NOVEL PROMOTERS FOR HIGH LEVEL EXPRESSION

CROSS-REFERENCE TO RELATED APPLICATION

[001] This application makes reference to and claims the benefit of priority of a Singapore patent application filed on 18 June 2014, and duly assigned application number 10201403371T. The content of said application filed on 18 June 2014 is incorporated herein by reference for all purposes, including an incorporation of any element or part of the description, claims or drawings not contained herein and referred to in Rule 20.5(a) of the PCT, pursuant to Rule 4.18 of the PCT.

FIELD OF THE INVENTION

[002] The present invention lies in the field of recombinant promoter variants capable of driving strong and sustained heterologous gene expression in *in vitro* and *in vivo* applications such as gene therapy and recombinant protein expression.

BACKGROUND OF THE INVENTION

[003] Strong promoters are desired for high level recombinant protein production, in order to provide large quantities of a desired recombinant protein permitting a wide range of possible uses including industrial processes, diagnosis and disease treatment.

[004] A typical promoter used for recombinant protein production contains a promoter element, an immediate upstream enhancer and if required other cis-acting regulatory elements. Optionally, transcription factors, which work in synergy to enhance transcription activity, are recruited to the site by specific sequence motifs.

[005] Increasing recombinant protein expression through improvements in transcription and through preventing promoter silencing is desirable for optimizing yield. In order to be able to provide functional proteins, mammalian proteins are often expressed in mammalian cell lines as these can ensure the required post-translational modifications, such as "native" mammalian glycosylation patterns and molecular folding steps. Thus, mammalian cells are an important host for the production of clinically relevant recombinant proteins. The most widely used approach for this purpose is to establish a cell line with an actively expressed recombinant gene stably integrated in its genome. Alternatively, proteins can be transiently produced in cells for a limited period of time without the necessity of recombinant gene integration.

[006] Chinese hamster ovary cells (CHO) cells have been the most commonly used mammalian host for large-scale commercial production of therapeutic proteins. The first CHO cell line was derived through single cell cloning in 1957. The cell line CHO-K1 was later derived from this ancestral cell line and it contains a slightly lower amount of DNA than the original CHO. Subsequently, another derivative of the original CHO cell line was mutagenized

to yield CHO-DG44, a cell line with deletions of both dhfr alleles. While CHO cells are used in studies of genetics, toxicity screening, nutrition and gene expression, the most prominent use is recombinant protein expression.

[007] Process development using CHO cell lines focuses on achieving the maximum amount of active product. Optimization of the amount of active product can be achieved via increasing the specific productivity (i.e., the product per cell) and/or by cell line development. Cell line development may include both sub-cloning the cell line to select higher producing clones and use of gene amplification.

[008] Another way to achieve higher recombinant protein yields is to increase the cell yield (i.e., cells per volume) of the process. This may be accomplished through process development (e.g., batch, fed-batch, perfusion, etc.) and medium development. By increasing the cells per volume per day, higher levels of product may be produced.

[009] However, even though efficiency and output in recombinant protein production has substantially increased in recent years, there is still the need in the art for alternative methods that allow an even higher expression level.

SUMMARY OF THE INVENTION

[0010] The inventors of the present application have found that said need can be met by novel chimeric gene regulatory units.

[0011] In a first aspect the present invention therefore relates to an isolated nucleic acid molecule comprising a functional chimeric gene regulatory unit comprising (a) a functional enhancer nucleotide sequence, (b) a functional core promoter nucleotide sequence and (c) at least one nucleotide sequence encoding for an intron, wherein the enhancer nucleotide sequence is 5' to the promoter nucleotide sequence and the intron nucleotide sequence is 3' to the promoter sequence and wherein at least one nucleotide sequence of the enhancer nucleotide sequence, the promoter nucleotide sequence or the at least one nucleotide sequence encoding for the intron is derived from a different species than the other nucleotide sequences.

[0012] In various embodiments, the isolated nucleic acid molecule further comprises at least one nucleotide sequence encoding for a polypeptide, peptide or RNA molecule, wherein said sequence is operably linked to the chimeric gene regulatory unit. The at least one nucleotide sequence encoding for a polypeptide, peptide or RNA molecule of interest may lie 3' to the intron nucleotide sequence, preferably directly adjacent to the intron sequence. In various embodiments, where the nucleotide sequence encodes for a polypeptide of interest, said polypeptide of interest is a polypeptide chain of a naturally occurring or artificial immunoglobulin. In various embodiments, the polypeptide of interest may be an antibody or fragment thereof. The antibody may be a human or humanized antibody, or a fragment thereof.

[0013] In various embodiments, the chimeric gene regulation unit has an increased resistance

to transcriptional silencing.

[0014] In various embodiments, the isolated nucleic acid molecule further comprises at least one nucleotide sequence encoding for a recognition site of a restriction endonuclease. The at least one nucleotide sequence encoding for a recognition site of a restriction endonuclease may be (i) 3' to the enhancer nucleotide sequence and 5' to the promoter nucleotide sequence or (ii) 3' to the promoter nucleotide sequence and 5' to the at least one nucleotide sequence encoding for an intron.

[0015] In various embodiments, the enhancer sequence is derived from viruses, preferably from double-stranded DNA viruses. Said viruses may be of the group of Herpesviridae and Polyomaviridae, preferably of the group consisting of human cytomegalovirus, murine cytomegalovirus, and simian virus 40.

[0016] In various embodiments, any one or more of the enhancer sequence, the promoter sequence and the intron sequence are derived from human cytomegalovirus, murine cytomegalovirus, simian virus 40, the human EF-1α gene, and the chicken β-actin gene. More preferably, the promoter may be derived from human cytomegalovirus, murine cytomegalovirus, simian virus 40, the human EF-1α gene, or the chicken β-actin gene, the enhancer may be derived from human cytomegalovirus, murine cytomegalovirus, or simian virus 40, and/or the intron sequence may be derived from human cytomegalovirus, the human EF-1α gene, or the chicken β-actin gene.

[0017] In various embodiments, the enhancer sequence comprises, consists essentially of or consists of (i) a nucleotide sequence as set forth in any one of SEQ ID NO:1; SEQ ID NO:2; SEQ ID NO:3; or a complement thereof; or (ii) a nucleotide sequence that shares at least 75% sequence identity with a nucleotide sequence of (i) or a complement thereof.

[0018] In various embodiments, the promoter sequence comprises, consists essentially of or consists of (i) a nucleotide sequence as set forth in any one of SEQ ID NO:4; SEQ ID NO:5; SEQ ID NO:6; SEQ ID NO:7; SEQ ID NO:8; or a complement thereof; or (ii) a nucleotide sequence that shares at least 75% sequence identity with a nucleotide sequence of (I) or a complement thereof.

[0019] In various embodiments, the intron nucleotide sequence comprises, consists essentially of or consists of (i) a nucleotide sequence as set forth in any one of SEQ ID NO:9; SEQ ID NO:10; SEQ ID NO:11; or a complement thereof; or (ii) a nucleotide sequence that shares at least 75% sequence identity with a nucleotide sequence of (i) or a complement thereof.

[0020] In various embodiments, the chimeric gene regulatory unit comprises, consists essentially of or consists of

(1) the nucleotide sequences as set forth in SEQ ID NO:1; SEQ ID NO:4; and SEQ ID NO:11; or complements thereof;

(2) the nucleotide sequences as set forth in SEQ ID NO:2; SEQ ID NO:5; and SEQ ID NO:11; or complements thereof;

(3) the nucleotide sequences as set forth in SEQ ID NO:2; SEQ ID NO:4; and SEQ ID NO:11; or complements thereof;

(4) the nucleotide sequences as set forth in SEQ ID NO:2; SEQ ID NO:4; and SEQ ID NO:9; or complements thereof;

(5) the nucleotide sequences as set forth in SEQ ID NO:1; SEQ ID NO:5; and SEQ ID NO:11; or complements thereof;

(6) the nucleotide sequences as set forth in SEQ ID NO:1; SEQ ID NO:5; and SEQ ID NO:9; or complements thereof;

(7) the nucleotide sequences as set forth in SEQ ID NO:1; SEQ ID NO:7; and SEQ ID NO:11; or complements thereof;

(8) the nucleotide sequences as set forth in SEQ ID NO:1; SEQ ID NO:5; and SEQ ID NO:11; or complements thereof;

(9) the nucleotide sequences as set forth in SEQ ID NO:2; SEQ ID NO:7; and SEQ ID NO:9; or complements thereof;

(10) the nucleotide sequences as set forth in SEQ ID NO:2; SEQ ID NO:6; and SEQ ID NO:10; or complements thereof;

(11) the nucleotide sequences as set forth in SEQ ID NO:3; SEQ ID NO:7; and SEQ ID NO:10; or complements thereof;

(12) the nucleotide sequences as set forth in SEQ ID NO:1; SEQ ID NO:6; and SEQ ID NO:11; or complements thereof;

(13) the nucleotide sequences as set forth in SEQ ID NO:3; SEQ ID NO:5; and SEQ ID NO:10; or complements thereof;

(14) the nucleotide sequences as set forth in SEQ ID NO:1; SEQ ID NO:7; and SEQ ID NO:10; or complements thereof;

(15) the nucleotide sequences as set forth in SEQ ID NO:2; SEQ ID NO:6; and SEQ ID NO:11; or complements thereof;

(16) the nucleotide sequences as set forth in SEQ ID NO:2; SEQ ID NO:6; and SEQ ID NO:9; or complements thereof;

(17) the nucleotide sequences as set forth in SEQ ID NO:2; SEQ ID NO:7; and SEQ ID NO:11; or complements thereof;

(18) the nucleotide sequences as set forth in SEQ ID NO:1; SEQ ID NO:8; and SEQ ID NO:10; or complements thereof;

(19) the nucleotide sequences as set forth in SEQ ID NO:2; SEQ ID NO:5; and SEQ ID NO:10; or complements thereof;

(20) the nucleotide sequences as set forth in SEQ ID NO:3; SEQ ID NO:5; and SEQ ID NO:11; or complements thereof;

(21) the nucleotide sequences as set forth in SEQ ID NO:2; SEQ ID NO:5; and SEQ ID NO:9; or complements thereof;

(22) the nucleotide sequences as set forth in SEQ ID NO:2; SEQ ID NO:4; and SEQ ID NO:10; or complements thereof;

(23) the nucleotide sequences as set forth in SEQ ID NO:1; SEQ ID NO:7; and SEQ ID NO:11; or complements thereof;

(24) the nucleotide sequences as set forth in SEQ ID NO:2; SEQ ID NO:7; and SEQ ID NO:10; or complements thereof;

(25) the nucleotide sequences as set forth in SEQ ID NO:1; SEQ ID NO:5; and SEQ ID NO:10; or complements thereof; or

(26) a nucleotide sequence that shares at least 75% sequence identity with one nucleotide sequence of (1)-(25) or a complement thereof.

[0021] In various embodiments, the isolated nucleic acid molecule of the invention comprising the functional chimeric gene regulatory unit and the at least one nucleotide sequence encoding for a polypeptide, peptide or RNA molecule of interest has increased expression activity to express the polypeptide, peptide or RNA molecule of interest in CHO (Chinese Hamster Ovary) K1 or CHO DG44 cells compared to an isolated nucleic acid molecule comprising a naturally occurring gene regulatory unit and a nucleotide sequence encoding for the same polypeptide, peptide or RNA molecule of interest. The chimeric gene regulatory unit having increased expression activity in CHO K1 cells may comprise, consist essentially of or consist of (i) a nucleotide sequence as set forth in SEQ ID NO: 30, SEQ ID NO: 35, SEQ ID NO:59, SEQ ID NO:60, SEQ ID NO:62, SEQ ID NO: 64, SEQ ID NO: 65 ; or a complement thereof; or (ii) a nucleotide sequence that shares at least 75% sequence identity with a nucleotide sequence of (i) or a complement thereof. The chimeric gene regulatory unit having increased expression activity in CHO DG44 cells may comprise, consist essentially of or consist of (i) a nucleotide sequence as set forth in SEQ ID Nos. 34, 36, 37, 45, 47-52, 56, 57, 59-62, 64-67, 71 or a complement thereof; or (ii) a nucleotide sequence that shares at least 75% sequence identity with a nucleotide sequence of (i) or a complement thereof.

[0022] In various embodiments, the promoter comprises at least one binding site for a transcription factor. The transcription factor may be specificity protein 1 (Sp1) transcription factor. The Sp1 transcription factor may comprise, consist essentially of or consist of a polypeptide sequence as set forth in any one of SEQ ID NO:74 and SEQ ID NO:75, or a fragment thereof. In various embodiments, the at least one binding site for a transcription factor comprises, consists essentially of or consists of the nucleotide sequence set forth in SEQ ID NO:76 (5'-(G/T)GGGCGG(G/A)(G/A)(C/T)-3').

[0023] In another aspect, the present invention relates to a vector comprising the isolated nucleic acid molecule as described herein, preferably a plasmid.

[0024] In still another aspect, the present invention is also directed to a host cell comprising the isolated nucleic acid molecule or the vector as described herein. The host cell may be a eukaryotic cell, such as a CHO cell, preferably a CHO K1 cell or a CHO DG44 cell.

[0025] Another aspect of the invention is directed to the use of the isolated nucleic acid molecule of the invention for facilitating or enhancing the expression of a polypeptide, peptide or RNA of interest, wherein said isolated nucleic acid molecule comprises a nucleotide sequence encoding the polypeptide, peptide or RNA of interest, wherein said nucleotide sequence encoding the polypeptide, peptide or RNA of interest is operably linked to the chimeric gene regulatory unit of the isolated nucleic acid molecule.

[0026] Still another aspect is related to a method of producing a polypeptide, peptide or RNA of interest, comprising:

(i) providing the isolated nucleic acid molecule as described herein, wherein said isolated nucleic acid molecule comprises a nucleotide sequence encoding the polypeptide, peptide or RNA of interest, said nucleotide sequence encoding the polypeptide, peptide or RNA of interest being operably linked to the chimeric gene regulatory unit of the isolated nucleic acid molecule; and

(ii) producing the polypeptide, peptide or RNA of interest by *in vitro* transcription and translation or in a suitable host cell under conditions that allow production of the polypeptide, peptide or RNA of interest. In such methods, the host cell may be a eukaryotic cell, such as a CHO cell, preferably a CHO K1 cell or a CHO DG44 cell.

BRIEF DESCRIPTION OF THE DRAWINGS

[0027] The invention will be better understood with reference to the detailed description when considered in conjunction with the non-limiting examples and the accompanying drawings.

[0028] **Figure 1** shows a schematic overview of the design of the chimeric gene regulatory unit. Five natural gene regulatory units occurring upstream of the human cytomegalovirus immediate early gene (hCMV), of the murine cytomegalovirus immediate early gene (mCMV), the simian virus 40 (SV40), the human elongation factor-1α gene (hEF-1α) and the chicken β-actin gene (cA) were dissected into enhancers (E), core promoters (CP) and introns (I). These enhancers, core promoters, and introns from different sources were then combined to generate fifty-seven new enhancer-core promoter and enhancer-core promoter-intron combinations, referred to as chimeric gene regulatory units or hybrid promoters.

[0029] **Figure 2** shows a schematic representation of monoclonal antibody expressing vectors for comparison of different chimeric promoters. (A) Antibody expression vector for comparison

of chimeric promoters in CHO K1 cells. (B) Antibody expression vector for comparison of chimeric promoters in CHO DG44 cells. ChiP: chimeric gene regulatory unit; LC: antibody light chain encoding sequence; HC: antibody heavy chain encoding sequence; Zeo: zeocin encoding sequence; DHFR: dihydrofolate reductase encoding sequence; IRESwt: wild-type encephalomyocarditis virus internal ribosome entry site; mIRES, mutated IRES with reduced translation efficiency; pA: polyadenlyation signal.

[0030] **Figure 3** shows the results of the comparison of the newly generated chimeric gene regulatory units according to Figure 2 and Table 2 with the wild type promoters for expression level in stably transfected CHO K1 (A) and CHO DG44 (B) cells. Stably transfected pools were generated by transfection of CHO K1/CHO DG44 cells with monoclonal antibody (mAb) expressing vectors containing different chimeric promoters and selection of stable transfectants using zeocin. Antibody titers of stably transfected pools were determined in shake flask batch cultures. The black bar represents the titer from the strongest wild type promoter. Seven hybrid promoters exhibited higher recombinant protein production than any wild type promoters in CHO K1 cells. 21 hybrid promoters exhibit higher expression than any wild type promoters in CHO DG44 cells.

DETAILED DESCRIPTION OF THE INVENTION

[0031] The following detailed description refers to, by way of illustration, specific details and embodiments in which the invention may be practiced. These embodiments are described in sufficient detail to enable those skilled in the art to practice the invention. Other embodiments may be utilized and structural, and logical changes may be made without departing from the scope of the invention. The various embodiments are not necessarily mutually exclusive, as some embodiments can be combined with one or more other embodiments to form new embodiments.

[0032] Unless otherwise defined, all technical and scientific terms used herein have the same meaning as commonly understood by one of ordinary skill in the art. In case of conflict, the present document, including definitions, will control.

[0033] The object of the present invention is to provide novel chimeric gene regulatory units for high level expression of a molecule of interest.

[0034] In one first aspect, the present invention relates to an isolated nucleic acid molecule comprising a functional chimeric gene regulatory unit comprising (a) a functional enhancer nucleotide sequence, (b) a functional promoter nucleotide sequence and (c) at least one nucleotide sequence encoding for an intron, wherein the enhancer nucleotide sequence is 5' to the promoter nucleotide sequence and the intron nucleotide sequence is 3' to the promoter sequence and wherein at least one nucleotide sequence of the enhancer nucleotide sequence, the promoter nucleotide sequence or the at least one nucleotide sequence encoding for the intron is

derived from a different species than the other nucleotide sequences.

[0035] As used herein the term "functional" refers to an entity, which possesses either the native biological activity of the naturally-occurring entity of its type, or any specific desired activity, for example in case of a promoter as judged by its ability to initiate gene transcription.

[0036] As used herein the term "isolated nucleic acid molecule" relates to nucleic acid molecules that may appear independent of their natural genetic context and/or background and are preferably separated from other nucleic acids or cellular components. The separation may occur by purification, for which various techniques are known in the art.

[0037] The term "nucleic acid molecule" refers to the phosphate ester polymeric form of ribonucleosides (adenosine, guanosine, uridine or cytidine; "RNA molecules") or deoxyribonucleosides (deoxyadenosine, deoxyguanosine, deoxythymidine, or deoxycytidine; "DNA molecules"), any phosphoester analogs thereof, such as phosphorothioates and thioesters, in either single stranded form, or as a double-stranded helix as well as artificial nucleic acid analogs such as peptide nucleic acid, morpholino- and locked nucleic acid, as well as glycol nucleic acid and threose nucleic acid. Each of these artificial nucleic acid analogs is distinguished from naturally occurring DNA or RNA by changes to the backbone of the molecule. In preferred embodiments the isolated nucleic acid molecule is a DNA molecule.

[0038] "At least one", as used herein, relates to one or more, in particular 1, 2, 3, 4, 5, 6, 7, 8, 9, 10 or more.

[0039] The articles "a" and "an" are used herein to refer to one or to more than one (i.e., to at least one) of the grammatical object of the article. By way of example, "an element" means at least one element and can include more than one element.

[0040] The term "sequence", as used herein in relation to nucleic acids, relates to the primary sequence of nucleic acid molecules.

[0041] As used herein the term "functional chimeric gene regulatory unit" or "hybrid promoter" refers to the combination of enhancer, core promoter and at least one intron as described herein.

[0042] As used herein the term "chimeric" or "hybrid" refers to the fact that different elements of the regulatory unit are derived from different genes, i.e. in nature the combinations of elements of the regulatory unit as described herein do not exist. This may be achieved by using at least one of the elements from a different species and combining it with the other elements of the regulatory unit. At least one of the enhancer, the core promoter and the intron is thus heterologous with respect to at least one of the other two.

[0043] As used herein the term "functional enhancer" refers to a short region of DNA that can activate transcription (of a gene), for example by being capable of binding proteins (activators).

[0044] In general the term "promoter" refers to a region of DNA that initiates transcription of a particular gene.

[0045] As used herein the term "functional promoter" or "core promoter" refers to the core region in a promoter, which is the minimal portion of the promoter required to properly initiate gene transcription.

[0046] As used herein the term "intron" refers to a nucleotide sequence within a gene that is removed by RNA splicing during maturation of the final RNA product. The term intron refers to both the DNA sequence within a gene and the corresponding sequence in RNA transcripts. Sequences that are joined together in the final mature RNA after RNA splicing are exons.

[0047] The term "5'" as used herein refers to the directionality, i.e., the end-to-end chemical orientation of a single strand of nucleic acid. The chemical convention of naming carbon atoms in the nucleotide sugar-ring numerically gives rise to a 5-end and a 3-end. The relative positions of structures along a strand of nucleic acid, including genes and various protein binding sites, are usually noted as being either upstream (towards the 5-end) or downstream (towards the 3-end). This naming convention is important because nucleic acids can only be synthesized *in vivo* in the 5-to-3`direction, as the polymerase that assembles new strands only attaches new nucleotides to the 3-hydroxyl (-OH) group, via a phosphodiester bond.

[0048] In various embodiments, the isolated nucleic acid molecule further comprises at least one nucleotide sequence encoding for a peptide, polypeptide or RNA molecule of interest. Said molecules of interest are those to be expressed using the novel chimeric gene regulatory units if high level expression is desired. Preferably, it is a recombinant polypeptide or protein.

[0049] As used herein, the term "peptide" relates to two or more amino acids linked by a peptide bond and thus includes dipeptides, oligopeptides, and polypeptides.

[0050] The term "polypeptide", as used herein, refers to a long, continuous peptide chain, preferably of at least 50 amino acids in length.

[0051] The term "protein", as used herein, relates to one or more polypeptides arranged in a biologically functional way. A protein may consist of more than one polypeptide chains, such as an antibody, which consists of two light chains and two heavy chains, with each of the chains being a polypeptide. A protein may be bound to ligands such as coenzymes and cofactors or to another protein or other macromolecule.

[0052] In various embodiments, said sequence encoding the molecule of interest is operably linked to the chimeric gene regulatory unit. In preferred embodiments, the at least one nucleotide sequence encoding for a molecule of interest lies 3' (downstream) relative to the intron nucleotide sequence. In more preferred embodiments, the at least one nucleotide sequence encoding a molecule of interest lies directly adjacent to the intron sequence.

[0053] "Directly adjacent" means that the intron sequence and the coding sequence are directly linked by a phosphodiester bond and that no linker nucleotide sequence is interposed between the two elements.

[0054] As used herein the term "operably linked" means associated in such a way that the chimeric gene regulatory unit may control expression of the molecule of interest.

[0055] It is advantageous that the at least one nucleotide sequence encoding for a molecule of interest lies directly adjacent to the intron sequence, because this increases the chances of correct and high level expression.

[0056] In various embodiments, where the at least one nucleotide sequence encoding for a molecule of interest encodes for a polypeptide of interest, said polypeptide is a polypeptide chain of a naturally occurring or artificial immunoglobulin. In preferred embodiments, the polypeptide of interest is a protein and the protein is an antibody. In more preferred embodiments, the antibody is a human or humanized antibody, or a fragment thereof. It is understood that in such embodiments, wherein expression of an immunoglobulin, specifically an antibody is desired, the isolated nucleic acid molecules comprises nucleotide sequences that encode for more than one polypeptide. For example, in case antibody expression is desired, the isolated nucleic acid molecule may comprise two nucleic acid sequences encoding for a polypeptide of interest, namely one sequence encoding the heavy chain and one sequence encoding the light chain. In such embodiments, the different coding sequences may be directly linked or may be separated by linker nucleotide sequences. Said linker nucleotide sequences may be functional in that they allow ribosomal binding and may thus for example include internal ribosomal entry sites (IRES).

[0057] As used herein and in line with the above, the term "immunoglobulin" refers to a protein consisting of one or more polypeptides substantially encoded by immunoglobulin genes.

[0058] In various embodiments, the chimeric gene regulation unit has an increased resistance to transcriptional silencing.

[0059] The term "transcriptional silencing" refers to any mechanism, whereby gene expression is down-regulated on transcriptional level, e.g. via DNA methylation, histone modifications and chromatin remodeling, which make the DNA permanently inaccessible for future transcription.

[0060] It is advantageous if the chimeric gene regulation unit has an increased resistance to transcriptional silencing, as this will result in higher overall yields of expressed product.

[0061] In various embodiments, the isolated nucleic acid molecule further comprises at least one nucleotide sequence encoding for a recognition site of a restriction endonuclease. In preferred embodiments, said at least one nucleotide sequence encoding for a recognition site of a restriction endonuclease is 3' to the enhancer nucleotide sequence and 5' to the promoter nucleotide sequence. Alternatively, in various preferred embodiments, said nucleotide sequence encoding for a recognition site of a restriction endonuclease is 3' to the promoter nucleotide sequence and 5' to the at least one nucleotide sequence encoding for an intron. This location

allows separating and combining the different elements of the regulatory unit in a specific manner, e.g. linking enhancer, promoter and intron sequences.

[0062] As used herein, the term "restriction endonuclease" is intended to mean an enzyme that recognizes a specific nucleotide sequence in a nucleic acid and cleaves the nucleic acid. A restriction endonuclease can recognize a sequence that is, for example, 4, 5, 6, 7 or more nucleotides long. A restriction endonuclease can recognize more than one sequence, for example, two or more variants of a degenerate sequence that includes one of two or more different nucleotides at a particular position. Alternatively, a restriction endonuclease can be specific for a single recognition sequence.

[0063] As used herein, the term "recognition site" is intended to mean a portion of the nucleic acid having a nucleotide sequence that specifically binds to a particular binding moiety such as a restriction endonuclease, more specifically the substrate recognition and binding site of a restriction endonuclease. Typically, a restriction endonuclease recognition site is cleaved by a restriction endonuclease.

[0064] In various embodiments, the enhancer sequence is derived from viruses. In preferred embodiments, the enhancer sequence is derived from double-stranded DNA viruses. In more preferred embodiments, the enhancer sequence is derived from viruses consisting of the group of Herpesviridae and Polyomaviridae. In still more preferred embodiments, the enhancer sequence is derived from the group consisting of human cytomegalovirus; murine cytomegalovirus; and simian virus 40.

[0065] Cytomegalovirus is a viral genus of the Herpesviridae abbreviated as CMV. The species that infects humans is commonly known as human CMV (hCMV). Other CMV viruses such as murine cytomegalovirus in mice are found in several mammal species, but species isolated from animals differ from hCMV in terms of genomic structure.

[0066] Simian virus 40 (SV40) is a polyomavirus that is found in both monkeys and humans.

[0067] In various embodiments, the enhancer sequence comprises, consists essentially of or consists of (i) a nucleotide sequence as set forth in any one of SEQ ID NO:1; SEQ ID NO:2; SEQ ID NO:3; or a complement thereof; or (ii) a nucleotide sequence that shares at least 75%, 80%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 97.5%, 98.0%, 98.5%, 99.0%, or 99.5% sequence identity with a nucleotide sequence of (i) or a complement thereof.

[0068] "Complement", as used herein, relates to a nucleic acid molecule which is complementary to another nucleic acid molecule when both nucleic acid molecules are aligned antiparallel to each other in that essentially all nucleotides of either of the nucleic acid molecules form Watson-Crick base pairs with the corresponding nucleotides on the other molecule. In various embodiments, the complements are full complements in that each

nucleotide of the respective molecule or sequence forms a Watson-Crick base pair with a corresponding nucleotide on the other strand.

[0069] The term "sequence identity," as used herein, is generally expressed as a percentage and refers to the percent of amino acid residues or nucleotides, as appropriate, that are identical as between two sequences when optimally aligned. For the purposes of this invention, sequence identity means the sequence identity determined using the well-known Basic Local Alignment Search Tool (BLAST), which is publicly available through the National Cancer Institute/National Institutes of Health (Bethesda, Maryland) and has been described in printed publications (see, e.g., Altschul et al., J. Mol. Biol, 215(3), 403-10 (1990)).

[0070] In various embodiments, the sequence of the core promoter is derived from the group consisting of human cytomegalovirus; murine cytomegalovirus; simian virus 40; the human EF-1α gene promoter; and the chicken β-actin gene promoter.

[0071] Elongation factor 1-alpha 1 (EF-1α) is a protein that in humans is encoded by the EEF1A1 gene. This gene encodes an isoform of the alpha subunit of the elongation factor-1 complex, which is responsible for the enzymatic delivery of aminoacyl tRNAs to the ribosome.

[0072] In various embodiments, the core promoter sequence comprises, consists essentially of or consists of (i) a nucleotide sequence as set forth in any one of SEQ ID NO:4; SEQ ID NO:5; SEQ ID NO:6; SEQ ID NO:7; SEQ ID NO:8; or a complement thereof; or (ii) a nucleotide sequence that shares at least 75%, 80%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 97.5%, 98.0%, 98.5%, 99.0%, or 99.5% sequence identity with a nucleotide sequence of (i) or a complement thereof.

[0073] In various embodiments, the intron nucleotide sequence is selected from a sequence derived from the group consisting of human cytomegalovirus; the human EF-1α gene; and the chicken β-actin gene.

[0074] In various embodiments, the intron nucleotide sequence comprises, consists essentially of or consists of (i) a nucleotide sequence as set forth in any one of SEQ ID NO:9; SEQ ID NO:10; SEQ ID NO:11; or a complement thereof; (ii) a nucleotide sequence that shares at least 75%, 80%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 97.5%, 98.0%, 98.5%, 99.0%, or 99.5% sequence identity with a nucleotide sequence of (i) or a complement thereof.

[0075] The above elements may be combined, such that the chimeric gene regulatory unit comprises, consists essentially of or consists of

(1) the nucleotide sequences as set forth in SEQ ID NO:1; SEQ ID NO:4; and SEQ ID NO:11; or complements thereof;

(2) the nucleotide sequences as set forth in SEQ ID NO:2; SEQ ID NO:5; and SEQ ID NO:11; or complements thereof;

(3) the nucleotide sequences as set forth in SEQ ID NO:2; SEQ ID NO:4; and SEQ ID NO:11; or complements thereof;

(4) the nucleotide sequences as set forth in SEQ ID NO:2; SEQ ID NO:4; and SEQ ID NO:9; or complements thereof;

(5) the nucleotide sequences as set forth in SEQ ID NO:1; SEQ ID NO:5; and SEQ ID NO:11; or complements thereof;

(6) the nucleotide sequences as set forth in SEQ ID NO:1; SEQ ID NO:5; and SEQ ID NO:9; or complements thereof;

(7) the nucleotide sequences as set forth in SEQ ID NO:1; SEQ ID NO:7; and SEQ ID NO:11; or complements thereof; or

(8) a nucleotide sequence that shares at least 75%, 80%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 97.5%, 98.0%, 98.5%, 99.0%, or 99.5% sequence identity with one nucleotide sequence of (1)-(7) or a complement thereof.

[0076] Such chimeric gene regulatory units are advantageous as it was surprisingly found that they exhibit higher recombinant protein production levels in CHO KG1 cells compared with wild type gene regulatory units or different chimeric gene regulatory units.

[0077] The term "wild-type" (WT), as used herein, refers to the typical, most common or conventional form as it occurs in nature.

[0078] In various embodiments, the isolated nucleic acid molecule of the invention comprising the functional chimeric gene regulatory unit and the at least one nucleotide sequence encoding for a molecule of interest has increased expression activity in that it expresses a molecule of interest in Chinese Hamster Ovary (CHO) K1 cells in higher levels relative to an isolated nucleic acid molecule comprising a naturally occurring gene regulatory unit and a nucleotide sequence encoding for the same molecule of interest. In preferred embodiments, the increased expression activity of the functional chimeric gene regulatory unit is at least 1.1-fold, 1.15-fold, 1.2-fold, 1.4-fold, 1.5-fold, 1.6-fold or 1.75-fold higher compared to the naturally occurring gene regulatory unit.

[0079] CHO cells are advantageous due to their ability to produce glycoproteins with post-translational modifications compatible to humans, their refractory nature to human viruses, the availability of well-established gene amplification systems for CHO cells coupled with the cells ability to adapt and grow in serum-free suspension culture. These characteristics render the CHO cells ideal for large scale high-titer cultures in the industry.

[0080] In various embodiments, the chimeric gene regulatory unit comprises, consists essentially of or consists of (i) a nucleotide sequence as set forth in SEQ ID NO: 30, SEQ ID NO: 35, SEQ ID NO:59, SEQ ID NO:60, SEQ ID NO:62, SEQ ID NO: 64, SEQ ID NO: 65 or a complement thereof; or (ii) a nucleotide sequence that shares at least 75%, 80%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 97.5%, 98.0%, 98.5%, 99.0%,

or 99.5% sequence identity with a nucleotide sequence of (i) or a complement thereof. It was found that said constructs provide for increased expression activity in CHO K1 cells. Particularly preferred is a chimeric gene regulatory unit that comprises, consists essentially of or consists of the nucleotide sequence as set forth in SEQ ID NO:35 or a nucleotide sequence that shares at least 75%, 80%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 97.5%, 98.0%, 98.5%, 99.0%, or 99.5% sequence identity with said nucleotide sequence of SEQ ID NO:35 or the respective complements of these sequences. It was found that said sequence is particularly advantageous – even though it may not provide the highest titer – because the time used to generate stably transfected cell pools with said chimeric gene regulatory unit is significantly shorter – e.g. three weeks instead of two weeks - compared to the chimeric promoters set forth in SEQ ID Nos. 30, 59, 60, 62, 64 and 65.

[0081] In various other embodiments, the chimeric gene regulatory unit comprises, consists essentially of or consists of

(1) the nucleotide sequences as set forth in SEQ ID NO:2; SEQ ID NO:4; and SEQ ID NO:11; or complements thereof;

(2) the nucleotide sequences as set forth in SEQ ID NO:2; SEQ ID NO:5; and SEQ ID NO:11; or complements thereof;

(3) the nucleotide sequences as set forth in SEQ ID NO:1; SEQ ID NO:5; and SEQ ID NO:11; or complements thereof;

(4) the nucleotide sequences as set forth in SEQ ID NO:2; SEQ ID NO:7; and SEQ ID NO:9; or complements thereof;

(5) the nucleotide sequences as set forth in SEQ ID NO:2; SEQ ID NO:6; and SEQ ID NO:10; or complements thereof;

(6) the nucleotide sequences as set forth in SEQ ID NO:3; SEQ ID NO:7; and SEQ ID NO:10; or complements thereof;

(7) the nucleotide sequences as set forth in SEQ ID NO:1; SEQ ID NO:6; and SEQ ID NO:11; or complements thereof;

(8) the nucleotide sequences as set forth in SEQ ID NO:3; SEQ ID NO:5; and SEQ ID NO:10; or complements thereof;

(9) the nucleotide sequences as set forth in SEQ ID NO:1; SEQ ID NO:7; and SEQ ID NO:10; or complements thereof;

(10) the nucleotide sequences as set forth in SEQ ID NO:2; SEQ ID NO:6; and SEQ ID NO:11; or complements thereof;

(11) the nucleotide sequences as set forth in SEQ ID NO:2; SEQ ID NO:6; and SEQ ID NO:9; or complements thereof;

(12) the nucleotide sequences as set forth in SEQ ID NO:2; SEQ ID NO:7; and SEQ ID NO:11; or complements thereof;

(13) the nucleotide sequences as set forth in SEQ ID NO:1; SEQ ID NO:8; and SEQ ID NO:10; or complements thereof;

(14) the nucleotide sequences as set forth in SEQ ID NO:2; SEQ ID NO:5; and SEQ ID NO:10; or complements thereof;

(15) the nucleotide sequences as set forth in SEQ ID NO:3; SEQ ID NO:5; and SEQ ID NO:11; or complements thereof;

(16) the nucleotide sequences as set forth in SEQ ID NO:1; SEQ ID NO:4; and SEQ ID NO:11; or complements thereof;

(17) the nucleotide sequences as set forth in SEQ ID NO:2; SEQ ID NO:5; and SEQ ID NO:9; or complements thereof;

(18) the nucleotide sequences as set forth in SEQ ID NO:2; SEQ ID NO:4; and SEQ ID NO:10; or complements thereof;

(19) the nucleotide sequences as set forth in SEQ ID NO:1; SEQ ID NO:7; and SEQ ID NO:11; or complements thereof;

(20) the nucleotide sequences as set forth in SEQ ID NO:2; SEQ ID NO:7; and SEQ ID NO:10; or complements thereof;

(21) the nucleotide sequences as set forth in SEQ ID NO:1; SEQ ID NO:5; and SEQ ID NO:10; or complements thereof; or

(22) a nucleotide sequence that shares at least 75%, 80%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 97.5%, 98.0%, 98.5%, 99.0%, or 99.5% sequence identity with one nucleotide sequence of (1)-(21) or a complement thereof.

[0082] Such chimeric gene regulatory units are advantageous as it was surprisingly found that they exhibit higher recombinant protein production levels in CHO DG44 cells compared with wild type gene regulatory units or different chimeric gene regulatory units.

[0083] Accordingly, in various embodiments, the isolated nucleic acid molecule of the invention comprising the functional chimeric gene regulatory unit and the at least one nucleotide sequence encoding for a molecule of interest has increased expression activity to express a molecule of interest in Chinese Hamster Ovary (CHO) DG44 cells compared to an isolated nucleic acid molecule comprising a naturally occurring gene regulatory unit and a nucleotide sequence encoding for the molecule of interest. In preferred embodiments, the increased expression activity of the functional chimeric gene regulatory unit is at least 1.1-fold, 1.2-fold, 1.3-fold, 1.4-fold, 1.5-fold, 1.6-fold or 1.7-fold higher compared to the naturally occurring gene regulatory unit.

[0084] In various embodiments, the chimeric gene regulatory unit having increased expression activity in CHO DG44 cells comprises, consists essentially of or consists of (i) a nucleotide sequence as set forth in SEQ ID Nos. 34, 36, 37, 45, 47-52, 56, 57, 59-62, 64-67, 71 or a complement thereof; or (ii) a nucleotide sequence that shares at least 75%, 80%, 85%, 86%,

87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 97.5%, 98.0%, 98.5%, 99.0%, or 99.5% sequence identity with a nucleotide sequence of (i), or a complement thereof.

[0085] Such chimeric gene regulatory units are advantageous as it was surprisingly found that they exhibit higher recombinant protein production levels as achieved with wild type gene regulatory units or different chimeric gene regulatory units.

[0086] In various embodiments, the chimeric gene regulatory unit comprises at least one binding site for a transcription factor.

[0087] In preferred embodiments, the at least one binding site for a transcription factor is comprised in the enhancer, the core promoter or the intron.

[0088] As used herein the term "transcription factor" refers to a protein that binds to specific DNA sequences, thereby controlling the rate of transcription of genetic information from DNA to messenger RNA (mRNA). Transcription factors perform this function alone or with other proteins in a complex, by promoting (as an activator), or blocking (as a repressor) the recruitment of RNA polymerase to specific genes. A defining feature of transcription factors is that they contain one or more DNA-binding domains (DBDs), which attach to specific sequences of DNA adjacent to the genes that they regulate. Herein, it is preferred that the recruited transcription factors activate RNA polymerase binding and function.

[0089] In preferred embodiments, the transcription factor is specificity protein 1 (Sp1) transcription factor. This may be advantageous as it has been shown that the SP1 binding site may enhance expression during long term culture. The Sp1 transcription factor may comprise, consist essentially of or consist of the polypeptide sequence as set forth in SEQ ID NO:74 or SEQ ID NO:75, or may be a fragment thereof, with said fragment being functional in that it retains at least 50% activity of the full length sequence. Alternatively, in other preferred embodiments, the at least one binding site for a transcription factor contained in the nucleic acid molecules described herein comprises, consists essentially of or consists of the nucleotide sequence set forth in SEQ ID NO:76 (5'-(G/T)GGGCGG(G/A)(G/A)(C/T)-3').

[0090] The use of a transcription factor is advantageous as it represents an additional tool for controlling and improving the rate of transcription of genetic information from DNA to messenger RNA and hence achieving higher expression levels.

[0091] In a further aspect, the invention relates to a vector comprising the isolated nucleic acid molecule of the invention.

[0092] As used herein the term "vector" refers to a nucleic acid molecule used as a vehicle to artificially carry foreign genetic material into another cell, where it can be replicated and/or expressed. The four major types of vectors are plasmids, viral vectors, cosmids, and artificial chromosomes. Common to all engineered vectors are an origin of replication, a multicloning site, and a selectable marker. The vector itself is generally a nucleic acid sequence that consists of an insert (transgene) and a larger sequence that serves as the "backbone" of the vector. The

purpose of a vector, which transfers genetic information to another cell, is typically to isolate, multiply, or express the insert in the target cell. In preferred embodiments, the vector is a plasmid.

[0093] In a still further aspect, the invention relates to a host cell comprising the isolated nucleic acid molecule of the invention and/or the vector of the invention.

[0094] The term "host cell" as used herein means an organism that harbors the nucleic acid molecules comprising the chimeric gene regulatory unit as described herein. They may be integrated into the genome of the host cell or exist in separate form in the cell.

[0095] In various embodiments, said host cell is a eukaryotic cell. In preferred embodiments, said host cell is a mammalian cell. In even more preferred embodiments said host cell is a Chinese hamster ovary (CHO) cell. In more preferred embodiments, the host cell is a CHO K1 cell or a CHO DG44 cell.

[0096] The nucleic acid molecules described herein can be used to facilitate or enhance the expression of a given molecule of interest in a cell. It is understood that in such embodiments, said isolated nucleic acid molecule also comprises a nucleotide sequence encoding the molecule of interest being operably linked to the chimeric gene regulatory unit of the isolated nucleic acid molecule.

[0097] In such methods for the expression of molecules of interest, in particular polypeptides, the actual expression may be performed by by *in vitro* transcription and translation or, more preferably, recombinantly in a suitable host cell under conditions that allow production of the molecule of interest.

[0098] The host cell may be a cell as described above.

[0099] Conditions that allow production of the molecule of interest include the various parameters of cell culture, including selection of the medium and the cultivating conditions, such as temperature, time, etc. All of these factors are well-known to those skilled in the art and can be easily adapted by using routine techniques.

[00100] It is understood that all embodiments disclosed herein in relation to the nucleic acids of the invention are similarly applicable to the vectors, host cells, uses and methods, described herein, and vice versa.

[00101] The present invention is further illustrated by the following examples. However, it should be understood, that the invention is not limited to the exemplified embodiments.

EXAMPLES

[00102] Five natural promoters occurring upstream of the human cytomegalovirus immediate early gene (hCMV), of the murine cytomegalovirus immediate early gene (mCMV), the simian virus 40 (SV40), the human elongation factor-1α gene (hEF-1α) and the chicken β-actin gene (cA) were dissected into enhancers (E), core promoters (CP) and introns (I) (Figure 1). These enhancers, core promoters, and introns from different sources were then recombined to generate

fifty-seven new enhancer-core promoter and enhancer-core promoter-intron combinations, referred to as chimeric gene regulatory units or hybrid promoters.

[00103] Table 1 shows the different elements used for generation of the chimeric gene regulatory units while Table 2 shows the tested combinations.

Table 1: Naturally occurring enhancers, promoters, and introns

Origin	Enhancer	SEQ ID No.	Core Promoter	SEQ ID No.	Intron	SEQ ID No.
Human CMV (hCMV)	hCMVE	1	hCMVP	4	hCMV IntronA (vI)	9
Murine CMV (mCMV)	mCMVE	2	mCMVP	5		
SV40	SV40E	3	SV40P	6		
Human EF gene (hEF)			hEFP	7	EF Intron (fI)	10
Chicken beta actin (cA)			cAP	8	cA Intron (aI)	11

Table 2: Assessed gene regulatory units

	Name	Enhancer	Core promoter	Intron	SEQ ID No
1	WT hCMV	HCMVE	hCMVP		12
2	WT mCMV	MCMVE	mCMVP		13
3	WT SV40	SV40E	SV40P		14
4	WT hEF		hEFP	fI	15
5	WT cA		cAP	aI	16
6	hCmC	hCMVE	mCMVP		17
7	hCS	hCMVE	SV40P		18
8	hCE	hCMVE	hEFP		19
9	hCA	hCMVE	CAP		20
10	mChC	mCMVE	hCMVP		21
11	mCS	mCMVE	SV40P		22
12	mCE	mCMVE	hEFP		23
13	mCA	mCMVE	CAP		24
14	ShC	SV40E	hCMVP		25
15	SmC	SV40E	mCMVP		26
16	SE	SV40E	hEFP		27
17	SA	SV40E	CAP		28
18	WT hCMVvI	hCMVE	hCMVP	vI	29

19	hCmCvI	hCMVE	mCMVP	vI	30
20	hCSvI	hCMVE	SV40P	vI	31
21	hCEvI	hCMVE	hEFP	vI	32
22	hCAvI	hCMVE	CAP	vI	33
23	mCMVvI	mCMVE	mCMVP	vI	34
24	mChCvI	mCMVE	hCMVP	vI	35
25	mCSvI	mCMVE	SV40P	vI	36
26	mCEvI	mCMVE	hEFP	vI	37
27	mCAvI	mCMVE	CAP	vI	38
28	SV40vI	SV40E	SV40P	vI	39
29	ShCvI	SV40E	hCMVP	vI	40
30	SmCvI	SV40E	mCMVP	vI	41
31	SEvI	SV40E	hEFP	vI	42
32	SAvI	SV40E	CAP	vI	43
33	hCMVfI	hCMVE	hCMVP	fI	44
34	hCmCfI	hCMVE	mCMVP	fI	45
35	hCSfI	hCMVE	SV40P	fI	46
36	hCEfI	hCMVE	hEFP	fI	47
37	hCAfI	hCMVE	CAP	fI	48
38	mCMVfI	mCMVE	mCMVP	fI	49
39	mChCfI	mCMVE	hCMVP	fI	50
40	mCSfI	mCMVE	SV40P	fI	51
41	mCEfI	mCMVE	hEFP	fI	52
42	mCAfI	mCMVE	CAP	fI	53
43	SV40fI	SV40E	SV40P	fI	54
44	ShCfI	SV40E	hCMVP	fI	55
45	SmCfI	SV40E	mCMVP	fI	56
46	SEfI	SV40E	hEFP	fI	57
47	SAfI	SV40E	CAP	fI	58
48	hCMVaI	hCMVE	hCMVP	aI	59
49	hCmCaI	hCMVE	mCMVP	aI	60
50	hCSaI	hCMVE	SV40P	aI	61
51	hCEaI	hCMVE	hEFP	aI	62
52	hCAaI	hCMVE	CAP	aI	63
53	mCMVaI	mCMVE	mCMVP	aI	64
54	mChCaI	mCMVE	hCMVP	aI	65

55	mCSaI	mCMVE	SV40P	aI	66
56	mCEaI	mCMVE	hEFP	aI	67
57	mCAaI	mCMVE	CAP	aI	68
58	SV40aI	SV40E	SV40P	aI	69
59	ShCaI	SV40E	hCMVP	aI	70
60	SmCaI	SV40E	mCMVP	aI	71
61	SEaI	SV40E	hEFP	aI	72
62	SAaI	SV40E	CAP	aI	73

[00104] The different chimeric gene regulatory units were then inserted into antibody expression vectors for comparison of chimeric promoters in CHO K1 and CHO DG44 cells with the arrangement of the different elements in the vectors schematically shown in Figure 2.

[00105] Stably transfected CHO K1 pools were generated by transfecting 1×10^7 CHO K1 cells with 5 μg of an appropriate linearized mAb expressing plasmid containing a specific chimeric promoter and zeocin selection marker gene (Figure 2A). Transfections were carried out using Nucleofactor kit V (Lonza, VCA1003) and program U-24 on a Nucleofector II system (Lonza, Cologne, Germany) following the manufacturer's instructions. The transfected cells were then resuspended in 2 mL protein free medium in 6-well suspension culture plate. At 24 h post-transfection, the transfected cell culture were centrifuged at ~100×g for 5 min. Cell pellets were then resuspended in 25 mL protein free medium containing 600 μg/mL zeocin in 125 mL shake flasks to select for stable transfectants. The stably transfected pools were deemed successfully generated when viability of stably transfected pools recovered above 95%. Productivity of each stably transfected pool was determined in 125 mL shake flask batch cultures. Cells were seeded at 2×10^5 cells/mL. Cell density and viability were monitored using Vi-Cell every day until viability dropped to below 50%. The supernatant was collected at the end of culture and analyzed for mAb concentration using a nephelometric method on an IMMAGE 800 immunochemistry system (Beckman Coulter, Buckinghamshire, England). The IMMAGE 800 system uses anti-human Fc region antibodies for IgG detection. The average titer of duplicated pools generated using each promoter was shown in Figure 3A.

[00106] Transfection of CHO DG44 cells were carried out using the same protocol as for CHO K1 cells. The transfected cells were then resuspended in 2 mL protein free medium containing hypoxanthine and thymine (HT) in 6-well suspension culture plate. At 24 h post-transfection, the transfected cell culture were centrifuged at ~100×g for 5 min. Cell pellets were then resuspended in 25 mL protein free medium without HT in 125 mL shake flasks to select for stable transfectants. When viability of stably transfected pools recovered above 95%, stepwise methotrexate (MTX, Sigma, M8407) amplification was carried out with concentrations of 50 nM to 500 nM. Productivity of amplified pools at 500 nM was determined using the same

protocol as for stably transfected CHO K1 cells. The average titer of duplicated pools generated using each promoter was shown in Figure 3b.

P109649-seql-000001

SEQUENCE LISTING

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gggcgcggcg cggggctttg tgcgctccgc gtgtgcgcga ggggagcgcg gccgggggcg 360

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cggggctcgc cgtgccgggc ggggggtggc ggcaggtggg ggtgccgggc ggggcggggc 600

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acttcctttg tcccaaatct ggcggagccg aaatctggga ggcgccgccg cacccccctct 780

agcgggcgcg ggcgaagcgg tgcggcgccg gcaggaagga aatgggcggg gagggccttc 840

gtgcgtcgcc gcgccgccgt ccccttctcc atctccagcc tcggggctgc cgcaggggga 900

cggctgcctt cgggggggac ggggcagggc ggggttcggc ttctggcgtg tgaccggcgg 960

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<210> 12
<211> 620
<212> DNA
<213> Artificial Sequence

<220>
<223> gene regulatory unit

<400> 12
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ccgcccaacg acccccgccc attgacgtca ataatgacgt atgttcccat agtaacgcca 180

atagggactt tccattgacg tcaatgggtg gagtatttac ggtaaactgc ccacttggca 240

gtacatcaag tgtatcatat gccaagtacg ccccctattg acgtcaatga cggtaaatgg 300

cccgcctggc attatgccca gtacatgacc ttatgggact ttcctacttg gcagtacatc 360

tacgtattag tcatcgctat taccatggtg atgcggtttt ggcagtacat caatgggcgt 420

ggatagcggt ttgactcacg gggatttcca agtctccacc ccattgacgt caatgggagt 480

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aaccggcggc cgcaggatcc 620

<210> 13
<211> 728
<212> DNA
<213> Artificial Sequence

<220>
<223> gene regulatory unit

<400> 13
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cattgggttt tgcccagtac ataaggtcaa taggggtga gtcaacagga aagtcccatt 120

ggagccaagt acattgagtc aatagggact ttccaatggg ttttgcccag tacataaggt 180

caatgggagg taagccaatg ggtttttccc attactggca cgtatactga gtcattaggg 240

actttccaat gggttttgcc cagtacataa ggtcaatagg ggtgaatcaa caggaaagtc 300

ccattggagc caagtacact gagtcaatag ggactttcca ttgggttttg cccagtacaa 360

aaggtcaata gggggtgagt caatgggttt ttcccattat tggcacgtac ataaggtcaa 420

taggggtgag tcattgggtt tttccagcca atttaattaa aacgccatgt actttcccac 480

cattgacgtc aatgggctat tgaaactaat gcaacgtgac ctttaaacgg tactttccca 540

tagctgatta atgggaaagt accgttctcg agccaataca cgtcaatggg aagtgaaagg 600

gcagccaaaa cgtaacaccg ccccggtttt ccctggaaat tccatattgg cacgcattct 660

attggctgag ctgcgttcac gtgggtataa gaggcgcgac cagcgtcggt accgcggccg 720

caggatcc 728

<210> 14
<211> 298
<212> DNA

<213> Artificial Sequence

<220>
<223> gene regulatory unit

<400> 14
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gaagtatgca aagcatgcat ctcaattagt cagcaaccag gtgtggaaag tccccaggct 120

ccccagcagg cagaagtatg caaagcatgc atctcaatta gtcagcaacc atagtcccgc 180

ccctaactcc gcccatcccg cccctaactc cgcccagttc cgcccattct ccgccccatg 240

gctgactaat ttttttttatt tatgcagagg ccgaggccgc ctcgcggccg caggatcc 298

<210> 15
<211> 1200
<212> DNA
<213> Artificial Sequence

<220>
<223> gene regulatory unit

<400> 15
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actgggaaag tgatgtcgtg tactggctcc gccttttttcc cgagggtggg ggagaaccgt 180

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aggtaagtgc cgtgtgtggt tcccgcgggc ctggcctctt tacgggttat ggcccttgcg 300

tgccttgaat tacttccacg cccctggctg cagtacgtga ttcttgatcc cgagcttcgg 360

gttggaagtg ggtgggagag ttcgaggcct tgcgcttaag gagccccttc gcctcgtgct 420

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gcctgtctcg ctgctttcga taagtctcta gccatttaaa atttttgatg acctgctgcg 540

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aggcggggcc tgcgagcgcg gccaccgaga atcggacggg ggtagtctca agctggccgg 720

cctgctctgg tgcctggcct cgcgccgccg tgtatcgccc cgccctgggc ggcaaggctg 780

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ctcaagcctc agacagtggt tcaaagtttt tttcttccat ttcaggtgtc gtgaggatcc 1200

<210> 16
<211> 1293
<212> DNA
<213> Artificial Sequence

<220>
<223> gene regulatory unit

<400> 16
acgcgtacta gttcgaggtg agccccacgt tctgcttcac tctccccatc tccccccccc 60

ccccaccccc aattttgtat ttatttattt tttaattatt ttgtgcagcg atgggggcgg 120

gggggggggg ggcgcgcgcc aggcggggcg gggcggggcg aggggcgggg cggggcgagg 180

cggagaggtg cggcggcagc caatcagagc ggcgcgctcc gaaagtttcc ttttatggcg 240

aggcggcggc ggcggcggcc ctataaaaag cgaagcgcgc ggcgggcggg agtcgctgcg 300

ttgccttcgc cccgtgcccc gctccgcgcc gcctcgcgcc gcccgccccg gctctgactg 360

accgcgttac tcccacaggt gagcgggcgg gacggccctt ctcctccggg ctgtaattag 420

cgcttggttt aatgacggct cgtttctttt ctgtggctgc gtgaaagcct taaagggctc 480

cgggagggcc ctttgtgcgg gggggagcgg ctcgggggggt gcgtgcgtgt gtgtgtgcgt 540

ggggagcgcc gcgtgcggcc cgcgctgccc ggcggctgtg agcgctgcgg gcgcggcgcg 600

gggctttgtg cgctccgcgt gtgcgcgagg ggagcgcggc cgggggcggt gccccgcggt 660

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cgaagcggtg cggcgccggc aggaaggaaa tgggcgggga gggccttcgt gcgtcgccgc 1140

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gggggacgg ggcagggcgg ggttcggctt ctggcgtgtg accggcgggg tttatatctt 1260

cccttctctg ttcctccgca gccagccgga tcc 1293

<210> 17
<211> 683
<212> DNA
<213> Artificial Sequence

<220>
<223> chimeric gene regulatory unit

<400> 17
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catagcccat atatggagtt ccgcgttaca taacttacgg taaatggccc gcctggctga 120

ccgcccaacg acccccgccc attgacgtca ataatgacgt atgttcccat agtaacgcca 180

atagggactt tccattgacg tcaatgggtg gagtatttac ggtaaactgc ccacttggca 240

gtacatcaag tgtatcatat gccaagtccg cccctattg acgtcaatga cggtaaatgg 300

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catgtacttt cccaccattg acgtcaatgg gctattgaaa ctaatgcaac gtgaccttta 480

aacggtactt tcccatagct gattaatggg aaagtaccgt tctcgagcca atacacgtca 540

atgggaagtg aaagggcagc caaaacgtaa caccgccccg gttttccctg gaaattccat 600

attggcacgc attctattgg ctgagctgcg ttcacgtggg tataagaggc gcgaccagcg 660

tcggtaccgc ggccgcagga tcc 683

<210> 18
<211> 507
<212> DNA
<213> Artificial Sequence

<220>
<223> chimeric gene regulatory unit

<400> 18
acgcgttgac attgattatt gactagttat taatagtaat caattacggg gtcattagtt 60

catagcccat atatggagtt ccgcgttaca taacttacgg taaatggccc gcctggctga 120

ccgcccaacg acccccgccc attgacgtca ataatgacgt atgttcccat agtaacgcca 180

atagggactt tccattgacg tcaatgggtg gagtatttac ggtaaactgc ccacttggca 240

gtacatcaag tgtatcatat gccaagtacg ccccctattg acgtcaatga cggtaaatgg 300

cccgcctggc attatgccca gtacatgacc ttatgggact ttcctacttg gcagtacatc 360

tacgtattag tcatcgctat tactcccgcc cctaactccg cccatcccgc ccctaactcc 420

gcccagttcc gcccattctc cgccccatgg ctgactaatt ttttttattt atgcagaggc 480

cgaggccgcc tcgcggccgc aggatcc 507

<210> 19
<211> 607
<212> DNA
<213> Artificial Sequence

<220>
<223> chimeric gene regulatory unit

<400> 19

acgcgttgac attgattatt gactagttat taatagtaat caattacggg gtcattagtt 60

catagcccat atatggagtt ccgcgttaca taacttacgg taaatggccc gcctggctga 120

ccgcccaacg acccccgccc attgacgtca ataatgacgt atgttcccat agtaacgcca 180

atagggactt tccattgacg tcaatgggtg gagtatttac ggtaaactgc ccacttggca 240

gtacatcaag tgtatcatat gccaagtacg ccccctattg acgtcaatga cggtaaatgg 300

cccgcctggc attatgccca gtacatgacc ttatgggact ttcctacttg gcagtacatc 360

tacgtattag tcatcgctat tacactagtc gtgaggctcc ggtgcccgtc agtgggcaga 420

gcgcacatcg cccacagtcc ccgagaagtt gggggggaggg gtcggcaatt gaaccggtgc 480

ctagagaagg tggcgcgggg taaactggga aagtgatgtc gtgtactggc tccgcctttt 540

tcccgagggt gggggagaac cgtatataag tgcagtagtc gccgtgaacg ttgcggccgc 600

aggatcc 607

<210> 20
<211> 677
<212> DNA
<213> Artificial Sequence

<220>
<223> chimeric gene regulatory unit

<400> 20
acgcgttgac attgattatt gactagttat taatagtaat caattacggg gtcattagtt 60

catagcccat atatggagtt ccgcgttaca taacttacgg taaatggccc gcctggctga 120

ccgcccaacg acccccgccc attgacgtca ataatgacgt atgttcccat agtaacgcca 180

atagggactt tccattgacg tcaatgggtg gagtatttac ggtaaactgc ccacttggca 240

gtacatcaag tgtatcatat gccaagtacg ccccctattg acgtcaatga cggtaaatgg 300

cccgcctggc attatgccca gtacatgacc ttatgggact ttcctacttg gcagtacatc 360

tacgtattag tcatcgctat tacactagtt cgaggtgagc cccacgttct gcttcactct 420

ccccatctcc ccccccctccc caccccccaat tttgtattta tttatttttt aattattttg 480

tgcagcgatg ggggcggggg gggggggggc gcgcgccagg cggggcgggg cggggcgagg 540

ggcggggcgg ggcgaggcgg agaggtgcgg cggcagccaa tcagagcggc gcgctccgaa 600

agtttccttt tatggcgagg cggcggcggc ggcggcccta taaaaagcga agcgcgcggc 660

gggcggccgc aggatcc 677

<210> 21
<211> 671
<212> DNA
<213> Artificial Sequence

<220>
<223> chimeric gene regulatory unit

<400> 21
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cattgggttt tgcccagtac ataaggtcaa taggggtga gtcaacagga aagtcccatt 120

ggagccaagt acattgagtc aatagggact ttccaatggg ttttgcccag tacataaggt 180

caatgggagg taagccaatg ggtttttccc attactggca cgtatactga gtcattaggg 240

actttccaat gggttttgcc cagtacataa ggtcaatagg ggtgaatcaa caggaaagtc 300

ccattggagc caagtacact gagtcaatag ggactttcca ttgggttttg cccagtacaa 360

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taggggtgac tagtcatggt gatgcggttt tggcagtaca ccaatgggcg tggatagcgg 480

tttgactcac ggggatttcc aagtctccac cccattgacg tcaatgggag tttgttttgg 540

caccaaaatc aacgggactt tccaaaatgt cgtaataacc ccgccccgtt gacgcaaatg 600

ggcggtaggc gtgtacggtg ggaggtctat ataagcagag ctcgtttagt gaaccggcgg 660

ccgcaggatc c 671

<210> 22
<211> 558
<212> DNA
<213> Artificial Sequence

<220>
<223> chimeric gene regulatory unit

<400> 22
acgcgtagtc aatgggaaaa acccattgga gccaagtaca ctgactcaat agggactttc 60

cattgggttt tgcccagtac ataaggtcaa taggggggtga gtcaacagga aagtcccatt 120

ggagccaagt acattgagtc aatagggact ttccaatggg ttttgcccag tacataaggt 180

caatgggagg taagccaatg ggtttttccc attactggca cgtatactga gtcattaggg 240

actttccaat gggttttgcc cagtacataa ggtcaatagg ggtgaatcaa caggaaagtc 300

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taggggtgac tagttcccgc ccctaactcc gcccatcccg cccctaactc cgcccagttc 480

cgcccattct ccgccccatg gctgactaat ttttttttatt tatgcagagg ccgaggccgc 540

ctcgcggccg caggatcc 558

<210> 23
<211> 652
<212> DNA
<213> Artificial Sequence

<220>
<223> chimeric gene regulatory unit

<400> 23
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cattgggttt tgcccagtac ataaggtcaa taggggggtga gtcaacagga aagtcccatt 120

ggagccaagt acattgagtc aatagggact ttccaatggg ttttgcccag tacataaggt 180

caatgggagg taagccaatg ggtttttccc attactggca cgtatactga gtcattaggg 240

actttccaat gggttttgcc cagtacataa ggtcaatagg ggtgaatcaa caggaaagtc 300

ccattggagc caagtacact gagtcaatag ggactttcca ttgggttttg cccagtacaa 360

aaggtcaata gggggtgagt caatgggttt ttcccattat tggcacgtac ataaggtcaa 420

taggggtgac tagtcgtgag gctccggtgc ccgtcagtgg gcagagcgca catcgcccac 480

agtccccgag aagttggggg gaggggtcgg caattgaacc ggtgcctaga gaaggtggcg 540

cggggtaaac tgggaaagtg atgtcgtgta ctggctccgc ctttttcccg agggtggggg 600

agaaccgtat ataagtgcag tagtcgccgt gaacgttgcg gccgcaggat cc 652

<210> 24
<211> 722
<212> DNA
<213> Artificial Sequence

<220>
<223> chimeric gene regulatory unit

<400> 24
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cattgggttt tgcccagtac ataaggtcaa taggggtga gtcaacagga aagtcccatt 120

ggagccaagt acattgagtc aatagggact ttccaatggg ttttgcccag tacataaggt 180

caatgggagg taagccaatg ggtttttccc attactggca cgtatactga gtcattaggg 240

actttccaat gggttttgcc cagtacataa ggtcaatagg ggtgaatcaa caggaaagtc 300

ccattggagc caagtacact gagtcaatag ggactttcca ttgggttttg cccagtacaa 360

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taggggtgac tagttcgagg tgagccccac gttctgcttc actctcccca tctccccccc 480

ctccccaccc ccaattttgt atttatttat tttttaatta ttttgtgcag cgatgggggc 540

gggggggggg ggggcgcgcg ccaggcgggg cggggcgggg cgaggggcgg ggcggggcga 600

ggcggagagg tgcggcggca gccaatcaga gcggcgcgct ccgaaagttt ccttttatgg 660

cgaggcggcg gcggcggcgg ccctataaaa agcgaagcgc gcggcgggcg gccgcaggat 720

cc 722

<210> 25
<211> 418
<212> DNA

<213> Artificial Sequence

<220>
<223> chimeric gene regulatory unit

<400> 25
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gaagtatgca aagcatgcat ctcaattagt cagcaaccag gtgtggaaag tccccaggct 120

ccccagcagg cagaagtatg caaagcatgc atctcaatta gtcagcaacc atagactagt 180

catggtgatg cggttttggc agtacaccaa tgggcgtgga tagcggtttg actcacgggg 240

atttccaagt ctccacccca ttgacgtcaa tgggagtttg ttttggcacc aaaatcaacg 300

ggactttcca aaatgtcgta ataaccccgc cccgttgacg caaatgggcg gtaggcgtgt 360

acggtgggag gtctatataa gcagagctcg tttagtgaac cgtgcggccg caggatcc 418

<210> 26
<211> 480
<212> DNA
<213> Artificial Sequence

<220>
<223> chimeric gene regulatory unit

<400> 26
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gaagtatgca aagcatgcat ctcaattagt cagcaaccag gtgtggaaag tccccaggct 120

ccccagcagg cagaagtatg caaagcatgc atctcaatta gtcagcaacc atagactagt 180

agtcattggg tttttccagc caatttaatt aaaacgccat gtactttccc accattgacg 240

tcaatgggct attgaaacta atgcaacgtg acctttaaac ggtactttcc catagctgat 300

taatgggaaa gtaccgttct cgagccaata cacgtcaatg ggaagtgaaa gggcagccaa 360

aacgtaacac cgccccggtt ttccctggaa attccatatt ggcacgcatt ctattggctg 420

agctgcgttc acgtgggtat aagaggcgcg accagcgtcg gtaccgcggc cgcaggatcc 480

<210> 27

<211> 398
<212> DNA
<213> Artificial Sequence

<220>
<223> chimeric gene regulatory unit

<400> 27
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gaagtatgca aagcatgcat ctcaattagt cagcaaccag gtgtggaaag tccccaggct 120

ccccagcagg cagaagtatg caaagcatgc atctcaatta gtcagcaacc atagactagt 180

cgtgaggctc cggtgcccgt cagtgggcag agcgcacatc gcccacagtc cccgagaagt 240

tgggggggagg ggtcggcaat tgaaccggtg cctagagaag gtggcgcggg gtaaactggg 300

aaagtgatgt cgtgtactgg ctccgccttt ttcccgaggg tgggggagaa ccgtatataa 360

gtgcagtagt cgccgtgaac gttgcggccg caggatcc 398

<210> 28
<211> 471
<212> DNA
<213> Artificial Sequence

<220>
<223> chimeric gene regulatory unit

<400> 28
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gaagtatgca aagcatgcat ctcaattagt cagcaaccag gtgtggaaag tccccaggct 120

ccccagcagg cagaagtatg caaagcatgc atctcaatta gtcagcaacc atagactagt 180

tcgaggtgag ccccacgttc tgcttcactc tccccatctc ccccccctcc ccacccccaa 240

ttttgtattt atttatttttt taattatttt gtgcagcgat gggggcgggg gggggggggg 300

cgcgcgccag gcggggcggg gcggggcgag gggcggggcg gggcgaggcg gagaggtgcg 360

gcggcagcca atcagagcgg cgcgctccga aagtttcctt ttatggcgag gcggcggcgg 420

cggcggccct ataaaaagcg aagcgcgcgg cgggcggcgg ccgcaggatc c 471

<210> 29
<211> 1566
<212> DNA
<213> Artificial Sequence

<220>
<223> chimeric gene regulatory unit

<400> 29
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catagcccat atatggagtt ccgcgttaca taacttacgg taaatggccc gcctggctga 120

ccgcccaacg acccccgccc attgacgtca ataatgacgt atgttcccat agtaacgcca 180

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acgcaaatgg gcggtaggcg tgtacggtgg gaggtctata taagcagagc tcgtttagtg 600

aaccgtcaga tcgcctggag acgccatcca cgctgttttg acctccatag aagacaccgg 660

gaccgatcca gcctccgcgg ccgggaacgg tgcattggaa cgcggattcc ccgtgccaag 720

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<213> Artificial Sequence

<220>
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<220>
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<210> 32

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<220>
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<211> 1630
<212> DNA
<213> Artificial Sequence

<220>
<223> chimeric gene regulatory unit

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cgtcggatcc 1630

<210> 34
<211> 1680
<212> DNA
<213> Artificial Sequence

<220>
<223> chimeric gene regulatory unit

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caatgggagg taagccaatg ggtttttccc attactggca cgtatactga gtcattaggg 240

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gcagccaaaa cgtaacaccg ccccggtttt ccctggaaat tccatattgg cacgcattct 660

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gctgacagac taacagactg ttcctttcca tgggtctttt ctgcagtcac cgtcggatcc 1680

<210> 35
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<212> DNA
<213> Artificial Sequence

<220>
<223> chimeric gene regulatory unit

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ggagccaagt acattgagtc aatagggact ttccaatggg ttttgcccag tacataaggt 180

caatgggagg taagccaatg ggtttttccc attactggca cgtatactga gtcattaggg 240

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gcagtgtagt ctgagcagta ctcgttgctg ccgcgcgcgc caccagacat aatagctgac 1560

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<210> 36
<211> 1510
<212> DNA
<213> Artificial Sequence

<220>
<223> chimeric gene regulatory unit

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ggagccaagt acattgagtc aatagggact ttccaatggg ttttgcccag tacataaggt 180

caatgggagg taagccaatg ggtttttccc attactggca cgtatactga gtcattaggg 240

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<211> 1604
<212> DNA
<213> Artificial Sequence

<220>
<223> chimeric gene regulatory unit

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ctgagcagta ctcgttgctg ccgcgcgcgc caccagacat aatagctgac agactaacag 1560

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<210> 38

<211> 1682
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<213> Artificial Sequence

<220>
<223> chimeric gene regulatory unit

<400> 38
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ggagccaagt acattgagtc aatagggact ttccaatggg ttttgcccag tacataaggt 180

caatgggagg taagccaatg ggtttttccc attactggca cgtatactga gtcattaggg 240

actttccaat gggttttgcc cagtacataa ggtcaatagg ggtgaatcaa caggaaagtc 300

ccattggagc caagtacact gagtcaatag ggactttcca ttgggttttg cccagtacaa 360

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taggggtgac tagttcgagg tgagccccac gttctgcttc actctcccca tctccccccc 480

ctccccaccc ccaattttgt atttatttat tttttaatta ttttgtgcag cgatgggggc 540

gggggggggg ggggcgcgcg ccaggcgggg cggggcgggg cgaggggcgg ggcggggcga 600

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cgaggcggcg gcggcggcgg ccctataaaa agcgaagcgc gcggcgggcg gccgcgcggc 720

cgctcagatc gcctggagac gccatccacg ctgttttgac ctccatagaa gacaccggga 780

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cagctgagtt gttgtattct gataagagtc agaggtaact cccgttgcgg tgctgttaac 1560

ggtggagggc agtgtagtct gagcagtact cgttgctgcc gcgcgcgcca ccagacataa 1620

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cc 1682

<210> 39
<211> 1250
<212> DNA
<213> Artificial Sequence

<220>
<223> chimeric gene regulatory unit

<400> 39
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gaagtatgca aagcatgcat ctcaattagt cagcaaccag gtgtggaaag tccccaggct 120

ccccagcagg cagaagtatg caaagcatgc atctcaatta gtcagcaacc atagtcccgc 180

ccctaactcc gcccatcccg cccctaactc cgcccagttc cgcccattct ccgccccatg 240

gctgactaat ttttttttatt tatgcagagg ccgaggccgc ctcgcggccg ctcagatcgc 300

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tccataacat ggctctttgc cacaactatc tctattggct atatgccaat actctgtcct 660

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ttcacatata caacaacgcc gtcccccgtg cccgcagttt ttattaaaca tagcgtggga 780

tctccacgcg aatctcgggt acgtgttccg gacatgggct cttctccggt agcggcggag 840

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taacagactg ttcctttcca tgggtctttt ctgcagtcac cgtcggatcc 1250

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<212> DNA
<213> Artificial Sequence

<220>
<223> chimeric gene regulatory unit

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gaagtatgca aagcatgcat ctcaattagt cagcaaccag gtgtggaaag tccccaggct 120

ccccagcagg cagaagtatg caaagcatgc atctcaatta gtcagcaacc atagactagt 180

catggtgatg cggttttggc agtacaccaa tgggcgtgga tagcggtttg actcacgggg 240

atttccaagt ctccacccca ttgacgtcaa tgggagtttg ttttggcacc aaaatcaacg 300

ggactttcca aaatgtcgta ataaccccgc cccgttgacg caaatgggcg gtaggcgtgt 360

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gaacggtgca ttggaacgcg gattccccgt gccaagagtg acgtaagtac cgcctataga 540

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tgaccattat tgaccactcc cctattggtg acgatacttt ccattactaa tccataacat 720

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taagagtcag aggtaactcc cgttgcggtg ctgttaacgg tggagggcag tgtagtctga 1260

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ttcctttcca tgggtctttt ctgcagtcac cgtcggatcc 1360

<210> 41
<211> 1432
<212> DNA
<213> Artificial Sequence

<220>
<223> chimeric gene regulatory unit

<400> 41
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gaagtatgca aagcatgcat ctcaattagt cagcaaccag gtgtggaaag tccccaggct 120

ccccagcagg cagaagtatg caaagcatgc atctcaatta gtcagcaacc atagactagt 180

agtcattggg tttttccagc caatttaatt aaaacgccat gtactttccc accattgacg 240

tcaatgggct attgaaacta atgcaacgtg acctttaaac ggtactttcc catagctgat 300

taatgggaaa gtaccgttct cgagccaata cacgtcaatg ggaagtgaaa gggcagccaa 360

aacgtaacac cgccccggtt ttccctggaa attccatatt ggcacgcatt ctattggctg 420

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gccgcacaag gccgtggcgg tagggtatgt gtctgaaaat gagctcggag attgggctcg 1200

caccgtgacg cagatggaag acttaaggca gcggcagaag aagatgcagg cagctgagtt 1260

gttgtattct gataagagtc agaggtaact cccgttgcgg tgctgttaac ggtggagggc 1320

agtgtagtct gagcagtact cgttgctgcc gcgcgcgcca ccagacataa tagctgacag 1380

actaacagac tgttcctttc catgggtctt ttctgcagtc accgtcggat cc 1432

<210> 42
<211> 1350
<212> DNA
<213> Artificial Sequence

<220>
<223> chimeric gene regulatory unit

<400> 42

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ccccagcagg cagaagtatg caaagcatgc atctcaatta gtcagcaacc atagactagt 180

cgtgaggctc cggtgcccgt cagtgggcag agcgcacatc gcccacagtc cccgagaagt 240

tgggggggagg ggtcggcaat tgaaccggtg cctagagaag gtggcgcggg gtaaactggg 300

aaagtgatgt cgtgtactgg ctccgccttt ttcccgaggg tgggggagaa ccgtatataa 360

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tgggtctttt ctgcagtcac cgtcggatcc 1350

<210> 43
<211> 1423
<212> DNA
<213> Artificial Sequence

<220>
<223> chimeric gene regulatory unit

<400> 43
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gaagtatgca aagcatgcat ctcaattagt cagcaaccag gtgtggaaag tccccaggct 120

ccccagcagg cagaagtatg caaagcatgc atctcaatta gtcagcaacc atagactagt 180

tcgaggtgag ccccacgttc tgcttcactc tccccatctc ccccccctcc ccacccccaa 240

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<210> 44
<211> 1604
<212> DNA
<213> Artificial Sequence

<220>
<223> chimeric gene regulatory unit

<400> 44
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<211> 1667
<212> DNA
<213> Artificial Sequence

<220>
<223> chimeric gene regulatory unit

<400> 45
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<210> 46
<211> 1491
<212> DNA

<213> Artificial Sequence

<220>
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<210> 47
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<212> DNA
<213> Artificial Sequence

<220>
<223> chimeric gene regulatory unit

<400> 47
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<210> 48
<211> 1661
<212> DNA
<213> Artificial Sequence

<220>
<223> chimeric gene regulatory unit

<400> 48
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ccccatctcc ccccctcccc cacccccaat tttgtattta tttatttttt aattattttg 480

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<210> 49
<211> 1712
<212> DNA
<213> Artificial Sequence

<220>
<223> chimeric gene regulatory unit

<400> 49
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ggagccaagt acattgagtc aatagggact ttccaatggg ttttgcccag tacataaggt 180

caatgggagg taagccaatg ggtttttccc attactggca cgtatactga gtcattaggg 240

actttccaat gggttttgcc cagtacataa ggtcaatagg ggtgaatcaa caggaaagtc 300

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gcagccaaaa cgtaacaccg ccccggtttt ccctggaaat tccatattgg cacgcattct 660

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<210> 50
<211> 1655
<212> DNA
<213> Artificial Sequence

<220>
<223> chimeric gene regulatory unit

<400> 50
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ggagccaagt acattgagtc aatagggact ttccaatggg ttttgcccag tacataaggt 180

caatgggagg taagccaatg ggtttttccc attactggca cgtatactga gtcattaggg 240

actttccaat gggttttgcc cagtacataa ggtcaatagg ggtgaatcaa caggaaagtc 300

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ggcggtaggc gtgtacggtg ggaggtctat ataagcagag ctcgtttagt gaaccggcgg 660

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<210> 51
<211> 1542
<212> DNA
<213> Artificial Sequence

<220>
<223> chimeric gene regulatory unit

<400> 51
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caatgggagg taagccaatg ggtttttccc attactggca cgtatactga gtcattaggg 240

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gttcaaagtt tttttcttcc atttcaggtg tcgtgaggat cc 1542

<210> 52

<211> 1628
<212> DNA
<213> Artificial Sequence

<220>
<223> chimeric gene regulatory unit

<400> 52
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<210> 53
<211> 1714
<212> DNA
<213> Artificial Sequence

<220>
<223> chimeric gene regulatory unit

<400> 53
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caatgggagg taagccaatg ggtttttccc attactggca cgtatactga gtcattaggg 240

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ttttttтctt ccatttcagg tgtcgtgagg atcc 1714

<210> 54
<211> 1282
<212> DNA
<213> Artificial Sequence

<220>
<223> chimeric gene regulatory unit

<400> 54
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ccccagcagg cagaagtatg caaagcatgc atctcaatta gtcagcaacc atagtcccgc 180

ccctaactcc gcccatcccg cccctaactc cgcccagttc cgcccattct ccgccccatg 240

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ggagactgaa gttaggccag cttggcactt gatgtaattc tccttggaat ttgccctttt 1200

tgagtttgga tcttggttca ttctcaagcc tcagacagtg gttcaaagtt tttttcttcc 1260

atttcaggtg tcgtgaggat cc 1282

<210> 55
<211> 1402
<212> DNA
<213> Artificial Sequence

<220>
<223> chimeric gene regulatory unit

<400> 55
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gaagtatgca aagcatgcat ctcaattagt cagcaaccag gtgtggaaag tccccaggct 120

ccccagcagg cagaagtatg caaagcatgc atctcaatta gtcagcaacc atagactagt 180

catggtgatg cggttttggc agtacaccaa tgggcgtgga tagcggtttg actcacgggg 240

atttccaagt ctccacccca ttgacgtcaa tgggagtttg ttttggcacc aaaatcaacg 300

ggactttcca aaatgtcgta ataaccccgc cccgttgacg caaatgggcg gtaggcgtgt 360

acggtgggag gtctatataa gcagagctcg tttagtgaac cgtgcggccg ccttttcgc 420

aacgggtttg ccgccagaac acaggtaagt gccgtgtgtg gttcccgcgg gcctggcctc 480

tttacgggtt atggcccttg cgtgccttga attacttcca cgcccctggc tgcagtacgt 540

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ggggtagtct caagctggcc ggcctgctct ggtgcctggc ctcgcgccgc cgtgtatcgc 960

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atttcaggtg tcgtgaggat cc 1402

<210> 56
<211> 1464
<212> DNA
<213> Artificial Sequence

<220>
<223> chimeric gene regulatory unit

<400> 56
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gaagtatgca aagcatgcat ctcaattagt cagcaaccag gtgtggaaag tccccaggct 120

ccccagcagg cagaagtatg caaagcatgc atctcaatta gtcagcaacc atagactagt 180

agtcattggg tttttccagc caatttaatt aaaacgccat gtactttccc accattgacg 240

tcaatgggct attgaaacta atgcaacgtg acctttaaac ggtactttcc catagctgat 300

taatgggaaa gtaccgttct cgagccaata cacgtcaatg ggaagtgaaa gggcagccaa 360

aacgtaacac cgccccggtt ttccctggaa attccatatt ggcacgcatt ctattggctg 420

agctgcgttc acgtgggtat aagaggcgcg accagcgtcg gtaccgcggc cgccttttc 480

gcaacgggtt tgccgccaga acacaggtaa gtgccgtgtg tggttcccgc gggcctggcc 540

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ccgcttcccg gccctgctgc agggagctca aaatggagga cgcggcgctc gggagagcgg 1140

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gactccacgg agtaccgggc gccgtccagg cacctcgatt agttctcgag cttttggagt 1260

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tttgagtttg gatcttggtt cattctcaag cctcagacag tggttcaaag tttttttctt 1440

ccatttcagg tgtcgtgagg atcc 1464

<210> 57
<211> 1374
<212> DNA
<213> Artificial Sequence

<220>
<223> chimeric gene regulatory unit

<400> 57
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gaagtatgca aagcatgcat ctcaattagt cagcaaccag gtgtggaaag tccccaggct 120

ccccagcagg cagaagtatg caaagcatgc atctcaatta gtcagcaacc atagactagt 180

cgtgaggctc cggtgcccgt cagtgggcag agcgcacatc gcccacagtc cccgagaagt 240

tgggggggagg ggtcggcaat tgaaccggtg cctagagaag gtggcgcggg gtaaactggg 300

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agtgggtggg agagttcgag gccttgcgct taaggagccc cttcgcctcg tgcttgagtt 600

gaggcctggc ctgggcgctg gggccgccgc gtgcgaatct ggtggcacct tcgcgcctgt 660

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gcctttccgt cctcagccgt cgcttcatgt gactccacgg agtaccgggc gccgtccagg 1140

cacctcgatt agttctcgag cttttggagt acgtcgtctt taggttgggg ggaggggttt 1200

tatgcgatgg agtttcccca cactgagtgg gtggagactg aagttaggcc agcttggcac 1260

ttgatgtaat tctccttgga atttgccctt tttgagtttg gatcttggtt cattctcaag 1320

cctcagacag tggttcaaag ttttttttctt ccatttcagg tgtcgtgagg atcc 1374

<210> 58
<211> 1455
<212> DNA
<213> Artificial Sequence

<220>
<223> chimeric gene regulatory unit

<400> 58
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gaagtatgca aagcatgcat ctcaattagt cagcaaccag gtgtggaaag tccccaggct 120

ccccagcagg cagaagtatg caaagcatgc atctcaatta gtcagcaacc atagactagt 180

tcgaggtgag ccccacgttc tgcttcactc tccccatctc ccccccctcc ccacccccaa 240

ttttgtattt atttatttttt taattatttt gtgcagcgat gggggcgggg gggggggggg 300

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gcggcagcca atcagagcgg cgcgctccga aagtttcctt ttatggcgag gcggcggcgg 420

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tggtggcacc ttcgcgcctg tctcgctgct ttcgataagt ctctagccat ttaaaatttt 780

tgatgacctg ctgcgacgct ttttttctgg caagatagtc ttgtaaatgc gggccaagat 840

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cgcacatgtt cggcgaggcg gggcctgcga gcgcggccac cgagaatcgg acgggggtag 960

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gagtaccggg cgccgtccag gcacctcgat tagttctcga gcttttggag tacgtcgtct 1260

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gaagttaggc cagcttggca cttgatgtaa ttctccttgg aatttgccct ttttgagttt 1380

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gtgtcgtgag gatcc 1455

<210> 59
<211> 1618
<212> DNA
<213> Artificial Sequence

<220>
<223> chimeric gene regulatory unit

<400> 59
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gtgtgaccgg cggggtttat atcttccctt ctctgttcct ccgcagccag ccggatcc 1618

<210> 60
<211> 1681
<212> DNA
<213> Artificial Sequence

<220>
<223> chimeric gene regulatory unit

<400> 60
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c 1681

<210> 61
<211> 1505
<212> DNA
<213> Artificial Sequence

<220>
<223> chimeric gene regulatory unit

<400> 61
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gatcc 1505

<210> 62
<211> 1605
<212> DNA
<213> Artificial Sequence

<220>
<223> chimeric gene regulatory unit

<400> 62

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<210> 63
<211> 1670
<212> DNA
<213> Artificial Sequence

<220>
<223> chimeric gene regulatory unit

<400> 63
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<210> 64
<211> 1726
<212> DNA
<213> Artificial Sequence

<220>
<223> chimeric gene regulatory unit

<400> 64
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ggagccaagt acattgagtc aatagggact ttccaatggg ttttgcccag tacataaggt 180

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<210> 65
<211> 1669
<212> DNA

<213> Artificial Sequence

<220>
<223> chimeric gene regulatory unit

<400> 65
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caatgggagg taagccaatg ggtttttccc attactggca cgtatactga gtcattaggg 240

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<210> 66
<211> 1556
<212> DNA
<213> Artificial Sequence

<220>
<223> chimeric gene regulatory unit

<400> 66
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<210> 67
<211> 1650
<212> DNA
<213> Artificial Sequence

<220>
<223> chimeric gene regulatory unit

<400> 67
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ggagccaagt acattgagtc aatagggact ttccaatggg ttttgcccag tacataaggt 180

caatgggagg taagccaatg ggtttttccc attactggca cgtatactga gtcattaggg 240

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<210> 68

<211> 1715
<212> DNA
<213> Artificial Sequence

<220>
<223> chimeric gene regulatory unit

<400> 68
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<210> 69
<211> 1296
<212> DNA
<213> Artificial Sequence

<220>
<223> chimeric gene regulatory unit

<400> 69
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<210> 70
<211> 1416
<212> DNA
<213> Artificial Sequence

<220>
<223> chimeric gene regulatory unit

<400> 70
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ccccagcagg cagaagtatg caaagcatgc atctcaatta gtcagcaacc atagactagt 180

catggtgatg cggttttggc agtacaccaa tgggcgtgga tagcggtttg actcacgggg 240

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<210> 71
<211> 1478
<212> DNA
<213> Artificial Sequence

<220>
<223> chimeric gene regulatory unit

<400> 71
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ccccagcagg cagaagtatg caaagcatgc atctcaatta gtcagcaacc atagactagt 180

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tgggggggagg ggtcggcaat tgaaccggtg cctagagaag gtggcgcggg gtaaactggg 300

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35 40 45

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

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Gly Gln Tyr Val Val Ala Ala Ala Pro Asn Leu Gln Asn Gln Gln Val
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Pro Gln Phe Gln Thr Val Asp Gly Gln Gln Leu Gln Phe Ala Ala Thr
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Gly Ala Gln Val Gln Gln Asp Gly Ser Gly Gln Ile Gln Ile Ile Pro
145                 150                 155                 160

Gly Ala Asn Gln Gln Ile Ile Thr Asn Arg Gly Ser Gly Gly Asn Ile
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Leu Ala Asn Asn Val Leu Ser Gly Gln Thr Gln Tyr Val Thr Asn Val
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Pro Val Ala Leu Asn Gly Asn Ile Thr Leu Leu Pro Val Asn Ser Val
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Ser Ala Ala Thr Leu Thr Pro Ser Ser Gln Ala Val Thr Ile Ser Ser
225                 230                 235                 240

Ser Gly Ser Gln Glu Ser Gly Ser Gln Pro Val Thr Ser Gly Thr Thr
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Asn Ile Gln Gln Asn Gln Thr Ser Gly Gly Ser Leu Gln Ala Gly Gln
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Ala Ala Pro Leu Ser Gly Gln Thr Phe Thr Thr Gln Ala Ile Ser Gln
    370                 375                 380

Glu Thr Leu Gln Asn Leu Gln Leu Gln Ala Val Pro Asn Ser Gly Pro
385                 390                 395                 400

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Gln Thr Leu Gln Leu Gln Asn Leu Gln Val Gln Asn Pro Gln Ala Gln
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Ser Ser Asn Thr Thr Leu Thr Pro Ile Ala Ser Ala Ala Ser Ile Pro
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His Pro Ile Gln Gly Leu Pro Leu Ala Ile Ala Asn Ala Pro Gly Asp
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His Gly Ala Gln Leu Gly Leu His Gly Ala Gly Gly Asp Gly Ile His
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Asp Asp Thr Ala Gly Gly Glu Glu Gly Glu Asn Ser Pro Asp Ala Gln
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Pro Gln Ala Gly Arg Arg Thr Arg Arg Glu Ala Cys Thr Cys Pro Tyr
545                 550                 555                 560

Cys Lys Asp Ser Glu Gly Arg Gly Ser Gly Asp Pro Gly Lys Lys Lys
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Gln His Ile Cys His Ile Gln Gly Cys Gly Lys Val Tyr Gly Lys Thr
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Ser His Leu Arg Ala His Leu Arg Trp His Thr Gly Glu Arg Pro Phe
        595                 600                 605

Met Cys Thr Trp Ser Tyr Cys Gly Lys Arg Phe Thr Arg Ser Asp Glu
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Leu Gln Arg His Lys Arg Thr His Thr Gly Glu Lys Lys Phe Ala Cys
625                 630                 635                 640

Pro Glu Cys Pro Lys Arg Phe Met Arg Ser Asp His Leu Ser Lys His
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Ile Lys Thr His Gln Asn Lys Lys Gly Gly Pro Gly Val Ala Leu Ser
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Val Gly Thr Leu Pro Leu Asp Ser Gly Ala Gly Ser Glu Gly Ser Gly
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Thr Ala Thr Pro Ser Ala Leu Ile Thr Thr Asn Met Val Ala Met Glu
690 695 700

Ala Ile Cys Pro Glu Gly Ile Ala Arg Leu Ala Asn Ser Gly Ile Asn
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Ser Ser Gly Gly Gly Gly Gly Gln Glu Ser Gln Pro Ser Pro Leu Ala
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Leu Leu Ala Ala Thr Cys Ser Arg Ile Glu Ser Pro Asn Glu Asn Ser

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Asn Asn Ser Gln Gly Pro Ser Gln Ser Gly Gly Thr Gly Glu Leu Asp
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            340                 345                 350

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Ile Gln Gln Asn Gln Thr Ser Gly Gly Ser Leu Gln Gly Ser Gln Gln
    370                 375                 380

Lys Glu Gly Glu Gln Ser Gln Gln Thr Gln Gln Gln Gln Ile Leu Ile
385                 390                 395                 400

Gln Pro Gln Leu Val Gln Gly Gly Gln Ala Leu Gln Ala Leu Gln Ala
                405                 410                 415

Ala Pro Leu Ser Gly Gln Thr Phe Thr Thr Gln Ala Ile Ser Gln Glu
            420                 425                 430

Thr Leu Gln Asn Leu Gln Leu Gln Ala Val Gln Asn Ser Gly Pro Ile
        435                 440                 445

Ile Ile Arg Thr Pro Thr Val Gly Pro Asn Gly Gln Val Ser Trp Gln
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    450                 455                 460

Thr Leu Gln Leu Gln Asn Leu Gln Val Gln Asn Pro Gln Ala Gln Thr
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Ser Asn Thr Thr Leu Thr Pro Ile Ala Ser Ala Ala Ser Ile Pro Ala
            500                 505                 510

Gly Thr Val Thr Val Asn Ala Ala Gln Leu Ser Ser Met Pro Gly Leu
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Gln Thr Ile Asn Leu Ser Ala Leu Gly Thr Ser Gly Ile Gln Val His
    530                 535                 540

Gln Leu Pro Gly Leu Pro Leu Ala Ile Ala Asn Thr Pro Gly Asp His
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Gly Thr Gln Leu Gly Leu His Gly Ser Gly Gly Asp Gly Ile His Asp
                565                 570                 575

Glu Thr Ala Gly Gly Glu Gly Glu Asn Ser Ser Asp Leu Gln Pro Gln
            580                 585                 590

Ala Gly Arg Arg Thr Arg Arg Glu Ala Cys Thr Cys Pro Tyr Cys Lys
        595                 600                 605

Asp Ser Glu Gly Arg Ala Ser Gly Asp Pro Gly Lys Lys Lys Gln His
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Ile Cys His Ile Gln Gly Cys Gly Lys Val Tyr Gly Lys Thr Ser His
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Leu Arg Ala His Leu Arg Trp His Thr Gly Glu Arg Pro Phe Met Cys
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Claims:

1. Isolated nucleic acid molecule comprising a functional chimeric gene regulatory unit comprising

(a) a functional enhancer nucleotide sequence comprising, consisting essentially of or consisting of (i) a nucleotide sequence as set forth in any one of SEQ ID NO:1; SEQ ID NO:2; SEQ ID NO:3; or a complement thereof; or (ii) a nucleotide sequence that shares at least 90% sequence identity with a nucleotide sequence of (i) or a complement thereof;

(b) a functional core promoter nucleotide sequence comprising, consisting essentially of or consisting of (i) a nucleotide sequence as set forth in any one of SEQ ID NO:4; SEQ ID NO:5; SEQ ID NO:6; SEQ ID NO:7; SEQ ID NO:8; or a complement thereof; or (ii) a nucleotide sequence that shares at least 90% sequence identity with a nucleotide sequence of (i) or a complement thereof; and

(c) at least one nucleotide sequence encoding for an intron comprising, consisting essentially of or consisting of (i) a nucleotide sequence as set forth in any one of SEQ ID NO:9; SEQ ID NO:10; SEQ ID NO:11; or a complement thereof; or (ii) a nucleotide sequence that shares at least 90% sequence identity with a nucleotide sequence of (i) or a complement thereof, wherein the enhancer nucleotide sequence is 5' to the promoter nucleotide sequence and the intron nucleotide sequence is 3' to the promoter sequence and wherein at least one nucleotide sequence of the enhancer nucleotide sequence, the promoter nucleotide sequence or the at least one nucleotide sequence encoding for the intron is derived from a different species than the other nucleotide sequences.

2. The isolated nucleic acid molecule of claim 1, further comprising at least one nucleotide sequence encoding for a polypeptide, peptide or RNA molecule, wherein said sequence is operably linked to the chimeric gene regulatory unit.

3. The isolated nucleic acid molecule of claim 2, wherein the at least one nucleotide sequence encoding for a polypeptide, peptide or RNA molecule of interest lies 3' to the intron nucleotide sequence.

4. The isolated nucleic acid molecule of claim 3, wherein the at least one nucleotide sequence encoding for a polypeptide, peptide or RNA molecule of interest lies directly adjacent to the intron sequence.

5. The isolated nucleic acid molecule of any one of claims 2-4, wherein the polypeptide of interest is a polypeptide chain of a naturally occurring or artificial immunoglobulin.

6. The isolated nucleic acid molecule of claim 5, wherein the polypeptide of interest is an antibody or fragment thereof.

7. The isolated nucleic acid molecule of claim 6, wherein the antibody is a human or humanized antibody, or a fragment thereof.

8. The isolated nucleic acid molecule of any one of claims 1 to 7, wherein the chimeric gene regulation unit has an increased resistance to transcriptional silencing.

9. The isolated nucleic acid molecule of any one of claims 1 to 8, wherein the isolated nucleic acid molecule further comprises at least one nucleotide sequence encoding for a recognition site of a restriction endonuclease.

10. The isolated nucleic acid molecule of claim 9, wherein the at least one nucleotide sequence encoding for a recognition site of a restriction endonuclease is (i) 3' to the enhancer nucleotide sequence and 5' to the promoter nucleotide sequence or (ii) 3' to the promoter nucleotide sequence and 5' to the at least one nucleotide sequence encoding for an intron.

11. The isolated nucleic acid molecule of any one of claims 1 to 10, wherein the enhancer sequence is derived from viruses, preferably from double-stranded DNA viruses.

12. The isolated nucleic acid molecule of claim 11, wherein the enhancer sequence is derived from viruses consisting of the group of Herpesviridae and Polyomaviridae.

13. The isolated nucleic acid molecule of claim 12, wherein the enhancer sequence is derived from the group consisting of human cytomegalovirus; murine cytomegalovirus; and simian virus 40.

14. The isolated nucleic acid molecule of any one of claims 1 to 13, wherein any one or more of the enhancer sequence, the promoter sequence and the intron are independently derived from human cytomegalovirus; murine cytomegalovirus; simian virus 40; the human EF-1α gene; or the chicken β-actin gene.

15. The isolated nucleic acid molecule of claim 14, wherein (i) the promoter is derived from human cytomegalovirus, murine cytomegalovirus, simian virus 40, the human EF-1α gene, or the chicken β-actin gene, (ii) the enhancer is derived from human cytomegalovirus, murine cytomegalovirus, or simian virus 40, and/or (iii) the intron sequence is derived from human cytomegalovirus, the human EF-1α gene, or the chicken β-actin gene.

16. The isolated nucleic acid molecule of any one of claims 1 to 15, wherein the chimeric gene regulatory unit comprises, consists essentially of or consists of

(1) the nucleotide sequences as set forth in SEQ ID NO:1; SEQ ID NO:4; and SEQ ID NO:11; or complements thereof;

(2) the nucleotide sequences as set forth in SEQ ID NO:2; SEQ ID NO:5; and SEQ ID NO:11; or complements thereof;

(3) the nucleotide sequences as set forth in SEQ ID NO:2; SEQ ID NO:4; and SEQ ID NO:11; or complements thereof;

(4) the nucleotide sequences as set forth in SEQ ID NO:2; SEQ ID NO:4; and SEQ ID NO:9; or complements thereof;

(5) the nucleotide sequences as set forth in SEQ ID NO:1; SEQ ID NO:5; and SEQ ID NO:11; or complements thereof;

(6) the nucleotide sequences as set forth in SEQ ID NO:1; SEQ ID NO:5; and SEQ ID NO:9; or complements thereof;

(7) the nucleotide sequences as set forth in SEQ ID NO:1; SEQ ID NO:7; and SEQ ID NO:11; or complements thereof;

(8) the nucleotide sequences as set forth in SEQ ID NO:1; SEQ ID NO:5; and SEQ ID NO:11; or complements thereof;

(9) the nucleotide sequences as set forth in SEQ ID NO:2; SEQ ID NO:7; and SEQ ID NO:9; or complements thereof;

(10) the nucleotide sequences as set forth in SEQ ID NO:2; SEQ ID NO:6; and SEQ ID NO:10; or complements thereof;

(11) the nucleotide sequences as set forth in SEQ ID NO:3; SEQ ID NO:7; and SEQ ID NO:10; or complements thereof;

(12) the nucleotide sequences as set forth in SEQ ID NO:1; SEQ ID NO:6; and SEQ ID NO:11; or complements thereof;

(13) the nucleotide sequences as set forth in SEQ ID NO:3; SEQ ID NO:5; and SEQ ID NO:10; or complements thereof;

(14) the nucleotide sequences as set forth in SEQ ID NO:1; SEQ ID NO:7; and SEQ ID NO:10; or complements thereof;

(15) the nucleotide sequences as set forth in SEQ ID NO:2; SEQ ID NO:6; and SEQ ID NO:11; or complements thereof;

(16) the nucleotide sequences as set forth in SEQ ID NO:2; SEQ ID NO:6; and SEQ ID NO:9; or complements thereof;

(17) the nucleotide sequences as set forth in SEQ ID NO:2; SEQ ID NO:7; and SEQ ID NO:11; or complements thereof;

(18) the nucleotide sequences as set forth in SEQ ID NO:1; SEQ ID NO:8; and SEQ ID NO:10; or complements thereof;

(19) the nucleotide sequences as set forth in SEQ ID NO:2; SEQ ID NO:5; and SEQ ID NO:10; or complements thereof;

(20) the nucleotide sequences as set forth in SEQ ID NO:3; SEQ ID NO:5; and SEQ ID NO:11; or complements thereof;

(21) the nucleotide sequences as set forth in SEQ ID NO:2; SEQ ID NO:5; and SEQ ID NO:9; or complements thereof;

(22) the nucleotide sequences as set forth in SEQ ID NO:2; SEQ ID NO:4; and SEQ ID NO:10; or complements thereof;

(23) the nucleotide sequences as set forth in SEQ ID NO:1; SEQ ID NO:7; and SEQ ID NO:11; or complements thereof;

(24) the nucleotide sequences as set forth in SEQ ID NO:2; SEQ ID NO:7; and SEQ ID NO:10; or complements thereof;

(25) the nucleotide sequences as set forth in SEQ ID NO:1; SEQ ID NO:5; and SEQ ID NO:10; or complements thereof; or

(26) a nucleotide sequence that shares at least 90% sequence identity with one nucleotide sequence of (1)-(25) or a complement thereof.

17. The isolated nucleic acid molecule of any one of claims 1 to 16, wherein the isolated nucleic acid molecule of the invention comprising the functional chimeric gene regulatory unit and the at least one nucleotide sequence encoding for a polypeptide, peptide or RNA molecule of interest has increased expression activity to express the polypeptide, peptide or RNA molecule of interest in CHO (Chinese Hamster Ovary) K1 or CHO DG44 cells compared to an isolated nucleic acid molecule comprising a naturally occurring gene regulatory unit and a nucleotide sequence encoding for the same polypeptide, peptide or RNA molecule of interest.

18. The isolated nucleic acid molecule of any one of claims 1 to 17, wherein the chimeric gene regulatory unit having increased expression activity in CHO K1 cells comprises, consists essentially of or consists of (i) a nucleotide sequence as set forth in SEQ ID NO: 30, SEQ ID NO: 35, SEQ ID NO:59, SEQ ID NO:60, SEQ ID NO:62, SEQ ID NO: 64, SEQ ID NO: 65; or

a complement thereof; or (ii) a nucleotide sequence that shares at least 90% sequence identity with a nucleotide sequence of (i) or a complement thereof.

19. The isolated nucleic acid molecule of any one of claims 1 to 18, wherein the chimeric gene regulatory unit having increased expression activity in CHO DG44 cells comprises, consists essentially of or consists of (i) a nucleotide sequence as set forth in SEQ ID Nos. 34, 36, 37, 45, 47-52, 56, 57, 59-62, 64-67, 71 or a complement thereof; or (ii) a nucleotide sequence that shares at least 90% sequence identity with a nucleotide sequence of (i) or a complement thereof.

20. The isolated nucleic acid molecule of any one of claims 1 to 19, wherein the promoter comprises at least one binding site for a transcription factor.

21. Vector comprising the isolated nucleic acid molecule of any one of claims 1-20.

22. Host cell comprising the isolated nucleic acid molecule of any one of claims 1-20 or the vector of claim 21.

23. The host cell of claim 22, wherein the host cell is a eukaryotic cell.

24. The host cell of claim 23, wherein the host cell is a CHO cell, preferably a CHO K1 cell or a CHO DG44 cell.

25. Use of the isolated nucleic acid molecule of any one of claims 1-20 for facilitating or enhancing the expression of a polypeptide, peptide or RNA of interest, wherein said isolated nucleic acid molecule comprises a nucleotide sequence encoding the polypeptide, peptide or RNA of interest, wherein said nucleotide sequence encoding the polypeptide, peptide or RNA of interest is operably linked to the chimeric gene regulatory unit of the isolated nucleic acid molecule.

26. Method of producing a polypeptide, peptide or RNA of interest comprising:

(i) providing the isolated nucleic acid molecule of any one of claims 1-20, wherein said isolated nucleic acid molecule comprises a nucleotide sequence encoding the polypeptide, peptide or RNA of interest, said nucleotide sequence encoding the polypeptide, peptide or RNA of interest being operably linked to the chimeric gene regulatory unit of the isolated nucleic acid molecule; and

(ii) producing the polypeptide, peptide or RNA of interest by *in vitro* transcription and translation or in a suitable host cell under conditions that allow production of the polypeptide, peptide or RNA of interest.

27. The method of claim 26, wherein the host cell is a eukaryotic cell.

28. The method of claim 27, wherein the eukaryotic cell is a CHO cell, more preferably a CHO K1 cell or a CHO DG44 cell.