(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
11 June 2009 (11.06.2009)

PCT

(10) International Publication Number
WO 2009/073565 A2

(51) International Patent Classification:
C12Q 1/68 (2006.01)

(21) International Application Number:
PCT/US2008/085045

(22) International Filing Date:
26 November 2008 (26.11.2008)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
60/991,203 29 November 2007 (29.11.2007) US
PCT/US2008/064562 22 May 2008 (22.05.2008) US
61/192,268 17 September 2008 (17.09.2008) US

(71) Applicants *(for all designated States except US)*: **GENENTECH, INC.** [US/US]; 1 Dna Way, South San Francisco, CA 94080-4990 (US). **THE UNIVERSITY COURT OF THE UNIVERSITY OF EDINBURGH OF OLD COLLEGE** [GB/GB]; South Bridge, Edinburgh EH8 9YL (GB).

(72) Inventors; and

(75) Inventors/Applicants *(for US only)*: **ABBAS, Alexander, R.** [US/US]; 2007 Lyon Avenue, Belmont, CA 94002 (US). **CLARK, Hilary** [US/US]; 1504 Noe Street, San Francisco, CA 94131 (US). **DIEHL, Lauri** [US/US]; West Lothian, Los Altos, CA (US). **LEES, Charles** [GB/GB]; West Lothian (GB). **NOBLE, Colin, L.** [GB/GB]; Edinburgh, Scotland (GB). **SATSANGI, Jack** [GB/GB]; Midlothian (GB).

(74) Agents: **FARIS, Alissa** et al.; Goodwin Procter LLP, 135 Commonwealth Drive, Menlo Park, CA 94025 (US).

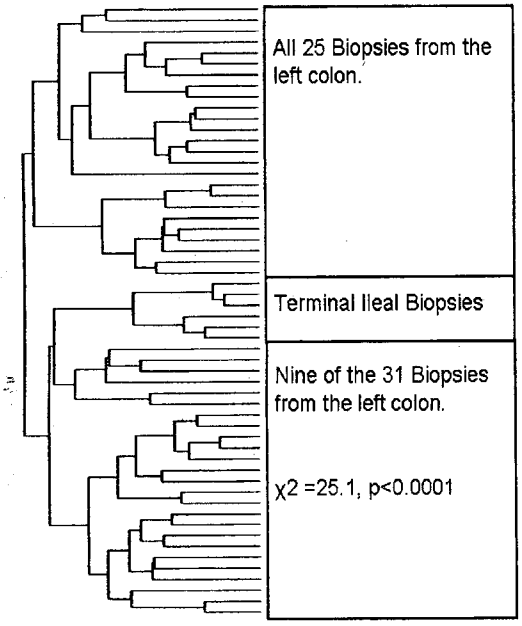
(81) Designated States *(unless otherwise indicated, for every kind of national protection available)*: AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RS, RU, SC, SD, SE, SG, SK, SL, SM, ST, SV, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW.

(84) Designated States *(unless otherwise indicated, for every kind of regional protection available)*: ARIPO (BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI,

[Continued on next page]

(54) Title: GENE EXPRESSION MARKERS FOR INFLAMMATORY BOWEL DISEASE

Figure 1: Unsupervised hierarchical clustering of healthy control biopsies showing the location of biopsy retrieval.



(57) Abstract: The present invention relates to methods of gene expression profiling for inflammatory bowel disease pathogenesis, in which the differential expression in a test sample from a mammalian subject of one or more IBD markers relative to a control is determined, wherein the differential expression in the test sample is indicative of an IBD in the mammalian subject from which the test sample was obtained.

WO 2009/073565 A2

FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MT, NL, NO, PL, PT, RO, SE, SI, SK, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Published:

— *without international search report and to be republished upon receipt of that report*

GENE EXPRESSION MARKERS FOR INFLAMMATORY BOWEL DISEASE

Background of the Invention

Cross-reference to Related Applications

This application claims priority under Section 119(e) and the benefit of United States Provisional Application Serial No. 60/991,203 filed November 29, 2007, United States Provisional Application Serial No. 61/192,268 filed September 17, 2008, and International Patent Application Serial No. PCT/US08/64562 filed May 22, 2008 the entire disclosures of which are incorporated herein by reference in their entirety.

Field of the Invention

The present invention relates to gene expression profiles in inflammatory bowel disease pathogenesis, including use in the detection and diagnosis of inflammatory bowel disease.

Description of Related Art

Immune related and inflammatory diseases are the manifestation or consequence of fairly complex, often multiple interconnected biological pathways which in normal physiology are critical to respond to insult or injury, initiate repair from insult or injury, and mount innate and acquired defense against foreign organisms. Disease or pathology occurs when these normal physiological pathways cause additional insult or injury either as directly related to the intensity of the response, as a consequence of abnormal regulation or excessive stimulation, as a reaction to self, or as a combination of these.

Though the genesis of these diseases often involves multistep pathways and often multiple different biological systems/pathways, intervention at critical points in one or more of these pathways can have an ameliorative or therapeutic effect. Therapeutic intervention can occur by either antagonism of a detrimental process/pathway or stimulation of a beneficial process/pathway.

Many immune related diseases are known and have been extensively studied. Such diseases include immune-mediated inflammatory diseases, non-immune-mediated inflammatory diseases, infectious diseases, immunodeficiency diseases, neoplasia, *etc.*

The term inflammatory bowel disorder ("IBD") describes a group of chronic inflammatory disorders of unknown causes in which the intestine (bowel) becomes inflamed, often causing recurring cramps or diarrhea. The prevalence of IBD in the US is estimated to be about 200 per 100,000 population. Patients with IBD can be divided into two major groups, those with ulcerative colitis ("UC") and those with Crohn's disease ("CD"). Both UC and CD are chronic relapsing diseases and are complex

clinical entities that occur in genetically susceptible individuals who are exposed to as yet poorly defined environmental stimuli. (Bonen and Cho, Gastroenterology. 2003; 124:521-536; Gaya et al. Lancet. 2006;367:1271-1284).

Although the cause of IBD remains unknown, several factors such as genetic, infectious and immunologic susceptibility have been implicated. IBD is much more common in Caucasians, especially those of Jewish descent. The chronic inflammatory nature of the condition has prompted an intense search for a possible infectious cause. Although agents have been found which stimulate acute inflammation, none has been found to cause the chronic inflammation associated with IBD. The hypothesis that IBD is an autoimmune disease is supported by the previously mentioned extraintestinal manifestation of IBD as joint arthritis, and the known positive response to IBD by treatment with therapeutic agents such as adrenal glucocorticoids, cyclosporine and azathioprine, which are known to suppress immune response. In addition, the GI tract, more than any other organ of the body, is continuously exposed to potential antigenic substances such as proteins from food, bacterial byproducts (LPS), etc.

There is sufficient overlap in the diagnostic criteria for UC and CD that it is sometimes impossible to say which a given patient has; however, the type of lesion typically seen is different, as is the localization. UC mostly appears in the colon, proximal to the rectum, and the characteristic lesion is a superficial ulcer of the mucosa; CD can appear anywhere in the bowel, with occasional involvement of stomach, esophagus and duodenum, and the lesions are usually described as extensive linear fissures.

The current therapy of IBD usually involves the administration of antiinflammatory or immunosuppressive agents, such as sulfasalazine, corticosteroids, 6-mercaptopurine/azathioprine, or cyclosporine, which usually bring only partial results. If anti-inflammatory/immunosuppressive therapies fail, colectomies are the last line of defense. The typical operation for CD not involving the rectum is resection (removal of a diseased segment of bowel) and anastomosis (reconnection) without an ostomy. Sections of the small or large intestine may be removed. About 30% of CD patients will need surgery within the first year after diagnosis. In the subsequent years, the rate is about 5% per year. Unfortunately, CD is characterized by a high rate of recurrence; about 5% of patients need a second surgery each year after initial surgery.

Refining a diagnosis of inflammatory bowel disease involves evaluating the progression status of the diseases using standard classification criteria. The classification systems used in IBD include the Truelove and Witts Index (Truelove S.C. and Witts, L.J. *Br Med J.* 1955;2:1041-1048), which classifies colitis as mild, moderate, or severe, as well as Lennard-Jones. (Lennard-Jones JE. Scand J Gastroenterol Suppl 1989;170:2-6) and the simple clinical colitis activity index (SCCAI). (Walmsley

et. al. Gut. 1998;43:29-32) These systems track such variables as daily bowel movements, rectal bleeding, temperature, heart rate, hemoglobin levels, erythrocyte sedimentation rate, weight, hematocrit score, and the level of serum albumin.

In approximately 10-15% of cases, a definitive diagnosis of ulcerative colitis or Crohn's disease cannot be made and such cases are often referred to as "indeterminate colitis." Two antibody detection tests are available that can help the diagnosis, each of which assays for antibodies in the blood. The antibodies are "perinuclear anti-neutrophil antibody" (pANCA) and "anti-Saccharomyces cervisiae antibody" (ASCA). Most patients with ulcerative colitis have the pANCA antibody but not the ASCA antibody, while most patients with Crohn's disease have the ASCA antibody but not the pANCA antibody. However, these two tests have shortcomings as some patients have neither antibody and some Crohn's disease patients may have only the pANCA antibody.For clinical practice, a reliable test that would indicate the presence and/or progression of an IBD based on molecular markers rather than the measurement of a multitude of variables would be useful for identifying and/or treating individuals with an IBD. Hypothesis free, linkage and association studies have identified genetic loci that have been associated with UC, notably the MHC region on chromosome 6,(Rioux et al. Am J Hum Genet. 2000;66:1863-1870; Stokkers et al. Gut. 1999; 45:395-401; Van Heel et al. Hum Mol Genet. 2004;13:763-770) the IBD2 locus on chromosome 12 (Parkes et al. Am J Hum Genet. 2000;67:1605-1610; Satsangi et al. Nat Genet. 1996;14:199-202) and the IBD5 locus on chromosome 5. (Giallourakis et. al. Am J. Hum Genet. 2003;73:205-211; Palmieri et. al Aliment Pharmacol Ther. 2006;23:497-506; Russell et. al. Gut. 2006;55:1114-1123; Waller et. al. Gut. 2006;55:809-814) Following a UK wide linkage scan identifying a putative loci of association for UC on chromosome 7q, further studies have implicated variants in the ABCB1 (MDR1) gene which is involved in cellular detoxification with UC. (Satsangi et. al. Nat Genet. 1996;14:199-202; Brant et.al. Am J Hum Genet. 2003;73:1282-1292; Ho et. al. Gastroenterology. 2005;128:288-296)

A complementary approach towards the identification and understanding of the complex gene- gene and gene- environment relationships that result in the chronic intestinal inflammation observed in inflammatory bowel disease (IBD) is microarray gene expression analysis. Microarrays allow a comprehensive picture of gene expression at the tissue and cellular level, thus helping understand the underlying patho-physiological processes. (Stoughton et. al. Annu Rev Biochem. 2005;74:53-82) Microarray analysis was first applied to patients with IBD in 1997, comparing expression of 96 genes in surgical resections of patients with CD to synovial tissue of patients with rheumatoid arthritis. (Heller et. al. Proc Natl Acad Sci U S A. 1997;94:2150-2155) Further studies using microarray platforms to interrogate surgical specimens from patients with IBD identified an number of novel genes that were differentially regulated when diseased samples were compared to controls.

(Dieckgraefe et.al. Physiol Genomics. 2000;4:1-11; Lawrance et. al. Hum Mol Genet. 2001;10:445-456)

A complementary approach towards the identification and understanding of the complex gene- gene and gene- environment relationships that result in the chronic intestinal inflammation observed in inflammatory bowel disease (IBD) is microarray gene expression analysis. Microarrays allow a comprehensive picture of gene expression at the tissue and cellular level, thus helping understand the underlying patho-physiological processes. (Stoughton et. al. Annu Rev Biochem. 2005;74:53-82) Microarray analysis was first applied to patients with IBD in 1997, comparing expression of 96 genes in surgical resections of patients with CD to synovial tissue of patients with rheumatoid arthritis. (Heller et. al. Proc Natl Acad Sci U S A. 1997;94:2150-2155) Further studies using microarray platforms to interrogate surgical specimens from patients with IBD identified a number of novel genes that were differentially regulated when diseased samples were compared to controls. (Dieckgraefe et.al. Physiol Genomics. 2000;4:1-11; Lawrance et. al. Hum Mol Genet. 2001;10:445-456)

Endoscopic pinch mucosal biopsies have allowed investigators to microarray tissue from a larger range of patients encompassing those with less severe disease. Langmann et. al. used microarray technology to analyze 22,283 genes in biopsy specimens from macroscopically non affected areas of the colon and terminal ileum. (Langmann et. al. Gastroenterology. 2004;127:26-40) Genes which were involved in cellular detoxification and biotransformation (Pregnane X receptor and MDR1) were significantly downregulated in the colon of patients with UC, however, there was no change in the expression of these genes in the biopsies from patients with CD. Costello and colleagues (Costello et. al. PLoS Med. 2005;2:e199) looked at the expression of 33792 sequences in endoscopic sigmoid colon biopsies obtained from healthy controls, patients with CD and UC. A number of sequences representing novel proteins were differentially regulated and *in silico* analysis suggested that these proteins had putative functions related to disease pathogenesis – transcription factors, signaling molecules and cell adhesion.

In a study of patients with UC, Okahara et al. (Aliment Pharmacol Ther. 2005;21:1091-1097) observed that (migration inhibitory factor- related protein 14 (MRP14), growth- related oncogene gamma (GROγ) and serum amyloid A1 (SAA1) were upregulated where as TIMP1 and elfin were down regulated in the inflamed biopsies when compared to the non- inflamed biopsies. When observing 41 chemokines and 21 chemokine receptors, Puleston et al demonstrated that chemokines CXCLs 1-3 and 8 and CCL20 were upregulated in active colonic CD and UC. (Aliment Pharmacol Ther. 2005;21:109-120) Overall these studies illustrate the heterogeneity of early microarray platforms and tissue collection. However, despite these problems differential expression of a number of genes was consistently observed.

Despite the above identified advances in IBD research, there is a great need for additional diagnostic and therapeutic agents capable of detecting IBD in a mammal and for effectively treating this disorder. Accordingly, the present invention provides polynucleotides and polypeptides that are overexpressed in IBD as compared to normal tissue, and methods of using those polypeptides, and their encoding nucleic acids, for to detect or diagnose the presence of an IBD in mammalian subjects and subsequently to treat those subjects in which an IBD is detected with suitable IBD therapeutic agents.

The present invention provides methods for detecting the presence of and determining the progression of inflammatory bowel disease (IBD), including ulcerative colitis (UC) and Crohn's disease (CD).

The invention disclosed herein provides methods and assays examining expression of one or more gene expression markers in a mammalian tissue or cell sample, wherein the expression of one or more such biomarkers is predictive of whether the mammalian subject from which the tissue or cell sample was taken is more likely to have an IBD. In various embodiments of the invention, the methods and assays examine the expression of gene expression markers such as those listed in Tables 1, 2, and 3 and determine whether expression is higher or lower than a control sample.

These and further embodiments of the present invention will be apparent to those of ordinary skill in the art.

Summary of the Invention

In one aspect, the invention concerns a method of detecting or diagnosing an inflammatory bowel disease (IBD) in a mammalian subject comprising determining, in a biological sample obtained from the subject, that expression levels of (i) one or more nucleic acids encoding one or more polypeptides selected from Tables 1, 2, or 3, or (ii) RNA transcripts or their expression products of one or more genes selected from Tables 1, 2, or 3, is different relative to the expression level in a control, wherein the difference in expression indicates the subject is more likely to have an IBD.

In one embodiment, the methods of diagnosing or detecting the presence of an IBD in a mammalian subject comprise determining that the expression level of (i) one or more nucleic acids encoding one or more polypeptides selected from Tables 1A, 2, or 3A; or (ii) RNA transcripts or expression products thereof of one or more genes selected from Tables 1A, 2 or 3A in a test sample obtained from the subject is higher relative to the level of expression in a control, wherein the higher level of expression is indicative of the presence of an IBD in the subject from which the test sample was obtained.

In another embodiment, the methods of diagnosing or detecting the presence of an IBD in a mammalian subject comprise determining that the expression level of (i) one or more nucleic acids encoding one or more polypeptides selected from Tables 1B or 3B; or (ii) RNA transcripts or expression products thereof of one or more genes selected from Tables 1B or 3B in a test sample obtained from the subject is lower relative to the level of expression in a control, wherein the lower level of expression is indicative of the presence of an IBD in the subject from which the test sample was obtained.

In one aspect, the methods are directed to diagnosing or detecting a flare-up of an IBD in mammalian subject that was previously diagnosed with an IBD and is currently in remission. The subject may have completed treatment for the IBD or is currently undergoing treatment for the IBD. In one embodiment, the methods comprise determining, in a biological sample obtained from the mammalian subject, that the expression level of (i) one or more nucleic acids encoding one or more polypeptides selected from Tables 1, 2, or 3; or (ii) RNA transcripts or expression products thereof of one or more genes selected from Tables 1, 2 or 3 is different relative to the expression level in a control, wherein the difference in expression indicates the subject is more likely to have an IBD flareup. Alternatively, the test sample may be compared to a prior test sample of the mammalian subject, if available, obtained before, after, or at the time of the intial IBD diagnosis.

In all aspects, the mammalian subject preferably is a human patient, such as a human patient diagnosed with or at risk of developing an IBD. The subject may also be an IBD patient who has received prior treatment for an IBD but is at risk of a recurrence of the IBD.

For all aspects of the method of the invention, determining the expression level of one or more genes described herein (or one or more nucleic acids encoding polypeptide(s) expressed by one or more of such genes) may be obtained, for example, by a method of gene expression profiling. The method of gene expression profiling may be, for example, a PCR-based method.

In various embodiments, the diagnosis includes quantification of the expression level of (i) one or more nucleic acids encoding one or more polypeptides selected from Tables 1, 2, or 3; or (ii) RNA transcripts or expression products thereof of one or more genes selected from Tables 1, 2 or 3, such as by immunohistochemistry (IHC) and/or fluorescence *in situ* hybridization (FISH).

For all aspects of the invention, the expression levels of the genes may be normalized relative to the expression levels of one or more reference genes, or their expression products.

For all aspects of the invention, the method may further comprise determining evidence of the expression levels of at least two, three, four, five, six, seven, eight, nine, ten, eleven, twelve, thirteen,

fourteen, fifteen, sixteen, seventeen, eighteen, nineteen, or twenty of said genes, or their expression products.

In another aspect, the methods of present invention also contemplate the use of a "panel" of such genes (i.e. IBD markers as disclosed herein) based on the evidence of their level of expression. In some embodiments, the panel of IBD markers will include at least one, two, three, four, five, six, seven, eight, nine, ten, eleven, twelve, thirteen, fourteen, fifteen, sixteen, seventeen, eighteen, nineteen or twenty IBD markers. The panel may include an IBD marker that is overexpressed in IBD relative to a control, an IBD marker that is underexpressed in IBD relative to a control, or IBD markers that are both overexpressed and underexpressed in IBD relative to a control. Such panels may be used to screen a mammalian subject for the differential expression of one or more IBD markers in order to make a determination on whether an IBD is present in the subject.

In one embodiment, the IBD markers that make up the panel are selected from Tables 1, 2, and 3. In a preferred embodiment, the methods of diagnosing or detecting the presence of an IBD in a mammalian subject comprise determining a differential expression level of RNA transcripts or expression products thereof from a panel of IBD markers in a test sample obtained from the subject relative to the level of expression in a control, wherein the differential level of expression is indicative of the presence of an IBD in the subject from which the test sample was obtained. The differential expression in the test sample may be higher and/or lower relative to a control as discussed herein.

For all aspects of the invention, the method may further comprise the step of creating a report summarizing said prediction.

For all aspects, the IBD diagnosed or detected according to the methods of the present invention is Crohn's disease (CD), ulcerative colitis (UC), or both CD and UC.

For all aspects of the invention, the test sample obtained from a mammalian subject may be derived from a colonic tissue biopsy. In a preferred embodiment, the biopsy is a tissue selected from the group consisting of terminal ileum, the ascending colon, the descending colon, and the sigmoid colon. In other preferred embodiments, the biopsy is from an inflamed colonic area or from a non-inflamed colonic area. The inflamed colonic area may be acutely inflamed or chronically inflamed.

For all aspects, determination of expression levels may occur at more than one time. For all aspects of the invention, the determination of expression levels may occur before the patient is subjected to any therapy before and/or after any surgery. In some embodiments, the determining step is indicative of a recurrence of an IBD in the mammalian subject following surgery or indicative of a flare-up of said IBD in said mammalian subject. In a preferred embodiment, the IBD is Crohn's disease.

In another aspect, the present invention concerns methods of treating a mammalian subject in which the presence of an IBD has been detected by the methods described herein. For example, following a determination that a test sample obtained from the mammalian subject exhibits differential expression relative to a control of one or more of the RNA transcripts or the corresponding gene products of an IBD marker described herein, the mammalian subject may be administered an IBD therapeutic agent.

In one embodiment, the methods of treating an IBD in a mammalian subject in need thereof, comprise (a) determining a differential level of expression of (i) one or more nucleic acids encoding one or more polypeptides selected from Tables 1, 2, or 3; or (ii) RNA transcripts or expression products thereof of one or more genes selected from Tables 1, 2 or 3 in a test sample obtained from said subject relative to the level of expression in a control, wherein said differential level of expression is indicative of the presence of an IBD in the subject from which the test sample was obtained; and (b) administering to said subject an effective amount of an IBD therapeutic agent. In a preferred embodiment, the methods of treating an IBD comprise (a) determining that the expression level of (i) one or more nucleic acids encoding one or more polypeptides selected from Tables 1A, 2, or 3A; or (ii) RNA transcripts or expression products thereof of one or more genes selected from Tables 1A, 2 or 3A in a test sample obtained from the subject is higher relative to the level of expression in a control, wherein the higher level of expression is indicative of the presence of an IBD in the subject from which the test sample was obtained; and (b) administering to said subject an effective amount of an IBD therapeutic agent. In another preferred embodiment, the methods of treating an IBD comprise (a) determining that the expression level of (i) one or more nucleic acids encoding one or more polypeptides selected from Tables 1B or 3B; or (ii) RNA transcripts or expression products thereof of one or more genes selected from Tables 1B or 3B in a test sample obtained from the subject is lower relative to the level of expression in a control, wherein the lower level of expression is indicative of the presence of an IBD in the subject from which the test sample was obtained. In some preferred embodiments, the IBD therapeutic agent is one or more of an aminosalicylate, a corticosteroid, and an immunosuppressive agent.

In one aspect, the panel of IBD markers discussed above is useful in methods of treating an IBD in a mammalian subject. In one embodiment, the mammalian subject is screened against the panel of markers and if the presence of an IBD is determined, IBD therapeutic agent(s) may be administered as discussed herein.

In a different aspect the invention concerns a kit comprising one or more of (1) extraction buffer/reagents and protocol; (2) reverse transcription buffer/reagents and protocol; and (3) qPCR buffer/reagents and protocol suitable for performing the methods of this invention. The kit may comprise data retrieval and analysis software.

In one embodiment, the gene whose differential expression is indicative of an IBD is GLI1. In another embodiment, the GLI1 gene is a GLI1 variant. In a preferred embodiment, the GLI1 variant is rs2228226C→G (Q1100E) as described in Example 4.

All publications mentioned herein are incorporated herein by reference to disclose and describe the methods and/or materials in connection with which the publications are cited. Publications cited herein are cited for their disclosure prior to the filing date of the present application. Nothing here is to be construed as an admission that the inventors are not entitled to antedate the publications by virtue of an earlier priority date or prior date of invention. Further the actual publication dates may be different from those shown and require independent verification.

Brief Description of Drawings

Figure 1 shows the histologically normal biopsies from control patients that were analysed by unsupervised hierarchical clustering.

Figure 2 shows the expression of defensins alpha 5 and 6 in ulcerative colitis patients and controls.

Figure 3 shows the expression of the matrix metalloproteinases (MMPs) 3 and 7 in ulcerative colitis and controls.

Figure 4 shows the real time PCR expression of SAA1, IL-8, defensin alpha 5, and defensin alpha 6 in control and ulcerative colitis inflamed and non-inflamed sigmoid colon biopsies.

Figure 5 shows the real time PCR expression of MMP3, MMP7, S100A8, and TLR4 in control and ulcerative colitis inflamed and non-inflamed sigmoid colon biopsies.

Figure 6 shows *in situ* hybridization of defensin alpha 5 in the terminal ileum and colon of patients with ulcerative colitis and controls.

Figure 7 shows *in situ* hybridization of defensin alpha 6 in the terminal ileum and colon of patients with ulcerative colitis and controls.

Figure 8A and 8B depict the nucleic acid sequence (SEQ ID NO:1) encoding human DEFA6 polypeptide and the amino acid sequence of human DEFA6 polypeptide (SEQ ID NO:2).

Figure 9A and 9B depict the nucleic acid sequence (SEQ ID NO:3) encoding human DEFA5 polypeptide and the amino acid sequence of human DEFA5 polypeptide (SEQ ID NO:4). Figure 9C and 9D depict the nucleic acid sequence (SEQ ID NO:210) encoding human DEFB14 polypeptide and the amino acid sequence of human DEFB14 polypeptide (SEQ ID NO:211).

Figure 10A and 10B depict the nucleic acid sequence (SEQ ID NO:5) encoding human IL3RA polypeptide and the amino acid sequence of human IL3RA polypeptide (SEQ ID NO:6).

Figure 11A and 11B depict the nucleic acid sequence (SEQ ID NO:7) encoding human IL2RA polypeptide and the amino acid sequence of human IL2RA polypeptide (SEQ ID NO:8).

Figure 12A and 12B depict the nucleic acid sequence (SEQ ID NO:9) encoding human REG3G polypeptide and the amino acid sequence of human REG3G polypeptide (SEQ ID NO:10).

Figure 13A and 13B depict the nucleic acid sequence (SEQ ID NO:11) encoding human REG1B polypeptide and the amino acid sequence of human REG1B polypeptide (SEQ ID NO:12).

Figure 14A and 14B depict the nucleic acid sequence (SEQ ID NO:13) encoding human KCND3 polypeptide and the amino acid sequence of human KCND3 polypeptide (SEQ ID NO:14).

Figure 15A and 15B depict the nucleic acid sequence (SEQ ID NO:15) encoding human MIP-3a polypeptide and the amino acid sequence of human MIP-3a polypeptide (SEQ ID NO:16).

Figure 16A and 16B depict the nucleic acid sequence (SEQ ID NO:17) encoding human ECGF1 polypeptide and the amino acid sequence of human ECGF1 polypeptide (SEQ ID NO:18).

Figure 17A and 17B depict the nucleic acid sequence (SEQ ID NO:19) encoding human IL1B polypeptide and the amino acid sequence of human IL1B polypeptide (SEQ ID NO:20).

Figure 18A and 18B depict the nucleic acid sequence (SEQ ID NO:21) encoding human MIP2BGRO-g polypeptide and the amino acid sequence of human MIP2BGRO-g polypeptide (SEQ ID NO:22).

Figure 19A and 19B depict the nucleic acid sequence (SEQ ID NO:23) encoding human CXCL1 polypeptide and the amino acid sequence of human CXCL1 polypeptide (SEQ ID NO:24).

Figure 20A and 20B depict the nucleic acid sequence (SEQ ID NO:25) encoding human IAP1 polypeptide and the amino acid sequence of human IAP1 polypeptide (SEQ ID NO:26).

Figure 21A and 21B depict the nucleic acid sequence (SEQ ID NO:27) encoding human CASP5 polypeptide and the amino acid sequence of human CASP5 polypeptide (SEQ ID NO:28).

Figure 22A and 22B depict the nucleic acid sequence (SEQ ID NO:29) encoding human DMBT1 polypeptide and the amino acid sequence of human DMBT1 polypeptide (SEQ ID NO:30).

Figure 23A and 23B depict the nucleic acid sequence (SEQ ID NO:31) encoding human PCDH17 polypeptide and the amino acid sequence of human PCDH17 polypeptide (SEQ ID NO:32).

Figure 24A and 24B depict the nucleic acid sequence (SEQ ID NO:33) encoding human IFITM1 polypeptide and the amino acid sequence of human IFITM1 polypeptide (SEQ ID NO:34).

Figure 25A and 25B depict the nucleic acid sequence (SEQ ID NO:35) encoding human PDZK1IP1 polypeptide and the amino acid sequence of human PDZK1IP1 polypeptide (SEQ ID NO:36).

Figure 26A and 26B depict the nucleic acid sequence (SEQ ID NO:37) encoding human IRTA2 polypeptide and the amino acid sequence of human IRTA2 polypeptide (SEQ ID NO:38).

Figure 27A and 27B depict the nucleic acid sequence (SEQ ID NO:39) encoding human SLC40A1 polypeptide and the amino acid sequence of human SLC40A1 polypeptide (SEQ ID NO:40).

Figure 28A and 28B depict the nucleic acid sequence (SEQ ID NO:41) encoding human IGHV4-4 polypeptide and the amino acid sequence of human IGHV4-4 polypeptide (SEQ ID NO:42).

Figure 29A and 29B depict the nucleic acid sequence (SEQ ID NO:43) encoding human REG3G polypeptide and the amino acid sequence of human REG3G polypeptide (SEQ ID NO:44).

Figure 30A and 30B depict the nucleic acid sequence (SEQ ID NO:45) encoding human AQP9 polypeptide and the amino acid sequence of human AQP9 polypeptide (SEQ ID NO:46).

Figure 31A and 31B depict the nucleic acid sequence (SEQ ID NO:47) encoding human OLFM4 polypeptide and the amino acid sequence of human OLFM4 polypeptide (SEQ ID NO:48).

Figure 32A and 32B depict the nucleic acid sequence (SEQ ID NO:49) encoding human S100A9 polypeptide and the amino acid sequence of human S100A9 polypeptide (SEQ ID NO:50).

Figure 33A and 33B depict the nucleic acid sequence (SEQ ID NO:51) encoding human UNC5CL polypeptide and the amino acid sequence of human UNC5CL polypeptide (SEQ ID NO:52).

Figure 34A and 34B depict the nucleic acid sequence (SEQ ID NO:53) encoding human GPR110 polypeptide and the amino acid sequence of human GPR110 polypeptide (SEQ ID NO:54).

Figure 35A and 35B depict the nucleic acid sequence (SEQ ID NO:55) encoding human HLA-G polypeptide and the amino acid sequence of human HLA-G polypeptide (SEQ ID NO:56).

Figure 36A and 36B depict the nucleic acid sequence (SEQ ID NO:57) encoding human TAP1 polypeptide and the amino acid sequence of human TAP1 polypeptide (SEQ ID NO:58).

Figure 37A and 37B depict the nucleic acid sequence (SEQ ID NO:59) encoding human MAP3K8 polypeptide and the amino acid sequence of human MAP3K8 polypeptide (SEQ ID NO:60).

Figure 38A and 38B depict the nucleic acid sequence (SEQ ID NO:61) encoding human UBD|GABBR1 polypeptide and the amino acid sequence of human UBD|GABBR1 polypeptide (SEQ ID NO:62).

Figure 39A and 39B depict the nucleic acid sequence (SEQ ID NO:63) encoding human DHX57 polypeptide and the amino acid sequence of human DHX57 polypeptide (SEQ ID NO:64).

Figure 40A and 40B depict the nucleic acid sequence (SEQ ID NO:65) encoding human MA polypeptide and the amino acid sequence of human MApolypeptide (SEQ ID NO:66).

Figure 41A and 41B depict the nucleic acid sequence (SEQ ID NO:67) encoding human IGLJCOR18 polypeptide and the amino acid sequence of human IGLJCOR18 polypeptide (SEQ ID NO:68).

Figure 42A and 42B depict the nucleic acid sequence (SEQ ID NO:69) encoding human HLA-G polypeptide and the amino acid sequence of human HLA-G polypeptide (SEQ ID NO:70).

Figure 43A and 43B depict the nucleic acid sequence (SEQ ID NO:71) encoding human SAA1 polypeptide and the amino acid sequence of human SAA1 polypeptide (SEQ ID NO:72).

Figure 44A and 44B depict the nucleic acid sequence (SEQ ID NO:73) encoding human TAP2 polypeptide and the amino acid sequence of human TAP2 polypeptide (SEQ ID NO:74).

Figure 45A and 45B depict the nucleic acid sequence (SEQ ID NO:75) encoding human PCAA17448 polypeptide and the amino acid sequence of human PCAA17448 polypeptide (SEQ ID NO:76).

Figure 46A and 46B depict the nucleic acid sequence (SEQ ID NO:77) encoding human LCN2 polypeptide and the amino acid sequence of human LCN2 polypeptide (SEQ ID NO:78).

Figure 47A and 47B depict the nucleic acid sequence (SEQ ID NO:79) encoding human ZBP1 polypeptide and the amino acid sequence of human ZBP1 polypeptide (SEQ ID NO:80).

Figure 48A and 48B depict the nucleic acid sequence (SEQ ID NO:81) encoding human TNIP3 polypeptide and the amino acid sequence of human TNIP3 polypeptide (SEQ ID NO:82).

Figure 49A and 49B depict the nucleic acid sequence (SEQ ID NO:83) encoding human ZC3H12A polypeptide and the amino acid sequence of human ZC3H12A polypeptide (SEQ ID NO:84).

Figure 50A and 50B depict the nucleic acid sequence (SEQ ID NO:85) encoding human CHI3L1 polypeptide and the amino acid sequence of human CHI3L1 polypeptide (SEQ ID NO:86).

Figure 51A and 51B depict the nucleic acid sequence (SEQ ID NO:87) encoding human FCGR3A polypeptide and the amino acid sequence of human FCGR3A polypeptide (SEQ ID NO:88).

Figure 52A and 52B depict the nucleic acid sequence (SEQ ID NO:89) encoding human SAMD9L polypeptide and the amino acid sequence of human SAMD9L polypeptide (SEQ ID NO:90).

Figure 53A and 53B depict the nucleic acid sequence (SEQ ID NO:91) encoding human MMP9 polypeptide and the amino acid sequence of human MMP9 polypeptide (SEQ ID NO:92).

Figure 54A and 54B depict the nucleic acid sequence (SEQ ID NO:93) encoding human MMP7 polypeptide and the amino acid sequence of human MMP7 polypeptide (SEQ ID NO:94).

Figure 55A and 55B depict the nucleic acid sequence (SEQ ID NO:95) encoding human BF polypeptide and the amino acid sequence of human BF polypeptide (SEQ ID NO:96).

Figure 56A and 56B depict the nucleic acid sequence (SEQ ID NO:97) encoding human S100P polypeptide and the amino acid sequence of human S100P polypeptide (SEQ ID NO:98).

Figure 57A and 57B depict the nucleic acid sequence (SEQ ID NO:99) encoding human GRO polypeptide and the amino acid sequence of human GRO polypeptide (SEQ ID NO:100).

Figure 58A and 58B depict the nucleic acid sequence (SEQ ID NO:101) encoding human INDO polypeptide and the amino acid sequence of human INDO polypeptide (SEQ ID NO:102).

Figure 59A and 59B depict the nucleic acid sequence (SEQ ID NO:103) encoding human TRIM22 polypeptide and the amino acid sequence of human TRIM22 polypeptide (SEQ ID NO:104).

Figure 60A and 60B depict the nucleic acid sequence (SEQ ID NO:105) encoding human SAA2 polypeptide and the amino acid sequence of human SAA2 polypeptide (SEQ ID NO:106).

Figure 61A and 61B depict the nucleic acid sequence (SEQ ID NO:107) encoding human NEU4 polypeptide and the amino acid sequence of human NEU4 polypeptide (SEQ ID NO:108).

Figure 62A and 62B depict the nucleic acid sequence (SEQ ID NO:109) encoding human IRTA2/FCRH5 polypeptide and the amino acid sequence of human IRTA2/FCRH5 polypeptide (SEQ ID NO:110).

Figure 63A and 63B depict the nucleic acid sequence (SEQ ID NO:111) encoding human IGLJCOR18 polypeptide and the amino acid sequence of human IGLJCOR18 polypeptide (SEQ ID NO:112).

Figure 64A and 64B depict the nucleic acid sequence (SEQ ID NO:113) encoding human IGHV4-4 polypeptide and the amino acid sequence of human IGHV4-4 polypeptide (SEQ ID NO:114).

Figure 65A and 65B depict the nucleic acid sequence (SEQ ID NO:115) encoding human MMP9 polypeptide and the amino acid sequence of human MMP9 polypeptide (SEQ ID NO:116).

Figure 66A and 66B depict the nucleic acid sequence (SEQ ID NO:117) encoding human GRO polypeptide and the amino acid sequence of human GRO polypeptide (SEQ ID NO:118).

Figure 67A and 67B depict the nucleic acid sequence (SEQ ID NO:119) encoding human MIP2BGRO-g polypeptide and the amino acid sequence of human MIP2BGRO-g polypeptide (SEQ ID NO:120).

Figure 68A and 68B depict the nucleic acid sequence (SEQ ID NO:121) encoding human IL1B polypeptide and the amino acid sequence of human IL1B polypeptide (SEQ ID NO:122).

Figure 69A and 69B depict the nucleic acid sequence (SEQ ID NO:123) encoding human IL3RA polypeptide and the amino acid sequence of human IL3RA polypeptide (SEQ ID NO:124).

Figure 70A and 70B depict the nucleic acid sequence (SEQ ID NO:125) encoding human CASP1 polypeptide and the amino acid sequence of human CASP1 polypeptide (SEQ ID NO:126).

Figure 71A and 71B depict the nucleic acid sequence (SEQ ID NO:127) encoding human BV8 polypeptide and the amino acid sequence of human BV8 polypeptide (SEQ ID NO:128).

Figure 72A and 72B depict the nucleic acid sequence (SEQ ID NO:129) encoding human HDAC7A polypeptide and the amino acid sequence of human HDAC7A polypeptide (SEQ ID NO:130).

Figure 73A and 73B depict the nucleic acid sequence (SEQ ID NO:131) encoding human ACVRL1 polypeptide and the amino acid sequence of human ACVRL1 polypeptide (SEQ ID NO:132).

Figure 74A and 74B depict the nucleic acid sequence (SEQ ID NO:133) encoding human NR4A1 polypeptide and the amino acid sequence of human NR4A1 polypeptide (SEQ ID NO:134).

Figure 75A and 75B depict the nucleic acid sequence (SEQ ID NO:135) encoding human K5B polypeptide and the amino acid sequence of human K5B polypeptide (SEQ ID NO:136).

Figure 76A and 76B depict the nucleic acid sequence (SEQ ID NO:137) encoding human SILV polypeptide and the amino acid sequence of human SILV polypeptide (SEQ ID NO:138).

Figure 77A and 77B depict the nucleic acid sequence (SEQ ID NO:139) encoding human IRAK3 polypeptide and the amino acid sequence of human IRAK3 polypeptide (SEQ ID NO:140).

Figure 78A and 78B depict the nucleic acid sequence (SEQ ID NO:141) encoding human IL-4 polypeptide and the amino acid sequence of human IL-4 polypeptide (SEQ ID NO:142).

Figure 79A and 79B depict the nucleic acid sequence (SEQ ID NO:143) encoding human IL-13 polypeptide and the amino acid sequence of human IL-13 polypeptide (SEQ ID NO:144).

Figure 80A and 80B depict the nucleic acid sequence (SEQ ID NO:145) encoding human RAD50 polypeptide and the amino acid sequence of human RAD50 polypeptide (SEQ ID NO:146).

Figure 81A and 81B depict the nucleic acid sequence (SEQ ID NO:147) encoding human IL-5 polypeptide and the amino acid sequence of human IL-5 polypeptide (SEQ ID NO:148).

Figure 82A and 82B depict the nucleic acid sequence (SEQ ID NO:149) encoding human IRF1 polypeptide and the amino acid sequence of human IRF1 polypeptide (SEQ ID NO:150).

Figure 83A and 83B depict the nucleic acid sequence (SEQ ID NO:151) encoding human PDLIM4 polypeptide and the amino acid sequence of human PDLIM4 polypeptide (SEQ ID NO:152).

Figure 84A and 84B depict the nucleic acid sequence (SEQ ID NO:153) encoding human CSF2 polypeptide and the amino acid sequence of human CSF2 polypeptide (SEQ ID NO:154).

Figure 85A and 85B depict the nucleic acid sequence (SEQ ID NO:155) encoding human IL-3 polypeptide and the amino acid sequence of human IL-3 polypeptide (SEQ ID NO:156).

Figure 86A and 86B depict the nucleic acid sequence (SEQ ID NO:157) encoding human MMP3 polypeptide and the amino acid sequence of human MMP3 polypeptide (SEQ ID NO:158).

Figure 87A and 87B depict the nucleic acid sequence (SEQ ID NO:159) encoding human IL-8 polypeptide and the amino acid sequence of human IL-8 polypeptide (SEQ ID NO:160).

Figure 88A and 88B depict the nucleic acid sequence (SEQ ID NO:161) encoding human TLR4 polypeptide and the amino acid sequence of human TLR4 polypeptide (SEQ ID NO:162).

Figure 89A and 89B depict the nucleic acid sequence (SEQ ID NO:163) encoding human HLA-DRB1 polypeptide and the amino acid sequence of human HLA-DRB1 polypeptide (SEQ ID NO:164).

Figure 90A and 90B depict the nucleic acid sequence (SEQ ID NO:165) encoding human MMP19 polypeptide and the amino acid sequence of human MMP19 polypeptide (SEQ ID NO:166).

Figure 91A and 91B depict the nucleic acid sequence (SEQ ID NO:167) encoding human TIMP1 polypeptide and the amino acid sequence of human TIMP1 polypeptide (SEQ ID NO:168).

Figure 92A and 92B depict the nucleic acid sequence (SEQ ID NO:169) encoding human Elfin polypeptide and the amino acid sequence of human Elfin polypeptide (SEQ ID NO:170).

Figure 93A and 93B depict the nucleic acid sequence (SEQ ID NO:171) encoding human CXCL1 polypeptide and the amino acid sequence of human CXCL1 polypeptide (SEQ ID NO:172).

Figure 94A and 94B depict the nucleic acid sequence (SEQ ID NO:173) encoding human DFKZP586A0522 polypeptide and the amino acid sequence of human DFKZP586A0522 polypeptide (SEQ ID NO:174).

Figure 95A and 95B depict the nucleic acid sequence (SEQ ID NO:175) encoding human SLC39A5 polypeptide and the amino acid sequence of human SLC39A5 polypeptide (SEQ ID NO:176).

Figure 96A and 96B depict the nucleic acid sequence (SEQ ID NO:177) encoding human GLI-1 polypeptide and the amino acid sequence of human GLI-1 polypeptide (SEQ ID NO:178).

Figure 97A and 97B depict the nucleic acid sequence (SEQ ID NO:179) encoding human HMGA2 polypeptide and the amino acid sequence of human HMGA2 polypeptide (SEQ ID NO:180).

Figure 98A and 98B depict the nucleic acid sequence (SEQ ID NO:181) encoding human SLC22A5 polypeptide and the amino acid sequence of human SLC22A5 polypeptide (SEQ ID NO:182).

Figure 99A and 99B depict the nucleic acid sequence (SEQ ID NO:183) encoding human SLC22A4 polypeptide and the amino acid sequence of human SLC22A4 polypeptide (SEQ ID NO:184).

Figure 100A and 100B depict the nucleic acid sequence (SEQ ID NO:185) encoding human P4HA2 polypeptide and the amino acid sequence of human P4HA2 polypeptide (SEQ ID NO:186).

Figure 101A and 101B depict the nucleic acid sequence (SEQ ID NO:187) encoding human TSLP polypeptide and the amino acid sequence of human TSLP polypeptide (SEQ ID NO:188).

Figure 102A and 102B depict the nucleic acid sequence (SEQ ID NO:189) encoding human tubulin alpha 5/alpha 3 polypeptide and the amino acid sequence of human tubulin alpha 5/alpha 3 polypeptide (SEQ ID NO:190).

Figure 103A and 103B depict the nucleic acid sequence (SEQ ID NO:191) encoding human tubulin alpha 6 polypeptide and the amino acid sequence of human tubulin alpha 6 polypeptide (SEQ ID NO:192).

Figure 104 shows a meta-analysis of non-synonymous GLI1 SNP rs2228226 in Scotland, Cambridge and Sweden using Mantel-Haenszel method.

Figure 105 shows Q1100E disrupts a conserved region of the GLI1 protein and reduces GLI1 transcriptional activity.

Figure 106 shows expression of hedgehog (HH) signalling components in the healthy human adult colon (HC) and ulcerative colitis (UC).

Figure 107 shows the results in which *Gli1+/-* animals show mortality, severe clinical symptoms, and profound weight loss after DSS treatment.

Figure 108 shows *Gli1+/-* animals demonstrate more severe intestinal inflammation than WT littermates in response to DSS treatment.

Figure 109 shows cytokine analysis of *Gli1+/-* and WT mice after DSS treatments demonstrates robust pro-inflammatory cytokine activation.

Figure 110A-B shows the (A) nucleic acid sequence encoding human arrestin domain containing 5 (ARRDC5) (LOC342959) and the (B) amino acid sequence of human ARRDC5 polypeptide.

Figure 111 shows the nucleic acid sequence corresponding to human ataxin 3-like (ATXN3L).

Figure 112A-B shows the (A) nucleic acid sequence encoding human follicle stimulating hormone receptor (FSHR) (LOC92552) and (B) the amino acid sequence of human FSHR polypeptide.

Figure 113A-B shows the (A) nucleic acid sequence encoding human Platelet-derived growth factor receptor, alpha polypeptide (PDGFRA) and (B) the amino acid sequence of human PDGFRA polypeptide.

Figure 114A-B shows the (A) nucleic acid sequence encoding human transforming growth factor beta 3 (TGFB3) and (B) the amino acid sequence of human TGFB3 polypeptide.

Figure 115A-B shows the (A) nucleic acid sequence encoding human potassium channel tetramerisation domain containing 8 (KCTD8) and (B) the amino acid sequence of human KCTD8 polypeptide.

Figure 116A-B shows the (A) nucleic acid sequence encoding human transglutaminase 4 (TGM4) and (B) the amino acid sequence of human TGM4 polypeptide.

Figure 117A-B shows the (A) nucleic acid sequence encoding human TPD52L3 tumor protein D52-like 3 (NYD-SP25) and (B) the amino acid sequence of human NYD-SP25 polypeptide.

Figure 118 shows the nucleic acid sequence corresponding to misc_RNA (C3orf53), FLJ33651.

Figure 119 shows the nucleic acid sequence corresponding to EMX2 opposite strand (non-protein coding) (EMX2OS) on chromosome 10.

Figure 120A-B shows the (A) nucleic acid sequence encoding human wingless-type MMTV integration site family, member 16 (WNT16) and (B) the amino acid sequence of human WNT16 polypeptide.

Figure 121A-C shows the (A-B) nucleic acid sequences encoding human sprouty-related, EVH1 domain containing 2 (SPRED2) and (C) the amino acid sequence of human SPRED2.

Figure 122A-C shows the (A-B) nucleic acid sequences encoding human chromosome 16 open reading frame 65 (C16orf65) and (C) the amino acid sequence of human chromosome 16 open reading frame 65 (C16orf65).

Figure 123A-B shows the (A) nucleic acid sequence encoding human chromosome 12 open reading frame 2 (C12orf2) and (B) the amino acid sequence of human chromosome 12 open reading frame 2 (C12orf2).

Figure 124A-B shows the (A) nucleic acid sequence encoding human multiple PDZ domain protein (MPDZ) and (B) the amino acid sequence of human MPDZ.

Figure 125A-B shows the (A) nucleic acid sequence encoding human phenylalanine-tRNA synthetase 2 (FARS2) and (B) the amino acid sequence of human FARS2.

Figure 126A-B shows the (A) nucleic acid sequence encoding human caspase 8, apoptosis-related cysteine protease (CASP8) and (B) the amino acid sequence of human CASP8.

Figure 127A-B shows the (A) nucleic acid sequence encoding human 5'-nucleotidase, ecto (CD73) (NT5E) and (B) the amino acid sequence of human NT5E.

Figure 128 shows the nucleic acid sequence corresponding to human teratocarcinoma-derived growth factor 3 (TDGF3).

Figure 129A-B shows the (A) nucleic acid sequence encoding human butyrophilin-like 3 (BTNL3) and (B) the amino acid sequence of human BTNL3.

Figure 130A-B shows the (A) nucleic acid sequence encoding human S100A8 and (B) the amino acid sequence of human S100A8.

Figure 131A-B shows the (A) nucleic acid sequence encoding human CCL20 and (B) the amino acid sequence of human CCL20.

Detailed Description of the Invention

A. Definitions

Unless defined otherwise, technical and scientific terms used herein have the same meaning as commonly understood by one of ordinary skill in the art to which this invention belongs. Singleton *et al.*, Dictionary of Microbiology and Molecular Biology 2nd ed., J. Wiley & Sons (New York, NY 1994), and March, Advanced Organic Chemistry Reactions, Mechanisms and Structure 4th ed., John Wiley & Sons (New York, NY 1992), provide one skilled in the art with a general guide to many of the terms used in the present application.

One skilled in the art will recognize many methods and materials similar or equivalent to those described herein, which could be used in the practice of the present invention. Indeed, the present invention is in no way limited to the methods and materials described. For purposes of the present invention, the following terms are defined below.

The term "inflammatory bowel disease" or "IBD" is used as a collective term for ulcerative colitis and Crohn's disease. Although the two diseases are generally considered as two different entities, their common characteristics, such as patchy necrosis of the surface epithelium, focal accumulations of leukocytes adjacent to glandular crypts, and an increased number of intraepithelial lymphocytes (IEL) and certain macrophage subsets, justify their treatment as a single disease group.

The term "Crohn's disease" or "CD" is used herein to refer to a condition involving chronic inflammation of the gastrointestinal tract. Crohn's-related inflammation usually affects the intestines, but may occur anywhere from the mouth to the anus. CD differs from UC in that the inflammation extends through all layers of the intestinal wall and involves mesentery as well as lymph nodes. The disease is often discontinuous, i.e., severely diseased segments of bowel are separated from apparently disease-free areas. In CD, the bowel wall also thickens which can lead to obstructions,

and the development of fistulas and fissures are not uncommon. As used herein, CD may be one or more of several types of CD, including without limitation, ileocolitis (affects the ileum and the large intestine); ileitis (affects the ileum); gastroduodenal CD (inflammation in the stomach and the duodenum); jejunoileitis (spotty patches of inflammation in the jejunum); and Crohn's (granulomatous) colitis (only affects the large intestine).

The term "ulcerative colitis" or "UC" is used herein to refer to a condition involving inflammation of the large intestine and rectum. In patients with UC, there is an inflammatory reaction primarily involving the colonic mucosa. The inflammation is typically uniform and continuous with no intervening areas of normal mucosa. Surface mucosal cells as well as crypt epithelium and submucosa are involved in an inflammatory reaction with neutrophil infiltration. Ultimately, this reaction typically progresses to epithelial damage and loss of epithelial cells resulting in multiple ulcerations, fibrosis, dysplasia and longitudinal retraction of the colon.

The term "inactive" IBD is used herein to mean an IBD that was previously diagnosed in an individual but is currently in remission. This is in contrast to an "active" IBD in which an individual has been diagnosed with and IBD but has not undergone treatment. In addition, the active IBD may be a recurrence of a previously diagnosed and treated IBD that had gone into remission (i.e. become an inactive IBD). Such recurrences may also be referred to herein as "flare-ups" of an IBD. Mammalian subjects having an active autoimmune disease, such as an IBD, may be subject to a flare-up, which is a period of heightened disease activity or a return of corresponding symptoms. Flare-ups may occur in response to severe infection, allegic reactions, physical stress, emotional trauma, surgery, or environmental factors.

The term "modulate" is used herein to mean that the expression of the gene, or level of RNA molecule or equivalent RNA molecules encoding one or more proteins or protein subunits, or activity of one or more proteins or protein subunits is up regulated or down regulated, such that expression, level, or activity is greater than or less than that observed in the absence of the modulator.

The terms "inhibit", "down-regulate", "underexpress" and "reduce" are used interchangeably and mean that the expression of a gene, or level of RNA molecules or equivalent RNA molecules encoding one or more proteins or protein subunits, or activity of one or more proteins or protein subunits, is reduced relative to one or more controls, such as, for example, one or more positive and/or negative controls.

The term "up-regulate" or "overexpress" is used to mean that the expression of a gene, or level of RNA molecules or equivalent RNA molecules encoding one or more proteins or protein subunits, or

activity of one or more proteins or protein subunits, is elevated relative to one or more controls, such as, for example, one or more positive and/or negative controls.

The term "diagnosis" is used herein to refer to the identification of a molecular or pathological state, disease or condition, such as the identification of IBD.

The term "prognosis" is used herein to refer to the prediction of the likelihood of IBD development or progression, including autoimmune flare-ups and recurrences following surgery. Prognostic factors are those variables related to the natural history of IBD, which influence the recurrence rates and outcome of patients once they have developed IBD. Clinical parameters that may be associated with a worse prognosis include, for example, an abdominal mass or tenderness, skin rash, swollen joints, mouth ulcers, and borborygmus (gurgling or splashing sound over the intestine). Prognostic factors may be used to categorize patients into subgroups with different baseline recurrence risks.

The "pathology" of an IBD includes all phenomena that compromise the well-being of the patient. IBD pathology is primarily attributed to abnormal activation of the immune system in the intestines that can lead to chronic or acute inflammation in the absence of any known foreign antigen, and subsequent ulceration. Clinically, IBD is characterized by diverse manifestations often resulting in a chronic, unpredictable course. Bloody diarrhea and abdominal pain are often accompanied by fever and weight loss. Anemia is not uncommon, as is severe fatigue. Joint manifestations ranging from arthralgia to acute arthritis as well as abnormalities in liver function are commonly associated with IBD. During acute "attacks" of IBD, work and other normal activity are usually impossible, and often a patient is hospitalized.

The aetiology of these diseases is unknown and the initial lesion has not been clearly defined; however, patchy necrosis of the surface epithelium, focal accumulations of leukocytes adjacent to glandular crypts, and an increased number of intraepithelial lymphocytes and certain macrophage subsets have been described as putative early changes, especially in Crohn's disease.

The term "treatment" refers to both therapeutic treatment and prophylactic or preventative measures for IBD, wherein the object is to prevent or slow down (lessen) the targeted pathologic condition or disorder. Those in need of treatment include those already with an IBD as well as those prone to have an IBD or those in whom the IBD is to be prevented. Once the diagnosis of an IBD has been made by the methods disclosed herein, the goals of therapy are to induce and maintain a remission.

Various agents that are suitable for use as an "IBD therapeutic agent" are known to those of ordinary skill in the art. As described herein, such agents include without limitation, aminosalicylates, corticosteroids, and immunosuppressive agents.

The term "test sample" refers to a sample from a mammalian subject suspected of having an IBD, known to have an IBD, or known to be in remission from an IBD. The test sample may originate from various sources in the mammalian subject including, without limitation, blood, semen, serum, urine, bone marrow, mucosa, tissue, etc.

The term "control" or "control sample" refers a negative control in which a negative result is expected to help correlate a positive result in the test sample. Controls that are suitable for the present invention include, without limitation, a sample known to have normal levels of gene expression, a sample obtained from a mammalian subject known not to have an IBD, and a sample obtained from a mammalian subject known to be normal. A control may also be a sample obtained from a subject previously diagnosed and treated for an IBD who is currently in remission; and such a control is useful in determining any recurrence of an IBD in a subject who is in remission. In addition, the control may be a sample containing normal cells that have the same origin as cells contained in the test sample. Those of skill in the art will appreciate other controls suitable for use in the present invention.

The term "microarray" refers to an ordered arrangement of hybridizable array elements, preferably polynucleotide probes, on a substrate.

The term "polynucleotide," when used in singular or plural, generally refers to any polyribonucleotide or polydeoxribonucleotide, which may be unmodified RNA or DNA or modified RNA or DNA. Thus, for instance, polynucleotides as defined herein include, without limitation, single- and double-stranded DNA, DNA including single- and double-stranded regions, single- and double-stranded RNA, and RNA including single- and double-stranded regions, hybrid molecules comprising DNA and RNA that may be single-stranded or, more typically, double-stranded or include single- and double-stranded regions. In addition, the term "polynucleotide" as used herein refers to triple-stranded regions comprising RNA or DNA or both RNA and DNA. The strands in such regions may be from the same molecule or from different molecules. The regions may include all of one or more of the molecules, but more typically involve only a region of some of the molecules. One of the molecules of a triple-helical region often is an oligonucleotide. The term "polynucleotide" specifically includes cDNAs. The term includes DNAs (including cDNAs) and RNAs that contain one or more modified bases. Thus, DNAs or RNAs with backbones modified for stability or for other reasons are "polynucleotides" as that term is intended herein. Moreover, DNAs or RNAs comprising unusual bases, such as inosine, or modified bases, such as tritiated bases, are included within the term "polynucleotides" as defined herein. In general, the term "polynucleotide" embraces all chemically, enzymatically and/or metabolically modified forms of unmodified polynucleotides, as well as the chemical forms of DNA and RNA characteristic of viruses and cells, including simple and complex cells.

The term "oligonucleotide" refers to a relatively short polynucleotide, including, without limitation, single-stranded deoxyribonucleotides, single- or double-stranded ribonucleotides, RNA:DNA hybrids and double-stranded DNAs. Oligonucleotides, such as single-stranded DNA probe oligonucleotides, are often synthesized by chemical methods, for example using automated oligonucleotide synthesizers that are commercially available. However, oligonucleotides can be made by a variety of other methods, including *in vitro* recombinant DNA-mediated techniques and by expression of DNAs in cells and organisms.

The terms "differentially expressed gene," "differential gene expression" and their synonyms, which are used interchangeably, refer to a gene whose expression is activated to a higher or lower level in a subject suffering from a disease, specifically an IBD, such as UC or CD, relative to its expression in a normal or control subject. The terms also include genes whose expression is activated to a higher or lower level at different stages of the same disease. It is also understood that a differentially expressed gene may be either activated or inhibited at the nucleic acid level or protein level, or may be subject to alternative splicing to result in a different polypeptide product. Such differences may be evidenced by a change in mRNA levels, surface expression, secretion or other partitioning of a polypeptide, for example. Differential gene expression may include a comparison of expression between two or more genes or their gene products, or a comparison of the ratios of the expression between two or more genes or their gene products, or even a comparison of two differently processed products of the same gene, which differ between normal subjects and subjects suffering from a disease, specifically an IBD, or between various stages of the same disease. Differential expression includes both quantitative, as well as qualitative, differences in the temporal or cellular expression pattern in a gene or its expression products among, for example, normal and diseased cells, or among cells which have undergone different disease events or disease stages. For the purpose of this invention, "differential gene expression" is considered to be present when there is at least an about two-fold, preferably at least about four-fold, more preferably at least about six-fold, most preferably at least about ten-fold difference between the expression of a given gene in normal and diseased subjects, or in various stages of disease development in a diseased subject.

The term "over-expression" with regard to an RNA transcript is used to refer to the level of the transcript determined by normalization to the level of reference mRNAs, which might be all transcripts detected in the specimen or a particular reference set of mRNAs.

The phrase "gene amplification" refers to a process by which multiple copies of a gene or gene fragment are formed in a particular cell or cell line. The duplicated region (a stretch of amplified DNA) is often referred to as "amplicon". Usually, the amount of the messenger RNA (mRNA) produced, *i.e.,* the level of gene expression, also increases in the proportion of the number of copies made of the particular gene expressed.

In general, the term "marker" or "biomarker" or refers to an identifiable physical location on a chromosome, such as a restriction endonuclease recognition site or a gene, whose inheritance can be monitored. The marker may be an expressed region of a gene referred to as a "gene expression marker", or some segment of DNA with no known coding function. An "IBD marker" as used herein refers those genes listed in Tables 1, 2, and 3.

"Stringency" of hybridization reactions is readily determinable by one of ordinary skill in the art, and generally is an empirical calculation dependent upon probe length, washing temperature, and salt concentration. In general, longer probes require higher temperatures for proper annealing, while shorter probes need lower temperatures. Hybridization generally depends on the ability of denatured DNA to reanneal when complementary strands are present in an environment below their melting temperature. The higher the degree of desired homology between the probe and hybridizable sequence, the higher the relative temperature which can be used. As a result, it follows that higher relative temperatures would tend to make the reaction conditions more stringent, while lower temperatures less so. For additional details and explanation of stringency of hybridization reactions, see Ausubel et al., Current Protocols in Molecular Biology, Wiley Interscience Publishers, (1995).

"Stringent conditions" or "high stringency conditions", as defined herein, typically: (1) employ low ionic strength and high temperature for washing, for example 0.015 M sodium chloride/0.0015 M sodium citrate/0.1% sodium dodecyl sulfate at 50°C; (2) employ during hybridization a denaturing agent, such as formamide, for example, 50% (v/v) formamide with 0.1% bovine serum albumin/0.1% Ficoll/0.1% polyvinylpyrrolidone/50mM sodium phosphate buffer at pH 6.5 with 750 mM sodium chloride, 75 mM sodium citrate at 42°C; or (3) employ 50% formamide, 5 x SSC (0.75 M NaCl, 0.075 M sodium citrate), 50 mM sodium phosphate (pH 6.8), 0.1% sodium pyrophosphate, 5 x Denhardt's solution, sonicated salmon sperm DNA (50 μg/ml), 0.1% SDS, and 10% dextran sulfate at 42°C, with washes at 42°C in 0.2 x SSC (sodium chloride/sodium citrate), 50% formamide, followed by a high-stringency wash consisting of 0.1 x SSC containing EDTA at 55°C.

"Moderately stringent conditions" may be identified as described by Sambrook et al., Molecular Cloning: A Laboratory Manual, New York: Cold Spring Harbor Press, 1989, and include the use of washing solution and hybridization conditions (e.g., temperature, ionic strength and %SDS) less stringent that those described above. An example of moderately stringent conditions is overnight incubation at 37°C in a solution comprising: 20% formamide, 5 x SSC (150 mM NaCl, 15 mM trisodium citrate), 50 mM sodium phosphate (pH 7.6), 5 x Denhardt's solution, 10% dextran sulfate, and 20 mg/ml denatured sheared salmon sperm DNA, followed by washing the filters in 1 x SSC at about 37-50°C. The skilled artisan will recognize how to adjust the temperature, ionic strength, etc. as necessary to accommodate factors such as probe length and the like.

In the context of the present invention, reference to "at least one," "at least two," "at least five," etc. of the genes listed in any particular gene set means any one or any and all combinations of the genes listed.

The terms "splicing" and "RNA splicing" are used interchangeably and refer to RNA processing that removes introns and joins exons to produce mature mRNA with continuous coding sequence that moves into the cytoplasm of an eukaryotic cell.

In theory, the term "exon" refers to any segment of an interrupted gene that is represented in the mature RNA product (B. Lewin. *Genes IV* Cell Press, Cambridge Mass. 1990). In theory the term "intron" refers to any segment of DNA that is transcribed but removed from within the transcript by splicing together the exons on either side of it. Operationally, exon sequences occur in the mRNA sequence of a gene as defined by Ref. SEQ ID numbers. Operationally, intron sequences are the intervening sequences within the genomic DNA of a gene, bracketed by exon sequences and having GT and AG splice consensus sequences at their 5' and 3' boundaries.

An "interfering RNA" or "small interfering RNA (siRNA)" is a double stranded RNA molecule usually less than about 30 nucleotides in length that reduces expression of a target gene. Interfering RNAs may be identified and synthesized using known methods (Shi Y., *Trends in Genetics* 19(1):9-12 (2003), WO/2003056012 and WO2003064621), and siRNA libraries are commercially available, for example from Dharmacon, Lafayette, Colorado.

A "native sequence" polypeptide is one which has the same amino acid sequence as a polypeptide derived from nature, including naturally occurring or allelic variants. Such native sequence polypeptides can be isolated from nature or can be produced by recombinant or synthetic means. Thus, a native sequence polypeptide can have the amino acid sequence of naturally occurring human polypeptide, murine polypeptide, or polypeptide from any other mammalian species.

The term "antibody" herein is used in the broadest sense and specifically covers monoclonal antibodies, polyclonal antibodies, multispecific antibodies (*e.g.* bispecific antibodies), and antibody fragments, so long as they exhibit the desired biological activity. The present invention particularly contemplates antibodies against one or more of the IBD markers disclosed herein. Such antibodies may be referred to as "anti-IBD marker antibodies".

The term "monoclonal antibody" as used herein refers to an antibody from a population of substantially homogeneous antibodies, *i.e.*, the individual antibodies comprising the population are identical and/or bind the same epitope(s), except for possible variants that may arise during production of the monoclonal antibody, such variants generally being present in minor amounts. Such monoclonal antibody typically includes an antibody comprising a polypeptide sequence that

binds a target, wherein the target-binding polypeptide sequence was obtained by a process that includes the selection of a single target binding polypeptide sequence from a plurality of polypeptide sequences.

The monoclonal antibodies herein specifically include "chimeric" antibodies in which a portion of the heavy and/or light chain is identical with or homologous to corresponding sequences in antibodies derived from a particular species or belonging to a particular antibody class or subclass, while the remainder of the chain(s) is identical with or homologous to corresponding sequences in antibodies derived from another species or belonging to another antibody class or subclass, as well as fragments of such antibodies, so long as they exhibit the desired biological activity (U.S. Patent No. 4,816,567; and Morrison *et al., Proc. Natl. Acad. Sci. USA*, 81:6851-6855 (1984)). Chimeric antibodies of interest herein include "primatized" antibodies comprising variable domain antigen-binding sequences derived from a non-human primate (*e.g.* Old World Monkey, Ape etc) and human constant region sequences, as well as "humanized" antibodies.

"Humanized" forms of non-human (*e.g.,* rodent) antibodies are chimeric antibodies that contain minimal sequence derived from non-human immunoglobulin. For the most part, humanized antibodies are human immunoglobulins (recipient antibody) in which residues from a hypervariable region of the recipient are replaced by residues from a hypervariable region of a non-human species (donor antibody) such as mouse, rat, rabbit or nonhuman primate having the desired specificity, affinity, and capacity.

An "intact antibody" herein is one which comprises two antigen binding regions, and an Fc region. Preferably, the intact antibody has a functional Fc region.

"Antibody fragments" comprise a portion of an intact antibody, preferably comprising the antigen binding region thereof. Examples of antibody fragments include Fab, Fab', $F(ab')_2$, and Fv fragments; diabodies; linear antibodies; single-chain antibody molecules; and multispecific antibodies formed from antibody fragment(s).

"Native antibodies" are usually heterotetrameric glycoproteins of about 150,000 daltons, composed of two identical light (L) chains and two identical heavy (H) chains. Each light chain is linked to a heavy chain by one covalent disulfide bond, while the number of disulfide linkages varies among the heavy chains of different immunoglobulin isotypes. Each heavy and light chain also has regularly spaced intrachain disulfide bridges. Each heavy chain has at one end a variable domain (V_H) followed by a number of constant domains. Each light chain has a variable domain at one end (V_L) and a constant domain at its other end. The constant domain of the light chain is aligned with the first constant domain of the heavy chain, and the light-chain variable domain is aligned with the

variable domain of the heavy chain. Particular amino acid residues are believed to form an interface between the light chain and heavy chain variable domains.

The term "variable" refers to the fact that certain portions of the variable domains differ extensively in sequence among antibodies and are used in the binding and specificity of each particular antibody for its particular antigen. However, the variability is not evenly distributed throughout the variable domains of antibodies. It is concentrated in three segments called hypervariable regions both in the light chain and the heavy chain variable domains. The more highly conserved portions of variable domains are called the framework regions (FRs). The variable domains of native heavy and light chains each comprise four FRs, largely adopting a β-sheet configuration, connected by three hypervariable regions, which form loops connecting, and in some cases forming part of, the β-sheet structure. The hypervariable regions in each chain are held together in close proximity by the FRs and, with the hypervariable regions from the other chain, contribute to the formation of the antigen-binding site of antibodies (see Kabat *et al., Sequences of Proteins of Immunological Interest*, 5th Ed. Public Health Service, National Institutes of Health, Bethesda, MD. (1991)).

The term "*hypervariable region*," "*HVR*," or "*HV*," when used herein refers to the regions of an antibody-variable domain that are hypervariable in sequence and/or form structurally defined loops. Generally, antibodies comprise six HVRs; three in the VH (H1, H2, H3), and three in the VL (L1, L2, L3). In native antibodies, H3 and L3 display the most diversity of the six HVRs, and H3 in particular is believed to play a unique role in conferring fine specificity to antibodies. See, *e.g.*, Xu *et al. Immunity* 13:37-45 (2000); Johnson and Wu in *Methods in Molecular Biology* 248:1-25 (Lo, ed., Human Press, Totowa, NJ, 2003)). Indeed, naturally occurring camelid antibodies consisting of a heavy chain only are functional and stable in the absence of light chain. See, *e.g.*, Hamers-Casterman *et al., Nature* 363:446-448 (1993) and Sheriff *et al., Nature Struct. Biol.* 3:733-736 (1996).

A number of hypervariable region delineations are in use and are encompassed herein. The Kabat Complementarity Determining Regions (CDRs) are based on sequence variability and are the most commonly used (Kabat *et al., Sequences of Proteins of Immunological Interest*, 5th Ed. Public Health Service, National Institutes of Health, Bethesda, MD. (1991)). Chothia refers instead to the location of the structural loops (Chothia and Lesk *J. Mol. Biol.* 196:901-917 (1987)). The end of the Chothia CDR-H1 loop when numbered using the Kabat numbering convention varies between H32 and H34 (see below) depending on the length of the loop (this is because the Kabat numbering scheme places the insertions at H35A and H35B; if neither 35A nor 35B is present, the loop ends at 32; if only 35A is present, the loop ends at 33; if both 35A and 35B are present, the loop ends at 34). The AbM hypervariable regions represent a compromise between the Kabat CDRs and Chothia structural loops, and are used by Oxford Molecular's AbM antibody modeling software. The "contact" hypervariable

regions are based on an analysis of the available complex crystal structures. The residues from each of these hypervariable regions are noted below.

Loop	Kabat	AbM	Chothia	Contact
L1	L24-L34	L24-L34	L24-L34	L30-L36
L2	L50-L56	L50-L56	L50-L56	L46-L55
L3	L89-L97	L89-L97	L89-L97	L89-L96
H1	H31-H35B	H26-H35B	H26-H32, 33 or 34	H30-H35B (Kabat Numbering)
H1	H31-H35	H26-H35	H26-H32	H30-H35 (Chothia Numbering)
H2	H50-H65	H50-H58	H52-H56	H47-H58
H3	H95-H102	H95-H102	H95-H102	H93-H101.

Hypervariable regions may comprise "extended hypervariable regions" as follows: 24-36 or 24-34 (L1), 46-56 or 50-56 (L2) and 89-97 (L3) in the VL and 26-35B (H1), 50-65, 47-65 or 49-65 (H2) and 93-102, 94-102 or 95-102 (H3) in the VH. These extended hypervariable regions are typically combinations of the Kabat and Chothia definitions, which may optionally further include residues identified using the Contact definition. The variable domain residues are numbered according to Kabat *et al.*, *supra* for each of these definitions.

Papain digestion of antibodies produces two identical antigen-binding fragments, called "Fab" fragments, each with a single antigen-binding site, and a residual "Fc" fragment, whose name reflects its ability to crystallize readily. Pepsin treatment yields an $F(ab')_2$ fragment that has two antigen-binding sites and is still capable of cross-linking antigen.

"Fv" is the minimum antibody fragment which contains a complete antigen-recognition and antigen-binding site. This region consists of a dimer of one heavy chain and one light chain variable domain in tight, non-covalent association. It is in this configuration that the three hypervariable regions of each variable domain interact to define an antigen-binding site on the surface of the V_H-V_L dimer. Collectively, the six hypervariable regions confer antigen-binding specificity to the antibody. However, even a single variable domain (or half of an Fv comprising only three hypervariable regions specific for an antigen) has the ability to recognize and bind antigen, although at a lower affinity than the entire binding site.

The Fab fragment also contains the constant domain of the light chain and the first constant domain (CH1) of the heavy chain. Fab' fragments differ from Fab fragments by the addition of a few residues at the carboxy terminus of the heavy chain CH1 domain including one or more cysteines from the antibody hinge region. Fab'-SH is the designation herein for Fab' in which the cysteine residue(s) of the constant domains bear at least one free thiol group. $F(ab')_2$ antibody fragments originally were produced as pairs of Fab' fragments which have hinge cysteines between them. Other chemical couplings of antibody fragments are also known.

The "light chains" of antibodies from any vertebrate species can be assigned to one of two clearly distinct types, called kappa (κ) and lambda (λ), based on the amino acid sequences of their constant domains.

The term "Fc region" herein is used to define a C-terminal region of an immunoglobulin heavy chain, including native sequence Fc regions and variant Fc regions. Although the boundaries of the Fc region of an immunoglobulin heavy chain might vary, the human IgG heavy chain Fc region is usually defined to stretch from an amino acid residue at position Cys226, or from Pro230, to the carboxyl-terminus thereof. The C-terminal lysine (residue 447 according to the EU numbering system) of the Fc region may be removed, for example, during production or purification of the antibody, or by recombinantly engineering the nucleic acid encoding a heavy chain of the antibody. Accordingly, a composition of intact antibodies may comprise antibody populations with all K447 residues removed, antibody populations with no K447 residues removed, and antibody populations having a mixture of antibodies with and without the K447 residue.

Unless indicated otherwise, herein the numbering of the residues in an immunoglobulin heavy chain is that of the EU index as in Kabat *et al., Sequences of Proteins of Immunological Interest*, 5th Ed. Public Health Service, National Institutes of Health, Bethesda, MD (1991), expressly incorporated herein by reference. The "EU index as in Kabat" refers to the residue numbering of the human IgG1 EU antibody.

A "native sequence Fc region" comprises an amino acid sequence identical to the amino acid sequence of an Fc region found in nature. Native sequence human Fc regions include a native sequence human IgG1 Fc region (non-A and A allotypes); native sequence human IgG2 Fc region; native sequence human IgG3 Fc region; and native sequence human IgG4 Fc region as well as naturally occurring variants thereof.

A "variant Fc region" comprises an amino acid sequence which differs from that of a native sequence Fc region by virtue of at least one amino acid modification, preferably one or more amino acid substitution(s). Preferably, the variant Fc region has at least one amino acid substitution compared to

a native sequence Fc region or to the Fc region of a parent polypeptide, *e.g.* from about one to about ten amino acid substitutions, and preferably from about one to about five amino acid substitutions in a native sequence Fc region or in the Fc region of the parent polypeptide. The variant Fc region herein will preferably possess at least about 80% homology with a native sequence Fc region and/or with an Fc region of a parent polypeptide, and most preferably at least about 90% homology therewith, more preferably at least about 95% homology therewith.

Depending on the amino acid sequence of the constant domain of their heavy chains, intact antibodies can be assigned to different "classes". There are five major classes of intact antibodies: IgA, IgD, IgE, IgG, and IgM, and several of these may be further divided into "subclasses" (isotypes), *e.g.*, IgG1, IgG2, IgG3, IgG4, IgA, and IgA2. The heavy-chain constant domains that correspond to the different classes of antibodies are called α, δ, ε, γ, and μ, respectively. The subunit structures and three-dimensional configurations of different classes of immunoglobulins are well known.

"Single-chain Fv" or "scFv" antibody fragments comprise the V_H and V_L domains of antibody, wherein these domains are present in a single polypeptide chain. Preferably, the Fv polypeptide further comprises a polypeptide linker between the V_H and V_L domains which enables the scFv to form the desired structure for antigen binding. For a review of scFv see Plückthun in *The Pharmacology of Monoclonal Antibodies*, vol. 113, Rosenburg and Moore eds., Springer-Verlag, New York, pp. 269-315 (1994).

The term "diabodies" refers to small antibody fragments with two antigen-binding sites, which fragments comprise a variable heavy domain (V_H) connected to a variable light domain (V_L) in the same polypeptide chain (V_H - V_L). By using a linker that is too short to allow pairing between the two domains on the same chain, the domains are forced to pair with the complementary domains of another chain and create two antigen-binding sites. Diabodies are described more fully in, for example, EP 404,097; WO 93/11161; and Hollinger *et al., Proc. Natl. Acad. Sci. USA*, 90:6444-6448 (1993).

A "naked antibody" is an antibody that is not conjugated to a heterologous molecule, such as a small molecule or radiolabel.

An "isolated" antibody is one which has been identified and separated and/or recovered from a component of its natural environment. Contaminant components of its natural environment are materials which would interfere with diagnostic or therapeutic uses for the antibody, and may include enzymes, hormones, and other proteinaceous or nonproteinaceous solutes. In preferred embodiments, the antibody will be purified (1) to greater than 95% by weight of antibody as determined by the Lowry method, and most preferably more than 99% by weight, (2) to a degree

sufficient to obtain at least 15 residues of N-terminal or internal amino acid sequence by use of a spinning cup sequenator, or (3) to homogeneity by SDS-PAGE under reducing or nonreducing conditions using Coomassie blue or, preferably, silver stain. Isolated antibody includes the antibody *in situ* within recombinant cells since at least one component of the antibody's natural environment will not be present. Ordinarily, however, isolated antibody will be prepared by at least one purification step.

An "affinity matured" antibody is one with one or more alterations in one or more hypervariable regions thereof which result an improvement in the affinity of the antibody for antigen, compared to a parent antibody which does not possess those alteration(s). Preferred affinity matured antibodies will have nanomolar or even picomolar affinities for the target antigen. Affinity matured antibodies are produced by procedures known in the art. Marks *et al. Bio/Technology* 10:779-783 (1992) describes affinity maturation by VH and VL domain shuffling. Random mutagenesis of HVR and/or framework residues is described by: Barbas *et al. Proc Nat. Acad. Sci, USA* 91:3809-3813 (1994); Schier *et al. Gene* 169:147-155 (1995); Yelton *et al. J. Immunol.* 155:1994-2004 (1995); Jackson *et al., J. Immunol.* 154(7):3310-9 (1995); and Hawkins *et al, J. Mol. Biol.* 226:889-896 (1992).

An "amino acid sequence variant" antibody herein is an antibody with an amino acid sequence which differs from a main species antibody. Ordinarily, amino acid sequence variants will possess at least about 70% homology with the main species antibody, and preferably, they will be at least about 80%, more preferably at least about 90% homologous with the main species antibody. The amino acid sequence variants possess substitutions, deletions, and/or additions at certain positions within or adjacent to the amino acid sequence of the main species antibody. Examples of amino acid sequence variants herein include an acidic variant (*e.g.* deamidated antibody variant), a basic variant, an antibody with an amino-terminal leader extension (*e.g.* VHS-) on one or two light chains thereof, an antibody with a C-terminal lysine residue on one or two heavy chains thereof, etc., and includes combinations of variations to the amino acid sequences of heavy and/or light chains. The antibody variant of particular interest herein is the antibody comprising an amino-terminal leader extension on one or two light chains thereof, optionally further comprising other amino acid sequence and/or glycosylation differences relative to the main species antibody.

A "glycosylation variant" antibody herein is an antibody with one or more carbohydrate moieities attached thereto which differ from one or more carbohydrate moieties attached to a main species antibody. Examples of glycosylation variants herein include antibody with a G1 or G2 oligosaccharide structure, instead a G0 oligosaccharide structure, attached to an Fc region thereof, antibody with one or two carbohydrate moieties attached to one or two light chains thereof, antibody with no carbohydrate attached to one or two heavy chains of the antibody, etc., and combinations of glycosylation alterations.

Where the antibody has an Fc region, an oligosaccharide structure may be attached to one or two heavy chains of the antibody, *e.g.* at residue 299 (298, Eu numbering of residues). For pertuzumab, G0 was the predominant oligosaccharide structure, with other oligosaccharide structures such as G0-F, G-1, Man5, Man6, G1-1, G1(1-6), G1(1-3) and G2 being found in lesser amounts in the pertuzumab composition.

Unless indicated otherwise, a "G1 oligosaccharide structure" herein includes G-1, G1-1, G1(1-6) and G1(1-3) structures.

An "amino-terminal leader extension" herein refers to one or more amino acid residues of the amino-terminal leader sequence that are present at the amino-terminus of any one or more heavy or light chains of an antibody. An exemplary amino-terminal leader extension comprises or consists of three amino acid residues, VHS, present on one or both light chains of an antibody variant.

A "deamidated" antibody is one in which one or more asparagine residues thereof has been derivatized, *e.g.* to an aspartic acid, a succinimide, or an iso-aspartic acid.

B.1 General Description of the Invention

The practice of the present invention will employ, unless otherwise indicated, conventional techniques of molecular biology (including recombinant techniques), microbiology, cell biology, and biochemistry, which are within the skill of the art. Such techniques are explained fully in the literature, such as, "Molecular Cloning: A Laboratory Manual", 2nd edition (Sambrook et al., 1989); "Oligonucleotide Synthesis" (M.J. Gait, ed., 1984); "Animal Cell Culture" (R.I. Freshney, ed., 1987); "Methods in Enzymology" (Academic Press, Inc.); "Handbook of Experimental Immunology", 4th edition (D.M. Weir & C.C. Blackwell, eds., Blackwell Science Inc., 1987); "Gene Transfer Vectors for Mammalian Cells" (J.M. Miller & M.P. Calos, eds., 1987); "Current Protocols in Molecular Biology" (F.M. Ausubel et al., eds., 1987); and "PCR: The Polymerase Chain Reaction", (Mullis et al., eds., 1994).

As discussed above, the detection or diagnosis of IBD is currently obtained by various classification systems that rely on a number of variables observed in a patient. The present invention is based on the identification of genes that are associated with IBD. Accordingly, the expression levels of such genes can serve as diagnostic markers to identify patients with IBD. As described in the Examples, the differential expression of a number of genes in IBD patients has been observed. Thus, according to the present invention, the genes listed in Tables 1A-B, 2, and 3A-B have been identified as differentially expressed in IBD.

Table 1A provides a list of genes that are upregulated in IBD.

Table 1A

Gene	Indication(s)	SEQ ID NO nucleic acid, amino acid	Figure
Defensin, alpha 6 (DEFA6)	CD, UC	1, 2	8
Defensin, alpha 5 (DEFA5)	UC	3, 4	9A-B
Defensin beta 14 (DEFB14)	UC	229, 230	9C-D
IL-3 receptor, alpha low affinity (IL3RA)	CD	5, 6	10
IL-2 receptor, alpha (IL2RA)	CD, UC	7, 8	11
Regenerating islet-derived 3 gamma (REG3G)	CD, UC	9, 10	12
Regenerating islet-derived 1 beta pancreatic stone protein (REG1B)	CD, UC	11, 12	13
Potassium voltage-gated channel, Shal-related subfamily (KCND3)	CD, UC	13, 14	14
Human macrophage inflammatory protein 3 (MIP-3a)	CD, UC	15, 16	15
Endothelial cell growth factor 1 platelet-derived (ECGF1)	CD, UC	17, 18	16
Interleukin 1 beta (IL1B)	CD, UC	19, 20	17
Growth regulated protein gamma (MIP2BGRO-g)	CD, UC	21, 22	18
Chemokine C-X-C motif ligand 1 (CXCL1)	CD, UC	23, 24	19
Inhibitor of apoptosis protein 1 (IAP1)	CD, UC	25, 26	20
Caspase 5, apoptosis-related cysteine protease (CASP5)	CD, UC	27, 28	21
Deleted in malignant brain tumors 1 (DMBT1)	CD, UC	29, 30	22
Protocadherin 17 (PCDH17)	CD, UC	31, 32	23
Interferon-inducible protein 9-27 (IFITM1)	CD, UC	33, 34	24
PDZK1 interacting protein 1 (PDZK1IP1)	CD, UC	35, 36	25
IRTA2 / FCRH5 (IRTA2)	CD	37, 38	26
Solute carrier family 40 iron-regulated transporter, member 1 (SLC40A1)	CD, UC	39, 40	27
Immunoglobulin heavy variable 4-4 (IGHV4-4)	CD, UC	41, 42	28
Regenerating islet-derived 3 gamma (REG3G)	CD, UC	43, 44	29
Aquaporin 9 (AQP9)	CD, UC	45, 46	30
Olfactomedin 4 (OLFM4)	CD, UC	47, 48	31

S100 calcium binding protein A9 calgranulin B (S100A9)	CD, UC	49, 50	32
unc-5 homolog C C. elegans-like (UNC5CL)	CD, UC	51, 52	33
G protein-coupled receptor 110 (GPR110)	CD, UC	53, 54	34
HLA-G histocompatibility antigen, class I, G (HLA-G)	CD, UC	55, 56	35
Transporter 1, ATP-binding cassette, sub-family B MDR/TAP (TAP1)	CD, UC	57, 58	36
Mitogen-activated protein kinase kinase kinase 8 (MAP3K8)	CD, UC	59, 60	37
Ubiquitin D| Gamma-aminobutyric acid GABA B receptor, 1 (UBD|GABBR1)	CD, UC	61, 62	38
DEAH Asp-Glu-Ala-Asp/His box polypeptide 57 (DHX57)	CD, UC	63, 64	39
Metastasis-associate (MA) LY6/PLAUR domain containing 5 (LYPD5)	CD, UC	65, 66	40
Immunoglobulin lambda joining-constant/OR18 (IGLJCOR18)	CD, UC	67, 68	41
TNF R superfamily, member 6b, decoy (TNFRSF6B)	CD, UC	69, 70	42
serum amyloid A1 (SAA1)	CD, UC	71, 72	43
Transporter 2, ATP-binding cassette, sub-family B MDR/TAP (TAP2)	CD, UC	73, 74	44
PCAA17448	CD, UC	75, 76	45
lipocalin 2 oncogene 24p3 (LCN2)	CD, UC	77, 78	46
Z-D binding protein 1 (ZBP1)	CD, UC	79, 80	47
TNFAIP3 interacting protein 3 (TNIP3)	CD, UC	81, 82	48
Zinc finger CCCH-type containing 12A (ZC3H12A)	CD, UC	83, 84	49
Chitinase 3-like 1 cartilage glycoprotein-39 (CHI3L1)	CD, UC	85, 86	50
Fc fragment of IgG, low affinity IIIa, receptor CD16a (FCGR3A)	CD, UC	87, 88	51
Sterile alpha motif domain containing 9-like (SAMD9L)	CD, UC	89, 90	52
Matrix metalloproteinase 9 gelatinase B, 92kDa gelatinase, 92kDa type IV collagenase (MMP9)	CD	91, 92	53

Matrix metalloproteinase 7 matrilysin, uterine (MMP7)	CD, UC	93, 94	54
B-factor, properdin (BF)	CD, UC	95, 96	55
S100 calcium binding protein P (S100P)	CD, UC	97, 98	56
Growth regulated protein (GRO)	CD, UC	99, 100	57
Indoleamine-pyrrole 2,3 dioxygenase INDO (INDO)	CD, UC	101, 102	58
Tripartite motif-containing 22 (TRIM22)	CD, UC	103, 104	59
Serum amyloid A2 (SAA2)	CD, UC	105, 106	60
Arrestin domain containing 5 (ARRDC5) (LOC342959)	CD, UC	193, 194	110
ataxin 3-like (ATXN3L) (A_24_P910246)	CD, UC	195	111
follicle stimulating hormone receptor (FSHR) (LOC92552)	CD, UC	196, 197	112
platelet-derived growth factor receptor, alpha polypeptide (PDGFRA)	CD, UC	198, 199	113
transforming growth factor beta 3 (TGFB3)	CD, UC	200, 201	114
potassium channel tetramerisation domain containing 8 (KCTD8)	CD, UC	202, 203	115
transglutaminase 4 (TGM4)	CD, UC	204, 205	116
TPD52L3 tumor protein D52-like 3 (NYD-SP25)	CD, UC	206, 207	117
misc_RNA (C3orf53) (FLJ33651)	CD, UC	208	118
EMX2 opposite strand (non-protein coding) (EMX2OS) on chromosome 10	CD, UC	209	119A
S100A8	UC	231, 232	130
CCL20	UC	233, 234	131

Table 1B provides a list of genes that are downregulated in IBD.

Gene	Indication(s)	SEQ ID NO nucleic acid, amino acid	Figure
Sialidase 4 (NEU4)	CD, UC	107, 108	61
wingless-type MMTV integration site family,	CD, UC	210, 211	120

member 16 (WNT16)			
sprouty-related, EVH1 domain containing 2 (SPRED2)	CD, UC	212, 213	121
chromosome 16 open reading frame 65 (C16orf65) (MGC50721)	CD, UC	214, 215	122
chromosome 12 open reading frame 2 (C12orf2)	CD, UC	216, 217	123
multiple PDZ domain protein (MPDZ)	CD, UC	218, 219	124
phenylalanine-tRNA synthetase 2 (FARS2)	CD, UC	220, 221	125
caspase 8, apoptosis-related cysteine protease (CASP8)	CD, UC	222, 223	126
5'-nucleotidase, ecto (CD73)(NT5E)	CD, UC	224, 225	127
teratocarcinoma-derived growth factor 3 (TDGF3)	CD, UC	226	128
butyrophilin-like 3 (BTNL3)	CD, UC	227, 228	129

Table 2 provides a list of genes that are upregulated in IBD. These genes were identified from the immune response in silico (IRIS) collection of genes (Abbas, A. et al. Genes and Immunity, 6:319-331 (2005) hereby incorporated by reference in its entirety).

Table 2

Gene	Indication(s)	SEQ ID NO nucleic acid, amino acid	Figure
Immunoglobulin domain IRTA2/FCRH5	CD, UC	109, 110	62
Immunoglobulin lambda joining-constant/OR18 (IGLJCOR18)	CD, UC	111, 112	63
Immunoglobulin heavy variable 4-4 (IGHV4-4)	CD, UC	113, 114	64
Matrix metalloproteinase 9 gelatinase B, 92kDa gelatinase, 92kDa type IV collagenase (MMP9)	CD, UC	115, 116	65
Growth regulated protein (GRO)	CD, UC	117, 118	66
Growth regulated protein gamma (MIP2BGRO-g)	CD, UC	119, 120	67
interleukin 1, beta (IL1B)	CD, UC	121, 122	68
IL-3 receptor, alpha low affinity (IL3RA)	CD, UC	123, 124	69
Caspase 1, apoptosis-related cysteine protease	CD, UC	125, 126	70

interleukin 1, beta, convertase (CASP1)			
Bv8 protein (BV8)	CD, UC	127, 128	71

Table 3A provides a list of genes that are upregulated in IBD and were identified based on the experiments described in Example 2. In some instances, the locus/chromosome of the gene is provided.

Table 3A

Gene	Indication(s)	Locus/ Chromosome (if known)	SEQ ID NO nucleic acid, amino acid	Figure
HDAC7A	UC	IBD2/12	129, 130	72
ACVRL1	UC	IBD2/12	131, 132	73
NR4A1	UC	IBD2/12	133, 134	74
K5B	UC	IBD2/12	135, 136	75
SILV	UC	IBD2/12	137, 138	76
IRAK3	UC	IBD2/12	139, 140	77
IL-4	UC	IBD5/5	141, 142	78
IL-13	UC	IBD5/5	143, 144	79
RAD50	UC	IBD5/5	145, 146	80
IL-5	UC	IBD5/5	147, 148	81
IRF1	UC	IBD5/5	149, 150	82
PDLIM4	UC	IBD5/5	151, 152	83
CSF2	UC	IBD5/5	153, 154	84
IL-3	UC	IBD5/5	155, 156	85
MMP3	UC		157, 158	86
IL-8	UC		159, 160	87
TLR4	UC		161, 162	88
HLA-DRB1	UC		163, 164	89
MMP19	UC		165, 166	90
TIMP1	UC		167, 168	91
Elfin	UC		169, 170	92
CXCL1	UC		171, 172	93

Table 3B provides a list of genes that are down-regulated in IBD and were identified based on the experiments described in Example 2. In some instances, the locus/chromosome of the gene is provided.

Table 3B

Gene	Indication(s)	Locus/ Chromosome	SEQ ID NO nucleic acid, amino acid	Figure
DFKZP586A0522	UC	IBD2/12	173, 174	94
SLC39A5	UC	IBD2/12	175, 176	95
GLI-1	UC	IBD2/12	177, 178	96
HMGA2	UC	IBD2/12	179, 180	97
SLC22A5	UC	IBD5/5	181, 182	98
SLC22A4	UC	IBD5/5	183, 184	99
P4HA2	UC	IBD5/5	185, 186	100
TSLP	UC		187, 188	101
tubulin alpha 5/alpha 3	UC		189, 190	102
tubulin alpha 6	UC		191, 192	103

a. Biomarkers of the Invention

The present invention provides numerous gene expression markers or biomarkers for IBD listed in Tables 1A, 1B, 2, 3A, and 3B. In one embodiment of the present invention, the biomarkers are suitable for use in a panel of markers (as described herein). Such panels may include one or more markers from Table 1A; one or more markers from Table 1B; the marker from Table 2; one or markers from Table 3A; and one or more markers from Table 3B. In addition, the present invention also contemplates panels of markers selected from two or more of Tables 1A, 1B, 2, 3A, and 3B. For example, a panel might contain one or more markers from Table 1A and one or more markers from Table 1B; or one or more markers from Table 1A and the marker from Table 2; or one or more markers from Table 1B and the marker from Table 2; or one or more markers from Table 1A and one or more markers from Table 3A, etc. Those of ordinary skill in the art will appreciate the various combinations of biomarkers from Tables 1-3 that are suitable for use in the panels described herein.

In one embodiment of the present invention, a preferred set of IBD markers identified by microarray analysis, includes markers that are upregulated in an IBD. Preferably, the set of upregulated markers includes DEFA5 (SEQ ID NOS:3-4), DEFA6(SEQ ID NO:1-2), TNIP3(SEQ ID NO:81-82), REG3-

gamma(SEQ ID NO:9-10), MMP7(SEQ ID NO:93-94), and SAA1(SEQ ID NO:71-72) in Table 1A; and IL-8(SEQ ID NO:159-160), Keratin 5B (K5B)(SEQ ID NO:135-136), SLC22A4(SEQ ID NO:183-184), SLC22A5(SEQ ID NO:181-182), MMP3(SEQ ID NO:157-158), and MMP19(SEQ ID NO:165-166) in Tables 3A. A preferred downregulated marker is GLI-1 (SEQ ID NO: 175-176) in in Table 3B. A panel of biomarkers as described herein may include one of, more than one of, or all of these markers. Alternatively, the set of markers include 1, 2, 3, 4, 5, 6 of the indicated markers from Table 1A, and/or 1, 2, 3, 4, 5, 6 of the indicated markers from Table 3A and/or 1 or 2 of the indicated markers in Table 3B.

Members of lists provided above, as single markers or in any combination, are preferred for use in prognostic and diagnostic assays of the present invention. The IBD markers of the present invention are differentially expressed genes or regions of genes. A differential level of expression of one or more markers in a test sample from a mammalian subject relative to a control can determined from the level of RNA transcripts or expression products detected by one or more of the methods described in further detail below.

Based on evidence of differential expression of RNA transcripts in normal cells and cells from a mammalian subject having IBD, the present invention provides gene markers for IBD. The IBD markers and associated information provided by the present invention allow physicians to make more intelligent treatment decisions, and to customize the treatment of IBD to the needs of individual patients, thereby maximizing the benefit of treatment and minimizing the exposure of patients to unnecessary treatments, which do not provide any significant benefits and often carry serious risks due to toxic side-effects.

Multi-analyte gene expression tests can measure the expression level of one or more genes involved in each of several relevant physiologic processes or component cellular characteristics. In some instances the predictive power of the test, and therefore its utility, can be improved by using the expression values obtained for individual genes to calculate a score which is more highly correlated with outcome than is the expression value of the individual genes. For example, the calculation of a quantitative score (recurrence score) that predicts the likelihood of recurrence in estrogen receptor-positive, node-negative breast cancer is describe in U.S. Published Patent Application No. 20050048542. The equation used to calculate such a recurrence score may group genes in order to maximize the predictive value of the recurrence score. The grouping of genes may be performed at least in part based on knowledge of their contribution to physiologic functions or component cellular characteristics such as discussed above. The formation of groups, in addition, can facilitate the mathematical weighting of the contribution of various expression values to the recurrence score. The weighting of a gene group representing a physiological process or component cellular characteristic can reflect the contribution of that process or characteristic to the pathology of the IBD and clinical

outcome. Accordingly, in an important aspect, the present invention also provides specific groups of the genes identified herein, that together are more reliable and powerful predictors of outcome than the individual genes or random combinations of the genes identified.

In addition, based on the determination of a recurrence score, one can choose to partition patients into subgroups at any particular value(s) of the recurrence score, where all patients with values in a given range can be classified as belonging to a particular risk group. Thus, the values chosen will define subgroups of patients with respectively greater or lesser risk.

The utility of a gene marker in predicting the development or progression of an IBD may not be unique to that marker. An alternative marker having a expression pattern that is closely similar to a particular test marker may be substituted for or used in addition to a test marker and have little impact on the overall predictive utility of the test. The closely similar expression patterns of two genes may result from involvement of both genes in a particular process and/or being under common regulatory control. The present invention specifically includes and contemplates the use of such substitute genes or gene sets in the methods of the present invention.

The markers and associated information provided by the present invention predicting the development and/or progression of an IBD also have utility in screening patients for inclusion in clinical trials that test the efficacy of drug compounds for the treatment of patients with IBD.

The markers and associated information provided by the present invention predicting the presence, development and/or progression of an IBD are useful as criterion for determing whether IBD treatment is appropriate. For example, IBD treatment may be appropriate where the results of the test indicate that an IBD marker is differentially expressed in a test sample from an individual relative to a control sample. The individual may be an individual not known to have an IBD, an individual known to have an IBD, an individual previously diagnosed with an IBD undergoing treatment for the IBD, or an individual previously diagnosed with an IBD and having had surgery to address the IBD. In addition, the present invention contemplates methods of treating an IBD. As described below, the diagnostic methods of the present invention may further comprise the step of administering an IBD therapeutic agent to the mammalian subject that provided the test sample in which the differential expression of one or more IBD markers was observed relative to a control. Such methods of treatment would therefore comprise (a) determining the presence of an IBD in a mammalian subject, and (b) administering an IBD therapeutic agent to the mammalian subject.

In another embodiment, the IBD markers and associated information are used to design or produce a reagent that modulates the level or activity of the gene's transcript or its expression product. Said reagents may include but are not limited to an antisense RNA, a small inhibitory RNA (siRNA), a

ribozyme, a monoclonal or polyclonal antibody. In a further embodiment, said gene or its transcript, or more particularly, an expression product of said transcript is used in an (screening) assay to identify a drug compound, wherein said drug compounds is used in the development of a drug to treat an IBD.

In various embodiments of the inventions, various technological approaches described below are available for determination of expression levels of the disclosed genes. In particular embodiments, the expression level of each gene may be determined in relation to various features of the expression products of the gene including exons, introns, protein epitopes and protein activity. In other embodiments, the expression level of a gene may be inferred from analysis of the structure of the gene, for example from the analysis of the methylation pattern of gene's promoter(s).

b. *Diagnostic Methods of the Invention*

The present invention provides methods of detecting or diagnosing an IBD in a mammalian subject based on differential expression of an IBD marker. In a one embodiment, the methods comprise the use of a panel of IBD markers as discussed above. The panels may include one or more IBD markers selected from Tables 1-3.

In some embodiments, the panel of IBD markers will include at least 1 IBD marker, at least two IBD markers, at least three IBD markers, at least 4 IBD markers, at least five IBD markers, at least 6 IBD markers, at least 7 IBD marker, at least 8 IBD markers, at least 9 IBD markers, at least 10 IBD markers, at least 11 IBD markers, at least 12 IBD markers, at least 13 IBD markers, at least 14 IBD markers, at least 15 IBD markers, at least 16 IBD markers, at least 17 IBD markers, at least 18 IBD markers, at least 19 IBD markers, or at least 20 IBD markers. In one embodiment, the panel includes markers in increments of five. In another embodiment, the panel includes markers in increments of ten. The panel may include an IBD marker that is overexpressed in IBD relative to a control, an IBD marker that is underexpressed in IBD relative to a control, or IBD markers that are both overexpressed and underexpressed in IBD relative to a control. In a preferred embodiment, the panel includes one or more markers that are upregulated in CD and one or more markers that are downregulated in CD. In another preferred embodiment, the panel includes one or more markers that are upregulated in UC and one or more markers that are downregulated in UC.

In another embodiment, the panels of the present invention may include an IBD marker that is overexpressed in an active IBD relative to a control, underexpressed in an active IBD relative to a control, or IBD markers that are both overexpressed and underexpressed in an active IBD relative to a control. In another embodiment, the panels of the present invention may include an IBD marker that is overexpressed in an inactive IBD relative to a control, underexpressed in an inactive IBD

relative to a control, or IBD markers that are both overexpressed and underexpressed in an inactive IBD relative to a control. In a preferred embodiment, the active IBD is CD. In another preferred embodiment, the inactive IBD is CD.

In a preferred embodiment, the methods of diagnosing or detecting the presence of an IBD in a mammalian subject comprise determining a differential expression level of RNA transcripts or expression products thereof from a panel of IBD markers in a test sample obtained from the subject relative to the level of expression in a control, wherein the differential level of expression is indicative of the presence of an IBD in the subject from which the test sample was obtained. The differential expression in the test sample may be higher and/or lower relative to a control as discussed herein.

Differential expression or activity of one or more of the genes provided in the lists above, or the corresponding RNA molecules or encoded proteins in a biological sample obtained from the patient, relative to control, indicates the presence of an IBD in the patient. The control can, for example, be a gene, present in the same cell, which is known to be up-regulated (or down-regulated) in an IBD patient (positive control). Alternatively, or in addition, the control can be the expression level of the same gene in a normal cell of the same cell type (negative control). Expression levels can also be normalized, for example, to the expression levels of housekeeping genes, such as glyceraldehyde-3-phosphate-dehydrogenase (GAPDH) and/or β-actin, or to the expression levels of all genes in the sample tested. In one embodiment, expression of one or more of the above noted genes is deemed positive expression if it is at the median or above, *e.g.* compared to other samples of the same type. The median expression level can be determined essentially contemporaneously with measuring gene expression, or may have been determined previously. These and other methods are well known in the art, and are apparent to those skilled in the art.

Methods for identifying IBD patients are provided herein. Of this patient population, patients with an IBD can be identified by determining the expression level of one or more of the genes, the corresponding RNA molecules or encoded proteins in a biological sample comprising cells obtained from the patient. The biological sample can, for example, be a tissue biopsy as described herein.

The methods of the present invention concern IBD diagnostic assays, and imaging methodologies. In one embodiment, the assays are performed using antibodies as described herein. The invention also provides various immunological assays useful for the detection and quantification of proteins. These assays are performed within various immunological assay formats well known in the art, including but not limited to various types of radioimmunoassays, enzyme-linked immunosorbent assays (ELISA), enzyme-linked immunofluorescent assays (ELIFA), and the like. In addition, immunological imaging methods capable of detecting an IBD characterized by expression of a molecule described herein are also

provided by the invention, including but not limited to radioscintigraphic imaging methods using labeled antibodies. Such assays are clinically useful in the detection, monitoring, diagnosis and prognosis of IBD characterized by expression of one or more molecules described herein.

Another aspect of the present invention relates to methods for identifying a cell that expresses a molecule described herein. The expression profile of a molecule(s) described herein make it a diagnostic marker for IBD. Accordingly, the status of the expression of the molecule(s) provides information useful for predicting a variety of factors including susceptibility to advanced stages of disease, rate of progression, and/or sudden and severe onset of symptoms in an active IBD or an inactive IBD, i.e. flare-ups.

In one embodiment, the present invention provides methods of detecting an IBD. A test sample from a mammalian subject and a control sample from a known normal mammal are each contacted with an anti-IBD marker antibody or a fragment thereof. The level of IBD marker expression is measured and a differential level of expression in the test sample relative to the control sample is indicative of an IBD in the mammalian subject from which the test sample was obtained. In some embodiments, the level of IBD marker expression in the test sample is determined to be higher than the level of expression in the control, wherein the higher level of expression indicates the presence of an IBD in the subject from which the test sample was obtained. In another embodiments, the level of IBD marker expression in the test sample is determined to be lower than the level of expression in the control, wherein the lower level of expression indicates the presence of an IBD in the subject from which the test sample was obtained.

In another embodiment, the IBD detected by the methods of the present invention is the recurrence or flareup of an IBD in the mammalian subject.

In preferred embodiments, the methods are employed to detect the flare-up of an IBD or a recurrence of an IBD in a mammalian subject previously determined to have an IBD who underwent treatment for the IBD, such as drug therapy or a surgical procedure. Following initial detection of an IBD, additional test samples may be obtained from the mammalian subject found to have an IBD. The additional sample may be obtained hours, days, weeks, or months after the initial sample was taken. Those of skill in the art will appreciate the appropriate schedule for obtaining such additional samples, which may include second, third, fourth, fifth, sixth, etc. test samples. The intial test sample and the additional sample (and alternately a control sample as described herein) are contacted with an anti-IBD marker antibody. The level of IBD marker expression is measured and a differential level of expression in the additional test sample as compared to the initial test sample is indicative of a flare-up in or a recurrence of an IBD in the mammalian subject from which the test sample was obtained.

In one aspect, the methods of the present invention are directed to a determining step. In one embodiment, the determining step comprises measuring the level of expression of one or more IBD markers in a test sample relative to a control. Typically, measuring the level of IBD marker expression, as described herein, involves analyzing a test sample for differential expression of an IBD marker relative to a control by performing one or more of the techniques described herein. The expression level data obtained from a test sample and a control are compared for differential levels of expression. In another embodiment, the determining step further comprises an examination of the test sample and control expression data to assess whether an IBD is present in the subject from which the test sample was obtained.

In some embodiments, the determining step comprises the use of a software program executed by a suitable processor for the purpose of (i) measuring the differential level of IBD marker expression in a test sample and a control; and/or (ii) analyzing the data obtained from measuring differential level of IBD marker expression in a test sample and a control. Suitable software and processors are well known in the art and are commercially available. The program may be embodied in software stored on a tangible medium such as CD-ROM, a floppy disk, a hard drive, a DVD, or a memory associated with the processor, but persons of ordinary skill in the art will readily appreciate that the entire program or parts thereof could alternatively be executed by a device other than a processor, and/or embodied in firmware and/or dedicated hardware in a well known manner.

Following the determining step, the measurement results, findings, diagnoses, predictions and/or treatment recommendations are typically recorded and communicated to technicians, physicians and/or patients, for example. In certain embodiments, computers will be used to communicate such information to interested parties, such as, patients and/or the attending physicians. In some embodiments, the assays will be performed or the assay results analyzed in a country or jurisdiction which differs from the country or jurisdiction to which the results or diagnoses are communicated.

In a preferred embodiment, a diagnosis, prediction and/or treatment recommendation based on the level of expression of one or more IBD markers disclosed herein measured in a test subject of having one or more of the IBD markers herein is communicated to the subject as soon as possible after the assay is completed and the diagnosis and/or prediction is generated. The results and/or related information may be communicated to the subject by the subject's treating physician. Alternatively, the results may be communicated directly to a test subject by any means of communication, including writing, electronic forms of communication, such as email, or telephone. Communication may be facilitated by use of a computer, such as in case of email communications. In certain embodiments, the communication containing results of a diagnostic test and/or conclusions drawn from and/or treatment recommendations based on the test, may be generated and delivered automatically to the subject using a combination of computer hardware and software which will be familiar to artisans

skilled in telecommunications. One example of a healthcare-oriented communications system is described in U.S. Pat. No. 6,283,761; however, the present invention is not limited to methods which utilize this particular communications system. In certain embodiments of the methods of the invention, all or some of the method steps, including the assaying of samples, diagnosing of diseases, and communicating of assay results or diagnoses, may be carried out in diverse (e.g., foreign) jurisdictions.

The invention provides assays for detecting the differential expression of an IBD marker in tissues associated with the gastrointestinal tract including, without limitation, ascending colon tissue, descending colon tissue, sigmoid colon tissue, and terminal ileum tissue; as well expression in other biological samples such as serum, semen, bone, prostate, urine, cell preparations, and the like. Methods for detecting differential expression of an IBD marker are also well known and include, for example, immunoprecipitation, immunohistochemical analysis, Western blot analysis, molecular binding assays, ELISA, ELIFA and the like. For example, a method of detecting the differential expression of an IBD marker in a biological sample comprises first contacting the sample with an anti-IBD marker antibody, an IBD marker-reactive fragment thereof, or a recombinant protein containing an antigen-binding region of an anit-IBD marker antibody; and then detecting the binding of an IBD marker protein in the sample.

In various embodiments of the inventions, various technological approaches are available for determination of expression levels of the disclosed genes, including, without limitation, RT-PCR, microarrays, serial analysis of gene expression (SAGE) and Gene Expression Analysis by Massively Parallel Signature Sequencing (MPSS), which will be discussed in detail below. In particular embodiments, the expression level of each gene may be determined in relation to various features of the expression products of the gene including exons, introns, protein epitopes and protein activity. In other embodiments, the expression level of a gene may be inferred from analysis of the structure of the gene, for example from the analysis of the methylation pattern of gene's promoter(s).

c. *Therapeutic Methods of the Invention*

The present invention provides therapeutic methods of treating an IBD in a subject in need that comprise detecting the presence of an IBD in a mammalian subject by the diagnostic methods described herein and then administering to the mammalian subject an IBD therapeutic agent. Those of ordinary skill in the art will appreciate the various IBD therapeutic agents that may be suitable for use in the present invention (see St Clair Jones, Hospital Pharmacist, May 2006, Vol. 13; pages 161-166, hereby incorporated by reference in its entirety). The present invention contemplates methods of IBD treatment in which one or more IBD therapeutic agents are administered to a subject in need. In one embodiment, the IBD therapeutic agent is one or more of an aminosalicylate, a corticosteroid,

and an immunosuppressive agent. In a preferred embodiment, the aminosalicylate is one of sulfasalazine, olsalazine, mesalamine, balsalazide, and asacol. In another preferred embodiment, multiple aminosalicylates are co-administered, such as a combination of sulfasalazine and olsalazine. In other preferred embodiments, the corticosteroid may be budesonide, prednisone, prednisolone, methylprednisolone, 6-mercaptopurine (6-MP), azathioprine, methotrexate, and cyclosporin. In other preferred embodiments, the IBD therapeutic agent may an antibiotic, such as ciprofloxacin and/or metronidazole; or an antibody-based agent such as infliximab (Remicade®).

The least toxic IBD therapeutic agents which patients are typically treated with are the aminosalicylates. Sulfasalazine (Azulfidine), typically administered four times a day, consists of an active molecule of aminosalicylate (5-ASA) which is linked by an azo bond to a sulfapyridine. Anaerobic bacteria in the colon split the azo bond to release active 5-ASA. However, at least 20% of patients cannot tolerate sulfapyridine because it is associated with significant side-effects such as reversible sperm abnormalities, dyspepsia or allergic reactions to the sulpha component. These side effects are reduced in patients taking olsalazine. However, neither sulfasalazine nor olsalazine are effective for the treatment of small bowel inflammation. Other formulations of 5-ASA have been developed which are released in the small intestine (e.g. mesalamine and asacol). Normally it takes 6-8 weeks for 5-ASA therapy to show full efficacy. Patients who do not respond to 5-ASA therapy, or who have a more severe disease, are prescribed corticosteroids. However, this is a short term therapy and cannot be used as a maintenance therapy. Clinical remission is achieved with corticosteroids within 2-4 weeks, however the side effects are significant and include Cushing goldface, facial hair, severe mood swings and sleeplessness. The response to sulfasalazine and 5-aminosalicylate preparations is poor in CD, fair to mild in early ulcerative colitis and poor in severe UC. If these agents fail, powerful immunosuppressive agents such as cyclosporine, prednisone, 6-mercaptopurine or azathioprine (converted in the liver to 6-mercaptopurine) are typically tried. For CD patients, the use of corticosteroids and other immunosuppressives must be carefully monitored because of the high risk of intra-abdominal sepsis originating in the fistulas and abscesses common in this disease. Approximately 25% of IBD patients will require surgery (colectomy) during the course of the disease.

Treatment of an IBD may include a surgical procedure, including without limitation, a bowel resection, anastomosis, a colectomy, a proctocolectomy, and an ostomy, or any combination thereof.

In addition to pharmaceutical medicine and surgery, nonconventional treatments for IBD such as nutritional therapy have also been attempted. For example, Flexical®, a semi-elemental formula, has been shown to be as effective as the steroid prednisolone. Sanderson *et al.*, *Arch. Dis. Child.* 51:123-7 (1987). However, semi-elemental formulas are relatively expensive and are typically unpalatable-thus their use has been restricted. Nutritional therapy incorporating whole proteins has also been

attempted to alleviate the symptoms of IBD. Giafer *et al.*, *Lancet* 335: 816-9 (1990). U.S. Patent No. 5,461,033 describes the use of acidic casein isolated from bovine milk and TGF-2. Beattie *et al.*, *Aliment. Pharmacol. Ther.* 8: 1-6 (1994) describes the use of casein in infant formula in children with IBD. U.S.P. 5,952,295 describes the use of casein in an enteric formulation for the treatment of IBD. However, while nutrional therapy is non-toxic, it is a palliative treatment and does not treat the underlying cause of the disease.

The present invention contemplates methods of IBD treatment, including for example, in vitro, ex vivo and in vivo therapeutic methods. The invention provides methods useful for treating an IBD in a subject in need upon the detection of an IBD disease state in the subject associated with the expression of one or more IBD markers disclosed herein, such as increased and/or decreased IBD marker expression. In one preferred embodiment, the method comprises (a) determining that the level of expression of (i) one or more nucleic acids encoding one or more polypeptides selected from Tables 1, 2, or 3; or (ii) RNA transcripts or expression products thereof of one or more genes listed in Tables 1, 2, and 3 in a test sample obtained from said subject is higher and/or lower relative to the level of expression in a control, wherein said higher and/or lower level of expression is indicative of the presence of an IBD in the subject from which the test sample was obtained; and (b) administering to said subject an effective amount of an IBD therapeutic agent. The determining step (a) may comprise the measurement of the expression of multiple IBD marker

The method of treatment comprises detecting the IBD and administering an effective amount of an IBD therapeutic agent to a subject in need of such treatment. In some embodiments, the IBD disease state is associated with an increased and/or decrease in expression of one or more IBD markers.

In one aspect, the invention provides methods for treating or preventing an IBD, the methods comprising detecting the presence of an IBD in a subject and administering an effective amount of an IBD therapeutic agent to the subject. It is understood that any suitable IBD therapeutic agent may be used in the methods of treatment, including aminosalicylates, corticosteroids, and immunosuppressive agents as discussed herein.

In any of the methods herein, one may administer to the subject or patient along with a single IBD therapeutic agent discussed herein an effective amount of a second medicament (where the single IBD therapeutic agent herein is a first medicament), which is another active agent that can treat the condition in the subject that requires treatment. For instance, an aminosalicylate may be co-administered with a corticosteroid, an immunsuppressive agent, or another aminosalicylate. The type of such second medicament depends on various factors, including the type of IBD, its severity, the condition and age of the patient, the type and dose of first medicament employed, etc.

Such treatments using first and second medicaments include combined administration (where the two or more agents are included in the same or separate formulations), and separate administration, in which case, administration of the first medicament can occur prior to, and/or following, administration of the second medicament. In general, such second medicaments may be administered within 48 hours after the first medicaments are administered, or within 24 hours, or within 12 hours, or within 3-12 hours after the first medicament, or may be administered over a pre-selected period of time, which is preferably about 1 to 2 days, about 2 to 3 days, about 3 to 4 days, about 4 to 5 days, about 5 to 6 days, or about 6 to 7 days.

The first and second medicaments can be administered concurrently, sequentially, or alternating with the first and second medicament or upon non-responsiveness with other therapy. Thus, the combined administration of a second medicament includes co-administration (concurrent administration), using separate formulations or a single pharmaceutical formulation, and consecutive administration in either order, wherein preferably there is a time period while both (or all) medicaments simultaneously exert their biological activities. All these second medicaments may be used in combination with each other or by themselves with the first medicament, so that the express "second medicament" as used herein does not mean it is the only medicament besides the first medicament, respectively. Thus, the second medicament need not be one medicament, but may constitute or comprise more than one such drug. These second medicaments as set forth herein are generally used in the same dosages and with administration routes as the first medicaments, or about from 1 to 99% of the dosages of the first medicaments. If such second medicaments are used at all, preferably, they are used in lower amounts than if the first medicament were not present, especially in subsequent dosings beyond the initial dosing with the first medicament, so as to eliminate or reduce side effects caused thereby.

Where the methods of the present invention comprise administering one or more IBD therapeutic agent to treat or prevent an IBD, it may be particularly desirable to combine the administering step with a surgical procedure that is also performed to treat or prevent the IBD. The IBD surgical procedures contemplated by the present invention include, without limitation, a bowel resection, anastomosis, a colectomy, a proctocolectomy, and an ostomy, or any combination thereof. For instance, an IBD therapeutic agent described herein may be combined with a colectomy in a treatment scheme, e.g. in treating an IBD. Such combined therapies include and separate administration, in which case, administration of the IBD therapeutic agent can occur prior to, and/or following, the surgical procedure.

Treatment with a combination of one or more IBD therapeutic agents; or a combination of one or more IBD therapeutic agents and a surgical procedure described herein preferably results in an improvement in the signs or symptoms of an IBD. For instance, such therapy may result in an

improvement in the subject receiving the IBD therapeutic agent treatment regimen and a surgical procedure, as evidenced by a reduction in the severity of the pathology of the IBD.

The IBD therapeutic agent(s) is/are administered by any suitable means, including parenteral, subcutaneous, intraperitoneal, intrapulmonary, and intranasal, and, if desired for local treatment, intralesional administration. Parenteral infusions include intramuscular, intravenous, intraarterial, intraperitoneal, or subcutaneous administration. Dosing can be by any suitable route, e.g. by injections, such as intravenous or subcutaneous injections, depending in part on whether the administration is brief or chronic.

The IBD therapeutic agent(s) compositions administered according to the methods of the invention will be formulated, dosed, and administered in a fashion consistent with good medical practice. Factors for consideration in this context include the particular disorder being treated, the particular mammal being treated, the clinical condition of the individual patient, the cause of the disorder, the site of delivery of the agent, the method of administration, the scheduling of administration, and other factors known to medical practitioners. The first medicament(s) need not be, but is optionally formulated with one or more additional medicament(s) (e.g. second, third, fourth, etc. medicaments) described herein. The effective amount of such additional medicaments depends on the amount of the first medicament present in the formulation, the type of disorder or treatment, and other factors discussed above. These are generally used in the same dosages and with administration routes as used hereinbefore or about from 1 to 99% of the heretofore employed dosages.

For the prevention or treatment of an IBD, the appropriate dosage of an IBD therapeutic agent (when used alone or in combination with other agents) will depend on the type of disease to be treated, the type of IBD therapeutic agent(s), the severity and course of the disease, whether the IBD therapeutic agent is administered for preventive or therapeutic purposes, previous therapy, the patient's clinical history and response to the IBD therapeutic agent, and the discretion of the attending physician. The IBD therapeutic agent is suitably administered to the patient at one time or over a series of treatments. Depending on the type and severity of the disease, about 1 ug/kg to 15 mg/kg (e.g. 0.1 mg/kg-10 mg/kg) of IBD therapeutic agent is an initial candidate dosage for administration to the patient, whether, for example, by one or more separate administrations, or by continuous infusion. One typical daily dosage might range from about 1 ug/kg to 100 mg/kg or more, depending on the factors mentioned above. For repeated administrations over several days or longer, depending on the condition, the treatment is sustained until a desired suppression of disease symptoms occurs. One exemplary dosage of the IBD therapeutic agent would be in the range from about 0.05 mg/kg to about 10 mg/kg. Thus, one or more doses of about 0.5 mg/kg, 2.0 mg/kg, 4.0 mg/kg or 10 mg/kg (or any combination thereof) may be administered to the patient. Such doses may be administered intermittently, e.g. every week or every three weeks (e.g. such that the patient receives from about

two to about twenty, e.g. about six doses of the IBD therapeutic agent). An initial higher loading dose, followed by one or more lower doses may be administered. An exemplary dosing regimen comprises administering an initial loading dose of about 4 mg/kg, followed by a weekly maintenance dose of about 2 mg/kg of the IBD therapeutic agent. However, other dosage regimens may be useful. The progress of this therapy is easily monitored by conventional techniques and assays.

B.2. Gene Expression Profiling

In general, methods of gene expression profiling can be divided into two large groups: methods based on hybridization analysis of polynucleotides, and other methods based on biochemical detection or sequencing of polynucleotides. The most commonly used methods known in the art for the quantification of mRNA expression in a sample include northern blotting and in situ hybridization (Parker & Barnes, Methods in Molecular Biology 106:247-283 (1999)); RNAse protection assays (Hod, Biotechniques 13:852-854 (1992)); and reverse transcription polymerase chain reaction (RT-PCR) (Weis et al., Trends in Genetics 8:263-264 (1992)). Alternatively, antibodies may be employed that can recognize specific duplexes, including DNA duplexes, RNA duplexes, and DNA-RNA hybrid duplexes or DNA-protein duplexes. Various methods for determining expression of mRNA or protein include, but are not limited to, gene expression profiling, polymerase chain reaction (PCR) including quantitative real time PCR (qRT-PCR), microarray analysis that can be performed by commercially available equipment, following manufacturer's protocols, such as by using the Affymetrix GenChip technology, serial analysis of gene expression (SAGE) (Velculescu et al., Science 270:484-487 (1995); and Velculescu et al., Cell 88:243-51 (1997)), MassARRAY, Gene Expression Analysis by Massively Parallel Signature Sequencing (MPSS) (Brenner et al., Nature Biotechnology 18:630-634 (2000)), proteomics, immunohistochemistry (IHC), etc. Preferably mRNA is quantified. Such mRNA analysis is preferably performed using the technique of polymerase chain reaction (PCR), or by microarray analysis. Where PCR is employed, a preferred form of PCR is quantitative real time PCR (qRT-PCR).

a. *Reverse Transcriptase PCR (RT-PCR)*

Of the techniques listed above, the most sensitive and most flexible quantitative method is RT-PCR, which can be used to compare mRNA levels in different sample populations, in normal and test sample tissues, to characterize patterns of gene expression, to discriminate between closely related mRNAs, and to analyze RNA structure.

The first step is the isolation of mRNA from a target sample. The starting material is typically total RNA isolated from colonic tissue biopsies. Thus, RNA can be isolated from a variety of tissues, including without limitation, the terminal ileum, the ascending colon, the descending colon, and the

sigmoid colon. In addition, the colonic tissue from which a biopsy is obtained may be from an inflamed and/or a non-inflamed colonic area.

In one embodiment, the mRNA is obtained from a biopsy as defined above wherein the biopsy is obtained from the left colon or from the right colon. As used herein, the "left colon" refers to the sigmoideum and rectosigmoideum and the "right colon" refers to the cecum.

General methods for mRNA extraction are well known in the art and are disclosed in standard textbooks of molecular biology, including Ausubel et al., Current Protocols of Molecular Biology, John Wiley and Sons (1997). In particular, RNA isolation can be performed using purification kit, buffer set and protease from commercial manufacturers, such as Qiagen, according to the manufacturer's instructions. Total RNA from tissue samples can be isolated using RNA Stat-60 (Tel-Test). RNA prepared from a biopsy can be isolated, for example, by cesium chloride density gradient centrifugation.

As RNA cannot serve as a template for PCR, the first step in gene expression profiling by RT-PCR is the reverse transcription of the RNA template into cDNA, followed by its exponential amplification in a PCR reaction. The two most commonly used reverse transcriptases are avilo myeloblastosis virus reverse transcriptase (AMV-RT) and Moloney murine leukemia virus reverse transcriptase (MMLV-RT). The reverse transcription step is typically primed using specific primers, random hexamers, or oligo-dT primers, depending on the circumstances and the goal of expression profiling. For example, extracted RNA can be reverse-transcribed using a GeneAmp RNA PCR kit (Perkin Elmer, CA, USA), following the manufacturer's instructions. The derived cDNA can then be used as a template in the subsequent PCR reaction.

Although the PCR step can use a variety of thermostable DNA-dependent DNA polymerases, it typically employs the Taq DNA polymerase, which has a 5'-3' nuclease activity but lacks a 3'-5' proofreading endonuclease activity. Thus, TaqMan® PCR typically utilizes the 5'-nuclease activity of Taq or Tth polymerase to hydrolyze a hybridization probe bound to its target amplicon, but any enzyme with equivalent 5' nuclease activity can be used. Two oligonucleotide primers are used to generate an amplicon typical of a PCR reaction. A third oligonucleotide, or probe, is designed to detect nucleotide sequence located between the two PCR primers. The probe is non-extendible by Taq DNA polymerase enzyme, and is labeled with a reporter fluorescent dye and a quencher fluorescent dye. Any laser-induced emission from the reporter dye is quenched by the quenching dye when the two dyes are located close together as they are on the probe. During the amplification reaction, the Taq DNA polymerase enzyme cleaves the probe in a template-dependent manner. The resultant probe fragments disassociate in solution, and signal from the released reporter dye is free from the quenching effect of the second fluorophore. One molecule of reporter dye is liberated for

each new molecule synthesized, and detection of the unquenched reporter dye provides the basis for quantitative interpretation of the data.

TaqMan® RT-PCR can be performed using commercially available equipment, such as, for example, ABI PRISM 7700TM Sequence Detection SystemTM (Perkin-Elmer-Applied Biosystems, Foster City, CA, USA), or Lightcycler (Roche Molecular Biochemicals, Mannheim, Germany). In a preferred embodiment, the 5' nuclease procedure is run on a real-time quantitative PCR device such as the ABI PRISM 7700TM Sequence Detection SystemTM. The system consists of a thermocycler, laser, charge-coupled device (CCD), camera and computer. The system amplifies samples in a 96-well format on a thermocycler. During amplification, laser-induced fluorescent signal is collected in real-time through fiber optics cables for all 96 wells, and detected at the CCD. The system includes software for running the instrument and for analyzing the data.

5'-Nuclease assay data are initially expressed as Ct, or the threshold cycle. As discussed above, fluorescence values are recorded during every cycle and represent the amount of product amplified to that point in the amplification reaction. The point when the fluorescent signal is first recorded as statistically significant is the threshold cycle (Ct).

To minimize errors and the effect of sample-to-sample variation, RT-PCR is usually performed using an internal standard. The ideal internal standard is expressed at a constant level among different tissues, and is unaffected by the experimental treatment. RNAs most frequently used to normalize patterns of gene expression are mRNAs for the housekeeping genes glyceraldehyde-3-phosphate-dehydrogenase (GAPDH) and β-actin.

A more recent variation of the RT-PCR technique is the real time quantitative PCR, which measures PCR product accumulation through a dual-labeled fluorigenic probe (i.e., TaqMan® probe). Real time PCR is compatible both with quantitative competitive PCR, where internal competitor for each target sequence is used for normalization, and with quantitative comparative PCR using a normalization gene contained within the sample, or a housekeeping gene for RT-PCR. For further details see, e.g. Held et al., Genome Research 6:986-994 (1996).

According to one aspect of the present invention, PCR primers and probes are designed based upon intron sequences present in the gene to be amplified. In this embodiment, the first step in the primer/probe design is the delineation of intron sequences within the genes. This can be done by publicly available software, such as the DNA BLAT software developed by Kent, W.J., Genome Res. 12(4):656-64 (2002), or by the BLAST software including its variations. Subsequent steps follow well established methods of PCR primer and probe design.

In order to avoid non-specific signals, it is important to mask repetitive sequences within the introns when designing the primers and probes. This can be easily accomplished by using the Repeat Masker program available on-line through the Baylor College of Medicine, which screens DNA sequences against a library of repetitive elements and returns a query sequence in which the repetitive elements are masked. The masked intron sequences can then be used to design primer and probe sequences using any commercially or otherwise publicly available primer/probe design packages, such as Primer Express (Applied Biosystems); MGB assay-by–design (Applied Biosystems); Primer3 (Steve Rozen and Helen J. Skaletsky (2000) Primer3 on the WWW for general users and for biologist programmers. In: Krawetz S, Misener S (eds) Bioinformatics Methods and Protocols: Methods in Molecular Biology. Humana Press, Totowa, NJ, pp 365-386).

The most important factors considered in PCR primer design include primer length, melting temperature (Tm), and G/C content, specificity, complementary primer sequences, and 3'-end sequence. In general, optimal PCR primers are generally 17-30 bases in length, and contain about 20-80%, such as, for example, about 50-60% G+C bases. Tm's between 50 and 80 °C, e.g. about 50 to 70 °C are typically preferred.

For further guidelines for PCR primer and probe design see, e.g. Dieffenbach, C.W. et al., "General Concepts for PCR Primer Design" in: PCR Primer, A Laboratory Manual, Cold Spring Harbor Laboratory Press, New York, 1995, pp. 133-155; Innis and Gelfand, "Optimization of PCRs" in: PCR Protocols, A Guide to Methods and Applications, CRC Press, London, 1994, pp. 5-11; and Plasterer, T.N. Primerselect: Primer and probe design. Methods Mol. Biol. 70:520-527 (1997), the entire disclosures of which are hereby expressly incorporated by reference.

Further PCR-based techniques include, for example, differential display (Liang and Pardee, Science 257:967-971 (1992)); amplified fragment length polymorphism (iAFLP) (Kawamoto et al., Genome Res. 12:1305-1312 (1999)); BeadArray™ technology (Illumina, San Diego, CA; Oliphant et al., Discovery of Markers for Disease (Supplement to Biotechniques), June 2002; Ferguson et al., Analytical Chemistry 72:5618 (2000)); BeadsArray for Detection of Gene Expression (BADGE), using the commercially available Luminex100 LabMAP system and multiple color-coded microspheres (Luminex Corp., Austin, TX) in a rapid assay for gene expression (Yang et al., Genome Res. 11:1888-1898 (2001)); and high coverage expression profiling (HiCEP) analysis (Fukumura et al., Nucl. Acids. Res. 31(16) e94 (2003)).

b. *Microarrays*

Differential gene expression can also be identified, or confirmed using the microarray technique. Thus, the expression profile of IBD-associated genes can be measured in either fresh or paraffin-

embedded tissue, using microarray technology. In this method, polynucleotide sequences of interest (including cDNAs and oligonucleotides) are plated, or arrayed, on a microchip substrate. The arrayed sequences are then hybridized with specific DNA probes from cells or tissues of interest. Just as in the RT-PCR method, the source of mRNA typically is total RNA isolated from biopsy tissue or cell lines derived from cells obtained from a subject having an IBD, and corresponding normal tissues or cell lines. Thus RNA can be isolated from a variety of colonic tissues or colonic tissue-based cell lines.

In a specific embodiment of the microarray technique, PCR amplified inserts of cDNA clones are applied to a substrate in a dense array. Preferably at least 10,000 nucleotide sequences are applied to the substrate. The microarrayed genes, immobilized on the microchip at 10,000 elements each, are suitable for hybridization under stringent conditions. Fluorescently labeled cDNA probes may be generated through incorporation of fluorescent nucleotides by reverse transcription of RNA extracted from tissues of interest. Labeled cDNA probes applied to the chip hybridize with specificity to each spot of DNA on the array. After stringent washing to remove non-specifically bound probes, the chip is scanned by confocal laser microscopy or by another detection method, such as a CCD camera. Quantitation of hybridization of each arrayed element allows for assessment of corresponding mRNA abundance. With dual color fluorescence, separately labeled cDNA probes generated from two sources of RNA are hybridized pairwise to the array. The relative abundance of the transcripts from the two sources corresponding to each specified gene is thus determined simultaneously. The miniaturized scale of the hybridization affords a convenient and rapid evaluation of the expression pattern for large numbers of genes. Such methods have been shown to have the sensitivity required to detect rare transcripts, which are expressed at a few copies per cell, and to reproducibly detect at least approximately two-fold differences in the expression levels (Schena et al., Proc. Natl. Acad. Sci. USA 93(2):106-149 (1996)). Microarray analysis can be performed by commercially available equipment, following manufacturer's protocols, such as by using the Affymetrix GenChip technology, or Incyte's microarray technology, or Agilent's Whole Human Genome microarray technology.

c. *Serial Analysis of Gene Expression (SAGE)*

Serial analysis of gene expression (SAGE) is a method that allows the simultaneous and quantitative analysis of a large number of gene transcripts, without the need of providing an individual hybridization probe for each transcript. First, a short sequence tag (about 10-14 bp) is generated that contains sufficient information to uniquely identify a transcript, provided that the tag is obtained from a unique position within each transcript. Then, many transcripts are linked together to form long serial molecules, that can be sequenced, revealing the identity of the multiple tags simultaneously. The expression pattern of any population of transcripts can be quantitatively evaluated by

determining the abundance of individual tags, and identifying the gene corresponding to each tag. For more details see, e.g. Velculescu *et al., Science* 270:484-487 (1995); and Velculescu *et al., Cell* 88:243-51 (1997).

d. *MassARRAY Technology*

In the MassARRAY-based gene expression profiling method, developed by Sequenom, Inc. (San Diego, CA) following the isolation of RNA and reverse transcription, the obtained cDNA is spiked with a synthetic DNA molecule (competitor), which matches the targeted cDNA region in all positions, except a single base, and serves as an internal standard. The cDNA/competitor mixture is PCR amplified and is subjected to a post-PCR shrimp alkaline phosphatase (SAP) enzyme treatment, which results in the dephosphorylation of the remaining nucleotides. After inactivation of the alkaline phosphatase, the PCR products from the competitor and cDNA are subjected to primer extension, which generates distinct mass signals for the competitor- and cDNA-derives PCR products. After purification, these products are dispensed on a chip array, which is pre-loaded with components needed for analysis with matrix-assisted laser desorption ionization time-of-flight mass spectrometry (MALDI-TOF MS) analysis. The cDNA present in the reaction is then quantified by analyzing the ratios of the peak areas in the mass spectrum generated. For further details see, e.g. Ding and Cantor, Proc. Natl. Acad. Sci. USA 100:3059-3064 (2003).

e. *Gene Expression Analysis by Massively Parallel Signature Sequencing (MPSS)*

This method, described by Brenner *et al., Nature Biotechnology* 18:630-634 (2000), is a sequencing approach that combines non-gel-based signature sequencing with *in vitro* cloning of millions of templates on separate 5 μm diameter microbeads. First, a microbead library of DNA templates is constructed by *in vitro* cloning. This is followed by the assembly of a planar array of the template-containing microbeads in a flow cell at a high density (typically greater than 3 x 10^6 microbeads/cm^2). The free ends of the cloned templates on each microbead are analyzed simultaneously, using a fluorescence-based signature sequencing method that does not require DNA fragment separation. This method has been shown to simultaneously and accurately provide, in a single operation, hundreds of thousands of gene signature sequences from a yeast cDNA library.

The steps of a representative protocol for profiling gene expression using fixed, paraffin-embedded tissues as the RNA source, including mRNA isolation, purification, primer extension and amplification are given in various published journal articles (for example: Godfrey *et al. J. Molec. Diagnostics* 2: 84-91 (2000); Specht *et al., Am. J. Pathol.* 158: 419-29 (2001)). Briefly, a representative process starts with cutting about 10 microgram thick sections of paraffin-embedded tissue samples. The mRNA is then extracted, and protein and DNA are removed. General methods

for mRNA extraction are well known in the art and are disclosed in standard textbooks of molecular biology, including Ausubel *et al.*, Current Protocols of Molecular Biology, John Wiley and Sons (1997). Methods for RNA extraction from paraffin embedded tissues are disclosed, for example, in Rupp and Locker, *Lab Invest.* 56:A67 (1987), and De Andrés *et al., BioTechniques* 18:42044 (1995). In particular, RNA isolation can be performed using purification kit, buffer set and protease from commercial manufacturers, such as Qiagen, according to the manufacturer's instructions. For example, total RNA from cells in culture can be isolated using Qiagen RNeasy mini-columns. Other commercially available RNA isolation kits include MasterPure™ Complete DNA and RNA Purification Kit (EPICENTRE®, Madison, WI), and Paraffin Block RNA Isolation Kit (Ambion, Inc.). Total RNA from tissue samples can be isolated using RNA Stat-60 (Tel-Test). RNA prepared from tissues can be isolated, for example, by cesium chloride density gradient centrifugation. After analysis of the RNA concentration, RNA repair and/or amplification steps may be included, if necessary, and RNA is reverse transcribed using gene specific promoters followed by PCR. Peferably, real time PCR is used, which is compatible both with quantitative competitive PCR, where internal competitor for each target sequence is used for normalization, and with quantitative comparative PCR using a normalization gene contained within the sample, or a housekeeping gene for RT-PCR. For further details see, e.g. "PCR: The Polymerase Chain Reaction", Mullis et al., eds., 1994; and Held *et al., Genome Research* 6:986-994 (1996). Finally, the data are analyzed to identify the best treatment option(s) available to the patient on the basis of the characteristic gene expression pattern identified in the sample examined.

f. *Immunohistochemistry*

Immunohistochemistry methods are also suitable for detecting the expression levels of the IBD markers of the present invention. Thus, antibodies or antisera, preferably polyclonal antisera, and most preferably monoclonal antibodies specific for each marker are used to detect expression. The antibodies can be detected by direct labeling of the antibodies themselves, for example, with radioactive labels, fluorescent labels, hapten labels such as, biotin, or an enzyme such as horse radish peroxidase or alkaline phosphatase. Alternatively, unlabeled primary antibody is used in conjunction with a labeled secondary antibody, comprising antisera, polyclonal antisera or a monoclonal antibody specific for the primary antibody. Immunohistochemistry protocols and kits are well known in the art and are commercially available.

Expression levels can also be determined at the protein level, for example, using various types of immunoassays or proteomics techniques.

In immunoassays, the target diagnostic protein marker is detected by using an antibody specifically binding to the markes. The antibody typically will be labeled with a detectable moiety. Numerous labels are available which can be generally grouped into the following categories:

Radioisotopes, such as 35S, 14C, 125I, 3H, and 131I. The antibody can be labeled with the radioisotope using the techniques described in Current Protocols in Immunology, Volumes 1 and 2, Coligen et al. (1991) Ed. Wiley-Interscience, New York, New York, Pubs. for example and radioactivity can be measured using scintillation counting.

Fluorescent labels such as rare earth chelates (europium chelates) or fluorescein and its derivatives, rhodamine and its derivatives, dansyl, Lissamine, phycoerythrin and Texas Red are available. The fluorescent labels can be conjugated to the antibody using the techniques disclosed in Current Protocols in Immunology, supra, for example. Fluorescence can be quantified using a fluorimeter.

Various enzyme-substrate labels are available and U.S. Patent No. 4,275,149 provides a review of some of these. The enzyme generally catalyzes a chemical alteration of the chromogenic substrate which can be measured using various techniques. For example, the enzyme may catalyze a color change in a substrate, which can be measured spectrophotometrically. Alternatively, the enzyme may alter the fluorescence or chemiluminescence of the substrate. Techniques for quantifying a change in fluorescence are described above. The chemiluminescent substrate becomes electronically excited by a chemical reaction and may then emit light which can be measured (using a chemiluminometer, for example) or donates energy to a fluorescent acceptor. Examples of enzymatic labels include luciferases (e.g., firefly luciferase and bacterial luciferase; U.S. Patent No. 4,737,456), luciferin, 2,3-dihydrophthalazinediones, malate dehydrogenase, urease, peroxidase such as horseradish peroxidase (HRPO), alkaline phosphatase, β-galactosidase, glucoamylase, lysozyme, saccharide oxidases (e.g., glucose oxidase, galactose oxidase, and glucose-6-phosphate dehydrogenase), heterocyclic oxidases (such as uricase and xanthine oxidase), lactoperoxidase, microperoxidase, and the like. Techniques for conjugating enzymes to antibodies are described in O'Sullivan et al. (1981) Methods for the Preparation of Enzyme-Antibody Conjugates for use in Enzyme Immunoassay, in Methods in Enzym. (ed J. Langone & H. Van Vunakis), Academic press, New York 73:147-166.

Examples of enzyme-substrate combinations include, for example: horseradish peroxidase (HRPO) with hydrogen peroxidase as a substrate, wherein the hydrogen peroxidase oxidizes a dye precursor (e.g.,orthophenylene diamine (OPD) or 3,3',5,5'-tetramethyl benzidine hydrochloride (TMB)); alkaline phosphatase (AP) with para-Nitrophenyl phosphate as chromogenic substrate; and β-D-galactosidase (β-D-Gal) with a chromogenic substrate (e.g., p-nitrophenyl-β-D-galactosidase) or fluorogenic substrate 4-methylumbelliferyl-β-D-galactosidase.

Numerous other enzyme-substrate combinations are available to those skilled in the art. For a general review of these, see U.S. Patent Nos. 4,275,149 and 4,318,980.

Sometimes, the label is indirectly conjugated with the antibody. The skilled artisan will be aware of various techniques for achieving this. For example, the antibody can be conjugated with biotin and any of the three broad categories of labels mentioned above can be conjugated with avidin, or vice versa. Biotin binds selectively to avidin and thus, the label can be conjugated with the antibody in this indirect manner. Alternatively, to achieve indirect conjugation of the label with the antibody, the antibody is conjugated with a small hapten (e.g., digoxin) and one of the different types of labels mentioned above is conjugated with an anti-hapten antibody (e.g., anti-digoxin antibody). Thus, indirect conjugation of the label with the antibody can be achieved.

In other versions of immunoassay techniques, the antibody need not be labeled, and the presence thereof can be detected using a labeled antibody which binds to the antibody.

Thus, the diagnostic immunoassays herein may be in any assay format, including, for example, competitive binding assays, direct and indirect sandwich assays, and immunoprecipitation assays. Zola, Monoclonal Antibodies: A Manual of Techniques, pp.147-158 (CRC Press, Inc. 1987).

Competitive binding assays rely on the ability of a labeled standard to compete with the test sample analyze for binding with a limited amount of antibody. The amount of antigen in the test sample is inversely proportional to the amount of standard that becomes bound to the antibodies. To facilitate determining the amount of standard that becomes bound, the antibodies generally are insolubilized before or after the competition, so that the standard and analyze that are bound to the antibodies may conveniently be separated from the standard and analyze which remain unbound.

Sandwich assays involve the use of two antibodies, each capable of binding to a different immunogenic portion, or epitope, of the protein to be detected. In a sandwich assay, the test sample analyze is bound by a first antibody which is immobilized on a solid support, and thereafter a second antibody binds to the analyze, thus forming an insoluble three-part complex. See, e.g.,U.S. Pat No. 4,376,110. The second antibody may itself be labeled with a detectable moiety (direct sandwich assays) or may be measured using an anti-immunoglobulin antibody that is labeled with a detectable moiety (indirect sandwich assay). For example, one type of sandwich assay is an ELISA assay, in which case the detectable moiety is an enzyme.

g. *Proteomics*

The term "proteome" is defined as the totality of the proteins present in a sample (e.g. tissue, organism, or cell culture) at a certain point of time. Proteomics includes, among other things, study

of the global changes of protein expression in a sample (also referred to as "expression proteomics"). Proteomics typically includes the following steps: (1) separation of individual proteins in a sample by 2-D gel electrophoresis (2-D PAGE); (2) identification of the individual proteins recovered from the gel, e.g. my mass spectrometry or N-terminal sequencing, and (3) analysis of the data using bioinformatics. Proteomics methods are valuable supplements to other methods of gene expression profiling, and can be used, alone or in combination with other methods, to detect the products of the markers of the present invention.

h. *5'-multiplexed Gene Specific Priming of Reverse Transcription*

RT-PCR requires reverse transcription of the test RNA population as a first step. The most commonly used primer for reverse transcription is oligo-dT, which works well when RNA is intact. However, this primer will not be effective when RNA is highly fragmented.

The present invention includes the use of gene specific primers, which are roughly 20 bases in length with a Tm optimum between about 58 °C and 60 °C. These primers will also serve as the reverse primers that drive PCR DNA amplification.

An alternative approach is based on the use of random hexamers as primers for cDNA synthesis. However, we have experimentally demonstrated that the method of using a multiplicity of gene-specific primers is superior over the known approach using random hexamers.

i. *Promoter Methylation Analysis*

A number of methods for quantization of RNA transcripts (gene expression analysis) or their protein translation products are discussed herein. The expression level of genes may also be inferred from information regarding chromatin structure, such as for example the methylation status of gene promoters and other regulatory elements and the acetylation status of histones.

In particular, the methylation status of a promoter influences the level of expression of the gene regulated by that promoter. Aberrant methylation of particular gene promoters has been implicated in expression regulation, such as for example silencing of tumor suppressor genes. Thus, examination of the methylation status of a gene's promoter can be utilized as a surrogate for direct quantization of RNA levels.

Several approaches for measuring the methylation status of particular DNA elements have been devised, including methylation-specific PCR (Herman J.G. et al. (1996) Methylation-specific PCR: a novel PCR assay for methylation status of CpG islands. Proc. Natl Acad. Sci. USA. **93**, 9821–9826.) and bisulfite DNA sequencing (Frommer M. et al. (1992) A genomic sequencing protocol that yields

a positive display of 5-methylcytosine residues in individual DNA strands. Proc. Natl Acad. Sci. USA. **89**, 1827–1831.). More recently, microarray-based technologies have been used to characterize promoter methylation status (Chen C.M. (2003) Methylation target array for rapid analysis of CpG island hypermethylation in multiple tissue genomes. Am. J. Pathol. 163, 37–45.).

j. *Coexpression of Genes*

A further aspect of the invention is the identification of gene expression clusters. Gene expression clusters can be identified by analysis of expression data using statistical analyses known in the art, including pairwise analysis of correlation based on Pearson correlation coefficients (Pearson K. and Lee A. (1902) Biometrika 2, 357).

In one embodiment, an expression cluster identified herein includes genes upregulated in the left colon (Fig. 1).

In another embodiment, an expression cluster identified herein includes genes upregulated in the right colon (Fig. 1).

In one other embodiment, an expression cluster identified herein includes genes upregulated in the terminal ileum (Fig. 1).

In other embodiments, the expression cluster identified herein includes genes in the IBD2 locus (Table 7); or in the IBD5 locus (Table 8).

In some embodiments, the expression cluster identified herein includes genes classified under an immune response.

In other embodiments, the expression cluster identified herein includes genes classified under a response to wounding.

k. *Design of Intron-Based PCR Primers and Probes*

According to one aspect of the present invention, PCR primers and probes are designed based upon intron sequences present in the gene to be amplified. Accordingly, the first step in the primer/probe design is the delineation of intron sequences within the genes. This can be done by publicly available software, such as the DNA BLAT software developed by Kent, W.J., Genome Res. 12(4):656-64 (2002), or by the BLAST software including its variations. Subsequent steps follow well established methods of PCR primer and probe design.

In order to avoid non-specific signals, it is important to mask repetitive sequences within the introns when designing the primers and probes. This can be easily accomplished by using the Repeat

Masker program available on-line through the Baylor College of Medicine, which screens DNA sequences against a library of repetitive elements and returns a query sequence in which the repetitive elements are masked. The masked intron sequences can then be used to design primer and probe sequences using any commercially or otherwise publicly available primer/probe design packages, such as Primer Express (Applied Biosystems); MGB assay-by–design (Applied Biosystems); Primer3 (Steve Rozen and Helen J. Skaletsky (2000) Primer3 on the WWW for general users and for biologist programmers. In: Krawetz S, Misener S (eds) Bioinformatics Methods and Protocols: Methods in Molecular Biology. Humana Press, Totowa, NJ, pp 365-386).

The most important factors considered in PCR primer design include primer length, melting temperature (Tm), and G/C content, specificity, complementary primer sequences, and 3'-end sequence. In general, optimal PCR primers are generally 17-30 bases in length, and contain about 20-80%, such as, for example, about 50-60% G+C bases. Tm's between 50 and 80 °C, e.g. about 50 to 70 °C are typically preferred.

For further guidelines for PCR primer and probe design see, e.g. Dieffenbach, C.W. et al., "General Concepts for PCR Primer Design" in: PCR Primer, A Laboratory Manual, Cold Spring Harbor Laboratory Press, New York, 1995, pp. 133-155; Innis and Gelfand, "Optimization of PCRs" in: PCR Protocols, A Guide to Methods and Applications, CRC Press, London, 1994, pp. 5-11; and Plasterer, T.N. Primerselect: Primer and probe design. Methods Mol. Biol. 70:520-527 (1997), the entire disclosures of which are hereby expressly incorporated by reference.

l. *IBD Gene Set, Assayed Gene Subsequences, and Clinical Application of Gene Expression Data*

An important aspect of the present invention is to use the measured expression of certain genes by colonic issue to provide diagnostic information. For this purpose it is necessary to correct for (normalize away) both differences in the amount of RNA assayed and variability in the quality of the RNA used. Therefore, the assay typically measures and incorporates the expression of certain normalizing genes, including well known housekeeping genes, such as GAPDH and Cyp1. Alternatively, normalization can be based on the mean or median signal (Ct) of all of the assayed genes or a large subset thereof (global normalization approach). On a gene-by-gene basis, measured normalized amount of a patient colonic tissue mRNA is compared to the amount found in an appropriate tissue reference set. The number (N) of tissues in this reference set should be sufficiently high to ensure that different reference sets (as a whole) behave essentially the same way. If this condition is met, the identity of the individual colonic tissues present in a particular set will have no significant impact on the relative amounts of the genes assayed. Usually, the tissue reference set consists of at least about 30, preferably at least about 40 different IBD tissue specimens. Unless noted otherwise, normalized expression levels for each mRNA/tested tissue/patient will be expressed

as a percentage of the expression level measured in the reference set. More specifically, the reference set of a sufficiently high number (e.g. 40) of IBD samples yields a distribution of normalized levels of each mRNA species. The level measured in a particular sample to be analyzed falls at some percentile within this range, which can be determined by methods well known in the art. Below, unless noted otherwise, reference to expression levels of a gene assume normalized expression relative to the reference set although this is not always explicitly stated.

m. *Production of antibodies*

The present invention further provides anti-IBD marker antibodies. Exemplary antibodies include polyclonal, monoclonal, humanized, bispecific, and heteroconjugate antibodies. As discussed herein, the antibodies may be used in the diagnostic methods for IBD, and in some cases in methods of treatment of IBD.

(1) Polyclonal antibodies

Polyclonal antibodies are preferably raised in animals by multiple subcutaneous (sc) or intraperitoneal (ip) injections of the relevant antigen and an adjuvant. It may be useful to conjugate the relevant antigen to a protein that is immunogenic in the species to be immunized, e.g., keyhole limpet hemocyanin, serum albumin, bovine thyroglobulin, or soybean trypsin inhibitor using a bifunctional or derivatizing agent, for example, maleimidobenzoyl sulfosuccinimide ester (conjugation through cysteine residues), N-hydroxysuccinimide (through lysine residues), glutaraldehyde, succinic anhydride, SOCl2, or R1N=C=NR, where R and R1 are different alkyl groups.

Animals are immunized against the antigen, immunogenic conjugates, or derivatives by combining, e.g., 100 μg or 5 μg of the protein or conjugate (for rabbits or mice, respectively) with 3 volumes of Freund's complete adjuvant and injecting the solution intradermally at multiple sites. One month later the animals are boosted with 1/5 to 1/10 the original amount of peptide or conjugate in Freund's complete adjuvant by subcutaneous injection at multiple sites. Seven to 14 days later the animals are bled and the serum is assayed for antibody titer. Animals are boosted until the titer plateaus. Preferably, the animal is boosted with the conjugate of the same antigen, but conjugated to a different protein and/or through a different cross-linking reagent. Conjugates also can be made in recombinant cell culture as protein fusions. Also, aggregating agents such as alum are suitably used to enhance the immune response.

(2) Monoclonal antibodies

Various methods for making monoclonal antibodies herein are available in the art. For example, the monoclonal antibodies may be made using the hybridoma method first described by Kohler et al., Nature, 256:495 (1975), by recombinant DNA methods (U.S. Patent No. 4,816,567).

In the hybridoma method, a mouse or other appropriate host animal, such as a hamster, is immunized as hereinabove described to elicit lymphocytes that produce or are capable of producing antibodies that will specifically bind to the protein used for immunization. Alternatively, lymphocytes may be immunized *in vitro*. Lymphocytes then are fused with myeloma cells using a suitable fusing agent, such as polyethylene glycol, to form a hybridoma cell (Goding, *Monoclonal Antibodies: Principles and Practice*, pp.59-103 (Academic Press, 1986)).

The hybridoma cells thus prepared are seeded and grown in a suitable culture medium that preferably contains one or more substances that inhibit the growth or survival of the unfused, parental myeloma cells. For example, if the parental myeloma cells lack the enzyme hypoxanthine guanine phosphoribosyl transferase (HGPRT or HPRT), the culture medium for the hybridomas typically will include hypoxanthine, aminopterin, and thymidine (HAT medium), which substances prevent the growth of HGPRT-deficient cells.

Preferred myeloma cells are those that fuse efficiently, support stable high-level production of antibody by the selected antibody-producing cells, and are sensitive to a medium such as HAT medium. Among these, preferred myeloma cell lines are murine myeloma lines, such as those derived from MOPC-21 and MPC-11 mouse tumors available from the Salk Institute Cell Distribution Center, San Diego, California USA, and SP-2 or X63-Ag8-653 cells available from the American Type Culture Collection, Rockville, Maryland USA. Human myeloma and mouse-human heteromyeloma cell lines also have been described for the production of human monoclonal antibodies (Kozbor, J. Immunol., 133:3001 (1984); and Brodeur et al., Monoclonal Antibody Production Techniques and Applications, pp. 51-63 (Marcel Dekker, Inc., New York, 1987)).

Culture medium in which hybridoma cells are growing is assayed for production of monoclonal antibodies directed against the antigen. Preferably, the binding specificity of monoclonal antibodies produced by hybridoma cells is determined by immunoprecipitation or by an in vitro binding assay, such as radioimmunoassay (RIA) or enzyme-linked immunoabsorbent assay (ELISA).

The binding affinity of the monoclonal antibody can, for example, be determined by the Scatchard analysis of Munson et al., Anal. Biochem., 107:220 (1980).

After hybridoma cells are identified that produce antibodies of the desired specificity, affinity, and/or activity, the clones may be subcloned by limiting dilution procedures and grown by standard methods (Goding, Monoclonal Antibodies: Principles and Practice, pp.59-103 (Academic Press, 1986)). Suitable culture media for this purpose include, for example, D-MEM or RPMI-1640 medium. In addition, the hybridoma cells may be grown in vivo as ascites tumors in an animal.

The monoclonal antibodies secreted by the subclones are suitably separated from the culture medium, ascites fluid, or serum by conventional antibody purification procedures such as, for example, protein A-Sepharose, hydroxylapatite chromatography, gel electrophoresis, dialysis, or affinity chromatography.

DNA encoding the monoclonal antibodies is readily isolated and sequenced using conventional procedures (e.g., by using oligonucleotide probes that are capable of binding specifically to genes encoding the heavy and light chains of murine antibodies). The hybridoma cells serve as a preferred source of such DNA. Once isolated, the DNA may be placed into expression vectors, which are then transfected into host cells such as E. coli cells, simian COS cells, Chinese Hamster Ovary (CHO) cells, or myeloma cells that do not otherwise produce antibody protein, to obtain the synthesis of monoclonal antibodies in the recombinant host cells. Review articles on recombinant expression in bacteria of DNA encoding the antibody include Skerra et al., Curr. Opinion in Immunol., 5:256-262 (1993) and Plückthun, Immunol. Revs., 130:151-188 (1992).

In a further embodiment, monoclonal antibodies or antibody fragments can be isolated from antibody phage libraries generated using the techniques described in McCafferty et al., Nature, 348:552-554 (1990). Clackson et al., Nature, 352:624-628 (1991) and Marks et al., J. Mol. Biol., 222:581-597 (1991) describe the isolation of murine and human antibodies, respectively, using phage libraries. Subsequent publications describe the production of high affinity (nM range) human antibodies by chain shuffling (Marks et al., Bio/Technology, 10:779-783 (1992)), as well as combinatorial infection and in vivo recombination as a strategy for constructing very large phage libraries (Waterhouse et al., Nuc. Acids. Res., 21:2265-2266 (1993)). Thus, these techniques are viable alternatives to traditional monoclonal antibody hybridoma techniques for isolation of monoclonal antibodies.

The DNA also may be modified, for example, by substituting the coding sequence for human heavy chain and light chain constant domains in place of the homologous murine sequences (U.S. Patent No. 4,816,567; and Morrison, et al., Proc. Natl Acad. Sci. USA, 81:6851 (1984)), or by covalently joining to the immunoglobulin coding sequence all or part of the coding sequence for a non-immunoglobulin polypeptide.

Typically such non-immunoglobulin polypeptides are substituted for the constant domains of an antibody, or they are substituted for the variable domains of one antigen-combining site of an antibody to create a chimeric bivalent antibody comprising one antigen-combining site having specificity for an antigen and another antigen-combining site having specificity for a different antigen.

(3) Humanized antibodies

Methods for humanizing non-human antibodies have been described in the art. Preferably, a humanized antibody has one or more amino acid residues introduced into it from a source which is non-human. These non-human amino acid residues are often referred to as "import" residues, which are typically taken from an "import" variable domain. Humanization can be essentially performed following the method of Winter and co-workers (Jones et al., Nature, 321:522-525 (1986); Riechmann et al., Nature, 332:323-327 (1988); Verhoeyen et al., Science, 239:1534-1536 (1988)), by substituting hypervariable region sequences for the corresponding sequences of a human antibody. Accordingly, such "humanized" antibodies are chimeric antibodies (U.S. Patent No. 4,816,567) wherein substantially less than an intact human variable domain has been substituted by the corresponding sequence from a non-human species. In practice, humanized antibodies are typically human antibodies in which some hypervariable region residues and possibly some FR residues are substituted by residues from analogous sites in rodent antibodies. An example of a humanized antibody used to treat IBD is infliximab (Remicade®), an engineered murine-human chimeric monoclonal antibody. The antibody binds the cytokine TNF-alpha and prevents it from binding its receptors to trigger and sustain an inflammatory response. Infliximab is used to treat both CD and UC.

The choice of human variable domains, both light and heavy, to be used in making the humanized antibodies is very important to reduce antigenicity. According to the so-called "best-fit" method, the sequence of the variable domain of a rodent antibody is screened against the entire library of known human variable-domain sequences. The human sequence which is closest to that of the rodent is then accepted as the human framework region (FR) for the humanized antibody (Sims et al., J. Immunol., 151:2296 (1993); Chothia et al., J. Mol. Biol., 196:901 (1987)). Another method uses a particular framework region derived from the consensus sequence of all human antibodies of a particular subgroup of light or heavy chains. The same framework may be used for several different humanized antibodies (Carter et al., Proc. Natl. Acad. Sci. USA, 89:4285 (1992); Presta et al., J. Immunol., 151:2623 (1993)).

It is further important that antibodies be humanized with retention of high affinity for the antigen and other favorable biological properties. To achieve this goal, according to a preferred method,

humanized antibodies are prepared by a process of analysis of the parental sequences and various conceptual humanized products using three-dimensional models of the parental and humanized sequences. Three-dimensional immunoglobulin models are commonly available and are familiar to those skilled in the art. Computer programs are available which illustrate and display probable three-dimensional conformational structures of selected candidate immunoglobulin sequences. Inspection of these displays permits analysis of the likely role of the residues in the functioning of the candidate immunoglobulin sequence, i.e., the analysis of residues that influence the ability of the candidate immunoglobulin to bind its antigen. In this way, FR residues can be selected and combined from the recipient and import sequences so that the desired antibody characteristic, such as increased affinity for the target antigen(s), is achieved. In general, the hypervariable region residues are directly and most substantially involved in influencing antigen binding.

Various forms of the humanized antibody are contemplated. For example, the humanized antibody may be an antibody fragment, such as a Fab, which is optionally conjugated with one or more cytotoxic agent(s) in order to generate an immunoconjugate. Alternatively, the humanized antibody may be an intact antibody, such as an intact IgG1 antibody.

(4) Human antibodies

As an alternative to humanization, human antibodies can be generated. For example, it is now possible to produce transgenic animals (e.g., mice) that are capable, upon immunization, of producing a full repertoire of human antibodies in the absence of endogenous immunoglobulin production. For example, it has been described that the homozygous deletion of the antibody heavy-chain joining region (JH) gene in chimeric and germ-line mutant mice results in complete inhibition of endogenous antibody production. Transfer of the human germ-line immunoglobulin gene array in such germ-line mutant mice will result in the production of human antibodies upon antigen challenge. See, e.g., Jakobovits et al., Proc. Natl. Acad. Sci. USA, 90:2551 (1993); Jakobovits et al., Nature, 362:255-258 (1993); Bruggermann et al., Year in Immuno., 7:33 (1993); and U.S. Patent Nos. 5,591,669, 5,589,369 and 5,545,807. Alternatively, phage display technology (McCafferty et al., Nature 348:552-553 (1990)) can be used to produce human antibodies and antibody fragments in vitro, from immunoglobulin variable (V) domain gene repertoires from unimmunized donors. According to this technique, antibody V domain genes are cloned in-frame into either a major or minor coat protein gene of a filamentous bacteriophage, such as M13 or fd, and displayed as functional antibody fragments on the surface of the phage particle. Because the filamentous particle contains a single-stranded DNA copy of the phage genome, selections based on the functional properties of the antibody also result in selection of the gene encoding the antibody exhibiting those properties. Thus, the phage mimics some of the properties of the B-cell. Phage display can be performed in a variety of formats; for their review see, e.g., Johnson, Kevin S. and Chiswell, David J., Current Opinion in

Structural Biology 3:564-571 (1993). Several sources of V-gene segments can be used fc display. Clackson et al., Nature, 352:624-628 (1991) isolated a diverse array of anti-ox antibodies from a small random combinatorial library of V genes derived from the sp immunized mice. A repertoire of V genes from unimmunized human donors can be constru antibodies to a diverse array of antigens (including self-antigens) can be isolated es following the techniques described by Marks et al., J. Mol. Biol. 222:581-597 (1991), or G al., EMBO J. 12:725-734 (1993). See, also, U.S. Patent Nos. 5,565,332 and 5,573,905.

As discussed above, human antibodies may also be generated by *in vitro* activated B cells (Patents 5,567,610 and 5,229,275).

(5) Antibody fragments

Various techniques have been developed for the production of antibody fragments comprisin more antigen binding regions. Traditionally, these fragments were derived via proteolytic d of intact antibodies (see, e.g., Morimoto et al., Journal of Biochemical and Biophysical I 24:107-117 (1992); and Brennan et al., Science, 229:81 (1985)). However, these fragments be produced directly by recombinant host cells. For example, the antibody fragments can be from the antibody phage libraries discussed above. Alternatively, Fab'-SH fragments can be recovered from E. coli and chemically coupled to form F(ab')2 fragments (Carter Bio/Technology 10:163-167 (1992)). According to another approach, F(ab')2 fragments isolated directly from recombinant host cell culture. Other techniques for the production of a fragments will be apparent to the skilled practitioner. In other embodiments, the antibody o is a single chain Fv fragment (scFv). See WO 93/16185; U.S. Patent No. 5,571,894; and U.S No. 5,587,458. The antibody fragment may also be a Alinear antibody@, *e.g.*, as described Patent 5,641,870 for example. Such linear antibody fragments may be monospecific or bispe

(6) Bispecific antibodies

Bispecific antibodies are antibodies that have binding specificities for at least two different e Exemplary bispecific antibodies may bind to two different epitopes of an IBD marker Bispecific antibodies may also be used to localize agents to cells which express an IBD protein.

These antibodies possess an IBD marker-binding arm and an arm which binds an agent aminosalicylate). Bispecific antibodies can be prepared as full length antibodies or a fragments (e.g. F(ab')2 bispecific antibodies).

Methods for making bispecific antibodies are known in the art. Traditional production of full length bispecific antibodies is based on the coexpression of two immunoglobulin heavy chain-light chain pairs, where the two chains have different specificities (Millstein *et al., Nature*, 305:537-539 (1983)). Because of the random assortment of immunoglobulin heavy and light chains, these hybridomas (quadromas) produce a potential mixture of 10 different antibody molecules, of which only one has the correct bispecific structure. Purification of the correct molecule, which is usually done by affinity chromatography steps, is rather cumbersome, and the product yields are low. Similar procedures are disclosed in WO 93/08829, and in Traunecker *et al., EMBO J.*, 10:3655-3659 (1991).

According to a different approach, antibody variable domains with the desired binding specificities (antibody-antigen combining sites) are fused to immunoglobulin constant domain sequences. The fusion preferably is with an immunoglobulin heavy chain constant domain, comprising at least part of the hinge, CH2, and CH3 regions. It is preferred to have the first heavy-chain constant region (CH1) containing the site necessary for light chain binding, present in at least one of the fusions. DNAs encoding the immunoglobulin heavy chain fusions and, if desired, the immunoglobulin light chain, are inserted into separate expression vectors, and are co-transfected into a suitable host organism. This provides for great flexibility in adjusting the mutual proportions of the three polypeptide fragments in embodiments when unequal ratios of the three polypeptide chains used in the construction provide the optimum yields. It is, however, possible to insert the coding sequences for two or all three polypeptide chains in one expression vector when the expression of at least two polypeptide chains in equal ratios results in high yields or when the ratios are of no particular significance.

In a preferred embodiment of this approach, the bispecific antibodies are composed of a hybrid immunoglobulin heavy chain with a first binding specificity in one arm, and a hybrid immunoglobulin heavy chain-light chain pair (providing a second binding specificity) in the other arm. It was found that this asymmetric structure facilitates the separation of the desired bispecific compound from unwanted immunoglobulin chain combinations, as the presence of an immunoglobulin light chain in only one half of the bispecific molecule provides for a facile way of separation. This approach is disclosed in WO 94/04690. For further details of generating bispecific antibodies see, for example, Suresh *et al., Methods in Enzymology*, 121:210 (1986).

According to another approach described in U.S. Patent No. 5,731,168, the interface between a pair of antibody molecules can be engineered to maximize the percentage of heterodimers which are recovered from recombinant cell culture. The preferred interface comprises at least a part of the C_H3 domain of an antibody constant domain. In this method, one or more small amino acid side chains from the interface of the first antibody molecule are replaced with larger side chains (*e.g.* tyrosine or tryptophan). Compensatory "cavities" of identical or similar size to the large side chain(s) are

created on the interface of the second antibody molecule by replacing large amino acid side chains with smaller ones (*e.g.* alanine or threonine). This provides a mechanism for increasing the yield of the heterodimer over other unwanted end-products such as homodimers.

Bispecific antibodies include cross-linked or "heteroconjugate" antibodies. For example, one of the antibodies in the heteroconjugate can be coupled to avidin, the other to biotin. Such antibodies have, for example, been proposed to target immune system cells to unwanted cells (U.S. Patent No. 4,676,980), and for treatment of HIV infection (WO 91/00360, WO 92/200373, and EP 03089). Heteroconjugate antibodies may be made using any convenient cross-linking methods. Suitable cross-linking agents are well known in the art, and are disclosed in U.S. Patent No. 4,676,980, along with a number of cross-linking techniques.

Techniques for generating bispecific antibodies from antibody fragments have also been described in the literature. For example, bispecific antibodies can be prepared using chemical linkage. Brennan *et al., Science*, 229: 81 (1985) describe a procedure wherein intact antibodies are proteolytically cleaved to generate $F(ab')_2$ fragments. These fragments are reduced in the presence of the dithiol complexing agent sodium arsenite to stabilize vicinal dithiols and prevent intermolecular disulfide formation. The Fab' fragments generated are then converted to thionitrobenzoate (TNB) derivatives. One of the Fab'-TNB derivatives is then reconverted to the Fab'-thiol by reduction with mercaptoethylamine and is mixed with an equimolar amount of the other Fab'-TNB derivative to form the bispecific antibody. The bispecific antibodies produced can be used as agents for the selective immobilization of enzymes.

Various techniques for making and isolating bispecific antibody fragments directly from recombinant cell culture have also been described. For example, bispecific antibodies have been produced using leucine zippers. Kostelny *et al., J. Immunol.*, 148(5):1547-1553 (1992). The leucine zipper peptides from the Fos and Jun proteins were linked to the Fab' portions of two different antibodies by gene fusion. The antibody homodimers were reduced at the hinge region to form monomers and then re-oxidized to form the antibody heterodimers. This method can also be utilized for the production of antibody homodimers. The "diabody" technology described by Hollinger *et al., Proc. Natl. Acad. Sci. USA*, 90:6444-6448 (1993) has provided an alternative mechanism for making bispecific antibody fragments. The fragments comprise a heavy-chain variable domain (V_H) connected to a light-chain variable domain (V_L) by a linker which is too short to allow pairing between the two domains on the same chain. Accordingly, the V_H and V_L domains of one fragment are forced to pair with the complementary V_L and V_H domains of another fragment, thereby forming two antigen-binding sites. Another strategy for making bispecific antibody fragments by the use of single-chain Fv (sFv) dimers has also been reported. See Gruber *et al., J. Immunol.*, 152:5368 (1994).

Antibodies with more than two valencies are contemplated. For example, trispecific antibodies can be prepared. Tutt *et al. J. Immunol.* 147: 60 (1991).

(7) Other amino acid sequence modifications

Amino acid sequence modification(s) of the antibodies described herein are contemplated. For example, it may be desirable to improve the binding affinity and/or other biological properties of the antibody. Amino acid sequence variants of the antibody are prepared by introducing appropriate nucleotide changes into the antibody nucleic acid, or by peptide synthesis. Such modifications include, for example, deletions from, and/or insertions into and/or substitutions of, residues within the amino acid sequences of the antibody. Any combination of deletion, insertion, and substitution is made to arrive at the final construct, provided that the final construct possesses the desired characteristics. The amino acid changes also may alter post-translational processes of the antibody, such as changing the number or position of glycosylation sites.

A useful method for identification of certain residues or regions of the antibody that are preferred locations for mutagenesis is called "alanine scanning mutagenesis" as described by Cunningham and Wells *Science*, 244:1081-1085 (1989). Here, a residue or group of target residues are identified (*e.g.*, charged residues such as arg, asp, his, lys, and glu) and replaced by a neutral or negatively charged amino acid (most preferably alanine or polyalanine) to affect the interaction of the amino acids with antigen. Those amino acid locations demonstrating functional sensitivity to the substitutions then are refined by introducing further or other variants at, or for, the sites of substitution. Thus, while the site for introducing an amino acid sequence variation is predetermined, the nature of the mutation *per se* need not be predetermined. For example, to analyze the performance of a mutation at a given site, ala scanning or random mutagenesis is conducted at the target codon or region and the expressed antibody variants are screened for the desired activity.

Amino acid sequence insertions include amino- and/or carboxyl-terminal fusions ranging in length from one residue to polypeptides containing a hundred or more residues, as well as intrasequence insertions of single or multiple amino acid residues. Examples of terminal insertions include antibody with an N-terminal methionyl residue or the antibody fused to a cytotoxic polypeptide. Other insertional variants of the antibody molecule include the fusion to the N- or C-terminus of the antibody to an enzyme (*e.g.* for ADEPT) or a polypeptide which increases the serum half-life of the antibody.

Another type of variant is an amino acid substitution variant. These variants have at least one amino acid residue in the antibody molecule replaced by a different residue. The sites of greatest interest for substitutional mutagenesis include the hypervariable regions, but FR alterations are also

contemplated. Conservative substitutions are shown in Table 1 under the heading of "preferred substitutions". If such substitutions result in a change in biological activity, then more substantial changes, denominated "exemplary substitutions" in the following table, or as further described below in reference to amino acid classes, may be introduced and the products screened.

Original Residue	Exemplary Substitutions	Preferred Substitutions
Ala (A)	val; leu; ile	val
Arg (R)	lys; gln; asn	lys
Asn (N)	gln; his; lys; arg	gln
Asp (D)	glu	glu
Cys (C)	ser	ser
Gln (Q)	asn	asn
Glu (E)	asp	asp
Gly (G)	pro; ala	ala
His (H)	asn; gln; lys; arg	arg
Ile (I)	leu; val; met; ala; phe; norleucine	leu
Leu (L)	norleucine; ile; val; met; ala; phe	ile
Lys (K)	arg; gln; asn	arg
Met (M)	leu; phe; ile	leu
Phe (F)	leu; val; ile; ala; tyr	leu
Pro (P)	ala	ala
Ser (S)	thr	thr
Thr (T)	ser	ser
Trp (W)	tyr; phe	tyr
Tyr (Y)	trp; phe; thr; ser	phe
Val (V)	ile; leu; met; phe; ala; norleucine	leu

Substantial modifications in the biological properties of the antibody are accomplished by selecting substitutions that differ significantly in their effect on maintaining (a) the structure of the polypeptide backbone in the area of the substitution, for example, as a sheet or helical conformation, (b) the charge or hydrophobicity of the molecule at the target site, or (c) the bulk of the side chain. Amino acids may be grouped according to similarities in the properties of their side chains (in A. L. Lehninger, in *Biochemistry*, second ed., pp. 73-75, Worth Publishers, New York (1975)): non-polar: Ala (A), Val (V), Leu (L), Ile (I), Pro (P), Phe (F), Trp (W), Met (M); uncharged polar: Gly (G), Ser (S), Thr (T), Cys (C), Tyr (Y), Asn (N), Gln (Q); acidic: Asp (D), Glu (E); and basic: Lys (K), Arg (R), His(H).

Alternatively, naturally occurring residues may be divided into groups based on common side-chain properties: hydrophobic : Norleucine, Met, Ala, Val, Leu, Ile; neutral hydrophilic: Cys, Ser, Thr,

Asn, Gln; acidic: Asp, Glu; basic: His, Lys, Arg; residues that influence chain orientation: Gly, Pro; and aromatic: Trp, Tyr, Phe.

Non-conservative substitutions will entail exchanging a member of one of these classes for another class.

Any cysteine residue not involved in maintaining the proper conformation of the antibody also may be substituted, generally with serine, to improve the oxidative stability of the molecule and prevent aberrant crosslinking. Conversely, cysteine bond(s) may be added to the antibody to improve its stability (particularly where the antibody is an antibody fragment such as an Fv fragment).

A particularly preferred type of substitutional variant involves substituting one or more hypervariable region residues of a parent antibody (*e.g.* a humanized or human antibody). Generally, the resulting variant(s) selected for further development will have improved biological properties relative to the parent antibody from which they are generated. A convenient way for generating such substitutional variants involves affinity maturation using phage display. Briefly, several hypervariable region sites (*e.g.* 6-7 sites) are mutated to generate all possible amino substitutions at each site. The antibody variants thus generated are displayed in a monovalent fashion from filamentous phage particles as fusions to the gene III product of M13 packaged within each particle. The phage-displayed variants are then screened for their biological activity (*e.g.* binding affinity) as herein disclosed. In order to identify candidate hypervariable region sites for modification, alanine scanning mutagenesis can be performed to identify hypervariable region residues contributing significantly to antigen binding. Alternatively, or additionally, it may be beneficial to analyze a crystal structure of the antigen-antibody complex to identify contact points between the antibody and an IBD marker protein. Such contact residues and neighboring residues are candidates for substitution according to the techniques elaborated herein. Once such variants are generated, the panel of variants is subjected to screening as described herein and antibodies with superior properties in one or more relevant assays may be selected for further development.

Engineered antibodies with three or more (preferably four) functional antigen binding sites are also contemplated (U.S. Published Patent Application No. US2002/0004587 A1, Miller *et al.*).

Nucleic acid molecules encoding amino acid sequence variants of the antibody are prepared by a variety of methods known in the art. These methods include, but are not limited to, isolation from a natural source (in the case of naturally occurring amino acid sequence variants) or preparation by oligonucleotide-mediated (or site-directed) mutagenesis, PCR mutagenesis, and cassette mutagenesis of an earlier prepared variant or a non-variant version of the antibody.

B.3 Kits of the invention

The materials for use in the methods of the present invention are suited for preparation of kits produced in accordance with well known procedures. The invention thus provides kits comprising agents, which may include gene-specific or gene-selective probes and/or primers, for quantitating the expression of the disclosed genes for IBD. Such kits may optionally contain reagents for the extraction of RNA from samples, in particular fixed paraffin-embedded tissue samples and/or reagents for RNA amplification. In addition, the kits may optionally comprise the reagent(s) with an identifying description or label or instructions relating to their use in the methods of the present invention. The kits may comprise containers (including microtiter plates suitable for use in an automated implementation of the method), each with one or more of the various reagents (typically in concentrated form) utilized in the methods, including, for example, pre-fabricated microarrays, buffers, the appropriate nucleotide triphosphates (e.g., dATP, dCTP, dGTP and dTTP; or rATP, rCTP, rGTP and UTP), reverse transcriptase, DNA polymerase, RNA polymerase, and one or more probes and primers of the present invention (e.g., appropriate length poly(T) or random primers linked to a promoter reactive with the RNA polymerase).

B.4 Reports of the invention

The methods of this invention, when practiced for commercial diagnostic purposes generally produce a report or summary of the normalized expression levels of one or more of the selected genes. The methods of this invention will produce a report comprising a prediction of the clinical outcome of a subject diagnosed with an IBD before and after any surgical procedure to treat the IBD. The methods and reports of this invention can further include storing the report in a database. Alternatively, the method can further create a record in a database for the subject and populate the record with data. In one embodiment the report is a paper report, in another embodiment the report is an auditory report, in another embodiment the report is an electronic record. It is contemplated that the report is provided to a physician and/or the patient. The receiving of the report can further include establishing a network connection to a server computer that includes the data and report and requesting the data and report from the server computer.

The methods provided by the present invention may also be automated in whole or in part.

All aspects of the present invention may also be practiced such that a limited number of additional genes that are co-expressed with the disclosed genes, for example as evidenced by high Pearson correlation coefficients, are included in a prognostic or predictive test in addition to and/or in place of disclosed genes.

Having described the invention, the same will be more readily understood through reference to the following Examples, which is provided by way of illustration, and is not intended to limit the invention in any way.

Examples

Example 1 - Microarray analysis

Clinically, IBD is characterized by diverse manifestations often resulting in a chronic, unpredictable course. Bloody diarrhea and abdominal pain are often accompanied by fever and weight loss. Anemia is common, as is severe fatigue. Joint manifestations ranging from arthralgia to acute arthritis as well as abnormalities in liver function are commonly associated with IBD. Patients with IBD also have an increased risk of colon carcinomas compared to the general population. During acute "attacks" of IBD, work and other normal activity are usually impossible, and often a patient is hospitalized.

Although the cause of IBD remains unknown, several factors such as genetic, infectious and immunologic susceptibility have been implicated. IBD is much more common in Caucasians, especially those of Jewish descent. The chronic inflammatory nature of the condition has prompted an intense search for a possible infectious cause. Although agents have been found which stimulate acute inflammation, none has been found to cause the chronic inflammation associated with IBD. The hypothesis that IBD is an autoimmune disease is supported by the previously mentioned extraintestinal manifestation of IBD as joint arthritis, and the known positive response to IBD by treatment with therapeutic agents such as adrenal glucocorticoids, cyclosporine and azathioprine, which are known to suppress immune response. In addition, the GI tract, more than any other organ of the body, is continuously exposed to potential antigenic substances such as proteins from food, bacterial byproducts (LPS), etc. The subtypes of IBD are UC and CD.

CD differs from UC in that the inflammation extends through all layers of the intestinal wall and involves mesentery as well as lymph nodes. CD may affect any part of the alimentary canal from mouth to anus. The disease is often discontinuous, i.e., severely diseased segments of bowel are separated from apparently disease-free areas. In CD, the bowel wall also thickens which can lead to obstructions. In addition, fistulas and fissures are not uncommon.

Both UC and CD are typically diagnosed by endoscopy, which shows the afflicted areas. However, the use of microarray technology has shed light on the molecular pathology of UC. A study published in 2000 used microarray technology to analyze eight UC patients. (Dieckgraefe et al., Physiol. Genomics 2000; 4:1-11). 6500 genes were analyzed in this study and the results confirmed increased expression of genes previously implicated in UC pathogenesis, namely IL-1, IL-1RA and IL-8. Endoscopic diagnosis coupled with the ability to take pinch mucosal biopsies have allowed investigators to further diagnose UC using microarray analysis, and allowed investigators to analyze afflicted tissue against normal tissue and to analyze tissue from a larger range of patients with

varying degrees of severity. Biopsies of macroscopically unaffected areas of the colon and terminal ileum were microarrayed. (Langman et al., Gastroent. 2004; 127:26-40). Langman analyzed 22,283 genes and found that genes involved in cellular detoxification, such as pregnane X receptor and MDR1 were significantly downregulated in the colon of patients with UC, but there was no change in expression of these genes in CD patients.

Nucleic acid microarrays, often containing thousands of gene sequences, are useful for identifying differentially expressed genes in diseased tissues as compared to their normal counterparts. Using nucleic acid microarrays, test and control mRNA samples from test and control tissue samples are reverse transcribed and labeled to generate cDNA probes. The cDNA probes are then hybridized to an array of nucleic acids immobilized on a solid support. The array is configured such that the sequence and position of each member of the array is known. For example, a selection of genes known to be expressed in certain disease states may be arrayed on a solid support. Hybridization of a labeled probe with a particular array member indicates that the sample from which the probe was derived expresses that gene. If the hybridization signal of a probe from a test (for example, disease tissue) sample is greater than hybridization signal of a probe from a control, normal tissue sample, the gene or genes overexpressed in the disease tissue are identified. The implication of this result is that an overexpressed protein in a disease tissue is useful not only as a diagnostic marker for the presence of the disease condition, but also as a therapeutic target for treatment of the disease condition.

The methodology of hybridization of nucleic acids and microarray technology is well known in the art. In one example, the specific preparation of nucleic acids for hybridization and probes, slides, and hybridization conditions are all detailed in PCT Patent Application Serial No. PCT/US01/10482, filed on March 30, 2001 and which is herein incorporated by reference.

Microarray analysis was used to find genes that are overexpressed in CD as compared to normal bowel tissue. For this study, sixty seven patients with CD and thirty-one control patients undergoing colonoscopy were recruited. Patient symptoms were evaluated at the time of colonoscopy using the simple clinical colitis activity index (SCCAI). (Walmsley et al., Gut. 1998; 43:29-32). Quiescent disease showing no histological inflammation was defined as a SCCAI of 2 or less. Active disease with histologially acute or chronic inflammation was defined as a SCCAI of greater than 2. The severity of the CD itself was determined by the criteria of Leonard-Jones. (Lennard-Jones Scand. J. Gastroent. 1989; 170:2-6). The CD patients provided well phenotyped biopsies for analysis of inflammatory pathways of CD at the molecular level, thus identifying novel candidate genes and potential pathways for therapeutic intervention. Paired biopsies were taken from each anatomical location.

All biopsies were stored at -70°C until ready for RNA isolation. The biopsies were homogenized in 600µl of RLT buffer (+ BME) and RNA was isolated using Qiagen™ Rneasy Mini columns (Qiagen) with on-column DNase treatment following the manufacturer's guidelines. Following RNA isolation, RNA was quantitated using RiboGreen™ (Molecular Probes) following the manufacturer's guidelines and checked on agarose gels for integrity. Appropriate amounts of RNA were labeled for microarray analysis and samples were run on proprietary Genentech microarray and Affymetrics™ microarrays. Genes were compared whose expression was upregulated in UC tissue vs normal bowel, matching biopsies from normal bowel and CD tissue from the same patient. The results of this experiment showed that the nucleic acids as shown in Tables 1A, 1B, and 2A (provided above) are differentially expressed in CD and/or UC tissue in comparision to normal tissue.

The genes listed in Table 1A-1B demonstrated a minimum 1.5 fold difference in expression and also acceptable probe hybridization strength was observed. The genes listed in Table 2 were found to have a minimum within-group Pearson correlation of approximately 0.65 and a three-fold upregulation of gene expression was observed.

More specifically, the SEQ ID NOS listed in Tables 1A and 2 represent polynucleotides and their encoded polypeptide which are significantly up-regulated/overexpressed in CD and/or UC.

The SEQ ID NO listed in Table 1B represents a polynucleotide and its encoded polypeptide which is significantly down-regulated/under-expressed in CD and/or UC.

SEQ ID NOS: listed in Table 3A represent polynucleotides and their encoded polypeptide which are significantly up-regulated/overexpressed in UC.

SEQ ID NOS: listed in Table 3B represent polynucleotides and their encoded polypeptide which are significantly down-regulated/underexpressed in UC.

Example 2: Characterisation of Distinct Intestinal Gene Expression Profiles in Ulcerative Colitis by Microarray Analysis

Microarray analysis allows a comprehensive picture of gene expression at the cellular level. The aim of this study was to investigate differential intestinal gene expression in patients with ulcerative colitis (UC) and controls.

Methods: 67 UC and 31 control subjects- 23 normal and 8 inflamed non-inflammatory bowel disease patients were studied. Paired endoscopic biopsies were taken from 5 specific anatomical locations for RNA extraction and histology. 41058 expression sequence tags were analyzed in 215 biopsies using the Agilent platform. Confirmation of results was undertaken by real time PCR and immunohistochemistry. Results: In healthy control biopsies, cluster analysis showed differences in

gene expression between the right and left colon. (χ^2=25.1, p<0.0001). Developmental genes HOXA13, (p=2.3x10^{-16}), HOXB13 (p <1x10^{-45}), GLI1 (p=4.0x10^{-24}), and GLI3 (p=2.1x10^{-28}) primarily drove this separation. When all UC biopsies and control biopsies were compared, 143 sequences had a fold change of >1.5 in the UC biopsies (0.01>p>10^{-45}) and 54 sequences had a fold change of <-1.5 (0.01>p>10^{-20}). Differentially upregulated in UC genes included SAA1 (p<10^{-45}) the alpha defensins, DEFA5&6 (p=0.00003 and p=6.95x10^{-7} respectively), MMP3 (p=5.6x10^{-10}) and MMP7 (p=2.3x10^{-7}). Increased DEFA5&6 expression was further characterized to Paneth cell metaplasia by immunohistochemistry and *in-situ* hybridization. Sub-analysis of the IBD2 & IBD5 loci, and the ABC transporter genes revealed a number of differentially regulated genes in the UC biopsies. Conclusions: These data implicate a number of novel gene families, as well as established candidate genes in the pathogenesis of UC, and may allow characterisation of potential therapeutic targets.

The aim of the current study was to use microarray gene expression analysis to investigate genome wide expression in endoscopic mucosal biopsies of patients with UC and controls. In order to resolve previous inconsistencies and to further delineate inflammatory pathways in UC, substantially more patients and biopsies were included than in previous studies.

MATERIALS AND METHODS

Patients and Controls. Sixty seven patients with UC and 31 control patients who were undergoing colonoscopy were recruited. Their demographics are shown in Table 4.

Table 4

	UC
Number of patients	67
Male/ Female	33/34
Median age at diagnosis (years)	37
Median duration of follow up (years)	7.8
Disease Group	
New Diagnosis (1)	8
Quiescent disease (2)	41
Active disease (3)	18
Disease extent at time of Endoscopy	
Proctitis	15
L sided colitis	27
Extensive colitis	25
Current Smoker	6
Family history of IBD	5
5 ASA Therapy	40
Corticosteroid therapy	10
Immunosuppressant therapy (AZA, 6MP, MTX, MMF)	11

Sixty seven patients with UC and 31 control patients who were undergoing colonoscopy were recruited (Table 4). All UC patients attended the clinic at the Western General Hospital, Edinburgh and the diagnosis of UC adhered to the criteria of Lennard-Jones. (Lennard-Jones JE. Scand J Gastroenterol Suppl 1989;170:2-6) Phenotypic data were collected by interview and case-note review and comprised of demographics, date of diagnosis, disease location, disease behavior, progression, extra-intestinal manifestations, surgical operations, current medication, smoking history, joint symptoms, family history and ethnicity. At the time of colonoscopy patients symptoms were evaluated using the simple clinical colitis activity index (SCCAI). (Walmsley et. al. Gut. 1998;43:29-32)

Patients were recorded as having a 'new diagnosis' of UC if the colonoscopy took place at the time of their index presentation and they had had less than 24 hours of oral/IV therapy. Quiescent disease was defined as a SCCAI of 2 or less and histology showing no inflammation or mild chronic inflammation and active disease was defined as a SCCAI of greater than 2 and histology showing acute or chronic inflammation.

Eleven of the controls were male, 20 were female with a median age of 43 at the time of endoscopy. Six of the controls had normal colonoscopies for colon cancer screening, 9 controls had symptoms consistent with irritable bowel syndrome and had a normal colonoscopic investigation and 7 patients had a colonoscopy for another indication and histologically normal biopsies were obtained. Eight control patients had abnormal inflamed colonic biopsies (1 pseudomembranous colitis, 1 diverticulitis, 1 amoebiasis, 2 microscopic colitis, 1 eosoinophilic infiltrate, 2 scattered lymphoid aggregates and a history of gastroenteritis). Written informed consent was obtained from all patients. Lothian Local Research Ethics Committee approved the study protocol: REC 04/S1103/22.

Biopsy Collection. Anatomical location was confirmed by an experienced operator, distance of endoscope insertion and endoscope configuration using a Scope Guide ™. Paired biopsies were taken from each anatomical location. One biopsy was sent for histological examination and the other was snap frozen in liquid nitrogen for RNA extraction. Each biopsy was graded histologically, by an experienced gastrointestinal pathologist as having no evidence on inflammation, biopsies with evidence of chronic inflammation and predominately chronic inflammatory cell infiltrate or simply those with acute inflammation and an acute inflammatory cell infiltrate. One hundred and thirty nine paired UC biopsies and 76 paired control biopsies were collected. The number of paired biopsies in UC patients and controls from each anatomical location are shown in Table 5.

Table 5

	UC (n =67)	*Controls (n =31)*
Total number of paired biopsies	139	76

Terminal Ileum	4	6
Ascending colon	33	17
Descending colon	35	23
Sigmoid colon biopsies.	57	27
Removed from analysis	10	3

RNA Isolation. The biopsies weighed between 0.2mg and 16.5 mg with a median weight of 5.5 mg. Total RNA was extracted from each biopsy using the micro total RNA isolation from animal tissues protocol (Qiagen, Valencia, CA), according to the manufacturer's instructions. To evaluate purity and integrity 1 μL of total RNA was assessed each sample with the Agilent technologies 2100 bioanalyzer using the Pico LabChip reagent set (Agilent Technologies, Palo Alto, CA).

Microarray Analysis. 1 μg of total RNA was amplified using the Low RNA Input Fluorescent Linear Amplification protocol (Agilent Technologies, Palo Alto, CA). A T7 RNA polymerase single round of linear amplification was carried out to incorporate Cyanine-3 and Cyanine-5 label into cRNA. The cRNA was purified using the RNeasy Mini Kit (Qiagen, Valencia, CA). 1 μl of cRNA was quantified using the NanoDrop ND-1000 spectrophotometer (NanoDrop Technologies, Wilmington, Delaware).

750 ng of Universal Human Reference (Stratagene, La Jolla, CA) cRNA labeled with Cyanine-3 and 750 ng of the test sample cRNA labeled with Cyanine-5 were fragmented for 30 minutes at 60°C before loading onto Agilent Whole Human Genome microarrays (Agilent technologies, Palo Alto, CA). The samples were hybridized for 18 hours at 60°C with constant rotation. Microarrays were washed, dried and scanned on the Agilent scanner according to the manufacturer's protocol (Agilent technologies, Palo Alto, CA). Microarray image files were analyzed using Agilent's Feature Extraction software version 7.5 (Agilent Technologies, Palo Alto, CA). The distribution of log intensities for each sample was plotted and outlier samples (i.e. greater than 2 standard deviations from the mean) were excluded from analysis. 10 UC samples and 3 control samples were designated as outliers using these criteria.

Real Time PCR. Confirmation real time PCR analysis was carried out on 8 genes- SAA1, IL8, DEFA5, DEFA6, MMP3, MMP7, S100A8 and TLR4. Ten healthy control sigmoid colon biopsies with normal histology, 9 quiescent UC sigmoid biopsies and 11 UC sigmoid biopsies with an acute (6 biopsies) or chronic (5 biopsies) inflammatory cell infiltrate were selected to represent the different disease groups after stratifying to represent a range of SAA1 and IL-8 expression.

Prior to RTPCR analysis 1 RNA amplification cycle was carried out using the MessageAmp™ II aRNA Amplification Kit protocol (Ambion technologies, Austin, TX). Reverse transcription PCR was then performed on 50ng of RNA using Stratagene model MX4000 (La Jolla, Ca, USA). TaqMan

primers and probes were manufactured in house (Genentech Inc, South San Francisco, CA). The sequences for the forward probe, the reverse probe and the TaqMan probe were as follows-

SAA1, forward- agcgatgccagagagaata, reverse- ggaagtgattggggtctttg, Taq- ctttggccatggtgcggagg, [SEQ ID NO:235]

IL-8, forward- actcccagtcttgtcattgc, reverse- caagtttcaaccagcaagaa, Taq- tgtgttggtagtgctgtgttgaattacgg, [SEQ ID NO:236]

DEFA5, forward- gctacccgtgagtccctct, reverse- tcttgcactgctttggtttc, Taq- tgtgtgaaatcagtggccgcct, [SEQ ID NO:237]

DEFA6, forward- agagctttgggctcaacaag, reverse- atgacagtgcaggtcccata, Taq- cacttgccattgcagaaggtcctg, [SEQ ID NO:238]

MMP3, forward- aagggaacttgagcgtgaat, reverse- gagtgcttccccttctcttg, Taq- ggcattcaaatgggctgctgc, [SEQ ID NO:239]

MMP7, forward- cacttcgatgaggatgaacg, reverse- gtcccatacccaaagaatgg, Taq- ctggacggatggtagcagtctaggga, [SEQ ID NO:240]

S100A8, forward- ttgaccgagctggagaaag, reverse- tcaggtcatccctgtagacg, Taq- tccctgataaaggggaatttccatgc [SEQ ID NO:241] and

TLR4, forward- agagccgctggtgtatcttt, reverse- ccttctgcaggacaatgaag, Taq- tggcagtttctgagcagtcgtgc [SEQ ID NO:242].

PCR conditions comprised of 48°C for 30 minutes, 95°C hold for 10 minutes, followed by 40 cycles of 30 second 95°C melt and 1 minute 60°C anneal/extend. Absolute quantification of product was calculated by normalizing to RPL19. Results were analyzed using SAS and JMP software (SAS, North Carolina).

In Situ Hybridization for Defensin Alpha 5.

PCR primers were designed to amplify a 318 bp fragment of DEFA5 spanning from nt 55-372 of NM_021010 (upper- 5' catcccttgctgccattct [SEQ ID NO:243] and lower- 5' gaccttgaactgaatcttgc [SEQ ID NO:244]). Primers included extensions encoding 27-nucleotide T7 or T3 RNA polymerase initiation sites to allow in vitro transcription of sense or antisense probes, respectively, from the amplified products. Endoscopic biopsies were fixed in 10% neutral buffered formalin and paraffin-embedded. Sections 5 μm thick were deparaffinized, deproteinated in 10 ug/ml Proteinase K (Amresco) for 45 minutes at 37 °C, and further processed for *in situ* hybridization as previously described. (Jubb et. al. Methods Mol Biol. 2006;326:255-264) ^{33}P-UTP labeled sense and antisense probes were hybridized to the sections at 55°C overnight. Unhybridized probe was removed by incubation in 20μg/ml RNase A for 30 min at 37°C, followed by a high stringency wash at 55°C in 0.1 X SSC for 2 hours and dehydration through graded ethanols. The slides were dipped in NTB

nuclear track emulsion (Eastman Kodak), exposed in sealed plastic slide boxes containing desiccant for 4 weeks at 4°C , developed and counterstained with hematoxylin and eosin.

Immunohistochemistry for Rabbit Anti-Human Lysozyme and Rabbit Anti-Human Defensin Alpha 6

Formalin fixed paraffin embedded tissue sections were rehydrated prior to quenching of endogenous peroxidase activity (KPL, Gathersburg, MD) and blocking of avidin and biotin (Vector, Burlingame, CA). Sections were blocked for 30 minutes with 10% normal goat serum in PBS with 3% BSA. Tissue sections were then incubated with primary antibodies for 60 minutes at room temperature, biotinylated secondary antibodies for 30 min, and incubated in ABC reagent (Vector, Burlingame, CA) for 30 minutes followed by a 5 minute incubation in metal enhanced DAB (Pierce, Rockford, IL). The sections were then counterstained with Mayer's hematoxylin. Primary antibodies used were rabbit anti-human lysozyme at 5.0 µg/ml (Dako, Carpinteria, CA) and rabbit anti-human DEFA6 at 5.0 µg/ml (Alpha Diagnostics, SanAntonio, TX). Secondary antibody used was biotinylated goat anti-rabbit IgG at 7.5 µg/ml (Vector, Burlingame, CA). DEFA6 alpha staining required pre-treatment with Target Retrieval High pH (Dako, Carpenteria,CA) at 99°C for 20 minutes, lysozyme staining did not require pretreatment. All other steps were performed at room temperature.

Data Analysis. Microarray data were analyzed using the Rosetta Resolver software (Rosetta Inpharmatics, Seattle). Statistical significance of the microarray data was determined by Student's unpaired *t* test. $p < 0.01$ and a fold change of greater or less than 1.5 were considered statistically significant. Fold change data was calculated using the Rosetta Resolver software. Gene ontology was analyzed using Ingenuity software (Ingenuity Systems, Mountain View, CA). The Mann-Whitney U test was used to analyze the real time PCR data. $p < 0.05$ was considered significant.

RESULTS

Influence of anatomical location on gene expression in the healthy colon and terminal ileum. 56 histologically normal biopsies from control patients were analyzed by unsupervised hierarchical clustering. Clear separation by anatomical location was observed on one side of the dendrogram 25/25 biopsies were from the left colon (descending colon or sigmoid colon) where as on the other side of the dendrogram 20/31 biopsies were from the ascending colon (χ^2 =25.1, $p<0.0001$) (Figure 1). 6/6 of the terminal ileal biopsies were clustered together. Biopsies from individual patients did not cluster together. The genes driving the differential expression between the right and left colon that were causing the observed clustering were predominately involved in the embryological development of the GI tract- HOXA13, (FC +4.93, $p = 2.3x10^{-16}$), HOXB13 (FC +16.96, $p <1x10^{-45}$), GLI1 (FC +2.2, $p = 4.0x10^{-24}$), and GLI3 (FC +2.3, $p = 2.1x10^{-28}$) were all upregulated in the left colon.

Analysis of expression in UC and control biopsies.

Using unsupervised hierarchical clustering we were unable to differentiate between biopsies from UC patients and controls patients. In addition no clustering based on the inflammation status of the biopsies was observed. The only clustering that was observed was with biopsies from the terminal ileum where both UC and control biopsies clustered together. When all of the UC biopsies (129) and control biopsies (73) were compared, 143 sequences had a fold change of greater than 1.5 in the UC biopsies ($0.01 > p > 10^{-45}$) and 54 sequences had a fold change of less than 1.5 ($0.01 > p > 10^{-20}$) (data not shown).

Serum amyloid A1 (SAA1) was the most up regulated gene (Fold change (FC) +8.19, $p < 10^{-45}$). Other notably upregulated genes were S100A8 (FC +3.50, $p = 2.3x10^{-17}$), S100A9 (FC +3.06, $p = 4.1x10^{-13}$), the alpha defensins, alpha 5 (DEFA5) (FC +3.25, p = 0.00003), alpha 6 (DEFA6) (FC +2.18, $p = 6.95x10^{-7}$) and the matrix metalloproteinases MMP3 (FC +2.17, $p = 5.6x10^{-10}$) and MMP7 (FC +2.29, $p = 2.3x10^{-7}$).

A list of the genes found to be differentially expressed in UC patients when compared to normal patients can be found in Tables 1A, 1B, and 2A as described above.

The differential gene expression of a number of candidate genes across more than one experiment is shown in Table 6. Table 6 shows fold changes and p values are shown in a number of different genes in four different experiments. The number of biopsies analyzed in each experiment is shown in brackets. Significant consistent changes in expression across more than one experiment were observed for the genes of interest in this table.

Table 6

Genes Analyzed	*All UC (129 biopsies) v controls (73 biopsies) Fold change*	*p value*	*Non-inflamed UC sigmoid (22) v non- inflamed control sigmoid (18) Fold change*	*p value*	*Inflamed UC sigmoid (35) v inflamed control sigmoid (8) Fold change*	*p value*	*Inflamed UC sigmoid (35) v non-inflamed sigmoid UC (22) Fold change*	*p value*
SAA1	+8.19	$<10^{-45}$	+2.0	0.00024	+17.5	2.9×10^{-21}	+16.51	$<10^{-45}$
Def alpha 5	+3.25	0.00003	+1.02	0.89	+7.27	6.3×10^{-30}	+8.44	$<10^{-45}$
Def alpha 6	+2.18	6.95×10^{-7}	-1.09	0.34	+4.41	9.7×10^{-9}	+6.72	4.16×10^{-19}
S100A8	+3.50	2.3×10^{-17}	+1.21	0.19	+9.75	2.4×10^{-24}	+6.84	1.16×10^{-19}
S100A9	+3.06	4.1×10^{-13}	+1.05	0.16	+7.53	6.4×10^{-12}	+7.11	1.96×10^{-32}
MMP3	+2.17	5.6×10^{-10}	-1.55	0.0088	+11.0	1.22×10^{-37}	+8.15	2.32×10^{-35}
MMP7	+2.29	2.3×10^{-7}	+1.16	0.080	+7.31	4.9×10^{-24}	+5.53	1.01×10^{-23}
IL8	+2.05	4.2×10^{-11}	+1.10	0.26	+6.36	9.27×10^{-17}	+7.24	8.42×10^{-19}
TLR4	+1.34	4.5×10^{-7}	+1.15	0.18	+1.50	0.0044	+1.54	0.00073
TNIP3	+8.02	1.1×10^{-17}	-1.30	0.20	+7.53	2.93×10^{-13}	+10.5	1×10^{-38}
CCL20	+1.30	0.00011	+1.25	0.020	+1.79	0.00002	+2.36	4.68×10^{-11}
ABCB1	-1.32	0.00091	+1.10	0.40	-1.82	5.6×10^{-6}	-1.92	9.0×10^{-10}
HLA-DRB1	+1.03	0.88	-3.0	0.0010	+3.30	0.033	+2.67	0.0011
TSLP	-1.12	0.31	-2.73	2.7×10^{-10}	-1.15	0.61	+1.23	0.092

Gene ontology analysis involving the genes differentially expressed between the UC and control biopsies showed a preponderance of differentially expressed genes were involved in immune response (48 genes out of a total of 679 genes classified under immune response, $p = 2.1x10^{-9}$, OR 2.61, CI 1.85-3.56) and response to wounding (30 genes out of a total of 359 genes classified under response to wounding, $p = 6.42 x10^{-9}$, OR 3.14, CI 2.09- 4.53) when biological systems were considered.

Analysis of expression in sigmoid colon biopsies in patients with quiescent UC and non-inflamed control biopsies. To compare expression in biopsies without an acute inflammatory signal and to remove the effect of anatomical variation, 22 biopsies from the sigmoid colon with no histological evidence of inflammation from patients with UC were compared to 18 histologically normal control sigmoid colon biopsies. 102 sequences had a fold change greater than 1.5 ($0.01 > p > 4.77x10^{-13}$) and 84 sequences had a fold change of less than 1.5 ($0.01 > p > 1.8x10^{-21}$) (data not shown).

Upregulated genes included defensin beta 14 (FC +2.11, p = 0.00002) and SAA1 (FC +2.01, p = 0.00024). Interesting genes that were down regulated included HLA-DRB1 (FC -3.0, p = 0.0010) and TSLP (FC -2.73, $p = 2.7x10^{-10}$) (Table 6).

Analysis of expression in sigmoid colon biopsies in patients with active UC and inflamed control biopsies. Expression of 35 histologically inflamed sigmoid biopsies from patients with UC were compared to 8 histologically inflamed control sigmoid biopsies. Reflecting the more severe inflammation in the UC biopsies a number of genes involved in the acute inflammatory response were upregulated in the UC biopsies v the control biopsies- SAA1 (FC +17.5, $p = 2.9x10^{-21}$), MMP3 (FC +11.0, $p = 1.22x10^{-37}$), MMP7 (FC +7.31, $p = 4.9x10^{-24}$) and IL-8 (FC +6.36, $p = 9.27x10^{-17}$) (Table 6). Overall 623 sequences had a fold change of greater than 1.5 and 509 sequences had a fold change of -1.5 or less ($p < 0.01$) (data not shown).

Inflamed versus non-inflamed UC sigmoid colon biopsies. When expression signals were compared between 35 histologically inflamed and 22 non- inflamed sigmoid colon UC biopsies 700 sequences had a fold change of greater than 1.5 ($0.01 > p > 1x10^{-45}$) and 518 sequences ($0.01 > p > 1x10^{-45}$) had a fold change of less than 1.5 in the inflamed biopsies (data not shown).

Notably upregulated genes included SAA1 (FC +16.51, $p = <10^{-45}$), TNFAIP3 interacting protein 3 (TNIP3) (FC +10.5, $p = 1x10^{-38}$), DEFA5 (FC +8.44, $p = <10^{-45}$), DEFA6 (FC +6.72, $p = 4.16x10^{-19}$) and regenerating islet-derived 3 gamma (REG3γ) (FC +6.99, $p = <10^{-45}$).

Analysis of Specific Gene Families- Alpha Defensins 5 and 6.

Expression of a number of genes of interest was further analysed, taking into consideration anatomical location and degree of inflammation in the UC samples. When DEFA5 and DEFA6 were analysed

expression in the normal controls and the non- inflamed UC biopsies was similar across the different anatomical locations with there being high expression in the terminal ileum, and expression decreasing as the biopsy location became more distal in the colon (Figure 2).

In Figure 2, the expression of each array sample is plotted against the Agilent universal reference. Each endoscopic biopsy has been separated by patient status, biopsy inflammation status and anatomical location. The mean expression levels for each anatomical location are linked in blue. High alpha defensin 5 (panel A) and 6 (B) (DEFA5 and DEFA6) expression levels are seen in the terminal ileum of the controls and the non inflamed UC samples. The expression in these 2 groups decreased the more distally in the colon the biopsies were retrieved from. In the acute and chronically inflamed UC samples and to a lesser extent in the inflamed control samples there was a marked increase in DEFA5 and DEFA6 expression throughout the ascending , descending and sigmoid colon- sigmoid colon inflamed v non-inflamed UC samples (FC +8.44, $p = <10^{-45}$) for DEFA5, (FC +6.72, $p = 4.16x10^{-19}$) for DEFA6.

In the acute and chronically inflamed UC biopsies there was marked upregulation of DEFA5 and DEFA6 expression throughout the ascending, descending and sigmoid colon (Table 6).

Matrix metalloproteinases 3 and 7.

Increased expression of MMP3 and MMP7 was observed in the acutely and chronically inflamed UC biopsies when compared to the non- inflamed UC biopsies- sigmoid colon inflamed v non- inflamed UC samples MMP3 (FC +8.15, $p = 2.3x10^{-35}$) and MMP7 (FC +5.53, $p = 1.0x10^{-23}$) (Figure 3).

In Figure 3, the expression of each array sample is plotted against the Agilent universal reference. Each endoscopic biopsy has been separated by patient status, biopsy inflammation status and anatomical location. The mean expression levels for each anatomical location are linked in blue. Increased expression of MMP3 (panel A) and MMP7 (B) was observed in the acutely and chronically inflamed UC biopsies when compared to the non inflamed UC biopsies- sigmoid colon inflamed v non inflamed UC samples MMP3 (FC +8.15, $p = 2.3x10^{-35}$) and MMP7 (FC +5.53, $p = 1.0x10^{-23}$). In contrast when the inflamed and non- inflamed control samples were analysed, a decrease in the expression levels of MMP3 and MMP7 in the inflamed control biopsies was observed (FC -1.62, p = 0.012 and FC -2.0, p = 0.0002 respectively).

ATP- binding cassette (ABC) transporter family and the Xenobiotic- transcription regulators. To further investigate this gene family, expression patterns from probes representing 48 transcriptional genes and their key mediators (PXR, FXR, LXR and CAR) were analysed. When these genes were compared in all the UC and control biopsies, 7 genes were found to significantly down regulated in the UC samples when compared to the control samples- ABCA1 (p= 0.01), ABCA8 (p= 0.0064), ABCB1 (p= 0.0091), ABCC6

(p=0.0050), ABCB7 (p= 0.0068), ABCF1 (p=0.0005) and ABCF2 (p<0.00001). Only one probe representing ABCB2 was significantly upregulated in UC (p= 0.0048).

A number of ABC genes were found to be down-regulated in IBD patients as compared to normal patients (data not shown). The changes observed in ABCB1 expression appeared to be primarily driven by the inflamed UC biopsies which were significantly downregulated when compared to the non-inflamed UC biopsies in the sigmoid colon (FC -1.82, p= $5.6x10^{-6}$)(Table 6). Of interest, no difference in the expression of PXR between UC and controls was observed in any of the analysis including disease location and activity.

RTPCR Analysis. In the case of 8 genes implicated by microarray expression results, confirmatory real time PCR analysis using 10 healthy control colon sigmoid biopsies with normal histology, 9 quiescent UC sigmoid biopsies and 11 UC sigmoid biopsies with an acute (6 biopsies) or chronic (5 biopsies) inflammatory cell infiltrate was undertaken. Increased SAA1 expression in the inflamed UC sigmoid colon biopsies compared to the normal control sigmoid colon biopsies and the non-inflamed UC sigmoid colon biopsies (p = 0.041 and p = 0.044 respectively) was observed. Elevated IL-8 expression was also confirmed in the inflamed UC sigmoid biopsies when compared to the control sigmoid biopsies (p = 0.031) and a trend was observed towards there being higher IL-8 expression in the inflamed UC sigmoid colon biopsies when compared to the non-inflamed UC biopsies (p = 0.089) (Figure 4).

Figure 4 shows the real time PCR expression data comparing expression in 10 healthy control sigmoid biopsies with normal histology, 9 quiescent UC sigmoid biopsies and 11 UC sigmoid biopsies with an acute or chronic inflammatory cell infiltrate. Expression of SAA1 (A), IL-8 (B), defensin alpha 5 (C) and defensin alpha (D) were compared between the control and the inflamed and non-inflamed UC biopsies. Standard error bars are illustrated in green in each graph.

Increased expression of DEFA5 and DEFA6 in the inflamed UC sigmoid colon biopsies when compared to the non- inflamed UC sigmoid colon biopsies (p = 0.0008 and p = 0.0005 respectively) and the control sigmoid colon biopsies (p = 0.0002 and p = 0.0001 respectively) was observed (Figure 4). Increased expression in the inflamed UC sigmoid colon biopsies when compared to the non inflamed UC sigmoid colon biopsies was also observed when MMP7, (p = 0.0005), S100A8, (p = 0.0029) and TLR4, (p = 0.019) were examined (Figure 5).

Figure 5 shows the real time PCR expression data comparing expression in 10 healthy control sigmoid biopsies with normal histology, 9 quiescent UC sigmoid biopsies and 11 UC sigmoid biopsies with an acute or chronic inflammatory cell infiltrate. Expression of MMP3 (A), MMP7 (B), S100A8 (C) and TLR4 (D) were compared between the different patient groups. Standard error bars are illustrated in

green in each graph. No significant change in MMP3 expression was observed when the inflamed, non-inflamed UC sigmoid colon biopsies and the control sigmoid colon biopsies were analysed.

In- Situ Hybridization and Immunohistochemistry.

To further investigate the cellular localization of the excess DEFA5& 6 expression in the colon of patients with UC, *in- situ* hybridization and immunohistochemistry was undertaken in a cohort of biopsies of patients with UC and controls (Figures 6 and 7).

Figure 6 shows the *in- situ* hybridization of the terminal ileal biopsies for DEFA5 showed strong hybridization in the basal crypts consistent with Paneth cell location. In the upper panel terminal ileum (TI), the antisense probe shows strong hybridization in the basal crypts consistent with Paneth cell location. In the lower panel terminal ileum (TI), no significant hybridization was observed with sense control probe. Panel A shows the sigmoid colon biopsy of a non- inflamed control patient. Panels B,C, & D show strong, multifocal hybridization in the basal crypt region of UC sigmoid colon biopsies consistent with Paneth cell metaplasia. In the UC biopsies taken from the sigmoid colon strong, multifocal hybridization in the basal crypt region of these biopsies was observed and this would be consistent with Paneth cell metaplasia. This was not observed in the non- inflamed control biopsies.

Figure 7 shows the *in- situ* hybridization of the terminal ileal biopsies for DEFA6. In panel A, terminal ileum immunohistochemistry shows positive staining in the basal crypts consistent with Paneth cell location. In panels B & C, no significant staining was observed in the non- inflamed control patients. In panels D, E, & F, strong, multifocal staining in the basal crypt region of UC sigmoid colon biopsies consistent with Paneth cell metaplasia. Immunohistochemistry for DEFA6 confirmed that in the sigmoid colon UC biopsies, staining was observed in the basal crypt region of these biopsies consistent with Paneth cell metaplasia. Again, this was not observed in the non- inflamed control biopsies (Figure 7).

Expression of Genes within the IBD2 Locus. Using the markers defining the IBD2 locus we identified 526 Agilent probes representing genes or expressed sequence tags within this locus on chromosome 12. 12 probes had a greater or less than 1.5 fold change in expression with $p < 0.01$ when expression of acute and chronically inflamed UC sigmoid colon biopsies were compared to non- inflamed UC sigmoid colon biopsies (Table 7).

Table 7

Agilent Probe	*Gene Symbol*	**UC sigmoid inflamed (35 biopsies) v non-inflamed (25) fold change**	*p value*
A_23_P98876	SLC39A5	-1.52855	$1.36x10^{-7}$
A_24_P647146	HDAC7A	1.53876	$3.15x10^{-16}$
A_24_P941773	DKFZP586A0522	-2.27306	$2.31x10^{-11}$
A_24_P945113	ACVRL1	1.57956	$6.33x10^{-9}$
A_23_P128230	NR4A1	1.81844	0.00005
A_23_P331098	K5B	2.3845	0.0004
A_24_P246636	A_24_P246636	-1.69754	$7.06x10^{-8}$
A_23_P2233	SILV	1.51557	$9.07x10^{-9}$
A_23_P105251	GLI	-1.54447	$7.73x10^{-9}$
A_32_P3783	HMGA2	-1.94107	$2.37x10^{-9}$
A_23_P162300	IRAK3	1.7382	$3.11x10^{-15}$
A_32_P83256	IRAKM	1.70847	$4.56x10^{-10}$

Analysis of the 526 expression probes located within the IBD2 locus identified 12 probes that were significantly differentially regulated when the inflamed UC sigmoid colon biopsies were compared to the non- inflamed UC sigmoid colon biopsies.

Table 3A (provided above) lists those genes from the IBD2 locus on chromosome 12 that were found to be up-regulated in IBD patients as compared to normal patients.

Table 3B (provided above) lists those genes from the IBD2 locus on chromosome 12 that were found to be down-regulated in IBD patients as compared to normal patients.

Interesting candidate genes that were differentially regulated in the inflamed UC sigmoid samples included keratin 5B (FC +2.38, p = 0.0004), MMP19 (FC +1.95, p = 0.0084), GLI 1(FC -1.54, p = $7.3x10^{-9}$), interleukin-1 receptor-associated kinase 3 (FC +1.74, p = $3.1x10^{-15}$) and interleukin-1 receptor-associated kinase M (FC +1.71, p = 0.0014).

When the acute inflammatory signal was removed and non- inflamed UC sigmoid biopsies and non-inflamed control sigmoid biopsies were compared, no sequences had a fold change greater or less than 1.5. However, notably downregulated genes included tubulin alpha 5 (FC -1.32, p = $9.0x10^{-6}$) and tubulin alpha 6 (FC -1.45, p = $1.2x10^{-5}$), molecules involved in the microtubule cytoskeleton and barrier integrity of the bowel.

Expression of Genes within the IBD5 Locus. Agilent probes representing 11 genes within the with IBD5 locus were identified and compared in healthy control, non- inflamed and inflamed UC biopsies (Table

8). Table 8 shows the fold changes in expression of genes within the IBD5 locus comparing controls and patients with UC, who have been stratified for the degree of inflammation observed in their sigmoid biopsies. Significant down regulation of the organic cation transporters SLC22A4 and SLC22A5 was observed when inflamed UC sigmoid biopsies were compared to non-inflamed UC sigmoid biopsies.

Table 8

Genes Analyzed	**All UC (129) v controls (73) Fold change**	**p value**	**Inflamed sigmoid (35) v non-inflamed sigmoid (22) (UC) Fold change**	**p value**	**Non-inflamed UC sigmoid (22) v non inflamed control sigmoid (18) Fold change**	*p value*
IL4	+1.00	0.96	+1.06	0.62	+1.14	0.40
IL13	+1.12	0.057	-1.02	0.82	1.00	0.98
RAD50	+1.02	0.20	-1.20	$3.5x10^{-6}$	+1.08	0.062
IL5	+1.09	0.037	+1.10	0.17	+1.04	0.53
IRF1	+1.10	0.35	+1.12	$2.9x10^{-6}$	-1.01	0.62
SLC22A5	-1.26	$3.37x10^{-6}$	-1.50	$2.2x10^{-6}$	+1.02	0.75
SLC22A4	-1.18	0.11	-1.79	$1.53x10^{-9}$	+1.22	0.63
PDLIM4	+1.10	0.0056	+1.14	0.00039	+1.01	0.78
P4HA2	-1.05	0.13	1.00	0.98	-1.05	0.28
CSF2	+1.10	0.056	+1.19	0.052	-1.04	0.63
IL3	-1.01	0.39	+1.02	0.67	+1.01	0.75

Table 3A (provided above) lists those genes from the IBD5 locus on chromosome 5 that were found to be up-regulated.

Non significant, but consistent fold increases in expression were observed when IRF1 and PDLIM4 expression was compared in inflamed and non-inflamed UC sigmoid colon biopsies, (FC +1.12, $p = 2.9x10^{-6}$ and FC +1.14, p = 0.00039, respectively).

Table 3B (provided above) lists those genes from the IBD5 locus on chromosome 5 that were found to be down-regulated in IBD patients as compared to normal patients. SLC22A5 (OCTN2) was downregulated in UC biopsies compared to controls (FC -1.26 $p = 3.37x10^{-6}$) and when inflamed UC sigmoid colon biopsies were compared to non- inflamed UC sigmoid colon biopsies (FC -1.50, $p = 2.2x10^{-6}$). Expression of SLC22A4 (OCTN1) was also downregulated in inflamed UC sigmoid colon biopsies compared to non- inflamed UC sigmoid colon biopsies (FC -1.79, $p = 1.5x10^{-9}$), however when all UC biopsies were compared to controls, no change was observed (FC -1.18, p = 0.11).

Gene Expression and Disease Activity. Sigmoid colon biopsies from newly diagnosed UC patients who were undergoing endoscopy (8 biopsies) and sigmoid biopsies from patients with established active UC (18 biopsies) were compared. In the newly diagnosed UC sigmoid biopsies, 861 sequences were upregulated with a fold change of greater than 1.5 and $p < 0.01$, and 373 sequences were downregulated with a fold change of less than 1.5 and $p < 0.01$ (data not shown).

The 3 most upregulated genes in the newly diagnosed patients were Selectin E (FC +10.95, $p = 1.8x10^{-6}$), CCL19 (FC +7.42, $p = 4.7x10^{-15}$) and IL-8 (FC +7.32, $p = 2.9x10^{-7}$), and down regulated genes included S100P (FC -6.4, $p = 2.0x10^{-9}$).

Sigmoid colon biopsies from patients from UC patients with a simple clinical colitis activity index (SCCAI) of more than 2 (27 biopsies) were compared to sigmoid colon biopsies from UC patients with a SCCAI of 2 or less (30 biopsies). 813 sequences were upregulated and 444 sequences were downregulated. Among the most upregulated genes were those that were involved in the acute inflammatory response IL-8 (FC +8.86, $p = 4.4x10^{-12}$), MMP3 (FC +6.5, $p = 3.2x10^{-19}$), MMP7 (FC +5.3, $p = 3.4x10^{-21}$) and DEFA6 (FC +4.5, $p = 2.7x10^{-12}$). Down regulated genes included UGT2B15 (FC -4.5, p = 0.0013), UGT2B17 (FC -2.8, p = 0.0059) and UGT2B10 (FC -2.2, p = 0.0038), all members of the UGT family which are involved in cellular detoxification and excretion.

Table 3A (provided above) lists additional genes identified in the present study observed to be up-regulated in UC patients as compared to normal patients, while Table 3B (provided above) lists additional genes identified in the present study observed to be down-regulated in UC patients as compared to normal patients.

DISCUSSION

The present study represents the most rigorous microarray analysis yet reported comparing intestinal gene expression in patients with UC, with healthy controls as well as in patients with other causes of colonic inflammation. The data provide important information on anatomical pattern of gene expression in the healthy colon, with intriguing differences in the right and left colon. Moreover, strong evidence for dysregulated gene expression characteristic of UC has been provided and overall these data provide valuable insight into gene expression in normal physiological homeostasis and during the pathological process of UC.

The strengths of this data set are the size of the study undertaken, the meticulous assessment of disease phenotype, the documenting of anatomical location for each biopsy and the avoidance of confounding effects due to pooling of samples. Thereby, we have been able to remove a considerable amount of background variability that has hampered previous studies. (Marshall E. Science 2004;306:630-631; Ioannidis JP. Lancet 2005;365:454-455).

Moreover, the present study has addressed the potentially critical confounding effect of the strength of the non- specific acute inflammatory signature. Quiescent biopsies from patients with UC and controls were compared and from these analysis we were able to gain valuable insight into the pathogenesis of UC. In addition, the present study provided access to a proportion of patients with newly diagnosed disease, overcoming treatment related alterations in gene expression. A further strength of our study has been the fact that real time PCR analysis consistently confirmed the significant changes of in expression in all but one of the candidate genes of interest, strongly validating the microarray data and increasing substantially the confidence associated with the interpretation of the data.

This is the first microarray study to show a gradient in expression of a number of genes along the healthy adult colon. These results contrast with data from Costello and colleagues where no significant differences in expression patterns were observed when comparing biopsies from caecum, transverse colon, descending colon and sigmoid colon (Costello CM, et al. PLoS Med 2005;2:e199). The observed differences in these data sets may be explained by our analysis looking only at non- inflamed control samples where as Costello investigated control and diseased patients.

Genes involved in developmental pathways - the HOX family and the hedgehog signaling pathway appeared to be the most differentially regulated along the anatomical length of the healthy colon. HOXA13 has been shown play a crucial role in the development of the tail gut and mutations in the gene result in urogenital abnormalities, (De Santa et. al. Development. 2002;129:551-561) and interestingly it has been shown that HOXB13 expression is down regulated in colorectal tumours from the distal left colon. (Jung et. al. Br J Cancer. 2005;92:2233-2239)

The hedgehog signaling pathway is also crucial to the normal growth and development of the human gastrointestinal system and a number of congenital diseases that affect the gut are due to mutations in genes involved in this pathway. (Lees et. al. Gastroenterology. 2005;129:1696-1710) GLI-1 is one of the major effector molecules of the hedgehog signaling pathway and the GLI-1 gene lies within the IBD2 locus, an area that has previously been shown to be associated with UC. (Parkes et. al. Am J Hum Genet. 2000;67:1605-1610; Satsangi, et. al, Nat. Genet. 1996;14:199-202) Data from the present study would also suggest that GLI-1 is downregulated in inflamed UC biopsies compared to non inflamed biopsies from patients with UC. Recent data from our unit has shown a strong association between mutations in the GLI-1 gene and UC. (Lees et. al. Gastroenterology. 2006;130:A52)

Further recent data published by Varnat and colleagues have suggested that PPARβ negatively regulates Paneth cell differentiation by downregulating the expression of Indian hedgehog, another of the major effector molecules in the hedgehog signaling pathway. (Varnat et. al. Gastroenterology. 2006;131:538-553) Our data have shown upregulation of the alpha defensins 5 and 6 in the colon of patients with inflamed UC compared to non-inflamed biopsies from patients with UC and controls, and immunohistochemistry and *in-situ* hybridization have shown that this is largely mediated by Paneth cell metaplasia. It is intriguing to speculate that in patients with UC, further as yet undetermined defects in the Hedgehog signaling pathway may result in unregulated Paneth cell differentiation, Paneth cell metaplasia, increased alpha defensin 5 and 6 expression, and mucosal inflammation.

Indeed among the most stimulating observations in the present study were the data showing the upregulation of the alpha defensins 5 and 6 in patients with UC. Alpha defensins 5 and 6 are small cationic proteins that are part of the innate immune response and they have potent antimicrobial properties against gram positive and gram negative bacteria. (Ouellette AJ. Springer Semin Immunopathol. 2005;27:133-146) They are stored as pro-molecules in Paneth cells which in the healthy colon are largely restricted to the terminal ileum and on release into the mucosa they are cleaved by trypsin to the active antimicrobial peptide. (Ghosh et.al. Nat Immunol. 2002;3:583-590)

In our data set, high levels of alpha defensin expression were observed in the terminal ileal biopsies of non-inflamed controls and patients with UC. Levels of expression in the control patients and patients with quiescent UC fell as the location that the biopsies were retrieved from became more distal in the colon – ascending colon, descending colon and sigmoid colon. However, in the inflamed UC biopsies increased expression of both alpha defensins 5 and 6 was observed at each anatomical location that was biopsied. Lawrance and colleagues also noted the defensins alpha 5 and 6 were upregulated in patients with UC compared to controls, (Lawrance et. al. Hum Mol Genet. 2001;10:445-456) although, RNA was extracted from surgical resections and no details about the anatomical location of these specimens were given.

Recent data examining the expression of the alpha defensins 5 and 6 in patients with CD in the terminal ileum would suggest that expression levels are reduced irrespective of the degree of inflammation when compared to control terminal ileal tissue and this may be responsible for the terminal ileal phenotype observed in CD. (Wehkamp et. al. Proc Natl Acad Sci U S A. 2005;102:18129-18134) Whether the observed increase in alpha defensin 5 and 6 expression in our data set is a primary phenomenon related to disease pathogenesis, or whether it is secondary phenomenon protecting a previously damaged epithelial surface to microbial invasion may be resolved by looking for critical variants within these genes that are associated with disease susceptibility and altered function of these peptides.

It is of interest that many but not all of our results are broadly in line with two of the landmark microarray papers in IBD. Consistent with data from Lawrance and colleagues (Lawrance et. al. Hum Mol Genet. 2001;10:445-456) we have shown upregulation of S100A8 & A9 and the alpha defensins 5 & 6 in UC. However, no overlap was observed in the differentially expressed probes in the IBD2 locus in the present study and in that of Lawrance. Dieckgraefe and colleagues (Dieckgraefe et.al. Physiol Genomics. 2000;4:1-11) observed upregulation of a number of the MMP genes, consistent with our data and interestingly members of the REG family were shown to be upregulated in the colon of patients with UC, probably as a result of Paneth cell metaplasia.

The downregulation of ABCB1 in our dataset is of significant interest, and consistent with earlier microarray data from Langman, Dieckgraefe and Lawrance and colleagues. (Dieckgraefe et.al. Physiol Genomics. 2000;4:1-11; Lawrance et. al. Hum Mol Genet. 2001;10:445-456; Langmann et. al. Gastroenterology. 2004;127:26-40) In addition to this, we have observed that the expression in ABCB1 displayed a decreasing gradient, with gene expression lowest in the sigmoid colon in UC. This pattern of expression is perhaps consistent with the hypothesis associating loss-of-function of P-glycoprotein (gene product of ABCB1) in UC, and in line with the clinical presentation of UC. The current data illustrate the importance of ABCB1 in the disease pathogenesis of UC, as highlighted in recent genetic and animal functional data. (Moodie et. al. *Glucocorticoid access and action in the rat colon: expression and regulation of multidrug resistance 1a gene (mdr1a), glucocorticoid receptor (GR), mineralocorticoid receptor (MR) and 11-beta-hydroxysteroid dehydrogenase type 2* (11BHDS2). 197 ed. 2003)

ABCB1 encodes P-glycoprotein 170, an efflux epithelial transporter involved in gut barrier defence and xenobiotic metabolism. It is pertinent that when the entire class of proteins sharing homology with ABCB1 were analyzed, a further 6 out of 48 genes (12.5%) of the ABC transporters were significantly dysregulated in UC; suggesting an important role in this class of protein in the aetiopathogenesis of UC.

In contrast to data produced by Langmann we did not observe any changes in expression of the transcriptional regulator Pregnane-X receptor. These negative data are consistent with genetic studies carried out in the IBD population in Edinburgh- using a haplotype tagging approach, there was an

association between the ABCB1 gene and UC , (Ho et. al. Hum Mol Genet. 2006;15:797-805) but no association between the Pregnane- X receptor and UC. (Ho GT et. al. Gut. 2006;55:1676-1677) Aspects of study design may explain the differences observed in this context between our data and those of Langmann and colleagues, as our analysis took in to consideration the inflammation status of the biopsies and anatomical location. In our data set we did not pool samples, thus carrying out a large number of microarrays, where as Langmann and colleagues pooled terminal ileal and colon biopsies and this difference in methodology may also account for the different results.

The matrix metalloproteinases (MMPs) comprise of a family of greater than 23 zinc-dependent enzymes that are end stage effecter molecules involved in the degradation of extra cellular matrix components during morphogenesis and tissue remodeling. (Brinckerhoff et. al. Nat Rev Mol Cell Biol. 2002;3:207-214) Consistent with our data, previous studies in patients with IBD have shown a marked increase in expression of MMP3 in the inflamed biopsies when compared to non inflamed biopsies and control biopsies. (Heuschkel et. al. Gut. 2000;47:57-62; von LBet. al. Gut. 2000;47:63-73) Data for MMP3 -/- mice have also demonstrated delayed clearance of bacteria, a compensatory increase in MMP7 and reduced $CD4^+$ T lymphocyte recruitment to the lamina propria. (Li et. al. J Immunol. 2004;173:5171-5179) Furthermore, recent data have also shown a proinflammatory effect of MMP3 mediated through CXCL7 causing dose dependant neutrphil recruitment in colonic cell lines. (Kruidenier et. al. Gastroenterology. 2006;130:127-136)

In our data set we observed a decrease in MMP3 expression in our inflamed controls compared to our non-inflamed controls suggesting that the changes observed in MMP3 and MMP7 expression in UC may be disease specific. Transmission disequilibrium testing of the 5A variant of MMP3 in the German population showed an association with CD and not UC that was not replicated in the English population. (Pender et. al. J Med Genet. 2004;41:e112)

We have also used this dataset to analyse the relative expression of genes mapping to susceptibility loci implicated by genome wide analysis, notably within IBD2 and IBD5. The present data will be of use in gene identification, complementing results of fine-mapping studies, and genome- wide case- control studies currently underway. In this context it is of considerable interest to review our data concerning the IBD5 locus which spans a cytokine cluster containing a number of attractive candidate genes was initially discovered by genome wide scanning in 2000. (Rioux et. al. Am J Hum Genet. 2000;66:1863-1870; Ma et. al. Inflamm Bowel Dis. 1999;5:271-278) The tight linkage disequilibrium spanning the IBD5 linkage interval, has limited previous genetic studies, and these have not been sufficiently powered to identify the susceptibility gene within this region. (Waller, et. al. Gut. 2006;55:809-814; Fisher et. al. Hum Mutat. 2006;27:778-785; Noble et. al. Gastroenterology. 2005;129:1854-1864)

Downregulation of the positional candidate gene encoding the organic cation transporter SLC22A5 (OCTN2) was observed when UC biopsies were compared to control biopsies and in both SLC22A4 (OCTN1) and SLC22A5 down regulation was observed in the inflamed UC sigmoid colon biopsies compared to non-inflamed sigmoid biopsies. These provocative data would suggest that decreased expression of these genes may after all be involved in the pathogenesis of UC, and these data thereby may sustain interest in these genes. Peltekova and colleagues suggested that two variants in these genes- SLC22A4 (1672C→T) and the SLC22A5 variant (-207G→C) conferred disease susceptibility to CD, (Peltekova et. al. Nat Genet. 2004;36:471-475) however, when expression was compared in the small number of patients in this study who had been genotyped for these mutations no change in expression was observed between wild type and TC homozygote patients (data not shown). Expression of IRF-1 and PDLIM4, both plausible candidates within IBD5 was also dysregulated, emphasizing the uncertainties pertaining to this locus at present. Within the IBD2 locus, a series of dysregulated genes were identified in the present dataset, of which only GLI 1 has been subjected to detailed mutation analysis.

In conclusion these data have rigorously characterized expression of the whole genome in the terminal ileum and colon of patients which UC and controls. The studies provide new insights into regional variation of gene expression in the healthy colon, and also considerably extend previous studies in UC. These data identify a number of key regulators of intestinal inflammation, notably the alpha defensin family, hedgehog signaling molecules, and matrix metalloproteinases.

Example 3 - Immunohistochemistry

DefA6 Expression in IBD Biopsies.

Defensin alpha 6 is normally expressed by Paneth cells in the small intestine crypt epithelium and not in colon epithelial cells. We had observed increased DefA6 expression at the RNA level in ulcerative colitis and Crohn's disease patients using Agilent microarray and in taqman on biopsy lysates. This experiment evaluated if increased DefA6 protein expression could be seen in formalin fixed colon biopsies.

Our studies show, as expected, that there was no DefA6 staining in colon biopsies from non-IBD control patients with no histologic evidence of inflammation. We also evaluated one non-IBD control patient with a diagnosis of microscopic colitis. In that patient, DefA6 was present in sigmoid colon crypt epithelial cells.

In ulcerative colitis patients, 21 patients had scattered or clustered DefA6 staining in crypt epithelial cells of the sigmoid colon, descending colon, transverse colon, or rectum. Twenty of 21 positive patients had histologic evidence of chronic or chronic-active inflammation in their biopsy tissue. The remaining patient had predominantly acute (neutrophilic) inflammation. No patients with positive DefA6 staining in the colon had uninflamed biopsies.

There were 18 ulcerative colitis patients with no evidence of DefA6 staining in colon epithelium. The majority of these patients (10) had no histologic evidence of inflammation in the biopsy tissue. Six of the remaining patients had predominantly neutrophilic inflammation (acute inflammation) and two had chronic/chronic-active inflammation.

In summary, DefA6 expression in ulcerative colitis appears to correlated with the local inflammation status observed in the biopsy. None of the uninflamed biopsies had DefA6 staining. In addition, patients with chronic or chronic-active inflammation were more likely to have positive DefA6 staining than patients with acute inflammation.

Experimental Design: The scoring of inflammation status was based on inflammatory cell type predominance: neutrophil predominance = acute inflammation; neutrophils and mononuclear inflammatory cells = chronic active; and predominantly mononuclear inflammatory cells = chronic.

Table 9 shows the histologic findings. The expression of DefA6 is shown as "-", "+", or "++" and the corresponding inflammation score is provided in some cases.

Table 9

Patient	HP #	Tissue	DefA6	Inflammation status
115	HP-19891	sigmoid	+	microscopic colitis
119	HP-19893	descending	-	
122	HP-19898	sigmoid	-	
124	HP-19899	sigmoid	-	
125	HP-19900	sigmoid	NA	this is a section of terminal ileum
125	HP-19901	sigmoid	-	
130	HP-19905	rectum	-	
131	HP-19906	sigmoid	-	
135	HP-19908	sigmoid	-	
136	HP-19909	sigmoid	-	
222	HP-19912	rectum	+	chronic active
223	HP-19914	sigmoid	+	chronic
224	HP-19916	sigmoid	+	minimal chronic active
225	HP-19919	sigmoid	-	no inflammation
226	HP-19920	descending	-	no inflammation
227	HP-19922	sigmoid	+	minimal chronic active
230	HP-19924	sigmoid	-	no inflammation
230	HP-19925	rectum	-	no inflammation
231	HP-19926	descending	-	acute inflammation
233	HP-19927	sigmoid	-	no inflammation
234	HP-19928	descending	-	minimal chronic active HP
235	HP-19929	rectum	-	acute inflammation
238	HP-19930	sigmoid	+	chronic active
239	HP-19932	rectum	+	minimal chronic
240	HP-19933	rectum	-	minimal acute
241	HP-19934	rectum	-	no inflammation
244	HP-19935	sigmoid	-	no inflammation
246	HP-19936	sigmoid	+	minimal chronic
247	HP-19937	rectum	+	minimal chronic
248	HP-19938	rectum	+	minimal chronic
249	HP-19939	rectum	+	chronic active
250	HP-19940	sigmoid	+	chronic active
251	HP-19941	rectum	+	chronic active
253	HP-19942	sigmoid	+	chronic active
255	HP-19943	sigmoid	NA	fragmented section
256	HP-19944	sigmoid	+	chronic active
257	HP-19947	rectum	++	chronic active
258	HP-19948	rectum	+	chronic
259	HP-19949	sigmoid	++	chronic active
260	HP-19950	sigmoid	+	chronic active
261	HP-19951	sigmoid	-	mild acute
262	HP-19952	sigmoid	-	acute inflammation
262	HP-19953	rectum	-	no inflammation
263	HP-19954	rectum	-	no inflammation
265	HP-19955	sigmoid	+	chronic active
266	HP-19956	rectum	+	acute inflammation
267	HP-19957	transverse	++	Chronic active
270	HP-19958	rectum	-	Chronic active
245	HP-19965	sigmoid	-	no inflammation
245	HP-19966	rectum	-	acute inflammation

Example 4 – Analysis of Germline GLI1 Variation

Ulcerative colitis (UC) and Crohn's disease (CD) are polygenic chronic inflammatory bowel diseases (IBD) of high prevalence that are associated with considerable morbidity. The hedgehog (HH) signalling pathway plays vital roles in gastrointestinal tract development, homeostasis and malignancy. We identified a germline variation in *GLI1* (within the IBD2 linkage region, 12q13) in patients with IBD. Since this IBD-associated variant encodes a GLI1 protein with reduced function, we tested whether mice with reduced Gli1 activity are susceptible to chemically induced colitis. Using a gene-wide haplotype-tagging approach, germline *GLI1* variation was examined in three independent populations of IBD patients and healthy controls from Northern Europe (Scotland, England and Sweden) totalling over 5000 individuals. On log-likelihood analysis, *GLI1* was associated with IBD, predominantly UC, in Scotland and England ($p<0.0001$). A non-synonymous SNP (rs2228226C→G), in exon 12 of *GLI1* (Q1100E) was strongly implicated, with pooled odds ratio of 1.194 (C.I.=1.09-1.31, p=0.0002). *GLI1* variants were tested in vitro for transcriptional activity in luciferase assays. Q1100E falls within a conserved motif near the C-terminus of GLI1; the variant GLI protein exhibited reduced transactivation function in vitro. In complementary expression studies, we noted the colonic HH response, including GLI1, PTCH and HHIP, to be down-regulated in patients with UC. Finally, *Gli1*+/- mice were tested for susceptibility to DSS-induced colitis. Clinical response, histology and expression of inflammatory cytokines were recorded. *Gli1*+/- mice rapidly developed severe intestinal inflammation, with considerable morbidity and mortality compared with wild-type. Local myeloid cells were shown to be direct targets of HH signals and cytokine expression studies revealed robust up-regulation of IL-12, IL-17 and IL-23 in this model. HH signalling through GLI1 is required for proper modulation of the intestinal response to acute inflammatory challenge. Reduced GLI1 function predisposes to IBD pathogenesis, suggesting novel therapeutic avenues.

Ulcerative colitis (UC; MIM 191390) and Crohn's disease (CD; MIM 266600) are chronic, relapsing, inflammatory bowel diseases (IBD) of high prevalence (200-400 cases per 100,000 in N Europe and N America [Loftus EV, Jr. (2004) Gastroenterology 126: 1504-1517]) and are associated with considerable morbidity. Precise aetio-pathogenetic mechanisms are not understood but several lines of evidence implicate the central importance of a dysregulated host response to intestinal bacteria [Xavier RJ, Podolsky DK (2007) Nature 448: 427-434]. Epidemiological data, detailed molecular studies, and recent genome-wide association studies strongly suggest that UC and CD are related polygenic diseases that share some susceptibility loci (IL-23R, IL-12B, and NKX2.3 [Wellcome Trust Case Control Consortium (2007) Nature 447: 661-678; Duerr et al. (2006) Science 314: 1461-1463; Parkes et al. (2007) Nat Genet Jul;39(7):830-2. Epub 2007 Jun 6]), but differ at others: NOD2, ATG16L1 and IRGM are specific CD genes; the ECM1 locus is associated with UC [Parkes et al. (2007) Nat Genet Jul;39(7):830-2. Epub 2007 Jun 6; Fisher et al. (2008). Nat Genet 40(6):710-2. Epub 2008 Apr 27; Hampe et al. (2007) Nat Genet 39:

207-211; Hugot et al. (2001). Nature 411: 599-603; Ogura Y et al. (2001). Nature 411: 603-606]. The IBD2 locus (OMIM 601458) on chromosome 12q13 was first identified in a UK genome-wide scan (peak LOD score 5.47 at D12S83) [Satsangi et al. (1996). Nat Genet 14: 199-202] involving both UC and CD patients. Later studies showed that IBD2 contributes significantly to UC, notably extensive disease, but perhaps in a more minor way to CD susceptibility [Achkar et al. (2006). Am J Gastroenterol 101: 572-580; Parkes M et al. (2000) Am J Hum Genet 67: 1605-1610]. A strong candidate gene that maps to the IBD2 locus is *GLI1*, one of three related GLI transcription factors that transduce secreted hedgehog (HH) signals. HH signalling is key in gut development, homeostasis and malignancy, but has not been carefully studied in IBD [Lees et al. (2005) Gastroenterology 129: 1696-1710]. In developing intestine, Sonic (SHH) and Indian Hedgehog (IHH) provide a paracrine signal from epithelium to the mesenchymal receptor patched (PTCH). PTCH controls HH signal transduction through the membrane protein smoothened (SMO) and zinc finger transcription factors GLI1, GLI2, and GLI3 to direct tissue pattern and cell fate [Madison et al. (2005) Development 132: 279-289]. Chronic injury, inflammation and repair are critical aspects of IBD, and thus it is pertinent that the HH pathway is centrally involved in these processes in several other tissues, including muscle [Pola et al. (2003) Circulation 108: 479-485], liver [Jung et al. (2008) Gastroenterology 134: 1532-1543; Omenetti et al. (2008) Gut May;134(5):1532-43. Epub 2008 Feb 14.], and lung [Stewart et al. (2003) J Pathol 199: 488-495; Watkins et al. (2003) Nature 422: 313-317]. Indeed, HH signalling may play a central role in the inflammatory response since SHH is critical for T lymphocyte development [El Andaloussi et al. (2006). Nat Immunol 7: 418-426], adult human CD4+ T cell activation [Lowrey et al. (2002) J Immunol 169: 1869-1875; Stewart et al. (2002). J Immunol 169: 5451-5457], and myeloid cell maturation in the spleen [Varas et al., (2008) J Leukoc Biol Jun;83(6):1476-83. Epub 2008 Mar 11]. Dysregulation of components of the HH pathway has also been noted in inflammatory diseases of the gut, including Barrett's esophagus, chronic gastritis and IBD [Nielsen et al., (2004) Lab Invest 84: 1631-1642]. Using microarray gene expression analyses of colonoscopic biopsies, we recently demonstrated that GLI1 is downregulated in the intestinal mucosa in inflamed UC compared with non-inflamed samples [Noble et al. (2008) Gut. Oct;57(10):1398-405. Epub 2008 Jun 3]. To further explore the possible association between GLI1 and IBD susceptibility, we examined haplotype variation at the *GLI1* locus in several Northern European populations using a gene-wide haplotype-tagging approach. We identified a significant association with IBD strongly implicating a non-synonymous SNP in the C-terminal region of GLI1. Functional analysis of the associated variant in vitro demonstrated a 50% reduction in GLI1 transcriptional activation, evidence that this may be a functional variant increasing disease risk. These findings together led us to hypothesize that a reduced dosage of functional GLI1 protein might play an important role in colonic inflammation. To test this directly, we challenged *Gli1*+/- mice and their wild type (WT) littermates with dextran sodium sulphate (DSS) to induce acute intestinal inflammation. *Gli1*+/- mice rapidly developed severe colitis, suggesting that functional Gli1 activity is crucial to response to inflammatory stimuli in mouse and man.

Subjects and Samples. Table 10 provides detailed demographics and phenotypic data on Scottish and Cambridge IBD population. (HC – healthy control; CD – Crohn's disease; UC – ulcerative colitis; IC – indeterminate colitis.

Table 10

	Scottish Panel	*Cambridge Panel*
Total number	**2183** **(1374 HC; 474 UC; 335 CD)**	**2337** **(589 HC; 928 UC; 737 CD; 83 IC)**
Sex - % male	HC 48.7%; UC 52.0%; CD 39.6%	HC 45.0%; UC 52.6%; CD 37.0%
Median age at diagnosis/ recruitment -years (IQR)	HC 50.0 (43.0-55.0) UC 34.1 (25.2-49.9) CD 27.8 (20.8-41.1)	HC 60.0 (53.0-69.0) UC 36.7 (26.84-50.35) CD 26.1 (20.3-37.2)
CD location		
Terminal ileum (L1)	38.4%	31.8%
Colon (L2)	36.5%	36.5%
Ileocolon (L3)	25.1%	31.7%
UC location		
Proctitis (E1)	17.3%	14.8%
Left-sided colitis (E2)	40.5%	34.1%
Extensive colitis (E3)	42.2%	51.1%
CD 5 year behaviour		
Inflammatory (B1)	64.8%	52.3%
Stricturing (B2)	14.8%	35.2%
Penetrating (B3)	20.3%	12.5%
Perianal involvement (p)	17.4%	24.4%
Surgery CD	CD 59.3% UC 18.5%	CD 52.0% UC 11.8%
Smoking at diagnosis of CD	YES 40.7% NO 47.4% EX 11.9%	YES 41.8% NO 45.0% EX 13.2%
Smoking at diagnosis of UC	YES 19.0% NO 49.5% EX 31.5%	YES 12.1%

Genotyping. Scotland and Sweden: Genomic DNA was extracted from blood samples using a modified salting-out technique as previously described, and Nucleon kits. Genotypes were derived using the

Taqman system for allelic discrimination; the assays were available from Applied Biosystems as Taqman SNP Genotyping Assays (7900HT sequence detection system; Applied Biosystems), except for SNPs rs10783819, rs3809114, rs507562, rs542278, rs730560, rs1669296, rs775322 which were genotyped on the Illumina platform. The accuracy of each Taqman assay was checked by repeat analysis in 5% of cases, with 100% concordance. Genotype distributions in control populations were consistent with Hardy-Weinberg Equilibrium ($p>0.01$) for all SNPs. Genotypes, in cases for the four tSNPs that could not be derived by Taqman were obtained by direct sequencing. Cambridge: DNA was extracted using Nucleon kits. Genotyping of CD cases and controls was performed using the Taqman biallelic discrimination system using an ABI 7900HT analyser (Applied Biosystems). Genotyping of UC cases was performed using a 1536 SNP Golden Gate bead array (Illumina). Concordance between platforms was assessed by genotyping 92 UC cases for SNPs rs2228224 and rs2228226 with concordance rates of 100% and 97.9% respectively and no evidence of systematic bias between platforms. Genotype distributions in case and control populations were consistent with Hardy-Weinberg Equilibrium ($p>0.01$) for all SNPs.

Gene expression by microarray and QPCR. The cohort of patients used in the microarray studies consisted of 67 patients with UC, 53 with CD and 31 healthy controls (HC). For demographics, generation of microarray dataset and QPCR methodology [see Noble et al. (2008) Gut. Oct;57(10):1398-405. Epub 2008 Jun 3].

Induction of DSS-induced colitis and histological analysis. Groups of two to four wild type *Gli1+/lacZ* or wild type littermate controls in mixed cages (on a C57BL/6 background) were administered 3% DSS in drinking water for 4-6 days. The amount of DSS consumed was not significantly different between WT and *Gli1+/-* animals (data not shown). *Gli1+/-* animals tended to weigh more than their WT littermates (mean = 28g for *Gli1+/-* animals and 24g for WT animals). Therefore, DSS-treated weight matched WT C57Bl/6 animals (n= 4) were also tested along with *Gli1+/-* animals and WT littermates. No differences were evident between WT littermates and weight matched C57Bl/6. All animals were monitored daily for diarrhoea, bloody stool, and weight loss. Clinical scoring was as follows: 0 = no symptoms, 1 = diarrhoea, 2 = bloody stool, 4 = severe rectal bleeding and morbidity to the point of immobility/death. For histology, a segment of large intestine tissue of equal length and location for all animals was fixed overnight in 4% paraformaldehyde, dehydrated, infiltrated with paraffin, and sectioned at 5μm. Slides were stained with hematoxylin/eosin and scored histologically by a gastrointestinal pathologist (HA) blinded to the source of the tissue.

Protein Mutagenesis and Luciferase Assay GLI1 E1100 was amplified from Image Clone #3531657, and cloned into pCMVTag2b. GLI1 Q1100 was obtained by inducing a point mutation using the QuikChange II Site-Directed Mutagenesis Kit (Stratagene) following the manufacturer's protocol. Plasmids encoding 8xGli-Luciferase, m8x Gli-Luciferase (mutated Gli sites) and Gli2ΔN were gifts of

Dr. Andrzej Dlugosz. 293T cells were plated in 12 well plates, transfected with 0.7μg/well transcription factor, 0.4μg/well reporter plasmid, and 2ng/well pRL-TK Renilla (Promega) and analyzed for luciferase expression 36 hours after transfection using the Dual-Luciferase Reporter Kit (Promega) following the manufacturer's protocol. Firefly luciferase expression was normalized by well to Renilla, and fold changes were calculated by comparing to 8xGli-Luciferase transfected alone.

Cytokine Expression QPCR Whole colonic mRNA was collected using Trizol, followed by RNA clean-up with DNase digestion using the RNeasy Mini Kit (Qiagen). cDNA was synthesized using the iScript cDNA synthesis kit (Biorad), and SybrGreen QPCR was performed on a Biorad iCycler machine. Expression levels were normalized to GAPDH, and statistical analysis was performed using the Student's T-test.

Statistical analysis. Haplotype frequencies of the tSNPs were inferred using the expectation-maximization algorithm and these used to test whether haplotype frequencies were different in cases and controls as implemented in the EH and PM programmes. The test statistic 2*(ln(Lcase) + ln(Lcontrol) – ln(Lcase/Lcontrol)), which has a χ^2 distribution with n-1 degrees of freedom (where n = number of possible haplotypes) was calculated and empirical p values obtained by permuting the data 10,000 times. Haplotypes were examined using the Haploview programme v3.2 (www.hapmap.org). Individual SNP analysis was performed using χ^2 or Fisher's exact test, where appropriate, with twotailed p-values given and odds ratios (OR) presented with 95% confidence intervals (C.I.). The meta-analysis of SNP rs2228226 was performed using the Mantel-Haenszel method using a fixed effects model (R-software package). Details for calculation of false positive report probability are provided in supplementary methods. Expression profiles were analysed using Mann-Whitney U test and Kruskal-Wallis test, assuming a non-parametric distribution of all datasets (GraphPad Prism 4, GraphPad Software Inc.).

RESULTS

Gene-wide variation in *GLI1* is associated with IBD and attributable to a nonsynonymous SNP (rs2228226) in the Scottish population

Four multi-marker tagging single nucleotide polymorphisms (tSNPs; $r^2 \geq 0.8$) were identified (rs3817474, rs2228225, rs2228224, and rs2228226) to describe haplotypic variation of *GLI1*, detecting haplotypes of a frequency >1%. We genotyped these 4 tSNPs in a Scottish IBD population consisting of 474 UC and 335 CD cases, and 1364 well-matched healthy controls (Table 10). We then used a model-free analysis [Zhao et al. (2000) Hum Hered 50: 133-139] to test the association of *GLI1* and IBD susceptibility. In the Scottish population, we demonstrate a highly significant association in IBD ($p<0.0001$) and UC ($p<0.0001$), and an association with CD of borderline significance ($p=0.03$). On analysis of individual estimated haplotype frequencies in Haploview, 3 common haplotypes were described (DATA NOT

SHOWN). We confirmed that this effect was confined to the *GLI1* gene by genotyping an additional 7 haplotypetagging SNPs, chosen from Phase II HapMap data, to tag neighbouring blocks, in 166 CD and 170 UC patients. This confirmed the presence of a *GLI1* spanning haplotype block that did not extend into neighbouring genes (*INHBE* and *ARHGAP9*) (DATA NOT SHOWN).

Table 11 shows minor allelic frequencies for GLI1 non-synonymous SNP rs2228226 (tSNP4) in Scottish, English, and Swedish healthy controls (HC), inflammatory bowel disease (IBD), Crohn's disease (CD) and ulcerative colitis (UC).

Table 11

	HC		IBD			UC			CD		
	N	%	N	%	p value OR (C.I.)	N	%	p value OR (C.I.)	N	%	p value OR (C.I.)
Scotland	1374	30.3	884	34.8	0.0026 1.23 (1.07-1.40)	474	33.9	0.042 1.19 (1.01-1.39)	335	36.1	0.0053 1.30 (1.08-1.55)
Cambridge	589	26.4	1737	29.6	0.042 1.17 (1.0-136)	928	30.8	0.017 1.21 (1.03-1.42)	737	27.9	0.40 1.08 (0.90-1.28)
Sweden	281	30.6	493	35	0.27 1.14 (0.90-1.45)	288	34.4	0.43 1.11 (0.90-1.45)	205	35.9	0.24 1.19 (0.90-1.58)

Odds ratios and two-tailed p-values are given for $\chi 2$ analysis of IBD vs. HC, UC vs. HC and CD vs. HC in each of these three populations. Meta-analysis of these data are presented in Figure 1. Frequencies of estimated haplotypes in all three populations and the full genotype data for the Scottish population are detailed in supplementary materials (Supplemental Tables 1 and 2).

The association on haplotype testing and log-likelihood analysis was largely attributable to a non-synonymous SNP in exon 12 of *GLI1* (rs2228226C→G; tSNP4). rs2228226 was associated with IBD (allelic frequency OR=1.23, C.I. 1.07-1.40, p=0.0026; homozygotes OR=1.56, C.I. 1.15-2.11, p=0.0047), CD (allelic frequency OR=1.30, C.I. 1.08-1.55, p=0.0053, homozygotes OR=1.79, C.I. 1.21-2.65, p=0.0048) and UC (allelic frequency OR=1.19, C.I. 1.01-1.39, p=0.04) (Table 11 and DATA NOT SHOWN). These data suggest an allele specific dose response with a greater odds ratio for homozygotes than heterozygote patients. Mutation screening of the *GLI1* coding regions by direct sequencing failed to

identify any novel SNPs. There was no association between 7 additional *GLI1* variants from dbSNP and IBD (DATA NOT SHOWN).

Replication of *GLI1* association in two independent North European IBD cohorts and meta-analysis. We then sought to replicate these findings in other populations. In a large IBD panel from Cambridge, England (n=928 UC, 737 CD, 83 indeterminate colitis and 589 HC) association with *GLI1* was replicated by log-likelihood analysis in IBD (p=0.009) and UC (p<0.0001). rs2228226 was associated with IBD (OR 1.17, C.I. 1.00-1.36, p=0.042) and UC (OR 1.21, C.I. 1.03-1.42, p=0.017) but not CD in this population (Table 11). As in Scotland, there was no association with tSNPs1-3 (DATA NOT SHOWN). In the smaller Swedish cohort (n=770), there was a non-significant trend to association of rs2228226 with IBD (OR 1.14, C.I. 0.90-1.45) (Table 11).

Figure 104 shows a meta-analysis, using the Mantel-Haenszel method with a fixed effects model on the IBD cases and healthy controls in Scotland, England and Sweden confirmed the association with rs2228226 (OR 1.194, C.I. 1.089-1.309, p=0.0002). The meta-analysis is of non-synonymous *GLI1* SNP rs2228226 (tSNP4) in Scotland, Cambridge and Sweden using Mantel-Haenszel method (n=5352 individuals). There was no evidence of heterogeneity in the contribution of rs2228226 between the 3 cohorts (p=0.825). Recognising the current problem with the publication of false positive findings in genetic association studies we estimated the probability that the association with disease risk found in the meta-analysis of *GLI1* SNP rs2228226 represents a true (rather than false positive) association by adopting the false positive report probability (FPRP) approach described by Wacholder et al. (2004) J Natl Cancer Inst 96: 434-442. This gives an estimated probability that these findings represent a true finding of at least 92% (FPRP < 0.08). This method is designed to avoid overinterpretation of statistically significant findings that are not likely to signify a true positive but in our study gives clear support to our interpretation of these data.

The GLI1 variant encoded by rs2228226 is functionally deficient in activating GLI-responsive transcription in vitro rs2228226C→G is a mis-sense mutation in exon 12 of *GLI1*, encoding a change from glutamine to glutamic acid (Q1100E).

Figure 105 shows Q1100E disrupts a conserved region of the GLI1 protein and reduces GLI1 transcriptional activity. A) Conservation of known functional domains in the Gli1 protein. Previously described Sufu binding, DNA binding, and transactivation domains [Yoon et al. (1998) J Biol Chem 273: 3496-3501; 27 Kinzler et al. (1988) Nature 332:371-374; Kogerman et al. (1999) Nat Cell Biol 1: 312-319] are shown schematically. Amino acid conservation of each domain is represented numerically and by shading of the bar below the domain. Red boxes indicate regions known to regulate GLI1 protein stability [Huntzicker et al. (2006) Genes Dev 20: 276-281]. The conserved C-terminal domain that includes Q1100E is adjacent to a known transactivation domain. B) Alignment of the C-terminus of

mammalian Gli1 proteins. This region (AA 1080-1106) is highly conserved in mammalian lineages. C, D) GLI1 Q1100 and E1100 have similar cellular localization in 293T cells. E) GLI1 E1100 is deficient in driving activation of the 8xGli-Luciferase reporter compared to GLI1 Q1100. Gli2ΔN is a strong activator of 8xGli-Luciferase and serves as a positive control for GLI1 activation. The m8xGli-Luciferase construct contains only mutant Gli binding sites and serves as a negative control. Data shown from 6 triplicate experiments done using two different plasmid preparations (N=18).

The mutation falls within a well conserved motif at the C-terminus of mammalian GLI1 proteins, near a recognized transactivation domain (Figure 105a) [Yoon et al. (1998) J Biol Chem 273: 3496-3501]. The Q1100 residue is itself 100% conserved in all mammals examined (Figure 105b). In order to evaluate the functional consequences of the Q1100E mutation, we transfected either GLI1 Q1100 or the variant GLI1 E1100 into 293T cells. No differences in level of expression or cellular localization were detected between these GLI1 variants; both proteins were readily detectable in the nucleus of transfected cells (Figure 105c-d). We further evaluated the ability of each variant to activate the well-characterized GLI reporter 8xGli-Luciferase [Saitsu et al. (2005) Dev Dyn 232: 282-292]. We utilized GliΔ2N, a very strong activator of 8xGli-Luciferase, as a positive control for GLI1 transcriptional activity [Roessler et al. (2005) Hum Mol Genet 14: 2181-2188]. While both GLI1 variants activated 8xGli-Luciferase above baseline, WT GLI1 Q1100 was two-fold more efficient as a transcriptional activator than the variant GLI1 E1100 (Figure 105e).

Hedgehog pathway activity is dysregulated in colonic inflammation. We have previously reported that GLI1 expression is greater in the distal compared with the proximal colon in man [Noble et al. (2008) Gut. Oct;57(10):1398-405. Epub 2008 Jun 3].

Figure 106 shows expression of hedgehog (HH) signalling components in the healthy human adult colon (HC) and ulcerative colitis (UC). A) Patched (PTCH), Hedgehog-interacting protein (HHIP), and GLI1 mRNA levels increase along the length of the healthy adult colon, from ascending colon (AC) to descending colon (DC) and sigmoid colon (SC). **B)** HH protein expression in terminally differentiated enterocytes at the luminal surface, is greater in the distal colon compared with the proximal. **C)** Quantitative analysis of mRNA levels of Indian hedgehog (IHH), PTCH, GLI1, and HHIP in UC compared with non-inflamed HC. To account for the gradients identified along the length of the healthy colon (**a-b**), the data from SC only are shown. QPCR data is presented for IHH as this gene was not present on the Agilent microarray chip. Disease specimens are sub-categorised into non-inflamed (N-I) and inflamed (I) tissues. There was no change in levels of DHH, PTCH2, GLI2, GLI3, SUFU or DISP1 in either UC or CD compared with HC, or in non-IBD inflammation (data not shown). Analysis of SHH mRNA demonstrated a mild increase in expression levels related to inflammation that is consistent with the known expression of SHH in inflammatory cells (data not shown) [Lowrey et al. (2002) J Immunol 169: 1869-1875].

Individual data points are plotted with horizontal lines representing the medians for each dataset. P-values presented are derived from Kruskal-Wallis test, comparing levels in AC, DC and SC, and from Mann-Whitney U-tests (UC vs. HC (N-I)).

Extended in silico analysis of this microarray dataset now demonstrates that mRNA transcripts of PTCH and HHIP, along with HH protein, mirror this expression gradient (Figure 106a-b). GLI1, PTCH and HHIP are pathway response elements whose expression levels predict pathway activity. GLI1 ($p=0.0003$), PTCH ($p=0.002$), and HHIP ($p=0.0003$) were lower in inflamed UC compared with HC from equivalent location (Figure 106c). IHH was lower in UC regardless of inflammation ($p=0.02$). GLI1 expression was lower in CD than HC ($p=0.004$) irrespective of inflammatory status (DATA NOT SHOWN), a noteworthy finding given that *GLI1* variation was also associated with CD in Scotland. PTCH was lower in inflamed CD compared with non-inflamed CD and HC ($p=0.007$). GLI1 and PTCH were both lower in non-IBD inflammation versus HC (DATA NOT SHOWN). These data demonstrate overall down-regulation of HH pathway activity, including GLI1, PTCH, and HHIP, in areas of colonic inflammation.

Gli1+/- animals exhibit mortality and heightened morbidity in response to intestinal inflammation induced by 3% DSS treatment. In vitro analysis of the GLI1 1100E variant demonstrated a 50% deficiency in transactivation function compared to WT GLI1, and our genetic analysis demonstrates an allele-specific dosage response, suggesting that a moderate reduction in GLI1 function was sufficient to predispose to intestinal inflammatory disease. To specifically test this hypothesis, we treated *Gli1*+/- mice [Park et al. (2000) Development 127: 1593-1605], and their WT littermates with 3% DSS for 6 days to induce acute intestinal inflammation. *Gli1*+/- animals were rapidly and severely affected by DSS treatment.

Figure 107 shows the results in which *Gli1*+/- animals show mortality, severe clinical symptoms, and profound weight loss after DSS treatment. A) WT animals are 100% viable over the 6 day treatment period (N=14). Nearly 50% of *Gli1*+/- animals (4/9) die in response to 3% DSS treatment for 6 days. **B)** *Gli1*+/- animals display markedly more severe symptoms than WT animals after 4 or 6 days of 3% DSS treatment. 1=diarrhoea, 2=bloody diarrhoea, 4=severe bleeding/death. Each dot represents an individual animal and the solid line shows the mean observation in each cohort. **C)** *Gli1*+/- animals (N=9) have lose weight more rapidly than their WT littermates (N=10). * = $p < 0.05$

After 6 days, 4/9 had died, and 3 of the survivors demonstrated severe morbidity, with significant rectal bleeding and almost complete immobility (Figure 107a). In contrast, no WT animals (N=14) died, all were mobile and showed less morbidity on days 5 and 6 after treatment. *Gli1*+/- animals developed bloody diarrhoea and significant weight loss by day 4, whereas WT animals did not develop clinical signs or measurable weight loss until day 6 (Figure 107b-c).

Gli1+/- animals develop more severe colonic pathology than WT littermates in response to DSS treatment. We examined colonic tissue from *Gli1*+/- and WT animals taken after 4 and 6 days of DSS treatment. *Gli1*+/- animals developed severe tissue lesions more rapidly than WT.

Figure 108 shows *Gli1*+/- animals demonstrate more severe intestinal inflammation than WT littermates in response to DSS treatment. A) WT animals (N=4) exhibit mild colonic inflammation but do not develop substantial epithelial or ulcerative inflammatory pathology within 4 days of DSS treatment. **B)** *Gli1*+/- animals (N=4) develop significant inflammatory infiltration, epithelial damage, and ulceration within 4 days of DSS treatment. **C-D)** *Gli1*+/- animals develop profound intestinal inflammation in response to 3% DSS treatment, with severe epithelial damage in long stretches of their colonic mucosa (N=9). **E)** Blinded histological scoring of colonic damage after 6 days of DSS treatment. Standard lengths of tissue from the mid colon and distal descending colon were scored in each animal. *Gli1*+/- animals (N=6) have more overall inflammatory foci and more long foci (10+ crypt units affected) than WT animals (N=6). Each dot represents the number of observed foci in an individual animal; the solid line shows the mean observation in each cohort. Red dots indicate the animals that were analyzed for cytokine expression. **F)** Resident mucosal myeloid cells respond directly to Hh signalling and express LacZ in the homeostatic colon of *Gli1*+/- animals. Arrows indicate cells with LacZ-positive nuclei and Cd11b membranes.

After 4 days, WT colons showed evidence of inflammatory change but with few destructive lesions Figure 108a), while extensive inflammatory infiltration and destructive colonic ulcers were prominent in *Gli1*+/- mice (Figure 108b). After 6 days, inflammation in surviving *Gli1*+/- animals was markedly more severe. The number (Figure 108e), size and invasiveness of inflammatory lesions (Figure 108c-e) were significantly greater in *Gli1*+/- animals. Taken together, these results demonstrate that the loss of a single *Gli1* allele leads to increased sensitivity to DSS treatment as reflected by severe intestinal inflammatory pathology and obvious clinical signs.

Intestinal myeloid cells respond directly to HH signals. We have demonstrated that HH signalling is exclusively paracrine in murine intestine and colon [Madison et al. (2005) Development 132: 279-28914]. Here we confirm that Gli1 is expressed in inflammatory cells in mouse, utilizing *Gli1*+/lacZ animals, which allow Hh-responsive cells to be easily visualized [Park et al. (2000) Development 127: 1593-1605]. In resting adult colon, lamina propria resident CD11b-positive myeloid cells express LacZ and are therefore responding directly to Hh signals (Figure 108e).

Gli1+/- animals have increased IL-23p19 and pro-inflammatory cytokine expression.

Figure 109 shows cytokine analysis of *Gli1*+/- and WT mice after DSS treatments demonstrates robust pro-inflammatory cytokine activation. A) Cytokine expression in WT and *Gli1*+/- animals (N=4) after 6

days of 3% DSS treatment. Cytokine expression normalized to GAPDH is plotted on the Y-axis for *Gli1*+/- mice, and on the X-axis for WT animals. Gene expression levels that are changed in a statistically significant manner are shown with stars. The dotted diagonal trendline indicates identical expression levels between WT and *Gli1*+/-mice. **B)** Table showing the average cytokine expression, standard deviation, and fold change in *Gli1*+/- animals compared to WT controls (* = $p<0.05$). Several pro-inflammatory cytokines are upregulated in *Gli1*+/- animals, but anti-inflammatory cytokines are largely unchanged.

QPCR examination of cytokine expression on whole colonic tissue taken after 6 days of DSS confirms the histological and clinical data; *Gli1*+/- animals demonstrate very significant inflammation compared to WT (Figure 109). We detect robust expression of TH1 cytokines, including IFNγ, in *Gli1*+/- animals, not surprising given the severity of the inflammation in these animals and the prominence of TH1 cells in DSS-induced colitis. We did not detect a significant difference in TGFβ and IL-10 between *Gli1*+/- and WT animals, suggesting that down-regulation of anti-inflammatory cytokines was not the primary mechanism of increased inflammation in this model. The most highly expressed cytokine in *Gli1*+/- animals was IL-23p19, which is known to drive differentiation of TH17 lymphocytes, key mediators of inflammation in several systems, including IBD [Hue et al. (2006) J Exp Med 203: 2473-2483; Yen et al. (2006) J Clin Invest 116: 1310-1316]. IL-12 and IL-17, cytokines closely associated with IL-23, were also upregulated in *Gli1*+/- animals. These data are particularly significant since the IL-23 pathway has recently been strongly implicated in IBD pathogenesis both in humans [Duerr et al. (2006) Science 314: 1461-1463] and mice [Yen et al. (2006) J Clin Invest 116: 1310-1316]. Our data provide a potential link between this key inflammatory pathway and the robust inflammation seen with reduced GLI1 dosage or function.

DISCUSSION

The data presented here provide the first evidence that intact HH signalling is critical in the mammalian gut response to inflammatory challenge, and that reduced GLI1 function is implicated in IBD pathogenesis. We confirm that the HH signaling pathway is downregulated in colonic inflammation in man. We identify a specific *GLI1* variant that is highly associated with UC/IBD, and demonstrate that the variant protein is functionally deficient as a transcriptional activator in vitro. Finally, we demonstrate that a 50% reduction in murine *Gli1* results in a heightened intestinal inflammatory response to DSS with significant upregulation of the IL-23 pathway. Not only do these findings have clear implications for the understanding of IBD pathogenesis with potential for therapeutic intervention, they are the first clear description of a functional role for HH signalling and GLI1 in bowel inflammation. The inherited variation in the *GLI1* gene that we have detected is associated with IBD and UC, in both Scotland and England, with findings for rs2228226 confirmed by meta-analysis of over 5000 individuals, with odds ratio of 1.19. Evidence for an effect in CD is seen in the present study, but the predominant effect is

clearly related to UC. The magnitude of this association is entirely in line with the effect size noted in a number of recent studies of complex disease genetics, including CD, colo-rectal cancer [Tenesa et al. (2008) Nat Genet 40: 631-637], and coeliac disease [Hunt et al. (2008) Nat Genet 40: 395-402]. The level of significance attained satisfies suggested criteria of $p < 10^{-4}$ - 10^{-6} for gene-centric studies [Burton et al. (2007) Nat Genet 39: 1329-1337; Thomas et al. (2004) J Natl Cancer Inst 96: 421-423]. The three Northern European populations studied have previously demonstrated similar contribution of other IBD susceptibility genes / loci, including NOD2 and IBD5 [Gaya et al. (2006) Lancet 367: 1271-1284]. Whilst the minor allelic frequencies for this SNP are very similar in Scotland and Sweden (30.3% and 30.6%), they differ by 3.9% between Scotland and Cambridge (30.3% and 26.4%). This difference is in keeping with that noted for a number of SNPs analysed for population stratification in the recent WTCCC study [Wellcome Trust Case Control Consortium (2007) Nature 447: 661-678]. Whilst our resequencing efforts identify rs2228226 as the only coding variant associated with IBD, the haplotype analysis and log-likelihood analyses raise the possibility that other germ-line variants may also contribute to IBD risk. These need be explored formally – specifically the role of intronic variants, long-range promoter effects and / or copy number variation. In this context, several complex disease genes, including NOD2 [Hugot et al. (2001). Nature 411: 599-603; Ogura Y et al. (2001). Nature 411: 603-606], have multiple independent mutations conferring disease risk, some disease genes have no causative mutations within coding sequences (e.g. *IRGM* in CD [Parkes et al. Am J Hum Genet. 2000;67:1605-16105]), and synonymous SNPs may be associated with functional effects [Kimchi-Sarfaty et al. (2007) Science 315: 525-528]. rs2228226C→G encodes a change from glutamine to glutamic acid (Q1100E). Our in vitro data demonstrates that GLI1 1100E is a subfunctional transcriptional activator compared to WT GLI1, though it is synthesized and localized appropriately. The Q1100E mutation causes a significant charge change in a conserved region directly adjacent to the known transactivation region of GLI1; this change could directly modify transactivation activity, disrupt the structure of the transactivation domain, or affect protein stabilization [Huntzicker et al. (2006) Genes Dev 20: 276-281] decreasing activity. Our data suggest that reductions in GLI1 activity or amount also produce a robust phenotype. *Gli1+/-* animals, which have only 50% of the WT level of Gli1, develop severe inflammation rapidly in response to moderate stimuli. These data, to our knowledge the first description of a phenotype for reduced Gli1 function [Park et al. (2000) Development 127: 1593-1605], demonstrate the key role that a full complement of Hh response plays in protection from inflammatory disease. In addition, our in vitro data demonstrates that GLI1 E1100 is capable of activating some Gli response, suggesting that under homeostatic conditions, GLI1 E1100 could perform adequately. Similar to the situation in *Gli1+/-* animals, however, under conditions of inflammatory stress, GLI1 E1100 can only function at 50% of the level of WT GLI1. Whether the predisposition to inflammation in these systems is a direct result of lowered HH signal transduction within inflammatory cells or reflects the effect of lower HH signals on stromal target cells that, in turn, release signals that impact the integrity of the epithelial layer is not yet clear. Addressing this question will be a key avenue of future investigation. We have shown that the HH

pathway may directly modify the innate immune response through signalling to myeloid target cells. This finding is in accordance with recent data demonstrating a crucial role for Hh signalling in myeloid cell maturation in the spleen [Varas et al., (2008) J Leukoc Biol Jun;83(6):1476-83. Epub 2008 Mar 1123]. Interestingly, myeloid cell populations can differentially modify the intestinal inflammatory milieu through a significant impact on the IL-23/IL-17 pathway [Denning et al. (2007) Nat Immunol 8: 1086-1094]. Together, our findings demonstrating direct HH response by innate immune populations and increased IL-23 after DSS treatment in Gli1+/- animals suggest that HH signalling may normally promote a tolerogenic phenotype in mucosal myeloid cells; reduced HH signal transduction may instead trigger an inflammatory response in these cells.

In conclusion, we demonstrate here for the first time the altered expression of a developmental signalling pathway in IBD, opening up novel lines of investigation. Furthermore, we show that these effects are in part genetically determined, with evidence implicating *GLI1* as an IBD2 gene, and identification of a specific variant with reduced transcriptional activity. The functional relevance of Gli1 is demonstrated by the severe intestinal inflammation that develops in the face of a 50% reduction in Gli1 concentration in an established mouse model of colitis. Taken together, these data strongly argue for the importance of a robust HH pathway activation in the protective response of the intestinal mucosa to inflammatory stimuli. These findings have important implications for the pathogenesis of UC and potentially for other forms of chronic inflammation. [Lees et al. (2006) Gastroenterology 131: 1657-1658].

Example 5 – IBD gene expression profiles from whole blood samples

Genome wide expression profiles from human endoscopic colonic biopsies have started to help dissect out the pathogenic inflammatory pathways at the cellular level in IBD (Noble CL et al . Gut, 2008 Jun 3. [Epub ahead of print]). Whole blood genome wide expression profiles may complement conventional endoscopic techniques to help in the diagnosis of IBD- Crohn's disease (CD) and ulcerative colitis (UC). The aim of this study was to investigate whole blood gene expression profiles to try to differentiate patients with IBD- CD, UC, and controls (HC).

Patients. 21 UC, 19 CD, and 10 controls (HC) were studied. 2 of the UC patients were newly diagnosed, 15 had quiescent disease and 4 had active disease. In CD 1 new diagnosis, 11 quiescent disease and 7 active disease patients were investigated.

Methods. 41058 expression sequence tags (representing 33296 genes) were analyzed in 50 whole blood samples using the Agilent platform. Total RNA was extracted from the blood using the micro total RNA isolation from animal tissues protocol (*Qiagen, Valencia, CA*). A T7 RNA polymerase single round of linear amplification was carried out to incorporate Cyanine-3 and Cyanine-5 label into cRNA. The samples were hybridized for 18 hours at 60°C with constant rotation. Microarrays were washed, dried

and scanned on the Agilent scanner according to the manufacturer's protocol. Microarray image files were analysed using Agilent's Feature Extraction software version 7.5. The genes were normalized using the *Stratagene* Universal Human Reference.

Using clustering analysis with all the IBD and HC patients, and probes that had a > or < than 1.5 fold change in expression, HC patients were more prevalent on one side of the dendrogram 1/21 v 9/29 ($p=0.02$ OR 1.8) (data not shown). No difference was observed in the distribution of the CD and UC samples. When all of the IBD samples were compared to controls 493 sequences had a fold change of greater than 1.5 ($1.7x10\text{-}41<p<0.01$) and 595 sequences had a fold change of less than 1.5 ($4.0x10^{-40}<p<0.01$). When CD and UC were compared, 293 sequences had a fold change of greater than 1.5 ($5.4x10^{-27}<p<0.01$) and 301 sequences had a fold change of less than 1.5 ($5.2x10^{-18}<p<0.01$).

By using a panel of 10 of the up regulated and down regulated genes sequences we were able to predict with a >90% sensitivity IBD samples from controls. Table 12 below lists 20 differentially regulated genes in IBD when compared to controls.

Table 12

Sequence Name	Sequence Code	Fold Change	P-value
LOC342959 (AARDC5)	A_32_P30271	4.92527	8.62E-18
A_24_P910246 (ATXN3L)	A_24_P910246	2.92405	1.41E-07
LOC92552 (FSHR)	A_23_P361744	2.78494	4.12E-13
PDGFRA	A_23_P332536	2.7178	0.00004
TGFB3	A_24_P373096	2.67234	5.89E-09
KCTD8	A_23_P94902	2.65574	0.00005
TGM4	A_23_P41241	2.64262	0.0005
NYD-SP25	A_24_P309216	2.62905	7.76E-15
FLJ33651	A_24_P306032	2.62873	0.0034
EMX2OS	A_24_P892472	2.55683	0.00029
WNT16	A_23_P134601	-2.96773	3.46E-10
SPRED2	A_24_P315535	-2.97751	3.12E-16
MGC50721 (C16orf65)	A_23_P412508	-3.06148	0.0088
C12orf2	A_24_P78556	-3.17916	0.0129
MPDZ	A_23_P396328	-3.19437	1.87E-40
FARS2	A_24_P456422	-3.35391	0.00097
CASP8	A_24_P157087	-3.41412	3.90E-09
NT5E	A_24_P316430	-3.63046	0
TDGF3	A_24_P179646	-3.71928	7.31E-23

BTNL3	A_23_P158297	-5.22514	2.09E-12

Whole blood genome wide expression signature provides a starting point for differentiating between patients with IBD and controls and this may provide complimentary diagnostic evidence of the diagnosis of IBD.

5

WHAT IS CLAIMED:

1. A method of diagnosing the presence of an inflammatory bowel disease (IBD) in a mammalian subject, comprising determining that the level of expression of a nucleic acid encoding a polypeptide shown as any one of SEQ ID NOS: 2, 4, 6, 8, 10, 12, 14, 16, 18, 20, 22, 24, 26, 28, 30, 32, 34, 36, 38, 40, 42, 44, 46, 48, 50, 52, 54, 56, 58, 60, 62, 64, 66, 68, 70, 72, 74, 76, 78, 80, 82, 84, 86, 88, 90, 92, 94, 96, 98, 100, 102, 104, 106, 110, 112, 114, 116, 118, 120, 122, 124, 126, 128, 130, 132, 134, 136, 138, 140, 142, 144, 146, 148, 150, 152, 154, 156, 158, 160, 162, 164, 166, 168, 170, 172, 194, 197, 199, 201, 203, 205, 207, and 230 in a test sample obtained from said subject is higher relative to the level of expression in a control, wherein said higher level of expression is indicative of the presence of an IBD in the subject from which the test sample was obtained.

2. A method of diagnosing the presence of an inflammatory bowel disease (IBD) in a mammalian subject, comprising determining that the level of expression of a nucleic acid encoding a polypeptide shown as any one of SEQ ID NOS: 108, 174, 176, 178, 180, 182, 184, 186, 188, 190, 192, 211, 213, 215, 217, 219, 221, 223, 225, and 228, in a test sample obtained from said subject is lower relative to the level of expression in a control, wherein said lower level of expression is indicative of the presence of an IBD in the subject from which the test sample was obtained.

3. The method of claim 1 or 2 wherein said mammalian subject is a human patient.

4. The method of claim 3 wherein evidence of said expression level is obtained by a method of gene expression profiling.

5. The method of claim 3 wherein said method is a PCR-based method.

6. The method of claim 4 wherein said expression levels are normalized relative to the expression levels of one or more reference genes, or their expression products.

7. The method of claim 1 or 2 comprising determining evidence of the expression levels of at least two of said genes, or their expression products.

8. The method of claim 1 or 2 comprising determining evidence of the expression levels of at least three of said genes, or their expression products.

9. The method of claim 1 or 2 comprising determining evidence of the expression levels of at least four of said genes, or their expression products.

10. The method of claim 1 or 2 comprising determining evidence of the expression levels of at least five of said genes, or their expression products.

11. The method of claim 1 or 2 further comprising the step of creating a report summarizing said IBD detection.

12. The method of claim 1 or 2, wherein said IBD is ulcerative colitis.

13. The method of claim 1 or 2, wherein said IBD is Crohn's disease.

14. The method of claim 1 or 2, wherein said IBD is ulcerative colitis and Crohn's disease.

15. The method of claim 1 or 2, wherein said test sample is from a colonic tissue biopsy.

16. The method of claim 15, wherein said biopsy is from a tissue selected from the group consisting of the terminal ileum, the ascending colon, the descending colon, and the sigmoid colon.

17. The method of claim 15, wherein said biopsy is from an inflamed colonic area.

18. The method of claim 15, wherein said biopsy is from a non-inflamed colonic area.

19. The method of claim 1 or 2, wherein said determining step is indicative of a recurrence of an IBD in said mammalian subject, and wherein said mammalian subject was previously diagnosed with an IBD and treated for said previously diagnosed IBD.

20. The method of claim 19, wherein said treatment comprised surgery.

21. The method of claim 1 or 2, wherein said determining step is indicative of a flare-up of said IBD in said mammalian subject.

22. A method of treating an inflammatory bowel disorder (IBD) in a mammalian subject in need thereof, the method comprising the steps of

(a) determining that the level of expression of a nucleic acid encoding a polypeptide shown as any one of SEQ ID NOS: 2, 4, 6, 8, 10, 12, 14, 16, 18, 20, 22, 24, 26, 28, 30, 32, 34, 36, 38, 40, 42, 44, 46, 48, 50, 52, 54, 56, 58, 60, 62, 64, 66, 68, 70, 72, 74, 76, 78, 80, 82, 84, 86, 88, 90, 92, 94, 96, 98, 100, 102, 104, 106, 110, 112, 114, 116, 118, 120, 122, 124, 126, 128, 130, 132, 134, 136, 138, 140, 142, 144, 146, 148, 150, 152, 154, 156, 158, 160, 162, 164, 166, 168, 170, 172, 194, 197, 199, 201, 203, 205, 207, and 230 in a test sample obtained from said subject is higher relative to the level of expression in a control, wherein said higher level of expression is indicative of the presence of an IBD in the subject from which the test sample was obtained; and

(b) administering to said subject an effective amount of an IBD therapeutic agent.

23. A method of treating an inflammatory bowel disorder (IBD) in a mammalian subject in need thereof, the method comprising the steps of

(a) determining that the level of expression of a nucleic acid encoding a polypeptide shown as any one of SEQ ID NOS: 108, 174, 176, 178, 180, 182, 184, 186, 188, 190, 192, 211, 213, 215, 217, 219, 221, 223, 225, and 228, in a test sample obtained from said subject is lower relative to the level of expression in a control, wherein said lower level of expression is indicative of the presence of an IBD in the subject from which the test sample was obtained; and

(b) administering to said subject an effective amount of an IBD therapeutic agent.

24. The method of claim 22 or 23 wherein said mammalian subject is a human patient.

25. The method of claim 24 wherein evidence of said expression level is obtained by a method of gene expression profiling.

26. The method of claim 24 wherein said method is a PCR-based method.

27. The method of claim 25 wherein said expression levels are normalized relative to the expression levels of one or more reference genes, or their expression products.

28. The method of claim 22 or 23 comprising determining evidence of the expression levels of at least two of said genes, or their expression products.

29. The method of claim 22 or 23 comprising determining evidence of the expression levels of at least three of said genes, or their expression products.

30. The method of claim 22 or 23 comprising determining evidence of the expression levels of at least four of said genes, or their expression products.

31. The method of claim 22 or 23 comprising determining evidence of the expression levels of at least five of said genes, or their expression products.

32. The method of claim 22 or 23 further comprising the step of creating a report summarizing said IBD detection.

33. The method of claim 22 or 23, wherein said IBD is ulcerative colitis.

34. The method of claim 22 or 23, wherein said IBD is Crohn's disease.

35. The method of claim 22 or 23, wherein said IBD is ulcerative colitis and Crohn's disease.

36. The method of claim 22 or 23, wherein said test sample is from a colonic tissue biopsy.

37. The method of claim 36, wherein said biopsy is from a tissue selected from the group consisting of the terminal ileum, the ascending colon, the descending colon, and the sigmoid colon.

38. The method of claim 36, wherein said biopsy is from an inflamed colonic area.

39. The method of claim 36, wherein said biopsy is from a non-inflamed colonic area.

40. The method of claim 22 or 23, wherein said determining step is indicative of a recurrence of an IBD in said mammalian subject, and wherein said mammalian subject was previously diagnosed with an IBD and treated for said previously diagnosed IBD.

41. The method of claim 40, wherein said treatment comprised surgery.

42. The method of claim 22 or 23, wherein said determining step is indicative of a flare-up of said IBD in said mammalian subject.

43. The method of claim 22 or 23, wherein said IBD therapeutic agent is an aminosalicylate.

44. The method of claim 22 or 23, wherein said IBD therapeutic agent is a corticosteroid.

45. The method of claim 22 or 23, wherein said IBD therapeutic agent is an immunosuppressive agent.

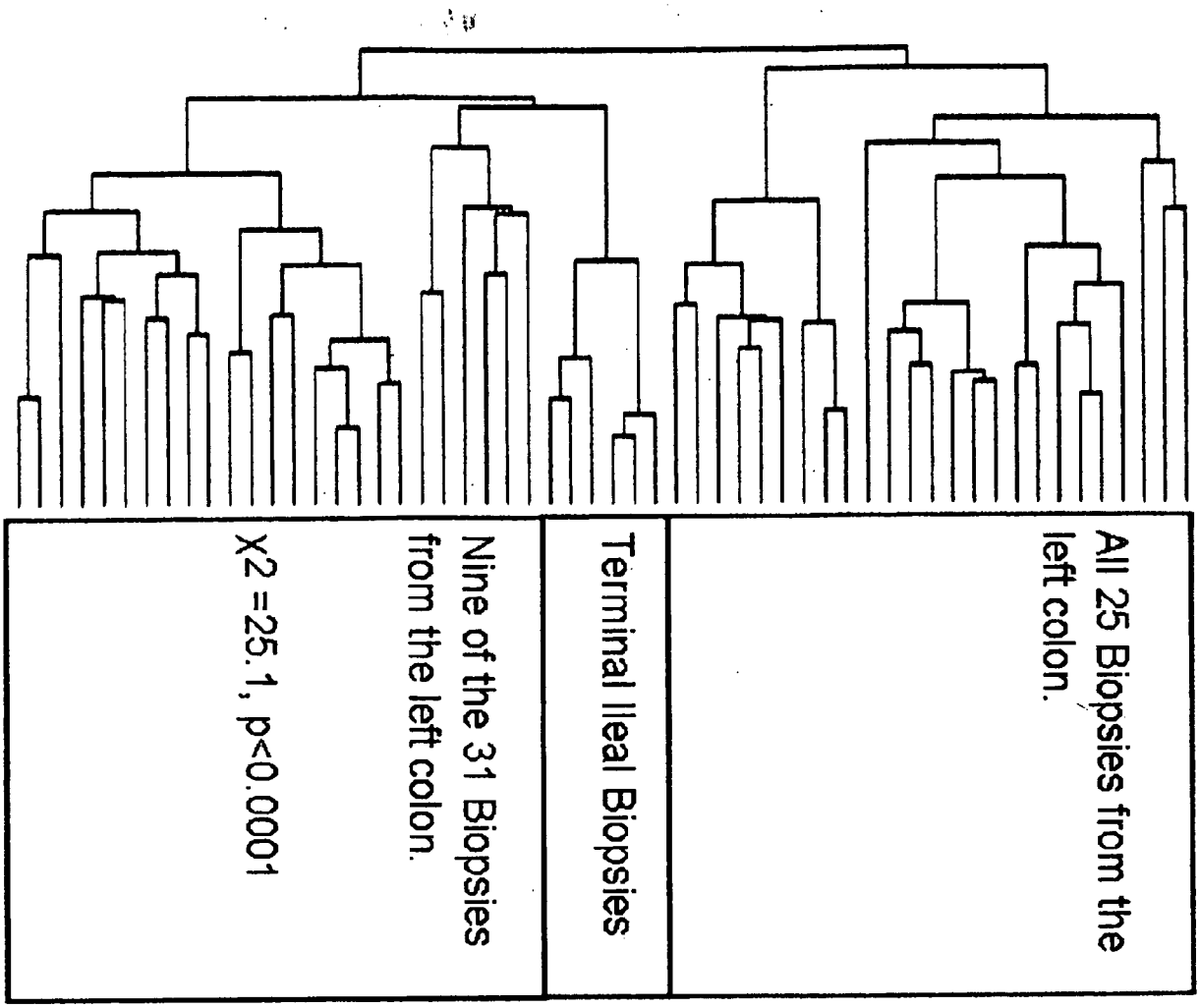


Figure 1: Unsupervised hierarchical clustering of healthy control biopsies showing the location of biopsy retrieval.

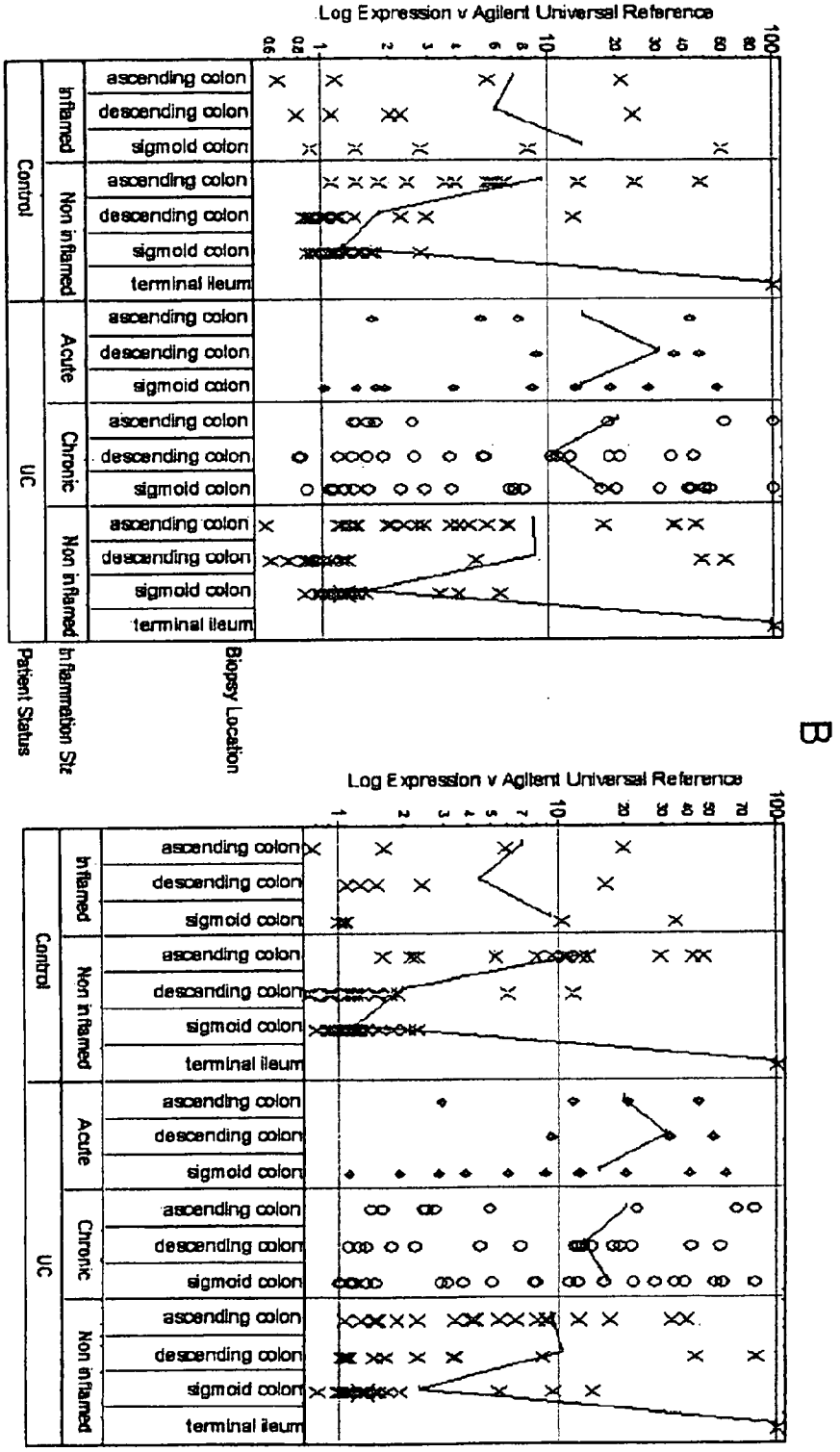


Figure 2: Expression of defensins alpha 5 and 6 in ulcerative colitis patients and controls

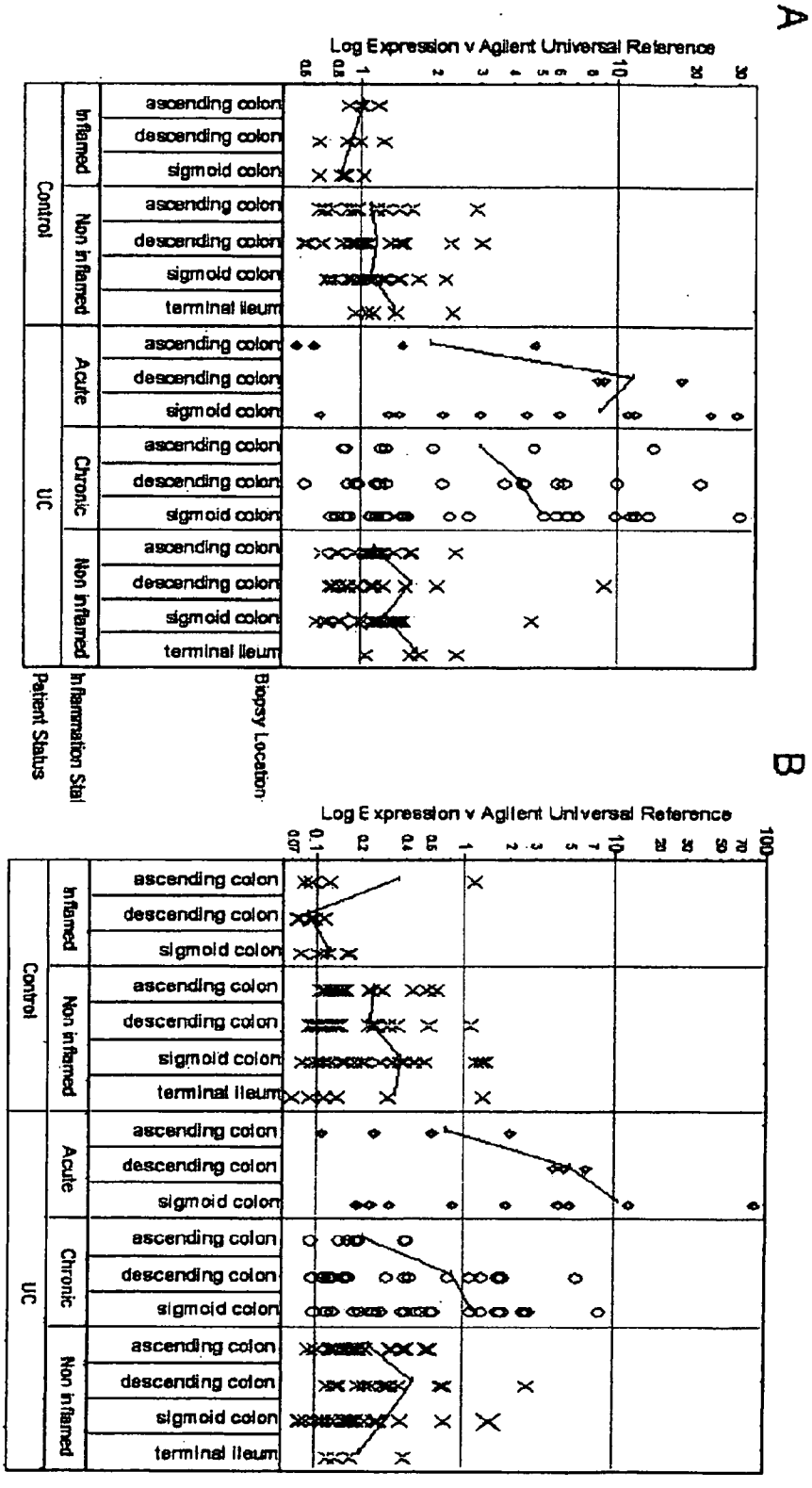


Figure 3: Expression of the matrix metalloproteinases (MMP's) 3 and 7 in ulcerative colitis patients and controls

Figure 4: Real time PCR expression of SAA1, IL-8 defensin alpha 5 and defensin alpha 6 in control and ulcerative colitis inflamed and non-inflamed sigmoid colon biopsies.

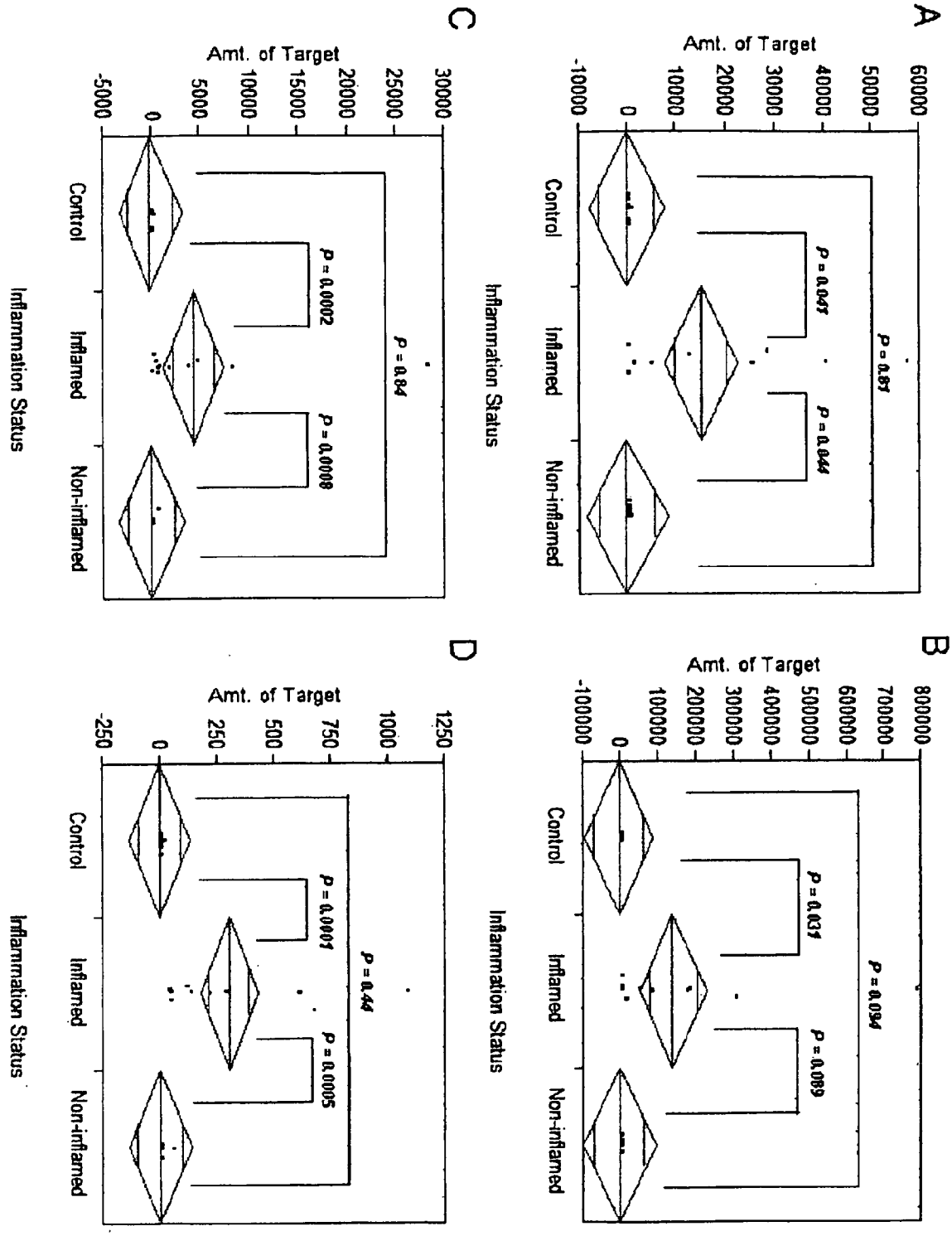
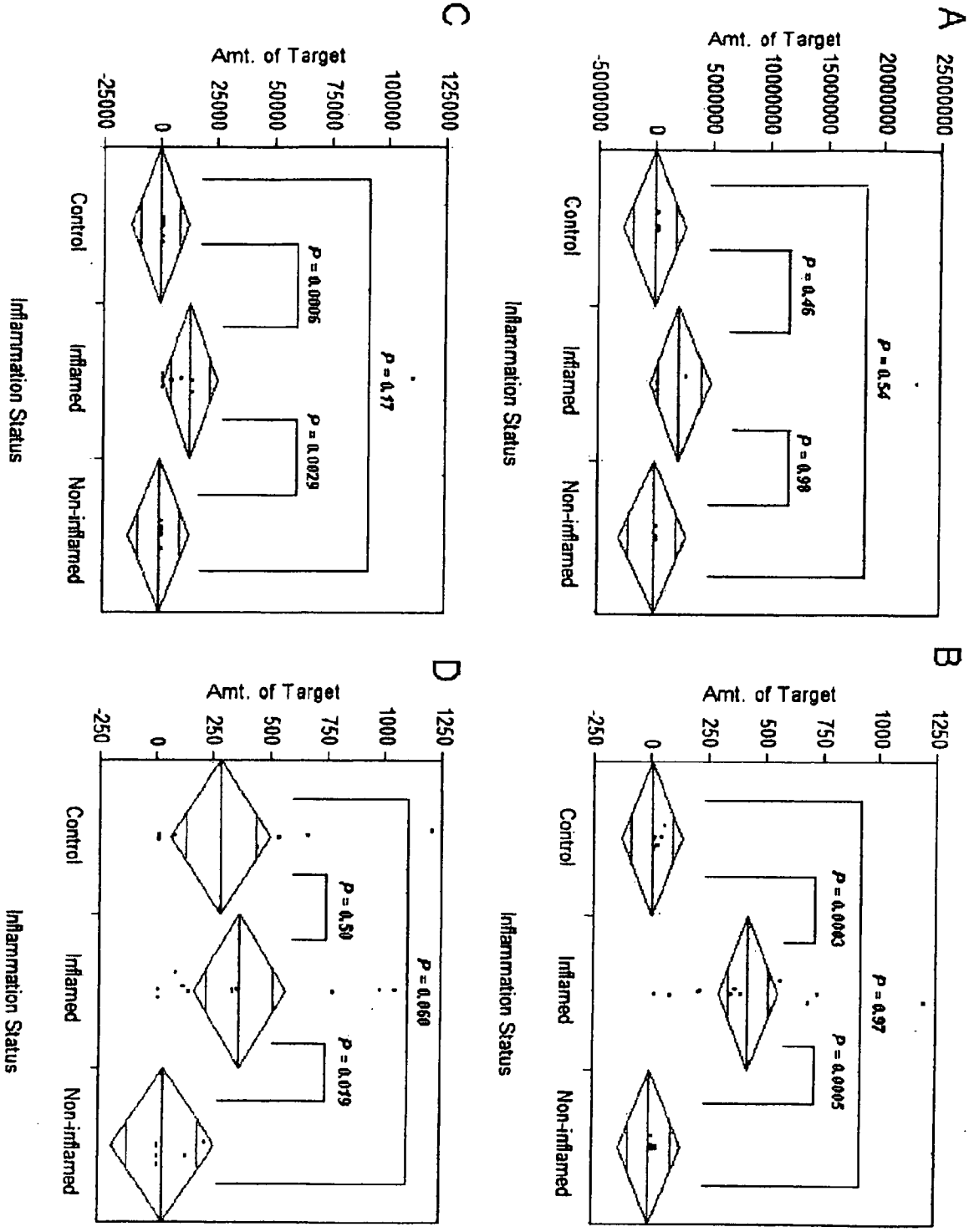


Figure 5: Real time PCR expression of MMP3, MMP7, S100A8 and TLR4 in control and ulcerative colitis inflamed and non- inflamed sigmoid colon biopsies.



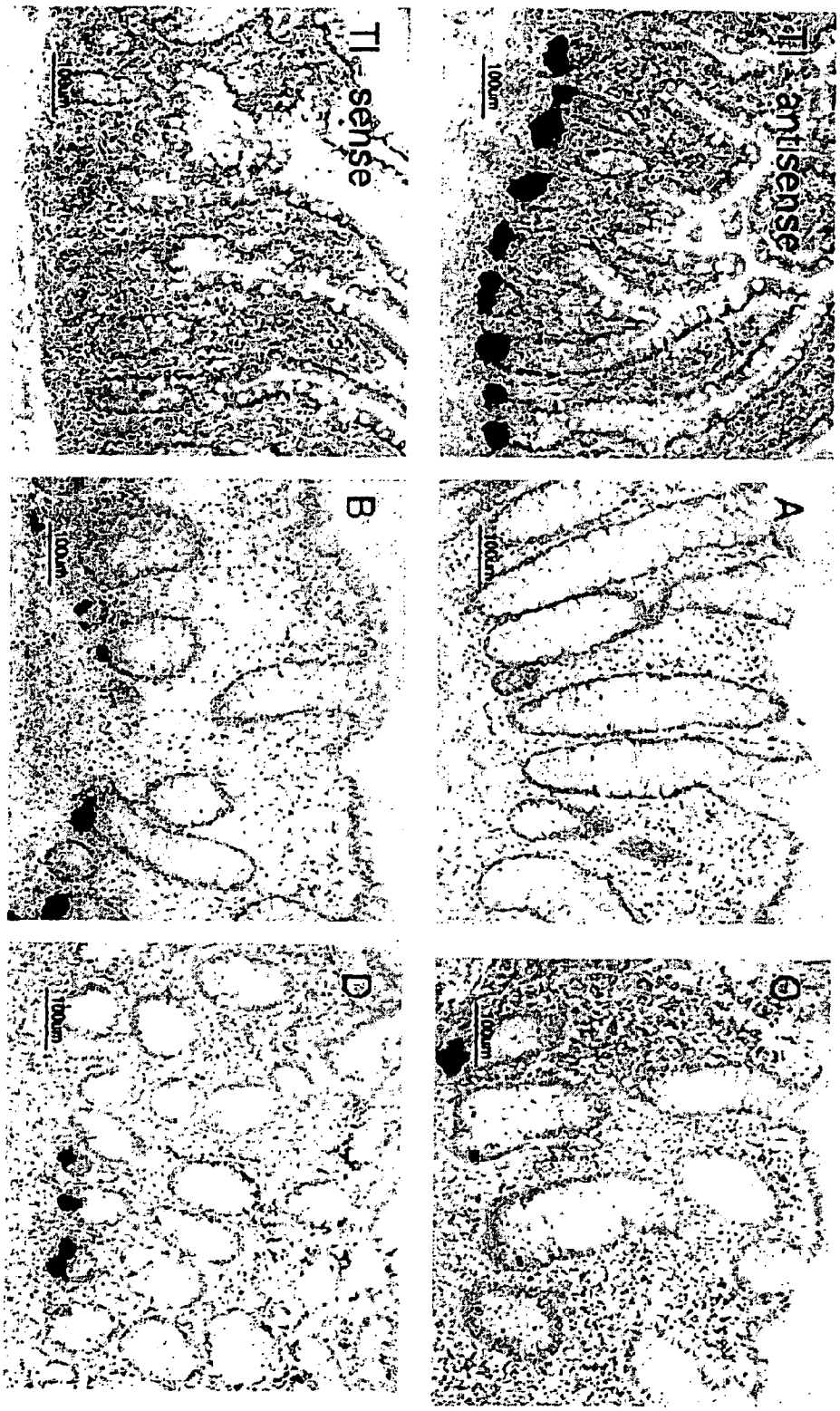


Figure 6: Defensin alpha 5 In- Situ Hybridization in the terminal ileum and colon of patients with ulcerative colitis and controls.

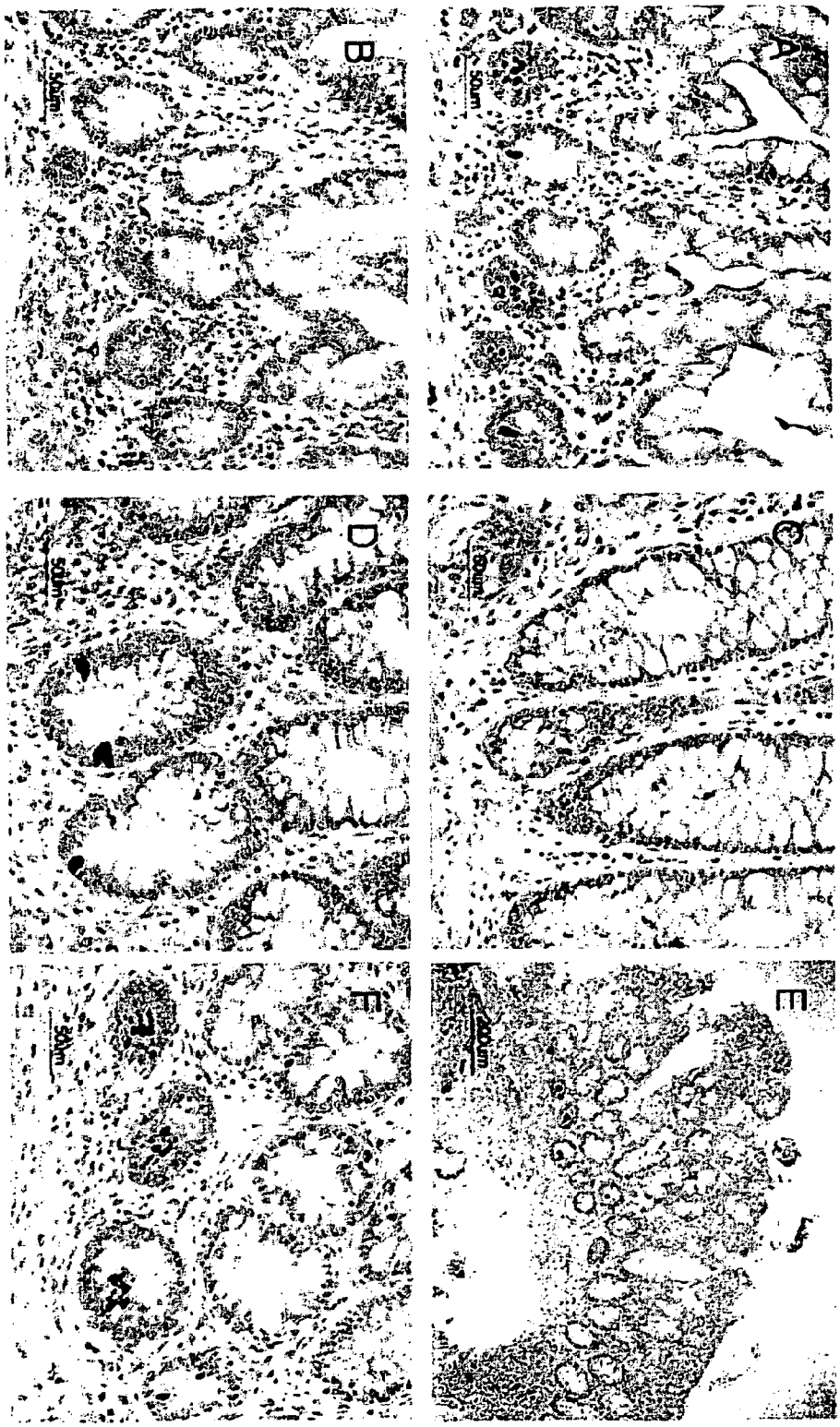


Figure 7: Defensin alpha 6 Immunohistochemistry in the terminal ileum and colon of patients with ulcerative colitis and controls.

1 acacatctgc tcctgctctc tctcctccag cgaccctagc catgagaacc ctcaccatcc
61 tcactgctgt tctcctcgtg gccctccagg ccaaggctga gccactccaa gctgaggatg
121 atccactgca ggcaaaaget tatgaggctg atgcccagga gcagcgtggg gcaaatgacc
181 aggactttgc cgtctccttt gcagaggatg caagctcaag tcttagagct ttgggctcaa
241 caagggcttt cacttgccat tgcagaaggt cctgttattc aacagaatat tcctatggga
301 cctgcactgt catgggtatt aaccacagat tctgctgcct ctgagggatg agaacagaga
361 gaaatatatt cataatttac tttatgacct agaaggaaac tgtcgtgtgt cccatacatt
421 gccatcaact ttgtttcctc atctcaaata aagtccttte agcaaaaaaa aaaaa

Figure 8A

MRTLTILTAVLLVALQAKAEPLQAEDDPLQAKAYEADAQEQRGANDQDFAVSFAEDASSSL
RALGSTRAFTCHCRRSCYSTEYSYGTCTVMGINHRFCCL

Figure 8B

1 atatccactc ctgctctccc tcctgcaggt gaccccagcc atgaggacca tcgccatcct
61 tgctgccatt ctcctggtgg ccctgcaggc ccaggctgag tcactccagg aaagagctga
121 tgaggctaca acccagaagc agtctgggga agacaaccag gaccttgcta tctccttgc
181 aggaaatgga ctctctgctc ttagaacctc aggttctcag gcaagagcca cctgctattg
241 ccgaaccggc cgttgtgcta cccgtgagtc cctctccggg gtgtgtgaaa tcagtggccg
301 cctctacaga ctctgctgtc gctgagcttc ctagatagaa accaaagcag tgcaagattc
361 agttcaaggt cctgaaaaaa gaaaaacatt ttactctgtg taccttgtgt ctttctaaat
421 ttctctctcc aaaataaagt tcaagcatt

Figure 9A

MRTIAILAAILLVALQAQAESLQERADEATTQKQSGEDNQDLAISFAGNGLSALRTSGSQARA
TCYCRTGRCATRESLSGVCEISGRLYRLCCR

Figure 9B

1 atgaggatct tttactatct ccatttttctg tgttatgtga ccttcattct accagccaca
61 tgtaccttgg tgaatgctga tcgttgcacc aaacgttacg gtcgttgtaa aagagactgt
121 cttgagagtg aaaagcaaat agacatatgt tccttaccaa gaaaaatttg ctgcactgag
181 aaattgtatg aagaagatga tatgttttga

Figure 9C

MRIFYYLHFLCYVTFILPATCTLVNADRCTKRYGRCKRDCLESEKQIDICSLPRKICCTEKLYE
EDDMF

Figure 9D

1 gtcaggttca tggttacgaa gctgctgacc ccaggatccc agcccgtggg agagaagggg
61 gtctctgaca gcccccaccc ctccccactg ccagatcctt attgggtctg agtttcaggg
121 gtggggcccc agctggaggt tataaaacag ctcaatcggg gagtacaacc ttcggtttct
181 cttcggggaa agctgcttic agcgcacacg ggaagatatc agaaacatcc taggatcagg
241 acaccccaga tcttctcaac tggaaccacg aaggctgttt cttccacaca gcactttgat
301 ctccatttaa gcaggcacct ctgtcctgcg ttccggagct gcgttcccga tggtcctcct
361 ttggctcacg ctgctcctga tcgccctgcc ctgtctcctg caaacgaagg aagatccaaa
421 cccaccaatc acgaacctaa ggatgaaagc aaaggctcag cagttgacct gggaccttaa
481 cagaaatgtg accgatatcg agtgtgttaa agacgccgac tattctatgc cggcagtgaa
541 caatagctat tgccagtttg gagcaatttc cttatgtgaa gtgaccaact acaccgtccg
601 agtggccaac ccaccattct ccacgtggat cctcttccct gagaacagtg ggaagccttg
661 ggcaggtgcg gagaatctga cctgctggat tcatgacgtg gatttcttga gctgcagctg
721 ggcggtaggc ccgggggccc ccgcggacgt ccagtacgac ctgtacttga acgttgccaa
781 caggcgtcaa cagtacgagt gtcttcacta caaaacggat gctcagggaa cacgtatcgg
841 gtgtcgtttc gatgacatct ctcgactctc cagcggttct caaagttccc acatcctggt
901 gcgggggcagg agcgcagcct tcggtatccc ctgcacagat aagtttgtcg tcttttcaca
961 gattgagata ttaactccac ccaacatgac tgcaaagtgt aataagacac attcctttat
1021 gcactggaaa atgagaagtc atttcaatcg caaatttcgc tatgagcttc agatacaaaa
1081 gagaatgcag cctgtaatca cagaacaggt cagagacaga acctccttcc agctactcaa
1141 tcctggaacg tacacagtac aaataagagc ccgggaaaga gtgtatgaat tcttgagcgc
1201 ctggagcacc ccccagcgct tcgagtgcga ccaggaggag ggcgcaaaca cacgtgcctg
1261 gcggacgtcg ctgctgatcg cgctggggac gctgctggcc ctggtctgtg tcttcgtgat
1321 ctgcagaagg tatctggtga tgcagagact ctttccccgc atccctcaca tgaaagaccc
1381 catcggtgac agcttccaaa acgacaagct ggtggtctgg gaggcgggca aagccggcct
1441 ggaggagtgt ctggtgactg aagtacaggt cgtgcagaaa acttgagact ggggttcagg
1501 gcttgtgggg gtctgcctca atctccctgg ccgggccagg cgcctgcaca gactggctgc
1561 tggacctgcg cacgcagccc aggaatggac attcctaacg ggtggtgggc atgggagatg
1621 cctgtgtaat ttcgtccgaa gctgccagga agaagaacag aactttgtgt gtttatttca
1681 tgataaagtg attttttttt ttttaaccca aaaaaaaaaa aaaaaa

Figure 10A

MVLLWLTLLLIALPCLLQTKEDPNPPITNLRMKAKAQQLTWDLNRNVTDIECVKDADYSMP
AVNNSYCQFGAISLCEVTNYTVRVANPPFSTWILFPENSGKPWAGAENLTCWIHDVDFLSCS
WAVGPGAPADVQYDLYLNVANRRQQYECLHYKTDAQGTRIGCRFDDISRLSSGSQSSHILVR
GRSAAFGIPCTDKFVVFSQIEILTPPNMTAKCNKTHSFMHWKMRSHFNRKFRYELQIQKRMQ
PVITEQVRDRTSFQLLNPGTYTVQIRARERVYEFLSAWSTPQRFECDQEEGANTRAWRTSLLI
ALGTLLALVCVFVICRRYLVMQRLFPRIPHMKDPIGDSFQNDKLVVWEAGKAGLEECLVTEV
QVVQKT

Figure 10B

gagagactgg atggacccac aagggtgaca gcccaggcgg accgatcttc ccatcccaca tcctccggcg cgatgccaaa
aagaggctga cggcaactgg gccttctgca gagaaagacc tccgcttcac tgccccggct ggtcccaagg gtcaggaaga tggattcata
cctgctgatg tggggactgc tcacgttcat catggtgcct ggctgccagg cagagctctg tgacgatgac ccgccagaga tcccacacgc
cacattcaaa gccatggcct acaaggaagg aaccatgttg aactgtgaat gcaagagagg tttccgcaga ataaaaagcg ggtcactcta
tatgctctgt
acaggaaact ctagccactc gtcctgggac aaccaatgtc aatgcacaag ctctgccact cggaacacaa cgaaacaagt gacacctcaa
cctgaagaac agaaagaaag gaaaaccaca gaaatgcaaa gtccaatgca gccagtggac caagcgagcc ttccaggtca
ctgcagggaa
cctccaccat gggaaaatga agccacagag agaatttatc atttcgtggt ggggcagatg gtttattatc agtgcgtcca gggatacagg
gctctacaca gaggtcctgc tgagagcgtc tgcaaaatga cccacgggaa gacaaggtgg acccagcccc agctcatatg
cacaggtgaa
atggagacca gtcagtttcc aggtgaagag aagcctcagg caagccccga aggccgtcct gagagtgaga cttcctgcct cgtcacaaca
acagattttc aaatacagac agaaatggct gcaaccatgg agacgtccat atttacaaca gagtaccagg tagcagtggc cggctgtgtt
ttcctgctga tcagcgtcct cctcctgagt gggctcacct ggcagcggag acagaggaag agtagaagaa caatctagaa aaccaaaaga
acaagaattt cttggtaaga agccgggaac agacaacaga agtcatgaag cccaagtgaa atcaaaggtg ctaaatggtc gcccaggaga
catccgttgt gcttgcctgc gttttggaag ctctgaagtc acatcacagg acacggggca gtggcaacct tgtctctatg ccagctcagt
cccatcagag agcgagcgct acccacttct aaatagcaat ttcgccgttg aagaggaagg gcaaaaccac tagaactctc catcttattt
tcatgtatat gtgttcatta aagcatgaat ggtatggaac tctctccacc ctatatgtag tataaagaaa agtaggttta cattcatctc
attccaactt cccagttcag gagtcccaag gaaagcccca gcactaacgt aaatacacaa cacacacact ctaccctata caactggaca
ttgtctgcgt ggttcctttc tcagccgctt ctgactgctg attctcccgt tcacgttgcc taataaacat ccttcaagaa ctctgggctg
ctacccagaa atcattttac ccttggctca atcctctaag ctaacccccc tctactgagc cttcagtctt gaatttctaa aaaacagagg
ccatggcaga ataatctttg ggtaacttca aaacggggca gccaaaccca tgaggcaatg tcaggaacag aaggatgaat gaggtcccag
gcagagaatc atacttagca aagttttacc tgtgcgttac taattggcct ctttaagagt tagtttcttt gggattgcta tgaatgatac
cctgaatttg gcctgcacta atttgatgtt tacaggtgga cacacaaggt gcaaatcaat gcgtacgttt cctgagaagt gtctaaaaac
accaaaaagg gatccgtaca ttcaatgttt
atgcaaggaa ggaaagaaag aaggaagtga agagggagaa gggatggagg tcacactggt agaacgtaac cacggaaaag
agcgcatcag gcctggcacg gtggctcagg cctataaccc cagctcccta ggagaccaag gcgggagcat ctcttgaggc
caggagtttg agaccagcct
gggcagcata gcaagacaca tccctacaaa aaattagaaa ttggctggat gtggtggcat acgcctgtag tcctagccac tcaggaggct
gaggcaggag gattgcttga gcccaggagt tcgaggctgc agtcagtcat gatggcacca ctgcactcca gcctgggcaa
cagagcaaga
tcctgtcttt aaggaaaaaa agacaagg

Figure 11A

MDSYLLMWGLLTFIMVPGCQAELCDDDPPEIPHATFKAMAYKEGTMLNCECKRGFRRIKSG
SLYMLCTGNSSHSSWDNQCQCTSSATRNTTKQVTPQPEEQKERKTTEMQSPMQPVDQASLP
GHCREPPPWENEATERIYHFVVGQMVYYQCVQGYRALHRGPAESVCKMTHGKTRWTQPQL
ICTGEMETSQFPGEEKPQASPEGRPESETSCLVTTTDFQIQTEMAATMETSIFTTEYQVAVAGC
VFLLISVLLLSGLTWQRRQRKSRRTI

Figure 11B

1 aaaccatacc atatcccacc agagagtgac tcctgattgc ctcctcaagt cgcagacact
61 atgctgcctc ccatggccct gcccagtgta tcttggatgc tgctttcctg cctcatgctg
121 ctgtctcagg ttcaaggtga agaaccccag agggaactgc cctctgcacg gatccgctgt
181 cccaaaggct ccaaggccta tggctcccac tgctatgcct tgtttttgtc accaaaatcc
241 tggacagatg cagatctggc ctgccagaag cggccctctg gaaacctggt gtctgtgctc
301 agtggggctg agggatcctt cgtgtcctcc ctggtgaaga gcattggtaa cagctactca
361 tacgtctgga ttgggctcca tgaccccaca cagggcaccg agcccaatgg agaaggttgg
421 gagtggagta gcagtgatgt gatgaattac tttgcatggg agagaaatcc ctccaccatc
481 tcaagccccg gccactgtgc gagcctgtcg agaagcacag catttctgag gtggaaagat
541 tataactgta atgtgaggtt accctatgtc tgcaagttca ctgactagtg caggagggaa
601 gtcagcagcc tgtgtttggt gtgcaactca tcatgggcat gagaccagtg tgaggactca
661 ccctggaaga gaatattcgc ttaattcccc caacctgacc acctcattct tatctttctt
721 ctgtttcttc ctccccgctg tcatttcagt ctcttcattt tgtcatacgg cctaaggctt
781 taaagagcaa taaaattttt agtctgc

Figure 12A

MLPPMALPSVSWMLLSCLMLLSQVQGEEPQRELPSARIRCPKGSKAYGSHCYALFLSPKSWT
DADLACQKRPSGNLVSVLSGAEGSFVSSLVKSIGNSYSYVWIGLHDPTQGTEPNGEGWEWSS
SDVMNYFAWERNPSTISSPGHCASLSRSTAFLRWKDYNCNVRLPYVCKFTD

Figure 12B

1 aagccacctc aagtggacaa ggcacttacc aacagagatt gctgatttgc tccttaagca
61 agagattcac tgccgctaag catggctcag accaactcgt tcttcatgct gatctcctcc
121 ctgatgttcc tgtctctgag ccaaggccag gagtcccaga cagagctgcc taatccccga
181 atcagctgcc cagaaggcac caatgcctat cgctcctact gctactactt taatgaagac
241 cctgagacct gggttgatgc agatctctat tgccagaaca tgaattcagg caacctggtg
301 tctgtgctca cccaggcgga gggtgccttc gtggcctcac tgattaagga gagtagcact
361 gatgacagca atgtctggat tggcctccat gacccaaaaa agaaccgccg ctggcactgg
421 agtagtgggt ccctggtctc ctacaagtcc tgggacactg gatccccgag cagtgctaat
481 gctggctact gtgcaagcct gacttcatgc tcaggattca agaaatggaa ggatgaatct
541 tgtgagaaga agttctcctt tgtttgcaag ttcaaaaact agaggaagct gaaaaatgga
601 tgtctagaac tggtcctgca attactatga agtcaaaaat taaactagac tatgtctcca
661 actcagttca gaccatctcc tcctaatga gtttgcatcg ctgatcttca gtaccttcac
721 ctgtctcagt ctctagagcc ctgaaaaata aaaacaaact tatttttatc cag

Figure 13A

MAQTNSFFMLISSLMFLSLSQGQESQTELPNPRISCPEGTNAYRSYCYYFNEDPETWVDADLY
CQNMNSGNLVSVLTQAEGAFVASLIKESSTDDSNVWIGLHDPKKNRRWHWSSGSLVSYKSW
DTGSPSSANAGYCASLTSCSGFKKWKDESCEKKFSFVCKFKN

Figure 13B

1 ggagagaaat ggctgaaagt ggaaacccgg agcggtttgg ggcgcttcgc aaagttctcc
61 agctcggcga gccggcggtg tgtctaccag aggctggggg ccagtccatc tggtcctgcc
121 cgacgccact tccacccccgc gagctctggg aaaggtctct acgtgacgcc aagggccgtc
181 gcggcccccgg ggagagggat cgaaagactc actctgcgag gtgtttacac tggaggtggg
241 ggacgggaag ggactgggca aagttacctg gactcaacta aattcctgcg cttgcttagt
301 gttgacattt gaataggatc cgagatgttc tgcttttatc ccgggcagcc ctgatatgtc
361 agcaacaggc tgaggttcca gacctgaaat cgcactgcaa gaaaaagggg tttgctgaac
421 taactccaag ctggtgtgcc tagcgtccgc gcggctgccg gcccaagagc tggagtcacc
481 atggcggccg gagttgcggc ctggctgcct tttgcccggg ctgcggccat cgggtggatg
541 ccggtggcca actgccccat gcccctggcc ccggccgaca agaacaagcg gcaggatgag
601 ctgattgtcc tcaacgtgag tgggcggagg ttccagacct ggaggaccac gctggagcgc
661 tacccggaca ccctgctggg cagcacggag aaggagttct tcttcaacga ggacaccaag
721 gagtacttct tcgaccgggg ccccgaggtg ttccgctgcg tgctcaactt ctaccgcacg
781 gggaagctgc actacccgcg ctacgagtgc atctctgcct acgacgacga gctggccttc
841 tacggcatcc tcccggagat catcggggac tgctgctacg aggagtacaa ggaccgcaag
901 agggagaacg ccgagcggct catggacgac aacgactcgg agaacaacca ggagtccatg
961 ccctcgctca gcttccgcca gaccatgtgg cgggccttcg agaacccccca caccagcacg
1021 ctggccctgg tcttctacta cgtgactggc ttcttcatcg ctgtctcggt catcaccaac
1081 gtggtggaga cggtgccgtg cggcacggtc ccgggcagca aggagctgcc gtgcggggag
1141 cgctactcgg tggccttctt ctgcctggac acggcgtgcg tcatgatctt caccgtggag
1201 tacctcctgc ggctcttcgc ggctcccagc cgctaccgct tcatccgcag cgtcatgagc
1261 atcatcgacg tggtggccat catgccctac tacatcggtc tggtcatgac caacaacgag
1321 gacgtgtccg gcgccttcgt cacgctccgg gtcttccgcg tcttcaggat cttcaagttt
1381 tcccgccact cccagggcct gcggatcctg ggctacacac tgaagagctg tgcctccgaa
1441 ctgggctttc ttctcttctc cctcaccatg gccatcatca tctttgccac tgtgatgttt
1501 tatgccgaga agggctcctc ggccagcaag ttcacaagca tccctgcctc gttttggtac
1561 accattgtca ccatgaccac actggggtac ggagacatgg tgcctaagac gattgcaggg
1621 aagatcttcg gctccatctg ctccttgagt ggcgtcctgg tcattgccct gccagtccct
1681 gtgattgttt ccaactttag ccggatttac caccagaatc agagagctga taaacgcagg
1741 gcacaaaaga aggcccgcct tgccaggatc cgtgtggcca aaacaggcag ttcgaatgca
1801 tacctgcaca gcaagcgcaa cgggctcctc aacgaggcgc tggagctgac gggcacccca
1861 gaagaggagc acatgggcaa gaccacctca ctcatcgaga gccagcatca tcacctgctg
1921 cactgcctgg aaaaaaccac tgggttgtcc tatcttgtgg atgatccccct gttatctgta
1981 cgaacctcca ccatcaagaa ccacgagttt attgatgagc agatgtttga gcagaactgc
2041 atggagagtt caatgcagaa ctaccccatcc acaagaagtc cctcactgtc cagccaccca
2101 ggcctcacta ccacctgctg ctcccgtcgt agtaagaaga ccacacacct gcccaattct
2161 aacctgccag ctactcgcct gcgcagcatg caagagctca gcacgatcca catccagggc
2221 agtgagcagc cctccctcac aaccagtcgc tccagcctta atttgaaagc agacgacgga
2281 ctgagaccaa actgcaaaac atcccagatc accacagcca tcatcagcat ccccactccc
2341 ccagcgctaa ccccagaggg ggaaagtcgg ccacccccctg ccagcccagg ccccaacacg
2401 aacattcctt ccatagccag caatgttgtc aaggtctccg ccttgtaaaa ccactggaca
2461 gagggccaga gtgggtagtg gggaatgaag gggactggca tgttggtggg tggtcactga
2521 gaccactccc tccccccttt ccccactatt tctgcctgcc ccattgtacc cctagcactg
2581 agacttgtgc ctggaaggaa aaagaggtag caaaggggca cctgaggttc acgctgctag
2641 cgtggacata gccctgtgat actgcatctc actggggcca gaggaaggga ggg

Figure 14A

MAAGVAAWLPFARAAAIGWMPVANCPMPLAPADKNKRQDELIVLNVSGRRFQTWRTTLER
YPDTLLGSTEKEFFFNEDTKEYFFDRDPEVFRCVLNFYRTGKLHYPRYECISAYDDELAFYGI
LPEIIGDCCYEEYKDRKRENAERLMDDNDSENNQESMPSLSFRQTMWRAFENPHTSTLALVF
YYVTGFFIAVSVITNVVETVPCGTVPGSKELPCGERYSVAFFCLDTACVMIFTVEYLLRLFAA
PSRYRFIRSVMSIIDVVAIMPYYIGLVMTNNEDVSGAFVTLRVFRVFRIFKFSRHSQGLRILGY
TLKSCASELGFLLFSLTMAIIIFATVMFYAEKGSSASKFTSIPASFWYTIVTMTTLGYGDMVPK
TIAGKIFGSICSLSGVLVIALPVPVIVSNFSRIYHQNQRADKRRAQKKARLARIRVAKTGSSNA
YLHSKRNGLLNEALELTGTPEEEHMGKTTSLIESQHHHLLHCLEKTTGLSYLVDDPLLSVRTS
TIKNHEFIDEQMFEQNCMESSMQNYPSTRSPSLSSHPGLTTTCCSRRSKKTTHLPNSNLPATRL
RSMQELSTIHIQGSEQPSLTTSRSSLNLKADDGLRPNCKTSQITTAIISIPTPPALTPEGESRPPPA
SPGPNTNIPSIASNVVKVSAL

Figure 14B

1 cactcccaaa gaactgggta ctcaacactg agcagatctg ttctttgagc taaaaaccat
61 gtgctgtacc aagagtttgc tcctggctgc tttgatgtca gtgctgctac tccacctctg
121 cggcgaatca gaagcagcaa gcaactttga ctgctgtctt ggatacacag accgtattct
181 tcatcctaaa tttattgtgg gcttcacacg gcagctggcc aatgaaggct gtgacatcaa
241 tgctatcatc tttcacacaa agaaaaagtt gtctgtgtgc gcaaatccaa aacagacttg
301 ggtgaaatat attgtgcgtc tcctcagtaa aaaagtcaag aacatgtaaa aactgtggct
361 tttctggaat ggaattggac atagcccaag aacagaaaga accttgctgg ggttggaggt
421 ttcacttgca catcatggag ggtttagtgc ttatctaatt tgtgcctcac tggacttgtc
481 caattaatga agttgattca tattgcatca tagtttgctt tgtttaagca tcacattaaa
541 gttaaactgt attttatgtt atttatagct gtaggttttc tgtgtttagc tatttaatac
601 taatttttcca taagctattt tggtttagtg caaagtataa aattatattt ggggggggaat
661 aagattatat ggactttctt gcaagcaaca agctattttt taaaaaaact atttaacatt
721 cttttgttta tattgttttg tctcctaaat tgttgtaatt gcattataaa ataagaaaaa
781 cattaataag acaaatatt

Figure 15A

MCCTKSLLLAALMSVLLLHLCGESEAASNFDCCLGYTDRILHPKFIVGFTRQLANEGCDINAII
FHTKKKLSVCANPKQTWVKYIVRLLSKKVKNM

Figure 15B

1 gaagcgggaa agggccacaa tggggtctgg gaggtgggcg gggcggagcg gggatgtcca
61 gccacgtcgc tttgttttcc cacgctagga gctaccacaa caggtgctgc gagccgtaag
121 cgcccccccac ccgcgctatg ggctcggacg cctgggtggg cctttggcgg ccacaccggc
181 cccgcggccc catcgcggcg cactacggag gccccgggcc caaatacaag ctgccgccca
241 acaccggcta cgccctgcat gaccccgtcgc ggccgcgcgc ccccgccttc accttcggcg
301 cgcgcttccc cacgcagcag acgacgtgcg gccccgggcc aggccacctg gtgccccgctc
361 gcatgaccgt gcgcggcacc gacggcgccc ccgcctactc catctacggc cgccccacgcc
421 gctcagcgcc cttcctcact ccgggacctg gcaggtactt ccccggagcga gcggggaacg
481 cgacgtaccc cagtgcgcct cggcacacca ttgctccccg aaactggggt gtccaggcgg
541 aacagcagag cccaggtccc gcggcctata cggtgccctc gctcttgggt ccgcgcgtca
601 tcggcaaagt ctccgccccca acttgctcca tctacggccg cagagcggct ggcagtttct
661 tcgaggacct cagcaagacc ccgggccccct gcgcctatca ggtcgtgagt ccaggggtct
721 acaagtcccg ggcccccccag ttcacgattc tggcgcggac ttcgctcccc caagacaaca
781 ctcggaagcc agggcccgcg gcctacaacg tggatcagca ccggaagccc cgcggctgga
841 gtttcgggat ccggcactcg gactacctgg ccccgctggt gaccgacgcg gacaactgac
901 ccgccaggcg ggagcggccc cacacgtgtt tgcttaaagt ctgcgagtcc gcaaaaaaaa
961 aaaaaaaaaa

Figure 16A

MGSDAWVGLWRPHRPRGPIAAHYGGPGPKYKLPPNTGYALHDPSRPRAPAFTFGARFPTQQ
TTCGPGPGHLVPARMTVRGTDGAPAYSIYGRPRRSAPFLTPGPGRYFPERAGNATYPSAPRHT
IAPRNWGVQAEQQSPGPAAYTVPSLLGPRVIGKVSAPTCSIYGRRAAGSFFEDLSKTPGPCAY
QVVSPGVYKSRAPQFTILARTSLPQDNTRKPGPAAYNVDQHRKPRGWSFGIRHSDYLAPLVT
DADN

Figure 16B

1 accaaacctc ttcgaggcac aaggcacaac aggctgctct gggattctct tcagccaatc
61 ttcattgctc aagtgtctga agcagccatg gcagaagtac ctgagctcgc cagtgaaatg
121 atggcttatt acagtggcaa tgaggatgac ttgttctttg aagctgatgg ccctaaacag
181 atgaagtgct ccttccagga cctggacctc tgccctctgg atggcggcat ccagctacga
241 atctccgacc accactacag caagggcttc aggcaggccg cgtcagttgt tgtggccatg
301 gacaagctga ggaagatgct ggttccctgc ccacagacct tccaggagaa tgacctgagc
361 accttctttc ccttcatctt tgaagaagaa cctatcttct tcgacacatg ggataacgag
421 gcttatgtgc acgatgcacc tgtacgatca ctgaactgca cgctccggga ctcacagcaa
481 aaaagcttgg tgatgtctgg tccatatgaa ctgaaagctc tccacctcca gggacaggat
541 atggagcaac aagtggtgtt ctccatgtcc tttgtacaag gagaagaaag taatgacaaa
601 atacctgtgg ccttgggcct caaggaaaag aatctgtacc tgtcctgcgt gttgaaagat
661 gataagccca ctctacagct ggagagtgta gatcccaaaa attacccaaa gaagaagatg
721 gaaaagcgat ttgtcttcaa caagatagaa atcaataaca agctggaatt tgagtctgcc
781 cagttcccca actggtacat cagcacctct caagcagaaa acatgccccgt cttcctggga
841 gggaccaaag gcggccagga tataactgac ttcaccatgc aatttgtgtc ttcctaaaga
901 gagctgtacc cagagagtcc tgtgctgaat gtggactcaa tccctagggc tggcagaaag
961 ggaacagaaa ggtttttgag tacggctata gcctggactt tcctgttgtc tacaccaatg
1021 cccaactgcc tgccttaggg tagtgctaag aggatctcct gtccatcagc caggacagtc
1081 agctctctcc tttcagggcc aatccccagc ccttttgttg agccaggcct ctctcacctc
1141 tcctactcac ttaaagcccg cctgacagaa accacggcca catttggttc taagaaaccc
1201 tctgtcattc gctcccacat tctgatgagc aaccgcttcc ctatttattt atttatttgt
1261 ttgtttgttt tattcattgg tctaatttat tcaaaggggg caagaagtag cagtgtctgt
1321 aaaagagcct agtttttaat agctatggaa tcaattcaat ttggactggt gtgctctctt
1381 taaatcaagt cctttaatta agactgaaaa tatataagct cagattattt aaatgggaat
1441 atttataaat gagcaaatat catactgttc aatggttctg aaataaactt cactgaag

Figure 17A

MAEVPELASEMMAYYSGNEDDLFFEADGPKQMKCSFQDLDLCPLDGGIQLRISDHHYSKGF
RQAASVVVAMDKLRKMLVPCPQTFQENDLSTFFPFIFEEEPIFFDTWDNEAYVHDAPVRSLN
CTLRDSQQKSLVMSGPYELKALHLQGQDMEQQVVFSMSFVQGEESNDKIPVALGLKEKNLY
LSCVLKDDKPTLQLESVDPKNYPKKKMEKRFVFNKIEINNKLEFESAQFPNWYISTSQAENMP
VFLGGTKGGQDITDFTMQFVSS

Figure 17B

1 cacagagccc gggccgcagg cacctcctcg ccagctcttc cgctcctctc acagccgcca
61 gacccgcctg ctgagcccca tggccccgcgc tgctctctcc gccgcccccca gcaatccccg
121 gctcctgcga gtggcactgc tgctcctgct cctggtagcc gctggccggc gcgcagcagg
181 agcgtccgtg gccactgaac tgcgctgcca gtgcttgcag accctgcagg gaattcaccc
241 caagaacatc caaagtgtga acgtgaagtc ccccggaccc cactgcgccc aaaccgaagt
301 catagccaca ctcaagaatg ggcggaaagc ttgcctcaat cctgcatccc ccatagttaa
361 gaaaatcatc gaaaagatgc tgaacagtga caaatccaac tgaccagaag ggaggaggaa
421 gctcactggt ggctgttcct gaaggaggcc ctgcccttat aggaacagaa gaggaaagag
481 agacacagct gcagaggcca cctggattgt gcctaatgtg tttgagcatc gcttaggaga
541 agtcttctat ttatttattt attcattagt tttgaagatt ctatgttaat attttaggtg
601 taaaataatt aagggtatga ttaactctac ctgcacactg tcctattata ttcattcttt
661 ttgaaatgtc aaccccaagt tagttcaatc tggatttcata tttaatttga aggtagaatg
721 ttttcaaatg ttctccagtc attatgttaa tatttctgag gagcctgcaa catgccagcc
781 actgtgatag aggctggcgg atccaagcaa atggccaatg agatcattgt gaaggcaggg
841 gaatgtatgt gcacatctgt tttgtaactg tttagatgaa tgtcagttgt tatttattga
901 aatgatttca cagtgtgtgg tcaacatttc tcatgttgaa actttaagaa ctaaaatgtt
961 ctaaatatcc cttggacatt ttatgtcttt cttgtaaggc atactgcctt gtttaatggt
1021 agttttacag tgtttctggc ttagaacaaa ggggcttaat tattgatgtt ttcatagaga
1081 atataaaaat aaagcactta tag

Figure 18A

MARAALSAAPSNPRLLRVALLLLLLVAAGRRAAGASVATELRCQCLQTLQGIHPKNIQSVNV
KSPGPHCAQTEVIATLKNGRKACLNPASPIVKKIIEKMLNSDKSN

Figure 18B

1 cacagagccc gggccgcagg cacctcctcg ccagctcttc cgctcctctc acagccgcca
61 gacccgcctg ctgagcccca tggccccgcgc tgctctctcc gccgcccccca gcaatccccg
121 gctcctgcga gtggcactgc tgctcctgct cctggtagcc gctggccggc gcgcagcagg
181 agcgtccgtg gccactgaac tgcgctgcca gtgcttgcag accctgcagg gaattcaccc
241 caagaacatc caaagtgtga acgtgaagtc ccccggaccc cactgcgccc aaaccgaagt
301 catagccaca ctcaagaatg ggcggaaagc ttgcctcaat cctgcatccc ccatagttaa
361 gaaaatcatc gaaaagatgc tgaacagtga caaatccaac tgaccagaag ggaggaggaa
421 gctcactggt ggctgttcct gaaggaggcc ctgcccttat aggaacagaa gaggaaagag
481 agacacagct gcagaggcca cctggattgt gcctaatgtg tttgagcatc gcttaggaga
541 agtcttctat ttatttattt attcattagt tttgaagatt ctatgttaat attttaggtg
601 taaaataatt aagggtatga ttaactctac ctgcacactg tcctatttata ttcattcttt
661 ttgaaatgtc aaccccaagt tagttcaatc tggattcata tttaatttga aggtagaatg
721 ttttcaaatg ttctccagtc attatgttaa tatttctgag gagcctgcaa catgccagcc
781 actgtgatag aggctggcgg atccaagcaa atggccaatg agatcattgt gaaggcaggg
841 gaatgtatgt gcacatctgt tttgtaactg tttagatgaa tgtcagttgt tatttattga
901 aatgatttca cagtgtgtgg tcaacatttc tcatgttgaa actttaagaa ctaaaatgtt
961 ctaaatatcc cttggacatt ttatgtcttt cttgtaaggc atactgcctt gtttaatggt
1021 agttttacag tgtttctggc ttagaacaaa ggggcttaat tattgatgtt ttcatagaga
1081 atataaaaat aaagcactta tag

Figure 19A

MARAALSAAPSNPRLLRVALLLLLLVAAGRRAAGASVATELRCQCLQTLQGIHPKNIQSVNV
KSPGPHCAQTEVIATLKNGRKACLNPASPIVKKIIEKMLNSDKSN

Figure 19B

1 agcgtgagac tcgcgccctc cggcacggaa aaggccaggc gacaggtgtc gcttgaaaag
61 actgggcttg tccttgctgg tgcatgcgtc gtcggcctct gggcagcagg tttacaaagg
121 aggaaaacga cttcttctag attttttttt cagtttcttc tataaatcaa aacatctcaa
181 aatggagacc taaaatcctt aaagggactt agtctaatct cgggagggtag ttttgtgcat
241 gggtaaacaa attaagtatt aactggtgtt ttactatcca aagaatgcta attttataaa
301 catgatcgag ttatataagg tataccataa tgagtttgat tttgaatttg atttgtggaa
361 ataaaggaaa agtgattcta gctggggcat attgttaaag catttttttc agagttggcc
421 aggcagtctc ctactggcac attctcccat tatgtagaat agaaatagta cctgtgtttg
481 ggaaagattt taaaatgagt gacagttatt tggaacaaag agctaataat caatccactg
541 caaattaaag aaacatgcag atgaaagttt tgacacatta aaatacttct acagtgacaa
601 agaaaaatca agaacaaagc tttttgatat gtgcaacaaa tttagaggaa gtaaaaagat
661 aaatgtgatg attggtcaag aaattatcca gttatttaca aggccactga tattttaaac
721 gtccaaaagt ttgtttaaat gggctgttac cgctgagaat gatgaggatg agaatgatgg
781 ttgaaggtta catttagga aatgaagaaa cttagaaaat taatataaag acagtgatga
841 atacaaagaa gatttttata acaatgtgta aaatttttgg ccagggaaag gaatattgaa
901 gttagataca attacttacc tttgagggaa ataattgttg gtaatgagat gtgatgtttc
961 tcctgccacc tggaaacaaa gcattgaagt ctgcagttga aaagcccaac gtctgtgaga
1021 tccaggaaac catgcttgca aaccactggt aaaaaaaaaa aaaaaaaaaa aaaaagccca
1081 cagtgacttg cttattggtc attgctagta ttatcgactc agaacctctt tactaatggc
1141 tagtaaatca taattgagaa attctgaatt ttgacaaggt ctctgctgtt gaaatggtaa
1201 atttattatt ttttttgtca tgataaattc tggttcaagg tatgctatcc atgaaataat
1261 ttctgaccaa aactaaattg atgcaatttg attatccatc ttagcctaca gatggcatct
1321 ggtaacttit gactgtttta aaaaataaat ccactatcag agtagatttg atgttggctt
1381 cagaaacatt tagaaaaaca aaagttcaaa aatgtttica ggaggtgata agttgaataa
1441 ctctacaatg ttagttcttt gagggggaca aaaaatttaa aatctttgaa aggtcttatt
1501 ttacagccat atctaaatta tcttaagaaa atttttaaca aagggaatga aatatatatc
1561 atgattctgt ttttccaaaa gtaacctgaa tatagcaatg aagttcagtt ttgttattgg
1621 tagtttgggc agagtctctt tttgcagcac ctgttgtcta ccataattac agaggacatt
1681 tccatgttct agccaagtat actattagaa taaaaaaact taacattgag ttgcttcaac
1741 agcatgaaac tgagtccaaa agaccaaatg aacaaacaca ttaatctctg attatttatt
1801 ttaaatagaa tatttaattg tgtaagatct aatagtatca ttatacttaa gcaatcatat
1861 tcctgatgat ctatgggaaa taactattat ttaattaata ttgaaaccag gttttaagat
1921 gtgttagcca gtcctgttac tagtaaatct ctttatttgg agagaaattt tagattgttt
1981 tgttctcctt attagaagga ttgtagaaag aaaaaaatga ctaattggag aaaaattggg
2041 gatatatcat atttcactga attcaaaatg tcttcagttg taaatcttac cattatttta
2101 cgtacctcta agaaataaaa gtgcttctaa ttaaaatatg atgtcattaa ttatgaaata
2161 cttcttgata acagaagttt taaaatagcc atcttagaat cagtgaaata tggtaatgta
2221 ttattttcct cctttgagtt aggtcttgtg cttttttttc ctggccacta aatttcacaa
2281 tttccaaaaa gcaaaataaa catattctga atatttttgc tgtgaaacac ttgacagcag
2341 agctttccac catgaaaaga agcttcatga gtcacacatt acatctttgg gttgattgaa
2401 tgccactgaa acattctagt agcctggaga agttgaccta cctgtggaga tgcctgccat
2461 taaatggcat cctgatggct taatacacat cactcttctg tgaagggttt taattttcaa
2521 cacagcttac tctgtagcat catgtttaca ttgtatgtat aaagattata caaaggtgca
2581 attgtgtatt tcttccttaa aatgtatcag tataggattt agaatctcca tgttgaaact
2641 ctaaatgcat agaaataaaa ataataaaaa atttttcatt ttggcttttc agcctagtat
2701 taaaactgat aaaagcaaag ccatgcacaa aactacctcc ctagagaaag gctagtccct
2761 tttcttcccc attcatttca ttatgaacat agtagaaaac agcatattct tatcaaattt
2821 gatgaaaagc gccaacacgt ttgaactgaa atacgacttg tcatgtgaac tgtaccgaat
2881 gtctacgtat tccacttttc ctgctggggt tcctgtctca gaaaggagtc ttgctcgtgc

Figure 20A

2941 tggtttctat tacactggtg tgaatgacaa ggtcaaatgc ttctgttgtg gcctgatgct
3001 ggataactgg aaaagaggag acagtcctac tgaaaagcat aaaaagttgt atcctagctg
3061 cagattcgtt cagagtctaa attccgttaa caacttggaa gctacctctc agcctacttt

3121 tccttcttca gtaacaaatt ccacacactc attacttccg ggtacagaaa acagtggata
3181 tttccgtggc tcttattcaa actctccatc aaatcctgta aactccagag caaatcaaga
3241 ttttctgcc ttgatgagaa gttcctacca ctgtgcaatg aataacgaaa atgccagatt
3301 acttactttt cagacatggc cattgacttt tctgtcgcca acagatctgg caaaagcagg
3361 cttttactac ataggacctg gagacagagt ggcttgcttt gcctgtggtg gaaaattgag
3421 caattgggaa ccgaaggata atgctatgtc agaacacctg agacattttc ccaaatgccc
3481 atttatagaa aatcagcttc aagacacttc aagatacaca gtttctaatc tgagcatgca
3541 gacacatgca gcccgcttta aaacattctt taactggccc tctagtgttc tagttaatcc
3601 tgagcagctt gcaagtgcgg gtttttatta tgtgggtaac agtgatgatg tcaaatgctt
3661 ttgctgtgat ggtggactca ggtgttggga atctggagat gatccatggg ttcaacatgc
3721 caagtggttt ccaaggtgtg agtacttgat aagaattaaa ggacaggagt tcatccgtca
3781 agttcaagcc agttacccctc atctacttga acagctgcta tccacatcag acagcccagg
3841 agatgaaaat gcagagtcat caattatcca ttttgaacct ggagaagacc attcagaaga
3901 tgcaatcatg atgaatactc ctgtgattaa tgctgccgtg gaaatgggct ttagtagaag
3961 cctggtaaaa cagacagttc agagaaaaat cctagcaact ggagagaatt atagactagt
4021 caatgatctt gtgttagact tactcaatgc agaagatgaa ataagggaag aggagagaga
4081 aagagcaact gaggaaaaag aatcaaatga tttattatta atccggaaga atagaatggc
4141 acttttcaa catttgactt gtgtaattcc aatcctggat agtctactaa ctgccggaat
4201 tattaatgaa caagaacatg atgttattaa acagaagaca cagacgtctt tacaagcaag
4261 agaactgatt gatacgattt tagtaaaagg aaatattgca gccactgtat tcagaaactc
4321 tctgcaagaa gctgaagctg tgttatatga gcatttattt gtgcaacagg acataaaata
4381 tattcccaca gaagatgttt cagatctacc agtggaagaa caattgcgga gactacaaga
4441 agaaagaaca tgtaaagtgt gtatggacaa agaagtgtcc atagtgttta ttccttgtgg
4501 tcatctagta gtatgcaaag attgtgctcc ttctttaaga aagtgtccta tttgtaggag
4561 tacaatcaag ggtacagttc gtacatttct ttcatgaaga agaaccaaaa catcgtctaa
4621 actttagaat taatttatta aatgtattat aactttaact tttatcctaa tttggtttcc
4681 ttaaaatttt tatttattta caactcaaaa aacattgttt tgtgtaacat atttatatat
4741 gtatctaaac catatgaaca tatatttttt agaaactaag agaatgatag gcttttgttc
4801 ttatgaacga aaaagaggta gcactacaaa cacaatattc aatcaaaatt tcagcattat
4861 tgaaattgta agtgaagtaa aacttaagat atttgagtta acctttaaga attttaaata
4921 ttttggcatt gtactaatac cgggaacatg aagccaggtg tggtggtatg tgcctgtagt
4981 cccaggctga ggcaagagaa ttacttgagc ccaggagttt gaatccatcc tgggcagcat
5041 actgagaccc tgcctttaaa aacaaacaga acaaaaacaa aacaccaggg acacatttct
5101 ctgtcttttt tgatcagtgt cctatacatc gaaggtgtgc atatatgttg aatgacattt
5161 tagggacatg gtgtttttat aaagaattct gtgagaaaaa atttaataaa gcaacaaaaa
5221 ttactcttaa aaaaaaaaaa aaa

Figure 20A (Continued)

MNIVENSIFLSNLMKSANTFELKYDLSCELYRMSTYSTFPAGVPVSERSLARAGFYYTGVND
KVKCFCCGLMLDNWKRGDSPTEKHKKLYPSCRFVQSLNSVNNLEATSQPTFPSSVTNSTHSL
LPGTENSGYFRGSYSNSPSNPVNSRANQDFSALMRSSYHCAMNNENARLLTFQTWPLTFLSP
TDLAKAGFYYIGPGDRVACFACGGKLSNWEPKDNAMSEHLRHFPKCPFIENQLQDTSRYTVS
NLSMQTHAARFKTFFNWPSSVLVNPEQLASAGFYYVGNSDDVKCFCCDGGLRCWESGDDP
WVQHAKWFPRCEYLIRIKGQEFIRQVQASYPHLLEQLLSTSDSPGDENAESSIIHFEPGEDHSE
DAIMMNTPVINAAVEMGFSRSLVKQTVQRKILATGENYRLVNDLVLDLLNAEDEIREEERER
ATEEKESNDLLLIRKNRMALFQHLTCVIPILDSLLTAGIINEQEHDVIKQKTQTSLQARELIDTI
LVKGNIAATVFRNSLQEAEAVLYEHLFVQQDIKYIPTEDVSDLPVEEQLRRLQEERTCKVCM
DKEVSIVFIPCGHLVVCKDCAPSLRKCPICRSTIKGTVRTFLS

Figure 20B

1 cggcaaaaaa aaaaggcgta agaattttga agctatgttc aaaggtatcc ttcagagtgg
61 attggataac ttcgtgataa accacatgct aaagaacaac gtggctggac aaacatctat
121 ccagacccta gtacctaata cggatcaaaa gtcgaccagt gtaaaaaaag acaaccacaa
181 aaaaaaaaca gttaagatgt tggaatacct gggcaaagat gttcttcatg gtgttttaa
241 ttatttggca aaacacgatg ttctgacatt gaaggaagag gaaaagaaaa aatattatga
301 tgccaaaatt gaagacaagg ccctgatctt ggtagactct ttgcgaaaga atcgcgtggc
361 tcatcaaatg tttacccaaa cacttctcaa tatggaccaa aagatcacca gtgtaaaacc
421 tcttctgcaa atcgaggctg gaccacctga gtcagcagaa tctacaaata tactcaaact
481 ttgtcctcgt gaagaattcc tgagactgtg taaaaaaaat catgatgaga tctatccaat
541 aaaaaagaga gaggaccgca gacgcctggc tctcatcata tgcaatacaa agtttgatca
601 cctgcctgca aggaatgggg ctcactatga catcgtgggg atgaaaaggc tgcttcaagg
661 cctgggctac actgtggttg acgaaaagaa tctcacagcc agggatatgg agtcagtgct
721 gagggcattt gctgccagac cagagcacaa gtcctctgac agcacgttct tggtactcat
781 gtctcatggc atcctagagg gaatctgcgg aactgcgcat aaaaagaaaa aaccggatgt
841 gctgctttat gacaccatct tccagatatt caacaaccgc aactgcctca gtctaaagga
901 caaacccaag gtcatcattg tccaggcctg cagaggtgaa aaacatgggg aactctgggt
961 cagagactct ccagcatcct tggcagtcat ctcttcacag tcatctgaga acctggaggc
1021 agattctgtt tgcaagatcc acgaggagaa ggacttcatt gctttctgtt cttcaacacc
1081 acataacgtg tcctggagag accgcacaag gggctccatc ttcattacgg aactcatcac
1141 atgcttccag aaatattctt gctgctgcca cctaatggaa atatttcgga aggtacagaa
1201 atcatttgaa gttccacagg ctaaagccca gatgcccacc atagaacgag caaccttgac
1261 aagagatttc tacctctttc ctggcaattg aaaatgaaac cacaggcagc ccagccctcc
1321 tctgtcaaca tcaaagagca catttaccag tatagcttgc atagtcaata tttggtattt
1381 caataaaagt aaagactgta

Figure 21A

MFKGILQSGLDNFVINHMLKNNVAGQTSIQTLVPNTDQKSTSVKKDNHKKKTVKMLEYLGK
DVLHGVFNYLAKHDVLTLKEEEKKKYYDAKIEDKALILVDSLRKNRVAHQMFTQTLLNMD
QKITSVKPLLQIEAGPPESAESTNILKLCPREEFLRLCKKNHDEIYPIKKREDRRRLALIICNTKF
DHLPARNGAHYDIVGMKRLLQGLGYTVVDEKNLTARDMESVLRAFAARPEHKSSDSTFLVL
MSHGILEGICGTAHKKKKPDVLLYDTIFQIFNNRNCLSLKDKPKVIIVQACRGEKHGELWVRD
SPASLAVISSQSSENLEADSVCKIHEEKDFIAFCSSTPHNVSWRDRTRGSIFITELITCFQKYSCC
CHLMEIFRKVQKSFEVPQAKAQMPTIERATLTRDFYLFPGN

Figure 21B

1 tttatagcag cagtagaaat ataccaccct agaggacaca cctcctttta gctaggtacc
61 tataaatgtc caggattttc tattcaattg agaagaaccc agcaaaatgg ggatctccac
121 agtcatcctt gaaatgtgtc ttttatgggg acaagttcta tctacaggtg ggtggatccc
181 aaggactaca gactacgctt cactgattcc ctcggaggtg cccttggatc caactgtagc
241 agaaggttct ccatttccct cggagtcgac cctggagtca actgtagcag aaggttctcc
301 gatttccttg gagtcaaccc tggagtcaac cgtagcagaa ggttctctga ttccctcaga
361 gtcaaccctg gagtcaactg tagcagaagg atctgattct ggtttggccc tgaggctggt
421 gaatggagat ggcaggtgtc agggccgagt ggagatccta taccgaggct cctggggcac
481 cgtgtgtgat gacagctggg acaccaatga tgccaacgtg gtctgtaggc agctgggttg
541 tggctgggcc atgtcagctc caggaaatgc ctggtttggc cagggctcag gacccattgc
601 cctggatgat gtgcgctgct caggacacga atcctacctg tggagctgcc cccacaatgg
661 ctggctctcc cataactgtg gccatggtga agatgctggt gttatctgct cagctgccca
721 gcctcagtca acactcaggc cagaaagttg gcctgtcagg atatcaccac ctgtacccac
781 agaaggatct gaatccagtt tggccctgag gctggtgaat ggaggcgaca ggtgtcgagg
841 ccgagtggag gtcctatacc gaggctcctg gggcaccgtg tgtgatgact actgggacac
901 caatgatgcc aatgtggtct gcaggcagct gggctgtggc tgggccatgt cagccccagg
961 aaatgcccag tttggccagg gctcaggacc cattgtcctg gatgatgtgc gctgctcagg
1021 acatgagtcc tacctgtgga gctgccccca caatggctgg ctcacccaca actgtggcca
1081 tagtgaagac gctggtgtca tctgctcagc tccccagtcc cggccgacac ccagcccaga
1141 tacttggccg acctcacatg catcaacagc aggacctgaa tccagtttgg ccctgaggct
1201 ggtgaatgga ggtgacaggt gtcagggccg agtggaggtc ctataccgag gctcctgggg
1261 caccgtgtgt gatgatagct gggacaccag tgacgccaat gtggtctgcc ggcagctggg
1321 ctgtggctgg gccacgtcag ccccaggaaa tgcccggttt ggccagggtt caggacccat
1381 tgtcctggat gacgtgcgct gctcaggcta tgagtcctac ctgtggagct gccccccaca
1441 tggctggctc tcccataact gtcagcacag tgaagacgct ggtgtcatct gctcagctgc
1501 ccactcctgg tcgacgccca gtccagacac attgccgacc atcaccttgc ctgcatcgac
1561 agtaggatct gaatccagtt tggccctgag gctggtgaat ggaggtgaca ggtgtcaggg
1621 ccgagtggag gtcctatacc aaggctcctg gggcaccgtg tgcgatgaca gctgggacac
1681 caatgatgcc aatgtcgtct gcaggcaact gggctgtggc tgggccatgt cagccccagg
1741 aaatgcccgg tttggtcagg gctcaggacc cattgtcctg gatgatgtgc gctgctcagg
1801 acacgagtct tacctgtgga gctgccccca caatggctgg ctctcccaca actgtggcca
1861 tagtgaagac gctggtgtca tctgctcagc ttcccagtcc cggccaacac ctagtccaga
1921 cacttggcca acctcacatg catcaacagc aggatctgaa tccagtttgg ccctgaggct
1981 ggtgaatgga ggtgacaggt gtcagggccg agtggaggtc ctataccgag gctcctgggg
2041 caccgtgtgt gatgactact gggacaccaa tgatgccaat gtggtttgca ggcagctggg
2101 ctgtggctgg gccatgtcag ccccaggaaa tgcccggttt ggccagggtt caggacccat
2161 tgtcctggat gatgtgcgct gctcaggaca tgagtcctat ctgtggagct gccccccaca
2221 tggctggctc tcccacaact gtggccatca tgaagacgct ggtgtcatct gctcagcttc
2281 ccagtcccag ccgacaccca gcccagacac ttggccaacc tcacatgcat caacagcagg
2341 atctgaatcc agtttggccc tgaggctggt gaatggaggt gacaggtgtc agggccgagt
2401 ggaggtccta taccgaggct cctggggcac cgtgtgtgat gactactggg acaccaatga
2461 tgccaatgtg gtttgcaggc agctgggctg tggctgggcc acgtcagccc caggaaatgc
2521 ccggtttggc cagggttcag gacccattgt cctggatgat gtgcgctgct caggacatga
2581 gtcctatctg tggagctgcc cccacaatgg ctggctctcc cacaactgtg gccatcatga
2641 agacgctggt gtcatctgct cagcttccca gtcccagccg acacccagcc cagacacttg
2701 gccaacctct cgtgcatcaa cagcaggatc tgaatccact ttggccctga gactggtgaa
2761 tggaggtgac aggtgtcgag gccgagtgga ggtcctatac caaggctcct ggggcaccgt
2821 gtgtgatgac tactgggaca ccaatgatgc caacgtggtc tgcaggcagc tgggctgtgg
2881 ctgggccatg tcagccccag gaaatgccca gtttggccag ggctcaggac ccattgtcct

Figure 22A

2941 ggatgatgtg cgctgctcag gacacgagtc ttacctgtgg agctgccccc acaatggctg
3001 gctctcccac aactgtggcc atcatgaaga tgctggtgtc atctgctcag ctgctcagtc
3061 ccagtcaacg cccaggccag atacttggct gaccaccaac ttaccggcat tgacagtagg
3121 atctgaatcc agtttggctc tgaggctggt gaatggaggt gacaggtgtc gaggccgagt

3181 ggaggtcctg tatcgaggct cctggggaac cgtgtgtgat gacagctggg acaccaatga
3241 tgccaatgtg gtctgcaggc agctgggctg tggctgggcc atgtcggccc caggaaatgc
3301 ccggtttggc cagggctcag gacccattgt cctggatgat gtgcgctgct cagggaatga
3361 gtcctacctg tggagctgcc cccacaaagg ctggctcacc cacaactgtg gccatcacga
3421 agacgctggt gtcatctgct cagccaccca aataaattct actacgacag attggtggca
3481 tccaacaact acaaccactg caagaccctc ttcaaattgt ggtggcttct tattctatgc
3541 cagtgggaca ttctccagcc catcctaccc tgcatactac cccaacaatg ctaagtgtgt
3601 ttgggaaata gaagtgaatt ctggttatcg cataaacctg ggcttcagta atctgaaatt
3661 ggaggcacac cataactgca gttttgatta tgttgaaatc tttgatggat cattgaatag
3721 cagtctcctg ctggggaaaa tctgtaatga taccaggcaa atatttacat cttcttacaa
3781 ccgaatgacc attcactttc gaagtgacat cagtttccaa aacactggct ttttggcttg
3841 gtataactcc ttcccaagcg atgccacctt gaggttggtc aatttaaatt catcctatgg
3901 tctatgtgcc gggcgtgtag aaatttacca tggtggcacc tgggggacag tttgtgatga
3961 ctcctggacc attcaggaag ctgaggtggt ctgcagacag ctagggtgtg gacgtgcagt
4021 ttcagcccct ggaaatgcat attttggctc tggctctggc cccatcaccc tggacgatgt
4081 agagtgctca gggacggaat ccactctctg gcagtgccgg aaccgaggct ggttctccca
4141 caactgtaat catcgtgaag atgctggtgt catctgctca ggaaaccatc tatcgacacc
4201 tgctcctttt ctcaacatca cccgtccaaa cacagattat tcctgcggag gcttcctatc
4261 ccaaccatca ggggacttit ccagcccatt ctatcccggg aactatccaa acaatgccaa
4321 gtgtgtgtgg gacattgagg tgcaaaacaa ctaccgtgtg actgtgatct tcagagatgt
4381 ccagcttgaa ggtggctgca actatgatta tattgaagtt ttcgatggcc cctaccgcag
4441 ttccccctct attgctcgag tttgtgatgg ggccagaggc tccttcactt cttcctccaa
4501 cttcatgtcc attcgcttca tcagtgacca cagcatcaca aggagagggt tccgggctga
4561 gtactactcc agtcccttca atgacagcac caacctgctc tgtctgccaa atcacatgca
4621 agccagtgtg agcaggagct atctccaatc cttgggcttt tctgccagtg accttgtcat
4681 ttccacctgg aatggatact acgagtgtcg gccccagata acgccgaacc tggtgatatt
4741 cacaattccc tactcaggct gcggcacctt caagcaggca gacaatgaca ccatcgacta
4801 ttccaacttc ctcacagcag ctgtctcagg tggcatcatc aagaggagga cagacctccg
4861 tattcacgtc agctgcagaa tgcttcagaa cacctgggtc gacaccatgt acattgctaa
4921 tgacaccatc cacgttgcta ataacaccat ccaggtcgag gaagtccagt atggcaattt
4981 tgacgtgaac atttccttit atacttcctc atctttcttg tatcctgtga ccagccgccc
5041 ttactacgtg gacctgaacc aggacttgta cgttcaggct gaaatcctcc attctgatgc
5101 tgtactgacc ttgtttgtgg acacctgcgt ggcatcacca tactccaatg acttcacgtc
5161 tttgacttat gatctaatcc ggagtggatg cgtgagggat gacacctacg gaccctactc
5221 ctcgccatct cttcgcattg cccgcttccg gttcagggcc ttccacttcc tgaaccgctt
5281 ccctccgtg tacctgcgtt gtaaaatggt ggtgtgcaga gcgtatgacc cctcttcccg
5341 ctgctaccga ggctgtgtgt tgaggtcgaa gagggatgtg ggctcctacc aggaaaaggt
5401 ggacgtcgtc ctgggtccca tccagctgca gacccccccca cgccgagaag aggagcctcg
5461 gtaggtggtc gctctcagac cccactgtcc accggggcgc agaccccctga ctcggggact
5521 tgggatgttc ctcttggtgt catattccaa ctcagattga gccctacatt gtgctgcacc
5581 tggtcatacg gagttgaatc agacctggtt cccgcctccc ccaaggctca tggtccttgg
5641 aggacccgtt gcagggtgag gtcaagagag ttctgaccig gatggcccat agacctgacg
5701 tcccagaatc catgcttctc atctgcaaaa tgaaaatgtc aatacttact tcttagcact
5761 gttgagaggg ttacttacat aaaggaattt tggtgaaact gc

Figure 22A (Continued)

MGISTVILEMCLLWGQVLSTGGWIPRTTDYASLIPSEVPLDPTVAEGSPFPSESTLESTVAEGSP
ISLESTLESTVAEGSLIPSESTLESTVAEGSDSGLALRLVNGDGRCQGRVEILYRGSWGTVCDD
SWDTNDANVVCRQLGCGWAMSAPGNAWFGQGSGPIALDDVRCSGHESYLWSCPHNGWLS
HNCGHGEDAGVICSAAQPQSTLRPESWPVRISPPVPTEGSESSLALRLVNGGDRCRGRVEVLY
RGSWGTVCDDYWDTNDANVVCRQLGCGWAMSAPGNAQFGQGSGPIVLDDVRCSGHESYL
WSCPHNGWLTHNCGHSEDAGVICSAPQSRPTPSPDTWPTSHASTAGPESSLALRLVNGGDRC
QGRVEVLYRGSWGTVCDDSWDTSDANVVCRQLGCGWATSAPGNARFGQGSGPIVLDDVRC
SGYESYLWSCPHNGWLSHNCQHSEDAGVICSAAHSWSTPSPDTLPTITLPASTVGSESSLALR
LVNGGDRCQGRVEVLYQGSWGTVCDDSWDTNDANVVCRQLGCGWAMSAPGNARFGQGS
GPIVLDDVRCSGHESYLWSCPHNGWLSHNCGHSEDAGVICSASQSRPTPSPDTWPTSHASTA
GSESSLALRLVNGGDRCQGRVEVLYRGSWGTVCDDYWDTNDANVVCRQLGCGWAMSAPG
NARFGQGSGPIVLDDVRCSGHESYLWSCPHNGWLSHNCGHHEDAGVICSASQSQPTPSPDT
WPTSHASTAGSESSLALRLVNGGDRCQGRVEVLYRGSWGTVCDDYWDTNDANVVCRQLG
CGWATSAPGNARFGQGSGPIVLDDVRCSGHESYLWSCPHNGWLSHNCGHHEDAGVICSASQ
SQPTPSPDTWPTSRASTAGSESTLALRLVNGGDRCRGRVEVLYQGSWGTVCDDYWDTNDA
NVVCRQLGCGWAMSAPGNAQFGQGSGPIVLDDVRCSGHESYLWSCPHNGWLSHNCGHHE
DAGVICSAAQSQSTPRPDTWLTTNLPALTVGSESSLALRLVNGGDRCRGRVEVLYRGSWGT
VCDDSWDTNDANVVCRQLGCGWAMSAPGNARFGQGSGPIVLDDVRCSGNESYLWSCPHK
GWLTHNCGHHEDAGVICSATQINSTTTDWWHPTTTTTARPSSNCGGFLFYASGTFSSPSYPA
YYPNNAKCVWEIEVNSGYRINLGFSNLKLEAHHNCSFDYVEIFDGSLNSSLLLGKICNDTRQI
FTSSYNRMTIHFRSDISFQNTGFLAWYNSFPSDATLRLVNLNSSYGLCAGRVEIYHGGTWGTV
CDDSWTIQEAEVVCRQLGCGRAVSALGNAYFGSGSGPITLDDVECSGTESTLWQCRNRGWF
SHNCNHREDAGVICSGNHLSTPAPFLNITRPNTDYSCGGFLSQPSGDFSSPFYPGNYPNNAKC
VWDIEVQNNYRVTVIFRDVQLEGGCNYDYIEVFDGPYRSSPLIARVCDGARGSFTSSSNFMSI
RFISDHSITRRGFRAEYYSSPSNDSTNLLCLPNHMQASVSRSYLQSLGFSASDLVISTWNGYYE
CRPQITPNLVIFTIPYSGCGTFKQADNDTIDYSNFLTAAVSGGIIKRRTDLRIHVSCRMLQNTW
VDTMYIANDTIHVANNTIQVEEVQYGNFDVNISFYTSSSFLYPVTSRPYYVDLNQDLYVQAEI
LHSDAVLTLFVDTCVASPYSNDFTSLTYDLIRSGCVRDDTYGPYSSPSLRIARFRFRAFHFLNR
FPSVYLRCKMVVCRAYDPSSRCYRGCVLRSKRDVGSYQEKVDVVLGPIQLQTPPRREEEPR

Figure 22B

1 gtagatgcag tccgccgccg ccgctgcctc agccagcaat gcaagattag atctctaaat
61 gcagcaaaac actgcctgaa aacagaccgg cccgcgcagc aagcagacat ttcacggtgc
121 gctggggaag cttcaaaata tatctgtgac tctgtcttcg ttgctcttca tccccatcaa
181 tttcatcacg ggaggcgagc agcaagtaag aatttcactt tcggatctgc ctagagacac
241 acctccctgc tccctccccc actcgatgtg aagagtattc cggagtctcc gggcgggagt
301 agatttgcag caccctagcg ggagcgagga aaacctactg attctttagc tcattatcat
361 ctctcccaga cgagatttcc ttcttatcgc ctgcctcatc gctcaagttt gagcctcccg
421 aagtccgggc gggagagacg aaaccccctgg ctcaccccca gccgcaggaa gccaccgcct
481 tgctccaagc ccctgcagct ctgctgcacc gcagcttctc acccagtgcg gatgctgtag
541 atcaacaggt tcagggaact tgagcagaat aaggagagac caccgggtgc cgcagctcgg
601 gtgcagaggg aaaaaaggac ccatagactt gtggctcgcg tcgcgcgcgc acgctgcgcc
661 agggccccag gctggcgcgc actccctctc tggctcctcc agtccgattg ctcctgcccc
721 cacttacag gtctgggatg taccttttca tctgttgctg ctttcttcta tgggcccctg
781 ccctcactct caagaaccte aactactccg tgccggagga gcaaggggcc ggcacggtga
841 tcgggaacat cggcagggat gctcgactgc agcctgggct tccgcctgca gagcgcggcg
901 gcggagggcg cagcaagtcg ggtagctacc gggtgctgga gaactccgca ccgcacctgc
961 tggacgtgga cgcagacagc gggctcctct acaccaagca gcgcatcgac cgcgagtccc
1021 tgtgccgcca caatgccaag tgccagctgt ccctcgaggt gttcgccaac gacaaggaga
1081 tctgcatgat caaggtagag atccaggaca tcaacgacaa cgcgcccctcc ttctcctcgg
1141 accagatcga aatggacatc tcggagaacg ctgctccggg cacccgcttc ccctcaccca
1201 gcgcacatga ccccgacgcc ggcgagaatg ggctccgcac ctacctgctc acgcgcgacg
1261 atcacggcct ctttggactg gacgttaagt cccgcggcga cggcaccaag ttcccagaac
1321 tggtcatcca gaaggctctg gaccgcgagc aacagaatca ccatacgctc gtgctgactg
1381 ccctggacgg tggcgagcct ccacgttccg ccaccgtaca gatcaacgtg aaggtgattg
1441 actccaacga caacagcccg gtcttcgagg cgccatccta cttggtggaa ctgccccgaga
1501 acgctccgct gggtacagtg gtcatcgatc tgaacgccac cgacgccgat gaaggtccca
1561 atggtgaagt gctctactct ttcagcagct acgtgcctga ccgcgtgcgg gagctcttct
1621 ccatcgaccc caagaccggc ctaatccgtg tgaagggcaa tctggactat gaggaaaacg
1681 ggatgctgga gattgacgtg caggcccgag acctggggcc taaccctatc ccagcccact
1741 gcaaagtcac ggtcaagctc atcgaccgca acgacaatgc gccgtccatc ggtttcgtct
1801 ccgtgcgcca gggggcgctg agcgaggccg ccctcccgg caccgtcatc gccctggtgc
1861 gggtcactga ccgggactct ggcaagaacg gacagctgca gtgtcgggtc ctaggcggag
1921 gagggacggg cggcggcggg ggcctgggcg ggccgggggg ttccgtcccc ttcaagcttg
1981 aggagaacta cgacaacttc tacacggtgg tgactgaccg cccgctggac cgcgagacac
2041 aagacgagta caacgtgacc atcgtggcgc gggacggggg ctctcctccc ctcaactcca
2101 ccaagtcgtt cgcgatcaag attctagacg agaacgacaa cccgcctcgg ttcaccaaag
2161 ggctctacgt gcttcaggtg cacgagaaca acatcccggg agagtacctg ggctctgtgc
2221 tcgcccagga tcccgaccta ggccagaacg gcaccgtatc ctactctatc ctgccctcgc
2281 acatcggcga cgtgtctatc tacacctatg tgtctgtgaa tcccacgaac ggggccatct
2341 acgccctgcg ctccttaac ttcgagcaga ccaaggcttt tgagttcaag gtgcttgcta
2401 aggactcggg ggcgcccgcg cacttggaga gcaacgccac ggtgagggtg acagtgctag
2461 acgtgaatga caacgcgcca gtgatcgtgc tccccacgct gcagaacgac accgcggagc
2521 tgcaggtgcc gcgcaacgct ggcctgggct atctggtgag cactgtgcgc gccctagaca
2581 gcgacttcgg cgagagcggg cgtctcacct acgagatcgt ggacggcaac gacgaccacc
2641 tgtttgagat cgacccgtcc agcggcgaga tccgcacgct gcaccctttc tgggaggacg
2701 tgacgcccgt ggtggagctg gtggtgaagg tgaccgacca cggcaagcct accctgtccg

Figure 23A

2761 cagtggccaa gctcatcatc cgctcggtga gcggatccct tcccgagggg gtaccacggg
2821 tgaatggcga gcagcaccac tgggacatgt cgctgccgct catcgtgact ctgagcacta
2881 tctccatcat cctcctagcg gccatgatca ccatcgccgt caagtgcaag cgcgagaaca

2941 aggagatccg cacttacaac tgccgcatcg ccgagtacag ccacccgcag ctgggtgggg
3001 gcaagggcaa gaagaagaag atcaacaaaa atgatatcat gctggtgcag agcgaagtgg
3061 aggagaggaa cgccatgaac gtcatgaacg tggtgagcag cccctccctg gccacctccc
3121 ccatgtactt cgactaccag acccgcctgc ccctcagctc gccccggtcg gaggtgatgt
3181 atctcaaacc ggcctccaac aacctgactg tccctcaggg gcacgcgggc tgccacacca
3241 gcttcaccgg acaagggact aatgcaagcg agacccctgc cactcggatg tccataattc
3301 agacagacaa ttttcccgca gagcccaatt acatgggcag caggcagcag tttgttcaaa
3361 gtatttcagt agctccacgt ttaaggaccc agaaagagcc agcctgagag acagtgggca
3421 cggggacagt gatcaggctg acagtgacca agacactaac aaaggctcct gctgtgacat
3481 gtctgttagg gaggcactca agatgaaaac tacttcaact aaaagccaac cacttgaaca
3541 agaaccagaa gagtgtgtta attgcacaga tgaatgccga gtgcttggtc attctgacag
3601 gtgctggatg ccacagttcc ctgcagccaa tcaggctgaa aatgcagatt accgcacaaa
3661 tctctttgta cctacagttg aagctaatgt tgagactgag actacgaaa ctgtgaatcc
3721 cactgggaaa aagacttttt gtacatttgg aaaagacaag cgagagcaca ctattctcat
3781 tgccaacgtt aaaccttatt taaaagccaa acgtgccctg agccctctcc tccaagaggt
3841 cccctcagca tcaagcagcc caaccaaggc gtgcatcgag ccttgcacct caacaaaagg
3901 ctccctggat ggctgtgaag caaaaccagg agccctggct gaagcaagca gtcagtactt
3961 gcccactgac agtcaatatc tgtcacctag taagcaacca agagaccctc ccttcatggc
4021 ttccgatcag atggcaaggg tctttgcaga tgtgcattcc agagccagcc gggattccag
4081 tgagatgggt gctgttcttg agcagcttga ccaccccaac agggatctgg gcagagagtc
4141 tgtggatgca gaggaagttg tgagagaaat tgataagctt ttgcaagact gccggggaaa
4201 cgaccctgtg gctgtgagaa agtgaaaaaa gaaaaaaaaa aaggcattgg catttcttg
4261 tctcttctgt tgatttaaaa atgatcccte ctggtgataa cccattttac agggatgaag
4321 aaagaccaat gctgctttaa ggcttttagt gaacatctga agtgcccaca agtatgttct
4381 ttccactgct gatttctttt tcagagataa caatggtttc gttttgacca aacttgtatt
4441 aggacagaat taatgatgct taaagagaaa agaaaaaaag agagaagaaa aaggagagat
4501 gaaaaaggag gatgaggaga agaattacct tttgacaatc tgttaggaag gtatgcagtg
4561 tgagaactga agtatttctg atcactctca gactgtcctc cgtgatttat gctgacttaa
4621 ctgtttacct ataaacccca tacaaagcag ggtcataatt tgtgatctgt ggtggatttc
4681 tagcagtcat cacaggcttc tactgaaagt cctgaaaaga ccttgcagta gtccaagcta
4741 caccaaacat taacacatat ttgtggtaaa catttctgta taaagttacc tgacacacat
4801 ataaacacaa ggaacattcc atatcattag tcgaaaacaa aaacaaaaaa aaaacctttg
4861 gtcatttgta agacatctca tgtcatataa aagttaaatg taaaaagata cagtccattt
4921 tgtcctgcac acacgtagac taattcacgt caaaaaaaaa aaaaaa

Figure 23A (Continued)

MYLSICCCFLLWAPALTLKNLNYSVPEEQGAGTVIGNIGRDARLQPGLPPAERGGGGRSKSG
SYRVLENSAPHLLDVDADSGLLYTKQRIDRESLCRHNAKCQLSLEVFANDKEICMIKVEIQDI
NDNAPSFSSDQIEMDISENAAPGTRFPLTSAHDPDAGENGLRTYLLTRDDHGLFGLDVKSRG
DGTKFPELVIQKALDREQQNHHTLVLTALDGGEPPRSATVQINVKVIDSNDNSPVFEAPSYLV
ELPENAPLGTVVIDLNATDADEGPNGEVLYSFSSYVPDRVRELFSIDPKTGLIRVKGNLDYEE
NGMLEIDVQARDLGPNPIPAHCKVTVKLIDRNDNAPSIGFVSVRQGALSEAAPPGTVIALVRV
TDRDSGKNGQLQCRVLGGGGTGGGGGLGGPGGSVPFKLEENYDNFYTVVTDRPLDRETQD
EYNVTIVARDGGSPPLNSTKSFAIKILDENDNPPRFTKGLYVLQVHENNIPGEYLGSVLAQDP
DLGQNGTVSYSILPSHIGDVSIYTYVSVNPTNGAIYALRSFNFEQTKAFEFKVLAKDSGAPAH
LESNATVRVTVLDVNDNAPVIVLPTLQNDTAELQVPRNAGLGYLVSTVRALDSDFGESGRLT
YEIVDGNDDHLFEIDPSSGEIRTLHPFWEDVTPVVELVVKVTDHGKPTLSAVAKLIIRSVSGSL
PEGVPRVNGEQHHWDMSLPLIVTLSTISIILLAAMITIAVKCKRENKEIRTYNCRIAEYSHPQL
GGGKGKKKKINKNDIMLVQSEVEERNAMNVMNVVSSPSLATSPMYFDYQTRLPLSSPRSEV
MYLKPASNNLTVPQGHAGCHTSFTGQGTNASETPATRMSIIQTDNFPAEPNYMGSRQQFVQS
ISVAPRLRTQKEPA

Figure 23B

1 aaacagcagg aaatagaaac ttaagagaaa tacacacttc tgagaaactg aaacgacagg
61 ggaaaggagg tctcactgag caccgtccca gcatccggac accacagcgg cccttcgctc
121 cacgcagaaa accacacttc tcaaaccttc actcaacact tccttcccca aagccagaag
181 atgcacaagg aggaacatga ggtggctgtg ctgggggcac ccccagcac catccttcca
241 aggtccaccg tgatcaacat ccacagcgag acctccgtgc ccgaccatgt cgtctggtcc
301 ctgttcaaca ccctcttctt gaactggtgc tgtctgggct tcatagcatt cgcctactcc
361 gtgaagtcta gggacaggaa gatggttggc gacgtgaccg gggcccaggc ctatgcctcc
421 accgccaagt gcctgaacat ctgggccctg attctgggca tcatcatgac cattggattc
481 atcctgttac tggtattcgg ctctgtgaca gtctaccata ttatgttaca gataatacag
541 gaaaaacggg gttactagta gccgcccata gcctgcaacc tttgcactcc actgtgcaat
601 gctggccctg cacgctgggg ctgttgcccc tgcccccttg gtcctgcccc tagatacagc
661 agtttatacc cacacacctg tctacagtgt cattcaataa agtgcacgtg cttgtgaaaa
721 aaaaaaaaaa aaa

Figure 24A

MHKEEHEVAVLGAPPSTILPRSTVINIHSETSVPDHVVWSLFNTLFLNWCCLGFIAFAYSVKSR
DRKMVGDVTGAQAYASTAKCLNIWALILGILMTIGFILLLVFGSVTVYHIMLQIIQEKRGY

Figure 24B

1 gcccgtcttc gtgtctcctc cctccctcgc cttcctcctt cctagctcct ctcctccagg
61 gccagactga gcccaggttg atttcaggcg gacaccaata gactccacag cagctccagg
121 agcccagaca ccggcggcca gaagcaaggc taggagctgc tgcagccatg tcggccctca
181 gcctcctcat tctgggcctg ctcacggcag tgccacctgc cagctgtcag caaggcctgg
241 ggaaccttca gccctggatg cagggcctta tcgcggtggc cgtgttcctg gtcctcgttg
301 caatcgcctt tgcagtcaac cacttctggt gccaggagga gccggagcct gcacacatga
361 tcctgaccgt cggaaacaag gcagatggag tcctggtggg aacagatgga aggtactctt
421 cgatggcggc cagtttcagg tccagtgagc atgagaatgc ctatgagaat gtgcccgagg
481 aggaaggcaa ggtccgcagc accccgatgt aaccttctct gtggctccaa ccccaagact
541 cccaggcaca tgggatggat gtccagtgct accacccaag ccccctcctt ctttgtgtgg
601 aatctgcaat agtgggctga ctcctccag ccccatgccg gcctaccccg ccttgaagt
661 atagccagcc aaggttggag ctcagaccgt gtctaggttg gggctcggct gtggccctgg
721 ggtctcctgc tcagctcaga agagccttct ggagaggaca gtcagctgag cacctcccat
781 cctgctcaca cgtccttccc cataactatg gaaatggccc taatttctgt gaaataaaga
841 ctttttgtat ttctgggggct gaggctcagc aacagcccct caggcttcca gtga

Figure 25A

MSALSLLILGLLTAVPPASCQQGLGNLQPWMQGLIAVAVFLVLVAIAFAVNHFWCQEEPEPA
HMILTVGNKADGVLVGTDGRYSSMAASFRSSEHENAYENVPEEEGKVRSTPM

Figure 25B

1 aattcactaa tgcattctgc tcttttgag agcacagctt ctcagatgtg ctccttggag
61 ctggtgtgca gtgtcctgac tgtaagatca agtccaaacc tgttttggaa ttgaggaaac
121 ttctcttttg atctcagccc ttggtggtcc aggtcttcat gctgctgtgg gtgatattac
181 tggtcctggc tcctgtcagt ggacagtttg caaggacacc caggcccatt attttcctcc
241 agcctccatg gaccacagtc ttccaaggag agagagtgac cctcacttgc aagggatttc
301 gcttctactc accacagaaa acaaaatggt accatcggta ccttgggaaa gaaatactaa
361 gagaaacccc agacaatatc cttgaggttc aggaatctgg agagtacaga tgccaggccc
421 agggctcccc tctcagtagc cctgtgcact tggatttttc ttcagcttcg ctgatcctgc
481 aagctccact ttctgtgttt gaaggagact ctgtggttct gaggtgccgg gcaaaggcgg
541 aagtaacact gaataatact atttacaaga atgataatgt cctggcattc cttaataaaa
601 gaactgactt ccatattcct catgcatgtc tcaaggacaa tggtgcatat cgctgtactg
661 gatataagga aagttgttgc cctgtttctt ccaatacagt caaaatccaa gtccaagagc
721 catttacacg tccagtgctg agagccagct ccttccagcc catcagcggg aacccagtga
781 ccctgaccta tgagacccag ctctctctag agaggtcaga tgtcccgctc cggttccgct
841 tcttcagaga tgaccagacc ctgggattag gctggagtct ctcccccgaat ttccagatta
901 ctgccatgtg gagtaaagat tcagggttct actggtgtaa ggcagcaaca atgccttaca
961 gcgtcatatc tgacagcccg agatcctgga tacaggtgca gatccctgca tctcatcctg
1021 tcctcactct cagccctgaa aaggctctga attttgaggg aaccaaggtg acacttcact
1081 gtgaaaccca ggaagattct ctgcgcactt tgtacaggtt ttatcatgag ggtgtccccc
1141 tgaggcacaa gtcagtccgc tgtgaaaggg gagcatccat cagcttctca ctgactacag
1201 agaattcagg gaactactac tgcacagctg acaatggcct tggcgccaag cccagtaagg
1261 ctgtgagcct ctcagtcact gttcccgtgt ctcatcctgt cctcaacctc agctctcctg
1321 aggacctgat ttttgaggga gccaaggtga cacttcactg tgaagcccag agaggttcac
1381 tccccatcct gtaccagttt catcatgagg gtgctgccct ggagcgtagg tcggccaact
1441 ctgcaggagg agtggccatc agcttctctc tgactgcaga gcattcaggg aactactact
1501 gcacagctga caatggcttt ggcccccagc gcagtaaggc ggtgagcctc tccgtcactg
1561 tccctgtgtc tcatcctgtc ctcaccctca gctctgctga ggccctgact tttgaaggag
1621 ccactgtgac acttcactgt gaagtccaga gaggttcccc acaaatccta taccagtttt
1681 atcatgagga catgcccctg tggagcagct caacaccctc tgtgggaaga gtgtccttca
1741 gcttctctct gactgaagga cattcaggga attactactg cacagctgac aatggctttg
1801 gtccccagcg cagtgaagtg gtgagccttt ttgtcactgt tccagtgtct cgccccatcc
1861 tcaccctcag ggttcccagg gcccaggctg tggtgggggа cctgctggag cttcactgtg
1921 aggccccgag aggctctccc ccaatcctgt actggtttta tcatgaggat gtcaccctgg
1981 ggagcagctc agccccctct ggaggagaag cttctttcaa cctctctctg actgcagaac
2041 attctggaaa ctactcatgt gaggccaaca atggcctagt ggcccagcac agtgacacaa
2101 tatcactcag tgttatagtt ccagtatctc gtcccatcct caccttcagg gctcccaggg
2161 cccaggctgt ggtgggggac ctgctggagc ttcactgtga ggccctgaga ggctcctccc
2221 caatcctgta ctggttttat catgaagatg tcaccctggg taagatctca gccccctctg
2281 gaggaggggc ctccttcaac ctctctctga ctacagaaca ttctggaatc tactcctgtg
2341 aggcagacaa tggtctggag gcccagcgca gtgagatggt gacactgaaa gttgcagttc
2401 cggtgtctcg cccggtcctc accctcaggg ctcccgggac ccatgctgcg gtgggggacc
2461 tgctggagct tcactgtgag gccctgagag gctctcccct gatcctgtac cggttttttc
2521 atgaggatgt caccctagga aataggtcgt ccccctctgg aggagcgtcc ttaaacctct
2581 ctctgactgc agagcactct ggaaactact cctgtgaggc cgacaatggc ctcggggccc
2641 agcgcagtga gacagtgaca cttatatca cagggctgac cgcgaacaga agtggccctt
2701 ttgccacagg agtcgccggg ggcctgctca gcatagcagg ccttgctgcg ggggcactgc
2761 tgctctactg ctggctctcg agaaaagcag ggagaaagcc tgcctctgac cccgccagga
2821 gcccttcaga ctcggactcc caagagccca cctatcacaa tgtaccagcc tgggaagagc

Figure 26A

2881 tgcaaccagt gtacactaat gcaaatccta gaggagaaaa tgtggtttac tcagaagtac
2941 ggatcatcca agagaaaaag aaacatgcag tggcctctga ccccaggcat ctcaggaaca
3001 agggttcccc tatcatctac tctgaagtta aggtggcgtc aaccccggtt tccggatccc
3061 tgttcttggc ttcctcagct cctcacagat gagtccacac gtctctccaa ctgctgtttc

3121 agcctctgca ccccaaagtt ccccttgggg gagaagcagc attgaagtgg gaagatttag
3181 gctgccccag accatatcta ctggcctttg tttcacatgt cctcattctc agtctgacca
3241 gaatgcaggg ccctgctgga ctgtcacctg tttcccagtt aaagccctga ctggcaggtt
3301 ttttaatcca gtggcaaggt gctcccactc cagggcccag cacatctcct ggattcctta
3361 gtgggcttca gctgtggttg ctgttctgag tactgctctc atcacacccc cacagagggg
3421 gtcttaccac acaaagggag agtgggcctt caggagatgc cgggctggcc taacagctca
3481 ggtgctccta aactccgaca cagagttcct gctttgggtg gatgcatttc tcaattgtca
3541 tcagcctggt ggggctactg cagtgtgctg ccaaatggga cagcacacag cctgtgcaca
3601 tgggacatgt gatgggtctc cccacggggg ctgcatttca cactcctcca cctgtctcaa
3661 actctaaggt cggcacttga caccaaggta acttctctcc tgctcatgtg tcagtgtcta
3721 cctgccccaag taagtggctt tcatacacca agtcccaagt tcttcccatc ctaacagaag
3781 taacccagca agtcaaggcc aggaggacca ggggtgcaga cagaacacat actggaacac
3841 aggaggtgct caattactat ttgactgact gactgaatga atgaatgaat gaggaagaaa
3901 actgtgggta atcaaactgg cataaaatcc agtgcactcc ctaggaaatc cgggaggtat
3961 tctggcttcc ctaagaaaca atggaagaga aggagcttgg atgaggaaac tgttcagcaa
4021 gaggaagggc ttctcacact ttcatgtgct tgtggatcac ctgaggatcc tgtgaaaata
4081 cagatactga ttcagtgggt ctgcgtagag cctgagactg ccattctaac atgttcccag
4141 gggatgctga tgctgctggc cctgggactg cactgcatgc atgtgaagcc ctataggtct
4201 cagcagaggc ccatggagag ggaatgtgtg gctctggctg cccagggccc aactcggttc
4261 acacggatcg tgctgctccc tggccagcct ttggccacag caccaccagc tgctgttgct
4321 gagagagctt cttctctgtg acatgttggc tttcatcagc cacccctggga agcggaaagt
4381 agctgccact atctttgttt ccccacctca ggcctcacac tttcccatga aaagggtgaa
4441 tgtatataac ctgagccctc tccattcaga gttgttctcc catctctgag caatgggatg
4501 ttctgttccg cttttatgat atccatcaca tcttatcttg atctttgctc ccagtggatt
4561 gtacagtgat gacttttaag ccccacggcc ctgaaataaa atccttccaa gggcattgga
4621 agctcactcc acctgaacca tggcttttca tgcttccaag tgtcagggcc ttgcccagat
4681 agacagggct ggctctgctg ccccaaccct tcaaggagga aaccagacac ctgagacagg
4741 agcctgtatg cagcccagtg cagccttgca gaggacaagg ctggaggcat ttgtcatcac
4801 tacagatatg caactaaaat agacgtggag caagagaaat gcattcccac cgaggccgct
4861 tttttaggcc tagttgaaag tcaagaagga cagcagcaag cataggctca ggattaaaga
4921 aaaaaatctg ctcacagtct gttctggagg tcacatcacc aacaaagctc acgccctatg
4981 cagttctgag aaggtggagg caccaggctc aaaagaggaa atttagaatt tctcattggg
5041 agagtaaggt accccccatcc cagaatgata actgcacagt ggcagaacaa actccaccct
5101 aatgtgggtg gaccccgtcc agtctgttga aggcctgaat gtaacaaaag ggcttattct
5161 tcctcaagta agggggaact cctgctttgg gctgggacat aagtttttct gctttcagac
5221 gcaaactgaa aaatggctct tcttgggtct tgagcttgct ggcatatgga ctgaaagaaa
5281 ctatgctatt ggatctcctg gatctccagc ttgctgactg cagatcttga gatatgtcag
5341 cctctacagt cacaagagct aattcattct aataaaccaa tctttctgta aaaaa

Figure 26A (Continued)

MLLWVILLVLAPVSGQFARTPRPIIFLQPPWTTVFQGERVTLTCKGFRFYSPQKTKWYHRYLG
KEILRETPDNILEVQESGEYRCQAQGSPLSSPVHLDFSSASLILQAPLSVFEGDSVVLRCRAKA
EVTLNNTIYKNDNVLAFLNKRTDFHIPHACLKDNGAYRCTGYKESCCPVSSNTVKIQVQEPF
TRPVLRASSFQPISGNPVTLTCETQLSLERSDVPLRFRFFRDDQTLGLGWSLSPNFQITAMWSK
DSGFYWCKAATMPYSVISDSPRSWIQVQIPASHPVLTLSPEKALNFEGTKVTLHCETQEDSLR
TLYRFYHEGVPLRHKSVRCERGASISFSLTTENSGNYYCTADNGLGAKPSKAVSLSVTVPVSH
PVLNLSSPEDLIFEGAKVTLHCEAQRGSLPILYQFHHEGAALERRSANSAGGVAISFSLTAEHS
GNYYCTADNGFGPQRSKAVSLSVTVPVSHPVLTLSSAEALTFEGATVTLHCEVQRGSPQILY
QFYHEDMPLWSSSTPSVGRVSFSFSLTEGHSGNYYCTADNGFGPQRSEVVSLFVTVPVSRPIL
TLRVPRAQAVVGDLLELHCEAPRGSPPILYWFYHEDVTLGSSSAPSGGEASFNLSLTAEHSGN
YSCEANNGLVAQHSDTISLSVIVPVSRPILTFRAPRAQAVVGDLLELHCEALRGSSPILYWFYH
EDVTLGKISAPSGGGASFNLSLTTEHSGIYSCEADNGLEAQRSEMVTLKVAVPVSRPVLTLRA
PGTHAAVGDLLELHCEALRGSPLILYRFFHEDVTLGNRSSPSGGASLNLSLTAEHSGNYSCEA
DNGLGAQRSETVTLYITGLTANRSGPFATGVAGGLLSIAGLAAGALLLYCWLSRKAGRKPAS
DPARSPSDSDSQEPTYHNVPAWEELQPVYTNANPRGENVVYSEVRIIQEKKKHAVASDPRHL
RNKGSPIIYSEVKVASTPVSGSLFLASSAPHR

Figure 26B

1 gggacgcccg ggcggccctg aaggggacgg ggcggcccca gtcggaggtc gcagggagct
61 ccgccccccga ctcggtataa gagctgggcc cggcccacgg cggcggcggc ggcggcggag
121 agagctggct cagggcgtcc gctaggctcg gacgacctgc tgagcctccc aaaccgcttc
181 cataaggctt tgcctttcca acttcagcta cagtgttagc taagtttgga aagaaggaaa
241 aaagaaaatc cctgggcccc ttttcttttg ttctttgcca aagtcgtcgt tgtagtcttt
301 ttgcccaagg ctgttgtgtt ttagaggtc ctatctccag ttccttgcac tcctgttaac
361 aagcacctca gcgagagcag cagcagcgat agcagccgca gaagagccag cggggtcgcg
421 tagtgtcatg accagggcgg gagatcacaa ccgccagaga ggatgctgtg gatccttggc
481 cgactacctg acctctgcaa aattccttct ctaccttggt cattctctct ctacttgggg
541 agatcggatg tggcacttta cggtgtctgt gtttctggta gagctctatg gaaacagcct
601 ccttttgaca gcagtctacg ggctggtggt ggcagggtct gttctggtcc tgggagccat
661 catcggtgac tgggtggaca agaatgctag acttaaagtg gcccagacct cgctggtggt
721 acagaatgtt tcagtcatcc tgtgtggaat catcctgatg atggttttct tacataaaca
781 tgagcttctg accatgtacc atggatgggt tctcacttcc tgctatatcc tgatcatcac
841 tattgcaaat attgcaaatt tggccagtac tgctactgca atcacaatcc aaagggattg
901 gattgttgtt gttgcaggag aagacagaag caaactagca aatatgaatg ccacaatacg
961 aaggattgac cagttaacca acatcttagc ccccatggct gttggccaga ttatgacatt
1021 tggctcccca gtcatcggct gtggctttat ttcgggatgg aacttggtat ccatgtgcgt
1081 ggagtacgtt ctgctctgga aggtttacca gaaaacccca gctctagctg tgaaagctgg
1141 tcttaaagaa gaggaaactg aattgaaaca gctgaattta cacaaagata ctgagccaaa
1201 acccctggag ggaactcatc taatgggtgt gaaagactct aacatccatg agcttgaaca
1261 tgagcaagag cctacttgtg cctcccagat ggctgagccc ttccgtacct tccgagatgg
1321 atgggtctcc tactacaacc agcctgtgtt tctggctggc atgggtcttg ctttccttta
1381 tatgactgtc ctgggctttg actgcatcac cacagggtac gcctacactc agggactgag
1441 tggttccatc ctcagtattt tgatgggagc atcagctata actggaataa tgggaactgt
1501 agcttttact tggctacgtc gaaaatgtgg tttggttcgg acaggtctga tctcaggatt
1561 ggcacagctt tcctgtttga tcttgtgtgt gatctctgta ttcatgcctg gaagcccccc
1621 ggacttgtcc gtttctcctt ttgaagatat ccgatcaagg ttcattcaag gagagtcaat
1681 tacacctacc aagataccctg aaattacaac tgaaatatac atgtctaatg ggtctaattc
1741 tgctaatatt gtcccggaga caagtcctga atctgtgccc ataatctctg tcagtctgct
1801 gtttgcaggc gtcattgctg ctagaatcgg tctttggtcc tttgatttaa ctgtgacaca
1861 gttgctgcaa gaaaatgtaa ttgaatctga aagaggcatt ataaatggtg tacagaactc
1921 catgaactat cttcttgatc ttctgcattt catcatggtc atcctggctc caaatcctga
1981 agcttttggc ttgctcgtat tgatttcagt ctcctttgtg gcaatgggcc acattatgta
2041 tttccgattt gcccaaaata ctctgggaaa caagctcttt gcttgcggtc ctgatgcaaa
2101 agaagttagg aaggaaaatc aagcaaatac atctgttgtt tgagacagtt taactgttgc
2161 tatcctgtta ctagattata tagagcacat gtgcttattt tgtactgcag aattccaata
2221 aatggctggg tgttttgctc tgttttacc acagctgtgc cttgagaact aaaagctgtt
2281 taggaaacct aagtcagcag aaattaactg attaatttcc cttatgttga ggcatggaaa
2341 aaaaattgga aaagaaaaac tcagtttaaa tacggagact ataatgataa cactgaattc
2401 ccctatttct catgagtaga tacaatctta cgtaaaagag tggttagtca cgtgaattca
2461 gttatcattt gacagattct tatctgtact agaattcaga tatgtcagtt ttctgcaaaa
2521 ctcactcttg ttcaagacta gctaatttat ttttttgcat cttagttatt tttaaaaaca
2581 aattcttcaa gtatgaagac taaattttga taactaatat tatccttatt gatcctattg
2641 atcttaaggt atttacatgt atgtggaaaa acaaaacact taactagaat tctctaataa
2701 ggtttatggt ttagcttaaa gagcaccttt gtatttttat tatcagatgg ggcaacatat
2761 tgtatgaagc atatgtagca cttcacagca tggttatcat gtaagctgca ggtagaagca
3061 cacactcagg tagaatattt ttatttttac tgttttatac ccagaagtta tttctacatt

Figure 27A

2821 aagctgtaaa gtagatttat cacacaatga ctgcatacag acttcaaata tgtcaatagt
2881 ttggtcatag aacctagaag ccaaaagcca cacagaaggg caagaatccc aatttaactc
2941 atgttatcat cattagtgat ctgtgttgta gaacatgagg gtgtaagcct tcagcctggc

3001 aagttacatg tagaaagccc acacttgtga aggttttgtt ttacaaatca cttgatttaa
3121 gttctacagc aagaatattc ataaaagtat ccctttcaaa tgcctttgag aagaatagaa
3181 gaaaaaaagt ttgtatatat tttaaaaaat tgttttaaaa gtcagtttgc aacatgtctg
3241 taccaagatg gtactttgcc ttaaccgttt atatgcactt tcatggagac tgcaatacgt
3301 tgctatgagc actttcttta tccttggagt ttaatccttt gcttcatctt tctacagtat
3361 gacataatga tttgctatgt tgtaaaatct ttgtaaaaaa tttctatata aaaatatttt
3421 gaaaatctta aaaaaaaaaa aaaaaaaaaa aaaaaaa

Figure 27A (Continued)

MTRAGDHNRQRGCCGSLADYLTSAKFLLYLGHSLSTWGDRMWHFAVSVFLVELYGNSLLL
TAVYGLVVAGSVLVLGAIIGDWVDKNARLKVAQTSLVVQNVSVILCGIILMMVFLHKHELL
TMYHGWVLTSCYILIITIANIANLASTATAITIQRDWIVVVAGEDRSKLANMNATIRRIDQLTN
ILAPMAVGQIMTFGSPVIGCGFISGWNLVSMCVEYVLLWKVYQKTPALAVKAGLKEEETEL
KQLNLHKDTEPKPLEGTHLMGVKDSNIHELEHEQEPTCASQMAEPFRTFRDGWVSYYNQPV
FLAGMGLAFLYMTVLGFDCITTGYAYTQGLSGSILSILMGASAITGIMGTVAFTWLRRKCGL
VRTGLISGLAQLSCLILCVISVFMPGSPLDLSVSPFEDIRSRFIQGESITPTKIPEITTEIYMSNGSN
SANIVPETSPESVPIISVSLLFAGVIAARIGLWSFDLTVTQLLQENVIESERGIINGVQNSMNYLL
DLLHFIMVILAPNPEAFGLLVLISVSFVAMGHIMYFRFAQNTLGNKLFACGPDAKEVRKENQ
ANTSVV

Figure 27B

GCTCTAGAACTAGTGGATCCCCCGGGCTGCAGGAATTCTCTAAAGAAGCCCCTGGGAGC
A
CAGCTCATCACCATGGACTGGACCTGGAGGTTCCTCTTTGTGGTGGCAGCAGCTACAGGT
GTCCAGTCCCAGGTGCAGCTGGTGCAGTCTGGGGCTGAGGTGAAGAAGCCTGGGTCCTC
G
GTGAAGGTCTCCTGCAAGGCTTCTGGAGGCACCTTCAGCAGCTATGCTATCAGCTGGGTG
CGACAGGCCCCTGGACAAGGGCTTGAGTGGATGGGAGGGATCATCCCTATCTTTGGTAC
A
GCAAACTACGCACAGAAGTTCCAGGGCAGAGTCACGATTACCGCGGACGAATCCACGAG
C
ACAGCCTACATGGAGCTGAGCAGCCTGAGATCTGAGGACACGGCCGTGTATTACTGTGC
G
AAAACCGGGATCCTGGGGCCGTATAGCAGTGGCTGGTACCCGAACTCGGACTACTACTA
C
TACGGTATGGACGTCTGGGGCCAAGGGACCACGGTCACCGTCTCCTCAGGGAGTGCATC
C
GCCCCAACCCTTTTCCCCCTCGTCTCCTGTGAGAATTCCCCGTCGGATACGAGCAGCGTG
GCCGTTGGCTGCCTCGCACAGGACTTCCTTCCCGACTCCATCACTTTCTCCTGGAAATAC
AAGAACAACTCTGACATCAGCAGCACCCGGGGCTTCCCATCAGTCCTGAGAGGGGGCAA
G
TACGCAGCCACCTCACAGGTGCTGCTGCCTTCCAAGGACGTCATGCAGGGCACAGACGA
A
CACGTGGTGTGCAAAGTCCAGCACCCCAACGGCAACAAAGAAAAGAACGTGCCTCTTCC
A
GTGATTGCTGAGCTGCCTCCCAAAGTGAGCGTCTTCGTCCCACCCCGCGACGGCTTCTTC
GGCAACCCCCGCAGCAAGTCCAAGCTCATCTGCCAGGCCACGGGTTTCAGTCCCCGGCA
G
ATTCAGGTGTCCTGGCTGCGCGAGGGGAAGCAGGTGGGGTCTGGCGTCACCACGGACCA
G
GTGCAGGCTGAGGCCAAAGAGTCTGGGCCCACGACCTACAAGGTGACCAGCACACTGAC
C
ATCAAAGAGAGCGACTGGCTCAGCCAGAGCATGTTCACCTGCCGCGTGGATCACAGGGG
C
CTGACCTTCCAGCAGAATGCGTCCTCCATGTGTGTCCCCGATCAAGACACAGCCATCCGG
GTCTTCGCCATCCCCCCATCCTTTGCCAGCATCTTCCTCACCAAGTCCACCAAGTTGACC
TGCCTGGTCACAGACCTGACCACCTATGACAGCGTGACCATCTCCTGGACCCGCCAGAAT
GGCGAAGCTGTGAAAACCCACACCAACATCTCCGAGAGCCACCCCAATGCCACTTTCAG
C
GCCGTGGGTGAGGCCAGCATCTGCGAGGATGACTGGAATTCCGGGGAGAGGTTCACGTG
C
ACCGTGACCCACACAGACCTGCCCTCGCCACTGAAGCAGACCATCTCCCGGCCCAAGGG
G
GTGGCCCTGCACAGGCCCGATGTCTACTTGCTGCCACCAGCCCGGGAGCAGCTGAACCTG
CGGGAGTCGGCCACCATCACGTGCCTGGTGACGGGCTTCTCTCCCGCGGACGTCTTCGTG
CAGTGGATGCAGAGGGGGCAGCCCTTGTCCCCGGAGAAGTATGTGACCAGCGCCCCAAT
G
CCTGAGCCCCAGGCCCCAGGCCGGTACTTCGCCCACAGCATCCTGACCGTGTCCGAAGA
G
GAATGGAACACGGGGGAGACCTACACCTGCGTGGTGGCCCATGAGGCCCTGCCCAACAG
G
GTCACCGAGAGGACCGTGGACAAGTCCACCGAGGGGGAGGTGAGCGCCGACGAGGAGG
GC
TTTGAGAACCTGTGGGCCACCGCCTCCACCTTCATCGTCCTCTTCCTCCTGAGCCTCTTC
TACAGTACCACCGTCACCTTGTTCAAGGTGAAATGATCCCAACAGAAGAACATCGGAGA
C

CAGAGAGAGGAACTCAAAGGGGCGCTGCCTCCGGGTCTGGGGTCCTGGCCTGCGTGGCC
T
GTTGGCACGTGTTTCTCTTCCCGCCCGGCCTCCAGTTGTGTGCTCTCACACAGGCTTCCT
TCTCGACCGGCAGGGGCTGGCTGGCTTGCAGGCCACGAGGTGGGCTCTACCCCACACTG
C
TTTGCTGTGTATACGCTTGTTGCCCTGAAATAAATATGCACATTTTATCCATG

Figure 28A

MDWTWRFLFVVAAATGVQSQVQLVQSGAEVKKPGSSVKVSCKASGGTFSSYAISWVRQAP
GQGLEWMGGIIPIFGTANYAQKFQGRVTITADESTSTAYMELSSLRSEDTAVYYCAKTGILGP
YSSGWYPNSDYYYYGMDVWGQGTTVTVSSGSASAPTLFPLVSCENSPSDTSSVAVGCLAQD
FLPDSITFSWKYKNNSDISSTRGFPSVLRGGKYAATSQVLLPSKDVMQGTDEHVVCKVQHPN
GNKEKNVPLPVIAELPPKVSVFVPPRDGFFGNPRSKSKLICQATGFSPRQIQVSWLREGKQVG
SGVTTDQVQAEAKESGPTTYKVTSTLTIKESDWLSQSMFTCRVDHRGLTFQQNASSMCVPD
QDTAIRVFAIPPSFASIFLTKSTKLTCLVTDLTTYDSVTISWTRQNGEAVKTHTNISESHPNATF
SAVGEASICEDDWNSGERFTCTVTHTDLPSPLKQTISRPKGVALHRPDVYLLPPAREQLNLRE
SATITCLVTGFSPADVFVQWMQRGQPLSPEKYVTSAPMPEPQAPGRYFAHSILTVSEEEWNT
GETYTCVVAHEALPNRVTERTVDKSTEGEVSADEEGFENLWATASTFIVLFLLSLFYSTTVTL
FKVK

Figure 28B

1 ccatccctga gatcttttta taaaaaaccc agtctttgct gaccagacaa agcataccag
61 atctcaccag agagtcctag gggactacag aaggaaaaag acaagaggca gtaggatatc
121 tgtgtgtcct cccgctgacc acacttcctt tagtgacccg attgcctcct caagtcgcag
181 acactatgct gcctcccatg gccctgccca gtgtgtcctg gatgctgctt tcctgcctca
241 ttctcctgtg tcaggttcaa ggtgaagaaa cccagaagga actgccctct ccacggatca
301 gctgtcccaa aggctccaag gcctatggct ccccctgcta tgccttgttt ttgtcaccaa
361 aatcctggat ggatgcagat ctggcttgcc agaagcggcc ctctggaaaa ctggtgtctg
421 tgctcagtgg ggctgaggga tccttcgtgt cctccctggt gaggagcatt agtaacagct
481 attcatacat ctggattggg ctccatgacc ccacacaggg ctctgagcct gatggagatg
541 gatgggagtg gagtagcact gatgtgatga attactttgc atgggagaaa aatccctcca
601 ccatcttaaa ccctggccac tgtgggagcc tgtcaagaag cacaggattt ctgaagtgga
661 aagattataa ctgtgatgca aagttaccct atgtctgcaa gttcaaggac tagggcaggt
721 gggaagtcag cagcctgagc ttggcgtgca gctcatcatg gacatgagac cagtgtgaag
781 actcaccctg gaagagaata ttctccccaa actgccctac ctgactacct tgtcatgatc
841 ctccttcttt ttccttttc ttcaccttca tttcaggctt ttctctgtct tccatgtctt
901 gagatctcag agaataataa taaaaatgtt actttatacg taaaaaa

Figure 29A

MLPPMALPSVSWMLLSCLILLCQVQGEETQKELPSPRISCPKGSKAYGSPCYALFLSPKSWMD
ADLACQKRPSGKLVSVLSGAEGSFVSSLVRSISNSYSYIWIGLHDPTQGSEPDGDGWEWSSTD
VMNYFAWEKNPSTILNPGHCGSLSRSTGFLKWKDYNCDAKLPYVCKFKD

Figure 29B

aacacaactg gcacatctct tttctcatct cttgaaaaaa accaacagag aaaaaagtac cttgagaata aaggtaatga ttaatctgtc
aggcacaaaa gggattgttt tggggatttc gggttctaag tcgcagattc aaacaaatag cagcgaacag ggaatgacag ttccaccaga
agacgattaa gccacagcct ctaattggaa cggcatttgt acagtcagag actcttacca gacatctcca ggaatctgtg agccattgtc
aaaacgtcca ttttcatctg gctgtgaaag tgaggaccac aacaggtagg tattggtaga aacaggagtc ctcagagaag ccccaagatg
cagcctgagg gagcagaaaa gggaaaaagc ttcaagcaga gactggtctt gaagagcagc ttagcgaaag aaaccctctc tgagttcttg
ggcacgttca tcttgattgt ccttggatgt ggctgtgttg cccaagctat tctcagtcga ggacgttttg gaggggtcat cactatcaat
gttggatttt caatggcagt tgcaatggcc atttatgtgg ctggcggtgt ctctggtggt cacatcaacc cagctgtgtc tttagcaatg
tgtctctttg gacggatgaa atggttcaaa ttgccatttt atgtgggagc ccagttcttg ggagcctttg tgggggctgc aaccgtcttt
ggcatttact atgatggact tatgtccttt gctggtggaa aactgctgat cgtgggagaa aatgcaacag cacacatttt tgcaacatac
ccagctccgt atctatctct ggcgaacgcatttgcagatc aagtggtggc caccatgata ctcctcataa tcgtctttgc catctttgac
tccagaaact tgggagcccc cagaggccta gagcccattg ccatcggcct cctgattatt gtcattgctt cctccctggg actgaacagt
ggctgtgcca tgaacccagc tcgagacctg agtcccagac ttttcactgc cttggcaggc tgggggtttg aagtcttcag agctggaaac
aacttctggt ggattcctgt agtgggccct ttggttggtg ctgtcattgg aggcctcatc tatgttcttg tcattgaaat ccaccatcca
gagcctgact cagtctttaa gacagaacaa tctgaggaca aaccagagaa atatgaactc agtgtcatca tgtagtggca tgctcagctc
tggatttgca gtcagtttgg gattctcttc agaaagatgg catctaagtg tctgtgttct tgtaagcctg aggtggaatc cacccagttt
tgtctgctag ccatatggga catctaattg
gaaaagcatc tgcataaaag tttggaaaca atgaccactt ctctaccatt gtccccccacc cccacccccc agaataacgc tgactgtccc
ctgaaacagc cttctctcct gccctgttta tttcatcctc gatgggaatt cttgctaggt aagcactaat aactcggcat cttgacgata
gtcccatttg ggtggtttca gctgcactat ctgtatgaaa tggtgtcacc aaaacccttt tcttcagtat cgacaaagat tacattctga
gtaccaacca aaccctaaat tgaaagacaa aactatggtt tcagtcaaca tattcatgaa ttagggagct aatgggttaa gcttccagtt
cccgctatgc tactggattt gtataaatac tgatattctc caaacctagt ggtgtaggga gcaagagaat gcagctggaa ggcacaaggg
gaggacattg tggcattcag aaactgcagg agacaagatg aatttgagaa gccaaatgga atttttaatg gaaaccattt atcagattaa
tctcttgctc tcctgcattt tagaggacac caattaattt cctggtcttt agtatataat aacctaaaat accattgtaa cctcagtcat
gaaaaataca tcactctgtc ttttagctc aaatgtattt tcctaattgc ccacttgaga acagacattt gacaagttat atcaacgact
gtgcttgtcc attattttac acatgcccta gaagccaaaa ctgaaagcca ctggatcctg gtctagctga atcttcagag tgggaggtct
ccaaaaagat attaccttat tgggcttaac aattcacaag gcactttcac acccattatc taatttaatc ctcataatga ctatgtgagg
caaatgccac attgcccatt tttcagataa agaaacaaaa tcttagggaa gataagttga gttgtccaag agcacactga aagttgaatg
ttatctaatg cattcctcta cctttcagaa
gatcagtagc tggctgagaa tctttgccaa atcttccttg ctagccagaa gtggaattgg cagcttctag aatatgtaca cctctggaca
aaatgttcct caatcttaag atacaaagac cctcattgtc tgggtctatt cccacactta ctgagtacag atgaaggaaa gtggtagcaa
tttaatcata actttcattt gctgaaaaac attatgagaa ggcctcccct cctaagccac ctctggtctt gctaagtctt gatcttgctt
cctgccagca ccaaacatta cattcagggg atttcctctg gctcagtctt ttcccttga agttctctaa tagatgttac ttttgacaaa
agatcgccta tgagttacaa gcaccagggg atgctctaca tcaagggatg caccttcagt caaactgtca aaaagcccag aattcccaaa
ggcattaggt ttcccaactg ctttgtgctg atatcagaac agcagaaatt aaatgtgaaa tgtttctgat gacttatgtt ctacaatcta
tggacatacg ggatttttt ttcttgcttt gaagctacct ggatatttcc tatttgaaat aaaattgttc ggtcattgtt gaaaaaaaaa aaa

Figure 30A

MQPEGAEKGKSFKQRLVLKSSLAKETLSEFLGTFILIVLGCGCVAQAILSRGRFGGVITINVGF
SMAVAMAIYVAGGVSGGHINPAVSLAMCLFGRMKWFKLPFYVGAQFLGAFVGAATVFGIY
YDGLMSFAGGKLLIVGENATAHIFATYPAPYLSLANAFADQVVATMILLIIVFAIFDSRNLGAP
RGLEPIAIGLLIIVIASSLGLNSGCAMNPARDLSPRLFTALAGWGFEVFRAGNNFWWIPVVGPL
VGAVIGGLIYVLVIEIHHPEPDSVFKTEQSEDKPEKYELSVIM

Figure 30B

1 atgaggcccg gcctctcatt tctcctagcc cttctgttct tccttggcca agctgcaggg
61 gatttggggg atgtgggacc tccaattccc agccccggct tcagctcttt cccaggtgtt
121 gactccagct ccagcttcag ctccagctcc aggtcgggct ccagctccag ccgcagctta
181 ggcagcggag gttctgtgtc ccagttgttt tccaatttca ccggctccgt ggatgaccgt
241 gggacctgcc agtgctctgt ttccctgcca gacaccacct ttcccgtgga cagagtggaa
301 cgcttggaat tcacagctca tgttctttct cagaagtttg agaaagaact ttccaaagtg
361 agggaatatg tccaattaat tagtgtgtat gaaaagaaac tgttaaacct aactgtccga
421 attgacatca tggagaagga taccatttct tacactgaac tggacttcga gctgatcaag
481 gtagaagtga aggagatgga aaaactggtc atacagctga aggagagttt tggtggaagc
541 tcagaaattg ttgaccagct ggaggtggag ataagaaata tgactctctt ggtagagaag
601 cttgagacac tagacaaaaa caatgtcctt gccattcgcc gagaaatcgt ggctctgaag
661 accaagctga aagagtgtga ggcctctaaa gatcaaaaca ccctgtcgt ccaccctcct
721 cccactccag ggagctgtgg tcatggtggt gtggtgaaca tcagcaaacc gtctgtggtt
781 cagctcaact ggagagggtt ttcttatcta tatggtgctt ggggtaggga ttactctccc
841 cagcatccaa acaaaggact gtattgggtg gcgccattga atacagatgg gagactgttg
901 gagtattata gactgtacaa cacactggat gatttgctat tgtatataaa tgctcgagag
961 ttgcggatca cctatggcca aggtagtggt acagcagttt acaacaacaa catgtacgtc
1021 aacatgtaca acaccgggaa tattgccaga gttaacctga ccaccaacac gattgctgtg
1081 actcaaactc tccctaatgc tgcctataat aaccgctttt catatgctaa tgttgcttgg
1141 caagatattg actttgctgt ggatgagaat ggattgtggg ttatttattc aactgaagcc
1201 agcactggta acatggtgat tagtaaactc aatgacacca cacttcaggt gctaaacact
1261 tggtatacca agcagtataa accatctgct tctaacgcct tcatggtatg tggggttctg
1321 tatgccaccc gtactatgaa caccagaaca gaagagattt tttactatta tgacacaaac
1381 acagggaaag agggcaaact agacattgta atgcataaga tgcaggaaaa agtgcagagc
1441 attaactata acccttttga ccagaaactt tatgtctata acgatggtta ccttctgaat
1501 tatgatcttt ctgtcttgca gaagccccag taagctgttt aggagttagg gtgaaagaga
1561 aaatgtttgt tgaaaaaata gtcttctcca cttacttaga tatctgcagg ggtgtctaaa
1621 agtgtgttca ttttgcagca atgtttaggt gcatagttct accacactag agatctagga
1681 catttgtctt gatttggtga gttctcttgg gaatcatctg cctcttcagg cgcatttgc
1741 aataaagtct gtctagggtg ggattgtcag aggtctaggg gcactgtggg cctagtgaag
1801 cctactgtga ggaggcttca ctagaagcct taaattagga attaaggaac ttaaaactca
1861 gtatggcgtc tagggattct ttgtacagga aatattgccc aatgactagt cctcatccat
1921 gtagcaccac taattcttcc atgcctggaa gaaacctggg gacttagtta ggtagattaa
1981 tatctggagc tcctcgaggg accaaatctc caacttttt ttccctcac tagcacctgg
2041 aatgatgctt tgtatgtggc agataagtaa atttggcatg cttatatatt ctacatctgt
2101 aaagtgctga gttttatgga gagaggcctt tttatgcatt aaattgtaca tggcaaataa
2161 atcccagaag gatctgtaga tgaggcacct gcttttctt ttctctcatt gtccaccttа
2221 ctaaaagtca gtagaatctt ctacctcata acttccttcc aaaggcagct cagaagatta
2281 gaaccagact tactaaccaa ttccaccccc caccaacccc cttctactgc ctacttaaa
2341 aaaattaata gttttctatg gaactgatct aagattagaa aaattaattt tctttaattt
2401 cattatgaac ttttatttac atgactctaa gactataaga aaatctgatg gcagtgacaa
2461 agtgctagca tttattgtta tctaataaag accttggagc atatgtgcaa cttatgagtg
2521 tatcagttgt tgcatgtaat ttttgccttt gtttaagcct ggaacttgta agaaaatgaa
2581 aatttaattt ttttttctag gacgagctat agaaaagcta ttgagagtat ctagttaatc
2641 agtgcagtag ttggaaacct tgctggtgta tgtgatgtgc ttctgtgctt ttgaatgact
2701 ttatcatcta gtctttgtct attttccttt tgatgttcaa gtcctagtct ataggattgg
2761 cagtttaaat gctttactcc ccctttaaa ataaatgatt aaaatgtgct ttgaaaaaaa
2821 aaaaaaaaaa aaaaaaaaaa aaaa

Figure 31A

MRPGLSFLLALLFFLGQAAGDLGDVGPPIPSPGFSSFPGVDSSSSFSSSSRSGSSSSRSLGSGGS
VSQLFSNFTGSVDDRGTCQCSVSLPDTTFPVDRVERLEFTAHVLSQKFEKELSKVREYVQLIS
VYEKKLLNLTVRIDIMEKDTISYTELDFELIKVEVKEMEKLVIQLKESFGGSSEIVDQLEVEIRN
MTLLVEKLETLDKNNVLAIRREIVALKTKLKECEASKDQNTPVVHPPPTPGSCGHGGVVNIS
KPSVVQLNWRGFSYLYGAWGRDYSPQHPNKGLYWVAPLNTDGRLLEYYRLYNTLDDLLLY
INARELRITYGQGSGTAVYNNNMYVNMYNTGNIARVNLTTNTIAVTQTLPNAAYNNRFSYA
NVAWQDIDFAVDENGLWVIYSTEASTGNMVISKLNDTTLQVLNTWYTKQYKPSASNAFMV
CGVLYATRTMNTRTEEIFYYYDTNTGKEGKLDIVMHKMQEKVQSINYNPFDQKLYVYNDG
YLLNYDLSVLQKPQ

Figure 31B

1 aaacactctg tgtggctcct cggctttgac agagtgcaag acgatgactt gcaaaatgtc
61 gcagctggaa cgcaacatag agaccatcat caacaccttc caccaatact ctgtgaagct
121 ggggcaccca gacaccctga accaggggga attcaaagag ctggtgcgaa aagatctgca
181 aaattttctc aagaaggaga ataagaatga aaaggtcata gaacacatca tggaggacct
241 ggacacaaat gcagacaagc agctgagctt cgaggagttc atcatgctga tggcgaggct
301 aacctgggcc tcccacgaga agatgcacga gggtgacgag ggccctggcc accaccataa
361 gccaggcctc ggggagggca ccccctaaga ccacagtggc caagatcaca gtggccacgg
421 ccacggccac agtcatggtg gccacggcca cagccactaa tcaggaggcc aggccaccct
481 gcctctaccc aaccagggcc ccggggcctg ttatgtcaaa ctgtcttggc tgtggggcta
541 ggggctgggg ccaaataaag tctcttcctc caagtcaaaa aaaaaa

Figure 32A

MTCKMSQLERNIETIINTFHQYSVKLGHPDTLNQGEFKELVRKDLQNFLKKENKNEKVIEHIM
EDLDTNADKQLSFEEFIMLMARLTWASHEKMHEGDEGPGHHHKPGLGEGTP

Figure 32B

1 gccagcagcc tctaagagct cctagacggc ctttggcttt ggctggcaca ggggtgaagg
61 agagccagcg gcattgagta accaggcgaa tgtgccccca ggagagttca ttccaaccct
121 cccagttcct actgctggtg ggggtcccag tggcaagtgt cctccttctg gcccaatgcc
181 ttcgatggca ctgccctaga aggctgctgg gggcctgctg gacactgaat ggtcaagagg
241 aaccagtgtc ccagcctacc ccccaactag aaaatgaggt ctcaaggcag cacctgccag
301 ccacactgcc agagatggtt gccttctacc aggagctaca cacacccact caaggccaga
361 ccatggtccg ccagttgatg cacaaactgt tggtgttttc ggctcgagag gtggatcacc
421 gcggcggttg cctgatgctc caggatacag gcatctcctt gctcatccca ccaggtgctg
481 tggctgtggg ccgccaggag cgggtgtctt tgatcctggt gtgggacctg tcggacgccc
541 catcgctgtc ccaagcccag gggctggtaa gccctgtggt ggcatgtggc ccccatgggg
601 cctccttcct gaagccttgc actctcacgt tcaaacactg tgccgagcag cccagccatg
661 ctcgcaccta cagcagcaac actaccctgc tggatgccaa ggtatggagg cccctggggc
721 ggccgggggc ccacgcctcc cgggatgagt gtcgcatcca cctctcccac ttcagcctct
781 acacctgtgt gctggaggca cctgtggggc gcgaagcccg caaatggctg cagctggccg
841 tattctgctc accgctggtg ccaggacagt cccatctgca actgcgtatc tacttcctca
901 acaacacgcc ctgcgcccctg cagtgggcac tgaccaacga gcagccccat ggtgggcgcc
961 tgcgtgggcc ctgccagctc ttcgacttca atggggctag gggcgaccag tgcctgaagc
1021 tcacgtacat ctcagagggt tgggagaatg tggatgacag cagttgccag ctggttcccc
1081 atctccacat ctggcatgga aagtgccccc tccgctcctt ctgcttccgg agaaaagcag
1141 ccgatgagaa tgaggactgt tcagcactaa ccaatgagat cattgtcacc atgcacacct
1201 tccaggatgg cttggagacc aagtatatgg aaatcctcag attccaggca tcagaggagg
1261 aatcctgggc agcgccacca cctgtttccc agccgccccc atgcaatagg ctgccccccag
1321 agctctttga gcagctgcgg atgttattgg agccaaacag catcaccggc aatgactggc
1381 gcggactggc ctcccacctg gggcttgcg gcatgaagat ccggttcctg tcctgccagc
1441 gcagcccccgc agcggccatc ctggagttgt ttgaggagca gaacggcagc ctgcaggagc
1501 tgcactacct catgaccgtc atggagcggc tagactgcgc ctccgccatc cagaactacc
1561 tgagtgggac acacggcggc agcccaggcc ccgagcgcgg gggcgccccgg gataaccagg
1621 gcctggagct ggacgagaag ctctgagcgc ccagcgggca gggccggagg aggtgtaggg
1681 gcgagagggg ttgttctcct acgcctaaga ggaacacagc agctgttcct ggctgtgccc
1741 accacccttc ccagaaccct cggacggtgc cagggccgcc cgcgtcctcg ccagcctccc
1801 agcagcaggc gcgcccttcc ggccgcgagc tgtcccgcgt gcgggtcccc tcctggccgg
1861 cagagggcgc aggagcccag gagatggcct cagcgtggcc agcctgccaa actgaccagg
1921 ggacggccac ggtccccgcg tgcacttag ggccggtcag gccctaaagt attcactgag
1981 cacttaggaa gaccgggcat tgggctggtg tcatgaagaa tactggaata taggaggtag
2041 ggtctggagc cctgacaagc acacagttct tttgcaggag tcaagatgtg ctcataggag
2101 ccaagggcaa actcgaaaac agccctgccc tgtggttagg ggaggtgggt gtggctttag
2161 gagttgagag gggaagagct gagtgcgggc tggagcagcg agaatgcttc acggaggatg
2221 ttggggagag aggatttgat ttgccgagtg gtttggagat ctttaggggc gggtagggga
2281 agagggtggc tggacttaag gtaggagccg aaagtgggca tgggagccca tccccgtggg
2341 tgtgaggccg gggtaggacc aggcttcccg gctaggcacg cctggctggc tgcctctgcc
2401 tctactaact tcctttgtct ctttatcctc ctgcttaggc cgtgtcttcc tctctctctg
2461 ccatttctc tatcagaaaa cattaaagct gagtagaaac ttcaagatga tcattctggc
2521 ccagcccttt tatctcttta tctccaatgg tgtgcgtttt aagttttctct gacttggttt
2581 ttctgtccct gtctcccaca gttgttcccg ctctgcacct gtgtttcagt tactctctct
2641 ctctgtctta gatcttttg tttctgccta gtctctgtgc cctgtctttg tgtgtttctt
2701 tctctgcctg aaaccctccc tcttttccct tcaggcatat gtctctaaac caatgttatg
2761 tatcaaagac tgttgaaaga gacagggcta ctctaggaat ggatgggtgg ggatattttc
2821 cccatggatc aagatccagt ttagggttgg gaaataaagg atagggataa aagaggcacc
2881 ccattcagtc agcagatact tattcagcac ctactatgtg tttgatactg tatacaaaag
2941 acatgaatgg gctgggtcct gaacagagaa taaagggttt gactccaaaa aaaaaaaaaa
3001 aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa
3061 aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaa

Figure 33A

MCPQESSFQPSQFLLLVGVPVASVLLLAQCLRWHCPRRLLGACWTLNGQEEPVSQPTPQLEN
EVSRQHLPATLPEMVAFYQELHTPTQGQTMVRQLMHKLLVFSAREVDHRGGCLMLQDTGIS
LLIPPGAVAVGRQERVSLILVWDLSDAPSLSQAQGLVSPVVACGPHGASFLKPCTLTFKHCAE

QPSHARTYSSNTTLLDAKVWRPLGRPGAHASRDECRIHLSHFSLYTCVLEAPVGREARKWLQ
LAVFCSPLVPGQSHLQLRIYFLNNTPCALQWALTNEQPHGGRLRGPCQLFDFNGARGDQCLK
LTYISEGWENVDDSSCQLVPHLHIWHGKCPFRSFCFRRKAADENEDCSALTNEIIVTMHTFQD
GLETKYMEILRFQASEEESWAAPPPVSQPPPCNRLPPELFEQLRMLLEPNSITGNDWRGLASH
LGLCGMKIRFLSCQRSPAAAILELFEEQNGSLQELHYLMTVMERLDCASAIQNYLSGTHGGSP
GPERGGARDNQGLELDEKL

Figure 33B

1 attgctgatg gatcagtgag cctgtgttca tgccagtgag ctgctgtggc tcagatactg
61 atactttctt tccaaacagc ataagaagtg attgagccac aagtatactg aaggaagggc
121 tccctcgagt tctggtgtga agagataaat caccagtcac agactatgca cccgactgct
181 gctgttcagt ccagggaaaa tgaaagttgg agtgctgtgg ctcatttctt tcttcacctt
241 cactgacggc cacggtggct tcctggggaa aaatgatggc atcaaaacaa aaaaagaact
301 cattgtgaat aagaaaaaac atctaggccc agtcgaagaa tatcagctgc tgcttcaggt
361 gacctataga gattccaagg agaaaagaga tttgagaaat tttctgaagc tcttgaagcc
421 tccattatta tggtcacatg ggctaattag aattatcaga gcaaaggcta ccacagactg
481 caacagcctg aatggagtcc tgcagtgtac ctgtgaagac agctacacct ggtttcctcc
541 ctcatgcctt gatccccaga actgctacct tcacacggct ggagcactcc caagctgtga
601 atgtcatctc aacaacctca gccagagtgt caatttctgt gagagaacaa agatttgggg
661 cactttcaaa attaatgaaa ggtttacaaa tgacctttg aattcatctt ctgctatata
721 ctccaaatat gcaaatggaa ttgaaattca acttaaaaaa gcatatgaaa gaattcaagg
781 ttttgagtcg gttcaggtca cccaatttcg aatgtcactc ttgtcgccca agttggagtg
841 caatggcaca atctaggctc actgcaaccc tgcaacctct gcctaccggg ttcaagagat
901 tcccctgcct cagcctccca agtagctgga attacaggca cctgccacca catccagcta
961 actttttttg tatttttact agagacaggg tttcaccatg ttggccacac tggtctcaaa
1021 ctcctgacct caggtgatcc gcctgcctcg gcccccaaag tgctgggatt acaggcatga
1081 gccaccacat ctggcctagg accttaaata ttggaaagca tcctcaaaac tgtgggtcag
1141 tgagtagaac tacaaaacaa tagcagtagg gcagaaactt gaaagaaggc aggagatcat
1201 ggtgacagtg gatgggaaaa agtgagggtt ggggataagg gttgcgggtt gtcgaagggt
1261 ggattttctc cttcagcaac tacaggagat atgatgcctc ataattcgga gccagaagtg
1321 gggcttggg tgagatatct ttgcacagat aacatgtata catcatagtt caaaacccag
1381 tagtcattgt ttacagcaaa taaagaaata tttagtaaat taaaaaaaaa aaaaaaa

Figure 34A

MKVGVLWLISFFTFTDGHGGFLGKNDGIKTKKELIVNKKKHLGPVEEYQLLLQVTYRDSKEK
RDLRNFLKLLKPPLLWSHGLIRIIRAKATTDCNSLNGVLQCTCEDSYTWFPPSCLDPQNCYLH
TAGALPSCECHLNNLSQSVNFCERTKIWGTFKINERFTNDLLNSSSAIYSKYANGIEIQLKKAY
ERIQGFESVQVTQFRMSLLSPKLECNGTI

Figure 34B

ATGGTGCTCATGGCGCCCCGAACCCTCCTCCTGCTGCTCTCAGGGGCCCTGGCCCTGACC
CAGACCTGGGCGCGCTCCCACTCCATGAGGTATTTCTACACCACCATGTCCCGGCCCGGC
CGCGGGGAGCCCCGCTTCATCTCCGTCGGCTACGTGGACGATACGCAGTTCGTGCGGTTC
GACAGCGACGCCGCGAGCCAGAGGATGGAGCCGCGGGCGCCGTGGATGGAGCGGGAGG
GG
CCGGAGTATTGGGACCGGAACACACAGATCTGCAAGGCCCAGGCACAGACTGAACGAG
AG
AACCTGCGGATCGCGCTCCGCTACTACAACCAGAGCGAGGGCGGTTCTCACACCATGCA
G
GTGATGTATGGCTGCGACGTGGGGCCCGACGGGCGCTTCCTCCGCGGGTATGAACAGCA
C
GCCTACGACAGCAAGGATTACATCGCTCTGAACGAGGACCTGCGCTCCTGGACCGCGGC
G
GACATGGCAGCTCAGATCACCAAGCGCAAGTGGGAGGCGGCCCGTCAGGCGGAGCAGCT
G
AGAGCCTACCTGGAGGGCGAGTTCGTGGAGTGGCTCCGCAGATACCTGGAGAACGGGAA
G
GAGACGCTGCAGCGCGCGGACCCCCCCAAGACACATATGACCCACCACCCCATCTCTGA
C
CATGAGGCCACCCTGAGGTGCTGGGCCCTGGGCTTCTACCCTGCGGAGATCACACTGACC
TGGCAGCGGGATGGGGAGGACCAGACCCACACACGGAGCTCATGGAGACCAGGCCTGC
AG
GGGATGGAACCTTCCAGAAGTGGGCGGCTGTGGTGGTGCCTTCTGGAGAGGAGCAGAGA
T
ACACCTGCCATGTGCAGCATGAGGGTCTGCCAGAGCCCCTCACCCTGAGATGGGAGCCA
T
CTTCCCAGCCCACCATCCCCATCGTGGGCATCGTTGCTGGCCTGGTTCTACTTGTAGCTG
TGGTCACTGGAGCTGTGGTCGCTGCTGTAATGTGGAGGAAGAAGAGCTCAGATAGAAAA
G
GAGGGAGCTACTCTCAGGCTGCAAGCGGCAACAGTGCCCAGGGCTCTGATGTGTCTCTC
A
CGGCGTGAAAGTGTGA

Figure 35A

MVLMAPRTLLLLLSGALALTQTWARSHSMRYFYTTMSRPGRGEPRFISVGYVDDTQFVRFD
SDAASQRMEPRAPWMEREGPEYWDRNTQICKAQAQTERENLRIALRYYNQSEGGSHTMQV
MYGCDVGPDGRFLRGYEQHAYDSKDYIALNEDLRSWTAADMAAQITKRKWEAARQAEQL
RAYLEGEFVEWLRRYLENGKETLQRADPPKTHMTHHPISDHEATLRCWALGFYPAEITLTW
QRDGEDQTHTRSSWRPGLQGMEPSRSGRLWWCLLERSRDTPAMCSMRVCQSPSP

Figure 35B

```
   1 gtgtgcgtga tggagaaaat tgggcaccag ggctgctccc gagattctca gatctgattt
  61 ccacgcttgc taccaaaata gtctgggcag gccacttttg gaagtaggcg ttatctagtg
 121 agcaggcggc cgctttcgat ttcgctttcc cctaaatggc tgagcttctc gccagcgcag
 181 gatcagcctg ttcctgggac tttccgagag ccccgccctc gttccctccc ccagccgcca
 241 gtaggggagg actcggcggt accccggagct tcaggcccca ccggggcgcg gagagtcccca
 301 ggccccggccg ggaccgggac ggcgtccgag tgccaatggc tagctctagg tgtccccgctc
 361 cccgcgggtg ccgctgcctc cccggagctt ctctcgcatg gctggggaca gtactgctac
 421 ttctcgccga ctgggtgctg ctccggaccg cgctgccccg catattctcc ctgctggtgc
 481 ccaccgcgct gccactgctc cgggtctggg cggtgggcct gagccgctgg gccgtgctct
 541 ggctgggggc ctgcgggggtc ctcagggcaa cggttggctc caagagcgaa aacgcaggtg
 601 cccagggctg gctggctgct ttgaagccat tagctgcggc actgggcttg gccctgccgg
 661 gacttgcctt gttccgagag ctgatctcat ggggagcccc cgggtccgcg gatagcacca
 721 ggctactgca ctggggaagt caccctaccg ccttcgttgt cagttatgca gcggcactgc
 781 ccgcagcagc cctgtggcac aaactcggga gcctctgggt gcccggcggt cagggcggct
 841 ctggaaaccc tgtgcgtcgg cttctaggct gcctgggctc ggagacgcgc cgcctctcgc
 901 tgttcctggt cctggtggtc ctctcctctc ttggggagat ggccattcca ttctttacgg
 961 gccgcctcac tgactggatt ctacaagatg gctcagccga taccttcact cgaaacttaa
1021 ctctcatgtc cattctcacc atagccagtg cagtgctgga gttcgtgggt gacgggatct
1081 ataacaacac catgggccac gtgcacagcc acttgcaggg agaggtgttt ggggctgtcc
1141 tgcgccagga gacggagttt ttccaacaga accagacagg taacatcatg tctcgggtaa
1201 cagaggacac gtccaccctg agtgattctc tgagtgagaa tctgagctta tttctgtggt
1261 acctggtgcg aggcctatgt ctcttgggga tcatgctctg gggatcagtg tccctcacca
1321 tggtcaccct gatcaccctg cctctgcttt tccttctgcc caagaaggtg ggaaaatggt
1381 accagttgct ggaagtgcag gtgcgggaat ctctggcaaa gtccagccag gtggccattg
1441 aggctctgtc ggccatgcct acagttcgaa gctttgccaa cgaggagggc gaagcccaga
1501 agtttaggga aaagctgcaa gaaataaaga cactcaacca gaaggaggct gtggcctatg
1561 cagtcaactc ctggaccact agtatttcag gtatgctgct gaaagtggga atcctctaca
1621 ttggtgggca gctggtgacc agtggggctg taagcagtgg gaaccttgtc acatttgttc
1681 tctaccagat gcagttcacc caggctgtgg aggtactgct ctccatctac cccagagtac
1741 agaaggctgt gggctcctca gagaaaatat ttgagtacct ggaccgcacc cctcgctgcc
1801 cacccagtgg tctgttgact cccttacact tggagggcct tgtccagttc caagatgtct
1861 cctttgccta cccaaaccgc ccagatgtct tagtgctaca ggggctgaca ttcaccctac
1921 gccctggcga ggtgacgggg ctggtgggac ccaatgggtc tgggaagagc acagtggctg
1981 ccctgctgca gaatctgtac cagcccaccg ggggacagct gctgttggat gggaagcccc
2041 ttcccaata tgagcaccgc tacctgcaca ggcaggtggc tgcagtggga caagagccac
2101 aggtatttgg aagaagtctt caagaaaata ttgcctatgg cctgacccag aagccaacta
2161 tggaggaaat cacagctgct gcagtaaagt ctggggccca tagtttcatc tctggactcc
2221 ctcagggcta tgacacagag gtagacgagg ctgggagcca gctgtcaggg ggtcagcgac
2281 aggcagtggc gttggcccga gcattgatcc ggaaaccgtg tgtacttatc ctggatgatg
2341 ccaccagtgc cctggatgca aacagccagt tacaggtgga gcagctcctg tacgaaagcc
2401 ctgagcggta ctcccgctca gtgcttctca tcacccagca cctcagcctg gtggagcagg
2461 ctgaccacat cctctttctg gaaggaggcg ctatccggga ggggggaacc caccagcagc
2521 tcatggagaa aaaggggtgc tactgggcca tggtgcaggc tcctgcagat gctccagaat
2581 gaaagccttc tcagacctgc gcactccatc tccctccctt ttcttctctc tgtggtggag
2641 aaccacagct gcagagtagg cagctgcctc caggatgagt tacttgaaat ttgccttgag
2701 tgtgttacct cctttccaag ctcctcgtga taatgcagac ttcctggagt acaaacacag
2761 gatttgtaat tccttactgt aacggagttt agagccaggg ctgatgcttt ggtgtggcca
2821 gcactctgaa actgagaaat gttcagaatg tacggaaaga tgatcagcta ttttcaacat
2881 aactgaaggc atatgctggc ccataaacac cctgtaggtt cttgatattt ataataaaat
2941 tggtgttttg taaaaaaaaa aaaaaaaaaa aaaa
```

Figure 36A

MAELLASAGSACSWDFPRAPPSFPPPAASRGGLGGTRSFRPHRGAESPRPGRDRDGVRVPMA
SSRCPAPRGCRCLPGASLAWLGTVLLLLADWVLLRTALPRIFSLLVPTALPLLRVWAVGLSR
WAVLWLGACGVLRATVGSKSENAGAQGWLAALKPLAAALGLALPGLALFRELISWGAPGS

ADSTRLLHWGSHPTAFVVSYAAALPAAALWHKLGSLWVPGGQGGSGNPVRRLLGCLGSET
RRLSLFLVLVVLSSLGEMAIPFFTGRLTDWILQDGSADTFTRNLTLMSILTIASAVLEFVGDGI
YNNTMGHVHSHLQGEVFGAVLRQETEFFQQNQTGNIMSRVTEDTSTLSDSLSENLSLFLWYL
VRGLCLLGIMLWGSVSLTMVTLITLPLLFLLPKKVGKWYQLLEVQVRESLAKSSQVAIEALS
AMPTVRSFANEEGEAQKFREKLQEIKTLNQKEAVAYAVNSWTTSISGMLLKVGILYIGGQLV
TSGAVSSGNLVTFVLYQMQFTQAVEVLLSIYPRVQKAVGSSEKIFEYLDRTPRCPPSGLLTPL
HLEGLVQFQDVSFAYPNRPDVLVLQGLTFTLRPGEVTALVGPNGSGKSTVAALLQNLYQPTG
GQLLLDGKPLPQYEHRYLHRQVAAVGQEPQVFGRSLQENIAYGLTQKPTMEEITAAAVKSG
AHSFISGLPQGYDTEVDEAGSQLSGGQRQAVALARALIRKPCVLILDDATSALDANSQLQVE
QLLYESPERYSRSVLLITQHLSLVEQADHILFLEGGAIREGGTHQQLMEKKGCYWAMVQAPA
DAPE

Figure 36B

```
   1 cgggcgccca gagggcaaat gaggggcggc ggggtggcgg gtcgggggga gacgcggaat
  61 ttcccagcgc gggggctctg gcttaccctg caaccgggca gtctctttct gtttacggag
 121 agaaaggggа aatggaaaag tcggggaggc ggtggctggc gtccgctgcg ccgcccctgg
 181 gcaggctcag acgccgtgag tcaggggcag agcagggcgg tctgagcgtg cgggcgacgc
 241 gggtctcact cgtccgctcc gctctggact gcgcgccacg ctctgggggtc cggcgccctg
 301 gttcctgctt ctgccgctgc cgccgccgga tcccagtggc ccggcgtgct cggctcccac
 361 aggcctgcag ccagcatcgc accgaacctt cgggggggcg cggctggagc gctcggccgg
 421 cgtgggagcg ccaaggccgc agatgcaatc ttcttaccgc gaagaagcca ggggaatagg
 481 tagccacatc ttgtttgcag ataagaaagg aagctaacgc agtatctgca aagccaggag
 541 tctgactcag tacttttctc actcatgcat acaaagcagc taaaaatgac acagcttatt
 601 taccatgccc ctgacactgc actgagcact ttatgagctt gaactctgtt aatcctcacg
 661 accacctcat gagactctcc agaaagagca acagtaatgg agtacatgag cactggaagt
 721 gacaataaag aagagattga tttattaatt aaacatttaa atgtgtctga tgtaatagac
 781 attatggaaa atctttatgc aagtgaagag ccagcagttt atgaacccag tctaatgacc
 841 atgtgtcaag acagtaatca aaacgatgag cgttctaagt ctctgctgct tagtggccaa
 901 gaggtaccat ggttgtcatc agtcagatat ggaactgtgg aggatttgct tgcttttgca
 961 aaccatatat ccaacactgc aaagcatttt tatggacaac gaccacagga atctggaatt
1021 ttattaaaca tggtcatcac tccccaaaat ggacgttacc aaatagattc cgatgttctc
1081 ctgatcccct ggaagctgac ttacaggaat attggttctg attttattcc tcggggcgcc
1141 tttggaaagg tatacttggc acaagatata aagacgaaga aaagaatggc gtgtaaactg
1201 atcccagtag atcaatttaa gccatctgat gtggaaatcc aggcttgctt ccggcacgag
1261 aacatcgcag agctgtatgg cgcagtcctg tggggtgaaa ctgtccatct ctttatggaa
1321 gcaggcgagg gagggtctgt tctggagaaa ctggagagct gtggaccaat gagagaattt
1381 gaaattattt gggtgacaaa gcatgttctc aagggacttg atttctaca ctcaaagaaa
1441 gtgatccatc atgatattaa acctagcaac attgttttca tgtccacaaa agctgttttg
1501 gtggattttg gcctaagtgt tcaaatgacc gaagatgtct attttcctaa ggacctccga
1561 ggaacagaga tttacatgag cccagaggtc atcctgtgca ggggccattc aaccaaagca
1621 gacatctaca gcctgggggc cacgctcatc cacatgcaga cgggcacccc acccctgggtg
1681 aagcgctacc ctcgctcagc ctatccctcc tacctgtaca taatccacaa gcaagcacct
1741 ccactggaag acattgcaga tgactgcagt ccagggatga gagagctgat agaagcttcc
1801 ctggagagaa accccaatca ccgcccaaga gccgcagacc tactaaaaca tgaggccctg
1861 aacccgccca gagaggatca gccacgctgt cagagtctgg actctgccct cttggagcgc
1921 aagaggctgc tgagtaggaa ggagctggaa cttcctgaga acattgctga ttcttcgtgc
1981 acaggaagca ccgaggaatc tgagatgctc aagaggcaac gctctctcta catcgacctc
2041 ggcgctctgg ctggctactt caatcttgtt cggggaccac caacgcttga atatggctga
2101 aggatgccat gtttgctcta aattaagaca gcattgatct cctggaggct ggttctgctg
2161 cctctacaca ggggccctgt acagtgaatg gtgccatttt cgaaggagca gtgtgacctc
2221 ctgtgaccca tgaatgtgcc tccaagcggc cctgtgtgtt tgacatgtga agctatttga
2281 tatgcaccag gtctcaaggt tctcatttct caggtgacgt gattctaagg caggaatttg
2341 agagttcaca gaaggatcgt gtctgctgac tgtttcattc actgtgcact ttgctcaaaa
2401 ttttaaaaat accaatcaca aggataatag agtagcctaa aattactatt cttggttctt
2461 atttaagtat ggaatattca ttttactcag aatagctgtt ttgtgtatat tggtgtatat
2521 tatataactc tttgagcctt tattggtaaa ttctggtata cattgaattc attataattt
2581 gggtgactag aacaacttga agattgtagc aataagctgg actagtgtcc taaaaatggc
2641 taactgatga attagaagcc atctgacagc aggccactag tgacagtttc ttttgtgttc
2701 ctatggaaac attttatact gtacatgcta tgctgaagac attcaaaacg tgatgttttg
2761 aatgtggata aaactgtgta aaccacataa ttttttgtaca tcccaaagga tgagaatgtg
2821 acctttaaga aaaatgaaaa cttttgtaaa ttattgatga ttttgtaatt cttatgacta
2881 aattttcttt taagcatttg tatattaaaa tagcatactg tgtatgtttt atatcaaatg
2941 ccttcatgaa tcttcatac atatatatat ttgtaacatt gtaaagtatg tgagtagtct
3001 tatgtaaagt atgtttttac attatgcaaa taaaacccaa tacttttgtc caatgtggtt
3061 ggtcaaatca actgaataaa ttcagtattt tgcctt
```

Figure 37A

MEYMSTGSDNKEEIDLLIKHLNVSDVIDIMENLYASEEPAVYEPSLMTMCQDSNQNDERSKS
LLLSGQEVPWLSSVRYGTVEDLLAFANHISNTAKHFYGQRPQESGILLNMVITPQNGRYQIDS
DVLLIPWKLTYRNIGSDFIPRGAFGKVYLAQDIKTKKRMACKLIPVDQFKPSDVEIQACFRHE

NIAELYGAVLWGETVHLFMEAGEGGSVLEKLESCGPMREFEIIWVTKHVLKGLDFLHSKKVI
HHDIKPSNIVFMSTKAVLVDFGLSVQMTEDVYFPKDLRGTEIYMSPEVILCRGHSTKADIYSL
GATLIHMQTGTPPWVKRYPRSAYPSYLYIIHKQAPPLEDIADDCSPGMRELIEASLERNPNHRP
RAADLLKHEALNPPREDQPRCQSLDSALLERKRLLSRKELELPENIADSSCTGSTEESEMLKR
QRSLYIDLGALAGYFNLVRGPPTLEYG

Figure 37B

1 cgctccccgc tcccgtggct gccgccgccc cggggaagaa gagacagggg tggggtttgg
61 gggaagcgag agaggagggg agagaccctg gccaggctgg agcctggatt cgaggggagg
121 agggacggga ggaggagaaa ggtggaggag aagggagggg ggagcgggga ggagcggccg
181 ggcctggggc ctlgaggccc ggggagagcc ggggagccgg gcccgcgcgc cgagatgttg
241 ctgctgctgt tactggcgcc actcttcctc cgccccccgg gcgcgggcgg ggcgcagacc
301 cccaacgcca cctcagaagg ttgccagatc atacacccgc cctgggaagg gggcatcagg
361 taccggggcc tgactcggga ccaggtgaag gctatcaact tcctgccagt ggactatgag
421 attgaglatg tgtgccgggg ggagcgcgag gtggtggggc ccaaggtccg caagtgcctg
481 gccaacggct cctggacaga tatggacaca cccagccgct gtgtccgaat ctgctccaag
541 tcttatttga ccctggaaaa tgggaaggtt ttcctgacgg gtggggacct cccagctctg
601 gacggagccc gggtggattt ccggtgtgac cccgacttcc atctggtggg cagctcccgg
661 agcatctgta gtcagggcca gtggagcacc cccaagcccc actgccaggt gaatcgaacg
721 ccacactcag aacggcgcgc agtgtacatc ggggcactgt ttcccatgag cgggggctgg
781 ccagggggcc aggcctgcca gcccgcggtg gagatggcgc tggaggacgt gaatagccgc
841 agggacatcc tgccggacta tgagctcaag ctcatccacc acgacagcaa gtgtgatcca
901 ggccaagcca ccaagtacct atatgagctg ctctacaacg accctatcaa gatcatcctt
961 atgcctggct gcagctctgt ctccacgctg gtggctgagg ctgctaggat gtggaacctc
1021 attgtgcttt cctatggctc cagctcacca gccctgtcaa accggcagcg tttccccact
1081 ttcttccgaa cgcacccatc agccacactc cacaacccta cccgcgtgaa actctttgaa
1141 aagtggggct ggaagaagat tgctaccatc cagcagacca ctgaggtctt cacttcgact
1201 ctggacgacc tggaggaacg agtgaaggag gctggaattg agattacttt ccgccagagt
1261 ttcttctcag atccagctgt gcccgtcaaa aacctgaagc gccaggatgc ccgaatcatc
1321 gtgggacttt tctatgagac tgaagcccgg aaagttttt gtgaggtgta caaggagcgt
1381 ctctttggga agaagtacgt ctggttcctc attgggtggt atgctgacaa ttggttcaag
1441 atctacgacc cttctatcaa ctgcacagtg gatgagatga ctgaggcggt ggagggccac
1501 atcacaactg agattgtcat gctgaatcct gccaataccc gcagcatttc caacatgaca
1561 tcccaggaat ttgtggagaa actaaccaag cgactgaaaa gacaccctga ggagacagga
1621 ggcttccagg aggcaccgct ggcctatgat gccatctggg ccttggcact ggccctgaac
1681 aagacatctg gaggaggcgg ccgttctggt gtgcgcctgg aggacttcaa ctacaacaac
1741 cagaccatta ccgaccaaat ctaccgggca atgaactctt cgtcctttga gggtgtctct
1801 ggccatgtgg tgtttgatgc cagcggctct cggatggcat ggacgcttat cgagcagctt
1861 cagggtggca gctacaagaa gattggctac tatgacagca ccaaggatga tctttcctgg
1921 tccaaaacag ataaatggat tggagggtcc cccccagctg accagaccct ggtcatcaag
1981 acattccgct tcctgtcaca gaaactcttt atctccgtct cagttctctc cagcctgggc
2041 attgtcctag ctgttgtctg tctgtccttt aacatctaca actcacatgt ccgttatatc
2101 cagaactcac agcccaacct gaacaacctg actgctgtgg gctgctcact ggctttagct
2161 gctgtcttcc ccctggggct cgatggttac cacattggga ggaaccagtt tcctttcgtc
2221 tgccaggccc gcctctggct cctgggcctg ggctttagtc tgggctacgg ttccatgttc
2281 accaagattt ggtgggtcca cacggtcttc acaaagaagg aagaaaagaa ggagtggagg
2341 aagactctgg aaccctggaa gctgtatgcc acagtgggcc tgctggtggg catggatgtc
2401 ctcactctcg ccatctggca gatcgtggac cctctgcacc ggaccattga gacatttgcc
2461 aaggaggaac ctaaggaaga tattgacgtc tctattctgc cccagctgga gcattgcagc
2521 tccaggaaga tgaatacatg gcttggcatt ttctatggtt acaaggggct gctgctgctg
2581 ctgggaatct tccttgctta tgagaccaag agtgtgtcca ctgagaagat caatgatcac
2641 cgggctgtgg gcatggctat ctacaatgtg gcagtcctgt gcctcatcac tgctcctgtc
2701 accatgattc tgtccagcca gcaggatgca gcctttgcct ttgcctctct tgccatagtt
2761 ttctcctcct atatcactct tgttgtgctc tttgtgccca agatgcgcag gctgatcacc
2821 cgaggggaat ggcagtcgga ggcgcaggac accatgaaga cagggtcatc gaccaacaac
2881 aacgaggagg agaagtcccg gctgttggag aaggagaacc gtgaactgga aaagatcatt
2941 gctgagaaag aggagcgtgt ctctgaactg cgccatcaac tccagtctcg gcagcagctc
3001 cgctcccggc gccacccacc gacaccccca gaaccctctg ggggcctgcc caggggaccc

Figure 38A

3061 cctgagcccc ccgaccggct tagctgtgat gggagtcgag tgcatttgct ttataagtga
3121 gggtagggtg agggaggaca ggccagtagg gggagggaaa gggagagggg aagggcaggg
3181 gactcaggaa gcagggggtc cccatcccca gctgggaaga acatgctatc caatctcatc

3241 tcttgtaaat acatgtcccc ctgtgagttc tgggctgatt tgggtctctc atacctctgg
3301 gaaacagacc tttttctctc ttactgcttc atgtaatttt gtatcacctc ttcacaattt
3361 agttcgtacc tggcttgaag ctgctcactg ctcacacgct gcctcctcag cagcctcact
3421 gcatctttct cttcccatgc aacaccctct tctagttacc acggcaaccc ctgcagctcc
3481 tctgcctttg tgctctgttc ctgtccagca ggggtctccc aacaagtgct ctttccaccc
3541 caaaggggcc tctccttttc tccactgtca taatctcttt ccatcttact tgcccttcta
3601 tactttctca catgtggctc ccccctgaatt ttgcttcctt tgggagctca ttcttttcgc
3661 caaggctcac atgctccttg cctctgctct gtgcactcac gctcagcaca catgcatcct
3721 cccctctcct gcgtgtgccc actgaacatg ctcatgtgta cacacgcttt tcccgtatgc
3781 tttcttcatg ttcagtcaca tgtgctctcg ggtgccctgc attcacagct acgtgtgccc
3841 ctctcatggt catgggtctg cccttgagcg tgtttgggta ggcatgtgca atttgtctag
3901 catgctgagt catgtctttc ctatttgcac acgtccatgt ttatccatgt actttccctg
3961 tgtaccctcc atgtaccttg tgtactttct tcccttaaat catggtattc ttctgacaga
4021 gccatatgta ccctaccctg cacattgtta tgcacttttc cccaattcat gtttggtggg
4081 gccatccaca ccctctcctt gtcacagaat ctccatttct gctcagattc ccccccatct
4141 cattgcattc atgtactacc ctcagtctac actcacaatc atcttctccc aagactgctc
4201 cctttgttt tgtgttttt tgaggggaat taaggaaaaa taagtggggg caggtttgga
4261 gagctgcttc cagtggatag ttgatgagaa tcctgaccaa aggaaggcac ccttgactgt
4321 tgggatagac agatggacct atggggtggg aggtggtgtc cctttcacac tgtggtgtct
4381 cttggggaag gatctccccg aatctcaata aaccagtgaa cagtgtgact cggcaaaaaa
4441 aaaaa

Figure 38A (Continued)

MLLLLLLAPLFLRPPGAGGAQTPNATSEGCQIIHPPWEGGIRYRGLTRDQVKAINFLPVDYEIE
YVCRGEREVVGPKVRKCLANGSWTDMDTPSRCVRICSKSYLTLENGKVFLTGGDLPALDGA
RVDFRCDPDFHLVGSSRSICSQGQWSTPKPHCQVNRTPHSERRAVYIGALFPMSGGWPGGQA
CQPAVEMALEDVNSRRDILPDYELKLIHHDSKCDPGQATKYLYELLYNDPIKIILMPGCSSVS
TLVAEAARMWNLIVLSYGSSSPALSNRQRFPTFFRTHPSATLHNPTRVKLFEKWGWKKIATIQ
QTTEVFTSTLDDLEERVKEAGIEITFRQSFFSDPAVPVKNLKRQDARIIVGLFYETEARKVFCE
VYKERLFGKKYVWFLIGWYADNWFKIYDPSINCTVDEMTEAVEGHITTEIVMLNPANTRSIS
NMTSQEFVEKLTKRLKRHPEETGGFQEAPLAYDAIWALALALNKTSGGGGRSGVRLEDFNY
NNQTITDQIYRAMNSSSFEGVSGHVVFDASGSRMAWTLIEQLQGGSYKKIGYYDSTKDDLS
WSKTDKWIGGSPPADQTLVIKTFRFLSQKLFISVSVLSSLGIVLAVVCLSFNIYNSHVRYIQNS
QPNLNNLTAVGCSLALAAVFPLGLDGYHIGRNQFPFVCQARLWLLGLGFSLGYGSMFTKIW
WVHTVFTKKEEKKEWRKTLEPWKLYATVGLLVGMDVLTLAIWQIVDPLHRTIETFAKEEPK
EDIDVSILPQLEHCSSRKMNTWLGIFYGYKGLLLLLGIFLAYETKSVSTEKINDHRAVGMAIY
NVAVLCLITAPVTMILSSQQDAAFAFASLAIVFSSYITLVVLFVPKMRRLITRGEWQSEAQDT
MKTGSSTNNNEEEKSRLLEKENRELEKIIAEKEERVSELRHQLQSRQQLRSRRHPPTPPEPSGG
LPRGPPEPPDRLSCDGSRVHLLYK

Figure 38B

1 gtacttacac aaccccagat ggtacaacct acaacacacc taggctgtat gatgtagcca
61 attgctccta gactacaaat ctatacagca tgttgctgta ctgaatactc taagcaatta
121 taacacaatg acctagcaac agtaacataa gcaaaggaga gtcacgccca aaatggaaac
181 ccaaagccaa agtacccctt cagactctac atatgacttc tgagaatcaa gagaaagtga
241 aagctcttct ccgagacctg caagaacaag atgctgatgc tggatctgaa agaggccttt
301 ctggggagga ggaagatgat gagcctgatt gctgtaacga tgagcggtac tggccagctg
361 gacaggaacc ttcctcgtt cccgacttgg atccttgga atatgctggc ttagcctcag
421 tggagccta tgttccagaa tttacagtct ccccatttgc agtgcaaaaa ctttccaggt
481 atggtttcaa tactgaacgc tgtcaagcgg tcctgaggat gtgtgatgga gatgtgggag
541 catcactaga gcatctcctt acccagtgtt tttcagagac atttggagag aggatgaaga
601 tctctgaggc agtcaaccag ataagcttgg atgagtgtat ggaacagcga caggaagagg
661 catttgctct caagtccatc tgtggagaaa aatttataga aagaattcag aacagagtct
721 ggaccattgg gttagaactg gagtatctga caagtagatt ccgcaaatcc aagccaaaag
781 aaagtaccaa aaatgtacaa gagaattcac ttgaaatctg taaattttac ctcaaaggaa
841 attgtaaatt tggatcaaaa tgcagattca aacatgaagt gcccccaaat caaattgttg
901 gaagaataga aagaagtgta gatgattctc atcttaatgc tattgaagat gcatcttttt
961 tatatgaact tgaaattcga ttttctaaag accacaaata tccctaccaa gctccgctcg
1021 tggcatttta ttccaccaat gagaacctac ctctggcttg tcgtttacat atttctgagt
1081 ttctttatga caaggccttg acatttgcgg aaacttcgga acctgtcgta tattctttga
1141 taacccttt agaggaagag tcggaaatag tcaagttact aacgaatacc caccacaagt
1201 atagtgaccc tcctgtgaac tttctgccag taccctctag gaccagaata aataatcctg
1261 cctgtcataa aacagtgatt ccaaataatt cttttgtttc taatcaaatt ccagaagttg
1321 aaaaagcatc agaatctgag gagtcagatg aggatgacgg tcctgcacct gttatagtag
1381 agaatgaaag ctatgtgaac cttaagaaaa agatttccaa aagatatgac tggcaggcaa
1441 agtcagtaca tgctgaaaat ggtaaaatct gcaagcagtt ccgaatgaaa caggtgctca
1501 atagccacat gtagccaggt gttgctgtat tggacagcac aggtatagaa catttccatc
1561 aacacggaaa gttctattgg acagtactgg tatagagact cttgttggga agaactggat
1621 atgtgctaag caagagggct ttatttcacc cagaaaatct ttcggtttat tcagatgttg
1681 gaaaactaat gtacagattc cacaactcat tctggctgat tctctgagca gcattctgaa
1741 taaagtcttc tacatccaat cccaacaaat ccaacaaagg atcactcaag gccaggagtg
1801 caagaccatc cagggcaaca taacaagact ctgtctctat aattaaaaaa aaaaaaaagc
1861 tgtaatccca aa

Figure 39A

MTSENQEKVKALLRDLQEQDADAGSERGLSGEEEDDEPDCCNDERYWPAGQEPSLVPDLDP
LEYAGLASVEPYVPEFTVSPFAVQKLSRYGFNTERCQAVLRMCDGDVGASLEHLLTQCFSET
FGERMKISEAVNQISLDECMEQRQEEAFALKSICGEKFIERIQNRVWTIGLELEYLTSRFRKSK
PKESTKNVQENSLEICKFYLKGNCKFGSKCRFKHEVPPNQIVGRIERSVDDSHLNAIEDASFLY
ELEIRFSKDHKYPYQAPLVAFYSTNENLPLACRLHISEFLYDKALTFAETSEPVVYSLITLLEEE
SEIVKLLTNTHHKYSDPPVNFLPVPSRTRINNPACHKTVIPNNSFVSNQIPEVEKASESEESDED
DGPAPVIVENESYVNLKKKISKRYDWQAKSVHAENGKICKQFRMKQVLNSHM

Figure 39B

1 agtaaggaga accagccagg cagaacatca cagcgggagg agctgtccca ggtggcccag
61 ctcagcaatg gcaatggggg tccccagagt cattctgctc tgcctctttg gggctgcact
121 ctgcctgaca gggtcccaag ccctgcagtg ctacagcttt gagcacacct actttggccc
181 ctttgacctc agggccatga agctgcccag catcicctgt cctcatgagt gctttgaggc
241 tatcctgtct ctggacaccg ggtatcgcgc gccggtgacc ctggtgcgga agggctgctg
301 gaccgggcct cctgcgggcc agacgcaatc gaacgcggac gcgctgccgc cagactactc
361 ggtggtgcgc ggctgcacaa ctgacaaatg caacgcccac ctcatgactc atgacgccct
421 ccccaacctg agccaagcac ccgacccgcc gacgctcagc ggcgccgagt gctacgcctg
481 tatcggggtc caccaggatg actgcgctat cggcaggtcc cgacgagtcc agtgtcacca
541 ggaccagacc gcctgcttcc agggcaatgg cagaatgaca gttggcaatt tctcagtccc
601 tgtgtacatc agaacctgcc accggcccic ctgcaccacc gagggcagca ccagcccctg
661 gacagccatc gacctccagg gctcctgctg tgaggggtac ctctgcaaca ggaaatccat
721 gacccagccc ttcaccagtg cttcagccac cacccctccc cgagcactac aggtcctggc
781 cctgctcctc ccagtcctcc tgctggtggg gctctcagca tagaccgccc ctccaggatg
841 ctggggacag ggctcacaca cctcattctt gctgcttcag cccctatcac atagctcact
901 ggaaaatgat gttaaagtaa gaattgcact cctgtcccic tggccttcca tctctcccgc
961 ccttgtgccc cacaacctgg ccaacagtac tggaagaaac tggacacagt caccagcatc
1021 cccggggagg gcaaaacagc catgtcgtgc cctgatgaag agcaattctg atcacagctg
1081 ttactcactg agcaccagcc aggcaccagg caccccataa cacggcttcc tgtgctctcc
1141 ctccagagcc tgtcgcagct ctaggaggga gctatacaat gatgtcttta ttagtgtcat
1201 catgagaagc ccaataagca gtatgcccta acagttagta ggccaggctc tggagctaag
1261 ctgcatgggt tcaaatccca gctccaccat tcagcctgca gagaccatga gcgagttact
1321 taagccaggc tctggagcta agctgcatgg gttcaaatcc cagctccagc attcagccta
1381 cagagaccat gggtgagtta cttaagccag gctctggagc taagctgcat gggttcaaat
1441 cccagctcca ccattcagcc tgcagagact gtgggtgagt tacttgagct ctctgtgcca
1501 atattttctc acctataagg tggaggtgaa aataaactct ataacatgac aagaactact
1561 tcacagtagt tgcagtgagg attcaacgag atgaacattt agtacttggg acacagcagt
1621 ggcccagtgt aaatgggcta cttgtcataa gccctaagtc acaggtcaac aaactgagag
1681 gcaaaagcac ttggttgagc ttgtgtatct agtgagtatg gattcaggga ccagattccc
1741 agccccacga actgctaagc aaccccacct cctaaacaca tgagtgccga ttaacttcac
1801 agaaaaacac acaaggcaaa gttcagcgag gtgaaattct ccaagctata aagatcaggg
1861 aagacttcct ggaggaattc accettgagc aaaatcctaa aggatcaata gtagctggca
1921 aaaagaagca ggaggaagcg cattctaggt agaggagaca gcctggacaa aggtctgagg
1981 gaggaaggag cacaaggagt gcaggacact ttcatgagtg caggacactt tcataactgc
2041 atgaacttca tagagatggg atcctttagc atgttctctg tgcacatgct tgaccatgtt
2101 ctttcacatg ctttttgcca cttgatcttt ccagcaactc agtgagagaa gcaaaaaagt
2161 aagttgcatc caaaaaaaaa aaaaaa

Figure 40A

MKLPSISCPHECFEAILSLDTGYRAPVTLVRKGCWTGPPAGQTQSNADALPPDYSVVRGCTT
DKCNAHLMTHDALPNLSQAPDPPTLSGAECYACIGVHQDDCAIGRSRRVQCHQDQTACFQG
NGRMTVGNFSVPVYIRTCHRPSCTTEGSTSPWTAIDLQGSCCEGYLCNRKSMTQPFTSASATT
PPRALQVLALLLPVLLLVGLSA

Figure 40B

GGCACGAGGCCCAGCACTAGAAGTCGGCGGTGTTTCCTTTCGGTGATCAGCACTGAACA
C
AGAGGACTCGCCATGGAGTTTGGGCTGAGCTGGGTTTTCCTCGTTGCTCTTTTAAGAGGT
GTCCAGTGTCAGGCGCAGTTGGTGGAGTCTGGGGGAGGCGTGGTCCAGCCCGGGAGCTC
C
CTGAGACTCTCCTGTGCAGCCTCTGGTTTCAGGTTCAGCAATTATGGCATGCACTGGGTC
CGCCAGGCTCCAGGCAAGGGGCTGGAGTGGGTGGCAGTTTTTTCATATGATGAAAGTGA
T
AAATATTATGCAGCCTCCGTGAAGGGTCGATTTACCATCTCCAGAGACAACTCCAAGAAC
ACGTTGTCTCTGCAAATGAACAGCCTGAGAGTTGAGGACACGGCTGTTTACTACTGTGCG
AAAGATCAGAAGCCCTGGTACAGCAACAGCTGGTTTCTAACCAACTTTGACTCTTGGGGC
CGGGGCACCCTGGTCACCGTCTCCTCAGCCTCCACCAAGGGCCCATCGGTCTTCCCCCTG
GCACCCTCCTCCAAGAGCACCTCTGGGGGCACAGCGGCCCTGGGCTGCCTGGTCAAGGA
C
TACTTCCCCGAACCGGTGACGGTGTCGTGGAACTCAGGCGCCCTGACCAGCGGCGTGCA
C
ACCTTCCCGGCTGTCCTACAGTCCTCAGGACTCTACTCCCTCAGCAGCGTGGTGACCGTG
CCCTCCAGCAGCTTGGGCACCCAGACCTACATCTGCAACGTGAATCACAAGCCCAGCAA
C
ACCAAGGTGGACAAGAAAGTTGAGCCCAAATCTTGTGACAAAACTCACACATGCCCACC
G
TGCCCAGCACCTGAACTCCTGGGGGGACCGTCAGTCTTCCTCTTCCCCCCAAAACCCAAG
GACACCCTCATGATCTCCCGGACCCCTGAGGTCACATGCGTGGTGGTGGACGTGAGCCAC
GAAGACCCTGAGGTCAAGTTCAACTGGTACGTGGACGGCGTGGAGGTGCATAATGCCAA
G
ACAAAGCCGCGGGAGGAGCAGTACAACAGCACGTACCGTGTGGTCAGCGTCCTCACCGT
C
CTGCACCAGGACTGGCTGAATGGCAAGGAGTACAAGTGCAAGGTCTCCAACAAAGCCCT
C
CCAGCCCCCATCGAGAAAACCATCTCCAAAGCCAAAGGGCAGCCCCGAGAACCACAGGT
G
TACACCCTGCCCCCATCCCGGGATGAGCTGACCAAGAACCAGGTCAGCCTGACCTGCCTG
GTCAAAGGCTTCTATCCCAGCGACATCGCCGTGGAGTGGGAGAGCAATGGGCAGCCGGA
G
AACAACTACAAGACCACGCCTCCCGTGCTGGACTCCGACGGCTCCTTCTTCCTCTACAGC
AAGCTCACCGTGGACAAGAGCAGGTGGCAGCAGGGGAACGTCTTCTCATGCTCCGTGAT
G
CATGAGGCTCTGCACAACCACTACACGCAGAAGAGCCTCTCCCTGTCTCCGGAGCTGCAA
CTGGAGGAGAGCTGTGCGGAGGCGCAGGACGGGGAGCTGGACGGGCTGTGGACGACCA
TC
ACCATCTTCATCACACTCTTCCTGTTAAGCGTGTGCTACAGTGCCACCGTCACCTTCTTC
AAGGTGAAGTGGATCTTCTCCTCGGTGGTGGACCTGAAGCAGACCATCATCCCCGACTAC
AGGAACATGATCGGACAGGGGGCCTAGGGCCACCCTCTGCGGGGTGTCCAGGGCCGCCC
A
GACCCCACACACCAGCCATGGGCCATGCTCAGCCACCACCCAGGCCACACCTGCCCCCG
A
CCTCACCGCCCTCAACCCCATGGCTCTCTGGCCTCGCAGTTGCCCTCTGACCCTGACACA
CCTGACACGCCCCCCTTCCAGACCCTGTGCATAGCAGGTCTACCCCAGACCTCCGCTGCT
TGGTGCATGCAGGGCACTGGGGGCCAGGTGTCCCCTCAGCAGGACATCCTTGCCCTCCGG
ACCACAAGGTGCTCACACAAAAGGAGGCAGTGACCGGTATCCCAGGCCCCCACCCAGGC
A
GGAGCTGGCCCTGGAGCCAACCCCGTCCACGCCAGCCTCCTGAACACAGGCGTGGTTTCC
AGATGGTGAGTGGGAGCATCAGCCGCCAAGGTAGGGAAGCCACAGCACCATCAGGCCCT
G

TTGGGGAGGCTTCCGAGAGCTGCGAAGGCTCACTCAGACGGCCTTCCTCCCAGCCCGCA
G
CCAGCCAGCCTCCATTCCGGGCACTCCCGTGAACTCCTGACATGAGGAATGAGGTTGTTC
TGATTTCAAGCAAAGAACGCTGCTCTCTGGCTCCTGGGAACAGTCTCGGTGCCAGCACCA
CCCCTTGGCTGCCTGCCCACACTGCTGGATTCTCGGGTGGAACTGGACCCGCAGGGACAG
CCAGCCCCAGAGTCCGCACTGGGGAGAGAAGGGGCCAGGCCCAGGACACTGCCACCTCC
C
ACCCACTCCAGTCCACCGAGATCACTCAGAGAAGAGCCTGGGCCATGTGGCCGCTGCAG
G
AGCCCCACAGTGCAAGGGTGAGGATAGCCCAAGGAAGGGCTGGGCATCTGCCCAGACA
GG
CCTCCCAGAGAAGGCTGGTGACCAGGTCCCAGGCGGGCAAGACTCAGCCTTGGTGGGGC
C
TGAGGACAGAGGAGGCCCAGGAGCATCGGGGAGAGAGGTGGAGGGACACCGGGAGAGC
CA

Figure 41A

GGAGCGTGGACACAGCCAGAACTCATCACAGAGGCTGGCGTCCAGTCCCGGGTCACGTG
C
AGCAGGAACAAGCAGCCACTCTGGGGGCACCAGGTGGAGAGGCAAGACGACAAAGAGG
GT
GCCCGTGTTCTTGCGAAAGCGGGGCTGCTGGCCACGAGTGCTGGACAGAGGCCCCCACG
C
TCTGCTGCCCCCATCACGCCGTTCCGTGACTGTCACGCAGAATCCGCAGACAGGAAGGG
A
GACTCGAGCGGGAGTGCGGCCAGCGCCTGCCTCGGCCGTCAGGGAGGACTCCCGGGCTC
A
CTCGAAGGAGGTGCCACCATTTCAGCTTTGGTAGCTTTTCTTCTTCTTTTAAATTTTCTA
AAGCTCATTAATTGTCTTTGATGTTTCTTTTGTGATGACAATAAAATATCCTTTTTAAGT
CTTGTAAAAAAAAAAAAAAAAAA

Figure 41A (Continued)

MEFGLSWVFLVALLRGVQCQAQLVESGGGVVQPGSSLRLSCAASGFRFSNYGMHWVRQAP
GKGLEWVAVFSYDESDKYYAASVKGRFTISRDNSKNTLSLQMNSLRVEDTAVYYCAKDQK
PWYSNSWFLTNFDSWGRGTLVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPV
TVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEP
KSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVD
GVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKG
QPREPQVYTLPPSRDELTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSF
FLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPELQLEESCAEAQDGELDGLW
TTITIFITLFLLSVCYSATVTFFKVKWIFSSVVDLKQTIIPDYRNMIGQGA

Figure 41B

1 tccgcaggcg gaccgggggc aaaggaggtg gcatgtcggt caggcacagc agggtcctgt
61 gtccgcgctg agccgcgctc tccctgctcc agcaaggacc atgagggcgc tggaggggcc
121 aggcctgtcg ctgctgtgcc tggtgttggc gctgcctgcc ctgctgccgg tgccggctgt
181 acgcggagtg gcagaaacac ccacctaccc ctggcgggac gcagagacag gggagcggct
241 ggtgtgcgcc cagtgccccc caggcacctt tgtgcagcgg ccgtgccgcc gagacagccc
301 cacgacgtgt ggcccgtgtc caccgcgcca ctacacgcag ttctggaact acctggagcg
361 ctgccgctac tgcaacgtcc tctgcgggga gcgtgaggag gaggcacggg cttgccacgc
421 cacccacaac cgtgcctgcc gctgccgcac cggcttcttc gcgcacgctg gtttctgctt
481 ggagcacgca tcgtgtccac ctggtgccgg cgtgattgcc ccgggcaccc ccagccagaa
541 cacgcagtgc cagccgtgcc ccccaggcac cttctcagcc agcagctcca gctcagagca
601 gtgccagccc caccgcaact gcacggccct gggcctggcc ctcaatgtgc caggctcttc
661 ctcccatgac accctgtgca ccagctgcac tggcttcccc ctcagcacca gggtaccagg
721 agctgaggag tgtgagcgtg ccgtcatcga ctttgtggct ttccaggaca tctccatcaa
781 gaggctgcag cggctgctgc aggccctcga ggccccggag ggctggggtc cgacaccaag
841 ggcgggccgc gcggccttgc agctgaagct gcgtcggcgg ctcacggagc tcctgggggc
901 gcaggacggg gcgctgctgg tgcggctgct gcaggcgctg cgcgtggcca ggatgccccgg
961 gctggagcgg agcgtccgtg agcgcttcct ccctgtgcac tgatcctggc ccctcttat
1021 ttattctaca tccttggcac cccacttgca ctgaaagagg cttttttta aatagaagaa
1081 atgaggtttc ttaaagctta ttttataaa gctttttcat aaaa

Figure 42A

MRALEGPGLSLLCLVLALPALLPVPAVRGVAETPTYPWRDAETGERLVCAQCPPGTFVQRPC
RRDSPTTCGPCPPRHYTQFWNYLERCRYCNVLCGEREEEARACHATHNRACRCRTGFFAHA
GFCLEHASCPPGAGVIAPGTPSQNTQCQPCPPGTFSASSSSSEQCQPHRNCTALGLALNVPGSS
SHDTLCTSCTGFPLSTRVPGAEECERAVIDFVAFQDISIKRLQRLLQALEAPEGWGPTPRAGRA
ALQLKLRRRLTELLGAQDGALLVRLLQALRVARMPGLERSVRERFLPVH

Figure 42B

1 aggctcagta taaatagcag ccaccgctcc ctggcaggca gggacccgca gctcagctac
61 agcacagatc aggtgaggag cacaccaagg agtgatttt aaaacttact ctgttttctc
121 tttcccaaca agattatcat ttcctttaaa aaaaatagtt atcctggggc atacagccat
181 accattctga aggtgtctta tctcctctga tctagagagc accatgaagc ttctcacggg
241 cctggttttc tgctccttgg tcctgggtgt cagcagccga agcttctttt cgttccttgg
301 cgaggctttt gatggggctc gggacatgtg gagagcctac tctgacatga gagaagccaa
361 ttacatcggc tcagacaaat acttccatgc tcgggggaac tatgatgctg ccaaaagggg
421 acctgggggt gcctgggctg cagaagtgat cagcgatgcc agagagaata tccagagatt
481 ctttggccat ggtgcggagg actcgctggc tgatcaggct gccaatgaat ggggcaggag
541 tggcaaagac cccaatcact tccgacctgc tggcctgcct gagaaatact gagcttcctc
601 ttcactctgc tctcaggaga tctggctgtg aggcctcag ggcagggata caaagcgggg
661 agagggtaca caatgggtat ctaataaata cttaagaggt ggaatttgtg gaaact

Figure 43A

MKLLTGLVFCSLVLGVSSRSFFSFLGEAFDGARDMWRAYSDMREANYIGSDKYFHARGNYD
AAKRGPGGAWAAEVISDARENIQRFFGHGAEDSLADQAANEWGRSGKDPNHFRPAGLPEKY

Figure 43B

```
   1 ctaaagctgg gttggtagct cctacctact gtgtggcaag aaggtatggg tcatgaacag
  61 aaccaaggag ctgcgctgct acagatgtta ccacttctgt ggctgctacc ccactcctgg
 121 gccgtcccctg aagctcctac tccaatgtgg ccagatgacc tgcaaaacca cacattcctg
 181 cacacagtgt actgccagga tgggagtccc agtgtgggac tctctgaggc ctacgacgag
 241 gaccagcttt tcttcttcga ctttcccag aacactcggg tgcctcgcct gcccgaattt
 301 gctgactggg ctcaggaaca gggagatgct cctgccattt tatttgacaa agagttctgc
 361 gagtggatga tccagcaaat agggccaaaa cttgatggga aaatcccggt gtccagaggg
 421 tttcctatcg ctgaagtgtt cacgctgaag ccccctggagt ttggcaagcc caacactttg
 481 gtctgttttg tcagtaatct cttcccaccc atgctgacag tgaactggca gcatcattcc
 541 gtccctgtgg aaggatttgg gcctactttt gtctcagctg tcgatggact cagcttccag
 601 gccttttctt acttaaactt cacaccagaa ccttctgaca tttctcctg cattgtgact
 661 cacgaaattg accgctacac agcaattgcc tattgggtac cccggaacgc actgccctca
 721 gatctgctgg agaatgtgct gtgtggcgtg gcctttggcc tgggtgtgct gggcatcatc
 781 gtgggcattg ttctcatcat ctacttccgg aagccttgct caggtgactg attcttccag
 841 accagagttt gatgccagca gcttcggcca tccaaacaga ggatgctcag atttctcaca
 901 tcctgcccag gatctcctct tagggtagaa gaagtctctg ggacatccct ggggtgtgtg
 961 tgtagatttc ccacctgggg actctgctgt ccctgggctt gcatcccagg gatcccagag
1021 tggcctgcct atcacaacca catcccttcc ccccacaagg caataaatct catttcttta
1081 aaaaaaaaaa aaaaaaaaaa
```

Figure 44A

MGHEQNQGAALLQMLPLLWLLPHSWAVPEAPTPMWPDDLQNHTFLHTVYCQDGSPSVGLS
EAYDEDQLFFFDFSQNTRVPRLPEFADWAQEQGDAPAILFDKEFCEWMIQQIGPKLDGKIPVS
RGFPIAEVFTLKPLEFGKPNTLVCFVSNLFPPMLTVNWQHHSVPVEGFGPTFVSAVDGLSFQA
FSYLNFTPEPSDIFSCIVTHEIDRYTAIAYWVPRNALPSDLLENVLCGVAFGLGVLGIIVGIVLII
YFRKPCSGD

Figure 44B

1 ggcaggtgca gctgccacag tgagacgggc accccgaccc gggcatggag gggggcaagg
61 ggcccaggct cagagacttc ctgagtggga gtctggctac ctgggcgctg ggactggccg
121 ggctggtcgg ggaggcggag gactcggagg gggaagaaga ggaagaggag gaagagccgc
181 cccttggtt ggagaagaga ttcctgcgcc tcagcgatgg ggccctgctc ctccgggtgc
241 tgggcatcat tgcccccagc tcccgagggg gacctcggat gctcagaggc cttgacggac
301 ctgctgcctg gcgagtgtgg aacctgaacc acctgtgggg ccgactgagg gacttctacc
361 aggaggagct gcagctgctg atcctgtcgc caccccccaga cctccagaca ttgggatttg
421 accctctctc agaagaagcg gtggagcagc tggaaggcgt tcttcggcta ctgttgggag
481 cgtcagtaca gtgtgagcac cgggaactct tcatccgcca catccagggc ctcagtctcg
541 aggtccagag cgagctggcc gctgccatcc aggaggtgac ccagccgggg gccggcgtgg
601 tgctggcact gtctgggcca gatcctgggg agctggcacc tgccgagctg gagatgctgt
661 cccggagcct gatggggaca ctgtcgaagc tggcacggga gcgtgacctg ggggcccagc
721 ggctggctga actgctgctg gagcgagaac ccctctgctt gaggcctgag gctccctcta
781 gggctcccgc cgagggcccc tcgcaccatc tggccctgca gctggccaac gccaaggctc
841 agctgcggcg tctgcggcag gagctggagg agaaggccga gctgctgcta gactcccagg
901 ccgaggtgca gggtttggag gccgaaataa gaaggctccg ccaggaggcc caggcgctgt
961 cgggacaggc caagcgggcc gagctgtacc gcgaggaggc agaggcgctg cgggagcggg
1021 ccggccgcct gccccgcctg caggaggagc tgaggcgctg ccgcgagcgg ctgcaggcgg
1081 ctgaggccta caagagtcag ctggaggagg agcgggtgct ctcgggggtg ctggaggcgt
1141 ccaaggcgct gctggaagag cagctggagg ctgcccgaga gcgctgcgcc cggctgcacg
1201 agacccagcg cgagaacctg ctgctgcgaa cccggctggg cgaggcccat gcggagctgg
1261 actctctgcg gcatcaggtg gaccagctgg ctgaggagaa tgtggagctg gagctggagc
1321 ttcagcggag cttggagcca cctccaggat cccctgggga ggcaccccta gcaggagcgg
1381 ccccctcgct gcaagatgag gtgagggagg cagaggctgg gcggcttcgg acccttgaga
1441 gggagaaccg ggagcttcgg gggctgcttc aggtgcttca ggggcagcca gggggccagc
1501 acccccctgct ggaggcaccg agagaggacc ctgttcttcc agtgctggag gaggctcccc
1561 agactcctgt ggccttcgac cacagcccte agggcttggt tcagaaggca agggatggag
1621 gccccaggc cttggacttg gctcccccgg cattagactc agtgctcgag gcatcagctg
1681 agtgtcccca ggcacctgat tcagacccac aggaggcaga gagtccccct caggcagctg
1741 ccatggaccc ccaggcctca gactggtccc cgcaagagtc aggctctcct gtggagacac
1801 aggagtcccc ggagaaggct ggccgtagat cctctctcca gagccctgcc tctgtggccc
1861 cacctcaggg tccagggacc aaaattcagg ccccgcagtt gctgggagga gagacagagg
1921 gaagagaggc tccccaaggc gagttggtgc ctgaggcctg ggggttgaga caggagggcc
1981 ctgagcacaa gccagggcct tcggagccca gctctgtgca gctggaggag caggagggcc
2041 caaaccaggg cctggacctg gccacgggac aagcagaggc cagagagcat gaccagaggc
2101 tggaagggac ggtcagggac ccagcctggc aaaaaccaca gcagaagtca gaaggggctc
2161 ttgaggtcca ggtctgggaa ggcccaatcc caggggagag cctggccagt ggtgtcgcag
2221 agcaggaggc cctcagggag gaggtggcac agttgaggag aaaggctgag gcccttggag
2281 atgagctgga agcccaggcc cgcaagctgg aggcccaaaa cacggaggct gcccgcctct
2341 ccaaggagct ggcccaagcg cgaagggcag aggccgaggc ccaccgggag gcagaggccc
2401 aggcctggga gcaagcccgg ctgcgggagg cagtggaggc tgctggccag gagctggagt
2461 ctgcgtccca ggaacgggag gcgctggtgg aggcgctggc agcagcgggc cgggagcgga
2521 ggcagtggga gcgtgagggg tccaggctgc gggcccagtc ggaggccgcc gaggaacgga
2581 tgcaggtgct ggagagcgag ggccgccagc acttggagga ggctgagagg gagcgccggg
2641 agaaggaggc cctccaggcg gagctggaga aagctgtggt gcggggcaag gagttggggg
2701 cccggctgga gcatttgcag cgtgagctgg agcaggcggc tctcgagcgc caggaatttc
2761 tgcgagaaaa ggaaagccag caccagaggt accagggctt ggagcagcgg ctggaagctg
2821 agctgcaggc ggcggcgacc agcaaggagg aggcgctgat ggagctcaag accagggccc
2881 tgcagctgga agaggagctg ttccagctgc gccagggccc cgcggggctg gggcccaaaa
2941 agcgtgcgga gcctcagctg gtggagaccc agaatgtgcg gcttattgag gtggagcgca

Figure 45A

3001 gtaatgcgat gctggtggca gagaaggcag ctttgcaggg gcagctgcag cacctggagg
3061 ggcagctggg gagcctgcag ggccgtgccc aggagctgct gctgcagagc cagcgggcgc
3121 aggagcacag cagccgcctg caggccgaga agtctgtgct ggagattcag ggccaggagc
3181 tgcaccggaa gctggaggtg ctggaggagg aggtgcgggc ggcacggcag tcccaggagg

3241 agacccgcgg gcagcagcag gccctgcttc gggaccacaa ggccctggca cagctgcagc
3301 ggcggcagga ggccgagcta gagggactgc tggtgcggca ccgagaccte aaggccaaca
3361 tgcgggcact ggagctggcc caccgggagc tgcagggccg gcacgagcag ctgcaggccc
3421 agcgggccag cgtggaggca caggaggtgg ccctgctggc agagcgtgaa cgcctgatgc
3481 aagatgggca tcggcagcgg ggcctggagg aggagctgcg gaggcttcag agcgagcacg
3541 acagggctca gatgctgctg gcagagttgt ctcgggagcg gggtgagctg cagggtgaac
3601 gcggggagct acggggccgg ctggcgcggc tggagctgga gcgggcacag ctggagatgc
3661 agagccagca gctgcgcgag tccaaccagc agctggacct gagcgcctgc cggctgacca
3721 cgcagtgtga gctattgaca cagctgcgaa gtgcccagga agaggagaac cggcagctgc
3781 tggctgaagt tcaggccctg agccgggaga acagggagct cctggagcgc agcctggaga
3841 gtcgggacca cctgcaccgc gaacagcggg agtacctgga ccagcttaat gccctgcgcc
3901 gcgagaagca gaagctcgtg gagaagatca tggaccaata ccgcgtgctg gagcctgtgc
3961 ccctgccccg gaccaagaag ggcagctggc tggcagacaa ggtgaagagg ctgatgcggc
4021 cccggcggga ggggggcccc cctggggggc tgcgcctggg ggccgatggg gctggcagca
4081 ccgagagcct ggggggcccc ccggagacgg agcttcctga gggcagggag gcagatggga
4141 cagggtcccc ttccccggca cccatgcgcc gggcccagag ctcccctctgc ctgcgggatg
4201 agaccttggc aggcgggcag cggcggaaac tcagctcaag gttcccggtg gggcgaagct
4261 ctgagtcatt cagccctggg gacaccccta ggcaacgatt ccgacagcgc catccaggcc
4321 ccctgggggc gcccgtctcc cacagcaaag gacctggtgt gggatgggag aactccgctg
4381 agaccctgca ggaacacgaa acagatgcca accgagaggg ccctgaggta caggaaccgg
4441 agaaacgtcc cctcacccca tccctcagcc agtgacaccg tgggaacagc aggcttggga
4501 gtgcagcctt ctcggcactg gagtgtcagc ggaggcccca ggcagccccaa gagctcaggg
4561 agccagggac cccaagggga gtccttggac aaggaggcct gggccctgag atcctccacg
4621 gtcagcgccg gggccccggag atggagctgg gacgagtgtg tggacagggg ggatggctgg
4681 cccccacgag cagctccagg ctggagttct ggttcttcca ggtggctccc gctgaggcag
4741 cggtctctgg gggatccccc agctgaagga ggctggcagg agttggcaag agaacccccct
4801 gccctgtcca ggtgggaagc tgagtcccag tgctgggggа ctgtggcctg ggctgatctt
4861 gagccttaac tggacatgag gggcatgaga ataaagctga actgcagcct cctgaaaaaa
4921 aaaaaaa

Figure 45A (Continued)

MEGGKGPRLRDFLSGSLATWALGLAGLVGEAEDSEGEEEEEEEEPPLWLEKRFLRLSDGALL
LRVLGHAPSSRGGPRMLRGLDGPAAWRVWNLNHLWGRLRDFYQEELQLLILSPPPDLQTLG
FDPLSEEAVEQLEGVLRLLLGASVQCEHRELFIRHIQGLSLEVQSELAAAIQEVTQPGAGVVL
ALSGPDPGELAPAELEMLSRSLMGTLSKLARERDLGAQRLAELLLEREPLCLRPEAPSRAPAE
GPSHHLALQLANAKAQLRRLRQELEEKAELLLDSQAEVQGLEAEIRRLRQEAQALSGQAKR
AELYREEAEALRERAGRLPRLQEELRRCRERLQAAEAYKSQLEEERVLSGVLEASKALLEEQ
LEAARERCARLHETQRENLLLRTRLGEAHAELDSLRHQVDQLAEENVELELELQRSLEPPPGS
PGEAPLAGAAPSLQDEVREAEAGRLRTLERENRELRGLLQVLQGQPGGQHPLLEAPREDPVL
PVLEEAPQTPVAFDHSPQGLVQKARDGGPQALDLAPPALDSVLEASAECPQAPDSDPQEAES
PLQAAAMDPQASDWSPQESGSPVETQESPEKAGRRSSLQSPASVAPPQGPGTKIQAPQLLGGE
TEGREAPQGELVPEAWGLRQEGPEHKPGPSEPSSVQLEEQEGPNQGLDLATGQAEAREHDQR
LEGTVRDPAWQKPQQKSEGALEVQVWEGPIPGESLASGVAEQEALREEVAQLRRKAEALGD
ELEAQARKLEAQNTEAARLSKELAQARRAEAEAHREAEAQAWEQARLREAVEAAGQELES
ASQEREALVEALAAAGRERRQWEREGSRLRAQSEAAEERMQVLESEGRQHLEEAERERREK
EALQAELEKAVVRGKELGARLEHLQRELEQAALERQEFLREKESQHQRYQGLEQRLEAELQ
AAATSKEEALMELKTRALQLEEELFQLRQGPAGLGPKKRAEPQLVETQNVRLIEVERSNAML
VAEKAALQGQLQHLEGQLGSLQGRAQELLLQSQRAQEHSSRLQAEKSVLEIQGQELHRKLE
VLEEEVRAARQSQEETRGQQQALLRDHKALAQLQRRQEAELEGLLVRHRDLKANMRALEL
AHRELQGRHEQLQAQRASVEAQEVALLAERERLMQDGHRQRGLEEELRRLQSEHDRAQML
LAELSRERGELQGERGELRGRLARLELERAQLEMQSQQLRESNQQLDLSACRLTTQCELLTQ
LRSAQEEENRQLLAEVQALSRENRELLERSLESRDHLHREQREYLDQLNALRREKQKLVEKI
MDQYRVLEPVPLPRTKKGSWLADKVKRLMRPRREGGPPGGLRLGADGAGSTESLGGPPETE
LPEGREADGTGSPSPAPMRRAQSSLCLRDETLAGGQRRKLSSRFPVGRSSESFSPGDTPRQRF
RQRHPGPLGAPVSHSKGPGVGWENSAETLQEHETDANREGPEVQEPEKRPLTPSLSQ

Figure 45B

1 actcgccacc tcctcttcca ccccctgccag gcccagcagc caccacagcg cctgcttcct
61 cggccctgaa atcatgcccc taggtctcct gtggctgggc ctagccctgt tgggggctct
121 gcatgcccag gcccaggact ccacctcaga cctgatccca gccccacctc tgagcaaggt
181 ccctctgcag cagaacttcc aggacaacca attccagggg aagtggtatg tggtaggcct
241 ggcagggaat gcaattctca gagaagacaa agacccgcaa aagatgtatg ccaccatcta
301 tgagctgaaa gaagacaaga gctacaatgt cacctccgtc ctgtttagga aaaagaagtg
361 tgactactgg atcaggactt ttgttccagg ttgccagccc ggcgagttca cgctgggcaa
421 cattaagagt taccctggat taacgagtta cctcgtccga gtggtgagca ccaactacaa
481 ccagcatgct atggtgttct tcaagaaagt ttctcaaaac agggagtact tcaagatcac
541 cctctacggg agaaccaagg agctgacttc ggaactaaag gagaacttca tccgcttctc
601 caaatctctg ggcctccctg aaaaccacat cgtcttccct gtcccaatcg accagtgtat
661 cgacggctga gtgcacaggt gccgccagct gccgcaccag cccgaacacc attgagggag
721 ctgggagacc ctccccacag tgccacccat gcagctgctc cccaggccac cccgctgatg
781 gagccccacc ttgtctgcta ataaacatg tgccctcagg ccaaaaaaaa aaaaaaaaaa

Figure 46A

MPLGLLWLGLALLGALHAQAQDSTSDLIPAPPLSKVPLQQNFQDNQFQGKWYVVGLAGNAI
LREDKDPQKMYATIYELKEDKSYNVTSVLFRKKKCDYWIRTFVPGCQPGEFTLGNIKSYPGL
TSYLVRVVSTNYNQHAMVFFKKVSQNREYFKITLYGRTKELTSELKENFIRFSKSLGLPENHI
VFPVPIDQCIDG

Figure 46B

```
   1 gctgacacct gcccagtgga agctggcatc cctccccttg tgggttcaga gctgcaagaa
  61 gcaccaggct cggccacttc agaagcccca gcctcgacct agcccaccct ctcagggcca
 121 cagtgcagaa gcctgcacac ctgccaagtc tctccgactc cttgcagctg ctgtcagcat
 181 ggcccaggct cctgctgacc cgggcagaga aggccacctt gaacaaagaa tcctgcaggt
 241 gctgacagag gctggctccc cggtgaaact tgcccagctg gtgaaggaat gccaagcacc
 301 caagagggag ctcaaccaag tcctctaccg aatgaaaaag gagttgaaag tctccctcac
 361 atcccctgcc acctggtgct tgggcgggac tgatcctgaa ggcgagggtc ctgcagagct
 421 ggccttgtcc agccctgccg agaggcccca gcaacatgca gctacaattc cagagacccc
 481 tggccctcag ttcagccaac aacgggagga agacatctac aggtttctca aagacaatgg
 541 tccccagagg gccctggtca tcgcccaagc actgggaatg aggacagcaa aagatgtgaa
 601 ccgagacttg tacaggatga agagcaggca ccttctggac atggatgagc agtccaaagc
 661 atggacgatt taccgcccag aagattctgg aagaagagca aagtcagcct caattattta
 721 ccagcacaat ccaatcaaca tgatctgcca gaatggaccc aacagctgga tttccattgc
 781 aaactccgaa gccatccaga ttggacacgg gaacatcatt acaagacaga cagtctccag
 841 ggaggacggt tccgccggtc cacgccacct cccttcaatg gcaccaggtg attcctcaac
 901 ttgggggacc ctagttgatc cctgggggcc ccaggacatc cacatggagc ggtccatact
 961 gagacgggtg cagctgggac acagcaatga gatgaggctc cacggcgtcc cgtccgaggg
1021 ccctgcccac atccccccctg gcagcccccc agtctctgcc actgctgccg gcccagaagc
1081 ttcgtttgaa gcaagaattc ccagtccagg aactcaccct gagggggaag ccgcccagag
1141 aatccacatg aaatcgtgct ttctcgagga cgccaccatc ggcaacagca acaaaatgtc
1201 tatcagccca ggggtggctg gcccaggagg agtcgcaggg tctggagagg gggagccagg
1261 ggaggacgca ggtcgtcgtc ccgcagacac acaatccaga agtcactttc ctcgagacat
1321 tggtcagccc atcactccca gccactcgaa gctcaccccc aagctggaaa ctatgactct
1381 tggaaacagg agtcacaaag ctgcagaagg cagccactat gtggatgaag cctcacacga
1441 ggggagctgg tggggaggtg ggatttagtg cacagcctca cgtggggctt ggacacaggc
1501 tgggggtggg cgcatgctag ggagactagc ctgctgctct ctgcattcct tagcgtcttg
1561 tttgacctgc ttgcttccag acataaacctg catgaatcag ttttgggggа atggacctgg
1621 catggggatg ggttcaggcc aggtcttttg atggccagga gtagatgaca gggagttgcc
1681 ttggggaacc tttggtgtgc caagaggagg tgggtagatg ggagtggggc tcggtccccc
1741 aggcccaggg gactctctcc actctttcct gggctcgggg catctgcctg gagttacctt
1801 ccatcatggc tacctgctgt ggtttgaatg tttgagtccc aacaaaattc atatcaaaac
1861 ataatcccaa ctgggtgcag tggctcacgc ctgtaatccc agcactttgg gaggccgagg
1921 cgggcggatc aataggtcag gaaatccaga ccgtcctggc taacatggtg aaaccccgtc
1981 tctactaaaa aaaaaaatac aaaaaattag ccgggcgttg tggcgggcac ctggagtccc
2041 agctacttcg gaggctgagg gaggagaatg gtgtgaaccc gggaggtgga gcttccagtg
2101 agccgagatc gcgccactgc actccaggct gggcgacaga gcgagactcc gtctcaaaaa
2161 aataaataca taaataaaaa ataaaccacc cataaaaaaa aaaaaaaaaa aaaaaaaaaa
2221 aaaa
```

Figure 47A

MAQAPADPGREGHLEQRILQVLTEAGSPVKLAQLVKECQAPKRELNQVLYRMKKELKVSLT
SPATWCLGGTDPEGEGPAELALSSPAERPQQHAATIPETPGPQFSQQREEDIYRFLKDNGPQR
ALVIAQALGMRTAKDVNRDLYRMKSRHLLDMDEQSKAWTIYRPEDSGRRAKSASIIYQHNPI
NMICQNGPNSWISIANSEAIQIGHGNIITRQTVSREDGSAGPRHLPSMAPGDSSTWGTLVDPW
GPQDIHMERSILRRVQLGHSNEMRLHGVPSEGPAHIPPGSPPVSATAAGPEASFEARIPSPGTH
PEGEAAQRIHMKSCFLEDATIGNSNKMSISPGVAGPGGVAGSGEGEPGEDAGRRPADTQSRS
HFPRDIGQPITPSHSKLTPKLETMTLGNRSHKAAEGSHYVDEASHEGSWWGGGI

Figure 47B

1 acgcggggat tctgtgtaat tcctatccac agtcacttct gttcattttt aatgaaaacc
61 tattgctgtt attttctatt atgagttaac ggtgatgtgt gttttttaaa ttttgtatac
121 ttgctctcac cctaaaatat accttaagag acttttcccc tgtttttctt tctgctttcc
181 aagactccag gaaaaacagc ttccatggca cattttgtac agggcacatc tagaatgatt
241 gccgcagaaa gttctacgga gcataaagag tgtgctgaac catcaacaag aaagaacttg
301 atgaattctc ttgaacaaaa gataaggtgt ttggaaaaac aaagaaaaga gctcctggaa
361 gttaaccagc aatgggatca gcaatttaga agtatgaaag agttatatga aagaaaggta
421 gcagagctga agacgaaact ggacgccgcg gaaagattcc tcagcacgcg ggagaaggat
481 ccgcatcaga ggcagagaaa ggacgacagg cagagagagg acgacaggca gcgcgacctg
541 acccgggacc ggctgcagcg ggaggagaag gaaaaggaac gcctaaatga agaattacat
601 gaattgaaag aagagaataa acttttaaag ggaaaaaata ctcttgcgaa caaggaaaag
661 gaacattacg aatgtgaaat aaaacgcctc aataaggctc ttcaggatgc cttgaatatc
721 aagtgttcat tttccgagga ctgtttgagg aagtctcgag tggaattctg ccatgaggag
781 atgagaacag aaatggaagt tctgaagcag caggtgcaaa tatacgaaga agacttcaaa
841 aaggaacgat cggatcgaga gagacttaat caagagaaag aggagctaca gcaaattaat
901 gaaacttccc aatcccagtt gaacaggctg aattcccaga taaaagcttg tcagatggag
961 aaagaaaaac tagaaaagca attaaaacag atgtattgcc caccctgtaa ctgcggcttg
1021 gttttccacc tgcaagatcc atgggtacca acaggccctg gagctgtgca gaagcaacgg
1081 gagcacccac cagactgtca gtggtatgct cttgaccagc ttccgccaga tgtacaacac
1141 aaggcaaatg gtttatcctc agtaaagaaa gtccatccgt agaagtacac actaacagag
1201 agagacaaca ggcaacgagg gagcgtggct gaggaccctc ttcttgttt atactgaggc
1261 ttgtttctgc cacaaaggca catcatctac cctgttattt gtgcctggtc atgttttcct
1321 ttggtatgaa tacaggaaaa ggcttctgac agctaagatc ctgatcaaat tggaggagcc
1381 agttattata caaccaaata caacttccag tttccttgaa atgagacttg gcagatggat
1441 gatgcacgac tccctgaaaa tctcttcagc atattgctgt tggatgcaca aaaatgattc
1501 tatgatttag gcaactcagt gtttgctgca gggatattgt atgttgattt aaagtgcata
1561 tgtgtgtgtg tgtgtgtgtg tgtgtgtgtg tttcctgggg taaaaatttc tgcagttgta
1621 aacgtttaac attgctccca ttcttcttcc acagggcctt agttctttag ctatttgact
1681 acatattgtt gacctcagtg atcctaaacg tagaattgaa gaggtgtata tacctcgtta
1741 aattaaataa gtggttcaat ctgaataaga tggttaattg gaagctattc cttagacaga
1801 tcatttcttt aagatggtga gaaattgtgc gcctgcatca caagacttga ttatgaaaga
1861 taaagtcttg ggctgggtgc agtggctcat gcctataatc ccagcacttt gggaggctga
1921 ggcaggtgga ttgctttgag gccaggagtt ctagaccagc ctggccagca tggtgaaacc
1981 ccatctctac taaaatacta aaaattagcc aggctcgtgg cacacacctа taaacccagc
2041 tactcaggag gcttgaggcg ggaggatcac ttgagcccag ggaggcagag gttgctgtaa
2101 gttgagatcg ccactgcact ccagcctggg aaatagagtg agcaagactc agtgcccccc
2161 acccacccac tccacaccac caaaaaaaaa aaaaaaaaaa aaaggaagac aaagtcctga
2221 tgggatgatg atggctatat ggctatgctg tgtccatata tacttacaga aatatttcag
2281 acatatggat ttatagttaa atctgtgttt ttccttccta tggatttgat taattttaat
2341 gaaaaactta attctgactc ctcaagccaa ttaaaatgaa aatggaattt atttaaaaaa
2401 aaaaaaaaaa aaaaaaaaaa aaaaa

Figure 48A

MAHFVQGTSRMIAAESSTEHKECAEPSTRKNLMNSLEQKIRCLEKQRKELLEVNQQWDQQF
RSMKELYERKVAELKTKLDAAERFLSTREKDPHQRQRKDDRQREDDRQRDLTRDRLQREEK
EKERLNEELHELKEENKLLKGKNTLANKEKEHYECEIKRLNKALQDALNIKCSFSEDCLRKS
RVEFCHEEMRTEMEVLKQQVQIYEEDFKKERSDRERLNQEKEELQQINETSQSQLNRLNSQI
KACQMEKEKLEKQLKQMYCPPCNCGLVFHLQDPWVPTGPGAVQKQREHPPDCQWYALDQ
LPPDVQHKANGLSSVKKVHP

Figure 48B

1 agtgcctcac caccacctgc ccgcgcgccg ccccatataa aggcgccgcc gtccttaccc
61 ccaggactcg gccccatgga gacgccgccg gccgccgctg gcgcatggcg ggtaggagct
121 gtggcgcggg gccttccagg agtctgagct atgagtggcc cctgtggaga gaagcctgtc
181 ctggaagcca gccccaccat gagtctgtgg gaatttgagg acagccacag ccgtcagggc
241 accccaaggc cgggtcaaga gctggccgct gaggaggcct cggccctgga actgcagatg
301 aaggtggact tcttccggaa gctgggctat tcatccacgg agatccacag cgtcctgcag
361 aagctgggcg tccaggcaga caccaacacg gtgctgggtg agctggtgaa acacgggaca
421 gccaccgagc gggagcgcca gacctcaccg gaccccctgc ctcagctccc tctagtcccg
481 cggggtggtg gcacccctaa ggctcccaac ctggagcctc cactcccaga agaggaaaag
541 gagggcagcg acctgagacc agtggtcatc gatgggagca acgtggccat gagccatggg
601 aacaaggagg tcttctcctg ccggggcatc ctgctggcag tgaactggtt tctggagcgg
661 ggccacacag acatcacagt gtttgtgcca tcctggagga aggagcagcc tcggcccgac
721 gtgcccatca cagaccagca catcctgcgg gaactggaga agaagaagat cctggtgttc
781 acaccatcac gacgcgtggg tggcaagcgg gtggtgtgct atgacgacag attcattgtg
841 aagctggcct acgagtctga cgggatcgtg gtttccaacg acacataccg tgacctccaa
901 ggcgagcggc aggagtggaa gcgcttcatc gaggagcggc tgctcatgta ctccttcgtc
961 aatgacaagt ttatgccccc tgatgaccca ctgggccggc acgggcccag cctggacaac
1021 ttcctgcgta agaagccact cactttggag cacaggaagc agccgtgtcc ctatggaagg
1081 aaatgcacct atgggatcaa gtgccgattc ttccacccag agcggccaag ctgccccccag
1141 cgctctgtgg cagatgagct ccgtgccaat gctctcctct cacccccccag agccccaagc
1201 aaggacaaaa atggccgggg gccttcacct tcatcccagt ccagctctct gctaacagag
1261 agtgagcagt gcagcctgga tgggaagaag ctgggggccc aggcatcccc agggtcccgc
1321 caagagggtc taacacagac ctatgcccca tcaggcagga gcctcgcacc tagcgggggc
1381 agtggcagca gctttgggcc cacagactgg ctcccacaga cgctggactc actcccgtac
1441 gtctcccagg attgcctgga ctcgggcatt ggctccctgg agagccagat gtcggaactt
1501 tgggggttc gaggaggagg ccctggtgag ccgggcccac cccgagcccc ttacacgggc
1561 tacagtccct atggatctga gctcccagcc accgcagcct tctctgcctt tggccgggcc
1621 atgggtgctg gccacttcag tgtccctgcc gactacccac ccgcgccccc tgccttttca
1681 cctcgagagt actggtctga accatacccа ctgccccccac ccacatcagt ccttcaggag
1741 ccccccagtgc agagccccagg ggctggcagg agcccgtggg gcagggcagg cagcctggcc
1801 aaggagcagg ccagcgtgta tactaagctg tgtggtgtgt ttcccccgca cctggtggag
1861 gctgtgatgg ggcgcttccc acagctcctg gacccccagc agctggctgc cgagatcctc
1921 tcctacaagt cccagcaccc cagtgagtaa gctgcctgtg gctggcaagg gcagcacccc
1981 cagcctccaa gggccgtcag gctgggcttt gggccattga gcagcccatt cccagccctg
2041 aggcccaccc cagaggctgg acagagggag gattcaagtc gggaaggaaa cccacaaacc
2101 aaagatactg taggattggt tctggcccat gcagcacctc tagctgtctg cctcagtggg
2161 tcagaagcga tcaccctgtt gatacacatt gtatctctgt agtttaagga gacgctgccg
2221 gtaacggcgt cggtccgtgg ctgaggccca aaccgtcttt tctctcagag ggtggggagg
2281 gaggtggggg cagcagaggc ctgggctggg tgccctgtgc acgccacccc acttccgccc
2341 taccccctggg acgttggcct tggctggcta gttgggcacc gtgtgcctgc cctccaaggg
2401 cctcctctac gccaatgagg cctcatctgt gctctcgctg ggcacgtggc ttcatgtcag
2461 taagcaagat gcttcttaat aacccacctt ctgccccact ctattcctta tcctgctgcc
2521 cctgtagggg tcaagggccc tccgtctaca ccctcttctt ctcctccatc ctttattcag
2581 agtcatctcg cccttcccca tgggtggggg aaccctgtgtt tgtttgtgtg cacatgtaaa
2641 ttttaaatat tttaagcaga aagtccttac ctcctgtaac acatcaataa agtacaatca
2701 ttgtgagccc tttcaaaaaa aaaaaaaaaa aaaaaaa

Figure 49A

MSGPCGEKPVLEASPTMSLWEFEDSHSRQGTPRPGQELAAEEASALELQMKVDFFRKLGYSS
TEIHSVLQKLGVQADTNTVLGELVKHGTATERERQTSPDPCPQLPLVPRGGGTPKAPNLEPPL
PEEEKEGSDLRPVVIDGSNVAMSHGNKEVFSCRGILLAVNWFLERGHTDITVFVPSWRKEQP
RPDVPITDQHILRELEKKKILVFTPSRRVGGKRVVCYDDRFIVKLAYESDGIVVSNDTYRDLQ

GERQEWKRFIEERLLMYSFVNDKFMPPDDPLGRHGPSLDNFLRKKPLTLEHRKQPCPYGRKC
TYGIKCRFFHPERPSCPQRSVADELRANALLSPPRAPSKDKNGRRPSPSSQSSSLLTESEQCSLD
GKKLGAQASPGSRQEGLTQTYAPSGRSLAPSGGSGSSFGPTDWLPQTLDSLPYVSQDCLDSGI
GSLESQMSELWGVRGGGPGEPGPPRAPYTGYSPYGSELPATAAFSAFGRAMGAGHFSVPAD
YPPAPPAFPPREYWSEPYPLPPPTSVLQEPPVQSPGAGRSPWGRAGSLAKEQASVYTKLCGVF
PPHLVEAVMGRFPQLLDPQQLAAEILSYKSQHPSE

Figure 49B

1 cacatagctc agttcccata aaagggctgg tttgccgcgt cggggagtgg agtgggacag
61 gtatataaag gaagtacagg gcctggggaa gaggccctgt ctaggtagct ggcaccagga
121 gccgtgggca agggaagagg ccacaccctg ccctgctctg ctgcagccag aatgggtgtg
181 aaggcgtctc aaacaggctt tgtggtcctg gtgctgctcc agtgctgctc tgcatacaaa
241 ctggtctgct actacaccag ctggtcccag taccgggaag gcgatgggag ctgcttccca
301 gatgcccttg accgcttcct ctgtacccac atcatctaca gctttgccaa tataagcaac
361 gatcacatcg acacctggga gtggaatgat gtgacgctct acggcatgct caacacactc
421 aagaacagga accccaacct gaagactctc ttgtctgtcg gaggatggaa ctttgggtct
481 caaagatttt ccaagatagc ctccaacacc cagagtcgcc ggactttcat caagtcagta
541 ccgccatttc tgcgcaccca tggctttgat gggctggacc ttgcctggct ctaccctgga
601 cggagagaca aacagcattt taccacccta atcaaggaaa tgaaggccga atttataaag
661 gaagcccagc cagggaaaaa gcagctcctg ctcagcgcag cactgtctgc ggggaaggtc
721 accattgaca gcagctatga cattgccaag atatcccaac acctggattt cattagcatc
781 atgacctacg attttcatgg agcctggcgt gggaccacag gccatcacag tcccctgttc
841 cgaggtcagg aggatgcaag tcctgacaga ttcagcaaca ctgactatgc tgtggggtac
901 atgttgaggc tgggggctcc tgccagtaag ctggtgatgg gcatccccac cttcgggagg
961 agcttcactc tggcttcttc tgagactggt gttggagccc caatctcagg accgggaatt
1021 ccaggccggt tcaccaagga ggcagggacc cttgcctact atgagatctg tgacttcctc
1081 cgcggagcca cagtccatag aatcctcggc cagcaggtcc cctatgccac caagggcaac
1141 cagtgggtag gatacgacga ccaggaaagc gtcaaaagca aggtgcagta cctgaaggac
1201 aggcagctgg cgggcgccat ggtatgggcc ctggacctgg atgacttcca gggctccttc
1261 tgcggccagg atctgcgctt cctctctacc aatgccatca aggatgcact cgctgcaacg
1321 tagccctctg ttctgcacac agcacggggg ccaaggatgc ccgtcccccc tctggctcca
1381 gctggccggg agcctgatca cctgccctgc tgagtcccag gctgagcctc agtctccctc
1441 ccttggggcc tatgcagagg tccacaacac acagatttga gctcagccct ggtgggcaga
1501 gaggtaggga tggggctgtg gggatagtga ggcatcgcaa tgtaagactc gggattagta
1561 cacacttgtt gattaatgga aatgtttaca gatccccaag cctggcaagg gaatttcttc
1621 aactccctgc ccccagccc tccttatcaa aggacaccat tttggcaagc tctatcacca
1681 aggagccaaa catcctacaa gacacagtga ccatactaat tatacccccc gcaaagccca
1741 gcttgaaacc ttcacttagg aacgtaatcg tgtcccctat cctacttccc cttcctaatt
1801 ccacagctgc tcaataaagt acaagagctt aacagtgaaa aaaaaaaaaa aaaaaaaaaa
1861 aaaaaaa

Figure 50A

MGVKASQTGFVVLVLLQCCSAYKLVCYYTSWSQYREGDGSCFPDALDRFLCTHIIYSFANIS
NDHIDTWEWNDVTLYGMLNTLKNRNPNLKTLLSVGGWNFGSQRFSKIASNTQSRRTFIKSVP
PFLRTHGFDGLDLAWLYPGRRDKQHFTTLIKEMKAEFIKEAQPGKKQLLLSAALSAGKVTID
SSYDIAKISQHLDFISIMTYDFHGAWRGTTGHHSPLFRGQEDASPDRFSNTDYAVGYMLRLG
APASKLVMGIPTFGRSFTLASSETGVGAPISGPGIPGRFTKEAGTLAYYEICDFLRGATVHRILG
QQVPYATKGNQWVGYDDQESVKSKVQYLKDRQLAGAMVWALDLDDFQGSFCGQDLRFPL
TNAIKDALAAT

Figure 50B

1 gattctgtgt gtgtcctcag atgctcagcc acagaccttt gagggagtaa agggggcaga
61 cccacccacc ttgcctccag gctctttcct tcctggtcct gttctatggt ggggctccct
121 tgccagactt cagactgaga agtcagatga agtttcaaga aaaggaaatt ggtgggtgac
181 agagatgggt ggaggggctg gggaaaggct gtttacttcc tcctgtctag tcggtttggt
241 ccctttaggg ctccggatat ctttggtgac ttgtccactc cagtgtggca tcatgtggca
301 gctgctcctc ccaactgctc tgctacttct agtttcagct ggcatgcgga ctgaagatct
361 cccaaaggct gtggtgttcc tggagcctca atggtacagg gtgctcgaga aggacagtgt
421 gactctgaag tgccagggag cctactcccc tgaggacaat tccacacagt ggtttcacaa
481 tgagagcctc atctcaagcc aggcctcgag ctacttcatt gacgctgcca cagtcgacga
541 cagtggagag tacaggtgcc agacaaacct ctccaccctc agtgacccgg tgcagctaga
601 agtccatatc ggctggctgt tgctccaggc ccctcggtgg gtgttcaagg aggaagaccc
661 tattcacctg aggtgtcaca gctggaagaa cactgctctg cataaggtca catatttaca
721 gaatggcaaa ggcaggaagt attttcatca taattctgac ttctacattc caaaagccac
781 actcaaagac agcggctcct acttctgcag ggggcttttt gggagtaaaa atgtgtcttc
841 agagactgtg aacatcacca tcactcaagg tttggcagtg tcaaccatct catcattctt
901 tccacctggg taccaagtct ctttctgctt ggtgatggta ctccttttg cagtggacac
961 aggactatat ttctctgtga agacaaacat tcgaagctca acaagagact ggaaggacca
1021 taaatttaaa tggagaaagg accctcaaga caaatgaccc ccatcccatg ggggtaataa
1081 gagcagtagc agcagcatct ctgaacattt ctctggattt gcaaccccat catcctcagg
1141 cctctctaca agcagcagga aacatagaac tcagagccag atcccttatc caactctcga
1201 cttttccttg gtctccagtg gaagggaaaa gcccatgatc ttcaagcagg gaagccccag
1261 tgagtagctg cattcctaga aattgaagtt tcagagctac acaaacactt tttctgtccc
1321 aaccgttccc tcacagcaaa gcaacaatac aggctaggga tggtaatcct ttaaacatac
1381 aaaaattgct cgtgttataa attacccagt ttagagggga aaaaaaaaca attattccta
1441 aataaatgga taagtagaat taatggttga ggcaggacca tacagagtgt gggaactgct
1501 ggggatctag ggaattcagt gggaccaatg aaagcatggc tgagaaatag caggtagtcc
1561 aggatagtct aagggaggtg ttcccatctg agcccagaga taagggtgtc ttcctagaac
1621 attagccgta gtggaattaa caggaaatca tgagggtgac gtagaattga gtcttccagg
1681 ggactctatc agaactggac catctccaag tatataacga tgagtcctct taatgctagg
1741 agtagaaaat ggtcctagga aggggactga ggattgcggt ggggggtggg gtggaaaaga
1801 aagtacagaa caaaccctgt gtcactgtcc caagttgcta agtgaacaga actatctcag
1861 catcagaatg agaaagcctg agaagaaaga accaaccaca agcacacagg aaggaaagcg
1921 caggaggtga aaatgcttte ttggccaggg tagtaagaat tagaggttaa tgcagggact
1981 gtaaaaccac cttttctgct tcaatatcta attcctgtgt agctttgttc attgcattta
2041 ttaaacaaat gttgtataac caatactaaa tgtactactg agcttcgctg agttaagtta
2101 tgaaactttc aaatccttca tcatgtcagt tccaatgagg tggggatgga gaagacaatt
2161 gttgcttatg aaagaaagct ttagctgtct ctgttttgta agctttaagc gcaacatttc
2221 ttggttccaa taaagcattt tacaagatct tgcatgctac tcttagatag aagatgggaa
2281 aaccatggta ataaaatatg aatgataaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa
2341 aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa
2401 aaaaaa

Figure 51A

MGGGAGERLFTSSCLVGLVPLGLRISLVTCPLQCGIMWQLLLPTALLLLVSAGMRTEDLPKA
VVFLEPQWYRVLEKDSVTLKCQGAYSPEDNSTQWFHNESLISSQASSYFIDAATVDDSGEYR
CQTNLSTLSDPVQLEVHIGWLLLQAPRWVFKEEDPIHLRCHSWKNTALHKVTYLQNGKGRK
YFHHNSDFYIPKATLKDSGSYFCRGLFGSKNVSSETVNITITQGLAVSTISSFFPPGYQVSFCLV
MVLLFAVDTGLYFSVKTNIRSSTRDWKDHKFKWRKDPQDK

Figure 51B

1 aaagtcagag tactgggaga acagaagact tcacaattta atgcctcagt ttttaaaaaa
61 ggatccttac acttcatgtc tcctagccat cagaagagga atgagacagc aaaagttcaa
121 atggcctgtt tcaagtttct gatataaaac gatgacattt tcaggaaaat cctgcatttc
181 cagagagaga ctggctggtt aaatttctga aagaggacac cagctaaaag aaggtattgc
241 atctcacccg agcagactgt gtctgtggaa agtgtaagcc ccttgccaga agagcagctt
301 cccagcaaag gcagagggtg aaaacagcaa aggtcttaag acactgggga cctagagtca
361 aaagggacct cctccaggga aaacgctgtg tgagaaatgg cctcattcgg tgactgtgag
421 tgacacagca gaaagttggg tcattccggc tgcttttttg agaagtccct gaagagatca
481 ataacagcaa gagggaacct ggcaaggaag ctattcctat aatccaggaa agagatgagg
541 aaggcttgga ccaggtggta gtggtgtcag gtagtcaaat gctgggtata ttttgaagat
601 acaccccata ggatttgctc cacattgaat gtggaatgct ggaagagaga taaagtgtac
661 ctgtcacata ctttttgagt tttatttatt ttcttagaag taagtacaca aagagatgct
721 acctaggaga agggtattct tttcactatt ctttcaaatt ttctgtatgt tcgaacattt
781 tcatagtaga aagttggggg gaaaatctgt ttcataaaca tttcctcagc agcagtccag
841 tctattgcat tttaattggt tgtgatatca ttgttttatg caatacgttc tcaacaagta
901 tatcctccgg caaactgaac aaggaccaag tctgttctgc ctacagctct gcttcctcat
961 agctgctttc cagaacgtga ctcttgcaaa ttatcaagaa aggggaacta atctaaggga
1021 tccagatcaa acagcctcat gaagacttat tttatgtttc taatataaag atagaagttt
1081 tcagaaaagc cctgctacac agaggatcag agcaggggtg ggcctgctgg gctgcagctg
1141 ggattctgag catcctttcc cggaggcacg gaaagtgagt gagtgagccc agtgaggaag
1201 aagttgaagc tttgatatga gtaaacaagt atctctacct gaaatgatta aagactggac
1261 caaagagcat gtgaaaaaat gggtaaatga agaccttaag attaatgagc aatacgggca
1321 aattctgctc agtgaagaag taacaggatt agtcctgcag gaattaactg agaaggacct
1381 tgtagaaatg gggctaccat ggggtccagc acttttgata aaacgttcat acaacaaatt
1441 gaatagtaag tcccctgaaa gtgacaatca tgatccggga caattagata attcaaaacc
1501 gtccaaaaca gaacaccaga aaaatccaaa acacaccaaa aaggaagaag aaaattcaat
1561 gtcatctaat attgattatg atcccagaga gatcagagat atcaaacaag aagaatcaat
1621 tcttatgaaa gaaaatgtgt tagatgaagt agcaaatgct aaacacaaga aaaagggtaa
1681 gctaaaacct gaacaattga cttgtatgcc atatcctttt gatcagttcc atgacagcca
1741 tcgctacata gaacattata ctctacaacc tgaaacagga gcactcaatc tcattgatcc
1801 aatacatgag ttcaaagctc tcacaaacac agaaacagcc acggaagtgg acattaagat
1861 gaaattcagc aatgaagtct tccgatttgc atcagcttgt atgaattcac gcaccaatgg
1921 caccatccat tttggagtca aggacaaacc ccatggagaa attgttggtg tgaaaatcac
1981 cagtaaggct gccttcattg accacttcaa tgtaatgatc aaaaagtatt ttgaagaaag
2041 tgagatcaat gaagccaaga agtgtattcg ggagccaagg tttgtggaag tccttctgca
2101 gaacaataca ccatctgaca gatttgtcat tgaagttgat actattccaa aacactctat
2161 atgtaatgat aagtatttct acattcagat gcaaatttgt aaagataaaa tatggaaaca
2221 aaaccaaaat ctttcactgt ttgtaagaga aggggctagc tctagggata tcctggccaa
2281 ttccaagcaa cgggatgtag atttcaaggc atttttacaa aatttaaagt cactggtagc
2341 atctagaaaa gaggctgaag aagagtatgg aatgaaggca atgaagaagg agagtgaagg
2401 actaaagctg gttaaacttc tcataggaaa ccgagactca ctggataatt catactatga
2461 ctggtacatt cttgtaacaa ataaatgcca tccaaaccaa ataaagcact tagatttttt
2521 aaaagaaatt aaatggtttg ctgtgttgga gtttgatcct gaatctatga tcaatggagt
2581 ggtcaaagct tacaaagaaa gtcgggtggc aaaccttcac tttccaaatc aatatgaaga
2641 caagacaact aacatgtggg agaagatttc tactcttaat ctttaccaac agcccagctg
2701 gattttctgc aacggcagat cagacctgaa aagcgagaca tataaacctc tagaaccaca
2761 tttatggcag agagaaagag cttcagaagt caggaaacta attttatttc tcacagatga

Figure 52A

2821 aaatataatg acaagaggaa aatttttggt agtgtttcta ttactctctt cagtggaaag
2881 cccaggagat ccactcattg aaactttctg ggctttctat caagctctca aaggaatgga
2941 aaatatgttg tgtatctctg taaactcaca tatttatcaa cgatggaaag atctactaca
3001 aacaagaatg aagatggaag atgaactaac aaaccacagt atttccactt taaatataga

3061 actggtaaac agcactatcc ttaaactaaa atcggtgact cggtcatcaa gaaggttttt
3121 gcccgcccgt ggatcttctt cagttatcct agagaaaaag aaagaggatg tcttgactgc
3181 actggaaatc ctctgtgaaa atgagtgtac agagacagac atcgagaaag acaaatctaa
3241 attcctggag tttaagaaat caaaagaaga acacttttat cgaggtggca aagtatcctg
3301 gtggaacttc tatttttctt ctgaaaacta ttcttcagat tttgttaaaa gggacagtta
3361 tgaaaagctt aaagatttaa tacactgctg ggcagagtct cctaaaccaa tatttgcaaa
3421 aatcatcaat ctttatcatc atccaggctg tggaggtacc acactggcta tgcatgttct
3481 ctgggactta aagaaaaact tcagatgtgc tgtgttaaaa aacaagacaa ctgattttgc
3541 agaaattgca gagcaagtga tcaatctggt cacctatagg gcaaagagcc atcaggatta
3601 cattcctgtg cttctccttg tggatgattt tgaagaacaa gaaaatgtct actttctaca
3661 aaatgccatc cattccgttt tagcagaaaa ggatttgcga tatgaaaaaa cattggtaat
3721 tatcttaaac tgcatgagat cccggaatcc agatgaaagt gcaaaattgg cagacagtat
3781 tgcactaaat taccaacttt cttccaagga acaaagagct tttggtgcca aactgaagga
3841 aattgaaaag cagcacaaga actgtgaaaa cttttattcc ttcatgatca tgaaaagcaa
3901 ttttgatgaa acatatatag aaaatgtagt caggaatatc ctaaaaggac aggatgttga
3961 cagcaaggaa gcacaactca tttccttcct ggctttactc agctcttatg ttactgactc
4021 tacaatttca gtttcacagt gtgaaatatt tttgggaatc atatacacta gtacaccctg
4081 ggaacctgaa agcttagaag acaagatggg aacttattct acacttctaa taaaaacaga
4141 agttgcagaa tatgggagat acacaggtgt gcgtatcatt caccctctga ttgccctgta
4201 ctgtctaaaa gaactggaaa gaagctatca cttggataaa tgtcaaattg cattgaatat
4261 attagaagag aatttattct atgattctgg aataggaaga gacaaatttc aacatgatgt
4321 tcaaactctt ctgcttacaa gacagcgcaa ggtgtatgga gatgaaacag acactctgtt
4381 ttccccatta atggaagctt tacagaataa agacattgaa aaggtcttga gtgcaggaag
4441 tagacgattc ccacaaaatg cattcatttg tcaagcctta gcaagacatt tctacattaa
4501 agagaaggac tttaacacag ctctggactg ggcacgtcag gccaaaatga aagcacctaa
4561 aaattcctat atttcagata cactaggtca agtctacaaa agtgaaatca aatggtggtt
4621 ggatgggaac aaaaactgta ggagcattac tgttaatgac ctaacacatc tcctagaagc
4681 tgcggaaaaa gcctcaagag ctttcaaaga atcccaaagg caaactgata gtaaaaacta
4741 tgaaaccgag aactggtcac cacagaagtc ccagagacga tatgacatgt ataacacagc
4801 ttgtttcttg ggtgaaatag aagttggtct ttacactatc cagattcttc agctcactcc
4861 ctttttccac aaagaaaatg aattatccaa aaaacatatg gtgcaatttt tatcaggaaa
4921 gtggaccatt cctcctgatc ccagaaatga atgttatttg gctcttagca agttcacatc
4981 ccacctaaaa aatttacaat cagatctgaa aaggtgcttt gacttttta ttgattatat
5041 ggttcttctg aaaatgaggt atacccaaaa agaaattgca gaaatcatgt taagcaagaa
5101 agtcagtcgt tgtttcagga aatacacaga acttttctgt catttggatc catgtctatt
5161 acaaagtaaa gagagtcaat tactccagga ggagaattgc aggaaaaagc tagaagctct
5221 gagagcagat aggtttgctg gactcttgga atatcttaat ccaaactaca aagatgctac
5281 caccatggaa agtatagtga atgaatatgc cttcctactg cagcaaaact caaaaaagcc
5341 catgacaaat gagaaacaaa attccatttt ggccaacatt attctgagtt gtctaaagcc
5401 caactccaag ttaattcaac cacttaccac gctaaaaaaa caactccgag aggtcttgca
5461 atttgtagga ctaagtcatc aatatccagg tccttatttc ttggcctgcc tcctgttctg
5521 gccagaaaat caagagctag atcaagattc caaactaata gaaaagtatg tttcatcctt
5581 aaatagatcc ttcaggggac agtacaagcg catgtgcagg tccaagcagg caagcacact

Figure 52A (continued)

5641 tttctatctg ggcaaaagga agggtctaaa cagtattgtt cacaaggcca aaatagagca
5701 gtactttgat aaagcacaaa atacaaattc cctctggcac agtggggatg tgtggaaaaa
5761 aaatgaagtc aaagacctcc tgcgtcgtct aactggtcag gctgaaggca agctaatctc
5821 tgtagaatat ggaacagagg aaaaaataaa aataccagta atatctgttt attcaggtcc
5881 actcagaagt ggtaggaaca tagaaagagt gtctttctac ctaggatttt ccattgaagg
5941 ccctctggca tatgatatag aagtaattta agacaataca tcacctgtag ttcaaatacg
6001 tttatttata tctttatgat tttattctct ctctctattc tcatggcact ttcataacat
6061 tatggctaac ctctaattac agattttgct tttgcctccc tgaatgaatt acaagccttt

6121 ttaagatatg aaatatgcct acccgcagag cttggcacaa agtggagtca atcttttaat
6181 gttttaaata tgcattttca gactcaaata attaagaagt ttcattgata tccactggtc
6241 acatcataac tgtctatagg gcaataaaat ctgtgttaaa ctcaattgct tttataagtt
6301 ttctaaatta tttcttcact gtgacagcaa agatttaaat aagatgaatg taaaagagaa
6361 agcttattgg actcaaaccc acagatccac accagagttc tatttacctc atcttggtat
6421 caataaaaac ttatgtggaa ggtaaatata ttgttcccca tccaccacat aacactctcc
6481 ccaacacaca cacacacaca cacacacaca cacacacaca cacacactcc ttgtaccccc
6541 tgcccttctc ccagctcatt gctccaggag agagaagagt tcaaaaaata aagtaatcat
6601 aaacttgaac tctctccatt ctcttgttcc catttacagg tgaatctctt cctttaagcc
6661 atttttgtct cctgtgaata cagccttatc tccacctgtt tcttagatcc catctccccc
6721 ggcttatttt ttccattcat taccctcttt gttcccttta cttctcaacc tgtgctatat
6781 acatgctgtt ctctctgttg agattgcctt atttccatct aacattctct ctcctgctat
6841 tctgatttgt cattcacaac tgatttcaag agtcaccttc accaggaagt cttccttgac
6901 caccatcatt cctgcctgat tagagggctt cctcatggta atatgtgttc tcaagttttc
6961 agtgtcaagg aatgccatcc cagaagctca ttctcagatg cacaacagcc agaacagtct
7021 caagcagcat tctagagctt ggaatttaag aactacgcat tgcctataaa gtgaaacata
7081 ggctaatata gattaaattg aatattgaat aaaaaatata tttatttatc cac

Figure 52A (Continued)

MSKQVSLPEMIKDWTKEHVKKWVNEDLKINEQYGQILLSEEVTGLVLQELTEKDLVEMGLP
WGPALLIKRSYNKLNSKSPESDNHDPGQLDNSKPSKTEHQKNPKHTKKEEENSMSSNIDYDP
REIRDIKQEESILMKENVLDEVANAKHKKKGKLKPEQLTCMPYPFDQFHDSHRYIEHYTLQP
ETGALNLIDPIHEFKALTNTETATEVDIKMKFSNEVFRFASACMNSRTNGTIHFGVKDKPHGEI
VGVKITSKAAFIDHFNVMIKKYFEESEINEAKKCIREPRFVEVLLQNNTPSDRFVIEVDTIPKHS
ICNDKYFYIQMQICKDKIWKQNQNLSLFVREGASSRDILANSKQRDVDFKAFLQNLKSLVAS
RKEAEEEYGMKAMKKESEGLKLVKLLIGNRDSLDNSYYDWYILVTNKCHPNQIKHLDFLKEI
KWFAVLEFDPESMINGVVKAYKESRVANLHFPNQYEDKTTNMWEKISTLNLYQQPSWIFCN
GRSDLKSETYKPLEPHLWQRERASEVRKLILFLTDENIMTRGKFLVVFLLLSSVESPGDPLIET
FWAFYQALKGMENMLCISVNSHIYQRWKDLLQTRMKMEDELTNHSISTLNIELVNSTILKLK
SVTRSSRRFLPARGSSSVILEKKKEDVLTALEILCENECTETDIEKDKSKFLEFKKSKEEHFYRG
GKVSWWNFYFSSENYSSDFVKRDSYEKLKDLIHCWAESPKPIFAKIINLYHHPGCGGTTLAM
HVLWDLKKNFRCAVLKNKTTDFAEIAEQVINLVTYRAKSHQDYIPVLLLVDDFEEQENVYFL
QNAIHSVLAEKDLRYEKTLVIILNCMRSRNPDESAKLADSIALNYQLSSKEQRAFGAKLKEIE
KQHKNCENFYSFMIMKSNFDETYIENVVRNILKGQDVDSKEAQLISFLALLSSYVTDSTISVSQ
CEIFLGIIYTSTPWEPESLEDKMGTYSTLLIKTEVAEYGRYTGVRIIHPLIALYCLKELERSYHL
DKCQIALNILEENLFYDSGIGRDKFQHDVQTLLLTRQRKVYGDETDTLFSPLMEALQNKDIEK
VLSAGSRRFPQNAFICQALARHFYIKEKDFNTALDWARQAKMKAPKNSYISDTLGQVYKSEI
KWWLDGNKNCRSITVNDLTHLLEAAEKASRAFKESQRQTDSKNYETENWSPQKSQRRYDM
YNTACFLGEIEVGLYTIQILQLTPFFHKENELSKKHMVQFLSGKWTIPPDPRNECYLALSKFTS
HLKNLQSDLKRCFDFFIDYMVLLKMRYTQKEIAEIMLSKKVSRCFRKYTELFCHLDPCLLQS
KESQLLQEENCRKKLEALRADRFAGLLEYLNPNYKDATTMESIVNEYAFLLQQNSKKPMTN
EKQNSILANIILSCLKPNSKLIQPLTTLKKQLREVLQFVGLSHQYPGPYFLACLLFWPENQELD
QDSKLIEKYVSSLNRSFRGQYKRMCRSKQASTLFYLGKRKGLNSIVHKAKIEQYFDKAQNTN
SLWHSGDVWKKNEVKDLLRRLTGQAEGKLISVEYGTEEKIKIPVISVYSGPLRSGRNIERVSF
YLGFSIEGPLAYDIEVI

Figure 52B

1 agacacctct gccctcacca tgagcctctg gcagcccctg gtcctggtgc tcctggtgct
61 gggctgctgc tttgctgccc ccagacagcg ccagtccacc cttgtgctct tccctggaga
121 cctgagaacc aatctcaccg acaggcagct ggcagaggaa tacctgtacc gctatggtta
181 cactcgggtg gcagagatgc gtggagagtc gaaatctctg gggcctgcgc tgctgcttct
241 ccagaagcaa ctgtccctgc ccgagaccgg tgagctggat agcgccacgc tgaaggccat
301 gcgaacccca cggtgcgggg tcccagacct gggcagattc caaaccttig agggcgacct
361 caagtggcac caccacaaca tcacctattg gatccaaaac tactcggaag acttgccgcg
421 ggcggtgatt gacgacgcct ttgcccgcgc cttcgcactg tggagcgcgg tgacgccgct
481 caccttcact cgcgtgtaca gccgggacgc agacatcgtc atccagtttg gtgtcgcgga
541 gcacggagac gggtatccct tcgacgggaa ggacgggctc ctggcacacg cctttcctcc
601 tggccccggc attcagggag acgcccattt cgacgatgac gagttgtggt ccctgggcaa
661 gggcgtcgtg gttccaactc ggtttggaaa cgcagatggc gcggcctgcc acttccccct
721 catcttcgag ggccgctcct actctgcctg caccaccgac ggtcgctccg acggcttgcc
781 ctggtgcagt accacggcca actacgacac cgacgaccgg tttggcttct gccccagcga
841 gagactctac acccaggacg gcaatgctga tgggaaaccc tgccagtttc cattcatctt
901 ccaaggccaa tcctactccg cctgcaccac ggacggtcgc tccgacggct accgctggtg
961 cgccaccacc gccaactacg accgggacaa gctcttcggc ttctgcccga cccgagctga
1021 ctcgacggtg atgggggtca actcggcggg ggagctgtgc gtcttcccct tcactttcct
1081 gggtaaggag tactcgacct gtaccagcga gggccgcgga gatgggcgcc tctggtgcgc
1141 taccacctcg aactttgaca gcgacaagaa gtggggcttc tgcccggacc aaggatacag
1201 tttgttcctc gtggcggcgc atgagttcgg ccacgcgctg ggcttagatc attcctcagt
1261 gccggaggcg ctcatgtacc ctatgtaccg cttcactgag gggccccccct tgcataagga
1321 cgacgtgaat ggcatccggc acctctatgg tcctcgccct gaacctgagc cacggcctcc
1381 aaccaccacc acaccgcagc ccacggctcc cccgacggtc tgccccaccg gaccccccac
1441 tgtccacccc tcagagcgcc ccacagctgg ccccacaggt ccccccctcag ctggccccac
1501 aggtcccccc actgctggcc cttctacggc cactactgtg cctttgagtc cggtggacga
1561 tgcctgcaac gtgaacatct tcgacgccat cgcggagatt gggaaccagc tgtatttgtt
1621 caaggatggg aagtactggc gattctctga gggcaggggg agccggccgc agggcccctt
1681 ccttatcgcc gacaagtggc ccgcgctgcc ccgcaagctg gactcggtct ttgaggagcg
1741 gctctccaag aagcttttct tcttctctgg gcgccaggtg tgggtgtaca caggcgcgtc
1801 ggtgctgggc ccgaggcgtc tggacaagct gggcctggga gccgacgtgg cccaggtgac
1861 cggggccctc cggagtggca gggggaagat gctgctgttc agcgggcggc gcctctggag
1921 gttcgacgtg aaggcgcaga tggtggatcc ccggagcgcc agcgaggtgg accggatgtt
1981 ccccggggtg cctttggaca cgcacgacgt cttccagtac cgagagaaag cctatttctg
2041 ccaggaccgc ttctactggc gcgtgagttc ccggagtgag ttgaaccagg tggaccaagt
2101 gggctacgtg acctatgaca tcctgcagtg ccctgaggac tagggctccc gtcctgcttt
2161 ggcagtgcca tgtaaatccc cactgggacc aaccctgggg aaggagccag tttgccggat
2221 acaaactggt attctgttct ggaggaaagg gaggagtgga ggtgggctgg gccctctctt
2281 ctcaccttig ttttttgttg gagtgtttct aataaacttg gattctctaa cctttaaaaa
2341 aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaa

Figure 53A

MSLWQPLVLVLLVLGCCFAAPRQRQSTLVLFPGDLRTNLTDRQLAEEYLYRYGYTRVAEMR
GESKSLGPALLLLQKQLSLPETGELDSATLKAMRTPRCGVPDLGRFQTFEGDLKWHHHNITY
WIQNYSEDLPRAVIDDAFARAFALWSAVTPLTFTRVYSRDADIVIQFGVAEHGDGYPFDGKD
GLLAHAFPPGPGIQGDAHFDDDELWSLGKGVVVPTRFGNADGAACHFPFIFEGRSYSACTTD
GRSDGLPWCSTTANYDTDDRFGFCPSERLYTQDGNADGKPCQFPFIFQGQSYSACTTDGRSD
GYRWCATTANYDRDKLFGFCPTRADSTVMGGNSAGELCVFPFTFLGKEYSTCTSEGRGDGR
LWCATTSNFDSDKKWGFCPDQGYSLFLVAAHEFGHALGLDHSSVPEALMYPMYRFTEGPPL
HKDDVNGIRHLYGPRPEPEPRPPTTTTPQPTAPPTVCPTGPPTVHPSERPTAGPTGPPSAGPTGP
PTAGPSTATTVPLSPVDDACNVNIFDAIAEIGNQLYLFKDGKYWRFSEGRGSRPQGPFLIADK
WPALPRKLDSVFEERLSKKLFFFSGRQVWVYTGASVLGPRRLDKLGLGADVAQVTGALRSG
RGKMLLFSGRRLWRFDVKAQMVDPRSASEVDRMFPGVPLDTHDVFQYREKAYFCQDRFYW
RVSSRSELNQVDQVGYVTYDILQCPED

Figure 53B

1 accaaatcaa ccataggtcc aagaacaatt gtctctggac ggcagctatg cgactcaccg
61 tgctgtgtgc tgtgtgcctg ctgcctggca gcctggccct gccgctgcct caggaggcgg
121 gaggcatgag tgagctacag tgggaacagg ctcaggacta tctcaagaga ttttatctct
181 atgactcaga aacaaaaaat gccaacagtt tagaagccaa actcaaggag atgcaaaaat
241 tctttggcct acctataact ggaatgttaa actcccgcgt catagaaata atgcagaagc
301 ccagatgtgg agtgccagat gttgcagaat actcactatt tccaaatagc ccaaaatgga
361 cttccaaagt ggtcacctac aggatcgtat catatactcg agacttaccg catattacag
421 tggatcgatt agtgtcaaag gctttaaaca tgtggggcaa agagatcccc ctgcatttca
481 ggaaagttgt atggggaact gctgacatca tgattggctt tgcgcgagga gctcatgggg
541 actcctaccc atttgatggg ccaggaaaca cgctggctca tgccttgcg cctgggacag
601 gtctcggagg agatgctcac ttcgatgagg atgaacgctg gacggatggt agcagtctag
661 ggattaactt cctgtatgct gcaactcatg aacttggcca ttctttgggt atgggacatt
721 cctctgatcc taatgcagtg atgtatccaa cctatggaaa tggagatccc caaaatttta
781 aactttccca ggatgatatt aaaggcattc agaaactata tggaaagaga agtaattcaa
841 gaaagaaata gaaacttcag gcagaacatc cattcattca ttcattggat tgtatatcat
901 tgttgcacaa tcagaattga taagcactgt tcctccactc catttagcaa ttatgtcacc
961 ctttttatt gcagttggtt tttgaatgtc tttcactcct tttaaggata aactccttta
1021 tggtgtgact gtgtcttatt catctatact tgcagtgggt agatgtcaat aaatgttaca
1081 tacacaaata aataaaatgt ttattccatg gtaaatttaa aaaaaaaaaa aaaaaaaaaa
1141 aaaaaaa

Figure 54A

MRLTVLCAVCLLPGSLALPLPQEAGGMSELQWEQAQDYLKRFYLYDSETKNANSLEAKLKE
MQKFFGLPITGMLNSRVIEIMQKPRCGVPDVAEYSLFPNSPKWTSKVVTYRIVSYTRDLPHIT
VDRLVSKALNMWGKEIPLHFRKVVWGTADIMIGFARGAHGDSYPFDGPGNTLAHAFAPGTG
LGGDAHFDEDERWTDGSSLGINFLYAATHELGHSLGMGHSSDPNAVMYPTYGNGDPQNFKL
SQDDIKGIQKLYGKRSNSRKK

Figure 54B

```
   1 ttggatgttc cgggaaagtg atgtgggtag gacaggcggg gcgagccgca ggtgccagaa
  61 cacagattgt ataaaaggct gggggctggt ggggagcagg ggaagggaat gtgaccaggt
 121 ctaggtctgg agtttcagct tggacactga gccaagcaga caagcaaagc aagccaggac
 181 acaccatcct gccccaggcc cagcttctct cctgccttcc aacgccatgg ggagcaatct
 241 cagcccccaa ctctgcctga tgccctttat cttgggcctc ttgtctggag gtgtgaccac
 301 cactccatgg tctttggccc ggccccaggg atcctgctct ctggaggggg tagagatcaa
 361 aggcggctcc ttccgacttc tccaagaggg ccaggcactg gagtacgtgt gtccttctgg
 421 cttctacccg taccctgtgc agacacgtac ctgcagatct acggggtcct ggagcaccct
 481 gaagactcaa gaccaaaaga ctgtcaggaa ggcagagtgc agagcaatcc actgtccaag
 541 accacacgac ttcgagaacg gggaatactg gccccggtct ccctactaca atgtgagtga
 601 tgagatctct ttccactgct atgacggtta cactctccgg ggctctgcca atcgcacctg
 661 ccaagtgaat ggccgatgga gtgggcagac agcgatctgt gacaacggag cggggtactg
 721 ctccaacccg ggcatcccca ttggcacaag gaaggtgggc agccagtacc gccttgaaga
 781 cagcgtcacc taccactgca gccgggggct taccctgcgt ggctcccagc ggcgaacgtg
 841 tcaggaaggt ggctcttgga gcgggacgga gccttcctgc caagactcct tcatgtacga
 901 cacccctcaa gaggtggccg aagctttcct gtcttcccctg acagagacca tagaaggagt
 961 cgatgctgag gatgggcacg gcccagggga acaacagaag cggaagatcg tcctggaccc
1021 ttcaggctcc atgaacatct acctggtgct agatggatca gacagcattg gggccagcaa
1081 cttcacagga gccaaaaagt gtctagtcaa cttaattgag aaggtggcaa gttatggtgt
1141 gaagccaaga tatggtctag tgacatatgc cacataccc aaaatttggg tcaaagtgtc
1201 tgaagcagac agcagtaatg cagactgggt cacgaagcag ctcaatgaaa tcaattatga
1261 agaccacaag ttgaagtcag ggactaacac caagaaggcc ctccaggcag tgtacagcat
1321 gatgagctgg ccagatgacg tccctcctga aggctggaac cgcaccccgcc atgtcatcat
1381 cctcatgact gatggattgc acaacatggg cggggaccca attactgtca ttgatgagat
1441 ccgggacttg ctatacattg gcaaggatcg caaaaaccca agggaggatt atctggatgt
1501 ctatgtgttt ggggtcgggc ctttggtgaa ccaagtgaac atcaatgctt tggcttccaa
1561 gaaagacaat gagcaacatg tgttcaaagt caaggatatg gaaaacctgg aagatgtttt
1621 ctaccaaatg atcgatgaaa gccagtctct gagtctctgt ggcatggttt gggaacacag
1681 gaagggtacc gattaccaca agcaaccatg gcaggccaag atctcagtca ttcgcccttc
1741 aaagggacac gagagctgta tgggggctgt ggtgtctgag tactttgtgc tgacagcagc
1801 acattgttc actgtggatg acaaggaaca ctcaatcaag gtcagcgtag gaggggagaa
1861 gcgggacctg gagatagaag tagtcctatt tcaccccaac tacaacatta atgggaaaaa
1921 agaagcagga attcctgaat tttatgacta tgacgttgcc ctgatcaagc tcaagaataa
1981 gctgaaatat ggccagacta tcaggcccat ttgtctcccc tgcaccgagg gaacaactcg
2041 agctttgagg cttcctccaa ctaccacttg ccagcaacaa aaggaagagc tgctccctgc
2101 acaggatatc aaagctctgt ttgtgtctga ggaggagaaa aagctgactc ggaaggaggt
2161 ctacatcaag aatggggata agaaaggcag ctgtgagaga gatgctcaat atgccccagg
2221 ctatgacaaa gtcaaggaca tctcagaggt ggtcaccct cggttccttt gtactggagg
2281 agtgagtccc tatgctgacc ccaatacttg cagaggtgat tctggcggcc ccttgatagt
2341 tcacaagaga agtcgtttca ttcaagttgg tgtaatcagc tggggagtag tggatgtctg
2401 caaaaaccag aagcggcaaa agcaggtacc tgctcacgcc cgagactttc acatcaacct
2461 ctttcaagtg ctgccctggc tgaaggagaa actccaagat gaggatttgg gttttctata
2521 aggggtttcc tgctggacag gggcgtggga ttgaattaaa acagctgcga caac
```

Figure 55A

MGSNLSPQLCLMPFILGLLSGGVTTTPWSLARPQGSCSLEGVEIKGGSFRLLQEGQALEYVCP
SGFYPYPVQTRTCRSTGSWSTLKTQDQKTVRKAECRAIHCPRPHDFENGEYWPRSPYYNVSD
EISFHCYDGYTLRGSANRTCQVNGRWSGQTAICDNGAGYCSNPGIPIGTRKVGSQYRLEDSV
TYHCSRGLTLRGSQRRTCQEGGSWSGTEPSCQDSFMYDTPQEVAEAFLSSLTETIEGVDAED
GHGPGEQQKRKIVLDPSGSMNIYLVLDGSDSIGASNFTGAKKCLVNLIEKVASYGVKPRYGL
VTYATYPKIWVKVSEADSSNADWVTKQLNEINYEDHKLKSGTNTKKALQAVYSMMSWPDD
VPPEGWNRTRHVIILMTDGLHNMGGDPITVIDEIRDLLYIGKDRKNPREDYLDVYVFGVGPL
VNQVNINALASKKDNEQHVFKVKDMENLEDVFYQMIDESQSLSLCGMVWEHRKGTDYHK
QPWQAKISVIRPSKGHESCMGAVVSEYFVLTAAHCFTVDDKEHSIKVSVGGEKRDLEIEVVL
FHPNYNINGKKEAGIPEFYDYDVALIKLKNKLKYGQTIRPICLPCTEGTTRALRLPPTTTCQQQ
KEELLPAQDIKALFVSEEEKKLTRKEVYIKNGDKKGSCERDAQYAPGYDKVKDISEVVTPRF
LCTGGVSPYADPNTCRGDSGGPLIVHKRSRFIQVGVISWGVVDVCKNQKRQKQVPAHARDF
HINLFQVLPWLKEKLQDEDLGFL

Figure 55B

1 tgaggctgcc ttataaagca ccaagaggct gccagtggga cattttctcg gccctgccag
61 cccccaggag gaaggtgggt ctgaatctag caccatgacg gaactagaga cagccatggg
121 catgatcata gacgtctttt cccgatattc gggcagcgag ggcagcacgc agaccctgac
181 caagggggag ctcaaggtgc tgatggagaa ggagctacca ggcttcctgc agagtggaaa
241 agacaaggat gccgtggata aattgctcaa ggacctggac gccaatggag atgcccaggt
301 ggacttcagt gagttcatcg tgttcgtggc tgcaatcacg tctgcctgtc acaagtactt
361 tgagaaggca ggactcaaat gatgccctgg agatgtcaca gattcctggc agagccatgg
421 tcccaggctt cccaaaagtg tttgttggca attattcccc taggctgagc ctgctcatgt
481 acctctgatt aataaatgct tatgaaatga

Figure 56A

MTELETAMGMIIDVFSRYSGSEGSTQTLTKGELKVLMEKELPGFLQSGKDKDAVDKLLKDL
DANGDAQVDFSEFIVFVAAITSACHKYFEKAGLK

Figure 56B

1 cacagagccc gggccgcagg cacctcctcg ccagctcttc cgctcctctc acagccgcca
61 gacccgcctg ctgagcccca tggccccgcgc tgctctctcc gccgcccccca gcaatccccg
121 gctcctgcga gtggcactgc tgctcctgct cctggtagcc gctggccggc gcgcagcagg
181 agcgtccgtg gccactgaac tgcgctgcca gtgcttgcag accctgcagg gaattcaccc
241 caagaacatc caaagtgtga acgtgaagtc ccccggaccc cactgcgccc aaaccgaagt
301 catagccaca ctcaagaatg ggcggaaagc ttgcctcaat cctgcatccc ccatagttaa
361 gaaaatcatc gaaaagatgc tgaacagtga caaatccaac tgaccagaag ggaggaggaa
421 gctcactggt ggctgttcct gaaggaggcc ctgcccttat aggaacagaa gaggaaagag
481 agacacagct gcagaggcca cctggattgt gcctaatgtg tttgagcatc gcttaggaga
541 agtcttctat ttatttattt attcattagt tttgaagatt ctatgttaat attttaggtg
601 taaaataatt aagggtatga ttaactctac ctgcacactg tcctattata ttcattcttt
661 ttgaaatgtc aaccccaagt tagttcaatc tggattcata tttaatttga aggtagaatg
721 ttttcaaatg ttctccagtc attatgttaa tatttctgag gagcctgcaa catgccagcc
781 actgtgatag aggctggcgg atccaagcaa atggccaatg agatcattgt gaaggcaggg
841 gaatgtatgt gcacatctgt tttgtaactg tttagatgaa tgtcagttgt tatttattga
901 aatgatttca cagtgtgtgg tcaacatttc tcatgttgaa actttaagaa ctaaaatgtt
961 ctaaatatcc cttggacatt ttatgtcttt cttgtaaggc atactgcctt gtttaatggt
1021 agttttacag tgtttctggc ttagaacaaa ggggcttaat tattgatgtt ttcatagaga
1081 atataaaaat aaagcactta tag

Figure 57A

MARAALSAAPSNPRLLRVALLLLLLVAAGRRAAGASVATELRCQCLQTLQGIHPKNIQSVNV
KSPGPHCAQTEVIATLKNGRKACLNPASPIVKKIIEKMLNSDKSN

Figure 57B

1 aatttctcac tgcccctgtg ataaactgtg gtcactggct gtggcagcaa ctattataag
61 atgctctgaa aactcttcag acactgaggg gcaccagagg agcagactac aagaatggca
121 cacgctatgg aaaactcctg gacaatcagt aaagagtacc atattgatga agaagtgggc
181 tttgctctgc caaatccaca ggaaaatcta cctgattttt ataatgactg gatgttcatt
241 gctaaacatc tgcctgatct catagagtct ggccagcttc gagaaagagt tgagaagtta
301 aacatgctca gcattgatca tctcacagac cacaagtcac agcgccttgc acgtctagtt
361 ctgggatgca tcaccatggc atatgtgtgg ggcaaaggtc atggagatgt ccgtaaggtc
421 ttgccaagaa atattgctgt tccttactgc caactctcca agaaactgga actgcctcct
481 attttggttt atgcagactg tgtcttggca aactggaaga aaaaggatcc taataagccc
541 ctgacttatg agaacatgga cgttttgttc tcatttcgtg atggagactg cagtaaagga
601 ttcttcctgg tctctctatt ggtggaaata gcagctgctt ctgcaatcaa agtaattcct
661 actgtattca aggcaatgca aatgcaagaa cgggacactt tgctaaaggc gctgttggaa
721 atagcttctt gcttggagaa agcccttcaa gtgtttcacc aaatccacga tcatgtgaac
781 ccaaaagcat ttttcagtgt tcttcgcata tatttgtctg gctggaaagg caacccccag
841 ctatcagacg gtctggtgta tgaagggttc tgggaagacc caaaggagtt tgcagggggc
901 agtgcaggcc aaagcagcgt ctttcagtgc tttgacgtcc tgctgggcat ccagcagact
961 gctggtggag gacatgctgc tcagttcctc caggacatga gaagatatat gccaccagct
1021 cacaggaact tcctgtgctc attagagtca aatccctcag tccgtgagtt tgtcctttca
1081 aaaggtgatg ctggcctgcg ggaagcttat gacgcctgtg tgaaagctct ggtctccctg
1141 aggagctacc atctgcaaat cgtgactaag tacatcctga ttcctgcaag ccagcagcca
1201 aaggagaata agaccictga agacccttca aaactggaag ccaaaggaac tggaggcact
1261 gatttaatga atttcctgaa gactgtaaga agtacaactg agaaatccct tttgaaggaa
1321 ggttaatgta acccaacaag agcacatttt atcatagcag agacatctgt atgcattcct
1381 gtcattaccc attgtaacag agccacaaac taatactatg caatgtttta ccaataatgc
1441 aatacaaaag acctcaaaat acctgtgcat ttcttgtagg aaaacaacaa aaggtaatta
1501 tgtgtaatta tactagaagt tttgtaatct gtatcttatc attggaataa aatgacattc
1561 aataaataaa aa

Figure 58A

MAHAMENSWTISKEYHIDEEVGFALPNPQENLPDFYNDWMFIAKHLPDLIESGQLRERVEKL
NMLSIDHLTDHKSQRLARLVLGCITMAYVWGKGHGDVRKVLPRNIAVPYCQLSKKLELPPIL
VYADCVLANWKKKDPNKPLTYENMDVLFSFRDGDCSKGFFLVSLLVEIAAASAIKVIPTVFK
AMQMQERDTLLKALLEIASCLEKALQVFHQIHDHVNPKAFFSVLRIYLSGWKGNPQLSDGLV
YEGFWEDPKEFAGGSAGQSSVFQCFDVLLGIQQTAGGGHAAQFLQDMRRYMPPAHRNFLCS
LESNPSVREFVLSKGDAGLREAYDACVKALVSLRSYHLQIVTKYILIPASQQPKENKTSEDPS
KLEAKGTGGTDLMNFLKTVRSTTEKSLLKEG

Figure 58B

1 cagggtttat tgttatgtaa gttcttgttc agcttccttt gttttctttc acttctgaga
61 atttaacttt cgtttctcac tcagctcctg tggggaaact catttgtgga gaccagccct
121 ctggcttggt gagtgaatct ggtttacacc ggctcctgcc ctgccttcac tcttctcccc
181 tgattcaaga ctcctctgct ttggactgaa gcactgcagg agtttgtgac caagaacttc
241 aagagtcaag acagaaggaa gccaagggag cagtgcaatg gatttctcag taaaggtaga
301 catagagaag gaggtgacct gccccatctg cctggagctc ctgacagaac ctctgagcct
361 agattgtggc cacagcttct gccaagcctg catcactgca aagatcaagg agtcagtgat
421 catctcaaga ggggaaagca gctgtcctgt gtgtcagacc agattccagc ctgggaacct
481 ccgacctaat cggcatctgg ccaacatagt tgagagagtc aaagaggtca agatgagccc
541 acaggagggg cagaagagag atgtctgtga gcaccatgga aaaaaactcc agatcttctg
601 taaggaggat ggaaaagtca tttgctgggt ttgtgaactg tctcaggaac accaaggtca
661 ccaaacattc cgcataaacg aggtggtcaa ggaatgtcag gaaaagctgc aggtagccct
721 gcagaggctg ataaaggagg atcaagaggc tgagaagctg gaagatgaca tcagacaaga
781 gagaaccgcc tggaagaatt atatccagat cgagagacag aagattctga aagggttcaa
841 tgaaatgaga gtcatcttgg acaatgagga gcagagagag ctgcaaaagc tggaggaagg
901 tgaggtgaat gtgctggata acctggcagc agctacagac cagctggtcc agcagaggca
961 ggatgccagc acgctcatct cagatctcca gcggaggttg aggggatcgt cagtagagat
1021 gctgcaggat gtgattgacg tcatgaaaag gagtgaaagc tggacattga agaagccaaa
1081 atctgtttcc aagaaactaa agagtgtatt ccgagtacca gatctgagtg ggatgctgca
1141 agttcttaaa gagctgacag atgtccagta ctactgggtg gacgtgatgc tgaatccagg
1201 cagtgccact tcgaatgttg ctatttctgt ggatcagaga caagtgaaaa ctgtacgcac
1261 ctgcacattt aagaattcaa atccatgtga ttttctgct ttggtgtct tcggctgcca
1321 atatttctct tcggggaaat attactggga agtagatgtg tctggaaaga ttgcctggat
1381 cctgggcgta cacagtaaaa taagtagtct gaataaaagg aagagctctg ggtttgcttt
1441 tgatccaagt gtaaattatt caaaagttta ctccagatat agacctcaat atggctactg
1501 ggttatagga ttacagaata catgtgaata taatgctttt gaggactcct cctcttctga
1561 tcccaaggtt ttgactctct ttatggctgt gcctccctgt cgtattgggg ttttcctaga
1621 ctatgaggca ggcattgtct catttttcaa tgtcacaaac cacggagcac tcatctacaa
1681 gttctctgga tgtcgctttt ctcgacctgc ttatccgtat ttcaatcctt ggaactgcct
1741 agtccccatg actgtgtgcc caccgagctc ctgagtgttc tcattccttt acccacttct
1801 gcatagtagc ccttgtgctg agactcagat tctgcacctg agttcatctc tactgagacc
1861 atctcttcct ttctttcccc ttctttact tagaatgtct ttgtattcat ttgctagggc
1921 ttccatagca aagcatcata gattgctgat ttaaactgta attgtattgc cgtactgtgg
1981 gctggaaatc ccaaatctag attccagcag agttggttct ttctgaggtc tgcaaggaag
2041 ggctctgttc catgcctctc tccttggctt gtagaaggca tcttgtccct atgactcttc
2101 acattgtctt tatgtacatc tctgtgccca agttttccct tttattaag acaccagtca
2161 tactggctca gggcccaccg ctaatgcctt aatgaaatca ttttaacatt atattctcta
2221 caaagacctt atttccaaat aagataatat ttggaggtat tgggaataaa aactccaaca
2281 tataaatttg aggaaggcac gatttcactc ataacaatct taccctttct tgcaagagat
2341 gcttgtacat tattttccta ataccttggt ttcactagta gtaaacatta ttatttttt
2401 tatatttgca aaggaaacat atctaatcct tcctatagaa agaacagtat tgctgtaatt
2461 ccttttcttt tcttcctcat ttcctctgcc ccttaaaaga ttgaagaaag agaaacttgt
2521 caactcatat ccacgttatc tagcaaagta cataagaatc tatcactaag taatgtatcc
2581 ttcagaatgt gttggtttac cagtgacacc ccatattcat cacaaaatta aagcaagaag
2641 tccatagtaa tttatttgct aatagtggat ttttaatgct cagagtttct gaggtcaaat
2701 tttatctttt cacttacaag ctctatgatc ttaaataatt tacttaatgt attttggtgt
2761 attttcctca aattaatatt ggtgttcaag actatatcta attcctctga tcactttgag
2821 aaacaaactt ttattaaatg taaggcactt ttctatgaat tttaaatata aaaataaata
2881 ttgttctgat tattactgaa aagatgtcag ccatttcaat gtcttgggaa acaatttttt
2941 gttttgttc tgttttcttt ttgcttcaat aaaacaatag ctggctctaa aaaaaaaaaa
3001 aaaaaaaaaa aaaaa

Figure 59A

MDFSVKVDIEKEVTCPICLELLTEPLSLDCGHSFCQACITAKIKESVIISRGESSCPVCQTRFQPG
NLRPNRHLANIVERVKEVKMSPQEGQKRDVCEHHGKKLQIFCKEDGKVICWVCELSQEHQG

HQTFRINEVVKECQEKLQVALQRLIKEDQEAEKLEDDIRQERTAWKNYIQIERQKILKGFNEM
RVILDNEEQRELQKLEEGEVNVLDNLAAATDQLVQQRQDASTLISDLQRRLRGSSVEMLQD
VIDVMKRSESWTLKKPKSVSKKLKSVFRVPDLSGMLQVLKELTDVQYYWVDVMLNPGSAT
SNVAISVDQRQVKTVRTCTFKNSNPCDFSAFGVFGCQYFSSGKYYWEVDVSGKIAWILGVHS
KISSLNKRKSSGFAFDPSVNYSKVYSRYRPQYGYWVIGLQNTCEYNAFEDSSSSDPKVLTLFM
AVPPCRIGVFLDYEAGIVSFFNVTNHGALIYKFSGCRFSRPAYPYFNPWNCLVPMTVCPPSS

Figure 59B

1 aggctcagta taaatagcag ccaccgctcc ctggcaggca gggacccgca gctcagctac
61 agcacagatc aggtgaggag cacaccaagg agtgattttt aaaacttact ctgttttctc
121 tttcccaaca agattatcat ttcctttaaa aaaaatagtt atcctggggc atacagccat
181 accattctga aggtgtctta tctcctctga tctagagagc accatgaagc ttctcacggg
241 cctggttttc tgctccttgg tcctgggtgt cagcagccga agcttctttt cgttccttgg
301 cgaggctttt gatggggctc gggacatgtg gagagcctac tctgacatga gagaagccaa
361 ttacatcggc tcagacaaat acttccatgc tcgggggaac tatgatgctg ccaaaagggg
421 acctgggggt gcctgggctg cagaagtgat cagcgatgcc agagagaata tccagagatt
481 ctttggccat ggtgcggagg actcgctggc tgatcaggct gccaatgaat ggggcaggag
541 tggcaaagac cccaatcact tccgacctgc tggcctgcct gagaaatact gagcttcctc
601 ttcactctgc tctcaggaga tctggctgtg aggccctcag ggcagggata caaagcgggg
661 agagggtaca caatgggtat ctaataaata cttaagaggt ggaatttgtg gaaact

Figure 60A

MKLLTGLVFCSLVLGVSSRSFFSFLGEAFDGARDMWRAYSDMREANYIGSDKYFHARGNYD
AAKRGPGGAWAAEVISDARENIQRFFGHGAEDSLADQAANEWGRSGKDPNHFRPAGLPEKY

Figure 60B

```
1 tcacctgccc cacagcccgca ccctgcctgt gcctgcaccc tggggagccc agagccggca
61 ggggccgagg cggtgggacc tcgggggagc tcaagcctcg actgtcccct cgctggaggc
121 cagaggccaa gatgatgtcc atgctgggcg gcttgcagag atacttccgg gtcatcctcc
181 tcctcctcct ggccctgact ctgctcctgc tggccggatt cctgcactcg gacttagagc
241 tggacacacc cctgtttggg ggccaggctg aggggccgcc ggtcaccaac atcatgttcc
301 tgaagacgca caagacggcc agcagcacgg tgctcaacat cctctaccgc ttcgccgaga
361 cccacaacct gtccgtggcg ctgcccgccg gctcacgcgt ccacctgggc taccctggc
421 tcttcctggc gcgctacgtg gaaggcgtgg ggtcgcagca gcgcttcaac atcatgtgca
481 accacctgag gttcaacctg cctcaggtgc agaaagtcat gcccaacgac accttctact
541 tctccatcct gaggaacccc gtgttccagc tggagtcctc cttcatctac tacaaaacct
601 acgccccccgc cttccggggc gccccgagcc tggacgcgtt cctggcctcg ccgcggacgt
661 tctacaacga cagccgccac ctcaggaacg tctacgccaa gaacaacatg tggttcgact
721 tcggcttcga ccccaacgcg cagtgcgagg agggctacgt gcgcgcgcgc atcgccgagg
781 tggagcggcg cttccggctg gtgctcatcg ccgagcacct ggacgagtcc ctggtgctgc
841 tgcggcgccg gctgcgctgg gcgctggacg acgtggtggc cttcaggctc aactccgca
901 gcgcgcgctc cgtggccccgc ctgtcgcccg agaccccggga gcgcgcgcgg agctggtgcg
961 cgctggactg gcgcctgtac gagcatttca accgcaccct ctgggcgcag ctgcgcgccg
1021 agctggggcc gcggcggctg cgcggggagg tggagcggct gcgcgccccgg aggcgcgaac
1081 tcgcgagcct gtgcctgcag gacggcggcg cgctcaagaa ccacacgcag atcagagacc
1141 cgcgcctgcg ccctaccag tccggcaagg ccgacatcct gggttacaac ctccggccgg
1201 gcctggacaa ccagacgctg ggcgtgtgcc agaggcttgt gatgcctgag ctccagtaca
1261 tggccccgcct gtacgccctg cagttccccgg agaagccccct caagaacatc ccgttcctgg
1321 gggcgtagag gggccgggcc ggggacgagg cctcctgcgg acaccagctc ctctctccgc
1381 cgtcaccggg gaggccgggg atccttgcag ggcttctggg gcgttgggaa acccaggccc
1441 gccggccac
```

Figure 61A

```
MMSMLGGLQRYFRVILLLLLALTLLLLAGFLHSDLELDTPLFGGQAEGPPVTNIMFLKTHKT
ASSTVLNILYRFAETHNLSVALPAGSRVHLGYPWLFLARYVEGVGSQQRFNIMCNHLRFNLP
QVQKVMPNDTFYFSILRNPVFQLESSFIYYKTYAPAFRGAPSLDAFLASPRTFYNDSRHLRNV
YAKNNMWFDFGFDPNAQCEEGYVRARIAEVERRFRLVLIAEHLDESLVLLRRRLRWALDDV
VAFRLNSRSARSVARLSPETRERARSWCALDWRLYEHFNRTLWAQLRAELGPRRLRGEVER
LRARRRELASLCLQDGGALKNHTQIRDPRLRPYQSGKADILGYNLRPGLDNQTLGVCQRLV
MPELQYMARLYALQFPEKPLKNIPFLGA
```

Figure 61B

AATTCACTAATGCATTCTGCTCTTTTTGAGAGCACAGCTTCTCAGATGTGCTCCTTGGAG
CTGGTGTGCAGTGTCCTGACTGTAAGATCAAGTCCAAACCTGTTTTGGAATTGAGGAAAC
TTCTCTTTTGATCTCAGCCCTTGGTGGTCCAGGTCTTCATGCTGCTGTGGGTGATATTAC
TGGTCCTGGCTCCTGTCAGTGGACAGTTTGCAAGGACACCCAGGCCCATTATTTTCCTCC
AGCCTCCATGGACCACAGTCTTCCAAGGAGAGAGAGTGACCCTCACTTGCAAGGGATTT
C
GCTTCTACTCACCACAGAAAACAAAATGGTACCATCGGTACCTCGGGAAAGAAATACTA
A
GAGAAACCCCAGACAATATCCTTGAGGTTCAGGAATCTGGAGAGTACAGATGCCAGGCC
C
AGGGCTCCCCTCTCAGTAGCCCTGTGCACTTGGATTTTTCTTCAGCTTCGCTGATCCTGC
AAGCTCCACTTTCTGTGTTTGAAGGAGACTCTGTGGTTCTGAGGTGCCGGGCAAAGGCGG
AAGTAACACTGAATAATACTATTTACAAGAATGATAATGTCCTGGCATTCCTTAATAAAA
GAACTGACTTCCATATTCCTCATGCATGTCTCAAGGACAATGGTGCATATCGCTGTACTG
GATATAAGGAAAGTTGTTGCCCTGTTTCTTCCAATACAGTCAAAATCCAAGTCCAAGAGC
CATTTACACGTCCAGTGCTGAGAGCCAGCTCCTTCCAGCCCATCAGCGGGAACCCAGTGA
CCCTGACCTGTGAGACCCAGCTCTCTCTAGAGAGGTCAGATGTCCCGCTCCGGTTCCGCT
TCTTCAGAGATGACCAGACCCTGGGATTAGGCTGGAGTCTCTCCCCGAATTTCCAGATTA
CTGCCATGTGGAGTAAAGATTCAGGGTTCTACTGGTGTAAGGCAGCAACAATGCCTCAC
A
GCGTCATATCTGACAGCCCGAGATCCTGGATACAGGTGCAGATCCCTGCATCTCATCCTG
TCCTCACTCTCAGCCCTGAAAAGGCTCTGAATTTTGAGGGAACCAAGGTGACACTTCACT
GTGAAACCCAGGAAGATTCTCTGCGCACTTTGTACAGGTTTTATCATGAGGGTGTCCCCC
TGAGGCACAAGTCAGTCCGCTGTGAAAGGGGAGCATCCATCAGCTTCTCACTGACTACA
G
AGAATTCAGGGAACTACTACTGCACAGCTGACAATGGCCTTGGCGCCAAGCCCAGTAAG
G
CTGTGAGCCTCTCAGTCACTGTTCCCGTGTCTCATCCTGTCCTCAACCTCAGCTCTCCTG
AGGACCTGATTTTTGAGGGAGCCAAGGTGACACTTCACTGTGAAGCCCAGAGAGGTTCA
C
TCCCCATCCTGTACCAGTTTCATCATGAGGATGCTGCCCTGGAGCGTAGGTCGGCCAACT
CTGCAGGAGGAGTGGCCATCAGCTTCTCTCTGACTGCAGAGCATTCAGGGAACTACTACT
GCACAGCTGACAATGGCTTTGGCCCCCAGCGCAGTAAGGCGGTGAGCCTCTCCATCACTG
TCCCTGTGTCTCATCCTGTCCTCACCCTCAGCTCTGCTGAGGCCCTGACTTTTGAAGGAG
CCACTGTGACACTTCACTGTGAAGTCCAGAGAGGTTCCCCACAAATCCTATACCAGTTTT
ATCATGAGGACATGCCCCTGTGGAGCAGCTCAACACCCTCTGTGGGAAGAGTGTCCTTCA
GCTTCTCTCTGACTGAAGGACATTCAGGGAATTACTACTGCACAGCTGACAATGGCTTTG
GTCCCCAGCGCAGTGAAGTGGTGAGCCTTTTTGTCACTGTTCCAGTGTCTCGCCCCATCC
TCACCCTCAGGGTTCCCAGGGCCCAGGCTGTGGTGGGGGACCTGCTGGAGCTTCACTGTG
AGGCCCCGAGAGGCTCTCCCCCAATCCTGTACTGGTTTTATCATGAGGATGTCACCCTGG
GGAGCAGCTCAGCCCCCTCTGGAGGAGAAGCTTCTTTCAACCTCTCTCTGACTGCAGAAC
ATTCTGGAAACTACTCATGTGAGGCCAACAATGGCCTAGTGGCCCAGCACAGTGACACA
A
TATCACTCAGTGTTATAGTTCCAGTATCTCGTCCCATCCTCACCTTCAGGGCTCCCAGGG
CCCAGGCTGTGGTGGGGGACCTGCTGGAGCTTCACTGTGAGGCCCTGAGAGGCTCCTCCC
CAATCCTGTACTGGTTTTATCATGAAGATGTCACCCTGGGTAAGATCTCAGCCCCCTCTG
GAGGAGGGGCCTCCTTCAACCTCTCTCTGACTACAGAACATTCTGGAATCTACTCCTGTG
AGGCAGACAATGGTCCGGAGGCCCAGCGCAGTGAGATGGTGACACTGAAAGTTGCAGTT
C
CGGTGTCTCGCCCGGTCCTCACCCTCAGGGCTCCCGGGACCCATGCTGCGGTGGGGGACC
TGCTGGAGCTTCACTGTGAGGCCCTGAGAGGCTCTCCCCTGATCCTGTACCGGTTTTTTC
ATGAGGATGTCACCCTAGGAAATAGGTCGTCCCCCTCTGGAGGAGCGTCCTTAAACCTCT
CTCTGACTGCAGAGCACTCTGGAAACTACTCCTGTGAGGCCGACAATGGCCTCGGGGCCC
AGCGCAGTGAGACAGTGACACTTTATATCACAGGGCTGACCGCGAACAGAAGTGGCCCT
T

TTGCCACAGGAGTCGCCGGGGGCCTGCTCAGCATAGCAGGCCTTGCTGCGGGGGCACTG
C

Figure 62A

TGCTCTACTGCTGGCTCTCGAGAAAAGCAGGGAGAAAGCCTGCCTCTGACCCCGCCAGG
A
GCCCTCCAGACTCGGACTCCCAAGAGCCCACCTATCACAATGTACCAGCCTGGGAAGAG
C
TGCAACCAGTGTACACTAATGCAAATCCTAGAGGAGAAAATGTGGTTTACTCAGAAGTA
C
GGATCATCCAAGAGAAAAAGAAACATGCAGTGGCCTCTGACCCCAGGCATCTCAGGAAC
A
AGGGTTCCCCTATCATCTACTCTGAAGTTAAGGTGGCGTCAACCCCGGTTTCCGGATCCC
TGTTCTTGGCTTCCTCAGCTCCTCACAGATGAGTCCACACGTCTCTCCAACTGCTGTTTC
AGCCTCTGCACCCCAAAGTTCCCCTTGGGGGAGAAGCAGCATTGAAGTGGGAAGATTTA
G
GCTGCCCCAGACCATATCTACTGGCCTTTGTTTCACATGTCCTCATTCTCAGTCTGACCA
GAATGCAGGGCCCTGCTGGACTGTCACCTGTTTCCCAGTTAAAGCCCTGACTGGCAGGTT
TTTTAATCCAGTGGCAAGGTGCTCCCACTCCAGGGCCCAGCACATCTCCTGGATTCCTTA
GTGGGCTTCAGCTGTGATTGCTGTTCTGAGTACTGCTCTCATCACACCCCCACAGAGGGG
GTCTTACCACACAAAGGGAGAGTGGGCCTTCAGGAGATGCCGGGCTGGCCTAACAGCTC
A
GGTGCTCCTAAACTCCGACACAGAGTTCCTGCTTTGGGTGGATGCATTTCTCAATTGTCA
TCAGCCTGGTGGGGCTACTGCAGTGTGCTGCCAAATGGGACAGCACACAGCCTGTGCAC
A
TGGGACATGTGATGGGTCTCCCCACGGGGGCTGCATTTCACACTCCTCCACCTGTCTCAA
ACTCTAAGGTCGGCACTTGACACCAAGGTAACTTCTCTCCTGCTCATGTGTCAGTGTCTA
CCTGCCCAAGTAAGTGGCTTTCATACACCAAGTCCCAAGTTCTTCCCATCCTAACAGAAG
TAACCCAGCAAGTCAAGGCCAGGAGGACCAGGGGTGCAGACAGAACACATACTGGAAC
AC
AGGAGGTGCTCAATTACTATTTGACTGACTGACTGAATGAATGAATGAATGAGGAAGAA
A
ACTGTGGGTAATCAAACTGGCATAAAATCCAGTGCACTCCCTAGGAAATCCGGGAGGTA
T
TCTGGCTTCCCTAAGAAACAACGGAAGAGAAGGAGCTTGGATGAGGAAACTGTTCAGCA
A
GAGGAAGGGCTTCTCACACTTTCATGTGCTTGTGGATCACCTGAGGATCCTGTGAAAATA
CAGATACTGATTCAGTGGGTCTGTGTAGAGCCTGAGACTGCCATTCTAACATGTTCCCAG
GGGATGCTGATGCTGCTGGCCCTGGGACTGCACTGCATGCATGTGAAGCCCTATAGGTCT
CAGCAGAGGCCCATGGAGAGGGAATGTGTGGCTCTGGCTGCCCAGGGCCCAACTCGGTT
C
ACACGGATCGTGCTGCTCCCTGGCCAGCCTTTGGCCACAGCACCACCAGCTGCTGTTGCT
GAGAGAGCTTCTTCTCTGTGACATGTTGGCTTTCATCAGCCACCCTGGGAAGCGGAAAGT
AGCTGCCACTATCTTTGTTTCCCCACCTCAGGCCTCACACTTTCCCATGAAAAGGGTGAA
TGTATATAACCTGAGCCCTCTCCATTCAGAGTTGTTCTCCCATCTCTGAGCAATGGGATG
TTCTGTTCCGCTTTTATGATATCCATCACATCTTATCTTGATCTTTGCTCCCAGTGGATT
GTACAGTGATGACTTTTAAGCCCCACGGCCCTGAAATAAAATCCTTCCAAGGGCATTGGA
AGCTCTCTCCACCTGAACCATGGCTTTTCATGCTTCCAAGTGTCAGGGCCTTGCCCAGAT
AGACAGGGCTGACTCTGCTGCCCCAACCTTTCAAGGAGGAAACCAGACACCTGAGACAG
G
AGCCTGTATGCAGCCCAGTGCAGCCTTGCAGAGGACAAGGCTGGAGGCATTTGTCATCA
C

TACAGATATGCAACTAAAATAGACGTGGAGCAAGAGAAATGCATTCCCACCGAGGCCGC
T
TTTTTAGGCCTAGTTGAAAGTCAAGAAGGACAGCAGCAAGCATAGGCTCAGGATTAAAG
A
AAAAAATCTGCTCACAGTTTGTTCTGGAGGTCACATCACCAACAAAGCTCACGCCCTATG
CAGTTCTGAGAAGGTGGAGGCACCAGGCTCAAAAGAGGAAATTTAGAATTTCTCATTGG
G
AGAGTAAGGTACCCCCATCCCAGAATGATAACTGCACAGTGGCAGAACAAACTCCACCC
T
AATGTGGGTGGACCCCATCCAGTCTGTTGAAGGCCTGAGTGTAACAAAAGGGCTTATTCT
TCCTCAAGTAAGGGGGAACTCCTGCTTTGGGCTGGGACATAAGTTTTTCTGCTTTCAGAC
GCAAACTGAAAAATGGCTCTTCTTGGGTCTTGAGCTTGCTGGCATATGGACTGAAAGAAA
CTATGCTATTGGATCTCCTGGATCTCCAGCTTGCTGACTGCAGATCTTGAGATATGTCAG
CCTCTACAGTCACAAGAGCTAATTCATTCTAATAAACCAATCTTTCTGTAAA

Figure 62A (Continued)

MLLWVILLVLAPVSGQFARTPRPIIFLQPPWTTVFQGERVTLTCKGFRFYSPQKTKWYHR

YLGKEILRETPDNILEVQESGEYRCQAQGSPLSSPVHLDFSSASLILQAPLSVFEGDSVV

LRCRAKAEVTLNNTIYKNDNVLAFLNKRTDFHIPHACLKDNGAYRCTGYKESCCPVSSNT

VKIQVQEPFTRPVLRASSFQPISGNPVTLTCETQLSLERSDVPLRFRFFRDDQTLGLGWS

LSPNFQITAMWSKDSGFYWCKAATMPHSVISDSPRSWIQVQIPASHPVLTLSPEKALNFE

GTKVTLHCETQEDSLRTLYRFYHEGVPLRHKSVRCERGASISFSLTTENSGNYYCTADNG

LGAKPSKAVSLSVTVPVSHPVLNLSSPEDLIFEGAKVTLHCEAQRGSLPILYQFHHEDAA

LERRSANSAGGVAISFSLTAEHSGNYYCTADNGFGPQRSKAVSLSITVPVSHPVLTLSSA

EALTFEGATVTLHCEVQRGSPQILYQFYHEDMPLWSSSTPSVGRVSFSFSLTEGHSGNYY

CTADNGFGPQRSEVVSLFVTVPVSRPILTLRVPRAQAVVGDLLELHCEAPRGSPPILYWF

YHEDVTLGSSSAPSGGEASFNLSLTAEHSGNYSCEANNGLVAQHSDTISLSVIVPVSRPI

LTFRAPRAQAVVGDLLELHCEALRGSSPILYWFYHEDVTLGKISAPSGGGASFNLSLTTE

HSGIYSCEADNGPEAQRSEMVTLKVAVPVSRPVLTLRAPGTHAAVGDLLELHCEALRGSP

LILYRFFHEDVTLGNRSSPSGGASLNLSLTAEHSGNYSCEADNGLGAQRSETVTLYITGL

TANRSGPFATGVAGGLLSIAGLAAGALLLYCWLSRKAGRKPASDPARSPPDSDSQEPTYH

NVPAWEELQPVYTNANPRGENVVYSEVRIIQEKKKHAVASDPRHLRNKGSPIIYSEVKVA

STPVSGSLFLASSAPHR

Figure 62B

GGCACGAGGCCCAGCACTAGAAGTCGGCGGTGTTTCCTTTCGGTGATCAGCACTGAACA
C
AGAGGACTCGCCATGGAGTTTGGGCTGAGCTGGGTTTTCCTCGTTGCTCTTTTAAGAGGT
GTCCAGTGTCAGGCGCAGTTGGTGGAGTCTGGGGGAGGCGTGGTCCAGCCCGGGAGCTC
C
CTGAGACTCTCCTGTGCAGCCTCTGGTTTCAGGTTCAGCAATTATGGCATGCACTGGGTC
CGCCAGGCTCCAGGCAAGGGGCTGGAGTGGGTGGCAGTTTTTTCATATGATGAAAGTGA
T
AAATATTATGCAGCCTCCGTGAAGGGTCGATTTACCATCTCCAGAGACAACTCCAAGAAC
ACGTTGTCTCTGCAAATGAACAGCCTGAGAGTTGAGGACACGGCTGTTTACTACTGTGCG
AAAGATCAGAAGCCCTGGTACAGCAACAGCTGGTTTCTAACCAACTTTGACTCTTGGGGC
CGGGGCACCCTGGTCACCGTCTCCTCAGCCTCCACCAAGGGCCCATCGGTCTTCCCCCTG
GCACCCTCCTCCAAGAGCACCTCTGGGGGCACAGCGGCCCTGGGCTGCCTGGTCAAGGA
C
TACTTCCCCGAACCGGTGACGGTGTCGTGGAACTCAGGCGCCCTGACCAGCGGCGTGCA
C
ACCTTCCCGGCTGTCCTACAGTCCTCAGGACTCTACTCCCTCAGCAGCGTGGTGACCGTG
CCCTCCAGCAGCTTGGGCACCCAGACCTACATCTGCAACGTGAATCACAAGCCCAGCAA
C
ACCAAGGTGGACAAGAAAGTTGAGCCCAAATCTTGTGACAAAACTCACACATGCCCACC
G
TGCCCAGCACCTGAACTCCTGGGGGGACCGTCAGTCTTCCTCTTCCCCCCAAAACCCAAG
GACACCCTCATGATCTCCCGGACCCCTGAGGTCACATGCGTGGTGGTGGACGTGAGCCAC
GAAGACCCTGAGGTCAAGTTCAACTGGTACGTGGACGGCGTGGAGGTGCATAATGCCAA
G
ACAAAGCCGCGGGAGGAGCAGTACAACAGCACGTACCGTGTGGTCAGCGTCCTCACCGT
C
CTGCACCAGGACTGGCTGAATGGCAAGGAGTACAAGTGCAAGGTCTCCAACAAAGCCCT
C
CCAGCCCCCATCGAGAAAACCATCTCCAAAGCCAAAGGGCAGCCCCGAGAACCACAGGT
G
TACACCCTGCCCCCATCCCGGGATGAGCTGACCAAGAACCAGGTCAGCCTGACCTGCCTG
GTCAAAGGCTTCTATCCCAGCGACATCGCCGTGGAGTGGGAGAGCAATGGGCAGCCGGA
G
AACAACTACAAGACCACGCCTCCCGTGCTGGACTCCGACGGCTCCTTCTTCCTCTACAGC
AAGCTCACCGTGGACAAGAGCAGGTGGCAGCAGGGGAACGTCTTCTCATGCTCCGTGAT
G
CATGAGGCTCTGCACAACCACTACACGCAGAAGAGCCTCTCCCTGTCTCCGGAGCTGCAA
CTGGAGGAGAGCTGTGCGGAGGCGCAGGACGGGGAGCTGGACGGGCTGTGGACGACCA
TC
ACCATCTTCATCACACTCTTCCTGTTAAGCGTGTGCTACAGTGCCACCGTCACCTTCTTC
AAGGTGAAGTGGATCTTCTCCTCGGTGGTGGACCTGAAGCAGACCATCATCCCCGACTAC
AGGAACATGATCGGACAGGGGGCCTAGGGCCACCCTCTGCGGGGTGTCCAGGGCCGCCC
A
GACCCCACACACCAGCCATGGGCCATGCTCAGCCACCACCCAGGCCACACCTGCCCCCG
A
CCTCACCGCCCTCAACCCCATGGCTCTCTGGCCTCGCAGTTGCCCTCTGACCCTGACACA
CCTGACACGCCCCCCTTCCAGACCCTGTGCATAGCAGGTCTACCCCAGACCTCCGCTGCT
TGGTGCATGCAGGGCACTGGGGGCCAGGTGTCCCCTCAGCAGGACATCCTTGCCCTCCGG
ACCACAAGGTGCTCACACAAAAGGAGGCAGTGACCGGTATCCCAGGCCCCCACCCAGGC
A
GGAGCTGGCCCTGGAGCCAACCCCGTCCACGCCAGCCTCCTGAACACAGGCGTGGTTTCC
AGATGGTGAGTGGGAGCATCAGCCGCCAAGGTAGGGAAGCCACAGCACCATCAGGCCCT
G

TTGGGGAGGCTTCCGAGAGCTGCGAAGGCTCACTCAGACGGCCTTCCTCCCAGCCCGCA
G
CCAGCCAGCCTCCATTCCGGGCACTCCCGTGAACTCCTGACATGAGGAATGAGGTTGTTC
TGATTTCAAGCAAAGAACGCTGCTCTCTGGCTCCTGGGAACAGTCTCGGTGCCAGCACCA
CCCCTTGGCTGCCTGCCCACACTGCTGGATTCTCGGGTGGAACTGGACCCGCAGGGACAG
CCAGCCCCAGAGTCCGCACTGGGGAGAGAAGGGGCCAGGCCCAGGACACTGCCACCTCC
C
ACCCACTCCAGTCCACCGAGATCACTCAGAGAAGAGCCTGGGCCATGTGGCCGCTGCAG
G
AGCCCCACAGTGCAAGGGTGAGGATAGCCCAAGGAAGGGCTGGGCATCTGCCCAGACA
GG
CCTCCCAGAGAAGGCTGGTGACCAGGTCCCAGGCGGGCAAGACTCAGCCTTGGTGGGGC
C
TGAGGACAGAGGAGGCCCAGGAGCATCGGGGAGAGAGGTGGAGGGACACCGGGAGAGC
CA

Figure 63A

GGAGCGTGGACACAGCCAGAACTCATCACAGAGGCTGGCGTCCAGTCCCGGGTCACGTG
C
AGCAGGAACAAGCAGCCACTCTGGGGGCACCAGGTGGAGAGGCAAGACGACAAAGAGG
GT
GCCCGTGTTCTTGCGAAAGCGGGGCTGCTGGCCACGAGTGCTGGACAGAGGCCCCCACG
C
TCTGCTGCCCCCATCACGCCGTTCCGTGACTGTCACGCAGAATCCGCAGACAGGAAGGG
A
GACTCGAGCGGGAGTGCGGCCAGCGCCTGCCTCGGCCGTCAGGGAGGACTCCCGGGCTC
A
CTCGAAGGAGGTGCCACCATTTCAGCTTTGGTAGCTTTTCTTCTTCTTTTAAATTTTCTA
AAGCTCATTAATTGTCTTTGATGTTTCTTTTGTGATGACAATAAAATATCCTTTTTAAGT
CTTGTAAAAAAAAAAAAAAAAA

Figure 63A (Continued)

MEFGLSWVFLVALLRGVQCQAQLVESGGGVVQPGSSLRLSCAASGFRFSNYGMHWVRQAP
GKGLEWVAVFSYDESDKYYAASVKGRFTISRDNSKNTLSLQMNSLRVEDTAVYYCAKDQK
PWYSNSWFLTNFDSWGRGTLVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPV
TVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEP
KSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVD
GVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKG
QPREPQVYTLPPSRDELTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSF
FLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPELQLEESCAEAQDGELDGLW
TTITIFITLFLLSVCYSATVTFFKVKWIFSSVVDLKQTIIPDYRNMIGQGA

Figure 63B

GCTCTAGAACTAGTGGATCCCCCGGGCTGCAGGAATTCTCTAAAGAAGCCCCTGGGAGC
A
CAGCTCATCACCATGGACTGGACCTGGAGGTTCCTCTTTGTGGTGGCAGCAGCTACAGGT
GTCCAGTCCCAGGTGCAGCTGGTGCAGTCTGGGGCTGAGGTGAAGAAGCCTGGGTCCTC
G
GTGAAGGTCTCCTGCAAGGCTTCTGGAGGCACCTTCAGCAGCTATGCTATCAGCTGGGTG
CGACAGGCCCCTGGACAAGGGCTTGAGTGGATGGGAGGGATCATCCCTATCTTTGGTAC
A
GCAAACTACGCACAGAAGTTCCAGGGCAGAGTCACGATTACCGCGGACGAATCCACGAG
C
ACAGCCTACATGGAGCTGAGCAGCCTGAGATCTGAGGACACGGCCGTGTATTACTGTGC
G
AAAACCGGGATCCTGGGGCCGTATAGCAGTGGCTGGTACCCGAACTCGGACTACTACTA
C
TACGGTATGGACGTCTGGGGCCAAGGGACCACGGTCACCGTCTCCTCAGGGAGTGCATC
C
GCCCCAACCCTTTTCCCCCTCGTCTCCTGTGAGAATTCCCCGTCGGATACGAGCAGCGTG
GCCGTTGGCTGCCTCGCACAGGACTTCCTTCCCGACTCCATCACTTTCTCCTGGAAATAC
AAGAACAACTCTGACATCAGCAGCACCCGGGGCTTCCCATCAGTCCTGAGAGGGGGCAA
G
TACGCAGCCACCTCACAGGTGCTGCTGCCTTCCAAGGACGTCATGCAGGGCACAGACGA
A
CACGTGGTGTGCAAAGTCCAGCACCCCAACGGCAACAAAGAAAAGAACGTGCCTCTTCC
A
GTGATTGCTGAGCTGCCTCCCAAAGTGAGCGTCTTCGTCCCACCCCGCGACGGCTTCTTC
GGCAACCCCCGCAGCAAGTCCAAGCTCATCTGCCAGGCCACGGGTTTCAGTCCCCGGCA
G
ATTCAGGTGTCCTGGCTGCGCGAGGGGAAGCAGGTGGGGTCTGGCGTCACCACGGACCA
G
GTGCAGGCTGAGGCCAAAGAGTCTGGGCCCACGACCTACAAGGTGACCAGCACACTGAC
C
ATCAAAGAGAGCGACTGGCTCAGCCAGAGCATGTTCACCTGCCGCGTGGATCACAGGGG
C
CTGACCTTCCAGCAGAATGCGTCCTCCATGTGTGTCCCCGATCAAGACACAGCCATCCGG
GTCTTCGCCATCCCCCCATCCTTTGCCAGCATCTTCCTCACCAAGTCCACCAAGTTGACC
TGCCTGGTCACAGACCTGACCACCTATGACAGCGTGACCATCTCCTGGACCCGCCAGAAT
GGCGAAGCTGTGAAAACCCACACCAACATCTCCGAGAGCCACCCCAATGCCACTTTCAG
C
GCCGTGGGTGAGGCCAGCATCTGCGAGGATGACTGGAATTCCGGGGAGAGGTTCACGTG
C
ACCGTGACCCACACAGACCTGCCCTCGCCACTGAAGCAGACCATCTCCCGGCCCAAGGG
G
GTGGCCCTGCACAGGCCCGATGTCTACTTGCTGCCACCAGCCCGGGAGCAGCTGAACCTG
CGGGAGTCGGCCACCATCACGTGCCTGGTGACGGGCTTCTCTCCCGCGGACGTCTTCGTG
CAGTGGATGCAGAGGGGGCAGCCCTTGTCCCCGGAGAAGTATGTGACCAGCGCCCCAAT
G
CCTGAGCCCCAGGCCCCAGGCCGGTACTTCGCCCACAGCATCCTGACCGTGTCCGAAGA
G
GAATGGAACACGGGGGAGACCTACACCTGCGTGGTGGCCCATGAGGCCCTGCCCAACAG
G
GTCACCGAGAGGACCGTGGACAAGTCCACCGAGGGGGAGGTGAGCGCCGACGAGGAGG
GC
TTTGAGAACCTGTGGGCCACCGCCTCCACCTTCATCGTCCTCTTCCTCCTGAGCCTCTTC
TACAGTACCACCGTCACCTTGTTCAAGGTGAAATGATCCCAACAGAAGAACATCGGAGA
C

CAGAGAGAGGAACTCAAAGGGGCGCTGCCTCCGGGTCTGGGGTCCTGGCCTGCGTGGCC
T
GTTGGCACGTGTTTCTCTTCCCGCCCGGCCTCCAGTTGTGTGCTCTCACACAGGCTTCCT
TCTCGACCGGCAGGGGCTGGCTGGCTTGCAGGCCACGAGGTGGGCTCTACCCCACACTG
C
TTTGCTGTGTATACGCTTGTTGCCCTGAAATAAATATGCACATTTTATCCATG

Figure 64A

MDWTWRFLFVVAAATGVQSQVQLVQSGAEVKKPGSSVKVSCKASGGTFSSYAISWVRQAP
GQGLEWMGGIIPIFGTANYAQKFQGRVTITADESTSTAYMELSSLRSEDTAVYYCAKTGI
LGPYSSGWYPNSDYYYYGMDVWGQGTTVTVSSGSASAPTLFPLVSCENSPSDTSSVAVGC
LAQDFLPDSITFSWKYKNNSDISSTRGFPSVLRGGKYAATSQVLLPSKDVMQGTDEHVVC
KVQHPNGNKEKNVPLPVIAELPPKVSVFVPPRDGFFGNPRSKSKLICQATGFSPRQIQVS
WLREGKQVGSGVTTDQVQAEAKESGPTTYKVTSTLTIKESDWLSQSMFTCRVDHRGLTFQ
QNASSMCVPDQDTAIRVFAIPPSFASIFLTKSTKLTCLVTDLTTYDSVTISWTRQNGEAV
KTHTNISESHPNATFSAVGEASICEDDWNSGERFTCTVTHTDLPSPLKQTISRPKGVALH
RPDVYLLPPAREQLNLRESATITCLVTGFSPADVFVQWMQRGQPLSPEKYVTSAPMPEPQ
APGRYFAHSILTVSEEEWNTGETYTCVVAHEALPNRVTERTVDKSTEGEVSADEEGFENL
WATASTFIVLFLLSLFYSTTVTLFKVK

Figure 64B

1 agacacctct gccctcacca tgagcctctg gcagccccctg gtcctggtgc tcctggtgct
61 gggctgctgc tttgctgccc ccagacagcg ccagtccacc cttgtgctct tccctggaga
121 cctgagaacc aatctcaccg acaggcagct ggcagaggaa tacctgtacc gctatggtta
181 cactcgggtg gcagagatgc gtggagagtc gaaatctctg gggcctgcgc tgctgcttct
241 ccagaagcaa ctgtccctgc ccgagaccgg tgagctggat agcgccacgc tgaaggccat
301 gcgaacccca cggtgcgggg tcccagacct gggcagattc caaaccttig agggcgacct
361 caagtggcac caccacaaca tcacctattg gatccaaaac tactcggaag acttgccgcg
421 ggcggtgatt gacgacgcct ttgcccgcgc cttcgcactg tggagcgcgg tgacgccgct
481 caccttcact cgcgtgtaca gccgggacgc agacatcgtc atccagtttg gtgtcgcgga
541 gcacggagac gggtatccct tcgacgggaa ggacgggctc ctggcacacg cctttcctcc
601 tggccccggc attcagggag acgcccattt cgacgatgac gagttgtggt ccctgggcaa
661 gggcgtcgtg gttccaactc ggtttggaaa cgcagatggc gcggcctgcc acttccccctt
721 catcttcgag ggccgctcct actctgcctg caccaccgac ggtcgctccg acggcttgcc
781 ctggtgcagt accacggcca actacgacac cgacgaccgg tttggcttct gccccagcga
841 gagactctac acccaggacg gcaatgctga tgggaaaccc tgccagtttc catcatctt
901 ccaaggccaa tcctactccg cctgcaccac ggacggtcgc tccgacggct accgctggtg
961 cgccaccaac gccaactacg accgggacaa gctcttcggc ttctgcccga cccgagctga
1021 ctcgacggtg atgggggggca actcggcggg ggagctgtgc gtcttcccct tcactttcct
1081 gggtaaggag tactcgacct gtaccagcga gggccgcgga gatgggcgcc tctggtgcgc
1141 taccacctcg aactttgaca gcgacaagaa gtggggcttc tgcccggacc aaggatacag
1201 tttgttcctc gtggcggcgc atgagttcgg ccacgcgctg ggcttagatc attcctcagt
1261 gccggaggcg ctcatgtacc ctatgtaccg cttcactgag gggccccccct tgcataagga
1321 cgacgtgaat ggcatccggc acctctatgg tcctcgccct gaacctgagc cacggcctcc
1381 aaccaccacc acaccgcagc ccacggctcc cccgacggtc tgcccccaccg gaccccccac
1441 tgtccacccc tcagagcgcc ccacagctgg ccccacaggt ccccccctcag ctggccccac
1501 aggtcccccc actgctggcc cttctacggc cactactgtg cctttgagtc cggtggacga
1561 tgcctgcaac gtgaacatct tcgacgccat cgcggagatt gggaaccagc tgtatttgtt
1621 caaggatggg aagtactggc gattctctga gggcaggggg agccggccgc agggccccctt
1681 ccttatcgcc gacaagtggc ccgcgctgcc ccgcaagctg gactcggtct ttgaggagcg
1741 gctctccaag aagcttttct tcttctctgg gcgccaggtg tgggtgtaca caggcgcgtc
1801 ggtgctgggc ccgaggcgtc tggacaagct gggcctggga gccgacgtgg cccaggtgac
1861 cggggccctc cggagtggca gggggaagat gctgctgttc agcgggcggc gcctctggag
1921 gttcgacgtg aaggcgcaga tggtggatcc ccggagcgcc agcgaggtgg accggatgtt
1981 ccccggggtg cctttggaca cgcacgacgt cttccagtac cgagagaaag cctatttctg
2041 ccaggaccgc ttctactggc gcgtgagttc ccggagtgag ttgaaccagg tggaccaagt
2101 gggctacgtg acctatgaca tcctgcagtg ccctgaggac tagggctccc gtcctgcttt
2161 ggcagtgcca tgtaaatccc cactgggacc aaccctgggg aaggagccag tttgccggat
2221 acaaactggt attctgttct ggaggaaagg gaggagtgga ggtgggctgg gccctctctt
2281 ctcacctttg ttttttgttg gagtgtttct aataaacttg gattctctaa cctttaaaaa
2341 aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaa

Figure 65A

MSLWQPLVLVLLVLGCCFAAPRQRQSTLVLFPGDLRTNLTDRQLAEEYLYRYGYTRVAEMR
GESKSLGPALLLLQKQLSLPETGELDSATLKAMRTPRCGVPDLGRFQTFEGDLKWHHHNITY
WIQNYSEDLPRAVIDDAFARAFALWSAVTPLTFTRVYSRDADIVIQFGVAEHGDGYPFDGKD
GLLAHAFPPGPGIQGDAHFDDDELWSLGKGVVVPTRFGNADGAACHFPFIFEGRSYSACTTD
GRSDGLPWCSTTANYDTDDRFGFCPSERLYTQDGNADGKPCQFPFIFQGQSYSACTTDGRSD
GYRWCATTANYDRDKLFGFCPTRADSTVMGGNSAGELCVFPFTFLGKEYSTCTSEGRGDGR
LWCATTSNFDSDKKWGFCPDQGYSLFLVAAHEFGHALGLDHSSVPEALMYPMYRFTEGPPL
HKDDVNGIRHLYGPRPEPEPRPPTTTTPQPTAPPTVCPTGPPTVHPSERPTAGPTGPPSAGPTGP
PTAGPSTATTVPLSPVDDACNVNIFDAIAEIGNQLYLFKDGKYWRFSEGRGSRPQGPFLIADK
WPALPRKLDSVFEERLSKKLFFFSGRQVWVYTGASVLGPRRLDKLGLGADVAQVTGALRSG
RGKMLLFSGRRLWRFDVKAQMVDPRSASEVDRMFPGVPLDTHDVFQYREKAYFCQDRFYW
RVSSRSELNQVDQVGYVTYDILQCPED

Figure 65B

1 cacagagccc gggccgcagg cacctcctcg ccagctcttc cgctcctctc acagccgcca
61 gaccccgcctg ctgagccccca tggccccgcgc tgctctctcc gccgcccccca gcaatccccg
121 gctcctgcga gtggcactgc tgctcctgct cctggtagcc gctggccggc gcgcagcagg
181 agcgtccgtg gccactgaac tgcgctgcca gtgcttgcag accctgcagg gaattcaccc
241 caagaacatc caaagtgtga acgtgaagtc ccccggaccc cactgcgccc aaaccgaagt
301 catagccaca ctcaagaatg ggcggaaagc ttgcctcaat cctgcatccc ccatagttaa
361 gaaaatcatc gaaaagatgc tgaacagtga caaatccaac tgaccagaag ggaggaggaa
421 gctcactggt ggctgttcct gaaggaggcc ctgcccttat aggaacagaa gaggaaagag
481 agacacagct gcagaggcca cctggattgt gcctaatgtg tttgagcatc gcttaggaga
541 agtcttctat ttatttattt attcattagt tttgaagatt ctatgttaat attttaggtg
601 taaaataatt aagggtatga ttaactctac ctgcacactg tcctattata ttcattcttt
661 ttgaaatgtc aaccccaagt tagttcaatc tggattcata tttaatttga aggtagaatg
721 ttttcaaatg ttctccagtc attatgttaa tatttctgag gagcctgcaa catgccagcc
781 actgtgatag aggctggcgg atccaagcaa atggccaatg agatcattgt gaaggcaggg
841 gaatgtatgt gcacatctgt tttgtaactg tttagatgaa tgtcagttgt tatttattga
901 aatgatttca cagtgtgtgg tcaacatttc tcatgttgaa actttaagaa ctaaaatgtt
961 ctaaatatcc cttggacatt ttatgtcttt cttgtaaggc atactgcctt gtttaatggt
1021 agttttacag tgtttctggc ttagaacaaa ggggcttaat tattgatgtt ttcatagaga
1081 atataaaaat aaagcactta tag

Figure 66A

MARAALSAAPSNPRLLRVALLLLLLVAAGRRAAGASVATELRCQCLQTLQGIHPKNIQSVNV
KSPGPHCAQTEVIATLKNGRKACLNPASPIVKKIIEKMLNSDKSN

Figure 66B

CTATAGAAGAGCTATGACGTCGCATGCACGCGTACGTAAGCTCGGAATTCGGCTCGAGG
C
TTCTCGCACAGCTTCCCGACGCGTCTGCTGAGCCCCATGGCCCACGCCACGCTCTCCGCC
GCCCCCAGCAATCCCCGGCTCCTGCGGGTGGCGCTGCTGCTCCTGCTCCTGGTGGCCGCC
AGCCGGCGCGCAGCAGGAGCGTCCGTGGTCACTGAACTGCGCTGCCAGTGCTTGCAGAC
A
CTGCAGGGAATTCACCTCAAGAACATCCAAAGTGTGAATGTTAGGTCCCCCGGACCCCA
C
TGCGCCCAAACCGAAGTCATAGCCACACTCAAGAATGGGAAGAAAGCTTGTCTCAACCC
C
GCATCCCCCATGGTTCAGAAAATCATCGAAAAGATACTGAACAAGGGGAGCACCAACTG
A
CAGGAGAGAAGTAAGAAGCTTATCAGCGTATCATTGACACTTCCTGCAGGGTGGTCCCT
G
CCCTTACCAGAGCTGAAAATGAAAAAGAGAACAGCAGCTTTCTAGGGACAGCTGGAAAG
G
ACTTAATGTGTTTGACTATTTCTTACGAGGGTTCTACTTATTTATGTATTTATTTTTGAA
AGCTTGTATTTTAATATTTTACATGCTGTTATTTAAAGATGTGAGTGTGTTTCATCAAAC
ATAGCTCAGTCCTGATTATTTAATTGGAATATGATGGGTTTTAAATGTGTCATTAAACTA
ATATTTAGTGGGAGACCATAATGTGTCAGCCACCTTGATAAATGACAGGGTGGGGAACT
G
GAGGGTGGGGGGATTGAAATGCAAGCAATTAGTGGATCACTGTTAGGGTAAGGGAATGT
A
TGTACACATCTATTTTTTATACTTTTTTTTTAAAAAAAAAATGTCAGTTGTTATTTATTC
AAATTATCTCACATTATGTGTTCAACATTTTTATGCTGAAGTTTCCCTTAGACATTTTAT
GTCTTGCTTGTAGGGCATAATGCCTTGTTTAATGTCCATTCTGCAGCGTTTCTCTTTCCC
TTGGAAAAGAGAATTTATCATTACTGTTACATTTGTACAAATGACATGATAATAAAAGTT
TTATGAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAGG

Figure 67A

MAHATLSAAPSNPRLLRVALLLLLLVAASRRAAGASVVTELRCQCLQTLQGIHLKNIQSVNV
RSPGPHCAQTEVIATLKNGKKACLNPASPMVQKIIEKILNKGSTN

Figure 67B

1 accaaacctc ttcgaggcac aaggcacaac aggctgctct gggattctct tcagccaatc
61 ttcattgctc aagtgtctga agcagccatg gcagaagtac ctgagctcgc cagtgaaatg
121 atggcttatt acagtggcaa tgaggatgac ttgttctttg aagctgatgg ccctaaacag
181 atgaagtgct ccttccagga cctggacctc tgccctctgg atggcggcat ccagctacga
241 atctccgacc accactacag caagggcttc aggcaggccg cgtcagttgt tgtggccatg
301 gacaagctga ggaagatgct ggttccctgc ccacagacct tccaggagaa tgacctgagc
361 accttctttc ccttcatctt tgaagaagaa cctatcttct tcgacacatg ggataacgag
421 gcttatgtgc acgatgcacc tgtacgatca ctgaactgca cgctccggga ctcacagcaa
481 aaaagcttgg tgatgtctgg tccatatgaa ctgaaagctc tccacctcca gggacaggat
541 atggagcaac aagtggtgtt ctccatgtcc tttgtacaag gagaagaaag taatgacaaa
601 atacctgtgg ccttgggcct caaggaaaag aatctgtacc tgtcctgcgt gttgaaagat
661 gataagccca ctctacagct ggagagtgta gatcccaaaa attacccaaa gaagaagatg
721 gaaaagcgat ttgtcttcaa caagatagaa atcaataaca agctggaatt tgagtctgcc
781 cagttcccca actggtacat cagcacctct caagcagaaa acatgcccgt cttcctggga
841 gggaccaaag gcggccagga tataactgac ttcaccatgc aatttgtgtc ttcctaaaga
901 gagctgtacc cagagagtcc tgtgctgaat gtggactcaa tccctagggc tggcagaaag
961 ggaacagaaa ggtttttgag tacggctata gcctggactt tcctgttgtc tacaccaatg
1021 cccaactgcc tgccttaggg tagtgctaag aggatctcct gtccatcagc caggacagtc
1081 agctctctcc tttcagggcc aatccccagc cttttgttg agccaggcct ctctcacctc
1141 tcctactcac ttaaagcccg cctgacagaa accacggcca catttggttc taagaaaccc
1201 tctgtcattc gctcccacat tctgatgagc aaccgcttcc ctatttattt atttatttgt
1261 ttgtttgttt tattcattgg tctaatttat tcaaaggggg caagaagtag cagtgtctgt
1321 aaaagagcct agtttttaat agctatggaa tcaattcaat ttggactggt gtgctctctt
1381 taaatcaagt cctttaatta agactgaaaa tatataagct cagattattt aaatgggaat
1441 atttataaat gagcaaatat catactgttc aatggttctg aaataaactt cactgaag

Figure 68A

MAEVPELASEMMAYYSGNEDDLFFEADGPKQMKCSFQDLDLCPLDGGIQLRISDHHYSKGF
RQAASVVVAMDKLRKMLVPCPQTFQENDLSTFFPFIFEEEPIFFDTWDNEAYVHDAPVRSLN
CTLRDSQQKSLVMSGPYELKALHLQGQDMEQQVVFSMSFVQGEESNDKIPVALGLKEKNLY
LSCVLKDDKPTLQLESVDPKNYPKKKMEKRFVFNKIEINNKLEFESAQFPNWYISTSQAENMP
VFLGGTKGGQDITDFTMQFVSS

Figure 68B

1 gtcaggttca tggttacgaa gctgctgacc ccaggatccc agcccgtggg agagaagggg
61 gtctctgaca gcccccaccc ctccccactg ccagatcctt attgggtctg agtttcaggg
121 gtggggcccc agctggaggt tataaaacag ctcaatcggg gagtacaacc ttcggtttct
181 cttcggggaa agctgctttc agcgcacacg ggaagatatc agaaacatcc taggatcagg
241 acaccccaga tcttctcaac tggaaccacg aaggctgttt cttccacaca gcactttgat
301 ctccatttaa gcaggcacct ctgtcctgcg ttccggagct gcgttcccga tggtcctcct
361 ttggctcacg ctgctcctga tcgccctgcc ctgtctcctg caaacgaagg aagatccaaa
421 cccaccaatc acgaacctaa ggatgaaagc aaaggctcag cagttgacct gggaccttaa
481 cagaaatgtg accgatatcg agtgtgttaa agacgccgac tattctatgc cggcagtgaa
541 caatagctat tgccagtttg gagcaatttc cttatgtgaa gtgaccaact acaccgtccg
601 agtggccaac ccaccattct ccacgtggat cctcttccct gagaacagtg ggaagccttg
661 ggcaggtgcg gagaatctga cctgctggat tcatgacgtg gatttcttga gctgcagctg
721 ggcggtaggc ccgggggccc ccgcggacgt ccagtacgac ctgtacttga acgttgccaa
781 caggcgtcaa cagtacgagt gtcttcacta caaaacggat gctcagggaa cacgtatcgg
841 gtgtcgtttc gatgacatct ctcgactctc cagcggttct caaagttccc acatcctggt
901 gcggggcagg agcgcagcct tcggtatccc ctgcacagat aagtttgtcg tcttttcaca
961 gattgagata ttaactccac ccaacatgac tgcaaagtgt aataagacac attcctttat
1021 gcactggaaa atgagaagtc atttcaatcg caaatttcgc tatgagcttc agatacaaaa
1081 gagaatgcag cctgtaatca cagaacaggt cagagacaga acctccttcc agctactcaa
1141 tcctggaacg tacacagtac aaataagagc ccgggaaaga gtgtatgaat tcttgagcgc
1201 ctggagcacc ccccagcgct tcgagtgcga ccaggaggag ggcgcaaaca cacgtgcctg
1261 gcggacgtcg ctgctgatcg cgctggggac gctgctggcc ctggtctgtg tcttcgtgat
1321 ctgcagaagg tatctggtga tgcagagact ctttccccgc atccctcaca tgaaagaccc
1381 catcggtgac agcttccaaa acgacaagct ggtggtctgg gaggcgggca aagccggcct
1441 ggaggagtgt ctggtgactg aagtacaggt cgtgcagaaa acttgagact ggggttcagg
1501 gcttgtgggg gtctgcctca atctccctgg ccgggccagg cgcctgcaca gactggctgc
1561 tggacctgcg cacgcagccc aggaatggac attcctaacg ggtggtgggc atgggagatg
1621 cctgtgtaat ttcgtccgaa gctgccagga agaagaacag aactttgtgt gtttatttca
1681 tgataaagtg attttttttt ttttaaccca aaaaaaaaaa aaaaaa

Figure 69A

MVLLWLTLLLIALPCLLQTKEDPNPPITNLRMKAKAQQLTWDLNRNVTDIECVKDADYSMP
AVNNSYCQFGAISLCEVTNYTVRVANPPFSTWILFPENSGKPWAGAENLTCWIHDVDFLSCS
WAVGPGAPADVQYDLYLNVANRRQQYECLHYKTDAQGTRIGCRFDDISRLSSGSQSSHILVR
GRSAAFGIPCTDKFVVFSQIEILTPPNMTAKCNKTHSFMHWKMRSHFNRKFRYELQIQKRMQ
PVITEQVRDRTSFQLLNPGTYTVQIRARERVYEFLSAWSTPQRFECDQEEGANTRAWRTSLLI
ALGTLLALVCVFVICRRYLVMQRLFPRIPHMKDPIGDSFQNDKLVVWEAGKAGLEECLVTEV
QVVQKT

Figure 69B

```
   1 gggaggagag aaaagccatg gccgacaagg tcctgaagga gaagagaaag ctgtttatcc
  61 gttccatggg tgaaggtaca ataaatggct tactggatga attattacag acaagggtgc
 121 tgaacaagga agagatggag aaagtaaaac gtgaaaatgc tacagttatg gataagaccc
 181 gagctttgat tgactccgtt attccgaaag gggcacaggc atgccaaatt tgcatcacat
 241 acatttgtga agaagacagt tacctggcag ggacgctggg actctcagca gctcctcagg
 301 cagtgcagga caacccagct atgcccacat cctcaggctc agaagggaat gtcaagcttt
 361 gctccctaga agaagctcaa aggatatgga aacaaaagtc ggcagagatt tatccaataa
 421 tggacaagtc aagccgcaca cgtcttgctc tcattatctg caatgaagaa tttgacagta
 481 ttcctagaag aactggagct gaggttgaca tcacaggcat gacaatgctg ctacaaaatc
 541 tggggtacag cgtagatgtg aaaaaaaatc tcactgcttc ggacatgact acagagctgg
 601 aggcatttgc acaccgccca gagcacaaga cctctgacag cacgttcctg gtgttcatgt
 661 ctcatggtat tcgggaaggc atttgtggga agaaacactc tgagcaagtc ccagatatac
 721 tacaactcaa tgcaatcttt aacatgttga ataccaagaa ctgcccaagt ttgaaggaca
 781 aaccgaaggt gatcatcatc caggcctgcc gtggtgacag ccctggtgtg gtgtggttta
 841 aagattcagt aggagtttct ggaaacctat ctttaccaac tacagaagag tttgaggatg
 901 atgctattaa gaaagcccac atagagaagg attttatcgc tttctgctct tccacaccag
 961 ataatgtttc ttggagacat cccacaatgg gctctgtttt tattggaaga ctcattgaac
1021 atatgcaaga atatgcctgt tcctgtgatg tggaggaaat tttccgcaag gttcgatttt
1081 catttgagca gccagatggt agagcgcaga tgcccaccac tgaaagagtg actttgacaa
1141 gatgtttcta cctcttccca ggacattaaa ataaggaaac tgtatgaatg tctgtgggca
1201 ggaagtgaag agatccttct gtaaaggttt ttggaattat gtctgctgaa taataaactt
1261 ttttgaaata ataaatctgg tagaaaaatg aaaaaaaaaa a
```

Figure 70A

MADKVLKEKRKLFIRSMGEGTINGLLDELLQTRVLNKEEMEKVKRENATVMDKTRALIDSVI
PKGAQACQICITYICEEDSYLAGTLGLSAAPQAVQDNPAMPTSSGSEGNVKLCSLEEAQRIWK
QKSAEIYPIMDKSSRTRLALIICNEEFDSIPRRTGAEVDITGMTMLLQNLGYSVDVKKNLTASD
MTTELEAFAHRPEHKTSDSTFLVFMSHGIREGICGKKHSEQVPDILQLNAIFNMLNTKNCPSL
KDKPKVIIIQACRGDSPGVVWFKDSVGVSGNLSLPTTEEFEDDAIKKAHIEKDFIAFCSSTPDN
VSWRHPTMGSVFIGRLIEHMQEYACSCDVEEIFRKVRFSFEQPDGRAQMPTTERVTLTRCFYL
FPGH

Figure 70B

```
   1 gagggcgcca tgaggagcct gtgctgcgcc ccactcctgc tcctcttgct gctgccgccg
  61 ctgctgctca cgccccgcgc tggggacgcc gccgtgatca ccggggcttg tgacaaggac
 121 tcccaatgtg gtggaggcat gtgctgtgct gtcagtatct gggtcaagag cataaggatt
 181 tgcacaccta tgggcaaact gggagacagc tgccatccac tgactcgtaa agttccattt
 241 tttgggcgga ggatgcatca cacttgccca tgtctgccag gcttggcctg tttacggact
 301 tcatttaacc gatttatttg tttagcccaa aagtaatcgc tctggagtag aaaccaaatg
 361 tgaatagcca catcttacct gtaaagtctt actgtgatt gtgccaaaca aaaaatgtgc
 421 cagaaagaaa tgctcttgct tcctcaactt tccaagtaac atttttatct ttgatttgta
 481 aatgatttit ttttttttt ttatcgaaag agaattttac ttttggatag aaatatgaag
 541 tgtaaggcat tatggaactg gttcttattt ccctgtttgt gttttggttt gatttggctt
 601 ttttcttaaa tgtcaaaaac gtacccattt tcacaaaaat gaggaaaata agaatttgat
 661 attttgttag aaaaacttit ttttttttt ctcaccaccc caagccccat ttgtgccctg
 721 ccgcacaaat acacctacag cttttggtcc cttgcctctt ccacctcaaa gaatttcaag
 781 gctcttacct tactttattt ttgtccattt ctcttccctc ctcttgcatt ttaaagtgga
 841 gggtttgtct ctttgagttt gatggcagaa tcactgatgg gaatccagct ttttgctggc
 901 atttaaatag tgaaaagagt gtatatgtga acttgacact ccaaactcct gtcatggcac
 961 ggaagctagg agtgctgctg gacccttcct aaacctgtca ctcaagagga cttcagctct
1021 gctgttgggc tggtgtgtgg acagaaggaa tggaaagcca aattaattta gtccagattt
1081 ctaggtttgg gtttttctaa aaataaaaga ttacatttac ttcttttact ttttataaag
1141 ttttttttcc ttagtctcct acttagagat attctagaaa atgtcacttg aagaggaagt
1201 atttatttta atctggcaca acactaatta ccatttttaa agcggtatta agttgtaatt
1261 taaaccttgt ttgtaactga aaggtcgatt gtaatggatt gccgtttgta cctgtatcag
1321 tattgctgtg taaaaattct gtatcagaat aataacagta ctgtatatca tttgatttat
1381 tttaatatta tatccttatt tttgtc
```

Figure 71A

MRSLCCAPLLLLLLLPPLLLTPRAGDAAVITGACDKDSQCGGGMCCAVSIWVKSIRICTPMG
KLGDSCHPLTRKVPFFGRRMHHTCPCLPGLACLRTSFNRFICLAQK

Figure 71B

ATAATACCTACCTTGCAGGACCACGACAGGATTAAGTGAGGAAAAACCCCCATGAGAGT
GTTTTGCCATTGTCAAGTGAGCCTGAGGGAGGCTGAGGGGGGATCAGGCTGTATCATGC
CCCCGAGGACAAACTTTCCAGTTTACCCTGCTCCCTCTCTCTGTCCCTAGGCTGCCCCAGG
CCCTGTGCAGACACACCAGGCCCTCAGCCGCAGCCCATGGACCTGCGGGTGGGCCAGCG
GCCCCCAGTGGAGCCCCCACCAGAGCCCACATTGCTGGCCCTGCAGCGTCCCCAGCGCCT
GCACCACCACCTCTTCCTAGCAGGCCTGCAGCAGCAGCGCTCGGTGGAGCCCATGAGGC
TCTCCATGGACACGCCGATGCCCGAGTTGCAGGTGGGACCCCAGGAACAAGAGCTGCGG
CAGCTTCTCCACAAGGACAAGAGCAAGCGAAGTGCTGTAGCCAGCAGCGTGGTCAAGCA
GAAGCTAGCGGAGGTGATTCTGAAAAAACAGCAGGCGGCCCTAGAAAGAACAGTCCATC
CCAACAGCCCCCGGCATTCCCTACAGAACCCTGGAGCCCCTGGAGACGGAAGGAGCCACC
CGCTCCATGCTCAGCAGCTTTTTGCCTCCTGTTCCCAGCCTGCCCAGTGACCCCCCAGAGC
ACTTCCCTCTGCGCAAGACAGTCTCTGAGCCCAACCTGAAGCTGCGCTATAAGCCCAAGA
AGTCCCTGGAGCGGAGGAAGAATCCACTGCTCCGAAAGGAGAGTGCGCCCCCCAGCCTC
CGGCGGCGGCCCGCAGAGACCCTCGGAGACTCCTCCCCAAGTAGTAGCAGCACGCCCGC
ATCAGGGTGCAGCTCCCCCAATGACAGCGAGCACGGCCCCAATCCCATCCTGGGCTCGG
AGGCGCTCTTGGGCCAGCGGCTGCGGCTGCAGGAGACTTCTGTGGCCCCGTTCGCCTTGC
CGACAGTGTCCTTGCTGCCCGCAATCACTCTGGGGCTGCCCGCCCCTGCCAGGGCTGACA
GTGACCGCAGGACCCATCCGACTCTGGGCCCTCGGGGGCCAATCCTGGGGAGCCCCCAC
ACTCCCCTCTTCCTGCCCCATGGCTTGGAGCCCGAGGCTGGGGGCACCTTGCCCTCTCGC
CTGCAGCCCATTCTCCTCCTGGACCCCTCAGGCTCTCATGCCCCCGCTGCTGACTGTGCCCG
GGCTTGGGCCCTTGCCCTTCCACTTTGCCCAGTCCTTAATGACCACCGAGCGGCTCTCTGG
GTCAGGCCTCCACTGGCCACTGAGCCGGACTCGCTCAGAGCCCCTGCCCCCCCAGTGCCAC
CGCTCCCCCACCGCCGGGCCCCATGCAGCCCCGCCTGGAGCAGCTCAAAACTCACGTCCA
GGTGATCAAGAGGTCAGCCAAGCCGAGTGAGAAGCCCCGGCTGCGGCAGATACCCTCGG
CTGAAGACCTGGAGACAGATGGCGGGGGACCGGGCCAGGTGGTGGACGATGGCCTGGA
GCACAGGGAGCTGGGCCATGGGCAGCCTGAGGCCAGAGGCCCCGCTCCTCTCCAGCAGC
ACCCTCAGGTGTTGCTCTGGGAACAGCAGCGACTGGCTGGGCGGCTCCCCCGGGGCAGC
ACCGGGGACACTGTGCTGCTTCCTCTGGCCCAGGGTGGGCACCGGCCTCTGTCCCGGGCT
CAGTCTTCCCCAGCCGCACCTGCCTCACTGTCAGCCCCAGAGCCTGCCAGCCAGGCCCGA
GTCCTCTCCAGCTCAGAGACCCCTGCCAGGACCCTGCCCTTCACCACAGGGCTGATCTAT
GACTCGGTCATGCTGAAGCACCAGTGCTCCTGCGGTGACAACAGCAGGCACCCGGAGCA
CGCCGGCCGCATCCAGAGCATCTGGTCCCGGCTGCAGGAGCGGGGGCTCCGGAGCCAGT
GTGAGTGTCTCCGAGGCCGGAAGGCCTCCCTGGAAGAGCTGCAGTCGGTCCACTCTGAG
CGGCACGTGCTCCTCTACGGCACCAACCCGCTCAGCCGCCTCAAACTGGACAACGGGAA
GCTGGCAGGGCTCCTGGCACAGCGGATGTTTGTGATGCTGCCCTGTGGTGGGGTTGGGGT
GGACACTGACACCATCTGGAATGAGCTTCATTCCTCCAATGCAGCCCGCTGGGCCGCTGG
CAGTGTCACTGACCTCGCCTTCAAAGTGGCTTCTCGTGAGCTAAAGAATGGTTTCGCTGT
GGTGCGGCCCCCAGGACACCATGCAGATCATTCAACAGCCATGGGCTTCTGCTTCTTCAA
CTCAGTGGCCATCGCCTGCCGGCAGCTGCAACAGCAGAGCAAGGCCAGCAAGATCCTCA
TTGTAGACTGGGACGTGCACCATGGCAACGGCACCCAGCAAACCTTCTACCAAGACCCC
AGTGTGCTCTACATCTCCCTGCATCGCCATGACGACGGCAACTTCTTCCCGGGGAGTGGG
GCTGTGGATGAGGTAGGGGCTGGCAGCGGTGAGGGCTTCAATGTCAATGTGGCCTGGGC
TGGAGGTCTGGACCCCCCCATGGGGGATCCTGAGTACCTGGCTGCTTTCAGGATAGTCGT
GATGCCCATCGCCCGAGAGTTCTCTCCAGACCTAGTCCTGGTGTCTGCTGGATTTGATGC
TGCTGAGGGTCACCCGGCCCCACTGGGTGGCTACCATGTTTCTGCCAAATGTTTTGGATA
CATGACGCAGCAACTGATGAACCTGGCAGGAGGCGCAGTGGTGCTGGCCTTGGAGGGTG
GCCATGACCTCACAGCCATCTGTGACGCCTCTGAGGCCTGTGTGGCTGCTCTTCTGGGTA
ACAGGGTGGATCCCCTTTCAGAAGAAGGCTGGAAACAGAAACCCAACCTCAATGCCATC
CGCTCTCTGGAGGCCGTGATCCGGGTGCACAGTAAATACTGGG

Figure 72A

GCTGCATGCAGCGCCTGGCCTCCTGTCCAGACTCCTGGGTGCCTAGAGTGCCAGGGGCTG
ACAAAGAAGAAGTGGAGGCAGTGACCGCACTGGCGTCCCTCTCTGTGGGCATCCTGGCT
GAAGATAGGCCCTCGGAGCAGCTGGTGGAGGAGGAAGAACCTATGAATCTCTAAGGCTC
TGGAACCATCTGCCCGCCCACCATGCCCTTGGGACCTGGTTCTCTTCTAACCCCTGGCAA
TAGCCCCCATTCCTGGGTCTTTAGAGATCCTGTGGGCAAGTAGTTGGAACCAGAGAACAG
CCTGCCTGCTTTGACAGTTATCCCAGGGAGCGTGAGAAAATCCCTGGGTCTAGAATGGGA
ACTGGAGAGGACCCTGAGAGGAGACGGGCTGGGCGGCGACCCCCACAGGGCTCTCGAG
AACAGATTCTCCCCTCCAGTATGGGCCCTGGCTGTGGCCCCCATTCCTCAGGACTGCACA
GAGGAGGACTGGCTCCGGCTCCGTCGGGCTCACCCTTAACCACTATTCCTGGCTCTGCAA
ACCCCAGACTTTGCACACAGCCCCAGGCTCCACACAGAAATGTGAACTTGGCCTCAGAC
AGGCTGGCCCTTCCTAGGCTCTAGGGGCTAGGGGGGAGTGGGGAGCCAAGAGGTCCCAT
ATTCCTGAGTGCAGGGGTAGTCCCTCTCACCTGCTTCCTCAGACGACTCTGGAAGCTTCC
CTCTACCACCGGGCACTGAGACGAAGCTCCCTGACAGCCGAGACTGGCAGCCCTCCATCT
GGTCCGTACCCTCGCCAGAGGCCCCCCTACATCAACCTCCTGGCGATGCCCTGGTGGAGC
AGATGGGTGCTCTGGGAGTCCTGTGCTTCCTGATCCAATGGTGCCAAACCCTTCATCTCC
CCCAGAAGCGCAGCATACCCCTGGGACCCCTCGGCCACTGCCCACTCGGGGAGCCTTCTC
TGTTTCTGGGGCCTCCCCCACCATAGCTCTGATTCCCACCCCACATAGGAATAGCCTGAC
TGAGGGGGAAGGGGTGGGAGAGAAGATACAGACATGGAGGAGGGGAGGCTGCTCTGGC
AAAGTCTTCAAGGCTTTTGGGGGTCCAGGCCTGGGGTCAAGAAGGAAAATGTGTGTGAG
CATGTGTGTGAGTGAGGCGTGTGTGTGAGCGTGTGTGTGAGTGAGGCGTGTGTGTGTGTC
TTTCCTAGGACCCACCATACCCTGTGTATGTATGCATGTTTTTGTAAAAAGGAAGAAAAT
GGAAAAAAATCTGAACAATAAATGTTTTATTTGCTTTAAAAAAAAAAAAAAAAA

Figure 72A (continued)

MDLRVGQRPPVEPPPEPTLLALQRPQRLHHHLFLAGLQQQRSVEPMRLSMDTPMPELQVGPQ
EQELRQLLHKDKSKRSAVASSVVKQKLAEVILKKQQAALERTVHPNSPGIPYRTLEPLETEGA
TRSMLSSFLPPVPSLPSDPPEHFPLRKTVSEPNLKLRYKPKKSLERRKNPLLRKESAPPSLRRRP
AETLGDSSPSSSSTPASGCSSPNDSEHGPNPILGSEALLGQRLRLQETSVAPFALPTVSLLPAITL
GLPAPARADSDRRTHPTLGPRGPILGSPHTPLFLPHGLEPEAGGTLPSRLQPILLLDPSGSHAPL
LTVPGLGPLPFHFAQSLMTTERLSGSGLHWPLSRTRSEPLPPSATAPPPPGPMQPRLEQLKTHV
QVIKRSAKPSEKPRLRQIPSAEDLETDGGGPGQVVDDGLEHRELGHGQPEARGPAPLQQHPQ
VLLWEQQRLAGRLPRGSTGDTVLLPLAQGGHRPLSRAQSSPAAPASLSAPEPASQARVLSSSE
TPARTLPFTTGLIYDSVMLKHQCSCGDNSRHPEHAGRIQSIWSRLQERGLRSQCECLRGRKAS
LEELQSVHSERHVLLYGTNPLSRLKLDNGKLAGLLAQRMFVMLPCGGVGVDTDTIWNELHS
SNAARWAAGSVTDLAFKVASRELKNGFAVVRPPGHHADHSTAMGFCFFNSVAIACRQLQQ
QSKASKILIVDWDVHHGNGTQQTFYQDPSVLYISLHRHDDGNFFPGSGAVDEVGAGSGEGFN
VNVAWAGGLDPPMGDPEYLAAFRIVVMPIAREFSPDLVLVSAGFDAAEGHPAPLGGYHVSA
KCFGYMTQQLMNLAGGAVVLALEGGHDLTAICDASEACVAALLGNRVDPLSEEGWKQKPN
LNAIRSLEAVIRVHSKYWGCMQRLASCPDSWVPRVPGADKEEVEAVTALASLSVGILAEDRP
SEQLVEEEEPMNL

Figure 72B

AGGAAACGGTTTATTAGGAGGGAGTGGTGGAGCTGGGCCAGGCAGGAAGACGCTGGAA
TAAGAAACATTTTTGCTCCAGCCCCCATCCCAGTCCCGGGAGGCTGCCGCGCCAGCTGCG
CCGAGCGAGCCCCTCCCCGGCTCCAGCCCGGTCCGGGGCCGCGCCGGACCCCAGCCCGC
CGTCCAGCGCTGGCGGTGCAACTGCGGCCGCGCGGTGGAGGGGAGGTGGCCCCGGTCCG
CCGAAGGCTAGCGCCCCGCCACCCGCAGAGCGGGCCCAGAGGGACCATGACCTTGGGCT
CCCCCAGGAAAGGCCTTCTGATGCTGCTGATGGCCTTGGTGACCCAGGGAGACCCTGTGA
AGCCGTCTCGGGGCCCGCTGGTGACCTGCACGTGTGAGAGCCCACATTGCAAGGGGCCT
ACCTGCCGGGGGGCCTGGTGCACAGTAGTGCTGGTGCGGGAGGAGGGGAGGCACCCCCA
GGAACATCGGGGCTGCGGGAACTTGCACAGGGAGCTCTGCAGGGGGCGCCCCACCGAGT
TCGTCAACCACTACTGCTGCGACAGCCACCTCTGCAACCACAACGTGTCCCTGGTGCTGG
AGGCCACCCAACCTCCTTCGGAGCAGCCGGGAACAGATGGCCAGCTGGCCCTGATCCTG
GGCCCCGTGCTGGCCTTGCTGGCCCTGGTGGCCCTGGGTGTCCTGGGCCTGTGGCATGTC
CGACGGAGGCAGGAGAAGCAGCGTGGCCTGCACAGCGAGCTGGGAGAGTCCAGTCTCAT
CCTGAAAGCATCTGAGCAGGGCGACACGATGTTGGGGGACCTCCTGGACAGTGACTGCA
CCACAGGGAGTGGCTCAGGGCTCCCCTTCCTGGTGCAGAGGACAGTGGCACGGCAGGTT
GCCTTGGTGGAGTGTGTGGGAAAAGGCCGCTATGGCGAAGTGTGGCGGGGCTTGTGGCA
CGGTGAGAGTGTGGCCGTCAAGATCTTCTCCTCGAGGGATGAACAGTCCTGGTTCCGGGA
GACTGAGATCTATAACACAGTATTGCTCAGACACGACAACATCCTAGGCTTCATCGCCTC
AGACATGACCTCCCGCAACTCGAGCACGCAGCTGTGGCTCATCACGCACTACCACGAGC
ACGGCTCCCTCTACGACTTTCTGCAGAGACAGACGCTGGAGCCCCATCTGGCTCTGAGGC
TAGCTGTGTCCGCGGCATGCGGCCTGGCGCACCTGCACGTGGAGATCTTCGGTACACAGG
GCAAACCAGCCATTGCCCACCGCGACTTCAAGAGCCGCAATGTGCTGGTCAAGAGCAAC
CTGCAGTGTTGCATCGCCGACCTGGGCCTGGCTGTGATGCACTCACAGGGCAGCGATTAC
CTGGACATCGGCAACAACCCGAGAGTGGGCACCAAGCGGTACATGGCACCCGAGGTGCT
GGACGAGCAGATCCGCACGGACTGCTTTGAGTCCTACAAGTGGACTGACATCTGGGCCTT
TGGCCTGGTGCTGTGGGAGATTGCCCGCCGGACCATCGTGAATGGCATCGTGGAGGACT
ATAGACCACCCTTCTATGATGTGGTGCCCAATGACCCCAGCTTTGAGGACATGAAGAAG
GTGGTGTGTGTGGATCAGCAGACCCCCACCATCCCTAACCGGCTGGCTGCAGACCCGGTC
CTCTCAGGCCTAGCTCAGATGATGCGGGAGTGCTGGTACCCAAACCCCTCTGCCCGACTC
ACCGCGCTGCGGATCAAGAAGACACTACAAAAAATTAGCAACAGTCCAGAGAAGCCTAA
AGTGATTCAATAGCCCAGGAGCACCTGATTCCTTTCTGCCTGCAGGGGGCTGGGGGGGTG
GGGGGCAGTGGATGGTGCCCTATCTGGGTAGAGGTAGTGTGAGTGTGGTGTGTGCTGGG
GATGGGCAGCTGCGCCTGCCTGCTCGGCCCCCAGCCCACCCAGCCAAAAATACAGCTGG
GCTGAAACCTG

Figure 73A

MTLGSPRKGLLMLLMALVTQGDPVKPSRGPLVTCTCESPHCKGPTCRGAWCTVVLVREEGR
HPQEHRGCGNLHRELCRGRPTEFVNHYCCDSHLCNHNVSLVLEATQPPSEQPGTDGQLALIL
GPVLALLALVALGVLGLWHVRRRQEKQRGLHSELGESSLILKASEQGDTMLGDLLDSDCTT
GSGSGLPFLVQRTVARQVALVECVGKGRYGEVWRGLWHGESVAVKIFSSRDEQSWFRETEI
YNTVLLRHDNILGFIASDMTSRNSSTQLWLITHYHEHGSLYDFLQRQTLEPHLALRLAVSAAC
GLAHLHVEIFGTQGKPAIAHRDFKSRNVLVKSNLQCCIADLGLAVMHSQGSDYLDIGNNPRV
GTKRYMAPEVLDEQIRTDCFESYKWTDIWAFGLVLWEIARRTIVNGIVEDYRPPFYDVVPND
PSFEDMKKVVCVDQQTPTIPNRLAADPVLSGLAQMMRECWYPNPSARLTALRIKKTLQKISN
SPEKPKVIQ

Figure 73B

CGGAAACTTGGGGGAGTGCACAGAAGAACTTCGGGAGCGCACGCGGGACCAGGGACCA
GGCTGAGACTCGGGGCGCCAGTCCGGGCAGGGGCAGCGGGACGCGGCCGGAGATGCCC
TGTATCCAAGCCCAATATGGGACACCAGCACCGAGTCCGGGACCCCGTGACCACCTGGC
AAGCGACCCCCTGACCCCTGAGTTCATCAAGCCCACCATGGACCTGGCCAGCCCCGAGG
CAGCCCCCGCTGCCCCCACTGCCCTGCCCAGCTTCAGCACGTTCATGGACGGCTACACAG
GAGAGTTTGACACCTTCCTCTACCAGCTGCCAGGAACAGTCCAGCCATGCTCCTCAGCCT
CCTCCTCGGCCTCCTCCACATCCTCGTCCTCAGCCACCTCCCCTGCCTCTGCCTCCTTCAA
GTTCGAGGACTTCCAGGTGTACGGCTGCTACCCCGGCCCCCTGAGCGGCCCAGTGGATGA
GGCCCTGTCCTCCAGTGGCTCTGACTACTATGGCAGCCCCTGCTCGGCCCCGTCGCCCTC
CACGCCCAGCTTCCAGCCGCCCCAGCTCTCTCCCTGGGATGGCTCCTTCGGCCACTTCTCG
CCCAGCCAGACTTACGAAGGCCTGCGGGCATGGACAGAGCAGCTGCCCAAAGCCTCTGG
GCCCCCACAGCCTCCAGCCTTCTTTTCCTTCAGTCCTCCCACTGGCCCCAGCCCCAGCCTG
GCCCAGAGCCCCCTGAAGTTGTTCCCCTCACAGGCCACCCACCAGCTGGGGGAGGGAGA
GAGCTATTCCATGCCTACGGCCTTCCCAGGTTTGGCACCCACTTCTCCACACCTTGAGGG
CTCGGGGATACTGGATACACCCGTGACCTCAACCAAGGCCCGGAGCGGGGCCCCAGGTC
CAAGTGAAGGCCGCTGTGCTGTGTGTGGGGACAACGCTTCATGCCAGCATTATGGTGTCC
GCACATGTGAGGGCTGCAAGGGCTTCTTCAAGCGCACAGTGCAGAAAAACGCCAAGTAC
ATCTGCCTGGCTAACAAGGACTGCCCTGTGGACAAGAGGCGGCGAAACCGCTGCCAGTT
CTGCCGCTTCCAGAAGTGCCTGGCGGTGGGCATGGTGAAGGAAGTTGTCCGAACAGACA
GCCTGAAGGGGCGGCGGGGCCGGCTACCTTCAAAACCCAAGCAGCCCCCAGATGCCTCC
CCTGCCAATCTCCTCACTTCCCTGGTCCTTGCACACCTGGATTCAGGGCCCAGCACTGCC
AAACTGGACTACTCCAAGTTCCAGGAGCTGGTGCTGCCCCACTTTGGGAAGGAAGATGC
TGGGGATGTACAGCAGTTCTACGACCTGCTCTCCGGTTCTCTGGAGGTCATCCGAAAGTG
GGCGGAGAAGATCCCTGGCTTTGCTGAGCTGTCACCGGCTGACCAGGACCTGTTGCTGGA
GTCGGCCTTCCTGGAGCTCTTCATCCTCCGCCTGGCGTACAGGTCTAAGCCAGGCGAGGG
CAAGCTCATCTTCTGCTCAGGCCTGGTGCTACACCGGCTGCAGTGTGCCCGTGGCTTCGG
GGACTGGATTGACAGTATCCTGGCCTTCTCAAGGTCCCTGCACAGCTTGCTTGTCGATGT
CCCTGCCTTCGCCTGCCTCTCTGCCCTTGTCCTCATCACCGACCGGCATGGGCTGCAGGA
GCCGCGGCGGGTGGAGGAGCTGCAGAACCGCATCGCCAGCTGCCTGAAGGAGCACGTGG
CAGCTGTGGCGGGCGAGCCCCAGCCAGCCAGCTGCCTGTCACGTCTGTTGGGCAAACTG
CCCGAGCTGCGGACCCTGTGCACCCAGGGCCTGCAGCGCATCTTCTACCTCAAGCTGGAG
GACTTGGTGCCCCCTCCACCCATCATTGACAAGATCTTCATGGACACGCTGCCCTTCTGA
CCCCTGCCTGGGAACACGTGTGCACATGCGCACTCTCATATGCCACCCCATGTGCCTTTA
GTCCACGGACCCCCAGAGCACCCCCAAGCCTGGGCTTGAGCTGCAGAATGACTCCACCTT
CTCACCTGCTCCAGGAGGTTTGCAGGGAGCTCAAGCCCTTGGGGAGGGGGATGCCTTCAT
GGGGGTGACCCCACGATTTGTCTTATCCCCCCCAGCCTGGCCCCGGCCTTTATGTTTTTTG
TAAGATAAACCGTTTTTAACACATAGCGCCGTGCTGTAAATAAGCCCAGTGCTGCTGTAA
ATACAGGAAGAAAGAGCTTGAGGTGGGAGCGGGGCTGGGAGGAAGGGATGGGCCCCGC
CTTCCTGGGCAGCCTTTCCAGCCTCCTGCCTGGCTCTCTCTTCCTACCCTCCTTCCACATGT
ACATAAACTGTCACTCTAGGAAGAAGACAAATGACAGATTCTGACATTTATATTTGTGTA
TTTTCCTGGATTTATAGTATGTGACTTTTCTGATTAATATATTTAATATATTGAATAAAAA
ATAGACATGTAGTTG

Figure 74A (continued)

MPCIQAQYGTPAPSPGPRDHLASDPLTPEFIKPTMDLASPEAAPAAPTALPSFSTFMDGYTGEF
DTFLYQLPGTVQPCSSASSSASSTSSSSATSPASASFKFEDFQVYGCYPGPLSGPVDEALSSSGS
DYYGSPCSAPSPSTPSFQPPQLSPWDGSFGHFSPSQTYEGLRAWTEQLPKASGPPQPPAFFSFS
PPTGPSPSLAQSPLKLFPSQATHQLGEGESYSMPTAFPGLAPTSPHLEGSGILDTPVTSTKARSG
APGPSEGRCAVCGDNASCQHYGVRTCEGCKGFFKRTVQKNAKYICLANKDCPVDKRRRNR
CQFCRFQKCLAVGMVKEVVRTDSLKGRRGRLPSKPKQPPDASPANLLTSLVLAHLDSGPSTA
KLDYSKFQELVLPHFGKEDAGDVQQFYDLLSGSLEVIRKWAEKIPGFAELSPADQDLLLESAF
LELFILRLAYRSKPGEGKLIFCSGLVLHRLQCARGFGDWIDSILAFSRSLHSLLVDVPAFACLS
ALVLITDRHGLQEPRRVEELQNRIASCLKEHVAAVAGEPQPASCLSRLLGKLPELRTLCTQGL
QRIFYLKLEDLVPPPPIIDKIFMDTLPF

Figure 74B

AGAAACTCACACACCTTGACAATCTGTCTGTCCGTCTGCAGCTGCGTGACTGTCTGTCTCT
GCCATGTCTCTCTCCCCATGCCGGGCCCAGAGGGGCTTCAGCGCTCGCTCAGCCTGTTCT
GCTCGCTCAAGGGGCCGCAGCAGGGGAGGCTTCAGCAGCAGGGGCGGCTTCAGCAGCAG
GAGCCTTAATTCCTTTGGGGGGTGCCTGGAAGGCTCTCGTGGGAGTACCTGGGGGTCAGG
GGGTAGGCTGGGGGTGCGGTTTGGGGAGTGGAGTGGTGGGCCTGGGCTCTCCCTGTGCC
CTCCGGGGGGCATCCAAGAAGTGACCATCAACCAGAATCCGCTGACCCCACTGAAGATT
GAGATCGATCCCCAGTTCCAGGTGGTGCGGACGCAGGAGACCCAGGAGATCAGAACCCT
CAACAACCAGTTTGCTTCCTTCATTGACAAGGTGCGGTTCCTGGAGCAGCAGAACAAGGT
CCTGGAGACGAAGTGGCATCTGCTGCAGCAACAGGGGTTGAGTGGCAGCCAGCAGGGCC
TGGAGCCTGTCTTTGAGGCCTGCCTGGATCAGCTCAGGAAGCAGCTGGAGCAGCTCCAG
GGAGAACGAGGGGCTCTGGATGCTGAGTTGAAGGCCTGCCGGGACCAGGAGGAGGAGT
ATAAGTCCAAGTATGAGGAGGAGGCCCACAGGCGTGCCACACTTGAGAACGACTTTGTG
GTCCTCAAGAAGGATGTGGATGGGGTTTTCCTGAGCAAGATGGAGTTGGAGGGCAAGCT
GGAGGCTCTGAGAGAGTACCTCTACTTCTTGAAGCATCTGAATGAAGAAGAGCTGGGCC
AGCTCCAGGCCCAGGCCAGCGACACGTCTGTGGTGCTGTCCATGGACAACAACCGCTAC
CTGGACTTCAGCAGCATCATCACTGAGGTCCGCGCCCGGTACGAGGAGATCGCCCGGAG
CAGCAAGGCTGAGGCTGAGGCCTTGTACCAGACCAAGTACCAGGAACTTCAGGTGTCTG
CCCAGCTTCATGGGGACAGGATGCAGGAAACGAAAGTCCAGATCTCTCAGCTACACCAA
GAGATTCAGAGGCTGCAGAGTCAGACTGAGAACCTCAAGAAGCAGAACGCCAGCCTGCA
GGCCGCCATCACTGATGCTGAGCAGCGTGGGGAGCTGGCCCTCAAGGACGCTCAGGCCA
AGGTGGACGAGCTGGAGGCTGCTCTGAGGATGGCCAAGCAGAACCTGGCCCGGCTGCTG
TGCGAGTACCAGGAGCTGACGAGCACGAAGCTTTCCCTGGATGTGGAGATTGCCACTTA
CCGCAGGCTGCTGGAGGGCGAGGAGTGCAGGATGTCTGGGGAGTGCACCAGCCAGGTCA
CTATCTCCTCGGTGGGAGGCAGCGCTGTCATGTCTGGAGGAGTTGGTGGAGGCTTGGGG
AGCACTTGTGGACTCGGTAGTGGGAAAGGCAGCCCTGGGTCCTGCTGCACCAGCATTGT
GACTGGAGGCTCCAACATCATTCTGGGCTCTGGGAAGGACCCTGTTTTGGATTCCTGCTC
TGTGTCTGGCTCCAGCGCTGGCTCCAGCTGCCACACCATCCTGAAGAAGACAGTTGAGTC
GAGTCTGAAGACATCCATCACCTACTGAGCGACCCAGCAGCCACCTCCTTCCTGAACACA
TTTGGCCCACTCCCCCCATCAGCCGGCTCTGCAAGGCCAACTCCGTGTCCGCTGCCCACA
GCCCAAGCCAGCCCACAGCGGATGCTGCAAAAATCAATAAAGTCTCCCCTCCTGCTGTTC
TGAATGCTCTAAGTGCTTGCACACCTCACCCAGCAAAACAAAAGCTGTGTGGCTCCCCAG
CTTCCTCTCCTCGGAAGGCAATTGTGGCATATCTGTGTCCAGACGTGTTCTATTGGTATCT
CACTCCACATCCCAGCCACTCTATCAAGGAAACTAAATTCATCCAAGGTAGTTCAATTAA
ATTGACTTTTTGAAAAGT

Figure 75A

MSLSPCRAQRGFSARSACSARSRGRSRGGFSSRGGFSSRSLNSFGGCLEGSRGSTWGSGGRLG
VRFGEWSGGPGLSLCPPGGIQEVTINQNPLTPLKIEIDPQFQVVRTQETQEIRTLNNQFASFIDK
VRFLEQQNKVLETKWHLLQQQGLSGSQQGLEPVFEACLDQLRKQLEQLQGERGALDAELKA
CRDQEEEYKSKYEEEAHRRATLENDFVVLKKDVDGVFLSKMELEGKLEALREYLYFLKHLN
EEELGQLQAQASDTSVVLSMDNNRYLDFSSIITEVRARYEEIARSSKAEAEALYQTKYQELQV
SAQLHGDRMQETKVQISQLHQEIQRLQSQTENLKKQNASLQAAITDAEQRGELALKDAQAK
VDELEAALRMAKQNLARLLCEYQELTSTKLSLDVEIATYRRLLEGEECRMSGECTSQVTISSV
GGSAVMSGGVGGGLGSTCGLGSGKGSPGSCCTSIVTGGSNIILGSGKDPVLDSCSVSGSSAGS
SCHTILKKTVESSLKTSITY

Figure 75B

GAGGGAAGAACACAATGGATCTGGTGCTAAAAAGATGCCTTCTTCATTTGGCTGTGATA
GGTGCTTTGCTGGCTGTGGGGGCTACAAAAGTACCCAGAAACCAGGACTGGCTTGGTGT
CTCAAGGCAACTCAGAACCAAAGCCTGGAACAGGCAGCTGTATCCAGAGTGGACAGAAG
CCCAGAGACTTGACTGCTGGAGAGGTGGTCAAGTGTCCCTCAAGGTCAGTAATGATGGG
CCTACACTGATTGGTGCAAATGCCTCCTTCTCTATTGCCTTGAACTTCCCTGGAAGCCAAA
AGGTATTGCCAGATGGGCAGGTTATCTGGGTCAACAATACCATCATCAATGGGAGCCAG
GTGTGGGGAGGACAGCCAGTGTATCCCCAGGAAACTGACGATGCCTGCATCTTCCCTGAT
GGTGGACCTTGCCCATCTGGCTCTTGGTCTCAGAAGAGAAGCTTTGTTTATGTCTGGAAG
ACCTGGGGCCAATACTGGCAAGTTCTAGGGGGCCCAGTGTCTGGGCTGAGCATTGGGAC
AGGCAGGGCAATGCTGGGCACACACACCATGGAAGTGACTGTCTACCATCGCCGGGGAT
CCCGGAGCTATGTGCCTCTTGCTCATTCCAGCTCAGCCTTCACCATTACTGACCAGGTGCC
TTTCTCCGTGAGCGTGTCCCAGTTGCGGGCCTTGGATGGAGGGAACAAGCACTTCCTGAG
AAATCAGCCTCTGACCTTTGCCCTCCAGCTCCATGACCCCAGTGGCTATCTGGCTGAAGC
TGACCTCTCCTACACCTGGGACTTTGGAGACAGTAGTGGAACCCTGATCTCTCGGGCACT
TGTGGTCACTCATACTTACCTGGAGCCTGGCCCAGTCACTGCCCAGGTGGTCCTGCAGGC
TGCCATTCCTCTCACCTCCTGTGGCTCCTCCCCAGTTCCAGGCACCACAGATGGGCACAG
GCCAACTGCAGAGGCCCCTAACACCACAGCTGGCCAAGTGCCTACTACAGAAGTTGTGG
GTACTACACCTGGTCAGGCGCCAACTGCAGAGCCCTCTGGAACCACATCTGTGCAGGTGC
CAACCACTGAAGTCATAAGCACTGCACCTGTGCAGATGCCAACTGCAGAGAGCACAGGT
ATGACACCTGAGAAGGTGCCAGTTTCAGAGGTCATGGGTACCACACTGGCAGAGATGTC
AACTCCAGAGGCTACAGGTATGACACCTGCAGAGGTATCAATTGTGGTGCTTTCTGGAAC
CACAGCTGCACAGGTAACAACTACAGAGTGGGTGGAGACCACAGCTAGAGAGCTACCTA
TCCCTGAGCCTGAAGGTCCAGATGCCAGCTCAATCATGTCTACGGAAAGTATTACAGGTT
CCCTGGGCCCCCTGCTGGATGGTACAGCCACCTTAAGGCTGGTGAAGAGACAAGTCCCC
CTGGATTGTGTTCTGTATCGATATGGTTCCTTTTCCGTCACCCTGGACATTGTCCAGGGTA
TTGAAAGTGCCGAGATCCTGCAGGCTGTGCCGTCCGGTGAGGGGGATGCATTTGAGCTG
ACTGTGTCCTGCCAAGGCGGGCTGCCCAAGGAAGCCTGCATGGAGATCTCATCGCCAGG
GTGCCAGCCCCCTGCCCAGCGGCTGTGCCAGCCTGTGCTACCCAGCCCAGCCTGCCAGCT
GGTTCTGCACCAGATACTGAAGGGTGGCTCGGGGACATACTGCCTCAATGTGTCTCTGGC
TGATACCAACAGCCTGGCAGTGGTCAGCACCCAGCTTATCATGCCTGGTCAAGAAGCAG
GCCTTGGGCAGGTTCCGCTGATCGTGGGCATCTTGCTGGTGTTGATGGCTGTGGTCCTTG
CATCTCTGATATATAGGCGCAGACTTATGAAGCAAGACTTCTCCGTACCCCAGTTGCCAC
ATAGCAGCAGTCACTGGCTGCGTCTACCCCGCATCTTCTGCTCTTGTCCCATTGGTGAGA
ACAGCCCCCTCCTCAGTGGGCAGCAGGTCTGAGTACTCTCATATGATGCTGTGATTTTCC
TGGAGTTGACAGAAACACCTATATTTCCCCCAGTCTTCCCTGGGAGACTACTATTAACTG
AAATAAATACTCAGAGCCTGA

Figure 76A

MDLVLKRCLLHLAVIGALLAVGATKVPRNQDWLGVSRQLRTKAWNRQLYPEWTEAQRLD
CWRGGQVSLKVSNDGPTLIGANASFSIALNFPGSQKVLPDGQVIWVNNTIINGSQVWGGQPV
YPQETDDACIFPDGGPCPSGSWSQKRSFVYVWKTWGQYWQVLGGPVSGLSIGTGRAMLGT
HTMEVTVYHRRGSRSYVPLAHSSSAFTITDQVPFSVSVSQLRALDGGNKHFLRNQPLTFALQ
LHDPSGYLAEADLSYTWDFGDSSGTLISRALVVTHTYLEPGPVTAQVVLQAAIPLTSCGSSPV
PGTTDGHRPTAEAPNTTAGQVPTTEVVGTTPGQAPTAEPSGTTSVQVPTTEVISTAPVQMPTA
ESTGMTPEKVPVSEVMGTTLAEMSTPEATGMTPAEVSIVVLSGTTAAQVTTTEWVETTAREL
PIPEPEGPDASSIMSTESITGSLGPLLDGTATLRLVKRQVPLDCVLYRYGSFSVTLDIVQGIESA
EILQAVPSGEGDAFELTVSCQGGLPKEACMEISSPGCQPPAQRLCQPVLPSPACQLVLHQILKG
GSGTYCLNVSLADTNSLAVVSTQLIMPGQEAGLGQVPLIVGILLVLMAVVLASLIYRRRLMK
QDFSVPQLPHSSSHWLRLPRIFCSCPIGENSPLLSGQQV

Figure 76B

GCCTGTCGCAGGCGTGCAGGGACCTGGACTCCGCCTCGTCCCCGGGGCTCGGGCAGCCG
AGCCATGGCGGGGAACTGTGGGGCCCGCGGCGCGCTGTCGGCGCACACGCTGCTGTTCG
ACCTGCCGCCCGCGCTGCTCGGAGAGCTCTGCGCTGTTCTGGACAGCTGCGACGGCGCGC
TGGGCTGGCGCGGCCTGGCAGAGAGACTTTCAAGCAGCTGGCTGGATGTTCGTCATATTG
AAAAGTATGTAGACCAAGGTAAAAGTGGAACAAGAGAATTACTTTGGTCCTGGGCACAG
AAAAACAAGACCATCGGTGACCTTTTACAGGTCCTCCAGGAGATGGGACATCGTCGAGC
TATTCATTTAATTACAAACTATGGAGCAGTGTTGAGTCCTTCAGAGAAGAGTTATCAGGA
AGGTGGATTTCCAAATATATTATTCAAGGAAACAGCCAATGTCACCGTGGATAATGTTCT
TATTCCTGAACATAATGAAAAAGGAGTACTGCTTAAATCTTCCATCAGCTTTCAAAATAT
CATAGAAGGAACTAGAAATTTCCACAAAGACTTCCTAATTGGAGAAGGAGAGATTTTTG
AGGTATACAGAGTGGAGATTCAAAACCTAACATATGCTGTCAAATTATTTAAACAGGAG
AAAAAAATGCAGTGTAAGAAGCATTGGAAGAGGTTTTTATCTGAGCTTGAAGTTTTACTA
CTGTTTCATCACCCAAACATACTAGAGTTGGCTGCATATTTTACAGAGACTGAGAAGTTC
TGTCTGATTTATCCATACATGAGAAATGGAACACTTTTTGACAGATTGCAGTGTGTAGGT
GACACGGCCCCACTCCCTTGGCACATTCGAATCGGTATATTAATAGGAATATCCAAAGCC
ATTCACTACCTGCACAACGTTCAACCATGCTCGGTCATCTGTGGCAGTATATCAAGTGCA
AACATCCTTTTGGATGATCAGTTTCAACCCAAACTAACTGATTTTGCCATGGCACACTTCC
GGTCCCACCTAGAACATCAGAGTTGTACCATAAATATGACCAGCAGCAGCAGTAAACAT
CTGTGGTACATGCCAGAAGAGTACATCAGACAGGGGAAACTTTCCATTAAAACAGATGT
CTACAGCTTTGGAATTGTAATAATGGAAGTTCTAACAGGATGTAGAGTAGTGTTAGATGA
TCCAAAACATATCCAGCTGCGGGATCTCCTTAGAGAATTGATGGAGAAGAGAGGCCTGG
ATTCATGTCTCTCATTTCTAGATAAGAAAGTGCCTCCCTGCCCTCGGAATTTCTCTGCCAA
GCTCTTCTGTTTGGCAGGCCGGTGTGCTGCAACGCGGGCAAAGTTAAGACCATCAATGGA
TGAAGTTTTAAATACTCTTGAAAGTACTCAAGCCAGCTTGTATTTTGCTGAAGATCCTCCC
ACATCACTAAAGTCCTTCAGGTGTCCTTCTCCTCTATTCCTGGAGAATGTACCAAGTATTC
CAGTGGAAGATGATGAAAGCCAGAATAACAATTTACTACCTTCTGATGAAGGCCTGAGG
ATAGACAGAATGACTCAGAAAACTCCTTTTGAATGCAGCCAGTCTGAGGTTATGTTTCTG
AGCTTGGACAAAAAGCCAGAGAGCAAGAGAAATGAGGAAGCTTGCAACATGCCCAGTT
CTTCTTGTGAAGAAAGTTGGTTCCCAAAGTATATAGTTCCATCCCAGGACTTAAGGCCCT
ATAAGGTAAATATAGATCCTTCTTCAGAAGCTCCAGGGCATTCTTGCAGGAGCAGGCCA
GTGGAGAGCAGCTGTTCCTCCAAATTTTCCTGGGATGAATATGAACAGTACAAAAAAGA
ATAAATTCTACCAGAAGATAAAGAAAAAAGCAAGT

Figure 77A

ATTGCATAGGCACCTGAGCATAGGTATGACCTTGGGAAGACATTGGCTCCATAAGCAAT
GCCAAGAGAATGATCAATAGTGAGTTTGGGTGATGCAGATAAACAATCTGGATAATTCC
ATTTCTTTTTTCCCAAACCCTCAAACAGAGTGCCTTAAAAAATTGTTTTATCAGGATAATT
GTCTCATGACCAAATCCACGCTCAATTAGAGCCATTCAAAATTCCTTAAGATCATGGGTT
CTGACTTCAGCCAAACAAAACAATCAAAACCTACCAAAAAGGGACTGGATTGTAATGTC
CTCTCCATCATCCTCAGTGTGAGTCCTCAGAGCCTCCATCTGCCAAGAACATTCAGTTGG
ATTCCATCGTTTGGTTTAGCTTGCTTGCACGGGTTGTAGGAAATG

Figure 77A (continued)

MAGNCGARGALSAHTLLFDLPPALLGELCAVLDSCDGALGWRGLAERLSSSWLDVRHIEKY
VDQGKSGTRELLWSWAQKNKTIGDLLQVLQEMGHRRAIHLITNYGAVLSPSEKSYQEGGFP
NILFKETANVTVDNVLIPEHNEKGVLLKSSISFQNIIEGTRNFHKDFLIGEGEIFEVYRVEIQNLT
YAVKLFKQEKKMQCKKHWKRFLSELEVLLLFHHPNILELAAYFTETEKFCLIYPYMRNGTLF
DRLQCVGDTAPLPWHIRIGILIGISKAIHYLHNVQPCSVICGSISSANILLDDQFQPKLTDFAMA
HFRSHLEHQSCTINMTSSSSKHLWYMPEEYIRQGKLSIKTDVYSFGIVIMEVLTGCRVVLDDP
KHIQLRDLLRELMEKRGLDSCLSFLDKKVPPCPRNFSAKLFCLAGRCAATRAKLRPSMDEVL
NTLESTQASLYFAEDPPTSLKSFRCPSPLFLENVPSIPVEDDESQNNNLLPSDEGLRIDRMTQKT
PFECSQSEVMFLSLDKKPESKRNEEACNMPSSSCEESWFPKYIVPSQDLRPYKVNIDPSSEAPG
HSCRSRPVESSCSSKFSWDEYEQYKKE

Figure 77B

CTGATAAACTAATTGCCTCACATTGTCACTGCAAATCGACACCTATTAATGGGTCTCACC
TCCCAACTGCTTCCCCCTCTGTTCTTCCTGCTAGCATGTGCCGGCAACTTTGTCCACGGAC
ACAAGTGCGATATCACCTTACAGGAGATCATCAAAACTTTGAACAGCCTCACAGAGCAG
AAGACTCTGTGCACCGAGTTGACCGTAACAGACATCTTTGCTGCCTCCAAGAACACAACT
GAGAAGGAAACCTTCTGCAGGGCTGCGACTGTGCTCCGGCAGTTCTACAGCCACCATGA
GAAGGACACTCGCTGCCTGGGTGCGACTGCACAGCAGTTCCACAGGCACAAGCAGCTGA
TCCGATTCCTGAAACGGCTCGACAGGAACCTCTGGGGCCTGGCGGGCTTGAATTCCTGTC
CTGTGAAGGAAGCCAACCAGAGTACGTTGGAAAACTTCTTGGAAAGGCTAAAGACGATC
ATGAGAGAGAAATATTCAAAGTGTTCGAGCTGAATATTTTAATTTATGAGTTTTTGATAG
CTTTATTTTTTAAGTATTTATATATTTATAACTCATCATAAAATAAAGTATATATAGAATC
TAA

Figure 78A

MGLTSQLLPPLFFLLACAGNFVHGHKCDITLQEIIKTLNSLTEQKTLCTELTVTDIFAASKNTT
EKETFCRAATVLRQFYSHHEKDTRCLGATAQQFHRHKQLIRFLKRLDRNLWGLAGLNSCPV
KEANQSTLENFLERLKTIMREKYSKCSS

Figure 78B

AAGCCACCCAGCCTATGCATCCGCTCCTCAATCCTCTCCTGTTGGCACTGGGCCTCATGG
CGCTTTTGTTGACCACGGTCATTGCTCTCACTTGCCTTGGCGGCTTTGCCTCCCCAGGCCC
TGTGCCTCCCTCTACAGCCCTCAGGGAGCTCATTGAGGAGCTGGTCAACATCACCCAGAA

CCAGAAGGCTCCGCTCTGCAATGGCAGCATGGTATGGAGCATCAACCTGACAGCTGGCA
TGTACTGTGCAGCCCTGGAATCCCTGATCAACGTGTCAGGCTGCAGTGCCATCGAGAAGA
CCCAGAGGATGCTGAGCGGATTCTGCCCGCACAAGGTCTCAGCTGGGCAGTTTTCCAGCT
TGCATGTCCGAGACACCAAAATCGAGGTGGCCCAGTTTGTAAAGGACCTGCTCTTACATT
TAAAGAAACTTTTTCGCGAGGGACGGTTCAACTGAAACTTCGAAAGCATCATTATTTGCA
GAGACAGGACCTGACTATTGAAGTTGCAGATTCATTTTTCTTTCTGATGTCAAAAATGTC
TTGGGTAGGCGGGAAGGAGGGTTAGGGAGGGGTAAAATTCCTTAGCTTAGACCTCAGCC
TGTGCTGCCCGTCTTCAGCCTAGCCGACCTCAGCCTTCCCCTTGCCCAGGGCTCAGCCTG
GTGGGCCTCCTCTGTCCAGGGCCCTGAGCTCGGTGGACCCAGGGATGACATGTCCCTACA
CCCCTCCCCTGCCCTAGAGCACACTGTAGCATTACAGTGGGTGCCCCCCTTGCCAGACAT
GTGGTGGGACAGGGACCCACTTCACACACAGGCAACTGAGGCAGACAGCAGCTCAGGCA
CACTTCTTCTTGGTCTTATTTATTATTGTGTGTTATTTAAATGAGTGTGTTTGTCACCGTTG
GGGATTGGGGAAGACTGTGGCTGCTGGCACTTGGAGCCAAGGGTTCAGAGACTCAGGGC
CCCAGCACTAAAGCAGTGGACCCCAGGAGTCCCTGGTAATAAGTACTGTGTACAGAATT
CTGCTACCTCACTGGGGTCCTGGGGCCTCGGAGCCTCATCCGAGGCAGGGTCAGGAGAG
GGGCAGAACAGCCGCTCCTGTCTGCCAGCCAGCAGCCAGCTCTCAGCCAACGAGTAATT
TATTGTTTTTCCTCGTATTTAAATATTAAATATGTTAGCAAAGAGTTAATATATAGAAGG
GTACCTTGAACACTGGGGGAGGGGACATTGAACAAGTTGTTTCATTGACTATCAAACTGA
AGCCAGAAATAAAGTTGGTGACAGAT

Figure 79A

MALLLTTVIALTCLGGFASPGPVPPSTALRELIEELVNITQNQKAPLCNGSMVWSINLTAGMY
CAALESLINVSGCSAIEKTQRMLSGFCPHKVSAGQFSSLHVRDTKIEVAQFVKDLLLHLKKLF
REGRFN

Figure 79B

TGCGGAGTTTTGGAATAGAGGACAAAGATAAGCACGCCCAGAATGCTCATCTTTTCGGTC
CGGGACATGTTTGCAAAGATGAGCATTCTGGGCGTGCGGAGTTTTGGAATAGAGGACAA
AGATAAGCAAATTATCACTTTCTTCAGCCCCCTTACAATTTTGGTTGGACCCAATGGGGC
GGGAAAGACGACCATCATTGAATGTCTAAAATATATTTGTACTGGAGATTTCCCTCCTGG
AACCAAAGGAAATACATTTGTACACGATCCCAAGGTTGCTCAAGAAACAGATGTGAGAG
CCCAGATTCGTCTGCAATTTCGTGATGTCAATGGAGAACTTATAGCTGTGCAAAGATCTA
TGGTGTGTACTCAGAAAAGCAAAAAGACAGAATTTAAAACCCTGGAAGGAGTCATTACT
AGAACAAAGCATGGTGAAAAGGTCAGTCTGAGCTCTAAGTGTGCAGAAATTGACCGAGA
AATGATCAGTTCTCTTGGGGTTTCCAAGGCTGTGCTAAATAATGTCATTTTCTGTCATCAA
GAAGATTCTAATTGGCCTTTAAGTGAGGGAAAGGCTTTGAAGCAAAAGTTTGATGAGAT
TTTTTCAGCAACAAGATACATTAAAGCCCTAGAAACACTTCGGCAGGTACGTCAGACAC
AAGGTCAGAAAGTAGAAGAATATCAAATGGAACTAAAATATCTGAAGCAATATAAGGA
AAAAGCTTGTGAGATTCGTGATCAGATTACAAGTAAGGAAGCCCAGTTAACATCTTCAA
AGGAAATTGTCAAATCCTATGAGAATGAACTTGATCCATTGAAGAATCGTCTAAAAGAA
ATTGAACATAATCTCTCTAAAATAATGAAACTTGACAATGAAATTAAAGCCTTGGATAGC
CGAAAGAAGCAAATGGAGAAAGATAATAGTGAACTGGAAGAGAAAATGGAAAAGGTTT
TTCAAGGGACTGATGAGCAACTAAATGACTTATATCACAATCACCAGAGAACAGTAAGG
GAGAAAGAAAGGAAATTGGTAGACTGTCATCGTGAACTGGAAAAACTAAATAAAGAAT
CTAGGCTTCTCAATCAGGAAAAATCAGAACTGCTTGTTGAACAGGGTCGTCTACAGCTGC
AAGCAGATCGCCATCAAGAACATATCCGAGCTAGAGATTCATTAATTCAGTCTTTGGCAA
CACAGCTAGAATTGGATGGCTTTGAGCGTGGACCATTCAGTGAAAGACAGATTAAAAAT
TTTCACAAACTTGTGAGAGAGAGACAAGAAGGGGAAGCAAAAACTGCCAACCAACTGAT
GAATGACTTTGCAGAAAAAGAGACTCTGAAACAAAAACAGATAGATGAGATAAGAGAT
AAGAAAACTGGACTGGGAAGAATAATTGAGTTAAAATCAGAAATCCTAAGTAAGAAGC
AGAATGAGCTGAAAAATGTGAAGTATGAATTACAGCAGTTGGAAGGATCTTCAGACAGG
ATTCTTGAACTGGACCAGGAGCTCATAAAAGCTGAACGTGAGTTAAGCAAGGCTGAGAA
AAACAGCAATGTAGAAACCTTAAAAATGGAAGTAATAAGTCTCCAAAATGAAAAAGCA
GACTTAGACAGGACCCTGCGTAAACTTGACCAGGAGATGGAGCAGTTAAACCATCATAC
AACAACACGTACCCAAATGGAGATGCTGACCAAAGACAAAGCTGACAAAGATGAACAA
ATCAGAAAAATAAAATCTAGGCACAGTGATGAATTAACCTCACTGTTGGGATATTTTCCC
AACAAAAAACAGCTTGAAGACTGGCTACATAGTAAATCAAAAGAAATTAATCAGACCAG
GGACAGACTTGCCAAATTGAACAAGGAACTAGCTTCATCTGAGCAGAATAAAAATCATA
TAAATAATGAACTAGAAAGAAAGGAAGAGCAGTTGTCCAGTTACGAAGACAAGCTGTTT
GATGTTTGTGGTAGCCAGGATTTTGAAAGTGATTTAGACAGGCTTAAAGAGGAAATTGA
AAAATCATCAAAACAGCGAGCCATGCTGGCTGGAGCCACAGCAGTTTACTCCCAGTTCA
TTACTCAGCTAACAGACGAAAACCAGTCATGTTGCCCCGTTTGTCAGAGAGTTTTTCAGA
CAGAGGCTGAGTTACAAGAAGCCATCAGTGATTTGCAGTCTAAACTGCGACTTGCTCCAG
ATAAACTCAAGTCAACAGAATCAGAGCTAAAAAAAAAAGGAAAAGCGGCGTGATGAAAT
GCTGGGACTTGCGCCCATGAGGCAAAGCATAATTGATTTGAAGGAGAAGGAAATACCAG
AATTAAGAAACAAACTGCAGAATGTCAATAGAGACATACAGCGCCTAAAGAACGACATA
GAAGAACAAGAAACACTCTTGGGTACAATAATGCCTGAAGAAGAAAGTGCCAAAGT

Figure 80A

ATGCCTGACAGATGTTACAATTATGGAGAGGTTCCAGATGGAACTTAAAGATGTTGAAA
GAAAAATTGCACAACAAGCAGCTAAGCTACAAGGAATAGACTTAGATCGAACTGTCCAA
CAAGTCAACCAGGAGAAACAAGAGAAACAGCACAAGTTAGACACAGTTTCTAGTAAGAT
TGAATTGAATCGTAAGCTTATACAGGACCAGCAGGAACAGATTCAACATCTAAAAAGTA
CAACAAATGAGCTAAAATCTGAGAAACTTCAGATATCCACTAATTTGCAACGTCGTCAGC
AACTGGAGGAGCAGACTGTGGAATTATCCACTGAAGTTCAGTCTTTGTACAGAGAGATA
AAGGATGCTAAAGAGCAGGTAAGCCCTTTGGAAACAACATTGGAAAAGTTCCAGCAAGA
AAAAGAAGAATTAATCAACAAAAAAAATACAAGCAACAAAATAGCACAGGATAAACTG
AATGATATTAAAGAGAAGGTTAAAAATATTCATGGCTATATGAAAGACATTGAGAATCA
TATTCAAGATGGGAAAGACGACTATATGAAGCAAAAAGAAACTGAACTTAATAAAGTAA
TAGCTCAACTAAGTGAATGCGAGAAACACAAAGAAAAGATAAATGAAGATATGAGACT
CATGAGACAAGATATTGATACACAGAAGATACAAGAAAGGTGGCTACAAGATAACCTTA
CTTTAAGAAAAAGAAATGAGGAACTAAAAGAAGTTGAAGAAGAAGGAAAACAACATTT
GAAGGAAATGGGTCAAATGCAGGTTTTGCAAATGAAAAGTGAACATCAGAAGTTGGAAG
AGAACATAGACAATATAAAAAGAAATCATAATTTGGCATTAGGGCGACAGAAAGGTTAT
GAAGAAGAAATTATTCATTTTAAGAAAGAACTTCGAGAACCACAATTTCGGGATGCTGA
GGAAAAGTATAGAGAAATGATGATTGTTATGAGGACAACAGAACTTGTGAACAAGGATC
TGGATATTTATTATAAGACTCTTGACCAAGCAATAATGAAATTTCACAGTATGAAGATGG
AAGAAATCAATAAAATTATACGTGACCTGTGGCGAAGTACCTATCGTGGACAAGATATT
GAATACATAGAAATACGGTCTGATGCCGATGAAAATGTATCAGCTTCTGATAAAAGGCG
GAATTATAACTACCGAGTGGTGATGCTGAAGGGAGACACAGCCTTGGATATGCGAGGAC
GATGCAGTGCTGGACAAAAGGTATTAGCCTCACTCATCATTCGCCTGGCCCTGGCTGAAA
CGTTCTGCCTCAACTGTGGCATCATTGCCTTGGATGAGCCAACAACAAATCTTGACCGAG
AAAACATTGAATCTCTTGCACATGCTCTGGTTGAGATAATAAAAAGTCGCTCACAGCAGC
GTAACTTCCAGCTTCTGGTAATCACTCATGATGAAGATTTTGTGGAGCTTTTAGGACGTTC
TGAATATGTGGAGAAATTCTACAGGATTAAAAAGAACATCGATCAGTGCTCAGAGATTG
TGAAATGCAGTGTTAGCTCCCTGGGATTCAATGTTCATTAAAAATATCCAAGATTTAAAT
GCCATAGAAATGTAGGTCCTCAGAAAGTGTATAATAAGAAACTTATTTCTCATATCAACT
TAGTCAATAAGAAAATATATTCTTTCAAAGGAAAAAAAAAAAAAA

Figure 80A (continued)

MLIFSVRDMFAKMSILGVRSFGIEDKDKQIITFFSPLTILVGPNGAGKTTIIECLKYICTGDFPPG
TKGNTFVHDPKVAQETDVRAQIRLQFRDVNGELIAVQRSMVCTQKSKKTEFKTLEGVITRTK
HGEKVSLSSKCAEIDREMISSLGVSKAVLNNVIFCHQEDSNWPLSEGKALKQKFDEIFSATRYI
KALETLRQVRQTQGQKVEEYQMELKYLKQYKEKACEIRDQITSKEAQLTSSKEIVKSYENEL
DPLKNRLKEIEHNLSKIMKLDNEIKALDSRKKQMEKDNSELEEKMEKVFQGTDEQLNDLYH
NHQRTVREKERKLVDCHRELEKLNKESRLLNQEKSELLVEQGRLQLQADRHQEHIRARDSLI
QSLATQLELDGFERGPFSERQIKNFHKLVRERQEGEAKTANQLMNDFAEKETLKQKQIDEIR
DKKTGLGRIIELKSEILSKKQNELKNVKYELQQLEGSSDRILELDQELIKAERELSKAEKNSNV
ETLKMEVISLQNEKADLDRTLRKLDQEMEQLNHHTTTRTQMEMLTKDKADKDEQIRKIKSR
HSDELTSLLGYFPNKKQLEDWLHSKSKEINQTRDRLAKLNKELASSEQNKNHINNELERKEE
QLSSYEDKLFDVCGSQDFESDLDRLKEEIEKSSKQRAMLAGATAVYSQFITQLTDENQSCCPV
CQRVFQTEAELQEAISDLQSKLRLAPDKLKSTESELKKKEKRRDEMLGLAPMRQSIIDLKEKE
IPELRNKLQNVNRDIQRLKNDIEEQETLLGTIMPEEESAKVCLTDVTIMERFQMELKDVERKI
AQQAAKLQGIDLDRTVQQVNQEKQEKQHKLDTVSSKIELNRKLIQDQQEQIQHLKSTTNELK
SEKLQISTNLQRRQQLEEQTVELSTEVQSLYREIKDAKEQVSPLETTLEKFQQEKEELINKKNT
SNKIAQDKLNDIKEKVKNIHGYMKDIENHIQDGKDDYMKQKETELNKVIAQLSECEKHKEKI
NEDMRLMRQDIDTQKIQERWLQDNLTLRKRNEELKEVEEEGKQHLKEMGQMQVLQMKSE
HQKLEENIDNIKRNHNLALGRQKGYEEEIIHFKKELREPQFRDAEEKYREMMIVMRTTELVN
KDLDIYYKTLDQAIMKFHSMKMEEINKIIRDLWRSTYRGQDIEYIEIRSDADENVSASDKRRN
YNYRVVMLKGDTALDMRGRCSAGQKVLASLIIRLALAETFCLNCGIIALDEPTTNLDRENIES
LAHALVEIIKSRSQQRNFQLLVITHDEDFVELLGRSEYVEKFYRIKKNIDQCSEIVKCSVSSLGF
NVH

Figure 80B

ATGCACTTTCTTTGCCAAAGGCAAACGCAGAACGTTTCAGAGCCATGAGGATGCTTCTGC
ATTTGAGTTTGCTAGCTCTTGGAGCTGCCTACGTGTATGCCATCCCCACAGAAATTCCCA
CAAGTGCATTGGTGAAAGAGACCTTGGCACTGCTTTCTACTCATCGAACTCTGCTGATAG
CCAATGAGACTCTGAGGATTCCTGTTCCTGTACATAAAAATCACCAACTGTGCACTGAAG
AAATCTTTCAGGGAATAGGCACACTGGAGAGTCAAACTGTGCAAGGGGGTACTGTGGAA
AGACTATTCAAAAACTTGTCCTTAATAAAGAAATACATTGACGGCCAAAAAAAAAAGTG
TGGAGAAGAAAGACGGAGAGTAAACCAATTCCTAGACTACCTGCAAGAGTTTCTTGGTG
TAATGAACACCGAGTGGATAATAGAAAGTTGAGACTAAACTGGTTTGTTGCAGCCAAAG
ATTTTGGAGGAGAAGGACATTTTACTGCAGTGAGAATGAGGGCCAAGAAAGAGTCAGGC
CTTAATTTTCAATATAATTTAACTTCAGAGGGAAAGTAAATATTTCAGGCATACTGACAC
TTTGCCAGAAAGCATAAAATTCTTAAAATATATTTCAGATATCAGAATCATTGAAGTATT
TTCCTCCAGGCAAAATTGATATACTTTTTTCTTATTTAACTTAACATTCTGTAAAATGTCT
GTTAACTTAATAGTATTTATGAAATGGTTAAGAATTTGGTAAATTAGTATTTATTTAATGT
TATGTTGTGTTCTAATAAAACAAAAATAGACAACTGTTC

Figure 81A

MRMLLHLSLLALGAAYVYAIPTEIPTSALVKETLALLSTHRTLLIANETLRIPVPVHKNH
QLCTEEIFQGIGTLESQTVQGGTVERLFKNLSLIKKYIDGQKKKCGEERRRVNQFLDYLQ
EFLGVMNTEWIIES

Figure 81B

CGAGCCCCGCCGAACCGAGGCCACCCGGAGCCGTGCCCAGTCCACGCCGGCCGTGCCCG
GCGGCCTTAAGAACCAGGCAACCTCTGCCTTCTTCCCTCTTCCACTCGGAGTCGCGCTCC
GCGCGCCCTCACTGCAGCCCCTGCGTCGCCGGGACCCTCGCGCGCGACCAGCCGAATCG
CTCCTGCAGCAGAGCCAACATGCCCATCACTCGGATGCGCATGAGACCCTGGCTAGAGA
TGCAGATTAATTCCAACCAAATCCCGGGGCTCATCTGGATTAATAAAGAGGAGATGATCT
TCCAGATCCCATGGAAGCATGCTGCCAAGCATGGCTGGGACATCAACAAGGATGCCTGT
TTGTTCCGGAGCTGGGCCATTCACACAGGCCGATACAAAGCAGGGGAAAAGGAGCCAGA
TCCCAAGACGTGGAAGGCCAACTTTCGCTGTGCCATGAACTCCCTGCCAGATATCGAGGA
GGTGAAAGACCAGAGCAGGAACAAGGGCAGCTCAGCTGTGCGAGTGTACCGGATGCTTC
CACCTCTCACCAAGAACCAGAGAAAAGAAAGAAAGTCGAAGTCCAGCCGAGATGCTAA
GAGCAAGGCCAAGAGGAAGTCATGTGGGGATTCCAGCCCTGATACCTTCTCTGATGGAC
TCAGCAGCTCCACTCTGCCTGATGACCACAGCAGCTACACAGTTCCAGGCTACATGCAGG
ACTTGGAGGTGGAGCAGGCCCTGACTCCAGCACTGTCGCCATGTGCTGTCAGCAGCACTC
TCCCCGACTGGCACATCCCAGTGGAAGTTGTGCCGGACAGCACCAGTGATCTGTACAACT
TCCAGGTGTCACCCATGCCCTCCACCTCTGAAGCTACAACAGATGAGGATGAGGAAGGG
AAATTACCTGAGGACATCATGAAGCTCTTGGAGCAGTCGGAGTGGCAGCCAACAAACGT
GGATGGGAAGGGGTACCTACTCAATGAACCTGGAGTCCAGCCCACCTCTGTCTATGGAG
ACTTTAGCTGTAAGGAGGAGCCAGAAATTGACAGCCCAGGGGGGGATATTGGGCTGAGT
CTACAGCGTGTCTTCACAGATCTGAAGAACATGGATGCCACCTGGCTGGACAGCCTGCTG
ACCCCAGTCCGGTTGCCCTCCATCCAGGCCATTCCCTGTGCACCGTAGCAGGGCCCCTGG
GCCCCTCTTATTCCTCTAGGCAAGCAGGACCTGGCATCATGGTGGATATGGTGCAGAGAA
GCTGGACTTCTGTGGGCCCCTCAACAGCCAAGTGTGACCCCACTGCCAAGTGGGGATGG
GCCTCCCTCCTTGGGTCATTGACCTCTCAGGGCCTGGCAGGCCAGTGTCTGGGTTTTTCTT
GTGGTGTAAAGCTGGCCCTGCCTCCTGGGAAGATGAGGTTCTGAGACCAGTGTATCAGGT
CAGGGACTTGGACAGGAGTCAGTGTCTGGCTTTTTCCTCTGAGCCCAGCTGCCTGGAGAG
GGTCTCGCTGTCACTGGCTGGCTCCTAGGGGAACAGACCAGTGACCCCAGAAAAGCATA
ACACCAATCCCAGGGCTGGCTCTGCACTAAGCGAAAATTGCACTAAATGAATCTCGTTCC
AAAGAACTACCCCTTTTCAGCTGAGCCCTGGGGACTGTTCCAAAGCCAGTGAATGTGAA
GGAAACTCCCCTCCTTCGGGGCAATGCTCCCTCAGCCTCAGAGGAGCTCTACCCTGCTCC
CTGCTTTGGCTGAGGGGCTTGGGAAAAAAACTTGGCACTTTTTCGTGTGGATCTTGCCAC
ATTTCTGATCAGAGGTGTACACTAACATTTCCCCCGAGCTCTTGGCCTTTGCATTTATTTA
TACAGTGCCTTGCTCGGGGCCCACCACCCCCTCAAGCCCCAGCAGCCCTCAACAGGCCCA
GGGAGGGAAGTGTGAGCGCCTTGGTATGACTTAAAATTGGAAATGTCATCTAACCATTA
AGTCATGTGTGAACACATAAGGACGTGTGTAAATATGTACATTTGTCTTTTTATAAAAAG
TAAAATTGTT

Figure 82A

MPITRMRMRPWLEMQINSNQIPGLIWINKEEMIFQIPWKHAAKHGWDINKDACLFRSWAIHT
GRYKAGEKEPDPKTWKANFRCAMNSLPDIEEVKDQSRNKGSSAVRVYRMLPPLTKNQRKER
KSKSSRDAKSKAKRKSCGDSSPDTFSDGLSSSTLPDDHSSYTVPGYMQDLEVEQALTPALSPC
AVSSTLPDWHIPVEVVPDSTSDLYNFQVSPMPSTSEATTDEDEEGKLPEDIMKLLEQSEWQPT
NVDGKGYLLNEPGVQPTSVYGDFSCKEEPEIDSPGGDIGLSLQRVFTDLKNMDATWLDSLLT
PVRLPSIQAIPCAP

Figure 82B

TCAGAGTCCGGCTCAGGCTCCGGCTGCGGCTCCAGCCCGCGATGCCCCATTCCGTGACCC
TGCGCGGGCCTTCGCCCTGGGGCTTCCGCCTGGTGGGCGGCCGGGACTTCAGCGCGCCCC
TCACCATCTCACGGGTCCATGCTGGCAGCAAGGCTGCATTGGCTGCCCTGTGCCCAGGAG
ACCTGATCCAGGCCATCAATGGTGAGAGCACAGAGCTCATGACACACCTGGAGGCACAG
AACCGCATCAAGGGCTGCCACGATCACCTCACACTGTCTGTGAGCAGGCCTGAGGGCAG
GAGCTGGCCCAGTGCCCCTGATGACAGCAAGGCTCAGGCACACAGGATCCACATCGATC
CTGAGATCCAGGACGGCAGCCCAACAACCAGCAGGCGGCCCTCAGGCACCGGGACTGGG
CCAGAAGATGGCAGACCAAGCCTGGGATCTCCATATGGACAACCCCCTCGCTTTCCAGTC
CCTCACAATGGCAGCAGCGAGGCCACCCTGCCAGCCCAGATGAGCACCCTGCATGTGTC
TCCACCCCCCAGCGCTGACCCAGCCAGAGGCCTCCCGCGGAGCCGGGACTGCAGAGTCG
ACCTGGGCTCCGAGGTGTACAGGATGCTGCGGGAGCCAGCCGAGCCCGTGGCCGCGGAG
CCCAAGCAGTCAGGCTCCTTCCGCTACTTGCAGGGCATGCTAGAGGCCGGCGAGGGCGG
GGATTGGCCCGGGCCTGGCGGCCCCCGGAACCTCAAGCCCACGGCCAGCAAGCTGGGCG
CTCCGCTGAGCGGCCTGCAGGGGCTGCCCGAGTGCACGCGCTGCGGCCACGGCATCGTG
GGCACCATCGTCAAGGCACGGGACAAGCTCTACCATCCCGAGTGCTTCATGTGCAGTGA
CTGCGGCCTGAACCTCAAGCAGCGTGGTTACTTCTTTCTGGACGAGCGGCTCTACTGTGA
GAGCCACGCCAAGGCGCGCGTGAAGCCGCCCGAGGGCTACGACGTGGTGGCGGTGTACC
CCAATGCCAAGGTGGAACTCGTCTGAGCTGGGACCCTGCTCCCACGCCTGCTTCTTAAGG
TCCCTGCTCGGCCGGTGTAAATATGTTTCACCCTGTCCCTCTAATAAAGCTCCTCTGCTCC
ACCTTGAACCTGTCACCTGGCCTGCCACCCTCCTGCGCAGGCCATGCATGGCTCCCGAGT
ACAGTAGTATCTGCTTAGGTGCCAGGCATGTCCTAGGCTCTGGGTGCAGTAGTGAGCAGG
ACGGGTACCATGCTGCCCTGAAGGGGCCACAGCCTGGGTGGAAGGCAGACCTGAATCAC
AACGGGCCAGCTCTAGTAATACGAAGGTGAGGTCTGGGATGCTGCGTGCGGCGCGACGA
CAGGAGGTATGACCTGGGTGGGGTCAGGGAAAGTCTTAGCTGAGAACTAAGAGATGAGG
GAGGCACAAACTCTGCACGGGGGAACTGTGTGTGCAAAGGTGAGCTGGGGGCGAGAAA
GGCCTCTGTGGCCGTCATCGGCACTAGCGGGTTGGGGGTGGTGGTGGGGTGCTGGCAGC
CTCAGGAGCGATCGCTCCCCTGGAGAGGGTGATTGAGTGTGGAGATCACCGGGGCCGCC
GCGGGCCGTCTGCACTTCTGTTCCAGGTTTTTCTGGCATTTTCTGTTCCAGGTTTCTTCCAC
CCACGAGCACTTTATTCTCCTCCGAGACCCCCTTTTCTTCCCCTTCCTCTCTCCCACCAGG
GGGCGCGCTTAAATTTCCAGACAGAGACCAGAAGGAAGGTTTAGAAAGAAAAGAACAC
TTGCCCAGGGCAGCTTTGCCCTCCAAGAGGCTCCCTCCTGTCTCTAAGTCAATTCCACCCC
TCCTCGAAGTCCCGGCTTCCACCCCTCTCCTCAGAGTCCCGGCGTTTACCTCGTGGTGTGT
TTGCCTTGGGCCTTTCATGCCCCGGCTGCACACATCGTCTGTGAATTGTGGCTGTTCACTC
CCGAGGATGTGTCCTAGACTCCGGGTCGCGTGGATCTACCCTCTAGTTTACTTGCTCGGG
AGAAGAAACTGACTCGTTTTATTTAGTGCCTATTTAGCGAGCCCAGAGTAACGTACATTT
GTGCTGTTTTCAATTTTGTGCTATCGCAAATCACAAAAAAACTGTTATCAATTCACATTCA
TCATCAGCACGAGACCCATTTCCTTGTGCTCCTGCCAGCTCAGGATATTATGTTTCTTTTT
TCATTTTTGCCAGTCTGTTAAGTAAAATGTCATATGCGTTTGTTTTAA

Figure 83A

MPHSVTLRGPSPWGFRLVGGRDFSAPLTISRVHAGSKAALAALCPGDLIQAINGESTELMTHL
EAQNRIKGCHDHLTLSVSRPEGRSWPSAPDDSKAQAHRIHIDPEIQDGSPTTSRRPSGTGTGPE
DGRPSLGSPYGQPPRFPVPHNGSSEATLPAQMSTLHVSPPPSADPARGLPRSRDCRVDLGSEV
YRMLREPAEPVAAEPKQSGSFRYLQGMLEAGEGGDWPGPGGPRNLKPTASKLGAPLSGLQG
LPECTRCGHGIVGTIVKARDKLYHPECFMCSDCGLNLKQRGYFFLDERLYCESHAKARVKPP
EGYDVVAVYPNAKVELV

Figure 83B

AGGAAAGGCTAAAGTTCTCTGGAGGATGTGGCTGCAGAGCCTGCTGCTCTTGGGCACTGT
GGCCTGCAGCATCTCTGCACCCGCCCGCTCGCCCAGCCCCAGCACGCAGCCCTGGGAGC
ATGTGAATGCCATCCAGGAGGCCCGGCGTCTCCTGAACCTGAGTAGAGACACTGCTGCT
GAGATGAATGAAACAGTAGAAGTCATCTCAGAAATGTTTGACCTCCAGGAGCCGACCTG

CCTACAGACCCGCCTGGAGCTGTACAAGCAGGGCCTGCGGGGCAGCCTCACCAAGCTCA
AGGGCCCCTTGACCATGATGGCCAGCCACTACAAGCAGCACTGCCCTCCAACCCCGGAA
ACTTCCTGTGCAATCCAGACTATCACCTTTGAAAGTTTCAAAGAGAACCTGAAGGACTTT
CTGCTTGTCATCCCCTTTGACTGCTGGGAGCCAGTCCAGGAGTGAGACCGGCCAGATGAG
GCTGGCCAAGCCGGGGAGCTGCTCTCTCATGAAACAAGAGCTAGAAACTCAGGATGGTC
ATCTTGGAGGGACCAAGGGGTGGGCCACAGCCATGGTGGGAGTGGCCTGGACCTGCCCT
GGGCCACACTGACCCTGATACAGGCATGGCAGAAGAATGGGAATATTTTATACTGACAG
AAATCAGTAATATTTATATATTTATATTTTTAAAATATTTATTTATTTATTTATTTAAGTTC
ATATTCCATATTTATTCAAGATGTTTTACCGTAATAATTATTATTAAAAATATGCTTCTAC
TTA

Figure 84A

MWLQSLLLLGTVACSISAPARSPSPSTQPWEHVNAIQEARRLLNLSRDTAAEMNETVEVISEM
FDLQEPTCLQTRLELYKQGLRGSLTKLKGPLTMMASHYKQHCPPTPETSCAIQTITFESFKEN
LKDFLLVIPFDCWEPVQE

Figure 84B

CCCGGGGTTGTGGGCACCTTGCTGCTGCACATATAAGGCGGGAGGTTGTTGCCAACTCTT
CAGAGCCCCACGAAGGACCAGAACAAGACAGAGTGCCTCCTGCCGATCCAAACATGAGC
CGCCTGCCCGTCCTGCTCCTGCTCCAACTCCTGGTCCGCCCCGGACTCCAAGCTCCCATG
ACCCAGACAACGTCCTTGAAGACAAGCTGGGTTAACTGCTCTAACATGATCGATGAAATT
ATAACACACTTAAAGCAGCCACCTTTGCCTTTGCTGGACTTCAACAACCTCAATGGGGAA
GACCAAGACATTCTGATGGAAAATAACCTTCGAAGGCCAAACCTGGAGGCATTCAACAG
GGCTGTCAAGAGTTTACAGAACGCATCAGCAATTGAGAGCATTCTTAAAAATCTCCTGCC
ATGTCTGCCCCTGGCCACGGCCGCACCCACGCGACATCCAATCCATATCAAGGACGGTG
ACTGGAATGAATTCCGGAGGAAACTGACGTTCTATCTGAAAACCCTTGAGAATGCGCAG
GCTCAACAGACGACTTTGAGCCTCGCGATCTTTTGAGTCCAACGTCCAGCTCGTTCTCTG
GGCCTTCTCACCACAGAGCCTCGGGACATCAAAAACAGCAGAACTTCTGAAACCTCTGG
GTCATCTCTCACACATTCCAGGACCAGAAGCATTTCACCTTTTCCTGCGGCATCAGATGA
ATTGTTAATTATCTAATTTCTGAAATGTGCAGCTCCCATTTGGCCTTGTGCGGTTGTGTTC
TCATTTTTATCCCATTGAGACTATTTATTTATGTATGTATGTATTTATTTATTTATTGCCTG
GAGTGTGAACTGTATTTATTTTAGCAGAGGAGCCATGTCCTGCTGCTTCTGCAAAAAACT
CAGAGTGGGGTGGGGAGCATGTTCATTTGTACCTCGAGTTTTAAACTGGTTCCTAGGGAT
GTGTGAGAATAAACTAGACTCTGAACA

Figure 85A

MSRLPVLLLLQLLVRPGLQAPMTQTTSLKTSWVNCSNMIDEIITHLKQPPLPLLDFNNLNGED
QDILMENNLRRPNLEAFNRAVKSLQNASAIESILKNLLPCLPLATAAPTRHPIHIKDGDWNEFR
RKLTFYLKTLENAQAQQTTLSLAIF

Figure 85B

ACAAGGAGGCAGGCAAGACAGCAAGGCATAGAGACAACATAGAGCTAAGTAAAGCCAG
TGGAAATGAAGAGTCTTCCAATCCTACTGTTGCTGTGCGTGGCAGTTTGCTCAGCCTATC
CATTGGATGGAGCTGCAAGGGGTGAGGACACCAGCATGAACCTTGTTCAGAAATATCTA
GAAAACTACTACGACCTCAAAAAAGATGTGAAACAGTTTGTTAGGAGAAAGGACAGTGG
TCCTGTTGTTAAAAAAATCCGAGAAATGCAGAAGTTCCTTGGATTGGAGGTGACGGGGA
AGCTGGACTCCGACACTCTGGAGGTGATGCGCAAGCCCAGGTGTGGAGTTCCTGATGTTG
GTCACTTCAGAACCTTTCCTGGCATCCCGAAGTGGAGGAAAACCCACCTTACATACAGGA
TTGTGAATTATACACCAGATTTGCCAAAAGATGCTGTTGATTCTGCTGTTGAGAAAGCTC
TGAAAGTCTGGGAAGAGGTGACTCCACTCACATTCTCCAGGCTGTATGAAGGAGAGGCT
GATATAATGATCTCTTTTGCAGTTAGAGAACATGGAGACTTTTACCCTTTTGATGGACCT
GGAAATGTTTTGGCCCATGCCTATGCCCCTGGGCCAGGGATTAATGGAGATGCCCACTTT
GATGATGATGAACAATGGACAAAGGATACAACAGGGACCAATTTATTTCTCGTTGCTGCT
CATGAAATTGGCCACTCCCTGGGTCTCTTTCACTCAGCCAACACTGAAGCTTTGATGTAC
CCACTCTATCACTCACTCACAGACCTGACTCGGTTCCGCCTGTCTCAAGATGATATAAAT
GGCATTCAGTCCCTCTATGGACCTCCCCCTGACTCCCCTGAGACCCCCCTGGTACCCACG
GAACCTGTCCCTCCAGAACCTGGGACGCCAGCCAACTGTGATCCTGCTTTGTCCTTTGAT
GCTGTCAGCACTCTGAGGGGAGAAATCCTGATCTTTAAAGACAGGCACTTTTGGCGCAA
ATCCCTCAGGAAGCTTGAACCTGAATTGCATTTGATCTCTTCATTTTGGCCATCTCTTCCT
TCAGGCGTGGATGCCGCATATGAAGTTACTAGCAAGGACCTCGTTTTCATTTTTAAAGGA
AATCAATTCTGGGCCATCAGAGGAAATGAGGTACGAGCTGGATACCCAAGAGGCATCCA
CACCCTAGGTTTCCCTCCAACCGTGAGGAAAATCGATGCAGCCATTTCTGATAAGGAAAA
GAACAAAACATATTTCTTTGTAGAGGACAAATACTGGAGATTTGATGAGAAGAGAAATT
CCATGGAGCCAGGCTTTCCCAAGCAAATAGCTGAAGACTTTCCAGGGATTGACTCAAAG
ATTGATGCTGTTTTTGAAGAATTTGGGTTCTTTTATTTCTTTACTGGATCTTCACAGTTGG
AGTTTGACCCAAATGCAAAGAAAGTGACACACACTTTGAAGAGTAACAGCTGGCTTAAT
TGTTGAAAGAGATATGTAGAAGGCACAATATGGGCACTTTAAATGAAGCTAATAATTCTT
CACCTAAGTCTCTGTGAATTGAAATGTTCGTTTTCTCCTGCCTGTGCTGTGACTCGAGTCA
CACTCAAGGGAACTTGAGCGTGAATCTGTATCTTGCCGGTCATTTTTATGTTATTACAGG
GCATTCAAATGGGCTGCTGCTTAGCTTGCACCTTGTCACATAGAGTGATCTTTCCCAAGA
GAAGGGGAAGCACTCGTGTGCAACAGACAAGTGACTGTATCTGTGTAGACTATTTGCTTA
TTTAATAAAGACGATTTGTCAGTTGTTTT

Figure 86A

MKSLPILLLLCVAVCSAYPLDGAARGEDTSMNLVQKYLENYYDLKKDVKQFVRRKDSGPV
VKKIREMQKFLGLEVTGKLDSDTLEVMRKPRCGVPDVGHFRTFPGIPKWRKTHLTYRIVNYT
PDLPKDAVDSAVEKALKVWEEVTPLTFSRLYEGEADIMISFAVREHGDFYPFDGPGNVLAHA
YAPGPGINGDAHFDDDEQWTKDTTGTNLFLVAAHEIGHSLGLFHSANTEALMYPLYHSLTDL
TRFRLSQDDINGIQSLYGPPPDSPETPLVPTEPVPPEPGTPANCDPALSFDAVSTLRGEILIFKDR
HFWRKSLRKLEPELHLISSFWPSLPSGVDAAYEVTSKDLVFIFKGNQFWAIRGNEVRAGYPRG
IHTLGFPPTVRKIDAAISDKEKNKTYFFVEDKYWRFDEKRNSMEPGFPKQIAEDFPGIDSKIDA
VFEEFGFFYFFTGSSQLEFDPNAKKVTHTLKSNSWLNC

Figure 86B

GAAGAAACCACCGGAAGGAACCATCTCACTGTGTGTAAACATGACTTCCAAGCTGGCCG
TGGCTCTCTTGGCAGCCTTCCTGATTTCTGCAGCTCTGTGTGAAGGTGCAGTTTTGCCAAG
GAGTGCTAAAGAACTTAGATGTCAGTGCATAAAGACATACTCCAAACCTTTCCACCCCAA
ATTTATCAAAGAACTGAGAGTGATTGAGAGTGGACCACACTGCGCCAACACAGAAATTA
TTGTAAAGCTTTCTGATGGAAGAGAGCTCTGTCTGGACCCCAAGGAAAACTGGGTGCAG
AGGGTTGTGGAGAAGTTTTTGAAGAGGGCTGAGAATTCATAAAAAAATTCATTCTCTGTG
GTATCCAAGAATCAGTGAAGATGCCAGTGAAACTTCAAGCAAATCTACTTCAACACTTCA
TGTATTGTGTGGGTCTGTTGTAGGGTTGCCAGATGCAATACAAGATTCCTGGTTAAATTT
GAATTTCAGTAAACAATGAATAGTTTTTCATTGTACCATGAAATATCCAGAACATACTTA
TATGTAAAGTATTATTTATTTGAATCTACAAAAAACAACAAATAATTTTTAAATATAAGG
ATTTTCCTAGATATTGCACGGGAGAATATACAAATAGCAAAATTGAGGCCAAGGGCCAA
GAGAATATCCGAACTTTAATTTCAGGAATTGAATGGGTTTGCTAGAATGTGATATTTGAA
GCATCACATAAAAATGATGGGACAATAAATTTTGCCATAAAGTCAAATTTAGCTGGAAA
TCCTGGATTTTTTTCTGTTAAATCTGGCAACCCTAGTCTGCTAGCCAGGATCCACAAGTCC
TTGTTCCACTGTGCCTTGGTTTCTCCTTTATTTCTAAGTGGAAAAAGTATTAGCCACCATC
TTACCTCACAGTGATGTTGTGAGGACATGTGGAAGCACTTTAAGTTTTTTCATCATAACA
TAAATTATTTTCAAGTGTAACTTATTAACCTATTTATTATTTATGTATTTATTTAAGCATCA
AATATTTGTGCAAGAATTTGGAAAAATAGAAGATGAATCATTGATTGAATAGTTATAAA
GATGTTATAGTAAATTTATTTTATTTTAGATATTAAATGATGTTTTATTAGATAAATTTCA
ATCAGGGTTTTTAGATTAAACAAACAAACAATTGGGTACCCAGTTAAATTTTCATTTCAG
ATATACAACAAATAATTTTTTAGTATAAGTACATTATTGTTTATCTGAAATTTTAATTGAA
CTAACAATCCTAGTTTGATACTCCCAGTCTTGTCATTGCCAGCTGTGTTGGTAGTGCTGTG
TTGAATTACGGAATAATGAGTTAGAACTATTAAAACAGCCAAAACTCCACAGTCAATATT
AGTAATTTCTTGCTGGTTGAAACTTGTTTATTATGTACAAATAGATTCTTATAATATTATT
TAAATGACTGCATTTTTAAATACAAGGCTTTATATTTTTAACTTTAAGATGTTTTTATGTG
CTCTCCAAATTTTTTTTACTGTTTCTGATTGTATGGAAATATAAAAGTAAATATGAAACAT
TTAAAATATAATTTGTTGTCAAAGTAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAA
AAAA

Figure 87A

MTSKLAVALLAAFLISAALCEGAVLPRSAKELRCQCIKTYSKPFHPKFIKELRVIESGPHCANT
EIIVKLSDGRELCLDPKENWVQRVVEKFLKRAENS

Figure 87B

CCTCTCACCCTTTAGCCCAGAACTGCTTTGAATACACCAATTGCTGTGGGGCGGCTCGAG
GAAGAGAAGACACCAGTGCCTCAGAAACTGCTCGGTCAGACGGTGATAGCGAGCCACGC
ATTCACAGGGCCACTGCTGCTCACAGAAGCAGTGAGGATGATGCCAGGATGATGTCTGC
CTCGCGCCTGGCTGGGACTCTGATCCCAGCCATGGCCTTCCTCTCCTGCGTGAGACCAGA
AAGCTGGGAGCCCTGCGTGGAGACTTGGCCCTAAACCACACAGAAGAGCTGGCATGAAA
CCCAGAGCTTTCAGACTCCGGAGCCTCAGCCCTTCACCCCGATTCCATTGCTTCTTGCTAA
ATGCTGCCGTTTTATCACGGAGGTGGTTCCTAATATTACTTATCAATGCATGGAGCTGAA
TTTCTACAAAATCCCCGACAACCTCCCCTTCTCAACCAAGAACCTGGACCTGAGCTTTAA
TCCCCTGAGGCATTTAGGCAGCTATAGCTTCTTCAGTTTCCCAGAACTGCAGGTGCTGGA
TTTATCCAGGTGTGAAATCCAGACAATTGAAGATGGGGCATATCAGAGCCTAAGCCACC
TCTCTACCTTAATATTGACAGGAAACCCCATCCAGAGTTTAGCCCTGGGAGCCTTTTCTG
GACTATCAAGTTTACAGAAGCTGGTGGCTGTGGAGACAAATCTAGCATCTCTAGAGAAC
TTCCCCATTGGACATCTCAAAACTTTGAAAGAACTTAATGTGGCTCACAATCTTATCCAA
TCTTTCAAATTACCTGAGTATTTTTCTAATCTGACCAATCTAGAGCACTTGGACCTTTCCA
GCAACAAGATTCAAAGTATTTATTGCACAGACTTGCGGGTTCTACATCAAATGCCCCTAC
TCAATCTCTCTTTAGACCTGTCCCTGAACCCTATGAACTTTATCCAACCAGGTGCATTTAA
AGAAATTAGGCTTCATAAGCTGACTTTAAGAAATAATTTTGATAGTTTAAATGTAATGAA
AACTTGTATTCAAGGTCTGGCTGGTTTAGAAGTCCATCGTTTGGTTCTGGGAGAATTTAG
AAATGAAGGAAACTTGGAAAAGTTTGACAAATCTGCTCTAGAGGGCCTGTGCAATTTGA
CCATTGAAGAATTCCGATTAGCATACTTAGACTACTACCTCGATGATATTATTGACTTATT
TAATTGTTTGACAAATGTTTCTTCATTTTCCCTGGTGAGTGTGACTATTGAAAGGGTAAAA
GACTTTTCTTATAATTTCGGATGGCAACATTTAGAATTAGTTAACTGTAAATTTGGACAGT
TTCCCACATTGAAACTCAAATCTCTCAAAAGGCTTACTTTCACTTCCAACAAAGGTGGGA
ATGCTTTTTCAGAAGTTGATCTACCAAGCCTTGAGTTTCTAGATCTCAGTAGAAATGGCTT
GAGTTTCAAAGGTTGCTGTTCTCAAAGTGATTTTGGGACAACCAGCCTAAAGTATTTAGA
TCTGAGCTTCAATGGTGTTATTACCATGAGTTCAAACTTCTTGGGCTTAGAACAACTAGA
ACATCTGGATTTCCAGCATTCCAATTTGAAACAAATGAGTGAGTTTTCAGTATTCCTATC
ACTCAGAAACCTCATTTACCTTGACATTTCTCATACTCACACCAGAGTTGCTTTCAATGGC
ATCTTCAATGGCTTGTCCAGTCTCGAAGTCTTGAAAATGGCTGGCAATTCTTTCCAGGAA
AACTTCCTTCCAGATATCTTCACAGAGCTGAGAAACTTGACCTTCCTGGACCTCTCTCAGT
GTC

Figure 88A

AACTGGAGCAGTTGTCTCCAACAGCATTTAACTCACTCTCCAGTCTTCAGGTACTAAATA
TGAGCCACAACAACTTCTTTTCATTGGATACGTTTCCTTATAAGTGTCTGAACTCCCTCCA
GGTTCTTGATTACAGTCTCAATCACATAATGACTTCCAAAAAACAGGAACTACAGCATTT
TCCAAGTAGTCTAGCTTTCTTAAATCTTACTCAGAATGACTTTGCTTGTACTTGTGAACAC
CAGAGTTTCCTGCAATGGATCAAGGACCAGAGGCAGCTCTTGGTGGAAGTTGAACGAAT
GGAATGTGCAACACCTTCAGATAAGCAGGGCATGCCTGTGCTGAGTTTGAATATCACCTG
TCAGATGAATAAGACCATCATTGGTGTGTCGGTCCTCAGTGTGCTTGTAGTATCTGTTGT
AGCAGTTCTGGTCTATAAGTTCTATTTTCACCTGATGCTTCTTGCTGGCTGCATAAAGTAT
GGTAGAGGTGAAAACATCTATGATGCCTTTGTTATCTACTCAAGCCAGGATGAGGACTGG
GTAAGGAATGAGCTAGTAAAGAATTTAGAAGAAGGGGTGCCTCCATTTCAGCTCTGCCTT
CACTACAGAGACTTTATTCCCGGTGTGGCCATTGCTGCCAACATCATCCATGAAGGTTTC
CATAAAAGCCGAAAGGTGATTGTTGTGGTGTCCCAGCACTTCATCCAGAGCCGCTGGTGT
ATCTTTGAATATGAGATTGCTCAGACCTGGCAGTTTCTGAGCAGTCGTGCTGGTATCATC
TTCATTGTCCTGCAGAAGGTGGAGAAGACCCTGCTCAGGCAGCAGGTGGAGCTGTACCG
CCTTCTCAGCAGGAACACTTACCTGGAGTGGGAGGACAGTGTCCTGGGGCGGCACATCTT
CTGGAGACGACTCAGAAAAGCCCTGCTGGATGGTAAATCATGGAATCCAGAAGGAACAG
TGGGTACAGGATGCAATTGGCAGGAAGCAACATCTATCTGAAGAGGAAAAATAAAAACC
TCCTGAGGCATTTCTTGCCCAGCTGGGTCCAACACTTGTTCAGTTAATAAGTATTAAATG
CTGCCACATGTCAGGCCTTATGCTAAGGGTGAGTAATTCCATGGTGCACTAGATATGCAG
GGCTGCTAATCTCAAGGAGCTTCCAGTGCAGAGGGAATAAATGCTAGACTAAAATACAG
AGTCTTCCAGGTGGGCATTTCAACCAACTCAGTCAAGGAACCCATGACAAAGAAAGTCA
TTTCAACTCTTACCTCATCAAGTTGAATAAAGACAGAGAAAACAGAAAGAGACATTGTT
CTTTTCCTGAGTCTTTTGAATGGAAATTGTATTATGTTATAGCCATCATAAAACCATTTTG
GTAGTTTTGACTGAACTGGGTGTTCACTTTTTCCTTTTTGATTGAATACAATTTAAATTCT
ACTTGATGACTGCAGTCGTCAAGGGGCTCCTGATGCAAGATGCCCCTTCCATTTTAAGTC
TGTCTCCTTACAGAGGTTAAAGTCTAGTGGCTAATTCCTAAGGAAACCTGATTAACACAT
GCTCACAACCATCCTGGTCATTCTCGAGCATGTTCTATTTTTTAACTAATCACCCCTGATA
TATTTTTATTTTTATATATCCAGTTTTCATTTTTTTACGTCTTGCCTATAAGCTAATATCAT
AAATAAGGTTGTTTAAGACGTGCTTCAAATATCCATATTAACCACTATTTTTCAAGGAAG
TATGGAAAAGTACACTCTGTCACTTTGTCACTCGATGTCATTCCAAAGTTATTGCCTACTA
AGTAATGACTGTCATGAAAGCAGCATTGAAATAATTTGTTTAAAGGGGGCACTCTTTTAA
ACGGGAAGAAAATTTCCGCTTCCTGGTCTTATCATGGACAATTTGGGCTAGAGGCAGGA
AGGAAGTGGGATGACCTCAGGAGGTCACCTTTTCTTGATTCCAGAAACATATGGGCTGAT
AAACCCGGGGTGACCTCATGAAATGAGTTGCAGCAGAAGTTTATTTTTTTCAGAACAAGT
GATGTTTGATGGACCTCTGAATCTCTTTAGGGAGACACAGATGGCTGGGATCCCTCCCCT
GTACCCTTCTCACTGCCAGGAGAACTA

Figure 88A (continued)

MELNFYKIPDNLPFSTKNLDLSFNPLRHLGSYSFFSFPELQVLDLSRCEIQTIEDGAYQSLSHLS
TLILTGNPIQSLALGAFSGLSSLQKLVAVETNLASLENFPIGHLKTLKELNVAHNLIQSFKLPEY
FSNLTNLEHLDLSSNKIQSIYCTDLRVLHQMPLLNLSLDLSLNPMNFIQPGAFKEIRLHKLTLR
NNFDSLNVMKTCIQGLAGLEVHRLVLGEFRNEGNLEKFDKSALEGLCNLTIEEFRLAYLDYY
LDDIIDLFNCLTNVSSFSLVSVTIERVKDFSYNFGWQHLELVNCKFGQFPTLKLKSLKRLTFTS
NKGGNAFSEVDLPSLEFLDLSRNGLSFKGCCSQSDFGTTSLKYLDLSFNGVITMSSNFLGLEQ
LEHLDFQHSNLKQMSEFSVFLSLRNLIYLDISHTHTRVAFNGIFNGLSSLEVLKMAGNSFQENF
LPDIFTELRNLTFLDLSQCQLEQLSPTAFNSLSSLQVLNMSHNNFFSLDTFPYKCLNSLQVLDY
SLNHIMTSKKQELQHFPSSLAFLNLTQNDFACTCEHQSFLQWIKDQRQLLVEVERMECATPS
DKQGMPVLSLNITCQMNKTIIGVSVLSVLVVSVVAVLVYKFYFHLMLLAGCIKYGRGENIYD
AFVIYSSQDEDWVRNELVKNLEEGVPPFQLCLHYRDFIPGVAIAANIIHEGFHKSRKVIVVVS
QHFIQSRWCIFEYEIAQTWQFLSSRAGIIFIVLQKVEKTLLRQQVELYRLLSRNTYLEWEDSVL
GRHIFWRRLRKALLDGKSWNPEGTVGTGCNWQEATSI

Figure 88B

TAGTTCTCCCTGAGTGAGACTTGCCTGCTTCTCTGGCCCCTGGTCCTGTCCTGTTCTCCAG
CATGGTGTGTCTGAAGCTCCCTGGAGGCTCCTGCATGACAGCGCTGACAGTGACACTGAT
GGTGCTGAGCTCCCCACTGGCTTTGGCTGGGGACACCCGACCACGTTTCTTGTGGCAGCT
TAAGTTTGAATGTCATTTCTTCAATGGGACGGAGCGGGTGCGGTTGCTGGAAAGATGCAT
CTATAACCAAGAGGAGTCCGTGCGCTTCGACAGCGACGTGGGGGAGTACCGGGCGGTGA
CGGAGCTGGGGCGGCCTGATGCCGAGTACTGGAACAGCCAGAAGGACCTCCTGGAGCAG
AGGCGGGCCGCGGTGGACACCTACTGCAGACACAACTACGGGGTTGGTGAGAGCTTCAC
AGTGCAGCGGCGAGTTGAGCCTAAGGTGACTGTGTATCCTTCAAAGACCCAGCCCCTGC
AGCACCACAACCTCCTGGTCTGCTCTGTGAGTGGTTTCTATCCAGGCAGCATTGAAGTCA
GGTGGTTCCGGAACGGCCAGGAAGAGAAGGCTGGGGTGGTGTCCACAGGCCTGATCCAG
AATGGAGATTGGACCTTCCAGACCCTGGTGATGCTGGAAACAGTTCCTCGGAGTGGAGA
GGTTTACACCTGCCAAGTGGAGCACCCAAGTGTGACGAGCCCTCTCACAGTGGAATGGA
GAGCACGGTCTGAATCTGCACAGAGCAAGATGCTGAGTGGAGTCGGGGGCTTCGTGCTG
GGCCTGCTCTTCCTTGGGGCCGGGCTGTTCATCTACTTCAGGAATCAGAAAGGACACTCT
GGACTTCAGCCAACAGGATTCCTGAGCTGAAATGCAGATGACCACATTCAAGGAAGAAC
CTTCTGTCCCAGCTTTGCAGAATGAAAAGCTTTCCTGCTTGGCAGTTATTCTTCCACAAGA
GAGGGCTTTCTCAGGACCTGGTTGCTACTGGTTCGGCAACTGCAGAAAATGTCCTCCCTT
GTGGCTTCCTCAGCTCCTGCCCTTGGCCTGAAGTCCCAGCATTGATGACAGCGCCTCATC
TTCAACTTTTGTGCTCCCCTTTGCCTAAACCGTATGGCCTCCCGTGCATCTGTACTCACCC
TGTACGACAAACACATTACATTATTAAATGTTTCTCAAAGATGGAGTT

Figure 89A

MVCLKLPGGSCMTALTVTLMVLSSPLALAGDTRPRFLWQLKFECHFFNGTERVRLLERCIYN
QEESVRFDSDVGEYRAVTELGRPDAEYWNSQKDLLEQRRAAVDTYCRHNYGVGESFTVQR
RVEPKVTVYPSKTQPLQHHNLLVCSVSGFYPGSIEVRWFRNGQEEKAGVVSTGLIQNGDWTF
QTLVMLETVPRSGEVYTCQVEHPSVTSPLTVEWRARSESAQSKMLSGVGGFVLGLLFLGAGL
FIYFRNQKGHSGLQPTGFLS

Figure 89B

ACGTCACTGTCTTGAAGCAGCAGTAGCCTGGGAAGTGAGGCAGGAGGAATTGAGAGGCA
GGAAGGGNGCTGGAGACACAGCTGAGCCTGGAAATGAGAGTGGGCATCGCCGTGGTCAT
CATGACTCCTCTGCGGCGTGGTCACCATGTTGGTTCACTGTGTTGGGCTCTTATTGACGGG
TCTCCTGCTAGGCCTGACCTTGGGTGCCGGAGCCCTGCTGGCTTCTGAGCCTATCTACCA
ACCACCTTCAGCCTGGGTGCCAGCTGGGGGGCTGGTGGGGCTGGCGCTGCTGGGAGCCC
TGCTCACACTTCGGTGGCCACGTCCATTCACAGTTCTGGGCACAACCCTGCTGGGTTCTG
CAGTGCTTGTGGCCTGTGTTGACTACTTCCTGGAGGGGCTGGCACTGGGGAGTTGGCTGG
GCCAACGCCTGCAGACACTTCCAGCCTTGCCTTCTCTCTGCTGATATAGCTGGGTCTTACT
GGGGATCTGGCCAGCCTTGGGGGCCCTTGGAGCCCTGGCCCAGTGGAAGCTCGTGCCTG
AGGAACATGGAGGCCACGCTAATGGGTCTGTTCCTGGTTTCCCAGATGCATAAAGGAAG
ACATATCCCTCCCCTGGGCAGCAAGGCTACAATGGGAGGGAGGGAGAACATGGGAGCAT
GTGAATAAAATGGCATTAAATACTG

Figure 90A

MLVHCVGLLLTGLLLGLTLGAGALLASEPIYQPPSAWVPAGGLVGLALLGALLTLRWPRPFT
VLGTTLLGSAVLVACVDYFLEGLALGSWLGQRLQTLPALPSLC

Figure 90B

CCGGGTCGACTACTACTACTACTAAATTCGCGGCCGCGTCGACCGCCCCTTGGCTTCTGC
ACTGATGGTGGGTGGATGAGTAATGCATCCAGGAAGCCTGGAGGCCTGTGGTTTCCGCA
CCCGCTGCCACCCCCGCCCCTAGCGTGGACATTTATCCTCTAGCGCTCAGGCCCTGCCGC
CATCGCCGCAGATCCAGCGCCCAGAGAGACACCAGAGAACCCACCATGGCCCCCTTTGA
GCCCCTGGCTTCTGGCATCCTGTTGTTGCTGTGGCTGATAGCCCCCAGCAGGGCCTGCAC
CTGTGTCCCACCCCACCCACAGACGGCCTTCTGCAATTCCGACCTCGTCATCAGGGCCAA
GTTCGTGGGGACACCAGAAGTCAACCAGACCACCTTATACCAGCGTTATGAGATCAAGA
TGACCAAGATGTATAAAGGGTTCCAAGCCTTAGGGGATGCCGCTGACATCCGGTTCGTCT
ACACCCCCGCCATGGAGAGTGTCTGCGGATACTTCCACAGGTCCCACAACCGCAGCGAG
GAGTTTCTCATTGCTGGAAAACTGCAGGATGGACTCTTGCACATCACTACCTGCAGTTTC
GTGGCTCCCTGGAACAGCCTGAGCTTAGCTCAGCGCCGGGGCTTCACCAAGACCTACACT
GTTGGCTGTGAGGAATGCACAGTGTTTCCCTGTTTATCCATCCCCTGCAAACTGCAGAGT
GGCACTCATTGCTTGTGGACGGACCAGCTCCTCCAAGGCTCTGAAAAGGGCTTCCAGTCC
CGTCACCTTGCCTGCCTGCCTCGGGAGCCAGGGCTGTGCACCTGGCAGTCCCTGCGGTCC
CAGATAGCCTGAATCCTGCCCGGAGTGGAAGCTGAAGCCTGCACAGTGTCCACCCTGTTC
CCACTCCCATCTTTCTTCCGGACAATGAAATAAAGAGTTACCACCCAGCA

Figure 91A

MAPFEPLASGILLLLWLIAPSRACTCVPPHPQTAFCNSDLVIRAKFVGTPEVNQTTLYQRYEIK
MTKMYKGFQALGDAADIRFVYTPAMESVCGYFHRSHNRSEEFLIAGKLQDGLLHITTCSFVA
PWNSLSLAQRRGFTKTYTVGCEECTVFPCLSIPCKLQSGTHCLWTDQLLQGSEKGFQSRHLA
CLPREPGLCTWQSLRSQIA

Figure 91B

GCCCGCGCCGCGCCGCTCTTTCTCCGACAGCTGCCGGGGGTGCCCTGCAAGCTGTTCCGC
GCGTCCTGCCCGTCTGTCCCCGCGGGTCGTCGCCCGCCACAGCCGCGCCATGACCACCCA
GCAGATAGACCTCCAGGGCCCGGGGCCGTGGGGCTTCCGCCTCGTGGGCGGCAAGGACT
TCGAGCAGCCTCTCGCCATTTCCCGGGTCACTCCTGGAAGCAAGGCGGCTCTAGCTAATT
TATGTATTGGAGATGTAATCACAGCCATTGATGGGGAAAATACTAGCAATATGACACAC
TTGGAAGCTCAGAACAGAATCAAAGGCTGCACAGACAACTTGACTCTCACTGTAGCCAG
ATCTGAACATAAAGTCTGGTCTCCTCTGGTGACGGAGGAAGGGAAGCGTCATCCATACA
AGATGAATTTAGCCTCTGAACCCCAGGAGGTCCTGCACATAGGAAGCGCCCACAACCGA
AGTGCCATGCCCTTTACCGCCTCGCCTGCCTCCAGCACTACTGCCAGGGTCATCACAAAC
CAGTACAACAACCCAGCTGGCCTCTACTCTTCTGAAAATATCTCCAACTTCAACAATGCC
CTGGAGTCAAAGACTGCTGCCAGCGGGGTGGAGGCGAACAGCAGACCCTTAGACCATGC
TCAGCCTCCAAGCAGCCTTGTCATCGACAAAGAATCTGAAGTTTACAAGATGCTTCAGGA
GAAACAGGAGTTGAATGAGCCCCCGAAACAGTCCACGTCTTTCTTGGTTTTGCAGGAAAT
CCTGGAGTCTGAAGAAAAAGGGGATCCCAACAAGCCCTCAGGATTCAGAAGTGTTAAAG
CTCCTGTCACTAAAGTGGCTGCGTCGATTGGAAATGCTCAGAAGTTGCCTATGTGTGACA
AATGTGGCACTGGGATTGTTGGTGTGTTTGTGAAGCTGCGGGACCGTCACCGCCACCCTG
AGTGTTATGTGTGCACTGACTGTGGCACCAACCTGAAACAGAAGGGCCATTTCTTTGTGG
AGGATCAAATCTACTGTGAGAAGCATGCCCGGGAGCGAGTCACACCACCTGAGGGTTAT
GAAGTGGTCACTGTGTTCCCCAAGTGAGCCAGCAGATCTGACCACTGTTCTCCAGCAGGC
CTCTGCTGCAGCTTTTTCTCTCAGTGTTCTGGCCCTCTCCTCTCTTGAAAGTTCTCTGCTTA
CTTTGGTTTTCCCTCTGCTTGTAAAACATTGAGTCCCCTCCCTGCCTTGGTTAATTGACTC
ACACCAGCTGTGCGATGCCCGCTTTTACAATTAAAGGAAAACTGTTTTGTTCAGTGTCAC
CTTGTCAGCAACACTGTGTCCCTTCGCCCCACCGTTCTTCTCTGCTGCATTTGGACATCAG
CCAAATTTGAACCCAATCAAATATAACGTGTCTGACACTGATTTTGTTTTTACTCAATAA
ATGTATAGACTACAAAAAAAAAAAAA

Figure 92A

MTTQQIDLQGPGPWGFRLVGGKDFEQPLAISRVTPGSKAALANLCIGDVITAIDGENTSNMTH
LEAQNRIKGCTDNLTLTVARSEHKVWSPLVTEEGKRHPYKMNLASEPQEVLHIGSAHNRSA
MPFTASPASSTTARVITNQYNNPAGLYSSENISNFNNALESKTAASGVEANSRPLDHAQPPSSL
VIDKESEVYKMLQEKQELNEPPKQSTSFLVLQEILESEEKGDPNKPSGFRSVKAPVTKVAASI
GNAQKLPMCDKCGTGIVGVFVKLRDRHRHPECYVCTDCGTNLKQKGHFFVEDQIYCEKHA
RERVTPPEGYEVVTVFPK

Figure 92B

1 cacagagccc gggccgcagg cacctcctcg ccagctcttc cgctcctctc acagccgcca
61 gacccgcctg ctgagcccca tggcccgcgc tgctctctcc gccgccccca gcaatccccg
121 gctcctgcga gtggcactgc tgctcctgct cctggtagcc gctggccggc gcgcagcagg
181 agcgtccgtg gccactgaac tgcgctgcca gtgcttgcag accctgcagg gaattcaccc
241 caagaacatc caaagtgtga acgtgaagtc ccccggaccc cactgcgccc aaaccgaagt
301 catagccaca ctcaagaatg ggcggaaagc ttgcctcaat cctgcatccc ccatagttaa
361 gaaaatcatc gaaaagatgc tgaacagtga caaatccaac tgaccagaag ggaggaggaa
421 gctcactggt ggctgttcct gaaggaggcc ctgcccttat aggaacagaa gaggaaagag
481 agacacagct gcagaggcca cctggattgt gcctaatgtg tttgagcatc gcttaggaga
541 agtcttctat ttatttattt attcattagt tttgaagatt ctatgttaat attttaggtg
601 taaaataatt aagggtatga ttaactctac ctgcacactg tcctattata ttcattcttt
661 ttgaaatgtc aaccccaagt tagttcaatc tggattcata tttaatttga aggtagaatg
721 ttttcaaatg ttctccagtc attatgttaa tatttctgag gagcctgcaa catgccagcc
781 actgtgatag aggctggcgg atccaagcaa atggccaatg agatcattgt gaaggcaggg
841 gaatgtatgt gcacatctgt tttgtaactg tttagatgaa tgtcagttgt tatttattga
901 aatgatttca cagtgtgtgg tcaacatttc tcatgttgaa actttaagaa ctaaaatgtt
961 ctaaatatcc cttggacatt ttatgtcttt cttgtaaggc atactgcctt gtttaatggt
1021 agttttacag tgtttctggc ttagaacaaa ggggcttaat tattgatgtt ttcatagaga
1081 atataaaaat aaagcactta tag

Figure 93A

MARAALSAAPSNPRLLRVALLLLLLVAAGRRAAGASVATELRCQCLQTLQGIHPKNIQSVNV
KSPGPHCAQTEVIATLKNGRKACLNPASPIVKKIIEKMLNSDKSN

Figure 93B

TGCAATTAAAGGAGTCGGGTCTCTAACTGTTGATCTGTTTTTTTCCCTTCTGAGCAATGGA
GCTTACCATCTTTATCCTGAGACTGGCCATTTACATCCTGACATTTCCCTTGTACCTGCTG
AACTTTCTGGGCTTGTGGAGCTGGATATGCAAAAAATGGTTCCCCTACTTCTTGGTGAGG
TTCACTGTGATATACAACGAACAGATGGCAAGCAAGAAGCGGGAGCTCTTCAGTAACCT
GCAGGAGTTTGCGGGCCCCTCCGGGAAACTCTCCCTGCTGGAAGTGGGCTGTGGCACGG
GGGCCAACTTCAAGTTCTACCCACCTGGGTGCAGGGTGACCTGTATTGACCCCAACCCCA
ACTTTGAGAAGTTTTTGATCAAGAGCATTGCAGAGAACCGACACCTGCAGTTTGAGCGCT
TTGTGGTAGCTGCCGGGGAGAACATGCACCAGGTGGCTGATGGCTCTGTGGATGTGGTG
GTCTGCACCCTGGTGCTGTGCTCTGTGAAGAACCAGGAGCGGATTCTCCGCGAGGTGTGC
AGAGTGCTGAGACCGGGAGGGGCTTTCTATTTCATGGAGCATGTGGCAGCTGAGTGTTCG
ACTTGGAATTACTTCTGGCAACAAGTCCTGGATCCTGCCTGGCACCTTCTGTTTGATGGGT
GCAACCTGACCAGAGAGAGCTGGAAGGCCCTGGAGCGGGCCAGCTTCTCTAAGCTGAAG
CTGCAGCACATCCAGGCCCCACTGTCCTGGGAGTTGGTGCGCCCTCATATCTATGGATAT
GCTGTGAAATAGTGTGAGCTGGCAGTTAAGAGCTGAATGGCTCAAAGAATTTAAAGCTT
CAGTTTTACATTTAAAATGCTAAGTGGGAGAAGAGAAACCTTTTTTTTGGGGGGCGGTTT
TTTTGGTTTGTTGTTGGTTTTTTTTTTTTTTTGGCAGGAGAATCTCTTGAACCCAGAAGGC
GAAGGTTGCAGTGAACCGAGATCATGCCATTGTACTCTAGCCTGGGTGACAAGAGCAAG
ACTCCGTCTCAAAAAAAAAAAAAAAAAAAAAAAGAAGTAGAGACAGGGAGACGGGGTC
TCACTGTGTTGCCTAGGCCGGTCTTGAACTCCTGGGCTCAAGTGATTCTCCCACCTTGACC
TCCTAAATTGTTGGGATTACAGGTGTGAGACAGTGCACCTGGCCGAAATAGCTCAAGTTT
CTGAAAAACAAATCTGAATCTATTTGTTATTCTTAGCGTCACTGGTCTGGCTTTCAGAATT
AACATACAAGGTTGCCACACCTAGTTCTGCCCAGCTTTATGTCTTTTATTCCAGTATTCCA
CCAAAGTTTGTTTTCCTGCATTCCAGTTCTCAAGTCTTAAGATAAAGATTGTACTTGACAG
TTTAGTATATCCATAAAACTATTTGAGGTGGTTAAGGTTCTTGGGTTCATTTTCCTTAATA
CTTTGCTGAATATTGTAGATTGTAGGCAATGAAAAAGTCTACTAAATTAGGAAAACCTTG
AATAATTAGGTATCCTAGGTAAGAGCCCCTAAACATCAAGCAATCTGTGAGTCTGTAAA
GAAATAAATATTTTTTGGATTATTCTTATCTAATTCCACCCCTGTTGGAAGATGATTTCTT
TGTTCTTTGCAACTATGGAAGCTGTGAAAATCATCACAAGTGCCTCTGAAAGCGAGTGTT
AGGTTGGTTAGAGGGTTTAATATTTTCTGCAATGGTTTGTAGGAATTTTAATAAATGTAG
TATATTTTCTGAGATGATTTTGTAAAAGTACTATTTTAAATATCAAATCAACCAATAAATT
CACATTTGTGTTAGGAACAAAA

Figure 94A

MELTIFILRLAIYILTFPLYLLNFLGLWSWICKKWFPYFLVRFTVIYNEQMASKKRELFSNLQE
FAGPSGKLSLLEVGCGTGANFKFYPPGCRVTCIDPNPNFEKFLIKSIAENRHLQFERFVVAAGE
NMHQVADGSVDVVVCTLVLCSVKNQERILREVCRVLRPGGAFYFMEHVAAECSTWNYFWQ
QVLDPAWHLLFDGCNLTRESWKALERASFSKLKLQHIQAPLSWELVRPHIYGYAVK

Figure 94B

GTCTCCTGCTATCAGGTAATGCCAACCTCAACCCCCTGGACCAGTCACCCCGATCAGACT
TTGCTTGCCTGATTTTAGGCCAGGTCAGACATCAGAGGAGAGCCCAGATCCTTGTTTCCT
CTCCCCCCGCAGGGCTTCCCCTTTCTTGGTCATCGATCCCTAGAGCTCTGGCTCTTTCTCT
TCTTGGGGTGAGAAACTGCTAAGAACAGTTTATTTCCCATGCATGCATCTGGGCTTGCCA
CTGATCTGCCTTTTCCCCCCTCCTCCCCAGGTTAGGGACACCTGGGTCCAACCTTCCCAAG
GAATATGGGGATGGGGGTTGGAGATGAAGTTTAGTGCTAGACTGTAAGGTAGGTGGGGT
GGAAGTACATGAGGGAAAGGGCTAAAATGGTACTAATGGTGTTAAGGATAGGGTGAATT
ATTTAAGAGGAAAAAGACTAGGCCCAGGTTCTCCTTAGCCATGTGGCTTTCCCAGGGCAG
AGGGTGGCCCCTCCCTACCCAGGGGCCCAGCAGAGACTGACTTTTGATCCCTACCCCAGA
GACCAGTGAACCATTAACTCCTCTCTTATGTGAGCCTTCACACACTGGCCCCACCCCTGA
CCCCGCCCCAAGGCAGGTGGGCTAGGAGGGGGTGCATGTCCATCTCAGCCTTCTATGTGA
CGTGGCCTCCGATCCACCTGGACACCTGGAGGCTAAGCCTGGATTCCCCCTTCCCTGACT
CAGGAACTGCTTAACGTCTACAGCAAGGCCTAATAGGGGACCTGAGGGCACAGTCCTCA
GGATGTTTCGGGGAGAATAGGAGCCAGAACCTGAGCCCCTAAGCTATTCCCCTCACCAA
TGATGGGGTCCCCAGTGAGTCATCTGCTGGCCGGCTTCTGTGTGTGGGTCGTCTTGGGCT
GGGTAGGGGGCTCAGTCCCCAACCTGGGCCCTGCTGAGCAGGAGCAGAACCATTACCTG
GCCCAGCTGTTTGGCCTGTACGGCGAGAATGGGACGCTGACTGCAGGGGGCTTGGCGCG
GCTTCTCCACAGCCTGGGGCTAGGCCGAGTTCAGGGGCTTCGCCTGGGACAGCATGGGC
CTCTGACTGGACGGGCTGCATCCCCAGCTGCAGACAATTCCACACACAGGCCACAGAAC
CCTGAGCTGAGTGTGGATGTCTGGGCAGGGATGCCTCTGGGTCCCTCAGGGTGGGGTGA
CCTGGAAGAGTCAAAGGCCCCTCACCTACCCCGTGGGCCAGCCCCCTCGGGCCTGGACCT
CCTTCACAGGCTTCTGTTGCTGGACCACTCATTGGCTGACCACCTGAATGAGGATTGTCT
GAACGGCTCCCAGCTGCTGGTCAATTTTGGCTTGAGCCCCGCTGCTCCTCTGACCCCTCGT
CAGTTTGCTCTGCTGTGCCCAGCCCTGCTTTATCAGATCGACAGCCGCGTCTGCATCGGC
GCTCCGGCCCCTGCACCCCCAGGGGATCTACTATCTGCCCTGCTTCAGAGTGCCCTGGCA
GTCCTGTTGCTCAGCCTCCCTTCTCCCCTATCCCTGCTGCTGCTGCGGCTCCTGGGACCTC
GTCTACTACGGCCCTTGCTGGGCTTCCTGGGGGCCCTGGCGGTGGGCACTCTTTGTGGGG
ATGCACTGCTACATCTGCTACCGCATGCACAAGAAGGGCGGCACGCAGGACCTGGCGGA
CTACCAGAGAAGGACCTGGGCCCGGGGCTGTCAGTGCTCGGAGGCCTCTTCCTGCTCTTT
GTGCTGGAGAACATGCTGGGGCTTTTGCGGCACCGAGGGCTCAGGCCAAGATGCTGCAG
GCGAAAACGAAGGAATCTCGAAACACGCAACTTGGATCCGGAGAATGGCAGTGGGATG
GCCCTTCAGCCCCTACAGGCAGCTCCAGAGCCAGGGGCTCAGGGCCAGAGGGAGAAGAA
CAGCCAGCACCCACCAGCTCTGGCCCCTCCTGGGCACCAAGGCCACAGTCATGGGCACC
AGGGTGGCACTGATATCACGTGGATGGTCCTCCTGGGAGATGGTCTACACAACCTCACTG
ATGGGCTGGCCATAGGTGCTGCCTTCTCTGATGGCTTCTCCAGCGGCCTCAGTACCACCT
TAGCGGTCTTCTGCCATGAGCTGCCCCACGAACTGGGTGACTTTGCCATGCTGCTCCAGT
CAGGGCTGTCCTTTCGGCGGCTGCTGCTGCTGAGCCTCGTGTCTGGAGCCCTGGGATTGG
GGGGTGCAGTCCTGGGGGTGGGGCTCAGCCTGGGCCCTGTCCCCCTCACTCCCTGGGTGT
TTGGGGTCACTGCTGGGGTCTTCCTCTATGTGGCCCTTGTGGACATGCTACCAGCCCTGCT
TCGTCCTCCGGAGCCCCTGCCTACGCCCCATGTGCTCCTGCAGGGGCTGGGGCTGCTGCT
GGGGGGCGGCCTCATGCTTGCCATAACCCTGCTGGAGGAGCGGCTACTGCCCGTGACCA
CTGAGGGCTGATGGGGCCAGTGGAAAGGGGTCGGGTTGCCCTTCCTTCCCCCCAACCAC
AGGAATGGAGGCGGGACACAGGGCCAGTAGGAGCAATAGGATTTTAATAAACAGAACC
CATCCCAAAGCCATGACTACGACAGTTGTACTTGCACCAAAACAGCATAGAAAACCAGA
GTGTGGTGGGAGGACCCGAAGCCGGTTGGGGGAGGATGTGAGTAGGGGCCTGGAGGGT
GCAGGGTCATTAATCTGCGGGGAGAACATTGTGCTTTAGCCCAGGGAGGGGAGGGGTGG
GGCAAATGCACCGAGGTCCCCACTTTTTCCTGCTGCCCTCGGCACCCTGGGGATGCAGGC
ATCTGGGCACATCTGCCCCTTATTGCTGCCCACCAGCGTT

Figure 95A

AAACGCCCCCGATCCCAACACTAGCACCACAGGTGGTTCCGGGGCAGGGAGAGGCAGGA
ATGGGAAAATTGCTTAGAGAAAGATTCCACTAGAATCCAGTGAATTGTGCTCAGTTCTCT
TTACTTCCTACAACCGAGTACATGGGTCACAGGGTGGAGGGTGCAACAGGACATGGAAC
ATGCCCCTCCGTGCCCCCCAACACACACCTGCACACAGGATGGTGGTGTCTGCAGCATCA
CAGGTCATGCAGGGCATGGGGAAGGGGAGGTTCACACACACATAGATGCCCACAGCGG
GTACCAGACGGAGAACACCCCTGAATATACATAGCTGTACATGGGGAACCCCCAGGTCC
CCACCCCAACCCTCTCCCCTGTCTTGCTGTCCCCCGCAGGGGAACTATATTGCTTTGAGA
GAGCCACCCCAGGGGCTGCTCTGCCAGGCACCCTCCCCTCCCACCCACCCCCATTTTGGC
ACATCTGCAAGACACACAGCAGCGAGAGTAGGCACCCTCCCTTCCCAGGCTTCTGTGGCC
TGGAGCTGGAGAAGGGGGTAGGAGACTTCATCCTCCATCCTCCCCTAACCCTTCCCAAAC
CCCTGCCAAACCCACTCAAGCCAGAACCCACCCCCACCCCCCAAACACACATACAAAGC
TGAGCTATCCAGGAACACAAGGGAAACAAGGAGATTGTCCAGGGTGGGAGCGGAGGCA
GCGGGGGAAGAAGACTGGAAGCAGAGACCTCCCCCCTTGTGGGGGGCAGACTGGCACA
ACAGCTACTTTAGTGCAATTGGAGAGGGTGCCCAGAGTGAGAGGTGGAGAAGGGAGGG
AAGGCGGTCCCCAACTTCCCTGGGGGCAAAGTCAGGCTTCCAGATTCCCCAGGGAAAGG
GCCTAGCAGGAGTGGGTGAGGGCCAAGGTGGATCCTCTGGTTACCCGCCACCCTCTGCCC
TCCCAAATGCAGTGACAGTGTCCCCCTCACACCTAAGTGGGCAACAGCAGCCTTGGAGTC
AGTACCTTCAAGTAATTCAAAGAGCAGACCCTCCCCACCCCAGCTTCACCCCATCTCTGG
GATTTGGTCGCTTCTCTAGGGGTTGGGTTGGGAGGAGGGAGCCCCCAAGGCAGACCCTTC
CCTCTCTACCTCCCGATTCCCAGACCACTGGGCTTGGTCCTCAAAGATTCCTCACCTCCGC
CCTTGCCCAACCTGGGTCAAGGCTGCAGAAGGCTGGAGCCACCACAATTAGAGGGGAAG
GGGCTGCTTTGTTCCTTATCCCTCCTTCTTAAAAGGTAGGGTTCAAACTAGGCGGGATGG
GGGCCCATACTGGTTTGCCCCAGGAGTAGGGTTTCTGGGCTAGGGTCTGTAAGGCTATTT
TCCTTTGCGGTGGGAAGGGGAGGTAGGGGATGAACACTGGGTATGGGAAGTGGGTGAGA
AATGGCTGAGAGGGAAGGAGGAAGGGGCCTCCCCGCTGGAGCAGTCACTGGAGTCATTT
AGACAAAAACACTCATGTGCATAAGATACACAGTGCGCAAACTCAGCCCTGCCAGCCCG
GCCCCAATCCCACCTCTCAGGACTCCTTCCAAGACCCTGGAGGAGGTTCTGGGGATACAG
CTGTAGAACCGTTCACTCTGGCCCCATCCACCCCACCTCCAGCCTCTTCTCCCCTTCTAGG
TCCAGGGAGTAAGAAGGTGCTCGGGTGGGCAGACAGTGGTGGAAACAGTATTGAGTTTT
CCTTTGGTTACATATTGAAGGCAAAGGTGAGCTGGACTTACAGTCAAAACGGATAGGGG
TGAGGAAGGAAGAGGGGCCATGGCTGGGGTTGGAGAGGGAGGTAGGCCCTCCTCAGCC
CCTCCACCCCAAGAAACACATCTACGTGGGGTGGCAGTCCCTCAGTCTTTTCTCTCCCAC
GCCCCACAGCACCAAACAAAAGGAGAAGCCCCCTCCCCCAGGGGCTGCTCCCCACCCCA
ACCTGGGCTGTACATTCAGTGGTTTTCAGCAGTCCTATGGCTCAGGGGGCCACGGGGCAG
GGGAGGTGGCCCGTCAGTCTCAGTGGACAGTGGCAGTGACCCGGGTCTGCTGGTCCTTCC
TGGGACCCACGGTTTGTGCCATTCGTTTTTCTGAAGGATAGTATATGACCCTACCAGAGC
CACCGCCCAATCAGAAATAGCTCCCCCAAAATCAGAAACTAAAAACTGGCTCTTTCCATC
TCACCCTCTGATTCACACGTCTGTTTCCCTGTCTCCTATGTCGCCCTCGCTCTGTTTCCTTT
GCTGGGACCTGGGGCTGCTCCCAGGGTCCTCGCTTAAAATAGGCCTTTTCACAAAAGTGC
TTATTACTTGAAGCAAGTGCTTTAGGGCTGCGGTGGGGAGAGGGGGGAGGGGGAGGGCA
AAGGGAAGGCGCTGTTCCCTCCCCGCCCTCCCCCATGAAGACTGGGGGGCATTCTGCCTG
TTTTACTTCTCCACACCCGTTTAAGTCAAAGAGGTTTAAAAAAAAATCTTAACATTAAAAT
AAATATGCAGTGGCCATGAGAATGGTCAAAATGCTTCAAAAAACACTAGGGCTGGGGAG
CCCAGGGTGGGGCGTGGGGTTTCCTTTGGCATAAGGAGAGGAGGCTGCTTGTCCCCCAG
GCTTCCTCACAGCCACATATGGAGGGACAGAGGACTCCCCACCACCTCCCAGCACTGCTG
ACAGTGCGCTGAGGGCAGCAGGGCGCAGACAGCCCCCAGAAATCTCATCTAGCAAGACA
ACGGGGCTCTGACACTCAGACGCTTCCCGCCATCACCAAACATCACGAAAGGAGAACAC
GACTCACACCCGGCAAGTTCTCTCTGGAGGACCCATCT

Figure 95A (continued)

TCTCACTCCCCTTGCCCCCCACCACCTAATTCCCAGCACCAAGATGAGAGGGAGGGGGTG
GAATGGGAAGATTTCAGGAGAGAGAATTGAAGGGAAGGCAAGCTTTGCAGAGCCAGCA
GGGTTGGGGATGGGGGCTGCAGCCCTTAAGAGAGGTCACATTGATTGTCATATAGGGGA
GGACACGGTGTGGAGGGAGGTGGGCAAGAGGGGCGTCACAAGGCCCTTTGGCTTTGAAA
ATAAAAATAAAAACTAAAAGCTGCACAATCCTTCTCATCAATAATGGTCATTTGGAAGCC
TTGAAATGATTTAGGAACTGAGGGTTGGGAGAAGCAAAACACAGAGAGACAGGGGATC
AAAAGGGACCATGAAAAGATAAGGACTTGGACAACACCCCAGGCTTCTGGAAACCAGC
ATGAGGTATGGTTAAAGGTATCCGTTGGGGAGGGAGGGGGTCCCTGGGACGCCCCCCTC
CCCTCAGCCCACCCTTGACAAGGGTGGCAAGACATTCAGGGTATACAACTAAAAGATGG
GTAAGACTGTGAATAAAGCAAACTTGAGTAGGGGAGGGAGGCTGAAGGATCCCCCCTCA
GGGGAGACCCTGTACTGTGTAAACGAAGCCTGTCCAGTTCTCAGGGGACAATACTGATG
GCAGCCAAACTGGGCAAGGATGCAGTGTGGGGGCGGAGGGGGCATGACCTCTATTCAAG
TTCTGTGTCTTGGCCCCTGGCTGAGGTATTGAGTGTGAGGAAGGGAACACTGGGCTGCAG
GAGTGGGTCCAACTGTCCAGGAGGCTGCACTAGGAGATGGGTGGACAGAGCACTTAAAG
GGACCAGGGCCAAATTCAATGCTACATTTAGAGAGAAAACTGCCCCCTCTTCACTCCAGC
CCAGTTTGGCTTTTGGGGTGCGACTTTAGAAATCTTATCAGTGCAGCCCCCAGCTCAATC
CCATCTTTCCTCCCTGCTGGGAAGGCAGGGACCAAGCCCCAGTACCTATTCATCTCTCTCT
AGGTCAGAGCTTCTTCCTCACACTGGAGGGGAAGCCTGGGTCCCGAGTAGCCACGGTCC
CTTGTCGGCCCTGCCCCTCCTACCATCTTTGGCTTCAGATCAGGAGTGACTGGGGCAGTG
GGTACTCTTGGACATAACGGAAGGTGGAGGCAGATAGGGAGCACAGATAAACTATGGGC
TTGGCGGCACAGGAGGAAGAACATGGTCCCTCCCTCCATATACATGCAAACACATGCCT
GAAACACAGTGGACATACTAGGGCTGTGGTTTTGAAATGGGCAGGAAATTAATTTGTTTC
TTCCCCTAAAGGATAAAACGCTTACTTAAAAATTCATGACAAGCCTCAAAGTTCAAGGG
AAGGAGAGCCAGGGCAGGAATGACCACAGGCTCTGCCCTCCCAAAAGAAGATAAAAGA
AAGAAGCAAGGTTAAAGTGCGTGGTTAGGGGCCAGGCTAGGAGTGGGAGGGAATGGGG
AGGGGGCAGGCTGTGGGGGCAGAACCAGCCCTTGATTTGCATATGAGGAGCCAGGGGAG
AGTGCAGGATTGGGGCCCAGGTACAGTAGTTGCTGCTTCAAGTGTTTTGCATTTGAACTT
TAGGGGTGATAGGGTACAGAAGTGGGGAAAAAGCTCCAGGCCCCAGTGCTAAATATCCT
CCCCCCTCATCCTCTAGCTGCCCCTGAAGGGGGGAGGGGGACACCCCCAGAGTGCTCAC
ACAGTACCAGAAATTAAGGCTTCTCACTGCTGCGGGGATGGAGGGACCGGCCGAGCAGG
GAGGCAGTGATGGGTATGGAAGAAGAGGGGATCTGCCTGGCAGTAGGGGCAGGGGAGA
AGGGGGACACAGAGAGGAGTCCCCAGGGAAGAGTCGGGGGAGCTGGCAGCAGAAAGAG
GGAACCAAGAGATGGAGTCAAAGAGTGGGGGAGCCAGGCATTTAGCAATCATTTTGGGA
CACTTGGCAGAAGGGGTCGCCCTGGGGGTACCAAGGGCCTGGGGTGCTCCCTGTCAGTC
CCAGACCCCTGCCAGGCCAAGATGGTGTGGCAAAGGGGTGAGCAGCTGCTCCCCAGGGC
TTCCTTCCCCTCCGCCCCCTCCACCCAGTCGTGTTCTCCTTTAAAGTGCCCTAAATGTTTA
GACTTTTTCTAAATAAATAGAATTAGATATCAAGCCACCGGCGGGGGAGGGACACTGGA
GGGGGCTACTCAGAGTAGCAGCCATCTAACCCAATGGCGCCGGGCCGCTCCTGGCTGTA
GGGGCAGGAGGCCCCATGGGGCAGGGCGCCGCAGCCACCCACCGTCTTGGCGGCTGCAA
TGCTGCAGTTCTTGAGCAGGCTGAAGCTGAAAGGACTGACGGCGTCCTTGGGTGGGAAA

Figure 95A (continued)

MMGSPVSHLLAGFCVWVVLGWVGGSVPNLGPAEQEQNHYLAQLFGLYGENGTLTAGGLA
RLLHSLGLGRVQGLRLGQHGPLTGRAASPAADNSTHRPQNPELSVDVWAGMPLGPSGWGD
LEESKAPHLPRGPAPSGLDLLHRLLLLDHSLADHLNEDCLNGSQLLVNFGLSPAAPLTPRQFA
LLCPALLYQIDSRVCIGAPAPAPPGDLLSALLQSALAVLLLSLPSPLSLLLLRLLGPRLLRPLLG
FLGALAVGTLCGDALLHLLPHAQEGRHAGPGGLPEKDLGPGLSVLGGLFLLFVLENMLGLLR
HRGLRPRCCRRKRRNLETRNLDPENGSGMALQPLQAAPEPGAQGQREKNSQHPPALAPPGH
QGHSHGHQGGTDITWMVLLGDGLHNLTDGLAIGAAFSDGFSSGLSTTLAVFCHELPHELGDF
AMLLQSGLSFRRLLLLSLVSGALGLGGAVLGVGLSLGPVPLTPWVFGVTAGVFLYVALVDM
LPALLRPPEPLPTPHVLLQGLGLLLGGGLMLAITLLEERLLPVTTEG

Figure 95B

CCCAGACTCCAGCCCTGGACCGCGCATCCCGAGCCCAGCGCCCAGACAGAGTGTCCCCA
CACCCTCCTCTGAGACGCCATGTTCAACTCGATGACCCCACCACCAATCAGTAGCTATGG
CGAGCCCTGCTGTCTCCGGCCCCTCCCCAGTCAGGGGGCCCCCAGTGTGGGGACAGAAG
GACTGTCTGGCCCGCCCTTCTGCCACCAAGCTAACCTCATGTCCGGCCCCCACAGTTATG
GGCCAGCCAGAGAGACCAACAGCTGCACCGAGGGCCCACTCTTTTCTTCTCCCCGGAGTG
CAGTCAAGTTGACCAAGAAGCGGGCACTGTCCATCTCACCTCTGTCGGATGCCAGCCTGG
ACCTGCAGACGGTTATCCGCACCTCACCCAGCTCCCTCGTAGCTTTCATCAACTCGCGAT
GCACATCTCCAGGAGGCTCCTACGGTCATCTCTCCATTGGCACCATGAGCCCATCTCTGG
GATTCCCAGCCCAGATGAATCACCAAAAAGGGCCCTCGCCTTCCTTTGGGGTCCAGCCTT
GTGGTCCCCATGACTCTGCCCGGGGTGGGATGATCCCACATCCTCAGTCCCGGGGACCCT
TCCCAACTTGCCAGCTGAAGTCTGAGCTGGACATGCTGGTTGGCAAGTGCCGGGAGGAA
CCCTTGGAAGGTGATATGTCCAGCCCCAACTCCACAGGCATACAGGATCCCCTGTTGGGG
ATGCTGGATGGGCGGGAGGACCTCGAGAGAGAGGAGAAGCGTGAGCCTGAATCTGTGTA
TGAAACTGACTGCCGTTGGGATGGCTGCAGCCAGGAATTTGACTCCCAAGAGCAGCTGG
TGCACCACATCAACAGCGAGCACATCCACGGGGAGCGGAAGGAGTTCGTGTGCCACTGG
GGGGGCTGCTCCAGGGAGCTGAGGCCCTTCAAAGCCCAGTACATGCTGGTGGTTCACAT
GCGCAGACACACTGGCGAGAAGCCACACAAGTGCACGTTTGAAGGGTGCCGGAAGTCAT
ACTCACGCCTCGAAAACCTGAAGACGCACCTGCGGTCACACACGGGTGAGAAGCCATAC
ATGTGTGAGCACGAGGGCTGCAGTAAAGCCTTCAGCAATGCCAGTGACCGAGCCAAGCA
CCAGAATCGGACCCATTCCAATGAGAAGCCGTATGTATGTAAGCTCCCTGGCTGCACCAA
ACGCTATACAGATCCTAGCTCGCTGCGAAAACATGTCAAGACAGTGCATGGTCCTGACG
CCCATGTGACCAAACGGCACCGTGGGGATGGCCCCCTGCCTCGGGCACCATCCATTTCTA
CAGTGGAGCCCAAGAGGGAGCGGGAAGGAGGTCCCATCAGGGAGGAAAGCAGACTGAC
TGTGCCAGAGGGTGCCATGAAGCCACAGCCAAGCCCTGGGGCCCAGTCATCCTGCAGCA
GTGACCACTCCCCGGCAGGGAGTGCAGCCAATACAGACAGTGGTGTGGAAATGACTGGC
AATGCAGGGGGCAGCACTGAAGACCTCTCCAGCTTGGACGAGGGACCTTGCATTGCTGG
CACTGGTCTGTCCACTCTTCGCCGCCTTGAGAACCTCAGGCTGGACCAGCTACATCAACT
CCGGCCAATAGGGACCCGGGGTCTCAAACTGCCCAGCTTGTCCCACACCGGTACCACTGT
GTCCCGCCGCGTGGGCCCCCCAGTCTCTCTTGAACGCCGCAGCAGCAGCTCCAGCAGCAT
CAGCTCTGCCTATACTGTCAGCCGCCGCTCCTCCCTGGCCTCTCCTTTCCCCCCTGGCTCC
CCACCAGAGAATGGAGCATCCTCCCTGCCTGGCCTTATGCCTGCCCAGCACTACCTGCTT
CGGGCAAGATATGCTTCAGCCAGAGGGGGTGGTACTTCGCCCACTGCAGCATCCAGCCT
GGATCGGATAGGTGGTCTTCCCATGCCTCCTTGGAGAAGCCGAGCCGAGTATCCAGGAT
ACAACCCCAATGCAGGGGTCACCCGGAGGGCCAGTGACCCAGCCCAGGCTGCTGACCGT
CCTGCTCCAGCTAGAGTCCAGAGGTTCAAGAGCCTGGGCTGTGTCCATACCCCACCCACT
GTGGCAGGGGGAGGACAGAACTTTGATCCTTACCTCCCAACCTCTGTCTACTCACCACAG
CCCCCCAGCATCACTGAGAATGCTGCCATGGATGCTAGAGGGCTACAGGAAGAGCCAGA
AGTTGGGACCTCCATGGTGGGCAGTGGTCTGAACCCCTATATGGACTTCCCACCTACTGA
TACTCTGGGATATGGGGGACCTGAAGGGGCAGCAGCTGAGCCTTATGGAGCGAGGGGTC
CAGGCTCTCTGCCTCTTGGGCCTGGTCCACCCACCAACTATGGCCCCAACCCCTGTCCCC
AGCAGGCCTCATATCCTGACCCCACCCAAGAAACATGGGGTGAGTTCCCTTCCCACTCTG
GGCTGTACCCAGGCCCCAAGGCTCTAGGTGGAACCTACAGCCAGTGTCCTCGACTTGAAC
ATTATGGACAAGTGCAAGTCAAGCCAGAACAGGGGTGCCCAGTGGGGTCTGACTCCACA
GGACTGGCACCCTGCCTCAATGCCCACCCCAGTGAGGGGCCCCCACATCCACAGCCTCTC
TTTTCCCATTACCCCCAGCCCTCTCCTCCCCAATATCTCCAGTCAGGCCCCTATACCCAGC
CACCCCCTGATTATCTTCCTTCAGAACCCAGGCCTTGCCTGGACTTTGATTCCCCCACCCA
TTCCACAGGGCAGCTCAAGGCTCAGCTTGTGTGTAATTATGTTCAATCTCAACAGGAGCT
ACTGTGGGAGGGTGGGGGCAGGGAAGATGCCCCCG

Figure 96A

CCCAGGAACCTTCCTACCAGAGTCCCAAGTTTCTGGGGGGTTCCCAGGTTAGCCCAAGCC
GTGCTAAAGCTCCAGTGAACACATATGGACCTGGCTTTGGACCCAACTTGCCCAATCACA
AGTCAGGTTCCTATCCCACCCCTTCACCATGCCATGAAAATTTTGTAGTGGGGGCAAATA
GGGCTTCACATAGGGCAGCAGCACCACCTCGACTTCTGCCCCCATTGCCCACTTGCTATG
GGCCTCTCAAAGTGGGAGGCACAAACCCCAGCTGTGGTCATCCTGAGGTGGGCAGGCTA
GGAGGGGGTCCTGCCTTGTACCCTCCTCCCGAAGGACAGGTATGTAACCCCCTGGACTCT
CTTGATCTTGACAACACTCAGCTGGACTTTGTGGCTATTCTGGATGAGCCCCAGGGGCTG
AGTCCTCCTCCTTCCCATGATCAGCGGGGCAGCTCTGGACATACCCCACCTCCCTCTGGG
CCCCCCAACATGGCTGTGGGCAACATGAGTGTCTTACTGAGATCCCTACCTGGGGAAACA
GAATTCCTCAACTCTAGTGCCTAAAGAGTAGGGAATCTCATCCATCACAGATCGCATTTC
CTAAGGGGTTTCTATCCTTCCAGAAAAATTGGGGGAGCTGCAGTCCCCTGCACAAGATGC
CCCAGGGATGGGAGGTATGGGCTGGGGGCTATGTATAGTCTGTATACGTTTTGAGGAGA
AATTTGATAATGACACTGTTTCCTGATAATAAAGGAACTGCATCAG

Figure 96A (continued)

MFNSMTPPPISSYGEPCCLRPLPSQGAPSVGTEGLSGPPFCHQANLMSGPHSYGPARETNSCTE
GPLFSSPRSAVKLTKKRALSISPLSDASLDLQTVIRTSPSSLVAFINSRCTSPGGSYGHLSIGTMS
PSLGFPAQMNHQKGPSPSFGVQPCGPHDSARGGMIPHPQSRGPFPTCQLKSELDMLVGKCRE
EPLEGDMSSPNSTGIQDPLLGMLDGREDLEREEKREPESVYETDCRWDGCSQEFDSQEQLVH
HINSEHIHGERKEFVCHWGGCSRELRPFKAQYMLVVHMRRHTGEKPHKCTFEGCRKSYSRL
ENLKTHLRSHTGEKPYMCEHEGCSKAFSNASDRAKHQNRTHSNEKPYVCKLPGCTKRYTDP
SSLRKHVKTVHGPDAHVTKRHRGDGPLPRAPSISTVEPKREREGGPIREESRLTVPEGAMKPQ
PSPGAQSSCSSDHSPAGSAANTDSGVEMTGNAGGSTEDLSSLDEGPCIAGTGLSTLRRLENLR
LDQLHQLRPIGTRGLKLPSLSHTGTTVSRRVGPPVSLERRSSSSSSISSAYTVSRRSSLASPFPPG
SPPENGASSLPGLMPAQHYLLRARYASARGGGTSPTAASSLDRIGGLPMPPWRSRAEYPGYN
PNAGVTRRASDPAQAADRPAPARVQRFKSLGCVHTPPTVAGGGQNFDPYLPTSVYSPQPPSIT
ENAAMDARGLQEEPEVGTSMVGSGLNPYMDFPPTDTLGYGGPEGAAAEPYGARGPGSLPLG
PGPPTNYGPNPCPQQASYPDPTQETWGEFPSHSGLYPGPKALGGTYSQCPRLEHYGQVQVKP
EQGCPVGSDSTGLAPCLNAHPSEGPPHPQPLFSHYPQPSPPQYLQSGPYTQPPPDYLPSEPRPC
LDFDSPTHSTGQLKAQLVCNYVQSQQELLWEGGGREDAPAQEPSYQSPKFLGGSQVSPSRAK
APVNTYGPGFGPNLPNHKSGSYPTPSPCHENFVVGANRASHRAAAPPRLLPPLPTCYGPLKV
GGTNPSCGHPEVGRLGGGPALYPPPEGQVCNPLDSLDLDNTQLDFVAILDEPQGLSPPPSHDQ
RGSSGHTPPPSGPPNMAVGNMSVLLRSLPGETEFLNSSA

Figure 96B

ACACACCACACACACTCACACTCACACACACTCACACACACTCATCCCCTTGAATCTTGG
GGCAGGAACTCAGAAAACTTCCAGCCCGGGCAGCGCGCGCTTGGTGCAAGACTCAGGAG
CTAGCAGCCCGTCCCCCTCCGACTCTCCGGTGCCGCCGCTGCCTGCTCCCGCCACCCTAG
GAGGCGCGGTGCCACCCACTACTCTGTCCTCTGCCTGTGCTCCGTGCCCGACCCTATCCC
GGCGGAGTCTCCCCATCCTCCTTTGCTTTCCGACTGCCCAAGGCACTTTCAATCTCAATCT
CTTCTCTCTCTCTCTCTCTCTCTCTCTGTCTCTCTCTCTCTCTCTCTCTCTCTCTCTCGCAGG
GTGGGGGGAAGAGGAGGAGGAATTCTTTCCCCGCCTAACATTTCAAGGGACACAATTCA
CTCCAAGTCTCTTCCCTTTCCAAGCCGCTTCCGAAGTGCTCCCGGTGCCCGCAACTCCTGA
TCCCAACCCGCGAGAGGAGCCTCTGCGACCTCAAAGCCTCTCTTCCTTCTCCCTCGCTTCC
CTCCTCCTCTTGCTACCTCCACCTCCACCGCCACCTCCACCTCCGGCACCCACCCACCGCC
GCCGCCGCCACCGGCAGCGCCTCCTCCTCTCCTCCTCCTCCCCTCTTCTCTTTTTGGC
AGCCGCTGGACGTCCGGTGTTGATGGTGGCAGCGGCGGCAGCCTAAGCAACAGCAGCCC
TCGCAGCCCGCCAGCTCGCGCTCGCCCCGCCGGCGTCCCCAGCCCTATCACCTCATCTCC
CGAAAGGTGCTGGGCAGCTCCGGGGCGGTCGAGGCGAAGCGGCTGCAGCGGCGGTAGC
GGCGGCGGGAGGCAGGATGAGCGCACGCGGTGAGGGCGCGGGGCAGCCGTCCACTTCA
GCCCAGGGACAACCTGCCGCCCCAGCGCCTCAGAAGAGAGGACGCGGCCGCCCCAGGA
AGCAGCAGCAAGAACCAACCGGTGAGCCCTCTCCTAAGAGACCCAGGGGAAGACCCAA
AGGCAGCAAAAACAAGAGTCCCTCTAAAGCAGCTCAAAAGAAAGCAGAAGCCACTGGA
GAAAAACGGCCAAGAGGCAGACCTAGGAAATGGCCACAACAAGTTGTTCAGAAGAAGC
CTGCTCAGGAGGAAACTGAAGAGACATCCTCACAAGAGTCTGCCGAAGAGGACTAGGGG
GCGCAACGTTCGATTTCTACCTCAGCAGCAGTTGGATCTTTTGAAGGGAGAAGACACTGC
AGTGACCACTTATTCTGTATTGCCATGGTCTTTCCACTTTCATCTGGGGTGGGGTGGGGTG
GGGTGGGGGAGGGGGGGGTGGGGTGGGGAGAAATCACATAACCTTAAAAAGGACTATA
TTAATCACCTTCTTTGTAATCCCTTCACAGTCCCAGGTTTAGTGAAAAACTGCTGTAAACA
CAGGGGACACAGCTTAACAATGCAACTTTTAATTACTGTTTTCTTTTTTCTTAACCTACTA
ATAGTTTGTTGATCTGATAAGCAAGAGTGGGCGGGTGAGAAAAACCGAATTGGGTTTAG
TCAATCACTGCACTGCATGCAAACAAGAAACGTGTCACACTTGTGACGTCGGGCATTCAT
ATAGGAAGAACGCGGTGTGTAACACTGTGTACACCTCAAATACCACCCCAACCCACTCC
CTGTAGTGAATCCTCTGTTTAGAACACCAAAGATAAGGACTAGATACTACTTTCTCTTTTT
CGTATAATCTTGTAGACACTTACTTGATGATTTTTAACTTTTTATTTCTAAATGAGACGAA
ATGCTGATGTATCCTTTCATTCAGCTAACAAACTAGAAAAGGTTATGTTCATTTTTCAAA
AAGGGAAGTAAGCAAACAAATATTGCCAACTCTTCTATTTATGGATATCACACATATCAG
CAGGAGTAATAAATTTACTCACAGCACTTGTTTTCAGGACAACACTTCATTTTCAGGAAA
TCTACTTCCTACAGAGCCAAAATGCCATTTAGCAATAAATAACACTTGTCAGCCTCAGAG
CATTTAAGGAAACTAGACAAGTAAAATTATCCTCTTTGTAATTTAATGAAAAGGTACAAC
AGAATAATGCATGATGAACTCACCTAATTATGAGGTGGGAGGAGCGAAATCTAAATTTC
TTTTGCTATAGTTATACATCAATTTAAAAAGCAAAAAAAAAAAAGGGGGGGGCAATCTCT
CTCTGTGTCTTTCTCTCTCTCTCTCCCTCTCCCTCTCTCTTTTCATGTGTATCAGTTTCCATG
AAAGACCTGAATACCACTTACCTCAAATTAAGCATATGTGTTACTTCAAGTAATACGTTT
TGACATAAGATGGTTGACCAAGGTGCTTTTCTTCGGCTTGAGTTCACCATCTCTTCATTCA
AACTGCACTTTTAGCCAGAGATGCAATATATCCCCACTACTCAATACTACCTCTGAATGT
TACAACGAATTTACAGTCTAGTACTTATTACATGCTGCTATACACAAGCAATGCAAGAAA
AAAACTTACTGGGTAGGTGATTCTAATCATCTGCAGTTCTTTTTGTACACTTAATTACAGT
TAAAGAAGCAATCTCCTTACTGTGTTTCAGCATGACTATGTATTTTTCTATGTTTTTTTAA
TTAAAAATTTTTAAAATACTTGTTTCAGCTTCTCTGCTAGATTTCTACATTAACTTGAAAA
TTTTTTAACCAAGTCGCTCCTAGGTTCTTAAGGATAATTTTCCTCAATCACACTACACATC
ACACAAGATTTGACTGTAATATTTAAATATTACCCTCCAAGTCTGTACCTCAAATGAATT
CTTTAAGGAGATGGACTAATTGACTTGCAAAGACCTACCTCCAG

Figure 97A

ACTTCAAAAGGAATGAACTTGTTACTTGCAGCATTCATTTGTTTTTTCAATGTTTGAAATA
GTTCAAACTGCAGCTAACCCTAGTCAAAACTATTTTTGTAAAAGACATTTGATAGAAAGG
AACACGTTTTTACATACTTTTGCAAAATAAGTAAATAATAAATAAAATAAAGCCAACCTT
CAAAGAACTTGAAGCTTTGTAGGTGAGATGCAACAAGCCCTGCTTTTGCATAATGCAATC
AAAAATATGTGTTTTTAAGATTAGTTGAATATAAGAAAATGCTTGACAAATATTTTCATG
TATTTTACACAAATGTGATTTTTGTAATATGTCTCAACCAGATTTATTTTAAACGCTTCTT
ATGTAGAGTTTTTATGCCTTTCTCTCCTAGTGAGTGTGCTGACTTTTTAACATGGTATTAT
CAACTGGGCCAGGAGGTAGTTTCTCATGACGGCTTTTGTCAGTATGGCTTTTAGTACTGA
AGCCAAATGAAACTCAAAACCATCTCTCTTCCAGCTGCTTCAGGGAGGTAGTTTCAAAGG
CCACATACCTCTCTGAGACTGGCAGATCGCTCACTGTTGTGAATCACCAAAGGAGCTATG
GAGAGAATTAAAACTCAACATTACTGTTAACTGTGCGTTAAATAAGCAAATAAACAGTG
GCTCATAAAAATAAAAGTCGCATTCCATATCTTTGGATGGGCCTTTTAGAAACCTCATTG
GCCAGCTCATAAAATGGAAGCAATTGCTCATGTTGGCCAAACATGGTGCACCGAGTGAT
TTCCATCTCTGGTAAAGTTACACTTTTATTTCCTGTATGTTGTACAATCAAAACACACTAC
TACCTCTTAAGTCCCAGTATACCTCATTTTTCATACTGAAAAAAAAAGCTTGTGGCCAAT
GGAACAGTAAGAACATCATAAAATTTTTATATATATAGTTTATTTTTGTGGGAGATAAAT
TTTATAGGACTGTTCTTTGCTGTTGTTGGTCGCAGCTACATAAGACTGGACATTTAACTTT
TCTACCATTTCTGCAAGTTAGGTATGTTTGCAGGAGAAAAGTATCAAGACGTTTAACTGC
AGTTGACTTTCTCCCTGTTCCTTTGAGTGTCTTCTAACTTTATTCTTTGTTCTTTATGTAGA
ATTGCTGTCTATGATTGTACTTTGAATCGCTTGCTTGTTGAAAATATTTCTCTAGTGTATT
ATCACTGTCTGTTCTGCACAATAAACATAACAGCCTCTGTGA

Figure 97A (continued)

MSARGEGAGQPSTSAQGQPAAPAPQKRGRGRPRKQQQEPTGEPSPKRPRGRPKGSKNKSPSK
AAQKKAEATGEKRPRGRPRKWPQQVVQKKPAQEETEETSSQESAEED

Figure 97B

GCGGCCCAGGCCCGGAACCTTCCCTGGTCGTGCGCCCTATGTAAGGCCAGCCGCGGCAG
GACCAAGGCGGCGGTGTCAGCTCGCGAGCCTACCCTCCGCGGACGGTCTTGGGTCGCCT
GCTGCCTGGCTTGCCTGGTCGGCGGCGGGTGCCCCGCGCGCACGCGCAAAGCCCGCCGC
GTTCCCCGACCCCAGGCCGCGCTCTGTGGGCCTCTGAGGGCGGCATGCGGGACTACGAC
GAGGTGACCGCCTTCCTGGGCGAGTGGGGGCCCTTCCAGCGCCTCATCTTCTTCCTGCTC
AGCGCCAGCATCATCCCCAATGGCTTCACCGGCCTGTCCTCCGTGTTCCTGATAGCGACC
CCGGAGCACCGCTGCCGGGTGCCGGACGCCGCGAACCTGAGCAGCGCCTGGCGCAACCA
CACTGTCCCACTGCGGCTGCGGGACGGCCGCGAGGTGCCCCACAGCTGCCGCCGCTACC
GGCTCGCCACCATCGCCAACTTCTCGGCGCTCGGGCTGGAGCCGGGGCGCGACGTGGAC
CTGGGGCAGCTGGAGCAGGAGAGCTGTCTGGATGGCTGGGAGTTCAGTCAGGACGTCTA
CCTGTCCACCATTGTGACCGAGTGGAACCTGGTGTGTGAGGACGACTGGAAGGCCCCAC
TCACAATCTCCTTGTTCTTCGTGGGTGTGCTGTTGGGCTCCTTCATTTCAGGGCAGCTGTC
AGACAGGTTTGGCCGGAAGAATGTGCTGTTCGTGACCATGGGCATGCAGACAGGCTTCA
GCTTCCTGCAGATCTTCTCGAAGAATTTTGAGATGTTTGTCGTGCTGTTTGTCCTTGTAGG
CATGGGCCAGATCTCCAACTATGTGGCAGCATTTGTCCTGGGGACAGAAATTCTTGGCAA
GTCAGTTCGTATAATATTCTCTACGTTAGGAGTGTGCATATTTTATGCATTTGGCTACATG
GTGCTGCCACTGTTTGCTTACTTCATCCGAGACTGGCGGATGCTGCTGGTGGCGCTGACG
ATGCCGGGGGTGCTGTGCGTGGCACTCTGGTGGTTCATCCCTGAGTCCCCCCGATGGCTC
ATCTCTCAGGGACGATTTGAAGAGGCAGAGGTGATCATCCGCAAGGCTGCCAAAGCCAA
TGGGATTGTTGTGCCTTCCACTATCTTTGACCCGAGTGAGTTACAAGACCTAAGTTCCAA
GAAGCAACAGTCCCACAACATTCTGGATCTGCTTCGAACCTGGAATATCCGGATGGTCAC
CATCATGTCCATAATGCTGTGGATGACCATATCAGTGGGCTATTTTGGGCTTTCGCTTGAT
ACTCCTAACTTGCATGGGGACATCTTTGTGAACTGCTTCCTTTCAGCGATGGTTGAAGTCC
CAGCATATGTGTTGGCCTGGCTGCTGCTGCAATATTTGCCCCGGCGCTATTCCATGGCCA
CTGCCCTCTTCCTGGGTGGCAGTGTCCTTCTCTTCATGCAGCTGGTACCCCCAGACTTGTA
TTATTTGGCTACAGTCCTGGTGATGGTGGGCAAGTTTGGAGTCACGGCTGCCTTTTCCAT
GGTCTACGTGTACACAGCCGAGCTGTATCCCACAGTGGTGAGAAACATGGGTGTGGGAG
TCAGCTCCACAGCATCCCGCCTGGGCAGCATCCTGTCTCCCTACTTCGTTTACCTTGGTGC
CTACGACCGCTTCCTGCCCTACATTCTCATGGGAAGTCTGACCATCCTGACAGCCATCCT
CACCTTGTTTCTCCCAGAGAGCTTCGGTACCCCACTCCCAGACACCATTGACCAGATGCT
AAGAGTCAAAGGAATGAAACACAGAAAAACTCCAAGTCACACAAGGATGTTAAAAGAT
GGTCAAGAAAGGCCCACAATCCTTAAAAGCACAGCCTTCTAACATCGCTTCCAGTAAGG
GAGAAACTGAAGAGGAAAGACTGTCTTGCTAGAAATGGCCAGCTTGTGCAGACTCCGAG
TCCTTCAGTGACAAAGGCCTTTGCTGTTTGTCCTCTTGACCTGTGTCTGACTTGCTCCTGG
ATGGGCACCCACACTCAGAGGCTACATATGGCCCTAGAGCACCACCTTCCTCTAGGGAC
ACTGGGGCTACCTACAGACAACTTCATCTAAGTCCTAACTATTACAATGATGGACTCAGC
ACCTCCAAAGCAGTTAATTTTTCACTAGAACCAGTGAGATCTGGAGGAATGTGAGAAGC
ATATGCTAAATGTACATTTTAATTTTAGACTACTTGAAAAGGCCCCTAATAAGGCTAGAG
GTCTAAGTCCCCCACCCCTTTCCCCACTCCCCTCTAGTGGTGAACTTTAGAGGAAAAGGA
AGTAATTGCACAAGGAGTTTGATTCTTACCTTTTCTCAGTTACAGAGGACATTAACTGGA
TCATTGCTTCCCCAGGGCAGGAGAGCGCAGAGCTAGGGAAAGTGAAAGGTAATGAAGAT
GGAGCAGAATGAGCAGATGCAGATCACCAGCAAAGTGCACTGATGTGTGAGCTCTTAAG
ACCACTCAGCATGACGACTGAGTAGACTTGTTTACATCTGATCAAAGCACTGGGCTTGTC
CAGGCTCATAATAAATGCTCCATTGAATCTACTATTCTTGTTTTCCACTGCTGTGGAAACC
TCCTTGCTACTATAGCGTCTTATGTATGGTTTAAAGGAAATTTATCAGGTGAGAGAGATG
AGCAACGTTGTCTTTTCTCTCAAAGCTGTAATGTGGGTTTTGTTTTACTGTTTATTTGTTTG
TTGTTGTATCCTTTTCTCCTTGTTATTTGCCCTTCAGAATGCACTTGGGAAAGGCTGGTTC
CTTAGCCTCCTGGTTTGTGTCTTTTTTTTTTTTTTTTTAAACACAGAATCACTCTGGCAATT
GTCTGCAGCTGCCACTGGTGCAAGGCCTTACCAGCCCTAGCCTCTAGC

Figure 98A

ACTTCTCTAAGTGCCAAAAACAGTGTCATTGTGTGTGTTCCTTTCTTGATACTTAGTCATG
GGAGGATATTACAAAAAAGAAATTTAAATTGTGTTCATAGTCTTTCAGAGTAGCTCACTT
TAGTCCTGTAACTTTATTGGGTGATATTTTGTGTTCAGTGTAATTGTCTTCTCTTTGCTGAT
TATGTTACCATGGTACTCCTAAAGCATATGCCTCACCTGGTTAAAAAAGAACAAACATGT
TTTTGTGAAAGCTACTGAAGTGCCTTGGGAAATGAGAAAGTTTTAATAAGTAAAATGATT
TTTTAAATATCAAAAAAAAAAAAAAAA

Figure 98A (continued)

MRDYDEVTAFLGEWGPFQRLIFFLLSASIIPNGFTGLSSVFLIATPEHRCRVPDAANLSSAWRN
HTVPLRLRDGREVPHSCRRYRLATIANFSALGLEPGRDVDLGQLEQESCLDGWEFSQDVYLS
TIVTEWNLVCEDDWKAPLTISLFFVGVLLGSFISGQLSDRFGRKNVLFVTMGMQTGFSFLQIF
SKNFEMFVVLFVLVGMGQISNYVAAFVLGTEILGKSVRIIFSTLGVCIFYAFGYMVLPLFAYFI
RDWRMLLVALTMPGVLCVALWWFIPESPRWLISQGRFEEAEVIIRKAAKANGIVVPSTIFDPS
ELQDLSSKKQQSHNILDLLRTWNIRMVTIMSIMLWMTISVGYFGLSLDTPNLHGDIFVNCFLS
AMVEVPAYVLAWLLLQYLPRRYSMATALFLGGSVLLFMQLVPPDLYYLATVLVMVGKFGV
TAAFSMVYVYTAELYPTVVRNMGVGVSSTASRLGSILSPYFVYLGAYDRFLPYILMGSLTILT
AILTLFLPESFGTPLPDTIDQMLRVKGMKHRKTPSHTRMLKDGQERPTILKSTAF

CCCCGGCTTCGCGCCCCAATTTCTAACAGCCTGCCTGTCCCCCGGGAACGTTCTAACATC
CTTGGGGAGCGCCCCAGCTACAAGACACTGTCCTGAGAACGCTGTCATCACCCGTAGTTG
CAAGTTTCGGAGCGGCAGTGGGAAGCATGCGGGACTACGACGAGGTGATCGCCTTCCTG
GGCGAGTGGGGGCCCTTCCAGCGCCTCATCTTCTTCCTGCTCAGCGCCAGCATCATCCCC
AATGGCTTCAATGGTATGTCAGTCGTGTTCCTGGCGGGGACCCCGGAGCACCGCTGTCGA
GTGCCGGACGCCGCGAACCTGAGCAGCGCCTGGCGCAACAACAGTGTCCCGCTGCGGCT
GCGGGACGGCCGCGAGGTGCCCCACAGCTGCAGCCGCTACCGGCTCGCCACCATCGCCA
ACTTCTCGGCGCTCGGGCTGGAGCCGGGGCGCGACGTGGACCTGGGGCAGCTGGAGCAG
GAGAGCTGCCTGGATGGCTGGGAGTTCAGCCAGGACGTCTACCTGTCCACCGTCGTGACC
GAGTGGAATCTGGTGTGTGAGGACAACTGGAAGGTGCCCCTCACCACCTCCCTGTTCTTC
GTAGGCGTGCTCCTCGGCTCCTTCGTGTCCGGGCAGCTGTCAGACAGGTTTGGCAGGAAG
AACGTTCTCTTCGCAACCATGGCTGTACAGACTGGCTTCAGCTTCCTGCAGATTTTCTCCA
TCAGCTGGGAGATGTTCACTGTGTTATTTGTCATCGTGGGCATGGGCCAGATCTCCAACT
ATGTGGTAGCCTTCATACTAGGAACAGAAATTCTTGGCAAGTCAGTTCGTATTATATTCT
CTACATTAGGAGTGTGCACATTTTTTGCAGTTGGCTATATGCTGCTGCCACTGTTTGCTTA
CTTCATCAGAGACTGGCGGATGCTGCTGCTGGCGCTGACGGTGCCGGGAGTGCTGTGTGT
CCCGCTGTGGTGGTTCATTCCTGAATCTCCCCGATGGCTGATATCCCAGAGAAGATTTAG
AGAGGCTGAAGATATCATCCAAAAAGCTGCAAAAATGAACAACACAGCTGTACCAGCAG
TGATATTTGATTCTGTGGAGGAGCTAAATCCCCTGAAGCAGCAGAAAGCTTTCATTCTGG
ACCTGTTCAGGACTCGGAATATTGCCATAATGACCATTATGTCTTTGCTGCTATGGATGCT
GACCTCAGTGGGTTACTTTGCTCTGTCTCTGGATGCTCCTAATTTACATGGAGATGCCTAC
CTGAACTGTTTCCTCTCTGCCTTGATTGAAATTCCAGCTTACATTACAGCCTGGCTGCTAT
TGCGAACGCTGCCCAGGCGTTATATCATAGCTGCAGTACTGTTCTGGGGAGGAGGTGTGC
TTCTCTTCATTCAACTGGTACCTGTGGATTATTACTTCTTATCCATTGGTCTGGTCATGCTG
GGAAAATTTGGGATCACCTCTGCTTTCTCCATGCTGTATGTCTTCACTGCTGAGCTCTACC
CAACCCTGGTCAGGAACATGGCGGTGGGGGTCACATCCACGGCCTCCAGAGTGGGCAGC
ATCATTGCCCCCTACTTTGTTTACCTCGGTGCTTACAACAGAATGCTGCCCTACATCGTCA
TGGGTAGTCTGACTGTCCTGATTGGAATCTTCACCCTTTTTTTCCCTGAAAGTTTGGGAAT
GACTCTTCCAGAAACCTTAGAGCAGATGCAGAAAGTGAAATGGTTCAGATCTGGGAAAA
AAACAAGAGACTCAATGGAGACAGAAGAAAATCCCAAGGTTCTAATAACTGCATTCTGA
AAAAATATCTACCCCATTTGGTGAAGTGAAAAACAGAAAAATAAGACCCTGTGGAGAAA
TTCGTTGTTCCCACTGAAATGGACTGACTGTAACGATTGACACCAAAATGAACCTTGCTA
TCAAGAAATGCTCGTCATACAGTAAACTCTGGATGATTCTTCCAGATAATGTCCTTGCTTT
ACAAACCAACCATTTCTAGAGAGTCTCCTTACTCATTAATTCAATGAAATGGATTGGTAA
GATGTCTTGAAAACATGTTAGTCAAGGACTGGTAAAATACATATAAAGATTAACACTCAT
TTCCAATCATACAAATACTATCCAAATAAAAAT

Figure 99A

MRDYDEVIAFLGEWGPFQRLIFFLLSASIIPNGFNGMSVVFLAGTPEHRCRVPDAANLSSAWR
NNSVPLRLRDGREVPHSCSRYRLATIANFSALGLEPGRDVDLGQLEQESCLDGWEFSQDVYL
STVVTEWNLVCEDNWKVPLTTSLFFVGVLLGSFVSGQLSDRFGRKNVLFATMAVQTGFSFL
QIFSISWEMFTVLFVIVGMGQISNYVVAFILGTEILGKSVRIIFSTLGVCTFFAVGYMLLPLFAY
FIRDWRMLLLALTVPGVLCVPLWWFIPESPRWLISQRRFREAEDIIQKAAKMNNTAVPAVIFD
SVEELNPLKQQKAFILDLFRTRNIAIMTIMSLLLWMLTSVGYFALSLDAPNLHGDAYLNCFLS
ALIEIPAYITAWLLLRTLPRRYIIAAVLFWGGGVLLFIQLVPVDYYFLSIGLVMLGKFGITSAFS
MLYVFTAELYPTLVRNMAVGVTSTASRVGSIIAPYFVYLGAYNRMLPYIVMGSLTVLIGIFTL
FFPESLGMTLPETLEQMQKVKWFRSGKKTRDSMETEENPKVLITAF

Figure 99B

GCGAGTGTCCAGCTGCGGAGACCCGTGATAATTCGTTAACTAATTCAACAAACGGGACC
CTTCTGTGTGCCAGAAACCGCAAGCAGTTGCTAACCCAGTGGGACAGGCGGATTGGAAG
AGCGGGAAGGTCCTGGCCCAGAGCAGTGTGACACTTCCCTCTGTGACCATGAAACTCTG
GGTGTCTGCATTGCTGATGGCCTGGTTTGGTGTCCTGAGCTGTGTGCAGGCCGAATTCTTC
ACCTCTATTGGGCACATGACTGACCTGATTTATGCAGAGAAAGAGCTGGTGCAGTCTCTG
AAAGAGTACATCCTTGTGGAGGAAGCCAAGCTTTCCAAGATTAAGAGCTGGGCCAACAA
AATGGAAGCCTTGACTAGCAAGTCAGCTGCTGATGCTGAGGGCTACCTGGCTCACCCTGT
GAATGCCTACAAACTGGTGAAGCGGCTAAACACAGACTGGCCTGCGCTGGAGGACCTTG
TCCTGCAGGACTCAGCTGCAGGTTTTATCGCCAACCTCTCTGTGCAGCGGCAGTTCTTCCC
CACTGATGAGGACGAGATAGGAGCTGCCAAAGCCCTGATGAGACTTCAGGACACATACA
GGCTGGACCCAGGCACAATTTCCAGAGGGGAACTTCCAGGAACCAAGTACCAGGCAATG
CTGAGTGTGGATGACTGCTTTGGGATGGGCCGCTCGGCCTACAATGAAGGGGACTATTAT
CATACGGTGTTGTGGATGGAGCAGGTGCTAAAGCAGCTTGATGCCGGGGAGGAGGCCAC
CACAACCAAGTCACAGGTGCTGGACTACCTCAGCTATGCTGTCTTCCAGTTGGGTGATCT
GCACCGTGCCCTGGAGCTCACCCGCCGCCTGCTCTCCCTTGACCCAAGCCACGAACGAGC
TGGAGGGAATCTGCGGTACTTTGAGCAGTTATTGGAGGAAGAGAGAGAAAAAACGTTAA
CAAATCAGACAGAAGCTGAGCTAGCAACCCCAGAAGGCATCTATGAGAGGCCTGTGGAC
TACCTGCCTGAGAGGGATGTTTACGAGAGCCTCTGTCGTGGGGAGGGTGTCAAACTGAC
ACCCCGTAGACAGAAGAGGCTTTTCTGTAGGTACCACCATGGCAACAGGGCCCCACAGC
TGCTCATTGCCCCCTTCAAAGAGGAGGACGAGTGGGACAGCCCGCACATCGTCAGGTAC
TACGATGTCATGTCTGATGAGGAAATCGAGAGGATCAAGGAGATCGCAAAACCTAAACT
TGCACGAGCCACCGTTCGTGATCCCAAGACAGGAGTCCTCACTGTCGCCAGCTACCGGGT
TTCCAAAAGCTCCTGGCTAGAGGAAGATGATGACCCTGTTGTGGCCCGAGTAAATCGTCG
GATGCAGCATATCACAGGGTTAACAGTAAAGACTGCAGAATTGTTACAGGTTGCAAATT
ATGGAGTGGGAGGACAGTATGAACCGCACTTCGACTTCTCTAGGCGACCTTTTGACAGCG
GCCTCAAAACAGAGGGGAATAGGTTAGCGACGTTTCTTAACTACATGAGTGATGTAGAA
GCTGGTGGTGCCACCGTCTTCCCTGATCTGGGGGCTGCAATTTGGCCTAAGAAGGGTACA
GCTGTGTTCTGGTACAACCTCTTGCGGAGCGGGGAAGGTGACTACCGAACAAGACATGC
TGCCTGCCCTGTGCTTGTGGGCTGCAAGTGGGTCTCCAATAAGTGGTTCCATGAACGAGG
ACAGGAGTTCTTGAGACCTTGTGGATCAACAGAAGTTGACTGACATCCTTTTCTGTCCTT
CCCCTTCCTGGTCCTTCAGCCCATGTCAACGTGACAGACACCTTTGTATGTTCCTTTGTAT
GTTCCTATCAGGCTGATTTTTGGAGAAATGAATGTTTGTCTGGAGCAGAGGGAGACCATA
CTAGGGCGACTCCTGTGTGACTGAAGTCCCAGCCCTTCCATTCAGCCTGTGCCATCCCTG
GCCCCAAGGCTAGGATCAAAGTGGCTGCAGCAGAGTTAGCTGTCTAGCGCCTAGCAAGG
TGCCTTTGTACCTCAGGTGTTTTAGGTGTGAGATGTTTCAGTGAACCAAAGTTCTGATACC
TTGTTTACATGTTTGTTTTTATGGCATTTCTATCTATTGTGGCTTTACCAAAAAATAAAAT
GTCCCTACCAGAAAAAAAAAA

Figure 100A

MKLWVSALLMAWFGVLSCVQAEFFTSIGHMTDLIYAEKELVQSLKEYILVEEAKLSKIKSWA
NKMEALTSKSAADAEGYLAHPVNAYKLVKRLNTDWPALEDLVLQDSAAGFIANLSVQRQFF
PTDEDEIGAAKALMRLQDTYRLDPGTISRGELPGTKYQAMLSVDDCFGMGRSAYNEGDYYH
TVLWMEQVLKQLDAGEEATTTKSQVLDYLSYAVFQLGDLHRALELTRRLLSLDPSHERAGG
NLRYFEQLLEEEREKTLTNQTEAELATPEGIYERPVDYLPERDVYESLCRGEGVKLTPRRQKR
LFCRYHHGNRAPQLLIAPFKEEDEWDSPHIVRYYDVMSDEEIERIKEIAKPKLARATVRDPKT
GVLTVASYRVSKSSWLEEDDDPVVARVNRRMQHITGLTVKTAELLQVANYGVGGQYEPHF
DFSRRPFDSGLKTEGNRLATFLNYMSDVEAGGATVFPDLGAAIWPKKGTAVFWYNLLRSGE
GDYRTRHAACPVLVGCKWVSNKWFHERGQEFLRPCGSTEVD

Figure 100B

GCAGCCAGAAAGCTCTGGAGCATCAGGGAGACTCCAACTTAAGGCAACAGCATGGGTGA
ATAAGGGCTTCCTGTGGACTGGCAATGAGAGGCAAAACCTGGTGCTTGAGCACTGGCCC
CTAAGGCAGGCCTTACAGATCTCTTACACTCGTGGTGGGAAGAGTTTAGTGTGAAACTGG
GGTGGAATTGGGTGTCCACGTATGTTCCCTTTTGCCTTACTATATGTTCTGTCAGTTTCTTT
CAGGAAAATCTTCATCTTACAACTTGTAGGGCTGGTGTTAACTTACGACTTCACTAACTG
TGACTTTGAGAAGATTAAAGCAGCCTATCTCAGTACTATTTCTAAAGACCTGATTACATA
TATGAGTGGGACCAAAAGTACCGAGTTCAACAACACCGTCTCTTGTAGCAATCGGCCAC
ATTGCCTTACTGAAATCCAGAGCCTAACCTTCAATCCCACCGCCGGCTGCGCGTCGCTCG
CCAAAGAAATGTTCGCCATGAAAACTAAGGCTGCCTTAGCTATCTGGTGCCCAGGCTATT
CGGAAACTCAGATAAATGCTACTCAGGCAATGAAGAAGAGGAGAAAAAGGAAAGTCAC
AACCAATAAATGTCTGGAACAAGTGTCACAATTACAAGGATTGTGGCGTCGCTTCAATCG
ACCTTTACTGAAACAACAGTAAACCATCTTTATTATGGTCATATTTCACAGCACCAAAAT
AAATCATCTTTATTAAGT

Figure 101A

MFPFALLYVLSVSFRKIFILQLVGLVLTYDFTNCDFEKIKAAYLSTISKDLITYMSGTKSTEFNN
TVSCSNRPHCLTEIQSLTFNPTAGCASLAKEMFAMKTKAALAIWCPGYSETQINATQAMKKR
RKRKVTTNKCLEQVSQLQGLWRRFNRPLLKQQ

Figure 101B

AGGTTCTCTTACATCGACCGCCTAAGAGTCGCGCTGTAAGAAGCAACAACCTCTCCTCTT
CGTCTCCGCCATCAGCTCGGCAGTCGCGAAGCAGCAACCATGCGTGAGTGCATCTCCATC
CACGTTGGCCAGGCTGGTGTCCAGATTGGCAATGCCTGCTGGGAGCTCTACTGCCTGGAA
CACGGCATCCAGCCCGATGGCCAGATGCCAAGTGACAAGACCATTGGGGGAGGAGATGA
TTCCTTCAACACCTTCTTCAGTGAGACGGGGGCTGGCAAGCATGTGCCCCGGGCAGTGTT
TGTAGACTTGGAACCCACAGTCATTGATGAAGTTCGCACTGGCACCTACCGCCAGCTCTT
CCACCCTGAGCAACTTATCACAGGCAAAGAAGATGCTGCCAATAACTATGCCCGAGGGC
ACTACACCATTGGCAAGGAGATCATTGACCTCGTGTTGGACCGAATTCGCAAGCTGGCCG
ACCAGTGCACGGGTCTCCAGGGCTTCTTGGTTTTCCACAGCTTTGGTGGGGGAACTGGTT
CTGGGTTCACCTCGCTGCTCATGGAACGTCTCTCAGTTGATTATGGCAAGAAGTCCAAGC
TGGAGTTCTCTATTTACCCGGCGCCCCAGGTTTCCACAGCTGTAGTTGAGCCCTACAACT
CCATCCTCACCACCCACACCACCCTGGAGCACTCTGATTGTGCCTTCATGGTAGACAATG
AGGCCATCTATGACATCTGTCGTAGAAACCTCGATATTGAGCGTCCAACCTATACTAACC
TGAATAGGTTAATAGGTCAAATTGTGTCCTCCATCACTGCTTCCCTGAGATTTGATGGAG
CCCTGAATGTTGACCTGACAGAATTCCAGACCAACCTGGTGCCCTATCCCCGCATCCACT
TCCCTCTGGCCACATATGCCCCTGTCATCTCTGCTGAGAAAGCCTACCATGAACAGCTTT
CTGTAGCAGAGATCACCAATGCTTGCTTTGAGCCAGCCAACCAGATGGTGAAATGTGAC
CCTCGCCATGGTAAATACATGGCTTGCTGCCTGTTGTACCGTGGTGACGTGGTTCCCAAA
GATGTCAATGCTGCCATTGCCACCATCAAGACCAAGCGTACCATCCAGTTTGTGGATTGG
TGCCCCACTGGCTTCAAGGTTGGCATCAACTACCAGCCTCCCACTGTGGTGCCTGGTGGA
GACCTGGCCAAGGTACAGAGAGCTGTGTGCATGCTGAGCAACACCACAGCCATTGCTGA
GGCCTGGGCTCGCCTGGACCACAAGTTTGACCTGATGTATGCCAAACGTGCCTTTGTTCA
CTGGTACGTTGGGGAGGGGATGGAGGAAGGTGAGTTTTCAGAGGCCCGTGAGGACATGG
CTGCCCTTGAGAAGGATTATGAGGAGGTTGGTGTGGATTCTGTTGAAGGAGAGGGTGAG
GAAGAAGGAGAGGAATACTAAAGTTAAAACGTCACAAAGGTGCTGCTTTTACAGGGAAG
CTTATTCTGTTTTAAACATTGAAAAGTTGTGGTCTGATCAGTTAATTTGTATGTAGCAGTG
TATGCTCTCATATACAATTACTGACCTATGCTCTAAAACATGAATGCTTTGTTACAGACCC
AAGCTGTCCATTTCTGTGATGGGTTTTGAATAAAGTATTCCCTGTCTTAAAAAAAAAAAA
AA

Figure 102A

MRECISIHVGQAGVQIGNACWELYCLEHGIQPDGQMPSDKTIGGGDDSFNTFFSETGAGKHV
PRAVFVDLEPTVIDEVRTGTYRQLFHPEQLITGKEDAANNYARGHYTIGKEIIDLVLDRIRKLA
DQCTGLQGFLVFHSFGGGTGSGFTSLLMERLSVDYGKKSKLEFSIYPAPQVSTAVVEPYNSIL
TTHTTLEHSDCAFMVDNEAIYDICRRNLDIERPTYTNLNRLIGQIVSSITASLRFDGALNVDLT
EFQTNLVPYPRIHFPLATYAPVISAEKAYHEQLSVAEITNACFEPANQMVKCDPRHGKYMAC
CLLYRGDVVPKDVNAAIATIKTKRTIQFVDWCPTGFKVGINYQPPTVVPGGDLAKVQRAVC
MLSNTTAIAEAWARLDHKFDLMYAKRAFVHWYVGEGMEEGEFSEAREDMAALEKDYEEV
GVDSVEGEGEEEGEEY

Figure 102B

CTTGGTAGTCTGTTAGTGGGAGATCCTTGTTGCCGTCCCTTCGCCTCCTTCACCGCCGCAG
ACCCCTTCAAGTTCTAGTCATGCGTGAGTGCATCTCCATCCACGTTGGCCAGGCTGGTGT
CCAGATTGGCAATGCCTGCTGGGAGCTCTACTGCCTGGAACACGGCATCCAGCCCGATG
GCCAGATGCCAAGTGACAAGACCATTGGGGGAGGAGATGATTCCTTCAACACCTTCTTC
AGTGAAACGGGTGCTGGCAAGCATGTGCCCCGGGCAGTGTTTGTAGACTTGGAACCCAC
AGTCATTGATGAAGTTCGCACTGGCACCTACCGCCAGCTCTTCCACCCTGAGCAGCTCAT
CACAGGCAAGGAAGATGCTGCCAATAACTATGCCCGAGGGCACTACACCATTGGCAAGG
AGATCATTGACCTCGTGTTGGACCGAATTCGCAAGCTGGCTGACCAGTGCACCGGTCTTC
AGGGCTTCTTGGTTTTCCACAGCTTTGGTGGGGGAACTGGTTCTGGGTTCACCTCGCTGCT
CATGGAACGTCTCTCAGTTGATTATGGCAAGAAGTCCAAGCTGGAGTTCTCTATTTACCC
GGCGCCCCAGGTTTCCACAGCTGTAGTTGAGCCCTACAACTCCATCCTCACCACCCACAC
CACCCTGGAGCACTCTGATTGTGCCTTCATGGTAGACAATGAGGCCATCTATGACATCTG
TCGTAGAAACCTCGATATCGAGCGCCCAACCTACACTAACCTTAACCGCCTTATTAGCCA
GATTGTGTCCTCCATCACTGCTTCCCTGAGATTTGATGGAGCCCTGAATGTTGACCTGAC
AGAATTCCAGACCAACCTGGTGCCCTACCCCCGCATCCACTTCCCTCTGGCCACATATGC
CCCTGTCATCTCTGCTGAGAAAGCCTACCATGAACAGCTTACTGTAGCAGAGATCACCAA
TGCTTGCTTTGAGCCAGCCAACCAGATGGTGAAATGTGACCCTCGCCATGGTAAATACAT
GGCTTGCTGCCTGTTATACCGTGGTGACGTGGTTCCCAAAGATGTCAATGCTGCCATTGC
CACCATCAAAACCAAGCGTACCATCCAGTTTGTGGATTGGTGCCCCACTGGCTTCAAGGT
TGGCATTAATTACCAGCCTCCCACTGTGGTGCCTGGCGGAGACCTGGCCAAGGTACAGA
GAGCTGTGTGCATGCTGAGCAATACCACAGCTGTTGCTGAGGCCTGGGCTCGCCTGGACC
ACAAGTTTGACCTGATGTATGCCAAGCGTGCCTTTGTTCACTGGTACGTGGGTGAGGGGA
TGGAGGAAGGCGAGTTTTCAGAGGCCCGTGAGGACATGGCTGCCCTTGAGAAGGATTAT
GAGGAGGTTGGAGCAGATAGTGCTGACGGAGAGGATGAGGGTGAAGAGTATTAACCTGT
GTGCTGTACTTTTACACTCCTTTGTCTTGGAACTGTCTTATTTTTGTTCTGTAAATGTCTAT
TGCCGTAAATTGTTAATAAAATTGATGTTTCCATTTTAAAAAAAAAAAAAAAAAAAAAA
AA

Figure 103A

MRECISIHVGQAGVQIGNACWELYCLEHGIQPDGQMPSDKTIGGGDDSFNTFFSETGAGKHV
PRAVFVDLEPTVIDEVRTGTYRQLFHPEQLITGKEDAANNYARGHYTIGKEIIDLVLDRIRKLA
DQCTGLQGFLVFHSFGGGTGSGFTSLLMERLSVDYGKKSKLEFSIYPAPQVSTAVVEPYNSIL
TTHTTLEHSDCAFMVDNEAIYDICRRNLDIERPTYTNLNRLISQIVSSITASLRFDGALNVDLTE
FQTNLVPYPRIHFPLATYAPVISAEKAYHEQLTVAEITNACFEPANQMVKCDPRHGKYMACC
LLYRGDVVPKDVNAAIATIKTKRTIQFVDWCPTGFKVGINYQPPTVVPGGDLAKVQRAVCM
LSNTTAVAEAWARLDHKFDLMYAKRAFVHWYVGEGMEEGEFSEAREDMAALEKDYEEVG
ADSADGEDEGEEY

Figure 103B

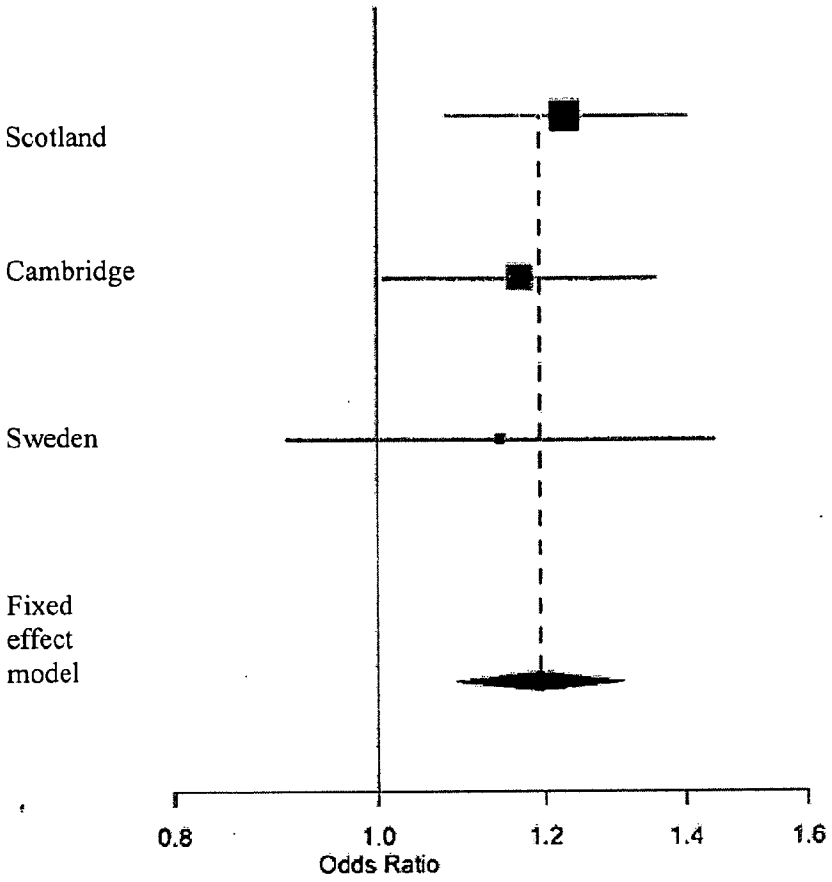

Scotland
Cambridge
Sweden
Fixed
effect
model
0.8
1.0
1.2
1.4
1.6
Odds Ratio

Figure 104

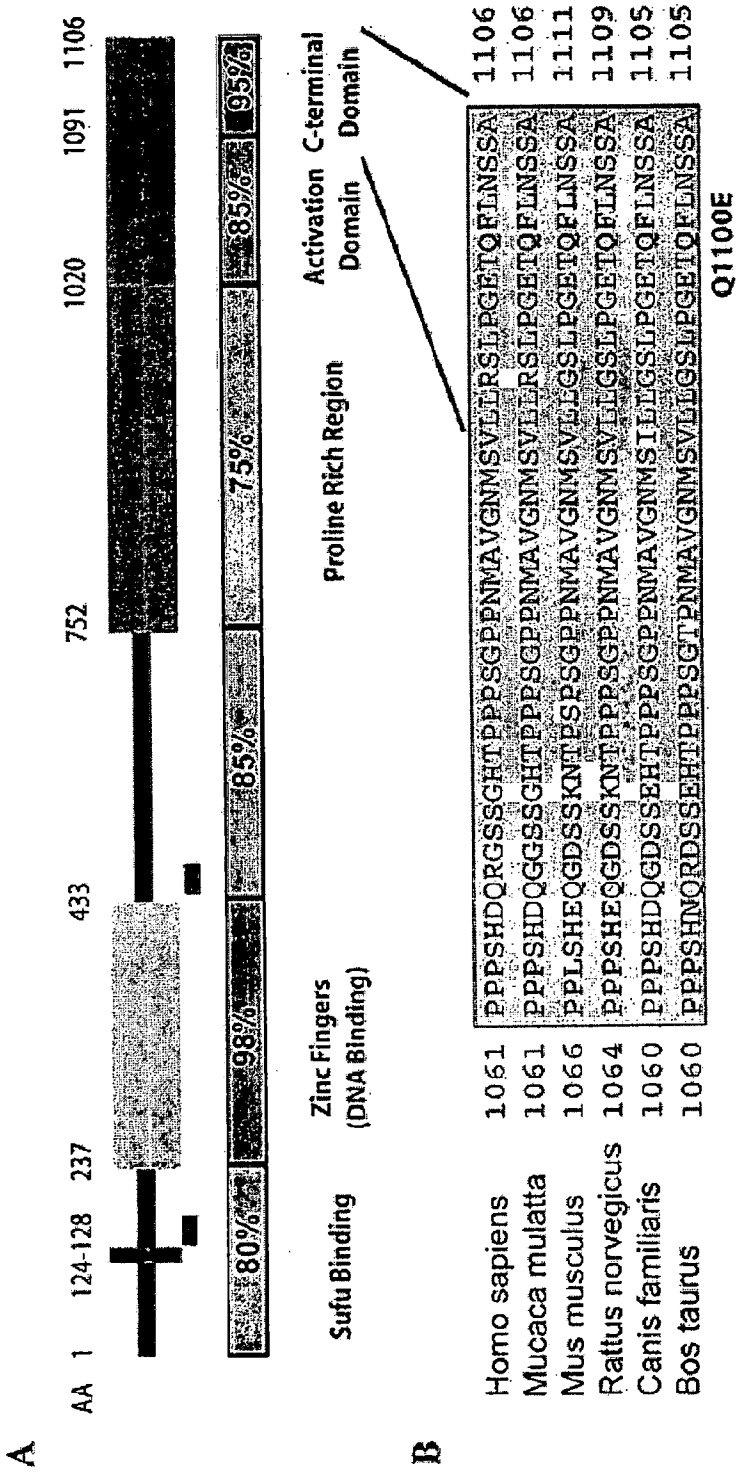
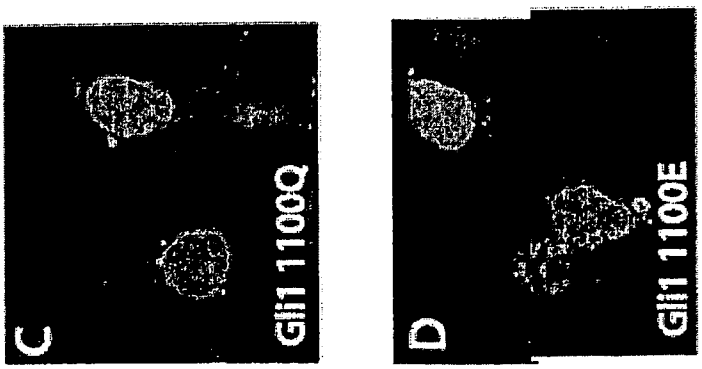


Figure 105 A-B



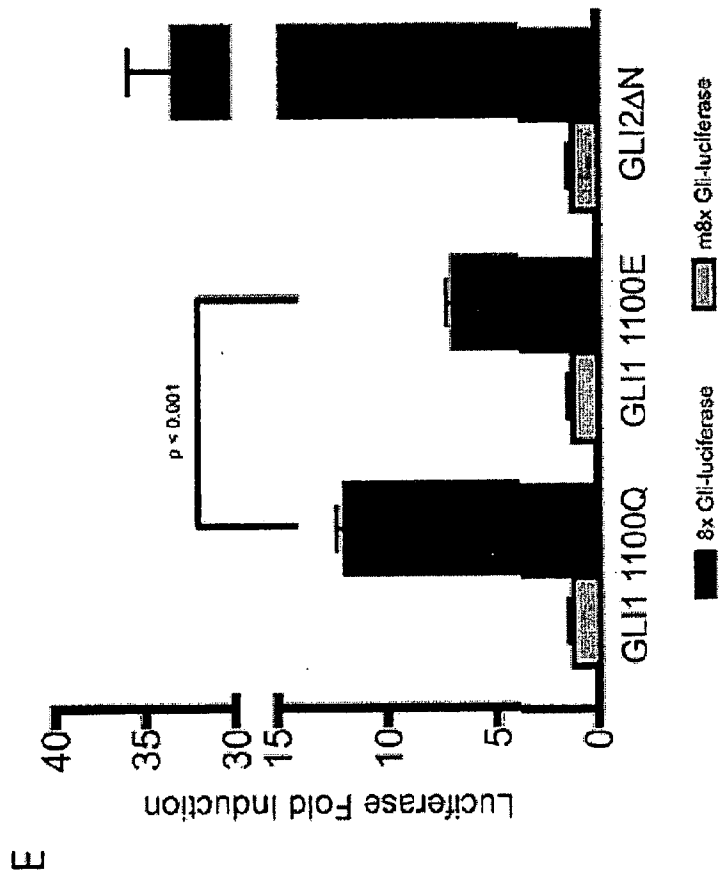


Figure 105 C-E

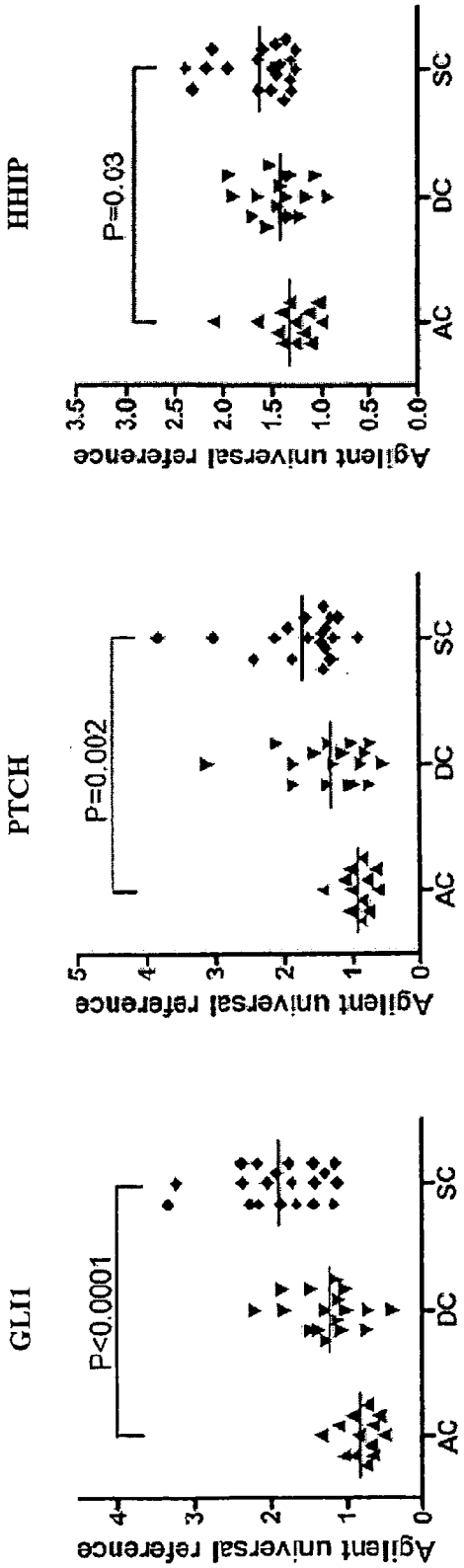

GLI1
P<0.0001
Agilent universal reference
0
1
2
3
4
AC
DC
SC
PTCH
P=0.002
Agilent universal reference
0
1
2
3
4
5
AC
DC
SC
HHIP
P=0.03
Agilent universal reference
0.0
0.5
1.0
1.5
2.0
2.5
3.0
3.5
AC
DC
SC

Figure 106A

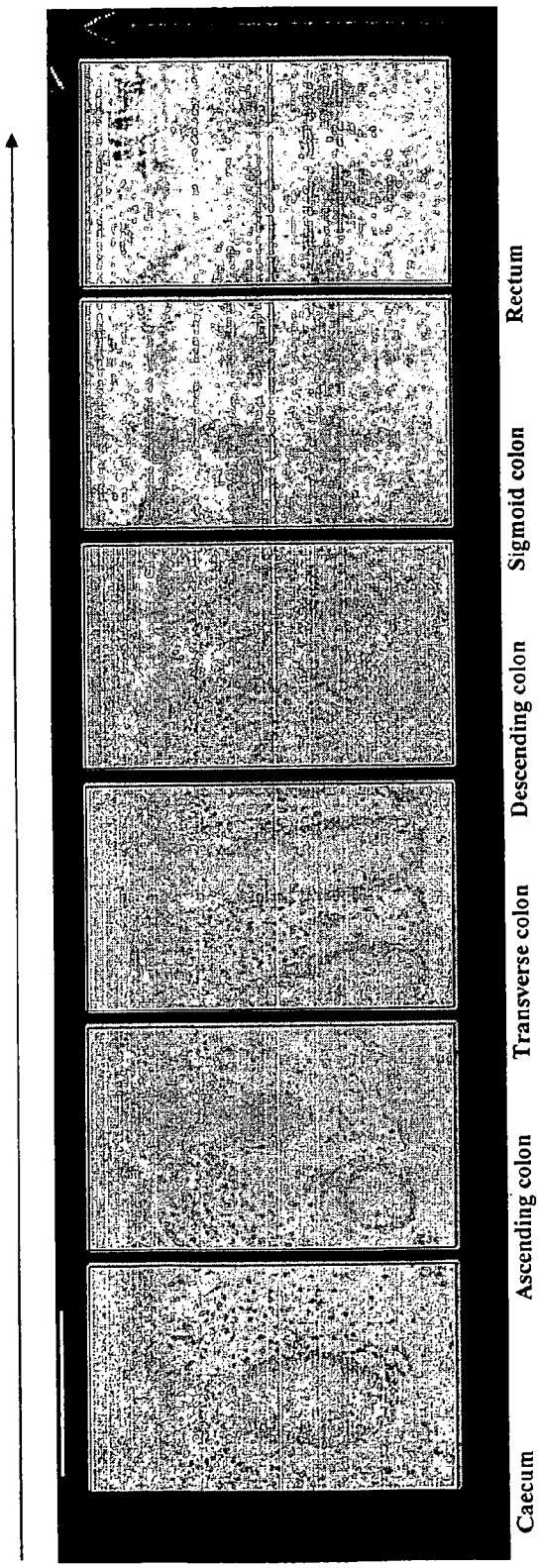

Caecum
Ascending colon
Transverse colon
Descending colon
Sigmoid colon
Rectum

Figure 106B

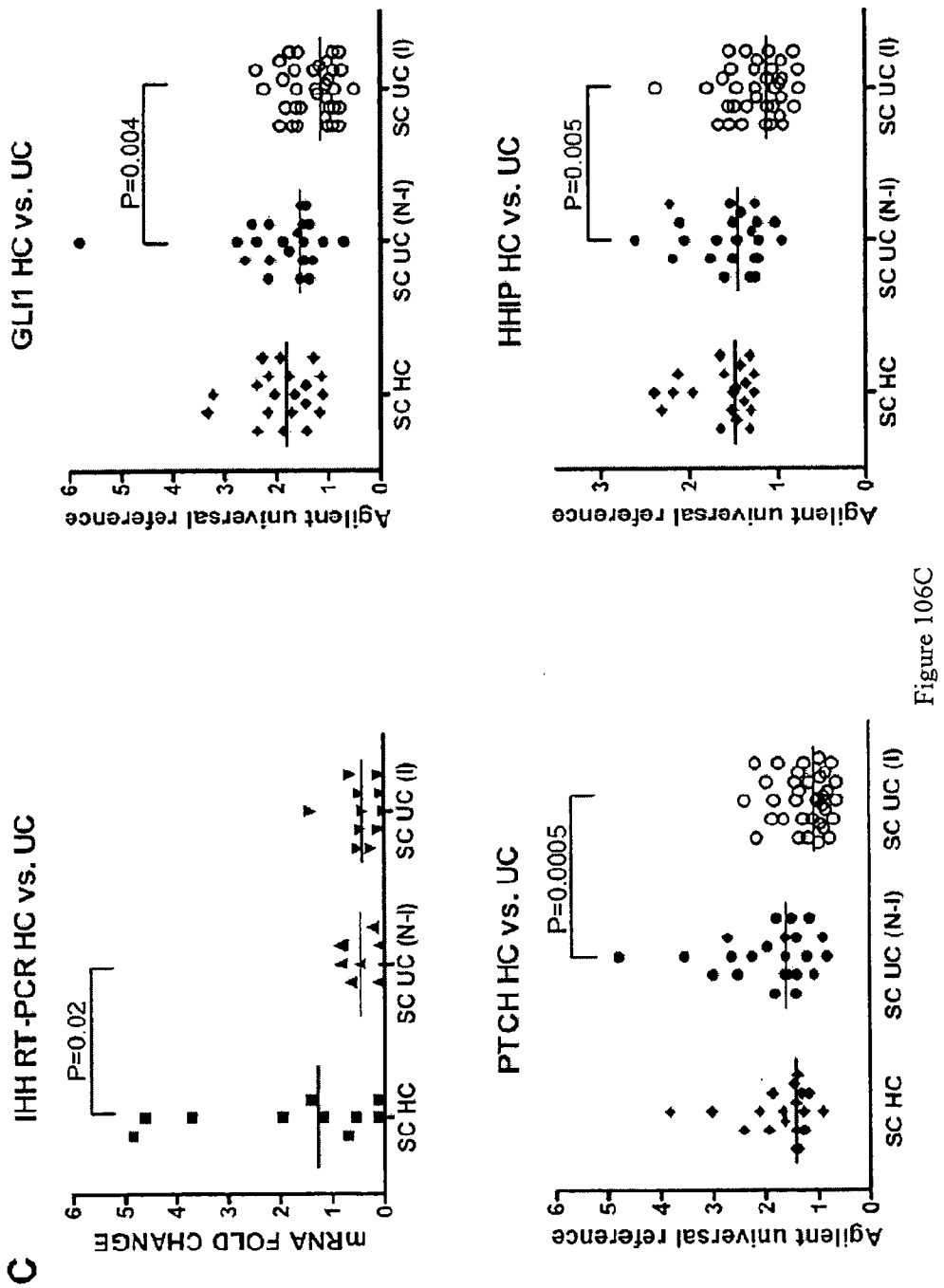

C
IHH RT-PCR HC vs. UC
mRNA FOLD CHANGE
P=0.02
SC HC
SC UC (N-I)
SC UC (I)
GLI1 HC vs. UC
Agilent universal reference
P=0.004
HHIP HC vs. UC
P=0.005
PTCH HC vs. UC
P=0.0005

Figure 106C

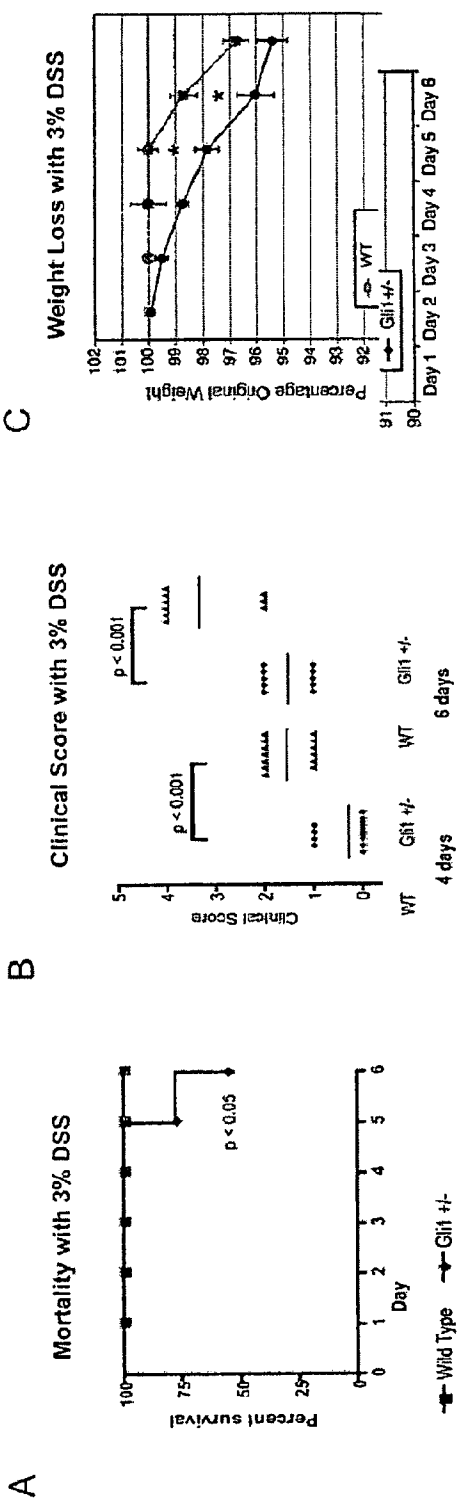

A
Mortality with 3% DSS
Percent survival
Day
p < 0.05
Wild Type
Gli1 +/-
B
Clinical Score with 3% DSS
Clinical Score
p < 0.001
p < 0.001
WT
Gli1 +/-
4 days
WT
Gli1 +/-
6 days
C
Weight Loss with 3% DSS
Percentage Original Weight
Day 1
Day 2
Day 3
Day 4
Day 5
Day 6
WT
Gli1+/-

Figure 107

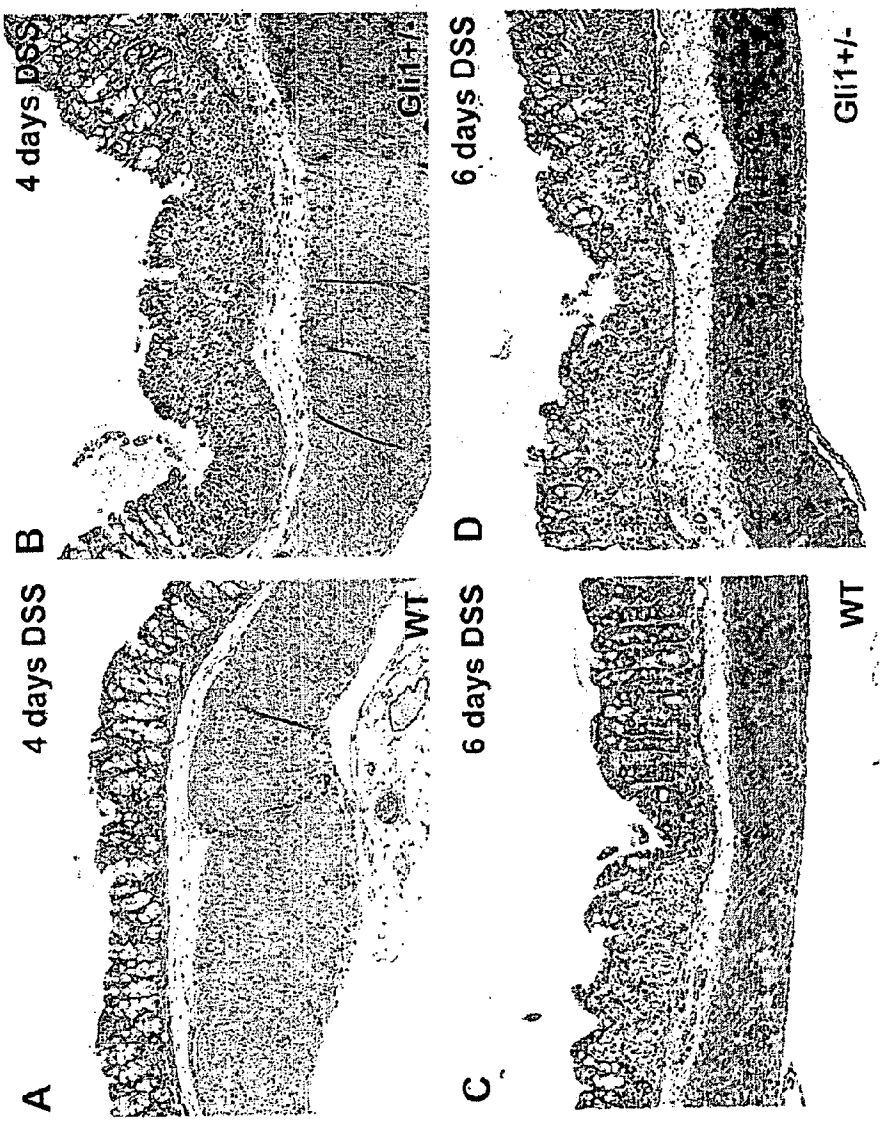


Figure 108 A-D

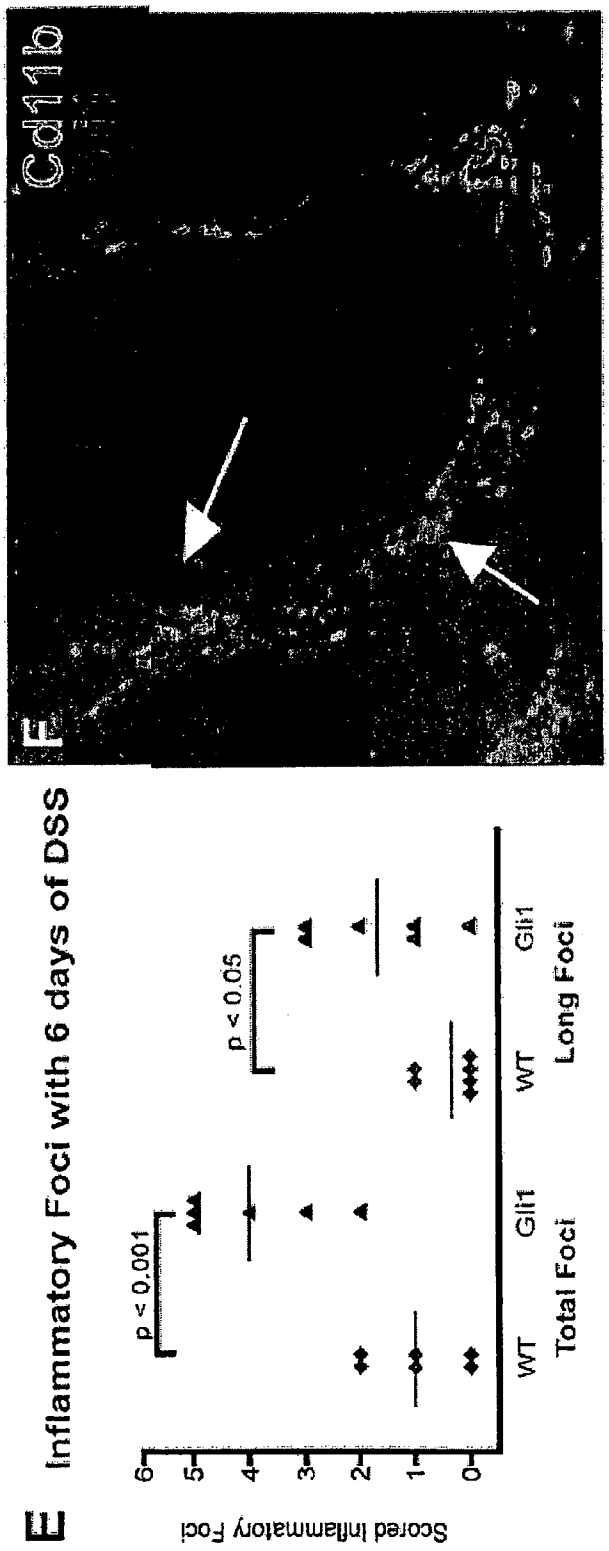
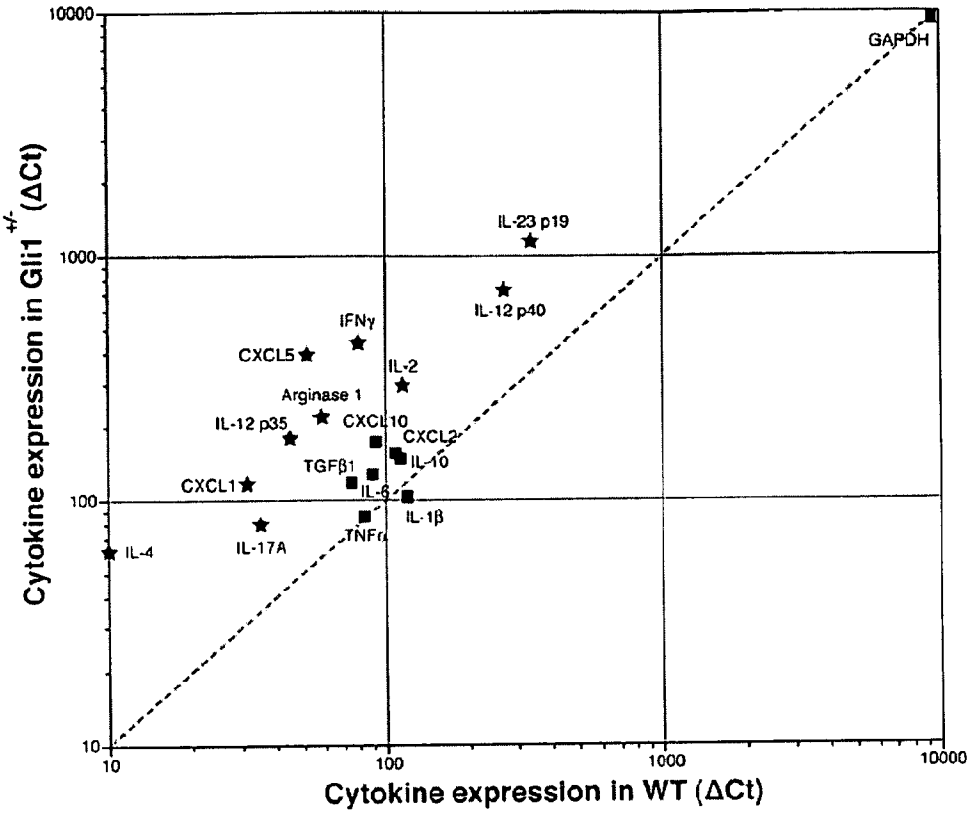


Figure 108 E-F

A



B

Gene	WT Avg	WT SD	Gli1$^{+/-}$ Avg	Gli1$^{+/-}$ SD	Fold Change
IL-23 p19	446.3	136.0	1129.9	330.0	2.5*
IL-12 p40	280.6	120.0	703.8	221.0	2.5*
IFNγ	78.3	21.5	439.0	103.4	5.6*
CXCL5	51.8	16.3	410.8	64.8	7.9*
IL-2	112.0	21.0	298.1	44.2	2.7*
Arginase 1	59.0	17.3	222.2	43.0	3.8*
IL-12 p35	50.2	6.6	206.3	36.2	4.1*
CXCL1	29.8	9.0	113.6	83.0	3.8*
IL-17A	35.5	8.7	80.0	30.4	2.3*
IL-4	6.3	2.1	65.4	10.2	10.4*
CXCL10	91.4	47.9	173.4	62.5	1.9
CXCL2	107.6	43.4	156.5	77.9	1.5
IL-6	111.3	40.4	148.7	50.6	1.3
IL-10	88.7	21.9	127.9	97.8	1.4
TGFβ1	74.6	14.3	118.1	46.1	1.6
IL-1β	118.5	25.6	104.1	62.8	0.9
TNFα	82.6	22.1	86.1	49.8	1.0

Figure 109

GAATGTCTCTCTACCCCCCAACCCCCCATGTCTGTGGTGAAGTCGATCGAATTAGTGCTG
CCCGAGGATAGAATCTACCTGGCTGGCTCCAGCATAAAAGGGCAGGTGATCTTAACCCTG
AACAGCACCCTGGTGGACCCCATAGTGAAGGTGGAGCTCGTGGGAAGGGGTTACGTCGAA
TGGAGTGAAGAAGCCGGGGCATCCTGTGATTATAGCAGAAATGTTATTTGCAACAACAAG
GCAGACTACGTGCATAAGACAAAGACATTCCCAGTGGAGGATAATTGGTTAAGTGCAGGC
AGCCACACCTTTGACTTCCATTTCAACTTACCTCCCAGGCTTCCTTCTACCTTCACCAGC
AAATTTGGCCATGTCTTCTATTTCGTACAAGCTTCCTGCATGGGCAGGGAACACATTTTA
GCCAAGAAGAGGATGTACTTATTGGTTCAAGGAACTTCCACCTTCCACAAAGAAACCCCA
TTCCAGGTACCGATGGGGGAAAGGTGGAGGTGGGAACAATCTCCAAGCTCCAAGGAGGAA
GAGGGAAGGAGAGGAGGGGGAGCTCCAGCTGCTCCTGAAAAGGCTGAAGAGAAGCCAGAG
GCAGAAAAGTGGGAGAACCCCTTGTTCGTGGAGGCTGAGGAGAAAGTCTCCTACAACTGC
TGCCGCCAGGGCACTGTCTGTTTGCAAATCCAGATGGAAAGGAACACCTTCACGCCAGGA
GAGAAGGTCGTCTTCACAACAGAGATCAACAACCAGACCAGCAAATGCATCAAGACGGTC
GTATTCGCCCTGTATGCCCACATACAGTACGAGGGCTTCACGCCCAGTGCAGAGCGGCGG
TCTCGGCTGGACAGCAGCGAGCTTCTGAGGCAGGAGGCCAACACCCCCGTGACCCGCTTC
AACACCACCAAGGTTGTCAGCACCTTCAACCTGCCGTTGCTGCTGTCCGTGAGCAGCAGC
ACGCAGGACGGTGAGATCATGCACACTCGCTACGAGCTGGTCACCACCGTGCACCTGCCC
TGGTCCCTGACCAGCCTCAAGGCCAAAGTTCCCATCATCATCACCAGCGCCTCAGTGGAC
TCTGCCATCTGCCAGCTGTCAGAGGACGGAGTGTTACCCGTGAACCCAGATCACCAGAAT
TAA

Figure 110A

MGDREECLSTPQPPMSVVKSIELVLPEDRIYLAGSSIKGQVILTLNSTLVDPIVKVELVGRGYVEWSE
EAGASCDYSRNVICNNKADYVHKTKTFPVEDNWLSAGSHTFDFHFNLPPRLPSTFTSKFGHVFYFV
QASCMGREHILAKKRMYLLVQGTSTFHKETPFQNPLFVEAEEKVSYNCCRQGTVCLQIQMERNTFT
PGEKVVFTTEINNQTSKCIKTVVFALYAHIQYEGFTPSAERRSRLDSSELLRQEANTPVTRFNTTKVV
STFNLPLLLSVSSSTQDGEIMHTRYELVTTVHLPWSLTSLKAKVPIIITSASVDSAICQLSEDGVLPVN
PDHQN

Figure 110B

ATGGATTTCATCTTTCATGAGAAACAGGAAGGTTTCCTGTGTGCTCAGCACTGTCTGAAC
AATCTATTGCAAGGAGAATATTTTAGCCCTGTGGAATTAGCCTCAATTGCACATCAGCTA
GATGAAGAAGAGAGGATGAGAATGGCAGAAGGAGGAGTCACCAGTGAAGAGTATCTTGCA
TTTTTACAGCAGCCTTCAGAAAACATGGATGATACCGGTTTCTTCTCCATTCAGGTAATA
AGCAATGCCTTGAAGTTCTGGGGTTTAGAGATCATCCATTTCAATAATCCTGAATATCAG
AAGCTCGGCATTGATCCTATAAATGAAAGATCTTTTATATGTAATTATAAACAACACTGG
TTTACTATTAGAAAATTTGGAAAACACTGGTTTAACTTGAATTCTCTCTTGGCGGGTCCA
GAATTAATATCAGATACATGCCTTGCAAATTTCTTGGCTCGATTACAACAACAAGCATAT
TCTGTATTTGTTGTCAAGGGTGATCTGCCAGACTGTGAAGCTGACCAACTCCTGCAGATC
ATCAGTGTCGAAGAGATGGATACACCAAAACTTAATGGAAAAAAATTAGTAAAACAAAAA
GAGCATAGAGTCTATAAAACAGTCCTTGAAAAAGTATCAGAAGAAAGTGATGAGTCTGGA
ACATCAGACCAAGATGAGGAGGATTTTCAGAGGGCCCTTGAACTAAGCCGCCAAGAAACC
AATAGAGAAGATGAACATCTCCGCAGTACTATTGAGTTAAGCATGCAAGGTAGTTCCGGA
AACACATCGCAAGATCTTCCAAAGACATCATGTGTAACTCCTGCTTCAGAACAGCCGAAG
AAAATAAAAGAAGACTATTTTGAAAAGCATCAGCAGGAACAGAAGCAGCAGCAACAACAG
TCAGATCTGCCGGGCCACAGTTCATACCTACACGAAAGGCCAACAACAAGTTCGAGAGCA
ATTGAGAGTGATCTCAGTGATGACATCAGTGAAGGCACAGTACAGGCCGCTGTCGACACC
ATTTTAGAAATTATGAGAAAGAATTTGAAAATCAAAGGGGAAAAATAA

Figure 111

CGCTGAGATCTGTGGAGGTTTTTCTCTGCAAATGCAGAAAGAAATCAGGTGGATGGATGCATA
ATTATGGCCCTGCTCCTGGTCTCTTTGCTGGCATTCCTGAGCTTGGGCTCAGGATGTCATCATCG
GATCTGTCACTGCTCTAACAGGGTTTTTCTCTGCCAAGAGAGCAAGGTGACAGAGATTCCTTCT
GACCTCCCGAGGAATGCCATTGAACTGAGGTTTGTCCTCACCAAGCTTCGAGTCATCCAAAAA
GGTGCATTTTCAGGATTTGGGGACCTGGAGAAAATAGAGATCTCTCAGAATGATGTCTTGGAG
GTGATAGAGGCAGATGTGTTCTCCAACCTTCCCAAATTACATGAAATTAGAATTGAAAAGGCC
AACAACCTGCTCTACATCACCCCTGAGGCCTTCCAGAACCTTCCCAACCTTCAATATCTGTTAA
TATCCAACACAGGTATTAAGCACCTTCCAGATGTTCACAAGATTCATTCTCTCCAAAAGGTTTT
ACTTGACATTCAAGATAACATAAACATCCACACAATTGAAAGAAATTCTTTCGTGGGGCTGAG
CTTTGAAAGTGTGATTCTATGGCTGAATAAGAATGGGATTCAAGAAATACACAACTGTGCATTC
AATGGAACCCAACTAGATGCAGTGAATCTAAGCGATAATAATAATTTAGAAGAATTGCCTAAT
GATGTTTTCCACGGAGCCTCTGGACCAGTCATTCTAGATATTTCAAGAACAAGGATCCATTCCC
TGCCTAGCTATGGCTTAGAAAATCTTAAGAAGCTGAGGGCCAGGTCGACTTACAACTTAAAAA
AGCTGCCTACTCTGGAAAAGCTTGTCGCCCTCATGGAAGCCAGCCTCACCTATCCCAGCCATTG
CTGTGCCTTTGCAAACTGGAGACGGCAAATCTCTGAGCTTCATCCAATTTGCAACAAATCTATT
TTAAGGCAAGAAGTTGATTATATGACTCAGGCTAGGGGTCAGAGATCCTCTCTGGCAGAAGAC
AATGAGTCCAGCTACAGCAGAGGATTTGACATGACGTACACTGAGTTTGACTATGACTTATGC
AATGAAGTGGTTGACGTGACCTGCTCCCCTAAGCCAGATGCATTCAACCCATGTGAAGATATC
ATGGGGTACAACATCCTCAGAGTCCTGATATGGTTTATCAGCATCCTGGCCATCACTGGGAACA
TCATAGTGCTAGTGATCCTAACTACCAGCCAATATAAACTCACAGTCCCCAGGTTCCTTATGTG
CAACCTGGCCTTTGCTGATCTCTGCATTGGAATCTACCTGCTGCTCATTGCATCAGTTGATATCC
ATACCAAGAGCCAATATCACAACTATGCCATTGACTGGCAAACTGGGGCAGGCTGTGATGCTG
CTGGCTTTTTCACTGTCTTTGCCAGTGAGCTGTCAGTCTACACTCTGACAGCTATCACCTTGGAA
AGATGGCATACCATCACGCATGCCATGCAGCTGGACTGCAAGGTGCAGCTCCGCCATGCTGCC
AGTGTCATGGTGATGGGCTGGATTTTTGCTTTTGCAGCTGCCCTCTTTCCCATCTTTGGCATCAG
CAGCTACATGAAGGTGAGCATCTGCCTGCCCATGGATATTGACAGCCCTTTGTCACAGCTGTAT
GTCATGTCCCTCCTTGTGCTCAATGTCCTGGCCTTTGTGGTCATCTGTGGCTGCTATATCCACAT
CTACCTCACAGTGCGGAACCCCAACATCGTGTCCTCCTCTAGTGACACCAGGATCGCCAAGCGC
ATGGCCATGCTCATCTTCACTGACTTCCTCTGCATGGCACCCATTTCTTTCTTTGCCATTTCTGCC
TCCCTCAAGGTGCCCCTCATCACTGTGTCCAAAGCAAAGATTCTGCTGGTTCTGTTTCACCCCAT
CAACTCCTGTGCCAACCCCTTCCTCTATGCCATCTTTACCAAAAACTTTCGCAGAGATTTCTTCA
TTCTGCTGAGCAAGTGTGGCTGCTATGAAATGCAAGCCCAAATTTATAGGACAGAAACTTCATC
CACTGTCCACAACACCCATCCAAGGAATGGCCACTGCTCTTCAGCTCCCAGAGTCACCAGTGGT
TCCACTTACATACTTGTCCCTCTAAGTCATTTAGCCCAAAACTAAAACACAATGTGAAAATGTA
TCTGAGTATTGAATGATAATTCAGTCCTTGCCTTTGAAGGGTATGTCACAAGGAGCTGACAGTG
CTTCTACACATTTCATCTAATTTAATATTCCTGGCATACCTTTAAGGTAAATTGGTCAGGAACTA
TTAATTCCATGTGATACATTAGGAAGCTGAATTATTAGTAACAACAATAATAATTAAAGAATGC
AATACTGTAAAAAAGCGGCCGCGAATT

Figure 112A

MALLLVSLLAFLSLGSGCHHRICHCSNRVFLCQESKVTEIPSDLPRNAIELRFVLTKLRVIQKGAFSG
FGDLEKIEISQNDVLEVIEADVFSNLPKLHEIRIEKANNLLYINPEAFQNLPNLQYLLISNTGIKHLPDV
HKIHSLQKVLLDIQDNINIHTIERNSFVGLSFESVILWLNKNGIQEIHNCAFNGTQLDELNLSDNNNLE
ELPNDVFHGASGPVILDISRTRIHSLPSYGLENLKKLRARSTYNLKKLPTLEKLVALMEASLTYPSHC
CAFANWRRQISELHPICNKSILRQEVDYMTQARGQRSSLAEDNESSYSRGFDMTYTEFDYDLCNEV
VDVTCSPKPDAFNPCEDIMGYNILRVLIWFISILAITGNIIVLVILTTSQYKLTVPRFLMCNLAFADLCI
GIYLLLIASVDIHTKSQYHNYAIDWQTGAGCDAAGFFTVFASELSVYTLTAITLERWHTITHAMQLD
CKVQLRHAASVMVMGWIFAFAAALFPIFGISSYMKVSICLPMDIDSPLSQLYVMSLLVLNVLAFVVI
CGCYIHIYLTVRNPNIVSSSSDTRIAKRMAMLIFTDFLCMAPISFFAISASLKVPLITVSKAKILLVLFH
PINSCANPFLYAIFTKNFRRDFFILLSKCGCYEMQAQIYRTETSSTVHNTHPRNGHCSSAPRVTSGST
YILVPLSHLAQN

Figure 112B

CCCATTACTGTTGGAGCTACAGGGAGAGAAACAGGAGGAGACTGCAAGAGATCATTTGGG
AAGGCCGTGGGCACGCTCTTTACTCCATGTGTGGGACATTCATTGCGGAATAACATCGGA
GGAGAAGTTTCCCAGAGCTATGGGGACTTCCCATCCGGCGTTCCTGGTCTTAGGCTGTCT
TCTCACAGGGCTGAGCCTAATCCTCTGCCAGCTTTCATTACCCTCTATCCTTCCAAATGA
AAATGAAAAGGTTGTGCAGCTGAATTCATCCTTTTCTCTGAGATGCTTTGGGGAGAGTGA
AGTGAGCTGGCAGTACCCCATGTCTGAAGAAGAGAGCTCCGATGTGGAAATCAGAAATGA
AGAAAACAACAGCGGCCTTTTTGTGACGGTCTTGGAAGTGAGCAGTGCCTCGGCGGCCCA
CACAGGGTTGTACACTTGCTATTACAACCACACTCAGACAGAAGAGAATGAGCTTGAAGG
CAGGCACATTTACATCTATGTGCCAGACCCAGATGTAGCCTTTGTACCTCTAGGAATGAC
GGATTATTTAGTCATCGTGGAGGATGATGATTCTGCCATTATACCTTGTCGCACAACTGA
TCCCGAGACTCCTGTAACCTTACACAACAGTGAGGGGGTGGTACCTGCCTCCTACGACAG
CAGACAGGGCTTTAATGGGACCTTCACTGTAGGGCCCTATATCTGTGAGGCCACCGTCAA
AGGAAAGAAGTTCCAGACCATCCCATTTAATGTTTATGCTTTAAAAGCAACATCAGAGCT
GGATCTAGAAATGGAAGCTCTTAAAACCGTGTATAAGTCAGGGGAAACGATTGTGGTCAC
CTGTGCTGTTTTTAACAATGAGGTGGTTGACCTTCAATGGACTTACCCTGGAGAAGTGAA
AGGCAAAGGCATCACAATGCTGGAAGAAATCAAAGTCCCATCCATCAAATTGGTGTACAC
TTTGACGGTCCCCGAGGCCACGGTGAAAGACAGTGGAGATTACGAATGTGCTGCCCGCCA
GGCTACCAGGGAGGTCAAAGAAATGAAGAAAGTCACTATTTCTGTCCATGAGAAAGGTTT
CATTGAAATCAAACCCACCTTCAGCCAGTTGGAAGCTGTCAACCTGCATGAAGTCAAACA
TTTTGTTGTAGAGGTGCGGGCCTACCCACCTCCCAGGATATCCTGGCTGAAAAACAATCT
GACTCTGATTGAAAATCTCACTGAGATCACCACTGATGTGGAAAAGATTCAGGAAATAAG
GTATCGAAGCAAATTAAAGCTGATCCGTGCTAAGGAAGAAGACAGTGGCCATTATACTAT
TGTAGCTCAAAATGAAGATGCTGTGAAGAGCTATACTTTTGAACTGTTAACTCAAGTTCC
TTCATCCATTCTGGACTTGGTCGATGATCACCATGGCTCAACTGGGGGACAGACGGTGAG
GTGCACAGCTGAAGGCACGCCGCTTCCTGATATTGAGTGGATGATATGCAAAGATATTAA
GAAATGTAATAATGAAACTTCCTGGACTATTTTGGCCAACAATGTCTCAAACATCATCAC
GGAGATCCACTCCCGAGACAGGAGTACCGTGGAGGGCCGTGTGACTTTCGCCAAAGTGGA
GGAGACCATCGCCGTGCGATGCCTGGCTAAGAATCTCCTTGGAGCTGAGAACCGAGAGCT
GAAGCTGGTGGCTCCCACCCTGCGTTCTGAACTCACGGTGGCTGCTGCAGTCCTGGTGCT
GTTGGTGATTGTGATCATCTCACTTATTGTCCTGGTTGTCATTTGGAAACAGAAACCGAG
GTATGAAATTCGCTGGAGGGTCATTGAATCAATCAGCCCGGATGGACATGAATATATTTA
TGTGGACCCGATGCAGCTGCCTTATGACTCAAGATGGGAGTTTCCAAGAGATGGACTAGT
GCTTGGTCGGGTCTTGGGGTCTGGAGCGTTTGGGAAGGTGGTTGAAGGAACAGCCTATGG
ATTAAGCCGGTCCCAACCTGTCATGAAAGTTGCAGTGAAGATGCTAAAACCCACGGCCAG
ATCCAGTGAAAAACAAGCTCTCATGTCTGAACTGAAGATAATGACTCACCTGGGGCCACA
TTTGAACATTGTAAACTTGCTGGGAGCCTGCACCAAGTCAGGCCCCATTTACATCATCAC
AGAGTATTGCTTCTATGGAGATTTGGTCAACTATTTGCATAAGAATAGGGATAGCTTCCT
GAGCCACCACCCAGAGAAGCCAAAGAAAGAGCTGGATATCTTTGGATTGAACCCTGCTGA
TGAAAGCACACGGAGCTATGTTATTTTATCTTTTGAAAACAATGGTGACTACATGGACAT
GAAGCAGGCTGATACTACACAGTATGTCCCCATGCTAGAAAGGAAAGAGGTTTCTAAATA
TTCCGACATCCAGAGATCACTCTATGATCGTCCAGCCTCATATAAGAAGAAATCTATGTT
AGACTCAGAAGTCAAAAACCTCCTTTCAGATGATAACTCAGAAGGCCTTACTTTATTGGA
TTTGTTGAGCTTCACCTATCAAGTTGCCCGAGGAATGGAGTTTTTGGCTTCAAAAAATTG
TGTCCACCGTGATCTGGCTGCTCGCAACGTCCTCCTGGCACAAGGAAAAATTGTGAAGAT
CTGTGACTTTGGCCTGGCCAGAGACATCATGCATGATTCGAACTATGTGTCGAAAGGCAG
TACCTTTCTGCCCGTGAAGTGGATGGCTCCTGAGAGCATCTTTGACAACCTCTACACCAC
ACTGAGTGATGTCTGGTCTTATGGCATTCTGCTCTGGGAGATCTTTTCCCTTGGTGGCAC
CCCTTACCCCGGCATGATGGTGGATTCTACTTTCTACAATAAGATCAAGAGTGGGTACCG
GATGGCCAAGCCTGACCACGCTACCAGTGAAGTCTACGAGATCATGGTGAAATGCTGGAA
CAGTGAGCCGGAGAAGAGACCCTCCTTTTACCACCTGAGTGAGATTGTGGAGAATCTGCT
GCCTGGACAATATAAAAAGAGTTATGAAAAAATTCACCTGGACTTCCTGAAGAGTGACCA
TCCTGCTGTGGCACGCATGCGTGTGGACTCAGACAATGCATACATTGGTGTCACCTACAA
AAACGAGGAAGACAAGCTGAAGGACTGGGAGGGTGGTCTGGATGAGCAGAGACTGAGCGC

Figure 113A

TGACAGTGGCTACATCATTCCTCTGCCTGACATTGACCCTGTCCCTGAGGAGGAGGACCT
GGGCAAGAGGAACAGACACAGCTCGCAGACCTCTGAAGAGAGTGCCATTGAGACGGGTTC
CAGCAGTTCCACCTTCATCAAGAGAGAGGACGAGACCATTGAAGACATCGACATGATGGA
CGACATCGGCATAGACTCTTCAGACCTGGTGGAAGACAGCTTCCTGTAACTGGCGGATTC
GAGGGGTTCCTTCCACTTCTGGGGCCACCTCTGGATCCCGTTCAGAAAACCACTTTATTG
CAATGCGGAGGTTGAGAGGAGGACTTGGTTGATGTTTAAAGAGAAGTTCCCAGCCAAGGG
CCTCGGGGAGCGTTCTAAATATGAATGAATGGGATATTTTGAAATGAACTTTGTCAGTGT
TGCCTCTCGCAATGCCTCAGTAGCATCTCAGTGGTGTGTGAAGTTTGGAGATAGATGGAT
AAGGGAATAATAGGCCACAGAAGGTGAACTTTGTGCTTCAAGGACATTGGTGAGAGTCCA
ACAGACACAATTTATACTGCGACAGAACTTCAGCATTGTAATTATGTAAATAACTCTAAC
CAAGGCTGTGTTTAGATTGTATTAACTATCTTCTTTGGACTTCTGAAGAGACCACTCAAT
CCATCCATGTACTTCCCTCTTGAAACCTGATGTCAGCTGCTGTTGAACTTTTTAAAGAAG
TGCATGAAAAACCATTTTTGAACCTTAAAAGGTACTGGTACTATAGCATTTTGCTATCTT
TTTTAGTGTTAAGAGATAAAGAATAATAATTAACCAACCTTGTTTAATAGATTTGGGTCA
TTTAGAAGCCTGACAACTCATTTTCATATTGTAATCTATGTTTATAATACTACTACTGTT
ATCAGTAATGCTAAATGTGTAATAATGTAACATGATTTCCCTCCAGAGAAAGCACAATTT
AAAACAATCCTTACTAAGTAGGTGATGAGTTTGACAGTTTTTGACATTTATATTAAATAA
CATGTTTCTCTATAAAGTATGGTAATAGCTTTAGTGAATTAAATTTAGTTGAGCATAGAG
AACAAAGTAAAAGTAGTGTTGTCCAGGAAGTCAGAATTTTTAACTGTACTGAATAGGTTC
CCCAATCCATCGTATTAAAAAACAATTAACTGCCCTCTGAAATAATGGGATTAGAAACAA
ACAAAACTCTTAAGTCCTAAAAGTTCTCAATGTAGAGGCATAAACCTGTGCTGAACATAA
CTTCTCATGTATATTACCCAATGGAAAATATAATGATCAGCAAAAAGACTGGATTTGCAG
AAGTTTTTTTTTTTTTTCTTCATGCCTGATGAAAGCTTTGGCAACCCCAATATATGTATT
TTTTGAATCTATGAACCTGAAAAGGGTCAGAAGGATGCCCAGACATCAGCCTCCTTCTTT
CACCCCTTACCCCAAAGAGAAAGAGTTTGAAACTCGAGACCATAAAGATATTCTTTAGTG
GAGGCTGGATGTGCATTAGCCTGGATCCTCAGTTCTCAAATGTGTGTGGCAGCCAGGATG
ACTAGATCCTGGGTTTCCATCCTTGAGATTCTGAAGTATGAAGTCTGAGGGAAACCAGAG
TCTGTATTTTTCTAAACTCCCTGGCTGTTCTGATCGGCCAGTTTTCGGAAACACTGACTT
AGGTTTCAGGAAGTTGCCATGGGAAACAAATAATTTGAACTTTGGAACAGGGTTGGAATT
CAACCACGCAGGAAGCCTACTATTTAAATCCTTGGCTTCAGGTTAGTGACATTTAATGCC
ATCTAGCTAGCAATTGCGACCTTAATTTAACTTTCCAGTCTTAGCTGAGGCTGAGAAAGC
TAAAGTTTGGTTTTGACAGGTTTTCCAAAAGTAAAGATGCTACTTCCCACTGTATGGGGG
AGATTGAACTTTCCCCGTCTCCCGTCTTCTGCCTCCCACTCCATACCCCGCCAAGGAAAG
GCATGTACAAAAATTATGCAATTCAGTGTTCCAAGTCTCTGTGTAACCAGCTCAGTGTTT
TGGTGGAAAAAACATTTTAAGTTTTACTGATAATTTGAGGTTAGATGGGAGGATGAATTG
TCACATCTATCCACACTGTCAAACAGGTTGGTGTGGGTTCATTGGCATTCTTTGCAATAC
TGCTTAATTGCTGATACCATATGAATGAAACATGGGCTGTGATTACTGCAATCACTGTGC
TATCGGCAGATGATGCTTTGGAAGATGCAGAAGCAATAATAAAGTACTTGACTACCTACT
GGTGTAATCTCAATGCAAGCCCCAACTTTCTTATCCAACTTTTTCATAGTAAGTGCGAAG
ACTGAGCCAGATTGGCCAATTAAAAACGAAAACCTGACTAGGTTCTGTAGAGCCAATTAG
ACTTGAAATACGTTTGTGTTTCTAGAATCACAGCTCAAGCATTCTGTTTATCGCTCACTC
TCCCTTGTACAGCCTTATTTTGTTGGTGCTTTGCATTTTGATATTGCTGTGAGCCTTGCA
TGACATCATGAGGCCGGATGAAACTTCTCAGTCCAGCAGTTTCCAGTCCTAACAAATGCT
CCCACCTGAATTTGTATATGACTGCATTTGTGGGTGTGTGTGTGTTTTCAGCAAATTCCA
GATTTGTTTCCTTTTGGCCTCCTGCAAAGTCTCCAGAAGAAAATTTGCCAATCTTTCCTA
CTTTCTATTTTTATGATGACAATCAAAGCCGGCCTGAGAAACACTATTTGTGACTTTTTA
AACGATTAGTGATGTCCTTAAAATGTGGTCTGCCAATCTGTACAAAATGGTCCTATTTTT
GTGAAGAGGGACATAAGATAAAATGATGTTATACATCAATATGTATATATGTATTTCTAT
ATAGACTTGGAGAATACTGCCAAAACATTTATGACAAGCTGTATCACTGCCTTCGTTTAT
ATTTTTTTAACTGTGATAATCCCCACAGGCACATTAACTGTTGCACTTTTGAATGTCCAA
AATTTATATTTTAGAAATAATAAAAAGAAAGATACTTACATGTTCCCAAAACAATGGTGT
GGTGAATGTGTGAGAAAAACTAACTTGATAGGGTCTACCAATACAAAATGTATTACGAAT
GCCCCTGTTCATGTTTTTGTTTTAAAACGTGTAAATGAAGATCTTTATATTTCAATAAAT
GATATATAATTTAAAGTT

Figure 113A (continued)

MGTSHPAFLVLGCLLTGLSLILCQLSLPSILPNENEKVVQLNSSFSLRCFGESEVSWQYPMSEEESSD
VEIRNEENNSGLFVTVLEVSSASAAHTGLYTCYYNHTQTEENELEGRHIYIYVPDPDVAFVPLGMTD
YLVIVEDDDSAIIPCRTTDPETPVTLHNSEGVVPASYDSRQGFNGTFTVGPYICEATVKGKKFQTIPF
NVYALKATSELDLEMEALKTVYKSGETIVVTCAVFNNEVVDLQWTYPGEVKGKGITMLEEIKVPSI
KLVYTLTVPEATVKDSGDYECAARQATREVKEMKKVTISVHEKGFIEIKPTFSQLEAVNLHEVKHF
VVEVRAYPPPRISWLKNNLTLIENLTEITTDVEKIQEIRYRSKLKLIRAKEEDSGHYTIVAQNEDAVK
SYTFELLTQVPSSILDLVDDHHGSTGGQTVRCTAEGTPLPDIEWMICKDIKKCNNETSWTILANNVS
NIITEIHSRDRSTVEGRVTFAKVEETIAVRCLAKNLLGAENRELKLVAPTLRSELTVAAAVLVLLVIV
IISLIVLVVIWKQKPRYEIRWRVIESISPDGHEYIYVDPMQLPYDSRWEFPRDGLVLGRVLGSGAFGK
VVEGTAYGLSRSQPVMKVAVKMLKPTARSSEKQALMSELKIMTHLGPHLNIVNLLGACTKSGPIYII
TEYCFYGDLVNYLHKNRDSFLSHHPEKPKKELDIFGLNPADESTRSYVILSFENNGDYMDMKQADT
TQYVPMLERKEVSKYSDIQRSLYDRPASYKKKSMLDSEVKNLLSDDNSEGLTLLDLLSFTYQVARG
MEFLASKNCVHRDLAARNVLLAQGKIVKICDFGLARDIMHDSNYVSKGSTFLPVKWMAPESIFDNL
YTTLSDVWSYGILLWEIFSLGGTPYPGMMVDSTFYNKIKSGYRMAKPDHATSEVYEIMVKCWNSE
PEKRPSFYHLSEIVENLLPGQYKKSYEKIHLDFLKSDHPAVARMRVDSDNAYIGVTYKNEEDKLKD
WEGGLDEQRLSADSGYIIPLPDIDPVPEEEDLGKRNRHSSQTSEESAIETGSSSSTFIKREDETIEDIDM
MDDIGIDSSDLVEDSFL

Figure 113B

TGATTTTGGGACCCAGCCATGGTCCTTCTGCTTCTTCTTTAAAATACCCACTTTCTCCCC
ATCGCCAAGCGGCGTTTGGCAATATCAGATATCCACTCTATTTATTTTTACCTAAGGAA
AAACTCCAGCTCCCTTCCCACTCCCAGCTGCCTTGCCACCCCTCCCAGCCCTCTGCTTG
CCCTCCACCTGGCCTGCTGGGAGTCAGAGCCCAGCAAAACCTGTTTAGACACATGGAC
AAGAATCCCAGCGCTACAAGGCACACAGTCCGCTTCTTCGTCCTCAGGGTTGCCAGCG
CTTCCTGGAAGTCCTGAAGCTCTCGCAGTGCAGTGAGTTCATGCACCTTCTTGCCAAGC
CTCAGTCTTTGGGATCTGGGGAGGCCGCCTGGTTTTCCTCCCTCCTTCTGCACGTCTGCT
GGGGTCTCTTCCTCTCCAGGCCTTGCCGTCCCCCTGGCCTCTCTTCCCAGCTCACACAT
GAAGATGCACTTGCAAAGGGCTCTGGTGGTCCTGGCCCTGCTGAACTTTGCCACGGTC
AGCCTCTCTCTGTCCACTTGCACCACCTTGGACTTCGGCCACATCAAGAAGAAGAGGG
TGGAAGCCATTAGGGGACAGATCTTGAGCAAGCTCAGGCTCACCAGCCCCCCTGAGCC
AACGGTGATGACCCACGTCCCCTATCAGGTCCTGGCCCTTTACAACAGCACCCGGGAG
CTGCTGGAGGAGATGCATGGGGAGAGGGAGGAAGGCTGCACCCAGGAAAACACCGAG
TCGGAATACTATGCCAAAGAAATCCATAAATTCGACATGATCCAGGGGCTGGCGGAGC
ACAACGAACTGGCTGTCTGCCCTAAAGGAATTACCTCCAAGGTTTTCCGCTTCAATGTG
TCCTCAGTGGAGAAAAATAGAACCAACCTATTCCGAGCAGAATTCCGGGTCTTGCGGG
TGCCCAACCCCAGCTCTAAGCGGAATGAGCAGAGGATCGAGCTCTTCCAGATCCTTCG
GCCAGATGAGCACATTGCCAAACAGCGCTATATCGGTGGCAAGAATCTGCCCACACGG
GGCACTGCCGAGTGGCTGTCCTTTGATGTCACTGACACTGTGCGTGAGTGGCTGTTGAG
AAGAGAGTCCAACTTAGGTCTAGAAATCAGCATTCACTGTCCATGTCACACCTTTCAG
CCCAATGGAGATATCCTGGAAAACATTCACGAGGTGATGGAAATCAAATTCAAAGGC
GTGGACAATGAGGATGACCATGGCCGTGGAGATCTGGGGCGCCTCAAGAAGCAGAAG
GATCACCACAACCCTCATCTAATCCTCATGATGATTCCCCCACACCGGCTCGACAACCC
GGGCCAGGGGGGTCAGAGGAAGAAGCGGGCTTTGGACACCAATTACTGCTTCCGCAA
CTTGGAGGAGAACTGCTGTGTGCGCCCCCTCTACATTGACTTCCGACAGGATCTGGGCT
GGAAGTGGGTCCATGAACCTAAGGGCTACTATGCCAACTTCTGCTCAGGCCCTTGCCC
ATACCTCCGCAGTGCAGACACAACCCACAGCACGGTGCTGGGACTGTACAACACTCTG
AACCCTGAAGCATCTGCCTCGCCTTGCTGCGTGCCCCAGGACCTGGAGCCCCTGACCA
TCCTGTACTATGTTGGGAGGACCCCCAAAGTGGAGCAGCTCTCCAACATGGTGGTGAA
GTCTTGTAAATGTAGCTGAGACCCCACGTGCGACAGAGAGAGGGGAGAGAGAACCAC
CACTGCCTGACTGCCCGCTCCTCGGGAAACACACAAGCAACAAACCTCACTGAGAGGC
CTGGAGCCCACAACCTTCGGCTCCGGGCAAATGGCTGAGATGGAGGTTTCCTTTTGGA
ACATTTCTTTCTTGCTGGCTCTGAGAATCACGGTGGTAAAGAAAGTGTGGGTTTGGTTA
GAGGAAGGCTGAACTCTTCAGAACACACAGACTTTCTGTGACGCAGACAGAGGGGAT
GGGGATAGAGGAAAGGGATGGTAAGTTGAGATGTTGTGTGGCAATGGGATTTGGGCT
ACCCTAAAGGGAGAAGGAAGGGCAGAGAATGGCTGGGTCAGGGCCAGACTGGAAGA
CACTTCAGATCTGAGGTTGGATTTGCTCATTGCTGTACCACATCTGCTCTAGGGAATCT
GGATTATGTTATACAAGGCAAGCATTTTTTTTTTTTTTTTAAAGACAGGTTACGAAGAC
AAAGTCCCAGAATTGTATCTCATACTGTCTGGGATTAAGGGCAAATCTATTACTTTTGC
AAACTGTCCTCTACATCAATTAACATCGTGGGTCACTACAGGGAGAAAATCCAGGTCA
TGCAGTTCCTGGCCCATCAACTGTATTGGGCCTTTTGGATATGCTGAACGCAGAAGAA
AGGGTGGAAATCAACCCTCTCCTGTCTGCCCTCTGGGTCCCTCCTCTCACCTCTCCCTC
GATCATATTTCCCCTTGGACACTTGGTTAGACGCCTTCCAGGTCAGGATGCACATTTCT
GGATTGTGGTTCCATGCAGCCTTGGGGCATTATGGGTTCTTCCCCCACTTCCCCTCCAA
GACCCTGTGTTCATTTGGTGTTCCTGGAAGCAGGTGCTACAACATGTGAGGCATTCGG
GGAAGCTGCACATGTGCCACACAGTGACTTGGCCCCAGACGCATAGACTGAGGTATAA
AGACAAGTATGAATATTACTCTCAAAATCTTTGTATAAATAAATATTTTTGGGGCATCC
TGGATGATTTCATCTTCTGGAATATTGTTTCTAGAACAGTAAAAGCCTTATTCTAAAAA
AAAAAAAAAAA

Figure 114A

MKMHLQRALVVLALLNFATVSLSLSTCTTLDFGHIKKKRVEAIRGQILSKLRLTSPPEPTVMTHVPY
QVLALYNSTRELLEEMHGEREEGCTQENTESEYYAKEIHKFDMIQGLAEHNELAVCPKGITSKVFR
FNVSSVEKNRTNLFRAEFRVLRVPNPSSKRNEQRIELFQILRPDEHIAKQRYIGGKNLPTRGTAEWLS
FDVTDTVREWLLRRESNLGLEISIHCPCHTFQPNGDILENIHEVMEIKFKGVDNEDDHGRGDLGRLK
KQKDHHNPHLILMMIPPHRLDNPGQGGQRKKRALDTNYCFRNLEENCCVRPLYIDFRQDLGWKW
VHEPKGYYANFCSGPCPYLRSADTTHSTVLGLYNTLNPEASASPCCVPQDLEPLTILYYVGRTPKVE
QLSNMVVKSCKCS

Figure 114B

ACTTCCCCGCCCTCGCCCCAAAGGAGCAGCAGCTCCTTCTTGCCTCTCCATTGCCGCCGC
CGCACCGGCGGAGCTCCTCTCTCGCGCGTCTCTCCTCCGATGGAGCTCGGGCGCCGCCGA
CGCCGCCGCTGCCCCGAACCCTGAGCGGGGCCGCCCCGGTCGGAGGAACGCGCCGCCCAG
TCCGAGGGCGCAGAGCGCCAGGAGCACGCGGAGGGCTGGGGCGCGGGCTCCGGGAACGAG
AAAGTGCAGCTCTCTCGGGTCACTGGGCCGGCGGCGGGGGGACTATGGCTCTGAAGGACA
CGGGCAGCGGCGGCAGCACCATCCTGCCCATTAGCGAGATGGTTTCCTCGTCCAGCTCGC
CCGGCGCGTCGGCCGCCGCCGCCCCGGGGCCCTGCGCACCCTCGCCCTTCCCTGAAGTAG
TGGAGCTGAACGTAGGCGGCCAGGTTTATGTGACCAAGCACTCGACGCTGCTCAGCGTCC
CGGACAGTACTTTGGCCAGCATGTTCTCGCCCTCTAGTCCCCGTGGCGGCGCCCGGCGCC
GGGGCGAGCTGCCCAGGGACAGCCGGGCGCGCTTCTTCATCGACCGGGACGGCTTCCTTT
TCAGGTACGTGCTGGATTATCTGCGGGACAAGCAACTCGCGCTGCCGGAGCACTTCCCCG
AGAAGGAGCGGCTGCTGCGCGAGGCCGAGTATTTCCAGCTCACCGACTTGGTCAAGCTGC
TGTCGCCCAAGGTCACCAAGCAGAACTCTCTCAACGACGAGGGCTGCCAGAGCGACCTGG
AGGACAACGTCTCGCAGGGTAGCAGCGACGCGCTGCTGCTGCGCGGGGCGGCGGCCGCCG
TGCCCTCGGGCCCGGGAGCGCACGGTGGTGGCGGCGGCGGCGGCGCGCAGGACAAGCGCT
CGGGCTTCCTCACGCTGGGCTACCGGGGCTCCTACACCACCGTGCGCGACAACCAGGCCG
ACGCCAAATTCCGGCGTGTGGCGCGCATCATGGTGTGCGGGCGCATCGCGCTGGCCAAGG
AGGTCTTCGGGGACACGCTCAACGAGAGCCGCGACCCCGACCGGCAGCCGGAGAAGTACA
CGTCCCGCTTCTACCTCAAGTTCACCTACTTGGAGCAGGCCTTTGATCGCCTGTCCGAGG
CCGGCTTCCACATGGTGGCGTGTAACTCCTCGGGCACCGCCGCCTTCGTCAACCAGTACC
GCGACGACAAGATCTGGAGCAGCTACACCGAGTACATTTTCTTCCGACCACCTCAGAAAA
TAGTATCACCTAAACAAGAACATGAAGATAGGAAACATGACAAAGTCACTGATAAAGGAA
GTGAAAGTGGGACTTCCTGTAATGAGCTCTCCACTTCCAGTTGTGACAGCCATTCAGAGG
CAAGCACTCCCCAGGACAACCCATCCAGTGCCCAGCAGGCAACAGCTCACCAACCTAACA
CTTTAACATTGGATCGCCCCTCTAAAAAAGCACCTGTACAATGGATACCCCCACCAGACA
AACGCAGAAACAGTGAACTCTTTCAGACCCTCATCAGCAAGTCCCGGGAAACAAATCTGT
CCAAAAAGAAAGTCTGTGAGAAGCTAAGTGTGGAAGAAGAAATGAAAAAGTGTATTCAGG
ATTTTAAAAAAATCCACATTCCAGATTATTTTCCAGAGCGCAAACGCCAATGGCAATCTG
AACTGTTGCAGAAGTATGGGTTATAGTAATTGTCACATTCCTGCAGTATTTTGATGACAT
TCAATGTTTACTACAGTGTCACCACCTGACTGATGTCCTAACAATGGTCAGTGTGATTCT
TGCTGCTCTTCCTTGTTGTGAACAGTGGATGTGGGACAGTATTTTCTTTTATGTTTTAGT
TGTTGTTCTTTTTAGAAACATGATTAAAAAGGAAAAAATATTAAATCAATAAGTGTTAAA
TCAAAATGGAATATCTGATTCAAACCATTTTACAAGAATGAAAGTAAAATGTGCATGATC
AAGCTTAGTATCTTGGTTTTTGAACTCTGGTCAACTGGATATGTTTGTCATTTTGTAACT
TACCAAAAACAAACCATCATATCATACCAACTAAAATGATATATGGATGAAGCAACATCA
AGTAAAATTTTAGACGATGGCTATAGGACCCAAATCTAAAGCTGTCTAAATGTTAATTCA
ATGAAACAAGTATTATTTTTGCATGAATACAATGTTACAAATAAATCACAAGAAATAGGG
AAGATCTGTTTGTTGCTTGG

Figure 115A

MALKDTGSGGSTILPISEMVSSSSSPGASAAAAPGPCAPSPFPEVVELNVGGQVYVTKHSTLLSVPDS
TLASMFSPSSPRGGARRRGELPRDSRARFFIDRDGFLFRYVLDYLRDKQLALPEHFPEKERLLREAE
YFQLTDLVKLLSPKVTKQNSLNDEGCQSDLEDNVSQGSSDALLLRGAAAAVPSGPGAHGGGGGGG
AQDKRSGFLTLGYRGSYTTVRDNQADAKFRRVARIMVCGRIALAKEVFGDTLNESRDPDRQPEKY
TSRFYLKFTYLEQAFDRLSEAGFHMVACNSSGTAAFVNQYRDDKIWSSYTEYIFFRPPQKIVSPKQE
HEDRKHDKVTDKGSESGTSCNELSTSSCDSHSEASTPQDNPSSAQQATAHQPNTLTLDRPSKKAPV
QWIPPPDKRRNSELFQTLISKSRETNLSKKKVCEKLSVEEEMKKCIQDFKKIHIPDYFPERKRQWQSE
LLQKYGL

Figure 115B

AGAGATAGAGTCTTCCCTGGCATTGCAGGAGAGAATCTGAAGGGATGATGGATGCATCAAAAG
AGCTGCAAGTTCTCCACATTGACTTCTTGAATCAGGACAACGCCGTTTCTCACCACACATGGGA
GTTCCAAACGAGCAGTCCTGTGTTCCGGCGAGGACAGGTGTTTCACCTGCGGCTGGTGCTGAAC
CAGCCCCTACAATCCTACCACCAACTGAAACTGGAATTCAGCACAGGGCCGAATCCTAGCATC
GCCAAACACACCCTGGTGGTGCTCGACCCGAGGACGCCCTCAGACCACTACAACTGGCAGGCA
ACCCTTCAAAATGAGTCTGGCAAAGAGGTCACAGTGGCTGTCACCAGTTCCCCCAATGCCATCC
TGGGCAAGTACCAACTAAACGTGAAAACTGGAAACCACATCCTTAAGTCTGAAGAAAACATCC
TATACCTTCTCTTCAACCCATGGTGTAAAGAGGACATGGTTTTCATGCCTGATGAGGACGAGCG
CAAAGAGTACATCCTCAATGACACGGGCTGCCATTACGTGGGGGCTGCCAGAAGTATCAAATG
CAAACCCTGGAACTTTGGTCAGTTTGAGAAAAATGTCCTGGACTGCTGCATTTCCCTGCTGACT
GAGAGCTCCCTCAAGCCCACAGATAGGAGGGACCCCGTGCTGGTGTGCAGGGCCATGTGTGCT
ATGATGAGCTTTGAGAAAGGCCAGGGCGTGCTCATTGGGAATTGGACTGGGGACTATGAAGGT
GGCACAGCCCCATACAAGTGGACAGGCAGTGCCCCGATCCTGCAGCAGTACTACAACACGAAG
CAGGCTGTGTGCTTTGGCCAGTGCTGGGTGTTTGCTGGGATCCTGACTACAGTGCTGAGAGCGT
TGGGCATCCCAGCACGCAGTGTGACAGGCTTCGATTCAGCTCACGACACAGAAAGGAACCTCA
CGGTGGACACCTATGTGAATGAGAATGGCAAGAAAATCACCAGTATGACCCACGACTCTGTCT
GGAATTTCCATGTGTGGACGGATGCCTGGATGAAGCGACCGGATCTGCCCAAGGGCTACGACG
GCTGGCAGGCTGTGGACGCAACGCCGCAGGAGCGAAGCCAGGGTGTCTTCTGCTGTGGGCCAT
CACCACTGACCGCCATCCGCAAAGGTGACATCTTTATTGTCTATGACACCAGATTCGTCTTCTC
AGAAGTGAATGGTGACAGGCTCATCTGGTTGGTGAAGATGGTGAATGGGCAGGAGGAGTTACA
CGTAATTTCAATGGAGACCACAAGCATCGGGAAAAACATCAGCACCAAGGCAGTGGGCCAAG
ACAGGCGGAGAGATATCACCTATGAGTACAAGTATCCAGAAGGCTCCTCTGAGGAGAGGCAG
GTCATGGATCATGCCTTCCTCCTTCTCAGTTCTGAGAGGGAGCACAGACGACCTGTAAAAGAG
AACTTTCTTCACATGTCGGTACAATCAGATGATGTGCTGCTGGGAAACTCTGTTAATTTCACCG
TGATTCTTAAAAGGAAGACCGCTGCCCTACAGAATGTCAACATCTTGGGCTCCTTTGAACTACA
GTTGTACACTGGCAAGAAGATGGCAAAACTGTGTGACCTCAATAAGACCTCGCAGATCCAAGG
TCAAGTATCAGAAGTGACTCTGACCTTGGACTCCAAGACCTACATCAACAGCCTGGCTATATTA
GATGATGAGCCAGTTATCAGAGGTTTCATCATTGCGGAAATTGTGGAGTCTAAGGAAATCATG
GCCTCTGAAGTATTCACGTCTTTCCAGTACCCTGAGTTCTCTATAGAGTTGCCTAACACAGGCA
GAATTGGCCAGCTACTTGTCTGCAATTGTATCTTCAAGAATACCCTGGCCATCCCTTTGACTGA
CGTCAAGTTCTCTTTGGAAAGCCTGGGCATCTCCTCACTACAGACCTCTGACCATGGGACGGTG
CAGCCTGGTGAGACCATCCAATCCCAAATAAAATGCACCCCAATAAAAACTGGACCCAAGAAA
TTTATCGTCAAGTTAAGTTCCAAACAAGTGAAAGAGATTAATGCTCAGAAGATTGTTCTCATCA
CCAAGTAGCCTTGTCTGATGCTGTGGAGCCTTAGTTGAGATTTCAGCATTTCCTACCTTGTGCTT
AGCTTTCAGATTATGGATGATTAAATTTGATGACTTATATGAGGGCAGATTCAAGAGCCAGCA
GGTCAAAAAGGCCAACACAACCATAAGCAGCCAGACCCACAAGGCCAGGTCCTGTGCTATCAC
AGGGTCACCTCTTTTACAGTTAGAAACACCAGCCGAGGCCACAGAATCCCATCCCTTTCCTGAG
TCATGGCCTCAAAAATCAGGGCCACCATTGTCTCAATTCAAATCCATAGATTTCGAAGCCACAG
AGTCTCTCCCTGGAGCAGCAGACTATGGGCAGCCCAGTGCTGCCACCTGCTGACGACCCTTGA
GAAGCTGCCATATCTTCAGGCCATGGGTTCACCAGCCCTGAAGGCACCTGTCAACTGGAGTGCT
CTCTCAGCACTGGGATGGGCCTGATAGAAGTGCATTCTCCTCCTATTGCCTCCATTCTCCTCTCT
CTATCCCTGAAATCCAGGAAGTCCCTCTCCTGGTGCTCCAAGCAGTTTGAAGCCCAATCTGCAA
GGACATTTCTCAAGGGCCATGTGGTTTTGCAGACAACCCTGTCCTCAGGCCTGAACTCACCATA
GAGACCCATGTCAGCAAACGGTGACCAGCAAATCCTCTTCCCTTATTCTAAAGCTGCCCCTTGG
GAGACTCCAGGGAGAAGGCATTGCTTCCTCCCTGGTGTGAACTCTTTCTTTGGTATTCCATCCA
CTATCCTGGCAACTCAAGGCTGCTTCTGTTAACTGAAGCCTGCTCCTTCTTGTTCTGCCCTCCAG
AGATTTGCTCAAATGATCAATAAGCTTTAAATTAAACTCTACTTCAAGAAAAAAAAACCG

Figure 116A

MMDASKELQVLHIDFLNQDNAVSHHTWEFQTSSPVFRRGQVFHLRLVLNQPLQSYHQLKLEFSTG
PNPSIAKHTLVVLDPRTPSDHYNWQATLQNESGKEVTVAVTSSPNAILGKYQLNVKTGNHILKSEE
NILYLLFNPWCKEDMVFMPDEDERKEYILNDTGCHYVGAARSIKCKPWNFGQFEKNVLDCCISLLT
ESSLKPTDRRDPVLVCRAMCAMMSFEKGQGVLIGNWTGDYEGGTAPYKWTGSAPILQQYYNTKQ
AVCFGQCWVFAGILTTVLRALGIPARSVTGFDSAHDTERNLTVDTYVNENGEKITSMTHDSVWNF
HVWTDAWMKRPDLPKGYDGWQAVDATPQERSQGVFCCGPSPLTAIRKGDIFIVYDTRFVFSEVNG
DRLIWLVKMVNGQEELHVISMETTSIGKNISTKAVGQDRRRDITYEYKYPEGSSEERQVMDHAFLL
LSSEREHRRPVKENFLHMSVQSDDVLLGNSVNFTVILKRKTAALQNVNILGSFELQLYTGKKMAKL
CDLNKTSQIQGQVSEVTLTLDSKTYINSLAILDDEPVIRGFIIAEIVESKEIMASEVFTSFQYPEFSIELP
NTGRIGQLLVCNCIFKNTLAIPLTDVKFSLESLGISSLQTSDHGTVQPGETIQSQIKCTPIKTGPKKFIV
KLSSKQVKEINAQKIVLITK

Figure 116B

AGTGAACACCACGAGCTAGCGTGTCTACTTCACAGGCCAGGTCGTCAACTCAACTGTCAA
GGTGTCCATTGTACCAGCTGGGCCATGGATCCCTCCCGCCTGAAATCTGACTCCACCTGC
CAAGAGTCTGAGCCTGCAGGCCTAGATTTCGACTCTGCTGGCCAAGATTATTTCTCTGCA
GCCCAATAATTCGACTCTTTCTACCAAGAATTGGACCTGGACTCTCTTAACGAAGATCTT
CTTTCCCAGTCCATGCCACATGCCAGGACAGAGACCTCTGTGGGCACATATGAATCCCAC
TCGACTTCTGAACTGGAGGATCTGACAGAGCCCGAGCAAAGAGAGCTCAAAACCAAACTC
ACTAAATTGGAGGCTGAAATTGTAACCCTACGCCACGTACTAGCAGCCAAAGAGAGACGC
TGTGGGGAACTCAAGAGGAAGTTAGGCCTCACCGCCTTGGTAGGGCTGAGACAGAATCTG
TCCAAGAGCTGGCTTGATGTTCAGGTCTCCAACACCTATGTGAAACAGAAGACATCAGCT
GCTCTGTCCACCATGGGCACTCTCATCTGCAGGAAGCTTGGAGGCGTGAAGAAGTCGGCC
ACATTCAGATCTTTTGAAGGAAACCCTAAAGGAGAAGGAAGCAGAATATAACCCTCTGGA
GAGCTCAAGACAGTAGGAACCTGGACGGTGCTTGTTTGAATTTTCTGATATCTGATTTTC
ACACGAATATACTTTTTGTTTGTTTTCCTTTTCCATTTTCAAAATGCCAAGATCTGGGAG
CCTCTTTCACTCCTCTAGACACACTGCCTGAGATAGAAGTTTGCATCTTATTGGCTGTGG
GCAGAGACTAGGACCCTTATGGGTACATTTCAGTAATCTCTCACTGCCTAAAATGGTAAT
CCCTCCAGCCTAAGAGGATGATTCTGTTTTGTTGACTCTTGAATGCTCCCCCAACATTCC
TTTGGTTTTCCTATAAGCAAAACCAAATACCACTATAAATACAAAAGCATCTGGTAAACT
GTAAAGTTACTCATGTATCCCAACCCTCCACAGATTTCTGAAGACAAAGTTTTGCTTGGA
TTAAAACAAGATGTTTTACTATTTTGCATGTTCGATTTTTAATTTGTTGTGTTTATCAAC
CAAAATGGCTTTGTATGCTGGAGAACAAGAGG

Figure 117A

MPHARTETSVGTYESHSTSELEDLTEPEQRELKTKLTKLEAEIVTLRHVLAAKERRCGELKRKLGLT
ALVGLRQNLSKSWLDVQVSNTYVKQKTSAALSTMGTLICRKLGGVKKSATLRSFEGNPKGEGSRI

Figure 117B

AGTTCATCCTGAGCCAGCTGCTGAGGCGGCGGCTGGGGCTGGGGCGGCTGTGGCGGCGCC
TGGCAGGCTCCGCCAGCCCCCTGGGAGCGGGGGATGGGCTCCGGGCGCGGAGAAACTCCC
TCAACATCCATCTCCATCTTCCCATTCACTGGAGGGCAAGACAAAAGCGGAGTGGAGACT
TGGCAGCGGCGCCCGGCAGCTACTCAGCTGCCCGTGGCACGCATGGCTCGCCGAGGAGGG
GCCGCCTCCCGCGCGCCCTCCCTTCTGCCACCCTTCGCCCCCGCTCCCCGCAGCTCCGCT
CGCCTGCTTGGCTCCGGCCCTGGCGGCGTCTGGGCCGGGGTGCGCGAGGAGCGGGTGGCC
GCGTGTCCTTGGAGCGCTGGCCTTCAGGCGCCCCCGGCAGTCCCGCTAAGCAGAGCGCAT
CCCGGCGGCGGCGGCGGCGGCGGCGCCTCCCAGCCGCGCTCCCAGCCTCAGGGCCGCTTG
GGTACTTGCTCTCCAGCCCGGCCCACGCTCCTAGCCGCTTTCCAGCGTCTCTTGGGGCCC
CTTGGCGTTTCTCCTCCCTACCAACCTTCTGAACAAAGTTGCTGGAAGAACCAACCTGGT
CGCCGGGCTTTGCCCCGGCGAAGCTGGCAAATTCCGGGCAACAGAGGGTCGATGGGGTAGG
AGGAAGGAGAAGCGAGAAGTCGCTGCCAGGCATTTACTGCAATGTGCCCGGGGCGGGCGC
CAGCTGGGCGCCGTCTCTTTTTGGTGGTGAGTTCTGTGCTGGAAGAGCGTCCTCAGCAGG
GCAGGGCTCCACCAGGAGGCTTCGGTGGTGACCCCAGGGCAGGCAGTGCGTTGCGTCTAT
AAATTTAAATAGAGATGGCGAGGGTAGCCTTGGAAATTCTTAAATCAGGGTTCACCACTA
GTCAGGTGAACAGGATGACTTCTCAATTTAACACCACTTGATCCTGGGTAGTAGCTTACA
ACTTCATGGGAACTGCCACTGCAACTCTGCACGTCCAGGAGGGACTTTCAAGCAGCTCTG
GAGAGAAATGGCGGGTTATCAAGAACCTGTTCAATATTAAATAGAGCCCATTATTCTGGG
CTTTGAATTCCATAATGCTCCCAAATGGATCAGCAGATTAATGAACTATTCATGCGTTTC
TTGGCAGAGGATGGCTTTTTTCCCCTAGCATGTATCACAGATCACACTTGCTTGATGAAA
CTGGAAAATTGCATTGCTCATCCCATGAATGCTTTGCATTAACTTAAACACAACTTTTAC
ATATCAAGACACACTGTCCCATTGATGCAGTTACACAAGAACACATCATTAGGTTGTATC
CCTCAATGCTATCTTTTAATCTGACTCTGCATGTGTGACAGAAATTAATTGCCACTTTCA
TCAGTGTAGACAACCAATCTGGGTAATGCAATGTGAACAAGTTTTTGAAAAAGAAGAAAA
AGTTTAGGGACCAAATTACCCATTCTCTTTTTCTTCAGATTTTCTAAAAATCAGATTTCA
AGTTCGTTTTCTAAATTGGGAATTGTTGAAAATAGAGTGAGCTCCTCCCCAGTACCTGGT
AATAAACCAACAATCATTATAGAACGTTTATAATGGTAAATTAGATTATATGTGTAATGT
GCTTAGCAGAGTGTCTTTGTGCATATCGAGCACCTAACATTGTTATACCGAGAACAGTAA
GATGATATATGTCCACACTGAGTGTTCATCTGAAGACCTTGATTTACAAAATAGAAGCTA
CCGGTTTAAATCACCTTTATTTAAATTTCCTAAAAGATATTTGGTATCTTTAGAGAATGA
AGCCCCTTCTGAAGACAGGAAGAAAGTCAATAATATTTTGTGCAATAAAGGTTTGAATTT
GTCAGGTTTTTGTTTTTTTTTTTTTCCCTACAGTGTAGCAATAAAAATCACATGTCAGTT
CAGACAGCAGCAGGAATAGCTGACTGGTAAGTTATTATTCTTCCATGCTTGCTACTTCCA
AAATACGTTTGTGAACTTCTTTCAAGGCTTAAATGAAGATTAAATCAAAATAAAGATACA
ATACTTCAATT

Figure 118

CGCCTCCTCCTCCACCAGCACCACTCCCTCCGGGGCACCCCGGTCCCTGCAGAGTCCCTGGCCGGCGCCG
CCTCCGCTGCGGCCCCCTGAATCCCGAGCCTGCCTCGCCCAAGCTGGTAGGACAGAAGGACAGACAGATT
CCTCTAGCCTAGCGCTCCGCCGCTGCTGCCTTACGCGGCCCCGCGTCGGGAGAACTGGGATCGCCCCAAG
AGCACCGCGAGGGGTCATCTCAGGCTGGCTGCATGCCTCAGCTGAAGATCCCAGCTCCTGTCAATGCCAC
CTCTCTGCTTGACTGTCTCCTTCCAGATTCGAGCAGGTATGAGCTGGGAAGAATGAAGGCAGGGCATGCC
CGTGTGCCAGCTCTGCACAGCTGGATAGCTGAGGAAAGATGTGGAGGAGAAGCCGGGGATTGTGTGGAA
GTCTAAGGGTGTTGTTTGCCCTTTGGGTTCCAGAAGATGCATGCCAGGACCCTGGGTGGCACTGCCAGGA
AGCAACAGAGAGGAGATAAAACTCACAGCAGACAGACTTGCCTTAACAACAACTCCCTTGAATTAAAAC
ACGCTTTTCAAGAAAACAAATTATCAGTTCGATCAGCAAACAGCAGAGAAGTTTCTCTCATAATGGCAAA
GAAGGGCCGGGTTGCTGACCAGTGAAAGAGCTTCAGAAAAGGAGAGGGGAGATGAGATGGCCAGAAGG
AGCAAGAGCACCGTACATCCCTGGACAACCTCATTCTAATGGGTCAGGGGCTGGGACGTGCATTTTGGAG
TGCAGGAGAAGTGGCAACTCACAAATGCTAGATTTTCTTCTAGAGATGACCAAGCTGTAGTTCTTAAAGC
AGTGGCACTAGGGCAGAAAACTCTCACACTTTGATGTGCACACACAGCCCCTGGGGATCTTGTTGACATG
TAGATTCTGATTCCGTAAGTCGGGCTGAGATTCTGCATTTCCAACAAGCTCCTAGATGAGGTCCATTTTGC
TGGTCCATGAAACACACTTAGAATAAGTAGCAAGGTATAGGAGGATACTGACTTTGCTCAGTGATGCTTG
GGCTTCCGTCCAAACTAAAATAAAACAAAAGCAGACATAAATGGCCCAATTCAACAGCCTGAGAAGTTT
GGTGATAATGACCCAAGCCCTGGCCTGGTGACCAAGTGGCTGCTCAGAGAGCTCTATCTCCAAACTCCTT
CCCTTCCTGCCTCCCCTCCAAGAGTGAGTAATGTGCCAGAGTTCATTGGGGTCTGCTGTCCCCAGGGAAA
GGTGGCCCAGTTGCCAAGTGCAAGTGTATAGAACGGCTTACCTGTGCAAAGCTATCAGCCCTGGACCTAT
GGGCCTAGAAACATTACTTGCCACTCACTCACTCACTATCATTCATTCATTTCTGCAACAAACACTTCCTG
AGCATATGCTATACACCAGGCCCTGAGCTCAGCTCTGGGGATACAGGATGAATGGCAGATTGTGCCATCA
GGAAGCCGACTGCACAGTCAGCCCGCTGGAGCACATATGAAAAACAATACGGATGTTTTGATTTATTATC
ATATTGATCATTATGATGGTAGCGTATACTTTTGGAAGGCTTGCCATACATTAGGCATTGTGCTAAGCACA
TTATATGGTTAATCTCATCAATCTTCACAACCTATGTGGCAGGTACTATTATTAAACCCACTTCAAAGAGG
AGGGAACTGAACCTCAGAGAGGGTAAGTGACTTGCACAAGGACACAAGCTAGTGAGGAGAGGAACTGA
GAGGAATGGCCAGACAGGCCATCAGCCTCTGTCCCCACATGCTGGGTCTGAGTGTCTGACGGTGGACACA
TTCCCTTCCTGGAGGGAGAGCTCCTAGGGAGCTGATGGCAGCACTGAGTCTGGAATGTGATGGGAGTGCA
TTAGATGACGTGGGTGATCTGATGAGTACAGAGGCGTCACACTGCAATGACTTCATGCACATATCTCCCC
TTGAATGCACAGAGATTCAGCAGAGGCCAGGAGCTCAAGTTTCTGGCCCAGTGTCCCCCTCTTCCCCTGG
GGAAAGCCAGGGACACACTGCCTGGCTTTGCTACACCTTTCTAGGCAAAGGCAGTATGCTCTCCCTCTCC
TTGGCCTCCCTGGCTGTCCACACATCCACACCCACTCACACACACATGCACATGATCATACACATTACAC
AAGCCCACATGCCCACAGACATGCTCACACTCACACTCACATGCATACACTGCCATACACAACACACATA
CATACATTCACACACACTTGCACACACACACACACACAGTTCTGATGGCCAATCTTTTGGGGCTATGT
TGACACTGTGAAGCAGGTGAAACAAAGTCTTTGCCACTCCCTGCTTTGGGCCTATTATGTTTGTTTTATAG
TTTAACTCTCAAAAGACAACTTTATTTTCCAAAATTATTCAGGTTCCCAGCCAGGTGCAGTGGCTCACACC
TGTAATCCCAGTACTTTGGGAGGCCAAGGCGGGCAGATCACCTGAGGTCAGGAGTTTGAGACCAGCTTG
GCCAACATGGTGAAACCCAGTCTCTACTAAAAATACAAAAATTAGCCAGACATGGTGGCACACACATGT
AATCCCAGCTATTCGGGAGGCTGAGGCAGGAGAATCGCTTGAACCCGGGAGGCGGAGGTTGCAGTGGGC
CAAGATCGTGCCACTGCACTCCAGCCTGGGCAACAGAGCAAGACTCCATCTCAAAAAACAAAAACAAAA
TCATTCAGGTTCTGTAGGGGACCCTCACTGTGTCCTGGATTCCATTCCACTTTTAAAGTCCCAAACAGCTT
GTATGGCCACTTCCCTTGACACCCAAACCAGATAGGAGTCTTAAATGACACAGAGTATTGATGGTTTCTT
TAAAAGGAAATCCACTCTCAATGGGAAGCTGGATAACTTCGCATCCAGATTTCATCCATCTTGGGCTTTG
GTGGCTGCTGTTTGTTTTTGTGCAGGAGAATCTCTCCCAGCCAACGTCGATTTCACTAACACAGTGGTTAA
CCTTTGCTCTCTACTCCTGCATCAATCTTCCGCCTACCGCATGTTGAGCCATGCTGCTTTCTGGCATTCCTT
TTGGATTTTCAGTTTACTACCCAACTACCAGTCCTAATAACATCAGATAAAAGGGCTTCCGCTGTGCTGCA
CTTGTTTTCAAAAACTATAAATGCCATCGACCCAGAGTTAAGTCCAGCCTCAGAGAGACAGAATATAAAT
ACCCAAGTGGCCCTGGGCCACTGAGTTCCTCAGACATTATGTGCTATGGGAGTTCCAGAAAGGGGGATTG
CCTGGTTTTGAGTGCAGAAGGCTTCCTGGAGGAGGCGAGATTTCTGATGGGCCTCTGTTATGAGCTAAAT
TGAGTCCACCCCAAAATTCAGATGTTCAAATCCTAACCTGTAGTACCTAAGCATGTGGCCTTATTTGGAA
GCAGAAGCATAACAGAGGTAATTCGTTAAGATGAGGTCACAGTGGAAGAGGGTGGACCCCAATCTGATA
CAACTCGTGTCCTTATAAAAAGCAGAAATTTGAAGACAGACACACAAGAAGATGAAG

Figure 119

CCCGCATCTCCTGCACATCTCCACCCCTGCGCAGGAGGAGATCCCCAGGCTGCTCTCTCCATCTCTCCTAC
AGCTCCCTGCAAACGAGGGGGAAGCTGCTGAGAGTCCCTATCACTGCTGGCCTTTTAATGTTGTATGCAA
GGAGGAAGAGGGCGAGGGATAACTTGGTGCTGGACAACTGACCTGCGGCCCGAAGGGCCTCTGGGGAG
GGGGTGCAAAAGAGGAGCGGCTGGGCTGGGGGACTCCATGCGGGGGCGATGGACAGGGCGGCGCTCCT
GGGACTGGCCCGCTTGTGCGCGCTGTGGGCAGCCCTGCTCGTGCTGTTCCCCTACGGAGCCCAAGGAAAC
TGGATGTGGTTGGGCATTGCCTCCTTCGGGGTTCCAGAGAAGCTGGGCTGCGCCAATTTGCCGCTGAACA
GCCGCCAGAAGGAGCTGTGCAAGAGGAAACCGTACCTGCTGCCGAGCATCCGAGAGGGCGCCCGGCTGG
GCATTCAGGAGTGCGGGAGCCAGTTCAGACACGAGAGATGGAACTGCATGATCACCGCCGCCGCCACTA
CCGCCCCGATGGGCGCCAGCCCCCTCTTTGGCTACGAGCTGAGCAGCGGCACCAAAGAGACAGCATTTAT
TTATGCTGTGATGGCTGCAGGCCTGGTGCATTCTGTGACCAGGTCATGCAGTGCAGGCAACATGACAGAG
TGTTCCTGTGACACCACCTTGCAGAACGGCGGCTCAGCAAGTGAAGGCTGGCACTGGGGGGGCTGCTCCG
ATGATGTCCAGTATGGCATGTGGTTCAGCAGAAAGTTCCTAGATTTCCCCATCGGAAACACCACGGGCAA
AGAAAACAAAGTACTATTAGCAATGAACCTACATAACAATGAAGCTGGAAGGCAGGCTGTCGCCAAGTT
GATGTCAGTAGACTGCCGCTGCCACGGAGTTTCCGGCTCCTGTGCTGTGAAAACATGCTGGAAAACCATG
TCTTCTTTTGAAAAGATTGGCCATTTGTTGAAGGATAAATATGAAAACAGTATCCAGATATCAGACAAAA
CAAAGAGGAAAATGCGCAGGAGAGAAAAAGATCAGAGGAAAATACCAATCCATAAGGATGATCTGCTC
TATGTTAATAAGTCTCCCAACTACTGTGTAGAAGATAAGAAACTGGGAATCCCAGGGACACAAGGCAGA
GAATGCAACCGTACATCAGAGGGTGCAGATGGCTGCAACCTCCTCTGCTGTGGCCGAGGTTACAACACCC
ATGTGGTCAGGCACGTGGAGAGGTGTGAGTGTAAGTTCATCTGGTGCTGCTATGTCCGTTGCAGGAGGTG
TGAAAGCATGACTGATGTCCACACTTGCAAGTAACCACTCCATCCAGCCTTGGGCAAGATGCCTCAGCAA
TATACAATGGCATTGCAACCAGAGAGGTGCCCATCCCTGTGCAGCGCTAGTAAAGTTGACTCTTGCAGTG
GAATCCCTAGAACCTTGGACCTGAGAGTTTCCCTTACCTGATCGACATATTTTCCTTTATCTGATCAACCC
ATCAATCATGTGGATTTCTTGGGATTCTAATGTTGAAAAGGTTTATATTCACCTTTTGATGATTTGGGGAA
TATATATTGACATACAAGGAAGATAATCTGTTTCCTAAGCAAGAAATAACAGGAAAGATCCCTTATGCCA
GGAGGCCTGCCATACTCAGGATAAGATCCTTGAATATGGAACTTAGTTACAGGACTCAATAATGGTGGGT
GAACATTAGTCATTTTTAAAAGACACCTCTTATAGCAATAAGGAGACATTAACATGAATCTCATTTATTCT
CTCAGTATTTTAACTGAAGAAATTATACTGTTTGTGTGTGGATAGAAGATGTTGAAAAGTTAACATAAGC
ATTGGGTGCTGACTTACCCTTTCATGTACTTCCAAAGAAAGGTAATCAAAAAGAATCTTCTTAAGTGATA
TAATATCCCTAAAAAAATGATCATTACAGATGTTTAGTGACAAAGAATCAATATGTAAAAAGTATAATGA
ATGATTTAGATTTTAAGTGCCTTTTCACTGGGAGAATCTGGAAAAACCTCCATAAGGTATATAGCAATCTT
TGATCTTTAGATTCATACTTTTATCACAGATCAGTTTCAACTGTTAAAAACCCACCTCTGAGATACTGGGG
GGAGGATCCTGAAACATGCGGGAAAAGGAGAGGTAAACAGTGGAGGTAAAAATATAATTTCATACATTG
TAAAGAAAAGCACCCTTTAAATGTGTAAAGACAGTGTTTTGTAAAGAATTTTGTTTAAAAAGTTTCTATTT
TGTAAATACAGTACTTAAGTTATATGATTTATATTAAAACATTTATTGACAAAGCCTAAGAGCTAAGGCA
GTAAAATTATCTCATAAATAATATTAGCTTATTTTTTTTCATACTATTAATGCTATTTTTTTGGACATCGAA
GAGAATTTAACTTAGCAGTTAGTTATATGGATGTGTATTTCTTGCTAAAATGACAGTTTTATATGTTATAG
ATTAAAATATGTTGCAAAATATCAAAAATTTGTGTTATTTCAGCAGTAAGATTAATTGAATTCTCTTTTCA
CATTAGTTATGCTTAACTCATAAGGTTATTATAATAAATTATATTAGTAAAAGTCTTAACTGGAAAAAAG
AATCTAAATCAGAATAGTGATCAATTTGTGGATTTGATATCCTGGATATTTATTATATTTTATGTAATGCT
GCATTTCTATTTGAATGTTAAGTGGTCTTTCTTGTTTTTAATATTCATGCATGTATATTCATCATATTTTAC
AAGGTTCCTGGTAAAAATTACAGGGCTCTATTTAAGGATGTATTTTAATGTAAATGCTTATGTTTTTTATG
AATTGTTAAATATTTCAGTATTATATAGAAAAAAATAGATTTTTAAAATTCAGAATGGACAAAGAGAAATA
TTCATTTTCTTATTAATAAGATAAAGAAATGTTTCCCTGCCCCACAGTCTTCATTCTATTTCTCTTTAATTT
TATTCACTGAGGCAGAGAAACAATTTTTGAAAAAGAGCAAACCCATGGAAAATGTCTCAGATCTAATATT
AAAATCAAGACTAAGCATTTAACTGTGAAAAAAAAAAAAAAAAAA

Figure 120A

MDRAALLGLARLCALWAALLVLFPYGAQGNWMWLGIASFGVPEKLGCANLPLNSRQKELCKRKP
YLLPSIREGARLGIQECGSQFRHERWNCMITAAATTAPMGASPLFGYELSSGTKETAFIYAVMAAGL
VHSVTRSCSAGNMTECSCDTTLQNGGSASEGWHWGGCSDDVQYGMWFSRKFLDFPIGNTTGKEN
KVLLAMNLHNNEAGRQAVAKLMSVDCRCHGVSGSCAVKTCWKTMSSFEKIGHLLKDKYENSIQIS
DKTKRKMRRREKDQRKIPIHKDDLLYVNKSPNYCVEDKKLGIPGTQGRECNRTSEGADGCNLLCC
GRGYNTHVVRHVERCECKFIWCCYVRCRRCESMTDVHTCK

Figure 120B

CCAGTTTCCACTTTTGAGAAGCAGGATGTTGAATGTGAGTAATGACACAACAGGCCTATAAAA
TGCGGACTAACCCTCGGATGACTCATCCGGTACAATGCAGCTACTATTTGTCAAGGAGACTGA
ACTCATACTATGGGGGAAACCACTTCTCAGGCAGCCAGCTGGTTCTCAGGTCAGCAAGAGACG
ATCCATTTTTATCGGAAGCTTTATAGTAGCAATAATGCTAATACCCAGCACTCGGGCTCCACAA
TGTAGAGGAAATGGCATCGCCTGGCAGTGACAGCTATATTGTGCGTGTCAAGGCTGTGGTTAT
GACCAGAGATGACTCCAGCGGGGGATGGTTCCCACAGGAAGGAGGCGGGATCAGTCGCGTCG
GGGTCTGTAAGGTCATGCACCCCGAAGGCAATGGACGAAGCGGCTTTCTCATCCATGGTGAAC
GACAGAAAGACAAACTGGTGGTATTGGAATGCTATGTAAGAAAGGACTTGGTCTACACCAAAG
CCAATCCAACGTTTCATCACTGGAAGGTCGATAATAGGAAGTTTGGACTTACTTTCCAAAGCCC
TGCTGATGCCCGAGCCTTTGACAGGGGAGTAAGGAAAGCAATCGAAGACCTTATAGAAGGTTC
AACAACGTCATCTTCCACCATCCATAATGAAGCTGAGCTTGGCGATGATGACGTTTTTACAACA
GCTACAGACAGTTCTTCTAATTCCTCTCAGAAGAGAGAGCAACCTACTCGGACAATCTCCTCTC
CCACATCCTGTGAGCACCGGAGGATTTATACCCTGGGCCACCTCCACGACTCATACCCCACAGA
CCACTATCACCTCGATCAGCCGATGCCAAGGCCCTACCGCCAGGTGAGCTTCCCGGACGACGA
CGAGGAGATCGTGCGCATCAACCCCCGGGAGAAGATCTGGATGACGGGGTACGAGGATTACC
GGCACGCACCCGTCAGGGGCAAGTACCCGGACCCCTCGGAGGACGCGGACTCCTCCTACGTGC
GCTTCGCCAAGGGCGAGGTCCCCAAGCATGACTACAACTACCCCTACGTGGACTCCTCAGACTT
TGGCCTAGGCGAGGACCCCAAAGGCCGCGGGGGCAGCGTGATCAAGACGCAGCCCTCCCGGG
GCAAGTCGCGGCGGCGGAAGGAGGACGGAGAGCGCTCGCGGTGCGTGTACTGCAGGGACATG
TTCAACCACGAGGAGAACCGCCGGGGCCACTGCCAGGACGCGCCCGACTCCGTGAGAACTTGC
ATCCGCCGGGTGAGCTGCATGTGGTGCGCGGACAGCATGCTCTATCACTGTATGTCGGACCCCG
AGGGAGACTATACAGACCCTTGCTCGTGCGATACTAGCGACGAGAAGTTTTGCCTCCGGTGGA
TGGCTCTTATTGCCTTGTCTTTCCTGGCCCCCTGTATGTGCTGTTACCTGCCCCTTCGGGCCTGCT
ACCACTGCGGAGTGATGTGCAGGTGCTGTGGCGGGAAGCACAAAGCGGCCGCGTGACTCAGTT
TCCCTCCCTTCTCCCTCCATCCGCAGCCACAGGGGAACTCGTCTCTTACATACTCTCATCTTCTC
CCCCGCTCCCTTCCACTCCAAGGAGCGAGGAGGGCAAGCGGCCTCCCAGCTCCCTGGTACCTC
GAGGCACCATTCCAGCCAGGGACGCTGCCGGGTAGACTCTCCACTCCCCCTGCCGCCCACACT
GCAGCAGCCACATCCATACACACACGCTCGCACAGTGTTCTGAGGAAGGAACCTTCGCCACAG
ACTCCTGTACTATTAACAATCTGTAACCAAGCTAACTGTCTCATCCATGTGTTGATTTCCTGTTT
CCTCCTCCCCCCGCCTCTTCCAGTTCAAAGGAGTCTGCAATTGGAACTGCTGATTTTCGGTGGGTT
TTGTAGTTGATTTTTCCAAGAGCGTCGAAGACTCTCTTTCTCTTGGTTCACCTTGCCTGTCGCTA
GCAAGCATCTGGTTCAGCGGAAATGGGATGTGAGAATGATGAAACCCGACAGAAGTATCTCAG
CCTGCAGTCAGTTATTATGTATAGGAGGTGAGCTAGTTAACAAACTTGTACCACAAAACAATAT
CGCTTTAACTTTTCTAAAGCCAAATTTCCCATGTAAGCTGCAGTTTCTATCTTTAGCCCATCATC
ATTTTCTGCCCCCCCAAAATCTGTTGAAATGATTCACTGATGCAAAACATTCACCCGTAATAGA
CTGAGAATTGAGCCTTAACTTCAGATTAACTTGTGAGAATCAGGAAAATTCCTTCAACTGCATT
GCATCCTCTTGGACCAGGGCTAGAATGGGGATTTCAGGTTTCTATGAGCCTCCCCATTACCCCT
AAAGTAGAACATTTTTTAAATTGTGTTGCCACCACTTCTAAAAATTTAGCAATATTAGAATAGG
ATACTAGTGAAGTAAGAAATTTTGCTTGTTGTTTTGCAAACCAAATAGTTTCCTCAAACACAAA
TCAGTGTTCCCACGAACAAGTTCCAGTTGAGAAACACTAAGGTTATGGTGAATAAAACCATAG
GGAGCTTCTTCCCCCCAACCCCTGGCTATTTTATATTAATGGGGAGAGGGGATTTTTAAATGTC
ATAAATTTGAAGAGTGGTGGGTTGCATTTTCTTCATGGGTTTATGTTTTCGTTTCATTTTGGACT
CAATTTCACATCACCAAATTCCTCATTTATACTTGGGGAAAAAACAAGGCCATATGTAAAAACC
CTTCCAATGCCTAAGTGTCTTTCTCCTGCAACTCCAAACCCAGACTCGCCACTTTGGGTGCACA
GGTGGTTAGGTCAGCCAACTGGTTCTGCCTGTCGCCTTGCCACGGAGGAGGCTTCTAATTAGCT
GGAAAAGAGTATTTTTCTAATACGTTGCAAGGATTAGCCAAATCTTCTTA

Figure 121A

TTGAAGAAAGAAGAAAAGTGAAGAGTGGTTACCTATACCTAGCATAGTACAATCAGAACCTCG
TGGAGACCACCGGGGACAGGCTTGCGGACGCCGGCTGTTCTTCCCGCCACGATCTTTCTGTGGT
AGCGGCCAGCAGAAGACATGGCCTGCTCCCCACTCCCTTTCCCCACTCCTTCTTTATTGCACAC
AGGACACCAGTCTTCAAGGAAAGGGACTTTTTTCCAGTCTGCCAATCATATTGGGAAAGTGCTA
GCTGTGCTCACCTTCATGGGGCTGTTTCCAGCTCGTCCACAAGCTCATCGATTTTCTTTAGTAGA
TTACCGGTGTAAATACCCAGTGTGCTTATGAGTCAGTTAGTAGACGTCTTCATTCATTGGAGTA
ACTGGTTTAGGCTTTCCAGTTTGGAAAAGGAGCAGAGAGCTGTCCATCTGGATTGATGGAAGA
AAAGAGAACCTCATCCATGCCTGGAGAACATCTAGAAAACCTTCAGCCAGCCTCCAGTGCTGT
CGAGAGACCACCTTCCCCCGACCCGGAGGCACTTCCTTGGGGTCTTTCTCTAGGGTCTCTTCTCT
ACAAAGCACAACACTAATGTTCGTTTCCTTAGACCTCAGTTCAAGTGCCCCTATTTATTTCAAT
AAGAACGCACATATCCCAGCTGTTTTTTGTTTGTCACCTCTATTTAGTTGTTACCTGTTTCTCTCT
TCTTTCACCCCTTGTCCTTTTCCACCCTTTTAAGAGTTACGCTAGCAGATCTTACTCCACGTATA
CTTTTTGGTTTGTGAAGGCATCGGTTAAGGGCACAAAGACAGCCATGGGGACATTTATGTAAAT
ACGTCTCTAATTGCCACACTGCAGCTGAACAGTGTGTAGTATTTTCCCAGTCAGCTTTGCCATA
CTGACGTCAATCATTTGAGAGAAATTATTCAGATTTTATTTTTGTATCTGTGGTAACAAAACATT
AACCAAAAGATTTTCTGTCCAGAAGCCTCCCCGACCCCCCAAGCTATTTGCTCACATTAACAAA
TTAAAGTGCCTGAAGCATAATTCATTCTTTACCTGTATACTAAAAACCCTGTTGTATTGATTTTT
TTATAATAAGCCTTTTTACCTCTGTGTAAAAAATATATATACAAGTGTATGATGTACATTTTAGT
TCTTAACTTTTTTTTATGGTTTCTAATATGTATGACCAATGTAGCCATTGCTTTAAAATGTACCG
TGTAAATATAAACACATCCTATCAGAAAAGAAAAAATCNAGAACGAA

Figure 121A (continued)

1 atgaccgaag aaacacaccc agacgatgac agctatattg tgcgtgtcaa ggctgtggtt
61 atgaccagag atgactccag cgggggatgg ttcccacagg aaggaggcgg gatcagtcgc
121 gtcggggtct gtaaggtcat gcaccccgaa ggcaatggac gaagcggctt tctcatccat
181 ggtgaacgac agaaagacaa actggtggta ttggaatgct atgtaagaaa ggacttggtc
241 tacaccaaag ccaatccaac gtttcatcac tggaaggtcg ataataggaa gtttggactt
301 actttccaaa gccctgctga tgcccgagcc tttgacaggg gagtaaggaa agcaatcgaa
361 gaccttatag aaggttcaac aacgtcatct tccaccatcc ataatgaagc tgagcttggc
421 gatgatgacg tttttacaac agctacagac agttcttcta attcctctca gaagagagag
481 caacctactc ggacaatctc ctctcccaca tcctgtgagc accggaggat ttataccctg
541 ggccacctcc acgactcata ccccacagac cactatcacc tcgatcagcc gatgccaagg
601 ccctaccgcc aggtgagctt cccggacgac gacgaggaga tcgtgcgcat caaccccccgg
661 gagaagatct ggatgacggg gtacgaggat taccggcacg cacccgtcag gggcaagtac
721 ccggaccccc cggaggacgc ggactcctcc tacgtgcgct tcgccaaggg cgaggtcccc
781 aagcatgact acaactaccc ctacgtggac tcctcagact ttggcctagg cgaggacccc
841 aaaggccgcg ggggcagcgt gatcaagacg cagcccctcc ggggcaagtc gcggcggcgg
901 aaggaggacg gagagcgctc gcggtgcgtg tactgcaggg acatgttcaa ccacgaggag
961 aaccgcccggg gccactgcca ggacgcgccc gactccgtga gaacttgcat ccgccgggtg
1021 agctgcatgt ggtgcgcgga cagcatgctc tatcactgta tgtcggaccc cgagggagac
1081 tatacagacc cttgctcgtg cgatactagc gacgagaagt tttgcctccg gtggatggct
1141 cttattgcct tgtctttcct ggccccctgt atgtgctgtt acctgccccct tcgggcctgc
1201 taccactgcg gagtgatgtg caggtgctgt ggcgggaagc acaaagcggc cgcgtga

Figure 121B

MTEETHPDDDSYIVRVKAVVMTRDDSSGGWFPQEGGGISRVGVCKVMHPEGNGRSGFLIHGERQK
DKLVVLECYVRKDLVYTKANPTFHHWKVDNRKFGLTFQSPADARAFDRGVRKAIEDLIEGSTTSSS
TIHNEAELGDDDVFTTATDSSSNSSQKREQPTRTISSPTSCEHRRIYTLGHLHDSYPTDHYHLDQPMP
RPCRQVSFPDDDEEIVRINPREKIWMTGYEDYRHAPVRGKYPDPSEDADSSYVRFAKGEVPKHDYN
YPYVDSSDFGLGEDPKGRGGSVIKTQPSRGKSRRRKEDGERSRCVYCRDMFNHEENRRGHCQDAP
DSVRTCIRRVSCMWCADSMLYHCMSDPEGDYTDPCSCDTSDEKFCLRWMALIALSFLAPCMCCYL
PLRACYHCGVMCRCCGGKHKAAA

Figure 121C

ATTTCAGCACACCAAAGAAAATTGAGCTGGCAAAAGATGAATCTTTCACAAGCAGTGATG
ATNATGAAAATGTAGATTTAGATAAAAGACTTCAATATTATAGATATCCGTGGTCAACTG
TGCATNANCCTGCAAGGAGACCANTATCCATCTCCAGAGACTGGCATGGATATAAGAAGA
AGANCCATACTATTAGTGTAGGANAAGACATTAATTGTGACGTGATGATTCACAGAGACG
ACAAGTATAGTATAGTGAGGGCCCCTTCTCCATGCTGGATAATGGTGAAGCAAGACNCAT
GTAAGCTCTTCCTCCTCTACCTCCTCTACCTCAGATGCATTTTGGCTGGGAGATTGTGCC
CAAGTTGTATAGAGGGTAAAGCCCAACTGGTATCAAAGGTTGGTTAGCTAATCTGTGGTC
ATATGAGCATTTATCTTGCAGACACCCAAGTTTTGTGCCTCACCAGGCACAAGTTTGCTG
TACTTATCAACGGTCTGTCTGTAGACTCACCAATTCTCTTCTCTTATGACTGCGTTATAA
AGCCTTTAGAGATGTTCTTCAACAGGATTATCTAAAGACTTCCTTGGGTTCTTGCAGGCC
TCACAAATCTTATTTTCAGAATAAGACCCTCCTTTTTGAGAAGAATTTCTTTCTTTTAGA
AAATGCCGTAGAGAAATCCAATATCAGAATGTCTGAACATAGTAGAGAATGTCACTTTAT
GTAAACACTACATTTTTCTTTAAATATTTAGTTTCTCTCTTTTTTTTGGTAAACTTCAAG
TACTATAATTAAAATAACTAAGAGACATAAAAAA

Figure 122A

1 atggcagaag gtgaagagga aggaggtgat gttctgatta gtgttggcca tgccaatgtg
61 ttaggatata ctcttcgaga atttttacag cttttgcaac atatcactat tggaacagtg
121 ctacaaatca aggtttaccg agattttatt aacattcctg aagaatggca agaaatatat
181 gatttaatcc ctgaggccaa attcccagta acaagcacac caaagaaaat tgagctggca
241 aaagatgaat ctttcacaag cagtgatgat aatgaaaatg tagatttaga taaaagactt
301 caatattata gatatccgtg gtcaactgtg catcaccctg caaggagacc aatatccatc
361 tccagagact ggcatggata taagaagaag aaccatacta ttagtgtagg aaaagacatt
421 aattgtgacg tgatgattca cagagacgac aagaaagaag tgagggcccc ttctccatac
481 tggataatgg tgaagcaaga caatgaaagc tcttcctcct ctacctcctc tacctcagat
541 gcattttggc tggaagattg tgcccaagtt gaagagggta aagcccaact ggtatcaaag
601 gttggttag

Figure 122B

MAEGEEEGGDVLISVGHANVLGYTLREFLQLLQHITIGTVLQIKVYRDFINIPEEWQEIYDLIPEAKFP
VTSTPKKIELAKDESFTSSDDNENVDLDKRLQYYRYPWSTVHHPARRPISISRDWHGYKKKNHTISV
GKDINCDVMIHRDDKKEVRAPSPYWIMVKQDNESSSSSTSSTSDAFWLEDCAQVEEGKAQLVSKV
G

Figure 122C

AGCGGAGGCGGCGCGGGGACGGGCGCTGGGCGGCCGCGGAGCTCCGGGTGCCGCCGC
GTC

CCCAGCGCCCCGGCCGGCCCCTCTGGGCGGCCTGCGGGGGCGGCGCAGTTGCGAAACTGA
GTGCCTGTGTAGATCATCCTAGAATACCTGTGTGGTGCTGTCCTTCCTCAAGACTACCTC
ATTCTCACTGGCTCGGAGACTCCTGCCTGCTGAGCTGACTACACAGACTTAGTCTTCTCC
ACTCCGTGTTCCTGCAGCTAGAGACATGACCTAACACCCTGATGACCACTCTCAGGGACC
TTGAGTGACTGGCCGGTGCACCATGGAACTTAAAGTATGGGTGGATGGAGTTCAGAGGAT
TGTTTGTGGAGTCACTGAAGTCACAACTTGCCAGGAGGTTGTCATAGCCTTAGCTCAAGC
AATAGGTCGAACTGGAAGGTACACCCTTATAGAGAAATGGAGAGATACTGAAAGACACTT
AGCACCTCATGAAAATCCTATCATATCCTTAAACAAATGGGGGCAGTATGCTAGTGATGT
GCAGCTCATTCTACGACGAACTGGGCCGTCTCTCAGTGAGCGACCCACTTCAGACAGTGT
GGCTCGAATTCCTGAAAGAACTTTATACAGGCAGAGTCTGCCCCCCTTAGCTAAACTGAG
GCCTCAGATTGACAAATCAATCAAAAGGAGGGAACCGAAAAGGAAATCACTGACATTTAC
AGGAGGTGCCAAAGGATTAATGGACATTTTTGGAAAAGGTAAAGAAACTGAGTTTAAGCA
AAAGGTGCTGAATAACTGCAAAACAACAGCAGATGAGTTGAAGAAGCTAATCCGTCTGCA
GACAGAGAAGCTTCAATCCATTGAGAAACAGCTGGAATCTAATGAAATAGAAATAAGATT
TTGGGAGCAAAAGTATAATTCCAACCTTGAAGAGGAAATTGTCCGTCTAGAGCAAAAGAT
CAAAAGAAACGATGTAGAAATTGAGGAGGAAGAATTCTGGGAAAATGAATTACAGATTGA
ACAGGAAAATGAAAAACAGCTGAAGGATCAACTTCAAGAAATAAGACAGAAAATAACAGA
ATGTGAAAACAAATTAAAGGACTATTTGGCACAGATCCGGACTATGGAAAGTGGTCTTGA
AGCAGAAAAATTGCAACGGGAAGTTCAAGAGGCACAGGTCAATGAGGAAGAGGTTAAAGG
AAAGATCGGTAAGGTCAAAGGGGAGATTGACATTCAAGGCCAGCAGAGTCTGAGGTTGGA
AAATGGCATCAAAGCTGTGGAAAGATCTCTTGGACAAGCCACCAAACGCTTACAGGACAA
AGAACAGGAACTGGAGCAGTTGACTAAGGAGTTGCGGCAAGTCAATCTCCAGCAGTTCAT
CCAGCAGACAGGGACAAAAGTTACCGTTTTGCCAGCGGAGCCCATTGAAATAGAGGCCTC
ACATGCAGACATTGAAAGGGGGATCATCATTCTTTCTGATAAGCAGGAGTGTAAAGATTA
GATATCACACCAAAAGCTCAGGCAAGAAAAGCAAAAATGAACAAGTGGGACTACATTAAA
CCCAAAACTCCTGCACAACAAAGGAAACGATCACCAAAATGAAAAGGTGGACTGTAGATT
GGGAGAAAATATTTGCAAACCGTTATCTGGTAGGGGTTTAATATCCAAACTATATAAGGA
ACTCACAGAACTTAAAGAAAACAAATAATCCAATTAAAAATGGTCAAAGGGGCTGGGCAT
GGTGGCTCACGCCTGTAATCTCAGCACTTTGGGAGGCCGAGGTGGGAGAATCACAAGGTC
AGGAGACTGAGACCATCCTGGCTAACACCATGATGGGCTAACACCCATCTCTACTAAAAA
TACGAAACATTAGCCAGGTGTGGTGGCACGCGCCTGTAATCCCAGCTACTCGGGAGGCTG
AGGCAGAAGGATTGCTTGAACCCGGGAGGTGGAGGTTGCAGTGAGCCGAGATCGCATTAC
TGCACTCCAGCCTGGGTAACAGAGTGAGACTCCATCTCAAAAAAAAAAAAAAAAATAGATA
TTTTTCCAAAGAAGACATAAAAACAGCCAACAGGTATATGAAAAAGTGCTCAACATCACT
GATCAGCAGGGAAATGCAAATCAAAGCCACAATGAGATACCACCTCACACCTGTTAGGTT
ACATCTGCTATTGTCAAAAAGATAAGAGATAGCAAGTGTCAGCAAGGGTCTGGAGAAAAG
GGAATTTTTGTATACTGTTGGTGGGAATGTAAATCAGTACGGCTATTGTGGAAAACAGTG
TAGAGGTTTCTCAAAAAATTAAAACTATCATACAACCCAGCAAAAAAAAAAAAAAAA

Figure 123A

MELKVWVDGVQRIVCGVTEVTTCQEVVIALAQAIGRTGRYTLIEKWRDTERHLAPHENPIISLNKW
GQYASDVQLILRRTGPSLSERPTSDSVARIPERTLYRQSLPPLAKLRPQIDKSIKRREPKRKSLTFTGG
AKGLMDIFGKGKETEFKQKVLNNCKTTADELKKLIRLQTEKLQSIEKQLESNEIEIRFWEQKYNSNL
EEEIVRLEQKIKRNDVEIEEEEFWENELQIEQENEKQLKDQLQEIRQKITECENKLKDYLAQIRTMES
GLEAEKLQREVQEAQVNEEEVKGKIGKVKGEIDIQGQQSLRLENGIKAVERSLGQATKRLQDKEQE
LEQLTKELRQVNLQQFIQQTGTKVTVLPAEPIEIEASHADIERGIIILSDKQECKD

Figure 123B

1 cgtgagtgtc tgtgcgtttt gatcccgaag ctcctcgccg ggtcgttact tcagaagaga
61 agacagtgag cgtgggcgag gcgaggcatc cagaggcccc ggcgacccct gctccccagt
121 cctccgcccc ctcgcgtcgc ggccctgggc gggcgccgcg agccggagtt ccattttaat
181 tgctgttaat catttcagag aagaacactg aactttgaaa aaaatgttgg aagccattga
241 caaaaatcgg gccctgcatg cagcagagcg cttgcaaacc aagctgcgag aacgtgggga
301 tgtagcaaat gaagacaaac tgagccttct gaagtcagtc ctgcagagcc ctctcttcag
361 tcagattctg agccttcaga cttctgtaca gcagctgaaa gaccaggtaa atattgcaac
421 ttcagcaact tcaaatattg aatatgccca cgttcctcat ctcagcccag ctgtgattcc
481 tactctgcaa aatgaatcgt ttttattatc cccaaacaat gggaatctgg aagcacttac
541 aggacctggt attccacaca ttaatgggaa acctgcttgt gatgaatttg atcagcttat
601 caaaaatatg gcccagggtc gccatgtaga agttttgag ctcctcaaac ctccatctgg
661 aggccttggg tttagtgttg tgggactaag aagtgaaaac agaggagagc tgggaatatt
721 tgttcaagag atacaagagg gcagtgtggc ccatagagat ggaagattga aagaaactga
781 tcaaattctt gctatcaatg gacaggctct tgatcagaca attacacatc agcaggctat
841 cagcatcctg cagaaagcca aagatactgt ccagctagtt attgccagag gctcattgcc
901 tcagcttgtc agccccatag tttcccgttc tccatctgca gccagcacaa tttcagctca
961 ctctaatccg gttcactggc aacacatgga aacgattgaa ttggtgaatg atggatctgg
1021 tttgggattt ggcatcatag gaggaaaagc aactggtgtg atagtaaaaa ccattctgcc
1081 tggaggagta gctgatcagc atgggcgttt atgcagtgga gaccacattc taaagattgg
1141 tgacacagat ctagcaggaa tgagcagtga gcaagtagca caagtccttа ggcaatgtgg
1201 aaatagagtt aagttgatga ttgcaagagg tgccatagaa gaacgtacag cacccactgc
1261 tttgggcatc accctctcct catccccaac ttcaacacca gagttgcggg ttgatgcttc
1321 tactcagaaa ggtgaagaaa gtgagacatt tgatgtagaa ctcactaaaa atgtccaagg
1381 attaggaatt accattgctg gctacattgg agataaaaaa ttggaacctt caggaatctt
1441 tgtaaagagc attacaaaaa gcagtgccgt tgagcatgat ggaagaatcc aaattggaga
1501 ccaaattata gcagtagatg gcacaaacct tcagggtttt actaatcagc aagcagtaga
1561 ggtattgcga catacaggac aaactgtgct cctgacacta atgaggagag gaatgaagca
1621 ggaagccgag ctcatgtcaa gggaagacgt cacaaaagat gcagatttgt ctcctgttaa
1681 tgccagcata atcaaagaaa attatgaaaa agatgaagat tttttatctt cgacgagaaa
1741 caccaacata ttaccaactg aagaagaagg gtatccatta ctgtcagctg agatagaaga
1801 aatagaagat gcacaaaaac aagaagctgc tctgctgaca aaatggcaaa ggattatggg
1861 aattaactat gaaatagtgg tggcccatgt gagcaagttt agtgagaaca gtggattggg
1921 gataagcctg gaagcgacag tgggacatca ttttatccga tctgttctac cagagggtcc
1981 tgttggacac agcgggaagc tcttcagtgg agacgagcta ttggaagtaa atggcataac
2041 tttacttggg gaaaatcacc aagatgtggt gaatatctta aaagaactgc ctatagaagt
2101 gacaatggtg tgctgtcgtc gaactgtgcc acccaccacc caatcagaat tggatagcct
2161 ggacttatgt gatattgagc taacagaaaa gcctcacgta gatctaggtg agttcatcgg
2221 gtcatcagag acagaggatc cagtgctggc gatgactgat gcgggtcaga gtacagaaga
2281 ggttcaagca cctttggcca tgtgggaggc tggcattcag cacatagagc tggagaaagg
2341 gagcaaagga cttggtttta gcattttaga ttatcaggat ccaattgatc cagcaagcac
2401 tgtgattata attcgttctt tggtgcctgg cggcattgct gaaaaggatg gacgacttct
2461 tcctggtgac cgactcatgt ttgtaaacga tgttaacttg gaaaacagca gtcttgagga
2521 agctgtagaa gcactgaagg gagcaccgtc agggactgtg agaataggag ttgctaagcc
2581 tttacccctt tcaccagaag aaggttatgt ttctgctaag gaggatttcc tictctaccc
2641 accacactcc tgtgaggaag cagggctggc tgacaaaccc ctcttcaggg ctgacttggc
2701 tctggtgggc acaaatgatg ctgacttagt agatgaatcc acatttgagt ctccatactc
2761 tcctgaaaat gacagcatct actctactca agcctctatt ttatctcttc atggcagttc
2821 ttgtggtgat ggcctgaact atggttcttc ccttccatca tctcctccta aggatgttat
2881 tgaaaattct tgtgatccag tacttgatct gcatatgtct ctggaggaac tatataccca
2941 gaatctcctg caaagacagg atgagaatac accttcggtg gacataagta tggggcctgc
3001 ttctggcttt actataaatg actacacacc tgcaaatgct attgaacaac aatatgaatg
3061 tgaaaacaca atagtgtgga ctgaatctca tttaccaagt gaagttatat caagtgcaga

Figure 124A

3121 acttccttct gtgctacccg attcagctgg aaagggctct gagtacctgc ttgaacagag
3181 ctccctggcc tgtaatgctg agtgtgtcat gcttcaaaat gtatctaaag aatcttttga
3241 aaggactatt aatatagcaa aaggcaattc tagcctagga atgacagtta gtgctaataa
3301 agatggcttg gggatgatcg ttcgaagcat tattcatgga ggtgccatta gtcgagatgg
3361 ccggattgcc attggggact gcatcttgtc cattaatgaa gagtctacca tcagtgtaac
3421 caatgcccag gcacgagcta tgttgagaag acattctctc attggccctg acataaaaat
3481 tacttatgtg cctgcagaac atttggaaga gttcaaaata agcttgggac aacaatctgg
3541 aagagtaatg gcactggata ttttttcttc atacactggc agagacattc cagaattacc
3601 agagcgagaa gagggagagg gtgaagaaag cgaacttcaa aacacagcat atagcaattg
3661 gaatcagccc aggcgggtgg aactctggag agaaccaagc aaatccttag gcatcagcat
3721 tgttggtgga cgagggatgg ggagtcggct aagcaatgga gaagtgatga ggggcatttt
3781 catcaaacat gttctggaag atagtccagc tggcaaaaat ggaaccttga aacctggaga
3841 tagaatcgta gaggtggatg gaatggacct cagagatgca agccatgaac aagctgtgga
3901 agccattcgg aaagcaggca accctgtagt ctttatggta cagagcatta taaacagacc
3961 aaggaaatcc cctttgcctt ccttgctgca caacctttac cctaagtaca acttcagcag
4021 cactaaccca tttgctgact ctctacaaat caacgccgac aaggcaccca gtcagtcaga
4081 gtcagagcca gagaaggctc cattgtgcag tgtgccccca ccccctcctt cagcctttgc
4141 cgaaatgggt agtgatcaca cacagtcatc tgcaagcaaa atctcacaag atgtggacaa
4201 agaggatgag tttggttaca gctggaaaaa tatcagagag cgttatggaa ccctaacagg
4261 cgagctgcat atgattgaac tggagaaagg tcatagtggt ttgggcctaa gtcttgctgg
4321 gaacaaagac cgatccagga tgagtgtctt catagtgggg attgatccaa atggagctgc
4381 aggaaaagat ggtcgattgc aaattgcaga tgagcttcta gagatcaatg gtcagatttt
4441 atatggaaga agtcatcaga atgcctcatc aatcattaaa tgtgcccctt ctaaagtgaa
4501 aataattttt atcagaaata aagatgcagt gaatcagatg gccgtatgtc ctggaaatgc
4561 agtagaacct ttgccttcta actcagaaaa tcttcaaaat aaggagacag agccaactgt
4621 tactacttct gatgcagctg tggacctcag ttcatttaaa aatgtgcaac atctggagct
4681 tcccaaggat caggggggtt tgggtattgc tatcagcgaa gaagatacac tcagtggagt
4741 catcataaag agcttaacag agcatggggt agcagccacg gatggacgac tcaaagtcgg
4801 agatcagata ctggctgtag atgatgaaat tgttgttggt taccctattg aaaagtttat
4861 tagccttctg aagacagcaa agatgacagt aaaacttacc atccatgctg agaatccaga
4921 ttcccaggct gttccttcag cagctggtgc agccagtgga gaaaaaaaga acagctccca
4981 gtctctgatg gtcccacagt ctggctcccc agaaccggag tccatccgaa atacaagcag
5041 atcatcaaca ccagcaattt ttgcttctga tcctgcaacc tgccccatta tccctggctg
5101 cgaaacaacc atcgagattt ccaaagggcg aacagggctg ggcctgagca tcgttggggg
5161 ttcagacacg ctgctgggtg ccattattat ccatgaagtt tatgaagaag gagcagcatg
5221 taaagatgga agactctggg ctggagatca gatcttagag gtgaatggaa ttgacttgag
5281 aaaggccaca catgatgaag caatcaatgt cctgagacag acgccacaga gagtgcgcct
5341 gacactctac agagatgagg ccccatacaa agaggaggaa gtgtgtgaca ccctcactat
5401 tgagctgcag aagaagccgg gaaaaggcct aggattaagt attgttggta aaagaaacga
5461 tactggagta tttgtgtcag acattgtcaa aggaggaatt gcagatgccg atggaagact
5521 gatgcaggga gaccagatat taatggtgaa tggggaagac gttcgtaatg ccacccaaga
5581 agcggttgcc gctttgctaa aggtgagtga aggcagcctg tcatctttca ctttccact
5641 ctctggatcc agtacatctg agtcactgga aagtagctca aagaagaatg cattggcatc
5701 tgaaatacag ggattaagaa cagtcgaaat gaaaaagggc cctactgact cactgggaat
5761 cagcatcgct ggaggagtag gcagcccact tggtgatgtg cctatattta ttgcaatgat
5821 gcacccaact ggagttgcag cacagaccca aaaactcaga gttggggata ggattgtcac
5881 catctgtggc acatccactg agggcatgac tcacacccaa gcagttaacc tactgaaaaa
5941 tgcatctggc tccattgaaa tgcaggtggt tgctggagga gacgtgagtg tggtcacagg
6001 tcatcagcag gagcctgcaa gttccagtct ttctttcact gggctgacgt caagcagtat
6061 atttcaggat gatttaggac ctcctcaatg taagtctatt acactagagc gaggaccaga
6121 tggcttaggc ttcagtatag ttggaggata tggcagccct catggagact tacccattta
6181 tgttaaaaca gtgtttgcaa agggagcagc ctctgaagac ggacgtctga aaaggggcga

Figure 124A (continued)

6241 tcagatcatt gctgtcaatg ggcagagtct agaaggagtc acccatgaag aagctgttgc
6301 catccttaaa cggacaaaag gcactgtcac tttgatggtt ctctcttgaa ttggctgcca
6361 gaattgaacc aacccaaccc ctagctcacc tcctactgta aagagaatgc actggtcctg
6421 acaatttta tgctgtgttc agccgggtct tcaaaactgt agggggggaaa taacacttaa
6481 gtttcttttt ctcatctaga aatgctttcc ttactgacaa cctaacatca ttttcttttt
6541 cttcttgcat tttgtgaact taaagagaag gaatatttgt gtaggtgaat ctcgttttta
6601 tttgtggaga tatctaatgt tttgtagtca catgggcaag aattattaca tgctaagctg
6661 gttagtataa agaaagataa ttctaaagct aaccaaagaa aatggcttca gtaagttagg
6721 atgaaaaatg aaaatataaa ataaagaaga aaatctcggg gagtttaaaa aaaatgcctc
6781 aatttggcaa tctacctcct ctccccaccc caaactaaaa aaagaaaaaa aggttttcta
6841 atgaaaatct ttaaaaatac tgtcagtatt ttaaaatttt caacagtatt ataaaaacat
6901 tgcatctccc cacctctaat atgcatatat attttcctg ctaaaattgg tttctacaat
6961 tgagtaaatg gcaaatacat gaagcaatgt ccctaaattt tataaagaaa ttatatttaa
7021 tgcacatttc aattttcatt cttatttttg acctttgta aaatattttc atgttgctat
7081 aagtaaatga tgatgccacc ccatgttgac tatggttttt ctagaaagca actatgctgc
7141 taaccataga ggaacataga agggttccag aatctttagt gctggtttta acaaccgatg
7201 caacattaaa aatgtgttag tgtgctgtgc aattggtttt caattcatat taatcttaat
7261 gacagagaac aatgtgttac taattatttt ggttgtatgc cattagtaaa ttgatagaaa
7321 aattaagggg attaacataa cttcatttca ttgccttata ttaacatctt ataatacaat
7381 agtttaagac taagggaaac agatggagct gtttattgag acaactggtg aggaattatc
7441 atgtgttcat tcccatttta gagcgtgaaa ctcctacatt agaatatata aagtcacttt
7501 aaatatctat atttgtaaca gaagtagtgt acagatattt tattacagca tttttgtgta
7561 aatgcagaat taaagtgaat aaataagaat tttcagtggt gcac

Figure 124A (continued)

TLKKMLEAIDKNRALHAAERLQTKLRERGDVANEDKLSLLKSVLQSPLFSQILSLQTSVQQLKDQV
NIATSATSNIEYAHVPHLSPAVIPTLQNESFLLSPNNGNLEALTGPGIPHINGKPACDEFDQLIKNMAQ
GRHVEVFELLKPPSGGLGFSVVGLRSENRGELGIFVQEIQEGSVAHRDGRLKETDQILAINGQALDQ
TITHQQAISILQKAKDTVQLVIARGSLPQLVSPIVSRSPSAASTISAHSNPVHWQHMETIELVNDGSGL
GFGIIGGKATGVIVKTILPGGVADQHGRLCSGDHILKIGDTDLAGMSSEQVAQVLRQCGNRVKLMI
ARGAIEERTAPTALGITLSSSPTSTPELRVDASTQKGEESETFDVELTKNVQGLGITIAGYIGDKKLEP
SGIFVKSITKSSAVEHDGRIQIGDQIIAVDGTNLQGFTNQQAVEVLRHTGQTVLLTLMRRGMKQEAE
LMSREDVTKDADLSPVNASIIKENYEKDEDFLSSTRNTNILPTEEEGYPLLSAEIEEIEDAQKQEAALL
TKWQRIMGINYEIVVAHVSKFSENSGLGISLEATVGHHFIRSVLPEGPVGHSGKLFSGDELLEVNGIT
LLGENHQDVVNILKELPIEVTMVCCRRTVPPTTQSELDSLDLCDIELTEKPHVDLGEFIGSSETEDPV
LAMTDAGQSTEEVQAPLAMWEAGIQHIELEKGSKGLGFSILDYQDPIDPASTVIIIRSLVPGGIAEKD
GRLLPGDRLMFVNDVNLENSSLEEAVEALKGAPSGTVRIGVAKPLPLSPEEGYVSAKEDSFLYPPHS
CEEAGLADKPLFRADLALVGTNDADLVDESTFESPYSPENDSIYSTQASILSLHGSSCGDGLNYGSSL
PSSPPKDVIENSCDPVLDLHMSLEELYTQNLLQRQDENTPSVDISMGPASGFTINDYTPANAIEQQYE
CENTIVWTESHLPSEVISSAELPSVLPDSAGKGSEYLLEQSSLACNAECVMLQNVSKESFERTINIAK
GNSSLGMTVSANKDGLGMIVRSIIHGGAISRDGRIAIGDCILSINEESTISVTNAQARAMLRRHSLIGP
DIKITYVPAEHLEEFKISLGQQSGRVMALDIFSSYTGRDIPELPEREEGEGEESELQNTAYSNWNQPR
RVELWREPSKSLGISIVGGRGMGSRLSNGEVMRGIFIKHVLEDSPAGKNGTLKPGDRIVEVDGMDL
RDASHEQAVEAIRKAGNPVVFMVQSIINRPRKSPLPSLLHNLYPKYNFSSTNPFADSLQINADKAPSQ
SESEPEKAPLCSVPPPPPSAFAEMGSDHTQSSASKISQDVDKEDEFGYSWKNIRERYGTLTGELHMIE
LEKGHSGLGLSLAGNKDRSRMSVFIVGIDPNGAAGKDGRLQIADELLEINGQILYGRSHQNASSIIKC
APSKVKIIFIRNKDAVNQMAVCPGNAVEPLPSNSENLQNKETEPTVTTSDAAVDLSSFKNVQHLELP
KDQGGLGIAISEEDTLSGVIIKSLTEHGVAATDGRLKVGDQILAVDDEIVVGYPIEKFISLLKTAKMT
VKLTIHAENPDSQAVPSAAGAASGEKKNSSQSLMVPQSGSPEPESIRNTSRSSTPAIFASDPATCPIIP
GCETTIEISKGRTGLGLSIVGGSDTLLGAIIIHEVYEEGAACKDGRLWAGDQILEVNGIDLRKATHDE
AINVLRQTPQRVRLTLYRDEAPYKEEEVCDTLTIELQKKPGKGLGLSIVGKRNDTGVFVSDIVKGGI
ADADGRLMQGDQILMVNGEDVRNATQEAVAALLKVSEGSLSSFTFPLSGSSTSESLESSSKKNALA
SEIQGLRTVEMKKGPTDSLGISIAGGVGSPLGDVPIFIAMMHPTGVAAQTQKLRVGDRIVTICGTSTE
GMTHTQAVNLLKNASGSIEMQVVAGGDVSVVTGHQQEPASSSLSFTGLTSSSIFQDDLGPPQCKSIT
LERGPDGLGFSIVGGYGSPHGDLPIYVKTVFAKGAASEDGRLKRGDQIIAVNGQSLEGVTHEEAVAI
LKRTKGTVTLMVLS

Figure 124B

GGAATTTCTACAATGGTGGGCTCAGCTCTCAGGAGAGGTGCCCATGCATATGTCTACCTG
GTGAGTAAGGCCAGTCACATCTCCAGAGGCCATCAGCACCAGGCCTGGGGATCGAGGCCT
CCTGCAGCAGAGTGTGCCACCCAAAGAGCTCCAGGCAGTGTGGTGGAGCTGCTGGGCAAA
TCCTACCCTCAGGACGACCACAGCAACCTCACCCGGAAGGTCCTCACCAGAGTTGGCAGG
AACCTGCACAACCAGCAGCATCACCCTCTGTGGCTGATCAAGGAGAGGGTGAAGGAGCAC
TTCTACAAGCAGTATGTGGGCCGCTTTGGGACCCCGTTGTTCTCGGTCTACGACAACCTT
TCTCCAGTGGTCACGACCTGGCAGAACTTTGACAGCCTGCTCATCCCAGCTGATCACCCC
AGCAGGAAGAAGGGGGACAACTATTACCTGAATCGGACTCACATGCTGAGAGCGCACACG
TCTGCACACCAGTGGGACTTGCTGCACGCGGGACTGGATGCCTTCCTGGTGGTGGGTGAT
GTCTACAGGCGTGACCAGATCGACTCCCAGCACTACCCTATTTTCCACCAGCTGGAGGCC
GTGCGGCTCTTCTCCAAGCATGAGTTATTTGCTGGTATAAAGGATGGAGAAAGCCTGCAG
CTCTTTGAACAAAGTTCTCGCTCTGCGCATAAACAAGAGACACACACCATGGAGGCCGTG
AAGCTTGTAGAGTTTGATCTTAAGCAAACGCTTACCAGGCTCATGGCACATCTTTTTGGA
GATGAGCTGGAGATAAGATGGGTAGACTGCTACTTCCCTTTTACACATCCTTCCTTTGAG
ATGGAGATCAACTTTCATGGAGAATGGCTGGAAGTTCTTGGCTGCGGGGTGATGGAACAA
CAACTGGTCAATTCAGCTGGTGCTCAAGACCGAATCGGCTGGGCTTTTGGCCTAGGATTA
GAAAGGCTAGCCATGATCCTCTACGACATCCCTGATATCCGTCTCTTCTGGTGTGAGGAC
GAGCGCTTCCTGAAGCAGTTCTGTGTATCCAACATTAATCAGAAGGTGAAGTTTCAGCCT
CTTAGCAAATATCCGGCTGTGATCAATGATATTTCATTCTGGTTGCCCTCTGAGAATTAC
GCAGAAAATGATTTCTATGACTTAGTCCGAACAATTGGAGGAGACCTGGTGGAAAAGGTT
GATCTCATAGACAAGTTTGTACATCCAAAGACGCACAAGACCAGCCACTGCTACCGCATC
ACGTACCGCCACATGGAACGGACTCTGTCCCAGAGAGAGGTCAGGCACATCCACCAGGCC
TTGCAGGAGGCTGCAGTCCAGCTGTTGGGTGTGGAGGGCAGGTTCTGATGTCACCACTTC
ACTCAGGCTGCAGCCCTCTTGGGGCTCCAGGATTTGCTGAAAGAGAAAAAGATATGGTTT
GTGAACTGGGGCATCAATCATCTTTTGATAAATGGATCAGTTTTAGGACTTTCAGAAAAT
AAAAGATCGCTCTTGAAAAAAAAAAAAAAAAAAAAAAAAAA

Figure 125A

MVGSALRRGAHAYVYLVSKASHISRGHQHQAWGSRPPAAECATQRAPGSVVELLGKSYPQDDHS
NLTRKVLTRVGRNLHNQQHHPLWLIKERVKEHFYKQYVGRFGTPLFSVYDNLSPVVTTWQNFDSL
LIPADHPSRKKGDNYYLNRTHMLRAHTSAHQWDLLHAGLDAFLVVGDVYRRDQIDSQHYPIFHQL
EAVRLFSKHELFAGIKDGESLQLFEQSSRSAHKQETHTMEAVKLVEFDLKQTLTRLMAHLFGDELEI
RWVDCYFPFTHPSFEMEINFHGEWLEVLGCGVMEQQLVNSAGAQDRIGWAFGLGLERLAMILYDI
PDIRLFWCEDERFLKQFCVSNINQKVKFQPLSKYPAVINDISFWLPSENYAENDFYDLVRTIGGDLV
EKVDLIDKFVHPKTHKTSHCYRITYRHMERTLSQREVRHIHQALQEAAVQLLGVEGRF

Figure 125B

TGAAGGCTGGTTGTTCAGACTGAGCTTCCTGCCTGCCTGTACCCCGCCAACAGCTTCAGA
AGAAGGTGACTGGTGGCTGCCTGAGGAATACCAGTGGGCAAGAGAATTAGCATTTCTGGA
GCATCTGCTGTCTGAGCAGCCCCTGGGTGCGTCCACTTTCTGGGCACGTGAGGTTGGGCC
TTGGCCGCCTGAGCCCTTGAGTTGGTCACTTGAACCTTGGGAATATTGAGATTATATTCT
CCTGCCTTTTAAAAAGATGGACTTCAGCAGAAATCTTTATGATATTGGGGAACAACTGGA
CAGTGAAGATCTGGCCTCCCTCAAGTTCCTGAGCCTGGACTACATTCCGCAAAGGAAGCA
AGAACCCATCAAGGATGCCTTGATGTTATTCCAGAGACTCCAGGAAAAGAGAATGTTGGA
GGAAAGCAATCTGTCCTTCCTGAAGGAGCTGCTCTTCCGAATTAATAGACTGGATTTGCT
GATTACCTACCTAAACACTAGAAAGGAGGAGATGGAAAGGGAACTTCAGACACCAGGCAG
GGCTCAAATTTCTGCCTACAGGTTCCACTTCTGCCGCATGAGCTGGGCTGAAGCAAACAG
CCAGTGCCAGACACAGTCTGTACCTTTCTGGCGGAGGGTCGATCATCTATTAATAAGGGT
CATGCTCTATCAGATTTCAGAAGAAGTGAGCAGATCAGAATTGAGGTCTTTTAAGTTTCT
TTTGCAAGAGGAAATCTCCAAATGCAAACTGGATGATGACATGAACCTGCTGGATATTTT
CATAGAGATGGAGAAGAGGGTCATCCTGGGAGAAGGAAAGTTGGACATCCTGAAAAGAGT
CTGTGCCCAAATCAACAAGAGCCTGCTGAAGATAATCAACGACTATGAAGAATTCAGCAA
AGGGGAGGAGTTGTGTGGGGTAATGACAATCTCGGACTCTCCAAGAGAACAGGATAGTGA
ATCACAGACTTTGGACAAAGTTTACCAAATGAAAAGCAAACCTCGGGGATACTGTCTGAT
CATCAACAATCACAATTTTGCAAAAGCACGGGAGAAAGTGCCCAAACTTCACAGCATTAG
GGACAGGAATGGAACACACTTGGATGCAGGGGCTTTGACCACGACCTTTGAAGAGCTTCA
TTTTGAGATCAAGCCCCACCATGACTGCACAGTAGAGCAAATCTATGAGATTTTGAAAAT
CTACCAACTCATGGACCACAGTAACATGGACTGCTTCATCTGCTGTATCCTCTCCCATGG
AGACAAGGGCATCATCTATGGCACTGATGGACAGGAGGCCCCCATCTATGAGCTGACATC
TCAGTTCACTGGTTTGAAGTGCCCTTCCCTTGCTGGAAAACCCAAAGTGTTTTTTATTCA
GGCTTGTCAGGGGGATAACTACCAGAAAGGTATACCTGTTGAGACTGATTCAGAGGAGCA
ACCCTATTTAGAAATGGATTTATCATCACCTCAAACGAGATATATCCCGGATGAGGCTGA
CTTTCTGCTGGGGATGGCCACTGTGAATAACTGTGTTTCCTACCGAAACCCTGCAGAGGG
AACCTGGTACATCCAGTCACTTTGCCAGAGCCTGAGAGAGCGATGTCCTCGAGGCGATGA
TATTCTCACCATCCTGACTGAAGTGAACTATGAAGTAAGCAACAAGGATGACAAGAAAAA
CATGGGGAAACAGATGCCTCAGCCTACTTTCACACTAAGAAAAAAACTTGTCTTCCCTTC
TGATTGATGGTGCTATTTTGTTTGTTTTGTTTTGTTTTGTTTTTTTGAGACAGAATCTCG
CTCTGTCGCCCAGGCTGGAGTGCAGTGGCGTGATCTCGGCTCACCGCAAGCTCCGCCTCC
CGGGTTCAGGCCATTCTCCTGCT

Figure 126A

MDFSRNLYDIGEQLDSEDLASLKFLSLDYIPQRKQEPIKDALMLFQRLQEKRMLEESNLSFLKELLF
RINRLDLLITYLNTRKEEMERELQTPGRAQISAYRFHFCRMSWAEANSQCQTQSVPFWRRVDHLLI
RVMLYQISEEVSRSELRSFKFLLQEEISKCKLDDDMNLLDIFIEMEKRVILGEGKLDILKRVCAQINK
SLLKIINDYEEFSKGEELCGVMTISDSPREQDSESQTLDKVYQMKSKPRGYCLIINNHNFAKAREKV
PKLHSIRDRNGTHLDAGALTTTFEELHFEIKPHDDCTVEQIYEILKIYQLMDHSNMDCFICCILSHGD
KGIIYGTDGQEAPIYELTSQFTGLKCPSLAGKPKVFFIQACQGDNYQKGIPVETDSEEQPYLEMDLSS
PQTRYIPDEADFLLGMATVNNCVSYRNPAEGTWYIQSLCQSLRERCPRGDDILTILTEVNYEVSNKD
DKKNMGKQMPQPTFTLRKKLVFPSD

Figure 126B

GCACTCGCCCGGCTCGCCCGCTTTCGCACCCAGTTCACGCGCCACAGCTATGTGTCCCCGAGCCGCGCGG
GCGCCCGCGACGCTACTCCTCGCCCTGGGCGCGGTGCTGTGGCCTGCGGCTGGCGCCTGGGAGCTTACGA
TTTTGCACACCAACGACGTGCACAGCCGGCTGGAGCAGACCAGCGAGGACTCCAGCAAGTGCGTCAACG
CCAGCCGCTGCATGGGTGGCGTGGCTCGGCTCTTCACCAAGGTTCAGCAGATCCGCCGCGCCGAACCCAA
CGTGCTGCTGCTGGACGCCGGCGACCAGTACCAGGGCACTATCTGGTTCACCGTGTACAAGGGCGCCGAG
GTGGCGCACTTCATGAACGCCCTGCGCTACGATGCCATGGCACTGGGAAATCATGAATTTGATAATGGTG
TGGAAGGACTGATCGAGCCACTCCTCAAAGAGGCCAAATTTCCAATTCTGAGTGCAAACATTAAAGCAA
AGGGGCCACTAGCATCTCAAATATCAGGACTTTATTTGCCATATAAAGTTCTTCCTGTTGGTGATGAAGTT
GTGGGAATCGTTGGATACACTTCCAAAGAAACCCCTTTTCTCTCAAATCCAGGGACAAATTTAGTGTTTG
AAGATGAAATCACTGCATTACAACCTGAAGTAGATAAGTTAAAAACTCTAAATGTGAACAAAATTATTGC
ACTGGGACATTCGGGTTTTGAAATGGATAAACTCATCGCTCAGAAAGTGAGGGGTGTGGACGTCGTGGTG
GGAGGACACTCCAACACATTTCTTTACACAGGCAATCCACCTTCCAAAGAGGTGCCTGCTGGGAAGTACC
CATTCATAGTCACTTCTGATGATGGGCGGAAGGTTCCTGTAGTCCAGGCCTATGCTTTTGGCAAATACCTA
GGCTATCTGAAGATCGAGTTTGATGAAAGAGGAAACGTCATCTCTTCCCATGGAAATCCCATTCTTCTAA
ACAGCAGCATTCCTGAAGATCCAAGCATAAAAGCAGACATTAACAAATGGAGGATAAAATTGGATAATT
ATTCTACCCAGGAATTAGGGAAAACAATTGTCTATCTGGATGGCTCCTCTCAATCATGCCGCTTTAGAGA
ATGCAACATGGGCAACCTGATTTGTGATGCAATGATTAACAACAACCTGAGACACACGGATGAAATGTTC
TGGAACCACGTATCCATGTGCATTTTAAATGGAGGTGGTATCCGGTCGCCCATTGATGAACGCAACAATG
GCACAATTACCTGGGAGAACCTGGCTGCTGTATTGCCCTTTGGAGGCACATTTGACCTAGTCCAGTTAAA
AGGTTCCACCCTGAAGAAGGCCTTTGAGCATAGCGTGCACCGCTACGGCCAGTCCACTGGAGAGTTCCTG
CAGGTGGGCGGAATCCATGTGGTGTATGATCTTTCCCGAAAACCTGGAGACAGAGTAGTCAAATTAGATG
TTCTTTGCACCAAGTGTCGAGTGCCCAGTTATGACCCTCTCAAAATGGACGAGGTATATAAGGTGATCCT
CCCAAACTTCCTGGCCAATGGTGGAGATGGGTTCCAGATGATAAAAGATGAATTATTAAGACATGACTCT
GGTGACCAAGATATCAACGTGGTTTCTACATATATCTCCAAAATGAAAGTAATTTATCCAGCAGTTGAAG
GTCGGATCAAGTTTTCCACAGGAAGTCACTGCCATGGAAGCTTTTCTTTAATATTTCTTTCACTTTGGGCA
GTGATCTTTGTTTTATACCAATAGCCAAAAATTCTCCTTGCCTTTAATGTGTGAAACTGCATTTTTTCAAGT
GAGATTCAAATCTGCCTTTTAGGACCTGGCTTTGTGACAGCAAAAACCATCTTTACAGGCTCCTAGAAGC
TGAAGGTTAGAGCATTATAAAATGAAGAGACAGACATGATTACTCAGGGTCAGCAACCTAGTGAGTTAG
AAAAAAAATTAACATAGGGCCCTATAAGGAGAAAGCCAACTATGTTAAGTTTACGTGTCCAAATTTTAAT
GAAATTTTACTAACAATTTTAAACCATATTTTTCTTCTTCATATCCATTTCTAATCCATCAAACAGCTTATG
TTTACATAAAATTTTATCATTCACAAGGAAGTTTTAAGCACACTGTCTCATTTGATATCCACAACTTATTT
TTGGTAGGAAAGAGAGATGTTTTTCCCACCTGTCAGATGAAAAAACTGAAGCTCAAAAAGGGTTGACTTG
ACCATACAGCTAATGCTGACAGATCCAAGACCTAGACCTAGGTCTTTTGAACTCAAGTCCAGCATTCTCA
ACTATATCAAGTTACTGTTCAGAATACTTAATATCTCCTCTCTTCATAATTATCAATAGCCCCAAGCTCAT
GGATGACAAATCTCTGCTTTATTTCTTGTCTCTATTTTTTCACTTTATAGCTCCTGTTATAATAGCAAGTTT
AATGGTATAAACACAGGATACCATCCTCTCTTGCAACACCCATGTGCCTTTGATGAGTCAGGTAGCAAGC
TGTAGTAGATAATGAGAAAGGCCAGAGGCTGCAAAGACAGTCAAAGGACACGAGAGAAAGGAAGGGGA
AGAACAGGACTCCAGGACTGTTTTATATTATAGAAAAGCAAGAGCTAAAGAGCATTTACACATGTTAAA
CAGATACTTGTTAAGCATAGTGCCTGACACACGGCATTAGCTGTTATTTTATGAGATTCCATCAGCTCTGC
CTCTGTCCTCTTTCTTCTAACATGAAGGTATCATGAGAAGAGAACCTTCTAACATAAGCTGTAATTCTAAA
CCTGCACTTGTCCCTCTCCAGCAAGAGGCTAGCACTGAATTCATTCTACTCATACTACACACCCAGTTATG
GAATGTCCAGAGTTCTCGAAGAAAATAAATGACTTTAGGAAGAGGTATACATTTTTTAAGTCGCTCTGCC
TCCAAATCTGAACAGTCACTGTAAATCATTCTTAAGCCCAGATATGAGAACTTCTGCTGGAAAGTGGGAC
CCTCTGAGTGGGTGGTCAGAAAATACCCATGCTGATGAAATGACCTATGCCCAAAGAACAAATACTTAAC
GTGGGAGTGGAACCACATGAGCCTGCTCAGCTCTGCATAAGTAATTCAAGAAATGGGAGGCTTCACCTTA
AAAACAGTGTGCAAATGGCAGCTAGAGGTTTTGATAGGAAGTATGTTTGTTTCTTAGTGTTTACAAATAT
TAAGTACTCTTGATACAAAATATACTTTTAAACTTCATAACCTTTTTATAAAAGTTGTTGCAGCAAAATAA
TAGCCTCGGTTCTATGCATATATGGATTGCTATAAAAAATGTCAATAAGATTGTACAAGGAAAATTAGAG
AAAGTCACATTTAGGGTTTATTTTTTACACTTGGCCAGTAAAATAGGGTAAATCCTATTAGAAATTTTTTA
AAGAACTTTTTTTAAGTTTCCTAAATCTGTGTGTGTATTGTGAAGTGGTATAAGAAATGACTTTGAACCAC
TTTGCAATTGTAGATTCCCAACAATAAAATTGAAGAT

Figure 127A

MCPRAARAPATLLLALGAVLWPAAGAWELTILHTNDVHSRLEQTSEDSSKCVNASRCMGGVARLF
TKVQQIRRAEPNVLLLDAGDQYQGTIWFTVYKGAEVAHFMNALRYDAMALGNHEFDNGVEGLIE
PLLKEAKFPILSANIKAKGPLASQISGLYLPYKVLPVGDEVVGIVGYTSKETPFLSNPGTNLVFEDEIT
ALQPEVDKLKTLNVNKIIALGHSGFEMDKLIAQKVRGVDVVVGGHSNTFLYTGNPPSKEVPAGKYP
FIVTSDDGRKVPVVQAYAFGKYLGYLKIEFDERGNVISSHGNPILLNSSIPEDPSIKADINKWRIKLDN
YSTQELGKTIVYLDGSSQSCRFRECNMGNLICDAMINNNLRHTDEMFWNHVSMCILNGGGIRSPID
ERNNGTITWENLAAVLPFGGTFDLVQLKGSTLKKAFEHSVHRYGQSTGEFLQVGGIHVVYDLSRKP
GDRVVKLDVLCTKCRVPSYDPLKMDEVYKVILPNFLANGGDGFQMIKDELLRHDSGDQDINVVST
YISKMKVIYPAVEGRIKFSTGSHCHGSFSLIFLSLWAVIFVLYQ

Figure 127B

AAGCTTGCGCGCCATGTAAGGTAAAGTGACTGATTCTATAGCAATCCAATTGTTCCTTTG
TCTGCCCGTTTACATATAACAATGTTGTCAATGTTTGATTGAAAATACCTAGCAGGCGAC
ACACACACACCTAGCTCCTCAGGCGGAGAGCACCCCTTTCTTGGCCACCCGGGTATCCCC
CAGGGAGTACGGGGCTCAAAACACCCTTTTGGAGAACAAGGTGGAAGCAAATTTCAGGAA
GTAAAACTTCCTGAAATAAAATAAAATATCGAATGCCTTGAGACCCATACATTTTCAGGT
TTTCCTAATTAAAGCAATTACTTTCCACCACCCCTCCAACCTGGAATCACCAACTTGGTT
AGAGAAACTGATTTTTCTTTTTTCTTTTTTTTTTCCCAAAAGAGTACATCTGATCATTTTA
GCCTGCAACTAATGATAGAGATATTAGGGCTAGTTAACCACAGTTTTACAAGACTCCTCT
CCCGCGTGTGGGCCATTGTCATGCTGTCGGTCCCGCCCACCTGAAAGGTCTCCCCGCCCC
GACTGGGGTTTGTTGTTGAAGAAGGAGAATCCCCGGAAAGGCTGAGTCTCCAGCTCAAGG
TCAAAACGTCCAAGGCCGAAAGCCCTCCAGTTTCCCCTGGACACCTTGCTCCTGCTTCTG
CTACGACCTTCTGGGAACGCGAATTTCTCATTTTCTTCTTAAATTGCCATTTTCGCTTTA
GGAGATGAATGTTTTCCTTTGGCTGTTTTGGCAATGACTCTGAATTAAAGCGATGCTAAC
GCCTCTTTTCCCCCTAATTGTTAAAAGCTATGGACTGCAGGAAGATGGTCCGCTTCTCTT
ACAGTGTGATTTGGATCATGGCCATTTCTAAAGCCTTTGAACTGGGATTAGTTGCCGGGC
TGGGCCATCAGGAATTTGCTCGTCCATCTCGGGGAGACCTGGCCTTCAGAGATGACAGCA
TTTGGCCCCAGGAGGAGCCTGCAATTCGGCCTCGGTCTTCCCAGCGTGTGCTGCCCATGG
GAATACAGCACAGTAAGGAGCTAAACAGAACCTGCTGCCTGAATGGGGGAACCTGCATGC
TGGAGTCCTTTTGTGCCTGCCCTCCCTCCTTCTACGGACGGAACTGTGAGCACGATGTGC
GCAAAGAGAACTGTGGGTCTGTGCCCCATGACACCTGGCTGCCCAAGAAGTGTTCCCTGT
GTAAATGCTGGCACGGTCAGCTCCGCTGCTTTCCTCAGGCATTTCTACCCGGCTGTGATG
GCCTTGTGATGGATGAGCACCTCGTGGCTTCCAGGACTCCAGAACTACCACCGTCTGCAC
GTACTACCACTTTTATGCTAGCTGGCATCTGCCTTTCTATACAAAGCTACTATTAATCGA
CATTGACCTATTTCCAGAAATACAATTTTAGATATTATGCAAATTTCATGACCCGTAAAG
GCTGCTGCTACAATGTCCTAACTGAAAGATGATCATTTGTAGTTGCCTTAAAATAATGAA
TACAATTTCCAAAACGGTCTCTAACATTTCCTTACAGAACTAACTACTTCTTACCTCTTT
GCCCTGCCCTCTCCCAAAAAACTACTTCTTTTTTCAAAAGAAAGTCAGCCATATCTCCAT
TGTGCCCAAGTCCAGTGTTTCTTTTTTTTTTTTGAGACGGAGTCTCACTCTGTCACCCAG
GCTGGACTGCAATGACGCGATCTCGGTTCACTGCAACCTCCGCATCCGGGGTTCAAGCCA
TTCTCCTGCCTCAGCCTCCCAAGTAGCTGGGATTACAGGCATGTGTCACCATGCCGGCTA
ATTTTTTTGTATTTTAGTAGAGACGGGGGTTTCACCATATTGGCCAGCTGGTCTCGAACT
CTGACCTTGTGATCCATCGCTCGCCTCTCGAGTGCTGAGATTACACACGTGAGCAACTGT
GCAAGGCCTGGTGTTTCTTGATACATGTAATTCTACCAAGGTCTTCTTAATATGTTCTTT
TAAATGATTGAATTATACACTCAGATTATTGGAGACTAAGTCTAATGTGGACCTTAGAAT
ACAGTTTTGAGTAGAGTTGATCAAAATCAATTAAAATAGTCTCTTTAAAAGGAAAGAAAA
CATCTTTAAGGGGAGGAACCAGAGTGCTGAAGGAATGGAAGTCCATCTGCGTGTGTGCAG
GGAGACTGGGTAGGAAAGAGGAAGCAAATAGAAGAGAGAGGTTGAAAAACAAAATGGGTT
ACTTGATTGGTGATTAGGTGGTGGTAGAGAAGCAAGTAAAAAGGCTAAATGGAAGGGCAA
GTTTCCATCATCTATAGAAAGCTATGTAAGACAAGGACTCCCCTTTTTTTCCCAAAGGCA
TTGTAAAAAGAATGAAGTCTCCTTAGAAAAAAAATTATACCTCAATGTCCCCAACAAGAT
TGCTTAATAAATTGTGTTTCCTCCAAGCTATTCAATTCTTTTAACTGTTGTAGAAGAGAA
AATGTTCACAATATATTTAGTTGTAAACCAAGTGATCAAACTACATATTGTAAAGCCCAT
TTTTAAAATACATTGTATATATGTGTATGCACAGTAAAAATGGAAACTATATTGACCTAA
AAAAAAAAAAAGGAAACCACCCTTAGGCAGGCAGGACATGCTCTTCAGAACTCTGCTCTT
CAGAGTTCCAAAGAAGGGATAAAACATCTTTTATXXCCATCAAATAGC

Figure 128

CGGCTCGAGCGGCTCGAGTGAAGAGCCTCTCCACGGCTCCTGCGCCTGAGACAGCTGGCC
TGACCTCCAAATCATCCATCCACCCCTGCTGTCATCTGTTTTCATAGTGTGAGATCAACC
CACAGGAATATCCATGGCTTTTGTGCTCATTTTGGTTCTCAGTTTCTACGAGCTGGTGTC
AGGACAGTGGCAAGTCACTGGACCGGGCAAGTTTGTCCAGGCCTTGGTGGGGGAGGACGC
CGTGTTCTCCTGCTCCCTCTTTCCTGAGACCAGTGCAGAGGCTATGGAAGTGCGGTTCTT
CAGGAATCAGTTCCATGCTGTGGTCCACCTCTACAGAGATGGGGAAGACTGGGAATCTAA
GCAGATGCCACAGTATCGAGGGAGAACTGAGTTTGTGAAGGACTCCATTGCAGGGGGGCG
TGTCTCTCTAAGGCTAAAAAACATCACTCCCTCGGACATCGGCCTGTATGGGTGCTGGTT
CAGTTCCCAGATTTACGATGAGGAGGCCACCTGGGAGCTGCGGGTGGCAGCACTGGGCTC
ACTTCCTCTCATTTCCATCGTGGGATATGTTGACGGAGGTATCCAGTTACTCTGCCTGTC
CTCAGGCTGGTTCCCCCAGCCCACAGCCAAGTGGAAAGGTCCACAAGGACAGGATTTGTC
TTCAGACTCCAGAGCAAATGCAGATGGGTACAGCCTGTATGATGTGGAGATCTCCATTAT
AGTCCAGGAAAATGCTGGGAGCATATTGTGTTCCATCCACCTTGCTGAGCAGAGTCATGA
GGTGGAATCCAAGGTATTGATAGGAGAGACGTTTTTCCAGCCCTCACCTTGGCGCCTGGC
TTCTATTTTACTCGGGTTACTCTGTGGTGCCCTGTGTGGTGTTGTCATGGGGATGATAAT
TGTTTTCTTCAAATCCAAAGGGAAAATCCAGGCGGAACTGGACTGGAGAAGAAAGCACGG
ACAGGCAGAATTGAGAGACGCCCGGAAACACGCAGTGGAGGTGACTCTGGATCCAGAGAC
GGCTCACCCGAAGCTCTGCGTTTCTGATCTGAAAACTGTAACCCATAGAAAAGCTCCCCA
GGAGGTGCCTCACTCTGAGAAGAGATTTACAAGGAAGAGTGTGGTGGCTTCTCAGGGTTT
CCAAGCAGGGAGACATTACTGGGAGGTGGACGTGGGACAAAATGTAGGGTGGTATGTGGG
AGTGTGTCGGGATGACGTAGACAGGGGGAAGAACAATGTGACTTTGTCTCCCAACAATGG
GTATTGGGTCCTCAGACTGACAACAGAACATTTGTATTTCACATTCAATCCCCATTTTAT
CAGCCTCCCCCCCAGCACCCCTCCTACACGAGTAGGGGTCTTCCTGGACTATGAGGGTGG
GACCATCTCCTTCTTCAATACAAATGACCAGTCCCTTATTTATACCCTGCTGACATGTCA
GTTTGAAGGCTTGTTGAGACCCTATATCCAGCATGCGATGTATGACGAGGAAAAGGGGAC
TCCCATATTCATATGTCCAGTGTCCTGGGGATGAGACAGAGAAGACCCTGCTTAAAGGGC
CCCACACCACAGACCCAGACACAGCCAAGGGAGAGTGCTCCCGACAGGTGGCCCCAGCTT
CCTCTCCGGAGCCTGCGCACAGAGAGTCACGCCCCCCACTCTCCTTTAGGGAGCTGAGGT
TCTTCTGCCCTGAGCCCTGCAGCAGCGGCAGTCACAGCTTCCAGATGAGGGGGGATTGGC
CTGACCCTGTGGGAGTCAGAAGCCATGGCTGCCCTGAAGTGGGGACGGAATAGACTCACA
TTAGGTTTAGTTTGTGAAAACTCCATCCAGCTAAGCGATCTTGAACAAGTCACAACCTCC
CAGGCTCCTCATTTGCTAGTCACGGACAGTGATTCCTGCCTCACAGGTGAAGATTAAAGA
GACAACGAATGTGAATCATGCTTGCAGGTTTGAGGGCACAGTGTTTGCTAATGATGTGTT
TTTATATTATACATTTTCCCACCATAAACTCTGTTTGCTTATTCCACATTAATTTACTTT
TCTCTATACCAAATCACCCATGGAATAGTTATTGAACACCTGCTTTGTGAGGCTCAAAGA
ATAAAGAGGAGGTAGGATTTTTCACTGATTCTATAAGCCCAGCATTACCTGATACCAAAA
CCAGGCAAAGAAAACAGAAGAAGAGGAAGGAAAACTACAGGTCCATATCCCTCATTAACA
CAGACACAAAAATTCTAAATAAAATTTTAACAAATTAAACTAAACAATATATTTAAAGAT
GATATATAACTACTCAGTGTGGTTTGTCCCACAAATGCAGAGTTGGTTTAATATTTAAAT
ATCAACCAGTGTAATTCAGCACATTAATAAAGTAAAAAAGAAAACCATAAAAAAAAAAAA
AAA

Figure 129A

MAFVLILVLSFYELVSGQWQVTGPGKFVQALVGEDAVFSCSLFPETSAEAMEVRFFRNQFHAVVHLYRDGED
WESKQMPQYRGRTEFVKDSIAGGRVSLRLKNITPSDIGLYGCWFSSQIYDEEATWELRVAALGSLPLISIVGYV
DGGIQLLCLSSGWFPQPTAKWKGPQGQDLSSDSRANADGYSLYDVEISIIVQENAGSILCSIHLAEQSHEVESK
VLIGETFFQPSPWRLASILLGLLCGALCGVVMGMIIVFFKSKGKIQAELDWRRKHGQAELRDARKHAVEVTLD
PETAHPKLCVSDLKTVTHRKAPQEVPHSEKRFTRKSVVASQGFQAGKHYWEVDVGQNVGWYVGVCRDDVD
RGKNNVTLSPNNGYWVLRLTTEHLYFTFNPHFISLPPSTPPTRVGVFLDYEGGTISFFNTNDQSLIYTLLTCQFE
GLLRPYIQHAMYDEEKGTPIFICPVSWG

Figure 129B

ctcttgtcag ctgtctttca gaagacctgg tggggnaagt ccgtgggcat catgttgacc gagctggaga aagccttgaa ctctatcatc gacgtctacc acaagtactc cctgataaag gggaatttcc atgccgtcta cagggatgac ctgaagaaat tgctagagac cgagtgtcct cagtatatca ggaaaaaggg tgcagacgtc tggttcaaag agttggatat caacactgat ggtgcagtta acttccagga gttcctcatt ctggtgataa agatgggctg gcagcccaca aaaaaagcca tgaagaaagc cacaaagagt agctgagtta ctgcccagag gctgggcccc tgacatgtac ctgcagaata ataaagtcat caatacctca aaaaaaaaaa aaaaaaaaaa

Figure 130A

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

Figure 130B

gcactcccaa agaactgggt actcaacact gagcagatct gttctttgag ctaaaaacca tgtgctgtac caagagtttg ctcctggctg ctttgatgtc agtgctgcta ctccacctct gcggcgaatc agaagcagca agcaacttig actgctgtct tggatacaca gaccgtattc ttcatcctaa atttattgtg ggcttcacac ggcagctggc caatgaaggc tgtgacatca atgctatcat ctttcacaca aagaaaaagt tgtctgtgtg cgcaaatcca aaacagactt gggtgaaata tattgtgcgt ctcctcagta aaaaagtcaa gaacatgtaa aaactgtggc ttttctggaa tggaattgga catagcccaa gaacagaaag aaccttgctg gggttggagg tttcacttgc acatcatgga gggtttagtg cttatctaat ttgtgcctca ctggacttgt ccaattaatg aagttgattc atattgcatc atagtttgct ttgtttaagc atcacattaa agttaaactg tattttatgt tatttatagc tgtaggtttt ctgtgtttag ctatttaata ctaattttcc ataagctatt ttggtttagt gcaaagtata aaattatatt tgggggggaa taagattata tggactttct tgcaagcaac aagctatttt ttaaaaaaaa ctatttaaca ttcttttgtt tatattgttt tgtctcctaa attgttgtaa ttgcattata aaataagaaa aatattaata agacaaatat tgaaaataaa gaaacaaaaa gttcttctgt ta

Figure 131A

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

Figure 131B