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(54) Title: TUMOR THERAPY WITH REPLICATION COMPETENT SINDBIS VIRAL VECTORS

(57) Abstract: Disclosed herein are methods for treating a mamma! harboring a solid tumor which expresses higher levels of High Affinity Laminin Receptors (LAMR) than normal cells: of the same lineage comprising systematically administering to a mammal in need of such treatment a therapeutically effective amount of a Replication Competent (RC) Sindbis virus vector, wherein said vector encodes a suicide gene.



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Tumor Therapy with Replication Competent Sindbis Viral Vectors

Cross Reference To Related Applications

5 The present application claims the benefit of U.S. Provisional Patent Application Serial No. 61/030,367, filed February 21, 2008, the contents of which are hereby incorporated by reference in their entirety.

The United States government has certain rights to this invention, by virtue of the funding received from grant CA100687 from the National Institutes of Health.

Field of the Invention

10 The present invention is directed to methods to treat mammals suffering from tumors and to monitor anticancer therapy using Sindbis viral vectors and pharmaceutical formulations for use in the methods. In particular, the vectors are replication competent Sindbis Viral Vectors and the tumors are solid tumors expressing increased levels of High Affinity Laminin Receptors (LAMR) compared to normal cells of the same lineage.

Background of the Invention

15 One type of gene therapy of tumors, gene-directed enzyme-prodrug therapy (GDEPT), holds considerable promise, although practical considerations limit its clinical applicability. These include the lack of acceptable noninvasive methods that are adaptable to humans for selective tumor targeting of the therapeutic genetic material. Sindbis virus is an oncolytic, alphavirus that
20 selectively targets tumors through the 67-kDa laminin receptor (LAMR).

Gene therapy targets the genome of tumor cells as a basis for a highly selective and nontoxic anticancer therapy. To enhance selectivity and specificity to the killing of cancer cells, several enzyme/prodrug systems—such as carboxylesterase/CPT-11 (1), cytosine deaminase/5-fluoro-

cytosine (2), and herpes simplex virus thymidine kinase type 1 (HSVtk)/ganciclovir (GCV) (3,4)---have been developed for gene-directed enzyme-prodrug therapy (GDEPT). In this strategy, tumor cells are transduced with therapeutic genes that encode enzymes for specific conversion/activation of prodrugs, which are toxicologically inert at relatively high doses, into highly toxic metabolites for tumor killing.

In addition to a proper vector system, cancer GDEPT therapy would greatly benefit from a means to noninvasively monitor the GDEPT enzyme activity after vector treatments *in vivo*. Such capability could improve the Sindbis-based HSVtk/GCV GDEPT in clinical settings by providing important information to address 2 critical questions: (i) Do the vectors systemically target tumor cells and spare normal tissues? (i) Do the tumors have sufficient expression levels of the enzyme for tumor eradication by subsequent prodrug activation? In addition, monitoring during the therapy could facilitate optimizing the dose and dosing schedule of the prodrug to reduce unwanted side affects.

U.S. Patent No. 7,306,712 discloses that vectors based on Sindbis virus, a blood-borne alphavirus transmitted through mosquito bites, infect tumor cells specifically and systemically throughout the body. The tumor specificity of Sindbis vectors may be mediated by the 67-kDa high-affinity laminin receptor (LAMR), which is over expressed in several types of human tumors. Another advantageous property of Sindbis vectors for cancer therapy is that, without carrying cytotoxic genes, they have been shown to induce apoptosis in mammalian cells. Furthermore, as Sindbis vectors are capable of expressing very high levels of their transduced suicide genes in infected tumor cells, the efficient production of the enzymes for sufficient prodrug conversion is ensured.

U.S. Patent Application Serial No. 10/920,030 discloses methods and compositions for detecting cancer cells and monitoring cancer therapy using replication defective Sindbis virus vectors.

U.S. Patent No. 7,303,798 discloses novel defective Sindbis virus vectors and their use in treating tumors in mammals.

Summary of the Invention

The present inventors have unexpectedly discovered that replication competent (RC) Sindbis viral vectors have enhanced anti-tumor and cancer therapy monitoring activities when used with tumors which express higher levels of LAMR than normal cells of the same lineage. The RC
5 Sindbis virus vectors are based on the mut-4 replication defective Sindbis virus vector disclosed in the '798 patent.

In one aspect, the present invention provides a method for treating a mammal harboring a solid tumor which expresses higher levels of High Affinity Laminin Receptors (LAMR) than normal cells of the same lineage comprising systematically administering to a mammal in need of such
10 treatment a therapeutically effective amount of a Replication Competent (RC) Sindbis virus vector, wherein said vector encodes a suicide gene.

In another aspect, the present invention provides a method for monitoring anti-cancer therapy in a mammal harboring a solid tumor which expresses higher levels of LAMR than normal cells of the same lineage comprising administering to a mammal in need of such treatment a
15 diagnostically effective amount of a Replication Competent (RC) Sindbis virus vector comprising a gene encoding a detectable label, and determining the amount of cancer cells in the body of said mammal, wherein the amount of cancer cells is proportional to the amount of label produced by said cancer cells and said vector encodes a suicide gene.

In a further aspect, the present invention provides a method for identifying cancer cells which
20 expresses higher levels of LAMR than normal cells of the same lineage in the body of a mammal comprising administering to a mammal in need of such treatment a diagnostically effective amount of a mut-4 RC Sindbis virus vector comprising a gene encoding a detectable label, and assaying for said label, wherein said cell is a cancer cell if it expresses said label and said vector encodes a suicide gene.

In a still further aspect, the present invention provides a method for determining the amount of
25 cancer cells which expresses higher levels of LAMR than normal cells of the same lineage in the body of a mammal comprising the steps of (a) administering to a mammal in need of such treatment a diagnostically effective amount of a mut-4 RC Sindbis virus vector comprising a

gene encoding a detectable label, and (b) determining the amount of said detectable label, wherein the amount of cancer cells in the body of said mammal is proportional to the amount of said label and said vector encodes a suicide gene.

In yet another aspect, the present invention provides a Replication Competent mut-4 Sindbis virus vector, wherein said vector encodes a suicide gene.

In a still further aspect, the present invention provides a pharmaceutical formulation or dosage form for administration to a mammal suffering from a solid tumor which expresses higher levels of LAMR than normal cells of the same lineage comprising a mut-4 RC Sindbis virus vector and a pharmaceutically acceptable carrier or diluent, wherein said vector further comprises a suicide gene.

These and other aspects of the present invention will be apparent to those of ordinary skill in the art in light of the present description and drawings.

Brief Description of the Drawings

Figure 1 (A-D). Various Sindbis vector systems. (A) The wild-type Sindbis virus RNA genome has two major groups of genes: non-structural genes on the 5' side and structural genes on the 3' side. (B) The conventional two-component replication defective (RD) system contains a replicon RNA for therapeutic gene expression, and a helper RNA to provide structural genes for vector production. (C) A replication-capable (RC) vector system with integrated structural genes. (D) a RC vector system with a suicide gene fused in-frame with the ns3 gene to achieve "controlled" vector propagation and replication in tumor cells. The ns3 gene encodes a protein which is critical for viral replication and survival.

Figure 2 (A-E). Replication-capable (RC) Sindbis virus vectors show superior tumor targeting and killing over conventional replication-defective (RD) systems. (A and B) Design of conventional RD-Sindbis/Fluc and a prototype RC-Sindbis/Fluc both carrying the firefly luciferase gene as reporter. (C) Bioluminescent imaging of tumor-bearing mice that received two consecutive daily treatments of RD- or RC-Sindbis/Fluc. The first dose was on day 0 and the last dose was on day 1. Subcutaneous BHK tumors were implanted on the right hind limb.

(D) Quantitative representation of tumor signals after two consecutive treatments on day 2. (E) Tumor volume measured on day 10.

Figure 3. (A-D). A suicide gene further enhances the therapeutic efficacy of Sindbis virus vectors. (A) Design of a conventional RD vector capable of expressing HSVtk for prodrug activation. (B) Bioluminescent imaging of ES2/Fluc ovarian cancer cells that express firefly luciferase for monitoring disease progression. SCID mice were inoculated with ES2/Fluc cells on day 0. Daily treatments with RD-Sindbis/HSVtk and GCV started on day 3. The combination of Sindbis virus vectors and the prodrug ganciclovir (GCV) significantly improved anti-tumor efficacy. (C and D) Quantitative representations of the imaging data.

Figure 4 is a map of the pSP6-R/NS3-HSVtk/Fluc-Mut4 plasmid. pSP6-R/NS3-HSVtk/Fluc-Mut4 is a Sindbis RC vector construction based on pSP6-R and Mut-4, which provides the replicase genes and structural genes respectively.

Detailed Description of the Invention

The instant invention takes advantage of the natural affinity of an alphavirus, particularly Sindbis virus, for tumor cells, in particular, for solid tumors that express higher levels of high affinity laminin receptors (alternatively referred to herein as LAMR or HALR), as compared to normal cells of the same lineage. The term "high affinity laminin receptor" or "LAMR" has its ordinary meaning in the art, i.e., the Mr 67,000 laminin receptor that can function as the receptor for Sindbis virus entry into cells (Wang *et al.*, J. Virol. 1992, 66:4992-5001; Strauss *et al.*, Arch. Virol. Suppl. 1994, 9:473-84).

Accordingly, the present invention provides a method for treating a mammal (*e.g.*, human) suffering from a tumor that expresses greater levels of high affinity laminin receptor (LAMR) compared to normal cells of the same lineage. The method comprises administering to a mammal harboring such a tumor an amount of a vector effective to treat the tumor, wherein the vector has a preferential affinity for LAMR and the vector genome comprises a single component.

While not bound by any particular theory, three sets of observations may account for the remarkable anti-tumor efficiency of Sindbis vector-based therapy of the present invention. First, the LAMR can function as the receptor for Sindbis virus entry into cells of most species (Wang *et al.*, J. Virol., 1992, 66:4992-5001; and Strauss *et al.*, Arch. Virol. Suppl., 1994, 9:473-484).

5 Second, it is widely recognized that expression of the LAMR is markedly elevated in many types of cancers (Menard *et al.*, Breast Cancer Res. Treat., 1998, 52:137-145). In fact, a significant correlation has been established between the increased expression of Mr 67,000 LAMR and cancers of the breast (Menard *et al.*, 1998, *supra*; Paolo Viacava *et al.*, J. Pathol., 1997, 182:36-44; Martignone *et al.*, J. Natl. Cancer Inst., 1993, 85:398-402), thyroid (Basolo *et al.*, Clin. Cancer Res., 1996, 2:1777-1780), colon (San Juan *et al.*, J Pathol., 1996, 179:376-380), prostate (Menard S *et al.*, Breast Cancer Res. Treat., 1998, 52:137-145), stomach (de Manzoni *et al.*, Jpn J Clin. Oncol., 1998, 28:534-537), pancreas (Pelosi *et al.*, J Pathol., 1997, 183:62-69), ovary (Menard *et al.*, Breast Cancer Res. Treat., 1998, 52:137-145; and van den Brule *et al.*, Eur J Cancer, 1996, 32A:1598-1602.), melanocytes (Taraboletti *et al.*, J Natl. Cancer Inst., 1993, 85:235-240), lung (Menard *et al.*, Breast Cancer Res. Treat., 1998, 52:137-145), liver (Ozaki *et al.*, Gut, 1998, 43:837-842), endometrium, and uterus (van den Brule *et al.*, Hum Pathol, 1996, 27:1185-1191). Indeed, data on more than 4000 cases of different tumors from diverse organs studied by immunohistochemistry are all concordant with a role for HALR in invasiveness, metastasis, and tumor growth (Menard *et al.*, Breast Cancer Res. Treat., 1998, 52:137-145).

20 Sindbis vectors, which are naturally blood-borne, can easily travel through the circulation and specifically home to and target growing and metastatic tumors expressing increased levels of LAMR. Finally, Sindbis virus is well known to be highly apoptotic for mammalian cells (Levine *et al.*, Nature 1993, 739-742; Jan *et al.* J Virol., 1999: 10296-10302; Jan *et al.* J Virol 2000 6425-6432). Cell death begins within a few hours of infection and by 48-96 hours virtually all infected

25 cells are dead (Sawai *et al.*, Mol Genet Metab. 1999, 67:36-42; Griffin *et al.*, Ann. Rev., 1997, Microbiol. 51:565-592).

The Sindbis vectors of the present invention, do not infect normal cells to the same extent *in vivo* compared to tumor cells. This allows for a differential effect in vector therapy, *e.g.*, infection by Sindbis vectors results in the death of tumor cells leading to tumor elimination without apparent deleterious effects to other tissues and organs of the treated subjects. This phenomenon may be

explained by the observation that an increased number of LAMR in tumors versus normal cells leads to a high number of exposed or unoccupied receptors on tumor cells (Liotta, L.A. Cancer Research, 1986, 46:1-7; Aznavoorian *et al.*, 1992, Molecular Aspects of Tumor Cell Invasion and Metastasis, pp. 1368-1383). For example, it has been demonstrated that breast carcinoma and colon carcinoma tissues contain a higher number of exposed (unoccupied) LAMR compared to benign lesions (Liotta *et al.*, 1985, Exp. Cell Res., 156:117-26; Barsky *et al.*, Breast Cancer Res. Treat., 1984, 4:181-188; Terranova *et al.*, Proc. Natl. Acad. Sci. USA, 1983, 80: 444-448). These excess unoccupied LAMR receptors on tumor cells, which are not found in normal cells, may be available for Sindbis virus binding, infection, and induction of cell death.

The invention advantageously provides a method for treating a mammal suffering from a tumor, in which the cells of the tumor express greater levels of LAMR compared to normal cells of the same lineage. The different levels of LAMRs result in target-mediated delivery, i.e., preferential binding of vectors of the invention to tumor cells. "Greater levels" of expression generally refer herein to levels that are expressed by tumor cells (as compared to non-tumor cells) and result in such preferential binding, e.g., at least a 3-fold greater binding, preferably at least a 30-fold greater binding and, most preferably at least a 300-fold greater binding. The increased level of expression in tumor cells can be evaluated on an absolute scale, i.e., relative to any other LAMR expressing non-tumor cells described, or on a relative scale, i.e., relative to the level expressed by untransformed cells in the same lineage as the transformed cancer cells (e.g., melanocytes in the case of melanoma; hepatocytes in the case of hepatic carcinoma; ovarian endothelial cells in the case of ovarian adenocarcinoma, renal endothelial or epithelial cells in the case of renal carcinoma).

As used herein, the term "infectious", "replication competent" or "replication capable", when used to describe a Sindbis virus vector RNA molecule, means an RNA molecule which is self-replicating and provides for transcription in a host cell. The term "replication", when used in conjunction with a Sindbis virus genomic RNA vector RNA molecule means production of full-length equivalents of (+)-strand RNA using (-)-strand RNA as a template.

As used herein, the term "tumor" refers to a malignant tissue comprising transformed cells that grow uncontrollably. Tumors include leukemias, lymphomas, myelomas, plasmacytomas, and

the like; and solid tumors. Examples of solid tumors that can be treated according to the invention include sarcomas and carcinomas such as, but not limited to: fibrosarcoma, myxosarcoma, liposarcoma, chondrosarcoma, osteogenic sarcoma, chordoma, angiosarcoma, endotheliosarcoma, lymphangiosarcoma, lymphangioendotheliosarcoma, synovioma, mesothelioma, Ewing's tumor, leiomyosarcoma, rhabdomyosarcoma, colon carcinoma, pancreatic cancer, breast cancer, ovarian cancer, prostate cancer, squamous cell carcinoma, basal cell carcinoma, epidermoid carcinoma, adenocarcinoma, sweat gland carcinoma, sebaceous gland carcinoma, papillary carcinoma, papillary adenocarcinomas, cystadenocarcinoma, medullary carcinoma, bronchogenic carcinoma, renal cell carcinoma, hepatoma, bile duct carcinoma, choriocarcinoma, seminoma, embryonal carcinoma, Wilms' tumor, cervical cancer, testicular tumor, lung carcinoma, small cell lung carcinoma, bladder carcinoma, epithelial carcinoma, glioma, astrocytoma, medulloblastoma, craniopharyngioma, ependymoma, pinealoma, hemangioblastoma, acoustic neuroma, oligodendroglioma, meningioma, melanoma, neuroblastoma, neuroglioma, and retinoblastoma. As noted above, the method of the invention depends on expression of LAMRs by cells of the tumor targeted for treatment.

The term "about" or "approximately" usually means within an acceptable error range for the type of value and method of measurement. For example, it can mean within 20%, more preferably within 10%, and most preferably still within 5% of a given value or range. Alternatively, especially in biological systems, the term "about" means within about a log (*i.e.*, an order of magnitude) preferably within a factor of two of a given value.

The phrase "pharmaceutically acceptable", as used in connection with compositions of the invention, refers to molecular entities and other ingredients of such compositions that are physiologically tolerable and do not typically produce untoward reactions when administered to a human. Preferably, as used herein, the term "pharmaceutically acceptable" means approved by a regulatory agency of the Federal or a state government or listed in the U.S. Pharmacopeia or other generally recognized pharmacopeia for use in mammals, and more particularly in humans.

The term "therapeutically effective" when applied to a dose or an amount refers to that quantity of a compound or pharmaceutical composition that is sufficient to result in a desired activity upon administration to a mammal in need thereof. As used herein with respect to viral vectors of

the invention, the term "therapeutically effective amount/dose" refers to the amount/dose of a vector or pharmaceutical composition containing the vector that is sufficient to produce an effective anti-tumor response upon administration to a mammal.

As disclosed in Serial No. 10/920,030 the present inventors previously discovered and devised methods for detecting tumor cells and monitoring cancer therapy. The methods are based on the natural preference of Sindbis virus to infect human cancer cells that express higher level of 37/67-KDa laminin receptor (LAMR) than normal, non-cancerous cells.

Various Sindbis viral vectors for cancer gene therapy have been designed based on the RNA genome of wild-type virus (Figure 1A). The wild-type genome contains two major parts. The first part, located on the 5' side of the genome, carries all of the non-structural genes (ns1, ns2, ns3, and ns4) and a packaging signal in the ns1 region. The expression of the ns1-4 genes leads to synthesis of the non-structural proteins nsp 1-4 that form the viral replicase. The replicase is necessary for expression of the structural genes in the second part of the genome at 3' side for virus formation. In order to do so, the replicase specifically recognizes a short stretch of sequences between the non-structural and structural genes, called the sub-genomic promoter (P_{SG}). One structural protein, the capsid protein, specifically recognizes the packaging signal at the ns1 region and picks it up to form viral particles with the rest of the structural proteins.

Figure 1B depicts the conventional design of a replication defective Sindbis viral vector that is capable of efficient delivery of therapeutic genes while being unable to propagate and generate more vector particles. This particular system has two components. Replicon RNA contains all of the non-structural genes, while the structural genes are replaced with the therapeutic gene to be delivered. In order to generate vector particles, the structural genes are provided in trans using a helper RNA, the second component of this system. Unlike replicon RNA, the helper RNA contains the non-structural genes and lacks the packaging signal. Therefore, the produced vector particles only carry replicon RNA with the gene of interest.

One major advantage of such conventional dual-component vector systems is that the produced vector particle is replication-defective (RD) and is safer for clinical use. However, this advantage may become a significant drawback for cancer genes therapy. The goal of cancer

gene therapy is to infect the majority of tumor cells and deliver the therapeutic genes for tumor detection or eradication. To achieve this goal using a replication-defective system may require a repetitive treatment regime and high doses of vectors. In some cases, such high doses may not be easily obtained using a replication defective system.

- 5 On the other hand, a Sindbis vector system that is capable of “controlled” replication and propagation is of great interest for cancer gene therapy. Such a replication-capable (RC) system should comprise a single-component to ensure efficient propagation of the vector in the tumor. That is, the system does not require a helper component for replication. One major benefit of such a system is that fewer treatments would be required and a lower dose should be sufficient to
10 achieve successful therapeutic outcomes while retaining the same tumor targeting capability as RD vectors. Preferably, a safety mechanism is incorporated in the vector to ensure that the vector is eliminated in order to prevent unwanted toxicity, if any, associated with the propagation of the vector.

- The present invention provides a replication-capable (RC) Sindbis viral vector (Figure 1C) which
15 was tested to see if a single-component system performed better than the conventional dual-component system. Instead of using a separate helper RNA vector to carry the structural genes, the structural genes are directly inserted into a conventional replicon vector, along with a dedicated sub-genomic promoter following the therapeutic gene. The dedicated second promoter guarantees that the efficient expression of the structural genes for high-level vector production
20 occurs. A simple dual-promoter RC system was first developed in order to study the function of the sub-genomic promoter in mammalian cells (5,6). This type of RC system was later used to deliver antigen encoding genes for vaccination purposes (7-9). Since Sindbis virus infects mosquito cells, a simple RC system was also used to study Sindbis virus spreading in mosquitoes (10). In light of the present inventors’ discovery that RD Sindbis vectors can target tumors in
25 living animals, a single-component RC Sindbis vector has been used to detect/treat tumors in mouse tumor models (11). However, instead of using a dedicated sub-genomic promoter, the prior art RC system used a cleavable component to release the reporter protein from the structural proteins and, therefore, significantly reduced the titer of vector production (12).

Figure 2 shows the results of an experiment comparing the anti-tumor activity of replication defective (RD, Figure 2A) and replication competent (RC, Figure 2B) Sindbis virus vectors. In this set of experiments, a subcutaneously induced BHK tumor model (on the right hind limb of SCID mice) was used to test and compare these two vector systems. In order to evaluate specific tumor targeting and elimination in this model, both vector systems carry a firefly luciferase gene as a reporter. The bioluminescent signals generated in the tumors can be easily detected and analyzed using the IVIS™ imaging system. Mice received only two consecutive treatments of RD or RC vectors via systemic (intravenous) injections on a day 0 and day 1. No further treatment was administrated. Figure 2C depicts the imaging result on day 2 and Figure 2D quantitatively shows the level of bioluminescent signals in tumors that directly reflects vector infection level. The data indicate that the RC vector system has about a 30 fold increase in infectivity compared to the conventional RD vector system. Higher infectivity is also reflected in enhanced tumor killing as evidenced by tumor size reduction on day 10 (Figure 2E).

These data provide proof-of-concept results in support of the use of a RC Sindbis vector system for cancer gene therapy. The capability of the RC vector to propagate and spread to the tumor dramatically enhances the ability of Sindbis vectors to target and kill cancer cells. The data also show that the same level of tumor detection can be achieved using a lower range of effective doses of the RC vector compared to conventional RD vectors. In the example depicted in Figure 2, 10^6 RD or RC vector particles were intravenously administered into mice. The signals from tumors treated with the RC vectors were about 30 fold higher than the RD signals. Therefore, the same imaging intensity in tumors was achieved using a lower dose (10^4 to 10^5) of RC vectors. Interestingly, no toxicity was associated with this prototype RC vector administered at 10^6 level and no bioluminescent signals, except in residual tumors, were observed in animals up to 20 days after vector injections, suggesting that using the same level of RC vector, as high as 10^6 per dose, should not cause side effects. The higher dose is useful not only for detecting small lesions but also for better tumor killing and therapeutic effects. Since humans are about 1000 times the body weight of mice, the expected range of effective amounts for humans will range between about 10^7 and about 10^{10} particles per dose. The lower range (10^7 - 10^8) is sufficient to detect tumor masses and higher range (10^8 - 10^{10}) are better for tumor eradication.

For use in the present invention, the RC Sindbis virus vectors can be produced as described in U.S. Patent Nos. 7,306,712 and 7,303,798 and in the example below. This involves the described *in vitro* transcription/electroporation method.

However, as mentioned above, a safety mechanism significantly reduces the risk, if any, of toxicity by controlling the propagation of the RC vector system. In a preferred embodiment, a “suicide gene” is incorporated into one of the Sindbis virus non-structural genes that are essential for viral propagation and survival. Figure 1C depicts the concept of such a design. A suicide gene, which encodes an enzyme capable of activating inert prodrugs into cytotoxic metabolites, is fused in frame with the ns3 gene to ensure co-expression with non-structural protein 3, an essential component of viral replicase. A particular region of the ns3 gene has been shown to be suitable for fusion without compromising the function of nsp3. Therefore, by such design the RC vector is genetically tagged with this safety mechanism which can shut-off vector propagation by killing the vector producing cell during or after the treatment regime.

In addition to serving as a safety feature, the fused suicide gene provides another advantage. The tumor cells that are selectively infected by the vector are more susceptible and sensitive to the prodrug treatment, since they would not only face the killing imposed by Sindbis infection, but also are exposed to toxic metabolites as a result of prodrug activation. In this regard, it has been discovered that activated toxic metabolites can passively diffuse to neighboring uninfected tumor cells to further enhance tumor killing. This is called a “bystander effect”. The bystander effect plays an important role in the eradication of surrounding untransduced (uninfected) tumor cells. This is caused by transmission of the activated prodrug from the transduced tumor cells (which may be only a small fraction of total tumor mass) to uninfected tumor cells. In the HSVtk/GCV system, the activated GCV is not membrane permeable because of its highly charged phosphate groups. However, it can be transferred to uninfected cells via the gap junctions or through the exchange of apoptotic vesicles that kill the surrounding untransduced tumor cells (14).

Several suicide genes and their appropriate prodrugs are available and suitable for use with the Sindbis virus vector in this embodiment. For example, as disclosed herein, a conventional Sindbis virus vector carrying a thymidine kinase gene isolated from herpes simplex virus (HSVtk) significantly enhanced tumor killing (Figure 3A) (Horsburgh BC et al, Recurrent

acyclovir-resistant herpes simplex in an immunocompromised patient; can strain differences compensate for loss of thymidine kinase in pathogenesis? J. Infect. Dis., 178 (3), 618-625, 1998). A specific prodrug, ganciclovir (GCV), has been developed to target HSVtk, and has been clinically approved for treatment of cytomegalovirus and herpes simplex virus infection in humans. (Ganciclovir, GCV, is marketed under the trade name CYTOVENE™ by Roche Laboratories Inc.)

Additional examples of suicide genes are thymidine kinase of Varicella Zoster virus (VZV-tk) (disclosed in Lacey SF et al, Analysis of mutations in the thymidine kinase genes of drug-resistant varicella-zoster virus populations using the polymerase chain reaction, J. Gen. Virol. 72 (PT 3), 623-630, 1991) and the bacterial gene cytosine deaminase (Perna NT et al, Genome sequence of enterohaemorrhagic Escherichia coli O157:H7, Nature 409 (6819), 529-533, 2001).

The prodrugs useful in the methods of the present invention are any that can be converted to a toxic product, *i.e.*, toxic to tumor cells. A preferred prodrug is ganciclovir, which is converted *in vivo* to a toxic compound by HSV-tk (Chen *et al.*, Cancer Res. 1996, 56: 3758-3762). Other representative examples of prodrugs include acyclovir, FIAU [1- (2-deoxy-2-fluoro-β-D-arabinofuranosyl) -5-iodouracil] (FIALURIDINE™, Moravek Biochemicals and Radiochemicals), 6-methoxypurine arabinoside (converted by VZV-tk), and 5-fluorocytosine (converted by cytosine deaminase) (5-fluorocytosine, Roche).

Prodrugs, may be readily administered to patients by physicians having ordinary skill in the art. Using methods known in the field, such physicians would also be able to determine the most appropriate dose and route for the administration of the prodrug. For example, ganciclovir is preferably administered systemically (e.g. orally or parenterally) in a dose of about 1-20 mg/day/kg body weight; acyclovir is administered in a dose of about 1-100 mg/day/kg body weight, and FIAU is administered in a dose of about 1-50 mg/day/kg body weight.

In the example below, SCID mice were intraperitoneally implanted with ES2 human ovarian cancer cells. In order to track and monitor disease progression, the ES2 cells were genetically engineered to express a firefly luciferase gene for bioluminescent imaging. Therefore, the bioluminescent signal intensity is proportional to the tumor load in these animals (Figure 3B).

Tumor-bearing mice were either mock treated or received daily treatments with a conventional RD-Sindbis/HSVtk vector. Some mice also received daily GCV treatments to determine if the prodrug enhanced tumor killing in conjunction with Sindbis vector treatment. Quantitative analysis indicated that, without HSVtk expression, unactivated GCV confers no therapeutic effect on tumor loading (Figure 3C). On the contrary, GCV dramatically enhanced the Sindbis/HSVtk vector treatments and suppressed tumor growth (Figure 3D).

In an alternate embodiment, the vectors of the present invention can be used to detect cancer cells and monitor anti-cancer therapy. Previously, the present inventors used an optical bioluminescence imaging system and RD Sindbis virus vectors to detect tumor-specific targeting of Sindbis virus vectors in small animals (15, 16 and Serial No. 10/920,030). The advantages of bioluminescent imaging include short imaging time, low costs, and ease of use. However, optical imaging methods suffer from very substantial attenuation of the light signal and, thus, are not amenable to applications in large animals and in patients. Recent advances in optical and radionuclide imaging technology provide several methods for non-invasive monitoring of marker gene expression in living animals. On the other hand, radionuclide imaging methods such as gamma-camera, SPECT, and PET have excellent depth sensitivity and can detect accumulation of gene expression within the transfected tumors anywhere in the body and on the basis of gene expression imaging (17,18,19). A major advantage of PET is the ability to generate quantitative high spatial resolution, 3-dimensional images. When combined with other forms of tomographic imaging, such as CT or MRI, fusion images of functional and anatomic data provides more detailed in situ information of marker genes' expression and localization.

As disclosed in copending Serial No. 10/920,030, the present inventors have discovered that imaging can be translated into photon counts produced by the detectable label delivered to cancer cells and that these are proportional to the amount of tumor cells that remain alive. Therefore, the present invention can be used to monitor anti-cancer therapy as follows. Patients can be administered a diagnostically-effective amount of the RC Sindbis vector of the present invention comprising a detectable label before the onset of treatment, and this value can be compared to one obtained upon administration of a diagnostically effective amount of a Sindbis virus comprising a detectable label after therapy has been completed. In this way, it is possible to

determine the extent of tumor kill. Since only living tumor cells would contain the label, therapy would continue only until a minimal amount of label is detected.

Since Sindbis virus vectors are gene transfer vectors, the cancer cells are labeled using genetic markers incorporated into the RC Sindbis virus vectors. In this embodiment, the genes useful for live tumor monitoring or labeling include but are not limited to the Green Fluorescence Protein (GFP) gene, [Cormack, B. P. *et al.* (1966) FACS-optimized mutants of the green fluorescent protein (GFP). *Gene* **173**:33-38] the Firefly luciferase (Fluc) gene, [de Wet, J.R., *et al.* (1987) Firefly luciferase gene: structure and expression in mammalian cells *Mol. Cell Biol.* **7** (2), 725-737], the Renilla luciferase (Rluc) gene [Lorenz, W.W. *et al.* (1991) Isolation and expression of a cDNA encoding Renilla reinformis luciferase, *Proc. Natl. Acad. Sci. U.S.A.* **88** (10), 4438-4442] and the dopamine-2 receptor (D₂R) gene. The use of the D₂R gene as a reporter gene in living animals is disclosed in MacLaren *et al.* (*Gene Therapy* **6**:785-791 (1999)) and Yaghoubi *et al.* (*Gene Therapy* **8**:1072-1080 (2001)) These genes can be incorporated into the Sindbis virus vectors of the present invention using techniques well known to those of ordinary skill in the art, as described in Bredenbeek P.J. *et al.* (1993) (Sindbis virus expression vectors: packaging of RNA replicons by using defective helper RNAs, *J. Virol.*; **67**(11):6439-46.)

Cells expressing the genetic markers of the present invention can be identified as follows: for the HSV-tk gene, the subject can be administered radiolabeled 9-[(4-[¹⁸F]fluro-3-hydroxymethylbutyl)guanine (FHBG), administered intravenously, about 6000 µCi/Kg body weight of the recipient, (commercially available from PET Imaging Science Center, U. of South California). Expression of HSV-tk activity in tumor cells results in the accumulation of radiolabeled FHBG and can be monitored by Positron Emission Tomography (PET). *In vivo* GFP expressing tumor cells can be monitored by fluorescence microscopic examination of tissue sections. Tissue sections of Fluc or Rluc expressing tumor cells can be monitored by Cooled Charge-Coupled Device (CCD) cameras *in vivo* (commercially available from Xenogen Corp., Alamenda, CA). D₂R activity can be identified by administering 3-(2-[¹⁸F]fluoroethyl)spiperone ([¹⁸F]FESP) and monitored by PET.

A subject to whom the diagnostic compound of the present invention has been administered as an effective diagnostic monitor for a disease or disorder is preferably a human, but can be any

animal, including a laboratory animal in the context of a clinical trial or screening or activity experiment. Thus, as can be readily appreciated by those of ordinary skill in the art, the methods and compositions of the present invention are particularly suited to administration to any animal, particularly a mammal, and including, but by no means limited to, domestic animals, such as feline or canine subjects, farm animals, such as but not limited to bovine, equine, caprine, ovine, and porcine subjects, wild animals (whether in the wild or in a zoological garden), research animals, such as mice, rats, rabbits, goats, sheep, pigs, dogs, cats, etc., avian species, such as chickens, turkeys, songbirds, etc., *i.e.*, for veterinary medical use.

In summary, the single-component RC Sindbis vector system of the present invention dramatically enhances the tumor targeting, monitoring and killing capability of replication-capable Sindbis vectors, and incorporation of suicide genes provides an additional layer of protection to achieve “controlled” propagation in tumors and enhances tumor cell killing by RC Sindbis virus vectors.

In a preferred embodiment, the RC vectors are derived from the RD mut-4 vector disclosed in U.S. Patent No. 7,303,798. The mut-4 vector is similar to the SinRep5 system (Invitrogen Corp.), except for changes in the amino acid sequences in the E2 protein. Since this protein is directly involved in vector binding and targeting to tumor cells, it is expected that RC vectors derived from the mut-4 vector will have the same improved binding capability as the RD vectors.

The construction of the RC mut-4 vector containing the HSV-tk gene is shown in Paper Example 1 below.

The present invention also provides pharmaceutical formulations or dosage forms for administration to mammals.

When formulated in a pharmaceutical composition, the vectors of the present invention can be admixed with a pharmaceutically acceptable carrier or excipient. The phrase “pharmaceutically acceptable” refers to molecular entities and compositions that are “generally regarded as safe”, *e.g.*, that are physiologically tolerable and do not typically produce an allergic or similar untoward reaction, such as gastric upset, dizziness and the like, when administered to a human. Preferably, as used herein, the term “pharmaceutically acceptable” means approved by a

regulatory agency of the Federal or a state government or listed in the U.S. Pharmacopeia or other generally recognized pharmacopeia for use in animals, and more particularly in humans. The term "carrier" refers to a diluent, adjuvant, excipient, or vehicles with which the compound is administered. Such pharmaceutical carriers can be sterile liquids, such as water and oils, including those of petroleum, animal, vegetable or synthetic origin, such as peanut oil, soybean oil, mineral oil, sesame oil and the like. Water or aqueous saline solutions and aqueous dextrose and glycerol solutions are preferably employed as carriers, particularly for injectable solutions. Alternatively, the carrier can be a solid dosage form carrier, including but not limited to one or more of a binder (for compressed pills), an encapsulating agent, a flavorant, and a colorant. Suitable pharmaceutical carriers are described in "Remington's Pharmaceutical Sciences" by E.W. Martin.

The preferred route of administration of the vectors of the present invention, for treatment and monitoring, is parenteral and most preferably systemic. This includes, but is not limited to intravenous, intraperitoneal, intra-arteriole, intra-muscular, intradermal, subcutaneous, intranasal and oral. These routes of administration will permit homing of the vector to tumor cells wherein, only Sindbis virus is a blood-borne virus. Therefore, gene therapy vectors based on this virus have an advantage over other viral vectors that are not adapted to travel in the bloodstream. This property is largely responsible for the observation that systemic administration of Sindbis viral vectors by i.p. or i.v. injections, target and infect only tumors expressing greater amounts of LAMR than normal cells of the same lineage growing s.c., i.p., intrapancreatically, or in the lungs. Thus, the blood-borne nature of Sindbis viral vectors provides them with the capacity to treat malignancies and monitor cancer therapy.

The present invention is described below in examples which are intended to further describe the invention without limiting the scope therapy.

Materials and Methods

Vector Construction

The prototype RC-Sindbis/Fluc vector was constructed using the pSinRep5/Fluc plasmid as a backbone. In order to make the vector replication competent, a DNA segment containing a sub-genomic promoter and the Sindbis viral structural genes was excised from the pRNA-DHBB plasmid (Invitrogen Corp., Carlsbad, CA) using *NsiI* and *BamHI* enzymes and then inserted into pSinRep5/Fluc at the *StuI* site. Therefore the constructed pSinRep5/Fluc-tBB plasmid has two independent sub-genomic promoters to drive expression of firefly luciferase and Sindbis viral structural proteins.

For construction of a RC vector with a suicide gene in the HSVtk gene was fused in-frame with the *ns3* gene at the *SpeI* site in pSinRep5/Fluc-tBB. The HSVtk gene (from the pORF-HSVtk plasmid, Invivogen, San Diego, CA) was inserted at this site to generate the pSinRep5-*ns3*-HSVtk/Fluc-tBB plasmid.

Vector preparation

The RC-Sindbis/Fluc vector was prepared using an *in vitro* transcription/electroporation method as described U.S. Patent Nos. 7,306,712 and 7,303,798. The plasmid pSinRep5/Fluc-tBB was linearized using the *NotI* restriction enzyme. The linearized plasmid DNA was then used as template for *in vitro* transcription. The *in vitro* transcription was done in a total volume of 20 μ L using a commercially available SP6 *in vitro* transcription kit (Ambion Inc., Austin, TX).

Transcribed RNA (20 μ L) was then electroporated into 6×10^6 BHK cells and cultured at 37°C in a 10 cm dish containing 10mL of α MEM (Invitrogen Corp.) with 10% FCS. The next day, the culture media was replaced with 9mL of OptiMEM (Invitrogen). The OptiMEM was then harvested and stored at -80°C.

In vivo imaging

BHK tumors were induced in female SCID mice (Taconic, Germantown, NY) by subcutaneous injection of 2 million BHK cells. Ten days later, on day 0, mice were split into two groups. One group of five mice received the first intravenous injection of 10^6 particles of RD-Sindbis/Fluc, and the other group received the first i.v. injection of 10^6 particles of RC-Sindbis/Fluc. The next day (day 1), both groups received a second dose (10^6) of i.v. treatments. Twenty-four hours later (day 2), tumor luminescence signals were measured using the IVIS® spectrum imaging system (Caliper LifeSciences, Hopkinton, MA) and tumor specific signals were analyzed using Living Image 3.0 software. Five minutes before imaging, 0.3 mL of 15mg/mL D-luciferin (Promega, Madison, WI) was i.p. injected in order to generate bioluminescent signals. Tumor sizes were measured using calipers and volumes were calculated using the formula: $4 \pi /3 \times \text{length} \times \text{width} \times \text{height}$.

An ES-2/Fluc ovarian cancer model was used to test if the HSVtk suicide gene enhanced the therapeutic effects of Sindbis vectors. The prodrug GCV (CYTOVENE-IV®, The Roche Laboratories Inc.) enhanced the killing of Sindbis/tk-infected ES-2/Fluc cells *in vivo*, as determined by the IVIS® system, which is capable of non-invasive detection of bioluminescent signal generated by ES-2/Fluc tumors. SCID mice were inoculated with ES-2/Fluc on day 0. Daily GDEPT treatments involving i.p. injections of RD-Sindbis/tk and GCV (25mg/Kg of body weight) were started on day 3. The Sindbis/tk –GCV group (n = 5) received Sindbis/tk treatments but no GCV. The Sindbis/tk +GCV group (n = 5) received both Sindbis/tk and GCV treatments. The Control group (n = 5) was neither treated with Sindbis/tk nor GCV. The Control +GCV group (n = 5) received no Sindbis/tk but was treated with GCV. Disease progression was monitored and the whole body photon counts were determined using the IVIS® system on days 1, 3, 6, 8, 12 and 14. Representative images of each treatment group are shown in Figure 2.

In Figure 2, tumor luciferase signals were higher and tumor volumes were lower using the RC vector compared to the RD vector. The average tumor luciferase signal in RC-treated mice was 43,970,000 photons, which was much higher than the average of 1,776,000 photons in RD-

treated animals. The average tumor size of RC-treated tumors was 410 mm³ and for RD-treated tumor the average size was 1609 mm³.

Paper Example 1

The plasmid pSP6-R/NS3-HSVtk/Fluc-Mut4 encodes a Sindbis virus RC vector construction based on pSP6-R and Mut-4, which provide replicase genes and structural genes respectively. Its sequence is set forth in Appendix A and a map of the plasmid is shown in Figure 4. In an alternate embodiment, the promoter is T7 (Ambun, Austin, TX ??) Its construction is described as follows.

A DNA segment containing a sub-genomic promoter and the Sindbis viral structural genes is excised from the pSP6-Mut4 plasmid (disclosed in U.S. Patent No. 7,303,798) using NsiI and BamHI enzymes and then inserted into pSP6-R/Fluc at the PmlI site. In addition, the HSVtk gene fragment (from the pORF-HSVtk plasmid (Invivogen, San Diego, CA) is inserted at the SpeI site in the ns3 region on pSP6-R/Fluc-tBB to generate the pSP6-R/nsp3-HSVtk/Fluc-tBB plasmid. A map showing the pSP6-R/nsp3-HSVtk/Fluc-tBB plasmid is shown in Figure 4 and its sequence is set forth in Appendix A below.

In Figure 4, the location of the genes is set forth below:

Sindbis non-structural genes locations (bp):

NS1	60 – 1979 (SEQ. ID NO.: 2)
NS2	1980 – 4100 (SEQ. ID NO.: 3)
NS3	4101 – 5261 and 6399 – 6878 (SEQ. ID NO.: 4)
NS4	6879 – 8729 (SEQ. ID NO.: 5)
First Psg	8722 – 8734 (SEQ. ID NO.: 6)
Second Psg	10766 – 10789 (SEQ. ID NO. 7)
Structural Genes:	10833 – 14567 (SEQ. ID NO.: 8)

In addition, the vector may also comprise a suicide gene, such as the thymidine kinase (TK) gene located within the NS3 gene (Nucleotide 5262 - 6398).

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Appendix ApSP6-R/nsp3-HSVtk/Fluc-Mut4

1	ATTGACGGCG	TAGTACACAC	TATTGAATCA	AACAGCCGAC	CAATTGCACT
	TAACTGCCGC	ATCATGTGTG	ATAACTTAGT	TTGTCGGCTG	GTAAACGTGA
51	ACCATCACAA	TGGAGAAGCC	AGTAGTAAAC	GTAGACGTAG	ACCCCCAGAG
	TGGTAGTGTT	ACCTCTTCGG	TCATCATTTG	CATCTGCATC	TGGGGGTCTC
101	TCCGTTTGTC	GTGCAACTGC	AAAAAAGCTT	CCCGCAATTT	GAGGTAGTAG
	AGGCAAACAG	CACGTTGACG	TTTTTTTCGAA	GGGCGTTAAA	CTCCATCATC
151	CACAGCAGGT	CACTCCAAAT	GACCATGCTA	ATGCCAGAGC	ATTTTCGCAT
	GTGTCGTCCA	GTGAGGTTTA	CTGGTACGAT	TACGGTCTCG	TAAAAGCGTA
201	CTGGCCAGTA	AACTAATCGA	GCTGGAGGTT	CCTACCACAG	CGACGATCTT
	GACCGGTCAT	TTGATTAGCT	CGACCTCCAA	GGATGGTGTC	GCTGCTAGAA
251	GGACATAGGC	AGCGCACCGG	CTCGTAGAAT	GTTTTCCGAG	CACCAGTATC
	CCTGTATCCG	TCGCGTGGCC	GAGCATCTTA	CAAAGGCTC	GTGGTCATAG
301	ATTGTGTCTG	CCCCATGCGT	AGTCCAGAAG	ACCCGGACCG	CATGATGAAA
	TAACACAGAC	GGGGTACGCA	TCAGGTCTTC	TGGGCCTGGC	GTACTACTTT
351	TATGCCAGTA	AACTGGCGGA	AAAAGCGTGC	AAGATTACAA	ACAAGAACTT
	ATACGGTCAT	TTGACCGCCT	TTTTCGCAGC	TTCTAATGTT	TGTTCTTGAA
401	GCATGAGAAG	ATTAAGGATC	TCCGGACCGT	ACTTGATACG	CCGGATGCTG
	CGTACTCTTC	TAATTCCTAG	AGGCCTGGCA	TGAACTATGC	GGCCTACGAC
451	AAACACCATC	GCTCTGCTTT	CACAACGATG	TTACCTGCAA	CATGCGTGCC
	TTTGTGGTAG	CGAGACGAAA	GTGTTGCTAC	AATGGACGTT	GTACGCACGG
501	GAATATTCCG	TCATGCAGGA	CGTGTATATC	AACGCTCCCG	GAACTATCTA
	CTTATAAGGC	AGTACGTCCT	GCACATATAG	TTGCGAGGGC	CTTGATAGAT
551	TCATCAGGCT	ATGAAAGGCG	TGCGGACCCT	GTACTGGATT	GGCTTCGACA
	AGTAGTCCGA	TACTTTCCGC	ACGCCTGGGA	CATGACCTAA	CCGAAGCTGT
601	CCACCCAGTT	CATGTTCTCG	GCTATGGCAG	GTTCGTACCC	TGCGTACAAC
	GGTGGGTCAA	GTACAAGAGC	CGATACCGTC	CAAGCATGGG	ACGCATGTTG
651	ACCAACTGGG	CCGACGAGAA	AGTCCTTGAA	GCGCGTAACA	TCGGACTTTG
	TGGTTGACCC	GGCTGCTCTT	TCAGGAACTT	CGCGCATTGT	AGCCTGAAAC
701	CAGCACAAAG	CTGAGTGAAG	GTAGGACAGG	AAAATTGTCG	ATAATGAGGA
	GTCGTGTTTC	GACTCACTTC	CATCCTGTCC	TTTAAACAGC	TATTACTCCT
751	AGAAGGAGTT	GAAGCCCCGG	TCGCGGGTTT	ATTTCTCCGT	AGGATCGACA
	TCTTCCTCAA	CTTCGGGCCC	AGCGCCCAA	TAAAGAGGCA	TCCTAGCTGT
801	CTTTATCCAG	AACACAGAGC	CAGCTTGCA	AGCTGGCATC	TTCCATCGGT
	GAAATAGGTC	TTGTGTCTCG	GTCGAACGTC	TCGACCGTAG	AAGGTAGCCA
851	GTTCCACTTG	AATGGAAAGC	AGTCGTACAC	TTGCCGCTGT	GATACAGTGG
	CAAGGTGAAC	TTACCTTTCG	TCAGCATGTG	AACGGCGACA	CTATGTCACC
901	TGAGTTGCGA	AGGCTACGTA	GTGAAGAAAA	TCACCATCAG	TCCCCGGGATC
	ACTCAACGCT	TCCGATGCAT	CACTTCTTTT	AGTGGTAGTC	AGGGCCCTAG

951	ACGGGAGAAA	CCGTGGGATA	CGCGGTTACA	CACAATAGCG	AGGGCTTCTT
	TGCCCTCTTT	GGCACCTAT	GCGCCAATGT	GTGTTATCGC	TCCCGAAGAA
1001	GCTATGCAAA	GTTACTGACA	CAGTAAAAGG	AGAACGGGTA	TCGTTCCCTG
	CGATACGTTT	CAATGACTGT	GTCATTTTCC	TCTTGCCCAT	AGCAAGGGAC
1051	TGTGCACGTA	CATCCCGGCC	ACCATATGCG	ATCAGATGAC	TGGTATAATG
	ACACGTGCAT	GTAGGGCCGG	TGGTATACGC	TAGTCTACTG	ACCATATTAC
1101	GCCACGGATA	TATCACCTGA	CGATGCACAA	AAACTTCTGG	TTGGGCTCAA
	CGGTGCCTAT	ATAGTGGACT	GCTACGTGTT	TTTGAAGACC	AACCCGAGTT
1151	CCAGCGAATT	GTCATTAACG	GTAGGACTAA	CAGGAACACC	AACACCATGC
	GGTCGCTTAA	CAGTAATTGC	CATCCTGATT	GTCCTTGTGG	TTGTGGTACG
1201	AAAATTACCT	TCTGCCGATC	ATAGCACAAG	GGPTCAGCAA	ATGGGCTAAG
	TTTTAATGGA	AGACGGCTAG	TATCGTGTTC	CCAAGTCGTT	TACCCGATTC
1251	GAGCGCAAGG	ATGATCTTGA	TAACGAGAAA	ATGCTGGGTA	CTAGAGAACG
	CTCGCGTTCC	TACTAGAACT	ATTGCTCTTT	TACGACCCAT	GATCTCTTGC
1301	CAAGCTTACG	TATGGCTGCT	TGTGGGCGTT	TCGCACTAAG	AAAGTACATT
	GTTTGAATGC	ATACCGACGA	ACACCCGCAA	AGCGTGATTC	TTTCATGTAA
1351	CGTTTTATCG	CCCACCTGGA	ACGCAGACCA	TCGTAAAAGT	CCCAGCCTCT
	GCAAAATAGC	GGGTGGACCT	TGCGTCTGGT	AGCATTTTCA	GGGTCCGAGA
1401	TTTAGCGCTT	TTCCCATGTC	GTCCGTATGG	ACGACCTCTT	TGCCCATGTC
	AAATCGCGAA	AAGGGTACAG	CAGGCATACC	TGCTGGAGAA	ACGGGTACAG
1451	GCTGAGGCAG	AAATTGAAAC	TGGCATTGCA	ACCAAAGAAG	GAGGAAAAAC
	CGACTCCGTC	TTTAACTTTG	ACCGTAACGT	TGGTTTCTTC	CTCCTTTTTG
1501	TGCTGCAGGT	CTCGGAGGAA	TTAGTCATGG	AGGCCAAGGC	TGCTTTTGAG
	ACGACGTCCA	GAGCCTCCTT	AATCAGTACC	TCCGGTTCCG	ACGAAAATC
1551	GATGCTCAGG	AGGAAGCCAG	AGCGGAGAAG	CTCCGAGAAG	CACTTCCACC
	CTACGAGTCC	TCCTTCGGTC	TCGCCTCTTC	GAGGCTCTTC	GTGAAGGTGG
1601	ATTAGTGGCA	GACAAAGGCA	TCGAGGCAGC	CGCAGAAGTT	GTCTGCGAAG
	TAATCACCGT	CTGTTTCCGT	AGCTCCGTCG	GCGTCTTCAA	CAGACGCTTC
1651	TGGAGGGGCT	CCAGGCGGAC	ATCGGAGCAG	CATTAGTTGA	AACCCGCGC
	ACCTCCCCGA	GGTCCGCCTG	TAGCCTCGTC	GTAATCAACT	TTGGGGCGCG
1701	GGTCACGTAA	GGATAATACC	TCAAGCAAAT	GACCGTATGA	TCGGACAGTA
	CCAGTGCAAT	CCTATTATGG	AGTTTCGTTT	CTGGCATACT	AGCCTGTCT
1751	TATCGTTGTC	TCGCCAAACT	CTGTGCTGAA	GAATGCCAAA	CTCGCACCAG
	ATAGCAACAG	AGCGGTTTGA	GACACGACTT	CTTACGGTTT	GAGCGTGGTC
1801	CGCACCCGCT	AGCAGATCAG	GTTAAGATCA	TAACACACTC	CGGAAGATCA
	GCGTGGGCGA	TCGTCTAGTC	CAATTCTAGT	ATTGTGTGAG	GCCTTCTAGT
1851	GGAAGGTACG	CGGTGCAACC	ATACGACGCT	AAAGTACTGA	TGCCAGCAGG
	CCTTCCATGC	GCCAGCTTGG	TATGCTGCGA	TTTCATGACT	ACGGTCGTCC
1901	AGGTGCCGTA	CCATGGCCAG	AATTCCTAGC	ACTGAGTGAG	AGCGCCACGT
	TCCACGGCAT	GGTACCGGTC	TTAAGGATCG	TGACTCACTC	TCGCGGTGCA
1951	TAGTGTACAA	CGAAAGAGAG	TTTGTGAACC	GCAAACCTATA	CCACATTGCC
	ATCACATGTT	GCTTTCTCTC	AAACACTTGG	CGTTTGATAT	GGTGTAACGG
2001	ATGCATGGCC	CCGCCAAGAA	TACAGAAGAG	GAGCAGTACA	AGGTTACAAA

	TACGTACCGG	GGCGGTTCTT	ATGTCTTCTC	CTCGTCATGT	TCCAATGTTT
2051	GGCAGAGCTT	GCAGAAACAG	AGTACGTGTT	TGACGTGGAC	AAGAAGCGTT
	CCGTCTCGAA	CGTCTTTGTC	TCATGCACAA	ACTGCACCTG	TTCTTCGCAA
2101	GCGTTAAGAA	GGAAGAAGCC	TCAGGTCTGG	TCCTCTCGGG	AGAACTGACC
	CGCAATTCTT	CCTTCTTCGG	AGTCCAGACC	AGGAGAGCCC	TCTTGACTGG
2151	AACCCCTCCCT	ATCATGAGCT	AGCTCTGGAG	GGACTGAAGA	CCCACCTGCT
	TTGGGAGGGA	TAGTACTCGA	TCGAGACCTC	CCTGACTTCT	GGGCTGGACG
2201	GGTCCCGTAC	AAGGTCGAAA	CAATAGGAGT	GATAGGCACA	CCGGGGTCGG
	CCAGGGCATG	TTCCAGCTTT	GTTATCCTCA	CTATCCGTGT	GGCCCCAGCC
2251	GCAAGTCAGC	TATTATCAAG	TCAACTGTCA	CGGCACGAGA	TCTTGTTACC
	CGTTTCAGTCG	ATAATAGTTC	AGTTGACAGT	GCCGTGCTCT	AGAACAAATGG
2301	AGCGGAAAGA	AAGAAAATTG	TCGCGAAATT	GAGGCCGACG	TGCTAAGACT
	TCGCCCTTCT	TTCTTTTAAC	AGCGCTTTAA	CTCCGGCTGC	ACGATTCTGA
2351	GAGGGGTATG	CAGATTACGT	CGAAGACAGT	AGATTTCGGT	ATGCTCAACG
	CTCCCCATAC	GTCTAATGCA	GCTTCTGTCA	TCTAAGCCAA	TACGAGTTGC
2401	GATGCCACAA	AGCCGTAGAA	GTGCTGTACG	TTGACGAAGC	GTTTCGGTGC
	CTACGGTGTT	TCGGCATCTT	CACGACATGC	AACTGCTTCG	CAAGCGCAGC
2451	CACGCAGGAG	CACTACTTGC	CTTGATTGCT	ATCGTCAGGC	CCCACAAGAA
	GTGCGTCCTC	GTGATGAACG	GAACAAACGA	TAGCAGTCCG	GGGCGTTCTT
2501	GGTAGTACTA	TGCGGAGACC	CCATGCAATG	CGGATTCTTC	AACATGATGC
	CCATCATGAT	ACGCCTCTGG	GGTACGTTAC	GCCTAAGAAG	TTGTACTACG
2551	AACTAAAGGT	ACATTTCAAT	CACCCTGAAA	AAGACATATG	CACCAAGACA
	TTGATTTCCA	TGTAAAGFTA	GTGGGACTTT	TTCTGTATAC	GTGGTTCCTGT
2601	TTCTACAAGT	ATATCTCCCG	GCGTTGCACA	CAGCCAGTTA	CAGCTATTGT
	AAGATGTTCA	TATAGAGGGC	CGCAACGTGT	GTCGGTCAAT	GTCGATAACA
2651	ATCGACACTG	CATTACGATG	GAAAGATGAA	AACCACGAAC	CCGTGCAAGA
	TAGCTGTGAC	GTAATGCTAC	CTTTCTACTT	TTGGTGCTTG	GGCAGCTTCT
2701	AGAACATTGA	AATCGATATT	ACAGGGGGCCA	CAAAGCCGAA	GCCAGGGGAT
	TCTTGTAAC	TTAGCTATAA	TGTCCCCGGT	GTTTCGGCTT	CGGTCCCCTA
2751	ATCATCCTGA	CATGTTTCCG	CGGGTGGGTT	AAGCAATTGC	AAATCGACTA
	TAGTAGGACT	GTACAAAGGC	GCCCAACCAA	TTCGTAAACG	TTTAGCTGAT
2801	TCCCGGACAT	GAAGTAATGA	CAGCCGCGGC	CTCACAAGGG	CTAACCAGAA
	AGGGCCTGTA	CTTCATTACT	GTCGGCGCCG	GAGTGTTCCT	GATTGGTCTT
2851	AAGGAGTGTA	TGCCGTCCGG	CAAAAAGTCA	ATGAAAACCC	ACTGTACGCG
	TTCTTCACAT	ACGGCAGGCC	GTTTTCAGT	TACTTTTGGG	TGACATGCGC
2901	ATCACATCAG	AGCATGTGAA	CGTGTGCTC	ACCCGCACTG	AGGACAGGCT
	TAGTGATGTC	TCGTACACTT	GCACAACGAG	TGGGCGTGAC	TCCTGTCCGA
2951	AGTGTGGAAG	ACCTTGACAG	GCGACCCATG	GATTAAGCAG	CTCACTAACA
	TCACACCTTT	TGGAACGTCC	CGCTGGGTAC	CTAATTCGTC	GAGTGATTGT
3001	TACCTAAAGG	AAACTTTTCAG	GCTACTATAG	AGGACTGGGA	AGCTGAACAC
	ATGGATTTCC	TTTGAAAGTC	CGATGATATC	TCCTGACCCT	TCGACTGTGT
3051	AAGGGAATAA	TTGCTGCAAT	AAACAGCCCC	ACTCCCCGTG	CCAATCCGTT
	TTCCCTTATT	AACGACGTTA	TTTGTGCGGG	TGAGGGGCAC	GGTTAGGCAA

3101	CAGCTGCAAG	ACCAACGTTT	GCTGGGCGAA	AGCATTGGAA	CCGATACTAG
	GTCGACGTTT	TGGTTGCAAA	CGACCCGCTT	TCGTAACTT	GGCTATGATC
3151	CCACGGCCGG	TATCGTACTT	ACCGGTTGCC	AGTGGAGCGA	ACTGTTCCCA
	GGTGCCGGCC	ATAGCATGAA	TGGCCAACGG	TCACCTCGCT	TGACAAGGGT
3201	CAGTTTGCGG	ATGACAAACC	ACATTGCGCC	ATTTACGCCT	TAGACGTAAT
	GTCAAACGCC	TACTGTTTGG	TGTAAGCCGG	TAAATGCGGA	ATCTGCATTA
3251	TTGCATTAAAG	TTTTTTCGGCA	TGGACTTGAC	AAGCGGACTG	TTTTCTAAAC
	AACGTAATTC	AAAAAGCCGT	ACCTGAACTG	TTCGCCTGAC	AAAAGATTTG
3301	AGAGCATCCC	ACTAACGTAC	CATCCCGCCG	ATTCAGCGAG	GCCGGTAGCT
	TCTCGTAGGG	TGATTGCATG	GTAGGGCCGG	TAAGTCGCTC	CGGCCATCGA
3351	CATTGGGACA	ACAGCCCAGG	AACCCGCAAG	TATGGGTACG	ATCACGCCAT
	GTAACCCTGT	TGTCGGGTCC	TTGGGCGTTC	ATACCCATGC	TAGTGCGGTA
3401	TGCCGCCGAA	CTCTCCCGTA	GATTTCCGGT	GTTCCAGCTA	GCTGGGAAGG
	ACGGCGGCTT	GAGAGGGCAT	CTAAAGGCCA	CAAGGTCGAT	CGACCCTTCC
3451	GCACACAAC	TGATTTGCAG	ACGGGGAGAA	CCAGAGTTAT	CTCTGCACAG
	CGTGTGTTGA	ACTAAACGTC	TGCCCCCTCT	GGTCTCAATA	GAGACGTGTC
3501	CATAACCTGG	TCCCGGTGAA	CCGCAATCTT	CCTCACGCCT	TAGTCCCCGA
	GTATTGGACC	AGGGCCACTT	GGCGTTAGAA	GGAGTGCGGA	ATCAGGGGCT
3551	GTACAAGGAG	AAGCAACCCG	GCCCGGTCGA	AAAATTCTTG	AACCAGTTCA
	CATGTTCTCT	TTCGTTGGGC	CGGGCCAGCT	TTTTAAGAAC	TTGGTCAAGT
3601	AACACCACTC	AGTACTTGTG	GTATCAGAGG	AAAAAATTGA	AGCTCCCCGT
	TTGTGGTGAG	TCATGAACAC	CATAGTCTCC	TTTTTTAACT	TCGAGGGGCA
3651	AAGAGAATCG	AATGGATCGC	CCCGATTGGC	ATAGCCGGTG	CAGATAAGAA
	TTCTCTTAGC	TTACCTAGCG	GGGCTAACCG	TATCGGCCAC	GTCTATTCTT
3701	CTACAACCTG	GCTTTCGGGT	TTCCGCCGCA	GGCACGGTAC	GACCTGGTGT
	GATGTTGGAC	CGAAAGCCCA	AAGGCGGCGT	CCGTGCCATG	CTGGACCACA
3751	TCATCAACAT	TGGAACATAA	TACAGAAACC	ACCACTTTCA	GCAGTGCGAA
	AGTAGTTGTA	ACCTTGATTT	ATGTC'TTTGG	TGGTGAAAGT	CGTCACGCTT
3801	GACCATGCGG	CGACCTTAAA	AACCC'TTTCG	CGTTCGGCCC	TGAATTGCCT
	CTGGTACGCC	GCTGGAATTT	TTGGGAAAGC	GCAAGCCGGG	ACTTAACGGA
3851	TAACCCAGGA	GGCACCCTCG	TGGTGAAGTC	CTATGGCTAC	GCCGACCGCA
	ATTGGGTCCT	CCGTGGGAGC	ACCACTTCAG	GATACCGATG	CGGCTGGCGT
3901	ACAGTGAGGA	CGTAGTCACC	GCTCTTGCCA	GAAAGTTTGT	CAGGGTGTCT
	TGTCACTCCT	GCATCAGTGG	CGAGAACGGT	CTTTCAAACA	GTCCACAGAA
3951	GCAGCGAGAC	CAGATTGTGT	CTCAAGCAAT	ACAGAAATGT	ACCTGATTTT
	CGTCGCTCTG	GTCTAACACA	GAGTTCGTTA	TGTCTTTACA	TGGACTAAAA
4001	CCGACAACTA	GACAACAGCC	GTACACGGCA	ATTCACCCCG	CACCATCTGA
	GGCTGTTGAT	CTGTTGTCGG	CATGTGCCGT	TAAGTGGGGC	GTGGTAGACT
4051	ATTGCGTGAT	TTCGTCCGTG	TATGAGGGTA	CAAGAGATGG	AGTTGGAGCC
	TAACGCACTA	AAGCAGGCAC	ATACTCCCAT	GTTCTCTACC	TCAACCTCGG
4101	GCGCCGTCAT	ACCGCACCAA	AAGGGAGAAT	ATTGCTGACT	GTCAAGAGGA
	CGCGGCAGTA	TGGCGTGGTT	TTCCCTCTTA	TAACGACTGA	CAGTTCTCCT
4151	AGCAGTTGTC	AACGCAGCCA	ATCCGCTGGG	TAGACCAGGC	GAAGGAGTCT

	TCGTCAACAG	TTGCGTCGGT	TAGGCGACCC	ATCTGGTCCG	CTTCCTCAGA
4201	GCCGTGCCAT	CTATAAACGT	TGGCCGACCA	GTTTTACCGA	TTCAGCCACG
	CGGCACGGTA	GATATTTGCA	ACCGGCTGGT	CAAAATGGCT	AAGTCGGTGC
4251	GAGACAGGCA	CCGCAAGAAT	GA CTGTGTGC	CTAGGAAAGA	AAGTGATCCA
	CTCTGTCCGT	GGCGTTCCTA	CTGACACACG	GATCCTTTCT	TTCCTAGGT
4301	CGCGGTCGGC	CCTGATTTCC	GGAAGCACCC	AGAAGCAGAA	GCCTTGAAAT
	GCGCCAGCCG	GGACTAAAGG	CCTTCGTGGG	TCTTCGTCTT	CGGAACCTTA
4351	TGCTACAAAA	CGCCTACCAT	GCAGTGGCAG	ACTTAGTAAA	TGAACATAAC
	ACGATGTTTT	GCGGATGGTA	CGTCACCGTC	TGAATCATTT	ACTTGATTG
4401	ATCAAGTCTG	TCGCCATTCC	ACTGCTATCT	ACAGGCATTT	ACGCAGCCGG
	TAGTTCAGAC	AGCGGTAAGG	TGACGATAGA	TGTCCGTAAA	TGCGTCGGCC
4451	AAAAGACCGC	CTTGAAGTAT	CACTTAACTG	CTTGACAACC	GCGCTAGACA
	TTTTCTGGCG	GAACCTCATA	GTGAATTGAC	GAACGTGTTG	CGCGATCTGT
4501	GAACGTGACG	GGACGTAACC	ATCTATTGCC	TGGATAAGAA	GTGGAAGGAA
	CTTGACTGCG	CCTGCATTGG	TAGATAACGG	ACCTATTCTT	CACCTTCCTT
4551	AGAATCGACG	CGGCACTCCA	ACTTAAGGAG	TCTGTAACAG	AGCTGAAGGA
	TCTTAGCTGC	GCCGTGAGGT	TGAATTCCTC	AGACATTGTC	TCGACTTCCT
4601	TGAAGATATG	GAGATCGACG	ATGAGTTAGT	ATGGATCCAT	CCAGACAGTT
	ACTTCTATAC	CTCTAGCTGC	TACTCAATCA	TACCTAGGTA	GGTCTGTCAA
4651	GCTTGAAGGG	AAGAAAGGGA	TTCAGTACTA	CAAAAGGAAA	ATTGTATTCTG
	CGAACTTCCC	TTCTTTCCTT	AAGTCATGAT	GTTTTCTTTT	TAACATAAGC
4701	TACTTCGAAG	GCACCAAATT	CCATCAAGCA	GCAAAAGACA	TGGCGGAGAT
	ATGAAGCTTC	CGTGGTTTTAA	GGTAGTTTCG	CGTTTTCTGT	ACCGCCTCTA
4751	AAAGGTCCTG	FTCCCTAATG	ACCAGGAAAG	TAATGAACAA	CTGTGTGCCT
	TTTCCAGGAC	AAGGGATTAC	TGGTCCTTTC	ATTACTTGTT	GACACACGGA
4801	ACATATTGGG	TGAGACCATG	GAAGCAATCC	GCGAAAAGTG	CCCGGTCGAC
	TGTATAACCC	ACTCTGGTAC	CTTCGTTAGG	CGCTTTTCAC	GGGCCAGCTG
4851	CATAACCCGT	CGTCTAGCCC	GCCCAAACG	TTGCCGTGCC	TTTGCATGTA
	GTATTGGGCA	GCAGATCGGG	CGGGTTTTGC	AACGGCACGG	AAACGTACAT
4901	TGCCATGACG	CCAGAAAGGG	TCCACAGACT	TAGAAGCAAT	AACGTCAAAG
	ACGGTACTGC	GGTCTTTCCC	AGGTGTCTGA	ATCTTCGTTA	TTGCAGTTTC
4951	AAGTTACAGT	ATGCTCCTCC	ACCCCCCTTC	CTAAGCACAA	AATTAAGAAT
	TTCAATGTCA	TACGAGGAGG	TGGGGGGAAG	GATTCGTGTT	TTAATTCTTA
5001	GTTTCAAGAG	TTCAGTGCAC	GAAAGTAGTC	CTGTTTAATC	CGCACACTCC
	CAAGTCTTCC	AAGTCACGTG	CTTTCATCAG	GACAAATTAG	GCGTGTGAGG
5051	CGCATTCGTT	CCCGCCCGTA	AGTACATAGA	AGTGCCAGAA	CAGCCTACCG
	GCGTAAGCAA	GGGCGGGCAT	TCATGTATCT	TCACGGTCTT	GTCGGATGGC
5101	CTCCTCCTGC	ACAGGCCGAG	GAGGCCCCCG	AAGTTGTAGC	GACACCGTCA
	GAGGAGGACG	TGTCCGGCTC	CTCCGGGGGC	TTCAACATCG	CTGTGGCAGT
5151	CCATCTACAG	CTGATAACAC	CTCGCTTGAT	GTCACAGACA	TCTCACTGGA
	GGTAGATGTC	GACTATTGTG	GAGCGAACTA	CAGTGTCTGT	AGAGTGACCT
5201	TATGGATGAC	AGTAGCGAAG	GCTCACTTTT	TTCGAGCTTT	AGCGGATCGG
	ATACCTACTG	TCATCGCTTC	CGAGTGAAAA	AAGCTCGAAA	TCGCCTAGCC

5251	ACAACTCTAT	TACTAGTGCC	TCGTACCCCG	GCCATCAACA	CGCGTCTGCG
	TGTTGAGATA	ATGATCACGG	AGCATGGGGC	CGGTAGTTGT	GCGCAGACGC
5301	TTCGACCAGG	CTGCGCGTTC	TCGCGGCCAT	AGCAACCGAC	GTACGGCGTT
	AAGCTGGTCC	GACGCGCAAG	AGCGCCGGTA	TCGTTGGCTG	CATGCCGCAA
5351	GCGCCCTCGC	CGGCAGCAAG	AAGCCACGGA	AGTCCGCCCG	GAGCAGAAAA
	CGCGGGAGCG	GCCGTCGTTC	TTCGGTGCCT	TCAGGCGGGC	CTCGTCTTTT
5401	TGCCCACGCT	ACTGCGGGTT	TATATAGACG	GTCCCCACGG	GATGGGGAAA
	ACGGGTGCGA	TGACGCCCAA	ATATATCTGC	CAGGGGTGCC	CTACCCCTTT
5451	ACCACCACCA	CGCAACTGCT	GGTGGCCCTG	GGTTCGCGCG	ACGATATCGT
	TGGTGGTGGT	GCGTTGACGA	CCACCGGGAC	CCAAGCGCGC	TGCTATAGCA
5501	CTACGTACCC	GAGCCGATGA	CTTACTGGCG	GGTGCTGGGG	GCTTCCGAGA
	GATGCATGGG	CTCGGCTACT	GAATGACCGC	CCACGACCCC	CGAAGGCTCT
5551	CAATCGCGAA	CATCTACACC	ACACAACACC	GCCTCGACCA	GGGTGAGATA
	GTTAGCGCTT	GTAGATGTGG	TGTGTTGTGG	CGGAGCTGGT	CCCACTCTAT
5601	TCGGCCGGGG	ACGCGGCGGT	GGTAATGACA	AGCGCCCAGA	TAACAATGGG
	AGCCGGCCCC	TGCGCCGCCA	CCATTACTGT	TCGCGGGTCT	ATTGTTACCC
5651	CATGCCTTAT	GCCGTGACCG	ACGCCGTTCT	GGCTCCTCAT	ATCGGGGGGG
	GTACCGGAATA	CGGCACTGGC	TGCGGCAAGA	CCGAGGAGTA	TAGCCCCCCC
5701	AGGCTGGGAG	CTCACATGCC	CCGCCCCCGG	CCCTCACCCCT	CATCTTCGAC
	TCCGACCCTC	GAGTGTACGG	GGCGGGGGCC	GGGAGTGGGA	GTAGAAGCTG
5751	CGCCATCCCA	TCGCCGCCCT	CCTGTGCTAC	CCGGCCGCGC	GGTACCTTAT
	GCGGTAGGGT	AGCGGCGGGA	GGACACGATG	GGCCGGCGCG	CCATGGAATA
5801	GGGCAGCATG	ACCCCCCAGG	CCGTGCTGGC	GTTCGTGGCC	CTCATCCCGC
	CCCGTCGTAC	TGGGGGGTCC	GGCACGACCG	CAAGCACCGG	GAGTAGGGCG
5851	CGACCTTGCC	CGGCACCAAC	ATCGTGCTTG	GGGCCCTTCC	GGAGGACAGA
	GCTGGAACGG	GCCGTGGFTG	TAGCACGAAC	CCCGGGAAGG	CCTCCTGTCT
5901	CACATCGACC	GCCTGGCCAA	ACGCCAGCGC	CCCGGCGAGC	GGCTGGACCT
	GTGTAGCTGG	CGGACCGGTT	TGCGGTCGCG	GGGCCGCTCG	CCGACCTGGA
5951	GGCTATGCTG	GCTGCGATTC	GCCGCGTTTA	CGGGCTACTT	GCCAATACGG
	CCGATACGAC	CGACGCTAAG	CGGCGCAAAT	GCCCGATGAA	CGGTTATGCC
6001	TGCGGTATCT	GCAGTGCGGC	GGGTGCTGGC	GGGAGGACTG	GGGACAGCTT
	ACGCCATAGA	CGTCACGCCG	CCCAGCACCG	CCCTCCTGAC	CCCTGTCGAA
6051	TCGGGGACGG	CCGTGCCGCC	CCAGGGTGCC	GAGCCCAGAG	GCAACGCGGG
	AGCCCCTGCC	GGCACGGCGG	GGTCCCACGG	CTCGGGGTCT	CGTTGCGCCC
6101	CCCACGACCC	CATATCGGGG	ACACGTTATT	TACCCTGTTT	CGGGCCCCCG
	GGGTGCTGGG	GTATAGCCCC	TGTGCAATAA	ATGGGACAAA	GCCCCGGGGC
6151	AGTTGCTGGC	CCCCAACGGC	GACCTGTATA	ACGTGTTTGC	CTGGGCCTTG
	TCAACGACCG	GGGGTTGCCG	CTGGACATAT	TGCACAAACG	GACCCGGAAC
6201	GACGTCTTGG	CCAAACGCCT	CCGTTCCATG	CACGTCTTTA	TCCTGGATTA
	CTGCAGAACC	GGTTTGCGGA	GGCAAGGTAC	GTGCAGAAAT	AGGACCTAAT
6251	CGACCAATCG	CCCGCCGGCT	GCCGGGACGC	CCTGCTGCAA	CTTACCTCCG
	GCTGGTTAGC	GGGCGGCCGA	CGGCCCTGCG	GGACGACGTT	GAATGGAGGC
6301	GGATGGTCCA	GACCCACGTC	ACCACCCCCG	GCTCCATACC	GACGATATGC

	CCTACCAGGT	CTGGGTGCAG	TGGTGGGGGC	CGAGGTATGG	CTGCTATACG
6351	GACCTGGCGC	GCACGTTTGC	CCGGGAGATG	GGGGAGGCTA	ACACTAGTAT
	CTGGACCGCG	CGTGCAAACG	GGCCCTCTAC	CCCCTCCGAT	TGTGATCATA
6401	GGACAGTTGG	TCGTCAGGAC	CTAGTTCACT	AGAGATAGTA	GACCGAAGGC
	CCTGTCAACC	AGCAGTCCTG	GATCAAGTGA	TCTCTATCAT	CTGGCTTCCG
6451	AGGTGGTGGT	GGCTGACGTT	CATGCCGTCC	AAGAGCCTGC	CCCTATTCCA
	TCCACCACCA	CCGACTGCAA	GTACGGCAGG	TTCTCGGACG	GGGATAAGGT
6501	CCGCCAAGGC	TAAAGAAGAT	GGCCCGCCTG	GCAGCGGCAA	GAAAAGAGCC
	GGCGGTTCGG	ATTTCTTCTA	CCGGGCGGAC	CGTCGCCGTT	CTTTTCTCGG
6551	CACTCCACCG	GCAAGCAATA	GCTCTGAGTC	CCTCCACCTC	TCTTTTGGTG
	GTGAGGTGGC	CGTTCGTTAT	CGAGACTCAG	GGAGGTGGAG	AGAAAACCAC
6601	GGGTATCCAT	GTCCCTCGGA	TCAATTTTCG	ACGGAGAGAC	GGCCCGCCAG
	CCCATAGGTA	CAGGGAGCCT	AGTTAAAAGC	TGCCTCTCTG	CCGGGCGGTC
6651	GCAGCGGTAC	AACCCCTGGC	AACAGGCCCC	ACGGATGTGC	CTATGTCCTT
	CGTCGCCATG	TTGGGGACCG	TTGTCCGGGG	TGCCTACACG	GATACAGAAA
6701	CGGATCGTTT	TCCGACGGAG	AGATTGATGA	GCTGAGCCGC	AGAGTAACTG
	GCCTAGCAAA	AGGCTGCCTC	TCTAACTACT	CGACTCGGCG	TCTCATPGAC
6751	AGTCCGAACC	CGTCCTGTTT	GGATCATTTG	AACCGGGCGA	AGTGAACCTA
	TCAGGCTTGG	GCAGGACAAA	CCTAGTAAAC	TTGGCCCGCT	TCACTTGAGT
6801	ATTATATCGT	CCCGATCAGC	CGTATCTTTT	CCACTACGCA	AGCAGAGACG
	TAATATAGCA	GGGCTAGTCG	GCATAGAAAA	GGTGATGCGT	TCGTCTCTGC
6851	TAGACGCAGG	AGCAGGAGGA	CTGAATACTG	ACTAACC GGG	GTAGGTGGGT
	ATCTGCGTCC	TCGTCTCTCT	GACTTATGAC	TGATTGGCCC	CATCCACCCA
6901	ACATATTTTC	GACGGACACA	GGCCCTGGGC	ACTTGCAAAA	GAAGTCCGTT
	TGTATAAAAG	CTGCCTGTGT	CCGGGACCCG	TGAACGTTTT	CTTCAGGCAA
6951	CTGCAGAACC	AGCTTACAGA	ACCGACCTTG	GAGCGCAATG	TCCTGGAAAG
	GACGTCTTGG	TCGAATGTCT	TGGCTGGAAC	CTCGCGTTAC	AGGACCTTTC
7001	AATTCATGCC	CCGGTGCTCG	ACACGTCGAA	AGAGGAACAA	CTCAAACCTCA
	TTAAGTACGG	GGCCACGAGC	TGTGCAGCTT	TCTCCTTGTT	GAGTTTGAGT
7051	GGTACCAGAT	GATGCCACCC	GAAGCCAACA	AAAGTAGGTA	CCAGTCTCGT
	CCATGGTCTA	CTACGGGTGG	CTTCGGTGTG	TTTCATCCAT	GGTCAGAGCA
7101	AAAGTAGAAA	ATCAGAAAGC	CATAACCACT	GAGCGACTAC	TGTCAGGACT
	TTTCATCTTT	TAGTCTTTTCG	GTATTGGTGA	CTCGCTGATG	ACAGTCCTGA
7151	ACGACTGTAT	AACTCTGCCA	CAGATCAGCC	AGAATGCTAT	AAGATCACCT
	TGCTGACATA	TTGAGACGGT	GTCTAGTCGG	TCTTACGATA	TTCTAGTGGA
7201	ATCCGAAACC	ATTGTACTCC	AGTAGCGTAC	CGGCGAACTA	CTCCGATCCA
	TAGGCTTTTG	TAACATGAGG	TCATCGCATG	GCCGCTTGAT	GAGGCTAGGT
7251	CAGTTCGCTG	TAGCTGTCTG	TAACAACCTAT	CTGCATGAGA	ACTATCCGAC
	GTCAAGCGAC	ATCGACAGAC	ATTGTTGATA	GACGTACTCT	TGATAGGCTG
7301	AGTAGCATCT	TATCAGATTA	CTGACGAGTA	CGATGCTTAC	TTGGATATGG
	TCATCGTAGA	ATAGTCTAAT	GACTGCTCAT	GCTACGAATG	AACCTATACC
7351	TAGACGGGAC	AGTCGCCTGC	CTGGATACTG	CAACCTTCTG	CCCCGCTAAG
	ATCTGCCCTG	TCAGCGGACG	GACCTATGAC	GTTGGAAGAC	GGGGCGATTTC

7401	CTTAGAAGTT	ACCCGAAAAA	ACATGAGTAT	AGAGCCCCGA	ATATCCGCAG
	GAATCTTCAA	TGGGCTTTTT	TGTACTCATA	TCTCGGGGCT	TATAGGCGTC
7451	TGCGGTCCA	TCAGCGATGC	AGAACACGCT	ACAAAATGTG	CTCATTGCCG
	ACGCCAAGGT	AGTCGCTACG	TCTTGTGCGA	TGTTTTACAC	GAGTAACGGC
7501	CAACTAAAAG	AAATTGCAAC	GTCACGCAGA	TGCGTGAAC	GCCAACACTG
	GTTGATTTTC	TTTAACGTTG	CAGTGCGTCT	ACGCACTTGA	CGGTTGTGAC
7551	GACTCAGCGA	CATTCAATGT	CGAATGCTTT	CGAAAATATG	CATGTAATGA
	CTGAGTCGCT	GTAAGTTACA	GCTTACGAAA	GCTTTTATAC	GTACATTACT
7601	CGAGTATTGG	GAGGAGTTCG	CTCGGAAGCC	AATTAGGATT	ACCACTGAGT
	GCTCATAACC	CTCCTCAAGC	GAGCCTTCGG	TTAATCCTAA	TGGTGACTCA
7651	TTGTCACCGC	ATATGTAGCT	AGACTGAAAG	GCCCTAAGGC	CGCCGCACTA
	AACAGTGGCG	TATACATCGA	TCTGACTTTC	CGGGATTCCG	GCGGCGTGAT
7701	TTTGCAAAGA	CGTATAATTT	GGTCCCATTG	CAAGAAAGTGC	CTATGGATAG
	AAACGTTTCT	GCATATTAAA	CCAGGGTAAC	GTTCTTCACG	GATACCTATC
7751	APTCGTCATG	GACATGAAAA	GAGACGTGAA	AGTTACACCA	GGCACGAAAC
	TAAGCAGTAC	CTGTACTTTT	CTCTGCACTT	TCAATGTGGT	CCGTGCTTTG
7801	ACACAGAAGA	AAGACCGAAA	GTACAAGTGA	TACAAGCCGC	AGAACCCCTG
	TGTGTCCTTCT	TTCTGGCTTT	CATGTTCACT	ATGTTCCGGCG	TCTTGGGGAC
7851	GCGACTGCTT	ACTTATGCGG	GATTACCCGG	GAATTAGTGC	GTAGGCTTAC
	CGCTGACGAA	TGAATACGCC	CTAAGTGGCC	CTTAATCACG	CATCCGAATG
7901	GGCCGTCTTG	CTTCCAAACA	TTCACACGCT	TTTTGACATG	TCGGCGGAGG
	CCGGCAGAAC	GAAGGTTTGT	AAGTGTGCGA	AAAACGTGAC	AGCCGCCCTC
7951	APTTTGATGC	AATCATAGCA	GAACACTTCA	AGCAAGGCCA	CCCGGTACTG
	TAAAACTACG	TTAGTATCGT	CTTGTGAAGT	TCGTTCCGCT	GGGCCATGAC
8001	GAGACGGATA	TCGCATCATT	CGACAAAAGC	CAAGACGACG	CTATGGCGTT
	CTCTGCCTAT	AGCGTAGTAA	GCTGTTTTCT	GTTCTGCTGC	GATACCGCAA
8051	AACCGGTCTG	ATGATCTTGG	AGGACCTGGG	TGTGGATCAA	CCACTACTCG
	TTGGCCAGAC	TACTAGAACC	TCCTGGACCC	ACACCTAGTT	GGTGATGAGC
8101	ACTTGATCGA	GTGCGCCTTT	GGAGAAATAT	CATCCACCCA	TCTACCTACG
	TGAAGTAGCT	CACGCGGAAA	CCTCTTTATA	GTAGGTGGGT	AGATGGATGC
8151	GGTACTCGTT	TTAAATTCGG	GGCGATGATG	AAATCCGGAA	TGTTCTCTAC
	CCATGAGCAA	AATTTAAGCC	CCGCTACTAC	TTTAGGCCTT	ACAAGGAGTG
8201	ACTTTTGTG	AACACAGTTT	TGAATGTCGT	TATCGCCAGC	AGAGTACTAG
	TGAAAAACAG	TTGTGTCAAA	ACTTACAGCA	ATAGCGGTCT	TCTCATGATC
8251	AAGAGCGGCT	TAAAACGTCC	AGATGTGCAG	CGTTCATTGG	CGACGACAAC
	TTCTCGCCGA	ATTTTGCAGG	TCTACACGTC	GCAAGTAACC	GCTGCTGTTG
8301	ATCATACATG	GAGTAGTATC	TGACAAAGAA	ATGGCTGAGA	GGTGCGCCAC
	TAGTATGTAC	CTCATCATAG	ACTGTTTCTT	TACCGACTCT	CCACGCGGTG
8351	CTGGCTCAAC	ATGGAGGTTA	AGATCATCGA	CGCAGTCATC	GGTGAGAGAC
	GACCGAGTTG	TACCTCCAAT	TCTAGTAGCT	GCGTCAGTAG	CCACTCTCTG
8401	CACCTTACTT	CTGCGGCGGA	TTTATCTTGC	AAGATTCGGT	TACTTCCACA
	GTGGAATGAA	GACGCCGCCT	AAATAGAACG	TTCTAAGCCA	ATGAAGGTGT
8451	GCGTGCCGCG	TGGCGGACCC	CCTGAAAAGG	CTGTTTAAGT	TGGGTAAACC

	CGCACGGCGC	ACCGCCTGGG	GGACTTTTCC	GACAAATTCA	ACCCATTTGG
8501	GCTCCCAGCC	GACGACGAGC	AAGACGAAGA	CAGAAGACGC	GCTCTGCTAG
	CGAGGGTTCGG	CTGCTGCTCG	TTCTGCTTCT	GTCTTCTGCG	CGAGACGATC
8551	ATGAAACAAA	GGCGTGGTTT	AGAGTAGGTA	TAACAGGCAC	TTTAGCAGTG
	TACTTTGTTT	CCGCACCAAA	TCTCATCCAT	ATTGTCCGTG	AAATCGTCAC
8601	GCCGTGACGA	CCCGGTATGA	GGTAGACAAT	ATTACACCTG	TCCTACTGGC
	CGGCACTGCT	GGGCCATACT	CCATCTGTTA	TAATGTGGAC	AGGATGACCG
8651	ATTGAGAACT	TTTGCCCAGA	GCAAAAGAGC	ATTCCAAGCC	ATCAGAGGGG
	TAACTCTTGA	AAACGGGTCT	CGTTTTCTCG	TAAGGTTCGG	TAGTCTCCCC
8701	AAATAAAGCA	TCTCTACGGT	GGTCCTAAAT	AGTCAGCATA	GTACATTTCA
	TTTATTTTCGT	AGAGATGCCA	CCAGGATTTA	TCAGTCGTAT	CATGTAAAGT
8751	TCTGACTAAT	ACTACAACAC	CACCACCTCT	AGCCCGGGCT	CGAGATCTGC
	AGACTGATTA	TGATGTTGTG	GTGGTGGAGA	TCGGGCCCGA	GCTCTAGACG
8801	GATCTAAGTA	AGCTTGGCAT	TCCGGTACTG	TTGGTAAAGC	CACCATGGAA
	CTAGATTCAT	TCGAACCGTA	AGGCCATGAC	AACCATTTCT	GTGGTACCTT
8851	GACGCCAAAA	ACATAAAGAA	AGGCCCGGCG	CCATTCTATC	CGCTGGAAGA
	CTGCGGTTTT	TGTATTTCTT	TCCGGGCCGC	GGTAAGATAG	GCGACCTTCT
8901	TGGAACCGCT	GGAGAGCAAC	TGCATAAGGC	TATGAAGAGA	TACGCCCTGG
	ACCTTGCGCA	CCTCTCGTTG	ACGTATTCCG	ATACTTCTCT	ATGCGGGACC
8951	TTCTTGGAAC	AATTGCTTTT	ACAGATGCAC	ATATCGAGGT	GGACATCACT
	AAGGACCTTG	TTAACGAAAA	TGTCTACGTG	TATAGCTCCA	CCTGTAGTGA
9001	TACGCTGAGT	ACTTCGAAAT	GTCCGTTCGG	TTGGCAGAAG	CTATGAAACG
	ATGCGACTCA	TGAAGCTTTA	CAGGCAAGCC	AACCGTCTTC	GATACTTTGC
9051	ATATGGGCTG	AATACAAATC	ACAGAATCGT	CGTATGCAGT	GAAAACTCTC
	TATACCCGAC	TTATGTTTAA	TGTCTTAGCA	GCATACGTCA	CTTTTGAGAG
9101	TTCAATTCTT	TATGCCGGTG	TTGGGCGCGT	TATTTATCGG	AGTTGCAGTT
	AAGTTAAGAA	ATACGGCCAC	AACCCGCGCA	ATAAATAGCC	TCAACGTCAA
9151	GCGCCCGCGA	ACGACATTTA	TAATGAACGT	GAATTGCTCA	ACAGTATGGG
	CGCGGGCGCT	TGCTGTAAAT	ATTACTTGCA	CTTAACGAGT	TGTCATACCC
9201	CATTTTCGAG	CCTACCGTGG	TGTTTCGTTT	CAAAAAGGGG	TTGCAAAAAA
	GTAAAGCGTC	GGATGGCACC	ACAAGCAAAG	GTTTTTCCCC	AACGTTTTTT
9251	TTTTGAACGT	GCAAAAAAAG	CTCCCAATCA	TCCAAAAAAT	TATTATCATG
	AAAACCTGCA	CGTTTTTTTC	GAGGGTTAGT	AGGTTTTTTA	ATAATAGTAC
9301	GATTCTAAAA	CGGATTACCA	GGGATTTTCA	TCGATGTACA	CGTTTCGTCAC
	CTAAGATTTT	GCCTAATGGT	CCCTAAAGTC	AGCTACATGT	GCAAGCAGTG
9351	ATCTCATCTA	CCTCCCGGTT	TTAATGAATA	CGATTTTGTG	CCAGAGTCCT
	TAGAGTAGAT	GGAGGGCCAA	AATTACTTAT	GCTAAAACAC	GGTCTCAGGA
9401	TCGATAGGGA	CAAGACAATT	GCACTGATCA	TGAACTCCTC	TGGATCTACT
	AGCTATCCCT	GTTCTGTTAA	CGTGACTAGT	ACTTGAGGAG	ACCTAGATGA
9451	GGTCTGCCTA	AAGGTGTGCG	TCTGCCTCAT	AGAACTGCCT	GCGTGAGATT
	CCAGACGGAT	TTCCACAGCG	AGACGGAGTA	TCTTGACGGA	CGCACTCTAA
9501	CTCGCATGCC	AGAGATCCTA	TTTTTGGCAA	TCAAATCATT	CCGGATACTG
	GAGCGTACGG	TCTCTAGGAT	AAAAACCGTT	AGPTTAGTAA	GGCCTATGAC

9551	CGATTTTAAAG	TGTTGTTCCA	TTCCATCACG	GTTTTGGAAT	GTTTACTACA
	GCTAAAATTTC	ACAACAAGGT	AAGGTAGTGC	CAAAACCTTA	CAAATGATGT
9601	CTCGGATATT	TGATATGTGG	ATTTCGAGTC	GTCTTAATGT	ATAGATTTGA
	GAGCCTATAA	ACTATACACC	TAAAGCTCAG	CAGAATTACA	TATCTAAACT
9651	AGAAGAGCTG	TTTCTGAGGA	GCCTTCAGGA	TTACAAGATT	CAAAGTGCGC
	TCTTCTCGAC	AAAGACTCCT	CGGAAGTCCT	AATGTTCTAA	GTTTCACGCG
9701	TGCTGGTGCC	AACCTTATTC	TCCTTCCTCG	CCAAAAGCAC	TCTGATTGAC
	ACGACCACGG	TTGGGATAAG	AGGAAGAAGC	GGTTTTCTGT	AGACTAACTG
9751	AAATACGATT	TATCTAATTT	ACACGAAATT	GCTTCTGGTG	GCGCTCCCCT
	TTTATGCTAA	ATAGATTAAA	TGTGCTTTAA	CGAAGACCAC	CGCGAGGGGA
9801	CTCTAAGGAA	GTCCGGGGAAG	CGGTTGCCAA	GAGGTTCCAT	CTGCCAGGTA
	GAGATTCCCTT	CAGCCCCTTC	GCCAACGGTT	CTCCAAGGTA	GACGGTCCAT
9851	TCAGGCAAGG	ATATGGGCTC	ACTGAGACTA	CATCAGCTAT	TCTGATTACA
	AGTCCGTTCC	TATACCCGAG	TGACTCTGAT	GTAGTCGATA	AGACTAATGT
9901	CCCGAGGGGG	ATGATAAACC	GGGCGCGGTC	GGTAAAGTTG	TTCCATTTTTT
	GGGCTCCCCC	TACTATTTGG	CCGCGGCCAG	CCATTTCAAC	AAGGTAAAAA
9951	TGAAGCGAAG	GTTGTGGATC	TGGATACCGG	GAAAACGCTG	GGCGTTAATC
	ACTTCGCTTC	CAACACCTAG	ACCTATGGCC	CTTTTGCGAC	CCGCAATTAG
10001	AAAGAGGCGA	ACTGTGTGTG	AGAGGTCCTA	TGATTATGTC	CGGTTATGTA
	TTTCTCCGCT	TGACACACAC	TCTCCAGGAT	ACTAATACAG	GCCAATACAT
10051	AACAATCCGG	AAGCGACCAA	CGCCTTGATT	GACAAGGATG	GATGGCTACA
	TTGTTAGGCC	TTGCTGGTT	GCGGAACATA	CTGTTCTTAC	CTACCGATGT
10101	TTCTGGAGAC	ATAGCTTACT	GGGACGAAGA	CGAACACTTC	TTCATCGTTG
	AAGACCTCTG	TATCGAATGA	CCCTGCTTCT	GCTTGTGAAG	AAGTAGCAAC
10151	ACCGCCTGAA	GTCTCTGATT	AAGTACAAAG	GCTATCAGGT	GGCTCCCGCT
	TGGCGGACTT	CAGAGACTAA	PTCATGTTTC	CGATAGTCCA	CCGAGGGCGA
10201	GAATTGGAAT	CCATCTTGCT	CCAACACCCC	AACATCTTCG	ACGCAGGTGT
	CTTAACCTTA	GGTAGAACGA	GGTTGTGGGG	TTGTAGAAGC	TGCGTCCACA
10251	CGCAGGTCTT	CCCGACGATG	ACGCCGGTGA	ACTTCCCGCC	GCCGTTGTTG
	GCGTCCAGAA	GGGCTGCTAC	TGCGGCCACT	TGAAGGGCGG	CGGCAACAAC
10301	TTTTGGAGCA	CGGAAAGACG	ATGACGGAAA	AAGAGATCGT	GGATTACGTC
	AAAACCTCGT	GCCTTTCTGC	TACTGCCTTT	TTCTCTAGCA	CCTAATGCAG
10351	GCCAGTCAAG	TAACAACCGC	GAAAAAGTTG	CGCGGAGGAG	TTGTGPTTGT
	CGGTCAGTTC	ATTGTTGGCG	CTTTTTCAAC	GCGCCTCCTC	AACACAAACA
10401	GGACGAAGTA	CCGAAAGGTC	TTACCGGAAA	ACTCGACGCA	AGAAAAATCA
	CCTGCTTCAT	GGCTTTCCAG	AATGGCCTTT	TGAGCTGCGT	TCTTTTTAGT
10451	GAGAGATCCT	CATAAAGGCC	AAGAAGGGCG	GAAAGATCGC	CGTGTAATTC
	CTCTCTAGGA	GTATTTCCGG	TTCTTCCCGC	CTTTCTAGCG	GCACATTAAG
10501	TAGAGGCGCG	CCGATCTCAC	GATCCCCTGA	AAAGGCTGTT	TAAGTTGGGT
	ATCTCCGCGC	GGCTAGAGTG	CTAGGGGACT	TTTCCGACAA	ATTCAACCCA
10551	AAACCGCTCC	CAGCCGACGA	CGAGCAAGAC	GAAGACAGAA	GACGCGCTCT
	TTTGGCGAGG	GTCGGCTGCT	GCTCGTTCTG	CTTCTGTCTT	CTGCGCGAGA
10601	GCTAGATGAA	ACAAAGGCGT	GGTTTAGAGT	AGGTATAACA	GGCACTTTAG

	CGATCTACTT	TGTTTCCGCA	CCAAATCTCA	TCCATATTGT	CCGTGAAATC
10651	CAGTGGCCGT	GACGACCCGG	TATGAGGTAG	ACAATATTAC	ACCTGTCCTA
	GTCACCGGCA	CTGCTGGGCC	ATACTCCATC	TGTTATAATG	TGGACAGGAT
10701	CTGGCATTGA	GAACFTTTGC	CCAGAGCAAA	AGAGCATTCC	AAGCCATCAG
	GACCGTAACT	CTTGAAAACG	GGTCTCGTTT	TCTCGTAAGG	TTCGGTAGTC
10751	AGGGGAAATA	AAGCATCTCT	ACGGTGGTCC	TAAATAGTCA	GCATAGTACA
	TCCCCTTTAT	TTCGTAGAGA	TGCCACCAGG	ATTTATCAGT	CGTATCATGT
10801	TTTCATCTGA	CTAATACTAC	AACACCACCA	CCATGAATAG	AGGATTCTTT
	AAAGTAGACT	GATTATGATG	TTGTGGTGGT	GGTACTTATC	TCCTAAGAAA
10851	AACATGCTCG	GCCGCCGCC	CTTCCCGGCC	CCCACTGCCA	TGTGGAGGCC
	TTGTACGAGC	CGGCGGCGGG	GAAGGGCCGG	GGGTGACGGT	ACACCTCCGG
10901	GCGGAGAAGG	AGGCAGGCGG	CCCCGATGCC	TGCCCCGAAC	GGGCTGGCTT
	CGCCTCTTCC	TCCGTCCGCC	GGGGCTACGG	ACGGGCGTTG	CCCGACCGAA
10951	CTCAAATCCA	GCAACTGACC	ACAGCCGTCA	GTGCCCTAGT	CATTGGACAG
	GAGTTTAGGT	CGTTGACTGG	TGTCGGCAGT	CACGGGATCA	GTAACCTGTC
11001	GCAACTAGAC	CTCAACCCCC	ACGTCCACGC	CAGCCACCGC	GCCAGAAGAA
	CGTTGATCTG	GAGTTGGGGG	TGCAGGTGCG	GTCGGTGGCG	CGGTCTTCTT
11051	GCAGGCGCCC	AAGCAACCAC	CGAAGCCGAA	GAAACCAAAA	ACGCAGGAGA
	CGTCCGCGGG	TTCGTTGGTG	GCTTCGGCTT	CTTTGGTTTT	TGCGTCCTCT
11101	AGAAGAAGAA	GCAACCTGCA	AAACCCAAAC	CCGGAAGAG	ACAGCGCATG
	TCTTCTTCTT	CGTTGGACGT	PTTGGGTTTG	GGCCTTTCTC	TGTCGCGTAC
11151	GCACTTAAGT	TGGAGGCCGA	CAGATTGTTT	GACGTCAAGA	ACGAGGACGG
	CGTGAATTCA	ACCTCCGGCT	GTCTAACAAG	CTGCAGTTCT	TGCTCCTGCC
11201	AGATGTCATC	GGGCACGCAC	TGGCCATGGA	AGGAAAGGTA	ATGAAACCTC
	TCTACAGTAG	CCCGTGCGTG	ACCGGTACCT	TCCTTTCCAT	TACTTTGGAG
11251	TGCACGTGAA	AGGAACCATC	GACCACCCTG	TGCTATCAAA	GCTCAAATTT
	ACGTGCACCT	TCCCTGGTAG	CTGGTGGGAC	ACGATAGTTT	CGAGTTTAAA
11301	ACCAAGTCGT	CAGCATACGA	CATGGAGTTC	GCACAGTTGC	CAGTCAACAT
	TGGTTCAGCA	GTCGTATGCT	GTACCTCAAG	CGTGTCAACG	GTCAGTTGTA
11351	GAGAAGTGAG	GCATTCACCT	ACACCAGTGA	ACACCCCGAA	GGATTCTATA
	CTCTTCACTC	CGTAAGTGGA	TGTGGTCACT	TGTGGGGCTT	CCTAAGATAT
11401	ACTGGCACCA	CGGAGCGGTG	CAGTATAGTG	GAGGTAGATT	TACCATCCCT
	TGACCGTGGT	GCCTCGCCAC	GTCATATCAC	CTCCATCTAA	ATGGTAGGGA
11451	CGCGGAGTAG	GAGGCAGAGG	AGACAGCGGT	CGTCCGATCA	TGGATAACTC
	GCGCCTCATC	CTCCGTCTCC	TCTGTGCGCA	GCAGGCTAGT	ACCTAFTGAG
11501	CGGTGCGGTT	GTCGCGATAG	TCCTCGGTGG	AGCTGATGAA	GGAACACGAA
	GCCAGCCCAA	CAGCGCTATC	AGGAGCCACC	TCGACTACTT	CCTTGTGCTT
11551	CTGCCCTTTC	GGTCGTCACC	TGGAATAGTA	AAGGGAAGAC	AATTAAGACG
	GACGGGAAAG	CCAGCAGTGG	ACCTTATCAT	TTCCCTTCTG	TTAATTCTGC
11601	ACCCCGGAAG	GGACAGAAGA	GTGGTCCGCA	GCACCACTGG	TCACGGCAAT
	TGGGGCCTTC	CCTGTCTTCT	CACCAGGCGT	CGTGGTGACC	AGTGCCGTTA
11651	GTGTTTGCTC	GGAAATGTGA	GCTTCCCATG	CGACCGCCCG	CCCACATGCT
	CACAAACGAG	CCTTTACACT	CGAAGGGTAC	GCTGGCGGGC	GGGTGTACGA

11701	ATACCCGCGA	ACCTTCCAGA	GCCCTCGACA	TCCTTGAAGA	GAACGTGAAC
	TATGGGCGCT	TGGAAGGTCT	CGGGAGCTGT	AGGAAC TTCT	CTTGCACTTG
11751	CATGAGGCCT	ACGATACCCT	GCTCAATGCC	ATATTGCGGT	GCGGATCGTC
	GTACTCCGGA	TGCTATGGGA	CGAGTTACGG	TATAACGCCA	CGCCTAGCAG
11801	TGGCAGAAGC	AAAAGAAGCG	TCATCGATGA	CTTTACCCTG	ACCAGCCCCCT
	ACCGTCTTCG	TTTTCTTCGC	AGTAGCTACT	GAAATGGGAC	TGGTCGGGGA
11851	ACTTGGGCAC	ATGCTCGTAC	TGCCACCATA	CTGAACCGTG	CTTCAGCCCCT
	TGAACCCGTG	TACGAGCATG	ACGGTGGTAT	GACTTGGCAC	GAAGTCGGGA
11901	GTTAAGATCG	AGCAGGTCTG	GGACGAAGCG	GACGATAACA	CCATACGCAT
	CAATTCTAGC	TCGTCCAGAC	CCTGCTTCGC	CTGCTATTGT	GGTATGCGTA
11951	ACAGACTTCC	GCCCAGTTTG	GATACGACCA	AAGCGGAGCA	GCAAGCGCAA
	TGTCTGAAGG	CGGGTCAAAC	CTATGCTGGT	TTGCGCTCGT	CGTTCGCGTT
12001	ACAAGTACCG	CTACATGTCT	CTTAAGCAGG	ATCACACCGT	TAAAGAAGGC
	TGTTTCATGGC	GATGTACAGC	GAATTCGTCC	TAGTGTGGCA	ATTTCTTCCG
12051	ACCATGGATG	ACATCAAGAT	TAGCACCTCA	GGACCGTGTA	GAAGGCTTAG
	TGGTACCTAC	TGTAGTTCTA	ATCGTGGAGT	CCTGGCACAT	CTTCCGAATC
12101	CTACAAAGGA	TACTTTCTCC	TCGCAAAATG	CCCTCCAGGG	GACAGCGTAA
	GATGTTTCCT	ATGAAAGAGG	AGCGTTTTAC	GGGAGGTCCC	CTGTGCGATT
12151	CGGTTAGCAT	AGTGAGTAGC	AACTCAGCAA	CGTCATGTAC	ACTGGCCCCG
	GCCAATCGTA	TCACTCATCG	TTGAGTCGTT	GCAGTACATG	TGACCGGGCG
12201	AAGATAAAAC	CAAAATTTCG	GGGACGGGAA	AAATATGATC	TACCTCCCCG
	TTCTATTTTG	GTTTAAAGCA	CCCTGCCCTT	TTTATACTAG	ATGGAGGGCA
12251	TCACGGTAAA	AAAATTTCCT	GCACAGTGTA	CGACCGTCTG	AAAGAAACAA
	AGTGCCATTT	TTTTAAGGAA	CGTGTCACAT	GCTGGCAGAC	TTTCTTTGTT
12301	CTGCAGGCTA	CATCACTATG	CACAGGCCGG	GCCCGCACGC	TTATACATCC
	GACGTCCGAT	GTAGTGATAC	GTGTCCGGCC	CGGGCGTGCG	AATATGTAGG
12351	TACCTGGAAG	AATCATCAGG	GAAAGTTTAC	GCAAAGCCGC	CATCTGGGAA
	ATGGACCTTC	TTAGTAGTCC	CTTTCAAATG	CGTTTCGGCG	GTAGACCCTT
12401	GAACATTACG	TATGAGTGCA	AGTGCGGCGA	CTACAAGACC	GGAACCGTTT
	CTTGTAATGC	ATACTCACGT	TCACGCCGCT	GATGTTCTGG	CCTTGGCAAA
12451	CGACCCGCAC	CGAAATCACT	GGTTGCACCG	CCATCAAGCA	GTGCGTCGCC
	GCTGGGCGTG	GCTTTAGTGA	CCAACGTGGC	GGTAGTTTCG	CACGCAGCGG
12501	TATAAGAGCG	ACCAAACGAA	GTGGGTCTTC	AACTCACCGG	ACTTGATCCG
	ATATTCTCGC	TGGTTTGCTT	CACCCAGAAG	TTGAGTGGCC	TGAAC TAGGC
12551	ACATGACGAC	CACACGGTCC	AAGGGAAATT	GCATTTGCCT	TTCAAGTTGA
	TGTACTGCTG	GTGTGCCAGG	TTCCCTTTAA	CGTAAACGGA	AAGTTCAACT
12601	TCCCGAGTAC	CTGCATGGTC	CCTGTTGCC	ACGCGCCGAA	TGTAATACAT
	AGGGCTCATG	GACGTACCAG	GGACAACGGG	TGCGCGGCTT	ACATTATGTA
12651	GGCTTTAAAC	ACATCAGCCT	CCAATTAGAT	ACAGACCACT	TGACATTGCT
	CCGAAATTTG	TGTAGTCGGA	GGTTAATCTA	TGTCTGGTGA	ACTGTAACGA
12701	CACCACCAGG	AGACTAGGGG	CAAACCCGGA	ACCAACCACT	GAATGGATCG
	GTGGTGGTCC	TCTGATCCCC	GTTTGGGCCT	TGGTTGGTGA	CTTACCTAGC
12751	TCGGAAAGAC	GGTCAGAAAC	TTCACCGTCG	ACCGAGATGG	CCTGGAATAC

	AGCCTTTCTG	CCAGTCTTTG	AAGTGGCAGC	TGGCTCTACC	GGACCTTATG
12801	ATATGGGGAA	ATCATGAGCC	AGTGAGGGTC	TATGCCCCAAG	AGTCAGCACC
	TATACCCCTT	TAGTACTCGG	TCACTCCCAG	ATACGGGTTC	TCAGTCGTGG
12851	AGGAGACCCT	CACGGATGGC	CACACGAAAT	AGTACAGCAT	TACTACCATC
	TCCTCTGGGA	GTGCCTACCG	GTGTGCTTTA	TCATGTCGTA	ATGATGGTAG
12901	GCCATCCTGT	GTACACCATC	TTAGCCGTCG	CATCAGCTAC	CGTGGCGATG
	CGGTAGGACA	CATGTGGTAG	AATCGGCAGC	GTAGTCGATG	GCACCGCTAC
12951	ATGATTGGCG	TAACGTGTTG	AGTGTATATG	GCCTGTAAAG	CGCGCCGTGA
	TACTAACCGC	ATTGACAACG	TCACAATACA	CGGACATTTC	GCGCGGCACT
13001	GTGCCTGACG	CCATACGCCC	TGGCCCCAAA	CGCCGTAATC	CCAACCTTCG
	CACGGACTGC	GGTATGCGGG	ACCGGGGTTT	GCGGCATTAG	GGTTGAAGCG
13051	TGGCACTCPT	GTGCTGCGTT	AGGTCGGCCA	ATGCTGAAAC	GTTCAACGAG
	ACCGTGAGAA	CACGACGCAA	TCCAGCCGGT	TACGACTTTG	CAAGTGGCTC
13101	ACCATGAGTT	ACTTGTGGTC	GAACAGTCAG	CCGTTCTTCT	GGGTCCAGTT
	TGGTACTCAA	TGAACACCAG	CTTGTCAGTC	GGCAAGAAGA	CCCAGGTCAA
13151	GTGCATACCT	TTGGCCGCTT	TCATCGTTCT	AATGCGCTGC	TGCTCCTGCT
	CACGTATGGA	AACCGGCGAA	AGTAGCAAGA	TTACGCGACG	ACGAGGACGA
13201	GCCTGCCTTT	TTTAGTGGTT	GCCGGCGCCT	ACCTGGCGAA	GGTAGACGCC
	CGGACGGAAA	AAATCACCAA	CGGCCGCGGA	TGGACCGCTT	CCATCTGCGG
13251	TACGAACATG	CGACCACTGT	TCCAAATGTG	CCACAGATAC	CGTATAAGGC
	ATGCTTGTAC	GCTGGTGACA	AGGTTTACAC	GGTGTCTATG	GCATATTCCG
13301	ACTTGTTGAA	AGGGCAGGGT	ATGCCCGCT	CAATTTGGAG	ATCACTGTCA
	TGAACAACCT	TCCCGTCCCA	TACGGGGCGA	GTAAACCTC	TAGTGACAGT
13351	TGTCCTCGGA	GGTTTTGCCT	TCCACCAACC	AAGAGTACAT	TACCTGCAAA
	ACAGGAGCCT	CCAAAACGGA	AGGTGGTTGG	TTCTCATGTA	ATGGACGTTT
13401	TTCACCACTG	TGGTCCCCTC	CCCAAAAATC	AAATGCTGCG	GCTCCTTGGA
	AAGTGGTGAC	ACCAGGGGAG	GGGTTTTTAG	TTTACGACGC	CGAGGAACCT
13451	ATGTCAGCCG	GCCGTTTCATG	CAGACTATAC	CTGCAAGGTC	TTCGGAGGGG
	TACAGTCGGC	CGGCAAGTAC	GTCTGATATG	GACGTTCCAG	AAGCCTCCCC
13501	TCTACCCCTT	TATGTGGGGA	GGAGCGCAAT	GTTTTTGCGA	CAGTGAGAAC
	AGATGGGGAA	ATACACCCCT	CCTCGCGTTA	CAAAAACGCT	GTCACTCTTG
13551	AGCCAGATGA	GTGAGGCGTA	CGTCGAACTG	TCAGCAGATT	GCGCGTCTGA
	TCGGTCTACT	CACTCCGCAT	GCAGCTTGAC	AGTCGTCTAA	CGCGCAGACT
13601	CCACGCGCAG	GCGATTAAGG	TGCACACTGC	CGCGATGAAA	GTAGGACTGC
	GGTGCGCGTC	CGCTAATTCC	ACGTGTGACG	GCGCTACTTT	CATCCTGACG
13651	GTATAGTGTA	CGGGAACACT	ACCAGTTTCC	TAGATGTGTA	CGTGAACGGA
	CATATCACAT	GCCCTTGTGA	TGGTCAAAGG	ATCTACACAT	GCACTTGCCCT
13701	GTCACACCAG	GAACGTCTAA	AGACTTGAAA	GTCATAGCTG	GACCAATTTT
	CAGTGTGGTC	CTTGCAAGAT	TCTGAACTTT	CAGTATCGAC	CTGGTTAAAG
13751	AGCATCGTTT	ACGCCATTCT	ATCATAAGGT	CGTTATCCAT	CGCGGCCTGG
	TCGTAGCAAA	TGCGGTAAGC	TAGTATTCCA	GCAATAGGTA	GCGCCGGACC
13801	TGTACAACCTA	TGACTTCCCG	GAATATGGAG	CGATGAAACC	AGGAGCGTTT
	ACATGTTGAT	ACTGAAGGGC	CTTATACCTC	GCTACTTTGG	TCCTCGCAAA

13851	GGAGACATTC	AAGCTACCTC	CTTGACTAGC	AAGGATCTCA	TCGCCAGCAC
	CCTCTGTAAG	TTCGATGGAG	GAACGTGATCG	TTCTTAGAGT	AGCGGTCGTG
13901	AGACATTAGG	CTACTCAAGC	CTTCCGCCAA	GAACGTGCAT	GTCCCGTACA
	TCTGTAATCC	GATGAGTTCG	GAAGGCGGTT	CTTGACAGTA	CAGGGCATGT
13951	CGCAGGCCGC	ATCAGGATTT	GAGATGTGGA	AAAACAACCTC	AGGCCGCCCA
	GCGTCCGGCG	TAGTCCTAAA	CTCTACACCT	TTTTGTTGAG	TCCGGCGGGT
14001	CTGCAGGAAA	CCGCACCTTT	CGGGTGTAAG	ATTGCAGTAA	ATCCGCTCCG
	GACGTCCTTT	GGCGTGGA	GCCCACATTC	TAACGTCATT	TAGGCGAGGC
14051	AGCGGTGGAC	TGTTCATACG	GGAACATTCC	CATTTCTATT	GACATCCCGA
	TCGCCACCTG	ACAAGTATGC	CCTTGTAAGG	GTAAAGATAA	CTGTAGGGCT
14101	ACGCTGCCTT	TATCAGGACA	TCAGATGCAC	CACTGGTCTC	AACAGTCAAA
	TGCGACGGAA	ATAGTCCTGT	AGTCTACGTG	GTGACCAGAG	TTGTCACTTT
14151	TGTGAAGTCA	GTGAGTGCAC	TTATTCAGCA	GACTTCGGCG	GGATGGCCAC
	ACACTTCAGT	CACTCACGTG	AATAAGTCGT	CTGAAGCCGC	CCTACCGGTG
14201	CCTGCAGTAT	GTATCCGACC	GCGAAGGTCA	ATGCCCCGTA	CATTCGCATT
	GGACGTCATA	CATAGGCTGG	CGCTTCCAGT	TACGGGGCAT	GTAAGCGTAA
14251	CGAGCACAGC	AACTCTCCAA	GAGTCGACAG	TACATGTCTT	GGAGAAAGGA
	GCTCGTGTCG	TTGAGAGGTT	CTCAGCTGTC	ATGTACAGGA	CCTCTTTCCT
14301	GCGGTGACAG	TACACTTTAG	CACCGCGAGT	CCACAGGCGA	ACTTTATCGT
	CGCCACTGTC	ATGTGAAATC	GTGGCGCTCA	GGTGTCCGCT	TGAAATAGCA
14351	ATCGCTGTGT	GGGAAGAAGA	CAACATGCAA	TGCAGAATGT	AAACCACCAG
	TAGCGACACA	CCCTTCTTCT	GTTGTACGTT	ACGTCTTACA	TTTGGTGGTC
14401	CTGACCATAT	CGTGAGCACC	CCGCACAAAA	ATGACCAAGA	ATTTCAAGCC
	GACTGGTATA	GCACTCGTGG	GGCGTGTTTT	TACTGGTTCT	TAAAGTTCCG
14451	GCCATCTCAA	AAACATCATG	GAGTTGGCTG	TTTGCCCTTT	TCGGCGGCGC
	CGGTAGAGTT	TTTGTAGTAC	CTCAACCGAC	AAACGGGAAA	AGCCGCCGCG
14501	CTCGTCGCTA	TTAATTATAG	GACTTATGAT	TTTTGCTTGC	AGCATGATGC
	GAGCAGCGAT	AATTAATATC	CTGAATACTA	AAAACGAACG	TCGTACTACG
14551	TGACTAGCAC	ACGAAGATGA	CCGCTACGCC	CCAATGATCC	GACCAGCAAA
	ACTGATCGTG	TGCTTCTACT	GGCGATGCGG	GGTTACTAGG	CTGGTCGTTT
14601	ACTCGATGTA	CTTCCGAGGA	ACTGATGTGC	ATAAGTGAGC	ATGCGTTTAA
	TGAGCTACAT	GAAGGCTCCT	TGACTACACG	TATTCACCTG	TACGCAAATT
14651	ACTGGGCCCA	ATGTTCCCCA	ATGATCCGAC	CAGCAAACT	CGATGTACTT
	TGACCCGGGT	TACAAGGGGT	TACTAGGCTG	GTCGTTTTGA	GCTACATGAA
14701	CCGAGGAACT	GATGTGCATA	ATGCATCAGG	CTGGTACATT	AGATCCCCGC
	GGCTCCTTGA	CTACACGTAT	TACGTAGTCC	GACCATGTAA	TCTAGGGGCG
14751	TTACCGCGGG	CAATATAGCA	ACACTAAAAA	CTCGATGTAC	TTCCGAGGAA
	AATGGCGCCC	GTTATATCGT	TGTGATTTTT	GAGCTACATG	AAGGCTCCTT
14801	GCGCAGTGCA	TAATGCTGCG	CAGTGTTGCC	ACATAACCAC	TATATTAACC
	CGCGTCACGT	ATTACGACGC	GTCACAACGG	TGTATTGGTG	ATATAATTGG
14851	ATTTATCTAG	CGGACGCCAA	AAACTCAATG	TATTTCTGAG	GAAGCGTGGT
	TAAATAGATC	GCCTGCGGTT	TTTGAGTTAC	ATAAAGACTC	CTTCGCACCA
14901	GCATAATGCC	ACGCAGCGTC	TGCATAACTT	TTATTATTTT	TTTTATTAA

	CGTATTACGG	TGCGTCGCAG	ACGTATTGAA	AATAATAAAG	AAAATAATTA
14951	CAACAAAATT	TTGTTTTTAA	CATTTCAAAA	AAAAAAAAAA	AAAAAAAAAA
	GTTGTTTTAA	AACAAAATT	GTAAAGTTTT	TTTTTTTTTT	TTTTTTTTTT
15001	AAAAAAAAAA	AAAATTTAAA	TTAATTAAGC	GGCCGCCTCG	AGGACGTCAG
	TTTTTTTTTT	TTTTAAATTT	AATTAATTCT	CCGGCGGAGC	TCCTGCAGTC
15051	GTGGCACTTT	TCGGGGAAAT	GTGCGCGGAA	CCCCTATTTG	TTTATTTTTTC
	CACCGTGAAA	AGCCCCTTTA	CACGCGCCTT	GGGGATAAAC	AAATAAAAAAG
15101	TAAATACATT	CAAATATGTA	TCCGCTCATG	AGACAATAAC	CCTGATAAAT
	ATTTATGTAA	GTTTATACAT	AGGCGAGTAC	TCTGTTATTG	GGACTATTTA
15151	GCTTCAATAA	TATTGAAAAA	GGAAGAGTAT	GAGTATTCAA	CATTTCCGTG
	CGAAGTTATT	ATAACTTTTT	CCTTCTCATA	CTCATAAGTT	GTAAAGGCAC
15201	TCGCCCTTAT	TCCCTTTTTT	GCGGCATTTT	GCCTTCCTGT	TTTTTGCTCAC
	AGCGGGAATA	AGGGAAAAAA	CGCCGTAAAA	CGGAAGGACA	AAAACGAGTG
15251	CCAGAAACGC	TGGTGAAAGT	AAAAGATGCT	GAAGATCAGT	TGGGTGCACG
	GGTCTTTGCG	ACCACTTTCA	TTTTCTACGA	CTTCTAGTCA	ACCCACGTGC
15301	AGTGGGTTAC	ATCGAACTGG	ATCTCAACAG	CGGTAAGATC	CTTGAGAGTT
	TCACCCAATG	TAGCTTGACC	TAGAGTTGTC	GCCATTCTAG	GAACCTCTCA
15351	TTCGCCCCGA	AGAACGTTTT	CCAATGATGA	GCACTTTTAA	AGTTCTGCTA
	AAGCGGGGCT	TCTTGCAAAA	GGTTACTACT	CGTGAAAATT	TCAAGACGAT
15401	TGTGGCGCGG	TATTATCCCG	TATPGACGCC	GGGCAAGAGC	AACTCGGTCC
	ACACCGCGCC	ATAATAGGGC	ATAACTGCGG	CCCGTTCTCG	TTGAGCCAGC
15451	CCGCATACAC	TATTCTCAGA	ATGACTTGGT	TGAGTACTCA	CCAGTCACAG
	GGCGTATGTG	ATAAGAGTCT	TACTGAACCA	ACTCATGAGT	GGTCAGTGTC
15501	AAAAGCATCT	TACGGATGGC	ATGACAGTAA	GAGAATTATG	CAGTGCTGCC
	TTTTCGTAGA	ATGCCTACCG	TACTGTCATT	CTCTTAATAC	GTCACGACGG
15551	ATAACCATGA	GTGATAACAC	TGCGGCCAAC	TTACTTCTGA	CAACGATCGG
	TATTGGTACT	CACTATTGTG	ACGCCGGTTG	AATGAAGACT	GTTGCTAGCC
15601	AGGACCGAAG	GAGCTAACCG	CTTTTTTGCA	CAACATGGGG	GATCATGTAA
	TCCTGGCTTC	CTCGATTGGC	GAAAAAACGT	GTTGTACCCC	CTAGTACATT
15651	CTCGCCTTGA	TCGTTGGGAA	CCGGAGCTGA	ATGAAGCCAT	ACCAAACGAC
	GAGCGGAAC	AGCAACCCTT	GGCCTCGACT	TACTTCGGTA	TGGTTTGCTG
15701	GAGCGTGACA	CCACGATGCC	TGTAGCAATG	GCAACAACGT	TGCGCAAAC
	CTCGCACTGT	GGTGCTACGG	ACATCGTTAC	CGTTGTTGCA	ACGCGTTTGA
15751	ATTAACCTGG	GAACACTTAA	CTCTAGCTTC	CCGGCAACAA	TTAATAGACT
	TAATTGACCG	CTTGATGAAT	GAGATCGAAG	GGCCGTTGTT	AATTATCTGA
15801	GGATGGAGGC	GGATAAAGTT	GCAGGACCAC	TTCTGCGCTC	GGCCCTTCCG
	CCTACCTCCG	CCTATTTCAA	CGTCCTGGTG	AAGACGCGAG	CCGGGAAGGC
15851	GCTGGCTGGT	TTATTGCTGA	TAAATCTGGA	GCCGGTGAGC	GTGGGTCTCG
	CGACCGACCA	AATAACGACT	ATTTAGACCT	CGGCCACTCG	CACCCAGAGC
15901	CGGTATCATT	GCAGCACTGG	GGCCAGATGG	TAAGCCCTCC	CGTATCGTAG
	GCCATAGTAA	CGTCGTGACC	CCGGTCTACC	ATTCGGGAGG	GCATAGCATC
15951	TTATCTACAC	GACGGGGAGT	CAGGCAACTA	TGGATGAACG	AAATAGACAG
	AATAGATGTG	CTGCCCTTCA	GTCCGTTGAT	ACCTACTTGC	TTTATCTGTC

16001	ATCGCTGAGA	TAGGTGCCTC	ACTGATTAAG	CATTGGTAAC	TGTCAGACCA
	TAGCGACTCT	ATCCACGGAG	TGACTAATTC	GTAACCATTG	ACAGTCTGGT
16051	AGTTTACTCA	TATATACTTT	AGATTGATTT	AAAAC TTCAT	TTT TAATTTA
	TCAAATGAGT	ATATATGAAA	TCTAACTAAA	TTTTGAAGTA	AAAAT TAAAT
16101	AAAGGATCTA	GGTGAAGATC	CTTTTTGATA	ATCTCATGAC	CAAAATCCCT
	TTTCCTAGAT	CCACTTCTAG	GAAAAACTAT	TAGAGTACTG	GTTTTAGGGA
16151	TAACGTGAGT	TTTCGTTCCA	CTGAGCGTCA	GACCCCGTAG	AAAAGATCAA
	ATTGCACTCA	AAAGCAAGGT	GACTCGCAGT	CTGGGGCATC	TTTTCTAGTT
16201	AGGATCTTCT	TGAGATCCTT	TTTTTCTGCG	CGTAATCTGC	TGCTTGCAAA
	TCCTAGAAGA	ACTCTAGGAA	AAAAAGACGC	GCATTAGACG	ACGAACGTTT
16251	CAAAAAAACC	ACCGCTACCA	GCGGTGGTTT	GTTTGCCGGA	TCAAGAGCTA
	GTTTTTTTTGG	TGGCGATGGT	CGCCACCAAA	CAAACGGCCT	AGTTCTCGAT
16301	CCAAC TCTTT	TTCCGAAGGT	AACTGGCTTC	AGCAGAGCGC	AGATACCAAA
	GGTTGAGAAA	AAGGCTTCCA	TTGACCGAAG	TCGTCTCGCG	TCTATGGTTT
16351	TACTGGTCTT	CTAGTGTAGC	CGTAGTTAGG	CCACCACTTC	AAGAACTCTG
	ATGACCAGAA	GATCACATCG	GCATCAATCC	GGTGGTGAAG	TTCTTGAGAC
16401	TAGCACCGCC	TACATACCTC	GCTCTGCTAA	TCTGT TACC	AGTGGCTGCT
	ATCGTGGCGG	ATGTATGGAG	CGAGACGATT	AGGACAATGG	TCACCGACGA
16451	GCCAGTGGCG	ATAAGTCGTG	TCTTACCGGG	TTGGACTCAA	GACGATAGTT
	CGGTCACCGC	TATTCAGCAC	AGAATGGCCC	AACCTGAGTT	CTGCTATCAA
16501	ACCGGATAAG	GCGCAGCGGT	CGGGCTGAAC	GGGGGGTTTC	TGCACACAGC
	TGGCCTATTTC	CGCGTCGCCA	GCCCCACTTG	CCCCCAAGC	ACGTGTGTGC
16551	CCAGCTTGGA	GCGAACGACC	TACACCGAAC	TGAGATACCT	ACAGCGTGAG
	GGTCGAACCT	CGCTTGCTGG	ATGTGGCTTG	ACTCTATGGA	TGTCGCACTC
16601	CTATGAGAAA	GCGCCACGCT	TCCC GAAGGG	AGAAAGGCGG	ACAGGTATCC
	GATACTCTTT	CGCGGTGCGA	AGGGCTTCCC	TCTTTCCGCC	TGTCCATAGG
16651	GGTAAGCGGC	AGGGTCGGAA	CAGGAGAGCG	CACGAGGGAG	CTTCCAGGGG
	CCATTCGCCG	TCCCAGCCTT	GTCCTCTCGC	GTGCTCCCTC	GAAGGTCCCC
16701	GAAACGCCTG	GTATCTTTAT	AGTCCTGTCT	GGTTTCGCCA	CCTCTGACTT
	CTTTGCGGAC	CATAGAAATA	TCAGGACAGC	CCAAAGCGGT	GGAGACTGAA
16751	GAGCGTCGAT	TTTTGTGATG	CTCGTCAGGG	GGGCGGAGCC	TATGGAAAAA
	CTCGCAGCTA	AAAACACTAC	GAGCAGTCCC	CCCGCCTCGG	ATACCTTTTT
16801	CGCCAGCAAC	GCGGCCTTTT	TACGGTTCCT	GGCCTTTTGC	TGGCCTTTTG
	GCGGTCGTTG	CGCCGGA AAA	ATGCCAAGGA	CCGGA AAACG	ACCGG AAAAC
16851	CTCACATGTG	GGAGGCTAGA	GTACATTTAG	GTGACACTAT	AGAA
	GAGTGTACAC	CCTCCGATCT	CATGTAAATC	CACTGTGATA	TCTT

The present invention is not to be limited in scope by the specific embodiments described herein. Indeed, various modifications of the invention in addition to those described herein will become apparent to those skilled in the art from the foregoing description and the accompanying figures. Such modifications are intended to fall within the scope of the appended claims.

- 5 It is further to be understood that all values are approximate, and are provided for description.

Patents, patent applications, publications, product descriptions, and protocols are cited throughout this application, the disclosures of which are incorporated herein by reference in their entireties for all purposes.

WHAT IS CLAIMED IS:

1. A method for treating a mammal harboring a solid tumor which expresses higher levels of High Affinity Laminin Receptors (LAMR) than normal cells of the same lineage comprising systematically administering to a mammal in
5 need of such treatment a therapeutically effective amount of a Replication Competent (RC) Sindbis virus vector, wherein said vector encodes a suicide gene.
2. The method of claim 1 comprising administering a therapeutically effective amount of a prodrug.
3. The method of claim 1 wherein said RC Sindbis virus vector is a RC
10 mut-4 vector comprising SEQ. ID NOS.: 2 - 8..
4. The method of claim 1 wherein said suicide gene is the Herpes virus thymidine kinase gene.
5. The method of claim 1 wherein said suicide gene is the Varicella zoster virus thymidine kinase gene.
- 15 6. The method of claim 1 wherein said suicide gene is the cytosine deaminase gene.
7. The method of claim 4 wherein said prodrug is ganciclovir.
8. The method of claim 5 wherein said prodrug is 5- fluorocytosine.
9. The method of claim 4 wherein said prodrug is acyclovir.
- 20 10. The method of claim 6 wherein said prodrug is FIAU.
11. A method for monitoring anti-cancer therapy in a mammal harboring a solid tumor which expresses higher levels of LAMR than normal cells of the same lineage comprising administering to a mammal in need of such treatment a diagnostically effective amount of a Replication Competent (RC) Sindbis virus vector

comprising a gene encoding a detectable label, and determining the amount of cancer cells in the body of said mammal, wherein the amount of cancer cells is proportional to the amount of label produced by said cancer cells and said vector encodes a suicide gene.

5 12. The method of claim 11 wherein said RC Sindbis virus vector is administered before, substantially simultaneously with or after said anti-cancer therapy.

 13. The method of claim 12, wherein said gene is selected from Herpes virus thymidine kinase, dopamine-2 receptor, green fluorescent protein, Firefly
10 luciferase and Renilla luciferase.

 14. The method of claim 11 wherein said RC Sindbis virus vector is a RC mut-4 vector comprising SEQ. ID NOS.: 2 - 8.

 15. The method of claim 11 further comprising administering a means for detecting said label.

15 16. The method of claim 15 wherein said detectable label is the Herpes virus thymidine kinase gene and said means for detecting said label is radiolabeled 2'-fluoro-2'-deoxy-1-beta-D-arabinofuranosyl-5-iodouracil (FIAU).

 17. The method of claim 16 wherein said means is identified by Positron Emission Tomography.

20 18. The method of claim 14 wherein said label is green fluorescent protein and said label is detected by (a) obtaining a tissue section of said cancer cells and (b) examining said tissue section by fluorescence microscopy.

 19. The method of claim 14 wherein said label is Firefly or Renilla luciferase and said label is detected by Cooled Charge-Coupled Device cameras.

25 20. The method of claim 11 wherein said Sindbis virus is administered after said anti-cancer therapy.

21. A method for identifying cancer cells which expresses higher levels of LAMR than normal cells of the same lineage in the body of a mammal comprising administering to a mammal in need of such treatment a diagnostically effective amount of a mut-4 RC Sindbis virus vector comprising SEQ. ID NOS.: 2 - 8 and
5 further comprising a gene encoding a detectable label, and assaying for said label, wherein said cell is a cancer cell if it expresses said label and said vector encodes a suicide gene.

22. The method of claim 21 wherein said gene encoding said detectable label is selected from Herpes virus thymidine kinase, green fluorescent protein,
10 Firefly luciferase and Renilla luciferase.

23. The method of claim 13 wherein said cancer cell is identified before anti-cancer suicide gene therapy is administered to said mammal.

24. The method of claim 23 wherein said cancer cell is identified after the administration of anti-cancer therapy.

15 25. The method of claim 23 further comprising administering a means for detecting said label.

26. A method for determining the amount of cancer cells which express higher levels of LAMR than normal cells of the same lineage in the body of a mammal comprising the steps of (a) administering to a mammal in need of such
20 treatment a diagnostically effective amount of a mut-4 RC Sindbis virus vector comprising SEQ. ID NOS.: 2 - 8 and further comprising a gene encoding a detectable label, and (b) determining the amount of said detectable label, wherein the amount of cancer cells in the body of said mammal is proportional to the amount of said label and the vector encodes a suicide gene.

25 27. The method of claim 26 wherein said gene is selected from Herpes simplex thymidine kinase, dopamine-2 receptor, green fluorescent protein, Firefly luciferase and Renilla luciferase.

28. The method of claim 27 further comprising administering a means for detecting said label.

29. The method of claim 28 wherein said detectable label is the Herpes virus thymidine kinase gene and said means for detecting said label is radiolabeled 2'-fluoro-2'-deoxy-1-beta-D-arabinofuranosyl-5-iodouracil (FIAU).

30. The method of claim 29 wherein said means is identified by Positron Emission Tomography.

31. The method of claim 27 wherein said label is green fluorescent protein and said label is detected by (a) obtaining a tissue section of said cancer cells and (b) examining said tissue section by fluorescence microscopy.

32. The method of claim 27 wherein said label is Firefly or Renilla luciferase and said label is detected by cooled Charge-Coupled Device cameras.

33. A Replication competent mut-4 Sindbis virus vector comprising SEQ. ID NOS.: 2 - 8.

34. The RC mut-4 Sindbis virus vector of claim 33 further comprising a suicide gene.

35. The RC mut-4 Sindbis virus vector of claim 34 wherein said suicide gene is HSVtk.

36. The RC mut-4 Sindbis virus vector of claim 34 wherein said suicide gene is cytosine deaminase.

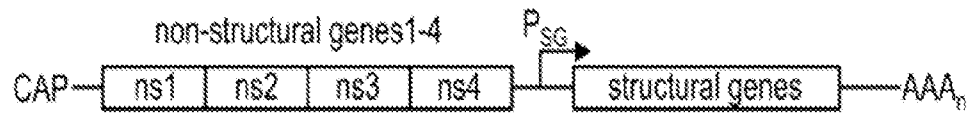
37. The RC mut-4 Sindbis virus vector of claim 34 wherein said suicide gene is Varicella Zoster virus thymidine kinase.

38. The RC mut-4 Sindbis virus vector of claim 34 wherein the genome of said vector is in a single component.

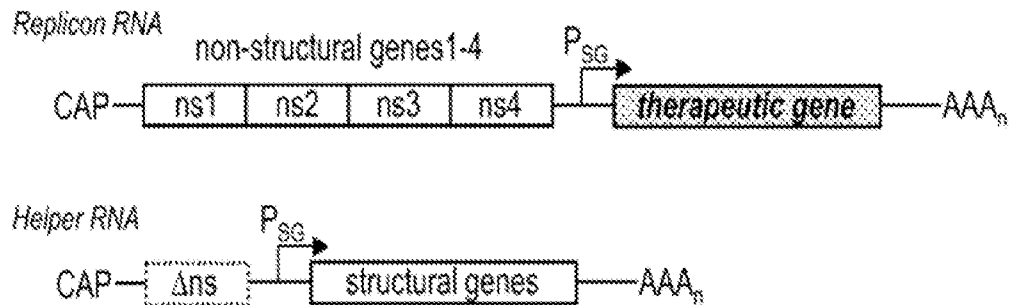
39. A pharmaceutical formulation or dosage form for administration to a mammal suffering from a solid tumor which expresses higher levels of LAMR than normal cells of the same lineage comprising a mut-4 RC Sindbis virus vector comprising SEQ. ID NOS.: 2 - 8 and a pharmaceutically acceptable carrier or diluent, wherein said vector further comprises a suicide gene.

FIGURE 1

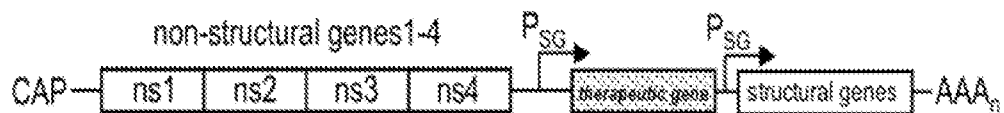
(A)

Wild-type Sindbis virus genomic RNA: single component

(B)

Replication-defective (RD) Sindbis viral vector system: dual components

(C)

Replication-capable (RC) Sindbis viral vector system: Single components

(D)

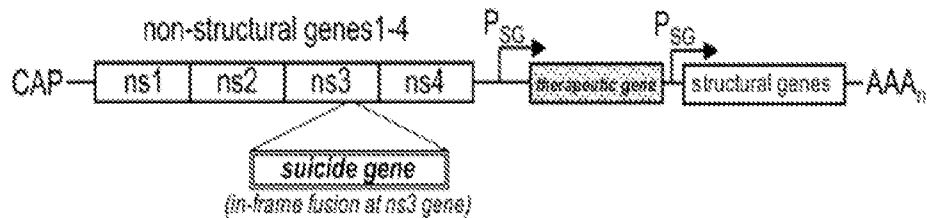
Replication-capable (RC) Sindbis viral vector system with safety feature: Single components

FIGURE 2

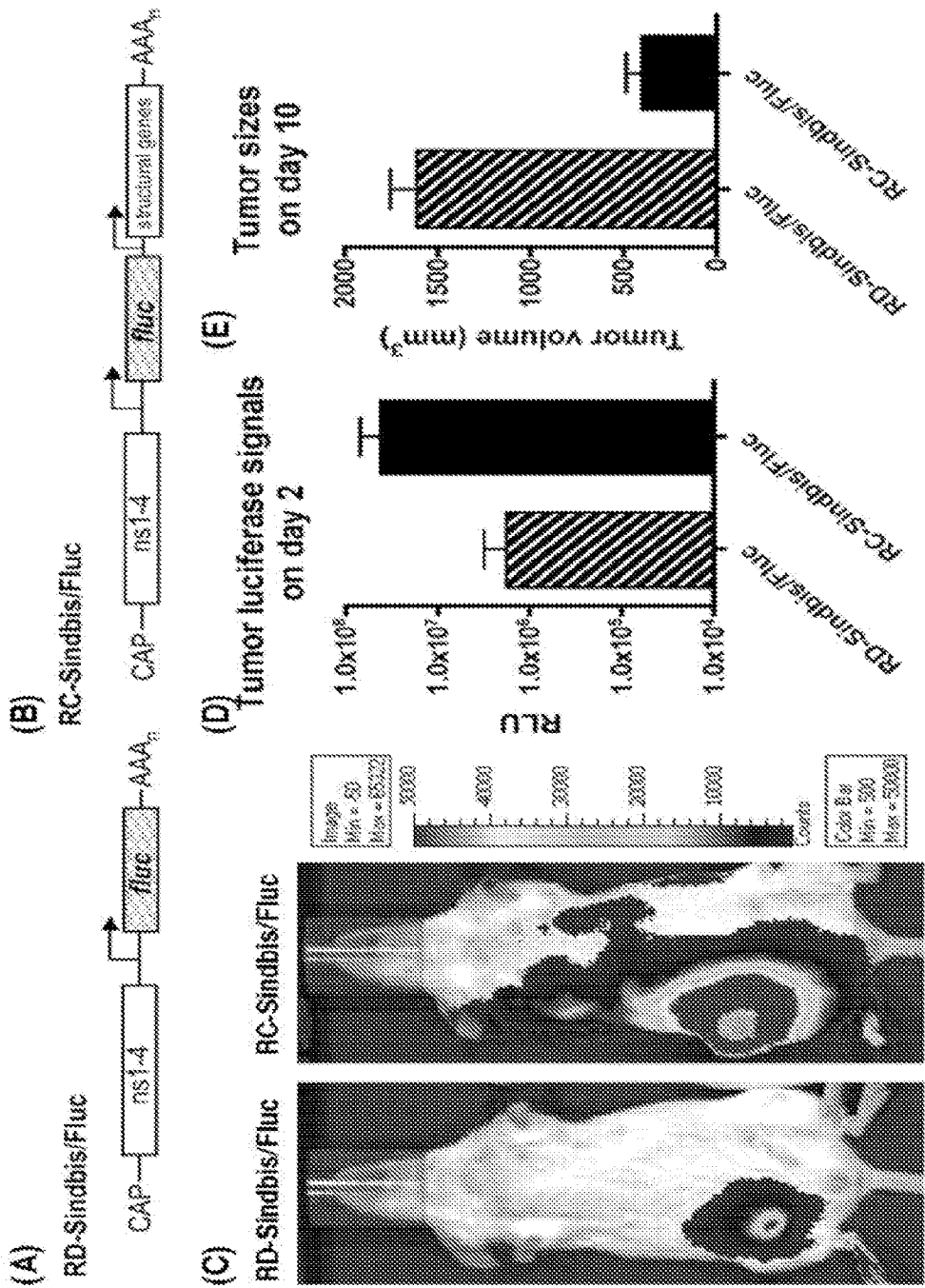


FIGURE 3

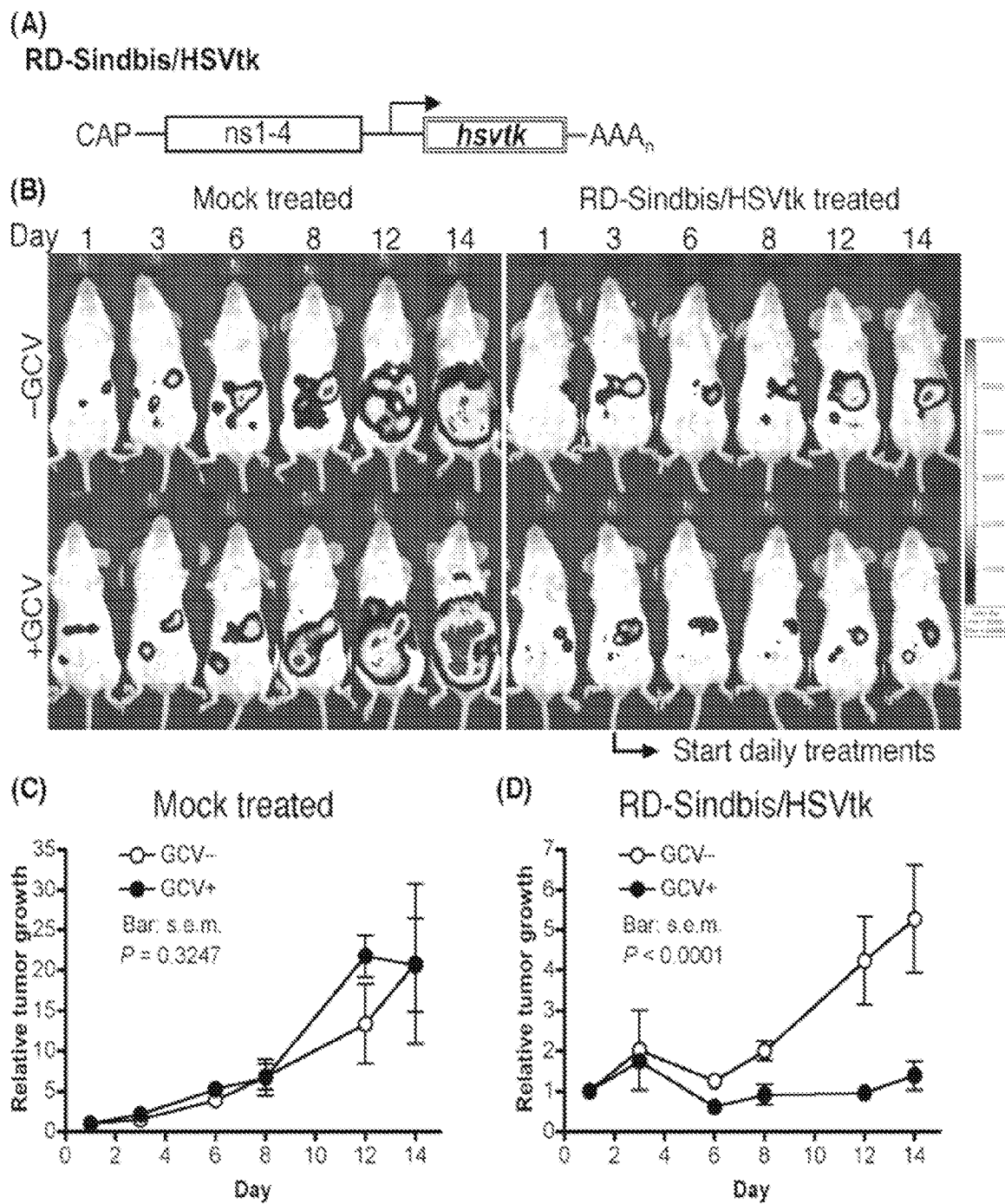


FIGURE 4

