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## DESCRIPTION

**[0001]** The present invention relates to a method, in particular an *in vitro* method, for identifying CD3CD4 and/or CD3CD8 positive T lymphocytes of a mammal, based on the methylation status in the T-lymphocyte specific methylated regions (TLSDRs) in the CD3 gamma-delta intergenic region, wherein a demethylation of at least one CpG in the analyzed sample to at least 90% is indicative for memory and naive CD4<sup>+</sup> T lymphocytes and memory and naive CD8<sup>+</sup> T lymphocytes. The method may further comprise analyzing the methylation status of at least one CpG position in the genes SLA2, CHRNA3, C16orf24, LCK, FASLG, CD7, SIT1, IL32, CXCR6, UBASH3A, GRAP2, ITGB7 and TXK which also allows the unambiguously identification of all CD3 positive T lymphocytes. For further unambiguous identification of all CD8 cells, also the equivalent analysis GNMT2, CRTAM, IL2RB and ZBTB32 can be employed. Among the CD3 positive T lymphocytes, these markers are capable to segregate between CD8 and CD4 positive cells. Equivalently, FLJ00060, FLJ38379, PPP6C, CD226, ZBTB7B and TNFAIP8 are capable of positively identifying CD4 expressing cells in whole blood and segregate between CD4 and CD8 positive CD3 positive cells.

**[0002]** Furthermore, the present invention relates to the use of a kit for performing the above methods. The present invention allows for a precise analysis even from sub-optimal quality samples, such as non-freshly obtained blood or serum samples. It is one aim of this invention to provide a novel, more robust means to quantitatively detect and measure particular subsets of the blood within any solid organs or any body fluid of a mammal.

**[0003]** Employing this method, the inventors provide for novel, not previously known means of determining, quantitating and routinely measuring T lymphocytes.

### Background of the invention

**[0004]** T-lymphocytes are a major component of the mammalian immune system. Both CD4 and CD8 T-cells are responsible for proper functioning of said immune system. Whereas CD8 T-cells mediate the cytotoxic immune defence, CD4 cells - the so called helper T-cells - assist both the humoral and the cell mediated immune defence. The heterodimeric T-cell antigen receptor (TCR) is bound to a monomorphic protein complex called CD3. CD3 consists of subelements CD3  $\gamma$ ,  $\delta$ , and  $\epsilon$ , and is expressed on all peripheral T-cells, but only on a subset of the thymocytes. The genes for CD3  $\gamma$ ,  $\delta$ , and  $\epsilon$  are encoded on neighbouring loci on chromosome 11 (11q23).

**[0005]** Role of CD3 in signal transduction - The function of the CD3-chains is both the formation and the transport of the full CD3 complex to the cell surface, as well as the signal transduction upon stimulation through the heterodimeric T-cell antigen receptor. The amino acid sequence of the cytoplasmatic part of CD3 $\gamma$ ,  $\delta$ ,  $\epsilon$  each contains a motif that becomes phosphorylated upon stimulation, and thus activated. This so called ITAM (immunoreceptor tyrosine-based activated motif) serves as docking point for different tyrosine kinases. Individuals with defective CD3 $\gamma$  or  $\epsilon$ -chains suffer from a severe clinical autoimmune deficiency.

**[0006]** Even though almost all cells in an individual contain the exact same complement of DNA code, higher organisms must impose and maintain different patterns of gene expression in the various types of tissue. Most gene regulation is transitory, depending on the current state of the cell and changes in external stimuli. Persistent regulation, on the other hand, is a primary role of epigenetics - heritable regulatory patterns that do not alter the basic genetic coding of the DNA. DNA methylation is the archetypical form of epigenetic regulation; it serves as the stable memory for cells and performs a crucial role in maintaining the long-term identity of various cell types.

**[0007]** The primary target of methylation is the two-nucleotide sequence Cytosine-Guanine (a 'CpG site'); within this context cytosine (C) can undergo a simple chemical modification to become 5-methyl-cytosine. In the human genome, the CG sequence is much rarer than expected, except in certain relatively dense clusters called 'CpG islands'. CpG islands are frequently associated with gene promoters, and it has been estimated that more than half of the human genes have CpG islands (Antequera and Bird, Proc Natl Acad Sci USA 90: 11995-9, 1993). Aberrant methylation of DNA is frequently associated with the transformation from healthy to cancerous cells. Among the observed effects are genome-wide hypomethylation, increased methylation of tumour suppressor genes, and hypomethylation of many oncogenes (reviewed, for example, by Jones and Laird, Nature Genetics 21:163-167, 1999; Esteller, Oncogene 21:5427-5440, 2002; and Laird, Nature Reviews/Cancer 3:253-266, 2003). Methylation profiles have been recognized to be tumour specific (i.e., changes in the methylation pattern of particular genes or even individual CpGs are diagnostic of particular tumour types), and there is now an extensive collection of diagnostic markers for bladder, breast, colon, oesophagus, stomach, liver, lung, and prostate cancers (summarized, for example, by Laird, Nature Reviews/Cancer 3:253-266, 2003).

**[0008]** Hamerman et al. (in: Hamerman JA, Page ST, Pullen AM. Distinct methylation states of the CD8 beta gene in peripheral T cells and intraepithelial lymphocytes. J Immunol. 1997 Aug 1;159(3):1240-6) distinguish between CD4 and CD8 T-lymphocytes.

**[0009]** EP 1 213 360 describes a method of identifying a cell, tissue or nucleus, comprising collecting information on the methylation pattern of DNA isolated from the cell, tissue or nucleus and analyzing the resultant information.

**[0010]** WO 2004/050706 describes a sub-group of T-cells, and relates to characteristics of regulatory T-cells which define them as such. The application also describes the uses of such T-cells, compositions comprising them, and chemokines which recruit them in the modulation of an immune response.

**[0011]** Flanagan et al (Immunogenetics, vol.3 1, pp. 13-20, 1990) discloses hypomethylation of the CD3 gamma-delta region in some T-cells.

**[0012]** Finally, EP 1 826 279 describes a method, in particular an *in vitro* method, for identifying FoxP3-positive regulatory T cells, preferably CD25<sup>+</sup> CD4<sup>+</sup> regulatory T cells of a mammal, comprising analyzing the methylation status of at least one CpG position in the gene *foxp3* or an orthologous or paralogous gene thereof, and the use of DNA-methylation analysis of the gene of the transcription factor FoxP3 for a detection and quality assurance and control of regulatory T cells. While the measurement and determination of CD4 and CD8 cells is generally easy and is usually achieved through analyzing the expression of said antigens on the cellular surface, clinically, it remains challenging to determine these cell types, since for the commonly used FACS analysis the cell samples need to be freshly isolated or immediately fixated in order to keep the cell entities intact. Thus, the detection of T lymphocytes, while desirous, is problematic, particularly for routine applications.

**[0013]** In view of the above, it is an object of the present invention to provide an improved and in particular robust method based on DNA methylation analysis as a superior tool in order to more conveniently and reliably identify T-lymphocytes.

**[0014]** The present invention solves the above object by providing a method for identifying CD3<sup>+</sup>CD4<sup>+</sup> and/or CD3<sup>+</sup>CD8<sup>+</sup> naive and/or memory T-lymphocytes in a sample derived from a mammal comprising T cells, comprising analyzing the methylation status of at least one CpG position in the T-lymphocyte specific demethylated region (TLSDR) located in amplicon 1405 (SEQ ID No.6), amplicon 1406 (SEQ ID No.7) and/or amplicon 1408 (SEQ ID No.8), and identifying CD3<sup>+</sup> CD4<sup>+</sup> and/or CD3<sup>+</sup>CD8<sup>+</sup> naive and/or memory T-lymphocytes based on said methylation status, wherein a demethylation of at least one CpG position to at least 90% in said amplicon is indicative for a CD3<sup>+</sup> CD4<sup>+</sup>, and/or CD3<sup>+</sup> CD8<sup>+</sup> naive and/or memory T-lymphocyte cell.

**[0015]** The present invention is based on the surprising finding of the inventors that the identification of said TLSDRs in the CD3 gene as a specific epigenetic marker can greatly facilitate the clinical routine application of the analysis of the above markers. In contrast to FACS and mRNA measurements, the respective measurement(s) can be done independent of purification, storage and to quite some extent also to tissue quality.

**[0016]** In another preferred embodiment of the method according to the present invention, said at least one CpG position in said sample is demethylated to more than 91 % and preferably more than 92% and most preferred more than 95%.

**[0017]** This concept is based on specific demethylation of the TLSDR regions in CD3 positive T-lymphocytes. Using a simple and precise quantitative PCR method, the inventors show that CD3 demethylation in said regions represents a surrogate marker for these T-lymphocyte counts in blood or tissues. The present inventors have thus identified particular regions within the CD3 gene, which are functionally involved in, or mandatory associated with, the existence of CD3 positive T-lymphocytes.

**[0018]** The regions are the TLSDRs within the nucleotide sequence according to SEQ ID No.1 containing CpG motifs, which display a differential methylation status when cells expressing CD3 in either CD4<sup>+</sup> or CD8<sup>+</sup> cells compared with all other cells, not expressing CD3 if, for example, the bisulphite sequencing method is used.

**[0019]** The inventors could demonstrate that in said CD3<sup>+</sup> cells the CpG motifs are almost completely demethylated (i.e. to more than 70%, preferably 80%, preferably, more than 90% and most preferred more than 95%), whereas the same motifs are completely methylated in all CD3<sup>-</sup>cells. The differential methylation of the CpG motifs within the aforementioned region correlates with CD3 expression. Thus, determination of the methylation status of the TLSDRs in the CD3 locus could become a valuable tool to identify T-lymphocytes, such as will be required/or at least of some value for measuring T-lymphocytes in autoimmune diseases, transplant rejections, cancer, allergy, or just the T-lymphocytes related immune status in any envisionable context,

when desired. The assays allows measurement if T-lymphocytes without purification or any staining procedures. It even reports in solid tumors or other solid tissues the number of cells demethylated in said region, thus showing the total amount of CD3 positive tumor infiltrating T-lymphocytes.

**[0020]** The inventors have shown that the potential for constitutive expression of CD3 in T-lymphocytes coincides with epigenetic, i.e., DNA methylation based regulation. DNA methylation is a biologically and chemically stable epigenetic modification, resulting in long-term gene expression changes. The inventors found demethylation at the human CD3 locus to be restricted to T-lymphocytes when tested against all major peripheral blood cell types and a selection of non-blood cells. These data indicated that epigenetic modifications in the CD3 locus serve as valuable marker for the identification of cells with the phenotype of T-lymphocyte, regardless of the expression of the specific delta or gamma sub-chains. In another preferred aspect of the method according to the present invention the methylation status of at least one CpG position in the genes SLA2, CHRNA3, C16orf24, LCK, FASLG, CD7, SIT1, IL32, CXCR6, UBASH3A, GRAP2, ITGB7 and TXK is additionally analysed in analogy to what is described herein for CD3. These genes thus also allow the unambiguous identification of all CD3 positive T lymphocytes. Thus, in a preferred embodiment of the method according to the present invention, said at least one CpG position is present in the 5' region upstream from the transcription start, promoter region, intron, and/or exon/intron border within the gene(s) SLA2, CHRNA3, C16orf24, LCK, FASLG, CD7, SIT1, IL32, CXCR6, UBASH3A, GRAP2, ITGB7 and TXK.

**[0021]** In order to further unambiguously identify all CD8 cells, the present invention in another preferred aspect thereof provides the equivalent analysis of the genes GNGT2, CRTAM, IL2RB and ZBTB32 among the CD3 positive T lymphocytes, as these markers are capable to segregate between CD8 and CD4 positive cells. This analysis is preferably performed simultaneously or subsequently to the analysis for the CD3 phenotype of the T-lymphocytes. Equivalently, FLJ00060, FLJ38379, PPP6C, CD226, ZBTB7B and TNFAIP8 are capable of positively identifying CD4 expressing cells in whole blood and segregate between CD4 and CD8 positive CD3 positive cells.

**[0022]** The present invention provides the surprising finding that in particular regions of the gene for CD3, the so-called "TLSDRs" (T lymphocyte specific demethylated regions), the CpG motifs are almost completely demethylated (i.e. to more than 90%, preferably 91%, preferably, more than 92% and most preferred more than 95%), whereas the same motifs are completely methylated in all non T lymphocytes. Thus, these regions and the diagnostic uses thereof also provides a valuable and reliable tool for a diagnostic analysis according to the present invention. The TLSDR according to the present invention are located in amplicon No. 1405 (SEQ ID No. 6), amplicon No. 1406 (SEQ ID No. 7), and/or amplicon No. 1408 (SEQ ID No. 8). All of these amplicons are parts of the overall region of interest depicted in SEQ ID No.1.

**[0023]** In a preferred embodiment of the method according to the present invention, said analysis of the methylation status comprises amplification with at least one primer of suitable primer pairs that can be suitably designed based on SEQ ID No. 1, preferably oligomers according to any of SEQ ID No. 2 to 5.

**[0024]** Preferably, the amplification involves a polymerase enzyme, a PCR or chemical amplification reaction, or other amplification methods as known to the person of skill as described below, e.g. in the context of MSP, HeavyMethyl, Scorpion, MS-SNUPE, MethylLight, bisulfite sequencing, methyl specific restriction assays. With the amplification, the amplicon of the TLSDR or any other region in the CD3 gene or any paralog or ortholog as described herein is produced that is a particularly preferred "tool" for performing the method(s) according to the present invention. Consequently, an oligomer according to any of SEQ ID No. 2 to 5 or the amplicon as amplified by a primer pair as mentioned above constitute preferred embodiments of the present invention.

**[0025]** The person of skill will furthermore be able to select specific subsets of CpG positions in order to minimise the amount of sites to be analyzed, for example at least one of CpG position 1, 2, 3, 4, 5, 6, 7, 8, 9, and 10 of the amplicon No. 1405 (SEQ ID No. 6), amplicon No. 1406 (SEQ ID No. 7), and amplicon No. 1408 (SEQ ID No. 8).

**[0026]** The positions are numerically counted from the 5'-end of the amplicon as generated and analysed. Preferred are combinations of 4, 5, 6, or 7 positions, which are producing enough information in order to be informative in the context of the present invention.

**[0027]** In order to analyze the methylation status of CpG positions, any known method to analyse DNA methylation can be used. In a preferred embodiment of the method according to the present invention, the analysis of the methylation status comprises a method selected from methylation specific enzymatic digests, bisulphite sequencing, analysis selected from promoter methylation, CpG island methylation, MSP, HeavyMethyl, MethylLight, Ms-SNuPE or other methods relying on a detection of amplified DNA. These methods are well known to the person of skill, and can be found in the respective literature.

**[0028]** In a preferred embodiment of the method according to the present invention, said method is suitable for routine

application, for example on a DNA-chip. Based on the above information and the respective literature, the person of skill will be able to adjust the method above to such settings.

**[0029]** In another preferred embodiment of the method according to the present invention, the identification comprises a distinction of said T-lymphocytes from all major peripheral blood cell types or non-blood cells, preferably, but not limited to, CD14, CD15, CD19, and CD56.

**[0030]** In yet another preferred embodiment of the method according to the present invention, the sample is selected from a mammalian body fluid, including human blood samples, or a tissue, organ or cell type blood sample, a sample of blood lymphocytes or a fraction thereof. Preferably, said mammal is a mouse, rat, monkey or human. The samples can be suitably pooled, if required.

**[0031]** Another preferred aspect of the method according to the present invention then further comprises the step of concluding on the immune status of said mammal based on said T-lymphocytes as identified. The general lymphocyte population can be quantified and either be used as a benchmark to relatively quantify further detailed subpopulations such as the CD3CD4CD25 positive regulatory T cells (als Bezugspunkt) or it can be used to finally detect this population to determine the overall immune activity status.

**[0032]** In yet another preferred embodiment of the methods according to the present invention, the mammal suffers from or is likely to suffer from autoimmune diseases, transplant rejections, cancer, and/or allergy.

**[0033]** Yet another preferred aspect of the present invention then relates to the use of a kit for identifying and/or monitoring CD3<sup>+</sup> CD4<sup>+</sup>, and/or CD3<sup>+</sup> CD8<sup>+</sup> T-lymphocytes in a mammal according to the method of present invention as described herein. Said kit comprises a) a bisulfite reagent, and b) materials for the methylation analysis of CpG positions as comprised by the amplicon No. 1405 (SEQ ID No. 6), amplicon No. 1406 (SEQ ID No. 7), and amplicon No. 1408 (SEQ ID No. 8). The positions consist of positions 1, 2, 3, 4, 5, 6, 7, 8, 9, and 10 of amplicon 1405, CpG positions 1, 2, 3, 4, 5, 6, 7 and 8 of amplicon 1408 and CpG positions 1, 2, 3, 4, 5, 6 and 7 of amplicon 1408. Most preferred are 5, 6, or 7 or all positions on said amplicon.

**[0034]** In summary, using the CD3 marker, the inventors very specifically identified (but not differentiated) both CD3/CD4 positive as well as CD3/CD8 positive naive and memory T lymphocytes. Using the marker CD8beta, for example CD8 positive lymphocytes could then be distinguished from CD4 lymphocytes. This, when using a combination of the present marker(s) and the CD8beta marker, CD4 and CD8 cells can be specifically distinguished. This was not possible before the invention, since all CD4 looked identical to non-T lymphocytes.

**[0035]** The invention will now be further described based on the following examples and with reference to the accompanying figures and the sequence protocol, without being limited thereto. In the Figures and Sequences,

Figure 1 shows the differentially methylated gene region as found for CD3 g and d and are indicated by red lines as "blast hits".

Figure 2 shows the analysis of amplicon No. 1405 (SEQ ID No. 6), bisulfite strand 2, sequencing direction: forward. Relevant positions are indicated in bold.

Figure 3 shows the analysis of amplicon No. 1406, bisulfite strand 2, sequencing direction: reverse. Relevant positions are indicated in bold.

Figure 4 shows the analysis of amplicon No. 1406 (SEQ ID No. 7), bisulfite strand: 2, sequencing direction: forward. Relevant positions are indicated in bold.

Figure 5 shows the analysis of amplicon No. 1408 (SEQ ID No. 8), bisulfite strand: 2, sequencing direction: forward. Relevant positions are indicated in bold.

Figure 6 shows the regulatory regions of the  $\gamma\delta$ -T-cell receptor, including regions Nr. 1405 1406 und 1408 on chromosome 11 (NCBI36:11:117714000:117730500:1). Exon sequences are underlined for CD3  $\delta$ , and double underlined for CD3  $\gamma$ . CGs are in bold. SEQ ID No. 1 shows the sequence of the region as considered to have a specific methylation pattern in CD3 cells.

SEQ ID No. 2 to 5 and 9 show the sequences of oligonucleotides used in the Illumina Chip-Fragment assay for CD3 $\gamma$  and CD3 $\delta$  and CD3 $\epsilon$ .

SEQ ID No. 6 to 8 show the reference sequences of amplicon No. 1405 (SEQ ID No. 6), amplicon No. 1406 (SEQ ID No. 7), and amplicon No. 1408 (SEQ ID No. 8).

SEQ ID No. 10 to 38 show the sequences around the CpG positions as analyzed in other preferred T-lymphocyte markers of the present invention according to example 2.

## EXAMPLES

### Example 1 - CD3-Analysis

[0036] The inventors have purified various blood subsets, including CD3/CD4, CD3/CD8 naïve and memory T lymphocytes, CD56 natural killer cells, CD19 naïve and memory B cells, CD14 monocytes and CD15 granulocytes. DNA from the purified cells was bisulfite-treated and analysed at various CpG dinucleotide motifs. The inventors then compared the methylation status (finding C as for Cytosine that was methylated in the original sequence versus T for cytosine that was unmethylated in the original sequence).

[0037] The data showed various CpG motifs and areas in the CD3  $\gamma$ ,  $\delta$  and  $\epsilon$  that were demethylated in all CD3CD4 and CD3CD8 cell types while methylated in all other blood cell types. The differentially methylated gene regions as found for CD3  $\gamma$ ,  $\delta$  and  $\epsilon$  are shown below in Figure 1 and are indicated in bold as "blast hits"

[0038] The data, as observed with Illumina Golden Gate technology, show that all CD4 and CD8 positive memory (0.06 and 0.06 respectively) and naïve (0.03 and 0.06, respectively) T cells are subject to much lower methylation rates than all other tested cell types, including CD15 (0.92), CD14 (0.90), CD19 memory and naïve (0.81 and 0.67, respectively), CD56 (0.86) positive blood cells as well as cells derived (0.78) from non-blood tissues. The experimental results are further depicted in the following table.

**Table 1: Methylation analysis results**

| Gene | Chr. | S1<br>n=12;<br>female | S2<br>n=5;<br>male | S3<br>Pool;<br>female | S4<br>Pool;<br>(5<br>male) | S5<br>Pool;<br>(5<br>male) | S6<br>Pool;<br>(5<br>male) | S7<br>Pool;<br>(5<br>male) | S8<br>Pool;<br>(5<br>male) | S9<br>Pool;<br>(5<br>male) | S10<br>Pool; (5<br>male) | S11<br>Pool; (5<br>male) | S12<br>Pool; (5<br>male) |
|------|------|-----------------------|--------------------|-----------------------|----------------------------|----------------------------|----------------------------|----------------------------|----------------------------|----------------------------|--------------------------|--------------------------|--------------------------|
| CD3D | 11   | 0.8                   | 0.6                | 0.6                   | 0.9                        | 0.9                        | 0.9                        | 0.0                        | 0.1                        | 0.1                        | 0.1                      | 0.7                      | 0.8                      |
|      |      | 0.9                   | 0.7                | 0.7                   | 0.9                        | 0.9                        | 0.9                        | 0.1                        | 0.1                        | 0.2                        | 0.2                      | 0.7                      | 0.8                      |
| CD3G | 11   | 0.7                   | 0.6                | 0.7                   | 0.9                        | 0.9                        | 0.8                        | 0.1                        | 0.1                        | 0.1                        | 0.1                      | 0.8                      | 0.9                      |
|      |      | 0.4                   | 0.6                | 0.5                   | 0.7                        | 0.8                        | 0.7                        | 0.1                        | 0.1                        | 0.1                        | 0.1                      | 0.3                      | 0.6                      |

S1 = ovarian tissue, S2 = whole blood, S3 peripheral blood mononuclear cells, S4 = granulocytes, S5 = monocytes, S6 = NK cells, S7 = naïve T helper cells, S8 = memory T helper cells, S9 = naïve cytotoxic T cells, S10 = memory cytotoxic T cells, S11 = naïve B-cells, S12 = memory B-cells., Chr = chromosome

[0039] The data showing the high specificity were obtained using a Illumina Golden Gate technology, with the following genomic CpGs regions analysed

#### CD3 $\gamma$

cg15880738 (SEQ ID No. 2)

(+1)AGCTGCTGCACAGGCTGGCTGGCTGGCTGGCTGCTAAGGGCTGCTCC**CG** cg07545925 (SEQ ID No. 3)

(+1)**CG**GAAAAACAAAAGGCATCTGCACCTGCAGCCCTGCTGAGGCCCTGCTG

#### CD3 $\delta$

cg24841244 (SEQ ID No. 4)

(-1) ACCCAGGCTGATAGTT**CG**GTGACCTGGCTTTATCTACTGGATGAGTTCCG cg07728874 (SEQ ID No. 5)

(-1) TGGACATAGCA**CG**TTTCTCTCTGGCCTGGTACTGGCTACCCTTCTCTCG

#### CD3 $\epsilon$

cg24612198 (Seq ID No. 9)

AGTCATCTGTTTTGCTTTTTTCCAGAAGTAGTAAGTCTGCTGGCCTCCG

[0040] Since the Illumina technology does only allow the analysis of a single CpG (or rather 2 CpGs per gene locus) the inventors verified the methylation properties using bisulfite sequencing. For that, the inventors bisulfite treated the samples using the Qiagen EpiTect kit, and sequenced the samples using an ABI 3100 prism sequencer. For data interpretation, the KB base calling software supplied by ABI was used.

[0041] While not providing entirely quantitative results calculating the percentile of methylated (i.e., CG signal on the plus strand sequence) versus unmethylated (i.e., TG on the plus strand sequence), the data were unambiguous for the purified cell types. All T-lymphocytes were overwhelmingly demethylated at all CG positions analysed, whereas all other analysed cell types were methylated at identical positions.

#### Example 2 -Analysis of additional markers in analogy to CD3

[0042] In order to identify further suitable markers distinguishing and monitoring T-lymphocytes, other markers in addition to CD3 have been identified and tested through methylation analysis. It was found that methylation in the CpG positions in the genes for SLA2, CHRNA3, C16orf24, LCK, FASLG, CD7, SIT1, IL32, CXCR6, UBASH3A, GRAP2, ITGB7 and TXK can also be used in the context of the present invention, as these markers are also able to identify CD3 positive T lymphocytes.

[0043] Furthermore, other markers have been identified that identify the subset of the CD8 and CD4 positive cells in the group of CD3 positive T lymphocytes. The genes for GNGT2, CRTAM, IL2RB and ZBTB32 have been found to segregate between CD8 and CD4 positive cells. Equivalently, FLJ00060, FLJ38379, PPP6C, CD226, ZBTB7B and TNFAIP8 are capable of positively identifying CD4 expressing cells in whole blood and segregate between CD4 and CD8 positive CD3 positive cells.

[0044] The following table 2 summarizes the Illumina-data as obtained for the above markers at selected CpG positions. It can be seen that several other markers can be used in order to selectively identify CD4+ (for CD3+ lymphocyte subset-identification), namely FLJ00060; FLJ38379; PPP6C; CD226; ZBTB7B and/or TNFAIP8, in order to selectively identify CD8+ (for CD3+ lymphocyte subset-identification), namely GNGT2; CRTAM; IL2RB and/or ZBTB32, and in order to selectively identify CD3+ lymphocytes, namely CD3D; CD3G, and/or CD3E, and/or SLA2,CHRNA3, C16orf24; LCK; FASLG; FASLG; CD7; SIT1; IL32; CXCR6; UBASH3A; GRAP2; ITGB7 and/or TXK, as shown with selected CpG sites as preferred examples. Based on the table, the person of skill will be able to extend the teaching regarding CD3 as herein to these markers and their CpG sites.

Table 2: Illumina-data as obtained selected markers at CpG positions Chr. = chromosome

| CD4+ marker<br>CpG-ID | Gene Name    | Chr | SEQ ID<br>No. /<br>Accession<br>No. | Ovar<br>Tissue<br>(mean,<br>n=12) | Whole<br>Blood<br>(Pool) | PBMC<br>(Pro-<br>mega) | BCST1<br>8<br>Granu-<br>loocyte<br>(CD15<br>+) | BCST1<br>9<br>Mono-<br>cyte<br>(CD14<br>+) | BCST2<br>0<br>NK<br>(CD56<br>+) | BCST21<br>T naive<br>(CD4+<br>CD27<br>+CD45R<br>A+) | BCST22<br>T mem<br>(CD4+<br>CD27+<br>CD45RA<br>-) | BCST23<br>CTL<br>naive<br>(CD8-C<br>D27+<br>CD45RA<br>-) | BCST24<br>CTL<br>mem<br>(CD8-C<br>D27+<br>CD45RA<br>+) | BCST2<br>5<br>B naive<br>(CD19<br>+) | BCST2<br>6<br>B mem<br>(CD19<br>+) | Mean<br>Value<br>Target<br>Cell<br>Type | Mean<br>Value<br>Rest | Delta<br>Meth<br>(Target-<br>Rest) |
|-----------------------|--------------|-----|-------------------------------------|-----------------------------------|--------------------------|------------------------|------------------------------------------------|--------------------------------------------|---------------------------------|-----------------------------------------------------|---------------------------------------------------|----------------------------------------------------------|--------------------------------------------------------|--------------------------------------|------------------------------------|-----------------------------------------|-----------------------|------------------------------------|
| cg03602<br>500        | FLJ000<br>60 | 19  | NM_0332<br>117                      | 0.802                             | 0.728                    | 0.779                  | 0.858                                          | 0.851                                      | 0.873                           | 0.325                                               | 0.279                                             | 0.521                                                    | 0.687                                                  | 0.655                                | 0.747                              | 0.257                                   | 0.75                  | -0.493                             |
| cg16173<br>109        | FLJ383<br>79 | 2   | XR_00102<br>6.1                     | 0.614                             | 0.675                    | 0.719                  | 0.833                                          | 0.844                                      | 0.784                           | 0.1141                                              | 0.113                                             | 0.341                                                    | 0.383                                                  | 0.418                                | 0.385                              | 0.113                                   | 0.599                 | -0.486                             |
| cg00620<br>024        | PPP6C        | 9   | NM_0027<br>137                      | 0.641                             | 0.619                    | 0.692                  | 0.801                                          | 0.851                                      | 0.836                           | 0.107                                               | 0.169                                             | 0.269                                                    | 0.420                                                  | 0.404                                | 0.502                              | 0.138                                   | 0.603                 | -0.465                             |
| cg13164<br>537        | CD226        | 18  | NM_0065<br>147                      | 0.458                             | 0.470                    | 0.508                  | 0.582                                          | 0.557                                      | 0.601                           | 0.029                                               | 0.071                                             | 0.351                                                    | 0.543                                                  | 0.366                                | 0.501                              | 0.05                                    | 0.494                 | -0.443                             |
| cg01782<br>486        | ZBTB7<br>B   | 1   | NM_0158<br>157                      | 0.789                             | 0.725                    | 0.720                  | 0.823                                          | 0.809                                      | 0.886                           | 0.190                                               | 0.428                                             | 0.875                                                    | 0.864                                                  | 0.586                                | 0.414                              | 0.309                                   | 0.749                 | -0.44                              |
| cg07066<br>380        | TNFAIP<br>8  | 5   | NM_0143<br>50.1                     | 0.728                             | 0.579                    | 0.635                  | 0.857                                          | 0.733                                      | 0.793                           | 0.110                                               | 0.106                                             | 0.288                                                    | 0.148                                                  | 0.309                                | 0.208                              | 0.108                                   | 0.528                 | -0.419                             |
| CD8+ marker<br>CpG-ID | Gene Name    | Chr | SEQ ID<br>No. /<br>Accession<br>No. | Ovar<br>Tissue<br>(mean,<br>n=12) | Whole<br>Blood<br>(Pool) | PBMC<br>(Pro-<br>mega) | BCST1<br>8<br>Granu-<br>loocyte<br>(CD15<br>+) | BCST1<br>9<br>Mono-<br>cyte<br>(CD14<br>+) | BCST2<br>0<br>NK<br>(CD56<br>+) | BCST21<br>T naive<br>(CD4+<br>CD27<br>+CD45R<br>A+) | BCST22<br>T mem<br>(CD4+<br>CD27+<br>CD45RA<br>-) | BCST23<br>CTL<br>naive<br>(CD8-C<br>D27+<br>CD45RA<br>-) | BCST24<br>CTL<br>mem<br>(CD8-C<br>D27+<br>CD45RA<br>+) | BCST2<br>5<br>B naive<br>(CD19<br>+) | BCST2<br>6<br>B mem<br>(CD19<br>+) | Mean<br>Value<br>Target<br>Cell<br>Type | Mean<br>Value<br>Rest | Delta<br>Meth<br>(Target-<br>Rest) |
| cg17839<br>611        | GNGT<br>2    | 17  | NM_0314<br>177                      | 0.779                             | 0.629                    | 0.088                  | 0.828                                          | 0.867                                      | 0.207                           | 0.340                                               | 0.562                                             | 0.09                                                     | 0.119                                                  | 0.854                                | 0.722                              | 0.104                                   | 0.648                 | -0.543                             |
| cg22512<br>551        | CRTA<br>M    | 11  | NM_0196<br>187                      | 0.651                             | 0.634                    | 0.709                  | 0.835                                          | 0.735                                      | 0.5                             | 0.363                                               | 0.630                                             | 0.079                                                    | 0.082                                                  | 0.194                                | 0.336                              | 0.08                                    | 0.559                 | -0.478                             |
| cg26757<br>673        | IL2RB        | 22  | NM_0008<br>187                      | 0.799                             | 0.662                    | 0.752                  | 0.878                                          | 0.9                                        | 0.092                           | 0.573                                               | 0.086                                             | 0.157                                                    | 0.061                                                  | 0.411                                | 0.403                              | 0.109                                   | 0.555                 | -0.446                             |
| cg08539<br>991        | ZBTB32       | 19  | NM_0143                             | 0.823                             | 0.736                    | 0.791                  | 0.912                                          | 0.926                                      | 0.674                           | 0.563                                               | 0.153                                             | 0.303                                                    | 0.085                                                  | 0.648                                | 0.140                              | 0.194                                   | 0.637                 | -0.442                             |

| 83.1                                |              |           |                                |                        |                          |                        |                                               |                                            |                                  |                                           |                                                    |                                                           |                                                         |                                      |                                    |                                         |                       |                                    |
|-------------------------------------|--------------|-----------|--------------------------------|------------------------|--------------------------|------------------------|-----------------------------------------------|--------------------------------------------|----------------------------------|-------------------------------------------|----------------------------------------------------|-----------------------------------------------------------|---------------------------------------------------------|--------------------------------------|------------------------------------|-----------------------------------------|-----------------------|------------------------------------|
| CD4+ /<br>CD8+<br>marker<br>Cell-ID | Gene<br>Name | Chr<br>No | SEQ ID<br>Accession<br>No      | Over<br>Time<br>(n=12) | Whole<br>Blood<br>(Pool) | PBMC<br>(Pro-<br>mega) | BCST1<br>8<br>Granu-<br>locyte<br>(CD15<br>-) | BCST1<br>9<br>Mono-<br>cyte<br>(CD14<br>+) | BCST2<br>0<br>NK<br>(CD356<br>+) | BCST21<br>T naive<br>(CD4+ C<br>D27<br>-) | BCST22<br>T mem<br>(CD4+ C<br>D27+<br>CD45RA<br>-) | BCST23<br>CTL<br>naive<br>(CD8+ C<br>D27+<br>CD45RA<br>-) | BCST24<br>CTL<br>mem<br>(CD8+ C<br>D27+<br>CD45RA<br>-) | BCST2<br>5<br>B naive<br>(CD19<br>-) | BCST2<br>6<br>B mem<br>(CD19<br>+) | Mean<br>Value<br>Target<br>Cell<br>Type | Mean<br>Value<br>Rest | Delta<br>Meth<br>(Target-<br>Rest) |
| cg24841<br>244                      | CD3D         | 11        | NM_0007<br>12.2<br>21/         | 0.783                  | 0.582                    | 0.644                  | 0.917                                         | 0.904                                      | 0.857                            | 0.025                                     | 0.057                                              | 0.057                                                     | 0.058                                                   | 0.673                                | 0.810                              | 0.049                                   | 0.771                 | -0.721                             |
| cg07728<br>874                      | CD3D         | 11        | NM_0007<br>12.2<br>22/         | 0.854                  | 0.683                    | 0.727                  | 0.911                                         | 0.901                                      | 0.881                            | 0.128                                     | 0.149                                              | 0.175                                                     | 0.155                                                   | 0.744                                | 0.807                              | 0.152                                   | 0.814                 | -0.661                             |
| cg15880<br>738                      | CD3G         | 11        | NM_0000<br>73.1<br>23/         | 0.714                  | 0.616                    | 0.682                  | 0.874                                         | 0.876                                      | 0.836                            | 0.061                                     | 0.091                                              | 0.093                                                     | 0.103                                                   | 0.811                                | 0.898                              | 0.087                                   | 0.788                 | -0.701                             |
| cg07545<br>925                      | CD3G         | 11        | NM_0000<br>73.1<br>24/         | 0.370                  | 0.552                    | 0.545                  | 0.737                                         | 0.771                                      | 0.739                            | 0.133                                     | 0.149                                              | 0.132                                                     | 0.131                                                   | 0.303                                | 0.601                              | 0.132                                   | 0.49                  | -0.358                             |
| cg24612<br>198                      | CD3E         | 11        | NM_0007<br>33.2<br>25/         | 0.679                  | 0.485                    | 0.563                  | 0.794                                         | 0.793                                      | 0.698                            | 0.064                                     | 0.036                                              | 0.093                                                     | 0.051                                                   | 0.206                                | 0.279                              | 0.061                                   | 0.562                 | -0.501                             |
| cg04759<br>756                      | SLA2         | 20        | NM_0322<br>14.2<br>26/         | 0.857                  | 0.673                    | 0.754                  | 0.892                                         | 0.925                                      | 0.711                            | 0.363                                     | 0.228                                              | 0.129                                                     | 0.211                                                   | 0.756                                | 0.849                              | 0.233                                   | 0.802                 | -0.569                             |
| cg22670<br>733                      | CHRN<br>A3   | 15        | NM_0007<br>41.2<br>27/         | 0.792                  | 0.733                    | 0.721                  | 0.911                                         | 0.888                                      | 0.8                              | 0.122                                     | 0.180                                              | 0.092                                                     | 0.315                                                   | 0.456                                | 0.668                              | 0.177                                   | 0.746                 | -0.568                             |
| cg09830<br>866                      | C16orf<br>24 | 16        | NM_0239<br>31.1<br>28/         | 0.493                  | 0.629                    | 0.647                  | 0.842                                         | 0.79                                       | 0.076                            | 0.041                                     | 0.056                                              | 0.033                                                     | 0.058                                                   | 0.72                                 | 0.510                              | 0.047                                   | 0.588                 | -0.541                             |
| cg17078<br>393                      | LCK          | 1         | NM_0053<br>56.2<br>29/         | 0.807                  | 0.575                    | 0.666                  | 0.920                                         | 0.884                                      | 0.26                             | 0.05                                      | 0.037                                              | 0.036                                                     | 0.041                                                   | 0.144                                | 0.27                               | 0.041                                   | 0.566                 | -0.524                             |
| cg10161<br>121                      | FASLG        | 1         | NM_0006<br>39.1<br>30/         | 0.704                  | 0.587                    | 0.697                  | 0.903                                         | 0.892                                      | 0.068                            | 0.051                                     | 0.06                                               | 0.088                                                     | 0.06                                                    | 0.353                                | 0.441                              | 0.065                                   | 0.581                 | -0.516                             |
| cg00071<br>250                      | FASLG        | 1         | NM_0006<br>39.1<br>31/         | 0.659                  | 0.498                    | 0.602                  | 0.871                                         | 0.838                                      | 0.075                            | 0.061                                     | 0.069                                              | 0.139                                                     | 0.051                                                   | 0.391                                | 0.4144<br>6208                     | 0.08                                    | 0.543                 | -0.463                             |
| cg02473<br>123                      | CD7          | 17        | NM_0061<br>37.6<br>32/         | 0.811                  | 0.681                    | 0.767                  | 0.942                                         | 0.898                                      | 0.359                            | 0.102                                     | 0.328                                              | 0.168                                                     | 0.372                                                   | 0.767                                | 0.81                               | 0.243                                   | 0.752                 | -0.509                             |
| cg15518<br>883                      | SET1         | 9         | 37.6<br>32/<br>NM_0144<br>50.2 | 0.817                  | 0.601                    | 0.696                  | 0.911                                         | 0.885                                      | 0.9033                           | 0.11                                      | 0.142                                              | 0.154                                                     | 0.358                                                   | 0.392                                | 0.373                              | 0.191                                   | 0.697                 | -0.506                             |
| cg18350<br>391                      | IL32         | 16        | NM_0010<br>12631.1<br>34/      | 0.332                  | 0.724                    | 0.794                  | 0.937                                         | 0.901                                      | 0.658                            | 0.296                                     | 0.169                                              | 0.15                                                      | 0.192                                                   | 0.881                                | 0.406                              | 0.202                                   | 0.704                 | -0.502                             |
| cg25226<br>014                      | CXCR6        | 3         | NM_0065<br>64.1<br>35/         | 0.702                  | 0.481                    | 0.548                  | 0.789                                         | 0.89                                       | 0.35                             | 0.028                                     | 0.046                                              | 0.046                                                     | 0.193                                                   | 0.258                                | 0.514                              | 0.078                                   | 0.567                 | -0.488                             |
| cg13578<br>652                      | UBAS<br>H3A  | 21        | NM_0189<br>61.2<br>36/         | 0.564                  | 0.444                    | 0.475                  | 0.537                                         | 0.703                                      | 0.169                            | 0.027                                     | 0.04                                               | 0.035                                                     | 0.05                                                    | 0.602                                | 0.673                              | 0.038                                   | 0.521                 | -0.483                             |
| cg25712<br>380                      | GRAP2        | 22        | NM_0048<br>10.2<br>37/         | 0.633                  | 0.602                    | 0.639                  | 0.824                                         | 0.83                                       | 0.506                            | 0.097                                     | 0.093                                              | 0.089                                                     | 0.1                                                     | 0.179                                | 0.310                              | 0.095                                   | 0.565                 | -0.470                             |
| cg19812<br>619                      | ITGB7        | 12        | NM_0008<br>89.1<br>38/         | 0.819                  | 0.651                    | 0.785                  | 0.874                                         | 0.897                                      | 0.645                            | 0.3374                                    | 0.275                                              | 0.199                                                     | 0.177                                                   | 0.608                                | 0.4337                             | 0.247                                   | 0.714                 | -0.467                             |
| cg02600<br>394                      | TXK          | 4         | NM_0033<br>28.1                | 0.775                  | 0.576                    | 0.682                  | 0.867                                         | 0.909                                      | 0.082                            | 0.036                                     | 0.075                                              | 0.051                                                     | 0.354                                                   | 0.376                                | 0.484                              | 0.129                                   | 0.594                 | -0.465                             |

SEQUENCE LISTING

[0045]

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## REFERENCES CITED IN THE DESCRIPTION

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- **HAMERMAN JAPAGE STPULLEN AM.** Distinct methylation states of the CD8 beta gene in peripheral T cells and intraepithelial lymphocytes J Immunol., 1997, vol. 159, 31240-6 [0008]
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## PATENTKRAV

1. Fremgangsmåde til identifikation af CD3<sup>+</sup> CD4<sup>+</sup> og/eller CD3<sup>+</sup> CD8<sup>+</sup> naive og/eller hukommelses-T-lymfocytter i en af et pattedyr afledt prøve, der omfatter T-celler,
  - 5 omfattende
    - a) analyse af methyleringsstatus for mindst én CpG-stilling i den T-lymfocyt-specifikke demethylerede region, som er placeret i amplicon 1405 (SEQ ID NO: 6), amplicon 1406 (SEQ ID NO: 7) og/eller amplicon 1408 (SEQ ID NO: 8), og
    - 10 b) identifikation af CD3<sup>+</sup> CD4<sup>+</sup> og/eller CD3<sup>+</sup> CD8<sup>+</sup> naive og/eller hukommelses-T-lymfocytter på grundlag af den nævnte methyleringsstatus, idet demethylering af mindst én CpG-stilling i ampliconet til mindst 90% er tegn på en CD3<sup>+</sup> CD4<sup>+</sup> og/eller CD3<sup>+</sup> CD8<sup>+</sup> naiv og/eller hukommelses-T-lymfocytcelle.
- 15 2. Fremgangsmåde ifølge krav 1, ved hvilken den mindst ene CpG-stilling i prøven demethyleres til mere end 91%, fortrinsvis mere end 92% og især mere end 95%.
  3. Fremgangsmåde ifølge krav 1 eller 2, ved hvilken analysen af demethyleringsstatussen omfatter en fremgangsmåde valgt blandt methyleringsspecifikke
    - 20 enzymatiske fordøjelser, bisulfit-sekvensbestemmelse, analyse valgt blandt promotor-methylering, CpG-ø-methylering, MSP, HeavyMethyl, MethyLight, Ms-SNuPE eller andre fremgangsmåder, der beror på påvisning af mangfoldiggjort DNA.
  4. Fremgangsmåde ifølge et hvilket som helst af kravene 1 til 3, som endvidere
    - 25 omfatter en methyleringsanalyse af mindst én CpG-stilling i generne for CD4<sup>+</sup> og/eller CD8, især CD8-β, eller i generne for GNGT2, CRTAM, IL2RB og ZBTB32 eller FLJ00060, FLJ38379, PPP6C, CD226, ZBTB7B og TNFAIP8 eller i generne SLA2, CHRNA3, C16orf24, LCK, FASLG, CD7, SIT1, IL32, CXCR6, UBASH3A, GRAP2, ITGB7 eller TXK.
    - 30
  5. Fremgangsmåde ifølge et hvilket som helst af kravene 1 til 4, hvilken fremgangsmåde er egnet til rutineanvendelse, f.eks. på en DNA-chip.
  6. Fremgangsmåde ifølge et hvilket som helst af kravene 1 til 5, ved hvilken
    - 35 identifikationen omfatter skelnen af lymfocytterne fra alle betydningsfulde typer blod-legemer eller ikke-blod-celler i perifert blod.

7. Fremgangsmåde ifølge et hvilket som helst af kravene 1 til 6, ved hvilken prøven er valgt blandt en human legemsvæske, herunder humane blodprøver, eller en vævs-, organ- eller celletype-blodprøve, en prøve af blod-lymfocytter eller en fraktion deraf.

5

8. Fremgangsmåde ifølge et hvilket som helst af kravene 1 til 7, som endvidere omfatter det trin at drage konklusion med hensyn til menneskets immunstatus på grundlag af T-lymfocytterne som identificeret.

10 9. Fremgangsmåde ifølge et hvilket som helst af kravene 1 til 8, ved hvilken mennesket lider af eller er udsat for at lide af autoimmunsygdomme, transplantat-afstødninger, cancer og/eller allergi.

15 10. Anvendelse af et sæt, der omfatter materialer til udøvelse af fremgangsmåden ifølge krav 1, til identifikation af CD3<sup>+</sup> CD4<sup>+</sup> og/eller CD3<sup>+</sup> CD8<sup>+</sup> naive og/eller hukommelses-T-lymfocytter i en prøve, idet sættet omfatter:

a) et bisulfitreagens og

20 b) materialer til udførelse af en metyleringsanalyse med hensyn til CpG-stillinger i TLSDR-regionen valgt blandt CpG-stilling 1, 2, 3, 4, 5, 6, 7, 8, 9 og 10 som talt numerisk fra 5'-enden af den sekvens, der er placeret i amplicon 1405 (SEQ ID NO: 6), CpG-stilling 1, 2, 3, 4, 5, 6, 7 og 8 i den sekvens, der er placeret i amplicon 1406 (SEQ ID NO: 7), og CpG-stilling 1, 2, 3, 4, 5, 6 og 7 i den sekvens, der er placeret i amplicon 1408 (SEQ ID NO: 8), til identifikation af CD3<sup>+</sup> CD4<sup>+</sup> og/eller CD3<sup>+</sup> CD8<sup>+</sup> naive og/eller hukommelses-T-lymfocytter i  
25 et pattedyr.

DRAWINGS

Figure 1

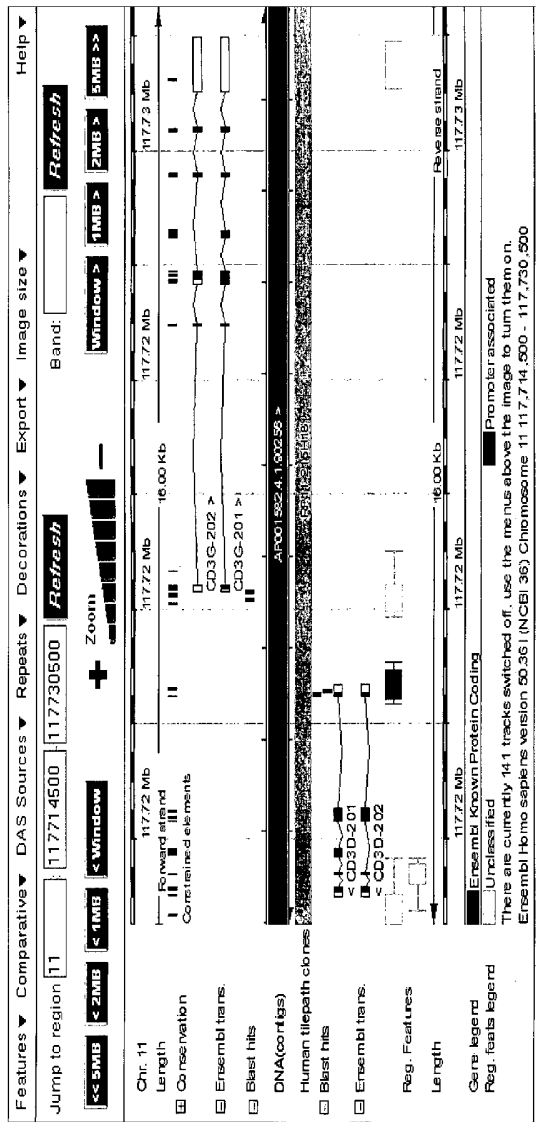


Figure 2 (Ref-Seq is SEQ ID No. 6)

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Monocytes      -----AGCCTCTTT-ATAA-TCTCAAAAAA 24
NK-Cells      -----AGCCTCTTT-ATAA-TCTCAAAAAA 24
AMP1405 Ref-Seq  TTATTCACCTATTACCTCCAAACGCCTCTTTTCATAA-TCTCAAAAAA 49
Granulocytes   -----CGCCTCTTT-ATAA-TCTCAAAAAA 24
mem. T-cells   -----TACCTCTTT-ATAAATCTCAAAAAA 25
mem. CTL       -----GACCTCTTT-ATAA-TCTCAAAAAA 24
naive CTL      -----CGCCTCTTT-ATA--TCTAAAAA-- 22
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Monocytes      TAATAAAACCAATACCGTATCTCAGCCTATAATCCCAACACTTTAAAA 74
NK-Cells      TAATAAAACCAATACCGTATCTCAGCCTATAATCCCAACACTTTAAAA 74
AMP1405 Ref-Seq TAATAAAACCAATACCGTATCTCAGCCTATAATCCCAACACTTTAAAA 99
Granulocytes   TAATAAAACCAATACCGTATCTCAGCCTATAATCCCAACACTTTAAAA 74
mem. T-cells   TAATAAAACCAATACCATATCTCAGCCTATAATCCCAACACTTTAAAA 75
mem. CTL       TAATAAAACCAATACCATATCTCAGCCTATAATCCCAACACTTTAAAA 74
naive CTL      --TATAAACCAATACCGTATCTCAGCCTATAATCCCAACACTT-AAAA 68
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Monocytes      AACTAAAACCAATAAATCAGAAATCAAAATTCG-AAACCAACCTAAC 123
NK-Cells      AACTAAAACCAATAAATCAGAAATCAAAATTCG-AAACCAACCTAAC 123
AMP1405 Ref-Seq AACTAAAACCAATAAATCAGAAATCAAAATTCG-AAACCAACCTAAC 148
Granulocytes   AACTAAAACCAATAAATCAGAAATCAAAATTCG-AAACCAACCTAAC 123
mem. T-cells   AACTAAAACCAATAAATCAGAAATCAAAATTCG-AAACCAACCTAAC 124
mem. CTL       AACTAAAACCAATAAATCAGAAATCAAAATTCG-AAACCAACCTAAC 123
naive CTL      AACTAAAACCAATAAATCAGAAATCAAAATTCGAAACCAACCTAAC 118
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Monocytes      AACAAATAAACCCCGTCTCTACTAAAAATACAAATTAACCGAAGCTT 173
NK-Cells      AACAAATAAACCCCGTCTCTACTAAAAATACAAATTAACCGAAGCTT 173
AMP1405 Ref-Seq AACAAATAAACCCCGTCTCTACTAAAAATACAAATTAACCGAAGCTT 198
Granulocytes   AACAAATAAACCCCGTCTCTACTAAAAATACAAATTAACCGAAGCTT 173
mem. T-cells   AACAAATAAACCCCGTCTCTACTAAAAATACAAATTAACCGAAGCTT 174
mem. CTL       AACAAATAAACCCCGTCTCTACTAAAAATACAAATTAACCGAAGCTT 173
naive CTL      AACAAATAAACCCCGTCTCTACTAAAAATACAAATTAACCGAAGCTT 168
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Monocytes      ACTAACACGACCTATAATCTCAACTACTCAAAAACTAAACAAAAAA 223
NK-Cells      ACTAACACGACCTATAATCTCAACTACTCAAAAACTAAACAAAAAA 223
AMP1405 Ref-Seq ACTAACACGACCTATAATCTCAACTACTCAAAAACTAAACAAAAAA 248
Granulocytes   ACTAACACGACCTATAATCTCAACTACTCAAAAACTAAACAAAAAA 223
mem. T-cells   ACTAACACGACCTATAATCTCAACTACTCAAAAACTAAACAAAAAA 224
mem. CTL       ACTAACACGACCTATAATCTCAACTACTCAAAAACTAAACAAAAAA 223
naive CTL      ACTAACACGACCTATAATCTCAACTACTCAAAAACTAAACAAAAAA 218
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Monocytes      TCGCTTAAACCCCGAAAAATAAAATTAACAATAAACTAAATAACGCCACT 273
NK-Cells      TCGCTTAAACCCCGAAAAATAAAATTAACAATAAACTAAATAACGCCACT 273
AMP1405 Ref-Seq TCGCTTAAACCCCGAAAAATAAAATTAACAATAAACTAAATAACGCCACT 298
Granulocytes   TCGCTTAAACCCCGAAAAATAAAATTAACAATAAACTAAATAACGCCACT 273
mem. T-cells   TCACTTAAACCCCGAAAAATAAAATTAACAATAAACTAAATAACGCCACT 274
mem. CTL       TCACTTAAACCCCGAAAAATAAAATTAACAATAAACTAAATAACGCCACT 273
naive CTL      TCACTTAAACCCCGAAAAATAAAATTAACAATAAACTAAATAACGCCACT 268
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Monocytes      ACACTCCAACCTAAACAACAAATAAACTCTATCTCAAAAAA 323
NK-Cells      ACACTCCAACCTAAACAACAAATAAACTCTATCTCAAAAAA 323
AMP1405 Ref-Seq ACACTCCAACCTAAACAACAAATAAACTCTATCTCAAAAAA 348
Granulocytes   ACACTCCAACCTAAACAACAAATAAACTCTATCTCAAAAAA 323
mem. T-cells   ACACTCCAACCTAAACAACAAATAAACTCTATCTCAAAAAA 324
mem. CTL       ACACTCCAACCTAAACAACAAATAAACTCTATCTCAAAAAA 323

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naive CTL      ACACTCCAACCTAAACAACAAAATAAACTCTATCTCAAAAAAAAAAAAA 318
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Monocytes     AAAAAAAAAA-AAAAAAAAATTCTAAAAAAAAAACCAAAAAAAAAAAAACT 372
NK-Cells      AAAAAAAAAA-AAAAAAAAATTCCAAAAAAAAAACCAAAAAAAAAAAAACT 372
AMP1405 Ref-Seq AAAAAAAAAATAAAAAAAAAATTCTAAATAAAACCTAAACTAAATAACT 398
Granulocytes  AAAAAAAAAA-AAAAAAAAATTCCAAAAAAAAAACCAAAAAAAAAAAAACT 372
mem. T-cells  AAAAAAAAAA-AAAAAAAAATTCCAAAAAAAAAACCAAAAAAAAAAAAACT 373
mem. CTL      AAAAAAAAAA-AAAAAAAAATTCCAAAAAAAAAACCAAAAAAAAAAAAACT 372
naive CTL     AAAAAAAAAA-AAAAAAAAATTCCAAAAAAAAAACCAAAAAAAAAAAAACT 367
                ***** * ** *
Monocytes     TTCCCTTTAAAAAACCCCCCAAAATTT----- 402
NK-Cells      TTCCCTTTAAAAAACCCCCCA----- 394
AMP1405 Ref-Seq TTCCATTTAAAAATCCAACCCCAACATCTAAAAATC 435
Granulocytes  TTCCCTTTAAAAAACCCCCCAAAAA----- 399
mem. T-cells  TTCCCTTTAAAAAACCCCCCA----- 394
mem. CTL      TTCCCTTTAAAAAACCCCCCA----- 396
naive CTL     TTCCCTTTAAAAAACCCCCCA----- 387
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```

**Figure 3** (Ref-Seq is SEQ ID No. 7, reverse)

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Granulocytes      -----CTGATTGTTA--TAGGGACGTTA--A 22
NK-Cells          -----ATGATTGTTAA--TAGGGACGTTA--A 23
mem. T-cells      -----CTATTGATGGGAGAAGTGAGGT-GTTAATA 30
naive CTL         -----CTATTGATGGGAGAAGTGAGGTGTTAATA 31
mem. CTL          -----CATTGATGGGAAGTAGAGGATTGATA--A 27
naive T-cells     -----ATTGGTATCTGTTAAGTATGGCATGCTGA--A 30
Monocytes         -----CTG-ATTGTTAA--TAGGGACGTTA--A 23
AMP1406 Ref-Seq   TTTAGGTTGTGTGTAATGTGGTGTATTGTTAA--TAGGGACGTTA--A 46
                  *           *           **  *

Granulocytes      AGTTTAGGTTATTTTTTTATATTTTTTGTAGTTTTTGTGTTAGAGATA 72
NK-Cells          AGTTTAGGTTATTTTTTTATATTTTTTGTAGTTTTTGTGTTAGAGATA 73
mem. T-cells      AGTTTAGGTTATTTTTTTATATTTTTTGTAGTTTTTGTGTTAGAGATA 80
naive CTL         AGTTTAGGTTATTTTTTTATATTTTTTGTAGTTTTTGTGTTAGAGATA 81
mem. CTL          AGTTTAGGTTATTTTTTTATATTTTTTGTAGTTTTTGTGTTAGAGATA 77
naive T-cells     AGTTTAGGTTATTTTTTTATATTTTTTGTAGTTTTTGTGTTAGAGATA 80
Monocytes         AGTTTAGGTTATTTTTTTATATTTTTTGTAGTTTTTGTGTTAGAGATA 73
AMP1406 Ref-Seq   AGTTTAGGTTATTTTTTTATATTTTTTGTAGTTTTTGTGTTAGAGATA 96
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Granulocytes      GAGTAATTTATATCGTTTTTTTTTATTTTATTTTATTTTATTTTATTT 122
NK-Cells          GAGTAATTTATATCGTTTTTTTTTATTTTATTTTATTTTATTTTATTT 123
mem. T-cells      GAGTAATTTATATCGTTTTTTTTTATTTTATTTTATTTTATTTTATTT 130
naive CTL         GAGTAATTTATATCGTTTTTTTTTATTTTATTTTATTTTATTTTATTT 131
mem. CTL          GAGTAATTTATATCGTTTTTTTTTATTTTATTTTATTTTATTTTATTT 127
naive T-cells     GAGTAATTTATATCGTTTTTTTTTATTTTATTTTATTTTATTTTATTT 130
Monocytes         GAGTAATTTATATCGTTTTTTTTTATTTTATTTTATTTTATTTTATTT 123
AMP1406 Ref-Seq   GAGTAATTTATATCGTTTTTTTTTATTTTATTTTATTTTATTTTATTT 146
                  *****

Granulocytes      TTGAAAATTTTTTATTATTAAACGGTAGAAAAGTAGAGAAGTAGATATTTT 172
NK-Cells          TTGAAAATTTTTTATTATTAAACGGTAGAAAAGTAGAGAAGTAGATATTTT 173
mem. T-cells      TTGAAAATTTTTTATTATTAAACGGTAGAAAAGTAGAGAAGTAGATATTTT 180
naive CTL         TTGAAAATTTTTTATTATTAAACGGTAGAAAAGTAGAGAAGTAGATATTTT 181
mem. CTL          TTGAAAATTTTTTATTATTAAACGGTAGAAAAGTAGAGAAGTAGATATTTT 177
naive T-cells     TTGAAAATTTTTTATTATTAAACGGTAGAAAAGTAGAGAAGTAGATATTTT 180
Monocytes         TTGAAAATTTTTTATTATTAAACGGTAGAAAAGTAGAGAAGTAGATATTTT 173
AMP1406 Ref-Seq   TTGAAAATTTTTTATTATTAAACGGTAGAAAAGTAGAGAAGTAGATATTTT 196
                  *****

Granulocytes      TAGTTTTTTTTTATTTTTTTTTTTTCCGGTTTTTGGGATTAATTAAGGGG 222
NK-Cells          TAGTTTTTTTTTATTTTTTTTTTTTCCGGTTTTTGGGATTAATTAAGGGG 223
mem. T-cells      TAGTTTTTTTTTATTTTTTTTTTTTCCGGTTTTTGGGATTAATTAAGGGG 230
naive CTL         TAGTTTTTTTTTATTTTTTTTTTTTCCGGTTTTTGGGATTAATTAAGGGG 231
mem. CTL          TAGTTTTTTTTTATTTTTTTTTTTTCCGGTTTTTGGGATTAATTAAGGGG 227
naive T-cells     TAGTTTTTTTTTATTTTTTTTTTTTCCGGTTTTTGGGATTAATTAAGGGG 230
Monocytes         TAGTTTTTTTTTATTTTTTTTTTTTCCGGATTTGTGAGTTAGTAGGGGG 223
AMP1406 Ref-Seq   TAGTTTTTTTTTATTTTTTTTTTTTCCGGATTTGTGAGTTAGTTAGGGG 246
                  *****

Granulocytes      GGGGTATTTTTTTTTTAGCTTGAAATTCGGGGATTGGGTTTTATTTATG 272
NK-Cells          GGGGTGTTTTTTTTTGGGTTGATAGTTCCGGGATTTGGTTTTATTTATG 273
mem. T-cells      GGGGTGTTTTTTTTTGGGTTGATAGTTCCGGGATTTGGTTTTATTTATG 280
naive CTL         GGGGAATTTTTTTTTTAGGTTGAAATTTGGGGGATTTGGTTTTATTTATG 281
mem. CTL          GGGGAATTTTTTTTTTAGGTTGAAATTTGGGGGATTTGGTTTTATTTATG 277
naive T-cells     GGGGAATTTTTTTTTTAGGTTGAAATTTGGGGGATTTGGTTTTATTTATG 280
Monocytes         AGGGTAGTTTTTTATTTAGGTTGATAGTTCCGGTATTTGGTTTAATTTATT 273
AMP1406 Ref-Seq   AGGGTAGTTTTTTATTTAGGTTGATAGTTCCGGTATTTGGTTTTATTTATT 296
                  ***  *

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|                 |                                                     |     |
|-----------------|-----------------------------------------------------|-----|
| Granulocytes    | GGAGGAAATTCCTGGGG-AAAGGAAAAAAAACCC--TTTTTTTTTGGGTT  | 319 |
| NK-Cells        | GGAGGATTCCTGGGG-AAAGGAAAAAAAACCC--TTTTTTTTTGGGTT    | 320 |
| mem. T-cells    | GGAGGATTTTTGTGGGG-AAAGGAAATAAAATTT--TTTTTTTTTGGGTT  | 327 |
| naive CTL       | GGAGGATTTTTGTGGGG-AAAGGAAAAAAAATTTT--TTTTTTTTTGGGTT | 328 |
| mem. CTL        | GGAGAAATTTTGTGGGG-AAAGGAAATAAATTTT--TTTTTTTTTGGGTT  | 324 |
| naive T-cells   | GGAGGATTTTTGTGGGG-AAAGGAAAAAAAATTTT--TTTTTTTTTCGGTT | 327 |
| Monocytes       | GAATGACTTTCGTTGGGGAGTGAATATAGTACGTTTTTTTTGGTTT      | 323 |
| AMPl406 Ref-Seq | GGATGAGTTTCGTTGGG-AGATGGAATATAGTACG--TTTTTTTTTGGTTT | 344 |
|                 | * * * * *                                           |     |

|                 |                                                    |     |
|-----------------|----------------------------------------------------|-----|
| Granulocytes    | GGGTTTGGGTTATTTTTTTTCGGAAGGG---AAGGTTTTTTAAGGGGGG  | 366 |
| NK-cells        | GGGTTTGGGTTATTTTTTTTCGGAAGGG---AAGGTTTTTTAAGGGGGG  | 367 |
| mem. T-cells    | G-----                                             | 328 |
| naive CTL       | GGGTTTGGGTTATTTTTTTTCGAAGGG---AAGGTTTTTTTGGGGGGG   | 375 |
| mem. CTL        | GGGTTTGGGTTTTTTTTTTTTGGGAAGGG---AAGGTTTTTTTGGGGGGG | 371 |
| naive T-cells   | CGGTTTGGGTTATTTTTTTTCGGAAGGG---AAGGTTTTTTTGGGGGGG  | 374 |
| Monocytes       | CGGTATCGGTATTTTTTTTCGGAAGGGGTAAGGGTATTTAGTGCGGG    | 373 |
| AMP1406 Ref-Seq | GGTATGGTTATTTTTTTTCGTAAGGT---AAGGTTATTTAGTGCGGT    | 391 |
|                 | *                                                  |     |

|                 |                                                   |     |
|-----------------|---------------------------------------------------|-----|
| Granulocytes    | --GGGGGAAGGGTTTTG-----                            | 382 |
| NK-Cells        | --GGGGGAAGGGTTTTAAAGGAAA--                        | 391 |
| -----           |                                                   |     |
| mem. T-cells    |                                                   |     |
| naive CTL       | --GGGGGAAGGGCTT-----                              | 388 |
| mem. CTL        | --GGGGGAGGGCTTTAAAGGAATTTTTGGG--                  | 401 |
| naive T-cells   | --GGGGGAAGGGCTT-----                              | 387 |
| Monocytes       | TGGGGGAAGGGATTTTGGAGAGGGATTATATTGATGGGGAGTGAAGGTT | 423 |
| AMP1406 Ref-Seq | --GGGGGAAGGGATT--GAGAGGGATATTATTGATGGG-ACTGAGGTTT | 436 |

**Figure 4** (Ref-Seq is SEQ ID No. 7)

|                 |                                                         |     |
|-----------------|---------------------------------------------------------|-----|
| Monocytes       | -----TATCCCTCTCA--AATCCCTTCCCCCA                        | 25  |
| NK-Cells        | -----TATCCCTCTCA--AATCCCTTCCCCCA                        | 25  |
| AMPl406 Ref-Seq | ATAAACCTCACTCCCATCAATATATCCCTTCA--AATCCCTTCCCCCA        | 48  |
| Granulocytes    | -----GTATCCCTTCTCA--AATCCCTTCCCCCA                      | 26  |
| mem. T-cells    | -----GCCATCTTACCCA--CAACCTCTAACCCCA                     | 28  |
| naive CTL       | -----GCCATCTTACCCA--CAACCTCTAACCCCA                     | 27  |
| mem. CTL        | -----TATATCTCTCACTCACTCTCCATCCCCA                       | 29  |
| naive T-cells   | -----CATCCCTCTCT--AATGCCCTTCCCCCA                       | 25  |
|                 | *** * *                                                 |     |
| Monocytes       | CCCACCTAAAAAACCCTTACCTTACGAAAAAAAAAATACCAATACCAAC       | 75  |
| NK-Cells        | CCCACCTAAAAAACCCTTACCTTACGAAAAAAAAAATACCAATACCAAC       | 75  |
| AMPl406 Ref-Seq | CCCACCTAAAAAACCCTTACCTTACGAAAAAAAAAATACCAATACCAAC       | 98  |
| Granulocytes    | CCCACCTAAAAAACCCTTACCTTACGAAAAAAAAAATACCAATACCAAC       | 76  |
| mem. T-cells    | CCCACCTAAAAAACCCTTACCTTACGAAAAAAAAAATACCAATACCAAC       | 77  |
| naive CTL       | CCCACCTAAAAAACCCTTACCTTACGAAAAAAAAAATACCAATACCAAC       | 78  |
| mem. CTL        | CCCACCTAAAAAACCCTTACCTTACGAAAAAAAAAATACCAATACCAAC       | 79  |
| naive T-cells   | CCCACCTAAAAAACCCTTACCTTACGAAAAAAAAAATACCAATACCAAC       | 75  |
|                 | * * * * *                                               |     |
| Monocytes       | CAAAAAAAAAACGTACTATATTCATCTCCCAACGAACTCATCCAATAAA       | 125 |
| NK-Cells        | CAAAAAAAAAACGTACTATATTCATCTCCCAACGAACTCATCCAATAAA       | 125 |
| AMPl406 Ref-Seq | CAAAAAAAAAACGTACTATATTCATCTCCCAACGAACTCATCCAATAAA       | 148 |
| Granulocytes    | CAAAAAAAAAACGTACTATATTCATCTCCCAACGAACTCATCCAATAAA       | 126 |
| mem. T-cells    | CAAAAAAAAAACGTACTATATTCATCTCCCAACGAACTCATCCAATAAA       | 128 |
| naive CTL       | CAAAAAAAAAACGTACTATATTCATCTCCCAACGAACTCATCCAATAAA       | 127 |
| mem. CTL        | CAAAAAAAAAACGTACTATATTCATCTCCCAACGAACTCATCCAATAAA       | 129 |
| naive T-cells   | CAAAAAAAAAACGTACTATATTCATCTCCCAACGAACTCATCCAATAAA       | 125 |
|                 | *****                                                   |     |
| Monocytes       | TAAACCAAAATCACCAGAACTATCAACCTAAATAAAACATCCCTCCCGTA      | 175 |
| NK-Cells        | TAAACCAAAATCACCAGAACTATCAACCTAAATAAAACATCCCTCCCGTA      | 175 |
| AMPl406 Ref-Seq | TAAACCAAAATCACCAGAACTATCAACCTAAATAAAACATCCCTCCCGTA      | 198 |
| Granulocytes    | TAAACCAAAATCACCAGAACTATCAACCTAAATAAAACATCCCTCCCGTA      | 176 |
| mem. T-cells    | TAAACCAAAATCACCAGAACTATCAACCTAAATAAAACATCCCTCCCGTA      | 178 |
| naive CTL       | TAAACCAAAATCACCAGAACTATCAACCTAAATAAAACATCCCTCCCGTA      | 177 |
| mem. CTL        | TAAACCAAAATCACCAGAACTATCAACCTAAATAAAACATCCCTCCCGTA      | 179 |
| naive T-cells   | TAAACCAAAATCACCAGAACTATCAACCTAAATAAAACATCCCTCCCGTA      | 175 |
|                 | *****                                                   |     |
| Monocytes       | ACTAATCTCACAATACCGAAAAAAAAAAAAATAAAAAAAAAACTTAAAAAT     | 225 |
| NK-Cells        | ACTAATCTCACAATACCGAAAAAAAAAAAAATAAAAAAAAAACTTAAAAAT     | 225 |
| AMPl406 Ref-Seq | ACTAATCTCACAATACCGAAAAAAAAAAAAATAAAAAAAAAACTTAAAAAT     | 218 |
| Granulocytes    | ACTAATCTCACAATACCGAAAAAAAAAAAAATAAAAAAAAAACTTAAAAAT     | 226 |
| mem. T-cells    | ACTAATCTCACAATACCGAAAAAAAAAAAAATAAAAAAAAAACTTAAAAAT     | 227 |
| naive CTL       | ACTAATCTCACAATACCGAAAAAAAAAAAAATAAAAAAAAAACTTAAAAAT     | 228 |
| mem. CTL        | ACTAATCTCACAATACCGAAAAAAAAAAAAATAAAAAAAAAACTTAAAAAT     | 229 |
| naive T-cells   | ACTAATCTCACAATACCGAAAAAAAAAAAAATAAAAAAAAAACTTAAAAAT     | 225 |
|                 | *****                                                   |     |
| Monocytes       | TTTTCTCTTCTTCTTCTCTCCCGTTAAAAAAAATAATTTTCAAAAAAAA       | 275 |
| NK-Cells        | TTTTCTCTTCTTCTTCTCTCCCGTTAAAAAAAATAATTTTCAAAAAAAA       | 275 |
| AMPl406 Ref-Seq | TTTCTACTCTCTACTCTTCTACCGTTTATATATAAAAAATTTTCAAAAAAAA    | 298 |
| Granulocytes    | TTTTTTTTTTTTTTTTTTTTTCTCCCGTTATATAAAAAATTTTAAAAATAAA    | 276 |
| mem. T-cells    | TTTTTTTTTTTTTTTTTTTTTCTCCCGTTTAAAAAAAATAATTTTAAAAATAAA  | 278 |
| naive CTL       | TTCTCTTCTCTCTCTTTTCTCCCGTTAAAAAAAATAATTTTAAAAATAAA      | 279 |
| mem. CTL        | TTTTCTTTTTTTTTTTTTTTTTTCTCCCGTTAAAAAAAATAATTTTAAAAATAAA | 277 |
| naive T-cells   | TTTTCTTTTTTTTTTTTTTTTTTCTCCCGTTAAAAAAAATAATTTTAAAAATAAA | 275 |

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Monocytes      AATAACCTAAAAAAAAAAAAAAAAAACCGTTTAAATTCCTTTTTTTT 325
NK-Cells       AATAACCTAAAAATAAAAAAAAAAAAAAACCGTTTAAATTCCTTTTTTTT 325
AMP1406 Ref-Seq AATAAACTAAAAATAAAATAAAAAAAAAACGATATAAATTACTCTATCTC 348
Granulocytes   AATAACCTAAAAATAAAATAAAAAAAAAAACCGTTTAAATTCCTTTTTTTT 326
mem. T-cells   AAAAACCTAAAAAAAAAAAAAAAAAACCATTTTAAATTCCTTTTTTTT 328
naive CTL      AAAAACCTAAAAAAAAAAAAAAAAAACCATTTTAAATTCCTTTTTTTT 327
mem. CTL       AAAAACCTAAAAAAAAAAAAAAAAAACCGTTTAAATTCCTTTCTT 329
naive T-cells  ATTAACCTAAAAATAAAAAAAAAAACCATTTTAAATTTCTTTTTTTT 325
*  *  *  *  *  *  *  *  *  *  *  *  *  *  *  *  *  *  *  *  *  *

Monocytes      TAACCAAAAAATTAACAAAAATTTAAAAAAATACCCAAATTTTACCG 375
NK-Cells       TAACCAAAAACTTAACAAAAATTTAAAAAAACCCTAACTTTACCG 375
AMP1406 Ref-Seq TAACCAAAAACTTAACAAAAATATAAAAAATAACCTAACTTTACCG 398
Granulocytes   TAACCAAAAACTTAACAAAAATTTAAAAAAATACCCTAACTTTACCG 376
mem. T-cells   TAACCAAAAACTTAACAAAAATTTAAAAAAATACCCAACTTTAACC 377
naive CTL      TAACCAAAAACTTAACAAAAATTTAAAAAAATACCCAACTTTTACC 376
mem. CTL       TAACCAAAAACTTAACAAAAATTTAAAAAAATACCCAACTTTTACC 378
naive T-cells  TAACCAAAAACTTAACAAAAATTTAAAAAAATACCCAACTTTTACC 374
***  *  *  *  *  *  *  *  *  *  *  *  *  *  *  *  *  *  *  *  *  *

Monocytes      CCCCTTTAAACAATCCACCCACTTTTCCCCACACCTAAAAA- 416
NK-Cells       CCCCTTTAAACAATCCACCCCTTTTCCCCCACCTAAAA- 416
AMP1406 Ref-Seq TCCCTTTAAACAATCAACACACATTTACACACAACCTAAAA- 438
Granulocytes   CCCCTTTAAAAAAACCCACCCCTTTTCCCCCACCCAAAAA 418
mem. T-cells   CCCCTTTAAAAAAACCCACCCCTTTTCCCCCCCCCAAAAA 419
naive CTL      CCCCTTTAAAAAAACCCACCCCTTTTCCCCCCCCCAAAAA 418
mem. CTL       CCCCTTTAAAAAAACCCACCCCTTTTCCCCCCCCCAAAAA- 419
naive T-cells  CCCCTTTAAAAAAACCCACCCCTTTTCCCCCCCCCAAAAA 416
*  *  *  *  *  *  *  *  *  *  *  *  *  *  *  *  *  *  *  *  *  *

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Figure 5 (Ref-Seq is SEQ ID No. 8)

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naive Th-cells      -----CTATAACACACAACTAACACAAATAA 29
mem. Th-cells      -----CTATAACACACAACTAACACAAATAA 29
mem. CTL            -----CTATAACACACAACTAACACAAATAA 29
naive CTL           -----GTATAACACACAACTAACACAAATAA 29
AMPl408 Ref-Seq    AATCCCTCCTAATTCATTACCTACACACACAACTAACACAAATAA 50
Granulocytes       -----TATAACACACAACTAACACAAATAA 28
Monocytes          -----TATAACACACAACTAACACAAATAA 28
NK-Cells           -----GATAACACACAACTAACACAAATAA 28
                    * *****

naive Th-cells      CAACTAACTACAATCCTAACAACTAATAACAAAAACATTTATCTCCCTCA 79
mem. Th-cells      CAACTAACTACAATCCTAACAACTAATAACAAAAACATTTATCTCCCTCA 79
mem. CTL            CAACTAACTACAATCCTAACAACTAATAACAAAAACATTTATCTCCCTCA 79
naive CTL           CAACTAACTACAATCCTAACAACTAATAACAAAAACATTTATCTCCCTCA 79
AMPl408 Ref-Seq    CAACTAACTACGATCCTAACAACTAATAACAAAAACATTTATCTCCCTCA 100
Granulocytes       CAACTAACTACGATCCTAACAACTAATAACAAAAACATTTATCTCCCTCA 78
Monocytes          CAACTAACTACGATCCTAACAACTAATAACAAAAACATTTATCTCCCTCA 78
NK-Cells           CAACTAACTACGATCCTAACAACTAATAACAAAAACATTTATCTCCCTCA 78
                    *****

naive Th-cells      TAAAAAAACAATCCCAAACCATCTCCACCCCAACATCCATTACAATTCC 129
mem. Th-cells      TAAAAAAACAATCCCAAACCATCTCCACCCCAACATCCATTACAATTCC 129
mem. CTL            TAAAAAAACAATCCCAAACCATCTCCACCCCAACATCCATTACAATTCC 129
naive CTL           TAAAAAAACAATCCCAAACCATCTCCACCCCAACATCCATTACAATTCC 129
AMPl408 Ref-Seq    TAAAAAAACGATCCCAAACCATCTCCACCCCAACATCCATTACGATTCC 150
Granulocytes       TAAAAAAACGATCCCAAACCATCTCCACCCCAACATCCATTACGATTCC 128
Monocytes          TAAAAAAACGATCCCAAACCATCTCCACCCCAACATCCATTACGATTCC 128
NK-Cells           TAAAAAAACGATCCCAAACCATCTCCACCCCAACATCCATTACGATTCC 128
                    *****

naive Th-cells      CTATACAAAATAAATCTCTAAATAAAAATCCAACACTCTCTCCCTCTTCT 179
mem. Th-cells      CTATACAAAATAAATCTCTAAATAAAAATCCAACACTCTCTCCCTCTTCT 179
mem. CTL            CTATACAAAATAAATCTCTAAATAAAAATCCAACACTCTCTCCCTCTTCT 179
naive CTL           CTATACAAAATAAATCTCTAAATAAAAATCCAACACTCTCTCCCTCTTCT 179
AMPl408 Ref-Seq    CTATACAAAATAAATCTCTAAATAAAAATCCAACACTCTCTCCCTCTTCT 200
Granulocytes       CTATACAAAATAAATCTCTAAATAAAAATCCAACACTCTCTCCCTCTTCT 178
Monocytes          CTATACAAAATAAATCTCTAAATAAAAATCCAACACTCTCTCCCTCTTCT 178
NK-Cells           CTATACAAAATAAATCTCTAAATAAAAATCCAACACTCTCTCCCTCTTCT 178
                    *****

naive Th- cells     TCCCCACCACCTTCACCCCTCCTTAACAAAAAACAAAAACATCTACACC 229
mem. Th-cells      TCCCCACCACCTTCACCCCTCCTTAACAAAAAACAAAAACATCTACACC 229
mem. CTL            TCCCCACCACCTTCACCCCTCCTTAACAAAAAACAAAAACATCTACACC 229
naive CTL           TCCCCACCACCTTCACCCCTCCTTAACAAAAAACAAAAACATCTACACC 229
AMPl408 Ref-Seq    TCCCCACCACCTTCACCCCTCCTTAACGAAAAAACAAAAACATCTACACC 250
Granulocytes       TCCCCACCACCTTCACCCCTCCTTAACGAAAAAACAAAAACATCTACACC 228
Monocytes          TCCCCACCACCTTCACCCCTCCTTAACGAAAAAACAAAAACATCTACACC 228
NK-Cells           TCCCCACCACCTTCACCCCTCCTTAACGAAAAAACAAAAACATCTACACC 228
                    *****

naive Th-cells      TACAACCTACTAAAACCCCTACTACTCACACTTACAACAAAAATAAAA 279
mem. Th-cells      TACAACCTACTAAAACCCCTACTACTCACACTTACAACAAAAATAAAA 279
mem. CTL            TACAACCTACTAAAACCCCTACTACTCACACTTACAACAAAAATAAAA 279
naive CTL           TACAACCTACTAAAACCCCTACTACTCACACTTACAACAAAAATAAAA 279
AMPl408 Ref-Seq    TACAACCTACTAAAACCCCTACTACTCACACTTACAACAAAAATAAAA 300
Granulocytes       TACAACCTACTAAAACCCCTACTACTCACACTTACAACAAAAATAAAA 278
Monocytes          TACAACCTACTAAAACCCCTACTACTCACACTTACAACAAAAATAAAA 278
NK-Cells           TACAACCTACTAAAACCCCTACTACTCACACTTACAACAAAAATAAAA 278
                    *****

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naive Th-cells      ACTCTAAATTCCTTACCTTCTCTCAAAAACCCCAACCCCAACAATAATAAA 329
mem. Th-cells      ACTCTAAATTCCTTACCTTCTCTCAAAAACCCCAACCCCAACAATAATAAA 329
mem. CTL           ACTCTAAATTCCTTACCTTCTCTCAAAAACCCCAACCCCAACAATAATAAA 329
naive CTL          ACTCTAAATTCCTTACCTTCTCTCAAAAACCCCAACCCCAACAATAATAAA 329
AMP1408 Ref-Seq    ACTCTAAATTCCTTACCTTCTCTCAAAAACCCCAACCCCAACAATAATAAA 350
Granulocytes       ACTCTAAATTCCTTACCTTCTCTCAAAAACCCCAACCCCAACAATAATAAA 328
Monocytes          ACTCTAAATTCCTTACCTTCTCTCAAAAACCCCAACCCCAACAATAATAAA 328
NK-Cells           ACTCTAAATTCCTTACCTTCTCTCAAAAACCCCAACCCCAACAATAATAAA 328
*****

naive Th-cells      TAAACCAATCTAACTACTACACAACTAACTAACTAACTAACTACAAAA 379
mem. Th-cells      TAAACCAATCTAACTACTACACAACTAACTAACTAACTAACTACAAAA 379
mem. CTL           TAAACCAATCTAACTACTACACAACTAACTAACTAACTAACTACTAAA 379
naive CTL          TAAACCAATCTAACTACTACACAACTAACTAACTAACTAACTACTAAA 379
AMP1408 Ref-Seq    TAAACCAATCTAACTACTACACAACTAACTAACTAACTAACTACTAAA 400
Granulocytes       TAAACCAATCTAACTACTACACAACTAACTAACTAACTAACTACTAAA 378
Monocytes          TAAACCAATCTAACTACTACACAACTAACTAACTAACTAACTACTAAA 378
NK-Cells           TAAACCAATCTAACTACTACACAACTAACTAACTAACTAACTACTAAA 378
*****

naive Th-cells      AACTACTCCTTACTTTTACCAAAAAACACAACTAACATAAAACAAAAAA 429
mem. Th-cells      AACTACTCCTTACTTTTACCAAAAAACACAACTAACATAAAACAAAAAA 429
mem. CTL           AACTACTCCTTACTTTTACCAAAAAACACAACTAACATAAAACAAAAAA 429
naive CTL          AACTACTCCTTACTTTTACCAAAAAACACAACTAACATAAAACAAAAAA 429
AMP1408 Ref-Seq    AACTACTCCTTACTTTTACCAAAAAACACAACTAACATAAAACAAAAAA 450
Granulocytes       AACTACTCCTTACTTTTACCAAAAAACACAACTAACATAAAACAAAAAA 428
Monocytes          AACTACTCCTTACTTTTACCAAAAAACACAACTAACATAAAACAAAAAA 428
NK-Cells           AACTACTCCTTACTTTTACCAAAAAACACAACTAACATAAAACAAAAAA 428
*   *   *   *   *   *   *   *   *   *   *   *   *   *   *   *

naive Th cells      AAAACCTAT----- 438
mem. Th-cells      AAAACCTATCTTT----- 442
mem. CTL           AAAACCTATCTTTCTT----- 445
naive CTL          AAAACCTA----- 437
AMP1408 Ref-Seq    AAAACCTAACTATCCTCATCCT 472
Granulocytes       AAAACCTATCTTTCCCAACCT 450
Monocytes          AAAACCTATCTTTCCCT--- 446
NK-Cells           CAAACCTATCTTTCTCCCAA-- 448
*****

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Figure 6 (SEQ ID No. 1)

AGATGACATCTATTGAAATATCCCTGTCTCAGCCAGGTGCAGTGGCTCATGCCCTCTAATCCAGCAGCTTTTGGG  
 GGCTGAGTGAAGTGGATCATTTGAGGTCAAGAGTTCGAGACCAGCCTGGCCACATGATGAAACCTGTCTCTACT  
 AAAAAACAAAAATAGCTGAACCTTGGTGACACATGCTTGCAATCCCAGCTACTCAGGAGGCTGAGGCAGGAGAA  
 TCACTTTGACTCCAGGAGACAGAGGTTGAGTAAGCCAAGATCATGCCACAGCCTCCAGGCTGAGCAACAGAGCA  
 AGACTCCATCTCAAAAAAAGAAAAATCCCTGTCTCAAACTCCTGCTTTCCAGGTAGATGGAGCGGGATATGTG  
 CTTTAATTTGGTGAAGGGTTTCTGATCCCTATTTATCATGCAAGAGGAGGAGCAAGCCAGAGACAGGTCCTGGCG  
 AAAGGAAGCTAAAAATGGTGCTTTGATACAGGGGAAAGGGATACGAAAGGGGCTTAGGTGAGACCTCCTTACAGC  
 TAGTGGCAGCTGGTGAGCAGGGCCGTAGAGTTGAGGCCATCCCTTAGCAGCAGTGGGACTTTGTTACACACACC  
 CTCTGAGTCTTTGGTGAGAACTAGTCCAGGGCCCTTTGTTGTCTCTGCCACTCCCATTCATGACATCATGGAAA  
 CTCTGTGCGGCTGGGCTCCTGAACACAGCAGCTGCCTCGGCTGGATGAGGCAGCCAAACCTTAAAGGGTT  
 GTGATAGGACTGGACTCAACAAGTAGCTGTGGAAAGTGGTGGCGAGACCTTCACCCAGGAGCCCTGTGGG  
 CTAGAAACACAGACAGCAGGATGTGGCAGAGACTGCCAACACACTGTCTGTGTGAGGCAGAGGAAGGAAGG  
 AGATGAAGGAAGAAACAGGTAGGTAGGAGGGCGAGATCCCAAGCAAGTCAGGACAACCTCCACGGCTTGCCAGG  
 AGCCTTAAGAAAGCCAGGCACCTGTGAGTGAAAGAGGATATTTATTGGCTGAGCAAGAGGGAAGGTACAGT  
 TGGTAATGGCTGCTCTAGAGAGCCAGCAGTCTCAGGTTCACTTTGTTCCAGGAGCCAGTTTCTCCAAGGTGGCTGT  
 ACTGAGCATCATCTCGATCTCGGAGGGGCTAAGAGAGGAGAAAGAAAAAGGTCAGGAGGAGGGTTAGAACTCT  
 TCAAGGAAGGGCCAGCAGGCGCTGACGATGAGAGCTCCTGCCTGACCTCTCCAGTCACACCCAGCAATGAAC  
 CCCCAGTAGGACCTTCCCAAGTGAACACAGCATTCAGTGTGAGCCTCTCTATCCCACTTACCTCCTCTCAT  
 CTTGCTCCTCTTCCCTCAAGCTCAGCTGATAGAGCTGGTCATCTCTCAACAGAGCTTTGTGTGCGGAGCTAGA  
 AGAAACAGAGAGACATCAATGGCTAGCAGATGGGACTGTGAGATCCACCTCCACACCTCAGAGTCTGCG  
 ATGATGATATGAACACACAGTCTTTCAACAGTCAGAGTCTTAGGAGTCTTTAGGAGATTCAGAGATTAAC  
 CAGCTGAGACTAAACCTTACCACAGCCCTTCTTAGCTGGTGATAGCTCACTGGTACACACACACACACA  
 CACACACACACACACACAAACACACTCTCATGCTCTGCTCTTCCACTAACCCACAGACAGCCTTCCAGTCTCATG  
 TCCACGAAAGCAGAGAGCTCCCAAGGCAAGGAGCAGAGTGGCAATGACATCAGTGACATGATGCCAGCCACGGT  
 GGTGGATCCAGCTCCAGCTCCAGCTCTGGCACACTGTGGGGGAAGGAGAGAGAGGAGGTTGAGAGCCTTTAA  
 GATCAGGGAACCATCTCTGCTCTTAGGGCAACCTTAGATCTCTTATGCCAAACCCAACTTCAATTAAGACC  
 CTGGGAGAAAGGCTGGTGATGGCTTGGCACACCTTCTCCACCTGCATCCTAAGGAATCCCTGGGAAGAGCC  
 AAGAGTAATCTCAGCTTTTGGGACCTTGAACAGGTGGTGGGCCAAACCTCTACCCCAACCAAGGCTCGAGTAA  
 CATGACCCCTACTGCTCTGCTCTGCTGAGTTAAGCTCTCTCTTCACTTTGAAGGTCCCAATCTGGCTTTGTAC  
 CATTACAATAGTGACCTCACTTTGTTTAGAGAACAGATGGGTCAACATATCCCTCTACGCCAGAAATTTCTCA  
 CATCCAGAAGCCCTATCCATTTCAACCCCAAGGGTTTCAGGAAGCAGTACTTCGATAATGAACCTTGACGGTGA  
 TTTCTTGTCTGTATATATCTGCTCCATTACACCTATATATTTCTCGTGGGTCCAGGATGGCTTTTCCAGGTG  
 CAGTCTTGTAATGCTGAGAGCAGTGTTCACACCGTTCCCTCTACCCATGTGATGCTGGTATTGCAATTCACAAA  
 CACTCTGCTCAGGTTCCCTCTATAGGTAICTTGAAGGGGCTCACTAAAGGGGAAAAAATATCAGAGTTGGAGAC  
 AGCTCTTTGATCTGCACCAAGCCCTTTGTTCTGGGAAGCTCATACTTAACAGAGACCATTTTCTGTGTCAGGA  
 CAGTTTATGGCTTCCATCAAGAGAGACAGAAAGTCAAGAAAAAGCCTTCAGAAAGTTCCCAACCACTGCAGGG  
 GTCAGGGGGACATGAGGATGCCATTCAAGCAGAGGACAGGCTTGGGGCTTGGTGCAAGAGAGGACCCCTCAG  
 AGCAGGATTGACCAAGCAGCTTCTTGGAAATGAATCCAGACCACTGATGAGGAGTAGGGGGAGCACGGACCACT  
 GAACCACTGGAAGATGTGGAAGACAGAGAAATCTTCCGATTGGAATGTCTGCATTTTCTCTCAAGGAAA  
 CATCTAATTTCCATTTCCAGCCATCTACAACACTCCCACTTCACTTCTTATCTCTCATCTTCTCTATTGCCCT  
 GCTCCATTGACAAACAGAAAGCGGGGCTCTCAACACTGAAGCCTTTCCAGGGCCAGGGATGGCTGTGGGTGGA  
 GACCACTGCTTTACAGCCCTGAATTAACAGCAAGTGGTCCAGAACGGGACAGGGCAAAATCCCATGTACAG  
 TTTTCCACCTTGGTTAGAAAGGAGAGAAACAGAAAAAATTTTATTGAATCCATCCCTACAGCTCCTCACAAGT  
 CAAGTCTTGTGGGAGACTTTTAGGGCTGGAGTGAGTGCAGCAACATTCCAGATGCACTGAGTTCTCTGACAGC  
 CTGAGCATCTCCACAGGCCACAGGGCACTACAGTCTATGCCCTCAAAACACAGGGAAAGTGGAGGCTACATT  
 CATTCATCTGGGCTTCACTAAGTCCCAAAATTTGGATACAAGGACATTTCTAGAAAACTTGAACAGCTGT  
 TGCTCACACTTCTGAAGCAGGTTGGAAGTATATGATGTATCTCAGGGAGACACATGCACATCAATGCTTCAC  
 GTCTACAGTCGGCTCTCTCAGGGATCTGTCTCCAGTGGAAATCTGAGTGCCTAGTGCAAGCAATATTAG  
 GTGACCATTTGACCCAGTTTGGCTTAGTGTGAAGGGGTTCTCGACATGGGACTTCCATTTTAAACTGAAT  
 TGGCAAACTGAGATGAGTTAAATCTACCATGTAAACACCCCTCAATCTTCCCTCCGTCCTGCTCAACCTAAA  
 GTTAACCTCTCTTAAAGCATTCACATAAGTGCTAGGACATGCCCTCCAGGGATGACATAATCATGGCCAAACAAAC  
 AAGAGTCTGATTCCAGAGGCCATCAGGCCTAAAAGGAGTAGTGACAGGAGCTGTGCTCCCATGGCCACTCCAG  
 ATTCAGGTACATACCTACTGAGCTATTTCTGACAGATCTGTGSCCTAAGGCCTTCTGAGAGACATTTAGGCCCA  
 CATGCACCCATGGCTGGAGTCACTCAAAGCCAAAGAGCCTGTTTCCAGACTCTATGCTACATCTGCCCCCTGCC  
 TCTGACACCCCTGGGTGCTGGTGAAGTGAAGCTAGCAGGAGAGGACTTTTCTTTTGTGAGATAAGGT  
 CTCACAGTTGCTAGGTTGAGGGCAGTGGCATGATCAGAGCTCACTGAAGCCTTGAATCCCGGGCTCAAGT  
 ACCCTCTGCTCAGCTCTCAATAGCTGGGACTACAGTTGTGACCCACCATGCTGGCTAATTTCTTTGTTT  
 TTGTAAGATAGAGTCTCATCATGTTGCTCAGACTGGTCTCAAACTCCTGGCTCAAAGGATCTTCCCACTTCGG  
 CCTCCAAAGCTCTGGGATTACTGCTGTGAGCCACCGTGCCTGGCAAGAAACACTTTCAAGTGGGCTCACTCCC  
 ATCAGTAATGTCCCTCTCAGGTCCTTCCCCACCCACCTGGAGTAGCCTTACCTTGGGAGAAAGGTAGCCAG

TACGACGGCCAGAGAGAAACGTGCTATGTTCCATCTCCAGCAGGAACTCATCCAGTAGATAATACAGGTCACCGA  
ACTTACAGCCTGGGTGAGAGCTGCCCTCCCCTAGCTGATCCAGAGTACCGGAAAGAGAGAGTGGGGAGAGGAT  
TAGAAGATGCTGCTGCTTCTCTGCTTTCTGCGTGTGATGTTGGAAATTTTCAGATGGGGTGGCGTAGGGTAGG  
CTTAGAGGAAGAGCGGTGTAAATTGCTATCTCTGACAGGGAGCTGGCAGAGAAATAGGAAGAAAGTGGCCCTAA  
TTTTAGGCTCCCTATTGCAATGCAACACATATTACACACACTAACCAATGCCCATCTCGAAGCCCCTTGAG  
AGAACGCTCGGCCCGGCTACAGCCAAGCGTAGCAGCTAGATTGTTGATGGGCTGATCTTTCTCAGGACAGCCTTC  
ACTAGGACGGCCGGGACACCAAGTCTAGACAGCTCTTGTCAGTGGGATGTTGGGCTTTAGAGACAGCCGACAGAG  
ATTTGATCTCTGGGTCCAAATAGTCCCTACCTGTGGGGCTGGGCACAGCATAAATTTTTCAGATGCTTATTTCA  
TTAGTACCAATTAGSATTCAACACAGATTTGATGTTGCTGCTCCAGCATATGTTGGCTCATTAAGGGGTAG  
TTATTAATAATAATAATTAATTGACTGACAGCCAAATTTGACCTCCGGCTGGACAAATGGACCTTTTCCCCTCT  
GGCTCAGGAGGATCTGAACCTTTCCAGCTGGCTGAGTGTAGACTTACCTTACCTGGGACAGAGTACGCTCT  
CTGTCTACGCTGTGATCTGTGCTGTGGCATTACAGGGAGCTTCGACATTTTGTGGCTCACTGACTGACTG  
GCTGAGGAGAAATAGGGGCTGATCTCGGCATCTCAGTCCGGGCTCTGGCCCTCGAAATGTGTGGCTGTGCT  
TCGGAATTTGTCATCATTTGCTCTCCAGCGCCTCTTTTCATGATCTCAAAAGAAATGATGAACCAAGGTGCGCT  
TCTCCAGCTCTGTAATCCCAACACTTTGGGAGCTGAGGACAGGTGGAATCAACAGCTCAGAGTCTGGAGACAGCCT  
GACCAACAGGTGAACCCGGTCTCTATAAAATCAAAATTTAGCCGGGCTGCTGGCAGCCAGCTGTAATCT  
CAGCTACTCAGGAGGCTCAGGACAGGAAATCGCTGAACCCCGAGGTTGGAGTTGCACTGAGGTGAGTAGACG  
CATGCACTACAGCCTGGSCCAAAAGTGAAGACTTGTCCTCAAAAAGAAAGAAAAAAAGTGAAAAAAAT  
CCTGAATGAAGGCTGAGCTGAGTGGCTTTCCATTTTGGAGTCTCAGGCCCAAGCTCTTGAGACTCTCTTAA  
TCTATTCTCAGCAGCAACCACTAGCAGCAAGATAACACTGCTCAGCTCTTAACACTAATGACAGGCACT  
TTATCTCCCTCTAGAGAAACGGTCCAGGACCATCTCCACCCAGCATCATTCGGTTCCTGTGCAAGATGA  
GCTCTCTGAGTGGGAATCAGCAGCTCTCTCCCTCTCTCTCCCAACCACTTCAGCTCTCTACGGAAAAACAAA  
GGCATCTGCACCTCGACSCCTGTCTGAGCCCTCTGCTCTCAAGTCTCAGACAGGGTGGAGGCTCTGGGTTTCT  
GCCCTCTCTCAAGGCGCCGAGCCCAAGAGTGTAGGTTGGAGCGACTTAGCTGTGTCACAGCTGGCTGGCTGG  
CTGGCTGTCAAGGGCTGTCTCAGGCTTTTCCGGAGGACAGAGACTGACATGTGAAGCAGGGAAGCCGCTGGCTGT  
CTCATCTCTGGCTCATCTCTCTTCAGGTTAGGGCTCTACACGGTCTGGAAGCTGGGAGGGCTGAAGGG  
AAGAGCCCATCATGACTCAGACAGGAAATTTGTTTCCCTAACCTTCAGGCTACCTCTGCTCTGACTCTAGAGTT  
CAAGAAGGCGAAAAATGAGGCTCTTAAGCTGTTCTCTCTAGAGAGAGGCTCTCCATCGGAGAGAGGAATCT  
CTGTGCTCTGAAATATCAAAACAGAGTCTTAATGGCTGAAGAGAGGCCCTCTTACGCCCACTTAGATTGA  
ATGCACCCCAAAAGGCGATAGGCCAGAGAAATAAAGAAAGAAATATGTTCCCTACTTCAGAGCTGGGGCTA  
CGACTCGACCTAGGAATGTCCATCTCAGTTCAGGTCAGTGGCAAGTTGGTCAACAAGAGAGGTTGAGGCCCT  
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