMP (sodium salt) and incubated without disturbance at 37°C for 12-18 hours. Following this incubation, the cultures were seeded with sufficient AV_3 cells in Richter's Modified Minimal Essential Medium (IMEMZO) (supplemented with insulin, zinc and HEPES buffer, 2 mM L-glutamine, 200 Units penicillin/mL, 100 pg streptomycin/mL, 5-10% (v/v) fetal calf serum, pH between 6.8 and 7.0) to yield a net cell concentration of 2 x 10^5 cells per mL (for all cells in the culture) and were reincubated at 37°C. Once the cultures reached confluence (2-3 days), the monolayer was chelated with a solution of 0.02% w/v EDTA in CMF-PBS (calcium and magnesium free phosphate buffered saline), the cells were dispersed, and passaged at 2 x 10^5 cells /mL in IMEMZO as before.

The cultures were then blindly passaged in the same way when confluent every 3-4 days (roughly twice a week) for 2-3 weeks. After two weeks, a slide culture was prepared to examine the cells for the presence of *Cryptovirus*-specific inclusions in the cytoplasm using a *Cryptovirus*-specific indirect fluorescent antibody technique (exposure to hyperimmune rabbit anti-*Cryptovirus* antisera followed by labeling with fluorescein-conjugated goat anti-rabbit IgG).

When 5-10% of the cells were positive for *Cryptovirus*-specific inclusions, the cultures were ready for co-cultivation with the permissive CV-l_c cells mentioned above. This involved the 1:1

cocultivation of the passaged primary PBMNC/AV_3 cultures with CV-l_c cells in Richter's Modified Minimal Essential Medium diluted to yield a net concentration of 2 X 10^5 cells/mL. These cultures were then monitored for the development of subtle cytopathic effects (CPE; stellation and rounding of cells or the formation of multinucleated cells containing three or more nuclei) over the ensuing 4-5 days. If no CPE developed before the cultures become confluent, they were passaged and monitored again. If no CPE developed after three such passages, the cultures were discarded.

Once CPE was observed, the whole culture was frozen at -70°C, thawed, and the cells were dispersed and dispensed into 1.0 mL aliquots. These aliquots represented the putative primary isolation of the virus. The virus was then plaque-purified by titration on monolayers of CV-l_c cells overlaid with a semi-solid solution of 1% w/v sodium carboxymethylcellulose (NaCMC) containing 2% fetal calf serum, which was made up in Richter's Modified Minimal Essential Medium. The cultures were incubated at 37°C in a partial CO_2 atmosphere (5% v/v). Plaques formed in 8-12 days and were then picked and replaqued, as above. Once triply plaque-purified, the virus was aliquoted onto CV-l_c monolayers (in IMEMZO media containing 5% fetal calf serum and supplements listed above) in 25-75 cm^2 tissue culture flasks. Once sufficient CPE developed, involving half or more of the cultured cells, the whole cultures were frozen, thawed, and the lysate was dispersed, re-aliquoted and refrozen at -70°C. Samples of the virus stock were then titrated for further use by the method of Robbins *et al.* (Robbins *et al.*, *J. Infect. Disease* 143:396-403, 1981).

Density Gradient Purification: Virions and intracellular nucleocapsids isolated from productively- (Vero and CV-1_C) and nonproductively-infected (AV_3/SSPE) cells were further purified on sucrose-potassium tartrate gradients (virions) and CsCl gradients (nucleocapsids) by the method of Robbins *et al.* (Robbins *et al.*, *J. Infect. Disease* 143:396-403, 1981; Rapp and Robbins, *Intervirology* 16:160-167, 1981; Robbins and Rapp, *Arch. Virol.* 71:85-91, 1982; and Robbins and Abbott-Smith, *J. Virol. Meth.* 11:253-257, 1985).

Example 2. *Cryptovirus* Propagation and Virion Isolation and Purification.

Once isolated, cell-free virus stocks were grown in simian epithelial cell lines (*e.g.* Vero or CV-1 cells). The *Cryptovirus* isolates used in the studies described herein were triply-plaque purified and grown in a clonal subline of CV-1 cells designated CV-l_C. Optimal production of infectious virus occurred when using IMEMZO supplemented with insulin, zinc and HEPES buffer, 2 mM L-glutamine, 200 Units penicillin/mL, 100 μg streptomycin/ml, 5-10% (v/v) fetal calf serum, at a pH between 6.8 and 7.0.

The presence of insulin, and optionally zinc dication, in the tissue culture medium was useful in obtaining viable titers of infectious virus. Independent attempts to grow the virus in CV-1 cells using standard media (*e.g.* MEM) produced very poor results. Conversely, the expression of *Cryptovirus* proteins and the productivity of *Cryptovirus* infections in primate cell cultures was dramatically enhanced (50- to 100-fold) by addition of cyclic GMP (1 mM; sodium salt) to standard media (specifically MEM). The enhancement obtained was very similar to the enhancement of measles virus replication published earlier (Robbins, *Intervirology* 32:204-208, 1991).

Virion Isolation and Purification. Virions were isolated and further purified from the supernatant tissue culture medium of acutely infected CV-1 cells 72 hours after infection. The procedure employed involved the separation of the virus particles by differential centrifugation.

The supernatant medium of infected cultures was decanted into a sterile plastic 50-mL Falcon centrifuge tube and clarified at 2000 rpm for 10 minutes. The supernatant was then transferred to an impact resistant glass centrifuge tube (Sorvall) and further clarified at 10,000 rpm for 10 minutes. All clarifications took place at 4° C in an RC2B Sorvall centrifuge. The supernatant fluid from the second clarification step was layered over a 60% w/v sucrose cushion (in 10 mM Tris, 5 mM EDTA, pH 7.2) and centrifuged at approximately 130,000 x G in a Beckman SW-28 rotor at 4° C for 90 minutes in a Beckman L70 ultracentrifuge. Materials were collected from the tissue culture medium-sucrose interface, pooled, diluted with tissue culture medium and recentrifuged onto another 60% sucrose cushion as described above. The materials at the interface were again removed, diluted with tissue culture medium, and centrifuged at 35,000 rpm (280,000 x G) for 60 minutes through a 30% w/v over 60% w/v discontinuous (i.e. layered) sucrose gradient prepared in the Tris EDTA buffer described above). The virions were collection from the 30%:60% sucrose interface, diluted with cold Tris EDTA buffer and pelleted in a Beckman SW41 rotor at 41,000 rpm and 4° C for 60 minutes. Pelleted virions were resuspended in a variable amount of the cold Tris EDTA buffer and frozen at –70° C until further use. Total protein in each virion preparation was determined by the method of Lowry et al. (1951).

Example 3. Preparation of Antisera.

Antisera were raised in adult New Zealand White rabbits against sucrose-potassium tartrate gradient-purified virions of *Cryptovirus*, CsCl gradient-purified nucleocapsids (from infected CV-1_c cell cytoplasm), and against the major viral nucleocapsid protein, NP, eluted from polyacrylamide gels after SDS-PAGE. Rabbit antisera were also raised against the NIH 21005-2WR strain of SV5, and the Edmonston strain of measles virus.

Animals were inoculated by a pincushion technique which involved three series of three separate inoculations in each animal using a sterile 27 gauge needle and 1.0-mL syringe (one inoculation intradermally on the back; one inoculation intraperitoneally and one inoculation in a hind foot pad). The first series of inoculations were made using gradient purified and dialyzed virions (100 μg of virions in 0.3 mL of a 10 mM Tris 5 mM EDTA solution) mixed 1:1 with Freund's Complete Adjuvant and each inoculation contained approximately 200 μL of the virion:adjuvant mixture. The second series of inoculations were made two weeks later in the same locations but on the opposite side of each animal and consisted of the same amount of virions mixed with Freund's Incomplete Adjuvant. The third series of inoculations were made two weeks later in the same locations as the first inoculations but using only virions (diluted in 0.6 mL of the Tris-EDTA solution described above). Blood was harvested by intracardiac exsanguination of the animals two weeks after the final series of inoculations. The harvested blood was centrifuged (2000 rpm for 10 minutes) and allowed to clot on ice. The upper serum component was harvested and adsorbed against the pelleted component (2000 rpm for 10 minutes) of saline-washed freeze-dried acetone:methanol-extracted monkey kidney tissue (4° C for 1 hour with agitation every 15 minutes). The adsorbed serum was harvested by centrifugation (2,000 for 10 minutes) and stored in 1.0-mL aliquots at –20° C).

All of the anti-*Cryptovirus* antisera were strongly reactive with the corresponding *Cryptovirus*-specific materials from which they were generated when analyzed by (1) immunoprecipitation, (2) immunofluorescence, (3) immunoblotting, (4) ultrastructural immunolabelling techniques (immunogold), and (5) in the case of antisera generated against gradient-purified virus particles, neutralization titration assays. All the hyperimmune virus-specific antisera that were generated in the rabbits had homologous neutralization titers in excess of 1280 and, usually, in excess of 2560 (reciprocal dilution of PRD_{50}).

All experimentally-generated antisera were adsorbed against saline washed, freeze-dried, acetone:methanol extracts of monkey kidney tissue or similar extracts of AV_3 cells and/or CV-1_C cells.

While clinical sera were similarly adsorbed, CSF specimens were NOT preadsorbed due to the small volumes that were usually available and the requirement to retain aliquots for duplicate and parallel studies.

The precipitating "titers" of the experimental sera raised against purified nucleocapsids and purified viruses were not specifically determined although, routinely, 5-10 μL were used in positive control immunoprecipitation reactions and 25 μL of positive control antisera (diluted 1:10 or 1:20) for positive controls in ELISA assays.

Cryptovirus-specific antisera were also produced in mice experimentally inoculated with gradient-purified infectious *Cryptovirus* virions. These antisera were analyzed by immunoprecipitation, and were found to strongly precipitate all *Cryptovirus* envelope proteins.

There was clear *asymmetric* cross-reactivity between the antisera raised against *Cryptovirus* virions and antiserum raised against virions of the NIH 2WR-21005 strain of SV5. The asymmetry observed in this regard was always such that the heterologous reactions (i.e., *Cryptovirus*-specific antisera vs. SV5 materials and SVS-specific antiserum vs. *Cryptovirus* materials) were two- to four-fold weaker that the homologous reactions (i.e., *Cryptovirus*-specific antisera vs. *Cryptovirus* materials and SVS-specific antisera vs. SV5 materials). Another antiserum, which was independently prepared against NIH 21005-2WR strain of SV5 and kindly provided by Dr. Purnell Choppin, behaved in a similar asymmetric manner to the antiserum against SV5 described hereinabove.

Such cross reactivity is not surprising. Precisely the same sort of asymmetric cross-reactivity occurs when examining other paramyxovirus systems (*e.g.*, there is also a two to four fold *asymmetric* cross-reactivity between measles virus antibodies when reacted with the closely related viruses of canine distemper and rinderpest and *vice versa*). There was also limited (*i.e.*, much weaker) cross-reactivity between *Cryptovirus*-specific antibodies and other paramyxoviruses (*e.g.*, measles virus).

Example 4. Characterization of isolated *Cryptovirus*.

Cryptovirus Neurovirulence and Neurotropism. As shown in Fig. 24A, *Cryptovirus* demonstrated a tropism for neurons. Intracranial inoculation of mice with infectious *Cryptovirus* or nonproductive virus-carrying cells (AV_3/SSPE) resulted in the subacute/slow development of a spectrum of neuropathological conditions that had epileptiform, neurological and/or neuropsychological components. These responses were similar to the "experimental SSPE" reported earlier in animals following inoculation with "cell-associated measles-like" virus such as Niigata, Kitaken and Biken (see Fig. 24B; Doi *et al., Japan. J. Med. Sci. Biol.* 25:321-333, 1972; Ueda *et al.*,

Biken Journal 18:179-181, 1975; Yamanouchi *et al., Japan. J. Med. Sci. Biol.* 29:177-186, 1976; Ohuchi *et al., Microbiol. Immunol.* 25:887-983, 1981).

Cryptovirus Presence in Neurovirulent SSPE-derived Virus-carrying Cell Lines. Four virus-carrying cell lines derived from patients with SSPE were tested by immunofluorescence for the presence of measles virus- and/or *Cryptovirus* specific antigens. These were AV_3/SSPE/MV (an SSPE-derived cell line derived from PBMNC from an SSPE patient cocultivated with AV_3 cells which was experimentally-infected with Edmonston strain measles virus; Robbins, unpublished data); the nonproductive SSPE-derived cell line designated "Kitaken" (Ueda *et al., Biken Journal* 18:179-181, 1975); the nonproductive SSPE-derived cell line designated "Niigata" (Doi *et al., Japan. J. Med. Sci. Biol.* 25:321-333, 1972); and the nonproductive SSPE-derived cell line designated "Biken" (Yamanouchi *et al., Japan. J. Med. Sci. Biol* 29:177-186, 1976; Ohuchi *et al., Microbiol. Immunol.* 25:887-983, 1981). With the possible exception of the Niigata cell line, all of these virus-carrying cell lines expressed both measles virus-specific and *Cryptovirus*-specific antigens when examined by virus-specific immunofluorescent techniques (shown in Fig. 6). Given that no cell-free clinical isolates of measles virus have ever been shown to cause SSPE-like illnesses in experimentally-infected animals, the presence of *Crytovirus* in these cultures strongly suggests that the subacute/slow neuropathies seen in these animals are due to the presence of *Cryptovirus* in the cultures—not measles virus.

Cryptovirus inclusion bodies (i.e. cytoplasmic nucleocapsids) displayed the same sort of "peppery" and or "splattered" distribution in both acutely-infected cells ($CV\text{-}1_C$) and nonproductively- and persistently-infected cells (AV_3/SSPE) as that previously described in CNS biopsy and autopsy materials from SSPE patients and in SSPE-derived nonproductive virus-carrying cell lines (e.g., de Felici *et al.*, Annales Microbiologie 126:523-538 [1975]; Makino *et al.*, Microbiology and Immunology 21:193-205 [1977]; Brown *et al.*, Acta Neuropathologica 50:181-186 [1980]). This is most clearly evident in Panels B, D, F, H and J of Fig. 6. These characteristics were in sharp contrast to the discrete and "coalescing" distribution and morphology of intracellular measles virus inclusions bodies (see Panels A, C, E and G of Fig. 6).

Neutralization Titration Assay. Formation of macroscopically visible plaques on monolayers of mammalian cells (e.g., BHK, Vero and $CV\text{-}1_C$) can be used to quantitate preparations of infectious *Cryptovirus.* Plaque formation can be inhibited by serial dilutions of clinical serum specimens and

Cryptovirus-specific antisera generated in rabbits (*see* Robbins *et al.*, *J. Infect. Disease* 143:396-403, 1981). Plaque titration assays were conducted to determine the PRD_{50} of isolated *Cryptovirus*.

Briefly, ten-fold serial dilutions of serum or CSF specimens to be tested were incubated for one hour at 4°C with sufficient infectious virus to yield a net plating concentration of between 100-200 plaque forming units of the virus / 0.2 mL of final diluent (including the diluted serum or CSF). After incubation, 0.2 mL of the diluted virus-serum (or virus-CSF) mixtures was then plated onto monolayers of susceptible cells (*e.g.* Vero or CV-1_c) and the cells were incubated at 37°C in a partial CO_2 atmosphere (5%v/v) (with redistribution of the inoculum every 15 minutes). At the end of the incubation period, inoculated monolayers were overlayed with sufficient volumes of a 2% (w/v) solution of carboxymethylcellulose (made up in IMEMZO medium containing 2% fetal calf serum, insulin, zinc, and HEPES buffer, 2 mM L-glutamine, 200 Units penicillin / mL, 100 μg streptomycin / mL, pH between 6.8 and 7.0) to last 10-12 days (*i.e.*, enough volume so that the monolayers won't dry out). The plates were not moved during the incubation period. After 10-12 days, the overlay was aspirated and the cells were fixed with formalin fixative and stained with a protein stain (*e.g.*, Giemsa). The number of plaques formed on each plate was then enumerated and the PRD_{50} calculated.

In particular, cross neutralization assays involved the determination of the titer of antisera made against each species of virus which would neutralize 50% of the plaque forming units (PFUs) of each virus. Virus stocks of the BBR strain of *Cryptovirus* and the NIH 21005-2WR strain of SV5 were diluted in serum-free minimal essential medium (Eagle's MEM containing 2mM L-glutamine, 200 units of penicillin and 100 μg of streptomycin/ml with the pH adjusted to between 6.8 and 7.0 with $NaHCO_3$) to a titer of 1,000 PFUs per mL (resulting in 100 PFUs per well after dilution and plating). Antiserum raised in New Zealand White rabbits was serially-diluted in 10-fold increments in the same serum-free MEM. Aliquots (0.5 mL) of the diluted virus stocks were then mixed with 0.5 ml aliquots of each dilution of the antisera, gently mixed with a vortex and incubated on ice for one hour with gentle mixing every 15 minutes. Following this incubation period, the medium was aspirated from monolayers of CV-1 cells in 6-well cluster plates (NUNC), the monolayers were washed with warm saline, the saline was aspirated and 0.2 mL of each of the diluted antisera-virus incubates were plated onto two monolayers. The inoculated cluster plates were subsequently incubated at 37° C in a CO_2 incubator (containing 5% CO_2 v/v) for 1 hour with manual redistribution of the inocula every 15 minutes. Following this adsorption period, each well was overlayed with 10.0 mL of a semisolid overlay medium (1% w/v sodium carboxymethylcellulose in Eagle's MEM containing 2 mM L-glutamine, 200 units of penicillin and 100 μg of streptomycin/ml, 2% v/v fetal

calf serum with the pH adjusted to between 6.8 and 7.0 with $NaHCO_3$) and incubated for 10-12 days at 37° C in a CO_2 incubator (containing 5% CO_2 v/v) without being disturbed. Following this incubation period, the overlay was aspirated, the monolayers were gently washed with warm saline, and then fixed in formalin fixative (3.7% by weight formaldehyde gas in saline) for 1 hour or longer. Following fixation, the fixative was aspirated and the fixed monolayers were gently washed with distilled water and stained with 1-2 mL per well of Giemsa stain (0.5 gm Giemsa powder dissolved in 42 mL of warmed [55° C] glycerin, 42 mL of absolute methanol, filtered and diluted 1:5 with formalin fixative immediately before use) for 1 hour at room temperature. The stain was subsequently decanted and the monolayers were washed under tap water and allowed to dry at room temperature. Plaques on monolayers were illuminated on a light box, enumerated under a magnifying lens and recorded for each dilution, virus and antisera series. The neutralization titer of each antiserum virus series was calculated to be the reciprocal of the dilution of antisera resulting in a 50% decrease in the number of plaques formed.

The calculated neutralization titer for each crossed neutralization set (i.e. anti-*Cryptovirus* antiserum versus *Cryptovirus* and anti-*Cryptovirus* antiserum versus SV5; anti-SV5 antiserum versus Cryptovirus and anti-SV5 antisera versus SV5) was consistently 2-4 fold less for the heterologous mixtures (i.e. anti-*Crytovirus* antisera versus SV5 and anti-SV5 antisera versus *Cryptovirus*) than for the homologous mixtures (anti-Cryptovirus antisera versus Cryptovirus and anti-SV5 antisera versus SV5). On no occasion did any heterologous mixture have less than a 2-fold difference when compared to the homologous pair (in three separate trials).

Cryptovirus Ultrastructural and Immunoultrastructural Characterization. AV_3/SSPE/MV cells (AV_3/SSPE cells persistently and nonproductively infected with the Edmonston strain of measles virus), AV_3/SSPE cells, and CV-1_c cells acutely infected with the BBR strain of *Cryptovirus* were fixed in situ (on glass cover slips) in 2% formaldehyde and picric acid and 3% glutaraldehyde in 0.1 M cacodylate buffer, pH 7.2, for 15 minutes at room temperature. Osmium tetroxide post-fixation was omitted for specimens that were to be treated with antibody (i.e. which were prepared for immunoultrastructural studies). Cover slips with fixed cells were washed in three changes of cacodylate buffer, dehydrated to 70% ethanol and embedded in LR White resin. Resin was polymerized at 50°C for 24 hours. Ultrathin sections were cut and mounted on uncoated nickel grids.

Stained thin sections of CV-1_C cells acutely-infected with the BBR strain of *Cryptovirus* and AV_3/SSPE cells were examined by electron microscopy. In infected CV-1_C cells, pleomorphic virion particles, 100-120 nm in diameter, were seen budding from the surface of acutely-infected cells and

numerous accumulations of filamentous structures (helical nucleocapsids, 15-17 nm in diameter) were observed in the cell cytoplasm (data not shown). Both the virions and nucleocapsids were similar to those described for other members of the Paramyxoviridae. While virions were not observed budding from the surfaces of AV_3/SSPE cells, inclusions of intracellular nucleocapsids were seen in abundance and these were identical to those seen in the acutely-infected cells.

The intracellular nucleocapsids of nonproductively and productively-infected mammalian cells can readily be localized under the electron microscope using *Cryptovirus*-specific or *Cryptovirus* nucleocapsid-specific hyperimmune rabbit antibodies and an indirect immunogold labeling technique.

Immunolabelling was performed on sections of AV_3/SSPE/MV cells by floating sections mounted on nickel grids (processed as described without osmium tetroxide post-fixation) on drops of solution (see below) in a closed, humid chamber. Sections were etched according to the method of Ingram *et al.* (Parasitology Research 74:208-215, 1988). Non-specific labeling was reduced by incubation of the sections with 5% bovine serum albumin in modified Tris buffer (20 mM Tris, 0.5 M NaCl, 20 mM sodium azide and 0.05% Tween 20, pH 8.2) for 30 minutes at 37°C prior to immunolabeling. The modified Tris buffer was used for all dilutions and washes.

In single labeling experiments, sections were incubated with rabbit antisera (anti-Edmonston measles virus or anti-BBR strain of Cryptovirus) diluted 1:20 in modified Tris buffer for 2 hours at 37°C, washed in three changes of buffer, and incubated with a goat anti-rabbit IgG colloidal gold (10 or 15 nm particle size, 1:20 dilution, 1 hour at 37°C). After washing with two changes of buffer, followed by two changes of distilled water, sections were lightly contrasted with 2% uranyl acetate and led citrate, and examined in a JEOL 1200EX transmission electron microscope.

In double labeling experiments, sections were immunolabeled on one face, as described for single labeling, using rabbit anti-Edmonston measles virus and 15 nm colloidal gold particles, and ensuring that the reverse face of the section was not contaminated by labeling solutions. The labeled face was then coated with a thin film of Celloidin to reduce possible cross reaction of antibodies while the reverse face of the section was labeled. Immunolabeling of the reverse face of the sections was performed as described above, using the second antiserum (rabbit anti-BBR strain of *Cryptovirus*) and 10 nm colloidal gold particles. Examination of these double labeled sections allowed simultaneous comparison of labeling patterns of the two antisera.

The results of these studies were unequivocal and are shown in Fig. 25. The first labeling sequence (15 nm gold beads) labeled only the wider "fuzzy" measles virus nucleocapsids (as shown

in Fig. 25B), while the second labeling sequence (10 nm gold beads) labeled only the narrower smooth *Cryptovirus* nucleocapsids (as shown in Fig. 25A).

Example 5. Characterization of Isolated *Cryptovirus* Proteins

Radioimmunoprecipitation (RIP) *Assay*: Extensive data were generated by the comparative analysis of *Cryptovirus*-specific immunoprecipitates of [^{35}S]-methionine-labeled uninfected, nonproductively- and productively-infected human and primate cells by sodium dodecyl sulfate polyacrylamide gel electrophoresis (SDS-PAGE; see below).

CV-1$_c$ or Vero cell monolayers were infected with the BBR strain of Cryptovirus, the NIH 21005-2WR strain of SV5 or the Edmonston strain of measles virus at a multiplicity of infection of 1-2 PFU/cell using procedures as described elsewhere (Robbins and Rapp, Virology 106:317-326, 1981).

Labeling was accomplished twenty-four hours after infection by the following procedure. Tissue culture medium was removed from infected cell monolayers and the cells were washed with a serum and methionine-free Eagle's based MEM (starvation medium). The infected cultures were then supplemented with the starvation medium for 60-90 minutes and incubated at 37°C. Following the starvation period, cultures were labeled with the starvation medium containing 100 μCi/mL of [^{35}S]-methionine (Amersham). Labeling was carried out at 37°C in a 5% CO_2 atmosphere for 5-6 hours. Immunoprecipitations were carried out according to the procedure of Lamb *et al.*, Virology 91:60-78, 1978.

SDS-PAGE: Virions and immunoprecipitates were analyzed under denaturing and reducing conditions on 10% (or to detect the presence of very small peptide species [e.g., SH protein], 20%) polyacrylamide slab gels (Laemmli, 1970). After electrophoresis, gels were treated with a fluor solution (Amersham), were dried, and were then exposed to X-ray film.

Purified virions of the virus were analyzed by SDS-PAGE under reducing and non-reducing conditions (see Fig. 11, an autoradiogram of gradient-purified [^{35}S]-methionine-labeled *Cryptovirus* virions produced in acutely-infected Vero cells after SDS-PAGE under reducing conditions). The approximate molecular weights of the proteins indicated on the right side of the figure were calculated by comparing their migrations to marker proteins of known molecular weights (Sigma Chemical Co., St. Louis, MO). The annotations are defined in the brief description of the drawing.

The SH protein, a small envelope-associated protein having a MW of about 5 kD, is not shown because it has run off the gel (see below).

SH Protein. Due apparently to the small size of the SH protein and its relatively low methionine content, the SH protein was difficult to detect in radio-labeled virion preparations of both the BBR strain of *Cryptovirus* and the NIH 21005-2WR strain of SV5. When unlabeled purified virion preparations of both viruses were run on 20% polyacrylamide slab gels under denaturing and reducing conditions alongside of low molecular weight marker proteins (BioRad) and stained with a silver-staining technique (BioRad), a small protein with an M_r of approximately 5 kD, identified as the SH protein, was found in both *Cryptovirus* and SV5 virion preparations. There was no detectable difference between the migration of the SH protein from the BBR strain of *Cryptovirus* or the NIH 21005-2WR strain of SV5.

F_0 and HN Co-migration Anomaly. Although the major envelope proteins (F_0 and HN) of many Rubulaviruses (*e.g.*, SV5) were readily discernible as separate bands on SDS-PAGE gels, the larger size of the *Cryptovirus* F_0 protein (*i.e.*, +22 amino acids) resulted in a significantly slower rate of migration for this protein (M_r = 69 kD). As shown in Figs. 13A-B, close examination of such gels enabled one to discern both proteins, albeit with some difficulty. Figs. 13A and 13B show photographs of migration patterns of the major *Cryptovirus* envelope proteins, F_0 and HN. Fig. 13A illustrates the observed near co-migration of the major *Cryptovirus* envelope proteins, F_0 and HN. Enlargement of the RIP from the CSF-positive patient (right lane) in Fig. 13A shows the "bowed" or "crested" structure that resulted from the near co-migration of the F_0 and HN proteins of *Cryptovirus*. A diagrammatic interpretation of the near co-migration of the F_0 and HN proteins of *Cryptovirus* and the discrete migration of the analogous proteins of Simian virus 5 are shown in Fig. 13B.

Example 6. Experimental Infection of Mice: Creation of an Animal Model.

Infectious *Cryptovirus* stocks (prepared in CV-1_C cells) and live nonproductively-infected AV_3/SSPE cells were used to intracerebrally inoculate two strains of laboratory mice (Quackenbush and Colored, an outbred strain of C57 Black).

Briefly, neonatal mice (1-2 days old) were inoculated by injection with 0.025 mL (phosphate buffered saline, pH 7.4) containing either 5 x 10^4 PFU of cell-free *Cryptovirus* or 5 x 10^3 nonproductively infected human amnion cells (AV_3/SSPE). Following inoculation, the neonatal mice were returned to their mothers who were provided food and water *ad libitum*. Observations of

inoculated mice were made daily. Symptom of disease first appeared in affected animals after 21 days, and in others not until after more than 60 days. Observed symptoms included cachexia, muscle spasms, tremors, compulsive behaviors (e.g., extended periods of scratching, rubbing, or running in circles), hyperactivity/hyperesthesia, seizures and convulsions, and stupor. These results demonstrated that intracerebral inoculation with *Cryptovirus* results in subacute central nervous system (CNS) disease. Neurological, neurodegenerative, and/or neuropsychiatric disease presentation in mice is virtually indistinguishable from presentation in humans.

While all of the inoculated animals developed antibodies to the nucleocapsid protein of the virus (NP), not all of them developed antibodies to the envelope proteins (F, HN, and SH). More than 90% of the mice inoculated with *Cryptovirus* virions developed antibodies to the envelope proteins but only 33% of those inoculated with AV_3/SSPE cells did so.

Concurrently, while many of the animals inoculated with infectious *Cryptovirus* stocks developed profound neuropathological disease, fewer of the animals inoculated with nonproductively-infected AV_3/SSPE cells developed such illnesses, and there was a strong correlation between development of antibodies to the envelope proteins of the virus and the development of CNS symptoms. This suggests that the development of CNS disease depends on the establishment of an acute or subacute CNS infection by the virus and the expression of all of the virus' structural proteins in some cells or tissues.

More detailed examples follow:

Quackenbush mice. Two litters of 1-2 day old Quackenbush mice were intracerebrally-inoculated (in the right cerebral hemisphere) with 5×10^4 PFUs of either *Cryptovirus* (strain BBR)(10 individuals) or measles virus (Edmonston strain)(8 individuals), were returned to their mothers and were periodically observed over a period of three months. Two animals (one inoculated with *Cryptovirus* and one inoculated with measles virus) were found dead and partially consumed the next morning. Their deaths were attributed to "needle trauma" and/or maternal cannibalism. While none of the mice inoculated with measles virus developed any neurological, neurodegenerative, physiological or neuropsychiatric symptoms over the course of the study, two of the male mice inoculated with *Cryptovirus* developed atrophy and contralateral hindlimb paralysis (in their left hind legs) three to four weeks after inoculation. A third (female) mouse was observed dragging its left hind leg (unatrophied) approximately four weeks after inoculation but was found killed and partially eaten a day later. While 3 of 9 animals inoculated with *Cryptovirus* developed hind limb paralysis (33%), none of the animals showed overt signs of seizure, wasting or neurophychiatric symptoms

over the course of the study. Hind limb paralysis was also seen in a number of the offspring of adult female Quackenbush mice that had been inoculated with *Cryptovirus* as newborns but that did not develop any overt symptomology. The frequency of this phenomenon was difficult to assess because the mothers tended to cannibalize the newborn animals that were born with, or subsequently developed, such characteristics.

Colored mice. Three litters of 1-2 day old Colored mice (comprising 26 individuals) were observed daily following intracerebral inoculation with 5 x 10^4 PFUs of *Cryptovirus* (strain BBR), Simian Virus 5 (NIH 21005-2WR strain) or measles virus (Edmonston strain) or mock-infected cells. Half of each litter was inoculated with *Cryptovirus* (13 animals) while the other half was apportioned into three groups and inoculated with either Simian Virus 5 (6 animals), measles virus (4 animals) or mock-infected CV-1_C lysate (3 animals). Each group was marked with phenol red stain on the upper skin of one foot to distinguish them (i.e. right front, left front, right rear, left rear). One animal inoculated with *Cryptovirus* died between 24 and 48 hours post-inoculation and this was attributed to "needle trauma/starvation" as it had stopped feeding (or was rejected) when it was returned to its mother. Between three and four weeks later, one male and one female animal were found dead in their cages in tonic-clonic posture—both having been inoculated with *Cryptovirus*. It was noted that both also appeared to be underweight when compared to their littermates. Two months after inoculation with *Cryptovirus*, a third mouse (male) was observed to have cachexia, anorectic wasting, tremors and seizures (Fig. 7A). Over the next month (approximately 11 weeks after inoculation), a fourth animal (also male) developed tremors and seizures although no wasting was observed (data not shown). A male littermate of the *Cryptovirus*-infected mouse shown in Fig 7A, which was inoculated with the NIH 21005-2WR strain of SV5, is shown in Fig. 7B. The same results were obtained when mice were inoculated with either the *Edmonston* strain of measles virus, mock-infected CV-1_C cells, or homogenized AV_3/SSPE cells (i.e. all remained healthy and none developed neurological, neurodegenerative or neuropsychiatric symptoms; data not shown).

Over the ensuing six months (observed up to nine months post inoculation), a significant number of the remaining animals (4 of the remaining 8) inoculated with *Cryptovirus* developed physiological, neurological and/or neuropsychiatric symptoms. Such late onset animals presented with symptoms that were in marked contrast to the overt seizure disorders observed in the subacute onset animals (i.e. those that developed symptoms in first three months post inoculation). These symptoms were dominated by physiological, neuropsychiatric and behavioral disturbances rather than more overt neurological symptoms and included: marked weight gain, extreme aggressive/passive

responses to stimuli, obsessive/compulsive behaviors, ataxia and tremor. Aggression was most frequently characterized in afflicted animals by physical agitation and a predisposition to biting when handled. Passive animals tended to eat excessively, gain weight, and sleep. Repetitive behavior was also sporadically observed and consisted primarily of endless pacing and/or facial washing so extreme as to result in the loss of fur on the head and neck and the development of abrasive wounds. One of the animals (a female shown in Fig. 8A) had abnormal cranial structure (microcephaly) and manifested a spectrum of physiological and behavioral symptoms at six months including obesity, tics and muscle twitching (along the back and left side) and obsessive/compulsive facial washing and scratching. Episodes of such obsessive/compulsive behavior were observed to last for an hour or more. A second female animal (shown in Fig. 8B) appeared overtly normal during the first five months post inoculation but between five and six months began displaying marked ataxia, tremors and aggression. While this animal maintained a normal body weight and appearance, it was prone to splaying its feet to maintain its balance when resting and stumbling when walking and biting and hissing/snarling when handled or disturbed. Neither animal shown in Fig. 8 developed overt (*grand mal*) seizures, in contrast to the animal shown in Fig. 7A. Two other animals (one male and one female) also developed mixtures of the slow onset symptomology (data not shown). Overt seizure activity was never observed in any of the late onset animals and none of the animals inoculated with SV5, measles virus or mock-infected cells developed any similar symptoms.

Of the 13 neonate animals inoculated with *Cryptovirus*, one died from needle trauma (sex uncertain), two died in tonic-clonic posture with signs of wasting (indicative of sudden death due to *status epilepticus* (one male; one female); two became wasted and developed grand mal seizures (both males); four developed a spectrum of slow onset neurological/neuropsychological symptoms (three females, one male); one committed infanticide after being bred (a female); and three never developed any symptoms (two females and one male). Removing the needle trauma death from the equation, 9 of 12 animals developed neurological, degenerative and/or neuropsychiatric symptoms (75%). Removing the two clonic-posture deaths as well, 7 of 10 animals developed symptoms (70%). This was highly significant compared to the combined results for the control inoculated mice (7 of 10 mice inoculated with *Cryptovirus* presenting with neurological symptoms versus 0 of 13 mice in the control groups; P = 0.0005, 2-sided Fisher exact test), and was also significant compared to just the SV5 inoculated mice (7 of 10 versus 0 of 6; P = 0.01, 2-sided Fisher exact test) and even when compared to just the measles inoculated mice (7 of 10 versus 0 of 4; P = 0.035, one-sided Fisher exact test). Statistical significance was not quite reached compared to the mice inoculated with uninfected cell lysate, because of the small number of mice in this group (7 of 10 versus 0 of 3, P = 0.069,

single-sided Fisher exact). However, when the two clonic-posture deaths were included even this small control group was significantly different (9 of 12 versus 0 of 3, P = 0.044, 2-sided Fisher exact). Thus, the disease(s) and symptoms resulting from *Cryptovirus* infection was profoundly significant.

Infanticide. Of the four Colored mice which were inoculated as neonates with *Cryptovirus* but did not develop subacute or slow onset symptoms over the first nine months of the study, three were female and were subsequently bred with uninfected males at nine months of age. While all of the offspring of two of the three resulting litters developed normally, all of the offspring in one of the litters (comprising 10 animals) were killed and wholly or partially cannibalized by their mother. Such infanticide did not occur in litters to females that had been inoculated with SV5, measles or mock-infected cells. In a separate study (see below), one of the females which was inoculated with live AV3/SSPE cells—but did not develop any overt neurological symptoms—developed late physiological and behavioral symptoms and also committed infanticide of its whole litter after being bred with an uninfected male.

Animal Model Employing Inoculation of Nonproductively Infected AV_3/SSPE cells. In a separate study, two litters of neonatal mice (18 animals) were inoculated (1-2 days after birth) with either live or homogenized AV_3/SSPE cells (six animals each) or live or homogenized AV_3 cells (three animals each). There were no needle trauma deaths. While none of the animals inoculated with the homogenized AV_3/SSPE cells, live AV_3 cells or homogenized AV_3 cells (12 animals) developed any subacute or slow onset symptoms whatsoever, one of the six animals inoculated with live AV_3/SSPE cells developed subacute degenerative and neurological symptoms (a male) and one developed slow onset symptoms (1 female). The animal that developed subacute symptomology began presenting with symptoms 24 days after intracerebral inoculation. Over a five day period, the symptoms presented included cachexia, wasting, hunched posture, repetitive chirping and clicking, hyperesthesia, incontinence of urine, tremors, muscle spasms and coma. Overt seizures were not observed. It was sacrificed when coma developed. The animal that developed slow onset symptomology (a female) presented at five to six months (post-inoculation) with repetitive pacing, aggression and progressive obesity. The animal was bred at six months with an uninfected male. Seven days after delivering a litter of eight offspring, it killed the whole litter and partially consumed each individual. No seizures or other signs of overt neurological symptoms were observed. None of the other females which were inoculated with homogenized AV_3/SSPE cells, AV_3 cells or homogenized AV_3 cells and bred (six animals in total) committed infanticide.

Example 7. *Cryptovirus*-Specific Antibodies Are Present In The Serum And Cerebrospinal Fluid (CSF) Of Human Patients Diagnosed With Neurological, Neurodegenerative And/Or Neuropsychiatric Diseases.

Evidence for the presence of *Cryptovirus*-specific antibodies to the major envelope proteins of the virus (F_0 and HN) in the serum and CSF of patients was determined by immunoprecipitation of [^{35}S]-methionine-labeled *Cryptovirus*-specific proteins produced in acutely-infected CV-1_C cells. Figs. 12A and 12B are photographs of autoradiograms, which serve as examples of RIP profiles of measles virus- or *Cryptovirus*-specific proteins precipitated from [^{35}S]-methionine-labeled acutely infected CV-1_c cells by clinical CSF specimens followed by SDS-PAGE (reduced). In Fig. 12A, lane "V" contains gradient-purified *Cryptovirus* virions from acutely-infected, ^{35}[S]methionine-labeled CV-1_C cells (BBR Strain). Lane "MV" contains proteins precipitated by the CSF of an 11-year old male SSPE patient from radiolabled CV-1_c cells acutely-infected with measles virus *(Edmonston Strain)*. Lane "B" contains proteins precipitated by the same CSF specimen from a 1:1 mixture of radiolabled CV-1_c cells acutely-infected with either measles virus or *Cryptovirus*. Lane "CV" contains proteins precipitated by the same CSF specimen from radio-labeled CV-1_c cells acutely-infected with *Cryptovirus*. In Fig. 12B are shown RIP profiles of the *Cryptovirus*-specific proteins precipitated by the CSFs of six randomly-selected neurology/neurosurgery patients who had CSF taken for diagnostic screening. The patient whose sample appears in Lane 2 was an adult male who had presented with ataxia, confusion and memory loss (tentatively diagnosed with *ataxic cerebellar syndrome*). The patient whose sample appears in Lane 4 was an infant female who presented with hydrocephalus and intractable seizures and who subsequently died in *status epilepticus*.

Example 8. *Cryptovirus* Is Implicated In The Aetiopathogenesis Of Disease in Patients Diagnosed with Idiopathic Human Neurological, Neurodegenerative, And/Or Neuropsychiatric Diseases.

Cryptovirus is implicated in the aetiopathogenesis of disease in patients diagnosed with idiopathic neurological, neurodegenerative, and/or neuropsychiatric diseases, including anorexia nervosa, multiple sclerosis (MS), epilepsy, subacute sclerosing panencephalitis (SSPE), autism, mental retardation, affective disorder, dysthymia (clinical depression), schizophrenia, obsessive compulsive disorder, manic depression (bipolar disorder), chronic fatigue syndrome (CFS), hydrocephalus, ataxic cerebellar syndrome and atypical viral meningitis. Most patients who had *Cryptovirus*-specific antibodies in their CSF had been given multiple diagnoses. Thus, there is a

correlation between the presence of *Cryptovirus*-specific antibody to the major envelope proteins of the virus (F_0 and HN) in the CSF of neurology or neurosurgery patients and prior diagnosis of a condition with a significant "iterative" or compulsive component.

Although *Cryptovirus* seropositivity did not necessarily correlate to CSF positivity (*i.e.*, the presence of antibody to the *Cryptovirus* F_0 and HN proteins in the CSF) or a diagnosis of any neuropathological condition, CSF positivity strongly correlated with a prior diagnosis of a significant disorder of the central nervous system. These correlations were consistently found for patients with certain diagnoses (*e.g.*, SSPE, MS, CFS, and certain forms of idiopathic epilepsy) and incidentally found for specimens from patients with other diagnoses (*e.g.*, Alzheimer's Disease).

Similar results were obtained for two CSF specimens analyzed by an immunblotting technique (data not shown), or for serum and CSF specimens analyzed by an enzyme-linked-immunosorbent-assay (ELISA; see Fig. 14), although these assays were performed on only a proportion of CSF specimens due to the limited volumes available in some samples.

Although some patients presented with some of the above-mentioned symptoms and did not have antibody to the virus in their CSF specimens, in no instances were *Cryptovirus*-specific antibodies found in the CSF of patients that did not present with many of the symptoms and who had not been diagnosed with a significant neuropathological or neuropsychological disorder.

In addition, seropositive individuals (*i.e.*, those who have *Cryptovirus*-specific antibodies in their serum) harbor the virus in a nonproductive, inapparent but inducible state in their PBMNCs.

While the presence of the virus in an individual patient's PBMNCs did not symmetrically correlate with the development of neuropathological disorder, these findings imply that the virus can gain entry into the CNS via a microvascular incident (*i.e.*, leakage of *Cryptovirus* carrying PBMNCs into the CNS) or by immune system responses to other CNS stimuli (*i.e.*, diapedisis of *Cryptovirus*-carrying lymphocytes into the CNS as part of an inflammatory response to another infection; a Trojan Horse phenomenon). Reference to a lack of symmetrical correlation means that, while all individuals whose PBMNCs were examined and had *Cryptovirus*-specific antibodies in their CSF carried the virus in those cells, not all individuals who were found to be carrying the virus in their PBMNCs were, at that time, suffering from any neurological, neurodegenerative, and/or neuropsychiatric disorder.

The following examples reveal more detail.

(a) *Alzheimer's Disease.* As shown in Fig. 15, three matched sets of serum and CSF (provided by the National Neurological Research Specimen Bank (NNRSB) in Los Angeles, CA)

were examined by RIP analysis for the ability to precipitate the *Cryptovirus* F_0 and HN proteins from radiolabeled acutely-infected CV-1_C cells. While all three had *Cryptovirus*-specific antibodies in their serum, only Patient 3 had these antibodies in his or her CSF. This implies that the illness Patient 3 was suffering, diagnosed as Alzheimer's disease, was complicated by concurrent *Cryptovirus* infection of the CNS tissues. Alternatively, Patient 3 could have been misdiagnosed, in which case he or she could actually be suffering from a *Cryptovirus*-related neuropathy.

Even though the sample size is small, it is interesting that all three of the Alzheimer's disease patients had been exposed to *Cryptovirus* and were probably carrying it in their lymphocytes. It appeared, unlikely, however, that *Cryptovirus* plays a role in the development of Alzheimer's disease, because Patients 1 and 2 did not appear to have the virus in their CNS tissues.

(b) *Ataxic Cerebellar Syndrome, Atypical Viral Meningitis, Hydrocephalus, Idiopathic Parasthesia and Status Epilepticus*. A blind screen (i.e., none of the diagnoses or medical histories pertaining to any of the specimens was provided prior to specimen screening) was conducted of 66 CSF specimens from neurology or neurosurgery patients who had CSF specimens taken for diagnostic screening by the Department of Clinical Microbiology at the Royal Brisbane and Royal Children's Hospitals, in Brisbane, Queensland, Australia. Of these CSF specimens, ten were *Cryptovirus*-positive (see Fig. 17). One of the ten *Cryptovirus*-positive CSF specimens was identified as being from an adult male patient who had been diagnosed with ataxic cerebellar syndrome. (see Fig. 12B). Another of the ten *Cryptovirus*-positive CSF specimens was identified as being from an adult female patient who had been diagnosed with atypical viral meningitis (data not shown). A third positive CSF specimen came from a 55 year old male that had presented with ataxia, memory loss, blackouts, seizures, diplopia and headache and had been diagnosed with hydrocephalus, chronic fatigue syndrome and possible epilepsy; a fourth positive CSF specimen was from an adult male who had been diagnosed with idiopathic parasthesia; and a fifth positive CSF specimen was from a female infant who presented with clonic hand movements and intractable seizures and was diagnosed with hydrocephalus and *status epilepticus* (see also c and d, below). Diagnoses and symptoms of the remaining five *Cryptovirus*-positive CSF specimens were unavailable.

(c) *Chronic Fatigue Syndrome (CFS)*. A number of adolescent and adult patients who presented with symptoms of CFS were subsequently found to have high titers of anti-*Cryptovirus* antibodies in their sera, demonstrating that primary infection with the virus can manifest as a chronic febrile tracheo-bronchial illness with associated chronic malaise and lymphadenopathy. This is not

unlike infectious mononucleosis in presentation (i.e., a sore throat and persistent "glandular fever"). There was no evidence of acute encephalitic (or encephalopathic) disease in such patients or in any other patient found to have *Cryptovirus*-specific antibodies in his or her serum or CSF. "Acute" is taken here to mean presenting with rapid onset and symptoms within seven days.

Fifty-six serum specimens from patients who had been diagnosed with CFS were provided for *Cryptovirus* screening by regional physicians (Brisbane and Southeast Queensland). Eleven matching CSF specimens were subsequently obtained. RIP analysis revealed that 54/56 (96.4%) of the serum samples and 10/11 (90.9%) of the CSF specimens contained *Cryptovirus*-specific antibodies (Fig. 16).

Including the patient who had been codiagnosed with hydrocephalus, epilepsy and CFS (see Fig. 17 and data for Epilepsy, below), a total of 12 CSF specimens from CFS patients were analyzed by RIP analysis and 11/12 (91.7%) had *Cryptovirus*-specific antibodies in them.

Patients who had been diagnosed with CFS almost always had two, or more, concurrent diagnoses. These included: anorexia nervosa, MS, epilepsy, dysthymia (clinical depression), schizophrenia, and manic depression (bipolar disorder). For example, one adolescent girl who was co-diagnosed with both anorexia nervosa and chronic fatigue syndrome (CFS) had *Cryptovirus*-specific antibodies in her CSF. It is of note that the etiology of virtually all of these disorders is idiopathic.

While the symptoms presented by CFS patients cover a broad spectrum, the spectrum is, in fact, fairly discrete and representative of the illness. This is perhaps best illustrated by examination of the medical records of five patients, presented below:

Patient PR was an adult male, 55 years of age, who was suffering primarily from mental confusion, lethargy, memory loss, blurred vision, dysthymia, and *petit mal* seizures. EEG results were abnormal, which indicates epileptiform disease. Patient PR was ambulatory with progressively deteriorating CNS symptoms.

Patient DF was an adult male, 52 years of age, who was suffering primarily from mental confusion, lethargy, memory loss, dysthymia, and *petit mal* seizures. EEG results were abnormal, showing epileptiform responses in cortical and subcortical functions of the anterior hemispheres. Patient DF was ambulatory with progressively deteriorating CNS symptoms.

Patient NB was an adult female, 36 years of age, who was suffering primarily from mental confusion, lethargy and extreme fatigue, memory loss, dysthymia, ataxia, blurred vision, and parathesias, and had a history of glandular fever, recurrent sore throats of prolonged duration,

tremors, and *petit mal* seizures. NB's sister was diagnosed with anorexia and myoclonus. Patient NB was bedridden or partially ambulatory with progressively deteriorating CNS symptoms.

Patient KT was an adult female, 27 years of age, who was suffering primarily from mental confusion, loss of concentration, memory loss, anorexia, lethargy and extreme fatigue, and tremors, and had a history of recurrent febrile lymphadenopathy. Patient KT was stable but bedridden and only partially ambulatory.

Patient SS was an adult female, 23 years of age, who was suffering primarily from loss of concentration, memory loss, and lethargy, and had a history of dysthymia beginning at age 14 and EBV-negative glandular fever. Immediate family members (mother, father, two sisters, and one brother) were all seropositive. In addition, SS's mother had a 9 year history of dysthymia, and *Cryptovirus* antigens were detected in her cultured PBMNC. Two years after sampling, Patient SS was stable and ambulatory.

(d) *Epilepsy and Hydrocephalus.* RIP analysis was used to determine the presence of *Cryptovirus*-specific antibodies in two clinical collections of CSF specimens. The first collection included 66 specimens that were selected at random from those submitted to the Department of Clinical Microbiology at Royal Brisbane Hospital in Brisbane, Queensland by physicians in the Department of Neurology and Neurosurgery (see b above). None of the diagnoses or medical histories pertaining to any of the specimens was provided prior to specimen screening. Fig. 17 illustrates the results of RIP assays conducted with CSF from this collection. The positive CSF precipitate in Lane 2 was subsequently found to have come from a 55-year old adult male (RW) who presented with ataxia, memory loss, blackouts, seizures, diplopia, and headaches. He was determined to have a hydrocephalic condition and underwent surgery to insert a ventricular shunt to alleviate the condition. He had been diagnosed with hydrocephalus, epilepsy and Chronic Fatigue Syndrome (CFS).

Ten of the 66 CSF specimens in Collection 1 were found to contain *Cryptovirus*-specific antibody (15%). Diagnoses were obtained for five of these patients and included: (1) hydrocephalus and intractable seizures in an infant female who subsequently died (see Fig. 12B), (2) ataxic cerebellar syndrome in an adult male (see Fig. 12B), (3) atypical viral meningitis in a female child, (4) parathesia in an adult male, and (5) hydrocephalus, epilepsy and CFS in the patient described in connection with Fig. 17.

Diagnoses were obtained for only two of the 56 *Cryptovirus*-negative CSF specimens: one patient (WK, a male) was diagnosed with acute viral meningitis and one (SG, a female) was diagnosed with idiopathic intracranial hypertension.

The second collection (Collection 2) included 20 CSF specimens from children (<12 years old) that were collected by neurologists at Camperdown Children's Hospital in Sydney, New South Wales, Australia. Again, none of the diagnoses or medical histories pertaining to any of the specimens was provided prior to specimen screening. However, in this collection a request had been made to include an undisclosed number of CSF specimens from children who had either presented with epileptiform illness or had been diagnosed with some form of idiopathic epilepsy.

Fig. 18 illustrates the results of RIP assays conducted with CSF from Collection 2. The CSF precipitate analyzed in Lane 1 was from a newborn infant who developed intractable seizures and died in *status epilepticus* (Patient CT, below) and the precipitate analyzed in Lane 2 was from a child who had been given a diagnosis of Lennox-Gasteau/generalized epilepsy (Patient LB, below), respectively. The background noise in this autoradiogram was high as a result of the long-term exposure (30 days) required to see the bands.

Six of the 20 CSF specimens provided in the (biased) Collection 2 were found to have *Cryptovirus*-specific antibodies, and it was subsequently learned that this screening had identified 6 of the 7 specimens from patients who had been diagnosed with epilepsy or other forms of epileptiform illness and had been included in the collection. The six *Cryptovirus*-positive CSF specimens came from the following patients: (1) CT, a neonate with intractable fits and seizures, who died in *status epilepticus*, (2) LB, who was diagnosed with Lennox-Gasteau epilepsy and generalized epilepsy, (3) BM, who was diagnosed with severe retardation and epilepsy, (4) FZ, a two-month old child with intractable seizures who died in *status epilepticus*, (5) CN, who had hydrocephalus, cerebral palsy, and epileptiform seizures, and (6) LD, who had primary infantile spasms. Hydrocephalus was codiagnosed in 3 of 8 patients diagnosed with epilepsy or other epileptiform illness.

Although one of the 14 *Cryptovirus*-negative CSF specimens was obtained from a patient who had been diagnosed with epilepsy, diagnoses were not provided for the remaining specimens. They were simply characterized as pediatric neurology or neurosurgery specimens from asymptomatic patients (*i.e.*, patients who had not presented with epileptiform symptoms or been diagnosed with epileptiform illness).

(e) *Multiple Sclerosis (MS).* Clinical specimens from patients with MS comprise one of the largest groups of materials screened (38 serum samples and 30 CSF samples including 30 matched sets of each). Eight of the serum samples came from MS patients in Brisbane, Queensland who had debilitating disease and were living in a nursing home run by the National Multiple Sclerosis Society of Australia. No CSF specimens were acquired from these patients. The 30 matched sets of serum and CSF were provided by the National Neurological Research Specimen Bank (NNRSB) in Los Angeles.

Fig. 19 illustrates the results of RIP assays conducted with serum samples of 5/30 MS patients provided by the NNRSB. The results obtained from an additional 25 serum specimens provided by the NNRSB are shown in Fig. 20, and the RIP results from 16/30 of the CSF specimens from MS patients provided by the NNRSB are shown in Fig. 21. RIPs performed using the remaining 8 specimens resulted in similar profiles (data not shown). As shown in Figs. 19-21, the results of these analyses demonstrated that all patients had high levels of *Cryptovirus*-specific antibodies in their serum (100%) and 29/30 had *Cryptovirus*-specific antibodies in their CSF (96.7%).

(f) *Subacute Sclerosing Panencephalitis (SSPE).* The anomalies that have been observed which are inconsistent with measles virus alone being the sole cause of SSPE (see Discussion of Related Art) can be explained by the evidence that the aetiopathogenesis of SSPE involves dual infection of the CNS by measles and *Cryptovirus* (which was isolated from SSPE patients).

Sera from SSPE patients were found to precipitate the major nucleocapsid protein of the virus (NP, 63 kD) from nonproductively-infected AV_3/SSPE cells (see Fig. 22). Fig. 22 is a photograph of an autoradiogram obtained following creation of RIP profiles of the *Cryptovirus* NP protein (p63) precipitated from [^{35}S]-methionine-labeled AV_3/SSPE cells by the sera of six Australian SSPE patients (Lanes 1-6) and six control sera (Lanes 7-12; sera from pediatric patients without antibodies to the *Cryptovirus* major envelope proteins (F_0, HN).

Fig. 23 is a photograph of an autoradiogram of RIP profiles of measles virus-specific and *Cryptovirus*-specific proteins precipitated from [^{35}S]-methionine-labeled measles virus-infected CV-1_C cells (Lane MV), *Cryptovirus*-infected CV-1_C cells (Lane CV) or a mixture of both (Lane B) by CSF sampled from an 11-year old male diagnosed with SSPE. Lane V = gradient-purified *Cryptovirus* virions from [^{35}S]-methionine-labeled *Cryptovirus*-infected CV-1_C cells. Fig. 23 shows that CSF from this SSPE patient precipitated both *Cryptovirus* and measles virus proteins. The results of this assay demonstrate that SSPE CSF contains both measles virus-specific and *Cryptovirus*-specific antibodies (i.e. antibody to the HN protein of measles virus (Lane MV) and the

HN and F_0 proteins of *Cryptovirus* virus (Lane CV) and that both are present in nearly equal amounts. This was unique, since none of the other CSFs samples that precipitated *Cryptovirus* proteins (e.g., from MS, CFS, or epilepsy patients) also preciptated the measles virus HN protein.

The RIP profile of *Cryptovirus*-specific proteins precipitated by this CSF specimen is typical of those produced by the "*Cryptovirus*-positive" CSFs of MS patients, CFS patients and idiopathic epilepsy patients tested to date (compare Figs. 12A and 17). While there was considerable variation in the strength of the antibody response to the F_0 and HN proteins, there appeared to be little variation in the presence of antibody to one protein or the other. There was, however, a variable response to the F_1 and F_2 proteins (*i.e.*, in many patients, such responses appeared to be absent). This paradox may relate to the proteolytic cleavage of the protein *in situ* and corresponding immune responses (*i.e.*, the F_0 protein is efficiently cleaved by some patients, generating the F_1 and F_2 fragments and ultimately exposing their immune system to them); in other patients the protein may be cleaved less efficiently (or not at all) and, therefore, these patients do not generate as much of an antibody response to the fragments).

Example 9. Correlations Between Affected Human Patients and Experimentally-Infected Animals

Some of the examples herein highlight the epileptiform symptomology presented by many of the patients who have *Cryptovirus*-specific antibodies in their cerebrospinal fluid (CSF) or by mice experimentally-infected with the virus. This association is strong, but not all patients with *Cryptovirus*-specific antibodies in their CSF present with overt seizures or convulsions. There is instead a spectrum of responses, from little or no seizure activity, through mild activity (*petit mal* or "absence" seizures), to recurrent and intractable *grand mal* seizures (the occurrence of which is often misunderstood by the lay public to be the defining symptom of all forms of epilepsy; *see Epilepsy: A Comprehensive Textbook*, Engel, Jr. J. and Pedley, T.A., Eds., Lippincott-Raven, 1997).

With regard to the development of symptoms and manifestations of human *Cryptovirus*-infections, it is essential to be cognizant of the spatial ("where"), temporal ("when"), and quantum ("what else") factors involved: (1) which cells, tissues, neural tracts and CNS structures become infected by the virus, (2) the developmental state of those systems at the time of infection, and (3) the role of environmental and host factors in development and progress of the infection, respectively.

For example, the data presented here establish a strong correlation between the development of epileptiform symptomology and *early* CNS infection with the virus (*i.e.*, in infancy, early childhood or adolescence and in experimentally-infected neonatal mice), this correlation is less strong

in adults (and adult mice who do not develop epileptiform symptoms) and the spectrum of CNS manifestations observed is much wider.

Generally, the characteristic most frequently and consistently presented by humans or animals that have been experimentally infected with the virus is the development of "iterative" or "compulsive" neuropathies and behaviors. This is most likely due to the selective loss of (or immunopathological damage done to) neurons (*e.g.* interneurons) or neuron tracts in different parts of the central nervous system (CNS) at different times or at different stages of CNS development.

When the medical records of patients who had *Cryptovirus*-specific antibodies in their CSF were examined, all of the patients had been diagnosed with one or more serious neurological disorders. These included, but were not limited to:

(1) subacute sclerosing panencephalitis (SSPE): 4 of 4 CSFs tested (100%), all adolescent patients);

(2) idiopathic / cryptogenic epilepsy: 6 of 7 CSFs tested (85.7%), from infants and children presenting with seizures and diagnosed with idiopathic or cryptogenic forms of epilepsy;

(3) multiple sclerosis (MS): 29 of 30 CSFs tested (96.7%) all adult specimens; and

(4) chronic fatigue syndrome (CFS) / clinical depression: 11 of 12 CSFs tested (91.7%), all adult specimens.

These results demonstrate a clear correlation between *Cryptovirus*-specific antibodies in the CSF and a narrow spectrum of CNS diseases. Although the diseases listed above have been defined as representatives of discrete pathognomonic entities, there is in reality substantial overlap between the symptoms presented by these patients and their diagnoses. For example, virtually every patient eventually diagnosed with SSPE is initially diagnosed with epilepsy. Similarly, early stage MS is extremely similar in presentation to CFS, and clinical depression is a common characteristic of both. Not surprisingly, another name for CFS is "atypical multiple sclerosis" (in Bell, *The Disease of a Thousand Names*, Pollard Publications, Lyndonville, NY [1991]).

There is a strong correlation between (1) the age of those patients who had severe epileptiform illness (SSPE and epilepsy, the majority of whom are infants, children, or adolescents) and (2) the age of those patients who had more diffuse or subtle neurological dysfunction (e.g., MS and CFS patients who were all adults). Furthermore, SSPE, certain forms of idiopathic and cryptogenic epilepsy, and MS have many neuropathological characteristics in common. These include areas of discrete, focal or disseminated sclerosis (scar formation in CNS tissue), dysplastic lesions (either as the result of immunopathological processes or neuron tract loss), and perivascular cuffing of immune cells (evidence of inflammatory processes in the vicinity of lesions). Thus, each

of these diseases could represent a different pathological "complex" of spatial, temporal, and quantum factors that have *Cryptovirus* infection of CNS tissues as a shared characteristic. With respect to SSPE, previous data have established (and the data here confirm) that measles virus is also involved in this illness. SSPE is caused by widespread CNS infection by both viruses (resulting in inflammatory and disseminated sclerosis across the white matter of the brain) while certain forms of idiopathic epilepsy represent early infection of the CNS by *Cryptovirus* alone (resulting in the loss of susceptible interneurons and neuron tracts and the development of discrete dysplastic lesions). MS, occurring almost exclusively in adults, represents the pathological outcome of late and focal *Cryptovirus* infection of the CNS – due to the restriction of *Cryptovirus* replication in fully differentiated CNS tissues and the effective partitioning of brain by the mature glial architecture.

In summary, intracranial inoculation of mice with the virus, or with cells nonproductively-infected with the virus, results in the subacute development of neuropathological diseases in a significant proportion of the animals. These diseases are closely akin to the spectrum of human neuropathies seen in patients with *Cryptovirus*-specific antibodies in their cerebrospinal fluids.

Further, although patients with *Cryptovirus*-positive CSF had been diagnosed with a spectrum of illnesses, there was a clear partitioning of patients into two groups (1) infants, children and adolescents with illnesses dominated by subacute epileptiform physical symptoms which were often life-threatening and (2) young adults and adults with slowly-developing chronic illnesses which presented with less pronounced physical symptoms but significant neuropsychological components which were usually not life-threatening.

These findings support the conclusion that *Cryptovirus* is responsible for a neurological spectrum disorder whose ultimate manifestation depends on (1) the age of the individual when they contract the primary infection, (2) the mechanism by which the virus gains entry into the CNS tissue, (3) the extent of the infection at that time, (4) the stage of development of the CNS when it becomes infected, (5) the part of the CNS which becomes infected, (6) genetic factors (*e.g.*, immune system defects, neurological malformations, the presence for absence of virus receptors on CNS tissues, etc.) and (7) other environmental factors (*e.g.*, the occurrence of head trauma, neurosurgery of any kind, prior or concurrent infection of CNS tissue by other agents, exposure to drugs or toxic chemicals, *etc.*).

A number of embodiments of the invention have been described. Nevertheless, it will be understood that various modifications can be made without departing from the spirit and scope of the invention. Accordingly, other embodiments are within the scope of the following claims.

The claims defining the invention are as follows:

1. An isolated nucleic acid, comprising:

(A) contiguous nucleotide positions 1-15246 of (SEQ ID NO: 1);

(B) a nucleotide sequence complementary to (A); or

(C) *Cryptovirus*-specific fragment of (A) or (B), comprising a nucleic acid segment selected from the group consisting of:

(i) contiguous nucleotide positions 152-1678 of (SEQ ID NO:1), a complementary sequence, or a degenerate coding sequence;

(ii) contiguous nucleotide positions 1850-2515 of (SEQ ID NO:1), a complementary sequence, or a degenerate coding sequence;

(iii) contiguous nucleotide positions 1850-3023 of (SEQ ID NO:1), a complementary sequence, or a degenerate coding sequence;

(iv) contiguous nucleotide positions 1850-3023 of (SEQ ID NO:1) combined with a further insertion of two guanine residues between nucleotide position 2339 of (SEQ ID NO:1) and nucleotide position 2340 of (SEQ ID NO:1), a complementary sequence, or a degenerate coding sequence;

(v) contiguous nucleotide positions 3141-4271 of (SEQ ID NO:1), a complementary sequence, or a degenerate coding sequence;

(vi) contiguous nucleotide positions 4530-6182 of (SEQ ID NO:1), a complementary sequence, or a degenerate sequence;

(vii) contiguous nucleotide positions 4587-6182 of (SEQ ID NO:1), a complementary sequence, or a degenerate sequence;

(viii) contiguous nucleotide positions 4587-4835 of (SEQ ID NO:1), a complementary sequence, or a degenerate sequence;

(ix) contiguous nucleotide positions 4836-6182 of (SEQ ID NO:1), a complementary sequence, or a degenerate sequence;

(x) contiguous nucleotide positions 4272-6515 of (SEQ ID NO:1), a complementary sequence, or a degenerate coding sequence;

(xi) contiguous nucleotide positions 6303-6434 of (SEQ ID NO:1), a complementary sequence, or a degenerate coding sequence;

(xii) contiguous nucleotide positions 6584-8278 of (SEQ ID. NO:1), a complementary sequence, or a degenerate coding sequence; and

(xiii) contiguous nucleotide positions 8414-15178 of (SEQ ID NO:1), a complementary sequence, or a degenerate coding sequence; and

(xiv) contiguous nucleotide positions 1684-1701 (of SEQ ID NO:1), a complementary sequence, or a degenerate coding sequence; and

(xv) contiguous nucleotide positions 1700-1717 (of SEQ ID NO:1), a complementary sequence, or a degenerate coding sequence; and

(xvi) contiguous nucleotide positions 4283-4300 (of SEQ ID NO:1), a complementary sequence, or a degenerate coding sequence; and

(xvii) contiguous nucleotide positions 4299-4316 (of SEQ ID NO:1), a complementary sequence, or a degenerate coding sequence; and

(xviii) contiguous nucleotide positions 4285-4302 (of SEQ ID NO:1), a complementary sequence, or a degenerate coding sequence; and

(xix) contiguous nucleotide positions 4300-4317 (of SEQ ID NO:1), a complementary sequence, or a degenerate coding sequence; and

(xx) contiguous nucleotide positions 4518-4535 (of SEQ ID NO:1), a complementary sequence, or a degenerate coding sequence; and

(xxi) contiguous nucleotide positions 4533-4550 (of SEQ ID NO:1), a complementary sequence, or a degenerate coding sequence; and

(xxii) contiguous nucleotide positions 6191-6208 (of SEQ ID NO:1), a complementary sequence, or a degenerate coding sequence; and

(xxiii) contiguous nucleotide positions 6116-6133 (of SEQ ID NO:1), a complementary sequence, or a degenerate coding sequence; and

(xxiv) contiguous nucleotide positions 6192-6209 (of SEQ ID NO:1), a complementary sequence, or a degenerate coding sequence; and

(xxv) contiguous nucleotide positions 7501-7518 (of SEQ ID NO:1), a complementary sequence, or a degenerate coding sequence; and

(xxvi) contiguous nucleotide positions 7517-7534 (of SEQ ID NO:1), a complementary sequence, or a degenerate coding sequence; and

(xxvii) contiguous nucleotide positions 4292-4549 (of SEQ ID NO:1), a complementary sequence, or a degenerate coding sequence.

2. The nucleic acid of Claim 1, wherein the nucleic acid is RNA.

3. The nucleic acid of Claim 1, wherein the nucleic acid is cDNA.

4. A nucleic acid construct, comprising the nucleic acid of any one of claims 1 to 3.

5. An expression vector, comprising the nucleic acid construct of Claim 4

6. A cloning vector, comprising the nucleic acid construct of Claim 4.

7. A host cell, comprising the expression vector of Claim 5 or the cloning vector of Claim 6.

8. The host cell of Claim 7, wherein the cell is a mammalian cell.

9. An isolated *Cryptovirus* protein encoded by a nucleic acid segment comprising:

(A) contiguous nucleotide positions 152-1678 of (SEQ ID NO:1) or a degenerate sequence;

(B) contiguous nucleotide positions 1850-2515 of (SEQ ID NO:1) or a degenerate sequence;

(C) contiguous nucleotide positions 1850-3023 of (SEQ ID NO:1) combined with a further insertion of two guanine residues between nucleotide position 2339 of (SEQ ID NO:1) and nucleotide position 2340 of (SEQ ID NO:1), or a degenerate sequence;

(D) contiguous nucleotide positions 3141-4271 of (SEQ ID NO:1) or a degenerate sequence;

(E) contiguous nucleotide positions 4530-6182 of (SEQ ID NO:1) or a degenerate sequence;

(F) contiguous nucleotide positions 4587-6182 of (SEQ ID NO:1) or a degenerate sequence;

(G) contiguous nucleotide positions 4587-4835 of (SEQ ID NO:1) or a degenerate sequence;

(H) contiguous nucleotide positions 4836-6182 of (SEQ ID NO:1) or a degenerate sequence;

(I) contiguous nucleotide positions 6303-6434 of (SEQ ID NO:1) or a degenerate sequence;

(J) contiguous nucleotide positions 6584-8278 of (SEQ ID NO:1) or a degenerate sequence; or

(K) contiguous nucleotide positions 8414-15178 of (SEQ ID NO:1) or a degenerate sequence.

10. The protein of Claim 9, wherein the protein is a *Cryptovirus* envelope protein encoded by a nucleic acid segment comprising (E), (F), (G), (H), (I), or (J).

11. A chimeric protein, comprising a *Cryptovirus* protein encoded by a nucleic acid segment comprising:

(A) contiguous nucleotide positions 152-1678 of (SEQ ID NO:1) or a degenerate sequence;

(B) contiguous nucleotide positions 1850-2515 of (SEQ ID NO:1) or a degenerate sequence;

(C) contiguous nucleotide positions 1850-3023 of (SEQ ID NO:1) combined with a further insertion of two guanine residues into the nucleotide sequence between nucleotide position 2339 of (SEQ ID NO:1) and nucleotide position 2340 of (SEQ ID NO:1), or a degenerate sequence;

(D) contiguous nucleotide positions 3141-4271 of (SEQ ID NO:1) or a degenerate sequence;

(E) contiguous nucleotide positions 4530-6182 of (SEQ ID NO:1) or a degenerate sequence;

(F) contiguous nucleotide positions 4587-6182 of (SEQ ID NO:1) or a degenerate sequence;

(G) contiguous nucleotide positions 4587-4835 of (SEQ ID NO:1) or a degenerate sequence;

(H) contiguous nucleotide positions 4836-6182 of (SEQ ID NO:1) or a degenerate sequence;

(I) contiguous nucleotide positions 6303-6434 of (SEQ ID NO:1) or a degenerate sequence;

(J) contiguous nucleotide positions 6584-8278 of (SEQ ID NO:1) or a degenerate sequence; or

(K) contiguous nucleotide positions 8414-15178 of (SEQ ID NO:1) or a degenerate sequence.

12. The chimeric protein of claim 11 wherein the *Cryptovirus* protein is a *Cryptovirus* envelope protein encoded by a nucleic acid segment comprising (E), (F), (G), (H), (I) or (J).

13. Use of the protein of any one of claims 9 to 12 in producing a *Cryptovirus*-specific antibody.

14. An isolated antibody that specifically binds the protein of claim 9 or 10.

15. The antibody of claim 14, that specifically binds a *Cryptovirus* envelope protein encoded by:

(A) contiguous nucleotide positions 4530-6182 of (SEQ ID NO:1) or a degenerate sequence;

(B) contiguous nucleotide positions 4587-6182 of (SEQ ID NO:1) or a degenerate sequence;

(C) contiguous nucleotide positions 4587-4835 of (SEQ ID NO:1) or a degenerate sequence;

(D) contiguous nucleotide positions 4836-6182 of (SEQ ID NO:1) or a degenerate sequence;

(E) contiguous nucleotide positions 6303-6434 of (SEQ ID NO:1) or a degenerate sequence;

(F) contiguous nucleotide positions 6584-8278 of (SEQ ID NO:1) or a degenerate sequence.

16. The antibody of claim 14 or 15, wherein the antibody is a polyclonal.

17. The antibody of claim 14 or 15, wherein the antibody is monoclonal.

18. The antibody of claim 14 or 15, wherein the antibody is chimeric.

19. Use of the antibody of any one of claims 14 to 18 in manufacturing a medicament for the treatment of *Cryptovirus* infections.

20. An isolated viral particle comprising the nucleic acid of claim 1.

21. A composition of matter, comprising the nucleic acid of any one of claims 1 to 3, the protein of any one of claims 9 to 12, the antibody of any one of claims 14 to 18, or the virion of claim 20; and a carrier.

22. An isolated viral particle, comprising the protein of any one of claims 9 to 12.

23. An isolated *Cryptovirus* particle, comprising a genome having a nucleotide sequence entirely complementary to (SEQ ID NO:1).

24. Use of the nucleic acid of any one of claims 1 to 3, the nucleic acid construct of claim 4, the protein of any one of claims 9 to 12, the viral particle of claim 20 or 22, or *Cryptovirus* particle of claim 23, in manufacturing a vaccine.

25. The use according to claim 24, wherein the viral particle is an attenuated virion.

26. The use according to claim 24, wherein the viral particle is a killed virion.

27. An isolated *Cryptovirus* particle, wherein the *Cryptovirus* is Strain BBR.

28. A probe or primer, comprising the nucleic acid of any one of claims 1 to 3.

29. A method of detecting the presence or absence of a *Cryptovirus* protein in a sample of a biological material, comprising:

contacting the sample of the biological material with the antibody of any one of claims 14 to 18; and

detecting specific binding of the antibody to a constituent of the sample, wherein the presence of specific binding indicates the presence of the *Cryptovirus* protein in the sample.

30. A method of detecting the presence or absence of a *Cryptovirus*-specific RNA in a sample of a biological material, comprising:

obtaining a sample of a biological material comprising RNA;

contacting the sample with the probe of claim 28 under at least moderately stringent hybridization conditions, wherein the formation of detectable hybridization product indicates the presence of the *Cryptovirus*-specific RNA in the sample.

31. A method of detecting the presence or absence of a *Cryptovirus*-specific RNA in a sample of a biological material, comprising:

obtaining a sample of a biological material comprising RNA;

amplifying *Cryptovirus*-specific RNA in the sample using at least one primer of claim 28 in an amplification reaction mixture;

then detecting the presence or absence of *Cryptovirus*-specific nucleic acid amplification products in the amplification reaction mixture, wherein the presence of the amplification products in the reaction mixture indicates the presence of the *Cryptovirus* RNA in the sample.

32. The method of any one of claims 29 to 31, wherein the biological material is a cellular material.

33. The method of any one of claims 29 to 31, wherein the biological material is blood or serum.

34. The method of any one of claims 29 to 31, wherein the biological material is cerebrospinal fluid.

35. The method of any one of claims 29 to 31, wherein the biological material is lymphoid tissue.

36. The method of any one of claims 29 to 31, wherein the biological material is nervous tissue.

37. The method of claim 36, wherein the nervous tissue is brain tissue.

38. A method of detecting the presence or absence of a *Cryptovirus*-specific antibody in a sample of a biological material, comprising:

contacting the sample with the protein of claim 9 or 10;

allowing the formation of a specific protein-antibody complex;

detecting the presence of the specific protein-antibody complex, wherein the presence of a specific protein-antibody complex indicates the presence of the *Cryptovirus*-specific antibody in the sample.

39. A method of detecting the presence of a *Cryptovirus*-specific antibody in a sample of a biological material, comprising:

contacting the sample with the protein of claim 11 or 12;

allowing the formation of a specific protein-antibody complex;

detecting the presence of the specific protein-antibody complex, wherein the presence of a specific protein-antibody complex indicates the presence of *Cryptovirus*-specific antibody in the sample.

40. An assay method for detecting the presence or absence of an antibody that selectively binds *Cryptovirus* in a sample of an antibody-containing biological material originating from a human, comprising:

contacting the sample, the sample originating from an individual suspected of having a *Cryptovirus* infection, with the envelope protein of claim 10, such that, if antibody selectively binding *Cryptovirus* is present, an antibody-bound envelope protein complex forms;

contacting any antibody-bound envelope protein complexes thus formed with anti-human antibody-binding antibody, and allowing the formation of complexes of the antibody, with the antibody-bound envelope protein complexes; and

detecting the presence or absence of any antibody-bound envelope protein complexes thus formed, the presence of such complexes indicating the presence in the sample of antibody selectively binding *Cryptovirus*.

41. An assay method for detecting the presence or absence of antibody that selectively binds *Cryptovirus* antigen in a sample of an antibody-containing biological material originating from a human, the method comprising:

contacting the sample, the sample originating from an individual suspected of having a *Cryptovirus* infection, with the viral particle of claim 22, such that, if antibody selectively binding *Cryptovirus* antigen is present, an antibody-bound virus complex forms;

contacting any antibody-bound virus complexes thus formed with anti-human antibody-binding antibody, and allowing the formation of complexes of the anti-human antibody-binding antibody with the antibody-bound virus complexes; and

detecting the presence or absence of any complexes formed, the presence of such complexes indicating the presence in the sample of antibody selectively binding *Cryptovirus* antigen.

42. A method of detecting *Cryptovirus* infection in a mammal, comprising:

obtaining a sample of a biological material from the mammal; and

performing the method of any one of claims 29 to 41, using the sample, whereby detecting the presence of the *Cryptovirus* protein, *Cryptovirus*-specific RNA, and/or *Cryptovirus*-specific antibody in the sample indicates a *Cryptovirus* infection in the mammal.

43. The method according to any one of claims 38 to 42, wherein the biological material is cellular material.

44. The method according to any one of claims 38 to 42, wherein the biological material is blood or serum.

45. The method according to any one of claims 38 to 42, wherein the biological material is cerebrospinal fluid.

46. The method according to any one of claims 38 to 42, wherein the biological material is lymphoid tissue.

47. The method according to any one of claims 38 to 42, wherein the biological material is nervous tissue.

48. The method according to claim 47, wherein the nervous tissue is brain tissue.

49. The method of claim 42, wherein the mammal is a human.

50. The method of claim 49, wherein the human has a neurological, neurodegenerative, and/or neuropsychiatric disease.

51. The method of claim 49, wherein the human has a primary tracheobronchial and/or lymphadenopathy-associated illness.

52. A method of isolating a *Cryptovirus* virion, comprising:

(a) culturing a plurality of peripheral blood mononuclear cells that have been obtained from a human having a *Cryptovirus* infection, in an artificial aqueous medium comprising an agent that increases cellular guanylyl cyclise activity.

(b) co-culturing the plurality of peripheral blood mononuclear cells with a plurality of mammalian amnion cells in fresh artificial aqueous medium comprising an agent that increases cellular guanylyl cyclise activity.

(c) passaging the peripheral blood mononuclear cells with the mammalian amnion cells in co-culture.

(d) co-cultivating a plurality of mammalian epithelial cells together with the peripheral blood mononuclear cells and the mammalian amnion cells in fresh artificial aqueous medium comprising an agent that increases cellular guanylyl cyclise activity; and

(e) separating a supernatant of the aqueous medium from the cells, to obtain a *Cryptovirus* virion in the supernatant.

53. A method of propagating a *Cryptovirus*, comprising:

(a) exposing a plurality of mammalian epithelial cells to a plurality of cell free *Cryptovirus* virions, said *Cryptovirus* virions having been isolated by the method of claim 52; and

(b) further cultivating the mammalian epithelial cells, thus virion-exposed, in an artificial aqueous medium comprising an agent that increases the activity of cellular guanylyl cyclise.

54. A method of producing a mammalian cell line non-productively infected with *Cryptovirus,* comprising:

(a) co-culturing peripheral blood mononuclear cells that have been obtained from a human having a *Cryptovirus* infection, with mammalian amnion cells, in an artificial aqueous medium comprising an agent that increases cellular guanylyl cyclise activity, such that the mammalian amnion cells become non-productively infected by *Cryptovirus;* and

(b) passaging the non-productively infected mammalian amnion cells with the peripheral blood mononuclear cells, whereby the co-culture becomes a monoculture of the non-productively infected mammalian amnion cells.

55. The method according to any one of claims 52 to 54, wherein the mammalian amnion cells are human amnion cells.

56. The method of claim 55, wherein the human amnion cells are AV_3 cells.

57. The method of any one of claims 52 to 54, wherein the mammalian epithelial cells are simian epithelial cells selected from the group consisting of Vero or CV-1 cells.

58. The method of claim 57, wherein the CV-1 cells are subline CV-1 cells.

59. The method of any one of claims 52 to 58, wherein the agent that increases cellular guanylyl cyclase activity is cyclic GMP, insulin, zinc dication, or a combination of any of these.

60. The method of claim 59 wherein the cyclic GMP is in a concentration of about 0.05 to about 5mM in the artificial aqueous medium.

61. The method of any one of claims 52 to 58, wherein the agent that increases cellular guanylyl cyclase activity is nitric oxide or a nitric oxide donor selected from the group consisting of organic nitrate compounds, iron nitrosyl compounds, S-nitrosothiol compounds, sydnonimine compounds, and nonoate compounds.

62. The method of any one of claims 52 to 61, wherein the aqueous medium further comprises glutamine.

63. A method of producing a mammalian epithelial cell line acutely infected with *Cryptovirus*, comprising the method of claim 53.

64. A mammalian epithelial cell acutely infected with *Cryptovirus*, said cell being produced by the method of claim 53 or 63.

65. A cell non-productively infected with *Cryptovirus*, wherein said cell is produced in accordance with the method of claim 54.

66. An *in vitro* method of screening a potential antiviral therapeutic agent, comprising:

(a) culturing the cell of claim 64;

(b) exposing the cells to the potential antiviral therapeutic agent; and

(c) measuring the effect of the agent on *Cryptovirus* replication and/or *Cryptovirus* virion assembly, wherein inhibition of *Cryptovirus* replication and/or *Cryptovirus* virion assembly relative to a control indicates antiviral activity of the potential therapeutic agent.

67. An *in vitro* method of screening a potential antiviral therapeutic agent, comprising:

(a) culturing the cell of claim 65;

(b) exposing the cells to the potential antiviral therapeutic agent; and

(c) measuring the effect of the agent *Cryptovirus* replication, *Cryptovirus* genome replication, and/or *Cryptovirus*-specific transcription, wherein inhibition of *Cryptovirus* replication, *Cryptovirus* genome replication, and/or *Cryptovirus*-specific transcription, relative to a control, indicates antiviral activity of the potential therapeutic agent.

68. An animal model for the study of human diseases, comprising a non-human mammal, said non-human mammal having been artificially inoculated with an infectious cell-free *Cryptovirus* having a genome comprising a single stranded RNA complementary to (SEQ ID NO:1), or having been inoculated with a cell non-productively-infected with the *Cryptovirus,* whereby the non-human mammal exhibits at

least one symptom characteristic of a human disease after being thus inoculated, said symptom not being previously exhibited by the non-human mammal.

69. The animal model of claim 68, wherein the non-human mammal is a rodent or lagomorph.

70. The animal model of claim 68, wherein the non-human mammal is a non-human primate.

71. The animal model of any one of claims 68 to 70, wherein the human disease is a neurological, neurodegenerative, and/or neuropsychiatric disease.

72. An *in vivo* method of screening a potential therapeutic agent, comprising:

(a) administering the potential therapeutic agent to be screened to the animal model of any one of claims 68 to 71, wherein the non-human mammal exhibits, before administration of the potential therapeutic agent, at least one symptom characteristic of a human disease; and

(b) detecting the presence or absence of a beneficial antiviral effect of the potential therapeutic agent, wherein the presence of a beneficial antiviral effect indicates activity of the potential therapeutic agent.

73. An *in vivo* method of screening a potential prophylactic agent, comprising:

(a) administering the potential prophylactic agent to be screened, to a non-human mammal not previously having a symptom of a human disease;

(b) inoculating the non-human mammal with an infectious cell-free *Cryptovirus* having a genome comprising a single stranded RNA complementary to (SEQ ID NO:1), or with a mammalian cell non-productively-infected with the *Cryptovirus*; and

(c) detecting the subsequent presence or absence in the non-human mammal of a beneficial antiviral effect, whereby the presence of a beneficial antiviral effect in the inoculated non-human mammal indicates activity of the potential prophylactic agent.

74. The method of claim 73, wherein the potential prophylactic agent is an immunoprophylactic agent.

75. The method of claim 72 or 73, wherein the non-human mammal is a rodent or a lagomorph.

76. The method of claim 72 or 73, wherein the non-human mammal is a non-human primate.

77. The method of any one of claims 72 to 76, wherein the human disease is a neurological, neurodegenerative, and/or neuropsychiatric disease.

78. An anti-*Cryptovirus* antibody detecting kit, comprising:

the *Cryptovirus* particle of claim 22 or 23; and

a labelled anti-human antibody-binding antibody.

79. The detecting kit of claim 78, wherein the kit further comprises a solid matrix for supporting said *Cryptovirus* particle.

80. An anti-*Cryptovirus* antibody detecting kit, comprising:

the protein of any one of claims 9 to 12; and

a labelled anti-human antibody-binding antibody.

81. The detecting kit of claim 80, wherein the kit further comprises a solid matrix for supporting said protein.

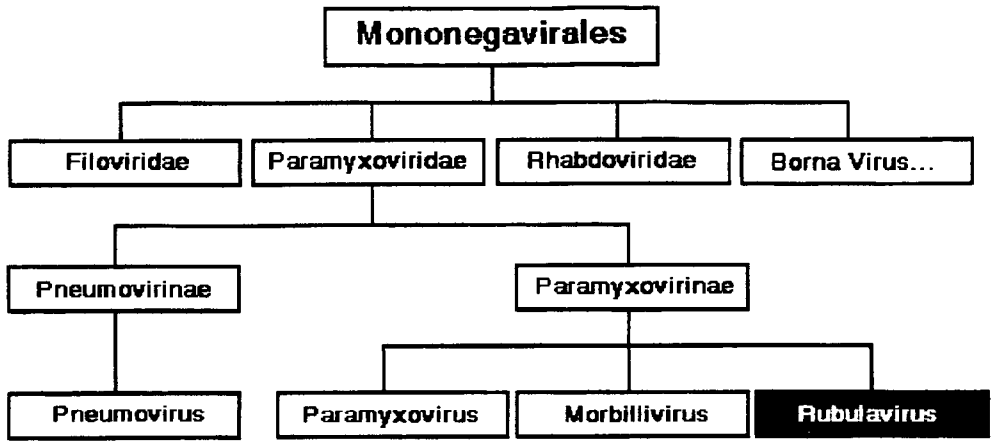

Mononegavirales
Filoviridae
Paramyxoviridae
Rhabdoviridae
Borna Virus...
Pneumovirinae
Paramyxovirinae
Pneumovirus
Paramyxovirus
Morbillivirus
Rubulavirus

Fig. 1

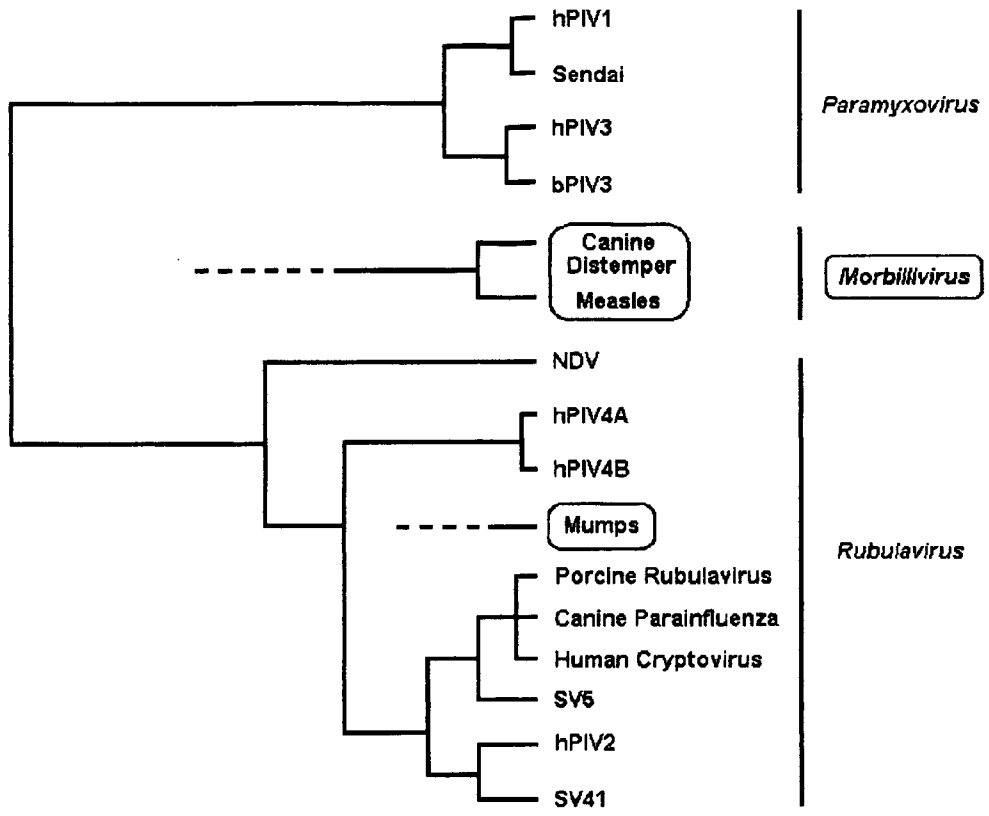
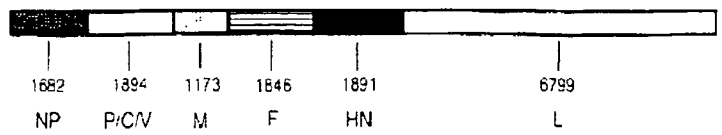
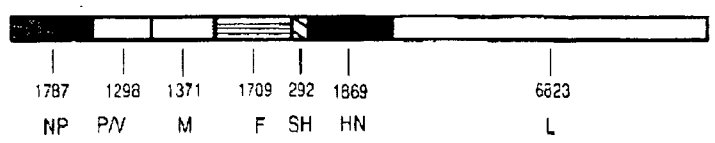

hPIV1
Sendai
hPIV3
bPIV3
Paramyxovirus
Canine Distemper
Measles
Morbillivirus
NDV
hPIV4A
hPIV4B
Mumps
Porcine Rubulavirus
Canine Parainfluenza
Human Cryptovirus
SV5
hPIV2
SV41
Rubulavirus

Fig. 2

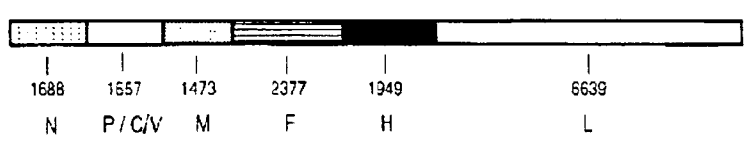
Parainfluenza virus - Sendai virus



Rubula virus - SV5



Morbillivirus - Measles



Pneumovirus - Respiratory Syncytial Virus

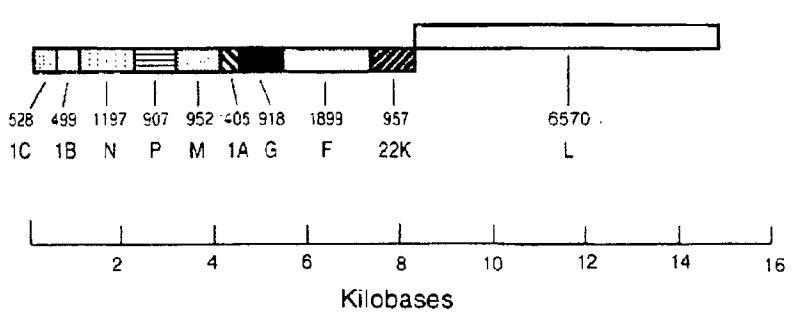
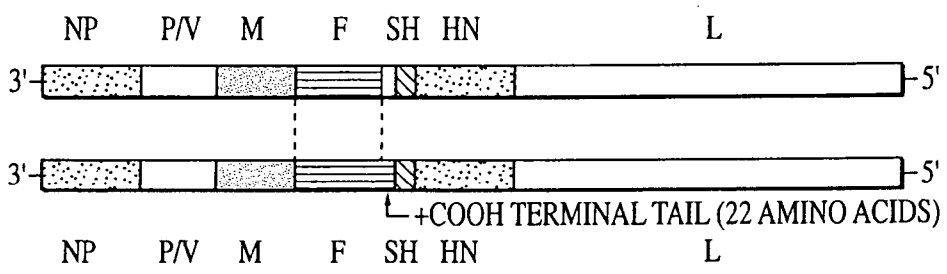


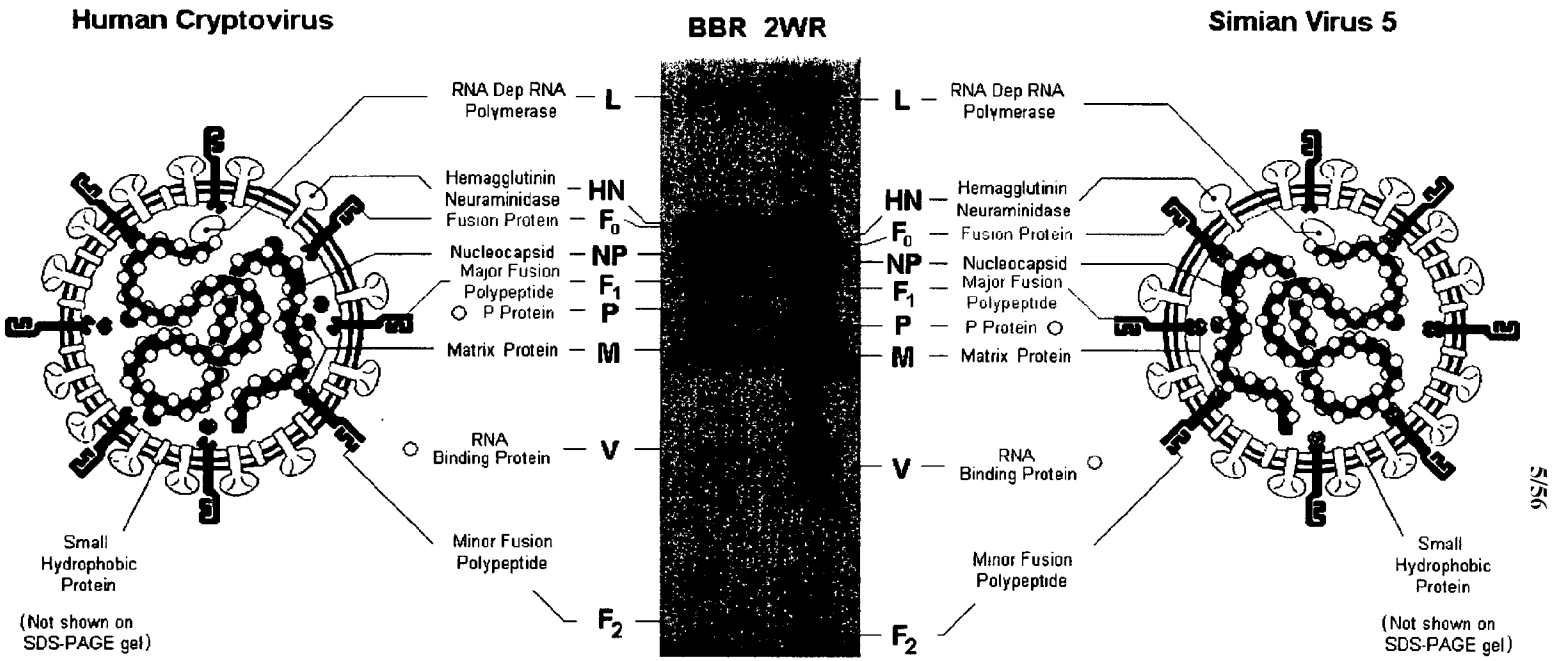
Fig. 3

SIMIAN VIRUS 5
RUBULAVIRUS



RUBULAVIRUS
NEUROTROPIC SPECIES
HUMAN CRYPTOVIRUS, CANINE PARAINFLUENZA TYPE 2 AND PORCINE RUBULAVIRUS

FIG. 4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BBR 2WR
Simian Virus 5
RNA Dep RNA Polymerase
L
Hemagglutinin Neuraminidase
HN
Fusion Protein
F0
Nucleocapsid
NP
Major Fusion Polypeptide
F1
P Protein
P
Matrix Protein
M
RNA Binding Protein
V
Minor Fusion Polypeptide
F2
Small Hydrophobic Protein
(Not shown on SDS-PAGE gel)

Fig. 5

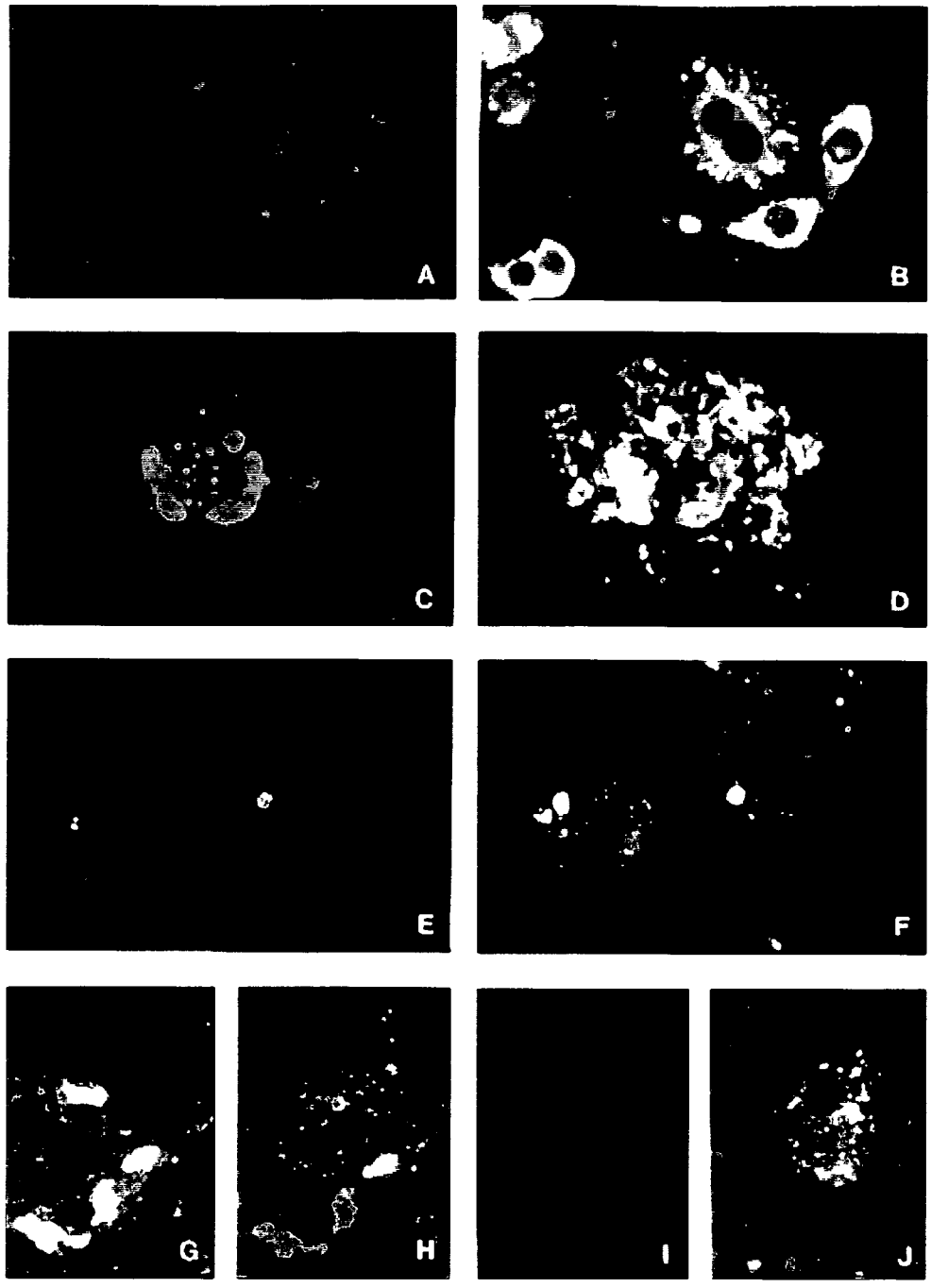

Fig. 6

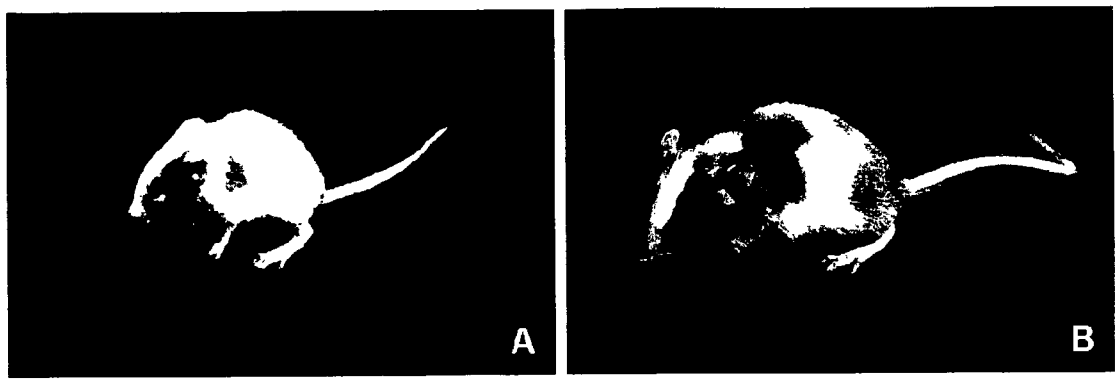

Fig. 7

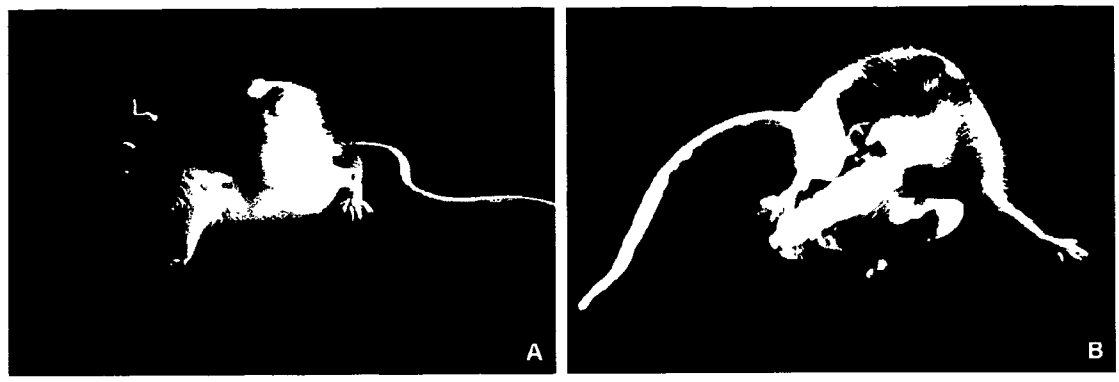

Fig. 8

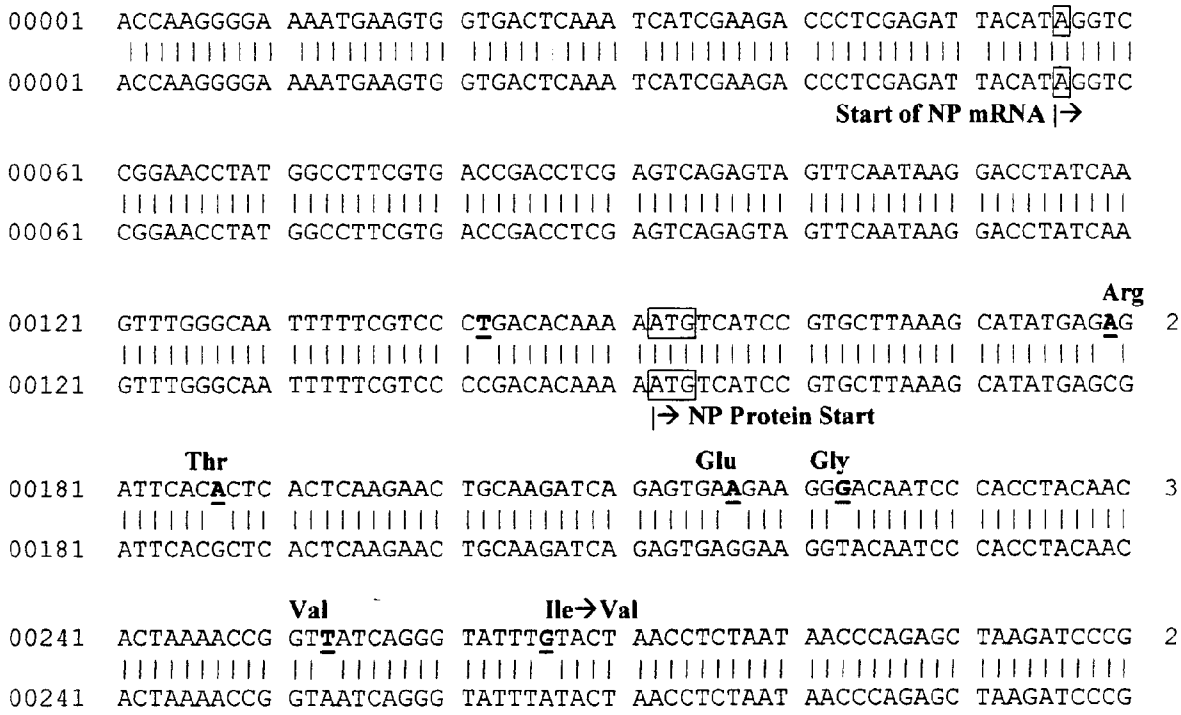

Figure 9
Page 1 of 25

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                   Leu                                 Ala
00361  TGGAGCATTA CTTACAATGT TTTCGCTACC ATCAGCTACA ATGCTCAATC ATGTCAAATT  2
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00421  AGCTGACCAG TCACCAGAAG CTGATATCGA AAGGGTAGAG ATCGATGGCT TTGAGGAGGG
       ||||||||||| ||||||||||| ||||||||||| ||||||||||| ||||||||||| |||||||||||
00421  AGCTGACCAG TCACCAGAAG CTGATATCGA AAGGGTAGAG ATCGATGGCT TTGAGGAGGG

                       Ile          Ala Arg
00481  ATCATTCCGC TTAATTCCCA ATGCTCGCTC AGGTATGAGC CGTGGAGAGA TCAATGCCTA  3
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00541  TGCTGCACTT GCAGAAGATC TACCTGACAC ACTAAACCAT GCAACACCTT TCGTTGATTC
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00541  TGCTGCACTT GCAGAAGATC TACCTGACAC ACTAAACCAT GCAACACCTT TCGTTGATTC

                                Asp
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       ||||||||||| ||||||||||| |||| ||||| |||||||||| |||||||||| ||||||||||
00601  CGAAGTCGAG GGAACTGCAT GGGATGAGAT TGAGACTTTC TTAGATATGT GTTACAGTGT

00661  CCTAATGCAG GCATGGATAG TGACTTGCAA GTGCATGACT GCGCCAGACC AACCTGCTGC
       ||||||||||| ||||||||||| ||||||||||| ||||||||||| ||||||||||| |||||||||||
00661  CCTAATGCAG GCATGGATAG TGACTTGCAA GTGCATGACT GCGCCAGACC AACCTGCTGC

                                                          Pro
00721  TTCTATTGAG AAACGCCTGC AAAAATATCG TCAGCAAGGC AGGATCAACC CAAGATATCT  1
       ||||||||||| ||||||||||| ||||||||||| ||||||||||| ||||||||||| | |||||||||
00721  TTCTATTGAG AAACGCCTGC AAAAATATCG TCAGCAAGGC AGGATCAACC CGAGATATCT

00781  CCTGCAACCG GAGGCTCGAC GAATAATCCA GAATGTAATC CGGAAGGGAA TGGTGGTCAG
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00841  ACATTTCCTC ACCTTTGAAC TGCAGCTTGC CCGAGCACAA AGCCTTGTAT CAAATAGGTA
       ||||||||||| ||||||||||| ||||||||||| ||||||||||| ||||||||||| |||||||||||
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00901  TTATGCTATG GTAGGGGATG TTGGAAAGTA TATAGAGAAT TGTGGAATGG GAGGCTTCTT
       ||||||||||| ||||||||||| ||||||||||| ||||||||||| ||||||||||| |||||||||||
00901  TTATGCTATG GTAGGGGATG TTGGAAAGTA TATAGAGAAT TGTGGAATGG GAGGCTTCTT
```

Figure 9

```
                                    Thr
00961  TTTGACACTA AAATATGCAT TAGGAACCAG ATGGCCCACA CTTGCTTTAG CTGCATTTTC  1
       ||||||||||| ||||||||||| ||||||| || |||||||||| |||||||||| ||||||||||
00961  TTTGACACTA AAATATGCAT TAGGAACTAG ATGGCCCACA CTTGCTTTAG CTGCATTTTC

                                                 Leu
01021  AGGAGAGCTA ACAAAGCTAA AGTCCCTCAT GGCATTGTAC CAGACCCTTG GTGAGCAGGC  1
       ||||||||||| ||||||||||| ||||||||| |||||| ||| |||||||||| ||||||||||
01021  AGGAGAGCTA ACAAAGCTAA AGTCCCTCAT GGCATTATAC CAGACCCTTG GTGAGCAGGC

                                         His                        Tyr
01081  CCGATATTTG GCCCTATTGG AGTCACCACA CTTGATGGAT TTTGCTGCAG CAAACTATCC  2
       ||||||||||| ||||||||||| ||||||||| ||||||||| |||||||||| ||||||| ||
01081  CCGATATTTG GCCCTATTGG AGTCACCACA TTTGATGGAT TTTGCTGCAG CAAACTACCC

       Leu
01141  ATTGCTATAT AGCTATGCTA TGGGAATAGG CTATGTGTTA GATGTCAACA TGAGGAACTA  1
       | |||||||| |||||||||| ||||||||| |||||||||| |||||||||| ||||||||||
01141  ACTGCTATAT AGCTATGCTA TGGGAATAGG CTATGTGTTA GATGTCAACA TGAGGAACTA

                                   Asn
01201  CGCTTTCTCC AGATCATACA TGAATAAGAC ATATTTCCAA TTGGGAATGG AAACTGCAAG  1
       |||||||||| |||||||||| |||| ||||| |||||||||| |||||||||| ||||||||||
01201  CGCTTTCTCC AGATCATACA TGAACAAGAC ATATTTCCAA TTGGGAATGG AAACTGCAAG

01261  AAAACAACAG GGTGCAGTTG ACATGAGGAT GGCAGAAGAT CTCGGTCTAA CTCAAGCCGA
       |||||||||| |||||||||| |||||||||| |||||||||| |||||||||| ||||||||||
01261  AAAACAACAG GGTGCAGTTG ACATGAGGAT GGCAGAAGAT CTCGGTCTAA CTCAAGCCGA

01321  ACGCACCGAG ATGGCAAATA CACTTGCCAA ATTGACCACA GCAAATCGAG GGGCAGACAC
       |||||||||| |||||||||| |||||||||| |||||||||| |||||||||| ||||||||||
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                                                        Val→Met
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       |||||||||| |||||||||| |||||||||| |||||||||| |||||| || ||||||||||
01381  CAGGGGAGGA GTCAACCCGT TCTCATCTGT CACTGGGACA ACTCAGGTGC CCGCTGCAGC

                     Leu→Phe
01441  AACAGGTGAC ACATTCGAGA GTTACATGGC AGCGGATCGA CTGAGGCAGA GATATGCTGA  1
       |||||||||| ||| |||||| |||||||||| |||||||||| |||||||||| ||||||||||
01441  AACAGGTGAC ACACTCGAGA GTTACATGGC AGCGGATCGA CTGAGGCAGA GATATGCTGA

                                            Leu
01501  TGCAGGCACC CATGATGATG AGATGCCACC ATTAGAAGAG GAGGAAGAGG ACGACACATC  1
       |||||||||| |||||||||| |||||||||| ||| |||||| |||||||||| ||||||||||
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                         Gly→Glu      Leu→Pro                    Asn→Ser
01561  TGCAGGTCCA CGCACTGAAC CAACTCCTGA ACAAGTGGCC TTGGACATCC AGAGCGCAGC  3
       |||||||||| ||||||| || |||||| ||| |||||||||| |||||||||| ||| ||||||
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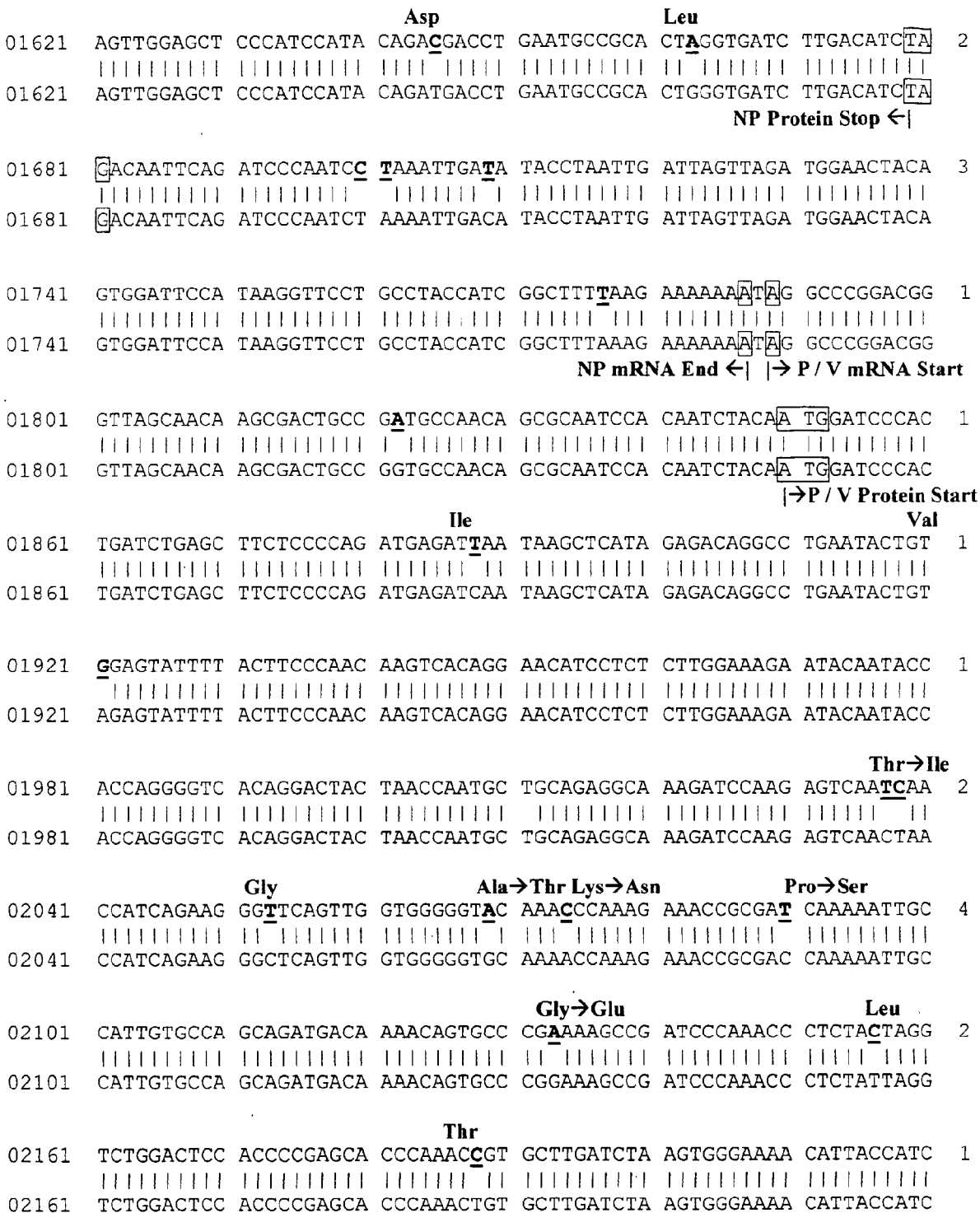
Figure 9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Leu
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NP mRNA End ←| |→ P / V mRNA Start
01801 GTTAGCAACA AGCGACTGCC GATGCCAACA GCGCAATCCA CAATCTACAA TGGATCCCAC 1
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|→P / V Protein Start
Ile
Val
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01861 TGATCTGAGC TTCTCCCCAG ATGAGATCAA TAAGCTCATA GAGACAGGCC TGAATACTGT
01921 GGAGTATTTT ACTTCCCAAC AAGTCACAGG AACATCCTCT CTTGGAAAGA ATACAATACC 1
01921 AGAGTATTTT ACTTCCCAAC AAGTCACAGG AACATCCTCT CTTGGAAAGA ATACAATACC
Thr→Ile
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01981 ACCAGGGGTC ACAGGACTAC TAACCAATGC TGCAGAGGCA AAGATCCAAG AGTCAACTAA
Gly
Ala→Thr Lys→Asn
Pro→Ser
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Gly→Glu
Leu
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02101 CATTGTGCCA GCAGATGACA AAACAGTGCC CGGAAAGCCG ATCCCAAACC CTCTATTAGG
Thr
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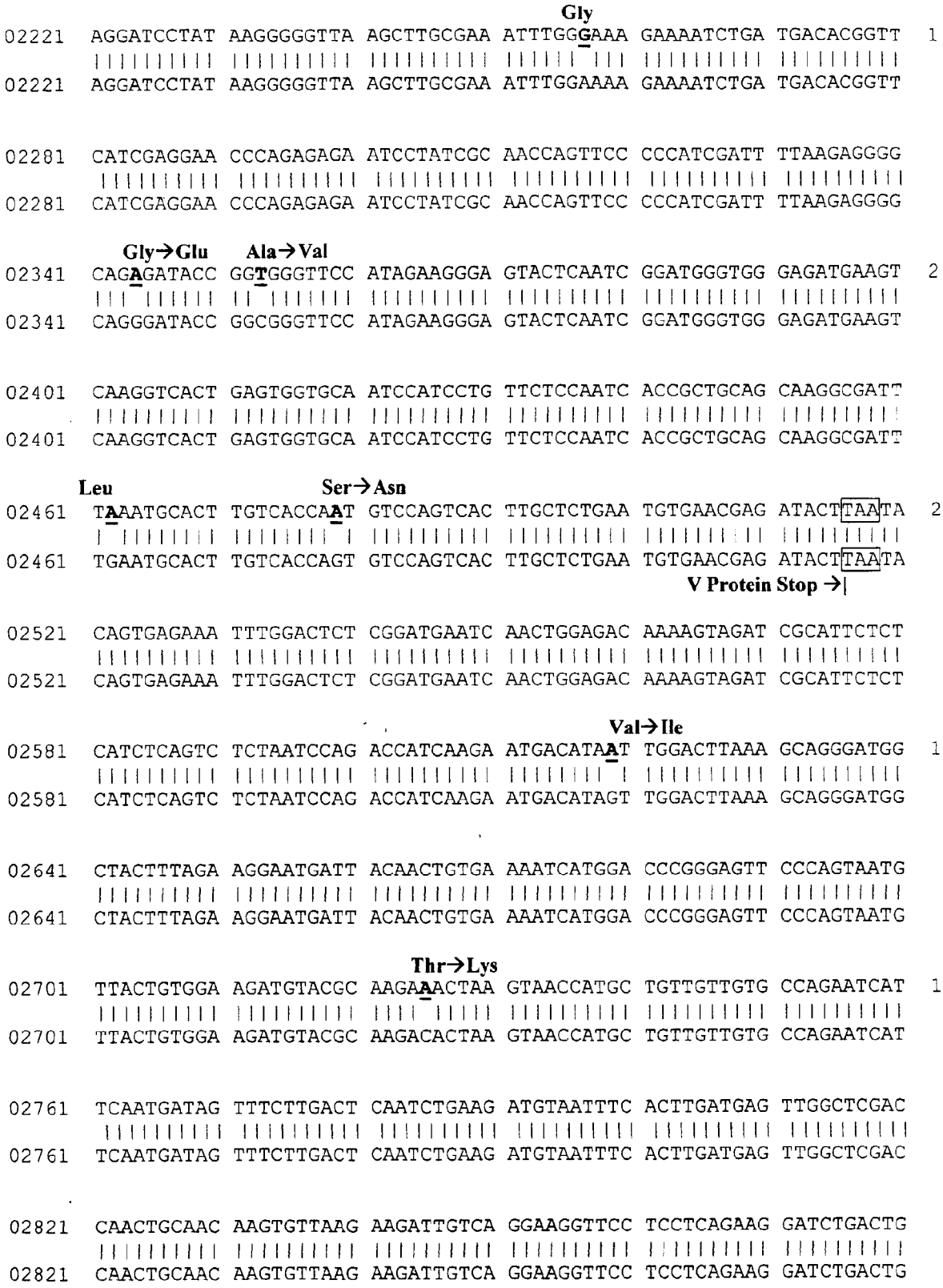
Figure 9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Gly→Glu
Ala→Val
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02341 CAGGGATACC GGCGGGTTCC ATAGAAGGGA GTACTCAATC GCATGGGTGG GAGATGAAGT
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02401 CAAGGTCACT GAGTGGTGCA ATCCATCCTG TTCTCCAATC ACCGCTGCAG CAAGGCGATT
Leu
Ser→Asn
02461 TAAATGCACT TGTCACCAAT GTCCAGTCAC TTGCTCTGAA TGTGAACGAG ATACTTAATA 2
02461 TGAATGCACT TGTCACCAGT GTCCAGTCAC TTGCTCTGAA TGTGAACGAG ATACTTAATA
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02521 CAGTGAGAAA TTTGGACTCT CGGATGAATC AACTGGAGAC AAAAGTAGAT CGCATTCTCT
Val→Ile
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02581 CATCTCAGTC TCTAATCCAG ACCATCAAGA ATGACATAGT TGGACTTAAA GCAGGGATGG
02641 CTACTTTAGA AGGAATGATT ACAACTGTGA AAATCATGGA CCCGGGAGTT CCCAGTAATG
02641 CTACTTTAGA AGGAATGATT ACAACTGTGA AAATCATGGA CCCGGGAGTT CCCAGTAATG
Thr→Lys
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02701 TTACTGTGGA AGATGTACGC AAGACACTAA GTAACCATGC TGTTGTTGTG CCAGAATCAT
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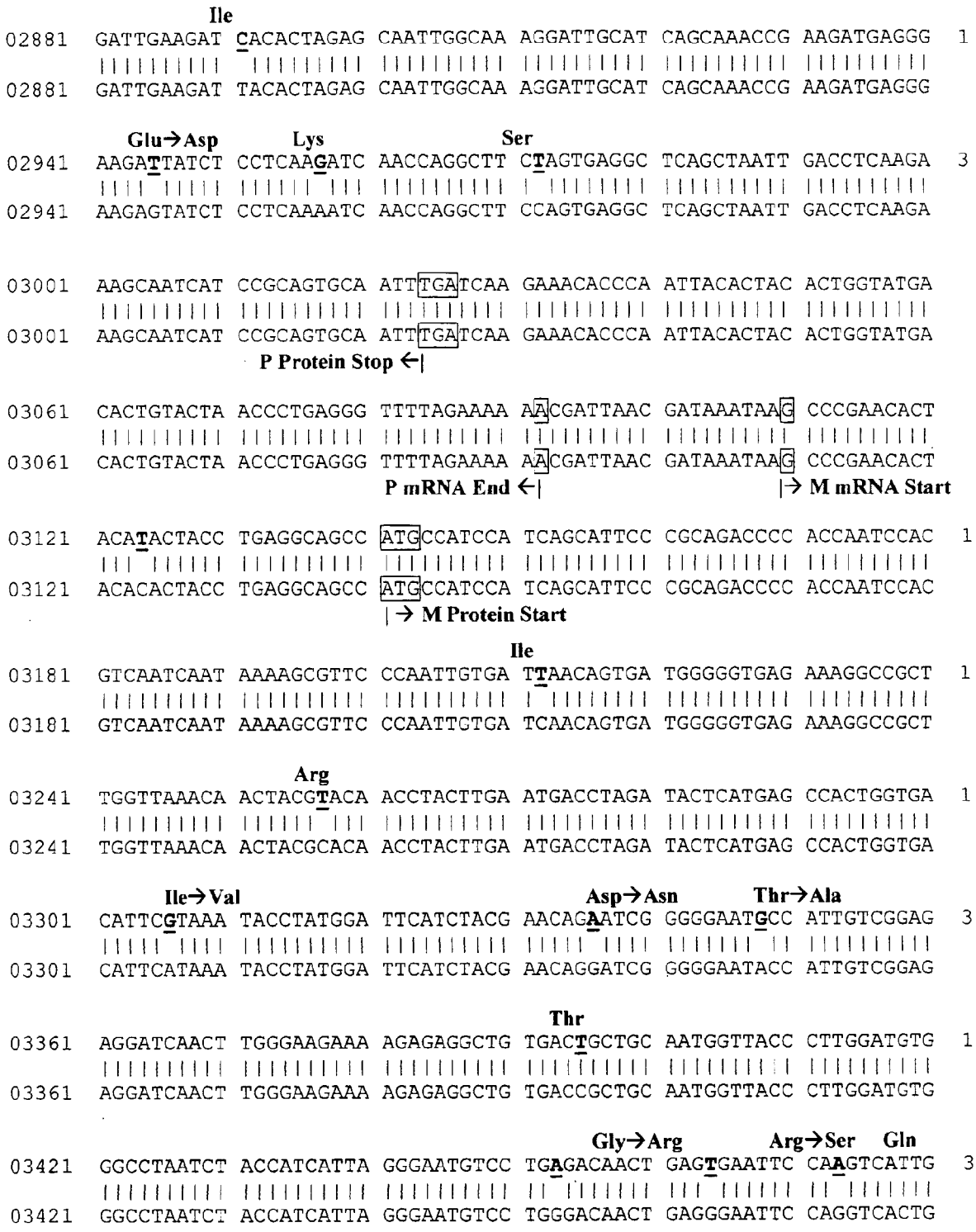
Figure 9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|→ M Protein Start
Ile
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03181 GTCAATCAAT AAAAGCGTTC CCAATTGTGA TCAACAGTGA TGGGGGTGAG AAAGGCCGCT
Arg
03241 TGGTTAAACA ACTACGTACA ACCTACTTGA ATGACCTAGA TACTCATGAG CCACTGGTGA 1
03241 TGGTTAAACA ACTACGCACA ACCTACTTGA ATGACCTAGA TACTCATGAG CCACTGGTGA
Ile→Val Asp→Asn Thr→Ala
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03301 CATTCATAAA TACCTATGGA TTCATCTACG AACAGGATCG GGGGAATACC ATTGTCGGAG
Thr
03361 AGGATCAACT TGGGAAGAAA AGAGAGGCTG TGACTGCTGC AATGGTTACC CTTGGATGTG 1
03361 AGGATCAACT TGGGAAGAAA AGAGAGGCTG TGACCGCTGC AATGGTTACC CTTGGATGTG
Gly→Arg Arg→Ser Gln
03421 GGCCTAATCT ACCATCATTA GGGAATGTCC TGAGACAACT GAGTGAATTC CAAGTCATTG 3
03421 GGCCTAATCT ACCATCATTA GGGAATGTCC TGGGACAACT GAGGGAATTC CAGGTCACTG

Figure 9

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03481  TTAGGAAGAC ATCCAGCAAA GCGGAAGAGA TGGTCTTTGA AATTGTTAAG TATCCGAGAA
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03481  TTAGGAAGAC ATCCAGCAAA GCGGAAGAGA TGGTCTTTGA AATTGTTAAG TATCCGAGAA

03541  TATTTCGGGG TCATACATTA ATCCAGAAAG GACTAGTCTG TGTCTCCGCA GAAAAATTTG
       ||||||||||| ||||||||||| ||||||||||| ||||||||||| ||||||||||| ||||||||||
03541  TATTTCGGGG TCATACATTA ATCCAGAAAG GACTAGTCTG TGTCTCCGCA GAAAAATTTG

                          Ile→Val
03601  TTAAGTCACC AGGGAAAGTA CAATCTGGAA TGGACTATCT CTTCATTCCG ACATTTCTGT  1
       ||||||||||| ||||||| || ||||||||||| ||||||||||| ||||||||||| ||||||||||
03601  TTAAGTCACC AGGGAAAATA CAATCTGGAA TGGACTATCT CTTCATTCCG ACATTTCTGT

                  Tyr
03661  CAGTGACTTA TTGTCCAGCT GCAATCAAAT TTCAGGTACC TGGCCCCATG TTGAAAATGA  1
       ||||||||||  ||||||||| ||||||||||| ||||||||||| |||||||||| ||||||||||
03661  CAGTGACTTA CTGTCCAGCT GCAATCAAAT TTCAGGTACC TGGCCCCATG TTGAAAATGA

       Arg
03721  GGTCAAGATA CACTCAGAGC TTACAACTTG AACTAATGAT AAGAATCCTG TGTAAGCCCG  1
       | |||||||| ||||||||||| ||||||||||| ||||||||||  ||||||||| ||||||||||
03721  GATCAAGATA CACTCAGAGC TTACAACTTG AACTAATGAT AAGAATCCTG TGTAAGCCCG

                                  Thr→Ile
03781  ATTCGCCACT TATGAAGGTC CATATCCCTG ACAAGGAGGG AAGAGGATGT CTTGTATCAG  1
       |||| ||||| |||||||||  |||| ||||| ||||||||||| ||||||||||| ||||||||||
03781  ATTCGCCACT TATGAAGGTC CATACCCCTG ACAAGGAGGG AAGAGGATGT CTTGTATCAG

03841  TATGGCTGCA TGTATGCAAC ATCTTCAAAT CAGGAAACAA GAATGGCAGT GAGTGGCAGG
       ||||||||||| ||||||||||| ||||||||||| ||||||||||| ||||||||||| ||||||||||
03841  TATGGCTGCA TGTATGCAAC ATCTTCAAAT CAGGAAACAA GAATGGCAGT GAGTGGCAGG

03901  AATACTGGAT GAGAAAGTGT GCTAACATGC AACTTGAAGT GTCGATTGCA GATATGTGGG
       ||||||||||| ||||||||||| ||||||||||| ||||||||||| ||||||||||| ||||||||||
03901  AATACTGGAT GAGAAAGTGT GCTAACATGC AACTTGAAGT GTCGATTGCA GATATGTGGG

03961  GACCAACTAT CATAATTCAT GCCAGAGGTC ACATTCCCAA AAGTGCTAAG TTGTTTTTTG
       ||||||||||| ||||||||||| ||||||||||| ||||||||||| ||||||||||| ||||||||||
03961  GACCAACTAT CATAATTCAT GCCAGAGGTC ACATTCCCAA AAGTGCTAAG TTGTTTTTTG

                                                  Val→Ile
04021  GAAAGGGTGG ATGGAGCTGC CATCCACTTC ACGAAATTGT TCCAAGTGTC ACTAAAACAC  1
       ||||||||||| ||||||||||| ||||||||||| ||||| |||| |||||||||| ||||||||||
04021  GAAAGGGTGG ATGGAGCTGC CATCCACTTC ACGAAGTTGT TCCAAGTGTC ACTAAAACAC

               Val       Glu
04081  TATGGTCCGT AGGTTGTGAA ATTACAAAGG CGAAGGCAAT AATACAAGAG AGTAGCATCT  2
       ||||||||||  ||||||||  |||||||||| |||||||||| |||||||||| ||||||||||
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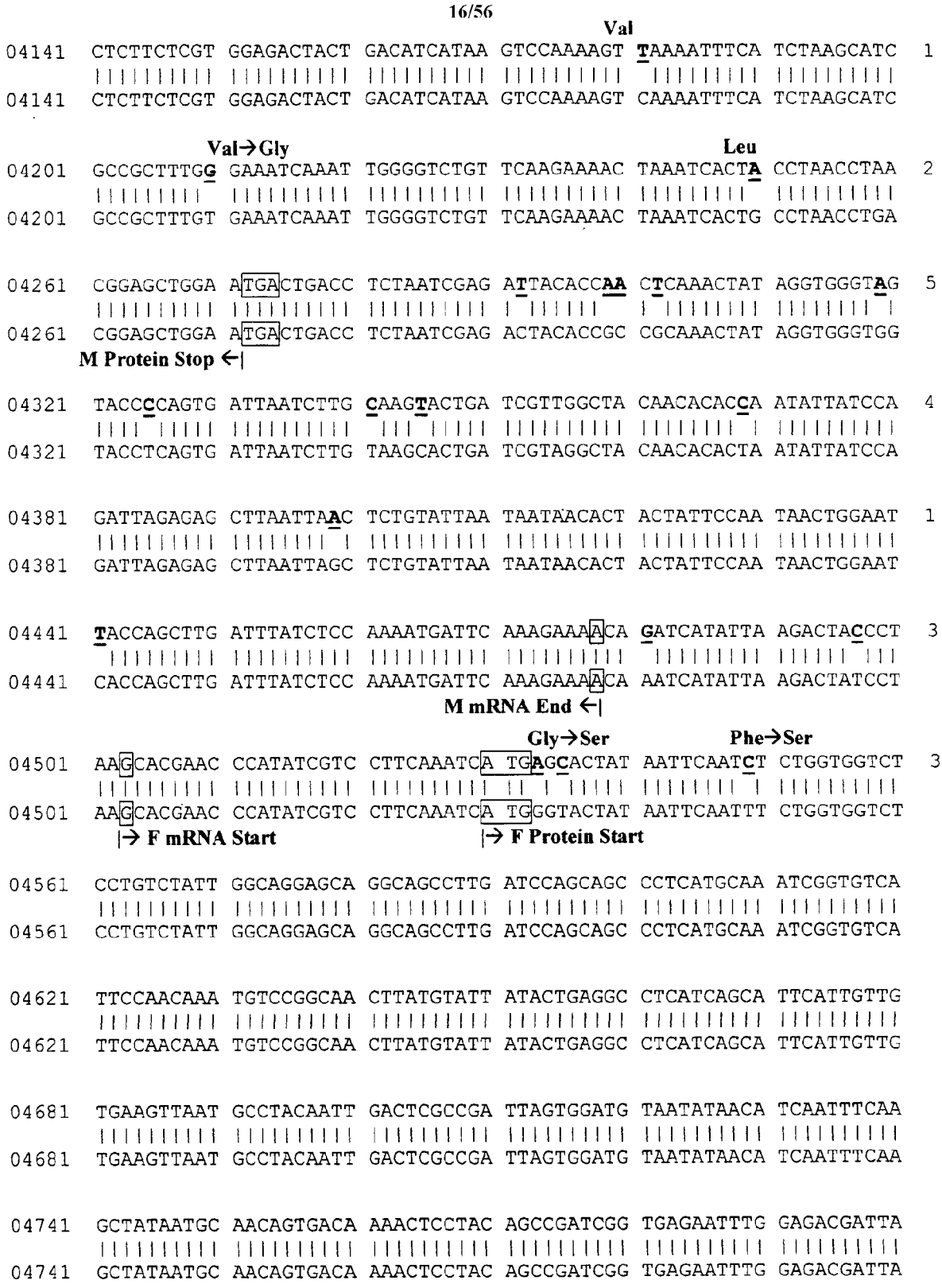
Figure 9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Leu
M Protein Stop ←|
M mRNA End ←|
Gly→Ser
Phe→Ser
|→ F mRNA Start
|→ F Protein Start

Figure 9

```
04801  GGAACCAGTT GATTCCAACT CGGAGGAGAC GCCGGTTTGC AGGGGTGGTG ATTGGATTAG
       |||||||||| |||||||||| |||||||||| |||||||||| |||||||||| ||||||||||
04801  GGAACCAGTT GATTCCAACT CGGAGGAGAC GCCGGTTTGC AGGGGTGGTG ATTGGATTAG

                                        Gln                 Val       Val
04861  CTGCATTAGG AGTAGCTACT GCCGCACAAG TCACTGCCGC AGTAAGCACTA GTTAAGGCAA  3
       |||||||||| |||||||||| |||||||| | |||||||||| ||| |||||| || |||||||
04861  CTGCATTAGG AGTAGCTACT GCCGCACAGG TCACTGCCGC AGTGGCACTA GTAAAGGCAA

             Ala→Thr
04921  ATGAAAATAC TGCGGCTATA CTCAATCTCA AAAATGCAAT CCAAAAAACA AATGCAGCAG  1
       |||||||| | |||||||||| |||||||||| |||||||||| |||||||||| ||||||||||
04921  ATGAAAATGC TGCGGCTATA CTCAATCTCA AAAATGCAAT CCAAAAAACA AATGCAGCAG

04981  TTGCAGATGT GGTCCAGGCC ACACAATCAC TAGGAACGGC AGTTCAAGCA GTTCAAGATC
       |||||||||| |||||||||| |||||||||| |||||||||| |||||||||| ||||||||||
04981  TTGCAGATGT GGTCCAGGCC ACACAATCAC TAGGAACGGC AGTTCAAGCA GTTCAAGATC

                    Val→Ile
05041  ACATAAACAG TGTGATAAGT CCAGCAATTA CAGCAGCCAA TTGTAAGGCC CAAGATGCTA  1
       |||||||||| |||| ||||| |||||||||| |||||||||| |||||||||| ||||||||||
05041  ACATAAACAG TGTGGTAAGT CCAGCAATTA CAGCAGCCAA TTGTAAGGCC CAAGATGCTA

                                                  Thr
05101  TCATTGGCTC AATCCTCAAT CTCTATTTGA CCGAGTTGAC AACTATCTTC CACAATCAAA  1
       |||||||||| |||||||||| |||||||||| |||||||||| ||| |||||| ||||||||||
05101  TCATTGGCTC AATCCTCAAT CTCTATTTGA CCGAGTTGAC AACCATCTTC CACAATCAAA

                          Pro
05161  TTACAAACCC TGCATTGAGT CCTATTACAA TTCAAGCTTT AAGGATCCTA CTGGGGAGTA  1
       |||||||||| |||||||||| || ||||||| |||||||||| |||||||||| ||||||||||
05161  TTACAAACCC TGCATTGAGT CCCATTACAA TTCAAGCTTT AAGGATCCTA CTGGGGAGTA

05221  CCTTGCCGAC TGTGGTCGAA AAATCTTTCA ATACCCAGAT AAGTGCAGCT GAGCTTCTCT
       |||||||||| |||||||||| |||||||||| |||||||||| |||||||||| ||||||||||
05221  CCTTGCCGAC TGTGGTCGAA AAATCTTTCA ATACCCAGAT AAGTGCAGCT GAGCTTCTCT

          Leu
05281  CATCAGGGTT GTTGACAGGC CAGATTGTGG GATTAGATTT GACCTATATG CAGATGGTCA  1
       |||||||||| |||||||||| |||||||||| |||||||||| |||||||||| ||||||||||
05281  CATCAGGGTT ATTGACAGGC CAGATTGTGG GATTAGATTT GACCTATATG CAGATGGTCA

05341  TAAAAATTGA GCTGCCAACT TTAACTGTAC AACCTGCAAC CCAGATCATA GATCTGGCCA
       |||||||||| |||||||||| |||||||||| |||||||||| |||||||||| ||||||||||
05341  TAAAAATTGA GCTGCCAACT TTAACTGTAC AACCTGCAAC CCAGATCATA GATCTGGCCA

                                                                Met→Ile
05401  CCATTTCTGC ATTCATTAAC AATCAAGAAG TCATGGCCCA ATTACCAACA CGTGTTATTG  1
       |||||||||| |||||||||| |||||||||| |||||||||| |||||||||| ||||||||||
05401  CCATTTCTGC ATTCATTAAC AATCAAGAAG TCATGGCCCA ATTACCAACA CGTGTTATGG
```

Figure 9
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```
                                                    Thr
05461  TGACTGGCAG CTTGATCCAA GCCTATCCCG CATCGCAATG CACTATTACA CCCAACACTG  1
       |||||||||| |||||||||| |||||||||| |||||||||| ||| |||||| ||||||||||
05461  TGACTGGCAG CTTGATCCAA GCCTATCCCG CATCGCAATG CACCATTACA CCCAACACTG

                                                    Thr
05521  TGTACTGTAG GTATAATGAT GCCCAAGTAC TCTCAGATGA TACGATGGCT TGCCTCCAAG  1
       |||||||||| |||||||||| |||||||||| |||||||||| ||| |||||| ||||||||||
05521  TGTACTGTAG GTATAATGAT GCCCAAGTAC TCTCAGATGA TACTATGGCT TGCCTCCAAG

05581  GTAACTTGAC AAGATGCACC TTCTCTCCAG TGGTTGGGAG CTTTCTCACT CGATTCGTGC
       |||||||||| |||||||||| |||||||||| |||||||||| |||||||||| ||||||||||
05581  GTAACTTGAC AAGATGCACC TTCTCTCCAG TGGTTGGGAG CTTTCTCACT CGATTCGTGC

                                                Leu
05641  TGTTCGATGG AATAGTTTAT GCAAATTGCA GGTCGATGCT GTGCAAGTGC ATGCAACCTG  1
       |||||||||| |||||||||| |||||||||| ||||||||| |||||||||| ||||||||||
05641  TGTTCGATGG AATAGTTTAT GCAAATTGCA GGTCGATGTT GTGCAAGTGC ATGCAACCTG

         Ala                                                   Tyr→His
05701  CTGCCGTGAT CCTACAGCCG AGTTCATCCC CTGTAACTGT CATTGACATG CACAAATGTG  2
       |||| ||||| |||||||||| |||||||||| |||||||||| |||||||||| |||||||||
05701  CTGCTGTGAT CCTACAGCCG AGTTCATCCC CTGTAACTGT CATTGACATG TACAAATGTG

                          Asn→Asp
05761  TGAGTCTGCA GCTTGACGAT CTCAGATTCA CCATCACTCA ATTGGCCAAT GTAACCTACA  1
       |||||||||| ||||||| || |||||||||| |||||||||| |||||||||| ||||||||||
05761  TGAGTCTGCA GCTTGACAAT CTCAGATTCA CCATCACTCA ATTGGCCAAT GTAACCTACA

                                Ser→Thr          Ser→Pro
05821  ATAGCACCAT CAAGCTTGAA ACATCCCAGA TCTTGCCTAT TGATCCGTTG GATATATCCC  2
       |||||||||| |||||||||| |||||||| ||||| |||| |||||||||| ||||||||||
05821  ATAGCACCAT CAAGCTTGAA TCATCCCAGA TCTTGTCTAT TGATCCGTTG GATATATCCC

       Gln   Leu
05881  AGAATTTAGC TGCGGTGAAT AAGAGTCTAA GTGATGCACT ACAACACTTA GCACAAAGTG  2
       | ||| |||| |||||||||| |||||||||| |||||||||| |||||||||| ||||||||||
05881  AAAATCTAGC TGCGGTGAAT AAGAGTCTAA GTGATGCACT ACAACACTTA GCACAAAGTG

            Tyr
05941  ACACATACCT TTCTGCAATC ACATCAGCTA CGACTACAAG TGTATTATCC ATAATAGCAA  1
       ||||||| || |||||||||| |||||||||| |||||||||| |||||||||| ||||||||||
05941  ACACATATCT TTCTGCAATC ACATCAGCTA CGACTACAAG TGTATTATCC ATAATAGCAA

06001  TCTGTCTTGG ATCGTTAGGT TTAATATTAA TAATCTTGCT CAGTGTAGTT GTGTGGAAGT
       |||||||||| |||||||||| |||||||||| |||||||||| |||||||||| ||||||||||
06001  TCTGTCTTGG ATCGTTAGGT TTAATATTAA TAATCTTGCT CAGTGTAGTT GTGTGGAAGT
```

Figure 9

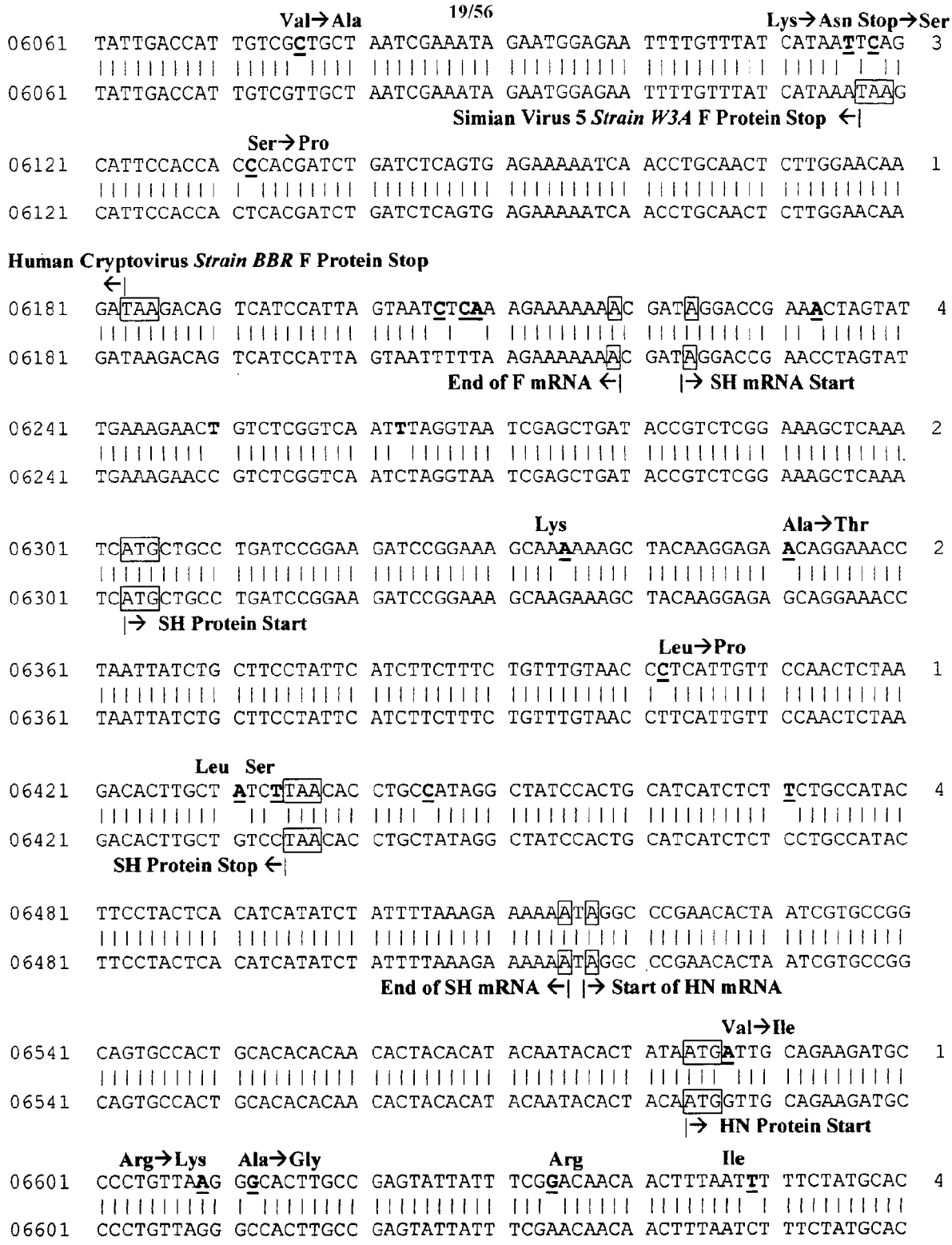
Val→Ala
Lys→Asn Stop→Ser
06061 TATTGACCAT TGTCGCTGCT AATCGAAATA GAATGGAGAA TTTTGTTTAT CATAATTCAG 3
06061 TATTGACCAT TGTCGTTGCT AATCGAAATA GAATGGAGAA TTTTGTTTAT CATAAATAAG
Simian Virus 5 Strain W3A F Protein Stop ←|
Ser→Pro
06121 CATTCCACCA CCCACGATCT GATCTCAGTG AGAAAAATCA ACCTGCAACT CTTGGAACAA 1
06121 CATTCCACCA CTCACGATCT GATCTCAGTG AGAAAAATCA ACCTGCAACT CTTGGAACAA
Human Cryptovirus Strain BBR F Protein Stop
←|
06181 GATAAGACAG TCATCCATTA GTAATCTCAA AGAAAAAAAC GATAGGACCG AAACTAGTAT 4
06181 GATAAGACAG TCATCCATTA GTAATTTTTA AGAAAAAAAC GATAGGACCG AACCTAGTAT
End of F mRNA ←| |→ SH mRNA Start
06241 TGAAAGAACT GTCTCGGTCA ATTTAGGTAA TCGAGCTGAT ACCGTCTCGG AAAGCTCAAA 2
06241 TGAAAGAACC GTCTCGGTCA ATCTAGGTAA TCGAGCTGAT ACCGTCTCGG AAAGCTCAAA
Lys
Ala→Thr
06301 TCATGCTGCC TGATCCGGAA GATCCGGAAA GCAAAAAAGC TACAAGGAGA ACAGGAAACC 2
06301 TCATGCTGCC TGATCCGGAA GATCCGGAAA GCAAGAAAGC TACAAGGAGA GCAGGAAACC
|→ SH Protein Start
Leu→Pro
06361 TAATTATCTG CTTCCTATTC ATCTTCTTTC TGTTTGTAAC CCTCATTGTT CCAACTCTAA 1
06361 TAATTATCTG CTTCCTATTC ATCTTCTTTC TGTTTGTAAC CTTCATTGTT CCAACTCTAA
Leu Ser
06421 GACACTTGCT ATCTTAACAC CTGCCATAGG CTATCCACTG CATCATCTCT TCTGCCATAC 4
06421 GACACTTGCT GTCCTAACAC CTGCTATAGG CTATCCACTG CATCATCTCT CCTGCCATAC
SH Protein Stop ←|
06481 TTCCTACTCA CATCATATCT ATTTTAAAGA AAAAATAGGC CCGAACACTA ATCGTGCCGG
06481 TTCCTACTCA CATCATATCT ATTTTAAAGA AAAAATAGGC CCGAACACTA ATCGTGCCGG
End of SH mRNA ←| |→ Start of HN mRNA
Val→Ile
06541 CAGTGCCACT GCACACACAA CACTACACAT ACAATACACT ATAATGATTG CAGAAGATGC 1
06541 CAGTGCCACT GCACACACAA CACTACACAT ACAATACACT ACAATGGTTG CAGAAGATGC
|→ HN Protein Start
Arg→Lys
Ala→Gly
Arg
Ile
06601 CCCTGTTAAG GGCACTTGCC GAGTATTATT TCGGACAACA ACTTTAATTT TTCTATGCAC 4
06601 CCCTGTTAGG GCCACTTGCC GAGTATTATT TCGAACAACA ACTTTAATCT TTCTATGCAC

Figure 9

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06661  ACTACTAGCA TTAAGCATCT CTATCCTTTA TGAGAGTTTA ATAACCCAAA AGCAAATCAT
       ||||||||||| ||||||||||| ||||||||||| ||||||||||| ||||||||||| |||||||||||
06661  ACTACTAGCA TTAAGCATCT CTATCCTTTA TGAGAGTTTA ATAACCCAAA AGCAAATCAT

          Ser                                          Ser→Gly Ile
06721  GAGTCAAGCA GGCTCAACTG GATCTAATTC TGGATTAGGA GGTATTACTG ATCTTCTTAA  3
       ||| |||||| ||||||||||| ||||||||||| ||||||||||  |||| |||| ||||||||||
06721  GAGCCAAGCA GGCTCAACTG GATCTAATTC TGGATTAGGA AGTATCACTG ATCTTCTTAA

               Leu
06781  TAATATTCTT TCTGTCGCAA ATCAGATTAT ATATAACTCT GCAGTCGCTC TACCTCTACA  1
       |||||||||  |||||||||| |||||||||| |||||||||| |||||||||| ||||||||||
06781  TAATATTCTC TCTGTCGCAA ATCAGATTAT ATATAACTCT GCAGTCGCTC TACCTCTACA

06841  ATTGGACACT CTTGAATCAA CACTCCTTAC AGCCATTAAG TCTCTTCAAA CCAGTGACAA
       |||||||||| |||||||||| |||||||||| |||||||||| |||||||||| ||||||||||
06841  ATTGGACACT CTTGAATCAA CACTCCTTAC AGCCATTAAG TCTCTTCAAA CCAGTGACAA

                                  Ser→Gly
06901  GCTAGAACAG AACTGCTCGT GGGGGTGCTGC ACTGATTAAT GATAATAGAT ACATTAATGG  1
       |||||||||| |||||||||| ||  ||||||| |||||||||| |||||||||| ||||||||||
06901  GCTAGAACAG AACTGCTCGT GGAGTGCTGC ACTGATTAAT GATAATAGAT ACATTAATGG

                           Phe
06961  CATCAATCAG TTCTATTTCT CAATTGCTGA GGGTCGCAAT CTGACACTTG GCCCACTTCT  1
       ||||||||||| ||||||||  |||||||||| |||||||||| |||||||||| ||||||||||
06961  CATCAATCAG TTCTATTTTT CAATTGCTGA GGGTCGCAAT CTGACACTTG GCCCACTTCT

          Met→Ile
07021  TAATATACCT AGTTTCATTC CAACTGCCAC GACACCAGAG GGCTGCACCA GGATCCCATC  1
       ||||||  ||| |||||||||| |||||||||| |||||||||| |||||||||| ||||||||||
07021  TAATATGCCT AGTTTCATTC CAACTGCCAC GACACCAGAG GGCTGCACCA GGATCCCATC

                                        Thr
07081  ATTCTCGCTC ACTAAGACAC ACTGGTGTTA TACGCACAAT GTTATCCTGA ATGGATGCCA  1
       |||||||||| |||||||||| |||||||||| ||| |||||| |||||||||| ||||||||||
07081  ATTCTCGCTC ACTAAGACAC ACTGGTGTTA TACACACAAT GTTATCCTGA ATGGATGCCA

07141  GGATCATGTA TCCTCAAATC AATTTGTTTC CATGGGAATC ATTGAACCCA CTTCTGCCGG
       |||||||||| |||||||||| |||||||||| |||||||||| |||||||||| ||||||||||
07141  GGATCATGTA TCCTCAAATC AATTTGTTTC CATGGGAATC ATTGAACCCA CTTCTGCCGG

             Phe→Ser
07201  GTTTCCATCC TTTCGAACCT TAAAGACTCT ATATCTCAGC GATGGGGTCA ATCGTAAGAG  1
       |||||||| | |||||||||| |||||||||| |||||||||| |||||||||| ||||||||||
07201  GTTTCCATTC TTTCGAACCC TAAAGACTCT ATATCTCAGC GATGGGGTCA ATCGTAAGAG

                                                 Val
07261  CTGCTCTATC AGTACAGTTC CGGGGGGTTG TATGATGTAC TGTTTTGTCT CTACTCAACC  1
       |||||||||| |||||||||| |||||||||| |||||||||| ||||||||  | ||||||||||
07261  CTGCTCTATC AGTACAGTTC CGGGGGGTTG TATGATGTAC TGTTTTGTTT CTACTCAACC
```

Figure 9
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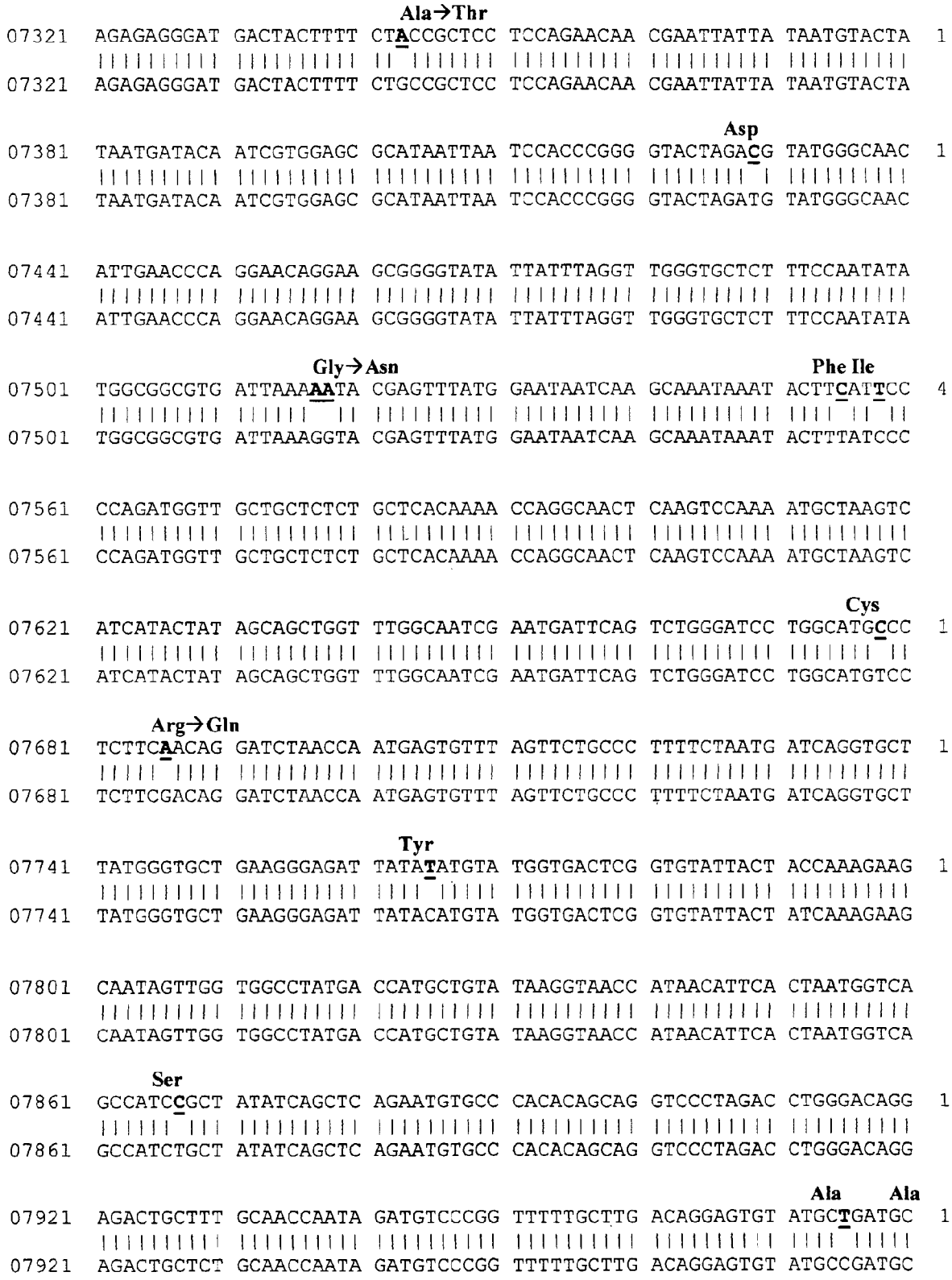

Figure 9

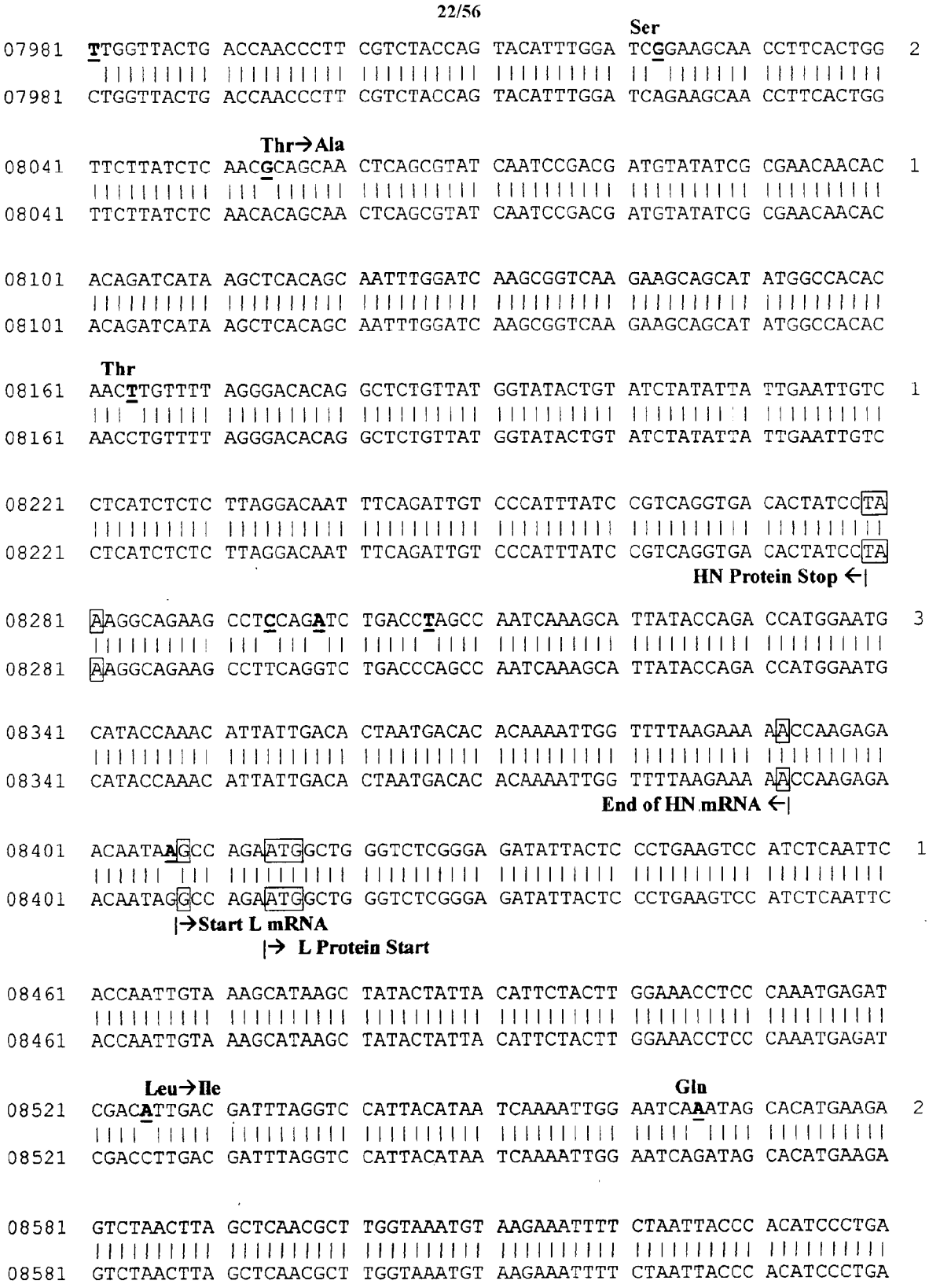
Ser
07981 TTGGTTACTG ACCAACCCTT CGTCTACCAG TACATTTGGA TCGGAAGCAA CCTTCACTGG 2
07981 CTGGTTACTG ACCAACCCTT CGTCTACCAG TACATTTGGA TCAGAAGCAA CCTTCACTGG
Thr→Ala
08041 TTCTTATCTC AACGCAGCAA CTCAGCGTAT CAATCCGACG ATGTATATCG CGAACAACAC 1
08041 TTCTTATCTC AACACAGCAA CTCAGCGTAT CAATCCGACG ATGTATATCG CGAACAACAC
08101 ACAGATCATA AGCTCACAGC AATTTGGATC AAGCGGTCAA GAAGCAGCAT ATGGCCACAC
08101 ACAGATCATA AGCTCACAGC AATTTGGATC AAGCGGTCAA GAAGCAGCAT ATGGCCACAC
Thr
08161 AACTTGTTTT AGGGACACAG GCTCTGTTAT GGTATACTGT ATCTATATTA TTGAATTGTC 1
08161 AACCTGTTTT AGGGACACAG GCTCTGTTAT GGTATACTGT ATCTATATTA TTGAATTGTC
08221 CTCATCTCTC TTAGGACAAT TTCAGATTGT CCCATTTATC CGTCAGGTGA CACTATCCTA
08221 CTCATCTCTC TTAGGACAAT TTCAGATTGT CCCATTTATC CGTCAGGTGA CACTATCCTA
HN Protein Stop ←|
08281 AAGGCAGAAG CCTCCAGATC TGACCTAGCC AATCAAAGCA TTATACCAGA CCATGGAATG 3
08281 AAGGCAGAAG CCTTCAGGTC TGACCCAGCC AATCAAAGCA TTATACCAGA CCATGGAATG
08341 CATACCAAAC ATTATTGACA CTAATGACAC ACAAAATTGG TTTTAAGAAA AACCAAGAGA
08341 CATACCAAAC ATTATTGACA CTAATGACAC ACAAAATTGG TTTTAAGAAA AACCAAGAGA
End of HN mRNA ←|
08401 ACAATAAGCC AGAATGGCTG GGTCTCGGGA GATATTACTC CCTGAAGTCC ATCTCAATTC 1
08401 ACAATAGGCC AGAATGGCTG GGTCTCGGGA GATATTACTC CCTGAAGTCC ATCTCAATTC
|→Start L mRNA
|→ L Protein Start
08461 ACCAATTGTA AAGCATAAGC TATACTATTA CATTCTACTT GGAAACCTCC CAAATGAGAT
08461 ACCAATTGTA AAGCATAAGC TATACTATTA CATTCTACTT GGAAACCTCC CAAATGAGAT
Leu→Ile
Gln
08521 CGACATTGAC GATTTAGGTC CATTACATAA TCAAAATTGG AATCAAATAG CACATGAAGA 2
08521 CGACCTTGAC GATTTAGGTC CATTACATAA TCAAAATTGG AATCAGATAG CACATGAAGA
08581 GTCTAACTTA GCTCAACGCT TGGTAAATGT AAGAAATTTT CTAATTACCC ACATCCCTGA
08581 GTCTAACTTA GCTCAACGCT TGGTAAATGT AAGAAATTTT CTAATTACCC ACATCCCTGA

Figure 9

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                                        Val
08641  TCTTAGAAAG GGCCATTGGC AAGAGTATGT AAATGTAATA CTGTGGCCGC GAATTCTTCC  1
       ||||||||||| |||||||||| |||||||||| |||||||||| |||||||||| ||||||||||
08641  TCTTAGAAAG GGCCATTGGC AAGAGTATGT CAATGTAATA CTGTGGCCGC GAATTCTTCC

08701  CTTGATCCCG GATTTTAAAA TCAATGACCA ATTGCCTCTG CTCAAAAATT GGGACAAGTT
       ||||||||||| |||||||||| |||||||||| |||||||||| |||||||||| ||||||||||
08701  CTTGATCCCG GATTTTAAAA TCAATGACCA ATTGCCTCTG CTCAAAAATT GGGACAAGTT

                                        Ala
08761  AGTTAAAGAA TCATGTTCAG TAATCAATGC GGGTACTTCC CAGTGCATTC AGAATCTCAG  1
       ||||||||||| |||||||||| |||||||||| |||||||||| |||||||||| ||||||||||
08761  AGTTAAAGAA TCATGTTCAG TAATCAATGC AGGTACTTCC CAGTGCATTC AGAATCTCAG

08821  CTATGGACTG ACAGGTCGTG GGAACCTCTT TACACGATCA CGTGAACTCT CTGGTGACCG
       ||||||||||| |||||||||| |||||||||| |||||||||| |||||||||| ||||||||||
08821  CTATGGACTG ACAGGTCGTG GGAACCTCTT TACACGATCA CGTGAACTCT CTGGTGACCG

                                  Thr
08881  CAGGGATATT GATCTTAAGA CGGTTGTGGC AGCATGGCAT GACTCAGACT GGAAAAGAAT  1
       ||||||||||| |||||||||| | |||||||| |||||||||| |||||||||| ||||||||||
08881  CAGGGATATT GATCTTAAGA CAGTTGTGGC AGCATGGCAT GACTCAGACT GGAAAAGAAT

08941  AAGTGATTTT TGGATTATGA TCAAATTCCA GATGAGACAA TTAATTGTTA GGCAAACAGA
       ||||||||||| |||||||||| |||||||||| |||||||||| |||||||||| ||||||||||
08941  AAGTGATTTT TGGATTATGA TCAAATTCCA GATGAGACAA TTAATTGTTA GGCAAACAGA

                  Ser→Pro
09001  TCATAATGAT CCTGATTTAA TCACGTATAT CGAAAATAGA GAAGGCATAA TCATCATAAC  1
       ||||||||||  |||||||||| |||||||||| |||||||||| |||||||||| ||||||||||
09001  TCATAATGAT TCTGATTTAA TCACGTATAT CGAAAATAGA GAAGGCATAA TCATCATAAC

                                  Asn
09061  CCCTGAACTG GTAGCATTAT TTAATACTGA GAATCATACA CTAACATACA TGACCTTTGA  1
       ||||||||||| |||||||||| |||| ||||| |||||||||| |||||||||| ||||||||||
09061  CCCTGAACTG GTAGCATTAT TTAACACTGA GAATCATACA CTAACATACA TGACCTTTGA

09121  AATTGTACTG ATGGTTTCAG ATATGTACGA AGGTCGTCAC AACATTTTAT CACTATGCAC
       ||||||||||| |||||||||| |||||||||| |||||||||| |||||||||| ||||||||||
09121  AATTGTACTG ATGGTTTCAG ATATGTACGA AGGTCGTCAC AACATTTTAT CACTATGCAC

09181  AGTTAGCACT TACCTGAATC CTCTGAAGAA AAGAATAACA TATTTATTGA GCCTTGTAGA
       ||||||||||| |||||||||| |||||||||| |||||||||| |||||||||| ||||||||||
09181  AGTTAGCACT TACCTGAATC CTCTGAAGAA AAGAATAACA TATTTATTGA GCCTTGTAGA
```

Figure 9

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09241  TAACTTAGCT TTTCAGATAG GTGATGCTGT ATATAACATA ATTGCTTTGC TAGAATCCTT
       ||||||||||| ||||||||||| ||||||||||| ||||||||||| ||||||||||| ||||||||||
09241  TAACTTAGCT TTTCAGATAG GTGATGCTGT ATATAACATA ATTGCTTTGC TAGAATCCTT

09301  TGTATATGCA CAGTTGCAAA TGTCAGATCC CATCCCAGAA CTCAGAGGAC AATTCCATGC
       ||||||||||| ||||||||||| ||||||||||| ||||||||||| ||||||||||| ||||||||||
09301  TGTATATGCA CAGTTGCAAA TGTCAGATCC CATCCCAGAA CTCAGAGGAC AATTCCATGC

                                                  Arg
09361  ATTCGTATGT TCTGAGATTC TTGATGCACT AAGGGGAACT AATAGTTTCA CCCAGGATGA  1
       ||||||||||| ||||||||||| ||||||||||| ||| |||||| ||||||||||| ||||||||||
09361  ATTCGTATGT TCTGAGATTC TTGATGCACT AAGAGGAACT AATAGTTTCA CCCAGGATGA

09421  ATTAAGAACT GTGACAACTA ATTTGATATC CCCATTCCAA GATCTGACCC CAGATCTTAC
       ||||||||||| ||||||||||| ||||||||||| ||||||||||| ||||||||||| ||||||||||
09421  ATTAAGAACT GTGACAACTA ATTTGATATC CCCATTCCAA GATCTGACCC CAGATCTTAC

09481  GGCTGAATTG CTCTGTATAA TGAGGCTTTG GGGACACCCC ATGCTCACTG CCAGTCAAGC
       ||||||||||| ||||||||||| ||||||||||| ||||||||||| ||||||||||| ||||||||||
09481  GGCTGAATTG CTCTGTATAA TGAGGCTTTG GGGACACCCC ATGCTCACTG CCAGTCAAGC

         Ala                                      Gly        Leu          Thr
09541  TGCGGGAAAG GTACGCGAGT CTATGTGTGC TGGGAAAGTA CTGGACTTTC CCACTATTAT  5
       ||| |||||| ||||||||||| ||||||||||| ||| |||||| | ||||||| |||| |||||
09541  TGCAGGAAAG GTACGCGAGT CTATGTGTGC TGGAAAAGTA TTAGACTTTC CCACCATTAT

09601  GAAAACACTA GCCTTTTTCC ATACTATTCT GATCAATGGA TACAGGAGGA AGCATCATGG
       ||||||||||.||||||||||| ||||||||||| ||||||||||| ||||||||||| ||||||||||
09601  GAAAACACTA GCCTTTTTCC ATACTATTCT GATCAATGGA TACAGGAGGA AGCATCATGG

                                    Pro                              Thr
09661  AGTATGGCCA CCCTTAAACT TACCAGGTAA TGCTTCAAAG GGTCTCACAG AACTTATGAA  2
       |||||||||| |||||||||| |||| || || |||||||||| |||||||| | ||||||||||
09661  AGTATGGCCA CCCTTAAACT TACCGGGTAA TGCTTCAAAG GGTCTCACGG AACTTATGAA

         Asn    Glu                                                 Val→Ile
09721  TGACAACACT GAGATAAGCT ATGAATTCAC ACTTAAGCAT TGGAAGGAAA TCTCTCTTAT  3
       |||||| ||| || ||||||| |||||||||| |||||||||| ||||||||| ||||||||||
09721  TGACAATACT GAAATAAGCT ATGAATTCAC ACTTAAGCAT TGGAAGGAAG TCTCTCTTAT

09781  AAAATTCAAG AAATGTTTTG ATGCAGACGC AGGTGAGGAA CTCAGTATAT TTATGAAAGA
       ||||||||||| ||||||||||| ||||||||||| ||||||||||| ||||||||||| ||||||||||
09781  AAAATTCAAG AAATGTTTTG ATGCAGACGC AGGTGAGGAA CTCAGTATAT TTATGAAAGA

       Lys
09841  TAAAGCAATT AGTGCCCCAA AACAAGACTG GATGAGTGTG TTTAGAAGAA GCCTAATCAA  1
       ||| |||||| |||||||||| |||||||||| |||||||||| |||||||||| ||||||||||
09841  TAAGGCAATT AGTGCCCCAA AACAAGACTG GATGAGTGTG TTTAGAAGAA GCCTAATCAA
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Figure 9
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                                                                  Leu
09901  ACAGCGCCAT CAGCATCATC AGGTCCCCCT ACCAAATCCA TTCAATCGAC GGCTATTGCT  1
       ||||||||||| ||||||||||| ||||||||||| ||||||||||| |||||||||| |||||
09901  ACAGCGCCAT CAGCATCATC AGGTCCCCCT ACCAAATCCA TTCAATCGAC GGCTGTTGCT

09961  AAACTTTCTC GGAGATGACA AATTCGACCC GAATGTGGAG CTACAGTATG TAACATCAGG
       ||||||||||| ||||||||||| ||||||||||| ||||||||||| ||||||||||| |||||
09961  AAACTTTCTC GGAGATGACA AATTCGACCC GAATGTGGAG CTACAGTATG TAACATCAGG

10021  TGAGTATCTA CATGATGACA CGTTTTGTGC ATCATATTCA CTAAAAGAGA AGGAAATTAA
       ||||||||||| ||||||||||| ||||||||||| ||||||||||| ||||||||||| |||||
10021  TGAGTATCTA CATGATGACA CGTTTTGTGC ATCATATTCA CTAAAAGAGA AGGAAATTAA

10081  ACCTGATGGT CGAATTTTTG CAAAGTTGAC TAAGAGAATG AGATCATGTC AAGTTATAGC
       ||||||||||| ||||||||||| ||||||||||| ||||||||||| ||||||||||| |||||
10081  ACCTGATGGT CGAATTTTTG CAAAGTTGAC TAAGAGAATG AGATCATGTC AAGTTATAGC

10141  AGAATCTCTT TTAGCGAACC ATGCTGGGAA GTTAATGAAA GAGAATGGTG TTGTGATGAA
       ||||||||||| ||||||||||| ||||||||||| ||||||||||| ||||||||||| |||||
10141  AGAATCTCTT TTAGCGAACC ATGCTGGGAA GTTAATGAAA GAGAATGGTG TTGTGATGAA

                                                              Lys→Arg
10201  TCAGCTATCA TTAACAAAAT CACTATTAAC AATGAGTCAG ATTGGAATAA TATCCGAGAG  1
       ||||||||||| ||||||||||| ||||||||||| ||||||||||| ||||||||||| |||||
10201  TCAGCTATCA TTAACAAAAT CACTATTAAC AATGAGTCAG ATTGGAATAA TATCCGAGAA

                 Ser                          Gln→Arg
10261  AGCTAGAAAG TCGACTCGAG ATAACATAAA TCGACCTGGT TTCCAGAATA TCCAGAGAAA  2
       ||||||||||| || ||||||| ||||||||||| || ||||||| ||||||||||| |||||
10261  AGCTAGAAAG TCAACTCGAG ATAACATAAA TCAACCTGGT TTCCAGAATA TCCAGAGAAA

10321  TAAATCACAT CACTCCAAGC AAGTCAATCA GCGAGATCCA AGTGATGACT TTGAATTGGC
       ||||||||||| ||||||||||| ||||||||||| ||||||||||| ||||||||||| |||||
10321  TAAATCACAT CACTCCAAGC AAGTCAATCA GCGAGATCCA AGTGATGACT TTGAATTGGC

                                                          Asn
10381  AGCATCTTTT TTAACTACTG ATCTCAAAAA ATATTGTTTA CAATGGAGGT ATCAGACAAT  1
       ||||||||||| ||||||||||| ||||||||||| ||||||||||| ||||||||||| |||||
10381  AGCATCTTTT TTAACTACTG ATCTCAAAAA ATATTGTTTA CAATGGAGGT ACCAGACAAT

                          Leu                                 Phe
10441  TATCCCATTT GCTCAATCAC TAAACAGAAT GTATGGTTAT CCTCATCTCT TCGAGTGGAT  2
       ||||||||||| ||||||||| ||||||||||| ||||||||||| ||||||||||| |||||
10441  TATCCCATTT GCTCAATCAT TAAACAGAAT GTATGGTTAT CCTCATCTCT TTGAGTGGAT
```

Figure 9

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                Leu                                                 Asp
10501  TCACTTGCGG CTAATGCGTA GTACACTTTA CGTGGGGGAC CCCTTCAACC CACCAGCAGA  2
       |||||| ||| |||||||||| |||||||||| |||||||||  |||||||||| ||||||||||
10501  TCACTTACGG CTAATGCGTA GTACACTTTA CGTGGGGGAT CCCTTCAACC CACCAGCAGA

10561  TACCAGTCAA TTTGATCTAG ATAAAGTAAT TAATGGAGAT ATCTTCATTG TATCACCCAG
       |||||||||| |||||||||| |||||||||| |||||||||| |||||||||| ||||||||||
10561  TACCAGTCAA TTTGATCTAG ATAAAGTAAT TAATGGAGAT ATCTTCATTG TATCACCCAG

                                    Lys                          Ala→Ser
10621  AGGTGGAATT GAAGGGCTGT GTCAAAAAGC TTGGACAATG ATATCTATCT CTGTGATAAT  2
       |||||||||| |||||||||| |||||| || |||||||||| |||||||||  ||||||||||
10621  AGGTGGAATT GAAGGGCTGT GTCAAAAGGC TTGGACAATG ATATCTATCG CTGTGATAAT

                                                Ser
10681  TCTATCTGCC ACAGAGTCTG GCACACGAGT AATGAGCATG GTGCAGGGAG ATAATCAAGC  1
       |||||||||| |||||||||| |||||||||| |||||| ||| |||||||||| ||||||||||
10681  TCTATCTGCC ACAGAGTCTG GCACACGAGT AATGAGTATG GTGCAGGGAG ATAATCAAGC

10741  AATTGCTGTC ACCACACGAG TACCAAGGAG CCTGCCGACT CTTGAGAAAA AGACTATTGC
       |||||||||| |||||||||| |||||||||| |||||||||| |||||||||| ||||||||||
10741  AATTGCTGTC ACCACACGAG TACCAAGGAG CCTGCCGACT CTTGAGAAAA AGACTATTGC

                          Leu
10801  TTTTAGATCT TGTAATTTAT TCTTTGAGAG GTTAAAATGT AATAATTTTG GATTAGGTCA  1
       |||||||||| |||||| ||| |||||||||| |||||||||| |||||||||| ||||||||||
10801  TTTTAGATCT TGTAATCTAT TCTTTGAGAG GTTAAAATGT AATAATTTTG GATTAGGTCA

10861  CCATTTGAAA GAACAAGAGA CTATCATTAG TTCTCACTTC TTTGTTTATA GCAAGAGAAT
       |||||||||| |||||||||| |||||||||| |||||||||| |||||||||| ||||||||||
10861  CCATTTGAAA GAACAAGAGA CTATCATTAG TTCTCACTTC TTTGTTTATA GCAAGAGAAT

10921  ATTCTATCAG GGGAGGATTC TAACGCAAGC CTTAAAAAAT GCTAGTAAGC TCTGCTTGAC
       |||||||||| |||||||||| |||||||||| |||||||||| |||||||||| ||||||||||
10921  ATTCTATCAG GGGAGGATTC TAACGCAAGC CTTAAAAAAT GCTAGTAAGC TCTGCTTGAC

10981  AGCTGATGTC CTAGGAGAAT GCACCCAATC ATCATGTTCT AATCTTGCAA CTACTGTCAT
       |||||||||| |||||||||| |||||||||| |||||||||| |||||||||| ||||||||||
10981  AGCTGATGTC CTAGGAGAAT GCACCCAATC ATCATGTTCT AATCTTGCAA CTACTGTCAT

11041  GAGGTTAACT GAGAATGGTG TTGAAAAAGA TATCTGTTTC TACTTGAATA TCTATATGAC
       |||||||||| |||||||||| |||||||||| |||||||||| |||||||||| ||||||||||
11041  GAGGTTAACT GAGAATGGTG TTGAAAAAGA TATCTGTTTC TACTTGAATA TCTATATGAC

                                                           Ser
11101  CATCAAACAG CTCTCCTATG ATATCATCTT CCCTCAAGTG TCGATTCCTG GAGATCAGAT  1
       |||||||||| |||||||||| |||||||||| |||||||||| ||  ||||||| ||||||||||
11101  CATCAAACAG CTCTCCTATG ATATCATCTT CCCTCAAGTG TCAATTCCTG GAGATCAGAT
```

Figure 9
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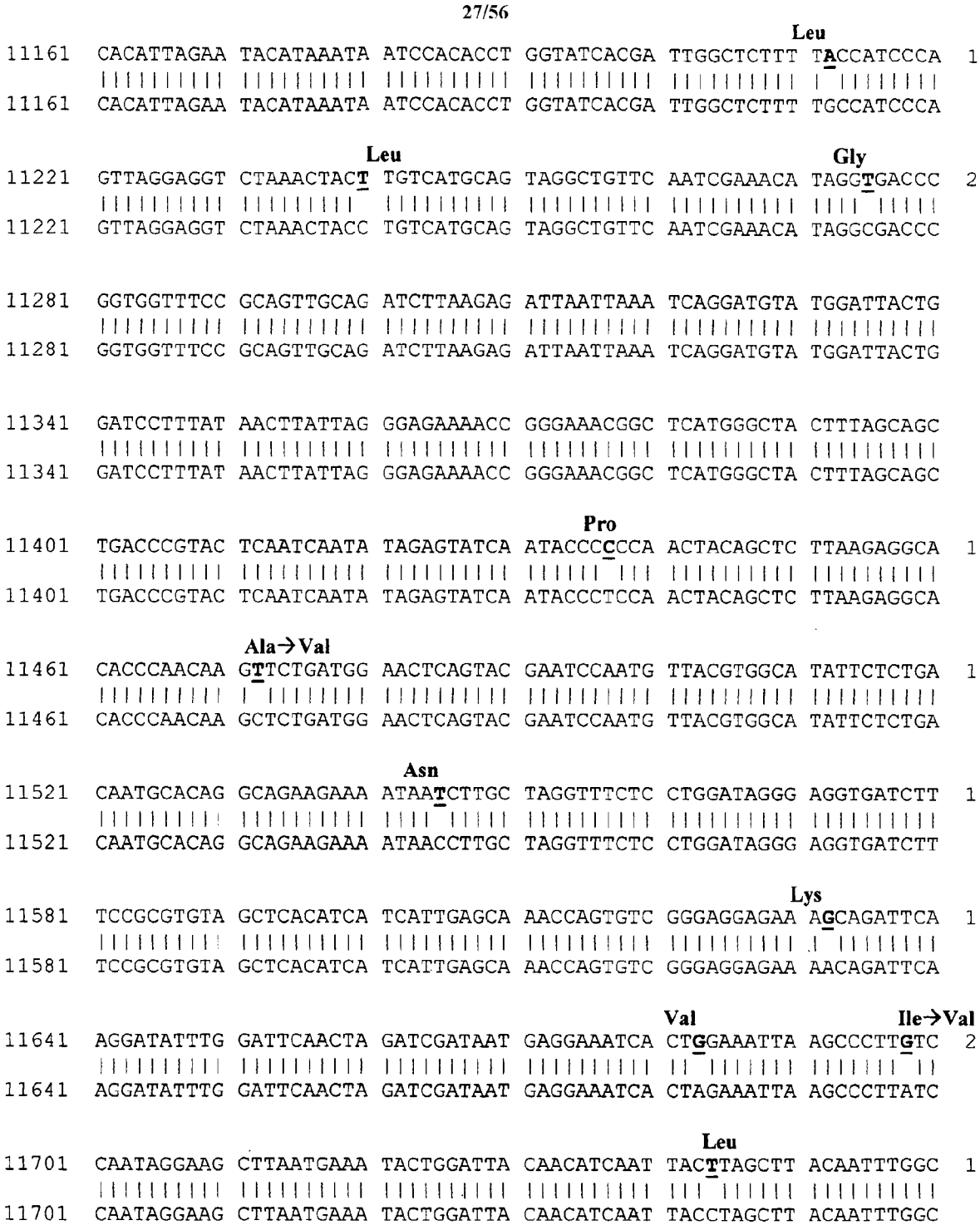
Leu
11161 CACATTAGAA TACATAAATA ATCCACACCT GGTATCACGA TTGGCTCTTT TACCATCCCA 1
11161 CACATTAGAA TACATAAATA ATCCACACCT GGTATCACGA TTGGCTCTTT TGCCATCCCA
Leu
Gly
11221 GTTAGGAGGT CTAAACTACT TGTCATGCAG TAGGCTGTTC AATCGAAACA TAGGTGACCC 2
11221 GTTAGGAGGT CTAAACTACC TGTCATGCAG TAGGCTGTTC AATCGAAACA TAGGCGACCC
11281 GGTGGTTTCC GCAGTTGCAG ATCTTAAGAG ATTAATTAAA TCAGGATGTA TGGATTACTG
11281 GGTGGTTTCC GCAGTTGCAG ATCTTAAGAG ATTAATTAAA TCAGGATGTA TGGATTACTG
11341 GATCCTTTAT AACTTATTAG GGAGAAAACC GGGAAACGGC TCATGGGCTA CTTTAGCAGC
11341 GATCCTTTAT AACTTATTAG GGAGAAAACC GGGAAACGGC TCATGGGCTA CTTTAGCAGC
Pro
11401 TGACCCGTAC TCAATCAATA TAGAGTATCA ATACCCCCCA ACTACAGCTC TTAAGAGGCA 1
11401 TGACCCGTAC TCAATCAATA TAGAGTATCA ATACCCTCCA ACTACAGCTC TTAAGAGGCA
Ala→Val
11461 CACCCAACAA GTTCTGATGG AACTCAGTAC GAATCCAATG TTACGTGGCA TATTCTCTGA 1
11461 CACCCAACAA GCTCTGATGG AACTCAGTAC GAATCCAATG TTACGTGGCA TATTCTCTGA
Asn
11521 CAATGCACAG GCAGAAGAAA ATAATCTTGC TAGGTTTCTC CTGGATAGGG AGGTGATCTT 1
11521 CAATGCACAG GCAGAAGAAA ATAACCTTGC TAGGTTTCTC CTGGATAGGG AGGTGATCTT
Lys
11581 TCCGCGTGTA GCTCACATCA TCATTGAGCA AACCAGTGTC GGGAGGAGAA AGCAGATTCA 1
11581 TCCGCGTGTA GCTCACATCA TCATTGAGCA AACCAGTGTC GGGAGGAGAA AACAGATTCA
Val
Ile→Val
11641 AGGATATTTG GATTCAACTA GATCGATAAT GAGGAAATCA CTGGAAATTA AGCCCTTGTC 2
11641 AGGATATTTG GATTCAACTA GATCGATAAT GAGGAAATCA CTAGAAATTA AGCCCTTATC
Leu
11701 CAATAGGAAG CTTAATGAAA TACTGGATTA CAACATCAAT TACTTAGCTT ACAATTTGGC 1
11701 CAATAGGAAG CTTAATGAAA TACTGGATTA CAACATCAAT TACCTAGCTT ACAATTTGGC

Figure 9

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                                                                  Thr
11761  ATTACTCAAG AATGCTATTG AACCTCCGAC TTATTTGAAG GCAATGACCC TTGAAACATG  1
       |||||||||| |||||||||| |||||||||| |||||||||| |||||||| | ||||||||||
11761  ATTACTCAAG AATGCTATTG AACCTCCGAC TTATTTGAAG GCAATGACAC TTGAAACATG

                                Asn→Ser
11821  TAGCATCGAC ATTGCAAGGA GCCTCCGGAA GCTCTCCTGG GCCCCACTCT TGGGTGGGAG  1
       |||||||||| |||||||||| ||||||||| |||||||||| |||||||||| ||||||||||
11821  TAGCATCGAC ATTGCAAGGA ACCTCCGGAA GCTCTCCTGG GCCCCACTCT TGGGTGGGAG

                       Leu                                Ile
11881  AAATCTTGAA GGACTAGAGA CGCCAGATCC CATTGAAATC ACTGCAGGAG CATTAATTGT  2
       |||||||||| ||| |||||| |||||||||| ||||||||| |||||||||| ||||||||||
11881  AAATCTTGAA GGATTAGAGA CGCCAGATCC CATTGAAATT ACTGCAGGAG CATTAATTGT

11941  TGGATCGGGC TACTGTGAAC AGTGTGCTGC AGGAGACAAT CGATTCACAT GGTTTTTCTT
       |||||||||| |||||||||| |||||||||| |||||||||| |||||||||| ||||||||||
11941  TGGATCGGGC TACTGTGAAC AGTGTGCTGC AGGAGACAAT CGATTCACAT GGTTTTTCTT

12001  GCCATCTGGT ATCGAGATAG GAGGGGATCC CCGTGATAAT CCTCCTATCC GTGTACCGTA
       |||||||||| |||||||||| |||||||||| |||||||||| |||||||||| ||||||||||
12001  GCCATCTGGT ATCGAGATAG GAGGGGATCC CCGTGATAAT CCTCCTATCC GTGTACCGTA

12061  CATTGGCTCC AGGACTGATG AGAGGAGGGT AGCCTCAATG GCATACATCA GGGGTGCCTC
       |||||||||| |||||||||| |||||||||| |||||||||| |||||||||| ||||||||||
12061  CATTGGCTCC AGGACTGATG AGAGGAGGGT AGCCTCAATG GCATACATCA GGGGTGCCTC

     Ser       Leu
12121  AAGTAGCCTA AAAGCAGTTC TTAGACTGGC GGGAGTGTAC ATCTGGGCAT TCGGAGATAC  2
         |||||| || |||||||||| |||||||||| |||||||||| |||||||||| ||||||||||
12121  GAGTAGCTTA AAAGCAGTTC TTAGACTGGC GGGAGTGTAC ATCTGGGCAT TCGGAGATAC

12181  TCTGGAGAAT TGGATAGATG CACTGGATTT GTCTCACACT AGAGTTAACA TCACACTTGA
       |||||||||| |||||||||| |||||||||| |||||||||| |||||||||| ||||||||||
12181  TCTGGAGAAT TGGATAGATG CACTGGATTT GTCTCACACT AGAGTTAACA TCACACTTGA

          Leu
12241  ACAGTTACAA TCCCTCACCC CACTTCCAAC CTCTGCCAAT CTAACCCATC GGTTGGATGA  2
       |||| | ||| |||||||||| |||||||||| |||||||||| |||||||||| ||||||||||
12241  ACAGCTGCAA TCCCTCACCC CACTTCCAAC CTCTGCCAAT CTAACCCATC GGTTGGATGA

                                      Ala
12301  TGGCACAACT ACCCTAAAGT TTACTCCTGC AAGCTCTTAC ACCTTTTCAA GTTTCACTCA  1
       |||||||||| |||||||||| |||||||||| ||||||||| |||||||||| ||||||||||
12301  TGGCACAACT ACCCTAAAGT TTACTCCTGC GAGCTCTTAC ACCTTTTCAA GTTTCACTCA

                                Tyr
12361  TATATCAAAT GATGAGCAAT ATCTGACAAT TAATGACAAA ACTGCAGATT CAAATATAAT  1
       |||||||||| |||||||||| | |||||||| |||||||||| |||||||||| ||||||||||
12361  TATATCAAAT GATGAGCAAT ACCTGACAAT TAATGACAAA ACTGCAGATT CAAATATAAT
```

Figure 9

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                                        Gly
12421  CTACCAACAG TTAATGATCA CTGGACTCGG GATCTTAGAA ACATGGAATA ATCCCCCAAT  1
       |||||||||| |||||||||| |||||||||| |||||||||| |||||||||| ||||||||||
12421  CTACCAACAG TTAATGATCA CTGGACTCGG AATCTTAGAA ACATGGAATA ATCCCCCAAT

12481  CAATAGAACA TTCGAAGAAT CTACCCTACA TTTGCACACT GGTGCATCAT GTTGTGTCCG
       |||||||||| |||||||||| |||||||||| |||||||||| |||||||||| ||||||||||
12481  CAATAGAACA TTCGAAGAAT CTACCCTACA TTTGCACACT GGTGCATCAT GTTGTGTCCG

                          Leu→Ile
12541  ACCTGTGGAC TCCTGCATTA TCTCAGAAGC ATTAACAGTC AAGCCACATA TTACAGTACC  1
       |||||||||| |||||||||| |||||||||| |||||||||| |||||||||| ||||||||||
12541  ACCTGTGGAC TCCTGCATTC TCTCAGAAGC ATTAACAGTC AAGCCACATA TTACAGTACC

                                   Glu                    Glu
12601  GTACAGCAAT AAATTTGTAT TTGATGAAGA CCCGCTATCT GAATATGAGA CTGCAAAACT  2
       |||||||||| |||||||||| ||||||| || |||||||||| |||||||| | ||||||||||
12601  GTACAGCAAT AAATTTGTAT TTGATGAGGA CCCGCTATCT GAATATGAAA CTGCAAAACT

12661  GGAATCGTTA TCATTCCAAG CCCAATTAGG CAACATTGAT GCTGTAGATA TGACAGGTAA
       |||||||||| |||||||||| |||||||||| |||||||||| |||||||||| ||||||||||
12661  GGAATCGTTA TCATTCCAAG CCCAATTAGG CAACATTGAT GCTGTAGATA TGACAGGTAA

12721  ATTAACATTA TTGTCCCAAT TCACTGCAAG GCAGATTATC AATGCAATCA CTGGACTCGA
       |||||||||| |||||||||| |||||||||| |||||||||| |||||||||| ||||||||||
12721  ATTAACATTA TTGTCCCAAT TCACTGCAAG GCAGATTATC AATGCAATCA CTGGACTCGA

             Val
12781  TGAGTCTGTT TCTCTTACTA ATGATGCCAT TGTTGCATCA GACTATGTCT CCAATTGGAT  1
       |||||||||  |||||||||| |||||||||| |||||||||| |||||||||| ||||||||||
12781  TGAGTCTGTC TCTCTTACTA ATGATGCCAT TGTTGCATCA GACTATGTCT CCAATTGGAT

12841  TAGTGAATGC ATGTATACCA AATTAGATGA ATTATTTATG TATTGTGGGT GGGAACTACT
       |||||||||| |||||||||| |||||||||| |||||||||| |||||||||| ||||||||||
12841  TAGTGAATGC ATGTATACCA AATTAGATGA ATTATTTATG TATTGTGGGT GGGAACTACT

12901  ATTGGAACTA TCCTATCAAA TGTATTATCT GAGGGTAGTT GGGTGGAGTA ATATAGTGGA
       |||||||||| |||||||||| |||||||||| |||||||||| |||||||||| ||||||||||
12901  ATTGGAACTA TCCTATCAAA TGTATTATCT GAGGGTAGTT GGGTGGAGTA ATATAGTGGA

12961  TTATTCTTAC ATGATCTTGA GAAGAATCCC GGGTGCAGCA TTAAACAATC TGGCATCTAC
       |||||||||| |||||||||| |||||||||| |||||||||| |||||||||| ||||||||||
12961  TTATTCTTAC ATGATCTTGA GAAGAATCCC GGGTGCAGCA TTAAACAATC TGGCATCTAC

13021  ATTAAGTCAT CCAAAACTTT TCCGACGAGC TATCAACCTA GATATAGTTG CCCCCTTAAA
       |||||||||| |||||||||| |||||||||| |||||||||| |||||||||| ||||||||||
13021  ATTAAGTCAT CCAAAACTTT TCCGACGAGC TATCAACCTA GATATAGTTG CCCCCTTAAA
```

Figure 9

Val→Met

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13081  TGCTCCTCAT TTTGCATCTC TGGACTACAT CAAGATGAGT ATGGATGCAA TACTCTGGGG  1
       ||||||||||| ||||||||||| ||||||||||| ||||||||||  |||||||||| ||||||||||
13081  TGCTCCTCAT TTTGCATCTC TGGACTACAT CAAGATGAGT GTGGATGCAA TACTCTGGGG

13141  CTGTAAAAGA GTCATCAATG TGCTCTCCAA TGGAGGGGAC TTAGAATTAG TTGTGACATC
       ||||||||||| ||||||||||| ||||||||||| ||||||||||| |||||||||| ||||||||||
13141  CTGTAAAAGA GTCATCAATG TGCTCTCCAA TGGAGGGGAC TTAGAATTAG TTGTGACATC

13201  TGAAGATAGC CTTATTCTCA GTGACCGATC CATGAATCTC ATTGCAAGGA AATTAACTTT
       ||||||||||| ||||||||||| ||||||||||| ||||||||||| |||||||||| ||||||||||
13201  TGAAGATAGC CTTATTCTCA GTGACCGATC CATGAATCTC ATTGCAAGGA AATTAACTTT

13261  ATTATCACTG ATTCACCATA ATGGTTTGGA ACTACCAAAG ATTAAGGGGT TCTCTCCTGA
       ||||||||||| ||||||||||| ||||||||||| ||||||||||| |||||||||| ||||||||||
13261  ATTATCACTG ATTCACCATA ATGGTTTGGA ACTACCAAAG ATTAAGGGGT TCTCTCCTGA

13321  TGAGAAGTGT TTCGCTTTGA CAGAATTTTT GAGGAAAGTG GTGAACTCAG GGTTGAGTTC
       ||||||||||| ||||||||||| ||||||||||| ||||||||||| |||||||||| ||||||||||
13321  TGAGAAGTGT TTCGCTTTGA CAGAATTTTT GAGGAAAGTG GTGAACTCAG GGTTGAGTTC

13381  AATAGAGAAC CTATCAAATT TTATGTACAA TGTGGAGAAC CCACGGCTTG CAGCATTCGC
       ||||||||||| ||||||||||| ||||||||||| ||||||||||| |||||||||| ||||||||||
13381  AATAGAGAAC CTATCAAATT TTATGTACAA TGTGGAGAAC CCACGGCTTG CAGCATTCGC
```

Ser

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13441  CAGCAACAAT TACTACCTGA CCAGAAAATT ATTGAATTCA ATACGAGATA CTGAGTCAGG  1
       ||||||||||| ||||||||||| ||||||||||| ||||||||||| |||||||||| |||||||  ||
13441  CAGCAACAAT TACTACCTGA CCAGAAAATT ATTGAATTCA ATACGAGATA CTGAGTCGGG

13501  TCAAGTAGCA GTCACCTCAT ATTATGAATC ATTAGAATAT ATTGATAGTC TTAAGCTAAC
       ||||||||||| ||||||||||| ||||||||||| ||||||||||| |||||||||| ||||||||||
13501  TCAAGTAGCA GTCACCTCAT ATTATGAATC ATTAGAATAT ATTGATAGTC TTAAGCTAAC

13561  CCCACATGTG CCTGGCACCT CATGCATTGA GGATGATAGT CTATGTACAA ATGATTACAT
       ||||||||||| ||||||||||| ||||||||||| ||||||||||| |||||||||| ||||||||||
13561  CCCACATGTG CCTGGCACCT CATGCATTGA GGATGATAGT CTATGTACAA ATGATTACAT

13621  AATCTGGATC ATAGAGTCTA ATGCAAACTT GGAGAAGTAT CCAATTCCAA ATAGCCCTGA
       ||||||||||| ||||||||||| ||||||||||| ||||||||||| |||||||||| ||||||||||
13621  AATCTGGATC ATAGAGTCTA ATGCAAACTT GGAGAAGTAT CCAATTCCAA ATAGCCCTGA

13681  GGATGATTCC AATTTCCATA ACTTTAAGTT GAATGCTCCA TCGCACCATA CCTTACGCCC
       ||||||||||| ||||||||||| ||||||||||| ||||||||||| |||||||||| ||||||||||
13681  GGATGATTCC AATTTCCATA ACTTTAAGTT GAATGCTCCA TCGCACCATA CCTTACGCCC
```

Figure 9

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                    Ser
13741  ATTAGGGTTG TCATCGACTG CTTGGTATAA GGGTATAAGC TGCTGCAGGT ACCTTGAGCG  1
       |||||||||| ||||| |||| |||||||||| |||||||||| |||||||||| ||||||||||
13741  ATTAGGGTTG TCATCAACTG CTTGGTATAA GGGTATAAGC TGCTGCAGGT ACCTTGAGCG

13801  ATTAAAGCTA CCACAAGGTG ATCATTTATA TATTGCAGAA GGTAGTGGTG CCAGTATGAC
       |||||||||| |||||||||| |||||||||| |||||||||| |||||||||| ||||||||||
13801  ATTAAAGCTA CCACAAGGTG ATCATTTATA TATTGCAGAA GGTAGTGGTG CCAGTATGAC

13861  AATCATAGAA TACCTATTCC CAGGAAGAAA GATATATTAC AATTCTTTAT TTAGTAGTGG
       |||||||||| |||||||||| |||||||||| |||||||||| |||||||||| ||||||||||
13861  AATCATAGAA TACCTATTCC CAGGAAGAAA GATATATTAC AATTCTTTAT TTAGTAGTGG

13921  TGACAATCCC CCACAAAGAA ATTATGCACC AATGCCTACT CAGTTCATTG AGAGTGTCCC
       |||||||||| |||||||||| |||||||||| |||||||||| |||||||||| ||||||||||
13921  TGACAATCCC CCACAAAGAA ATTATGCACC AATGCCTACT CAGTTCATTG AGAGTGTCCC

13981  ATACAAGCTC TGGCAAGCAC ACACAGATCA ATATCCCGAG ATTTTTGAGG ACTTCATCCC
       |||||||||| |||||||||| |||||||||| |||||||||| |||||||||| ||||||||||
13981  ATACAAGCTC TGGCAAGCAC ACACAGATCA ATATCCCGAG ATTTTTGAGG ACTTCATCCC

14041  TCTATGGAAC GGAAACGCCG CCATGACTGA CATAGGAATG ACAGCTTGTG TAGAATTCAT
       |||||||||| |||||||||| |||||||||| |||||||||| |||||||||| ||||||||||
14041  TCTATGGAAC GGAAACGCCG CCATGACTGA CATAGGAATG ACAGCTTGTG TAGAATTCAT

                    Val
14101  CATCAATCGA GTTGGCCCAA GGACTTGCAG TTTAGTACAT GTAGATTTGG AATCAAGTGC  1
       |||||||||| ||  ||||||| |||||||||| |||||||||| |||||||||| ||||||||||
14101  CATCAATCGA GTCGGCCCAA GGACTTGCAG TTTAGTACAT GTAGATTTGG AATCAAGTGC

14161  AAGCTTAAAT CAACAATGCC TGTCAAAGCC GATAATTAAT GCTATCATCA CTGCTACAAC
       |||||||||| |||||||||| |||||||||| |||||||||| |||||||||| ||||||||||
14161  AAGCTTAAAT CAACAATGCC TGTCAAAGCC GATAATTAAT GCTATCATCA CTGCTACAAC

14221  TGTTTTGTGC CCTCATGGGG TGCTTATTCT GAAATATAGT TGGTTGCCAT TTACTAGATT
       |||||||||| |||||||||| |||||||||| |||||||||| |||||||||| ||||||||||
14221  TGTTTTGTGC CCTCATGGGG TGCTTATTCT GAAATATAGT TGGTTGCCAT TTACTAGATT

14281  TAGTACTTTG ATCACTTTCT TATGGTGCTA CTTTGAGAGA ATCACTGTTC TTAGGAGCAC
       |||||||||| |||||||||| |||||||||| |||||||||| |||||||||| ||||||||||
14281  TAGTACTTTG ATCACTTTCT TATGGTGCTA CTTTGAGAGA ATCACTGTTC TTAGGAGCAC
```

Figure 9

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14341  ATATTCTGAT CCAGCTAATC ATGAGGTTTA TTTAATTTGT ATCCTTGCCA ACAACTTTGC
       ||||||||||| ||||||||||| ||||||||||| ||||||||||| ||||||||||| ||||||||||
14341  ATATTCTGAT CCAGCTAATC ATGAGGTTTA TTTAATTTGT ATCCTTGCCA ACAACTTTGC

                                                          Thr
14401  ATTCCAGACT GTCTCGCAGG CAACAGGAAT GGCGATGACT TTAACCGATC AAGGGTTTAC  1
       ||||||||||| ||||||||||| ||||||||||| ||||||||||| ||||| |||| ||||||||||
14401  ATTCCAGACT GTCTCGCAGG CAACAGGAAT GGCGATGACT TTAACTGATC AAGGGTTTAC

       Thr                                                Leu
14461  CTTGATATCA CCTGAAAGAA TAAATCAGTA TTGGGATGGT CACTTAAAGC AAGAACGTAT  2
        |||||||||| ||||||||||| ||||||||||| ||||||||||| ||||| |||| ||||||||||
14461  TTTGATATCA CCTGAAAGAA TAAATCAGTA TTGGGATGGT CACTTGAAGC AAGAACGTAT

14521  CGTAGCAGAA GCAATTGATA AGGTGGTTCT AGGAGAAAAT GCTCTATTTA ATTCGAGTGA
       ||||||||||| ||||||||||| ||||||||||| ||||||||||| ||||||||||| ||||||||||
14521  CGTAGCAGAA GCAATTGATA AGGTGGTTCT AGGAGAAAAT GCTCTATTTA ATTCGAGTGA

                                                                Leu
14581  TAATGAATTA ATTCTCAAAT GTGGAGGGAC ACCAAATGCA CGGAATCTTA TCGATATCGA  1
       ||||||||||| ||||||||||| ||||||||||| ||||||||||| |||||||| | ||||||||||
14581  TAATGAATTA ATTCTCAAAT GTGGAGGGAC ACCAAATGCA CGGAATCTCA TCGATATCGA

                                                    Leu
14641  GCCAGTCGCA ACTTTCATAG AATTTGAACA ACTAATCTGC ACAATGTTGA CAACCCACTT  2
       ||||||||||| ||||||||||| ||||||||||| | | |||||| ||||||||||| ||||||||||
14641  GCCAGTCGCA ACTTTCATAG AATTTGAACA ATTGATCTGC ACAATGTTGA CAACCCACTT

14701  GAAGGAAATA ATTGATATAA CAAGGTCTGG AACCCAGGAT TATGAAAGTT TATTACTCAC
       ||||||||||| ||||||||||| ||||||||||| ||||||||||| ||||||||||| ||||||||||
14701  GAAGGAAATA ATTGATATAA CAAGGTCTGG AACCCAGGAT TATGAAAGTT TATTACTCAC

14761  TCCTTACAAT TTAGGTCTTC TTGGTAAAAT CAGTACGATA GTGAGATTAT TAACAGAAAG
       ||||||||||| ||||||||||| ||||||||||| ||||||||||| ||||||||||| ||||||||||
14761  TCCTTACAAT TTAGGTCTTC TTGGTAAAAT CAGTACGATA GTGAGATTAT TAACAGAAAG

14821  GATTCTAAAT CATACTATCA GGAATTGGTT GATCCTCCCA CCTTCGCTCC AGATGATCGT
       ||||||||||| ||||||||||| ||||||||||| ||||||||||| ||||||||||| ||||||||||
14821  GATTCTAAAT CATACTATCA GGAATTGGTT GATCCTCCCA CCTTCGCTCC GGATGATCGT

14881  GAAGCAGGAC TTGGAATTCG GCATATTCAG GATTACTTCC ATCCTCAATT CTGATCGGTT
       ||||||||||| ||||||||||| ||||||||||| ||||||||||| ||||||||||| ||||||||||
14881  GAAGCAGGAC TTGGAATTCG GCATATTCAG GATTACTTCC ATCCTCAATT CTGATCGGTT

          Lys                                  Ala→Thr
14941  CCTGAAACTT TCTCCAAATA GGAAATACTT GATTACACAA TTAACTGCAG GCTACATTAG  2
       |||||| ||| |||||||||| |||||||||| |||| ||||| |||||||||| ||||||||||
14941  CCTGAAGCTT TCTCCAAATA GGAAATACTT GATTGCACAA TTAACTGCAG GCTACATTAG
```

Figure 9
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Cys

```
15001  GAAATTGATT GAGGGGGATT GTAATATCGA TCTAACCAGA CCTATCCAAA AGCAAATCTG  1
       ||||||||||| |||||||||| | |||||||| |||||||||| |||||||||| ||||||||||
15001  GAAATTGATT GAGGGGGATT GCAATATCGA TCTAACCAGA CCTATCCAAA AGCAAATCTG
```

Tyr

```
15061  GAAAGCATTA GGTTGTGTAG TCTACTGTCA CGATCCAATG GATCAAAGGG AGTCAACAGA  1
       ||||||||||| |||||||||| |||| ||||| |||||||||| |||||||||| ||||||||||
15061  GAAAGCATTA GGTTGTGTAG TCTATTGTCA CGATCCAATG GATCAAAGGG AGTCAACAGA

15121  GTTTATTGAT ATAAATATTA ATGAAGAAAT AGACCGCGGG ATCGATGGCG AGGAAATCTA
       ||||||||||| |||||||||| |||||||||| |||||||||| |||||||||| ||||||||||
15121  GTTTATTGAT ATAAATATTA ATGAAGAAAT AGACCGCGGG ATCGATGGCG AGGAAATCTA
                                                    L Protein Stop ←|

15181  AATATATCAA GAATCAGAAT TAATTTAAGA AAAAAGAAGC GGATTAATCT TGGTTTTCCC  3
       || ||||||| |||||||||| || ||||||| ||||||||| |||||||||| ||||||||||
15181  AACATATCAA GAATCAGAAT TAGTTTAAGA AAAAAGAAGA GGATTAATCT TGGTTTTCCC
                                  L mRNA End ←|

15241  CTTGGT  // (SEQ ID NO:1)

15241  CTTGGT  // (SEQ ID NO:2)
```

15,246 nucleotides 237

Of the 15,246 nucleotides, that comprise the genome of CV, there are 237 nucleotide differences between its sequence and that of the W3A strain of SV5 (1.55% different; 98.45% homology).

Figure 9

```
CV-0001   ATGAGCACTA TAATTCAATC TCTGGTGGTC TCCTGTCTAT TGGCAGGAGC AGGCAGCCTT
CPV-0001  ATGGGTACTA GAATTCAATT TCTGGTGGTC TCCTGTCTAT TGGCAGGAAC AGGCAGCCTT  5
PR-0001   ATGGGTACTA TAATTCAATT TCTGGTGGTC TCCTGTCTAT TGGCAGGAGC AGGCAGCCTT  3
W3A-0001  ATGGGTACTA TAATTCAATT TCTGGTGGTC TCCTGTCTAT TGGCAGGAGC AGGCAGCCTT  3
WR-0001   ATGGGTACTA TTATTCAATT TCTGGTGGTC TCCTGTCTAT TGGCAGGAGC AGGCAGCCTT  4

CV-0061   GATCCAGCAG CCCTCATGCA AATCGGTGTC ATTCCAACAA ATGTCCGGCA ACTTATGTAT
CPV-0061  GATCCAGCAG CCCTCATGCA AATCGGTGTC ATTCCAACAA ATGTCCGGCA ACTTATGTAT
PR-0061   GATCCAGCAG CCCTCATGCA AATCGGTGTC ATTCCAACAA ATGTCCGGCA ACTTATGTAT
W3A-0061  GATCCAGCAG CCCTCATGCA AATCGGTGTC ATTCCAACAA ATGTCCGGCA ACTTATGTAT
WR-0061   GATCTAGCAG CCCTCATGCA AATCGGTGTC ATTCCAACAA ATGTCCGGCA ACTTATGTAT  1

CV-0121   TATACTGAGG CCTCATCAGC ATTCATTGTT GTGAAGTTAA TGCCTACAAT TGACTCGCCG
CPV-0121  TATACTGAGG CTTCATCAGC ATTCATTGTT GTGAAGTTAA TGCCTACAAT TGACTCGCCG  1
PR-0121   TATACTGAGG CCTCATCAGC ATTCATTGTT GTGAAGTTAA TGCCTACAAT TGACTCGCCG
W3A-0121  TATACTGAGG CCTCATCAGC ATTCATTGTT GTGAAGTTAA TGCCTACAAT TGACTCGCCG
WR-0121   TATACTGAGG CCTCATCGGC ATTCATTGTT GTGAAGTTAA TGCCTACAAT TGACTCGCCG  1

CV-0181   ATTAGTGGAT GTAATATAAC ATCAATTTCA AGCTATAATG CAACAGTGAC AAAACTCCTA
CPV-0181  ATTAGTGGGT GTAATATAAC ATCCATTTCA AGCTATAATG CAACAATGAC AAAACTTCTA  4
PR-0181   ATTAGTGGAT GTAATATAAC ATCAATTTCA AGCTATAATG CAACAGTGAC AAAACTCCTA
W3A-0181  ATTAGTGGAT GTAATATAAC ATCAATTTCA AGCTATAATG CAACAGTGAC AAAACTCCTA
WR-0181   ATTAGTGGAT GTAATATAAC ATCAATTTCA AGCTATAATG CAACAGTGAC AAAACTCCTA
```

Figure 10A
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CV-0241   CAGCCGATCG GTGAGAATTT GGAGACGATT AGGAACCAGT TGATTCCAAC TCGGAGGAGA
          |||||||||| |||||||||| |||||||||  ||| |||||| |||||||||| ||||||||||
CPV-0241  CAGCCGATCG GTGAGAATTT AGAGACGATT AGGTACCAGT TGATTCCAAC TCGGAGGAGA  2
          |||||||||| |||||||||| ||  |||||| ||| |||||| |||||||||| ||||||||||
PR-0241   CAGCCGATCG GTGAGAATTT GGAAACGATT AGGAACCAGT TGATTCCAAC TCGGAGGAGA  1
          |||||||||| |||||||||| |||  |||||| |||||||||| |||||||||| ||||||||||
W3A-0241  CAGCCGATCG GTGAGAATTT GGAGACGATT AGGAACCAGT TGATTCCAAC TCGGAGGAGA
          |||||||||| |||||||||| |||||||||| |||||||||| |||||||||| |||||| |||
WR-0241   CAGCCGATCG GTGAGAATTT GGAGACGATT AGGAACCAGT TGATTCCAAC TCGGAGAAGA  1

CV-0301   CGCCGGTTTG CAGGGGTGGT GATTGGATTA GCTGCATTAG GAGTAGCTAC TGCCGCACAA
          |||||||||| |||||||||| |||||||||| || ||||||| |||||||||| ||| |||||
CPV-0301  CGCCGGTTTG CAGGGGTGGT GATTGGATTA GCCGCATTAG GAGTAGCTAC TGCAGCACAG  3
          |||||||||| |||||||||| |||||||||| || ||||||| |||||||||| ||| ||||||
PR-0301   CGCCGGTTTG CAGGGGTGGT GATTGGATTA GCTGCATTAG GAGTAGCTAC TGCCGCACAG  1
          |||||||||| |||||||||| |||||||||| |||||||||| |||||||||| ||||||||||
W3A-0301  CGCCGGTTTG CAGGGGTGGT GATTGGATTA GCTGCATTAG GAGTAGCTAC TGCCGCACAG  1
          |||||||||| |||||||||| |||||||||| |||||||||| |||||||||| ||||||||||
WR-0301   CGCCGGTTTG CAGGGGTGGT GATTGGATTA GCTGCATTAG GAGTAGCTAC TGCCGCACAG  1

CV-0361   GTCACTGCCG CAGTAGCACT AGTTAAGGCA AATGAAAATA CTGCGGCTAT ACTCAATCTC
          |||||||||| |||||||||| ||| |||||  ||| |||||  ||| |||||| ||||||||||
CPV-0361  GTCACTGCCG CAGTAGCACT AGTAAAGGCG AATAAAAATG CTGTGGCTAT ACTCAATCTC  5
          |||||||||| |||||||||| |||||||||  |||||||||| ||| |||||| ||||||||||
PR 0361   GTCACTGCCG CAGTAGCACT AGTAAAGGCA AATAAAAATG CTGCGGCTAT ACTCAATCTC  3
          |||||||||| |||| ||||| |||||||||| ||| |||||| |||||||||| ||||||||||
W3A-0361  GTCACTGCCG CAGTGGCACT AGTAAAGGCA AATGAAAATG CTGCGGCTAT ACTCAATCTC  3
          |||||||||| |||| ||||| |||||||||| |||||||||| |||||||||| ||||||||||
WR-0361   GTCACTGCCG CAGTAGCACT AGTAAAGGCA AATGAAAATG CTGCGGCTAT ACTCAATCTC  2

CV-0421   AAAAATGCAA TCCAAAAAAC AAATGCAGCA GTTGCAGATG TGGTCCAGGC CACACAATCA
          ||||| |||| |||||||||| |||||||||| |||||||| | |||| ||||| ||||||||||
CPV-0421  AAAAACGCAA TCCAAAAAAC AAATGCAGCA GTTGCAGACG TGGTTCAGGC CACACAATCA  3
          ||||| |||| |||||||||| |||| ||||| |||||||| | |||| ||||| ||||||||||
PR-0421   AAAAATGCAA TCCAAAAAAC AAATACAGCA GTTGCAGATG TGGTCCAGGC CACACAATCA  1
          |||||||||| |||||||||| |||| ||||| |||||||||| |||||||||| ||||||||||
W3A-0421  AAAAATGCAA TCCAAAAAAC AAATGCAGCA GTTGCAGATG TGGTCCAGGC CACACAATCA
          |||||||||| |||||||||| |||||||||| |||||||||| |||||||||| ||||||||||
WR-0421   AAAAATGCAA TCCAAAAAAC AAATGCAGCA GTTGCAGATG TGGTCCAGGC CACACAATCA

CV-0481   CTAGGAACGG CAGTTCAAGC AGTTCAAGAT CACATAAACA GTGTGATAAG TCCAGCAATT
          |||||||||| |||||||||| |||||||||| |||||||| | ||||| |||| ||||||||||
CPV-0481  CTAGGAACGG CAGTTCAAGC AGTTCAAGAT CACATAAATA GTGTGGTAAG TCCAGCAATT  2
          |||||||||| |||||||||| |||||||||| |||||||| | |||||||||| ||||||||||
PR-0481   CTAGGAACGG CAGTTCAAGC AGTTCAAGAT CACATAAACA GTGTGGTAAG TCCAGCAATT  1
          |||||||||| |||||||||| |||||||||| |||||||||| |||||||||| ||||||||||
W3A-0481  CTAGGAACGG CAGTTCAAGC AGTTCAAGAT CACATAAACA GTGTGGTAAG TCCAGCAATT  1
          |||||||||| |||||||||| |||||||||| |||||||||| |||||||||| ||||||||||
WR-0481   CTAGGAACGG CAGTTCAAGC AGTTCAAGAT CACATAAACA GTGTGGTAAG TCCAGCAATT  1
```

Figure 10A
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CV-0541   ACAGCAGCCA ATTGTAAGGC CCAAGATGCT ATCATTGGCT CAATCCTCAA TCTCTATTTG
          |||||||||| |||| || || |||||||||| |||||||||| |||| ||||| ||||||||||
CPV-0541  ACAGCAGCCA ATTGCAAAGC CCAAGATGCT ATCATTGGCT CAATTCTCAA TCTCTATTTG  3
          |||||||||| |||| || || |||||||||| |||||||||| |||| ||||| ||||||||||
PR-0541   ACAGCAGCCA ATTGTAAGGC CCAAGATGCT ATCATTGGCT CAATCCTCAA TCTCTATTTG
          |||||||||| |||||||||| |||||||||| |||||||||| |||||||||| ||||||||||
W3A-0541  ACAGCAGCCA ATTGTAAGGC CCAAGATGCT ATCATTGGCT CAATCCTCAA TCTCTATTTG
          |||||||||| |||||||||| |||||||||| |||||||||| |||||||||| ||||||||||
WR-0541   ACAGCAGCCA ATTGTAAGGC CCAAGATGCT ATCATTGGCT CAATCCTCAA TCTCTATTTG

CV-0601   ACCGAGTTGA CAACTATCTT CCACAATCAA ATTACAAACC CTGCATTGAG TCCTATTACA
          |||||||||| |||||||||| |||||||||| |||||||||| | |||||||| ||||||||||
CPV-0601  ACCGAGTTGA CAACTATCTT CCACAATCAA ATTACAAACC CCGCATTGAG TCCTATTACA  1
          |||||||||| |||||||||| |||||||||| |||||||||| | |||||||| ||||||||||
PR-0601   ACCGAGTTGA CAACTATCTT CCACAATCAA ATTACAAACC CTGCATTGAG TCCTATTACA
          |||||||||| |||| ||||| |||||||||| |||||||||| |||||||||| ||| ||||||
W3A-0601  ACCGAGTTGA CAACCATCTT CCACAATCAA ATTACAAACC CTGCATTGAG TCCCATTACA  2
          |||||||||| |||||||||| |||||||||| |||||||||| |||||||||| ||||||||||
WR-0601   ACCGAGTTGA CAACCATCTT CCACAATCAA ATTACAAACC CTGCATTGAG TCCCATTACA  2

CV-0661   ATTCAAGCTT TAAGGATCCT ACTGGGGAGT ACCTTGCCGA CTGTGGTCGA AAAATCTTTC
          |||||||||| | |||||||| ||| |||||| |||||||||| | |||||||| ||||||||||
CPV-0661  ATTCAAGCTT TGAGGATCCT ACTAGGGAGT ACCTTGCCGA CCGTGGTCGA AAAATCTTTC  3
          |||||||||| | |||||||| ||| |||||| |||||||||| | |||||||| ||||||||||
PR-0661   ATTCAAGCTT TAAGGATCCT ACTGGGGAGT ACCTTGCCGA CTGTGGTCGA AAAATCTTTC
          |||||||||| |||||||||| |||||||||| |||||||||| |||||||||| ||||||||||
W3A-0661  ATTCAAGCTT TAAGGATCCT ACTGGGGAGT ACCTTGCCGA CTGTGGTCGA AAAATCTTTC
          |||||||||| |||||||||| |||||||||| |||||||||| |||||||||| ||||||||||
WR-0661   ATTCAAGCTT TAAGGATCCT ACTGGGGAGT ACCTTGCCGA CTGTGGTCGA AAAATCTTTC

CV-0721   AATACCCAGA TAAGTGCAGC TGAGCTTCTC TCATCAGGGT TGTTGACAGG CCAGATTGTG
          |||||||||| |||||||||| |||||||||| |||||||||| | |||||||| ||||||||||
CPV-0721  AATACCCAGA TAAGTGCAGC TGAGCTTCTC TCATCAGGGT TATTGACAGG CCAGATTGTG  1
          |||||||||| |||||||||| |||||||||| |||||||||| |||||||||| ||||||||||
PR-0721   AATACCCAGA TAAGTGCAGC TGAGCTTCTC TCATCAGGGT TATTGACAGG CCAGATTGTG  1
          |||||||||| |||||||||| |||||||||| |||||||||| |||||||||| ||||||||||
W3A-0721  AATACCCAGA TAAGTGCAGC TGAGCTTCTC TCATCAGGGT TATTGACAGG CCAGATTGTG  1
          |||||||||| |||||||||| |||||||||| |||||||||| |||||||||| ||||||||||
WR-0721   AATACCCAGA TAAGTGCAGC TGAGCTTCTC TCATCAGGGT TATTGACAGG CCAGATTGTG  1

CV-0781   GGATTAGATT TGACCTATAT GCAGATGGTC ATAAAAATTG AGCTGCCAAC TTTAACTGTA
          |||||||||| ||||||| || |||||||||| |||||||||| |||||||||| ||||||||||
CPV-0781  GGATTAGATT TGACCTACAT GCAGATGGTC ATAAAAATTG AGCTGCCAAC TTTAACTGTA  1
          |||||||||| ||||||| || |||||||||| |||||||||| |||||||||| ||||||||||
PR-0781   GGATTAGATT TGACCTATAT GCAGATGGTC ATAAAAATTG AGCTGCCAAC TTTAACTGTA
          |||||||||| |||||||||| |||||||||| |||||||||| |||||||||| ||||||||||
W3A-0781  GGATTAGATT TGACCTATAT GCAGATGGTC ATAAAAATTG AGCTGCCAAC TTTAACTGTA
          |||||||||| |||||||||| |||||||||| |||||||||| |||||||||| ||||||||||
WR-0781   GGATTAGATT TGACCTATAT GCAGATGGTC ATAAAAATTG AGCTGCCAAC TTTAACTGTA
```

Figure 10A
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CV-0841   CAACCTGCAA CCCAGATCAT AGATCTGGCC ACCATTTCTG CATTCATTAA CAATCAAGAA
          ||||||||||| |||||||||| |||||||| | |||||||||| |||||||||| ||||||||||
CPV-0841  CAACCTGCAA CCCAGATCAT AGATCTGGTC ACCATTTCTG CATTCATTAA CAATCAAGAA  1
          ||||||||||| |||||||||| |||||||| | |||||||||| |||||||||| ||||||||||
PR-0841   CAACCTGCAA CCCAGATCAT AGATCTGGCC ACCATTTCTG CATTCATTAA CAATCAAGAA
          ||||||||||| |||||||||| |||||||||| |||||||||| |||||||||| ||||||||||
W3A-0841  CAACCTGCAA CCCAGATCAT AGATCTGGCC ACCATTTCTG CATTCATTAA CAATCAAGAA
          ||||||||||| |||||||||| |||||||||| |||||||||| |||||||||| ||||||||||
WR-0841   CAACCTGCAA CCCAGATCAT AGATCTGGCC ACCATTTCTG CATTCATTAA CAATCAAGAA

CV-0901   GTCATGGCCC AATTACCAAC ACGTGTTATT GTGACTGGCA GCTTGATCCA AGCCTATCCC
          || ||||||| |||||||||| |||||||||| |||||||||| |||||||||| ||||||||||
CPV-0901  GTTATGGCCC AATTACCAAC ACGTGTTATT GTGACTGGCA GCTTGATCCA AGCCTATCCC  1
          || ||||||| |||||||||| |||||||||| |||||||||| |||||||||| ||||||||||
PR-0901   GTCATGGCCC AATTACCAAC ACGTGTTATT GTGACTGGCA GCTTGATCCA AGCCTATCCC
          |||||||||| |||||||||| |||||||||  |||||||||| |||||||||| ||||||||||
W3A-0901  GTCATGGCCC AATTACCAAC ACGTGTTATG GTGACTGGCA GCTTGATCCA AGCCTATCCC  1
          |||||||||| |||||||||| |||||||||| |||||||||| |||||||||| ||||||||||
WR-0901   GTCATGGCCC AATTACCAAC ACGTGTTATG GTGACTGGCA GCTTGATCCA AGCCTATCCC  1

CV-0961   GCATCGCAAT GCACTATTAC ACCCAACACT GTGTACTGTA GGTATAATGA TGCCCAAGTA
          |||||||||| |||||||  ||  ||||||||| |||||||||| |||||||||| ||||||||||
CPV-0961  GCATCGCAAT GCACTATCAC CCCCAACACT GTGTACTGTA GGTATAATGA TGCCCAAGTA  2
          |||||||||| |||||||  ||  ||||||||| |||||||||| |||||||||| ||||||||||
PR-0961   GCATCGCAAT GCACTATTAC ACCCAACACT GTGTACTGTA GGTATAATGA TGCCCAAGTA
          |||||||||| ||||  ||||| |||||||||| |||||||||| |||||||||| ||||||||||
W3A-0961  GCATCGCAAT GCACCATTAC ACCCAACACT GTGTACTGTA GGTATAATGA TGCCCAAGTA  1
          |||||||||| |||||||||| |||||||||| |||||||||| |||||||||| ||||||||||
WR-0961   GCATCGCAAT GCACCATTAC ACCCAACACT GTGTACTGTA GGTATAATGA TGCCCAAGTA  1

CV-1021   CTCTCAGATG ATACGATGGC TTGCCTCCAA GGTAACTTGA CAAGATGCAC CTTCTCTCCA
          |||||||||| |||||||||| |||||||||| |||||||||| |||||||||| ||||||||||
CPV-1021  CTCTCAGATG ATACGATGGC TTGCCTCCAA GGTAACTTGA CAAGATGCAC CTTCTCTCCA
          |||||||||| |||||||||| |||||||||| |||||||||| |||||||||| |||||||||
PR-1021   CTCTCAGATG ATACGATGGC TTGCCTCCAA GGTAACTTGA CAAGATGCAC CTTCTCTCCG  1
          |||||||||  ||||  ||||| |||||||||| |||||||||| ||||||||||  |||||||||
W3A-1021  CTCTCAGATG ATACTATGGC TTGCCTCCAA GGTAACTTGA CAAGATGCAC CTTCTCTCCA  1
          |||||||||| |||||||||| |||||||||| |||||||||| |||||||||| ||||||||||
WR-1021   CTCTCAGATG ATACTATGGC TTGCCTCCAA GGTAACTTGA CAAGATGCAC CTTCTCTCCA  1

CV-1081   GTGGTTGGGA GCTTTCTCAC TCGATTCGTG CTGTTCGATG GAATAGTTTA TGCAAATTGC
          |||||||||| |||||||||| |||||||||| |||||  |||| |||||||||| ||||||||||
CPV-1081  GTGGTTGGGA GCTTTCTCAC TCGATTCGTG CTGTTTGATG GAATAGTTTA TGCAAATTGC  1
          |||||||||  |||||||||| |||||||  || |||||  |||| |||||||||| ||||||||||
PR-1081   GTGGTTGGGA GCTTTCTCAC TCGATTCATG CTGTTCGATG GAATAGTTTA TGCAAATTGC  1
          |||||||||| |||||||||| |||||||  || |||||||||| |||||||||| ||||||||||
W3A-1081  GTGGTTGGGA GCTTTCTCAC TCGATTCGTG CTGTTCGATG GAATAGTTTA TGCAAATTGC
          |||||||||| |||||||||| |||||||||| |||||||||| |||||||||| ||||||||||
WR-1081   GTGGTTGGGA GCTTTCTCAC TCGATTCGTG CTGTTCGATG GAATAGTTTA TGCAAATTGC
```

Figure 10 A

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CV-1141   AGGTCGATGC TGTGCAAGTG CATGCAACCT GCTGCCGTGA TCCTACAGCC GAGTTCATCC
          ||||||||||  ||||||||||| |||||| ||| ||||| || | |||||||||| ||| ||||||
CPV-1141  AGGTCGATGT TGTGCAAGTG CATGCAGCCT GCTGCTGTTA TCCTACAGCC GAGCTCATCC  5
          ||||||||||  | ||||||||| |||||||||| |||||||| | |||||||||| ||| ||||||
PR-1141   AGGTCGATGT TATGCAAGTG CATGCAGCCT GCTGCTGTGA TCCTACAGCC GAGTTCATCC  4
          ||||||||||  | ||||||||| |||||| ||| |||||||||| |||||||||| ||||||||||
W3A-1141  AGGTCGATGT TGTGCAAGTG CATGCAACCT GCTGCTGTGA TCCTACAGCC GAGTTCATCC  2
          ||||||||||  ||||||||||| |||||||||| |||||||||| |||||||||| ||||||||||
WR-1141   AGGTCGATGT TGTGCAAGTG CATGCAACCT GCTGCTGTGA TCCTACAGCC GAGTTCATCC  2

CV-1201   CCTGTAACTG TCATTGACAT GCACAAATGT GTGAGTCTGC AGCTTGACGA TCTCAGATTC
          ||||||||||  ||||||||||| | ||||||||| |||||||||| |||||||| | ||||||||||
CPV-1201  CCTGTAACTG TCATTGACAT GTACAAATGT GTGAGTCTGC AGCTTGACAA TCTCAGATTC  2
          ||||||||||  ||||||||||| ||||||||||| |||||||||| |||||||||| ||||||||||
PR-1201   CCTGTAACTG TCATTGACAT GTACAAATGT GTGAGTCTGC AGCTTGACAA TCTCAGATTC  2
          ||||||||||  ||||||||||| ||||||||||| |||||||||| |||||||||| ||||||||||
W3A-1201  CCTGTAACTG TCATTGACAT GTACAAATGT GTGAGTCTGC AGCTTGACAA TCTCAGATTC  2
          ||||||||||  ||||||||||| ||||||||||| |||||||||| |||||||||| ||||||||||
WR-1201   CCTGTAACTG TCATTGACAT GTACAAATGT GTGAGTCTGC AGCTTGACAA TCTCAGATTC  2

CV-1261   ACCATCACTC AATTGGCCAA TGTAACCTAC AATAGCACCA TCAAGCTTGA AACATCCCAG
          ||||||||||  ||||||||||| | ||||||||| |||||||||| |||||||||| ||||||||||
CPV-1261  ACCATCACTC AATTGGCCAA TATAACCTAC AATAGCACCA TCAAGCTTGA AACATCCCAG  1
          ||||||||||  ||||||||||| | ||||||||| |||||||||| |||||||||| ||||||||||
PR-1261   ACCATCACTC AATTGGCCAA TGTAACCTAC AATAGCACCA TCAAGCTTGA AACATCCCAG
          ||||||||||  ||||||||||| ||||||||||| |||||||||| |||||||||| | ||||||||
W3A-1261  ACCATCACTC AATTGGCCAA TGTAACCTAC AATAGCACCA TCAAGCTTGA ATCATCCCAG  1
          ||||||||||  ||||||||||| ||||||||||| |||||||||| |||||||||| ||||||||||
WR-1261   ACCATCACTC AATTGGCCAA TGTAACCTAC AATAGCACCA TCAAGCTTGA ATCATCCCAG  1

CV-1321   ATCTTGCCTA TTGATCCGTT GGATATATCC CAGAATTTAG CTGCGGTGAA TAAGAGTCTA
          ||||||||||  | ||||||||| |||||||||| |||||| ||| |||||||||| ||||||||||
CPV-1321  ATCTTGCCTA TCGATCCGTT GGATATATCC CAGAATCTAG CTGCGGTGAA TAAGAGTCTA  2
          ||||||||||  | ||||||||| |||||||||| |||||||||| |||||||||| ||||||||||
PR-1321   ATCTTGCCTA TTGATCCGTT GGATATATCC CAGAATCTAG CTGCGGTGAA TAAGAGTCTA  1
          ||||||  ||| |||||||||| |||||||||| || ||||||| |||||||||| ||||||||||
W3A-1321  ATCTTGTCTA TTGATCCGTT GGATATATCC CAAAATCTAG CTGCGGTGAA TAAGAGTCTA  3
          ||||||  ||| |||||||||| |||||||||| || ||||||| |||||||||| ||||||||||
WR-1321   ATCTTGCCTA TTGATCCGTT GGATATATCC CAGAATCTAG CTGCGGTGAA TAAGAGTCTA  1

CV-1381   AGTGATGCAC TACAACACTT AGCACAAAGT GACACATACC TTTCTGCAAT CACATCAGCT
          ||||||||||  ||||||||||| |||||||||| |||||||||| |||||||||| ||||||||||
CPV-1381  AGTGATGCAC TACAACACTT AGCACAAAGT GACACATACC TTTCTGCAAT CACATCAGCT
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W3A-1381  AGTGATGCAC TACAACACTT AGCACAAAGT GACACATATC TTTCTGCAAT CACATCAGCT  1
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Figure 10 *A*

```
CV-1441   ACGACTACAA GTGTATTATC CATAATAGCA ATCTGTCTTG GATCGTTAGG TTTAATATTA
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PR-1441   ACGACTACAA GTGTATTATC CATAATGGCA ATCTGTCTTG GATCGTTAGG TTTAATATTA  1
          |||||||||| |||||||||| |||||| ||| |||||||||| |||||||||| ||||||||||
W3A-1441  ACGACTACAA GTGTATTATC CATAATAGCA ATCTGTCTTG GATCGTTAGG TTTAATATTA
          |||||||||| |||||||||| |||||||||| |||||||||| |||||||||| ||||||||||
WR-1441   ACGACTACAA GTGTATTATC CATAATAGCA ATCTGTCTTG GATCGTTAGG TTTAATATTA

CV-1501   ATAATCTTGC TCAGTGTAGT TGTGTGGAAG TTATTGACCA TTGTCGCTGC TAATCGAAAT
          |||||||||| |||||||||| |||||||||| |||||||||| |||| ||||| ||||||||||
CPV-1501  ATAATCTTGC TCAGTGTAGT TGTGTGGAAG TTATTGACCA TTGTTGCTGC TAATCGAAAT  1
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PR-1501   ATAATCTTGC TCAGTGTAGT TGTGTGGAAG TTATTGACCA TTGTCACTGC TAATCGAAAT  1
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CV-1561   AGAATGGAGA ATTTTGTTTA TCATAATTCA GCATTCCACC ACCCACGATC TGATCTCAGT
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CPV-1561  AGAATGGAGA ATTTTGTTTA TCATAATTCA GCATTCCACC ACTCACGGTC TGATCTCAGT  2
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PR-1561   AGAATGGAGA ATTTTGTTTA TCATAATTCA GCATTCCACC ACTCACGATC TGATCTCAGT  1
          |||||||||| |||||||||| |||||| | | |||||||||| |||||||||| ||||||||||
W3A-1561  AGAATGGAGA ATTTTGTTTA TCATAAATAA GCATTCCACC ACTCACGATC TGATCTCAGT  3
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WR-1561   AGAATGGAGA ATTTTGTTTA TCATAAATAA GCATTCCACC ACTCACGATC TGATCTCAGT  3
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Termination Codon for W3A and WR (TAA)

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CV-1621   GAGAAAAATC AACCTGCAAC TCTTGGAACA AGATAA   //(SEQ ID NO:49)
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CPV-1621  GAGAAAAATC AACCTGCAAC TCTTGGAACA AGATAA   //(SEQ ID NO:25)
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PR-1621   GAGAAAAATC AACCTGCAAC TCTTGGAACA AGATAA   //(SEQ ID NO:27)
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W3A-1621  GAGAAAAATC AACCTGCAAC TCTTGGAACA AGATAA   //(SEQ ID NO:29)
          |||||||||| |||||||||| |||||||||| ||||||
WR-1621   GAGAAAAATC AACCTGCAAC TCTTGGAACA AGATAA   //(SEQ ID NO:31)
```

Termination Codon for CV, PR and CPV (TAA)

Figure 10 A
Page 6 of 6

```
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CPV 001  MGTRIQFLVV SCLLAGTGSL DPAALMQIGV IPTNVRQLMY YTEASSAFIV VKLMPTIDSP  4
PR  001  MGTIIQFLVV SCLLAGAGSL DPAALMQIGV IPTNVRQLMY YTEASSAFIV VKLMPTIDSP  2
W3A 001  MGTIIQFLVV SCLLAGAGSL DPAALMQIGV IPTNVRQLMY YTEASSAFIV VKLMPTIDSP  2
WR  001  MGTIIQFLVV SCLLAGAGSL DLAALMQIGV IPTNVRQLMY YTEASSAFIV VKLMPTIDSP  3

CV  061  ISGCNITSIS SYNATVTKLL QPIGENLETI RNQLIPTRRR RRFAGVVIGL AALGVATAAQ
CPV 061  ISGCNITSIS SYNATMTKLL QPIGENLETI RYQLIPTRRR RRFAGVVIGL AALGVATAAQ  2
PR  061  ISGCNITSIS SYNATVTKLL QPIGENLETI RNQLIPTRRR RRFAGVVIGL AALGVATAAQ
W3A 061  ISGCNITSIS SYNATVTKLL QPIGENLETI RNQLIPTRRR RRFAGVVIGL AALGVATAAQ
WR  061  ISGCNITSIS SYNATVTKLL QPIGENLETI RNQLIPTRRR RRFAGVVIGL AALGVATAAQ

CV  121  VTAAVALVKA NENTAAILNL KNAIQKTNAA VADVVQATQS LGTAVQAVQD HINSVISPAI
CPV 121  VTAAVALVKA NKNAVAILNL KNAIQKTNAA VADVVQATQS LGTAVQAVQD HINSVVSPAI  4
PR  121  VTAAVALVKA NKNAAAILNL KNAIQKTNTA VADVVQATQS LGTAVQAVQD HINSVVSPAI  3
W3A 121  VTAAVALVKA NENAAAILNL KNAIQKTNAA VADVVQATQS LGTAVQAVQD HINSVVSPAI  2
WR  121  VTAAVALVKA NENAAAILNL KNAIQKTNAA VADVVQATQS LGTAVQAVQD HINSVVSPAI  2

CV  181  TAANCKAQDA IIGSILNLYL TELTTIFHNQ ITNPALSPIT IQALRILLGS TLPTVVEKSF
CPV 181  TAANCKAQDA IIGSILNLYL TELTTIFHNQ ITNPALSPIT IQALRILLGS TLPTVVEKSF
PR  181  TAANCKAQDA IIGSILNLYL TELTTIFHNQ ITNPALSPIT IQALRILLGS TLPTVVEKSF
W3A 181  TAANCKAQDA IIGSILNLYL TELTTIFHNQ ITNPALSPIT IQALRILLGS TLPTVVEKSF
WR  181  TAANCKAQDA IIGSILNLYL TELTTIFHNQ ITNPALSPIT IQALRILLGS TLPTVVEKSF

CV  241  NTQISAAELL SSGLLTGQIV GLDLTYMQMV IKIELPTLTV QPATQIIDLA TISAFINNQE
CPV 241  NTQISAAELL SSGLLTGQIV GLDLTYMQMV IKIELPTLTV QPATQIIDLV TISAFINNQE  1
PR  241  NTQISAAELL SSGLLTGQIV GLDLTYMQMV IKIELPTLTV QPATQIIDLA TISAFINNQE
W3A 241  NTQISAAELL SSGLLTGQIV GLDLTYMQMV IKIELPTLTV QPATQIIDLA TISAFINNQE
WR  241  NTQISAAELL SSGLLTGQIV GLDLTYMQMV IKIELPTLTV QPATQIIDLA TISAFINNQE

CV  301  VMAQLPTRVI VTGSLIQAYP ASQCTITPNT VYCRYNDAQV LSDDTMACLQ GNLTRCTFSP
CPV 301  VMAQLPTRVI VTGSLIQAYP ASQCTITPNT VYCRYNDAQV LSDDTMACLQ GNLTRCTFSP
PR  301  VMAQLPTRVI VTGSLIQAYP ASQCTITPNT VYCRYNDAQV LSDDTMACLQ GNLTRCTFSP
W3A 301  VMAQLPTRVM VTGSLIQAYP ASQCTITPNT VYCRYNDAQV LSDDTMACLQ GNLTRCTFSP  1
WR  301  VMAQLPTRVM VTGSLIQAYP ASQCTITPNT VYCRYNDAQV LSDDTMACLQ GNLTRCTFSP  1

CV  361  VVGSFLTRFV LFDGIVYANC RSMLCKCMQP AAVILQPSSS PVTVIDMHKC VSLQLDDLRF
CPV 361  VVGSFLTRFV LFDGIVYANC RSMLCKCMQP AAVILQPSSS PVTVIDMYKC VSLQLDNLRF  2
PR  361  VVGSFLTRFM LFDGIVYANC RSMLCKCMQP AAVILQPSSS PVTVIDMYKC VSLQLDNLRF  3
W3A 361  VVGSFLTRFV LFDGIVYANC RSMLCKCMQP AAVILQPSSS PVTVIDMYKC VSLQLDNLRF  2
WR  361  VVGSFLTRFV LFDGIVYANC RSMLCKCMQP AAVILQPSSS PVTVIDMYKC VSLQLDNLRF  2
```

Figure 10B
Page 1 of 2

```
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CPV 421  TITQLANITY NSTIKLETSQ ILPIDPLDIS QNLAAVNKSL SDALQHLAQS DTYLSAITSA  1
PR  421  TITQLANVTY NSTIKLETSQ ILPIDPLDIS QNLAAVNKSL SDALQHLAQS DTYLSAITSA
W3A 421  TITQLANVTY NSTIKLESSQ ILSIDPLDIS QNLAAVNKSL SDALQHLAQS DTYLSAITSA  2
WR  421  TITQLANVTY NSTIKLESSQ ILPIDPLDIS QNLAAVNKSL SDALQHLAQS DTYLSAITSA  1

CV  481  TTTSVLSIIA ICLGSLGLIL IILLSVVVWK LLTIVAANRN RMENFVYHNS AFHHPRSDLS
CPV 481  TTTSVLSIIA ICLGSLGLIL IILLSVVVWK LLTIVAANRN RMENFVYHNS AFHHSRSDLS  1
PR  481  TTTSVLSIMA ICLGSLGLIL IILLSVVVWK LLTIVTANRN RMENFVYHNS AFHHSRSDLS  3
W3A 481  TTTSVLSIIA ICLGSLGLIL IILLSVVVWK LLTIVVANRN RMENFVYHK ← 529 AA     3
WR  481  TTTSVLSIIA ICLGSLGLIL IILLSVVVWK LLTIVAANRN RMENFVYHK ← 529 AA     2

CV  541  EKNQPATLGT R ← 551 AA   (SEQ ID NO:12)
CPV 541  EKNQPATLGT R ← 551 AA   (SEQ ID NO:26)
PR  541  EKNQPATLGT R ← 551 AA   (SEQ ID NO:28)
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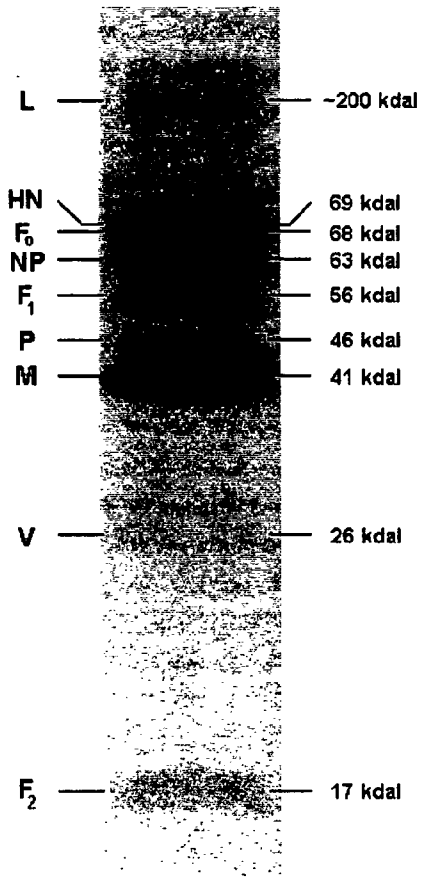
(SEQ ID NO:30)
(SEQ ID NO:32)

Figure 10 B
Page 2 of 2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V
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F2
17 kdal

Fig. 11

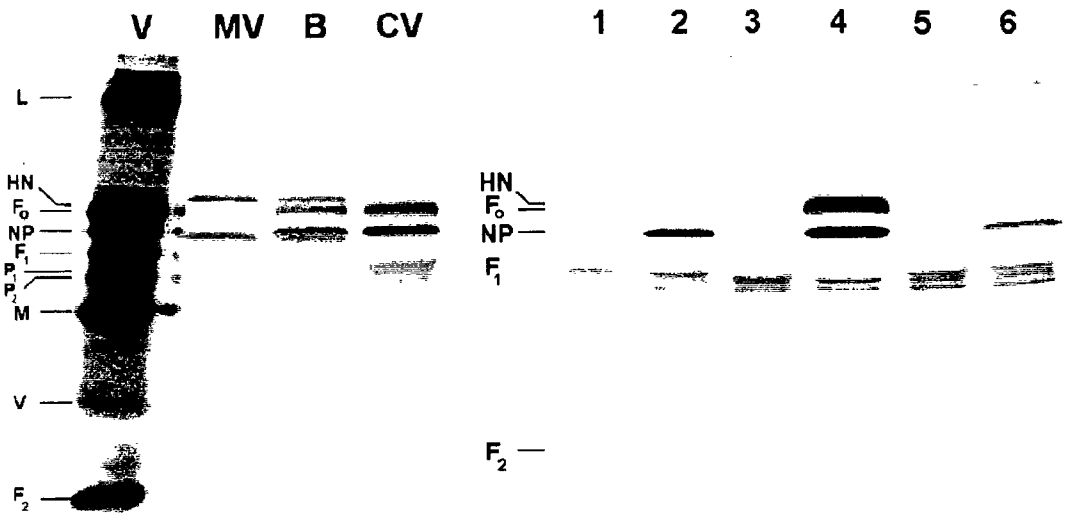


Fig. 12A

Fig. 12B

Fig. 12

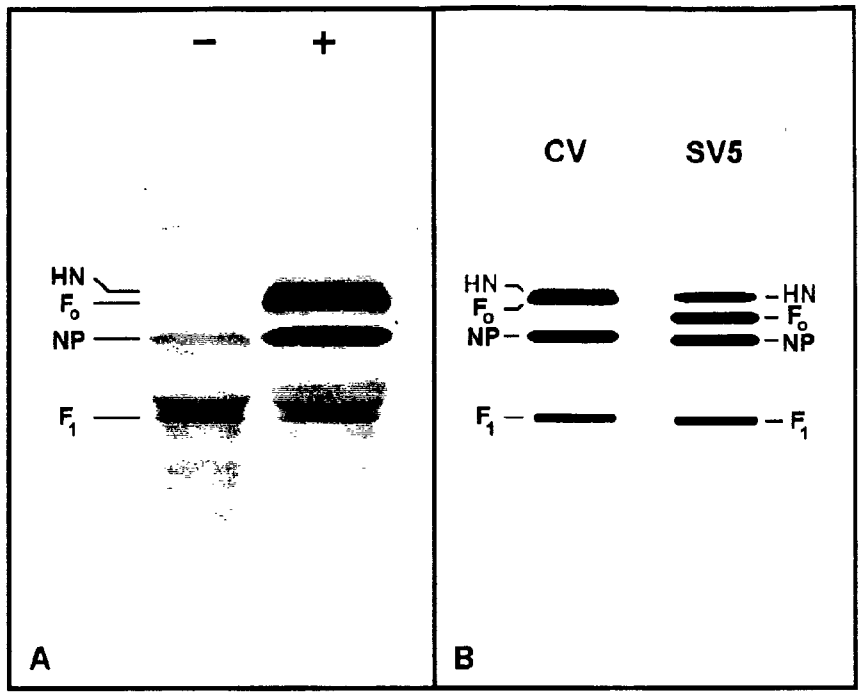


Fig. 13

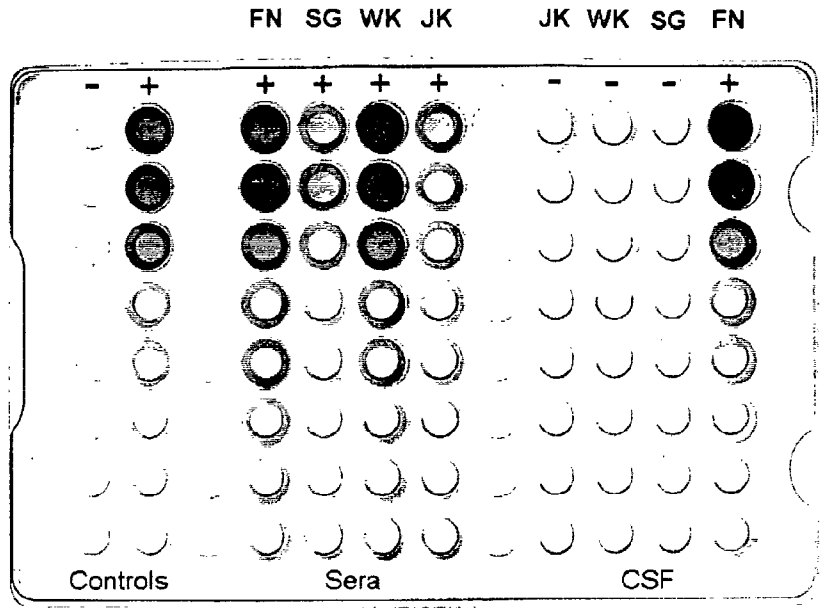
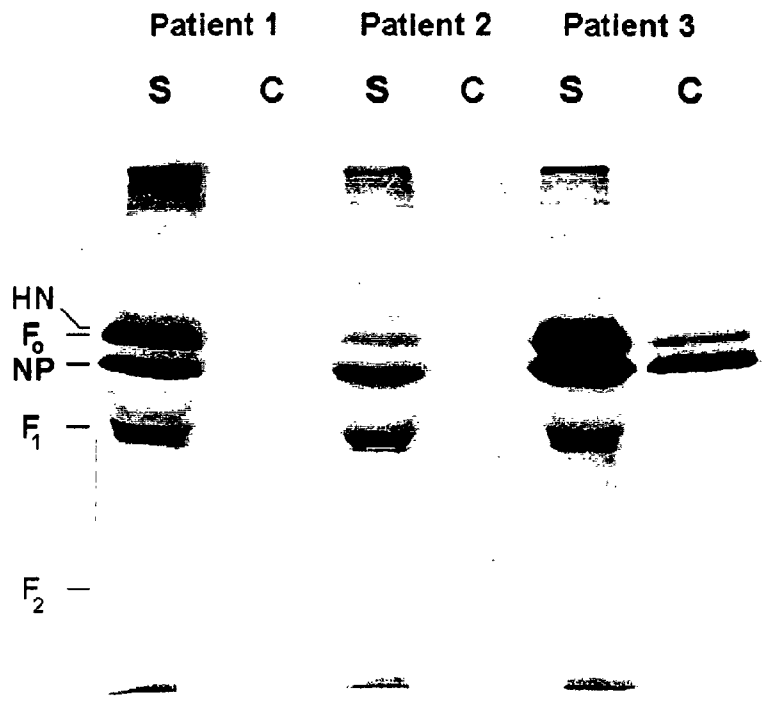


Fig. 14



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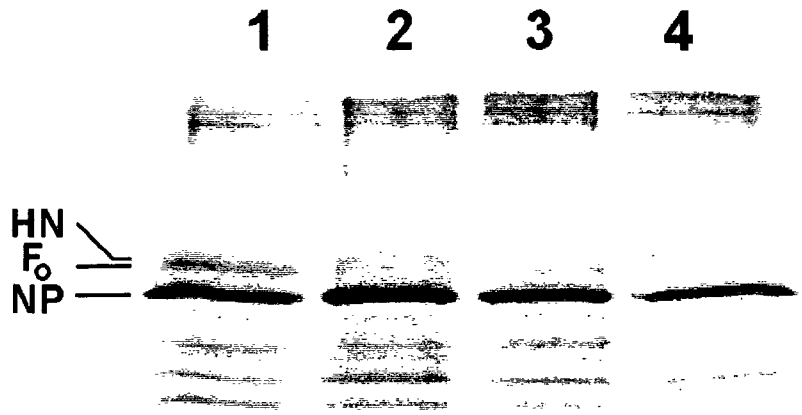
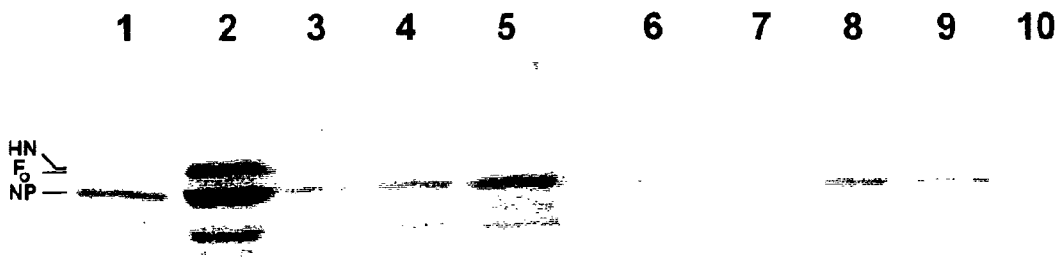


Fig. 16



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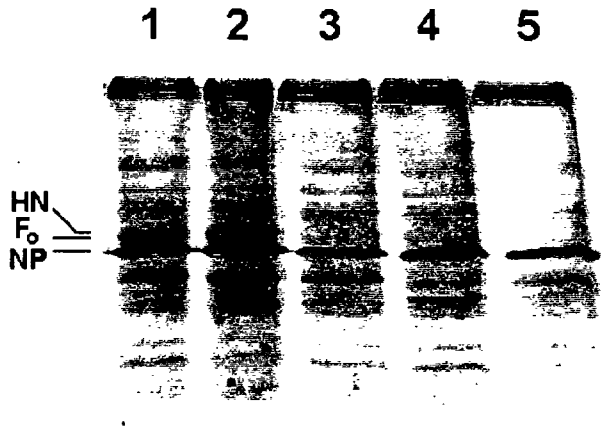

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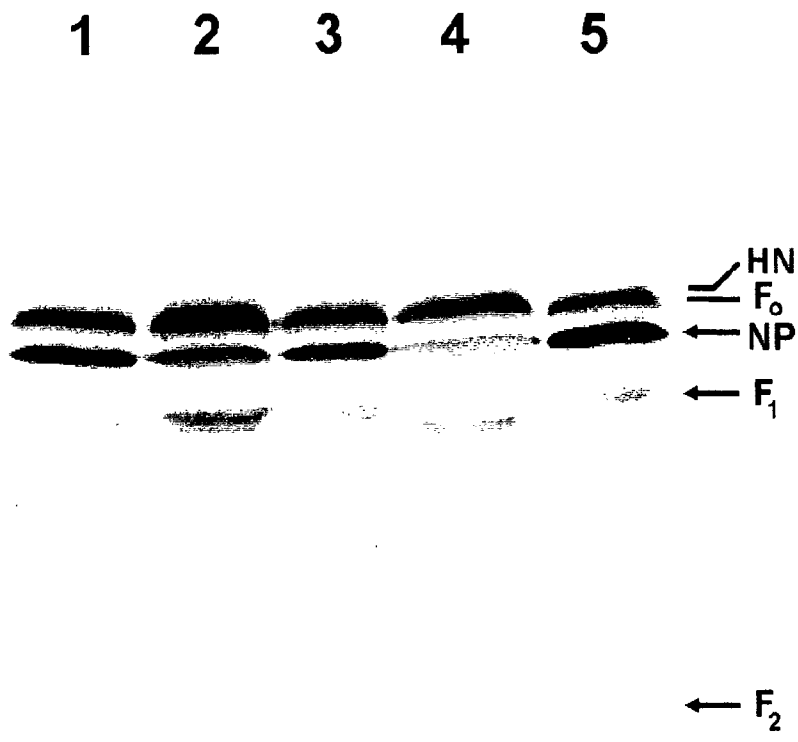

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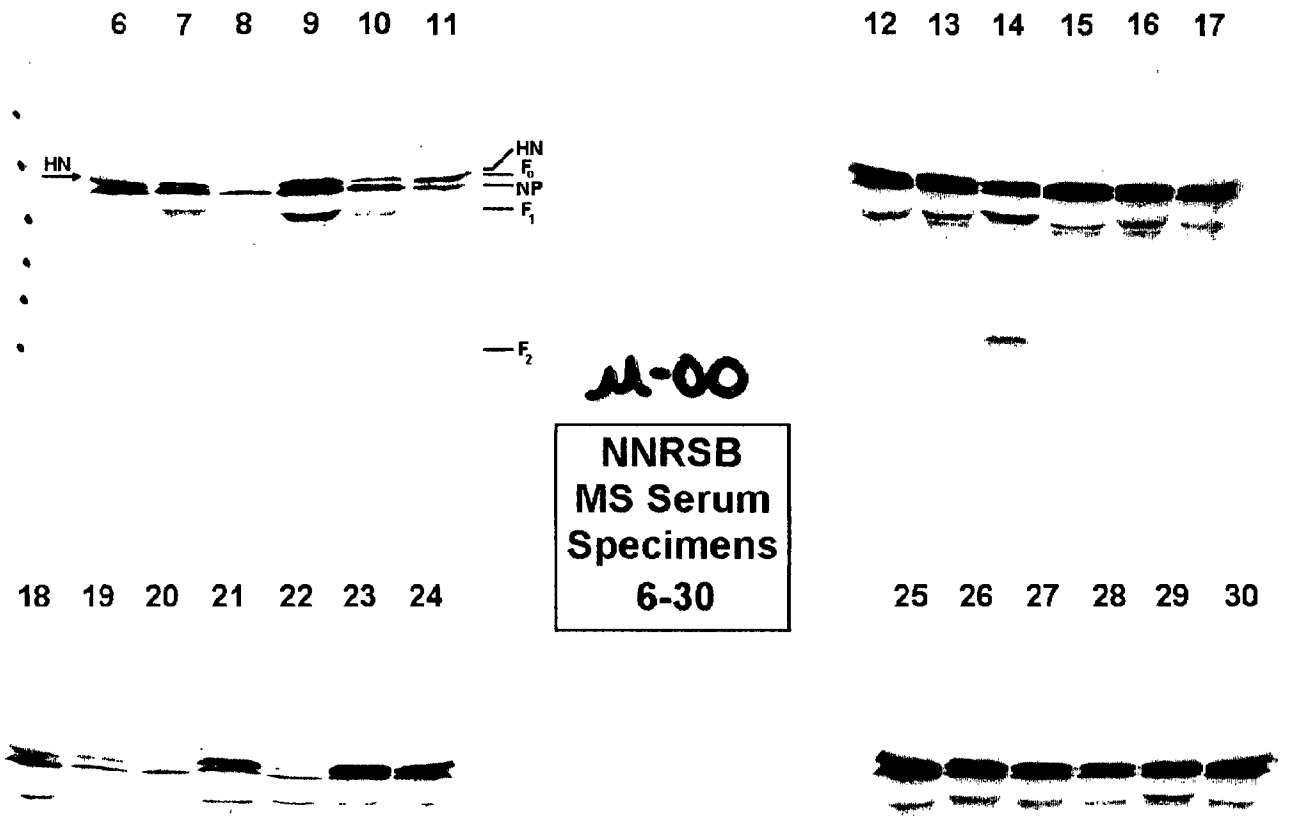
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Fig. 20

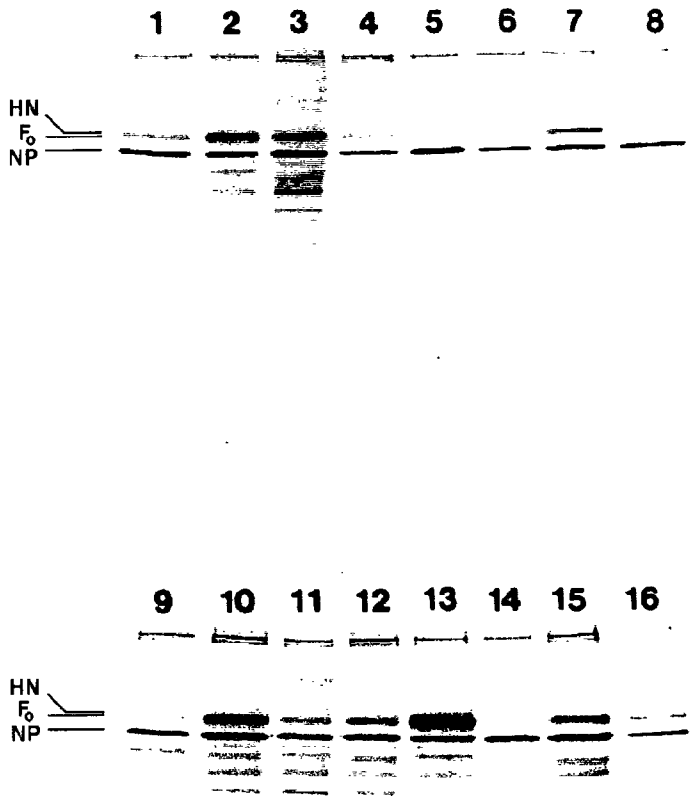


Fig. 21

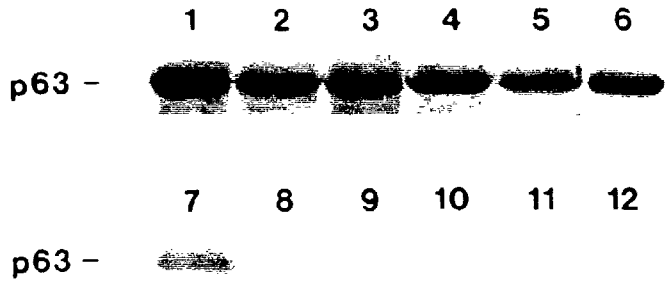
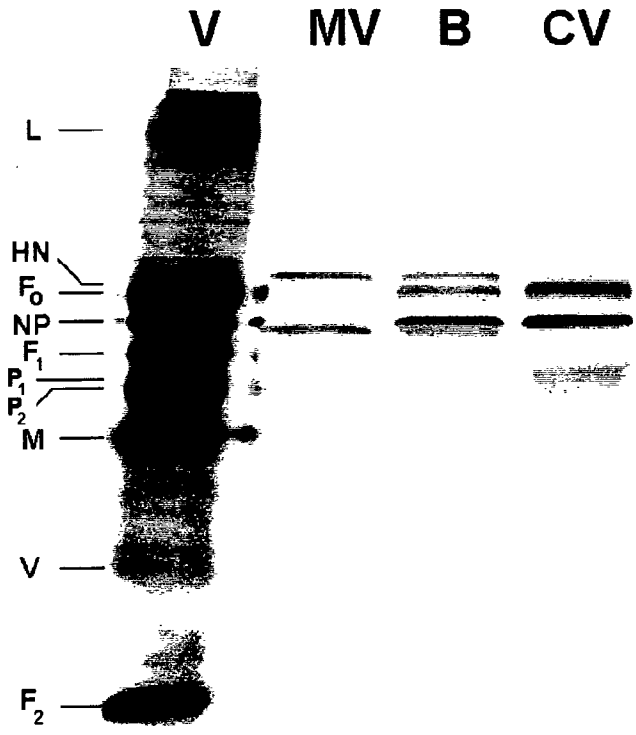


Fig. 22



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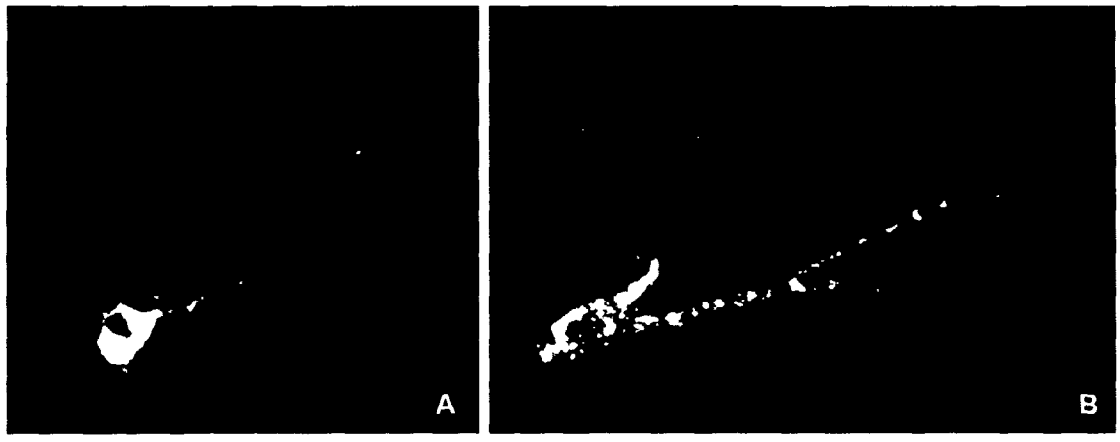

Fig. 24

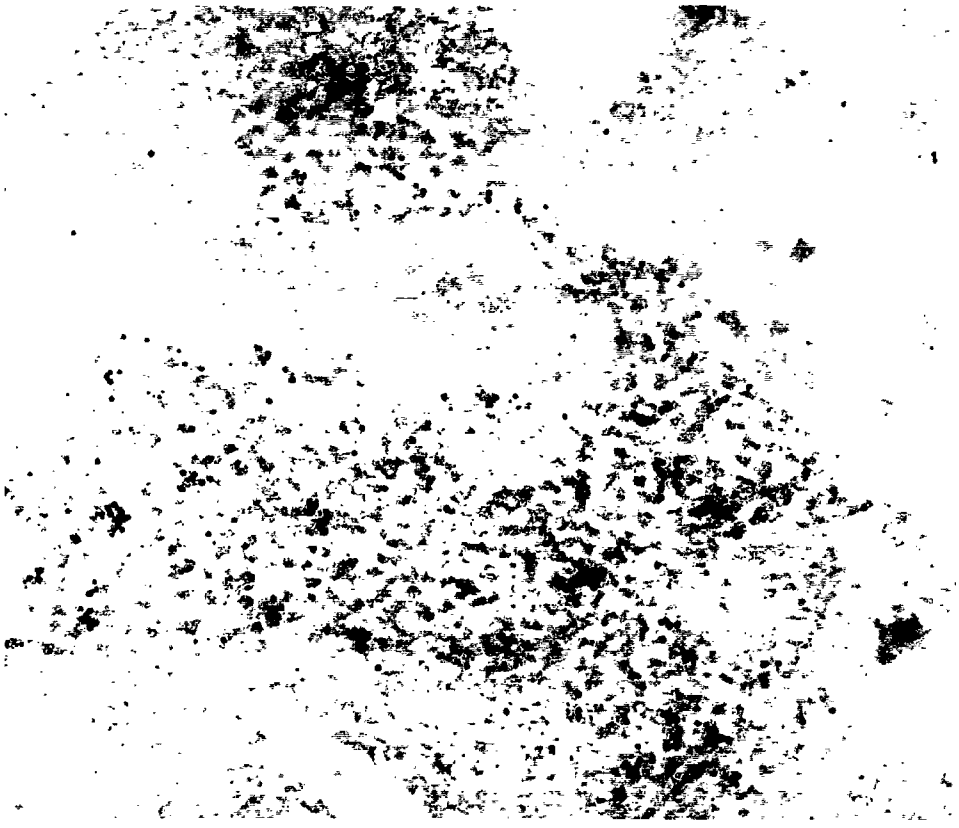

Fig. 25B

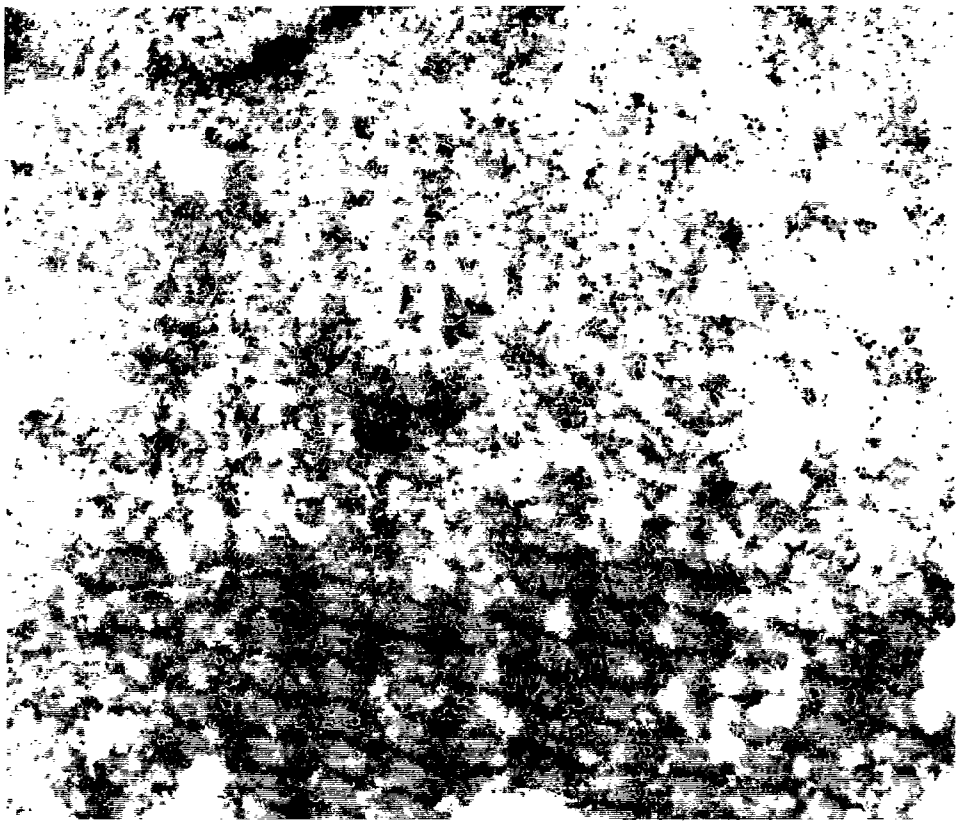

Fig. 25A

SEQUENCE LISTING

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Steven J. Robbins (Inventor)

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Ser Arg Leu Leu Leu Phe Cys Leu Arg Ile Val Leu Ser Asn Gly Ala
    50                  55                  60

agg gat tcc cat cgc ttt gga gca tta ctt aca atg ttt tcg cta cca   240
Arg Asp Ser His Arg Phe Gly Ala Leu Leu Thr Met Phe Ser Leu Pro
65                  70                  75                  80

tca gct aca atg ctc aat cat gtc aaa tta gct gac cag tca cca gaa   288
Ser Ala Thr Met Leu Asn His Val Lys Leu Ala Asp Gln Ser Pro Glu
                85                  90                  95

gct gat atc gaa agg gta gag atc gat ggc ttt gag gag gga tca ttc   336
Ala Asp Ile Glu Arg Val Glu Ile Asp Gly Phe Glu Glu Gly Ser Phe
            100                 105                 110

cgc tta att ccc aat gct cgc tca ggt atg agc cgt gga gag atc aat   384
Arg Leu Ile Pro Asn Ala Arg Ser Gly Met Ser Arg Gly Glu Ile Asn
        115                 120                 125

gcc tat gct gca ctt gca gaa gat cta cct gac aca cta aac cat gca   432
Ala Tyr Ala Ala Leu Ala Glu Asp Leu Pro Asp Thr Leu Asn His Ala
```

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    130                 135                 140

aca cct ttc gtt gat tcc gaa gtc gag gga act gca tgg gac gag att   480
Thr Pro Phe Val Asp Ser Glu Val Glu Gly Thr Ala Trp Asp Glu Ile
145                 150                 155                 160

gag act ttc tta gat atg tgt tac agt gtc cta atg cag gca tgg ata   528
Glu Thr Phe Leu Asp Met Cys Tyr Ser Val Leu Met Gln Ala Trp Ile
                165                 170                 175

gtg act tgc aag tgc atg act gcg cca gac caa cct gct gct tct att   576
Val Thr Cys Lys Cys Met Thr Ala Pro Asp Gln Pro Ala Ala Ser Ile
            180                 185                 190

gag aaa cgc ctg caa aaa tat cgt cag caa ggc agg atc aac cca aga   624
Glu Lys Arg Leu Gln Lys Tyr Arg Gln Gln Gly Arg Ile Asn Pro Arg
        195                 200                 205

tat ctc ctg caa ccg gag gct cga cga ata atc cag aat gta atc cgg   672
Tyr Leu Leu Gln Pro Glu Ala Arg Arg Ile Ile Gln Asn Val Ile Arg
    210                 215                 220

aag gga atg gtg gtc aga cat ttc ctc acc ttt gaa ctg cag ctt gcc   720
Lys Gly Met Val Val Arg His Phe Leu Thr Phe Glu Leu Gln Leu Ala
225                 230                 235                 240

cga gca caa agc ctt gta tca aat agg tat tat gct atg gta ggg gat   768
Arg Ala Gln Ser Leu Val Ser Asn Arg Tyr Tyr Ala Met Val Gly Asp
                245                 250                 255

gtt gga aag tat ata gag aat tgt gga atg gga ggc ttc ttt ttg aca   816
Val Gly Lys Tyr Ile Glu Asn Cys Gly Met Gly Gly Phe Phe Leu Thr
            260                 265                 270

cta aaa tat gca tta gga acc aga tgg ccc aca ctt gct tta gct gca   864
Leu Lys Tyr Ala Leu Gly Thr Arg Trp Pro Thr Leu Ala Leu Ala Ala
        275                 280                 285

ttt tca gga gag cta aca aag cta aag tcc ctc atg gca ttg tac cag   912
Phe Ser Gly Glu Leu Thr Lys Leu Lys Ser Leu Met Ala Leu Tyr Gln
    290                 295                 300

acc ctt ggt gag cag gcc cga tat ttg gcc cta ttg gag tca cca cac   960
Thr Leu Gly Glu Gln Ala Arg Tyr Leu Ala Leu Leu Glu Ser Pro His
305                 310                 315                 320

ttg atg gat ttt gct gca gca aac tat cca ttg cta tat agc tat gct  1008
Leu Met Asp Phe Ala Ala Ala Asn Tyr Pro Leu Leu Tyr Ser Tyr Ala
                325                 330                 335

atg gga ata ggc tat gtg tta gat gtc aac atg agg aac tac gct ttc  1056
Met Gly Ile Gly Tyr Val Leu Asp Val Asn Met Arg Asn Tyr Ala Phe
            340                 345                 350

tcc aga tca tac atg aat aag aca tat ttc caa ttg gga atg gaa act  1104
```

```
Ser Arg Ser Tyr Met Asn Lys Thr Tyr Phe Gln Leu Gly Met Glu Thr
        355                 360                 365

gca aga aaa caa cag ggt gca gtt gac atg agg atg gca gaa gat ctc   1152
Ala Arg Lys Gln Gln Gly Ala Val Asp Met Arg Met Ala Glu Asp Leu
    370                 375                 380

ggt cta act caa gcc gaa cgc acc gag atg gca aat aca ctt gcc aaa   1200
Gly Leu Thr Gln Ala Glu Arg Thr Glu Met Ala Asn Thr Leu Ala Lys
385                 390                 395                 400

ttg acc aca gca aat cga ggg gca gac acc agg gga gga gtc aac ccg   1248
Leu Thr Thr Ala Asn Arg Gly Ala Asp Thr Arg Gly Gly Val Asn Pro
                405                 410                 415

ttc tca tct gtc act ggg aca act cag atg ccc gct gca gca aca ggt   1296
Phe Ser Ser Val Thr Gly Thr Thr Gln Met Pro Ala Ala Ala Thr Gly
            420                 425                 430

gac aca ttc gag agt tac atg gca gcg gat cga ctg agg cag aga tat   1344
Asp Thr Phe Glu Ser Tyr Met Ala Ala Asp Arg Leu Arg Gln Arg Tyr
        435                 440                 445

gct gat gca ggc acc cat gat gat gag atg cca cca tta gaa gag gag   1392
Ala Asp Ala Gly Thr His Asp Asp Glu Met Pro Pro Leu Glu Glu Glu
    450                 455                 460

gaa gag gac gac aca tct gca ggt cca cgc act gaa cca act cct gaa   1440
Glu Glu Asp Asp Thr Ser Ala Gly Pro Arg Thr Glu Pro Thr Pro Glu
465                 470                 475                 480

caa gtg gcc ttg gac atc cag agc gca gca gtt gga gct ccc atc cat   1488
Gln Val Ala Leu Asp Ile Gln Ser Ala Ala Val Gly Ala Pro Ile His
                485                 490                 495

aca gac gac ctg aat gcc gca cta ggt gat ctt gac atc               1527
Thr Asp Asp Leu Asn Ala Ala Leu Gly Asp Leu Asp Ile
            500                 505


<210> 4
<211> 509
<212> PRT
<213> Cryptovirus NP Protein

<400> 4
Met Ser Ser Val Leu Lys Ala Tyr Glu Arg Phe Thr Leu Thr Gln Glu
 1               5                  10                  15
Leu Gln Asp Gln Ser Glu Glu Gly Thr Ile Pro Pro Thr Thr Leu Lys
            20                  25                  30
Pro Val Ile Arg Val Phe Val Leu Thr Ser Asn Asn Pro Glu Leu Arg
        35                  40                  45
Ser Arg Leu Leu Leu Phe Cys Leu Arg Ile Val Leu Ser Asn Gly Ala
    50                  55                  60
Arg Asp Ser His Arg Phe Gly Ala Leu Leu Thr Met Phe Ser Leu Pro
```

```
65                  70                  75                  80
Ser Ala Thr Met Leu Asn His Val Lys Leu Ala Asp Gln Ser Pro Glu
                85                  90                  95
Ala Asp Ile Glu Arg Val Glu Ile Asp Gly Phe Glu Glu Gly Ser Phe
            100                 105                 110
Arg Leu Ile Pro Asn Ala Arg Ser Gly Met Ser Arg Gly Glu Ile Asn
        115                 120                 125
Ala Tyr Ala Ala Leu Ala Glu Asp Leu Pro Asp Thr Leu Asn His Ala
    130                 135                 140
Thr Pro Phe Val Asp Ser Glu Val Glu Gly Thr Ala Trp Asp Glu Ile
145                 150                 155                 160
Glu Thr Phe Leu Asp Met Cys Tyr Ser Val Leu Met Gln Ala Trp Ile
                165                 170                 175
Val Thr Cys Lys Cys Met Thr Ala Pro Asp Gln Pro Ala Ala Ser Ile
            180                 185                 190
Glu Lys Arg Leu Gln Lys Tyr Arg Gln Gln Gly Arg Ile Asn Pro Arg
        195                 200                 205
Tyr Leu Leu Gln Pro Glu Ala Arg Arg Ile Ile Gln Asn Val Ile Arg
    210                 215                 220
Lys Gly Met Val Val Arg His Phe Leu Thr Phe Glu Leu Gln Leu Ala
225                 230                 235                 240
Arg Ala Gln Ser Leu Val Ser Asn Arg Tyr Tyr Ala Met Val Gly Asp
                245                 250                 255
Val Gly Lys Tyr Ile Glu Asn Cys Gly Met Gly Gly Phe Phe Leu Thr
            260                 265                 270
Leu Lys Tyr Ala Leu Gly Thr Arg Trp Pro Thr Leu Ala Leu Ala Ala
        275                 280                 285
Phe Ser Gly Glu Leu Thr Lys Leu Lys Ser Leu Met Ala Leu Tyr Gln
    290                 295                 300
Thr Leu Gly Glu Gln Ala Arg Tyr Leu Ala Leu Leu Glu Ser Pro His
305                 310                 315                 320
Leu Met Asp Phe Ala Ala Ala Asn Tyr Pro Leu Leu Tyr Ser Tyr Ala
                325                 330                 335
Met Gly Ile Gly Tyr Val Leu Asp Val Asn Met Arg Asn Tyr Ala Phe
            340                 345                 350
Ser Arg Ser Tyr Met Asn Lys Thr Tyr Phe Gln Leu Gly Met Glu Thr
        355                 360                 365
Ala Arg Lys Gln Gln Gly Ala Val Asp Met Arg Met Ala Glu Asp Leu
    370                 375                 380
Gly Leu Thr Gln Ala Glu Arg Thr Glu Met Ala Asn Thr Leu Ala Lys
385                 390                 395                 400
Leu Thr Thr Ala Asn Arg Gly Ala Asp Thr Arg Gly Gly Val Asn Pro
                405                 410                 415
Phe Ser Ser Val Thr Gly Thr Thr Gln Met Pro Ala Ala Ala Thr Gly
            420                 425                 430
Asp Thr Phe Glu Ser Tyr Met Ala Ala Asp Arg Leu Arg Gln Arg Tyr
        435                 440                 445
Ala Asp Ala Gly Thr His Asp Asp Glu Met Pro Pro Leu Glu Glu Glu
    450                 455                 460
Glu Glu Asp Asp Thr Ser Ala Gly Pro Arg Thr Glu Pro Thr Pro Glu
465                 470                 475                 480
Gln Val Ala Leu Asp Ile Gln Ser Ala Ala Val Gly Ala Pro Ile His
                485                 490                 495
Thr Asp Asp Leu Asn Ala Ala Leu Gly Asp Leu Asp Ile
            500                 505
```

<210> 5
<211> 666
<212> DNA
<213> Cryptovirus

<220>
<221> CDS
<222> (1)...(666)
<223> Cryptovirus V protein encoding sequence; cDNA in mRNA sense

<400> 5

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atg gat ccc act gat ctg agc ttc tcc cca gat gag att aat aag ctc   48
Met Asp Pro Thr Asp Leu Ser Phe Ser Pro Asp Glu Ile Asn Lys Leu
 1               5                  10                  15

ata gag aca ggc ctg aat act gtg gag tat ttt act tcc caa caa gtc   96
Ile Glu Thr Gly Leu Asn Thr Val Glu Tyr Phe Thr Ser Gln Gln Val
             20                  25                  30

aca gga aca tcc tct ctt gga aag aat aca ata cca cca ggg gtc aca   144
Thr Gly Thr Ser Ser Leu Gly Lys Asn Thr Ile Pro Pro Gly Val Thr
         35                  40                  45

gga cta cta acc aat gct gca gag gca aag atc caa gag tca atc aac   192
Gly Leu Leu Thr Asn Ala Ala Glu Ala Lys Ile Gln Glu Ser Ile Asn
     50                  55                  60

cat cag aag ggt tca gtt ggt ggg ggt aca aac cca aag aaa ccg cga   240
His Gln Lys Gly Ser Val Gly Gly Gly Thr Asn Pro Lys Lys Pro Arg
 65                  70                  75                  80

tca aaa att gcc att gtg cca gca gat gac aaa aca gtg ccc gaa aag   288
Ser Lys Ile Ala Ile Val Pro Ala Asp Asp Lys Thr Val Pro Glu Lys
                 85                  90                  95

ccg atc cca aac cct cta cta ggt ctg gac tcc acc ccg agc acc caa   336
Pro Ile Pro Asn Pro Leu Leu Gly Leu Asp Ser Thr Pro Ser Thr Gln
            100                 105                 110

acc gtg ctt gat cta agt ggg aaa aca tta cca tca gga tcc tat aag   384
Thr Val Leu Asp Leu Ser Gly Lys Thr Leu Pro Ser Gly Ser Tyr Lys
        115                 120                 125

ggg gtt aag ctt gcg aaa ttt ggg aaa gaa aat ctg atg aca cgg ttc   432
Gly Val Lys Leu Ala Lys Phe Gly Lys Glu Asn Leu Met Thr Arg Phe
    130                 135                 140

atc gag gaa ccc aga gag aat cct atc gca acc agt tcc ccc atc gat   480
Ile Glu Glu Pro Arg Glu Asn Pro Ile Ala Thr Ser Ser Pro Ile Asp
145                 150                 155                 160

ttt aag agg ggc aga gat acc ggt ggg ttc cat aga agg gag tac tca   528
```

```
Phe Lys Arg Gly Arg Asp Thr Gly Gly Phe His Arg Arg Glu Tyr Ser
                165                 170                 175

atc gga tgg gtg gga gat gaa gtc aag gtc act gag tgg tgc aat cca   576
Ile Gly Trp Val Gly Asp Glu Val Lys Val Thr Glu Trp Cys Asn Pro
            180                 185                 190

tcc tgt tct cca atc acc gct gca gca agg cga ttt aaa tgc act tgt   624
Ser Cys Ser Pro Ile Thr Ala Ala Ala Arg Arg Phe Lys Cys Thr Cys
        195                 200                 205

cac caa tgt cca gtc act tgc tct gaa tgt gaa cga gat act           666
His Gln Cys Pro Val Thr Cys Ser Glu Cys Glu Arg Asp Thr
    210                 215                 220
```

<210> 6
<211> 222
<212> PRT
<213> Cryptovirus V Protein

<400> 6

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Met Asp Pro Thr Asp Leu Ser Phe Ser Pro Asp Glu Ile Asn Lys Leu
 1               5                  10                  15
Ile Glu Thr Gly Leu Asn Thr Val Glu Tyr Phe Thr Ser Gln Gln Val
            20                  25                  30
Thr Gly Thr Ser Ser Leu Gly Lys Asn Thr Ile Pro Pro Gly Val Thr
        35                  40                  45
Gly Leu Leu Thr Asn Ala Ala Glu Ala Lys Ile Gln Glu Ser Ile Asn
    50                  55                  60
His Gln Lys Gly Ser Val Gly Gly Gly Thr Asn Pro Lys Lys Pro Arg
65                  70                  75                  80
Ser Lys Ile Ala Ile Val Pro Ala Asp Asp Lys Thr Val Pro Glu Lys
                85                  90                  95
Pro Ile Pro Asn Pro Leu Leu Gly Leu Asp Ser Thr Pro Ser Thr Gln
            100                 105                 110
Thr Val Leu Asp Leu Ser Gly Lys Thr Leu Pro Ser Gly Ser Tyr Lys
        115                 120                 125
Gly Val Lys Leu Ala Lys Phe Gly Lys Glu Asn Leu Met Thr Arg Phe
    130                 135                 140
Ile Glu Glu Pro Arg Glu Asn Pro Ile Ala Thr Ser Ser Pro Ile Asp
145                 150                 155                 160
Phe Lys Arg Gly Arg Asp Thr Gly Gly Phe His Arg Arg Glu Tyr Ser
                165                 170                 175
Ile Gly Trp Val Gly Asp Glu Val Lys Val Thr Glu Trp Cys Asn Pro
            180                 185                 190
Ser Cys Ser Pro Ile Thr Ala Ala Ala Arg Arg Phe Lys Cys Thr Cys
        195                 200                 205
His Gln Cys Pro Val Thr Cys Ser Glu Cys Glu Arg Asp Thr
    210                 215                 220
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<210> 7
<211> 1176

<212> DNA
<213> Cryptovirus

<220>
<221> CDS
<222> (1)...(1176)
<223> Cryptovirus P protein encoding sequence; cDNA in mRNA sense

<400> 7

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atg gat ccc act gat ctg agc ttc tcc cca gat gag att aat aag ctc   48
Met Asp Pro Thr Asp Leu Ser Phe Ser Pro Asp Glu Ile Asn Lys Leu
 1               5                  10                  15

ata gag aca ggc ctg aat act gtg gag tat ttt act tcc caa caa gtc   96
Ile Glu Thr Gly Leu Asn Thr Val Glu Tyr Phe Thr Ser Gln Gln Val
             20                  25                  30

aca gga aca tcc tct ctt gga aag aat aca ata cca cca ggg gtc aca   144
Thr Gly Thr Ser Ser Leu Gly Lys Asn Thr Ile Pro Pro Gly Val Thr
         35                  40                  45

gga cta cta acc aat gct gca gag gca aag atc caa gag tca atc aac   192
Gly Leu Leu Thr Asn Ala Ala Glu Ala Lys Ile Gln Glu Ser Ile Asn
     50                  55                  60

cat cag aag ggt tca gtt ggt ggg ggt aca aac cca aag aaa ccg cga   240
His Gln Lys Gly Ser Val Gly Gly Gly Thr Asn Pro Lys Lys Pro Arg
 65                  70                  75                  80

tca aaa att gcc att gtg cca gca gat gac aaa aca gtg ccc gaa aag   288
Ser Lys Ile Ala Ile Val Pro Ala Asp Asp Lys Thr Val Pro Glu Lys
                 85                  90                  95

ccg atc cca aac cct cta cta ggt ctg gac tcc acc ccg agc acc caa   336
Pro Ile Pro Asn Pro Leu Leu Gly Leu Asp Ser Thr Pro Ser Thr Gln
            100                 105                 110

acc gtg ctt gat cta agt ggg aaa aca tta cca tca gga tcc tat aag   384
Thr Val Leu Asp Leu Ser Gly Lys Thr Leu Pro Ser Gly Ser Tyr Lys
        115                 120                 125

ggg gtt aag ctt gcg aaa ttt ggg aaa gaa aat ctg atg aca cgg ttc   432
Gly Val Lys Leu Ala Lys Phe Gly Lys Glu Asn Leu Met Thr Arg Phe
    130                 135                 140

atc gag gaa ccc aga gag aat cct atc gca acc agt tcc ccc atc gat   480
Ile Glu Glu Pro Arg Glu Asn Pro Ile Ala Thr Ser Ser Pro Ile Asp
145                 150                 155                 160

ttt aag agg ggg gca gag ata ccg gtg ggt tcc ata gaa ggg agt act   528
Phe Lys Arg Gly Ala Glu Ile Pro Val Gly Ser Ile Glu Gly Ser Thr
                165                 170                 175

caa tcg gat ggg tgg gag atg aag tca agg tca ctg agt ggt gca atc   576
```

```
Gln Ser Asp Gly Trp Glu Met Lys Ser Arg Ser Leu Ser Gly Ala Ile
            180                 185                 190

cat cct gtt ctc caa tca ccg ctg cag caa ggc gat tta aat gca ctt   624
His Pro Val Leu Gln Ser Pro Leu Gln Gln Gly Asp Leu Asn Ala Leu
        195                 200                 205

gtc acc aat gtc cag tca ctt gct ctg aat gtg aac gag ata ctt aat   672
Val Thr Asn Val Gln Ser Leu Ala Leu Asn Val Asn Glu Ile Leu Asn
    210                 215                 220

aca gtg aga aat ttg gac tct cgg atg aat caa ctg gag aca aaa gta   720
Thr Val Arg Asn Leu Asp Ser Arg Met Asn Gln Leu Glu Thr Lys Val
225                 230                 235                 240

gat cgc att ctc tca tct cag tct cta atc cag acc atc aag aat gac   768
Asp Arg Ile Leu Ser Ser Gln Ser Leu Ile Gln Thr Ile Lys Asn Asp
                245                 250                 255

ata att gga ctt aaa gca ggg atg gct act tta gaa gga atg att aca   816
Ile Ile Gly Leu Lys Ala Gly Met Ala Thr Leu Glu Gly Met Ile Thr
            260                 265                 270

act gtg aaa atc atg gac ccg gga gtt ccc agt aat gtt act gtg gaa   864
Thr Val Lys Ile Met Asp Pro Gly Val Pro Ser Asn Val Thr Val Glu
        275                 280                 285

gat gta cgc aag aaa cta agt aac cat gct gtt gtt gtg cca gaa tca   912
Asp Val Arg Lys Lys Leu Ser Asn His Ala Val Val Val Pro Glu Ser
    290                 295                 300

ttc aat gat agt ttc ttg act caa tct gaa gat gta att tca ctt gat   960
Phe Asn Asp Ser Phe Leu Thr Gln Ser Glu Asp Val Ile Ser Leu Asp
305                 310                 315                 320

gag ttg gct cga cca act gca aca agt gtt aag aag att gtc agg aag  1008
Glu Leu Ala Arg Pro Thr Ala Thr Ser Val Lys Lys Ile Val Arg Lys
                325                 330                 335

gtt cct cct cag aag gat ctg act gga ttg aag atc aca cta gag caa  1056
Val Pro Pro Gln Lys Asp Leu Thr Gly Leu Lys Ile Thr Leu Glu Gln
            340                 345                 350

ttg gca aag gat tgc atc agc aaa ccg aag atg agg gaa gat tat ctc  1104
Leu Ala Lys Asp Cys Ile Ser Lys Pro Lys Met Arg Glu Asp Tyr Leu
        355                 360                 365

ctc aag atc aac cag gct tct agt gag gct cag cta att gac ctc aag  1152
Leu Lys Ile Asn Gln Ala Ser Ser Glu Ala Gln Leu Ile Asp Leu Lys
    370                 375                 380

aaa gca atc atc cgc agt gca att                                 1176
Lys Ala Ile Ile Arg Ser Ala Ile
385                 390
```

<210> 8
<211> 392
<212> PRT
<213> Cryptovirus P Protein

<400> 8

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Met Asp Pro Thr Asp Leu Ser Phe Ser Pro Asp Glu Ile Asn Lys Leu
 1               5                  10                  15
Ile Glu Thr Gly Leu Asn Thr Val Glu Tyr Phe Thr Ser Gln Gln Val
            20                  25                  30
Thr Gly Thr Ser Ser Leu Gly Lys Asn Thr Ile Pro Pro Gly Val Thr
        35                  40                  45
Gly Leu Leu Thr Asn Ala Ala Glu Ala Lys Ile Gln Glu Ser Ile Asn
    50                  55                  60
His Gln Lys Gly Ser Val Gly Gly Gly Thr Asn Pro Lys Lys Pro Arg
65                  70                  75                  80
Ser Lys Ile Ala Ile Val Pro Ala Asp Asp Lys Thr Val Pro Glu Lys
                85                  90                  95
Pro Ile Pro Asn Pro Leu Leu Gly Leu Asp Ser Thr Pro Ser Thr Gln
            100                 105                 110
Thr Val Leu Asp Leu Ser Gly Lys Thr Leu Pro Ser Gly Ser Tyr Lys
        115                 120                 125
Gly Val Lys Leu Ala Lys Phe Gly Lys Glu Asn Leu Met Thr Arg Phe
    130                 135                 140
Ile Glu Glu Pro Arg Glu Asn Pro Ile Ala Thr Ser Ser Pro Ile Asp
145                 150                 155                 160
Phe Lys Arg Gly Ala Glu Ile Pro Val Gly Ser Ile Glu Gly Ser Thr
                165                 170                 175
Gln Ser Asp Gly Trp Glu Met Lys Ser Arg Ser Leu Ser Gly Ala Ile
            180                 185                 190
His Pro Val Leu Gln Ser Pro Leu Gln Gln Gly Asp Leu Asn Ala Leu
        195                 200                 205
Val Thr Asn Val Gln Ser Leu Ala Leu Asn Val Asn Glu Ile Leu Asn
    210                 215                 220
Thr Val Arg Asn Leu Asp Ser Arg Met Asn Gln Leu Glu Thr Lys Val
225                 230                 235                 240
Asp Arg Ile Leu Ser Ser Gln Ser Leu Ile Gln Thr Ile Lys Asn Asp
                245                 250                 255
Ile Ile Gly Leu Lys Ala Gly Met Ala Thr Leu Glu Gly Met Ile Thr
            260                 265                 270
Thr Val Lys Ile Met Asp Pro Gly Val Pro Ser Asn Val Thr Val Glu
        275                 280                 285
Asp Val Arg Lys Lys Leu Ser Asn His Ala Val Val Val Pro Glu Ser
    290                 295                 300
Phe Asn Asp Ser Phe Leu Thr Gln Ser Glu Asp Val Ile Ser Leu Asp
305                 310                 315                 320
Glu Leu Ala Arg Pro Thr Ala Thr Ser Val Lys Lys Ile Val Arg Lys
                325                 330                 335
Val Pro Pro Gln Lys Asp Leu Thr Gly Leu Lys Ile Thr Leu Glu Gln
            340                 345                 350
Leu Ala Lys Asp Cys Ile Ser Lys Pro Lys Met Arg Glu Asp Tyr Leu
        355                 360                 365
Leu Lys Ile Asn Gln Ala Ser Ser Glu Ala Gln Leu Ile Asp Leu Lys
    370                 375                 380
```

```
Lys Ala Ile Ile Arg Ser Ala Ile
385                 390
```

<210> 9
<211> 1131
<212> DNA
<213> Cryptovirus

<220>
<221> CDS
<222> (1)...(1131)
<223> Crypotovirus M protein encoding sequence; cDNA in mRNA sense

<400> 9

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atg cca tcc atc agc att ccc gca gac ccc acc aat cca cgt caa tca   48
Met Pro Ser Ile Ser Ile Pro Ala Asp Pro Thr Asn Pro Arg Gln Ser
 1               5                  10                  15

ata aaa gcg ttc cca att gtg att aac agt gat ggg ggt gag aaa ggc   96
Ile Lys Ala Phe Pro Ile Val Ile Asn Ser Asp Gly Gly Glu Lys Gly
            20                  25                  30

cgc ttg gtt aaa caa cta cgt aca acc tac ttg aat gac cta gat act   144
Arg Leu Val Lys Gln Leu Arg Thr Thr Tyr Leu Asn Asp Leu Asp Thr
        35                  40                  45

cat gag cca ctg gtg aca ttc gta aat acc tat gga ttc atc tac gaa   192
His Glu Pro Leu Val Thr Phe Val Asn Thr Tyr Gly Phe Ile Tyr Glu
    50                  55                  60

cag aat cgg ggg aat gcc att gtc gga gag gat caa ctt ggg aag aaa   240
Gln Asn Arg Gly Asn Ala Ile Val Gly Glu Asp Gln Leu Gly Lys Lys
65                  70                  75                  80

aga gag gct gtg act gct gca atg gtt acc ctt gga tgt ggg cct aat   288
Arg Glu Ala Val Thr Ala Ala Met Val Thr Leu Gly Cys Gly Pro Asn
                85                  90                  95

cta cca tca tta ggg aat gtc ctg aga caa ctg agt gaa ttc caa gtc   336
Leu Pro Ser Leu Gly Asn Val Leu Arg Gln Leu Ser Glu Phe Gln Val
            100                 105                 110

att gtt agg aag aca tcc agc aaa gcg gaa gag atg gtc ttt gaa att   384
Ile Val Arg Lys Thr Ser Ser Lys Ala Glu Glu Met Val Phe Glu Ile
        115                 120                 125

gtt aag tat ccg aga ata ttt cgg ggt cat aca tta atc cag aaa gga   432
Val Lys Tyr Pro Arg Ile Phe Arg Gly His Thr Leu Ile Gln Lys Gly
    130                 135                 140

cta gtc tgt gtc tcc gca gaa aaa ttt gtt aag tca cca ggg aaa gta   480
Leu Val Cys Val Ser Ala Glu Lys Phe Val Lys Ser Pro Gly Lys Val
145                 150                 155                 160
```

```
caa tct gga atg gac tat ctc ttc att ccg aca ttt ctg tca gtg act   528
Gln Ser Gly Met Asp Tyr Leu Phe Ile Pro Thr Phe Leu Ser Val Thr
                165                 170                 175

tat tgt cca gct gca atc aaa ttt cag gta cct ggc ccc atg ttg aaa   576
Tyr Cys Pro Ala Ala Ile Lys Phe Gln Val Pro Gly Pro Met Leu Lys
            180                 185                 190

atg agg tca aga tac act cag agc tta caa ctt gaa cta atg ata aga   624
Met Arg Ser Arg Tyr Thr Gln Ser Leu Gln Leu Glu Leu Met Ile Arg
        195                 200                 205

atc ctg tgt aag ccc gat tcg cca ctt atg aag gtc cat atc cct gac   672
Ile Leu Cys Lys Pro Asp Ser Pro Leu Met Lys Val His Ile Pro Asp
    210                 215                 220

aag gag gga aga gga tgt ctt gta tca gta tgg ctg cat gta tgc aac   720
Lys Glu Gly Arg Gly Cys Leu Val Ser Val Trp Leu His Val Cys Asn
225                 230                 235                 240

atc ttc aaa tca gga aac aag aat ggc agt gag tgg cag gaa tac tgg   768
Ile Phe Lys Ser Gly Asn Lys Asn Gly Ser Glu Trp Gln Glu Tyr Trp
                245                 250                 255

atg aga aag tgt gct aac atg caa ctt gaa gtg tcg att gca gat atg   816
Met Arg Lys Cys Ala Asn Met Gln Leu Glu Val Ser Ile Ala Asp Met
            260                 265                 270

tgg gga cca act atc ata att cat gcc aga ggt cac att ccc aaa agt   864
Trp Gly Pro Thr Ile Ile Ile His Ala Arg Gly His Ile Pro Lys Ser
        275                 280                 285

gct aag ttg ttt ttt gga aag ggt gga tgg agc tgc cat cca ctt cac   912
Ala Lys Leu Phe Phe Gly Lys Gly Gly Trp Ser Cys His Pro Leu His
    290                 295                 300

gaa att gtt cca agt gtc act aaa aca cta tgg tcc gta ggt tgt gaa   960
Glu Ile Val Pro Ser Val Thr Lys Thr Leu Trp Ser Val Gly Cys Glu
305                 310                 315                 320

att aca aag gcg aag gca ata ata caa gag agt agc atc tct ctt ctc  1008
Ile Thr Lys Ala Lys Ala Ile Ile Gln Glu Ser Ser Ile Ser Leu Leu
                325                 330                 335

gtg gag act act gac atc ata agt cca aaa gtt aaa att tca tct aag  1056
Val Glu Thr Thr Asp Ile Ile Ser Pro Lys Val Lys Ile Ser Ser Lys
            340                 345                 350

cat cgc cgc ttt ggg aaa tca aat tgg ggt ctg ttc aag aaa act aaa  1104
His Arg Arg Phe Gly Lys Ser Asn Trp Gly Leu Phe Lys Lys Thr Lys
        355                 360                 365

tca cta cct aac cta acg gag ctg gaa                             1131
Ser Leu Pro Asn Leu Thr Glu Leu Glu
```

370 375

<210> 10
<211> 377
<212> PRT
<213> Cryptovirus M Protein

<400> 10

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Met Pro Ser Ile Ser Ile Pro Ala Asp Pro Thr Asn Pro Arg Gln Ser
 1               5                  10                  15
Ile Lys Ala Phe Pro Ile Val Ile Asn Ser Asp Gly Gly Glu Lys Gly
            20                  25                  30
Arg Leu Val Lys Gln Leu Arg Thr Thr Tyr Leu Asn Asp Leu Asp Thr
        35                  40                  45
His Glu Pro Leu Val Thr Phe Val Asn Thr Tyr Gly Phe Ile Tyr Glu
    50                  55                  60
Gln Asn Arg Gly Asn Ala Ile Val Gly Glu Asp Gln Leu Gly Lys Lys
65                  70                  75                  80
Arg Glu Ala Val Thr Ala Ala Met Val Thr Leu Gly Cys Gly Pro Asn
                85                  90                  95
Leu Pro Ser Leu Gly Asn Val Leu Arg Gln Leu Ser Glu Phe Gln Val
            100                 105                 110
Ile Val Arg Lys Thr Ser Ser Lys Ala Glu Glu Met Val Phe Glu Ile
        115                 120                 125
Val Lys Tyr Pro Arg Ile Phe Arg Gly His Thr Leu Ile Gln Lys Gly
    130                 135                 140
Leu Val Cys Val Ser Ala Glu Lys Phe Val Lys Ser Pro Gly Lys Val
145                 150                 155                 160
Gln Ser Gly Met Asp Tyr Leu Phe Ile Pro Thr Phe Leu Ser Val Thr
                165                 170                 175
Tyr Cys Pro Ala Ala Ile Lys Phe Gln Val Pro Gly Pro Met Leu Lys
            180                 185                 190
Met Arg Ser Arg Tyr Thr Gln Ser Leu Gln Leu Glu Leu Met Ile Arg
        195                 200                 205
Ile Leu Cys Lys Pro Asp Ser Pro Leu Met Lys Val His Ile Pro Asp
    210                 215                 220
Lys Glu Gly Arg Gly Cys Leu Val Ser Val Trp Leu His Val Cys Asn
225                 230                 235                 240
Ile Phe Lys Ser Gly Asn Lys Asn Gly Ser Glu Trp Gln Glu Tyr Trp
                245                 250                 255
Met Arg Lys Cys Ala Asn Met Gln Leu Glu Val Ser Ile Ala Asp Met
            260                 265                 270
Trp Gly Pro Thr Ile Ile Ile His Ala Arg Gly His Ile Pro Lys Ser
        275                 280                 285
Ala Lys Leu Phe Phe Gly Lys Gly Gly Trp Ser Cys His Pro Leu His
    290                 295                 300
Glu Ile Val Pro Ser Val Thr Lys Thr Leu Trp Ser Val Gly Cys Glu
305                 310                 315                 320
Ile Thr Lys Ala Lys Ala Ile Ile Gln Glu Ser Ser Ile Ser Leu Leu
                325                 330                 335
Val Glu Thr Thr Asp Ile Ile Ser Pro Lys Val Lys Ile Ser Ser Lys
            340                 345                 350
His Arg Arg Phe Gly Lys Ser Asn Trp Gly Leu Phe Lys Lys Thr Lys
        355                 360                 365
```

```
Ser Leu Pro Asn Leu Thr Glu Leu Glu
    370                 375


<210> 11
<211> 1653
<212> DNA
<213> Cryptovirus

<220>
<221> CDS
<222> (1)...(1653)
<223> Cryptovirus F protein encoding sequence; cDNA in
      mRNA sense

<400> 11
atg agc act ata att caa tct ctg gtg gtc tcc tgt cta ttg gca gga   48
Met Ser Thr Ile Ile Gln Ser Leu Val Val Ser Cys Leu Leu Ala Gly
 1               5                  10                  15

gca ggc agc ctt gat cca gca gcc ctc atg caa atc ggt gtc att cca   96
Ala Gly Ser Leu Asp Pro Ala Ala Leu Met Gln Ile Gly Val Ile Pro
            20                  25                  30

aca aat gtc cgg caa ctt atg tat tat act gag gcc tca tca gca ttc   144
Thr Asn Val Arg Gln Leu Met Tyr Tyr Thr Glu Ala Ser Ser Ala Phe
        35                  40                  45

att gtt gtg aag tta atg cct aca att gac tcg ccg att agt gga tgt   192
Ile Val Val Lys Leu Met Pro Thr Ile Asp Ser Pro Ile Ser Gly Cys
    50                  55                  60

aat ata aca tca att tca agc tat aat gca aca gtg aca aaa ctc cta   240
Asn Ile Thr Ser Ile Ser Ser Tyr Asn Ala Thr Val Thr Lys Leu Leu
65                  70                  75                  80

cag ccg atc ggt gag aat ttg gag acg att agg aac cag ttg att cca   288
Gln Pro Ile Gly Glu Asn Leu Glu Thr Ile Arg Asn Gln Leu Ile Pro
                85                  90                  95

act cgg agg aga cgc cgg ttt gca ggg gtg gtg att gga tta gct gca   336
Thr Arg Arg Arg Arg Arg Phe Ala Gly Val Val Ile Gly Leu Ala Ala
            100                 105                 110

tta gga gta gct act gcc gca caa gtc act gcc gca gta gca cta gtt   384
Leu Gly Val Ala Thr Ala Ala Gln Val Thr Ala Ala Val Ala Leu Val
        115                 120                 125

aag gca aat gaa aat act gcg gct ata ctc aat ctc aaa aat gca atc   432
Lys Ala Asn Glu Asn Thr Ala Ala Ile Leu Asn Leu Lys Asn Ala Ile
    130                 135                 140

caa aaa aca aat gca gca gtt gca gat gtg gtc cag gcc aca caa tca   480
Gln Lys Thr Asn Ala Ala Val Ala Asp Val Val Gln Ala Thr Gln Ser
145                 150                 155                 160
```

```
cta gga acg gca gtt caa gca gtt caa gat cac ata aac agt gtg ata   528
Leu Gly Thr Ala Val Gln Ala Val Gln Asp His Ile Asn Ser Val Ile
                165                 170                 175

agt cca gca att aca gca gcc aat tgt aag gcc caa gat gct atc att   576
Ser Pro Ala Ile Thr Ala Ala Asn Cys Lys Ala Gln Asp Ala Ile Ile
            180                 185                 190

ggc tca atc ctc aat ctc tat ttg acc gag ttg aca act atc ttc cac   624
Gly Ser Ile Leu Asn Leu Tyr Leu Thr Glu Leu Thr Thr Ile Phe His
        195                 200                 205

aat caa att aca aac cct gca ttg agt cct att aca att caa gct tta   672
Asn Gln Ile Thr Asn Pro Ala Leu Ser Pro Ile Thr Ile Gln Ala Leu
    210                 215                 220

agg atc cta ctg ggg agt acc ttg ccg act gtg gtc gaa aaa tct ttc   720
Arg Ile Leu Leu Gly Ser Thr Leu Pro Thr Val Val Glu Lys Ser Phe
225                 230                 235                 240

aat acc cag ata agt gca gct gag ctt ctc tca tca ggg ttg ttg aca   768
Asn Thr Gln Ile Ser Ala Ala Glu Leu Leu Ser Ser Gly Leu Leu Thr
                245                 250                 255

ggc cag att gtg gga tta gat ttg acc tat atg cag atg gtc ata aaa   816
Gly Gln Ile Val Gly Leu Asp Leu Thr Tyr Met Gln Met Val Ile Lys
            260                 265                 270

att gag ctg cca act tta act gta caa cct gca acc cag atc ata gat   864
Ile Glu Leu Pro Thr Leu Thr Val Gln Pro Ala Thr Gln Ile Ile Asp
        275                 280                 285

ctg gcc acc att tct gca ttc att aac aat caa gaa gtc atg gcc caa   912
Leu Ala Thr Ile Ser Ala Phe Ile Asn Asn Gln Glu Val Met Ala Gln
    290                 295                 300

tta cca aca cgt gtt att gtg act ggc agc ttg atc caa gcc tat ccc   960
Leu Pro Thr Arg Val Ile Val Thr Gly Ser Leu Ile Gln Ala Tyr Pro
305                 310                 315                 320

gca tcg caa tgc act att aca ccc aac act gtg tac tgt agg tat aat  1008
Ala Ser Gln Cys Thr Ile Thr Pro Asn Thr Val Tyr Cys Arg Tyr Asn
                325                 330                 335

gat gcc caa gta ctc tca gat gat acg atg gct tgc ctc caa ggt aac  1056
Asp Ala Gln Val Leu Ser Asp Asp Thr Met Ala Cys Leu Gln Gly Asn
            340                 345                 350

ttg aca aga tgc acc ttc tct cca gtg gtt ggg agc ttt ctc act cga  1104
Leu Thr Arg Cys Thr Phe Ser Pro Val Val Gly Ser Phe Leu Thr Arg
        355                 360                 365

ttc gtg ctg ttc gat gga ata gtt tat gca aat tgc agg tcg atg ctg  1152
Phe Val Leu Phe Asp Gly Ile Val Tyr Ala Asn Cys Arg Ser Met Leu
```

```
    370                 375                 380

tgc aag tgc atg caa cct gct gcc gtg atc cta cag ccg agt tca tcc   1200
Cys Lys Cys Met Gln Pro Ala Ala Val Ile Leu Gln Pro Ser Ser Ser
385                 390                 395                 400

cct gta act gtc att gac atg cac aaa tgt gtg agt ctg cag ctt gac   1248
Pro Val Thr Val Ile Asp Met His Lys Cys Val Ser Leu Gln Leu Asp
                405                 410                 415

gat ctc aga ttc acc atc act caa ttg gcc aat gta acc tac aat agc   1296
Asp Leu Arg Phe Thr Ile Thr Gln Leu Ala Asn Val Thr Tyr Asn Ser
            420                 425                 430

acc atc aag ctt gaa aca tcc cag atc ttg cct att gat ccg ttg gat   1344
Thr Ile Lys Leu Glu Thr Ser Gln Ile Leu Pro Ile Asp Pro Leu Asp
        435                 440                 445

ata tcc cag aat tta gct gcg gtg aat aag agt cta agt gat gca cta   1392
Ile Ser Gln Asn Leu Ala Ala Val Asn Lys Ser Leu Ser Asp Ala Leu
    450                 455                 460

caa cac tta gca caa agt gac aca tac ctt tct gca atc aca tca gct   1440
Gln His Leu Ala Gln Ser Asp Thr Tyr Leu Ser Ala Ile Thr Ser Ala
465                 470                 475                 480

acg act aca agt gta tta tcc ata ata gca atc tgt ctt gga tcg tta   1488
Thr Thr Thr Ser Val Leu Ser Ile Ile Ala Ile Cys Leu Gly Ser Leu
                485                 490                 495

ggt tta ata tta ata atc ttg ctc agt gta gtt gtg tgg aag tta ttg   1536
Gly Leu Ile Leu Ile Ile Leu Leu Ser Val Val Val Trp Lys Leu Leu
            500                 505                 510

acc att gtc gct gct aat cga aat aga atg gag aat ttt gtt tat cat   1584
Thr Ile Val Ala Ala Asn Arg Asn Arg Met Glu Asn Phe Val Tyr His
        515                 520                 525

aat tca gca ttc cac cac cca cga tct gat ctc agt gag aaa aat caa   1632
Asn Ser Ala Phe His His Pro Arg Ser Asp Leu Ser Glu Lys Asn Gln
    530                 535                 540

cct gca act ctt gga aca aga                                      1653
Pro Ala Thr Leu Gly Thr Arg
545                 550
```

<210> 12
<211> 551
<212> PRT
<213> Cryptovirus F protein

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<400> 12
Met Ser Thr Ile Ile Gln Ser Leu Val Val Ser Cys Leu Leu Ala Gly
 1               5                  10                  15
```

```
Ala Gly Ser Leu Asp Pro Ala Ala Leu Met Gln Ile Gly Val Ile Pro
            20                  25                  30
Thr Asn Val Arg Gln Leu Met Tyr Tyr Thr Glu Ala Ser Ser Ala Phe
        35                  40                  45
Ile Val Val Lys Leu Met Pro Thr Ile Asp Ser Pro Ile Ser Gly Cys
    50                  55                  60
Asn Ile Thr Ser Ile Ser Ser Tyr Asn Ala Thr Val Thr Lys Leu Leu
65                  70                  75                  80
Gln Pro Ile Gly Glu Asn Leu Glu Thr Ile Arg Asn Gln Leu Ile Pro
                85                  90                  95
Thr Arg Arg Arg Arg Arg Phe Ala Gly Val Val Ile Gly Leu Ala Ala
            100                 105                 110
Leu Gly Val Ala Thr Ala Ala Gln Val Thr Ala Ala Val Ala Leu Val
        115                 120                 125
Lys Ala Asn Glu Asn Thr Ala Ala Ile Leu Asn Leu Lys Asn Ala Ile
    130                 135                 140
Gln Lys Thr Asn Ala Ala Val Ala Asp Val Val Gln Ala Thr Gln Ser
145                 150                 155                 160
Leu Gly Thr Ala Val Gln Ala Val Gln Asp His Ile Asn Ser Val Ile
                165                 170                 175
Ser Pro Ala Ile Thr Ala Ala Asn Cys Lys Ala Gln Asp Ala Ile Ile
            180                 185                 190
Gly Ser Ile Leu Asn Leu Tyr Leu Thr Glu Leu Thr Thr Ile Phe His
        195                 200                 205
Asn Gln Ile Thr Asn Pro Ala Leu Ser Pro Ile Thr Ile Gln Ala Leu
    210                 215                 220
Arg Ile Leu Leu Gly Ser Thr Leu Pro Thr Val Val Glu Lys Ser Phe
225                 230                 235                 240
Asn Thr Gln Ile Ser Ala Ala Glu Leu Leu Ser Ser Gly Leu Leu Thr
                245                 250                 255
Gly Gln Ile Val Gly Leu Asp Leu Thr Tyr Met Gln Met Val Ile Lys
            260                 265                 270
Ile Glu Leu Pro Thr Leu Thr Val Gln Pro Ala Thr Gln Ile Ile Asp
        275                 280                 285
Leu Ala Thr Ile Ser Ala Phe Ile Asn Asn Gln Glu Val Met Ala Gln
    290                 295                 300
Leu Pro Thr Arg Val Ile Val Thr Gly Ser Leu Ile Gln Ala Tyr Pro
305                 310                 315                 320
Ala Ser Gln Cys Thr Ile Thr Pro Asn Thr Val Tyr Cys Arg Tyr Asn
                325                 330                 335
Asp Ala Gln Val Leu Ser Asp Asp Thr Met Ala Cys Leu Gln Gly Asn
            340                 345                 350
Leu Thr Arg Cys Thr Phe Ser Pro Val Val Gly Ser Phe Leu Thr Arg
        355                 360                 365
Phe Val Leu Phe Asp Gly Ile Val Tyr Ala Asn Cys Arg Ser Met Leu
    370                 375                 380
Cys Lys Cys Met Gln Pro Ala Ala Val Ile Leu Gln Pro Ser Ser Ser
385                 390                 395                 400
Pro Val Thr Val Ile Asp Met His Lys Cys Val Ser Leu Gln Leu Asp
                405                 410                 415
Asp Leu Arg Phe Thr Ile Thr Gln Leu Ala Asn Val Thr Tyr Asn Ser
            420                 425                 430
Thr Ile Lys Leu Glu Thr Ser Gln Ile Leu Pro Ile Asp Pro Leu Asp
        435                 440                 445
Ile Ser Gln Asn Leu Ala Ala Val Asn Lys Ser Leu Ser Asp Ala Leu
```

```
    450                 455                 460
Gln His Leu Ala Gln Ser Asp Thr Tyr Leu Ser Ala Ile Thr Ser Ala
465                 470                 475                 480
Thr Thr Thr Ser Val Leu Ser Ile Ile Ala Ile Cys Leu Gly Ser Leu
                485                 490                 495
Gly Leu Ile Leu Ile Ile Leu Leu Ser Val Val Val Trp Lys Leu Leu
            500                 505                 510
Thr Ile Val Ala Ala Asn Arg Asn Arg Met Glu Asn Phe Val Tyr His
        515                 520                 525
Asn Ser Ala Phe His His Pro Arg Ser Asp Leu Ser Glu Lys Asn Gln
    530                 535                 540
Pro Ala Thr Leu Gly Thr Arg
545                 550
```

<210> 13
<211> 1596
<212> DNA
<213> Cryptovirus

<220>
<221> CDS
<222> (1)...(1596)
<223> Cryptovirus F0 protein encoding sequence; cDNA in mRNA sense

<400> 13

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ctt gat cca gca gcc ctc atg caa atc ggt gtc att cca aca aat gtc   48
Leu Asp Pro Ala Ala Leu Met Gln Ile Gly Val Ile Pro Thr Asn Val
 1               5                  10                  15

cgg caa ctt atg tat tat act gag gcc tca tca gca ttc att gtt gtg   96
Arg Gln Leu Met Tyr Tyr Thr Glu Ala Ser Ser Ala Phe Ile Val Val
            20                  25                  30

aag tta atg cct aca att gac tcg ccg att agt gga tgt aat ata aca   144
Lys Leu Met Pro Thr Ile Asp Ser Pro Ile Ser Gly Cys Asn Ile Thr
        35                  40                  45

tca att tca agc tat aat gca aca gtg aca aaa ctc cta cag ccg atc   192
Ser Ile Ser Ser Tyr Asn Ala Thr Val Thr Lys Leu Leu Gln Pro Ile
    50                  55                  60

ggt gag aat ttg gag acg att agg aac cag ttg att cca act cgg agg   240
Gly Glu Asn Leu Glu Thr Ile Arg Asn Gln Leu Ile Pro Thr Arg Arg
65                  70                  75                  80

aga cgc cgg ttt gca ggg gtg gtg att gga tta gct gca tta gga gta   288
Arg Arg Arg Phe Ala Gly Val Val Ile Gly Leu Ala Ala Leu Gly Val
                85                  90                  95

gct act gcc gca caa gtc act gcc gca gta gca cta gtt aag gca aat   336
Ala Thr Ala Ala Gln Val Thr Ala Ala Val Ala Leu Val Lys Ala Asn
            100                 105                 110
```

```
gaa aat act gcg gct ata ctc aat ctc aaa aat gca atc caa aaa aca   384
Glu Asn Thr Ala Ala Ile Leu Asn Leu Lys Asn Ala Ile Gln Lys Thr
        115                 120                 125

aat gca gca gtt gca gat gtg gtc cag gcc aca caa tca cta gga acg   432
Asn Ala Ala Val Ala Asp Val Val Gln Ala Thr Gln Ser Leu Gly Thr
    130                 135                 140

gca gtt caa gca gtt caa gat cac ata aac agt gtg ata agt cca gca   480
Ala Val Gln Ala Val Gln Asp His Ile Asn Ser Val Ile Ser Pro Ala
145                 150                 155                 160

att aca gca gcc aat tgt aag gcc caa gat gct atc att ggc tca atc   528
Ile Thr Ala Ala Asn Cys Lys Ala Gln Asp Ala Ile Ile Gly Ser Ile
                165                 170                 175

ctc aat ctc tat ttg acc gag ttg aca act atc ttc cac aat caa att   576
Leu Asn Leu Tyr Leu Thr Glu Leu Thr Thr Ile Phe His Asn Gln Ile
            180                 185                 190

aca aac cct gca ttg agt cct att aca att caa gct tta agg atc cta   624
Thr Asn Pro Ala Leu Ser Pro Ile Thr Ile Gln Ala Leu Arg Ile Leu
        195                 200                 205

ctg ggg agt acc ttg ccg act gtg gtc gaa aaa tct ttc aat acc cag   672
Leu Gly Ser Thr Leu Pro Thr Val Val Glu Lys Ser Phe Asn Thr Gln
    210                 215                 220

ata agt gca gct gag ctt ctc tca tca ggg ttg ttg aca ggc cag att   720
Ile Ser Ala Ala Glu Leu Leu Ser Ser Gly Leu Leu Thr Gly Gln Ile
225                 230                 235                 240

gtg gga tta gat ttg acc tat atg cag atg gtc ata aaa att gag ctg   768
Val Gly Leu Asp Leu Thr Tyr Met Gln Met Val Ile Lys Ile Glu Leu
                245                 250                 255

cca act tta act gta caa cct gca acc cag atc ata gat ctg gcc acc   816
Pro Thr Leu Thr Val Gln Pro Ala Thr Gln Ile Ile Asp Leu Ala Thr
            260                 265                 270

att tct gca ttc att aac aat caa gaa gtc atg gcc caa tta cca aca   864
Ile Ser Ala Phe Ile Asn Asn Gln Glu Val Met Ala Gln Leu Pro Thr
        275                 280                 285

cgt gtt att gtg act ggc agc ttg atc caa gcc tat ccc gca tcg caa   912
Arg Val Ile Val Thr Gly Ser Leu Ile Gln Ala Tyr Pro Ala Ser Gln
    290                 295                 300

tgc act att aca ccc aac act gtg tac tgt agg tat aat gat gcc caa   960
Cys Thr Ile Thr Pro Asn Thr Val Tyr Cys Arg Tyr Asn Asp Ala Gln
305                 310                 315                 320

gta ctc tca gat gat acg atg gct tgc ctc caa ggt aac ttg aca aga   1008
Val Leu Ser Asp Asp Thr Met Ala Cys Leu Gln Gly Asn Leu Thr Arg
                325                 330                 335
```

```
tgc acc ttc tct cca gtg gtt ggg agc ttt ctc act cga ttc gtg ctg   1056
Cys Thr Phe Ser Pro Val Val Gly Ser Phe Leu Thr Arg Phe Val Leu
            340                 345                 350

ttc gat gga ata gtt tat gca aat tgc agg tcg atg ctg tgc aag tgc   1104
Phe Asp Gly Ile Val Tyr Ala Asn Cys Arg Ser Met Leu Cys Lys Cys
        355                 360                 365

atg caa cct gct gcc gtg atc cta cag ccg agt tca tcc cct gta act   1152
Met Gln Pro Ala Ala Val Ile Leu Gln Pro Ser Ser Ser Pro Val Thr
    370                 375                 380

gtc att gac atg cac aaa tgt gtg agt ctg cag ctt gac gat ctc aga   1200
Val Ile Asp Met His Lys Cys Val Ser Leu Gln Leu Asp Asp Leu Arg
385                 390                 395                 400

ttc acc atc act caa ttg gcc aat gta acc tac aat agc acc atc aag   1248
Phe Thr Ile Thr Gln Leu Ala Asn Val Thr Tyr Asn Ser Thr Ile Lys
                405                 410                 415

ctt gaa aca tcc cag atc ttg cct att gat ccg ttg gat ata tcc cag   1296
Leu Glu Thr Ser Gln Ile Leu Pro Ile Asp Pro Leu Asp Ile Ser Gln
            420                 425                 430

aat tta gct gcg gtg aat aag agt cta agt gat gca cta caa cac tta   1344
Asn Leu Ala Ala Val Asn Lys Ser Leu Ser Asp Ala Leu Gln His Leu
        435                 440                 445

gca caa agt gac aca tac ctt tct gca atc aca tca gct acg act aca   1392
Ala Gln Ser Asp Thr Tyr Leu Ser Ala Ile Thr Ser Ala Thr Thr Thr
    450                 455                 460

agt gta tta tcc ata ata gca atc tgt ctt gga tcg tta ggt tta ata   1440
Ser Val Leu Ser Ile Ile Ala Ile Cys Leu Gly Ser Leu Gly Leu Ile
465                 470                 475                 480

tta ata atc ttg ctc agt gta gtt gtg tgg aag tta ttg acc att gtc   1488
Leu Ile Ile Leu Leu Ser Val Val Val Trp Lys Leu Leu Thr Ile Val
                485                 490                 495

gct gct aat cga aat aga atg gag aat ttt gtt tat cat aat tca gca   1536
Ala Ala Asn Arg Asn Arg Met Glu Asn Phe Val Tyr His Asn Ser Ala
            500                 505                 510

ttc cac cac cca cga tct gat ctc agt gag aaa aat caa cct gca act   1584
Phe His His Pro Arg Ser Asp Leu Ser Glu Lys Asn Gln Pro Ala Thr
        515                 520                 525

ctt gga aca aga                                                  1596
Leu Gly Thr Arg
    530
```

<210> 14

<211> 532
<212> PRT
<213> Cryptovirus F0 protein

<400> 14

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Leu Asp Pro Ala Ala Leu Met Gln Ile Gly Val Ile Pro Thr Asn Val
 1               5                  10                  15
Arg Gln Leu Met Tyr Tyr Thr Glu Ala Ser Ser Ala Phe Ile Val Val
            20                  25                  30
Lys Leu Met Pro Thr Ile Asp Ser Pro Ile Ser Gly Cys Asn Ile Thr
        35                  40                  45
Ser Ile Ser Ser Tyr Asn Ala Thr Val Thr Lys Leu Leu Gln Pro Ile
    50                  55                  60
Gly Glu Asn Leu Glu Thr Ile Arg Asn Gln Leu Ile Pro Thr Arg Arg
65                  70                  75                  80
Arg Arg Arg Phe Ala Gly Val Val Ile Gly Leu Ala Ala Leu Gly Val
                85                  90                  95
Ala Thr Ala Ala Gln Val Thr Ala Ala Val Ala Leu Val Lys Ala Asn
            100                 105                 110
Glu Asn Thr Ala Ala Ile Leu Asn Leu Lys Asn Ala Ile Gln Lys Thr
        115                 120                 125
Asn Ala Ala Val Ala Asp Val Val Gln Ala Thr Gln Ser Leu Gly Thr
    130                 135                 140
Ala Val Gln Ala Val Gln Asp His Ile Asn Ser Val Ile Ser Pro Ala
145                 150                 155                 160
Ile Thr Ala Ala Asn Cys Lys Ala Gln Asp Ala Ile Ile Gly Ser Ile
                165                 170                 175
Leu Asn Leu Tyr Leu Thr Glu Leu Thr Thr Ile Phe His Asn Gln Ile
            180                 185                 190
Thr Asn Pro Ala Leu Ser Pro Ile Thr Ile Gln Ala Leu Arg Ile Leu
        195                 200                 205
Leu Gly Ser Thr Leu Pro Thr Val Val Glu Lys Ser Phe Asn Thr Gln
    210                 215                 220
Ile Ser Ala Ala Glu Leu Leu Ser Ser Gly Leu Leu Thr Gly Gln Ile
225                 230                 235                 240
Val Gly Leu Asp Leu Thr Tyr Met Gln Met Val Ile Lys Ile Glu Leu
                245                 250                 255
Pro Thr Leu Thr Val Gln Pro Ala Thr Gln Ile Ile Asp Leu Ala Thr
            260                 265                 270
Ile Ser Ala Phe Ile Asn Asn Gln Glu Val Met Ala Gln Leu Pro Thr
        275                 280                 285
Arg Val Ile Val Thr Gly Ser Leu Ile Gln Ala Tyr Pro Ala Ser Gln
    290                 295                 300
Cys Thr Ile Thr Pro Asn Thr Val Tyr Cys Arg Tyr Asn Asp Ala Gln
305                 310                 315                 320
Val Leu Ser Asp Asp Thr Met Ala Cys Leu Gln Gly Asn Leu Thr Arg
                325                 330                 335
Cys Thr Phe Ser Pro Val Val Gly Ser Phe Leu Thr Arg Phe Val Leu
            340                 345                 350
Phe Asp Gly Ile Val Tyr Ala Asn Cys Arg Ser Met Leu Cys Lys Cys
        355                 360                 365
Met Gln Pro Ala Ala Val Ile Leu Gln Pro Ser Ser Ser Pro Val Thr
    370                 375                 380
Val Ile Asp Met His Lys Cys Val Ser Leu Gln Leu Asp Asp Leu Arg
385                 390                 395                 400
```

```
Phe Thr Ile Thr Gln Leu Ala Asn Val Thr Tyr Asn Ser Thr Ile Lys
                405                 410                 415
Leu Glu Thr Ser Gln Ile Leu Pro Ile Asp Pro Leu Asp Ile Ser Gln
            420                 425                 430
Asn Leu Ala Ala Val Asn Lys Ser Leu Ser Asp Ala Leu Gln His Leu
        435                 440                 445
Ala Gln Ser Asp Thr Tyr Leu Ser Ala Ile Thr Ser Ala Thr Thr Thr
    450                 455                 460
Ser Val Leu Ser Ile Ile Ala Ile Cys Leu Gly Ser Leu Gly Leu Ile
465                 470                 475                 480
Leu Ile Ile Leu Leu Ser Val Val Val Trp Lys Leu Leu Thr Ile Val
                485                 490                 495
Ala Ala Asn Arg Asn Arg Met Glu Asn Phe Val Tyr His Asn Ser Ala
            500                 505                 510
Phe His His Pro Arg Ser Asp Leu Ser Glu Lys Asn Gln Pro Ala Thr
        515                 520                 525
Leu Gly Thr Arg
    530
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<210> 15
<211> 249
<212> DNA
<213> Cryptovirus

<220>
<221> CDS
<222> (1)...(249)
<223> Cryptovirus F2 coding sequence; cDNA in mRNA sense

<400> 15

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ctt gat cca gca gcc ctc atg caa atc ggt gtc att cca aca aat gtc   48
Leu Asp Pro Ala Ala Leu Met Gln Ile Gly Val Ile Pro Thr Asn Val
 1               5                  10                  15

cgg caa ctt atg tat tat act gag gcc tca tca gca ttc att gtt gtg   96
Arg Gln Leu Met Tyr Tyr Thr Glu Ala Ser Ser Ala Phe Ile Val Val
             20                  25                  30

aag tta atg cct aca att gac tcg ccg att agt gga tgt aat ata aca   144
Lys Leu Met Pro Thr Ile Asp Ser Pro Ile Ser Gly Cys Asn Ile Thr
         35                  40                  45

tca att tca agc tat aat gca aca gtg aca aaa ctc cta cag ccg atc   192
Ser Ile Ser Ser Tyr Asn Ala Thr Val Thr Lys Leu Leu Gln Pro Ile
     50                  55                  60

ggt gag aat ttg gag acg att agg aac cag ttg att cca act cgg agg   240
Gly Glu Asn Leu Glu Thr Ile Arg Asn Gln Leu Ile Pro Thr Arg Arg
 65                  70                  75                  80

aga cgc cgg                                                      249
Arg Arg Arg
```

<210> 16
<211> 83
<212> PRT
<213> Cryptovirus F2 protein

<400> 16
Leu Asp Pro Ala Ala Leu Met Gln Ile Gly Val Ile Pro Thr Asn Val
1 5 10 15
Arg Gln Leu Met Tyr Tyr Thr Glu Ala Ser Ser Ala Phe Ile Val Val
20 25 30
Lys Leu Met Pro Thr Ile Asp Ser Pro Ile Ser Gly Cys Asn Ile Thr
35 40 45
Ser Ile Ser Ser Tyr Asn Ala Thr Val Thr Lys Leu Leu Gln Pro Ile
50 55 60
Gly Glu Asn Leu Glu Thr Ile Arg Asn Gln Leu Ile Pro Thr Arg Arg
65 70 75 80
Arg Arg Arg

<210> 17
<211> 1347
<212> DNA
<213> Cryptovirus

<220>
<221> CDS
<222> (1)...(1347)
<223> Cryptovirus F1 protein encoding sequence; cDNA in mRNA sense

<400> 17
ttt gca ggg gtg gtg att gga tta gct gca tta gga gta gct act gcc 48
Phe Ala Gly Val Val Ile Gly Leu Ala Ala Leu Gly Val Ala Thr Ala
1 5 10 15

gca caa gtc act gcc gca gta gca cta gtt aag gca aat gaa aat act 96
Ala Gln Val Thr Ala Ala Val Ala Leu Val Lys Ala Asn Glu Asn Thr
20 25 30

gcg gct ata ctc aat ctc aaa aat gca atc caa aaa aca aat gca gca 144
Ala Ala Ile Leu Asn Leu Lys Asn Ala Ile Gln Lys Thr Asn Ala Ala
35 40 45

gtt gca gat gtg gtc cag gcc aca caa tca cta gga acg gca gtt caa 192
Val Ala Asp Val Val Gln Ala Thr Gln Ser Leu Gly Thr Ala Val Gln
50 55 60

gca gtt caa gat cac ata aac agt gtg ata agt cca gca att aca gca 240
Ala Val Gln Asp His Ile Asn Ser Val Ile Ser Pro Ala Ile Thr Ala
65 70 75 80

gcc aat tgt aag gcc caa gat gct atc att ggc tca atc ctc aat ctc 288
Ala Asn Cys Lys Ala Gln Asp Ala Ile Ile Gly Ser Ile Leu Asn Leu

```
                85                  90                  95

tat ttg acc gag ttg aca act atc ttc cac aat caa att aca aac cct   336
Tyr Leu Thr Glu Leu Thr Thr Ile Phe His Asn Gln Ile Thr Asn Pro
            100                 105                 110

gca ttg agt cct att aca att caa gct tta agg atc cta ctg ggg agt   384
Ala Leu Ser Pro Ile Thr Ile Gln Ala Leu Arg Ile Leu Leu Gly Ser
        115                 120                 125

acc ttg ccg act gtg gtc gaa aaa tct ttc aat acc cag ata agt gca   432
Thr Leu Pro Thr Val Val Glu Lys Ser Phe Asn Thr Gln Ile Ser Ala
    130                 135                 140

gct gag ctt ctc tca tca ggg ttg ttg aca ggc cag att gtg gga tta   480
Ala Glu Leu Leu Ser Ser Gly Leu Leu Thr Gly Gln Ile Val Gly Leu
145                 150                 155                 160

gat ttg acc tat atg cag atg gtc ata aaa att gag ctg cca act tta   528
Asp Leu Thr Tyr Met Gln Met Val Ile Lys Ile Glu Leu Pro Thr Leu
                165                 170                 175

act gta caa cct gca acc cag atc ata gat ctg gcc acc att tct gca   576
Thr Val Gln Pro Ala Thr Gln Ile Ile Asp Leu Ala Thr Ile Ser Ala
            180                 185                 190

ttc att aac aat caa gaa gtc atg gcc caa tta cca aca cgt gtt att   624
Phe Ile Asn Asn Gln Glu Val Met Ala Gln Leu Pro Thr Arg Val Ile
        195                 200                 205

gtg act ggc agc ttg atc caa gcc tat ccc gca tcg caa tgc act att   672
Val Thr Gly Ser Leu Ile Gln Ala Tyr Pro Ala Ser Gln Cys Thr Ile
    210                 215                 220

aca ccc aac act gtg tac tgt agg tat aat gat gcc caa gta ctc tca   720
Thr Pro Asn Thr Val Tyr Cys Arg Tyr Asn Asp Ala Gln Val Leu Ser
225                 230                 235                 240

gat gat acg atg gct tgc ctc caa ggt aac ttg aca aga tgc acc ttc   768
Asp Asp Thr Met Ala Cys Leu Gln Gly Asn Leu Thr Arg Cys Thr Phe
                245                 250                 255

tct cca gtg gtt ggg agc ttt ctc act cga ttc gtg ctg ttc gat gga   816
Ser Pro Val Val Gly Ser Phe Leu Thr Arg Phe Val Leu Phe Asp Gly
            260                 265                 270

ata gtt tat gca aat tgc agg tcg atg ctg tgc aag tgc atg caa cct   864
Ile Val Tyr Ala Asn Cys Arg Ser Met Leu Cys Lys Cys Met Gln Pro
        275                 280                 285

gct gcc gtg atc cta cag ccg agt tca tcc cct gta act gtc att gac   912
Ala Ala Val Ile Leu Gln Pro Ser Ser Ser Pro Val Thr Val Ile Asp
    290                 295                 300

atg cac aaa tgt gtg agt ctg cag ctt gac gat ctc aga ttc acc atc   960
```

```
Met His Lys Cys Val Ser Leu Gln Leu Asp Asp Leu Arg Phe Thr Ile
305                 310                 315                 320

act caa ttg gcc aat gta acc tac aat agc acc atc aag ctt gaa aca   1008
Thr Gln Leu Ala Asn Val Thr Tyr Asn Ser Thr Ile Lys Leu Glu Thr
                325                 330                 335

tcc cag atc ttg cct att gat ccg ttg gat ata tcc cag aat tta gct   1056
Ser Gln Ile Leu Pro Ile Asp Pro Leu Asp Ile Ser Gln Asn Leu Ala
            340                 345                 350

gcg gtg aat aag agt cta agt gat gca cta caa cac tta gca caa agt   1104
Ala Val Asn Lys Ser Leu Ser Asp Ala Leu Gln His Leu Ala Gln Ser
        355                 360                 365

gac aca tac ctt tct gca atc aca tca gct acg act aca agt gta tta   1152
Asp Thr Tyr Leu Ser Ala Ile Thr Ser Ala Thr Thr Thr Ser Val Leu
    370                 375                 380

tcc ata ata gca atc tgt ctt gga tcg tta ggt tta ata tta ata atc   1200
Ser Ile Ile Ala Ile Cys Leu Gly Ser Leu Gly Leu Ile Leu Ile Ile
385                 390                 395                 400

ttg ctc agt gta gtt gtg tgg aag tta ttg acc att gtc gct gct aat   1248
Leu Leu Ser Val Val Val Trp Lys Leu Leu Thr Ile Val Ala Ala Asn
                405                 410                 415

cga aat aga atg gag aat ttt gtt tat cat aat tca gca ttc cac cac   1296
Arg Asn Arg Met Glu Asn Phe Val Tyr His Asn Ser Ala Phe His His
            420                 425                 430

cca cga tct gat ctc agt gag aaa aat caa cct gca act ctt gga aca   1344
Pro Arg Ser Asp Leu Ser Glu Lys Asn Gln Pro Ala Thr Leu Gly Thr
        435                 440                 445

aga                                                               1347
Arg
```

<210> 18
<211> 449
<212> PRT
<213> Cryptovirus

<400> 18

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Phe Ala Gly Val Val Ile Gly Leu Ala Ala Leu Gly Val Ala Thr Ala
 1               5                  10                  15
Ala Gln Val Thr Ala Ala Val Ala Leu Val Lys Ala Asn Glu Asn Thr
            20                  25                  30
Ala Ala Ile Leu Asn Leu Lys Asn Ala Ile Gln Lys Thr Asn Ala Ala
        35                  40                  45
Val Ala Asp Val Val Gln Ala Thr Gln Ser Leu Gly Thr Ala Val Gln
    50                  55                  60
Ala Val Gln Asp His Ile Asn Ser Val Ile Ser Pro Ala Ile Thr Ala
```

```
65                  70                  75                  80
Ala Asn Cys Lys Ala Gln Asp Ala Ile Ile Gly Ser Ile Leu Asn Leu
                85                  90                  95
Tyr Leu Thr Glu Leu Thr Thr Ile Phe His Asn Gln Ile Thr Asn Pro
            100                 105                 110
Ala Leu Ser Pro Ile Thr Ile Gln Ala Leu Arg Ile Leu Leu Gly Ser
        115                 120                 125
Thr Leu Pro Thr Val Val Glu Lys Ser Phe Asn Thr Gln Ile Ser Ala
    130                 135                 140
Ala Glu Leu Leu Ser Ser Gly Leu Leu Thr Gly Gln Ile Val Gly Leu
145                 150                 155                 160
Asp Leu Thr Tyr Met Gln Met Val Ile Lys Ile Glu Leu Pro Thr Leu
                165                 170                 175
Thr Val Gln Pro Ala Thr Gln Ile Ile Asp Leu Ala Thr Ile Ser Ala
            180                 185                 190
Phe Ile Asn Asn Gln Glu Val Met Ala Gln Leu Pro Thr Arg Val Ile
        195                 200                 205
Val Thr Gly Ser Leu Ile Gln Ala Tyr Pro Ala Ser Gln Cys Thr Ile
    210                 215                 220
Thr Pro Asn Thr Val Tyr Cys Arg Tyr Asn Asp Ala Gln Val Leu Ser
225                 230                 235                 240
Asp Asp Thr Met Ala Cys Leu Gln Gly Asn Leu Thr Arg Cys Thr Phe
                245                 250                 255
Ser Pro Val Val Gly Ser Phe Leu Thr Arg Phe Val Leu Phe Asp Gly
            260                 265                 270
Ile Val Tyr Ala Asn Cys Arg Ser Met Leu Cys Lys Cys Met Gln Pro
        275                 280                 285
Ala Ala Val Ile Leu Gln Pro Ser Ser Ser Pro Val Thr Val Ile Asp
    290                 295                 300
Met His Lys Cys Val Ser Leu Gln Leu Asp Asp Leu Arg Phe Thr Ile
305                 310                 315                 320
Thr Gln Leu Ala Asn Val Thr Tyr Asn Ser Thr Ile Lys Leu Glu Thr
                325                 330                 335
Ser Gln Ile Leu Pro Ile Asp Pro Leu Asp Ile Ser Gln Asn Leu Ala
            340                 345                 350
Ala Val Asn Lys Ser Leu Ser Asp Ala Leu Gln His Leu Ala Gln Ser
        355                 360                 365
Asp Thr Tyr Leu Ser Ala Ile Thr Ser Ala Thr Thr Thr Ser Val Leu
    370                 375                 380
Ser Ile Ile Ala Ile Cys Leu Gly Ser Leu Gly Leu Ile Leu Ile Ile
385                 390                 395                 400
Leu Leu Ser Val Val Val Trp Lys Leu Leu Thr Ile Val Ala Ala Asn
                405                 410                 415
Arg Asn Arg Met Glu Asn Phe Val Tyr His Asn Ser Ala Phe His His
            420                 425                 430
Pro Arg Ser Asp Leu Ser Glu Lys Asn Gln Pro Ala Thr Leu Gly Thr
        435                 440                 445
Arg
```

<210> 19
<211> 132
<212> DNA
<213> Cryptovirus

<220>
<221> CDS
<222> (1)...(132)
<223> Cryptovirus SH protein encoding sequence; cDNA in
mRNA sense

<400> 19
atg ctg cct gat ccg gaa gat ccg gaa agc aaa aaa gct aca agg aga 48
Met Leu Pro Asp Pro Glu Asp Pro Glu Ser Lys Lys Ala Thr Arg Arg
1 5 10 15

aca gga aac cta att atc tgc ttc cta ttc atc ttc ttt ctg ttt gta 96
Thr Gly Asn Leu Ile Ile Cys Phe Leu Phe Ile Phe Phe Leu Phe Val
20 25 30

acc ctc att gtt cca act cta aga cac ttg cta tct 132
Thr Leu Ile Val Pro Thr Leu Arg His Leu Leu Ser
35 40

<210> 20
<211> 44
<212> PRT
<213> Cryptovirus

<400> 20
Met Leu Pro Asp Pro Glu Asp Pro Glu Ser Lys Lys Ala Thr Arg Arg
1 5 10 15
Thr Gly Asn Leu Ile Ile Cys Phe Leu Phe Ile Phe Phe Leu Phe Val
20 25 30
Thr Leu Ile Val Pro Thr Leu Arg His Leu Leu Ser
35 40

<210> 21
<211> 1695
<212> DNA
<213> Cryptovirus

<220>
<221> CDS
<222> (1)...(1695)
<223> Cryptovirus HN protein encoding sequence; cDNA in
mRNA sense

<400> 21
atg att gca gaa gat gcc cct gtt aag ggc act tgc cga gta tta ttt 48
Met Ile Ala Glu Asp Ala Pro Val Lys Gly Thr Cys Arg Val Leu Phe
1 5 10 15

cgg aca aca act tta att ttt cta tgc aca cta cta gca tta agc atc 96
Arg Thr Thr Thr Leu Ile Phe Leu Cys Thr Leu Leu Ala Leu Ser Ile
20 25 30

```
tct atc ctt tat gag agt tta ata acc caa aag caa atc atg agt caa   144
Ser Ile Leu Tyr Glu Ser Leu Ile Thr Gln Lys Gln Ile Met Ser Gln
         35                  40                  45

gca ggc tca act gga tct aat tct gga tta gga ggt att act gat ctt   192
Ala Gly Ser Thr Gly Ser Asn Ser Gly Leu Gly Gly Ile Thr Asp Leu
     50                  55                  60

ctt aat aat att ctt tct gtc gca aat cag att ata tat aac tct gca   240
Leu Asn Asn Ile Leu Ser Val Ala Asn Gln Ile Ile Tyr Asn Ser Ala
 65                  70                  75                  80

gtc gct cta cct cta caa ttg gac act ctt gaa tca aca ctc ctt aca   288
Val Ala Leu Pro Leu Gln Leu Asp Thr Leu Glu Ser Thr Leu Leu Thr
                 85                  90                  95

gcc att aag tct ctt caa acc agt gac aag cta gaa cag aac tgc tcg   336
Ala Ile Lys Ser Leu Gln Thr Ser Asp Lys Leu Glu Gln Asn Cys Ser
            100                 105                 110

tgg ggt gct gca ctg att aat gat aat aga tac att aat ggc atc aat   384
Trp Gly Ala Ala Leu Ile Asn Asp Asn Arg Tyr Ile Asn Gly Ile Asn
        115                 120                 125

cag ttc tat ttc tca att gct gag ggt cgc aat ctg aca ctt ggc cca   432
Gln Phe Tyr Phe Ser Ile Ala Glu Gly Arg Asn Leu Thr Leu Gly Pro
    130                 135                 140

ctt ctt aat ata cct agt ttc att cca act gcc acg aca cca gag ggc   480
Leu Leu Asn Ile Pro Ser Phe Ile Pro Thr Ala Thr Thr Pro Glu Gly
145                 150                 155                 160

tgc acc agg atc cca tca ttc tcg ctc act aag aca cac tgg tgt tat   528
Cys Thr Arg Ile Pro Ser Phe Ser Leu Thr Lys Thr His Trp Cys Tyr
                165                 170                 175

acg cac aat gtt atc ctg aat gga tgc cag gat cat gta tcc tca aat   576
Thr His Asn Val Ile Leu Asn Gly Cys Gln Asp His Val Ser Ser Asn
            180                 185                 190

caa ttt gtt tcc atg gga atc att gaa ccc act tct gcc ggg ttt cca   624
Gln Phe Val Ser Met Gly Ile Ile Glu Pro Thr Ser Ala Gly Phe Pro
        195                 200                 205

tcc ttt cga acc tta aag act cta tat ctc agc gat ggg gtc aat cgt   672
Ser Phe Arg Thr Leu Lys Thr Leu Tyr Leu Ser Asp Gly Val Asn Arg
    210                 215                 220

aag agc tgc tct atc agt aca gtt ccg ggg ggt tgt atg atg tac tgt   720
Lys Ser Cys Ser Ile Ser Thr Val Pro Gly Gly Cys Met Met Tyr Cys
225                 230                 235                 240

ttt gtc tct act caa cca gag agg gat gac tac ttt tct acc gct cct   768
Phe Val Ser Thr Gln Pro Glu Arg Asp Asp Tyr Phe Ser Thr Ala Pro
                245                 250                 255
```

```
cca gaa caa cga att att ata atg tac tat aat gat aca atc gtg gag   816
Pro Glu Gln Arg Ile Ile Ile Met Tyr Tyr Asn Asp Thr Ile Val Glu
            260                 265                 270

cgc ata att aat cca ccc ggg gta cta gac gta tgg gca aca ttg aac   864
Arg Ile Ile Asn Pro Pro Gly Val Leu Asp Val Trp Ala Thr Leu Asn
        275                 280                 285

cca gga aca gga agc ggg gta tat tat tta ggt tgg gtg ctc ttt cca   912
Pro Gly Thr Gly Ser Gly Val Tyr Tyr Leu Gly Trp Val Leu Phe Pro
    290                 295                 300

ata tat ggc ggc gtg att aaa aat acg agt tta tgg aat aat caa gca   960
Ile Tyr Gly Gly Val Ile Lys Asn Thr Ser Leu Trp Asn Asn Gln Ala
305                 310                 315                 320

aat aaa tac ttc att ccc cag atg gtt gct gct ctc tgc tca caa aac  1008
Asn Lys Tyr Phe Ile Pro Gln Met Val Ala Ala Leu Cys Ser Gln Asn
                325                 330                 335

cag gca act caa gtc caa aat gct aag tca tca tac tat agc agc tgg  1056
Gln Ala Thr Gln Val Gln Asn Ala Lys Ser Ser Tyr Tyr Ser Ser Trp
            340                 345                 350

ttt ggc aat cga atg att cag tct ggg atc ctg gca tgc cct ctt caa  1104
Phe Gly Asn Arg Met Ile Gln Ser Gly Ile Leu Ala Cys Pro Leu Gln
        355                 360                 365

cag gat cta acc aat gag tgt tta gtt ctg ccc ttt tct aat gat cag  1152
Gln Asp Leu Thr Asn Glu Cys Leu Val Leu Pro Phe Ser Asn Asp Gln
    370                 375                 380

gtg ctt atg ggt gct gaa ggg aga tta tat atg tat ggt gac tcg gtg  1200
Val Leu Met Gly Ala Glu Gly Arg Leu Tyr Met Tyr Gly Asp Ser Val
385                 390                 395                 400

tat tac tac caa aga agc aat agt tgg tgg cct atg acc atg ctg tat  1248
Tyr Tyr Tyr Gln Arg Ser Asn Ser Trp Trp Pro Met Thr Met Leu Tyr
                405                 410                 415

aag gta acc ata aca ttc act aat ggt cag cca tcc gct ata tca gct  1296
Lys Val Thr Ile Thr Phe Thr Asn Gly Gln Pro Ser Ala Ile Ser Ala
            420                 425                 430

cag aat gtg ccc aca cag cag gtc cct aga cct ggg aca gga gac tgc  1344
Gln Asn Val Pro Thr Gln Gln Val Pro Arg Pro Gly Thr Gly Asp Cys
        435                 440                 445

ttt gca acc aat aga tgt ccc ggt ttt tgc ttg aca gga gtg tat gct  1392
Phe Ala Thr Asn Arg Cys Pro Gly Phe Cys Leu Thr Gly Val Tyr Ala
    450                 455                 460

gat gct tgg tta ctg acc aac cct tcg tct acc agt aca ttt gga tcg  1440
Asp Ala Trp Leu Leu Thr Asn Pro Ser Ser Thr Ser Thr Phe Gly Ser
```

```
465                 470                 475                 480

gaa gca acc ttc act ggt tct tat ctc aac gca gca act cag cgt atc   1488
Glu Ala Thr Phe Thr Gly Ser Tyr Leu Asn Ala Ala Thr Gln Arg Ile
                485                 490                 495

aat ccg acg atg tat atc gcg aac aac aca cag atc ata agc tca cag   1536
Asn Pro Thr Met Tyr Ile Ala Asn Asn Thr Gln Ile Ile Ser Ser Gln
            500                 505                 510

caa ttt gga tca agc ggt caa gaa gca gca tat ggc cac aca act tgt   1584
Gln Phe Gly Ser Ser Gly Gln Glu Ala Ala Tyr Gly His Thr Thr Cys
        515                 520                 525

ttt agg gac aca ggc tct gtt atg gta tac tgt atc tat att att gaa   1632
Phe Arg Asp Thr Gly Ser Val Met Val Tyr Cys Ile Tyr Ile Ile Glu
    530                 535                 540

ttg tcc tca tct ctc tta gga caa ttt cag att gtc cca ttt atc cgt   1680
Leu Ser Ser Ser Leu Leu Gly Gln Phe Gln Ile Val Pro Phe Ile Arg
545                 550                 555                 560

cag gtg aca cta tcc                                               1695
Gln Val Thr Leu Ser
                565
```

<210> 22
<211> 565
<212> PRT
<213> Cryptovirus

<400> 22

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Met Ile Ala Glu Asp Ala Pro Val Lys Gly Thr Cys Arg Val Leu Phe
 1               5                  10                  15
Arg Thr Thr Thr Leu Ile Phe Leu Cys Thr Leu Leu Ala Leu Ser Ile
            20                  25                  30
Ser Ile Leu Tyr Glu Ser Leu Ile Thr Gln Lys Gln Ile Met Ser Gln
        35                  40                  45
Ala Gly Ser Thr Gly Ser Asn Ser Gly Leu Gly Gly Ile Thr Asp Leu
    50                  55                  60
Leu Asn Asn Ile Leu Ser Val Ala Asn Gln Ile Ile Tyr Asn Ser Ala
65                  70                  75                  80
Val Ala Leu Pro Leu Gln Leu Asp Thr Leu Glu Ser Thr Leu Leu Thr
                85                  90                  95
Ala Ile Lys Ser Leu Gln Thr Ser Asp Lys Leu Glu Gln Asn Cys Ser
            100                 105                 110
Trp Gly Ala Ala Leu Ile Asn Asp Asn Arg Tyr Ile Asn Gly Ile Asn
        115                 120                 125
Gln Phe Tyr Phe Ser Ile Ala Glu Gly Arg Asn Leu Thr Leu Gly Pro
    130                 135                 140
Leu Leu Asn Ile Pro Ser Phe Ile Pro Thr Ala Thr Thr Pro Glu Gly
145                 150                 155                 160
Cys Thr Arg Ile Pro Ser Phe Ser Leu Thr Lys Thr His Trp Cys Tyr
                165                 170                 175
```

```
Thr His Asn Val Ile Leu Asn Gly Cys Gln Asp His Val Ser Ser Asn
            180                 185                 190
Gln Phe Val Ser Met Gly Ile Ile Glu Pro Thr Ser Ala Gly Phe Pro
        195                 200                 205
Ser Phe Arg Thr Leu Lys Thr Leu Tyr Leu Ser Asp Gly Val Asn Arg
    210                 215                 220
Lys Ser Cys Ser Ile Ser Thr Val Pro Gly Gly Cys Met Met Tyr Cys
225                 230                 235                 240
Phe Val Ser Thr Gln Pro Glu Arg Asp Asp Tyr Phe Ser Thr Ala Pro
                245                 250                 255
Pro Glu Gln Arg Ile Ile Ile Met Tyr Tyr Asn Asp Thr Ile Val Glu
            260                 265                 270
Arg Ile Ile Asn Pro Pro Gly Val Leu Asp Val Trp Ala Thr Leu Asn
        275                 280                 285
Pro Gly Thr Gly Ser Gly Val Tyr Tyr Leu Gly Trp Val Leu Phe Pro
    290                 295                 300
Ile Tyr Gly Gly Val Ile Lys Asn Thr Ser Leu Trp Asn Asn Gln Ala
305                 310                 315                 320
Asn Lys Tyr Phe Ile Pro Gln Met Val Ala Ala Leu Cys Ser Gln Asn
                325                 330                 335
Gln Ala Thr Gln Val Gln Asn Ala Lys Ser Ser Tyr Tyr Ser Ser Trp
            340                 345                 350
Phe Gly Asn Arg Met Ile Gln Ser Gly Ile Leu Ala Cys Pro Leu Gln
        355                 360                 365
Gln Asp Leu Thr Asn Glu Cys Leu Val Leu Pro Phe Ser Asn Asp Gln
    370                 375                 380
Val Leu Met Gly Ala Glu Gly Arg Leu Tyr Met Tyr Gly Asp Ser Val
385                 390                 395                 400
Tyr Tyr Tyr Gln Arg Ser Asn Ser Trp Trp Pro Met Thr Met Leu Tyr
                405                 410                 415
Lys Val Thr Ile Thr Phe Thr Asn Gly Gln Pro Ser Ala Ile Ser Ala
            420                 425                 430
Gln Asn Val Pro Thr Gln Gln Val Pro Arg Pro Gly Thr Gly Asp Cys
        435                 440                 445
Phe Ala Thr Asn Arg Cys Pro Gly Phe Cys Leu Thr Gly Val Tyr Ala
    450                 455                 460
Asp Ala Trp Leu Leu Thr Asn Pro Ser Ser Thr Ser Thr Phe Gly Ser
465                 470                 475                 480
Glu Ala Thr Phe Thr Gly Ser Tyr Leu Asn Ala Ala Thr Gln Arg Ile
                485                 490                 495
Asn Pro Thr Met Tyr Ile Ala Asn Asn Thr Gln Ile Ile Ser Ser Gln
            500                 505                 510
Gln Phe Gly Ser Ser Gly Gln Glu Ala Ala Tyr Gly His Thr Thr Cys
        515                 520                 525
Phe Arg Asp Thr Gly Ser Val Met Val Tyr Cys Ile Tyr Ile Ile Glu
    530                 535                 540
Leu Ser Ser Ser Leu Leu Gly Gln Phe Gln Ile Val Pro Phe Ile Arg
545                 550                 555                 560
Gln Val Thr Leu Ser
                565
```

<210> 23
<211> 6765
<212> DNA

<213> Cryptovirus

<220>
<221> CDS
<222> (1)...(6765)
<223> Cryptovirus L protein encoding sequence; cDNA in mRNA sense

<400> 23

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atg gct ggg tct cgg gag ata tta ctc cct gaa gtc cat ctc aat tca   48
Met Ala Gly Ser Arg Glu Ile Leu Leu Pro Glu Val His Leu Asn Ser
 1               5                  10                  15

cca att gta aag cat aag cta tac tat tac att cta ctt gga aac ctc   96
Pro Ile Val Lys His Lys Leu Tyr Tyr Tyr Ile Leu Leu Gly Asn Leu
            20                  25                  30

cca aat gag atc gac att gac gat tta ggt cca tta cat aat caa aat   144
Pro Asn Glu Ile Asp Ile Asp Asp Leu Gly Pro Leu His Asn Gln Asn
        35                  40                  45

tgg aat caa ata gca cat gaa gag tct aac tta gct caa cgc ttg gta   192
Trp Asn Gln Ile Ala His Glu Glu Ser Asn Leu Ala Gln Arg Leu Val
    50                  55                  60

aat gta aga aat ttt cta att acc cac atc cct gat ctt aga aag ggc   240
Asn Val Arg Asn Phe Leu Ile Thr His Ile Pro Asp Leu Arg Lys Gly
65                  70                  75                  80

cat tgg caa gag tat gta aat gta ata ctg tgg ccg cga att ctt ccc   288
His Trp Gln Glu Tyr Val Asn Val Ile Leu Trp Pro Arg Ile Leu Pro
                85                  90                  95

ttg atc ccg gat ttt aaa atc aat gac caa ttg cct ctg ctc aaa aat   336
Leu Ile Pro Asp Phe Lys Ile Asn Asp Gln Leu Pro Leu Leu Lys Asn
            100                 105                 110

tgg gac aag tta gtt aaa gaa tca tgt tca gta atc aat gcg ggt act   384
Trp Asp Lys Leu Val Lys Glu Ser Cys Ser Val Ile Asn Ala Gly Thr
        115                 120                 125

tcc cag tgc att cag aat ctc agc tat gga ctg aca ggt cgt ggg aac   432
Ser Gln Cys Ile Gln Asn Leu Ser Tyr Gly Leu Thr Gly Arg Gly Asn
    130                 135                 140

ctc ttt aca cga tca cgt gaa ctc tct ggt gac cgc agg gat att gat   480
Leu Phe Thr Arg Ser Arg Glu Leu Ser Gly Asp Arg Arg Asp Ile Asp
145                 150                 155                 160

ctt aag acg gtt gtg gca gca tgg cat gac tca gac tgg aaa aga ata   528
Leu Lys Thr Val Val Ala Ala Trp His Asp Ser Asp Trp Lys Arg Ile
                165                 170                 175

agt gat ttt tgg att atg atc aaa ttc cag atg aga caa tta att gtt   576
Ser Asp Phe Trp Ile Met Ile Lys Phe Gln Met Arg Gln Leu Ile Val
```

```
            180                 185                 190

agg caa aca gat cat aat gat cct gat tta atc acg tat atc gaa aat   624
Arg Gln Thr Asp His Asn Asp Pro Asp Leu Ile Thr Tyr Ile Glu Asn
        195                 200                 205

aga gaa ggc ata atc atc ata acc cct gaa ctg gta gca tta ttt aat   672
Arg Glu Gly Ile Ile Ile Ile Thr Pro Glu Leu Val Ala Leu Phe Asn
    210                 215                 220

act gag aat cat aca cta aca tac atg acc ttt gaa att gta ctg atg   720
Thr Glu Asn His Thr Leu Thr Tyr Met Thr Phe Glu Ile Val Leu Met
225                 230                 235                 240

gtt tca gat atg tac gaa ggt cgt cac aac att tta tca cta tgc aca   768
Val Ser Asp Met Tyr Glu Gly Arg His Asn Ile Leu Ser Leu Cys Thr
                245                 250                 255

gtt agc act tac ctg aat cct ctg aag aaa aga ata aca tat tta ttg   816
Val Ser Thr Tyr Leu Asn Pro Leu Lys Lys Arg Ile Thr Tyr Leu Leu
            260                 265                 270

agc ctt gta gat aac tta gct ttt cag ata ggt gat gct gta tat aac   864
Ser Leu Val Asp Asn Leu Ala Phe Gln Ile Gly Asp Ala Val Tyr Asn
        275                 280                 285

ata att gct ttg cta gaa tcc ttt gta tat gca cag ttg caa atg tca   912
Ile Ile Ala Leu Leu Glu Ser Phe Val Tyr Ala Gln Leu Gln Met Ser
    290                 295                 300

gat ccc atc cca gaa ctc aga gga caa ttc cat gca ttc gta tgt tct   960
Asp Pro Ile Pro Glu Leu Arg Gly Gln Phe His Ala Phe Val Cys Ser
305                 310                 315                 320

gag att ctt gat gca cta agg gga act aat agt ttc acc cag gat gaa  1008
Glu Ile Leu Asp Ala Leu Arg Gly Thr Asn Ser Phe Thr Gln Asp Glu
                325                 330                 335

tta aga act gtg aca act aat ttg ata tcc cca ttc caa gat ctg acc  1056
Leu Arg Thr Val Thr Thr Asn Leu Ile Ser Pro Phe Gln Asp Leu Thr
            340                 345                 350

cca gat ctt acg gct gaa ttg ctc tgt ata atg agg ctt tgg gga cac  1104
Pro Asp Leu Thr Ala Glu Leu Leu Cys Ile Met Arg Leu Trp Gly His
        355                 360                 365

ccc atg ctc act gcc agt caa gct gcg gga aag gta cgc gag tct atg  1152
Pro Met Leu Thr Ala Ser Gln Ala Ala Gly Lys Val Arg Glu Ser Met
    370                 375                 380

tgt gct ggg aaa gta ctg gac ttt ccc act att atg aaa aca cta gcc  1200
Cys Ala Gly Lys Val Leu Asp Phe Pro Thr Ile Met Lys Thr Leu Ala
385                 390                 395                 400

ttt ttc cat act att ctg atc aat gga tac agg agg aag cat cat gga  1248
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Phe Phe His Thr Ile Leu Ile Asn Gly Tyr Arg Arg Lys His His Gly
                405                 410                 415

gta tgg cca ccc tta aac tta cca ggt aat gct tca aag ggt ctc aca   1296
Val Trp Pro Pro Leu Asn Leu Pro Gly Asn Ala Ser Lys Gly Leu Thr
            420                 425                 430

gaa ctt atg aat gac aac act gag ata agc tat gaa ttc aca ctt aag   1344
Glu Leu Met Asn Asp Asn Thr Glu Ile Ser Tyr Glu Phe Thr Leu Lys
        435                 440                 445

cat tgg aag gaa atc tct ctt ata aaa ttc aag aaa tgt ttt gat gca   1392
His Trp Lys Glu Ile Ser Leu Ile Lys Phe Lys Lys Cys Phe Asp Ala
    450                 455                 460

gac gca ggt gag gaa ctc agt ata ttt atg aaa gat aaa gca att agt   1440
Asp Ala Gly Glu Glu Leu Ser Ile Phe Met Lys Asp Lys Ala Ile Ser
465                 470                 475                 480

gcc cca aaa caa gac tgg atg agt gtg ttt aga aga agc cta atc aaa   1488
Ala Pro Lys Gln Asp Trp Met Ser Val Phe Arg Arg Ser Leu Ile Lys
                485                 490                 495

cag cgc cat cag cat cat cag gtc ccc cta cca aat cca ttc aat cga   1536
Gln Arg His Gln His His Gln Val Pro Leu Pro Asn Pro Phe Asn Arg
            500                 505                 510

cgg cta ttg cta aac ttt ctc gga gat gac aaa ttc gac ccg aat gtg   1584
Arg Leu Leu Leu Asn Phe Leu Gly Asp Asp Lys Phe Asp Pro Asn Val
        515                 520                 525

gag cta cag tat gta aca tca ggt gag tat cta cat gat gac acg ttt   1632
Glu Leu Gln Tyr Val Thr Ser Gly Glu Tyr Leu His Asp Asp Thr Phe
    530                 535                 540

tgt gca tca tat tca cta aaa gag aag gaa att aaa cct gat ggt cga   1680
Cys Ala Ser Tyr Ser Leu Lys Glu Lys Glu Ile Lys Pro Asp Gly Arg
545                 550                 555                 560

att ttt gca aag ttg act aag aga atg aga tca tgt caa gtt ata gca   1728
Ile Phe Ala Lys Leu Thr Lys Arg Met Arg Ser Cys Gln Val Ile Ala
                565                 570                 575

gaa tct ctt tta gcg aac cat gct ggg aag tta atg aaa gag aat ggt   1776
Glu Ser Leu Leu Ala Asn His Ala Gly Lys Leu Met Lys Glu Asn Gly
            580                 585                 590

gtt gtg atg aat cag cta tca tta aca aaa tca cta tta aca atg agt   1824
Val Val Met Asn Gln Leu Ser Leu Thr Lys Ser Leu Leu Thr Met Ser
        595                 600                 605

cag att gga ata ata tcc gag aga gct aga aag tcg act cga gat aac   1872
Gln Ile Gly Ile Ile Ser Glu Arg Ala Arg Lys Ser Thr Arg Asp Asn
    610                 615                 620
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ata aat cga cct ggt ttc cag aat atc cag aga aat aaa tca cat cac   1920
Ile Asn Arg Pro Gly Phe Gln Asn Ile Gln Arg Asn Lys Ser His His
625                 630                 635                 640

tcc aag caa gtc aat cag cga gat cca agt gat gac ttt gaa ttg gca   1968
Ser Lys Gln Val Asn Gln Arg Asp Pro Ser Asp Asp Phe Glu Leu Ala
                645                 650                 655

gca tct ttt tta act act gat ctc aaa aaa tat tgt tta caa tgg agg   2016
Ala Ser Phe Leu Thr Thr Asp Leu Lys Lys Tyr Cys Leu Gln Trp Arg
            660                 665                 670

tat cag aca att atc cca ttt gct caa tca cta aac aga atg tat ggt   2064
Tyr Gln Thr Ile Ile Pro Phe Ala Gln Ser Leu Asn Arg Met Tyr Gly
        675                 680                 685

tat cct cat ctc ttc gag tgg att cac ttg cgg cta atg cgt agt aca   2112
Tyr Pro His Leu Phe Glu Trp Ile His Leu Arg Leu Met Arg Ser Thr
    690                 695                 700

ctt tac gtg ggg gac ccc ttc aac cca cca gca gat acc agt caa ttt   2160
Leu Tyr Val Gly Asp Pro Phe Asn Pro Pro Ala Asp Thr Ser Gln Phe
705                 710                 715                 720

gat cta gat aaa gta att aat gga gat atc ttc att gta tca ccc aga   2208
Asp Leu Asp Lys Val Ile Asn Gly Asp Ile Phe Ile Val Ser Pro Arg
                725                 730                 735

ggt gga att gaa ggg ctg tgt caa aaa gct tgg aca atg ata tct atc   2256
Gly Gly Ile Glu Gly Leu Cys Gln Lys Ala Trp Thr Met Ile Ser Ile
            740                 745                 750

tct gtg ata att cta tct gcc aca gag tct ggc aca cga gta atg agc   2304
Ser Val Ile Ile Leu Ser Ala Thr Glu Ser Gly Thr Arg Val Met Ser
        755                 760                 765

atg gtg cag gga gat aat caa gca att gct gtc acc aca cga gta cca   2352
Met Val Gln Gly Asp Asn Gln Ala Ile Ala Val Thr Thr Arg Val Pro
    770                 775                 780

agg agc ctg ccg act ctt gag aaa aag act att gct ttt aga tct tgt   2400
Arg Ser Leu Pro Thr Leu Glu Lys Lys Thr Ile Ala Phe Arg Ser Cys
785                 790                 795                 800

aat tta ttc ttt gag agg tta aaa tgt aat aat ttt gga tta ggt cac   2448
Asn Leu Phe Phe Glu Arg Leu Lys Cys Asn Asn Phe Gly Leu Gly His
                805                 810                 815

cat ttg aaa gaa caa gag act atc att agt tct cac ttc ttt gtt tat   2496
His Leu Lys Glu Gln Glu Thr Ile Ile Ser Ser His Phe Phe Val Tyr
            820                 825                 830

agc aag aga ata ttc tat cag ggg agg att cta acg caa gcc tta aaa   2544
Ser Lys Arg Ile Phe Tyr Gln Gly Arg Ile Leu Thr Gln Ala Leu Lys
        835                 840                 845
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aat gct agt aag ctc tgc ttg aca gct gat gtc cta gga gaa tgc acc   2592
Asn Ala Ser Lys Leu Cys Leu Thr Ala Asp Val Leu Gly Glu Cys Thr
    850                 855                 860

caa tca tca tgt tct aat ctt gca act act gtc atg agg tta act gag   2640
Gln Ser Ser Cys Ser Asn Leu Ala Thr Thr Val Met Arg Leu Thr Glu
865                 870                 875                 880

aat ggt gtt gaa aaa gat atc tgt ttc tac ttg aat atc tat atg acc   2688
Asn Gly Val Glu Lys Asp Ile Cys Phe Tyr Leu Asn Ile Tyr Met Thr
                885                 890                 895

atc aaa cag ctc tcc tat gat atc atc ttc cct caa gtg tcg att cct   2736
Ile Lys Gln Leu Ser Tyr Asp Ile Ile Phe Pro Gln Val Ser Ile Pro
            900                 905                 910

gga gat cag atc aca tta gaa tac ata aat aat cca cac ctg gta tca   2784
Gly Asp Gln Ile Thr Leu Glu Tyr Ile Asn Asn Pro His Leu Val Ser
        915                 920                 925

cga ttg gct ctt tta cca tcc cag tta gga ggt cta aac tac ttg tca   2832
Arg Leu Ala Leu Leu Pro Ser Gln Leu Gly Gly Leu Asn Tyr Leu Ser
    930                 935                 940

tgc agt agg ctg ttc aat cga aac ata ggt gac ccg gtg gtt tcc gca   2880
Cys Ser Arg Leu Phe Asn Arg Asn Ile Gly Asp Pro Val Val Ser Ala
945                 950                 955                 960

gtt gca gat ctt aag aga tta att aaa tca gga tgt atg gat tac tgg   2928
Val Ala Asp Leu Lys Arg Leu Ile Lys Ser Gly Cys Met Asp Tyr Trp
                965                 970                 975

atc ctt tat aac tta tta ggg aga aaa ccg gga aac ggc tca tgg gct   2976
Ile Leu Tyr Asn Leu Leu Gly Arg Lys Pro Gly Asn Gly Ser Trp Ala
            980                 985                 990

act tta gca gct gac ccg tac tca atc aat ata gag tat caa tac ccc   3024
Thr Leu Ala Ala Asp Pro Tyr Ser Ile Asn Ile Glu Tyr Gln Tyr Pro
        995                 1000                1005

cca act aca gct ctt aag agg cac acc caa caa gtt ctg atg gaa ctc   3072
Pro Thr Thr Ala Leu Lys Arg His Thr Gln Gln Val Leu Met Glu Leu
    1010                1015                1020

agt acg aat cca atg tta cgt ggc ata ttc tct gac aat gca cag gca   3120
Ser Thr Asn Pro Met Leu Arg Gly Ile Phe Ser Asp Asn Ala Gln Ala
1025                1030                1035                1040

gaa gaa aat aat ctt gct agg ttt ctc ctg gat agg gag gtg atc ttt   3168
Glu Glu Asn Asn Leu Ala Arg Phe Leu Leu Asp Arg Glu Val Ile Phe
                1045                1050                1055

ccg cgt gta gct cac atc atc att gag caa acc agt gtc ggg agg aga   3216
Pro Arg Val Ala His Ile Ile Ile Glu Gln Thr Ser Val Gly Arg Arg
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            1060                1065                1070

aag cag att caa gga tat ttg gat tca act aga tcg ata atg agg aaa   3264
Lys Gln Ile Gln Gly Tyr Leu Asp Ser Thr Arg Ser Ile Met Arg Lys
        1075                1080                1085

tca ctg gaa att aag ccc ttg tcc aat agg aag ctt aat gaa ata ctg   3312
Ser Leu Glu Ile Lys Pro Leu Ser Asn Arg Lys Leu Asn Glu Ile Leu
    1090                1095                1100

gat tac aac atc aat tac tta gct tac aat ttg gca tta ctc aag aat   3360
Asp Tyr Asn Ile Asn Tyr Leu Ala Tyr Asn Leu Ala Leu Leu Lys Asn
1105                1110                1115                1120

gct att gaa cct ccg act tat ttg aag gca atg acc ctt gaa aca tgt   3408
Ala Ile Glu Pro Pro Thr Tyr Leu Lys Ala Met Thr Leu Glu Thr Cys
                1125                1130                1135

agc atc gac att gca agg agc ctc cgg aag ctc tcc tgg gcc cca ctc   3456
Ser Ile Asp Ile Ala Arg Ser Leu Arg Lys Leu Ser Trp Ala Pro Leu
            1140                1145                1150

ttg ggt ggg aga aat ctt gaa gga cta gag acg cca gat ccc att gaa   3504
Leu Gly Gly Arg Asn Leu Glu Gly Leu Glu Thr Pro Asp Pro Ile Glu
        1155                1160                1165

atc act gca gga gca tta att gtt gga tcg ggc tac tgt gaa cag tgt   3552
Ile Thr Ala Gly Ala Leu Ile Val Gly Ser Gly Tyr Cys Glu Gln Cys
    1170                1175                1180

gct gca gga gac aat cga ttc aca tgg ttt ttc ttg cca tct ggt atc   3600
Ala Ala Gly Asp Asn Arg Phe Thr Trp Phe Phe Leu Pro Ser Gly Ile
1185                1190                1195                1200

gag ata gga ggg gat ccc cgt gat aat cct cct atc cgt gta ccg tac   3648
Glu Ile Gly Gly Asp Pro Arg Asp Asn Pro Pro Ile Arg Val Pro Tyr
                1205                1210                1215

att ggc tcc agg act gat gag agg agg gta gcc tca atg gca tac atc   3696
Ile Gly Ser Arg Thr Asp Glu Arg Arg Val Ala Ser Met Ala Tyr Ile
            1220                1225                1230

agg ggt gcc tca agt agc cta aaa gca gtt ctt aga ctg gcg gga gtg   3744
Arg Gly Ala Ser Ser Ser Leu Lys Ala Val Leu Arg Leu Ala Gly Val
        1235                1240                1245

tac atc tgg gca ttc gga gat act ctg gag aat tgg ata gat gca ctg   3792
Tyr Ile Trp Ala Phe Gly Asp Thr Leu Glu Asn Trp Ile Asp Ala Leu
    1250                1255                1260

gat ttg tct cac act aga gtt aac atc aca ctt gaa cag tta caa tcc   3840
Asp Leu Ser His Thr Arg Val Asn Ile Thr Leu Glu Gln Leu Gln Ser
1265                1270                1275                1280

ctc acc cca ctt cca acc tct gcc aat cta acc cat cgg ttg gat gat   3888
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Leu Thr Pro Leu Pro Thr Ser Ala Asn Leu Thr His Arg Leu Asp Asp
                1285                1290                1295

ggc aca act acc cta aag ttt act cct gca agc tct tac acc ttt tca   3936
Gly Thr Thr Thr Leu Lys Phe Thr Pro Ala Ser Ser Tyr Thr Phe Ser
            1300                1305                1310

agt ttc act cat ata tca aat gat gag caa tat ctg aca att aat gac   3984
Ser Phe Thr His Ile Ser Asn Asp Glu Gln Tyr Leu Thr Ile Asn Asp
        1315                1320                1325

aaa act gca gat tca aat ata atc tac caa cag tta atg atc act gga   4032
Lys Thr Ala Asp Ser Asn Ile Ile Tyr Gln Gln Leu Met Ile Thr Gly
    1330                1335                1340

ctc ggg atc tta gaa aca tgg aat aat ccc cca atc aat aga aca ttc   4080
Leu Gly Ile Leu Glu Thr Trp Asn Asn Pro Pro Ile Asn Arg Thr Phe
1345                1350                1355                1360

gaa gaa tct acc cta cat ttg cac act ggt gca tca tgt tgt gtc cga   4128
Glu Glu Ser Thr Leu His Leu His Thr Gly Ala Ser Cys Cys Val Arg
                1365                1370                1375

cct gtg gac tcc tgc att atc tca gaa gca tta aca gtc aag cca cat   4176
Pro Val Asp Ser Cys Ile Ile Ser Glu Ala Leu Thr Val Lys Pro His
            1380                1385                1390

att aca gta ccg tac agc aat aaa ttt gta ttt gat gaa gac ccg cta   4224
Ile Thr Val Pro Tyr Ser Asn Lys Phe Val Phe Asp Glu Asp Pro Leu
        1395                1400                1405

tct gaa tat gag act gca aaa ctg gaa tcg tta tca ttc caa gcc caa   4272
Ser Glu Tyr Glu Thr Ala Lys Leu Glu Ser Leu Ser Phe Gln Ala Gln
    1410                1415                1420

tta ggc aac att gat gct gta gat atg aca ggt aaa tta aca tta ttg   4320
Leu Gly Asn Ile Asp Ala Val Asp Met Thr Gly Lys Leu Thr Leu Leu
1425                1430                1435                1440

tcc caa ttc act gca agg cag att atc aat gca atc act gga ctc gat   4368
Ser Gln Phe Thr Ala Arg Gln Ile Ile Asn Ala Ile Thr Gly Leu Asp
                1445                1450                1455

gag tct gtt tct ctt act aat gat gcc att gtt gca tca gac tat gtc   4416
Glu Ser Val Ser Leu Thr Asn Asp Ala Ile Val Ala Ser Asp Tyr Val
            1460                1465                1470

tcc aat tgg att agt gaa tgc atg tat acc aaa tta gat gaa tta ttt   4464
Ser Asn Trp Ile Ser Glu Cys Met Tyr Thr Lys Leu Asp Glu Leu Phe
        1475                1480                1485

atg tat tgt ggg tgg gaa cta cta ttg gaa cta tcc tat caa atg tat   4512
Met Tyr Cys Gly Trp Glu Leu Leu Leu Glu Leu Ser Tyr Gln Met Tyr
    1490                1495                1500
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tat ctg agg gta gtt ggg tgg agt aat ata gtg gat tat tct tac atg   4560
Tyr Leu Arg Val Val Gly Trp Ser Asn Ile Val Asp Tyr Ser Tyr Met
1505                1510                1515                1520

atc ttg aga aga atc ccg ggt gca gca tta aac aat ctg gca tct aca   4608
Ile Leu Arg Arg Ile Pro Gly Ala Ala Leu Asn Asn Leu Ala Ser Thr
                1525                1530                1535

tta agt cat cca aaa ctt ttc cga cga gct atc aac cta gat ata gtt   4656
Leu Ser His Pro Lys Leu Phe Arg Arg Ala Ile Asn Leu Asp Ile Val
            1540                1545                1550

gcc ccc tta aat gct cct cat ttt gca tct ctg gac tac atc aag atg   4704
Ala Pro Leu Asn Ala Pro His Phe Ala Ser Leu Asp Tyr Ile Lys Met
        1555                1560                1565

agt atg gat gca ata ctc tgg ggc tgt aaa aga gtc atc aat gtg ctc   4752
Ser Met Asp Ala Ile Leu Trp Gly Cys Lys Arg Val Ile Asn Val Leu
    1570                1575                1580

tcc aat gga ggg gac tta gaa tta gtt gtg aca tct gaa gat agc ctt   4800
Ser Asn Gly Gly Asp Leu Glu Leu Val Val Thr Ser Glu Asp Ser Leu
1585                1590                1595                1600

att ctc agt gac cga tcc atg aat ctc att gca agg aaa tta act tta   4848
Ile Leu Ser Asp Arg Ser Met Asn Leu Ile Ala Arg Lys Leu Thr Leu
                1605                1610                1615

tta tca ctg att cac cat aat ggt ttg gaa cta cca aag att aag ggg   4896
Leu Ser Leu Ile His His Asn Gly Leu Glu Leu Pro Lys Ile Lys Gly
            1620                1625                1630

ttc tct cct gat gag aag tgt ttc gct ttg aca gaa ttt ttg agg aaa   4944
Phe Ser Pro Asp Glu Lys Cys Phe Ala Leu Thr Glu Phe Leu Arg Lys
        1635                1640                1645

gtg gtg aac tca ggg ttg agt tca ata gag aac cta tca aat ttt atg   4992
Val Val Asn Ser Gly Leu Ser Ser Ile Glu Asn Leu Ser Asn Phe Met
    1650                1655                1660

tac aat gtg gag aac cca cgg ctt gca gca ttc gcc agc aac aat tac   5040
Tyr Asn Val Glu Asn Pro Arg Leu Ala Ala Phe Ala Ser Asn Asn Tyr
1665                1670                1675                1680

tac ctg acc aga aaa tta ttg aat tca ata cga gat act gag tca ggt   5088
Tyr Leu Thr Arg Lys Leu Leu Asn Ser Ile Arg Asp Thr Glu Ser Gly
                1685                1690                1695

caa gta gca gtc acc tca tat tat gaa tca tta gaa tat att gat agt   5136
Gln Val Ala Val Thr Ser Tyr Tyr Glu Ser Leu Glu Tyr Ile Asp Ser
            1700                1705                1710

ctt aag cta acc cca cat gtg cct ggc acc tca tgc att gag gat gat   5184
Leu Lys Leu Thr Pro His Val Pro Gly Thr Ser Cys Ile Glu Asp Asp
        1715                1720                1725
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agt cta tgt aca aat gat tac ata atc tgg atc ata gag tct aat gca   5232
Ser Leu Cys Thr Asn Asp Tyr Ile Ile Trp Ile Ile Glu Ser Asn Ala
    1730                1735                1740

aac ttg gag aag tat cca att cca aat agc cct gag gat gat tcc aat   5280
Asn Leu Glu Lys Tyr Pro Ile Pro Asn Ser Pro Glu Asp Asp Ser Asn
1745                1750                1755                1760

ttc cat aac ttt aag ttg aat gct cca tcg cac cat acc tta cgc cca   5328
Phe His Asn Phe Lys Leu Asn Ala Pro Ser His His Thr Leu Arg Pro
                1765                1770                1775

tta ggg ttg tca tcg act gct tgg tat aag ggt ata agc tgc tgc agg   5376
Leu Gly Leu Ser Ser Thr Ala Trp Tyr Lys Gly Ile Ser Cys Cys Arg
            1780                1785                1790

tac ctt gag cga tta aag cta cca caa ggt gat cat tta tat att gca   5424
Tyr Leu Glu Arg Leu Lys Leu Pro Gln Gly Asp His Leu Tyr Ile Ala
        1795                1800                1805

gaa ggt agt ggt gcc agt atg aca atc ata gaa tac cta ttc cca gga   5472
Glu Gly Ser Gly Ala Ser Met Thr Ile Ile Glu Tyr Leu Phe Pro Gly
    1810                1815                1820

aga aag ata tat tac aat tct tta ttt agt agt ggt gac aat ccc cca   5520
Arg Lys Ile Tyr Tyr Asn Ser Leu Phe Ser Ser Gly Asp Asn Pro Pro
1825                1830                1835                1840

caa aga aat tat gca cca atg cct act cag ttc att gag agt gtc cca   5568
Gln Arg Asn Tyr Ala Pro Met Pro Thr Gln Phe Ile Glu Ser Val Pro
                1845                1850                1855

tac aag ctc tgg caa gca cac aca gat caa tat ccc gag att ttt gag   5616
Tyr Lys Leu Trp Gln Ala His Thr Asp Gln Tyr Pro Glu Ile Phe Glu
            1860                1865                1870

gac ttc atc cct cta tgg aac gga aac gcc gcc atg act gac ata gga   5664
Asp Phe Ile Pro Leu Trp Asn Gly Asn Ala Ala Met Thr Asp Ile Gly
        1875                1880                1885

atg aca gct tgt gta gaa ttc atc atc aat cga gtt ggc cca agg act   5712
Met Thr Ala Cys Val Glu Phe Ile Ile Asn Arg Val Gly Pro Arg Thr
    1890                1895                1900

tgc agt tta gta cat gta gat ttg gaa tca agt gca agc tta aat caa   5760
Cys Ser Leu Val His Val Asp Leu Glu Ser Ser Ala Ser Leu Asn Gln
1905                1910                1915                1920

caa tgc ctg tca aag ccg ata att aat gct atc atc act gct aca act   5808
Gln Cys Leu Ser Lys Pro Ile Ile Asn Ala Ile Ile Thr Ala Thr Thr
                1925                1930                1935

gtt ttg tgc cct cat ggg gtg ctt att ctg aaa tat agt tgg ttg cca   5856
Val Leu Cys Pro His Gly Val Leu Ile Leu Lys Tyr Ser Trp Leu Pro
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            1940                1945                1950

ttt act aga ttt agt act ttg atc act ttc tta tgg tgc tac ttt gag   5904
Phe Thr Arg Phe Ser Thr Leu Ile Thr Phe Leu Trp Cys Tyr Phe Glu
        1955                1960                1965

aga atc act gtt ctt agg agc aca tat tct gat cca gct aat cat gag   5952
Arg Ile Thr Val Leu Arg Ser Thr Tyr Ser Asp Pro Ala Asn His Glu
    1970                1975                1980

gtt tat tta att tgt atc ctt gcc aac aac ttt gca ttc cag act gtc   6000
Val Tyr Leu Ile Cys Ile Leu Ala Asn Asn Phe Ala Phe Gln Thr Val
1985                1990                1995                2000

tcg cag gca aca gga atg gcg atg act tta acc gat caa ggg ttt acc   6048
Ser Gln Ala Thr Gly Met Ala Met Thr Leu Thr Asp Gln Gly Phe Thr
                2005                2010                2015

ttg ata tca cct gaa aga ata aat cag tat tgg gat ggt cac tta aag   6096
Leu Ile Ser Pro Glu Arg Ile Asn Gln Tyr Trp Asp Gly His Leu Lys
            2020                2025                2030

caa gaa cgt atc gta gca gaa gca att gat aag gtg gtt cta gga gaa   6144
Gln Glu Arg Ile Val Ala Glu Ala Ile Asp Lys Val Val Leu Gly Glu
        2035                2040                2045

aat gct cta ttt aat tcg agt gat aat gaa tta att ctc aaa tgt gga   6192
Asn Ala Leu Phe Asn Ser Ser Asp Asn Glu Leu Ile Leu Lys Cys Gly
    2050                2055                2060

ggg aca cca aat gca cgg aat ctt atc gat atc gag cca gtc gca act   6240
Gly Thr Pro Asn Ala Arg Asn Leu Ile Asp Ile Glu Pro Val Ala Thr
2065                2070                2075                2080

ttc ata gaa ttt gaa caa cta atc tgc aca atg ttg aca acc cac ttg   6288
Phe Ile Glu Phe Glu Gln Leu Ile Cys Thr Met Leu Thr Thr His Leu
                2085                2090                2095

aag gaa ata att gat ata aca agg tct gga acc cag gat tat gaa agt   6336
Lys Glu Ile Ile Asp Ile Thr Arg Ser Gly Thr Gln Asp Tyr Glu Ser
            2100                2105                2110

tta tta ctc act cct tac aat tta ggt ctt ctt ggt aaa atc agt acg   6384
Leu Leu Leu Thr Pro Tyr Asn Leu Gly Leu Leu Gly Lys Ile Ser Thr
        2115                2120                2125

ata gtg aga tta tta aca gaa agg att cta aat cat act atc agg aat   6432
Ile Val Arg Leu Leu Thr Glu Arg Ile Leu Asn His Thr Ile Arg Asn
    2130                2135                2140

tgg ttg atc ctc cca cct tcg ctc cag atg atc gtg aag cag gac ttg   6480
Trp Leu Ile Leu Pro Pro Ser Leu Gln Met Ile Val Lys Gln Asp Leu
2145                2150                2155                2160

gaa ttc ggc ata ttc agg att act tcc atc ctc aat tct gat cgg ttc   6528
```

```
Glu Phe Gly Ile Phe Arg Ile Thr Ser Ile Leu Asn Ser Asp Arg Phe
                2165                2170                2175

ctg aaa ctt tct cca aat agg aaa tac ttg att aca caa tta act gca   6576
Leu Lys Leu Ser Pro Asn Arg Lys Tyr Leu Ile Thr Gln Leu Thr Ala
            2180                2185                2190

ggc tac att agg aaa ttg att gag ggg gat tgt aat atc gat cta acc   6624
Gly Tyr Ile Arg Lys Leu Ile Glu Gly Asp Cys Asn Ile Asp Leu Thr
        2195                2200                2205

aga cct atc caa aag caa atc tgg aaa gca tta ggt tgt gta gtc tac   6672
Arg Pro Ile Gln Lys Gln Ile Trp Lys Ala Leu Gly Cys Val Val Tyr
    2210                2215                2220

tgt cac gat cca atg gat caa agg gag tca aca gag ttt att gat ata   6720
Cys His Asp Pro Met Asp Gln Arg Glu Ser Thr Glu Phe Ile Asp Ile
2225                2230                2235                2240

aat att aat gaa gaa ata gac cgc ggg atc gat ggc gag gaa atc       6765
Asn Ile Asn Glu Glu Ile Asp Arg Gly Ile Asp Gly Glu Glu Ile
                2245                2250                2255
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<210> 24
<211> 2255
<212> PRT
<213> Cryptovirus

<400> 24

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Met Ala Gly Ser Arg Glu Ile Leu Leu Pro Glu Val His Leu Asn Ser
 1               5                  10                  15
Pro Ile Val Lys His Lys Leu Tyr Tyr Tyr Ile Leu Leu Gly Asn Leu
            20                  25                  30
Pro Asn Glu Ile Asp Ile Asp Asp Leu Gly Pro Leu His Asn Gln Asn
        35                  40                  45
Trp Asn Gln Ile Ala His Glu Glu Ser Asn Leu Ala Gln Arg Leu Val
    50                  55                  60
Asn Val Arg Asn Phe Leu Ile Thr His Ile Pro Asp Leu Arg Lys Gly
65                  70                  75                  80
His Trp Gln Glu Tyr Val Asn Val Ile Leu Trp Pro Arg Ile Leu Pro
                85                  90                  95
Leu Ile Pro Asp Phe Lys Ile Asn Asp Gln Leu Pro Leu Leu Lys Asn
            100                 105                 110
Trp Asp Lys Leu Val Lys Glu Ser Cys Ser Val Ile Asn Ala Gly Thr
        115                 120                 125
Ser Gln Cys Ile Gln Asn Leu Ser Tyr Gly Leu Thr Gly Arg Gly Asn
    130                 135                 140
Leu Phe Thr Arg Ser Arg Glu Leu Ser Gly Asp Arg Arg Asp Ile Asp
145                 150                 155                 160
Leu Lys Thr Val Val Ala Ala Trp His Asp Ser Asp Trp Lys Arg Ile
                165                 170                 175
Ser Asp Phe Trp Ile Met Ile Lys Phe Gln Met Arg Gln Leu Ile Val
            180                 185                 190
```

```
Arg Gln Thr Asp His Asn Asp Pro Asp Leu Ile Thr Tyr Ile Glu Asn
        195                 200                 205
Arg Glu Gly Ile Ile Ile Ile Thr Pro Glu Leu Val Ala Leu Phe Asn
    210                 215                 220
Thr Glu Asn His Thr Leu Thr Tyr Met Thr Phe Glu Ile Val Leu Met
225                 230                 235                 240
Val Ser Asp Met Tyr Glu Gly Arg His Asn Ile Leu Ser Leu Cys Thr
                245                 250                 255
Val Ser Thr Tyr Leu Asn Pro Leu Lys Lys Arg Ile Thr Tyr Leu Leu
            260                 265                 270
Ser Leu Val Asp Asn Leu Ala Phe Gln Ile Gly Asp Ala Val Tyr Asn
        275                 280                 285
Ile Ile Ala Leu Leu Glu Ser Phe Val Tyr Ala Gln Leu Gln Met Ser
    290                 295                 300
Asp Pro Ile Pro Glu Leu Arg Gly Gln Phe His Ala Phe Val Cys Ser
305                 310                 315                 320
Glu Ile Leu Asp Ala Leu Arg Gly Thr Asn Ser Phe Thr Gln Asp Glu
                325                 330                 335
Leu Arg Thr Val Thr Thr Asn Leu Ile Ser Pro Phe Gln Asp Leu Thr
            340                 345                 350
Pro Asp Leu Thr Ala Glu Leu Leu Cys Ile Met Arg Leu Trp Gly His
        355                 360                 365
Pro Met Leu Thr Ala Ser Gln Ala Ala Gly Lys Val Arg Glu Ser Met
    370                 375                 380
Cys Ala Gly Lys Val Leu Asp Phe Pro Thr Ile Met Lys Thr Leu Ala
385                 390                 395                 400
Phe Phe His Thr Ile Leu Ile Asn Gly Tyr Arg Arg Lys His His Gly
                405                 410                 415
Val Trp Pro Pro Leu Asn Leu Pro Gly Asn Ala Ser Lys Gly Leu Thr
            420                 425                 430
Glu Leu Met Asn Asp Asn Thr Glu Ile Ser Tyr Glu Phe Thr Leu Lys
        435                 440                 445
His Trp Lys Glu Ile Ser Leu Ile Lys Phe Lys Lys Cys Phe Asp Ala
    450                 455                 460
Asp Ala Gly Glu Glu Leu Ser Ile Phe Met Lys Asp Lys Ala Ile Ser
465                 470                 475                 480
Ala Pro Lys Gln Asp Trp Met Ser Val Phe Arg Arg Ser Leu Ile Lys
                485                 490                 495
Gln Arg His Gln His His Gln Val Pro Leu Pro Asn Pro Phe Asn Arg
            500                 505                 510
Arg Leu Leu Leu Asn Phe Leu Gly Asp Asp Lys Phe Asp Pro Asn Val
        515                 520                 525
Glu Leu Gln Tyr Val Thr Ser Gly Glu Tyr Leu His Asp Asp Thr Phe
    530                 535                 540
Cys Ala Ser Tyr Ser Leu Lys Glu Lys Glu Ile Lys Pro Asp Gly Arg
545                 550                 555                 560
Ile Phe Ala Lys Leu Thr Lys Arg Met Arg Ser Cys Gln Val Ile Ala
                565                 570                 575
Glu Ser Leu Leu Ala Asn His Ala Gly Lys Leu Met Lys Glu Asn Gly
            580                 585                 590
Val Val Met Asn Gln Leu Ser Leu Thr Lys Ser Leu Leu Thr Met Ser
        595                 600                 605
Gln Ile Gly Ile Ile Ser Glu Arg Ala Arg Lys Ser Thr Arg Asp Asn
    610                 615                 620
Ile Asn Arg Pro Gly Phe Gln Asn Ile Gln Arg Asn Lys Ser His His
```

625 630 635 640
Ser Lys Gln Val Asn Gln Arg Asp Pro Ser Asp Asp Phe Glu Leu Ala
645 650 655
Ala Ser Phe Leu Thr Thr Asp Leu Lys Lys Tyr Cys Leu Gln Trp Arg
660 665 670
Tyr Gln Thr Ile Ile Pro Phe Ala Gln Ser Leu Asn Arg Met Tyr Gly
675 680 685
Tyr Pro His Leu Phe Glu Trp Ile His Leu Arg Leu Met Arg Ser Thr
690 695 700
Leu Tyr Val Gly Asp Pro Phe Asn Pro Pro Ala Asp Thr Ser Gln Phe
705 710 715 720
Asp Leu Asp Lys Val Ile Asn Gly Asp Ile Phe Ile Val Ser Pro Arg
725 730 735
Gly Gly Ile Glu Gly Leu Cys Gln Lys Ala Trp Thr Met Ile Ser Ile
740 745 750
Ser Val Ile Ile Leu Ser Ala Thr Glu Ser Gly Thr Arg Val Met Ser
755 760 765
Met Val Gln Gly Asp Asn Gln Ala Ile Ala Val Thr Thr Arg Val Pro
770 775 780
Arg Ser Leu Pro Thr Leu Glu Lys Lys Thr Ile Ala Phe Arg Ser Cys
785 790 795 800
Asn Leu Phe Phe Glu Arg Leu Lys Cys Asn Asn Phe Gly Leu Gly His
805 810 815
His Leu Lys Glu Gln Glu Thr Ile Ile Ser Ser His Phe Phe Val Tyr
820 825 830
Ser Lys Arg Ile Phe Tyr Gln Gly Arg Ile Leu Thr Gln Ala Leu Lys
835 840 845
Asn Ala Ser Lys Leu Cys Leu Thr Ala Asp Val Leu Gly Glu Cys Thr
850 855 860
Gln Ser Ser Cys Ser Asn Leu Ala Thr Thr Val Met Arg Leu Thr Glu
865 870 875 880
Asn Gly Val Glu Lys Asp Ile Cys Phe Tyr Leu Asn Ile Tyr Met Thr
885 890 895
Ile Lys Gln Leu Ser Tyr Asp Ile Ile Phe Pro Gln Val Ser Ile Pro
900 905 910
Gly Asp Gln Ile Thr Leu Glu Tyr Ile Asn Asn Pro His Leu Val Ser
915 920 925
Arg Leu Ala Leu Leu Pro Ser Gln Leu Gly Gly Leu Asn Tyr Leu Ser
930 935 940
Cys Ser Arg Leu Phe Asn Arg Asn Ile Gly Asp Pro Val Val Ser Ala
945 950 955 960
Val Ala Asp Leu Lys Arg Leu Ile Lys Ser Gly Cys Met Asp Tyr Trp
965 970 975
Ile Leu Tyr Asn Leu Leu Gly Arg Lys Pro Gly Asn Gly Ser Trp Ala
980 985 990
Thr Leu Ala Ala Asp Pro Tyr Ser Ile Asn Ile Glu Tyr Gln Tyr Pro
995 1000 1005
Pro Thr Thr Ala Leu Lys Arg His Thr Gln Gln Val Leu Met Glu Leu
1010 1015 1020
Ser Thr Asn Pro Met Leu Arg Gly Ile Phe Ser Asp Asn Ala Gln Ala
1025 1030 1035 1040
Glu Glu Asn Asn Leu Ala Arg Phe Leu Leu Asp Arg Glu Val Ile Phe
1045 1050 1055
Pro Arg Val Ala His Ile Ile Ile Glu Gln Thr Ser Val Gly Arg Arg
1060 1065 1070

Lys Gln Ile Gln Gly Tyr Leu Asp Ser Thr Arg Ser Ile Met Arg Lys
1075 1080 1085
Ser Leu Glu Ile Lys Pro Leu Ser Asn Arg Lys Leu Asn Glu Ile Leu
1090 1095 1100
Asp Tyr Asn Ile Asn Tyr Leu Ala Tyr Asn Leu Ala Leu Leu Lys Asn
1105 1110 1115 1120
Ala Ile Glu Pro Pro Thr Tyr Leu Lys Ala Met Thr Leu Glu Thr Cys
1125 1130 1135
Ser Ile Asp Ile Ala Arg Ser Leu Arg Lys Leu Ser Trp Ala Pro Leu
1140 1145 1150
Leu Gly Gly Arg Asn Leu Glu Gly Leu Glu Thr Pro Asp Pro Ile Glu
1155 1160 1165
Ile Thr Ala Gly Ala Leu Ile Val Gly Ser Gly Tyr Cys Glu Gln Cys
1170 1175 1180
Ala Ala Gly Asp Asn Arg Phe Thr Trp Phe Phe Leu Pro Ser Gly Ile
1185 1190 1195 1200
Glu Ile Gly Gly Asp Pro Arg Asp Asn Pro Pro Ile Arg Val Pro Tyr
1205 1210 1215
Ile Gly Ser Arg Thr Asp Glu Arg Arg Val Ala Ser Met Ala Tyr Ile
1220 1225 1230
Arg Gly Ala Ser Ser Ser Leu Lys Ala Val Leu Arg Leu Ala Gly Val
1235 1240 1245
Tyr Ile Trp Ala Phe Gly Asp Thr Leu Glu Asn Trp Ile Asp Ala Leu
1250 1255 1260
Asp Leu Ser His Thr Arg Val Asn Ile Thr Leu Glu Gln Leu Gln Ser
1265 1270 1275 1280
Leu Thr Pro Leu Pro Thr Ser Ala Asn Leu Thr His Arg Leu Asp Asp
1285 1290 1295
Gly Thr Thr Thr Leu Lys Phe Thr Pro Ala Ser Ser Tyr Thr Phe Ser
1300 1305 1310
Ser Phe Thr His Ile Ser Asn Asp Glu Gln Tyr Leu Thr Ile Asn Asp
1315 1320 1325
Lys Thr Ala Asp Ser Asn Ile Ile Tyr Gln Gln Leu Met Ile Thr Gly
1330 1335 1340
Leu Gly Ile Leu Glu Thr Trp Asn Asn Pro Pro Ile Asn Arg Thr Phe
1345 1350 1355 1360
Glu Glu Ser Thr Leu His Leu His Thr Gly Ala Ser Cys Cys Val Arg
1365 1370 1375
Pro Val Asp Ser Cys Ile Ile Ser Glu Ala Leu Thr Val Lys Pro His
1380 1385 1390
Ile Thr Val Pro Tyr Ser Asn Lys Phe Val Phe Asp Glu Asp Pro Leu
1395 1400 1405
Ser Glu Tyr Glu Thr Ala Lys Leu Glu Ser Leu Ser Phe Gln Ala Gln
1410 1415 1420
Leu Gly Asn Ile Asp Ala Val Asp Met Thr Gly Lys Leu Thr Leu Leu
1425 1430 1435 1440
Ser Gln Phe Thr Ala Arg Gln Ile Ile Asn Ala Ile Thr Gly Leu Asp
1445 1450 1455
Glu Ser Val Ser Leu Thr Asn Asp Ala Ile Val Ala Ser Asp Tyr Val
1460 1465 1470
Ser Asn Trp Ile Ser Glu Cys Met Tyr Thr Lys Leu Asp Glu Leu Phe
1475 1480 1485
Met Tyr Cys Gly Trp Glu Leu Leu Leu Glu Leu Ser Tyr Gln Met Tyr
1490 1495 1500
Tyr Leu Arg Val Val Gly Trp Ser Asn Ile Val Asp Tyr Ser Tyr Met

1505 1510 1515 1520
Ile Leu Arg Arg Ile Pro Gly Ala Ala Leu Asn Asn Leu Ala Ser Thr
1525 1530 1535
Leu Ser His Pro Lys Leu Phe Arg Arg Ala Ile Asn Leu Asp Ile Val
1540 1545 1550
Ala Pro Leu Asn Ala Pro His Phe Ala Ser Leu Asp Tyr Ile Lys Met
1555 1560 1565
Ser Met Asp Ala Ile Leu Trp Gly Cys Lys Arg Val Ile Asn Val Leu
1570 1575 1580
Ser Asn Gly Gly Asp Leu Glu Leu Val Val Thr Ser Glu Asp Ser Leu
1585 1590 1595 1600
Ile Leu Ser Asp Arg Ser Met Asn Leu Ile Ala Arg Lys Leu Thr Leu
1605 1610 1615
Leu Ser Leu Ile His His Asn Gly Leu Glu Leu Pro Lys Ile Lys Gly
1620 1625 1630
Phe Ser Pro Asp Glu Lys Cys Phe Ala Leu Thr Glu Phe Leu Arg Lys
1635 1640 1645
Val Val Asn Ser Gly Leu Ser Ser Ile Glu Asn Leu Ser Asn Phe Met
1650 1655 1660
Tyr Asn Val Glu Asn Pro Arg Leu Ala Ala Phe Ala Ser Asn Asn Tyr
1665 1670 1675 1680
Tyr Leu Thr Arg Lys Leu Leu Asn Ser Ile Arg Asp Thr Glu Ser Gly
1685 1690 1695
Gln Val Ala Val Thr Ser Tyr Tyr Glu Ser Leu Glu Tyr Ile Asp Ser
1700 1705 1710
Leu Lys Leu Thr Pro His Val Pro Gly Thr Ser Cys Ile Glu Asp Asp
1715 1720 1725
Ser Leu Cys Thr Asn Asp Tyr Ile Ile Trp Ile Ile Glu Ser Asn Ala
1730 1735 1740
Asn Leu Glu Lys Tyr Pro Ile Pro Asn Ser Pro Glu Asp Asp Ser Asn
1745 1750 1755 1760
Phe His Asn Phe Lys Leu Asn Ala Pro Ser His His Thr Leu Arg Pro
1765 1770 1775
Leu Gly Leu Ser Ser Thr Ala Trp Tyr Lys Gly Ile Ser Cys Cys Arg
1780 1785 1790
Tyr Leu Glu Arg Leu Lys Leu Pro Gln Gly Asp His Leu Tyr Ile Ala
1795 1800 1805
Glu Gly Ser Gly Ala Ser Met Thr Ile Ile Glu Tyr Leu Phe Pro Gly
1810 1815 1820
Arg Lys Ile Tyr Tyr Asn Ser Leu Phe Ser Ser Gly Asp Asn Pro Pro
1825 1830 1835 1840
Gln Arg Asn Tyr Ala Pro Met Pro Thr Gln Phe Ile Glu Ser Val Pro
1845 1850 1855
Tyr Lys Leu Trp Gln Ala His Thr Asp Gln Tyr Pro Glu Ile Phe Glu
1860 1865 1870
Asp Phe Ile Pro Leu Trp Asn Gly Asn Ala Ala Met Thr Asp Ile Gly
1875 1880 1885
Met Thr Ala Cys Val Glu Phe Ile Ile Asn Arg Val Gly Pro Arg Thr
1890 1895 1900
Cys Ser Leu Val His Val Asp Leu Glu Ser Ser Ala Ser Leu Asn Gln
1905 1910 1915 1920
Gln Cys Leu Ser Lys Pro Ile Ile Asn Ala Ile Ile Thr Ala Thr Thr
1925 1930 1935
Val Leu Cys Pro His Gly Val Leu Ile Leu Lys Tyr Ser Trp Leu Pro
1940 1945 1950

```
Phe Thr Arg Phe Ser Thr Leu Ile Thr Phe Leu Trp Cys Tyr Phe Glu
        1955                1960                1965
Arg Ile Thr Val Leu Arg Ser Thr Tyr Ser Asp Pro Ala Asn His Glu
    1970                1975                1980
Val Tyr Leu Ile Cys Ile Leu Ala Asn Asn Phe Ala Phe Gln Thr Val
1985                1990                1995                2000
Ser Gln Ala Thr Gly Met Ala Met Thr Leu Thr Asp Gln Gly Phe Thr
                2005                2010                2015
Leu Ile Ser Pro Glu Arg Ile Asn Gln Tyr Trp Asp Gly His Leu Lys
            2020                2025                2030
Gln Glu Arg Ile Val Ala Glu Ala Ile Asp Lys Val Val Leu Gly Glu
        2035                2040                2045
Asn Ala Leu Phe Asn Ser Ser Asp Asn Glu Leu Ile Leu Lys Cys Gly
    2050                2055                2060
Gly Thr Pro Asn Ala Arg Asn Leu Ile Asp Ile Glu Pro Val Ala Thr
2065                2070                2075                2080
Phe Ile Glu Phe Glu Gln Leu Ile Cys Thr Met Leu Thr Thr His Leu
                2085                2090                2095
Lys Glu Ile Ile Asp Ile Thr Arg Ser Gly Thr Gln Asp Tyr Glu Ser
            2100                2105                2110
Leu Leu Leu Thr Pro Tyr Asn Leu Gly Leu Leu Gly Lys Ile Ser Thr
        2115                2120                2125
Ile Val Arg Leu Leu Thr Glu Arg Ile Leu Asn His Thr Ile Arg Asn
    2130                2135                2140
Trp Leu Ile Leu Pro Pro Ser Leu Gln Met Ile Val Lys Gln Asp Leu
2145                2150                2155                2160
Glu Phe Gly Ile Phe Arg Ile Thr Ser Ile Leu Asn Ser Asp Arg Phe
                2165                2170                2175
Leu Lys Leu Ser Pro Asn Arg Lys Tyr Leu Ile Thr Gln Leu Thr Ala
            2180                2185                2190
Gly Tyr Ile Arg Lys Leu Ile Glu Gly Asp Cys Asn Ile Asp Leu Thr
        2195                2200                2205
Arg Pro Ile Gln Lys Gln Ile Trp Lys Ala Leu Gly Cys Val Val Tyr
    2210                2215                2220
Cys His Asp Pro Met Asp Gln Arg Glu Ser Thr Glu Phe Ile Asp Ile
2225                2230                2235                2240
Asn Ile Asn Glu Glu Ile Asp Arg Gly Ile Asp Gly Glu Glu Ile
                2245                2250                2255
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<210> 25
<211> 1656
<212> DNA
<213> Canine parainfluenza virus

<220>
<221> CDS
<222> (1)...(1656)
<223> Canine parainfluenza virus F protein encoding sequence with "TAA" termination codon; cDNA in mRNA sense

<400> 25

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atg ggt act aga att caa ttt ctg gtg gtc tcc tgt cta ttg gca gga   48
Met Gly Thr Arg Ile Gln Phe Leu Val Val Ser Cys Leu Leu Ala Gly
```

```
 1               5                  10                  15

aca ggc agc ctt gat cca gca gcc ctc atg caa atc ggt gtc att cca   96
Thr Gly Ser Leu Asp Pro Ala Ala Leu Met Gln Ile Gly Val Ile Pro
            20                  25                  30

aca aat gtc cgg caa ctt atg tat tat act gag gct tca tca gca ttc   144
Thr Asn Val Arg Gln Leu Met Tyr Tyr Thr Glu Ala Ser Ser Ala Phe
        35                  40                  45

att gtt gtg aag tta atg cct aca att gac tcg ccg att agt ggg tgt   192
Ile Val Val Lys Leu Met Pro Thr Ile Asp Ser Pro Ile Ser Gly Cys
    50                  55                  60

aat ata aca tcc att tca agc tat aat gca aca atg aca aaa ctt cta   240
Asn Ile Thr Ser Ile Ser Ser Tyr Asn Ala Thr Met Thr Lys Leu Leu
65                  70                  75                  80

cag ccg atc ggt gag aat tta gag acg att agg tac cag ttg att cca   288
Gln Pro Ile Gly Glu Asn Leu Glu Thr Ile Arg Tyr Gln Leu Ile Pro
                85                  90                  95

act cgg agg aga cgc cgg ttt gca ggg gtg gtg att gga tta gcc gca   336
Thr Arg Arg Arg Arg Arg Phe Ala Gly Val Val Ile Gly Leu Ala Ala
            100                 105                 110

tta gga gta gct act gca gca cag gtc act gcc gca gta gca cta gta   384
Leu Gly Val Ala Thr Ala Ala Gln Val Thr Ala Ala Val Ala Leu Val
        115                 120                 125

aag gcg aat aaa aat gct gtg gct ata ctc aat ctc aaa aac gca atc   432
Lys Ala Asn Lys Asn Ala Val Ala Ile Leu Asn Leu Lys Asn Ala Ile
    130                 135                 140

caa aaa aca aat gca gca gtt gca gac gtg gtt cag gcc aca caa tca   480
Gln Lys Thr Asn Ala Ala Val Ala Asp Val Val Gln Ala Thr Gln Ser
145                 150                 155                 160

cta gga acg gca gtt caa gca gtt caa gat cac ata aat agt gtg gta   528
Leu Gly Thr Ala Val Gln Ala Val Gln Asp His Ile Asn Ser Val Val
                165                 170                 175

agt cca gca att aca gca gcc aat tgc aaa gcc caa gat gct atc att   576
Ser Pro Ala Ile Thr Ala Ala Asn Cys Lys Ala Gln Asp Ala Ile Ile
            180                 185                 190

ggc tca att ctc aat ctc tat ttg acc gag ttg aca act atc ttc cac   624
Gly Ser Ile Leu Asn Leu Tyr Leu Thr Glu Leu Thr Thr Ile Phe His
        195                 200                 205

aat caa att aca aac ccc gca ttg agt cct att aca att caa gct ttg   672
Asn Gln Ile Thr Asn Pro Ala Leu Ser Pro Ile Thr Ile Gln Ala Leu
    210                 215                 220

agg atc cta cta ggg agt acc ttg ccg acc gtg gtc gaa aaa tct ttc   720
```

```
Arg Ile Leu Leu Gly Ser Thr Leu Pro Thr Val Val Glu Lys Ser Phe
225                 230                 235                 240

aat acc cag ata agt gca gct gag ctt ctc tca tca ggg tta ttg aca   768
Asn Thr Gln Ile Ser Ala Ala Glu Leu Leu Ser Ser Gly Leu Leu Thr
                245                 250                 255

ggc cag att gtg gga tta gat ttg acc tac atg cag atg gtc ata aaa   816
Gly Gln Ile Val Gly Leu Asp Leu Thr Tyr Met Gln Met Val Ile Lys
            260                 265                 270

att gag ctg cca act tta act gta caa cct gca acc cag atc ata gat   864
Ile Glu Leu Pro Thr Leu Thr Val Gln Pro Ala Thr Gln Ile Ile Asp
        275                 280                 285

ctg gtc acc att tct gca ttc att aac aat caa gaa gtt atg gcc caa   912
Leu Val Thr Ile Ser Ala Phe Ile Asn Asn Gln Glu Val Met Ala Gln
    290                 295                 300

tta cca aca cgt gtt att gtg act ggc agc ttg atc caa gcc tat ccc   960
Leu Pro Thr Arg Val Ile Val Thr Gly Ser Leu Ile Gln Ala Tyr Pro
305                 310                 315                 320

gca tcg caa tgc act atc acc ccc aac act gtg tac tgt agg tat aat   1008
Ala Ser Gln Cys Thr Ile Thr Pro Asn Thr Val Tyr Cys Arg Tyr Asn
                325                 330                 335

gat gcc caa gta ctc tca gat gat acg atg gct tgc ctc caa ggt aac   1056
Asp Ala Gln Val Leu Ser Asp Asp Thr Met Ala Cys Leu Gln Gly Asn
            340                 345                 350

ttg aca aga tgc acc ttc tct cca gtg gtt ggg agc ttt ctc act cga   1104
Leu Thr Arg Cys Thr Phe Ser Pro Val Val Gly Ser Phe Leu Thr Arg
        355                 360                 365

ttc gtg ctg ttt gat gga ata gtt tat gca aat tgc agg tcg atg ttg   1152
Phe Val Leu Phe Asp Gly Ile Val Tyr Ala Asn Cys Arg Ser Met Leu
    370                 375                 380

tgc aag tgc atg cag cct gct gct gtt atc cta cag ccg agc tca tcc   1200
Cys Lys Cys Met Gln Pro Ala Ala Val Ile Leu Gln Pro Ser Ser Ser
385                 390                 395                 400

cct gta act gtc att gac atg tac aaa tgt gtg agt ctg cag ctt gac   1248
Pro Val Thr Val Ile Asp Met Tyr Lys Cys Val Ser Leu Gln Leu Asp
                405                 410                 415

aat ctc aga ttc acc atc act caa ttg gcc aat ata acc tac aat agc   1296
Asn Leu Arg Phe Thr Ile Thr Gln Leu Ala Asn Ile Thr Tyr Asn Ser
            420                 425                 430

acc atc aag ctt gaa aca tcc cag atc ttg cct atc gat ccg ttg gat   1344
Thr Ile Lys Leu Glu Thr Ser Gln Ile Leu Pro Ile Asp Pro Leu Asp
        435                 440                 445
```

```
ata tcc cag aat cta gct gcg gtg aat aag agt cta agt gat gca cta   1392
Ile Ser Gln Asn Leu Ala Ala Val Asn Lys Ser Leu Ser Asp Ala Leu
    450                 455                 460

caa cac tta gca caa agt gac aca tac ctt tct gca atc aca tca gct   1440
Gln His Leu Ala Gln Ser Asp Thr Tyr Leu Ser Ala Ile Thr Ser Ala
465                 470                 475                 480

acg act aca agt gta tta tcc ata ata gca atc tgt ctt gga tcg tta   1488
Thr Thr Thr Ser Val Leu Ser Ile Ile Ala Ile Cys Leu Gly Ser Leu
                485                 490                 495

ggt tta ata tta ata atc ttg ctc agt gta gtt gtg tgg aag tta ttg   1536
Gly Leu Ile Leu Ile Ile Leu Leu Ser Val Val Val Trp Lys Leu Leu
            500                 505                 510

acc att gtt gct gct aat cga aat aga atg gag aat ttt gtt tat cat   1584
Thr Ile Val Ala Ala Asn Arg Asn Arg Met Glu Asn Phe Val Tyr His
        515                 520                 525

aat tca gca ttc cac cac tca cgg tct gat ctc agt gag aaa aat caa   1632
Asn Ser Ala Phe His His Ser Arg Ser Asp Leu Ser Glu Lys Asn Gln
    530                 535                 540

cct gca act ctt gga aca aga taa                                  1656
Pro Ala Thr Leu Gly Thr Arg  *
545                 550
```

<210> 26
<211> 551
<212> PRT
<213> Canine parainfluenza virus

<400> 26

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Met Gly Thr Arg Ile Gln Phe Leu Val Val Ser Cys Leu Leu Ala Gly
 1               5                  10                  15
Thr Gly Ser Leu Asp Pro Ala Ala Leu Met Gln Ile Gly Val Ile Pro
            20                  25                  30
Thr Asn Val Arg Gln Leu Met Tyr Tyr Thr Glu Ala Ser Ser Ala Phe
        35                  40                  45
Ile Val Val Lys Leu Met Pro Thr Ile Asp Ser Pro Ile Ser Gly Cys
    50                  55                  60
Asn Ile Thr Ser Ile Ser Ser Tyr Asn Ala Thr Met Thr Lys Leu Leu
65                  70                  75                  80
Gln Pro Ile Gly Glu Asn Leu Glu Thr Ile Arg Tyr Gln Leu Ile Pro
                85                  90                  95
Thr Arg Arg Arg Arg Arg Phe Ala Gly Val Val Ile Gly Leu Ala Ala
            100                 105                 110
Leu Gly Val Ala Thr Ala Ala Gln Val Thr Ala Ala Val Ala Leu Val
        115                 120                 125
Lys Ala Asn Lys Asn Ala Val Ala Ile Leu Asn Leu Lys Asn Ala Ile
    130                 135                 140
Gln Lys Thr Asn Ala Ala Val Ala Asp Val Val Gln Ala Thr Gln Ser
145                 150                 155                 160
```

```
Leu Gly Thr Ala Val Gln Ala Val Gln Asp His Ile Asn Ser Val Val
                165                 170                 175
Ser Pro Ala Ile Thr Ala Ala Asn Cys Lys Ala Gln Asp Ala Ile Ile
            180                 185                 190
Gly Ser Ile Leu Asn Leu Tyr Leu Thr Glu Leu Thr Thr Ile Phe His
        195                 200                 205
Asn Gln Ile Thr Asn Pro Ala Leu Ser Pro Ile Thr Ile Gln Ala Leu
    210                 215                 220
Arg Ile Leu Leu Gly Ser Thr Leu Pro Thr Val Val Glu Lys Ser Phe
225                 230                 235                 240
Asn Thr Gln Ile Ser Ala Ala Glu Leu Leu Ser Ser Gly Leu Leu Thr
                245                 250                 255
Gly Gln Ile Val Gly Leu Asp Leu Thr Tyr Met Gln Met Val Ile Lys
            260                 265                 270
Ile Glu Leu Pro Thr Leu Thr Val Gln Pro Ala Thr Gln Ile Ile Asp
        275                 280                 285
Leu Val Thr Ile Ser Ala Phe Ile Asn Asn Gln Glu Val Met Ala Gln
    290                 295                 300
Leu Pro Thr Arg Val Ile Val Thr Gly Ser Leu Ile Gln Ala Tyr Pro
305                 310                 315                 320
Ala Ser Gln Cys Thr Ile Thr Pro Asn Thr Val Tyr Cys Arg Tyr Asn
                325                 330                 335
Asp Ala Gln Val Leu Ser Asp Asp Thr Met Ala Cys Leu Gln Gly Asn
            340                 345                 350
Leu Thr Arg Cys Thr Phe Ser Pro Val Val Gly Ser Phe Leu Thr Arg
        355                 360                 365
Phe Val Leu Phe Asp Gly Ile Val Tyr Ala Asn Cys Arg Ser Met Leu
    370                 375                 380
Cys Lys Cys Met Gln Pro Ala Ala Val Ile Leu Gln Pro Ser Ser Ser
385                 390                 395                 400
Pro Val Thr Val Ile Asp Met Tyr Lys Cys Val Ser Leu Gln Leu Asp
                405                 410                 415
Asn Leu Arg Phe Thr Ile Thr Gln Leu Ala Asn Ile Thr Tyr Asn Ser
            420                 425                 430
Thr Ile Lys Leu Glu Thr Ser Gln Ile Leu Pro Ile Asp Pro Leu Asp
        435                 440                 445
Ile Ser Gln Asn Leu Ala Ala Val Asn Lys Ser Leu Ser Asp Ala Leu
    450                 455                 460
Gln His Leu Ala Gln Ser Asp Thr Tyr Leu Ser Ala Ile Thr Ser Ala
465                 470                 475                 480
Thr Thr Thr Ser Val Leu Ser Ile Ile Ala Ile Cys Leu Gly Ser Leu
                485                 490                 495
Gly Leu Ile Leu Ile Ile Leu Leu Ser Val Val Val Trp Lys Leu Leu
            500                 505                 510
Thr Ile Val Ala Ala Asn Arg Asn Arg Met Glu Asn Phe Val Tyr His
        515                 520                 525
Asn Ser Ala Phe His His Ser Arg Ser Asp Leu Ser Glu Lys Asn Gln
    530                 535                 540
Pro Ala Thr Leu Gly Thr Arg
545                 550
```

<210> 27
<211> 1656
<212> DNA

<213> Porcine Rubulavirus

<220>
<221> CDS
<222> (1)...(1656)
<223> Porcine Rubulavirus F protein encoding sequence
with "TAA" termination codon; cDNA in mRNA sense

<400> 27

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atg ggt act ata att caa ttt ctg gtg gtc tcc tgt cta ttg gca gga   48
Met Gly Thr Ile Ile Gln Phe Leu Val Val Ser Cys Leu Leu Ala Gly
 1               5                  10                  15

gca ggc agc ctt gat cca gca gcc ctc atg caa atc ggt gtc att cca   96
Ala Gly Ser Leu Asp Pro Ala Ala Leu Met Gln Ile Gly Val Ile Pro
             20                  25                  30

aca aat gtc cgg caa ctt atg tat tat act gag gcc tca tca gca ttc   144
Thr Asn Val Arg Gln Leu Met Tyr Tyr Thr Glu Ala Ser Ser Ala Phe
         35                  40                  45

att gtt gtg aag tta atg cct aca att gac tcg ccg att agt gga tgt   192
Ile Val Val Lys Leu Met Pro Thr Ile Asp Ser Pro Ile Ser Gly Cys
     50                  55                  60

aat ata aca tca att tca agc tat aat gca aca gtg aca aaa ctc cta   240
Asn Ile Thr Ser Ile Ser Ser Tyr Asn Ala Thr Val Thr Lys Leu Leu
 65                  70                  75                  80

cag ccg atc ggt gag aat ttg gaa acg att agg aac cag ttg att cca   288
Gln Pro Ile Gly Glu Asn Leu Glu Thr Ile Arg Asn Gln Leu Ile Pro
                 85                  90                  95

act cgg agg aga cgc cgg ttt gca ggg gtg gtg att gga tta gct gca   336
Thr Arg Arg Arg Arg Arg Phe Ala Gly Val Val Ile Gly Leu Ala Ala
            100                 105                 110

tta gga gta gct act gcc gca cag gtc act gcc gca gta gca cta gta   384
Leu Gly Val Ala Thr Ala Ala Gln Val Thr Ala Ala Val Ala Leu Val
        115                 120                 125

aag gca aat aaa aat gct gcg gct ata ctc aat ctc aaa aat gca atc   432
Lys Ala Asn Lys Asn Ala Ala Ala Ile Leu Asn Leu Lys Asn Ala Ile
    130                 135                 140

caa aaa aca aat aca gca gtt gca gat gtg gtc cag gcc aca caa tca   480
Gln Lys Thr Asn Thr Ala Val Ala Asp Val Val Gln Ala Thr Gln Ser
145                 150                 155                 160

cta gga acg gca gtt caa gca gtt caa gat cac ata aac agt gtg gta   528
Leu Gly Thr Ala Val Gln Ala Val Gln Asp His Ile Asn Ser Val Val
                165                 170                 175

agt cca gca att aca gca gcc aat tgt aag gcc caa gat gct atc att   576
Ser Pro Ala Ile Thr Ala Ala Asn Cys Lys Ala Gln Asp Ala Ile Ile
```

```
            180                 185                 190

ggc tca atc ctc aat ctc tat ttg acc gag ttg aca act atc ttc cac   624
Gly Ser Ile Leu Asn Leu Tyr Leu Thr Glu Leu Thr Thr Ile Phe His
        195                 200                 205

aat caa att aca aac cct gca ttg agt cct att aca att caa gct tta   672
Asn Gln Ile Thr Asn Pro Ala Leu Ser Pro Ile Thr Ile Gln Ala Leu
    210                 215                 220

agg atc cta ctg ggg agt acc ttg ccg act gtg gtc gaa aaa tct ttc   720
Arg Ile Leu Leu Gly Ser Thr Leu Pro Thr Val Val Glu Lys Ser Phe
225                 230                 235                 240

aat acc cag ata agt gca gct gag ctt ctc tca tca ggg tta ttg aca   768
Asn Thr Gln Ile Ser Ala Ala Glu Leu Leu Ser Ser Gly Leu Leu Thr
                245                 250                 255

ggc cag att gtg gga tta gat ttg acc tat atg cag atg gtc ata aaa   816
Gly Gln Ile Val Gly Leu Asp Leu Thr Tyr Met Gln Met Val Ile Lys
            260                 265                 270

att gag ctg cca act tta act gta caa cct gca acc cag atc ata gat   864
Ile Glu Leu Pro Thr Leu Thr Val Gln Pro Ala Thr Gln Ile Ile Asp
        275                 280                 285

ctg gcc acc att tct gca ttc att aac aat caa gaa gtc atg gcc caa   912
Leu Ala Thr Ile Ser Ala Phe Ile Asn Asn Gln Glu Val Met Ala Gln
    290                 295                 300

tta cca aca cgt gtt att gtg act ggc agc ttg atc caa gcc tat ccc   960
Leu Pro Thr Arg Val Ile Val Thr Gly Ser Leu Ile Gln Ala Tyr Pro
305                 310                 315                 320

gca tcg caa tgc act att aca ccc aac act gtg tac tgt agg tat aat  1008
Ala Ser Gln Cys Thr Ile Thr Pro Asn Thr Val Tyr Cys Arg Tyr Asn
                325                 330                 335

gat gcc caa gta ctc tca gat gat acg atg gct tgc ctc caa ggt aac  1056
Asp Ala Gln Val Leu Ser Asp Asp Thr Met Ala Cys Leu Gln Gly Asn
            340                 345                 350

ttg aca aga tgc acc ttc tct ccg gtg gtt ggg agc ttt ctc act cga  1104
Leu Thr Arg Cys Thr Phe Ser Pro Val Val Gly Ser Phe Leu Thr Arg
        355                 360                 365

ttc atg ctg ttc gat gga ata gtt tat gca aat tgc agg tcg atg tta  1152
Phe Met Leu Phe Asp Gly Ile Val Tyr Ala Asn Cys Arg Ser Met Leu
    370                 375                 380

tgc aag tgc atg cag cct gct gct gtg atc cta cag ccg agt tca tcc  1200
Cys Lys Cys Met Gln Pro Ala Ala Val Ile Leu Gln Pro Ser Ser Ser
385                 390                 395                 400

cct gta act gtc att gac atg tac aaa tgt gtg agt ctg cag ctt gac  1248
```

```
Pro Val Thr Val Ile Asp Met Tyr Lys Cys Val Ser Leu Gln Leu Asp
                405                 410                 415

aat ctc aga ttc acc atc act caa ttg gcc aat gta acc tac aat agc   1296
Asn Leu Arg Phe Thr Ile Thr Gln Leu Ala Asn Val Thr Tyr Asn Ser
            420                 425                 430

acc atc aag ctt gaa aca tcc cag atc ttg cct att gat ccg ttg gat   1344
Thr Ile Lys Leu Glu Thr Ser Gln Ile Leu Pro Ile Asp Pro Leu Asp
        435                 440                 445

ata tcc cag aat cta gct gcg gtg aat aag agt cta agt gat gca cta   1392
Ile Ser Gln Asn Leu Ala Ala Val Asn Lys Ser Leu Ser Asp Ala Leu
    450                 455                 460

caa cac tta gca caa agt gac aca tac ctt tct gca atc aca tca gct   1440
Gln His Leu Ala Gln Ser Asp Thr Tyr Leu Ser Ala Ile Thr Ser Ala
465                 470                 475                 480

acg act aca agt gta tta tcc ata atg gca atc tgt ctt gga tcg tta   1488
Thr Thr Thr Ser Val Leu Ser Ile Met Ala Ile Cys Leu Gly Ser Leu
                485                 490                 495

ggt tta ata tta ata atc ttg ctc agt gta gtt gtg tgg aag tta ttg   1536
Gly Leu Ile Leu Ile Ile Leu Leu Ser Val Val Val Trp Lys Leu Leu
            500                 505                 510

acc att gtc act gct aat cga aat aga atg gag aat ttt gtt tat cat   1584
Thr Ile Val Thr Ala Asn Arg Asn Arg Met Glu Asn Phe Val Tyr His
        515                 520                 525

aat tca gca ttc cac cac tca cga tct gat ctc agt gag aaa aat caa   1632
Asn Ser Ala Phe His His Ser Arg Ser Asp Leu Ser Glu Lys Asn Gln
    530                 535                 540

cct gca act ctt gga aca aga taa                                  1656
Pro Ala Thr Leu Gly Thr Arg  *
545                 550
```

<210> 28
<211> 551
<212> PRT
<213> Porcine Rubulavirus

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<400> 28
Met Gly Thr Ile Ile Gln Phe Leu Val Val Ser Cys Leu Leu Ala Gly
 1               5                  10                  15
Ala Gly Ser Leu Asp Pro Ala Ala Leu Met Gln Ile Gly Val Ile Pro
            20                  25                  30
Thr Asn Val Arg Gln Leu Met Tyr Tyr Thr Glu Ala Ser Ser Ala Phe
        35                  40                  45
Ile Val Val Lys Leu Met Pro Thr Ile Asp Ser Pro Ile Ser Gly Cys
    50                  55                  60
Asn Ile Thr Ser Ile Ser Ser Tyr Asn Ala Thr Val Thr Lys Leu Leu
```

```
65                  70                  75                  80
Gln Pro Ile Gly Glu Asn Leu Glu Thr Ile Arg Asn Gln Leu Ile Pro
                85                  90                  95
Thr Arg Arg Arg Arg Arg Phe Ala Gly Val Val Ile Gly Leu Ala Ala
            100                 105                 110
Leu Gly Val Ala Thr Ala Ala Gln Val Thr Ala Ala Val Ala Leu Val
        115                 120                 125
Lys Ala Asn Lys Asn Ala Ala Ala Ile Leu Asn Leu Lys Asn Ala Ile
    130                 135                 140
Gln Lys Thr Asn Thr Ala Val Ala Asp Val Val Gln Ala Thr Gln Ser
145                 150                 155                 160
Leu Gly Thr Ala Val Gln Ala Val Gln Asp His Ile Asn Ser Val Val
                165                 170                 175
Ser Pro Ala Ile Thr Ala Ala Asn Cys Lys Ala Gln Asp Ala Ile Ile
            180                 185                 190
Gly Ser Ile Leu Asn Leu Tyr Leu Thr Glu Leu Thr Thr Ile Phe His
        195                 200                 205
Asn Gln Ile Thr Asn Pro Ala Leu Ser Pro Ile Thr Ile Gln Ala Leu
    210                 215                 220
Arg Ile Leu Leu Gly Ser Thr Leu Pro Thr Val Val Glu Lys Ser Phe
225                 230                 235                 240
Asn Thr Gln Ile Ser Ala Ala Glu Leu Leu Ser Ser Gly Leu Leu Thr
                245                 250                 255
Gly Gln Ile Val Gly Leu Asp Leu Thr Tyr Met Gln Met Val Ile Lys
            260                 265                 270
Ile Glu Leu Pro Thr Leu Thr Val Gln Pro Ala Thr Gln Ile Ile Asp
        275                 280                 285
Leu Ala Thr Ile Ser Ala Phe Ile Asn Asn Gln Glu Val Met Ala Gln
    290                 295                 300
Leu Pro Thr Arg Val Ile Val Thr Gly Ser Leu Ile Gln Ala Tyr Pro
305                 310                 315                 320
Ala Ser Gln Cys Thr Ile Thr Pro Asn Thr Val Tyr Cys Arg Tyr Asn
                325                 330                 335
Asp Ala Gln Val Leu Ser Asp Asp Thr Met Ala Cys Leu Gln Gly Asn
            340                 345                 350
Leu Thr Arg Cys Thr Phe Ser Pro Val Val Gly Ser Phe Leu Thr Arg
        355                 360                 365
Phe Met Leu Phe Asp Gly Ile Val Tyr Ala Asn Cys Arg Ser Met Leu
    370                 375                 380
Cys Lys Cys Met Gln Pro Ala Ala Val Ile Leu Gln Pro Ser Ser Ser
385                 390                 395                 400
Pro Val Thr Val Ile Asp Met Tyr Lys Cys Val Ser Leu Gln Leu Asp
                405                 410                 415
Asn Leu Arg Phe Thr Ile Thr Gln Leu Ala Asn Val Thr Tyr Asn Ser
            420                 425                 430
Thr Ile Lys Leu Glu Thr Ser Gln Ile Leu Pro Ile Asp Pro Leu Asp
        435                 440                 445
Ile Ser Gln Asn Leu Ala Ala Val Asn Lys Ser Leu Ser Asp Ala Leu
    450                 455                 460
Gln His Leu Ala Gln Ser Asp Thr Tyr Leu Ser Ala Ile Thr Ser Ala
465                 470                 475                 480
Thr Thr Thr Ser Val Leu Ser Ile Met Ala Ile Cys Leu Gly Ser Leu
                485                 490                 495
Gly Leu Ile Leu Ile Ile Leu Leu Ser Val Val Val Trp Lys Leu Leu
            500                 505                 510
```

```
Thr Ile Val Thr Ala Asn Arg Asn Arg Met Glu Asn Phe Val Tyr His
        515                 520                 525
Asn Ser Ala Phe His His Ser Arg Ser Asp Leu Ser Glu Lys Asn Gln
    530                 535                 540
Pro Ala Thr Leu Gly Thr Arg
545                 550


<210> 29
<211> 1656
<212> DNA
<213> Simian virus 5

<220>
<221> CDS
<222> (1)...(1590)
<223> Simian virus 5 W3A strain F protein encoding
      sequence; cDNA in mRNA sense

<400> 29
atg ggt act ata att caa ttt ctg gtg gtc tcc tgt cta ttg gca gga   48
Met Gly Thr Ile Ile Gln Phe Leu Val Val Ser Cys Leu Leu Ala Gly
 1               5                  10                  15

gca ggc agc ctt gat cca gca gcc ctc atg caa atc ggt gtc att cca   96
Ala Gly Ser Leu Asp Pro Ala Ala Leu Met Gln Ile Gly Val Ile Pro
            20                  25                  30

aca aat gtc cgg caa ctt atg tat tat act gag gcc tca tca gca ttc   144
Thr Asn Val Arg Gln Leu Met Tyr Tyr Thr Glu Ala Ser Ser Ala Phe
        35                  40                  45

att gtt gtg aag tta atg cct aca att gac tcg ccg att agt gga tgt   192
Ile Val Val Lys Leu Met Pro Thr Ile Asp Ser Pro Ile Ser Gly Cys
    50                  55                  60

aat ata aca tca att tca agc tat aat gca aca gtg aca aaa ctc cta   240
Asn Ile Thr Ser Ile Ser Ser Tyr Asn Ala Thr Val Thr Lys Leu Leu
65                  70                  75                  80

cag ccg atc ggt gag aat ttg gag acg att agg aac cag ttg att cca   288
Gln Pro Ile Gly Glu Asn Leu Glu Thr Ile Arg Asn Gln Leu Ile Pro
                85                  90                  95

act cgg agg aga cgc cgg ttt gca ggg gtg gtg att gga tta gct gca   336
Thr Arg Arg Arg Arg Arg Phe Ala Gly Val Val Ile Gly Leu Ala Ala
            100                 105                 110

tta gga gta gct act gcc gca cag gtc act gcc gca gtg gca cta gta   384
Leu Gly Val Ala Thr Ala Ala Gln Val Thr Ala Ala Val Ala Leu Val
        115                 120                 125

aag gca aat gaa aat gct gcg gct ata ctc aat ctc aaa aat gca atc   432
Lys Ala Asn Glu Asn Ala Ala Ala Ile Leu Asn Leu Lys Asn Ala Ile
    130                 135                 140
```

```
caa aaa aca aat gca gca gtt gca gat gtg gtc cag gcc aca caa tca   480
Gln Lys Thr Asn Ala Ala Val Ala Asp Val Val Gln Ala Thr Gln Ser
145                 150                 155                 160

cta gga acg gca gtt caa gca gtt caa gat cac ata aac agt gtg gta   528
Leu Gly Thr Ala Val Gln Ala Val Gln Asp His Ile Asn Ser Val Val
                165                 170                 175

agt cca gca att aca gca gcc aat tgt aag gcc caa gat gct atc att   576
Ser Pro Ala Ile Thr Ala Ala Asn Cys Lys Ala Gln Asp Ala Ile Ile
            180                 185                 190

ggc tca atc ctc aat ctc tat ttg acc gag ttg aca acc atc ttc cac   624
Gly Ser Ile Leu Asn Leu Tyr Leu Thr Glu Leu Thr Thr Ile Phe His
        195                 200                 205

aat caa att aca aac cct gca ttg agt ccc att aca att caa gct tta   672
Asn Gln Ile Thr Asn Pro Ala Leu Ser Pro Ile Thr Ile Gln Ala Leu
    210                 215                 220

agg atc cta ctg ggg agt acc ttg ccg act gtg gtc gaa aaa tct ttc   720
Arg Ile Leu Leu Gly Ser Thr Leu Pro Thr Val Val Glu Lys Ser Phe
225                 230                 235                 240

aat acc cag ata agt gca gct gag ctt ctc tca tca ggg tta ttg aca   768
Asn Thr Gln Ile Ser Ala Ala Glu Leu Leu Ser Ser Gly Leu Leu Thr
                245                 250                 255

ggc cag att gtg gga tta gat ttg acc tat atg cag atg gtc ata aaa   816
Gly Gln Ile Val Gly Leu Asp Leu Thr Tyr Met Gln Met Val Ile Lys
            260                 265                 270

att gag ctg cca act tta act gta caa cct gca acc cag atc ata gat   864
Ile Glu Leu Pro Thr Leu Thr Val Gln Pro Ala Thr Gln Ile Ile Asp
        275                 280                 285

ctg gcc acc att tct gca ttc att aac aat caa gaa gtc atg gcc caa   912
Leu Ala Thr Ile Ser Ala Phe Ile Asn Asn Gln Glu Val Met Ala Gln
    290                 295                 300

tta cca aca cgt gtt atg gtg act ggc agc ttg atc caa gcc tat ccc   960
Leu Pro Thr Arg Val Met Val Thr Gly Ser Leu Ile Gln Ala Tyr Pro
305                 310                 315                 320

gca tcg caa tgc acc att aca ccc aac act gtg tac tgt agg tat aat  1008
Ala Ser Gln Cys Thr Ile Thr Pro Asn Thr Val Tyr Cys Arg Tyr Asn
                325                 330                 335

gat gcc caa gta ctc tca gat gat act atg gct tgc ctc caa ggt aac  1056
Asp Ala Gln Val Leu Ser Asp Asp Thr Met Ala Cys Leu Gln Gly Asn
            340                 345                 350

ttg aca aga tgc acc ttc tct cca gtg gtt ggg agc ttt ctc act cga  1104
Leu Thr Arg Cys Thr Phe Ser Pro Val Val Gly Ser Phe Leu Thr Arg
```

```
        355                 360                 365

ttc gtg ctg ttc gat gga ata gtt tat gca aat tgc agg tcg atg ttg   1152
Phe Val Leu Phe Asp Gly Ile Val Tyr Ala Asn Cys Arg Ser Met Leu
    370                 375                 380

tgc aag tgc atg caa cct gct gct gtg atc cta cag ccg agt tca tcc   1200
Cys Lys Cys Met Gln Pro Ala Ala Val Ile Leu Gln Pro Ser Ser Ser
385                 390                 395                 400

cct gta act gtc att gac atg tac aaa tgt gtg agt ctg cag ctt gac   1248
Pro Val Thr Val Ile Asp Met Tyr Lys Cys Val Ser Leu Gln Leu Asp
                405                 410                 415

aat ctc aga ttc acc atc act caa ttg gcc aat gta acc tac aat agc   1296
Asn Leu Arg Phe Thr Ile Thr Gln Leu Ala Asn Val Thr Tyr Asn Ser
            420                 425                 430

acc atc aag ctt gaa tca tcc cag atc ttg tct att gat ccg ttg gat   1344
Thr Ile Lys Leu Glu Ser Ser Gln Ile Leu Ser Ile Asp Pro Leu Asp
        435                 440                 445

ata tcc caa aat cta gct gcg gtg aat aag agt cta agt gat gca cta   1392
Ile Ser Gln Asn Leu Ala Ala Val Asn Lys Ser Leu Ser Asp Ala Leu
    450                 455                 460

caa cac tta gca caa agt gac aca tat ctt tct gca atc aca tca gct   1440
Gln His Leu Ala Gln Ser Asp Thr Tyr Leu Ser Ala Ile Thr Ser Ala
465                 470                 475                 480

acg act aca agt gta tta tcc ata ata gca atc tgt ctt gga tcg tta   1488
Thr Thr Thr Ser Val Leu Ser Ile Ile Ala Ile Cys Leu Gly Ser Leu
                485                 490                 495

ggt tta ata tta ata atc ttg ctc agt gta gtt gtg tgg aag tta ttg   1536
Gly Leu Ile Leu Ile Ile Leu Leu Ser Val Val Val Trp Lys Leu Leu
            500                 505                 510

acc att gtc gtt gct aat cga aat aga atg gag aat ttt gtt tat cat   1584
Thr Ile Val Val Ala Asn Arg Asn Arg Met Glu Asn Phe Val Tyr His
        515                 520                 525

aaa taa gcattccacc actcacgatc tgatctcagt gagaaaaatc aacctgcaac   1640
Lys  *


tcttggaaca agataa                                                1656

<210> 30
<211> 529
<212> PRT
<213> Simian virus 5

<400> 30
Met Gly Thr Ile Ile Gln Phe Leu Val Val Ser Cys Leu Leu Ala Gly
```

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 1               5                  10                  15
Ala Gly Ser Leu Asp Pro Ala Ala Leu Met Gln Ile Gly Val Ile Pro
            20                  25                  30
Thr Asn Val Arg Gln Leu Met Tyr Tyr Thr Glu Ala Ser Ser Ala Phe
        35                  40                  45
Ile Val Val Lys Leu Met Pro Thr Ile Asp Ser Pro Ile Ser Gly Cys
    50                  55                  60
Asn Ile Thr Ser Ile Ser Ser Tyr Asn Ala Thr Val Thr Lys Leu Leu
65                  70                  75                  80
Gln Pro Ile Gly Glu Asn Leu Glu Thr Ile Arg Asn Gln Leu Ile Pro
                85                  90                  95
Thr Arg Arg Arg Arg Arg Phe Ala Gly Val Val Ile Gly Leu Ala Ala
            100                 105                 110
Leu Gly Val Ala Thr Ala Ala Gln Val Thr Ala Ala Val Ala Leu Val
        115                 120                 125
Lys Ala Asn Glu Asn Ala Ala Ala Ile Leu Asn Leu Lys Asn Ala Ile
    130                 135                 140
Gln Lys Thr Asn Ala Ala Val Ala Asp Val Val Gln Ala Thr Gln Ser
145                 150                 155                 160
Leu Gly Thr Ala Val Gln Ala Val Gln Asp His Ile Asn Ser Val Val
                165                 170                 175
Ser Pro Ala Ile Thr Ala Ala Asn Cys Lys Ala Gln Asp Ala Ile Ile
            180                 185                 190
Gly Ser Ile Leu Asn Leu Tyr Leu Thr Glu Leu Thr Thr Ile Phe His
        195                 200                 205
Asn Gln Ile Thr Asn Pro Ala Leu Ser Pro Ile Thr Ile Gln Ala Leu
    210                 215                 220
Arg Ile Leu Leu Gly Ser Thr Leu Pro Thr Val Val Glu Lys Ser Phe
225                 230                 235                 240
Asn Thr Gln Ile Ser Ala Ala Glu Leu Leu Ser Ser Gly Leu Leu Thr
                245                 250                 255
Gly Gln Ile Val Gly Leu Asp Leu Thr Tyr Met Gln Met Val Ile Lys
            260                 265                 270
Ile Glu Leu Pro Thr Leu Thr Val Gln Pro Ala Thr Gln Ile Ile Asp
        275                 280                 285
Leu Ala Thr Ile Ser Ala Phe Ile Asn Asn Gln Glu Val Met Ala Gln
    290                 295                 300
Leu Pro Thr Arg Val Met Val Thr Gly Ser Leu Ile Gln Ala Tyr Pro
305                 310                 315                 320
Ala Ser Gln Cys Thr Ile Thr Pro Asn Thr Val Tyr Cys Arg Tyr Asn
                325                 330                 335
Asp Ala Gln Val Leu Ser Asp Asp Thr Met Ala Cys Leu Gln Gly Asn
            340                 345                 350
Leu Thr Arg Cys Thr Phe Ser Pro Val Val Gly Ser Phe Leu Thr Arg
        355                 360                 365
Phe Val Leu Phe Asp Gly Ile Val Tyr Ala Asn Cys Arg Ser Met Leu
    370                 375                 380
Cys Lys Cys Met Gln Pro Ala Ala Val Ile Leu Gln Pro Ser Ser Ser
385                 390                 395                 400
Pro Val Thr Val Ile Asp Met Tyr Lys Cys Val Ser Leu Gln Leu Asp
                405                 410                 415
Asn Leu Arg Phe Thr Ile Thr Gln Leu Ala Asn Val Thr Tyr Asn Ser
            420                 425                 430
Thr Ile Lys Leu Glu Ser Ser Gln Ile Leu Ser Ile Asp Pro Leu Asp
        435                 440                 445
```

```
Ile Ser Gln Asn Leu Ala Ala Val Asn Lys Ser Leu Ser Asp Ala Leu
    450                 455                 460
Gln His Leu Ala Gln Ser Asp Thr Tyr Leu Ser Ala Ile Thr Ser Ala
465                 470                 475                 480
Thr Thr Thr Ser Val Leu Ser Ile Ile Ala Ile Cys Leu Gly Ser Leu
                485                 490                 495
Gly Leu Ile Leu Ile Ile Leu Leu Ser Val Val Val Trp Lys Leu Leu
            500                 505                 510
Thr Ile Val Val Ala Asn Arg Asn Arg Met Glu Asn Phe Val Tyr His
        515                 520                 525
Lys
```

<210> 31
<211> 1656
<212> DNA
<213> Simian virus 5

<220>
<221> CDS
<222> (1)...(1590)
<223> Simian virus 5 WR strain F protein encoding sequence; cDNA in mRNA sense

<400> 31

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atg ggt act att att caa ttt ctg gtg gtc tcc tgt cta ttg gca gga   48
Met Gly Thr Ile Ile Gln Phe Leu Val Val Ser Cys Leu Leu Ala Gly
 1               5                  10                  15

gca ggc agc ctt gat cta gca gcc ctc atg caa atc ggt gtc att cca   96
Ala Gly Ser Leu Asp Leu Ala Ala Leu Met Gln Ile Gly Val Ile Pro
            20                  25                  30

aca aat gtc cgg caa ctt atg tat tat act gag gcc tca tcg gca ttc   144
Thr Asn Val Arg Gln Leu Met Tyr Tyr Thr Glu Ala Ser Ser Ala Phe
        35                  40                  45

att gtt gtg aag tta atg cct aca att gac tcg ccg att agt gga tgt   192
Ile Val Val Lys Leu Met Pro Thr Ile Asp Ser Pro Ile Ser Gly Cys
    50                  55                  60

aat ata aca tca att tca agc tat aat gca aca gtg aca aaa ctc cta   240
Asn Ile Thr Ser Ile Ser Ser Tyr Asn Ala Thr Val Thr Lys Leu Leu
65                  70                  75                  80

cag ccg atc ggt gag aat ttg gag acg att agg aac cag ttg att cca   288
Gln Pro Ile Gly Glu Asn Leu Glu Thr Ile Arg Asn Gln Leu Ile Pro
                85                  90                  95

act cgg aga aga cgc cgg ttt gca ggg gtg gtg att gga tta gct gca   336
Thr Arg Arg Arg Arg Arg Phe Ala Gly Val Val Ile Gly Leu Ala Ala
            100                 105                 110

tta gga gta gct act gcc gca cag gtc act gcc gca gta gca cta gta   384
```

```
Leu Gly Val Ala Thr Ala Ala Gln Val Thr Ala Ala Val Ala Leu Val
        115                 120                 125

aag gca aat gaa aat gct gcg gct ata ctc aat ctc aaa aat gca atc   432
Lys Ala Asn Glu Asn Ala Ala Ala Ile Leu Asn Leu Lys Asn Ala Ile
    130                 135                 140

caa aaa aca aat gca gca gtt gca gat gtg gtc cag gcc aca caa tca   480
Gln Lys Thr Asn Ala Ala Val Ala Asp Val Val Gln Ala Thr Gln Ser
145                 150                 155                 160

cta gga acg gca gtt caa gca gtt caa gat cac ata aac agt gtg gta   528
Leu Gly Thr Ala Val Gln Ala Val Gln Asp His Ile Asn Ser Val Val
                165                 170                 175

agt cca gca att aca gca gcc aat tgt aag gcc caa gat gct atc att   576
Ser Pro Ala Ile Thr Ala Ala Asn Cys Lys Ala Gln Asp Ala Ile Ile
            180                 185                 190

ggc tca atc ctc aat ctc tat ttg acc gag ttg aca acc atc ttc cac   624
Gly Ser Ile Leu Asn Leu Tyr Leu Thr Glu Leu Thr Thr Ile Phe His
        195                 200                 205

aat caa att aca aac cct gca ttg agt ccc att aca att caa gct tta   672
Asn Gln Ile Thr Asn Pro Ala Leu Ser Pro Ile Thr Ile Gln Ala Leu
    210                 215                 220

agg atc cta ctg ggg agt acc ttg ccg act gtg gtc gaa aaa tct ttc   720
Arg Ile Leu Leu Gly Ser Thr Leu Pro Thr Val Val Glu Lys Ser Phe
225                 230                 235                 240

aat acc cag ata agt gca gct gag ctt ctc tca tca ggg tta ttg aca   768
Asn Thr Gln Ile Ser Ala Ala Glu Leu Leu Ser Ser Gly Leu Leu Thr
                245                 250                 255

ggc cag att gtg gga tta gat ttg acc tat atg cag atg gtc ata aaa   816
Gly Gln Ile Val Gly Leu Asp Leu Thr Tyr Met Gln Met Val Ile Lys
            260                 265                 270

att gag ctg cca act tta act gta caa cct gca acc cag atc ata gat   864
Ile Glu Leu Pro Thr Leu Thr Val Gln Pro Ala Thr Gln Ile Ile Asp
        275                 280                 285

ctg gcc acc att tct gca ttc att aac aat caa gaa gtc atg gcc caa   912
Leu Ala Thr Ile Ser Ala Phe Ile Asn Asn Gln Glu Val Met Ala Gln
    290                 295                 300

tta cca aca cgt gtt atg gtg act ggc agc ttg atc caa gcc tat ccc   960
Leu Pro Thr Arg Val Met Val Thr Gly Ser Leu Ile Gln Ala Tyr Pro
305                 310                 315                 320

gca tcg caa tgc acc att aca ccc aac act gtg tac tgt agg tat aat  1008
Ala Ser Gln Cys Thr Ile Thr Pro Asn Thr Val Tyr Cys Arg Tyr Asn
                325                 330                 335
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gat gcc caa gta ctc tca gat gat act atg gct tgc ctc caa ggt aac   1056
Asp Ala Gln Val Leu Ser Asp Asp Thr Met Ala Cys Leu Gln Gly Asn
            340                 345                 350

ttg aca aga tgc acc ttc tct cca gtg gtt ggg agc ttt ctc act cga   1104
Leu Thr Arg Cys Thr Phe Ser Pro Val Val Gly Ser Phe Leu Thr Arg
        355                 360                 365

ttc gtg ctg ttc gat gga ata gtt tat gca aat tgc agg tcg atg ttg   1152
Phe Val Leu Phe Asp Gly Ile Val Tyr Ala Asn Cys Arg Ser Met Leu
    370                 375                 380

tgc aag tgc atg caa cct gct gct gtg atc cta cag ccg agt tca tcc   1200
Cys Lys Cys Met Gln Pro Ala Ala Val Ile Leu Gln Pro Ser Ser Ser
385                 390                 395                 400

cct gta act gtc att gac atg tac aaa tgt gtg agt ctg cag ctt gac   1248
Pro Val Thr Val Ile Asp Met Tyr Lys Cys Val Ser Leu Gln Leu Asp
                405                 410                 415

aat ctc aga ttc acc atc act caa ttg gcc aat gta acc tac aat agc   1296
Asn Leu Arg Phe Thr Ile Thr Gln Leu Ala Asn Val Thr Tyr Asn Ser
            420                 425                 430

acc atc aag ctt gaa tca tcc cag atc ttg cct att gat ccg ttg gat   1344
Thr Ile Lys Leu Glu Ser Ser Gln Ile Leu Pro Ile Asp Pro Leu Asp
        435                 440                 445

ata tcc cag aat cta gct gcg gtg aat aag agt cta agt gat gca cta   1392
Ile Ser Gln Asn Leu Ala Ala Val Asn Lys Ser Leu Ser Asp Ala Leu
    450                 455                 460

caa cac tta gca caa agt gac aca tat ctt tct gca atc aca tca gct   1440
Gln His Leu Ala Gln Ser Asp Thr Tyr Leu Ser Ala Ile Thr Ser Ala
465                 470                 475                 480

acg act aca agt gta tta tcc ata ata gca atc tgt ctt gga tcg tta   1488
Thr Thr Thr Ser Val Leu Ser Ile Ile Ala Ile Cys Leu Gly Ser Leu
                485                 490                 495

ggt tta ata tta ata atc ttg ctc agt gta gtt gtg tgg aag tta ttg   1536
Gly Leu Ile Leu Ile Ile Leu Leu Ser Val Val Val Trp Lys Leu Leu
            500                 505                 510

acc att gtc gct gct aat cga aat aga atg gag aat ttt gtt tat cat   1584
Thr Ile Val Ala Ala Asn Arg Asn Arg Met Glu Asn Phe Val Tyr His
        515                 520                 525

aaa taa gcattccacc actcacgatc tgatctcagt gagaaaaatc aacctgcaac   1640
Lys  *

tcttggaaca agataa                                               1656

<210> 32
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<211> 529
<212> PRT
<213> Simian virus 5

<400> 32
Met Gly Thr Ile Ile Gln Phe Leu Val Val Ser Cys Leu Leu Ala Gly
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Ala Gly Ser Leu Asp Leu Ala Ala Leu Met Gln Ile Gly Val Ile Pro
20 25 30
Thr Asn Val Arg Gln Leu Met Tyr Tyr Thr Glu Ala Ser Ser Ala Phe
35 40 45
Ile Val Val Lys Leu Met Pro Thr Ile Asp Ser Pro Ile Ser Gly Cys
50 55 60
Asn Ile Thr Ser Ile Ser Ser Tyr Asn Ala Thr Val Thr Lys Leu Leu
65 70 75 80
Gln Pro Ile Gly Glu Asn Leu Glu Thr Ile Arg Asn Gln Leu Ile Pro
85 90 95
Thr Arg Arg Arg Arg Arg Arg Phe Ala Gly Val Val Ile Gly Leu Ala Ala
100 105 110
Leu Gly Val Ala Thr Ala Ala Gln Val Thr Ala Ala Val Ala Leu Val
115 120 125
Lys Ala Asn Glu Asn Ala Ala Ala Ile Leu Asn Leu Lys Asn Ala Ile
130 135 140
Gln Lys Thr Asn Ala Ala Val Ala Asp Val Val Gln Ala Thr Gln Ser
145 150 155 160
Leu Gly Thr Ala Val Gln Ala Val Gln Asp His Ile Asn Ser Val Val
165 170 175
Ser Pro Ala Ile Thr Ala Ala Asn Cys Lys Ala Gln Asp Ala Ile Ile
180 185 190
Gly Ser Ile Leu Asn Leu Tyr Leu Thr Glu Leu Thr Thr Ile Phe His
195 200 205
Asn Gln Ile Thr Asn Pro Ala Leu Ser Pro Ile Thr Ile Gln Ala Leu
210 215 220
Arg Ile Leu Leu Gly Ser Thr Leu Pro Thr Val Val Glu Lys Ser Phe
225 230 235 240
Asn Thr Gln Ile Ser Ala Ala Glu Leu Leu Ser Ser Gly Leu Leu Thr
245 250 255
Gly Gln Ile Val Gly Leu Asp Leu Thr Tyr Met Gln Met Val Ile Lys
260 265 270
Ile Glu Leu Pro Thr Leu Thr Val Gln Pro Ala Thr Gln Ile Ile Asp
275 280 285
Leu Ala Thr Ile Ser Ala Phe Ile Asn Asn Gln Glu Val Met Ala Gln
290 295 300
Leu Pro Thr Arg Val Met Val Thr Gly Ser Leu Ile Gln Ala Tyr Pro
305 310 315 320
Ala Ser Gln Cys Thr Ile Thr Pro Asn Thr Val Tyr Cys Arg Tyr Asn
325 330 335
Asp Ala Gln Val Leu Ser Asp Asp Thr Met Ala Cys Leu Gln Gly Asn
340 345 350
Leu Thr Arg Cys Thr Phe Ser Pro Val Val Gly Ser Phe Leu Thr Arg
355 360 365
Phe Val Leu Phe Asp Gly Ile Val Tyr Ala Asn Cys Arg Ser Met Leu
370 375 380
Cys Lys Cys Met Gln Pro Ala Ala Val Ile Leu Gln Pro Ser Ser Ser
385 390 395 400

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Pro Val Thr Val Ile Asp Met Tyr Lys Cys Val Ser Leu Gln Leu Asp
                405                 410                 415
Asn Leu Arg Phe Thr Ile Thr Gln Leu Ala Asn Val Thr Tyr Asn Ser
            420                 425                 430
Thr Ile Lys Leu Glu Ser Ser Gln Ile Leu Pro Ile Asp Pro Leu Asp
        435                 440                 445
Ile Ser Gln Asn Leu Ala Ala Val Asn Lys Ser Leu Ser Asp Ala Leu
    450                 455                 460
Gln His Leu Ala Gln Ser Asp Thr Tyr Leu Ser Ala Ile Thr Ser Ala
465                 470                 475                 480
Thr Thr Thr Ser Val Leu Ser Ile Ile Ala Ile Cys Leu Gly Ser Leu
                485                 490                 495
Gly Leu Ile Leu Ile Ile Leu Leu Ser Val Val Val Trp Lys Leu Leu
            500                 505                 510
Thr Ile Val Ala Ala Asn Arg Asn Arg Met Glu Asn Phe Val Tyr His
        515                 520                 525
Lys
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<210> 33
<211> 1174
<212> DNA
<213> Cryptovirus

<220>
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aatacaatac caccaggggt cacaggacta ctaaccaatg ctgcagaggc aaagatccaa 180
gagtcaatca accatcagaa gggttcagtt ggtgggggta caaacccaaa gaaaccgcga 240
tcaaaaattg ccattgtgcc agcagatgac aaaacagtgc ccgaaaagcc gatcccaaac 300
cctctactag gtctggactc caccccgagc acccaaaccg tgcttgatct aagtgggaaa 360
acattaccat caggatccta taagggggtt aagcttgcga aatttgggaa agaaaatctg 420
atgacacggt tcatcgagga acccagagag aatcctatcg caaccagttc ccccatcgat 480
tttaagaggg gcagagatac cggtgggttc catagaaggg agtactcaat cggatgggtg 540
ggagatgaag tcaaggtcac tgagtggtgc aatccatcct gttctccaat caccgctgca 600
gcaaggcgat ttaaatgcac ttgtcaccaa tgtccagtca cttgctctga atgtgaacga 660
gatacttaat acagtgagaa atttggactc tcggatgaat caactggaga caaaagtaga 720
tcgcattctc tcatctcagt ctctaatcca gaccatcaag aatgacataa ttggacttaa 780
agcagggatg gctactttag aaggaatgat tacaactgtg aaaatcatgg acccgggagt 840
tcccagtaat gttactgtgg aagatgtacg caagaaacta agtaaccatg ctgttgttgt 900
gccagaatca ttcaatgata gtttcttgac tcaatctgaa gatgtaattt cacttgatga 960
gttggctcga ccaactgcaa caagtgttaa gaagattgtc aggaaggttc ctcctcagaa 1020
ggatctgact ggattgaaga tcacactaga gcaattggca aaggattgca tcagcaaacc 1080
gaagatgagg gaagattatc tcctcaagat caaccaggct tctagtgagg ctcagctaat 1140
tgacctcaag aaagcaatca tccgcagtgc aatt 1174

<210> 34
<211> 2244
<212> DNA
<213> Cryptovirus

<220>
<223> cDNA in mRNA sense

<400> 34
tgactgacct ctaatcgaga ttacaccaac tcaaactata ggtgggtagt accccagtga 60
ttaatcttgc aagtactgat cgttggctac aacacaccaa tattatccag attagagagc 120
ttaattaact ctgtattaat aataacacta ctattccaat aactggaatt accagcttga 180
tttatctcca aaatgattca aagaaaacag atcatattaa gactacccta agcacgaacc 240
catatcgtcc ttcaaatcat gagcactata attcaatctc tggtggtctc ctgtctattg 300
gcaggagcag gcagccttga tccagcagcc ctcatgcaaa tcggtgtcat tccaacaaat 360
gtccggcaac ttatgtatta tactgaggcc tcatcagcat tcattgttgt gaagttaatg 420
cctacaattg actcgccgat tagtggatgt aatataacat caatttcaag ctataatgca 480
acagtgacaa aactcctaca gccgatcggt gagaatttgg agacgattag gaaccagttg 540
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atcatatcta ttttaaagaa aaaa 2244

<210> 35
<211> 18
<212> DNA
<213> Cryptovirus

<220>
<223> cDNA in mRNA sense

<400> 35
aattcagatc ccaatcct 18

<210> 36

<211> 18
<212> DNA
<213> Cryptovirus

<220>
<223> cDNA in mRNA sense

<400> 36
ctaaattgat atacctaa 18

<210> 37
<211> 18
<212> DNA
<213> Cryptovirus

<220>
<223> cDNA in mRNA sense

<400> 37
taatcgagat tacaccaa 18

<210> 38
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<220>
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<400> 38
aactcaaact ataggtgg 18

<210> 39
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<220>
<223> cDNA in mRNA sense

<400> 39
atcgagatta caccaact 18

<210> 40
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<220>
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<400> 40
actcaaacta taggtggg 18

<210> 41

<211> 18
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<220>
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<400> 41
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<210> 42
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<220>
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<400> 42
agcactataa ttcaatct 18

<210> 43
<211> 18
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<220>
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<400> 43
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<210> 44
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<220>
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<400> 44
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<210> 45
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<220>
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<400> 45
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<210> 46

<211> 18
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<220>
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<400> 46
tggcggcgtg attaaaaa 18

<210> 47
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<220>
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<400> 47
aatacgagtt tatggaat 18

<210> 48
<211> 258
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<400> 48
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aataacacta ctattccaat aactggaatt accagcttga tttatctcca aaatgattca 180
aagaaaacag atcatattaa gactacccta agcacgaacc catatcgtcc ttcaaatcat 240
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<210> 49
<211> 1656
<212> DNA
<213> Cryptovirus

<220>
<223> cDNA in mRNA sense

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tatactgagg cctcatcagc attcattgtt gtgaagttaa tgcctacaat tgactcgccg 180
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gagaaaaatc aacctgcaac tcttggaaca agataa 1656