

CELLS FOR TREATING INFECTIONS

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

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Pathogens such as bacteria, fungi and viruses cause a multitude of diseases, many of which are contagious and life threatening. The majority of infections are currently treated with antimicrobial drugs (e.g. chemical substances), which generally act by fatally disrupting a cellular/molecular process of the pathogen.

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For example, antibiotics have been used in the treatment of bacterial infections for over 100 years, many of which disrupt DNA or protein synthesis of target bacteria. These antibiotics typically act on multiplying bacteria and have little efficacy against non-multiplying bacteria or persister cells, and therefore fail to clear the whole bacterial population. As a result, longer durations of antibiotic therapy are required, exacerbating the emergence of antibiotic resistance. This increasing emergence of antibiotic resistance has resulted in infectious disease becoming the second leading cause of mortality in the world, with drug-resistant bacteria killing approximately 25,000 people per year in Europe alone.

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This rise in antibiotic resistance has not been offset by an increase in the availability of new antibiotics, as the discovery and synthesis of new antibiotics has proven notoriously difficult. The same is true of chemical drugs which target other types of pathogen (e.g. anti-fungal and anti-viral agents). Furthermore, these drugs are generally very specific in nature, requiring the appropriate drug treatment and dosage to be identified for each type of infection, such that very few therapies are suitable for treating a multitude of infectious diseases.

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There therefore exists a need for alternative therapies for the treatment of infectious diseases, which overcome the issues of drug (e.g. antibiotic) resistance and new infectious strains for which there are no therapies or vaccinations currently available (e.g. new viruses) and which can be employed in the treatment of various infectious diseases. There also exists a need for methods of identifying and producing such therapies.

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The present invention addresses one or more of the above mentioned problems.

The present invention is predicated on the surprising finding that granulocytes can be isolated that have particular efficacy in the treatment of infections and/or overcome/reduce

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the need for conventional therapeutics, such as chemical antibiotics, against which pathogens are becoming increasingly resistant.

Thus, in one aspect the invention provides a granulocyte of the invention for use in treating an infection. In a related aspect, the invention also provides use of a granulocyte of the invention in the manufacture of a medicament for treating an infection as well as a method for treating an infection, the method comprising administering to a subject in need thereof the granulocyte according to the invention.

Granulocytes, such as neutrophils, generally act by ingesting and killing microorganisms or dying cells, or by secreting toxic proteins. They can recognise and kill both bacteria and fungi (e.g. following recognition through the presence of Pathogen Recognition Receptors (PRRs)), as well as viruses and larger (e.g. macroparasitic) pathogens such as helminths ("worms"). Thus, the generic modes of action of granulocyte cells make them particularly suitable for combating a variety of pathogen types (and thus a variety of infections/infectious diseases).

The present inventors have demonstrated the utility of granulocytes for killing different types of bacteria (both Gram negative and Gram positive). Advantageously, the granulocytes of the invention show improved efficacy against antibiotic-resistant (e.g. multiple antibiotic-resistant) bacteria. Moreover, the inventors have surprisingly shown that such granulocytes kill bacteria more rapidly than conventional chemical antibiotics.

Antibiotic resistance represents one of the largest public health concerns globally. An example of an antibiotic resistant bacterium is methicillin-resistant *Staphylococcus aureus* (MRSA), which has acquired resistance to a number of antibiotics (e.g. multiple drug resistance to beta-lactam antibiotics). Surprisingly, the present inventors have succeeded in providing granulocytes (and stem cells that differentiate into granulocytes) that have particular efficacy against MRSA.

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In one aspect, there is provided a method for producing a granulocyte for treating an infection, the method comprising:

- a. providing a stem cell obtainable from a sample from a donor, wherein a granulocyte of the donor kills a greater % of infective agents or cells infected by an infective agent when compared to a control;
- b. differentiating the stem cell into a granulocyte; and

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- c. optionally isolating the granulocyte.

In another aspect, there is provided a method for producing a stem cell for treating an infection, the method comprising:

- 5 a. providing a stem cell obtainable from a sample from a donor, wherein a granulocyte of the donor kills a greater % of infective agents or cells infected by an infective agent when compared to a control;
- b. differentiating the stem cell into a different stem cell (preferably a precursor cell); and
- 10 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.

- 15 A control sample for use in a method of the invention may be a sample comprising granulocytes from a donor that has granulocytes that are unsuitable for treating an infection (e.g. granulocytes that do not kill greater than 41.23% of the infective agent or cells infected by an infective agent in a method/assay described herein). In other embodiments, the control sample referred to may be a sample comprising granulocytes from a donor that has
- 20 granulocytes that are suitable for treating an infection (e.g. granulocytes that do kill greater than 41.23% of the infective agent or cells infected by an infective agent in a method/assay described herein), in which case the method may be used to detect donors having granulocytes with optimal therapeutic activity. Preferably, a control sample for use in a method of the invention is a sample comprising granulocytes from a donor that has
- 25 granulocytes that are unsuitable for treating an infection.

Preferably, the control sample comprises an infective agent or cells infected by an infective agent of the same type and a granulocyte obtainable from a different donor or wherein the granulocyte kills greater than 41.23% of the infective agent or cells infected by an infective

30 agent in an admixture.

Another aspect provides a method for selecting a granulocyte for treating an infection, said method comprising:

- 35 a. contacting an infective agent or a cell infected by an infective agent with a granulocyte obtainable from a donor to form a test sample, and incubating said test sample; and

- b. obtaining a granulocyte from a sample from said donor when the % of infective agent or cells infected by an infective agent killed in the test sample is greater than the % of infective agent or cells infected by an infective agent killed in a control sample, wherein the control sample comprises an infective agent or cells infected by an infective agent of the same type and a granulocyte obtainable from a different donor.

In another aspect, there is provided an *in vitro* method for obtaining a granulocyte for treating an infection, said method comprising obtaining a granulocyte from a sample obtainable from a donor wherein said donor produces granulocytes for treating an infection.

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In one embodiment a granulocyte is obtained from a sample from said donor when the % of infective agent or cells infected by an infective agent killed in the test sample is at least 5% greater than the % of infective agent or cells infected by an infective agent killed in the control sample. In some embodiments the % of infective agent or cells infected by an infective agent killed in the test sample is at least 10%, 15%, 20%, 25%, 30%, 40%, 50%, 60%, 70% or 80% greater than the % of infective agent or cells infected by an infective agent killed in the control sample. The skilled person would appreciate that reference to "kill", "killing an infective agent", "an infective agent killed" or the like encompasses "inactivate", "inactivating an infective agent" or "an infective agent inactivated" or the like.

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The methods of the invention may comprise the use of an infective agent or cells infected by an infective agent. In a preferred embodiment, methods of the invention comprise the use of an infective agent.

In one embodiment a granulocyte is produced when the % of infective agent or cells infected by an infective agent killed in the sample from a donor is at least 5% greater than the % of infective agent or cells infected by an infective agent killed in the control sample. In some embodiments the % of infective agent or cells infected by an infective agent killed in the test sample is at least 10%, 15%, 20%, 25%, 30%, 40%, 50%, 60%, 70% or 80% greater than the % of infective agent or cells infected by an infective agent killed in the control sample. The control sample preferably comprises an infective agent or cells infected by an infective agent of the same type and a granulocyte obtainable from a different donor.

Reference to "treating an infection" embraces alleviating the symptoms of an infection.

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In a further finding, the present inventors have surprisingly found that it is possible to select for stem cells (e.g. haematopoietic stem cells) that are capable of differentiating into granulocytes having the ability to kill pathogens (e.g. bacteria). Once such a stem cell (e.g. haematopoietic stem cell) has been selected from a donor, said cell can be either stored for subsequent therapeutic purposes, or used directly as a medicament, for example in the treatment of an infection. Advantageously stem cells (e.g. haematopoietic stem cells) obtainable by such a method of the invention can be immortalised thus providing a stable cell line that can be stored and/or propagated indefinitely. The present invention thus reduces the need for multiple rare donors, and/or for direct transfer of granulocytes collected from a donor to an infected patient. Thus the invention provides a viable, scalable, safe and/or reliable therapy.

For the first time, the present inventors have shown that the infective agent (e.g. bacteria) killing efficacy of granulocytes (e.g. neutrophils) is genetically-defined, rather than epigenetically-defined. In particular, it has been shown that granulocytes derived from stem cells (e.g. haematopoietic stem cells) isolated from a donor (who produces granulocytes suitable for treating an infection) have greater infective agent killing efficacy than mature granulocytes isolated directly from the same donor.

Advantageously, donors found to have granulocytes with a high infective agent killing activity can be used as a source of stem cells (e.g. haematopoietic stem cells) which can be differentiated into granulocytes with similarly high infective agent killing activity.

Such stem cells can advantageously be stored, and used for the production of high volumes of granulocytes for use in treating infections, thus overcoming problems of isolating sufficient quantities of fresh granulocytes from a donor.

Thus, a further aspect of the invention provides a method for obtaining a stem cell for treating an infection, said method comprising:

- a. contacting an infective agent or cell infected by an infective agent with a granulocyte obtainable from a donor to form a test sample, and incubating said test sample; and
- b. obtaining a stem cell from a sample from said donor when the % of infective agent or cells infected by an infective agent killed in the test sample is greater than the % of pathogens or pathogen-infected cells killed in a control sample, wherein the control sample comprises an infective agent or cells infected by an infective agent of the same type and a granulocyte obtainable from a different donor.

In another aspect, there is provided an *in vitro* method for obtaining a stem cell for treating an infection, said method comprising obtaining a stem cell from a sample obtainable from a donor wherein said donor produces granulocytes for treating an infection.

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In one embodiment a stem cell is obtained when the % of infective agent or cells infected by an infective agent killed in the sample from a donor is at least 5% greater than the % of infective agent or cells infected by an infective agent killed in the control sample. In some embodiments the % of infective agent or cells infected by an infective agent killed in the test sample is at least 10%, 15%, 20%, 25%, 30%, 40%, 50%, 60%, 70% or 80% greater than the % of infective agent or cells infected by an infective agent killed in the control sample.

The skilled person understands that where the methods of the invention comprise a comparison step between two samples (e.g. between a "test sample" and a "control sample") that conditions (e.g. assay conditions during the method) should be kept consistent. For example, the concentration ratio of granulocytes to infective agent or cells infected by an infective agent should be the same, as should the time conditions, etc. Where a comparison is made between two samples herein, suitably the samples are equivalent. For example, the samples being compared may be the same sample types (e.g. blood) and subjected to the same processing steps. In some embodiments the only difference between samples is the donor from which said samples are obtained. For example, in embodiments where the proportion of cells having a particular property is being determined, the total number of cells in each sample may be the same so that a proper comparison can be made.

The % of infective agent or cells infected by an infective agent killed in a control may be determined either prior to carrying out the present method or at the same time as carrying out the present method (preferably at the same time).

In some embodiments the method may comprise the use of a plurality of different test samples comprising granulocytes from further donors (e.g. second, third, fourth donors, etc.).

According to one aspect, there is provided a method for obtaining a stem cell for treating an infection, said method comprising:

- a. admixing a granulocyte obtainable from a donor with an infective agent or cells infected by an infective agent to form an admixture;
- b. incubating said admixture;

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c. measuring the % of infective agent or cells infected by an infective agent killed in said admixture; and

d. obtaining a stem cell from a sample from said donor when said granulocyte kills greater than 41.23% of the infective agent or cells infected by an infective agent in the admixture (suitably when the granulocyte from said subject kills at least 60%, preferably at least 80% or 90%, of the infective agent or cells infected by an infective agent in the test sample).

In a related aspect there is provided a method for selecting a granulocyte for treating an infection, said method comprising:

a. admixing a granulocyte with an infective agent or cells infected by an infective agent;

b. incubating said admixture;

c. measuring the % of infective agent or cells infected by an infective agent killed in said admixture; and

d. selecting a granulocyte that kills greater than 41.23% of the infective agent or cells infected by an infective agent in the admixture (suitably when the granulocyte from said subject kills at least 50% or 60%, preferably at least 80% or 90%, of the infective agent or cells infected by an infective agent in the test sample).

In one embodiment an infection is an infection with an infective agent (used synonymously herein with the term "infectious agent"). An infective agent may refer to a bacterium, a fungus, a virus, a macroparasite (e.g. a helminth), or a combination thereof. Preferably, an infective agent is a bacterium or a virus. For example, in one embodiment, an infective agent is a bacterium. In an alternative embodiment, an infective agent is a virus. In a preferred embodiment an infective agent is a pathogen.

Thus, in one embodiment the infection is one or more selected from bacterial, fungal, viral, macroparasitic, or a combination thereof (preferably bacterial).

As used herein the term "pathogen" refers to a microorganism that can cause disease and may also encompass opportunistic pathogens. The pathogen may be one or more selected from a pathogenic bacterium, a pathogenic fungus, a pathogenic virus, a pathogenic macroparasite (e.g. a pathogenic helminth), or a combination thereof. Preferably, the pathogen is a pathogenic bacterium or a pathogenic virus. For example, in one embodiment

the pathogen is a pathogenic bacterium. In an alternative embodiment, the pathogen is a pathogenic virus.

As used herein, a “cell infected by an infective agent” refers to a cell that is infected by an intracellular infective agent. Said intracellular infective agent is preferably a pathogen and the cell is therefore a “cell infected by a pathogen”. In one embodiment a cell may be infected by an intracellular bacterium or a virus, preferably a virus.

In one embodiment an infective agent is a Gram-negative bacterium or a Gram-positive bacterium. Preferably, an infective agent is a Gram-positive bacterium, such as a bacterium from the genus *Staphylococcus*.

A bacterium may be selected from one or more of *Staphylococcus* spp., multidrug resistant gram-negative bacteria (MRDGN bacteria), vancomycin-resistant *Enterococcus* (VRE), *Mycobacterium* spp., carbapenem-resistant *Enterobacteriaceae* (CRE) gut bacteria, *Acinetobacter* spp., *Actinomyces* spp., *Propionibacterium* spp., *Anaplasma* spp., *Bacillus* spp., *Arcanobacterium* spp., *Bacteroides* spp., *Bartonella* spp., *Brucella* spp., *Yersinia* spp., *Burkholderia* spp., *Campylobacter* spp., *Streptococcus* spp., *Haemophilus* spp., *Clostridium* spp., *Corynebacterium* spp., *Echinococcus* spp., *Ehrlichia* spp., *Enterococcus* spp., *Rickettsia* spp., *Fusobacterium* spp., *Neisseria* spp., *Klebsiella* spp., *Helicobacter* spp., *Escherichia* spp., *Kingella* spp., *Legionella* spp., *Listeria* spp., *Borrelia* spp., *Mycoplasma* spp., *Chlamydia* spp., *Nocardia* spp., *Pasteurella* spp., *Bordetella* spp., *Prevotella* spp., *Chlamydophila* spp., *Coxiella* spp., *Salmonella* spp., Group A *Streptococcus* spp., *Shigella* spp., *Staphylococcus* spp., *Treponema* spp., *Vibrio* spp., *Francisella* spp., *Pseudomonas* spp. and *Ureaplasma* spp.

In one embodiment the bacterium is selected from one or more of methicillin resistant *Staphylococcus aureus* (MRSA), multi-drug resistant *Mycobacterium tuberculosis* (MDR-TB), *Pseudomonas aeruginosa*, *Pseudomonas oryzae*, *Pseudomonas plecoglossicida*, *Acinetobacter baumannii*, *Actinomyces israelii*, *Actinomyces gerencseriae*, *Propionibacterium propionicus*, *Bacillus anthracis*, *Arcanobacterium haemolyticum*, *Bacillus cereus*, *Yersinia pestis*, *Mycobacterium ulcerans*, *Campylobacter jejuni*, *Bartonella bacilliformis*, *Bartonella henselae*, *Haemophilus ducreyi*, *Clostridium difficile*, *Corynebacterium diphtheria*, *Burkholderia mallei*, *Neisseria gonorrhoeae*, *Klebsiella granulomatis*, *Streptococcus pyogenes*, *Streptococcus agalactiae*, *Haemophilus influenzae*, *Helicobacter pylori*, *Escherichia coli* (e.g. O157:H7, O111 and O104:H4), *Kingella kingae*,

Legionella pneumophila, *Listeria monocytogenes*, *Burkholderia pseudomallei*, *Neisseria meningitidis*, *Mycoplasma pneumoniae*, *Mycoplasma genitalium*, *Chlamydia trachomatis*, *Bordetella pertussis*, *Streptococcus pneumoniae*, *Chlamydophila psittaci*, *Coxiella burnetii*, *Treponema pallidum*, *Clostridium tetani*, *Chlamydophila pneumoniae*, *Vibrio cholera*,
 5 *Mycobacterium tuberculosis*, *Salmonella enterica* subsp. *enterica*, serovartyphi, *Ureaplasma urealyticum*, and *Francisella tularensis*. Preferably *Mycobacterium tuberculosis*.

Preferably, in one embodiment the bacterium is selected from one or more of methicillin resistant *Staphylococcus aureus* (MRSA), multidrug resistant gram-negative bacteria
 10 (MRDGN bacteria), vancomycin-resistant *Enterococcus* (VRE), multi-drug resistant *Mycobacterium tuberculosis* (MDR-TB), and carbapenem-resistant *Enterobacteriaceae* (CRE) gut bacteria.

A virus may be selected from one or more family selected from Adenoviridae, Picornaviridae,
 15 Herpesviridae, Coronaviridae, Hepadnaviridae, Flaviviridae, Retroviridae, Orthomyxoviridae, Paramyxoviridae, Papovaviridae, Polyomavirus, Rhabdoviridae, Togaviridae and Bunyaviridae.

In one embodiment the virus may be selected from one or more of HIV-1 (Human
 20 immunodeficiency virus), HIV-2, Junin virus, BK virus, Machupo virus, Sabiá virus, Varicella zoster virus (VZV), Alphavirus, Colorado tick fever virus (CTFV), Rhinoviruses, Crimean-Congo hemorrhagic fever virus, Cytomegalovirus, Dengue virus, Ebolavirus (EBOV), Parvovirus B19, Human herpesvirus 6 (HHV-6), Human herpesvirus 7 (HHV-7), Enteroviruses (e.g. EV71), Coxsackie A virus, Sin Nombre virus, Heartland virus, Hanta
 25 virus, Hendra virus, Hepatitis A virus, Hepatitis B virus, Hepatitis C virus, Hepatitis D Virus, Hepatitis E virus, Herpes simplex virus 1 and 2 (HSV-1 and HSV-2), Human bocavirus (HBoV), Human metapneumovirus (hMPV), Human papillomaviruses, Human parainfluenza viruses (HPIV), Epstein–Barr virus (EBV), Lassa virus, Lymphocytic choriomeningitis virus (LCMV), Marburg virus, Measles virus, Middle East respiratory syndrome coronavirus,
 30 Molluscum contagiosum virus (MCV), Monkeypox virus, Mumps virus, Nipah virus, Norovirus, Poliovirus, JC virus, Respiratory syncytial virus (RSV), Rhinovirus, Rift Valley fever virus, Rotavirus, Rubella virus, SARS coronavirus, SARS-CoV-2, Variola major, Variola minor, Venezuelan equine encephalitis virus, Guanarito virus, West Nile virus, Yellow fever virus, and Zika virus.

A fungus may be selected from one or more of *Aspergillus* spp., *Piedraia* spp., *Blastomyces* spp., *Candida* spp., *Fonsecaea* spp., *Coccidioides* spp., *Cryptococcus* spp., *Cryptosporidium* spp., *Geotrichum* spp., *Histoplasma* spp., *Microsporidia* phylum, *Paracoccidioides* spp., *Pneumocystis* spp., *Sporothrix* spp., *Trichophyton* spp., *Epidermophyton* spp., *Hortaea* spp.,
 5 *Malassezia* spp., *Trichosporon* spp., and *Mucorales* order.

In one embodiment the pathogen is a fungus selected from one or more of *Aspergillus fumigatus*, *Aspergillus flavus*, *Piedraia hortae*, *Blastomyces dermatitidis*, *Candida albicans*, *Fonsecaea pedrosoi*, *Coccidioides immitis*, *Coccidioides posadasii*, *Cryptococcus*
 10 *neoformans*, *Geotrichum candidum*, *Histoplasma capsulatum*, *Paracoccidioides brasiliensis*, *Pneumocystis jirovecii*, *Sporothrix schenckii*, *Trichophyton tonsurans*, *Epidermophyton floccosum*, *Hortaea werneckii*, and *Trichosporon beigeli*.

A macroparasite may be one or more selected from *Angiostrongylus* spp., *Entamoeba*
 15 *Anisakis* spp., *Ascaris* spp., *Babesia* spp., *Balantidium* spp., *Baylisascaris* spp., *Blastocystis* spp., *Capillaria* spp., *Trypanosoma* spp., *Clonorchis* spp., *Ancylostoma* spp., *Cyclospora* spp., *Taenia* spp., *Desmodesmus* spp., *Dientamoeba* spp., *Dracunculus* spp., *Enterobius* spp., *Fasciola* spp., *Filarioidea* superfamily, *Giardia* spp., *Gnathostoma* spp., *Necator* spp.,
 20 *Hymenolepis* spp., *Isospora* spp., *Leptospira* spp., *Wuchereria* spp., *Rhinosporidium* spp., *Brugia* spp., *Plasmodium* spp., *Onchocerca* spp., *Opisthorchis* spp., *Paragonimus* spp., *Naegleria* spp., *Schistosoma* spp., *Strongyloides* spp., *Toxocara* spp., *Toxoplasma* spp., *Trichinella* spp., *Trichomonas* spp., and *Trichuris* spp.

In one embodiment the macroparasite is selected from one or more of *Entamoeba*
 25 *histolytica*, *Ascaris lumbricoides*, *Balantidium coli*, *Trypanosoma brucei*, *Trypanosoma cruzi*, *Clonorchis sinensis*, *Cyclospora cayetanensis*, *Taenia solium*, *Desmodesmus armatus*, *Dientamoeba fragilis*, *Dracunculus medinensis*, *Enterobius vermicularis*, *Fasciolopsis buski*, *Giardia lamblia*, *Necator americanus*, *Hymenolepis nana*, *Hymenolepis diminuta*, *Isospora belli*, *Wuchereria bancrofti*, *Rhinosporidium seeberi*, *Brugia malayi*, *Plasmodium vivax*,
 30 *Plasmodium falciparum*, *Plasmodium malariae*, *Plasmodium ovale*, *Plasmodium knowlesi*, *Onchocerca volvulus*, *Opisthorchis viverrini*, *Opisthorchis felinus*, *Naegleria fowleri*, *Strongyloides stercoralis*, *Toxoplasma gondii*, *Trichinella spiralis*, *Trichuris trichiura*, and *Trichomonas vaginalis*.

In one embodiment, the infective agent is an antibiotic-resistant bacterium (e.g. MRSA), preferably a multi-antibiotic resistant bacterium. An antibiotic resistant bacterium may be resistant to beta-lactams, such as methicillin.

- 5 Antibiotic resistance may be assessed using any technique known in the art, such as the Kirby-Baure method, Stokes method, Etest, and/or agar and broth dilution methods for minimum inhibitory concentration (MIC) determination.

- 10 In one embodiment a bacterium is resistant to one or more of a penicillin, a penicillinase-resistant penicillin, a cephalosporin, a beta-lactamase inhibitor, a tetracycline and combinations thereof, or pharmaceutically acceptable salts thereof.

- 15 In one embodiment a bacterium is resistant to one or more of: vancomycin, nafcillin, oxacillin, teicoplanin, penicillin, methicillin, flucloxacillin, dicloxacillin, cefazolin, cephalothin, cephalexin, cefuroxime, clindamycin, cefazolin, amoxicillin/clavulanate, ampicillin/sulbactam, lincomycin, erythromycin, trimethoprim, sulfamethoxazole, daptomycin, linezolid, rifampin, ciprofloxacin, gentamycin, tetracycline, doxycycline, minocycline, tigecycline and combinations thereof or pharmaceutically acceptable salts thereof. In one embodiment a bacterium may be resistant to vancomycin and/or teicoplanin, or pharmaceutically acceptable salts thereof.
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A multi-antibiotic resistant bacterium is resistant to at least 2, 3, 4, 5, 6, 7, 8, 9 or 10 antibiotics (e.g. chemical antibiotics).

- 25 In one embodiment, a granulocyte or stem cell of the invention kills an infective agent by phagocytosing a cell infected by the infective agent. For example, in one embodiment, a granulocyte or stem cell of the invention kills a virus by phagocytosing a cell infected by the virus. In one embodiment, a granulocyte or stem cell of the invention kills a bacterium by phagocytosing a cell infected by the bacterium. In one embodiment, a granulocyte or stem cell of the invention kills an infective agent by releasing one or more factors which kill the infective agent. For example, in one embodiment, a granulocyte or stem cell of the invention kills a virus by releasing one or more factors which kill the virus. In one embodiment, a granulocyte or stem cell of the invention kills a bacterium by releasing one or more factors which kill the bacterium. In some embodiments, a granulocyte or stem cell of the invention kills an infective agent by a combination of the above.
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In one embodiment the invention provides a method for selecting a granulocyte suitable for treating multi-antibiotic resistant *Pseudomonas aeruginosa*, said method comprising:

- a. admixing a granulocyte with multi-antibiotic resistant *Pseudomonas aeruginosa* cells to form an admixture;
- b. incubating said admixture;
- c. measuring the % of multi-antibiotic resistant *Pseudomonas aeruginosa* cells killed in said admixture; and
- d. selecting a granulocyte that kills greater than 41.23% of the multi-antibiotic resistant *Pseudomonas aeruginosa* cells in the admixture.

In one embodiment a method comprises selecting a granulocyte that kills at least 50%, 60%, 70% or 80% of the multi-antibiotic resistant *Pseudomonas aeruginosa* cells in the admixture.

- Preferably, the invention provides a method for selecting a granulocyte suitable for treating MRSA, said method comprising:
- a. admixing a granulocyte with MRSA cells to form an admixture;
 - b. incubating said admixture;
 - c. measuring the % of MRSA cells killed in said admixture; and
 - d. selecting a granulocyte that kills greater than 41.23% of the MRSA cells in the admixture.

In one embodiment a method comprises selecting a granulocyte that kills at least 50%, 60% or 70% of the MRSA cells in the admixture.

- The incubation step or contacting between a granulocyte and an infective agent/infective agent-infected cell may be carried out for between 1 hour and 100 hours. Preferably, the incubation step or contacting between a granulocyte and an infective agent/infective agent-infected cell may be carried out for between 5 hours and 75 hours, for example between 10 hours and 20 hours. The incubation step or contacting between a granulocyte and an infective agent/infective agent-infected cell may be carried out for between 6 hours to 6 days. Suitably, the incubation step or contacting between a granulocyte and an infective agent/infective agent-infected cell 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 or contacting between a granulocyte and an infective agent/infective agent-

infected cell is carried out for 48 hours. The incubation step or contacting between a granulocyte and an infective agent/infective agent-infected cell 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 or contacting between a granulocyte and an infective agent/infective agent-infected cell step is carried out at 37 or 39 °C for 24 hours. Preferably the incubation step or contacting between a granulocyte and an infective agent/infective agent-infected cell is carried out for 16-24 hours at 30-40 °C (e.g. 37°C).

- 10 The above-mentioned conditions may be particularly suitable when incubating/contacting a granulocyte with a cell infected by an infective agent.

The incubation step or contacting between a granulocyte and an infective agent/infective agent-infected cell may be carried out for between 30 minutes and 24 hours (e.g. prior to assessing % killing). Preferably, the incubation step or contacting between a granulocyte and an infective agent/infective agent-infected cell may be carried out for between 1-3 hours, for example for 2 hours. In other words, the assessment of % killing may be determined following contacting/incubating for 2 hours. The incubation step or contacting between a granulocyte and an infective agent/infective agent-infected cell 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 °C.

The above-mentioned conditions may be particularly suitable when incubating/contacting a granulocyte with an infective agent, such as a bacterium.

25 In one embodiment a contacting or incubation step is carried out in solution. In other words, the infective agent or cells infected with an infective agent may be growing in solution (i.e. not adhered to/growing on a surface, such as a surface of a plate).

30 Preferably, where the infective agent is a bacterium a contacting or incubation step is carried out in solution. In contrast, where the method employs cells infected with an infective agent it is preferred that said cells are growing on or adhered to a surface, such as a surface of a plate.

35 In one embodiment said contacting or incubation step is carried out under agitation, e.g. at 100-250 rpm, such as 120 rpm.

In one embodiment, where the method employs cells infected with an infective agent, the methods of the invention may comprise the use of at least a 1:1, 5:1 or 10:1 ratio of granulocytes to cells. Preferably the methods comprise the use of a 5:1 ratio of granulocytes
5 to cells. More preferably the methods comprise the use of a 10:1 ratio of granulocytes to cells.

The % of cells killed can be measured by reference to the total number of starting cells. The number of cells killed can be measured using any suitable means, for example by viability
10 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 cells killed may be determined within 24 hours (e.g. of incubating a cell and a granulocyte). The % of cells killed is preferably the maximum number
15 of cells killed when carrying out a method of the invention.

The number of 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
20 continuously by measuring electrical impedance. Such measurements may be carried out as detailed in the Examples. Said System is commercially available from ACEA Biosciences 6779 Mesa Ridge Road #100, San Diego, CA 92121 USA.

In one embodiment, where an infective agent is a bacterium, a ratio of at least 1:10, 1:5, 1:3
25 or 1:2 granulocytes to colony forming units may be used. Preferably a 1:2 ratio of granulocytes to colony forming units is used. More preferably a 1:1 ratio of granulocytes to colony forming units is used.

In one embodiment a method of the invention further comprises obtaining a stem cell from a
30 sample from a donor from whom a selected granulocyte is obtainable.

Furthermore, the present inventors have surprisingly identified a number of genes (and expression levels thereof) that are associated with a granulocyte's suitability for treating an infection. Advantageously, the expression levels of such genes can be determined using
35 transcriptomic or proteomic 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 an infection (e.g. where at least 90% of the granulocytes present are granulocytes suitable for treating an infection).

In one aspect the present invention provides a method for determining the suitability of a granulocyte for treating an infection, 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 an infection 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 an infection 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 an infection, 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 an infection 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 an infection based on the comparison.

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

- 5 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 an infection 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
- 10 b. identifying whether or not the donor produces granulocytes suitable for treating an infection based on the comparison.

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

- 15 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 an infection 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*;
- 20 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 an infection based on the comparison.

- 25 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
- 30 statistically-significantly different between granulocytes that are suitable for treating an infection and granulocytes that are unsuitable for treating an infection. 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
- 35 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.

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

10 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 an infection. In one embodiment a donor may be selected if said donor is a female. In another embodiment a donor may be selected if said donor is above the age of 40. Suitably, a donor may be selected if said donor is a female above the age of 40. Without wishing to be bound by theory, it is believed that females over 40 have a higher likelihood of producing granulocytes (e.g. neutrophils) that are suitable for treating an infection.

20 In one embodiment, a donor may be selected if said donor has been exposed to (e.g. vaccinated against) an infection of interest. For example, when obtaining a granulocyte or stem cell suitable for treating a viral infection (e.g. a Coronaviridae infection), a donor may be selected if said donor has been exposed to (or vaccinated against) the viral infection (e.g. the Coronaviridae infection) of interest. In one embodiment, a donor may be selected if said donor has developed immunity against the infection of interest. For example, when obtaining a granulocyte or stem cell suitable for treating a viral infection (e.g. a Coronaviridae infection), a donor may be selected if said donor has developed immunity against the viral infection (e.g. the Coronaviridae infection) of interest.

30 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.

35 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 SNPs, promoter sequences, gene copy number (e.g. duplications), and/or enhancers 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
5 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
10 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
15 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.

20 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
25 spectrometry, e.g. liquid chromatography and mass spectrometry (LC-MS/MS).

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

30

Thus, in one embodiment a method of the invention comprises measuring 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,
35 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 proteins 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.

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

5 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.

10 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.

15 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.

20 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
25 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
30 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/ is determined by RNA sequencing (RNA-Seq), e.g. *in toto*.

5 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.

10 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.

15 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.

25 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 an infection. Said genes are therefore referred to herein as genes associated with suitability for treating an infection. Thus, the term “one or more genes associated with suitability for treating an infection” (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*”.

35 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 an infection:

- a. locating and/or binding to an infective agent or a cell infected by an infective agent: *ANXA1*, *ATG7*, *ITGB1*, *SYK*, *DOCK8*, *CYBB*, *RAC1*, *CAP37*, *COMP*, and *PLEC*;
- b. killing an infective agent or a cell infected by an infective agent: *CYBB*, *SLC2A1*, *GZMK*, *CTSG*, *ATM*, *PERM*, *ACSL1*, *GM2A*, and *CAP37*; and/or
- 5 c. recruitment of immune mediators: *BCAP31*, *TAPBP*, *IKBKB*, *PPP3CB* and *PSMB2*.

In a preferred embodiment a method of the invention comprises measuring the expression of *ANXA1*. Advantageously, the inventors have shown that low levels of *ANXA1* expression are associated with high infective agent or infective agent-infected cell killing activity and
 10 therefore suitability for treating an infection. Without wishing to be bound by theory, it is believed 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 an infective agent or infective agent-infected cells.

15 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 an infection when compared to a granulocyte that is unsuitable for treating an infection. Alternatively or additionally, in one embodiment expression of *ANXA1* and/or *PPP3CB* is
 20 decreased in a granulocyte that is suitable for treating an infection when compared to a granulocyte that is unsuitable for treating an infection.

In one embodiment a method of the invention may further comprise measuring expression of one or more genes selected from: *S100A9* and *S100A8*. In one embodiment expression of
 25 *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 an infection.

In one embodiment a method of the invention comprises measuring and/or comparing
 30 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*,
 35 *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 an infection; 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 an infection.

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 an infection; 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 an infection.

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 an infection; 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 an infection.

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*,
5 *RAC1*, *GM2A*, and *PSMB2* when compared to a reference standard, wherein the reference standard is from a granulocyte unsuitable for treating an infection; or
decreased expression of *PPP3CB* when compared to a reference standard, wherein the reference standard is from a granulocyte unsuitable for treating an infection.

- 10 The term “for treating an infection” as used herein means “suitable for treating an infection”. In one embodiment a granulocyte that is “suitable for treating an infection” as used herein means that a granulocyte is capable of killing greater than 41.23% of MRSA strain USA300 cells in the “MRSA assay” described herein. In one embodiment a granulocyte is capable of
15 killing at least 50% (e.g. at least 60%) of MRSA strain USA300 cells in the “MRSA assay” described herein. Preferably a granulocyte is capable of killing at least 70% (e.g. at least 90% or 95%) of MRSA strain USA300 cells in the “MRSA assay” described herein. In one embodiment reference to a stem cell “for treating an infection” or that is “suitable for treating an infection” means that said stem cell is capable of differentiating into a granulocyte that is suitable for treating an infection.

- 20 In contrast, in one embodiment, a granulocyte that is “not suitable for treating an infection” or is “unsuitable for treating an infection” as used herein is a granulocyte that is not capable of killing greater than 41.23% of MRSA strain USA300 cells in the “MRSA assay” described herein, i.e. a granulocyte that kills less than or equal to 41.23% of MRSA strain USA300 cells
25 in the “MRSA assay” described herein. In one embodiment a granulocyte that is “not suitable for treating an infection” or is “unsuitable for treating an infection” is a granulocyte that is not capable of killing at least 50% (e.g. at least 60%) of MRSA strain USA300 cells in the “MRSA assay” described herein, i.e. a granulocyte that kills less than 50% (e.g. less than 60%) of MRSA strain USA300 cells in the “MRSA assay” described herein. Likewise, in one
30 embodiment, reference to a stem cell “not suitable for treating an infection” or that is “unsuitable for treating an infection” means that said stem cell is not capable of differentiating into a granulocyte that is suitable for treating an infection and/or that differentiates into a granulocyte that is unsuitable for treating an infection.

- 35 The “MRSA assay” is carried out as follows:

- a. admixing 100 μ l of a 1×10^7 CFU/ml solution of MRSA strain USA300 in RPMI 1640 with 100 μ l of a solution containing 1×10^7 granulocytes/ml;
- b. incubating the admixture at 37 °C under shaking at 120 rpm;
- c. taking a sample at 2 hours (diluting in sterile RPMI as needed) and plating on Tryptic Soy Agar;
- d. incubating the plated sample at 37 °C for 24 hours;
- e. counting the bacterial colonies; and
- f. quantifying the total CFU content; and
- g. calculating the % of MRSA cells killed based on the CFU content in steps a. and f using the formula $((\text{CFU content}_{\text{no effector}} - \text{CFU content}_{\text{effector}})/\text{CFU content}_{\text{no effector}}) \times 100$.

In a particularly preferred embodiment the term “suitable for treating an infection” as used herein further means that a granulocyte kills less than 15% of healthy (non-infected) cells in the “healthy (non-infected) cell assay” described herein. Preferably a granulocyte kills less than 10% (e.g. less than 5% or less than 1%) of healthy (non-infected) cells in the “healthy (non-infected) cell assay” described herein.

The “healthy (non-infected) cell assay” is carried out using an ACEA Biosciences xCELLigence RTCA DP Analyzer system® according to the manufacturer’s instructions and as follows:

- a. 6000 healthy (non-infected) 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-pathogen-infected cells) and incubated at 37 °C; and
- d. the % of healthy (non-infected) cells killed is the maximum % of non-pathogen-infected cells killed by 48 hours after the addition of the granulocytes as determined using the following formula: $((\text{Cell Index}_{\text{no effector}} - \text{Cell Index}_{\text{effector}})/\text{Cell Index}_{\text{no effector}}) \times 100$.

Preferably the healthy (non-infected) cells are MCF-12F, 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 healthy (non-infected) 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.

10 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. The sample may be any suitable biofluid sample 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
15 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
20 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 enhance 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
25 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
30 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.

35

A reference standard is preferably a reference standard for a granulocyte that is unsuitable for treating an infection (e.g. a transcriptomic or proteomic profile of a granulocyte that is unsuitable for treating an infection).

5 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 an infection. In one
10 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 an infection. 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
15 standard when the reference standard is from a granulocyte unsuitable for treating an infection 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 an infection.

A reference standard may be a reference standard for a granulocyte that is suitable for
20 treating an infection (e.g. a transcriptomic or proteomic profile of a granulocyte that is suitable for treating infection). 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
25 granulocyte suitable for treating an infection. 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 an infection.

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

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

In one embodiment a granulocyte is determined as being suitable for treating an infection 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 an infection; 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 an infection; 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 an infection; 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 an infection.
- In one embodiment a granulocyte is determined as being unsuitable for treating an infection 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 an infection; 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 an infection; 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 an infection; 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 an infection.

- 5 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 an infection, 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.

10

Accordingly, in one aspect, there is provided an *in vitro* method for obtaining a granulocyte for treating an infection, 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*,
15 *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 an infection; 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
20 treating an infection.

In a related aspect, there is provided an *in vitro* method for obtaining a stem cell for treating an infection, 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*,
25 *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 an infection; and/or
- b. decreased expression of *ANXA1* and/or *PPP3CB* when compared to a
30 reference standard, wherein the reference standard is from a granulocyte unsuitable for
treating an infection.

A method of the invention may comprise identifying whether or not a donor produces granulocytes suitable for treating an infection based on a comparison between a measured
35 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 an infection 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 an infection; 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 an infection; 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 an infection; 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 infection.

In one embodiment a donor is not identified as being a donor that produces granulocytes suitable for treating an infection (or is identified as a donor that produces granulocytes that are unsuitable for treating an infection) 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 an infection; 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 an infection; 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 an infection; 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 an infection.

5 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 an infection, a granulocyte may be obtained from a sample obtainable from said donor.

10 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 an infection
15 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 an infection, 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
20 reference standard is from a granulocyte unsuitable for treating an infection; and/or
b. decreased expression of *ANXA1* and/or *PPP3CB* when compared to a
25 reference standard, wherein the reference standard is from a granulocyte unsuitable for
treating an infection.

The term "obtainable" as used herein also encompasses the term "obtained". In one
30 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 an infection, wherein the granulocyte comprises:

- a. increased expression of one or more of *ITGB1*, *CYBB*, *SYK*, *DOCK8*, *COMP*,
35 *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 an infection; 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 an infection.

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 which are incorporated herein by reference.

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-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 for treating an infection, the method comprising:

- a. identifying a donor that produces granulocytes for treating an infection 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 an infection, 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 an infection; 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 an infection; 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).

5

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

10 In one aspect the invention provides a method for producing a granulocyte for treating an infection, the method comprising:

- a. providing a cell; and
- b. converting the cell into a granulocyte having an expression profile described herein, for example wherein:
 - 15 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 an infection; or
 - 20 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 an infection; or
 - 25 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 an infection; or
 - 30 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 an infection; and
- c. optionally isolating the granulocyte.

35 In one embodiment a method for producing a granulocyte for treating an infection 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 an infection; 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 an infection; 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 an infection; 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 an infection; 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 an infection 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 based on 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
5 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,
10 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
15 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-
20 beta.

The term "admix" as used herein means mixing one or more components together in any order, whether sequentially or simultaneously. The result of said admixing is an admixture. In one embodiment "admix" means contacting a first component with a second component
25 (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
30 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.

35 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 an infection, 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 an infection 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 an infection 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 an infection, 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 an infection 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 an infection based on the comparison.

5

The foregoing method allows for the identification of subjects who have granulocytes that are unsuitable for treating an infection 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.

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

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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 an infection; or

20

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 an infection; or

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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 an infection; or

30

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 an infection.

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

35

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 an infection; or

5 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 infection; or

10 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 an infection; or

15 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 an infection.

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

20 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 is CD11b high. Alternatively or additionally, the granulocyte may have a higher density than granulocytes unsuitable for treating an infection, and/or a positive cell surface charge (e.g. a net cell charge).

25 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.

30 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*;
- 5 thereby producing the engineered granulocyte, wherein the engineered granulocyte is suitable for treating an infection.

The granulocyte provided for use in the method is preferably a granulocyte that is unsuitable for treating an infection. Thus, in some embodiments a method of the invention converts a
10 cell that is unsuitable for treating an infection into a granulocyte that is suitable for treating an infection. 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). In some embodiments the engineered granulocyte may be used as a reference standard in a method of the invention (i.e. as a
15 reference standard from a granulocyte suitable for treating an infection).

The granulocyte provided for use in the method is preferably a granulocyte that is unsuitable for treating an infection. Thus, in some embodiments a method of the invention converts a
20 cell that is unsuitable for treating an infection into a granulocyte that is suitable for treating an infection. Said granulocyte may be identified by a method described herein and/or 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).

In a related aspect the invention provides a method for producing an engineered stem cell,
25 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*,
30 *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 an infection. 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
35 suitable for treating an infection).

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 an infection. 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 an infection).

- The stem cell provided for use in the method is preferably a stem cell that is unsuitable for treating an infection. Thus, in some embodiments a method of the invention converts a stem cell that is unsuitable for treating an infection into a stem cell that is suitable for treating an infection. 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).

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 an infection, a subject that is suitable for treatment with a granulocyte or stem cell of the invention, 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, 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 an infection 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

5 (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

10 *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 an infection in the

15 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 bacteria killing activity using a pre-validated gRNA targeting its exon. Lentiviral vectors may be prepared and suitable cells transduced

20 (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

25 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

30 lineage in stem cells and/or genes associated with suitability for treating an infection.

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

- a. increased expression of one or more of *ITGB1*, *CYBB*, *SYK*, *DOCK8*, *COMP*,
- 35 *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 an infection; 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 an infection.

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 an infection; 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 an infection.

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 an infection).

- 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 an infection. 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 infection killing activity of the granulocytes or stem cells. Accordingly, in some embodiments, the granulocyte or stem cell for treating an infection has not been activated *ex vivo*. For example, in some embodiments, the granulocyte or stem cell for treating an infection has not been activated *ex vivo* with flagellin. In some embodiments, the granulocyte or stem cell for treating an infection has not been activated *ex vivo* with a chemokine, cytokine or glucocorticoid. For example, in some embodiments, the granulocyte or stem cell for treating an infection has not been activated *ex vivo* with G-CSF. In some embodiments, the granulocyte or stem cell for treating an infection has not been activated *ex vivo* with prednisone. In some embodiments, the granulocyte or stem cell for treating an infection has not been activated *ex vivo* with the infective agent to be treated. For example, the granulocyte or stem cell for treating an infection may not have been activated *ex vivo* with the bacterium, virus, fungi, or pathogen of interest. In some embodiments, the granulocyte or stem cell for treating an infection has not been activated *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 some embodiments, the granulocyte or stem cell for treating an infection has not been activated *ex vivo* 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. Thus, in some embodiments, the granulocyte or stem cell for treating an infection 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 an infection *ex vivo*. For example, in some embodiments, the method does not comprise activating the granulocyte or stem cell for treating an infection *ex vivo* with flagellin. In some embodiments, the method does not comprise activating the granulocyte or stem cell for treating an infection *ex vivo* with a chemokine, cytokine or glucocorticoid. For example, in some embodiments, the method does not comprise activating the granulocyte or stem cell for treating an infection *ex vivo* with G-CSF. In some embodiments, the method does not comprise activating the granulocyte or stem cell for treating an infection *ex vivo* with prednisone. In some embodiments, the method does not comprise activating the granulocyte or stem cell for treating an infection *ex vivo* with a chemokine or cytokine. In some embodiments, the method does not comprise activating the granulocyte or stem cell for treating an infection *ex vivo* with the infective agent to be treated. For example, the method may not comprise activating the granulocyte or stem cell for treating an infection *ex vivo* with the bacterium, virus, fungi, or pathogen of interest. In some embodiments, the method does not comprise activating the granulocyte or stem cell for treating an infection 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 method does not comprise activating the granulocyte or stem cell for treating an infection 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. In some embodiments, the method does not comprise activating the granulocyte or stem cell for treating an infection *ex vivo* with IFN-gamma and GM-CSF.

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In alternative embodiments, the granulocyte or stem cell for treating an infection has been activated *ex vivo*. For example, in some embodiments, the granulocyte or stem cell for treating an infection has been activated *ex vivo* with flagellin. In some embodiments, the granulocyte or stem cell for treating an infection has been activated *ex vivo* with a chemokine, cytokine or glucocorticoid. For example, in some embodiments, the granulocyte or stem cell for treating an infection has been activated *ex vivo* with G-CSF. In some embodiments, the granulocyte or stem cell for treating an infection has been activated *ex vivo* with prednisone. In some embodiments, the granulocyte or stem cell for treating an infection has been activated *ex vivo* with a chemokine or cytokine. In preferred embodiments, the granulocyte or stem cell for treating an infection has been activated *ex vivo* with the infective agent to be treated. For example, the granulocyte or stem cell for treating an infection may have been activated *ex vivo* with the bacterium, virus, fungi, or pathogen of interest. In some embodiments, the granulocyte or stem cell for treating an infection 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 an infection has been activated with IFN-gamma and GM-CSF. In preferred embodiments, the granulocyte or stem cell for treating an infection has been activated with TNF-alpha. Thus, in some embodiments, the granulocyte or stem cell for treating an infection 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 an infection *ex vivo*. For example, in some embodiments, the method comprises activating the granulocyte or stem cell *ex vivo* with flagellin. In some embodiments, the method comprises activating the granulocyte or stem cell for treating an infection *ex vivo* with a chemokine, cytokine or glucocorticoid. For example, in some embodiments, the method comprises activating the granulocyte or stem cell for treating an infection *ex vivo* with G-CSF. In some embodiments, the method comprises activating the granulocyte or stem cell for treating an infection *ex vivo* with prednisone. In some

embodiments, the method comprises activating the granulocyte or stem cell for treating an infection *ex vivo* with a chemokine or cytokine. In preferred embodiments, the method comprises activating the granulocyte or stem cell for treating an infection *ex vivo* with the infective agent of interest. For example, the method may comprise activating the granulocyte or stem cell for treating an infection *ex vivo* with the bacterium, virus, fungi, or pathogen of interest. In some embodiments, the method comprises activating the granulocyte or stem cell for treating an infection 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 method comprises activating the granulocyte or stem cell for treating an infection 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. In some embodiments, the method comprises activating the granulocyte or stem cell for treating an infection *ex vivo* with IFN-gamma and GM-CSF.

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

25 In one embodiment granulocyte cell surface charge correlates with suitability for treating an infection, with granulocytes (e.g. neutrophils) that are more positively charged (or less negatively charged) being suitable for treating an infection and/or more efficacious in treating an infection. 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 an infection. In one embodiment a stem cell may be considered as suitable for treating an infection 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

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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 ($\text{SiO}_2\text{-OH}$) and creating the negative surface charge. Branched poly(ethylene imine) (PEI) molecules may be used to not only to cover the $\text{SiO}_2\text{-OH}$ 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 $\text{SiO}_2\text{-OH}$ 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 an infection may comprise:

- a. contacting an infective agent or cells infected with an infective agent with a granulocyte to form a test sample;
- b. incubating the test sample; and
- c. measuring the % of infective agent or cells infected with an infective agent 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 greater than 41.23% (e.g. at least 50%) of infective agent or cells infected with an infective agent in the test sample. In one embodiment, a granulocyte or stem cell is validated according to the assay when the granulocyte kills at least 60% or 70% of infective agent or cells infected with an infective agent in the test sample. In one embodiment, a granulocyte or stem cell is validated according to the assay when the granulocyte kills at least 80% or 90% of infective agent or cells infected with an infective agent in the test sample.

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).

- 5 The % of infective agent or cells infected by an infective agent killed as described herein can be measured by reference to the total number of starting infective agent or cells infected by an infective agent. The amount of infective agent or number of cells infected by an infective agent killed can be measured using any suitable means, for example by counting colony forming units in culture, viability staining (e.g. trypan blue staining), and microscopy. In some
10 embodiments the % of infective agent or cells infected by an infective agent killed may be determined within 24 hours (e.g. of incubating an infective agent or cells infected by an infective agent, and a granulocyte). The % of infective agent or cells infected by an infective agent killed is preferably the maximum amount of infective agent (e.g. number of infective agent cells killed) or cells infected by an infective agent killed when carrying out a method of
15 the invention.

In one embodiment, where an infective agent is a bacterium, a ratio of at least 1:10, 1:5, 1:3 or 1:2 granulocytes to colony forming units may be used. Preferably a 1:2 ratio of granulocytes to colony forming units is used. More preferably a 1:1 ratio of granulocytes to
20 colony forming units 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
25 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
30 preservation medium.

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

- 35 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 an infection; 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 an infection.

In one aspect the invention provides a composition for treating an infection, 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 an infection; 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 an infection.

In one aspect the invention provides a composition for treating an infection, 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 an infection; 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 an infection.

In one aspect the invention provides a composition for treating an infection, 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 an infection; 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 an infection.

5 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
10 reference standard is from a granulocyte unsuitable for treating an infection; 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 an infection.

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

The invention also provides a method for isolating granulocytes suitable for treating an infection based on the expression of one or more genes of the invention. Such methods may
20 provide a substantially homogeneous population of granulocytes that are suitable for treating an infection. In one embodiment, granulocytes for treating an infection 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*,
25 *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
30 (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,
35 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 an infection, 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 an infection.

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
5 a granulocyte for treating an infection.

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,
10 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
15 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
20 and the one or more polypeptides or between the binding means and the granulocyte. The method may comprise isolating a granulocyte for treating an infection based on the quantified amount of binding.

In one embodiment a granulocyte for treating an infection is isolated when there is a high
25 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 an infection is isolated when there is a low level
30 of binding between a binding means and ANXA1 and/or PPP3CB.

Preferably, a granulocyte for treating an infection 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,
35 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 an infection.

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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 an infection. 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

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unsuitable for treating an infection from a population of granulocytes.

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

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

In one aspect the invention provides a pharmaceutical composition comprising:

a.

a granulocyte, stem cell, or composition of the invention; and

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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, 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).

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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, foetal bovine serum (FBS), retinoic acid, lipopolysaccharide (LPS), IFN-gamma, IFN-beta or combinations thereof. Suitably, the pharmaceutical composition comprises IFN-gamma and 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 an infection). Suitably, the instructions may be for the use of the same in treating an infection 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 an infection, preferably MRSA.

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 infection 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 an infection), thus constituting a personalised medicine.

5 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.

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

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

25 In one embodiment the infection is an infection by any infective agent described herein. Preferably any pathogen described herein. In one embodiment an infection is a nosocomial infection.

Preferably an infection treated by the present invention is tuberculosis.

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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
35 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 an infection (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 an infection (or a symptom thereof). In some embodiments, the prophylactically effective amount prevents the onset or reoccurrence of an infection entirely. “Inhibiting” the onset means either lessening the likelihood of onset of an infection (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.

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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.

10 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).

15 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
20 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 $1/100^{\text{th}}$ and $1/700^{\text{th}}$, preferably a dose between $1/200^{\text{th}}$ and $1/400^{\text{th}}$, such as $1/300^{\text{th}}$, of the dose when compared to the dose of
25 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
30 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 2×10^9 cells or at least 2×10^{10} cells. Suitably, a subject for treatment may be dosed weekly
35 with at least 1×10^{11} or at least 2×10^{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 infection. 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 2×10^9 cells, wherein said cells are administered once weekly. Suitably a subject for treatment is dosed for 8 weeks with at least 2×10^9 cells (preferably at least 2×10^{10} or 2×10^{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, intrathecal injection, or combinations thereof. Suitably the medicament may be administered intravenously.

In one embodiment a medicament may be administered to an infected wound (e.g. as part of wound care). The medicament may comprise a stem cell or granulocyte of the invention. Preferably the medicament comprises a granulocyte of the invention.

In one embodiment, the medicament comprising a granulocyte of the invention is administered (e.g. sequentially or simultaneously) with infrared light treatment. In another embodiment, the medicament comprising a stem cell of the invention is administered (e.g. sequentially or simultaneously) with infrared light treatment. In another embodiment a donor or subject may be subjected to infrared light treatment. Said treatment may increase granulocyte function and proliferation.

The infrared light may have a wavelength of between 500-1500 nm, such as 750-1200 nm. In one embodiment, the subject is subjected to short bursts of high power (for example between 230-1500 W, preferably 300-1000 W, e.g. 300, 500, or 1000 W) near-infrared light. In one embodiment the subject is subjected to said near-infrared light for at least 30 seconds, e.g. at least 1, 10, 15, 20, 30, 40, or 60 minutes. The subject may be subjected for up to 5 times a day (e.g. 1, 2, 3 or 4 times per day) for up to 6 weeks (e.g. up to 1, 2, 3, 4 or 5 weeks).

In one embodiment, the subject is subjected to longer periods of low power (for example 50-220W, e.g. 100-200 W) near-infrared light. In one embodiment the subject is subjected to said near-infrared light for 1-10 hours, e.g. 2-6 hours, for up to 6 weeks (e.g. up to 1, 2, 3, 4 or 5 weeks).

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In one embodiment, the subject is subjected to a combination of high power and low power near-infrared light.

A white blood cell growth factor may be administered with a medicament of the invention.

10 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, 15 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 20 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), 25 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.

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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 35 simultaneously, preferably simultaneously) with a granulocyte-colony stimulating factor; and a growth hormone; and a serotonin; and an interleukin.

In one aspect the present invention provides a method for determining the suitability of a stem cell for treating an infection, 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 an infection 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 an infection based on the comparison.

In one aspect the present invention provides a method for determining the suitability of a stem cell for treating an infection, 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 an infection 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 an infection 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 an infection, 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 an infection 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 an infection 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 an infection, 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 an infection 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 an infection based on the comparison.

In one embodiment a stem cell is determined to be suitable for treating an infection or a donor is identified as producing stem cells suitable for treating an infection 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 an infection; 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 an infection; 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 an infection; 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 an infection.

Alternatively, in one embodiment a stem cell is determined to be unsuitable for treating an infection or a donor is identified as producing stem cells unsuitable for treating an infection 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 an infection; or

5 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 an infection; or

10 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 an infection; 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 an infection.

15 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 an infection; and/or

20 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 an infection.

25 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 an infection, the method comprising:

30 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 an infection 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 an infection 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 an infection, 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 an infection 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 an infection 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 an infection when:
 - i. 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 or the same when compared to the reference standard, when the reference standard is from a stem cell unsuitable for treating an infection; 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 an infection; 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 an infection; 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 an infection; or
- identifying the subject as unsuitable for treatment with a granulocyte or a stem cell for treating an infection 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 an infection; 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 an infection; 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 an infection; 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 an infection.

15

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.

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In alternative embodiments of any of the foregoing aspects, 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.

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In one aspect the invention provides a composition for treating an infection, 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:

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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 an infection; and/or

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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 an infection.

- 5 The invention also provides a method for isolating stem cells suitable for treating an infection 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 an infection. In one embodiment, stem cells for treating an infection are isolated using the expression of one or more cell-surface expressed polypeptides selected from: ATG7, CYBB,
 10 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 protein of the invention.
 15 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
 20 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 an infection, the method comprising:

- 25 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
 30 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
 35 '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 an infection.

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 an infection.

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 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 an infection based on the quantified amount of binding.

In one embodiment a stem cell for treating an infection 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 an infection 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 an infection is isolated when there is:

- 5 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.

- 10 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 an infection.

- The term "isolating" may mean providing a population of stem cells in which at least 50%,
15 60%, 70%, 80% or 90% (preferably at least 95%, 99% or 100%) are stem cells suitable for treating an infection. 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 an infection from a population of stem cells.

- 20 Thus, the methods for isolating suitably allow for the separation of a stem cell for treating an infection from stem cell that is unsuitable for treating an infection.

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

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In one aspect the invention provides a stem cell for treating an infection obtainable by a method of the invention (e.g. a stem cell capable of differentiating into granulocytes that are suitable to treat an infection). In one aspect the invention provides a stem cell for use in treating an infection (together with associated methods of treatment employing the same).

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

- a. providing a cell; and
 b. converting the cell into a stem cell having an expression profile described
35 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 an infection; or
- 5 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 an infection; or
- 10 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 an infection; or
- 15 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 an infection; and
- c. optionally isolating the stem cell.

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

In one embodiment the methods of the invention comprise:

- 25 not obtaining a stem cell from a sample from a donor when a granulocyte kills less than or equal to 41.23% of infective agent or cells infected with an infective agent;
- not obtaining a stem cell from a sample from a donor when the % of infective agent or cells infected with an infective agent is the same or less than the % killed in a control sample;
- not selecting a granulocyte when a granulocyte kills less than or equal to 41.23% of infective agent or cells infected with an infective agent; and/or
- 30 not obtaining a granulocyte from a sample from a donor when the % of infective agent or cells infected with an infective agent is the same or less than the % killed in a control sample.

35 In some embodiments of any of the foregoing aspects, a granulocyte unsuitable for treating an infection 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*.

5 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
10 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
15 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
20 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
25 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
30 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
35 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

5 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																		
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													
10 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								
15 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			
20 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:

25

Total number of identical matches

_____ x 100

[length of the longer sequence plus the
number of gaps introduced into the longer

30 sequence in order to align the two sequences]

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-

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

CONSERVATIVE AMINO ACID SUBSTITUTIONS

5	Basic:	arginine
		lysine
		histidine
	Acidic:	glutamic acid
		aspartic acid
10	Polar:	glutamine
		asparagine
	Hydrophobic:	leucine
		isoleucine
		valine
15	Aromatic:	phenylalanine
		tryptophan
		tyrosine
20	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.

5 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
10 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
15 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
20 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
25 example, reference to "a granulocyte" includes a plurality of such candidate agents and reference to "the granulocyte" includes reference to one or more haematopoietic cells 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
30 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.

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

BRIEF DESCRIPTION OF THE DRAWINGS

Embodiments of the invention will now be described, by way of example only, with reference to the following Figures, in which:

Figure 1 demonstrates validation of an *in vitro* assay of neutrophil mediated bacterial killing by neutrophils in suspension at concentrations of 1×10^5 , 5×10^5 or $1 \times 10^6/100\mu\text{l}$ which were incubated with 1×10^6 cfu *P. aeruginosa* RP73 for 2 hours at 37°C under 120rpm of shaking and quantified on TSA plates to calculate percentage of bacterial killing. Data are expressed as Mean $\pm$ SEM of bacterial killing (%), $n=2$, * = $P < 0.05$, ** = $P < 0.01$, *** = $P < 0.001$.

Figure 2 shows comparison of neutrophil mediated bacterial killing against Gram-negative and Gram-positive bacteria. $1 \times 10^6/100\mu\text{l}$ neutrophils were incubated with either 1×10^6 cfu *P. aeruginosa* RP73 (A) or MRSA USA300 (B) for 2 hours at 37°C under 120rpm of shaking and quantified on TSA plates to calculate percentage of bacterial killing. Data are expressed as Mean $\pm$ SEM of bacterial killing (%), $n=20$.

Figure 3 shows effects of tobramycin or vancomycin on bacterial killing at 2 hours. 1×10^6 cfu *P. aeruginosa* RP73 (A) or MRSA USA300 (B) were treated with either 1, 10 and $100\mu\text{g/ml}$ tobramycin (RP73) or vancomycin (MRSA) for 2 hours at 37°C under 120rpm of shaking and quantified on TSA plates to calculate percentage of bacterial killing. Data are expressed as Mean $\pm$ SEM of bacterial killing (%), $n=2$, * = $P < 0.05$, ** = $P < 0.01$, *** = $P < 0.001$.

Figure 4 shows comparison of neutrophil BKA against antibiotic therapy *in vitro*. 1×10^6 cfu *P. aeruginosa* RP73 (A) or MRSA USA300 (B) were treated with either $1\mu\text{g/ml}$ tobramycin (RP73), $1\mu\text{g/ml}$ vancomycin (MRSA) or 1×10^6 neutrophils for 2 hours at 37°C under 120rpm of shaking and quantified on TSA plates to calculate percentage of bacterial killing. Data are expressed as Mean $\pm$ SEM of bacterial killing (%), $n=2-3$, * = $P < 0.05$, ** = $P < 0.01$, *** = $P < 0.001$.

Figure 5 shows BKA assay results for Donor Derived Neutrophils and Stem Cell Derived Neutrophils for donors A, B, and C against MRSA.

Figure 6 shows BKA assay results for Donor Derived Neutrophils and Stem Cell Derived Neutrophils for donors A, B, and C against *P. aeruginosa* RP73.

Figure 7 shows significantly (*** $P < 0.001$, ** $P < 0.01$, * $P < 0.05$) upregulated expression of ITGB1, SYK, DOCK8 and CYBB in high BKA neutrophils (>41.23% MRSA BKA) compared with low BKA control neutrophils. Data are mean ($n = 3$ donor samples in duplicate) $\pm$ standard error of mean compared by two-way ANOVA.

Figure 8 shows significantly (** $P < 0.01$, * $P < 0.05$) upregulated expression of PLEC and COMP in high BKA neutrophils (>41.23% MRSA BKA) compared with low BKA control neutrophils. Data are mean ($n = 3$ donor samples in duplicate) $\pm$ standard error of mean compared by two-way ANOVA.

Figure 9 shows significantly (**P < 0.01, *P < 0.05) upregulated expression of ATG7, SLC2A1, S100A9, ACSL1, CTSG, PSMB2, ATM and S100A8 in high BKA neutrophils (>41.23% MRSA BKA) compared with low BKA control neutrophils. Data are mean (n = 3 donor samples in duplicate) ± standard error of mean compared by two-way ANOVA.

- 5 **Figure 10** shows significantly (**P < 0.01, *P < 0.05) downregulated expression of ANXA1 in high BKA neutrophils (>41.23% MRSA BKA) compared with low BKA control neutrophils. Data are mean (n = 3 donor samples in duplicate) ± standard error of mean compared by two-way ANOVA.

- 10 **Figure 11** shows significantly (**P < 0.01, *P < 0.05) upregulated expression of BCAP31 and TAPBP in high BKA neutrophils (>41.23% MRSA BKA) compared with low BKA control neutrophils. Data are mean (n = 3 donor samples in duplicate) ± standard error of mean compared by two-way ANOVA.

SEQUENCE LISTING

15

Gene Sequences

SEQ ID NO.	GENE	Accession No.	Ensembl Release No.
1	<i>CTSG</i>	ENSG00000100448	97
2	<i>CAP37</i>	ENSG00000172232	97
3	<i>ITGB1</i>	ENSG00000150093	97
4	<i>CYBB</i>	ENSG00000165168	97
5	<i>SYK</i>	ENSG00000165025	97
6	<i>DOCK8</i>	ENSG00000107099	97
7	<i>COMP</i>	ENSG00000105664	97
8	<i>ATG7</i>	ENSG00000197548	97
9	<i>SLC2A1</i>	ENSG00000117394	97
10	<i>GZMK</i>	ENSG00000113088	97
11	<i>S100A9</i>	ENSG00000163220	97
12	<i>S100A8</i>	ENSG00000143546	97
13	<i>ATM</i>	ENSG00000149311	97
14	<i>IKBKB</i>	ENSG00000104365	97
15	<i>BCAP31</i>	ENSG00000185825	97
16	<i>TAPBP</i>	ENSG00000231925	97
17	<i>PPP3CB</i>	ENSG00000107758	97
18	<i>ANXA1</i>	ENSG00000135046	97
19	<i>PERM</i>	ENSG00000005381	97
20	<i>PLEC</i>	ENSG00000178209	97
21	<i>ACSL1</i>	ENSG00000151726	97
22	<i>RAC1</i>	ENSG00000136238	97
23	<i>PSMB2</i>	ENSG00000126067	97
24	<i>GM2A</i>	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 AGLASSRAG SSPLLDIVGG RKARPRQFPF LASIQNQGRH FCGGALIHAR FVMTAASCFQ SQNPGVSTVV LGAYDLRRRE RQSRQTFSIS SMSSENGYDPQ QNLNDLMLLQ LDREANLTSS VTILPLPLQN ATVEAGTRCQ VAGWGSQSRG 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 GTAEKLPED ITQIQPQQLV LRLRSGEPT FTLKFKRAED YPIDLYYLM LSYSMKDDLE NVKSLGTDLM NEMRRITSDF RIGFGSFVEK TVMPYISTTP AKLRNPCTSE QNCTSPFSYK NVLSLTNKGE VFNELVGKQR ISGNLDSPEG GFDAIMQVAV CGSLIGWRNV TRLLVFSTDA GFHFAGDGKL GGIVLPNDGQ CHLENNMYTM SHYDYPsia HLVQKLSENN IQTIFAVTEE FQPVYKELKN LIPKSAVGTL SANSSNVIQL IIDAYNSLSS EVILENGKLS EGVTSYKSY CKNGVNGTGE NGRKCSNISI GDEVQFEISI TSNKCPKKDS DSFKIRPLGF TEEVEVILQY ICECECQSEG IPESPKCHEG NGTFECGACR CNEGRVGRHC ECSTDEVNSE DMDAYCRKEN

					SSEICSNNGE CVCQGQVCRK RDNTNEIYSG KFCECDNFNC DRSNGLICGG NGVCKCRVCE CNPNYTGSA C DCSLDTSTCE ASNGQICNGR GICECGVCKC TDPKFQGGTC EMCQTCLGVC AEHKECVQCR AFNKGEKKDT CTQECSYFNI TKVESRDKLP QPVQPDVSH CEKDVDDCW FYFTYSVNGN NEVMVHVVEN PECPTGPDII PIVAGVVAGI VLIGLALLLI WKLLMIHDR REFAKFEKEK MNAKWDGTEN PIYKSAVTTV VNPKEYGK
28	ITGB1	2	P05556-2	Entry version 242 (18 Sep 2019) Sequence version 2 (16 Dec 2008)	MNLQPIFWIG LISSVCCVFA QTDENRCLKA NAKSCGECIQ AGPNCGWCTN STFLQEGMPT SARCDDEAL KKKGCPPDDI ENPRGSKDIK KNKNVTNRSK GTAEKLPED ITQIQPQQLV LRLRSGEPQT FTLKFRAED YPIDLYYLM LSYSMKDDLE NVKSLGTDLM NEMRRITSDF RIGFGSFVEK TVMPYISTTP AKLRNPCTSE QNCTSPFSYK NVLSLTNKGE VFNELVGKQR ISGNLDSPEG GFDAMQVAV CGSLIGWRNV TRLLVFSTDA GFHFAGDGKL GGIVLPNDGQ CHLENNMYTM SHYYDYPsia HLVQKLSENN IQTIFAVTEE FQPVYKELKN LIPKSAVGTL SANSSNVIQL IIDAYNSLSS EVILENGKLS EGVTI SYKSY CKNGVNGTGE NGRKCSNISI GDEVQFEISI TSNKCPKKDS DSFKIRPLGF TEEVEVILQY ICECECQSEG IPESPKCHEG NGTFECGACR CNEGRVGRHC ECSTDEVNSE DMDAYCRKEN SSEICSNNGE CVCQGQVCRK RDNTNEIYSG KFCECDNFNC DRSNGLICGG NGVCKCRVCE CNPNYTGSA C DCSLDTSTCE ASNGQICNGR GICECGVCKC TDPKFQGGTC EMCQTCLGVC AEHKECVQCR AFNKGEKKDT CTQECSYFNI TKVESRDKLP QPVQPDVSH CEKDVDDCW FYFTYSVNGN NEVMVHVVEN PECPTGPDII PIVAGVVAGI VLIGLALLLI WKLLMIHDR REFAKFEKEK MNAKWDTVSY KTSKKQSG
29	ITGB1	3	P05556-3	Entry version 242 (18 Sep 2019) Sequence	MNLQPIFWIG LISSVCCVFA QTDENRCLKA NAKSCGECIQ AGPNCGWCTN STFLQEGMPT SARCDDEAL KKKGCPPDDI

				version 2 (16 Dec 2008)	ENPRGSKDIK KNKNVTNRSK GTAEKLPED ITQIQPQQLV LRLRSGEPQT FTLKFKRAED YPIDLYYLM LSYSMKDDLE NVKSLGTDLM NEMRRITSDF RIGFGSFVEK TVMPYISTTP AKLRNPCTSE QNCTSPFSYK NVLSLTNKGE VFNELVGKQR ISGNLDSPEG GFDAIMQVAV CGSLIGWRNV TRLLVFSTDA GFHFAGDGKL GGIVLPNDGQ CHLENNMYTM SHYYDYPSIA HLVQKLENN IQTIFAVTEE FQPVYKELKN LIPKSAVGTL SANSSNVIQL IIDAYNSLSS EVILENGKLS EGVTSYKSY CKNGVNGTGE NGRKCSNISI GDEVQFEISI TSNKCPKKDS DSFKIRPLGF TEEVEVILQY ICECECQSEG IPESPKCHEG NGTFECGACR CNEGRVGRHC ECSTDEVNSE DMDAYCRKEN SSEICSNNGE CVCGQCVCCK RDNTNEIYSG KFCECDNFNC DRNGLICGG NGVCKCRVCE CNPNYTGSA DCSLDTSTCE ASNGQICNGR GICECGVCKC TDPKFQGGTC EMCQTCLGVC AEHKECVQCR AFNKGEKKDT CTQEC SYFNI TKVESRDKLP QPVQPDVSH CKEKD VDDCW FYFTYSVNGN NEVMVHVVEN PECPTGPDII PIVAGVVAGI VLIGLALLI WKLLMIHDR 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 SARCDDEAL KKGCPDDI ENPRGSKDIK KNKNVTNRSK GTAEKLPED ITQIQPQQLV LRLRSGEPQT FTLKFKRAED YPIDLYYLM LSYSMKDDLE NVKSLGTDLM NEMRRITSDF RIGFGSFVEK TVMPYISTTP AKLRNPCTSE QNCTSPFSYK NVLSLTNKGE VFNELVGKQR ISGNLDSPEG GFDAIMQVAV CGSLIGWRNV TRLLVFSTDA GFHFAGDGKL GGIVLPNDGQ CHLENNMYTM SHYYDYPSIA HLVQKLENN IQTIFAVTEE FQPVYKELKN LIPKSAVGTL SANSSNVIQL IIDAYNSLSS EVILENGKLS EGVTSYKSY CKNGVNGTGE NGRKCSNISI

					GDEVQFEISI TSNKCPKKDS DSFKIRPLGF TEEVEVILQY ICECECQSEG IPESPKCHEG NGTFECGACR CNEGRVGRHC ECSTDEVNSE DMDAYCRKEN SSEICSNNGE CVCQGQVCRK RDNTNEIYSG KFCECDNFNC DRSNGLICGG NGVCKCRVCE CNPNYTGSA CDSLDTSTCE ASNGQICNGR GICECGVCKC TDPKFQGGTC EMCQTCLGVC AEHKECVQCR AFNKGEKKDT CTQECSYFNI TKVESRDKLP QPVQPDVSH CKEKDVDCCW FYFTYSVNGN NEVMVHVVEN PECPTGPDII PIVAGVVAGI VLIGLALLLI WKLLMIHHR REFAKFEKEK MNAKWDTPGV QWCDISSLOP LTRFQQFSC 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 SARCDDEAL KKKGCPDDI ENPRGSKDIK KNKNVTNRSK GTAEKLPED ITQIQPQQLV LRLRSSEPQT FTLKFKAED YPIDLYYLM LSYSMKDDLE NVKSLGTDLM NEMRRITSDF RIGFGSFVEK TVMPYISTTP AKLRNPCTSE QNCTSPFSYK NVLSLTNKGE VFNELVGKQR ISGNLDSPEG GFDAIMQVAV CGSLIGWRNV TRLLVFSTDA GFHFAGDGKL GGIVLPNDGQ CHLENNMYTM SHYYDYPsia HLVOQLSENN IQTIFAVTEE FQPVYKELKN LIPKSAVGTL SANSSNVIQL IIDAYNSLSS EVILENGKLS EGVTSYKSY CKNGVNGTGE NGRKCSNISI GDEVQFEISI TSNKCPKKDS DSFKIRPLGF TEEVEVILQY ICECECQSEG IPESPKCHEG NGTFECGACR CNEGRVGRHC ECSTDEVNSE DMDAYCRKEN SSEICSNNGE CVCQGQVCRK RDNTNEIYSG KFCECDNFNC DRSNGLICGG NGVCKCRVCE CNPNYTGSA CDSLDTSTCE ASNGQICNGR GICECGVCKC TDPKFQGGTC EMCQTCLGVC AEHKECVQCR AFNKGEKKDT CTQECSYFNI TKVESRDKLP QPVQPDVSH CKEKDVDCCW FYFTYSVNGN NEVMVHVVEN PECPTGPDII PIVAGVVAGI VLIGLALLLI WKLLMIHHR REFAKFEKEK MNAKWDTPGV

					PIYKSPINNF L	KNPNYGRKAG
32	CYBB	1	P04839	Entry version 213 (18 Sep 2019) Sequence version 2 (23 Jan 2007)	MGNWAVNEGL LNVFLFVWYY YTRKLLGSAL NFNCMLILLP GSSACCSTRV HKMVAVWMIAL FNVEWCVNAR LSELGDRQNE KNPEGGLYLA VITLCLILII YFEVFWYTHH IHGAERTVRG ITVCEQKISE QFAGNPPMTW LCERLVRFWR VTHPFKTIEL VGQYIFVKCP TLTSAPEEDF WTEGLFNACG KLPKIAVDGP YEVVMLVGAG KSVVYKCNN FYWLCRDTHA LESQMQRN TGWDESQANH VITGLKQKTL KTIASQHPNT ALAETLSKQS VHFIFNKENF	SIFVILVWLG RVYDIPPKFF ALARAPAACL VCRNLLSFLR RRQLDRNLTF HSAIHTIAHL VNNSDPYSA SYLNFARKRI VTLLAGITGV TSSTKTIRRS LFVIFFIGLA QTAEFLAVHN WGKIKECPIP KWIVGPMFLY SQQKVVTIKV QMKKKGFKME KVSKEWHHPF FSIHIRIVGD CDKQEFQDAW FGTASEDVFS IGVTFASIL ATNLKLLKIY FEWFADLLQL AGFLSYNIYL FAVHHDEEKD YGRPNWDNEF RIGVFLCGPE ISNSES GPRG
33	SYK	1	P43405	Entry version 224 (18 Sep 2019) Sequence version 1 (01 Nov 1995)	MASSGMADSA TREEAEDYLV LRQSRNYLGG AHHYTIEREL THASPADLCH CLLKKPFNRP EDLKENLIRE QALEQATISQ TAHEKMPWFH IVLIGSKTNG GSYALCLLHE DKTGKLSIPE VEHYSYKADG KIGTQGNVNF PATWSAGGII PGRKSSPAQ NPYEPELAPW LPMDETVYES KEVYLDKLL NFGTVKKGY VKILKNEAND ANVMQQLDNP AESWMLVMEM QQNRHVKDKN GMKYLEESNF LLVTQHYAKI ADENYYKAQT	NHLPFFFGNI QGGMSDGLYL FALSAVHGRK NGTYAIAGGR YHSQESDGLV QGVQPKTGPF YVKQTNLQG KPQLEKLIAT GKISREESEQ KFLIRARDNN GKVLHYRIDK GKKFDTLWQL LLRVLTVPQ GGRPQLPGSH SRIKSYSFPK GNRQESTVSF AADKGPQREA PYADPEEIRP TLEDKELGSG QMKKVVTVA PALKDELLAE YIVRMIGICE AELGPLNKYL IIELVHQVSM VHRDLAARNV SDFGLSKALR HGKWPVKWYA

					PECINYYKFS SKSDVWSFGV LMWEAFSYGQ KPYRGMKGSE VTAMLEKGER MGCPAGCPRE MYDLMNLCWT YDVENRPGFA AVELRLRNYY YDVPN
34	SYK	2	P43405-2	Entry version 224 (18 Sep 2019) Sequence version 1 (01 Nov 1995)	MASSGMADSA NHLPFFFGNI TREEAEDYLV QGGMSDGLYL LRQSRNYLGG FALSVAHGRK AHHTTIEREL NGTYAIAGGR THASPADLCH YHSQESDGLV CLLKKPFNRP QGVQPKTGPF EDLKENLIRE YVKQTNWLQG QALEQATISQ KPQLEKLIAT TAHEKMPWFH GKISREESEQ IVLIGSKTNG KFLIRARDNN GSYALCLLHE GKVLHYRIDK DKTGKLSIPE GKKFDTLWQL VEHYSYKADG LLRVLTVPQC KIGTQGNVNF GGRPQLPGSH PASSPAQGNR QESTVSFNPY EPELAPWAAD KGPQREALPM DTEVYESPYA DPEEIRPKEV YLDRKLLTLE DKELGSGNFG TVKKGYQMK KVVKTVAVKI LKNEANDPAL KDELLAEANV MQQLDNPYIV RMIGICEAES WMLVMEMAEL GPLNKYLQQN RHVKDKNIE LVHQVSMGMK YLEESNFVHR DLAARNVLLV TQHYAKISDF GLSKALRADE NYYKAQTHGK WPKWYAPEC INYYKFSSKS DVWSFGVLMW EAFSYGQKPY RGMKGSEVTA MLEKGERMGC PAGCPREMYD LMNLCWTYDV ENRPGFAAVE LRLRNYYDV VN
35	DOCK8	1	Q8NF50	Entry version 160 (18 Sep 2019) Sequence version 3 (21 Aug 2007)	MATLPSAERR AFALKINRYS SAEIRKQFTL PPNLGQYHRQ SISTSGFPSL QLPQFYDPVE PVDFEGLMT HLNSLDVQLA QELGDFDDED LDVVFTPKEC RTLQPSLPEE GVELDPHVRD CVQTYIREWL IVNRKNQGS EICGFKKTGS RKDFHKTLPK QTFESETLEC SEPAAQAGPR HLNVLCDVSG KGPVTACDFD LRSLQPDKRL ENLLQQVSAE DFKEQNEEAR RTNRQAELFA LYPSVDEEDA VEIRPVPECP KEHLGNRILV KLLTLKFEIE IEPLFASIAL YDVKERKKIS ENFHCDLNSD QFKGFLRAHT PSVAASSQAR SAVE'SVTYPS SDIYLVVKIE KVLQQGEIGD CAEPYTVIKE SDGKSKEKI EKLKLQAESF CQRLGKYRMP FAWAPISLSS FFNVSTLERE VTDVDSVGR SSVGERRTLA

					QSRRLSERAL	SLEENGVGSN
					FKTSTLSVSS	FFKQEGDRLS
					DEDLFKFLAD	YKRSSSLQRR
					VKSIPGLLRL	EISTAPEIIN
					CCLTPEMLPV	KPFPENRTRP
					HKEILEFPTR	EVYVPHTVYR
					NLLYVYPQRL	NFVNKLASAR
					NITIKIQFMC	GEDASNAMPV
					IFGKSSGPEF	LQEVYTAVTY
					HNKSPDFYEE	VKIKLPAKLT
					VNHLLFTFY	HISCOQKQGA
					SVETLLGYSW	LPILLNERLQ
					TGSYCLPVAL	EKLPPNYSMH
					SAEKVPLQNP	PIKWAEGHKG
					VFNIEVQAVS	SVHTQDNHLE
					KFFTLCBSLE	SQVTFPIRVL
					DQKISEMALE	HELKLSIICL
					NSSRLEPLVL	FLHLVLDKLF
					QLSVQPMVIA	GQTANFSQFA
					FESVVAIANS	LHNSKDLSKD
					QHGRNCLLAS	YVHYVFRLE
					VQRDVPKSGA	PTALLDPRSY
					HTYGRTSAAA	VSSKLLQARV
					MSSSNPDLAG	THSAADEEVK
					NIMSSKIADR	NCSRMSYYCS
					GSSDAPSSPA	APRPASKKHF
					HEELALQMVV	STGMVRETVF
					KYAWFFFELL	VKSMQHVHN
					MDKRDSFRRT	RFSDRFMDDI
					TTIVNVVTSE	IAALLVKPQK
					ENEQAQKMN	SLAFFLYDLL
					SLMDRGFVFN	LIRHYCSQLS
					AKLSNLPTLI	SMRLEFLRIL
					CSHEHYLNLN	LFFMNADTAP
					TSPCPSISSQ	NSSSCSSFQD
					QKIASMFDLT	SEYRQQHFLT
					GLLFTELA	LDAGEGISK
					VQRKAVSAIH	SLSSHDLDLP
					RCVKPEVKVK	IAALYLPLVG
					IILDALPQLC	DFTVADTRRY
					RTSGSDEEQE	GAGAINQNVA
					LAIAGNNFNL	KTSGIVLSSL
					PYKQYNMLNA	DTRNLMICF
					LWIMKNADQS	LIRKWIADLP
					STQLNRILDL	LFICVLCFEY
					KGKQSSDKVS	TQVLQKSRDV
					KARLEEALLR	GEGARGEMMR
					RRAPGNDRFP	GLNENLRWKK
					EQTHWRQANE	KLDKTKAELD
					QEALISGNLA	TEAHLIILDM
					QENIIQASSA	LDCKDSLGG
					VLRVLVNSLN	CDQSTTYLTH
					CFATLRALIA	KFGDLLFEEE
					VEQCFDLCHQ	VLHHCSSSMD
					VTRSQACATL	YLLMRFSGA
					TSNFARVKMQ	VTMSLASLVG
					RAPDFNEEHL	RRSLRTILAY
					SEEDTAMQMT	PFPTQVEELL
					CNLNSILYDT	VKMREFQEDP
					EMLMDLMYRI	AKSYQASPD

					RLTWLQNMAE KHTKKKCYTE AAMCLVHAAA LVAEYLSMLE DHSYLPVGSV SFQNISSNVL EESVVSIEDTL SPDEEDGVCAG QYFTESGLVG LLEQAAELFS TGGLYETVNE VYKLVIPILE AHREFRKLTL THSKLQRAFD SIVNKDHKRM FGTYFRVGFF GSKFGDLDEQ EFVYKEPAIT KLPEISHRLE AFYQCFGAE FVEVIKIDSTP VDKTKLDPNK AYIQITFVEP YFDEYEMKDR VTYFEKNFNL RRFMYTTPFT LEGRPRGELH EQYRRNTVLT TMHAFPIYKT RISVIQKEEF VLTPIEVAIE DMKKKTLQLA VAINQEPPDA KMLQMVQLGS VGATVNQGPI EVAQVFLAEI PADPKLYRHH NKLRLCFKEF IMRCGEAVEK NKRLITADQR EYQELKKNY NKLKENLRPM IERKIPELYK PIFRVESQKR DSFHRSSFRRK CETQLSQGS
36	DOCK8	2	Q8NF50-2	Entry version 160 (18 Sep 2019) Sequence version 3 (21 Aug 2007)	MATLPSAERR AFALKINRYS SAEIRKQFTL PPNLGQYHRQ SISTSGFPSL QLPQFYDPVE PVDFEGLMT HLNSLDVQLA QELGDFTDDE LDVVFTPKEC RTLQPSLPPEE GVLDPHVRD CVQTYIREWL IVNRKNQGS EICGFKKTGS RKDFHKTLPK QTFESETLEC SEPAAQAGPR HLNVLCDVSG KGPVTACDFD LRSLQPDKRL ENLLQQVSAE DFEKQNEEAR RTNRQAELFA LYPVDEEDA VEIRPVPECP KEHLGNRILV KLLTLKFEIE IEPLFASIAL YDVKERKKIS ENFHCDLNSD QFKGFLRAHT PSVAASSQAR SAVFSVTYPS SDIYLVVKIE KVLQQGEIGD CAEPYTVIKE SDGKSKEKI EKLKLQAESF CQRLGKYRMP FAWAPISLSS FFNVSTLERE VTDVDSVVGR SSVGERRTLA QSRRLSERAL SLEENGVSNS FKTSTLSVSS FFKQEGDRLS DEDLFKFLAD YKRSSSLQRR VKSIPGLLRL EISTAPEIIN CCLTPEMLPV KPFPENRTRP HKEILEFPTR EVYVPHTVYR NLLYVYPQRL NFVNKLASAR NITIKIQFMC GEDASNAMPV IFGKSSGPEF LQEVYTAVTY HNKSPDFYEE VKIKLPAKLT VNHLLFTFY HISCQQKQGA SVETLLGYSW LPILLNERLQ TGSYCLPVAL EKLPPNYSMH SAEKVPLQNP PIKWAEGHKG

					VFNIEVQAVS	SVHTQDNHLE
					KFFTLCHSLE	SQVTFPIRVL
					DQKISEMALE	HELKLSIICL
					NSSRLEPLVL	FLHLVLDKLF
					QLSVQPMVIA	GQTANFSQFA
					FESVVAIANS	LHNSKDL SKD
					QHGRNCLLAS	YVHYVFR LPE
					VQRDV PKSGA	PTALLDPRSY
					HTYGRTSAAA	VSSKLLQARV
					MSSSNPDLAG	THSAADEEVK
					NIMSSKHFE	ELALQM VVST
					GMVRETVFKY	AWFFFELLVK
					SMAQHVHNM	KRDSFRRTRF
					SDRFMDITT	IVNVVTSEIA
					ALLVKPQKEN	EQAEKMNISL
					AFFLYDLLSL	MDRGFVFNLI
					RHYCSQLSAK	LSNLPTLISM
					RLEFLRILCS	HEHYLNLNLF
					FMNADTAPTS	PCPSISSQNS
					SSCSSFQDQK	IASMF'DLTSE
					YRQQHFLTGL	LFTELAAALD
					AEEGEISKVQ	RKAVSAIHSL
					LSSHDLDP RC	VKPEVKVKIA
					ALYLPVGGII	LDALPQLCDF
					TVADTRRYRT	SGSDEE QEGA
					GAINQNVALA	IAGNNFN LKT
					SGIVLSSLPY	KQYNMLNADT
					TRNLMICFLW	IMKNADQSLI
					RKWIADLPST	QLNRILDLLF
					ICVLCFEYKG	KQSSDKVSTQ
					VLQKSRDVKA	RLEEALLRGE
					GARGEMMRRR	APGNDRFPGL
					NENLRWKKEQ	THWRQANEKL
					DKTKAELDQE	ALISGNLATE
					AHLIILDMQE	NIIQASSALD
					CKDSSLGGVL	RVLVNSLNCD
					QSTTYLTHCF	ATLRALIAKF
					GDLLFEEVE	QCFDLCHQVL
					HHCSSSMDVT	RSQACATLYL
					LMRFSFGATS	NFARVKMQVT
					MSLASLVGRA	PDFNEEHLRR
					SLRTILAYSE	EDTAMQMTPF
					PTQVEELLCN	LNSILYDTVK
					MREFQEDPEM	LMDLMYRIAK
					SYQASPDRL	TWLQNMAEKH
					TKKKCYTEAA	MCLVHAAALV
					AEYLSMLEDH	SYLPVGSVSF
					QNISSNVLEE	SVVSED TLSP
					DEDGVCAGQY	FTESGLVGLL
					EQAAELFSTG	GLYETVNEVY
					KLVIPILEAH	REFRKLTLTH
					SKLQRAFDSI	VNKDHKRMFG
					TYFRVGFFGS	KFGDLDEQEF
					VYKEPAITKL	PEISHRLEAF
					YGQCFGAEFV	EVIKDSTPVD
					KTKLDPNKAY	IQITFVEPYF
					DEYEMKDRVT	YFEKNFN LRR
					FMYTTPFTLE	GRPRGELHEQ
					YRRNTVLTTM	HAFPIKTRI
					SVIQKEEFVL	TPIEVAIEDM

					KKKTLQLAVA LQMVLQGSVG AQVFLAEIPA LRLCFKEFIM RLITADQREY LKENLRPMIE FRVESQKRDS TQLSQGS	INQEPPDAKM ATVNQGPLEV DPKLYRHHNK RCGEAVEKNK QQELKKNYNK RKIPELYKPI FHRSSFRKCE TQLSQGS
37	DOCK8	3	Q8NF50-3	Entry version 160 (18 Sep 2019) Sequence version 3 (21 Aug 2007)	MTHLNSLDVQ DDLDVVFTPK EEGVELDPHV WLIVNRKNQG GSRKDFHKT ECSEPAQAQ SGKGPVTACD RLENLLQQVS ARRTNRQAEL DAVEIRPVPE LVKLLTLKFE ALYDVKERKK SDQFKGFLRA ARSAVFSVTY IEKVLQQGEI KESDGGKSKE SFCQRLGKYR SSFFNVSTLE GRSSVGERRT ALSLEENGVG SSFFKQEGDR ADYKRSSLQ RLEISTAPEI PVKPFPENRT TREVVYPHTV RLNFVNKLAS MCGEDASNAM EFLQEVYTAV EEVKIKLPAK FYHISCQKQ SWLPILLNER ALEKLPPNYS NPPIKWAEGH VSSVHTQDNH LESQVTFPIR LEHELKLSII VLFLHLVLDK IAGQTANFSQ NSLHNSKDLS ASYVHYVFRL GAPALLDPR AAVSSKLLQA AGTHSAADEE DRNCSRMSYY PAAPRPASKK VVSTGMVRET LLVKSMAQHV RTRFSDRFMD SEIAALLVKP NISLAFFLYD FNLIRHYCSQ	LAQELGDFTD ECRTLQPSLP RDCVQTYIRE SPEICGFKKT PKQTFESETL PRHLNVLCDV FDLRLQPDK AEDFEKQNEE FALYPSVDEE CPKEHLGNRI IEIEPLFASI ISENFHCDLN HTPSVAASSQ PSSDIYLVVK GDCAEPTYVI KIEKLKLQAE MPFAWAPISL REVTDVDSVV LAQSRRLSER SNFKTSTLSV LSEDLFKFL RRVKSIPGLL INCCLTPEML RPHKEILEFP YRNLLYVYPQ ARNITIKIQF PVIFGKSSGP TYHNKSPDFY LTVNHLLFT GASVETLLGY LQTSYCLPV MHSAEKVPLQ KGVFNIEVQA LEKFTLCHS VLDQKISEMA CLNSSRLEPL LFQLSVQPMV FAFESVVAIA KDQHGRNCLL PEVQRDVPKS SYHTYGR TSA RVMSSSNPDL VKNIMSSKIA CSGSSDAPSS HFHEELALQM VFYAWFFFE HNMDKRDSFR DITTIVNVVT QKENEQAEM LLSLMDRGFV LSAKLSNLPT

					LISMRLEFLR LNLFFMNADT SQNSSSCSSF LTSEYRQQHF AALDAEGEGI IHSLLSSHDL VKIAALYLPL LCDFTVADTR QEGAGAINQN NLKTSIGIVLS NADTTRNLMI QSLIRKWIAD DLLFICVLCF VSTQVLQKSR LRGEARGEM FPGLNENLRW NEKLDKTKAE LATEAHLIIL SALDCKDSL LNCDQSTTYL IAKFGDLLFE HQVLHHCSSS TLYLLMRFSF MQVTMSLASL HLRRSLRIL MTPFPTQVEE DTVKMREFQE RIAKSYQASP AEKHTKKKCY AALVAEYLSM SVSFQNISSN TLSPDEDGVC VGLLEQAAEL NEVYKLVPI TLTHSKLQRA RMFGTYFRVG EQEFVYKEPA LEAFYGQCFG TPVDKTKLDP EPYFDEYEMK NLRRFMYTTP LHEQYRRNTV KTRISVIQKE IEDMKKKTLO DAKMLQMVLO PLEVAQVFLA HHNKLRLCFK EKNKRLITAD NYNKLKENLR YKPIFRVESQ RKCTQLSQGS	ILCSHEHYLN APTSPCPSIS QDQKIASMFD LTGLLFTELA SKVQRKAVSA DPRCVKPEVK VGIILDALPQ RYRTSGSDEE VALAIAGNNF SLPYKQYNML CFLWIMKNAD LPSTQLNRIL EYKKGQSSDK DVKARLEEAL MRRRAPGNDR KKEQTHWRQA LDQEALISGN DMQENIIQAS GGVLRLVNS THCFATLRAL EEVEQCFLDL MDVTRSQACA GATSNFARVK VGRAPDFNEE AYSEEDTAMQ LLCNLNSILY DPEMLMDLMY DLRLTWLQNM TEAMCLVHA LEDHSYLPVG VLEESVVSSED AGQYFTESGL FSTGGLYETV LEAHREFRKL FDSIVNKDHK FFGSKFGDLD ITKLPEISHR AEFVEVIKDS NKAYIQITFV DRVYFEKNF FTLEGRPRGE LTTMHAFPII EFVLTPIEVA LAVAINQEPP GSVGATVNQG EIPADPKLYR EFIMRCGEAV QREYQQELKK PMIERKIPEL KRDSFHRSSF
38	DOCK8	4	Q8NF50-4	Entry version 160 (18 Sep 2019) Sequence version 3 (21 Aug 2007)	MTHLNSLDVQ DDLDVVFTPK EEGVELDPHV WLIVNRKNQG GSRKDFHKT ECSEPAAQAG SGKGPVTACD RLENLLQQVS	LAQELGDFTD ECRTLQPSLP RDCVQTYIRE SPEICGFKKT PKQTFESETL PRHLNVLCDD FDLRLSLQPD AEDFEKQNEE

					ARRTNRQAEI	FALYPSVDEE
					DAVEIRPVPE	CPKEHLGNRI
					LVKLLTLKFE	IEIEPLFASI
					ALYDVKERKK	ISENFHCDLN
					SDQFKGFLRA	HTPSVAASSQ
					ARSAVFSVTY	PSSDIYLVVK
					IEKVLQQGEI	GDCAEPTYVI
					KESDGGKSKE	KIEKLLQAE
					SFCQRLGKYR	MPFAWAPISL
					SSFFNVSTLE	REVTDVDSVV
					GRSSVGERRT	LAQSRRLSER
					ALSLEENGVG	SNFKTSTLSV
					SSFFKQEGDR	LSDEDLFKFL
					ADYKRSSLQ	RRVKSIPGLL
					RLEISTAPEI	INCCLTPEML
					PVKPFPENRT	RPHKEILEFP
					TREVYVPHTV	YRNLLYVYPQ
					RLNFVNKLAS	ARNITIKIQF
					MCGEDASNAM	PVIFGKSSGP
					EFLQEVYTAV	TYHNKSPDFY
					EEVKIKLPAK	LTVNHLLFT
					FYHISCQQKQ	GASVETLLGY
					SWLPILLNER	LQTGSYCLPV
					ALEKLPPNYS	MHSAEKVPLQ
					NPPIKWAECH	KGVFNIEVQA
					VSSVHTQDNH	LEKFFTLCHS
					LESQVTFPIR	VLDQKISEMA
					LEHELKLSII	CLNSSRLEPL
					VLFLHLVLDK	LFQLSVQPMV
					IAGQTANFSQ	FAFESVVAIA
					NSLHNSKDLS	KDQHGRNCLL
					ASYVHYVFRL	PEVQRDVPKS
					GAPTALDPR	SYHTYGRISA
					AAVSSKLLQA	RVMSSSNPDL
					AGTHSAADEE	VKNIMSSKIA
					DRNCSRMSYY	CSGSSDAPSS
					PAAPRPASKK	HFHEELALQM
					VVSTGMVRET	VFKYAWFFFE
					LLVKSMQHV	HNMDKRDSFR
					RTRFSDRFMD	DITIVNVVT
					SEIAALLVKP	QKENEQAEKM
					NISLAFFLYD	LLSLMDRGFV
					FNLIRHYCSQ	LSAKLSNLPT
					LISMRLEFLR	ILCSHEHYLN
					LNLFMNAADT	APTSPCPSIS
					SQNSSSCSSF	QDQKIASMFD
					LTSEYRQQHF	LTGLLFTELA
					AALDAEGEGI	SKVQRKAVSA
					IHSLSSHDH	DPRCVKPEVK
					VKIAALYLPL	VGIILDALPQ
					LCDFTVADTR	RYRTSGSDEE
					QEGAGAINQN	VALAIAGNMF
					NLKTSGIVLS	SLPYKQYNML
					NADTTRNLMI	CFLWIMKNAD
					QSLIRKWIAD	LPSTQLNRIL
					DLLFICVLCF	EYKGKQSSDK
					VSTQVLQKSR	DVKARLEEAL
					LRGEGARGEM	MRRRAPGNDR
					FPGLNENLRW	KKEQTHWRQA
					NEKLDKTKAE	LDQEALISGN

					LATEAHLIIL DMQENIIQAS SALDCKDSL GGLRVLVNS LNCDQSTTYL THCFATLRAL IAKFGDLLFE EEVEQCFDLC HQVLHHCSSS MDVTRSQACA TLYLLMRFSF GATSNFARVK MQVTMSLASL VGRAPDFNEE HLRRSLRTIL AYSEEDTAMQ MTPFPTQVEE LLCNLNSILY DTVKMREFQE DPEMLMDLMY RIAKSYQASP DLRLTWLQNM AEKHTKKKCY TEAAMCLVHA AALVAEYLSM LEDHSYLPVG SVSFQNISSN VLEESVVSSED TLSPDEDGVC AGQYFTESGL VGLLEQAAEL FSTGGLYETV NEVYKLVIP I LEAHREFRKL TLTHSKLQRA FDSIVNKDHK RMFGTYFRVG FFGSKFGDLD EQEFVYKEPA ITKLPEISHR LEAFYGQCFG AEFVEVIKDS TPVDKTKLDP NKAYIQITFV EPYFDEYEMK DRVTYFEKNF NLRRFMYTTP FTLEGRPRGE LHEQYRRNTV LTTMHAFPIYI KTRISVIQKE EFVLTPIEVA IEDMKKKTLO LAVAINQEP DAKMLQMVLO 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 LTALAALGASG QGQSPLGSDL GPQMLRELQE TNAALQDVRE LLRQQVREIT FLKNTVMECD ACGMQQSVRT GLPSVRPLLH CAPGFCFPGV ACIQTESGAR CGPCPAGFTG NGSHCTDVNE CNAHPCFPRV RCINTSPGFR CEACPPGYSG PTHQGVGLAF AKANKQVCTD INECETGQHN CVPNSVCINT RGSFQCGPCQ PGFVGDAQSG CQRRARFCP DGSPSECHEH ADCVLERDGS RSCVCAVGWA GNGILCGRDT DLDGFPDEKL RCPERQCRKD NCVTVPNSSGQ EDVDRDGIGD ACDPDADGDG VPNEKDNCPL VRNPDQRNTD EDKWGDACDN CRSQKNDDQK DTDQDGRGDA CDDIDGDRI RNQADNCPRV PNSDQKSDSG DGIGDACDNC PQKSNPDQAD VDHDFVGDAC DSDQDQDGDG HQDSRDNCPT VPNSAQEDSD HDGQGDACDD DDDNDGVPDS RDNCRLLVNP GQEDADRDGV

					GDVCQDDFDA DKVVDKIDVC PENAETVLTLD FRAFQTVVLD PEGDAQIDPN WVVLNQGREI VQTMNSDPGL AVGYTAFNGV DFEGTFHVNT VTDDDYAGFI FGYQDSSSFY VVMWKQMEQT YWQANPFRAV AEPGIQLKAV KSSTGPGEQL RNALWHTGDT ESQVRLLWKD PRNVGWKDKK SYRWFLQHRP QVGYIRVRFY EGPELVADSN VVLDTTMRGG RLGVFCSFQE 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 PSECEHADDC VLERDGSRSR VCAVGWAGNG ILCGRDIDL GFPDEKLRCR ERQCRKDNVC TVPNSGQEDV DRDGIGDACD PDADGDGVPN EKDNCPLVRN PDQRNTDEDK WGDACDNCRS QKNDDQKDTD QDGRGDACDD DIDGDRIRNQ ADNCPRVVNS DQKSDSDGDI GDACDNCPCQ SNPDQADVDH DFVGDACDSD QDQDGDGHQD SRDNCPTVFN SAQEDSDHDG QGDACDDDDD NDGVPDSRDN CRLVPNPGQE DADRDGVGDV CQDDFDADKV VDKIDVCPEN AEVTLTDFRA FQTVVLDPEG DAQIDPNWVV LNQGRIEIVQT 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 KKLLEQAAN EIWESIKSGT ALENPVLLNK FLLLTADLKL KYHFYYWFCY PALCLPESLP LIQGPVGLDQ RFSCLKQIEAL

					ECAYDNLCQT EGV TALPYFL IKYDENMVLV SLLKHYSDF QGQRTKITIG VYDPCNLAQY PGWPLRNFLV LAAHRWSSSF QSVEVVCFRD RTMQGARDVA HSIIFEVKLP EMAFSPDCPK AVGWEKNQKG GMGPRMVNLS ECMDPKRLAE SSVDLNLKLM CWRLVPTLDL DKVSVKCLL LGAGTLGCNV ARTLMGWGVR HITFVDNAKI SYSNPVRQPL YEFEDCLGGG KPKALAAADR LQKIFPGVNA RGFNMSIPMP GHPVNFSSVT LEQARRDVEQ LEQLIESHDV VFLLMDTRES RWLPAVIAAS KRKLVINAAAL GFDTFVVMRH GLKKPKQQGA GDLCNHPVA SADLLGSSLF ANIPGYKLCG YFCNDVVAPG DSTRDRTLQD QCTVSRPGLA VIAGALAVEL MVSVLQHPEG GYAIASSSDD RMNEPPTSLG LVPHQIRGFL SRFDNVLPVS LAFDKCTACS SKVLDQYERE GFNFLAKVFN SSHSFLEDLT GLTLLHQETQ AAETWDMSSD 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 KKLLEQAAN EIWESIKSGT ALENPVLLNK FLLLTADL KYHFYYWFCY PALCLPESLP LIQGPVGLDQ RFLKQIEAL ECAYDNLCQT EGV TALPYFL IKYDENMVLV SLLKHYSDF QGQRTKITIG VYDPCNLAQY PGWPLRNFLV LAAHRWSSSF QSVEVVCFRD RTMQGARDVA HSIIFEVKLP EMAFSPDCPK AVGWEKNQKG GMGPRMVNLS ECMDPKRLAE SSVDLNLKLM CWRLVPTLDL DKVSVKCLL LGAGTLGCNV ARTLMGWGVR HITFVDNAKI SYSNPVRQPL YEFEDCLGGG KPKALAAADR LQKIFPGVNA RGFNMSIPMP GHPVNFSSVT LEQARRDVEQ LEQLIESHDV VFLLMDTRES RWLPAVIAAS KRKLVINAAAL GFDTFVVMRH GLKKPKQQGA GDLCNHPVA SADLLGSSLF ANIPGYKLCG YFCNDVVAPG DSTRDRTLQD QCTVSRPGLA VIAGALAVEL MVSVLQHPEG GYAIASSSDD RMNEPPTSLG LVPHQVLDQY EREGFNFLAK

					VFNSSHSFLE DLTGLTLLHQ ETQAAEIWDM SDETI
43	ATG7	3	O95352-3	Entry version 168 (18 Sep 2019) Sequence version 1 (01 May 1999)	MAAATGDPGL SKLQFAPFSS ALDVGFHWEL TQKKLNEYRL DEAPKDIKGY YYNGDSAGLP ARLTLEFSAF DMSAPTPARC CPAIGTLYNT NTLESFKTAD KKLLLEQAAN EIWESIKSGT ALENPVLLNK FLLLTFAIEA LECAYDNLCQ TEGVTALPYF LIKIDENMVL VSLKHYSDF FQGQRTKITI GVIDPCNLAQ YPGWPLRNFV VLAHRWSSS FQSVEVCFR DRTMQGARDV AHSIIFEVKL PEMAFSPDCP KAVGWEKNQK GGMGPRMVNL SECMDPKRLA ESSVDLNLKL MCWRLVPTLD LDKVSVKCL LLGAGTLGCN VARTLMGWGV RHITFVDNAK ISYSPVRQP LYEFEDCLGG GKPKALAAAD RLQKIFPGVN ARGFNMSIPM PGHPVNFSSV TLEQARRDVE QLEQLIESHD VVFLMDTRE SRWLPAVIAA SKRKLVINAA LGFDTFVVMR HGLKKPKQQG AGDLCPNHPV ASADLLGSSL FANIPGYKLG CYFCNDVVAP GDSTRDRLD 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 LGSQFGYNT GVINAPQKVI EEFYNTQWVH RYGESILPTT LTTLSLSVA IFSVGMIGS FSVGLFVNRF GRRNSMLMMN LLAFVSAVLM GFSKLKGSFE MLILGRFIIG VYCGLTGTFV PMYVGEVSPT ALRGALGTLH QLGIVVGILI AQVFGLDLIM GNKDLWPLLL SIIFIPALLQ CIVLPFCPEP PRFLLINRNE ENRAKSVLKK LRGTADVTHD LQEMKEESRQ MMREKKVTIL ELFRSPAYRQ PILIAVVLQL SQQLSGINAV FYYSTSIFEK AGVQQPVYAT IGSIVNTAF TVVSLFVVER AGRRTLHLIG LAGMAGCAIL MTIALALLEQ LPWMSYLSIV AIFGFVAFFE VGPGPIWFI VAELEFSQGP PAAIAVAGFS NWTSNFIVGM CFQYVEQLCG PYVFIIFTVL LVLFIFTYF KVPETKGRTE 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 WVLTAHCQY RFTKGQSPTV VLGAHSLSKN EASKQTLLEIK KFIPFSRVTS DPQSNIDMLV KLQTAAKLNK HVKMLHIRSK TSLRSGTKCK VTGWGATDPD SLRPSDTLRE VTVTVLSRKL CNSQSYNGD PFITKDMVCA GDAKGQKDSK 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 VRKDLQNFLL KENKNEKVIE HIMEDLDINA DKQLSFEEFI MLMARLTWAS HEKMHEGDEG PGHHHKPGLG EGTP
47	S100A8	1	P05109	Entry version 209 (18 Sep 2019) Sequence version 1 (01 Jan 1988)	MLTELEKALN SIIDVYHKYS LIKGNFHAVY RDDLLKLLLET ECPQYIRKKG ADVWFKELDI NTDGAVNFQE FLILVIKMGV AAHKSHEES HKE
48	ATM	1	Q13315	Entry version 236 (18 Sep 2019) Sequence version 4 (22 Jan 2014)	MSLVLNLLI 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 LNDLSKEVII ELFQLQIYIH HPKGAKTQEK GAYESTKWRS ILYNLYDLLV NEISHIGSRG KYSSGFRNIA VKENLIELMA DICHQVFNED TRSLEISQSY TTTQRESSDY SVPCKRRKIE LGWEVIKDHL QKSQNDFDLV PWLQIATQLI SKYPASLPNC ELSPLLMILS QLLPQQRHGE RTPYVLRCLT EVALCQDKRS NLESSQKSDL LKLWNKIWCI TFRGISSEQI QAENFGLLGA IIQGSLEVD REFWKLFSG ACRPSCPAVC CLTLALTTSI VPGTVKMGIE QNMCEVNRSF SLKESIMKWL LFYQLEGDLE NSTEVPPILH SNFPHLVLEK ILVSLTMKNC

					KAAMNFFQSV	PECEHHQKDK
					EELSFSEVEE	LFLQTTFDKM
					DFLTIVRECG	IEKHQSSIGF
					SVHQNLKESL	DRCLLGLSEQ
					LLNNYSSEIT	NSETLVRCSSR
					LLVGVLGCYC	YMGVIAEEEE
					YKSELFQKAK	SLMQCAGESI
					TLFKNKTNNEE	FRIGSLRNMM
					QLCTRCLSNC	TKKSPNKIAS
					GFFLRLLTSK	LMNDIADICK
					SLASFIKKPF	DRGEVESMED
					DTGNLMEVE	DQSSMNLFND
					YPDSSVSDAN	EPGESQSTIG
					AINPLAEEYL	SKQDLLFLDM
					LKFLCLCVTT	AQTNTVSFRA
					ADIRRKLLML	IDSSTLEPTK
					SLHLHMYLML	LKELPGEEYP
					LPMEDVLELL	KPLSNVCSLY
					RRDQDVCKTI	LNHVLHVKN
					LGQSNMDSN	TRDAQGQFLT
					VIGAFWHLTK	ERKYIFSVRM
					ALVNCLKTLL	EADPYSKWAI
					LNVMGKDFPV	NEVFTQFLAD
					NHHQVRMLAA	ESINRLFQDT
					KGDSSRLKA	LPLKLQQTAF
					ENAYLKAQEG	MREMSHSAEN
					PETLDEIYNR	KSVLLTLIAV
					VLSCSPICEK	QALFALCKSV
					KENGLEPHLV	KKVLEKVSET
					FGYRRLEDFM	ASHLDYLVLE
					WNLNQDTEYN	LSFPPFILLN
					YTNIEDFYRS	CYKVLIPHLV
					IRSHFDEVKS	IANQIQEDWK
					SLLTDCFPKI	LVNILPYFAY
					EGTRDSGMAQ	QRETATKVYD
					MLKSENLLGK	QIDHLFISNL
					PEIVVELLMT	LHEPANSSAS
					QSTDLCDFSG	DLDPAFNPPH
					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	VGSCLEGEVGP
					IDFSTIAIQH	SKDASYTKAL
					KLFEDKELQW	TFIMLTYLNN
					TLVEDCVKVR	SAAVTCLKNI
					LATKTGHSFW	EIYKMTTDPM
					LAYLQPFRTS	RKKFLEVPRF
					DKENPFEGLD	DINLWIPLSE
					NHDIWIKTLT	CAFLDSSGGTK

					CEILQLLKPM	CEVKTDFCQT
					VLPLYLIHDIL	LQDTNESWRN
					LLSTHVQGFF	TSCLRHFSQT
					SRSTTPANLD	SESEHFFRCC
					LDKKSQRTML	AVVDYMRRQK
					RPSSGTIFND	AFWLDLNYLE
					VAKVAQSCAA	HFTALLYAEI
					YADKKSMDDQ	EKRSLAFEEG
					SQSTTISSLS	EKSKEETGIS
					LQDLLLEIYR	SIGEPDSLYG
					CGGGKMLQPI	TRLRTYEHEA
					MWGKALVTD	LETAIPSSTR
					QAGIIQALQN	LGLCHILSVY
					LKGLDYENKD	WCPELEELHY
					QAAWRNMQWD	HCTSVSKEVE
					GTSYHESLYN	ALQSLRDREF
					STFYESLYA	RVKEVEEMCK
					RSLESVYSLY	PTLSRLQAIG
					ELESIGELFS	RSVTHRQLSE
					VYIKWQKHSQ	LLKDSDFSFO
					EPIMALRTVI	LEILMEKEMD
					NSQRECIKDI	LTKHLVELSI
					LARTFKNTQL	PERAIFQIKQ
					YNSVSCGVSE	WQLEEAQVFW
					AKKEQSLALS	ILKQMIKKLD
					ASCAANNPSL	KLTYTECLRV
					CGNWLAECL	ENPAVIMQTY
					LEKAVEVAGN	YDGESSDELR
					NGKMKAFSL	ARFSDTQYQR
					IENYMKSSSEF	ENKQALLKRA
					KEEVGLLREH	KIQTNRYTVK
					VQRELELDEL	ALRALKEDRK
					RFLCKAVENY	INCLLSGEEH
					DMWVFRCLSL	WLENSGVSEV
					NGMMKRDGMK	IPTYKFLPLM
					YQLAARMGTK	MMGGLGFHEV
					LNNLISRISM	DHPHHTLFII
					LALANANRDE	FLTKPEVARR
					SRITKNVPKQ	SSQLDEDRTE
					AANRIICTIR	SRRPQMVRSV
					EALCDAYIIL	ANLDATQWKT
					QRKGINIPAD	QPITKLNLE
					DVVVPTMEIK	VDHTGEYGNL
					VTIQSFKAEF	RLAGGVNLPK
					IIDCVGSDGK	ERRQLVKGRD
					DLRQDAVMQQ	VFQMCNTLLQ
					RNTETRKRL	TICTYKVVP
					SQRSGVLEWC	TGTVPIGEFL
					VNNEDGAHKL	YRPNDFAFQ
					CQKKMMEVQK	KSFEELYEVF
					MDVCQNFQPV	FRYFCMEKFL
					DPAIWFEKRL	AYTRSVATSS
					IVGYILGLGD	RHVQNILINE
					QSAELVHIDL	GVAFEQGKIL
					PTPETVPFRL	TRDIVDGMGI
					TGVEGVFRRC	CEKTMEVMRN
					SQETLLTIVE	VLLYDPLFDW
					TMNPLKALYL	QQRPEDETEL
					HPTLNADDQE	CKRNLSDIDQ
					SFNKVAERVL	MRLQEKLGKV

					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 GGDLRKLYNQ FENCCGLREG AILTLLSDIA SALRYLHENR IIHRDLKPEN IVLQQGEQRL IHKIIDLGYA KELDQGSLECT SFVGTQLQYLA PELLEQQKYT VTVDYWSFGT LAFECITGFR PFLPNWQPVQ WSKVRQKSE VDIVVSEDLN GTVKFSSSLP YPNNLNSVLA ERLEKWLQLM LMWHPRQRGT DPTYGPNCGF KALDDILNLK LVHILNMVTG TIHTYPVTED ESLQSLKARI QQDTGIPEED QELLQEAGLA LIPDKPATQC ISDGKLNESH TLDMDLVFLF DNSKITIYETQ ISPRQPESV SCILQEPKRN LAFFQLRKVW GQVWHSIQTL KEDCNRLQQG QRAAMNLLR NNSCLSKMKN SMASMSQQLK AKLDFFKTSI QIDLEKYSEQ TEFGITSCLK LLAWREMEQA VELCGRENEV KLLVERMMAL QTDIVDLQRS PMGRKQGGTL DDLEEQAREL YRRLREKPRD QRTEGDSQEM VRLLLQAIQS FEKKVRVIYT QLSKTVCKQ KALELLPKVE EVVSLMNEDE KTVVRLQEKR QKELWNLLKI ACSKVRGPVS GSPDSMNASR LSQPGQLMSQ PSTASNSLPE PAKKSEELVA EAHNLCTLLE NAIQDTVREQ DQSFTALDWS WLQTEEEHS CLEQAS
50	IKBKB	2	O14920- 2	Entry version 217 (18 Sep 2019) Sequence version 1 (01 Jan 1998)	MFSGGCHSPG FGRPSAPFPA PGSPPPAPRP CRQETGEQIA IKQCRQELSP RNRERWCLEI QIMRRLTHPN VVAARDVPEG MQNLAPNDLP LLAMEYCQGG DLRKLYNQFE NCCGLREGAI LTLLSDIASA LRYLHENRII HRDLKPENIV LQQGEQRLIH KIIDLGYAKE LDQGSLECTSF VGTLQYLAPL LLEQQKYTVT VDYWSFGTLA FECITGFRPF LPNWQPVQWH SKVRQKSEVD IVVSEDLNGT VKFSSSLPYP NNLNSVLAER LEKWLQLMLM WHPRQRGTD TPYGPNGCFKA LDDILNLKLV HILNMVTGTI HTYPVTEDES LQSLKARIQQ DTGIPEEDQE LLQEAGLALI

					PDKPATQCIS DGKLNIGHTL DMDLVFLFDN SKITYETQIS PRPQPESVSC ILQEPKRNLA FFQLRKVWQQ VWHSIQTLKE DCNRLQQGQR AAMNLLRNN SCLSKMKNSM ASMSQQLKAK LDFFKTSIQI DLEKYSEQTE FGITSDKLLL AWREMEQAVE LCGRENEVKL LVERMMALQT DIVDLQRSFM GRKQGGTLDD LEEQARELYR RLREKPRDQR TEGDSQEMVR LLLQAIQSFE KKVRIYITQL SKTVVCKQKA LELLPKVEEV VSLMNEDEKT VVRLQEKRQK ELWNLLKIAC SKVRGPVSGS PDSMNASRLS QPGQLMSQPS TASNLSPEPA KKSEELVAEA HNLCTLLENA IQDTVREQDQ SFTALDWSWL QTEEEHSCL 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 EGMQNLAEND LPLAMEYCQ GGDRLKYLNQ FENCCGLREG AILTLLSDIA SALRYLHENR IHRDLKPEN IVLQQGEQRL IHKIIDLGYA KELDQGSCLT SFVGTILQYLA PELLEQQKYT VTDVYWSFGT 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 DLPLAMEYC QGGDLRKYL N FENCCGLRE GAILTLLSDI ASALRYLHEN RIIHRDLKPE NIVLQQGEQR LIHKIIDLGY AKELDQGSCL TSFVGTILQYL APELLEQQKY TVTDVYWSFG TLAFCITGFR RPFLPNWQPV QWHSKVRQKS EVDIVVSEDL NGTVKFSSSL PYPNNLNSVL AERLEKWLQL MLMWHPRQRG TDPTYGPNGC FKALDDILNL KLVHILNMVT GTIHTYPVTE DESLQSLKAR IQQDTGIPEE DQELLQEAGL ALIPDKPATQ CISDGKLNEL HTLDMDLVFL FDNSKITIYET QISPRQPES VSCILQEPKR NLAFFQLRKV WQVWHSIQT LKEDCNRLQQ GQRAAMNLL RNNCLSKMK NSMASMSQQL KAKLDFFKTS IQIDLEKYSE QTEFGITSDK LLLAWREMEQ AVELCGRENE VKLLVERMMA LQTDIVDLQR SPMGRKQGGT

					LDDLEEQARE LYRRLREKPR DQRTEGDSQE MVRLLQAIQ SFEKKVRVIY TQLSKTVVCK QKALELLPKV EEVVSMLNED EKTIVVRLQEK RQKELWNLLK IACSKVRGPV SGSPDSMNAS RLSQPGQLMS QPSTASNSLP EPAKKSEELV AEAHNLCTLL ENAIQDTVRE QDQSFTALDW SWLQTEEEH 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 KEYDRLLLEEH AKLQAAVDGP MDKKEE
54	BCAP31	2	P51572- 2	Entry version 186 (18 Sep 2019) Sequence version 3 (23 Jan 2007)	MGAEASSSWC PGTALPEERL SVKRASEISG FLGQGSSGEA ALDVLTHVLE GAGNKLITSSC GKPSSNRMSL QWTAVATFLY AEVFVVLVLLC IPFISPKRWQ KIFKSRLVEL LVSYGNTFFV VLIVILVLLV IDAVREIRKY DDVTEKVNLO NNPGAMEHFH MKLFRAQRNL YIAGFSLLLS FLLRRLVTLI SQQATLLASN EAFKKQAESA SEAAKKYMEE NDQLKKGA AV DGGKLDVGNA EVKLEENRS LKADLQKLKD ELASTKQKLE KAENQVLAMR KQSEGLTKEY DRLLLEEHAKL QAAVDGPM D KEE
55	TAPBP	1	O15533	Entry version 190 (18 Sep 2019) Sequence version 1 (01 Jan 1998)	MKSLSLLLAV ALGLATAVSA GPAVIECWV EDASGKGLAK RPGALLLRQG PGEPPPRPDL DPELYLSVHD PAGALQAAFR RYPRGAPAPH CEMSFRVPLP ASAKWASGLT PAQNCPRALD GAWLMVSISS PVLSSLRLLR PQPEPQQEPV LITMATVVLT VLTHTPAPRV RLGQDALLDL SFAYMPPTSE AASSLAPGPP PFGLEWRRQH LGKGHLLAA TPGLNGQMPA AQEGAVAFAA WDDDEPWGPW TNGTFWLPR VQPFQEGTYL ATIHLPYLQG QVTLELAVYK PPKVSLMPAT LARAAPGEAP PELLCLVSHF YPSGGLEVEW ELRGPGGRS QKAEGQRWLS ALRHHSDGSV

					SLSGHLQPPP VTTEQHGARY ACRIHHPSLP ASGRSAEVTL EVAGLSGPSL EDSVGLFLSA FLLLGLFKAL GWAAYVLSTC KDSKKKAE
56	TAPBP	2	O15533-2	Entry version 190 (18 Sep 2019) Sequence version 1 (01 Jan 1998)	MKSLSLLLAV ALGLATAVSA GPAVIECWV EDASGKGLAK RPGALLLRQG PGEPPRPDL DPELYLSVHD PAGALQAAFR RYPRGAPAPH CEMSFRVPLP ASAKWASGLT PAQNCPRALD GAWLMVSISS PVLSSLSSLLR PQPEPQQEPV LITMATVVLT VLTHTPAPRV RLQDALLDL SFAYMPPTSE AASSLAPGPP PFGLEWRRQH LGKGHLLAA TPGLNGQMPA AQEGAVAFAA WDDDEPWGPW TGNGTFWLPR VQPFQEGTYL ATIHLPYLQG QVTLELAVYK PPKVSLMPAT LARAAPGEAP PELLCLVSHF YPSGGLEVEW ELRGGPGGRS QKAEGQRWLS ALRHSDGSV 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 GPAVIECWV EDASGKGLAK RPGALLLRQG PGEPPRPDL DPELYLSVHD PAGALQAAFR RYPRGAPAPH CEMSFRVPLP ASAKWASGLT PAQNCPRALD GAWLMVSISS PVLSSLSSLLR PQPEPQQEPV LITMATVVLT VLTHTPAPRV RLQDALLDL SFAYMPPTSE AASSLAPGPP PFGLEWRRQH LGKGHLLAA TPGLNGQMPA AQEGAVAFAA WDDDEPWGPW TGNGTFWLPR VQPFQEGTYL ATIHLPYLQG QVTLELAVYK PPKVSLMPAT LARAAPGEAP PELLCLVSHF YPSGGLEVEW ELRGGPGGRS QKAEGQRWLS ALRHSDGSV SLSGHLQPPP VTTEQHGARY ACRIHHPSLP ASGRSAEVTL EVAGLSGPSL EDSVGLFLSA FLLLGLFKAL GWAAYVLSTC KDSKKVQCST SLYLSLVTLS PHPISKPMEG GCWCGRQNLG LEFTLIWVKT WHYILTVGLF EHAT
58	TAPBP	4	O15533-4	Entry version 190 (18 Sep 2019) Sequence version 1 (01 Jan 1998)	MKSLSLLLAV ALGLATAVSA GPAVIECWV EDASGKGLAK RPGALLLRQG PGEPPRPDL DPELYLSVHV VLTVLTHTPA PRVRLGQDAL LDLSFAYMPP

				Jan 1998)	TSEAASSLAP RQHLGKGHLL MPAAQEGAVA GPWTGNGTFW TYLATIHLPY VYKPPKVSLM EAPPELLCLV VEWELRGPG WLSALRHHSD PPPVTTEQHG SLPASGRSAE PSLEDSVGLF KALGWAAVYL E	GPPPFGLEWR LAATPGLNGQ FAAWDDDEPW LPRVQPFQEG LQQQVTLLELA PATLARAAPG SHFYPSGGLE GRSQKAEGQR GSVSLSGHLQ ARYACRIHHP VTLEVAGLSG LSAFLLGLF STCKDSKKKA
59	PPP3CB	1	P16298	Entry version 166 (18 Sep 2019) Sequence version 2 (01 Feb 2005)	MAAPEPARAA PGADRVKAV EEVFDLDGIP KEGRVDEEIA LRREKTMIEV HGQFFDLMKL RYLFLGDYVD YLWVLKILYP ECRHLTEYFT ERVYEACMEA NQQFLCVHGG IRRLDRFKEP WSDPSEDFGN TVRGCSYFYN NNLLSIIRAH RKSQTTGFPS LDVYNNKAAV RQFNCSPPHY WSLPFVGEKV CSDDELMTEG RKEIIRNKIR VLREESESVL LPSGVLAGGR IEAEKAIRGF EAKGLDRINE QDGFNSLNTA HTAQ	PPPPPPPPPP PFPPTHRLTS RVDVLKNHLV LRIINEGAII EAPITVCGDI FEVGGSPANT RGYFSIECVL STLFLLRGNH FKQECHKIKYS FDSLPLAALL LSPEIHTLDD PAFGPMCDLL EKSQEHFSHN YPAVCEFLQN EAQDAGYRMY LITIFSAPNY LKYENNVMMNI WLPNFMDFVT TEMLVNVLSI EDQFDGSAAA AIGKMARVFS TLKGLTPTGM QTLQSATVEA SPPHRICSFE RMPPRKDAVQ HATENHGTGN
60	PPP3CB	2	P16298- 2	Entry version 166 (18 Sep 2019) Sequence version 2 (01 Feb 2005)	MAAPEPARAA PGADRVKAV EEVFDLDGIP KEGRVDEEIA LRREKTMIEV HGQFFDLMKL RYLFLGDYVD GTEDISINPH WVLKILYPST RHLTEYFTFK VYEACMEAFD QFLCVHGGLS RLDRFKEPPA DPSEDFGNEK RGCSYFYNY LLSIIRAHEA SQTTFPSLI	PPPPPPPPPP PFPPTHRLTS RVDVLKNHLV LRIINEGAII EAPITVCGDI FEVGGSPANT RGYFSIEHVL NNINECVLYL LFLLRGNHEC QECHKIKYSER SLPLAALLNQ PEIHTLDDIR FGPMCDLLWS SQEHFSHNTV AVCEFLQNNN QDAGYRMYRK TIFSAPNYLD

					VYNNKAAVLK YENNVNMIRQ FNCSPHPYWL PNFMDVFTWS LPFVGEKVTE MLVNVLSICS DDELMTEGED QFDGSAAARK EIIRNKIRAI GKMARVFSVL REESESVLTL KGLTPTGMLP SGVLAGGRQT LQSGNDVMQL AVPQMDWGT P HSFANNSHNA CREFLFFSS CLSS
61	PPP3CB	3	P16298-3	Entry version 166 (18 Sep 2019) Sequence version 2 (01 Feb 2005)	MAAPEPARAA PPPPPPPPPP PGADRVKAV 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 LKYENNVMMNI RQFNCSPHPY WLPNFMDVFT WSLPFVGEKV TEMLVNVLSI CSDDLMTEG EDQFDVGSAA ARKEIIRNKI RAIGKMARVF SVLREESESV LTLKGLTPTG MLPSGVLGG 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 PGADRVKAV 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 LKYENNVMMNI RQFNCSPHPY WLPNFMDVFT WSLPFVGEKV TEMLVNVLSI CSDDLMTEG EDQFDVGSAA ARKEIIRNKI RAIGKMARVF SVLREESESV LTLKGLTPTG MLPSGVLGG RQTLQSATVE

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

					NSYPRDFVNC WREAS	STLPALNLAS
65	PERM	2	P05164- 2	Entry version 221 (18 Sep 2019) Sequence version 1 (13 Aug 1987)	MELLSYFKQP ADYLHVALDL RPFNVTDLT SGCAYQDVG ITGMCNNRRS VRWLPAEYED GVKRNGFPVA RFPTDQLTPD GQLLDHDLDF VTGVNCTESC IPPNDPRIKN CPACPGSNIT FVDASMVYGS MSNQLGLLAV LLPFDNLHDD IPCFLAGDTR HTLLLRHNR RWDGERLYQE IITYRDYLP LPTYRSYND NAFRYGHITI YQPMENPRV RVVLEGGIDP KLNRQNIQAV VMRIGLDLPA LPGYNARWR QLGTVLRNLK TPNNIDIWGM RVGPLLACII DRFWWENEGV QISLPRIICD NIFMSNSYPR LNLASWREAS	VAATRTAVRA LERKLRSLWR PAQLNVLSKS TCPEQDKYRT PTLGASNRAF GFSLPYGWTP LARAVSNEIV QERSLMFMQW TPEPAARASF VQPPPCFPLK QADCIPFFRS IRNQINALTS EEPLARNLRN NQRFQDNGRA PCLLTNRSAR SSEMPELTSM LATELKSLNP ARKIVGAMVQ VLGPTAMRKY VDPRIANVFT QPFMFRDNR PLSRVFFASW ILRGLMATPA DEIRERLFEQ LNMQRSDHG CGLPQPETVG LARKLMEQYG GVSEPLKRRG GTQFRKLRDG FSMQQRQALA NTGITTVSKN DFVNCSTLPA
66	PERM	3	P05164- 3	Entry version 221 (18 Sep 2019) Sequence version 1 (13 Aug 1987)	MGVPPFFSSLR GGLTAEMKLL ATPQPSEGAA LVLSSMEEAK RESIKQRLRS YFKQPVAATR VALDLLERKL TDVLTQAQLN QDVGVTCEPQ NNRCGWLGA TPQASRCQRP GASNRAFVRW LPYGWTPGVK AVSNEIVRFP SLMFMQWGQL PAARASFVTG PPCFPLKIPP CIPFFRSCPA QINALTSFVD LARNLRNMSN FQDNGRALLP LTNRSARIPC MPELTSMHTL	CMVDLGPCWA LALAGLLAIL PAVLGEVDTS QLVDKAYKER GSASPMELLS TAVRAADYLH RSLWRRPFNV VLSKSSGCAY DKYRTITGMC AGTGLREASR VLPCRRSPTL LPAEYEDGFS RNGFPVALAR TDQLTPDQER LDHDLDFTE VNCETSCVQQ NDPRIKNQAD CPGSNITIRN ASMVYGSEEP QLGLLAVNQ FDNLHDDPCL FLAGDTRSS LLREHNRLAT

					ELKSLNPRWD GERLYQEAR IVGAMVQIIT YRDYLPVLV PTAMRKYLPT YRSYNDSDVP RIANVFTNAF RYGHTLIQPF MFRLDNRYQP MEPNPRVPLS RVFFASWRVV LEGGIDPILR GLMATPAKLN RQNQIAVDEI RERLFEQVMR IGLDLPALNM QRSRDHGLPG YNAWRRFCGL PQPETVGQLG TVLRNLKLAR KLMEQYGTPN NIDIWMGGVS EPLKRKGRVG PLLACIIGTQ FRKL RDGDRF 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 RRPRLPHPHV 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 QSEDMTAKK LLLWSQRMVE GYQGLRCDNF TSSWRDGRLF NAIHRHKPL LIDMNKVYRQ TNLENLDQAF SVAERDLGVT RLDPEDVDV PQPDEKSIIT YVSSLYDAMP RVPDVQDGVR ANELQLRWQE YRELVLVLLQ WMRHHTAAFE ERRFPSSFEE IEILWSQFLK FKEMELPAKE ADKNRSKGIY QSLEGAVQAG QLKVPPGYHP LDVEKEWGKL HVAILEREKQ LRSEFERLEC LQRIVTKLQM EAGLCEEQLN QADALLQSDV RLLAAGKVPQ RAGEVERDL KADSMIRLLF NDVQTLKDR HPQGEQMYRR VYRLHERLVA IRTEYNLRLK AGVAAPATQV AQVTLQSVQR RPELEDSTLR YLQDLLAWVE ENQHRVDGAE WGVLDPSVEA QLGSRLGLHQ SIEEFRAKIE RARSDEGQLS PATRGAYRDC LGRDLQYAK LLNSSKARLR SLESLSFVA AATKELMWLN EKEEEVGF WSDRNTNMTA KESYSALMR ELELKEKKIK ELQAGDRLL REDHPARPTV ESFQAALQTQ

					WSWMLQLCCC	IEAHLKENAA
					YFQFFSDVRE	AEGQLQKLQE
					ALRRKYSCDR	SATVTRLEDL
					LQDAQDEKEQ	LNEYKGHL SG
					LAKRAKAVVQ	LKPRHPAHPM
					RGRLLPLAVC	DYKQVEVT VH
					KGDECQLVGP	AQPSHWKVLS
					SSGSEAAVPS	VCFLVPPPNQ
					EAQEAVTRLE	AQHQAALVTLW
					HQLHVD MKSL	LAWQSLRRDV
					QLIRSWSLAT	FRTLKPEEQR
					QALHSLELHY	QAFLRDSQDA
					GGFGPEDRLM	AEREYGCSCSH
					HYQQLLQSLE	QGAQEESRCQ
					RCISELKDIR	LQLEACETRT
					VHRLRLPLDK	EPARECAQRI
					AEQQAQAEV	EGLGKGVARL
					SAEAEKVLAL	PEPSPAAPT L
					RSELELT LK	LEQVRSLSAI
					YLEKLKTISL	VIRGTQGAEE
					VLRAHEEQLK	EAQAVPATLP
					ELEATKASLK	KLRAQAE AQQ
					PTFDALRDEL	RGAQEVGERL
					QQRHGERDVE	VERWRERVAQ
					LLERWQAVLA	QTDVRQRELE
					QLGRQLRYR	ESADPLGAWL
					QDARRRQE QI	QAMPLADSQA
					VREQLRQEQA	LLEEIERHGE
					KVEECQRF AK	QYINAIKDYE
					LQLVTYKAQL	EPVASPAKKP
					KVQSGSESVI	QEYVDLRTHY
					SELTTLTSQY	IKFISETLRR
					MEEEERLAEQ	QRAEERERLA
					EVEAALEKQR	QLAEAHQAQAK
					AQAEREAKEL	QQRMQEEVVR
					REEAAVDAQQ	QKRSIQEELQ
					QLRQSSEAEI	QAKARQAEEA
					ERSRLRIEEE	IRVRLQLEA
					TERQRGGAEG	ELQALRARAE
					EAEAQKRQAQ	EEAERLRRQV
					QDESQRKRQA	EVELASRVKA
					EAEAAREKQR	ALQALEELRL
					QAEEAERRLR	QAEVERARQV
					QVALETAQRS	AEAELQSKRA
					SFAEKTAQLE	RSIQEEHVAV
					AQLREEAERR	AQQQAEEAERA
					REEAERELE R	WQLKANEALR
					LRLQAEEVAQ	QKSLAQAEAE
					KQKEEAEREA	RRRGKAEEQA
					VRQRELAEQE	LEKQRQLAEG
					TAQQRLAAEQ	ELIRLRAETE
					QGEQQRQLLE	EELARLQREA
					AAATQKRQEL	EAEALAKVRAE
					MEVLLASKAR	AEEESRSTSE
					KSKQRLEAEA	GRFRELAEEA
					ARLRALAE EA	KRQRQLAEED
					AARQRAEAER	VLAEKLA AIG
					EATRLKTEAE	IALKEKEAEN
					ERLRRLAEDE	AFQRRRLEE Q
					AAQHKADIEE	RLAQLRKASD

					SELERQKGLV	EDTLRQRRQV
					EEEILALKAS	FEKAAAGKAE
					LELELGRIRS	NAEDTLRSKE
					QAELEAARQR	QLAAEEERRR
					REAEERVQKS	LAAEEEAARQ
					RKAALEEVER	LKAKVEEARR
					LRERAEQESA	RQLQLAQEAA
					QKRLQAEEKA	HAFVQQKEQ
					ELQQTLLQEQ	SVLDQLRGEA
					EAARRAAEEA	EEARVQAERE
					AAQSRRQVEE	AERLKQSAEE
					QAQARAQAQA	AAEKLKKEAE
					QEAARRAQAE	QAALRQKQAA
					DAEMEKHKKF	AEQTLRQKAO
					VEQELTTLRL	QLEETDHQKN
					LLDEELQRLK	AEATEAARQR
					SQVEEELFSV	RVQMEELSKL
					KARIEAENRA	LILRDKDNTQ
					RFLQEEAEKM	KQVAEEAARL
					SVAAQEAAARL	RQLAEEDLAQ
					QRALAEKMLK	EKMQAVQEAT
					RLKAEAEELLQ	QQKELAQEQA
					RRLQEDKEQM	AQQLAEETQG
					FORTLEAERQ	RQLEMSAEAE
					RLKLRVAEMS	RAQARAEEA
					QRFRKQAEI	GEKLHRTCLA
					TQEKVTLVQT	LEIQRQQSDH
					DAERLREATA	ELEREKEKLQ
					QEAKLLQLKS	EEMQTVQEEQ
					LLQETQALQQ	SFLSEKDSLL
					QRERFIEQEK	AKLEQLFQDE
					VAKAQQLREE	QQRQQQQMEQ
					ERQRLVASME	EARRRQHEAE
					EGVRRKQEEL	QQLEQQRRQQ
					EELLAENQR	LREQLQLLEE
					QHRAALAHSE	EVTASQVAAT
					KTLPNGRDAL	DGPAAEAPE
					HSFDGLRRKV	SAQRLQEAGI
					LSAEELQRLA	QGHTTVDELA
					RREDVRHYLQ	GRSSIAGLLL
					KATNEKLSVY	AALQRQLLSP
					GTALILLEAQ	AASGFLLDPV
					RNRRLTVNEA	VKEGVVGPEL
					HHKLLSAERA	VTGYKDPYTG
					QQISLQAMQ	KGLIVREHGI
					RLLEAQIATG	GVIDPVHSHR
					VPVDVAYRRG	YFDEEMNRVL
					ADPSDDTKGF	FDPNTHNLT
					YLQLLERCVE	DPETGLCLLP
					LTDKAAKGGE	LVYTDSEARD
					VFEKATVSAP	FGKFQGKTVT
					IWEIINSEYF	TAEQRRDLLR
					QFRTGRITVE	KIIKIIITTV
					EEQEKGRLC	FEGRLSLVPA
					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
					DTKEKVSIE	AMRRGLLRAT
					TAALLLEAQA	ATGFLVDPVR
					NQRLYVHEAV	KAGVVGPELH
					EQLLSAEKAV	TGYRDPYSGS
					TISLFQAMQK	GLVLRQHGR
					LLEAQIATGG	IIDPVHSHRV
					PVDVAYQRCY	FSEEMNRVLA
					DPSDDTKGFF	DPNTHENLTY
					RQLLERCVED	PETGLRLLPL
					KGAEKAEVVE	TTQVYTEEET
					RRAFEETQID	IPGGGSHGGS
					TMSLWEVMQS	DLIPEEQRAQ
					LMADFQAGRV	TKERMIIIII
					EIIKTEIIR	QQGLASYDYV
					RRRLTAEDLF	EARIISLETY
					NLLREGTRSL	REALEAESAW
					CYLYGTGSVA	GVYLPGSRQT
					LSIYQALKKG	LLSAEVARLL
					LEAQAATGFL	LDPVKGERLT
					VDEAVRKGLV	GPELHDRLLS
					AERAVTGYRD	PYTEQTISLF
					QAMKKELIPT	EEALRLDDAQ
					LATGGIVDPR	LGFHLPLEVA
					YQRGYLNKDT	HDQLSEPSEV
					RSYVDPSTDE	RLSYTQLLRR
					CRRDDGTGQL	LLPLSDARKL
					TFRGLRKQIT	MEELVRSQVM
					DEATALQLRE	GLTSIEEVTK
					NLQKFLECTS	CIAGVFVDAT
					KERLSVYQAM	KKGIIRPGTA
					FELLEQAAT	GYVIDPIKGL
					KLTVEEAVRM	GIVGPEFKDK
					LLSAERAVTG	YKDPYSGKLI
					SLFQAMKKGL	ILKDHGIRLL
					EAQIATGGII	DPEESHRLPV
					EVAYKRGLED	EEMNEILTDP
					SDDTKGFFDP	NTEENLTYLQ
					LMERCITDPQ	TGLCLLPLKE
					KKRERKTSSK	SSVRKRRVVI
					VDPETGKEMS	VYEAYRKGLI
					DHQTYLELSE	QECEWEEITI
					SSSDGVVKSM	IIDRRSGRQY
					DIDDAIAKNL	IDRSALDQYR
					AGTLSITEFA	DMLSGNAGGF
					RSRSSSVGSS	SSYPISPAVS
					RTQLASWSDP	TEETGPVAGI
					LDTETLEKVS	ITEAMHRNLV

					DNITGQRLLE PSTGERFPVT IMVDRINLAQ TKTKMSAAQA GQRFLEVQYL GRVPLDEALQ KLRDVGAYSK ISYKDALDRS LEAAQSTKG GSTAGSRTGS GSFDATGSGF SSGYGRRYAS SAVA	AQACTGGIID DAVNKGLVDK KAFCGFEDPR LKKGWLYYEA TGGLIEPDTP RGTVDARTAQ YLTCPKTKLK MVEEGTGLRL YYSPYSVSGS RTGSRAGSRR SMTFSSSSYS GSSASLGGPE
68	PLEC	2	Q15149-2	Entry version 224 (18 Sep 2019) Sequence version 3 (14 Oct 2008)	MSGEDAEVRA GSPSPGDTLP RSGGGAGSNG IRIADERDRV KHLIKAQRHI HNLIISLLEVL RMRFHKLQNV QVKLVNIRND LGLIWTIILH QSEDMTAKK GYQGLRCDNF NAIHRHKPL TNLENLDQAF RLLDPEDVDV YVSSLYDAMP ANELQLRWQE WMRHHTAAFE IEILWSQFLK ADKNRSKGIY QLKVPPGYHP HVAILEREQ LQRIVTKLQM QADALLQSDV RAGEVERDL NDVQTLKDGR VYRLHERLVA AGVAAPATQV RPELEDSTLR ENQHRVDGAE QLGSHRGLHQ RARSDEGQLS LGRDLQYAK SLESLSFVA EKEEEVGF'D KKEYSALMR ELQNAGDRLL ESFQAALQTQ IEAHLKENAA AEGQLQKLQE SATVTRLEDL LNEYKGHLSG LKPRHPAHPM DYKQVEVTVH AQPSHWKVL VCFLVPPPNQ AQHQALVTLW	VSEDVSNSS WNLGKTQSR SVLDPARAV QKKTFTKWN SDLYEDLRDG SGDSLPREKG QIALDYLRR DIADGNPKLT FQISDIQVSG LLLWSQRMVE TSSWRDGRLE LIDMNKVYRQ SVAERDLGVT PQPDEKSIIT RVPDVQDGVR YRELVLALLQ ERFPSSFEE FKEMELPAKE QSLEGAVQAG LDVEKEWGKL LRSEFERLEC EAGLCEEQLN RLLAAGKVPQ KADSMIRLLF HPQGEQMYRR IRTEYNLRK AQVTLQSVQR YLQDLLAWVE WGVDLPSVEA SIEEFRAKIE PATRGAYRDC LLNSSKARLR AATKELMWLN WSDRNTNMTA EELKEKKIK REDHPARPTV WSWMLQLCCC YFQFFSDVRE ALRRKYSCDR LQDAQDEKEQ LAKRAKAVVQ RGRPLLLAVC KGDECQLVGP SSGSEAAVPS EAQEAATRL HQLHVDKMSL

					LAWQSLRRDV	QLIRSWSLAT
					FRTLKPEEQR	QALHSLELHY
					QAFRLRDSQDA	GGFGPEDRLM
					AEREYGSCSH	HYQQLQSL
					QGAQEESRCQ	RCISELKDIR
					LQLEACETRT	VHRLRLPLDK
					EPARECAQRI	AEQQKAQAEV
					EGLGKGVARL	SAEAEKVLAL
					PEPSPAAPTL	RSELELTGK
					LEQVRSLSAI	YLEKLKTISL
					VIRGTQGAE	VLRAHEEQLK
					EAQAVPATLP	ELEATKASLK
					KLRAQAEAAQ	PTFDALRDEL
					RGAEVGERL	QQRHGERDVE
					VERWRERVAQ	LLERWQAVLA
					QTDVRQRELE	QLGRQLRYR
					ESADPLGAWL	QDARRRQEIQ
					QAMPLADSQA	VREQLRQEQA
					LLEEIERHGE	KVEECQRFK
					QYINAIKDYE	LQLVTYKAQL
					EPVASPAKKP	KVQSGSESVI
					QEYVDLRTHY	SELTTLTSQY
					IKFISETLRR	MEEEEERLAEQ
					QRAEERERLA	EVEAALEKQR
					QLAEAHAQAK	AQAEREAKEL
					QORMQEEVVR	REEAAVDAQQ
					QKRSIQEELQ	QLRQSSEAEI
					QAKARQAEAA	ERSRLRIEEE
					IRVVRLQLEA	TERQRGGAEG
					ELQALRARAE	EAEAQKRQAQ
					EEAERLRRQV	QDESQRKRQA
					EVELASRVKA	EAEAAAREKQR
					ALQALEELRL	QAEAAERRLR
					QAEVERARQV	QVALETAQRS
					AEAELQSKRA	SFAEKTAQLE
					RSLQEEHVAV	AQLREEAERR
					AQQQAEEAERA	REEAERELE
					WOLKANEALR	LRLQAE EVAQ
					QKSLAQAEAE	KQKEEAERE
					RRRGKAEQA	VRQRELAEQE
					LEKQRQLAEG	TAQQRLAAEQ
					ELIRLRAETE	QGEQQRQLE
					EELARLQREA	AAATQKRQEL
					EAEAKVRAE	MEVLLASKAR
					AEESRSTSE	KSKQRLEAEA
					GRFRELAEEA	ARLRALAEAA
					KRQRQLAEE	AARQRAEAER
					VLAEKLAAG	EATRLKTEAE
					IALKEKEAEN	ERLRLAEDE
					AFQRRRLEEQ	AAQHKADIEE
					RLAQLRKASD	SELERQKGLV
					EDTLRQRRQV	EEETLALKAS
					FEKAAAGKAE	LELELGRIRS
					NAEDTLRSKE	QAELEAARQR
					QLAAEEEEERR	REAEERVQKS
					LAAEEEEAAQ	RKAALEEVER
					LKAKVEEARR	LRERAEQESA
					RQLQLAQEAA	QKRLQAE EKA
					HAFVQVQKEQ	ELQQTLOQEQ
					SVLDQLRGEA	EARRRAEEA

					EEARVQAERE	AAQSRQVEE
					AERLKQSAEE	QAQARAQAQA
					AAEKLKKEAE	QEAARRAQAE
					QAALRQKQAA	DAEMEKHKKF
					AEQTLRQKAQ	VEQELTTLRL
					QLEETDHQKN	LLDEELQRLK
					AEATEAARQR	SQVEEELFSV
					RVQMEELSKL	KARIEAENRA
					LILRDKDNTQ	RFLQEEAEKM
					KQVAEEAARL	SVAAQEAAARL
					RQLAEEDLAQ	QRALAEMMLK
					EKMQAVQEAT	RLKAEAEELLQ
					QQKELAQEQA	RRLQEDKEQM
					AQQLAEETQG	FQRTLEAERQ
					RQLEMSAEAE	RLKLRVAEMS
					RAQARAEEEDA	QRFRKQAEI
					GEKLHRTCLA	TQEKVTLVQT
					LEIQRQQSDH	DAERLREATA
					ELEREKEKLQ	QEAKLLQLKS
					EEMQTVQQEQ	LLQETQALQQ
					SFLSEKDSLL	QREFIEQEK
					AKLEQLFQDE	VAKAQQLREE
					QQRQQQQMEQ	ERQLVASME
					EARRRQHEAE	EGVRRKQEEL
					QQLEQQRRQQ	EELLAENQR
					LREQLQLLEE	QHRAALAHSE
					EVTASQVAAT	KTLPNGRDAL
					DGPAAEAEPE	HSFDGLRRKV
					SAQRLQEAGI	LSAEELQRLA
					QGHTTVDELA	RREDVRHYLQ
					GRSSIAGLLL	KATNEKLSVY
					AALQRQLLSP	GTALILLEAQ
					AASGFLLDPV	RNRRLTVNEA
					VKEGVVGPEL	HHKLLSAERA
					VTGYKDPYTG	QQISLQFQAMQ
					KGLIVREHGI	RLLEAQIATG
					GVIDPVHSHR	VPVDVAYRRG
					YFDEEMNRVL	ADPSDDTKGF
					FDPNTHENLT	YLQLLERCVE
					DPETGLCLLP	LTDKAAKGGE
					LVYTDSEARD	VFEKATVSAP
					FGKFQGKTVT	IWEIINSEYF
					TAEQRRDLLR	QFRTGRITVE
					KIIKIIITVV	EEQEKGRLC
					FEGLRSLVPA	AELLESRVID
					RELYQQLQRG	ERSVRDVAEV
					DTVRRALRGA	NVIAGVWLEE
					AGQKLSIYNA	LKKDLLPSDM
					AVALLEAQAG	TGHIIDPATS
					ARLTVDEAVR	AGLVGPEFHE
					KLLSAEKAVT	GYRDPYTGQS
					VSLFQALKKG	LIPREQGLRL
					LDAQLSTGGI	VDPSKSHRVP
					LDVACARGCL	DEETSRALSA
					PRADAKAYSD	PSTGEPATYG
					ELQQRCPDQ	LTGLSLLPLS
					EKAARARQEE	LYSELQARET
					FEKTPVEVPV	GGFKGRITVT
					WELISSEYFT	AEQRQELLRQ
					FRTGKVTVEK	VIKILITIVE

					EVETLRQERL	SFSGLRAPVP
					ASELLASGVL	SRAQFEQLKD
					GKTTVKDLSE	LGSVRTLLQG
					SGCLAGIYLE	DTKEKVSIEE
					AMRRGLLRAT	TAALLLEAQA
					ATGFLVDPVR	NQRLYVHEAV
					KAGVVGPELH	EQLLSAEKAV
					TGYRDPYSGS	TISLFQAMQK
					GLVLRQHGIR	LLEAQIATGG
					IIDPVHSHRV	PVDVAYQGRY
					FSEEMNRVLA	DPSDDTKGFF
					DPNTHENLTY	RQLLERCVED
					PETGLRLLPL	KGAEKAEVVE
					TTQVYTEEET	RRAFEETQID
					IPGGGSHGGS	TMSLWEVMQS
					DLIPEEQRAQ	LMADFQAGRV
					TKERMIIIII	EIIKTEIIR
					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	NLQKFLEGTG
					CIAGVFVDAT	KERLSVYQAM
					KKGIIRPGTA	FELLEAQAAT
					GYVIDPIKGL	KLTVEEAVRM
					GIVGPEFKDK	LLSAERAVTG
					YKDPYSGKLI	SLFQAMKKGL
					ILKDHGIRLL	EAQIATGGII
					DPEESHRLPV	EVAYKRGLFD
					EEMNEILTDP	SDDTKGFFDP
					NTEENLTYLQ	LMERCITDPQ
					TGLCLLPLKE	KKRERKTSSK
					SSVRKRRVVI	VDPETGKEMS
					VYEAYRKGLI	DHQTYLELSE
					QCEWEEITI	SSSDGVVKSM
					IIDRRSGRQY	DIDDAIAKNL
					IDRSALDQYR	AGTLSITEFA
					DMLSGNAGGF	RSRSSSVGSS
					SSYPISPAVS	RTQLASWSDP
					TEETGPVAGI	LDTETLEKVS
					ITEAMHRNLV	DNITGQRLLE
					AQACTGGIID	PSTGERFPVT
					DAVNKGLVDK	IMVDRINLAQ
					KAFCGFEDPR	TKTKMSAAQA
					LKKGWLYYEA	GQRFLEVQYL
					TGGLIEPDTF	GRVPLDEALQ
					RGTVDARTAQ	KLRDVGAYSK
					YLTCPKTKLK	ISYKDALDRS
					MVEEGTGLRL	LEAAAQSTKG
					YSPYSVSGS	GSTAGSRTGS

					RTGSRAGSRR GSFDATGSGF SMTFSSSSYS SSGYGRRYAS GSSASLGGPE SAVA
69	PLEC	3	Q15149-3	Entry version 224 (18 Sep 2019) Sequence version 3 (14 Oct 2008)	MSGEDAEVRA VSEDVSNSS GSPSPGDTLP WNLGKTQRRS RSGGGAGSNG SVLDPAERAV IRIADERDRV QKKTFTKWVN KHLIKAQRHI SDLYEDLRDG HNLISLLEVL SGDSLPREKG RMRFHKLQNV QIALDYLRHR QVKLVNIRND DIADGNPKLT LGLIWTTILH FQISDIQVSG QSEDMTAKK LLLWSQRMVE GYQGLRCDNF TSSWRDGRLF NAIIHRHKPL LIDMNKVYRQ TNLENLDQAF SVAERDLGVT RLDPEDVDV PQPDEKSIIT YVSSLYDAMP RVPDVQDDEL QLRWQEYREL VLLLLQWMRH HTAAFEERRF PSSFEEIEIL WSQFLKFKEM ELPAGEADKN RSKGIYQSLE GAVQAGQLKV PPGYHPLDVE KEWGKLHVAI LEREKQLRSE FERLECLQRI VTKLQMEAGL CEEQLNQADA LLQSDVRLLA AGKVPQRAGE VERDLKADS MIRLLFNDVQ TLKDGRHPQG EQMYRRVYRL HERLVAIRTE YNLRKAGVA APATQVAQVT LQSVQRRPEL EDSTLRYLQD LLAWVEENQH RVDGAEWGVD LPSVEAQLGS HRGLHQSIEE FRAKIERARS DEGQLSPATR GAYRDCLGRL DLQYAKLLNS SKARLRSLES LHSFVAAATK ELMWLNEKEE EEVGFDWSDR NTNMTAKKES YSALMRELEL KEKKIKELQN AGDRLLREDH PARPTVESFQ AALQTQWSWM LQLCCCIQAH LKENAAYFQF FSDVREAEQ LQKLQEALRR KYSCDRSATV TRLEDLLQDA QDEKEQLNEY KGHLISGLAKR AKAVVQLKPR HPAHPMRGRL PLLAVCDYKQ VEVTVHKGDE CQLVGPAQPS HWKVLSSSGS EAAVPSVCFL VPPPNQEAQE AVTRLEAQHQ ALVTLWHQLH VDMKSLLAQW SLRRDVQLIR SWSLATFRTL KPPEQRQALH SLELHYQAF RDSQDAGGFG PEDRLMAERE YGSCSHHYQQ LQSLQGAQ EESRCQRCIS ELKDRLQLE ACETRTRVHRL RLPLDKEPAR ECAQRIAEQQ KAAQAEVEGLG KGVARLSAEA EKVLAPEPS PAAPTLRSEL ELTLGKLEQV RSLSAIYLEK LKTISLVIRG

					TQGAEEVLRA VPATLPELEA QAEEQQPTFD EVGERLQQRH RERVAQLLER RQRELEQLGR PLGAWLQDAR LADSQAVREQ IERHGEKVEE AIKDYEQLV SPAKKPKVQS DLRTHYSELT SETLRRMEEE ERERLAEVEA AHAQAKAQAE QEEVVRREEA IQEELQQLRQ RQAEAAERSR RLQLEATERQ LRARAEEAEA RLRRQVQDES ASRVKAEAEA LEELRLQAE ERARQVQVAL LQSKRASFAE EEHVAVAQLR AEAERAREEA ANEALRLRLQ AQAEAEKQKE KAEQAVRQR RQLAEGTAQQ LRAETEQQEQ RLQREAAAAAT AKVRAEMEV SRSTSEKSKQ ELAEEAARLR QLAEDDAAEQ KLAAIGEATR EKEAENERLR RRLEEQAQAH LRKASDSELE RQRRQVEEEI AAGKAELELE TLRKEQAEL EEERRRREAE EEAARQRKAA VEEARRLRER LAQEAAQKRL VQQKEQELQQ QLRGEAEAAAR VQAEREAQAS KQSAEEQAQA LRKEAEQEAA RQKQADAEM LRQKAQVEQE TDHQKNLLDE EAARQRSQVE EELSKLKARI DKDNTQRFLQ EEAARLSVAA	HEEQLKEAQA TKASLKKLRA ALRDELGAQ GERDVEVERW WQAVLAQTDV QLRYRESAD RRQEIQAMP LRQEQALLEE CQRFAKQYIN TYKAQLEPVA GSESVIQEYV TLTSQYIKFI ERLAEQQRAE ALEKORQLAE REAKELQORM AVDAQQQRKS SSEAEIQAKA LRIEEIIRVV RGGAEQELQA QKRQAQEEAE QKRQAQEEVEL AREKQALQA AERRLRQAEV ETAQRSAAEAE KTAQLERSLQ EEAERRAQQQ ERELERWQLK AEEVAQQKSL EAEREARRRG ELAEQELEKQ RLAAEQELIR QRQLLEELA QKRQELEAEL LASKARAEAE RLEAEAGRFR ALAEEAKRQR RAEAEVLAEE LKTEAEIALK RLAEDEAFQR KADIEERLAQ RQKGLVEDTL LALKASFKA LGRIRSNAED EAARQRQLAA ERVQKSLAAE LEEVERLKAK AEQESARQLQ QAEEKAHAF TLQQEQSVLD RAAEEAEEAR RRQVEEAERL RAQAQAAAEK RRAQAEQAAL EKHKKFQET LTTLRQLLEE ELQRLKAEAT EELFSVRVQM EAENRALILR EEAEMKQVA QEAAARLRQLA
--	--	--	--	--	--	--

					EEDLAQQRAL	AEKMLKEKMQ
					AVQEATRLKA	EAELLQQQKE
					LAQEQARRLQ	EDKEQMAQQQ
					AEETQGFQRT	LEAERQRQLE
					MSAEAERLKL	RVAEMSRAQA
					RAEEDAQRFR	KQAEIIGEKL
					HRTELATQEK	VTLVQTLEIQ
					RQSDHDAER	LREAIAELER
					EKEKLQQEAK	LLQLKSEEMQ
					TVQQEQLLQE	TQALQQSFLS
					EKDSLLQRE	FIEQEKAKLE
					QLFQDEVAKA	QQLREEQQRQ
					QQQMEQERQR	LVASMEEARR
					RQHEAEEGVR	RKQEELQQLE
					QQRQQEELL	AEENQRLREQ
					LQLLEEQHRA	ALAHSEEVTA
					SQVAATKTL	NGRDALDGPA
					AEAPEHSFD	GLRRKVSQR
					LQEAGILSAE	ELQRLAQGHT
					TVDELARRED	VRHYLQGRSS
					IAGLLLKATN	EKLSVYAALQ
					RQLLSPGTAL	ILLEAQAASG
					FLLDPVRNRR	LTVNEAVKEG
					VVGPELHHKL	LSAERAVTGY
					KDPYTGQQIS	LFQAMQKGLI
					VREHGIRLLE	AQIATGGVID
					PVHSHRVPVD	VAYRRGYFDE
					EMNRVLADPS	DDTKGFFDPN
					THENLTYLQL	LERCVEDPET
					GLCLLPLTDK	AAKGCELVYT
					DSEARDVEFK	ATVSAPFGKF
					QGKTVTIWEI	INSEYFTAEQ
					RRDLLRQFRT	GRITVEKIIK
					IIITVVEEQE	QKGRLCFEG
					RSLVPAEELL	ESRVIDRELY
					QQLQRGERSV	RDVAEVDTVR
					RALRGANVIA	GVWLEEAGQK
					LSIYNALKKD	LLPSDMAVAL
					LEAQAGTCHI	IDPAT SARLT
					VDEAVRAGLV	GPEFHEKLLS
					AEKAVTGYRD	PYTCQSVSLF
					QALKKGLIPR	EQGLRLDLAQ
					LSTGGIVDPS	KSHRVPLDVA
					CARGCLDEET	SRALSAPRAD
					AKAYSDPSTG	EPATYGELQQ
					RCRPDQLTGL	SLLPLSEKAA
					RARQEELYSE	LQARETFEKT
					PVEVPVGGFK	GRTVTVWELI
					SSEYFTAEQR	QELLRQFRTG
					KVTVEKVIKI	LITIVEEVET
					LRQERLSFSG	LRAPVPASEL
					LASGVL SRAQ	FEQLKDGKTT
					VKDLSELGSV	RTLLQSGSCL
					AGIYLEDTKE	KVSIYEAMRR
					GLLRATTAAL	LLEAQAATGF
					LVDPVRNQRL	YVHEAVKAGV
					VGPELHEQLL	SAEKAVTGYR
					DPYSGSTISL	FQAMQKGLVL
					RQHGIRLLEA	QIATGGIIDP
					VHSHRVPVDV	AYQRGYFSEE

					MNRVLADPSD DTKGFFDPNT HENLTYRQLL ERCVEDPETG LRLPLKGA EAEVETTVQ YTEETTRAF EETQIDIPGG GSHGGSTMSL WEVMQSDLIP EEQRAQLMAD FQAGRVTKER MIIIIIEIE KTEIIRQQGL ASYDYVRRRL TAEDLFEARI ISLETYNLLR EGTRSLREAL EAESAWCYLY GTGSVAGVYL PGSRQTLSTY QALKKGLLSA EVARLLLEAQ AATGFLLDPV KGERLTVDEA VRKGLVGPPEL HDRLLSAERA VTGYRDPYTE QTISLFQAMK KELIPTEEAL RLDQAQLATG 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 KRRVVIDDPE TGKEMSVYEA YRKGLIDHQT YLELSEQECE WEEITISSSD GVVKSMIIDR RSGRQYDIDD AIAKNLIDRS ALDQYRAGTL SITEFADMLS GNAGGFRSRS SSVGSSSSYP ISPAVSRTQL ASWSDPTEET GPVAGILDTE TLEKVSITEA MHRNLVDNIT GQRLLEAQAC TGGIIDPSTG ERFPVTDVN KGLVDKIMVD RINLAQKAF GFEDPRTKTK MSAAQALKKG WLYYEAGQRF LEVQYLTGGL IEPDTPGRVP LDEALQRGTV DARTAQKL RD VGAYSKYLTC PKTKLKISYK DALDRSMVEE GTGLRLLEAA AQSTKGYYS YSVSGSGSTA GSRTGSRTGS RAGSRGSGFD ATGSGFSMTF SSSYSSSGY GRRYASGSSA SLGGPESAVA
70	PLEC	4	Q15149-4	Entry version 224 (18 Sep 2019) Sequence version 3 (14 Oct 2008)	MSQHQLRVPO PEGLRKRRTS SEDNLYLAVL RASEGKKDER DRVQKKFTK WVNKHLIKAQ RHISDLYEDL RDGHNLISLL EVLSGDSLPR EKGRMRFHKL QNVQIALDYL RHRQVKLVNI

					RNDDIADGNP	KLTGLIWTI
					ILHFQISDIQ	VSGQSEDMTA
					KEKLLWSQR	MVEGYQGLRC
					DNFTSSWRDG	RLFNAIHRH
					KPLLDIMNKV	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	RDCLGRDLQ
					YAKLLNSSKA	RLRSLESLHS
					FVAAATKELM	WLNEKEEEEV
					GFDWSDRNTN	MTAKKESYSA
					LMRELELKEK	KIKELQNAGD
					RLLREDHPAR	PTVESFQAAL
					QTQWSWMLQL	CCCIEAHLKE
					NAAYFQFFSD	VREAEGQLQK
					LQEALRRKYS	CDRSATVTRL
					EDLLQDAQDE	KEQLNEYKGH
					LSGLAKRAKA	VVQLKPRHPA
					HPMRGRLLPL	AVCDYKQVEV
					TVHKGDECQL	VGPAQPSHWK
					VLSSSGSEAA	VPSVCFLVPP
					PNQEAQEAVT	RLEAQHQALV
					TLWHQLHVDM	KSLLAWSLR
					RDVQLIRSW	LATFRTLKPE
					EQRQALHSLE	LHYQAFLRDS
					QDAGGFDPED	RLMAEREYGS
					CSHHYQQLLQ	SLEQGAQEE
					RCQRCISELK	DIRLQLEACE
					TRTVHRLRLP	LDKEPARECA
					QRIAEQQKAQ	AEVEGLGKGV
					ARLSAEAEKV	LALPEPSPAA
					PTLRSELELT	LGKLEQVRSL
					SAIYLEKLKT	ISLVIRGTQG
					AAEVLRHEE	QLKEAQAVPA
					TLPELEATKA	SLKKLRAQAE
					AQQPTFDALR	DELRGAQEVG
					ERLQQRHGER	DVEVERWRER
					VAQLLERWQA	VLAQTDVQR
					ELEQLGRQLR	YYRESADPLG
					AWLQDARRRQ	EQIQAMPLAD
					SQAVREQLRQ	EQALLEEIER
					HGEKVEECQR	FAQYINAIK
					DYELQLVTYK	AQLEPVASPA
					KKPKVQSGSE	SVIQEYVDLR

					THYSELTTLT	SQYIKFISSET
					LRRMEEEEERL	AEQQRAEERE
					RLAEVEAALE	KQRQLAEAHA
					QAKAQAREEA	KELQQRMQEE
					VVRREEAAVD	AQQQKRSIQE
					ELQQLRQSSE	AEIQAKARQA
					EEAERSRLRI	EEEIRVVRLQ
					LEATERQRGG	AEGELQALRA
					RAEEAEAQKR	QAQEEAERLR
					RQVQDESQRK	RQAEVELASR
					VKAEEAAARE	KQRALQALEE
					LRLQAEAAER	RLRQAEVERA
					RQVQVALETA	QRSAAELQS
					KRASFAEKTA	QLERSLQEEH
					VAVAQLREEA	ERRAQQQAEA
					ERAREEAERE	LERWQLKANE
					ALRLRLQAE	VAQQKSLAQ
					EAEKQKEEAE	REARRRGKAE
					EQAVRQRELA	EQELEKQRQL
					AEGTAQQRLA	AEQELIRLRA
					ETEQQEQQRQ	LLEELARLQ
					REAAAATQKR	QLEAELAKV
					RAEMEVLLAS	KARAEESRS
					TSEKSKQRLE	AEAGRFRELA
					EEAARLRALA	EEAKRQRQLA
					EEDAARQRAE	AERVLAEKLA
					AIGEATRLKT	EAEIALKEKE
					AENERLRRLA	EDEAFQRRRL
					EEQAAQHKAD	IEERLAQLRK
					ASDSELERQK	GLVEDTLRQR
					RQVEEELAL	KASFEKAAAG
					KAELELELGR	IRSNAEDTLR
					SKEQAELEAA	RQRQLAAEEE
					RRRREAEEERV	QKSLAAEEEA
					ARQRKAALEE	VERLKAKVEE
					ARRLRERAEQ	ESARQLQLAQ
					EAAQKRLQAE	EKAHAFVQQ
					KEQELQQTLO	QEQSVLDQLR
					GEAEAAARRAA	EEAEEARVQA
					EREAAQSRQ	VEEAERLKQS
					AEEQAQARAQ	AQAAAELKLR
					EAEQEAAARRA	QAEQAALRQK
					QAADAEMEKH	KKFAEQTLRQ
					KAQVEQELTT	LRLQLEETDH
					QKNLLDEELQ	RLKAEATEAA
					RQRSQVEEEL	FSVRVQMEEL
					SKLKARIEAE	NRALILRDKD
					NTQRFLQEEA	EKMKQVAEEA
					ARLSVAAQEA	ARLQQLAEED
					LAQQRALAEK	MLKEKMQAVQ
					EATRLKAEAE	LLQQQKELAQ
					EQARRLQEDK	EQMAQQLAEE
					TQGFQRTLEA	ERQRFQLEMSA
					EAERLKLRLVA	EMSRAQARAE
					EDAQRFRKQA	EEIGEKLRHT
					ELATQEKVTL	VQTLQIQRQQ
					SDHDAERLRE	ATAELEREKE
					KLQQEAKLLQ	LKSEEMQTVQ
					QEQLLQETQA	LQQSFLSEKD
					SLLQRERFIE	QEKAKLEQLF

					QDEVAKAQQ	REEQQRQQQ
					MEQERQRLVA	SMEEARRRQH
					EAEQGVRRKQ	EELQQLQQQR
					RQQEELLAEE	NQRLREQLQL
					LEEQHRAALA	HSEEVTAQV
					AATKTLPNCR	DALDGPAAEA
					EPEHSFDGLR	RKVSQRLQE
					AGILSAEELQ	RLAQGHHTVD
					ELARREDVRH	YLQGRSSIAG
					LLLKATNEKL	SVYAALQRQL
					LSPGTALILL	EAQAASGFLL
					DPVRNRRLTV	NEAVKEGVVG
					PELHHKLLSA	ERAVTGYKDP
					YTGQQISLFQ	AMQKGLIVRE
					HGIRLLEAQI	ATGGVIDPVH
					SHRVPVDVAY	RRGYFDEEMN
					RVLADPSDDT	KGFFDPNTHE
					NLTYLQLLER	CVEDPETGLC
					LLPLTDKAAK	GGELVYTDSE
					ARDVFEKATV	SAPFGKFQGG
					TVTIWEIINS	EYFTAEQRRD
					LLRQFRTGRI	TVEKIIKIII
					TVVEEQEQKG	RLCFEGLRSL
					VPAAELLESR	VIDRELYQQL
					QRGERSVRDV	AEVDTVRRAL
					RGANVIAGVW	LEEAGQKLSI
					YNALKKDLLP	SDMAVALLEA
					QAGTGHIIIDP	ATSARLTVDE
					AVRAGLVGPE	FHEKLLSAEK
					AVTGYRDPYT	GQSVSLFQAL
					KKGLIPREQG	LRLDDAQLST
					GGIVDPSKSH	RVPLDVACAR
					GCLDEETSRA	LSAPRADAKA
					YSDPSTGEPA	TYGELQQRGR
					PDQLTGLSLL	PLSEKAARAR
					QEELYSELQA	RETFEKTIVE
					VPVGGFKGRT	VTWELISSE
					YFTAEQRQEL	LRQFRTGKVT
					VEKVIKILIT	IVEEVETLRQ
					ERLSFSGLRA	PVPASELLAS
					GVLSRAQFEQ	LKDGKTTVKD
					LSELGSVRTL	LQSGGCLAGI
					YLEDTKKVS	IYEAMRRGLL
					RATTAALLLE	AQAATGFLVD
					PVRNQRLVH	EAVKAGVVG
					ELHEQLLSAE	KAVTGYRDPY
					SGSTISLFQA	MQKGLVLRQH
					GIRLLEAQIA	TGGIIDPVHS
					HRVPVDVAYQ	RGYFSEEMNR
					VLADPSDDTK	GFFDPNTHEN
					LTYRQLLERC	VEDPETGLRL
					LPLKGAEKAE	VVETTQVYTE
					EETRAFEET	QIDIPGGGSH
					GGSTMSLWEV	MQSDLIPEEQ
					RAQLMADFQA	GRVTKERMII
					IIIEIIIEKTE	IIRQQGLASY
					DYVRRRLTAE	DLFEARIISL
					ETYNLLREGT	RLREALEAE
					SAWCYLYGTG	SVAGVYLPGS
					RQTLSTIYQAL	KKGLLSAEVA

					RLLLEAQAAT GFLLDPVKGE RLTVDEAVRK GLVGPELHDR LLSAERAVTG YRDPYTEQTI SLFQAMKKEL IPTEEALRLL DAQLATGGIV DPRLGFHLPL EVAYQRGYLN KDTHDQLSEP SEVRSYVDPS TDERLSYTQL LRRCRRDDGT GQLLLPLSDA RKLTFRGLRK QITMEELVRS QVMDEATALQ LREGLTSIEE VTKNLQKFLE GTSCIAGVFF 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 TAQKL RDVGA YSKYLTCPKT KLIKISYKDAL DRSMVEEGTG LRLLEAAQSS TKGYYSPYSV SSGSGTAGSR TGSRTGSRAG SRRGSFDTG SGFSMTFSSS SYSSSGYGRR YASGSSASLG GPESAVA
71	PLEC	5	Q15149-5	Entry version 224 (18 Sep 2019) Sequence version 3 (14 Oct 2008)	MEPSGSLFPS LVVVGHVVTL AAVVHWRGR RWAQDEQDER DRVQKKTFK WVNKHLIKAQ RHISDLYEDL RDGHNLISSL EVLSGDSLPR EKGRMRFHKL QNVQIALDYL RHRQVKLVNI RNDDIADGNP KLTGLIWTI ILHFQISDIQ VSGQSEDMTA KEKLLWSQR MVEGYQGLRC DNFTSSWRDG RLFNAIHRH KPLLDIMNKV YRQTNLENLD QAFSVAERDL GVTRLDPED VDVPQPDEKS IITYVSSLYD AMPRVPDVQD GVRANELQLR WQEYRELVLL LLQWMRHHTA AFEERRFPSS FEEIEILWSQ FLKFKEMLP AKEADKNRSK

					GIYQSLEGAV	QAGQLKVPPG
					YHPLDVEKEW	GKLVHVAILER
					EKQLRSEFER	LECLQRIVTK
					LQMEAGLCEE	QLNQADALLQ
					SDVRLLAAGK	VPQRAGEVER
					DLDKADSMIR	LLFNDVQTLK
					DGRHPQGEQM	YRRVYRLHER
					LVAIRTEYNL	RLKAGVAAPA
					TQVAQVTLQS	VQRRPELEDS
					TLRYLQDLLA	WVEENQHRVD
					GAEWGVDLPS	VEAQLGSHRG
					LHQSIEEFRA	KIERARSDEG
					QLSPATRGAY	RDCLGRDLQ
					YAKLLNSSKA	RLRSLESLHS
					FVAAATKELM	WLNEKEEEV
					GFDWSDRNTN	MTAKKESYSA
					LMRELELKEK	KIKELQNAGD
					RLREDHPAR	PTVESFQAAL
					QTQWSWMLQL	CCCIEAHLKE
					NAAYFQFFSD	VREAEGQLQK
					LQEALRRKYS	CDRSATVTRL
					EDLLQDAQDE	KEQLNEYKGH
					LSGLAKRAKA	VVQLKPRHPA
					HPMRGRPLPL	AVCDYKQVEV
					TVHKGDECQL	VGPAQPSHWK
					VLSSSGSEAA	VPSVCFVPP
					PNQEAQEAUT	RLEAQHQALV
					TLWHQLHVDM	KSLAWQSLR
					RDVQLIRSWS	LATFRTLKPE
					EQRQALHSLE	LHYQAFLRDS
					QDAGGFGPED	RLMAEREYGS
					CSHHYQQLLQ	SLEQGAQEE
					RCQRCISELK	DIRLQLEACE
					TRTVHRLRLP	LDKEPARECA
					QRIAEQQKAQ	AEVEGLGKGV
					ARLSAEAEKV	LALPEPSPAA
					PTLRSELELT	LGKLEQVRS
					SAIYLEKLKT	ISLVIRGTQG
					AAEVLRHEE	QLKEAQAVPA
					TLPELEATKA	SLKKLRAQAE
					AQQPTFDALR	DELRCQAQEV
					ERLQQRHGER	DVEVERWRER
					VAQLLERWQA	VLAQTDVRQR
					ELEQLGRQLR	YYRESADPLG
					AWLQDARRRQ	EQIQAMPLAD
					SQAVREQLRQ	EQALLEEIER
					HGEKVEECQR	FAKQYINAIK
					DYELQLVITYK	AQLEPVASPA
					KKPKVQSGSE	SVIQEYVDLR
					THYSELTTLT	SQYIKFISSET
					LRRMEEEERL	AEQQRAEERE
					RLAEVEAALE	KQRQLAEAHA
					QAKAQAEAREA	KELQQRMQEE
					VVRREEAAVD	AQQQKRSIQE
					ELQQLRQSSE	AEIQAKARQA
					EEAERSRLRI	EEEIRVVRLQ
					LEATERQRGG	AEGLQALRA
					RAEEAEAQKR	QAQEEAERLR
					RQVQDESQRK	RQAEVELASR
					VKAEEAAARE	KQRALQALEE

					LRLQAEAAER	RLRQAEVERA
					RQVQVALETA	QRSAAELQS
					KRASFAEKTA	QLERSLQEEH
					VAVAQLREEA	ERRAQQQAEA
					ERAREEAERE	LERWQLKANE
					ALRLRLQAE	VAQQKSLAQ
					EAEKQKEEAE	REARRRGKAE
					EQAVRQRELA	EQELEKQRQL
					AEGTAQQRLA	AEQELIRLRA
					ETEQQEQQRQ	LLEEELARLQ
					REAAAAATQKR	QELEAELAKV
					RAEMEVLLAS	KARAEESRS
					TSEKSKQRLE	AEAGRFRELA
					EEAARLRALA	EEAKRQRQLA
					EEDAARQRAE	AERVLAEKLA
					AIGEATRLKT	EAEIALKEKE
					AENERLRRLA	EDEAFQRRRL
					EEQAAQHKAD	IEERLAQLRK
					ASDSELERQK	GLVEDTLRQR
					RQVEEELAL	KASFEKAAAG
					KAELELELGR	IRSNAEDTLR
					SKEQAELEAA	RQRQLAEEEE
					RRRREAEERV	QKSLAEEEEA
					ARQRKAALEE	VERLKAKVEE
					ARRLRERAEQ	ESARQLQLAQ
					EAAQKRLQAE	EKAHAFVQQ
					KEQELQQTQ	QEQSVLDQLR
					GEAAARRAA	EEAEEARVQA
					EREAAQSRQ	VEEAERLKQS
					AEEQAQARAQ	AQAAAEKLRK
					EAEQEARRA	QAEQAALRQK
					QAADAAMEKH	KKFAEQTLRQ
					KAQVEQELTT	LRLQLEETDH
					QKNLLDEELQ	RLKAEATEAA
					RQRSQVEEEL	FSVRVQMEEL
					SKLKARIEAE	NRALILRDKD
					NTQRFLQEEA	EKMKQVAEEA
					ARLSVAAQEA	ARLRQLAEED
					LAQQRALAEK	MLKEKMQAVQ
					EATRLKAEAE	LLQQQKELAQ
					EQARRLQEDK	EQMAQQLAEE
					TQGFQRTLEA	ERQRQLEMSA
					EAERLKLRLA	EMSRAQARAE
					EDAQRFRKQA	EEIGEKLHRT
					ELATQEKVTL	VQTLEIQRQQ
					SDHDAERLRE	ATAELEREKE
					KLQQAELLQ	LKSEEMQTVQ
					QEQLLQETQA	LQQSFLSEKD
					SLLREREFIE	QEKAKLEQLF
					QDEVAKAQQ	REEQQRQQQQ
					MEQERQRLVA	SMEEARRRQH
					EAEQGVRRKQ	EELQQLEQQR
					RQQEELLAAE	NQRLREQLQL
					LEEQHRAALA	HSEEVTSQV
					AATKTLPNGR	DALDGPAAEA
					EPEHSFDGLR	RKVSQRLQE
					AGILSAEELQ	RLAQGHITVD
					ELARREDVRH	YLQGRSSIAG
					LLLKATNEKL	SVYAALQRQL
					LSPGTALILL	EAQAASGFL

					DPVRNRRLTV	NEAVKEGVVG
					PELHHKLLSA	ERAVTGKDP
					YTQQISLFO	AMQKGLIVRE
					HGIRLLEAQI	ATGGVIDPVH
					SHRVPVDVAY	RRGYFDEEMN
					RVLADPSDDT	KGFFDPNTHE
					NLTYLQLLER	CVEDPETGLC
					LLPLTDKAAK	GGELVYTDSE
					ARDVFEKATV	SAPFGKFQ GK
					TVTIWEIINS	EYFTAEQRRD
					LLRQFRTGRI	TVEKIIKIII
					TVVEEQEQKG	RLCFEGLRSL
					VPAAELLESR	VIDRELYQQL
					QRGERSVRDV	AEVDTVRRAL
					RGANVIAGVW	LEEAGQKLSI
					YNALKKDLLP	SDMAVALLEA
					QAGTGHIIDP	ATSARLTVDE
					AVRAGLVGPE	FHEKLLSAEK
					AVTGYRDPYT	GQSVSLFQAL
					KKGLIPREQG	LRLDDAQLST
					GGIVDPSKSH	RVPLDVACAR
					GCLDEETSRA	LSAPRADAKA
					YSDPSTGEPA	TYGELQQRCR
					PDQLTGLSLL	PLSEKAARAR
					QEELYSELQA	RETFEKTPE
					VPVGGFKGRT	VTWELISSE
					YFTAEQRQEL	LRQFRTGKVT
					VEKVIKILIT	IVEEVETLRQ
					ERLSFSGLRA	PVPASELLAS
					GVLSRAQFEQ	LKDGKTTVKD
					LSELGSVRTL	LQSGGCLAGI
					YLEDTKEKVS	IYEAMRRGLL
					RATTAALLLE	AQAATGFLVD
					PVRNQRLVH	EAVKAGVVG
					ELHEQLLSAE	KAVTGYRDPY
					SGSTISLFOA	MQKGLVLRQH
					GIRLLEAQIA	TGGIIDPVHS
					HRVPVDVAYQ	RGYFSEEMNR
					VLADPSDDTK	GFFDPNTHEN
					LTYRQLLERC	VEDPETGLRL
					LPLKGAEKAE	VVETQVYTE
					EETRAFEET	QIDIPGGGSH
					GGSTMSLWEV	MQSDLIPEEQ
					RAQLMADFQA	GRVTKERMII
					IIIEIIEKTE	IIRQQGLASY
					DYVRRRLTAE	DLFEARIISL
					ETYNLLREGT	RSLREALEAE
					SAWCYLYGTG	SVAGVYLPGS
					RQTLSTYQAL	KKGLLSAEVA
					RLLEAQAAT	GFLLDPVKGE
					RLTVDEAVRK	GLVGPFLHDR
					LLSAERAVTG	YRDPYTEQTI
					SLFQAMKKEL	IPTEEALRLL
					DAQLATGGIV	DPRLGPHLPL
					EVAYQRGYLN	KDTHDQLSEP
					SEVRSYVDPS	TDERLSYTQL
					LRRCRDDGT	GQLLLPLSDA
					RKLTFRGLRK	QITMEELVRS
					QVMDEATALQ	LREGLTSIEE
					VTKNLQKFLE	GTSCIAGVFV

					DATKERLSVY GTAFELLEAQ KGLKLTVEEA KDKLLSAERA KLISLFQAMK RLLEAQIATG LPVEVAYKRG TDPSSDDTKGF YLQLMERCIT LKEKKRERKT VVIVDPETGK GLIDHQTYLE ITISSSDGVV RQYDIDDAIA QYRAGTLSIT GGFRSRSSSV AVSRTQLASW AGILDTETLE NLVDNITGQR IIDPSTGERF VDKIMVDRIN DPRTKTKMSA YEAGQRFLEV DTPGRVPLDE TAQKL RDVGA KLKISYKDAL LRLLEAAQAS SGSGSTAGSR SRRGSFDTG SYSSSGYGRR GPESAVA	QAMKKGIIRP AATGYVIDPI VRMGIVGPEF VTGYKDPYSG KGLILKDHGI GIIDPEESHR LFDEEMNEIL FDPNTEENLT DPQTGLCLLP SSKSSVRKRR EMSVYEAYRK LSEQECEWEE KSMIIDRRSG KNLIDRSALD EFADMLSGNA GSSSSYPISP SDPTEETGPV KVSITEAMHR LLEAQACTGG PVTDAVNKGL LAQKAF CGFE AQALKKGWLY QYLTGGLIEP ALQRGTVDAR YSKYLTCPKT DRSMVEEGTG TKGYSPYSV TGSRTGSRAG SGFSMTFSSS YASGSSASLG GPESAVA
72	PLEC	6	Q15149-6	Entry version 224 (18 Sep 2019) Sequence version 3 (14 Oct 2008)	MSGAGGAFAS WLDGGCEPAR VDERDRVQKK IKAQRHISDL ISLLEVLSGD FHKLQNVQIA LVNIRNDDIA IWTIILHFQI DMTAKEKLLL GLRCDNFTSS IHRHKPLLD ENLDQAFSVA DPEDVDVPQP SLYDAMP RVP LQLRWQEYRE HHTAAFEERR LWSQFLKFKE NRSKGIYQSL VPPGYHPLDV ILEREKQLRS IVTKLQMEAG ALLQSDVRL EVERDLKAD QTLKDGRHPQ LHERLVART AAPATQVAQV LEDSTLRYLQ HRVDGAEWGV	PREVLLERPC RGYLYQQ LCC TF TKWVNKHL YEDLRDGHNL SLPREKGRMR LDYLRHRQVK DGNPKLTLGL SDIQVSGQSE WSQRMVEGYQ WRDGRLFNAI MNKVYRQTNL ERDLGVTRLL DEKSIITYVS DVQDGV RANE LVLLLLQWMR FPSSFEEIEI MELPAKEADK EGAVQAGQLK EKEWGKLHVA EFERLECLQR LCEEQLNQAD AAGKVPQRAG SMIRLLFN DV GEQMYRRVYR EYNLRLKAGV TLQSVQRRPE DLLAWVEENQ DLPSVEAQLG

					SHRGLHQSTIE	EFRAKIERAR
					SDEGQLSPAT	RGAYRDCGLGR
					LDLQYAKLLN	SSKARLRSLE
					SLHSFVAAAT	KELMWLNEKE
					EEEVGFDWSD	RNTNMTAKKE
					SYSALMRELE	LKEKKIKELQ
					NAGDRLLRED	HPARPTVESF
					QAALQTQWSW	MLQLCCIEA
					HLKENAAYFQ	FFSDVREAEG
					QLQKLQEALR	RKYSCDRSAT
					VTRLEDLLQD	AQDEKEQLNE
					YKGHLSGLAK	RAKAVVQLKP
					RHPAHPMRGR	LPLLAVCDYK
					QVEVTVHKGD	ECQLVGPAQP
					SHWKVLSSSG	SEAAVPSVCF
					LVPPPQNEAQ	EAVTRLEAQH
					QALVTLWHQL	HVDMKSLLAW
					QSLRRDVQLI	RSWSLATFRT
					LKPEEQRQAL	HSLELHYQAF
					LRDSQDAGGF	GPEDRLMAER
					EYGSCSHHYQ	QLQSLEQGA
					QEESRCQRCI	SELKDIRLQL
					EACETRTVHR	LRLPLDKPEA
					RECAQRIAEQ	QKAQAEVEGL
					GKGVARLSAE	AEKVLALPEP
					SPAAPTLRSE	LELTGKLEQ
					VRSLSAIYLE	KLKTISLVIR
					GTQGAEEVLR	AHEEQLKEAQ
					AVPATLPELE	ATKASLKKLR
					AQAEAQQPTF	DALRDELPGA
					QEVGERLQQR	HGERDVEVER
					WRERVAQLLE	RWQAVLAQTD
					VRQRELEQLG	RQLRYRESA
					DPLGAWLQDA	RRRQEQIQAM
					PLADSQAVRE	QLRQEQALLE
					EIERHGKVE	ECQRFQKQYI
					NAIKDYELQL	VTYKAQLEPV
					ASPAKKPKVQ	SGSESVIQEY
					VDLRTHYSEL	TTLTSQYIKF
					ISETLRRMEE	EERLAEQQRA
					EERERLAEVE	AALEKQRQLA
					EAHAQAKAQA	EREAKELQQR
					MQEEVVRREE	AAVDAQQQR
					SIQEELQQLR	QSSEAEIQAK
					ARQAEAAERS	RLRIEEIIRV
					VRLQLEATER	QRGGAEGELQ
					ALRARAEAE	AQKRQAQEEA
					ERLRRQVQDE	SQRKRQAEVE
					LASRVKAEAE	AAREKQRALQ
					ALEELRLQAE	EAERRLRQAE
					VERARQVQVA	LETAQRSAEA
					ELQSKRASFA	EKTAQLERSL
					QEEHVAVAQL	REEAERRAQQ
					QAEAEAREEE	AERELERWQL
					KANEALRLRL	QAEVVAQQKS
					LAQAEAEKQK	EEAEREARRR
					GKAEQAVRQ	RELAEQELEK
					QRQLAEGTAQ	QRLAAEQELI
					RLRAETEQGE	QQRQLLEEL
					ARLQREAAAA	TQKRQELEAE

					LAKVRAEMEV	LLASKARAE
					ESRSTSEKSK	QRLEAEAGRF
					RELAEAAARL	RALAEAAKRO
					RQLAEEDAAR	QRAEAERVLA
					EKLAAIGEAT	RLKTEAEIAL
					KEKEAENERL	RRLAEDEAFQ
					RRRLEEQAQ	HKADIEERLA
					QLRKASDSEL	ERQKGLVEDT
					LRQRRQVEEE	ILALKASFKE
					AAAGKAELEL	ELGRIRSNAE
					DTLRSKEQAE	LEAARQRQLA
					AEERRRREA	EERVQKSLAA
					EEEEARQRKA	ALEEVERLKA
					KVEEARRLRE	RAEQESARQL
					QLAQEAAQKR	LQAEKKAHAF
					AVQQKEQELQ	QTLQQEQSVL
					DQLRGEAEAA	RRAEEAEAEA
					RVQAEREAAQ	SRRQVEEAER
					LKQSAEEQAQ	ARAQAQAAAE
					KLRKEAEQEA	ARRAQAEQAA
					LRQKQAADAE	MEKHKKFAEQ
					TLRQKAQVEQ	ELTTLRLQLE
					ETDHQKNLLD	EELQRLKAEA
					TEAARQRSQV	EEELFSVRVQ
					MEELSKLKAR	IEAENRALIL
					RDKDNTQRF	QEEAEKMKQV
					AEAAARLSVA	AQEAARLRQL
					AEEDLAQQRA	LAEKMLKEKM
					QAVQEATRLK	AEAEELLQQK
					ELAQEQARRL	QEDKEQMAQQ
					LAEETQGFQR	TLEAERQRQL
					EMSAEAERLK	LRVAEMSRAQ
					ARAEEDAQRF	RKQAEIIGEK
					LHRTELATQE	KVTLVQTLEI
					QRQSDHDAE	RLREAIAELE
					REKEKLQQEA	KLLQLKSEEM
					QTVQQEQLLQ	ETQALQQSFL
					SEKDSLLQRE	RFIEQEKAKL
					EQLFQDEVAK	AQQLREEQQR
					QQQQMEQERQ	RLVASMEEAR
					RRQHEAEECV	RRQEEELQQL
					EQRRRQEEEL	LAEENQRLRE
					QLQLLEEQHR	AALAHSEEV
					ASQVAATKTL	PNGRDALDGP
					AAEAPEHSF	DGLRRKVSAQ
					RLQEAGILSA	EELQRLAQGH
					TTVDELARRE	DVRHYLQGRS
					SIAGLLLKAT	NEKLSVYAAL
					QRQLLSPGTA	LILLEAQAAAS
					GFLDPVRNR	RLTVNEAVKE
					GTVGPPELHHK	LLSAERAVTG
					YKDPYTGQOI	SLFQAMQKGL
					IVREHGIRLL	EAQIATGGVI
					DPVHSHRVPV	DVAYRRGYFD
					EEMNRVLADP	SDDTKGFFDP
					NTHENLTYLQ	LLERCVEDPE
					TGLCLLPLTD	KAAKGGEVLV
					TDSEARDVFE	KATVSAPFGK
					FQKTVTIWE	IINSEYFTAE
					QRRDLLRQFR	TGRITVEKII

					KIIITVVEEQ	EQKGRLCFEG
					LRSLVPAAEL	LESRVIDREL
					YQQLQRGERS	VRDVAEVDTV
					RRALRGANVI	AGVWLEEAGQ
					KLSIYNALKK	DLLPSDMAVA
					LLEAQAGTGH	IIDPAT SARL
					TVDEAVRAGL	VGPEFHEKLL
					SAEKAVTGYR	DPYTGQSVSL
					FQALKKGLIP	REQGLRL LDA
					QLSTGGIVDP	SKSHRVPLDV
					ACARGCLDEE	TSRALSAPRA
					DAKAYSDPST	GEPATYGELQ
					QRCRPDQLTG	LSLLPLSEKA
					ARARQEELYS	ELQARETFEK
					TPVEVPVGGF	KGRITVTVWEL
					ISSEYFTAEQ	RQELLRQFRT
					GKVTVEKVIK	ILITIVEEVE
					TLRQERLSFS	GLRAPVPASE
					LLASGVLSRA	QFEQLKDGKT
					TVKDLSELGS	VRTLLQGSGC
					LAGIYLEDTK	EKVSIEAMR
					RGLLRATTAA	LLLEAQAATG
					FLVDPVRNQR	LYVHEAVKAG
					VVGPELHEQL	LSAEKAVTGY
					RDPSYSGTIS	LFQAMQKGLV
					LRQH GIRLLE	AQIATGGIID
					PVHSHRVPVD	VAYQRGYFSE
					EMNRVLADPS	DDTKGFFDPN
					THENLTYRQL	LERCVEDPET
					GLRLLPLKGA	EKAEEVETTQ
					VYTEEETRRA	FEETQIDIPG
					GGSHGGSTMS	LWEVMQSDLI
					PEEQRAQLMA	DFQAGRVTKE
					RMIIIIIEII	EKTEIIRQQG
					LASYDYVRRR	LTAEDLFEAR
					IISLETYNLL	REGTRSLREA
					LEAESAWCYL	YGTGSVAGVY
					LPGSRQTL SI	YQALKKGLLS
					AEVARLLLEA	QAATGFL LDP
					VKGERLTVDE	AVRKGLVGPE
					LHDRLLSAER	AVTG YRDPYT
					EQTISLFQAM	KKELIPTEEA
					LRLLDAQLAT	GGIVDPRLGF
					HLPLEVAYQR	GYLNK DTHDQ
					LSEPSEVRSY	VDPSTDERLS
					YTQLLRRCRR	DDGTGQLLLP
					LSDARKLTFR	GLRKQITMEE
					LVR SQVMDEA	TALQLREGLT
					SIEEVTKNLQ	KFLEGTSCIA
					GVFVDATKER	LSVYQAMKKG
					IIRPGTAFEL	LEAQAATGYV
					IDPIKGLKLT	VEEAVRMGIV
					GPEFKDKLLS	AERAVTGYKD
					PYSGKLISLF	QAMKKGLILK
					DHGIRLLEAQ	IATGGIIDPE
					ESHRLPVEVA	YKRGLFDEEM
					NEILTDPSDD	TKGFFDPNTE
					ENLTYLQLME	RCITDPQTGL
					CLLPLKEKKR	ERKTSSKSSV
					RKRRVIVDP	ETGKEMSVYE

					AYRKGLIDHQ TYLELSEQEC EWEEITISSS DGVVKSMIID RRSGRQYDID DATAKNLIDR SALDQYRAGT LSITEFADML SGNAGGFRSR SSSVGSSSSY PISPAVSRTQ LASWSDPTEE TGPVAGILDT ETLEKVSITE AMHRNLVDNI TGQRLLEAQA CTGGIIDPST GERFPVTDV NKGLVDKIMV DRINLAQKAF CGFEDPRTKT KMSAAQALKK GWLYYEAGQR FLEVQYLTGG LIEPDTPGRV PLDEALQRTG 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 VQKKFTTKWV NKHLIKAQRH ISDLYEDLRD GHNLISLLEV LSGDSLPREK GRMRFHKLQN VQIALDYLRH RQVKLVNIRN DDADGNPKL TLGLIWITIL HFQISDIQVS GQSEDMTAKK KLLLWSQRMV EGYQGLRCDN FTSSWRDGR FNATIIHRHKP LLIDMNKVYR QTNLENLDQA FSVAERDLGV TRLLDPEDVD VPQPEKSII TYVSSLYDAM PRVPDVQDGV RANELQLRWQ EYRELVLLLL QWMRHHTAAF EERRFPSSFE EIEILWSQFL KFKEMELPAK EADKNRSKGI YQSLGAVQA GQLKVPPGYH PLDVEKEWGK LHVAILEREK QLRSEFERLE CLQRIVTKLQ MEAGLCEEQL NQADALLQSD VRLAAGKVP QRAGEVERDL DKADSMIRLL FNDVQTLKDG RHPQGEQMYR RVYRLHERLV AIRTEYNLRL KAGVAAPATQ VAQVTLQSVQ RRPELEDSTL RYLQDLLAWV EENQHRVDGA EWGVDLPSVE AQLGSHRGLH QSIEEFRAKI ERARSDEGQL SPATRGAYRD CLGRDLQYA KLLNSSKARL RSLESLHSFV AAATKELMWL NEKEEEEVGF DWSDRNTNMT AKKESYSALM RELELKEKKI KELQNAGDRL LREDHPARPT VESFQAALQT QWSWMLQLCC CIEAHLKENA AYFQFFSDVR EAEGQLQKLQ EALRRKYSCD RSATVTRLED LLQDAQDEKE QLNEYKGHLS GLAKRAKAVV QLKPRHPAHP MRGRLPLLAV

					CDYKQVEVTV	HKGDECQLVG
					PAQPSHWKVL	SSSGSEAAMP
					SVCFLVPPPN	QEAQEAATRL
					EAQHQAALVT	WHQLHVDMS
					LLAWQSLRRD	VQLIRSWSLA
					TFRTLKPEEQ	RQALHSLELH
					YQAFRLRDSQD	AGGFGPEDRL
					MAEREYGSCL	HHYQQLLQSL
					EQGAQEESRC	QRCISELKDI
					RLQLEACETR	TVHRLRLPLD
					KEPARECAQR	IAEQQKAQAE
					VEGLGKGVAR	LSAEAEKVLA
					LPEPSPAAPT	LRSELELTG
					KLEQVRSLSA	IYLEKLKTI
					LVIRGTQGAE	EVLRAHEEQ
					KEAQAVPATL	PELEATKASL
					KKLRAQAEAQ	QPTFDALRDE
					LRGAQEVGER	LQQRHGERDV
					EVERWRERVA	QLLERWQAVL
					AQTDVRQREL	EQLGRQLRYY
					RESADPLGAW	LQDARRRQEQ
					IQAMPLADSQ	AVREQLRQEQ
					ALLEEIERHG	EKVEECQRFA
					KQYINAIKDY	ELQLVITYKAQ
					LEPVASPAKK	PKVQSGSESV
					IQEYVDLRTH	YSELTTLSQ
					YIKFISETLR	RMEEEERLAE
					QQRAEERERL	AEVEAALEKQ
					RQLAEAHQA	KAQAEREAKE
					LQORMQEEVV	RREEAAVDAQ
					QQRKSIQEE	QQLRQSSEAE
					IQAKARQAEA	AERSRLRIEE
					EIRVVRLQLE	ATERQRGGAE
					GELQALRARA	EEEAQKRQA
					QEEAERLRRQ	VQDESQRKRQ
					AEVELASRVK	AEAEAAAREKQ
					RALQALEELR	LQAEAAERRL
					RQAEVERARQ	VQVALETAQR
					SAEAEQLSKR	ASFAEKTAQL
					ERSLQEEHVA	VAQLREEAER
					RAQQQAEAE	AREEAERELE
					RWQLKANEAL	RLRLQAEVA
					QKSLAQAEA	EKQKEEAERE
					ARRRGKAEQ	AVRQRELAEQ
					ELEKQRQLAE	GTAQQRLAAE
					QELIRLRAET	EQGEQQRQLL
					EEELARLQRE	AAAATQKRQE
					LEAELAKVRA	EMEVLLASKA
					RAEEESRSTS	EKSKORLEAE
					AGRFRELAEE	AARLRALAE
					AKRQRQLAE	DAARQRAEAE
					RVLAEKLAAL	GEATRLKTEA
					EIALKEKEAE	NERLRRLAED
					EAFQRRRLAE	QAAQHKADIE
					ERLAQLRKAS	DSELERQKGL
					VEDTLRQRRQ	VEEEILALKA
					SFEKAAAGKA	ELELELGRIR
					SNAEDTLRSK	EQAELEAARQ
					RQLAAEEERR	RREAEEERVQK
					SLAAEEEAAR	QRKAALEEVE

					RLKAKVEEAR	RLRERAEQES
					ARQLQLAQEA	AQKRLQAEEK
					AHAFVQQKE	QELQQTLLQEE
					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	TRLKAEAEEL
					QQQKELAQEQ	ARRLQEDKEQ
					MAQQLAEETQ	GFQRTLEAER
					QRQLEMSAEA	ERLKL RVAEM
					SRAQARAED	AQRFKQAE
					IGEKLHRTTEL	ATQEKVTLVQ
					TLEIQRQQSD	HDAERLREAI
					AELEREKEKL	QQEAKLLQLK
					SEEMQTVQQE	QLLQETQALQ
					QSFLSEKDSL	LQRFIEQE
					KAKLEQLFQD	EVAKAQQLRE
					EQQRQQQOME	QERQLVASM
					EEARRRQHEA	EEGVRRQEE
					LQOLEQQRRQ	QEELLAENQ
					RLREQLLLE	EQHRAALAH
					EEVTASQVAA	TKTLPNGRDA
					LDGPAAEAEP	EHSFDGLRRK
					VSAQRLQEAG	ILSAEELQRL
					AQGHTTVDEL	ARREDVRHYL
					QGRSSIAGLL	LKATNEKLSV
					YAALQRQLLS	PGTALILLEA
					QAASGFLLD	VRNRRLTVNE
					AVKEGVVGPE	LHHKLLSAER
					AVTGYKDPYT	GQQISLFQAM
					QKGLIVREHG	IRLLEAQIAT
					GGVIDPVHSH	RVPVDVAYRR
					GYFDEEMNRV	LADPSDDTKG
					FFDPNTHENL	TYLQLLRCV
					EDPETGLCLL	PLTDKAAKGG
					ELVYTDSEAR	DVFEKATVSA
					PFGKFQKTV	TIWEIINSEY
					FTAEQRRDLL	RQFRTGRITV
					EKIIKIIITV	VEEQEQKGR
					CFEGLRSLVP	AAELLESRI
					DRELYQQLQR	GERSVRDVAE
					VDTVRRALRG	ANVIAGVWLE
					EAGQKLSIYN	ALKKDLLPSD
					MAVALLEAQA	GTGHIIDPAT
					SARLTVDEAV	RAGLVGPEFH
					EKLLSAEKAV	TGYRDPYTGQ
					SVSLFQALKK	GLIPREQGLR
					LLDAQSTGG	IVDPSKSHRV
					PLDVACARGC	LDEETSRLS
					APRADAKAYS	DPSTGEPATY
					GELQQRCRPD	QLTGLSLLPL

					SEKAARARQE	ELYSELQARE
					TFEKTPEVP	VGGEKGRITV
					VWELISSEYF	TAEQRQELLR
					QFRTGKVTVE	KVIKILITIV
					EEVETLRQER	LSFSGLRAPV
					PASELLASCV	LSRAQFEQLK
					DGKTTVKDLS	ELGSVRTLLQ
					GSGCLAGIYL	EDTKEKVSII
					EAMRRGLLRA	TTAALLLEAQ
					AATGFLVDPV	RNQRLYVHEA
					VKAGVVGPEL	HEQLLSAEKA
					VTGYRDPYSG	STISLFQAMQ
					KGLVLRQHGI	RLLEAQIATG
					GIIDPVHSHR	VPVDVAYQRG
					YFSEEMNRVL	ADPSDDTKGF
					FDPNTHENLT	YRQLLERCVE
					DPETGLRLLP	LKGAEKAEEV
					ETTQVYTEEE	TRRAFEETQI
					DIPGGGSHGG	STMSLWEVMQ
					SDLIPEEQRA	QLMADFQAGR
					VTKERMIIII	IEIIEKTEII
					RQQGLASYDY	VRRLTAEDL
					FEARIISLET	YNLLREGTRS
					LREALEAESA	WCYLYGTGSV
					AGVYLPGSRQ	TLSIYQALKK
					GLLSAEVARL	LLEAQAATGF
					LLDPVKGERL	TVDEAVRKGL
					VGPELHDRLL	SAERAVTGYR
					DPYTEQTISL	FQAMKKELIP
					TEEALRLDDA	QLATGGIVDP
					RLGFHLPLEV	AYQRGYLNKD
					THDQLSEPSE	VRSYVDPSTD
					ERLSYTQLLR	RCRRDDGTGQ
					LLLPLSDARK	LTFRGLRKQI
					TMEELVRSQV	MDEATALQLR
					EGLTSIEEVT	KNLQKFLEGT
					SCIAGVFVDA	TKERLSVYQA
					MKKGIIRPCT	AFELLEAQAA
					TGYVIDPIKG	LKLTVEEAVR
					MGIVGPEFKD	KLLSAERAVT
					GYKDPYSGKL	ISLFQAMKKG
					LILKDHGIRL	LEAQIATGGI
					IDPEESHRLP	VEVAYKRGFL
					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 KYLTCPKTKL SMVEEGTGLR GYSPYSVSG SRTGSRAGSR FSMTFSSSSY SGSSASLGGP	QKLRDVGAYS KISYKDALDR LLEAAAQSTK SGSTAGSRTG RGSF'DATGSG SSSGYGRRYA ESAVA
74	PLEC	8	Q15149-8	Entry version 224 (18 Sep 2019) Sequence version 3 (14 Oct 2008)	MDPSRAIQNE VQKKTFTKWV ISDLYEDLRD LSGDSLPREK VQIALDYLRL DDIADGNPKL HFQISDIQVS KLLLWSQRMV FTSSWRDGR LLIDMNKVYR FSVAERDLGV VPQPDEKSII PRVPDVQDGV EYRELVLLLL EERRFPSSFE KFKEMELPAK YQSLEGAVQA PLDVEKEWVK QLRSEFERLE MEAGLCEEQL VRLAAGKVP DKADSMIRLL RHPQGEQMYR AIRTEYNLRL VAQVTLQSVQ RYLQDLLAWV EWGVDLPSVE QSIEEFRAKI SPATRGAYRD KLLNSSKARL AAATKELMWL DWSDRNTNMT RELELKEKKI LREDHPARPT QWSWMLQLCC AYFQFFSDVR EALRRKYSCD LLQDAQDEKE GLAKRAKAVV MRGRLPLLAV HKGDECQLVG SSSGSEAAVP QEAQEAVTRL WHQLHVDMKS VQLIRSWSLA RQALHSLELH AGGFGPEDRL HHYQQLLQSL QRCISELKDI TVHRLRLPLD IAEQQKAQAE LSAEAEKVLA	ISSLKDERDR NKHLIKAQRH GHNLISSLLEV GRMRFHKLQN RQVKLVNIRN TLGLIWTIIL GQSEDMTAKE EGYQGLRCDN FNATIIHRHKKP QTNLNLDQA TRLLDPEDVD TYVSSLYDAM RANELQLRWQ QWMRHHTAAF EIEILWSQFL EADKNRSKGI GQLKVPPGYH LHVAILEREK CLQRIVTKLQ NQADALLQSD QRAGEVERDL FNDVQTLKDG RVYRLHERLV KAGVAAPATQ RRPELEDSTL EENQHRVDGA AQLGSHRGLH ERARSDEGQL CLGRDLQYA RSLESLHSFV NEKEEEEVGF AKKESYSALM KELQNAGDRL VESFQAALQT CIEAHLKENA EAEGQLQKLQ RSATVTRLED QLNEYKGHLS QLKPRHPAHP CDYKQVEVTV PAQPSHWKVL SVCFLVPPPN EAQHQAALVTL LLAWQSLRRD TFRTLKPEEQ YQAFLRDSQD MAEREYGSCS EQGAQEEESRC RLQLEACETR KEPARECAQR VEGLGKGVAR LPEPSPAAPT

					LRSELELTLC	KLEQVRSLSA
					IYLEKLKLTIS	LVIRGTQGAE
					EVLRAHEEQ	KEAQAVPATL
					PELEATKASL	KKLRAQAEAQ
					QPTFDALRDE	LRGAQEVGER
					LQQRHGERDV	EVERWRERVA
					QLLERWQAVL	AQTDVRQREL
					EQLGRQLRYY	RESADPLGAW
					LQDARRRQEQ	IQAMPLADSQ
					AVREQLRQEQ	ALLEEIERHG
					EKVEECQRFA	KQYINAIKDY
					ELQLVITYKAQ	LEPVASPAKK
					PKVQSGSESV	IQEYVDLRTH
					YSELTTLTSQ	YIKFISSETLR
					RMEEEERLAE	QQRAEERERL
					AEVEAALEKQ	RQLAEAHAQA
					KAQAEREAKE	LQQRMQEEVV
					RREEAAVDAQ	QQKRSIQEEL
					QQLRQSSEAE	IQAKARQAEA
					AERSRLRIEE	EIRVVRLQLE
					ATERQRGGAE	GELQALRARA
					EEAEAQKRQA	QEEAERLRRQ
					VQDESQRKRQ	AEVELASRVK
					AEAEAAAREKQ	RALQALEELR
					LQAEAAERRL	RQAEVERARQ
					VQVALETAQR	SAEAELQSKR
					ASFAEKTAQL	ERSLQEEHVA
					VAQLREEAER	RAQQQAEAER
					AREEAERELE	RWQLKANEAL
					RLRLQAEVA	QQKSLAQAEA
					EKQKEEAERE	ARRRGKAEQ
					AVRQRELAEQ	ELEKQRQLAE
					GTAQQRLAAE	QELIRLRAET
					EQGEQQRQLL	EEELARLQRE
					AAAATQKRQE	LEAELAKVRA
					EMEVLLASKA	RAEEESRSTS
					EKSKQRLEAE	AGRFRELAEE
					AARLRALAE	AKRQRQLAE
					DAARQRAEAE	RVLAEKLAAI
					GEATRLKTEA	EIALKEKEAE
					NERLRLAED	EAFQRRRLAE
					QAAQHKADIE	ERLAQLRKAS
					DSELERQKGL	VEDTLRQRRQ
					VEEEILALKA	SFEKAAAGKA
					ELELELGRIR	SNAEDTLRSK
					EQAELEAARQ	RQLAAEEERR
					RREAEEERVQK	SLAAEEEAAR
					QRKAAL EEVE	RLKAKVEEAR
					RLRERAEQES	ARQLQLAQEA
					AQKRLQAEK	AHAFVQQKE
					QELQQTLLQE	QSVLDQLRGE
					AEAARRAAEE	AEEARVQAER
					EAAQSRQVE	EAERLKQSAE
					EQAQARAQAQ	AAAEKLRKEA
					EQEAARRAQA	EQAALRQKQA
					ADAEMEKHKK	FAEQTLRQKA
					QVEQELTLR	LQLEETDHQK
					NLLDEELQRL	KAEATEAARQ
					RSQVEEELFS	VRVQMEELSK
					LKARIEAENR	ALILRDKDNT

					QRFLQEEAEK	MKQVAEEAAR
					LSVAAQEAAR	LRQLAEEDLA
					QQRALAEKML	KEKMQAVQEA
					TRLKAEAEEL	QQQKELAQEQ
					ARRLQEDKEQ	MAQQLAETQ
					GFQRTLEAER	QRQLEMSAEA
					ERLKLRAEM	SRAQARAEED
					AQRFRKQAE	IGEKLRHTEL
					ATQEKVTLVQ	TLEIQRQQSD
					HDAERLREAI	AELEREKEKL
					QQEAKLLQLK	SEEMQTVQQE
					QLLQETQALQ	QSFLSEKDSL
					LQRERFIEQE	KAKLEQLFQD
					EVAKAQQLR	EQQRQQQME
					QERQRLVASM	EEARRRQHEA
					EEGVRRKQEE	LQQLEQQRRQ
					QEELLAEEENQ	RLREQLQLLE
					EQHRAALAH	EEVTASQVAA
					TKTLPNGRDA	LDGPAAEAEP
					EHSFDGLRRK	VSAQRLQEAG
					ILSAEELQRL	AQGHTTVDEL
					ARREDVRHYL	QGRSSIAGLL
					LKATNEKLSV	YAALQRQLLS
					PGTALILLEA	QAASGFLDLP
					VRNRRLTVNE	AVKEGVVGPE
					LHHKLLSAER	AVTGKDPYT
					GQQISLQFAM	QKGLIVREHG
					IRLLEAQIAT	GGVIDPVHSH
					RVPVDVAYRR	GYFDEEMNRV
					LADPSDDTKG	FFDPNTHENL
					TYLQLLERC	EDPETGLCLL
					PLTDKAAKGG	ELVYTDSEAR
					DVFEKATVSA	PFGKFQGKTV
					TIWEIINSEY	FTAEQRRDLL
					RQFRTGRITV	EKI IKIITV
					VEEQEQKGRL	CFEGLRSLVP
					AAELLES RVI	DRELYQQLQR
					GERSVRDVAE	VDTVRRALRG
					ANVIAGVWLE	EAGQKLSIYN
					ALKKDLLPSD	MAVALLEAQA
					GTGHIIDPAT	SARLTVDEAV
					RAGLVGPEFH	EKLLSAEKAV
					TGYRDPYTGQ	SVSLFQALKK
					GLIPREQGLR	LLDAQ LSTGG
					IVDPSKSHRV	PLDVACARGC
					LDEETSRALS	APRADAKAYS
					DPSTGEPATY	GELQQRCRPD
					QLTGLSLLPL	SEKAARARQE
					ELYSELQARE	TFEKT PVEVP
					VGGFKGRITV	VWELISSEYF
					TAEQRQELLR	QFR TGKVTVE
					KVIKILITIV	EEVETLRQER
					LSFSGLRAPV	PASELLASGV
					LSRAQFEQLK	DGKTTVKDLS
					ELGSVRTLQ	GSGCLAGIYL
					EDTKEKVS IY	EAMRRG LLRA
					TTAALLLEAQ	AATGFLVDPV
					RNQRLYVHEA	VKAGVVGPEL
					HEQLLSAEKA	VTGYRDPYSG
					STISLQFAMQ	KGLVLRQHGI

					RLEAQIATG VPVDVAYQRG ADPSDDTKGF YRQLLERCVE LKGAEKAEVV TRRAFEETQI STMSLWEVMQ QLMADFQAGR IEIEKTEII VRRRLTAEDL YNLLREGTRS WCYLYGTGSV TSLIYQALKK LLEAQAAATGF TVDEAVRKGL SAERAVTGYR FQAMKKELIP QLATGGIVDP AYQRGYLNKD VRSYVDPSTD RCRRDDGTGQ LTFRGLRKQI MDEATALQLR KNLQKFLEGT TKERLSVYQA AFELLEAAQA LKLTVEEAVR KLLSAERAVT ISLFQAMKKG LEAQIATGGI VEVAYKRGLF PSDDTKGFFD QLMERCITDP EKKRERKTSS IVDPETGKEM IDHQTYLELS ISSSDGVVKS YDIDDAIAKN RAGTLSITEF FRSRSSSVGS SRTQLASWSD ILDTELEKV VDNITGQRLL DPSTGERFPV KIMVDRINLA RTKTKMSAAQ AGQRFLEVQY PGRVPLDEAL QKLRDVGAYS KISYKDALDR LLEAAQSTK SGSTAGSRTG RGSFDTATGSG SSSGYGRRYA ESAVA	GIIDPVHSHR YFSEEMNRVL FDPNTHENLT DPETGLRLLP ETTQVYTEEE DIPGGGSHGG SDLIPEEQRA VTKERMIIII RQQGLASYDY FEARIISLET LREALEAESA AGVYLPGRSQ GLLSAEVARL LLDPVKGERL VGPELHDLRL DPYTEQTISL TEEALRLLLDA RLGFHLPLEV THDQLSEPSE ERLSYTQLLR LLLPLSDARK TMEELVRSQV EGLTSIEEVT SCIAGVFVDA MKKGIIRPGT TGYVIDPIKG MGIVGPEFKD GYKDPYSGKL LILKDHGIRL IDPEESHRLP DEEMNEILTD PNTEENLTYL QTGLCLLPLK KSSVRKRRVV SVYEAYRKGL EQCEWEEIT MIIDRRSGRQ LIDRSALDQY ADMLSGNAGG SSSYPISPAV PTEETGPVAG SITEAMHRNL EAQACTGGII TDAVNKGLVD QKAFCGFEDP ALKKGWLYYE LTGGLIEPDT QRGTVDARTA KYLTCPKTKL SMVEEGTGLR GYYSPIYSVSG SRTGSRAGSR FSMTFSSSSY SGSSASLGGP
75	PLEC	9	Q15149-9	Entry version 224 (18 Sep 2019) Sequence	MAGPLPDEQD KYKDERDRVQ HLIKAQRHIS NLISLLEVL	FIQAYEEVRE KKTFTKWVVK DLYEDLRDGH GDSLPREKGR

				version 3 (14 Oct 2008)	MRFHKLQNVQ IALDYLRRHQ VKLVNIRNDD IADGNPKLTL GLIWTIILHF QISDIQVSGQ SEDMTAKEKL LLWSQRMVEG YQGLRCDNFT SSWRDGRLEFN AIIHRHKPLL IDMNKVYRQT NLENLDQAFS VAERDLGVTR LLDPEDVDVP QPDEKSIITY VSSLYDAMPR VPDVQDGVRA NELQLRWQEY RELVLLLLLQW MRHHTAAFEE RRFPSFEEI EILWSQFLKF KEMELPAKEA DKNRSKGIYQ SLEGAVQAGQ LKVPPGYHPL DVEKEWGKLH VAILEREKQL RSEFERLECL QRIVTKLQME AGLCEEQLNQ ADALLQSDVR LLAAGKVPQR AGEVERDLDK ADSMIRLLFN DVQTLKDGRH PQGEQMYRRV YRLHERLVAI RTEYNLRLLKA GVAAPATQVA QVTLQSVQRR PELEDSTLRY LQDLLAWVEE NQHRVDGAEW GVDLPSVEAQ LGSHRGLHQS IEEFRAKIER ARSDEGQLSP ATRGAYRDCL GRDLQYAKL LNSSKARLRS LESLHSFVAA ATKELMWLNE KEEEEVGFWD SDRNTNMTAK KESYSALMRE LELKEKKIKE LQAGDRLLR EDHPARPTVE SFQAALQTQW SWMLQLCCCI EAHLKENAAY FQFFSDVREA EGQLQKLQEA LRRKYSCDRS ATVTRLEDLL QDAQDEKEQL NEYKGHLSGL AKRAKAVVQL KPRHPAHPMR GRLLPLAVCD YKQVEVTVHK GDECQLVGPA QPSHWKVLSS SGSEAAVPSV CFLVPPPNQE AQEAVTRLEA QHQAALVTLWH QLHVDMKSLL AWQSLRRDVQ LIRSWSLATF RTLKPEEQRQ ALHSLELHYQ AFLRDSQDAG GFGPEDRLMA EREYGSCSHH YQQLQSLEQ GAQEESRCQR CISELKDIRL QLEACETRIV HRLRLPLDKE PARECAQRIA EQQKAQAEVE GLGKGVARLS AEAEKVLALP EPSPAAPTLLR SELELTGKGL EQVRSLSAIY LEKLKTIISLV IRGTQGAEV LRAHEEQLKE AQAVPATLPE LEATKASLKK LRAQAEAQQP TFDALRDELR GAQEVGERLQ QRHGERDVEV ERWRERVAQL LERWQAVLAQ TDVRQRELEQ LGRQLRYRE SADPLGAWLQ DARRRQEQIQ AMPLADSQAV REQLRQEQAL LEEIERHGEK VEECQRFAKQ YINAIKDVEL QLVITYKAQLE
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					PVASPAKKPK	VQSGSESVIQ
					EYVDLRTHYS	ELTTLTSQYI
					KFISSETLRRM	EEEERLAEQQ
					RAEERERLAE	VEAALEKQRQ
					LAEAHAQAKA	QAEREAKELQ
					QRMQEEVVR	EEAAVDAQQQ
					KRSIQEELQQ	LRQSSEAEIQ
					AKARQAEAAE	RSRLRIEEEEI
					RVVRLQLEAT	ERQRGGAEGE
					LQALRARAE	AEAQKRQAE
					EAERLRRQVQ	DESQRKRQAE
					VELASRVKAE	AEAAREKQRA
					LQALEELRLQ	AEAAERRLRQ
					AEVERARQVQ	VALETAQRSA
					EAELQSKRAS	FAEKTAQLER
					SLQEEHVAVA	QLREEAERRA
					QQQAEAEERAR	EEAERELEWR
					QLKANEALRL	RLQAE EVAQQ
					KSLAQAEAEK	QKEEAEREAR
					RRGKAEEQAV	RQRELAEQEL
					EKQRQLAEGT	AQQRLAAEQE
					LIRLRAETEQ	GEQQRQLLEE
					ELARLQREAA	AATQKRQELE
					AELAKVRAEM	EVLLASKARA
					EEESRSTSEK	SKQRLEAEAG
					RFRELAEEAA	RLRALAEAAK
					RQRQLAEEDA	ARQRAEAERV
					LAEKLAATGE	ATRLKTEAEI
					ALKEKEAENE	RLRLAEDEA
					FQRRRLEEQA	AQHKADIEER
					LAQLRKASDS	ELERQKGLVE
					DTLRQRRQVE	EETLALKASF
					EKAAAGKAEL	ELELGRIRSN
					AEDTLRSKEQ	AELEAARQRO
					LAAEEERRRR	EAEERVQKSL
					AAAAEAARQR	KAAL EEVERL
					KAKVEEARRL	RERA EQESAR
					QLQLAQEAAQ	KRLQAE EKAH
					AFVAVQQKEQ	LQQT LQQEQS
					VLDQLRGAE	AARRAAEEAE
					EARVQAEREA	AQSRRQVEEA
					ERLKQSAEEQ	AQARAQAQAA
					AEKLRKEAEQ	EAARRAQAEQ
					AALRQKQAAD	AEMEKKKKFA
					EQTLRQKAQV	EQELTTLRLQ
					LEETDHQKNL	LDEELQRLKA
					EATEAARQRS	QVEEELFSVR
					VQMEELSKLK	ARIEAENRAL
					ILRDKDNTQR	FLQEEAEKMK
					QVAEEAARLS	VAAQEAARLR
					QLAEEDLAQQ	RALAEKMLKE
					KMQAVQEATR	LKAEAE LLQQ
					QKELAQEQAR	RLQEDKEQMA
					QQLAEETQGF	QRTLEAERQR
					QLEMSAEAEER	LKLRVAEMSR
					AQARAEEDAQ	RFRKQAE EIG
					EKLHRTELAT	QEKVTLVQTL
					EIQRQQSDHD	AERLREAI AE
					LEREKEKLQQ	EAKLLQLKSE
					EMQTVQQEQL	LQETQALQQS

					FLSEKDSLLQ	RERFIEQEKA
					KLEQLFQDEV	AKAQQLRREEQ
					QRQQQQMEQE	RQRLVASMEE
					ARRRQHEAEE	GVRRKQEELQ
					QLEQQRRQQE	ELLAEENQRL
					REQLQLLEEQ	HRAALAHSEE
					VTASQVAATK	TLPNGRDALD
					GPAAEAPEEH	SFDGLRRKVS
					AQRLQEAGIL	SAEELQRLAQ
					GHTTVDELAR	REDVRHYLQG
					RSSIAGLLLK	ATNEKLSVYA
					ALQRQLLSPG	TALILLEAQA
					ASGFLLDPVR	NRRLTVNEAV
					KEGVVGPELH	HKLLSAERAV
					TGYKDPYTGQ	QISLFQAMQK
					GLIVREHGIR	LLEAQIATGG
					VIDPVHSHRV	PVDVAYRRGY
					FDEEMNRVLA	DPSDDTKGFF
					DPNTHENLTY	LQLLERCVED
					PETGLCLLPL	TDKAAKGCEL
					VYTDSEARDV	FEKATVSAPF
					GKFQGGKVTI	WEIINSEYFT
					AEQRRDLLRQ	FRTGRITVEK
					IIKIIITVVE	EQEKGKRLCF
					EGLRSLVPAA	ELLESRVDR
					ELYQQLQRGE	RSVRDVAEVD
					TVRRALRGAN	VIAGVWLEEA
					GQKLSIYNAL	KKDLLPSDMA
					VALLEAQAGT	GHIIDPATSA
					RLTVDEAVRA	GLVGPEFHEK
					LLSAEKAVTG	YRDPYTGQSV
					SLFQALKKGL	IPREQGLRLL
					DAQLSTGGIV	DPSKSHRVPL
					DVACARGCLD	EETSRALSAP
					RADAKAYSDP	STGEPATYGE
					LQQRCPDQL	TGLSLLPLSE
					KAARARQEEL	YSELQARETF
					EKTPVEVPVG	GFKGRTVTW
					ELISSEYFTA	EQRQELLRQF
					RTGKVTVEKV	IKILITIVEE
					VETLRQERLS	FSGLRAPVPA
					SELLASGVLS	RAQFEQLKDG
					KTTVKDLSEL	GSVRTLLQGS
					GCLAGIYLED	TKEKVSIEEA
					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	IEKTEIIRQ
					QGLASYDYVR	RRLTAEDLFE
					ARIISLETYN	LLREGTRSLR
					EALAEASAWC	YLYGTGSAVG

					VYLPGRQTL SIYQALKKGL LSAEVARLLL EAQAATGFLL DPVKGERLTV DEAVRKGLVG PELHDRLLSA ERAVTGYRDP YTEQTISLFQ AMKKELIPTE EALRLDDAQL ATGGIVDPRL GFHLPLEVAY QRGYLNKDTL DQLSEPSEVR SYVDPSTDER LSYTQLLRRC RRDDGTGQLL LPLSDARKLT FRGLRKQITM EELVRSQVMD EATALQLREG LTSIEEVTKN LQKFLEGTSC IAGVFVDATE ERLSVYQAMK KGIIRPGTAF ELLEAQAATG YVIDPIKGLK LTVEEAVRMG IVGPEFKDKL LSAERAVTGY KDPYSGKLIS LFQAMKKGLI LKDHGIRLLE AQIATGGIID PEESHRLPVE VAYKRGLFDE EMNEILTDPD DDTKGFFDPN TEENLTYLQL MERCITDPQT GLCLLPLKEK KRERKTSSKS SVRKRVRVIV DPETGKEMSV YEAYRKGLID HQTYLELSEQ ECEWEEITIS SSDGVVKSMI IDRRSGRQYD IDDAIAKNLI DRSALDQYRA GTLSITEFAD MLSGNAGGFR SRSSSVGSSS SYPISPAVSR TQLASWSDPT EETGPVAGIL DTETLEKSVI TEAMHRNLVD NITGQRLLEA QACTGGIIDP STGERFPVTD AVNKGVLVDKI MVDRLNLAQK AFCGFEDPRT KTKMSAAQAL KKGWLYYEAG QRFLEVQYLT GGLIEPDTFG 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 RMPVLVDFRQ YVRTLPNTNL MGFGAFAALT TFWYATRPKP LKPPCDLSMQ SVEVAGSGGA RRSALLDSDE PLVYFYDDVT TLYEGFQRGI QVSNNGPCLG SRKPDQPYEW LSYKQVAELS ECIGSALIQQ GFKTAPDQFI GIFAQNRPEW VIIEQGCFAI SMVIVPLYDT LGNEAITIYV NKAELSLVTV DKPEKAKLLL EGVENKLIPG LKIIIVMDAY GSELVERGQR CGVEVTSMA MEDLGRANRR KPKPPAPEDL AVICFTSGTT GNPKGAMVTH RNIVSDCSAF VKATENTVNP CPDDTLISFL

					PLAHMFERVV ECVMLCHGAK IGFFQGDRL LMDDLKVLQP TVFPVVPRL NRMFDRIFGQ ANTTLKRWLL DFASKRKEAE LRSGIIRNNS LWDRLIFHKV QSSLGGRVRL MVTGAAPVSA TVLTFLRAAL GCQFYEGYGQ TECTAGCCLT MPGDWTAGHV GAPMPCNLIK LVDVEEMNYM AAEGEGEVCV KGPNVFQGYL KDKGWLHTGD IGKWLPNGLT KIIDRKKHIF KLAQGEYIAP EKINIYMRS EPVAQVFVHG ESLQAFLIAI VVPDVETLCS WAQKRGFEGS FEELCRNKDV KKAILED MVR LGKDSGLKPF EQVKGITLHP ELFSIDNGLL TPTMKAKRPE LRNYFRSQID DLYSTIK
77	ACSLI	2	P33121-2	Entry version 186 (18 Sep 2019) Sequence version 1 (01 Oct 1993)	MQAHELFRYF RMPVLVDFRQ YVRTLPNTNL MGFGAFAALT TFWYATRPKP LKPPCDLSMQ SVEVAGSGGA RRSALLDSDE PLVYFYDDVT TLYEGFQIRI QVSNNGPCLG SRKPDQPYEW LSYKQVAELS ECIGSALIQK GFKTAPDQFI GIFAQNRPEW VIIEQGCFAV SMVIVPLYDT LGNEAITIYIV NKAELSLVFFV DKPEKAKLLL EGVENKLIPG LKIIIVMDAY GSELVERGQR CGVEVTSMKA MEDLGRANRR KKPAPAPEDL AVICFTSGTT GNPKGAMVTH RNIVSDCSAF VKATENTVNP CPDDTLISFL PLAHMFERVV ECVMLCHGAK IGFFQGDRL LMDDLKVLQP TVFPVVPRL NRMFDRIFGQ ANTTLKRWLL DFASKRKEAE LRSGIIRNNS LWDRLIFHKV QSSLGGRVRL MVTGAAPVSA TVLTFLRAAL GCQFYEGYGQ TECTAGCCLT MPGDWTAGHV GAPMPCNLIK LVDVEEMNYM AAEGEGEGLY KDKGWLHTGD IGKWLPNGLT KIIDRKKHIF KLAQGEYIAP EKINIYMRS EPVAQVFVHG ESLQAFLIAI VVPDVETLCS WAQKRGFEGS FEELCRNKDV KKAILED MVR LGKDSGLKPF EQVKGITLHP ELFSIDNGLL TPTMKAKRPE LRNYFRSQID DLYSTIKV
78	ACSLI	3	P33121-3	Entry version 186 (18 Sep 2019) Sequence	MQAHELFRYF RMPVLVDFRQ YVRTLPNTNL MGFGAFAALT TFWYATRPKP LKPPCDLSMQ SVEVAGSGGA RRSALLDSDE

				version 1 (01 Oct 1993)	PLVYFYDDVT QVSNNGPCLG LSYKQVAELS GFKTAPDQFI VIIEQGCFAF LGNEAITYIV DKPEKAKLLL LKIIIVMDAY CGVEVTSMA KPKPPAPEDL GNPKGAMVTH VKATEKALPL PLAHIYEQLL IGFFQGDTRL TVFPVVPRL ANTTLKRWLL LRSGIIRNNS QSSLGGRVRL TVLTFRLAAL TECTAGCCLT GAPMPCNLK AAEGEGEVCV KDKPAKTAEAL IGKWLPNGL KLAQGEYIAP EPVAQVFVHG VVPDVETLCS FEELCRNKDV LGKDSGLKPF ELFSIDNGLL LRNYFRSQID	TLYEGFQRCI SRKPDQPYEW ECIGSALIQL GIFAQNRPEW SMVIVPLYDT NKAELSLVFF EGVENKLIPG GSELVERGQR MEDLGRANRR AVICFTSGTT RNIVSDCSAF SASDTHISYL KCVMLCHGAK LMDDLKVLQP NRMFDRIFGQ DFASKRKEAE LWDRLIFHKV MVTGAAPVSA GCQFYEGYGQ MPGDWTAGHV LVDVEEMNYM KGPNVFQGYL DKDGLWHTGD KIIDRKKHIF EKIENIYMRS ESLQAFLIAI WAQKRGFEFS KKAILEDMVR EQVKGITLHP TPTMKAKRPE DLYSTIKV
79	RAC1	1	P63000	Entry version 192 (18 Sep 2019) Sequence version 1 (31 Aug 2004)	MQAIKCVVVG ISYTTNAFPG SANVMVDGKP QEDYDRLRPL CFSLVSPASF VRHHCNPPI DDKDTIEKLK QGLAMAKEIG TQRGLKTVFD PVKKRRKCLL	DGAVGKTCLL EYIPTVFDNY VNLGLWDTAG SYPQTDVFLI ENVRAKWYPE ILVGTKLDLR EKKLTPITYP AVKYLECSAL EAIKRAVLCPP LL
80	RAC1	2	P63000-2	Entry version 192 (18 Sep 2019) Sequence version 1 (31 Aug 2004)	MQAIKCVVVG ISYTTNAFPG SANVMVDGKP QEDYDRLRPL GKDITSRGKD FSLVSPASFE RHHCPNTPII DKDTIEKLKE GLAMAKEIGA QRGLKTVFDE VKKRRKRCCLL	DGAVGKTCLL EYIPTVFDNY VNLGLWDTAG SYPQTVGETY KPIADVFLIC NVRAKWYPEV LVGKLDLDRD KKLTPITYPQ VKYLECSALT AIRAVLCPPP L
81	PSMB2	1	P49721	Entry version 201 (18 Sep 2019) Sequence version 1 (01	MEYLIGIQGP AASNIVQMKD KILLLCVGEA QKNVQLYKMR ANFTRRLAD	DYVLVASDRV DHDKMFKMSE GDTVQFAEYI NGYELSPTAA CLRSRTPYHV

				Oct 1996)	NLLLAGYDEH EGPALYYMDY LAALAKAPFA AHGYGAFLTL SILDRYYTPT ISRERAVELL RKCLEELQKR FILNLPTFSV RIIDKNGIHD LDNISFPKQGS
82	GM2A	1	P17900	Entry version 190 (18 Sep 2019) Sequence version 4 (13 Nov 2007)	MQSLMQAPLL IALGLLLAAP AQAHLLKKPSQ LSSFSWDNCD EGKDPVIRS LTLEPDPIIV PGNVTLSVMG STSVPLSSPL KVDLVLEKEV AGLWIKIPCT DYIGSCTFEH FCDVLDMLIP TGEPCPEPLR TYGLPCHCPF KEGTYSLPKS EFVVPDLELP SWLTTGNYRI ESVLSSSGKR LGCICKIAASL KGI

Variant Gene Sequences

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

EXAMPLES

MATERIALS AND METHODS

Collection of granulocytes from donors

- 5 Neutrophils and stem cells collected from twenty healthy human volunteers were selected with equal weighting between the following 4 groups:

Group 1: Male Over 40

Group 2: Male Under 40

Group 3: Female Over 40

- 10 Group 4: Female Under 40

All donors were healthy and had confirmed that no anti-inflammatory drugs had been taken up to 10 days prior to blood donation. Cells were isolated using standard techniques.

Bacterial Culture

- 15 24 hours prior to use, overnight cultures (ONCs) of all strains (*P. aeruginosa*: multidrug resistant Cystic Fibrosis isolate RP73 (Di Lorenzo *et al* (2015), Mol. Immunol., 63, 166-175); MRSA: Community acquired strain USA300 (Diep *et al* (2006), Lancet, 367, 731-739)) were prepared by inoculating 20ml tryptic soy broth (3% w/v TSB in deionised water) with 2 stock
20 cryobeads for 24 hours at 37°C, under shaking at 120 rpm (Sciquip mini incu shake). After incubation, ONCs were centrifuged at 2,800 g for 20 minutes at 4°C. The pellet was then resuspended in 10ml Roswell Park Memorial Institute (RPMI) 1640 medium (commercially available from Sigma-Aldrich, UK). Optical density readings were then taken for all strains and diluted in RPMI 1640 to an OD of 0.015, equivalent of 1×10^7 cfu/ml.

25

Neutrophil Bacterial Co-culture assay

- Bacterial cultures were prepared as described above. 100µl of 1×10^7 cfu/ml bacterial strains were added to either 100µl RPMI 1640, 100µl 1×10^7 /ml neutrophils or increasing concentrations of Tobramycin (for *P. aeruginosa*) or Vancomycin (for MRSA) (1, 10,
30 100µg/ml). These cultures were then incubated at 37°C, under shaking at 120 rpm for up to 24 hours. At 2, 6 and 24 hours, 20µl aliquots of each sample were diluted in sterile RPMI at 1/10, 1/100, 1/1000, 1/10000, 1/100000 and 1/1000000 and plated on Tryptic Soy Agar (TSA) and incubated at 37°C for 24 hours. Post incubation, bacterial colonies were manually counted and the total cfu content quantified.

35

EXAMPLE 1**Validation of Neutrophil-Mediated Bacterial Killing**

To validate an *in vitro* model of neutrophil bacterial killing activity (BKA) assay, increasing concentrations of neutrophils (1×10^5 , 5×10^5 and 1×10^6 neutrophils per sample) were incubated with 1×10^6 cfu/ml of the *P. aeruginosa* strain RP73 under suspension. These neutrophil/bacterial cultures were then incubated for 2 hours at 37°C under 120rpm of shaking. After incubation 20 μl aliquots of each sample were diluted in sterile RPMI at 1/10, 1/100, 1/1000, 1/10000, 1/100000 and 1/1000000-fold dilutions and plated on Tryptic Soy Agar (TSA) and incubated at 37°C for 24 hours. Post incubation, bacterial colonies were manually counted and the total cfu content quantified. A concentration-dependent increase in bacterial killing was observed compared to negative controls (0: $0 \pm 0\%$; 1×10^5 : 25.00 ± 3.81 , $P < 0.05$; 5×10^5 : $47.67 \pm 2.54\%$, $P < 0.01$; 1×10^6 : 74.93 ± 1.98 , $P < 0.001$, Figure 1). From these data, for all future experiments a concentration of 1×10^6 neutrophils present in suspension was used to assess neutrophil bacterial killing.

EXAMPLE 2**Age and Gender differences in Neutrophil Mediated Bacterial Killing**

Neutrophils from the various donors indicated in the Materials & Methods section were assessed (using the assay described in Example 1) for bacterial killing activity (BKA) against the multi-drug resistant clinical isolate of the Gram-negative bacterium *P. aeruginosa* RP73 and the community acquired Methicillin Resistant *Staphylococcus aureus* (MRSA) strain USA300 over 2 hours.

Figure 2A shows that neutrophils from all donors induced at least some killing of RP73, and surprisingly a trend was observed demonstrating the highest level of killing in males and females over 40 years old, particularly in females (Male >40 : $63.70 \pm 11.12\%$; Male <40 : $46.32 \pm 13.00\%$; Female >40 : 70.14 ± 6.63 ; Female <40 : $46.06 \pm 8.91\%$, Figure 2A).

Figure 2B shows that neutrophils from all donors demonstrated at least some ability to kill the MRSA strain USA300. Similarly to the *P. aeruginosa* strain RP73, a surprising trend was observed suggesting that for both males and females (but particularly females), the over 40 cohort demonstrated enhanced killing over the gender controlled under 40 cohort (Male >40 : $38.03 \pm 13.35\%$; Male <40 : $26.46 \pm 7.89\%$; Female >40 : $68.41 \pm 5.93\%$; Female <40 : $50.69 \pm 11.39\%$, Figure 2B)

EXAMPLE 3**Neutrophil-Mediated Killing of Bacteria is Greater than Antibiotic Treatment at 2 Hours**

It was observed that neutrophils cultured from some human donors possessed a superior BKA compared to neutrophils cultured from other donors with 25% of tested donors demonstrating greater than 80% killing of RP73 in 2 hours. These donors were chosen to compare the BKA against the activity of the most common antibiotics used for the bacteria of interest (Tobramycin for *P. aeruginosa* and Vancomycin for *MRSA*).

Initial experiments were performed to produce a dose response for said most common antibiotics to be used against the bacterial strains RP73 (Tobramycin) and USA300 (Vancomycin) at 1, 10 and 100µg/ml over 2 hours. The multidrug resistant *P. aeruginosa* strain RP73 was only significantly killed at Tobramycin concentrations of 10 and 100µg/ml (1µg/ml: $6.60 \pm 2.22\%$; 10µg/ml: $77.78 \pm 13.40\%$, $P < 0.01$; 100µg/ml: $95.37 \pm 2.87\%$, $P < 0.01$, Figure 3A).

The community acquired strain of *MRSA* USA300 was only significantly killed at Vancomycin concentrations of 10 and 100µg/ml (1µg/ml: $5.73 \pm 3.70\%$; 10µg/ml: $250.5 \pm 6.13\%$, $P < 0.05$; 100µg/ml: $92.58 \pm 2.01\%$, $P < 0.01$, Figure 3B).

Both of these antibiotics are known to have cytotoxic side effects when given at high doses as demonstrated by the recommended serum trough concentrations of 2µg/ml for Tobramycin and 10-20µg/ml for Vancomycin by the British National Formulary. Therefore, in experiments comparing the BKA of neutrophils against the antibiotics, 1µg/ml was chosen for Tobramycin and 10µg/ml for Vancomycin. Neutrophils cultured from donors 12, 16 and 19 were selected for the comparison against antibiotic treatment as they had previously demonstrated superior BKA activity compared to the neutrophils cultured from other donors. (Figure 4).

When compared to the standard of care (SOC) serum trough dose of Tobramycin (1µg/ml) against the tobramycin resistant strain of *P. aeruginosa* RP73, neutrophils demonstrated significantly enhanced bacterial killing at 2 hours (1µg/ml Tobramycin: $6.60 \pm 2.22\%$ vs. 1×10^6 Neutrophils: $86.51 \pm 1.89\%$, $P < 0.001$, Figure 4A).

Similarly, neutrophils with superior BKA demonstrated significantly increased levels of killing of the Gram-positive bacterial strain of *MRSA* USA300 when compared to the SOC serum

trough dose of Vancomycin at 2 hours (10µg/ml Tobramycin: 25.05 ± 6.13% vs. 1x10⁶ Neutrophils: 70.55 ± 7.18%, P < 0.05, Figure 4B).

Advantageously, this shows that granulocytes (and preferably neutrophils) cultured from donors shown to produce granulocytes with higher BKA are particularly effective in the treatment of bacterial infections. This advantageous property is in contrast to the standard (chemical) antibiotics which show lower bacterial killing and are known to be associated with side effects, such as cytotoxic side effects (even at the doses typically used in the clinic).

10 **EXAMPLE 4**

Demonstrating variable BKA in Donor Derived Neutrophils

Figures 5 and 6 show the MRSA and *P. aeruginosa* RP73 (respectively) cytotoxicity (recorded by the BKA assay described in Example 1) for different donors. This assay is able to demonstrate differences in BKA between neutrophils from different donors. The assay can also demonstrate the most suitable donor based on the bacteria type to be targeted – donors D12 and D19 provided neutrophils with the highest BKA against MRSA, whereas donor D16 provided donors with the highest BKA against *P. aeruginosa* RP73.

20 **EXAMPLE 5**

Demonstrating BKA of Stem Cell Derived Neutrophils

Demonstrating that BKA of neutrophils is genetically encoded

Neutrophils isolated from three different donors (DDNs) mentioned above, as well as stem cell derived neutrophils (SCDNs) derived from CD34+ stem cells of the same donors according to standard techniques were tested for BKA as described in Example 1.

Figures 5 and 6 show the percentage cytotoxicity recorded by the BKA assay (after 2 hours) against MRSA and *P. aeruginosa* RP73 for DDNs and SCDNs from donors A, B and C. Surprisingly, the SCDNs demonstrated a BKA which had a highly similar profile to that of the DDNs from the same donor, demonstrating that BKA is encoded at the genetic level. Donors A and C provided neutrophils (and SCDNs) with the highest BKA against MRSA, while donor B provided neutrophils (and SCDNs) having lower BKA against MRSA.

Interestingly, the converse was demonstrated in a BKA assay with *P. aeruginosa* RP73, in which donor B provided neutrophils with the highest BKA, demonstrating the suitability for this method in optimising selection of donors based on pathogen type.

Results for *P. aeruginosa* RP73 are summarised in Table 1.

Table 1

RP73	Bacterial Killing (%)							
	Tobramycin (µg/ml)		Donor Derived Neutrophils			Stem Cell Derived Neutrophils		
	1	10	A	B	C	A	B	C
RP73	6.60	77.78	64.37	66.58	67.26	83.23	89.76	86.55

5 Results for MRSA are summarised in Table 2.

Table 2.

MRSA	Bacterial Killing (%)							
	Vancomycin (µg/ml)		Donor Derived Neutrophils			Stem Cell Derived Neutrophils		
	1	10	A	B	C	A	B	C
MRSA	5.73	25.05	67.23	41.23	68.25	77.78	56.19	77.69

10 This demonstrates that donors found to have neutrophils (e.g. DDNs) with a high BKA may also be used as a source of CD34+ stem cells which can be differentiated into neutrophils (e.g. SCDNs) with similarly high BKA.

15 Additionally, the results demonstrate that stem cells from different donors can a) be differentiated *in vitro* to produce neutrophils that demonstrate bacteria killing abilities, and b) that this bacteria killing activity varies by the source donor. Interestingly, the bacterial killing activity varies not only by the source donor, but also by the bacteria type (donor B was the best donor for RP73, but not for MRSA).

20 The results support the fact that the bacteria killing activity (BKA) by the innate immune system varies by individual and that the same innate variance in BKA seen in neutrophils taken directly from donors is also shown in a donor's stem cells. By selecting donors with proven high bacteria killing activity of their innate immune system, and using their stem cells (i.e. haematopoietic stem cells) for *ex vivo* expansion and differentiation, a cell bank can be created with said stem cells/neutrophils with high bacteria killing activity to be used in the
25 treatment of an infection.

EXAMPLE 6**Isolation of High-Density Neutrophils**

10 ml of heparinized (20 U/ml) human blood is mixed with an equal volume of 3% Dextran
5 T500 in saline and incubated for 30 minutes at room temperature to sediment erythrocytes.
A 50 ml conical polypropylene tube is prepared with 10 ml sucrose 1.077 g/ml and slowly
layered with a leukocyte-rich supernatant on top of the 1.077 g/ml sucrose layer prior to
centrifuging at 400 x g for 30 minutes at room temperature without brake. The high-density
neutrophils (HDN) appear in the pellet. Low-density neutrophils (LDN) co-purify with
10 monocytes and lymphocytes at the interface between the 1.077 g/ml sucrose layer and
plasma.

The HDNs may be tested in a BKA assay described herein. Haematopoietic cells are
suitably obtained from a donor having HDNs.

15

EXAMPLE 7**Differentiation of induced pluripotent stem cells (iPSCs) into neutrophils with high
BKA**

A donor comprising neutrophils with high BKA is identified. A somatic cell (e.g. fibroblast) is
20 isolated from the donor and used to establish a culture of iPSCs. The iPSCs are
differentiated into mature neutrophils, e.g. using the protocol as described by Sweeney CL,
Merling RK, Choi U, Priel DB, Kuhns DB, Wang H and Malech HL, Generation of functionally
mature neutrophils from induced pluripotent stem cells. Neutrophil Methods and Protocols,
Methods in Molecular Biology. 2014; 1124:189-206, and Sweeney et al (2016), Stem Cells,
25 34(6), 1513-1526 (the teaching of which is incorporated herein by reference).

The resulting mature neutrophils are shown to have similar BKA levels to those of the DDNs
and SCDNs from HSCs from the same donor.

30 The mature neutrophils are subsequently injected into the donor from which the iPSCs have
been originally derived, and do not provoke any immune response.

EXAMPLE 8**Treatment of a patient with MRSA**

A patient diagnosed with an MRSA infection is tested for suitability for treatment with the granulocytes of the invention. A blood sample is obtained from the patient and analysed in a
5 BKA assay (according to the method of Example 1).

The patient's granulocytes are unsuitable for treatment of infections and therefore the patient is found to be suitable for treatment with the granulocytes of the invention. The patient's details are processed through a cell database for a cell bank and suitable granulocytes
10 identified (suitable granulocytes are from a donor with the same blood group as the patient and that demonstrated >41.23% MRSA BKA).

The patient is treated once a week with the granulocytes of the invention. An infusion of 2×10^9 granulocytes is administered to the patient in the first week and the dose increased
15 incrementally for 3 subsequent weeks to a final dose of 2×10^{11} granulocytes in week 4. A change in symptoms (such as: redness and swelling of the skin; pus; pain; aches; confusion; fever; chills; and dizziness) is monitored. After 4 weeks of treatment the symptoms are vastly reduced/eliminated.

EXAMPLE 9**Treatment of a patient with vancomycin-resistant *Enterococcus* (VRE)**

A patient diagnosed with a vancomycin-resistant *Enterococcus* infection is tested for suitability for treatment with the granulocytes of the invention. A blood sample is obtained from the patient and analysed in a BKA assay (according to the method of Example 1).
25

The patient is found to be suitable for treatment with the granulocytes of the invention. The patient's details are processed through a cell database for a cell bank and suitable granulocytes identified (suitable granulocytes are from a donor with the same blood group as the patient and that demonstrated >41.23% MRSA BKA).
30

The patient is treated once a week with the granulocytes of the invention. An infusion of 2×10^9 granulocytes is administered to the patient in the first week and the dose increased incrementally for 3 subsequent weeks to a final dose of 2×10^{11} granulocytes in week 4. A change in symptoms (such as: redness and swelling of the skin; elevated heart rate; malaise; nausea; fever; chills) is monitored. After 4 weeks of treatment the symptoms are vastly
35 reduced/eliminated.

EXAMPLE 10**Infrared-Light Stimulates Neutrophil BKA**

A patient is diagnosed with a diabetic foot ulcer that is not healing. The patient is administered with the granulocytes of the invention and to increase the function and proliferation of the granulocytes is also subjected to short bursts of high-power near-infrared light (1000 W) for 30 minutes 3 times a day for 4 weeks. The infrared light is directed at the wound site. After the treatment course, the ulcer shows signs of significant healing, which is surprisingly improved when compared to a patient administered the granulocytes without the infrared light treatment.

EXAMPLE 11**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 ($50 \times 10^6/\text{ml}$) were frozen at -80°C in cryopreservative (10% FBS in DMSO).

Evaluation of Healthy Cell Killing using the xCelligence Assay

SCDN were thawed and decanted into complete Dulbecco's modified Eagle's medium (DMEM) before incubation for 72 hours with '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). Cell killing activity 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 healthy cells (MCF-12F) are placed in the bottom of a 16 well plate (the system can read up to 3 plates simultaneously).

5 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

10 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_{no effector} – Cell Index_{effector})/Cell Index_{no effector}) X 100.

15

SCDNs that demonstrated >41.23% BKA against MRSA by 2 hours in the assay carried out as per Example 1, and <10% non-bacterial target killing (i.e. killed <10% of 'healthy' breast epithelial cells (MCF-12F)) were designated high BKA neutrophils and cells that demonstrated less than or equal to 41.23% BKA against MRSA were designated low BKA

20 control neutrophils.

Table 3 shows BKA by 2 hours.

BKA type	Donor ID	BKA% MRSA	BKA% RP73
High BKA Neutrophil	A	77.78	83.23
High BKA Neutrophil	B	56.19	89.76
High BKA Neutrophil	C	77.69	86.55
High BKA Neutrophil	D	68.25	67.26
Low BKA Control	E	41.23	28.67
Low BKA Control	F	10.21	17.52

Proteomic Analysis

25 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).

Advantageously, the high BKA neutrophils showed significant upregulation of a number of polypeptides when compared to low BKA controls.

The following polypeptides (and thus genes) were upregulated compared to low BKA 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 polypeptides (and thus genes) were downregulated compared to low BKA controls:

ANXA1 and PPP3CB.

Table 4 presents a number of polypeptides with changed expression in high BKA cells compared to the typical low BKA cells.

Polypeptide	log2 (High BKA/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

- 5 The results are presented graphically in Figures 7-11 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 BKA cells from low BKA cells.
- 10 Advantageously, the expression of many of the genes (i.e. at the protein level) was highly statistically-significantly different (e.g. GM2A) between high BKA cells and low BKA cells, indicating that high BKA granulocytes could be identified using just one of the indicated genes.

EXAMPLE 12**Extracting haematopoietic stem cells from peripheral blood**

Upon giving consent the donors are given a granulocyte-colony stimulating factor (G-CSF) and/or a granulocyte-macrophage colony-stimulating factor (GM-CSF), e.g. Neupogen®
5 (commercially available from Amgen Inc. USA) to help harvest peripheral haematopoietic stem cells with minimal possible discomfort to donors. Cell surface polypeptide markers are used for identifying long-lasting multipotent stem-cells. Suitable markers may include CD 34⁺, CD59⁺, Thy1⁺, CD38^{low/-}, C-kit^{low}, and lin⁻.

EXAMPLE 13**Expansion and differentiation of haematopoietic cells**

The haematopoietic cells (e.g. haematopoietic stem cells) are stimulated using a supernatant growth factor suspension, to either develop more stem cells or differentiate into precursor cells (e.g. myeloid or granulocyte progenitor cells) or granulocytes. Suitable neutrophil
15 synthesis methods are disclosed in Lieber *et al*, Blood, 2004 Feb 1;103(3):852-9, and Choi *et al*, Nat. Protoc., 2011 Mar;6(3):296-313.

The protocol is composed of four major stages:

- culturing and proliferation of haematopoietic cells;
- 20 ▪ short-term expansion of multipotent myeloid progenitors with a high dose of granulocyte-macrophage colony-stimulating factor (GM-CSF), a granulocyte colony-stimulating factor (G-CSF), a human growth hormone (HGH); serotonin, vitamin C, vitamin D, glutamine (Gln), arachidonic acid, AGE-albumin, interleukin-3 (IL-3), interleukin 8 (IL-8), Interleukin-4 (IL-4), Interleukin-6 (IL-6), interleukin-18 (IL-18),
25 TNF-alpha, Flt-3 ligand, thrombopoietin, foetal bovine serum (FBS), or combinations thereof; and
- directed differentiation of myeloid progenitors into neutrophils, eosinophils, dendritic cells (DCs), Langerhans cells (LCs), macrophages and osteoclasts.

EXAMPLE 14**Preparation of cell banks**

Haematopoietic stem cells, granulocyte precursor cells and granulocytes obtainable therefrom, are cryogenically frozen and stored in appropriate cell banks.

- 35 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
5 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.