CELLS FOR TREATING CANCER

The present invention relates to a cell-based therapy suitable for treating cancer.

Cancer is a leading cause of morbidity and mortality worldwide, with an annual increase in cancer incidence in developed countries. The World Health Organisation stated that in 2012 alone there were approximately 14 million new cancer cases (and 8.2 million associated deaths), with a projected rise to 22 million cases over the next two decades. Current therapeutic strategies include combinations of surgery, radiation, and cytotoxic chemotherapy, however many of these treatments are ultimately ineffective and associated with harmful side-effects.

Safety and efficacy has been assessed for Haematopoietic Stem Cell Transplantation (HSCT) as a therapeutic technique for treating certain cancers, such as Renal Cell Carcinoma. However, this treatment is still largely seen as experimental due to potentially fatal safety issues, with recipients exhibiting severe Graft vs. Host Disease (GVHD) as a result of the uncontrolled multiplication of pluripotent stem cells. Thus, there is a need for improved and alternative cancer therapies.

In spite of the increased cancer incidence, it has been observed that approximately 50-60% of individuals do not develop cancer in their lifetime. Indeed, in rare cases, some individuals exhibit spontaneous cancer regression. This observation has led to the study of white blood cells from spontaneous regressor individuals, and use of said white blood cells in Leukocyte Infusion Therapy (LIFT).

Conventional LIFT is carried out using apheresis for direct transfer of granulocytes (e.g. neutrophils) taken from the donor to the cancer patient. Conventional approaches currently used in the clinic are not practical or scalable for use as a credible cancer therapeutic. First, granulocytes such as neutrophils have a very limited shelf-life (typically less than 24 hours) making them difficult to store. Secondly, apheresis requires approximately 5 (very rare) donors in order to acquire the required cell number. Thirdly, to avoid an allogeneic immune response from repeat exposure, the same donors cannot be used in a subsequent administration, thus requiring an increased pool of appropriate donors. Fourthly, it cannot be realistically expected that donors will be available on request, or willing to provide an endless

source of granulocytes for the LIFT procedure. Thus, there is need to quickly and reliably identify suitable donors that produce granulocytes with sufficient cancer killing activity.

Identifying donors that produce such granulocytes has conventionally been performed using functional assays that measure a percentage of cancer cells killed. However, such assays can be time-consuming. Thus, there is a need for improved/alternative assays that can sensitively and specifically and/or rapidly identify such granulocytes and donors and/or validate any results obtained using functional assays.

The present invention provides a solution to at least one of the problems described above.

The present inventors have surprisingly identified a number of genes (and expression levels thereof) that are associated with a granulocyte's suitability for treating cancer. Advantageously, the expression levels of such genes can be determined using transcriptomic, proteomic or genomic techniques to sensitively and specifically identify and/or rapidly identify granulocytes with therapeutic efficacy and/or donors producing such granulocytes.

Moreover, by determining the expression of the one or more genes described herein, the present invention allows for the preparation of substantially homogenous populations of granulocytes suitable for treating cancer (e.g. where at least 90% of the granulocytes present are granulocytes suitable for treating cancer).

In one aspect the present invention provides a method for determining the suitability of a granulocyte for treating cancer, the method comprising:

a. comparing a measured expression level of one or more genes by the granulocyte, wherein the one or more genes are associated with suitability for treating cancer and are selected from: *CTSG, CAP37, ITGB1, CYBB, SYK, DOCK8, COMP, ATG7, SLC2A1, GZMK, ATM, IKBKB, BCAP31, TAPBP, PPP3CB, ANXA1, PERM, PLEC, ACSL1, RAC1, GM2A,* and *PSMB2*, with the expression level of the same one or more genes in a reference standard; and

b. determining the suitability of the granulocyte for treating cancer based on the comparison.

Representative sequences for the genes for use in the invention are described in the Sequence Listing herein, together with the appropriate Ensembl Accession numbers. A gene for use in the invention may be one or more shown as SEQ ID NOs: 1-24 or 83-87 or a variant thereof. A gene for use in a method of the invention may comprise (or consist of) a nucleotide sequence having at least 70%, 80%, 90% or 95% sequence identity to any one of SEQ ID NOs: 1-24 or 83-87. Preferably, a gene for use in a method of the invention comprises (more preferably consists of) any one of SEQ ID NOs: 1-24 or 83-87.

In one aspect the present invention provides a method for determining the suitability of a granulocyte for treating cancer, the method comprising:

a. measuring an expression level of one or more genes by the granulocyte, wherein the one or more genes are associated with suitability for treating cancer and are selected from: *ITGB1, CYBB, SYK, DOCK8, COMP, ATG7, SLC2A1, GZMK, CTSG, ATM, IKBKB, BCAP31, TAPBP, PPP3CB, ANXA1, PERM, PLEC, ACSL1, RAC1, GM2A, CAP37,* and *PSMB2*;

b. comparing the measured expression level with the expression level of the same one or more genes in a reference standard; and

c. determining the suitability of the granulocyte for treating cancer based on the comparison.

In another aspect the invention provides a method for identifying whether or not a donor produces granulocytes suitable for treating cancer, the method comprising:

a. comparing a measured expression level of one or more genes by a granulocyte comprised in a sample obtainable from the donor, wherein the one or more genes are associated with suitability for treating cancer and are selected from: *CTSG, CAP37, ITGB1, CYBB, SYK, DOCK8, COMP, ATG7, SLC2A1, GZMK, ATM, IKBKB, BCAP31, TAPBP, PPP3CB, ANXA1, PERM, PLEC, ACSL1, RAC1, GM2A,* and *PSMB2*, with the expression level of the same one or more genes in a reference standard; and

b. identifying whether or not the donor produces granulocytes suitable for treating cancer based on the comparison.

In a related aspect the invention provides a method for identifying whether or not a donor produces granulocytes suitable for treating cancer, the method comprising:

a. measuring an expression level of one or more genes by a granulocyte comprised in a sample obtainable from the donor, wherein the one or more genes are associated with suitability for treating cancer and are selected from: *ITGB1, CYBB, SYK,*

DOCK8, COMP, ATG7, SLC2A1, GZMK, CTSG, ATM, IKBKB, BCAP31, TAPBP, PPP3CB, ANXA1, PERM, PLEC, ACSL1, RAC1, GM2A, CAP37, and *PSMB2*;

b. comparing the measured expression level with the expression level of the same one or more genes in a reference standard; and

c. identifying whether or not the donor produces granulocytes for treating cancer based on the comparison.

In a preferred embodiment, the methods referred to herein comprise measuring, and/or comparing a measured expression level of *GM2A, PLEC, CYBB, DOCK8*, and/or *PPP3CB* and optionally one or more further genes. Most preferably, the methods referred to herein comprise measuring and/or comparing a measured expression level of *GM2A* and optionally one or more further genes. Advantageously, the expression of said genes is highly statistically-significantly different between granulocytes that are suitable for treating cancer and granulocytes that are unsuitable for treating cancer. Thus, measuring, and/or comparing a measured expression level of at least one of those genes has particularly high predictive value. Thus, a gene used in any method described herein may be *GM2A, PLEC, CYBB, DOCK8*, and/or *PPP3CB* and optionally one or more further genes. Thus, a protein used in any method described herein may be GM2A, PLEC, CYBB, DOCK8, and/or PPP3CB and optionally one or more further proteins. Most preferably, GM2A or *GM2A* and optionally one or more further genes/proteins.

In one embodiment, the methods referred to herein are *in vitro* methods, such as *ex vivo* methods.

The term “donor” as used herein refers to a subject (suitably a human subject) from whom a sample is obtainable (e.g. obtained). Any suitable sample from which a stem cell or granulocyte cell is obtainable may be obtainable from the donor. The donor may be selected based on one or more of the following characteristics: sex, age, medical history, and/or blood group type. In one embodiment, a donor may be selected if said donor is a healthy donor. In one embodiment, a donor may be selected if said donor does not have cancer. In one embodiment a donor may be selected if said donor is a male. In another embodiment a donor may be selected if said donor is aged 18-55 and preferably 18-35 (more preferably 18-24). Suitably, a donor may be selected if said donor is a male aged between 18-55 and preferably 18-35 (more preferably 18-24). Without wishing to be bound by theory, it is believed that males in early adulthood have a higher likelihood of producing granulocytes (e.g. neutrophils) that are suitable for treating cancer.

The term "measuring" as used in reference to expression of one or more genes of the invention encompasses measuring both negative (e.g. no expression) and positive expression (e.g. expression). In one embodiment the expression is positive expression.

Measuring expression may be carried out by any means known to the person skilled in the art. In some embodiments expression may be measured using high-throughput techniques. For example, measuring expression may be at the level of transcription (e.g. transcriptomic techniques) or translation (e.g. proteomic techniques). Alternatively or additionally, the invention may employ the use of genomics, e.g. to detect the presence or absence of single nucleotide polymorphisms (SNPs), promoter sequences, gene copy number (e.g. duplications), and/or enhancer or other relevant genetic features, preferably those that determine the expression level of one or more genes of the invention. High-throughput techniques can be used to analyse whole genomes, proteomes and transcriptomes rapidly, providing data, including the expression levels, of all of the genes, polypeptides and transcripts in a cell. Proteomics is a technique for analysing the proteome of a cell (e.g. at a particular point in time). The proteome is different in different cell types. Typically, proteomics is carried out by mass-spectrometry, including tandem mass-spectrometry, and gel based techniques, including differential in-gel electrophoresis. Proteomics can be used to detect polypeptides expressed in a particular cell type and generate a proteomic profile to allow for the identification of specific cell types.

In one embodiment, mRNA of a target gene can be detected and quantified by e.g. Northern blotting or by quantitative reverse transcription PCR (RT-PCR). Single cell gene expression analysis may also be performed using commercially available systems (e.g. Fluidigm Dynamic Array). Alternatively, or in addition, gene expression levels can be determined by analysing polypeptide levels e.g. by using Western blotting techniques such as ELISA-based assays.

Thus, in one embodiment, gene expression levels are determined by measuring the mRNA/ cDNA levels of the genes of the present invention, such as RNA sequencing (RNA-Seq).

In a preferred embodiment, gene expression levels are determined by measuring the polypeptide levels produced by the genes of the present invention, such as by way of mass spectrometry, e.g. liquid chromatography and mass spectrometry (LC-MS/MS).

In one embodiment a granulocyte (or stem cell) for treating cancer may be detected using an enzyme-linked immunosorbent assay (ELISA) or a Luminex assay (commercially available from R&D Systems, USA).

Thus, in one embodiment a method of the invention comprises measuring and/or comparing an expression level of one or more polypeptides by a granulocyte, wherein the one or more polypeptides are selected from: CTSG, CAP37, ITGB1, CYBB, SYK, DOCK8, COMP, ATG7, SLC2A1, GZMK, CTSG, ATM, IKBKB, BCAP31, TAPBP, PPP3CB, ANXA1, PERM, PLEC, ACSL1, RAC1, GM2A, CAP37, and PSMB2.

Representative sequences for the polypeptides for use in the invention are described in the Sequence Listing herein, together with the appropriate UniProt Accession numbers. A polypeptide for use in the invention may be one or more shown as SEQ ID NOs: 25-82 or a variant thereof, such as a transcript isoform therefore. A polypeptide for use in a method of the invention may comprise (or consist of) a polypeptide sequence having at least 20%, 30%, 40%, 50%, or 60% sequence identity to any one of SEQ ID NOs: 25-82. In one embodiment a polypeptide for use in a method of the invention may comprise (or consist of) a polypeptide sequence having at least 70%, 80%, 90% or 95% sequence identity to any one of SEQ ID NOs: 25-82. Preferably, a polypeptide for use in a method of the invention comprises (more preferably consists of) any one of SEQ ID NOs: 25-82.

In one embodiment a method of the invention comprises measuring and/or comparing an amount of one or more polypeptides produced by a granulocyte, wherein the one or more polypeptides are selected from: CTSG, CAP37, ITGB1, CYBB, SYK, DOCK8, COMP, ATG7, SLC2A1, GZMK, CTSG, ATM, IKBKB, BCAP31, TAPBP, PPP3CB, ANXA1, PERM, PLEC, ACSL1, RAC1, GM2A, CAP37, and PSMB2.

In one embodiment a method of the invention comprises measuring and/or comparing an expression level of one or more polypeptides by a stem cell, wherein the one or more polypeptides are selected from: CTSG, CAP37, ITGB1, CYBB, SYK, DOCK8, COMP, ATG7, SLC2A1, GZMK, CTSG, ATM, IKBKB, BCAP31, TAPBP, PPP3CB, ANXA1, PERM, PLEC, ACSL1, RAC1, GM2A, CAP37, and PSMB2.

In one embodiment a method of the invention comprises measuring and/or comparing an amount of one or more polypeptides produced by a stem cell, wherein the one or more polypeptides are selected from: CTSG, CAP37, ITGB1, CYBB, SYK, DOCK8, COMP, ATG7,

SLC2A1, GZMK, CTSG, ATM, IKBKB, BCAP31, TAPBP, PPP3CB, ANXA1, PERM, PLEC, ACSL1, RAC1, GM2A, CAP37, and PSMB2.

In one embodiment a method of the invention employs a genome wide association study, which is compared to a reference standard (e.g. a reference standard from a reference population, such as a reference standard from: a suitable or unsuitable donor, or a suitable or unsuitable granulocyte, or a subject that is suitable or unsuitable for treatment with a granulocyte or stem cell of the invention, or a subject that is at risk or not at risk of cancer or combinations thereof).

Methods suitable for establishing a baseline or reference value for comparing expression levels are conventional techniques known to those skilled in the art.

The term “increased” as used herein in reference to expression of the one or more genes of the invention may refer to an expression level that is statistically-significantly increased when compared to a reference standard. Such a gene may be considered to be upregulated.

In one embodiment increased expression means greater than 1-fold, 1.25-fold to about 10-fold or more expression relative to a reference standard. In some embodiments, increased expression means greater than at least about 1.1-fold, 1.2-fold, 1.25-fold, 1.5-fold, 1.75-fold, 2-fold, 4-fold, 5-fold, 10-fold, 15-fold, 20-fold, 25-fold, 30-fold, 35-fold, 40-fold, 50-fold, 75-fold, 100-fold, 150-fold, 200-fold, or at least about 300-fold expression when compared to a reference standard.

The term “decreased” as used herein in reference to expression of the one or more genes of the invention may refer to an expression level that is statistically-significantly decreased when compared to a reference standard. Such a gene may be considered to be downregulated.

In one embodiment decreased expression means less than -1-fold, -1.25-fold to about -10-fold or more expression relative to a reference standard. In some embodiments, decreased expression means less than at least about -1.1-fold, -1.2-fold, -1.25-fold, -1.5-fold, -1.75-fold, -2-fold, -4-fold, -5-fold, -10-fold, -15-fold, -20-fold, 25-fold, -30-fold, -35-fold, -40-fold, -50-fold, -75-fold, -100-fold, -150-fold, -200-fold, or at least about -300-fold expression when compared to a reference standard.

The fold change difference can be in absolute terms (e.g. CPM: counts per million) or Log2CPM (a standard measure in the field) of the expression level in a sample. Preferably the fold change is Log2 fold change. In one embodiment a Log2 change is an increase of at least 0.1, 0.2, 0.3, 0.4, 0.5, 0.6, 0.7, 0.8, 0.9, 1.0, 1.1, 1.2, 1.3, 1.4, 1.5, 1.6, 1.7, 1.8, 1.9, 2.0, 2.1, 2.2, 2.3, 2.4, 2.5, 2.6 or 2.7. In one embodiment a Log2 change is a decrease of 0.1 or more, 0.2 or more, 0.3 or more, 0.4 or more, 0.5 or more, 0.6 or more, 0.7 or more, 0.8 or more, 0.9 or more, 1.0 or more, 1.1 or more, 1.2 or more or 1.3 or more. A decrease may be indicated by the presence of a "-" symbol prior to the value.

In one embodiment said fold-change is measured and/or is determined by RNA sequencing (RNA-Seq), e.g. *in toto*.

The term "unchanged" or "the same" as used herein in reference to expression of the one or more genes of the invention may refer to an expression level that is not statistically-significantly different to a reference standard. Preferably, an expression level that is the same as a reference standard.

The expression level may be an average such as a mean expression level. In one embodiment statistical significance is determined using two-way ANOVA, e.g. where n is at least 3 and data are presented as mean +/- standard error of mean.

In one embodiment the methods of the invention comprise measuring expression of combinations of the genes described herein.

The term "one or more" when used in the context of a gene described herein may mean at least 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21 or 22 of the genes. Preferably, the term "one of more" means all of the genes. Likewise, the term "one or more" when used in the context of a polypeptide described herein may mean at least 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21 or 22 of the polypeptides. Preferably, the term "one of more" means all of the polypeptides.

The expression of one or more of *ITGB1, CYBB, SYK, DOCK8, COMP, ATG7, SLC2A1, GZMK, CTSG, ATM, IKBKB, BCAP31, TAPBP, PPP3CB, ANXA1, PERM, PLEC, ACSL1, RAC1, GM2A, CAP37,* and *PSMB2* correlates with a granulocyte's suitability for treating cancer. Said genes are therefore referred to herein as genes associated with suitability for treating cancer. Thus, the term "one or more genes associated with suitability for treating

cancer" (and the like) may in be synonymous with (and thus replaced with) the term "one or more of *ITGB1, CYBB, SYK, DOCK8, COMP, ATG7, SLC2A1, GZMK, CTSG, ATM, IKBKB, BCAP31, TAPBP, PPP3CB, ANXA1, PERM, PLEC, ACSL1, RAC1, GM2A, CAP37,* and *PSMB2*". Thus, the term "one or more polypeptides associated with suitability for treating cancer" (and the like) may in be synonymous with (and thus replaced with) the term "one or more of ITGB1, CYBB, SYK, DOCK8, COMP, ATG7, SLC2A1, GZMK, CTSG, ATM, IKBKB, BCAP31, TAPBP, PPP3CB, ANXA1, PERM, PLEC, ACSL1, RAC1, GM2A, CAP37, and PSMB2".

Without wishing to be bound by theory, the inventors believe that, based on the data obtained in the Examples and the inventors' theorised mechanism of action, the one or more genes may have the following functions making them suitable for treating cancer:

a. killing cancer cells: *GM2A, CTSG, CAP37, CYBB, GZMK, ATM, PERM, ACSL1, ATG7, SYK, DOCK8, RAC1*, and *PSMB2*; and/or

b. locating and/or binding to cancer cells: *ANXA1, ITGB1, COMP, SLC2A1* and *PLEC*; and/or

c. recruitment of immune mediators: *BCAP31, TAPBP, IKBKB*, and *PPP3CB*.

In a preferred embodiment a method of the invention comprises measuring and/or comparing the expression of *ANXA1*. Advantageously, the inventors have shown that low levels of *ANXA1* expression are associated with high cancer killing activity and therefore suitability for treating cancer. Without wishing to be bound by theory, the inventors believe that *ANXA1* modulates chemotaxis and/or motility of granulocytes and, in particular, that low expression of *ANXA1* promotes granulocyte motility and thus location/binding to cancer cells.

In one embodiment expression of one or more of *ITGB1, CYBB, SYK, DOCK8, COMP, ATG7, SLC2A1, GZMK, CTSG, ATM, IKBKB, BCAP31, TAPBP, PERM, PLEC, ACSL1, RAC1, GM2A, CAP37,* and *PSMB2* is increased in a granulocyte that is suitable for treating cancer when compared to a granulocyte that is unsuitable for treating cancer. Alternatively or additionally, in one embodiment expression of *ANXA1* and/or *PPP3CB* is decreased in a granulocyte that is suitable for treating cancer when compared to a granulocyte that is unsuitable for treating cancer.

In one embodiment a method of the invention may further comprise measuring and/or comparing expression of one or more genes selected from: *S100A9* and *S100A8*. In one embodiment expression of *S100A9* and/or *S100A8* may be increased in a granulocyte of the

invention when compared to a reference standard, when the reference standard is from a granulocyte that is unsuitable for treating cancer.

In one embodiment a method of the invention comprises measuring and/or comparing expression of *CTSG* and at least one further gene selected from: *CAP37, ITGB1, CYBB, SYK, DOCK8, COMP, ATG7, SLC2A1, GZMK, ATM, IKBKB, BCAP31, TAPBP, PPP3CB, ANXA1, PERM, PLEC, ACSL1, RAC1, GM2A,* and *PSMB2*. Similarly, a granulocyte of the invention may comprise increased expression of *CTSG* and:

at least one further gene selected from: *CAP37, ITGB1, CYBB, SYK, DOCK8, COMP, ATG7, SLC2A1, GZMK, ATM, IKBKB, BCAP31, TAPBP, PERM, PLEC, ACSL1, RAC1, GM2A,* and *PSMB2* when compared to a reference standard, wherein the reference standard is from a granulocyte unsuitable for treating cancer; or

decreased expression of *ANXA1* and/or *PPP3CB* when compared to a reference standard, wherein the reference standard is from a granulocyte unsuitable for treating cancer.

In a particularly preferred embodiment, a method of the invention comprises measuring and/or comparing expression of *GM2A* and at least one further gene selected from: *CAP37, ITGB1, CYBB, SYK, DOCK8, COMP, ATG7, SLC2A1, GZMK, ATM, IKBKB, BCAP31, TAPBP, PPP3CB, ANXA1, PERM, PLEC, ACSL1, RAC1, CTSG,* and *PSMB2*. Similarly, a granulocyte of the invention may comprise increased expression of *GM2A* and:

at least one further gene selected from: *CAP37, ITGB1, CYBB, SYK, DOCK8, COMP, ATG7, SLC2A1, GZMK, ATM, IKBKB, BCAP31, TAPBP, PERM, PLEC, ACSL1, RAC1, CTSG,* and *PSMB2* when compared to a reference standard, wherein the reference standard is from a granulocyte unsuitable for treating cancer; or

decreased expression of *ANXA1* and/or *PPP3CB* when compared to a reference standard, wherein the reference standard is from a granulocyte unsuitable for treating cancer.

In one embodiment a method of the invention comprises measuring and/or comparing expression of *CAP37* and at least one further gene selected from: *CTSG, ITGB1, CYBB, SYK, DOCK8, COMP, ATG7, SLC2A1, GZMK, ATM, IKBKB, BCAP31, TAPBP, PPP3CB, ANXA1, PERM, PLEC, ACSL1, RAC1, GM2A,* and *PSMB2*. Similarly, a granulocyte of the invention may comprise increased expression of *CAP37* and:

at least one further gene selected from: *CTSG, ITGB1, CYBB, SYK, DOCK8, COMP, ATG7, SLC2A1, GZMK, ATM, IKBKB, BCAP31, TAPBP, PERM, PLEC, ACSL1, RAC1,*

GM2A, and *PSMB2* when compared to a reference standard, wherein the reference standard is from a granulocyte (or stem cell) unsuitable for treating cancer; or

decreased expression of *ANXA1* and/or *PPP3CB* when compared to a reference standard, wherein the reference standard is from a granulocyte unsuitable for treating cancer.

In another embodiment a method of the invention comprises measuring and/or comparing expression of *ANXA1* and at least one further gene selected from: *CTSG, CAP37, ITGB1, CYBB, SYK, DOCK8, COMP, ATG7, SLC2A1, GZMK, ATM, IKBKB, BCAP31, TAPBP, PPP3CB, PERM, PLEC, ACSL1, RAC1, GM2A,* and *PSMB2*. Similarly, a granulocyte of the invention may comprise decreased expression of *ANXA1* and:

at least one further gene selected from: *CTSG, CAP37, ITGB1, CYBB, SYK, DOCK8, COMP, ATG7, SLC2A1, GZMK, ATM, IKBKB, BCAP31, TAPBP, PERM, PLEC, ACSL1, RAC1, GM2A,* and *PSMB2* when compared to a reference standard, wherein the reference standard is from a granulocyte unsuitable for treating cancer; or

decreased expression of *PPP3CB* when compared to a reference standard, wherein the reference standard is from a granulocyte unsuitable for treating cancer.

The term "for treating cancer" as used herein means "suitable for treating cancer". A granulocyte that is "suitable for treating cancer" as used herein means that a granulocyte is capable of killing at least 51.5% of cancer cells in the "cancer killing activity (CKA) assay" described herein. In one embodiment a granulocyte is capable of killing at least 70% of cancer cells in the "cancer killing activity (CKA) assay" described herein. Preferably a granulocyte is capable of killing at least 80% (e.g. at least 90% or 95%) of cancer cells in the "cancer killing activity (CKA) assay" described herein. Reference to a stem cell "for treating cancer" or that is "suitable for treating cancer" means that said stem cell is capable of differentiating into a granulocyte that is suitable for treating cancer.

In contrast a granulocyte that is "not suitable for treating cancer" or is "unsuitable for treating cancer" is a granulocyte that is not capable of killing at least 51.5% of cancer cells in the "cancer killing activity (CKA) assay" described herein, i.e. a granulocyte that kills less than 51.5% of cancer cells in the "cancer killing activity (CKA) assay" described herein. In one embodiment a granulocyte that is "not suitable for treating cancer" or is "unsuitable for treating cancer" is a granulocyte that is not capable of killing at least 70% of cancer cells in the "cancer killing activity (CKA) assay" described herein, i.e. a granulocyte that kills less than 70% of cancer cells in the "cancer killing activity (CKA) assay" described herein.

Likewise, reference to a stem cell that is "not suitable for treating cancer" or is "unsuitable for treating cancer" is a stem cell that does not differentiate into a granulocyte that is suitable for treating cancer and/or that differentiates into a granulocyte that is unsuitable for treating cancer.

The "cancer killing activity (CKA) assay" or "CKA assay" is carried out using an ACEA Biosciences xCELLigence RTCA DP Analyzer system® according to the manufacturer's instructions and as follows:

a. 6000 cancer cells are placed in the bottom of a 16 well plate;
b. cells are grown to confluence as determined by plateauing of Cell Index (CI) values (i.e. the 'normalisation point');
c. 60,000 granulocytes are added (i.e. giving a ratio of 10 granulocytes to 1 cancer cells) and incubated at 37 °C; and
d. the % of cancer cells killed is the maximum % of cancer cells killed by 48 hours after addition of the granulocytes as determined using the following formula: ((Cell Index $_{\text{no effector}}$ – Cell Index $_{\text{effector}}$)/Cell Index $_{\text{no effector}}$) X 100.

The maximum % of cancer cells killed may be referred to herein as "% CKA".

Preferably the cancer cells are PANC-1 cells, which are commercially available from the American Type Culture Collection United Kingdom (U.K.), Guernsey, Ireland, Jersey and Liechtenstein, LGC Standards, Queens Road, Teddington, Middlesex, TW11 0LY, UK and have catalogue number ATCC CRL-1469.

In a particularly preferred embodminent the term "suitable for treating cancer" as used herein further means that a granulocyte kills less than 15% of non-cancer cells in the "non-cancer killing activity (NCKA) assay" described herein. Preferably a granulocyte kills less than 10% (e.g. less than 5% or less than 1%) of non-cancer cells in the "non-cancer killing activity (NCKA) assay" described herein.

The "non-cancer killing activity (NCKA) assay" or "NCKA assay" is carried out using an ACEA Biosciences xCELLigence RTCA DP Analyzer system® according to the manufacturer's instructions and as follows:

a. 6000 non-cancer cells are placed in the bottom of a 16 well plate;
b. cells are grown to confluence as determined by plateauing of Cell Index (CI) values (i.e. the 'normalisation point');

c. 60,000 granulocytes are added (i.e. giving a ratio of 10 granulocytes to 1 non-cancer cells) and incubated at 37 °C; and

d. the % of non-cancer cells killed is the maximum % of non-cancer cells killed by 48 hours after addition of the granulocytes as determined using the following formula: ((Cell Index $_{\text{no effector}}$ – Cell Index $_{\text{effector}}$)/Cell Index $_{\text{no effector}}$) X 100.

Preferably the non-cancer cells are MCF-12F non-cancer cells, which are commercially available from the American Type Culture Collection, 10801 University Boulevard. Manassas, VA 20110 USA and have catalogue number ATCC® CRL-10783™. In another embodiment the non-cancer cells are liver cells (e.g. primary non-transplantable liver tissue cells).

The expression level of one or more genes of the invention may be compared to a reference standard. The comparison may be carried out by any suitable technique known to the person skilled in the art, e.g. a bioinformatics technique. The detected gene expression in the reference standard may have been obtained (e.g. quantified) previously to a method of the invention. The expression level of the genes described herein is suitably known in said reference standard. A reference standard is preferably from the same sample type as that referred to in a method of the invention. For example, both the sample and reference standard may be blood samples.

In one embodiment the term “sample” as used herein (e.g. in reference to a sample from a donor) may be any sample comprising a granulocyte and/or a stem cell and/or other cell capable of differentiating into a granulocyte, preferably comprising a granulocyte. The sample may be any suitable biofluid sample from which a granulocyte and/or a stem cell and/or other cell capable of differentiating into a granulocyte is obtainable, preferably from which a granulocyte is obtainable. A sample may be a blood sample, such as a peripheral blood sample. The term “blood” as used herein encompasses whole blood, blood serum, and blood plasma. Blood may be subjected to centrifugation in order to separate red blood cells, white blood cells, and plasma. Following centrifugation, the mononuclear cell layer may be removed for use in the present invention.

The reference standard may be a proteomic profile (indicating an amount of polypeptide expressed by a granulocyte), a transcriptomic profile (indicating an amount of gene expression by a granulocyte, e.g. measured by way of RNA produced by said granulocyte) or a genomic profile. A genomic profile may be used to detect the presence or absence of

SNPs, promoter sequences, gene copy number (e.g. duplications), and/or enhancer or other relevant genetic features, preferably those that determine the expression level of one or more genes of the invention. The skilled person will appreciate that both the proteomic and transcriptomic profiles are measures of gene expression and will employ the appropriate reference standard depending on the technique used to measure gene expression in accordance with the invention. For example, where proteomics is used in practising the present invention the skilled person will employ a reference standard that is a proteomic profile, where transcriptomics is used in practising the present invention the skilled person will employ a reference standard that is a transcriptomic profile, and where genomics is used in practising the present invention the skilled person will employ a reference standard that is a genomic profile. A reference standard may refer to a database (e.g. a genomic database), e.g. which may include data from one or more sources, such as one or more subjects and/or cells.

A reference standard is preferably a reference standard for a granulocyte that is unsuitable for treating cancer (e.g. a transcriptomic or proteomic profile of a granulocyte that is unsuitable for treating cancer). Such a reference standard may be from a subject that does not have cancer (a healthy subject) or from a subject that has cancer. Preferably, such a reference standard is from a subject that does not have cancer. Figure 1 represents a selection of features that are different between those cells from a subject that has cancer, a normal subject that produces granulocytes unsuitable for treating cancer, and a subject that produces granulocytes that are suitable for treating cancer. Any one of said properties may be measured to characterise granulocytes present in a sample (e.g. in a reference standard).

In one embodiment expression of one or more of *ITGB1, CYBB, SYK, DOCK8, COMP, ATG7, SLC2A1, GZMK, CTSG, ATM, IKBKB, BCAP31, TAPBP, PERM, PLEC, ACSL1, RAC1, GM2A, CAP37,* and *PSMB2* is increased when compared to a reference standard when the reference standard is from a granulocyte unsuitable for treating cancer. In one embodiment expression of *ANXA1* and/or *PPP3CB* is decreased when compared to a reference standard, when the reference standard is from a granulocyte unsuitable for treating cancer. In one embodiment expression of one or more of *ITGB1, CYBB, SYK, DOCK8, COMP, ATG7, SLC2A1, GZMK, CTSG, ATM, IKBKB, BCAP31, TAPBP, PERM, PLEC, ACSL1, RAC1, GM2A, CAP37,* and *PSMB2* is increased when compared to a reference standard when the reference standard is from a granulocyte unsuitable for treating cancer and expression of *ANXA1* and/or *PPP3CB* is decreased when compared to a reference standard, when the reference standard is from a granulocyte unsuitable for treating cancer.

A reference standard may be a reference standard for a granulocyte that is suitable for treating cancer (e.g. a transcriptomic or proteomic profile of a granulocyte that is suitable for treating cancer). In one embodiment expression of one or more of *ITGB1, CYBB, SYK, DOCK8, COMP, ATG7, SLC2A1, GZMK, CTSG, ATM, IKBKB, BCAP31, TAPBP, PERM, PLEC, ACSL1, RAC1, GM2A, CAP37,* and *PSMB2* is increased or the same when compared to a reference standard, when the reference standard is from a granulocyte suitable for treating cancer. In one embodiment expression of *ANXA1* and/or *PPP3CB* is decreased or the same when compared to a reference standard, when the reference standard is from a granulocyte suitable for treating cancer.

In some embodiments the present invention may comprise the use of a reference standard for a granulocyte that is unsuitable for treating cancer and a reference standard for a granulocyte that is suitable for treating cancer.

A method of the invention may comprise determining the suitability of a granulocyte for treating cancer based on a comparison between a measured expression level of one or more genes of the invention and a reference standard.

In one embodiment a granulocyte is determined as being suitable for treating cancer when:

i. a measured expression level of one or more of *ITGB1, CYBB, SYK, DOCK8, COMP, ATG7, SLC2A1, GZMK, CTSG, ATM, IKBKB, BCAP31, TAPBP, PERM, PLEC, ACSL1, RAC1, GM2A, CAP37,* and *PSMB2* is increased when compared to the reference standard when the reference standard is from a granulocyte unsuitable for treating cancer; and/or

ii. a measured expression level of *ANXA1* and/or *PPP3CB* is decreased when compared to the reference standard, when the reference standard is from a granulocyte unsuitable for treating cancer; and/or

iii. a measured expression level of one or more of *ITGB1, CYBB, SYK, DOCK8, COMP, ATG7, SLC2A1, GZMK, CTSG, ATM, IKBKB, BCAP31, TAPBP, PERM, PLEC, ACSL1, RAC1, GM2A, CAP37,* and *PSMB2* is increased or the same when compared to the reference standard, when the reference standard is from a granulocyte suitable for treating cancer; and/or

iv. a measured expression level of *ANXA1* and/or *PPP3CB* is decreased or the same when compared to the reference standard, when the reference standard is from a granulocyte suitable for treating cancer.

In one embodiment a granulocyte is determined as being unsuitable for treating cancer when:

i. a measured expression level of one or more of *ITGB1, CYBB, SYK, DOCK8, COMP, ATG7, SLC2A1, GZMK, CTSG, ATM, IKBKB, BCAP31, TAPBP, PERM, PLEC, ACSL1, RAC1, GM2A, CAP37,* and *PSMB2* is decreased or the same when compared to the reference standard, when the reference standard is from a granulocyte unsuitable for treating cancer; and/or

ii. a measured expression level of *ANXA1* and/or *PPP3CB* is increased or the same when compared to the reference standard, when the reference standard is from a granulocyte unsuitable for treating cancer; and/or

iii. a measured expression level of one or more of *ITGB1, CYBB, SYK, DOCK8, COMP, ATG7, SLC2A1, GZMK, CTSG, ATM, IKBKB, BCAP31, TAPBP, PERM, PLEC, ACSL1, RAC1, GM2A, CAP37,* and *PSMB2* is decreased when compared to reference standard, when the reference standard is from a granulocyte suitable for treating cancer; and/or

iv. a measured expression level of *ANXA1* and/or *PPP3CB* is increased when compared to the reference standard, when the reference standard is from a granulocyte suitable for treating cancer.

The methods of the invention may further comprise selecting (or deselecting/discarding) a granulocyte based on the outcome of the method. In one embodiment, where a granulocyte has been determined to be suitable for treating cancer, a granulocyte may be obtained from a sample from which the tested granulocyte was originally obtained. Alternatively, or additionally a stem cell may be obtained from said sample.

Accordingly, in one aspect, there is provided an *in vitro* method for obtaining a granulocyte suitable for treating cancer, said method comprising obtaining a granulocyte from a sample obtainable from a donor wherein said donor produces granulocytes comprising:

a. increased expression of one or more of *ITGB1, CYBB, SYK, DOCK8, COMP, ATG7, SLC2A1, GZMK, CTSG, ATM, IKBKB, BCAP31, TAPBP, PERM, PLEC, ACSL1, RAC1, GM2A, CAP37,* and *PSMB2* when compared to a reference standard, wherein the reference standard is from a granulocyte unsuitable for treating cancer; and/or

b. decreased expression of *ANXA1* and/or *PPP3CB* when compared to a reference standard, wherein the reference standard is from a granulocyte unsuitable for treating cancer.

In a related aspect, there is provided an *in vitro* method for obtaining a stem cell suitable for treating cancer, said method comprising obtaining a stem cell from a sample obtainable from a donor wherein said donor produces granulocytes comprising:

a. increased expression of one or more of *ITGB1, CYBB, SYK, DOCK8, COMP, ATG7, SLC2A1, GZMK, CTSG, ATM, IKBKB, BCAP31, TAPBP, PERM, PLEC, ACSL1, RAC1, GM2A, CAP37,* and *PSMB2* when compared to a reference standard, wherein the reference standard is from a granulocyte unsuitable for treating cancer; and/or

b. decreased expression of *ANXA1* and/or *PPP3CB* when compared to a reference standard, wherein the reference standard is from a granulocyte unsuitable for treating cancer.

A method of the invention may comprise identifying whether or not a donor produces granulocytes suitable for treating cancer based on a comparison between a measured expression level of one or more genes of the invention and a reference standard.

In one embodiment a donor is identified as being a donor that produces granulocytes suitable for treating cancer when:

i. a measured expression level of one or more of *ITGB1, CYBB, SYK, DOCK8, COMP, ATG7, SLC2A1, GZMK, CTSG, ATM, IKBKB, BCAP31, TAPBP, PERM, PLEC, ACSL1, RAC1, GM2A, CAP37,* and *PSMB2* is increased when compared to the reference standard when the reference standard is from a granulocyte unsuitable for treating cancer; and/or

ii. a measured expression level of *ANXA1* and/or *PPP3CB* is decreased when compared to the reference standard, when the reference standard is from a granulocyte unsuitable for treating cancer; and/or

iii. a measured expression level of one or more of *ITGB1, CYBB, SYK, DOCK8, COMP, ATG7, SLC2A1, GZMK, CTSG, ATM, IKBKB, BCAP31, TAPBP, PERM, PLEC, ACSL1, RAC1, GM2A, CAP37,* and *PSMB2* is increased or the same when compared to the reference standard, when the reference standard is from a granulocyte suitable for treating cancer; and/or

iv. a measured expression level of *ANXA1* and/or *PPP3CB* is decreased or the same when compared to the reference standard, when the reference standard is from a granulocyte suitable for treating cancer.

In one embodiment a donor is not identified as being a donor that produces granulocytes suitable for treating cancer (or is identified as a donor that produces granulocytes that are unsuitable for treating cancer) when:

i. a measured expression level of one or more of *ITGB1, CYBB, SYK, DOCK8, COMP, ATG7, SLC2A1, GZMK, CTSG, ATM, IKBKB, BCAP31, TAPBP, PERM, PLEC, ACSL1, RAC1, GM2A, CAP37,* and *PSMB2* is decreased or the same when compared to the reference standard, when the reference standard is from a granulocyte unsuitable for treating cancer; and/or

ii. a measured expression level of *ANXA1* and/or *PPP3CB* is increased or the same when compared to the reference standard, when the reference standard is from a granulocyte unsuitable for treating cancer; and/or

iii. a measured expression level of one or more of *ITGB1, CYBB, SYK, DOCK8, COMP, ATG7, SLC2A1, GZMK, CTSG, ATM, IKBKB, BCAP31, TAPBP, PERM, PLEC, ACSL1, RAC1, GM2A, CAP37,* and *PSMB2* is decreased when compared to reference standard, when the reference standard is from a granulocyte suitable for treating cancer; and/or

iv. a measured expression level of *ANXA1* and/or *PPP3CB* is increased when compared to the reference standard, when the reference standard is from a granulocyte suitable for treating cancer.

The methods of the invention may further comprise selecting (or deselecting) a donor based on the outcome of the method. In one embodiment, where a donor has been identified as being a donor that produces granulocytes suitable for treating cancer, a granulocyte may be obtained from a sample obtainable from said donor.

In one aspect the invention provides a granulocyte obtainable by a method of the invention.

Alternatively, or additionally a stem cell may be obtained from a sample obtainable from said donor. Thus, in one aspect the invention provides a method comprising:

a. identifying a donor that produces granulocytes suitable for treating cancer according to a method of the invention; and

b. obtaining a stem cell from a sample obtainable from the donor.

Thus, in one aspect, the invention provides a stem cell obtainable by a method of the invention. The stem cell is capable of differentiating into a granulocyte for treating cancer, wherein the granulocyte comprises:

a. increased expression of one or more of *ITGB1, CYBB, SYK, DOCK8, COMP, ATG7, SLC2A1, GZMK, CTSG, ATM, IKBKB, BCAP31, TAPBP, PERM, PLEC, ACSL1, RAC1, GM2A, CAP37,* and *PSMB2* when compared to a reference standard, wherein the reference standard is from a granulocyte unsuitable for treating cancer; and/or

b. decreased expression of *ANXA1* and/or *PPP3CB* when compared to a reference standard, wherein the reference standard is from a granulocyte unsuitable for treating cancer.

The term "obtainable" as used herein also encompasses the term "obtained". In one embodiment the term "obtainable" means obtained.

In a related aspect, there is provided a stem cell which is capable of differentiating into a granulocyte for treating cancer, wherein the granulocyte comprises:

a. increased expression of one or more of *ITGB1, CYBB, SYK, DOCK8, COMP, ATG7, SLC2A1, GZMK, CTSG, ATM, IKBKB, BCAP31, TAPBP, PERM, PLEC, ACSL1, RAC1, GM2A, CAP37,* and *PSMB2* when compared to a reference standard, wherein the reference standard is from a granulocyte unsuitable for treating cancer; and/or

b. decreased expression of *ANXA1* and/or *PPP3CB* when compared to a reference standard, wherein the reference standard is from a granulocyte unsuitable for treating cancer.

The term "stem cell" as used herein encompasses any cell that is capable of differentiating into a granulocyte (preferably a neutrophil). For example, the term "stem cell" may encompass totipotent, pluripotent, multipotent, or unipotent cells. In one embodiment the term "stem cell" encompasses a haematopoietic stem cell, as well as a precursor cell (e.g. differentiated from a haematopoietic stem cell), wherein said precursor cell is capable of differentiating into a granulocyte (preferably a neutrophil). Preferably the term "stem cell" as used herein does not encompass a human embryonic stem cell.

A stem cell may be part of a stem cell culture.

The "stem cell" may be a natural stem cell or an artificial stem cell. In one embodiment a natural stem cell may be a cell of the haematopoiesis pathway or a cell equivalent thereto. In one embodiment an artificial stem cell may be an induced pluripotent stem cell (iPSC) or a cell equivalent thereto.

In one embodiment, an iPSC is obtainable from a somatic cell, such as a somatic cell of a donor. Generation of iPSCs is a well-known technique in the art, *see* Yu *et al* (2007), Science, 318:1917-1920 the teaching of which is incorporated herein by reference.

In another embodiment, an iPSC is obtainable from a stem cell (e.g. obtainable from a donor), such as from a stem cell of the hematopoietic pathway. Preferably an iPSC is obtainable from a hematopoietic stem cell or a precursor cell described herein.

In one embodiment, a stem cell is a nuclear transfer embryonic stem cell (NT-ESC) or equivalent thereto. In one embodiment, an NT-ESC is obtainable by injecting the nucleus of a cell from the donor into an egg cell from which the original nucleus has been removed. Generation of NT-ESCs is a well-known technique in the art, *see* Tachibana M, Amato P, Sparman M, *et al* (2013), Cell, 154(2): 465-466 the teaching of which is incorporated herein by reference.

In one embodiment where a stem cell is obtained from a sample from a donor, said stem cell may be isolated from said sample. In another embodiment where a stem cell is obtained from a sample from a donor, said sample is a sample comprising stem cells or somatic cells and the stem cell is obtained by inducing pluripotency of and/or reprogramming a cell (e.g. a somatic cell) in said sample to obtain a stem cell (e.g. an iPSC).

In one embodiment the cell is reprogrammed into an induced pluripotent stem. The cell which is reprogrammed may be a hematopoietic progenitor cell, a mononuclear myeloid cell or a peripheral blood mononuclear cell using methods based on the disclosure in Ohmine *et al*, Stem Cell Res Ther 2011 Nov;2(6):46 and/or Rim *et al*, J Vis Exp 2016;(118) which are incorporated herein by reference.

In another embodiment the cell is reprogrammed into a multipotent stem cell, for example a hematopoietic stem cell, or a progenitor cell, for example a multilineage blood progenitor. The cell which is reprogrammed may be a fibroblast or a blood cell using methods based on the disclosure in Riddell *et al*, Cell 2014; 157(3) 549-64 and/or Szabo *et al*, Nature 2010; 468(7323) 521-526.

In another embodiment where a stem cell is obtained from a sample from a donor, said sample is a sample comprising stem cells or somatic cells and the stem cell is obtained by

injecting the nucleus of a cell (e.g. a somatic cell) in said sample into an egg cell (e.g. from which the original nucleus has been removed) to obtain an NT-ESC.

In a preferred embodiment a stem cell is a haematopoietic stem cell. A haematopoietic stem cell may, in one embodiment, be selected on the basis of cell surface polypeptide markers, for example selected from CD34 (e.g. UniProt accession number P28906), CD59 (e.g. UniProt accession number P13987), Thy1 (e.g. UniProt accession number P04216), CD38 (e.g. UniProt accession number P28907), C-kit (e.g. UniProt accession number P10721), and lin. In one embodiment a haematopoietic stem cell comprises the cell surface polypeptide markers $CD34^+$, $CD59^+$, $Thy1^+$, $CD38^{low/-}$, $C\text{-}kit^{low/-}$, and lin^-. Preferably a haematopoietic cell expresses CD34. Antibodies to detect the presence or absence of said markers are commercially available and may be obtained from BD Biosciences Europe, ebioscience, Beckman Coulter and Pharmingen, for example.

Most preferably, a stem cell is a precursor cell (which may be referred to herein as a "granulocyte precursor cell"). In one embodiment a precursor cell is a granulocyte-committed progenitor, preferably a neutrophil-committed progenitor. A precursor cell may be one or more selected from a common myeloid progenitor cell, a myeloblast, a promyelocyte (e.g. a N. promyelocyte), a myelocyte (e.g. a N. myelocyte), a metamyelocyte (e.g. a N. metamyelocyte), a band (e.g. an N. band), or combinations thereof. Preferably, a precursor cell is a N. promyelocyte.

A stem cell of the present invention is preferably an isolated stem cell, e.g. a stem cell that has been isolated from its physiological surroundings, such as an *ex vivo* stem cell.

A stem cell may be differentiated into a granulocyte. A stem cell (e.g. a haematopoietic stem cell, an iPSC, or a NT-ESC) may be differentiated into another type of stem cell (e.g. a precursor cell). Differentiation may be carried out using any suitable method, such as a method based on the disclosure in Lengerke *et al*, Ann N Y Acad Sci, 2009 Sep; 1176:219-217, Pawlowski *et al*, Stem Cell Reports 2017 Apr 11;8(4):803-812, Doulatov *et al*, Cell Stem Cell, 2013, Oct 3;13(4)459-470, Lieber *et al*, Blood, 2004 Feb 1;103(3):852-9, and/ or Choi *et al*, Nat. Protoc., 2011 Mar;6(3):296-313, and/or Timmins *et. al*. Biotechnology and bioengineering. 2009;104(4):832–40, which are incorporated herein by reference.

In one aspect, the invention provides a method for preparing a stem cell suitable for treating cancer, the method comprising:

a. identifying a donor that produces granulocytes for treating cancer according to a method of the invention; and

b. obtaining the stem cell from a sample obtainable from said donor.

In another aspect, the invention provides a method for producing a stem cell for treating cancer, the method comprising:

a. providing a stem cell obtainable from a sample from a donor wherein said donor produces granulocytes comprising:

i. increased expression of one or more of *ITGB1, CYBB, SYK, DOCK8, COMP, ATG7, SLC2A1, GZMK, CTSG, ATM, IKBKB, BCAP31, TAPBP, PERM, PLEC, ACSL1, RAC1, GM2A, CAP37,* and *PSMB2* when compared to a reference standard, wherein the reference standard is from a granulocyte unsuitable for treating cancer; and/or

ii. decreased expression of *ANXA1* and/or *PPP3CB* when compared to a reference standard, wherein the reference standard is from a granulocyte unsuitable for treating cancer ; and

b. differentiating the stem cell into a different stem cell (preferably a precursor cell); and

c. optionally isolating the different stem cell (preferably the precursor cell).

In embodiments where the stem cell is a precursor cell, the different stem cell may be a different precursor cell.

In one embodiment, the sample comprises a somatic cell and obtaining the stem cell from the sample comprises reprograming the somatic cell into a stem cell.

In one aspect the invention provides a method for producing a granulocyte for treating cancer, the method comprising:

a. providing a cell; and

b. converting the cell into a granulocyte having an expression profile described herein, for example wherein:

i. the measured expression level of one or more of *GM2A, CTSG, CAP37, ITGB1, CYBB, SYK, DOCK8, COMP, ATG7, SLC2A1, GZMK, ATM, IKBKB, BCAP31, TAPBP, PERM, PLEC, ACSL1, RAC1,* and *PSMB2* is increased in the granulocyte when compared to a reference standard

when the reference standard is from a granulocyte unsuitable for treating cancer; or

ii. the measured expression level of *ANXA1* and/or *PPP3CB* is decreased in the granulocyte when compared to the reference standard, when the reference standard is from a granulocyte unsuitable for treating cancer; or

iii. the measured expression level of one or more of *GM2A, CTSG, CAP37, ITGB1, CYBB, SYK, DOCK8, COMP, ATG7, SLC2A1, GZMK, ATM, IKBKB, BCAP31, TAPBP, PERM, PLEC, ACSL1, RAC1,* and *PSMB2* is increased or the same when compared to the reference standard, when the reference standard is from a granulocyte suitable for treating cancer; or

iv. the measured expression level of *ANXA1* and/or *PPP3CB* is decreased or the same when compared to the reference standard, when the reference standard is from a granulocyte suitable for treating cancer; and

c. optionally isolating the granulocyte.

In one embodiment a method for producing a granulocyte for treating cancer comprises:

a. providing a cell; and

b. converting the cell into a granulocyte having an expression profile described herein, for example wherein:

i. the measured expression level of one or more of *GM2A, CTSG, CAP37, ITGB1, CYBB, SYK, DOCK8, COMP, ATG7, SLC2A1, GZMK, ATM, IKBKB, BCAP31, TAPBP, PERM, PLEC, ACSL1, RAC1,* and *PSMB2* is increased in the granulocyte when compared to a reference standard when the reference standard is from a granulocyte unsuitable for treating cancer; and/or (preferably and)

ii. the measured expression level of *ANXA1* and/or *PPP3CB* is decreased in the granulocyte when compared to the reference standard, when the reference standard is from a granulocyte unsuitable for treating cancer; and/or (preferably and)

iii. the measured expression level of one or more of *GM2A, CTSG, CAP37, ITGB1, CYBB, SYK, DOCK8, COMP, ATG7, SLC2A1, GZMK, ATM, IKBKB, BCAP31, TAPBP, PERM, PLEC, ACSL1, RAC1,* and *PSMB2* is increased or the same when compared to the reference standard, when the reference standard is from a granulocyte suitable for treating cancer; and/or (preferably and)

iv. the measured expression level of *ANXA1* and/or *PPP3CB* is decreased or the same when compared to the reference standard, when the reference standard is from a granulocyte suitable for treating cancer; and

c. optionally isolating the granulocyte.

The cell may be a stem cell according to the invention or a somatic/differentiated cell optionally from a donor who produces granulocytes suitable for treating cancer as determined by a method of the invention. In one embodiment, converting the cell into a granulocyte comprises transdifferentiating a somatic/differentiated cell into a granulocyte using standard techniques known in the art, for example those based on Szabo *et al*, Nature 2010; 468(7323) 521-526.

In one embodiment converting the cell into a granulocyte comprises differentiating a stem cell into a granulocyte based on standard techniques known in the art, for example those referenced herein. For example, in one embodiment a method of differentiating a stem cell comprises admixing said stem cell with a granulocyte-macrophage colony-stimulating factor (GM-CSF), a granulocyte colony-stimulating factor (G-CSF), a growth hormone; serotonin, vitamin C, vitamin D, glutamine (Gln), arachidonic acid, AGE-albumin, an interleukin, TNF-alpha, Flt-3 ligand, thrombopoietin, foetal bovine serum (FBS), retinoic acid, lipopolysaccharide (LPS), IFN-gamma, IFN-beta or combinations thereof. In some embodiments, a method of differentiating a stem cell comprises admixing said stem cell with IFN-gamma and GM-CSF. In preferable embodiments, a method of differentiating a stem cell comprises admixing said stem cell with TNF-alpha.

In one embodiment the invention provides a method of differentiating a stem cell comprising admixing said stem cell with a granulocyte-macrophage colony-stimulating factor (GM-CSF), and a granulocyte colony-stimulating factor (G-CSF), and a growth hormone, and serotonin, and vitamin C, and vitamin D, and glutamine (Gln), and arachidonic acid, and AGE-albumin, and an interleukin, and TNF-alpha, and Flt-3 ligand, and thrombopoietin, and foetal bovine serum (FBS).

In one embodiment the invention provides a method of differentiating a stem cell comprising admixing said stem cell with a granulocyte-macrophage colony-stimulating factor (GM-CSF), and a granulocyte colony-stimulating factor (G-CSF), and a growth hormone, and serotonin, and vitamin C, and vitamin D, and glutamine (Gln), and arachidonic acid, and AGE-albumin, and an interleukin, and TNF-alpha, and Flt-3 ligand, and thrombopoietin, and foetal bovine

serum (FBS), and retinoic acid, and lipopolysaccharide (LPS), and IFN-gamma, and IFN-beta.

The term "admix" as used herein means mixing one or more components together in any order, whether sequentially or simultaneously. In one embodiment "admix" means contacting a first component with a second component (e.g. a stem cell and GM-CSF).

In one embodiment differentiation of a stem cell comprises culturing said stem cell with one or more feeder cell(s). Suitably, a feeder cell may be an OP9 cell. OP9 cells (ATCC® CRL-2749™) are commercially available from the American Type Culture Collection United Kingdom (U.K.), Guernsey, Ireland, Jersey and Liechtenstein, LGC Standards, Queens Road, Teddington, Middlesex, TW11 0LY, UK. In one embodiment a stem cell may be cultured with one or more feeder cell(s) and Flt-3 ligand, thrombopoietin, fetal bovine serum (FBS), or combinations thereof.

Thus in one embodiment, a pharmaceutical composition or cell culture of the invention may further comprise a feeder cell, such as an OP9 cell.

A stem cell may be immortalised. The person skilled in the art is familiar with immortalisation techniques, which include *inter alia* introduction of a viral gene that deregulates the cell cycle (e.g. the adenovirus type 5 E1 gene), and artificial expression of telomerase. Immortalisation advantageously allows for the preparation of a cell line which can be stably cultured *in vitro*. Thus, in one aspect the invention provides an immortalised cell line obtainable (e.g. obtained) from a selected stem cell, as well as a stable stem cell culture. Suitably an immortalised cell line or stable stem cell culture is obtainable (e.g. obtained) by a method of the present invention.

The term "stable" as used in reference to a stem cell culture or cell line means that the cell culture or cell line has been modified such that it is more amenable to *in vitro* cell culture than an unmodified cell (i.e. a cell obtained from a donor and subjected directly to *in vitro* cell culture). Said "stable" cell culture or cell line is therefore capable of undergoing more rounds of replication (preferably for prolonged periods of time) when compared to an unmodified cell.

In one aspect the invention provides a method for selecting whether or not a subject is suitable for treatment with a granulocyte or a stem cell for treating cancer, the method comprising:

a. comparing a measured expression level of one or more genes by a granulocyte comprised in a sample obtainable from the subject, wherein the one or more genes are associated with suitability for treating cancer and are selected from: *CTSG, CAP37, ITGB1, CYBB, SYK, DOCK8, COMP, ATG7, SLC2A1, GZMK, ATM, IKBKB, BCAP31, TAPBP, PPP3CB, ANXA1, PERM, PLEC, ACSL1, RAC1, GM2A,* and *PSMB2* with the expression level of the same one or more genes in a reference standard; and

b. identifying whether or not the subject is suitable for treatment with a granulocyte or a stem cell for treating cancer based on the comparison.

In one aspect the invention provides a method for selecting whether or not a subject is suitable for treatment with a granulocyte or a stem cell for treating cancer, the method comprising:

a. measuring an expression level of one or more genes by a granulocyte comprised in a sample obtainable from the subject, wherein the one or more genes are associated with suitability for treating cancer and are selected from: *ITGB1, CYBB, SYK, DOCK8, COMP, ATG7, SLC2A1, GZMK, CTSG, ATM, IKBKB, BCAP31, TAPBP, PPP3CB, ANXA1, PERM, PLEC, ACSL1, RAC1, GM2A, CAP37,* and *PSMB2*;

b. comparing the measured expression level with the expression level of the same one or more genes in a reference standard; and

c. identifying whether or not the subject is suitable for treatment with a granulocyte or a stem cell for treating cancer based on the comparison.

The foregoing method allows for the identification of subjects who have granulocytes that are unsuitable for treating cancer and who are appropriate candidates for treatment with a granulocyte or stem cell of the invention. Advantageously, patients who are most likely to respond positively to treatment can be selected, thereby allowing for more cost-effective and/or economical prescribing of the granulocyte and/or stem cell of the invention and/or avoiding selection of an incorrect patient cohort for clinical trials.

In one embodiment a subject is identified as being suitable for treatment with a granulocyte or stem cell of the invention when:

i. a measured expression level of one or more of *ITGB1, CYBB, SYK, DOCK8, COMP, ATG7, SLC2A1, GZMK, CTSG, ATM, IKBKB, BCAP31, TAPBP, PERM, PLEC, ACSL1, RAC1, GM2A, CAP37,* and *PSMB2* is decreased or the same when compared to a reference standard, when the reference standard is from a granulocyte unsuitable for treating cancer; or

ii. a measured expression level of *ANXA1* and/or *PPP3CB* is increased or the same when compared to a reference standard, when the reference standard is from a granulocyte unsuitable for treating cancer; or

iii. a measured expression level of one or more of *ITGB1, CYBB, SYK, DOCK8, COMP, ATG7, SLC2A1, GZMK, CTSG, ATM, IKBKB, BCAP31, TAPBP, PERM, PLEC, ACSL1, RAC1, GM2A, CAP37,* and *PSMB2* is decreased when compared to a reference standard, when the reference standard is from a granulocyte suitable for treating cancer; or

iv. a measured expression level of *ANXA1* and/or *PPP3CB* is increased when compared to a reference standard, when the reference standard is from a granulocyte suitable for treating cancer.

In one embodiment a subject is identified as being unsuitable for treatment with a granulocyte or stem cell of the invention when:

i. a measured expression level of one or more of *ITGB1, CYBB, SYK, DOCK8, COMP, ATG7, SLC2A1, GZMK, CTSG, ATM, IKBKB, BCAP31, TAPBP, PERM, PLEC, ACSL1, RAC1, GM2A, CAP37,* and *PSMB2* is increased when compared to a reference standard when the reference standard is from a granulocyte unsuitable for treating cancer; or

ii. a measured expression level of *ANXA1* and/or *PPP3CB* is decreased when compared to a reference standard, when the reference standard is from a granulocyte unsuitable for treating cancer; or

iii. a measured expression level of one or more of *ITGB1, CYBB, SYK, DOCK8, COMP, ATG7, SLC2A1, GZMK, CTSG, ATM, IKBKB, BCAP31, TAPBP, PERM, PLEC, ACSL1, RAC1, GM2A, CAP37,* and *PSMB2* is increased or the same when compared to a reference standard, when the reference standard is from a granulocyte suitable for treating cancer; or

iv. a measured expression level of *ANXA1* and/or *PPP3CB* is decreased or the same when compared to a reference standard, when the reference standard is from a granulocyte suitable for treating cancer

The terms “subject” and “patient” are used synonymously herein. The “subject” may be a mammal, and preferably the subject is a human subject.

In another aspect the invention provides a method for determining a subject’s risk for developing cancer, the method comprising:

a. comparing a measured expression level of one or more genes by a granulocyte comprised in a sample obtainable from the subject, wherein the one or more

genes are associated with suitability for treating cancer and are selected from: *CTSG, CAP37, ITGB1, CYBB, SYK, DOCK8, COMP, ATG7, SLC2A1, GZMK, ATM, IKBKB, BCAP31, TAPBP, PPP3CB, ANXA1, PERM, PLEC, ACSL1, RAC1, GM2A,* and *PSMB2* with the expression level of the same one or more genes in a reference standard; and

b. determining the subject's risk for developing cancer based on the comparison.

In a related aspect there is provided a method for determining a subject's risk for developing cancer, the method comprising:

a. measuring an expression level of one or more genes by a granulocyte comprised in a sample obtainable from the subject, wherein the one or more genes are associated with suitability for treating cancer and are selected from: *ITGB1, CYBB, SYK, DOCK8, COMP, ATG7, SLC2A1, GZMK, CTSG, ATM, IKBKB, BCAP31, TAPBP, PPP3CB, ANXA1, PERM, PLEC, ACSL1, RAC1, GM2A, CAP37,* and *PSMB2*;

b. comparing the measured expression level with the expression level of the same one or more genes in a reference standard; and

c. determining the subject's risk for developing cancer based on the comparison.

In one embodiment a subject is determined as being at risk of developing cancer when:

i. a measured expression level of one or more of *ITGB1, CYBB, SYK, DOCK8, COMP, ATG7, SLC2A1, GZMK, CTSG, ATM, IKBKB, BCAP31, TAPBP, PERM, PLEC, ACSL1, RAC1, GM2A, CAP37,* and *PSMB2* is decreased or the same when compared to a reference standard, when the reference standard is from a granulocyte unsuitable for treating cancer; or

ii. a measured expression level of *ANXA1* and/or *PPP3CB* is increased or the same when compared to a reference standard, when the reference standard is from a granulocyte unsuitable for treating cancer; or

iii. a measured expression level of one or more of *ITGB1, CYBB, SYK, DOCK8, COMP, ATG7, SLC2A1, GZMK, CTSG, ATM, IKBKB, BCAP31, TAPBP, PERM, PLEC, ACSL1, RAC1, GM2A, CAP37,* and *PSMB2* is decreased when compared to a reference standard, when the reference standard is from a granulocyte suitable for treating cancer

iv. a measured expression level of ANXA1 and/or PPP3CB is increased when compared to a reference standard, when the reference standard is from a granulocyte suitable for treating cancer.

In one embodiment a subject is determined as not at risk of developing cancer when:

i. a measured expression level of one or more of *ITGB1, CYBB, SYK, DOCK8, COMP, ATG7, SLC2A1, GZMK, CTSG, ATM, IKBKB, BCAP31, TAPBP, PERM, PLEC, ACSL1, RAC1, GM2A, CAP37,* and *PSMB2* is increased when compared to a reference standard when the reference standard is from a granulocyte unsuitable for treating cancer; or

ii. a measured expression level of *ANXA1* and/or *PPP3CB* is decreased when compared to a reference standard, when the reference standard is from a granulocyte unsuitable for treating cancer; or

iii. a measured expression level of one or more of *ITGB1, CYBB, SYK, DOCK8, COMP, ATG7, SLC2A1, GZMK, CTSG, ATM, IKBKB, BCAP31, TAPBP, PERM, PLEC, ACSL1, RAC1, GM2A, CAP37,* and *PSMB2* is increased or the same when compared to a reference standard, when the reference standard is from a granulocyte suitable for treating cancer; or

iv. a measured expression level of *ANXA1* and/or *PPP3CB* is decreased or the same when compared to a reference standard, when the reference standard is from a granulocyte suitable for treating cancer

The term “granulocyte” encompasses the following cell types: neutrophils, basophils, and eosinophils. Preferably the granulocyte is a neutrophil. A granulocyte may express the cell surface polypeptide markers CD11b (e.g. UniProt accession number P11215) and CD15. A granulocyte may also produce reactive oxygen species (O_2^-). Preferably the granulocyte $CD11b^{high}$. Alternatively or additionally, the granulocyte may have a higher density than granulocytes unsuitable for treating cancer, and/or a positive cell surface charge (e.g. a net cell charge).

A granulocyte of the present invention is preferably an isolated granulocyte, e.g. a granulocyte that has been isolated from its physiological surroundings, such as an *ex vivo* granulocyte.

In some embodiments the granulocyte is obtainable from a sample obtainable from a donor. In another embodiment a granulocyte may be an engineered granulocyte. Such a granulocyte may be produced by a method comprising:

a. providing a granulocyte; and

b. engineering the granulocyte to:

i. increase expression of one or more genes selected from: *ITGB1, CYBB, SYK, DOCK8, COMP, ATG7, SLC2A1, GZMK, CTSG, ATM, IKBKB, BCAP31, TAPBP, PERM, PLEC, ACSL1, RAC1, GM2A, CAP37,* and *PSMB2*; and/or

ii. decrease expression of *ANXA1* and/or *PPP3CB*;

thereby producing the engineered granulocyte, wherein the engineered granulocyte is suitable for treating cancer. In some embodiments the engineered granulocyte may be used as a reference standard in a method of the invention (i.e. as a reference standard from a granulocyte suitable for treating cancer).

The granulocyte provided for use in the method is preferably a granulocyte that is unsuitable for treating cancer. Thus, in some embodiments a method of the invention converts a cell that is unsuitable for treating cancer into a granulocyte that is suitable for treating cancer. Said granulocyte may be identified by a method described herein, obtained from a donor identified by a method described herein (e.g. from a subject suitable for treatment with a granulocyte or stem cell of the invention), and/or from a subject identified as being at risk of developing cancer.

In a related aspect the invention provides a method for producing an engineered stem cell, the method comprising:

a. providing a stem cell; and

b. engineering the stem cell to:

i. increase expression of one or more genes selected from: *ITGB1, CYBB, SYK, DOCK8, COMP, ATG7, SLC2A1, GZMK, CTSG, ATM, IKBKB, BCAP31, TAPBP, PERM, PLEC, ACSL1, RAC1, GM2A, CAP37,* and *PSMB2*; and/or

ii. decrease expression of *ANXA1* and/or *PPP3CB*;

thereby producing the engineered stem cell, wherein the engineered stem cell is suitable for treating cancer. In some embodiments the engineered stem cell may be used as a reference standard in a method of the invention (i.e. as a reference standard from a stem cell suitable for treating cancer).

In a related aspect the invention provides a method for producing an engineered stem cell, the method comprising:

a. providing a stem cell; and

b. engineering the stem cell such that it is capable of differentiating into a granulocyte having:

i. increased expression of one or more genes selected from: *ITGB1, CYBB, SYK, DOCK8, COMP, ATG7, SLC2A1, GZMK, CTSG, ATM, IKBKB, BCAP31, TAPBP, PERM, PLEC, ACSL1, RAC1, GM2A, CAP37,* and *PSMB2*; and/or

ii. decreased expression of *ANXA1* and/or *PPP3CB*;

thereby producing the engineered stem cell, wherein the engineered stem cell is suitable for treating cancer. In some embodiments the engineered stem cell may be used as a reference standard in a method of the invention (i.e. as a reference standard from a stem cell suitable for treating cancer).

The stem cell provided for use in the method is preferably a stem cell that is unsuitable for treating cancer. Thus, in some embodiments a method of the invention converts a stem cell that is unsuitable for treating cancer into a stem cell that is suitable for treating cancer. Said stem cell may be identified by a method described herein, obtained from a donor identified by a method described herein (e.g. from a subject suitable for treatment with a granulocyte or stem cell of the invention), and/or from a subject identified as being at risk of developing cancer.

Engineering a stem cell or granulocyte may be carried out *in vivo*, for example in one aspect the invention comprises engineering a stem cell or granulocyte in a subject, preferably engineering a stem cell in a subject. In one embodiment the invention may comprise engineering a stem cell or granulocyte *in situ* in a subject (e.g. in the bone marrow of a subject). Suitably, said subject may be a subject that produces stem cells or granulocytes that are unsuitable for treating cancer, a subject that is suitable for treatment with a granulocyte or stem cell of the invention, a subject that is at risk of developing cancer, or combinations thereof.

The engineering may be carried out using any means known to the person skilled in the art. In one embodiment expression may be increased or decreased using genome editing. In one embodiment expression may be increased or decreased using CRISPR (e.g. the DNA-snipping CRISPR-associated endonuclease Cas9 genome-editing system), TALENS, Zinc finger proteins, adenoviruses (AV), retroviruses, vectors (e.g. inducible and/or over-expressible vectors), transgene insertion, cisgene over- or under-expression, silencing, or epigenetic modulation of promoter regions through histone deacetylase (HDAC) inhibitors, or combinations thereof. The expression of genes associated with suitability for treating cancer can be modulated in stem cells (e.g. myeloblasts) using methods of culturing (adapted from Gupta D, Shah HP, Malu K, Berliner N, Gaines P. Differentiation and characterization of myeloid cells. Curr Protoc Immunol. 2014;104:Unit 22F 25.), and in any suitable cells by using CRISPR methods (adapted from N.E. Sanjana, O. Shalem, F. Zhang Improved vectors and genome-wide libraries for CRISPR screening Nat. Methods, 11 (2014), pp. 783-784), TALEN systems (adapted from A.A. Nemudryi, K.R. Valetdinova, S.P. Medvedev, and S.M.

Zakian TALEN and CRISPR/Cas genome editing systems: tools of discovery. Acta Naturae. 2014; 6(3); 19-40), and Zinc finger proteins (adapted from M.C. Keightley et al. The Pu.1 target gene Zbtb11 regulates neutrophil development through its integrase-like HHCC zinc finger. Nat Commun. 2017;8;14911) to generate cells with key genes knocked-in or knocked-out. Where the cell is a stem cell, said cell can be differentiated to produce granulocytes. Briefly, by using lentiviral transduction of single guide CRISPR–Cas9 vectors, pre-validated CRISPR (guide) gRNA sequences to genes associated with suitability for treating cancer in the lentiviral vector lentiCRISPRv2 can be ordered from GenScript or AddGene. CRISPR knockout experiments may use targeting sequences within exons, whereas CRISPR activation or repression experiments may use targets within promoters. ANXA1 for instance, can be knocked-out of a cell to improve cancer killing activity using a pre-validated gRNA targeting its exon. Lentiviral vectors may be prepared and suitable cells transduced (according to previously published protocols (Satchwell TJ, Hawley BR, Bell AJ, Ribeiro ML, Toye AM. The cytoskeletal binding domain of band 3 is required for multiprotein complex formation and retention during erythropoiesis. Haematologica 2015;100(1):133–142.). Verification of CRISPR on- and off-target effects can be confirmed via whole genome sequencing by comparing the genomic differences between the unedited control and the modified samples. Modified myeloblasts may then be differentiated and identified using the methods of Gupta and colleagues (2014). In one embodiment said approaches may be applied to granulocytes or stem cells.

In some embodiments the engineering may be modulation of one or more cytokines driving lineage in stem cells and/or genes associated with suitability for treating cancer.

In one aspect of the invention, there is provided a granulocyte (or engineered granulocyte) for treating cancer, wherein the granulocyte comprises:

a. increased expression of one or more of *ITGB1, CYBB, SYK, DOCK8, COMP, ATG7, SLC2A1, GZMK, CTSG, ATM, IKBKB, BCAP31, TAPBP, PERM, PLEC, ACSL1, RAC1, GM2A, CAP37,* and *PSMB2* when compared to a reference standard, wherein the reference standard is from a granulocyte unsuitable for treating cancer; and/or

b. decreased expression of *ANXA1* and/or *PPP3CB* when compared to a reference standard, wherein the reference standard is from a granulocyte unsuitable for treating cancer.

In one embodiment a granulocyte comprises:

a. increased expression of one or more of *ITGB1, CYBB, SYK, DOCK8, COMP, ATG7, SLC2A1, GZMK, CTSG, ATM, IKBKB, BCAP31, TAPBP, PERM, PLEC, ACSL1, RAC1, GM2A, CAP37,* and *PSMB2* when compared to a reference standard, wherein the reference standard is from a granulocyte unsuitable for treating cancer; and

b. decreased expression of *ANXA1* and/or *PPP3CB* when compared to a reference standard, wherein the reference standard is from a granulocyte unsuitable for treating cancer.

In a particularly preferred embodiment a granulocyte of the invention has a positively charged cell surface (or a more positively charged cell surface when compared to a granulocyte that is unsuitable for treating cancer).

The skilled person would appreciate that the granulocytes or stem cells of the invention do not need to be activated *ex vivo* to be suitable for treating cancer. To the extent that the granulocytes or stem cells of the invention are activated *ex vivo*, the skilled person would appreciate that any activation would further increase the cancer killing activity of the granulocytes or stem cells. Accordingly, in some embodiments, the granulocyte or stem cell for treating cancer has not been activated *ex vivo*. In some embodiments, the granulocyte or stem cell for treating cancer has not been activated *ex vivo* with a chemokine or cytokine. For example, in some embodiments, the granulocyte or stem cell for treating cancer has not been activated *ex vivo* with TGFβ, CCL2, CCL3, CCL5, CXC1, CXC12 and/or CXC16. In preferred embodiments, the granulocyte or stem cell for treating cancer has not been activated *ex vivo* with CCL2. In preferred embodiments, the granulocyte or stem cell for treating cancer has not been activated *ex vivo* with TGFβ. In some embodiments, the granulocyte or stem cell for treating cancer has not been activated with a granulocyte-macrophage colony-stimulating factor (GM-CSF), a granulocyte colony-stimulating factor (G-CSF), a growth hormone; serotonin, vitamin C, vitamin D, glutamine (Gln), arachidonic acid, AGE-albumin, an interleukin, TNF-alpha, Flt-3 ligand, thrombopoietin, foetal bovine serum (FBS), retinoic acid, lipopolysaccharide (LPS), IFN-gamma, IFN-beta or combinations thereof. Thus, in some embodiments, the granulocyte or stem cell for treating cancer is an unactivated granulocyte or stem cell.

Accordingly, in some embodiments of a method of the invention, the method does not comprise activating a granulocyte or stem cell for treating cancer *ex vivo*. For example, in some embodiments, the method does not comprise activating the granulocyte or stem cell for treating cancer. In some embodiments, the method does not comprise activating the

granulocyte or stem cell for treating cancer *ex vivo* with a chemokine or cytokine. For example, in some embodiments, the method does not comprise activating the granulocyte or stem cell for treating cancer *ex vivo* with TGFβ, CCL2, CCL3, CCL5, CXC1, CXC12 and/or CXC16. In preferred embodiments, the method does not comprise activating the granulocyte or stem cell for treating cancer *ex vivo* with CCL2. In preferred embodiments, the method does not comprise activating the granulocyte or stem cell for treating cancer *ex vivo* with TGFβ. In some embodiments, the method does not comprise activating the granulocyte or stem cell for treating cancer *ex vivo* with a granulocyte-macrophage colony-stimulating factor (GM-CSF), a granulocyte colony-stimulating factor (G-CSF), a growth hormone; serotonin, vitamin C, vitamin D, glutamine (Gln), arachidonic acid, AGE-albumin, an interleukin, TNF-alpha, Flt-3 ligand, thrombopoietin, foetal bovine serum (FBS), retinoic acid, lipopolysaccharide (LPS), IFN-gamma, IFN-beta or combinations thereof.

In alternative embodiments, the granulocyte or stem cell for treating cancer has been activated *ex vivo*. In some embodiments, the granulocyte or stem cell for treating cancer has been activated *ex vivo* with a chemokine or cytokine. For example, in some embodiments, the granulocyte or stem cell for treating cancer has been activated *ex vivo* with TGFβ, CCL2, CCL3, CCL5, CXC1, CXC12 and/or CXC16. In preferred embodiments, the granulocyte or stem cell for treating cancer has been activated *ex vivo* with CCL2. In preferred embodiments, the granulocyte or stem cell for treating cancer has been activated *ex vivo* with TGFβ. In some embodiments, the granulocyte or stem cell has been activated with a granulocyte-macrophage colony-stimulating factor (GM-CSF), a granulocyte colony-stimulating factor (G-CSF), a growth hormone; serotonin, vitamin C, vitamin D, glutamine (Gln), arachidonic acid, AGE-albumin, an interleukin, TNF-alpha, Flt-3 ligand, thrombopoietin, foetal bovine serum (FBS), retinoic acid, lipopolysaccharide (LPS), IFN-gamma, IFN-beta or combinations thereof. In some embodiments, the granulocyte or stem cell for treating cancer has been activated with IFN-gamma and GM-CSF. In preferred embodiments, the granulocyte or stem cell for treating cancer has been activated with TNF-alpha. Thus, in some embodiments, the granulocyte or stem cell for treating cancer is an activated granulocyte or stem cell.

Accordingly, in some embodiments of a method of the invention, the method comprises activating a granulocyte or stem cell for treating cancer *ex vivo*. For example, in some embodiments, the method comprises activating the granulocyte or stem cell for treating cancer. In some embodiments, the method does comprises activating the granulocyte or stem cell for treating cancer *ex vivo* with a chemokine or cytokine. For example, in some

embodiments, the method comprises activating the granulocyte or stem cell for treating cancer *ex vivo* with TGFβ, CCL2, CCL3, CCL5, CXC1, CXC12 and/or CXC16. In some embodiments, the method comprises activating the granulocyte or stem cell for treating cancer *ex vivo* with CCL2. In some embodiments, the method comprises activating the granulocyte or stem cell for treating cancer *ex vivo* with TGFβ. In some embodiments, the method comprises activating the granulocyte or stem cell for treating cancer *ex vivo* with a granulocyte-macrophage colony-stimulating factor (GM-CSF), a granulocyte colony-stimulating factor (G-CSF), a growth hormone; serotonin, vitamin C, vitamin D, glutamine (Gln), arachidonic acid, AGE-albumin, an interleukin, TNF-alpha, Flt-3 ligand, thrombopoietin, foetal bovine serum (FBS), retinoic acid, lipopolysaccharide (LPS), IFN-gamma, IFN-beta or combinations thereof.

The present invention may further comprise the validation of a granulocyte or stem cell's suitability for treating cancer by a different means, e.g. by way of cell surface charge and/or by way of a functional assay.

In one embodiment granulocyte cell surface charge correlates with suitability for treating cancer, with granulocytes (e.g. neutrophils) that are more positively charged (or less negatively charged) being suitable for treating cancer and/or more efficacious in treating cancer. The level of cell surface charge may be determined when compared to a reference standard, preferably wherein the reference standard is from a granulocyte that is unsuitable for treating cancer. In one embodiment a stem cell may be considered as suitable for treating cancer if it is capable of differentiating into a granulocyte having a more positively charged (or less negatively charged) cell surface. A cell surface charge can be determined using any suitable technique known in the art. In one embodiment the cell surface charge is determined using electrophoresis. An electrophoretic mobility assay may be one described in "Cell Electrophoresis" edited by Johann Bauer (ISBN 0-8493-8918-6 published by CRC Press, Inc.) the teaching of which is incorporated herein in its entirety. In another embodiment cell surface charge can be determined using negatively and/or positively charged means. In one embodiment, a granulocyte has a positive cell surface charge when it can be bound by a negatively charged means, and not a positively charged means. In one embodiment, a granulocyte has a negative cell surface charge when it can be bound by a positively charged means, and not a negatively charged means. Such negatively and/or positively charged means may also be used to measure the concentration of a granulocyte cell in a sample. A positively charged means may be a positively charged particle, nanoprobe or nanoparticle, or a cation exchange media. Suitable nanoparticles may be

prepared by conjugating superparamagnetic Iron(II,III) oxide (Fe_3O_4) nanoparticles (NPs) with (3-Aminopropyl)triethoxysilane (APTES) to form a thin layer of Silicon dioxide (SiO_2) shell on the NPs' surface upon reaction with Tetraethyl orthosilicate (TEOS) and ammonium hydroxide (NH_4OH). Fluorescein isothiocyanates (FITCs) may be embedded in the SiO_2 shell, thus exposing the Si-linked hydroxyl groups (SiO_2-OH) and creating the negative surface charge. Branched poly(ethylene imine) (PEI) molecules may be used to not only to cover the SiO_2-OH groups in a non-covalently manner but also to expose the additional amine groups that carry the positive charges. Thus, in one embodiment a negatively charged nanoparticle is prepared by conjugating Fe_3O_4 nanoparticles with APTES to form a thin layer of SiO_2 shell on the nanoparticle surface upon reaction with Tetraethyl orthosilicate (TEOS) and ammonium hydroxide (NH_4OH), and embedding a FITC in the SiO_2 shell, thus exposing the SiO_2-OH groups (creating the negative surface charge). In another embodiment, a positively charged nanoparticle is prepared by contacting a negatively charged nanoparticle (as described herein) with a PEI molecule (e.g. to expose additional amine groups that carry a positive charge). In one embodiment, the negatively charged means (e.g. nanoparticle) may have a negative surface charge of at least -5 mV, -10 mV, -20 mV, -30 mV, or -40 mV. Preferably, the negatively charged means (e.g. nanoparticle) has may have a negative surface charge of at least -35 mV. In one embodiment, the positively charged means (e.g. nanoparticle) may have a positive surface charge of at least +5 mV, +10 mV, +20 mV, +30 mV, or +40 mV. Preferably, the positively charged means (e.g. nanoparticle) has may have a positive surface charge of at least +35 mV. The surface charge of said positively or negatively charged means (e.g. nanoparticle) may refer to the surface zeta potential of the positively or negatively charged means (e.g. nanoparticle). The surface zeta potential may be measured with a Dynamic light scattering particle size analyser (e.g. the Zetasizer Nano-ZS90, Malvern, UK). In one aspect the present invention involves isolating granulocytes comprising a (more) positive cell surface charge by way of said charge. For example, said cells may be isolated using a negatively charged means, such as a negatively charged particle, nanoprobe or nanoparticle, or an anion exchange media. Such techniques may be used to measure the cell surface charge of granulocytes or the concentration of granulocytes having a positive cell surface charge in the foregoing embodiments. The cells may be isolated from negatively charged, neutrally charged, or less positively charged granulocytes. In one embodiment, a positively or negatively charged means (e.g. nanoparticle) may be detectable by fluorescence. In another embodiment, a positively or negatively charged means (e.g. nanoparticle) may be capable of being captured by way of magnetism, thus allowing isolation of a cell that interacts with said means.

A functional assay for validating the suitability of a granulocyte or stem cell for treating cancer may comprise:

a. contacting cancer cells with a granulocyte to form a test sample;
b. incubating the test sample; and
c. measuring the % of cancer cells killed in the test sample.

To validate a stem cell's suitability, said stem cell may be differentiated into a granulocyte which is employed in the above-mentioned assay.

In one embodiment a granulocyte or stem cell is validated according to the assay when the granulocyte kills at least 70% of the cancer cells in the test sample. Preferably, a granulocyte or stem cell is validated according to the assay when the granulocyte kills at least 80% or 90% of the cancer cells in the test sample.

The cancer cell for use in an assay may be one or more selected from a pancreatic cancer cell line, a liver cancer cell line, an oesophageal cancer cell line, a stomach cancer cell line, a cervical cancer cell line, an ovarian cancer cell line, a lung cancer cell line, a bladder cancer cell line, a kidney cancer cell line, a brain cancer cell line, a prostate cancer cell line, a myeloma cancer cell line, a non-Hodgkin's lymphoma (NHL) cell line, a larynx cancer cell line, a uterine cancer cell line, or a breast cancer cell line. Suitable cell lines are available commercially from the American Type Culture Collection United Kingdom (U.K.), Guernsey, Ireland, Jersey and Liechtenstein, LGC Standards, Queens Road, Teddington, Middlesex, TW11 0LY, UK. For example, a pancreatic cell line may be one or more of Capan-2, ATCC HTB-80; Panc 10.05, ATCC CRL-2547; CFPAC-1, ATCC CRL-1918; HPAF-II, ATCC CRL-1997; SW 1990, ATCC CRL-2172; BxPC-3, ATCC CRL-1687; AsPC-1, ATCC CRL-1682; ATCC® TCP-1026™; SW1990, ATCC CRL-2172; SU.86.86, ATCC CRL-1837; BXPC-3, ATCC CRL-1687; Panc 10.05, ATCC CRL-2547; MIA-PaCa-2, ATCC CRL-1420; PANC-1, ATCC CRL-1469; or ATCC® TCP-2060™. Preferably the cancer cell line is pancreatic cancer cell line, such as PANC-1. In one embodiment the cancer cell line is a cervical cancer cell line, such as a HeLa cell.

The incubation step may be carried out for between 1 hour and 100 hours. Suitably, the incubation step may be carried out for between 5 hours and 75 hours, for example between 10 hours and 20 hours. The incubation step may be carried out for between 6 hours to 6 days. Suitably, the incubation step may be carried out for between 6 hours and 2 days, for example for between 12 hours to 36 hours, such as between 16 to 24 hours. In one

embodiment the incubation step is carried out for 24 hours. In another embodiment the incubation step is carried out for 48 hours. The incubation step may be carried out at any temperature suitable for cell growth and viability, for example at a temperature between 35 °C to 42 °C, suitably at 37 or 39 °C. Preferably the incubation step is carried out at 37 or 39 °C for 24 hours. Preferably the incubation step is carried out for 16-24 hours at 30-40 °C (e.g. 37°C).

The % of cancer cells killed can be measured by reference to the total number of starting cancer cells. The number of cancer cells killed can be measured using any suitable means, for example by viability staining (e.g. trypan blue staining), and microscopy, or using other automated means, for example by cell electronic sensing equipment, such as the RT-CES™ system available from ACEA Biosciences, Inc. (11585 Sorrento Valley Rd., Suite 103, San Diego, CA 92121, USA). In some embodiments the % of cancer cells killed may be determined within 24 hours (e.g. of incubating a cancer cell line and a granulocyte). The % of cancer cells killed is preferably the maximum number of cancer cells killed when carrying out a method of the invention.

The number of cancer cells killed can be also be measured using the ACEA Biosciences xCELLigence RTCA DP Analyzer system®. The xCELLigence System is a real-time cell analyser, allowing for label-free and dynamic monitoring of cellular phenotypic changes continuously by measuring electrical impedance. Such measurements may be carried out as detailed in Example 11. Said System is commercially available from ACEA Biosciences 6779 Mesa Ridge Road #100, San Diego, CA 92121 USA.

A ratio of at least 1:1, 5:1 or 10:1 of granulocytes to cancer cells may be used. Preferably a 5:1 ratio of granulocytes to cancer cells is used. More preferably a 10:1 ratio of granulocytes to cancer cells is used.

A granulocyte or stem cell described herein may be part of a cell culture (e.g. an *in vitro* cell culture). Accordingly, in one aspect, there is provided an *in vitro* culture of granulocytes of the invention. In a related aspect, there is provided an *in vitro* culture of stem cells of the invention.

A granulocyte or stem cell of the invention may be subjected to one or more further processing steps, such as cryogenic freezing. The further processing step may include

admixing said granulocyte or stem cell with a preservation medium, for example a cryogenic preservation medium.

In one aspect the invention provides a composition for treating cancer, the composition comprising granulocytes: wherein at least 90% of the granulocytes comprised in the composition have:

a. increased expression of one or more of *ITGB1, CYBB, SYK, DOCK8, COMP, ATG7, SLC2A1, GZMK, CTSG, ATM, IKBKB, BCAP31, TAPBP, PERM, PLEC, ACSL1, RAC1, GM2A, CAP37,* and *PSMB2* when compared to a reference standard, wherein the reference standard is from a granulocyte unsuitable for treating cancer; and/or

b. decreased expression of *ANXA1* and/or *PPP3CB* when compared to a reference standard, wherein the reference standard is from a granulocyte unsuitable for treating cancer.

In one aspect the invention provides a composition for treating cancer, the composition comprising granulocytes: wherein at least 95% of the granulocytes comprised in the composition have:

a. increased expression of one or more of *ITGB1, CYBB, SYK, DOCK8, COMP, ATG7, SLC2A1, GZMK, CTSG, ATM, IKBKB, BCAP31, TAPBP, PERM, PLEC, ACSL1, RAC1, GM2A, CAP37,* and *PSMB2* when compared to a reference standard, wherein the reference standard is from a granulocyte unsuitable for treating cancer; and/or

b. decreased expression of *ANXA1* and/or *PPP3CB* when compared to a reference standard, wherein the reference standard is from a granulocyte unsuitable for treating cancer.

In one aspect the invention provides a composition for treating cancer, the composition comprising granulocytes: wherein at least 99% of the granulocytes comprised in the composition have:

a. increased expression of one or more of *ITGB1, CYBB, SYK, DOCK8, COMP, ATG7, SLC2A1, GZMK, CTSG, ATM, IKBKB, BCAP31, TAPBP, PERM, PLEC, ACSL1, RAC1, GM2A, CAP37,* and *PSMB2* when compared to a reference standard, wherein the reference standard is from a granulocyte unsuitable for treating cancer; and/or

b. decreased expression of *ANXA1* and/or *PPP3CB* when compared to a reference standard, wherein the reference standard is from a granulocyte unsuitable for treating cancer.

In one aspect the invention provides a composition for treating cancer, the composition comprising granulocytes: wherein at least 100% of the granulocytes comprised in the composition have:

a. increased expression of one or more of *ITGB1, CYBB, SYK, DOCK8, COMP, ATG7, SLC2A1, GZMK, CTSG, ATM, IKBKB, BCAP31, TAPBP, PERM, PLEC, ACSL1, RAC1, GM2A, CAP37,* and *PSMB2* when compared to a reference standard, wherein the reference standard is from a granulocyte unsuitable for treating cancer; and/or

b. decreased expression of *ANXA1* and/or *PPP3CB* when compared to a reference standard, wherein the reference standard is from a granulocyte unsuitable for treating cancer.

In one embodiment at least 90%, 95%, 99% or 100% of the granulocytes comprised in the composition have:

a. increased expression of one or more of *ITGB1, CYBB, SYK, DOCK8, COMP, ATG7, SLC2A1, GZMK, CTSG, ATM, IKBKB, BCAP31, TAPBP, PERM, PLEC, ACSL1, RAC1, GM2A, CAP37,* and *PSMB2* when compared to a reference standard, wherein the reference standard is from a granulocyte unsuitable for treating cancer; and

b. decreased expression of *ANXA1* and/or *PPP3CB* when compared to a reference standard, wherein the reference standard is from a granulocyte unsuitable for treating cancer.

Advantageously, the compositions of the invention contain a substantially homogeneous population of granulocytes that are suitable for treating cancer.

The invention also provides a method for isolating granulocytes suitable for treating cancer based on the expression of one or more genes of the invention. Such methods may provide a substantially homogeneous population of granulocytes that are suitable for treating cancer. In one embodiment, granulocytes for treating cancer are isolated using the expression of one or more cell-surface expressed polypeptides selected from: ATG7, CYBB, DOCK8, CTSG, S100A9, COMP, S100A8, CTSG, SYK, ITGB1, SLC2A1, GZMK, ANXA1, RAC1, and CAP37, preferably one or more selected from: ATG7, S100A9, COMP, S100A8, CTSG, SYK, ITGB1, SLC2A1, GZMK, ANXA1, RAC1, and CAP37. The isolation may be performed using any suitable technique. In one embodiment a method for isolating granulocytes comprises the use of a binding means that binds to a polypeptide of the invention. Preferably the binding means is an antibody. Antibodies to detect the presence or absence of polypeptides of the invention are commercially available: anti-CYBB antibody (Cat#

M03328, BosterBio), anti-DOCK8 antibody (Ab227529, AbCam), anti-ATG7 antibody (Cat# HPA007639, Atlas Antibodies), anti-S100A9 antibody (HPA004193, Atlas Antibodies), anti-ACSL1 antibody (Cat# HPA011964, Atlas Antibodies), anti-ATM antibody (Cat# HPA067142, Atlas Antibodies), anti-COMP antibody (Cat# AF3134, R&D Systems), anti-TAPBP antibody (Cat# HPA007066, Atlas Antibodies), anti-S100A8 antibody (Cat# AF4570, R&D Systems), anti-PLEC antibody (Cat# HPA029906, Atlas Antibodies), anti-BCAP31 antibody (Cat# HPA003906, Atlas Antibodies), anti-CTSG antibody (Cat# C35667, Sab Biotech), anti-SYK antibody (Cat# Ab40781, AbCam), anti-ITGB1 antibody (Cat# P260111, Sino Biological), anti-PSMB2 antibody (Cat# HPA026322, Atlas Antibodies), anti-GM2A antibody (Cat# HPA008063, Atlas Antibodies), anti-SLC2A1 antibody (Cat# HPA031345, Atlas Antibodies), anti-GZMK antibody (Cat# HPA063181, Atlas Antibodies), anti-IKBKB antibody (Cat# HPA001249, Atlas Antibodies), anti-PPP3CB antibody (Cat# HPA008233, Atlas Antibodies), anti-ANXA1 antibody (Cat# HPA011271, Atlas Antibodies), anti-PERM antibody (Cat# HPA021147, Atlas Antibodies), anti-RAC1 antibody (Cat# HPA047820, Atlas Antibodies), and anti-CAP37 antibody (Cat# HPA055851, Atlas Antibodies). The method may comprise the use of flow cytometric techniques, preferably fluorescence activated cell sorting (FACS), e.g. together with appropriate 'gating'. Flow cytometric techniques may be particularly suitable when the method employs the use of a binding means coupled to a detectable label, such as a fluorophore.

In one aspect there is provided a method for isolating a granulocyte for treating cancer, the method comprising:

a) contacting a sample of granulocytes with a binding means, wherein the binding means binds to one or more polypeptides selected from CTSG, CAP37, ITGB1, CYBB, SYK, DOCK8, COMP, ATG7, SLC2A1, GZMK, ATM, IKBKB, BCAP31, TAPBP, PPP3CB, ANXA1, PERM, PLEC, ACSL1, RAC1, GM2A, and PSMB2; and

b) isolating the granulocyte based on the presence or absence of binding between the binding means and the one or more polypeptides.

Binding may be determined to be present when the amount of binding is statistically significant (e.g. when compared to a 'background' control). Binding may be determined to be absent when the amount of binding is statistically insignificant (e.g. when compared to a 'background' control). Preferably, binding is determined to be absent when there is no binding whatsoever.

In one embodiment the invention comprises detecting the presence of one or more polypeptides selected from CTSG, CAP37, ITGB1, CYBB, SYK, DOCK8, COMP, ATG7, SLC2A1, GZMK, ATM, IKBKB, BCAP31, TAPBP, PERM, PLEC, ACSL1, RAC1, GM2A, and PSMB2. When said one or more polypeptides are detected (i.e. where there is binding between the binding means and the polypeptide) the granulocyte may be isolated. Suitably, said isolated granulocyte may be a granulocyte for treating cancer.

In another embodiment the invention may comprise detecting the absence of ANXA1 and/or PPP3CB (e.g. not detecting ANXA1 and/or PPP3CB). When said one or more polypeptides are not detected (i.e. where there is an absence of binding between the binding means and the polypeptide) the granulocyte may be isolated. Suitably, said isolated granulocyte may be a granulocyte for treating cancer.

Preferably, the invention comprises detecting:

the presence of one or more polypeptides selected from CTSG, CAP37, ITGB1, CYBB, SYK, DOCK8, COMP, ATG7, SLC2A1, GZMK, ATM, IKBKB, BCAP31, TAPBP, PERM, PLEC, ACSL1, RAC1, GM2A, and PSMB2; and

the invention absence of ANXA1 and/or PPP3CB. In one embodiment, when said polypeptides are detected or not detected (as indicated), the granulocyte is isolated.

In one embodiment a method of isolating a granulocyte comprises the use of an immobilised binding means (e.g. a binding means conjugated to a bead, such as a magnetic bead, or chromatographic resin) to isolate a granulocyte of the invention. Such methods may be immuno-affinity methods.

The method may comprise quantifying the amount of binding between the binding means and the one or more polypeptides or between the binding means and the granulocyte. The method may comprise isolating a granulocyte for treating cancer based on the quantified amount of binding.

In one embodiment a granulocyte for treating cancer is isolated when there is a high level of binding between a binding means and one or more polypeptides selected from CTSG, CAP37, ITGB1, CYBB, SYK, DOCK8, COMP, ATG7, SLC2A1, GZMK, ATM, IKBKB, BCAP31, TAPBP, PERM, PLEC, ACSL1, RAC1, GM2A, and PSMB2.

In one embodiment a granulocyte for treating cancer is isolated when there is a low level of binding between a binding means and ANXA1 and/or PPP3CB.

Preferably, a granulocyte for treating cancer is isolated when there is:

a high level of binding between a binding means and one or more polypeptides selected from CTSG, CAP37, ITGB1, CYBB, SYK, DOCK8, COMP, ATG7, SLC2A1, GZMK, ATM, IKBKB, BCAP31, TAPBP, PERM, PLEC, ACSL1, RAC1, GM2A, and PSMB2; and

a low level of binding between a binding means and ANXA1 and/or PPP3CB.

A high/low level of binding is preferably relative to a level of binding between the same binding means and polypeptide under the same conditions for a granulocyte that is unsuitable for treating cancer.

The term “isolating” may mean providing a population of granulocytes in which at least 50%, 60%, 70%, 80% or 90% (preferably at least 95%, 99% or 100%) are granulocytes suitable for treating cancer. In other words, the term “isolating” may mean removing at least 50%, 60%, 70%, 80% or 90% (preferably at least 95%, 99% or 100%) of granulocytes that are unsuitable for treating cancer from a population of granulocytes.

Thus, the methods for isolating suitably allow for the separation of a granulocyte for treating cancer from granulocyte that is unsuitable for treating cancer.

In some embodiments a method described herein comprises discarding granulocytes that are unsuitable for treating cancer.

In one aspect the invention provides a pharmaceutical composition comprising:

a. a granulocyte, stem cell, or composition of the invention; and
b. a pharmaceutically acceptable carrier, excipient, adjuvant, and/or salt

The term “pharmaceutically acceptable carrier, excipient, adjuvant, and/or salt” as used herein means a carrier that can be administered to a subject (e.g. a patient) intravenously, intra-arterially, intraperitoneally, intra-tumourally, intrathecally or combinations thereof (preferably intravenously) without causing harm to said subject. In one embodiment a pharmaceutically acceptable carrier is an injectable carrier, such as a sterile physiological saline solution. In one embodiment a pharmaceutically acceptable carrier, excipient, adjuvant, and/or salt may be Plasma-Lyte A (e.g. commercially available from Baxter, USA),

dextrose, sodium chloride, human serum albumin, dextran (e.g. dextran 40 (LMD)), dextrose, DMS or combinations thereof. Plasma-Lyte A may be present at a concentration of 10-50% v/v (preferably 31.25% v/v). 5% dextrose/0.45% sodium chloride may be present at a concentration of 10-50% v/v (preferably 31.25% v/v). 25% HAS may be present at 10-30% v/v (preferably 20% v/v). 10% Dextran 40 (LMD)/5% dextrose may be present at a concentration of 1-30% v/v (preferably 10% v/v). DMS may be present at 1-15% v/v (preferably 7.5% v/v).

The pharmaceutical composition may comprise a granulocyte-macrophage colony-stimulating factor (GM-CSF), a granulocyte colony-stimulating factor (G-CSF), a growth hormone; serotonin, vitamin C, vitamin D, glutamine (Gln), arachidonic acid, AGE-albumin, an interleukin, TNF-alpha, Flt-3 ligand, thrombopoietin, serum (e.g. foetal bovine serum [FBS]), retinoic acid, lipopolysaccharide (LPS), IFN-gamma, IFN-beta, or combinations thereof. Suitably, the pharmaceutical composition comprises IFN-gamma and a GM-CSF. Preferably, the pharmaceutical composition comprises TNF-alpha. Particularly preferably, the pharmaceutical composition comprises a granulocyte-macrophage colony-stimulating factor (GM-CSF), and a granulocyte colony-stimulating factor (G-CSF), and a growth hormone, and serotonin, and vitamin C, and vitamin D, and glutamine (Gln), and arachidonic acid, and AGE-albumin, and an interleukin, and TNF-alpha, and Flt-3 ligand, and thrombopoietin, and foetal bovine serum (FBS). Preferably, the pharmaceutical composition comprises a granulocyte-macrophage colony-stimulating factor (GM-CSF), and a granulocyte colony-stimulating factor (G-CSF), and a growth hormone, and serotonin, and vitamin C, and vitamin D, and glutamine (Gln), and arachidonic acid, and AGE-albumin, and an interleukin, and TNF-alpha, and Flt-3 ligand, and thrombopoietin, and foetal bovine serum (FBS), and retinoic acid, and lipopolysaccharide (LPS), and IFN-gamma, and IFN-beta.

In a related aspect the invention provides a kit comprising a granulocyte, stem cell, composition or pharmaceutical composition of the invention; and instructions for use of the same in medicine (e.g. in treating cancer). Suitably, the instructions may be for the use of the same in treating a cancer described in any one of the foregoing embodiments. In some embodiments the instructions also detail an appropriate dosage regimen (e.g. as described in a foregoing embodiment). In one embodiment the instructions are for use of said kit in treating cancer, preferably pancreatic cancer.

The invention may further comprise depositing a granulocyte, stem cell, composition or pharmaceutical composition of the invention in a cell bank, and thus in a related aspect

provides a granulocyte, stem cell, composition or pharmaceutical composition. The term "cell bank" as used herein refers to a storage facility which maintains a cell under suitable conditions for cell viability. For example, the cell may be stored in a metabolically dormant state (e.g. cryogenically frozen). Suitably, a cell comprised within a cell bank is catalogued for appropriate retrieval (e.g. based on blood group, and/or human leukocyte antigen (HLA) type). In one embodiment a cell may be catalogued based on the type of cancer it (or a cell differentiated therefrom) kills. Where the cell bank is a granulocyte cell bank, said cell bank may be replenished using a stem cell of the invention. In some embodiments a stem cell or granulocyte obtained from a donor may be stored and later administered to said donor (e.g. if said donor is diagnosed with cancer), thus constituting a personalised medicine.

A granulocyte or stem cell of the invention may be formulated in any suitable manner, based on its downstream application (e.g. storage in a cell bank, or use in therapy).

Thus, one aspect of the invention provides a cell bank comprising the stem cell, granulocyte, composition, or pharmaceutical composition of the present invention.

The present invention provides granulocytes, stem cells, pharmaceutical compositions, and kits for use in medicine, particularly in the treatment of cancer.

Thus in one aspect the invention provides a granulocyte of the invention for use in treating cancer. In another aspect the invention provides a stem cell of the invention for use in treating cancer. In another aspect the invention provides a composition of the invention for use in treating cancer. In another aspect the invention provides a pharmaceutical composition of the invention for use in treating cancer. In another aspect the invention provides a kit of the invention for use in treating cancer. Similarly, the invention provides in one aspect use of a granulocyte, stem cell, composition, pharmaceutical composition, or kit of the invention in the manufacture of a medicament for treating cancer. In a related aspect there is provided a method for treating cancer comprising: administering to a subject in need thereof a granulocyte, stem cell, composition, pharmaceutical composition, or kit of the invention.

In one embodiment a cancer is a solid tumour cancer. The term "solid tumour cancer" refers to an abnormal, malignant mass of tissue that does not contain cysts or liquid inclusions. Examples of solid tumour cancers include carcinomas, sarcomas, and lymphomas.

A solid tumour cancer may be a carcinoma. A carcinoma may be selected from one or more of an adenocarcinoma, a basal cell carcinoma, a squamous cell carcinoma, an adenosquamous carcinoma, a renal cell carcinoma, a ductal carcinoma *in situ* (DCIS), an invasive ductal carcinoma, an anaplastic carcinoma, a large cell carcinoma, a small cell carcinoma or combinations thereof. A carcinoma may also be selected from epithelial neoplasms, squamous cell neoplasms, squamous cell carcinoma, basal cell neoplasms, basal cell carcinoma, transitional cell carcinomas, adenocarcinomas (such as Adenocarcinoma not otherwise specified (NOS), linitis plastica, vipoma, cholangiocarcinoma, hepatocellular carcinoma NOS, adenoid cystic carcinoma, renal cell carcinoma, Grawitz tumour), adnexal and skin appendage neoplasms, mucoepidermoid neoplasms, cystic mucinous and serous neoplasms, ductal lobular and medullary neoplasms, acinar cell neoplasms, or complex epithelial neoplasms.

Alternatively a solid tumour cancer may be a sarcoma. A sarcoma may be selected from Askin's tumour, sarcoma botryoides, chondrosarcoma, Ewing's, malignant hemangioendothelioma, malignant schwannoma, osteosarcoma, or soft tissue sarcomas (including alveolar soft part sarcoma, angiosarcoma, cystosarcoma phyllodes, dermatofibrosarcoma protuberans (DFSP), desmoid tumour, desmoplastic small round cell tumour, epithelioid sarcoma, extraskeletal chondrosarcoma, extraskeletal osteosarcoma, fibrosarcoma, gastrointestinal stromal tumour (GIST), hemangiopericytoma, hemangiosarcoma, Kaposi's sarcoma, leiomyosarcoma, liposarcoma, lymphangiosarcoma, malignant fibrous histiocytoma, undifferentiated pleomorphic sarcoma, malignant peripheral nerve sheath tumour (MPNST), neurofibrosarcoma, rhabdomyosarcoma, and synovial sarcoma).

Alternatively a solid tumour may be a lymphoma, such as a B-cell lymphoma, a T-cell lymphoma, a NK-cell lymphoma, or a Hodgkin’s lymphoma.

In one embodiment a granulocyte, stem cell, composition, pharmaceutical composition or kit of the invention is for use in treating one or more of: pancreatic cancer, liver cancer, oesophageal cancer, stomach cancer, cervical cancer, ovarian cancer, lung cancer, bladder cancer, kidney cancer, brain cancer, prostate cancer, myeloma cancer, non-Hodgkin’s lymphoma (NHL), larynx cancer, uterine cancer, or breast cancer.

Preferably a granulocyte, stem cell, composition, pharmaceutical composition or kit of the invention is for use in treating pancreatic cancer. The pancreatic cancer may be a pancreatic

solid tumour cancer, such as a pancreatic adenocarcinoma (e.g. a pancreatic ductal adenocarcinoma).

Pancreatic cancer is known to be one of the most difficult cancers to treat. However surprisingly, the present inventors have succeeded in providing granulocytes (and stem cells that differentiate into granulocytes) that have particular efficacy against pancreatic cancer cells.

In some embodiments a stem cell may be differentiated into a granulocyte prior to administration. In preferred embodiments a stem cell may be differentiated into a different stem cell (preferably a precursor cell) prior to administration. In other embodiments a stem cell may be administered to a subject. A stem cell may be administered by any suitable technique known in the art. In one embodiment a subject may be given a stem cell transplant, such as a bone marrow transplant.

Prior to administration there may be a matching step between a medicament of the invention (e.g. a granulocyte, stem cell, composition, pharmaceutical composition or kit of the invention) and the subject to be treated. Matching may be based on data derived from the donor from which the stem cell, or granulocyte is derived, and similar data obtained from the subject to be treated. Matching may be achieved on the basis of blood group type, human leukocyte antigen (HLA) type similarity, or combinations thereof.

A granulocyte, stem cell, composition, pharmaceutical composition or kit of the invention may be administered to a subject in a therapeutically effective amount or a prophylactically effective amount.

The term “treat” or “treating” as used herein encompasses prophylactic treatment (e.g. to prevent onset of a disease) as well as corrective treatment (treatment of a subject already suffering from a disease). Preferably “treat” or “treating” as used herein means corrective treatment.

The term “treat” or “treating” as used herein refers to the disorder and/or a symptom thereof.

A “therapeutically effective amount” is any amount of the granulocyte, stem cell, composition, pharmaceutical composition or kit of the invention, which when administered alone or in

combination to a subject for treating cancer (or a symptom thereof) is sufficient to effect such treatment of the disorder, or symptom thereof.

A "prophylactically effective amount" is any amount of the granulocyte, stem cell, composition, pharmaceutical composition or kit of the invention that, when administered alone or in combination to a subject inhibits or delays the onset or reoccurrence of cancer (or a symptom thereof). In some embodiments, the prophylactically effective amount prevents the onset or reoccurrence of a cancer entirely. "Inhibiting" the onset means either lessening the likelihood of cancer onset (or symptom thereof), or preventing the onset entirely.

In one embodiment a granulocyte is administered to a subject. Preferably, the granulocyte is a neutrophil.

In one embodiment a stem cell is administered to a subject. Preferably, the stem cell is a precursor cell, e.g. selected from a common myeloid progenitor cell, a myeloblast, a promyelocyte (e.g. a N. promyelocyte), a myelocyte (e.g. a N. myelocyte), a metamyelocyte (e.g. a N. metamyelocyte), a band (e.g. an N. band), or combinations thereof.

In some embodiments a stem cell and a granulocyte are administered to a subject. Preferably, a precursor cell and a neutrophil are administered to a subject.

An appropriate dosage range is one that produces the desired therapeutic effect (e.g. wherein the granulocyte, stem cell, composition, pharmaceutical composition or kit of the invention is dosed in a therapeutically or prophylactically effective amount).

A typical treatment regimen may include administering from 10^6, 10^7, 10^8 or 10^9 cells (e.g. granulocyte cells or stem cells) to a subject, or up to 10^{12}, 10^{13} or 10^{14} cells to a subject. In one embodiment a treatment regimen includes administering a dose of at least 1×10^9 cells to a subject. Suitably, a treatment regimen may include administering a dose of at least 2×10^9 cells or at least 5×10^9 cells to a subject. In one embodiment a treatment regimen may include administering a dose of at least 1×10^{10} cells or at least 5×10^{10} cells to a subject. At least 1×10^{11} or at least 2×10^{11} cells may be administered to a subject. In some embodiments between 1×10^9 to 3×10^{11} or 1×10^{10} to 3×10^{11} cells are administered to a subject. Suitably, between 5×10^{10} to 2.5×10^{11} cells are administered to a subject. In one embodiment when the cell is a stem cell, e.g. a precursor cell as defined herein, a treatment regimen includes administering a dose between $1/100^{th}$ and $1/700^{th}$, preferably a dose

between 1/200th and 1/400th, such as 1/300th, of the dose when compared to the dose of granulocytes administered.

A subject for treatment may be dosed once, twice, three times, four times, five times, or six times per week. Alternatively a subject may be dosed daily (e.g. once or twice daily). In other embodiments a subject may be dosed once weekly or bi-weekly. Preferably the dose is weekly. The skilled person will appreciate that the dose can be tailored based on the needs of the subject, and efficacy of the medicament. For example, where the medicament is highly efficacious, the dose may be lowered.

In one embodiment a subject for treatment is dosed weekly (e.g. once weekly) with at least 2 x 10^9 cells or at least 2 x 10^{10} cells. Suitably, a subject for treatment may be dosed weekly with at least 1 x 10^{11} or at least 2 x 10^{11} cells.

The treatment term can be varied based on the response of the subject to the treatment, and/or the type and/or severity of the cancer. For example, the subject for treatment may be dosed for at least 1 or 2 weeks. Suitably the subject for treatment may be dosed for at least 3 or 4 weeks. In one embodiment the subject for treatment is dosed for at least 5 or 6 weeks, suitably at least 7 or 8 weeks.

In one embodiment a subject for treatment is dosed for 4-8 weeks with at least 2 x 10^9 cells, wherein said cells are administered once weekly. Suitably a subject for treatment is dosed for 8 weeks with at least 2 x 10^9 cells (preferably at least 2 x 10^{10} or 2 x 10^{11} cells), wherein said cells are administered once weekly.

Administration may be by any suitable technique or route, including but not limited to intravenous injection, intra-arterial injection, intraperitoneal injection, injection into a tumour resection cavity, intrathecal injection, or combinations thereof. Suitably the medicament may be administered intravenously.

A white blood cell growth factor may be administered with a medicament of the invention. The administration may be sequential or simultaneous (suitably simultaneous). Suitable white blood cell growth factors may include a granulocyte-macrophage colony-stimulating factor (GM-CSF), a granulocyte colony-stimulating factor (G-CSF), a growth hormone; serotonin, vitamin C, vitamin D, glutamine (Gln), arachidonic acid, AGE-albumin, an interleukin, TNF-alpha, Flt-3 ligand, thrombopoietin, foetal bovine serum (FBS), retinoic acid,

lipopolysaccharide (LPS), IFN-gamma, IFN-beta, or combinations thereof. Suitably, the white blood cell growth factors comprises IFN-gamma and GM-CSF. Preferably, the white blood cell growth factors comprises TNF-alpha. Suitably the white blood cell growth factors may comprise a granulocyte-macrophage colony-stimulating factor (GM-CSF), and a granulocyte colony-stimulating factor (G-CSF), and a growth hormone, and serotonin, and vitamin C, and vitamin D, and glutamine (Gln), and arachidonic acid, and AGE-albumin, and an interleukin, and TNF-alpha, and Flt-3 ligand, and thrombopoietin, and foetal bovine serum (FBS). Suitably the white blood cell growth factors may comprise a granulocyte-macrophage colony-stimulating factor (GM-CSF), and a granulocyte colony-stimulating factor (G-CSF), and a growth hormone, and serotonin, and vitamin C, and vitamin D, and glutamine (Gln), and arachidonic acid, and AGE-albumin, and an interleukin, and TNF-alpha, and Flt-3 ligand, and thrombopoietin, and foetal bovine serum (FBS), and retinoic acid, and lipopolysaccharide (LPS), and IFN-gamma, and IFN-beta. Particular examples of the foregoing include but are not limited to LEUKINE® brand sargramostim, NEUPOGEN® brand filgrastim, and NEULAST A® brand 5 PEG-filgrastim.

In one embodiment a stem cell may be administered (e.g. sequentially or simultaneously, preferably simultaneously) with a granulocyte-colony stimulating factor; and a growth hormone; and a serotonin; and an interleukin. In one embodiment a granulocyte precursor cell (e.g. a granulocyte precursor cell culture) is administered (e.g. sequentially or simultaneously, preferably simultaneously) with a granulocyte-colony stimulating factor; and a growth hormone; and a serotonin; and an interleukin.

In some embodiments a granulocyte or stem cell of the invention may be used in combination with another therapeutic, e.g. in combination with an existing cancer therapy, such as radiotherapy, chemotherapy, and/or immunotherapy.

In one aspect the present invention provides a method for determining the suitability of a stem cell for treating cancer, the method comprising:

a. comparing a measured expression level of one or more genes by the stem cell, wherein the one or more genes are associated with suitability for treating cancer and are selected from: *CTSG, CAP37, ITGB1, CYBB, SYK, DOCK8, COMP, ATG7, SLC2A1, GZMK, ATM, IKBKB, BCAP31, TAPBP, PPP3CB, ANXA1, PERM, PLEC, ACSL1, RAC1, GM2A,* and *PSMB2*, with the expression level of the same one or more genes in a reference standard; and

b. determining the suitability of the stem cell for treating cancer based on the comparison.

In one aspect the present invention provides a method for determining the suitability of a stem cell for treating cancer, the method comprising:

a. measuring an expression level of one or more genes by the stem cell, wherein the one or more genes are associated with suitability for treating cancer and are selected from: *ITGB1, CYBB, SYK, DOCK8, COMP, ATG7, SLC2A1, GZMK, CTSG, ATM, IKBKB, BCAP31, TAPBP, PPP3CB, ANXA1, PERM, PLEC, ACSL1, RAC1, GM2A, CAP37,* and *PSMB2*;

b. comparing the measured expression level with the expression level of the same one or more genes in a reference standard; and

c. determining the suitability of the stem cell for treating cancer based on the comparison.

In another aspect the invention provides a method for identifying whether or not a donor produces stem cells suitable for treating cancer, the method comprising:

a. comparing a measured expression level of one or more genes by a stem cell comprised in a sample obtainable from the donor, wherein the one or more genes are associated with suitability for treating cancer and are selected from: *CTSG, CAP37, ITGB1, CYBB, SYK, DOCK8, COMP, ATG7, SLC2A1, GZMK, ATM, IKBKB, BCAP31, TAPBP, PPP3CB, ANXA1, PERM, PLEC, ACSL1, RAC1, GM2A,* and *PSMB2*, with the expression level of the same one or more genes in a reference standard; and

b. identifying whether or not the donor produces stem cells suitable for treating cancer based on the comparison.

In a related aspect the invention provides a method for identifying whether or not a donor produces stem cells for treating cancer, the method comprising:

a. measuring an expression level of one or more genes by a stem cell comprised in a sample obtainable from the donor, wherein the one or more genes are associated with suitability for treating cancer and are selected from: *ITGB1, CYBB, SYK, DOCK8, COMP, ATG7, SLC2A1, GZMK, CTSG, ATM, IKBKB, BCAP31, TAPBP, PPP3CB, ANXA1, PERM, PLEC, ACSL1, RAC1, GM2A, CAP37,* and *PSMB2*;

b. comparing the measured expression level with the expression level of the same one or more genes in a reference standard; and

c. identifying whether or not the donor produces stem cells for treating cancer based on the comparison.

In one embodiment a stem cell is determined to be suitable for treating cancer or a donor is identified as producing stem cells suitable for treating cancer when:

i. a measured expression level of one or more of *ITGB1, CYBB, SYK, DOCK8, COMP, ATG7, SLC2A1, GZMK, CTSG, ATM, IKBKB, BCAP31, TAPBP, PERM, PLEC, ACSL1, RAC1, GM2A, CAP37,* and *PSMB2* is increased when compared to the reference standard when the reference standard is from a stem cell unsuitable for treating cancer; or

ii. a measured expression level of *ANXA1* and/or *PPP3CB* is decreased when compared to the reference standard, when the reference standard is from a stem cell unsuitable for treating cancer; or

iii. a measured expression level of one or more of *ITGB1, CYBB, SYK, DOCK8, COMP, ATG7, SLC2A1, GZMK, CTSG, ATM, IKBKB, BCAP31, TAPBP, PERM, PLEC, ACSL1, RAC1, GM2A, CAP37,* and *PSMB2* is increased or the same when compared to the reference standard, when the reference standard is from a stem cell suitable for treating cancer; or

iv. a measured expression level of *ANXA1* and/or *PPP3CB* is decreased or the same when compared to the reference standard, when the reference standard is from a stem cell suitable for treating cancer.

Alternatively, in one embodiment a stem cell is determined to be unsuitable for treating cancer or a donor is identified as producing stem cells unsuitable for treating cancer when:

i. a measured expression level of one or more of *ITGB1, CYBB, SYK, DOCK8, COMP, ATG7, SLC2A1, GZMK, CTSG, ATM, IKBKB, BCAP31, TAPBP, PERM, PLEC, ACSL1, RAC1, GM2A, CAP37,* and *PSMB2* is decreased or the same when compared to the reference standard, when the reference standard is from a stem cell unsuitable for treating cancer; or

ii. a measured expression level of *ANXA1* and/or *PPP3CB* is increased or the same when compared to the reference standard, when the reference standard is from a stem cell unsuitable for treating cancer; or

iii. a measured expression level of one or more of *ITGB1, CYBB, SYK, DOCK8, COMP, ATG7, SLC2A1, GZMK, CTSG, ATM, IKBKB, BCAP31, TAPBP, PERM, PLEC, ACSL1, RAC1, GM2A, CAP37,* and *PSMB2* is decreased when compared to reference standard, when the reference standard is from a stem cell suitable for treating cancer; or

iv. a measured expression level of *ANXA1* and/or *PPP3CB* is increased when compared to the reference standard, when the reference standard is from a stem cell suitable for treating cancer.

In one aspect the invention provides a stem cell, wherein the stem cell comprises:

a. increased expression of one or more of *ITGB1, CYBB, SYK, DOCK8, COMP, ATG7, SLC2A1, GZMK, CTSG, ATM, IKBKB, BCAP31, TAPBP, PERM, PLEC, ACSL1, RAC1, GM2A, CAP37,* and *PSMB2* when compared to a reference standard, wherein the reference standard is from a stem cell unsuitable for treating cancer; and/or

b. decreased expression of *ANXA1* and/or *PPP3CB* when compared to a reference standard, wherein the reference standard is from a stem cell unsuitable for treating cancer.

In one aspect the invention provides a method for selecting whether or not a subject is suitable for treatment with a stem cell or granulocyte for treating cancer, the method comprising:

a. comparing a measured expression level of one or more genes by a stem cell comprised in a sample obtainable from the subject, wherein the one or more genes are associated with suitability for treating cancer and are selected from: *CTSG, CAP37, ITGB1, CYBB, SYK, DOCK8, COMP, ATG7, SLC2A1, GZMK, ATM, IKBKB, BCAP31, TAPBP, PPP3CB, ANXA1, PERM, PLEC, ACSL1, RAC1, GM2A,* and *PSMB2* with the expression level of the same one or more genes in a reference standard; and

b. identifying whether or not the subject is suitable for treatment with a stem cell or granulocyte for treating cancer based on the comparison.

In one aspect the invention provides a method for selecting whether or not a subject is suitable for treatment with a stem cell or granulocyte for treating cancer, the method comprising:

a. measuring an expression level of one or more genes by a stem cell comprised in a sample obtainable from the subject, wherein the one or more genes are associated with suitability for treating cancer and are selected from: *CTSG, CAP37, ITGB1, CYBB, SYK, DOCK8, COMP, ATG7, SLC2A1, GZMK, ATM, IKBKB, BCAP31, TAPBP, PPP3CB, ANXA1, PERM, PLEC, ACSL1, RAC1, GM2A,* and *PSMB2*;

b. comparing the measured expression level with the expression level of the same one or more genes in a reference standard; and

c. identifying whether or not the subject is suitable for treatment with a stem cell or granulocyte for treating cancer based on the comparison.

In another aspect the invention provides a method for determining a subject's risk for developing cancer, the method comprising:

a. comparing a measured expression level of one or more genes by a stem cell comprised in a sample obtainable from the subject, wherein the one or more genes are associated with suitability for treating cancer and are selected from: *CTSG, CAP37, ITGB1, CYBB, SYK, DOCK8, COMP, ATG7, SLC2A1, GZMK, ATM, IKBKB, BCAP31, TAPBP, PPP3CB, ANXA1, PERM, PLEC, ACSL1, RAC1, GM2A,* and *PSMB2* with the expression level of the same one or more genes in a reference standard; and

b. determining the subject's risk for developing cancer based on the comparison.

In another aspect the invention provides a method for determining a subject's risk for developing cancer, the method comprising:

a. measuring an expression level of one or more genes by a stem cell comprised in a sample obtainable from the subject, wherein the one or more genes are associated with suitability for treating cancer and are selected from: *CTSG, CAP37, ITGB1, CYBB, SYK, DOCK8, COMP, ATG7, SLC2A1, GZMK, ATM, IKBKB, BCAP31, TAPBP, PPP3CB, ANXA1, PERM, PLEC, ACSL1, RAC1, GM2A,* and *PSMB2*;

b. comparing the measured expression level with the expression level of the same one or more genes in a reference standard; and

c. determining the subject's risk for developing cancer based on the comparison.

In one embodiment, step c. of any one of the foregoing aspects comprises:

identifying the subject as suitable for treatment with a granulocyte or a stem cell for treating cancer or determining that the subject is at risk of developing cancer when:

i. the measured expression level of one or more of *CTSG, CAP37, ITGB1, CYBB, SYK, DOCK8, COMP, ATG7, SLC2A1, GZMKATM, IKBKB, BCAP31, TAPBP, PERM, PLEC, ACSL1, RAC1, GM2A,* and *PSMB2* is decreased or the same when compared to the reference standard, when the reference standard is from a stem cell unsuitable for treating cancer; or

ii. the measured expression level of *ANXA1* and/or *PPP3CB* is increased or the same when compared to the reference standard, when the reference standard is from a stem cell unsuitable for treating cancer; or

iii. the measured expression level of one or more of *CTSG, CAP37, ITGB1, CYBB, SYK, DOCK8, COMP, ATG7, SLC2A1, GZMK, ATM, IKBKB, BCAP31, TAPBP, PERM, PLEC, ACSL1, RAC1, GM2A,* and *PSMB2* is decreased when compared to the reference standard, when the reference standard is from a stem cell suitable for treating cancer; or

iv. the measured expression level of *ANXA1* and/or *PPP3CB* is increased when compared to the reference standard, when the reference standard is from a stem cell suitable for treating cancer; or

identifying the subject as unsuitable for treatment with a granulocyte or a stem cell for treating cancer when or determining that the subject is not at risk of developing cancer when:

v. the measured expression level of one or more of *CTSG, CAP37, ITGB1, CYBB, SYK, DOCK8, COMP, ATG7, SLC2A1, GZMK, ATM, IKBKB, BCAP31, TAPBP, PERM, PLEC, ACSL1, RAC1, GM2A,* and *PSMB2* is increased when compared to the reference standard when the reference standard is from a stem cell unsuitable for treating cancer; or

vi. the measured expression level of *ANXA1* and/or *PPP3CB* is decreased when compared to the reference standard, when the reference standard is from a stem cell unsuitable for treating cancer; or

vii. the measured expression level of one or more of *CTSG, CAP37, ITGB1, CYBB, SYK, DOCK8, COMP, ATG7, SLC2A1, GZMK, ATM, IKBKB, BCAP31, TAPBP, PERM, PLEC, ACSL1, RAC1, GM2A,* and *PSMB2* is increased or the same when compared to the reference standard, when the reference standard is from a stem cell suitable for treating cancer; or

viii. the measured expression level of *ANXA1* and/or *PPP3CB* is decreased or the same when compared to the reference standard, when the reference standard is from a stem cell suitable for treating cancer.

In some embodiments of any of the foregoing aspects, the method does not comprise measuring the expression level of CD10 and/or CD101 by a granulocyte or stem cell comprised in a sample from a donor. In some embodiments of any of the foregoing aspects, the method does not comprise comparing the measured expression level of CD10 and/or CD101 with the expression level with the same genes in a reference standard.

In alternative embodiments, the method comprises measuring the expression level of CD10 and/or CD101 by a granulocyte or stem cell comprised in a sample from a donor. In some embodiments of any of the foregoing aspects, the method comprises comparing the

measured expression level of CD10 and/or CD101 with the expression level with the same genes in a reference standard.

In one aspect the invention provides a composition for treating cancer, the composition comprising stem cells: wherein at least 90% (preferably at least 95%, 99% or 100%) of the stem cells comprised in the composition have:

a. increased expression of one or more of *CTSG, CAP37, ITGB1, CYBB, SYK, DOCK8, COMP, ATG7, SLC2A1, GZMK, ATM, IKBKB, BCAP31, TAPBP, PERM, PLEC, ACSL1, RAC1, GM2A, and PSMB2*ITGB1, CYBB, SYK, DOCK8, COMP, ATG7, SLC2A1, GZMK, *CTSG, ATM, IKBKB, BCAP31, TAPBP, PERM, PLEC, ACSL1, RAC1, GM2A, CAP37,* and *PSMB2* when compared to a reference standard, wherein the reference standard is from a stem cell unsuitable for treating cancer; and/or

b. decreased expression of *ANXA1* and/or *PPP3CB* when compared to a reference standard, wherein the reference standard is from a stem cell unsuitable for treating cancer.

The invention also provides a method for isolating stem cells suitable for treating cancer based on the expression of one or more genes of the invention. Such methods may provide a substantially homogeneous population of stem cells that are suitable for treating cancer. In one embodiment, stem cells for treating cancer are isolated using the expression of one or more cell-surface expressed polypeptides selected from: ATG7, CYBB, DOCK8, CTSG, S100A9, COMP, S100A8, CTSG, SYK, ITGB1, SLC2A1, GZMK, ANXA1, RAC1, and CAP37, preferably one or more selected from: ATG7, S100A9, COMP, S100A8, CTSG, SYK, ITGB1, SLC2A1, GZMK, ANXA1, RAC1, and CAP37. The isolation may be performed using any suitable technique. In one embodiment a method for isolating granulocytes comprises the use of a binding means that binds to a polypeptide of the invention. Preferably the binding means is an antibody. Antibodies to detect the presence or absence of polypeptides of the invention are commercially available and may be one or more of the antibodies described herein. The method may comprise the use of flow cytometric techniques, preferably fluorescence activated cell sorting (FACS), e.g. together with appropriate 'gating'. Flow cytometric techniques may be particularly suitable when the method employs the use of a binding means coupled to a detectable label, such as a fluorophore.

In one aspect there is provided a method for isolating a stem cell for treating cancer, the method comprising:

a) contacting a sample of stem cells with a binding means, wherein the binding means binds to one or more polypeptides selected from CTSG, CAP37, ITGB1, CYBB, SYK, DOCK8, COMP, ATG7, SLC2A1, GZMK, ATM, IKBKB, BCAP31, TAPBP, PPP3CB, ANXA1, PERM, PLEC, ACSL1, RAC1, GM2A, and PSMB2; and

b) isolating the stem cell based on the presence or absence of binding between the binding means and the one or more polypeptides.

Binding may be determined to be present when the amount of binding is statistically significant (e.g. when compared to a 'background' control). Binding may be determined to be absent when the amount of binding is statistically insignificant (e.g. when compared to a 'background' control). Preferably, binding is determined to be absent when there is no binding whatsoever.

In one embodiment the invention comprises detecting the presence of one or more polypeptides selected from CTSG, CAP37, ITGB1, CYBB, SYK, DOCK8, COMP, ATG7, SLC2A1, GZMK, ATM, IKBKB, BCAP31, TAPBP, PERM, PLEC, ACSL1, RAC1, GM2A, and PSMB2. When said one or more polypeptides are detected (i.e. where there is binding between the binding means and the polypeptide) the stem cell may be isolated. Suitably, said isolated stem cell may be a stem cell for treating cancer.

In another embodiment the invention may comprise detecting the absence of ANXA1 and/or PPP3CB (e.g. not detecting ANXA1 and/or PPP3CB). When said one or more polypeptides are not detected (i.e. where there is an absence of binding between the binding means and the polypeptide) the stem cell may be isolated. Suitably, said isolated stem cell may be a stem cell for treating cancer.

Preferably, the invention comprises detecting:

the presence of one or more polypeptides selected from CTSG, CAP37, ITGB1, CYBB, SYK, DOCK8, COMP, ATG7, SLC2A1, GZMK, ATM, IKBKB, BCAP31, TAPBP, PERM, PLEC, ACSL1, RAC1, GM2A, and PSMB2; and

the invention absence of ANXA1 and/or PPP3CB. In one embodiment, when said polypeptides are detected or not detected (as indicated), the stem cell is isolated.

In one embodiment a method of isolating a stem cell comprises the use of an immobilised binding means (e.g. a binding means conjugated to a bead, such as a magnetic bead, or

chromatographic resin) to isolate a stem cell of the invention. Such methods may be immuno-affinity methods.

The method may comprise quantifying the amount of binding between the binding means and the one or more polypeptides or between the binding means and the stem cell. The method may comprise isolating a stem cell for treating cancer based on the quantified amount of binding.

In one embodiment a stem cell for treating cancer is isolated when there is a high level of binding between a binding means and one or more polypeptides selected from CTSG, CAP37, ITGB1, CYBB, SYK, DOCK8, COMP, ATG7, SLC2A1, GZMK, ATM, IKBKB, BCAP31, TAPBP, PERM, PLEC, ACSL1, RAC1, GM2A, and PSMB2.

In one embodiment a stem cell for treating cancer is isolated when there is a low level of binding between a binding means and ANXA1 and/or PPP3CB.

Preferably, a stem cell for treating cancer is isolated when there is:

a high level of binding between a binding means and one or more polypeptides selected from CTSG, CAP37, ITGB1, CYBB, SYK, DOCK8, COMP, ATG7, SLC2A1, GZMK, ATM, IKBKB, BCAP31, TAPBP, PERM, PLEC, ACSL1, RAC1, GM2A, and PSMB2; and

a low level of binding between a binding means and ANXA1 and/or PPP3CB.

A high/low level of binding is preferably relative to a level of binding between the same binding means and polypeptide under the same conditions for a stem cell that is unsuitable for treating cancer.

The term “isolating” may mean providing a population of stem cells in which at least 50%, 60%, 70%, 80% or 90% (preferably at least 95%, 99% or 100%) are stem cells suitable for treating cancer. In other words, the term “isolating” may mean removing at least 50%, 60%, 70%, 80% or 90% (preferably at least 95%, 99% or 100%) of stem cells that are unsuitable for treating cancer from a population of stem cells.

Thus, the methods for isolating suitably allow for the separation of a stem cell for treating cancer from stem cell that is unsuitable for treating cancer.

In some embodiments a method described herein comprises discarding stem cells that are unsuitable for treating cancer.

In one aspect the invention provides a stem cell for treating cancer obtainable by a method of the invention (e.g. a stem cell capable of differentiating into granulocytes that are suitable to treat cancer).

In one aspect there is provided a method for producing a stem cell for treating cancer, the method comprising:

a. providing a cell; and

b. converting the cell into a stem cell having an expression profile described herein, for example a stem cell that is capable of differentiating into a granulocyte having an expression profile described herein, e.g. wherein:

i. the measured expression level of one or more of *GM2A, CTSG, CAP37, ITGB1, CYBB, SYK, DOCK8, COMP, ATG7, SLC2A1, GZMK, ATM, IKBKB, BCAP31, TAPBP, PERM, PLEC, ACSL1, RAC1,* and *PSMB2* is increased in the granulocyte when compared to a reference standard when the reference standard is from a granulocyte unsuitable for treating cancer; or

ii. the measured expression level of *ANXA1* and/or *PPP3CB* is decreased in the granulocyte when compared to the reference standard, when the reference standard is from a granulocyte unsuitable for treating cancer; or

iii. the measured expression level of one or more of *GM2A, CTSG, CAP37, ITGB1, CYBB, SYK, DOCK8, COMP, ATG7, SLC2A1, GZMK, ATM, IKBKB, BCAP31, TAPBP, PERM, PLEC, ACSL1, RAC1,* and *PSMB2* is increased or the same when compared to the reference standard, when the reference standard is from a granulocyte suitable for treating cancer; or

iv. the measured expression level of *ANXA1* and/or *PPP3CB* is decreased or the same when compared to the reference standard, when the reference standard is from a granulocyte suitable for treating cancer; and

c. optionally isolating the stem cell.

In one embodiment the cell is a somatic/differentiated cell, optionally from a donor who produces granulocytes suitable for treating cancer, for example as determined according to a method of the invention.

In some embodiments of any of the foregoing aspects, a granulocyte unsuitable for treating cancer is a viable granulocyte.

Embodiments related to the various methods of the invention are intended to be applied equally to other methods, the granulocytes, stem cells, compositions, pharmaceutical compositions or uses, and *vice versa*.

SEQUENCE IDENTITY

Any of a variety of sequence alignment methods can be used to determine percent identity, including, without limitation, global methods, local methods and hybrid methods, such as, e.g., segment approach methods. Protocols to determine percent identity are routine procedures within the scope of one skilled in the art. Global methods align sequences from the beginning to the end of the molecule and determine the best alignment by adding up scores of individual residue pairs and by imposing gap penalties. Non-limiting methods include, e.g., CLUSTAL W, see, e.g., Julie D. Thompson et al., CLUSTAL W: Improving the Sensitivity of Progressive Multiple Sequence Alignment Through Sequence Weighting, Position- Specific Gap Penalties and Weight Matrix Choice, 22(22) Nucleic Acids Research 4673-4680 (1994); and iterative refinement, see, e.g., Osamu Gotoh, Significant Improvement in Accuracy of Multiple Protein. Sequence Alignments by Iterative Refinement as Assessed by Reference to Structural Alignments, 264(4) J. Mol. Biol. 823-838 (1996). Local methods align sequences by identifying one or more conserved motifs shared by all of the input sequences. Non-limiting methods include, e.g., Match-box, see, e.g., Eric Depiereux and Ernest Feytmans, Match-Box: A Fundamentally New Algorithm for the Simultaneous Alignment of Several Protein Sequences, 8(5) CABIOS 501 -509 (1992); Gibbs sampling, see, e.g., C. E. Lawrence et al., Detecting Subtle Sequence Signals: A Gibbs Sampling Strategy for Multiple Alignment, 262(5131) Science 208-214 (1993); Align-M, see, e.g., Ivo Van Walle et al., Align-M - A New Algorithm for Multiple Alignment of Highly Divergent Sequences, 20(9) Bioinformatics:1428-1435 (2004).

Thus, percent sequence identity is determined by conventional methods. See, for example, Altschul et al., Bull. Math. Bio. 48: 603-16, 1986 and Henikoff and Henikoff, Proc. Natl. Acad. Sci. USA 89:10915-19, 1992. Briefly, two amino acid sequences are aligned to optimize the alignment scores using a gap opening penalty of 10, a gap extension penalty of 1, and the "blosum 62" scoring matrix of Henikoff and Henikoff (ibid.) as shown below (amino acids are indicated by the standard one-letter codes).

The "percent sequence identity" between two or more nucleic acid or amino acid sequences is a function of the number of identical positions shared by the sequences. Thus, % identity may be calculated as the number of identical nucleotides / amino acids divided by the total number of nucleotides / amino acids, multiplied by 100. Calculations of % sequence identity may also take into account the number of gaps, and the length of each gap that needs to be introduced to optimize alignment of two or more sequences. Sequence comparisons and the determination of percent identity between two or more sequences can be carried out using specific mathematical algorithms, such as BLAST, which will be familiar to a skilled person.

ALIGNMENT SCORES FOR DETERMINING SEQUENCE IDENTITY

	A	R	N	D	C	Q	E	G	H	I	L	K	M	F	P	S	T	W	Y	V
A	4																			
R	-1	5																		
N	-2	0	6																	
D	-2	-2	1	6																
C	0	-3	-3	-3	9															
Q	-1	1	0	0	-3	5														
E	-1	0	0	2	-4	2	5													
G	0	-2	0	-1	-3	-2	-2	6												
H	-2	0	1	-1	-3	0	0	-2	8											
I	-1	-3	-3	-3	-1	-3	-3	-4	-3	4										
L	-1	-2	-3	-4	-1	-2	-3	-4	-3	2	4									
K	-1	2	0	-1	-3	1	1	-2	-1	-3	-2	5								
M	-1	-1	-2	-3	-1	0	-2	-3	-2	1	2	-1	5							
F	-2	-3	-3	-3	-2	-3	-3	-3	-1	0	0	-3	0	6						
P	-1	-2	-2	-1	-3	-1	-1	-2	-2	-3	-3	-1	-2	-4	7					
S	1	-1	1	0	-1	0	0	0	-1	-2	-2	0	-1	-2	-1	4				
T	0	-1	0	-1	-1	-1	-1	-2	-2	-1	-1	-1	-1	-2	-1	1	5			
W	-3	-3	-4	-4	-2	-2	-3	-2	-2	-3	-2	-3	-1	1	-4	-3	-2	11		
Y	-2	-2	-2	-3	-2	-1	-2	-3	2	-1	-1	-2	-1	3	-3	-2	-2	2	7	
V	0	-3	-3	-3	-1	-2	-2	-3	-3	3	1	-2	1	-1	-2	-2	0	-3	-1	4

The percent identity is then calculated as:

$$\frac{\text{Total number of identical matches}}{[\text{length of the longer sequence plus the number of gaps introduced into the longer sequence in order to align the two sequences}]} \times 100$$

Substantially homologous polypeptides are characterized as having one or more amino acid substitutions, deletions or additions. These changes are preferably of a minor nature, that is conservative amino acid substitutions (see below) and other substitutions that do not significantly affect the folding or activity of the polypeptide; small deletions, typically of one to about 30 amino acids; and small amino- or carboxyl-terminal extensions, such as an amino-

terminal methionine residue, a small linker peptide of up to about 20-25 residues, or an affinity tag.

CONSERVATIVE AMINO ACID SUBSTITUTIONS

Basic:	arginine
	lysine
	histidine
Acidic:	glutamic acid
	aspartic acid
Polar:	glutamine
	asparagine
Hydrophobic:	leucine
	isoleucine
	valine
Aromatic:	phenylalanine
	tryptophan
	tyrosine
Small:	glycine
	alanine
	serine
	threonine
	methionine

In addition to the 20 standard amino acids, non-standard amino acids (such as 4-hydroxyproline, 6-N-methyl lysine, 2-aminoisobutyric acid, isovaline and α -methyl serine) may be substituted for amino acid residues of the polypeptides of the present invention. A limited number of non-conservative amino acids, amino acids that are not encoded by the genetic code, and unnatural amino acids may be substituted for polypeptide amino acid residues. The polypeptides of the present invention can also comprise non-naturally occurring amino acid residues.

Non-naturally occurring amino acids include, without limitation, trans-3-methylproline, 2,4-methano-proline, cis-4-hydroxyproline, trans-4-hydroxy-proline, N-methylglycine, allo-threonine, methyl-threonine, hydroxy-ethylcysteine, hydroxyethylhomo-cysteine, nitro-glutamine, homoglutamine, pipecolic acid, tert-leucine, norvaline, 2-azaphenylalanine, 3-azaphenyl-alanine, 4-azaphenyl-alanine, and 4-fluorophenylalanine. Several methods are

known in the art for incorporating non-naturally occurring amino acid residues into proteins. For example, an in vitro system can be employed wherein nonsense mutations are suppressed using chemically aminoacylated suppressor tRNAs. Methods for synthesizing amino acids and aminoacylating tRNA are known in the art. Transcription and translation of plasmids containing nonsense mutations is carried out in a cell free system comprising an E. coli S30 extract and commercially available enzymes and other reagents. Proteins are purified by chromatography. See, for example, Robertson et al., J. Am. Chem. Soc. 113:2722, 1991; Ellman et al., Methods Enzymol. 202:301, 1991; Chung et al., Science 259:806-9, 1993; and Chung et al., Proc. Natl. Acad. Sci. USA 90:10145-9, 1993). In a second method, translation is carried out in Xenopus oocytes by microinjection of mutated mRNA and chemically aminoacylated suppressor tRNAs (Turcatti et al., J. Biol. Chem. 271:19991-8, 1996). Within a third method, E. coli cells are cultured in the absence of a natural amino acid that is to be replaced (e.g., phenylalanine) and in the presence of the desired non-naturally occurring amino acid(s) (e.g., 2-azaphenylalanine, 3-azaphenylalanine, 4-azaphenylalanine, or 4-fluorophenylalanine). The non-naturally occurring amino acid is incorporated into the polypeptide in place of its natural counterpart. See, Koide et al., Biochem. 33:7470-6, 1994. Naturally occurring amino acid residues can be converted to non-naturally occurring species by in vitro chemical modification. Chemical modification can be combined with site-directed mutagenesis to further expand the range of substitutions (Wynn and Richards, Protein Sci. 2:395-403, 1993).

A limited number of non-conservative amino acids, amino acids that are not encoded by the genetic code, non-naturally occurring amino acids, and unnatural amino acids may be substituted for amino acid residues of polypeptides of the present invention.

Essential amino acids in the polypeptides of the present invention can be identified according to procedures known in the art, such as site-directed mutagenesis or alanine-scanning mutagenesis (Cunningham and Wells, Science 244: 1081-5, 1989). Sites of biological interaction can also be determined by physical analysis of structure, as determined by such techniques as nuclear magnetic resonance, crystallography, electron diffraction or photoaffinity labeling, in conjunction with mutation of putative contact site amino acids. See, for example, de Vos et al., Science 255:306-12, 1992; Smith et al., J. Mol. Biol. 224:899-904, 1992; Wlodaver et al., FEBS Lett. 309:59-64, 1992. The identities of essential amino acids can also be inferred from analysis of homologies with related components (e.g. the translocation or protease components) of the polypeptides of the present invention.

Multiple amino acid substitutions can be made and tested using known methods of mutagenesis and screening, such as those disclosed by Reidhaar-Olson and Sauer (Science 241:53-7, 1988) or Bowie and Sauer (Proc. Natl. Acad. Sci. USA 86:2152-6, 1989). Briefly, these authors disclose methods for simultaneously randomizing two or more positions in a polypeptide, selecting for functional polypeptide, and then sequencing the mutagenized polypeptides to determine the spectrum of allowable substitutions at each position. Other methods that can be used include phage display (e.g., Lowman et al., Biochem. 30:10832-7, 1991; Ladner et al., U.S. Patent No. 5,223,409; Huse, WIPO Publication WO 92/06204) and region-directed mutagenesis (Derbyshire et al., Gene 46:145, 1986; Ner et al., DNA 7:127, 1988).

Unless defined otherwise, all technical and scientific terms used herein have the same meaning as commonly understood by one of ordinary skill in the art to which this disclosure belongs. Singleton, et al., DICTIONARY OF MICROBIOLOGY AND MOLECULAR BIOLOGY, 20 ED., John Wiley and Sons, New York (1994), and Hale & Marham, THE HARPER COLLINS DICTIONARY OF BIOLOGY, Harper Perennial, NY (1991) provide the skilled person with a general dictionary of many of the terms used in this disclosure.

This disclosure is not limited by the exemplary methods and materials disclosed herein, and any methods and materials similar or equivalent to those described herein can be used in the practice or testing of embodiments of this disclosure. Numeric ranges are inclusive of the numbers defining the range. Unless otherwise indicated, any nucleic acid sequences are written left to right in 5' to 3' orientation; amino acid sequences are written left to right in amino to carboxy orientation, respectively.

The headings provided herein are not limitations of the various aspects or embodiments of this disclosure.

Amino acids are referred to herein using the name of the amino acid, the three letter abbreviation or the single letter abbreviation. The term “protein", as used herein, includes proteins, polypeptides, and peptides. As used herein, the term “amino acid sequence” is synonymous with the term “polypeptide” and/or the term “protein”. In some instances, the term “amino acid sequence” is synonymous with the term “peptide”. In some instances, the term “amino acid sequence” is synonymous with the term “enzyme”. The terms "protein" and "polypeptide" are used interchangeably herein. In the present disclosure and claims, the conventional one-letter and three-letter codes for amino acid residues may be used. The 3-

letter code for amino acids as defined in conformity with the IUPACIUB Joint Commission on Biochemical Nomenclature (JCBN). It is also understood that a polypeptide may be coded for by more than one nucleotide sequence due to the degeneracy of the genetic code.

Other definitions of terms may appear throughout the specification. Before the exemplary embodiments are described in more detail, it is to be understood that this disclosure is not limited to particular embodiments described, and as such may vary. It is also to be understood that the terminology used herein is for the purpose of describing particular embodiments only, and is not intended to be limiting, since the scope of the present disclosure will be defined only by the appended claims.

Where a range of values is provided, it is understood that each intervening value, to the tenth of the unit of the lower limit unless the context clearly dictates otherwise, between the upper and lower limits of that range is also specifically disclosed. Each smaller range between any stated value or intervening value in a stated range and any other stated or intervening value in that stated range is encompassed within this disclosure. The upper and lower limits of these smaller ranges may independently be included or excluded in the range, and each range where either, neither or both limits are included in the smaller ranges is also encompassed within this disclosure, subject to any specifically excluded limit in the stated range. Where the stated range includes one or both of the limits, ranges excluding either or both of those included limits are also included in this disclosure.

It must be noted that as used herein and in the appended claims, the singular forms “a”, “an”, and “the” include plural referents unless the context clearly dictates otherwise. Thus, for example, reference to “a granulocyte” includes a plurality of such candidate agents and reference to “the granulocyte” includes reference to one or more granulocytes and equivalents thereof known to those skilled in the art, and so forth.

The publications discussed herein are provided solely for their disclosure prior to the filing date of the present application. Nothing herein is to be construed as an admission that such publications constitute prior art to the claims appended hereto.

BRIEF DESCRIPTION OF THE DRAWINGS

Embodiments of the invention will now be described, by way of example only, with reference to the following Figures and Examples.

Figure 1 shows the distribution of different types of neutrophils in the general population. Defective neutrophils are characterised by an anti-inflammatory and proangiogenic phenotype whereas healthy neutrophils are characterised by a proinflammatory and antiangiogenic phenotype. Finally, exceptional neutrophils are present in a proportion of the general population and exhibit the extreme of all qualities found in healthy neutrophils.

Figure 2 shows significantly (***P < 0.001, **P < 0.01, *P < 0.05) upregulated expression of ITGB1, SYK, DOCK8 and CYBB in high CKA neutrophils (>80% CKA) compared with low CKA control neutrophils. Data are mean (n = 3 donor samples in duplicate) ± standard error of mean compared by two-way ANOVA.

Figure 3 shows significantly (**P < 0.01, *P < 0.05) upregulated expression of PLEC and COMP in high CKA neutrophils (>80% CKA) compared with low CKA control neutrophils. Data are mean (n = 3 donor samples in duplicate) ± standard error of mean compared by two-way ANOVA.

Figure 4 shows significantly (**P < 0.01, *P < 0.05) upregulated expression of ATG7, SLC2A1, S100A9, ACSL1, CTSG, PSMB2, ATM and S100A8 in high CKA neutrophils (>80% CKA) compared with low CKA control neutrophils. Data are mean (n = 3 donor samples in duplicate) ± standard error of mean compared by two-way ANOVA.

Figure 5 shows significantly (**P < 0.01, *P < 0.05) downregulated expression of ANXA1 in high CKA neutrophils (>80% CKA) compared with low CKA control neutrophils. Data are mean (n = 3 donor samples in duplicate) ± standard error of mean compared by two-way ANOVA.

Figure 6 shows significantly (**P < 0.01, *P < 0.05) upregulated expression of BCAP31 and TAPBP in high CKA neutrophils (>80% CKA) compared with low CKA control neutrophils. Data are mean (n = 3 donor samples in duplicate) ± standard error of mean compared by two-way ANOVA.

SEQUENCE LISTING

Gene Sequences

SEQ ID NO.	GENE	Accession No.	Ensembl Release No.
1	*CTSG*	ENSG00000100448	97
2	*CAP37*	ENSG00000172232	97
3	*ITGB1*	ENSG00000150093	97
4	*CYBB*	ENSG00000165168	97
5	*SYK*	ENSG00000165025	97
6	*DOCK8*	ENSG00000107099	97
7	*COMP*	ENSG00000105664	97
8	*ATG7*	ENSG00000197548	97
9	*SLC2A1*	ENSG00000117394	97
10	*GZMK*	ENSG00000113088	97

11	*S100A9*	ENSG00000163220	97
12	*S100A8*	ENSG00000143546	97
13	*ATM*	ENSG00000149311	97
14	*IKBKB*	ENSG00000104365	97
15	*BCAP31*	ENSG00000185825	97
16	*TAPBP*	ENSG00000231925	97
17	*PPP3CB*	ENSG00000107758	97
18	*ANXA1*	ENSG00000135046	97
19	*PERM*	ENSG00000005381	97
20	*PLEC*	ENSG00000178209	97
21	*ACSL1*	ENSG00000151726	97
22	*RAC1*	ENSG00000136238	97
23	*PSMB2*	ENSG00000126067	97
24	*GM2A*	ENSG00000196743	97

Polypeptide Sequences

SEQ ID NO.	POLY-PEPTIDE	ISOFORM	UniProt ID	UniProt Version Number	SEQUENCE
25	CTSG	1	P08311	Entry version 191 (18 Sep 2019) Sequence version 2 (01 Jan 1990)	MQPLLLLLAF LLPTGAEAGE IIGGRESRPH SRPYMAYLQI QSPAGQSRCG GFLVREDFVL TAAHCWGSNI NVTLGAHNIQ RRENTQQHIT ARRAIRHPQY NQRTIQNDIM LLQLSRRVRR NRNVNPVALP RAQEGLRPGT LCTVAGWGRV SMRRGTDTLR EVQLRVQRDR QCLRIFGSYD PRRQICVGDR RERKAAFKGD SGGPLLCNNV AHGIVSYGKS SGVPPEVFTR VSSFLPWIRT TMRSFKLLDQ METPL
26	CAP37	1	P20160	Entry version 191 (18 Sep 2019) Sequence version 3 (01 Oct 1993)	MTRLTVLALL AGLLASSRAG SSPLLDIVGG RKARPRQFPF LASIQNQGRH FCGGALIHAR FVMTAASCFQ SQNPGVSTVV LGAYDLRRRE RQSRQTFSIS SMSENGYDPQ QNLNDLMLLQ LDREANLTSS VTILPLPLQN ATVEAGTRCQ VAGWGSQRSG GRLSRFPRFV NVTVTPEDQC RPNNVCTGVL TRRGGICNGD GGTPLVCEGL AHGVASFSLG PCGRGPDFFT RVALFRDWID GVLNNPGPGP A
27	ITGB1	1	P05556	Entry version 242 (18 Sep 2019) Sequence version 2 (16 Dec 2008)	MNLQPIFWIG LISSVCCVFA QTDENRCLKA NAKSCGECIQ AGPNCGWCTN STFLQEGMPT SARCDDLEAL KKKGCPPDDI ENPRGSKDIK KNKNVTNRSK GTAEKLKPED ITQIQPQQLV LRLRSGEPQT FTLKFKRAED YPIDLYYLMD LSYSMKDDLE NVKSLGTDLM NEMRRITSDF RIGFGSFVEK TVMPYISTTP

					AKLRNPCTSE QNCTSPFSYK NVLSLTNKGE VFNELVGKQR ISGNLDSPEG GFDAIMQVAV CGSLIGWRNV TRLLVFSTDA GFHFAGDGKL GGIVLPNDGQ CHLENNMYTM SHYYDYPSIA HLVQKLSENN IQTIFAVTEE FQPVYKELKN LIPKSAVGTL SANSSNVIQL IIDAYNSLSS EVILENGKLS EGVTISYKSY CKNGVNGTGE NGRKCSNISI GDEVQFEISI TSNKCPKKDS DSFKIRPLGF TEEVEVILQY ICECECQSEG IPESPKCHEG NGTFECGACR CNEGRVGRHC ECSTDEVNSE DMDAYCRKEN SSEICSNNGE CVCGQCVCRK RDNTNEIYSG KFCECDNFNC DRSNGLICGG NGVCKCRVCE CNPNYTGSAC DCSLDTSTCE ASNGQICNGR GICECGVCKC TDPKFQGQTC EMCQTCLGVC AEHKECVQCR AFNKGEKKDT CTQECSYFNI TKVESRDKLP QPVQPDPVSH CKEKDVDDCW FYFTYSVNGN NEVMVHVVEN PECPTGPDII PIVAGVVAGI VLIGLALLLI WKLLMIIHDR REFAKFEKEK MNAKWDTGEN PIYKSAVTTV VNPKYEGK
28	ITGB1	2	P05556-2	Entry version 242 (18 Sep 2019) Sequence version 2 (16 Dec 2008)	MNLQPIFWIG LISSVCCVFA QTDENRCLKA NAKSCGECIQ AGPNCGWCTN STFLQEGMPT SARCDDLEAL KKKGCPPDDI ENPRGSKDIK KNKNVTNRSK GTAEKLKPED ITQIQPQQLV LRLRSGEPQT FTLKFKRAED YPIDLYYLMD LSYSMKDDLE NVKSLGTDLM NEMRRITSDF RIGFGSFVEK TVMPYISTTP AKLRNPCTSE QNCTSPFSYK NVLSLTNKGE VFNELVGKQR ISGNLDSPEG GFDAIMQVAV CGSLIGWRNV TRLLVFSTDA GFHFAGDGKL GGIVLPNDGQ CHLENNMYTM SHYYDYPSIA HLVQKLSENN IQTIFAVTEE FQPVYKELKN LIPKSAVGTL SANSSNVIQL IIDAYNSLSS EVILENGKLS EGVTISYKSY CKNGVNGTGE NGRKCSNISI GDEVQFEISI TSNKCPKKDS DSFKIRPLGF TEEVEVILQY ICECECQSEG IPESPKCHEG NGTFECGACR CNEGRVGRHC ECSTDEVNSE DMDAYCRKEN SSEICSNNGE CVCGQCVCRK RDNTNEIYSG KFCECDNFNC DRSNGLICGG NGVCKCRVCE

					CNPNYTGSAC DCSLDTSTCE ASNGQICNGR GICECGVCKC TDPKFQGQTC EMCQTCLGVC AEHKECVQCR AFNKGEKKDT CTQECSYFNI TKVESRDKLP QPVQPDPVSH CKEKDVDDCW FYFTYSVNGN NEVMVHVVEN PECPTGPDII PIVAGVVAGI VLIGLALLLI WKLLMIIHDR REFAKFEKEK MNAKWDTVSY KTSKKQSGL
29	ITGB1	3	P05556-3	Entry version 242 (18 Sep 2019) Sequence version 2 (16 Dec 2008)	MNLQPIFWIG LISSVCCVFA QTDENRCLKA NAKSCGECIQ AGPNCGWCTN STFLQEGMPT SARCDDLEAL KKKGCPPDDI ENPRGSKDIK KNKNVTNRSK GTAEKLKPED ITQIQPQQLV LRLRSGEPQT FTLKFKRAED YPIDLYYLMD LSYSMKDDLE NVKSLGTDLM NEMRRITSDF RIGFGSFVEK TVMPYISTTP AKLRNPCTSE QNCTSPFSYK NVLSLTNKGE VFNELVGKQR ISGNLDSPEG GFDAIMQVAV CGSLIGWRNV TRLLVFSTDA GFHFAGDGKL GGIVLPNDGQ CHLENNMYTM SHYYDYPSIA HLVQKLSENN IQTIFAVTEE FQPVYKELKN LIPKSAVGTL SANSSNVIQL IIDAYNSLSS EVILENGKLS EGVTISYKSY CKNGVNGTGE NGRKCSNISI GDEVQFEISI TSNKCPKKDS DSFKIRPLGF TEEVEVILQY ICECECQSEG IPESPKCHEG NGTFECGACR CNEGRVGRHC ECSTDEVNSE DMDAYCRKEN SSEICSNNGE CVCGQCVCRK RDNTNEIYSG KFCECDNFNC DRSNGLICGG NGVCKCRVCE CNPNYTGSAC DCSLDTSTCE ASNGQICNGR GICECGVCKC TDPKFQGQTC EMCQTCLGVC AEHKECVQCR AFNKGEKKDT CTQECSYFNI TKVESRDKLP QPVQPDPVSH CKEKDVDDCW FYFTYSVNGN NEVMVHVVEN PECPTGPDII PIVAGVVAGI VLIGLALLLI WKLLMIIHDR REFAKFEKEK MNAKWDTSLS VAQPGVQWCD ISSLQPLTSR FQQFSCLSLP STWDYRVKIL FIRVP
30	ITGB1	4	P05556-4	Entry version 242 (18 Sep 2019) Sequence version 2 (16 Dec 2008)	MNLQPIFWIG LISSVCCVFA QTDENRCLKA NAKSCGECIQ AGPNCGWCTN STFLQEGMPT SARCDDLEAL KKKGCPPDDI ENPRGSKDIK KNKNVTNRSK GTAEKLKPED ITQIQPQQLV

					LRLRSGEPQT FTLKFKRAED YPIDLYYLMD LSYSMKDDLE NVKSLGTDLM NEMRRITSDF RIGFGSFVEK TVMPYISTTP AKLRNPCTSE QNCTSPFSYK NVLSLTNKGE VFNELVGKQR ISGNLDSPEG GFDAIMQVAV CGSLIGWRNV TRLLVFSTDA GFHFAGDGKL GGIVLPNDGQ CHLENNMYTM SHYYDYPSIA HLVQKLSENN IQTIFAVTEE FQPVYKELKN LIPKSAVGTL SANSSNVIQL IIDAYNSLSS EVILENGKLS EGVTISYKSY CKNGVNGTGE NGRKCSNISI GDEVQFEISI TSNKCPKKDS DSFKIRPLGF TEEVEVILQY ICECECQSEG IPESPKCHEG NGTFECGACR CNEGRVGRHC ECSTDEVNSE DMDAYCRKEN SSEICSNNGE CVCGQCVCRK RDNTNEIYSG KFCECDNFNC DRSNGLICGG NGVCKCRVCE CNPNYTGSAC DCSLDTSTCE ASNGQICNGR GICECGVCKC TDPKFQGQTC EMCQTCLGVC AEHKECVQCR AFNKGEKKDT CTQECSYFNI TKVESRDKLP QPVQPDPVSH CKEKDVDDCW FYFTYSVNGN NEVMVHVVEN PECPTGPDII PIVAGVVAGI VLIGLALLLI WKLLMIIHDR REFAKFEKEK MNAKWDTPGV QWCDISSLQP LTSRFQQFSC LSLPSTWDYR VKILFIRVP
31	ITGB1	5	P05556-5	Entry version 242 (18 Sep 2019) Sequence version 2 (16 Dec 2008)	MNLQPIFWIG LISSVCCVFA QTDENRCLKA NAKSCGECIQ AGPNCGWCTN STFLQEGMPT SARCDDLEAL KKKGCPPDDI ENPRGSKDIK KNKNVTNRSK GTAEKLKPED ITQIQPQQLV LRLRSGEPQT FTLKFKRAED YPIDLYYLMD LSYSMKDDLE NVKSLGTDLM NEMRRITSDF RIGFGSFVEK TVMPYISTTP AKLRNPCTSE QNCTSPFSYK NVLSLTNKGE VFNELVGKQR ISGNLDSPEG GFDAIMQVAV CGSLIGWRNV TRLLVFSTDA GFHFAGDGKL GGIVLPNDGQ CHLENNMYTM SHYYDYPSIA HLVQKLSENN IQTIFAVTEE FQPVYKELKN LIPKSAVGTL SANSSNVIQL IIDAYNSLSS EVILENGKLS EGVTISYKSY CKNGVNGTGE NGRKCSNISI GDEVQFEISI TSNKCPKKDS DSFKIRPLGF TEEVEVILQY ICECECQSEG IPESPKCHEG NGTFECGACR CNEGRVGRHC

					ECSTDEVNSE DMDAYCRKEN SSEICSNNGE CVCGQCVCRK RDNTNEIYSG KFCECDNFNC DRSNGLICGG NGVCKCRVCE CNPNYTGSAC DCSLDTSTCE ASNGQICNGR GICECGVCKC TDPKFQGQTC EMCQTCLGVC AEHKECVQCR AFNKGEKKDT CTQECSYFNI TKVESRDKLP QPVQPDPVSH CKEKDVDDCW FYFTYSVNGN NEVMVHVVEN PECPTGPDII PIVAGVVAGI VLIGLALLLI WKLLMIIHDR REFAKFEKEK MNAKWDTQEN PIYKSPINNF KNPNYGRKAG L
32	CYBB	1	P04839	Entry version 213 (18 Sep 2019) Sequence version 2 (23 Jan 2007)	MGNWAVNEGL SIFVILVWLG LNVFLFVWYY RVYDIPPKFF YTRKLLGSAL ALARAPAACL NFNCMLILLP VCRNLLSFLR GSSACCSTRV RRQLDRNLTF HKMVAWMIAL HSAIHTIAHL FNVEWCVNAR VNNSDPYSVA LSELGDRQNE SYLNFARKRI KNPEGGLYLA VTLLAGITGV VITLCLILII TSSTKTIRRS YFEVFWYTHH LFVIFFIGLA IHGAERIVRG QTAESLAVHN ITVCEQKISE WGKIKECPIP QFAGNPPMTW KWIVGPMFLY LCERLVRFWR SQQKVVITKV VTHPFKTIEL QMKKKGFKME VGQYIFVKCP KVSKLEWHPF TLTSAPEEDF FSIHIRIVGD WTEGLFNACG CDKQEFQDAW KLPKIAVDGP FGTASEDVFS YEVVMLVGAG IGVTPFASIL KSVWYKYCNN ATNLKLKKIY FYWLCRDTHA FEWFADLLQL LESQMQERNN AGFLSYNIYL TGWDESQANH FAVHHDEEKD VITGLKQKTL YGRPNWDNEF KTIASQHPNT RIGVFLCGPE ALAETLSKQS ISNSESGPRG VHFIFNKENF
33	SYK	1	P43405	Entry version 224 (18 Sep 2019) Sequence version 1 (01 Nov 1995)	MASSGMADSA NHLPFFFGNI TREEAEDYLV QGGMSDGLYL LRQSRNYLGG FALSVAHGRK AHHYTIEREL NGTYAIAGGR THASPADLCH YHSQESDGLV CLLKKPFNRP QGVQPKTGPF EDLKENLIRE YVKQTWNLQG QALEQAIISQ KPQLEKLIAT TAHEKMPWFH GKISREESEQ IVLIGSKTNG KFLIRARDNN GSYALCLLHE GKVLHYRIDK DKTGKLSIPE GKKFDTLWQL VEHYSYKADG LLRVLTVPCQ

					KIGTQGNVNF GGRPQLPGSH PATWSAGGII SRIKSYSFPK PGHRKSSPAQ GNRQESTVSF NPYEPELAPW AADKGPQREA LPMDTEVYES PYADPEEIRP KEVYLDRKLL TLEDKELGSG NFGTVKKGYY QMKKVVKTVA VKILKNEAND PALKDELLAE ANVMQQLDNP YIVRMIGICE AESWMLVMEM AELGPLNKYL QQNRHVKDKN IIELVHQVSM GMKYLEESNF VHRDLAARNV LLVTQHYAKI SDFGLSKALR ADENYYKAQT HGKWPVKWYA PECINYYKFS SKSDVWSFGV LMWEAFSYGQ KPYRGMKGSE VTAMLEKGER MGCPAGCPRE MYDLMNLCWT YDVENRPGFA AVELRLRNYY YDVVN
34	SYK	2	P43405-2	Entry version 224 (18 Sep 2019) Sequence version 1 (01 Nov 1995)	MASSGMADSA NHLPFFFGNI TREEAEDYLV QGGMSDGLYL LRQSRNYLGG FALSVAHGRK AHHYTIEREL NGTYAIAGGR THASPADLCH YHSQESDGLV CLLKKPFNRP QGVQPKTGPF EDLKENLIRE YVKQTWNLQG QALEQAIISQ KPQLEKLIAT TAHEKMPWFH GKISREESEQ IVLIGSKTNG KFLIRARDNN GSYALCLLHE GKVLHYRIDK DKTGKLSIPE GKKFDTLWQL VEHYSYKADG LLRVLTVPCQ KIGTQGNVNF GGRPQLPGSH PASSPAQGNR QESTVSFNPY EPELAPWAAD KGPQREALPM DTEVYESPYA DPEEIRPKEV YLDRKLLTLE DKELGSGNFG TVKKGYYQMK KVVKTVAVKI LKNEANDPAL KDELLAEANV MQQLDNPYIV RMIGICEAES WMLVMEMAEL GPLNKYLQQN RHVKDKNIIE LVHQVSMGMK YLEESNFVHR DLAARNVLLV TQHYAKISDF GLSKALRADE NYYKAQTHGK WPVKWYAPEC INYYKFSSKS DVWSFGVLMW EAFSYGQKPY RGMKGSEVTA MLEKGERMGC PAGCPREMYD LMNLCWTYDV ENRPGFAAVE LRLRNYYYDV VN
35	DOCK8	1	Q8NF50	Entry version 160 (18 Sep 2019) Sequence version 3 (21 Aug 2007)	MATLPSAERR AFALKINRYS SAEIRKQFTL PPNLGQYHRQ SISTSGFPSL QLPQFYDPVE PVDFEGLLMT HLNSLDVQLA QELGDFTDDD LDVVFTPKEC RTLQPSLPEE GVELDPHVRD CVQTYIREWL IVNRKNQGSP EICGFKKTGS RKDFHKTLPK

					QTFESETLEC SEPAAQAGPR
					HLNVLCDVSG KGPVTACDFD
					LRSLQPDKRL ENLLQQVSAE
					DFEKQNEEAR RTNRQAELFA
					LYPSVDEEDA VEIRPVPECP
					KEHLGNRILV KLLTLKFEIE
					IEPLFASIAL YDVKERKKIS
					ENFHCDLNSD QFKGFLRAHT
					PSVAASSQAR SAVFSVTYPS
					SDIYLVVKIE KVLQQGEIGD
					CAEPYTVIKE SDGGKSKEKI
					EKLKLQAESF CQRLGKYRMP
					FAWAPISLSS FFNVSTLERE
					VTDVDSVVGR SSVGERRTLA
					QSRRLSERAL SLEENGVGSN
					FKTSTLSVSS FFKQEGDRLS
					DEDLFKFLAD YKRSSSLQRR
					VKSIPGLLRL EISTAPEIIN
					CCLTPEMLPV KPFPENRTRP
					HKEILEFPTR EVYVPHTVYR
					NLLYVYPQRL NFVNKLASAR
					NITIKIQFMC GEDASNAMPV
					IFGKSSGPEF LQEVYTAVTY
					HNKSPDFYEE VKIKLPAKLT
					VNHHLLFTFY HISCQQKQGA
					SVETLLGYSW LPILLNERLQ
					TGSYCLPVAL EKLPPNYSMH
					SAEKVPLQNP PIKWAEGHKG
					VFNIEVQAVS SVHTQDNHLE
					KFFTLCHSLE SQVTFPIRVL
					DQKISEMALE HELKLSIICL
					NSSRLEPLVL FLHLVLDKLF
					QLSVQPMVIA GQTANFSQFA
					FESVVAIANS LHNSKDLSKD
					QHGRNCLLAS YVHYVFRLPE
					VQRDVPKSGA PTALLDPRSY
					HTYGRTSAAA VSSKLLQARV
					MSSSNPDLAG THSAADEEVK
					NIMSSKIADR NCSRMSYYCS
					GSSDAPSSPA APRPASKKHF
					HEELALQMVV STGMVRETVF
					KYAWFFFELL VKSMAQHVHN
					MDKRDSFRRT RFSDRFMDDI
					TTIVNVVTSE IAALLVKPQK
					ENEQAEKMNI SLAFFLYDLL
					SLMDRGFVFN LIRHYCSQLS
					AKLSNLPTLI SMRLEFLRIL
					CSHEHYLNLN LFFMNADTAP
					TSPCPSISSQ NSSSCSSFQD
					QKIASMFDLT SEYRQQHFLT
					GLLFTELAAA LDAEGEGISK
					VQRKAVSAIH SLLSSHDLDP
					RCVKPEVKVK IAALYLPLVG
					IILDALPQLC DFTVADTRRY
					RTSGSDEEQE GAGAINQNVA
					LAIAGNNFNL KTSGIVLSSL
					PYKQYNMLNA DTTRNLMICF
					LWIMKNADQS LIRKWIADLP
					STQLNRILDL LFICVLCFEY
					KGKQSSDKVS TQVLQKSRDV

					KARLEEALLR GEGARGEMMR RRAPGNDRFP GLNENLRWKK EQTHWRQANE KLDKTKAELD QEALISGNLA TEAHLIILDM QENIIQASSA LDCKDSLLGG VLRVLVNSLN CDQSTTYLTH CFATLRALIA KFGDLLFEEE VEQCFDLCHQ VLHHCSSSMD VTRSQACATL YLLMRFSFGA TSNFARVKMQ VTMSLASLVG RAPDFNEEHL RRSLRTILAY SEEDTAMQMT PFPTQVEELL CNLNSILYDT VKMREFQEDP EMLMDLMYRI AKSYQASPDL RLTWLQNMAE KHTKKKCYTE AAMCLVHAAA LVAEYLSMLE DHSYLPVGSV SFQNISSNVL EESVVSEDTL SPDEDGVCAG QYFTESGLVG LLEQAAELFS TGGLYETVNE VYKLVIPILE AHREFRKLTL THSKLQRAFD SIVNKDHKRM FGTYFRVGFF GSKFGDLDEQ EFVYKEPAIT KLPEISHRLE AFYGQCFGAE FVEVIKDSTP VDKTKLDPNK AYIQITFVEP YFDEYEMKDR VTYFEKNFNL RRFMYTTPFT LEGRPRGELH EQYRRNTVLT TMHAFPYIKT RISVIQKEEF VLTPIEVAIE DMKKKTLQLA VAINQEPPDA KMLQMVLQGS VGATVNQGPL EVAQVFLAEI PADPKLYRHH NKLRLCFKEF IMRCGEAVEK NKRLITADQR EYQQELKKNY NKLKENLRPM IERKIPELYK PIFRVESQKR DSFHRSSFRK CETQLSQGS
36	DOCK8	2	Q8NF50-2	Entry version 160 (18 Sep 2019) Sequence version 3 (21 Aug 2007)	MATLPSAERR AFALKINRYS SAEIRKQFTL PPNLGQYHRQ SISTSGFPSL QLPQFYDPVE PVDFEGLLMT HLNSLDVQLA QELGDFTDDD LDVVFTPKEC RTLQPSLPEE GVELDPHVRD CVQTYIREWL IVNRKNQGSP EICGFKKTGS RKDFHKTLPK QTFESETLEC SEPAAQAGPR HLNVLCDVSG KGPVTACDFD LRSLQPDKRL ENLLQQVSAE DFEKQNEEAR RTNRQAELFA LYPSVDEEDA VEIRPVPECP KEHLGNRILV KLLTLKFEIE IEPLFASIAL YDVKERKKIS ENFHCDLNSD QFKGFLRAHT PSVAASSQAR SAVFSVTYPS SDIYLVVKIE KVLQQGEIGD CAEPYTVIKE SDGGKSKEKI EKLKLQAESF CQRLGKYRMP FAWAPISLSS FFNVSTLERE VTDVDSVVGR SSVGERRTLA

					QSRRLSERAL SLEENGVGSN
					FKTSTLSVSS FFKQEGDRLS
					DEDLFKFLAD YKRSSSLQRR
					VKSIPGLLRL EISTAPEIIN
					CCLTPEMLPV KPFPENRTRP
					HKEILEFPTR EVYVPHTVYR
					NLLYVYPQRL NFVNKLASAR
					NITIKIQFMC GEDASNAMPV
					IFGKSSGPEF LQEVYTAVTY
					HNKSPDFYEE VKIKLPAKLT
					VNHHLLFTFY HISCQQKQGA
					SVETLLGYSW LPILLNERLQ
					TGSYCLPVAL EKLPPNYSMH
					SAEKVPLQNP PIKWAEGHKG
					VFNIEVQAVS SVHTQDNHLE
					KFFTLCHSLE SQVTFPIRVL
					DQKISEMALE HELKLSIICL
					NSSRLEPLVL FLHLVLDKLF
					QLSVQPMVIA GQTANFSQFA
					FESVVAIANS LHNSKDLSKD
					QHGRNCLLAS YVHYVFRLPE
					VQRDVPKSGA PTALLDPRSY
					HTYGRTSAAA VSSKLLQARV
					MSSSNPDLAG THSAADEEVK
					NIMSSKHFHE ELALQMVVST
					GMVRETVFKY AWFFFELLVK
					SMAQHVHNMD KRDSFRRTRF
					SDRFMDDITT IVNVVTSEIA
					ALLVKPQKEN EQAEKMNISL
					AFFLYDLLSL MDRGFVFNLI
					RHYCSQLSAK LSNLPTLISM
					RLEFLRILCS HEHYLNLNLF
					FMNADTAPTS PCPSISSQNS
					SSCSSFQDQK IASMFDLTSE
					YRQQHFLTGL LFTELAAALD
					AEGEGISKVQ RKAVSAIHSL
					LSSHDLDPRC VKPEVKVKIA
					ALYLPLVGII LDALPQLCDF
					TVADTRRYRT SGSDEEQEGA
					GAINQNVALA IAGNNFNLKT
					SGIVLSSLPY KQYNMLNADT
					TRNLMICFLW IMKNADQSLI
					RKWIADLPST QLNRILDLLF
					ICVLCFEYKG KQSSDKVSTQ
					VLQKSRDVKA RLEEALLRGE
					GARGEMMRRR APGNDRFPGL
					NENLRWKKEQ THWRQANEKL
					DKTKAELDQE ALISGNLATE
					AHLIILDMQE NIIQASSALD
					CKDSLLGGVL RVLVNSLNCD
					QSTTYLTHCF ATLRALIAKF
					GDLLFEEEVE QCFDLCHQVL
					HHCSSSMDVT RSQACATLYL
					LMRFSFGATS NFARVKMQVT
					MSLASLVGRA PDFNEEHLRR
					SLRTILAYSE EDTAMQMTPF
					PTQVEELLCN LNSILYDTVK
					MREFQEDPEM LMDLMYRIAK
					SYQASPDLRL TWLQNMAEKH
					TKKKCYTEAA MCLVHAAALV

					AEYLSMLEDH SYLPVGSVSF QNISSNVLEE SVVSEDTLSP DEDGVCAGQY FTESGLVGLL EQAAELFSTG GLYETVNEVY KLVIPILEAH REFRKLTLTH SKLQRAFDSI VNKDHKRMFG TYFRVGFFGS KFGDLDEQEF VYKEPAITKL PEISHRLEAF YGQCFGAEFV EVIKDSTPVD KTKLDPNKAY IQITFVEPYF DEYEMKDRVT YFEKNFNLRR FMYTTPFTLE GRPRGELHEQ YRRNTVLTTM HAFPYIKTRI SVIQKEEFVL TPIEVAIEDM KKKTLQLAVA INQEPPDAKM LQMVLQGSVG ATVNQGPLEV AQVFLAEIPA DPKLYRHHNK LRLCFKEFIM RCGEAVEKNK RLITADQREY QQELKKNYNK LKENLRPMIE RKIPELYKPI FRVESQKRDS FHRSSFRKCE TQLSQGS
37	DOCK8	3	Q8NF50-3	Entry version 160 (18 Sep 2019) Sequence version 3 (21 Aug 2007)	MTHLNSLDVQ LAQELGDFTD DDLDVVFTPK ECRTLQPSLP EEGVELDPHV RDCVQTYIRE WLIVNRKNQG SPEICGFKKT GSRKDFHKTL PKQTFESETL ECSEPAAQAG PRHLNVLCDV SGKGPVTACD FDLRSLQPDK RLENLLQQVS AEDFEKQNEE ARRTNRQAEL FALYPSVDEE DAVEIRPVPE CPKEHLGNRI LVKLLTLKFE IEIEPLFASI ALYDVKERKK ISENFHCDLN SDQFKGFLRA HTPSVAASSQ ARSAVFSVTY PSSDIYLVVK IEKVLQQGEI GDCAEPYTVI KESDGGKSKE KIEKLKLQAE SFCQRLGKYR MPFAWAPISL SSFFNVSTLE REVTDVDSVV GRSSVGERRT LAQSRRLSER ALSLEENGVG SNFKTSTLSV SSFFKQEGDR LSDEDLFKFL ADYKRSSSLQ RRVKSIPGLL RLEISTAPEI INCCLTPEML PVKPFPENRT RPHKEILEFP TREVYVPHTV YRNLLYVYPQ RLNFVNKLAS ARNITIKIQF MCGEDASNAM PVIFGKSSGP EFLQEVYTAV TYHNKSPDFY EEVKIKLPAK LTVNHHLLFT FYHISCQQKQ GASVETLLGY SWLPILLNER LQTGSYCLPV ALEKLPPNYS MHSAEKVPLQ NPPIKWAEGH KGVFNIEVQA VSSVHTQDNH LEKFFTLCHS LESQVTFPIR VLDQKISEMA LEHELKLSII CLNSSRLEPL VLFLHLVLDK LFQLSVQPMV IAGQTANFSQ FAFESVVAIA

					NSLHNSKDLS KDQHGRNCLL ASYVHYVFRL PEVQRDVPKS GAPTALLDPR SYHTYGRTSA AAVSSKLLQA RVMSSSNPDL AGTHSAADEE VKNIMSSKIA DRNCSRMSYY CSGSSDAPSS PAAPRPASKK HFHEELALQM VVSTGMVRET VFKYAWFFFE LLVKSMAQHV HNMDKRDSFR RTRFSDRFMD DITTIVNVVT SEIAALLVKP QKENEQAEKM NISLAFFLYD LLSLMDRGFV FNLIRHYCSQ LSAKLSNLPT LISMRLEFLR ILCSHEHYLN LNLFFMNADT APTSPCPSIS SQNSSSCSSF QDQKIASMFD LTSEYRQQHF LTGLLFTELA AALDAEGEGI SKVQRKAVSA IHSLLSSHDL DPRCVKPEVK VKIAALYLPL VGIILDALPQ LCDFTVADTR RYRTSGSDEE QEGAGAINQN VALAIAGNNF NLKTSGIVLS SLPYKQYNML NADTTRNLMI CFLWIMKNAD QSLIRKWIAD LPSTQLNRIL DLLFICVLCF EYKGKQSSDK VSTQVLQKSR DVKARLEEAL LRGEGARGEM MRRRAPGNDR FPGLNENLRW KKEQTHWRQA NEKLDKTKAE LDQEALISGN LATEAHLIIL DMQENIIQAS SALDCKDSLL GGVLRVLVNS LNCDQSTTYL THCFATLRAL IAKFGDLLFE EEVEQCFDLC HQVLHHCSSS MDVTRSQACA TLYLLMRFSF GATSNFARVK MQVTMSLASL VGRAPDFNEE HLRRSLRTIL AYSEEDTAMQ MTPFPTQVEE LLCNLNSILY DTVKMREFQE DPEMLMDLMY RIAKSYQASP DLRLTWLQNM AEKHTKKKCY TEAAMCLVHA AALVAEYLSM LEDHSYLPVG SVSFQNISSN VLEESVVSED TLSPDEDGVC AGQYFTESGL VGLLEQAAEL FSTGGLYETV NEVYKLVIPI LEAHREFRKL TLTHSKLQRA FDSIVNKDHK RMFGTYFRVG FFGSKFGDLD EQEFVYKEPA ITKLPEISHR LEAFYGQCFG AEFVEVIKDS TPVDKTKLDP NKAYIQITFV EPYFDEYEMK DRVTYFEKNF NLRRFMYTTP FTLEGRPRGE LHEQYRRNTV LTTMHAFPYI KTRISVIQKE EFVLTPIEVA IEDMKKKTLQ LAVAINQEPP DAKMLQMVLQ GSVGATVNQG PLEVAQVFLA EIPADPKLYR HHNKLRLCFK EFIMRCGEAV

					EKNKRLITAD QREYQQELKK NYNKLKENLR PMIERKIPEL YKPIFRVESQ KRDSFHRSSF RKCETQLSQG S
38	DOCK8	4	Q8NF50-4	Entry version 160 (18 Sep 2019) Sequence version 3 (21 Aug 2007)	MTHLNSLDVQ LAQELGDFTD DDLDVVFTPK ECRTLQPSLP EEGVELDPHV RDCVQTYIRE WLIVNRKNQG SPEICGFKKT GSRKDFHKTL PKQTFESETL ECSEPAAQAG PRHLNVLCDV SGKGPVTACD FDLRSLQPDK RLENLLQQVS AEDFEKQNEE ARRTNRQAEL FALYPSVDEE DAVEIRPVPE CPKEHLGNRI LVKLLTLKFE IEIEPLFASI ALYDVKERKK ISENFHCDLN SDQFKGFLRA HTPSVAASSQ ARSAVFSVTY PSSDIYLVVK IEKVLQQGEI GDCAEPYTVI KESDGGKSKE KIEKLKLQAE SFCQRLGKYR MPFAWAPISL SSFFNVSTLE REVTDVDSVV GRSSVGERRT LAQSRRLSER ALSLEENGVG SNFKTSTLSV SSFFKQEGDR LSDEDLFKFL ADYKRSSSLQ RRVKSIPGLL RLEISTAPEI INCCLTPEML PVKPFPENRT RPHKEILEFP TREVYVPHTV YRNLLYVYPQ RLNFVNKLAS ARNITIKIQF MCGEDASNAM PVIFGKSSGP EFLQEVYTAV TYHNKSPDFY EEVKIKLPAK LTVNHHLLFT FYHISCQQKQ GASVETLLGY SWLPILLNER LQTGSYCLPV ALEKLPPNYS MHSAEKVPLQ NPPIKWAEGH KGVFNIEVQA VSSVHTQDNH LEKFFTLCHS LESQVTFPIR VLDQKISEMA LEHELKLSII CLNSSRLEPL VLFLHLVLDK LFQLSVQPMV IAGQTANFSQ FAFESVVAIA NSLHNSKDLS KDQHGRNCLL ASYVHYVFRL PEVQRDVPKS GAPTALLDPR SYHTYGRTSA AAVSSKLLQA RVMSSSNPDL AGTHSAADEE VKNIMSSKIA DRNCSRMSYY CSGSSDAPSS PAAPRPASKK HFHEELALQM VVSTGMVRET VFKYAWFFFE LLVKSMAQHV HNMDKRDSFR RTRFSDRFMD DITTIVNVVT SEIAALLVKP QKENEQAEKM NISLAFFLYD LLSLMDRGFV FNLIRHYCSQ LSAKLSNLPT LISMRLEFLR ILCSHEHYLN LNLFFMNADT APTSPCPSIS SQNSSSCSSF QDQKIASMFD LTSEYRQQHF LTGLLFTELA

					AALDAEGEGI SKVQRKAVSA IHSLLSSHDL DPRCVKPEVK VKIAALYLPL VGIILDALPQ LCDFTVADTR RYRTSGSDEE QEGAGAINQN VALAIAGNNF NLKTSGIVLS SLPYKQYNML NADTTRNLMI CFLWIMKNAD QSLIRKWIAD LPSTQLNRIL DLLFICVLCF EYKGKQSSDK VSTQVLQKSR DVKARLEEAL LRGEGARGEM MRRRAPGNDR FPGLNENLRW KKEQTHWRQA NEKLDKTKAE LDQEALISGN LATEAHLIIL DMQENIIQAS SALDCKDSLL GGVLRVLVNS LNCDQSTTYL THCFATLRAL IAKFGDLLFE EEVEQCFDLC HQVLHHCSSS MDVTRSQACA TLYLLMRFSF GATSNFARVK MQVTMSLASL VGRAPDFNEE HLRRSLRTIL AYSEEDTAMQ MTPFPTQVEE LLCNLNSILY DTVKMREFQE DPEMLMDLMY RIAKSYQASP DLRLTWLQNM AEKHTKKKCY TEAAMCLVHA AALVAEYLSM LEDHSYLPVG SVSFQNISSN VLEESVVSED TLSPDEDGVC AGQYFTESGL VGLLEQAAEL FSTGGLYETV NEVYKLVIPI LEAHREFRKL TLTHSKLQRA FDSIVNKDHK RMFGTYFRVG FFGSKFGDLD EQEFVYKEPA ITKLPEISHR LEAFYGQCFG AEFVEVIKDS TPVDKTKLDP NKAYIQITFV EPYFDEYEMK DRVTYFEKNF NLRRFMYTTP FTLEGRPRGE LHEQYRRNTV LTTMHAFPYI KTRISVIQKE EFVLTPIEVA IEDMKKKTLQ LAVAINQEPP DAKMLQMVLQ GSVGATVNQG PLEVAQVFLA EIPADPKLYR HHNKLRLCFK EFIMRCGEAV EKNKRLITAD QREYQQELKK NYNKLKENLR PMIERKIPEL YKPIFRVESQ KRDSFHRSSF RKCETQLSQG S
39	COMP	1	P49747	Entry version 195 (18 Sep 2019) Sequence version 2 (14 Oct 2008)	MVPDTACVLL LTLAALGASG QGQSPLGSDL GPQMLRELQE TNAALQDVRE LLRQQVREIT FLKNTVMECD ACGMQQSVRT GLPSVRPLLH CAPGFCFPGV ACIQTESGAR CGPCPAGFTG NGSHCTDVNE CNAHPCFPRV RCINTSPGFR CEACPPGYSG PTHQGVGLAF AKANKQVCTD INECETGQHN CVPNSVCINT RGSFQCGPCQ PGFVGDQASG CQRRAQRFCP DGSPSECHEH

					ADCVLERDGS RSCVCAVGWA GNGILCGRDT DLDGFPDEKL RCPERQCRKD NCVTVPNSGQ EDVDRDGIGD ACDPDADGDG VPNEKDNCPL VRNPDQRNTD EDKWGDACDN CRSQKNDDQK DTDQDGRGDA CDDDIDGDRI RNQADNCPRV PNSDQKDSDG DGIGDACDNC PQKSNPDQAD VDHDFVGDAC DSDQDQDGDG HQDSRDNCPT VPNSAQEDSD HDGQGDACDD DDDNDGVPDS RDNCRLVPNP GQEDADRDGV GDVCQDDFDA DKVVDKIDVC PENAEVTLTD FRAFQTVVLD PEGDAQIDPN WVVLNQGREI VQTMNSDPGL AVGYTAFNGV DFEGTFHVNT VTDDDYAGFI FGYQDSSSFY VVMWKQMEQT YWQANPFRAV AEPGIQLKAV KSSTGPGEQL RNALWHTGDT ESQVRLLWKD PRNVGWKDKK SYRWFLQHRP QVGYIRVRFY EGPELVADSN VVLDTTMRGG RLGVFCFSQE NIIWANLRYR CNDTIPEDYE THQLRQA
40	COMP	2	P49747-2	Entry version 195 (18 Sep 2019) Sequence version 2 (14 Oct 2008)	MVPDTACVLL LTLAALGASG QGQSPLGSDL GPQMLRELQE TNAALQDVRE LLRQQVREIT FLKNTVMECD ACGMQQSVRT GLPSVRPLLH CAPGFCFPGV ACIQTESGAR CGPCPAGFTG NGSHCTDVNE CETGQHNCVP NSVCINTRGS FQCGPCQPGF VGDQASGCQR RAQRFCPDGS PSECHEHADC VLERDGSRSC VCAVGWAGNG ILCGRDTDLD GFPDEKLRCP ERQCRKDNCV TVPNSGQEDV DRDGIGDACD PDADGDGVPN EKDNCPLVRN PDQRNTDEDK WGDACDNCRS QKNDDQKDTD QDGRGDACDD DIDGDRIRNQ ADNCPRVPNS DQKDSDGDGI GDACDNCPQK SNPDQADVDH DFVGDACDSD QDQDGDGHQD SRDNCPTVPN SAQEDSDHDG QGDACDDDDD NDGVPDSRDN CRLVPNPGQE DADRDGVGDV CQDDFDADKV VDKIDVCPEN AEVTLTDFRA FQTVVLDPEG DAQIDPNWVV LNQGREIVQT MNSDPGLAVG YTAFNGVDFE GTFHVNTVTD DDYAGFIFGY QDSSSFYVVM WKQMEQTYWQ ANPFRAVAEP GIQLKAVKSS TGPGEQLRNA LWHTGDTESQ VRLLWKDPRN VGWKDKKSYR WFLQHRPQVG YIRVRFYEGP ELVADSNVVL

					DTTMRGGRLG VFCFSQENII WANLRYRCND TIPEDYETHQ LRQA
41	ATG7	1	O95352	Entry version 168 (18 Sep 2019) Sequence version 1 (01 May 1999)	MAAATGDPGL SKLQFAPFSS ALDVGFWHEL TQKKLNEYRL DEAPKDIKGY YYNGDSAGLP ARLTLEFSAF DMSAPTPARC CPAIGTLYNT NTLESFKTAD KKLLLEQAAN EIWESIKSGT ALENPVLLNK FLLLTFADLK KYHFYYWFCY PALCLPESLP LIQGPVGLDQ RFSLKQIEAL ECAYDNLCQT EGVTALPYFL IKYDENMVLV SLLKHYSDFF QGQRTKITIG VYDPCNLAQY PGWPLRNFLV LAAHRWSSSF QSVEVVCFRD RTMQGARDVA HSIIFEVKLP EMAFSPDCPK AVGWEKNQKG GMGPRMVNLS ECMDPKRLAE SSVDLNLKLM CWRLVPTLDL DKVVSVKCLL LGAGTLGCNV ARTLMGWGVR HITFVDNAKI SYSNPVRQPL YEFEDCLGGG KPKALAAADR LQKIFPGVNA RGFNMSIPMP GHPVNFSSVT LEQARRDVEQ LEQLIESHDV VFLLMDTRES RWLPAVIAAS KRKLVINAAL GFDTFVVMRH GLKKPKQQGA GDLCPNHPVA SADLLGSSLF ANIPGYKLGC YFCNDVVAPG DSTRDRTLDQ QCTVSRPGLA VIAGALAVEL MVSVLQHPEG GYAIASSSDD RMNEPPTSLG LVPHQIRGFL SRFDNVLPVS LAFDKCTACS SKVLDQYERE GFNFLAKVFN SSHSFLEDLT GLTLLHQETQ AAEIWDMSDD ETI
42	ATG7	2	O95352-2	Entry version 168 (18 Sep 2019) Sequence version 1 (01 May 1999)	MAAATGDPGL SKLQFAPFSS ALDVGFWHEL TQKKLNEYRL DEAPKDIKGY YYNGDSAGLP ARLTLEFSAF DMSAPTPARC CPAIGTLYNT NTLESFKTAD KKLLLEQAAN EIWESIKSGT ALENPVLLNK FLLLTFADLK KYHFYYWFCY PALCLPESLP LIQGPVGLDQ RFSLKQIEAL ECAYDNLCQT EGVTALPYFL IKYDENMVLV SLLKHYSDFF QGQRTKITIG VYDPCNLAQY PGWPLRNFLV LAAHRWSSSF QSVEVVCFRD RTMQGARDVA HSIIFEVKLP EMAFSPDCPK AVGWEKNQKG GMGPRMVNLS ECMDPKRLAE SSVDLNLKLM CWRLVPTLDL DKVVSVKCLL LGAGTLGCNV ARTLMGWGVR

					HITFVDNAKI SYSNPVRQPL YEFEDCLGGG KPKALAAADR LQKIFPGVNA RGFNMSIPMP GHPVNFSSVT LEQARRDVEQ LEQLIESHDV VFLLMDTRES RWLPAVIAAS KRKLVINAAL GFDTFVVMRH GLKKPKQQGA GDLCPNHPVA SADLLGSSLF ANIPGYKLGC YFCNDVVAPG DSTRDRTLDQ QCTVSRPGLA VIAGALAVEL MVSVLQHPEG GYAIASSSDD RMNEPPTSLG LVPHQVLDQY EREGFNFLAK VFNSSHSFLE DLTGLTLLHQ ETQAAEIWDM SDDETI
43	ATG7	3	O95352-3	Entry version 168 (18 Sep 2019) Sequence version 1 (01 May 1999)	MAAATGDPGL SKLQFAPFSS ALDVGFWHEL TQKKLNEYRL DEAPKDIKGY YYNGDSAGLP ARLTLEFSAF DMSAPTPARC CPAIGTLYNT NTLESFKTAD KKLLLEQAAN EIWESIKSGT ALENPVLLNK FLLLTFAIEA LECAYDNLCQ TEGVTALPYF LIKYDENMVL VSLLKHYSDF FQGQRTKITI GVYDPCNLAQ YPGWPLRNFL VLAAHRWSSS FQSVEVVCFR DRTMQGARDV AHSIIFEVKL PEMAFSPDCP KAVGWEKNQK GGMGPRMVNL SECMDPKRLA ESSVDLNLKL MCWRLVPTLD LDKVVSVKCL LLGAGTLGCN VARTLMGWGV RHITFVDNAK ISYSNPVRQP LYEFEDCLGG GKPKALAAAD RLQKIFPGVN ARGFNMSIPM PGHPVNFSSV TLEQARRDVE QLEQLIESHD VVFLLMDTRE SRWLPAVIAA SKRKLVINAA LGFDTFVVMR HGLKKPKQQG AGDLCPNHPV ASADLLGSSL FANIPGYKLG CYFCNDVVAP GDSTRDRTLD QQCTVSRPGL AVIAGALAVE LMVSVLQHPE GGYAIASSSD DRMNEPPTSL GLVPHQIRGF LSRFDNVLPV SLAFDKCTAC SSKIWDMSDD ETI
44	SLC2A1	1	P11166	Entry version 230 (18 Sep 2019) Sequence version 2 (03 Oct 2006)	MEPSSKKLTG RLMLAVGGAV LGSLQFGYNT GVINAPQKVI EEFYNQTWVH RYGESILPTT LTTLWSLSVA IFSVGGMIGS FSVGLFVNRF GRRNSMLMMN LLAFVSAVLM GFSKLGKSFE MLILGRFIIG VYCGLTTGFV PMYVGEVSPT ALRGALGTLH QLGIVVGILI AQVFGLDSIM GNKDLWPLLL SIIFIPALLQ CIVLPFCPES PRFLLINRNE

					ENRAKSVLKK LRGTADVTHD LQEMKEESRQ MMREKKVTIL ELFRSPAYRQ PILIAVVLQL SQQLSGINAV FYYSTSIFEK AGVQQPVYAT IGSGIVNTAF TVVSLFVVER AGRRTLHLIG LAGMAGCAIL MTIALALLEQ LPWMSYLSIV AIFGFVAFFE VGPGPIPWFI VAELFSQGPR PAAIAVAGFS NWTSNFIVGM CFQYVEQLCG PYVFIIFTVL LVLFFIFTYF KVPETKGRTF DEIASGFRQG GASQSDKTPE ELFHPLGADS QV
45	GZMK	1	P49863	Entry version 152 (18 Sep 2019) Sequence version 1 (01 Oct 1996)	MTKFSSFSLF FLIVGAYMTH VCFNMEIIGG KEVSPHSRPF MASIQYGGHH VCGGVLIDPQ WVLTAAHCQY RFTKGQSPTV VLGAHSLSKN EASKQTLEIK KFIPFSRVTS DPQSNDIMLV KLQTAAKLNK HVKMLHIRSK TSLRSGTKCK VTGWGATDPD SLRPSDTLRE VTVTVLSRKL CNSQSYYNGD PFITKDMVCA GDAKGQKDSC KGDSGGPLIC KGVFHAIVSG GHECGVATKP GIYTLLTKKY QTWIKSNLVP PHTN
46	S100A9	1	P06702	Entry version 218 (18 Sep 2019) Sequence version 1 (01 Jan 1988)	MTCKMSQLER NIETIINTFH QYSVKLGHPD TLNQGEFKEL VRKDLQNFLK KENKNEKVIE HIMEDLDTNA DKQLSFEEFI MLMARLTWAS HEKMHEGDEG PGHHHKPGLG EGTP
47	S100A8	1	P05109	Entry version 209 (18 Sep 2019) Sequence version 1 (01 Jan 1988)	MLTELEKALN SIIDVYHKYS LIKGNFHAVY RDDLKKLLET ECPQYIRKKG ADVWFKELDI NTDGAVNFQE FLILVIKMGV AAHKKSHEES HKE
48	ATM	1	Q13315	Entry version 236 (18 Sep 2019) Sequence version 4 (22 Jan 2014)	MSLVLNDLLI CCRQLEHDRA TERKKEVEKF KRLIRDPETI KHLDRHSDSK QGKYLNWDAV FRFLQKYIQK ETECLRIAKP NVSASTQASR QKKMQEISSL VKYFIKCANR RAPRLKCQEL LNYIMDTVKD SSNGAIYGAD CSNILLKDIL SVRKYWCEIS QQQWLELFSV YFRLYLKPSQ DVHRVLVARI IHAVTKGCCS QTDGLNSKFL DFFSKAIQCA RQEKSSSGLN HILAALTIFL KTLAVNFRIR VCELGDEILP TLLYIWTQHR LNDSLKEVII ELFQLQIYIH HPKGAKTQEK GAYESTKWRS ILYNLYDLLV NEISHIGSRG KYSSGFRNIA VKENLIELMA DICHQVFNED TRSLEISQSY TTTQRESSDY

					SVPCKRKKIE LGWEVIKDHL QKSQNDFDLV PWLQIATQLI SKYPASLPNC ELSPLLMILS QLLPQQRHGE RTPYVLRCLT EVALCQDKRS NLESSQKSDL LKLWNKIWCI TFRGISSEQI QAENFGLLGA IIQGSLVEVD REFWKLFTGS ACRPSCPAVC CLTLALTTSI VPGTVKMGIE QNMCEVNRSF SLKESIMKWL LFYQLEGDLE NSTEVPPILH SNFPHLVLEK ILVSLTMKNC KAAMNFFQSV PECEHHQKDK EELSFSEVEE LFLQTTFDKM DFLTIVRECG IEKHQSSIGF SVHQNLKESL DRCLLGLSEQ LLNNYSSEIT NSETLVRCSR LLVGVLGCYC YMGVIAEEEA YKSELFQKAK SLMQCAGESI TLFKNKTNEE FRIGSLRNMM QLCTRCLSNC TKKSPNKIAS GFFLRLLTSK LMNDIADICK SLASFIKKPF DRGEVESMED DTNGNLMEVE DQSSMNLFND YPDSSVSDAN EPGESQSTIG AINPLAEEYL SKQDLLFLDM LKFLCLCVTT AQTNTVSFRA ADIRRKLLML IDSSTLEPTK SLHLHMYLML LKELPGEEYP LPMEDVLELL KPLSNVCSLY RRDQDVCKTI LNHVLHVVKN LGQSNMDSEN TRDAQGQFLT VIGAFWHLTK ERKYIFSVRM ALVNCLKTLL EADPYSKWAI LNVMGKDFPV NEVFTQFLAD NHHQVRMLAA ESINRLFQDT KGDSSRLLKA LPLKLQQTAF ENAYLKAQEG MREMSHSAEN PETLDEIYNR KSVLLTLIAV VLSCSPICEK QALFALCKSV KENGLEPHLV KKVLEKVSET FGYRRLEDFM ASHLDYLVLE WLNLQDTEYN LSSFPFILLN YTNIEDFYRS CYKVLIPHLV IRSHFDEVKS IANQIQEDWK SLLTDCFPKI LVNILPYFAY EGTRDSGMAQ QRETATKVYD MLKSENLLGK QIDHLFISNL PEIVVELLMT LHEPANSSAS QSTDLCDFSG DLDPAPNPPH FPSHVIKATF AYISNCHKTK LKSILEILSK SPDSYQKILL AICEQAAETN NVYKKHRILK IYHLFVSLLL KDIKSGLGGA WAFVLRDVIY TLIHYINQRP SCIMDVSLRS FSLCCDLLSQ VCQTAVTYCK DALENHLHVI VGTLIPLVYE QVEVQKQVLD LLKYLVIDNK DNENLYITIK LLDPFPDHVV FKDLRITQQK

					IKYSRGPFSL LEEINHFLSV
					SVYDALPLTR LEGLKDLRRQ
					LELHKDQMVD IMRASQDNPQ
					DGIMVKLVVN LLQLSKMAIN
					HTGEKEVLEA VGSCLGEVGP
					IDFSTIAIQH SKDASYTKAL
					KLFEDKELQW TFIMLTYLNN
					TLVEDCVKVR SAAVTCLKNI
					LATKTGHSFW EIYKMTTDPM
					LAYLQPFRTS RKKFLEVPRF
					DKENPFEGLD DINLWIPLSE
					NHDIWIKTLT CAFLDSGGTK
					CEILQLLKPM CEVKTDFCQT
					VLPYLIHDIL LQDTNESWRN
					LLSTHVQGFF TSCLRHFSQT
					SRSTTPANLD SESEHFFRCC
					LDKKSQRTML AVVDYMRRQK
					RPSSGTIFND AFWLDLNYLE
					VAKVAQSCAA HFTALLYAEI
					YADKKSMDDQ EKRSLAFEEG
					SQSTTISSLS EKSKEETGIS
					LQDLLLEIYR SIGEPDSLYG
					CGGGKMLQPI TRLRTYEHEA
					MWGKALVTYD LETAIPSSTR
					QAGIIQALQN LGLCHILSVY
					LKGLDYENKD WCPELEELHY
					QAAWRNMQWD HCTSVSKEVE
					GTSYHESLYN ALQSLRDREF
					STFYESLKYA RVKEVEEMCK
					RSLESVYSLY PTLSRLQAIG
					ELESIGELFS RSVTHRQLSE
					VYIKWQKHSQ LLKDSDFSFQ
					EPIMALRTVI LEILMEKEMD
					NSQRECIKDI LTKHLVELSI
					LARTFKNTQL PERAIFQIKQ
					YNSVSCGVSE WQLEEAQVFW
					AKKEQSLALS ILKQMIKKLD
					ASCAANNPSL KLTYTECLRV
					CGNWLAETCL ENPAVIMQTY
					LEKAVEVAGN YDGESSDELR
					NGKMKAFLSL ARFSDTQYQR
					IENYMKSSEF ENKQALLKRA
					KEEVGLLREH KIQTNRYTVK
					VQRELELDEL ALRALKEDRK
					RFLCKAVENY INCLLSGEEH
					DMWVFRLCSL WLENSGVSEV
					NGMMKRDGMK IPTYKFLPLM
					YQLAARMGTK MMGGLGFHEV
					LNNLISRISM DHPHHTLFII
					LALANANRDE FLTKPEVARR
					SRITKNVPKQ SSQLDEDRTE
					AANRIICTIR SRRPQMVRSV
					EALCDAYIIL ANLDATQWKT
					QRKGINIPAD QPITKLKNLE
					DVVVPTMEIK VDHTGEYGNL
					VTIQSFKAEF RLAGGVNLPK
					IIDCVGSDGK ERRQLVKGRD
					DLRQDAVMQQ VFQMCNTLLQ
					RNTETRKRKL TICTYKVVPL
					SQRSGVLEWC TGTVPIGEFL

					VNNEDGAHKR YRPNDFSAFQ CQKKMMEVQK KSFEEKYEVF MDVCQNFQPV FRYFCMEKFL DPAIWFEKRL AYTRSVATSS IVGYILGLGD RHVQNILINE QSAELVHIDL GVAFEQGKIL PTPETVPFRL TRDIVDGMGI TGVEGVFRRC CEKTMEVMRN SQETLLTIVE VLLYDPLFDW TMNPLKALYL QQRPEDETEL HPTLNADDQE CKRNLSDIDQ SFNKVAERVL MRLQEKLKGV EEGTVLSVGG QVNLLIQQAI DPKNLSRLFP GWKAWV
49	IKBKB	1	O14920	Entry version 217 (18 Sep 2019) Sequence version 1 (01 Jan 1998)	MSWSPSLTTQ TCGAWEMKER LGTGGFGNVI RWHNQETGEQ IAIKQCRQEL SPRNRERWCL EIQIMRRLTH PNVVAARDVP EGMQNLAPND LPLLAMEYCQ GGDLRKYLNQ FENCCGLREG AILTLLSDIA SALRYLHENR IIHRDLKPEN IVLQQGEQRL IHKIIDLGYA KELDQGSLCT SFVGTLQYLA PELLEQQKYT VTVDYWSFGT LAFECITGFR PFLPNWQPVQ WHSKVRQKSE VDIVVSEDLN GTVKFSSSLP YPNNLNSVLA ERLEKWLQLM LMWHPRQRGT DPTYGPNGCF KALDDILNLK LVHILNMVTG TIHTYPVTED ESLQSLKARI QQDTGIPEED QELLQEAGLA LIPDKPATQC ISDGKLNEGH TLDMDLVFLF DNSKITYETQ ISPRPQPESV SCILQEPKRN LAFFQLRKVW GQVWHSIQTL KEDCNRLQQG QRAAMMNLLR NNSCLSKMKN SMASMSQQLK AKLDFFKTSI QIDLEKYSEQ TEFGITSDKL LLAWREMEQA VELCGRENEV KLLVERMMAL QTDIVDLQRS PMGRKQGGTL DDLEEQAREL YRRLREKPRD QRTEGDSQEM VRLLLQAIQS FEKKVRVIYT QLSKTVVCKQ KALELLPKVE EVVSLMNEDE KTVVRLQEKR QKELWNLLKI ACSKVRGPVS GSPDSMNASR LSQPGQLMSQ PSTASNSLPE PAKKSEELVA EAHNLCTLLE NAIQDTVREQ DQSFTALDWS WLQTEEEEHS CLEQAS
50	IKBKB	2	O14920-2	Entry version 217 (18 Sep 2019) Sequence version 1 (01 Jan 1998)	MFSGGCHSPG FGRPSPAFPA PGSPPPAPRP CRQETGEQIA IKQCRQELSP RNRERWCLEI QIMRRLTHPN VVAARDVPEG MQNLAPNDLP LLAMEYCQGG DLRKYLNQFE NCCGLREGAI LTLLSDIASA LRYLHENRII HRDLKPENIV LQQGEQRLIH

					KIIDLGYAKE LDQGSLCTSF VGTLQYLAPE LLEQQKYTVT VDYWSFGTLA FECITGFRPF LPNWQPVQWH SKVRQKSEVD IVVSEDLNGT VKFSSSLPYP NNLNSVLAER LEKWLQLMLM WHPRQRGTDP TYGPNGCFKA LDDILNLKLV HILNMVTGTI HTYPVTEDES LQSLKARIQQ DTGIPEEDQE LLQEAGLALI PDKPATQCIS DGKLNEGHTL DMDLVFLFDN SKITYETQIS PRPQPESVSC ILQEPKRNLA FFQLRKVWGQ VWHSIQTLKE DCNRLQQGQR AAMMNLLRNN SCLSKMKNSM ASMSQQLKAK LDFFKTSIQI DLEKYSEQTE FGITSDKLLL AWREMEQAVE LCGRENEVKL LVERMMALQT DIVDLQRSPM GRKQGGTLDD LEEQARELYR RLREKPRDQR TEGDSQEMVR LLLQAIQSFE KKVRVIYTQL SKTVVCKQKA LELLPKVEEV VSLMNEDEKT VVRLQEKRQK ELWNLLKIAC SKVRGPVSGS PDSMNASRLS QPGQLMSQPS TASNSLPEPA KKSEELVAEA HNLCTLLENA IQDTVREQDQ SFTALDWSWL QTEEEEHSCL EQAS
51	IKBKB	3	O14920-3	Entry version 217 (18 Sep 2019) Sequence version 1 (01 Jan 1998)	MSWSPSLTTQ TCGAWEMKER LGTGGFGNVI RWHNQETGEQ IAIKQCRQEL SPRNRERWCL EIQIMRRLTH PNVVAARDVP EGMQNLAPND LPLLAMEYCQ GGDLRKYLNQ FENCCGLREG AILTLLSDIA SALRYLHENR IIHRDLKPEN IVLQQGEQRL IHKIIDLGYA KELDQGSLCT SFVGTLQYLA PELLEQQKYT VTVDYWSFGT LAFECITGFR PFLPNWQPVQ CVRMWPGTVA HSCNPSTLGG RGRWIS
52	IKBKB	4	O14920-4	Entry version 217 (18 Sep 2019) Sequence version 1 (01 Jan 1998)	MSSDGTIRLT HPNVVAARDV PEGMQNLAPN DLPLLAMEYC QGGDLRKYLN QFENCCGLRE GAILTLLSDI ASALRYLHEN RIIHRDLKPE NIVLQQGEQR LIHKIIDLGY AKELDQGSLC TSFVGTLQYL APELLEQQKY TVTVDYWSFG TLAFECITGF RPFLPNWQPV QWHSKVRQKS EVDIVVSEDL NGTVKFSSSL PYPNNLNSVL AERLEKWLQL MLMWHPRQRG TDPTYGPNGC FKALDDILNL KLVHILNMVT GTIHTYPVTE DESLQSLKAR IQQDTGIPEE DQELLQEAGL ALIPDKPATQ CISDGKLNEG

					HTLDMDLVFL FDNSKITYET QISPRPQPES VSCILQEPKR NLAFFQLRKV WGQVWHSIQT LKEDCNRLQQ GQRAAMMNLL RNNSCLSKMK NSMASMSQQL KAKLDFFKTS IQIDLEKYSE QTEFGITSDK LLLAWREMEQ AVELCGRENE VKLLVERMMA LQTDIVDLQR SPMGRKQGGT LDDLEEQARE LYRRLREKPR DQRTEGDSQE MVRLLLQAIQ SFEKKVRVIY TQLSKTVVCK QKALELLPKV EEVVSLMNED EKTVVRLQEK RQKELWNLLK IACSKVRGPV SGSPDSMNAS RLSQPGQLMS QPSTASNSLP EPAKKSEELV AEAHNLCTLL ENAIQDTVRE QDQSFTALDW SWLQTEEEEH SCLEQAS
53	BCAP31	1	P51572	Entry version 186 (18 Sep 2019) Sequence version 3 (23 Jan 2007)	MSLQWTAVAT FLYAEVFVVL LLCIPFISPK RWQKIFKSRL VELLVSYGNT FFVVLIVILV LLVIDAVREI RKYDDVTEKV NLQNNPGAME HFHMKLFRAQ RNLYIAGFSL LLSFLLRRLV TLISQQATLL ASNEAFKKQA ESASEAAKKY MEENDQLKKG AAVDGGKLDV GNAEVKLEEE NRSLKADLQK LKDELASTKQ KLEKAENQVL AMRKQSEGLT KEYDRLLEEH AKLQAAVDGP MDKKEE
54	BCAP31	2	P51572-2	Entry version 186 (18 Sep 2019) Sequence version 3 (23 Jan 2007)	MGAEASSSWC PGTALPEERL SVKRASEISG FLGQGSSGEA ALDVLTHVLE GAGNKLTSSC GKPSSNRMSL QWTAVATFLY AEVFVVLLLC IPFISPKRWQ KIFKSRLVEL LVSYGNTFFV VLIVILVLLV IDAVREIRKY DDVTEKVNLQ NNPGAMEHFH MKLFRAQRNL YIAGFSLLLS FLLRRLVTLI SQQATLLASN EAFKKQAESA SEAAKKYMEE NDQLKKGAAV DGGKLDVGNA EVKLEEENRS LKADLQKLKD ELASTKQKLE KAENQVLAMR KQSEGLTKEY DRLLEEHAKL QAAVDGPMDK KEE
55	TAPBP	1	O15533	Entry version 190 (18 Sep 2019) Sequence version 1 (01 Jan 1998)	MKSLSLLLAV ALGLATAVSA GPAVIECWFV EDASGKGLAK RPGALLLRQG PGEPPPRPDL DPELYLSVHD PAGALQAAFR RYPRGAPAPH CEMSRFVPLP ASAKWASGLT PAQNCPRALD GAWLMVSISS PVLSLSSLLR PQPEPQQEPV LITMATVVLT VLTHTPAPRV RLGQDALLDL SFAYMPPTSE AASSLAPGPP PFGLEWRRQH LGKGHLLLAA TPGLNGQMPA AQEGAVAFAA

					WDDDEPWGPW TGNGTFWLPR VQPFQEGTYL ATIHLPYLQG QVTLELAVYK PPKVSLMPAT LARAAPGEAP PELLCLVSHF YPSGGLEVEW ELRGGPGGRS QKAEGQRWLS ALRHHSDGSV SLSGHLQPPP VTTEQHGARY ACRIHHPSLP ASGRSAEVTL EVAGLSGPSL EDSVGLFLSA FLLLGLFKAL GWAAVYLSTC KDSKKKAE
56	TAPBP	2	O15533-2	Entry version 190 (18 Sep 2019) Sequence version 1 (01 Jan 1998)	MKSLSLLLAV ALGLATAVSA GPAVIECWFV EDASGKGLAK RPGALLLRQG PGEPPPRPDL DPELYLSVHD PAGALQAAFR RYPRGAPAPH CEMSRFVPLP ASAKWASGLT PAQNCPRALD GAWLMVSISS PVLSLSSLLR PQPEPQQEPV LITMATVVLT VLTHTPAPRV RLGQDALLDL SFAYMPPTSE AASSLAPGPP PFGLEWRRQH LGKGHLLLAA TPGLNGQMPA AQEGAVAFAA WDDDEPWGPW TGNGTFWLPR VQPFQEGTYL ATIHLPYLQG QVTLELAVYK PPKVSLMPAT LARAAPGEAP PELLCLVSHF YPSGGLEVEW ELRGGPGGRS QKAEGQRWLS ALRHHSDGSV SLSGHLQPPP VTTEQHGARY ACRIHHPSLP ASGRSAEVTL EVAGKSWELC GI
57	TAPBP	3	O15533-3	Entry version 190 (18 Sep 2019) Sequence version 1 (01 Jan 1998)	MKSLSLLLAV ALGLATAVSA GPAVIECWFV EDASGKGLAK RPGALLLRQG PGEPPPRPDL DPELYLSVHD PAGALQAAFR RYPRGAPAPH CEMSRFVPLP ASAKWASGLT PAQNCPRALD GAWLMVSISS PVLSLSSLLR PQPEPQQEPV LITMATVVLT VLTHTPAPRV RLGQDALLDL SFAYMPPTSE AASSLAPGPP PFGLEWRRQH LGKGHLLLAA TPGLNGQMPA AQEGAVAFAA WDDDEPWGPW TGNGTFWLPR VQPFQEGTYL ATIHLPYLQG QVTLELAVYK PPKVSLMPAT LARAAPGEAP PELLCLVSHF YPSGGLEVEW ELRGGPGGRS QKAEGQRWLS ALRHHSDGSV SLSGHLQPPP VTTEQHGARY ACRIHHPSLP ASGRSAEVTL EVAGLSGPSL EDSVGLFLSA FLLLGLFKAL GWAAVYLSTC KDSKKVQCST SLYLSLVTLS PHPISKPMEG GCWCGRQNLG LEFTLIWVKT WHYILTVGLF EHAT
58	TAPBP	4	O15533-	Entry version	MKSLSLLLAV ALGLATAVSA

			4	190 (18 Sep 2019) Sequence version 1 (01 Jan 1998)	GPAVIECWFV EDASGKGLAK RPGALLLRQG PGEPPPRPDL DPELYLSVHV VLTVLTHTPA PRVRLGQDAL LDLSFAYMPP TSEAASSLAP GPPPFGLEWR RQHLGKGHLL LAATPGLNGQ MPAAQEGAVA FAAWDDDEPW GPWTGNGTFW LPRVQPFQEG TYLATIHLPY LQGQVTLELA VYKPPKVSLM PATLARAAPG EAPPELLCLV SHFYPSGGLE VEWELRGGPG GRSQKAEGQR WLSALRHHSD GSVSLSGHLQ PPPVTTEQHG ARYACRIHHP SLPASGRSAE VTLEVAGLSG PSLEDSVGLF LSAFLLLGLF KALGWAAVYL STCKDSKKKA E
59	PPP3CB	1	P16298	Entry version 166 (18 Sep 2019) Sequence version 2 (01 Feb 2005)	MAAPEPARAA PPPPPPPPPP PGADRVVKAV PFPPTHRLTS EEVFDLDGIP RVDVLKNHLV KEGRVDEEIA LRIINEGAAI LRREKTMIEV EAPITVCGDI HGQFFDLMKL FEVGGSPANT RYLFLGDYVD RGYFSIECVL YLWVLKILYP STLFLLRGNH ECRHLTEYFT FKQECKIKYS ERVYEACMEA FDSLPLAALL NQQFLCVHGG LSPEIHTLDD IRRLDRFKEP PAFGPMCDLL WSDPSEDFGN EKSQEHFSHN TVRGCSYFYN YPAVCEFLQN NNLLSIIRAH EAQDAGYRMY RKSQTTGFPS LITIFSAPNY LDVYNNKAAV LKYENNVMNI RQFNCSPHPY WLPNFMDVFT WSLPFVGEKV TEMLVNVLSI CSDDELMTEG EDQFDGSAAA RKEIIRNKIR AIGKMARVFS VLREESESVL TLKGLTPTGM LPSGVLAGGR QTLQSATVEA IEAEKAIRGF SPPHRICSFE EAKGLDRINE RMPPRKDAVQ QDGFNSLNTA HATENHGTGN HTAQ
60	PPP3CB	2	P16298-2	Entry version 166 (18 Sep 2019) Sequence version 2 (01 Feb 2005)	MAAPEPARAA PPPPPPPPPP PGADRVVKAV PFPPTHRLTS EEVFDLDGIP RVDVLKNHLV KEGRVDEEIA LRIINEGAAI LRREKTMIEV EAPITVCGDI HGQFFDLMKL FEVGGSPANT RYLFLGDYVD RGYFSIEHVL GTEDISINPH NNINECVLYL WVLKILYPST LFLLRGNHEC RHLTEYFTFK QECKIKYSER VYEACMEAFD SLPLAALLNQ QFLCVHGGLS PEIHTLDDIR RLDRFKEPPA FGPMCDLLWS DPSEDFGNEK SQEHFSHNTV

					RGCSYFYNYP AVCEFLQNNN LLSIIRAHEA QDAGYRMYRK SQTTGFPSLI TIFSAPNYLD VYNNKAAVLK YENNVMNIRQ FNCSPHPYWL PNFMDVFTWS LPFVGEKVTE MLVNVLSICS DDELMTEGED QFDGSAAARK EIIRNKIRAI GKMARVFSVL REESESVLTL KGLTPTGMLP SGVLAGGRQT LQSGNDVMQL AVPQMDWGTP HSFANNSHNA CREFLLFFSS CLSS
61	PPP3CB	3	P16298-3	Entry version 166 (18 Sep 2019) Sequence version 2 (01 Feb 2005)	MAAPEPARAA PPPPPPPPPP PGADRVVKAV PFPPTHRLTS EEVFDLDGIP RVDVLKNHLV KEGRVDEEIA LRIINEGAAI LRREKTMIEV EAPITVCGDI HGQFFDLMKL FEVGGSPANT RYLFLGDYVD RGYFSIECVL YLWVLKILYP STLFLLRGNH ECRHLTEYFT FKQECKIKYS ERVYEACMEA FDSLPLAALL NQQFLCVHGG LSPEIHTLDD IRRLDRFKEP PAFGPMCDLL WSDPSEDFGN EKSQEHFSHN TVRGCSYFYN YPAVCEFLQN NNLLSIIRAH EAQDAGYRMY RKSQTTGFPS LITIFSAPNY LDVYNNKAAV LKYENNVMNI RQFNCSPHPY WLPNFMDVFT WSLPFVGEKV TEMLVNVLSI CSDDELMTEG EDQFDVGSAA ARKEIIRNKI RAIGKMARVF SVLREESESV LTLKGLTPTG MLPSGVLAGG RQTLQSAIRG FSPPHRICSF EEAKGLDRIN ERMPPRKDAV QQDGFNSLNT AHATENHGTG NHTAQ
62	PPP3CB	4	P16298-4	Entry version 166 (18 Sep 2019) Sequence version 2 (01 Feb 2005)	MAAPEPARAA PPPPPPPPPP PGADRVVKAV PFPPTHRLTS EEVFDLDGIP RVDVLKNHLV KEGRVDEEIA LRIINEGAAI LRREKTMIEV EAPITVCGDI HGQFFDLMKL FEVGGSPANT RYLFLGDYVD RGYFSIECVL YLWVLKILYP STLFLLRGNH ECRHLTEYFT FKQECKIKYS ERVYEACMEA FDSLPLAALL NQQFLCVHGG LSPEIHTLDD IRRLDRFKEP PAFGPMCDLL WSDPSEDFGN EKSQEHFSHN TVRGCSYFYN YPAVCEFLQN NNLLSIIRAH EAQDAGYRMY RKSQTTGFPS LITIFSAPNY LDVYNNKAAV LKYENNVMNI RQFNCSPHPY WLPNFMDVFT WSLPFVGEKV TEMLVNVLSI CSDDELMTEG EDQFDVGSAA ARKEIIRNKI RAIGKMARVF SVLREESESV LTLKGLTPTG

					MLPSGVLAGG RQTLQSATVE AIEAEKAIRG FSPPHRICSF EEAKGLDRIN ERMPPRKDAV QQDGFNSLNT AHATENHGTG NHTAQ
63	ANXA1	1	P04083	Entry version 244 (18 Sep 2019) Sequence version 2 (23 Jan 2007)	MAMVSEFLKQ AWFIENEEQE YVQTVKSSKG GPGSAVSPYP TFNPSSDVAA LHKAIMVKGV DEATIIDILT KRNNAQRQQI KAAYLQETGK PLDETLKKAL TGHLEEVVLA LLKTPAQFDA DELRAAMKGL GTDEDTLIEI LASRTNKEIR DINRVYREEL KRDLAKDITS DTSGDFRNAL LSLAKGDRSE DFGVNEDLAD SDARALYEAG ERRKGTDVNV FNTILTTRSY PQLRRVFQKY TKYSKHDMNK VLDLELKGDI EKCLTAIVKC ATSKPAFFAE KLHQAMKGVG TRHKALIRIM VSRSEIDMND IKAFYQKMYG ISLCQAILDE TKGDYEKILV ALCGGN
64	PERM	1	P05164	Entry version 221 (18 Sep 2019) Sequence version 1 (13 Aug 1987)	MGVPFFSSLR CMVDLGPCWA GGLTAEMKLL LALAGLLAIL ATPQPSEGAA PAVLGEVDTS LVLSSMEEAK QLVDKAYKER RESIKQRLRS GSASPMELLS YFKQPVAATR TAVRAADYLH VALDLLERKL RSLWRRPFNV TDVLTPAQLN VLSKSSGCAY QDVGVTCPEQ DKYRTITGMC NNRRSPTLGA SNRAFVRWLP AEYEDGFSLP YGWTPGVKRN GFPVALARAV SNEIVRFPTD QLTPDQERSL MFMQWGQLLD HDLDFTPEPA ARASFVTGVN CETSCVQQPP CFPLKIPPND PRIKNQADCI PFFRSCPACP GSNITIRNQI NALTSFVDAS MVYGSEEPLA RNLRNMSNQL GLLAVNQRFQ DNGRALLPFD NLHDDPCLLT NRSARIPCFL AGDTRSSEMP ELTSMHTLLL REHNRLATEL KSLNPRWDGE RLYQEARKIV GAMVQIITYR DYLPLVLGPT AMRKYLPTYR SYNDSVDPRI ANVFTNAFRY GHTLIQPFMF RLDNRYQPME PNPRVPLSRV FFASWRVVLE GGIDPILRGL MATPAKLNRQ NQIAVDEIRE RLFEQVMRIG LDLPALNMQR SRDHGLPGYN AWRRFCGLPQ PETVGQLGTV LRNLKLARKL MEQYGTPNNI DIWMGGVSEP LKRKGRVGPL LACIIGTQFR KLRDGDRFWW ENEGVFSMQQ RQALAQISLP RIICDNTGIT TVSKNNIFMS

					NSYPRDFVNC STLPALNLAS WREAS
65	PERM	2	P05164-2	Entry version 221 (18 Sep 2019) Sequence version 1 (13 Aug 1987)	MELLSYFKQP VAATRTAVRA ADYLHVALDL LERKLRSLWR RPFNVTDVLT PAQLNVLSKS SGCAYQDVGV TCPEQDKYRT ITGMCNNRRS PTLGASNRAF VRWLPAEYED GFSLPYGWTP GVKRNGFPVA LARAVSNEIV RFPTDQLTPD QERSLMFMQW GQLLDHDLDF TPEPAARASF VTGVNCETSC VQQPPCFPLK IPPNDPRIKN QADCIPFFRS CPACPGSNIT IRNQINALTS FVDASMVYGS EEPLARNLRN MSNQLGLLAV NQRFQDNGRA LLPFDNLHDD PCLLTNRSAR IPCFLAGDTR SSEMPELTSM HTLLLREHNR LATELKSLNP RWDGERLYQE ARKIVGAMVQ IITYRDYLPL VLGPTAMRKY LPTYRSYNDS VDPRIANVFT NAFRYGHTLI QPFMFRLDNR YQPMEPNPRV PLSRVFFASW RVVLEGGIDP ILRGLMATPA KLNRQNQIAV DEIRERLFEQ VMRIGLDLPA LNMQRSRDHG LPGYNAWRRF CGLPQPETVG QLGTVLRNLK LARKLMEQYG TPNNIDIWMG GVSEPLKRKG RVGPLLACII GTQFRKLRDG DRFWWENEGV FSMQQRQALA QISLPRIICD NTGITTVSKN NIFMSNSYPR DFVNCSTLPA LNLASWREAS
66	PERM	3	P05164-3	Entry version 221 (18 Sep 2019) Sequence version 1 (13 Aug 1987)	MGVPFFSSLR CMVDLGPCWA GGLTAEMKLL LALAGLLAIL ATPQPSEGAA PAVLGEVDTS LVLSSMEEAK QLVDKAYKER RESIKQRLRS GSASPMELLS YFKQPVAATR TAVRAADYLH VALDLLERKL RSLWRRPFNV TDVLTPAQLN VLSKSSGCAY QDVGVTCPEQ DKYRTITGMC NNRCGWLGVA AGTGLREASR TPQASRCQRP VLPCRRSPTL GASNRAFVRW LPAEYEDGFS LPYGWTPGVK RNGFPVALAR AVSNEIVRFP TDQLTPDQER SLMFMQWGQL LDHDLDFTPE PAARASFVTG VNCETSCVQQ PPCFPLKIPP NDPRIKNQAD CIPFFRSCPA CPGSNITIRN QINALTSFVD ASMVYGSEEP LARNLRNMSN QLGLLAVNQR FQDNGRALLP FDNLHDDPCL LTNRSARIPC FLAGDTRSSE MPELTSMHTL LLREHNRLAT ELKSLNPRWD GERLYQEARK

					IVGAMVQIIT YRDYLPLVLG PTAMRKYLPT YRSYNDSVDP RIANVFTNAF RYGHTLIQPF MFRLDNRYQP MEPNPRVPLS RVFFASWRVV LEGGIDPILR GLMATPAKLN RQNQIAVDEI RERLFEQVMR IGLDLPALNM QRSRDHGLPG YNAWRRFCGL PQPETVGQLG TVLRNLKLAR KLMEQYGTPN NIDIWMGGVS EPLKRKGRVG PLLACIIGTQ FRKLRDGDRF WWENEGVFSM QQRQALAQIS LPRIICDNTG ITTVSKNNIF MSNSYPRDFV NCSTLPALNL ASWREAS
67	PLEC	1	Q15149	Entry version 224 (18 Sep 2019) Sequence version 3 (14 Oct 2008)	MVAGMLMPRD QLRAIYEVLF REGVMVAKKD RRPRSLHPHV PGVTNLQVMR AMASLRARGL VRETFAWCHF YWYLTNEGIA HLRQYLHLPP EIVPASLQRV RRPVAMVMPA RRTPHVQAVQ GPLGSPPKRG PLPTEEQRVY RRKELEEVSP ETPVVPATTQ RTLARPGPEP APATDERDRV QKKTFTKWVN KHLIKAQRHI SDLYEDLRDG HNLISLLEVL SGDSLPREKG RMRFHKLQNV QIALDYLRHR QVKLVNIRND DIADGNPKLT LGLIWTIILH FQISDIQVSG QSEDMTAKEK LLLWSQRMVE GYQGLRCDNF TSSWRDGRLF NAIIHRHKPL LIDMNKVYRQ TNLENLDQAF SVAERDLGVT RLLDPEDVDV PQPDEKSIIT YVSSLYDAMP RVPDVQDGVR ANELQLRWQE YRELVLLLLQ WMRHHTAAFE ERRFPSSFEE IEILWSQFLK FKEMELPAKE ADKNRSKGIY QSLEGAVQAG QLKVPPGYHP LDVEKEWGKL HVAILEREKQ LRSEFERLEC LQRIVTKLQM EAGLCEEQLN QADALLQSDV RLLAAGKVPQ RAGEVERDLD KADSMIRLLF NDVQTLKDGR HPQGEQMYRR VYRLHERLVA IRTEYNLRLK AGVAAPATQV AQVTLQSVQR RPELEDSTLR YLQDLLAWVE ENQHRVDGAE WGVDLPSVEA QLGSHRGLHQ SIEEFRAKIE RARSDEGQLS PATRGAYRDC LGRLDLQYAK LLNSSKARLR SLESLHSFVA AATKELMWLN EKEEEEVGFD WSDRNTNMTA KKESYSALMR ELELKEKKIK ELQNAGDRLL REDHPARPTV ESFQAALQTQ WSWMLQLCCC IEAHLKENAA YFQFFSDVRE AEGQLQKLQE ALRRKYSCDR SATVTRLEDL

					LQDAQDEKEQ	LNEYKGHLSG
					LAKRAKAVVQ	LKPRHPAHPM
					RGRLPLLAVC	DYKQVEVTVH
					KGDECQLVGP	AQPSHWKVLS
					SSGSEAAVPS	VCFLVPPPNQ
					EAQEAVTRLE	AQHQALVTLW
					HQLHVDMKSL	LAWQSLRRDV
					QLIRSWSLAT	FRTLKPEEQR
					QALHSLELHY	QAFLRDSQDA
					GGFGPEDRLM	AEREYGSCSH
					HYQQLLQSLE	QGAQEESRCQ
					RCISELKDIR	LQLEACETRT
					VHRLRLPLDK	EPARECAQRI
					AEQQKAQAEV	EGLGKGVARL
					SAEAEKVLAL	PEPSPAAPTL
					RSELELTLGK	LEQVRSLSAI
					YLEKLKTISL	VIRGTQGAEE
					VLRAHEEQLK	EAQAVPATLP
					ELEATKASLK	KLRAQAEAQQ
					PTFDALRDEL	RGAQEVGERL
					QQRHGERDVE	VERWRERVAQ
					LLERWQAVLA	QTDVRQRELE
					QLGRQLRYYR	ESADPLGAWL
					QDARRRQEQI	QAMPLADSQA
					VREQLRQEQA	LLEEIERHGE
					KVEECQRFAK	QYINAIKDYE
					LQLVTYKAQL	EPVASPAKKP
					KVQSGSESVI	QEYVDLRTHY
					SELTTLTSQY	IKFISETLRR
					MEEEERLAEQ	QRAEERERLA
					EVEAALEKQR	QLAEAHAQAK
					AQAEREAKEL	QQRMQEEVVR
					REEAAVDAQQ	QKRSIQEELQ
					QLRQSSEAEI	QAKARQAEAA
					ERSRLRIEEE	IRVVRLQLEA
					TERQRGGAEG	ELQALRARAE
					EAEAQKRQAQ	EEAERLRRQV
					QDESQRKRQA	EVELASRVKA
					EAEAAREKQR	ALQALEELRL
					QAEEAERRLR	QAEVERARQV
					QVALETAQRS	AEAELQSKRA
					SFAEKTAQLE	RSLQEEHVAV
					AQLREEAERR	AQQQAEAERA
					REEAERELER	WQLKANEALR
					LRLQAEEVAQ	QKSLAQAEAE
					KQKEEAEREA	RRRGKAEEQA
					VRQRELAEQE	LEKQRQLAEG
					TAQQRLAAEQ	ELIRLRAETE
					QGEQQRQLLE	EELARLQREA
					AAATQKRQEL	EAELAKVRAE
					MEVLLASKAR	AEEESRSTSE
					KSKQRLEAEA	GRFRELAEEA
					ARLRALAEEA	KRQRQLAEED
					AARQRAEAER	VLAEKLAAIG
					EATRLKTEAE	IALKEKEAEN
					ERLRRLAEDE	AFQRRRLEEQ
					AAQHKADIEE	RLAQLRKASD
					SELERQKGLV	EDTLRQRRQV
					EEEILALKAS	FEKAAAGKAE
					LELELGRIRS	NAEDTLRSKE

					QAELEAARQR QLAAEEERRR REAEERVQKS LAAEEEAARQ RKAALEEVER LKAKVEEARR LRERAEQESA RQLQLAQEAA QKRLQAEEKA HAFAVQQKEQ ELQQTLQQEQ SVLDQLRGEA EAARRAAEEA EEARVQAERE AAQSRRQVEE AERLKQSAEE QAQARAQAQA AAEKLRKEAE QEAARRAQAE QAALRQKQAA DAEMEKHKKF AEQTLRQKAQ VEQELTTLRL QLEETDHQKN LLDEELQRLK AEATEAARQR SQVEEELFSV RVQMEELSKL KARIEAENRA LILRDKDNTQ RFLQEEAEKM KQVAEEAARL SVAAQEAARL RQLAEEDLAQ QRALAEKMLK EKMQAVQEAT RLKAEAELLQ QQKELAQEQA RRLQEDKEQM AQQLAEETQG FQRTLEAERQ RQLEMSAEAE RLKLRVAEMS RAQARAEEDA QRFRKQAEEI GEKLHRTELA TQEKVTLVQT LEIQRQQSDH DAERLREAIA ELEREKEKLQ QEAKLLQLKS EEMQTVQQEQ LLQETQALQQ SFLSEKDSLL QRERFIEQEK AKLEQLFQDE VAKAQQLREE QQRQQQQMEQ ERQRLVASME EARRRQHEAE EGVRRKQEEL QQLEQQRRQQ EELLAEENQR LREQLQLLEE QHRAALAHSE EVTASQVAAT KTLPNGRDAL DGPAAEAEPE HSFDGLRRKV SAQRLQEAGI LSAEELQRLA QGHTTVDELA RREDVRHYLQ GRSSIAGLLL KATNEKLSVY AALQRQLLSP GTALILLEAQ AASGFLLDPV RNRRLTVNEA VKEGVVGPEL HHKLLSAERA VTGYKDPYTG QQISLFQAMQ KGLIVREHGI RLLEAQIATG GVIDPVHSHR VPVDVAYRRG YFDEEMNRVL ADPSDDTKGF FDPNTHENLT YLQLLERCVE DPETGLCLLP LTDKAAKGGE LVYTDSEARD VFEKATVSAP FGKFQGKTVT IWEIINSEYF TAEQRRDLLR QFRTGRITVE KIIKIIITVV EEQEQKGRLC FEGLRSLVPA AELLESRVID RELYQQLQRG ERSVRDVAEV DTVRRALRGA NVIAGVWLEE AGQKLSIYNA LKKDLLPSDM AVALLEAQAG TGHIIDPATS ARLTVDEAVR AGLVGPEFHE KLLSAEKAVT GYRDPYTGQS VSLFQALKKG LIPREQGLRL LDAQLSTGGI VDPSKSHRVP LDVACARGCL

					DEETSRALSA PRADAKAYSD
					PSTGEPATYG ELQQRCRPDQ
					LTGLSLLPLS EKAARARQEE
					LYSELQARET FEKTPVEVPV
					GGFKGRTVTV WELISSEYFT
					AEQRQELLRQ FRTGKVTVEK
					VIKILITIVE EVETLRQERL
					SFSGLRAPVP ASELLASGVL
					SRAQFEQLKD GKTTVKDLSE
					LGSVRTLLQG SGCLAGIYLE
					DTKEKVSIYE AMRRGLLRAT
					TAALLLEAQA ATGFLVDPVR
					NQRLYVHEAV KAGVVGPELH
					EQLLSAEKAV TGYRDPYSGS
					TISLFQAMQK GLVLRQHGIR
					LLEAQIATGG IIDPVHSHRV
					PVDVAYQRGY FSEEMNRVLA
					DPSDDTKGFF DPNTHENLTY
					RQLLERCVED PETGLRLLPL
					KGAEKAEVVE TTQVYTEEET
					RRAFEETQID IPGGGSHGGS
					TMSLWEVMQS DLIPEEQRAQ
					LMADFQAGRV TKERMIIIII
					EIIEKTEIIR QQGLASYDYV
					RRRLTAEDLF EARIISLETY
					NLLREGTRSL REALEAESAW
					CYLYGTGSVA GVYLPGSRQT
					LSIYQALKKG LLSAEVARLL
					LEAQAATGFL LDPVKGERLT
					VDEAVRKGLV GPELHDRLLS
					AERAVTGYRD PYTEQTISLF
					QAMKKELIPT EEALRLLDAQ
					LATGGIVDPR LGFHLPLEVA
					YQRGYLNKDT HDQLSEPSEV
					RSYVDPSTDE RLSYTQLLRR
					CRRDDGTGQL LLPLSDARKL
					TFRGLRKQIT MEELVRSQVM
					DEATALQLRE GLTSIEEVTK
					NLQKFLEGTS CIAGVFVDAT
					KERLSVYQAM KKGIIRPGTA
					FELLEAQAAT GYVIDPIKGL
					KLTVEEAVRM GIVGPEFKDK
					LLSAERAVTG YKDPYSGKLI
					SLFQAMKKGL ILKDHGIRLL
					EAQIATGGII DPEESHRLPV
					EVAYKRGLFD EEMNEILTDP
					SDDTKGFFDP NTEENLTYLQ
					LMERCITDPQ TGLCLLPLKE
					KKRERKTSSK SSVRKRRVVI
					VDPETGKEMS VYEAYRKGLI
					DHQTYLELSE QECEWEEITI
					SSSDGVVKSM IIDRRSGRQY
					DIDDAIAKNL IDRSALDQYR
					AGTLSITEFA DMLSGNAGGF
					RSRSSSVGSS SSYPISPAVS
					RTQLASWSDP TEETGPVAGI
					LDTETLEKVS ITEAMHRNLV
					DNITGQRLLE AQACTGGIID
					PSTGERFPVT DAVNKGLVDK
					IMVDRINLAQ KAFCGFEDPR

					TKTKMSAAQA LKKGWLYYEA GQRFLEVQYL TGGLIEPDTP GRVPLDEALQ RGTVDARTAQ KLRDVGAYSK YLTCPKTKLK ISYKDALDRS MVEEGTGLRL LEAAAQSTKG YYSPYSVSGS GSTAGSRTGS RTGSRAGSRR GSFDATGSGF SMTFSSSSYS SSGYGRRYAS GSSASLGGPE SAVA
68	PLEC	2	Q15149-2	Entry version 224 (18 Sep 2019) Sequence version 3 (14 Oct 2008)	MSGEDAEVRA VSEDVSNGSS GSPSPGDTLP WNLGKTQRSR RSGGGAGSNG SVLDPAERAV IRIADERDRV QKKTFTKWVN KHLIKAQRHI SDLYEDLRDG HNLISLLEVL SGDSLPREKG RMRFHKLQNV QIALDYLRHR QVKLVNIRND DIADGNPKLT LGLIWTIILH FQISDIQVSG QSEDMTAKEK LLLWSQRMVE GYQGLRCDNF TSSWRDGRLF NAIIHRHKPL LIDMNKVYRQ TNLENLDQAF SVAERDLGVT RLLDPEDVDV PQPDEKSIIT YVSSLYDAMP RVPDVQDGVR ANELQLRWQE YRELVLLLLQ WMRHHTAAFE ERRFPSSFEE IEILWSQFLK FKEMELPAKE ADKNRSKGIY QSLEGAVQAG QLKVPPGYHP LDVEKEWGKL HVAILEREKQ LRSEFERLEC LQRIVTKLQM EAGLCEEQLN QADALLQSDV RLLAAGKVPQ RAGEVERDLD KADSMIRLLF NDVQTLKDGR HPQGEQMYRR VYRLHERLVA IRTEYNLRLK AGVAAPATQV AQVTLQSVQR RPELEDSTLR YLQDLLAWVE ENQHRVDGAE WGVDLPSVEA QLGSHRGLHQ SIEEFRAKIE RARSDEGQLS PATRGAYRDC LGRLDLQYAK LLNSSKARLR SLESLHSFVA AATKELMWLN EKEEEEVGFD WSDRNTNMTA KKESYSALMR ELELKEKKIK ELQNAGDRLL REDHPARPTV ESFQAALQTQ WSWMLQLCCC IEAHLKENAA YFQFFSDVRE AEGQLQKLQE ALRRKYSCDR SATVTRLEDL LQDAQDEKEQ LNEYKGHLSG LAKRAKAVVQ LKPRHPAHPM RGRLPLLAVC DYKQVEVTVH KGDECQLVGP AQPSHWKVLS SSGSEAAVPS VCFLVPPPNQ EAQEAVTRLE AQHQALVTLW HQLHVDMKSL LAWQSLRRDV QLIRSWSLAT FRTLKPEEQR QALHSLELHY QAFLRDSQDA GGFGPEDRLM AEREYGSCSH HYQQLLQSLE

					QGAQEESRCQ RCISELKDIR LQLEACETRT VHRLRLPLDK EPARECAQRI AEQQKAQAEV EGLGKGVARL SAEAEKVLAL PEPSPAAPTL RSELELTLGK LEQVRSLSAI YLEKLKTISL VIRGTQGAEE VLRAHEEQLK EAQAVPATLP ELEATKASLK KLRAQAEAQQ PTFDALRDEL RGAQEVGERL QQRHGERDVE VERWRERVAQ LLERWQAVLA QTDVRQRELE QLGRQLRYYR ESADPLGAWL QDARRRQEQI QAMPLADSQA VREQLRQEQA LLEEIERHGE KVEECQRFAK QYINAIKDYE LQLVTYKAQL EPVASPAKKP KVQSGSESVI QEYVDLRTHY SELTTLTSQY IKFISETLRR MEEEERLAEQ QRAEERERLA EVEAALEKQR QLAEAHAQAK AQAEREAKEL QQRMQEEVVR REEAAVDAQQ QKRSIQEELQ QLRQSSEAEI QAKARQAEAA ERSRLRIEEE IRVVRLQLEA TERQRGGAEG ELQALRARAE EAEAQKRQAQ EEAERLRRQV QDESQRKRQA EVELASRVKA EAEAAREKQR ALQALEELRL QAEEAERRLR QAEVERARQV QVALETAQRS AEAELQSKRA SFAEKTAQLE RSLQEEHVAV AQLREEAERR AQQQAEAERA REEAERELER WQLKANEALR LRLQAEEVAQ QKSLAQAEAE KQKEEAEREA RRRGKAEEQA VRQRELAEQE LEKQRQLAEG TAQQRLAAEQ ELIRLRAETE QGEQQRQLLE EELARLQREA AAATQKRQEL EAELAKVRAE MEVLLASKAR AEEESRSTSE KSKQRLEAEA GRFRELAEEA ARLRALAEEA KRQRQLAEED AARQRAEAER VLAEKLAAIG EATRLKTEAE IALKEKEAEN ERLRRLAEDE AFQRRRLEEQ AAQHKADIEE RLAQLRKASD SELERQKGLV EDTLRQRRQV EEEILALKAS FEKAAAGKAE LELELGRIRS NAEDTLRSKE QAELEAARQR QLAAEEERRR REAEERVQKS LAAEEEAARQ RKAALEEVER LKAKVEEARR LRERAEQESA RQLQLAQEAA QKRLQAEEKA HAFAVQQKEQ ELQQTLQQEQ SVLDQLRGEA EAARRAAEEA EEARVQAERE AAQSRRQVEE AERLKQSAEE QAQARAQAQA AAEKLRKEAE QEAARRAQAE QAALRQKQAA DAEMEKHKKF

					AEQTLRQKAQ VEQELTTLRL QLEETDHQKN LLDEELQRLK AEATEAARQR SQVEEELFSV RVQMEELSKL KARIEAENRA LILRDKDNTQ RFLQEEAEKM KQVAEEAARL SVAAQEAARL RQLAEEDLAQ QRALAEKMLK EKMQAVQEAT RLKAEAELLQ QQKELAQEQA RRLQEDKEQM AQQLAEETQG FQRTLEAERQ RQLEMSAEAE RLKLRVAEMS RAQARAEEDA QRFRKQAEEI GEKLHRTELA TQEKVTLVQT LEIQRQQSDH DAERLREAIA ELEREKEKLQ QEAKLLQLKS EEMQTVQQEQ LLQETQALQQ SFLSEKDSLL QRERFIEQEK AKLEQLFQDE VAKAQQLREE QQRQQQQMEQ ERQRLVASME EARRRQHEAE EGVRRKQEEL QQLEQQRRQQ EELLAEENQR LREQLQLLEE QHRAALAHSE EVTASQVAAT KTLPNGRDAL DGPAAEAEPE HSFDGLRRKV SAQRLQEAGI LSAEELQRLA QGHTTVDELA RREDVRHYLQ GRSSIAGLLL KATNEKLSVY AALQRQLLSP GTALILLEAQ AASGFLLDPV RNRRLTVNEA VKEGVVGPEL HHKLLSAERA VTGYKDPYTG QQISLFQAMQ KGLIVREHGI RLLEAQIATG GVIDPVHSHR VPVDVAYRRG YFDEEMNRVL ADPSDDTKGF FDPNTHENLT YLQLLERCVE DPETGLCLLP LTDKAAKGGE LVYTDSEARD VFEKATVSAP FGKFQGKTVT IWEIINSEYF TAEQRRDLLR QFRTGRITVE KIIKIIITVV EEQEQKGRLC FEGLRSLVPA AELLESRVID RELYQQLQRG ERSVRDVAEV DTVRRALRGA NVIAGVWLEE AGQKLSIYNA LKKDLLPSDM AVALLEAQAG TGHIIDPATS ARLTVDEAVR AGLVGPEFHE KLLSAEKAVT GYRDPYTGQS VSLFQALKKG LIPREQGLRL LDAQLSTGGI VDPSKSHRVP LDVACARGCL DEETSRALSA PRADAKAYSD PSTGEPATYG ELQQRCRPDQ LTGLSLLPLS EKAARARQEE LYSELQARET FEKTPVEVPV GGFKGRTVTV WELISSEYFT AEQRQELLRQ FRTGKVTVEK VIKILITIVE EVETLRQERL SFSGLRAPVP ASELLASGVL SRAQFEQLKD GKTTVKDLSE LGSVRTLLQG SGCLAGIYLE DTKEKVSIYE

					AMRRGLLRAT TAALLLEAQA ATGFLVDPVR NQRLYVHEAV KAGVVGPELH EQLLSAEKAV TGYRDPYSGS TISLFQAMQK GLVLRQHGIR LLEAQIATGG IIDPVHSHRV PVDVAYQRGY FSEEMNRVLA DPSDDTKGFF DPNTHENLTY RQLLERCVED PETGLRLLPL KGAEKAEVVE TTQVYTEEET RRAFEETQID IPGGGSHGGS TMSLWEVMQS DLIPEEQRAQ LMADFQAGRV TKERMIIIII EIIEKTEIIR QQGLASYDYV RRRLTAEDLF EARIISLETY NLLREGTRSL REALEAESAW CYLYGTGSVA GVYLPGSRQT LSIYQALKKG LLSAEVARLL LEAQAATGFL LDPVKGERLT VDEAVRKGLV GPELHDRLLS AERAVTGYRD PYTEQTISLF QAMKKELIPT EEALRLLDAQ LATGGIVDPR LGFHLPLEVA YQRGYLNKDT HDQLSEPSEV RSYVDPSTDE RLSYTQLLRR CRRDDGTGQL LLPLSDARKL TFRGLRKQIT MEELVRSQVM DEATALQLRE GLTSIEEVTK NLQKFLEGTS CIAGVFVDAT KERLSVYQAM KKGIIRPGTA FELLEAQAAT GYVIDPIKGL KLTVEEAVRM GIVGPEFKDK LLSAERAVTG YKDPYSGKLI SLFQAMKKGL ILKDHGIRLL EAQIATGGII DPEESHRLPV EVAYKRGLFD EEMNEILTDP SDDTKGFFDP NTEENLTYLQ LMERCITDPQ TGLCLLPLKE KKRERKTSSK SSVRKRRVVI VDPETGKEMS VYEAYRKGLI DHQTYLELSE QECEWEEITI SSSDGVVKSM IIDRRSGRQY DIDDAIAKNL IDRSALDQYR AGTLSITEFA DMLSGNAGGF RSRSSSVGSS SSYPISPAVS RTQLASWSDP TEETGPVAGI LDTETLEKVS ITEAMHRNLV DNITGQRLLE AQACTGGIID PSTGERFPVT DAVNKGLVDK IMVDRINLAQ KAFCGFEDPR TKTKMSAAQA LKKGWLYYEA GQRFLEVQYL TGGLIEPDTP GRVPLDEALQ RGTVDARTAQ KLRDVGAYSK YLTCPKTKLK ISYKDALDRS MVEEGTGLRL LEAAAQSTKG YYSPYSVSGS GSTAGSRTGS RTGSRAGSRR GSFDATGSGF SMTFSSSSYS SSGYGRRYAS GSSASLGGPE SAVA
69	PLEC	3	Q15149-	Entry version	MSGEDAEVRA VSEDVSNGSS

			3	224 (18 Sep 2019) Sequence version 3 (14 Oct 2008)	GSPSPGDTLP WNLGKTQRSR RSGGGAGSNG SVLDPAERAV IRIADERDRV QKKTFTKWVN KHLIKAQRHI SDLYEDLRDG HNLISLLEVL SGDSLPREKG RMRFHKLQNV QIALDYLRHR QVKLVNIRND DIADGNPKLT LGLIWTIILH FQISDIQVSG QSEDMTAKEK LLLWSQRMVE GYQGLRCDNF TSSWRDGRLF NAIIHRHKPL LIDMNKVYRQ TNLENLDQAF SVAERDLGVT RLLDPEDVDV PQPDEKSIIT YVSSLYDAMP RVPDVQDGEL QLRWQEYREL VLLLLQWMRH HTAAFEERRF PSSFEEIEIL WSQFLKFKEM ELPAKEADKN RSKGIYQSLE GAVQAGQLKV PPGYHPLDVE KEWGKLHVAI LEREKQLRSE FERLECLQRI VTKLQMEAGL CEEQLNQADA LLQSDVRLLA AGKVPQRAGE VERDLDKADS MIRLLFNDVQ TLKDGRHPQG EQMYRRVYRL HERLVAIRTE YNLRLKAGVA APATQVAQVT LQSVQRRPEL EDSTLRYLQD LLAWVEENQH RVDGAEWGVD LPSVEAQLGS HRGLHQSIEE FRAKIERARS DEGQLSPATR GAYRDCLGRL DLQYAKLLNS SKARLRSLES LHSFVAAATK ELMWLNEKEE EEVGFDWSDR NTNMTAKKES YSALMRELEL KEKKIKELQN AGDRLLREDH PARPTVESFQ AALQTQWSWM LQLCCCIEAH LKENAAYFQF FSDVREAEGQ LQKLQEALRR KYSCDRSATV TRLEDLLQDA QDEKEQLNEY KGHLSGLAKR AKAVVQLKPR HPAHPMRGRL PLLAVCDYKQ VEVTVHKGDE CQLVGPAQPS HWKVLSSSGS EAAVPSVCFL VPPPNQEAQE AVTRLEAQHQ ALVTLWHQLH VDMKSLLAWQ SLRRDVQLIR SWSLATFRTL KPEEQRQALH SLELHYQAFL RDSQDAGGFG PEDRLMAERE YGSCSHHYQQ LLQSLEQGAQ EESRCQRCIS ELKDIRLQLE ACETRTVHRL RLPLDKEPAR ECAQRIAEQQ KAQAEVEGLG KGVARLSAEA EKVLALPEPS PAAPTLRSEL ELTLGKLEQV RSLSAIYLEK LKTISLVIRG TQGAEEVLRA HEEQLKEAQA VPATLPELEA TKASLKKLRA QAEAQQPTFD ALRDELRGAQ EVGERLQQRH GERDVEVERW RERVAQLLER WQAVLAQTDV

					RQRELEQLGR QLRYYRESAD PLGAWLQDAR RRQEQIQAMP LADSQAVREQ LRQEQALLEE IERHGEKVEE CQRFAKQYIN AIKDYELQLV TYKAQLEPVA SPAKKPKVQS GSESVIQEYV DLRTHYSELT TLTSQYIKFI SETLRRMEEE ERLAEQQRAE ERERLAEVEA ALEKQRQLAE AHAQAKAQAE REAKELQQRM QEEVVRREEA AVDAQQQKRS IQEELQQLRQ SSEAEIQAKA RQAEAAERSR LRIEEEIRVV RLQLEATERQ RGGAEGELQA LRARAEEAEA QKRQAQEEAE RLRRQVQDES QRKRQAEVEL ASRVKAEAEA AREKQRALQA LEELRLQAEE AERRLRQAEV ERARQVQVAL ETAQRSAEAE LQSKRASFAE KTAQLERSLQ EEHVAVAQLR EEAERRAQQQ AEAERAREEA ERELERWQLK ANEALRLRLQ AEEVAQQKSL AQAEAEKQKE EAEREARRRG KAEEQAVRQR ELAEQELEKQ RQLAEGTAQQ RLAAEQELIR LRAETEQGEQ QRQLLEEELA RLQREAAAAT QKRQELEAEL AKVRAEMEVL LASKARAEEE SRSTSEKSKQ RLEAEAGRFR ELAEEAARLR ALAEEAKRQR QLAEEDAARQ RAEAERVLAE KLAAIGEATR LKTEAEIALK EKEAENERLR RLAEDEAFQR RRLEEQAAQH KADIEERLAQ LRKASDSELE RQKGLVEDTL RQRRQVEEEI LALKASFEKA AAGKAELELE LGRIRSNAED TLRSKEQAEL EAARQRQLAA EEERRRREAE ERVQKSLAAE EEAARQRKAA LEEVERLKAK VEEARRLRER AEQESARQLQ LAQEAAQKRL QAEEKAHAFA VQQKEQELQQ TLQQEQSVLD QLRGEAEAAR RAAEEAEEAR VQAEREAAQS RRQVEEAERL KQSAEEQAQA RAQAQAAAEK LRKEAEQEAA RRAQAEQAAL RQKQAADAEM EKHKKFAEQT LRQKAQVEQE LTTLRLQLEE TDHQKNLLDE ELQRLKAEAT EAARQRSQVE EELFSVRVQM EELSKLKARI EAENRALILR DKDNTQRFLQ EEAEKMKQVA EEAARLSVAA QEAARLRQLA EEDLAQQRAL AEKMLKEKMQ AVQEATRLKA EAELLQQQKE LAQEQARRLQ EDKEQMAQQL AEETQGFQRT LEAERQRQLE MSAEAERLKL RVAEMSRAQA

					RAEEDAQRFR KQAEEIGEKL HRTELATQEK VTLVQTLEIQ RQQSDHDAER LREAIAELER EKEKLQQEAK LLQLKSEEMQ TVQQEQLLQE TQALQQSFLS EKDSLLQRER FIEQEKAKLE QLFQDEVAKA QQLREEQQRQ QQQMEQERQR LVASMEEARR RQHEAEEGVR RKQEELQQLE QQRRQQEELL AEENQRLREQ LQLLEEQHRA ALAHSEEVTA SQVAATKTLP NGRDALDGPA AEAEPEHSFD GLRRKVSAQR LQEAGILSAE ELQRLAQGHT TVDELARRED VRHYLQGRSS IAGLLLKATN EKLSVYAALQ RQLLSPGTAL ILLEAQAASG FLLDPVRNRR LTVNEAVKEG VVGPELHHKL LSAERAVTGY KDPYTGQQIS LFQAMQKGLI VREHGIRLLE AQIATGGVID PVHSHRVPVD VAYRRGYFDE EMNRVLADPS DDTKGFFDPN THENLTYLQL LERCVEDPET GLCLLPLTDK AAKGGELVYT DSEARDVFEK ATVSAPFGKF QGKTVTIWEI INSEYFTAEQ RRDLLRQFRT GRITVEKIIK IIITVVEEQE QKGRLCFEGL RSLVPAAELL ESRVIDRELY QQLQRGERSV RDVAEVDTVR RALRGANVIA GVWLEEAGQK LSIYNALKKD LLPSDMAVAL LEAQAGTGHI IDPATSARLT VDEAVRAGLV GPEFHEKLLS AEKAVTGYRD PYTGQSVSLF QALKKGLIPR EQGLRLLDAQ LSTGGIVDPS KSHRVPLDVA CARGCLDEET SRALSAPRAD AKAYSDPSTG EPATYGELQQ RCRPDQLTGL SLLPLSEKAA RARQEELYSE LQARETFEKT PVEVPVGGFK GRTVTVWELI SSEYFTAEQR QELLRQFRTG KVTVEKVIKI LITIVEEVET LRQERLSFSG LRAPVPASEL LASGVLSRAQ FEQLKDGKTT VKDLSELGSV RTLLQGSGCL AGIYLEDTKE KVSIYEAMRR GLLRATTAAL LLEAQAATGF LVDPVRNQRL YVHEAVKAGV VGPELHEQLL SAEKAVTGYR DPYSGSTISL FQAMQKGLVL RQHGIRLLEA QIATGGIIDP VHSHRVPVDV AYQRGYFSEE MNRVLADPSD DTKGFFDPNT HENLTYRQLL ERCVEDPETG LRLLPLKGAE KAEVVETTQV YTEEETRRAF EETQIDIPGG GSHGGSTMSL WEVMQSDLIP

					EEQRAQLMAD FQAGRVTKER MIIIIIEIIE KTEIIRQQGL ASYDYVRRRL TAEDLFEARI ISLETYNLLR EGTRSLREAL EAESAWCYLY GTGSVAGVYL PGSRQTLSIY QALKKGLLSA EVARLLLEAQ AATGFLLDPV KGERLTVDEA VRKGLVGPEL HDRLLSAERA VTGYRDPYTE QTISLFQAMK KELIPTEEAL RLLDAQLATG GIVDPRLGFH LPLEVAYQRG YLNKDTHDQL SEPSEVRSYV DPSTDERLSY TQLLRRCRRD DGTGQLLLPL SDARKLTFRG LRKQITMEEL VRSQVMDEAT ALQLREGLTS IEEVTKNLQK FLEGTSCIAG VFVDATKERL SVYQAMKKGI IRPGTAFELL EAQAATGYVI DPIKGLKLTV EEAVRMGIVG PEFKDKLLSA ERAVTGYKDP YSGKLISLFQ AMKKGLILKD HGIRLLEAQI ATGGIIDPEE SHRLPVEVAY KRGLFDEEMN EILTDPSDDT KGFFDPNTEE NLTYLQLMER CITDPQTGLC LLPLKEKKRE RKTSSKSSVR KRRVVIVDPE TGKEMSVYEA YRKGLIDHQT YLELSEQECE WEEITISSSD GVVKSMIIDR RSGRQYDIDD AIAKNLIDRS ALDQYRAGTL SITEFADMLS GNAGGFRSRS SSVGSSSSYP ISPAVSRTQL ASWSDPTEET GPVAGILDTE TLEKVSITEA MHRNLVDNIT GQRLLEAQAC TGGIIDPSTG ERFPVTDAVN KGLVDKIMVD RINLAQKAFC GFEDPRTKTK MSAAQALKKG WLYYEAGQRF LEVQYLTGGL IEPDTPGRVP LDEALQRGTV DARTAQKLRD VGAYSKYLTC PKTKLKISYK DALDRSMVEE GTGLRLLEAA AQSTKGYYSP YSVSGSGSTA GSRTGSRTGS RAGSRRGSFD ATGSGFSMTF SSSSYSSSGY GRRYASGSSA SLGGPESAVA
70	PLEC	4	Q15149-4	Entry version 224 (18 Sep 2019) Sequence version 3 (14 Oct 2008)	MSQHQLRVPQ PEGLGRKRTS SEDNLYLAVL RASEGKKDER DRVQKKTFTK WVNKHLIKAQ RHISDLYEDL RDGHNLISLL EVLSGDSLPR EKGRMRFHKL QNVQIALDYL RHRQVKLVNI RNDDIADGNP KLTLGLIWTI ILHFQISDIQ VSGQSEDMTA KEKLLLWSQR MVEGYQGLRC DNFTSSWRDG RLFNAIIHRH KPLLIDMNKV YRQTNLENLD

					QAFSVAERDL GVTRLLDPED
					VDVPQPDEKS IITYVSSLYD
					AMPRVPDVQD GVRANELQLR
					WQEYRELVLL LLQWMRHHTA
					AFEERRFPSS FEEIEILWSQ
					FLKFKEMELP AKEADKNRSK
					GIYQSLEGAV QAGQLKVPPG
					YHPLDVEKEW GKLHVAILER
					EKQLRSEFER LECLQRIVTK
					LQMEAGLCEE QLNQADALLQ
					SDVRLLAAGK VPQRAGEVER
					DLDKADSMIR LLFNDVQTLK
					DGRHPQGEQM YRRVYRLHER
					LVAIRTEYNL RLKAGVAAPA
					TQVAQVTLQS VQRRPELEDS
					TLRYLQDLLA WVEENQHRVD
					GAEWGVDLPS VEAQLGSHRG
					LHQSIEEFRA KIERARSDEG
					QLSPATRGAY RDCLGRLDLQ
					YAKLLNSSKA RLRSLESLHS
					FVAAATKELM WLNEKEEEEV
					GFDWSDRNTN MTAKKESYSA
					LMRELELKEK KIKELQNAGD
					RLLREDHPAR PTVESFQAAL
					QTQWSWMLQL CCCIEAHLKE
					NAAYFQFFSD VREAEGQLQK
					LQEALRRKYS CDRSATVTRL
					EDLLQDAQDE KEQLNEYKGH
					LSGLAKRAKA VVQLKPRHPA
					HPMRGRLPLL AVCDYKQVEV
					TVHKGDECQL VGPAQPSHWK
					VLSSSGSEAA VPSVCFLVPP
					PNQEAQEAVT RLEAQHQALV
					TLWHQLHVDM KSLLAWQSLR
					RDVQLIRSWS LATFRTLKPE
					EQRQALHSLE LHYQAFLRDS
					QDAGGFGPED RLMAEREYGS
					CSHHYQQLLQ SLEQGAQEES
					RCQRCISELK DIRLQLEACE
					TRTVHRLRLP LDKEPARECA
					QRIAEQQKAQ AEVEGLGKGV
					ARLSAEAEKV LALPEPSPAA
					PTLRSELELT LGKLEQVRSL
					SAIYLEKLKT ISLVIRGTQG
					AEEVLRAHEE QLKEAQAVPA
					TLPELEATKA SLKKLRAQAE
					AQQPTFDALR DELRGAQEVG
					ERLQQRHGER DVEVERWRER
					VAQLLERWQA VLAQTDVRQR
					ELEQLGRQLR YYRESADPLG
					AWLQDARRRQ EQIQAMPLAD
					SQAVREQLRQ EQALLEEIER
					HGEKVEECQR FAKQYINAIK
					DYELQLVTYK AQLEPVASPA
					KKPKVQSGSE SVIQEYVDLR
					THYSELTTLT SQYIKFISET
					LRRMEEEERL AEQQRAEERE
					RLAEVEAALE KQRQLAEAHA
					QAKAQAEREA KELQQRMQEE
					VVRREEAAVD AQQQKRSIQE

					ELQQLRQSSE	AEIQAKARQA
					EAAERSRLRI	EEEIRVVRLQ
					LEATERQRGG	AEGELQALRA
					RAEEAEAQKR	QAQEEAERLR
					RQVQDESQRK	RQAEVELASR
					VKAEAEAARE	KQRALQALEE
					LRLQAEEAER	RLRQAEVERA
					RQVQVALETA	QRSAEAELQS
					KRASFAEKTA	QLERSLQEEH
					VAVAQLREEA	ERRAQQQAEA
					ERAREEAERE	LERWQLKANE
					ALRLRLQAEE	VAQQKSLAQA
					EAEKQKEEAE	REARRRGKAE
					EQAVRQRELA	EQELEKQRQL
					AEGTAQQRLA	AEQELIRLRA
					ETEQGEQQRQ	LLEEELARLQ
					REAAAATQKR	QELEAELAKV
					RAEMEVLLAS	KARAEEESRS
					TSEKSKQRLE	AEAGRFRELA
					EEAARLRALA	EEAKRQRQLA
					EEDAARQRAE	AERVLAEKLA
					AIGEATRLKT	EAEIALKEKE
					AENERLRRLA	EDEAFQRRRL
					EEQAAQHKAD	IEERLAQLRK
					ASDSELERQK	GLVEDTLRQR
					RQVEEEILAL	KASFEKAAAG
					KAELELELGR	IRSNAEDTLR
					SKEQAELEAA	RQRQLAAEEE
					RRRREAEERV	QKSLAAEEEA
					ARQRKAALEE	VERLKAKVEE
					ARRLRERAEQ	ESARQLQLAQ
					EAAQKRLQAE	EKAHAFAVQQ
					KEQELQQTLQ	QEQSVLDQLR
					GEAEAARRAA	EEAEEARVQA
					EREAAQSRRQ	VEEAERLKQS
					AEEQAQARAQ	AQAAAEKLRK
					EAEQEAARRA	QAEQAALRQK
					QAADAEMEKH	KKFAEQTLRQ
					KAQVEQELTT	LRLQLEETDH
					QKNLLDEELQ	RLKAEATEAA
					RQRSQVEEEL	FSVRVQMEEL
					SKLKARIEAE	NRALILRDKD
					NTQRFLQEEA	EKMKQVAEEA
					ARLSVAAQEA	ARLRQLAEED
					LAQQRALAEK	MLKEKMQAVQ
					EATRLKAEAE	LLQQQKELAQ
					EQARRLQEDK	EQMAQQLAEE
					TQGFQRTLEA	ERQRQLEMSA
					EAERLKLRVA	EMSRAQARAE
					EDAQRFRKQA	EEIGEKLHRT
					ELATQEKVTL	VQTLEIQRQQ
					SDHDAERLRE	AIAELEREKE
					KLQQEAKLLQ	LKSEEMQTVQ
					QEQLLQETQA	LQQSFLSEKD
					SLLQRERFIE	QEKAKLEQLF
					QDEVAKAQQL	REEQQRQQQQ
					MEQERQRLVA	SMEEARRRQH
					EAEEGVRRKQ	EELQQLEQQR
					RQQEELLAEE	NQRLREQLQL
					LEEQHRAALA	HSEEVTASQV

					AATKTLPNGR DALDGPAAEA
					EPEHSFDGLR RKVSAQRLQE
					AGILSAEELQ RLAQGHTTVD
					ELARREDVRH YLQGRSSIAG
					LLLKATNEKL SVYAALQRQL
					LSPGTALILL EAQAASGFLL
					DPVRNRRLTV NEAVKEGVVG
					PELHHKLLSA ERAVTGYKDP
					YTGQQISLFQ AMQKGLIVRE
					HGIRLLEAQI ATGGVIDPVH
					SHRVPVDVAY RRGYFDEEMN
					RVLADPSDDT KGFFDPNTHE
					NLTYLQLLER CVEDPETGLC
					LLPLTDKAAK GGELVYTDSE
					ARDVFEKATV SAPFGKFQGK
					TVTIWEIINS EYFTAEQRRD
					LLRQFRTGRI TVEKIIKIII
					TVVEEQEQKG RLCFEGLRSL
					VPAAELLESR VIDRELYQQL
					QRGERSVRDV AEVDTVRRAL
					RGANVIAGVW LEEAGQKLSI
					YNALKKDLLP SDMAVALLEA
					QAGTGHIIDP ATSARLTVDE
					AVRAGLVGPE FHEKLLSAEK
					AVTGYRDPYT GQSVSLFQAL
					KKGLIPREQG LRLLDAQLST
					GGIVDPSKSH RVPLDVACAR
					GCLDEETSRA LSAPRADAKA
					YSDPSTGEPA TYGELQQRCR
					PDQLTGLSLL PLSEKAARAR
					QEELYSELQA RETFEKTPVE
					VPVGGFKGRT VTVWELISSE
					YFTAEQRQEL LRQFRTGKVT
					VEKVIKILIT IVEEVETLRQ
					ERLSFSGLRA PVPASELLAS
					GVLSRAQFEQ LKDGKTTVKD
					LSELGSVRTL LQGSGCLAGI
					YLEDTKEKVS IYEAMRRGLL
					RATTAALLLE AQAATGFLVD
					PVRNQRLYVH EAVKAGVVGP
					ELHEQLLSAE KAVTGYRDPY
					SGSTISLFQA MQKGLVLRQH
					GIRLLEAQIA TGGIIDPVHS
					HRVPVDVAYQ RGYFSEEMNR
					VLADPSDDTK GFFDPNTHEN
					LTYRQLLERC VEDPETGLRL
					LPLKGAEKAE VVETTQVYTE
					EETRRAFEET QIDIPGGGSH
					GGSTMSLWEV MQSDLIPEEQ
					RAQLMADFQA GRVTKERMII
					IIIEIIEKTE IIRQQGLASY
					DYVRRRLTAE DLFEARIISL
					ETYNLLREGT RSLREALEAE
					SAWCYLYGTG SVAGVYLPGS
					RQTLSIYQAL KKGLLSAEVA
					RLLLEAQAAT GFLLDPVKGE
					RLTVDEAVRK GLVGPELHDR
					LLSAERAVTG YRDPYTEQTI
					SLFQAMKKEL IPTEEALRLL
					DAQLATGGIV DPRLGFHLPL

					EVAYQRGYLN KDTHDQLSEP SEVRSYVDPS TDERLSYTQL LRRCRRDDGT GQLLLPLSDA RKLTFRGLRK QITMEELVRS QVMDEATALQ LREGLTSIEE VTKNLQKFLE GTSCIAGVFV DATKERLSVY QAMKKGIIRP GTAFELLEAQ AATGYVIDPI KGLKLTVEEA VRMGIVGPEF KDKLLSAERA VTGYKDPYSG KLISLFQAMK KGLILKDHGI RLLEAQIATG GIIDPEESHR LPVEVAYKRG LFDEEMNEIL TDPSDDTKGF FDPNTEENLT YLQLMERCIT DPQTGLCLLP LKEKKRERKT SSKSSVRKRR VVIVDPETGK EMSVYEAYRK GLIDHQTYLE LSEQECEWEE ITISSSDGVV KSMIIDRRSG RQYDIDDAIA KNLIDRSALD QYRAGTLSIT EFADMLSGNA GGFRSRSSSV GSSSSYPISP AVSRTQLASW SDPTEETGPV AGILDTETLE KVSITEAMHR NLVDNITGQR LLEAQACTGG IIDPSTGERF PVTDAVNKGL VDKIMVDRIN LAQKAFCGFE DPRTKTKMSA AQALKKGWLY YEAGQRFLEV QYLTGGLIEP DTPGRVPLDE ALQRGTVDAR TAQKLRDVGA YSKYLTCPKT KLKISYKDAL DRSMVEEGTG LRLLEAAAQS TKGYYSPYSV SGSGSTAGSR TGSRTGSRAG SRRGSFDATG SGFSMTFSSS SYSSSGYGRR YASGSSASLG GPESAVA
71	PLEC	5	Q15149-5	Entry version 224 (18 Sep 2019) Sequence version 3 (14 Oct 2008)	MEPSGSLFPS LVVVGHVVTL AAVWHWRRGR RWAQDEQDER DRVQKKTFTK WVNKHLIKAQ RHISDLYEDL RDGHNLISLL EVLSGDSLPR EKGRMRFHKL QNVQIALDYL RHRQVKLVNI RNDDIADGNP KLTLGLIWTI ILHFQISDIQ VSGQSEDMTA KEKLLLWSQR MVEGYQGLRC DNFTSSWRDG RLFNAIIHRH KPLLIDMNKV YRQTNLENLD QAFSVAERDL GVTRLLDPED VDVPQPDEKS IITYVSSLYD AMPRVPDVQD GVRANELQLR WQEYRELVLL LLQWMRHHTA AFEERRFPSS FEEIEILWSQ FLKFKEMELP AKEADKNRSK GIYQSLEGAV QAGQLKVPPG YHPLDVEKEW GKLHVAILER EKQLRSEFER LECLQRIVTK LQMEAGLCEE QLNQADALLQ SDVRLLAAGK VPQRAGEVER

					DLDKADSMIR LLFNDVQTLK
					DGRHPQGEQM YRRVYRLHER
					LVAIRTEYNL RLKAGVAAPA
					TQVAQVTLQS VQRRPELEDS
					TLRYLQDLLA WVEENQHRVD
					GAEWGVDLPS VEAQLGSHRG
					LHQSIEEFRA KIERARSDEG
					QLSPATRGAY RDCLGRLDLQ
					YAKLLNSSKA RLRSLESLHS
					FVAAATKELM WLNEKEEEEV
					GFDWSDRNTN MTAKKESYSA
					LMRELELKEK KIKELQNAGD
					RLLREDHPAR PTVESFQAAL
					QTQWSWMLQL CCCIEAHLKE
					NAAYFQFFSD VREAEGQLQK
					LQEALRRKYS CDRSATVTRL
					EDLLQDAQDE KEQLNEYKGH
					LSGLAKRAKA VVQLKPRHPA
					HPMRGRLPLL AVCDYKQVEV
					TVHKGDECQL VGPAQPSHWK
					VLSSSGSEAA VPSVCFLVPP
					PNQEAQEAVT RLEAQHQALV
					TLWHQLHVDM KSLLAWQSLR
					RDVQLIRSWS LATFRTLKPE
					EQRQALHSLE LHYQAFLRDS
					QDAGGFGPED RLMAEREYGS
					CSHHYQQLLQ SLEQGAQEES
					RCQRCISELK DIRLQLEACE
					TRTVHRLRLP LDKEPARECA
					QRIAEQQKAQ AEVEGLGKGV
					ARLSAEAEKV LALPEPSPAA
					PTLRSELELT LGKLEQVRSL
					SAIYLEKLKT ISLVIRGTQG
					AEEVLRAHEE QLKEAQAVPA
					TLPELEATKA SLKKLRAQAE
					AQQPTFDALR DELRGAQEVG
					ERLQQRHGER DVEVERWRER
					VAQLLERWQA VLAQTDVRQR
					ELEQLGRQLR YYRESADPLG
					AWLQDARRRQ EQIQAMPLAD
					SQAVREQLRQ EQALLEEIER
					HGEKVEECQR FAKQYINAIK
					DYELQLVTYK AQLEPVASPA
					KKPKVQSGSE SVIQEYVDLR
					THYSELTTLT SQYIKFISET
					LRRMEEEERL AEQQRAEERE
					RLAEVEAALE KQRQLAEAHA
					QAKAQAEREA KELQQRMQEE
					VVRREEAAVD AQQQKRSIQE
					ELQQLRQSSE AEIQAKARQA
					EAAERSRLRI EEEIRVVRLQ
					LEATERQRGG AEGELQALRA
					RAEEAEAQKR QAQEEAERLR
					RQVQDESQRK RQAEVELASR
					VKAEAEAARE KQRALQALEE
					LRLQAEEAER RLRQAEVERA
					RQVQVALETA QRSAEAELQS
					KRASFAEKTA QLERSLQEEH
					VAVAQLREEA ERRAQQQAEA
					ERAREEAERE LERWQLKANE

					ALRLRLQAEE VAQQKSLAQA EAEKQKEEAE REARRRGKAE EQAVRQRELA EQELEKQRQL AEGTAQQRLA AEQELIRLRA ETEQGEQQRQ LLEEELARLQ REAAAATQKR QELEAELAKV RAEMEVLLAS KARAEEESRS TSEKSKQRLE AEAGRFRELA EEAARLRALA EEAKRQRQLA EEDAARQRAE AERVLAEKLA AIGEATRLKT EAEIALKEKE AENERLRRLA EDEAFQRRRL EEQAAQHKAD IEERLAQLRK ASDSELERQK GLVEDTLRQR RQVEEEILAL KASFEKAAAG KAELELELGR IRSNAEDTLR SKEQAELEAA RQRQLAAEEE RRRREAEERV QKSLAAEEEA ARQRKAALEE VERLKAKVEE ARRLRERAEQ ESARQLQLAQ EAAQKRLQAE EKAHAFAVQQ KEQELQQTLQ QEQSVLDQLR GEAEAARRAA EEAEEARVQA EREAAQSRRQ VEEAERLKQS AEEQAQARAQ AQAAAEKLRK EAEQEAARRA QAEQAALRQK QAADAEMEKH KKFAEQTLRQ KAQVEQELTT LRLQLEETDH QKNLLDEELQ RLKAEATEAA RQRSQVEEEL FSVRVQMEEL SKLKARIEAE NRALILRDKD NTQRFLQEEA EKMKQVAEEA ARLSVAAQEA ARLRQLAEED LAQQRALAEK MLKEKMQAVQ EATRLKAEAE LLQQQKELAQ EQARRLQEDK EQMAQQLAEE TQGFQRTLEA ERQRQLEMSA EAERLKLRVA EMSRAQARAE EDAQRFRKQA EEIGEKLHRT ELATQEKVTL VQTLEIQRQQ SDHDAERLRE AIAELEREKE KLQQEAKLLQ LKSEEMQTVQ QEQLLQETQA LQQSFLSEKD SLLQRERFIE QEKAKLEQLF QDEVAKAQQL REEQQRQQQQ MEQERQRLVA SMEEARRRQH EAEEGVRRKQ EELQQLEQQR RQQEELLAEE NQRLREQLQL LEEQHRAALA HSEEVTASQV AATKTLPNGR DALDGPAAEA EPEHSFDGLR RKVSAQRLQE AGILSAEELQ RLAQGHTTVD ELARREDVRH YLQGRSSIAG LLLKATNEKL SVYAALQRQL LSPGTALILL EAQAASGFLL DPVRNRRLTV NEAVKEGVVG PELHHKLLSA ERAVTGYKDP YTGQQISLFQ AMQKGLIVRE HGIRLLEAQI ATGGVIDPVH SHRVPVDVAY RRGYFDEEMN

					RVLADPSDDT KGFFDPNTHE
					NLTYLQLLER CVEDPETGLC
					LLPLTDKAAK GGELVYTDSE
					ARDVFEKATV SAPFGKFQGK
					TVTIWEIINS EYFTAEQRRD
					LLRQFRTGRI TVEKIIKIII
					TVVEEQEQKG RLCFEGLRSL
					VPAAELLESR VIDRELYQQL
					QRGERSVRDV AEVDTVRRAL
					RGANVIAGVW LEEAGQKLSI
					YNALKKDLLP SDMAVALLEA
					QAGTGHIIDP ATSARLTVDE
					AVRAGLVGPE FHEKLLSAEK
					AVTGYRDPYT GQSVSLFQAL
					KKGLIPREQG LRLLDAQLST
					GGIVDPSKSH RVPLDVACAR
					GCLDEETSRA LSAPRADAKA
					YSDPSTGEPA TYGELQQRCR
					PDQLTGLSLL PLSEKAARAR
					QEELYSELQA RETFEKTPVE
					VPVGGFKGRT VTVWELISSE
					YFTAEQRQEL LRQFRTGKVT
					VEKVIKILIT IVEEVETLRQ
					ERLSFSGLRA PVPASELLAS
					GVLSRAQFEQ LKDGKTTVKD
					LSELGSVRTL LQGSGCLAGI
					YLEDTKEKVS IYEAMRRGLL
					RATTAALLLE AQAATGFLVD
					PVRNQRLYVH EAVKAGVVGP
					ELHEQLLSAE KAVTGYRDPY
					SGSTISLFQA MQKGLVLRQH
					GIRLLEAQIA TGGIIDPVHS
					HRVPVDVAYQ RGYFSEEMNR
					VLADPSDDTK GFFDPNTHEN
					LTYRQLLERC VEDPETGLRL
					LPLKGAEKAE VVETTQVYTE
					EETRRAFEET QIDIPGGGSH
					GGSTMSLWEV MQSDLIPEEQ
					RAQLMADFQA GRVTKERMII
					IIIEIIEKTE IIRQQGLASY
					DYVRRRLTAE DLFEARIISL
					ETYNLLREGT RSLREALEAE
					SAWCYLYGTG SVAGVYLPGS
					RQTLSIYQAL KKGLLSAEVA
					RLLLEAQAAT GFLLDPVKGE
					RLTVDEAVRK GLVGPELHDR
					LLSAERAVTG YRDPYTEQTI
					SLFQAMKKEL IPTEEALRLL
					DAQLATGGIV DPRLGFHLPL
					EVAYQRGYLN KDTHDQLSEP
					SEVRSYVDPS TDERLSYTQL
					LRRCRRDDGT GQLLLPLSDA
					RKLTFRGLRK QITMEELVRS
					QVMDEATALQ LREGLTSIEE
					VTKNLQKFLE GTSCIAGVFV
					DATKERLSVY QAMKKGIIRP
					GTAFELLEAQ AATGYVIDPI
					KGLKLTVEEA VRMGIVGPEF
					KDKLLSAERA VTGYKDPYSG
					KLISLFQAMK KGLILKDHGI

					RLLEAQIATG GIIDPEESHR LPVEVAYKRG LFDEEMNEIL TDPSDDTKGF FDPNTEENLT YLQLMERCIT DPQTGLCLLP LKEKKRERKT SSKSSVRKRR VVIVDPETGK EMSVYEAYRK GLIDHQTYLE LSEQECEWEE ITISSSDGVV KSMIIDRRSG RQYDIDDAIA KNLIDRSALD QYRAGTLSIT EFADMLSGNA GGFRSRSSSV GSSSSYPISP AVSRTQLASW SDPTEETGPV AGILDTETLE KVSITEAMHR NLVDNITGQR LLEAQACTGG IIDPSTGERF PVTDAVNKGL VDKIMVDRIN LAQKAFCGFE DPRTKTKMSA AQALKKGWLY YEAGQRFLEV QYLTGGLIEP DTPGRVPLDE ALQRGTVDAR TAQKLRDVGA YSKYLTCPKT KLKISYKDAL DRSMVEEGTG LRLLEAAAQS TKGYYSPYSV SGSGSTAGSR TGSRTGSRAG SRRGSFDATG SGFSMTFSSS SYSSSGYGRR YASGSSASLG GPESAVA
72	PLEC	6	Q15149-6	Entry version 224 (18 Sep 2019) Sequence version 3 (14 Oct 2008)	MSGAGGAFAS PREVLLERPC WLDGGCEPAR RGYLYQQLCC VDERDRVQKK TFTKWVNKHL IKAQRHISDL YEDLRDGHNL ISLLEVLSGD SLPREKGRMR FHKLQNVQIA LDYLRHRQVK LVNIRNDDIA DGNPKLTLGL IWTIILHFQI SDIQVSGQSE DMTAKEKLLL WSQRMVEGYQ GLRCDNFTSS WRDGRLFNAI IHRHKPLLID MNKVYRQTNL ENLDQAFSVA ERDLGVTRLL DPEDVDVPQP DEKSIITYVS SLYDAMPRVP DVQDGVRANE LQLRWQEYRE LVLLLLQWMR HHTAAFEERR FPSSFEEIEI LWSQFLKFKE MELPAKEADK NRSKGIYQSL EGAVQAGQLK VPPGYHPLDV EKEWGKLHVA ILEREKQLRS EFERLECLQR IVTKLQMEAG LCEEQLNQAD ALLQSDVRLL AAGKVPQRAG EVERDLDKAD SMIRLLFNDV QTLKDGRHPQ GEQMYRRVYR LHERLVAIRT EYNLRLKAGV AAPATQVAQV TLQSVQRRPE LEDSTLRYLQ DLLAWVEENQ HRVDGAEWGV DLPSVEAQLG SHRGLHQSIE EFRAKIERAR SDEGQLSPAT RGAYRDCLGR LDLQYAKLLN SSKARLRSLE SLHSFVAAAT KELMWLNEKE EEEVGFDWSD RNTNMTAKKE

					SYSALMRELE LKEKKIKELQ NAGDRLLRED HPARPTVESF QAALQTQWSW MLQLCCCIEA HLKENAAYFQ FFSDVREAEG QLQKLQEALR RKYSCDRSAT VTRLEDLLQD AQDEKEQLNE YKGHLSGLAK RAKAVVQLKP RHPAHPMRGR LPLLAVCDYK QVEVTVHKGD ECQLVGPAQP SHWKVLSSSG SEAAVPSVCF LVPPPNQEAQ EAVTRLEAQH QALVTLWHQL HVDMKSLLAW QSLRRDVQLI RSWSLATFRT LKPEEQRQAL HSLELHYQAF LRDSQDAGGF GPEDRLMAER EYGSCSHHYQ QLLQSLEQGA QEESRCQRCI SELKDIRLQL EACETRTVHR LRLPLDKEPA RECAQRIAEQ QKAQAEVEGL GKGVARLSAE AEKVLALPEP SPAAPTLRSE LELTLGKLEQ VRSLSAIYLE KLKTISLVIR GTQGAEEVLR AHEEQLKEAQ AVPATLPELE ATKASLKKLR AQAEAQQPTF DALRDELRGA QEVGERLQQR HGERDVEVER WRERVAQLLE RWQAVLAQTD VRQRELEQLG RQLRYYRESA DPLGAWLQDA RRRQEQIQAM PLADSQAVRE QLRQEQALLE EIERHGEKVE ECQRFAKQYI NAIKDYELQL VTYKAQLEPV ASPAKKPKVQ SGSESVIQEY VDLRTHYSEL TTLTSQYIKF ISETLRRMEE EERLAEQQRA EERERLAEVE AALEKQRQLA EAHAQAKAQA EREAKELQQR MQEEVVRREE AAVDAQQQKR SIQEELQQLR QSSEAEIQAK ARQAEAAERS RLRIEEEIRV VRLQLEATER QRGGAEGELQ ALRARAEEAE AQKRQAQEEA ERLRRQVQDE SQRKRQAEVE LASRVKAEAE AAREKQRALQ ALEELRLQAE EAERRLRQAE VERARQVQVA LETAQRSAEA ELQSKRASFA EKTAQLERSL QEEHVAVAQL REEAERRAQQ QAEAERAREE AERELERWQL KANEALRLRL QAEEVAQQKS LAQAEAEKQK EEAEREARRR GKAEEQAVRQ RELAEQELEK QRQLAEGTAQ QRLAAEQELI RLRAETEQGE QQRQLLEEEL ARLQREAAAA TQKRQELEAE LAKVRAEMEV LLASKARAEE ESRSTSEKSK QRLEAEAGRF RELAEEAARL RALAEEAKRQ RQLAEEDAAR QRAEAERVLA EKLAAIGEAT RLKTEAEIAL

					KEKEAENERL RRLAEDEAFQ RRRLEEQAAQ HKADIEERLA QLRKASDSEL ERQKGLVEDT LRQRRQVEEE ILALKASFEK AAAGKAELEL ELGRIRSNAE DTLRSKEQAE LEAARQRQLA AEEERRRREA EERVQKSLAA EEEAARQRKA ALEEVERLKA KVEEARRLRE RAEQESARQL QLAQEAAQKR LQAEEKAHAF AVQQKEQELQ QTLQQEQSVL DQLRGEAEAA RRAAEEAEEA RVQAEREAAQ SRRQVEEAER LKQSAEEQAQ ARAQAQAAAE KLRKEAEQEA ARRAQAEQAA LRQKQAADAE MEKHKKFAEQ TLRQKAQVEQ ELTTLRLQLE ETDHQKNLLD EELQRLKAEA TEAARQRSQV EEELFSVRVQ MEELSKLKAR IEAENRALIL RDKDNTQRFL QEEAEKMKQV AEEAARLSVA AQEAARLRQL AEEDLAQQRA LAEKMLKEKM QAVQEATRLK AEAELLQQQK ELAQEQARRL QEDKEQMAQQ LAEETQGFQR TLEAERQRQL EMSAEAERLK LRVAEMSRAQ ARAEEDAQRF RKQAEEIGEK LHRTELATQE KVTLVQTLEI QRQQSDHDAE RLREAIAELE REKEKLQQEA KLLQLKSEEM QTVQQEQLLQ ETQALQQSFL SEKDSLLQRE RFIEQEKAKL EQLFQDEVAK AQQLREEQQR QQQQMEQERQ RLVASMEEAR RRQHEAEEGV RRKQEELQQL EQQRRQQEEL LAEENQRLRE QLQLLEEQHR AALAHSEEVT ASQVAATKTL PNGRDALDGP AAEAEPEHSF DGLRRKVSAQ RLQEAGILSA EELQRLAQGH TTVDELARRE DVRHYLQGRS SIAGLLLKAT NEKLSVYAAL QRQLLSPGTA LILLEAQAAS GFLLDPVRNR RLTVNEAVKE GVVGPELHHK LLSAERAVTG YKDPYTGQQI SLFQAMQKGL IVREHGIRLL EAQIATGGVI DPVHSHRVPV DVAYRRGYFD EEMNRVLADP SDDTKGFFDP NTHENLTYLQ LLERCVEDPE TGLCLLPLTD KAAKGGELVY TDSEARDVFE KATVSAPFGK FQGKTVTIWE IINSEYFTAE QRRDLLRQFR TGRITVEKII KIIITVVEEQ EQKGRLCFEG LRSLVPAAEL LESRVIDREL YQQLQRGERS VRDVAEVDTV RRALRGANVI AGVWLEEAGQ KLSIYNALKK DLLPSDMAVA

					LLEAQAGTGH IIDPATSARL TVDEAVRAGL VGPEFHEKLL SAEKAVTGYR DPYTGQSVSL FQALKKGLIP REQGLRLLDA QLSTGGIVDP SKSHRVPLDV ACARGCLDEE TSRALSAPRA DAKAYSDPST GEPATYGELQ QRCRPDQLTG LSLLPLSEKA ARARQEELYS ELQARETFEK TPVEVPVGGF KGRTVTVWEL ISSEYFTAEQ RQELLRQFRT GKVTVEKVIK ILITIVEEVE TLRQERLSFS GLRAPVPASE LLASGVLSRA QFEQLKDGKT TVKDLSELGS VRTLLQGSGC LAGIYLEDTK EKVSIYEAMR RGLLRATTAA LLLEAQAATG FLVDPVRNQR LYVHEAVKAG VVGPELHEQL LSAEKAVTGY RDPYSGSTIS LFQAMQKGLV LRQHGIRLLE AQIATGGIID PVHSHRVPVD VAYQRGYFSE EMNRVLADPS DDTKGFFDPN THENLTYRQL LERCVEDPET GLRLLPLKGA EKAEVVETTQ VYTEEETRRA FEETQIDIPG GGSHGGSTMS LWEVMQSDLI PEEQRAQLMA DFQAGRVTKE RMIIIIIEII EKTEIIRQQG LASYDYVRRR LTAEDLFEAR IISLETYNLL REGTRSLREA LEAESAWCYL YGTGSVAGVY LPGSRQTLSI YQALKKGLLS AEVARLLLEA QAATGFLLDP VKGERLTVDE AVRKGLVGPE LHDRLLSAER AVTGYRDPYT EQTISLFQAM KKELIPTEEA LRLLDAQLAT GGIVDPRLGF HLPLEVAYQR GYLNKDTHDQ LSEPSEVRSY VDPSTDERLS YTQLLRRCRR DDGTGQLLLP LSDARKLTFR GLRKQITMEE LVRSQVMDEA TALQLREGLT SIEEVTKNLQ KFLEGTSCIA GVFVDATKER LSVYQAMKKG IIRPGTAFEL LEAQAATGYV IDPIKGLKLT VEEAVRMGIV GPEFKDKLLS AERAVTGYKD PYSGKLISLF QAMKKGLILK DHGIRLLEAQ IATGGIIDPE ESHRLPVEVA YKRGLFDEEM NEILTDPSDD TKGFFDPNTE ENLTYLQLME RCITDPQTGL CLLPLKEKKR ERKTSSKSSV RKRRVVIVDP ETGKEMSVYE AYRKGLIDHQ TYLELSEQEC EWEEITISSS DGVVKSMIID RRSGRQYDID DAIAKNLIDR SALDQYRAGT LSITEFADML SGNAGGFRSR SSSVGSSSSY

					PISPAVSRTQ LASWSDPTEE TGPVAGILDT ETLEKVSITE AMHRNLVDNI TGQRLLEAQA CTGGIIDPST GERFPVTDAV NKGLVDKIMV DRINLAQKAF CGFEDPRTKT KMSAAQALKK GWLYYEAGQR FLEVQYLTGG LIEPDTPGRV PLDEALQRGT VDARTAQKLR DVGAYSKYLT CPKTKLKISY KDALDRSMVE EGTGLRLLEA AAQSTKGYYS PYSVSGSGST AGSRTGSRTG SRAGSRRGSF DATGSGFSMT FSSSSYSSSG YGRRYASGSS ASLGGPESAV A
73	PLEC	7	Q15149-7	Entry version 224 (18 Sep 2019) Sequence version 3 (14 Oct 2008)	MKIVPDERDR VQKKTFTKWV NKHLIKAQRH ISDLYEDLRD GHNLISLLEV LSGDSLPREK GRMRFHKLQN VQIALDYLRH RQVKLVNIRN DDIADGNPKL TLGLIWTIIL HFQISDIQVS GQSEDMTAKE KLLLWSQRMV EGYQGLRCDN FTSSWRDGRL FNAIIHRHKP LLIDMNKVYR QTNLENLDQA FSVAERDLGV TRLLDPEDVD VPQPDEKSII TYVSSLYDAM PRVPDVQDGV RANELQLRWQ EYRELVLLLL QWMRHHTAAF EERRFPSSFE EIEILWSQFL KFKEMELPAK EADKNRSKGI YQSLEGAVQA GQLKVPPGYH PLDVEKEWGK LHVAILEREK QLRSEFERLE CLQRIVTKLQ MEAGLCEEQL NQADALLQSD VRLLAAGKVP QRAGEVERDL DKADSMIRLL FNDVQTLKDG RHPQGEQMYR RVYRLHERLV AIRTEYNLRL KAGVAAPATQ VAQVTLQSVQ RRPELEDSTL RYLQDLLAWV EENQHRVDGA EWGVDLPSVE AQLGSHRGLH QSIEEFRAKI ERARSDEGQL SPATRGAYRD CLGRLDLQYA KLLNSSKARL RSLESLHSFV AAATKELMWL NEKEEEEVGF DWSDRNTNMT AKKESYSALM RELELKEKKI KELQNAGDRL LREDHPARPT VESFQAALQT QWSWMLQLCC CIEAHLKENA AYFQFFSDVR EAEGQLQKLQ EALRRKYSCD RSATVTRLED LLQDAQDEKE QLNEYKGHLS GLAKRAKAVV QLKPRHPAHP MRGRLPLLAV CDYKQVEVTV HKGDECQLVG PAQPSHWKVL SSSGSEAAVP SVCFLVPPPN QEAQEAVTRL EAQHQALVTL WHQLHVDMKS LLAWQSLRRD VQLIRSWSLA

					TFRTLKPEEQ RQALHSLELH YQAFLRDSQD AGGFGPEDRL MAEREYGSCS HHYQQLLQSL EQGAQEESRC QRCISELKDI RLQLEACETR TVHRLRLPLD KEPARECAQR IAEQQKAQAE VEGLGKGVAR LSAEAEKVLA LPEPSPAAPT LRSELELTLG KLEQVRSLSA IYLEKLKTIS LVIRGTQGAE EVLRAHEEQL KEAQAVPATL PELEATKASL KKLRAQAEAQ QPTFDALRDE LRGAQEVGER LQQRHGERDV EVERWRERVA QLLERWQAVL AQTDVRQREL EQLGRQLRYY RESADPLGAW LQDARRRQEQ IQAMPLADSQ AVREQLRQEQ ALLEEIERHG EKVEECQRFA KQYINAIKDY ELQLVTYKAQ LEPVASPAKK PKVQSGSESV IQEYVDLRTH YSELTTLTSQ YIKFISETLR RMEEEERLAE QQRAEERERL AEVEAALEKQ RQLAEAHAQA KAQAEREAKE LQQRMQEEVV RREEAAVDAQ QQKRSIQEEL QQLRQSSEAE IQAKARQAEA AERSRLRIEE EIRVVRLQLE ATERQRGGAE GELQALRARA EEAEAQKRQA QEEAERLRRQ VQDESQRKRQ AEVELASRVK AEAEAAREKQ RALQALEELR LQAEEAERRL RQAEVERARQ VQVALETAQR SAEAELQSKR ASFAEKTAQL ERSLQEEHVA VAQLREEAER RAQQQAEAER AREEAERELE RWQLKANEAL RLRLQAEEVA QQKSLAQAEA EKQKEEAERE ARRRGKAEEQ AVRQRELAEQ ELEKQRQLAE GTAQQRLAAE QELIRLRAET EQGEQQRQLL EEELARLQRE AAAATQKRQE LEAELAKVRA EMEVLLASKA RAEEESRSTS EKSKQRLEAE AGRFRELAEE AARLRALAEE AKRQRQLAEE DAARQRAEAE RVLAEKLAAI GEATRLKTEA EIALKEKEAE NERLRRLAED EAFQRRRLEE QAAQHKADIE ERLAQLRKAS DSELERQKGL VEDTLRQRRQ VEEEILALKA SFEKAAAGKA ELELELGRIR SNAEDTLRSK EQAELEAARQ RQLAAEEERR RREAEERVQK SLAAEEEAAR QRKAALEEVE RLKAKVEEAR RLRERAEQES ARQLQLAQEA AQKRLQAEEK AHAFAVQQKE QELQQTLQQE QSVLDQLRGE AEAARRAAEE AEEARVQAER EAAQSRRQVE

					EAERLKQSAE	EQAQARAQAQ
					AAAEKLRKEA	EQEAARRAQA
					EQAALRQKQA	ADAEMEKHKK
					FAEQTLRQKA	QVEQELTTLR
					LQLEETDHQK	NLLDEELQRL
					KAEATEAARQ	RSQVEEELFS
					VRVQMEELSK	LKARIEAENR
					ALILRDKDNT	QRFLQEEAEK
					MKQVAEEAAR	LSVAAQEAAR
					LRQLAEEDLA	QQRALAEKML
					KEKMQAVQEA	TRLKAEAELL
					QQQKELAQEQ	ARRLQEDKEQ
					MAQQLAEETQ	GFQRTLEAER
					QRQLEMSAEA	ERLKLRVAEM
					SRAQARAEED	AQRFRKQAEE
					IGEKLHRTEL	ATQEKVTLVQ
					TLEIQRQQSD	HDAERLREAI
					AELEREKEKL	QQEAKLLQLK
					SEEMQTVQQE	QLLQETQALQ
					QSFLSEKDSL	LQRERFIEQE
					KAKLEQLFQD	EVAKAQQLRE
					EQQRQQQQME	QERQRLVASM
					EEARRRQHEA	EEGVRRKQEE
					LQQLEQQRRQ	QEELLAEENQ
					RLREQLQLLE	EQHRAALAHS
					EEVTASQVAA	TKTLPNGRDA
					LDGPAAEAEP	EHSFDGLRRK
					VSAQRLQEAG	ILSAEELQRL
					AQGHTTVDEL	ARREDVRHYL
					QGRSSIAGLL	LKATNEKLSV
					YAALQRQLLS	PGTALILLEA
					QAASGFLLDP	VRNRRLTVNE
					AVKEGVVGPE	LHHKLLSAER
					AVTGYKDPYT	GQQISLFQAM
					QKGLIVREHG	IRLLEAQIAT
					GGVIDPVHSH	RVPVDVAYRR
					GYFDEEMNRV	LADPSDDTKG
					FFDPNTHENL	TYLQLLERCV
					EDPETGLCLL	PLTDKAAKGG
					ELVYTDSEAR	DVFEKATVSA
					PFGKFQGKTV	TIWEIINSEY
					FTAEQRRDLL	RQFRTGRITV
					EKIIKIIITV	VEEQEQKGRL
					CFEGLRSLVP	AAELLESRVI
					DRELYQQLQR	GERSVRDVAE
					VDTVRRALRG	ANVIAGVWLE
					EAGQKLSIYN	ALKKDLLPSD
					MAVALLEAQA	GTGHIIDPAT
					SARLTVDEAV	RAGLVGPEFH
					EKLLSAEKAV	TGYRDPYTGQ
					SVSLFQALKK	GLIPREQGLR
					LLDAQLSTGG	IVDPSKSHRV
					PLDVACARGC	LDEETSRALS
					APRADAKAYS	DPSTGEPATY
					GELQQRCRPD	QLTGLSLLPL
					SEKAARARQE	ELYSELQARE
					TFEKTPVEVP	VGGFKGRTVT
					VWELISSEYF	TAEQRQELLR
					QFRTGKVTVE	KVIKILITIV
					EEVETLRQER	LSFSGLRAPV

					PASELLASGV	LSRAQFEQLK
					DGKTTVKDLS	ELGSVRTLLQ
					GSGCLAGIYL	EDTKEKVSIY
					EAMRRGLLRA	TTAALLLEAQ
					AATGFLVDPV	RNQRLYVHEA
					VKAGVVGPEL	HEQLLSAEKA
					VTGYRDPYSG	STISLFQAMQ
					KGLVLRQHGI	RLLEAQIATG
					GIIDPVHSHR	VPVDVAYQRG
					YFSEEMNRVL	ADPSDDTKGF
					FDPNTHENLT	YRQLLERCVE
					DPETGLRLLP	LKGAEKAEVV
					ETTQVYTEEE	TRRAFEETQI
					DIPGGGSHGG	STMSLWEVMQ
					SDLIPEEQRA	QLMADFQAGR
					VTKERMIIII	IEIIEKTEII
					RQQGLASYDY	VRRRLTAEDL
					FEARIISLET	YNLLREGTRS
					LREALEAESA	WCYLYGTGSV
					AGVYLPGSRQ	TLSIYQALKK
					GLLSAEVARL	LLEAQAATGF
					LLDPVKGERL	TVDEAVRKGL
					VGPELHDRLL	SAERAVTGYR
					DPYTEQTISL	FQAMKKELIP
					TEEALRLLDA	QLATGGIVDP
					RLGFHLPLEV	AYQRGYLNKD
					THDQLSEPSE	VRSYVDPSTD
					ERLSYTQLLR	RCRRDDGTGQ
					LLLPLSDARK	LTFRGLRKQI
					TMEELVRSQV	MDEATALQLR
					EGLTSIEEVT	KNLQKFLEGT
					SCIAGVFVDA	TKERLSVYQA
					MKKGIIRPGT	AFELLEAQAA
					TGYVIDPIKG	LKLTVEEAVR
					MGIVGPEFKD	KLLSAERAVT
					GYKDPYSGKL	ISLFQAMKKG
					LILKDHGIRL	LEAQIATGGI
					IDPEESHRLP	VEVAYKRGLF
					DEEMNEILTD	PSDDTKGFFD
					PNTEENLTYL	QLMERCITDP
					QTGLCLLPLK	EKKRERKTSS
					KSSVRKRRVV	IVDPETGKEM
					SVYEAYRKGL	IDHQTYLELS
					EQECEWEEIT	ISSSDGVVKS
					MIIDRRSGRQ	YDIDDAIAKN
					LIDRSALDQY	RAGTLSITEF
					ADMLSGNAGG	FRSRSSSVGS
					SSSYPISPAV	SRTQLASWSD
					PTEETGPVAG	ILDTETLEKV
					SITEAMHRNL	VDNITGQRLL
					EAQACTGGII	DPSTGERFPV
					TDAVNKGLVD	KIMVDRINLA
					QKAFCGFEDP	RTKTKMSAAQ
					ALKKGWLYYE	AGQRFLEVQY
					LTGGLIEPDT	PGRVPLDEAL
					QRGTVDARTA	QKLRDVGAYS
					KYLTCPKTKL	KISYKDALDR
					SMVEEGTGLR	LLEAAAQSTK
					GYYSPYSVSG	SGSTAGSRTG
					SRTGSRAGSR	RGSFDATGSG

					FSMTFSSSSY SSSGYGRRYA SGSSASLGGP ESAVA
74	PLEC	8	Q15149-8	Entry version 224 (18 Sep 2019) Sequence version 3 (14 Oct 2008)	MDPSRAIQNE ISSLKDERDR VQKKTFTKWV NKHLIKAQRH ISDLYEDLRD GHNLISLLEV LSGDSLPREK GRMRFHKLQN VQIALDYLRH RQVKLVNIRN DDIADGNPKL TLGLIWTIIL HFQISDIQVS GQSEDMTAKE KLLLWSQRMV EGYQGLRCDN FTSSWRDGRL FNAIIHRHKP LLIDMNKVYR QTNLENLDQA FSVAERDLGV TRLLDPEDVD VPQPDEKSII TYVSSLYDAM PRVPDVQDGV RANELQLRWQ EYRELVLLLL QWMRHHTAAF EERRFPSSFE EIEILWSQFL KFKEMELPAK EADKNRSKGI YQSLEGAVQA GQLKVPPGYH PLDVEKEWGK LHVAILEREK QLRSEFERLE CLQRIVTKLQ MEAGLCEEQL NQADALLQSD VRLLAAGKVP QRAGEVERDL DKADSMIRLL FNDVQTLKDG RHPQGEQMYR RVYRLHERLV AIRTEYNLRL KAGVAAPATQ VAQVTLQSVQ RRPELEDSTL RYLQDLLAWV EENQHRVDGA EWGVDLPSVE AQLGSHRGLH QSIEEFRAKI ERARSDEGQL SPATRGAYRD CLGRLDLQYA KLLNSSKARL RSLESLHSFV AAATKELMWL NEKEEEEVGF DWSDRNTNMT AKKESYSALM RELELKEKKI KELQNAGDRL LREDHPARPT VESFQAALQT QWSWMLQLCC CIEAHLKENA AYFQFFSDVR EAEGQLQKLQ EALRRKYSCD RSATVTRLED LLQDAQDEKE QLNEYKGHLS GLAKRAKAVV QLKPRHPAHP MRGRLPLLAV CDYKQVEVTV HKGDECQLVG PAQPSHWKVL SSSGSEAAVP SVCFLVPPPN QEAQEAVTRL EAQHQALVTL WHQLHVDMKS LLAWQSLRRD VQLIRSWSLA TFRTLKPEEQ RQALHSLELH YQAFLRDSQD AGGFGPEDRL MAEREYGSCS HHYQQLLQSL EQGAQEESRC QRCISELKDI RLQLEACETR TVHRLRLPLD KEPARECAQR IAEQQKAQAE VEGLGKGVAR LSAEAEKVLA LPEPSPAAPT LRSELELTLG KLEQVRSLSA IYLEKLKTIS LVIRGTQGAE EVLRAHEEQL KEAQAVPATL PELEATKASL KKLRAQAEAQ QPTFDALRDE LRGAQEVGER

					LQQRHGERDV EVERWRERVA QLLERWQAVL AQTDVRQREL EQLGRQLRYY RESADPLGAW LQDARRRQEQ IQAMPLADSQ AVREQLRQEQ ALLEEIERHG EKVEECQRFA KQYINAIKDY ELQLVTYKAQ LEPVASPAKK PKVQSGSESV IQEYVDLRTH YSELTTLTSQ YIKFISETLR RMEEEERLAE QQRAEERERL AEVEAALEKQ RQLAEAHAQA KAQAEREAKE LQQRMQEEVV RREEAAVDAQ QQKRSIQEEL QQLRQSSEAE IQAKARQAEA AERSRLRIEE EIRVVRLQLE ATERQRGGAE GELQALRARA EEAEAQKRQA QEEAERLRRQ VQDESQRKRQ AEVELASRVK AEAEAAREKQ RALQALEELR LQAEEAERRL RQAEVERARQ VQVALETAQR SAEAELQSKR ASFAEKTAQL ERSLQEEHVA VAQLREEAER RAQQQAEAER AREEAERELE RWQLKANEAL RLRLQAEEVA QQKSLAQAEA EKQKEEAERE ARRRGKAEEQ AVRQRELAEQ ELEKQRQLAE GTAQQRLAAE QELIRLRAET EQGEQQRQLL EEELARLQRE AAAATQKRQE LEAELAKVRA EMEVLLASKA RAEEESRSTS EKSKQRLEAE AGRFRELAEE AARLRALAEE AKRQRQLAEE DAARQRAEAE RVLAEKLAAI GEATRLKTEA EIALKEKEAE NERLRRLAED EAFQRRRLEE QAAQHKADIE ERLAQLRKAS DSELERQKGL VEDTLRQRRQ VEEEILALKA SFEKAAAGKA ELELELGRIR SNAEDTLRSK EQAELEAARQ RQLAAEEERR RREAEERVQK SLAAEEEAAR QRKAALEEVE RLKAKVEEAR RLRERAEQES ARQLQLAQEA AQKRLQAEEK AHAFAVQQKE QELQQTLQQE QSVLDQLRGE AEAARRAAEE AEEARVQAER EAAQSRRQVE EAERLKQSAE EQAQARAQAQ AAAEKLRKEA EQEAARRAQA EQAALRQKQA ADAEMEKHKK FAEQTLRQKA QVEQELTTLR LQLEETDHQK NLLDEELQRL KAEATEAARQ RSQVEEELFS VRVQMEELSK LKARIEAENR ALILRDKDNT QRFLQEEAEK MKQVAEEAAR LSVAAQEAAR LRQLAEEDLA QQRALAEKML KEKMQAVQEA TRLKAEAELL QQQKELAQEQ ARRLQEDKEQ MAQQLAEETQ

					GFQRTLEAER QRQLEMSAEA
					ERLKLRVAEM SRAQARAEED
					AQRFRKQAEE IGEKLHRTEL
					ATQEKVTLVQ TLEIQRQQSD
					HDAERLREAI AELEREKEKL
					QQEAKLLQLK SEEMQTVQQE
					QLLQETQALQ QSFLSEKDSL
					LQRERFIEQE KAKLEQLFQD
					EVAKAQQLRE EQQRQQQQME
					QERQRLVASM EEARRRQHEA
					EEGVRRKQEE LQQLEQQRRQ
					QEELLAEENQ RLREQLQLLE
					EQHRAALAHS EEVTASQVAA
					TKTLPNGRDA LDGPAAEAEP
					EHSFDGLRRK VSAQRLQEAG
					ILSAEELQRL AQGHTTVDEL
					ARREDVRHYL QGRSSIAGLL
					LKATNEKLSV YAALQRQLLS
					PGTALILLEA QAASGFLLDP
					VRNRRLTVNE AVKEGVVGPE
					LHHKLLSAER AVTGYKDPYT
					GQQISLFQAM QKGLIVREHG
					IRLLEAQIAT GGVIDPVHSH
					RVPVDVAYRR GYFDEEMNRV
					LADPSDDTKG FFDPNTHENL
					TYLQLLERCV EDPETGLCLL
					PLTDKAAKGG ELVYTDSEAR
					DVFEKATVSA PFGKFQGKTV
					TIWEIINSEY FTAEQRRDLL
					RQFRTGRITV EKIIKIIITV
					VEEQEQKGRL CFEGLRSLVP
					AAELLESRVI DRELYQQLQR
					GERSVRDVAE VDTVRRALRG
					ANVIAGVWLE EAGQKLSIYN
					ALKKDLLPSD MAVALLEAQA
					GTGHIIDPAT SARLTVDEAV
					RAGLVGPEFH EKLLSAEKAV
					TGYRDPYTGQ SVSLFQALKK
					GLIPREQGLR LLDAQLSTGG
					IVDPSKSHRV PLDVACARGC
					LDEETSRALS APRADAKAYS
					DPSTGEPATY GELQQRCRPD
					QLTGLSLLPL SEKAARARQE
					ELYSELQARE TFEKTPVEVP
					VGGFKGRTVT VWELISSEYF
					TAEQRQELLR QFRTGKVTVE
					KVIKILITIV EEVETLRQER
					LSFSGLRAPV PASELLASGV
					LSRAQFEQLK DGKTTVKDLS
					ELGSVRTLLQ GSGCLAGIYL
					EDTKEKVSIY EAMRRGLLRA
					TTAALLLEAQ AATGFLVDPV
					RNQRLYVHEA VKAGVVGPEL
					HEQLLSAEKA VTGYRDPYSG
					STISLFQAMQ KGLVLRQHGI
					RLLEAQIATG GIIDPVHSHR
					VPVDVAYQRG YFSEEMNRVL
					ADPSDDTKGF FDPNTHENLT
					YRQLLERCVE DPETGLRLLP
					LKGAEKAEVV ETTQVYTEEE

					TRRAFEETQI DIPGGGSHGG STMSLWEVMQ SDLIPEEQRA QLMADFQAGR VTKERMIIII IEIIEKTEII RQQGLASYDY VRRRLTAEDL FEARIISLET YNLLREGTRS LREALEAESA WCYLYGTGSV AGVYLPGSRQ TLSIYQALKK GLLSAEVARL LLEAQAATGF LLDPVKGERL TVDEAVRKGL VGPELHDRLL SAERAVTGYR DPYTEQTISL FQAMKKELIP TEEALRLLDA QLATGGIVDP RLGFHLPLEV AYQRGYLNKD THDQLSEPSE VRSYVDPSTD ERLSYTQLLR RCRRDDGTGQ LLLPLSDARK LTFRGLRKQI TMEELVRSQV MDEATALQLR EGLTSIEEVT KNLQKFLEGT SCIAGVFVDA TKERLSVYQA MKKGIIRPGT AFELLEAQAA TGYVIDPIKG LKLTVEEAVR MGIVGPEFKD KLLSAERAVT GYKDPYSGKL ISLFQAMKKG LILKDHGIRL LEAQIATGGI IDPEESHRLP VEVAYKRGLF DEEMNEILTD PSDDTKGFFD PNTEENLTYL QLMERCITDP QTGLCLLPLK EKKRERKTSS KSSVRKRRVV IVDPETGKEM SVYEAYRKGL IDHQTYLELS EQECEWEEIT ISSSDGVVKS MIIDRRSGRQ YDIDDAIAKN LIDRSALDQY RAGTLSITEF ADMLSGNAGG FRSRSSSVGS SSSYPISPAV SRTQLASWSD PTEETGPVAG ILDTETLEKV SITEAMHRNL VDNITGQRLL EAQACTGGII DPSTGERFPV TDAVNKGLVD KIMVDRINLA QKAFCGFEDP RTKTKMSAAQ ALKKGWLYYE AGQRFLEVQY LTGGLIEPDT PGRVPLDEAL QRGTVDARTA QKLRDVGAYS KYLTCPKTKL KISYKDALDR SMVEEGTGLR LLEAAAQSTK GYYSPYSVSG SGSTAGSRTG SRTGSRAGSR RGSFDATGSG FSMTFSSSSY SSSGYGRRYA SGSSASLGGP ESAVA
75	PLEC	9	Q15149-9	Entry version 224 (18 Sep 2019) Sequence version 3 (14 Oct 2008)	MAGPLPDEQD FIQAYEEVRE KYKDERDRVQ KKTFTKWVNK HLIKAQRHIS DLYEDLRDGH NLISLLEVLS GDSLPREKGR MRFHKLQNVQ IALDYLRHRQ VKLVNIRNDD IADGNPKLTL GLIWTIILHF QISDIQVSGQ SEDMTAKEKL LLWSQRMVEG YQGLRCDNFT SSWRDGRLFN AIIHRHKPLL IDMNKVYRQT

					NLENLDQAFS VAERDLGVTR
					LLDPEDVDVP QPDEKSIITY
					VSSLYDAMPR VPDVQDGVRA
					NELQLRWQEY RELVLLLLQW
					MRHHTAAFEE RRFPSSFEEI
					EILWSQFLKF KEMELPAKEA
					DKNRSKGIYQ SLEGAVQAGQ
					LKVPPGYHPL DVEKEWGKLH
					VAILEREKQL RSEFERLECL
					QRIVTKLQME AGLCEEQLNQ
					ADALLQSDVR LLAAGKVPQR
					AGEVERDLDK ADSMIRLLFN
					DVQTLKDGRH PQGEQMYRRV
					YRLHERLVAI RTEYNLRLKA
					GVAAPATQVA QVTLQSVQRR
					PELEDSTLRY LQDLLAWVEE
					NQHRVDGAEW GVDLPSVEAQ
					LGSHRGLHQS IEEFRAKIER
					ARSDEGQLSP ATRGAYRDCL
					GRLDLQYAKL LNSSKARLRS
					LESLHSFVAA ATKELMWLNE
					KEEEEVGFDW SDRNTNMTAK
					KESYSALMRE LELKEKKIKE
					LQNAGDRLLR EDHPARPTVE
					SFQAALQTQW SWMLQLCCCI
					EAHLKENAAY FQFFSDVREA
					EGQLQKLQEA LRRKYSCDRS
					ATVTRLEDLL QDAQDEKEQL
					NEYKGHLSGL AKRAKAVVQL
					KPRHPAHPMR GRLPLLAVCD
					YKQVEVTVHK GDECQLVGPA
					QPSHWKVLSS SGSEAAVPSV
					CFLVPPPNQE AQEAVTRLEA
					QHQALVTLWH QLHVDMKSLL
					AWQSLRRDVQ LIRSWSLATF
					RTLKPEEQRQ ALHSLELHYQ
					AFLRDSQDAG GFGPEDRLMA
					EREYGSCSHH YQQLLQSLEQ
					GAQEESRCQR CISELKDIRL
					QLEACETRTV HRLRLPLDKE
					PARECAQRIA EQQKAQAEVE
					GLGKGVARLS AEAEKVLALP
					EPSPAAPTLR SELELTLGKL
					EQVRSLSAIY LEKLKTISLV
					IRGTQGAEEV LRAHEEQLKE
					AQAVPATLPE LEATKASLKK
					LRAQAEAQQP TFDALRDELR
					GAQEVGERLQ QRHGERDVEV
					ERWRERVAQL LERWQAVLAQ
					TDVRQRELEQ LGRQLRYYRE
					SADPLGAWLQ DARRRQEQIQ
					AMPLADSQAV REQLRQEQAL
					LEEIERHGEK VEECQRFAKQ
					YINAIKDYEL QLVTYKAQLE
					PVASPAKKPK VQSGSESVIQ
					EYVDLRTHYS ELTTLTSQYI
					KFISETLRRM EEEERLAEQQ
					RAEERERLAE VEAALEKQRQ
					LAEAHAQAKA QAEREAKELQ
					QRMQEEVVRR EEAAVDAQQQ

					KRSIQEELQQ	LRQSSEAEIQ
					AKARQAEAAE	RSRLRIEEEI
					RVVRLQLEAT	ERQRGGAEGE
					LQALRARAEE	AEAQKRQAQE
					EAERLRRQVQ	DESQRKRQAE
					VELASRVKAE	AEAAREKQRA
					LQALEELRLQ	AEEAERRLRQ
					AEVERARQVQ	VALETAQRSA
					EAELQSKRAS	FAEKTAQLER
					SLQEEHVAVA	QLREEAERRA
					QQQAEAERAR	EEAERELERW
					QLKANEALRL	RLQAEEVAQQ
					KSLAQAEAEK	QKEEAEREAR
					RRGKAEEQAV	RQRELAEQEL
					EKQRQLAEGT	AQQRLAAEQE
					LIRLRAETEQ	GEQQRQLLEE
					ELARLQREAA	AATQKRQELE
					AELAKVRAEM	EVLLASKARA
					EEESRSTSEK	SKQRLEAEAG
					RFRELAEEAA	RLRALAEEAK
					RQRQLAEEDA	ARQRAEAERV
					LAEKLAAIGE	ATRLKTEAEI
					ALKEKEAENE	RLRRLAEDEA
					FQRRRLEEQA	AQHKADIEER
					LAQLRKASDS	ELERQKGLVE
					DTLRQRRQVE	EEILALKASF
					EKAAAGKAEL	ELELGRIRSN
					AEDTLRSKEQ	AELEAARQRQ
					LAAEEERRRR	EAEERVQKSL
					AAEEEAARQR	KAALEEVERL
					KAKVEEARRL	RERAEQESAR
					QLQLAQEAAQ	KRLQAEEKAH
					AFAVQQKEQE	LQQTLQQEQS
					VLDQLRGEAE	AARRAAEEAE
					EARVQAEREA	AQSRRQVEEA
					ERLKQSAEEQ	AQARAQAQAA
					AEKLRKEAEQ	EAARRAQAEQ
					AALRQKQAAD	AEMEKHKKFA
					EQTLRQKAQV	EQELTTLRLQ
					LEETDHQKNL	LDEELQRLKA
					EATEAARQRS	QVEEELFSVR
					VQMEELSKLK	ARIEAENRAL
					ILRDKDNTQR	FLQEEAEKMK
					QVAEEAARLS	VAAQEAARLR
					QLAEEDLAQQ	RALAEKMLKE
					KMQAVQEATR	LKAEAELLQQ
					QKELAQEQAR	RLQEDKEQMA
					QQLAEETQGF	QRTLEAERQR
					QLEMSAEAER	LKLRVAEMSR
					AQARAEEDAQ	RFRKQAEEIG
					EKLHRTELAT	QEKVTLVQTL
					EIQRQQSDHD	AERLREAIAE
					LEREKEKLQQ	EAKLLQLKSE
					EMQTVQQEQL	LQETQALQQS
					FLSEKDSLLQ	RERFIEQEKA
					KLEQLFQDEV	AKAQQLREEQ
					QRQQQQMEQE	RQRLVASMEE
					ARRRQHEAEE	GVRRKQEELQ
					QLEQQRRQQE	ELLAEENQRL
					REQLQLLEEQ	HRAALAHSEE

					VTASQVAATK TLPNGRDALD GPAAEAEPEH SFDGLRRKVS AQRLQEAGIL SAEELQRLAQ GHTTVDELAR REDVRHYLQG RSSIAGLLLK ATNEKLSVYA ALQRQLLSPG TALILLEAQA ASGFLLDPVR NRRLTVNEAV KEGVVGPELH HKLLSAERAV TGYKDPYTGQ QISLFQAMQK GLIVREHGIR LLEAQIATGG VIDPVHSHRV PVDVAYRRGY FDEEMNRVLA DPSDDTKGFF DPNTHENLTY LQLLERCVED PETGLCLLPL TDKAAKGGEL VYTDSEARDV FEKATVSAPF GKFQGKTVTI WEIINSEYFT AEQRRDLLRQ FRTGRITVEK IIKIIITVVE EQEQKGRLCF EGLRSLVPAA ELLESRVIDR ELYQQLQRGE RSVRDVAEVD TVRRALRGAN VIAGVWLEEA GQKLSIYNAL KKDLLPSDMA VALLEAQAGT GHIIDPATSA RLTVDEAVRA GLVGPEFHEK LLSAEKAVTG YRDPYTGQSV SLFQALKKGL IPREQGLRLL DAQLSTGGIV DPSKSHRVPL DVACARGCLD EETSRALSAP RADAKAYSDP STGEPATYGE LQQRCRPDQL TGLSLLPLSE KAARARQEEL YSELQARETF EKTPVEVPVG GFKGRTVTVW ELISSEYFTA EQRQELLRQF RTGKVTVEKV IKILITIVEE VETLRQERLS FSGLRAPVPA SELLASGVLS RAQFEQLKDG KTTVKDLSEL GSVRTLLQGS GCLAGIYLED TKEKVSIYEA MRRGLLRATT AALLLEAQAA TGFLVDPVRN QRLYVHEAVK AGVVGPELHE QLLSAEKAVT GYRDPYSGST ISLFQAMQKG LVLRQHGIRL LEAQIATGGI IDPVHSHRVP VDVAYQRGYF SEEMNRVLAD PSDDTKGFFD PNTHENLTYR QLLERCVEDP ETGLRLLPLK GAEKAEVVET TQVYTEEETR RAFEETQIDI PGGGSHGGST MSLWEVMQSD LIPEEQRAQL MADFQAGRVT KERMIIIIIE IIEKTEIIRQ QGLASYDYVR RRLTAEDLFE ARIISLETYN LLREGTRSLR EALEAESAWC YLYGTGSVAG VYLPGSRQTL SIYQALKKGL LSAEVARLLL EAQAATGFLL DPVKGERLTV DEAVRKGLVG PELHDRLLSA ERAVTGYRDP YTEQTISLFQ AMKKELIPTE EALRLLDAQL ATGGIVDPRL

					GFHLPLEVAY QRGYLNKDTH DQLSEPSEVR SYVDPSTDER LSYTQLLRRC RRDDGTGQLL LPLSDARKLT FRGLRKQITM EELVRSQVMD EATALQLREG LTSIEEVTKN LQKFLEGTSC IAGVFVDATK ERLSVYQAMK KGIIRPGTAF ELLEAQAATG YVIDPIKGLK LTVEEAVRMG IVGPEFKDKL LSAERAVTGY KDPYSGKLIS LFQAMKKGLI LKDHGIRLLE AQIATGGIID PEESHRLPVE VAYKRGLFDE EMNEILTDPS DDTKGFFDPN TEENLTYLQL MERCITDPQT GLCLLPLKEK KRERKTSSKS SVRKRRVVIV DPETGKEMSV YEAYRKGLID HQTYLELSEQ ECEWEEITIS SSDGVVKSMI IDRRSGRQYD IDDAIAKNLI DRSALDQYRA GTLSITEFAD MLSGNAGGFR SRSSSVGSSS SYPISPAVSR TQLASWSDPT EETGPVAGIL DTETLEKVSI TEAMHRNLVD NITGQRLLEA QACTGGIIDP STGERFPVTD AVNKGLVDKI MVDRINLAQK AFCGFEDPRT KTKMSAAQAL KKGWLYYEAG QRFLEVQYLT GGLIEPDTPG RVPLDEALQR GTVDARTAQK LRDVGAYSKY LTCPKTKLKI SYKDALDRSM VEEGTGLRLL EAAAQSTKGY YSPYSVSGSG STAGSRTGSR TGSRAGSRRG SFDATGSGFS MTFSSSSYSS SGYGRRYASG SSASLGGPES AVA
76	ACSLI	1	P33121	Entry version 186 (18 Sep 2019) Sequence version 1 (01 Oct 1993)	MQAHELFRYF RMPELVDFRQ YVRTLPTNTL MGFGAFAALT TFWYATRPKP LKPPCDLSMQ SVEVAGSGGA RRSALLDSDE PLVYFYDDVT TLYEGFQRGI QVSNNGPCLG SRKPDQPYEW LSYKQVAELS ECIGSALIQK GFKTAPDQFI GIFAQNRPEW VIIEQGCFAY SMVIVPLYDT LGNEAITYIV NKAELSLVFV DKPEKAKLLL EGVENKLIPG LKIIVVMDAY GSELVERGQR CGVEVTSMKA MEDLGRANRR KPKPPAPEDL AVICFTSGTT GNPKGAMVTH RNIVSDCSAF VKATENTVNP CPDDTLISFL PLAHMFERVV ECVMLCHGAK IGFFQGDIRL LMDDLKVLQP TVFPVVPRLL NRMFDRIFGQ ANTTLKRWLL DFASKRKEAE LRSGIIRNNS LWDRLIFHKV QSSLGGRVRL MVTGAAPVSA TVLTFLRAAL GCQFYEGYGQ

					TECTAGCCLT MPGDWTAGHV GAPMPCNLIK LVDVEEMNYM AAEGEGEVCV KGPNVFQGYL KDPAKTAEAL DKDGWLHTGD IGKWLPNGTL KIIDRKKHIF KLAQGEYIAP EKIENIYMRS EPVAQVFVHG ESLQAFLIAI VVPDVETLCS WAQKRGFEGS FEELCRNKDV KKAILEDMVR LGKDSGLKPF EQVKGITLHP ELFSIDNGLL TPTMKAKRPE LRNYFRSQID DLYSTIK
77	ACSLI	2	P33121-2	Entry version 186 (18 Sep 2019) Sequence version 1 (01 Oct 1993)	MQAHELFRYF RMPELVDFRQ YVRTLPTNTL MGFGAFAALT TFWYATRPKP LKPPCDLSMQ SVEVAGSGGA RRSALLDSDE PLVYFYDDVT TLYEGFQRGI QVSNNGPCLG SRKPDQPYEW LSYKQVAELS ECIGSALIQK GFKTAPDQFI GIFAQNRPEW VIIEQGCFAY SMVIVPLYDT LGNEAITYIV NKAELSLVFV DKPEKAKLLL EGVENKLIPG LKIIVVMDAY GSELVERGQR CGVEVTSMKA MEDLGRANRR KPKPPAPEDL AVICFTSGTT GNPKGAMVTH RNIVSDCSAF VKATENTVNP CPDDTLISFL PLAHMFERVV ECVMLCHGAK IGFFQGDIRL LMDDLKVLQP TVFPVVPRLL NRMFDRIFGQ ANTTLKRWLL DFASKRKEAE LRSGIIRNNS LWDRLIFHKV QSSLGGRVRL MVTGAAPVSA TVLTFLRAAL GCQFYEGYGQ TECTAGCCLT MPGDWTAGHV GAPMPCNLIK LVDVEEMNYM AAEGEGEGYL KDPAKTAEAL DKDGWLHTGD IGKWLPNGTL KIIDRKKHIF KLAQGEYIAP EKIENIYMRS EPVAQVFVHG ESLQAFLIAI VVPDVETLCS WAQKRGFEGS FEELCRNKDV KKAILEDMVR LGKDSGLKPF EQVKGITLHP ELFSIDNGLL TPTMKAKRPE LRNYFRSQID DLYSTIKV
78	ACSLI	3	P33121-3	Entry version 186 (18 Sep 2019) Sequence version 1 (01 Oct 1993)	MQAHELFRYF RMPELVDFRQ YVRTLPTNTL MGFGAFAALT TFWYATRPKP LKPPCDLSMQ SVEVAGSGGA RRSALLDSDE PLVYFYDDVT TLYEGFQRGI QVSNNGPCLG SRKPDQPYEW LSYKQVAELS ECIGSALIQK GFKTAPDQFI GIFAQNRPEW VIIEQGCFAY SMVIVPLYDT LGNEAITYIV NKAELSLVFV DKPEKAKLLL EGVENKLIPG LKIIVVMDAY GSELVERGQR CGVEVTSMKA MEDLGRANRR

					KPKPPAPEDL AVICFTSGTT GNPKGAMVTH RNIVSDCSAF VKATEKALPL SASDTHISYL PLAHIYEQLL KCVMLCHGAK IGFFQGDIRL LMDDLKVLQP TVFPVVPRLL NRMFDRIFGQ ANTTLKRWLL DFASKRKEAE LRSGIIRNNS LWDRLIFHKV QSSLGGRVRL MVTGAAPVSA TVLTFLRAAL GCQFYEGYGQ TECTAGCCLT MPGDWTAGHV GAPMPCNLIK LVDVEEMNYM AAEGEGEVCV KGPNVFQGYL KDPAKTAEAL DKDGWLHTGD IGKWLPNGTL KIIDRKKHIF KLAQGEYIAP EKIENIYMRS EPVAQVFVHG ESLQAFLIAI VVPDVETLCS WAQKRGFEGS FEELCRNKDV KKAILEDMVR LGKDSGLKPF EQVKGITLHP ELFSIDNGLL TPTMKAKRPE LRNYFRSQID DLYSTIKV
79	RAC1	1	P63000	Entry version 192 (18 Sep 2019) Sequence version 1 (31 Aug 2004)	MQAIKCVVVG DGAVGKTCLL ISYTTNAFPG EYIPTVFDNY SANVMVDGKP VNLGLWDTAG QEDYDRLRPL SYPQTDVFLI CFSLVSPASF ENVRAKWYPE VRHHCPNTPI ILVGTKLDLR DDKDTIEKLK EKKLTPITYP QGLAMAKEIG AVKYLECSAL TQRGLKTVFD EAIRAVLCPP PVKKRKRKCL LL
80	RAC1	2	P63000-2	Entry version 192 (18 Sep 2019) Sequence version 1 (31 Aug 2004)	MQAIKCVVVG DGAVGKTCLL ISYTTNAFPG EYIPTVFDNY SANVMVDGKP VNLGLWDTAG QEDYDRLRPL SYPQTVGETY GKDITSRGKD KPIADVFLIC FSLVSPASFE NVRAKWYPEV RHHCPNTPII LVGTKLDLRD DKDTIEKLKE KKLTPITYPQ GLAMAKEIGA VKYLECSALT QRGLKTVFDE AIRAVLCPPP VKKRKRKCLL L
81	PSMB2	1	P49721	Entry version 201 (18 Sep 2019) Sequence version 1 (01 Oct 1996)	MEYLIGIQGP DYVLVASDRV AASNIVQMKD DHDKMFKMSE KILLLCVGEA GDTVQFAEYI QKNVQLYKMR NGYELSPTAA ANFTRRNLAD CLRSRTPYHV NLLLAGYDEH EGPALYYMDY LAALAKAPFA AHGYGAFLTL SILDRYYTPT ISRERAVELL RKCLEELQKR FILNLPTFSV RIIDKNGIHD LDNISFPKQG S
82	GM2A	1	P17900	Entry version 190 (18 Sep 2019)	MQSLMQAPLL IALGLLLAAP AQAHLKKPSQ LSSFSWDNCD EGKDPAVIRS LTLEPDPIIV

				Sequence version 4 (13 Nov 2007)	PGNVTLSVMG STSVPLSSPL KVDLVLEKEV AGLWIKIPCT DYIGSCTFEH FCDVLDMLIP TGEPCPEPLR TYGLPCHCPF KEGTYSLPKS EFVVPDLELP SWLTTGNYRI ESVLSSSGKR LGCIKIAASL KGI

Variant Gene Sequences

SEQ ID NO.	GENE	Accession No.	Ensembl Release No.
83	*CAP37*	ENSG00000278624	98
84	*TAPBP*	ENSG00000112493	98
85	*TAPBP*	ENSG00000206281	98
86	*TAPBP*	ENSG00000112493	98
87	*TAPBP*	ENSG00000236490	98

EXAMPLES

MATERIALS AND METHODS

Isolation of Stem Cell-Derived Neutrophils

Stem cell-derived neutrophils (SCDN) were synthesised according to standard techniques and cultured *ex vivo* for 25 days following Ficoll-separation to obtain PBMCs and CD34+ isolates from ten one-off donor buffy leukocyte cones. Aliquots of the SCDN (50 x 10^6/ml) were frozen at -80°C in cryopreservative (10% FBS in DMSO).

Evaluation of Cancer Killing Activity (CKA) using the xCelligence Assay

SCDN were thawed and decanted into complete Dulbecco's modified Eagle's medium (DMEM) before incubation for 72 hours with pancreatic cancer (PANC-1) cells and 'healthy' breast epithelial cells (MCF-12F) (commercially available from the American Type Culture Collection - United Kingdom (U.K.), Guernsey, Ireland, Jersey and Liechtenstein, LGC Standards, Queens Road, Teddington, Middlesex TW11 0LY, UK). CKA was recorded regularly throughout the 72 hour culture period by xCelligence Assay.

The ACEA Biosciences xCELLigence RTCA DP Analyzer system® was used and the manufacturer's instructions were followed. The xCELLigence System is a real-time cell analyser, allowing for label-free and dynamic monitoring of cellular phenotypic changes continuously by measuring electrical impedance. The system measures impedance using interdigitated gold microelectrodes integrated into the bottom of each well of the tissue culture E-Plates. Impedance measurements are displayed as Cell Index (CI) values, providing quantitative information about the biological status of the cells, including viability. Impedance-based monitoring of cell viability correlates with cell number and MTT-based readout. The kinetic aspect of impedance-based cell viability measurements provides the necessary temporal information when neutrophils are used to induce cytotoxic effects. In particular, the xCELLigence System can also pinpoint the optimal time points when the neutrophils achieve their maximal effect (where such data is desired), as indicated by the lowest CI values, in cytotoxicity and cell death assays. 6,000 cancer cells (PANC-1) or healthy, non-cancerous cells (MCF-12F) are placed in the bottom of a 16 well plate (the system can read up to 3 plates simultaneously). For the first few hours after cells have been added to a well there is a rapid increase in impedance. This is caused by cells falling out of suspension, depositing onto the electrodes, and forming focal adhesions. If the initial number of cells added is low and there is empty space on the well bottom, cells will proliferate, causing a gradual yet steady increase in CI. When cells reach confluence the CI value

plateaus, reflecting the fact that the electrode surface area that is accessible to bulk media is no longer changing. At this point, which is called the 'normalization point', the neutrophils (60,000 cells) are added (giving a 10:1 effector:target ratio) and incubated at 37 °C. The percentage of cytolysis is readily calculated using a simple formula: Percentage of cytolysis = ((Cell Index $_{\text{no effector}}$ – Cell Index $_{\text{effector}}$)/Cell Index $_{\text{no effector}}$) X 100.

SCDNs that demonstrated >80% CKA (against PANC-1) by 48 hours after addition, and <10% off-target killing (i.e. killed <10% of 'healthy' breast epithelial cells (MCF-12F) by 48 hours after addition) were designated high CKA neutrophils and cells that demonstrated <51.5% CKA were designated low CKA control neutrophils.

Proteomic Analysis

Neutrophils were lysed and underwent sonication and were analysed using the Pierce bicinchoninic acid (BCA) protein assay according to manufacturer's instructions (commercially available from ThermoFisher, Waltham, MA, catalogue number: 23225) to determine protein concentration. Typically samples contained around 20 micrograms of protein in <500 µl. Samples were digested, desalted and lyophilised prior to liquid chromatography and mass spectrometry (LC-MS/MS) using a Thermo Q-Exactive (Orbitrap) Plus Mass Spectrometer (Thermo Scientific™). First, chromatography separates the peptides in solution, the smaller hydrophilic peptides come off the column in the first fraction, and bigger hydrophobic peptides come off last over a 2 hour period. Secondly, a strongly acidic pH2 solution ensures all peptides have protons and are thus given a positive charge, the Mass Spectrometer only allows through positively charged ions of a given fraction to hit the detector. The Orbitrap device fluctuates between isolate and fragment, at around 20 Hz so the least 'sticky' peptides of a given mass/charge ratio are quantified first. The fluctuations are proportional to the intensity of the peptides detected, thus providing protein quantities for each cell type.

Bioinformatics was performed using the online DAVID system (Huang DW, Sherman BT, Lempicki RA. Bioinformatics enrichment tools: paths toward the comprehensive functional analysis of large gene lists. Nucleic Acids Res. 2009;37:1–13.; and Huang DW, Sherman BT, Lempicki RA. Systematic and integrative analysis of large gene lists using DAVID bioinformatics resources. Nat Protoc. 2009;4:44–57).

EXAMPLE 1

Proteomic analysis was carried out according to the Materials & Methods section herein. Advantageously, a number of proteins were significantly upregulated in the high CKA neutrophils when compared to low CKA controls.

The following proteins (and thus genes) were upregulated compared to low CKA controls:

S100A9, S100A8, ITGB1, CYBB, SYK, DOCK8, COMP, ATG7, SLC2A1, GZMK, CTSG, ATM, IKBKB, BCAP31, TAPBP, PERM, PLEC, ACSL1, RAC1, GM2A, CAP37, and PSMB2.

The following proteins (and thus genes) were downregulated compared to low CKA controls:

ANXA1 and PPP3CB.

Table 1 presents a number of proteins with changed expression in high CKA cells compared to the typical low CKA cells.

Protein	log2 (High CKA/Typical)	p-value (t-test)
GM2A	1.943649	7.66E-06
PLEC	0.855651	0.000199
CYBB	1.609576	0.00024
DOCK8	1.454172	0.000455
ATG7	1.163505	0.000737
SLC2A1	1.4505	0.001259
S100A9	1.435349	0.001681
ACSL1	1.065324	0.001746
CTSG	2.155855	0.002295
PSMB2	1.058384	0.002481
ATM	2.011409	0.002754
BCAP31	2.707073	0.003322
S100A8	0.699763	0.003776
ITGB1	1.143777	0.005138
TAPBP	1.277103	0.005596
COMP	0.99287	0.005695
SYK	1.722188	0.006851
GZMK	1.8696069	0.040591
IKBKB	2.2958852	0.017181
PPP3CB	-1.36037	0.000127
ANXA1	-1.17725	0.000792
PERM	2.00962408	0.0379030
RAC1	1.9456240	0.0100812
CAP37	2.70390702	0.01459156

The results are presented graphically in Figures 2-6 for a number of the proteins, including two-way ANOVA statistical analyses. Advantageously, said protein levels (and thus gene expression levels) provided a robust means for identifying and differentiating high CKA cells from low CKA cells.

Advantageously, the expression of many of the genes (i.e. at the protein level) was highly statistically-significantly different (e.g. GM2A) between high CKA cells and low CKA cells, indicating that high CKA granulocytes could be identified using just one of the indicated genes.

All publications mentioned in the above specification are herein incorporated by reference. Various modifications and variations of the described methods and system of the present

invention will be apparent to those skilled in the art without departing from the scope and spirit of the present invention. Although the present invention has been described in connection with specific preferred embodiments, it should be understood that the invention as claimed should not be unduly limited to such specific embodiments. Indeed, various modifications of the described modes for carrying out the invention which are obvious to those skilled in biochemistry and biotechnology or related fields are intended to be within the scope of the following claims.