βGI-IgG Intron for Enhanced Anti-IGF1R Expression

This application claims the benefit of U.S. provisional patent application no. 61/113,807; filed November 12, 2008; which is herein incorporated by reference in its entirety.

Field of the Invention

The present invention relates to polynucleotides comprising a target gene operably linked to a promoter/beta-globin-immunoglobin gamma (βGI-IgG) intron construct and methods of expressing such a target gene.

Background of the Invention

The clinical and commercial success of antibodies, antibody fragments and other therapeutic proteins has led to the need for very large-scale production in mammalian cell culture. This has resulted in rapid expansion of global manufacturing capacity, an increase in size of reactors (up to 20,000 L) and a greatly increased effort to improve process efficiency with concomitant manufacturing cost reduction.

For example, most antibody therapies require high doses over a long period of time, which requires large amounts of purified product per patient. Therefore, manufacturing capacity to meet the demands of antibody production is a real challenge; it is desirable to have highly productive manufacturing processes.

One means by which to improve *in vivo* production levels of an antibody or other protein is to generate novel polynucleotide expression constructs which cause enhanced levels of protein production as compared to that of standard constructs. The present invention addresses this need in the art.

Summary of the Invention

The present invention provides, in part, an isolated βGI-IgG intron polynucleotide comprising a beta-globin splice donor site and an immunoglobulin gamma splice acceptor site wherein said sites are separated by about 125 nucleotides. In addition to the βGI-IgG introns, the present invention includes methods of use for expressing target polypeptides at high levels. Plasmids, host cells, master cell banks and working cell banks also form part of the present invention.

For example, in an embodiment of the invention, the polynucleotides comprises a beta-globin splice donor site comprising the nucleotide sequence CAGGTAAGTTTA (SEQ ID NO: 4) and an immunoglobulin gamma splice acceptor site comprising the nucleotide sequence TTTCTCTCCACAGGC (SEQ ID NO: 5) wherein said sites are separated by about 125 nucleotides; e.g., wherein the splice donor site and the splice acceptor site are separated by the sequence

AAGCTCAGGT CGAGACCGGG CCTTTGTCCG GCGCTCCCTT GGAGCCTACC TAGACTCAGC CGGCTCTCCA CGCTTTGCCT GACCCTGCTT GCTCAACTCT ACGTCTTTGT TTCGTTTTCT GTTCC

(nucleotides 51-175 of SEQ ID NO: 3). In an embodiment of the invention, the βGI-IgG intron is upstream of a gene and downstream of a promoter that is operably associated with said gene. The gene can be of any type, for example, an immunoglobulin, for example, wherein the immunoglobulin is a light chain variable region (optionally including a signal peptide) or heavy chain variable region (optionally including a signal peptide), or both, of an antibody or antigen-binding fragment thereof which binds specifically to IGF1R, IL-23 p19, IL23 receptor (any subunit thereof, *e.g.*, IL-12β1 or IL-23R), IL-17A, PD1 or HGF, *e.g.*, wherein the gene encodes CDR-L1, CDR-L2 and CDR-L3 of a light chain immunoglobulin comprising amino acids 20-128 of SEQ ID NO: 6, 8-11, 18 or 26 or SEQ ID NO 31; and/or wherein the gene encodes CDR-H1, CDR-H2 and CDR-H3 of a heavy chain immunoglobulin comprising amino acids 20-137 of SEQ ID NO: 7, 12, 13, 14 or 22 or SEQ ID NO: 30. The βGI-IgG intron can be placed in any polynucleotide, for example, a vector such as a plasmid vector or viral vector.

The present invention includes within its scope, an isolated plasmid that includes a βGI-IgG intron characterized by the plasmid vector map of any of figures 1-10, for example, wherein the plasmid comprises βGI-IgG intron nucleotides 39-190 of the nucleotide sequence of SEQ ID NO: 3.

Host cells including a βGI-IgG intron of the present invention are also within the scope of the present invention. For example, in the host cell, the βGI-IgG intron polynucleotide can be integrated into the chromosomal DNA of the host cell or not integrated. Furthermore, the host cell can contain a high copy number of the polynucleotide, for example, 2 or more copies per cell.

Master cell banks (MCBs) also form part of the present invention. Accordingly, the present invention includes a method for making a master cell bank comprising introducing a βGI-IgG intron polynucleotide of the invention (*e.g.*, plasmid vector shown in any of figures 1-10) into a host cell (*e.g.*, a mammalian cell, *e.g.*, a CHO cell, such as a CHO-DG44, CHO-

K1 or CHO-DXB11), selecting a single clonal population of host cells comprising said polynucleotide, culturing said clonal population, determining if cells from said culture contain bacteria, viruses, fungi and/or mycoplasma and, if none are detected, storing cells from said culture in one or more containers under refrigeration. In an embodiment of the invention, the master cell bank is free of biological contaminants, such as bacteria, viruses, fungi and/or mycoplasma. The master cell bank can be stored under refrigeration. A master cell bank, for example, produced by the described method of making a MCB is also part of the present invention is also part of the present invention. The present invention further provides a method for making a working cell bank (WCB) by culturing cells from a master cell bank of the present invention and storing cells from said culture in one or more containers under refrigeration. Similar to the method for making a MCB, this method can include a step for testing the WCB for bacteria, viruses, fungi and/or mycoplasma and, if none are detected, storing cells from said culture under refrigeration. A working cell bank, for example, produced by the described method of making a WCB is also part of the present. For example, in an embodiment of the invention, in the MCB or WCB, the cells are in vials (*e.g.*, about 200 or more) comprising about 10^7 cells per vial and are free of detectable levels of bacteria, viruses, mycoplasma and fungi.

The present invention also provides a method for expressing a target polypeptide encoded by a gene which is operably associated with a promoter, in a host cell (*e.g.*, a mammalian cell, *e.g.*, a CHO cell, such as a CHO-K1, CHO-DXB11 or CHO-DG44 cell), comprising introducing a βGl-IgG intron polynucleotide comprising a beta-globin splice donor site and an immunoglobulin gamma splice acceptor wherein said sites are separated by about 125 nucleotides, between the promoter and the polynucleotide encoding the target polypeptide (*e.g.*, plasmid pAIG1FRLCb2V1, *e.g.*, that comprises the nucleotide sequence of SEQ ID NO: 35) into the host cell under conditions whereby the target polypeptide is expressed; and, optionally, purifying said target polypeptide. In an embodiment of the invention, the beta-globin splice donor site comprises the nucleotide sequence CAGGTAAGTTTA (SEQ ID NO: 4) and the immunoglobulin splice acceptor site comprises the nucleotide sequence TTTCTCTCCACAGGC (SEQ ID NO: 5), *e.g.*, wherein the splice donor site and the splice acceptor site are separated by the sequence

AAGCTCAGGT CGAGACCGGG CCTTTGTCCG GCGCTCCCTT GGAGCCTACC TAGACTCAGC CGGCTCTCCA CGCTTTGCCT GACCCTGCTT GCTCAACTCT ACGTCTTTGT TTCGTTTTCT GTTCC

(nucleotides 51-175 or SEQ ID NO: 3). In an embodiment of the invention, the gene is an immunoglobulin, for example, wherein the immunoglobulin is a light chain variable region or heavy chain variable region of an antibody which binds specifically to IGF1R, *e.g.*, wherein

the gene encodes CDR-L1, CDR-L2 and CDR-L3 of a light chain immunoglobulin comprising amino acids 20-128 of SEQ ID NO: 6, 8-11, 18 or 26 or SEQ ID NO 31; or wherein the gene encodes CDR-H1, CDR-H2 and CDR-H3 of a heavy chain immunoglobulin comprising amino acids 20-137 of SEQ ID NO: 7, 12, 13, 14 or 22 or SEQ ID NO: 30.

Brief Description of the Figures

Figure 1. Plasmid map for pAIG1FRLCb2V1. The feature map for this plasmid is set forth below:

AP(R)
Start: 3965 End: 4828
(Complementary)
VDJ
Start: 5966 End: 6393
IgG1
Start: 6393 End: 7373
IgG1 non genomic region
DHFR cDNA
Start: 601 End: 1347
(Complementary)
SV40 t Ag Intron
Start: 11916 End: 600
Kappa
Start: 10055 End: 10378
(Complementary)
Kappa Chain
VJ
Start: 10379 End: 10756
(Complementary)
VJ of IGF-1R (LCb, human germline sequence)
pBR322
Start: 2811 End: 3019
(Complementary)

pBR322
Start: 3020 End: 5033
TK-Hygromycinseq
Start: 7682 End: 9691
(Complementary)
Beta Globin Poly A signal
Start: 7398 End: 7636
Beta Globin Poly A signal
Start: 9784 End: 10032
(Complementary)
SV40 Poly A signal
Start: 11669 End: 11917
MMTV-LTR
Start: 1348 End: 2810
(Complementary)
hCMV/ βGl-IgG intron
Start: 5069 End: 5910
Human CMV promoter/βGl-IgG
intron
hCMV/ βGl-IgG intron
Start: 10778 End: 11619
(Complementary)
Human CMV promoter/βGl-IgG
intron
pBR ORI
Start: 3207 End: 3207

Figure 2. Plasmid map for pAIG1FRLCb2V3. The feature map for this plasmid is set forth below:

AP(R)
Start: 3965 End: 4828
(Complementary)
IgG1
Start: 7371 End: 8351

(Complementary)
IgG1 non genomic region
VDJ
Start: 8351 End: 8778
(Complementary)
DHFR cDNA
Start: 601 End: 1347
(Complementary)
SV40 t Ag Intron
Start: 11916 End: 600
Kappa
Start: 10055 End: 10378
(Complementary)
Kappa Chain
VJ
Start: 10379 End: 10756
(Complementary)
VJ of IGF-1R (LCb, human germline sequence)
pBR322
Start: 2811 End: 3019
(Complementary)
pBR322
Start: 3020 End: 5033
TK-Hygromycinseq
Start: 5053 End: 7062
Beta Globin Poly A signal
Start: 7108 End: 7346
(Complementary)
Beta globin pA signal
Start: 9784 End: 10032
(Complementary)
SV40 POLYA
Start: 11669 End: 11917

MMTV-LTR
Start: 1348 End: 2810
(Complementary)
hCMV/ βGl-IgG intron
Start: 8834 End: 9675
(Complementary)
Human CMV promoter with βGl-IgG
intron
hCMV/ βGl-IgG intron
Start: 10778 End: 11619
(Complementary)
Human CMV promoter and βGl-IgG
intron
pBR ORI
Start: 3207 End: 3207

Figure 3. Plasmid map for pAIG1FRV1.

AP(R)
Start: 3965 End: 4828 (Complementary)
VDJ
Start: 5824 End: 6251
VDJ of IGFR1 of 19D12 hybridoma
IgG1
Start: 6241 End: 7231
IgG1 non genomic region
DHFR cDNA
Start: 601 End: 1347 (Complementary)
SV40 t Ag Intron
Start: 11740 End: 600
Kap
Start: 9898 End: 10233 (Complementary)
Kappa chain of hu-antiIGFR gene
VJ
Start: 10234 End: 10614 (Complementary)
VJ Domain of hu-anti IGFR gene for light chain
pBR322
Start: 2811 End: 3019 (Complementary)
pBR322
Start: 3020 End: 5033

TK-Hygromycinseq
Start: 7540 End: 9549 (Complementary)
TK-hygromycin sequenced in Union U-3

Beta Globin Poly A signal
Start: 7256 End: 7494

Beta globin pA signal
Start: 9642 End: 9890 (Complementary)

SV40 POLYA
Start: 11493 End: 11741

MMTV-LTR
Start: 1348 End: 2810 (Complementary)

CMV
Start: 10801 End: 11455 (Complementary)

CMV
Start: 5069 End: 5723

T 7 promoter/priming site
Start: 5723 End: 5742

T 7 promoter/priming site
Start: 10782 End: 10801 (Complementary)

pBR ORI
Start: 3207 End: 3207

Figure 4. Plasmid map for pAIG1FRV3.

AP(R)
Start: 3965 End: 4828 (Complementary)

IgG1
Start: 7371 End: 8361 (Complementary)
IgG1 non genomic region

VDJ
Start: 8351 End: 8778 (Complementary)
VDJ of IGFR1 of 19D12 hybridoma

DHFR cDNA
Start: 601 End: 1347 (Complementary)

SV40 t Ag Intron
Start: 11740 End: 600

Kap
Start: 9898 End: 10233 (Complementary)
Kappa chain of hu-antiIGFR gene

VJ
Start: 10234 End: 10614 (Complementary)
VJ Domain of hu-anti IGFR gene for light chain

pBR322
Start: 2811 End: 3019 (Complementary)

pBR322

Start: 3020 End: 5033

TK-Hygromycinseq
Start: 5053 End: 7062
TK-hygromycin

Beta Globin Poly A signal
Start: 7108 End: 7346 (Complementary)

Beta globin pA signal
Start: 9642 End: 9890 (Complementary)

SV40 POLYA
Start: 11493 End: 11741

MMTV-LTR
Start: 1348 End: 2810 (Complementary)

CMV
Start: 10801 End: 11455 (Complementary)

T 7 promoter/priming site
Start: 8860 End: 8879 (Complementary)

CMV
Start: 8879 End: 9533 (Complementary)

T 7 promoter/priming site
Start: 10782 End: 10801 (Complementary)

pBR ORI
Start: 3207 End: 3207

Figure 5. Plasmid map for pAIG1FRLCB2-V1K.

AP(R)
Start: 3965 End: 4828 (Complementary)

VDJ
Start: 6356 End: 6356
VDJ region of anti-IL10 (12G8)

IgG1
Start: 6361 End: 7341
IgG1 non genomic region

VJ
Start: 10368 End: 10745 (Complementary)

IgK
Start: 10013 End: 10367 (Complementary)
VDJ-IgK for 12G8 light chain (anti-IL10)

DHFR cDNA
Start: 601 End: 1347 (Complementary)

SV40 t Ag Intron
Start: 11899 End: 600

pBR322
Start: 2811 End: 3019 (Complementary)

pBR322
Start: 3020 End: 5033

TK-Hygromycinseq
Start: 7650 End: 9659 (Complementary)
TK-hygromycin

Beta Globin Poly A signal
Start: 7366 End: 7604

Beta Globin Poly A signal
Start: 9763 End: 9996

SV40 POLYA
Start: 11652 End: 11900

MMTV-LTR
Start: 1348 End: 2810 (Complementary)

hCMV/ βGI-IgG intron
Start: 5069 End: 5910
Human CMV promoter with hybrid intron

hCMV/ βGI-IgG intron
Start: 10773 End: 11614 (Complementary)
Human CMV promoter and hybrid intron

pBR ORI
Start: 3207 End: 3207

Figure 6. Plasmid map for pAIL23V1K. Plasmid vector comprising hCMV promoter-(βGI-IgG intron)-anti-IL-23 Ig. light chain and hCMV promoter-(βGI-IgG intron)-anti-IL-23 Ig. heavy chain constructs. βGI-IgG intron is at nt. 10906-10755 and 5760-5911.

Figure 7. Plasmid map for pAIL23RV1. Plasmid vector comprising hCMV promoter-(βGI-IgG intron)-anti-IL-23R Ig. light chain and hCMV promoter-(βGI-IgG intron)-anti-IL-23R Ig. heavy chain constructs. βGI-IgG intron is at nt. 10914-10763 and 5760-5911.

Figure 8. Plasmid map for pAIL17AV1. Plasmid vector comprising hCMV promoter-(βGI-IgG intron)-anti-IL-17 Ig. light chain and hCMV promoter-(βGI-IgG intron)-anti-IL-17 Ig. heavy chain constructs. βGI-IgG intron is at nt. 10934-10783 and 5759-5910.

Figure 9. Plasmid map for pAPD16V1-GA. Plasmid vector comprising hCMV promoter-(βGI-IgG intron)-anti-PD1 Ig. light chain and hCMV promoter-(βGI-IgG intron)-anti-PD1 Ig. heavy chain constructs. βGI-IgG intron is at nt.10871-10720 and 5759-5910.

Figure 10. Plasmid map for pAHGFV1. Plasmid vector comprising hCMV promoter-(βGI-IgG intron)-anti-HGF Ig. light chain and hCMV promoter-(βGI-IgG intron)-anti-HGF Ig. heavy chain constructs. βGI-IgG intron is at nt. 10922-10771 and 5760-5911.

Detailed Description of the Invention

The present invention provides, in part, expression constructs from which target genes, such as immunoglobulin light or heavy chains, can be expressed at particularly high levels, relative to conventional expression constructs. For example, the present invention includes polynucleotides (*e.g.*, plasmid vectors) which include a target gene to be expressed (*e.g.*, an immunoglobulin light and/or heavy chain gene), operably linked to a promoter wherein, between the gene and promoter there is a construct comprising a beta-globin intron splice donor site, followed by about 125 nucleotides, followed, then, by an immunoglobulin-gamma intron acceptor site. The present invention also includes methods for expressing the target genes using the expression constructs of the present invention.

Molecular Biology

In accordance with the present invention there may be employed conventional molecular biology, microbiology, and recombinant DNA techniques within the skill of the art. Such techniques are explained fully in the literature. See, *e.g.*, Sambrook, Fritsch & Maniatis, Molecular Cloning: A Laboratory Manual, Second Edition (1989) Cold Spring Harbor Laboratory Press, Cold Spring Harbor, New York (herein "Sambrook, *et al.*, 1989"); DNA Cloning: A Practical Approach, Volumes I and II (D.N. Glover ed. 1985); Oligonucleotide Synthesis (M.J. Gait ed. 1984); Nucleic Acid Hybridization (B.D. Hames & S.J. Higgins eds. (1985)); Transcription And Translation (B.D. Hames & S.J. Higgins, eds. (1984)); Animal Cell Culture (R.I. Freshney, ed. (1986)); Immobilized Cells And Enzymes (IRL Press, (1986)); B. Perbal, A Practical Guide To Molecular Cloning (1984); F.M. Ausubel, *et al.* (eds.), Current Protocols in Molecular Biology, John Wiley & Sons, Inc. (1994).

A "polynucleotide", "nucleic acid " or "nucleic acid molecule" includes DNA and RNA.

A "polynucleotide sequence", "nucleic acid sequence" or "nucleotide sequence" is a series of nucleotides in a nucleic acid, such as DNA or RNA, and means any chain of two or more nucleotides.

A "coding sequence" or a sequence "encoding" an expression product, such as a RNA, polypeptide, protein, or enzyme, is a nucleotide sequence that, when expressed, results in production of the product.

The term "gene" includes DNA that codes for or corresponds to a particular sequence of ribonucleotides or amino acids which comprise all or part of one or more RNA molecules or proteins. Genes may be transcribed from DNA to RNA which may or may not be translated into an amino acid sequence. A "target gene" or a "target polynucleotide" is a polynucleotide, *e.g.*, that encodes a target polypeptide, which a practitioner intends to express or is expressing, for example, by introducing the polynucleotide into an expression construct for expression in *e.g.*, a host cell.

The terms "isolated polynucleotide" or "isolated polypeptide" or the like include a polynucleotide (*e.g.*, RNA or DNA molecule) or a polypeptide, respectively, which are partially or fully separated from other components that are normally found in cells or in recombinant DNA expression systems. These components include, but are not limited to, cell membranes, cell walls, ribosomes, polymerases, serum components and extraneous genomic sequences. An isolated polynucleotide or polypeptide will, in an embodiment of the invention, be an essentially homogeneous composition of molecules but may contain some heterogeneity.

"Amplification" of DNA as used herein includes the use of polymerase chain reaction (PCR) to increase the concentration of a particular DNA sequence within a mixture of DNA sequences. For a description of PCR see Saiki, *et al.*, Science (1988) 239: 487.

As used herein, the term "oligonucleotide" includes a nucleic acid, generally of at least 10 (*e.g.*, 10, 11, 12, 13 or 14), preferably at least 15 (*e.g.*, 15, 16, 17, 18 or 19), and more preferably at least 20 nucleotides (*e.g.*, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29 or 30), preferably no more than 100 nucleotides (*e.g.*, 40, 50, 60, 70, 80 or 90), that may be hybridizable to a genomic DNA molecule, a cDNA molecule, or an mRNA molecule encoding a gene, mRNA, cDNA, or other nucleic acid of interest. Oligonucleotides can be labeled, *e.g.*, by incorporation of ^{32}P-nucleotides, ^{3}H-nucleotides, ^{14}C-nucleotides, ^{35}S-nucleotides or nucleotides to which a label, such as biotin, has been covalently conjugated. In one embodiment of the invention, a labeled oligonucleotide can be used as a probe to detect the presence of a nucleic acid. In another embodiment, oligonucleotides (one or both of which may be labeled) can be used as PCR primers, either for cloning full length or a fragment of a gene, or to detect the presence of nucleic acids. Generally, oligonucleotides are prepared synthetically, *e.g.*, on a nucleic acid synthesizer.

The sequence of any nucleic acid may be sequenced by any method known in the art (*e.g.*, chemical sequencing or enzymatic sequencing). "Chemical sequencing" of DNA includes methods such as that of Maxam and Gilbert (1977) (Proc. Natl. Acad. Sci. USA 74:560), in which DNA is randomly cleaved using individual base-specific reactions. "Enzymatic sequencing" of DNA may includes methods such as that of Sanger (Sanger, *et al.*, (1977) Proc. Natl. Acad. Sci. USA 74:5463).

The nucleic acids of the invention may, in an embodiment of the invention, be flanked by natural regulatory (expression control) sequences, or may be associated with heterologous sequences, including promoters, internal ribosome entry sites (IRES) and other ribosome binding site sequences, enhancers, response elements, suppressors, signal sequences, polyadenylation sequences, introns, 5'- and 3'- non-coding regions, and the like.

A "promoter" or "promoter sequence" is, in an embodiment of the invention, a DNA regulatory region capable of binding an RNA polymerase in a cell (*e.g.*, directly or through other promoter-bound proteins or substances) and initiating transcription of a coding sequence (*e.g.*, an immunoglobulin such as an anti-IGF1R immunoglobulin). A promoter sequence is, in general, bounded at its 3' terminus by the transcription initiation site and extends upstream (5' direction) to include the minimum number of bases or elements necessary to initiate transcription at any level. Within the promoter sequence may be found a transcription initiation site (conveniently defined, for example, by mapping with nuclease S1), as well as protein binding domains (consensus sequences) responsible for the binding of RNA polymerase. The promoter may be operably associated with other expression control sequences, including enhancer and repressor sequences or with a nucleic acid of the invention. Promoters which may be used to control gene expression include, but are not limited to, cytomegalovirus (CMV) promoter (U.S. Patent Nos. 5,385,839 and 5,168,062), the SV40 early promoter region (Benoist, *et al.*, (1981) Nature 290:304-310), the promoter contained in the 3' long terminal repeat of Rous sarcoma virus (Yamamoto, *et al.*, (1980) Cell 22:787-797), the herpes thymidine kinase promoter (Wagner, *et al.*, (1981) Proc. Natl. Acad. Sci. USA 78:1441-1445), the regulatory sequences of the metallothionein gene (Brinster, *et al.*, (1982) Nature 296:39-42); prokaryotic expression vectors such as the β-lactamase promoter (Villa-Komaroff, *et al.*, (1978) Proc. Natl. Acad. Sci. USA 75:3727-3731), or the *tac* promoter (DeBoer, *et al.*, (1983) Proc. Natl. Acad. Sci. USA 80:21-25); see also "Useful proteins from recombinant bacteria" in Scientific American (1980) 242:74-94; and promoter elements from yeast or other fungi such as the *Gal 4* promoter, the *ADC*

(alcohol dehydrogenase) promoter, *PGK* (phosphoglycerol kinase) promoter or the alkaline phosphatase promoter.

A coding sequence is "under the control of", "functionally associated with" or "operably linked to" or "operably associated with" transcriptional or translational control sequences in a cell when the sequences direct RNA polymerase mediated transcription of the coding sequence into RNA, *e.g.*, mRNA, which then may be trans-RNA spliced (if it contains introns) and, optionally, translated into a protein encoded by the coding sequence. A promoter is operably linked to a βGl-IgG intron if the intron causes increased levels of expression from the promoter relative to the promoter without the βGl-IgG intron.

The terms "express" and "expression" mean allowing or causing the information in a gene, *e.g.*, an RNA or DNA, to become manifest; for example, producing a protein by activating the cellular functions involved in transcription and translation of a corresponding gene. A DNA sequence can be expressed in or by a cell to form an "expression product" such as an RNA (*e.g.*, mRNA) or a protein. The expression product itself may also be said to be "expressed" by the cell.

The terms "vector", "cloning vector" and "expression vector" include a vehicle (*e.g.*, a plasmid) by which a nucleic acid can be introduced into a host cell, so as to transform the host and, optionally, promote expression of a gene encoded by the nucleic acid and/or replication of the introduced nucleic acid. In an embodiment of the invention, the vector is an autonomously replicating nucleic acid such as a circular plasmid.

The term "transformation" means the introduction of a nucleic acid into a cell. The term includes the introduction of a nucleic acid encoding an anti-IGF1R, anti-IL23, anti-IL23R, anti-IL17, anti-PD1 or anti-HGF antibody or antigen-binding fragment thereof into a cell. The introduced gene or sequence may be called a "clone". A host cell that receives the introduced DNA or RNA has been "transformed" and is a "transformant" or a "clone". The DNA or RNA introduced to a host cell can come from any source, including cells of the same genus or species as the host cell, or cells of a different genus or species. Plasmids may be introduced into a cell by any of the many methods which are commonly known in the art. For example, a plasmid of the invention can be used to transform a cell by the calcium phosphate method, electroporation, the DEAE-dextran method or the liposome method.

The term "host cell" includes any cell of any organism that is selected, modified, transfected, transformed, grown, or used or manipulated in any way, for the production of a substance by the cell, for example the expression or replication, by the cell, of a gene, a

DNA or RNA sequence, a protein or an enzyme. Host cells include Chinese hamster ovary cells such as CHO-K1 cells (ATCC accession no. CRL-9618), CHO-DG44 cells, and CHO-DXB-11 cells.

An "expression construct" is a polynucleotide which is capable of driving expression of a target gene encoded within the polynucleotide. For example, wherein the gene is operably linked to a promoter (*e.g.*, CMV promoter) between which is located a βGl-IgG intron.

A "promoter/ βGl-IgG intron" is a promoter operably linked to a βGl-IgG intron. The βGl-IgG intron cause higher levels of expression from the promoter than in the absence of the βGl-IgG intron.

A "βGl-IgG intron" is an intron comprising splice donor (*e.g.*, beta-globin) and splice acceptor sites (*e.g.*, IgG).

In an embodiment of the invention, an expression construct comprises a Kozak consensus sequence, *e.g.*, gccgccaccatgg (SEQ ID NO: 1) or gccgccaccatg (SEQ ID NO: 2).

The term "expression system" means a host cell and compatible vector which, under suitable conditions, can express a protein or nucleic acid which is carried by the vector and introduced to the host cell. Common expression systems include *E. coli* host cells and plasmid vectors, insect host cells and Baculovirus vectors, and mammalian host cells and vectors. As mentioned above, host cells include CHO (Chinese hamster ovary) cells, such as CHO-K1or DXB-11; and also HeLa cells and NIH 3T3 cells and NSO cells (non-Ig-producing murine myeloma cell line).

Plasmid vectors of the present invention may include any of several amplifiable markers known in the art. Use of amplifiable markers is discussed in Maniatis, Molecular Biology: A Laboratory Manual, Cold Spring Harbor Laboratory, NY (1989)). Useful selectable markers for gene amplification in drug-resistant mammalian cells include DHFR (MTX (methotrexate) resistance) (Alt *et al.*, J. Biol. Chem. 253:1357 (1978); Wigler *et al.*, Proc. Natl. Acad. Sci. USA 77:3567 (1980)); metallothionein (cadmium resistance) (Beach *et al.*, Proc Natl. Acad. Sci. USA 78:210 (1981)); CAD (N-(phosphonoacetyl)-l-aspartate (PALA) resistance) (Wahl *et al.*, J. Biol. Chem. 254: 8679 (1979)); adenylate deaminase (coformycin resistance) (Debatisse *et al.*, Mol. Cell. Biol. 6:1776 (1986)); IMP 5'-dehydrogenase (mycophenolic acid resistance) (Huberman *et al.*, Proc. Natl. Acad. Sci. USA 78:3151 (1981)) and other markers known in the art (as reviewed, for example, in Kaufman *et al.*, Meth. Enzymology 185:537-566 (1988)).

The present invention contemplates any superficial or slight modification to the amino acid or nucleotide sequences which encode the target genes encoded by the plasmids of the present invention, *e.g.*, antibodies or antigen-binding fragments thereof of the invention. "Sequence-conservative variants" of a polynucleotide sequence are those in which a change of one or more nucleotides in a given codon results in no alteration in the amino acid encoded at that position. Function-conservative variants of the target genes of the invention are also contemplated by the present invention. "Function-conservative variants" are those in which one or more amino acid residues in a protein have been changed without altering the overall conformation and function of the polypeptide, including, but, by no means, limited to, replacement of an amino acid with one having similar properties. Amino acids with similar properties are well known in the art. For example, polar/hydrophilic amino acids which may be interchangeable include asparagine, glutamine, serine, cysteine, threonine, lysine, arginine, histidine, aspartic acid and glutamic acid; nonpolar/hydrophobic amino acids which may be interchangeable include glycine, alanine, valine, leucine, isoleucine, proline, tyrosine, phenylalanine, tryptophan and methionine; acidic amino acids which may be interchangeable include aspartic acid and glutamic acid and basic amino acids which may be interchangeable include histidine, lysine and arginine. Conservative substitutions of an amino acid sequence refer to those wherein an amino acid of one subtype (*e.g.*, polar/hydrophilic) is replaced with another amino acid of the same subtype; and, in an embodiment of the invention, wherein the conservatively substituted polypeptide retains essentially the same level of biological activity.

The present invention includes plasmids including nucleic acids encoding target genes as well as nucleic acids which hybridize thereto. In an embodiment of the invention, the nucleic acids hybridize under low stringency conditions, more preferably under moderate stringency conditions and most preferably under high stringency conditions. A nucleic acid molecule is "hybridizable" to another nucleic acid molecule, such as a cDNA, genomic DNA, or RNA, when a single stranded form of the nucleic acid molecule can anneal to the other nucleic acid molecule under the appropriate conditions of temperature and solution ionic strength (see Sambrook, *et al.*, *supra*). The conditions of temperature and ionic strength determine the "stringency" of the hybridization. Typical low stringency hybridization conditions include, in an embodiment of the invention, 55°C, 5X SSC, 0.1% SDS, 0.25% milk, and no formamide; or 30% formamide, 5X SSC, 0.5% SDS. Typical, moderate stringency hybridization conditions are similar to the low stringency conditions except the hybridization is carried out in 40% formamide, with 5X or 6X SSC. High

stringency hybridization conditions are similar to low stringency conditions except the hybridization conditions are carried out in 50% formamide, 5X or 6X SSC and, optionally, at a higher temperature (*e.g.*, 57°C, 59°C, 60°C, 62°C, 63°C, 65°C or 68°C). In general, SSC is 0.15M NaCl and 0.015M Na-citrate. Hybridization requires that the two nucleic acids contain complementary sequences, although, depending on the stringency of the hybridization, mismatches between bases are possible. The appropriate stringency for hybridizing nucleic acids depends on the length of the nucleic acids and the degree of complementation, variables well known in the art. The greater the degree of similarity or homology between two nucleotide sequences, the higher the stringency under which the nucleic acids may hybridize. For hybrids of greater than 100 nucleotides in length, equations for calculating the melting temperature have been derived (see Sambrook, *et al.*, *supra*, 9.50-9.51). For hybridization with shorter nucleic acids, *i.e.*, oligonucleotides, the position of mismatches becomes more important, and the length of the oligonucleotide determines its specificity (see Sambrook, *et al.*, *supra*, 11.7-11.8).

Also included in the present invention are plasmids including target nucleotide sequences which encode target polypeptides comprising amino acid sequences which are at least about 70% identical, preferably at least about 80% identical, more preferably at least about 90% identical and most preferably at least about 95% identical (*e.g.*, 95%, 96%, 97%, 98%, 99%, 100%) to the reference nucleotide and amino acid sequences (*e.g.*, any of SEQ ID NOs: 6-31) of the present invention when the comparison is performed by a BLAST algorithm wherein the parameters of the algorithm are selected to give the largest match between the respective sequences over the entire length of the respective reference sequences. Polypeptides comprising amino acid sequences which are at least about 70% similar, preferably at least about 80% similar, more preferably at least about 90% similar and most preferably at least about 95% similar (*e.g.*, 95%, 96%, 97%, 98%, 99%, 100%) to the reference amino acid sequences of the present invention (*e.g.*, any of SEQ ID NOs: 6-31) when the comparison is performed with a BLAST algorithm wherein the parameters of the algorithm are selected to give the largest match between the respective sequences over the entire length of the respective reference sequences, are also included in the present invention.

Sequence identity refers to exact matches between the nucleotides or amino acids of two sequences which are being compared. Sequence similarity refers to both exact matches between the amino acids of two polypeptides which are being compared in addition to matches between nonidentical, biochemically related amino acids.

Biochemically related amino acids which share similar properties and may be interchangeable are discussed above.

The following references regarding the BLAST algorithm are herein incorporated by reference: **BLAST ALGORITHMS:** Altschul, S.F., *et al.*, (1990) J. Mol. Biol. 215:403-410; Gish, W., *et al.*, (1993) Nature Genet. 3:266-272; Madden, T.L., *et al.*, (1996) Meth. Enzymol. 266:131-141; Altschul, S.F., *et al.*, (1997) Nucleic Acids Res. 25:3389-3402; Zhang, J., *et al.*, (1997) Genome Res. 7:649-656; Wootton, J.C., *et al.*, (1993) Comput. Chem. 17:149-163; Hancock, J.M. *et al.*, (1994) Comput. Appl. Biosci. 10:67-70; **ALIGNMENT SCORING SYSTEMS**: Dayhoff, M.O., *et al.*, "A model of evolutionary change in proteins." in Atlas of Protein Sequence and Structure, (1978) vol. 5, suppl. 3. M.O. Dayhoff (ed.), pp. 345-352, Natl. Biomed. Res. Found., Washington, DC; Schwartz, R.M., *et al.*, "Matrices for detecting distant relationships." in Atlas of Protein Sequence and Structure, (1978) vol. 5, suppl. 3." M.O. Dayhoff (ed.), pp. 353-358, Natl. Biomed. Res. Found., Washington, DC; Altschul, S.F., (1991) J. Mol. Biol. 219:555-565; States, D.J., *et al.*, (1991) Methods 3:66-70; Henikoff, S., *et al.*, (1992) Proc. Natl. Acad. Sci. USA 89:10915-10919; Altschul, S.F., *et al.*, (1993) J. Mol. Evol. 36:290-300; **ALIGNMENT STATISTICS**: Karlin, S., *et al.*, (1990) Proc. Natl. Acad. Sci. USA 87:2264-2268; Karlin, S., *et al.*, (1993) Proc. Natl. Acad. Sci. USA 90:5873-5877; Dembo, A., *et al.*, (1994) Ann. Prob. 22:2022-2039; and Altschul, S.F. "Evaluating the statistical significance of multiple distinct local alignments." in Theoretical and Computational Methods in Genome Research (S. Suhai, ed.), (1997) pp. 1-14, Plenum, New York.

Introns

The present invention comprises polynucleotides, such as vectors (*e.g.*, plasmids), comprising a promoter (*e.g.*, human cytomegalovirus (CMV) promoter, *e.g.*, immediate-early promoter-regulatory region of human cytomegalovirus) operably linked with a βGl-IgG intron that comprises a beta-globin splice donor and an immunoglobulin splice acceptor, which promoter/intron combination is operably linked with a target gene, such as an immunoglobulin. Methods of expressing such target genes using the polynucleotides of the present invention are also part of the present invention. As is discussed herein, it has been discovered that expression of a gene such as an anti-IGF1R immunoglobulin, from a human CMV promoter is greatly increased when the CMV promoter is linked with a βGl-IgG intron (beta-globin splice donor/Ig. splice acceptor).

For example, in an embodiment of the invention, the promoter/intron construct is upstream of the target gene to which it is operably linked. Methods for increasing expression of a target gene comprising operably linking the target gene to the promoter/intron are also within the scope of the present invention.

In an embodiment of the invention, the βGl-IgG intron, comprising the beta-globin splice donor and the IgG. splice acceptor, comprises the following nucleotide sequence:

ATTAATACGA CTCACTATAG CAATTGCACG TGTGGCCACA GGTAAGTTTA
AAGCTCAGGT CGAGACCGGG CCTTTGTCCG GCGCTCCCTT GGAGCCTACC
TAGACTCAGC CGGCTCTCCA CGCTTTGCCT GACCCTGCTT GCTCAACTCT
ACGTCTTTGT TTCGTTTTCT GTTCCTTTCT CTCCACAGGC TTAA

(SEQ ID NO: 3). The beta-globin splice donor site is underscored with a solid line and the immunoglobulin splice acceptor is underscored with a broken line. In an embodiment of the invention, the beta-globin spice donor site comprises the nucleotide sequence CAGGTAAGTTTA (SEQ ID NO: 4). In an embodiment of the invention, the immunoglobulin splice acceptor site is derived from an IgG variable region, for example, comprising the nucleotide sequence TTTCTCTCCACAGGC (SEQ ID NO: 5).

In an embodiment of the invention, the βGl-IgG intron comprises

CA GGTAAGTTTA AAGCTCAGGT CGAGACCGGG CCTTTGTCCG GCGCTCCCTT
GGAGCCTACC TAGACTCAGC CGGCTCTCCA CGCTTTGCCT GACCCTGCTT GCTCAACTCT
ACGTCTTTGT TTCGTTTTCT GTTCCTTTCT CTCCACAGGC

(nucleotides 39-190 of SEQ ID NO: 3).

Immunoglobulins

The present invention includes embodiments comprising polynucleotides (*e.g.*, plasmids) comprising a promoter/intron construct operably associated with a target gene such as an immunoglobulin. In an embodiment of the invention, the immunoglobulin comprises an anti-IGF1R immunoglobulin light or heavy chain variable region, optionally linked with an immunoglobulin constant region.

In an embodiment of the invention, the immunoglobulin chain encodes any of those set forth below; for example, any of the following immunoglobulin light or heavy chains or any of the CDRs thereof. Dotted, underscored type encodes the signal peptide. Solid underscored type encodes the CDRs. Plain type encodes the framework regions. In an embodiment of the invention, the antibody chains are mature fragments which lack the signal peptide. In an embodiment of the invention, non-processed immunoglobulin chains are expressed, including the signal peptide, secreted from the host cell whereby the signal

peptide is processed and removed to generate a mature immunoglobulin chain. Such compositions and methods of expression form part of the present invention.

Polynucleotides encoding any of the following target immunoglobulin amino acid sequences form part of the present invention.

19D12/15H12 Light Chain (SEQ ID NO: 6)

MSPSQLIGFLLLWVPASRGEIVLTQVPDFQSVTPKEKVTITCRASQSIGSSLHWYQQKPD
QSPKLLIKYASQSLSGVPSRFSGSGSGTDFTLTINSLEAEDAAAYYCHQSSRLPHTFGGG
TKVEIKRT

19D12/15H12 Heavy Chain (SEQ ID NO: 7)

MEFGLSWVFLVAILKGVQCEVQLVQSGGGLVHPGGSLRLSCAASGFTFSSFAMHWVRQAP
GKGLEWISVIDTRGATYYADSVKGRFTISRDNAKNSLYLQMNSLRAEDMAVYYCARLGNF
YYGMDVWGQGTTVTVSS

19D12/15H12 Light Chain-C (LCC) (SEQ ID NO: 8)

M S P S Q L I G F L L L W V P A S
R G E I V L T Q S P D S L S V T P
G E R V T I T C R A S Q S I G S S
L H W Y Q Q K P G Q S P K L L I K
Y A S Q S L S G V P S R F S G S G
S G T D F T L T I S S L E A E D A
A A Y Y C H Q S S R L P H T F G Q
G T K V E I K R T

19D12/15H12 Light Chain-D (LCD) (SEQ ID NO: 9)

M S P S Q L I G F L L L W V P A S
R G E I V L T Q S P D S L S V T P
G E R V T I T C R A S Q S I G S S
L H W Y Q Q K P G Q S P K L L I K
Y A S Q S L S G V P S R F S G S G
S G T D F T L T I S S L E A E D F
A V Y Y C H Q S S R L P H T F G Q
G T K V E I K R T

19D12/15H12 Light Chain-E (LCE) (SEQ ID NO: 10)

M S P S Q L I G F L L L W V P A S
R G E I V L T Q S P G T L S V S P
G E R A T L S C R A S Q S I G S S
L H W Y Q Q K P G Q A P R L L I K
Y A S Q S L S G I P D R F S G S G
S G T D F T L T I S R L E P E D A
A A Y Y C H Q S S R L P H T F G Q
G T K V E I K R T

19D12/15H12 Light Chain-F (LCF) (SEQ ID NO: 11)

M S P S Q L I G F L L L W V P A S
R G E I V L T Q S P G T L S V S P
G E R A T L S C R A S Q S I G S S
L H W Y Q Q K P G Q A P R L L I K
Y A S Q S L S G I P D R F S G S G
S G T D F T L T I S R L E P E D F
A V Y Y C H Q S S R L P H T F G Q
G T K V E I K R T

19D12/15H12 heavy chain-A (HCA) (SEQ ID NO: 12)

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

19D12/15H12 heavy chain-B (HCB) (SEQ ID NO: 13)

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

See international application publication no. WO2003/100008, wherein each sequence is disclosed; which is incorporated herein by reference in its entirety.

2C6 heavy chain

MELGLSWIFLLAILKGVQC
EVQLVESGGGLVQPGRSLRLSCAAS**GFTFDDYAMH**WVRQAPGKGLEWVS**GISWNSGSKGYVDSVKG**RFTISRDNAKN
SLYLQMNSLRAEDTALYYCAK**DIRIGVAASYYFGMDV**WGHGTTVTVSS (SEQ ID NO: 14)

2C6 CDR-H1: GFTFDDYAMH (SEQ ID NO: 15)
2C6 CDR-H2: GISWNSGSKGYVDSVKG (SEQ ID NO: 16)
2C6 CDR-H3: DIRIGVAASYYFGMDV (SEQ ID NO: 17)

2C6 Light chain

MDMRVPAQLLGLLLLWLPGARC
AIQLTQSPSSLSASVGDRVTITC**RASQGISSVLA**WYQQKPGKAPKLLIY**DASSLES**GVPSRFSGSGSGTDFTLTISS
LQPEDFATYYC**QQFNSYPYT**FGQGTKLEIK (SEQ ID NO: 18)

2C6 CDR-L1: RASQGISSVLA (SEQ ID NO: 19)
2C6 CDR-L2: DASSLES (SEQ ID NO: 20)
2C6 CDR-L3: QQFNSYPYT (SEQ ID NO: 21)

9H2 Heavy chain

MDWTWRILFLVAAATGAHS

QVQLVQSGAEVKKPGASVKVSCKAS**GYTFTSYVMH**WVRQAPGQRLEWMG**WINAGNGNTKYSQKFQG**RVTITRDTSAS TVYMELSSLRSEDTAVYYCAR**GGMPVAGPGYFYYYGMDV**WGQGTTVTVSS (SEQ ID NO: 22)

9H2 CDR-H1: GYTFTSYVMH (SEQ ID NO: 23)

9H2 CDR-H2: WINAGNGNTKYSQKFQG (SEQ ID NO: 24)

9H2 CDR-H3: GGMPVAGPGYFYYYGMDV (SEQ ID NO: 25)

9H2 Light chain

METPAQLLFLLLLWLPDTTG

EIVLTQSPGTLSLSPGERATLSC**RASQSVSRSYLA**WYQQKPGQAPRLLIY**GASSRAT**GIPDRFSGSGSGTDFTLTIS RLEPEDFAVYCC**QQYGSSPWT**FGQGTKVEIKRT (SEQ ID NO: 26)

9H2 CDR-L1: RASQSVSRSYLA (SEQ ID NO: 27)

9H2 CDR-L2: GASSRAT (SEQ ID NO: 28)

9H2 CDR-L3: QQYGSSPWT (SEQ ID NO: 29)

Heavy chain immunoglobulin variable region # 1.0 sequence

E VQLLESGGGL VQPGGSLRLS CTASGFTFSS YAMNWVRQAP GKGLEWVSAI SGSGGTTFYA DSVKGRFTIS RDNSRTTLYL QMNSLRAEDT AVYYCAKDLG WSDSYYYYYG MDVWGQGTTV TVSS (SEQ ID NO: 30);

Light chain immunoglobulin variable region # 1.0 sequence

DIQMTQFP SSLSASVGDR VTITCRASQG IRNDLGWYQQ KPGKAPKRLI YAASRLHRGV PSRFSGSGSG TEFTLTISSL QPEDFATYYC LQHNSYPCSF GQGTKLEIKR (SEQ ID NO: 31);

Embodiments of the invention include those wherein the polynucleotide (*e.g.*, plasmid) includes a promoter/βGI-IgG intron construct operably linked to more than one immunoglobulin, for example, a combination of any of those set forth herein (*e.g.*, heavy chain Ig. # 1.0 and light chain Ig. #1.0; or LCC and HCA; or LCF and HCA; or LCC and HCB).

Plasmids

The present invention provides, in part, isolated plasmids which exhibit high levels of expression of anti-IGF1R heavy and light chains. These plasmids are pAIG1FRLCb2V1

and pAIG1FRLCb2V3. These plasmid encode and direct expression of antibodies including the LCF and the HCA. The sequences of the plasmids are set forth below:

pAIG1FRLCB2V1:

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   1 GCACTATACA TCAAATATTC CTTATTAACC CCTTTACAAA TTAAAAAGCT AAAGGTACAC
  61 AATTTTTGAG CATAGTTATT AATAGCAGAC ACTCTATGCC TGTGTGGAGT AAGAAAAAAC
 121 AGTATGTTAT GATTATAACT GTTATGCCTA CTTATAAAGG TTACAGAATA TTTTTCCATA
 181 ATTTTCTTGT ATAGCAGTGC AGCTTTTTCC TTTGTGGTGT AAATAGCAAA GCAAGCAAGA
 241 GTTCTATTAC TAAACACAGC ATGACTCAAA AAACTTAGCA ATTCTGAAGG AAAGTCCTTG
 301 GGGTCTTCTA CCTTTCTCTT CTTTTTTGGA GGAGTAGAAT GTTGAGAGTC AGCAGTAGCC
 361 TCATCATCAC TAGATGGCAT TTCTTCTGAG CAAAACAGGT TTTCCTCATT AAAGGCATTC
 421 CACCACTGCT CCCATTCATC AGTTCCATAG GTTGGAATCT AAAATACACA AACAATTAGA
 481 ATCAGTAGTT TAACACATTA TACACTTAAA AATTTTATAT TTACCTTAGA GCTTTAAATC
 541 TCTGTAGGTA GTTTGTCCAA TTATGTCACA CCACAGAAGT AAGGTTCCTT CACAAAGATC
 601 GATCTAAAGC CAGCAAAAGT CCCATGGTCT TATAAAAATG CATAGCTTTA GGAGGGGAGC
 661 AGAGAACTTG AAAGCATCTT CCTGTTAGTC TTTCTTCTCG TAGACTTCAA ACTTATACTT
 721 GATGCCTTTT TCCTCCTGGA CCTCAGAGAG GACGCCTGGG TATTCTGGGA GAAGTTTATA
 781 TTTCCCCAAA TCAATTTCTG GGAAAAACGT GTCACTTTCA AATTCCTGCA TGATCCTTGT
 841 CACAAAGAGT CTGAGGTGGC CTGGTTGATT CATGGCTTCC TGGTAAACAG AACTGCCTCC
 901 GACTATCCAA ACCATGTCTA CTTTACTTGC CAATTCCGGT TGTTCAATAA GTCTTAAGGC
 961 ATCATCCAAA CTTTTGGCAA GAAAATGAGC TCCTCGTGGT GGTTCTTTGA GTTCTCTACT
1021 GAGAACTATA TTAATTCTGT CCTTTAAAGG TCGATTCTTC TCAGGAATGG AGAACCAGGT
1081 TTTCCTACCC ATAATCACCA GATTCTGTTT ACCTTCCACT GAAGAGGTTG TGGTCATTCT
1141 TTGGAAGTAC TTGAACTCGT TCCTGAGCGG AGGCCAGGGT AGGTCTCCGT TCTTGCCAAT
1201 CCCCATATTT TGGGACACGG CGACGATGCA GTTCAATGGT CGAACCATGA TGGCAGCGGG
1261 GATAAAATCC TACCAGCCTT CACGCTAGGA TTGCCGTCAA GTTTGGCGCG AAATCGCAGC
1321 CCTGAGCTGT CCCCCCCCCC AAGCTCAGAT CTGAGCTTGG TCCCTATGGT GAGTCCGTTC
1381 CGCTCTTGTG ATGATAGCCA GACAAGAAAG AGACAATACA AGACAAACAC CAAATAGTAG
1441 AAATAGAGAC AAGGGTCACT TATCCGAGGG TCCCTGTTCG GGCGCCAGCT GCCGCAGTCG
1501 GCCGACCTGA GGGTCGCCGG GGTCTGCGGG GGGACCCTCT GGAAAGTGAA GGATAAGTGA
1561 CGAGCGGAGA CGGGATGGCG AACAGACACA AACACACAAG AGGTGAATGT TAGGACTGTT
1621 GCAAGTTTAC TCAAAAAATC AGCACTCTTT TATATCTTGG TTTACATAAG CATTTACATA
1681 AGATTTGGAT AAATTCCAAA AGAACATAGG AAAATAGAAC ACTCAGAGCT CAGATCAGAA
1741 CCTTTGATAC CAAACCAAGT CAGGAAACCA CTTGTCTCAC ATCCTCGTTT TAAGAACAGT
1801 TTGTAACCAA AAACTTACTT AAGCCCTGGG AACCGCAAGG TTGGGCCAAT AAAGGCTATT
1861 CATAATAACT CATGCCATGA GTTTTTGCAG AATAATGTTC TATTAGTCCA GCCACTGTCC
1921 CCTCCTTGGT ATGGAAAATC TTTCCCCAAA AGTGCATTCC TGTTCCTAGA TAAATATAAT
1981 CATGTACCTG TTGTTTCATG TCGTCTTTTT CTTCTTGAGA CAACATACAC CAAGGAGGTC
2041 TAGCTCTGGC GAGTCTTTCA CGAAAAGGGA GGGATCTATA TAACACTTTA TAGCCATTGA
2101 CTGTAACCCA CCTATCCCAA TTTAAGTCAT ATCTTCCTGT ATATGGTAAG GGGGCATCTG
2161 TTGGTCTGTA GATGTAAGGT CCCCTATAAG TCCCTGGTTG CCACCACCTG TCTCCTATTT
2221 TGACAAAAAC ACTCTTTTTT CCCTTTTTTA CTTCTAGGCC TGTGGTCAAT AGTCCTTGCA
2281 CCTGTTCTTC AATTGAGGTT GAGCGTCTCT TTCTATTTTC TATTCCCATT TCTAACTTCT
2341 GAATTTGAGT AAAAATAGTA CTAAAAGATA ATGATTCATT TCTTAACATA GTAACTAATA
2401 ATCTACCTAT TGGATTGGTC TTATTGGTAA AAATATAATT TTTAGCAAGC ATTCTTATTT
2461 CTATTTCTGA AGGACAAAAT CGATGCGGCT TGTAAGAGGA AGTTGGCTGT GGTCCTTGCC
2521 TCAGGAGGAA GGTCGAGTTC TCCGAATTGT TTAGATTGTA ATCTTGCACA GAAGAGCTAT
2581 TAAAAGAGTC AAGGGTGAGA GCCCTGCGAG CACGAACCGC AACTTCCCCC AATAGCCCCA
2641 GGCAAAGCAG AGCTATGCCA AGTTTGCAGC AGAGAATGAA TATGTCTTTG TCTGATGGGC
2701 TCATCCGTTT GTGCGCAGAC GGGTCGTCCT TGGTGGGAAA CAACCCCTTG GCTGCTTCTC
2761 CCCTAGGTGT AGGACACTCT CGGGAGTTCA ACCATTTCTG CCCAAGCTCA GATCTGAGCT
2821 TTAATGCGGT AGTTTATCAC AGTTAAATTG CTAACGCAGT CAGGCACCGT GTATGAAATC
2881 TAACAATGCG CTCATCGTCA TCCTCGGCAC CGTCACCCTG GATGCTGTAG GCATAGGCTT
2941 GGTTATGCCG GTACTGCCGG GCCTCTTGCG GGATATCGTC CATTCCGACA GCATCGCCAG
3001 TCACTATGGC GTGCTGCTAG CGCTCTTCCG CTTCCTCGCT CACTGACTCG CTGCGCTCGG
3061 TCGTTCGGCT GCGGCGAGCG GTATCAGCTC ACTCAAAGGC GGTAATACGG TTATCCACAG
3121 AATCAGGGGA TAACGCAGGA AAGAACATGT GAGCAAAAGG CCAGCAAAAG GCCAGGAACC
3181 GTAAAAAGGC CGCGTTGCTG GCGTTTTTCC ATAGGCTCCG CCCCCCTGAC GAGCATCACA
3241 AAAATCGACG CTCAAGTCAG AGGTGGCGAA ACCCGACAGG ACTATAAAGA TACCAGGCGT
3301 TTCCCCCTGG AAGCTCCCTC GTGCGCTCTC CTGTTCCGAC CCTGCCGCTT ACCGGATACC
3361 TGTCCGCCTT TCTCCCTTCG GGAAGCGTGG CGCTTTCTCA TAGCTCACGC TGTAGGTATC
3421 TCAGTTCGGT GTAGGTCGTT CGCTCCAAGC TGGGCTGTGT GCACGAACCC CCCGTTCAGC
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3481 CCGACCGCTG CGCCTTATCC GGTAACTATC GTCTTGAGTC CAACCCGGTA AGACACGACT
3541 TATCGCCACT GGCAGCAGCC ACTGGTAACA GGATTAGCAG AGCGAGGTAT GTAGGCGGTG
3601 CTACAGAGTT CTTGAAGTGG TGGCCTAACT ACGGCTACAC TAGAAGGACA GTATTTGGTA
3661 TCTGCGCTCT GCTGAAGCCA GTTACCTTCG GAAAAAGAGT TGGTAGCTCT TGATCCGGCA
3721 AACAAACCAC CGCTGGTAGC GGTGGTTTTT TTGTTTGCAA GCAGCAGATT ACGCGCAGAA
3781 AAAAAGGATC TCAAGAAGAT CCTTTGATCT TTTCTACGGG GTCTGACGCT CAGTGGAACG
3841 AAAACTCACG TTAAGGGATT TTGGTCATGA GATTATCAAA AAGGATCTTC ACCTAGATCC
3901 TTTTAAATTA AAAATGAAGT TTTAAATCAA TCTAAAGTAT ATATGAGTAA ACTTGGTCTG
3961 ACAGTTACCA ATGCTTAATC AGTGAGGCAC CTATCTCAGC GATCTGTCTA TTTCGTTCAT
4021 CCATAGTTGC CTGACTCCCC GTCGTGTAGA TAACTACGAT ACGGGAGGGC TTACCATCTG
4081 GCCCCAGTGC TGCAATGATA CCGCGAGACC CACGCTCACC GGCTCCAGAT TTATCAGCAA
4141 TAAACCAGCC AGCCGGAAGG GCCGAGCGCA GAAGTGGTCC TGCAACTTTA TCCGCCTCCA
4201 TCCAGTCTAT TAATTGTTGC CGGGAAGCTA GAGTAAGTAG TTCGCCAGTT AATAGTTTGC
4261 GCAACGTTGT TGCCATTGCT ACAGGCATCG TGGTGTCACG CTCGTCGTTT GGTATGGCTT
4321 CATTCAGCTC CGGTTCCCAA CGATCAAGGC GAGTTACATG ATCCCCCATG TTGTGCAAAA
4381 AAGCGGTTAG CTCCTTCGGT CCTCCGATCG TTGTCAGAAG TAAGTTGGCC GCAGTGTTAT
4441 CACTCATGGT TATGGCAGCA CTGCATAATT CTCTTACTGT CATGCCATCC GTAAGATGCT
4501 TTTCTGTGAC TGGTGAGTAC TCAACCAAGT CATTCTGAGA ATAGTGTATG CGGCGACCGA
4561 GTTGCTCTTG CCCGGCGTCA ACACGGGATA TACCGCGCC ACATAGCAGA ACTTTAAAAG
4621 TGCTCATCAT TGGAAAACGT TCTTCGGGGC GAAAACTCTC AAGGATCTTA CCGCTGTTGA
4681 GATCCAGTTC GATGTAACCC ACTCGTGCAC CCAACTGATC TTCAGCATCT TTTACTTTCA
4741 CCAGCGTTTC TGGGTGAGCA AAAACAGGAA GGCAAAATGC CGCAAAAAAG GGAATAAGGG
4801 CGACACGGAA ATGTTGAATA CTCATACTCT TCCTTTTTCA ATATTATTGA AGCATTTATC
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4921 GGGTTCCGCG CACATTTCCC CGAAAAGTGC CACCTGACGT CTAAGAAACC ATTATTATCA
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 7501 GAGGAAGAAG GAGCCGTCGG AGTCCAGCAC GGGAGGCGTG GTCTTGTAGT TGTTCTCCGG
 7561 CTGCCCATTG CTCTCCCACT CCACGGCGAT GTCGCTGGGA TAGAAGCCTT TGACCAGGCA
 7621 GGTCAGGCTG ACCTGGTTCT TGGTCAGCTC ATCCCGGGAT GGGGGCAGGG TGTACACCTG
 7681 TGGTTCTCGG GGCTGCCCTT TGGCTTTGGA GATGGTTTTC TCGATGGGGG CTGGGAGGGC
 7741 TTTGTTGGAG ACCTTGCACT TGTACTCCTT GCCATTCAGC CAGTCCTGGT GCAGGACGGT
 7801 GAGGACGCTG ACCACACGGT ACGTGCTGTT GTACTGCTCC TCCCGCGGCT TTGTCTTGGC
 7861 ATTATGCACC TCCACGCCGT CCACGTACCA GTTGAACTTG ACCTCAGGGT CTTCGTGGCT
 7921 CACGTCCACC ACCACGCATG TGACCTCAGG GGTCCGGGAG ATCATGAGGG TGTCCTTGGG
 7981 TTTTGGGGGG AAGAGGAAGA CTGACGGTCC CCCCAGGAGT TCAGGTGCTG GGCACGGTGG
 8041 GCATGTGTGA GTTTTGTCAC AAGATTTGGG CTCAACTTTC TTGTCCACCT TGGTGTTGCT
 8101 GGGCTTGTGA TTCACGTTGC AGATGTAGGT CTGGGTGCCC AAGCTGCTGG AGGGCACGGT
 8161 CACCACGCTG CTGAGGGAGT AGAGTCCTGA GGACTGTAGG ACAGCCGGGA AGGTGTGCAC
 8221 GCCGCTGGTC AGGGCGCCTG AGTTCCACGA CACCGTCACC GGTTCGGGGA AGTAGTCCTT
 8281 GACCAGGCAG CCCAGGGCCG CTGTGCCCCC AGAGGTGCTC TTGGAGGAGG GTGCCAGGGG
 8341 GAAGACCGAT GGGCCCTTGG TGGAAGCTGA GGAGACGGTG ACCGTGGTCC CTTGGCCCCA
 8401 GACGTCCATA CCGTAGTAGA AGTTCCCCAG TCTTGCACAG TAATACACAG CAGTGTCCTC
 8461 GGCTCTCAGG CTGTTCATTT GAAGATACAA GGAGTTCTTG GCATTGTCTC TGGAGATGGT
 8521 GAATCGGCCC TTCACGGAGT CTGCATAGTA TGTGGCACCA CGAGTATCAA TAACTGATAT
 8581 CCACTCCAGA CCTTTTCCTG GAGCCTGGCG AACCCAGTGC ATAGCAAAGC TACTGAAGGT
 8641 GAATCCAGAG GCTGCACAGG AGAGTCTCAG GGACCCCCCA GGCTTTACCA AGCCTCCCCC
 8701 AGACTGCACC AGCTGAACCT CACACTGGAC ACCTTTTAAT ATAGCAACAA GGAAAACCCA
 8761 GCTCAGCCCA AACTCCATAA GGGCGAATTC CACCACACTG GACTAGTGGA TCCGAGCTCG
 8821 GTACCAAGCT TAAGCCTGTG GAGAGAAAGG AACAGAAAAC GAAACAAAGA CGTAGAGTTG
 8881 AGCAAGCAGG GTCAGGCAAA GCGTGGAGAG CCGGCTGAGT CTAGGTAGGC TCCAAGGGAG
 8941 CGCCGGACAA AGGCCCGGTC TCGACCTGAG CTTTAAACTT ACCTGTGGCC ACACGTGCAA
 9001 TTGCTATAGT GAGTCGTATT AATTTCGATA AGCCAGTAAG CAGTGGGTTC TCTAGTTAGC
 9061 CAGAGAGCTC TGCTTATATA GACCTCCCAC CGTACACGCC TACCGCCCAT TTGCGTCAAT
 9121 GGGGCGGAGT TGTTACGACA TTTTGGAAAG TCCCGTTGAT TTTGGTGCCA AAACAAACTC
 9181 CCATTGACGT CAATGGGGTG GAGACTTGGA AATCCCCGTG AGTCAAACCG CTATCCACGC
 9241 CCATTGATGT ACTGCCAAAA CCGCATCACC ATGGTAATAG CGATGACTAA TACGTAGATG
 9301 TACTGCCAAG TAGGAAAGTC CCATAAGGTC ATGTACTGGG CATAATGCCA GGCGGGCCAT
 9361 TTACCGTCAT TGACGTCAAT AGGGGGCGTA CTTGGCATAT GATACACTTG ATGTACTGCC
 9421 AAGTGGGCAG TTTACCGTAA ATACTCCACC CATTGACGTC AATGGAAAGT CCCTATTGGC
 9481 GTTACTATGG GAACATACGT CATTATTGAC GTCAATGGGC GGGGGTCGTT GGGCGGTCAG
 9541 CCAGGCGGGC CATTTACCGT AAGTTATGTA ACGCGGAACT CCATATATGG GCTATGAACT
 9601 AATGACCCCG TAATTGATTA CTATTAATAA CTAGTCAATA ATCAATGTCA ACGCGTATAT
 9661 CTGGCCCGTA CATCGGTAGC TGAGGGTTTA AACGGCGCGC GGCCGGCCGG TACCACGCGT
 9721 TGGCCACATA TGGCGGCCGC TCGCGATTAA TTAATCGCGA TGGCCACATA TGGAGCTCTC
 9781 TAGAGCTTGT CGACAGATCC CCCTCTTCAT TTCTTTATGT TTTAAATGCA CTGACCTCCC
 9841 ACATTCCCTT TTTAGTAAAA TATTCAGAAA TAATTTAAAT ACATCATTGC AATGAAAATA
 9901 AATGTTTTTT ATTAGGCAGA ATCCAGATGC TCAAGGCCCT TCATAATATC CCCCAGTTTA
 9961 GTAGTTGGAC TTAGGGAACA AAGGAACCTT TAATAGAAAT TGGACAGCAA GAAAGCGAGG
10021 GGGATCTGGA TCCTCCGGAG GGCCCCTTCT CCCTCTAACA CTCTCCCCTG TTGAAGCTCT
10081 TTGTGACGGG CGAGCTCAGG CCCTGATGGG TGACTTCGCA GGCGTAGACT TTGTGTTTCT
10141 CGTAGTCTGC TTTGCTCAGC GTCAGGGTGC TGCTGAGGCT GTAGGTGCTG TCCTTGCTGT
10201 CCTGCTCTGT GACACTCTCC TGGGAGTTAC CCGATTGGAG GGCGTTATCC ACCTTCCACT
10261 GTACTTTGGC CTCTCTGGGA TAGAAGTTAT TCAGCAGGCA CACAACAGAG GCAGTTCCAG
10321 ATTTCAACTG CTCATCAGAT GGCGGGAAGA TGAAGACAGA TGGTGCAGCC ACTGTACGTT
10381 TGATCTCCAC CTTGGTCCCT TGGCCGAAAG TGTGAGGTAA ACGACTACTC TGATGACAGT
10441 AATACACTGC GAAATCTTCA GGCTCCAGTC TACTGATGGT GAGGGTGAAA TCTGTCCCAG
10501 ATCCACTGCC ACTGAACCTA TCGGGGATCC CTGAGAGGGA CTGGGATGCA TACTTGATGA
10561 GAAGCCTTGG AGCCTGACCT GGTTTCTGCT GGTACCAGTG TAAGCTACTA CCAATGCTCT
10621 GACTGGCCCG GCAGGAGAGG GTGGCTCTCT CGCCTGGAGA CACAGACAGG GTACCTGGGC
10681 TCTGAGTCAG CACAATTTCA CCCCTGGAGG CTGGAACCCA GAGCAGCAGA AACCCAATGA
10741 GTTGTGATGG CGACATGTTA AACGCTAGAA TTCTTAAGCC TGTGGAGAGA AAGGAACAGA
10801 AAACGAAACA AAGACGTAGA GTTGAGCAAG CAGGGTCAGG CAAAGCGTGG AGAGCCGGCT
10861 GAGTCTAGGT AGGCTCCAAG GGAGCGCCGG ACAAAGGCCC GGTCTCGACC TGAGCTTTAA
10921 ACTTACCTGT GGCCACACGT GCAATTGCTA TAGTGAGTCG TATTAATTTC GATAAGCCAG
10981 TAAGCAGTGG GTTCTCTAGT TAGCCAGAGA GCTCTGCTTA TATAGACCTC CCACCGTACA
11041 CGCCTACCGC CCATTTGCGT CAATGGGGCG GAGTTGTTAC GACATTTTGG AAAGTCCCGT
11101 TGATTTTGGT GCCAAAACAA ACTCCCATTG ACGTCAATGG GGTGGAGACT TGGAAATCCC
11161 CGTGAGTCAA ACCGCTATCC ACGCCCATTG ATGTACTGCC AAAACCGCAT CACCATGGTA
11221 ATAGCGATGA CTAATACGTA GATGTACTGC CAAGTAGGAA AGTCCCATAA GGTCATGTAC
11281 TGGGCATAAT GCCAGGCGGG CCATTTACCG TCATTGACGT CAATAGGGGG CGTACTTGGC
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11341 ATATGATACA CTTGATGTAC TGCCAAGTGG GCAGTTTACC GTAAATACTC CACCCATTGA
11401 CGTCAATGGA AAGTCCCTAT TGGCGTTACT ATGGGAACAT ACGTCATTAT TGACGTCAAT
11461 GGGCGGGGGT CGTTGGGCGG TCAGCCAGGC GGGCCATTTA CCGTAAGTTA TGTAACGCGG
11521 AACTCCATAT ATGGGCTATG AACTAATGAC CCCGTAATTG ATTACTATTA ATAACTAGTC
11581 AATAATCAAT GTCAACGCGT ATATCTGGCC CGTACATCG TAACTAGTCG GACCGCCGCG
11641 GACTAGTGCC CGGGCCACCG GTGCTCGAAG CTTGGATCGA TCCAGACATG ATAAGATACA
11701 TTGATGAGTT TGGACAAACC ACAACTAGAA TGCAGTGAAA AAAATGCTTT ATTTGTGAAA
11761 TTTGTGATGC TATTGCTTTA TTTGTAACCA TTATAAGCTG CAATAAACAA GTTAACAACA
11821 ACAATTGCAT TCATTTTATG TTTCAGGTTC AGGGGGAGGT GTGGGAGGTT TTTTAAAGCA
11881 AGTAAAACCT CTACAAATGT GGTATGGCTG ATTATGATCT CTAGTCAAG
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(SEQ ID NO: 36)

The present invention further provides, in part, isolated plasmids which exhibit high levels of expression of anti-IL-23 p19 heavy and light chains. One plasmid is pAIL23V1-K. The sequence of the pAIL23V1-K plasmid is set forth below:

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   1 GGCACTATAC ATCAAATATT CCTTATTAAC CCCTTTACAA ATTAAAAAGC TAAAGGTACA
  61 CAATTTTTGA GCATAGTTAT TAATAGCAGA CACTCTATGC CTGTGTGGAG TAAGAAAAAA
 121 CAGTATGTTA TGATTATAAC TGTTATGCCT ACTTATAAAG GTTACAGAAT ATTTTTCCAT
 181 AATTTTCTTG TATAGCAGTG CAGCTTTTTC CTTTGTGGTG TAAATAGCAA AGCAAGCAAG
 241 AGTTCTATTA CTAAACACAG CATGACTCAA AAAACTTAGC AATTCTGAAG GAAAGTCCTT
 301 GGGGTCTTCT ACCTTTCTCT TCTTTTTTGG AGGAGTAGAA TGTTGAGAGT CAGCAGTAGC
 361 CTCATCATCA CTAGATGGCA TTTCTTCTGA GCAAAACAGG TTTTCCTCAT TAAAGGCATT
 421 CCACCACTGC TCCCATTCAT CAGTTCCATA GGTTGGAATC TAAAATACAC AAACAATTAG
 481 AATCAGTAGT TTAACACATT ATACACTTAA AAATTTTATA TTTACCTTAG AGCTTTAAAT
 541 CTCTGTAGGT AGTTTGTCCA ATTATGTCAC ACCACAGAAG TAAGGTTCCT TCACAAAGAT
 601 CGATCTAAAG CCAGCAAAAG TCCCATGGTC TTATAAAAAT GCATAGCTTT AGGAGGGGAG
 661 CAGAGAACTT GAAAGCATCT TCCTGTTAGT CTTTCTTCTC GTAGACTTCA AACTTATACT
 721 TGATGCCTTT TTCCTCCTGG ACCTCAGAGA GGACGCCTGG GTATTCTGGG AGAAGTTTAT
 781 ATTTCCCCAA ATCAATTTCT GGGAAAAACG TGTCACTTTC AAATTCCTGC ATGATCCTTG
 841 TCACAAAGAG TCTGAGGTGG CCTGGTTGAT TCATGGCTTC CTGGTAAACA GAACTGCCTC
 901 CGACTATCCA AACCATGTCT ACTTTACTTG CCAATTCCGG TTGTTCAATA AGTCTTAAGG
 961 CATCATCCAA ACTTTTGGCA AGAAAATGAG CTCCTCGTGG TGGTTCTTTG AGTTCTCTAC
1021 TGAGAACTAT ATTAATTCTG TCCTTTAAAG GTCGATTCTT CTCAGGAATG GAGAACCAGG
1081 TTTTCCTACC CATAATCACC AGATTCTGTT TACCTTCCAC TGAAGAGGTT GTGGTCATTC
1141 TTTGGAAGTA CTTGAACTCG TTCCTGAGCG GAGGCCAGGG TAGGTCTCCG TTCTTGCCAA
1201 TCCCCATATT TTGGGACACG GCGACGATGC AGTTCAATGG TCGAACCATG ATGGCAGCGG
1261 GGATAAAATC CTACCAGCCT TCACGCTAGG ATTGCCGTCA AGTTTGGCGC GAAATCGCAG
1321 CCCTGAGCTG TCCCCCCCCC CAAGCTCAGA TCTGAGCTTG GTCCCTATGG TGAGTCCGTT
1381 CCGCTCTTGT GATGATAGCC AGACAAGAAA GAGACAATAC AAGACAAACA CCAAATAGTA
1441 GAAATAGAGA CAAGGGTCAC TTATCCGAGG GTCCCTGTTC GGGCGCCAGC TGCCGCAGTC
1501 GGCCGACCTG AGGGTCGCCG GGGTCTGCGG GGGGACCCTC TGGAAAGTGA AGGATAAGTG
1561 ACGAGCGGAG ACGGGATGGC GAACAGACAC AAACACACAA GAGGTGAATG TTAGGACTGT
1621 TGCAAGTTTA CTCAAAAAAT CAGCACTCTT TTATATCTTG GTTTACATAA GCATTTACAT
1681 AAGATTTGGA TAAATTCCAA AAGAACATAG GAAAATAGAA CACTCAGAGC TCAGATCAGA
1741 ACCTTTGATA CCAAACCAAG TCAGGAAACC ACTTGTCTCA CATCCTCGTT TTAAGAACAG
1801 TTTGTAACCA AAAACTTACT TAAGCCCTGG GAACCGCAAG GTTGGGCCAA TAAAGGCTAT
1861 TCATAATAAC TCATGCCATG AGTTTTTGCA GAATAATGTT CTATTAGTCC AGCCACTGTC
1921 CCCTCCTTGG TATGGAAAAT CTTTCCCCAA AAGTGCATTC CTGTTCCTAG ATAAATATAA
1981 TCATGTACCT GTTGTTTCAT GTCGTCTTTT TCTTCTTGAG ACAACATACA CCAAGGAGGT
2041 CTAGCTCTGG CGAGTCTTTC ACGAAAAGGG AGGGATCTAT ATAACACTTT ATAGCCATTG
2101 ACTGTAACCC ACCTATCCCA ATTTAAGTCA TATCTTCCTG TATATGGTAA GGGGGCATCT
2161 GTTGGTCTGT AGATGTAAGG TCCCCTATAA GTCCCTGGTT GCCACCACCT GTCTCCTATT
2221 TTGACAAAAA CACTCTTTTT TCCCTTTTTT ACTTCTAGGC CTGTGGTCAA TAGTCCTTGC
2281 ACCTGTTCTT CAATTGAGGT TGAGCGTCTC TTTCTATTTT CTATTCCCAT TTCTAACTTC
2341 TGAATTTGAG TAAAAATAGT ACTAAAAGAT AATGATTCAT TTCTTAACAT AGTAACTAAT
2401 AATCTACCTA TTGGATTGGT CTTATTGGTA AAAATATAAT TTTTAGCAAG CATTCTTATT
2461 TCTATTTCTG AAGGACAAAA TCGATGCGGC TTGTAAGAGG AAGTTGGCTG TGGTCCTTGC
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2521  CTCAGGAGGA AGGTCGAGTT CTCCGAATTG TTTAGATTGT AATCTTGCAC AGAAGAGCTA
2581  TTAAAAGAGT CAAGGGTGAG AGCCCTGCGA GCACGAACCG CAACTTCCCC CAATAGCCCC
2641  AGGCAAAGCA GAGCTATGCC AAGTTTGCAG CAGAGAATGA ATATGTCTTT GTCTGATGGG
2701  CTCATCCGTT TGTGCGCAGA CGGGTCGTCC TTGGTGGGAA ACAACCCCTT GGCTGCTTCT
2761  CCCCTAGGTG TAGGACACTC TCGGGAGTTC AACCATTTCT GCCCAAGCTC AGATCTGAGC
2821  TTTAATGCGG TAGTTTATCA CAGTTAAATT GCTAACGCAG TCAGGCACCG TGTATGAAAT
2881  CTAACAATGC GCTCATCGTC ATCCTCGGCA CCGTCACCCT GGATGCTGTA GGCATAGGCT
2941  TGGTTATGCC GGTACTGCCG GGCCTCTTGC GGGATATCGT CCATTCCGAC AGCATCGCCA
3001  GTCACTATGG CGTGCTGCTA GCGCTCTTCC GCTTCCTCGC TCACTGACTC GCTGCGCTCG
3061  GTCGTTCGGC TGCGGCGAGC GGTATCAGCT CACTCAAAGG CGGTAATACG GTTATCCACA
3121  GAATCAGGGG ATAACGCAGG AAAGAACATG TGAGCAAAAG GCCAGCAAAA GGCCAGGAAC
3181  CGTAAAAAGG CCGCGTTGCT GGCGTTTTTC CATAGGCTCC GCCCCCCTGA CGAGCATCAC
3241  AAAAATCGAC GCTCAAGTCA GAGGTGGCGA AACCCGACAG GACTATAAAG ATACCAGGCG
3301  TTTCCCCCTG GAAGCTCCCT CGTGCGCTCT CCTGTTCCGA CCCTGCCGCT TACCGGATAC
3361  CTGTCCGCCT TTCTCCCTTC GGGAAGCGTG GCGCTTTCTC ATAGCTCACG CTGTAGGTAT
3421  CTCAGTTCGG TGTAGGTCGT TCGCTCCAAG CTGGGCTGTG TGCACGAACC CCCCGTTCAG
3481  CCCGACCGCT GCGCCTTATC CGGTAACTAT CGTCTTGAGT CCAACCCGGT AAGACACGAC
3541  TTATCGCCAC TGGCAGCAGC CACTGGTAAC AGGATTAGCA GAGCGAGGTA TGTAGGCGGT
3601  GCTACAGAGT TCTTGAAGTG GTGGCCTAAC TACGGCTACA CTAGAAGGAC AGTATTTGGT
3661  ATCTGCGCTC TGCTGAAGCC AGTTACCTTC GGAAAAAGAG TTGGTAGCTC TTGATCCGGC
3721  AAACAAACCA CCGCTGGTAG CGGTGGTTTT TTTGTTTGCA AGCAGCAGAT TACGCGCAGA
3781  AAAAAAGGAT CTCAAGAAGA TCCTTTGATC TTTTCTACGG GGTCTGACGC TCAGTGGAAC
3841  GAAAACTCAC GTTAAGGGAT TTTGGTCATG AGATTATCAA AAAGGATCTT CACCTAGATC
3901  CTTTTAAATT AAAAATGAAG TTTTAAATCA ATCTAAAGTA TATATGAGTA AACTTGGTCT
3961  GACAGTTACC AATGCTTAAT CAGTGAGGCA CCTATCTCAG CGATCTGTCT ATTTCGTTCA
4021  TCCATAGTTG CCTGACTCCC CGTCGTGTAG ATAACTACGA TACGGGAGGG CTTACCATCT
4081  GGCCCCAGTG CTGCAATGAT ACCGCGAGAC CCACGCTCAC CGGCTCCAGA TTTATCAGCA
4141  ATAAACCAGC CAGCCGGAAG GGCCGAGCGC AGAAGTGGTC CTGCAACTTT ATCCGCCTCC
4201  ATCCAGTCTA TTAATTGTTG CCGGGAAGCT AGAGTAAGTA GTTCGCCAGT TAATAGTTTG
4261  CGCAACGTTG TTGCCATTGC TACAGGCATC GTGGTGTCAC GCTCGTCGTT TGGTATGGCT
4321  TCATTCAGCT CCGGTTCCCA ACGATCAAGG CGAGTTACAT GATCCCCCAT GTTGTGCAAA
4381  AAAGCGGTTA GCTCCTTCGG TCCTCCGATC GTTGTCAGAA GTAAGTTGGC CGCAGTGTTA
4441  TCACTCATGG TTATGGCAGC ACTGCATAAT TCTCTTACTG TCATGCCATC CGTAAGATGC
4501  TTTTCTGTGA CTGGTGAGTA CTCAACCAAG TCATTCTGAG AATAGTGTAT GCGGCGACCG
4561  AGTTGCTCTT GCCCGGCGTC AACACGGGAT AATACCGCGC CACATAGCAG AACTTTAAAA
4621  GTGCTCATCA TTGGAAAACG TTCTTCGGGG CGAAAACTCT CAAGGATCTT ACCGCTGTTG
4681  AGATCCAGTT CGATGTAACC CACTCGTGCA CCCAACTGAT CTTCAGCATC TTTTACTTTC
4741  ACCAGCGTTT CTGGGTGAGC AAAAACAGGA AGGCAAAATG CCGCAAAAAA GGGAATAAGG
4801  GCGACACGGA AATGTTGAAT ACTCATACTC TTCCTTTTTC AATATTATTG AAGCATTTAT
4861  CAGGGTTATT GTCTCATGAG CGGATACATA TTTGAATGTA TTTAGAAAAA TAAACAAATA
4921  GGGGTTCCGC GCACATTTCC CCGAAAAGTG CCACCTGACG TCTAAGAGAC CATTATTATC
4981  ATGACATTAA CCTATAAAAA TAGGCGTATC ACGAGGCCCT TTCGTCTTCA AGAATTGTCT
5041  AGAGGCGCGC CGTTTAAACC CTCAGCTACC GATGTACGGG CCAGATATAC GCGTTGACAT
5101  TGATTATTGA CTAGTTATTA ATAGTAATCA ATTACGGGGT CATTAGTTCA TAGCCCATAT
5161  ATGGAGTTCC GCGTTACATA ACTTACGGTA AATGGCCCGC CTGGCTGACC GCCCAACGAC
5221  CCCCGCCCAT TGACGTCAAT AATGACGTAT GTTCCCATAG TAACGCCAAT AGGGACTTTC
5281  CATTGACGTC AATGGGTGGA CTATTTACGG TAAACTGCCC ACTTGGCAGT ACATCAAGTG
5341  TATCATATGC CAAGTACGCC CCCTATTGAC GTCAATGACG GTAAATGGCC CGCCTGGCAT
5401  TATGCCCAGT ACATGACCTT ATGGGACTTT CCTACTTGGC AGTACATCTA CGTATTAGTC
5461  ATCGCTATTA CCATGGTGAT GCGGTTTTGG CAGTACATCA ATGGGCGTGG ATAGCGGTTT
5521  GACTCACGGG GATTTCCAAG TCTCCACCCC ATTGACGTCA ATGGGAGTTT GTTTTGGCAC
5581  CAAAATCAAC GGGACTTTCC AAAATGTCGT AACAACTCCG CCCCATTGAC GCAAATGGGC
5641  GGTAGGCGTG TACGGTGGGA GGTCTATATA AGCAGAGCTC TCTGGCTAAC TAGAGAACCC
5701  ACTGCTTACT GGCTTATCGA AATTAATACG ACTCACTATA GCAATTGCAC GTGTGGCCAC
5761  AGGTAAGTTT AAAGCTCAGG TCGAGACCGG GCCTTTGTCC GGCGCTCCCT TGGAGCCTAC
5821  CTAGACTCAG CCGGCTCTCC ACGCTTTGCC TGACCCTGCT TGCTCAACTC TACGTCTTTG
5881  TTTCGTTTTC TGTTCCTTTC TCTCCACAGG CTTAAGCTCG AGGCCGCCAC CATGGCTGTG
5941  CTGGGGCTGC TGTTCTGCCT GGTGACATTC CCAAGCTGTG TGCTGTCCCA GGTGCAGCTG
6001  GTGCAGTCTG GCGCTGAGGT GAAGAAGCCT GGCGCCTCCG TGAAGGTCTC CTGCAAGGCT
6061  TCTGGCTACA TCTTCATCAC CTACTGGATG ACCTGGGTGC GGCAGGCCCC TGGCCAGGGG
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6121  CTGGAGTGGA TGGGCCAGAT CTTCCCTGCC AGCGGCTCTG CAGACTACAA CGAGAAGTTC
6181  GAAGGCAGAG TCACCATGAC CACAGACACA TCCACCAGCA CAGCCTACAT GGAGCTGAGG
6241  AGCCTGAGAT CTGACGACAC CGCCGTGTAT TACTGTGCCA GAGGCGGTGG CGGATTCGCT
6301  TACTGGGGCC AGGGCACCCT GGTCACCGTC TCCAGCGCTA GCACCAAGGG CCCATCGGTC
6361  TTCCCCCTGG CACCCTCCTC CAAGAGCACC TCTGGGGGCA CAGCGGCCCT GGGCTGCCTG
6421  GTCAAGGACT ACTTCCCCGA ACCGGTGACG GTGTCGTGGA ACTCAGGCGC CCTGACCAGC
6481  GGCGTGCACA CCTTCCCGGC TGTCCTACAG TCCTCAGGAC TCTACTCCCT CAGCAGCGTG
6541  GTGACCGTGC CCTCCAGCAG CTTGGGCACC CAGACCTACA TCTGCAACGT GAATCACAAG
6601  CCCAGCAACA CCAAGGTGGA CAAGAAAGTT GAGCCCAAAT CTTGTGACAA AACTCACACA
6661  TGCCCACCGT GCCCAGCACC TGAACTCCTG GGGGGACCGT CAGTCTTCCT CTTCCCCCCA
6721  AAACCCAAGG ACACCCTCAT GATCTCCCGG ACCCCTGAGG TCACATGCGT GGTGGTGGAC
6781  GTGAGCCACG AAGACCCTGA GGTCAAGTTC AACTGGTACG TGGACGGCGT GGAGGTGCAT
6841  AATGCCAAGA CAAAGCCGCG GGAGGAGCAG TACAACAGCA CGTACCGTGT GGTCAGCGTC
6901  CTCACCGTCC TGCACCAGGA CTGGCTGAAT GGCAAGGAGT ACAAGTGCAA GGTCTCCAAC
6961  AAAGCCCTCC CAGCCCCCAT CGAGAAAACC ATCTCCAAAG CCAAAGGGCA GCCCCGAGAA
7021  CCACAGGTGT ACACCCTGCC CCCATCCCGG GATGAGCTGA CCAAGAACCA GGTCAGCCTG
7081  ACCTGCCTGG TCAAAGGCTT CTATCCCAGC GACATCGCCG TGGAGTGGGA GAGCAATGGG
7141  CAGCCGGAGA ACAACTACAA GACCACGCCT CCCGTGCTGG ACTCCGACGG CTCCTTCTTC
7201  CTCTACAGCA AGCTCACCGT GGACAAGAGC AGGTGGCAGC AGGGGAACGT CTTCTCATGC
7261  TCCGTGATGC ATGAGGCTCT GCACAACCAC TACACGCAGA AGAGCCTCTC CCTGTCTCCG
7321  GGTAAATGAA TCGATGATTC TAGATACGGG TCCGGAGGAT CCAGATCCCC CTCGCTTTCT
7381  TGCTGTCCAA TTTCTATTAA AGGTTCCTTT GTTCCCTAAG TCCAACTACT AAACTGGGGG
7441  ATATTATGAA GGGCCTTGAG CATCTGGATT CTGCCTAATA AAAAACATTT ATTTTCATTG
7501  CAATGATGTA TTTAAATTAT TTCTGAATAT TTTACTAAAA AGGGAATGTG GGAGGTCAGT
7561  GCATTTAAAA CATAAAGAAA TGAAGAGGGG GATCTGTCGA CAAGCTCTAG AGAGCTCACG
7621  CGTTGATCAT GTACAGGCCG GCCAAGCTTT CGACTAGCTT GGCACGCCAG AAATCCGCGC
7681  GGTGGTTTTT GGGGGTCGGG GGTGTTTGGC AGCCACAGAC GCCCGGTGTT CGTGTCGCGC
7741  CAGTACATGC GGTCCATGCC CAGGCCATCC AAAAACCATG GGTCTGTCTG CTCAGTCCAG
7801  TCGTGGACCT GACCCCACGC AACGCCCAAA ATAATAACCC CCACGAACCA TAAACCATTC
7861  CCCATGGGGG ACCCCGTCCC TAACCCACGG GGCCAGTGGC TATGGCAGGG CCTGCCGCCC
7921  CGACGTTGGC TGCGAGCCCT GGGCCTTCAC CCGAACTTGG GGGGTGGGGT GGGGAAAAGG
7981  AAGAAACGCG GGCGTATTGG CCCCAATGGG GTCTCGGTGG GGTATCGACA GAGTGCCAGC
8041  CCTGGGACCG AACCCCGCGT TTATGAACAA ACGACCCAAC ACCCGTGCGT TTTATTCTGT
8101  CTTTTTATTG CCGTCATAGC GCGGGTTCCT TCCGGTATTG TCTCCTTCCG TGTTTCAGTT
8161  AGCCTCCCCC ATCTCCCGAT CCGGACGAGT GCTGGGGCGT CGGTTTCCAC TATCGGCGAG
8221  TACTTCTACA CAGCCATCGG TCCAGACGGC CGCGCTTCTG CGGGCGATTT GTGTACGCCC
8281  GACAGTCCCG GCTCCGGATC GGACGATTGC GTCGCATCGA CCCTGCGCCC AAGCTGCATC
8341  ATCGAAATTG CCGTCAACCA AGCTCTGATA GAGTTGGTCA AGACCAATGC GGAGCATATA
8401  CGCCCGGAGC CGCGGCGATC CTGCAAGCTC CGGATGCCTC CGCTCGAAGT AGCGCGTCTG
8461  CTGCTCCATA CAAGCCAACC ACGGCCTCCA GAAGAAGATG TTGGCGACCT CGTATTGGGA
8521  ATCCCCGAAC ATCGCCTCGC TCCAGTCAAT GACCGCTGTT ATGCGGCCAT TGTCCGTCAG
8581  GACATTGTTG GAGCCGAAAT CCGCGTGCAC GAGGTGCCGG ACTTCGGGGC AGTCCTCGGC
8641  CCAAAGCATC AGCTCATCGA GAGCCTGCGC GACGGACGCA CTGACGGTGT CGTCCATCAC
8701  AGTTTGCCAG TGATACACAT GGGGATCAGC AATCGCGCAT ATGAAATCAC GCCATGTAGT
8761  GTATTGACCG ATTCCTTGCG GTCCGAATGG GCCGAACCCG CTCGTCTGGC TAAGATCGGC
8821  CGCAGCGATC GCATCCATGG CCTCCGCGAC CGGCTGCAGA ACAGCGGGCA GTTCGGTTTC
8881  AGGCAGGTCT TGCAACGTGA CACCCTGTGC ACGGCGGGAG ATGCAATAGG TCAGGCTCTC
8941  GCTGAATTCC CCAATGTCAA GCACTTCCGG AATCGGGAGC GCGGCCGATG CAAAGTGCCG
9001  ATAAACATAA CGATCTTTGT AGAAACCATC GGCGCAGCTA TTTACCCGCA GGACATATCC
9061  ACGCCCTCCT ACATCGAAGC TGAAAGCACG AGATTCTTCG CCCTCCGAGA GCTGCATCAG
9121  GTCGGAGACG CTGTCGAACT TTTCGATCAG AAACTTCTCG ACAGACGTCG CGGTGAGTTC
9181  AGGCTTTTTC ATATCTCATT GCCCCCCGGG ATCTGCGGCA CGCTGTTGAC GCTGTTAAGC
9241  GGGTCGCTGC AGGGTCGCTC GGTGTTCGAG GCCACACGCG TCACCTTAAT ATGCGAAGTG
9301  GACCTCGGAC CGCGCCGCCC CGACTGCATC TGCGTGTTCG AATTCGCCAA TGACAAGACG
9361  CTGGGCGGGG TTTGTGTCAT CATAGAACTA AAGACATGCA AATATATTTC TTCCGGGGAC
9421  ACCGCCAGCA AACGCGAGCA ACGGGCCACG GGGATGAAGC AGGGCGGCAC CTCGCTAACG
9481  GATTCACCAC TCCAAGAATT GGAGCCAATC AATTCTTGCG GAGAACTGTG AATGCGCAAA
9541  CCAACCCTTG GCAGAACATA TCCATCGCGT CCGCCATCTC CAGCAGCCGC ACGCGGCGCA
9601  TCTCGGGGCC GACGCGCTGG GCTACGTCTT GCTGGCGTTC GCACAGGCCG GCCAGCGCGC
9661  GGCCGGCCGG TACCACGCGT TGGCCACATA TGGCGGCCGC TCGCGATTAA TTAATCGCGA
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 9721  TGGCCACATA TGGAGCTCTC TAGAGCTTGT CGACAGATCC CCCTCTTCAT TTCTTTATGT
 9781  TTTAAATGCA CTGACCTCCC ACATTCCCTT TTTAGTAAAA TATTCAGAAA TAATTTAAAT
 9841  ACATCATTGC AATGAAAATA AATGTTTTTT ATTAGGCAGA ATCCAGATGC TCAAGGCCCT
 9901  TCATAATATC CCCCAGTTTA GTAGTTGGAC TTAGGGAACA AAGGAACCTT TAATAGAAAT
 9961  TGGACAGCAA GAAAGCGAGG GGGATCTGGA TCCTCCTACG TATCTAGAAT CATCGATTAA
10021  CACTCTCCCC TGTTGAAGCT CTTTGTCACG GGGCTGCTCA GGCCCTGATG GGTCACCTCG
10081  CAGGCGTACA CCTTGTGTTT CTCGTAGTCT GCTTTGCTCA GGGTCAGGGT GCTGCTCAGG
10141  CTGTAGGTGC TGTCCTTGCT GTCCTGCTCT GTCACGCTCT CCTGGGAGTT GCCGCTCTGG
10201  AGGGCGTTAT CCACCTTCCA CTGCACCTTG GCCTCTCTGG GATAGAAGTT ATTCAGCAGG
10261  CACACCACGG AGGCAGTTCC AGACTTCAGC TGCTCATCAG ATGGAGGGAA GATGAACACA
10321  GATGGTGCAG CCACCGTACG CTTGATCTCC ACCTTGGTGC CCTGGCCGAA GGTGAATGGA
10381  ATTCCGTAGT GGTGCTGACA GTAGTAGGTG GCGAAGTCCT CAGGCTGCAG GCTGCTGATG
10441  GTCAGGGTGA AGTCTGTCCC AGAGCCGCTG CCGCTGAACC TGGATGGCAC CCCTTCAGCC
10501  AGGGTCTTGG CGTTATAGAT CAGCAGCTTA GGGGCCTTCC CTGGCTTCTG CTGATACCAG
10561  GCCAGGTAGC TGTAGATGTT CTCGCTGGTC CTGCAGGTGA TGGTCACTCT GTCGCCCACA
10621  GAGGCAGACA GGGAGGATGG AGACTGGGTC ATCTGGATAT CACATCTCAT GGCTGGCAGG
10681  AACAGCACCA GCAGCCCCAG CAGCTGCACT GGAGCCATGG TGGCGGCCTC GAGAAGCTTA
10741  AGTTTAATTC TTAAGCCTGT GGAGAGAAAG GAACAGAAAA CGAAACAAAG ACGTAGAGTT
10801  GAGCAAGCAG GGTCAGGCAA AGCGTGGAGA GCCGGCTGAG TCTAGGTAGG CTCCAAGGGA
10861  GCGCCGGACA AAGGCCCGGT CTCGACCTGA GCTTTAAACT TACCTGTGGC CACACGTGCA
10921  ATTGCTATAG TGAGTCGTAT TAATTTCGAT AAGCCAGTAA GCAGTGGGTT CTCTAGTTAG
10981  CCAGAGAGCT CTGCTTATAT AGACCTCCCA CCGTACACGC CTACCGCCCA TTTGCGTCAA
11041  TGGGGCGGAG TTGTTACGAC ATTTTGGAAA GTCCCGTTGA TTTTGGTGCC AAAACAAACT
11101  CCCATTGACG TCAATGGGGT GGAGACTTGG AAATCCCCGT GAGTCAAACC GCTATCCACG
11161  CCCATTGATG TACTGCCAAA ACCGCATCAC CATGGTAATA GCGATGACTA ATACGTAGAT
11221  GTACTGCCAA GTAGGAAAGT CCCATAAGGT CATGTACTGG GCATAATGCC AGGCGGGCCA
11281  TTTACCGTCA TTGACGTCAA TAGGGGGCGT ACTTGGCATA TGATACACTT GATGTACTGC
11341  CAAGTGGGCA GTTTACCGTA AATAGTCCAC CCATTGACGT CAATGGAAAG TCCCTATTGG
11401  CGTTACTATG GGAACATACG TCATTATTGA CGTCAATGGG CGGGGGTCGT TGGGCGGTCA
11461  GCCAGGCGGG CCATTTACCG TAAGTTATGT AACGCGGAAC TCCATATATG GGCTATGAAC
11521  TAATGACCCC GTAATTGATT ACTATTAATA ACTAGTCAAT AATCAATGTC AACGCGTATA
11581  TCTGGCCCGT ACATCGGTAA CTAGTCGGAC CGGCCCGGGC CACCGGTGCT CGAAGCTTGG
11641  ATCGATCCAG ACATGATAAG ATACATTGAT GAGTTTGGAC AAACCACAAC TAGAATGCAG
11701  TGAAAAAAAT GCTTTATTTG TGAAATTTGT GATGCTATTG CTTTATTTGT AACCATTATA
11761  AGCTGCAATA AACAAGTTAA CAACAACAAT TGCATTCATT TTATGTTTCA GGTTCAGGGG
11821  GAGGTGTGGG AGGTTTTTTA AAGCAAGTAA AACCTCTACA AATGTGGTAT GGCTGATTAT
11881  GATCTCTAGT CAA
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(SEQ ID NO: 44)

The present invention further provides, in part, isolated plasmids which exhibit high levels of expression of anti-IL-23R heavy and light chains. One plasmid is pAIL23RV1. The sequence of the pAIL23RV1 plasmid is set forth below:

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   1  GGCACTATAC ATCAAATATT CCTTATTAAC CCCTTTACAA ATTAAAAAGC TAAAGGTACA
  61  CAATTTTTGA GCATAGTTAT TAATAGCAGA CACTCTATGC CTGTGTGGAG TAAGAAAAAA
 121  CAGTATGTTA TGATTATAAC TGTTATGCCT ACTTATAAAG GTTACAGAAT ATTTTTCCAT
 181  AATTTTCTTG TATAGCAGTG CAGCTTTTTC CTTTGTGGTG TAAATAGCAA AGCAAGCAAG
 241  AGTTCTATTA CTAAACACAG CATGACTCAA AAAACTTAGC AATTCTGAAG GAAAGTCCTT
 301  GGGGTCTTCT ACCTTTCTCT TCTTTTTTGG AGGAGTAGAA TGTTGAGAGT CAGCAGTAGC
 361  CTCATCATCA CTAGATGGCA TTTCTTCTGA GCAAAACAGG TTTTCCTCAT TAAAGGCATT
 421  CCACCACTGC TCCCATTCAT CAGTTCCATA GGTTGGAATC TAAAATACAC AAACAATTAG
 481  AATCAGTAGT TTAACACATT ATACACTTAA AAATTTTATA TTTACCTTAG AGCTTTAAAT
 541  CTCTGTAGGT AGTTTGTCCA ATTATGTCAC ACCACAGAAG TAAGGTTCCT TCACAAAGAT
 601  CGATCTAAAG CCAGCAAAAG TCCCATGGTC TTATAAAAAT GCATAGCTTT AGGAGGGGAG
 661  CAGAGAACTT GAAAGCATCT TCCTGTTAGT CTTTCTTCTC GTAGACTTCA AACTTATACT
 721  TGATGCCTTT TTCCTCCTGG ACCTCAGAGA GGACGCCTGG GTATTCTGGG AGAAGTTTAT
 781  ATTTCCCCAA ATCAATTTCT GGGAAAAACG TGTCACTTTC AAATTCCTGC ATGATCCTTG
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 841  TCACAAAGAG TCTGAGGTGG CCTGGTTGAT TCATGGCTTC CTGGTAAACA GAACTGCCTC
 901  CGACTATCCA AACCATGTCT ACTTTACTTG CCAATTCCGG TTGTTCAATA AGTCTTAAGG
 961  CATCATCCAA ACTTTTGGCA AGAAAATGAG CTCCTCGTGG TGGTTCTTTG AGTTCTCTAC
1021  TGAGAACTAT ATTAATTCTG TCCTTTAAAG GTCGATTCTT CTCAGGAATG GAGAACCAGG
1081  TTTTCCTACC CATAATCACC AGATTCTGTT TACCTTCCAC TGAAGAGGTT GTGGTCATTC
1141  TTTGGAAGTA CTTGAACTCG TTCCTGAGCG GAGGCCAGGG TAGGTCTCCG TTCTTGCCAA
1201  TCCCCATATT TTGGGACACG GCGACGATGC AGTTCAATGG TCGAACCATG ATGGCAGCGG
1261  GGATAAAATC CTACCAGCCT TCACGCTAGG ATTGCCGTCA AGTTTGGCGC GAAATCGCAG
1321  CCCTGAGCTG TCCCCCCCCC CAAGCTCAGA TCTGAGCTTG GTCCCTATGG TGAGTCCGTT
1381  CCGCTCTTGT GATGATAGCC AGACAAGAAA GAGACAATAC AAGACAAACA CCAAATAGTA
1441  GAAATAGAGA CAAGGGTCAC TTATCCGAGG GTCCCTGTTC GGGCGCCAGC TGCCGCAGTC
1501  GGCCGACCTG AGGGTCGCCG GGGTCTGCGG GGGGACCCTC TGGAAAGTGA AGGATAAGTG
1561  ACGAGCGGAG ACGGGATGGC GAACAGACAC AAACACACAA GAGGTGAATG TTAGGACTGT
1621  TGCAAGTTTA CTCAAAAAAT CAGCACTCTT TTATATCTTG GTTTACATAA GCATTTACAT
1681  AAGATTTGGA TAAATTCCAA AAGAACATAG GAAAATAGAA CACTCAGAGC TCAGATCAGA
1741  ACCTTTGATA CCAAACCAAG TCAGGAAACC ACTTGTCTCA CATCCTCGTT TTAAGAACAG
1801  TTTGTAACCA AAAACTTACT TAAGCCCTGG GAACCGCAAG GTTGGGCCAA TAAAGGCTAT
1861  TCATAATAAC TCATGCCATG AGTTTTTGCA GAATAATGTT CTATTAGTCC AGCCACTGTC
1921  CCCTCCTTGG TATGGAAAAT CTTTCCCCAA AAGTGCATTC CTGTTCCTAG ATAAATATAA
1981  TCATGTACCT GTTGTTTCAT GTCGTCTTTT TCTTCTTGAG ACAACATACA CCAAGGAGGT
2041  CTAGCTCTGG CGAGTCTTTC ACGAAAAGGG AGGGATCTAT ATAACACTTT ATAGCCATTG
2101  ACTGTAACCC ACCTATCCCA ATTTAAGTCA TATCTTCCTG TATATGGTAA GGGGGCATCT
2161  GTTGGTCTGT AGATGTAAGG TCCCCTATAA GTCCCTGGTT GCCACCACCT GTCTCCTATT
2221  TTGACAAAAA CACTCTTTTT TCCCTTTTTT ACTTCTAGGC CTGTGGTCAA TAGTCCTTGC
2281  ACCTGTTCTT CAATTGAGGT TGAGCGTCTC TTTCTATTTT CTATTCCCAT TTCTAACTTC
2341  TGAATTTGAG TAAAAATAGT ACTAAAAGAT AATGATTCAT TTCTTAACAT AGTAACTAAT
2401  AATCTACCTA TTGGATTGGT CTTATTGGTA AAAATATAAT TTTTAGCAAG CATTCTTATT
2461  TCTATTTCTG AAGGACAAAA TCGATGCGGC TTGTAAGAGG AAGTTGGCTG TGGTCCTTGC
2521  CTCAGGAGGA AGGTCGAGTT CTCCGAATTG TTTAGATTGT AATCTTGCAC AGAAGAGCTA
2581  TTAAAAGAGT CAAGGGTGAG AGCCCTGCGA GCACGAACCG CAACTTCCCC CAATAGCCCC
2641  AGGCAAAGCA GAGCTATGCC AAGTTTGCAG CAGAGAATGA ATATGTCTTT GTCTGATGGG
2701  CTCATCCGTT TGTGCGCAGA CGGGTCGTCC TTGGTGGGAA ACAACCCCTT GGCTGCTTCT
2761  CCCCTAGGTG TAGGACACTC TCGGGAGTTC AACCATTTCT GCCCAAGCTC AGATCTGAGC
2821  TTTAATGCGG TAGTTTATCA CAGTTAAATT GCTAACGCAG TCAGGCACCG TGTATGAAAT
2881  CTAACAATGC GCTCATCGTC ATCCTCGGCA CCGTCACCCT GGATGCTGTA GGCATAGGCT
2941  TGGTTATGCC GGTACTGCCG GGCCTCTTGC GGGATATCGT CCATTCCGAC AGCATCGCCA
3001  GTCACTATGG CGTGCTGCTA GCGCTCTTCC GCTTCCTCGC TCACTGACTC GCTGCGCTCG
3061  GTCGTTCGGC TGCGGCGAGC GGTATCAGCT CACTCAAAGG CGGTAATACG GTTATCCACA
3121  GAATCAGGGG ATAACGCAGG AAAGAACATG TGAGCAAAAG GCCAGCAAAA GGCCAGGAAC
3181  CGTAAAAAGG CCGCGTTGCT GGCGTTTTTC CATAGGCTCC GCCCCCCTGA CGAGCATCAC
3241  AAAAATCGAC GCTCAAGTCA GAGGTGGCGA AACCCGACAG GACTATAAAG ATACCAGGCG
3301  TTTCCCCCTG GAAGCTCCCT CGTGCGCTCT CCTGTTCCGA CCCTGCCGCT TACCGGATAC
3361  CTGTCCGCCT TTCTCCCTTC GGGAAGCGTG GCGCTTTCTC ATAGCTCACG CTGTAGGTAT
3421  CTCAGTTCGG TGTAGGTCGT TCGCTCCAAG CTGGGCTGTG TGCACGAACC CCCCGTTCAG
3481  CCCGACCGCT GCGCCTTATC CGGTAACTAT CGTCTTGAGT CCAACCCGGT AAGACACGAC
3541  TTATCGCCAC TGGCAGCAGC CACTGGTAAC AGGATTAGCA GAGCGAGGTA TGTAGGCGGT
3601  GCTACAGAGT TCTTGAAGTG GTGGCCTAAC TACGGCTACA CTAGAAGGAC AGTATTTGGT
3661  ATCTGCGCTC TGCTGAAGCC AGTTACCTTC GGAAAAAGAG TTGGTAGCTC TTGATCCGGC
3721  AAACAAACCA CCGCTGGTAG CGGTGGTTTT TTTGTTTGCA AGCAGCAGAT TACGCGCAGA
3781  AAAAAAGGAT CTCAAGAAGA TCCTTTGATC TTTTCTACGG GGTCTGACGC TCAGTGGAAC
3841  GAAAACTCAC GTTAAGGGAT TTTGGTCATG AGATTATCAA AAAGGATCTT CACCTAGATC
3901  CTTTTAAATT AAAAATGAAG TTTTAAATCA ATCTAAAGTA TATATGAGTA AACTTGGTCT
3961  GACAGTTACC AATGCTTAAT CAGTGAGGCA CCTATCTCAG CGATCTGTCT ATTTCGTTCA
4021  TCCATAGTTG CCTGACTCCC CGTCGTGTAG ATAACTACGA TACGGGAGGG CTTACCATCT
4081  GGCCCCAGTG CTGCAATGAT ACCGCGAGAC CCACGCTCAC CGGCTCCAGA TTTATCAGCA
4141  ATAAACCAGC CAGCCGGAAG GGCCGAGCGC AGAAGTGGTC CTGCAACTTT ATCCGCCTCC
4201  ATCCAGTCTA TTAATTGTTG CCGGGAAGCT AGAGTAAGTA GTTCGCCAGT TAATAGTTTG
4261  CGCAACGTTG TTGCCATTGC TACAGGCATC GTGGTGTCAC GCTCGTCGTT TGGTATGGCT
4321  TCATTCAGCT CCGGTTCCCA ACGATCAAGG CGAGTTACAT GATCCCCCAT GTTGTGCAAA
4381  AAAGCGGTTA GCTCCTTCGG TCCTCCGATC GTTGTCAGAA GTAAGTTGGC CGCAGTGTTA
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4441  TCACTCATGG TTATGGCAGC ACTGCATAAT TCTCTTACTG TCATGCCATC CGTAAGATGC
4501  TTTTCTGTGA CTGGTGAGTA CTCAACCAAG TCATTCTGAG AATAGTGTAT GCGGCGACCG
4561  AGTTGCTCTT GCCCGGCGTC AACACGGGAT AATACCGCGC CACATAGCAG AACTTTAAAA
4621  GTGCTCATCA TTGGAAAACG TTCTTCGGGG CGAAAACTCT CAAGGATCTT ACCGCTGTTG
4681  AGATCCAGTT CGATGTAACC CACTCGTGCA CCCAACTGAT CTTCAGCATC TTTTACTTTC
4741  ACCAGCGTTT CTGGGTGAGC AAAAACAGGA AGGCAAAATG CCGCAAAAAA GGGAATAAGG
4801  GCGACACGGA AATGTTGAAT ACTCATACTC TTCCTTTTTC AATATTATTG AAGCATTTAT
4861  CAGGGTTATT GTCTCATGAG CGGATACATA TTTGAATGTA TTTAGAAAAA TAAACAAATA
4921  GGGGTTCCGC GCACATTTCC CCGAAAAGTG CCACCTGACG TCTAAGAGAC CATTATTATC
4981  ATGACATTAA CCTATAAAAA TAGGCGTATC ACGAGGCCCT TTCGTCTTCA AGAATTGTCT
5041  AGAGGCGCGC CGTTTAAACC CTCAGCTACC GATGTACGGG CCAGATATAC GCGTTGACAT
5101  TGATTATTGA CTAGTTATTA ATAGTAATCA ATTACGGGGT CATTAGTTCA TAGCCCATAT
5161  ATGGAGTTCC GCGTTACATA ACTTACGGTA AATGGCCCGC CTGGCTGACC GCCCAACGAC
5221  CCCCGCCCAT TGACGTCAAT AATGACGTAT GTTCCCATAG TAACGCCAAT AGGGACTTTC
5281  CATTGACGTC AATGGGTGGA CTATTTACGG TAAACTGCCC ACTTGGCAGT ACATCAAGTG
5341  TATCATATGC CAAGTACGCC CCCTATTGAC GTCAATGACG GTAAATGGCC CGCCTGGCAT
5401  TATGCCCAGT ACATGACCTT ATGGGACTTT CCTACTTGGC AGTACATCTA CGTATTAGTC
5461  ATCGCTATTA CCATGGTGAT GCGGTTTTGG CAGTACATCA ATGGGCGTGG ATAGCGGTTT
5521  GACTCACGGG GATTTCCAAG TCTCCACCCC ATTGACGTCA ATGGGAGTTT GTTTTGGCAC
5581  CAAAATCAAC GGGACTTTCC AAAATGTCGT AACAACTCCG CCCCATTGAC GCAAATGGGC
5641  GGTAGGCGTG TACGGTGGGA GGTCTATATA AGCAGAGCTC TCTGGCTAAC TAGAGAACCC
5701  ACTGCTTACT GGCTTATCGA AATTAATACG ACTCACTATA GCAATTGCAC GTGTGGCCAC
5761  AGGTAAGTTT AAAGCTCAGG TCGAGACCGG GCCTTTGTCC GGCGCTCCCT TGGAGCCTAC
5821  CTAGACTCAG CCGGCTCTCC ACGCTTTGCC TGACCCTGCT TGCTCAACTC TACGTCTTTG
5881  TTTCGTTTTC TGTTCCTTTC TCTCCACAGG CTTAAGCTCG AGGCCGCCAC CATGGCTGTG
5941  CTGGGGCTGC TGTTCTGCCT GGTGACATTC CCAAGCTGTG TGCTGTCCCA GGTGCAGCTG
6001  GTGCAGTCTG GCGCTGAGGT GAAGAAGCCT GGCGCCTCCG TGAAGGTCTC CTGCAAGGCT
6061  TCTGGCTACA CATTCACCAA CTACGCTATG AACTGGGTGC GGCAGGCCCC TGGCCAGGGG
6121  CTGGAGTGGA TGGGCTGGAT CAACACTTAC ACCGGTGAGC CAACCTACAG CGACGACTTC
6181  AAGGGCAGAG TCACCTTCAC CCTGGACACA TCCACCAGCA CAGCCTACAT GGAGCTGAGG
6241  AGCCTGAGAT CTGACGACAC CGCCGTGTAT TACTGTGCCA GAGGTGGAGG CTACGATGAG
6301  GACTACTTCG ACTACTGGGG CCAGGGCACC CTGGTCACCG TCTCCAGCGC TAGCACCAAG
6361  GGCCCATCGG TCTTCCCCCT GGCACCCTCC TCCAAGAGCA CCTCTGGGGG CACAGCGGCC
6421  CTGGGCTGCC TGGTCAAGGA CTACTTCCCC GAACCGGTGA CGGTGTCGTG GAACTCAGGC
6481  GCCCTGACCA GCGGCGTGCA CACCTTCCCG GCTGTCCTAC AGTCCTCAGG ACTCTACTCC
6541  CTCAGCAGCG TGGTGACCGT GCCCTCCAGC AGCTTGGGCA CCCAGACCTA CATCTGCAAC
6601  GTGAATCACA AGCCCAGCAA CACCAAGGTG GACAAGAAAG TTGAGCCCAA ATCTTGTGAC
6661  AAAACTCACA CATGCCCACC GTGCCCAGCA CCTGAACTCC TGGGGGGACC GTCAGTCTTC
6721  CTCTTCCCCC CAAAACCCAA GGACACCCTC ATGATCTCCC GGACCCCTGA GGTCACATGC
6781  GTGGTGGTGG ACGTGAGCCA CGAAGACCCT GAGGTCAAGT TCAACTGGTA CGTGGACGGC
6841  GTGGAGGTGC ATAATGCCAA GACAAAGCCG CGGGAGGAGC AGTACAACAG CACGTACCGT
6901  GTGGTCAGCG TCCTCACCGT CCTGCACCAG GACTGGCTGA ATGGCAAGGA GTACAAGTGC
6961  AAGGTCTCCA ACAAAGCCCT CCCAGCCCCC ATCGAGAAAA CCATCTCCAA AGCCAAAGGG
7021  CAGCCCCGAG AACCACAGGT GTACACCCTG CCCCCATCCC GGGATGAGCT GACCAAGAAC
7081  CAGGTCAGCC TGACCTGCCT GGTCAAAGGC TTCTATCCCA GCGACATCGC CGTGGAGTGG
7141  GAGAGCAATG GGCAGCCGGA GAACAACTAC AAGACCACGC CTCCCGTGCT GGACTCCGAC
7201  GGCTCCTTCT TCCTCTACAG CAAGCTCACC GTGGACAAGA GCAGGTGGCA GCAGGGGAAC
7261  GTCTTCTCAT GCTCCGTGAT GCATGAGGCT CTGCACAACC ACTACACGCA GAAGAGCCTC
7321  TCCCTGTCTC CGGGTAAATA AATCGATGAT TCTAGATACG GGTCCGGAGG ATCCAGATCC
7381  CCCTCGCTTT CTTGCTGTCC AATTTCTATT AAAGGTTCCT TTGTTCCCTA AGTCCAACTA
7441  CTAAACTGGG GGATATTATG AAGGGCCTTG AGCATCTGGA TTCTGCCTAA TAAAAAACAT
7501  TTATTTTCAT TGCAATGATG TATTTAAATT ATTTCTGAAT ATTTTACTAA AAAGGGAATG
7561  TGGGAGGTCA GTGCATTTAA AACATAAAGA AATGAAGAGG GGGATCTGTC GACAAGCTCT
7621  AGAGAGCTCA CGCGTTGATC ATGTACAGGC CGGCCAAGCT TTCGACTAGC TTGGCACGCC
7681  AGAAATCCGC GCGGTGGTTT TTGGGGGTCG GGGGTGTTTG GCAGCCACAG ACGCCCGGTG
7741  TTCGTGTCGC GCCAGTACAT GCGGTCCATG CCCAGGCCAT CCAAAAACCA TGGGTCTGTC
7801  TGCTCAGTCC AGTCGTGGAC CTGACCCCAC GCAACGCCCA AAATAATAAC CCCCACGAAC
7861  CATAAACCAT TCCCCATGGG GGACCCCGTC CCTAACCCAC GGGGCCAGTG GCTATGGCAG
7921  GGCCTGCCGC CCCGACGTTG GCTGCGAGCC CTGGGCCTTC ACCCGAACTT GGGGGGTGGG
7981  GTGGGGAAAA GGAAGAAACG CGGGCGTATT GGCCCCAATG GGGTCTCGGT GGGGTATCGA
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 8041  CAGAGTGCCA GCCCTGGGAC CGAACCCCGC GTTTATGAAC AAACGACCCA ACACCCGTGC
 8101  GTTTTATTCT GTCTTTTTAT TGCCGTCATA GCGCGGGTTC CTTCCGGTAT TGTCTCCTTC
 8161  CGTGTTTCAG TTAGCCTCCC CCATCTCCCG ATCCGGACGA GTGCTGGGGC GTCGGTTTCC
 8221  ACTATCGGCG AGTACTTCTA CACAGCCATC GGTCCAGACG GCCGCGCTTC TGCGGGCGAT
 8281  TTGTGTACGC CCGACAGTCC CGGCTCCGGA TCGGACGATT GCGTCGCATC GACCCTGCGC
 8341  CCAAGCTGCA TCATCGAAAT TGCCGTCAAC CAAGCTCTGA TAGAGTTGGT CAAGACCAAT
 8401  GCGGAGCATA TACGCCCGGA GCCGCGGCGA TCCTGCAAGC TCCGGATGCC TCCGCTCGAA
 8461  GTAGCGCGTC TGCTGCTCCA TACAAGCCAA CCACGGCCTC CAGAAGAAGA TGTTGGCGAC
 8521  CTCGTATTGG GAATCCCCGA ACATCGCCTC GCTCCAGTCA ATGACCGCTG TTATGCGGCC
 8581  ATTGTCCGTC AGGACATTGT TGGAGCCGAA ATCCGCGTGC ACGAGGTGCC GGACTTCGGG
 8641  GCAGTCCTCG GCCCAAAGCA TCAGCTCATC GAGAGCCTGC GCGACGGACG CACTGACGGT
 8701  GTCGTCCATC ACAGTTTGCC AGTGATACAC ATGGGGATCA GCAATCGCGC ATATGAAATC
 8761  ACGCCATGTA GTGTATTGAC CGATTCCTTG CGGTCCGAAT GGGCCGAACC CGCTCGTCTG
 8821  GCTAAGATCG GCCGCAGCGA TCGCATCCAT GGCCTCCGCG ACCGGCTGCA GAACAGCGGG
 8881  CAGTTCGGTT TCAGGCAGGT CTTGCAACGT GACACCCTGT GCACGGCGGG AGATGCAATA
 8941  GGTCAGGCTC TCGCTGAATT CCCCAATGTC AAGCACTTCC GGAATCGGGA GCGCGGCCGA
 9001  TGCAAAGTGC CGATAAACAT AACGATCTTT GTAGAAACCA TCGGCGCAGC TATTTACCCG
 9061  CAGGACATAT CCACGCCCTC CTACATCGAA GCTGAAAGCA CGAGATTCTT CGCCCTCCGA
 9121  GAGCTGCATC AGGTCGGAGA CGCTGTCGAA CTTTTCGATC AGAAACTTCT CGACAGACGT
 9181  CGCGGTGAGT TCAGGCTTTT TCATATCTCA TTGCCCCCCG GGATCTGCGG CACGCTGTTG
 9241  ACGCTGTTAA GCGGGTCGCT GCAGGGTCGC TCGGTGTTCG AGGCCACACG CGTCACCTTA
 9301  ATATGCGAAG TGGACCTCGG ACCGCGCCGC CCCGACTGCA TCTGCGTGTT CGAATTCGCC
 9361  AATGACAAGA CGCTGGGCGG GGTTTGTGTC ATCATAGAAC TAAAGACATG CAAATATATT
 9421  TCTTCCGGGG ACACCGCCAG CAAACGCGAG CAACGGGCCA CGGGGATGAA GCAGGGCGGC
 9481  ACCTCGCTAA CGGATTCACC ACTCCAAGAA TTGGAGCCAA TCAATTCTTG CGGAGAACTG
 9541  TGAATGCGCA AACCAACCCT TGGCAGAACA TATCCATCGC GTCCGCCATC TCCAGCAGCC
 9601  GCACGCGGCG CATCTCGGGG CCGACGCGCT GGGCTACGTC TTGCTGGCGT TCGCACAGGC
 9661  CGGCCAGCGC GCGGCCGGCC GGTACCACGC GTTGGCCACA TATGGCGGCC GCTCGCGATT
 9721  AATTAATCGC GATGGCCACA TATGGAGCTC TCTAGAGCTT GTCGACAGAT CCCCCTCTTC
 9781  ATTTCTTTAT GTTTTAAATG CACTGACCTC CCACATTCCC TTTTTAGTAA AATATTCAGA
 9841  AATAATTTAA ATACATCATT GCAATGAAAA TAAATGTTTT TTATTAGGCA GAATCCAGAT
 9901  GCTCAAGGCC CTTCATAATA TCCCCCAGTT TAGTAGTTGG ACTTAGGGAA CAAAGGAACC
 9961  TTTAATAGAA ATTGGACAGC AAGAAAGCGA GGGGGATCTG GATCCTTTAA CACTCTCCCC
10021  TGTTGAAGCT CTTTGTGACG GGCGAGCTCA GGCCCTGATG GGTGACTTCG CAGGCGTAGA
10081  CTTTGTGTTT CTCGTAGTCT GCTTTGCTCA GCGTCAGGGT GCTGCTGAGG CTGTAGGTGC
10141  TGTCCTTGCT GTCCTGCTCT GTGACACTCT CCTGGGAGTT ACCCGATTGG AGGGCGTTAT
10201  CCACCTTCCA CTGTACTTTG GCCTCTCTGG GATAGAAGTT ATTCAGCAGG CACACAACAG
10261  AGGCAGTTCC AGATTTCAAC TGCTCATCAG ATGGCGGGAA GATGAAGACA GATGGTGCAG
10321  CCACCGTACG TTTGATTTCC ACCTTGGTCC CCTGTCCAAA GGTCCATGGT GTGTCATAGT
10381  GCTGCTGACA GTAGTACACG CCCACATCTT CGGCCTCCAC CCGGCTGATC TTCAGAGTGA
10441  AATCTGTCCC AGATCCGCTG CCGCTGAACC TGTCTGGCAC CCCGCTCTCG CGAGTGCTGG
10501  CGAAATAGAT CAGCAGCTGA GGGCTCTGCC CTGGTTTCTG CAGATACCAG GCCAGGTAGG
10561  TCTTCTGGTT GATGGTGTTG AACAGGCTCT GGCTGCTCTT GCAGCTGATG CTGGCTGGCT
10621  CTCCGGGTGT CACAGGCAGG GACAGTGGAG ACTGGGTCAT CACGATATCA CATCTCATGG
10681  CTGGCAGGAA CAGCACCAGC AGCCCCAGCA GCTGCACTGG AGCCATGGTG GCGGCCTCGA
10741  GAAGCTTAAG TTTAATTCTT AAGCCTGTGG AGAGAAAGGA ACAGAAAACG AAACAAAGAC
10801  GTAGAGTTGA GCAAGCAGGG TCAGGCAAAG CGTGGAGAGC CGGCTGAGTC TAGGTAGGCT
10861  CCAAGGGAGC GCCGGACAAA GGCCCGGTCT CGACCTGAGC TTTAAACTTA CCTGTGGCCA
10921  CACGTGCAAT TGCTATAGTG AGTCGTATTA ATTTCGATAA GCCAGTAAGC AGTGGGTTCT
10981  CTAGTTAGCC AGAGAGCTCT GCTTATATAG ACCTCCCACC GTACACGCCT ACCGCCCATT
11041  TGCGTCAATG GGGCGGAGTT GTTACGACAT TTTGGAAAGT CCCGTTGATT TTGGTGCCAA
11101  AACAAACTCC CATTGACGTC AATGGGGTGG AGACTTGGAA ATCCCCGTGA GTCAAACCGC
11161  TATCCACGCC CATTGATGTA CTGCCAAAAC CGCATCACCA TGGTAATAGC GATGACTAAT
11221  ACGTAGATGT ACTGCCAAGT AGGAAAGTCC CATAAGGTCA TGTACTGGGC ATAATGCCAG
11281  GCGGGCCATT TACCGTCATT GACGTCAATA GGGGGCGTAC TTGGCATATG ATACACTTGA
11341  TGTACTGCCA AGTGGGCAGT TTACCGTAAA TAGTCCACCC ATTGACGTCA ATGGAAAGTC
11401  CCTATTGGCG TTACTATGGG AACATACGTC ATTATTGACG TCAATGGGCG GGGGTCGTTG
11461  GGCGGTCAGC CAGGCGGGCC ATTTACCGTA AGTTATGTAA CGCGGAACTC CATATATGGG
11521  CTATGAACTA ATGACCCCGT AATTGATTAC TATTAATAAC TAGTCAATAA TCAATGTCAA
11581  CGCGTATATC TGGCCCGTAC ATCGGTAACT AGTCGGACCG GCCCGGGCCA CCGGTGCTCG
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11641    AAGCTTGGAT CGATCCAGAC ATGATAAGAT ACATTGATGA GTTTGGACAA ACCACAACTA
11701    GAATGCAGTG AAAAAAATGC TTTATTTGTG AAATTTGTGA TGCTATTGCT TTATTTGTAA
11761    CCATTATAAG CTGCAATAAA CAAGTTAACA ACAACAATTG CATTCATTTT ATGTTTCAGG
11821    TTCAGGGGGA GGTGTGGGAG GTTTTTTAAA GCAAGTAAAA CCTCTACAAA TGTGGTATGG
11881    CTGATTATGA TCTCTAGTCA A
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(SEQ ID NO: 45)

The present invention further provides, in part, isolated plasmids which exhibit high levels of expression of anti-IL-17 heavy and light chains. One plasmid is pAIL17AV1. The sequence of the pAIL17AV1 plasmid is set forth below:

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   1    GCACTATACA TCAAATATTC CTTATTAACC CCTTTACAAA TTAAAAAGCT AAAGGTACAC
  61    AATTTTTGAG CATAGTTATT AATAGCAGAC ACTCTATGCC TGTGTGGAGT AAGAAAAAAC
 121    AGTATGTTAT GATTATAACT GTTATGCCTA CTTATAAAGG TTACAGAATA TTTTTCCATA
 181    ATTTTCTTGT ATAGCAGTGC AGCTTTTTCC TTTGTGGTGT AAATAGCAAA GCAAGCAAGA
 241    GTTCTATTAC TAAACACAGC ATGACTCAAA AAACTTAGCA ATTCTGAAGG AAAGTCCTTG
 301    GGGTCTTCTA CCTTTCTCTT CTTTTTTGGA GGAGTAGAAT GTTGAGAGTC AGCAGTAGCC
 361    TCATCATCAC TAGATGGCAT TTCTTCTGAG CAAAACAGGT TTTCCTCATT AAAGGCATTC
 421    CACCACTGCT CCCATTCATC AGTTCCATAG GTTGGAATCT AAAATACACA AACAATTAGA
 481    ATCAGTAGTT TAACACATTA TACACTTAAA AATTTTATAT TTACCTTAGA GCTTTAAATC
 541    TCTGTAGGTA GTTTGTCCAA TTATGTCACA CCACAGAAGT AAGGTTCCTT CACAAAGATC
 601    GATCTAAAGC CAGCAAAAGT CCCATGGTCT TATAAAAATG CATAGCTTTA GGAGGGGAGC
 661    AGAGAACTTG AAAGCATCTT CCTGTTAGTC TTTCTTCTCG TAGACTTCAA ACTTATACTT
 721    GATGCCTTTT TCCTCCTGGA CCTCAGAGAG GACGCCTGGG TATTCTGGGA GAAGTTTATA
 781    TTTCCCCAAA TCAATTTCTG GGAAAAACGT GTCACTTTCA AATTCCTGCA TGATCCTTGT
 841    CACAAAGAGT CTGAGGTGGC CTGGTTGATT CATGGCTTCC TGGTAAACAG AACTGCCTCC
 901    GACTATCCAA ACCATGTCTA CTTTACTTGC CAATTCCGGT TGTTCAATAA GTCTTAAGGC
 961    ATCATCCAAA CTTTTGGCAA GAAAATGAGC TCCTCGTGGT GGTTCTTTGA GTTCTCTACT
1021    GAGAACTATA TTAATTCTGT CCTTTAAAGG TCGATTCTTC TCAGGAATGG AGAACCAGGT
1081    TTTCCTACCC ATAATCACCA GATTCTGTTT ACCTTCCACT GAAGAGGTTG TGGTCATTCT
1141    TTGGAAGTAC TTGAACTCGT TCCTGAGCGG AGGCCAGGGT AGGTCTCCGT TCTTGCCAAT
1201    CCCCATATTT TGGGACACGG CGACGATGCA GTTCAATGGT CGAACCATGA TGGCAGCGGG
1261    GATAAAATCC TACCAGCCTT CACGCTAGGA TTGCCGTCAA GTTTGGCGCG AAATCGCAGC
1321    CCTGAGCTGT CCCCCCCCCC AAGCTCAGAT CTGAGCTTGG TCCCTATGGT GAGTCCGTTC
1381    CGCTCTTGTG ATGATAGCCA GACAAGAAAG AGACAATACA AGACAAACAC CAAATAGTAG
1441    AAATAGAGAC AAGGGTCACT TATCCGAGGG TCCCTGTTCG GGCGCCAGCT GCCGCAGTCG
1501    GCCGACCTGA GGGTCGCCGG GGTCTGCGGG GGGACCCTCT GGAAAGTGAA GGATAAGTGA
1561    CGAGCGGAGA CGGGATGGCG AACAGACACA AACACACAAG AGGTGAATGT TAGGACTGTT
1621    GCAAGTTTAC TCAAAAAATC AGCACTCTTT TATATCTTGG TTTACATAAG CATTTACATA
1681    AGATTTGGAT AAATTCCAAA AGAACATAGG AAAATAGAAC ACTCAGAGCT CAGATCAGAA
1741    CCTTTGATAC CAAACCAAGT CAGGAAACCA CTTGTCTCAC ATCCTCGTTT TAAGAACAGT
1801    TTGTAACCAA AAACTTACTT AAGCCCTGGG AACCGCAAGG TTGGGCCAAT AAAGGCTATT
1861    CATAATAACT CATGCCATGA GTTTTTGCAG AATAATGTTC TATTAGTCCA GCCACTGTCC
1921    CCTCCTTGGT ATGGAAAATC TTTCCCCAAA AGTGCATTCC TGTTCCTAGA TAAATATAAT
1981    CATGTACCTG TTGTTTCATG TCGTCTTTTT CTTCTTGAGA CAACATACAC CAAGGAGGTC
2041    TAGCTCTGGC GAGTCTTTCA CGAAAAGGGA GGGATCTATA TAACACTTTA TAGCCATTGA
2101    CTGTAACCCA CCTATCCCAA TTTAAGTCAT ATCTTCCTGT ATATGGTAAG GGGGCATCTG
2161    TTGGTCTGTA GATGTAAGGT CCCCTATAAG TCCCTGGTTG CCACCACCTG TCTCCTATTT
2221    TGACAAAAAC ACTCTTTTTT CCCTTTTTTA CTTCTAGGCC TGTGGTCAAT AGTCCTTGCA
2281    CCTGTTCTTC AATTGAGGTT GAGCGTCTCT TTCTATTTTC TATTCCCATT TCTAACTTCT
2341    GAATTTGAGT AAAAATAGTA CTAAAAGATA ATGATTCATT TCTTAACATA GTAACTAATA
2401    ATCTACCTAT TGGATTGGTC TTATTGGTAA AAATATAATT TTTAGCAAGC ATTCTTATTT
2461    CTATTTCTGA AGGACAAAAT CGATGCGGCT TGTAAGAGGA AGTTGGCTGT GGTCCTTGCC
2521    TCAGGAGGAA GGTCGAGTTC TCCGAATTGT TTAGATTGTA ATCTTGCACA GAAGAGCTAT
2581    TAAAAGAGTC AAGGGTGAGA GCCCTGCGAG CACGAACCGC AACTTCCCCC AATAGCCCCA
2641    GGCAAAGCAG AGCTATGCCA AGTTTGCAGC AGAGAATGAA TATGTCTTTG TCTGATGGGC
2701    TCATCCGTTT GTGCGCAGAC GGGTCGTCCT TGGTGGGAAA CAACCCCTTG GCTGCTTCTC
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2761  CCCTAGGTGT AGGACACTCT CGGGAGTTCA ACCATTTCTG CCCAAGCTCA GATCTGAGCT
2821  TTAATGCGGT AGTTTATCAC AGTTAAATTG CTAACGCAGT CAGGCACCGT GTATGAAATC
2881  TAACAATGCG CTCATCGTCA TCCTCGGCAC CGTCACCCTG GATGCTGTAG GCATAGGCTT
2941  GGTTATGCCG GTACTGCCGG GCCTCTTGCG GGATATCGTC CATTCCGACA GCATCGCCAG
3001  TCACTATGGC GTGCTGCTAG CGCTCTTCCG CTTCCTCGCT CACTGACTCG CTGCGCTCGG
3061  TCGTTCGGCT GCGGCGAGCG GTATCAGCTC ACTCAAAGGC GGTAATACGG TTATCCACAG
3121  AATCAGGGGA TAACGCAGGA AAGAACATGT GAGCAAAAGG CCAGCAAAAG GCCAGGAACC
3181  GTAAAAAGGC CGCGTTGCTG GCGTTTTTCC ATAGGCTCCG CCCCCCTGAC GAGCATCACA
3241  AAAATCGACG CTCAAGTCAG AGGTGGCGAA ACCCGACAGG ACTATAAAGA TACCAGGCGT
3301  TTCCCCCTGG AAGCTCCCTC GTGCGCTCTC CTGTTCCGAC CCTGCCGCTT ACCGGATACC
3361  TGTCCGCCTT TCTCCCTTCG GGAAGCGTGG CGCTTTCTCA TAGCTCACGC TGTAGGTATC
3421  TCAGTTCGGT GTAGGTCGTT CGCTCCAAGC TGGGCTGTGT GCACGAACCC CCCGTTCAGC
3481  CCGACCGCTG CGCCTTATCC GGTAACTATC GTCTTGAGTC CAACCCGGTA AGACACGACT
3541  TATCGCCACT GGCAGCAGCC ACTGGTAACA GGATTAGCAG AGCGAGGTAT GTAGGCGGTG
3601  CTACAGAGTT CTTGAAGTGG TGGCCTAACT ACGGCTACAC TAGAAGGACA GTATTTGGTA
3661  TCTGCGCTCT GCTGAAGCCA GTTACCTTCG GAAAAAGAGT TGGTAGCTCT TGATCCGGCA
3721  AACAAACCAC CGCTGGTAGC GGTGGTTTTT TTGTTTGCAA GCAGCAGATT ACGCGCAGAA
3781  AAAAAGGATC TCAAGAAGAT CCTTTGATCT TTTCTACGGG GTCTGACGCT CAGTGGAACG
3841  AAAACTCACG TTAAGGGATT TTGGTCATGA GATTATCAAA AAGGATCTTC ACCTAGATCC
3901  TTTTAAATTA AAAATGAAGT TTTAAATCAA TCTAAAGTAT ATATGAGTAA ACTTGGTCTG
3961  ACAGTTACCA ATGCTTAATC AGTGAGGCAC CTATCTCAGC GATCTGTCTA TTTCGTTCAT
4021  CCATAGTTGC CTGACTCCCC GTCGTGTAGA TAACTACGAT ACGGGAGGGC TTACCATCTG
4081  GCCCCAGTGC TGCAATGATA CCGCGAGACC CACGCTCACC GGCTCCAGAT TTATCAGCAA
4141  TAAACCAGCC AGCCGGAAGG GCCGAGCGCA GAAGTGGTCC TGCAACTTTA TCCGCCTCCA
4201  TCCAGTCTAT TAATTGTTGC CGGGAAGCTA GAGTAAGTAG TTCGCCAGTT AATAGTTTGC
4261  GCAACGTTGT TGCCATTGCT ACAGGCATCG TGGTGTCACG CTCGTCGTTT GGTATGGCTT
4321  CATTCAGCTC CGGTTCCCAA CGATCAAGGC GAGTTACATG ATCCCCCATG TTGTGCAAAA
4381  AAGCGGTTAG CTCCTTCGGT CCTCCGATCG TTGTCAGAAG TAAGTTGGCC GCAGTGTTAT
4441  CACTCATGGT TATGGCAGCA CTGCATAATT CTCTTACTGT CATGCCATCC GTAAGATGCT
4501  TTTCTGTGAC TGGTGAGTAC TCAACCAAGT CATTCTGAGA ATAGTGTATG CGGCGACCGA
4561  GTTGCTCTTG CCCGGCGTCA ACACGGGATA TACCGCGCC ACATAGCAGA ACTTTAAAAG
4621  TGCTCATCAT TGGAAAACGT TCTTCGGGGC GAAAACTCTC AAGGATCTTA CCGCTGTTGA
4681  GATCCAGTTC GATGTAACCC ACTCGTGCAC CCAACTGATC TTCAGCATCT TTTACTTTCA
4741  CCAGCGTTTC TGGGTGAGCA AAAACAGGAA GGCAAAATGC CGCAAAAAAG GGAATAAGGG
4801  CGACACGGAA ATGTTGAATA CTCATACTCT TCCTTTTTCA ATATTATTGA AGCATTTATC
4861  AGGGTTATTG TCTCATGAGC GGATACATAT TTGAATGTAT TTAGAAAAAT AAACAAATAG
4921  GGGTTCCGCG CACATTTCCC CGAAAAGTGC CACCTGACGT CTAAGAGACC ATTATTATCA
4981  TGACATTAAC CTATAAAAAT AGGCGTATCA CGAGGCCCTT TCGTCTTCAA GAATTGTCTA
5041  GAGGCGCGCC GTTTAAACCC TCAGCTACCG ATGTACGGGC CAGATATACG CGTTGACATT
5101  GATTATTGAC TAGTTATTAA TAGTAATCAA TTACGGGGTC ATTAGTTCAT AGCCCATATA
5161  TGGAGTTCCG CGTTACATAA CTTACGGTAA ATGGCCCGCC TGGCTGACCG CCCAACGACC
5221  CCCGCCCATT GACGTCAATA ATGACGTATG TTCCCATAGT AACGCCAATA GGGACTTTCC
5281  ATTGACGTCA ATGGGTGGAC TATTTACGGT AAACTGCCCA CTTGGCAGTA CATCAAGTGT
5341  ATCATATGCC AAGTACGCCC CCTATTGACG TCAATGACGG TAAATGGCCC GCCTGGCATT
5401  ATGCCCAGTA CATGACCTTA TGGGACTTTC CTACTTGGCA GTACATCTAC GTATTAGTCA
5461  TCGCTATTAC CATGGTGATG CGGTTTTGGC AGTACATCAA TGGGCGTGGA TAGCGGTTTG
5521  ACTCACGGGG ATTTCCAAGT CTCCACCCCA TTGACGTCAA TGGGAGTTTG TTTTGGCACC
5581  AAAATCAACG GGACTTTCCA AAATGTCGTA ACAACTCCGC CCCATTGACG CAAATGGGCG
5641  GTAGGCGTGT ACGGTGGGAG GTCTATATAA GCAGAGCTCT CTGGCTAACT AGAGAACCCA
5701  CTGCTTACTG GCTTATCGAA ATTAATACGA CTCACTATAG CAATTGCACG TGTGGCCACA
5761  GGTAAGTTTA AAGCTCAGGT CGAGACCGGG CCTTTGTCCG GCGCTCCCTT GGAGCCTACC
5821  TAGACTCAGC CGGCTCTCCA CGCTTTGCCT GACCCTGCTT GCTCAACTCT ACGTCTTTGT
5881  TTCGTTTTCT GTTCCTTTCT CTCCACAGGC TTAAGAGTAC TGCCGCCACC ATGGCTGTGC
5941  TGGGGCTGCT GTTCTGCCTG GTGACATTCC CAAGCTGTGT GCTGTCCCAG GTGCAGCTGC
6001  AGGAGTCTGG ACCAGGCCTG GTGAAGCCTA GCGAGACCCT GAGCCTGACC TGTACCGTGT
6061  CTGGATTCAG CCTGCCCAGC CACAGCGTGA GCTGGATCAG ACAGCCTCCA GGCAAGGGAC
6121  TGGAGTGGAT CGGCATCATT TGGAATCAAG GCGGCACTGA CTATAACAGC GCCTTCAAGA
6181  GCCGCGTGAC CATCTCCGTG GACACCTCCA AGAACCAGTT CAGCCTGAAG CTGAGCAGCG
6241  TGACCGCTGC CGACACCGCT GTGTATTACT GTGCCAGAAA TGCATACATC ACCGACTACT
6301  ATTACGAGAA CTACTTCATG GATGCCTGGG GACAGGGCAC CCTGGTGACC GTGAGCTCCG
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6361 CTAGCACCAA GGGCCCATCG GTCTTCCCCC TGGCACCCTC CTCCAAGAGC ACCTCTGGGG
6421 GCACAGCGGC CCTGGGCTGC CTGGTCAAGG ACTACTTCCC CGAACCGGTG ACGGTGTCGT
6481 GGAACTCAGG CGCCCTGACC AGCGGCGTGC ACACCTTCCC GGCTGTCCTA CAGTCCTCAG
6541 GACTCTACTC CCTCAGCAGC GTGGTGACCG TGCCCTCCAG CAGCTTGGGC ACCCAGACCT
6601 ACATCTGCAA CGTGAATCAC AAGCCCAGCA ACACCAAGGT GGACAAGAAA GTTGAGCCCA
6661 AATCTTGTGA CAAAACTCAC ACATGCCCAC CGTGCCCAGC ACCTGAACTC CTGGGGGGAC
6721 CGTCAGTCTT CCTCTTCCCC CCAAAACCCA AGGACACCCT CATGATCTCC CGGACCCCTG
6781 AGGTCACATG CGTGGTGGTG GACGTGAGCC ACGAAGACCC TGAGGTCAAG TTCAACTGGT
6841 ACGTGGACGG CGTGGAGGTG CATAATGCCA AGACAAAGCC GCGGGAGGAG CAGTACAACA
6901 GCACGTACCG TGTGGTCAGC GTCCTCACCG TCCTGCACCA GGACTGGCTG AATGGCAAGG
6961 AGTACAAGTG CAAGGTCTCC AACAAAGCCC TCCCAGCCCC CATCGAGAAA ACCATCTCCA
7021 AAGCCAAAGG GCAGCCCCGA GAACCACAGG TGTACACCCT GCCCCCATCC CGGGATGAGC
7081 TGACCAAGAA CCAGGTCAGC CTGACCTGCC TGGTCAAAGG CTTCTATCCC AGCGACATCG
7141 CCGTGGAGTG GGAGAGCAAT GGGCAGCCGG AGAACAACTA CAAGACCACG CCTCCCGTGC
7201 TGGACTCCGA CGGCTCCTTC TTCCTCTACA GCAAGCTCAC CGTGGACAAG AGCAGGTGGC
7261 AGCAGGGGAA CGTCTTCTCA TGCTCCGTGA TGCATGAGGC TCTGCACAAC CACTACACGC
7321 AGAAGAGCCT CTCCCTGTCT CCGGGTAAAT GAATCGATGA TTCTAGATAC GGGTCCGGAG
7381 GATCCAGATC CCCCTCGCTT TCTTGCTGTC CAATTTCTAT TAAAGGTTCC TTTGTTCCCT
7441 AAGTCCAACT ACTAAACTGG GGGATATTAT GAAGGGCCTT GAGCATCTGG ATTCTGCCTA
7501 ATAAAAAACA TTTATTTTCA TTGCAATGAT GTATTTAAAT TATTTCTGAA TATTTTACTA
7561 AAAAGGGAAT GTGGGAGGTC AGTGCATTTA AAACATAAAG AAATGAAGAG GGGGATCTGT
7621 CGACAAGCTC TAGAGAGCTC ACGCGTTGAT CATGTACAGG CCGGCCAAGC TTTCGACTAG
7681 CTTGGCACGC CAGAAATCCG CGCGGTGGTT TTTGGGGGTC GGGGGTGTTT GGCAGCCACA
7741 GACGCCCGGT GTTCGTGTCG CGCCAGTACA TGCGGTCCAT GCCCAGGCCA TCCAAAAACC
7801 ATGGGTCTGT CTGCTCAGTC CAGTCGTGGA CCTGACCCCA CGCAACGCCC AAAATAATAA
7861 CCCCCACGAA CCATAAACCA TTCCCCATGG GGGACCCCGT CCCTAACCCA CGGGGCCAGT
7921 GGCTATGGCA GGGCCTGCCG CCCCGACGTT GGCTGCGAGC CCTGGGCCTT CACCCGAACT
7981 TGGGGGGTGG GGTGGGGAAA AGGAAGAAAC GCGGGCGTAT TGGCCCCAAT GGGGTCTCGG
8041 TGGGGTATCG ACAGAGTGCC AGCCCTGGGA CCGAACCCCG CGTTTATGAA CAAACGACCC
8101 AACACCCGTG CGTTTTATTC TGTCTTTTTA TTGCCGTCAT AGCGCGGGTT CCTTCCGGTA
8161 TTGTCTCCTT CCGTGTTTCA GTTAGCCTCC CCCATCTCCC GATCCGGACG AGTGCTGGGG
8221 CGTCGGTTTC CACTATCGGC GAGTACTTCT ACACAGCCAT CGGTCCAGAC GGCCGCGCTT
8281 CTGCGGGCGA TTTGTGTACG CCCGACAGTC CCGGCTCCGG ATCGGACGAT TGCGTCGCAT
8341 CGACCCTGCG CCCAAGCTGC ATCATCGAAA TTGCCGTCAA CCAAGCTCTG ATAGAGTTGG
8401 TCAAGACCAA TGCGGAGCAT ATACGCCCGG AGCCGCGGCG ATCCTGCAAG CTCCGGATGC
8461 CTCCGCTCGA AGTAGCGCGT CTGCTGCTCC ATACAAGCCA ACCACGGCCT CCAGAAGAAG
8521 ATGTTGGCGA CCTCGTATTG GGAATCCCCG AACATCGCCT CGCTCCAGTC AATGACCGCT
8581 GTTATGCGGC CATTGTCCGT CAGGACATTG TTGGAGCCGA AATCCGCGTG CACGAGGTGC
8641 CGGACTTCGG GGCAGTCCTC GGCCCAAAGC ATCAGCTCAT CGAGAGCCTG CGCGACGGAC
8701 GCACTGACGG TGTCGTCCAT CACAGTTTGC CAGTGATACA CATGGGGATC AGCAATCGCG
8761 CATATGAAAT CACGCCATGT AGTGTATTGA CCGATTCCTT GCGGTCCGAA TGGGCCGAAC
8821 CCGCTCGTCT GGCTAAGATC GGCCGCAGCG ATCGCATCCA TGGCCTCCGC GACCGGCTGC
8881 AGAACAGCGG GCAGTTCGGT TTCAGGCAGG TCTTGCAACG TGACACCCTG TGCACGGCGG
8941 GAGATGCAAT AGGTCAGGCT CTCGCTGAAT TCCCCAATGT CAAGCACTTC CGGAATCGGG
9001 AGCGCGGCCG ATGCAAAGTG CCGATAAACA TAACGATCTT TGTAGAAACC ATCGGCGCAG
9061 CTATTTACCC GCAGGACATA TCCACGCCCT CCTACATCGA AGCTGAAAGC ACGAGATTCT
9121 TCGCCCTCCG AGAGCTGCAT CAGGTCGGAG ACGCTGTCGA ACTTTTCGAT CAGAAACTTC
9181 TCGACAGACG TCGCGGTGAG TTCAGGCTTT TTCATATCTC ATTGCCCCCC GGGATCTGCG
9241 GCACGCTGTT GACGCTGTTA AGCGGGTCGC TGCAGGGTCG CTCGGTGTTC GAGGCCACAC
9301 GCGTCACCTT AATATGCGAA GTGGACCTCG GACCGCGCCG CCCCGACTGC ATCTGCGTGT
9361 TCGAATTCGC CAATGACAAG ACGCTGGGCG GGGTTTGTGT CATCATAGAA CTAAAGACAT
9421 GCAAATATAT TTCTTCCGGG GACACCGCCA GCAAACGCGA GCAACGGGCC ACGGGGATGA
9481 AGCAGGGCGG CACCTCGCTA ACGGATTCAC CACTCCAAGA ATTGGAGCCA ATCAATTCTT
9541 GCGGAGAACT GTGAATGCGC AAACCAACCC TTGGCAGAAC ATATCCATCG CGTCCGCCAT
9601 CTCCAGCAGC CGCACGCGGC GCATCTCGGG GCCGACGCGC TGGGCTACGT CTTGCTGGCG
9661 TTCGCACAGG CCGGCCAGCG CGCGGCCGGC CGGTACCACG CGTTGGCCAC ATATGGCGGC
9721 CGCTCGCGAT TAATTAATCG CGATGGCCAC ATATGGAGCT CTCTAGAGCT TGTCGACAGA
9781 TCCCCCTCTT CATTTCTTTA TGTTTTAAAT GCACTGACCT CCCACATTCC CTTTTTAGTA
9841 AAATATTCAG AAATAATTTA AATACATCAT TGCAATGAAA ATAAATGTTT TTTATTAGGC
9901 AGAATCCAGA TGCTCAAGGC CCTTCATAAT ATCCCCCAGT TTAGTAGTTG GACTTAGGGA

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 9961    ACAAAGGAAC CTTTAATAGA AATTGGACAG CAAGAAAGCG AGGGGGATCT GGATCCTCCG
10021    GAGGGCCCCT TCTCCCTCTA ACACTCTCCC CTGTTGAAGC TCTTTGTGAC GGGCGAGCTC
10081    AGGCCCTGAT GGGTGACTTC GCAGGCGTAG ACTTTGTGTT TCTCGTAGTC TGCTTTGCTC
10141    AGCGTCAGGG TGCTGCTGAG GCTGTAGGTG CTGTCCTTGC TGTCCTGCTC TGTGACACTC
10201    TCCTGGGAGT TACCCGATTG GAGGGCGTTA TCCACCTTCC ACTGTACTTT GGCCTCTCTG
10261    GGATAGAAGT TATTCAGCAG GCACACAACA GAGGCAGTTC CAGATTTCAA CTGCTCATCA
10321    GATGGCGGGA AGATGAAGAC AGATGGTGCA GCCACCGTAC GTTTGATTTC CACCTTGGTC
10381    CCCTGTCCAA AGGTGTAGGG TGTGTAATAG CTCTGCTGAC AGTAGTACAC GCCCACATCT
10441    TCGGCCTCCA CCCGGCTGAT CTTCAGAGTG AAATCTGTCC CAGATCCGCT GCCGCTGAAC
10501    CTGTCTGGCA CCCCGCTCTG CCGGGTGCTG GTCCAATAGA TCAGCAGCTG AGGGCTCTGC
10561    CCTGGTTTCT GCAGATACCA GGCCAGGTAG TTCTTCTGGT TCTCGCTGAA CAGCAGGCTC
10621    TGGCTGCTCT TGCAGCTGAT GCTGGCTGGC TCTCCGGGTG TCACAGGCAG GGACAGTGGA
10681    GACTGGGTCA TCACGATATC ACATCTCATG GCTGGCAGGA ACAGCACCAG CAGCCCCAGC
10741    AGCTGCACTG GAGCCATGGT GGCGGCGCTA GCGAATTCTT AAGCCTGTGG AGAGAAAGGA
10801    ACAGAAAACG AAACAAAGAC GTAGAGTTGA GCAAGCAGGG TCAGGCAAAG CGTGGAGAGC
10861    CGGCTGAGTC TAGGTAGGCT CCAAGGGAGC GCCGGACAAA GGCCCGGTCT CGACCTGAGC
10921    TTTAAACTTA CCTGTGGCCA CACGTGCAAT TGCTATAGTG AGTCGTATTA ATTTCGATAA
10981    GCCAGTAAGC AGTGGGTTCT CTAGTTAGCC AGAGAGCTCT GCTTATATAG ACCTCCCACC
11041    GTACACGCCT ACCGCCCATT TGCGTCAATG GGGCGGAGTT GTTACGACAT TTTGGAAAGT
11101    CCCGTTGATT TTGGTGCCAA AACAAACTCC CATTGACGTC AATGGGGTGG AGACTTGGAA
11161    ATCCCCGTGA GTCAAACCGC TATCCACGCC CATTGATGTA CTGCCAAAAC CGCATCACCA
11221    TGGTAATAGC GATGACTAAT ACGTAGATGT ACTGCCAAGT AGGAAAGTCC CATAAGGTCA
11281    TGTACTGGGC ATAATGCCAG GCGGGCCATT TACCGTCATT GACGTCAATA GGGGGCGTAC
11341    TTGGCATATG ATACACTTGA TGTACTGCCA AGTGGGCAGT TTACCGTAAA TAGTCCACCC
11401    ATTGACGTCA ATGGAAAGTC CCTATTGGCG TTACTATGGG AACATACGTC ATTATTGACG
11461    TCAATGGGCG GGGGTCGTTG GGCGGTCAGC CAGGCGGGCC ATTTACCGTA AGTTATGTAA
11521    CGCGGAACTC CATATATGGG CTATGAACTA ATGACCCCGT AATTGATTAC TATTAATAAC
11581    TAGTCAATAA TCAATGTCAA CGCGTATATC TGGCCCGTAC ATCGGTAACT AGTCGGACCG
11641    GCCCGGGCCA CCGGTGCTCG AAGCTTGGAT CGATCCAGAC ATGATAAGAT ACATTGATGA
11701    GTTTGGACAA ACCACAACTA GAATGCAGTG AAAAAAATGC TTTATTTGTG AAATTTGTGA
11761    TGCTATTGCT TTATTTGTAA CCATTATAAG CTGCAATAAA CAAGTTAACA ACAACAATTG
11821    CATTCATTTT ATGTTTCAGG TTCAGGGGGA GGTGTGGGAG GTTTTTTAAA GCAAGTAAAA
11881    CCTCTACAAA TGTGGTATGG CTGATTATGA TCTCTAGTCA AG
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(SEQ ID NO: 46)

The present invention further provides, in part, isolated plasmids which exhibit high levels of expression of anti-PD1 (Programmed Death 1) heavy and light chains. One plasmid is pAPD16V1-GA. The sequence of the pAPD16V1-GA plasmid is set forth below:

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    1    GCACTATACA TCAAATATTC CTTATTAACC CCTTTACAAA TTAAAAAGCT AAAGGTACAC
   61    AATTTTTGAG CATAGTTATT AATAGCAGAC ACTCTATGCC TGTGTGGAGT AAGAAAAAAC
  121    AGTATGTTAT GATTATAACT GTTATGCCTA CTTATAAAGG TTACAGAATA TTTTTCCATA
  181    ATTTTCTTGT ATAGCAGTGC AGCTTTTTCC TTTGTGGTGT AAATAGCAAA GCAAGCAAGA
  241    GTTCTATTAC TAAACACAGC ATGACTCAAA AAACTTAGCA ATTCTGAAGG AAAGTCCTTG
  301    GGGTCTTCTA CCTTTCTCTT CTTTTTTGGA GGAGTAGAAT GTTGAGAGTC AGCAGTAGCC
  361    TCATCATCAC TAGATGGCAT TTCTTCTGAG CAAAACAGGT TTTCCTCATT AAAGGCATTC
  421    CACCACTGCT CCCATTCATC AGTTCCATAG GTTGGAATCT AAAATACACA AACAATTAGA
  481    ATCAGTAGTT TAACACATTA TACACTTAAA AATTTTATAT TTACCTTAGA GCTTTAAATC
  541    TCTGTAGGTA GTTTGTCCAA TTATGTCACA CCACAGAAGT AAGGTTCCTT CACAAAGATC
  601    GATCTAAAGC CAGCAAAAGT CCCATGGTCT TATAAAAATG CATAGCTTTA GGAGGGGAGC
  661    AGAGAACTTG AAAGCATCTT CCTGTTAGTC TTTCTTCTCG TAGACTTCAA ACTTATACTT
  721    GATGCCTTTT TCCTCCTGGA CCTCAGAGAG GACGCCTGGG TATTCTGGGA GAAGTTTATA
  781    TTTCCCCAAA TCAATTTCTG GGAAAAACGT GTCACTTTCA AATTCCTGCA TGATCCTTGT
  841    CACAAAGAGT CTGAGGTGGC CTGGTTGATT CATGGCTTCC TGGTAAACAG AACTGCCTCC
  901    GACTATCCAA ACCATGTCTA CTTTACTTGC CAATTCCGGT TGTTCAATAA GTCTTAAGGC
  961    ATCATCCAAA CTTTTGGCAA GAAAATGAGC TCCTCGTGGT GGTTCTTTGA GTTCTCTACT
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1021 GAGAACTATA TTAATTCTGT CCTTTAAAGG TCGATTCTTC TCAGGAATGG AGAACCAGGT
1081 TTTCCTACCC ATAATCACCA GATTCTGTTT ACCTTCCACT GAAGAGGTTG TGGTCATTCT
1141 TTGGAAGTAC TTGAACTCGT TCCTGAGCGG AGGCCAGGGT AGGTCTCCGT TCTTGCCAAT
1201 CCCCATATTT TGGGACACGG CGACGATGCA GTTCAATGGT CGAACCATGA TGGCAGCGGG
1261 GATAAAATCC TACCAGCCTT CACGCTAGGA TTGCCGTCAA GTTTGGCGCG AAATCGCAGC
1321 CCTGAGCTGT CCCCCCCCCC AAGCTCAGAT CTGAGCTTGG TCCCTATGGT GAGTCCGTTC
1381 CGCTCTTGTG ATGATAGCCA GACAAGAAAG AGACAATACA AGACAAACAC CAAATAGTAG
1441 AAATAGAGAC AAGGGTCACT TATCCGAGGG TCCCTGTTCG GGCGCCAGCT GCCGCAGTCG
1501 GCCGACCTGA GGGTCGCCGG GGTCTGCGGG GGGACCCTCT GGAAAGTGAA GGATAAGTGA
1561 CGAGCGGAGA CGGGATGGCG AACAGACACA AACACACAAG AGGTGAATGT TAGGACTGTT
1621 GCAAGTTTAC TCAAAAAATC AGCACTCTTT TATATCTTGG TTTACATAAG CATTTACATA
1681 AGATTTGGAT AAATTCCAAA AGAACATAGG AAAATAGAAC ACTCAGAGCT CAGATCAGAA
1741 CCTTTGATAC CAAACCAAGT CAGGAAACCA CTTGTCTCAC ATCCTCGTTT TAAGAACAGT
1801 TTGTAACCAA AAACTTACTT AAGCCCTGGG AACCGCAAGG TTGGGCCAAT AAAGGCTATT
1861 CATAATAACT CATGCCATGA GTTTTTGCAG AATAATGTTC TATTAGTCCA GCCACTGTCC
1921 CCTCCTTGGT ATGGAAAATC TTTCCCCAAA AGTGCATTCC TGTTCCTAGA TAAATATAAT
1981 CATGTACCTG TTGTTTCATG TCGTCTTTTT CTTCTTGAGA CAACATACAC CAAGGAGGTC
2041 TAGCTCTGGC GAGTCTTTCA CGAAAAGGGA GGGATCTATA TAACACTTTA TAGCCATTGA
2101 CTGTAACCCA CCTATCCCAA TTTAAGTCAT ATCTTCCTGT ATATGGTAAG GGGGCATCTG
2161 TTGGTCTGTA GATGTAAGGT CCCCTATAAG TCCCTGGTTG CCACCACCTG TCTCCTATTT
2221 TGACAAAAAC ACTCTTTTTT CCCTTTTTTA CTTCTAGGCC TGTGGTCAAT AGTCCTTGCA
2281 CCTGTTCTTC AATTGAGGTT GAGCGTCTCT TTCTATTTTC TATTCCCATT TCTAACTTCT
2341 GAATTTGAGT AAAAATAGTA CTAAAAGATA ATGATTCATT TCTTAACATA GTAACTAATA
2401 ATCTACCTAT TGGATTGGTC TTATTGGTAA AAATATAATT TTTAGCAAGC ATTCTTATTT
2461 CTATTTCTGA AGGACAAAAT CGATGCGGCT TGTAAGAGGA AGTTGGCTGT GGTCCTTGCC
2521 TCAGGAGGAA GGTCGAGTTC TCCGAATTGT TTAGATTGTA ATCTTGCACA GAAGAGCTAT
2581 TAAAAGAGTC AAGGGTGAGA GCCCTGCGAG CACGAACCGC AACTTCCCCC AATAGCCCCA
2641 GGCAAAGCAG AGCTATGCCA AGTTTGCAGC AGAGAATGAA TATGTCTTTG TCTGATGGGC
2701 TCATCCGTTT GTGCGCAGAC GGGTCGTCCT TGGTGGGAAA CAACCCCTTG GCTGCTTCTC
2761 CCCTAGGTGT AGGACACTCT CGGGAGTTCA ACCATTTCTG CCCAAGCTCA GATCTGAGCT
2821 TTAATGCGGT AGTTTATCAC AGTTAAATTG CTAACGCAGT CAGGCACCGT GTATGAAATC
2881 TAACAATGCG CTCATCGTCA TCCTCGGCAC CGTCACCCTG GATGCTGTAG GCATAGGCTT
2941 GGTTATGCCG GTACTGCCGG GCCTCTTGCG GGATATCGTC CATTCCGACA GCATCGCCAG
3001 TCACTATGGC GTGCTGCTAG CGCTCTTCCG CTTCCTCGCT CACTGACTCG CTGCGCTCGG
3061 TCGTTCGGCT GCGGCGAGCG GTATCAGCTC ACTCAAAGGC GGTAATACGG TTATCCACAG
3121 AATCAGGGGA TAACGCAGGA AAGAACATGT GAGCAAAAGG CCAGCAAAAG GCCAGGAACC
3181 GTAAAAAGGC CGCGTTGCTG GCGTTTTTCC ATAGGCTCCG CCCCCCTGAC GAGCATCACA
3241 AAAATCGACG CTCAAGTCAG AGGTGGCGAA ACCCGACAGG ACTATAAAGA TACCAGGCGT
3301 TTCCCCCTGG AAGCTCCCTC GTGCGCTCTC CTGTTCCGAC CCTGCCGCTT ACCGGATACC
3361 TGTCCGCCTT TCTCCCTTCG GGAAGCGTGG CGCTTTCTCA TAGCTCACGC TGTAGGTATC
3421 TCAGTTCGGT GTAGGTCGTT CGCTCCAAGC TGGGCTGTGT GCACGAACCC CCCGTTCAGC
3481 CCGACCGCTG CGCCTTATCC GGTAACTATC GTCTTGAGTC CAACCCGGTA AGACACGACT
3541 TATCGCCACT GGCAGCAGCC ACTGGTAACA GGATTAGCAG AGCGAGGTAT GTAGGCGGTG
3601 CTACAGAGTT CTTGAAGTGG TGGCCTAACT ACGGCTACAC TAGAAGGACA GTATTTGGTA
3661 TCTGCGCTCT GCTGAAGCCA GTTACCTTCG GAAAAAGAGT TGGTAGCTCT TGATCCGGCA
3721 AACAAACCAC CGCTGGTAGC GGTGGTTTTT TTGTTTGCAA GCAGCAGATT ACGCGCAGAA
3781 AAAAAGGATC TCAAGAAGAT CCTTTGATCT TTTCTACGGG GTCTGACGCT CAGTGGAACG
3841 AAAACTCACG TTAAGGGATT TTGGTCATGA GATTATCAAA AAGGATCTTC ACCTAGATCC
3901 TTTTAAATTA AAAATGAAGT TTTAAATCAA TCTAAAGTAT ATATGAGTAA ACTTGGTCTG
3961 ACAGTTACCA ATGCTTAATC AGTGAGGCAC CTATCTCAGC GATCTGTCTA TTTCGTTCAT
4021 CCATAGTTGC CTGACTCCCC GTCGTGTAGA TAACTACGAT ACGGGAGGGC TTACCATCTG
4081 GCCCCAGTGC TGCAATGATA CCGCGAGACC CACGCTCACC GGCTCCAGAT TTATCAGCAA
4141 TAAACCAGCC AGCCGGAAGG GCCGAGCGCA GAAGTGGTCC TGCAACTTTA TCCGCCTCCA
4201 TCCAGTCTAT TAATTGTTGC CGGGAAGCTA GAGTAAGTAG TTCGCCAGTT AATAGTTTGC
4261 GCAACGTTGT TGCCATTGCT ACAGGCATCG TGGTGTCACG CTCGTCGTTT GGTATGGCTT
4321 CATTCAGCTC CGGTTCCCAA CGATCAAGGC GAGTTACATG ATCCCCCATG TTGTGCAAAA
4381 AAGCGGTTAG CTCCTTCGGT CCTCCGATCG TTGTCAGAAG TAAGTTGGCC GCAGTGTTAT
4441 CACTCATGGT TATGGCAGCA CTGCATAATT CTCTTACTGT CATGCCATCC GTAAGATGCT
4501 TTTCTGTGAC TGGTGAGTAC TCAACCAAGT CATTCTGAGA ATAGTGTATG CGGCGACCGA
4561 GTTGCTCTTG CCCGGCGTCA ACACGGGATA ATACCGCGCC ACATAGCAGA ACTTTAAAAG

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4621  TGCTCATCAT TGGAAAACGT TCTTCGGGGC GAAAACTCTC AAGGATCTTA CCGCTGTTGA
4681  GATCCAGTTC GATGTAACCC ACTCGTGCAC CCAACTGATC TTCAGCATCT TTTACTTTCA
4741  CCAGCGTTTC TGGGTGAGCA AAAACAGGAA GGCAAAATGC CGCAAAAAAG GGAATAAGGG
4801  CGACACGGAA ATGTTGAATA CTCATACTCT TCCTTTTTCA ATATTATTGA AGCATTTATC
4861  AGGGTTATTG TCTCATGAGC GGATACATAT TTGAATGTAT TTAGAAAAAT AAACAAATAG
4921  GGGTTCCGCG CACATTTCCC CGAAAAGTGC CACCTGACGT CTAAGAGACC ATTATTATCA
4981  TGACATTAAC CTATAAAAAT AGGCGTATCA CGAGGCCCTT TCGTCTTCAA GAATTGTCTA
5041  GAGGCGCGCC GTTTAAACCC TCAGCTACCG ATGTACGGGC CAGATATACG CGTTGACATT
5101  GATTATTGAC TAGTTATTAA TAGTAATCAA TTACGGGGTC ATTAGTTCAT AGCCCATATA
5161  TGGAGTTCCG CGTTACATAA CTTACGGTAA ATGGCCCGCC TGGCTGACCG CCCAACGACC
5221  CCCGCCCATT GACGTCAATA ATGACGTATG TTCCCATAGT AACGCCAATA GGGACTTTCC
5281  ATTGACGTCA ATGGGTGGAC TATTTACGGT AAACTGCCCA CTTGGCAGTA CATCAAGTGT
5341  ATCATATGCC AAGTACGCCC CCTATTGACG TCAATGACGG TAAATGGCCC GCCTGGCATT
5401  ATGCCCAGTA CATGACCTTA TGGGACTTTC CTACTTGGCA GTACATCTAC GTATTAGTCA
5461  TCGCTATTAC CATGGTGATG CGGTTTTGGC AGTACATCAA TGGGCGTGGA TAGCGGTTTG
5521  ACTCACGGGG ATTTCCAAGT CTCCACCCCA TTGACGTCAA TGGGAGTTTG TTTTGGCACC
5581  AAAATCAACG GGACTTTCCA AAATGTCGTA ACAACTCCGC CCCATTGACG CAAATGGGCG
5641  GTAGGCGTGT ACGGTGGGAG GTCTATATAA GCAGAGCTCT CTGGCTAACT AGAGAACCCA
5701  CTGCTTACTG GCTTATCGAA ATTAATACGA CTCACTATAG CAATTGCACG TGTGGCCACA
5761  GGTAAGTTTA AAGCTCAGGT CGAGACCGGG CCTTTGTCCG GCGCTCCCTT GGAGCCTACC
5821  TAGACTCAGC CGGCTCTCCA CGCTTTGCCT GACCCTGCTT GCTCAACTCT ACGTCTTTGT
5881  TTCGTTTTCT GTTCCTTTCT CTCCACAGGC TTAAGCTCGA GGCCGCCACC ATGGCCGTGC
5941  TGGGCCTGCT GTTCTGCCTG GTGACCTTCC CTTCCTGCGT GCTGTCCCAG GTGCAGCTGG
6001  TGCAGTCCGG CGTGGAGGTG AAGAAGCCTG GCGCCTCCGT CAAGGTGTCC TGTAAGGCCT
6061  CCGGCTACAC CTTCACCAAC TACTACATGT ACTGGGTGCG GCAGGCCCCA GGCCAGGGAC
6121  TGGAGTGGAT GGGCGGCATC AACCCTTCCA ACGGCGGCAC CAACTTCAAC GAGAAGTTCA
6181  AGAACCGGGT GACCCTGACC ACCGACTCCT CCACCACAAC CGCCTACATG GAACTGAAGT
6241  CCCTGCAGTT CGACGACACC GCCGTGTACT ACTGCGCCAG GCGGGACTAC CGGTTCGACA
6301  TGGGCTTCGA CTACTGGGGC CAGGGCACCA CCGTGACCGT GTCCTCCGCT AGCACCAAGG
6361  GCCCTTCCGT GTTCCCTCTG GCCCCTTGCT CCCGGTCCAC CTCCGAGTCC ACCGCCGCTC
6421  TGGGCTGTCT GGTGAAGGAC TACTTCCCTG AGCCTGTGAC CGTGAGCTGG AACTCTGGCG
6481  CCCTGACCTC CGGCGTGCAC ACCTTCCCTG CCGTGCTGCA GTCCTCCGGC CTGTACTCCC
6541  TGTCCTCCGT GGTGACCGTG CCTTCCTCCT CCCTGGGCAC CAAGACCTAC ACCTGCAACG
6601  TGGACCACAA GCCTTCCAAC ACCAAGGTGG ACAAGCGGGT GGAGTCCAAG TACGGCCCTC
6661  CTTGCCCTCC CTGCCCTGCC CCTGAGTTCC TGGGCGGACC CTCCGTGTTC CTGTTCCCTC
6721  CTAAGCCTAA GGACACCCTG ATGATCTCCC GGACCCCTGA GGTGACCTGC GTGGTGGTGG
6781  ACGTGTCCCA GGAAGATCCT GAGGTCCAGT TCAATTGGTA CGTGGATGGC GTGGAGGTGC
6841  ACAACGCCAA GACCAAGCCT CGGGAGGAAC AGTTCAACTC CACCTACCGG GTGGTGTCTG
6901  TGCTGACCGT GCTGCACCAG GACTGGCTGA ACGGCAAGGA ATACAAGTGC AAGGTCAGCA
6961  ACAAGGGCCT GCCCTCCTCC ATCGAGAAAA CCATCTCCAA GGCCAAGGGC CAGCCTCGCG
7021  AGCCTCAGGT GTACACCCTG CCTCCTAGCC AGGAAGAGAT GACCAAGAAT CAGGTGTCCC
7081  TGACATGCCT GGTGAAGGGC TTCTACCCTT CCGATATCGC CGTGGAGTGG GAGAGCAACG
7141  GCCAGCCAGA GAACAACTAC AAGACCACCC CTCCTGTGCT GGACTCCGAC GGCTCCTTCT
7201  TCCTGTACTC CAGGCTGACC GTGGACAAGT CCCGGTGGCA GGAAGGCAAC GTCTTTTCCT
7261  GCTCCGTGAT GCACGAGGCC CTGCACAACC ACTACACCCA GAAGTCCCTG TCCCTGTCTC
7321  TGGGCAAGTG AATCGATGGA TCCAGATCCC CCTCGCTTTC TTGCTGTCCA ATTTCTATTA
7381  AAGGTTCCTT TGTTCCCTAA GTCCAACTAC TAAACTGGGG GATATTATGA AGGGCCTTGA
7441  GCATCTGGAT TCTGCCTAAT AAAAAACATT TATTTTCATT GCAATGATGT ATTTAAATTA
7501  TTTCTGAATA TTTTACTAAA AAGGGAATGT GGGAGGTCAG TGCATTTAAA ACATAAAGAA
7561  ATGAAGAGGG GGATCTGTCG ACAAGCTCTA GAGAGCTCAC GCGTTGATCA TGTACAGGCC
7621  GGCCAAGCTT TCGACTAGCT TGGCACGCCA GAAATCCGCG CGGTGGTTTT TGGGGGTCGG
7681  GGGTGTTTGG CAGCCACAGA CGCCCGGTGT TCGTGTCGCG CCAGTACATG CGGTCCATGC
7741  CCAGGCCATC CAAAAACCAT GGGTCTGTCT GCTCAGTCCA GTCGTGGACC TGACCCCACG
7801  CAACGCCCAA AATAATAACC CCCACGAACC ATAAACCATT CCCCATGGGG GACCCCGTCC
7861  CTAACCCACG GGGCCAGTGG CTATGGCAGG GCCTGCCGCC CCGACGTTGG CTGCGAGCCC
7921  TGGGCCTTCA CCCGAACTTG GGGGGTGGGG TGGGGAAAAG GAAGAAACGC GGGCGTATTG
7981  GCCCCAATGG GGTCTCGGTG GGGTATCGAC AGAGTGCCAG CCCTGGGACC GAACCCCGCG
8041  TTTATGAACA AACGACCCAA CACCCGTGCG TTTTATTCTG TCTTTTTATT GCCGTCATAG
8101  CGCGGGTTCC TTCCGGTATT GTCTCCTTCC GTGTTTCAGT TAGCCTCCCC CATCTCCCGA
8161  TCCGGACGAG TGCTGGGGCG TCGGTTTCCA CTATCGGCGA GTACTTCTAC ACAGCCATCG
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8221 GTCCAGACGG CCGCGCTTCT GCGGGCGATT TGTGTACGCC CGACAGTCCC GGCTCCGGAT
8281 CGGACGATTG CGTCGCATCG ACCCTGCGCC CAAGCTGCAT CATCGAAATT GCCGTCAACC
8341 AAGCTCTGAT AGAGTTGGTC AAGACCAATG CGGAGCATAT ACGCCCGGAG CCGCGGCGAT
8401 CCTGCAAGCT CCGGATGCCT CCGCTCGAAG TAGCGCGTCT GCTGCTCCAT ACAAGCCAAC
8461 CACGGCCTCC AGAAGAAGAT GTTGGCGACC TCGTATTGGG AATCCCCGAA CATCGCCTCG
8521 CTCCAGTCAA TGACCGCTGT TATGCGGCCA TTGTCCGTCA GGACATTGTT GGAGCCGAAA
8581 TCCGCGTGCA CGAGGTGCCG GACTTCGGGG CAGTCCTCGG CCCAAAGCAT CAGCTCATCG
8641 AGAGCCTGCG CGACGGACGC ACTGACGGTG TCGTCCATCA CAGTTTGCCA GTGATACACA
8701 TGGGGATCAG CAATCGCGCA TATGAAATCA CGCCATGTAG TGTATTGACC GATTCCTTGC
8761 GGTCCGAATG GGCCGAACCC GCTCGTCTGG CTAAGATCGG CCGCAGCGAT CGCATCCATG
8821 GCCTCCGCGA CCGGCTGCAG AACAGCGGGC AGTTCGGTTT CAGGCAGGTC TTGCAACGTG
8881 ACACCCTGTG CACGGCGGGA GATGCAATAG GTCAGGCTCT CGCTGAATTC CCCAATGTCA
8941 AGCACTTCCG GAATCGGGAG CGCGGCCGAT GCAAAGTGCC GATAAACATA ACGATCTTTG
9001 TAGAAACCAT CGGCGCAGCT ATTTACCCGC AGGACATATC CACGCCCTCC TACATCGAAG
9061 CTGAAAGCAC GAGATTCTTC GCCCTCCGAG AGCTGCATCA GGTCGGAGAC GCTGTCGAAC
9121 TTTTCGATCA GAAACTTCTC GACAGACGTC GCGGTGAGTT CAGGCTTTTT CATATCTCAT
9181 TGCCCCCCGG GATCTGCGGC ACGCTGTTGA CGCTGTTAAG CGGGTCGCTG CAGGGTCGCT
9241 CGGTGTTCGA GGCCACACGC GTCACCTTAA TATGCGAAGT GGACCTCGGA CCGCGCCGCC
9301 CCGACTGCAT CTGCGTGTTC GAATTCGCCA ATGACAAGAC GCTGGGCGGG GTTTGTGTCA
9361 TCATAGAACT AAAGACATGC AAATATATTT CTTCCGGGGA CACCGCCAGC AAACGCGAGC
9421 AACGGGCCAC GGGGATGAAG CAGGGCGGCA CCTCGCTAAC GGATTCACCA CTCCAAGAAT
9481 TGGAGCCAAT CAATTCTTGC GGAGAACTGT GAATGCGCAA ACCAACCCTT GGCAGAACAT
9541 ATCCATCGCG TCCGCCATCT CCAGCAGCCG CACGCGGCGC ATCTCGGGGC CGACGCGCTG
9601 GGCTACGTCT TGCTGGCGTT CGCACAGGCC GGCCAGCGCG CGGCCGGCCG GTACCACGCG
9661 TTGGCCACAT ATGGCGGCCG CTCGCGATTA ATTAATCGCG ATGGCCACAT ATGGAGCTCT
9721 CTAGAGCTTG TCGACAGATC CCCCTCTTCA TTTCTTTATG TTTTAAATGC ACTGACCTCC
9781 CACATTCCCT TTTTAGTAAA ATATTCAGAA ATAATTTAAA TACATCATTG CAATGAAAAT
9841 AAATGTTTTT TATTAGGCAG AATCCAGATG CTCAAGGCCC TTCATAATAT CCCCCAGTTT
9901 AGTAGTTGGA CTTAGGGAAC AAAGGAACCT TTAATAGAAA TTGGACAGCA AGAAAGCGAG
9961 GGGGATCTGG ATCCCTCCCT TCAGCACTCG CCCCGGTTGA AGGACTTGGT CACAGGGCTG
10021 GACAGGCCCT GGTGGGTCAC CTCGCAGGCG TACACCTTGT GCTTCTCGTA GTCGGCCTTG
10081 GACAGGGTCA GGGTGGAGGA CAGGGAGTAG GTGCTGTCCT TGGAGTCCTG CTCGGTGACG
10141 GATTCCTGGG AGTTGCCGGA CTGCAGGGCA TTGTCCACCT TCCACTGCAC CTTGGCCTCC
10201 CGAGGGTAGA AGTTGTTCAG CAGGCACACC ACGGAGGCGG TGCCGGACTT CAGCTGCTCG
10261 TCGGAGGGAG GGAAGATGAA CACGGAAGGA GCGGCCACCG TACGCTTGAT CTCCAGCTTG
10321 GTGCCCTGGC CGAAGGTCAG AGGCAGGTCC CGGGAGTGCT GGCAGTAGTA CACGCCCACG
10381 TCCTCGGCCT CCACCCGGGA GATCTTCAGG GTGAAGTCGG TGCCGCTGCC GGAGCCGGAG
10441 AACCGGTCAG GCACGCCGGA CTCCAGGTAG GAGGCCAGGT AGATCAGCAG CTGGGGGGAC
10501 TGGCCAGGCT TCTGCAGATA CCAGTGCAGG TAGGAGTAGC CGGAGGTGGA CACGCCCTTG
10561 GAGGCCCGGC AGGAGATGGA GGCAGGCTCG CCAGGGGTCA CAGGCAGGGA CAGAGGGGAC
10621 TGGGTCAGCA CGATCTCGCA CCGCATGGCA GGCAGGAACA GCACCAGCAG GCCCAGCAGC
10681 TGCACAGGGG CCATGGTGGC GGCCTCGAGG AATTCTTAAG CCTGTGGAGA GAAAGGAACA
10741 GAAAACGAAA CAAAGACGTA GAGTTGAGCA AGCAGGGTCA GGCAAAGCGT GGAGAGCCGG
10801 CTGAGTCTAG GTAGGCTCCA AGGGAGCGCC GGACAAAGGC CCGGTCTCGA CCTGAGCTTT
10861 AAACTTACCT GTGGCCACAC GTGCAATTGC TATAGTGAGT CGTATTAATT TCGATAAGCC
10921 AGTAAGCAGT GGGTTCTCTA GTTAGCCAGA GAGCTCTGCT TATATAGACC TCCCACCGTA
10981 CACGCCTACC GCCCATTTGC GTCAATGGGG CGGAGTTGTT ACGACATTTT GGAAAGTCCC
11041 GTTGATTTTG GTGCCAAAAC AAACTCCCAT TGACGTCAAT GGGGTGGAGA CTTGGAAATC
11101 CCCGTGAGTC AAACCGCTAT CCACGCCCAT TGATGTACTG CCAAAACCGC ATCACCATGG
11161 TAATAGCGAT GACTAATACG TAGATGTACT GCCAAGTAGG AAAGTCCCAT AAGGTCATGT
11221 ACTGGGCATA ATGCCAGGCG GGCCATTTAC CGTCATTGAC GTCAATAGGG GGCGTACTTG
11281 GCATATGATA CACTTGATGT ACTGCCAAGT GGGCAGTTTA CCGTAAATAG TCCACCCATT
11341 GACGTCAATG GAAAGTCCCT ATTGGCGTTA CTATGGGAAC ATACGTCATT ATTGACGTCA
11401 ATGGGCGGGG GTCGTTGGGC GGTCAGCCAG GCGGGCCATT TACCGTAAGT TATGTAACGC
11461 GGAACTCCAT ATATGGGCTA TGAACTAATG ACCCCGTAAT TGATTACTAT TAATAACTAG
11521 TCAATAATCA ATGTCAACGC GTATATCTGG CCCGTACATC GGTAACTAGT CGGACCGGCC
11581 CGGGCCACCG GTGCTCGAAG CTTGGATCGA TCCAGACATG ATAAGATACA TTGATGAGTT
11641 TGGACAAACC ACAACTAGAA TGCAGTGAAA AAAATGCTTT ATTTGTGAAA TTTGTGATGC
11701 TATTGCTTTA TTTGTAACCA TTATAAGCTG CAATAAACAA GTTAACAACA ACAATTGCAT
11761 TCATTTTATG TTTCAGGTTC AGGGGGAGGT GTGGGAGGTT TTTTAAAGCA AGTAAAACCT

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11821    CTACAAATGT GGTATGGCTG ATTATGATCT CTAGTCAAG
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(SEQ ID NO: 47)

The present invention further provides, in part, isolated plasmids which exhibit high levels of expression of anti-HGF (hepatocyte growth factor) heavy and light chains. One plasmid is pAHGFV1. The sequence of the pAHGFV1 plasmid is set forth below:

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     1    GGCACTATAC ATCAAATATT CCTTATTAAC CCCTTTACAA ATTAAAAAGC TAAAGGTACA
    61    CAATTTTTGA GCATAGTTAT TAATAGCAGA CACTCTATGC CTGTGTGGAG TAAGAAAAAA
   121    CAGTATGTTA TGATTATAAC TGTTATGCCT ACTTATAAAG GTTACAGAAT ATTTTTCCAT
   181    AATTTTCTTG TATAGCAGTG CAGCTTTTTC CTTTGTGGTG TAAATAGCAA AGCAAGCAAG
   241    AGTTCTATTA CTAAACACAG CATGACTCAA AAAACTTAGC AATTCTGAAG GAAAGTCCTT
   301    GGGGTCTTCT ACCTTTCTCT TCTTTTTTGG AGGAGTAGAA TGTTGAGAGT CAGCAGTAGC
   361    CTCATCATCA CTAGATGGCA TTTCTTCTGA GCAAAACAGG TTTTCCTCAT TAAAGGCATT
   421    CCACCACTGC TCCCATTCAT CAGTTCCATA GGTTGGAATC TAAAATACAC AAACAATTAG
   481    AATCAGTAGT TTAACACATT ATACACTTAA AAATTTTATA TTTACCTTAG AGCTTTAAAT
   541    CTCTGTAGGT AGTTTGTCCA ATTATGTCAC ACCACAGAAG TAAGGTTCCT TCACAAAGAT
   601    CGATCTAAAG CCAGCAAAAG TCCCATGGTC TTATAAAAAT GCATAGCTTT AGGAGGGGAG
   661    CAGAGAACTT GAAAGCATCT TCCTGTTAGT CTTTCTTCTC GTAGACTTCA AACTTATACT
   721    TGATGCCTTT TTCCTCCTGG ACCTCAGAGA GGACGCCTGG GTATTCTGGG AGAAGTTTAT
   781    ATTTCCCCAA ATCAATTTCT GGGAAAAACG TGTCACTTTC AAATTCCTGC ATGATCCTTG
   841    TCACAAAGAG TCTGAGGTGG CCTGGTTGAT TCATGGCTTC CTGGTAAACA GAACTGCCTC
   901    CGACTATCCA AACCATGTCT ACTTTACTTG CCAATTCCGG TTGTTCAATA AGTCTTAAGG
   961    CATCATCCAA ACTTTTGGCA AGAAAATGAG CTCCTCGTGG TGGTTCTTTG AGTTCTCTAC
  1021    TGAGAACTAT ATTAATTCTG TCCTTTAAAG GTCGATTCTT CTCAGGAATG GAGAACCAGG
  1081    TTTTCCTACC CATAATCACC AGATTCTGTT TACCTTCCAC TGAAGAGGTT GTGGTCATTC
  1141    TTTGGAAGTA CTTGAACTCG TTCCTGAGCG GAGGCCAGGG TAGGTCTCCG TTCTTGCCAA
  1201    TCCCCATATT TTGGGACACG GCGACGATGC AGTTCAATGG TCGAACCATG ATGGCAGCGG
  1261    GGATAAAATC CTACCAGCCT TCACGCTAGG ATTGCCGTCA AGTTTGGCGC GAAATCGCAG
  1321    CCCTGAGCTG TCCCCCCCCC CAAGCTCAGA TCTGAGCTTG GTCCCTATGG TGAGTCCGTT
  1381    CCGCTCTTGT GATGATAGCC AGACAAGAAA GAGACAATAC AAGACAAACA CCAAATAGTA
  1441    GAAATAGAGA CAAGGGTCAC TTATCCGAGG GTCCCTGTTC GGGCGCCAGC TGCCGCAGTC
  1501    GGCCGACCTG AGGGTCGCCG GGGTCTGCGG GGGGACCCTC TGGAAAGTGA AGGATAAGTG
  1561    ACGAGCGGAG ACGGGATGGC GAACAGACAC AAACACACAA GAGGTGAATG TTAGGACTGT
  1621    TGCAAGTTTA CTCAAAAAAT CAGCACTCTT TTATATCTTG GTTTACATAA GCATTTACAT
  1681    AAGATTTGGA TAAATTCCAA AAGAACATAG GAAAATAGAA CACTCAGAGC TCAGATCAGA
  1741    ACCTTTGATA CCAAACCAAG TCAGGAAACC ACTTGTCTCA CATCCTCGTT TTAAGAACAG
  1801    TTTGTAACCA AAAACTTACT TAAGCCCTGG GAACCGCAAG GTTGGGCCAA TAAAGGCTAT
  1861    TCATAATAAC TCATGCCATG AGTTTTTGCA GAATAATGTT CTATTAGTCC AGCCACTGTC
  1921    CCCTCCTTGG TATGGAAAAT CTTTCCCCAA AAGTGCATTC CTGTTCCTAG ATAAATATAA
  1981    TCATGTACCT GTTGTTTCAT GTCGTCTTTT TCTTCTTGAG ACAACATACA CCAAGGAGGT
  2041    CTAGCTCTGG CGAGTCTTTC ACGAAAAGGG AGGGATCTAT ATAACACTTT ATAGCCATTG
  2101    ACTGTAACCC ACCTATCCCA ATTTAAGTCA TATCTTCCTG TATATGGTAA GGGGGCATCT
  2161    GTTGGTCTGT AGATGTAAGG TCCCCTATAA GTCCCTGGTT GCCACCACCT GTCTCCTATT
  2221    TTGACAAAAA CACTCTTTTT TCCCTTTTTT ACTTCTAGGC CTGTGGTCAA TAGTCCTTGC
  2281    ACCTGTTCTT CAATTGAGGT TGAGCGTCTC TTTCTATTTT CTATTCCCAT TTCTAACTTC
  2341    TGAATTTGAG TAAAAATAGT ACTAAAAGAT AATGATTCAT TTCTTAACAT AGTAACTAAT
  2401    AATCTACCTA TTGGATTGGT CTTATTGGTA AAAATATAAT TTTTAGCAAG CATTCTTATT
  2461    TCTATTTCTG AAGGACAAAA TCGATGCGGC TTGTAAGAGG AAGTTGGCTG TGGTCCTTGC
  2521    CTCAGGAGGA AGGTCGAGTT CTCCGAATTG TTTAGATTGT AATCTTGCAC AGAAGAGCTA
  2581    TTAAAAGAGT CAAGGGTGAG AGCCCTGCGA GCACGAACCG CAACTTCCCC CAATAGCCCC
  2641    AGGCAAAGCA GAGCTATGCC AAGTTTGCAG CAGAGAATGA ATATGTCTTT GTCTGATGGG
  2701    CTCATCCGTT TGTGCGCAGA CGGGTCGTCC TTGGTGGGAA ACAACCCCTT GGCTGCTTCT
  2761    CCCCTAGGTG TAGGACACTC TCGGGAGTTC AACCATTTCT GCCCAAGCTC AGATCTGAGC
  2821    TTTAATGCGG TAGTTTATCA CAGTTAAATT GCTAACGCAG TCAGGCACCG TGTATGAAAT
  2881    CTAACAATGC GCTCATCGTC ATCCTCGGCA CCGTCACCCT GGATGCTGTA GGCATAGGCT
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2941  TGGTTATGCC GGTACTGCCG GGCCTCTTGC GGGATATCGT CCATTCCGAC AGCATCGCCA
3001  GTCACTATGG CGTGCTGCTA GCGCTCTTCC GCTTCCTCGC TCACTGACTC GCTGCGCTCG
3061  GTCGTTCGGC TGCGGCGAGC GGTATCAGCT CACTCAAAGG CGGTAATACG GTTATCCACA
3121  GAATCAGGGG ATAACGCAGG AAAGAACATG TGAGCAAAAG GCCAGCAAAA GGCCAGGAAC
3181  CGTAAAAAGG CCGCGTTGCT GGCGTTTTTC CATAGGCTCC GCCCCCCTGA CGAGCATCAC
3241  AAAAATCGAC GCTCAAGTCA GAGGTGGCGA AACCCGACAG GACTATAAAG ATACCAGGCG
3301  TTTCCCCCTG GAAGCTCCCT CGTGCGCTCT CCTGTTCCGA CCCTGCCGCT TACCGGATAC
3361  CTGTCCGCCT TTCTCCCTTC GGGAAGCGTG GCGCTTTCTC ATAGCTCACG CTGTAGGTAT
3421  CTCAGTTCGG TGTAGGTCGT TCGCTCCAAG CTGGGCTGTG TGCACGAACC CCCCGTTCAG
3481  CCCGACCGCT GCGCCTTATC CGGTAACTAT CGTCTTGAGT CCAACCCGGT AAGACACGAC
3541  TTATCGCCAC TGGCAGCAGC CACTGGTAAC AGGATTAGCA GAGCGAGGTA TGTAGGCGGT
3601  GCTACAGAGT TCTTGAAGTG GTGGCCTAAC TACGGCTACA CTAGAAGGAC AGTATTTGGT
3661  ATCTGCGCTC TGCTGAAGCC AGTTACCTTC GGAAAAAGAG TTGGTAGCTC TTGATCCGGC
3721  AAACAAACCA CCGCTGGTAG CGGTGGTTTT TTTGTTTGCA AGCAGCAGAT TACGCGCAGA
3781  AAAAAAGGAT CTCAAGAAGA TCCTTTGATC TTTTCTACGG GGTCTGACGC TCAGTGGAAC
3841  GAAAACTCAC GTTAAGGGAT TTTGGTCATG AGATTATCAA AAAGGATCTT CACCTAGATC
3901  CTTTTAAATT AAAAATGAAG TTTTAAATCA ATCTAAAGTA TATATGAGTA AACTTGGTCT
3961  GACAGTTACC AATGCTTAAT CAGTGAGGCA CCTATCTCAG CGATCTGTCT ATTTCGTTCA
4021  TCCATAGTTG CCTGACTCCC CGTCGTGTAG ATAACTACGA TACGGGAGGG CTTACCATCT
4081  GGCCCCAGTG CTGCAATGAT ACCGCGAGAC CCACGCTCAC CGGCTCCAGA TTTATCAGCA
4141  ATAAACCAGC CAGCCGGAAG GGCCGAGCGC AGAAGTGGTC CTGCAACTTT ATCCGCCTCC
4201  ATCCAGTCTA TTAATTGTTG CCGGGAAGCT AGAGTAAGTA GTTCGCCAGT TAATAGTTTG
4261  CGCAACGTTG TTGCCATTGC TACAGGCATC GTGGTGTCAC GCTCGTCGTT TGGTATGGCT
4321  TCATTCAGCT CCGGTTCCCA ACGATCAAGG CGAGTTACAT GATCCCCCAT GTTGTGCAAA
4381  AAAGCGGTTA GCTCCTTCGG TCCTCCGATC GTTGTCAGAA GTAAGTTGGC CGCAGTGTTA
4441  TCACTCATGG TTATGGCAGC ACTGCATAAT TCTCTTACTG TCATGCCATC CGTAAGATGC
4501  TTTTCTGTGA CTGGTGAGTA CTCAACCAAG TCATTCTGAG AATAGTGTAT GCGGCGACCG
4561  AGTTGCTCTT GCCCGGCGTC AACACGGGAT AATACCGCGC CACATAGCAG AACTTTAAAA
4621  GTGCTCATCA TTGGAAAACG TTCTTCGGGG CGAAAACTCT CAAGGATCTT ACCGCTGTTG
4681  AGATCCAGTT CGATGTAACC CACTCGTGCA CCCAACTGAT CTTCAGCATC TTTTACTTTC
4741  ACCAGCGTTT CTGGGTGAGC AAAAACAGGA AGGCAAAATG CCGCAAAAAA GGGAATAAGG
4801  GCGACACGGA AATGTTGAAT ACTCATACTC TTCCTTTTTC AATATTATTG AAGCATTTAT
4861  CAGGGTTATT GTCTCATGAG CGGATACATA TTTGAATGTA TTTAGAAAAA TAAACAAATA
4921  GGGGTTCCGC GCACATTTCC CCGAAAAGTG CCACCTGACG TCTAAGAGAC CATTATTATC
4981  ATGACATTAA CCTATAAAAA TAGGCGTATC ACGAGGCCCT TTCGTCTTCA AGAATTGTCT
5041  AGAGGCGCGC CGTTTAAACC CTCAGCTACC GATGTACGGG CCAGATATAC GCGTTGACAT
5101  TGATTATTGA CTAGTTATTA ATAGTAATCA ATTACGGGGT CATTAGTTCA TAGCCCATAT
5161  ATGGAGTTCC GCGTTACATA ACTTACGGTA AATGGCCCGC CTGGCTGACC GCCCAACGAC
5221  CCCCGCCCAT TGACGTCAAT AATGACGTAT GTTCCCATAG TAACGCCAAT AGGGACTTTC
5281  CATTGACGTC AATGGGTGGA CTATTTACGG TAAACTGCCC ACTTGGCAGT ACATCAAGTG
5341  TATCATATGC CAAGTACGCC CCCTATTGAC GTCAATGACG GTAAATGGCC CGCCTGGCAT
5401  TATGCCCAGT ACATGACCTT ATGGGACTTT CCTACTTGGC AGTACATCTA CGTATTAGTC
5461  ATCGCTATTA CCATGGTGAT GCGGTTTTGG CAGTACATCA ATGGGCGTGG ATAGCGGTTT
5521  GACTCACGGG GATTTCCAAG TCTCCACCCC ATTGACGTCA ATGGGAGTTT GTTTTGGCAC
5581  CAAAATCAAC GGGACTTTCC AAAATGTCGT AACAACTCCG CCCCATTGAC GCAAATGGGC
5641  GGTAGGCGTG TACGGTGGGA GGTCTATATA AGCAGAGCTC TCTGGCTAAC TAGAGAACCC
5701  ACTGCTTACT GGCTTATCGA AATTAATACG ACTCACTATA GCAATTGCAC GTGTGGCCAC
5761  AGGTAAGTTT AAAGCTCAGG TCGAGACCGG GCCTTTGTCC GGCGCTCCCT TGGAGCCTAC
5821  CTAGACTCAG CCGGCTCTCC ACGCTTTGCC TGACCCTGCT TGCTCAACTC TACGTCTTTG
5881  TTTCGTTTTC TGTTCCTTTC TCTCCACAGG CTTAAAACGC CGCCACCATG GGGTCAACCG
5941  CCATCCTCGC CCTCCTCCTG GCTGTTCTCC AAGGAGTCTG TGCCGAAGTG CAGCTGGTGC
6001  AGTCTGGAGC AGAGGTGAAA AAGCCCGGGG AGTCTCTGAA GATCTCCTGT AAGGGTTCTG
6061  GATACAGCTT TACCACCTAC TGGATGCACT GGGTGCGCCA GATGCCCGGG AAAGGCCTGG
6121  AGTGGATGGG GGAGATTAAT CCTACCAACG GTCATACTAA CTACAATCCG TCCTTCCAAG
6181  GCCAGGTCAC CATCTCAGCT GACAAGTCCA TCAGCACTGC CTACCTGCAG TGGAGCAGCC
6241  TGAAGGCCTC GGACACCGCC ATGTATTACT GTGCGAGAAA CTATGTTGGT AGCATCTTTG
6301  ACTACTGGGG CCAAGGAACC CTGGTCACCG TCTCCTCAGC TAGCACCAAG GGCCCATCGG
6361  TCTTCCCCCT GGCACCCTCC TCCAAGAGCA CCTCTGGGGG CACAGCGGCC CTGGGCTGCC
6421  TGGTCAAGGA CTACTTCCCC GAACCGGTGA CGGTGTCGTG GAACTCAGGC GCCCTGACCA
6481  GCGGCGTGCA CACCTTCCCG GCTGTCCTAC AGTCCTCAGG ACTCTACTCC CTCAGCAGCG
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6541  TGGTGACCGT GCCCTCCAGC AGCTTGGGCA CCCAGACCTA CATCTGCAAC GTGAATCACA
6601  AGCCCAGCAA CACCAAGGTG GACAAGAAAG TTGAGCCCAA ATCTTGTGAC AAAACTCACA
6661  CATGCCCACC GTGCCCAGCA CCTGAACTCC TGGGGGGACC GTCAGTCTTC CTCTTCCCCC
6721  CAAAACCCAA GGACACCCTC ATGATCTCCC GGACCCCTGA GGTCACATGC GTGGTGGTGG
6781  ACGTGAGCCA CGAAGACCCT GAGGTCAAGT TCAACTGGTA CGTGGACGGC GTGGAGGTGC
6841  ATAATGCCAA GACAAAGCCG CGGGAGGAGC AGTACAACAG CACGTACCGT GTGGTCAGCG
6901  TCCTCACCGT CCTGCACCAG GACTGGCTGA ATGGCAAGGA GTACAAGTGC AAGGTCTCCA
6961  ACAAAGCCCT CCCAGCCCCC ATCGAGAAAA CCATCTCCAA AGCCAAAGGG CAGCCCCGAG
7021  AACCACAGGT GTACACCCTG CCCCCATCCC GGGATGAGCT GACCAAGAAC CAGGTCAGCC
7081  TGACCTGCCT GGTCAAAGGC TTCTATCCCA GCGACATCGC CGTGGAGTGG GAGAGCAATG
7141  GGCAGCCGGA GAACAACTAC AAGACCACGC CTCCCGTGCT GGACTCCGAC GGCTCCTTCT
7201  TCCTCTACAG CAAGCTCACC GTGGACAAGA GCAGGTGGCA GCAGGGGAAC GTCTTCTCAT
7261  GCTCCGTGAT GCATGAGGCT CTGCACAACC ACTACACGCA GAAGAGCCTC TCCCTGTCTC
7321  CGGGTAAATG AATCGATGAT TCTAGATACG GGTCCGGAGG ATCCAGATCC CCCTCGCTTT
7381  CTTGCTGTCC AATTTCTATT AAAGGTTCCT TTGTTCCCTA AGTCCAACTA CTAAACTGGG
7441  GGATATTATG AAGGGCCTTG AGCATCTGGA TTCTGCCTAA TAAAAAACAT TTATTTTCAT
7501  TGCAATGATG TATTTAAATT ATTTCTGAAT ATTTTACTAA AAAGGGAATG TGGGAGGTCA
7561  GTGCATTTAA AACATAAAGA AATGAAGAGG GGGATCTGTC GACAAGCTCT AGAGAGCTCA
7621  CGCGTTGATC ATGTACAGGC CGGCCAAGCT TTCGACTAGC TTGGCACGCC AGAAATCCGC
7681  GCGGTGGTTT TTGGGGGTCG GGGGTGTTTG GCAGCCACAG ACGCCCGGTG TTCGTGTCGC
7741  GCCAGTACAT GCGGTCCATG CCCAGGCCAT CCAAAAACCA TGGGTCTGTC TGCTCAGTCC
7801  AGTCGTGGAC CTGACCCCAC GCAACGCCCA AAATAATAAC CCCCACGAAC CATAAACCAT
7861  TCCCCATGGG GGACCCCGTC CCTAACCCAC GGGGCCAGTG GCTATGGCAG GGCCTGCCGC
7921  CCCGACGTTG GCTGCGAGCC CTGGGCCTTC ACCCGAACTT GGGGGGTGGG GTGGGGAAAA
7981  GGAAGAAACG CGGGCGTATT GGCCCCAATG GGGTCTCGGT GGGGTATCGA CAGAGTGCCA
8041  GCCCTGGGAC CGAACCCCGC GTTTATGAAC AAACGACCCA ACACCCGTGC GTTTTATTCT
8101  GTCTTTTTAT TGCCGTCATA GCGCGGGTTC CTTCCGGTAT TGTCTCCTTC CGTGTTTCAG
8161  TTAGCCTCCC CCATCTCCCG ATCCGGACGA GTGCTGGGGC GTCGGTTTCC ACTATCGGCG
8221  AGTACTTCTA CACAGCCATC GGTCCAGACG GCCGCGCTTC TGCGGGCGAT TTGTGTACGC
8281  CCGACAGTCC CGGCTCCGGA TCGGACGATT GCGTCGCATC GACCCTGCGC CCAAGCTGCA
8341  TCATCGAAAT TGCCGTCAAC CAAGCTCTGA TAGAGTTGGT CAAGACCAAT GCGGAGCATA
8401  TACGCCCGGA GCCGCGGCGA TCCTGCAAGC TCCGGATGCC TCCGCTCGAA GTAGCGCGTC
8461  TGCTGCTCCA TACAAGCCAA CCACGGCCTC CAGAAGAAGA TGTTGGCGAC CTCGTATTGG
8521  GAATCCCCGA ACATCGCCTC GCTCCAGTCA ATGACCGCTG TTATGCGGCC ATTGTCCGTC
8581  AGGACATTGT TGGAGCCGAA ATCCGCGTGC ACGAGGTGCC GGACTTCGGG GCAGTCCTCG
8641  GCCCAAAGCA TCAGCTCATC GAGAGCCTGC GCGACGGACG CACTGACGGT GTCGTCCATC
8701  ACAGTTTGCC AGTGATACAC ATGGGGATCA GCAATCGCGC ATATGAAATC ACGCCATGTA
8761  GTGTATTGAC CGATTCCTTG CGGTCCGAAT GGGCCGAACC CGCTCGTCTG GCTAAGATCG
8821  GCCGCAGCGA TCGCATCCAT GGCCTCCGCG ACCGGCTGCA GAACAGCGGG CAGTTCGGTT
8881  TCAGGCAGGT CTTGCAACGT GACACCCTGT GCACGGCGGG AGATGCAATA GGTCAGGCTC
8941  TCGCTGAATT CCCCAATGTC AAGCACTTCC GGAATCGGGA GCGCGGCCGA TGCAAAGTGC
9001  CGATAAACAT AACGATCTTT GTAGAAACCA TCGGCGCAGC TATTTACCCG CAGGACATAT
9061  CCACGCCCTC CTACATCGAA GCTGAAAGCA CGAGATTCTT CGCCCTCCGA GAGCTGCATC
9121  AGGTCGGAGA CGCTGTCGAA CTTTTCGATC AGAAACTTCT CGACAGACGT CGCGGTGAGT
9181  TCAGGCTTTT TCATATCTCA TTGCCCCCCG GGATCTGCGG CACGCTGTTG ACGCTGTTAA
9241  GCGGGTCGCT GCAGGGTCGC TCGGTGTTCG AGGCCACACG CGTCACCTTA ATATGCGAAG
9301  TGGACCTCGG ACCGCGCCGC CCCGACTGCA TCTGCGTGTT CGAATTCGCC AATGACAAGA
9361  CGCTGGGCGG GGTTTGTGTC ATCATAGAAC TAAAGACATG CAAATATATT TCTTCCGGGG
9421  ACACCGCCAG CAAACGCGAG CAACGGGCCA CGGGGATGAA GCAGGGCGGC ACCTCGCTAA
9481  CGGATTCACC ACTCCAAGAA TTGGAGCCAA TCAATTCTTG CGGAGAACTG TGAATGCGCA
9541  AACCAACCCT TGGCAGAACA TATCCATCGC GTCCGCCATC TCCAGCAGCC GCACGCGGCG
9601  CATCTCGGGG CCGACGCGCT GGGCTACGTC TTGCTGGCGT TCGCACAGGC CGGCCAGCGC
9661  GCGGCCGGCC GGTACCACGC GTTGGCCACA TATGGCGGCC GCTCGCGATT AATTAATCGC
9721  GATGGCCACA TATGGAGCTC TCTAGAGCTT GTCGACAGAT CCCCCTCTTC ATTTCTTTAT
9781  GTTTTAAATG CACTGACCTC CCACATTCCC TTTTTAGTAA AATATTCAGA AATAATTTAA
9841  ATACATCATT GCAATGAAAA TAAATGTTTT TTATTAGGCA GAATCCAGAT GCTCAAGGCC
9901  CTTCATAATA TCCCCCAGTT TAGTAGTTGG ACTTAGGGAA CAAAGGAACC TTTAATAGAA
9961  ATTGGACAGC AAGAAAGCGA GGGGGATCTG GATCCTCCTA CGTATCTAGA ATCATCGATT
10021 AACACTCTCC CCTGTTGAAG CTCTTTGTCA CGGGGCTGCT CAGGCCCTGA TGGGTCACCT
10081 CGCAGGCGTA CACCTTGTGT TTCTCGTAGT CTGCTTTGCT CAGGGTCAGG GTGCTGCTCA
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10141    GGCTGTAGGT GCTGTCCTTG CTGTCCTGCT CTGTCACGCT CTCCTGGGAG TTGCCGCTCT
10201    GGAGGGCGTT ATCCACCTTC CACTGCACCT TGGCCTCTCT GGGATAGAAG TTATTCAGCA
10261    GGCACACCAC GGAGGCAGTT CCAGACTTCA GCTGCTCATC AGATGGAGGG AAGATGAACA
10321    CAGATGGTGC AGCCACCGTA CGTTTGATCT CCAGCTTGGT CCCCTGGCCA AACGTGTACG
10381    GATAGTTGTA ACTCTGCCCA CAGTAGTAAG TTGCAAAATC TTCAGGTTGC AGACTGCTGA
10441    TGGTGAGAGT GAAATCTGTC CCAGATCCAC TGCCACTGAA CCTTGATGGG ACCCCAGTGT
10501    TCCGGTTGGA TGCCCCATAG ATCAGGAGCT TAGGGGCTTT CCCTGGTTTC TGCTGATACC
10561    AGGATACATA AGAAACCACA TTCTCACTGG CCTTGCAAGT GATGGTGACT CTGTCTCCTA
10621    CAGATGCAGA CAGGGAGGAT GGAGACTGGG TCATCTGGAT GTCACATCTG GCACCTCGGA
10681    GCCAGAGTAG CAGGAGCCCC AGGAGCTGAG CGGGGACCCT CATGTCCATG GTGGCGGCGA
10741    ATTCTCGAGA AGCTTAAGTT TAATTCTTAA GCCTGTGGAG AGAAAGGAAC AGAAAACGAA
10801    ACAAAGACGT AGAGTTGAGC AAGCAGGGTC AGGCAAAGCG TGGAGAGCCG GCTGAGTCTA
10861    GGTAGGCTCC AAGGGAGCGC CGGACAAAGG CCCGGTCTCG ACCTGAGCTT TAAACTTACC
10921    TGTGGCCACA CGTGCAATTG CTATAGTGAG TCGTATTAAT TTCGATAAGC CAGTAAGCAG
10981    TGGGTTCTCT AGTTAGCCAG AGAGCTCTGC TTATATAGAC CTCCCACCGT ACACGCCTAC
11041    CGCCCATTTG CGTCAATGGG GCGGAGTTGT TACGACATTT TGGAAAGTCC CGTTGATTTT
11101    GGTGCCAAAA CAAACTCCCA TTGACGTCAA TGGGGTGGAG ACTTGGAAAT CCCCGTGAGT
11161    CAAACCGCTA TCCACGCCCA TTGATGTACT GCCAAAACCG CATCACCATG GTAATAGCGA
11221    TGACTAATAC GTAGATGTAC TGCCAAGTAG GAAAGTCCCA TAAGGTCATG TACTGGGCAT
11281    AATGCCAGGC GGGCCATTTA CCGTCATTGA CGTCAATAGG GGGCGTACTT GGCATATGAT
11341    ACACTTGATG TACTGCCAAG TGGGCAGTTT ACCGTAAATA GTCCACCCAT TGACGTCAAT
11401    GGAAAGTCCC TATTGGCGTT ACTATGGGAA CATACGTCAT TATTGACGTC AATGGGCGGG
11461    GGTCGTTGGG CGGTCAGCCA GGCGGGCCAT TTACCGTAAG TTATGTAACG CGGAACTCCA
11521    TATATGGGCT ATGAACTAAT GACCCCGTAA TTGATTACTA TTAATAACTA GTCAATAATC
11581    AATGTCAACG CGTATATCTG GCCCGTACAT CGGTAACTAG TCGGACCGGC CCGGGCCACC
11641    GGTGCTCGAA GCTTGGATCG ATCCAGACAT GATAAGATAC ATTGATGAGT TTGGACAAAC
11701    CACAACTAGA ATGCAGTGAA AAAAATGCTT TATTTGTGAA ATTTGTGATG CTATTGCTTT
11761    ATTTGTAACC ATTATAAGCT GCAATAAACA AGTTAACAAC AACAATTGCA TTCATTTTAT
11821    GTTTCAGGTT CAGGGGGAGG TGTGGGAGGT TTTTTAAAGC AAGTAAAACC TCTACAAATG
11881    TGGTATGGCT GATTATGATC TCTAGTCAA
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(SEQ ID NO: 48)

Plasmid maps for these plasmids are also provided herein in figures 1-10.

Expression

Vectors, such as plasmids (*e.g.*, figures 1-10), including a target gene to be expressed may be introduced into a host cell by any of several methods known in the art. If cells without cell wall barriers are used as host cells, transformation can be carried out by the calcium phosphate precipitation method as described by Graham and Van der Eb, Virology, 52: 546 (1978). However, other methods for introducing DNA into cells such as by nuclear injection or by protoplast fusion may also be used. Other methods for transformation include electroporation, liposomal transformation and DEAE-Dextran transformation.

If prokaryotic cells (*e.g.*, *E.coli* such as BL21 or BD21DE3 or HB101 or DH1 or DH5) or cells which contain substantial cell wall constructions (such as *S.cerevisiae*) are used, transformation can be by calcium treatment using calcium chloride as described by Cohen, F. N. *et al.* Proc. Natl. Acad. Sci. (USA) 69: 2110 (1972).

Host cells comprising a vector (*e.g.*, figures 1-10) of the present invention may be selected and screened to identify the clone with the requisite characteristics for expression of a target gene. In Chinese hamster ovary (CHO) cells, one common approach to achieve maximal expression involves the use of mutant cell lines and a gradual increase in the selection pressure over several months for a co-transfected selection marker such as dihydrofolate reductase (DHFR) (Kaufman *et al.* (1982) J. Mol. Biol. 159: 601–621; Schimke *et al.* (1982) Natl. Cancer Inst. Monogr. 60: 79–86). In order to achieve high production rates, a dihydrofolate reductase (DHFR) negative cell line (*e.g.*, a CHO cell line) (Urlaub *et al.* (1980) Proc. Natl. Acad. Sci. USA 77: 4216–4220) is transformed with an expression vector containing a functional *DHFR* gene in combination with the target gene to be expressed. Amplification of the vector-inserted target genes occurs in response to addition of increasing amounts of the DHFR antagonist methotrexate (MTX) to the culture medium and clones or subpopulations carrying multiple copies of the recombinant genes are generated and can be selected (Wurm (1990) Biologicals 18:159–164). The gene amplification process typically takes several months until stable cell lines are obtained which show high target gene copy numbers and high production rates of the desired protein.

In an embodiment of the invention, a polynucleotide of the present invention is integrated into host cell (*e.g.*, CHO, CHO-K1, CHO-D1 DXB11) DNA or is ectopic (non-integrated). In an embodiment of the invention, the polynucleotide of the present invention is present in the cell at several copies per cell (*e.g.*, 2, 3, 4, 5, 6, 7, 8, 9, 10, 15, 20). Where an expression vector has been integrated into the genomic DNA of the host cell to improve stability, the copy number of the vector DNA, and, concomitantly, the amount of product which could be expressed, can be increased by selecting for cell lines in which the vector sequences have been amplified after integration into the DNA of the host cell.

Any of several cell culture mediums known in the art can be used to propagate cells expressing a target gene. Several commercially available culture mediums are available. If expressing a protein to be used therapeutically, animal-product-free media (*e.g.*, serum-free media (SFM)) may be desirable. There are several methods known in the art by which to cells may be adapted to growth in serum-free medium. For example, direct adaption includes merely switching cells from serum supplemented media to serum-free media. Sequential adaptation or weaning includes switching cells from a serum-supplemented medium into a serum-free medium in several steps (*e.g.*, 25% SFM, 50% SFM, 75% SFM, then, 90% SFM for about 3 passages, then 100% SFM). Sequential adaptation tends to be

less harsh on cells than direct adaptation. Generally, to adapt cells to serum-free media, the culture should be in mid-logarithmic phase, > 90% viable and seeded at a higher initial cell inoculum than during adaptation.

A cell line containing a host cell of the present invention may also be stored in a master cell bank (MCB) and working cell bank (WCB). Typically, when a cell line is to be used over many manufacturing cycles, a two-tiered cell banking system consisting of a master cell bank or master seed bank (MSB) and a working cell bank can be established. A cell line is established from a single host cell clone and this cell line is used to make-up the MCB. Generally, this MCB must be characterized and extensively tested for contaminants such as bacteria, fungi, viruses and mycoplasma. A sample of cells from the MCB can be expanded to form the WCB, which is characterized for cell viability prior to use in a manufacturing process. The cells in a MCB or WCB can be stored in vials, for example, at low temperature (*e.g.*, 0°C or lower, -20°C or -80°C).

Typically, the working cell bank includes cells from one vial of the master bank which have been grown for several passages before storage. In general, when future cells are needed, they are taken from the working cell bank; whereas, the master cell bank is used only when necessary, ensuring a stock of cells with a low passage number to avoid genetic variation within the cell culture.

Thus, the present invention includes a method for making a master cell bank comprising transforming a cell, *e.g.*, a CHO cell, with a plasmid of the present invention, selecting a single clonal population of said transformed cells (*e.g.*, a single colony growth on a culture plate), culturing said clonal population (*e.g.*, in liquid growth media), determining if the cells from said culture contains bacteria, viruses, mycoplasma and/or fungi, and, if the cells of the culture are free of detectable levels of such agents, storing cells taken from such culture, *e.g.*, in one or more separate containers, such as vials (*e.g.*, comprising about 10^7 cells per vial), under refrigeration (*e.g.*, at -80°C). The present invention also includes methods for preparing a working cell bank comprising selecting a sample of cells from a master cell bank, growing the cells and storing the cells in one or more containers, such as vials. Cells used to make a working cell bank can also be tested for bacteria, viruses, mycoplasma or fungi as with the master cell bank.

The present invention also includes a master cell bank and/or a working cell bank including any host cell of the present invention (*e.g.*, as set forth herein) or one or more cells therefrom. Cells in a master cell bank or working cell bank can be stored in hundreds

(*e.g.*, 100, 200, 500, 700, 1000, or 2000 vials or more) of containers, such as vials (*e.g.*, glass vials) under refrigeration (*e.g.*, 0°C or lower, -20°C or -80°C).

Examples

These examples are intended to further clarify the present invention and not to limit the invention. Any composition or method, in whole or in part, set forth in the examples form a part of the present invention.

Example 1: Evaluation of an intron element in the antibody expression cassette.

A βGl-IgG intron containing the β-globin splice donor that is present in plasmid pDSRG along with a part of the sequence of pDSRG and an immunoglobulin splice acceptor

was synthesized by PCR:

ATTAATACGA CTCACTATAG CAATTGCACG TGTGGCCACA G/GTAAGTTTA
AAGCTCAGGT CGAGACCGGG CCTTTGTCCG GCGCTCCCTT GGAGCCTACC TAGACTCAGC
CGGCTCTCCA CGCTTTGCCT GACCCTGCTT GCTCAACTCT ACGTCTTTGT TTCGTTTTCT
GTTCCTTTCT CTCCACAG/GC TTAAGAATTC ATAT

(SEQ ID NO: 3)

The sequence containing CAGGTAAGTTTA (SEQ ID NO: 4) is the β-globin splice donor, and the sequence containing TTTCTCTCCACAGGC (SEQ ID NO: 5) is immunoglobulin acceptor site. The slashes represent the predicted splice site between the donor and acceptor sequences.

The intron was inserted downstream of the human CMV promoter, within the 5' flanking region of the expression cassette in anticipation of expression enhancement. To do this, the 5' end of the βGl-IgG intron was extended by PCR to contain a partial sequence of the CMV promoter. The resulting extended PCR product was digested with EcoRI, filled in with Klenow polymerase and digested with NcoI. Simultaneously, the light chain expression plasmid, pUhCMVIGFRLCb2, was also digested with NheI, filled in with Klenow polymerase, and digested with NcoI. The intron was then ligated to pUhCMVIGFRLCb2 to construct pUIGFRLCb2 (SEQ ID NO: 32). To insert the intron into the heavy chain expression plasmid, the PCR-extended, intron-containing fragment was digested with SnaBI and AflII. Simultaneously, pUhyg(-)IG1FRhuH was digested by SnaBI and AflII, and the intron was inserted to construct pUIG1FRmodH (SEQ ID NO: 33). Subsequently, a single plasmid vector containing both the heavy and light chain expression cassettes was

constructed as follows: pUIGFRLCb2 was digested by RsrII and PacI to transfer the light chain expression cassette. pXBLS was also digested by RsrII and PacI and the LCB2-containing light chain expression cassette was inserted to construct pAIGFRLCb2 (SEQ ID NO: 34). pUIG1FRmodH was then digested by BssHII to release the fragment carrying heavy chain and hygromycin-B phosphotransferase expression cassettes. pAIGFRLCb2 was also digested by BssHII and the heavy chain expression cassette was inserted at the site to construct pAIG1FRLCb2V1 (SEQ ID NO: 35) and pAIG1FRLCb2V3 (SEQ ID NO: 36).

The intron containing plasmids were evaluated for antibody expression in a transient transfection by ELISA. The results demonstrated that when the transfection was performed with plasmids carrying the intron in both the heavy and light chain expression cassettes, expression of anti-IGF1R was about two- to three-fold higher than that obtained from transfection by similar plasmids without the intron.

The two single expression plasmids, pAIG1FRLCb2V1 and pAIG1FRLCb2V3, were evaluated for bioactivity in the KIRA (kinase receptor activation) assay. The result suggests that both of the single expression plasmids show equivalent bioactivity to that shown by the purified antibody obtained from 19D12 hybridoma.

Some plasmid vectors were further modified through PCR to incorporate the Kozak consensus sequence (shown below in bold) at the 5' end of the heavy and light chain cDNA sequences. The restriction sites in the primers, noted below, are underlined, and the initiating methionine codons (atg) are in bold and italics.

The primer pair for the heavy chain is as follows:

5' primer: 5'- gcttggtacc**gccgccacc*atg*g**agtttgggctgagctgggtttt-3' (SEQ ID NO: 37)

3' primer: 5'- agaccgatgggcccttggtggaagctgagg -3' (SEQ ID NO: 38)

The 5' primer has a KpnI (ggtacc) site along with the Kozak sequence and the 3' primer has an ApaI site (gggccc).

For the light chain the following primers were used:

5' primer: 5'-gaattcgtttaaac**gccgccacc*atg***tcgccatcacaactcattgggt-3' (SEQ ID NO: 39)

3' primer: 5'-ccaccgtacgtttgatctccaccttggtccctt-3' (SEQ ID NO: 40)

The 5' primer for the light chain has an EcoRI (gaattc) and a PmeI (gtttaaac) site along with the Kozak sequence, and the 3' primer has a BsiWI site (cgtacg). The PmeI site was added to the 5' primer to serve as an indicator of successful ligation of the PCR product to the plasmid.

The amplified heavy chain sequence was cloned in pUIG1FRmodH/Kan at the

KpnI and ApaI sites to construct pAIG1FRH-K (SEQ ID NO: 41), and the light chain sequence was cloned in pAIGFRLCb2 at the EcoRI and BsiWI sites to construct pAIGFRLCb2(-)L-K (SEQ ID NO: 42).

pAIG1FRH-K was then digested by BssHII to transfer the heavy chain expression cassette along with the hygromycin-B resistance gene expression cassette to pAIGFRLCb2(-)L-K. pAIGFRLCb2(-)L-K was also digested by BssHII, and the heavy chain expression cassette was inserted at the same site to construct pAIG1FRLCb2V1-K (SEQ ID NO: 43).

DXB11 cells were transfected with expression plasmids with and without introns. The presence of the βGl-IgG intron brought about a two- to three-fold increase in expression of anti-IGF1R in DXB11 cells. pAIG1FRV1 and pAIG1FRV3 were the plasmids carrying both heavy and light chain expression cassettes of anti-IGF1R without the intron. pAIG1FRLCB2V1 and pAIGFRLCB2V3 were the plasmids that carried both heavy and light chain expression cassettes of anti-IGF1R along with the intron. The supernatants from day 3 and 5 post-transfection were analyzed by ELISA. The data from the ELISA analyses are set forth below in table 1.

ELISA Procedure

Reagents-

- Anti-IGF1R 20.24 mg/mL concentrate
- Human IgG-coated plates
- HRP-conjugated goat anti-human IgG
- ELISA Diluent - 0.1% BSA (bovine serum albumin) / PBST (Phosphate buffer saline and Tween 20
- TMB liquid substrate system: 1 step turbo system from Pierce
- Stopping Reagent (~2M H_2SO_4)

Procedure-

A. Preparation of Standard Curve

Diluted purified anti-IGF1R to 200 ng/mL in ELISA Diluent.

20,240,000 ng/mL ÷ 200 ng/mL = 1:101200 dilution

Added 10μL Human IgG1 standard to 990 μL ELISA diluent (I).

Diluted to 200ng/mL by adding 49.4μL of (I) to 49950.6 μL ELISA diluent.

Prepared 4 mL aliquots of the 200 ng/mL standard and stored at 4°C. On day of assay, prepared remainder of the standard curve by loading 200μL of standard to row A and performed 1:2, serial dilutions from the top standard to the bottom (3.125 ng/mL). Used ELISA Diluent as the blank or 0 ng/mL standard.

B. Preparation of Control

Prepared control at 300 ng/mL.

Added 74.1 μL of (I), (see Preparation of Standard Curve) 49925.9 μL of ELISA diluent. Prepared 2.5 mL aliquots and stored at 4°C.

C. Assay

Allowed all reagents to warm to room temperature before using them.

1. Set up a template denoting positions of standard curve and unknowns.

2. Washed plate 1X with EIA Wash Buffer

3. Added standards, controls, and samples to the appropriate wells as per the template. Final volume in each well was 100 μL.

   Covered the plate and incubated for 1 hour at room temperature.

4. Diluted the HRP-conjugated anti-huIgG 1:10,000 in ELISA diluent.

   Performed an initial 1:100 dilution by adding 10 μL of anti-huIgG stock to 990μL of 0.1% BSA-PBST, then performed an additional 1:100 dilution by adding 350μL of the initial dilution to 34650 μL of 0.1% BSA-PBST. The final dilution of this solution was 1:10000.

5. Aspirated the liquid in the wells. Washed the wells 4 times with EIA Wash Buffer.

6. Added 100 µL of the HRP conjugate to all wells. Covered the plate and incubated for 30 minutes at room temperature.

7. Washed the wells as in Step 5.

8. Developed color in the wells by adding 100 µL of TMB substrate to each well.

9. Depending upon the amount of blue color in the wells, added 50 µL of Stopping Reagent to all the wells in the same order as dispensed in Step 8. This took approximately 2 - 4 minutes. Plate developed for 2 minutes.

10. Within 30 minutes of adding the Stopping Reagent, read the absorbance of each well using a microplate reader, setting the wavelengths at 450-650 nm.

D. Data Analysis-

Analyzed data using a 4-parameter logistics curve fit.

Kinase Receptor Activation (KIRA) Assay Procedure

1) Prepared MCF-7 cells at 200,000 cells/well ($2.0x10^6$ cells/mL - 0.1 mL) in culture media without Bovine Insulin. Seeded cells in 96-well tissue culture plates (Falcon # 35-3075). Prepared duplicate wells/sample. Incubated plates overnight in CO_2 incubator (5-6% CO_2, 35-37°C).

2) Coated ELISA plate(s) (NUNC MAXI-SORP) with 100µL/well anti-IGF1R capture antibody (a commercially available IgG1 specific antibody). Prepared purified hybridoma derived 19D12 to 1.0 µg/mL. Each batch was tested for use. Incubated ELISA plate at 4°C overnight.

3) Removed tissue culture plate(s) from incubator. Withdrew media from all wells except the untreated (EMEM) control wells. Using a 12-channel multichannel pipet, removed the media one row at a time to prevent wells from drying prior to sample addition.

4) For dilution curves in a 96-well dilution plate, added 100 µl/mL EMEM to columns 1-10 and 12. Added 200 µL/well control Ab at 5.0 µg/mL to appropriate wells of column 11. Add 200 µl/well samples to appropriate wells of column 11. Using serial diluting apparatus transferred 100µl (1:2) from column 11 to column 1 (column 12 is untreated cell control). Removed media from wells of cell plate. Transferred 50 µl/well from dilution plate to

corresponding wells of cell plate. Incubated for 30 minutes in CO_2 incubator (5-6% CO_2, 35-37°C).

5) Prepared IGF-I (R&D Systems; Minneapolis, MN) at 75 ng/mL in EMEM (no FBS). Removed tissue culture plates from incubator. Withdrew the contents from all the wells (1 plate at a time). Added 100µL/well IGF-I to the sample wells, and the IGF-I control wells. Added 100 µl/well EMEM to column 12.

6) While cell plates were incubating, blocked the previously coated ELISA plate(s). Discarded the capture antibody (dumping into a container is acceptable) and blotted on paper towel. Added 150 µL/well blocking buffer (see reagent sheet). Gently shook plate(s) on a plate shaker at room temperature for 1 hour.

7) Following IGF-I incubation of cell plate(s), withdrew contents of all wells of tissue culture plate(s) (all wells can be withdrawn/96-well plate). Added 100 µL/well lyse buffer. Shook plate(s) on a plate shaker at room temperature for 1 hour.

8) Following blocking buffer incubation of ELISA plate(s), discarded block buffer (dump, blot). Washed plate 6x with 150 µL/well wash buffer (see reagent sheet). Dumped and blotted after each wash.

9) Following lyse buffer incubation of cell plate(s), transferred 85 µL from cell plate(s) wells to corresponding wells of ELISA plate(s). A whole row was transferred at one time using a 12 channel multichannel pipet. Prior to transfer, gently pipetted, up and down, the transfer volume in order to break up some of the remaining cell clumps. Avoided producing bubbles when pipeting the lysates. Shook plate(s) on a plate shaker at room temperature for 2 hours.

10) Prepared biotinylated anti-phosphotyrosine detection Ab - 4G10 (Upstate USA; Lake Placid, NY) at 0.2 µg/mL in dilution buffer (see reagent sheet). Brought to room temperature. Following incubation of lysates, discarded the lysates (dump, blot). Washed ELISA plate(s) 4x with 100 µL/well wash buffer. Dumped and blotted after each wash.

11) Added 100 µL/well 4G10 Ab (anti-phosphotyrosine antibody) to ELISA plate(s). Gently shook plate(s) on a plate shaker at room temperature for 2 hours.

12) Prepared HRP conjugated Streptavidin (Kirkegaard and Perry Laboratories Inc.; Gaithersburg, MD) at 0.025 µg/mL in dilution buffer. Brought to room temperature. Following the 4G10 (anti-phosphotyrosine antibody) incubation, discarded the detection antibody (dump, blot). Washed ELISA plate(s) 4x with 100 µL/well wash buffer. Dumped and blotted after each wash.

13) Added 100 µL/well HRP conjugated Streptavidin. Gently shook plate(s) on a plate shaker at room temperature for 30 minutes.

14) Prepared TMB substrate (2 component system, R&D Systems) at a 1:1 mixture of component A to component B. Brought to room temperature. Following the Streptavidin incubation in ELISA plate(s), discarded the Streptavidin (dump, blot). Washed ELISA plate 4X with 100 µL/well wash buffer. Dumped and blotted after each wash.

15) Added 100µL/well TMB substrate to ELISA plate(s). Shook plate(s) on a plate shaker at room temperature for 15 minutes.

16) Following TMB incubation, added 50 µL/well 1N H_2SO_4 stop agent. Read plate(s) on plate reader (Molecular Devices) at 450 nm/570 nm. Plate was read within 20 minutes of adding stop agent.

Table 1. Anti-IGF1R expression level from various plasmids.

	Day 3*	Day 5*
pAIG1FRV1 (LC/HCA)	1.04	1.09
pAIG1FRV3 (LC/HCA)	0.76	0.83
pAIG1FRLCB2V1 (LCF/HCA)	2.42	2.91
pAIG1FRLCB2V3 (LCF/HCA)	3.03	3.26
pAIG1FRLCB2V1 (LCF/HCA)	2.61	2.76
pAIG1FRLCB2-V1K (LCF/HCA)	3.23	4.06

*mAb production expressed in (ug/ml)

These data demonstrate the superior expression levels associated with βGl-IgG – containing plasmids, pAIG1FRLCB2V1 and pAIG1FRLCB2V3, compared to related plasmids lacking the βGl-IgG intron, pAIG1FRV1 and pAIG1FRV3. Even greater levels of expression were possible when a Kozak consensus sequence was operably associated with the immunoglobulin genes of plasmid pAIG1FRLCB2V1 to generate pAIG1FRLCB2-V1K.

The biological activity of the 19D12 antibodies from the 19D12 parental hybridoma and from the plasmids pAIG1FRLCB2V1 and pAIG1FRLCB2V3 were analyzed by KIRA assay. These data are set forth below in table 2.

Table 2. Evaluation of anti-IGF1R antibodies from a 19D12 hybridoma and from CHO-DXB11 cells containing plasmids pAIG1FRLCB2V1 and pAIG1FRLCB2V3.

	% Inhibition		
nM Ab	19D12	pAIG1FRLCb2V1 (LCF/HCA)	pAIG1FRLCb2V3 (LCF/HCA)
0.01	-3.26	-4.68	1.11
0.01	-0.34	-5.72	-3.10
0.03	-3.18	-9.34	-2.88
0.05	0.87	-1.78	-4.33
0.10	3.82	-1.78	-0.90
0.21	10.10	2.74	6.41
0.42	18.01	11.06	10.41
0.83	39.39	28.24	20.38
1.67	40.51	39.05	34.20
3.34	54.59	56.00	49.82
6.67	69.59	76.34	63.30

"nM Ab" indicates the concentration (nanomolar) of antibody used in each assay.

19D12 corresponds to signal generated using the 19D12 antibody.

pAIG1FRLCb2V1 and pAIG1FRLCb2V3 correspond to data generated using the antibody expressed and purified from these two plasmid (light chain F/heavy chain A).

These data demonstrated that the pAIG1FRLCb2V1 and pAIG1FRLCb2V3 plasmids generated anti-IGF1R antibody that was biologically active.

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The present invention is not to be limited in scope by the specific embodiments described herein. Indeed, the scope of the present invention includes embodiments specifically set forth herein and other embodiments not specifically set forth herein; the embodiments specifically set forth herein are not necessarily intended to be exhaustive. Various modifications of the invention in addition to those described herein will become apparent to those skilled in the art from the foregoing description. Such modifications are intended to fall within the scope of the claims.

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

I claim:

1. An isolated polynucleotide comprising a beta-globin splice donor site and an immunoglobulin gamma splice acceptor site wherein said sites are separated by about 125 nucleotides; which is operably linked to a promoter, which sites and promoter are operably linked to a gene encoding an anti-IGF1R, anti-IL-23 p19, anti-IL23 receptor, anti-IL-17, anti-PD1 or anti-HGF antibody immunoglobulin light chain or heavy chain which chains are optionally fused to an immunoglobulin constant region.

2. The isolated polynucleotide of claim 1 comprising a beta-globin splice donor site comprising the nucleotide sequence CAGGTAAGTTTA (SEQ ID NO: 4) and an immunoglobulin gamma splice acceptor site comprising the nucleotide sequence TTTCTCTCCACAGGC (SEQ ID NO: 5) wherein said sites are separated by about 125 nucleotides.

3. The polynucleotide of claim 2 wherein the splice donor site and the splice acceptor site are separated by the sequence
AAGCTCAGGT CGAGACCGGG CCTTTGTCCG GCGCTCCCTT GGAGCCTACC TAGACTCAGC CGGCTCTCCA CGCTTTGCCT GACCCTGCTT GCTCAACTCT ACGTCTTTGT TTCGTTTTCT GTTCC
(nucleotides 51-175 of SEQ ID NO: 3).

4. The polynucleotide of claim 1 wherein the promoter is a CMV promoter.

5. The polynucleotide of claim 1 wherein the gene encodes an immunoglobulin light chain fused to a kappa immunoglobulin constant region.

6. The polynucleotide of claim 1 wherein the gene encodes an immunoglobulin heavy chain fused to a gamma-1 immunoglobulin constant region.

7. The polynucleotide of claim 6 wherein the gene encodes CDR-L1, CDR-L2 and CDR-L3 of a light chain immunoglobulin comprising amino acids 20-128 of SEQ ID NO: 6, 8-11, 18 or 26 or SEQ ID NO 31; or wherein the gene encodes CDR-H1, CDR-H2 and CDR-H3 of a heavy chain immunoglobulin comprising amino acids 20-137 of SEQ ID NO: 7, 12, 13, 14 or 22 or SEQ ID NO: 30.

8. The polynucleotide of claim 7 wherein the gene encodes amino acids 20-128 of SEQ ID NO: 8, 9, 10 or 11.

9. The polynucleotide of claim 7 wherein the gene encodes amino acids 20-137 of SEQ ID NO: 12 or 13.

10. An isolated plasmid vector comprising the polynucleotide of claim 1.

11. An isolated plasmid vector characterized by a plasmid map set forth in a figure selected from the group consisting of figures 1-10.

12. The plasmid of claim 10 comprising nucleotides 39-190 of the nucleotide sequence of SEQ ID NO: 3.

13. An isolated host cell comprising the polynucleotide of claim 1.

14. The host cell of claim 13 wherein the polynucleotide is integrated into the chromosomal DNA of the host cell.

15. The host cell of claim 14 comprising two or more copies of the polynucleotide

16. The host cell of claim 13 wherein the polynucleotide is not integrated into the chromosomal DNA of the host cell.

17. The host cell of claim 16 comprising two or more copies of the polynucleotide.

18. A method for making a master cell bank comprising introducing a polynucleotide of claim 1 into a host cell, selecting a single clonal population of host cells comprising said polynucleotide, culturing said clonal population, determining if cells from said culture contain bacteria, viruses, fungi and/or mycoplasma and, if none are detected, storing cells from said culture in one or more containers under refrigeration.

19. The method of claim 18 wherein said polynucleotide is in a plasmid that comprises a plasmid map of figure 1 or 2.

20. The method of claim 18 wherein said polynucleotide is in a plasmid that comprises a plasmid map of figure 6, 7, 8, 9 or 10.

21. The method of claim 18 wherein said bacteria, viruses, fungi and/or mycoplasma are one or more members selected from the group consisting of human immunodeficiency virus, hepatitis A virus, hepatitis B virus, hepatitis C virus, human papilloma virus, human cytomegalovirus, human T-lymphotropic virus, Epstein-Barr virus, human herpes simplex virus, *Escherichia coli* and *Staphylococcus aureus.*

22. A master cell bank produced by the method of claim 18.

23. A method for making a working cell bank comprising culturing cells from the master cell bank of claim 22 and storing cells from said culture in one or more containers under refrigeration.

24. The method of claim 23 wherein said polynucleotide is in a plasmid that comprises a plasmid map of figure 1 or 2.

25. The method of claim 23 wherein said polynucleotide is in a plasmid that comprises a plasmid map of figure 6, 7, 8, 9 or 10.

26. The method of claim 23 wherein said cultured cells are tested for bacteria, viruses, fungi and/or mycoplasma and, if none are detected, storing cells from said culture under refrigeration.

27. A working cell bank produced by the method of claim 23.

28. A master cell bank comprising host cells of claim 13.

29. The master cell bank of claim 28 wherein said cells are in vials comprising about 10^7 cells per vial and are free of detectable levels of bacteria, viruses, mycoplasma and fungi.

30.The master cell bank of claim 29 comprising 200 or more vials of said cells.

31. The master cell bank of claim 28 comprising CHO-DXB11 cells comprising a plasmid characterized by the plasmid map of figure 1.

32. The master cell bank of claim 28 comprising CHO-DXB11 cells comprising a plasmid characterized by the plasmid map of figure 2.

33. A working cell bank comprising host cells of claim 13.

34. The working cell bank of claim 33 wherein said cells are in vials comprising about 10^7 cells per vial and are free of detectable levels of bacteria, viruses, mycoplasma and fungi.

35. The working cell bank of claim 34 comprising 200 or more vials of said cells.

36. The working cell bank of claim 33 comprising CHO-DXB11 cells comprising a plasmid characterized by the plasmid map of figure 1.

37. The working cell bank of claim 33 comprising CHO-DXB11 cells comprising a plasmid characterized by the plasmid map of figure 2.

38. A method for expressing a target polypeptide encoded by a gene which is operably associated with a promoter, in a host cell, comprising introducing a βGI-IgG intron polynucleotide comprising a beta-globin splice donor site and an immunoglobulin gamma splice acceptor wherein said sites are separated by about 125 nucleotides, between the promoter and the polynucleotide encoding the target polypeptide, into the host cell, and culturing the host cell under conditions whereby the target polypeptide is expressed.

39. The method of claim 38, further comprising purifying said target polypeptide.

40. The method of claim 38 wherein the beta-globin splice donor site comprises the nucleotide sequence CAGGTAAGTTTA (SEQ ID NO: 4) and the immunoglobulin splice acceptor site comprises the nucleotide sequence TTTCTCTCCACAGGC (SEQ ID NO: 5).

41. The method of claim 40 wherein the splice donor site and the splice acceptor site are separated by the sequence
AAGCTCAGGT CGAGACCGGG CCTTTGTCCG GCGCTCCCTT GGAGCCTACC TAGACTCAGC CGGCTCTCCA CGCTTTGCCT GACCCTGCTT GCTCAACTCT ACGTCTTTGT TTCGTTTTCT GTTCC
(nucleotides 51-175 or SEQ ID NO: 3).

42. The method of claim 38 wherein the gene encodes an immunoglobulin.

43. The method of claim 42 wherein the immunoglobulin is a light chain variable region or heavy chain variable region of an antibody which binds specifically to IGF1R, IL-23, IL-23 receptor, IL-17, PD1 or HGF.

44. The method of claim 43 wherein the gene encodes CDR-L1, CDR-L2 and CDR-L3 of a light chain immunoglobulin comprising amino acids 20-128 of SEQ ID NO: 6, 8-11, 18 or 26 or SEQ ID NO 31; or wherein the gene encodes CDR-H1, CDR-H2 and CDR-H3 of a heavy chain immunoglobulin comprising amino acids 20-137 of SEQ ID NO: 7, 12, 13, 14 or 22 or SEQ ID NO: 30.

45. The method of claim 44 wherein the gene encodes amino acids 20-128 of SEQ ID NO: 8, 9, 10 or 11.

46. The method of claim 44 wherein the gene encodes amino acids 20-137 of SEQ ID NO: 12 or 13.

47. The method of claim 44 further comprising isolating the polypeptide.

48. The method of claim 44 wherein the gene, promoter and polynucleotide are in a plasmid characterized by the plasmid map of figure 1.

49. The method of claim 48 wherein the plasmid characterized by the plasmid map of figure 1 comprises the nucleotide sequence of SEQ ID NO: 35.

50. The method of claim 49 wherein the host cell is a Chinese hamster ovary cell.