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(54) Title: MODIFIED RECOMBINASE

(57) Abstract: The present invention concerns a fusion protein comprising a recombinase protein, preferably the site-specific DNA recombinase C31-Int of phage (C31, and a peptide sequence which directs the nuclear uptake of the fusion protein in eucaryotic cells, and the use of this fusion protein to recombine, invert or delete DNA molecules containing recognition sequences for said recombinase in eucaryotic cells at high efficiency. In addition the invention relates to a cell, preferably a mammalian cell which contains recognition sequences for said recombinase in its genome and wherein the genome is recombined by the action of said fusion protein. Moreover, the invention relates to the use of said cell to study the function of genes and for the creation of transgenic organisms to study gene function at various developmental stages, including the adult. In conclusion, the present invention provides a process which enables the highly efficient modification of the genome of mammalian cells by site-specific recombination.

Modified Recombinase

The present invention concerns a fusion protein comprising a recombinase protein, preferably the site-specific DNA recombinase C31-Int of phage ΦC31, and a peptide sequence which directs the nuclear uptake of the fusion protein in eucaryotic cells, and the use of this fusion protein to recombine, invert or delete DNA molecules containing recognition sequences for said recombinase in eucaryotic cells at high efficiency. In addition the invention relates to a cell, preferably a mammalian cell which contains recognition sequences for said recombinase in its genome and wherein the genome is recombined by the action of said fusion protein. Moreover, the invention relates to the use of said cell to study the function of genes and for the creation of transgenic organisms to study gene function at various developmental stages, including the adult. In conclusion, the present invention provides a process which enables the highly efficient modification of the genome of mammalian cells by site-specific recombination.

Background of the invention

The controlled and permanent modification of the genome of eucaryotic cells and organisms is an important method for research applications, e.g. for studying gene function, for medical applications like gene therapy and the creation of disease models and for the design of economically important animals and crops. The basic methods for genome manipulations by the engineering of endogenous genes through gene targeting in murine embryonic stem (ES) cells are well established and used since many years (Capecchi, Trends in Genetics, 5, 70-76 (1989)). Since ES cells can pass mutations induced in vitro to transgenic offspring in vivo it is possible to analyse the consequences of gene disruption in the context of the entire organism. Thus, numerous mouse strains with functionally inactivated genes ("knock-out mice") have been created by this technology and utilised to study the biological function of a variety of genes (Koller et al., Ann. Rev. Immunol., 10, 705 - 730 (1992)). More importantly, mouse mutants created by this procedure (also known as "conventional, complete or classical mutants"), contain the inactivated gene in all cells and

tissues throughout life. Thus, classical mouse mutants represent the best animal model for inherited human diseases as the mutation is introduced into the germline but are not the optimal model to study gene function in adults, e.g. to validate potential drug target genes.

A refined method of targeted mutagenesis, referred to as conditional mutagenesis, employs the Cre/loxP site-specific recombination system which enables the temporally and/or spatially restricted inactivation of target genes in cells or mice (Rajewsky et al., J. Clin. Invest., 98, 600 - 603 (1996)). The phage P1 derived Cre recombinase recognises a 34 bp sequence referred to as loxP site which is structured as an inverted repeat of 13 bp separated by an asymmetric 8 bp sequence which defines the direction of the loxP site. If two loxP sites are located on a DNA molecule in the same orientation the intervening DNA sequence is excised by Cre recombinase from the parental molecule as a closed circle leaving one loxP site on each of the reaction products (Kilby et al., TIG, 9, 413-421 (1993)). The creation of conditional mouse mutants initially requires the generation of two mouse strains, one containing two or more Cre recombinase recognition (loxP) sites in its genome while the other harbours a Cre transgene. The former strain is generated by homologous recombination in ES cells as described above, except that the exon(s) of the target gene is (are) flanked by two loxP sites which reside in introns and do not interfere with gene expression. The Cre transgenic strain contains a transgene whose expression is either constitutively active in certain cells and tissues or is inducible by external agents, depending on the promoter region used. Crossing of the loxP-flanked mouse strain with the Cre recombinase expressing strain enables the deletion of the loxP-flanked exons in the genome of doubly transgenic offspring in a prespecified temporally and/or spatially restricted manner. Thus, the method allows the analysis of gene function in particular cell types and tissues of otherwise widely expressed genes. Moreover, it enables the analysis of gene function in the adult organism by circumventing embryonic lethality which is often the consequence of complete (germline) gene inactivation. For pharmaceutical research, aiming to validate the utility of genes and their products for drug development, gene inactivation which is inducible in adults provides an excellent genetic tool as this mimicks the biological effects of target inhibition upon drug application.

Since the first description of the concept of conditional gene targeting using the Cre/loxP system in mice in 1994 (Gu et al., Science 265, 103-106 (1994)) this method became increasingly popular among the research community and resulted in a broad collection of genetic tools for biological research in the mouse. More than 30 Cre transgenic mouse strains with various tissue specificities for gene inactivation have been created, including several "deleter" strains which allow to remove the loxP-flanked target gene segment in the male or female germline (Cohen-Tannoudji et al., Mol. Hum. Reprod. 4, 929-938 (1998); Metzger et al., Curr. Op. Biotech., 10, 470-476 (1999)). The need to characterise the expression pattern of Cre mediated recombination in newly generated strains stimulated the construction of a number of "Cre-reporter" strains which harbour a silent reporter gene the expression of which is activated upon Cre-mediated deletion (Nagy, Genesis, 26, 99-109 (2000)). Conditional mouse mutants have been reported for about 20 different genes, many of them could not be studied in adults as their complete inactivation leads to embryonic lethality (Cohen-Tannoudji et al., Mol. Hum. Reprod. 4, 929-938 (1998)).

Great efforts have also been made to control the expression of Cre recombinase in an inducible fashion in mice. After the first demonstration that inducible gene knock-out is feasible in adult mice using an interferon controlled promoter (Kühn et al., Science, 269, 1427-1429 (1995)), mainly two methods were applied to control the activity of Cre recombinase. First, it has been demonstrated that the fusion of Cre with the ligand binding domain of a mutant estrogen receptor allows to control recombinase activity by a specific steroid-like inducer. Several transgenic mouse strains expressing such a fusion protein have been generated and allow to induce gene inactivation in specific tissues (Metzger et al., Curr. Op. Biotech., 10, 470-476 (1999)). Furthermore, the tetracycline-regulated gene expression system has been successfully used to control the expression of Cre in transgenic mice and thus provides a second system for inducible gene inactivation using doxycycline as inducer (Saam et al., J. Biol. Chem. 274, 38071-38082 (1999)).

In addition to the application of Cre/loxP for gene inactivation by deletion of a gene segment this recombination system has been proved to be useful also for a number of other genomic manipulations in ES cells or mice. These include the

conditional activation of transgenes in mice, chromosome engineering to obtain deletion, translocation or inversion, the simple removal of selection marker genes, gene replacement, the targeted insertion of transgenes and the (in)activation of genes by inversion (Nagy, Genesis, 26, 99-109 (2000); Cohen-Tannoudji et al., Mol. Hum. Reprod. 4, 929-938 (1998)). In conclusion, the Cre/loxP recombination system has been proven to be extremely useful for the analysis of gene function in mice by broadening the methodological spectrum for genome engineering. It can be expected that many of the protocols now established for the mouse may be applied in future also to other animals or plants.

In contrast to the huge diversity of genome manipulations which have been developed for the Cre/loxP system, very limited efforts have been made to develop further site-specific recombination systems for the use in mammalian cells. Alternative recombination systems of different specificity but with an efficiency comparable to Cre/loxP could further enhance the flexibility of genome engineering by the side to side use of two or more systems in the same cell or organism. Furthermore, unidirectional recombination systems which follow a different mechanism than the reversible Cre/loxP-mediated recombination should allow to develop new applications for genome engineering which cannot be performed with the current systems.

The reasons for the almost exclusive use of the Cre/loxP system for site-specific recombination in mammalian cells are readily explained by a number of requirements which must be fulfilled for the efficient use of a recombinase in mammalian cells:

i) the recombinase should act independent of cofactors like helper proteins,

ii) it should act independent of the supercoiling status of the target DNA and also on mammalian chromatin,

iii) it should be efficiently active and stable at a temperature of 37°C, and

iv) it should recognize a target sequence which is sufficiently long to be unique among large genomes, and it should exhibit a very high affinity to its target site for efficient action (Kilby et al., TIG, 9, 413-421 (1993)).

Among the more than 200 described members of the integrase and resolvase/invertase recombinase families only the Cre/loxP system is presently known to fulfill all of these requirements (Nunes-Düby et al., Nucleic Acids Res., 26, 391-406 (1998); Kilby et al., TIG, 9, 413-421 (1993); Ringrose et al., J. Mol. Biol., 284, 363 - 384 (1998)). Besides Cre/loxP a few recombinases have been shown to exhibit some activity in mammalian cells but their practical value is presently unclear as their efficieny has not been compared to the Cre/loxP system on the same genomic recombination substrate and in some cases it is known that one or more of the criteria listed above are not met. The best characterised examples are the yeast derived FLP and Kw recombinases which exhibit a temperature optimum at 30°C but which are unstable at 37°C (Buchholz et al., Nature Biotech., 16, 657 - 662 (1998); Ringrose et al., Eur. J. Biochem., 248, 903 - 912). For FLP it has been shown in addition that its affinity to the FRT target site is much lower as compared to the affinity of Cre to loxP sites (Ringrose et al., J. Mol. Biol., 284, 363 - 384 (1998)). Other recombinases which show in principle some activity in mammalian cells are a mutant integrase of phage λ, the integrases of phages ΦC31 and HK022, mutant γδ-resolvase and β-recombinase (Lorbach et al., J. Mol. Biol., 296, 1175 - 81 (2000); Groth et al., Proc. Natl. Acad. Sci. USA, 97, 5995 - 6000 (2000); Kolot et al., Mol. Biol. Rep. 26, 207 - 213 (1999); Schwikardi et al., FEBS Lett., 471, 147 - 150 (2000); Diaz et al., J. Biol. Chem., 274, 6634 - 6640 (1999)). Other phage integrase systems include coliphage P4 recombinase, Listeria phage recombinase, bacteriophage R4 Sre recombinase, CisA recombinase, XisF recombinase and transposon Tn*4451* TnpX recombinase (Stark et al. Trends in Genetics 8, 432-439 (1992); Hatfull & Gridley, in Genetic Recombination. Eds. Kucherlipati & Smith, Am. Soc. Microbiol., Washington DC, 357-396 (1988)).

However, the practical value of these recombinases and integrases for use in mammalian cells is limited as their efficiency to recombine mammalian genomic DNA has not been tested or compared with the Cre/loxP system. From the data available it can be assumed that these recombinases are much less effective than the Cre/loxP system.

In a few cases attempts have been made to improve the performance of recombinases in mammalian cells: for FLP a mutant showing improved thermostability and acticity at 37°C has been isolated but this mutant is still considerably more heat labile as compared to Cre (Buchholz et al., Nature Biotech., 16, 657 - 662 (1998)). In the case of λ-integrase and γδ-resolvase the absolute requirement for coproteins and supercoiled DNA could be eliminated by the introduction of specific point mutations (Schwikardi et al. FEBS Lett 471, pp147-50 (2000)).

The import of cytoplasmic proteins into the nucleus of eucaryotic cells through nuclear pores is a regulated, energy dependent process mediated by specific receptors (Görlich et al., Science, 271, 1513 - 1518 (1996)). Proteins which do not posses a signal sequence recognised by the nuclear import machinery are excluded from the nucleus and remain in the cytoplasm. Numerous of such nuclear localisation signal sequences (NLS), which share a high proportion of basic amino acids in common, have been characterised (Boulikas, Crit. Rev. Eucar. Gene Expression, 3, 193 - 227 (1993)), the prototype of which is the 7 amino acid NLS derived from the T-antigen of the SV40 virus (Kalderon et. al, Cell, 39, 499 - 509 (1984)).

It was believed that the fusion of such an NLS peptide to a recombinase possibly would enhance the efficiency of the recombinase by mediating its import into the nucleus and therewith increasing the concentration of the recombinase inside the nucleus. However, for Cre recombinase it has been shown that the addition of the SV-40 T-antigen NLS does not improve its recombination efficiency in mammalian cells (Le et al., Nucleic Acid Res., 27, 4703 -4709 (1999)). Nevertheless, both Cre and a Cre-NLS-fusion protein are widely used. Schwikardi (Schwikardi et al., FEBS Lett. 471, pp147-50 (2000)) reported a γδ-resolvase-SV-40 T-antigen NLS fusion protein, which also did not enhance the recombination efficiency.

The level of activity exhibited by recombinases of diverse prokaryotic origin in mammalian cells may be the result of the intrinsic properties of an enzyme depending on parameters like its temperature optimum, its target site affinity, protein structure and stability, the degree of cooperativity, the stability of the

synaptic complex and the dependence on coproteins or supercoiled DNA. Within the specific environment of mammalian cells the activity of a prokaryotic recombinase could be limited by additional factors such as a short half-life of the recombinase transcript, a short half-life of its protein, its inability to act on histone-complexed and higher order structured mammalian genomic DNA, exclusion from the nucleus or the recognition of cryptic splice sites within its mRNA resulting in a nonfunctional transcript. Due to the lack of information on the parameters listed above for almost all recombinases it is presently not possible to rationally optimise their performance in mammalian cells.

Summary of the Invention

The object to be solved by the invention of the present application is the provision of a recombination system alternative to the Cre/loxP system, which has a different specificity but an efficiency comparable to Cre/loxP. Such an alternative recombination system is particularly desirable for all those applications which require more than one potent recombination system for being successfully carried out (e.g. the methods disclosed in PCT/EP01/00060 and PCT/EP00/10162). Most surprisingly, it was found that the above object can be solved by fusing a signal peptide capable directing the nuclear import (hereinafter shortly referred to as nuclear localisation signal sequences (NLS)) to specific recombinases.

In contrast to the wildtype recombinases, the resulting modified recombinases allow a highly efficient recombination of extrachromosomal and chromosomal DNA in mammalian cells, and a highly efficient excision of extrachromosomal and chromosomal DNA-stretches, which are flanked by suitable recognition sites for said modified recombinases.

The present invention thus provides:

(1) A fusion protein (hereinafter also referred to as "modified recombinase") comprising

(a) a recombinase domain comprising a recombinase protein or fragment thereof and

(b) a signal peptide domain being linked to (a) and directing the nuclear import

of said fusion protein in eucaryotic cells,
preferably the activity of the fusion protein in eucaryotic cells is significantly higher as compared to the acitivity of the wildtype recombinase corresponding to the recombinase of the recombinase domain;

(2) in a preferred embodiment of the fusion protein defined in (1) above, the recombinase domain comprises an integrase protein, preferably a phage ΦC31 integrase (C31-Int) protein or a mutant thereof;

(3) a DNA coding for the fusion protein as defined in (1) or (2) above;

(4) a vector containing the DNA as defined in (3) above;

(5) a microorganism containing the DNA of (3) above and/or the vector of (4) above;

(6) a process for preparing the fusion protein as defined in (1) or (2) above which comprises culturing a microorganism as defined in (5) above;

(7) the use of the fusion protein as defined in (1) or (2) above to recombine DNA molecules, which contain recombinase recognition sequences for the recombinase protein of the recombinase domain, in eucaryotic cells;

(8) a cell, preferably a mammalian cell containing the DNA sequence of (3) above in its genome;

(9) the use of the cell of (8) above for studying the function of genes and for the creation of transgenic organisms;

(10) a transgenic organism, preferably a transgenic mammal containing the DNA sequence of (3) above in its genome;

(11) the use of the transgenic organism of (10) above for studying gene function at various developmental stages; and

(12) a method for recombining DNA molecules of cells or organisms containing recognition sequences for the recombinase protein of the recombinase domain as defined in (1) or (2) above, which method comprises supplying the cells or organisms with a fusion protein as defined in (1) or (2) above, or with a DNA sequence of (3) above and/or a vector of (4) above which are capable of expressing said fusion protein in the cell or organism.

The present invention combines the use of prokaryotic recombinases such as the C31-Int with a eukaryotic signal sequence which increases its efficiency in mammalian cells such that it is equal to the widely used Cre/loxP recombination system. The improved recombination system of the present invention provides

an alternative recombination system for use in mammalian cells and organisms which allows to perform the same types of genomic modifications as shown for Cre/loxP, including conditional gene inactivation by recombinase-mediated deletion, the conditional activation of transgenes in mice, chromosome engineering to obtain deletion, translocation or inversion, the simple removal of selection marker genes, gene replacement, the targeted insertion of transgenes and the (in)activation of genes by inversion.

Short Description of Figures

Fig. 1: C31-Int and Cre recombinase expression vectors and a recombinase reporter vector used for transient and stable transfections

Fig. 2: Results of transient transfections of C31 Int and Cre expression vectors and reporter vectors into CHO cells.

Fig. 3: Results of transient transfections of XisA and Ssv recombinase expression vectors with and without nuclear localisation signals and reporter vectors into CHO cells.

Fig. 4: Results of transient transfections of C31-Int and Cre recombinase vectors into a stable reporter cell line.

Fig. 5: In situ detection of ß-galactosidase in 3T3(pRK64)-3 cells transfected with recombinase expression vectors

Fig. 6: Test vector for C31-Int mediated deletion, pRK64, and the expected deletion product.

Fig. 7: PCR products generated with the primers P64-1 and P64-4 and sequence comparison.

Fig. 8: ROSA26 locus of the C31 reporter mice carrying a C31 reporter construct.

Fig. 9: *In situ* detection of β-galactosidase in a cryosection of the testis of: (A) a double transgenic mouse carrying both the recombinase and the reporter; and

(B) a transgenic mouse carrying only the reporter as a control.

Detailed Description of the Invention

The "organisms" according to the present invention are multi-cell organisms and can be vertebrates such as mammals (humans and non-human animals including rodents such as mice or rats) or non-mammals (e.g. fish), or can be invertebrates such as insects or worms, or can be plants (higher plants, algi or fungi). Most preferred living organisms are mice and fish.

"Cells" and "eucaryotic cells" according to the present invention include cells isolated from the above defined living organism and cultured *in vitro*. These cells can be transformed (immortalized) or untransformed (directly derived from the living organism; primary cell culture).

"Microorganism" according to the present invention relates to procaryotes (e.g. *E. coli*) and eucaryotic microorganisms (e.g. yeasts).

According to embodiment (1) of the present invention, the activity of the fusion protein in eucaryotic cells is significantly higher as compared to the acitivity of the wildtype recombinase corresponding to the recombinase of the recombinase domain. A "significantly higher activity" in accordance with the present invention refers to an increase in activity of at least 50%, preferably at least 75%, more preferably at least 100% relative to the corresponding wildtyp recombinase in eucaryotic cells. A "significantly higher activty" also implies that the resulting fusion protein has at least 25%, preferably at least 50% and more preferably at least 75%, of the activity of Cre/loxP in 3T3 cells with a stably integrated target sequence.

Recombinase proteins which can be used in the recombinase domain of the fusion protein of the present invention (i.e., giving a fusion having a "significantly higher activty" as defined above) include , but are not limited to, a certain type of recombinases belonging to the family of of large serine recombinases (Thorpe et al., Control of directionalty in the site-specific recombination system of the streptomyces phage ϕC31, Molecular Microbiology 38(2), 232-241 (2000)). This family includes bacteriophage ΦC31 integrase ("C31-Int"; the amino acid

sequence of said integrase and a DNA sequence coding therefor are shown in SEQ ID NOs:21 and 20, respectively), coliphage P4 recombinase, Listeria phage recombinase, bacteriophage R4 Sre recombinase ("R4 Sre" deposited under GI 793758; the amino acid sequence of said recombinase and a DNA sequence coding therefor are shown in SEQ ID NOs:55 and 54, respectively), bacillus subtilis CisA recombinase ("CisA" deposited under GI 142689; the amino acid sequence of said recombinase and a DNA sequence coding therefor are shown in SEQ ID NOs:57 and 56, respectively), XisF recombinase from annabaena sp. Strain PCC 7120 (Cyanobacterium; "XisF" deposited under GI 349678; the amino acid sequence of said integrase and a DNA sequence coding therefor are shown in SEQ ID NOs:59 and 58, respectively), transposon Tn*4451* TnpX recombinase ("TnpX" deposited under GI 551135; the amino acid sequence of said recombinase and a DNA sequence coding therefor are shown in SEQ ID NOs:61 and 60, respectively), "XisA" recombinase from annabaena sp. Strain PCC 7120 (Cyanobacterium; the amino acid sequence of said recombinase and a DNA sequence coding therefor are shown in SEQ ID NOs:63 and 62, respectively), "SSV" recombinase from phage of sulfolobus shibatae (the amino acid sequence of said recombinase and a DNA sequence coding therefor are shown in SEQ ID NOs:65 and 64, respectively), lactococcal bacteriophage TP901-1 recombinase (TP901-1 complete genome deposited under GI 13786531; the amino acid sequence of said recombinase and a DNA sequence coding therefor are shown in SEQ ID NOs:108 and 107, respectively), and the like, or mutants thereof. Other procaryotic recombinases known in the art are also applicable.

A "mutant" of the above recombinases in accordance with the present invention relates to a mutant of the respective original (viz. wild-type) recombinase having a recombinase activity similar (e.g. at least about 90%) to that of said wild-type recombinase. Mutants include truncated forms of the recombinase (such as N- or C-terminal truncated recombinase proteins), deletion-type mutants (where one or more amino acid residues or segments having more than one continuous amino acid residue have been deleted from the primary sequence of the wildtyp recombinase), replacement-type mutants (where one or more amino acid residues or segments of the primary sequence of the wildtyp recombinase have been replaced with alternative amino acid residues or segments), or combinations thereof.

According to embodiment (2) of the invention, the recombinase domain comprises an integrase protein, preferably a phage ΦC31 integrase (C31-Int) protein or a mutant thereof. Thus, the present invention provides a fusion protein comprising

(a) an integrase domain being a C31-Int protein or a mutant thereof, and

(b) a signal peptide domain being linked to (a) and directing the nuclear import of said fusion protein into eucaryotic cells.

In the fusion protein of embodiment (2), the integrase domain is preferably a C31-Int having the amino acid sequence shown in SEQ ID NO:21 or a C-terminal truncated form thereof. Suitable truncated forms of the C31-Int comprise amino acid residues 306 to 613 of SEQ ID NO:21.

The signal peptide domain (hereinafter also referred to as "NLS") is preferably derived from yeast GAL4, SKI3, L29 or histone H2B proteins, polyoma virus large T protein, VP1 or VP2 capsid protein, SV40 VP1 or VP2 capsid protein, Adenovirus E1a or DBP protein, influenza virus NS1 protein, hepatitis virus core antigen or the mammalian lamin, c-myc, max, c-myb, p53, c-erbA, jun, Tax, steroid receptor or Mx proteins (see Boulikas, Crit. Rev. Eucar. Gene Expression, 3, 193 - 227 (1993)), simian virus 40 ("SV40") T-antigen (Kalderon et. al, Cell, 39, 499 – 509 (1984)) or other proteins with known nuclear localisation. The NLS is preferably derived from the SV40 T-antigen.

Furthermore, the signal peptide domain preferably has a length of 5 to 74, preferably 7 to 15 amino acid residues. More preferred is that the signal peptide domain comprises a segment of 6 amino acid residues wherein at least 2 amino acid residues, preferably at least 3 amino acid residues are positively charged basic amino acids. Basic amino acids include, but are not limited to, Lysin, Arginin and Histidine. Particularly preferred signal peptides are show in the following table.

Organism	Sequence/(SEQ ID NO:)	
yeast GAL4	MKx11CRLKKLKCSKEKPKCAKCLKx5Rx3KTKR	(24)
yeast SKI3	IKYFKKFPKD	(25)

yeast L29	MTGSKTRKHRGSGA	(26)
	(MTGSKHRKHPGSGA)	(27)
yeast histone H2B	(GKKRSKA)	(28)
polyoma virus large T protein	(PKKAREDVSRKRPR)	(29)
polyoma virus VP1 capsid protein	(APKRKSGVSKC)	(30)
polyoma virus VP2 capsid protein	(EEDGPQKKKRRL)	(31)
SV40 VP1 capsid protein	(APTKRKGS)	(32)
SV40 VP2 capsid protein,	(PNKKKRK)	(33)
Adenovirus E1a protein	(KRPRP)	(34)
	(CGGLSSKRPRP)	(35)
Adenovirus DBP protein	(PPKKRMRRRIEPKKKKKRP)	(36)
influenza virus NS1 protein	(PFLDRLRRDQK)	(37)
	(PKQKRKMAR)	(38)
human laminA	(SVTKKRKLE)	(39)
human c-myc	(CGGAAKRVKLD)	(40)
	(PAAKRVKLD)	(41)
	(RQRRNELKRSP)	(42)
HUMAN max	(PQSRKKLR)	(43)
HUMAN c-myb	(PLLKKIKQ)	(44)
HUMAN p53	(PQPKKKP)	(45)
HUMAN c-erbA	(SKRVAKRKL)	(46)
VIRAL jun	(ASKSRKRKL)	(47)
HUMAN Tax	(GGLCSARLHRHALLAT)	(48)
Mammalian glucocorticoid receptor	(RKTKKKIK)	(49)
HUMAN ANDROGEN RECEPTOR	(RKLKKLGN)	(50)
MAMMALIAN ESTROGEN RECEPTOR	(RKDRRGGR)	(51)
Mx proteins	(DTREKKKFLKRRLLRLDE)	(52)
SV40 T-antigen	(PKKKRKV)	(53)

The most preferred signal peptide domain is that of SV40 T-antigen having the sequence Pro-Lys-Lys-Lys-Arg-Lys-Val.

The signal peptide domain may be linked to the N-terminal or C-terminal of the integrase domain or may be integrated into the integrase domain, preferably the signal peptide domain is linked to the C-terminal of the integrase domain. With

regard to phage ΦC31 integrase protein of embodiment (2) of the invention it was found that the fusion of an NLS-peptide to the C-terminus of the integrase provided a much higher increase of activity as compared to the fusion of the same NLS-peptide to the N-terminus of the integrase (see Example 1, figures 3 and 4).

According to the present invention, the signal peptide domain may be linked to the integrase domain directly or through a linker peptide. Suitable linkers include peptides having from 1 to 30, preferably 1 to 15 amino acid residues, said amino acid residues being essentially neutral amino acids such as Gly, Ala and Val.

The most preferred fusion protein of the present invention comprises the amino acid sequence shown in SEQ ID NO:23 (a suitable DNA sequence coding for said fusion protein being shown in SEQ ID NO:22).

Further preferred fusion proteins of the present invention are "NLS-XisA" and "NLS-SSV" (having the NLS-peptide fused to the N-terminus of the recombinases) as shown in SEQ ID NO:67 and 69, respectively (suitable DNA sequences coding for said fusion proteins being shown in SEQ ID NO:66 and 68, respectively).

In embodiments (7), (8), (10) and (12) of the invention the DNA molecules, the cell or transgenic organism may also contain recognition sequences for the recombinase protein of the recombinase domain. Thus, when utilizing the fusion protein of embodiment (2), the C31-Int recognition sequences attP and attB are present in DNA molecules, the cell or transgenic organism.

The term "mammal" as used in embodiment (10) of the invention includes non-human mammals (viz. animals as defined above) and humans (if such subject matter is patentable with the respective patent authority).

Since the modified recombinase of the invention, in particular the modified C31-Int, acts in mammalian cells as efficient (or at least almost as efficient) as the widely used Cre/loxP system it can be used for a large variety of genomic modifications (including the methods disclosed in PCT/EP01/00060 and

PCT/EP00/10162, the content of which is herewith incorporated by reference). Concerning embodiment (11) it is to be noted that the mammals of embodiment (10) can be used to study the function of genes, e.g. in mice, by conditional gene targeting. For this purpose suitable recognition sequences - when utilizing the fusion protein of embodiment (2), one attP and one attB site (C31-Int recognition sequences) in the same orientation - can be introduced into introns of a gene by homologous recombination of a gene targeting vector in ES cells such that the two sites flank one or more exons of the gene to be studied but do not interfere with gene expression. A selection marker gene, needed to isolate recombinant ES cell clones, can be flanked by two recognition sites of another recombinase such as loxP or FRT sites to enable deletion of the marker gene upon transient expression of the respective recombinase in ES cells. These ES cells can be used to generate germline chimaeric mice which transmit the target gene modified by att sites to their offspring and allow to establish a modified mouse strain. The crossing of this strain with a C31-Int recombinase transgenic line or the application of C31-Int protein will result in the deletion of the att-flanked gene segment from the genome of doubly transgenic offspring and the inactivation of the target gene in doubly transgenic offspring in a prespecified temporally and/or spatially restricted manner. The C31-Int transgenic strain contains a transgene whose expression is either constitutively active in certain cells and tissues or is inducible by external agents, depending on the promoter region used. If an attB and an attP site are placed into the genome in opposite orientation C31-Int mediated recombination results in the irreversible inversion of the flanked gene segment leading the functional loss of on or more exons of the target gene. Thus, the method allows the analysis of gene function in particular cell types and tissues of otherwise widely expressed genes and circumvents embryonic lethality which is often the consequence of complete (germline) gene inactivation. For the validation of genes and their products for drug development, gene inactivation which is inducible in adults provides an excellent genetic tool as this mimicks the biological effects of target inhibition upon drug application. If a pair of attB/P sites is placed in the same or opposite orientation into a chromosome at large distance using two gene targeting vectors, C31-Int recombination allows to delete or invert chromosome segments containing one or more genes, or chromosomal translocations if the two sites are located on different chromosomes. In another application of the method a pair of attB/P sites is

placed in the same orientation within a transgene such that the deletion of the att-flanked DNA segment results in gene expression, e.g. of a toxin or reporter gene for cell lineage studies, or in the inactivation of the transgene.

In addition, according with embodiment (12) of the invention, the recombination system of embodiment (1), in particular the C31-Int recombination system of embodiment (2), can also be used for the site specific integration of foreign DNA into the genome of mammalian cells, e.g. for gene therapy. For this purpose, and if the C31-Int recombination system of embodiment (2) is utilized, only one attB (or attP) site is initially introduced into the genome by homologous recombination, or an endogenous genomic sequence which resembles attB or attP is used . The application of a vector containing an attP (or attB) site to such cells or mice in conjunction with the expression of C31-Int recombinase will lead to the site specific integration of the vector into the genomic att site.

Thus, the present invention provides a process which enables the highly efficient modification of the genome of mammalian cells by site-specific recombination. Said process possesses the following advantages over current technology:

(i) the modified recombinase, in particular the modified C31-Integrase, allows to recombine extrachromosomal and genomic DNA in mammalian cells at much higher efficiency as compared to the use of its wildtype form;

(ii) the modified recombinase, in particular the modified C31-Integrase, is the first described alternative recombination system with equal efficiency to Cre/loxP for the recombination of chromosomal DNA in mammalian cells.

The appended figures further explain the present invention:

Figure 1 shows C31-Int and Cre recombinase expression vectors and a recombinase reporter vector used for transient and stable transfections.
A-D: Mammalian expression vectors for recombinases which contain the CMV immediate early promoter followed by a hybrid intron, the coding region of the recombinase to be tested, and an artificial polyadenylation signal sequence (pA).

A: pCMV-C31Int(wt) containing the nonmodified (wildtype) 1.85 kb coding region of C31-Int as found in the genome of phage ΦX31.

B: pCMV-C31Int(NNLS) containing a modified C31-Int gene coding for the full length C31-Int protein with a N-terminal fusion to the SV40 virus large T antigen nuclear localisation signal (NLS).

C: pCMV-C31Int(CNLS) containing a modified C31-Int gene coding for the full length C31-Int protein with a C-terminal fusion to the SV40 virus large T antigen nuclear localisation signal (NLS).

D: pCMV-Cre contains the 1.1 kb Cre coding region with an N-terminal fusion to the SV40 T antigen NLS.

E: Recombination substrate vector pRK64 contains a SV40 promoter region followed by a 1.1 kb cassette consisting of the coding region of the puromycin resistance gene and a polyadenylation signal sequence, flanked 5` by the 84 bp attB and 3´ by the 84 bp attP recognition site of C31-Int. pRK64 contains in addition two Cre recognition (loxP) sites in direct orientation next to the att sites.

Figure 2 shows results of transient transfections of C31-Int and Cre recombinase and reporter vectors into CHO cells.

All transfections were performed with a fixed amount of the reporter plasmid pRK64 and 0.5 ng or 1 ng of the recombinase expression plasmids pCMV-C31-Int(wt) (samples 4-5), pCMV-C31-Int(NNLS) (samples 6-7), pCMV-C31-Int(CNLS) (samples 8-9) or pCMV-Cre (samples 10-11). Negative controls: transfection with pRK64 (sample 3) or pUC19 alone (sample 1). Positive control: transfection with the Cre-recombined reporter pRK64(ΔCre) (sample 2).

The vertical rows show the mean values and standard deviation of "Relative Light Units" obtained from lysates with the assay for ß-galactosidase (RLU (ß-Gal)), the RLU from the assay for Luciferase, the ratio of the ß-galactosidase and Luciferase values with standard deviation (RLU x 10^5 (Gal/Luc)), and the relative activity of the various recombinases as compared to the positive control defined as 1.

Figure 3 shows results of transient transfections of XisA and Ssv recombinases and reporter vectors into CHO cells.

All transfections were performed with fixed amounts of the reporter plasmids pPGKnif (for XisA) and pPGKattA (for SSV) and 25 ng or 100 ng of the

recombinase expression plasmids pCMV-XisA, pCMV-XisA(NNLS) and 10 ng or 20 ng of the expression plasmids pCMV-Ssv and pCMV-Ssv(NNLS). Negative controls: transfection with pPGKnif or pPGKattA alone.

The vertical rows show the mean values and standard deviation of "Relative Light Units" obtained from lysates with the assay for ß-galactosidase (RLU (ß-Gal)), the RLU from the assay for Luciferase, the ratio of the ß-galactosidase and "Luciferase" values with standard deviation (RLU x 10^5 (Gal/Luc)).

Figure 4 shows results of transient transfections of recombinase vectors into a stable reporter cell line.

All transfections were performed with a NIH 3T3 derived clone containing stably integrated copies of the pRK64 recombination substrate vector. Either 32 ng or 64 ng of the recombinase expression plasmids pCMV-C31-Int(wt) (samples 2-3), pCMV-C31-Int(NNLS) (samples 4-5), pCMV-C31-Int(CNLS) (samples 6-7) or pCMV-Cre(NNLS) (samples 8-9). Negative control: transfection with pUC19 alone (sample 1).

The vertical rows show the mean values and standard deviation of "Relative Light Units" obtained from lysates with the assay for ß-galactosidase (RLU (ß-Gal)) and the relative activity of the various recombinases as compared to the value obtained with pCMV-Cre(NNLS) defined as 1.

Figure 5 shows the in situ detection of ß-galactosidase in 3T3(pRK64)-3 cells transfected with recombinase expression vectors.

The Cre and C31-Int recombinase reporter cell line 3T3(pRK64)-3 was either not transfected with DNA (A), transfected with the Cre expression vector pCMV-Cre (B) or with the C31-Int expression vector pCMV-C31-Int(CNLS). Two days after tranfection the cells were fixed and incubated with the histochemical X-Gal assay which develops a blue stain in ß-galactosidase positive cells indicating recombinase mediated activation of the reporter gene.

Figure 6 shows the test vector for C31-Int mediated deletion, pRK64, and the expected product of deletion, pRK64(ΔInt).

Plasmid pRK64 contains the 1.1 kb cassette of the coding region of the puromycin resistance gene and a polyadenylation signal, which is flanked 5` by the 84 bp attB and 3´ by the 84 bp attP recognition site (large triangles) of C31-

Int. These attB and attP sites are oriented in the same way to each other (thick black arrows) which is used by the ΦX31 phage to integrate into the bacterial genome. In addition, the cassette is flanked by two Cre recombinase recognition (loxP) sites in the same orientation (black small triangles). For better orientation the half sites of the att sequences are labelled by a direction (thin arrow) and numbered 1-4. The 3 bp sequence within the att sites at which recombination occurs is framed by a box. The positions at which the PCR primers P64-1 and P64-4 hybridise to the pRK64 vector are indicated by arrows, pointing into the 3` direction of both oligonucleotides.

PRK64(ΔInt) depicts the deletion product expected from the C31-Int mediated recombination between the att sites of pRK64. The recombination between a pair of attB/attP sites generates an attR site remaining on the parental DNA molecule while the puromycin cassette is excised. In this configuration the primers P64-1 and P64-4 will amplify a PCR product of 630 bp from pRK64(ΔInt).

Figure 7 shows PCR products generated with the primers P64-1 and P64-4 and a sequence comparison of the PCR product.

A: Analysis of PCR products on an agarose gel from PCR reactions using the Primers P64-1 and P64-4 on DNA extracted from MEF5-5 cells transfected 2 days before with plasmid pRK64 alone (lane 4), with pRK64 + CMV-Cre (lane 3), with pRK64 + pCMV-C31-Int(wt) (lane 2), and from a control reaction which did not contain cellular DNA (lane 1). The product with an apparent size around 650 bp, as compared to the size marker used, from lane 2 was excised from the agarose gel and purified. The PCR product was cloned into a sequencing plasmid vector and gave rise to the plasmid pRK80d. The insert of this plasmid was sequenced using reverse primer (seq80d) and compared to the predicted sequence of the pRK64 vector after C31-Int mediated deletion of the att flanked cassette, pRK64(ΔInt). The cloned PCR product shows a 100% identity with the predicted attR sequence after deletion. The generated attR site is shown in a box, with the same sequence designation used in Figure 5. The nucleotide positions (pos.) of the compared sequences pRK64(ΔInt) and Seq80d are indicated.

Figure 8 shows the modified ROSA26 locus of C31 reporter mice (Seq ID NO:106). A recombination substrate has been inserted in the ROSA26 locus. The substate consists of a splice acceptor (SA) followed by a cassette consisting of

the hygromycin resistance gene driven by a PGK promoter and flanked by the recombination sites attB and attP. In addition the reporter contains two Cre recognition sites (loxP) in direct orientation next to the att sites. This cassette is followed by the coding region for β-galactosidase, which is only expressed when the hygromycin resistance gene has been deleted by recombination.

Figure 9 shows the in situ detection of β-galactosidase activity. A cryosection of the testis of a double transgenic mouse carrying both the C31-int recombinase and the recombination substrate was stained with X-Gal (A). The blue colour indicates recombination of the substrate, which leads to the expression of β-galactosidase. As a control a cryosection of testis of a transgenic mouse carrying only the recombination substrate was stained with X-Gal (B).

The present invention is further illustrated by the following Examples which are, however, not to be construed as to limit the invention.

Examples

Example 1

As compared to Cre recombinase the wildtype form of C31-Int exhibits a significantly lower recombination activity in mammalian cells which falls in the range of 10 – 40% of Cre, depending on the assay system used (see below). As a measure which may increase C31-Int efficiency in eukaryotic cells we designed mammalian expression vectors for N- or C-terminal fusion proteins of C31-Int with a peptide was designed which is recognised by the nuclear import machinery. The recombination efficiency obtained by this modified C31-Int recombinase in mammalian cells was compared side by side to the unmodified (wildtype) form of C31-Int and to Cre recombinase. For the quantification of recombinase activities the expression vectors were transiently introduced into a mammalian cell line together with a reporter vector which contains C31-Int and Cre target sites and leads to the expression of ß-galactosidase upon recombinase mediated deletion of a vector segment flanked by recombinase recognition sites.

A. Plasmid constructions:

Construction of the recombination test vectors pPGKnif and pPGKattA: first a nifD site (Haselkorn, Annu Rev.Genet. 26, 113-130 (1992)) generated by the annealing of the two synthetic oligonucleotides nifD3 (SEQ ID NO:89) and nifD4 (SEQ ID NO:90), was ligated into the BamHI restriction site of the vector PSV-Pax1 (Buchholz et al., Nucleic Acids Res., 24, 4256-4262 (1996)), 3`of its puromycin resistance gene and loxP site, giving rise to plasmid pPGKnifD3' (SEQ ID NO:79). Next, another nifD site, generated by the annealing of the two synthetic oligonucleotides nifD1 (SEQ ID NO:87) and nifD2 (SEQ ID NO:88), was ligated into the BstBI restriction site of plasmid pPGKnifD3', upstream of the puromycin resistance gene and loxP site, giving rise to plasmid pPGKnifD (SEQ ID NO:78). For pPGKattA (Muskhelishvili et al., Mol.Gen.Genet. 237, 334-342 (1993)) first a 352bp-fragment was amplified from genomic DNA from the thermophilic bacterium Sulfolobus shibatae (DSM-5389, DSMZ Braunschweig-Deutsche Sammlung von Mikroorganismen und Zellkulturen GmbH, Mascheroder Weg 1b, D-38124 Braunschweig, Germany) with oligonucleotides SSV5 (SEQ ID NO:96) and SSV6 (SEQ ID NO:97) including restriction sites for BamHI and BstBI. The amplified fragment was cloned into the BamHI site of the vector PSV-Pax1 giving rise to plasmid pPGKattA1 (SEQ ID NO:82), subsequently the same 352 bp-fragment was cloned into the BstBI site of pPGKattA1 giving rise to the plasmid pPGKattA2 (SEQ ID NO:83). The sequence and orientation of both nifD sites and attA sites was confirmed by DNA sequence analysis. In pPGKnifD/pPGKattA2 the newly cloned nifD/attA sites (positions 535-619 and 1722-1787/ positions 6718-7081 and 12-363) are in the same orientation flanking the puromycin resistance gene and the SV40 early polyadenylation sequence. The nifD/attA sites are followed by loxP sites in the same orientation (positions 623 – 656 and 1794 – 1827/ positions 7085-7118 and 369-402). The puromycin cassette is transcribed from the SV40 early enhancer/promoter region and followed by the coding region for E. coli ß-galactosidase and the SV40 late region polyadenylation sequence.

Construction of XisA and SSV expression vectors: First the XisA gene of cyanobacterium PCC7120 was amplified by PCR from genomic DNA from Nostoc strain PCC7120 (CNCM-Collection Nationale de Cultures de Microorganismes, Institut Pasteur, Paris) using the primers XisA1 (SEQ ID NO:84) and XisA3 (SEQ ID NO:86), and XisA1 (SEQ ID NO:84) and XisA2 (SEQ ID NO:85) (with NLS).

The ends of the PCR product were digested with NotI and the product was ligated into plasmid pBluescript II KS, opened with NotI, giving rise to plasmids pRK42a and pRK43 (with NNLS). The DNA sequence of the insert was determined and found to be identical to the published XisA sequence (Genbank GI:3953452) apart from four silent point mutations. The XisA gene was isolated as a 1.4 kb fragment from pRK42a and pRK43 by digestion with NotI and ligated into the generic mammalian expression vector pRK50 (see below), opened with NotI, giving rise to the XisA expression vectors pCMV-XisA (SEQ ID NO:76) and pCMV-XisA(NNLS) (SEQ ID NO:77). pCMV-XisA(wt) contains a Cytomegalovirus immediated early gene promoter (position 1 - 616), a 240 bp hybrid intron (position 716 - 953), the XisA gene (position 974 - 2392), and a synthetic polyadenylation sequence (position 2413 - 2591).

The SSV gene was amplified from genomic DNA from the thermophilic bacterium Sulfolobus shibatae (DSM-5389, DSMZ Braunschweig- Deutsche Sammlung von Mikroorganismen und Zellkulturen GmbH, Mascheroder Weg 1b, D-38124 Braunschweig, Germany) in two PCR steps because of an internal attP sequence. First, two overlapping PCR fragments were created with the oligonucleotides SSV1-1 (SEQ ID NO:91) (or SSV1-2 for the SSV(NNLS) gene) and SSV2 (SEQ ID NO:93) and oligonucleotides SSV3 (SEQ ID NO:94) and SSV4 (SEQ ID NO:95). Using these overlapping fragments as template, a 1000bp fragment containing the complete SSV coding sequence was amplified with primers SSV1-1 (or SSV1-2 for the SSV(NNLS) gene) and SSV4. The 5' 620 bp-fragments of these PCR products were isolated by digestion with NotI-XhoI and cloned into vector pBluescript II KS giving rise to plasmids pRK47 and pRK48 (with NLS). The 3' 380 bp fragment generated by XhoI-digestion was cloned into the XhoI restriction site of vector pBluescript II KS giving rise to the plasmid pBS-SSVs (SEQ ID NO:72). The 380bp SSV-fragment was then isolated by digestion of pBS-SSVs with XhoI and ligated into pRK47 and pRK48 opened by XhoI giving rise to plasmids pBS-SSV3 (SEQ ID NO:70) and pBS-SSV4 (SEQ ID NO:71) (with NLS) containing the complete SSV gene. Sequencing of the plasmids confirmed one point mutation in both plasmids. Therefore 312 bp/ 91 bp fragments generated by digestion with EcoRV-SmaI/ EcoRV-XhoI of another clone of pRK47 were exchanged in plasmids pBS-SSV3/ pBS-SSV4. Sequences were confirmed by sequencing. The SSV gene was isolated from pRK47 and pRK48 by digestion with NotI and KpnI and ligated into the generic mammalian expression vector

pRK50 (see below), opened with NotI and SalI, giving rise to the SSV expression vectors pCMV-SSV(wt) (SEQ ID NO:74) and pCMV-SSV(NNLS) (SEQ ID NO:75).

Construction of the recombination test vector pRK64: first an attB site (Thorpe et al. Proc. Natl. Acad. Sci. USA, 95, 5505 - 5510 (1998)), generated by the annealing of the two synthetic oligonucleotides C31-4 (SEQ ID NO:1) and C31-5 (SEQ ID NO:2), was ligated into the BstBI restriction site of the vector PSV-Pax1 (Buchholz et al., Nucleic Acids Res., 24, 4256-4262 (1996)), 5` of its puromycin resistance gene and loxP site, giving rise to plasmid pRK52. The sequence and orientation of the cloned attB site was confirmed by DNA sequence analysis. Next, an attP site site (Thorpe et al. Proc. Natl. Acad. Sci. USA, 95, 5505 - 5510 (1998)), generated by the annealing of the two synthetic oligonucleotides C31-6 (SEQ ID NO:3) and C31-7-2 (SEQ ID NO:4), was ligated into the BamHI restriction site of plasmid pRK52, downstream of the puromycin resistance gene and loxP site, giving rise to plasmid pRK64 (SEQ ID NO:5). The sequence and orientation of the attP site was confirmed by DNA sequence analysis. In pRK64 the newly cloned attB (position 348 - 431) and attP (position 1534 - 1617) sites are in the same orientation flanking the puromycin resistance gene and the SV40 early polyadenylation sequence. The attB and attP sites are followed by loxP sites in the same orientation (positions 435 - 469 and 1624 - 1658). The puromycin cassette is transcribed from the SV40 early enhancer/promoter region and followed by the coding region for E. coli ß-galactosidase and the SV40 late region polyadenylation sequence.

Construction of C31-Int expression vectors: First the C31-Int gene of phage ΦC31 was amplified by PCR from phage DNA (DSM-49156, DSMZ-Deutsche Sammlung von Mikroorganismen und Zellkulturen GmbH, Mascheroder Weg 1b, D-38124 Braunschweig, Germany) using the primers C31-1 (SEQ ID NO:6) and C31-3 (SEQ ID NO:7). The ends of the PCR product were digested with NotI and the product was ligated into plasmid pBluescript II KS, opened with NotI, giving rise to plasmid pRK40. The DNA sequence of the 1.85 kb insert was determined and found to be identical to the published C31-Int gene (Kuhstoss et al., J. Mol. Biol. 222, 897-908 (1991)), except for an error in the stop codon. This error was repaired by PCR amplification of a 300 bp fragment from plasmid pRK40 using the primers C31-8 (SEQ ID NO:8) and C31-9 (SEQ ID NO:9), which provide a

corrected Stop codon. The ends of this PCR fragment were digested with Eco47III and XhoI, the fragment was ligated into plasmid pRK40 and opened with Eco47III and XhoI to remove the fragment containing the defective stop codon. The resulting plasmid pRK55 contains the correct C31-Int gene as confirmed by DNA sequence analysis.

The C31-Int gene was isolated from pRK55 as 1.85 kb fragment by digestion with NotI and XhoI and ligated into the generic mammalian expression vector pRK50 (see below), opened with NotI and XhoI, giving rise to the C31-Int expression vector pCMV-C31-Int(wt). pCMV-C31-Int(wt) (SEQ ID NO:10) contains a 700 bp cytomegalovirus immediated early gene promoter (position 1 - 700), a 270 bp hybrid intron (position 701 - 970), the C31-Int gene (position 978 - 2819), and a 189 bp synthetic polyadenylation sequence (position 2831 - 3020).

For the construction of pCMV-C31-Int(NNLS) a 1.5 kb fragment was amplified by PCR from phage DNA using oligonucleotides C31-2 (SEQ ID NO:98) and C31-3 (SEQ ID NO:7). The ends of the PCR product were digested with NotI and the product was ligated into plasmid pBluescript II KS, opened with NotI, giving rise to plasmid pRK41 (SEQ ID NO: 99). A 1100 bp fragment generated by digestion of plasmid pRK41 with NcoI and NotI was then ligated into plasmid pRK55 (SEQ ID NO:80), opened with NcoI and NotI, giving rise to the plasmid pRK63 (SEQ ID NO:81). The C31-Int gene with N-terminal NLS was isolated as a 1.8 kb fragment from pRK63 by digestion with NotI and XhoI and ligated into the mammalian expression vector pRK50, opened with NotI and XhoI, giving rise to the C31-Int expression vector pCMV-C31-Int(NNLS). pCMV-C31-Int(NNLS) (SEQ ID NO:73) contains a 700 bp Cytomegalovirus immediated early gene promoter (position 1 - 700), a 270 bp hybrid intron (position 701 - 970), the C31-Int gene with N-terminal NLS (position 976 - 2838), and a 189 bp synthetic polyadenylation sequence (position 2851 - 3040).

For the construction of pCMV-C31-Int(CNLS), the 3`-end of the C31-Int gene was amplified from pCMV-C31-Int(wt) as a 300 bp PCR fragment using the primers C31-8 (SEQ ID NO:8) and C31-2-2 (SEQ ID NO:11). Primer C31-2-2 modifies the 3`-end of the wildtype C31-Int gene such that the stop codon is replaced by a sequence of 21 basepairs coding for the SV40 T-antigen nuclear localisation sequence of 7 amino acids (Prolin-Lysin-Lysin-Lysin-Arginin-Lysin-Valin) (Kalderon et. al, Cell, 39, 499 - 509 (1984)), followed by a new stop

codon. The ends of this 300 bp PCR fragment were digested with with Eco47III and XhoI, the fragment was ligated into plasmid pCMV-C31-Int(wt) and opened with Eco47III and XhoI to replace the 3´-end of the wildtype C31-Int gene resulting in the plasmid pCMV-C31-Int(CNLS). The identity of the new gene segment was verified by DNA sequence analysis. pCMV-C31-Int(CNLS) (SEQ ID NO:12) contains a 700 bp cytomegalovirus immediated early gene promoter (position 12 - 711), a 270 bp hybrid intron (position 712 - 981), the modified C31-Int gene (position 989 - 2851), and a 189 bp synthetic polyadenylation sequence (position 2854 - 3043).

To generate the Cre expression plasmid pCMV-Cre (SEQ ID NO:13), the coding sequence of Cre recombinase (Sternberg et al., J. Mol. Biol., 187, 197 - 212 (1986)) with a N-terminal fusion of the 7 amino acid SV40 T-antigen NLS (see above) was recovered from plasmid pgk-Cre and cloned into the NotI and XhoI sites of plasmid pRK50. PRK50 (SEQ ID NO:14) is a generic expression vector for mammalian cells based on the cloning vector pNEB193 (New England Biolabs Inc, Beverly, MA, USA). PRK50 was built by insertion into pNEB193 of a 700 bp cytomegalovirus immediated early gene (CMV-IE) promoter (position 1-700) from plasmid pIREShyg (GenBank#U89672; Clontech Laboratories Inc, Palo Alto, CA, USA), a synthetic 270 bp hybrid intron (position 701-970), consisting of a adenovirus derived splice donor and an IgG derived splice acceptor sequence (Choi et al., Mol. Cell. Biol., 11, 3070 - 3074 (1991)), and a 189 bp synthetic polyadenylation sequence (position 1000-1188) build from the polyadenylation consensus sequence and 4 MAZ polymerase pause sites (Levitt et al., Genes&Dev., 3, 1019 - 1025 (1989); The EMBO J. 13, 5656 - 5667 (1994)). The positive control plasmid pRK64(ΔCre) (SEQ ID NO:15) was generated from pRK64 by transformation into the Cre expressing E. coli strain 294-Cre (Buchholz et al., Nucleic Acids Res., 24, 3118 - 3119 (1996)).

One of the transformed subclones was confirmed for the Cre mediated deletion of the loxP-flanked cassette by restriction mapping and further expanded. Plasmid pUC19 is a cloning vector without eukaryotic control elements used to equalise DNA amounts for transfections (GenBank#X02514; New England Biolabs Inc, Beverly, MA, USA). All plasmids were propagated in DH5α E. coli cells (Life Technologies GmbH, Karlsruhe, Germany) grown in Luria-Bertani medium and

purified with the plasmid DNA purification reagents "Plasmid-Maxi-Kit" (Quiagen GmbH, Hilden, Germany) or "Concert high purity plasmid purification system" (Life Technologies GmbH, Karlsruhe, Germany). Following purification, the plasmid DNA concentrations were determined by absorption at 260 nm and 280 nm in UVette cuvettes (Eppendorf-Netheler-Hinz GmbH, Hamburg, Germany) using a BioPhotometer (Eppendorf-Netheler-Hinz GmbH, Hamburg, Germany) and the plasmids were diluted to the same concentration; finally these were confirmed by separation of 10 ng of each plasmid on an ethidiumbromide-stained agarose gel.

B. Cell culture and transfections: Chinese hamster ovary (CHO) cells (Puck et al., J. Exp. Med., 108, 945 (1958)) were obtained from the Institute for Genetics (University of Cologne, Germany) as a population adapted to growth in DMEM medium. The cells were grown in DMEM/Glutamax medium (Life Technologies) supplemented with 10% fetal calf serum at 37°C, 10% CO_2 in humid atmosphere and passaged upon trypsinisation. One day before transfection 10^6 cells were plated into a 48-well plate (Falcon). For the transient transfection of cells with plasmids each well received into 250 ml of medium a total amount of 300 ng supercoiled plasmid DNA complexed before with the FuGene6 transfection reagent (Roche Diagnostics GmbH, Mannheim, Germany) according to the manufacturers protocol. Each 300 ng DNA preparation (Fig.2 sample 4 to 11) contained 50 ng of the luciferase expression vector pUHC13-1 (Gossen et al., Proc Natl Acad Sci USA., 89 5547-5551 (1992)), 50 ng of the substrate vector pRK64, 0.5 ng or 1 ng of one of the recombinase expression vectors pCMV-C31Int(wt), pCMV-C31Int(NNLS), pCMV-C31Int(CNLS) or pCMV-Cre and 199 ng or 199.5 ng of pUC19 plasmid, except for the controls which received 50 ng of pUHC13-1 together with 50 ng of pRK64 (sample 3) or pRK64(Δcre) (sample 2) and 200 ng pUC19, or 50 ng pUHC13-1 with 250 ng pUC19 (sample 1). Transfections of Ssv and XisA recombinases (Fig.3) also contained 50 ng of the luciferase expression vector pUHC13-1, 50 ng of substrate vectors pPGKattA and pPGKnif and 10 ng or 20 ng of recombinase expression vector pCMV-SSV or pCMV-SSV(NNLS) or 25 ng or 100 ng of expression vectors pCMV-XisA/ pCMV-XisA(NNLS). Plasmid pUC19 was added to a total amount of 300 ng plasmid DNA. As the C31-Int expression vectors are 15% larger in size than pCMV-Cre and the same amounts of DNA of the three plasmids were used for transfection, the

samples with C31-Int vectors received 15% less plasmid molecules as compared to the samples with Cre expression vector. The ß-galactosidase values from C31-Int transfected samples by this value were not corrected and thus is a slight underestimation of the calculated C31-Int activities. For each sample to be tested four individual wells were transfected. One day after the addition of the DNA preparations each well received additional 250 ml of growth medium. The cells of each well were lysed 48 hours after transfection with 100 ml lysate reagent supplemented with protease inhibitors (Roche Diagnostics). The lysates were centrifuged and 20 ml were used to determine the ß-galactosidase activities using the ß-galactosidase reporter gene assay (Roche Diagnostics) according to the manufacturers protocol in a Lumat LB 9507 luminometer (Berthold). To measure luciferase activity, 20ml lysate was diluted into 250ml assay buffer (50mM glycylglycin, 5mM $MgCl_2$, 5mM ATP) and the "Relative Light Units" (RLU) were counted in a Lumat LB 9507 luminometer after addition of 100 ml of a 1 mM luciferin (Roche Diagnostics) solution. The mean value and standard deviation of the samples was calculated from the ß-galactosidase and luciferase RLU values obtained from the four transfected wells of each sample.

C. Results: To set up an assay system for the measurement of C31-Int and Cre recombinase efficiency in mammalian cells the recombination substrate vector pRK64 shown in Figure 1E was first constructed. pRK64 contains a SV40 promoter region for expression in mammalian cells followed by a 1.1 kb cassette which consists of the coding region of the puromycin resistance gene and a polyadenylation signal sequence. This cassette is flanked at the 5`-end by the 84 bp attB and at the 3´-end by the 84 bp attP recognition site of C31-Int (Fig.1 and 6). These attB and attP sites are located on the same DNA molecule and oriented in a way to each other which allows the deletion of the flanked DNA segment. The same orientation of attB and attP sites is used naturally by the ΦC31 phage and the bacterial genome, leading to the integration of the phage genome when both sites are located on different DNA molecules (Thorpe et al., Proc. Natl. Acad. Sci. USA, 95, 5505 – 5510 (1998)). To measure C31-Int and Cre recombinase activities with the same substrate vector, pRK64 contains in addition two Cre recognition (loxP) sites in direct orientation next to the att sites. Since the att/lox-flanked cassette in plasmid pRK64 is inserted between the SV40 promoter and the coding region of the ß-galactosidase gene, its presence inhibits

ß-galactosidase expression as the SV40 promoter derived transcripts are terminated at the polyadenylation signal of the puromycin gene. Plasmid pRK64 is turned into a ß-galactosidase expression vector upon C31-Int or Cre mediated deletion of the att/lox-flanked puromycin cassette since the remaining single att and loxP site do not substantially interfere with gene expression.

For the expression of recombinases a mammalian expression vector was designed which contains the CMV immediate early promoter followed by a hybrid intron, the coding region of the recombinase to be tested, and an artificial polyadenylation signal sequence. The backbone sequence of the four recombinase expression vectors shown in Figure 1A-D is identical to each other except for the recombinase coding region. Plasmid pCMV-C31Int(wt) (Fig. 1A) contains the nonmodified (wildtype) 1.85 kb coding region of C31-Int as found in the genome of phage ΦC31 (Kuhstoss, et al., J. Mol. Biol. 222, 897-908 (1991)). Plasmid pCMV-C31Int(NNLS) (Fig. 1B) contains a modified C31-Int gene coding for the full length C31-Int protein with a N-terminal extension of 7 amino acids derived from the SV40 virus large T antigen which serves as a nuclear localisation signal (NLS). Plasmid pCMV-C31Int(CNLS) (Fig. 1C) contains a C-terminal extension of 7 amino acids derived from the SV40 virus large T antigen which serves as a nuclear localisation signal (NLS). Plasmid pCMV-Cre (Fig. 1D) contains the 1.1 kb Cre coding region with an N-terminal fusion of the 7 amino acid NLS of the SV40 T-antigen. For Cre recombinase it has been shown that the N-terminal addition of the SV40 T-antigen NLS does not increase its recombination efficiency in mammalian cells (Le et al., Nucleic Acids Res., 27, 4703 - 4709 (1999)).

As a test system to compare the efficiency of the 4 recombinases the same amount of plasmid DNA of each of the recombinase expression vectors together with a fixed amount of the reporter plasmid pRK64 was transiently introduced into Chinese Hamster Ovary (CHO) cells. Thus, in this assay design the efficiency of the various recombinases on an extrachromosomal substrate introduced into the CHO cells was compared as a circular plasmid. Two days after transfection the cells from the various samples were lysed and the activity of ß-galactosidase in the lysates was determined by a specific chemiluminescense assay and expressed in "Relative Light Units" (RLU (ß-Gal)) (Fig. 2). In addition all samples

contained a fixed amount of a luciferase expression vector to control for the experimental variation of cell transfection and lysis. For this purpose the lysates of each sample were also tested for luciferase activity with a specific chemiluminescense assay and the values expressed as "Relative Light Units" (RLU (Luciferase)) (Fig. 2). All transfection samples contained in addition varying amounts of the unrelated cloning plasmid pUC19 so that all samples were equalised to the same amount of plasmid DNA. As a positive control for ß-galactosidase a derivative of the recombination reporter pRK64 was used in which the loxP flanked 1.1 kb cassette has been removed through Cre mediated recombination in E. coli giving rise to plasmid pRK64(ΔCre). As negative controls served samples which received the unrecombined reporter plasmid pRK64 but no recombinase expression vector as well as samples set up with the pUC19 plasmid alone.

To determine the relative efficiency of the tested recombinases the RLU values of ß-galactosidase were divided individually for each sample by the RLU values obtained for luciferase and multiplied with 10^5. From the values of the four data points of each sample the mean value and standard deviation was calculated as an indicator of recombinase activity (Gal/Luc) (Fig. 2). The relative activity of the tested recombinases was then compared to the positive control defined as an activity of 1.

As shown in Fig. 2, the expression of Cre recombinase (samples 10 and 11) resulted in a 150 to 170-fold increase of ß-galactosidase activity as compared to the negative control (sample 3), demonstrating the wide dynamic range of our test system. Each recombinase vector was tested using two different amounts of DNA for transfection (0.5 and 1ng/sample), which in the case of Cre resulted in 63% and 72% recombinase activity (samples 10 and 11 as compared to the positive control). These two values establish that the DNA amounts used are close to the test systems saturation for recombinase expression as the doubling of DNA amounts resulted only in a minor increase of recombinase activity.

In comparison to Cre, the expression of wildtype C31-Int resulted in a considerably lower recombinase activity of 23% and 30% (Fig. 2, samples 4 and 5) as compared to the positive control. These values represent 37% and 42%

recombinase activity for wildtype C31-Int as compared to Cre recombinase (compare samples 4 and 5 with 10 and 11). Upon the expression of C31-Int fused with the N-terminal NLS (C31-Int(NNLS)) values of 32% and 36% recombinase activity (samples 6 and 7) were obtained as compared to the positive control. The C31-Int(NNLS) values represent 51% and 50% recombinase activity as compared to Cre (compare samples 6 and 7 to 10 and 11). Thus, the activity of C31-Int in mammalian cells is just moderately enhanced by the addition of a NLS signal.

Surprisingly, upon the expression of C31-Int fused with the C-terminal NLS (C31-Int(CNLS)) values of 50% and 65% recombinase activity (samples 8 and 9) were obtained as compared to the positive control. The C31-Int(CNLS) values represent 79% and 90% recombinase activity as compared to Cre recombinase (compare samples 84 and 9 to 10 and 11). Unexpectedly,C31-Int(CNLS) exhibits a dramatic, more than twofold increase of recombinase activity in comparison to C31-Int(wt) (compare samples 8 and9 to 4 and 5).

In order to test whether the addition of a NLS sequence may be a general, simple method to enhance recombinase activity in mammalian cells we extended our studies by two additional recombinases: XisA recombinase (XisA) derived from the cyanobacterium Anabaena, and SSV-Integrase (SSV-Int) derived from the SSV1 virus of the thermophilic bacterium Sulfolobus shibatae. To this end we constructed mammalian expression vectors for the wildtype forms of XisA and SSV recombinases and compared their activity to versions which were modified by the N-terminal addition of the 7 amino acid NLS of the SV40 T-antigen. These recombinases were compared by the use of the reporter vector shown in Fig.1E, except that the att elements of C31-Int were replaced by the nif recognition sequences for XisA or the att sequences for SSV-Int. As described above for C31-Int, recombinase activities were tested by transient transfection into CHO cells using the reporter vector derived β-galactosidase activity as readout and cotransfected luciferase as internal control.

As shown in Fig.3 for both, XisA and SSV recombinases the addition of a NLS sequence did not improve their activity in a mammalian cell line as compared to the wildtype forms. At both DNA concentrations tested wildtype XisA exhibits a significant recombination activity as compared to the reporter vector alone (compare samples 2 and 3 to sample 1), but this activity is not altered by the

addition of an NLS (compare samples 2 and 3 to samples 4 and 5). SSV-Int exhibits only a low recombination activity (compare samples 7 and 8 with sample 6) which is also not enhanced by the addition of a NLS (compare samples 9 and 10 with samples 7 and 8). From these results we conclude that the addition of a NLS to an inefficient recombinase is not a general, simple method to improve its performance in mammalian cells.

Taken together, in the transient transfection test system shown in Figure 2 a more than twofold activity increase of the ΦC31 Integrase could be achieved by the C-terminal, but not the N-terminal addition of the SV40 T antigen NLS signal. As this signal sequence has been characterised to act as a nuclear localisation signal (Kalderon et. al, Cell, 39, 499 - 509 (1984)) we conclude that the efficiency increase of C31-Int(CNLS) is the result of the improved nuclear accumulation of this recombinase. The relative inefficiency of C31-Int (NNLS) may be explained by the inaccessibility of the NLS peptide to the nuclear import machinery at the N-terminal position of the C31-Int protein.
In particular, it could be shown that C31-Int(CNLS) recombines extrachromosomal DNA in mammalian cells almost as efficient as the widely used Cre recombinase and thus provides an additional or alternative recombination system of highest activity. The efficiency increase of C31-Int(CNLS) as compared to its wildtype form is regarded as an invention of substantial use for biotechnology.

Example 2

As demonstrated in example 1 C31-Int recombinase with the C-terminal fusion of the SV40 T-antigen NLS (C31-Int(CNLS)) shows in mammalian cells a recombination activity comparable to Cre recombinase on an extrachromosomal plasmid vector. It was further tried to test whether C31-Int(CNLS) exhibits a similar activity on a recombination substrate which is chromosomally integrated into the genome of mammalian cells. This question is critical for the use of a recombination system for genome engineering as it is possible that a recombinase may act efficiently on extrachromosomal substrates but is impaired if the recognition sites are part of the mammalian chromatin. To characterise the recombination activity of C31-Int(CNLS) and C31-Int(NNLS) on a chromosomal substrate the pRK64 reporter plasmid (Fig. 1E) was stably integrated, containing

a pair of loxP and att sites, into the genome of a mammalian cell line. One of the stable transfected clones was chosen for further analysis and was transiently transfected with recombinase expression vectors coding for C31-Int(CNLS), C31-Int(NNLS), C31-Int(wt) or Cre recombinase. The activity of ß-galactosidase derived from the Cre expression vector recombined in these cells was taken as a measure of recombination efficiency.

A. Plasmid constructions: all plasmids used and their purification are described in example 1.

B. Cell culture and transfections: To generate a stably transfected C31-Int reporter cell line 2.5 x 10^6 NIH-3T3 cells (Andersson et al., Cell, 16, 63-75 (1979); DSMZ#ACC59; DSMZ-Deutsche Sammlung von Mikroorganismen und Zellkulturen GmbH, Mascheroder Weg 1b, D-38124 Braunschweig, Germany) were electroporated with 5 µg pRK64 plasmid DNA linearised with ScaI and plated into 10cm petri dishes. The cells were grown in DMEM/Glutamax medium (Life Technologies) supplemented with 10% fetal calf serum at 37°C, 10% CO_2 in humid atmosphere, and passaged upon trypsinisation. Two days after tranfection the medium was supplemented with 1mg/ml of puromycin (Calbiochem) for the selection of stable integrants. Upon the growth of resistant colonies these were isolated under a stereomicroscope and individually expanded in the absence of puromycin. To demonstrate stable integration of the transfected vector, genomic DNA of puromycin resistant clones was prepared according to standard methods and 5–10 µg were digested with EcoRV. Digested DNA was separated in a 0.8% agarose gel and transferred to nylon membranes (GeneScreen Plus, NEN DuPont) under alkaline conditions for 16 hours. The filter was dried and hybridised for 16 hours at 65°C with a probe representing the 5` part of the E. coli ß-galactosidase gene (1.25 kb NotI - EcoRV fragment of plasmid CMV-ß-pA (R. Kühn, unpublished). The probe was radiolabelled with P32-marked α-dCTP (Amersham) using the Megaprime Kit (Amersham). Hybridisation was performed in a buffer consisting of 10% dextranesulfate, 1% SDS, 50 mM Tris and 100 mM NaCl, pH7.5). After hybridisation the filter was washed with 2x SSC/1%SDS and exposed to BioMax MS1 X-ray films (Kodak) at – 80°C.

Transfections of the selected clone 3T3(pRK64)-3 with plasmid DNAs and the measurement of ß-galactosidase activities in lysates were essentially performed

as described in example 1 for CHO cells, except that 32ng or 64ng of the recombinase expression plasmids and 218 or 186 ng of pUC19 plasmid were used and the pRK64 plasmid was omitted from all samples.

C. Histochemical detection of ß-galactosidase activity in transfected 3T3(pRK64)-3 cells

To directly demonstrate ß-galactosidase expression in recombinase transfected cells, 10^4 3T3(pRK64)-3 cells were plated one day before transfection into each well of a 48-well tissue culture plate (Falcon). For the transient transfection of cells with plasmids each well received into 250 µl of medium a total amount of 150 ng supercoiled plasmid DNA complexed before with the FuGene6 transfection reagent (Roche Diagnostics GmbH, Mannheim, Germany) according to the manufacturers protocol. Each 150 ng DNA preparation contained 50 ng of the recombinase expression vector pCMV-Cre or pCMV-C31Int(CNLS) and 100ng of the pUC19 plasmid. After 2 days the culture medium was removed from the wells, the wells were washed once with phosphate buffered saline (PBS), and the cells were fixed for 5 minutes at room temperature in a solution of 2% formaldehyde and 1% glutaraldehyde in PBS. Next, the cells were washed twice with PBS and finally incubated in X-Gal staining solution for 24 hours at 37°C (staining solution: 5 mM $K_3(Fe(CN)_6)$, 5 mM $K_4(Fe(CN)_6)$, 2 mM $MgCl_2$, 1mg/ml X-Gal (BioMol) in PBS) until photographs were taken.

D. Results

To generate a mammalian cell clone with a stable genomic integration of the C31-Int and Cre recombinase reporter plasmid pRK64, the murine fibroblast cell line NIH-3T3 was electroporated with linearised pRK64 DNA (Fig.1D; see also example 1) and subjected to selection in puromycin containing growth medium. Plasmid pRK64 contains in between the pair of loxP and att sites the coding region of the puromycin resistance gene expressed from the SV40-IE promoter. Thirty-six puromycin resistant clones were isolated and the genomic DNA of 19 clones was analysed for the presence and copy number of the pRK64 DNA. Three clones, which apparently contain 2 - 4 copies of pRK64, were further characterised on the single cell level for the expression of ß-galactosidase upon transient transfection with the Cre expression vector pCMV-Cre (Fig. 1C). The cell clone with the largest proportion of ß-galactosidase positive cells, 3T3(pRK64)-3,

was selected as most useful for the planned studies on C31-Int and Cre recombinase efficiency.

To compare the efficiency of wildtype C31-Int (C31-Int(wt)), C31-Int(CNLS), C31-Int(NNLS), and Cre recombinases 32ng or 64 ng of the recombinase expression vectors pCMV-C31Int(wt), pCMV-C31Int(CNLS), pCMV-C31Int(NNLS), or pCMV-Cre (Fig. 1 A-D) together with the unrelated cloning plasmid pUC19 were transiently introduced into 3T3(pRK64)-3 cells, such that all samples contained the same amount of plasmid DNA. As a negative control a sample prepared with the pUC19 plasmid alone was used. Two days after transfection the cells from the various samples were lysed and the activity of ß-galactosidase in the lysates was determined by a specific chemiluminescense assay and expressed in "Relative Light Units" (RLU)(ß-Gal) (Fig. 4). From the values of the four data points of each sample the mean value and standard deviation was calculated as an indicator of recombinase activity (Fig.4). The relative activity of the tested recombinases was then compared to the highest value obtained with the Cre expression vector, defined as an activity of 1.

As shown in Figure 4 the expression of Cre recombinase (samples 8 and 9) resulted in a 36 to 49-fold increase of ß-galactosidase activity as compared to the negative control (sample 1), demonstrating the dynamic range of the test system used. Each recombinase vector was tested using two different amounts of DNA for transfection (32 ng and 64 ng/sample), which in the case of Cre resulted in 73% and 100% recombinase activity (samples 8 and 9). These two values establish that the DNA amounts used are not far from the linear scale of the test systems ability for recombinase expression as the twofold increase of the amount of DNA also resulted in a significant increase of recombinase activity.

The expression of wildtype C31-Int (Fig. 4, samples 2 and 3) resulted in a low recombinase activity of 4% and 10% as compared to thevalues obtained by Cre transfection (compare samples 2 and 3 with 8 and 9). This activity was only moderately enhanced by the expression of C31-Int(NNLS) to values of 19% and 22% of Cre activity (compare samples 4 and 5 with samples 8 and 9). Upon the expression of C31-Int(CNLS) values of 48% and 78% recombinase activity were obtained as compared to Cre recombinase (compare samples 6 and 7 to 8 and

9). Hence, C31-Int(CNLS) exhibits an 12-fold higher activity than C31-Int(wt) at 32 ng plasmid DNA (Fig.4, compare samples 6 and 2) and an 8-fold higher activity than C31-Int(wt) at 64 ng plasmid DNA (Fig.4, compare samples 7 and 3).

In addition, it was aimed to directly demonstrate in situ the expression of ß-galactosidase in 3T3(pRK64)-3 cells after transfection with Cre or C31-Int(CNLS) recombinase plasmid. Two days after transfection the cells were fixed in situ and incubated with the histochemical X-Gal assay which detects ß-galactosidase positive cells by a blue precipitate. As shown in Figure 5 stained cells were found at a comparable frequency in the samples transfected with the Cre or C31-Int(CNLS) expression vectors but not in the nontransfected control. This result confirms that the ß-galactosidase activities measured by chemiluminescense upon recombinase transfection (Fig. 4) results from a population of individual, recombined reporter cells.

In conclusion, upon the transient transfection of recombinase expression vectors into a cell line with a genomic integration of the recombination substrate vector, a 8 – 12-fold activity increase of the ΦC31 Integrase by the C-terminal fusion with the SV40 T-antigen NLS signal was found. As this signal sequence has been characterised to act as a nuclear localisation signal (Kalderon et. al, Cell, 39, 499 – 509 (1984)), it was concluded that the dramatic efficiency increase of C31-Int(CNLS) is the result of the improved nuclear accumulation of this recombinase. The approximately tenfold activity increase of C31-Int(CNLS) upon expression in a cell line with a genomic integration of the substrate vector is considerably higher than the activity increase found upon the transient expression of both vectors (see example 1). Thus, a substrate vector integrated into the chromatin of a mammalian cell may pose more stringent requirements on recombinase activity to be recombined as compared to an extrachromosomal substrate.

The dramatic activity increase of C31-Int(CNLS), as compared to its wildtype form, on a stable integrated substrate in mammalian cells is an invention of significant practical use as this recombinase is as efficient as the widely used

Cre/loxP system; thus, C31-Int(CNLS) provides an additional or alternative recombination system of highest activity.

Example 3

To demonstrate that the increase in ß-galactosidase activity obtained by the cotransfection of a C31-Int expression vector and the reporter vector pRK64 into mammalian cells is in fact the result of recombinase mediated deletion, one of the recombination products was detected by a specific polymerase chain reaction (PCR). The amplified PCR product was cloned and its sequence determined. The obtained sequence confirms that C31-Int mediated deletion of the test vector occurs in a mammalian cell line and that the recombination occurs at the known breakpoint within the attB and attP sites.

A. Plasmid constructions: The construction of plasmids pRK64, pCMV-Cre and pCMV-C31-Int(wt) is described in Example 1. To simulate the recombination of pRK64 by C31-Int, the sequence between the CAA motives of the att sites (boxed in Fig.5) was deleted from the computerfile of pRK64, giving rise to the sequence of pRK64(ΔInt) (SEQ ID NO:16).

B. Transfection of Cells and PCR amplification: MEF5-5 mouse fibroblasts (Schwenk et al., 1998) (20000 cells per well of a 12 well plate (Falcon)) were transfected with 0.5 µg pRK64 alone or together with 250 ng pCMV-Int(wt) or pCMV-Cre using the FuGene6 transfection reagent following the manufacturers protocol (Roche Diagnostics). After 2 days DNA was extracted from these cells according to standard methods and used for PCR amplification with Primers P64-1 (SEQ ID NO:17; complementary to position 111-135 of pRK64(ΔInt)) and P64-4 (SEQ ID NO:18; complementary to position 740-714 of pRK64(ΔInt)) using the Expand High Fidelity PCR kit (Roche Diagnostics). PCR products were separated on a 0.8% agarose gel, extracted with the QuiaEx kit (Quiagen) and cloned into the pCR2.1 vector using the TA cloning kit (Invitrogen) resulting in plasmid pRK80d. The sequence of its insert, seq80d (SEQ ID NO:19), was determined using the reverse sequencing primer and standard sequencing methods (MWG Biotech).

For the measurement of ß-galactosidase activity the cells were lysed 2 days after

transfection and the ß-galactosidase activities were determined with the ß-galactosidase reporter gene assay (Roche Diagnostics) as described in example 1.

C. Results: As a test vector for C31-Int mediated DNA recombination plasmid pRK64 was used, which contains the 1.1 kb coding region of the puromycin resistance gene flanked 5` by the 84 bp attB and 3´ by the 84 bp attP recognition site of C31-Int (Fig. 5). These attB and attP sites are located on the same DNA molecule and oriented in a way to each other which allows the deletion of the att-flanked DNA segment. The same orientation of attB and attP sites is used naturally by the ΦC31 phage and the bacterial genome for the integration of the phage genome when both sites are located on different DNA molecules (Thorpe et al., Proc. Natl. Acad. Sci. USA, 95, 5505 - 5510 (1998)). As a positive control, vector pRK64 contains in addition two Cre recombinase recognition (loxP) sites in direct orientation next to the att sites. Since the att-flanked DNA segment in plasmid pRK64 is inserted between a promoter active in mammalian cells and the ß-galactosidase gene, its deletion can be measured by the increase of ß-galactosidase activity. The expected product of C31-Int mediated deletion of plasmid pRK64 is shown in Fig. 6, designated as pRK64(ΔInt). If the recombination between attB and attP occurs as described in bacteria (Thorpe et al., Proc. Natl. Acad. Sci. USA, 95, 5505 - 5510 (1998)), a single attR site is generated and left on the parental plasmid (Fig. 6) while the flanked DNA is excised and contains an attL site. Beside the measurement of ß-galactosidase activity, C31-Int mediated recombination of pRK64 can be directly detected on the DNA level by a specific polymerase chain reaction (PCR) using the primers P64-1 and P64-4 (Fig. 6). These primers, located 5` of the attB site (P64-1) and 3` of the attP site, are designed to amplify a PCR product of 630 bp lenght upon the C31-Int mediated recombination of pRK64. For the expression of C31-Int in mammalian cells plasmid pCMV-C31(wt) was used, which contains the CMV-IE-Promoter upstream of the C31-Int coding region followed by a synthetic polyadenylation signal (see Example 1 and Fig.1).

The recombination substrate vector pRK64 was transiently transfected into the murine fibroblast cell line MEF5-5 either alone, or together with the C31-Int expression vector pCMV-C31(wt), or together with an expression vector for Cre recombinase, pCMV-Cre. Two days after transfection half the cells of each sample

was lysed and used to measure ß-galactosidase activity by chemiluminescense, and the other half was used for the preparation of DNA from the transfected cells for PCR analysis. The ß-galactosidase levels of the 3 samples were found as following (expressed as "Relative Light Units" (RLU) with standard deviation (SD) of the ß-galactosidase assay):

Sample	RLU (SD)
1) pRK64	692 ± 5
2) pRK64 + pCMV-Cre	8527 ± 269
3) pRK64 + pCMV-C31(wt)	1288 ± 93

As the coexpression of the test vector pRK64 together with the C31-Int expression vector in sample 3 leads to a significant increase of ß-galactosidase activity as compared to pRK64 alone, this result suggests that pRK64 is recombined by C31-Int as anticipated in Fig. 6.

Next, cellular DNA was prepared from the three samples and tested for the occurrence of the expected Cre or C31-Int generated deletion product by PCR using primers P64-1 and P64-4 for amplification. As shown in Fig. 7 an amplification product of the expected size was found only in the samples cotransfected with the Cre or C31-Int recombinase expression vectors (Fig. 7A, lane3 and lane 4). The PCR products amplified from pRK64 recombined by C31-Int or Cre are of the same size but should be recombined via the attB/P or loxP sites, respectively.

To prove that the PCR product found after cotransfection of plasmids pRK64 and pCMV-C31(wt) represents in fact the deletion product of C31-Int mediated recombination, this DNA fragment was cloned into a plasmid vector and its DNA sequence determined. One clone, pRK80d, was analysed, and its sequence showed exactly the sequence of an attR site as expected from C31-Int mediated deletion of pRK64 (Fig. 7B, compare to Fig. 6).

In conclusion, this experiment demonstrates that C31-Int mediated deletion of a vector containing a pair of attB/attP sites occurs in a mammalian cell line, and that the recombination occurs within the same 3 bp breakpoint region of attB and attP as found in bacteria (Thorpe et al., Proc. Natl. Acad. Sci. USA, 95, 5505 –

5510 (1998)). Thus, it was concluded that an increase of ß-galactosidase activity observed by cotransfection of the pRK64 reporter vector and a C31-Int expression vector in mammalian cells truly reflects C31-Int recombinase activity.

Example 4

As has been demonstrated in examples 1-3, the C31-Int recombinase with the C-terminal fusion of the SV40 T-antigen NLS (C31-Int(CNLS)) shows a recombination activity comparable to Cre recombinase on an extrachromosomal as well as a chromosomally integrated target in mammalian cells in vitro. To test whether C31-Int(CNLS) exhibits activity in mice, transgenic mice carrying a C31-Int(CNLS) expression vector were generated. These transgenic mice were crossed with reporter mice carrying the recombinase substrate. Recombination-mediated expression of β-galactosidase, which can be measured by staining with the substrate X-Gal, was analyzed in testes of double transgenic progeny carrying both the recombinase and the reporter.

A. Plasmid constructions: For the construction of the C31-Int(CNLS) transgene expression vector, the C31Int gene with C-terminal NLS was isolated as a 2 kb-fragment generated by restriction of pCMV-C31Int(CNLS) (SEQ ID NO: 12) with BglII. The fragment was ligated into the BglII restriction site of the vector pCAGGS-Cre-pA (SEQ ID NO:104) giving rise to the plasmid pCAGGS-C31CNLS-pA (SEQ ID NO:105). In pCAGGS-C31CNLS-pA the C31-Int(CNLS) (position 1891-3753) is transcribed from the CAGGS promoter (position 1-1616) and followed by the SV40 late region polyadenylation sequence (position 3763-3941).

B. Production of transgenic mice: For the embryo injections a 3.95 kb-fragment was generated by restriction of the plasmid pCAGGS-C31CNLS-pA with PstI and AscI. This fragment was purified as follows: DNA bands were separated on an agarose-gel without ethidiumbromide. One part of the gel was stained with ethidiumbromide to locate the band to excise. The DNA was electroeluted from the excised band with S&S Biotrap Elution Chamber in 1x TAE (40 mM Tris-acetate, 1 mM EDTA) overnight. The DNA was precipitated from the eluate with 1/10 volume 3M sodium acetate and 2.5 volumes ethanol at -20 °C for several

hours. The DNA was pelleted by centrifugation at 13000 rpm for 30 min and washed twice with 70 % ethanol. The dried DNA pellet was resuspended in TE (10 mM Tris, 1 mM EDTA, pH 8). Subsequently the precipitation procedure was repeated once and the DNA resuspended in injection buffer (10 mM Tris pH 7.2, 0.1 mM EDTA). The sample was dialysed with Slide-A-Lyse Mini Dialysis Unit (Pierce) in injection buffer with several changes of buffer at 4°C overnight. Different amounts of the sample were checked on a gel to determine concentration. To generate transgenic mice, 5-10 fg of the purified fragment were injected into one pronucleus of (B6CBA)F2 mouse one-cell embryos. The injected embryos were subsequently transferred into the oviduct of 0.5 day pseudopregnant NMRI females.

C. Analysis of transgenic mice: Mice were analyzed for the presence of the pCAGGS-C31CNLS-pA transgene by PCR using tail DNA and the primers C31-screen 1 (SEQ ID NO:100) and C31-screen 2 (SEQ ID NO:101) amplifying a fragment of 500 bp. The PCR reaction contained 5 µl PCR buffer (Invitrogen), 2 µl 50 mM $MgCl_2$, 1.5 µl 10 mM dNTP-mix, 2 µl (10 pmol) of each primer, 0.5 µl Taq-polymerase (5 U/ µl) and water to a volume of 50 µl. The program used for the PCR reactions was: 94 °C for 30 s, 55 °C for 30 s and 72 °C for 1 min in 30 cycles.

D. Analysis of C31-Int(CNLS) activity: Founder mice transgenic for the pCAGGS-C31CNLS-pA transgene were crossed to heterozygous C31 reporter mice carrying the C31 reporter construct in the ROSA26 locus (SEQ ID NO:106) (Fig. 8). Offspring of the crosses were genotyped for the presence of the pCAGGS-C31CNLS-pA transgene by the PCR assay described in section C as well as for the ROSA26-C31 reporter allele by a LacZ-specific PCR assay. The PCR was performed using tail DNA and the primers β-Gal 3 (SEQ ID NO:102) and β-Gal 4 (SEQ ID NO:103) amplifying a fragment of 315 bp. The PCR reaction contained 5 µl PCR buffer (Invitrogen), 2.5 µl 50 mM $MgCl_2$, 2 µl 10 mM dNTP-mix, 1 µl (10 pmol) of each primer, 0.4 µl Taq-polymerase (5 U/ µl) and water to a volume of 50 µl. The program used for the PCR reactions was: 94 °C for 1 min, 60 °C for 1 min and 72 °C for 1 min in 30 cycles.

Testes from mice carrying the pCAGGS-C31CNLS-pA transgene as well as the reporter locus and from a control mouse carrying the reporter allele only were

dissected. The tissues were imbedded in OCT Tissue freezing medium (Leica/Jung) and frozen in liquid nitrogen. Cryosections were generated from the embedded tissues using a Leica CM3050 cryomicrotome, dried on polylysine-coated slides for 1-4 hours and then stained as follows: Sections were fixed in 0.2 % glutaraldehyde, 5 mM EGTA, 2 mM $MgCl_2$ in 0.1 M PB (K_2HPO_4/ KH_2PO_4, pH 7.3) for 5 min at room temperature and washed in wash buffer (2 mM $MgCl_2$, 0.02 % Nonidet-40 in PB in 0.1 M PB) 3 times for 15 min. Then sections were stained in X-Gal-solution (0.6 mg/ ml X-Gal in DMSO, 5 mM potassium hexacyanoferrat III, 5 mM potassium hexacyanoferrat II in LacZ wash buffer) overnigth at 37 °C. After staining sections were washed in 1x PBS twice for 5 min. Dehydration was performed by washing the sections first with 70 %, 96 % and 100 % ethanol for 2 min each, then with a 1:1 mix of ethanol and xylol for 5 min and in the end only with xylol for 5 min. Before taking pictures sections were mounted in Entellan.

E. Results: To identify transgenic founder mice carrying the pCAGGS-C31CNLS-pA transgene, 29 mice born from the injection experiment were analyzed for the presence of the transgene. 5 founder mice (3 females and 2 males) were identified. To analyze the activity of the C31-Int(CNLS) recombinase in transgenic mice, 2 of the female founder mice were crossed to heterozygous C31 reporter mice carrying a C31 reporter construct in the ROSA26 locus (Fig. 8). From each of these crosses, one offspring carrying the pCAGGS-C31CNLS-pA transgene as well as the C31 reporter allele was sacrificed. In oder to determine whether pCAGGS-C31CNLS-pA transgenic mice are able to delete an attB/P flanked DNA sequence in the mouse germline, tissue sections from the testes of the sacrificed animals were prepared and stained for ß-galactosidase activity with X-Gal. Fig. 9 shows the result of the staining experiment for one of these mice (A) as well as a control mouse carrying only the reporter allele, but lacking the pCAGGS-C31CNLS-pA transgene (B). Clear staining can be detected in the maturing sperm cells in about 50% of the tubules with the proportion of ß-galactosidase expressing cells ranging between 10 and 100. No staining could be detected for the control mouse. This clearly demonstrates that C31-int-mediated recombination has taken place during spermatogenesis in the pCAGGS-C31CNLS-pA transgenic mice. These results show that the C31-int is functional in vivo, in a

transgenic mouse system and therefore provides a new tool to introduce specific deletions, inversions or integrations into the mouse germline.

Claims

1. A fusion protein comprising
(a) a recombinase domain comprising a recombinase protein or or a mutant thereof having a recombinase activity similar to that of the corresponding wild-type recombinase and
(b) a signal peptide domain linked to said recombinase domain which directs nuclear import of said fusion protein in eucaryotic cells.

2. The fusion protein of claim 1, wherein the activity of the fusion protein in eucaryotic cells is significantly higher as compared to that of the wild-type recombinase corresponding to the recombinase of the recombinase domain.

3. The fusion protein of claim 1 or 2, wherein the recombinase domain comprises a recombinase protein belonging to the family of large serine recombinases or a mutant thereof, preferably the recombinase domain comprises a recombinase protein selected from the group consisting of bacteriophage ΦC31 integrase (C31-Int), coliphage P4 recombinase, Listeria phage recombinase, bacteriophage R4 Sre recombinase, CisA recombinase, XisF recombinase, transposon Tn*4451* TnpX recombinase and lactococcal bacteriophage TP901-1 recombinase, or a mutant thereof; most preferably the recombinase protein is a C31-Int protein or a mutant thereof.

4. The fusion protein of claim 3, wherein the recombinase protein comprises a C31-Int having the amino acid sequence shown in SEQ ID NO:21 or a C-terminal truncated form thereof, said truncated form of the C31-Int preferably comprising amino acid residues of 306 to 613 of SEQ ID NO:21.

5. The fusion protein according to any one of claims 1 to 4, wherein the signal peptide domain is derived from yeast GAL4, SKI3, L29 or histone H2B proteins, polyoma virus large T protein, VP1 or VP2 capsid protein, SV40 VP1 or VP2 capsid protein, adenovirus E1a or DBP protein, influenza virus NS1 protein, hepatitis virus core antigen or the mammalian lamin, c-myc, max, c-myb, p53, c-erbA, jun, Tax, steroid receptor or Mx proteins, SV40 T-antigen or other proteins with

known nuclear localisation, preferably the signal peptide domain comprises a peptide which is derived from the SV40 T-antigen.

6. The fusion protein according to any one of claims 1 to 5, wherein the signal peptide domain

(i) has a length of 5 to 74, preferably 7 to 15 amino acid residues, and/or

(ii) comprises a segment of 6 amino acid residues having at least 2 positively charged basic amino acid residues, said basic amino acid residues being preferably selected from lysine, arginine and histidine.

7. The fusion protein of claim 5 or 6, wherein the signal peptide domain comprises a peptide selected from a sequence shown in SEQ ID NOs:24 to 53, preferably the signal peptide comprises the amino acid sequence Pro-Lys-Lys-Lys-Arg-Lys-Val (SEQ ID NO:53).

8. The fusion protein according to any one of claims 1 to 6, wherein

(i) the signal peptide domain is linked to the N-terminal or C-terminal of the recombinase domain or is integrated into the recombinase domain, preferably the signal peptide domain is linked to the C-terminal of the recombinase domain; and/or

(ii) the signal peptide domain is linked to the recombinase domain directly or through a linker peptide, said linker preferably having 1 to 30 essentially neutral amino acid residues.

9. The fusion protein of claim 1 comprising the amino acid sequence shown in SEQ ID NO:23.

10. A DNA coding for the fusion protein according to any one of claims 1 to 9.

11. A vector containing the DNA as defined in claim 10.

12. A microorganism containing the DNA of claim 10 and/or the vector of claim 11.

13. A process for preparing the fusion protein as defined in any one of claims 1 to 9 which comprises culturing a microorganism as defined in claim 11 under conditions suitable for expression of said fusion protein and recovering said fusion protein.

14. Use of the fusion protein as defined in any one of claims 1 to 9 to recombine DNA molecules, which contain recombinase recognition sequences for the recombinase protein of the recombinase domain, in eucaryotic cells.

15. A cell, preferably a mammalian cell containing the DNA sequence of claim 10 in its genome.

16. The cell of claim 15, also containing recognition sequences for the recombinase protein of the recombinase domain in its genome.

17. Use of the cell of claim 15 or 16 for studying the function of genes and for the creation of transgenic organisms.

18. A transgenic organism, preferably a transgenic non-human mammal containing the DNA sequence of claim 10 in its genome.

19. The transgenic organism of claim 18 also containing recognition sequences for the recombinase protein of the recombinase domain in its genome.

20. Use of the transgenic organism of claim 18 or 19 for studying gene function at various developmental stages.

21. A method for recombining DNA molecules of cells or organisms containing recombinase recognition sequences for the recombinase protein of the recombinase domain as defined in claims 1 to 9, which method comprises supplying the cells or organisms with a fusion protein as defined in claims 1 to 9 or with a DNA sequence of claim 10 and/or a vector of claim 11 which are capable of expressing said fusion protein in the cell or organism.

22. A method for recombining a DNA molecule containing recognition sequences

for a recombinase protein in a eucaryotic cell, said method comprising contacting the cell with a fusion protein according to claim 1 that recognizes said recognition sequences, wherein the fusion protein catalyzes recombination of the DNA molecule.

23. The fusion protein according to any one of claims 1 to 9 which catalyzes recombination at recognition sequences for the recombinase protein.

24 A transgenic organism, preferably a transgenic non-human mammal, comprising a cell containing a DNA sequence coding for a recombinase fusion protein as defined in claims 1 to 9 and 23 in its genome.

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<213> Artificial Sequence

<220>
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<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: primer C31-2-2

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<211> 5723
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<212> DNA
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<220>
<223> Description of Artificial Sequence: vector pCMV-Cre

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<210> 16
<211> 6252
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: vector
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<210> 17
<211> 25
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: primer P64-1

<400> 17
tcagcaacca ggctccccag caggc 25

<210> 18
<211> 27
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: primer 64-4

<400> 18
gacgacagta tcggcctcag gaagatc 27

<210> 19
<211> 840
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence:
oligonucleotide 80d

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<210> 20
<211> 1842
<212> DNA

<213> Bacteriophage phi-C31

<220>
<221> CDS
<222> (1)..(1839)

<400> 20

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Met Thr Gln Gly Val Val Thr Gly Val Asp Thr Tyr Ala Gly Ala Tyr
 1               5                  10                  15

gac cgt cag tcg cgc gag cgc gag aat tcg agc gca gca agc cca gcg   96
Asp Arg Gln Ser Arg Glu Arg Glu Asn Ser Ser Ala Ala Ser Pro Ala
            20                  25                  30

aca cag cgt agc gcc aac gaa gac aag gcg gcc gac ctt cag cgc gaa   144
Thr Gln Arg Ser Ala Asn Glu Asp Lys Ala Ala Asp Leu Gln Arg Glu
        35                  40                  45

gtc gag cgc gac ggg ggc cgg ttc agg ttc gtc ggg cat ttc agc gaa   192
Val Glu Arg Asp Gly Gly Arg Phe Arg Phe Val Gly His Phe Ser Glu
    50                  55                  60

gcg ccg ggc acg tcg gcg ttc ggg acg gcg gag cgc ccg gag ttc gaa   240
Ala Pro Gly Thr Ser Ala Phe Gly Thr Ala Glu Arg Pro Glu Phe Glu
65                  70                  75                  80

cgc atc ctg aac gaa tgc cgc gcc ggg cgg ctc aac atg atc att gtc   288
Arg Ile Leu Asn Glu Cys Arg Ala Gly Arg Leu Asn Met Ile Ile Val
                85                  90                  95

tat gac gtg tcg cgc ttc tcg cgc ctg aag gtc atg gac gcg att ccg   336
Tyr Asp Val Ser Arg Phe Ser Arg Leu Lys Val Met Asp Ala Ile Pro
            100                 105                 110

att gtc tcg gaa ttg ctc gcc ctg ggc gtg acg att gtt tcc act cag   384
Ile Val Ser Glu Leu Leu Ala Leu Gly Val Thr Ile Val Ser Thr Gln
        115                 120                 125

gaa ggc gtc ttc cgg cag gga aac gtc atg gac ctg att cac ctg att   432
Glu Gly Val Phe Arg Gln Gly Asn Val Met Asp Leu Ile His Leu Ile
    130                 135                 140

atg cgg ctc gac gcg tcg cac aaa gaa tct tcg ctg aag tcg gcg aag   480
Met Arg Leu Asp Ala Ser His Lys Glu Ser Ser Leu Lys Ser Ala Lys
145                 150                 155                 160

att ctc gac acg aag aac ctt cag cgc gaa ttg ggc ggg tac gtc ggc   528
Ile Leu Asp Thr Lys Asn Leu Gln Arg Glu Leu Gly Gly Tyr Val Gly
                165                 170                 175

ggg aag gcg cct tac ggc ttc gag ctt gtt tcg gag acg aag gag atc   576
Gly Lys Ala Pro Tyr Gly Phe Glu Leu Val Ser Glu Thr Lys Glu Ile
            180                 185                 190

acg cgc aac ggc cga atg gtc aat gtc gtc atc aac aag ctt gcg cac   624
Thr Arg Asn Gly Arg Met Val Asn Val Val Ile Asn Lys Leu Ala His
        195                 200                 205

tcg acc act ccc ctt acc gga ccc ttc gag ttc gag ccc gac gta atc   672
Ser Thr Thr Pro Leu Thr Gly Pro Phe Glu Phe Glu Pro Asp Val Ile
    210                 215                 220

cgg tgg tgg tgg cgt gag atc aag acg cac aaa cac ctt ccc ttc aag   720
Arg Trp Trp Trp Arg Glu Ile Lys Thr His Lys His Leu Pro Phe Lys
225                 230                 235                 240
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ccg ggc agt caa gcc gcc att cac ccg ggc agc atc acg ggg ctt tgt   768
Pro Gly Ser Gln Ala Ala Ile His Pro Gly Ser Ile Thr Gly Leu Cys
                245                 250                 255

aag cgc atg gac gct gac gcc gtg ccg acc cgg ggc gag acg att ggg   816
Lys Arg Met Asp Ala Asp Ala Val Pro Thr Arg Gly Glu Thr Ile Gly
            260                 265                 270

aag aag acc gct tca agc gcc tgg gac ccg gca acc gtt atg cga atc   864
Lys Lys Thr Ala Ser Ser Ala Trp Asp Pro Ala Thr Val Met Arg Ile
        275                 280                 285

ctt cgg gac ccg cgt att gcg ggc ttc gcc gct gag gtg atc tac aag   912
Leu Arg Asp Pro Arg Ile Ala Gly Phe Ala Ala Glu Val Ile Tyr Lys
    290                 295                 300

aag aag ccg gac ggc acg ccg acc acg aag att gag ggt tac cgc att   960
Lys Lys Pro Asp Gly Thr Pro Thr Thr Lys Ile Glu Gly Tyr Arg Ile
305                 310                 315                 320

cag cgc gac ccg atc acg ctc cgg ccg gtc gag ctt gat tgc gga ccg  1008
Gln Arg Asp Pro Ile Thr Leu Arg Pro Val Glu Leu Asp Cys Gly Pro
                325                 330                 335

atc atc gag ccc gct gag tgg tat gag ctt cag gcg tgg ttg gac ggc  1056
Ile Ile Glu Pro Ala Glu Trp Tyr Glu Leu Gln Ala Trp Leu Asp Gly
            340                 345                 350

agg ggg cgc ggc aag ggg ctt tcc cgg ggg caa gcc att ctg tcc gcc  1104
Arg Gly Arg Gly Lys Gly Leu Ser Arg Gly Gln Ala Ile Leu Ser Ala
        355                 360                 365

atg gac aag ctg tac tgc gag tgt ggc gcc gtc atg act tcg aag cgc  1152
Met Asp Lys Leu Tyr Cys Glu Cys Gly Ala Val Met Thr Ser Lys Arg
    370                 375                 380

ggg gaa gaa tcg atc aag gac tct tac cgc tgc cgt cgc cgg aag gtg  1200
Gly Glu Glu Ser Ile Lys Asp Ser Tyr Arg Cys Arg Arg Arg Lys Val
385                 390                 395                 400

gtc gac ccg tcc gca cct ggg cag cac gaa ggc acg tgc aac gtc agc  1248
Val Asp Pro Ser Ala Pro Gly Gln His Glu Gly Thr Cys Asn Val Ser
                405                 410                 415

atg gcg gca ctc gac aag ttc gtt gcg gaa cgc atc ttc aac aag atc  1296
Met Ala Ala Leu Asp Lys Phe Val Ala Glu Arg Ile Phe Asn Lys Ile
            420                 425                 430

agg cac gcc gaa ggc gac gaa gag acg ttg gcg ctt ctg tgg gaa gcc  1344
Arg His Ala Glu Gly Asp Glu Glu Thr Leu Ala Leu Leu Trp Glu Ala
        435                 440                 445

gcc cga cgc ttc ggc aag ctc act gag gcg cct gag aag agc ggc gaa  1392
Ala Arg Arg Phe Gly Lys Leu Thr Glu Ala Pro Glu Lys Ser Gly Glu
    450                 455                 460

cgg gcg aac ctt gtt gcg gag cgc gcc gac gcc ctg aac gcc ctt gaa  1440
Arg Ala Asn Leu Val Ala Glu Arg Ala Asp Ala Leu Asn Ala Leu Glu
465                 470                 475                 480

gag ctg tac gaa gac cgc gcg gca ggc gcg tac gac gga ccc gtt ggc  1488
Glu Leu Tyr Glu Asp Arg Ala Ala Gly Ala Tyr Asp Gly Pro Val Gly
                485                 490                 495

agg aag cac ttc cgg aag caa cag gca gcg ctg acg ctc cgg cag caa  1536
Arg Lys His Phe Arg Lys Gln Gln Ala Ala Leu Thr Leu Arg Gln Gln
            500                 505                 510
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ggg gcg gaa gag cgg ctt gcc gaa ctt gaa gcc gcc gaa gcc ccg aag   1584
Gly Ala Glu Glu Arg Leu Ala Glu Leu Glu Ala Ala Glu Ala Pro Lys
        515                 520                 525

ctt ccc ctt gac caa tgg ttc ccc gaa gac gcc gac gct gac ccg acc   1632
Leu Pro Leu Asp Gln Trp Phe Pro Glu Asp Ala Asp Ala Asp Pro Thr
    530                 535                 540

ggc cct aag tcg tgg tgg ggg cgc gcg tca gta gac gac aag cgc gtg   1680
Gly Pro Lys Ser Trp Trp Gly Arg Ala Ser Val Asp Asp Lys Arg Val
545                 550                 555                 560

ttc gtc ggg ctc ttc gta gac aag atc gtt gtc acg aag tcg act acg   1728
Phe Val Gly Leu Phe Val Asp Lys Ile Val Val Thr Lys Ser Thr Thr
                565                 570                 575

ggc agg ggg cag gga acg ccc atc gag aag cgc gct tcg atc acg tgg   1776
Gly Arg Gly Gln Gly Thr Pro Ile Glu Lys Arg Ala Ser Ile Thr Trp
            580                 585                 590

gcg aag ccg ccg acc gac gac gac gaa gac gac gcc cag gac ggc acg   1824
Ala Lys Pro Pro Thr Asp Asp Asp Glu Asp Asp Ala Gln Asp Gly Thr
        595                 600                 605

gaa gac gta gcg gcg tag                                          1842
Glu Asp Val Ala Ala
    610
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<210> 21
<211> 613
<212> PRT
<213> Bacteriophage phi-C31

<400> 21

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Asp Arg Gln Ser Arg Glu Arg Glu Asn Ser Ser Ala Ala Ser Pro Ala
             20                  25                  30

Thr Gln Arg Ser Ala Asn Glu Asp Lys Ala Ala Asp Leu Gln Arg Glu
         35                  40                  45

Val Glu Arg Asp Gly Gly Arg Phe Arg Phe Val Gly His Phe Ser Glu
     50                  55                  60

Ala Pro Gly Thr Ser Ala Phe Gly Thr Ala Glu Arg Pro Glu Phe Glu
 65                  70                  75                  80

Arg Ile Leu Asn Glu Cys Arg Ala Gly Arg Leu Asn Met Ile Ile Val
                 85                  90                  95

Tyr Asp Val Ser Arg Phe Ser Arg Leu Lys Val Met Asp Ala Ile Pro
            100                 105                 110

Ile Val Ser Glu Leu Leu Ala Leu Gly Val Thr Ile Val Ser Thr Gln
        115                 120                 125

Glu Gly Val Phe Arg Gln Gly Asn Val Met Asp Leu Ile His Leu Ile
    130                 135                 140

Met Arg Leu Asp Ala Ser His Lys Glu Ser Ser Leu Lys Ser Ala Lys
145                 150                 155                 160

Ile Leu Asp Thr Lys Asn Leu Gln Arg Glu Leu Gly Gly Tyr Val Gly
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165 170 175

Gly Lys Ala Pro Tyr Gly Phe Glu Leu Val Ser Glu Thr Lys Glu Ile
180 185 190

Thr Arg Asn Gly Arg Met Val Asn Val Val Ile Asn Lys Leu Ala His
195 200 205

Ser Thr Thr Pro Leu Thr Gly Pro Phe Glu Phe Glu Pro Asp Val Ile
210 215 220

Arg Trp Trp Trp Arg Glu Ile Lys Thr His Lys His Leu Pro Phe Lys
225 230 235 240

Pro Gly Ser Gln Ala Ala Ile His Pro Gly Ser Ile Thr Gly Leu Cys
245 250 255

Lys Arg Met Asp Ala Asp Ala Val Pro Thr Arg Gly Glu Thr Ile Gly
260 265 270

Lys Lys Thr Ala Ser Ser Ala Trp Asp Pro Ala Thr Val Met Arg Ile
275 280 285

Leu Arg Asp Pro Arg Ile Ala Gly Phe Ala Ala Glu Val Ile Tyr Lys
290 295 300

Lys Lys Pro Asp Gly Thr Pro Thr Thr Lys Ile Glu Gly Tyr Arg Ile
305 310 315 320

Gln Arg Asp Pro Ile Thr Leu Arg Pro Val Glu Leu Asp Cys Gly Pro
325 330 335

Ile Ile Glu Pro Ala Glu Trp Tyr Glu Leu Gln Ala Trp Leu Asp Gly
340 345 350

Arg Gly Arg Gly Lys Gly Leu Ser Arg Gly Gln Ala Ile Leu Ser Ala
355 360 365

Met Asp Lys Leu Tyr Cys Glu Cys Gly Ala Val Met Thr Ser Lys Arg
370 375 380

Gly Glu Glu Ser Ile Lys Asp Ser Tyr Arg Cys Arg Arg Arg Lys Val
385 390 395 400

Val Asp Pro Ser Ala Pro Gly Gln His Glu Gly Thr Cys Asn Val Ser
405 410 415

Met Ala Ala Leu Asp Lys Phe Val Ala Glu Arg Ile Phe Asn Lys Ile
420 425 430

Arg His Ala Glu Gly Asp Glu Glu Thr Leu Ala Leu Leu Trp Glu Ala
435 440 445

Ala Arg Arg Phe Gly Lys Leu Thr Glu Ala Pro Glu Lys Ser Gly Glu
450 455 460

Arg Ala Asn Leu Val Ala Glu Arg Ala Asp Ala Leu Asn Ala Leu Glu
465 470 475 480

Glu Leu Tyr Glu Asp Arg Ala Ala Gly Ala Tyr Asp Gly Pro Val Gly
485 490 495

Arg Lys His Phe Arg Lys Gln Gln Ala Ala Leu Thr Leu Arg Gln Gln
500 505 510

Gly Ala Glu Glu Arg Leu Ala Glu Leu Glu Ala Ala Glu Ala Pro Lys
515 520 525

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Leu Pro Leu Asp Gln Trp Phe Pro Glu Asp Ala Asp Ala Asp Pro Thr
    530                 535                 540

Gly Pro Lys Ser Trp Trp Gly Arg Ala Ser Val Asp Asp Lys Arg Val
545                 550                 555                 560

Phe Val Gly Leu Phe Val Asp Lys Ile Val Val Thr Lys Ser Thr Thr
                565                 570                 575

Gly Arg Gly Gln Gly Thr Pro Ile Glu Lys Arg Ala Ser Ile Thr Trp
            580                 585                 590

Ala Lys Pro Pro Thr Asp Asp Asp Glu Asp Asp Ala Gln Asp Gly Thr
        595                 600                 605

Glu Asp Val Ala Ala
    610
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<210> 22
<211> 1863
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: DNA sequence coding for fusion protein C31-Int(CNLS)

<220>
<221> CDS
<222> (1)..(1860)

<400> 22

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atg aca caa ggg gtt gtg acc ggg gtg gac acg tac gcg ggt gct tac   48
Met Thr Gln Gly Val Val Thr Gly Val Asp Thr Tyr Ala Gly Ala Tyr
  1               5                  10                  15

gac cgt cag tcg cgc gag cgc gag aat tcg agc gca gca agc cca gcg   96
Asp Arg Gln Ser Arg Glu Arg Glu Asn Ser Ser Ala Ala Ser Pro Ala
             20                  25                  30

aca cag cgt agc gcc aac gaa gac aag gcg gcc gac ctt cag cgc gaa   144
Thr Gln Arg Ser Ala Asn Glu Asp Lys Ala Ala Asp Leu Gln Arg Glu
         35                  40                  45

gtc gag cgc gac ggg ggc cgg ttc agg ttc gtc ggg cat ttc agc gaa   192
Val Glu Arg Asp Gly Gly Arg Phe Arg Phe Val Gly His Phe Ser Glu
     50                  55                  60

gcg ccg ggc acg tcg gcg ttc ggg acg gcg gag cgc ccg gag ttc gaa   240
Ala Pro Gly Thr Ser Ala Phe Gly Thr Ala Glu Arg Pro Glu Phe Glu
 65                  70                  75                  80

cgc atc ctg aac gaa tgc cgc gcc ggg cgg ctc aac atg atc att gtc   288
Arg Ile Leu Asn Glu Cys Arg Ala Gly Arg Leu Asn Met Ile Ile Val
                 85                  90                  95

tat gac gtg tcg cgc ttc tcg cgc ctg aag gtc atg gac gcg att ccg   336
Tyr Asp Val Ser Arg Phe Ser Arg Leu Lys Val Met Asp Ala Ile Pro
            100                 105                 110

att gtc tcg gaa ttg ctc gcc ctg ggc gtg acg att gtt tcc act cag   384
Ile Val Ser Glu Leu Leu Ala Leu Gly Val Thr Ile Val Ser Thr Gln
        115                 120                 125
```

```
gaa ggc gtc ttc cgg cag gga aac gtc atg gac ctg att cac ctg att   432
Glu Gly Val Phe Arg Gln Gly Asn Val Met Asp Leu Ile His Leu Ile
    130                 135                 140

atg cgg ctc gac gcg tcg cac aaa gaa tct tcg ctg aag tcg gcg aag   480
Met Arg Leu Asp Ala Ser His Lys Glu Ser Ser Leu Lys Ser Ala Lys
145                 150                 155                 160

att ctc gac acg aag aac ctt cag cgc gaa ttg ggc ggg tac gtc ggc   528
Ile Leu Asp Thr Lys Asn Leu Gln Arg Glu Leu Gly Gly Tyr Val Gly
                165                 170                 175

ggg aag gcg cct tac ggc ttc gag ctt gtt tcg gag acg aag gag atc   576
Gly Lys Ala Pro Tyr Gly Phe Glu Leu Val Ser Glu Thr Lys Glu Ile
            180                 185                 190

acg cgc aac ggc cga atg gtc aat gtc gtc atc aac aag ctt gcg cac   624
Thr Arg Asn Gly Arg Met Val Asn Val Val Ile Asn Lys Leu Ala His
        195                 200                 205

tcg acc act ccc ctt acc gga ccc ttc gag ttc gag ccc gac gta atc   672
Ser Thr Thr Pro Leu Thr Gly Pro Phe Glu Phe Glu Pro Asp Val Ile
    210                 215                 220

cgg tgg tgg tgg cgt gag atc aag acg cac aaa cac ctt ccc ttc aag   720
Arg Trp Trp Trp Arg Glu Ile Lys Thr His Lys His Leu Pro Phe Lys
225                 230                 235                 240

ccg ggc agt caa gcc gcc att cac ccg ggc agc atc acg ggg ctt tgt   768
Pro Gly Ser Gln Ala Ala Ile His Pro Gly Ser Ile Thr Gly Leu Cys
                245                 250                 255

aag cgc atg gac gct gac gcc gtg ccg acc cgg ggc gag acg att ggg   816
Lys Arg Met Asp Ala Asp Ala Val Pro Thr Arg Gly Glu Thr Ile Gly
            260                 265                 270

aag aag acc gct tca agc gcc tgg gac ccg gca acc gtt atg cga atc   864
Lys Lys Thr Ala Ser Ser Ala Trp Asp Pro Ala Thr Val Met Arg Ile
        275                 280                 285

ctt cgg gac ccg cgt att gcg ggc ttc gcc gct gag gtg atc tac aag   912
Leu Arg Asp Pro Arg Ile Ala Gly Phe Ala Ala Glu Val Ile Tyr Lys
    290                 295                 300

aag aag ccg gac ggc acg ccg acc acg aag att gag ggt tac cgc att   960
Lys Lys Pro Asp Gly Thr Pro Thr Thr Lys Ile Glu Gly Tyr Arg Ile
305                 310                 315                 320

cag cgc gac ccg atc acg ctc cgg ccg gtc gag ctt gat tgc gga ccg   1008
Gln Arg Asp Pro Ile Thr Leu Arg Pro Val Glu Leu Asp Cys Gly Pro
                325                 330                 335

atc atc gag ccc gct gag tgg tat gag ctt cag gcg tgg ttg gac ggc   1056
Ile Ile Glu Pro Ala Glu Trp Tyr Glu Leu Gln Ala Trp Leu Asp Gly
            340                 345                 350

agg ggg cgc ggc aag ggg ctt tcc cgg ggg caa gcc att ctg tcc gcc   1104
Arg Gly Arg Gly Lys Gly Leu Ser Arg Gly Gln Ala Ile Leu Ser Ala
        355                 360                 365

atg gac aag ctg tac tgc gag tgt ggc gcc gtc atg act tcg aag cgc   1152
Met Asp Lys Leu Tyr Cys Glu Cys Gly Ala Val Met Thr Ser Lys Arg
    370                 375                 380

ggg gaa gaa tcg atc aag gac tct tac cgc tgc cgt cgc cgg aag gtg   1200
Gly Glu Glu Ser Ile Lys Asp Ser Tyr Arg Cys Arg Arg Arg Lys Val
385                 390                 395                 400
```

```
gtc gac ccg tcc gca cct ggg cag cac gaa ggc acg tgc aac gtc agc   1248
Val Asp Pro Ser Ala Pro Gly Gln His Glu Gly Thr Cys Asn Val Ser
            405                 410                 415

atg gcg gca ctc gac aag ttc gtt gcg gaa cgc atc ttc aac aag atc   1296
Met Ala Ala Leu Asp Lys Phe Val Ala Glu Arg Ile Phe Asn Lys Ile
        420                 425                 430

agg cac gcc gaa ggc gac gaa gag acg ttg gcg ctt ctg tgg gaa gcc   1344
Arg His Ala Glu Gly Asp Glu Glu Thr Leu Ala Leu Leu Trp Glu Ala
    435                 440                 445

gcc cga cgc ttc ggc aag ctc act gag gcg cct gag aag agc ggc gaa   1392
Ala Arg Arg Phe Gly Lys Leu Thr Glu Ala Pro Glu Lys Ser Gly Glu
450                 455                 460

cgg gcg aac ctt gtt gcg gag cgc gcc gac gcc ctg aac gcc ctt gaa   1440
Arg Ala Asn Leu Val Ala Glu Arg Ala Asp Ala Leu Asn Ala Leu Glu
465                 470                 475                 480

gag ctg tac gaa gac cgc gcg gca ggc gcg tac gac gga ccc gtt ggc   1488
Glu Leu Tyr Glu Asp Arg Ala Ala Gly Ala Tyr Asp Gly Pro Val Gly
            485                 490                 495

agg aag cac ttc cgg aag caa cag gca gcg ctg acg ctc cgg cag caa   1536
Arg Lys His Phe Arg Lys Gln Gln Ala Ala Leu Thr Leu Arg Gln Gln
        500                 505                 510

ggg gcg gaa gag cgg ctt gcc gaa ctt gaa gcc gcc gaa gcc ccg aag   1584
Gly Ala Glu Glu Arg Leu Ala Glu Leu Glu Ala Ala Glu Ala Pro Lys
    515                 520                 525

ctt ccc ctt gac caa tgg ttc ccc gaa gac gcc gac gct gac ccg acc   1632
Leu Pro Leu Asp Gln Trp Phe Pro Glu Asp Ala Asp Ala Asp Pro Thr
530                 535                 540

ggc cct aag tcg tgg tgg ggg cgc gcg tca gta gac gac aag cgc gtg   1680
Gly Pro Lys Ser Trp Trp Gly Arg Ala Ser Val Asp Asp Lys Arg Val
545                 550                 555                 560

ttc gtc ggg ctc ttc gta gac aag atc gtt gtc acg aag tcg act acg   1728
Phe Val Gly Leu Phe Val Asp Lys Ile Val Val Thr Lys Ser Thr Thr
            565                 570                 575

ggc agg ggg cag gga acg ccc atc gag aag cgc gct tcg atc acg tgg   1776
Gly Arg Gly Gln Gly Thr Pro Ile Glu Lys Arg Ala Ser Ile Thr Trp
        580                 585                 590

gcg aag ccg ccg acc gac gac gac gaa gac gac gcc cag gac ggc acg   1824
Ala Lys Pro Pro Thr Asp Asp Asp Glu Asp Asp Ala Gln Asp Gly Thr
    595                 600                 605

gaa gac gta gcg gcg cct aag aag aag agg aag gtt tag               1863
Glu Asp Val Ala Ala Pro Lys Lys Lys Arg Lys Val
610                 615                 620
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<210> 23
<211> 620
<212> PRT
<213> Artificial Sequence
<223> Description of Artificial Sequence: DNA sequence coding for fusion protein C31-Int(CNLS)

<400> 23
Met Thr Gln Gly Val Val Thr Gly Val Asp Thr Tyr Ala Gly Ala Tyr

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1               5                  10                  15

Asp Arg Gln Ser Arg Glu Arg Glu Asn Ser Ser Ala Ala Ser Pro Ala
            20                  25                  30

Thr Gln Arg Ser Ala Asn Glu Asp Lys Ala Ala Asp Leu Gln Arg Glu
        35                  40                  45

Val Glu Arg Asp Gly Gly Arg Phe Arg Phe Val Gly His Phe Ser Glu
    50                  55                  60

Ala Pro Gly Thr Ser Ala Phe Gly Thr Ala Glu Arg Pro Glu Phe Glu
65                  70                  75                  80

Arg Ile Leu Asn Glu Cys Arg Ala Gly Arg Leu Asn Met Ile Ile Val
                85                  90                  95

Tyr Asp Val Ser Arg Phe Ser Arg Leu Lys Val Met Asp Ala Ile Pro
            100                 105                 110

Ile Val Ser Glu Leu Leu Ala Leu Gly Val Thr Ile Val Ser Thr Gln
        115                 120                 125

Glu Gly Val Phe Arg Gln Gly Asn Val Met Asp Leu Ile His Leu Ile
    130                 135                 140

Met Arg Leu Asp Ala Ser His Lys Glu Ser Ser Leu Lys Ser Ala Lys
145                 150                 155                 160

Ile Leu Asp Thr Lys Asn Leu Gln Arg Glu Leu Gly Gly Tyr Val Gly
                165                 170                 175

Gly Lys Ala Pro Tyr Gly Phe Glu Leu Val Ser Glu Thr Lys Glu Ile
            180                 185                 190

Thr Arg Asn Gly Arg Met Val Asn Val Val Ile Asn Lys Leu Ala His
        195                 200                 205

Ser Thr Thr Pro Leu Thr Gly Pro Phe Glu Phe Glu Pro Asp Val Ile
    210                 215                 220

Arg Trp Trp Trp Arg Glu Ile Lys Thr His Lys His Leu Pro Phe Lys
225                 230                 235                 240

Pro Gly Ser Gln Ala Ala Ile His Pro Gly Ser Ile Thr Gly Leu Cys
                245                 250                 255

Lys Arg Met Asp Ala Asp Ala Val Pro Thr Arg Gly Glu Thr Ile Gly
            260                 265                 270

Lys Lys Thr Ala Ser Ser Ala Trp Asp Pro Ala Thr Val Met Arg Ile
        275                 280                 285

Leu Arg Asp Pro Arg Ile Ala Gly Phe Ala Ala Glu Val Ile Tyr Lys
    290                 295                 300

Lys Lys Pro Asp Gly Thr Pro Thr Thr Lys Ile Glu Gly Tyr Arg Ile
305                 310                 315                 320

Gln Arg Asp Pro Ile Thr Leu Arg Pro Val Glu Leu Asp Cys Gly Pro
                325                 330                 335

Ile Ile Glu Pro Ala Glu Trp Tyr Glu Leu Gln Ala Trp Leu Asp Gly
            340                 345                 350

Arg Gly Arg Gly Lys Gly Leu Ser Arg Gly Gln Ala Ile Leu Ser Ala
        355                 360                 365
```

Met Asp Lys Leu Tyr Cys Glu Cys Gly Ala Val Met Thr Ser Lys Arg
370 375 380

Gly Glu Glu Ser Ile Lys Asp Ser Tyr Arg Cys Arg Arg Arg Lys Val
385 390 395 400

Val Asp Pro Ser Ala Pro Gly Gln His Glu Gly Thr Cys Asn Val Ser
405 410 415

Met Ala Ala Leu Asp Lys Phe Val Ala Glu Arg Ile Phe Asn Lys Ile
420 425 430

Arg His Ala Glu Gly Asp Glu Glu Thr Leu Ala Leu Leu Trp Glu Ala
435 440 445

Ala Arg Arg Phe Gly Lys Leu Thr Glu Ala Pro Glu Lys Ser Gly Glu
450 455 460

Arg Ala Asn Leu Val Ala Glu Arg Ala Asp Ala Leu Asn Ala Leu Glu
465 470 475 480

Glu Leu Tyr Glu Asp Arg Ala Ala Gly Ala Tyr Asp Gly Pro Val Gly
485 490 495

Arg Lys His Phe Arg Lys Gln Gln Ala Ala Leu Thr Leu Arg Gln Gln
500 505 510

Gly Ala Glu Glu Arg Leu Ala Glu Leu Glu Ala Ala Glu Ala Pro Lys
515 520 525

Leu Pro Leu Asp Gln Trp Phe Pro Glu Asp Ala Asp Ala Asp Pro Thr
530 535 540

Gly Pro Lys Ser Trp Trp Gly Arg Ala Ser Val Asp Asp Lys Arg Val
545 550 555 560

Phe Val Gly Leu Phe Val Asp Lys Ile Val Val Thr Lys Ser Thr Thr
565 570 575

Gly Arg Gly Gln Gly Thr Pro Ile Glu Lys Arg Ala Ser Ile Thr Trp
580 585 590

Ala Lys Pro Pro Thr Asp Asp Asp Glu Asp Asp Ala Gln Asp Gly Thr
595 600 605

Glu Asp Val Ala Ala Pro Lys Lys Lys Arg Lys Val
610 615 620

<210> 24
<211> 43
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: NLS

<400> 24
Met Lys Lys Lys Lys Lys Lys Lys Lys Lys Lys Lys Cys Arg Leu Lys
1 5 10 15

Lys Leu Lys Cys Ser Lys Glu Lys Pro Lys Cys Ala Lys Cys Leu Lys
20 25 30

Lys Lys Lys Lys Arg Arg Arg Lys Thr Lys Arg

35 40

<210> 25
<211> 10
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: NLS

<400> 25
Ile Lys Tyr Phe Lys Lys Phe Pro Lys Asp
1 5 10

<210> 26
<211> 14
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: NLS

<400> 26
Met Thr Gly Ser Lys Thr Arg Lys His Arg Gly Ser Gly Ala
1 5 10

<210> 27
<211> 14
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: NLS

<400> 27
Met Thr Gly Ser Lys His Arg Lys His Pro Gly Ser Gly Ala
1 5 10

<210> 28
<211> 7
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: NLS

<400> 28
Gly Lys Lys Arg Ser Lys Ala
1 5

<210> 29
<211> 14
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: NLS

<400> 29
Pro Lys Lys Ala Arg Glu Asp Val Ser Arg Lys Arg Pro Arg
1 5 10

<210> 30
<211> 11
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: NLS

<400> 30
Ala Pro Lys Arg Lys Ser Gly Val Ser Lys Cys
1 5 10

<210> 31
<211> 12
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: NLS

<400> 31
Glu Glu Asp Gly Pro Gln Lys Lys Lys Arg Arg Leu
1 5 10

<210> 32
<211> 8
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: NLS

<400> 32
Ala Pro Thr Lys Arg Lys Gly Ser
1 5

<210> 33
<211> 7
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: NLS

<400> 33
Pro Asn Lys Lys Lys Arg Lys
1 5

<210> 34
<211> 5
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: NLS

<400> 34
Lys Arg Pro Arg Pro
1 5

<210> 35

<211> 11
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: NLS

<400> 35
Cys Gly Gly Leu Ser Ser Lys Arg Pro Arg Pro
1 5 10

<210> 36
<211> 19
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: NLS

<400> 36
Pro Pro Lys Lys Arg Met Arg Arg Arg Ile Glu Pro Lys Lys Lys Lys
1 5 10 15

Lys Arg Pro

<210> 37
<211> 11
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: NLS

<400> 37
Pro Phe Leu Asp Arg Leu Arg Arg Asp Gln Lys
1 5 10

<210> 38
<211> 9
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: NLS

<400> 38
Pro Lys Gln Lys Arg Lys Met Ala Arg
1 5

<210> 39
<211> 9
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: NLS

<400> 39
Ser Val Thr Lys Lys Arg Lys Leu Glu
1 5

<210> 40
<211> 11
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: NLS

<400> 40
Cys Gly Gly Ala Ala Lys Arg Val Lys Leu Asp
1 5 10

<210> 41
<211> 9
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: NLS

<400> 41
Pro Ala Ala Lys Arg Val Lys Leu Asp
1 5

<210> 42
<211> 11
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: NLS

<400> 42
Arg Gln Arg Arg Asn Glu Leu Lys Arg Ser Pro
1 5 10

<210> 43
<211> 8
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: NLS

<400> 43
Pro Gln Ser Arg Lys Lys Leu Arg
1 5

<210> 44
<211> 8
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: NLS

<400> 44
Pro Leu Leu Lys Lys Ile Lys Gln
1 5

<210> 45
<211> 7

<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: NLS

<400> 45
Pro Gln Pro Lys Lys Lys Pro
1 5

<210> 46
<211> 9
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: NLS

<400> 46
Ser Lys Arg Val Ala Lys Arg Lys Leu
1 5

<210> 47
<211> 9
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: NLS

<400> 47
Ala Ser Lys Ser Arg Lys Arg Lys Leu
1 5

<210> 48
<211> 16
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: NLS

<400> 48
Gly Gly Leu Cys Ser Ala Arg Leu His Arg His Ala Leu Leu Ala Thr
1 5 10 15

<210> 49
<211> 8
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: NLS

<400> 49
Arg Lys Thr Lys Lys Lys Ile Lys
1 5

<210> 50
<211> 8
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: NLS

<400> 50
Arg Lys Leu Lys Lys Leu Gly Asn
1 5

<210> 51
<211> 8
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: NLS

<400> 51
Arg Lys Asp Arg Arg Gly Gly Arg
1 5

<210> 52
<211> 18
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: NLS

<400> 52
Asp Thr Arg Glu Lys Lys Lys Phe Leu Lys Arg Arg Leu Leu Arg Leu
1 5 10 15

Asp Glu

<210> 53
<211> 7
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: NLS

<400> 53
Pro Lys Lys Lys Arg Lys Val
1 5

<210> 54
<211> 1410
<212> DNA
<213> Bacteriophage R4

<220>
<221> CDS
<222> (1)..(1407)

<400> 54
atg aat cga ggg ggg ccc act gta cgg gcc gac atc tac gtc cga atc 48
Met Asn Arg Gly Gly Pro Thr Val Arg Ala Asp Ile Tyr Val Arg Ile
1 5 10 15

agc ctg gac cgc aca ggg gaa gag ctc ggg gtc gag cgc cag gag gag 96
Ser Leu Asp Arg Thr Gly Glu Glu Leu Gly Val Glu Arg Gln Glu Glu

30

20 25 30

```
tcg tgt cgc gag ctc tgc aag agc ctc ggc atg gag gtg ggg cag gtg   144
Ser Cys Arg Glu Leu Cys Lys Ser Leu Gly Met Glu Val Gly Gln Val
          35                  40                  45

tgg gtc gac aac gac ctg agc gcc acc aag aag aac gtc gtc cgc cct   192
Trp Val Asp Asn Asp Leu Ser Ala Thr Lys Lys Asn Val Val Arg Pro
     50                  55                  60

gac ttc gag gcg atg atc gcg agc aac ccg cag gcg atc gtc tgc tgg   240
Asp Phe Glu Ala Met Ile Ala Ser Asn Pro Gln Ala Ile Val Cys Trp
 65                  70                  75                  80

cac acc gac cgg ctc atc cgc gtc acg cgg gac ctg gag cgg gtg atc   288
His Thr Asp Arg Leu Ile Arg Val Thr Arg Asp Leu Glu Arg Val Ile
                 85                  90                  95

gac ctc gga gtc aac gtc cac gcc gtg atg gcc gga cac ctg gac ctg   336
Asp Leu Gly Val Asn Val His Ala Val Met Ala Gly His Leu Asp Leu
            100                 105                 110

tcc acc ccg gcc ggc cga gcc gtc gcc cgc acg gtg acg gcc tgg gcc   384
Ser Thr Pro Ala Gly Arg Ala Val Ala Arg Thr Val Thr Ala Trp Ala
        115                 120                 125

acg tac gag ggc gag cag aag gct gag cgc cag aag ctc gcc aac atc   432
Thr Tyr Glu Gly Glu Gln Lys Ala Glu Arg Gln Lys Leu Ala Asn Ile
    130                 135                 140

cag aac gcc cgc gcc ggc aag ccg tac acc ccc ggc atc cgc ccc ttc   480
Gln Asn Ala Arg Ala Gly Lys Pro Tyr Thr Pro Gly Ile Arg Pro Phe
145                 150                 155                 160

ggg tac ggc gac gac cac atg acc atc gtg acg gcc gag gcg gac gcc   528
Gly Tyr Gly Asp Asp His Met Thr Ile Val Thr Ala Glu Ala Asp Ala
                165                 170                 175

atc cgc gac ggc gcg aag atg atc ctc gac ggc tgg tcc ctg tcg gcc   576
Ile Arg Asp Gly Ala Lys Met Ile Leu Asp Gly Trp Ser Leu Ser Ala
            180                 185                 190

gtg gct cgc tac tgg gag gag ctc aag ctc cag tcg ccc cgg agt atg   624
Val Ala Arg Tyr Trp Glu Glu Leu Lys Leu Gln Ser Pro Arg Ser Met
        195                 200                 205

gcc gca ggc ggc aag ggc tgg tct ctg cgg ggc gta aag aag gtg ctg   672
Ala Ala Gly Gly Lys Gly Trp Ser Leu Arg Gly Val Lys Lys Val Leu
    210                 215                 220

acc tcc ccg cgc tac gtc ggg cgg tcc agc tac ctc ggg gag gtc gtg   720
Thr Ser Pro Arg Tyr Val Gly Arg Ser Ser Tyr Leu Gly Glu Val Val
225                 230                 235                 240

ggc gat gct cag tgg ccg ccc atc ctc gac ccg gac gtc tac tac ggg   768
Gly Asp Ala Gln Trp Pro Pro Ile Leu Asp Pro Asp Val Tyr Tyr Gly
                245                 250                 255

gtc gtg gcc atc ctg aac aac ccc gac cgc ttc agc ggg ggc cct cgg   816
Val Val Ala Ile Leu Asn Asn Pro Asp Arg Phe Ser Gly Gly Pro Arg
            260                 265                 270

acc ggc cgc acc ccc ggc acg ctg ctc gca ggc atc gcc ttg tgc ggt   864
Thr Gly Arg Thr Pro Gly Thr Leu Leu Ala Gly Ile Ala Leu Cys Gly
        275                 280                 285

gag tgc ggc aag acg gtc agt gga cgc ggc tac cga ggt gtc ctg gtc   912
```

```
Glu Cys Gly Lys Thr Val Ser Gly Arg Gly Tyr Arg Gly Val Leu Val
    290                 295                 300

tac gga tgt aag gac acg cac act cgg acg cct cgg agc atc gct gac   960
Tyr Gly Cys Lys Asp Thr His Thr Arg Thr Pro Arg Ser Ile Ala Asp
305                 310                 315                 320

ggc cgc gcg agc agc tcg acc ctc gcc cgg ctc atg ttc ccc gac ttc   1008
Gly Arg Ala Ser Ser Ser Thr Leu Ala Arg Leu Met Phe Pro Asp Phe
                325                 330                 335

ctg ccc ggc ctc ctg gcc tct ggg cag gcc gag gac ggc cag tcg gca   1056
Leu Pro Gly Leu Leu Ala Ser Gly Gln Ala Glu Asp Gly Gln Ser Ala
            340                 345                 350

gca tcc aag cac tcg gag gcc cag acg ctg cgc gag cgc ctt gac ggg   1104
Ala Ser Lys His Ser Glu Ala Gln Thr Leu Arg Glu Arg Leu Asp Gly
        355                 360                 365

ctg gct acg gcc tac gcg gag ggt gcg atc agc ctg tct cag atg acg   1152
Leu Ala Thr Ala Tyr Ala Glu Gly Ala Ile Ser Leu Ser Gln Met Thr
    370                 375                 380

gcc ggc tcg gaa gca ctg cgg aag aag ctg gag gtg atc gaa gcc gac   1200
Ala Gly Ser Glu Ala Leu Arg Lys Lys Leu Glu Val Ile Glu Ala Asp
385                 390                 395                 400

ctc gtg ggc tcg gca ggc atc ccg ccc ttc gat cca gtg gcc gga gtg   1248
Leu Val Gly Ser Ala Gly Ile Pro Pro Phe Asp Pro Val Ala Gly Val
                405                 410                 415

gct ggc ctg atc tcc ggc tgg ccc acc acg cct ctc ccg acg cgt cga   1296
Ala Gly Leu Ile Ser Gly Trp Pro Thr Thr Pro Leu Pro Thr Arg Arg
            420                 425                 430

gca tgg gtg gac ttc tgc ctg gtg gtc acg ctg aac acc cag aag ggg   1344
Ala Trp Val Asp Phe Cys Leu Val Val Thr Leu Asn Thr Gln Lys Gly
        435                 440                 445

cgc cat gcg tcg agc atg acc gtg gac gac cac gtc acc atc gag tgg   1392
Arg His Ala Ser Ser Met Thr Val Asp Asp His Val Thr Ile Glu Trp
    450                 455                 460

cga gac gtg gcc gag tag                                          1410
Arg Asp Val Ala Glu
465
```

<210> 55
<211> 469
<212> PRT
<213> Bacteriophage R4

<400> 55

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Met Asn Arg Gly Gly Pro Thr Val Arg Ala Asp Ile Tyr Val Arg Ile
  1               5                  10                  15

Ser Leu Asp Arg Thr Gly Glu Glu Leu Gly Val Glu Arg Gln Glu Glu
             20                  25                  30

Ser Cys Arg Glu Leu Cys Lys Ser Leu Gly Met Glu Val Gly Gln Val
         35                  40                  45

Trp Val Asp Asn Asp Leu Ser Ala Thr Lys Lys Asn Val Val Arg Pro
     50                  55                  60

Asp Phe Glu Ala Met Ile Ala Ser Asn Pro Gln Ala Ile Val Cys Trp
```

65 70 75 80

His Thr Asp Arg Leu Ile Arg Val Thr Arg Asp Leu Glu Arg Val Ile
85 90 95

Asp Leu Gly Val Asn Val His Ala Val Met Ala Gly His Leu Asp Leu
100 105 110

Ser Thr Pro Ala Gly Arg Ala Val Ala Arg Thr Val Thr Ala Trp Ala
115 120 125

Thr Tyr Glu Gly Glu Gln Lys Ala Glu Arg Gln Lys Leu Ala Asn Ile
130 135 140

Gln Asn Ala Arg Ala Gly Lys Pro Tyr Thr Pro Gly Ile Arg Pro Phe
145 150 155 160

Gly Tyr Gly Asp Asp His Met Thr Ile Val Thr Ala Glu Ala Asp Ala
165 170 175

Ile Arg Asp Gly Ala Lys Met Ile Leu Asp Gly Trp Ser Leu Ser Ala
180 185 190

Val Ala Arg Tyr Trp Glu Glu Leu Lys Leu Gln Ser Pro Arg Ser Met
195 200 205

Ala Ala Gly Gly Lys Gly Trp Ser Leu Arg Gly Val Lys Lys Val Leu
210 215 220

Thr Ser Pro Arg Tyr Val Gly Arg Ser Ser Tyr Leu Gly Glu Val Val
225 230 235 240

Gly Asp Ala Gln Trp Pro Pro Ile Leu Asp Pro Asp Val Tyr Tyr Gly
245 250 255

Val Val Ala Ile Leu Asn Asn Pro Asp Arg Phe Ser Gly Gly Pro Arg
260 265 270

Thr Gly Arg Thr Pro Gly Thr Leu Leu Ala Gly Ile Ala Leu Cys Gly
275 280 285

Glu Cys Gly Lys Thr Val Ser Gly Arg Gly Tyr Arg Gly Val Leu Val
290 295 300

Tyr Gly Cys Lys Asp Thr His Thr Arg Thr Pro Arg Ser Ile Ala Asp
305 310 315 320

Gly Arg Ala Ser Ser Ser Thr Leu Ala Arg Leu Met Phe Pro Asp Phe
325 330 335

Leu Pro Gly Leu Leu Ala Ser Gly Gln Ala Glu Asp Gly Gln Ser Ala
340 345 350

Ala Ser Lys His Ser Glu Ala Gln Thr Leu Arg Glu Arg Leu Asp Gly
355 360 365

Leu Ala Thr Ala Tyr Ala Glu Gly Ala Ile Ser Leu Ser Gln Met Thr
370 375 380

Ala Gly Ser Glu Ala Leu Arg Lys Lys Leu Glu Val Ile Glu Ala Asp
385 390 395 400

Leu Val Gly Ser Ala Gly Ile Pro Pro Phe Asp Pro Val Ala Gly Val
405 410 415

Ala Gly Leu Ile Ser Gly Trp Pro Thr Thr Pro Leu Pro Thr Arg Arg
420 425 430

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Ala Trp Val Asp Phe Cys Leu Val Val Thr Leu Asn Thr Gln Lys Gly
        435                 440                 445

Arg His Ala Ser Ser Met Thr Val Asp Asp His Val Thr Ile Glu Trp
    450                 455                 460

Arg Asp Val Ala Glu
465
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<210> 56
<211> 1503
<212> DNA
<213> CisA recombinase

<220>
<221> CDS
<222> (1)..(1500)

<400> 56

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gtg ata gca ata tat gta agg gta tcg acc gag gaa caa gcg atc aag   48
Val Ile Ala Ile Tyr Val Arg Val Ser Thr Glu Glu Gln Ala Ile Lys
  1               5                  10                  15

gga tcg agc atc gac agc caa atc gag gcc tgt ata aag aaa gca ggg   96
Gly Ser Ser Ile Asp Ser Gln Ile Glu Ala Cys Ile Lys Lys Ala Gly
            20                  25                  30

act aaa gat gtg ctg aag tat gca gat gaa gga ttt tca gga gag ctt   144
Thr Lys Asp Val Leu Lys Tyr Ala Asp Glu Gly Phe Ser Gly Glu Leu
        35                  40                  45

tta gaa cgt ccg gct ttg aat cgc ttg agg gag gat gca agc aag gga   192
Leu Glu Arg Pro Ala Leu Asn Arg Leu Arg Glu Asp Ala Ser Lys Gly
    50                  55                  60

ctt ata agt caa gtc att tgt tac gat cct gac cgt ctt tct cgg aaa   240
Leu Ile Ser Gln Val Ile Cys Tyr Asp Pro Asp Arg Leu Ser Arg Lys
65                  70                  75                  80

tta atg aat cag cta atc att gat gac gaa ttg cga aag cga aac ata   288
Leu Met Asn Gln Leu Ile Ile Asp Asp Glu Leu Arg Lys Arg Asn Ile
                85                  90                  95

cct ttg att ttt gta aat ggt gaa tac gcc aat tct cca gaa ggt caa   336
Pro Leu Ile Phe Val Asn Gly Glu Tyr Ala Asn Ser Pro Glu Gly Gln
            100                 105                 110

ttg ttt ttc gca atg cgc ggg gca atc tca gaa ttt gaa aaa gcc aaa   384
Leu Phe Phe Ala Met Arg Gly Ala Ile Ser Glu Phe Glu Lys Ala Lys
        115                 120                 125

atc aaa gaa cgg aca tca agc ggc cga ctt caa aaa atg aaa aaa ggc   432
Ile Lys Glu Arg Thr Ser Ser Gly Arg Leu Gln Lys Met Lys Lys Gly
    130                 135                 140

atg atc att aaa gat tct aaa cta tat ggc tat aaa ttt gtt aaa gag   480
Met Ile Ile Lys Asp Ser Lys Leu Tyr Gly Tyr Lys Phe Val Lys Glu
145                 150                 155                 160

aaa aga act ctt gag ata tta gaa gag gaa gca aaa atc att cgg atg   528
Lys Arg Thr Leu Glu Ile Leu Glu Glu Glu Ala Lys Ile Ile Arg Met
                165                 170                 175

att ttt aac tat ttc acc gat cat aaa agc cct ttt ttc ggc aga gta   576
```

```
Ile Phe Asn Tyr Phe Thr Asp His Lys Ser Pro Phe Phe Gly Arg Val
            180                 185                 190

aat ggt att gct cta cat tta act cag atg ggg gtt aaa aca aaa aaa   624
Asn Gly Ile Ala Leu His Leu Thr Gln Met Gly Val Lys Thr Lys Lys
        195                 200                 205

ggc gcc aaa gta tgg cac agg cag gtt gtt cgg caa ata tta atg aac   672
Gly Ala Lys Val Trp His Arg Gln Val Val Arg Gln Ile Leu Met Asn
    210                 215                 220

tct tcc tat aag ggt gaa cat aga cag tat aaa tat gat aca gag ggt   720
Ser Ser Tyr Lys Gly Glu His Arg Gln Tyr Lys Tyr Asp Thr Glu Gly
225                 230                 235                 240

tcc tat gtt tca aag cag gca ggg aac aaa tct ata att aaa ata agg   768
Ser Tyr Val Ser Lys Gln Ala Gly Asn Lys Ser Ile Ile Lys Ile Arg
                245                 250                 255

cct gaa gaa gaa caa atc act gtg aca att cca gca att gtt cca gct   816
Pro Glu Glu Glu Gln Ile Thr Val Thr Ile Pro Ala Ile Val Pro Ala
            260                 265                 270

gaa caa tgg gat tat gct caa gaa ctc tta ggt caa agt aaa aga aaa   864
Glu Gln Trp Asp Tyr Ala Gln Glu Leu Leu Gly Gln Ser Lys Arg Lys
        275                 280                 285

cac ttg agt atc agc cct cac aat tac ttg tta tcg ggt ttg gtt aga   912
His Leu Ser Ile Ser Pro His Asn Tyr Leu Leu Ser Gly Leu Val Arg
    290                 295                 300

tgc gga aaa tgc gga aat acc atg aca ggg aag aaa aga aaa tca cat   960
Cys Gly Lys Cys Gly Asn Thr Met Thr Gly Lys Lys Arg Lys Ser His
305                 310                 315                 320

ggt aaa gac tac tat gta tat act tgc cgg aaa aat tat tct ggc gca  1008
Gly Lys Asp Tyr Tyr Val Tyr Thr Cys Arg Lys Asn Tyr Ser Gly Ala
                325                 330                 335

aag gac cgc ggc tgc gga aaa gaa atg tct gag aat aaa ttg aac cgg  1056
Lys Asp Arg Gly Cys Gly Lys Glu Met Ser Glu Asn Lys Leu Asn Arg
            340                 345                 350

cat gta tgg ggt gaa att ttt aaa ttc atc aca aat cct caa aag tat  1104
His Val Trp Gly Glu Ile Phe Lys Phe Ile Thr Asn Pro Gln Lys Tyr
        355                 360                 365

gtt tct ttt aaa gag gct gaa caa tca aat cac ctg tct gat gaa tta  1152
Val Ser Phe Lys Glu Ala Glu Gln Ser Asn His Leu Ser Asp Glu Leu
    370                 375                 380

gaa ctt att gaa aaa gag ata gag aaa aca aaa aaa ggc cgc aag cgt  1200
Glu Leu Ile Glu Lys Glu Ile Glu Lys Thr Lys Lys Gly Arg Lys Arg
385                 390                 395                 400

ctt tta acg cta atc agc cta agc gat gac gat gat tta gac ata gat  1248
Leu Leu Thr Leu Ile Ser Leu Ser Asp Asp Asp Asp Leu Asp Ile Asp
                405                 410                 415

gaa atc aaa gca caa att att gaa ctg caa aaa aag caa aat cag ctt  1296
Glu Ile Lys Ala Gln Ile Ile Glu Leu Gln Lys Lys Gln Asn Gln Leu
            420                 425                 430

act gaa aag tgt aac aga atc cag tca aaa atg aaa gtc cta gat gat  1344
Thr Glu Lys Cys Asn Arg Ile Gln Ser Lys Met Lys Val Leu Asp Asp
        435                 440                 445
```

```
acg agc tca agt gaa aat gct cta aaa aga gcc atc gac tat ttt caa   1392
Thr Ser Ser Ser Glu Asn Ala Leu Lys Arg Ala Ile Asp Tyr Phe Gln
    450                 455                 460

tca atc ggt gca gat aac tta act ctt gaa gat aaa aaa aca att gtt   1440
Ser Ile Gly Ala Asp Asn Leu Thr Leu Glu Asp Lys Lys Thr Ile Val
465                 470                 475                 480

aac ttt atc gtg aaa gaa gtt acc att gtg gat tct gac acc ata tat   1488
Asn Phe Ile Val Lys Glu Val Thr Ile Val Asp Ser Asp Thr Ile Tyr
                485                 490                 495

att gaa acg tat taa                                              1503
Ile Glu Thr Tyr
            500
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<210> 57
<211> 500
<212> PRT
<213> CisA recombinase

<400> 57

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Val Ile Ala Ile Tyr Val Arg Val Ser Thr Glu Glu Gln Ala Ile Lys
 1               5                  10                  15

Gly Ser Ser Ile Asp Ser Gln Ile Glu Ala Cys Ile Lys Lys Ala Gly
            20                  25                  30

Thr Lys Asp Val Leu Lys Tyr Ala Asp Glu Gly Phe Ser Gly Glu Leu
        35                  40                  45

Leu Glu Arg Pro Ala Leu Asn Arg Leu Arg Glu Asp Ala Ser Lys Gly
    50                  55                  60

Leu Ile Ser Gln Val Ile Cys Tyr Asp Pro Asp Arg Leu Ser Arg Lys
65                  70                  75                  80

Leu Met Asn Gln Leu Ile Ile Asp Asp Glu Leu Arg Lys Arg Asn Ile
                85                  90                  95

Pro Leu Ile Phe Val Asn Gly Glu Tyr Ala Asn Ser Pro Glu Gly Gln
            100                 105                 110

Leu Phe Phe Ala Met Arg Gly Ala Ile Ser Glu Phe Glu Lys Ala Lys
        115                 120                 125

Ile Lys Glu Arg Thr Ser Ser Gly Arg Leu Gln Lys Met Lys Lys Gly
    130                 135                 140

Met Ile Ile Lys Asp Ser Lys Leu Tyr Gly Tyr Lys Phe Val Lys Glu
145                 150                 155                 160

Lys Arg Thr Leu Glu Ile Leu Glu Glu Glu Ala Lys Ile Ile Arg Met
                165                 170                 175

Ile Phe Asn Tyr Phe Thr Asp His Lys Ser Pro Phe Phe Gly Arg Val
            180                 185                 190

Asn Gly Ile Ala Leu His Leu Thr Gln Met Gly Val Lys Thr Lys Lys
        195                 200                 205

Gly Ala Lys Val Trp His Arg Gln Val Val Arg Gln Ile Leu Met Asn
    210                 215                 220

Ser Ser Tyr Lys Gly Glu His Arg Gln Tyr Lys Tyr Asp Thr Glu Gly
225                 230                 235                 240
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```
Ser Tyr Val Ser Lys Gln Ala Gly Asn Lys Ser Ile Ile Lys Ile Arg
                245                 250                 255

Pro Glu Glu Glu Gln Ile Thr Val Thr Ile Pro Ala Ile Val Pro Ala
            260                 265                 270

Glu Gln Trp Asp Tyr Ala Gln Glu Leu Leu Gly Gln Ser Lys Arg Lys
        275                 280                 285

His Leu Ser Ile Ser Pro His Asn Tyr Leu Leu Ser Gly Leu Val Arg
    290                 295                 300

Cys Gly Lys Cys Gly Asn Thr Met Thr Gly Lys Lys Arg Lys Ser His
305                 310                 315                 320

Gly Lys Asp Tyr Tyr Val Tyr Thr Cys Arg Lys Asn Tyr Ser Gly Ala
                325                 330                 335

Lys Asp Arg Gly Cys Gly Lys Glu Met Ser Glu Asn Lys Leu Asn Arg
            340                 345                 350

His Val Trp Gly Glu Ile Phe Lys Phe Ile Thr Asn Pro Gln Lys Tyr
        355                 360                 365

Val Ser Phe Lys Glu Ala Glu Gln Ser Asn His Leu Ser Asp Glu Leu
    370                 375                 380

Glu Leu Ile Glu Lys Glu Ile Glu Lys Thr Lys Lys Gly Arg Lys Arg
385                 390                 395                 400

Leu Leu Thr Leu Ile Ser Leu Ser Asp Asp Asp Asp Leu Asp Ile Asp
                405                 410                 415

Glu Ile Lys Ala Gln Ile Ile Glu Leu Gln Lys Lys Gln Asn Gln Leu
            420                 425                 430

Thr Glu Lys Cys Asn Arg Ile Gln Ser Lys Met Lys Val Leu Asp Asp
        435                 440                 445

Thr Ser Ser Ser Glu Asn Ala Leu Lys Arg Ala Ile Asp Tyr Phe Gln
    450                 455                 460

Ser Ile Gly Ala Asp Asn Leu Thr Leu Glu Asp Lys Lys Thr Ile Val
465                 470                 475                 480

Asn Phe Ile Val Lys Glu Val Thr Ile Val Asp Ser Asp Thr Ile Tyr
                485                 490                 495

Ile Glu Thr Tyr
            500
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<210> 58
<211> 1545
<212> DNA
<213> XisF recombinase

<220>
<221> CDS
<222> (1)..(1542)

<400> 58

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atg gaa aat tgg ggt tac gcg aga gtg agc ggt gag gaa cag caa aca   48
Met Glu Asn Trp Gly Tyr Ala Arg Val Ser Gly Glu Glu Gln Gln Thr
  1               5                  10                  15
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```
gat aaa ggt gcg ttg cgt aaa caa ata gaa cgc ttg cgt aat gct gga   96
Asp Lys Gly Ala Leu Arg Lys Gln Ile Glu Arg Leu Arg Asn Ala Gly
            20                  25                  30

tgt tca aaa gtg tac tgg gat att caa tcg cgg aca act gaa gtc aga  144
Cys Ser Lys Val Tyr Trp Asp Ile Gln Ser Arg Thr Thr Glu Val Arg
        35                  40                  45

gaa ggg cta caa caa tta att aat gac tta aag aca tct tca aca ggt  192
Glu Gly Leu Gln Gln Leu Ile Asn Asp Leu Lys Thr Ser Ser Thr Gly
    50                  55                  60

aag gta aaa tca ctg caa ttt acc cgc att gat cgc atc ggc tca tca  240
Lys Val Lys Ser Leu Gln Phe Thr Arg Ile Asp Arg Ile Gly Ser Ser
65                  70                  75                  80

tcg cgg ttg ttt tat tca ttg tta gag gta tta cgt tcc aag gga att  288
Ser Arg Leu Phe Tyr Ser Leu Leu Glu Val Leu Arg Ser Lys Gly Ile
                85                  90                  95

aaa ctg ata gcc tta gat caa ggc gtt gac cca gac agc ctt ggc ggg  336
Lys Leu Ile Ala Leu Asp Gln Gly Val Asp Pro Asp Ser Leu Gly Gly
            100                 105                 110

gaa cta aca att gat atg tta ctg gct gct gcc aaa ttt gag gta aga  384
Glu Leu Thr Ile Asp Met Leu Leu Ala Ala Ala Lys Phe Glu Val Arg
        115                 120                 125

atg gtg acg gag agg tta aaa agc gaa cgt cgt cat agg gtg aac caa  432
Met Val Thr Glu Arg Leu Lys Ser Glu Arg Arg His Arg Val Asn Gln
    130                 135                 140

gga aaa agt cac cga gtt gcc cca tta gga tac cgc aaa gat aaa gat  480
Gly Lys Ser His Arg Val Ala Pro Leu Gly Tyr Arg Lys Asp Lys Asp
145                 150                 155                 160

aaa tat ata cgc gat cgc tca cca tgt gtt tgc tta cta gaa gga cgc  528
Lys Tyr Ile Arg Asp Arg Ser Pro Cys Val Cys Leu Leu Glu Gly Arg
                165                 170                 175

aga gaa tta acg gtg tct gac tta gcc cag tat att ttt cac act ttt  576
Arg Glu Leu Thr Val Ser Asp Leu Ala Gln Tyr Ile Phe His Thr Phe
            180                 185                 190

ttt gag tgc ggt tcc gtt gct gct act gtg cgt aag ctg cac tca gat  624
Phe Glu Cys Gly Ser Val Ala Ala Thr Val Arg Lys Leu His Ser Asp
        195                 200                 205

ttt ggt ata gaa aca aaa gtt ctg aat tgg aac aag cta gaa aaa tct  672
Phe Gly Ile Glu Thr Lys Val Leu Asn Trp Asn Lys Leu Glu Lys Ser
    210                 215                 220

tcc cgg att gtt ggc gac gac gac tta gat aaa att gca ttt aca cca  720
Ser Arg Ile Val Gly Asp Asp Asp Leu Asp Lys Ile Ala Phe Thr Pro
225                 230                 235                 240

aat aaa act aac cac ccc ttg cgt tat ccc tgg tct ggg cta aga tgg  768
Asn Lys Thr Asn His Pro Leu Arg Tyr Pro Trp Ser Gly Leu Arg Trp
                245                 250                 255

tca atc cct ggt tta aaa gcg tta tta gtt aac cct gtt tac gcc ggg  816
Ser Ile Pro Gly Leu Lys Ala Leu Leu Val Asn Pro Val Tyr Ala Gly
            260                 265                 270

ggt ttg ccc ttt gat act tac gtt aaa tca aaa gga aaa cgc aag cat  864
Gly Leu Pro Phe Asp Thr Tyr Val Lys Ser Lys Gly Lys Arg Lys His
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```
          275                 280                 285

ttt gac gag tgg aaa gta aaa tgg gga acc cac gac gat gag gca atc   912
Phe Asp Glu Trp Lys Val Lys Trp Gly Thr His Asp Asp Glu Ala Ile
    290                 295                 300

att acc tgt gag gaa cat gaa aga ata aaa cag atg att cga gac aat   960
Ile Thr Cys Glu Glu His Glu Arg Ile Lys Gln Met Ile Arg Asp Asn
305                 310                 315                 320

cgc aat aat cga tgg gct gca aga gaa gaa aac gaa gta aac cca ttt   1008
Arg Asn Asn Arg Trp Ala Ala Arg Glu Glu Asn Glu Val Asn Pro Phe
                325                 330                 335

tct aat tta ctt aaa tgt acc cat tgc ggc ggc tca atg aca cgc cac   1056
Ser Asn Leu Leu Lys Cys Thr His Cys Gly Gly Ser Met Thr Arg His
            340                 345                 350

gcc aaa cgt gta gat aag agt gga caa gct atc tat tat tat cag tgc   1104
Ala Lys Arg Val Asp Lys Ser Gly Gln Ala Ile Tyr Tyr Tyr Gln Cys
        355                 360                 365

cga ttg tat aaa gct ggc aac tgt agc aat aaa aat atg att tca tcc   1152
Arg Leu Tyr Lys Ala Gly Asn Cys Ser Asn Lys Asn Met Ile Ser Ser
    370                 375                 380

aaa ata tta gat atc caa gta atg gat tta ttg gca caa gaa gcc gaa   1200
Lys Ile Leu Asp Ile Gln Val Met Asp Leu Leu Ala Gln Glu Ala Glu
385                 390                 395                 400

cgt tta gca aat ttg gtg gaa aca gat gag ccg ctt att gta gaa gaa   1248
Arg Leu Ala Asn Leu Val Glu Thr Asp Glu Pro Leu Ile Val Glu Glu
                405                 410                 415

ccc cca gaa gta aaa acg ctg cgc gca tcc ctg aat agt ctg gaa aca   1296
Pro Pro Glu Val Lys Thr Leu Arg Ala Ser Leu Asn Ser Leu Glu Thr
            420                 425                 430

ttg cca gca agt tca gca att gaa caa att aaa aat gac ctc aaa gaa   1344
Leu Pro Ala Ser Ser Ala Ile Glu Gln Ile Lys Asn Asp Leu Lys Glu
        435                 440                 445

cag att gcg atc gca cta gga gca acc aat aat gct tct aaa caa tct   1392
Gln Ile Ala Ile Ala Leu Gly Ala Thr Asn Asn Ala Ser Lys Gln Ser
    450                 455                 460

ctg att gcc aag gaa aga att ata caa gct ttt gct cat aaa agt tac   1440
Leu Ile Ala Lys Glu Arg Ile Ile Gln Ala Phe Ala His Lys Ser Tyr
465                 470                 475                 480

tgg caa gga cta aac gct caa gat aaa cga gca atc ctc aat ggt tgc   1488
Trp Gln Gly Leu Asn Ala Gln Asp Lys Arg Ala Ile Leu Asn Gly Cys
                485                 490                 495

gta aaa aaa atc tcc gta gat ggt aac ttt gtt aca gct att gag tat   1536
Val Lys Lys Ile Ser Val Asp Gly Asn Phe Val Thr Ala Ile Glu Tyr
            500                 505                 510

cgt tac tag                                                      1545
Arg Tyr
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<210> 59
<211> 514
<212> PRT
<213> XisF recombinase

<400> 59

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Met Glu Asn Trp Gly Tyr Ala Arg Val Ser Gly Glu Glu Gln Gln Thr
 1               5                  10                  15

Asp Lys Gly Ala Leu Arg Lys Gln Ile Glu Arg Leu Arg Asn Ala Gly
            20                  25                  30

Cys Ser Lys Val Tyr Trp Asp Ile Gln Ser Arg Thr Thr Glu Val Arg
        35                  40                  45

Glu Gly Leu Gln Gln Leu Ile Asn Asp Leu Lys Thr Ser Ser Thr Gly
    50                  55                  60

Lys Val Lys Ser Leu Gln Phe Thr Arg Ile Asp Arg Ile Gly Ser Ser
65                  70                  75                  80

Ser Arg Leu Phe Tyr Ser Leu Leu Glu Val Leu Arg Ser Lys Gly Ile
                85                  90                  95

Lys Leu Ile Ala Leu Asp Gln Gly Val Asp Pro Asp Ser Leu Gly Gly
            100                 105                 110

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

Met Val Thr Glu Arg Leu Lys Ser Glu Arg Arg His Arg Val Asn Gln
    130                 135                 140

Gly Lys Ser His Arg Val Ala Pro Leu Gly Tyr Arg Lys Asp Lys Asp
145                 150                 155                 160

Lys Tyr Ile Arg Asp Arg Ser Pro Cys Val Cys Leu Leu Glu Gly Arg
                165                 170                 175

Arg Glu Leu Thr Val Ser Asp Leu Ala Gln Tyr Ile Phe His Thr Phe
            180                 185                 190

Phe Glu Cys Gly Ser Val Ala Ala Thr Val Arg Lys Leu His Ser Asp
        195                 200                 205

Phe Gly Ile Glu Thr Lys Val Leu Asn Trp Asn Lys Leu Glu Lys Ser
    210                 215                 220

Ser Arg Ile Val Gly Asp Asp Asp Leu Asp Lys Ile Ala Phe Thr Pro
225                 230                 235                 240

Asn Lys Thr Asn His Pro Leu Arg Tyr Pro Trp Ser Gly Leu Arg Trp
                245                 250                 255

Ser Ile Pro Gly Leu Lys Ala Leu Leu Val Asn Pro Val Tyr Ala Gly
            260                 265                 270

Gly Leu Pro Phe Asp Thr Tyr Val Lys Ser Lys Gly Lys Arg Lys His
        275                 280                 285

Phe Asp Glu Trp Lys Val Lys Trp Gly Thr His Asp Asp Glu Ala Ile
    290                 295                 300

Ile Thr Cys Glu Glu His Glu Arg Ile Lys Gln Met Ile Arg Asp Asn
305                 310                 315                 320

Arg Asn Asn Arg Trp Ala Ala Arg Glu Glu Asn Glu Val Asn Pro Phe
                325                 330                 335

Ser Asn Leu Leu Lys Cys Thr His Cys Gly Gly Ser Met Thr Arg His
            340                 345                 350
```

```
Ala Lys Arg Val Asp Lys Ser Gly Gln Ala Ile Tyr Tyr Tyr Gln Cys
        355                 360                 365

Arg Leu Tyr Lys Ala Gly Asn Cys Ser Asn Lys Asn Met Ile Ser Ser
    370                 375                 380

Lys Ile Leu Asp Ile Gln Val Met Asp Leu Leu Ala Gln Glu Ala Glu
385                 390                 395                 400

Arg Leu Ala Asn Leu Val Glu Thr Asp Glu Pro Leu Ile Val Glu Glu
                405                 410                 415

Pro Pro Glu Val Lys Thr Leu Arg Ala Ser Leu Asn Ser Leu Glu Thr
            420                 425                 430

Leu Pro Ala Ser Ser Ala Ile Glu Gln Ile Lys Asn Asp Leu Lys Glu
        435                 440                 445

Gln Ile Ala Ile Ala Leu Gly Ala Thr Asn Asn Ala Ser Lys Gln Ser
    450                 455                 460

Leu Ile Ala Lys Glu Arg Ile Ile Gln Ala Phe Ala His Lys Ser Tyr
465                 470                 475                 480

Trp Gln Gly Leu Asn Ala Gln Asp Lys Arg Ala Ile Leu Asn Gly Cys
                485                 490                 495

Val Lys Lys Ile Ser Val Asp Gly Asn Phe Val Thr Ala Ile Glu Tyr
            500                 505                 510

Arg Tyr
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<210> 60
<211> 2124
<212> DNA
<213> Transposon Tn4451

<220>
<221> CDS
<222> (1)..(2121)

<400> 60
atg tca agg act tca aga att aca gca ctt tac gag cgt ttg tca aga   48
Met Ser Arg Thr Ser Arg Ile Thr Ala Leu Tyr Glu Arg Leu Ser Arg
  1               5                  10                  15

gat gat gac ctt act ggc gag agt aat tct att acc aat caa aag aaa   96
Asp Asp Asp Leu Thr Gly Glu Ser Asn Ser Ile Thr Asn Gln Lys Lys
             20                  25                  30

tac ctc gaa gat tat gcc cgt agg aat ggt ttt gag aac att cgc cat   144
Tyr Leu Glu Asp Tyr Ala Arg Arg Asn Gly Phe Glu Asn Ile Arg His
         35                  40                  45

ttt acc gat gac gga ttt tcg ggt gta aat ttc aat cgc cct ggc ttt   192
Phe Thr Asp Asp Gly Phe Ser Gly Val Asn Phe Asn Arg Pro Gly Phe
     50                  55                  60

caa tct ctg ata aaa gaa gtt gaa gca gga aat gta gaa acc ttg att   240
Gln Ser Leu Ile Lys Glu Val Glu Ala Gly Asn Val Glu Thr Leu Ile
 65                  70                  75                  80

gtt aag gat atg agc cga ttg ggg cga aat tat ctg caa gta ggt ttt   288
Val Lys Asp Met Ser Arg Leu Gly Arg Asn Tyr Leu Gln Val Gly Phe
```

```
                    85                  90                  95

tat acg gaa gtt ctg ttt cca cag aaa aat gtc cgt ttc ctt gca att   336
Tyr Thr Glu Val Leu Phe Pro Gln Lys Asn Val Arg Phe Leu Ala Ile
            100                 105                 110

aac aac agt att gac agt aac aac gct tcg gat aat gac ttt gct ccg   384
Asn Asn Ser Ile Asp Ser Asn Asn Ala Ser Asp Asn Asp Phe Ala Pro
        115                 120                 125

ttt ttg aat att atg aac gaa tgg tat gcc aaa gac aca agc aac aaa   432
Phe Leu Asn Ile Met Asn Glu Trp Tyr Ala Lys Asp Thr Ser Asn Lys
    130                 135                 140

atc aag gct ata ttc gat gcc cgt atg aaa gac gga aag cgt tgt agc   480
Ile Lys Ala Ile Phe Asp Ala Arg Met Lys Asp Gly Lys Arg Cys Ser
145                 150                 155                 160

ggt tct atc cct tat ggg tat aac cga ctg ccg agc gac aaa caa acg   528
Gly Ser Ile Pro Tyr Gly Tyr Asn Arg Leu Pro Ser Asp Lys Gln Thr
                165                 170                 175

ctt gtg gtt gac cct gtg gct tcg gaa gtg gta aag cgt atc ttt act   576
Leu Val Val Asp Pro Val Ala Ser Glu Val Val Lys Arg Ile Phe Thr
            180                 185                 190

ctt gcc aat gat ggc aaa agt aca agg gca atc gca gaa ata ctg acc   624
Leu Ala Asn Asp Gly Lys Ser Thr Arg Ala Ile Ala Glu Ile Leu Thr
        195                 200                 205

gaa gaa aaa gtt tta acc cct gcg gca tac gca aag gaa tac cac ccc   672
Glu Glu Lys Val Leu Thr Pro Ala Ala Tyr Ala Lys Glu Tyr His Pro
    210                 215                 220

gaa cag tac aac ggc aac aag ttc aca aac cct tat ctt tgg gca atg   720
Glu Gln Tyr Asn Gly Asn Lys Phe Thr Asn Pro Tyr Leu Trp Ala Met
225                 230                 235                 240

tca acg ata aga aat att tta ggc agg cag gaa tat ctc ggt cac acc   768
Ser Thr Ile Arg Asn Ile Leu Gly Arg Gln Glu Tyr Leu Gly His Thr
                245                 250                 255

gtt ttg cga aag tcg gta agc aca aat ttc aaa ctt cac aag aga aaa   816
Val Leu Arg Lys Ser Val Ser Thr Asn Phe Lys Leu His Lys Arg Lys
            260                 265                 270

agc aca gac gaa gaa gaa cag tat gta ttt ccg aat aca cac gag cct   864
Ser Thr Asp Glu Glu Glu Gln Tyr Val Phe Pro Asn Thr His Glu Pro
        275                 280                 285

atc ata tcg cag gaa ctt tgg gac agc gtt caa aaa cgc aga agc aga   912
Ile Ile Ser Gln Glu Leu Trp Asp Ser Val Gln Lys Arg Arg Ser Arg
    290                 295                 300

gta aat cgt gcc tcg gct tgg gga acg cac agc aac cgt tta agc gga   960
Val Asn Arg Ala Ser Ala Trp Gly Thr His Ser Asn Arg Leu Ser Gly
305                 310                 315                 320

tat ttg tac tgt gcc gat tgc gga aga aga atg act ttg cag aca cat  1008
Tyr Leu Tyr Cys Ala Asp Cys Gly Arg Arg Met Thr Leu Gln Thr His
                325                 330                 335

tac agc aaa aaa gac ggt tct gtg cag tat tct tac cgt tgc ggt ggg  1056
Tyr Ser Lys Lys Asp Gly Ser Val Gln Tyr Ser Tyr Arg Cys Gly Gly
            340                 345                 350

tat gca agc aga gtg aac agt tgt acc agt cat tcg att agt acc gat  1104
```

```
Tyr Ala Ser Arg Val Asn Ser Cys Thr Ser His Ser Ile Ser Thr Asp
        355                 360                 365

aat gtt gaa gcc ttg ata tta tca tct gtc aaa cgc ttt tca agg ttt   1152
Asn Val Glu Ala Leu Ile Leu Ser Ser Val Lys Arg Phe Ser Arg Phe
    370                 375                 380

gtt ctg aat gat gaa caa gca ttt gct ttg gaa ctg caa tct ctt tgg   1200
Val Leu Asn Asp Glu Gln Ala Phe Ala Leu Glu Leu Gln Ser Leu Trp
385                 390                 395                 400

aat gaa aaa cag gag gaa aag ccg aaa cac aat caa tcg gaa ctg caa   1248
Asn Glu Lys Gln Glu Glu Lys Pro Lys His Asn Gln Ser Glu Leu Gln
                405                 410                 415

cgc tgt cag aaa cgc tat gac gaa ctc tct acc ctt gtt cgt ggc ttg   1296
Arg Cys Gln Lys Arg Tyr Asp Glu Leu Ser Thr Leu Val Arg Gly Leu
            420                 425                 430

tat gaa aat ctt atg tcg gga tta ctg ccc gaa aga cag tat aag caa   1344
Tyr Glu Asn Leu Met Ser Gly Leu Leu Pro Glu Arg Gln Tyr Lys Gln
        435                 440                 445

ctg atg aaa cag tat gat gac gag cag gca gag ttg gaa acg aaa atg   1392
Leu Met Lys Gln Tyr Asp Asp Glu Gln Ala Glu Leu Glu Thr Lys Met
    450                 455                 460

gaa acg atg aaa aca gaa ctt gcc gaa gaa aaa gta agt tcc gtt gat   1440
Glu Thr Met Lys Thr Glu Leu Ala Glu Glu Lys Val Ser Ser Val Asp
465                 470                 475                 480

att aag cat ttc att tcg ctg ata cgc aag tgt aaa aat cct acg gaa   1488
Ile Lys His Phe Ile Ser Leu Ile Arg Lys Cys Lys Asn Pro Thr Glu
                485                 490                 495

atc tcc gat aca atg ttt aat gaa ctt gtt gat aag ata gtg gtt tat   1536
Ile Ser Asp Thr Met Phe Asn Glu Leu Val Asp Lys Ile Val Val Tyr
            500                 505                 510

gaa gca gag ggt gtg gga aaa gca cga aca caa aag gtc gat att tat   1584
Glu Ala Glu Gly Val Gly Lys Ala Arg Thr Gln Lys Val Asp Ile Tyr
        515                 520                 525

ttt aac tat gtc ggt caa gtg gat att gcc tat acc gaa gaa gaa ctt   1632
Phe Asn Tyr Val Gly Gln Val Asp Ile Ala Tyr Thr Glu Glu Glu Leu
    530                 535                 540

gcc gag ata gaa aca cag aaa gag cag gag gaa cag caa cgc ttg gca   1680
Ala Glu Ile Glu Thr Gln Lys Glu Gln Glu Glu Gln Gln Arg Leu Ala
545                 550                 555                 560

aga cag cgc aag cgt gaa aaa gcc tac cga gaa aag cga aag gca cag   1728
Arg Gln Arg Lys Arg Glu Lys Ala Tyr Arg Glu Lys Arg Lys Ala Gln
                565                 570                 575

aaa atc gct gaa aac ggt ggc gaa atc gtt aag aca aag gtt tgc cct   1776
Lys Ile Ala Glu Asn Gly Gly Glu Ile Val Lys Thr Lys Val Cys Pro
            580                 585                 590

cat tgc aac aaa gag ttt atc ccg aca agc aac cga cag gtg ttc tgt   1824
His Cys Asn Lys Glu Phe Ile Pro Thr Ser Asn Arg Gln Val Phe Cys
        595                 600                 605

tcc aaa gag tgc tgc tat caa gca agg caa gac aaa aag aaa aca gac   1872
Ser Lys Glu Cys Cys Tyr Gln Ala Arg Gln Asp Lys Lys Lys Thr Asp
    610                 615                 620
```

```
cga gaa gca gaa cga gga aat cac tat tac cga cag cgt gta tgt gct   1920
Arg Glu Ala Glu Arg Gly Asn His Tyr Tyr Arg Gln Arg Val Cys Ala
625                 630                 635                 640

gtg tgc ggc aat tcc tat tgg cct aca cac agc caa cag aaa ttc tgc   1968
Val Cys Gly Asn Ser Tyr Trp Pro Thr His Ser Gln Gln Lys Phe Cys
                645                 650                 655

tcc gaa gaa tgt caa agg gta aat cac aat aag aaa aca ttg gaa ttt   2016
Ser Glu Glu Cys Gln Arg Val Asn His Asn Lys Lys Thr Leu Glu Phe
            660                 665                 670

tac cac cat aaa aaa gaa aag gag aag ctg caa tgc aaa gat tta tca   2064
Tyr His His Lys Lys Glu Lys Glu Lys Leu Gln Cys Lys Asp Leu Ser
        675                 680                 685

cag acg aaa gaa cgg gta tcc gat atg aac tta tcg ggg act att act   2112
Gln Thr Lys Glu Arg Val Ser Asp Met Asn Leu Ser Gly Thr Ile Thr
    690                 695                 700

acc cct gct taa                                                 2124
Thr Pro Ala
705
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<210> 61
<211> 707
<212> PRT
<213> Transposon Tn4451

<400> 61

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Met Ser Arg Thr Ser Arg Ile Thr Ala Leu Tyr Glu Arg Leu Ser Arg
  1               5                  10                  15

Asp Asp Asp Leu Thr Gly Glu Ser Asn Ser Ile Thr Asn Gln Lys Lys
             20                  25                  30

Tyr Leu Glu Asp Tyr Ala Arg Arg Asn Gly Phe Glu Asn Ile Arg His
         35                  40                  45

Phe Thr Asp Asp Gly Phe Ser Gly Val Asn Phe Asn Arg Pro Gly Phe
     50                  55                  60

Gln Ser Leu Ile Lys Glu Val Glu Ala Gly Asn Val Glu Thr Leu Ile
 65                  70                  75                  80

Val Lys Asp Met Ser Arg Leu Gly Arg Asn Tyr Leu Gln Val Gly Phe
                 85                  90                  95

Tyr Thr Glu Val Leu Phe Pro Gln Lys Asn Val Arg Phe Leu Ala Ile
            100                 105                 110

Asn Asn Ser Ile Asp Ser Asn Asn Ala Ser Asp Asn Asp Phe Ala Pro
        115                 120                 125

Phe Leu Asn Ile Met Asn Glu Trp Tyr Ala Lys Asp Thr Ser Asn Lys
    130                 135                 140

Ile Lys Ala Ile Phe Asp Ala Arg Met Lys Asp Gly Lys Arg Cys Ser
145                 150                 155                 160

Gly Ser Ile Pro Tyr Gly Tyr Asn Arg Leu Pro Ser Asp Lys Gln Thr
                165                 170                 175

Leu Val Val Asp Pro Val Ala Ser Glu Val Val Lys Arg Ile Phe Thr
            180                 185                 190
```

Leu Ala Asn Asp Gly Lys Ser Thr Arg Ala Ile Ala Glu Ile Leu Thr
195 200 205

Glu Glu Lys Val Leu Thr Pro Ala Ala Tyr Ala Lys Glu Tyr His Pro
210 215 220

Glu Gln Tyr Asn Gly Asn Lys Phe Thr Asn Pro Tyr Leu Trp Ala Met
225 230 235 240

Ser Thr Ile Arg Asn Ile Leu Gly Arg Gln Glu Tyr Leu Gly His Thr
245 250 255

Val Leu Arg Lys Ser Val Ser Thr Asn Phe Lys Leu His Lys Arg Lys
260 265 270

Ser Thr Asp Glu Glu Glu Gln Tyr Val Phe Pro Asn Thr His Glu Pro
275 280 285

Ile Ile Ser Gln Glu Leu Trp Asp Ser Val Gln Lys Arg Arg Ser Arg
290 295 300

Val Asn Arg Ala Ser Ala Trp Gly Thr His Ser Asn Arg Leu Ser Gly
305 310 315 320

Tyr Leu Tyr Cys Ala Asp Cys Gly Arg Arg Met Thr Leu Gln Thr His
325 330 335

Tyr Ser Lys Lys Asp Gly Ser Val Gln Tyr Ser Tyr Arg Cys Gly Gly
340 345 350

Tyr Ala Ser Arg Val Asn Ser Cys Thr Ser His Ser Ile Ser Thr Asp
355 360 365

Asn Val Glu Ala Leu Ile Leu Ser Ser Val Lys Arg Phe Ser Arg Phe
370 375 380

Val Leu Asn Asp Glu Gln Ala Phe Ala Leu Glu Leu Gln Ser Leu Trp
385 390 395 400

Asn Glu Lys Gln Glu Glu Lys Pro Lys His Asn Gln Ser Glu Leu Gln
405 410 415

Arg Cys Gln Lys Arg Tyr Asp Glu Leu Ser Thr Leu Val Arg Gly Leu
420 425 430

Tyr Glu Asn Leu Met Ser Gly Leu Leu Pro Glu Arg Gln Tyr Lys Gln
435 440 445

Leu Met Lys Gln Tyr Asp Asp Glu Gln Ala Glu Leu Glu Thr Lys Met
450 455 460

Glu Thr Met Lys Thr Glu Leu Ala Glu Glu Lys Val Ser Ser Val Asp
465 470 475 480

Ile Lys His Phe Ile Ser Leu Ile Arg Lys Cys Lys Asn Pro Thr Glu
485 490 495

Ile Ser Asp Thr Met Phe Asn Glu Leu Val Asp Lys Ile Val Val Tyr
500 505 510

Glu Ala Glu Gly Val Gly Lys Ala Arg Thr Gln Lys Val Asp Ile Tyr
515 520 525

Phe Asn Tyr Val Gly Gln Val Asp Ile Ala Tyr Thr Glu Glu Glu Leu
530 535 540

Ala Glu Ile Glu Thr Gln Lys Glu Gln Glu Glu Gln Gln Arg Leu Ala

545 550 555 560

Arg Gln Arg Lys Arg Glu Lys Ala Tyr Arg Glu Lys Arg Lys Ala Gln
565 570 575

Lys Ile Ala Glu Asn Gly Gly Glu Ile Val Lys Thr Lys Val Cys Pro
580 585 590

His Cys Asn Lys Glu Phe Ile Pro Thr Ser Asn Arg Gln Val Phe Cys
595 600 605

Ser Lys Glu Cys Cys Tyr Gln Ala Arg Gln Asp Lys Lys Lys Thr Asp
610 615 620

Arg Glu Ala Glu Arg Gly Asn His Tyr Tyr Arg Gln Arg Val Cys Ala
625 630 635 640

Val Cys Gly Asn Ser Tyr Trp Pro Thr His Ser Gln Gln Lys Phe Cys
645 650 655

Ser Glu Glu Cys Gln Arg Val Asn His Asn Lys Lys Thr Leu Glu Phe
660 665 670

Tyr His His Lys Lys Glu Lys Glu Lys Leu Gln Cys Lys Asp Leu Ser
675 680 685

Gln Thr Lys Glu Arg Val Ser Asp Met Asn Leu Ser Gly Thr Ile Thr
690 695 700

Thr Pro Ala
705

<210> 62
<211> 1420
<212> DNA
<213> XisA recombinase

<220>
<221> CDS
<222> (1)..(1416)

<400> 62

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atg caa aat cag ggt caa gac aaa tat caa caa gcc ttt gca gac tta   48
Met Gln Asn Gln Gly Gln Asp Lys Tyr Gln Gln Ala Phe Ala Asp Leu
  1               5                  10                  15

gag cca ctt tca tct acc gac ggc agt ttt ctc ggc tca agt ctg caa   96
Glu Pro Leu Ser Ser Thr Asp Gly Ser Phe Leu Gly Ser Ser Leu Gln
             20                  25                  30

gca cag cag caa aga gaa cac atg aga aca aaa gta cta caa gac cta   144
Ala Gln Gln Gln Arg Glu His Met Arg Thr Lys Val Leu Gln Asp Leu
          35                  40                  45

gac aag gta aat ctg cgt ttg aag tct gca aag acg aaa gtc tca gtt   192
Asp Lys Val Asn Leu Arg Leu Lys Ser Ala Lys Thr Lys Val Ser Val
      50                  55                  60

cga gaa tct aac gga agt ctg caa tta cga gca acg tta cca att aaa   240
Arg Glu Ser Asn Gly Ser Leu Gln Leu Arg Ala Thr Leu Pro Ile Lys
  65                  70                  75                  80

cct gga gat aag gac acc aac ggt aca ggc aga aag caa tac aat ctc   288
Pro Gly Asp Lys Asp Thr Asn Gly Thr Gly Arg Lys Gln Tyr Asn Leu
                  85                  90                  95
```

```
agc ttg aat atc cct gca aac ttg gat gga ctg aag acg gct gag gaa   336
Ser Leu Asn Ile Pro Ala Asn Leu Asp Gly Leu Lys Thr Ala Glu Glu
            100                 105                 110

gaa gct tat gaa tta ggt aaa tta atc gct cgg aaa acc ttt gaa tgg   384
Glu Ala Tyr Glu Leu Gly Lys Leu Ile Ala Arg Lys Thr Phe Glu Trp
        115                 120                 125

aat gat aaa tat tta ggc aaa gaa gcc act aaa aaa gat tca caa aca   432
Asn Asp Lys Tyr Leu Gly Lys Glu Ala Thr Lys Lys Asp Ser Gln Thr
    130                 135                 140

ata ggt gat tta cta gaa aaa ttt gca gaa gag tat ttt aaa acc cat   480
Ile Gly Asp Leu Leu Glu Lys Phe Ala Glu Glu Tyr Phe Lys Thr His
145                 150                 155                 160

aaa cgc acc act aaa agc gaa cat acc ttt ttt tac tat ttt tcc cgc   528
Lys Arg Thr Thr Lys Ser Glu His Thr Phe Phe Tyr Tyr Phe Ser Arg
                165                 170                 175

acc caa cga tat acc aat tcc aaa gat tta gca acg gcg gaa aat ctc   576
Thr Gln Arg Tyr Thr Asn Ser Lys Asp Leu Ala Thr Ala Glu Asn Leu
            180                 185                 190

atc aat tca att gag caa atc gat aaa gaa tgg gcg aga tat aat gcc   624
Ile Asn Ser Ile Glu Gln Ile Asp Lys Glu Trp Ala Arg Tyr Asn Ala
        195                 200                 205

gcc aga gcc ata tca gct ttt tgc ata aca ttc aat ata gaa att gat   672
Ala Arg Ala Ile Ser Ala Phe Cys Ile Thr Phe Asn Ile Glu Ile Asp
    210                 215                 220

ttg tcc cag tat tcc aaa atg cct gat cgc aat tcg cgc aac atc ccc   720
Leu Ser Gln Tyr Ser Lys Met Pro Asp Arg Asn Ser Arg Asn Ile Pro
225                 230                 235                 240

aca gat gca gaa ata cta tca gga att acc aaa ttt gaa gac tat cta   768
Thr Asp Ala Glu Ile Leu Ser Gly Ile Thr Lys Phe Glu Asp Tyr Leu
                245                 250                 255

gtt acc aga gga aat caa gtt aat gaa gat gta aaa gat agc tgg caa   816
Val Thr Arg Gly Asn Gln Val Asn Glu Asp Val Lys Asp Ser Trp Gln
            260                 265                 270

ctt tgg cgc tgg aca tat gga atg tta gca gtt ttt ggt tta cgc ccc   864
Leu Trp Arg Trp Thr Tyr Gly Met Leu Ala Val Phe Gly Leu Arg Pro
        275                 280                 285

agg gaa att ttt att aac cct aat att gat tgg tgg tta agc aaa gag   912
Arg Glu Ile Phe Ile Asn Pro Asn Ile Asp Trp Trp Leu Ser Lys Glu
    290                 295                 300

aat ata gac ctc aca tgg aaa gta gac aaa gaa tgt aaa act ggt gaa   960
Asn Ile Asp Leu Thr Trp Lys Val Asp Lys Glu Cys Lys Thr Gly Glu
305                 310                 315                 320

aga caa gca tta ccc tta cat aaa gaa tgg att gat gag ttt gat tta  1008
Arg Gln Ala Leu Pro Leu His Lys Glu Trp Ile Asp Glu Phe Asp Leu
                325                 330                 335

aga aat ccg aaa tat tta gaa atg ctg gca aca gca att agt aaa aaa  1056
Arg Asn Pro Lys Tyr Leu Glu Met Leu Ala Thr Ala Ile Ser Lys Lys
            340                 345                 350

gat aaa aca aat cat gct gaa ata aca gcc tta act cag cgt att agt  1104
Asp Lys Thr Asn His Ala Glu Ile Thr Ala Leu Thr Gln Arg Ile Ser
```

```
          355                 360                 365

tgg tgg ttt cgg aaa gtc gaa tta gat ttt aaa ccc tat gat tta cgt   1152
Trp Trp Phe Arg Lys Val Glu Leu Asp Phe Lys Pro Tyr Asp Leu Arg
 370                 375                 380

cac gcc tgg gca atc aga gcg cat att tta ggc ata cca atc aaa gcg   1200
His Ala Trp Ala Ile Arg Ala His Ile Leu Gly Ile Pro Ile Lys Ala
385                 390                 395                 400

gcg gct gat aat ttg ggg cat agt atg cag gtt cat aca caa acc tat   1248
Ala Ala Asp Asn Leu Gly His Ser Met Gln Val His Thr Gln Thr Tyr
                405                 410                 415

cag cgc tgg ttc tcg cta gat atg cgg aag tta gcg att aat cag gct   1296
Gln Arg Trp Phe Ser Leu Asp Met Arg Lys Leu Ala Ile Asn Gln Ala
            420                 425                 430

ttg act aag agg aat gaa ttt gag gtg att agg gag gag aat gct aaa   1344
Leu Thr Lys Arg Asn Glu Phe Glu Val Ile Arg Glu Glu Asn Ala Lys
        435                 440                 445

ttg cag ata gaa aat gaa agg ttg agg atg gaa att gag aag tta aag   1392
Leu Gln Ile Glu Asn Glu Arg Leu Arg Met Glu Ile Glu Lys Leu Lys
 450                 455                 460

atg gaa ata gct tat aag aat agt tgag                             1420
Met Glu Ile Ala Tyr Lys Asn Ser
465                 470
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<210> 63
<211> 472
<212> PRT
<213> XisA recombinase

<400> 63

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Met Gln Asn Gln Gly Gln Asp Lys Tyr Gln Gln Ala Phe Ala Asp Leu
  1               5                  10                  15

Glu Pro Leu Ser Ser Thr Asp Gly Ser Phe Leu Gly Ser Ser Leu Gln
            20                  25                  30

Ala Gln Gln Gln Arg Glu His Met Arg Thr Lys Val Leu Gln Asp Leu
        35                  40                  45

Asp Lys Val Asn Leu Arg Leu Lys Ser Ala Lys Thr Lys Val Ser Val
    50                  55                  60

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

Pro Gly Asp Lys Asp Thr Asn Gly Thr Gly Arg Lys Gln Tyr Asn Leu
                85                  90                  95

Ser Leu Asn Ile Pro Ala Asn Leu Asp Gly Leu Lys Thr Ala Glu Glu
            100                 105                 110

Glu Ala Tyr Glu Leu Gly Lys Leu Ile Ala Arg Lys Thr Phe Glu Trp
        115                 120                 125

Asn Asp Lys Tyr Leu Gly Lys Glu Ala Thr Lys Lys Asp Ser Gln Thr
    130                 135                 140

Ile Gly Asp Leu Leu Glu Lys Phe Ala Glu Glu Tyr Phe Lys Thr His
145                 150                 155                 160
```

Lys Arg Thr Thr Lys Ser Glu His Thr Phe Phe Tyr Tyr Phe Ser Arg
165 170 175

Thr Gln Arg Tyr Thr Asn Ser Lys Asp Leu Ala Thr Ala Glu Asn Leu
180 185 190

Ile Asn Ser Ile Glu Gln Ile Asp Lys Glu Trp Ala Arg Tyr Asn Ala
195 200 205

Ala Arg Ala Ile Ser Ala Phe Cys Ile Thr Phe Asn Ile Glu Ile Asp
210 215 220

Leu Ser Gln Tyr Ser Lys Met Pro Asp Arg Asn Ser Arg Asn Ile Pro
225 230 235 240

Thr Asp Ala Glu Ile Leu Ser Gly Ile Thr Lys Phe Glu Asp Tyr Leu
245 250 255

Val Thr Arg Gly Asn Gln Val Asn Glu Asp Val Lys Asp Ser Trp Gln
260 265 270

Leu Trp Arg Trp Thr Tyr Gly Met Leu Ala Val Phe Gly Leu Arg Pro
275 280 285

Arg Glu Ile Phe Ile Asn Pro Asn Ile Asp Trp Trp Leu Ser Lys Glu
290 295 300

Asn Ile Asp Leu Thr Trp Lys Val Asp Lys Glu Cys Lys Thr Gly Glu
305 310 315 320

Arg Gln Ala Leu Pro Leu His Lys Glu Trp Ile Asp Glu Phe Asp Leu
325 330 335

Arg Asn Pro Lys Tyr Leu Glu Met Leu Ala Thr Ala Ile Ser Lys Lys
340 345 350

Asp Lys Thr Asn His Ala Glu Ile Thr Ala Leu Thr Gln Arg Ile Ser
355 360 365

Trp Trp Phe Arg Lys Val Glu Leu Asp Phe Lys Pro Tyr Asp Leu Arg
370 375 380

His Ala Trp Ala Ile Arg Ala His Ile Leu Gly Ile Pro Ile Lys Ala
385 390 395 400

Ala Ala Asp Asn Leu Gly His Ser Met Gln Val His Thr Gln Thr Tyr
405 410 415

Gln Arg Trp Phe Ser Leu Asp Met Arg Lys Leu Ala Ile Asn Gln Ala
420 425 430

Leu Thr Lys Arg Asn Glu Phe Glu Val Ile Arg Glu Glu Asn Ala Lys
435 440 445

Leu Gln Ile Glu Asn Glu Arg Leu Arg Met Glu Ile Glu Lys Leu Lys
450 455 460

Met Glu Ile Ala Tyr Lys Asn Ser
465 470

<210> 64
<211> 1008
<212> DNA
<213> Artificial Sequence

<220>
<221> CDS
<222> (1)..(1005)

<220>
<223> Description of Artificial Sequence: vector pBS-SSV3

<400> 64

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atg acg aaa gat aag acg cgt tat aaa tac ggg gat tat att tta cgc   48
Met Thr Lys Asp Lys Thr Arg Tyr Lys Tyr Gly Asp Tyr Ile Leu Arg
  1               5                  10                  15

gag agg aaa ggg cgg tat tat gtt tac aag cta gag tat gaa aac ggt   96
Glu Arg Lys Gly Arg Tyr Tyr Val Tyr Lys Leu Glu Tyr Glu Asn Gly
            20                  25                  30

gag gta aaa gag cgt tac gtg ggt cct tta gct gac gtc gtt gaa tca   144
Glu Val Lys Glu Arg Tyr Val Gly Pro Leu Ala Asp Val Val Glu Ser
        35                  40                  45

tat cta aaa atg aaa tta ggg gtc gta ggg gat act ccc cta caa gcg   192
Tyr Leu Lys Met Lys Leu Gly Val Val Gly Asp Thr Pro Leu Gln Ala
    50                  55                  60

gat ccc ccc ggt ttc gag ccc ggg aca agc gga agc ggt ggt gga aaa   240
Asp Pro Pro Gly Phe Glu Pro Gly Thr Ser Gly Ser Gly Gly Gly Lys
65                  70                  75                  80

gag gga act gaa cga cgt aaa ata gcg ttg gtt gcc aat ttg cgc caa   288
Glu Gly Thr Glu Arg Arg Lys Ile Ala Leu Val Ala Asn Leu Arg Gln
                85                  90                  95

tac gcg acg gac ggc aac ata aag gcg ttc tac aac tat ctc atg aac   336
Tyr Ala Thr Asp Gly Asn Ile Lys Ala Phe Tyr Asn Tyr Leu Met Asn
            100                 105                 110

gaa agg ggg ata agc gaa aaa act gca aag gac tac atc aat gct ata   384
Glu Arg Gly Ile Ser Glu Lys Thr Ala Lys Asp Tyr Ile Asn Ala Ile
        115                 120                 125

tca aag ccg tat aaa gag acg aga gac gca cag aag gct tac cga ctc   432
Ser Lys Pro Tyr Lys Glu Thr Arg Asp Ala Gln Lys Ala Tyr Arg Leu
    130                 135                 140

ttt gca cgt ttc tta gcg tca cgc aat atc ata cat gat gaa ttt gcg   480
Phe Ala Arg Phe Leu Ala Ser Arg Asn Ile Ile His Asp Glu Phe Ala
145                 150                 155                 160

gat aaa ata ttg aaa gcg gta aag gtg aag aag gcg aac gct gat atc   528
Asp Lys Ile Leu Lys Ala Val Lys Val Lys Lys Ala Asn Ala Asp Ile
                165                 170                 175

tac att cca acg ttg gaa gag ata aaa agg acg tta caa tta gca aaa   576
Tyr Ile Pro Thr Leu Glu Glu Ile Lys Arg Thr Leu Gln Leu Ala Lys
            180                 185                 190

gac tat agc gaa aac gtc tac ttc atc tac cgt atc gct ctc gag tcg   624
Asp Tyr Ser Glu Asn Val Tyr Phe Ile Tyr Arg Ile Ala Leu Glu Ser
        195                 200                 205

ggc gtt agg ctg agc gaa ata ctg aaa gtg ctg aag gaa ccc gaa agg   672
Gly Val Arg Leu Ser Glu Ile Leu Lys Val Leu Lys Glu Pro Glu Arg
    210                 215                 220

gac att tgc ggt aac gac gtc tgt tat tat ccg ctt agt tgg act agg   720
Asp Ile Cys Gly Asn Asp Val Cys Tyr Tyr Pro Leu Ser Trp Thr Arg
```

```
225                 230                 235                 240

gga tat aag ggc gtc ttc tat gta ttc cac ata acg cct ctg aag aga   768
Gly Tyr Lys Gly Val Phe Tyr Val Phe His Ile Thr Pro Leu Lys Arg
                245                 250                 255

gta gag gtg acg aag tgg gca ata gcg gac ttt gaa cga cgt cat aag   816
Val Glu Val Thr Lys Trp Ala Ile Ala Asp Phe Glu Arg Arg His Lys
            260                 265                 270

gac gct ata gcg ata aag tac ttc cgc aaa ttc gta gcg tct aag atg   864
Asp Ala Ile Ala Ile Lys Tyr Phe Arg Lys Phe Val Ala Ser Lys Met
        275                 280                 285

gct gag cta agc gta ccg tta gat att atc gat ttt att caa ggg cgt   912
Ala Glu Leu Ser Val Pro Leu Asp Ile Ile Asp Phe Ile Gln Gly Arg
    290                 295                 300

aaa ccg aca cgc gtt tta acg caa cat tac gta tcg ctc ttc ggc ata   960
Lys Pro Thr Arg Val Leu Thr Gln His Tyr Val Ser Leu Phe Gly Ile
305                 310                 315                 320

gcg aaa gag caa tat aaa aag tat gcg gaa tgg cta aaa ggg gtc tga  1008
Ala Lys Glu Gln Tyr Lys Lys Tyr Ala Glu Trp Leu Lys Gly Val
                325                 330                 335
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<210> 65
<211> 335
<212> PRT
<213> Artificial Sequence
<223> Description of Artificial Sequence: vector pBS-SSV3

<400> 65

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Met Thr Lys Asp Lys Thr Arg Tyr Lys Tyr Gly Asp Tyr Ile Leu Arg
  1               5                  10                  15

Glu Arg Lys Gly Arg Tyr Tyr Val Tyr Lys Leu Glu Tyr Glu Asn Gly
             20                  25                  30

Glu Val Lys Glu Arg Tyr Val Gly Pro Leu Ala Asp Val Val Glu Ser
         35                  40                  45

Tyr Leu Lys Met Lys Leu Gly Val Val Gly Asp Thr Pro Leu Gln Ala
     50                  55                  60

Asp Pro Pro Gly Phe Glu Pro Gly Thr Ser Gly Ser Gly Gly Gly Lys
 65                  70                  75                  80

Glu Gly Thr Glu Arg Arg Lys Ile Ala Leu Val Ala Asn Leu Arg Gln
                 85                  90                  95

Tyr Ala Thr Asp Gly Asn Ile Lys Ala Phe Tyr Asn Tyr Leu Met Asn
            100                 105                 110

Glu Arg Gly Ile Ser Glu Lys Thr Ala Lys Asp Tyr Ile Asn Ala Ile
        115                 120                 125

Ser Lys Pro Tyr Lys Glu Thr Arg Asp Ala Gln Lys Ala Tyr Arg Leu
    130                 135                 140

Phe Ala Arg Phe Leu Ala Ser Arg Asn Ile Ile His Asp Glu Phe Ala
145                 150                 155                 160

Asp Lys Ile Leu Lys Ala Val Lys Val Lys Lys Ala Asn Ala Asp Ile
                165                 170                 175
```

```
Tyr Ile Pro Thr Leu Glu Glu Ile Lys Arg Thr Leu Gln Leu Ala Lys
            180                 185                 190

Asp Tyr Ser Glu Asn Val Tyr Phe Ile Tyr Arg Ile Ala Leu Glu Ser
        195                 200                 205

Gly Val Arg Leu Ser Glu Ile Leu Lys Val Leu Lys Glu Pro Glu Arg
    210                 215                 220

Asp Ile Cys Gly Asn Asp Val Cys Tyr Tyr Pro Leu Ser Trp Thr Arg
225                 230                 235                 240

Gly Tyr Lys Gly Val Phe Tyr Val Phe His Ile Thr Pro Leu Lys Arg
                245                 250                 255

Val Glu Val Thr Lys Trp Ala Ile Ala Asp Phe Glu Arg Arg His Lys
            260                 265                 270

Asp Ala Ile Ala Ile Lys Tyr Phe Arg Lys Phe Val Ala Ser Lys Met
        275                 280                 285

Ala Glu Leu Ser Val Pro Leu Asp Ile Ile Asp Phe Ile Gln Gly Arg
    290                 295                 300

Lys Pro Thr Arg Val Leu Thr Gln His Tyr Val Ser Leu Phe Gly Ile
305                 310                 315                 320

Ala Lys Glu Gln Tyr Lys Lys Tyr Ala Glu Trp Leu Lys Gly Val
                325                 330                 335
```

<210> 66
<211> 1441
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: DNA sequence coding for fusion protein NLS-XisA

<220>
<221> CDS
<222> (1)..(1437)

<400> 66

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atg ccc aag aag aag agg aag gtg caa aat cag ggt caa gac aaa tat   48
Met Pro Lys Lys Lys Arg Lys Val Gln Asn Gln Gly Gln Asp Lys Tyr
  1               5                  10                  15

caa caa gcc ttt gca gac tta gag cca ctt tca tct acc gac ggc agt   96
Gln Gln Ala Phe Ala Asp Leu Glu Pro Leu Ser Ser Thr Asp Gly Ser
             20                  25                  30

ttt ctc ggc tca agt ctg caa gca cag cag caa aga gaa cac atg aga   144
Phe Leu Gly Ser Ser Leu Gln Ala Gln Gln Gln Arg Glu His Met Arg
         35                  40                  45

aca aaa gta cta caa gac cta gac aag gta aat ctg cgt ttg aag tct   192
Thr Lys Val Leu Gln Asp Leu Asp Lys Val Asn Leu Arg Leu Lys Ser
     50                  55                  60

gca aag acg aaa gtc tca gtt cga gaa tct aac gga agt ctg caa tta   240
Ala Lys Thr Lys Val Ser Val Arg Glu Ser Asn Gly Ser Leu Gln Leu
 65                  70                  75                  80
```

```
cga gca acg tta cca att aaa cct gga gat aag gac acc aac ggt aca   288
Arg Ala Thr Leu Pro Ile Lys Pro Gly Asp Lys Asp Thr Asn Gly Thr
                 85                  90                  95

ggc aga aag caa tac aat ctc agc ttg aat atc cct gca aac ttg gat   336
Gly Arg Lys Gln Tyr Asn Leu Ser Leu Asn Ile Pro Ala Asn Leu Asp
            100                 105                 110

gga ctg aag acg gct gag gaa gaa gct tat gaa tta ggt aaa tta atc   384
Gly Leu Lys Thr Ala Glu Glu Glu Ala Tyr Glu Leu Gly Lys Leu Ile
        115                 120                 125

gct cgg aaa acc ttt gaa tgg aat gat aaa tat tta ggc aaa gaa gcc   432
Ala Arg Lys Thr Phe Glu Trp Asn Asp Lys Tyr Leu Gly Lys Glu Ala
    130                 135                 140

act aaa aaa gat tca caa aca ata ggt gat tta cta gaa aaa ttt gca   480
Thr Lys Lys Asp Ser Gln Thr Ile Gly Asp Leu Leu Glu Lys Phe Ala
145                 150                 155                 160

gaa gag tat ttt aaa acc cat aaa cgc acc act aaa agc gaa cat acc   528
Glu Glu Tyr Phe Lys Thr His Lys Arg Thr Thr Lys Ser Glu His Thr
                165                 170                 175

ttt ttt tac tat ttt tcc cgc acc caa cga tat acc aat tcc aaa gat   576
Phe Phe Tyr Tyr Phe Ser Arg Thr Gln Arg Tyr Thr Asn Ser Lys Asp
            180                 185                 190

tta gca acg gcg gaa aat ctc atc aat tca att gag caa atc gat aaa   624
Leu Ala Thr Ala Glu Asn Leu Ile Asn Ser Ile Glu Gln Ile Asp Lys
        195                 200                 205

gaa tgg gcg aga tat aat gcc gcc aga gcc ata tca gct ttt tgc ata   672
Glu Trp Ala Arg Tyr Asn Ala Ala Arg Ala Ile Ser Ala Phe Cys Ile
    210                 215                 220

aca ttc aat ata gaa att gat ttg tcc cag tat tcc aaa atg cct gat   720
Thr Phe Asn Ile Glu Ile Asp Leu Ser Gln Tyr Ser Lys Met Pro Asp
225                 230                 235                 240

cgc aat tcg cgc aac atc ccc aca gat gca gaa ata cta tca gga att   768
Arg Asn Ser Arg Asn Ile Pro Thr Asp Ala Glu Ile Leu Ser Gly Ile
                245                 250                 255

acc aaa ttt gaa gac tat cta gtt acc aga gga aat caa gtt aat gaa   816
Thr Lys Phe Glu Asp Tyr Leu Val Thr Arg Gly Asn Gln Val Asn Glu
            260                 265                 270

gat gta aaa gat agc tgg caa ctt tgg cgc tgg aca tat gga atg tta   864
Asp Val Lys Asp Ser Trp Gln Leu Trp Arg Trp Thr Tyr Gly Met Leu
        275                 280                 285

gca gtt ttt ggt tta cgc ccc agg gaa att ttt att aac cct aat att   912
Ala Val Phe Gly Leu Arg Pro Arg Glu Ile Phe Ile Asn Pro Asn Ile
    290                 295                 300

gat tgg tgg tta agc aaa gag aat ata gac ctc aca tgg aaa gta gac   960
Asp Trp Trp Leu Ser Lys Glu Asn Ile Asp Leu Thr Trp Lys Val Asp
305                 310                 315                 320

aaa gaa tgt aaa act ggt gaa aga caa gca tta ccc tta cat aaa gaa   1008
Lys Glu Cys Lys Thr Gly Glu Arg Gln Ala Leu Pro Leu His Lys Glu
                325                 330                 335

tgg att gat gag ttt gat tta aga aat ccg aaa tat tta gaa atg ctg   1056
Trp Ile Asp Glu Phe Asp Leu Arg Asn Pro Lys Tyr Leu Glu Met Leu
            340                 345                 350
```

```
gca aca gca att agt aaa aaa gat aaa aca aat cat gct gaa ata aca   1104
Ala Thr Ala Ile Ser Lys Lys Asp Lys Thr Asn His Ala Glu Ile Thr
        355                 360                 365

gcc tta act cag cgt att agt tgg tgg ttt cgg aaa gtc gaa tta gat   1152
Ala Leu Thr Gln Arg Ile Ser Trp Trp Phe Arg Lys Val Glu Leu Asp
    370                 375                 380

ttt aaa ccc tat gat tta cgt cac gcc tgg gca atc aga gcg cat att   1200
Phe Lys Pro Tyr Asp Leu Arg His Ala Trp Ala Ile Arg Ala His Ile
385                 390                 395                 400

tta ggc ata cca atc aaa gcg gcg gct gat aat ttg ggg cat agt atg   1248
Leu Gly Ile Pro Ile Lys Ala Ala Ala Asp Asn Leu Gly His Ser Met
                405                 410                 415

cag gtt cat aca caa acc tat cag cgc tgg ttc tcg cta gat atg cgg   1296
Gln Val His Thr Gln Thr Tyr Gln Arg Trp Phe Ser Leu Asp Met Arg
            420                 425                 430

aag tta gcg att aat cag gct ttg act aag agg aat gaa ttt gag gtg   1344
Lys Leu Ala Ile Asn Gln Ala Leu Thr Lys Arg Asn Glu Phe Glu Val
        435                 440                 445

att agg gag gag aat gct aaa ttg cag ata gaa aat gaa agg ttg agg   1392
Ile Arg Glu Glu Asn Ala Lys Leu Gln Ile Glu Asn Glu Arg Leu Arg
    450                 455                 460

atg gaa att gag aag tta aag atg gaa ata gct tat aag aat agt tgag  1441
Met Glu Ile Glu Lys Leu Lys Met Glu Ile Ala Tyr Lys Asn Ser
465                 470                 475
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<210> 67
<211> 479
<212> PRT
<213> Artificial Sequence
<223> Description of Artificial Sequence: DNA sequence coding for fusion protein NLS-XisA

<400> 67

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Met Pro Lys Lys Lys Arg Lys Val Gln Asn Gln Gly Gln Asp Lys Tyr
  1               5                  10                  15

Gln Gln Ala Phe Ala Asp Leu Glu Pro Leu Ser Ser Thr Asp Gly Ser
             20                  25                  30

Phe Leu Gly Ser Ser Leu Gln Ala Gln Gln Gln Arg Glu His Met Arg
         35                  40                  45

Thr Lys Val Leu Gln Asp Leu Asp Lys Val Asn Leu Arg Leu Lys Ser
     50                  55                  60

Ala Lys Thr Lys Val Ser Val Arg Glu Ser Asn Gly Ser Leu Gln Leu
 65                  70                  75                  80

Arg Ala Thr Leu Pro Ile Lys Pro Gly Asp Lys Asp Thr Asn Gly Thr
                 85                  90                  95

Gly Arg Lys Gln Tyr Asn Leu Ser Leu Asn Ile Pro Ala Asn Leu Asp
            100                 105                 110

Gly Leu Lys Thr Ala Glu Glu Glu Ala Tyr Glu Leu Gly Lys Leu Ile
        115                 120                 125

Ala Arg Lys Thr Phe Glu Trp Asn Asp Lys Tyr Leu Gly Lys Glu Ala
```

130 135 140

Thr Lys Lys Asp Ser Gln Thr Ile Gly Asp Leu Leu Glu Lys Phe Ala
145 150 155 160

Glu Glu Tyr Phe Lys Thr His Lys Arg Thr Thr Lys Ser Glu His Thr
165 170 175

Phe Phe Tyr Tyr Phe Ser Arg Thr Gln Arg Tyr Thr Asn Ser Lys Asp
180 185 190

Leu Ala Thr Ala Glu Asn Leu Ile Asn Ser Ile Glu Gln Ile Asp Lys
195 200 205

Glu Trp Ala Arg Tyr Asn Ala Ala Arg Ala Ile Ser Ala Phe Cys Ile
210 215 220

Thr Phe Asn Ile Glu Ile Asp Leu Ser Gln Tyr Ser Lys Met Pro Asp
225 230 235 240

Arg Asn Ser Arg Asn Ile Pro Thr Asp Ala Glu Ile Leu Ser Gly Ile
245 250 255

Thr Lys Phe Glu Asp Tyr Leu Val Thr Arg Gly Asn Gln Val Asn Glu
260 265 270

Asp Val Lys Asp Ser Trp Gln Leu Trp Arg Trp Thr Tyr Gly Met Leu
275 280 285

Ala Val Phe Gly Leu Arg Pro Arg Glu Ile Phe Ile Asn Pro Asn Ile
290 295 300

Asp Trp Trp Leu Ser Lys Glu Asn Ile Asp Leu Thr Trp Lys Val Asp
305 310 315 320

Lys Glu Cys Lys Thr Gly Glu Arg Gln Ala Leu Pro Leu His Lys Glu
325 330 335

Trp Ile Asp Glu Phe Asp Leu Arg Asn Pro Lys Tyr Leu Glu Met Leu
340 345 350

Ala Thr Ala Ile Ser Lys Lys Asp Lys Thr Asn His Ala Glu Ile Thr
355 360 365

Ala Leu Thr Gln Arg Ile Ser Trp Trp Phe Arg Lys Val Glu Leu Asp
370 375 380

Phe Lys Pro Tyr Asp Leu Arg His Ala Trp Ala Ile Arg Ala His Ile
385 390 395 400

Leu Gly Ile Pro Ile Lys Ala Ala Ala Asp Asn Leu Gly His Ser Met
405 410 415

Gln Val His Thr Gln Thr Tyr Gln Arg Trp Phe Ser Leu Asp Met Arg
420 425 430

Lys Leu Ala Ile Asn Gln Ala Leu Thr Lys Arg Asn Glu Phe Glu Val
435 440 445

Ile Arg Glu Glu Asn Ala Lys Leu Gln Ile Glu Asn Glu Arg Leu Arg
450 455 460

Met Glu Ile Glu Lys Leu Lys Met Glu Ile Ala Tyr Lys Asn Ser
465 470 475

<210> 68
<211> 1029
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: DNA sequence coding for fusion protein NLS-Ssv

<220>
<221> CDS
<222> (1)..(1026)

<400> 68

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atg ccc aag aag aag agg aag gtg acg aaa gat aag acg cgt tat aaa   48
Met Pro Lys Lys Lys Arg Lys Val Thr Lys Asp Lys Thr Arg Tyr Lys
  1               5                  10                  15

tac ggg gat tat att tta cgc gag agg aaa ggg cgg tat tat gtt tac   96
Tyr Gly Asp Tyr Ile Leu Arg Glu Arg Lys Gly Arg Tyr Tyr Val Tyr
             20                  25                  30

aag cta gag tat gaa aac ggt gag gta aaa gag cgt tac gtg ggt cct   144
Lys Leu Glu Tyr Glu Asn Gly Glu Val Lys Glu Arg Tyr Val Gly Pro
         35                  40                  45

tta gct gac gtc gtt gaa tca tat cta aaa atg aaa tta ggg gtc gta   192
Leu Ala Asp Val Val Glu Ser Tyr Leu Lys Met Lys Leu Gly Val Val
     50                  55                  60

ggg gat act ccc cta caa gcg gat ccc ccc ggt ttc gag ccc ggg aca   240
Gly Asp Thr Pro Leu Gln Ala Asp Pro Pro Gly Phe Glu Pro Gly Thr
 65                  70                  75                  80

agc gga agc ggt ggt gga aaa gag gga act gaa cga cgt aaa ata gcg   288
Ser Gly Ser Gly Gly Gly Lys Glu Gly Thr Glu Arg Arg Lys Ile Ala
                 85                  90                  95

ttg gtt gcc aat ttg cgc caa tac gcg acg gac ggc aac ata aag gcg   336
Leu Val Ala Asn Leu Arg Gln Tyr Ala Thr Asp Gly Asn Ile Lys Ala
            100                 105                 110

ttc tac aac tat ctc atg aac gaa agg ggg ata agc gaa aaa act gca   384
Phe Tyr Asn Tyr Leu Met Asn Glu Arg Gly Ile Ser Glu Lys Thr Ala
        115                 120                 125

aag gac tac atc aat gct ata tca aag ccg tat aaa gag acg aga gac   432
Lys Asp Tyr Ile Asn Ala Ile Ser Lys Pro Tyr Lys Glu Thr Arg Asp
    130                 135                 140

gca cag aag gct tac cga ctc ttt gca cgt ttc tta gcg tca cgc aat   480
Ala Gln Lys Ala Tyr Arg Leu Phe Ala Arg Phe Leu Ala Ser Arg Asn
145                 150                 155                 160

atc ata cat gat gaa ttt gcg gat aaa ata ttg aaa gcg gta aag gtg   528
Ile Ile His Asp Glu Phe Ala Asp Lys Ile Leu Lys Ala Val Lys Val
                165                 170                 175

aag aag gcg aac gct gat atc tac att cca acg ttg gaa gag ata aaa   576
Lys Lys Ala Asn Ala Asp Ile Tyr Ile Pro Thr Leu Glu Glu Ile Lys
            180                 185                 190

agg acg tta caa tta gca aaa gac tat agc gaa aac gtc tac ttc atc   624
Arg Thr Leu Gln Leu Ala Lys Asp Tyr Ser Glu Asn Val Tyr Phe Ile
        195                 200                 205

tac cgt atc gct ctc gag tcg ggc gtt agg ctg agc gaa ata ctg aaa   672
```

```
Tyr Arg Ile Ala Leu Glu Ser Gly Val Arg Leu Ser Glu Ile Leu Lys
    210                 215                 220

gtg ctg aag gaa ccc gaa agg gac att tgc ggt aac gac gtc tgt tat   720
Val Leu Lys Glu Pro Glu Arg Asp Ile Cys Gly Asn Asp Val Cys Tyr
225                 230                 235                 240

tat ccg ctt agt tgg act agg gga tat aag ggc gtc ttc tat gta ttc   768
Tyr Pro Leu Ser Trp Thr Arg Gly Tyr Lys Gly Val Phe Tyr Val Phe
                245                 250                 255

cac ata acg cct ctg aag aga gta gag gtg acg aag tgg gca ata gcg   816
His Ile Thr Pro Leu Lys Arg Val Glu Val Thr Lys Trp Ala Ile Ala
            260                 265                 270

gac ttt gaa cga cgt cat aag gac gct ata gcg ata aag tac ttc cgc   864
Asp Phe Glu Arg Arg His Lys Asp Ala Ile Ala Ile Lys Tyr Phe Arg
        275                 280                 285

aaa ttc gta gcg tct aag atg gct gag cta agc gta ccg tta gat att   912
Lys Phe Val Ala Ser Lys Met Ala Glu Leu Ser Val Pro Leu Asp Ile
    290                 295                 300

atc gat ttt att caa ggg cgt aaa ccg aca cgc gtt tta acg caa cat   960
Ile Asp Phe Ile Gln Gly Arg Lys Pro Thr Arg Val Leu Thr Gln His
305                 310                 315                 320

tac gta tcg ctc ttc ggc ata gcg aaa gag caa tat aaa aag tat gcg   1008
Tyr Val Ser Leu Phe Gly Ile Ala Lys Glu Gln Tyr Lys Lys Tyr Ala
                325                 330                 335

gaa tgg cta aaa ggg gtc tga                                      1029
Glu Trp Leu Lys Gly Val
            340
```

<210> 69
<211> 342
<212> PRT
<213> Artificial Sequence
<223> Description of Artificial Sequence: DNA sequence coding for fusion protein NLS-Ssv

<400> 69

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Met Pro Lys Lys Lys Arg Lys Val Thr Lys Asp Lys Thr Arg Tyr Lys
  1               5                  10                  15

Tyr Gly Asp Tyr Ile Leu Arg Glu Arg Lys Gly Arg Tyr Tyr Val Tyr
             20                  25                  30

Lys Leu Glu Tyr Glu Asn Gly Glu Val Lys Glu Arg Tyr Val Gly Pro
         35                  40                  45

Leu Ala Asp Val Val Glu Ser Tyr Leu Lys Met Lys Leu Gly Val Val
     50                  55                  60

Gly Asp Thr Pro Leu Gln Ala Asp Pro Pro Gly Phe Glu Pro Gly Thr
 65                  70                  75                  80

Ser Gly Ser Gly Gly Gly Lys Glu Gly Thr Glu Arg Arg Lys Ile Ala
                 85                  90                  95

Leu Val Ala Asn Leu Arg Gln Tyr Ala Thr Asp Gly Asn Ile Lys Ala
            100                 105                 110

Phe Tyr Asn Tyr Leu Met Asn Glu Arg Gly Ile Ser Glu Lys Thr Ala
        115                 120                 125
```

Lys Asp Tyr Ile Asn Ala Ile Ser Lys Pro Tyr Lys Glu Thr Arg Asp
130 135 140

Ala Gln Lys Ala Tyr Arg Leu Phe Ala Arg Phe Leu Ala Ser Arg Asn
145 150 155 160

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

Lys Lys Ala Asn Ala Asp Ile Tyr Ile Pro Thr Leu Glu Glu Ile Lys
180 185 190

Arg Thr Leu Gln Leu Ala Lys Asp Tyr Ser Glu Asn Val Tyr Phe Ile
195 200 205

Tyr Arg Ile Ala Leu Glu Ser Gly Val Arg Leu Ser Glu Ile Leu Lys
210 215 220

Val Leu Lys Glu Pro Glu Arg Asp Ile Cys Gly Asn Asp Val Cys Tyr
225 230 235 240

Tyr Pro Leu Ser Trp Thr Arg Gly Tyr Lys Gly Val Phe Tyr Val Phe
245 250 255

His Ile Thr Pro Leu Lys Arg Val Glu Val Thr Lys Trp Ala Ile Ala
260 265 270

Asp Phe Glu Arg Arg His Lys Asp Ala Ile Ala Ile Lys Tyr Phe Arg
275 280 285

Lys Phe Val Ala Ser Lys Met Ala Glu Leu Ser Val Pro Leu Asp Ile
290 295 300

Ile Asp Phe Ile Gln Gly Arg Lys Pro Thr Arg Val Leu Thr Gln His
305 310 315 320

Tyr Val Ser Leu Phe Gly Ile Ala Lys Glu Gln Tyr Lys Lys Tyr Ala
325 330 335

Glu Trp Leu Lys Gly Val
340

<210> 70
<211> 3908
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: vector
pBS-SSV3

<400> 70
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cgagataggg ttgagtgttg ttccagtttg gaacaagagt ccactattaa agaacgtgga 180
ctccaacgtc aaagggcgaa aaaccgtcta tcagggcgat ggcccactac gtgaaccatc 240
accctaatca agtttttttgg ggtcgaggtg ccgtaaagca ctaaatcgga accctaaagg 300
gagccccccga tttagagctt gacggggaaa gccggcgaac gtggcgagaa aggaagggaa 360
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caccacaccc gccgcgctta atgcgccgct acagggcgcg tcccattcgc cattcaggct 480
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tcgtgcaccc aactgatctt cagcatcttt tactttcacc agcgtttctg ggtgagcaaa 3720
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catactcttc ctttttcaat attattgaag catttatcag ggttattgtc tcatgagcgg 3840
atacatattt gaatgtattt agaaaaataa acaaataggg gttccgcgca catttccccg 3900
aaaagtgc 3908

<210> 71
<211> 3927
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: vector
pBS-SSV4

<400> 71
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cgagataggg ttgagtgttg ttccagtttg gaacaagagt ccactattaa agaacgtgga 180
ctccaacgtc aaagggcgaa aaaccgtcta tcagggcgat ggcccactac gtgaaccatc 240
accctaatca agttttttgg ggtcgaggtg ccgtaaagca ctaaatcgga accctaaagg 300
gagcccccga tttagagctt gacggggaaa gccggcgaac gtggcgagaa aggaagggaa 360
gaaagcgaaa ggagcgggcg ctagggcgct ggcaagtgta gcggtcacgc tgcgcgtaac 420
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<220>
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<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: vector pCMVC31(NNLS)

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<220>
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<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: vector
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<213> Artificial Sequence

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Asp Thr Ser Ser Ala Met Gly Ser Leu Phe Leu Thr Ile Leu Ser Ala
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aaa cta ggg cga gcg aaa tct ggt aag tct atg atg tgg act aag aca   480
Lys Leu Gly Arg Ala Lys Ser Gly Lys Ser Met Met Trp Thr Lys Thr
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Ala Phe Gly Tyr Tyr His Asn Arg Lys Thr Gly Ile Leu Glu Ile Val
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Glu Gly Met His Lys Pro Ile Ile Pro Tyr Glu Thr Tyr Leu Lys Val
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Gln Lys Glu Leu Glu Glu Arg Gln Gln Gln Thr Tyr Glu Arg Asn Asn
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gat ttt atc act atg gat gag ttg aaa gat cgt act gat tcc ctt cag  1248
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gct gag aaa aag ctg ctt aaa gct aag att agc gaa aat aaa ttt aat  1296
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Pro Ile Asn Glu Leu Ser Tyr Asp Asn Lys Lys Lys Ile Val Asn Asn
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Lys Phe Gln Leu Ala
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Tyr Ala Glu Ala Met Gly Trp Gln Val Ser Asp Thr Tyr Thr Asp Ala
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Gly Phe Ser Gly Ala Lys Leu Glu Arg Pro Ala Met Gln Arg Leu Ile
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Asn Asp Ile Glu Asn Lys Ala Phe Asp Thr Val Leu Val Tyr Lys Leu
 65                  70                  75                  80

Asp Arg Leu Ser Arg Ser Val Arg Asp Thr Leu Tyr Leu Val Lys Asp
                 85                  90                  95

Val Phe Thr Lys Asn Lys Ile Asp Phe Ile Ser Leu Asn Glu Ser Ile
            100                 105                 110

Asp Thr Ser Ser Ala Met Gly Ser Leu Phe Leu Thr Ile Leu Ser Ala
        115                 120                 125

Ile Asn Glu Phe Glu Arg Glu Asn Ile Lys Glu Arg Met Thr Met Gly
    130                 135                 140

Lys Leu Gly Arg Ala Lys Ser Gly Lys Ser Met Met Trp Thr Lys Thr
145                 150                 155                 160

Ala Phe Gly Tyr Tyr His Asn Arg Lys Thr Gly Ile Leu Glu Ile Val
                165                 170                 175

Pro Leu Gln Ala Thr Ile Val Glu Gln Ile Phe Thr Asp Tyr Leu Ser
            180                 185                 190

Gly Ile Ser Leu Thr Lys Leu Arg Asp Lys Leu Asn Glu Ser Gly His
        195                 200                 205

Ile Gly Lys Asp Ile Pro Trp Ser Tyr Arg Thr Leu Arg Gln Thr Leu
    210                 215                 220

Asp Asn Pro Val Tyr Cys Gly Tyr Ile Lys Phe Lys Asp Ser Leu Phe
225                 230                 235                 240
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Glu Gly Met His Lys Pro Ile Ile Pro Tyr Glu Thr Tyr Leu Lys Val
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Gln Lys Glu Leu Glu Glu Arg Gln Gln Gln Thr Tyr Glu Arg Asn Asn
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Asn Pro Arg Pro Phe Gln Ala Lys Tyr Met Leu Ser Gly Met Ala Arg
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Pro Ile Asn Glu Leu Ser Tyr Asp Asn Lys Lys Lys Ile Val Asn Asn
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Lys Phe Gln Leu Ala
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Fig. 1

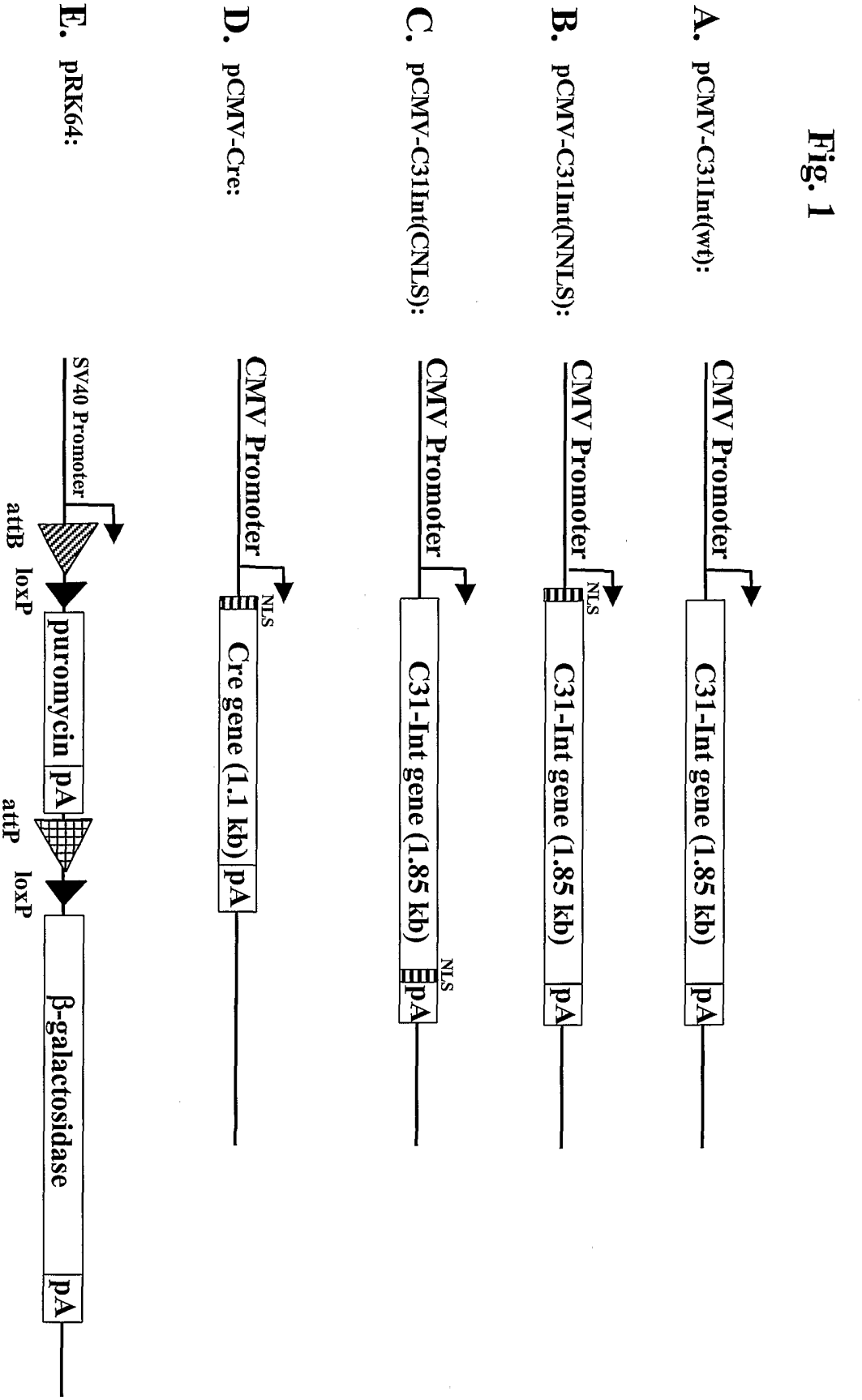

A. pCMV-C31Int(wt):
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C31-Int gene (1.85 kb)
pA
B. pCMV-C31Int(NNLS):
CMV Promoter
NLS
C31-Int gene (1.85 kb)
pA
C. pCMV-C31Int(CNLS):
CMV Promoter
C31-Int gene (1.85 kb)
NLS
pA
D. pCMV-Cre:
CMV Promoter
NLS
Cre gene (1.1 kb)
pA
E. pRK64:
SV40 Promoter
attB
loxP
puromycin
pA
attP
loxP
β-galactosidase
pA

Fig. 2

Sample	RLU (βGal)	RLU (Luciferase)	RLU x10^5 (Gal/Luc)	RLU x10^5 (Gal/Luc)	relative activity
				10^4 5 x 10^4	
1) pUC19 only	433 ± 37	1818700 ± 328970	**24** ± 4		
2) pRK64(ΔCre)	784932 ± 290524	1657062 ± 526562	**46975** ± 3696		1
3) pRK64 only	1936 ± 262	988144 ± 175116	**204** ± 62		0.004
4) pCMV-C31Int(wt) 0.5 ng	73318 ± 19084	677861 ± 145341	**10774** ± 972		0.23
5) pCMV-C31Int(wt) 1 ng	75838 ± 12628	527237 ± 53846	**14412** ± 2050		0.3
6) pCMV-C31Int(NNLS) 0.5 ng	158402 ± 75870	2560450 ± 736186	**15104** ± 3041		0.32
7) pCMV-C31Int(NNLS) 1 ng	206857 ± 76733	2677621 ± 504285	**17029** ± 2246		0.36
8) pCMV-C31Int(CNLS) 0.5 ng	274192 ± 78937	1173932 ± 291315	**23299** ± 3194		0.5
9) pCMV-C31Int(CNLS) 1 ng	262169 ± 60583	864752 ± 229935	**30560** ± 1585		0.65
10) pCMV-Cre(NNLS) 0.5 ng	231200 ± 96741	763121 ± 280687	**29595** ± 4632		0.63
11) pCMV-Cre(NNLS) 1 ng	297760 ± 83363	868905 ± 196404	**33872** ± 2609		0.72

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Fig. 3

	RLU (βGal)	RLU (Luciferase)	RLU x 10^5 (Gal/Luci)
1) pPGKnifD (reporter) only	1324 ± 876	3631598 ± 903012	34 ± 18
2) pCMV-XisA 25 ng	4650 ± 2273	2741969 ± 667568	164 ± 54
3) pCMV-XisA 100 ng	17529 ± 9304	3798872 ± 1288020	443 ± 151
4) pCMV-XisA(NNLS) 25 ng	4060 ± 1376	2471695 ± 611351	163 ± 36
5) pCMV-XisA(NNLS) 100 ng	17801 ± 3892	3570103 ± 750628	500 ± 65
6) pPGKattA (reporter) only	754 ± 70	195822 ± 81858	755 ± 601
7) pCMV-SSV 10 ng	925 ± 273	119043 ± 67451	906 ± 316
8) pCMV-SSV 20 ng	1033 ± 270	122557 ± 30054	879 ± 291
9) pCMV-SSV(NNLS) 10 ng	1108 ± 367	174380 ± 58876	694 ± 345
10) pCMV-SSV(NNLS) 20 ng	1306 ± 383	211182 ± 101011	874 ± 741

Fig. 4

Sample	RLU (βGal)	RLU (βGal)	relative activity
1) pUC19 only	754 ± 44	5 x 10³ / 4 x 10⁴	
2) pCMV-C31Int(wt) 32 ng	1386 ± 174		0.04
3) pCMV-C31Int(wt) 64 ng	3783 ± 1537		0.1
4) pCMV-C31Int(NNLS) 32 ng	7125 ± 1474		0.19
5) pCMV-C31Int(NNLS) 64 ng	8206 ± 2210		0.22
6) pCMV-C31Int(CNLS) 32 ng	17624 ± 5578		0.48
7) pCMV-C31Int(CNLS) 64 ng	28849 ± 6623		0.78
8) pCMV-Cre(NNLS) 32 ng	27064 ± 3769		0.73
9) pCMV-Cre(NNLS) 64 ng	36823 ± 3993		1

A.: Nontransfected control

B.: pCMV-Cre

C.: pCMV-C31Int(NLS)

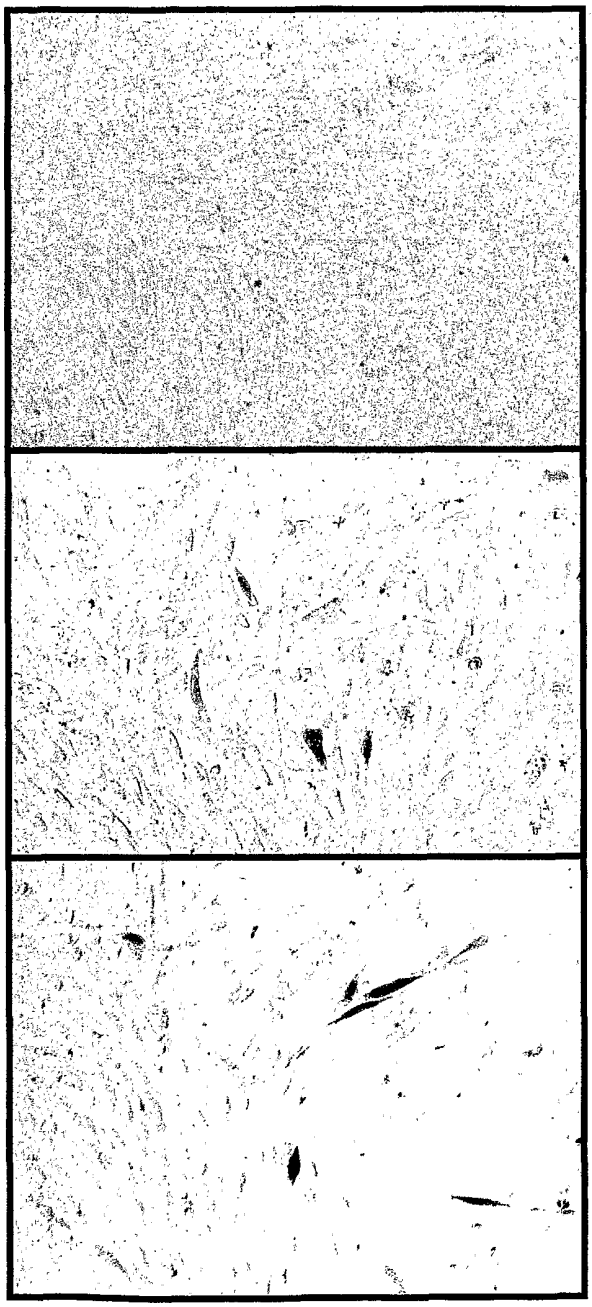


Fig. 5

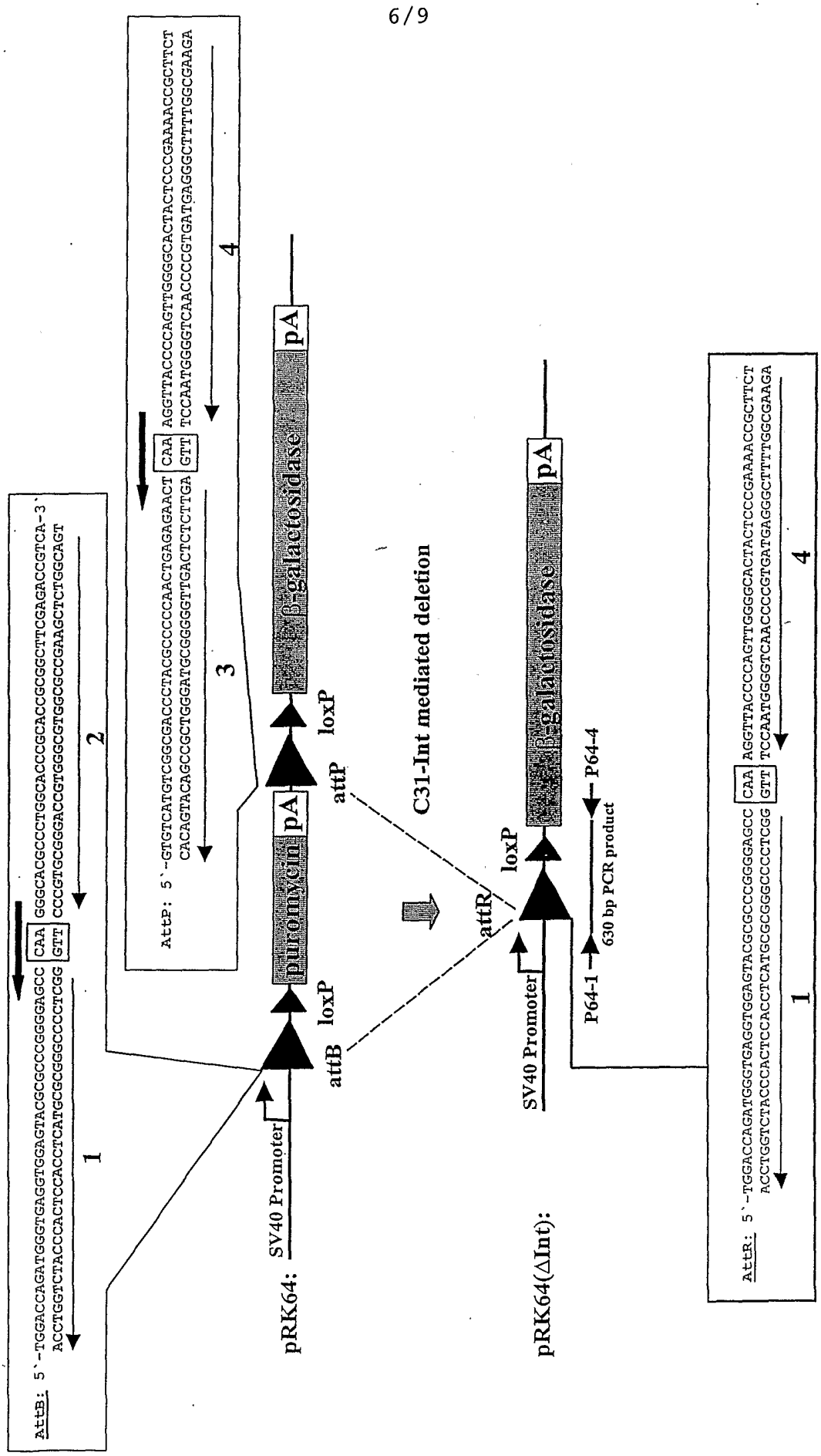

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β-galactosidase
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Fig. 6

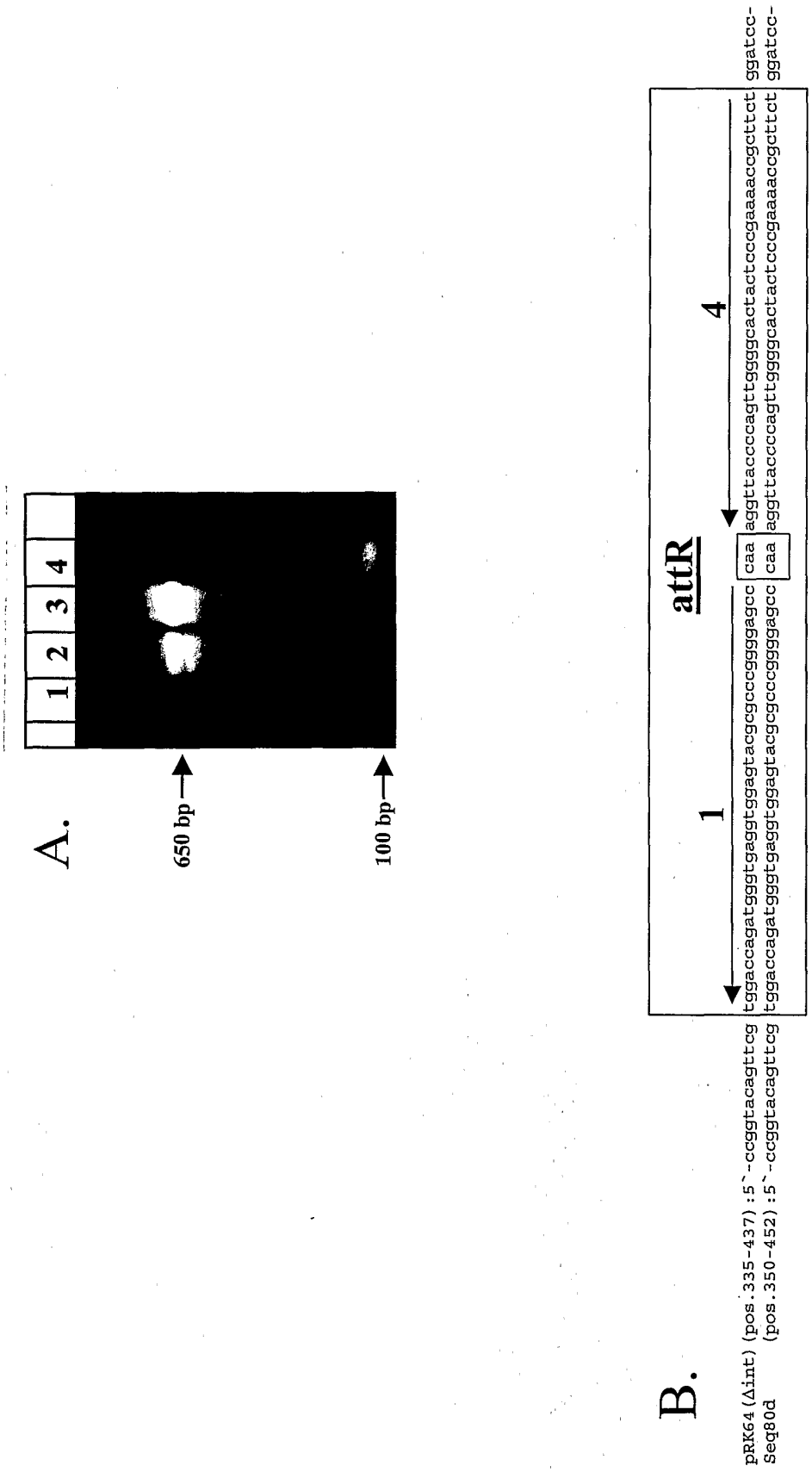
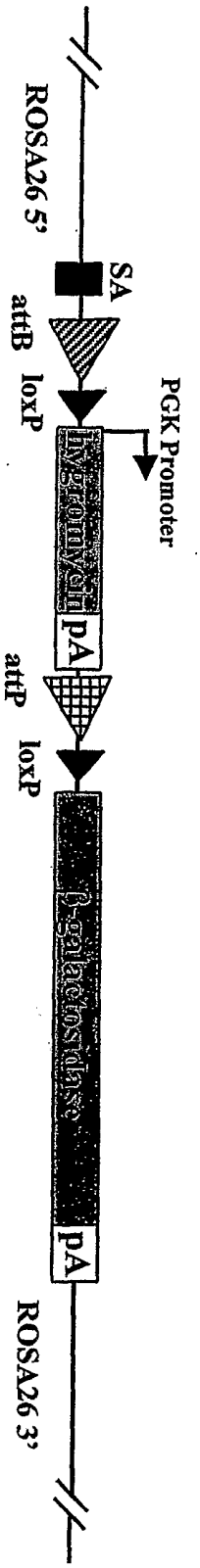

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100 bp
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Fig. 7

Fig. 8



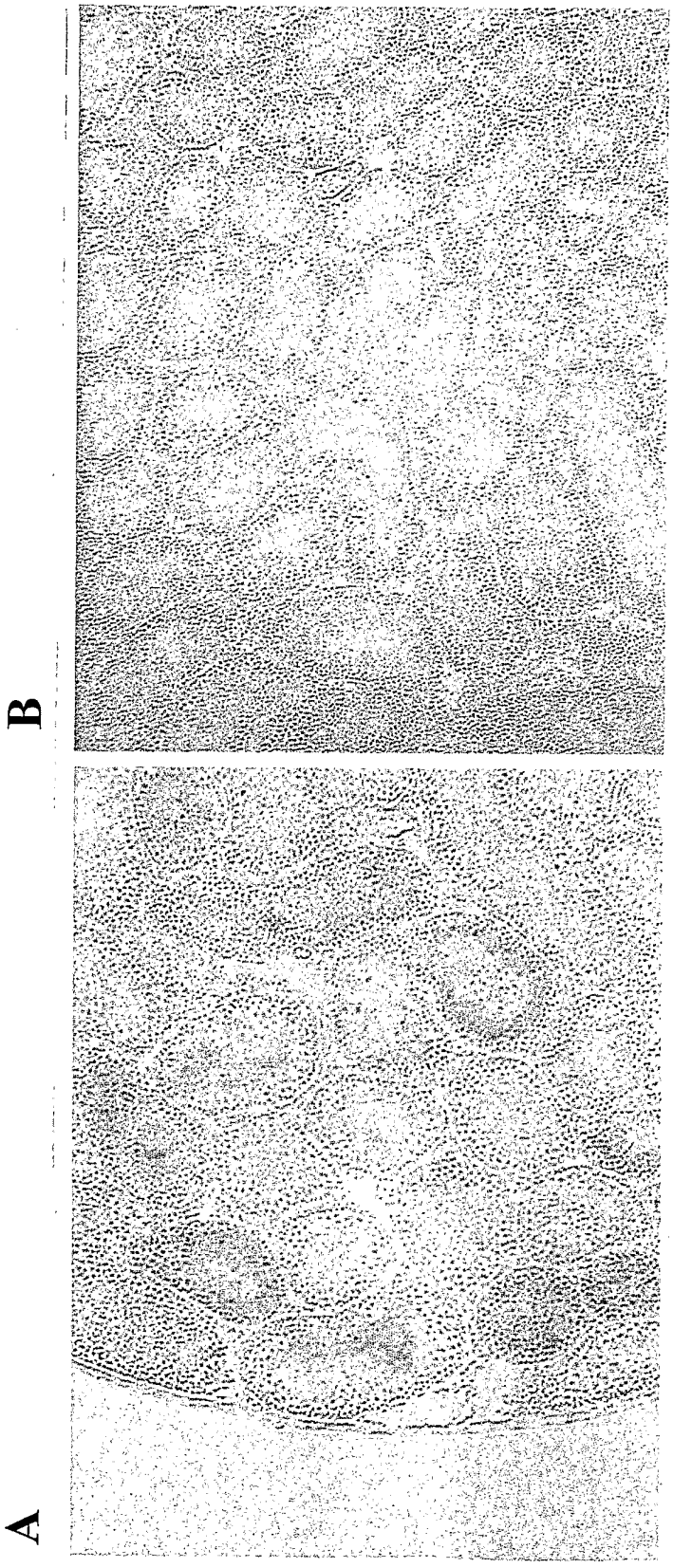


Fig. 9