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(54) **Title**: NOVEL CELL LINES AND METHODS

(57) **Abstract**: The invention relates to novel cells and cell lines, and methods for making and using them.

NOVEL CELL LINES AND METHODS

Field of the Invention

The invention relates to novel cells and cell lines, and methods for making and using them.

Background of the Invention

[0001] Currently, the industry average failure rate for drug discovery programs in pharmaceutical companies is reported to be approximately 98%. Although this includes failures at all stages of the process, the high failure rate points to a dire need for any improvements in the efficiency of the process.

[0002] One factor contributing to the high failure rate is the lack of cell lines expressing therapeutic targets for used in cell-based functional assays during drug discovery. Indisputably, research using cell-based assays, especially drug discovery research, would benefit from cells and cell lines for use in cell-based assays.

[0003] Consequently, there is a great need for rapid and effective establishment of cell based assays for more rapid discovery of new and improved drugs. Preferably, for more effective drug discovery, the assay system should provide a more physiologically relevant predictor of the effect of a modulator *in vivo*.

[0004] Beyond the need for cell-based assays is a need for improved cells for protein production, cell-based therapy and a variety of other uses.

[0005] Accordingly, there is an urgent need for cells and cell lines that express a function protein or RNA of interest.

Summary of the Invention

[0006] In some embodiments, the invention provides a cell that expresses a heterodimeric protein of interest from an introduced nucleic acid encoding at least one of the subunits of the heterodimeric protein of interest, said cell being characterized in that it produces the heterodimeric protein of interest in a form suitable for use in a functional assay, wherein said protein of interest does not comprise a protein tag, or said protein is produced in that form consistently and reproducibly such that the cell has a Z' factor of at least 0.4 in the functional assay, or said cell is cultured in the absence of selective pressure, or any combinations thereof

[0007] In some embodiments, the invention provides a cell that expresses a heterodimeric protein of interest, wherein the cell is engineered to activate transcription of an endogenous nucleic acid encoding at least one of the subunits of the heterodimeric protein of interest, said cell being characterized in that it produces the heterodimeric protein of interest in a form suitable for use in a functional assay, wherein said protein of interest does not comprise a protein tag, or said protein is produced in that form consistently and reproducibly such that the cell has a Z' factor of at least 0.4 in the functional assay, or said cell is cultured in the absence of selective pressure, or any combinations thereof.

[0008] In some embodiments, the invention provides a cell that expresses a heterodimeric protein of interest from an introduced nucleic acid encoding at least one of the subunits of the heterodimeric protein of interest, said cell being characterized in that it produces the protein of interest in a form that is or is capable of becoming biologically active, wherein the cell is cultured in the absence of selective pressure.

[0009] In some embodiments, the invention provides a cell that expresses a heterodimeric protein of interest wherein the cell is engineered to activate

transcription of an endogenous nucleic acid encoding at least one of the subunits of the heterodimeric protein of interest, said cell being characterized in that it produces the protein of interest in a form that is or is capable of becoming biologically active, wherein the cell is cultured in the absence of selective pressure.

[0010] In some embodiments, the nucleic acid encoding the second subunit of the heterodimeric protein of interest is endogenous. In other embodiments, the nucleic acid encoding the second subunit of the heterodimeric protein of interest is introduced. In yet other embodiments, the protein of interest does not comprise a protein tag.

[0011] In some embodiments, the heterodimeric protein of interest is selected from the group consisting of: an ion channel, a G protein coupled receptor (GPCR), tyrosine receptor kinase, cytokine receptor, nuclear steroid hormone receptor and immunological receptor. In some embodiments, the heterodimeric protein of interest is selected from the group consisting of: a sweet taste receptor and an umami taste receptor. In other embodiments, the heterodimeric protein of interest has no known ligand.

[0012] In some embodiments, the heterodimeric protein of interest is not expressed in a cell of the same type. In some embodiments the cell is a mammalian cell.

[0013] In some embodiments, the cell is further characterized in that it has an additional desired property selected from the group consisting of: a signal to noise ratio greater than 1, being stable over time, growth without selective pressure without losing expression, physiological EC50 values, and physiological IC50 values. In some embodiments, the heterodimeric protein of interest is produced in a form consistently and reproducibly for a period of time selected from: at least one week, at least two weeks, at least three weeks, at least one month, at least two months, at least three months at least four months, at least five months, at least six months, at least seven months, at least eight months, and at least nine months. In some embodiments, the functional assay is selected from the group consisting of : a cell-based assay, a fluorescent cell-based assay, a high throughput screening assay, a reporter cell-based assay, a G protein mediated cell-based assay, and a calcium flux cell-based assay. In other embodiments, the cell is suitable for utilization in a cell based high throughput screening.

[0014] In some embodiments, the selective pressure is an antibiotic. In other embodiments, the cell expresses the heterodimeric protein in the absence of selective pressure for at least 15 days, 30 days, 45 days, 60 days, 75 days, 100 days, 120 days, or 150 days.

[0015] In some embodiments, the invention provides a cell that expresses a heteromultimeric protein of interest wherein said heteromultimeric protein comprises at least 3 subunits, wherein at least one subunit of the heteromultimeric protein interest is encoded by an introduced nucleic acid, said cell being characterized in that it produces the heteromultimeric protein of interest in a form suitable for use in a functional assay, wherein said protein of interest does not comprise a protein tag, or said protein produced in that form consistently and reproducibly such that the cell has a Z' factor of at least 0.4 in the functional assay, or said cell is cultured in the absence of selective pressure, or any combinations thereof.

[0016] In some embodiments, the invention provides a cell that expresses a heteromultimeric protein of interest wherein said heteromultimeric protein comprises at least 3 subunits, wherein the cell is engineered to activate transcription of an endogenous nucleic acid encoding at least one of the subunits of the heteromultimeric protein of interest, said cell being characterized in that it produces the heteromultimeric protein of interest in a form suitable for use in a functional assay, wherein said protein of interest does not comprise a protein tag, or said protein produced in that form consistently and reproducibly such that the cell has a Z' factor of at least 0.4 in the functional assay, or said cell is cultured in the absence of selective pressure, or any combinations thereof.

[0017] In some embodiments, the invention provides a cell that expresses a heteromultimeric protein of interest wherein said heteromultimeric protein comprises at least 3 subunits, wherein at least one subunit of the heteromultimeric protein interest is encoded by an introduced nucleic acid, said cell being characterized in that it produces the protein of interest in a form that is or is capable of becoming biologically active.

[0018] In some embodiments, the invention provides a cell that expresses a heteromultimeric protein of interest wherein said heteromultimeric protein comprises at least 3 subunits, wherein the cell is engineered to activate transcription of an endogenous nucleic acid encoding at least one of the subunits of the

heteromultimeric protein of interest, said cell being characterized in that it produces the protein of interest in a form that is or is capable of becoming biologically active.

[0019] In some embodiments, the nucleic acid encoding at least one of the subunits of the heteromultimeric protein of interest is endogenous.

[0020] In some embodiments, the nucleic acid encoding at least one of the subunits of the heteromultimeric protein of interest is introduced.

[0021] In some embodiments, the protein of interest does not comprise a protein tag.

[0022] In some embodiments, the heteromultimeric protein of interest is selected from the group consisting of: an ion channel, a G protein coupled receptor (GPCR), tyrosine receptor kinase, cytokine receptor, nuclear steroid hormone receptor and immunological receptor. In other embodiments, the heteromultimeric protein of interest is selected from the group consisting of: GABA, ENaC and NaV. In some embodiments, the heteromultimeric protein of interest has no known ligand.

[0023] In some embodiments, the heteromultimeric protein of interest is not expressed in a cell of the same type. In other embodiments, the cell is a mammalian cell.

[0024] In some embodiments, the cell is further characterized in that it has an additional desired property selected from the group consisting of: a signal to noise ratio greater than 1, being stable over time, growth without selective pressure without losing expression, physiological EC50 values, and physiological IC50 values. In other embodiments, the heteromultimeric protein of interest is produced in a form consistently and reproducibly for a period of time selected from: at least one week, at least two weeks, at least three weeks, at least one month, at least two months, at least three months at least four months, at least five months, at least six months, at least seven months, at least eight months, and at least nine months.

[0025] In some embodiments, the functional assay is selected from the group consisting of: a cell-based assay, a fluorescent cell-based assay, a high throughput screening assay, a reporter cell-based assay, a G protein mediated cell-based assay, and a calcium flux cell-based assay. In other embodiments, the cell expressing the heteromultimeric protein is suitable for utilization in a cell based high throughput screening.

[0026] In some embodiments, the cells expressing the heteromultimeric protein are cultured in the absence of selective pressure. In some embodiments, the selective

pressure is an antibiotic. In other embodiments, The cell according to claim 35 or 36, wherein the cell expresses the heteromultimeric protein in the absence of selective pressure for at least 15 days, 30 days, 45 days, 60 days, 75 days, 100 days, 120 days, or 150 days.

[0027] In some embodiments, the invention provides a cell that expresses two or more proteins of interest from an introduced nucleic acid encoding at least one of the proteins of interest, said cell being characterized in that it produces the proteins of interest in a form suitable for use in a functional assay, wherein said proteins of interest do not comprise a protein tag, or said proteins are produced in that form consistently and reproducibly such that the cell has a Z' factor of at least 0.4 in the functional assay, or said cell is cultured in the absence of selective pressure, or any combinations thereof.

[0028] In some embodiments, the invention provides a cell that expresses two or more proteins of interest, wherein the cell is engineered to activate transcription of an endogenous nucleic acid encoding at least one of the proteins of interest, said cell being characterized in that it produces the proteins of interest in a form suitable for use in a functional assay, wherein said proteins of interest do not comprise a protein tag, or said proteins are produced in that form consistently and reproducibly such that the cell has a Z' factor of at least 0.4 in the functional assay, or said cell is cultured in the absence of selective pressure, or any combinations thereof.

[0029] In some embodiments, the invention provides a cell that expresses two or more proteins of interest from an introduced nucleic acid encoding at least one of the proteins of interest, said cell being characterized in that it produces the proteins of interest in a form that is or is capable of becoming biologically active.

[0030] In some embodiments, the invention provides a cell that expresses two or more proteins of interest, wherein the cell is engineered to activate transcription of an endogenous nucleic acid encoding at least one of the proteins of interest, said cell being characterized in that it produces the proteins of interest in a form that is or is capable of becoming biologically active.

[0031] In some embodiments, at least one of the two or more proteins of interest is a dimeric protein. In other embodiments, the dimeric protein of interest is a homodimeric protein. In other embodiments, the dimeric protein of interest is a heterodimeric protein. In some embodiments, at least one of the two or more proteins of interest is a multimeric protein. In other embodiments, the multimeric

protein of interest is a homomultimeric protein. In other embodiments, the multimeric protein of interest is a heteromultimeric protein.

[0032] In some of the embodiments, one of the two or more proteins of interest is encoded by an endogenous nucleic acid. In other embodiments, one of the two or more proteins of interest is encoded by an introduced nucleic acid. In other embodiments, the proteins of interest do not comprise a protein tag.

[0033] In some embodiments, one of the two or more proteins of interest is selected from the group consisting of: an ion channel, a G protein coupled receptor (GPCR), tyrosine receptor kinase, cytokine receptor, nuclear steroid hormone receptor and immunological receptor. In other embodiments one of the proteins of interest has no known ligand.

[0034] In some embodiments, one of the two or more proteins of interest is not expressed in a cell of the same type. In some embodiments, the cell expressing the two or more proteins is a mammalian cell.

[0035] In some embodiments, the cell expressing the two or more proteins is further characterized in that it has an additional desired property selected from the group consisting of: a signal to noise ratio greater than 1, being stable over time, growth without selective pressure without losing expression, physiological EC50 values, and physiological IC50 values.

[0036] In some embodiments, the two or more proteins of interest are produced in a form consistently and reproducibly for a period of time selected from: at least one week, at least two weeks, at least three weeks, at least one month, at least two months, at least three months at least four months, at least five months, at least six months, at least seven months, at least eight months, and at least nine months.

[0037] In some embodiments, the functional assay is selected from the group consisting of: a cell-based assay, a fluorescent cell-based assay, a high throughput screening assay, a reporter cell-based assay, a G protein mediated cell-based assay, and a calcium flux cell-based assay. In some embodiments, the cell expressing the two or more proteins is suitable for utilization in a cell based high throughput screening.

[0038] In some embodiments, the cell expressing the two or more proteins is cultured in the absence of selective pressure. In some embodiments, the selective pressure is an antibiotic. In some embodiments, the cell expresses the two or more

proteins in the absence of selective pressure for at least 15 days, 30 days, 45 days, 60 days, 75 days, 100 days, 120 days, or 150 days.

[0039] In some embodiments, the invention provides a cell that expresses at least one RNA of interest, wherein said RNA of interest is encoded by an introduced nucleic acid, said cell being characterized in that it produces the at least one RNA of interest in a form suitable for use in a functional assay, wherein said RNA of interest do not comprise a tag, or said RNA is produced in that form consistently and reproducibly such that the cell has a Z' factor of at least 0.4 in the functional assay, or said cell is cultured in the absence of selective pressure, or any combinations thereof.

[0040] In some embodiments, the invention provides a cell that expresses at least one RNA of interest, wherein the cell is engineered to activate transcription of an endogenous nucleic acid encoding the at least one RNA of interest, said cell being characterized in that it produces the at least one RNA of interest in a form suitable for use in a functional assay, wherein said RNA of interest do not comprise a tag, or said RNA is produced in that form consistently and reproducibly such that the cell has a Z' factor of at least 0.4 in the functional assay or said cell is cultured in the absence of selective pressure, or any combinations thereof.

[0041] In some embodiments, the cell expresses at least two RNAs of interest. In other embodiments, the cell expresses at least three RNAs of interest. In some embodiments, the cell further expresses a RNA encoded by an introduced nucleic acid. In some embodiments, the the RNA of interest is selected from the group consisting of : a RNA encoding an ion channel, a RNA encoding a G protein coupled receptor (GPCR), a RNA encoding a tyrosine receptor kinase, a RNA encodinga cytokine receptor, a RNA encoding a nuclear steroid hormone receptor and a RNA encoding an immunological receptor.

[0042] In some embodiments, the RNA of interest is not expressed in a cell of the same type. In some embodiments, the cell expressing the RNA of interest is a mammalian cell.

[0043] In some embodiments, the cell expressing the RNA of interest is further characterized in that it has an additional desired property selected from the group consisting of: a signal to noise ratio greater than 1, being stable over time, growth without selective pressure without losing expression, physiological EC50 values, and physiological IC50 values. In some embodiments, the RNA of interest is produced in

a form consistently and reproducibly for a period of time selected from: at least one week, at least two weeks, at least three weeks, at least one month, at least two months, at least three months at least four months, at least five months, at least six months, at least seven months, at least eight months, and at least nine months.

[0044] In some embodiments, the functional assay is selected from the group consisting of: a cell-based assay, a fluorescent cell-based assay, a high throughput screening assay, a reporter cell-based assay, a G protein mediated cell-based assay, and a calcium flux cell-based assay.

[0045] In some embodiments, the cell expressing the RNA of interest is suitable for utilization in a cell based high throughput screening.

[0046] In some embodiments, the invention provides a cell line produced from a cell described herein.

[0047] In some embodiments, the invention provides a method for producing a cell that expresses a protein of interest, wherein the cell has at least one desired property that is consistent over time, comprising the steps of:

a) providing a plurality of cells that express mRNA encoding the protein of interest;

b) dispersing cells individually into individual culture vessels, thereby providing a plurality of separate cell cultures

c) culturing the cells under a set of desired culture conditions using automated cell culture methods characterized in that the conditions are substantially identical for each of the separate cell cultures, during which culturing the number of cells per separate cell culture is normalized, and wherein the separate cultures are passaged on the same schedule;

d) assaying the separate cell cultures for at least one desired characteristic of the protein of interest at least twice; and

e) identifying a separate cell culture that has the desired characteristic in both assay.

[0048] In some embodiments, the plurality of cells in step a) of the methods described herein are cultured for some period of time prior to the dispersing in step b).

[0049] In some embodiments, the individual culture vessels used in the methods of this invention are selected from the group consisting of: individual wells of a multiwell plate and vials.

[0050] In some embodiments, the method further comprises the step of determining the growth rate of a plurality of the separate cell cultures and grouping the separate cell cultures by their growth rates into groups such that the difference between the fastest and slowest growth rates in any group is no more than 1, 2, 3, 4 or 5 hours between steps b) and c).

[0051] In some embodiments, the method further comprises the step of preparing a stored stock of one or more of the separate cultures. In some embodiments, the method further comprises the step of one or more replicate sets of the separate cell cultures and culturing the one or more replicate sets separately from the source separate cell cultures.

[0052] In some embodiments, the assaying in step d) of the method of this invention is a functional assay for the protein.

[0053] In some embodiments, the at least one characteristic that has remained constant in step e) is protein function.

[0054] In some embodiments, the culturing in step c) of the methods of this invention is in a robotic cell culture apparatus. In some embodiments, the robotic cell culture apparatus comprises a multi-channel robotic pipettor. In some embodiments, the multi-channel robotic pipettor comprises at least 96 channels. In some embodiments, the robotic cell culture apparatus further comprises a cherry-picking arm.

[0055] In some embodiments, the automated methods include one or more of: media removal, media replacement, cell washing, reagent addition, removal of cells, cell dispersal, and cell passaging.

[0056] In some embodiments, the plurality of separate cell cultures used in the methods of this invention is at least 50 cultures. In other embodiments, the plurality of separate cell cultures is at least 100 cultures. In other embodiments, the plurality of separate cell cultures is at least 500 cultures. In yet other embodiments, the plurality of separate cell cultures is at least 1000 cultures.

[0057] In some embodiments, the growth rate is determined by a method selected from the group consisting of: measuring ATP, measuring cell confluency, light scattering, optical density measurement. In some embodiments, the difference between the fastest and slowest growth rates in a group is no more than 1, 2, 3, 4, or 5 hours.

[0058] In some embodiments, the culturing in step c) of the methods of this invention is for at least 2 days.

[0059] In some embodiments, the growth rates of the plurality of separate cell cultures are determined by dispersing the cells and measuring cell confluency. In some embodiments, the cells in each separate cell culture of the methods of this invention are dispersed prior to measuring cell confluency. In some embodiments, the dispersing step comprises adding trypsin to the well and to eliminate clumps. In some embodiments, the cell confluency of the plurality of separate cell cultures is measured using an automated microplate reader.

[0060] In some embodiments, at least two confluency measurements are made before growth rate is calculated. In some embodiments, the cell confluency is measured by an automated plate reader and the confluency values are used with a software program that calculates growth rate.

[0061] In some embodiments, the separate cell cultures in step d) are characterization for a desired trait selected from one or more of: fragility, morphology, adherence to a solid surface; lack of adherence to a solid surface and protein function.

[0062] In some embodiments, the cells used in the methods of this invention are eukaryotic cells. In some embodiments, the eukaryotic cells used in the methods of this invention are mammalian cells. In some embodiments, the mammalian cell line is selected from the group consisting of: NS0 cells, CHO cells, COS cells, HEK-293 cells, HUVECs, 3T3 cells and HeLa cells.

[0063] In some embodiments, the protein of interest expressed in the methods of this invention is a human protein. In some embodiments, the protein of interest is a heteromultimer. In some embodiments, the protein of interest is a G protein coupled receptor. In other embodiments, the protein has no known ligand.

[0064] In some embodiments, the method of this invention, further comprises after the identifying step, the steps of:

a) expanding a stored aliquot of the cell culture identified in step e) under desired culture conditions;

b) determining if the expanded cell culture of a) has the desired characteristic.

[0065] In some embodiments, the invention provides a matched panel of clonal cell lines, wherein the clonal cell lines are of the same cell type, and wherein each cell

line in the panel expresses a protein of interest, and wherein the clonal cell lines in the panel are matched to share the same physiological property to allow parallel processing. In some embodiments, the physiological property is growth rate. In other embodiments, the physiological property is adherence to a tissue culture surface. In other embodiments, the physiological property is Z' factor. In other embodiments, the physiological property is expression level of RNA encoding the protein of interest. In yet other embodiments, the physiological property is expression level of the protein of interest.

[0066] In some embodiments, the growth rates of the clonal cell lines in the panel are within 1, 2, 3, 4, or 5 hours of each other. In other embodiments, the culture conditions used for the matched panel are the same for all clonal cell lines in the panel.

[0067] In some embodiments, the clonal cell line used in the matched panels is a eukaryotic cell line. In some embodiments, the eukaryotic cell line is a mammalian cell line. In some embodiments, the cell line cells used in the matched panels are selected from the group consisting of: primary cells and immortalized cells.

[0068] In some embodiments, the cell line cells used in the matched panels are prokaryotic or eukaryotic. In some embodiments, the cell line cells used in the matched panels are eukaryotic and are selected from the group consisting of: fungal cells, insect cells, mammalian cells, yeast cells, algae, crustacean cells, arthropod cells , avian cells, reptilian cells, amphibian cells and plant cells. In some embodiments, the cell line cells used in the matched panels are mammalian and are selected from the group consisting of: human, non-human primate, bovine, porcine, feline, rat, marsupial, murine, canine, ovine, caprine, rabbit, guinea pig hamster.

[0069] In some embodiments, the cells in the cell line of the matched panels are engineered to express the protein of interest. In some embodiments, the cells in the cell line of the matched panels express the protein of interest from an introduced nucleic acid encoding the protein or, in the case of a multimeric protein, encoding a subunit of the protein. In some embodiments, the cells express the protein of interest from an endogenous nucleic acid and wherein the cell is engineered to activate transcription of the endogenous protein or, in the case of a multimeric protein, activates transcription of a subunit of the protein.

[0070] In some embodiments, the panel comprises at least four clonal cell lines. In other embodiments, the panel comprises at least six clonal cell lines. In yet other embodiments, the panel comprises at least twenty five clonal cell lines.

[0071] In some embodiments, two or more of the clonal cell lines in the panel express the same protein of interest. In other embodiments, two or more of the clonal cell lines in the panel express a different protein of interest.

[0072] In some embodiments, the cell lines in the panel express different forms of a protein of interest, wherein the forms are selected from the group consisting of: isoforms, amino acid sequence variants, splice variants, truncated forms, fusion proteins, chimeras, or combinations thereof.

[0073] In some embodiments, the cell lines in the panel express different proteins in a group of proteins of interest, wherein the groups of proteins of interest are selected from the group consisting of: proteins in the same signaling pathway, expression library of similar proteins, monoclonal antibody heavy chain library, monoclonal antibody light chain library and SNPs.

[0074] In some embodiments, the protein of interest expressed in the panel is a single chain protein. In some embodiments, the single chain protein is a G protein coupled receptor. In some embodiments, the G protein coupled receptor is a taste receptor. In some embodiments, the taste receptor is selected from the group consisting of: a bitter taste receptor, a sweet taste receptor, a salt taste receptor and a umami taste receptor.

[0075] In other embodiments, the protein of interest expressed in the panel is a multimeric protein. In some embodiments, the protein is a heterodimer or a heteromultimer.

[0076] In some embodiments, the protein of interest expressed in the panel is selected from the group consisting of: an ion channel, an ion channel, a G protein coupled receptor (GPCR), tyrosine receptor kinase, cytokine receptor, nuclear steroid hormone receptor and immunological receptor. In some embodiments, the protein expressed in the matched panel is Epithelial sodium Channel (ENaC). In some embodiments, the ENaC comprises an alpha subunit, a beta subunit and a gamma subunit. In other embodiments, the cell lines in the panel express different ENaC isoforms. In other embodiments, the cell lines in the panel comprise different proteolyzed isoforms of ENaC. In some embodiments, the ENaC is human ENaC. In some embodiments the protein expressed in the matched panel is voltage gated

sodium channel (NaV). In some embodiments, the NaV comprises an alpha subunit and two beta subunits. In some embodiments, the NaV is human NaV.

[0077] In some embodiments, the protein expressed in the matched panel is selected from the group consisting of: gamma-aminobutyric acid A receptor ($GABA_A$ receptor), gamma-aminobutyric acid B receptor ($GABA_B$ receptor) and gamma-aminobutyric acid C receptor ($GABA_C$ receptor). In some embodiments, the protein is $GABA_A$ receptor. In some embodiments, the $GABA_A$ receptor comprises two alpha subunits, two beta subunits and a gamma or delta subunit.

[0078] In some embodiments, the clonal cell lines in the panel are produced simultaneously, or within no more than 4 weeks of each other.

[0079] In some embodiments, the invention provides a cell that expresses a monomeric protein of interest from an introduced nucleic acid encoding said monomeric protein of interest, characterized in that it produces the protein of interest in a form that is or is capable of becoming biologically active, wherein the cell is cultured in the absence of selective pressure and wherein the expression of the protein does not vary by more than 5% over 3 months. In some embodiments the expression of the protein does not vary by more than 5% over 6 months. In some embodiments, the monomeric protein of interest has no known ligand.

[0080] In some embodiments, the invention provides A method for identifying a modulator of a protein of interest comprising the steps of:

a) contacting a cell according to any one of the above-described cell embodiments with a test compound; and

b) detecting a change in the activity of the protein of interest in the cell contacted with the test compound compared to the activity of the protein in a cell not contacted by the test compound;

wherein a compound that produces a difference in the activity in the presence compared to in the absence is a modulator of the protein of interest.

[0081] In another embodiment, the invention provides a modulator identified by the method of the preceding paragraph.

Detailed Description

[0082] Unless otherwise defined, 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 invention belongs. Exemplary methods and materials are described

below, although methods and materials similar or equivalent to those described herein can also be used in the practice or testing of the present invention. In case of conflict, the present specification, including definitions, will control.

[0083] All publications and other references mentioned herein are incorporated by reference in their entirety. Although a number of documents are cited herein, this citation does not constitute an admission that any of these documents forms part of the common general knowledge in the art.

[0084] Throughout this specification and claims, the word "comprise," or variations such as "comprises" or "comprising" will be understood to imply the inclusion of a stated integer or group of integers but not the exclusion of any other integer or group of integers. Unless otherwise required by context, singular terms shall include pluralities and plural terms shall include the singular. The materials, methods, and examples are illustrative only and not intended to be limiting.

[0085] In order that the present invention may be more readily understood, certain terms are first defined. Additional definitions are set forth throughout the detailed description.

[0086] The term "stable" or "stably expressing" is meant to distinguish the cells and cell lines of the invention from cells that transiently express proteins as the terms "stable expression" and "transient expression" would be understood by a person of skill in the art.

[0087] As used herein, a "functional" RNA or protein of interest is one that has a signal to noise ratio greater than 1:1 in a cell based assay. In some embodiments, a functional protein or RNA of interest has one or more of the biological activities of the naturally occurring or endogenously expressed protein or RNA.

[0088] The term "cell line" or "clonal cell line" refers to a population of cells that is progeny of a single original cell. As used herein, cell lines are maintained *in vitro* in cell culture and may be frozen in aliquots to establish banks of clonal cells.

[0089] The term "stringent conditions" or "stringent hybridization conditions" describe temperature and salt conditions for hybridizing one or more nucleic acid probes to a nucleic acid sample and washing off probes that have not bound specifically to target nucleic acids in the sample. Stringent conditions are known to those skilled in the art and can be found in, for example, *Current Protocols in Molecular Biology*, John Wiley & Sons, N.Y. (1989), 6.3.1-6.3.6. Aqueous and nonaqueous methods are described in the Protocols and either can be used. One

example of stringent hybridization conditions is hybridization in 6X SSC at about 45°C, followed by at least one wash in 0.2X SSC, 0.1% SDS at 60°C. Another example of stringent hybridization conditions is hybridization in 6X SSC at about 45°C, followed by at least one wash in 0.2X SSC, 0.1% SDS at 65°C. Stringent hybridization conditions also include hybridization in 0.5M sodium phosphate, 7% SDS at 65°C, followed by at least one wash at 0.2X SSC, 1% SDS at 65°C.

[0090] The phrase "percent identical" or "percent identity" in connection with amino acid and/or nucleic acid sequences refers to the similarity between at least two different sequences. The percent identity can be determined by standard alignment algorithms, for example, the Basic Local Alignment Tool (BLAST) described by Altshul et al. ((1990) J. Mol. Biol., 215: 403-410); the algorithm of Needleman et al. ((1970) J. Mol. Biol., 48: 444-453); or the algorithm of Meyers et al. ((1988) Comput. Appl. Biosci., 4: 11-17). A set of parameters may be the Blosum 62 scoring matrix with a gap penalty of 12, a gap extend penalty of 4, and a frameshift gap penalty of 5. The percent identity between two amino acid or nucleotide sequences can also be determined using the algorithm of E. Meyers and W. Miller ((1989) CABIOS, 4:11-17) that has been incorporated into the ALIGN program (version 2.0), using a PAM120 weight residue table, a gap length penalty of 12 and a gap penalty of 4. The percent identity is usually calculated by comparing sequences of similar length.

[0091] Protein analysis software matches similar amino acid sequences using measures of similarity assigned to various substitutions, deletions and other modifications, including conservative amino acid substitutions. For instance, the GCG Wisconsin Package (Accelrys, Inc.) contains programs such as "Gap" and "Bestfit" that can be used with default parameters to determine sequence identity between closely related polypeptides, such as homologous polypeptides from different species or between a wild type protein and a mutein thereof. *See, e.g.*, GCG Version 6.1. Polypeptide sequences also can be compared using FASTA using default or recommended parameters. A program in GCG Version 6.1. FASTA (*e.g.,* FASTA2 and FASTA3) provides alignments and percent sequence identity of the regions of the best overlap between the query and search sequences (Pearson, Methods Enzymol. 183:63-98 (1990); Pearson, Methods Mol. Biol. 132:185-219 (2000)).

[0092] The length of polypeptide sequences compared for identity will generally be at least about 16 amino acid residues, usually at least about 20 residues, more usually at least about 24 residues, typically at least about 28 residues, and preferably more than about 35 residues. The length of a DNA sequence compared for identity will generally be at least about 48 nucleic acid residues, usually at least about 60 nucleic acid residues, more usually at least about 72 nucleic acid residues, typically at least about 84 nucleic acid residues, and preferably more than about 105 nucleic acid residues.

[0093] The phrase "substantially as set out," "substantially identical" or "substantially homologous" in connection with an amino acid or nucleotide sequence means that the relevant amino acid or nucleotide sequence will be identical to or have insubstantial differences (*e.g.*, conserved amino acid substitutions or nucleic acids encoding such substitutions) in comparison to the comparator sequences. Insubstantial differences include minor amino acid changes, such as 1 or 2 substitutions in a 50 amino acid sequence of a specified region and the nucleic acids that encode those sequences.

[0094] Modulators include any substance or compound that alters an activity of a protein of interest. The modulator can be an agonist (potentiator or activator) or antagonist (inhibitor or blocker), including partial agonists or antagonists, selective agonists or antagonists and inverse agonists, and can also be an allosteric modulator. A substance or compound is a modulator even if its modulating activity changes under different conditions or concentrations or with respect to different forms of a protein of interest. In other aspects, a modulator may change the ability of another modulator to affect the function of a protein of interest.

[0095] The terms "potentiator", "agonist" or "activator" refer to a compound or substance that increases one or more activities of a protein of interest.

[0096] The terms "inhibitor", "antagonist" or "blocker" refer to a compound or substance that decreases or blocks one or more activities of a protein of interest.

[0097] The invention provides for the first time novel cells and cell lines produced from the cells that meet the urgent need for cells that stably express a functional RNA of interest or a functional protein of interest, including complex proteins such as heteromultimeric proteins and proteins for which no ligand is known. The cells and cell lines of the invention are suitable for any use in which consistent, functional expression of an RNA or protein of interest are desirable. Applicants have produced

cell lines meeting this description for a variety of proteins, both single subunit and heteromultimeric (including heterodimeric and proteins with more than two different subunits), including membrane proteins, cytosolic proteins and secreted proteins, as well as various combinations of these.

[0098] In one aspect, the cells and cell lines of the invention are suitable for use in a cell-based assay. Such cells and cell lines provide consistent and reproducible expression of the protein of interest over time and, thus, are particularly advantageous in such assays.

[0099] In another aspect, the invention provides cells and cell lines that are suitable for the production of biological molecules. The cells and cell lines for such use are characterized, for example, by consistent expression of a protein or polypeptide that is functional or that is capable of becoming functional.

[0100] The invention further provides a method for producing cells and cell lines that stably express an RNA or a protein of interest. Using the method of the invention, one can produce cells and cell lines that express any desired protein in functional form, including complex proteins such as multimeric proteins, (e.g., heteromultimeric proteins) and proteins that are cytotoxic. The method disclosed herein makes possible the production of engineered cells and cell lines stably expressing functional proteins that prior to this invention have not previously been produced. Without being bound by theory, it is believed that because the method permits investigation of very large numbers of cells or cell lines under any desired set of conditions, it makes possible the identification of rare cells that would not have been produced in smaller populations or could not otherwise be found and that are optimally suited to express a desired protein in a functional form under desired conditions.

[0101] In a further aspect, the invention provides a matched panel of cell lines, i.e., a collection of clonal cell lines that are matched for one or more physiological properties. Because the method of the invention permits maintenance and characterization of large numbers of cell lines under identical conditions, it is possible to identify any number of cell lines with similar physiological properties. Using the method of the invention, it is possible to make matched panels comprising any desired number of cell lines or make up Such matched panels may be maintained under identical conditions, including cell density and, thus, are useful for high throughput screening and other uses where it is desired to compare and identify

differences between cell lines. Also within the invention are matched panels of cell lines that are matched for growth rate.

[0102] In another aspect, the invention provides a method for producing cells or cell lines that express a protein of previously unknown function and/or for which no ligand had previously been identified. Such a protein may be a known naturally occurring protein, a previously unknown naturally occurring protein, a previously unknown form of a known naturally occurring protein or a modified form of any of the foregoing.

[0103] Any desired cell type may be used for the cells of the invention. The cells may be prokaryotic or eukaryotic. The cells may express the protein of interest in their native state or not. Eukaryotic cells that may be used include but are not limited to fungi cells such as yeast cells, plant cells and animal cells. Animal cells that can be used include but are not limited to mammalian cells and insect cells, Primary or immortalized cells may be derived from mesoderm, ectoderm or endoderm layers of eukaryotic organisms. The cells may be endothelial, epidermal, mesenchymal, neural, renal, hepatic, hematopoietic, or immune cells. For example, the cells may be intestinal crypt or villi cells, clara cells, colon cells, intestinal cells, goblet cells, enterochromafin cells, enteroendocrine cells. Mammalian cells that are useful in the method include but are not limited to human, non-human primate, cow, horse, goat, sheep, pig, rodent (including rat, mouse, hamster, guinea pig), marsupial, rabbit, dog and cat. The cells can be differentiated cells or stem cells, including embryonic stem cells.

[0104] Cells of the invention can be primary, transformed, oncogenically transformed, virally transformed, immortalized, conditionally transformed, explants, cells of tissue sections, animals, plants, fungi, protists, archaebacteria and eubacteria, mammals, birds, fish, reptiles, amphibians, and arthropods, avian, chicken, reptile, amphibian, frog, lizard, snake, fish, worms, squid, lobster, sea urchin, sea slug, sea squirt, fly, squid, hydra, arthropods, beetles, chicken, lamprey, ricefish, zebra finch, pufferfish, and Zebrafish,

[0105] Additionally, cells such as blood/immune cells, endocrine (thyroid, parathyroid, adrenal), GI (mouth, stomach, intestine), liver, pancreas, gallbladder, respiratory (lung, trachea, pharynx), Cartilage, bone, muscle, skin, hair, urinary (kidney, bladder), reproductive (sperm, ovum, testis, uterus, ovary, penis, vagina), sensory (eye, ear, nose, mouth, tongue, sensory neurons), Blood/immune cells such

as_B cell, T cell (Cytotoxic T cell, Natural Killer T cell, Regulatory T cell, T helper cell, Tcell , Natural killer cell; granulocytes (basophil granulocyte, eosinophil granulocyte, neutrophil granulocyte/hypersegmented neutrophil), monocyte/macrophage, red blood cell (reticulocyte), mast cell, thrombocyte/Megakaryocyte, dendritic cell; endocrine cells such as: thyroid (thyroid epithelial cell, parafollicular cell), parathyroid (parathyroid chief cell, oxyphil cell), adrenal (chromaffin cell), nervous system cells such as: glial cells (astrocyte, microglia), magnocellular neurosecretory cell, stellate cell, nuclear chain cell, boettcher cell, pituitary, (gonadotrope, corticotrope, thyrotrope, somatotrope, lactotroph), respiratory system cells such as pneumocyte (type I pneumocyte, type II pneumocyte), clara cell, goblet cell; circulatory system cells such as myocardiocyte · pericyte; digestive system cells such as stomach (gastric chief cell, parietal cell), goblet cell, paneth cell, G cells, D cells, ECL cells, I cells, K cells, ,enteroendocrine cells, enterochromaffin cell, APUD cell, liver (hepatocyte, kupffer cell), pancreas (beta cells, alpha cells), gallbladder; cartilage/bone/muscle/integumentary system cells such as osteoblast, osteocyte, steoclast, tooth cells (cementoblast, ameloblast), cartilage cells: chondroblast, chondrocyte, skin/hair cells: trichocyte, keratinocyte, melanocyte, muscle cells: myocyte, adipocyte, fibroblast, urinary system cells such as podocyte, juxtaglomerular cell, intraglomerular mesangial cell/extraglomerular mesangial cell, kidney proximal tubule brush border cell, macula densa cell; reproductive system cells such as spermatozoon, sertoli cell, leydig cell, ovum, ovarian follicle cell; sensory cells such as organ of corti cells, olfactory epithelium, temperature sensitive sensory neurons, merckel cells, olfactory receptor neuron, pain sensitive neurons, photoreceptor cells, taste bud cells, hair cells of the vestibular apparatus, carotid body cells are useful to make cells or cell lines of the invention.

[0106] Plant cells that are useful include roots, stems and leaves and plant tissues include meristematic tissues, parenchyma collenchyma, sclerenchyma, secretory tissues, xylem, phloem, epidermis, periderm (bark).

[0107] Cells that are useful for the cells and cell lines of the invention also include but are not limited to: Chinese hamster ovary (CHO) cells, established neuronal cell lines, pheochromocytomas, neuroblastomas fibroblasts, rhabdomyosarcomas, dorsal root ganglion cells, NS0 cells, CV-1 (ATCC CCL 70), COS-1 (ATCC CRL 1650), COS-7 (ATCC CRL 1651), CHO-K1 (ATCC CCL 61), 3T3 (ATCC CCL 92), NIH/3T3

(ATCC CRL 1658), HeLa (ATCC CCL 2), C127I (ATCC CRL 1616), BS-C-1 (ATCC CCL 26), MRC-5 (ATCC CCL 171), L-cells, HEK-293 (ATCC CRL1573) and PC12 (ATCC CRL-1721), HEK293T (ATCC CRL-11268), RBL (ATCC CRL-1378), SH-SY5Y (ATCC CRL-2266), MDCK (ATCC CCL-34), SJ-RH30 (ATCC CRL-2061), HepG2 (ATCC HB-8065), ND7/23 (ECACC 92090903), CHO (ECACC 85050302), Vero (ATCC CCL 81), Caco-2 (ATCC HTB 37), K562 (ATCC CCL 243), Jurkat (ATCC TIB-152), Per.C6 (Crucell, Leiden, The Netherlands), Huvec (ATCC Human Primary PCS 100-010, Mouse CRL 2514, CRL 2515, CRL 2516), HuH-7D12 (ECACC 01042712), 293 (ATCC CRL 10852), A549 (ATCC CCL 185), IMR-90 (ATCC CCL 186), MCF-7 (ATC HTB-22), U-2 OS (ATCC HTB-96), T84 (ATCC CCL 248), or any established cell line (polarized or nonpolarized) or any cell line available from repositories such as American Type Culture Collection (ATCC, 10801 University Blvd. Manassas, Va. 20110-2209 USA) or European Collection of Cell Cultures (ECACC, Salisbury Wiltshire SP4 0JG England).

[0108] Further, cells that are useful in the method of the invention are mammalian cells amenable to growth in serum containing media, serum free media, fully defined media without any animal-derived products, and cells that can be converted from one of these conditions to another.

[0109] Cells of the invention include cells into which a nucleic acid that encodes the protein of interest (or in the case of a heteromultimeric protein, a nucleic acid that encodes one or more of the subunits of the protein) has been introduced. Engineered cells also include cells into which nucleic acids for transcriptional activation of an endogenous sequence encoding a protein of interest (or for transcriptional activation of endogenous sequence encoding one or more subunits of a heteromultimeric protein) have been introduced. Engineered cells also include cells comprising a nucleic acid encoding a protein of interest that is activated by contact with an activating compound. Engineered cells further include combinations of the foregoing, that is, cells that express one or more subunits of a heteromultimeric protein from an introduced nucleic acid encoding it and that express one or more subunits of the protein by gene activation.

[0110] Any of the nucleic acids may be introduced into the cells using known means. Techniques for introducing nucleic acids into cells are well-known and readily appreciated by the skilled worker. The methods include but are not limited to transfection, viral delivery, protein or peptide mediated insertion, coprecipitation

methods, lipid based delivery reagents (lipofection), cytofection, lipopolyamine delivery, dendrimer delivery reagents, electroporation or mechanical delivery. Examples of transfection reagents are GENEPORTER, GENEPORTER2, LIPOFECTAMINE, LIPOFECTAMINE 2000, FUGENE 6, FUGENE HD, TFX-10, TFX-20, TFX-50, OLIGOFECTAMINE, TRANSFAST, TRANSFECTAM, GENESHUTTLE, TROJENE, GENESILENCER, X-TREMEGENE, PERFECTIN, CYTOFECTIN, SIPORT, UNIFECTOR, SIFECTOR, TRANSIT-LT1, TRANSIT-LT2, TRANSIT-EXPRESS, IFECT, RNAI SHUTTLE, METAFECTENE, LYOVEC, LIPOTAXI, GENEERASER, GENEJUICE, CYTOPURE, JETSI, JETPEI, MEGAFECTIN, POLYFECT, TRANSMESSANGER, RNAiFECT, SUPERFECT, EFFECTENE, TF-PEI-KIT, CLONFECTIN, and METAFECTINE.

[0111] Where two or more nucleotide sequences are introduced, such as sequences encoding two or more subunits of a heteromultimeric protein or sequences encoding two or more different proteins of interest, the sequences may be introduced on the same vector or, preferably, on separate vectors. The DNA can be genomic DNA, cDNA, synthetic DNA or mixtures of them. In some embodiments, nucleic acids encoding a protein of interest or a partial protein of interest do not include additional sequences such that the protein of interest is expressed with additional amino acids that may alter the function of the cells compared to the physiological function of the protein.

[0112] In some embodiments, the nucleic acid encoding the protein of interest comprises one or more substitutions, insertions, mutations or deletions, as compared to a nucleic acid sequence encoding the wild-type protein. In embodiments comprising a nucleic acid comprising a mutation, the mutation may be a random mutation or a site-specific mutation. These nucleic acid changes may or may not result in an amino acid substitution. In some embodiments, the nucleic acid is a fragment of the nucleic acid that encodes the protein of interest. Nucleic acids that are fragments or have such modifications encode polypeptides that retain at least one biological property of the protein of interest.

[0113] The invention also encompasses cells and cell lines stably expressing a nucleic acid, whose sequence is at least about 85% identical to the "wild type" sequence encoding the protein of interest, or a counterpart nucleic acid derived from a species other than human or a nucleic acid that encodes the same amino acid sequence as any of those nucleic acids. In some embodiments, the sequence

identity is at least 85%, 90%, 95%, 96%, 97%, 98%, 99% or higher compared to those sequences. The invention also encompasses cells and cell lines wherein the nucleic acid encoding a protein of interest hybridizes under stringent conditions to the wild type sequence or a counterpart nucleic acid derived from a species other than human, or a nucleic acid that encodes the same amino acid sequence as any of those nucleic acids.

[0114] In some embodiments, the cell or cell line comprises a protein-encoding nucleic acid sequence comprising at least one substitution as compared to the wild-type sequence or a counterpart nucleic acid derived from a species other than human or a nucleic acid that encodes the same amino acid sequence as any of those nucleic acids. The substitution may comprise less than 10, 20, 30, or 40 nucleotides or, up to or equal to 1%, 5%, 10% or 20% of the nucleotide sequence. In some embodiments, the substituted sequence may be substantially identical to the wild-type sequence or a counterpart nucleic acid derived from a species other than human a nucleic acid that encodes the same amino acid sequence as any of those nucleic acids (*e.g.*, a sequence at least 85%, 90%, 95%, 96%, 97%, 98%, 99% or higher identical thereto), or be a sequence that is capable of hybridizing under stringent conditions to the wild type sequence or a counterpart nucleic acid derived from a species other than human or a nucleic acid that encodes the same amino acid sequence as any one of those nucleic acids.

[0115] In some embodiments, the cell or cell line comprises protein-encoding nucleic acid sequence comprising an insertion into or deletion from the wild type sequence or a counterpart nucleic acid derived from a species other than human or a nucleic acid that encodes the same amino acid sequence as any of those nucleic acids. The insertion or deletion may be less than 10, 20, 30, or 40 nucleotides or up to or equal to 1%, 5%, 10% or 20% of the nucleotide sequence. In some embodiments, the sequences of the insertion or deletion may be substantially identical to the wild type sequence or a counterpart nucleic acid derived from a species other than human or a nucleic acid that encodes the same amino acid sequence as any of those nucleic acids (*e.g.*, a sequence at least 85%, 90%, 95%, 96%, 97%, 98%, 99% or higher identical thereto), or be a sequence that is capable of hybridizing under stringent conditions to the wild-type sequence or a counterpart nucleic acid derived from a species other than human, or a nucleic acid that encodes the same amino acid sequence as any of those nucleic acids.

[0116] In some embodiments, the nucleic acid substitution or modification results in an amino acid change, such as an amino acid substitution. For example, an amino acid residue of the wild type protein of interest or a counterpart amino acid derived from a species other than human may be replaced by a conservative or a non-conservative substitution. In some embodiments, the sequence identity between the original and modified amino acid sequence can differ by about 1%, 5%, 10% or 20% or from a sequence substantially identical thereto (*e.g.*, a sequence at least 85%, 90%, 95%, 96%, 97%, 98%, 99% or higher identical thereto).

[0117] A "conservative amino acid substitution" is one in which an amino acid residue is substituted by another amino acid residue having a side chain R group with similar chemical properties to the parent amino acid residue (*e.g.*, charge or hydrophobicity). In cases where two or more amino acid sequences differ from each other by conservative substitutions, the percent sequence identity or degree of similarity may be adjusted upwards to correct for the conservative nature of the substitution. Means for making this adjustment are well-known to those of skill in the art. *See, e.g.*, Pearson, Methods Mol. Biol. 243:307-31 (1994).

[0118] Examples of groups of amino acids that have side chains with similar chemical properties include 1) aliphatic side chains: glycine, alanine, valine, leucine, and isoleucine; 2) aliphatic-hydroxyl side chains: serine and threonine; 3) amide-containing side chains: asparagine and glutamine; 4) aromatic side chains: phenylalanine, tyrosine, and tryptophan; 5) basic side chains: lysine, arginine, and histidine; 6) acidic side chains: aspartic acid and glutamic acid; and 7) sulfur-containing side chains: cysteine and methionine. Preferred conservative amino acids substitution groups are: valine-leucine-isoleucine, phenylalanine-tyrosine, lysine-arginine, alanine-valine, glutamate-aspartate, and asparagine-glutamine. Alternatively, a conservative amino acid substitution is any change having a positive value in the PAM250 log-likelihood matrix disclosed in Gonnet et al., Science 256:1443-45 (1992). A "moderately conservative" replacement is any change having a nonnegative value in the PAM250 log-likelihood matrix.

[0119] Conservative modifications in the protein of interest will produce proteins having functional and chemical characteristics similar (*i.e.* at least 50%, 60%, 70%, 80%, 90% or 95% the same) to those of the unmodified protein.

[0120] In one embodiment, the host cell is an embryonic stem cell that is then used as the basis for the generation of transgenic animals that produce the protein of

interest. Embryonic stem cells stably expressing a functional protein of interest, may be implanted into organisms directly, or their nuclei may be transferred into other recipient cells and these may then be implanted, or they may be used to create transgenic animals. In some embodiments the protein may be expressed in the animal with desired temporal and/or tissue specific expression.

[0121] As will be appreciated by those of skill in the art, any vector that is suitable for use with a chosen host cell may be used to introduce a nucleic acid encoding a protein of interest into a host cell. Where more than one vector is used, for example, to introduce two or more different subunits or two or more proteins of interest, the vectors may be the same type or may be of different types.

[0122] Examples of vectors that may be used to introduce the nucleic acids into host cells include but are not limited to plasmids, viruses, including retroviruses and lentiviruses, cosmids, artificial chromosomes and may include, for example, pCMVScript, pcDNA3.1 Hygro, pcDNA3.1neo, pcDNA3.1puro, pSV2neo, pIRES puro, pSV2 zeo. Exemplary mammalian expression vectors that are useful to make the cells and cell lines of the invention include: pFN11A (BIND) Flexi®, pGL4.31, pFC14A (HaloTag® 7) CMV Flexi®, pFC14K (HaloTag® 7) CMV Flexi®, pFN24A (HaloTag® 7) CMVd3 Flexi®, pFN24K (HaloTag® 7) CMVd3 Flexi®,HaloTag™ pHT2,pACT , pAdVAntage™, pALTER®-MAX,pBIND, pCAT®3-Basic, pCAT®3-Control, pCAT®3-Enhancer, pCAT®3-Promoter, pCI, pCMVTNT™ , pG5luc, pSI, pTARGET™, pTNT™, pF12A RM Flexi®, pF12K RM Flexi®, pReg neo,pYES2/GS, pAd/CMV/V5-DEST Gateway® Vector , pAd/PL-DEST™ Gateway® Vector,Gateway® pDEST™27 Vector , Gateway® pEF-DEST51 Vector , Gateway® pcDNA™-DEST47 vector , pCMV/Bsd Vector , pEF6/His A, B, & c,pcDNA™6.2-DEST, pLenti6/TR, pLP-AcGFP1-C, pLPS-AcGFP1-N,pLP-IRESneo, pLP-TRE2, pLP-RevTRE, pLP-LNCX, pLP-CMV-HA, pLP-CMV-Myc, pLP-RetroQ and pLP-CMVneo.

[0123] In some embodiments, the vectors comprise expression control sequences such as constitutive or conditional promoters, preferably, constitutive promoters are used. One of ordinary skill in the art will be able to select such sequences. For example, suitable promoters include but are not limited to CMV, TK, SV40 and EF-1α. In some embodiments, the promoters are inducible, temperature regulated, tissue specific, repressible, heat-shock, developmental, cell lineage specific, eukaryotic, prokaryotic or temporal promoters or a combination or recombination of

unmodified or mutagenized, randomized, shuffled sequences of any one or more of the above. In other embodiments, the protein of interest is expressed by gene activation or episomally.

[0124] In some embodiments, the vector lacks a selectable marker or drug resistance gene. In other embodiments, the vector optionally comprises a nucleic acid encoding a selectable marker, such as a protein that confers drug or antibiotic resistance or more generally any product that exerts selective pressure on the cell. Where more than one vector is used, each vector may have the same or a different drug resistance or other selective pressure marker. If more than one of the drug resistance or selective pressure markers are the same, simultaneous selection may be achieved by increasing the level of the drug. Suitable markers are well-known to those of skill in the art and include but are not limited to polypeptides products conferring resistance to any one of the following: Neomycin/G418, Puromycin, hygromycin, Zeocin, methotrexate and blasticidin. Although drug selection (or selection using any other suitable selection marker) is not a required step in producing the cells and cell lines of this invention, it may be used to enrich the transfected cell population for stably transfected cells, provided that the transfected constructs are designed to confer drug resistance. If subsequent selection of cells expressing the protein of interest is accomplished using signaling probes, selection too soon following transfection can result in some positive cells that may only be transiently and not stably transfected. However, this effect can be minimized by allowing sufficient cell passage to allow for dilution of transient expression in transfected cells.

[0125] In some embodiments, the protein-encoding nucleic acid sequence further comprises a tag. Such tags may encode, for example, a HIS tag, a myc tag, a hemagglutinin (HA) tag, protein C, VSV-G, FLU, yellow fluorescent protein (YFP), green fluorescent protein, FLAG, BCCP, maltose binding protein tag, Nus-tag, Softag-1, Softag-2, Strep-tag, S-tag, thioredoxin, GST, V5, TAP or CBP. A tag may be used as a marker to determine protein expression levels, intracellular localization, protein-protein interactions, regulation of the protein of interest, or the protein's function. Tags may also be used to purify or fractionate proteins.

[0126] In the case of cells and cell lines expressing an RNA of interest, the RNA can be of any type including antisense RNA, short interfering RNA (siRNA), transfer

RNA (tRNA), structural RNA, ribosomal RNA, heterogeneous nuclear RNA (hnRNA) and small nuclear RNA (snRNA).

[0127] In embodiments in which the cells and cell lines of the invention express a functional protein of interest, the protein can be any protein including but not limited to single chain proteins, multi-chain proteins, hetero-multimeric proteins. In the case of multimeric proteins, in some embodiments the cells express all of the subunits that make up the native protein. The protein can have a "wild type" sequence or may be a variant. In some embodiments, the cells express a protein that comprises a variant of one or more of the subunits including allelic variants, splice variants, truncated forms, isoforms, chimeric subunits and mutated forms that comprise amino acid substitutions (conservative or non-conservative), modified amino acids including chemically modified amino acids, and non-naturally occurring amino acids. A heteromultimeric protein expressed by cells or cell lines of the invention may comprise subunits from two or more species, such as from species homologs of the protein of interest.

[0128] In some embodiments, the cells of the invention express two or more functional proteins of interest. According to the invention, such expression can be from the introduction of a nucleic acid encoding all or part of a protein of interest, from the introduction of a nucleic acid that activates the transcription of all or part of a protein of interest from an endogenous sequence or from any combination thereof. The cells may express any desired number of proteins of interest. In various embodiments, the cells express three, four, five, six, or more proteins of interest. For example, the invention contemplates cells and cell lines that stably express functional proteins in a pathway of interest, proteins from intersecting pathways including enzymatic pathways, signaling pathways regulatory pathways and the like.

[0129] In particular, the protein expressed by the cells or cell lines used in the method are proteins for which stable functional cell lines have not previously been available. Without being bound by theory, it is believed that some reasons why such cell lines have not heretofore been possible include that the protein is highly complex and without preparing a large number of cells expressing the protein, it has not been possible to identify one in which the protein is properly assembled; or because no ligand or modulator of the protein is known for use in identifying a cell or cell line that expresses the protein in functional form; or because the protein is cytotoxic when

expressed outside its natural context, such as in a content that does not naturally express it.

[0130] Cells and cell lines of the invention can be made that consistently express any protein of interest either intracellular, surface or secreted. Such proteins include heteromultimeric ion channels, ligand gated (such as GABA A receptor), ion channels (such as CFTR), heteromultimeric ion channels, voltage gated (such as NaV), heteromultimeric ion channel, non-ligand gated (Epithelial sodium channel, ENaC), heterodimeric GPCRs (such as opioid receptors, taste receptors including sweet, umami and bitter), other GPCRs, Orphan GPCRs, GCC, opioid receptors, growth hormone receptors, estrogen/hgh, nuclear or membrane bound, TGF receptors, PPAR nuclear hormone receptor, nicotinics/Ach and immune receptors such as B-cell/T-cell receptors.

[0131] Cells and cell lines of the invention can express functional proteins including any protein or combination of proteins listed in Tables 2-13 (Mammalian G proteins, Human orphan GPCRs, Human opioid receptors, Human olfactory receptors, Canine olfactory receptors, Mosquito olfactory receptors, Other heteromultimeric receptors and GABA receptors.

[0132] The cells and cell lines of the invention have a number of attributes that make them particularly advantageous for any use where it is desired that cells provide consistent expression of a functional protein of interest over time. The terms "stable" or "consistent" as applied to the expression of the protein and the function of the protein is meant to distinguish the cells and cell lines of the invention from cells with transient expression or variable function, as the terms “stable expression” and “transient expression” would be understood by a person of skill in the art. A cell or cell line of the invention has stable or consistent expression of functional protein that has less than 10% variation for at least 2-4 days.

[0133] In various embodiments, the cells or cell lines of the invention express the functional RNA or protein of interest, i.e., the cells are consistently functional after growth for at least 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 35, 40, 45, 50, 55, 60, 65, 70, 75, 80, 85, 90, 95, 100, 110, 120, 130, 140, 150, 160, 170, 180, 190, 200 days or over 200 days, where consistent expression or consistently functional refers to a level of expression that does not vary by more than: 1%, 2%, 3%, 4%, 5%, 6%, 7%, 8% 9% or 10% over 2 to 4 days of continuous cell culture; 1%, 2%, 4%, 6%, 8%, 10% or 12% over 5 to 15

days of continuous cell culture; 1%, 2%, 4%, 6%, 8%, 10%, 12%, 14%, 16%, 18% or 20% over 16 to 20 days of continuous cell culture; 1%, 2%, 4%, 6%, 8%, 10%, 12%, 14%, 16%, 18%, 20%, 22%, 24% over 21 to 30 days of continuous cell culture; 1%, 2%, 4%, 6%, 8%, 10%, 12%, 14%, 16%, 18%, 20%, 22%, 24%, 26%, 28% or 30% over 30 to 40 days of continuous cell culture; 1%, 2%, 4%, 6%, 8%, 10%, 12%, 14%, 16%, 18%, 20%, 22%, 24%, 26%, 28% or 30% over 41 to 45 days of continuous cell culture; 1%, 2%, 4%, 6%, 8%, 10%, 12%, 14%, 16%, 18%, 20%, 22%, 24%, 26%, 28% or 30% over 45 to 50 days of continuous cell culture; 1%, 2%, 4%, 6%, 8%, 10%, 12%, 14%, 16%, 18%, 20%, 22%, 24%, 26%, 28%, 30% or 35% over 45 to 50 days of continuous cell culture; 1%, 2%, 4%, 6%, 8%, 10%, 12%, 14%, 16%, 18%, 20%, 22%, 24%, 26%, 28% or 30% or 35% over 50 to 55 days of continuous cell culture; 1%, 2%, 4%, 6%, 8%, 10%, 12%, 14%, 16%, 18%, 20%, 22%, 24%, 26%, 28%, 30% or 35% over 50 to 55 days of continuous cell culture; 1%, 2%, 3%, 4%, 5%, 10%, 15%, 20%, 25%, 30%, 35% or 40% over 55 to 75 days of continuous cell culture; 1%, 2%, 3%, 4%, 5%, 5%, 10%, 15%, 20%, 25%, 30%, 35%, 40% or 45% over 75 to 100 days of continuous cell culture; 1%, 2%, 3%, 4%, 5%, 5%, 10%, 15%, 20%, 25%, 30%, 35%, 40% or 45% over 101 to 125 days of continuous cell culture; 1%, 2%, 3%, 4%, 5%, 5%, 10%, 15%, 20%, 25%, 30%, 35%, 40% or 45% over 126 to 150 days of continuous cell culture; 1%, 2%, 3%, 4%, 5%, 5%, 10%, 15%, 20%, 25%, 30%, 35%, 40% or 45% over 151 to 175 days of continuous cell culture; 1%, 2%, 3%, 4%, 5%, 5%, 10%, 15%, 20%, 25%, 30%, 35%, 40% or 45% over 176 to 200 days of continuous cell culture; 1%, 2%, 3%, 4%, 5%, 5%, 10%, 15%, 20%, 25%, 30%, 35%, 40% or 45% over more than 200 days of continuous cell culture.

[0134] Cells may be selected that have desirable properties in addition to the stable expression of functional protein. Any desired property that can be detected may be selected for. Those of skill in the art will aware of such characteristics. By way of non-limiting example, such properties include:

fragility, morphology and adherence to a solid surface, monodispersion by trypsin or cell dissociation reagent, adaptability to the automated culture conditions, performance under serum-containing conditions, performance in serum-free conditions, convertability to serum-free suspension conditions, propensity to form clumps, propensity to form monodisperse cell layers following passaging, resilience, propensity to remain attached to growth chamber surfaces under fluid addition steps

of different force, non-fragmented nucleus, lack of intracellular vacuoles, lack of microbial contamination, lack of mycoplasma, lack of viral contamination, clonality, consistency of gross physical properties of cells within wells, propensity for growth below/at/above room temperature, propensity for tolerance of various temperatures for various time periods, propensity of cells to evenly uptake plasmid/oligonucleotides/fluorogenic probes/peptides/proteins/compounds, propensity of cells to withstand incubation with DMSO/EtOH/MeOH, organic solvent/detergent, propensity of cells to withstand maintained UPR induction, propensity of cells to withstand exposure to DTT, propensity of cells to be infected with viral/lentiviral/cosmid vectors, endogenous expression of desired RNA(s)/protein(s) or lack thereof, chromosomal number, chromosomal aberrations, amenable to growth at 5/6/7/8/9pH, tolerance to UV/mutagen/radiation, ability to maintain the above characteristics under altered/manual/scaled-up growth conditions (i.e., including reactors).

[0135] Cells and cell lines of the invention have enhanced properties as compared to cells and cell lines made by conventional methods. For example, the cells and cell lines of this invention have enhanced stability of expression and/or levels of expression (even when maintained in cultures without selective pressure, including, for example, antibiotics and other drugs). In other embodiments, the cells and cell lines of the invention have high Z' values in various assays. In still other embodiments, the cells and cell lines of this invention are improved in context of their expression of a physiologically relevant protein activity as compared to more conventionally engineered cells. These properties enhance and improve the ability of the cells and cell lines of this invention to be used for any use, whether in assays to identify modulators, for cell therapy, for protein production or any other use and improve the functional attributes of the identified modulators.

[0136] A further advantageous property of the cells and cell lines of the invention is that they stably express the protein of interest in the absence of drug or other selective pressure. Thus, in preferred embodiments, the cells and cell lines of the invention are maintained in culture without any selective pressure. In further embodiments, cells and cell lines are maintained without any drug or antibiotics. As used herein, cell maintenance refers to culturing cells after they have been selected as described for protein expression. Maintenance does not refer to the optional step of growing cells under selective pressure (*e.g.*, an antibiotic) prior to cell sorting

where marker(s) introduced into the cells allow enrichment of stable transfectants in a mixed population.

[0137] Drug-free and selective pressure-free cell maintenance of the cells and cell lines of this invention provides a number of advantages. For example, drug-resistant cells may not express the co-transfected transgene of interest at adequate levels, because the selection relies on survival of the cells that have taken up the drug resistant gene, with or without the transgene. Further, selective drugs and other selective pressure factors are often mutagenic or otherwise interfere with the physiology of the cells, leading to skewed results in cell-based assays. For example, selective drugs may decrease susceptibility to apoptosis (Robinson et al., Biochemistry, 36(37):11169-11178 (1997)), increase DNA repair and drug metabolism (Deffie et al., Cancer Res. 48(13):3595-3602 (1988)), increase cellular pH (Thiebaut et al., J Histochem Cytochem. 38(5):685-690 (1990); Roepe et al., Biochemistry. 32(41):11042-11056 (1993); Simon et al., Proc Natl Acad Sci U S A. 91(3):1128-1132 (1994)), decrease lysosomal and endosomal pH (Schindler et al., Biochemistry. 35(9):2811-2817 (1996); Altan et al., J Exp Med. 187(10):1583-1598 (1998)), decrease plasma membrane potential (Roepe et al., Biochemistry. 32(41):11042-11056 (1993)), increase plasma membrane conductance to chloride (Gill et al., Cell. 71(1):23-32 (1992)) and ATP (Abraham et al., Proc Natl Acad Sci U S A. 90(1):312-316 (1993)), and increase rates of vesicle transport (Altan et al., Proc Natl Acad Sci U S A. 96(8):4432-4437 (1999)). Thus, the cells and cell lines of this invention allow screening assays that are free from the artifacts caused by selective pressure. In some preferred embodiments, the cells and cell lines of this invention are not cultured with selective pressure factors, such as antibiotics, before or after cell sorting, so that cells and cell lines with desired properties are isolated by sorting, even when not beginning with an enriched cell population.

[0138] The cells and cell lines of the invention have enhanced stability as compared to cells and cell lines produced by conventional methods in the context of expression and expression levels (RNA or protein). To identify cells and cell lines characterized by such stable expression, a cell or cell line's expression of a protein of interest is measured over a timecourse and the expression levels are compared. Stable cell lines will continue expressing (RNA or protein) throughout the timecourse. In some aspects of the invention, the timecourse may be for at least one week, two

weeks, three weeks, etc., or at least one month, or at least two, three, four, five, six, seven, eight or nine months, or any length of time in between.

[0139] Isolated cells and cell lines may be further characterized, such as by PCR, RT-PCR, qRT-PCR and single end-point RT-PCR to determine the absolute amounts and relative amounts (in the case of multisubunit proteins or multiple proteins of interest) being expressed (RNA). Preferably, the expansion levels of the subunits of a multi-subunit protein are substantially the same in the cells and cell lines of this invention.

[0140] In other embodiments, the expression of a functional protein of interest is assayed over time. In these embodiments, stable expression is measured by comparing the results of functional assays over a timecourse. The assay of cell and cell line stability based on a functional assay provides the benefit of identifying cells and cell lines that not only stably express the protein (RNA or protein), but also stably produce and properly process (*e.g.,* post-translational modification, subunit assembly, and localization within the cell) the protein to produce a functional protein.

[0141] Cells and cell lines of the invention have the further advantageous property of providing assays with high reproducibility as evidenced by their Z' factor. *See* Zhang JH, Chung TD, Oldenburg KR, "A Simple Statistical Parameter for Use in Evaluation and Validation of High Throughput Screening Assays." *J. Biomol. Screen.* 1999;4(2):67-73, which is incorporated herein by reference in its entirety. Z' values relate to the quality of a cell or cell line because it reflects the degree to which a cell or cell line will respond consistently to modulators. Z' is a statistical calculation that takes into account the signal-to-noise range and signal variability (*i.e.*, from well to well) of the functional response to a reference compound across a multiwell plate. is Z' calculated using Z' data obtained from multiple wells with a positive control and multiple wells with a negative control. The ratio of their combined standard deviations multiplied by three to the difference factor, in their mean values is subtracted from one to give the Z' according the equation below:

$$Z' \text{ factor} = 1 - ((3\sigma_{\text{positive control}} + 3\sigma_{\text{negative control}})/ (\mu_{\text{positive control}} - \mu_{\text{negative control}}))$$

If the factor is 1.0, which would indicate an ideal assay with theoretical maximum Z' no variability and limitless dynamic range. As used herein, a "high Z'" refers to a Z'

factor of Z' of at least 0.6, at least 0.7, at least 0.75 or at least 0.8, or any decimal in between 0.6 and 1.0. In the case of a complex target, a high Z' means a Z' of at least 0.4 or greater. A score of close to 0 is undesirable because it indicates that there is overlap between positive and negative controls. In the industry, for simple cell-based assays, Z' scores up to 0.3 are considered marginal scores, Z' scores between 0.3 and 0.5 are considered acceptable, and Z' scores above 0.5 are considered excellent. Cell-free or biochemical assays may approach scores for cell-based systems tend to be lower because higher Z' scores, but Z' cell-based systems are complex.

[0142] As those of ordinary skill in the art will recognize cell-based assays using conventional cells expressing even a single chain protein do not typically achieve a Z' higher than 0.5 to 0.6. Cells with engineered expression (either from introduced coding sequences or gene activation) of multi-subunit proteins, if even reported in the art, would be lower due to their added complexity. Such cells would not be reliable for use in assays because the results would not be reproducible. Cells and cell lines of this invention, on the other hand, have higher Z' values and advantageously produce consistent results in assays. Indeed, the cells and cell lines of the invention provide the basis for high throughput screening (HTS) compatible assays because they generally have values than conventionally produced cells. In some aspects of the invention, the cells and cell lines result in Z' of at least 0.3, at least 0.4, at least 0.5, at least 0.6, at least 0.7, or at least 0.8. Even Z' values of at least 0.3 – 0.4 for the cells and cell lines of the invention are advantageous because the proteins of interest are multigene targets. In other aspects of the invention, the cells and cell lines of the invention result in a Z' of at least 0.7, at least 0.75 or at least 0.8 even after the cells are maintained for multiple passages, *e.g.*, between 5-20 passages, including any integer in between 5 and 20. In some aspects of the invention, the cells and cell lines result in a Z' of at least 0.7, at least 0.75 or at least 0.8 in cells and cell lines maintained for 1, 2, 3, 4 or 5 weeks or 2, 3, 4, 5, 6, 7, 8 or 9 months, including any period of time in between.

[0143] In a further aspect, the invention provides a method for producing the cells and cell lines of the invention. In one embodiment, the method comprises the steps of:

a) providing a plurality of cells that express mRNA encoding the protein of interest;

b) dispersing cells individually into individual culture vessels, thereby providing a plurality of separate cell cultures

c) culturing the cells under a set of desired culture conditions using automated cell culture methods characterized in that the conditions are substantially identical for each of the separate cell cultures, during which culturing the number of cells in each separate cell culture is normalized, and wherein the separate cultures are passaged on the same schedule;

d) assaying the separate cell cultures for at least one desired characteristic of the protein of interest at least twice; and

e) identifying a separate cell culture that has the desired characteristic in both assays.

[0144] According to the method, the cells are cultured under a desired set of culture conditions. The conditions can be any desired conditions. Those of skill in the art will understand what parameters are comprised within a set of culture conditions. For example, culture conditions include but are not limited to: the media (Base media (DMEM, MEM, RPMI, serum-free, with serum, fully chemically defined, without animal-derived components), mono and divalent ion (sodium, potassium, calcium, magnesium) concentration, additional components added (amino acids, antibiotics, glutamine, glucose or other carbon source, HEPES, channel blockers, modulators of other targets, vitamins, trace elements, heavy metals, co-factors, growth factors, anti-apoptosis reagents), fresh or conditioned media, with HEPES, pH, depleted of certain nutrients or limiting (amino acid, carbon source)), level of confluency at which cells are allowed to attain before split/passage, feeder layers of cells, or gamma-irradiated cells, CO_2, a three gas system (oxygen, nitrogen, carbon dioxide), humidity, temperature, still or on a shaker, and the like, which will be well known to those of skill in the art.

[0145] The cell culture conditions may be chosen for convenience or for a particular desired use of the cells. Advantageously, the invention provides cells and cell lines that are optimally suited for a particular desired use. That is, in embodiments of the invention in which cells are cultured under conditions for a particular desired use, cells are selected that have desired characteristics under the condition for the desired use.

By way of illustration, if cells will be used in assays in plates where it is desired that the cells are adherent, cells that display adherence under the conditions of the assay may be selected. Similarly, if the cells will be used for protein production, cells may be cultured under conditions appropriate for protein production and selected for advantageous properties for this use.

[0146] In some embodiments, the method comprises the additional step of measuring the growth rates of the separate cell cultures. Growth rates may be determined using any of a variety of techniques means that will be well known to the skilled worker. Such techniques include but are not limited to measuring ATP, cell confluency, light scattering, optical density (e.g., OD 260 for DNA). Preferably growth rates are determined using means that minimize the amount of time that the cultures spend outside the selected culture conditions.

[0147] In some embodiments, cell confluency is measured and growth rates are calculated from the confluency values. In some embodiments, cells are dispersed and clumps removed prior to measuring cell confluency for improved accuracy. Means for monodispersing cells are well-known and can be achieved, for example, by addition of a dispersing reagent to a culture to be measured. Dispersing agents are well-known and readily available, and include but are not limited to enzymatic dispering agents, such as trypsin, and EDTA-based dispersing agents. Growth rates can be calculated from confluency date using commercially available software for that purpose such as HAMILTON VECTOR. Automated confluency measurement, such as using an automated microscopic plate reader is particularly useful. Plate readers that measure confluency are commercially available and include but are not limited to the CLONE SELECT IMAGER (Genetix). Typically, at least 2 measurements of cell confluency are made before calculating a growth rate. The number of confluency values used to determine growth rate can be any number that is convenient or suitable for the culture. For example, confluency can be measured multiple times over e.g., a week, 2 weeks, 3 weeks or any length of time and at any frequency desired.

[0148] When the growth rates are known, according to the method, the plurality of separate cell cultures are divided into groups by similarity of growth rates. By grouping cultures into growth rate bins, one can manipulate the cultures in the group together, thereby providing another level of standardization that reduces variation between cultures. For example, the cultures in a bin can be passaged at the same

time, treated with a desired reagent at the same time, etc. Further, functional assay results are typically dependent on cell density in an assay well. A true comparison of individual clones is only accomplished by having them plated and assayed at the same density. Grouping into specific growth rate cohorts enables the plating of clones at a specific density that allows them to be functionally characterized in a high throughput format

[0149] The range of growth rates in each group can be any convenient range. It is particularly advantageous to select a range of growth rates that permits the cells to be passaged at the same time and avoid frequent renormalization of cell numbers. Growth rate groups can include a very narrow range for a tight grouping, for example, average doubling times within an hour of each other. But according to the method, the range can be up to 2 hours, up to 3 hours, up to 4 hours, up to 5 hours or up to 10 hours of each other or even broader ranges. The need for renormalization arises when the growth rates in a bin are not the same so that the number of cells in some cultures increases faster than others. To maintain substantially identical conditions for all cultures in a bin, it is necessary to periodically remove cells to renormalize the numbers across the bin. The more disparate the growth rates, the more frequently renormalization is needed.

[0150] In step d) the cells and cell lines may be tested for and selected for any physiological property including but not limited to: a change in a cellular process encoded by the genome ;a change in a cellular process regulated by the genome; a change in a pattern of chromosomal activity; a change in a pattern of chromosomal silencing; a change in a pattern of gene silencing; a change in a pattern or in the efficiency of gene activation; a change in a pattern or in the efficiency of gene expression; a change in a pattern or in the efficiency of RNA expression; a change in a pattern or in the efficiency of RNAi expression; a change in a pattern or in the efficiency of RNA processing; a change in a pattern or in the efficiency of RNA transport; a change in a pattern or in the efficiency of protein translation; a change in a pattern or in the efficiency of protein folding; a change in a pattern or in the efficiency of protein assembly; a change in a pattern or in the efficiency of protein modification; a change in a pattern or in the efficiency of protein transport; a change in a pattern or in the efficiency of transporting a membrane protein to a cell surface change in growth rate; a change in cell size; a change in cell shape; a change in cell morphology; a change in % RNA content; a change in % protein content; a change in

% water content; a change in % lipid content; a change in ribosome content; a change in mitochondrial content; a change in ER mass; a change in plasma membrane surface area; a change in cell volume; a change in lipid composition of plasma membrane; a change in lipid composition of nuclear envelope; a change in protein composition of plasma membrane; a change in protein; composition of nuclear envelope; a change in number of secretory vesicles; a change in number of lysosomes; a change in number of vacuoles; a change in the capacity or potential of a cell for: protein production, protein secretion, protein folding, protein assembly, protein modification, enzymatic modification of protein, protein glycosylation, protein phosphorylation, protein dephosphorylation, metabolite biosynthesis, lipid biosynthesis, DNA synthesis, RNA synthesis, protein synthesis, nutrient absorption, cell growth, mitosis, meiosis, cell division, to dedifferentiate, to transform into a stem cell, to transform into a pluripotent cell, to transform into a omnipotent cell, to transform into a stem cell type of any organ (i.e. liver, lung, skin, muscle, pancreas, brain, testis, ovary, blood, immune system, nervous system, bone, cardiovascular system, central nervous system, gastro-intestinal tract, stomach, thyroid, tongue, gall bladder, kidney, nose, eye, nail, hair, taste bud), to transform into a differentiated any cell type (i.e. muscle, heart muscle, neuron, skin, pancreatic, blood, immune, red blood cell, white blood cell, killer T-cell, enteroendocrine cell, taste, secretory cell, kidney, epithelial cell, endothelial cell, also including any of the animal or human cell types already listed that can be used for introduction of nucleic acid sequences), to uptake DNA, to uptake small molecules, to uptake fluorogenic probes, to uptake RNA, to adhere to solid surface, to adapt to serum-free conditions, to adapt to serum-free suspension conditions, to adapt to scaled-up cell culture, for use for large scale cell culture, for use in drug discovery, for use in high throughput screening, for use in a functional cell based assay, for use in membrane potential assays, for use in calcium flux assays, for use in G-protein reporter assays, for use in reporter cell based assays, for use in ELISA studies, for use in in vitro assays, for use in vivo applications, for use in secondary testing, for use in compound testing, for use in a binding assay, for use in panning assay, for use in an antibody panning assay, for use in imaging assays, for use in microscopic imaging assays, for use in multiwell plates, for adaptation to automated cell culture, for adaptation to miniaturized automated cell culture, for adaptation to large-scale automated cell culture, for adaptation to cell culture in multiwell plates (6, 12, 24, 48, 96, 384, 1536 or higher

density), for use in cell chips, for use on slides, for use on glass slides, for microarray on slides or glass slides, for immunofluorescence studies, for use in protein purification, for use in biologics production, for use in the production of industrial enzymes, for use in the production of reagents for research, for use in vaccine development, for use in cell therapy, for use in implantation into animals or humans, for use in isolation of factors secreted by the cell, for preparation of cDNA libraries, for purification of RNA, for purification of DNA, for infection by pathogens, viruses or other agent, for resistance to infection by pathogens, viruses or other agents, for resistance to drugs, for suitability to be maintained under automated miniaturized cell culture conditions, for use in the production of protein for characterization, including: protein crystallography, vaccine development, stimulation of the immune system, antibody production or generation or testing of antibodies. Those of skill in the art will readily recognize suitable tests for any of the above-listed properties.

[0151] Tests that may be used to characterize cells and cell lines of the invention and/or matched panels of the invention include but are not limited to: Amino acid analysis, DNA sequencing, Protein sequencing, NMR, A test for protein transport, A test for nucelocytoplasmic transport, A test for subcellular localization of proteins, A test for subcellular localization of nucleic acids, Microscopic analysis, Submicroscopic analysis, Fluorescence microscopy, Electron microscopy, Confocal microscopy, Laser ablation technology, Cell counting and Dialysis. The skilled worker would understand how to use any of the above-listed tests.

[0152] When collections or panels of cells or cell lines are produced, e.g., for drug screening, the cells or cell lines in the collection or panel may be matched such that they are the same (including substantially the same) with regard to one or more selective physiological properties. The “same physiological property” in this context means that the selected physiological property is similar enough amongst the members in the collection or panel such that the cell collection or panel can produce reliable results in drug screening assays; for example, variations in readouts in a drug screening assay will be due to, e.g., the different biological activities of test compounds on cells expressing different forms of a protein, rather than due to inherent variations in the cells. For example, the cells or cell lines may be matched to have the same growth rate, i.e., growth rates with no more than one, two, three, four, or five hour difference amongst the members of the cell collection or panel. This may be achieved by, for example, binning cells by their growth rate into five, six,

seven, eight, nine, or ten groups, and creating a panel using cells from the same binned group. Methods of determining cell growth rate are well known in the art. The cells or cell lines in a panel also can be matched to have the same Z' factor (e.g., Z' factors that do not differ by more than 0.1), protein expression level (e.g., CFTR expression levels that do not differ by more than 5%, 10%, 15%, 20%, 25%, or 30%), RNA expression level, adherence to tissue culture surfaces, and the like. Matched cells and cell lines can be grown under identical conditions, achieved by, e.g., automated parallel processing, to maintain the selected physiological property.

[0153] In one embodiment, the panel is matched for growth rate under the same set of conditions. Such a panel, also referred to herein as a matched panel, are highly desirable for use in a wide range of cell-based studies in which it is desirable to compare the effect of an experimental variable across two or more cell lines. Cell lines that are matched for growth rate maintain roughly the same number of cells per well over time thereby reducing variation in growth conditions, such as nutrient content between cell lines in the panel

[0154] According to the invention, matched panels may have growth rates within any desired range, depending on a number of factors including the characteristics of the cells, the intended use of the panel, the size of the panel, the culture conditions, and the like. Such factors will be readily appreciated by the skilled worker.

[0155] Growth rates may be determined by any suitable and convenient means, the only requirement being that the growth rates for all of the cell lines for a matched panel are determined by the same means. Numerous means for determining growth rate are known as described herein.

[0156] A matched panel of the invention can comprise any number of clonal cell lines. The maximum number of clonal cell lines in the panel will differ for each use and user and can be as many as can be maintained. In various embodiments, the panel may comprise 2, 3, 4, 5, 6, 7, 8, 9, 10 or more clonal cell lines, for example, at least 12, at least 15, at least 20, at least 24, at least 25, at least 30, at least 35, at least 40, at least 45, at least 48, at least 50, at least 75, at least 96, at least 100, at least 200, at least 300, at least 384, at least 400 or more clonal cell lines.

[0157] According to the invention, the panel comprises a plurality of clonal cell lines, that is, a plurality of cell lines generated from a different single parent cell. Any desired cell type may be used in the production of a matched panel. The panel can comprise cell lines of all the same cell type or cell lines of different cell types.

[0158] The clonal cell lines in the panel stably express one or more proteins of interest. The stable expression can be for any length of time that is suitable for the desired use of the panel but at a minimum, is sufficiently long to permit selection and use in a matched panel.

[0159] The clonal cell lines in the matched panel may all express the same one or more proteins of interest or some clonal cell lines in the panel may express different proteins of interest.

[0160] In some embodiments, the matched panel comprises one or more clonal cell lines that express different proteins of interest. That is, a first clonal cell line in the panel may express a first protein of interest, a second clonal cell line in the panel may express a second protein of interest, a third cell line may express a third protein of interest, etc. for as many different proteins of interest as are desired. The different proteins of interest may be different isoforms, allelic variants, splice variants, or mutated (including but not limited to sequence mutated or truncated), chimeric or chemically including enzymatically modified forms of a protein of interest. In some embodiments the different proteins can be members of a functionally defined group of proteins, such as a panel of bitter taste receptors or a panel of kinases. In some embodiments the different proteins may be part of the same or interrelated signaling pathways. In still other panels involving heteromultimeric proteins (including heterodimers), the panel may comprise two or more different combinations of subunits up to all possible combinations of subunits. The combinations may comprise subunit sequence variants, subunit isoform combinations, interspecies combinations of subunits and combinations of subunit types.

[0161] By way of example, Gamma-aminobutyric acid (GABA) $_A$ receptors typically comprise two alpha subunits, two beta subunits and a gamma subunit. There are 6 alpha isoforms, 5 beta isoforms, 4 gamma isoforms, and a delta, a pi, a theta and an epsilon subunit. The present invention contemplates panels comprising two or more combinations of any of these subunits including panels comprising every possible combination of alpha, beta, gamma, delta, pi, epsilon and theta subunit. Further, the GABA receptor family also includes $GABA_B$ and $GABA_C$ receptors. The invention also contemplates panels that comprise any combination of $GABA_{A,}$, $GABA_B$ and $GABA_C$ subunits. In some embodiments, such panels comprise human GABA subunits. mammalian GABA receptor panel such as a non-human primate (eg,

cynomolgus) GABA receptor , mouse, rat or human GABA receptor panels or mixtures thereof

[0162] In a further example, the invention contemplates one or more epithelial sodium channel (ENaC) panels, including any mammalian ENaC panel such as a non-human primate (eg, cynomolgus) ENaC, mouse, rat or human ENaC panels or mixtures thereof . Like GABA receptors, intact ENaC comprise multiple subunits: alpha or delta, beta and gamma. The invention contemplates panels with at least two different combinations of ENaC subunits and also contemplates all possible combinations of ENaC subunits, including combinations of subunits from different species, combinations of isoforms, allelic variants, SNPs, chimeric subunits, forms comprising modified and/or non-natural amino acids and chemically modified such as enzymatically modified subunits. The present invention also contemplates panels comprising any ENaC form set forth in International Application PCT/US09/31936, the contents of which are incorporated by reference in its entirety.

[0163] In a further particular embodiment, a matched panel of 25 bitter taste receptors comprising cell lines that express native (no tag) functional bitter receptors listed in Table 10. In some embodiments, the panel is matched for growth rate. In some embodiments the panel is matched for growth rate and an additional physiological property of interest. In some embodiments the cell lines in the panel were generated in parallel and/or screened in parallel.

[0164] Further exemplary but non-limited examples of panels and their uses are the following: a panel of odorant receptors (insect, canine, human, bed bug), for example to profile of fragrances or to discovery of modulators; panels of cells expressing a gene fused to a test peptide, i.e., to find a peptide that works to internalize a cargo such as a protein, including a monoclonal antibody or a non-protein drug into cells (the cargo could be a reporter such as GFP or AP). Related to this embodiment, supernatants from cells of this panel could be added to other cells for assessment of internalization. In such an embodiment, the panel may comprise different cell types to assess cell-type specific delivery. A panel of cell lines expressing different monoclonal antibody heavy chain/light chain combinations to identify active mAbs. An antibody panel also could provide a series of derivatized versions of a monoclonal antibody to identify one with improved characteristics, such as stability in serum, binding affinity and the like. Yet another panel could be used to express a target protein in the presence of various signaling molecules, such as

different G-proteins. Still another type of panel could be used to test variants of a target proteins for improved activity/stability. A panels could comprise single nucleotide polymorphs (SNPs) or other mutated forms of a target protein to select modulators that act on a subset, many or all forms. Other panels could be used to define the patterns of activity of test compounds on a family of proteins or isoforms of a protein (such as $GABA_A$ or other CNS ion channels). Differentially acting compounds could then be used in further study to determine the function/role/localization of corresponding subunit combinations *in vivo*. The test compounds could be known modulators that failed in the clinic or ones that have adverse off-target effects, to determine subunit combinations that may correlate with such effects. Still other panels could be used in HTS for parallel screening for reliable assessment of compounds' activity at multiple target subtypes to assist in finding compounds active at desired targets and that have minimal off target effects.

[0165] The panels can include any desired group of proteins and all such panels are contemplated by the invention.

[0166] A matched panel of the invention may be produced by generating the different cell lines for the panel sequentially, in parallel or a combination of both. For example, one can make each cell line individually and then match them. More preferably, to minimize difference between the cell lines, sequentially generated cell lines can be frozen at the same stage or passage number and thawed in parallel. Even more preferably, the cell lines are made in parallel.

[0167] In a preferred embodiments, the cell lines in a panel are screened or assayed in parallel.

[0168] According to the invention, the cell lines of the matched panel are maintained under the same cell culture conditions including but not limited to the same culture media, temperature, and the like. All of the cell lines in the panel are passaged at the same frequency which may be any desired frequency depending on a number of factors including cell type, growth rate, As will be appreciated, to maintain roughly equal numbers of cells from cell line to cell line of the panel, the number of cells should be normalized periodically.

[0169] According to the method, cells may be cultured in any cell culture format so long as the cells or cell lines are dispersed in individual cultures prior to the step of measuring growth rates. For example, for convenience, cells may be initially pooled

for culture under the desired conditions and then individual cells separated one cell per well or vessel.

Cells may be cultured in multi-well tissue culture plates with any convenient number of wells. Such plates are readily commercially available and will be well knows to a person of skill in the art. In some cases, cells may preferably be cultured in vials or in any other convenient format, the various formats will be known to the skilled worker and are readily commericially available.

[0170] In embodiments comprising the step of measuring growth rate, prior to measuring growth rates, the cells are cultured for a sufficient length of time for them to acclimate to the culture conditions. As will be appreciated by the skilled worker, the length of time will vary depending on a number of factors such as the cell type, the chosen conditions, the culture format and may be any amount of time from one day to a few days, a week or more.

[0171] Preferably, each individual culture in the plurality of separate cell cultures is maintained under substantially identical conditions a discussed below, including a standardized maintenance schedule. Another advantageous feature of the method is that large numbers of individual cultures can be maintained simultaneously, so that a cell with a desired set of traits may be identified even if extremely rare. For those and other reasons, according to the invention, the plurality of separate cell cultures are cultured using automated cell culture methods so that the conditions are substantially identical for each well. Automated cell culture prevents the unavoidable variability inherent to manual cell culture.

[0172] Any automated cell culture system may be used in the method of the invention. A number of automated cell culture systems are commercially available and will be well-known to the skilled worker. In some embodiments, the automated system is a robotic system. Preferably, the system includes independently moving channels, a multichannel head (for instance a 96–tip head) and a gripper or cherry-picking arm and a HEPA filtration device to maintain sterility during the procedure. The number of channels in the pipettor should be suitable for the format of the culture. Convenient pipettors have, e.g., 96 or 384 channels. Such systems are known and are commercially available. For example, a MICROLAB STAR™ instrument (Hamilton) may be used in the method of the invention. The automated system should be able to perform a variety of desired cell culture tasks. Such tasks will be known by a person of skill in the art. They include but are not limited to:

removing media, replacing media, adding reagents, cell washing, removing wash solution, adding a dispersing agent, removing cells from a culture vessel, adding cells to a culture vessel an the like.

[0173] The production of a cell or cell line of the invention may include any number of separate cell cultures. However, the advantages provided by the method increase as the number of cells increases. There is no theoretical upper limit to the number of cells or separate cell cultures that can be utilized in the method. According to the invention, the number of separate cell cultures can be two or more but more advantageously is at least 3, 4, 5, 6, 7, 8, 9, 10 or more separate cell cultures, for example, at least 12, at least 15, at least 20, at least 24, at least 25, at least 30, at least 35, at least 40, at least 45, at least 48, at least 50, at least 75, at least 96, at least 100, at least 200, at least 300, at least 384, at least 400, at least 500, at least 1000, at least 10,000, at least 100,000, at least 500,000 or more.

[0174] In some embodiments, the cells and cell lines of the invention that are cultured as described are cells that have previously been selected as positive for a nucleic acid of interest, which can be an introduced nucleic acid encoding all or part of a protein of interest or an introduced nucleic acid that activates transcription of a sequence encoding all or part of a protein of interest. In some embodiments, the cells that are cultured as described herein are cells that have been selected as positive for mRNA encoding the protein of interest.

[0175] To make cells and cell lines of the invention, one can use, for example, the technology described in U.S. Patent 6,692,965 and WO/2005/079462. Both of these documents are incorporated herein by reference in their entirety. This technology provides real-time assessment of millions of cells such that any desired number of clones (from hundreds to thousands of clones). Using cell sorting techniques, such as flow cytometric cell sorting (*e.g.,* with a FACS machine) or magnetic cell sorting (*e.g.,* with a MACS machine), one cell per well is automatically deposited with high statistical confidence in a culture vessel (such as a 96 well culture plate). The speed and automation of the technology allows multigene recombinant cell lines to be readily isolated.

[0176] Using the technology, the RNA sequence for a protein of interest may be detected using a signaling probe, also referred to as a molecular beacon or fluorogenic probe. In some embodiments, the vector containing the coding sequence has an additional sequence coding for an RNA tag sequence. “Tag

sequence" refers to a nucleic acid sequence that is an expressed RNA or portion of an RNA that is to be detected by a signaling probe. Signaling probes may detect a variety of RNA sequences, any of which may be used as tags, including those encoding peptide and protein tags described above. Signaling probes may be directed against the tag by designing the probes to include a portion that is complementary to the sequence of the tag. The tag sequence may be a 3' untranslated region of the plasmid that is cotranscribed with the transcript of the protein of interest and comprises a target sequence for signaling probe binding. The tag sequence can be in frame with the protein-coding portion of the message of the gene or out of frame with it, depending on whether one wishes to tag the protein produced. Thus, the tag sequence does not have to be translated for detection by the signaling probe. The tag sequences may comprise multiple target sequences that are the same or different, wherein one signaling probe hybridizes to each target sequence. The tag sequence may be located within the RNA encoding the gene of interest, or the tag sequence may be located within a 5'- or 3'-untranslated region. The tag sequences may be an RNA having secondary structure. The structure may be a three-arm junction structure. In some embodiments, the signaling probe detects a sequence within the coding sequence for the protein of interest.

[0177] Following transfection of the DNA constructs into cells and subsequent drug selection (if used), or following gene activation, molecular beacons (*e.g.,* fluorogenic probes), each of which is targeted to a different tag sequence and differentially labeled, may be introduced into the cells, and a flow cytometric cell sorter is used to isolate cells positive for their signals (multiple rounds of sorting may be carried out). In one embodiment, the flow cytometric cell sorter is a FACS machine. MACS (magnetic cell sorting) or laser ablation of negative cells using laser-enabled analysis and processing can also be used. Other fluorescence plate readers, including those that are compatible with high-throughput screening can also be used. Signal-positive cells take up and may integrate into their genomes at least one copy of the introduced sequence(s). Cells introduced with message for the protein of interest are then identified. By way of example, the coding sequences may be integrated at different locations of the genome in the cell. The expression level of the introduced sequence may vary based upon copy number or integration site. Further, cells comprising a protein of interest may be obtained wherein one or more of the introduced nucleic acids is episomal or results from gene activation.

[0178] Signaling probes useful in this invention are known in the art and generally are oligonucleotides comprising a sequence complementary to a target sequence and a signal emitting system so arranged that no signal is emitted when the probe is not bound to the target sequence and a signal is emitted when the probe binds to the target sequence. By way of non-limiting illustration, the signaling probe may comprise a fluorophore and a quencher positioned in the probe so that the quencher and fluorophore are brought together in the unbound probe. Upon binding between the probe and the target sequence, the quencher and fluorophore separate, resulting in emission of signal. International publication WO/2005/079462, for example, describes a number of signaling probes that may be used in the production of the present cells and cell lines. The methods described above for introducing nucleic acids into cells may be used to introduce signaling probes.

[0179] Where tag sequences are used, each vector (where multiple vectors are used) can comprise the same or a different tag sequence. Whether the tag sequences are the same or different, the signaling probes may comprise different signal emitters, such as different colored fluorophores and the like so that expression of each subunit may be separately detected. By way of illustration, the signaling probe that specifically detects a first mRNA of interest can comprise a red fluorophore, the probe that detects a second mRNA of interest can comprise a green fluorophore, and the probe that detects a third mRNA of interest can comprise a blue fluorophore. Those of skill in the art will be aware of other means for differentially detecting the expression of the three subunits with a signaling probe in a triply transfected cell.

[0180] In one embodiment, the signaling probes are designed to be complementary to either a portion of the RNA encoding the protein of interest or to portions of the 5' or 3' untranslated regions. Even if the signaling probe designed to recognize a messenger RNA of interest is able to detect spuriously endogenously expressed target sequences, the proportion of these in comparison to the proportion of the sequence of interest produced by transfected cells is such that the sorter is able to discriminate the two cell types.

[0181] The expression level of a protein of interest may vary from cell to cell or cell line to cell line. The expression level in a cell or cell line may also decrease over time due to epigenetic events such as DNA methylation and gene silencing and loss of transgene copies. These variations can be attributed to a variety of factors, for

example, the copy number of the transgene taken up by the cell, the site of genomic integration of the transgene, and the integrity of the transgene following genomic integration. One may use FACS or other cell sorting methods (i.e., MACS) to evaluate expression levels. Additional rounds of introducing signaling probes may be used, for example, to determine if and to what extent the cells remain positive over time for any one or more of the RNAs for which they were originally isolated.

[0182] Optionally, one or more replicate sets of cultures for one or more of the growth rate groups may be prepared. In some cases, it may be advantageous to freeze a replicate set of one or more growth bins, for example, to serve as a frozen stock. However, according to the method, frozen cell stocks can be made as often as desired and at any point and at as many points during their production. Methods for freezing cell cultures are well-known to those of skill in the art. By way of example, the replicate set can be frozen at any temperature, for example, at -70° to -80° C. In one embodiment, cells were incubated until 70-100% confluency was reached. Next, media was aspirated and a solution of 90% FBS and 10% media was added to the plates, insulated and frozen.

[0183] The invention contemplates performing the method with any number of replicate sets using different culture conditions. That is, the method can be formed with a first plurality (set) of separate cell cultures under a first set of culture conditions and with a second set of separate cell cultures that are cultured under a second set of conditions that are different from the first conditions, and so on for any desired number of sets of conditions. The methods using different sets of conditions can be performed simultaneously or sequentially or a combination of both (such as two sets simultaneously followed by two more sets, and so on).

[0184] One advantage of the method described herein for selecting a cell with consistent functional expression of a protein of interest is that cells are selected by function, not by the presence of a particular nucleic acid in the cell. Cells that comprise a nucleic acid encoding a protein of interest may not express it, or even if the protein is produced, for many reasons the protein may not be functional or have altered function compared to "native" function, i.e., function in a cell in its normal contextthat naturally expresses the protein. By selecting cells based on function, the methods described herein make it possible to identify novel functional forms. For example, it is possible to identify multiple cells that have various degrees of function in the same assay, such as with the same test compound or with a series of

compounds. The differential function provides a series of functional "profiles". Such profiles are useful, for example, to identify compounds that differentially affect different functional forms of a protein. Such compounds are useful to identify the functional form of a protein in a particular tissue or disease state, an the like.

[0185] A further advantage of the method for making cells and cell lines of the invention including cells that express complex proteins or multiple proteins of interest is that the cells can be produced in significantly less time that by conventional methods. For example, depending on a number of factors including the number of cells required for the functional assay, whether growth rate binning is done and other factors, cells expressing a demonstrably functional protein may be produced in as little as 2 day, or a week but even production time of 2 weeks, 3 weeks, 1 month, 2 months, 3 months or even 6 months are significantly faster than was possible by conventional methods, even for complex or multiple proteins.

[0186] In another aspect, the invention provides methods of using the cells and cell lines of the invention. The cells and cell lines of the invention may be used in any application for which the functional protein of interest are needed. The cells and cell lines may be used, for example, in an *in vitro* cell-based assay or an *in vivo* assay where the cells are implanted in an animal (*e.g.*, a non-human mammal) to, *e.g.*, screen for modulators; produce protein for crystallography and binding studies; and investigate compound selectivity and dosing, receptor/compound binding kinetic and stability, and effects of receptor expression on cellular physiology (*e.g.*, electrophysiology, protein trafficking, protein folding, and protein regulation). The cells and cell lines of the invention also can be used in knock down studies to examine the roles of the protein of interest.

[0187] Cells and cell lines of the invention also may be used to identify soluble biologic competitors, for functional assays, bio-panning (e.g., using phage display libraries), gene chip studies to assess resulting changes in gene expression, two-hybrid studies to identify protein-protein interactions, knock down of specific subunits in cell lines to assess its role, electrophysiology, study of protein trafficking, study of protein folding, study of protein regulation, production of antibodies to the protein, isolation of probes to the protein, isolation of fluorescent probes to the protein, study of the effect of the protein's expression on overall gene expression/processing, study of the effect of the protein's expression on overall protein expression and processing,

and study of the effect of protein's expression on cellular structure, properties, characteristics.

[0188] The cells and cell lines of the invention further are useful to characterize the protein of interest (DNA, RNA or protein) including DNA, RNA or protein stoichiometry, protein folding, assembly, membrane integration or surface presentation, conformation, activity state, activation potential, response, function, and the cell based assay function, where the protein of interest comprises a multigene system, complex or pathway whether all components of these are provided by one or more target genes introduced into cells or by any combination of introduced and endogenously expressed sequences.

[0189] The invention makes possible the producition of multiple cell lines expressing a protein of interest. Clonal cell lines of the invention will have different absolute and relative levels of such expression. A large panel of such clones can be screened for activity with a number of known reference compounds. In this way, each isolated cell line will have a "fingerprint" of responses to test compounds which represent the activities of differential functional expression of the protein. The cell lines can then be grouped based on the similarity of such responses to the compounds. At least one cell line representing each functionally distinct expression profile can be chosen for further study. A collection of these cell lines can then be used to screen a large number of compounds. In this way, compounds which selectively modulate one or more of the corresponding distinct functional forms of the protein may be identified. These modulators can then be tested in secondary assays or *in vivo* models to determine which demonstrate activity in these assays or models. In this connection, the modulators would be used as reference compounds to identify which corresponding functional forms of the protein may be present or play a role in the secondary assay or model system employed. Such testing may be used to determine the functional forms of a protein that may exist *in vivo* as well as those that may be physiologically relevant. These modulators could be used to discern which of the functionally distinct forms are involved in a particular phenotype or physiological function such as disease.

[0190] This method is also useful when creating cell lines for proteins that have not been well characterized. For such proteins, there is often little information regarding the nature of their functional response to known compounds. Such a lack of established functional benchmarks to assess the activity of clones may be one

challenge in producing physiologically relevant cell lines. The method described above provides a way to obtain physiologically relevant cell lines even for proteins that are not well characterized where there is a lack of such information. Cell lines comprising the physiologically relevant form of a protein may be obtained by pursuing clones representing a number or all of the functional forms that may result from the expression of genes comprising a protein.

[0191] The cells and cell lines of the invention may be used to identify the roles of different forms of the protein of interest in different pathologies by correlating the identity of *in vivo* forms of the protein with the identity of known forms of the protein based on their response to various modulators. This allows selection of disease- or tissue-specific modulators for highly targeted treatment of pathologies associated with the protein.

[0192] To identify a modulator, one exposes a cell or cell line of the invention to a test compound under conditions in which the protein would be expected to be functional and then detects a statistically significant change (*e.g.,* $p<0.05$) in protein activity compared to a suitable control, *e.g.,* cells that are not exposed to the test compound. Positive and/or negative controls using known agonists or antagonists and/or cells expressing the protein of interest may also be used. One of ordinary skill in the art would understand that various assay parameters may be optimized, *e.g.,* signal to noise ratio.

[0193] In some embodiments, one or more cells or cell lines of the invention are exposed to a plurality of test compounds, for example, a library of test compounds. Such libraries of test compounds can be screened using the cell lines of the invention to identify one or more modulators of the protein of interest. The test compounds can be chemical moieties including small molecules, polypeptides, peptides, peptide mimetics, antibodies or antigen-binding portions thereof, natural compounds, synthetic compounds , extracts, lipids, detergents, and the like. In the case of antibodies, they may be non-human antibodies, chimeric antibodies, humanized antibodies, or fully human antibodies. The antibodies may be intact antibodies comprising a full complement of heavy and light chains or antigen-binding portions of any antibody, including antibody fragments (such as Fab and Fab, Fab', $F(ab')_2$, Fd, Fv, dAb and the like), single chain antibodies (scFv), single domain antibodies, all or an antigen-binding portion of a heavy chain or light chain variable region.

[0194] In some embodiments, prior to exposure to a test compound, the cells or cell lines of the invention may be modified by pretreatment with, for example, enzymes, including mammalian or other animal enzymes, plant enzymes, bacterial enzymes, protein modifying enzymes and lipid modifying enzymes. Such enzymes can include, for example, kinases, proteases, phosphatases, glycosidases, oxidoreductases, transferases, hydrolases, lyases, isomerases, ligases bacterial proteases, proteases from the gut, proteases from the GI tract, proteases in saliva, in the oral cavity, proteases from lysol cells/bacteria, and the like. Alternatively, the cells and cell lines may be exposed to the test compound first followed by enzyme treatment to identify compounds that alter the modification of the protein by the treatment.

[0195] In some embodiments, large compound collections are tested for protein modulating activity in a cell-based, functional, high-throughput screen (HTS), *e.g.*, using 96-well, 384-well, 1536-well or higher density formats. In some embodiments, a test compound or multiple test compounds, including a library of test compounds, may be screened using more than one cell or cell line of the invention.

[0196] In some embodiments, the cells and cell lines of the invention have increased sensitivity to modulators of the protein of interest. Cells and cell lines of the invention also respond to modulators with a physiological range EC_{50} or IC_{50} values for the protein. As used herein, EC_{50} refers to the concentration of a compound or substance required to induce a half-maximal activating response in the cell or cell line. As used herein, IC_{50} refers to the concentration of a compound or substance required to induce a half-maximal inhibitory response in the cell or cell line. EC_{50} and IC_{50} values may be determined using techniques that are well-known in the art, for example, a dose-response curve that correlates the concentration of a compound or substance to the response of the protein -expressing cell line.

[0197] A further advantageous property of the cells and cell lines of the invention is that modulators identified in initial screening using those cells and cell lines are functional in secondary functional assays. As those of ordinary skill in the art will recognize, compounds identified in initial screening assays typically must be modified, such as by combinatorial chemistry, medicinal chemistry or synthetic chemistry, for their derivatives or analogs to be functional in secondary functional assays. However, due to the high physiological relevance of the cells and cell lines of this invention, many compounds identified using those cells and cell lines are

functional without further modification. In some embodiments, at least 25%, 30%, 40%, 50% or more of the modulators identified in an initial assay are functional in a secondary assay. Further, cell lines of the invention perform in functional assays on a par with the "gold standard" assays. For example, cell lines of the invention expressing GABA A receptors perform substantially the same in membrane potential assays and in electrophysiology.

[0198] These and other embodiments of the invention may be further illustrated in the following non-limiting Examples.

EXAMPLES

Example 1 Generating a Stable $GABA_A$-Expressing Cell Line

Generating Expression Vectors

[0199] Plasmid expression vectors that allowed streamlined cloning were generated based on pCMV-SCRIPT (Stratagene) and contained various necessary components for transcription and translation of a gene of interest, including: CMV and SV40 eukaryotic promoters; SV40 and HSV-TK polyadenylation sequences; multiple cloning sites; Kozak sequences; and neomycin/kanamycin resistance cassettes.

Step 1--Transfection

[0200] We transfected both 293T and CHO cells. The example focuses on CHO cells, where the CHO cells were cotransfected with three separate plasmids, one encoding a human GABA alpha subunit (SEQ ID NO: GABA1-GABA4), one encoding the human GABA beta 3 subunit (SEQ ID NO: GABA5) and the other encoding the human GABA gamma 2 subunit (SEQ ID NO: GABA6) in the following combinations: α1β3γ2s (α1), α2β3γ2s (α2), α3β3γ2s (α3) and α5β3γ2s (α5). As will be appreciated by those of skill in the art, any reagent that is suitable for use with a chosen host cell may be used to introduce a nucleic acid, e.g. plasmid, oligonucleotide, labeled oligonucleotide, into a host cell with proper optimization. Examples of reagents that may be used to introduce nucleic acids into host cells

include but are not limited to Lipofectamine, Lipofectamine 2000, Oligofectamine, TFX reagents, Fugene 6, DOTAP/DOPE, Metafectine, or Fecturin.

[0201] Although drug selection is optional in the methods of this invention, we included one drug resistance marker per plasmid. The sequences were under the control of the CMV promoter. An untranslated sequence encoding a tag for detection by a signaling probe was also present along with a sequence encoding a drug resistance marker. The target sequences utilized were GABA Target Sequence 1 (SEQ ID NO: GABA7), GABA Target Sequence 2 (SEQ ID NO: GABA8) and GABA Target Sequence 3 (SEQ ID NO: GABA9). In these examples, the GABA alpha subunit gene-containing vector contained GABA Target Sequence 1, the GABA beta subunit gene-containing vector contained GABA Target Sequence 2 and the GABA gamma subunit gene-containing vector contained the GABA Target Sequence 3.

Step 2 – Selection step

[0202] Transfected cells were grown for 2 days in HAMF12-FBS, followed by 14 days in antibiotic-containing HAMF12-FBS. The antibiotic containing period had antibiotics added to the media as follows: Puromycin (3.5 ug/ml), Hygromycin (150 ug/ml), and G418/Neomycin (300 ug/ml)

Step 3 – Cell passaging

[0203] Following antibiotic selection, and prior to introduction of fluorogenic probes, cells were passaged 6 to 18 times in the absence of antibiotics to allow time for expression that is not stable over the selected period of time to subside.

Step 4 – Exposure of cells to fluorogenic probes

[0204] Cells were harvested and transfected with GABA signaling probes (SEQ ID NO: GABA10-GABA12). As will be appreciated by those of skill in the art, any reagent that is suitable for use with a chosen host cell may be used to introduce a nucleic acid, e.g. plasmid, oligonucleotide, labeled oligonucleotide, into a host cell with proper optimization. Examples of reagents that may be used to introduce nucleic acids into host cells include but are not limited to Lipofectamine, Lipofectamine 2000, Oligofectamine, TFX reagents, Fugene 6, DOTAP/DOPE, Metafectine, or Fecturin.

[0205] GABA Signaling Probe 1 binds GABA Target Sequence 1, GABA Signaling Probe 2 binds GABA Target Sequence 2 and GABA Signaling Probe 3 binds GABA Target Sequence 3. The cells were then collected for analysis and sorted using a fluorescence activated cell sorter (below).

[0206] **Target Sequences detected by signaling probes**

GABA Target 1

5'-GTTCTTAAGGCACAGGAACTGGGAC-3' (SEQ ID NO:GABA7) (alpha subunit)

GABA Target 2

5'-GAAGTTAACCCTGTCGTTCTGCGAC-3' (SEQ ID NO: GABA8) (beta subunit)

GABA Target 3

5'-GTTCTATAGGGTCTGCTTGTCGCTC-3' (SEQ ID NO: GABA9) (gamma subunit)

Signaling probes

Supplied as 100μM stocks

[0207] A similar probe using a Quasar Dye (BioSearch) with spectral properties similar to Cy5 was used in certain experiments. Note also that 5-MedC and 2-aminodA mixmer probes rather than DNA probes were used in some instances.

GABA Signaling probe 1 - binds (GABA Target 1)

5' - Cy5 GCCAGTCCCAGTTCCTGTGCCTTAAGAACCTCGC **BHQ3 quench -3'** (SEQ ID NO:GABA10)

GABA Signaling probe 2 –binds (GABA Target 2)

5'- Cy5.5 GCGAGTCGCAGAACGACAGGGTTAACTTCCTCGC **BHQ3 quench -3'** (SEQ ID NO: GABA11)

Note that BHQ3 could be substituted with BHQ2 or a gold particle in Probe 1 or Probe 2.

GABA Signaling probe 3 –binds (GABA Target 3)

5'- Fam GCGAGAGCGACAAGCAGACCCTATAGAACCTCGC **BHQ1 quench -3''** (SEQ ID NO: GABA12)

Note that BHQ1 could be substituted with BHQ2 or Dabcyl in Probe 3.

Step 5 – Isolation of positive cells

[0208] The cells were dissociated and collected for analysis and sorting using a fluorescence activated cell sorter. Standard analytical methods were used to gate cells fluorescing above background and to isolate individual cells falling within the gate into barcoded 96-well plates. The gating hierarchy was as follows: Gating hierarchy: coincidence gate> singlets gate> live gate > Sort gate. With this gating strategy, the top 0.04-0.4% of triple positive cells were marked for sorting into barcoded 96-well plates.

Step 6 – Additional cycles of steps 1-5 and/or 3-5

[0209] Steps 1 to 5 and/or 3-5 were repeated to obtain a greater number of cells. Two independent rounds of steps 1-5 were completed, and for each of these cycles, at least three internal cycles of steps 3-5 were performed for the sum of independent rounds.

Step 7 – Estimation of growth rates for the populations of cells

[0210] The plates were transferred to a Hamilton Microlabstar automated liquid handler. Cells were incubated for 5-7 days in a 1:1 mix of 2-3 day conditioned growth medium:fresh growth medium (growth medium is Ham's F12/10% FBS) supplemented with 100 units penicillin/ml plus 0.1mg/ml streptomycin and then dispersed by trypsinization with 0.25% trypsin to minimize clumps and transferred to new 96-well plates. After the clones were dispersed, plates were imaged to determine confluency of wells (Genetix). Each plate was focused for reliable image acquisition across the plate. Reported confluencies of greater than 70% were not relied upon. Confluency measurements were obtained at days every 3 times over 9 days (between days 1 and 10 post-dispersal) and used to calculate growth rates.

Step 8 – Binning populations of cells according to growth rate estimates

[0211] Cells were binned (independently grouped and plated as a cohort) according to growth rate between 10-11 days following the dispersal step in step 7. Bins were independently collected and plated on individual 96 well plates for downstream handling, and there could be more than one target plate per specific bin. Bins were calculated by considering the spread of growth rates and bracketing a range covering a high percentage of the total number of populations of cells. Depending on the sort iteration (see Step 5), between 5 and 6 growth bins were used with a partition of 1-4 days. Therefore each bin

corresponded to a growth rate or population doubling time between 12 and 14.4 hours depending on the iteration.

Step 9 – Replica plating to speed parallel processing and provide stringent QC

[0212] The plates were incubated under standard and fixed conditions (humidified 37°C, 5% CO_2/95% air) in Ham's F12 media/10%FBS without antibiotics. The plates of cells were split to produce 4 sets (the set consists of all plates with all growth bins – these steps ensure there are 4 replicates of the initial set) of target plates. Up to 2 target plate sets were committed for cryopreservation (see below), and the remaining set was scaled and further replica plated for passage and for functional assay experiments. Distinct and independent tissue culture reagents, incubators, personnel and carbon dioxide sources were used for each independently carried set of plates. Quality control steps were taken to ensure the proper production and quality of all tissue culture reagents: each component added to each bottle of media prepared for use was added by one designated person in one designated hood with only that reagent in the hood while a second designated person monitored to avoid mistakes. Conditions for liquid handling were set to eliminate cross contamination across wells. Fresh tips were used for all steps or stringent tip washing protocols were used. Liquid handling conditions were set for accurate volume transfer, efficient cell manipulation, washing cycles, pipetting speeds and locations, number of pipetting cycles for cell dispersal, and relative position of tip to plate.

Step 10 – Freezing early passage stocks of populations of cells

[0213] At least two sets of plates were frozen at -70 to -80C. Plates in each set were first allowed to attain confluencies of 70 to 100%. Media was aspirated and 90%FBS and 10% DMSO was added. The plates were sealed with Parafilm and then individually surrounded by 1 to 5cm of foam and placed into a -80C freezer.

Step 11– Methods and conditions for initial transformative steps to produce VSF

[0214] The remaining set of plates were maintained as described in step 9 (above). All cell splitting was performed using automated liquid handling steps, including media removal, cell washing, trypsin addition and incubation, quenching and cell dispersal steps.

Step 12 – Normalization methods to correct any remaining variability of growth rates

The consistency and standardization of cell and culture conditions for all populations of cells was controlled. Any differences across plates due to slight differences in growth rates could be controlled by periodic normalization of cell numbers across plates.

Step 13 – Characterization of population of cells

[0215] The cells were maintained for 6 to 8 weeks of cell culture to allow for their in vitro evolution under these conditions. During this time, we observed size, morphology, fragility, response to trypsinization or dissociation, roundness/average circularity post-dissociation, percentage viability, tendency towards microconfluency, or other aspects of cell maintenance such as adherence to culture plate surfaces.

Step 14 – Assessment of potential functionality of populations of cells under VSF conditions

[0216] Populations of cells were tested using functional criteria. Membrane potential assay kits (Molecular Devices/MDS) were used according to manufacturer's instructions. Cells were tested at multiple different densities in 96 or 384-well plates and responses were analyzed. A variety of time points post plating were used, for instance 12-48 hours post plating. Different densities of plating were also tested for assay response differences.

Step 15

[0217] The functional responses from experiments performed at low and higher passage numbers were compared to identify cells with the most consistent responses over defined periods of time, ranging from 3 to 9 weeks. Other characteristics of the cells that changed over time are also noted, including morphology, tendency toward microconfluency, and time to attach to culture matrices post-plating.

Step 16

[0218] Populations of cells meeting functional and other criteria were further evaluated to determine those most amenable to production of viable, stable and functional cell lines. Selected populations of cells were expanded in larger tissue culture vessels and the characterization steps described above were continued or repeated under these conditions. At this point, additional standardization steps were introduced for consistent and reliable passages. These included different plating cell densities, time of passage, culture dish

size/format and coating, fluidics optimization, cell dissociation optimization (type, volume used, and length of time), as well as washing steps. Assay Z' scores were stable when tested every few days over the course of four weeks in culture.

[0219] Also, viability of cells at each passage were determined. Manual intervention was increased and cells were more closely observed and monitored. This information was used to help identify and select final cell lines that retained the desired properties Final cell lines and back-up cell lines were selected that showed consistent growth, appropriate adherence, as well as functional response.

Step 17 – Establishment of cell banks

[0220] The low passage frozen plates (see above) corresponding to the final cell line and back-up cell lines were thawed at 37°C, washed two times with Ham's F12/10% FBS and incubated in humidified 37°C/5% CO2 conditions. The cells were then expanded for a period of 2-3 weeks. Cell banks for each final and back-up cell line consisting of 25 vials each with 10 million cells were established.

Step 18

[0221] At least one vial from the cell bank was thawed and expanded in culture. The resulting cells were tested to confirm that they met the same characteristics for which they were originally selected.

Example 2 Verification of $GABA_A$ Cell Lines Response to GABA Ligand.

[0222] The response of CHO cell lines expressing $GABA_A$ (subunit combinations of α1β3γ2s (α1), α2β3γ2s (α2), α3β3γ2s (α3) and α5β3γ2s (α5)) GABA, the endogenous $GABA_A$ ligand, was evaluated. Interaction of cell lines with GABA was evaluated by measuring the membrane potential of $GABA_A$, in response to GABA using the following protocol.

[0223] Cells were plated 24 hours prior to assay at 10-25,000 cells per well in 384 well plates in growth media (Ham's F-12 media plus FBS and glutamine). Media removal was followed by the addition of membrane potential dye diluted in load buffer (137mM NaCl, 5mMKCl,1.25mM CaCl, 25mM HEPES, 10mM Glucose). Incubation was for 1 hour, followed by plate loading onto the high throughput fluorescent plate reader (Hamamastu FDSS). GABA ligand was diluted in MP assay buffer (137mM NaCl, 5mM KGluconate,1.25mM CaCl, 25mM HEPES, 10mM

Glucose) to the desired concentration (when needed, serial dilutions of GABA were generated, concentrations used: 3nM, 10nM, 30nM, 100nM, 300nM, 1uM, 3uM, 10uM) and added to each well. The plates were read for 90 seconds.

[0224] **Table GABA1** (below) demonstrates that each of the cell lines generated responds to GABA ligand. These results indicate that the $GABA_A$ cell lines produced, which respond as expected to the endogenous ligand, are physiologically relevant for use in high-throughput screening assays. Further, the replicate wells produced precise EC_{50} values from well to well indicating high reproducibility of the $GABA_A$ cell lines. Z' values generated using the membrane potential assay were α1β3γ2s 0.58, α2β3γ2s 0.67, α3β3γ2s 0.69 and α5β3γ2s 0.62.

Example 3 Additional Verification of $GABA_A$ Cell Lines Using A Known $GABA_A$ Modulator.

[0225] The $GABA_A$ cell lines and membrane potential assay were verified by the methods described in Example 2 using serial dilutions in assay buffer of bicuculline (a known antagonist) at 30uM, 10uM, 3uM, 1uM, 300nM, 100nM and 30nM.

[0226] Bicuculline was found to interact with all four $GABA_A$ cell lines in the presence of EC_{50} concentrations of GABA. These results indicate that the $GABA_A$ cell lines produced, which respond as expected to this known modulator of $GABA_A$, are physiologically and pharmacologically relevant for use in high-throughput screening assays.

Example 4 Characterization of Cell Line Expressing $GABA_A$ for Native $GABA_A$ Function Using Membrane Potential Assay

[0227] The interaction of CHO cell lines expressing $GABA_A$ (subunit combinations of α1β3γ2s (α1), α2β3γ2s (α2), α3β3γ2s (α3) and α5β3γ2s (α5)) with 1280 compounds from the LOPAC 1280 (Library of Pharmacologically Active Compounds) was evaluated (Sigma-RBI Prod. No. LO1280). The LOPAC 1280 library contains high purity, small organic ligands with well documented pharmacological activities. Interaction of cell lines with test compounds was evaluated by measuring the membrane potential of $GABA_A$, in response to test compounds using the following protocol.

[0228] Cells were plated 24 hours prior to assay at 10-25,000 cells per well in 384 well plates in growth media (Ham's F-12 media plus FBS and glutamine). Media

removal was followed by the addition of membrane potential dye diluted in load buffer (137mM NaCl, 5mMKCl,1.25mM CaCl, 25mM HEPES, 10mM Glucose). Incubation was for 1 hour, followed by plate loading onto the high throughput fluorescent plate reader (Hamamastu FDSS). Test compounds were diluted in MP assay buffer (137mM NaCl, 5mM KGluconate,1.25mM CaCl, 25mM HEPES, 10mM Glucose) to the desired concentration (when needed, serial dilutions of each test compound were generated, concentrations used: 3nM, 10nM, 30nM, 100nM, 300nM, 1uM, 3uM, 10uM) and added to each well. The plates were read for 90 seconds.

Results

[0229] The activity of each compound towards the $GABA_A$ cell lines produced was measured and compounds which exhibited similar or greater activity as GABA (the endogenous ligand) were scored as positive hits. Of the 1280 compounds screened, 34 activated at least one cell line (i.e., either α1, α2, α3 and α5) as well as, if not better, than GABA. The interaction of 17 of these compounds with the produced $GABA_A$ cell lines was confirmed in the following dose response studies. Modulators which require GABA to be present, partial agonists and low potency compounds were not included in the list.

[0230] The screening assay identified each of the $GABA_A$ agonists in the LOPAC library: GABA (endogenous ligand), propofol, isoguvacine hydrochloride, muscimol hydrobromide, piperidine-4-sulphonic acid, 3-alpha,21-dihydroxy-5-alpha-pregnan-20-one (a neurosteroid), 5-alpha-pregnan-3alpha-ol-11,20-dione (a neurosteroid), 5-alpha-pegnan-3alpha-ol-20-one (a neurosteroid), and tracazolate. The results indicate that the produced $GABA_A$ cell lines respond in a physiologically relevant manner (e.g., they respond to agonists of the endogenous receptor). EC_{50} values for these eight agonists were determined and are included in **Table GABA1** (below).

[0231] The screening assay also identified four compounds in the LOPAC library not described as GABA agonist but known to have other activities associated with $GABA_A$ which we noted: etazolate (a phospodiesterase inhibitor), androsterone (a steroid hormone), chlormezanone (a muscle relaxant), and ivermectin (an anti-parasitic known to effect chlorine channels). EC_{50} values for these four compounds were determined and are summarized in **Table GABA1** (below).

[0232] The screening assay further identified four compounds in the LOPAC library which, until now, were not known to interact with $GABA_A$. These novel compounds

include: dipyrimidole (an adenosine deaminase inhibitor), niclosamide (an anti-parasitic), tyrphosin A9 (a PDGFR inhibitor), and I-Ome-Tyrphosin AG 538 (an IGF RTK inhibitor). EC50 values for these four compounds were determined and are summarized in **Table GABA1** (below).

The results of the screening assays summarized in **Table GABA1**:

Compound	Description	Chromocell Target	EC_{50} Values
GABA	endogenous ligand	α1, α2, α3, α5	α1 3.29μM α2 374nM α3 131nM α5 144nM
Muscimol	agonist	α1, α2, α3, α5	α1 4μM α2 675nM α3 367nM α5 80nM
Propofol	agonist	α1, α2, α3, α5	α1 33.4μM α2 42.8μM α3 12.9μM α5 2.0μM
Isoguvacine hydrochloride	agonist	α1, α2, α3, α5	α1 3.57μM α2 3.42μM α3 6.78μM α5 1.13μM
Piperidine-4-sulphonic acid	agonist	α1, α2, α3, α5	α1 13μM α2 20μM α3 8.33μM α5 14.2μM
3-alpha, 21-dihydroxy-5-alpha-pregnan-20-one	neurosteroid (agonist)	α1, α2, α3, α5	α1 382nM α2 123nM α3 80.2nM α5 17.3nM
5-alpha-Pregnan-3alpha-ol-11,20-dione	neurosteroid (agonist)	α1, α2, α3, α5	α1 762nM α2 338nM α3 168nM α5 122nM
5-alpha-Pregnan-3alpha-ol-20-one	neurosteroid (agonist)	α1, α2, α3, α5	α1 692nM α2 140nM

			α3 80.0nM α5 33.6nM
Tracazolate	agonist	α1, α2, α3, α5	α1 10.6μM α2 8.9μM α3 4.3μM α5 762nM
Androsterone	Steroid with $GABA_A$ receptor activity	α1, α2, α3, α5	α1 1.48μM α2 1.52μM α3 1.12μM α5 337nM
Ivermectin	Phospho-diesterase inhibitor: Known GABAergic	α1, α2, α3, α5	α1 4.26μM α2 767nM α3 798nM α5 687nM
Chlormezanone	Muscle relaxant: known GABA ligand	α1, α2, α3, α5	α1 1.74nM α2 5.42nM α3 7.0nM α5 14.1nM
Etazolate	Anti-parasitic: known effector of chlorine channels	α1, α2, α3, α5	α1 2.54μM α2 790nM α3 569nM α5 281nM
Dipyridamole	Adenosine inhibitor known to effect GABA release in neurons (not known to bind to $GABA_A$)	α1, α2, α3, α5	α1 7.16μM α2 3.68μM α3 3.69μM α5 1.37μM
Niclosamide	Anti parasitic (side effects include drowsiness and dizziness)	α1, α2, α3, α5	α1 1.2μM α2 1.26μM α3 0.55μM α5 0.69μM
Tyrphostin A9	PDGFR inhibitor	α1, α2, α3, α5	α1 1.8μM α2 0.88μM α3 5.0 μM

			α5 54.0 μM
I-OMe Tyrphostin 538	IGF RTK inhibitor	α1, α2, α3, α5	α1 3.5μM α2 1.5μM α3 2.2μM α5 Not active

Example 5 Characterization $GABA_A$-CHO cells for native $GABA_A$ function using Electrophysiological Assay

[0233] The following voltage-clamp protocol was used: the membrane potential was clamped to a holding potential of -60 mV. Currents were evoked by 2-sec applications of increasing concentrations of GABA (0.10-100 μM) with intermediate wash with buffer.

[0234] Whole cell receptor current traces for the α2, α3, and α5 $GABA_A$ cell lines in response to 100uM GABA, and the α1 $GABA_A$ cell line in response to increasing concentrations of GABA (0.10-100μM in log increments), confirm that the $GABA_A$ cell lines can be used in traditional electrophysiology assays in addition to the High-Throughput Screening assays described above. These electrophysiology assay results, along with the membrane potential assay of Example 2, confirm the physiological and pharmacological relevance of the $GABA_A$ cell lines produced herein. Electrophysiology is accepted as a reliable method of detecting modulators of $GABA_A$ receptors. Our data indicate that the cell lines of the invention can produce similarly reliable results using a membrane potential assay. Cell lines of the prior art are not reliable or sensitive enough to effectively utilize this membrane potential assay, which is cheaper and faster than electrophysiology. Thus, the cell lines of the invention allow screening on a much larger scale than is available using electrophysiology (10,000's of assays per day using the membrane potential assay compared to less than 100 per day using electrophysiology).

Example 6 Characterization of an in-cell readout assay for native $GABA_A$ function using halide-sensitive meYFP

[0235] The response of $GABA_A$ (subunit combinations of α1β3γ2s (A1), α2β3γ2s (A2), α3β3γ2s (A3) and α5β3γ2s (A5)) expressing CHO cells of the invention to test compounds was evaluated using the following protocol for an in-cell readout assay.

[0236] Cells were plated 24 hours prior to assay at 10-25,000 cells per well in 384 well plates in growth media (Ham's F-12 media plus FBS and glutamine). Media removal was followed by the addition of loading buffer (135mM NaCl, 5mM KCl, 2mM $CaCl_2$, 1 mM $MgCl_2$, 10mM HEPES, 10mM glucose) and incubation for 1 hour. The assay plates were then loaded on the FDSS (Hamamatsu Corporation). Test compounds (*e.g.* GABA ligand) were diluted in assay buffer (150mM NaI, 5mMKCl, 1.25mM $CaCl_2$, 1 mM $MgCl_2$, 25mM HEPES, 10mM glucose) to the desired concentration (when needed, serial dilutions of each test compound were generated, effective concentrations used: 3nM, 10nM, 30nM, 100nM, 300nM, 1uM, 3uM, 10uM) and added to each well. The plates were read for 90 seconds.

[0237] In response to increasing concentrations of GABA ligand, $GABA_A$-meYFP-CHO cells show increasing quench of meYFP signal. This quench can be used to calculate dose response curves for GABA activation. The GABA dose response curves generated by the in-cell readout assay are similar to the curves generated by the Membrane Potential Blue assay described in Example 3. These data demonstrate that the cells of the invention can be used in an in-cell readout assay to determine modulators of $GABA_A$.

Example 8 Generating a stable GC-C-expressing cell line

[0238] 293T cells were transfected with a plasmid encoding the human GC-C gene (SEQ ID NO: GCC 3) using standard techniques. (Examples of reagents that may be used to introduce nucleic acids into host cells include, but are not limited to, LIPOFECTAMINE™, LIPOFECTAMINE™ 2000, OLIGOFECTAMINE™, TFX™ reagents, FUGENE® 6, DOTAP/DOPE, Metafectine or FECTURIN™.)

[0239] Although drug selection is optional in the methods of this invention, we included one drug resistance marker in the plasmid encoding the human GC-C gene. The GC-C sequence was under the control of the CMV promoter. An untranslated sequence encoding a tag for detection by a signaling probe was also present along with a sequence encoding a drug resistance marker. The target sequence utilized

was GC-C Target Sequence 1 (SEQ ID NO: GCC 1). In this example, the GC-C gene-containing vector contained GC-C Target Sequence 1.

[0240] Transfected cells were grown for 2 days in DMEM-FBS, followed by 10 days in 500µg/ml hygromycin-containing DMEM-FBS, then in DMEM-FBS for the remainder of the time, totaling between 4 and 5 weeks (depending on which independent isolation) in DMEM/10% FBS, prior to the addition of the signaling probe.

[0241] Following enrichment on antibiotic, cells were passaged 8-10 times in the absence of antibiotic selection to allow time for expression that is not stable over the selected period of time to subside.

[0242] Cells were harvested and transfected with GC-C Signaling Probe 1 (SEQ ID NO: GCC 2) using standard techniques. (Examples of reagents that may be used to introduce nucleic acids into host cells include, but are not limited to, LIPOFECTAMINE™, LIPOFECTAMINE™ 2000, OLIGOFECTAMINE™, TFX™ reagents, FUGENE® 6, DOTAP/DOPE, Metafectine or FECTURIN™.) The cells were then dissociated and collected for analysis and sorted using a fluorescence activated cell sorter.

GC-C Target Sequence 1 detected by GC-C Signaling probe 1

5'-GTTCTTAAGGCACAGGAACTGGGAC-3' (SEQ ID NO: GCC 1)

GC-C Signaling probe 1

(Supplied as 100µM stock)

5' - Cy5 GCCAGTCCCAGTTCCTGTGCCTTAAGAACCTCGC BHQ2 -3' (SEQ ID NO: GCC 2)

[0243] In addition, a similar probe using a QUASAR® Dye (BioSearch) with spectral properties similar to Cy5 was used in certain experiments. In some experiments, 5-MedC and 2-amino dA mixmers were used rather than DNA probes.

[0244] The cells were dissociated and collected for analysis and sorting using a fluorescence activated cell sorter. Standard analytical methods were used to gate cells fluorescing above background and to isolate individual cells falling within the gate into bar-coded 96-well plates. The following gating hierarchy was used: coincidence gate → singlets gate → live gate → Sort gate in plot FAM vs. Cy5: 0.3% of live cells

[0245] The above steps were repeated to obtain a greater number of cells. Two rounds of all the above steps were performed. In addition, the cell passaging, exposure to the signaling probe and isolation of positive cells by the fluorescence activated cell sorter sequence of steps was performed a total of two times for one of the independent transfection rounds.

[0246] The plates were transferred to a MICROLAB STAR™ (Hamilton Robotics). Cells were incubated for 9 days in 100µl of 1:1 mix of fresh complete growth medium and 2-day-conditioned growth medium, supplemented with 100U penicillin and 0.1mg/ml streptomycin, dispersed by trypsinization twice to minimize clumps and transferred to new 96-well plates. Plates were imaged to determine confluency of wells (Genetix). Each plate was focused for reliable image acquisition across the plate. Reported confluencies of greater than 70% were not relied upon. Confluency measurements were obtained on 3 consecutive days and used to calculate growth rates.

[0247] Cells were binned (independently grouped and plated as a cohort) according to growth rate 3 days following the dispersal step. Each of the 4 growth bins was separated into individual 96-well plates; some growth bins resulted in more than one 96-well plate. Bins were calculated by considering the spread of growth rates and bracketing a range covering a high percentage of the total number of populations of cells. Bins were calculated to capture 12-hour differences in growth rate.

[0248] Cells can have doubling times from less than 1 day to more than 2 weeks. In order to process the most diverse clones that at the same time can be reasonably binned according to growth rate, it is preferable to use 3-9 bins with a 0.25 to 0.7 day doubling time per bin. One skilled in the art will appreciate that the tightness of the bins and number of bins can be adjusted for the particular situation and that the tightness and number of bins can be further adjusted if cells were synchronized for their cell cycle.

[0249] The plates were incubated under standardized and fixed conditions (DMEM/FBS, 37°C, 5% CO_2) without antibiotics. The plates of cells were split to produce 5 sets of 96-well plates (3 sets for freezing, 1 for assay and 1 for passage). Distinct and independent tissue culture reagents, incubators, personnel and carbon dioxide sources were used downstream in the workflow for each of the sets of plates. Quality control steps were taken to ensure the proper production and quality of all

tissue culture reagents: each component added to each bottle of media prepared for use was added by one designated person in one designated hood with only that reagent in the hood while a second designated person monitors to avoid mistakes. Conditions for liquid handling were set to eliminate cross contamination across wells. Fresh tips were used for all steps, or stringent tip washing protocols were used. Liquid handling conditions were set for accurate volume transfer, efficient cell manipulation, washing cycles, pipetting speeds and locations, number of pipetting cycles for cell dispersal, and relative position of tip to plate.

[0250] One set of plates was frozen at -70 to -80°C. Plates in the set were first allowed to attain confluencies of 70 to 100%. Medium was aspirated and 90% FBS and 10% DMSO was added. The plates were individually sealed with Parafilm, surrounded by 1 to 5cm of foam and placed into a freezer.

[0251] The remaining two sets of plates were maintained under standardized and fixed conditions as described above. All cell splitting was performed using automated liquid handling steps, including media removal, cell washing, trypsin addition and incubation, quenching and cell dispersal steps.

[0252] The consistency and standardization of cell and culture conditions for all populations of cells was controlled. Differences across plates due to slight differences in growth rates were controlled by normalization of cell numbers across plates and occurred 3 passages after the rearray. Populations of cells that are outliers were detected and eliminated.

[0253] The cells were maintained for 3 to 6 weeks to allow for their *in vitro* evolution under these conditions. During this time, we observed size, morphology, tendency towards microconfluency, fragility, response to trypsinization and average circularity post-trypsinization, or other aspects of cell maintenance such as adherence to culture plate surfaces and resistance to blow-off upon fluid addition.

[0254] Populations of cells were tested using functional criteria. The Direct Cyclic GMP Enzyme Immunoassay Kit (Cat. 900-014; AssayDesigns, Inc.) was used according to manufacturer's instructions: (http://www.assaydesigns.com/objects/catalog//product/extras/900-014.pdf). Cells were tested at 4 different densities in 96- or 384-well plates and responses were analyzed. The following conditions were used for the GC-C-expressing cell lines of the invention:

- Clone screening: 1:2 and 1:3 splits of confluent 96-well plates 48 hour prior to assay, 30 minutes guanylin treatment.
- Dose-response studies: densities of 20,000, 40,000, 60,000, 80,000, 120,000 and 160,000 per well, 30 minutes guanylin treatment (see Example 9).
- Z' studies: densities of 160,000 and 200,000 per well were used, 30 minutes guanylin treatment (see Example 10).

[0255] The functional responses from experiments performed at low and higher passage numbers were compared to identify cells with the most consistent responses over defined periods of time, ranging from 4 to 10 weeks. Other characteristics of the cells that changed over time were also noted.

[0256] Populations of cells meeting functional and other criteria were further evaluated to determine those most amenable to production of viable, stable and functional cell lines. Selected populations of cells were expanded in larger tissue culture vessels, and the characterization steps described above were continued or repeated under these conditions. At this point, additional standardization steps, such as different cell densities; time of plating, length of cell culture passage; cell culture dishes format and coating; fluidics optimization, including speed and shear force; time of passage; and washing steps, were introduced for consistent and reliable passages. Also, viability of cells at each passage was determined. Manual intervention was increased, and cells were more closely observed and monitored. This information was used to help identify and select final cell lines that retain the desired properties. Final cell lines and back-up cell lines (20 clones total) were selected that showed appropriate adherence/stickiness and growth rate and even plating (lack of microconfluency) when produced following this process and under these conditions.

[0257] The initial frozen stock of 3 vials per each of the selected 20 clones was generated by expanding the non-frozen populations from the re-arrayed 96-well plates via 24-well, 6-well and 10cm dishes in DMEM/10%FBS/HEPES/L-Glu. The low passage frozen stocks corresponding to the final cell line and back-up cell lines were thawed at 37°C, washed two times with DMEM containing FBS and incubated in the same manner. The cells were then expanded for a period of 2 to 4 weeks. Two final clones were selected.

[0258] One vial from one clone of the initial freeze was thawed and expanded in culture. The resulting cells were tested to confirm that they met the same characteristics for which they were originally selected. Cell banks for each cell line consisting of 20 to over 100 vials may be established.

[0259] The following step can also be conducted to confirm that the cell lines are viable, stable and functional: At least one vial from the cell bank is thawed and expanded in culture; the resulting cells are tested to determine if they meet the same characteristics for which they were originally selected.

Example 9 Characterizing the cell lines for native GC-C function

[0260] A competitive ELISA for detection of cGMP was used to characterize native GC-C function in the produced GC-C-expressing cell line. Cells expressing GC-C were maintained under standard cell culture conditions in Dulbecco's Modified Eagles medium (DMEM) supplemented with 10% fetal bovine serum, glutamine and HEPES and grown in T175cm flasks. For the ELISA, the cells were plated into coated 96-well plates (poly-D-lysine).

Cell treatment and cell lysis protocol

[0261] Cells were washed twice with serum-free medium and incubated with 1 mM IBMX for 30 minutes. Desired activators (*i.e.*, guanylin, 0.001-40 μM) were then added to the cells and incubated for 30-40 minutes. Supernatant was removed, and the cells were washed with TBS buffer. The cells were lysed with 0.1 N HCl. This was followed by lysis with 0.1N HCl and a freeze/thaw cycle at -20°C/room temperature. Defrosted lysates (samples were spun in Eppendorf tubes at 10,000rpm) were centrifuged to pellet cell debris. The cleared supernatant lysate was then transferred to ELISA plates.

ELISA protocol

[0262] All of the following steps were performed at room temperature, unless otherwise indicated. ELISA plates were coated with anti-IgG antibodies in coating buffer (Na-carbonate/bi-carbonate buffer, 0.1M final, pH 9.6) overnight at 4°C. Plates were then washed with wash buffer (TBS-Tween 20, 0.05%), followed by blocking reagent addition. Incubation for 1 hour with blocking reagent at 37°C was followed by a wash of the plates with wash buffer. A rabbit anti-cGMP polyclonal antibody (Chemicon) was then added, followed by incubation for 1 hour and a subsequent wash with wash buffer. Cell lysate was then added, and incubated for 1

hour before the subsequent addition of a cGMP-biotin conjugate (1 and 10nM of 8-Biotin-AET-cGMP (Biolog)). Plates were incubated for 2 hours and then washed with wash buffer. Streptavidin-alkaline phosphate was then added and incubated for 1 hour, then washed with wash buffer. Plates were incubated for at least 1 hour (preferably 2-5 hours) with PNPP substrate (Sigma). The absorbance was then read at 405nm on a SAFIRE$^{2™}$ plate reader (Tecan).

[0263] Maximum absorbance was seen when no cell lysate was used in the ELISA (Control). Reduction in absorbance (corresponding to increased cGMP levels) was observed with cell lysate from the produced GC-C-expressing cell line treated with 100 nM guanylin (Clone).

[0264] The cGMP level in the produced GC-C-expressing cell line treated with 100 nM guanylin was also compared to that of parental cell line control samples not expressing GC-C (not shown) using the Direct Cyclic GMP Enzyme Immunoassay Kit (Cat. 900-014; AssayDesigns, Inc.). The GC-C-expressing cell line showed a greater reduction in absorbance (corresponding to increased cGMP levels) than parental cells treated and untreated with guanylin.

[0265] For guanylin dose-response experiments, cells of the produced GC-C-expressing cell line, plated at densities of 20,000, 40,000, 60,000, 80,000, 120,000 and 160,000 cells/well in a 96-well plate, were challenged with increasing concentration of guanylin for 30 minutes. The cellular response (*i.e.*, absorbance) as a function of changes in cGMP levels (as measured using the Direct Cyclic GMP Enzyme Immunoassay Kit (Cat. 900-014; AssayDesigns, Inc.) was detected using a SAFIRE$^{2™}$ plate reader (Tecan). Data were then plotted as a function of guanylin concentration and analyzed using non-linear regression analysis using GraphPad Prism 5.0 software, resulting in an EC_{50} value of 1.1 nM. The produced GC-C-expressing cell line shows a higher level of cGMP (6 pmol/ml) when treated with low concentrations of guanylin in comparison to that previously reported in other cell lines (3.5 pmol/ml) (Forte et al., Endocr. 140(4):1800-1806 (1999)), indicating the potency of the clone.

Example 10 Generation of GC-C-expressing cell line Z' value

[0266] Z' for the produced GC-C-expressing cell line was calculated using a direct competitive ELISA assay. The ELISA was performed using the Direct Cyclic GMP

Enzyme Immunoassay Kit (Cat. 900-014; AssayDesigns, Inc.). Specifically, for the Z' assay, 24 positive control wells in a 96-well assay plate (plated at a density of 160,000 or 200,000 cells/well) were challenged with a GC-C activating cocktail of 40μM guanylin and IBMX in DMEM media for 30 minutes. Considering the volume and surface area of the 96-well assay plate, this amount of guanylin created a concentration comparable to the 10μM used by Forte *et al.* (1999) *Endocr.* 140(4), 1800-1806. An equal number of wells containing clonal cells in DMEM/IMBX were challenged with vehicle alone (in the absence of activator). Absorbance (corresponding to cGMP levels) in the two conditions was monitored using a SAFIRE$^{2™}$ plate reader (Tecan). Mean and standard deviations in the two conditions were calculated and Z' was computed using the method of Zhang et al., J Biomol Screen, 4(2):67-73 (1999)). The Z' value of the produced GC-C-expressing cell line was determined to be 0.72.

Example 11 Short-circuit current measurements

[0267] Ussing chamber experiments are performed 7–14 days after plating GC-C-expressing cells (primary or immortalized epithelial cells, for example, lung, intestinal, mammary, uterine, or renal) on culture inserts (Snapwell, Corning Life Sciences). Cells on culture inserts are rinsed, mounted in an Ussing type apparatus (EasyMount Chamber System, Physiologic Instruments) and bathed with continuously gassed Ringer solution (5% CO_2 in O_2, pH 7.4) maintained at 37°C containing (in mM) 120 NaCl, 25 $NaHCO_3$, 3.3 KH_2PO_4, 0.8 K_2HPO_4, 1.2 $CaCl_2$, 1.2 $MgCl_2$, and 10 glucose. The hemichambers are connected to a multichannel voltage and current clamp (VCC-MC8, Physiologic Instruments). Electrodes [agar bridged (4% in 1 M KCl) Ag-AgCl] are used, and the inserts are voltage clamped to 0 mV. Transepithelial current, voltage and resistance are measured every 10 seconds for the duration of the experiment. Membranes with a resistance of <200mOhms are discarded. This secondary assay can provide confirmation that in the appropriate cell type (*i.e.*, cell that form tight junctions) the introduced GC-C is altering CFTR activity and modulating a transepithelial current.

Example 12 Generating a Stable CFTR-Expressing Cell Line

Generating Expression Constructs

[0268] Plasmid expression vectors that allowed streamlined cloning were generated based on pCMV-SCRIPT (Stratagene) and contained various necessary components for transcription and translation of a gene of interest, including: CMV and SV40 eukaryotic promoters; SV40 and HSV-TK polyadenylation sequences; multiple cloning sites; Kozak sequences; and drug resistance cassettes.

Generating Cell Lines

Step 1: Transfection

[0269] CHO cells were transfected with a plasmid encoding a human CFTR (SEQ ID NO: CFTR1) using standard techniques. (Examples of reagents that may be used to introduce nucleic acids into host cells include, but are not limited to, LIPOFECTAMINE™, LIPOFECTAMINE™ 2000, OLIGOFECTAMINE™, TFX™ reagents, FUGENE® 6, DOTAP/DOPE, Metafectine or FECTURIN™.)

[0270] Although drug selection is optional to produce the cells or cell lines of this invention, we included one drug resistance marker in the plasmid (*i.e.,* puromycin). The CFTR sequence was under the control of the CMV promoter. An untranslated sequence encoding a CFTR Target Sequence for detection by a signaling probe was also present along with the sequence encoding the drug resistance marker. The target sequence utilized was CFTR Target Sequence 1 (SEQ ID NO: CFTR2), and in this example, the CFTR gene-containing vector comprised CFTR Target Sequence 1 (SEQ ID NO: CFTR2).

Step 2: Selection

[0271] Transfected cells were grown for 2 days in Ham's F12-FBS media without antibiotics, followed by 10 days in 12.5 µg/ml puromycin-containing Ham's F12-FBS media. The cells were then transferred to Ham's F12-FBS media without antibiotics for the remainder of the time, prior to the addition of the signaling probe.

Step 3: Cell passaging

[0272] Following enrichment on antibiotic, cells were passaged 5 - 14 times in the absence of antibiotic selection to allow time for expression that was not stable over the selected period of time to subside.

Step 4: Exposure of cells to fluorogenic probes

[0273] Cells were harvested and transfected with CFTR Signaling Probe 1 (SEQ ID NO: CFTR3) using standard techniques. (Examples of reagents that may be used to introduce nucleic acids into host cells include, but are not limited to, LIPOFECTAMINE™, LIPOFECTAMINE™ 2000, OLIGOFECTAMINE™, TFX™ reagents, FUGENE® 6, DOTAP/DOPE, Metafectine or FECTURIN™.) CFTR Signaling Probe 1 (SEQ ID NO: CFTR3) bound CFTR Target Sequence 1 (SEQ ID NO: CFTR2). The cells were then collected for analysis and sorted using a fluorescence activated cell sorter.

Target Sequence detected by signaling probe

CFTR Target Sequence 1

5'- GTTCTTAAGGCACAGGAACTGGGAC -3' (SEQ ID NO: CFTR2)

Signaling probe

Supplied as 100µM stock

CFTR Signaling probe 1

5' - **Cy5** GCCAGTCCCAGTTCCTGTGCCTTAAGAACCTCGC **BHQ2** -3' (SEQ ID NO: CFTR3)

[0274] In addition, a similar probe using a Quasar® Dye (BioSearch) with spectral properties similar to Cy5 was used in certain experiments. In some experiments, 5-MedC and 2-amino dA mixmers were used rather than DNA probes. A non-targeting FAM labeled probe was also used as a loading control.

Step 5: Isolation of positive cells

[0275] The cells were dissociated and collected for analysis and sorting using a fluorescence activated cell sorter. Standard analytical methods were used to gate cells fluorescing above background and to isolate individual cells falling within the gate into bar-coded 96-well plates. The following gating hierarchy was used:

coincidence gate → singlets gate → live gate → Sort gate in plot FAM vs. Cy5: 0.1 – 0.4 % of cells.

Step 6: Additional cycles of steps 1-5 and/or 3-5

[0276] Steps 1-5 and/or 3-5 were repeated to obtain a greater number of cells. Two rounds of steps 1-5 were performed, and for each of these rounds, two internal cycles of steps 3-5 were performed.

Step 7: Estimation of growth rates for the populations of cells

[0277] The plates were transferred to a Microlab Star (Hamilton Robotics). Cells were incubated for 9 days in 100 µl of 1:1 mix of fresh complete growth media and 2 to 3 day-conditioned growth media, supplemented with 100 units/ml penicillin and 0.1 mg/ml streptomycin. Then the cells were dispersed by trypsinization once or twice to minimize clumps and later transferred to new 96-well plates. Plates were imaged to determine confluency of wells (Genetix). Each plate was focused for reliable image acquisition across the plate. Reported confluencies of greater than 70% were not relied upon. Confluency measurements were obtained on consecutive days between days 1 and 10 post-dispersal and used to calculate growth rates.

Step 8: Binning populations of cells according to growth rate estimates

[0278] Cells were binned (independently grouped and plated as a cohort) according to growth rate less than two weeks following the dispersal step in step 7. Each of the three growth bins was separated into individual 96 well plates; some growth bins resulted in more than one 96 well plate. Bins were calculated by considering the spread of growth rates and bracketing a high percentage of the total number of populations of cells. Bins were calculated to capture 12-16 hour differences in growth rate.

[0279] Cells can have doubling times from less 1 day to more than 2 week. In order to process the most diverse clones that at the same time can be reasonably binned according to growth rate, it may be preferable to use 3-9 bins with a 0.25 to 0.7 day doubling time per bin. One skilled in the art will appreciate that the tightness of the bins and number of bins can be adjusted for the particular situation and that the tightness and number of bins can be further adjusted if cells are synchronized for their cell cycle.

Step 9: Replica plating to speed parallel processing and provide stringent quality control

[0280] The plates were incubated under standardized and fixed conditions (*i.e.*, Ham's F12-FBS media, 37°C/5%CO2) without antibiotics. The plates of cells were split to produce 4 sets of 96 well plates (3 sets for freezing, 1 set for assay and passage). Distinct and independent tissue culture reagents, incubators, personnel, and carbon dioxide sources were used for each of the sets of the plates. Quality control steps were taken to ensure the proper production and quality of all tissue culture reagents: each component added to each bottle of media prepared for use was added by one designated person in one designated hood with only that reagent in the hood while a second designated person monitored to avoid mistakes. Conditions for liquid handling were set to eliminate cross contamination across wells. Fresh tips were used for all steps or stringent tip washing protocols were used. Liquid handling conditions were set for accurate volume transfer, efficient cell manipulation, washing cycles, pipetting speeds and locations, number of pipetting cycles for cell dispersal, and relative position of tip to plate.

Step 10: Freezing early passage stocks of populations of cells

[0281] Three sets of plates were frozen at -70 to -80°C. Plates in the set were first allowed to attain confluencies of 70 to 100%. Medium was aspirated and 90%FBS and 10% DMSO was added. The plates were individually sealed with Parafilm, individually surrounded by 1 to 5cm of foam, and then placed into a -80°C freezer.

Step 11: Methods and conditions for initial transformative steps to produce viable, stable and functional (VSF) cell lines

[0282] The remaining set of plates was maintained as described in step 9. All cell splitting was performed using automated liquid handling steps, including media removal, cell washing, trypsin addition and incubation, quenching and cell dispersal steps.

Step 12: Normalization methods to correct any remaining variability of growth rates

[0283] The consistency and standardization of cell and culture conditions for all populations of cells was controlled. Differences across plates due to slight

differences in growth rates were controlled by normalization of cell numbers across plates and occurred every 8 passages after the rearray. Populations of cells that were outliers were detected and eliminated.

Step 13: Characterization of population of cells

[0284] The cells were maintained for 6 to 10 weeks post rearray in culture to allow for their *in vitro* evolution under these conditions. During this time, we observed size, morphology, tendency towards microconfluency, fragility, response to trypsinization and average circularity post-trypsinization, or other aspects of cell maintenance such as adherence to culture plate surfaces and resistance to blow-off upon fluid addition.

Step 14: Assessment of potential functionality of populations of cells under VSF conditions

[0285] Populations of cells were tested using functional criteria. Membrane potential dye kits (Molecular Devices, MDS) were used according to manufacturer's instructions.

[0286] Cells were tested at varying densities in 384-well plates (*i.e.*, 12.5 x 10^3 to 20 x 10^3 cells/per well) and responses were analyzed. Time between cell plating and assay read was tested. Dye concentration was also tested. Dose response curves and Z' scores were both calculated as part of the assessment of potential functionality.

[0287] The following steps (*i.e.*, steps 15 -18) can also be conducted to select final and back-up viable, stable and functional cell lines.

Step 15:

[0288] The functional responses from experiments performed at low and higher passage numbers are compared to identify cells with the most consistent responses over defined periods of time (*e.g.*, 3 – 9 weeks). Other characteristics of the cells that change over time are also noted.

Step 16:

[0289] Populations of cells meeting functional and other criteria are further evaluated to determine those most amenable to production of viable, stable and

functional cell lines. Selected populations of cells are expanded in larger tissue culture vessels and the characterization steps described above are continued or repeated under these conditions. At this point, additional standardization steps, such as different cell densities; time of plating, length of cell culture passage; cell culture dishes format and coating; fluidics optimization, including speed and shear force; time of passage; and washing steps, are introduced for consistent and reliable passages.

[0290] In addition, viability of cells at each passage is determined. Manual intervention is increased and cells are more closely observed and monitored. This information is used to help identify and select final cell lines that retain the desired properties. Final cell lines and back-up cell lines are selected that show appropriate adherence/stickiness, growth rate, and even plating (lack of microconfluency) when produced following this process and under these conditions.

Step 17: Establishment of cell banks

[0291] The low passage frozen stocks corresponding to the final cell line and back-up cell lines are thawed at 37°C, washed two times with Ham's F12-FBS and then incubated in Ham's F12-FBS. The cells are then expanded for a period of 2 to 4 weeks. Cell banks of clones for each final and back-up cell line are established, with 25 vials for each clonal cells being cryopreserved.

Step 18:

[0292] At least one vial from the cell bank is thawed and expanded in culture. The resulting cells are tested to determine if they meet the same characteristics for which they are originally selected.

Example 13 Characterizing Stable Cell Lines for Native CFTR Function

[0293] We used a high-throughput compatible fluorescence membrane potential assay to characterize native CFTR function in the produced stable CFTR-expressing cell lines.

[0294] CHO cell lines stably expressing CFTR were maintained under standard cell culture conditions in Ham's F12 medium supplemented with 10% fetal bovine serum and glutamine. On the day before assay, the cells were harvested from stock plates and plated into black clear-bottom 384 well assay plates. The assay plates

were maintained in a 37°C cell culture incubator under 5% CO_2 for 22-24 hours. The media was then removed from the assay plates and blue membrane potential dye (Molecular Devices Inc.) diluted in loading buffer (137 mM NaCl, 5 mM KCl, 1.25 mM $CaCl_2$, 25 mM HEPES, 10 mM glucose) was added and allowed to incubate for 1 hour at 37°C. The assay plates were then loaded on a fluorescent plate reader (Hamamatsu FDSS) and a cocktail of forskolin and IBMX dissolved in compound buffer (137 mM sodium gluconate, 5 mM potassium gluconate, 1.25 mM $CaCl_2$, 25 mM HEPES, 10mM glucose) was added.

[0295] Representative data from the fluorescence membrane potential assay showed that the ion flux attributable to functional CFTR in stable CFTR-expressing CHO cell lines (cell line 1, M11, J5, E15, and O15) were all higher than control cells lacking CFTR as indicated by the assay response.

[0296] The ion flux attributable to functional CFTR in stable CFTR-expressing CHO cell lines (cell line 1, M11, J5, E15, and O15) were also all higher than transiently CFTR-transfected CHO cells. The transiently CFTR-transfected cells were generated by plating CHO cells at 5-16 million per 10cm tissue culture dish and incubating them for 18-20 hours before transfection. A transfection complex consisting of lipid transfection reagent and plasmids encoding CFTR was directly added to each dish. The cells were then incubated at 37°C in a CO_2 incubator for 6-12 hours. After incubation, the cells were lifted, plated into black clear-bottom 384 well assay plates, and assayed for function using the above-described fluorescence membrane potential assay.

[0297] For forskolin dose-response experiments, cells of the produced stable CFTR-expressing cell lines, plated at a density of 15,000 cells/well in a 384-well plate were challenged with increasing concentration of forskolin, a known CFTR agonist. The cellular response as a function of changes in cell fluorescence was monitored over time by a fluorescent plate reader (Hamamatsu FDSS). Data were then plotted as a function of forskolin concentration and analyzed using non-linear regression analysis using GraphPad Prism 5.0 software, resulting in an EC_{50} of 256 nM. The produced CFTR-expressing cell line shows a EC_{50} value of forskolin within the ranges of EC_{50} if forskolin previously reported in other cell lines (between 250 and 500 nM) (Galietta *et al.*, Am J Physiol Cell Physiol. 281(5): C1734-1742 (2001)), indicating the potency of the clone.

Example 14 Determination of Z' Value for CFTR Cell-Based Assay

[0298] Z' value for the produced stable CFTR-expressing cell line was calculated using a high-throughput compatible fluorescence membrane potential assay. The fluorescence membrane potential assay protocol was performed substantially according to the protocol in **Example 13**. Specifically for the Z' assay, 24 positive control wells in a 384-well assay plate (plated at a density of 15,000 cells/well) were challenged with a CFTR activating cocktail of forskolin and IBMX. An equal number of wells were challenged with vehicle alone and containing DMSO (in the absence of activators). Cell responses in the two conditions were monitored using a fluorescent plate reader (Hamamatsu FDSS). Mean and standard deviations in the two conditions were calculated and Z' was computed using the method disclosed in Zhang *et al.*, J Biomol Screen, 4(2): 67-73, (1999). The Z' value of the produced stable CFTR-expressing cell line was determined to be higher than or equal to 0.82.

Example 15 High-Throughput Screening and Identification of CFTR Modulators

[0299] A high-throughput compatible fluorescence membrane potential assay is used to screen and identify CFTR modulator. On the day before assay, the cells are harvested from stock plates into growth media without antibiotics and plated into black clear-bottom 384 well assay plates. The assay plates are maintained in a 37°C cell culture incubator under 5% CO_2 for 19-24 hours. The media is then removed from the assay plates and blue membrane potential dye (Molecular Devices Inc.) diluted in load buffer (137 mM NaCl, 5 mM KCl, 1.25 mM $CaCl_2$, 25 mM HEPES, 10 mM glucose) is added and the cells are incubated for 1 hr at 37°C. Test compounds are solubilized in dimethylsulfoxide, diluted in assay buffer (137 mM sodium gluconate, 5 mM potassium gluconate, 1.25 mM $CaCl_2$, 25 mM HEPES, 10mM glucose) and then loaded into 384 well polypropylene micro-titer plates. The cell and compound plates are loaded into a fluorescent plate reader (Hamamatsu FDSS) and run for 3 minutes to identify test compound activity. The instrument will then add a forskolin solution at a concentration of 300 nM – 1 μM to the cells to allow either modulator or blocker activity of the previously added compounds to be observed. The activity of the compound is determined by measuring the change in fluorescence produced following the addition of the test compounds to the cells and/or following the subsequent agonist addition.

Example 16 Characterizing Stable CFTR-Expressing Cell Lines for Native CFTR Function using Short-Circuit Current Measurements

[0300] Ussing chamber experiments are performed 7–14 days after plating CFTR-expressing cells (primary or immortalized epithelial cells including but not limited to lung and intestinal) on culture inserts (Snapwell, Corning Life Sciences). Cells on culture inserts are rinsed, mounted in an Ussing type apparatus (EasyMount Chamber System, Physiologic Instruments) and bathed with continuously gassed Ringer solution (5% CO_2 in O_2, pH 7.4) maintained at 37°C containing 120 mM NaCl, 25 mM $NaHCO_3$, 3.3 mM KH_2PO_4, 0.8 mM K_2HPO_4, 1.2 mM $CaCl_2$, 1.2 mM $MgCl_2$, and 10 mM glucose. The hemichambers are connected to a multichannel voltage and current clamp (VCC-MC8 Physiologic Instruments). Electrodes [agar bridged (4% in 1 M KCl) Ag-AgCl] are used and the inserts are voltage clamped to 0 mV. Transepithelial current, voltage and resistance are measured every 10 seconds for the duration of the experiment. Membranes with a resistance of < 200 mΩs are discarded.

Example 17 Characterizing Stable CFTR-expressing Cell Lines for Native CFTR Function using Electrophysiological Assay

[0301] While both manual and automated electrophysiology assays have been developed and both can be applied to assay this system, described below is the protocol for manual patch clamp experiments.

[0302] Cells are seeded at low densities and are used 2–4 days after plating. Borosilicate glass pipettes are fire-polished to obtain tip resistances of 2–4 mega Ω. Currents are sampled and low pass filtered. The extracellular (bath) solution contains: 150 mM NaCl, 1 mM $CaCl_2$, 1 mM $MgCl_2$, 10 mM glucose, 10 mM mannitol, and 10 mM TES, pH 7.4. The pipette solution contains: 120 mM CsCl, 1 mM $MgCl_2$, 10 mM TEA-Cl, 0.5 mM EGTA, 1 mM Mg-ATP, and 10 mM HEPES (pH 7.3). Membrane conductances are monitored by alternating the membrane potential between -80 mV and -100 mV. Current-voltage relationships are generated by applying voltage pulses between -100 mV and +100 mV in 20-mV steps.

Example 18 Generating a Stable NaV 1.7 Heterotrimer-Expressing Cell Line

Generating Expression Constructs

[0303] Plasmid expression vectors that allowed streamlined cloning were generated based on pCMV-SCRIPT (Stratagene) and contained various necessary components for transcription and translation of a gene of interest, including: CMV and SV40 eukaryotic promoters; SV40 and HSV-TK polyadenylation sequences; multiple cloning sites; Kozak sequences; and Neomycin/Kanamycin resistance cassettes (or Ampicillin, Hygromycin, Puromycin, Zeocin resistance cassettes).

Generation of Cell Lines

Step 1: Transfection

[0304] 293T cells were cotransfected with three separate plasmids, one encoding a human NaV 1.7 α subunit (SEQ ID NO: NAV-1), one encoding a human NaV 1.7 β1 subunit (SEQ ID NO: NAV-2) and one encoding a human NaV 1.7 β2 subunit (SEQ ID NO: NAV-3), using standard techniques. (Examples of reagents that may be used to introduce nucleic acids into host cells include, but are not limited to, LIPOFECTAMINE™, LIPOFECTAMINE™ 2000, OLIGOFECTAMINE™, TFX™ reagents, FUGENE® 6, DOTAP/DOPE, Metafectine or FECTURIN™.)

[0305] Although drug selection is optional to produce the cells or cell lines of this invention, we included one drug resistance marker per plasmid. The sequences were under the control of the CMV promoter. An untranslated sequence encoding a NaV Target Sequence for detection by a signaling probe was also present along with the sequence encoding the drug resistance marker. The NaV Target Sequences utilized were NaV Target Sequence 1 (SEQ ID NO: NAV-4), NaV Target Sequence 2 (SEQ ID NO: NAV-5) and NaV Target Sequence 3 (SEQ ID NO: NAV-6). In this example, the NaV 1.7 α subunit gene-containing vector comprised NaV Target Sequence 1 (SEQ ID NO: NAV-4); the NaV 1.7 β1 subunit gene-containing vector comprised NaV Target Sequence 2 (SEQ ID NO: NAV-5); and the NaV 1.7 β2 subunit gene-containing vector comprised NaV Target Sequence 3 (SEQ ID NO: NAV-6).

Step 2: Selection

[0306] Transfected cells were grown for 2 days in DMEM-FBS media, followed by 10 days in antibiotic-containing DMEM-FBS media. During the antibiotic containing period, antibiotics were added to the media as follows: puromycin (0.1 μg/ml), hygromycin (100 μg/ml), and zeocin (200 μg/ml).

Step 3: Cell passaging

[0307] Following enrichment on antibiotic, cells were passaged 6-18 times in the absence of antibiotic selection to allow time for expression that was not stable over the selected period of time to subside.

Step 4: Exposure of cells to fluorogenic probes

[0308] Cells were harvested and transfected with signaling probes (SEQ ID NOS: NaV-7, NaV-8, NaV-9) using standard techniques. (Examples of reagents that may be used to introduce nucleic acids into host cells include, but are not limited to, LIPOFECTAMINE™, LIPOFECTAMINE™ 2000, OLIGOFECTAMINE™, TFX™ reagents, FUGENE® 6, DOTAP/DOPE, Metafectine or FECTURIN™.)

[0309] NaV Signaling Probe 1(SEQ ID NO: NAV-7) bound NaV Target Sequence 1 (SEQ ID NO: NAV-4); NaV Signaling Probe 2 (SEQ ID NO: NAV-8) bound NaV Target Sequence 2 (SEQ ID NO: NAV-5); and NaV Signaling Probe 3 (SEQ ID NO: NAV-9) bound NaV Target Sequence 3 (SEQ ID NO: NAV-6). The cells were then dissociated and collected for analysis and sorted using a fluorescence activated cell sorter.

[0310] **Target Sequences detected by signaling probes**

The following tag sequences were used for the NaV 1.7 subunit transgenes.

NaV Target Sequence 1

5'-GTTCTTAAGGCACAGGAACTGGGAC-3' (SEQ ID NO: NAV-4) (NaV 1.7 α subunit)

NaV Target Sequence 2

5'-GAAGTTAACCCTGTCGTTCTGCGAC-3' (SEQ ID NO: NAV-5) (NaV 1.7 β1 subunit)

NaV Target Sequence 3

5'-GTTCTATAGGGTCTGCTTGTCGCTC-3' (SEQ ID NO: NAV-6) (NaV 1.7 β2 subunit)

[0311] **Signaling probes**

Supplied as 100 μM stocks.

NaV Signaling probe 1 - This probe binds target sequence 1.

5' - Cy5 GCCAGTCCCAGTTCCTGTGCCTTAAGAACCTCGC **BHQ3 quench -3'** (SEQ ID NO: NAV-7)

NaV Signaling probe 2 – This probe binds target sequence 2.

5'- Cy5.5 CGAGTCGCAGAACGACAGGGTTAACTTCCTCGC **BHQ3 quench -3' (**SEQ ID NO: NAV-8)

NaV Signaling probe 3 – This probe binds target sequence 3.

5'- Fam CGAGAGCGACAAGCAGACCCTATAGAACCTCGC **BHQ1 quench - 3' (**SEQ ID NO: NAV-9)

[0312] BHQ3 in NaV Signaling probes 1 and 2 can be replaced by BHQ2 or gold particle. BHQ1 in NaV Signaling probe 3 can be replaced by BHQ2, gold particle, or DABCYL.

[0313] In addition, a similar probe using a Quasar® Dye (BioSearch) with spectral properties similar to Cy5 was used in certain experiments. In some experiments, 5-MedC and 2-amino dA mixmer probes were used rather than DNA probes.

Step 5: Isolation of positive cells

[0314] Standard analytical methods were used to gate cells fluorescing above background and to isolate cells falling within the defined gate directly into 96-well plates. Flow cytometric cell sorting was operated such that a single cell was deposited per well. After selection, the cells were expanded in media lacking drug. The following gating hierarchy was used:

coincidence gate → singlets gate → live gate → Sort gate in plot FAM vs. Cy5: 0.1 – 1.0% of live cells.

Step 6: Additional cycles of steps 1-5 and/or 3-5

[0315] Steps 1-5 and/or 3-5 were repeated to obtain a greater number of cells. At least four independent rounds of steps 1-5 were completed, and for each of these cycles, at least two internal cycles of steps 3-5 were performed for each independent round.

Step 7: Estimation of growth rates for the populations of cells

[0316] The plates were transferred to a Microlabstar automated liquid handler (Hamilton Robotics). Cells were incubated for 5-7 days in a 1:1 mix of fresh complete growth medium (DMEM/10% FBS) and 2-3 day conditioned growth medium, supplemented with 100 units/ml penicillin and 0.1mg/ml streptomycin. Then the cells were dispersed by trypsinization to minimize clumps and transferred to new 96-well plates. After the clones were dispersed, plates were imaged to determine confluency of wells (Genetix). Each plate was focused for reliable image acquisition across the plate. Reported confluencies of greater than 70% were not relied upon. Confluency measurements were obtained at days every 3 times over 9 days (*i.e*, between days 1 and 10 post-dispersal) and used to calculate growth rates.

Step 8: Binning populations of cells according to growth rate estimates

[0317] Cells were binned (independently grouped and plated as a cohort) according to growth rate between 10-11 days following the dispersal step in step 7. Bins were independently collected and plated on individual 96 well plates for downstream handling; some growth bins resulted in more than one 96-well plate. Bins were calculated by considering the spread of growth rates and bracketing a high percentage of the total number of populations of cells. Depending on the sort iteration described in Step 5, between 5 and 9 growth bins were used with a partition of 1- 4 days. Therefore, each bin corresponded to a growth rate or population doubling time between 8 and 14.4 hours depending on the iteration.

[0318] Cells can have doubling times from less 1 day to more than 2 weeks. In order to process the most diverse clones that at the same time can be reasonably binned according to growth rate, it is preferable to use 3-9 bins with a 0.25 to 0.7 day doubling time per bin. One skilled in the art will appreciate that the tightness of the bins and number of bins can be adjusted for the particular situation and that the tightness and number of bins can be further adjusted if cells are synchronized for their cell cycle.

Step 9: Replica plating to speed parallel processing and provide stringent quality control

[0319] The plates were incubated under standard and fixed conditions (humidified 37°C, 5%CO2) in antibiotics-free DMEM-10%FBS media. The plates of cells were split to produce 4 sets of target plates. These 4 sets of plates comprised all plates with all growth bins to ensure there were 4 replicates of the initial set. Up to 3 target plate sets were committed for cryopreservation (described in step 10), and the remaining set was scaled and further replica plated for passage and functional assay experiments. Distinct and independent tissue culture reagents, incubators, personnel, and carbon dioxide sources were used for downstream replica plates. Quality control steps were taken to ensure the proper production and quality of all tissue culture reagents: each component added to each bottle of media prepared for use was added by one designated person in one designated hood with only that reagent in the hood while a second designated person monitored to avoid mistakes. Conditions for liquid handling were set to eliminate cross contamination across wells. Fresh tips were used for all steps, or stringent tip washing protocols were used. Liquid handling conditions were set for accurate volume transfer, efficient cell manipulation, washing cycles, pipetting speeds and locations, number of pipetting cycles for cell dispersal, and relative position of tip to plate.

Step 10: Freezing early passage stocks of populations of cells

[0320] Three sets of plates were frozen at -70 to -80°C. Plates in each set were first allowed to attain confluencies of 70 to 80%. Medium was aspirated and 90%FBS and 5%-10% DMSO was added. The plates were sealed with Parafilm, individually surrounded by 1 to 5cm of foam, and then placed into a -80°C freezer.

Step 11: Methods and conditions for initial transformative steps to produce viable, stable and functional (VSF) cell lines

[0321] The remaining set of plates was maintained as described in step 9. All cell splitting was performed using automated liquid handling steps, including media removal, cell washing, trypsin addition and incubation, quenching and cell dispersal steps. For some assay plating steps, cells were dissociated with cell dissociation buffer (*e.g.*, CDB, Invitrogen or CellStripper, CellGro) rather than trypsin.

Step 12: Normalization methods to correct any remaining variability of growth rates

[0322] The consistency and standardization of cell and culture conditions for all populations of cells was controlled. Differences across plates due to slight differences in growth rates were controlled by periodic normalization of cell numbers across plates every 2 to 8 passages. Populations of cells that were outliers were detected and eliminated.

Step 13: Characterization of population of cells

[0323] The cells were maintained for 3 to 8 weeks to allow for their *in vitro* evolution under these conditions. During this time, we observed size, morphology, fragility, response to trypsinization or dissociation, roundness/average circularity post-dissociation, percentage viability, tendency towards microconfluency, or other aspects of cell maintenance such as adherence to culture plate surfaces.

Step 14: Assessment of potential functionality of populations of cells under VSF conditions

[0324] Populations of cells were tested using functional criteria. Membrane potential assay kits (Molecular Devices/MDS) were used according to manufacturer's instructions. Cells were tested at multiple different densities in 96- or 384-well plates and responses were analyzed. A variety of post-plating time points were used, *e.g.*, 12-48 hours post plating. Different densities of plating were also tested for assay response differences.

Step 15:

[0325] The functional responses from experiments performed at low and higher passage numbers were compared to identify cells with the most consistent responses over defined periods of time, ranging from 3 to 9 weeks. Other characteristics of the cells that changed over time were also noted.

Step 16:

[0326] Populations of cells meeting functional and other criteria were further evaluated to determine those most amenable to production of viable, stable and functional cell lines. Selected populations of cells were expanded in larger tissue culture vessels and the characterization steps described above were continued or repeated under these conditions. At this point, additional standardization steps, such

as different plating cell densities; time of passage; culture dish size/format and coating); fluidics optimization; cell dissociation optimization (*e.g.*, type, volume used, and length of time); and washing steps, were introduced for consistent and reliable passages. Temperature differences were also used for standardization (*i.e.*, 30°C vs 37°C).

[0327] In addition, viability of cells at each passage was determined. Manual intervention was increased and cells were more closely observed and monitored. This information was used to help identify and select final cell lines that retained the desired properties. Final cell lines and back-up cell lines were selected that showed consistent growth, appropriate adherence, and functional response.

Step 17: Establishment of cell banks

[0328] The low passage frozen plates described above corresponding to the final cell line and back-up cell lines were thawed at 37°C, washed two times with DMEM-10% FBS and incubated in humidified 37°C /5% CO2 conditions. The cells were then expanded for a period of 2-3 weeks. Cell banks for each final and back-up cell line consisting of 15-20 vials were established.

Step 18:

[0329] The following step can also be conducted to confirm that the cell lines are viable, stable, and functional. At least one vial from the cell bank is thawed and expanded in culture. The resulting cells are tested to determine if they meet the same characteristics for which they were originally selected.

Example 19 Characterizing Relative Expression of Heterologous NaV 1.7 Subunits in Stable NaV 1.7-Expressing Cell Lines

[0330] Quantitative RT-PCR (qRT-PCR) was used to determine the relative expression of the heterologous human NaV 1.7 α, β1, and β2 subunits in the produced stable NaV 1.7-expressing cell lines. Total RNA was purified from 1-3x10^6 mammalian cells using an RNA extraction kit (RNeasy Mini Kit, Qiagen). DNase treatment was done according to rigorous DNase treatment protocol (TURBO DNA-free Kit, Ambion). First strand cDNA synthesis was performed using a reverse transcriptase kit (SuperScript III, Invitrogen) in 20 µL reaction volume with 1 µg DNA-free total RNA and 250 ng Random Primers (Invitrogen). Samples without reverse

transcriptase and sample without RNA were used as negative controls for this reaction. Synthesis was done in a thermal cycler (Mastercycler, Eppendorf) at the following conditions: 5 min at 25°C, 60 min at 50°C; reaction termination was conducted for 15 min at 70°C.

[0331] For analysis of gene expression, primers and probes for qRT-PCR (MGB TaqMan probes, Applied Biosystems) were designed to specifically anneal to the target sequences (SEQ ID NOS: NaV-4, NaV-5, NaV-6). For sample normalization, control (glyceraldehyde 3-phosphate dehydrogenase (GAPDH)) Pre-Developed Assay reagents (TaqMaN, Applied Biosystems) were used. Reactions, including negative controls and positive controls (plasmid DNA), were set up in triplicates with 40 ng of cDNA in 50 µL reaction volume. The relative amounts of each of the three NaV 1.7 subunits being expressed were determined. All three subunits were successfully expressed in the produced stable NaV 1.7-expressing cell line.

Example 20 Characterizing Stable NaV 1.7-Expressing Cell Lines for Native NaV Function using Electrophysiological Assay

[0332] Automated patch-clamp system was used to record sodium currents from the produced stable HEK293T cell lines expressing NaV 1.7 α, $\beta 1$, and $\beta 2$ subunits. The following illustrated protocol can also be used for QPatch, Sophion or Patchliner, Nanion systems. The extracellular Ringer's solution contained 140 mM NaCl, 4.7 mM KCl, 2.6 mM $MgCl_2$, 11 mM glucose and 5 mM HEPES, pH 7.4 at room temperature. The intracellular Ringer's solution contained 120 mM CsF, 20 mM Cs-EGTA, 1 mM $CaCl_2$, 1 mM $MgCl_2$, and 10 mM HEPES, pH 7.2. Experiments were conducted at room temperature.

[0333] Cells stably expressing NaV 1.7 α, $\beta 1$, and $\beta 2$ subunits were grown under standard culturing protocols as described in **Example 18**. Cells were harvested and kept in suspension with continuous stirring for up to 4 hours with no significant change in quality or ability to patch. Electrophysiological experiment (whole-cell) was performed using the standard patch plate. The patch-clamp hole (micro-etched in the chip) is approximately 1 µm in diameter and has a resistance of ~2 MΩ. The membrane potential was clamped to a holding potential of -100 mV.

[0334] Current-voltage relation and inactivation characteristics of voltage-gated human NaV 1.7 sodium channel stably expressed in HEK293T cells were

characterized. Sodium currents were measured in response to 20 ms depolarization pulses from - 80 mV to +50 mV with a holding potential of -100 mV. The resulting current-voltage (I-V) relationship for peak sodium channel currents was characterized. The activation threshold was - 35 mV (midpoint of activation, Va = - 24.9 mV +/- 3.7 mV), and the maximal current amplitude was obtained at -10 mV. The inactivation graph for the sodium channel was plotted. The membrane potential was held at a holding potential of - 100 mV, subsequently shifted to conditioning potentials ranging from -110 mV to +10 mV for 1000 ms, and finally the current was measured upon a step to 0 mV. The resulting current amplitude indicates the fraction of sodium channels in the inactivated state. At potentials more negative than - 85 mV the channels were predominantly in the closed state, whereas at potentials above -50 mV they were predominantly in the inactivated state. The curve represents the Boltzmann fit from which the $V_{1/2}$ for steady-state inactivation was estimated to be - 74 mV. The current-voltage profile for the produced stable NaV 1.7-expressing cell lines is consistent with previously reported current-voltage profile (Va= - 28.0 mV ±1.1 mV; $V_{1/2}$ = -71.3 mV ± 0.8 mV) (Sheets *et al.*, J Physiol. 581(Pt 3):1019-1031. (2007)).

Example 21 Characterizing Stable NaV 1.7-Expressing Cell Lines for Native NaV Function using Membrane Potential Assay

[0335] The produced stable cells expressing NaV 1.7 α, $\beta 1$, and $\beta 2$ subunits were maintained under standard cell culture conditions in Dulbecco's Modified Eagles medium supplemented with 10% fetal bovine serum, glutamine and HEPES. On the day before assay, the cells were harvested from stock plates using cell dissociation buffer, *e.g.*, CDB (GIBCO) or cell-stripper (Mediatech), and plated at 10, 000 - 25,000 cells per well in 384 well plates in growth media. The assay plates were maintained in a 37°C cell culture incubator under 5%CO2 for 22-24 hours. The media were then removed from the assay plates and blue fluorescence membrane potential dye (Molecular Devices Inc.) diluted in load buffer (137 mM NaCl, 5 mM KCl,1.25 mM $CaCl_2$, 25 mM HEPES, 10 mM glucose) was added. The cells were incubated with blue membrane potential dye for 1 hour at 37°C. The assay plates were then loaded onto the high-throughput fluorescent plate reader (Hamamastu

FDSS). The fluorescent plate reader measures cell fluorescence in images taken of the cell plate once per second and displays the data as relative florescence units.

[0336] The assay response of stable NaV 1.7-expressing cells and control cells (*i.e.*, HEK293T parental cells) to addition of buffer and channel activators (*i.e.*, veratridine and scorpion venom (SV)) were measured. In a first addition step (*i.e.*, Addition 1), only buffer was added, with no test compounds added. If desired, test compounds can be added in this step. In a second addition step, veratridine and scorpion venom, which are sodium channels activators, were diluted in assay buffer to the desired concentration (*i.e.*, 25 μM veratridine and 5 – 25 μg/ml scorpion venom) and added into 384 well polypropylene microtiter plates. Once bound, veratridine and scorpion venom proteins modulate the activity of voltage-gated sodium channels through a combination of mechanisms, including an alteration of the activation and inactivation kinetics. The resulted activation of sodium channels in stable NaV 1.7-expressing cells changes cells membrane potential and the fluorescent signal increases. The above-described functional assay can also be used to characterize the relative potencies of test compounds at NaV 1.7 ion channels.

Example 22 Characterizing Regulation of NaV 1.7 Alpha Subunit by Beta Subunits

Regulation of Alpha Subunit Gene Expression by Beta Subunits

[0337] Pools of HEK293T cells were engineered to express various ratios of α and β subunits by manipulating the molar ratios of independent plasmid DNAs or α and control plasmids (*e.g.*, α:β1:β2 = 1:1:1). After drug selection the subunits expression in six different cell pools were evaluated with qRT-PCR as described in **Example 19**. Comparative qRT-PCR indicated that α subunit expression in drug-selected cells detection was increased when all three human NaV 1.7 subunits (*i.e.*, α, β1, and β2) were co-transfected in compared to only α subunit and control plasmid transfected. The presence of the β subunit transcripts affects α subunit gene expression, demonstrating the importance of co-expressing all three NaV 1.7 subunits for a physiologically relevant functional assay.

Regulation of Pharmacological Properties by Beta Subunits

[0338] A membrane potential cell-based assay was used to measure the response to test compounds of the cells stably co-expressing all three NaV 1.7 subunits (*i.e.,* α, β1, and β2) and control cells stably expressing only a NaV 1.7 α subunit. Two compounds (*i.e.*, C18 and K21) were tested in the membrane potential assay performed substantially according to the protocol in **Example 21**. Specifically for this example, the test compounds were added in the first addition step.

[0339] C18 and K21 potentiated the response of clone C44 (expressing NaV 1.7 α, β1, and β2 subunits) and blocked the response of clone C60 (expressing NaV 1.7 α subunit only). The assay response of the two test compounds was normalized to the response of buffer alone for each of the two clones.

Table 2 Mammalian G proteins, their families and descriptions

Class	Family/*Subtype*	Protein # (UniProt)	Description
G-alpha	**G_s**		
	Gs	P04896	Galpha-s-Bos taurus
	Gs	P16052	Galpha-s-Cricetulus longicaudatus
	Gs	P63092	Galpha-s-Homo sapiens-2
	Gs	P63091	Galpha-s-Canis familiaris
	Gs	P63093	Galpha-s-Mesocricetus auratus
	Gs	P63094	Galpha-s-Mus musculus-2
	Gs	P63095	Galpha-s-Rattus norvegicus-2
	Gs	P29797	Galpha-s-Sus scrofa
	Gs	O60726	Galpha-s-Homo sapiens-4
	Gs	O75632	Galpha-s-Homo sapiens-5
	Gs	O75633	Galpha-s-Homo sapiens-6
	Gs	Q14433	Galpha-s-Homo sapiens-7
	Gs	Q14455	Galpha-s-Homo sapiens
	Gs	Q8R4A8	Galpha-s-Cricetulus griseus
	Gs	Q9JJ33	Galpha-s-Mus musculus
	Gs	Q9JLG1	Galpha-s-Rattus norvegicus-1
	Gs	Q5JWF2	Galpha-s-Homo sapiens-3
	Golf	P38405	Galpha-olf-Homo sapiens-2
	Golf	Q8CGK7	Galpha-olf-Mus musculus
	Golf	P38406	Galpha-olf-Rattus norvegicus
	Golf	Q86XU3	Galpha-olf-Homo sapiens-1
	$G_{i/o}$		
	Gi	Q29047	Galpha-i-Sus scrofa
	Gi1	P38401	Galpha-i1-Cavia porcellus
	Gi1	P50146	Galpha-i1-Gallus gallus
	Gi1	P63096	Galpha-i1-Homo sapiens-1
	Gi1	P63097	Galpha-i1-Bos taurus
	Gi1	P10824	Galpha-i1-Rattus norvegicus
	Gi1	O43383	Galpha-i1-Homo sapiens-2
	Gi1	Q61018	Galpha-i1-Mus musculus
	Gi2	P38400	Galpha-i2-Canis familiaris
	Gi2	P38402	Galpha-i2-Cavia porcellus
	Gi2	P50147	Galpha-i2-Gallus gallus
	Gi2	P04899	Galpha-i2-Homo sapiens-2
	Gi2	P08752	Galpha-i2-Mus musculus-2
	Gi2	P04897	Galpha-i2-Rattus norvegicus
	Gi2	Q7M3G8	Galpha-i2-Sus scrofa
	Gi2	Q7M3G9	Galpha-i2-Bos taurus-2
	Gi2	Q7M3H0	Galpha-i2-Bos taurus-1
	Gi2	Q8JZT4	Galpha-i2-Mus musculus-1
	Gi2	Q96C71	Galpha-i2-Homo sapiens-1
	Gi3	P38403	Galpha-i3-Cavia porcellus
	Gi3	Q60397	Galpha-i3-Cricetulus griseus
	Gi3	P08754	Galpha-i3-Homo sapiens
	Gi3	P08753	Galpha-i3-Rattus norvegicus
	Gi3	Q9DC51	Galpha-i3-Mus musculus
	Go	P59215	Galpha-o-Rattus norvegicus

	Go	Q8N6I9	Galpha-o-Homo sapiens
	Go1	P08239	Galpha-o1-Bos taurus
	Go1	P59216	Galpha-o1-Cricetulus longicaudatus
	Go1	P09471	Galpha-o1-Homo sapiens
	Go1	P18872	Galpha-o1-Mus musculus
	Gz	P19086	Galpha-z-Homo sapiens-2
	Gz	O70443	Galpha-z-Mus musculus
	Gz	P19627	Galpha-z-Rattus norvegicus
	Gz	Q8IY73	Galpha-z-Homo sapiens-3
	Gz	Q8N652	Galpha-z-Homo sapiens-1
	Gz	Q95LC0	Galpha-z-Sus scrofa
	Gt	Q16162	Galpha-t-Homo sapiens
	Gt	Q9D7B3	Galpha-t-Mus musculus
	Gt1	P04695	Galpha-t1-Bos taurus
	Gt1	Q28300	Galpha-t1-Canis familiaris
	Gt1	P11488	Galpha-t1-Homo sapiens
	Gt1	P20612	Galpha-t1-Mus musculus
	Gt2	P04696	Galpha-t2-Bos taurus
	Gt2	P19087	Galpha-t2-Homo sapiens
	Gt2	P50149	Galpha-t2-Mus musculus-2
	Gt2	Q8BSY7	Galpha-t2-Mus musculus-1
	Ggust	P29348	Galpha-gust-Rattus norvegicus
	$G_{q/11}$		
	Gq	Q6NT27	Galpha-q-Homo sapiens-2
	Gq	Q28294	Galpha-q-Canis familiaris
	Gq	P50148	Galpha-q-Homo sapiens-1
	Gq	P21279	Galpha-q-Mus musculus
	Gq	P82471	Galpha-q-Rattus norvegicus
	G11	Q71RI7	Galpha-11-Gallus gallus
	G11	P38409	Galpha-11-Bos taurus
	G11	P52206	Galpha-11-Canis familiaris
	G11	P29992	Galpha-11-Homo sapiens
	G11	P45645	Galpha-11-Meleagris gallopavo
	G11	P21278	Galpha-11-Mus musculus-2
	G11	Q9JID2	Galpha-11-Rattus norvegicus
	G11	Q8SPP3	Galpha-11-Macaca mulatta
	G11	Q91X95	Galpha-11-Mus musculus-1
	G14	P38408	Galpha-14-Bos taurus
	G14	O95837	Galpha-14-Homo sapiens
	G14	P30677	Galpha-14-Mus musculus-2
	G14	Q8C3M7	Galpha-14-Mus musculus-3
	G14	Q8CBT5	Galpha-14-Mus musculus-4
	G14	Q8R2X9	Galpha-14-Mus musculus-1
	G15	P30678	Galpha-15-Mus musculus
	G15	O88302	Galpha-15-Rattus norvegicus
	G16	P30679	Galpha-16-Homo sapiens
	$G_{12/13}$		
	G12	Q03113	Galpha-12-Homo sapiens
	G12	P27600	Galpha-12-Mus musculus
	G12	Q63210	Galpha-12-Rattus norvegicus
	G13	Q14344	Galpha-13-Homo sapiens

	G13	P27601	Galpha-13-Mus musculus-2
	G13	Q8C5L2	Galpha-13-Mus musculus-3
	G13	Q9D034	Galpha-13-Mus musculus-1
G-beta	**B_{1-5}**		
	B1	Q6TMK6	Gbeta-1-Cricetulus griseus
	B1	P62871	Gbeta-1-Bos taurus
	B1	P62872	Gbeta-1-Canis familiaris
	B1	P62873	Gbeta-1-Homo sapiens
	B1	P62874	Gbeta-1-Mus musculus
	B1	P54311	Gbeta-1-Rattus norvegicus-2
	B1	Q9QX36	Gbeta-1-Rattus norvegicus-1
	B2	P11017	Gbeta-2-Bos taurus
	B2	P62879	Gbeta-2-Homo sapiens
	B2	P62880	Gbeta-2-Mus musculus
	B2	P54313	Gbeta-2-Rattus norvegicus-2
	B2	Q9QX35	Gbeta-2-Rattus norvegicus-1
	B3	P79147	Gbeta-3-Canis familiaris
	B3	P16520	Gbeta-3-Homo sapiens-1
	B3	Q61011	Gbeta-3-Mus musculus
	B3	P52287	Gbeta-3-Rattus norvegicus
	B3	Q96B71	Gbeta-3-Homo sapiens-2
	B4	Q9HAV0	Gbeta-4-Homo sapiens
	B4	P29387	Gbeta-4-Mus musculus
	B4	O35353	Gbeta-4-Rattus norvegicus
	B5	O14775	Gbeta-5-Homo sapiens-2
	B5	P62881	Gbeta-5-Mus musculus-2
	B5	P62882	Gbeta-5-Rattus norvegicus
	B5	Q60525	Gbeta-5-Mesocricetus auratus
	B5	Q96F32	Gbeta-5-Homo sapiens-1
	B5	Q9CSQ0	Gbeta-5-Mus musculus-3
	B5	Q9CU21	Gbeta-5-Mus musculus-1
	$B_{unclassified}$		
	B unclassified	Q61621	unclassified_Gbeta-Mus musculus-1
	B unclassified	Q8BMQ1	unclassified_Gbeta-Mus musculus-2
	B unclassified	Q9UFT3	unclassified_Gbeta-Homo sapiens
G-gamma	**γ_{1-12}**		
	γ1	Q8R1U6	Ggamma-1-Mus musculus
	γ2	P59768	Ggamma-2-Homo sapiens
	γ2	P63212	Ggamma-2-Bos taurus
	γ2	P63213	Ggamma-2-Mus musculus
	γ2	O35355	Ggamma-2-Rattus norvegicus
	γ3	P63214	Ggamma-3-Bos taurus
	γ3	P63215	Ggamma-3-Homo sapiens
	γ3	P63216	Ggamma-3-Mus musculus
	γ3	O35356	Ggamma-3-Rattus norvegicus
	γ4	P50150	Ggamma-4-Homo sapiens
	γ4	P50153	Ggamma-4-Mus musculus
	γ4	O35357	Ggamma-4-Rattus norvegicus
	γ5	P63217	Ggamma-5-Bos taurus
	γ5	P63218	Ggamma-5-Homo sapiens-2

	γ5	Q80SZ7	Ggamma-5-Mus musculus
	γ5	P63219	Ggamma-5-Rattus norvegicus
	γ5	Q9Y3K8	Ggamma-5-Homo sapiens-1
	γ7	P30671	Ggamma-7-Bos taurus
	γ7	O60262	Ggamma-7-Homo sapiens
	γ7	Q61016	Ggamma-7-Mus musculus
	γ7	P43425	Ggamma-7-Rattus norvegicus
	γ8	Q9UK08	Ggamma-8-Homo sapiens-2
	γ8	P63078	Ggamma-8-Mus musculus-2
	γ8	P63077	Ggamma-8-Rattus norvegicus
	γ8	P50154	Ggamma-8-Bos taurus
	γ8	O14610	Ggamma-8-Homo sapiens-1
	γ8	Q61017	Ggamma-8-Mus musculus-1
	γ10	P50151	Ggamma-10-Homo sapiens-2
	γ10	O35358	Ggamma-10-Rattus norvegicus
	γ10	Q96BN9	Ggamma-10-Homo sapiens-1
	γ10	Q9CXP8	Ggamma-10-Mus musculus
	γ11	P61952	Ggamma-11-Homo sapiens
	γ11	P61953	Ggamma-11-Mus musculus
	γ11	P61954	Ggamma-11-Rattus norvegicus
	γ12	Q28024	Ggamma-12-Bos taurus
	γ12	Q9UBI6	Ggamma-12-Homo sapiens
	γ12	Q9DAS9	Ggamma-12-Mus musculus
	γ12	O35359	Ggamma-12-Rattus norvegicus
	γ13	Q9P2W3	Ggamma-13-Homo sapiens
	γ13	Q9JMF3	Ggamma-13-Mus musculus
	γt1	P02698	Ggamma-t1-Bos taurus
	γt1	P63211	Ggamma-t1-Homo sapiens
	γt1	P63210	Ggamma-t1-Canis familiaris
	γt1	Q61012	Ggamma-t1-Mus musculus
	$\gamma_{unclassified}$		
	γ unclassified	Q7M3H1	unclassified Ggamma-Bos indicus

Table 3 Human orphan GPCRs including their gene symbols and NCBI gene ID numbers

Family	Human Gene Symbol	Human Gene ID
Bombesin	BRS3	680
Free fatty acid	GPR42P	2866
N-Formylpeptide family	FPRL2	2359
Nicotinic acid	GPR81	27198
Opsin-like	OPN3	23596
OrphanA2	GPR52	9293
OrphanA2	GPR21	2844
OrphanA3	GPR78	27201
OrphanA3	GPR26	2849
OrphanA4	GPR37	2861
OrphanA4	GPR37L1	9283
OrphanA6	GPR63	81491
OrphanA6	GPR45	11250
OrphanA7	GPR83	10888
OrphanA9	GRCAe	27239

OrphanA9	GPR153	387509
OrphanA12	P2RY5	10161
OrphanA13	P2RY10	27334
OrphanA13	GPR174	84636
OrphanA14	GPR142	350383
OrphanA14	GPR139	124274
OrphanA15	ADMR	11318
OrphanA15	CMKOR1	57007
OrphanLGR	LGR4	55366
OrphanLGR	LGR5	8549
OrphanLGR	LGR6	59352
OrphanSREB	GPR85	54329
OrphanSREB	GPR27	2850
OrphanSREB	GPR173	54328
Orphan (chemokine receptor-like)	CCRL2	9034
Orphan (Mas-related)	MAS1	4142
Orphan (Mas-related)	MAS1L	116511
Orphan (Mas-related)	MRGPRE	116534
Orphan (Mas-related)	MRGPRF	116535
Orphan (Mas-related)	MRGPRG	386746
Orphan (Mas-related)	MRGX3e	117195
Orphan (Mas-related)	MRGX4e	117196
Orphan (melatonin-like)	GPR50	9248
Orphan (P2Y-like)	GPR87	53836
Orphan (trace amine-like)	TRAR3f	134860
Orphan (trace amine-like)	TRAR4	319100
Orphan (trace amine-like)	TRAR5	83551
Orphan (trace amine-like)	PNRe	9038
Orphan (trace amine-like)	GPR57g	9288
Orphan (trace amine-like)	GPR58	9287
Other orphan genes	EBI2	1880
Other orphan genes	GPR160	26996
Other orphan genes	GPRe	11245
Other orphan genes	GPR1	2825
Other orphan genes	GPR101	83550
Other orphan genes	GPR135	64582
Other orphan genes	OPN5	221391
Other orphan genes	GPR141	353345
Other orphan genes	GPR146	115330
Other orphan genes	GPR148	344561
Other orphan genes	GPR149	344758
Other orphan genes	GPR15	2838
Other orphan genes	GPR150	285601
Other orphan genes	GPR152	390212
Other orphan genes	GPR161	23432
Other orphan genes	GPR17	2840
Other orphan genes	GPR171	29909
Other orphan genes	GPR18	2841
Other orphan genes	GPR19	2842
Other orphan genes	GPR20	2843

Other orphan genes	GPR22	2845
Other orphan genes	GPR25	2848
Other orphan genes	GPR31	2853
Other orphan genes	GPR32	2854
Other orphan genes	GPR33	2856
Other orphan genes	GPR34	2857
Other orphan genes	GPR55	9290
Other orphan genes	GPR61	83873
Other orphan genes	GPR62	118442
Other orphan genes	GPR79h	27200
Other orphan genes	GPR82	27197
Other orphan genes	GPR84	53831
Other orphan genes	GPR88	54112
Other orphan genes	GPR92	57121
Other orphan genes	P2RY8	286530
Other orphan genes	GPR151	134391
LNB7TM	GPR64	10149
LNB7TM	GPR56	9289
LNB7TM	GPR115	221393
LNB7TM	GPR114	221188
LNB7TM:Brain specific angiogenesis inhibitor	BAI1	575
LNB7TM:Brain specific angiogenesis inhibitor	BAI2	576
LNB7TM:Brain specific angiogenesis inhibitor	BAI3	577
LNB7TM:Proto-cadherin	CELSR1	9620
LNB7TM:Proto-cadherin	CELSR2	1952
LNB7TM:Proto-cadherin	CELSR3	1951
LNB7TM:EGF, mucin-like receptor	EMR1	2015
LNB7TM:EGF, mucin-like receptor	EMR2	30817
LNB7TM	GPR97	222487
LNB7TM	GPR110	266977
LNB7TM	GPR111	222611
LNB7TM	GPR112	139378
LNB7TM	GPR113	165082
LNB7TM	GPR116	221395
LNB7TM	MASS1	84059
LNB7TM	ELTD1	64123
LNB7TM	GPR123	84435
LNB7TM	GPR124	25960
LNB7TM	GPR125	166647
LNB7TM	GPR126	57211
LNB7TM	GPR128	84873
LNB7TM	GPR144	347088
LNB7TM:EGF, mucin-like receptor	EMR3	84658
LNB7TM:EGF, mucin-like receptor	EMR4b	326342
LNB7TM	CD97	976
LNB7TM:Latrophilin substrate	LPHN2	23266
LNB7TM:Latrophilin substrate	LPHN3	23284
LNB7TM:Latrophilin substrate	LPHN1	22859

Unclassified	GPR157	80045
GABAB	GPR51	9568
GABAB	GPR156	165829
Calcium sensor	GPRC6A	222545
GPRC5	GPRC5A	9052
GPRC5	GPRC5B	51704
GPRC5	GPRC5C	55890
GPRC5	GPRC5D	55507
Unclassified	GPR158	57512
Unclassified	GPR158L1	342663

Table 4 Human opioid receptors, their gene symbols, NCBI gene ID numbers and related synonyms

Type	Subunit	Gene Symbol	Splice form	NCBI Gene ID	Synonyms
Opioid	Mu	OPRM1	1	4988	KIAA0403, MOR, MOR1, MOR-1, Mu-type opioid receptor, OPRM
			2		
	Delta	OPRD1	1	4985	Delta-type opioid receptor, DOR-1, OPRD
	Kappa	OPRK1	1	4986	Kappa-type opioid receptor, KOR, KOR-1, OPRK
	Sigma	OPRS1	1	10280	AAG8, Aging-associated gene 8 protein, FLJ25585, hSigmaR1, MGC3851, SIG-1R, Sigma1R, Sigma1-receptor, Sigma 1-type opioid receptor, SIGMAR1, SR31747-binding protein, SRBP, SR-BP, SR-BP1
			2		
			3		
			4		
			5		
Opioid Like Receptor		OPRL1	1	4987	Kappa-type 3 opioid receptor, KOR-3, MGC34578, Nociceptin receptor, NOCIR, OOR, ORL1, Orphanin FQ receptor
			2		
opioid binding protein/cell adhesion molecule-like		OPCML	1	4978	OBCAM, OPCM, Opioid-binding cell adhesion molecule, Opioid-binding protein/cell adhesion molecule precursor
opioid growth factor receptor		OGFR	1	11054	7-60, 7-60 protein, OGFr, Opioid growth factor receptor, Zeta-type opioid receptor
			2		
opioid		OGFRL1	1	79627	dJ331H24.1, FLJ21079,

growth factor receptor-like 1					MGC102783

Table 5 Human olfactory receptors, their gene symbols, and common names

Name	Common Name
ORL1003	OR2W1
ORL1004	OR10H1
ORL1009	OR1K1
ORL1011	sdolf
ORL1015	OR3A3
ORL1016	OR1E1
ORL1017	LOC113744
ORL1018	OR1D2
ORL1019	OR2B2
ORL1020	sdolf
ORL1021	LOC113117
ORL1022	OR1F2
ORL1023	OR1F1
ORL1025	LOC116408
ORL1026	LOC91013
ORL1027	LOC93312
ORL1028	OR7A17
ORL1029	OR7C2
ORL1030	OR12D3
ORL1031	OR5V1
ORL1032	OR2J2
ORL1033	OR2W1
ORL1037	OR2W1
ORL1038	LOC89905
ORL1040	OR2K2
ORL1041	OR3A2
ORL1043	OR11A1
ORL1046	OR2S2
ORL1048	JCG10
ORL1049	JCG4
ORL1050	PJCG1
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ORL3144	OR4F10/OR06.12.02
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ORL3422	OR8B8/OR11.38.10/HGPCR0539

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ORL3425	OR4C6/OR11.49.14/HGPCR0046
ORL3426	OR5D14/OR11.32.04/HGPCR0685
ORL3427	OR6Q1/OR11.46.01/HGPCR1025
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ORL3429	OR52I2/OR11.02.02/HGPCR0469
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ORL3430	OR2D3/OR11.22.02/HGPCR0950
ORL3431	OR52W1P/OR11.12.01/HGPCR0130
ORL3432	OR2D2/OR11.22.01/HGPCR0954
ORL3433	OR5M11/OR11.40.01/HGPCR0253
ORL3434	OR8G3P/OR11.40.04/HGPCR0380
ORL3435	OR4C16/OR11.49.04/HGPCR0692
ORL3436	OR52N5/OR11.17.01/HGPCR0053
ORL3438	OR6X1/OR11.44.01
ORL3440	OR51C1P/HGPCR0066
ORL3441	OR51J1P/HGPCR0768
ORL3442	OR51R1P/HGPCR0731
ORL3443	OR9I2P/HGPCR0326
ORL3444	OR51A4
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ORL3447	OR8J1
ORL3449	OR9G1
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ORL3451	OR5B2
ORL3452	OR52D1
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ORL3454	OR5AK2
ORL3455	OR8B3
ORL3456	OR8B2
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ORL3458	OR11.38.07
ORL3459	OR11.28.02
ORL3460	OR11.25.02
ORL3461	OR11.39.03
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ORL3473	OR8F1P

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ORL3476	OR7E5P
ORL3477	OR51B3P
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ORL3479	OR7E4P
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ORL3487	OR52J1P
ORL3488	OR51P1P
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ORL3499	OR52J2P
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ORL3563	OR52B3P
ORL3564	OR5BB1P
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ORL3579	OR5BN1P
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ORL3584	OR4A6P
ORL3585	OR4A7P
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ORL3594	OR4A14P
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ORL3613	OR52T1P
ORL3614	OR52H2P
ORL3615	OR52B5P
ORL3616	OR5BA1P
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ORL3633	OR10Y1P
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ORL3636	OR4A18P
ORL3637	OR4A19P
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ORL3639	OR10V3P
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ORL3652	OR4A21P
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ORL3654	OR4C14P
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ORL3659	OR9K1P/HGPCR0894
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ORL3667	OR9R1P
ORL3668	OR10P2P
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ORL3674	OR11H2P
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ORL3676	OR7E104P
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ORL3679	OR7E33P
ORL368	hsORL-144
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ORL3682	OR4K3/OR14.07.06
ORL3683	OR6J2/OR14.02.01
ORL3684	OR4K5/OR14.07.09
ORL3685	OR4N5/OR14.06.02
ORL3686	OR11H4/OR14.03.01
ORL3687	OR11G2/OR14.03.03
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ORL3689	OR4K13/OR14.07.04
ORL369	hsORL-145
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ORL3691	OR4K17/OR14.07.02
ORL3692	OR14.07.03/HGPCR0058
ORL3693	OR4N2/OR14.06.03/HGPCR0320
ORL3694	OR6S1/OR14.02.02/HGPCR0135
ORL3695	OR10G3/OR14.04.02/HGPCR0263
ORL3697	OR10G2/OR14.04.01/HGPCR0272
ORL3698	OR4E2/OR14.05.01/HGPCR0273
ORL3699	OR11H6/OR14.03.02/HGPCR0190
ORL37	HTPCRH02
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ORL3706	OR4K6P
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ORL3708	OR7E106P
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ORL3713	OR4Q2P
ORL3714	OR4K16P
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ORL3716	OR4H8P
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ORL3718	OR10G1P
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ORL372	hsORL-148
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ORL3722	OR4N4/OR15.02.02/HGPCR0703
ORL3723	OR4M2/OR15.02.01/HGPCR0928
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ORL3727	OR11K1P
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ORL3729	OR4H6P
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ORL3730	OR11H3P
ORL3731	OR4H10P
ORL3732	OR11J1P
ORL3733	OR11J2P
ORL3734	OR8B11P
ORL3735	OR11I2P
ORL3736	OR4C5P/OR16.03.03
ORL3737	OR4S1/OR16.03.01/HGPCR0474
ORL3738	OR4C3/OR16.03.02/HGPCR0976
ORL3739	OR4C2P
ORL374	hsORL-150
ORL3740	OR4C4P
ORL3741	OR4F11P
ORL3742	OR4G5P
ORL3743	OR2C2P
ORL3744	OR4G1P
ORL3745	OR4D2/OR17.06.02/HGPCR0095
ORL3746	OR3A2/OR17.01.04/HGPCR0766
ORL3747	OR1G1/OR17.05.01
ORL3748	OR17.06.01

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ORL3751	OR4K7P
ORL3752	OR1R2P
ORL3753	OR1D3P
ORL3754	OR1E9P
ORL3755	OR1R3P
ORL3756	OR4K9P
ORL3757	OR4K10P
ORL3758	OR5D12P
ORL3759	OR5D5P
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ORL3761	OR10H5/OR19.05.02/HGPCR0167
ORL3762	OR7G1/OR19.04.03/HGPCR0435
ORL3763	OR2Z1/OR19.01.01/HGPCR0216
ORL3764	OR2Z1/OR19.01.01/HGPCR0725
ORL3765	OR7G3/OR19.04.04/HGPCR0434
ORL3766	OR7D4P/OR19.04.05/HGPCR0977
ORL3767	OR7C1/OR19.04.08/HGPCR0887
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ORL3769	OR19.04.01/HGPCR0980
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ORL3771	OR7G2/HGPCR0436
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ORL3777	OR7D1P
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ORL3795	OR4G3P
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ORL3802	OR11H1/OR22.01.01/HGPCR0191
ORL3803	OR13H1/OR0X.01.01/HGPCR0012
ORL3804	H38g522/HGPCR0369
ORL3805	OR2D1
ORL3806	OR1F11
ORL3807	OR2A19
ORL3808	OR7E120
ORL3809	OR2M1
ORL381	AA042813
ORL3810	OR5AC2
ORL3811	OR5B3
ORL3812	OR6C2
ORL3813	OR52A2
ORL3814	OR4Q3
ORL3815	OR6C1
ORL3816	OR2A20
ORL3817	OR2M2
ORL3818	OR2A21
ORL3819	OR6C3
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ORL3821	HGPCR0003
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ORL3823	HGPCR0005
ORL3824	HGPCR0013
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ORL3827	HGPCR0017
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ORL3829	HGPCR0042
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ORL3832	HGPCR0060
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ORL3834	HGPCR0062
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ORL3837	HGPCR0078
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ORL3938	HGPCR0546
ORL3939	HGPCR0566
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ORL3998	HGPCR0832
ORL3999	HGPCR0836
ORL40	HTPCRX03
ORL400	af90d06.s1
ORL4000	HGPCR0837
ORL4001	HGPCR0844
ORL4002	HGPCR0845
ORL4003	HGPCR0848
ORL4004	HGPCR0858
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ORL4007	HGPCR0868
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ORL4074	OR1AA1P
ORL4075	OR7L1P
ORL4076	OR2AF2P
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ORL4083	OR2C5P
ORL4084	OR5B12P
ORL4085	OR7E39P
ORL4086	OR7E27P
ORL4087	OR5D10P
ORL4088	OR2I3P
ORL4089	OR7E119P
ORL4090	OR7E47P
ORL4091	OR7E42P
ORL4092	OR2M3P
ORL4093	OR7E57P
ORL4094	OR7E34P
ORL4095	OR7E56P
ORL4096	OR7E21P
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ORL4098	OR7E77P
ORL4099	OR7E81P
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ORL4102	OR7E59P
ORL4103	OR7E28P
ORL4104	OR7E54P
ORL4105	OR7E48P
ORL4106	OR51E3P
ORL4107	OR7E40P
ORL4108	OR7E52P
ORL4109	OR2I7P
ORL4110	OR7E30P
ORL4111	OR2I8P
ORL4112	OR52A3P
ORL4113	OR2I9P
ORL4114	OR7E20P
ORL4115	OR2A22P
ORL4116	OR5BH2P
ORL4117	OR1E8P
ORL4118	OR4W1P
ORL4119	OR7E124P

ORL4120	OR10J4P
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ORL4122	OR7E36P
ORL4123	OR4G2P
ORL4124	OR06.03.02
ORL4125	HGPCR0405
ORL4126	OR09.01.09/HGPCR019
ORL4127	OR09.01.08/HGPCR019
ORL4128	OR13E2/HGPCR0369
ORL4129	OR93
ORL42	HTPCRX09
ORL420	dJ88J8.1
ORL423	OR2C1
ORL43	HTPCRX10
ORL430	olfr89
ORL44	HTPCRX11
ORL45	HTPCRX12
ORL4501	HsOR1.4.9
ORL4502	HsOR1.5.1
ORL4503	HsOR1.1.1P
ORL4504	HsOR1.1.2P
ORL4505	HsOR1.1.3
ORL4506	HsOR1.2.1P
ORL4507	HsOR1.3.1P
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ORL4509	HsOR1.4.3P
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ORL4511	HsOR1.4.14P
ORL4512	HsOR1.4.15P
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ORL4523	HsOR1.5.16
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ORL4525	HsOR1.5.19
ORL4526	HsOR1.5.20P
ORL4527	HsOR1.5.22P
ORL4528	HsOR1.5.23
ORL4529	HsOR1.5.24
ORL4530	HsOR1.5.25
ORL4531	HsOR1.5.26P
ORL4532	HsOR1.5.28P
ORL4533	HsOR1.5.27

ORL4534	HsOR1.5.29
ORL4535	HsOR1.5.30
ORL4536	HsOR1.5.38
ORL4537	HsOR1.5.42
ORL4538	HsOR1.5.44
ORL4539	HsOR1.5.48
ORL4540	HsOR1.5.50
ORL4541	HsOR2.1.1P
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ORL4543	HsOR2.1.3P
ORL4544	HsOR2.2.1P
ORL4545	HsOR2.3.1P
ORL4546	HsOR2.3.2P
ORL4547	HsOR2.3.3P
ORL4548	HsOR2.4.1
ORL4549	HsOR2.4.2
ORL4550	HsOR2.4.3P
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ORL4552	HsOR3.2.1P
ORL4553	HsOR3.2.2P
ORL4554	HsOR3.2.3P
ORL4555	HsOR3.2.4P
ORL4556	HsOR3.3.1P
ORL4557	HsOR3.3.2
ORL4558	HsOR3.3.4
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ORL4563	HsOR3.3.8P
ORL4565	HsOR3.3.9P
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ORL4567	HsOR3.3.13P
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ORL4569	HsOR3.3.15
ORL4570	HsOR3.3.16
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ORL4577	HsOR3.6.1P
ORL4578	HsOR3.6.2P
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ORL4581	HsOR4.1.3P
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ORL4583	HsOR4.2.2P
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ORL4585	HsOR4.2.4P
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ORL4587	HsOR4.3.1P
ORL4588	HsOR4.4.1P
ORL4589	HsOR5.1.1P
ORL459	OLFR 17-30
ORL4590	HsOR5.2.1P
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ORL4593	HsOR5.4.3
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ORL4598	HsOR6.2.4P
ORL4599	HsOR6.2.5P
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ORL4601	HsOR6.2.7P
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ORL4605	HsOR6.3.5P
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ORL4618	HsOR7.1.1P
ORL4619	HsOR7.2.1P
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ORL4627	HsOR7.6.5P
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ORL4631	HsOR7.6.13
ORL4632	HsOR7.6.14P
ORL4633	HsOR7.6.16P
ORL4634	HsOR7.6.17P

ORL4635	HsOR7.6.18P
ORL4636	HsOR7.6.20P
ORL4637	HsOR7.6.21
ORL4638	HsOR7.6.22P
ORL4639	HsOR8.2.1P
ORL4640	HsOR8.3.1P
ORL4641	HsOR8.4.1P
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ORL4650	HsOR9.1.6P
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ORL4654	HsOR9.3.1P
ORL4655	HsOR9.3.2P
ORL4656	HsOR9.4.5P
ORL4657	HsOR9.4.9P
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ORL4659	HsOR9.4.12P
ORL4660	HsOR9.6.7P
ORL4661	HsOR10.1.1P
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ORL4663	HsOR10.1.3P
ORL4664	HsOR10.2.1P
ORL4665	HsOR11.8.13
ORL4666	HsOR11.9.7
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ORL4670	HsOR11.3.1P
ORL4671	HsOR11.3.2
ORL4672	HsOR11.3.3P
ORL4673	HsOR11.3.4P
ORL4674	HsOR11.3.5P
ORL4675	HsOR11.3.7P
ORL4676	HsOR11.3.9P
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ORL4679	HsOR11.3.19P
ORL4680	HsOR11.3.20P
ORL4681	HsOR11.3.21P
ORL4682	HsOR11.3.22
ORL4683	HsOR11.3.23P
ORL4684	HsOR11.3.26P

ORL4685	HsOR11.3.29P
ORL4686	HsOR11.3.31P
ORL4687	HsOR11.3.32P
ORL4688	HsOR11.3.36P
ORL4689	HsOR11.3.39P
ORL4690	HsOR11.3.41P
ORL4691	HsOR11.3.42P
ORL4692	HsOR11.3.45P
ORL4693	HsOR11.3.46P
ORL4694	HsOR11.3.47P
ORL4695	HsOR11.3.48P
ORL4696	HsOR11.3.49P
ORL4697	HsOR11.3.50
ORL4698	HsOR11.3.52P
ORL4699	HsOR11.3.53P
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ORL4701	HsOR11.3.56P
ORL4702	HsOR11.3.57
ORL4703	HsOR11.3.58P
ORL4704	HsOR11.3.59
ORL4705	HsOR11.3.60
ORL4706	HsOR11.3.61
ORL4707	HsOR11.3.62P
ORL4708	HsOR11.3.64P
ORL4709	HsOR11.3.67P
ORL4710	HsOR11.3.69P
ORL4711	HsOR11.3.71P
ORL4712	HsOR11.3.72P
ORL4713	HsOR11.3.73P
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ORL4715	HsOR11.3.75P
ORL4716	HsOR11.3.76P
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ORL4718	HsOR11.3.79
ORL4719	HsOR11.3.82P
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ORL4721	HsOR11.3.89P
ORL4722	HsOR11.3.91
ORL4723	HsOR11.3.92
ORL4724	HsOR11.3.95P
ORL4725	HsOR11.3.97P
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ORL4727	HsOR11.3.100P
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ORL4730	HsOR11.5.2P
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ORL4732	HsOR11.5.6P
ORL4733	HsOR11.6.1P

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ORL4749	HsOR11.9.1P
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ORL4752	HsOR11.9.6P
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ORL4756	HsOR11.10.4P
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ORL4758	HsOR11.10.7P
ORL4759	HsOR11.10.9P
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ORL4763	HsOR11.11.7P
ORL4764	HsOR11.11.8P
ORL4765	HsOR11.11.10P
ORL4766	HsOR11.11.11P
ORL4767	HsOR11.11.12P
ORL4768	HsOR11.11.13P
ORL4769	HsOR11.11.14P
ORL4770	HsOR11.11.21P
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ORL4773	HsOR11.11.24P
ORL4774	HsOR11.11.26P
ORL4775	HsOR11.11.32P
ORL4776	HsOR11.11.33P
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ORL4778	HsOR11.11.38P
ORL4779	HsOR11.11.40P
ORL4780	HsOR11.11.43P
ORL4781	HsOR11.11.44P
ORL4782	HsOR11.11.50P
ORL4783	HsOR11.11.52P

ORL4784	HsOR11.11.53P
ORL4785	HsOR11.11.58P
ORL4786	HsOR11.11.60P
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ORL4789	HsOR11.11.66P
ORL4790	HsOR11.11.68P
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ORL4792	HsOR11.11.73P
ORL4793	HsOR11.11.74P
ORL4794	HsOR11.11.75P
ORL4795	HsOR11.11.80P
ORL4796	HsOR11.11.81P
ORL4797	HsOR11.11.82P
ORL4798	HsOR11.11.83P
ORL4799	HsOR11.11.86P
ORL48	HTPCRX15
ORL4800	HsOR11.11.88P
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ORL4803	HsOR11.11.92P
ORL4804	HsOR11.11.93P
ORL4805	HsOR11.11.94P
ORL4806	HsOR11.11.97P
ORL4807	HsOR11.11.98P
ORL4808	HsOR11.12.2P
ORL4809	HsOR11.12.4P
ORL481	HOR 5'Beta3
ORL4810	HsOR11.12.6P
ORL4811	HsOR11.12.8
ORL4812	HsOR11.12.13P
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ORL4814	HsOR11.12.15P
ORL4815	HsOR11.12.16P
ORL4816	HsOR11.12.18P
ORL4817	HsOR11.12.19P
ORL4818	HsOR11.12.23
ORL4819	HsOR11.13.1P
ORL482	HOR 5
ORL4820	HsOR11.13.2P
ORL4821	HsOR11.13.9P
ORL4822	HsOR11.13.11
ORL4823	HsOR11.13.12P
ORL4824	HsOR11.13.14P
ORL4825	HsOR11.13.15P
ORL4826	HsOR11.14.1P
ORL4827	HsOR11.14.2P
ORL4828	HsOR11.14.3P
ORL4829	HsOR11.15.1P
ORL483	OR2D2

ORL4830	HsOR11.15.2P
ORL4831	HsOR11.15.3P
ORL4832	HsOR11.15.4P
ORL4833	HsOR11.16.1P
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ORL4835	HsOR11.16.3P
ORL4836	HsOR11.17.1P
ORL4837	HsOR11.17.2P
ORL4838	HsOR11.18.3P
ORL4839	HsOR11.18.4P
ORL484	OR10A1
ORL4840	HsOR11.18.10P
ORL4841	HsOR11.18.15P
ORL4842	HsOR11.18.17P
ORL4843	HsOR11.18.18P
ORL4844	HsOR11.18.20P
ORL4845	HsOR11.18.21P
ORL4846	HsOR11.18.22
ORL4847	HsOR11.18.23P
ORL4848	HsOR11.18.24P
ORL4849	HsOR11.18.28P
ORL485	OR5F1
ORL4850	HsOR11.18.29P
ORL4851	HsOR11.18.30P
ORL4852	HsOR11.18.31P
ORL4853	HsOR11.18.32P
ORL4854	HsOR11.18.33
ORL4855	HsOR11.18.34
ORL4856	HsOR11.18.37P
ORL4857	HsOR11.18.38P
ORL4858	HsOR11.18.39P
ORL4859	HsOR11.18.43P
ORL486	OR5D4
ORL4860	HsOR12.1.1P
ORL4861	HsOR12.1.2P
ORL4862	HsOR12.1.3P
ORL4862	HsOR12.2.1P
ORL4863	HsOR12.3.2P
ORL4864	HsOR12.3.3P
ORL4865	HsOR12.3.4P
ORL4866	HsOR12.3.5P
ORL4867	HsOR12.3.7P
ORL4868	HsOR12.3.8P
ORL4869	HsOR12.4.1P
ORL487	OR5D3
ORL4870	HsOR12.5.1P
ORL4871	HsOR12.5.3P
ORL4872	HsOR12.5.4P
ORL4873	HsOR12.5.6
ORL4874	HsOR12.5.7P

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ORL4877	HsOR12.5.10P
ORL4878	HsOR12.5.11
ORL4879	HsOR12.5.12
ORL4880	HsOR12.5.13P
ORL4881	HsOR12.5.14
ORL4882	HsOR12.5.15P
ORL4883	HsOR12.5.16
ORL4884	HsOR12.5.17
ORL4885	HsOR12.5.18
ORL4886	HsOR12.5.19
ORL4887	HsOR12.5.20
ORL4888	HsOR12.5.21
ORL4889	HsOR12.5.22P
ORL4890	HsOR12.5.25P
ORL4891	HsOR13.1.1P
ORL4892	HsOR13.1.2P
ORL4893	HsOR13.1.3P
ORL4894	HsOR13.3.1P
ORL4895	HsOR13.3.2P
ORL4896	HsOR13.4.1P
ORL4897	HsOR13.4.2P
ORL4898	HsOR14.1.1
ORL4899	HsOR14.1.2P
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ORL4902	HsOR14.1.6P
ORL4903	HsOR14.1.8P
ORL4904	HsOR14.1.9P
ORL4905	HsOR14.1.11P
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ORL4907	HsOR14.1.16P
ORL4908	HsOR14.1.19P
ORL4909	HsOR14.1.21P
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ORL4910	HsOR14.1.24P
ORL4911	HsOR14.1.26P
ORL4912	HsOR14.1.28P
ORL4913	HsOR14.2.3P
ORL4914	HsOR14.2.6P
ORL4915	HsOR14.3.2P
ORL4916	HsOR14.4.1P
ORL4917	HsOR14.5.1P
ORL4918	HsOR14.5.3P
ORL4919	HsOR15.2.6
ORL492	hsORL492
ORL4920	HsOR15.1.1P
ORL4921	HsOR15.1.2P

ORL4922	HsOR15.1.3P
ORL4923	HsOR15.1.4P
ORL4924	HsOR15.1.5P
ORL4925	HsOR15.1.6P
ORL4926	HsOR15.1.7P
ORL4927	HsOR15.1.10P
ORL4928	HsOR15.2.4P
ORL4929	HsOR15.2.5P
ORL493	hsORL493
ORL4930	HsOR15.2.7P
ORL4931	HsOR15.2.8P
ORL4932	HsOR16.1.2P
ORL4933	HsOR17.1.3P
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ORL4935	HsOR17.1.8P
ORL4936	HsOR17.1.9P
ORL4937	HsOR17.1.13
ORL4938	HsOR18.1.1P
ORL4939	HsOR19.1.1P
ORL494	hsORL494
ORL4940	HsOR19.1.2P
ORL4941	HsOR19.1.4P
ORL4942	HsOR19.2.2P
ORL4943	HsOR19.2.6P
ORL4944	HsOR19.2.10P
ORL4945	HsOR19.2.12P
ORL4946	HsOR19.2.13P
ORL4947	HsOR19.2.15P
ORL4948	HsOR19.2.17P
ORL4949	HsOR19.3.4P
ORL495	hsORL495
ORL4950	HsOR19.3.7P
ORL4951	HsOR19.3.9P
ORL4952	HsOR19.3.10P
ORL4953	HsOR19.3.13P
ORL4954	HsOR19.4.6P
ORL4955	HsOR19.5.1P
ORL4956	HsOR21.1.1P
ORL4957	HsOR21.1.2P
ORL4958	HsOR21.2.1P
ORL4959	HsORX.1.1P
ORL496	hsORL496
ORL4960	HsORX.1.2P
ORL4961	HsORX.1.3P
ORL4962	HsORX.1.4P
ORL4963	HsORX.1.6P
ORL4964	HsORX.2.1P
ORL4965	HsOR17.1.1
ORL4966	HsOR14.1.5
ORL497	hsORL497

ORL498	hsORL498
ORL499	hsORL499
ORL50	HTPCRX17
ORL500	hsORL500
ORL501	hsORL501
ORL502	hsORL502
ORL504	NCI_CGAP_Ut7
ORL505	
ORL506	NP_058638.1
ORL507	hsORL507
ORL508	hsORL508
ORL509	NCI_CGAP_Co14
ORL51	HTPCRX19
ORL510	HPFH6OR
ORL511	OR1D5
ORL512	OR1A1
ORL513	OR6A1
ORL520	OR3A1
ORL521	OR1D2
ORL522	Soares_NFL_T_GBC_S1
ORL523	OR12D2
ORL524	OR11A1
ORL525	OR10H1
ORL526	OR10C1
ORL527	OR10H3
ORL528	OR10H2
ORL536	hf30a07.x1
ORL589	OR17-2
ORL590	OR17-228
ORL591	OR17-4
ORL592	OR17-23
ORL593	OR17-24
ORL594	OR17-40
ORL671	6M1-3*02
ORL672	6M1-7P*01
ORL673	6M1-16*03
ORL674	6M1-16*02
ORL675	6M1-16*01
ORL676	6M1-15*03
ORL677	6M1-15*02
ORL678	6M1-15*01
ORL68	OR17-23
ORL680	6M1-10*02
ORL681	6M1-10*01
ORL682	6M1-6*03
ORL683	6M1-6*02
ORL684	6M1-6*01
ORL685	6M1-02P*02
ORL686	6M1-4P*04
ORL687	6M1-4P*05

ORL688	6M1-4P*03
ORL689	6M1-4P*02
ORL69	OR17-24
ORL690	6M1-4P*01
ORL691	6M1-3*04
ORL692	6M1-3*01
ORL693	6M1-1*02
ORL694	6M1-1*01
ORL697	6M1-7P*02
ORL70	OR17-32
ORL71	OR17-82
ORL72	OR17-93
ORL729	6M1-18*02
ORL73	OR17-207
ORL732	OR2A4
ORL735	OR6A1
ORL736	OR5I1
ORL737	OR1D4
ORL738	OR1E2
ORL739	OR1E1
ORL74	OR17-201
ORL740	OR1A2
ORL741	OR1A1
ORL742	LOC82475
ORL743	OR12D2
ORL75	OR17-209
ORL76	OR17-210
ORL77	OR17-219
ORL78	OR17-2
ORL79	OR17-4
ORL830	LOC83361
ORL869	
ORL870	hB2
ORL871	hP2
ORL872	hP4
ORL873	hP3
ORL874	hI7
ORL875	hT3
ORL925	OR51B2
ORL929	OR7A17
ORL931	OR10H2
ORL932	OR10H3
ORL933	OR1I1
ORL934	OR2B3
ORL935	OR2J3
ORL936	OR2J2
ORL937	OR7C1
ORL938	OR7A10
ORL939	OR2F2
ORL940	OR6B1

ORL941	OR4F3
ORL942	OR2A4
ORL943	OLFR89
ORL944	OR2H2
ORL946	OR52A1
ORL947	
ORL948	
ORL949	DJ25J61
ORL950	OR17-1
ORL993	
ORL994	
ORL995	OR5U1
ORL996	OR5V1
ORL997	OR12D3
ORL998	OLFR
ORL999	

Table 6 Canine olfactory receptors, their gene names

Name	Name	Name	Name
CfOLF1	cOR1J6	cOR52A13	cOR6K5P
CfOLF2	cOR1K2	cOR52A14	cOR6K7P
CfOLF3	cOR1L6	cOR52A15	cOR6K8
CfOLF4	cOR1L8	cOR52A16P	cOR6K9
TPCR62	cOR1L9	cOR52A17	cOR6M4
TPCR63	cOR1M1P	cOR52A6	cOR6M5
TPCR64	cOR1M2	cOR52A7	cOR6M6
TPCR71	cOR1P1P	cOR52A8	cOR6M7
TPCR72	cOR1P2	cOR52A9	cOR6M8
TPCR79	cOR1R4	cOR52AA1P	cOR6n
DTMT	cOR1S3P	cOR52AB1	cOR6N1
DOPCRH01	cOR1X2	cOR52AB2	cOR6P1
DOPCRH02	cOR2A13P	cOR52AB3	cOR6Q2
DOPCRH07	cOR2A29	cOR52AB4	cOR6T2
DOPCRX01	cOR2A30	cOR52AC1	cOR6U3
DOPCRX04	cOR2A31	cOR52AD1	cOR6V2
DOPCRX07	cOR2A32	cOR52AE1	cOR6W1
DOPCRX09	cOR2A33	cOR52B10P	cOR6Y3
DOPCRX16	cOR2A34P	cOR52B2	cOR6Z1
DTPCRH02	cOR2A35	cOR52B6	cOR6Z2
DTPCRH09	cOR2A36	cOR52B7	cOR6Z3
OR4A16/HGPCR0945	cOR2A37	cOR52B8	cOR7A21
cOR7C50P	cOR2A38	cOR52B9P	cOR7A22P
cOR7C49P	cOR2A39	cOR52D1P	cOR7A23
cOR7H8P	cOR2A40	cOR52D2	cOR7A24P
cOR13C22P	cOR2A7	cOR52D3	cOR7A25P
cOR5BW2P	cOR2AG1	cOR52D4P	cOR7A26
cOR13C20P	cOR2AG4P	cOR52E10P	cOR7A27
cOR5AN4P	cOR2AG5P	cOR52E11P	cOR7A28
cOR10Q4P	cOR2AG6	cOR52E12	cOR7C10P
cOR13Q2P	cOR2AG7	cOR52E13	cOR7C11
cOR5L3P	cOR2AG8	cOR52E14	cOR7C12P
cOR10J17P	cOR2AG9	cOR52E15P	cOR7C13
cOR10J15P	cOR2AI2	cOR52E16P	cOR7C14P
cOR2AG5P	cOR2AK3	cOR52E17	cOR7C15P
cOR1D9P	cOR2AT5P	cOR52E18	cOR7C16
cOR2AG4P	cOR2AT6	cOR52E19P	cOR7C17
cOR13N1P	cOR2AT7	cOR52E2	cOR7C18P
cOR5B22P	cOR2AT8P	cOR52E20P	cOR7C19
cOR7C52	cOR2AV1	cOR52E4	cOR7C20
cOR4Z5	cOR2AV2	cOR52E8	cOR7C21
cOR7D10	cOR2AV3	cOR52E9	cOR7C22
cOR1E12	cOR2AX1P	cOR52H1	cOR7C23P
cOR4X6	cOR2AX2	cOR52H10P	cOR7C24
cOR7G14	cOR2AZ1	cOR52H11	cOR7C25
cOR7H9	cOR2B10P	cOR52H2P	cOR7C26

cOR5F3	cOR2B2P	cOR52H3P	cOR7C27
cOR9I5	cOR2B7P	cOR52H4	cOR7C28
cOR4Z4	cOR2B9	cOR52H5	cOR7C29P
cOR5M22	cOR2BA1P	cOR52H6	cOR7C3
cOR9S20	cOR2C1	cOR52H7	cOR7C30
cOR2M12	cOR2C6	cOR52H8	cOR7C31
cOR2L19	cOR2D10P	cOR52H9	cOR7C32
cOR7C46	cOR2D2	cOR52I2	cOR7C33P
cOR4H14	cOR2D4	cOR52J5	cOR7C34
cOR13C21	cOR2D5P	cOR52J6P	cOR7C35
cOR7C45	cOR2D6	cOR52J7	cOR7C36
cOR7C44	cOR2D7P	cOR52J8	cOR7C37
cOR5D23	cOR2D8	cOR52J9P	cOR7C38
cOR4K23	cOR2D9	cOR52K4	cOR7C39
cOR8C6	cOR2G4	cOR52K5	cOR7C4
cOR5L7	cOR2G5	cOR52K6	cOR7C40
cOR2A40	cOR2H8	cOR52L3	cOR7C41
cOR11M3	cOR2H9P	cOR52M1P	cOR7C42
cOR7H7	cOR2K2	cOR52M5	cOR7C43
cOR7C43	cOR2L15P	cOR52M6P	cOR7C44
cOR3A13	cOR2L16	cOR52N10	cOR7C45
cOR10J21	cOR2L17	cOR52N11	cOR7C46
cOR3A12	cOR2L18	cOR52N12P	cOR7C47
cOR8S16	cOR2L19	cOR52N2P	cOR7C48
cOR8J6	cOR2M10	cOR52N6P	cOR7C49P
cOR7C40	cOR2M11	cOR52N7P	cOR7C50P
cOR2A36	cOR2M12	cOR52N8	cOR7C51
cOR7C39	cOR2M8	cOR52N9	cOR7C52
cOR7H6	cOR2M9P	cOR52P1P	cOR7C53
cOR12F3	cOR2Q1P	cOR52P2P	cOR7C5P
cOR7H4	cOR2S3P	cOR52P3	cOR7C6
cOR2AY1	cOR2T1	cOR52R2	cOR7C7
cOR2AG6	cOR2T13	cOR52R3P	cOR7C8
cOR2A31	cOR2T14P	cOR52S2	cOR7C9P
cOR7C14	cOR2T15	cOR52S3	cOR7D10
cOR10J16	cOR2T16P	cOR52S4P	cOR7D4P
cOR7H2	cOR2T17	cOR52S5	cOR7D5
cOR7C13	cOR2T18P	cOR52U2	cOR7D7
cOR10A9	cOR2T19	cOR52U3P	cOR7D8
cOR2D6	cOR2T20	cOR52V2	cOR7D9P
cOR7A21	cOR2T21	cOR52W2	cOR7E152
cOR10J13	cOR2T22	cOR52X2	cOR7E153
cOR1D7	cOR2T23	cOR52X3	cOR7E154
cOR1L9	cOR2T24	cOR52Z2	cOR7G10
cOR4Z1	cOR2T25	cOR52Z3	cOR7G11
cOR7C4	cOR2T26	cOR52Z4	cOR7G12
cOR13D4	cOR2V4	cOR52Z5	cOR7G13
cOR7C3	cOR2W10	cOR55B3	cOR7G14

cOR7G4	cOR2W11	cOR55D1	cOR7G4
CfOLF4	cOR2W12	cOR56A10	cOR7G5
CfOLF3	cOR2W13P	cOR56A11	cOR7G6
CfOLF2	cOR2W14	cOR56A12	cOR7G7
CfOLF1	cOR2W15	cOR56A13P	cOR7G8
cOR10A10	cOR2W16P	cOR56A14	cOR7G9
cOR10A11P	cOR2W9	cOR56A15	cOR7H2
cOR10A12P	cOR2Y2	cOR56A16	cOR7H3P
cOR10A13	cOR2Z2	cOR56A17	cOR7H4
cOR10A14	cOR2Z3	cOR56A18	cOR7H5P
cOR10A3	cOR2Z4	cOR56A19P	cOR7H6
cOR10A4P	cOR3A10	cOR56A20	cOR7H7
cOR10A5	cOR3A11	cOR56A21P	cOR7H8P
cOR10A4P	cOR3A12	cOR56A22	cOR7H9
cOR10A8P	cOR3A13	cOR56A23	cOR7P1
cOR10A5	cOR3A9	cOR56A24	cOR7R1
cOR10A9	cOR3n	cOR56A4	cOR8A1P
cOR10A8P	cOR4A26	cOR56A6	cOR8B14
cOR10A9	cOR4A27	cOR56A8	cOR8B15
cOR10AB2	cOR4A28	cOR56A9	cOR8B16
cOR10AD1	cOR4A29	cOR56B10P	cOR8B17
cOR10AD2	cOR4A30	cOR56B11	cOR8B18
cOR10AD3	cOR4A31P	cOR56B12P	cOR8B19
cOR10AG2P	cOR4A32P	cOR56B2	cOR8B1P
cOR10AH1P	cOR4A33P	cOR56B5	cOR8B20
cOR10AI1	cOR4A34	cOR56B6	cOR8B21
cOR10AJ1P	cOR4A35	cOR56B7	cOR8B3
cOR10B1P	cOR4A36	cOR56B8P	cOR8B8
cOR10D1P	cOR4A37P	cOR56B9P	cOR8C4
cOR10D4P	cOR4A38	cOR5A2	cOR8C5
cOR10D5P	cOR4A39	cOR5A3	cOR8C6
cOR10D7	cOR4A4P	cOR5A4P	cOR8D2P
cOR10D8	cOR4B1	cOR5AC3	cOR8D4
cOR10D9	cOR4B3P	cOR5AK6	cOR8D5
cOR10G11	cOR4B4	cOR5AK7	cOR8D6
cOR10G12	cOR4C11P	cOR5AL1P	cOR8F2
cOR10G13P	cOR4C18	cOR5AL3	cOR8F3
cOR10G11	cOR4C19	cOR5AN2P	cOR8F4
cOR10G7	cOR4C1P	cOR5AN3	cOR8G8P
cOR10H10	cOR4C20P	cOR5AN4P	cOR8G9P
cOR10G12	cOR4C21	cOR5AP3	cOR8H4
cOR10G13P	cOR4C22P	cOR5AP4P	cOR8I3P
cOR10G7	cOR4C23P	cOR5AR1P	cOR8J4
cOR10H10	cOR4C24	cOR5B22P	cOR8J5
cOR10H11P	cOR4C25P	cOR5B23	cOR8J6
cOR10H12P	cOR4C26	cOR5B24	cOR8J7
cOR10H13	cOR4C27	cOR5B25	cOR8K1
cOR10H14P	cOR4C28	cOR5B26	cOR8K6P

cOR10H6P	cOR4C29	cOR5B27P	cOR8S10
cOR10H7	cOR4C3	cOR5B28	cOR8S11
cOR10H8	cOR4C30	cOR5B29	cOR8S12
cOR10H9	cOR4C31	cOR5B30P	cOR8S13
cOR10J10P	cOR4C32	cOR5B31	cOR8S14
cOR10J11P	cOR4C33P	cOR5B32	cOR8S15
cOR10J12	cOR4C34	cOR5BA2	cOR8S16
cOR10J13	cOR4C35	cOR5BC2	cOR8S17
cOR10J14	cOR4C36	cOR5BC3	cOR8S18P
cOR10J15P	cOR4C37	cOR5BG2	cOR8S19P
cOR10J16	cOR4C38	cOR5BH3	cOR8S20
cOR10J17P	cOR4C39P	cOR5BU2	cOR8S2P
cOR10J18P	cOR4C40	cOR5BV1P	cOR8S3P
cOR10J19	cOR4C41P	cOR5BW1P	cOR8S4
cOR10J20	cOR4C42	cOR5BW2P	cOR8S5
cOR10J21	cOR4C43	cOR5C1G	cOR8S6P
cOR10J22	cOR4C44	cOR5D14	cOR8S7
cOR10J23	cOR4D11P	cOR5D19	cOR8S8
cOR10J7P	cOR4D13	cOR5D20	cOR8S9
cOR10K2	cOR4D14P	cOR5D21	cOR8T2
cOR10K3	cOR4D15	cOR5D22	cOR8T3P
cOR10K4	cOR4D2P	cOR5D23	cOR8T4
cOR10n	cOR4D5	cOR5E1P	cOR8T5
cOR10N1P	cOR4E1P	cOR5F3	cOR8U2
cOR10P4P	cOR4E3P	cOR5G1P	cOR8U3
cOR10Q1	cOR4F22	cOR5G3P	cOR8U4P
cOR10Q4P	cOR4F23P	cOR5G7P	cOR8U5
cOR10Q3	cOR4F24P	cOR5G8P	cOR8U6
cOR10Q5	cOR4F25	cOR5G9	cOR8U7
cOR10R4	cOR4F26P	cOR5H10	cOR8V10
cOR10R5	cOR4F27P	cOR5H11	cOR8V11
cOR10R6P	cOR4G10	cOR5H12	cOR8V2
cOR10R7	cOR4G7P	cOR5H13P	cOR8V3
cOR10S2P	cOR4G8	cOR5H9	cOR8V4
cOR10T3	cOR4G9	cOR5I1	cOR8V5
cOR10T4P	cOR4H13	cOR5I2	cOR8V6
cOR10V4P	cOR4H14	cOR5J1P	cOR8V7P
cOR10V5	cOR4K15P	cOR5J3	cOR8V8P
cOR10V6	cOR4K18	cOR5J4	cOR8V9
cOR10X2	cOR4K19P	cOR5K5	cOR9A7
cOR10Z1	cOR4K20	cOR5K6	cOR9A8
cOR11G10	cOR4K21P	cOR5K7	cOR9G1
cOR11G11	cOR4K22	cOR5L1P	cOR9G4
cOR11G1P	cOR4K23	cOR5L3P	cOR9G7
cOR11G3P	cOR4K24	cOR5L4P	cOR9G8P
cOR11G4	cOR4K6P	cOR5L5	cOR9I2P
cOR11G5P	cOR4L1	cOR5L6P	cOR9I4P
cOR11G6	cOR4L3P	cOR5L7	cOR9I5

cOR11G7	cOR4L4	cOR5M12P	cOR9K3
cOR11G8	cOR4M3P	cOR5M13P	cOR9K4
cOR11G9P	cOR4M3P	cOR5M17P	cOR9K5P
cOR11H10	cOR4N5	cOR5M16	cOR9K6
cOR11H11P	cOR4N6	cOR5M18P	cOR9Q3
cOR11H7P	cOR4P10	cOR5M19P	cOR9R2
cOR11H8	cOR4P5P	cOR5M20	cOR9R3P
cOR11H9	cOR4P6	cOR5M21	cOR9R4
cOR11I3	cOR4P7	cOR5M22	cOR9S10
cOR11J3	cOR4P8	cOR5M8	cOR9S11
cOR11J4	cOR4P9	cOR5P4P	cOR9S12
cOR11K3	cOR4Q4	cOR5P5	cOR9S13
cOR11K4	cOR4Q5	cOR5P6P	cOR9S14
cOR11L2	cOR4Q6	cOR5R2	cOR9S15
cOR11M2	cOR4Q7	cOR5T4	cOR9S16
cOR11M3	cOR4S3	cOR5T5	cOR9S17
cOR11S1	cOR4S4	cOR5T6	cOR9S18
cOR11S2	cOR4S5	cOR5T7	cOR9S19
cOR12E1	cOR4S6	cOR5W4	cOR9S1P
cOR12E2	cOR4S7P	cOR5W5	cOR9S2
cOR12E3	cOR4T2P	cOR5W6	cOR9S20
cOR12E4P	cOR4X3	cOR5W7	cOR9S21P
cOR12E5	cOR4X4	cOR5W8	cOR9S22P
cOR12E7P	cOR4X5P	cOR6A2P	cOR9S23
cOR12E8	cOR4X6	cOR6AA1P	cOR9S3P
cOR12F1	cOR4Y1	cOR6AB1P	cOR9S4
cOR12F2P	cOR4Y2	cOR6B4	cOR9S5P
cOR12G1	cOR4Y3P	cOR6B5P	cOR9S6
cOR12H1P	cOR4Y4	cOR6B6	cOR9S7P
cOR12J1	cOR4Y5	cOR6B7	cOR9S8P
cOR13C10	cOR4Z1	cOR6B8	cOR9S9P
cOR13C11	cOR4Z2	cOR6C10P	
cOR13C12	cOR4Z3	cOR6C11	
cOR13C13P	cOR4Z4	cOR6C12	
cOR13C14	cOR4Z5	cOR6C13P	
cOR13C15	cOR51A14P	cOR6C14	
cOR13C16	cOR51A15P	cOR6C15	
cOR13C17	cOR51A16	cOR6C16P	
cOR13C18	cOR51A17	cOR6C17	
cOR13C19	cOR51A18	cOR6C18P	
cOR13C20P	cOR51A19	cOR6C19P	
cOR13C21	cOR51A20P	cOR6C20P	
cOR13C22P	cOR51A21	cOR6C21	
cOR13C23	cOR51AA1	cOR6C22	
cOR13C9	cOR51B10	cOR6C23	
cOR13D1	cOR51B4	cOR6C25	
cOR13D4	cOR51B7	cOR6C27	
cOR13D5	cOR51B8P	cOR6C26	

cOR13D6P	cOR51B9	cOR6C28
cOR13D7P	cOR51C4	cOR6C29
cOR13E3	cOR51C5	cOR6C30
cOR13F2P	cOR51C6P	cOR6C31
cOR13F3	cOR51C7P	cOR6C32P
cOR13F4	cOR51D2P	cOR6C33
cOR13G1	cOR51E2P	cOR6C34P
cOR13L1	cOR51E4	cOR6C35
cOR13L2	cOR51F2P	cOR6C36
cOR13M1	cOR51F2P	cOR6C37
cOR13M2P	cOR51G2	cOR6C38
cOR13M3	cOR51G4	cOR6C39P
cOR13M4	cOR51H3	cOR6C4
cOR13N1P	cOR51H4	cOR6C40P
cOR13N2	cOR51H5	cOR6C41P
cOR13N3P	cOR51I1P	cOR6C42P
cOR13N4	cOR51I2	cOR6C43
cOR13N5	cOR51I3	cOR6C44P
cOR13P1	cOR51J3	cOR6C45P
cOR13P2P	cOR51K1P	cOR6C46
cOR13P3	cOR51I4P	cOR6C47P
cOR13P4	cOR51K2	cOR6C48P
cOR13P5	cOR51L2	cOR6C49P
cOR13Q1P	cOR51L2	cOR6C50P
cOR13Q2P	cOR51M1	cOR6C51
cOR13Q3	cOR51P3	cOR6C52P
cOR13R1	cOR51Q1P	cOR6C53P
cOR13R2	cOR51Q2P	cOR6C54P
cOR13S1P	cOR51Q3	cOR6C55
cOR1A3P	cOR51R2	cOR6C56P
cOR1AB2	cOR51T2	cOR6C57P
cOR1AB3	cOR51V2	cOR6C58P
cOR1AD1	cOR51V3	cOR6C59P
cOR1AE1	cOR51V4	cOR6C5P
cOR1AF1	cOR51V5P	cOR6C6
cOR1AG1P	cOR51V5P	cOR6C60
cOR1D10	cOR51V6	cOR6C61P
cOR1D11P	cOR51V6	cOR6C62
cOR1D12	cOR51V7	cOR6C63
cOR1D7	cOR51W1	cOR6C7
cOR1D8	cOR51X1	cOR6C8
cOR1D9P	cOR51X2	cOR6C9
cOR1E10	cOR51X3P	cOR6D3P
cOR1E11	cOR51X4	cOR6D4
cOR1E12	cOR51Z1P	cOR6D5
cOR1F14P	cOR52A10	cOR6D6P
cOR1F15	cOR52A11	cOR6D7P
cOR1I2	cOR52A12	cOR6K2P

Table 7 Mosquito olfactory receptors, gene symbols

Gene Symbol	Gene Symbol
GPRor53	GPRor18
GPRor54	GPRor19
GPRor55	GPRor20
GPRor56	GPRor21
GPRor57	GPRor22
GPRor58	GPRor23
GPRor59	GPRor24
GPRor60	GPRor25
GPRor61	GPRor26
GPRor62	GPRor27
GPRor63	GPRor28
GPRor64	GPRor29
GPRor65	GPRor30
GPRor66	GPRor31
GPRor67	GPRor32
GPRor68	GPRor33
GPRor69	GPRor34
GPRor70	GPRor35
GPRor71	GPRor36
GPRor72	GPRor37
GPRor73	GPRor38
GPRor74	GPRor39
GPRor75	GPRor40
GPRor76	GPRor41
GPRor77	GPRor42
GPRor78	GPRor43
GPRor79	GPRor44
GPRor12	GPRor45
GPRor1	GPRor46
GPRor2	GPRor47
GPRor3	GPRor48
GPRor4	GPRor49
GPRor5	GPRor50
GPRor6	GPRor51
GPRor7	GPRor52
GPRor8	
GPRor9	
GPRor10	
GPRor11	
GPRor13	
GPRor14	
GPRor15	
GPRor16	
GPRor17	

Table 8 Other heteromultimeric receptors, gene name, NCBI gene ID numbers and related synonyms

Type	Subunit	Gene	NCBI Gene ID	Synonyms
GABA A	gamma-aminobutyric acid (GABA) A receptor, alpha 1	*GABRA 1*	2554	ECA4, EJM, GABA(A) receptor, GABA(A) receptor subunit alpha-1, Gamma-aminobutyric-acid receptor alpha-1 subunit precursor, Gamma-aminobutyric-acid receptor subunit alpha-1 precursor
	gamma-aminobutyric acid (GABA) A receptor, alpha 2	*GABRA 2*	2555	GABA(A) receptor, GABA(A) receptor subunit alpha-2, Gamma-aminobutyric-acid receptor alpha-2 subunit precursor, Gamma-aminobutyric-acid receptor subunit alpha-2 precursor
	gamma-aminobutyric acid (GABA) A receptor, alpha 3	*GABRA 3*	2556	GABA(A) receptor, GABA(A) receptor subunit alpha-3, Gamma-aminobutyric-acid receptor alpha-3 subunit precursor, Gamma-aminobutyric-acid receptor subunit alpha-3 precursor
	gamma-aminobutyric acid (GABA) A receptor, alpha 4	*GABRA 4*	2557	GABA(A) receptor, GABA(A) receptor subunit alpha-4, Gamma-aminobutyric-acid receptor alpha-4 subunit precursor, Gamma-aminobutyric-acid receptor subunit alpha-4 precursor
	gamma-aminobutyric acid (GABA) A receptor, alpha 5	*GABRA 5*	2558	GABA(A) receptor, GABA(A) receptor subunit alpha-5, Gamma-aminobutyric-acid receptor alpha-5 subunit precursor, Gamma-aminobutyric-acid receptor subunit alpha-5 precursor
	gamma-aminobutyric acid (GABA) A receptor, alpha 6	*GABRA 6*	2559	GABA(A) receptor, GABA(A) receptor subunit alpha-6, Gamma-aminobutyric-acid receptor alpha-6 subunit precursor, Gamma-aminobutyric-acid receptor subunit alpha-6 precursor, MGC116903, MGC116904
	gamma-aminobutyric acid (GABA) A receptor, beta 1	*GABRB 1*	2560	GABA(A) receptor, GABA(A) receptor subunit beta-1, Gamma-aminobutyric-acid receptor beta-1 subunit precursor, Gamma-aminobutyric-acid receptor subunit beta-1 precursor
	gamma-aminobutyric acid (GABA) A	*GABRB 2*	2561	GABA(A) receptor, GABA(A) receptor subunit beta-2, Gamma-

	receptor, beta2			aminobutyric-acid receptor beta-2 subunit precursor, Gamma-aminobutyric-acid receptor subunit beta-2 precursor, MGC119386, MGC119388, MGC119389
	gamma-aminobutyric acid (GABA) A receptor, beta3	*GABRB 3*	2562	GABA(A) receptor, GABA(A) receptor subunit beta-3, Gamma-aminobutyric-acid receptor beta-3 subunit precursor, Gamma-aminobutyric-acid receptor subunit beta-3 precursor
	gamma-aminobutyric acid (GABA) A receptor, gamma1	*GABRG 1*	2565	DKFZp686H2042, GABA(A) receptor, GABA(A) receptor subunit gamma-1, Gamma-aminobutyric-acid receptor gamma-1 subunit precursor, Gamma-aminobutyric-acid receptor subunit gamma-1 precursor, MGC33838
	gamma-aminobutyric acid (GABA) A receptor, gamma2	*GABRG 2*	2566	CAE2, ECA2, GABA(A) receptor, GABA(A) receptor subunit gamma-2, Gamma-aminobutyric-acid receptor gamma-2 subunit precursor, Gamma-aminobutyric-acid receptor subunit gamma-2 precursor, GEFSP3
	gamma-aminobutyric acid (GABA) A receptor, gamma3	*GABRG 3*	2567	GABA(A) receptor, GABA(A) receptor subunit gamma-3, Gamma-aminobutyric-acid receptor gamma-3 subunit precursor, Gamma-aminobutyric-acid receptor subunit gamma-3 precursor
	gamma-aminobutyric acid (GABA) A receptor, delta	*GABRD*	2563	GABA(A) receptor, GABA(A) receptor subunit delta, Gamma-aminobutyric-acid receptor delta subunit precursor, Gamma-aminobutyric-acid receptor subunit delta precursor
	gamma-aminobutyric acid (GABA) A receptor, epsilon	*GABRE*	2564	GABA(A) receptor, GABA(A) receptor subunit epsilon, Gamma-aminobutyric-acid receptor epsilon subunit precursor, Gamma-aminobutyric-acid receptor subunit epsilon precursor
	gamma-aminobutyric acid (GABA) A receptor, pi	*GABRP*	2568	GABA(A) receptor, GABA(A) receptor subunit pi, Gamma-aminobutyric-acid receptor pi subunit precursor, Gamma-aminobutyric-acid receptor subunit pi precursor, MGC126386, MGC126387
	gamma-aminobutyric acid (GABA) A	*GABRQ*	55879	GABA(A) receptor, GABA(A) receptor subunit theta, Gamma-

	receptor, theta			aminobutyric-acid receptor subunit theta precursor, Gamma-aminobutyric-acid receptor theta subunit precursor, MGC129629, MGC129630, THETA
GABAC	gamma-aminobutyric acid (GABA) receptor, rho 1	*GABRR1*	2569	GABA(A) receptor, GABA(A) receptor subunit rho-1, Gamma-aminobutyric-acid receptor rho-1 subunit precursor, Gamma-aminobutyric-acid receptor subunit rho-1 precursor H
	gamma-aminobutyric acid (GABA) receptor, rho 2	*GABRR2*	2570	GABA(A) receptor, GABA(A) receptor subunit rho-2, Gamma-aminobutyric-acid receptor rho-2 subunit precursor, Gamma-aminobutyric-acid receptor subunit rho-2 precursor
	gamma-aminobutyric acid (GABA) receptor, rho 3	*GABRR3*	200959	gamma-aminobutyric acid (GABA) receptor, rho 3
nAChR	cholinergic receptor, nicotinic, alpha 1 (muscle)	*CHRNA1*	1134	Acetylcholine receptor protein, alpha subunit precursor, Acetylcholine receptor subunit alpha precursor, ACHRA, ACHRD, CHNRA, CHRNA, CMS2A, FCCMS, SCCMS
	cholinergic receptor, nicotinic, alpha 1 (muscle)		1134	Acetylcholine receptor protein, alpha subunit precursor, Acetylcholine receptor subunit alpha precursor, ACHRA, ACHRD, CHNRA, CHRNA, CMS2A, FCCMS, SCCMS
	cholinergic receptor, nicotinic, alpha 2 (neuronal)	*CHRNA2*	1135	Neuronal acetylcholine receptor protein, alpha-2 subunit precursor, Neuronal acetylcholine receptor subunit alpha-2 precursor
	cholinergic receptor, nicotinic, alpha 3	*CHRNA3*	1136	LNCR2, MGC104879, NACHRA3, Neuronal acetylcholine receptor protein, alpha-3 subunit precursor, Neuronal acetylcholine receptor subunit alpha-3 precursor, PAOD2
	cholinergic receptor, nicotinic, alpha 4	*CHRNA4*	1137	BFNC, EBN, EBN1, FLJ95812, NACHR, NACHRA4, NACRA4, Neuronal acetylcholine receptor protein, alpha-4 subunit precursor, Neuronal acetylcholine receptor subunit alpha-4 precursor
	cholinergic receptor, nicotinic, alpha 5	*CHRNA5*	1138	NACHRA5, Neuronal acetylcholine receptor protein, alpha-5 subunit precursor, Neuronal acetylcholine

				receptor subunit alpha-5 precursor
	cholinergic receptor, nicotinic, alpha 6	*CHRNA 6*	8973	Neuronal acetylcholine receptor protein, alpha-6 subunit precursor, Neuronal acetylcholine receptor subunit alpha-6 precursor
	cholinergic receptor, nicotinic, alpha 7	*CHRNA 7*	1139	CHRNA7-2, NACHRA7, Neuronal acetylcholine receptor protein, alpha-7 subunit precursor, Neuronal acetylcholine receptor subunit alpha-7 precursor
	cholinergic receptor, nicotinic, alpha 9	*CHRNA 9*	55584	HSA243342, MGC142109, MGC142135, NACHRA9, NACHR alpha 9, Neuronal acetylcholine receptor protein, alpha-9 subunit precursor, Neuronal acetylcholine receptor subunit alpha-9 precursor, Nicotinic acetylcholine receptor subunit alpha 9
	cholinergic receptor, nicotinic, alpha 10	*CHRNA 10*	57053	NACHRA10, NACHR alpha 10, Neuronal acetylcholine receptor protein, alpha-10 subunit precursor, Neuronal acetylcholine receptor subunit alpha-10 precursor, Nicotinic acetylcholine receptor subunit alpha 10
	cholinergic receptor, nicotinic, beta 1 (muscle)	*CHRNB 1*	1140	Acetylcholine receptor protein, beta subunit precursor, Acetylcholine receptor subunit beta precursor, ACHRB, CHRNB, CMS1D, CMS2A, SCCMS
	cholinergic receptor, nicotinic, beta 2 (neuronal)	*CHRNB 2*	1141	EFNL3, nAChRB2, Neuronal acetylcholine receptor protein, beta-2 subunit precursor, Neuronal acetylcholine receptor subunit beta-2 precursor
	cholinergic receptor, nicotinic, beta 3	*CHRNB 3*	1142	Neuronal acetylcholine receptor protein, beta-3 subunit precursor, Neuronal acetylcholine receptor subunit beta-3 precursor
	cholinergic receptor, nicotinic, beta 4	*CHRNB 4*	1143	Neuronal acetylcholine receptor protein, beta-4 subunit precursor, Neuronal acetylcholine receptor subunit beta-4 precursor
	cholinergic receptor, nicotinic, gamma	*CHRNG*	1146	Acetylcholine receptor protein, gamma subunit precursor, Acetylcholine receptor subunit gamma precursor, ACHRG, MGC133376
	cholinergic receptor, nicotinic, delta	*CHRND*	1144	Acetylcholine receptor protein, delta subunit precursor, Acetylcholine receptor subunit delta precursor, ACHRD, CMS2A,

				FCCMS, SCCMS
	cholinergic receptor, nicotinic, epsilon	*CHRNE*	1145	Acetylcholine receptor protein, epsilon subunit precursor, Acetylcholine receptor subunit epsilon precursor, ACHRE, CMS1D, CMS1E, CMS2A, FCCMS, SCCMS
5-HT3	5-hydroxytryptamine (serotonin) receptor 3A	*HTR3A*	3359	5-HT-3, 5-HT3A, 5HT3R, 5-HT3R, 5-hydroxytryptamine 3 receptor precursor, HTR3, Serotonin-gated ion channel receptor
	5-hydroxytryptamine (serotonin) receptor 3B	*HTR3B*	9177	5-HT3B
	5-hydroxytryptamine (serotonin) receptor 3C	*HTR3C*	170572	none
	5-hydroxytryptamine (serotonin) receptor 3D	*HTR3D*	200909	MGC119636, MGC119637
	5-hydroxytryptamine (serotonin) receptor 3E	*HTR3E*	285242	5-HT3c1, MGC120035, MGC120036, MGC120037
Glycine (GlyR)	glycine receptor, alpha 1	*GLRA1*	2741	glycine receptor, alpha 1 (startle disease/hyperekplexia, stiff man syndrome), Glycine receptor 48 kDa subunit, Glycine receptor alpha-1 chain precursor, Glycine receptor strychnine-binding subunit, Glycine receptor subunit alpha-1 precursor, MGC138878, MGC138879, STHE, Strychnine-binding subunit
	glycine receptor, alpha 2	*GLRA2*	2742	Glycine receptor alpha-2 chain precursor, Glycine receptor subunit alpha-2 precursor
	glycine receptor, alpha 3	*GLRA3*	8001	Glycine receptor alpha-3 chain precursor, Glycine receptor subunit alpha-3 precursor
	glycine receptor, alpha 4	*GLRA4*	441509	none
	glycine receptor, beta	*GLRB*	2743	Glycine receptor 58 kDa subunit, Glycine receptor beta chain precursor, Glycine receptor subunit beta precursor
Glutamate receptors:	glutamate receptor, ionotropic, AMPA 1	*GRIA1*	2890	AMPA-selective glutamate receptor 1, GLUH1, GLUR1, GluR-1, GLURA, GluR-A, GluR-K1, Glutamate receptor 1 precursor,

				Glutamate receptor ionotropic, AMPA 1, HBGR1, MGC133252
	glutamate receptor, ionotropic, AMPA 2	*GRIA2*	2891	AMPA-selective glutamate receptor 2, GLUR2, GluR-2, GLURB, GluR-B, GluR-K2, Glutamate receptor 2 precursor, Glutamate receptor ionotropic, AMPA 2, HBGR2
	glutamate receptor, ionotrophic, AMPA 3	*GRIA3*	2892	AMPA-selective glutamate receptor 3, GLUR3, GluR-3, GLURC, gluR-C, GluR-C, GLUR-C, GluR-K3, GLUR-K3, Glutamate receptor 3 precursor, Glutamate receptor ionotropic, AMPA 3, MRX94
	glutamate receptor, ionotrophic, AMPA 4	*GRIA4*	2893	AMPA-selective glutamate receptor 4, GluR4, GLUR4, GluR-4, GLUR4C, GLURD, GluR-D, Glutamate receptor 4 precursor, Glutamate receptor ionotropic, AMPA 4
	glutamate receptor, ionotropic, kainate 1	*GRIK1*	2897	EAA3, EEA3, Excitatory amino acid receptor 3, GLR5, GluR5, GLUR5, GluR-5, Glutamate receptor, ionotropic kainate 1 precursor, Glutamate receptor 5
	glutamate receptor, ionotropic, kainate 2	*GRIK2*	2898	EAA4, Excitatory amino acid receptor 4, GLR6, GLUK6, GluR6, GLUR6, GluR-6, Glutamate receptor, ionotropic kainate 2 precursor, Glutamate receptor 6, MGC74427, MRT6
	glutamate receptor, ionotropic, kainate 3	*GRIK3*	2899	EAA5, Excitatory amino acid receptor 5, GLR7, GluR7, GLUR7, GluR-7, GluR7a, Glutamate receptor, ionotropic kainate 3 precursor, Glutamate receptor 7
	glutamate receptor, ionotropic, kainate 4	*GRIK4*	2900	EAA1, Excitatory amino acid receptor 1, Glutamate receptor, ionotropic kainate 4 precursor, Glutamate receptor KA-1, GRIK, KA1
	glutamate receptor, ionotropic, kainate 5	*GRIK5*	2901	EAA2, Excitatory amino acid receptor 2, Glutamate receptor, ionotropic kainate 5 precursor, Glutamate receptor KA-2, GRIK2, KA2
	glutamate receptor, ionotropic, N-methyl D-aspartate 1	*GRIN1*	2902	NMDA1, NMDAR1, N-methyl-D-aspartate receptor subunit NR1, NR1
	glutamate receptor, ionotropic, N-methyl D-aspartate-like 1A	*GRINL1A*	81488	none
	glutamate receptor,	*GRINL1*	8453	GLURR2

	ionotropic, N-methyl D-aspartate-like 1B	*B*	4	
	glutamate receptor, ionotropic, N-methyl D-aspartate 2A	*GRIN2A*	2903	hNR2A, NMDAR2A, N-methyl D-aspartate receptor subtype 2A, NR2A
	glutamate receptor, ionotropic, N-methyl D-aspartate 2B	*GRIN2B*	2904	hNR3, MGC142178, MGC142180, NMDAR2B, N-methyl D-aspartate receptor subtype 2B, N-methyl-D-aspartate receptor subunit 3, NR2B, NR3
	glutamate receptor, ionotropic, N-methyl D-aspartate 2C	*GRIN2C*	2905	NMDAR2C, N-methyl D-aspartate receptor subtype 2C, NR2C
	glutamate receptor, ionotropic, N-methyl D-aspartate 2D	*GRIN2D*	2906	EB11, NMDAR2D, N-methyl D-aspartate receptor subtype 2D, NR2D
	glutamate receptor, ionotropic, N-methyl-D-aspartate 3A	*GRIN3A*	116443	FLJ45414, KIAA1973, NMDAR-L, N-methyl-D-aspartate receptor subtype NR3A, NR3A
	GluN3B	*GRIN3B*		
ATP-gated channels:	purinergic receptor P2X, ligand-gated ion channel, 1	*P2RX1*	5023	ATP receptor, P2X1, P2X purinoceptor 1, Purinergic receptor
	purinergic receptor P2X, ligand-gated ion channel, 2	*P2RX2*	22953	ATP receptor, MGC129601, P2X2, P2X purinoceptor 2, Purinergic receptor
	purinergic receptor P2X, ligand-gated ion channel, 3	*P2RX3*	5024	ATP receptor, MGC129956, P2X3, P2X purinoceptor 3, Purinergic receptor
	purinergic receptor P2X, ligand-gated ion channel, 4	*P2RX4*	5025	ATP receptor, P2X4, P2X4R, P2X purinoceptor 4, Purinergic receptor
	purinergic receptor P2X, ligand-gated ion channel, 5	*P2RX5*	5026	ATP receptor, MGC47755, P2X5, P2X5R, P2X purinoceptor 5, Purinergic receptor
	purinergic receptor P2X, ligand-gated ion channel, 6	*P2RX6*	9127	ATP receptor, MGC129625, P2RXL1, P2X6, P2XM, P2X purinoceptor 6, Purinergic receptor, Purinergic receptor P2X-like 1, purinergic receptor P2X-like 1, orphan receptor
	purinergic receptor P2X, ligand-gated ion channel, 7	*P2RX7*	5027	ATP receptor, MGC20089, P2X7, P2X purinoceptor 7, P2Z receptor, Purinergic receptor
ENaC/DEG family	sodium channel, nonvoltage-gated 1 alpha	*SCNN1A*	6337	Alpha ENaC, Alpha NaCH, Amiloride-sensitive sodium channel alpha-subunit, Amiloride-sensitive sodium channel subunit alpha,

				ENaCa, ENaCalpha, Epithelial Na(+) channel subunit alpha, Epithelial Na+ channel alpha subunit, FLJ21883, Nonvoltage-gated sodium channel 1 alpha subunit, Nonvoltage-gated sodium channel 1 subunit alpha, SCNEA, SCNN1
	sodium channel, nonvoltage-gated 1, beta	*SCNN1 B*	6338	Amiloride-sensitive sodium channel beta-subunit, Amiloride-sensitive sodium channel subunit beta, Beta ENaC, Beta NaCH, ENaCb, ENaCB, ENaCbeta, Epithelial Na(+) channel subunit beta, Epithelial Na+ channel beta subunit, Nonvoltage-gated sodium channel 1 beta subunit, Nonvoltage-gated sodium channel 1 subunit beta, SCNEB, sodium channel, nonvoltage-gated 1, beta (Liddle syndrome)
	sodium channel, nonvoltage-gated 1, gamma	*SCNN1 G*	6340	Amiloride-sensitive sodium channel gamma-subunit, Amiloride-sensitive sodium channel subunit gamma, ENaCg, ENaCgamma, Epithelial Na(+) channel subunit gamma, Epithelial Na+ channel gamma subunit, Gamma ENaC, Gamma NaCH, Nonvoltage-gated sodium channel 1 gamma subunit, Nonvoltage-gated sodium channel 1 subunit gamma, PHA1, SCNEG
	sodium channel, nonvoltage-gated 1, delta	*SCNN1 D*	6339	Amiloride-sensitive sodium channel delta-subunit, Amiloride-sensitive sodium channel subunit delta, Delta ENaC, Delta NaCH, dNaCh, DNACH, ENaCd, ENaCdelta, Epithelial Na(+) channel subunit delta, Epithelial Na+ channel delta subunit, MGC149710, MGC149711, Nonvoltage-gated sodium channel 1 delta subunit, Nonvoltage-gated sodium channel 1 subunit delta, SCNED
	amiloride-sensitive cation channel 1, neuronal	ACCN2	41	Acid-sensing ion channel 1, Amiloride-sensitive cation channel 2, neuronal, ASIC, ASIC1, ASIC1A, BNaC2, BNAC2, Brain sodium channel 2, hBNaC2
	amiloride-sensitive cation channel 2, neuronal	ACCN1	40	ACCN, Acid-sensing ion channel 2, Amiloride-sensitive brain sodium channel, Amiloride-sensitive cation channel 1, neuronal, amiloride-

				sensitive cation channel 1, neuronal (degenerin), Amiloride-sensitive cation channel neuronal 1, ASIC2, ASIC2a, BNaC1, BNAC1, BNC1, Brain sodium channel 1, hBNaC1, Mammalian degenerin homolog, MDEG
	amiloride-sensitive cation channel 3	ACCN3	9311	Acid-sensing ion channel 3, Amiloride-sensitive cation channel 3, ASIC3, DRASIC, hASIC3, hTNaC1, SLNAC1, Testis sodium channel 1, TNaC1, TNAC1
	amiloride-sensitive cation channel 4, pituitary	ACCN4	55515	Acid-sensing ion channel 4, Amiloride-sensitive cation channel 4, Amiloride-sensitive cation channel 4, pituitary, ASIC4, BNAC4, MGC17248, MGC24860
	amiloride-sensitive cation channel 5, intestinal	ACCN5	51802	HINAC, INAC
TRP family	transient receptor potential cation channel, subfamily A, member 1	TRPA1	8989	ANKTM1, Ankyrin-like with transmembrane domains protein 1, Transformation sensitive-protein p120, Transient receptor potential cation channel subfamily A member 1
	transient receptor potential cation channel, subfamily C, member 1	TRPC1	7220	HTRP-1, MGC133334, MGC133335, Short transient receptor potential channel 1, TRP1, TRP-1 protein, TrpC1
	transient receptor potential cation channel, subfamily C, member 2 (pseudogene)	TRPC2	7221	transient receptor potential cation channel, subfamily C, member 2, transient receptor potential channel 2
	transient receptor potential cation channel, subfamily C, member 3	TRPC3	7222	Htrp3, Htrp-3, Short transient receptor potential channel 3, TRP3, TrpC3
	transient receptor potential cation channel, subfamily C, member 4	TRPC4	7223	hTrp4, HTRP4, hTrp-4, MGC119570, MGC119571, MGC119572, MGC119573, Short transient receptor potential channel 4, TRP4, TrpC4, trp-related protein 4, Trp-related protein 4
	transient receptor potential cation channel, subfamily C, member 4 associated protein	TRPC4 AP	26133	C20orf188, dJ756N5.2, DKFZp586C1223, DKFZP727M231, Protein TRUSS, Short transient receptor potential channel 4-associated protein, TAP1 protein, TNF-receptor ubiquitous

				scaffolding/signaling protein, Trp4-associated protein, Trpc4-associated protein, TRRP4AP, TRUSS, TRUSS protein
	transient receptor potential cation channel, subfamily C, member 5	TRPC5	7224	Htrp5, Htrp-5, Short transient receptor potential channel 5, TRP5, TrpC5
	transient receptor potential cation channel, subfamily C, member 6	TRPC6	7225	FLJ11098, FLJ14863, FSGS2, Short transient receptor potential channel 6, TRP6, TrpC6
	transient receptor potential cation channel, subfamily C, member 6 pseudogene	TRPC6P	644218	LOC644218, similar to transient receptor potential cation channel, subfamily C, member 6, TRPC6L
	transient receptor potential cation channel, subfamily C, member 7	TRPC7	57113	Short transient receptor potential channel 7, TRP7, TRP7 protein, TrpC7
	transient receptor potential cation channel, subfamily M, member 1	TRPM1	4308	LTRPC1, MLSN, MLSN1
	transient receptor potential cation channel, subfamily M, member 2	TRPM2	7226	EREG1, Estrogen-responsive element-associated gene 1 protein, KNP3, Long transient receptor potential channel 2, LTrpC2, LTRPC2, LTrpC-2, MGC133383, NUDT9H, NUDT9L1, Transient receptor potential cation channel subfamily M member 2, Transient receptor potential channel 7, TrpC7, TRPC7
	transient receptor potential cation channel, subfamily M, member 3	TRPM3	80036	GON-2, KIAA1616, Long transient receptor potential channel 3, LTrpC3, LTRPC3, Melastatin-2, MLSN2, Transient receptor potential cation channel subfamily M member 3
	transient receptor potential cation channel, subfamily M, member 4	TRPM4	54795	Calcium-activated non-selective cation channel 1, FLJ20041, hTRPM4, Long transient receptor potential channel 4, LTRPC4, Melastatin-4, Transient receptor potential cation channel subfamily M member 4, TRPM4B
	transient receptor potential cation channel, subfamily M, member 5	TRPM5	29850	LTRPC5, MTR1

	transient receptor potential cation channel, subfamily M, member 6	TRPM6	140803	CHAK2, Channel kinase 2, FLJ22628, HMGX, HOMG, HOMG1, HSH, Melastatin-related TRP cation channel 6, Transient receptor potential cation channel subfamily M member 6
	transient receptor potential cation channel, subfamily M, member 7	TRPM7	54822	CHAK, CHAK1, Channel-kinase 1, FLJ20117, FLJ25718, Long transient receptor potential channel 7, LTrpC7, LTRPC7, Transient receptor potential cation channel subfamily M member 7, TRP-PLIK
	transient receptor potential cation channel, subfamily M, member 8	TRPM8	79054	Long transient receptor potential channel 6, LTrpC6, LTRPC6, MGC2849, Transient receptor potential cation channel subfamily M member 8, Transient receptor potential-p8, TRPP8, Trp-p8
	trichorhinophalangeal syndrome I	TRPS1	7227	GC79, LGCR, MGC134928, Tricho-rhino-phalangeal syndrome type I protein, Zinc finger protein GC79, Zinc finger transcription factor Trps1
	tRNA phosphotransferase 1	TRPT1	83707	MGC11134, tRNA 2'-phosphotransferase 1
	transient receptor potential cation channel, subfamily V, member 1	TRPV1	7442	Capsaicin receptor, DKFZp434K0220, osm-9-like TRP channel 1, OTRPC1, Transient receptor potential cation channel subfamily V member 1, TrpV1, Vanilloid receptor 1, VR1
	transient receptor potential cation channel, subfamily V, member 2	TRPV2	51393	MGC12549, osm-9-like TRP channel 2, OTRPC2, Transient receptor potential cation channel subfamily V member 2, TrpV2, Vanilloid receptor-like protein 1, VRL, VRL1, VRL-1
	transient receptor potential cation channel, subfamily V, member 3	TRPV3	162514	Transient receptor potential cation channel subfamily V member 3, TrpV3, Vanilloid receptor-like 3, VRL3, VRL-3
	transient receptor potential cation channel, subfamily V, member 4	TRPV4	59341	osm-9-like TRP channel 4, OTRPC4, Transient receptor potential cation channel subfamily V member 4, Transient receptor potential protein 12, TRP12, TrpV4, Vanilloid receptor-like channel 2, Vanilloid receptor-like protein 2, Vanilloid receptor-related osmotically-activated channel, VRL2, VRL-2, VROAC, VR-OAC
	transient receptor	TRPV5	5630	Calcium transport protein 2, CaT2,

	potential cation channel, subfamily V, member 5		2	CAT2, ECaC, ECaC1, ECAC1, Epithelial calcium channel 1, osm-9-like TRP channel 3, OTRPC3, Transient receptor potential cation channel subfamily V member 5, TrpV5
	transient receptor potential cation channel, subfamily V, member 6	TRPV6	55503	ABP/ZF, Calcium transport protein 1, CaT1, CAT1, CATL, CaT-L, CaT-like, ECaC2, ECAC2, Epithelial calcium channel 2, HSA277909, LP6728, Transient receptor potential cation channel subfamily V member 6, TrpV6, ZFAB
CNG family	cyclic nucleotide gated channel alpha 1	CNGA1	1259	cGMP-gated cation channel alpha 1, CNCG, CNCG1, CNG1, CNG-1, CNG channel alpha 1, Cyclic nucleotide-gated cation channel 1, Cyclic-nucleotide-gated cation channel 1, Cyclic nucleotide gated channel, photoreceptor, Cyclic nucleotide-gated channel, photoreceptor, Cyclic nucleotide gated channel alpha 1, Cyclic nucleotide-gated channel alpha 1, RCNC1, RCNCa, RCNCalpha, Rod photoreceptor cGMP-gated channel alpha subunit, Rod photoreceptor cGMP-gated channel subunit alpha
	cyclic nucleotide gated channel alpha 2	CNGA2	1260	CNCA, CNCA1, CNCG2, CNG2, CNG-2, CNG channel 2, Cyclic nucleotide-gated cation channel 2, Cyclic nucleotide-gated olfactory channel, FLJ46312, OCNC1, OCNCa, OCNCalpha, OCNCALPHA
	cyclic nucleotide gated channel alpha 3	CNGA3	1261	ACHM2, CCNC1, CCNCa, CCNCalpha, CNCG3, CNG3, CNG-3, CNG channel alpha 3, Cone photoreceptor cGMP-gated channel alpha subunit, Cone photoreceptor cGMP-gated channel subunit alpha, Cyclic nucleotide-gated cation channel alpha 3, Cyclic nucleotide-gated channel alpha 3
	cyclic nucleotide gated channel alpha 4	CNGA4	338753, 1262	CNCA2, CNG5, CNGB2, MGC126168, MGC126169, OCNC2, OCNCb, OCNCBETA
	cyclic nucleotide gated channel beta 1	CNGB1	1258	CNCG2, CNCG3L, CNCG4, CNG4, CNG-4, CNGB1B, CNG channel 4,

				Cyclic nucleotide-gated cation channel 4, Cyclic nucleotide-gated cation channel modulatory subunit, GAR1, GARP, RCNC2, RCNCb, RCNCbeta
	cyclic nucleotide gated channel beta 3	CNGB3	54714	ACHM1, ACHM3, CNG channel beta 3, Cone photoreceptor cGMP-gated channel beta subunit, Cone photoreceptor cGMP-gated channel subunit beta, Cyclic nucleotide-gated cation channel beta 3, Cyclic nucleotide-gated cation channel modulatory subunit, Cyclic nucleotide-gated channel beta 3, RMCH, RMCH1
HCN family	hyperpolarization activated cyclic nucleotide-gated potassium channel 1	HCN1	348980	BCNG1, BCNG-1, Brain cyclic nucleotide gated channel 1, Brain cyclic nucleotide-gated channel 1, HAC-2, Potassium/sodium hyperpolarization-activated cyclic nucleotide-gated channel 1
	hyperpolarization activated cyclic nucleotide-gated potassium channel 2	HCN2	610	BCNG2, BCNG-2, Brain cyclic nucleotide gated channel 2, Brain cyclic nucleotide-gated channel 2, HAC-1, Potassium/sodium hyperpolarization-activated cyclic nucleotide-gated channel 2
	hyperpolarization activated cyclic nucleotide-gated potassium channel 3	HCN3	57657	KIAA1535, MGC131493, Potassium/sodium hyperpolarization-activated cyclic nucleotide-gated channel 3
	hyperpolarization activated cyclic nucleotide-gated potassium channel 4	HCN4	10021	Potassium/sodium hyperpolarization-activated cyclic nucleotide-gated channel 4
KCN family	potassium voltage-gated channel, shaker-related subfamily, member 1 (episodic ataxia with myokymia)	KCNA1	3736	AEMK, EA1, HBK1, HUK1, HUKI, Kv1.1, KV1.1, MBK1, MGC126782, MGC138385, MK1, Potassium voltage-gated channel subfamily A member 1, RBK1, Voltage-gated potassium channel subunit Kv1.1
	potassium voltage-gated channel, shaker-related subfamily, member 2	KCNA2	3737	HBK5, HK4, HUKIV, Kv1.2, KV1.2, MGC50217, MK2, NGK1, Potassium voltage-gated channel subfamily A member 2, RBK2, Voltage-gated potassium channel subunit Kv1.2
	potassium voltage-gated channel, shaker-related	KCNA3	3738	HGK5, HLK3, HPCN3, HuKIII, HUKIII, Kv1.3, KV1.3, MK3, PCN3, Potassium voltage-gated channel

	subfamily, member 3			subfamily A member 3, Voltage-gated potassium channel subunit Kv1.3
	potassium voltage-gated channel, shaker-related subfamily, member 4	KCNA4	3739	HBK4, HK1, HPCN2, HUKII, KCNA4L, KCNA8, Kv1.4, KV1.4, PCN2, Potassium voltage-gated channel subfamily A member 4, Voltage-gated potassium channel subunit Kv1.4
	potassium voltage-gated channel, shaker-related subfamily, member 5	KCNA5	3741	ATFB7, HCK1, HK2, HPCN1, Kv1.5, KV1.5, MGC117058, MGC117059, PCN1, Potassium voltage-gated channel subfamily A member 5, Voltage-gated potassium channel subunit Kv1.5
	potassium voltage-gated channel, shaker-related subfamily, member 6	KCNA6	3742	FLJ25134, HBK2, Kv1.6, KV1.6, Potassium voltage-gated channel subfamily A member 6, Voltage-gated potassium channel subunit Kv1.6
	potassium voltage-gated channel, shaker-related subfamily, member 7	KCNA7	3743	HAK6, Kv1.7, KV1.7
	potassium voltage-gated channel, shaker-related subfamily, member 10	KCNA10	3744	Kcn1, Kv1.8
	potassium voltage-gated channel, shaker-related subfamily, beta member 1	KCNAB1	7881	AKR6A3, hKvb3, hKvBeta3, K(+) channel beta-1 subunit, K(+) channel subunit beta-1, KCNA1B, Kvb1.3, Kv-beta-1, KV-BETA-1, Voltage-gated potassium channel beta-1 subunit, Voltage-gated potassium channel subunit beta-1
	potassium voltage-gated channel, shaker-related subfamily, beta member 2	KCNAB2	8514	AKR6A5, HKvbeta2, HKvbeta2.1, HKvbeta2.2, K(+) channel beta-2 subunit, K(+) channel subunit beta-2, KCNA2B, KCNK2, Kv-beta-2, KV-BETA-2, MGC117289, Voltage-gated potassium channel beta-2 subunit, Voltage-gated potassium channel subunit beta-2
	potassium voltage-gated channel, shaker-related subfamily, beta member 3	KCNAB3	9196	AKR6A9, K(+) channel beta-3 subunit, K(+) channel subunit beta-3, KCNA3.1B, KCNA3B, Kv-beta-3, KV-BETA-3, MGC116886, Voltage-gated potassium channel beta-3 subunit, Voltage-gated potassium channel subunit beta-3
	potassium voltage-gated channel, Shab-	KCNB1	3745	DRK1, h-DRK1, Kv2.1, KV2.1, Potassium voltage-gated channel

	related subfamily, member 1			subfamily B member 1, Voltage-gated potassium channel subunit Kv2.1
	potassium voltage-gated channel, Shab-related subfamily, member 2	KCNB2	9312	Kv2.2, Potassium voltage-gated channel subfamily B member 2, Voltage-gated potassium channel subunit Kv2.2
	potassium voltage-gated channel, Shaw-related subfamily, member 1	KCNC1	3746	FLJ41162, FLJ42249, FLJ43491, Kv3.1, KV3.1, Kv4, KV4, MGC129855, NGK2, Potassium voltage-gated channel subfamily C member 1, Voltage-gated potassium channel subunit Kv3.1
	potassium voltage-gated channel, Shaw-related subfamily, member 2	KCNC2	3747	Kv3.2, KV3.2, MGC138196
	potassium voltage-gated channel, Shaw-related subfamily, member 3	KCNC3	3748	KSHIIID, Kv3.3, KV3.3, Potassium voltage-gated channel subfamily C member 3, SCA13, Voltage-gated potassium channel subunit Kv3.3
	potassium voltage-gated channel, Shaw-related subfamily, member 4	KCNC4	3749	HKSHIIIC, KSHIIIC, Kv3.4, KV3.4, MGC126818, Potassium voltage-gated channel subfamily C member 4, Voltage-gated potassium channel subunit Kv3.4
	potassium voltage-gated channel, Shal-related subfamily, member 1	KCND1	3750	Kv4.1, Potassium voltage-gated channel subfamily D member 1, Voltage-gated potassium channel subunit Kv4.1
	potassium voltage-gated channel, Shal-related subfamily, member 2	KCND2	3751	KIAA1044, Kv4.2, KV4.2, MGC119702, MGC119703, Potassium voltage-gated channel subfamily D member 2, RK5, Voltage-gated potassium channel subunit Kv4.2
	potassium voltage-gated channel, Shal-related subfamily, member 3	KCND3	3752	KCND3L, KCND3S, KSHIVB, Kv4.3, KV4.3, MGC142035, MGC142037, Potassium voltage-gated channel subfamily D member 3, Voltage-gated potassium channel subunit Kv4.3
	potassium voltage-gated channel, Isk-related family, member 1	KCNE1	3753	Delayed rectifier potassium channel subunit IsK, FLJ18426, FLJ38123, FLJ94103, IKs producing slow voltage-gated potassium channel beta subunit Mink, IKs producing slow voltage-gated potassium channel subunit beta Mink, ISK, JLNS, JLNS2, LQT2/5, LQT5, MGC33114, Minimal potassium channel, minK, MinK, Potassium

				voltage-gated channel subfamily E member 1
	KCNE1-like	KCNE1L	23630	AMMECR2 protein, AMME syndrome candidate gene 2 protein, Potassium voltage-gated channel subfamily E member 1-like protein
	potassium voltage-gated channel, Isk-related family, member 2	KCNE2	9992	LQT5, LQT6, MGC138292, Minimum potassium ion channel-related peptide 1, MinK-related peptide 1, MiRP1, MIRP1, Potassium channel beta subunit MiRP1, Potassium channel subunit beta MiRP1, Potassium voltage-gated channel subfamily E member 2
	potassium voltage-gated channel, Isk-related family, member 3	KCNE3	10008	DKFZp781H21101, HOKPP, MGC102685, MGC129924, Minimum potassium ion channel-related peptide 2, MinK-related peptide 2, MiRP2, Potassium channel beta subunit MiRP2, Potassium channel subunit beta MiRP2, Potassium voltage-gated channel subfamily E member 3
	potassium voltage-gated channel, Isk-related family, member 4	KCNE4	23704	MGC20353, Minimum potassium ion channel-related peptide 3, MinK-related peptide 3, MiRP3, MIRP3, Potassium channel beta subunit MiRP3, Potassium channel subunit beta MiRP3, Potassium voltage-gated channel subfamily E member 4
	potassium voltage-gated channel, subfamily F, member 1	KCNF1	3754	IK8, KCNF, kH1, Kv5.1, KV5.1, MGC33316, Potassium voltage-gated channel subfamily F member 1, Voltage-gated potassium channel subunit Kv5.1
	potassium voltage-gated channel, subfamily G, member 1	KCNG1	3755	K13, KCNG, kH2, Kv6.1, KV6.1, MGC12878, Potassium voltage-gated channel subfamily G member 1, Voltage-gated potassium channel subunit Kv6.1
	potassium voltage-gated channel, subfamily G, member 2	KCNG2	26251	Cardiac potassium channel subunit, KCNF2, Kv6.2, KV6.2, Potassium voltage-gated channel subfamily G member 2, Voltage-gated potassium channel subunit Kv6.2
	potassium voltage-gated channel, subfamily G, member 3	KCNG3	170850	Kv10.1, KV10.1, Kv6.3, KV6.3, Potassium voltage-gated channel subfamily G member 3, Voltage-gated potassium channel subunit

				Kv6.3
	potassium voltage-gated channel, subfamily G, member 4	KCNG4	93107	KCNG3, Kv6.3, KV6.3, Kv6.4, KV6.4, MGC129609, MGC4558, Potassium voltage-gated channel subfamily G member 4, Voltage-gated potassium channel subunit Kv6.4
	potassium voltage-gated channel, subfamily H (eag-related), member 1	KCNH1	3756	eag, EAG, eag1, EAG1, Ether-a-go-go potassium channel 1, h-eag, hEAG1, Kv10.1, MGC142269, Potassium voltage-gated channel subfamily H member 1, Voltage-gated potassium channel subunit Kv10.1
	potassium voltage-gated channel, subfamily H (eag-related), member 2	KCNH2	3757	eag homolog, Eag-related protein 1, ERG, erg1, Erg1, ERG1, Ether-a-go-go related gene potassium channel 1, Ether-a-go-go-related gene potassium channel 1, Ether-a-go-go related protein 1, Ether-a-go-go-related protein 1, HERG, H-ERG, HERG1, Kv11.1, LQT2, Potassium voltage-gated channel subfamily H member 2, SQT1, Voltage-gated potassium channel subunit Kv11.1
	potassium voltage-gated channel, subfamily H (eag-related), member 3	KCNH3	23416	BEC1, Brain-specific eag-like channel 1, elk2, ELK2, ELK channel 2, Ether-a-go-go-like potassium channel 2, KIAA1282, Kv12.2, Potassium voltage-gated channel subfamily H member 3, Voltage-gated potassium channel subunit Kv12.2
	potassium voltage-gated channel, subfamily H (eag-related), member 4	KCNH4	23415	BEC2, Brain-specific eag-like channel 2, elk1, ELK1, ELK channel 1, Ether-a-go-go-like potassium channel 1, Kv12.3, Potassium voltage-gated channel subfamily H member 4, Voltage-gated potassium channel subunit Kv12.3
	potassium voltage-gated channel, subfamily H (eag-related), member 5	KCNH5	27133	eag2, Eag2, EAG2, Ether-a-go-go potassium channel 2, hEAG2, H-EAG2, Kv10.2, Potassium voltage-gated channel subfamily H member 5, Voltage-gated potassium channel subunit Kv10.2
	potassium voltage-gated channel, subfamily H (eag-related), member 6	KCNH6	81033	Eag-related protein 2, erg2, ERG2, Ether-a-go-go-related gene potassium channel 2, Ether-a-go-go-related protein 2, HERG2,

				Kv11.2, Potassium voltage-gated channel subfamily H member 6, Voltage-gated potassium channel subunit Kv11.2
	potassium voltage-gated channel, subfamily H (eag-related), member 7	KCNH7	90134	Eag-related protein 3, erg3, ERG3, Ether-a-go-go-related gene potassium channel 3, Ether-a-go-go-related protein 3, HERG3, HERG-3, Kv11.3, MGC45986, Potassium voltage-gated channel subfamily H member 7, Voltage-gated potassium channel subunit Kv11.3
	potassium voltage-gated channel, subfamily H (eag-related), member 8	KCNH8	131096	ELK, ELK1, elk3, ELK3, ELK channel 3, Ether-a-go-go-like potassium channel 3, hElk1, Kv12.1, Potassium voltage-gated channel subfamily H member 8, Voltage-gated potassium channel subunit Kv12.1
	Kv channel interacting protein 1	KCNIP1	308200	A-type potassium channel modulatory protein 1, KChIP1, KCHIP1, Kv channel-interacting protein 1, MGC95, Potassium channel-interacting protein 1, VABP, Vesicle APC-binding protein
	Kv channel interacting protein 2	KCNIP2	30819	A-type potassium channel modulatory protein 2, Cardiac voltage gated potassium channel modulatory subunit, Cardiac voltage-gated potassium channel modulatory subunit, DKFZp566L1246, KChIP2, KCHIP2, Kv channel-interacting protein 2, MGC17241, Potassium channel-interacting protein 2
	Kv channel interacting protein 3, calsenilin	KCNIP3	30818	A-type potassium channel modulatory protein 3, calsenilin, Calsenilin, CSEN, DREAM, DRE-antagonist modulator, KChIP3, KCHIP3, Kv channel-interacting protein 3, MGC18289
	Kv channel interacting protein 4	KCNIP4	803303	A-type potassium channel modulatory protein 4, CALP, Calsenilin-like protein, KChIP4, KCHIP4, Kv channel-interacting protein 4, MGC44947, Potassium channel-interacting protein 4
	potassium inwardly-rectifying channel, subfamily J, member 1	KCNJ1	3758	ATP-regulated potassium channel ROM-K, ATP-sensitive inward rectifier potassium channel 1,

				Kir1.1, KIR1.1, Potassium channel, inwardly rectifying subfamily J member 1, ROMK, ROMK1
	potassium inwardly-rectifying channel, subfamily J, member 2	KCNJ2	3759	Cardiac inward rectifier potassium channel, HHBIRK1, HHIRK1, HIRK1, Inward rectifier K(+) channel Kir2.1, Inward rectifier potassium channel 2, IRK1, Kir2.1, KIR2.1, LQT7, Potassium channel, inwardly rectifying subfamily J member 2, SQT3
	potassium inwardly-rectifying channel, subfamily J, member 3	KCNJ3	3760	GIRK1, G protein-activated inward rectifier potassium channel 1, Inward rectifier K(+) channel Kir3.1, KGA, Kir3.1, KIR3.1, Potassium channel, inwardly rectifying subfamily J member 3
	potassium inwardly-rectifying channel, subfamily J, member 4	KCNJ4	3761	Hippocampal inward rectifier, HIR, hIRK2, HIRK2, HRK1, Inward rectifier K(+) channel Kir2.3, Inward rectifier potassium channel 4, IRK3, Kir2.3, MGC142066, MGC142068, Potassium channel, inwardly rectifying subfamily J member 4
	potassium inwardly-rectifying channel, subfamily J, member 5	KCNJ5	3762	Cardiac inward rectifier, CIR, GIRK4, G protein-activated inward rectifier potassium channel 4, Heart KATP channel, Inward rectifier K(+) channel Kir3.4, KATP1, KATP-1, Kir3.4, KIR3.4, Potassium channel, inwardly rectifying subfamily J member 5
	potassium inwardly-rectifying channel, subfamily J, member 6	KCNJ6	3763	BIR1, GIRK2, G protein-activated inward rectifier potassium channel 2, hiGIRK2, Inward rectifier K(+) channel Kir3.2, KATP2, KATP-2, KCNJ7, Kir3.2, KIR3.2, MGC126596, Potassium channel, inwardly rectifying subfamily J member 6
	potassium inwardly-rectifying channel, subfamily J, member 8	KCNJ8	3764	ATP-sensitive inward rectifier potassium channel 8, Inwardly rectifier K(+) channel Kir6.1, Kir6.1, KIR6.1, Potassium channel, inwardly rectifying subfamily J member 8, uKATP-1
	potassium inwardly-rectifying channel, subfamily J, member 9	KCNJ9	3765	GIRK3, G protein-activated inward rectifier potassium channel 3, Inwardly rectifier K(+) channel Kir3.3, Kir3.3, KIR3.3, Potassium channel, inwardly rectifying subfamily J member 9

	potassium inwardly-rectifying channel, subfamily J, member 10	KCNJ10	3766	ATP-dependent inwardly rectifying potassium channel Kir4.1, ATP-sensitive inward rectifier potassium channel 10, BIRK-10, Inward rectifier K(+) channel Kir1.2, KCNJ13-PEN, Kir1.2, KIR1.2, Kir4.1, KIR4.1, Potassium channel, inwardly rectifying subfamily J member 10
	potassium inwardly-rectifying channel, subfamily J, member 11	KCNJ11	3767	ATP-sensitive inward rectifier potassium channel 11, BIR, HHF2, IKATP, Inward rectifier K(+) channel Kir6.2, Kir6.2, KIR6.2, MGC133230, PHHI, Potassium channel, inwardly rectifying subfamily J member 11, TNDM3
	potassium inwardly-rectifying channel, subfamily J, member 12	KCNJ12	3768	ATP-sensitive inward rectifier potassium channel 12, FLJ14167, hIRK, hIRK1, hkir2.2x, Inward rectifier K(+) channel Kir2.2, Inward rectifying K(+) channel negative regulator Kir2.2v, IRK2, kcnj12x, KCNJN1, Kir2.2, Kir2.2v, Potassium channel, inwardly rectifying subfamily J member 12
	potassium inwardly-rectifying channel, subfamily J, member 13	KCNJ13	3769	Inward rectifier K(+) channel Kir7.1, Inward rectifier potassium channel 13, Kir1.4, KIR1.4, Kir7.1, KIR7.1, MGC33328, Potassium channel, inwardly rectifying subfamily J member 13, SVD
	potassium inwardly-rectifying channel, subfamily J, member 14	KCNJ14	3770	ATP-sensitive inward rectifier potassium channel 14, Inward rectifier K(+) channel Kir2.4, IRK4, Kir2.4, KIR2.4, MGC46111, Potassium channel, inwardly rectifying subfamily J member 14
	potassium inwardly-rectifying channel, subfamily J, member 15	KCNJ15	3772	ATP-sensitive inward rectifier potassium channel 15, Inward rectifier K(+) channel Kir4.2, IRKK, KCNJ14, Kir1.3, KIR1.3, Kir4.2, KIR4.2, MGC13584, Potassium channel, inwardly rectifying subfamily J member 15
	potassium inwardly-rectifying channel, subfamily J, member 16	KCNJ16	3773	BIR9, Inward rectifier K(+) channel Kir5.1, Inward rectifier potassium channel 16, Kir5.1, KIR5.1, MGC33717, Potassium channel, inwardly rectifying subfamily J member 16
	potassium channel, subfamily K, member	KCNK1	3775	DPK, HOHO, HOHO1, Inward rectifying potassium channel

	1			protein TWIK-1, K2p1.1, KCNO1, Potassium channel KCNO1, Potassium channel subfamily K member 1, TWIK1, TWIK-1
	potassium channel, subfamily K, member 2	KCNK2	3776	hTREK-1c, hTREK-1e, K2p2.1, MGC126742, MGC126744, Outward rectifying potassium channel protein TREK-1, Potassium channel subfamily K member 2, TPKC1, TREK, TREK1, TREK-1, TREK-1 K(+) channel subunit, Two-pore domain potassium channel TREK-1, Two-pore potassium channel TPKC1
	potassium channel, subfamily K, member 3	KCNK3	3777	Acid-sensitive potassium channel protein TASK-1, K2p3.1, OAT1, Potassium channel subfamily K member 3, TASK, TASK1, TASK-1, TBAK1, TWIK-related acid-sensitive K(+) channel 1, Two pore potassium channel KT3.1
	potassium channel, subfamily K, member 4	KCNK4	50801	K2p4.1, Potassium channel subfamily K member 4, TRAAK, TRAAK1, TWIK-related arachidonic acid-stimulated potassium channel protein, Two pore K(+) channel KT4.1
	potassium channel, subfamily K, member 5	KCNK5	8645	Acid-sensitive potassium channel protein TASK-2, FLJ11035, K2p5.1, Potassium channel subfamily K member 5, TASK2, TASK-2, TWIK-related acid-sensitive K(+) channel 2
	potassium channel, subfamily K, member 6	KCNK6	9424	FLJ12282, Inward rectifying potassium channel protein TWIK-2, K2p6.1, KCNK8, Potassium channel subfamily K member 6, TOSS, TWIK2, TWIK-2, TWIK-originated similarity sequence
	potassium channel, subfamily K, member 7	KCNK7	10089	K2p7.1, MGC118782, MGC118784, Potassium channel subfamily K member 7, PRO1716, TWIK3
	potassium channel, subfamily K, member 9	KCNK9	51305	Acid-sensitive potassium channel protein TASK-3, K2p9.1, KT3.2, MGC138268, MGC138270, Potassium channel subfamily K member 9, TASK3, TASK-3, TWIK-related acid-sensitive K(+) channel 3, Two pore potassium channel KT3.2
	potassium channel,	KCNK1	5420	K2p10.1, Outward rectifying

	subfamily K, member 10	0	7	potassium channel protein TREK-2, Potassium channel subfamily K member 10, TREK2, TREK-2, TREK-2 K(+) channel subunit
	potassium channel, subfamily K, member 12	KCNK12	56660	Potassium channel subfamily K member 12, Tandem pore domain halothane-inhibited potassium channel 2, THIK2, THIK-2
	potassium channel, subfamily K, member 13	KCNK13	56659	K2p13.1, Potassium channel subfamily K member 13, Tandem pore domain halothane-inhibited potassium channel 1, THIK1, THIK-1
	potassium channel, subfamily K, member 15	KCNK15	60598	Acid-sensitive potassium channel protein TASK-5, dJ781B1.1, K2p15.1, KCNK11, KCNK14, KIAA0237, KT3.3, Potassium channel subfamily K member 15, TASK5, TASK-5, TWIK-related acid-sensitive K(+) channel 5, Two pore potassium channel KT3.3
	potassium channel, subfamily K, member 16	KCNK16	83795	2P domain potassium channel Talk-1, K2p16.1, MGC133123, Potassium channel subfamily K member 16, TALK1, TALK-1, TWIK-related alkaline pH-activated K(+) channel 1
	potassium channel, subfamily K, member 17	KCNK17	89822	2P domain potassium channel Talk-2, K2p17.1, Potassium channel subfamily K member 17, TALK2, TALK-2, TASK4, TASK-4, TWIK-related acid-sensitive K(+) channel 4, TWIK-related alkaline pH-activated K(+) channel 2, UNQ5816/PRO19634
	potassium channel, subfamily K, member 18	KCNK18	338567	K2p18.1, TRESK, TRESK2, TRESK-2, TRIK
	potassium large conductance calcium-activated channel, subfamily M, alpha member 1	KCNMA1	3778	BKCA alpha, BK channel, BKTM, Calcium-activated potassium channel, subfamily M, alpha subunit 1, Calcium-activated potassium channel, subfamily M subunit alpha 1, Calcium-activated potassium channel alpha subunit 1, Calcium-activated potassium channel subunit alpha 1, DKFZp686K1437, hSlo, K(VCA)alpha, KCa1.1, KCNMA, MaxiK, Maxi K channel, MGC71881, mSLO1, SAKCA, SLO, Slo1, SLO1, Slo-alpha, SLO-

				ALPHA, Slo homolog, Slowpoke homolog
	potassium large conductance calcium-activated channel, subfamily M, beta member 1	KCNMB1	3779	BKbeta, BKbeta1, BK channel beta subunit 1, BK channel subunit beta 1, Calcium-activated potassium channel, subfamily M, beta subunit 1, Calcium-activated potassium channel, subfamily M subunit beta 1, Calcium-activated potassium channel beta-subunit, Calcium-activated potassium channel beta subunit 1, Calcium-activated potassium channel subunit beta, Calcium-activated potassium channel subunit beta 1, Charybdotoxin receptor beta subunit 1, Charybdotoxin receptor subunit beta 1, Hbeta1, hslo-beta, K(VCA)beta, K(VCA)beta 1, Maxi K channel beta subunit 1, Maxi K channel subunit beta 1, Slo-beta, SLO-BETA, Slo-beta 1
	potassium large conductance calcium-activated channel, subfamily M, beta member 2	KCNMB2	10242	BKbeta2, BK channel beta subunit 2, BK channel subunit beta 2, Calcium-activated potassium channel, subfamily M, beta subunit 2, Calcium-activated potassium channel, subfamily M subunit beta 2, Calcium-activated potassium channel beta subunit 2, Calcium-activated potassium channel subunit beta 2, Charybdotoxin receptor beta subunit 2, Charybdotoxin receptor subunit beta 2, Hbeta2, Hbeta3, K(VCA)beta 2, Maxi K channel beta subunit 2, Maxi K channel subunit beta 2, Slo-beta 2
	potassium large conductance calcium-activated channel, subfamily M beta member 3	KCNMB3	27094	BKbeta3, BK channel beta subunit 3, BK channel subunit beta 3, Calcium-activated potassium channel, subfamily M, beta subunit 3, Calcium-activated potassium channel, subfamily M subunit beta 3, Calcium-activated potassium channel beta subunit 3, Calcium-activated potassium channel subunit beta 3, Charybdotoxin receptor beta subunit 3, Charybdotoxin receptor subunit beta 3, Hbeta3, K(VCA)beta 3, KCNMB2, KCNMBL, Maxi K channel beta subunit 3, Maxi K

				channel subunit beta 3, Slo-beta 3
	potassium large conductance calcium-activated channel, subfamily M, beta member 3-like	KCNMB3L	27093	KCNMB2L, KCNMB3L1, KCNMBLP
	potassium large conductance calcium-activated channel, subfamily M, beta member 4	KCNMB4	27345	BKbeta4, BK channel beta subunit 4, BK channel subunit beta 4, Calcium-activated potassium channel, subfamily M, beta subunit 4, Calcium-activated potassium channel, subfamily M subunit beta 4, Calcium-activated potassium channel beta subunit 4, Calcium-activated potassium channel subunit beta 4, Charybdotoxin receptor beta subunit 4, Charybdotoxin receptor subunit beta 4, Hbeta4, K(VCA)beta 4, Maxi K channel beta subunit 4, Maxi K channel subunit beta 4, Slo-beta 4
	potassium intermediate/small conductance calcium-activated channel, subfamily N, member 1	KCNN1	3780	hSK1, KCa2.1, SK, SK1, SKCA1, Small conductance calcium-activated potassium channel protein 1
	potassium intermediate/small conductance calcium-activated channel, subfamily N, member 2	KCNN2	3781	hSK2, KCa2.2, SK2, SKCA2, Small conductance calcium-activated potassium channel protein 2
	potassium intermediate/small conductance calcium-activated channel, subfamily N, member 3	KCNN3	3782	hSK3, K3, KCa2.3, SK3, SKCa3, SKCA3, Small conductance calcium-activated potassium channel protein 3
	potassium intermediate/small conductance calcium-activated channel, subfamily N, member 4	KCNN4	3783	hIKCa1, hKCa4, hSK4, IK1, IKCa1, IKCA1, Intermediate conductance calcium-activated potassium channel protein 4, KCa3.1, KCa4, KCA4, Putative Gardos channel, SK4
	potassium voltage-gated channel, KQT-like subfamily, member 1	KCNQ1	3784	ATFB1, FLJ26167, IKs producing slow voltage-gated potassium channel alpha subunit KvLQT1, IKs producing slow voltage-gated potassium channel subunit alpha KvLQT1, JLNS1, KCNA8, KCNA9,

				KQT-like 1, Kv1.9, Kv7.1, KVLQT1, LQT, LQT1, Potassium voltage-gated channel subfamily KQT member 1, RWS, SQT2, Voltage-gated potassium channel subunit Kv7.1, WRS
	KCNQ1 downstream neighbor	KCNQ1 DN	55539	Beckwith-Wiedemann region transcript protein, BWRT, HSA404617, KCNQ1 downstream neighbor protein
	KCNQ1 overlapping transcript 1 (non-protein coding)	KCNQ1 OT1	10984	FLJ41078, KCNQ10T1, KCNQ1 overlapping transcript 1, KvDMR1, KvLQT1-AS, LIT1, long QT intronic transcript 1, NCRNA00012
	potassium voltage-gated channel, KQT-like subfamily, member 2	KCNQ2	3785	BFNC, EBN, EBN1, ENB1, HNSPC, KCNA11, KQT-like 2, Kv7.2, KV7.2, KVEBN1, Neuroblastoma-specific potassium channel alpha subunit KvLQT2, Neuroblastoma-specific potassium channel subunit alpha KvLQT2, Potassium voltage-gated channel subfamily KQT member 2, Voltage-gated potassium channel subunit Kv7.2
	potassium voltage-gated channel, KQT-like subfamily, member 3	KCNQ3	3786	BFNC2, EBN2, KQT-like 3, Kv7.3, KV7.3, Potassium channel alpha subunit KvLQT3, Potassium channel subunit alpha KvLQT3, Potassium voltage-gated channel subfamily KQT member 3, Voltage-gated potassium channel subunit Kv7.3
	potassium voltage-gated channel, KQT-like subfamily, member 4	KCNQ4	9132	DFNA2, KQT-like 4, Kv7.4, KV7.4, Potassium channel alpha subunit KvLQT4, Potassium channel subunit alpha KvLQT4, Potassium voltage-gated channel subfamily KQT member 4, Voltage-gated potassium channel subunit Kv7.4
	potassium voltage-gated channel, KQT-like subfamily, member 5	KCNQ5	56479	KQT-like 5, Kv7.5, Potassium channel alpha subunit KvLQT5, Potassium channel subunit alpha KvLQT5, Potassium voltage-gated channel subfamily KQT member 5, Voltage-gated potassium channel subunit Kv7.5
	potassium channel regulator	KCNRG	283518	None
	potassium voltage-gated channel, delayed-rectifier,	KCNS1	3787	Delayed-rectifier K(+) channel alpha subunit 1, Kv9.1, Potassium voltage-gated channel subfamily S

	subfamily S, member 1			member 1, Voltage-gated potassium channel subunit Kv9.1
	potassium voltage-gated channel, delayed-rectifier, subfamily S, member 2	KCNS2	3788	Delayed-rectifier K(+) channel alpha subunit 2, KIAA1144, Kv9.2, Potassium voltage-gated channel subfamily S member 2, Voltage-gated potassium channel subunit Kv9.2
	potassium voltage-gated channel, delayed-rectifier, subfamily S, member 3	KCNS3	3790	Delayed-rectifier K(+) channel alpha subunit 3, Kv9.3, KV9.3, MGC9481, Potassium voltage-gated channel subfamily S member 3, Voltage-gated potassium channel subunit Kv9.3
	potassium channel, subfamily T, member 1	KCNT1	57582	bA100C15.2, FLJ41282, KCa4.1, KIAA1422, Potassium channel subfamily T member 1, SLACK
	potassium channel, subfamily T, member 2	KCNT2	343350	KCa4.2, MGC119610, MGC119611, MGC119612, MGC119613, SLICK, SLO2.1
	potassium channel, subfamily U, member 1	KCNU1	157855	KCa5.1, Kcnma3, KCNMA3, KCNMC1, Slo3, SLO3
	potassium channel, subfamily V, member 1	KCNV1	27012	HNKA, KCNB3, KV2.3, Kv8.1, KV8.1
	potassium channel, subfamily V, member 2	KCNV2	169522	KV11.1, Kv8.2, MGC120515, Potassium voltage-gated channel subfamily V member 2, RCD3B, Voltage-gated potassium channel subunit Kv8.2
Receptor tyrosine kinases	Fibroblast growth factor receptor 1	FGFR1	2260	Basic fibroblast growth factor receptor 1 precursor, BFGFR, bFGF-R, CD331, CD331 antigen, CEK, c-fgr, C-FGR, FGFBR, FGFR-1, fibroblast growth factor receptor 1 (fms-related tyrosine kinase 2, Pfeiffer syndrome), FLG, FLJ99988, FLT2, Fms-like tyrosine kinase 2, H2, H3, H4, H5, HBGFR, KAL2, N-SAM
	Fibroblast growth factor receptor 2	FGFR2	2263	BEK, BFR-1, CD332, CD332 antigen, CEK3, CFD1, ECT1, FGFR-2, Fibroblast growth factor receptor 2 precursor, FLJ98662, JWS, Keratinocyte growth factor receptor 2, KGFR, KSAM, K-SAM, TK14, TK25
	Fibroblast growth factor receptor 3	FGFR3	2261	ACH, CD333, CD333 antigen, CEK2, FGFR-3, fibroblast growth factor receptor 3 (achondroplasia,

				thanatophoric dwarfism), Fibroblast growth factor receptor 3 precursor, HSFGFR3EX, JTK4
	Fibroblast growth factor receptor 4	FGFR4	2264	CD334, CD334 antigen, FGFR-4, Fibroblast growth factor receptor 4 precursor, JTK2, MGC20292, TKF
	Fibroblast growth factor receptor 6	FGFR6	2265	None
	platelet derived growth factor receptor A	PDGFRA	5156	Alpha platelet-derived growth factor receptor precursor, CD140a, CD140A, CD140a antigen, MGC74795, PDGFR2, PDGF-R-alpha, Rhe-PDGFRA
	platelet derived growth factor receptor B	PDGFRB	5159	Beta platelet-derived growth factor receptor precursor, CD140b, CD140B, CD140b antigen, JTK12, PDGFR, PDGFR1, PDGF-R-beta
	epidermal growth factor receptor	EGFR	1956	Epidermal growth factor receptor precursor, ERBB, ERBB1, HER1, mENA, PIG61, Receptor tyrosine-protein kinase ErbB-1
	v-erb-b2 erythroblastic leukemia viral oncogene homolog 2	ERBB2	2064	CD340, CD340 antigen, C-erbB-2, c-erb B2, HER2, HER-2, HER-2/neu, MLN 19, NEU, NEU proto-oncogene, NGL, p185erbB2, Receptor tyrosine-protein kinase erbB-2 precursor, TKR1, Tyrosine kinase-type cell surface receptor HER2
	v-erb-b2 erythroblastic leukemia viral oncogene homolog 3	ERBB3	2065	c-erbB3, c-erbB-3, ErbB-3, erbB3-S, HER3, LCCS2, MDA-BF-1, MGC88033, p180-ErbB3, p45-sErbB3, p85-sErbB3, Receptor tyrosine-protein kinase erbB-3 precursor, Tyrosine kinase-type cell surface receptor HER3
	v-erb-b2 erythroblastic leukemia viral oncogene homolog 4	ERBB4	266	HER4, MGC138404, p180erbB4, Receptor tyrosine-protein kinase erbB-4 precursor, Tyrosine kinase-type cell surface receptor HER4
Nuclear steroid receptors	estrogen receptor 1	ESR1	2099	DKFZp686N23123, ER, Era, ER-alpha, ESR, ESRA, Estradiol receptor, Estrogen receptor, major ORF, NR3A1
	estrogen receptor 2	ESR2	2100	Erb, ER-beta, ER-BETA, ESRB, ESR-BETA, ESTRB, Estrogen receptor beta, NR3A2
	Thyroid hormone receptor-α	THRA	7067	AR7, c-erbA-1, c-ERBA-1, C-erbA-alpha, c-ERBA-ALPHA-2, EAR7,

				EAR-7, EAR-7.1, EAR-7.1/EAR-7.2, EAR-7.2, ERBA, ERBA1, ERBA-ALPHA, ERB-T-1, MGC000261, MGC43240, NR1A1, THRA1, THRA2, THRA3, Thyroid hormone receptor alpha, TR-ALPHA-1
	Thyroid hormone receptor-β	THRB	7068	ERBA2, ERBA-BETA, GRTH, MGC126109, MGC126110, NR1A2, PRTH, THR1, THRB1, THRB2, Thyroid hormone receptor beta-1, Thyroid hormone receptor beta-2
	Retinoic acid receptor-α	RARA	5914	NR1B1, RAR
	Retinoic acid receptor-β	RARB	5915	HAP, HBV-activated protein, NR1B2, RAR-beta, RAR-epsilon, Retinoic acid receptor beta, RRB2
	Retinoic acid receptor-γ	RARG	5916	NR1B3, RARC, RAR-gamma-1, RAR-gamma-2, Retinoic acid receptor gamma-1, Retinoic acid receptor gamma-2
	Peroxisome proliferator-activated receptor-α	PPARA	5465	hPPAR, MGC2237, MGC2452, NR1C1, peroxisome proliferative activated receptor, alpha, Peroxisome proliferator-activated receptor alpha, PPAR, PPAR-alpha
	Peroxisome proliferator-activated receptor-β/δ	PPARD	5467	FAAR, MGC3931, NR1C2, NUC1, NUCI, NUCII, Nuclear hormone receptor 1, peroxisome proliferative activated receptor, delta, Peroxisome proliferator-activated receptor delta, PPARB, PPAR-beta, PPAR-delta
	Peroxisome proliferator-activated receptor-γ	PPARG	5468	HUMPPARG, NR1C3, peroxisome proliferative activated receptor, gamma, Peroxisome proliferator-activated receptor gamma, PPARG1, PPARG2, PPARgamma, PPAR-gamma
	Rev-ErbAα	NR1D1	9572	EAR1, ear-1, hRev, HREV, Orphan nuclear receptor NR1D1, Rev-ErbAalpha, Rev-erbA-alpha, THRA1, THRAL, V-erbA-related protein EAR-1
	Rev-ErbAβ	NR1D2	9975	BD73, EAR-1r, EAR-1R, Hs.37288, HZF2, Orphan nuclear hormone receptor BD73, Orphan nuclear receptor NR1D2, Rev-erb-beta, RVR
	RAR-related orphan	RORA	6095	MGC119326, MGC119329,

	receptor-α			NR1F1, Nuclear receptor ROR-alpha, Nuclear receptor RZR-alpha, Retinoid-related orphan receptor-alpha, ROR1, ROR2, ROR3, RZRA, RZR-ALPHA
	RAR-related orphan receptor-β	RORB	6096	bA133M9.1, NR1F2, Nuclear receptor ROR-beta, Nuclear receptor RZR-beta, Retinoid-related orphan receptor-beta, ROR-BETA, RZRB, RZR-BETA
	RAR-related orphan receptor-γ	RORC	6097	MGC129539, NR1F3, Nuclear receptor ROR-gamma, Nuclear receptor RZR-gamma, Retinoid-related orphan receptor-gamma, RORG, RZRG, RZR-GAMMA, TOR
	Liver X receptor-α	NR1H3	10062	Liver X receptor alpha, LXRA, LXR-a, Nuclear orphan receptor LXR-alpha, Oxysterols receptor LXR-alpha, RLD-1
	Liver X receptor-β	NR1H2	7376	Liver X receptor beta, LXRB, LXR-b, NER, NER-I, Nuclear orphan receptor LXR-beta, Nuclear receptor NER, Oxysterols receptor LXR-beta, RIP15, Ubiquitously-expressed nuclear receptor, UNR
	Farnesoid X receptor	NR1H4	9971	BAR, Bile acid receptor, Farnesoid X-activated receptor, Farnesol receptor HRR-1, FXR, HRR1, HRR-1, MGC163445, Retinoid X receptor-interacting protein 14, RIP14, RXR-interacting protein 14
	Vitamin D receptor	VDR	7421	1,25-dihydroxyvitamin D3 receptor, NR1I1, Vitamin D3 receptor
	Pregnane X receptor	NR1I2	8856	BXR, ONR1, Orphan nuclear receptor PAR1, Orphan nuclear receptor PXR, PAR, PAR1, PAR2, PARq, Pregnane X receptor, PRR, PXR, SAR, Steroid and xenobiotic receptor, SXR
	Constitutive androstane receptor	NR1I3	9970	CAR, CAR1, CAR-BETA, CAR-SV1, CAR-SV10, CAR-SV11, CAR-SV12, CAR-SV13, CAR-SV14, CAR-SV15, CAR-SV17, CAR-SV18, CAR-SV19, CAR-SV20, CAR-SV21, CAR-SV4, CAR-SV6, CAR-SV7, CAR-SV8, CAR-SV9, Constitutive activator of retinoid response, Constitutive active response, Constitutive androstane receptor, MB67, MGC150433, MGC97144, MGC97209, Orphan

				nuclear receptor MB67, Orphan nuclear receptor NR1I3
TGFbeta superfamily receptors	bone morphogenic protein receptor 1A	BMPR1A	657	Activin receptor-like kinase 3, ACVRLK3, ALK3, ALK-3, Bone morphogenetic protein receptor type IA precursor, CD292, CD292 antigen, Serine/threonine-protein kinase receptor R5, SKR5
	bone morphogenic protein receptor 1B	BMPR1B	658	ALK6, ALK-6, Bone morphogenetic protein receptor type IB precursor, CDw293, CDw293 antigen
	bone morphogenic protein receptor 2A	BMPR2	659	BMPR3, BMPR-II, BMP type II receptor, BMR2, Bone morphogenetic protein receptor type-2 precursor, Bone morphogenetic protein receptor type II, BRK-3, FLJ41585, FLJ76945, PPH1, T-ALK
	Activin receptor 2A	ACVR2A	92	Activin receptor type 2A precursor, Activin receptor type-2A precursor, Activin receptor type IIA, ACTRII, ACTRIIA, ACTR-IIA, ACVR2
	Activin receptor 1B	ACVR1B	91	Activin receptor-like kinase 4, Activin receptor type 1B precursor, ActRIB, ACTRIB, ACTR-IB, ACVRLK4, ALK4, ALK-4, Serine/threonine-protein kinase receptor R2, SKR2
	Activin receptor 2B	ACVR2B	93	Activin receptor type 2B precursor, Activin receptor type-2B precursor, Activin receptor type IIB, ACTRIIB, ActR-IIB, ACTR-IIB, MGC116908
	Activin receptor 1C	ACVR1C	130399	Activin receptor-like kinase 7, Activin receptor type 1C precursor, ACTR-IC, ACVRLK7, ALK7, ALK-7
	transforming growth factor beta receptor 1	TGFBRI	7046	AAT5, Activin receptor-like kinase 5, ACVRLK4, ALK5, ALK-5, LDS1A, LDS2A, Serine/threonine-protein kinase receptor R4, SKR4, TbetaR-I, TGF-beta receptor type-1 precursor, TGF-beta receptor type I, TGF-beta type I receptor, TGFR-1, transforming growth factor, beta receptor I (activin A receptor type II-like kinase, 53kDa), Transforming growth factor-beta receptor type I
	transforming growth factor beta receptor 2	TGFBRII	7048	AAT3, FAA3, HNPCC6, LDS1B, LDS2B, MFS2, RIIC, TAAD2, TbetaR-II, TGF-beta receptor type-2 precursor, TGF-beta receptor type II, TGFbeta-RII, TGF-beta type

				II receptor, TGFR-2, Transforming growth factor-beta receptor type II
	transforming growth factor beta receptor 3	TGFBRII	7049	betaglycan, Betaglycan, BGCAN, TGF-beta receptor type III precursor, TGFR-3, transforming growth factor, beta receptor III (betaglycan, 300kDa), Transforming growth factor beta receptor III
T- cell receptors	T- cell receptors	http://www.bioinf.org.uk/abs/		
B-cell receptors	B-cell receptors	http://www.bioinf.org.uk/abs/		

Table 9 GABA subunits from various species.

Receptor subunit	Gene name	Spicies
GABAA:		
gamma-aminobutyric acid (GABA) A receptor, alpha 1	GABRA1	Homo sapiens
gamma-aminobutyric acid (GABA) A receptor, alpha 1	Gabra1	Mus musculus
gamma-aminobutyric acid (GABA) A receptor, alpha 1	gabra1	Danio rerio
gamma-aminobutyric acid (GABA) A receptor, alpha 1	GABRA1	Pan troglodytes
gamma-aminobutyric acid (GABA) A receptor, alpha 1	GABRA1 (variant 1)	Bos taurus
gamma-aminobutyric acid (GABA) A receptor, alpha 1	GABRA1 (variant 2)	Bos taurus
gamma-aminobutyric acid (GABA) A receptor, alpha 1	GABRA1	Gallus gallus
gamma-aminobutyric acid (GABA) A receptor, alpha 1	GABRA1	Canis familiaris
gamma-aminobutyric acid (GABA) A receptor, alpha 1	Gabra1	Rattus norvegicus
gamma-aminobutyric acid (GABA) A receptor, alpha 2	GABRA2	Homo sapiens
gamma-aminobutyric acid (GABA) A receptor, alpha 2	Gabra2	Mus musculus
gamma-aminobutyric acid (GABA) A receptor, alpha 2	LOC100150704	Danio rerio
gamma-aminobutyric acid (GABA) A receptor, alpha 2	GABRA2	Pan troglodytes
gamma-aminobutyric acid (GABA) A receptor, alpha 2	GABRA2	Bos taurus

gamma-aminobutyric acid (GABA) A receptor, alpha 2	GABRA2	Gallus gallus
gamma-aminobutyric acid (GABA) A receptor, alpha 2	GABRA2	Canis familiaris
gamma-aminobutyric acid (GABA) A receptor, alpha 2	LOC289606	Rattus norvegicus
gamma-aminobutyric acid (GABA) A receptor, alpha 3	GABRA3	Homo sapiens
gamma-aminobutyric acid (GABA) A receptor, alpha 3	Gabra3	Mus musculus
gamma-aminobutyric acid (GABA) A receptor, alpha 3	Grd	Drosophila melanogaster
gamma-aminobutyric acid (GABA) A receptor, alpha 3	GABRA3	Bos taurus
gamma-aminobutyric acid (GABA) A receptor, alpha 3	GABRA3	Gallus gallus
gamma-aminobutyric acid (GABA) A receptor, alpha 3	GABRA3	Canis familiaris
gamma-aminobutyric acid (GABA) A receptor, alpha 3	Gabra3	Rattus norvegicus
gamma-aminobutyric acid (GABA) A receptor, alpha 4	GABRA4	Homo sapiens
gamma-aminobutyric acid (GABA) A receptor, alpha 4	Gabra4	Mus musculus
gamma-aminobutyric acid (GABA) A receptor, alpha 4	zgc:110204	Danio rerio
gamma-aminobutyric acid (GABA) A receptor, alpha 4	GABRA4	Pan troglodytes
gamma-aminobutyric acid (GABA) A receptor, alpha 4	GABRA4	Bos taurus
gamma-aminobutyric acid (GABA) A receptor, alpha 4	GABRA4	Gallus gallus
gamma-aminobutyric acid (GABA) A receptor, alpha 4	GABRA4	Canis familiaris
gamma-aminobutyric acid (GABA) A receptor, alpha 4	Gabra4	Rattus norvegicus
gamma-aminobutyric acid (GABA) A receptor, alpha 5	GABRA5	Homo sapiens
gamma-aminobutyric acid (GABA) A receptor, alpha 5	Gabra5	Mus musculus
gamma-aminobutyric acid (GABA) A receptor, alpha 5	CG8916	Drosophila melanogaster
gamma-aminobutyric acid (GABA) A receptor, alpha 5	lgc-37	Caenorhabditis elegans
gamma-aminobutyric acid (GABA) A receptor, alpha 5	LOC799124	Danio rerio
gamma-aminobutyric acid (GABA) A receptor, alpha 5	GABRA5	Bos taurus

gamma-aminobutyric acid (GABA) A receptor, alpha 5	GABRA5	Gallus gallus
gamma-aminobutyric acid (GABA) A receptor, alpha 5	GABRA5	Canis familiaris
gamma-aminobutyric acid (GABA) A receptor, alpha 5	Gabra5	Rattus norvegicus
gamma-aminobutyric acid (GABA) A receptor, alpha 6	GABRA6	Homo sapiens
gamma-aminobutyric acid (GABA) A receptor, alpha 6	Gabra6	Mus musculus
gamma-aminobutyric acid (GABA) A receptor, alpha 6	Rdl	Drosophila melanogaster
gamma-aminobutyric acid (GABA) A receptor, alpha 6	lgc-38	Caenorhabditis elegans
gamma-aminobutyric acid (GABA) A receptor, alpha 6	gabra6a	Danio rerio
gamma-aminobutyric acid (GABA) A receptor, alpha 6	gabra6b	Danio rerio
gamma-aminobutyric acid (GABA) A receptor, alpha 6	GABRA6	Pan troglodytes
gamma-aminobutyric acid (GABA) A receptor, alpha 6	GABRA6	Bos taurus
gamma-aminobutyric acid (GABA) A receptor, alpha 6	GABRA6	Gallus gallus
gamma-aminobutyric acid (GABA) A receptor, alpha 6	GABRA6	Canis familiaris
gamma-aminobutyric acid (GABA) A receptor, alpha 6	Gabra6	Rattus norvegicus
gamma-aminobutyric acid (GABA) A receptor, beta 1	GABRB1	Homo sapiens
gamma-aminobutyric acid (GABA) A receptor, beta 1	Gabrb1	Mus musculus
gamma-aminobutyric acid (GABA) A receptor, beta 1	GABRB1	Pan troglodytes
gamma-aminobutyric acid (GABA) A receptor, beta 1	GABRB1	Bos taurus
gamma-aminobutyric acid (GABA) A receptor, beta 1	GABRB1	Gallus gallus
gamma-aminobutyric acid (GABA) A receptor, beta 1	Gabrb1	Rattus norvegicus
gamma-aminobutyric acid (GABA) A receptor, beta 2	GABRB2	Homo sapiens
gamma-aminobutyric acid (GABA) A receptor, beta 2	Gabrb2	Mus musculus
gamma-aminobutyric acid (GABA) A receptor, beta 2	gabrb2	Danio rerio
gamma-aminobutyric acid (GABA) A receptor, beta 2	GABRB2	Pan troglodytes
gamma-aminobutyric acid (GABA) A receptor, beta 2	GABRB2	Bos taurus
gamma-aminobutyric acid (GABA) A receptor, beta 2	GABRB2	Gallus gallus
gamma-aminobutyric acid (GABA) A receptor, beta 2	GABRB2	Canis familiaris
gamma-aminobutyric acid (GABA) A receptor, beta 2	Gabrb2	Rattus norvegicus

gamma-aminobutyric acid (GABA) A receptor, beta 3	GABRB3	Homo sapiens
gamma-aminobutyric acid (GABA) A receptor, beta 3	Gabrb3	Mus musculus
gamma-aminobutyric acid (GABA) A receptor, beta 3	Lcch3	Drosophila melanogaster
gamma-aminobutyric acid (GABA) A receptor, beta 3	gab-1	Caenorhabditis elegans
gamma-aminobutyric acid (GABA) A receptor, beta 3	LOC566922	Danio rerio
gamma-aminobutyric acid (GABA) A receptor, beta 3	GABRB3	Pan troglodytes
gamma-aminobutyric acid (GABA) A receptor, beta 3	GABRB3	Gallus gallus
gamma-aminobutyric acid (GABA) A receptor, beta 3	GABRB3	Canis familiaris
gamma-aminobutyric acid (GABA) A receptor, beta 3	Gabrb3	Rattus norvegicus
gamma-aminobutyric acid (GABA) A receptor, gamma 1	GABRG1	Homo sapiens
gamma-aminobutyric acid (GABA) A receptor, gamma 1	Gabrg1	Mus musculus
gamma-aminobutyric acid (GABA) A receptor, gamma 1	LOC556202	Danio rerio
gamma-aminobutyric acid (GABA) A receptor, gamma 1	GABRG1	Pan troglodytes
gamma-aminobutyric acid (GABA) A receptor, gamma 1	GABRG1	Bos taurus
gamma-aminobutyric acid (GABA) A receptor, gamma 1	GABRG1	Gallus gallus
gamma-aminobutyric acid (GABA) A receptor, gamma 1	GABRG1	Canis familiaris
gamma-aminobutyric acid (GABA) A receptor, gamma 1	Gabrg1	Rattus norvegicus
gamma-aminobutyric acid (GABA) A receptor, gamma 2	GABRG2	Homo sapiens
gamma-aminobutyric acid (GABA) A receptor, gamma 2	Gabrg2	Mus musculus
gamma-aminobutyric acid (GABA) A receptor, gamma 2	LOC553402	Danio rerio
gamma-aminobutyric acid (GABA) A receptor, gamma 2	GABRG2	Bos taurus
gamma-aminobutyric acid (GABA) A receptor, gamma 2	GABRG2	Gallus gallus
gamma-aminobutyric acid (GABA) A receptor, gamma 2	GABRG2	Canis familiaris
gamma-aminobutyric acid (GABA) A receptor, gamma 2	Gabrg2	Rattus norvegicus
gamma-aminobutyric acid (GABA) A receptor, gamma 3	GABRG3	Homo sapiens
gamma-aminobutyric acid (GABA) A receptor,	Gabrg3	Mus musculus

gamma 3		
gamma-aminobutyric acid (GABA) A receptor, gamma 3	LOC567057	Danio rerio
gamma-aminobutyric acid (GABA) A receptor, gamma 3	GABRG3	Gallus gallus
gamma-aminobutyric acid (GABA) A receptor, gamma 3	Gabrg3	Rattus norvegicus
gamma-aminobutyric acid (GABA) A receptor, delta	GABRD	Homo sapiens
gamma-aminobutyric acid (GABA) A receptor, delta	Gabrd	Mus musculus
gamma-aminobutyric acid (GABA) A receptor, delta	DKEYP-87A12.2	Danio rerio
gamma-aminobutyric acid (GABA) A receptor, delta	GABRD	Pan troglodytes
gamma-aminobutyric acid (GABA) A receptor, delta	GABRD	Bos taurus
gamma-aminobutyric acid (GABA) A receptor, delta	GABRD	Gallus gallus
gamma-aminobutyric acid (GABA) A receptor, delta	GABRD	Canis familiaris
gamma-aminobutyric acid (GABA) A receptor, delta	Gabrd	Rattus norvegicus
gamma-aminobutyric acid (GABA) A receptor, epsilon	GABRE	Homo sapiens
gamma-aminobutyric acid (GABA) A receptor, epsilon	Gabre	Mus musculus
gamma-aminobutyric acid (GABA) A receptor, epsilon	GABRE	Pan troglodytes
gamma-aminobutyric acid (GABA) A receptor, epsilon	GABRE	Bos taurus
gamma-aminobutyric acid (GABA) A receptor, epsilon	GABRE	Canis familiaris
gamma-aminobutyric acid (GABA) A receptor, epsilon	Gabre	Rattus norvegicus
gamma-aminobutyric acid (GABA) A receptor, pi	GABRP	Homo sapiens
gamma-aminobutyric acid (GABA) A receptor, pi	Gabrp	Mus musculus
gamma-aminobutyric acid (GABA) A receptor, pi	GABRP	Pan troglodytes
gamma-aminobutyric acid (GABA) A receptor, pi	GABRP	Bos taurus
gamma-aminobutyric acid (GABA) A receptor, pi	GABRP	Gallus gallus
gamma-aminobutyric acid (GABA) A receptor, pi	GABRP	Canis familiaris
gamma-aminobutyric acid (GABA) A receptor, pi	Gabrp	Rattus norvegicus
gamma-aminobutyric acid (GABA) A receptor, theta	GABRQ	Homo sapiens
gamma-aminobutyric acid (GABA) A receptor, theta	Gabrq	Mus musculus
gamma-aminobutyric acid (GABA) A receptor, theta	GABRQ	Pan troglodytes
gamma-aminobutyric acid (GABA) A receptor, theta	GABRQ	Bos taurus
gamma-aminobutyric acid (GABA) A receptor, theta	GABRQ	Canis

		familiaris
gamma-aminobutyric acid (GABA) A receptor, theta	Gabrq	Rattus norvegicus
GABAB:		
gamma-aminobutyric acid (GABA) B receptor, 1	GABBR1	Homo sapiens
gamma-aminobutyric acid (GABA) B receptor, 1	Gabbr1	Mus musculus
gamma-aminobutyric acid (GABA) B receptor, 1	GABA-B-R1	Drosophila melanogaster
gamma-aminobutyric acid (GABA) B receptor, 1	Y41G9A.4	Caenorhabditis elegans
gamma-aminobutyric acid (GABA) B receptor, 1	gabbr1	Danio rerio
gamma-aminobutyric acid (GABA) B receptor, 1	GABBR1	Pan troglodytes
gamma-aminobutyric acid (GABA) B receptor, 1	GABBR1	Bos taurus
gamma-aminobutyric acid (GABA) B receptor, 1	GABBR1	Canis familiaris
gamma-aminobutyric acid (GABA) B receptor, 1	Gabbr1	Rattus norvegicus
gamma-aminobutyric acid (GABA) B receptor, 2	GABBR2	Homo sapiens
gamma-aminobutyric acid (GABA) B receptor, 2	Gabbr2	Mus musculus
gamma-aminobutyric acid (GABA) B receptor, 2	GABA-B-R2	Drosophila melanogaster
gamma-aminobutyric acid (GABA) B receptor, 2	si:dkey-190l1.2	Danio rerio
gamma-aminobutyric acid (GABA) B receptor, 2	GABBR2	Pan troglodytes
gamma-aminobutyric acid (GABA) B receptor, 2	GABBR2	Bos taurus
gamma-aminobutyric acid (GABA) B receptor, 2	GABBR2	Gallus gallus
gamma-aminobutyric acid (GABA) B receptor, 2	GABBR2	Canis familiaris
gamma-aminobutyric acid (GABA) B receptor, 2	Gabbr2	Rattus norvegicus
GABAC:		
gamma-aminobutyric acid (GABA) A receptor, rho1	GABRR1	Homo sapiens
gamma-aminobutyric acid (GABA) A receptor, rho1	Gabrr1	Mus musculus
gamma-aminobutyric acid (GABA) A receptor, rho1	gabrr1	Danio rerio
gamma-aminobutyric acid (GABA) A receptor, rho1	GABRR1	Pan troglodytes
gamma-aminobutyric acid (GABA) A receptor, rho1	GABRR1	Bos taurus
gamma-aminobutyric acid (GABA) A receptor, rho1	GABRR1	Gallus gallus
gamma-aminobutyric acid (GABA) A receptor, rho1	GABRR1	Canis familiaris
gamma-aminobutyric acid (GABA) A receptor, rho1	Gabrr1	Rattus norvegicus
gamma-aminobutyric acid (GABA) A receptor, rho2	GABRR2	Homo sapiens
gamma-aminobutyric acid (GABA) A receptor, rho2	Gabrr2	Mus musculus
gamma-aminobutyric acid (GABA) A receptor, rho2	si:dkey-181i3.1	Danio rerio

gamma-aminobutyric acid (GABA) A receptor, rho2	GABRR2	Pan troglodytes
gamma-aminobutyric acid (GABA) A receptor, rho2	GABRR2	Gallus gallus
gamma-aminobutyric acid (GABA) A receptor, rho2	GABRR2	Canis familiaris
gamma-aminobutyric acid (GABA) A receptor, rho2	Gabrr2	Rattus norvegicus
gamma-aminobutyric acid (GABA) A receptor, rho3	GABRR3	Homo sapiens
gamma-aminobutyric acid (GABA) A receptor, rho3	Gabrr3	Mus musculus
gamma-aminobutyric acid (GABA) A receptor, rho3	zgc:194845	Danio rerio
gamma-aminobutyric acid (GABA) A receptor, rho3	GABRR3	Pan troglodytes
gamma-aminobutyric acid (GABA) A receptor, rho3	GABRR3	Bos taurus
gamma-aminobutyric acid (GABA) A receptor, rho3	GABRR3	Gallus gallus
gamma-aminobutyric acid (GABA) A receptor, rho3	Gabrr3	Rattus norvegicus

Table 10. Human bitter receptors

Code	Receptor
F1	hTAS2R1
F5	hTAS2R3
F25	hTAS2R4
F11	hTAS2R5
F4	hTAS2R7
F2	hTAS2R8
F24	hTAS2R9
F16	hTAS2R10
F3	hTAS2R13
F15	hTAS2R14
F14	hTAS2R16
F7	hTAS2R38
F23	hTAS2R39
F19	hTAS2R40
F18	hTAS2R41
F6	hTAS2R43
F12	hTAS2R44
F8	hTAS2R45
F9	hTAS2R46
F22	hTAS2R47
F17	hTAS2R48
F21	hTAS2R49
F10	hTAS2R50
F13	hTAS2R55
F20	hTAS2R60

Preferred G proteins in making bitter receptor cell lines

Mouse Gα15
Human GNA15

Table 11 Sweet and Umami receptors

Type	Subunit	Gene Symbol	Splice form	NCBI Gene ID	Synonyms
Umami Taste	T1R1	T1R1	1 2 3 4	80835	TAS1R1, TR1, GPR70
Sweet Taste	T1R2	T1R2	1	80834	TAS1R2, TR2, GPR71
Umami/Sweet Taste	T1R3	T1R3	1	83756	TAS1R3

Table 12 Cystic Fibrosis Transmembrane-conductance Regulator

Class	Protein # (UniProt)	Description
		Homo sapiens cystic fibrosis transmembrane conductance regulator (CFTR)
		Homo sapiens cystic fibrosis transmembrane conductance regulator (CFTR) mutant (F508)

Table 13. Guanylyl Cyclases

Class	Family/ *Subtype*	Protein # (UniProt)	Description
Guanylyl cyclases			Guanylate cyclase-A/ natriuretic peptide receptor A
			Guanylate cyclase-B/ natriuretic peptide receptor B
			Guanylate cyclase-C
			Guanylate cyclase-D
			Guanylate cyclase-E
			Guanylate cyclase-F
			Guanylate cyclase-G
Related receptor lacking guanylyl cyclase domain			Natriuretic peptide receptor C (NPR3)

SEQUENCE TABLE

Human $GABA_A$ receptor alpha 1 subunit cDNA (SEQ ID NO: GABA1)

ATGAGGAAAAGTCCAGGTCTGTCTGACTGTCTTTGGGCCTGGATCCTC
CTTCTGAGCACACTGACTGGAAGAAGCTATGGACAGCCGTCATTACAA
GATGAACTTAAAGACAATACCACTGTCTTCACCAGGATTTTGGACAGA
CTCCTAGATGGTTATGACAATCGCCTGAGACCAGGATTGGGAGAGCG
TGTAACCGAAGTGAAGACTGATATCTTCGTCACCAGTTTCGGACCCGT
TTCAGACCATGATATGGAATATACAATAGATGTATTTTTCCGTCAAAGC
TGGAAGGATGAAAGGTTAAAATTTAAAGGACCTATGACAGTCCTCCGG
TTAAATAACCTAATGGCAAGTAAAATCTGGACTCCGGACACATTTTTCC
ACAATGGAAAGAAGTCAGTGGCCCACAACATGACCATGCCCAACAAA
CTCCTGCGGATCACAGAGGATGGCACCTTGCTGTACACCATGAGGCT
GACAGTGAGAGCTGAATGTCCGATGCATTTGGAGGACTTCCCTATGG
ATGCCCATGCTTGCCCACTAAAATTTGGAAGTTATGCTTATACAAGAG
CAGAAGTTGTTTATGAATGGACCAGAGAGCCAGCACGCTCAGTGGTT
GTAGCAGAAGATGGATCACGTCTAAACCAGTATGACCTTCTTGGACAA
ACAGTAGACTCTGGAATTGTCCAGTCAAGTACAGGAGAATATGTTGTT
ATGACCACTCATTTCCACTTGAAGAGAAAGATTGGCTACTTTGTTATTC
AAACATACCTGCCATGCATAATGACAGTGATTCTCTCACAAGTCTCCTT
CTGGCTCAACAGAGAGTCTGTACCAGCAAGAACTGTCTTTGGAGTAAC
AACTGTGCTCACCATGACAACATTGAGCATCAGTGCCAGAAACTCCCT
CCCTAAGGTGGCTTATGCAACAGCTATGGATTGGTTTATTGCCGTGTG
CTATGCCTTTGTGTTCTCAGCTCTGATTGAGTTTGCCACAGTAAACTAT
TTCACTAAGAGAGGTTATGCATGGGATGGCAAAAGTGTGGTTCCAGAA
AAGCCAAAGAAAGTAAAGGATCCTCTTATTAAGAAAAACAACACTTAC
GCTCCAACAGCAACCAGCTACACCCCTAATTTGGCCAGGGGCGACCC
GGGCTTAGCCACCATTGCTAAAAGTGCAACCATAGAACCTAAAGAGGT
CAAGCCCGAAACAAAACCACCAGAACCCAAGAAAACCTTTAACAGTGT
CAGCAAAATTGACCGACTGTCAAGAATAGCCTTCCCGCTGCTATTTGG
AATCTTTAACTTAGTCTACTGGGCTACGTATTTAAACAGAGAGCCTCAG
CTAAAAGCCCCCACACCACATCAATAG

Human $GABA_A$ receptor alpha 2 subunit cDNA (SEQ ID NO: GABA2)

ATGAAGACAAAATTGAACATCTACAACATGCAGTTCCTGCTTTTTGTTT
TCTTGGTGTGGGACCCTGCCAGGTTGGTGCTGGCTAACATCCAAGAA
GATGAGGCTAAAAATAACATTACCATCTTTACGAGAATTCTTGACAGAC
TTCTGGATGGTTACGATAATCGGCTTAGACCAGGACTGGGAGACAGT
ATTACTGAAGTCTTCACTAACATCTACGTGACCAGTTTTGGCCCTGTCT
CAGATACAGATATGGAATATACAATTGATGTTTTCTTTCGACAAAAATG
GAAAGATGAACGTTTAAAATTTAAAGGTCCTATGAATATCCTTCGACTA
AACAATTTAATGGCTAGCAAAATCTGGACTCCAGATACCTTTTTTCACA
ATGGGAAAAAATCAGTAGCTCATAATATGACAATGCCAAATAAGTTGCT
TCGAATTCAGGATGATGGGACTCTGCTGTATACCATGAGGCTTACAGT
TCAAGCTGAATGCCCAATGCACTTGGAGGATTTCCCAATGGATGCTCA
TTCATGTCCTCTGAAATTTGGCAGCTATGCATATACAACTTCAGAGGTC
ACTTATATTTGGACTTACAATGCATCTGATTCAGTACAGGTTGCTCCTG
ATGGCTCTAGGTTAAATCAATATGACCTGCTGGGCCAATCAATCGGAA

AGGAGACAATTAAATCCAGTACAGGTGAATATACTGTAATGACAGCTC
ATTTCCACCTGAAAAGAAAAATTGGGTATTTTGTGATTCAAACCTATCT
GCCTTGCATCATGACTGTCATTCTCTCCCAAGTTTCATTCTGGCTTAAC
AGAGAATCTGTGCCTGCAAGAACTGTGTTTGGAGTAACAACTGTCCTA
ACAATGACAACTCTAAGCATCAGTGCTCGGAATTCTCTCCCCAAAGTG
GCTTATGCAACTGCCATGGACTGGTTTATTGCTGTTTGTTATGCATTTG
TGTTCTCTGCCCTAATTGAATTTGCAACTGTTAATTACTTCACCAAAAG
AGGATGGACTTGGGATGGGAAGAGTGTAGTAAATGACAAGAAAAAAG
AAAAGGCTTCCGTTATGATACAGAACAACGCTTATGCAGTGGCTGTTG
CCAATTATGCCCCGAATCTTTCAAAAGATCCAGTTCTCTCCACCATCTC
CAAGAGTGCAACCACGCCAGAACCCAACAAGAAGCCAGAAAACAAGC
CAGCTGAAGCAAAGAAAACTTTCAACAGTGTTAGCAAAATTGACAGAA
TGTCCAGAATAGTTTTTCCAGTTTTGTTTGGTACCTTTAATTTAGTTTAC
TGGGCTACATATTTAAACAGAGAACCTGTATTAGGGGTCAGTCCTTGA

Human $GABA_A$ receptor alpha 3 subunit cDNA (SEQ ID NO: GABA3)

ATGATAATCACACAAACAAGTCACTGTTACATGACCAGCCTTGGGATT
CTTTTCCTGATTAATATTCTCCCTGGAACCACTGGTCAAGGGGAATCA
AGACGACAAGAACCCGGGGACTTTGTGAAGCAGGACATTGGCGGGCT
GTCTCCTAAGCATGCCCCAGATATTCCTGATGACAGCACTGACAACAT
CACTATCTTCACCAGAATCTTGGATCGTCTTCTGGACGGCTATGACAA
CCGGCTGCGACCTGGGCTTGGAGATGCAGTGACTGAAGTGAAGACTG
ACATCTACGTGACCAGTTTTGGCCCTGTGTCAGACACTGACATGGAGT
ACACTATTGATGTATTTTTTCGGCAGACATGGCATGATGAAAGACTGA
AATTTGATGGCCCCATGAAGATCCTTCCACTGAACAATCTCCTGGCTA
GTAAGATCTGGACACCGGACACCTTCTTCCACAATGGCAAGAAATCAG
TGGCTCATAACATGACCACGCCCAACAAGCTGCTCAGATTGGTGGAC
AACGGAACCCTCCTCTATACAATGAGGTTAACAATTCATGCTGAGTGT
CCCATGCATTTGGAAGATTTTCCCATGGATGTGCATGCCTGCCCACTG
AAGTTTGGAAGCTATGCCTATACAACAGCTGAAGTGGTTTATTCTTGG
ACTCTCGGAAAGAACAAATCCGTGGAAGTGGCACAGGATGGTTCTCG
CTTGAACCAGTATGACCTTTTGGGCCATGTTGTTGGGACAGAGATAAT
CCGGTCTAGTACAGGAGAATATGTCGTCATGACAACCCACTTCCATCT
CAAGCGAAAAATTGGCTACTTTGTGATCCAGACCTACTTGCCATGTAT
CATGACTGTCATTCTGTCACAAGTGTCGTTCTGGCTCAACAGAGAGTC
TGTTCCTGCCCGTACAGTCTTTGGTGTCACCACTGTGCTTACCATGAC
CACCTTGAGTATCAGTGCCAGAAATTCCTTACCTAAAGTGGCATATGC
GACGGCCATGGACTGGTTCATAGCCGTCTGTTATGCCTTTGTATTTTC
TGCACTGATTGAATTTGCCACTGTCAACTATTTCACCAAGCGGAGTTG
GGCTTGGGAAGGCAAGAAGGTGCCAGAGGCCCTGGAGATGAAGAAG
AAAACACCAGCAGCCCCAGCAAAGAAAACCAGCACTACCTTCAACATC
GTGGGGACCACCTATCCCATCAACCTGGCCAAGGACACTGAATTTTC
CACCATCTCCAAGGGCGCTGCTCCCAGTGCCTCCTCAACCCCAACAA
TCATTGCTTCACCCAAGGCCACCTACGTGCAGGACAGCCCGACTGAG
ACCAAGACCTACAACAGTGTCAGCAAGGTTGACAAAATTTCCCGCATC
ATCTTTCCTGTGCTCTTTGCCATATTCAATCTGGTCTATTGGGCCACAT
ATGTCAACCGGGAGTCAGCTATCAAGGGCATGATCCGCAAACAGTAG

Human $GABA_A$ receptor alpha 5 subunit cDNA (SEQ ID NO: GABA4)

ATGGACAATGGAATGTTCTCTGGTTTTATCATGATCAAAAACCTCCTTC
TCTTTTGTATTTCCATGAACTTATCCAGTCACTTTGGCTTTTCACAGAT
GCCAACCAGTTCAGTGAAAGATGAGACCAATGACAACATCACGATATT
TACCAGGATCTTGGATGGGCTCTTGGATGGCTACGACAACAGACTTC
GGCCCGGGCTGGGAGAGCGCATCACTCAGGTGAGGACCGACATCTA
CGTCACCAGCTTCGGCCCGGTGTCCGACACGGAAATGGAGTACACCA
TAGACGTGTTTTTCCGACAAAGCTGGAAAGATGAAAGGCTTCGGTTTA
AGGGGCCCATGCAGCGCCTCCCTCTCAACAACCTCCTTGCCAGCAAG
ATCTGGACCCCAGACACGTTCTTCCACAACGGGAAGAAGTCCATCGC
TCACAACATGACCACGCCCAACAAGCTGCTGCGGCTGGAGGACGACG
GCACCCTGCTCTACACCATGCGCTTGACCATCTCTGCAGAGTGCCCC
ATGCAGCTTGAGGACTTCCCGATGGATGCGCACGCTTGCCCTCTGAA
ATTTGGCAGCTATGCGTACCCTAATTCTGAAGTCGTCTACGTCTGGAC
CAACGGCTCCACCAAGTCGGTGGTGGTGGCGGAAGATGGCTCCAGA
CTGAACCAGTACCACCTGATGGGGCAGACGGTGGGCACTGAGAACAT
CAGCACCAGCACAGGCGAATACACAATCATGACAGCTCACTTCCACCT
GAAAAGGAAGATTGGCTACTTTGTCATCCAGACCTACCTTCCCTGCAT
AATGACCGTGATCTTATCACAGGTGTCCTTTTGGCTGAACCGGGAATC
AGTCCCAGCCAGGACAGTTTTTGGGGTCACCACGGTGCTGACCATGA
CGACCCTCAGCATCAGCGCCAGGAACTCTCTGCCCAAAGTGGCCTAC
GCCACCGCCATGGACTGGTTCATAGCCGTGTGCTATGCCTTCGTCTT
CTCGGCGCTGATAGAGTTTGCCACGGTCAATTACTTTACCAAGAGAGG
CTGGGCCTGGGATGGCAAAAAAGCCTTGGAAGCAGCCAAGATCAAGA
AAAAGCGTGAAGTCATACTAAATAAGTCAACAAACGCTTTTACAACTG
GGAAGATGTCTCACCCCCCAAACATTCCGAAGGAACAGACCCCAGCA
GGGACGTCGAATACAACCTCAGTCTCAGTAAAACCCTCTGAAGAGAA
GACTTCTGAAAGCAAAAAGACTTACAACAGTATCAGCAAAATTGACAA
AATGTCCCGAATCGTATTCCCAGTCTTGTTCGGCACTTTCAACTTAGTT
TACTGGGCAACGTATTTGAATAGGGAGCCGGTGATAAAAGGAGCCGC
CTCTCCAAAATAA

Human $GABA_A$ receptor beta 3 variant 1 subunit cDNA (SEQ ID NO: GABA5)

ATGTGGGGCCTTGCGGGAGGAAGGCTTTTCGGCATCTTCTCGGCCCC
GGTGCTGGTGGCTGTGGTGTGCTGCGCCCAGAGTGTGAACGATCCC
GGGAACATGTCCTTTGTGAAGGAGACGGTGGACAAGCTGTTGAAAGG
CTACGACATTCGCCTAAGACCCGACTTCGGGGGTCCCCCGGTCTGCG
TGGGGATGAACATCGACATCGCCAGCATCGACATGGTTTCCGAAGTC
AACATGGATTATACCTTAACCATGTATTTTCAACAATATTGGAGAGATA
AAAGGCTCGCCTATTCTGGGATCCCTCTCAACCTCACGCTTGACAATC
GAGTGGCTGACCAGCTATGGGTGCCCGACACATATTTCTTAAATGACA
AAAAGTCATTTGTGCATGGAGTGACAGTGAAAAACCGCATGATCCGTC
TTCACCCTGATGGGACAGTGCTGTATGGGCTCAGAATCACCACGACA
GCAGCATGCATGATGGACCTCAGGAGATACCCCCTGGACGAGCAGAA
CTGCACTCTGGAAATTGAAAGCTATGGCTACACCACGGATGACATTGA
GTTTTACTGGCGAGGCGGGGACAAGGCTGTTACCGGAGTGGAAAGG
ATTGAGCTCCCGCAGTTCTCCATCGTGGAGCACCGTCTGGTCTCGAG

GAATGTTGTCTTCGCCACAGGTGCCTATCCTCGACTGTCACTGAGCTT
TCGGTTGAAGAGGAACATTGGATACTTCATTCTTCAGACTTATATGCC
CTCTATACTGATAACGATTCTGTCGTGGGTGTCCTTCTGGATCAATTAT
GATGCATCTGCTGCTAGAGTTGCCCTCGGGATCACAACTGTGCTGAC
AATGACAACCATCAACACCCACCTTCGGGAGACCTTGCCCAAAATCCC
CTATGTCAAAGCCATTGACATGTACCTTATGGGCTGCTTCGTCTTTGT
GTTCCTGGCCCTTCTGGAGTATGCCTTTGTCAACTACATTTTCTTTGGA
AGAGGCCCTCAAAGGCAGAAGAAGCTTGCAGAAAAGACAGCCAAGGC
AAAGAATGACCGTTCAAAGAGCGAAAGCAACCGGGTGGATGCTCATG
GAAATATTCTGTTGACATCGCTGGAAGTTCACAATGAAATGAATGAGG
TCTCAGGCGGCATTGGCGATACCAGGAATTCAGCAATATCCTTTGACA
ACTCAGGAATCCAGTACAGGAAACAGAGCATGCCTCGAGAAGGGCAT
GGGCGATTCCTGGGGGACAGAAGCCTCCCGCACAAGAAGACCCATCT
ACGGAGGAGGTCTTCACAGCTCAAAATTAAAATACCTGATCTAACCGA
TGTGAATGCCATAGACAGATGGTCCAGGATCGTGTTTCCATTCACTTT
TTCTCTTTTCAACTTAGTTTACTGGCTGTACTATGTTAACTGA

Human $GABA_A$ receptor gamma 2 transcript variant 1 (short) subunit cDNA (SEQ ID NO: GABA6)

ATGAGTTCGCCAAATATATGGAGCACAGGAAGCTCAGTCTACTCGACT
CCTGTATTTTCACAGAAAATGACGGTGTGGATTCTGCTCCTGCTGTCG
CTCTACCCTGGCTTCACTAGCCAGAAATCTGATGATGACTATGAAGAT
TATGCTTCTAACAAAACATGGGTCTTGACTCCAAAAGTTCCTGAGGGT
GATGTCACTGTCATCTTAAACAACCTGCTGGAAGGATATGACAATAAA
CTTCGGCCTGATATAGGAGTGAAGCCAACGTTAATTCACACAGACATG
TATGTGAATAGCATTGGTCCAGTGAACGCTATCAATATGGAATACACT
ATTGATATATTTTTTGCGCAAACGTGGTATGACAGACGTTTGAAATTTA
ACAGCACCATTAAAGTCCTCCGATTGAACAGCAACATGGTGGGGAAAA
TCTGGATTCCAGACACTTTCTTCAGAAATTCCAAAAAAGCTGATGCACA
CTGGATCACCACCCCCAACAGGATGCTGAGAATTTGGAATGATGGTC
GAGTGCTCTACACCCTAAGGTTGACAATTGATGCTGAGTGCCAATTAC
AATTGCACAACTTTCCAATGGATGAACACTCCTGCCCCTTGGAGTTCT
CAAGTTATGGCTATCCACGTGAAGAAATTGTTTATCAATGGAAGCGAA
GTTCTGTTGAAGTGGGCGACACAAGATCCTGGAGGCTTTATCAATTCT
CATTTGTTGGTCTAAGAAATACCACCGAAGTAGTGAAGACAACTTCCG
GAGATTATGTGGTCATGTCTGTCTACTTTGATCTGAGCAGAAGAATGG
GATACTTTACCATCCAGACCTATATCCCCTGCACACTCATTGTCGTCCT
ATCCTGGGTGTCTTTCTGGATCAATAAGGATGCTGTTCCAGCCAGAAC
ATCTTTAGGTATCACCACTGTCCTGACAATGACCACCCTCAGCACCAT
TGCCCGGAAATCGCTCCCCAAGGTCTCCTATGTCACAGCGATGGATC
TCTTTGTATCTGTTTGTTTCATCTTTGTCTTCTCTGCTCTGGTGGAGTA
TGGCACCTTGCATTATTTTGTCAGCAACCGGAAACCAAGCAAGGACAA
AGATAAAAAGAAGAAAAACCCTGCCCCTACCATTGATATCCGCCCAAG
ATCAGCAACCATTCAAATGAATAATGCTACACACCTTCAAGAGAGAGA
TGAAGAGTACGGCTATGAGTGTCTGGACGGCAAGGACTGTGCCAGTT
TTTTCTGCTGTTTTGAAGATTGTCGAACAGGAGCTTGGAGACATGGGA
GGATACATATCCGCATTGCCAAAATGGACTCCTATGCTCGGATCTTCT

TCCCCACTGCCTTCTGCCTGTTTAATCTGGTCTATTGGGTCTCCTACC TCTACCTGTGA

GABA Target 1 (SEQ ID NO: GABA7)
5'-GTTCTTAAGGCACAGGAACTGGGAC-3'

GABA Target 2 (SEQ ID NO: GABA8)
5'-GAAGTTAACCCTGTCGTTCTGCGAC-3'

GABA Target 3 (SEQ ID NO: GABA9)
5'-GTTCTATAGGGTCTGCTTGTCGCTC-3'

GABA Signal Probe 1 (SEQ ID NO: GABA10)
5' - **Cy5** GCCAGTCCCAGTTCCTGTGCCTTAAGAACCTCGC **BHQ3 quench** -3'

GABA Signal Probe 2 (SEQ ID NO: GABA11)
5'- **Cy5.5** GCGAGTCGCAGAACGACAGGGTTAACTTCCTCGC **BHQ3 quench** -3'

GABA Signal Probe 3 (SEQ ID NO: GABA12)

5'- **Fam** GCGAGAGCGACAAGCAGACCCTATAGAACCTCGC **BHQ1 quench** -3"

SEQ ID NO: GCC1

5'-GTTCTTAAGGCACAGGAACTGGGAC-3'

SEQ ID NO: GCC 2

5' - Cy5 GCCAGTCCCAGTTCCTGTGCCTTAAGAACCTCGC BHQ2 -3'

SEQ ID NO: GCC 3 (GUCY2C (guanylate cyclase 2C) nucleotide sequence)

ATGAAGACGTTGCTGTTGGACTTGGCTTTGTGGTCACTGCTCTTCCAG CCCGGGTGGCTGTCCTTTAGTTCCCAGGTGAGTCAGAACTGCCACAA

TGGCAGCTATGAAATCAGCGTCCTGATGATGGGCAACTCAGCCTTTG
CAGAGCCCCTGAAAAACTTGGAAGATGCGGTGAATGAGGGGCTGGAA
ATAGTGAGAGGACGTCTGCAAAATGCTGGCCTAAATGTGACTGTGAAC
GCTACTTTCATGTATTCGGATGGTCTGATTCATAACTCAGGCGACTGC
CGGAGTAGCACCTGTGAAGGCCTCGACCTACTCAGGAAAATTTCAAAT
GCACAACGGATGGGCTGTGTCCTCATAGGGCCCTCATGTACATACTC
CACCTTCCAGATGTACCTTGACACAGAATTGAGCTACCCCATGATCTC
AGCTGGAAGTTTTGGATTGTCATGTGACTATAAAGAAACCTTAACCAG
GCTGATGTCTCCAGCTAGAAAGTTGATGTACTTCTTGGTTAACTTTTGG
AAAACCAACGATCTGCCCTTCAAAACTTATTCCTGGAGCACTTCGTAT
GTTTACAAGAATGGTACAGAAACTGAGGACTGTTTCTGGTACCTTAAT
GCTCTGGAGGCTAGCGTTTCCTATTTCTCCCACGAACTCGGCTTTAAG
GTGGTGTTAAGACAAGATAAGGAGTTTCAGGATATCTTAATGGACCAC
AACAGGAAAAGCAATGTGATTATTATGTGTGGTGGTCCAGAGTTCCTC
TACAAGCTGAAGGGTGACCGAGCAGTGGCTGAAGACATTGTCATTATT
CTAGTGGATCTTTTCAATGACCAGTACTTGGAGGACAATGTCACAGCC
CCTGACTATATGAAAAATGTCCTTGTTCTGACGCTGTCTCCTGGGAAT
TCCCTTCTAAATAGCTCTTTCTCCAGGAATCTATCACCAACAAAACGAG
ACTTTGCTCTTGCCTATTTGAATGGAATCCTGCTCTTTGGACATATGCT
GAAGATATTTCTTGAAAATGGAGAAAATATTACCACCCCCAAATTTGCT
CATGCTTTCAGGAATCTCACTTTTGAAGGGTATGACGGTCCAGTGACC
TTGGATGACTGGGGGGATGTTGACAGTACCATGGTGCTTCTGTATACC
TCTGTGGACACCAAGAAATACAAGGTTCTTTTGACCTATGATACCCAC
GTAAATAAGACCTATCCTGTGGATATGAGCCCCACATTCACTTGGAAG
AACTCTAAACTTCCTAATGATATTACAGGCCGGGGCCCTCAGATCCTG
ATGATTGCAGTCTTCACCCTCACTGGAGCTGTGGTGCTGCTCCTGCTC
GTCGCTCTCCTGATGCTCAGAAAATATAGAAAAGATTATGAACTTCGT
CAGAAAAAATGGTCCCACATTCCTCCTGAAAATATCTTTCCTCTGGAG
ACCAATGAGACCAATCATGTTAGCCTCAAGATCGATGATGACAAAAGA
CGAGATACAATCCAGAGACTACGACAGTGCAAATACGACAAAAAGCG
AGTGATTCTCAAAGATCTCAAGCACAATGATGGTAATTTCACTGAAAAA
CAGAAGATAGAATTGAACAAGTTGCTTCAGATTGACTATTACAACCTGA

CCAAGTTCTACGGCACAGTGAAACTTGATACCATGATCTTCGGGGTGA
TAGAATACTGTGAGAGAGGATCCCTCCGGGAAGTTTTAAATGACACAA
TTTCCTACCCTGATGGCACATTCATGGATTGGGAGTTTAAGATCTCTG
TCTTGTATGACATTGCTAAGGGAATGTCATATCTGCACTCCAGTAAGA
CAGAAGTCCATGGTCGTCTGAAATCTACCAACTGCGTAGTGGACAGTA
GAATGGTGGTGAAGATCACTGATTTTGGCTGCAATTCCATTTTACCTC
CAAAAAAGGACCTGTGGACAGCTCCAGAGCACCTCCGCCAAGCCAAC
ATCTCTCAGAAAGGAGATGTGTACAGCTATGGGATCATCGCACAGGA
GATCATTCTGCGGAAAGAAACCTTCTACACTTTGAGCTGTCGGGACCG
GAATGAGAAGATTTTCAGAGTGGAAAATTCCAATGGAATGAAACCCTT
CCGCCCAGATTTATTCTTGGAAACAGCAGAGGAAAAAGAGCTAGAAGT
GTACCTACTTGTAAAAAACTGTTGGGAGGAAGATCCAGAAAAGAGACC
AGATTTCAAAAAAATTGAGACTACACTTGCCAAGATATTTGGACTTTTT
CATGACCAAAAAAATGAAAGCTATATGGATACCTTGATCCGACGTCTA
CAGCTATATTCTCGAAACCTGGAACATCTGGTAGAGGAAAGGACACAG
CTGTACAAGGCAGAGAGGGACAGGGCTGACAGACTTAACTTTATGTT
GCTTCCAAGGCTAGTGGTAAAGTCTCTGAAGGAGAAAGGCTTTGTGG
AGCCGGAACTATATGAGGAAGTTACAATCTACTTCAGTGACATTGTAG
GTTTCACTACTATCTGCAAATACAGCACCCCCATGGAAGTGGTGGACA
TGCTTAATGACATCTATAAGAGTTTTGACCACATTGTTGATCATCATGA
TGTCTACAAGGTGGAAACCATCGGTGATGCGTACATGGTGGCTAGTG
GTTTGCCTAAGAGAAATGGCAATCGGCATGCAATAGACATTGCCAAGA
TGGCCTTGGAAATCCTCAGCTTCATGGGGACCTTTGAGCTGGAGCAT
CTTCCTGGCCTCCCAATATGGATTCGCATTGGAGTTCACTCTGGTCCC
TGTGCTGCTGGAGTTGTGGGAATCAAGATGCCTCGTTATTGTCTATTT
GGAGATACGGTCAACACAGCCTCTAGGATGGAATCCACTGGCCTCCC
TTTGAGAATTCACGTGAGTGGCTCCACCATAGCCATCCTGAAGAGAAC
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AAGAGGAAATGAGACTACCTACTGGCTGACTGGGATGAAGGACCAGA
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AAGCAGAATTTTCAGACATGATTGCCAACTCTTTACAGAAAAGACAGG
CAGCAGGGATAAGAAGCCAAAAACCCAGACGGGTAGCCAGCTATAAA

AAAGGCACTCTGGAATACTTGCAGCTGAATACCACAGACAAGGAGAG
CACCTATTTTTAA

[0340] Homo sapiens (H. s.) cystic fibrosis transmembrane conductance regulator (CFTR) nucleotide sequence (SEQ ID NO: CFTR1):

atgcagaggtcgcctctggaaaaggccagcgttgtctccaaacttttttcagctggaccagaccaatttt
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[0341] CFTR Target Sequence 1 (SEQ ID NO: CFTR2):

5'- GTTCTTAAGGCACAGGAACTGGGAC -3'

[0342] CFTR Signaling probe 1 (SEQ ID NO: CFTR3):

5' - **Cy5** GCCAGTCCCAGTTCCTGTGCCTTAAGAACCTCGC **BHQ2** -3'

H.s. SCN9A (SEQ ID NO: NAV-1)

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[0343] H.s. SCN1B (SEQ ID NO: NAV-2):

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[0344] H.s. SCN2B (SEQ ID NO: NAV-3):

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[0345] NaV Target sequence 1 (SEQ ID NO: NAV-4)

5'-GTTCTTAAGGCACAGGAACTGGGAC-3'

[0346] NaV Target sequence 2 (SEQ ID NO: NAV-5)

5'-GAAGTTAACCCTGTCGTTCTGCGAC-3'

[0347] NaV Target sequence 3 (SEQ ID NO: NAV-6)

5'-GTTCTATAGGGTCTGCTTGTCGCTC-3'

[0348] NaV Signaling probe 1 (binds target 1) (SEQ ID NO: NAV-7)

5' - Cy5 GCCAGTCCCAGTTCCTGTGCCTTAAGAACCTCGC **BHQ2 quench -3'**

[0349] NaV Signaling probe 2 – (binds target 2) (SEQ ID NO: NAV-8)

5'- Cy5.5 GCGAGTCGCAGAACGACAGGGTTAACTTCCTCGC **BHQ2 quench -3'**

[0350] NaV Signaling probe 3 – (binds target 3) (SEQ ID NO: NAV-9)

5'- Fam GCGAGAGCGACAAGCAGACCCTATAGAACCTCGC **BHQ1 quench -3'**

What is Claimed is:

1. A cell that expresses a heterodimeric protein of interest from an introduced nucleic acid encoding at least one of the subunits of the heterodimeric protein of interest, said cell being characterized in that it produces the heterodimeric protein of interest in a form suitable for use in a functional assay, wherein said protein of interest does not comprise a protein tag, or said protein is produced in that form consistently and reproducibly such that the cell has a Z' factor of at least 0.4 in the functional assay, or said cell is cultured in the absence of selective pressure, or any combinations thereof.

2. A cell that expresses a heterodimeric protein of interest, wherein the cell is engineered to activate transcription of an endogenous nucleic acid encoding at least one of the subunits of the heterodimeric protein of interest, said cell being characterized in that it produces the heterodimeric protein of interest in a form suitable for use in a functional assay, wherein said protein of interest does not comprise a protein tag, or said protein is produced in that form consistently and reproducibly such that the cell has a Z' factor of at least 0.4 in the functional assay, or said cell is cultured in the absence of selective pressure, or any combinations thereof.

3. A cell that expresses a heterodimeric protein of interest from an introduced nucleic acid encoding at least one of the subunits of the heterodimeric protein of interest, said cell being characterized in that it produces the protein of interest in a form that is or is capable of becoming biologically active, wherein the cell is cultured in the absence of selective pressure.

4. A cell that expresses a heterodimeric protein of interest wherein the cell is engineered to activate transcription of an endogenous nucleic acid encoding at least one of the subunits of the heterodimeric

protein of interest, said cell being characterized in that it produces the protein of interest in a form that is or is capable of becoming biologically active, wherein the cell is cultured in the absence of selective pressure.

5. The cell according to any one of claims 1-4, wherein the nucleic acid encoding the second subunit of the heterodimeric protein of interest is endogenous.

6. The cell according to claim 2 or 4, wherein the nucleic acid encoding the second subunit of the heterodimeric protein of interest is introduced.

7. The cell according to any one of claims 1-6, wherein the protein of interest does not comprise a protein tag.

8. The cell according to any one of claims 1-7, wherein the heterodimeric protein of interest is selected from the group consisting of: an ion channel, a G protein coupled receptor (GPCR), tyrosine receptor kinase, cytokine receptor, nuclear steroid hormone receptor and immunological receptor.

9. The cell according to claim 8, wherein the heterodimeric protein of interest is selected from the group consisting of: a sweet taste receptor and an umami taste receptor.

10. The cell according to any one of claims 1-8, wherein the heterodimeric protein of interest has no known ligand.

11. The cell according to any one of claims 1-10, wherein the heterodimeric protein of interest is not expressed in a cell of the same type.

12. The cell according to any one of claims 1-11, wherein the cell is a mammalian cell.

13. The cell according to any one of claims 1-12, wherein the cell is further characterized in that it has an additional desired property selected from the group consisting of: a signal to noise ratio greater than 1, being stable over time, growth without selective pressure without losing expression, physiological EC50 values, and physiological IC50 values.

14. The cell according to any one of claims 1, 2 and 5-13, wherein the heterodimeric protein of interest is produced in a form consistently and reproducibly for a period of time selected from: at least one week, at least two weeks, at least three weeks, at least one month, at least two months, at least three months at least four months, at least five months, at least six months, at least seven months, at least eight months, and at least nine months.

15. The cell according to any one of claims 1, 2 and 5-13, wherein the functional assay is selected from the group consisting of : a cell-based assay, a fluorescent cell-based assay, a high throughput screening assay, a reporter cell-based assay, a G protein mediated cell-based assay, and a calcium flux cell-based assay.

16. The cell according to any one of claims 1, 2, and 5-13, wherein the cell is suitable for utilization in a cell based high throughput screening.

17. The cell according to any one of claims 3-13, wherein the selective pressure is an antibiotic.

18. The cell according to any one of claims 3-13 and 17, wherein the cell expresses the heterodimeric protein in the absence of selective pressure for at least 15 days, 30 days, 45 days, 60 days, 75 days, 100 days, 120 days, or 150 days.

19. A cell that expresses a heteromultimeric protein of interest wherein said heteromultimeric protein comprises at least 3 subunits, wherein at least one subunit of the heteromultimeric protein

interest is encoded by an introduced nucleic acid, said cell being characterized in that it produces the heteromultimeric protein of interest in a form suitable for use in a functional assay, wherein said protein of interest does not comprise a protein tag, or said protein produced in that form consistently and reproducibly such that the cell has a Z' factor of at least 0.4 in the functional assay, or said cell is cultured in the absence of selective pressure, or any combinations thereof.

20. A cell that expresses a heteromultimeric protein of interest wherein said heteromultimeric protein comprises at least 3 subunits, wherein the cell is engineered to activate transcription of an endogenous nucleic acid encoding at least one of the subunits of the heteromultimeric protein of interest, said cell being characterized in that it produces the heteromultimeric protein of interest in a form suitable for use in a functional assay, wherein said protein of interest does not comprise a protein tag, or said protein produced in that form consistently and reproducibly such that the cell has a Z' factor of at least 0.4 in the functional assay, or said cell is cultured in the absence of selective pressure, or any combinations thereof.

21. A cell that expresses a heteromultimeric protein of interest wherein said heteromultimeric protein comprises at least 3 subunits, wherein at least one subunit of the heteromultimeric protein interest is encoded by an introduced nucleic acid, said cell being characterized in that it produces the protein of interest in a form that is or is capable of becoming biologically active.

22. A cell that expresses a heteromultimeric protein of interest wherein said heteromultimeric protein comprises at least 3 subunits, wherein the cell is engineered to activate transcription of an endogenous nucleic acid encoding at least one of the subunits of the heteromultimeric protein of interest, said cell being characterized in that it produces the protein of interest in a form that is or is capable of becoming biologically active.

23. The cell according to any one of claims 19-22, wherein the nucleic acid encoding at least one of the subunits of the heteromultimeric protein of interest is endogenous.

24. The cell according to claim 20 or 22, wherein the nucleic acid encoding at least one of the subunits of the heteromultimeric protein of interest is introduced.

25. The cell according to any one of claims 19-24, wherein the protein of interest does not comprise a protein tag.

26. The cell according to any one of claims 19-25, wherein the heteromultimeric protein of interest is selected from the group consisting of: an ion channel, a G protein coupled receptor (GPCR), tyrosine receptor kinase, cytokine receptor, nuclear steroid hormone receptor and immunological receptor.

27. The cell according to claim 26, wherein the heteromultimeric protein of interest is selected from the group consisting of: GABA, ENaC and NaV.

28. The cell according to any one of claims 19-26, wherein the heteromultimeric protein of interest has no known ligand.

29. The cell according to any one of claims 19-28, wherein the heteromultimeric protein of interest is not expressed in a cell of the same type.

30. The cell according to any one of claims 19-29, wherein the cell is a mammalian cell.

31. The cell according to any one of claims 19-30, wherein the cell is further characterized in that it has an additional desired property selected from the group consisting of: a signal to noise ratio greater than 1, being stable over time, growth without selective pressure without losing expression, physiological EC50 values, and physiological IC50 values.

32. The cell according to any one of claims 19, 20 and 23-31, wherein the heteromultimeric protein of interest is produced in a form consistently and reproducibly for a period of time selected from: at least one week, at least two weeks, at least three weeks, at least one month, at least two months, at least three months at least four months, at least five months, at least six months, at least seven months, at least eight months, and at least nine months.

33. The cell according to any one of claims 19, 20 and 23-31, wherein the functional assay is selected from the group consisting of: a cell-based assay, a fluorescent cell-based assay, a high throughput screening assay, a reporter cell-based assay, a G protein mediated cell-based assay, and a calcium flux cell-based assay.

34. The cell according to any one of claims 19, 20, and 23-31, wherein the cell is suitable for utilization in a cell based high throughput screening.

35. The cell according to any one of claims 21-31, wherein said cells are cultured in the absence of selective pressure.

36. The cell according to claims 35, wherein the selective pressure is an antibiotic.

37. The cell according to claim 35 or 36, wherein the cell expresses the heteromultimeric protein in the absence of selective pressure for at least 15 days, 30 days, 45 days, 60 days, 75 days, 100 days, 120 days, or 150 days.

38. A cell that expresses two or more proteins of interest from an introduced nucleic acid encoding at least one of the proteins of interest, said cell being characterized in that it produces the proteins of interest in a form suitable for use in a functional assay, wherein said proteins of interest do not comprise a protein tag, or said proteins are produced in that form consistently and reproducibly such that the cell has a

Z' factor of at least 0.4 in the functional assay, or said cell is cultured in the absence of selective pressure, or any combinations thereof.

39. A cell that expresses two or more proteins of interest, wherein the cell is engineered to activate transcription of an endogenous nucleic acid encoding at least one of the proteins of interest, said cell being characterized in that it produces the proteins of interest in a form suitable for use in a functional assay, wherein said proteins of interest do not comprise a protein tag, or said proteins are produced in that form consistently and reproducibly such that the cell has a Z' factor of at least 0.4 in the functional assay, or said cell is cultured in the absence of selective pressure, or any combinations thereof.

40. A cell that expresses two or more proteins of interest from an introduced nucleic acid encoding at least one of the proteins of interest, said cell being characterized in that it produces the proteins of interest in a form that is or is capable of becoming biologically active.

41. A cell that expresses two or more proteins of interest, wherein the cell is engineered to activate transcription of an endogenous nucleic acid encoding at least one of the proteins of interest, said cell being characterized in that it produces the proteins of interest in a form that is or is capable of becoming biologically active.

42. The cell according to any one of claims 38-41, wherein at least one protein of interest is a dimeric protein.

43. The cell according to claim 42, wherein the dimeric protein of interest is a homodimeric protein.

44. The cell according to claim 42, wherein the dimeric protein of interest is a heterodimeric protein.

45. The cell according to any one of claims 38-41, wherein at least one protein of interest is a multimeric protein.

46. The cell according to claim 45, wherein the multimeric protein of interest is a homomultimeric protein.

47. The cell according to claim 45, wherein the multimeric protein of interest is a heteromultimeric protein.

48. The cell according to any one of claims 38-47, wherein one of the proteins is encoded by an endogenous nucleic acid.

49. The cell according to claim 39 or 41, wherein one of the proteins is encoded by an introduced nucleic acid.

50. The cell according to any one of claims 38-49, wherein the proteins of interest do not comprise a protein tag.

51. The cell according to any one of claims 38-49, wherein one of the proteins of interest is selected from the group consisting of: an ion channel, a G protein coupled receptor (GPCR), tyrosine receptor kinase, cytokine receptor, nuclear steroid hormone receptor and immunological receptor.

52. The cell according to any one of claims 38-51, wherein one of the proteins of interest has no known ligand.

53. The cell according to any one of claims 38-52, wherein one of the proteins of interest is not expressed in a cell of the same type.

54. The cell according to any one of claims 38-53, wherein the cell is a mammalian cell.

55. The cell according to any one of claims 38-54, wherein the cell is further characterized in that it has an additional desired property selected from the group consisting of: a signal to noise ratio greater than 1, being stable over time, growth without selective pressure without losing expression, physiological EC50 values, and physiological IC50 values.

56. The cell according to any one of claims 38, 39 and 42-55, wherein the two or more proteins of interest are produced in a form consistently and reproducibly for a period of time selected from: at least one week, at least two weeks, at least three weeks, at least one month, at least two months, at least three months at least four months, at least five months, at least six months, at least seven months, at least eight months, and at least nine months.

57. The cell according to any one of claims 38, 39 and 42-55, wherein the functional assay is selected from the group consisting of: a cell-based assay, a fluorescent cell-based assay, a high throughput screening assay, a reporter cell-based assay, a G protein mediated cell-based assay, and a calcium flux cell-based assay.

58. The cell according to any one of claims 38, 39, and 42-55, wherein the cell is suitable for utilization in a cell based high throughput screening.

59. The cell according to any one of claims 40-55, wherein said cells are cultured in the absence of selective pressure.

60. The cell according to claims 59, wherein the selective pressure is an antibiotic.

61. The cell according to claim 59 or 60, wherein the cell expresses the two or more proteins in the absence of selective pressure for at least 15 days, 30 days, 45 days, 60 days, 75 days, 100 days, 120 days, or 150 days.

62. A cell that expresses at least one RNA of interest, wherein said RNA of interest is encoded by an introduced nucleic acid, said cell being characterized in that it produces the at least one RNA of interest in a form suitable for use in a functional assay, wherein said RNA of interest do not comprise a tag, or said RNA is produced in that form consistently and reproducibly such that the cell has a Z' factor of at least

0.4 in the functional assay, or said cell is cultured in the absence of selective pressure, or any combinations thereof.

63. A cell that expresses at least one RNA of interest, wherein the cell is engineered to activate transcription of an endogenous nucleic acid encoding the at least one RNA of interest, said cell being characterized in that it produces the at least one RNA of interest in a form suitable for use in a functional assay, wherein said RNA of interest do not comprise a tag, or said RNA is produced in that form consistently and reproducibly such that the cell has a Z' factor of at least 0.4 in the functional assay or said cell is cultured in the absence of selective pressure, or any combinations thereof.

64. A cell according to claim 62 or 63, wherein the cell expresses at least two RNAs of interest.

65. A cell according to claim 62 or 63, wherein the cell expresses at least three RNAs of interest.

66. The cell according to any one of claims 64-65, wherein the cell further expresses a RNA encoded by an introduced nucleic acid.

67. The cell according to any one of claims 62-66, wherein the RNA of interest is selected from the group consisting of : a RNA encoding an ion channel, a RNA encoding a G protein coupled receptor (GPCR), a RNA encoding a tyrosine receptor kinase, a RNA encodinga cytokine receptor, a RNA encoding a nuclear steroid hormone receptor and a RNA encoding an immunological receptor.

68. The cell according to any one of claims 62-67, wherein the RNA of interest is not expressed in a cell of the same type.

69. The cell according to any one of claims 62-68, wherein the cell is a mammalian cell.

70. The cell according to any one of claims 62-69, wherein the cell is further characterized in that it has an additional desired property selected from the group consisting of: a signal to noise ratio greater than 1, being stable over time, growth without selective pressure without losing expression, physiological EC50 values, and physiological IC50 values.

71. The cell according to any one of claims 62-70, wherein the RNA of interest is produced in a form consistently and reproducibly for a period of time selected from: at least one week, at least two weeks, at least three weeks, at least one month, at least two months, at least three months at least four months, at least five months, at least six months, at least seven months, at least eight months, and at least nine months.

72. The cell according to any one of claims 62-71, wherein the functional assay is selected from the group consisting of: a cell-based assay, a fluorescent cell-based assay, a high throughput screening assay, a reporter cell-based assay, a G protein mediated cell-based assay, and a calcium flux cell-based assay.

73. The cell according to any one of claims 61-72, wherein the cell is suitable for utilization in a cell based high throughput screening.

74. A cell line produced from the cell of any one of claims 1-73.

75. A method for producing a cell that expresses a protein of interest, wherein the cell has at least one desired property that is consistent over time, comprising the steps of:

a) providing a plurality of cells that express mRNA encoding the protein of interest;

b) dispersing cells individually into individual culture vessels, thereby providing a plurality of separate cell cultures

c) culturing the cells under a set of desired culture conditions using automated cell culture methods characterized in that the

conditions are substantially identical for each of the separate cell cultures, during which culturing the number of cells per separate cell culture is normalized from culture to culture, and wherein the separate cultures are passaged on the same schedule;

d) assaying the separate cell cultures for at least one desired characteristic of the protein of interest at least twice; and

e) identifying a separate cell culture that has the desired characteristic in both assays; wherein said cell is a cell that.

76. The method of claim 75, wherein the plurality of cells in step a) are cultured for some period of time prior to the dispersing in step b).

77. The method of claim 75, wherein the individual culture vessels are selected from the group consisting of: individual wells of a multiwell plate and vials.

78. The method of claim 75, further comprising the step of determining the growth rate of a plurality of the separate cell cultures and grouping the separate cell cultures by their growth rates into groups such that the difference between the fastest and slowest growth rates in any group is no more than 1, 2, 3, 4, or 5 days between steps b) and c).

79. The method of claim 75 or claim 78, further comprising the step of preparing a stored stock of one or more of the separate cultures.

80. The method of claim 75, further comprising the step of one or more replicate sets of the separate cell cultures and culturing the one or more replicate sets separately from the source separate cell cultures.

81. The method of claim 75, wherein the assaying in step d) is a functional assay for the protein.

82. The method of claim 75, wherein the at least one characteristic that has remained constant in step e) is protein function.

83. The method of claim 75, wherein the culturing in step c) is in a robotic cell culture apparatus.

84. The method of claim 83, wherein the robotic cell culture apparatus comprises a multi-channel robotic pipettor.

85. The method of claim 84, wherein the multi-channel robotic pipettor comprises at least 96 channels.

86. The method of claim 84, wherein the robotic cell culture apparatus further comprises a cherry-picking arm.

87. The method of claim 75, wherein the automated methods are include one or more of: media removal, media replacement, cell washing, reagent addition, removal of cells, cell dispersal, and cell passaging.

88. The method of claim 75, wherein the plurality of separate cell cultures is at least 50 cultures.

89. The method of claim 75, wherein the plurality of separate cell cultures is at least 100 cultures.

90. The method of claim 75, wherein the plurality of separate cell cultures is at least 500 cultures.

91. The method of claim 75, wherein the plurality of separate cell cultures is at least 1000 cultures.

92. The method of claim 78, wherein the growth rate is determined by a method selected from the group consisting of: measuring ATP, measuring cell confluency, light scattering, optical density measurement.

93. The method of claim 78, wherein the difference between the fastest and slowest growth rates in a group is no more than 1, 2, 3, 4, or 5 hours.

94. The method of claim 75, wherein the culturing in step c) is for at least 2 days.

95. The method of claim 78, wherein the growth rates of the plurality of separate cell cultures are determined by dispersing the cells and measuring cell confluency.

96. The method of claim 95, wherein the cells in each separate cell culture are dispersed prior to measuring cell confluency.

97. The method of claim 95 or 96, wherein the dispersing step comprises adding trypsin to the well and to eliminate clumps.

98. The method of claim 95, wherein the cell confluency of the plurality of separate cell cultures is measured using an automated microplate reader.

99. The method of claim 95, wherein at least two confluency measurements are made before growth rate is calculated.

100. The method of claim 98, wherein the cell confluency is measured by an automated plate reader and the confluency values are used with a software program that calculates growth rate.

101. The method of claim 75, wherein the separate cell cultures in step d) are characterization for a desired trait selected from one or more of: fragility, morphology, adherence to a solid surface; lack of adherence to a solid surface and protein function.

102. The method of claim 75, wherein the cells are eukaryotic cells.

103. The method of claim 75, wherein the eukaryotic cells are mammalian cells.

104. The method of claim 75, wherein the mammalian cell line is selected from the group consisting of: NS0 cells, CHO cells, COS cells, HEK-293 cells, HUVECs, 3T3 cells and HeLa cells.

105. The method of claim 75, wherein the protein of interest is a human protein.

106. The method of claim 75, wherein the protein of interest is a heteromultimer

107. The method of claim 75, wherein the protein of interest is a G protein coupled receptor.

108. The method of claim 75, wherein the protein has no known ligand.

109. The method of claim 75, further comprising after the identifying step, the steps of:

a) expanding a stored aliquot of the cell culture identified in step e) under desired culture conditions;

b) determining if the expanded cell culture of a) has the desired characteristic.

110. A matched panel of clonal cell lines, wherein the clonal cell lines are of the same cell type, and wherein each cell line in the panel expresses a protein of interest, and wherein the clonal cell lines in the panel are matched to share the same physiological property to allow parallel processing.

111. The matched panel of clonal cell lines of claim 110, wherein the physiological property is growth rate.

112. The matched panel of clonal cell lines of claim 110, wherein the physiological property is adherence to a tissue culture surface.

113. The matched panel of clonal cell lines of claim 110, wherein the physiological property is Z' factor.

114. The matched panel of clonal cell lines of claim 110, wherein the physiological property is expression level of RNA encoding the protein of interest.

115. The matched panel of clonal cell lines of claim 110, wherein the physiological property is expression level of the protein of interest.

116. The matched panel of clonal cell lines of claim 111, wherein the growth rates of the clonal cell lines in the panel are within 1, 2, 3, 4, or 5 hours of each other.

117. The matched panel of clonal cell lines of claim 110, wherein the culture conditions are the same for all clonal cell lines in the panel.

118. The matched panel of clonal cell lines of claim 110, wherein the clonal cell line is a eukaryotic cell line.

119. The matched panel of clonal cell lines of claim 110, wherein the eukaryotic cell line is a mammalian cell line.

120. The matched panel of clonal cell lines of claim 110, wherein the cell line cells are selected from the group consisting of: primary cells and immortalized cells.

121. The matched panel of clonal cell lines of claim 110, wherein the cell line cells are prokaryotic or eukaryotic.

122. The matched panel of clonal cell lines of claim 121, wherein the cell line cells are eukaryotic and are selected from the group

consisting of: fungal cells, insect cells, mammalian cells, yeast cells, algae, crustacean cells, arthropod cells , avian cells, reptilian cells, amphibian cells and plant cells.

123. The matched panel of clonal cell lines of claim 122, wherein the cell line cells are mammalian and are selected from the group consisting of: human, non-human primate, bovine, porcine, feline, rat, marsupial, murine, canine, ovine, caprine, rabbit, guinea pig hamster.

124. The matched panel of clonal cell lines of claim 110, wherein the cells in the cell line are engineered to express the protein of interest.

125. The matched panel of clonal cell lines of claim 110, wherein the cells in the cell line express the protein of interest from an introduced nucleic acid encoding the protein or, in the case of a multimeric protein, encoding a subunit of the protein.

126. The matched panel of clonal cell lines of claim 110, wherein the cells express the protein of interest from an endogenous nucleic acid and wherein the cell is engineered to activate transcription of the endogenous protein or, in the case of a multimeric protein, activates transcription of a subunit of the protein.

127. The matched panel of clonal cell lines of claim 110, wherein the panel comprises at least four clonal cell lines.

128. The matched panel of clonal cell lines of claim 110, wherein the panel comprises at least six clonal cell lines.

129. The matched panel of clonal cell lines of claim 110, wherein the panel comprises at least twenty five clonal cell lines.

130. The matched panel of clonal cell lines of claim 110, wherein two or more of the clonal cell lines in the panel express the same protein of interest.

131. The matched panel of clonal cell lines of claim 110, wherein two or more of the clonal cell lines in the panel express a different protein of interest.

132. The matched panel of clonal cell lines of claim 110, wherein the cell lines in the panel express different forms of a protein of interest, wherein the forms are selected from the group consisting of: isoforms, amino acid sequence variants, splice variants, truncated forms, fusion proteins, chimeras, or combinations thereof.

133. The matched panel of clonal cell lines of claim 110, wherein the cell lines in the panel express different proteins in a group of proteins of interest, wherein the groups of proteins of interest are selected from the group consisting of: proteins in the same signaling pathway, expression library of similar proteins, monoclonal antibody heavy chain library, monoclonal antibody light chain library and SNPs.

134. The matched panel of clonal cell lines of claim 110, wherein the protein of interest is a single chain protein.

135. The matched panel of clonal cell lines of claim 110, wherein the single chain protein is a G protein coupled receptor.

136. The matched panel of clonal cell lines of claim 135, wherein the G protein coupled receptor is a taste receptor.

137. The matched panel of clonal cell lines of claim 136, wherein the taste receptor is selected from the group consisting of: a bitter taste receptor, a sweet taste receptor, a salt taste receptor and a umami taste receptor.

138. The matched panel of clonal cell lines of claim 110, wherein the protein is a multimeric protein.

139. The matched panel of clonal cell lines of claim 110, wherein the protein is a heterodimer or a heteromultimer.

140. The matched panel of clonal cell lines of claim 110, wherein the protein is selected from the group consisting of: an ion channel, an ion channel, a G protein coupled receptor (GPCR), tyrosine receptor kinase, cytokine receptor, nuclear steroid hormone receptor and immunological receptor.

141. The matched panel of clonal cell lines of claim 140, wherein the protein is Epithelial sodium Channel (ENaC).

142. The matched panel of clonal cell lines of claim 140, wherein the ENaC comprises an alpha subunit, a beta subunit and a gamma subunit.

143. The matched panel of clonal cell lines of claim 110, wherein the cell lines in the panel express different ENaC isoforms.

144. The matched panel of clonal cell lines of claim 110, wherein the cell lines in the panel comprise different proteolyzed isoforms of ENaC.

145. The matched panel of clonal cell lines of any one of claims 141-143, wherein the ENaC is human ENaC.

146. The matched panel of clonal cell lines of claim 140, wherein the protein is voltage gated sodium channel (NaV).

147. The matched panel of clonal cell lines of claim146, wherein the NaV comprises an alpha subunit and two beta subunits.

148. The matched panel of clonal cell lines of claim 140, wherein the NaV is human NaV.

149. The matched panel of clonal cell lines of claim 110, wherein the protein is selected from the group consisting of: gamma-aminobutyric acid A receptor ($GABA_A$ receptor), gamma-aminobutyric acid

B receptor ($GABA_B$ receptor) and gamma-aminobutyric acid C receptor ($GABA_C$ receptor).

150. The matched panel of clonal cell lines of claim 110, wherein the protein is $GABA_A$ receptor.

151. The matched panel of clonal cell lines of claim 150, wherein the $GABA_A$ receptor comprises two alpha subunits, two beta subunits and a gamma or delta subunit.

152. The matched panel of clonal cell lines of claim 110, wherein the clonal cell lines in the panel were produced simultaneously, or within no more than 4 weeks of each other.

153. A cell that expresses a monomeric protein of interest from an introduced nucleic acid encoding said monomeric protein of interest, characterized in that it produces the protein of interest in a form that is or is capable of becoming biologically active, wherein the cell is cultured in the absence of selective pressure and wherein the expression of the protein does not vary by more than 5% over 3 months.

154. The cell according to claim 153, wherein the expression of the protein does not vary by more than 5% over 6 months

155. The cell according to claim 153 or 154, wherein the protein of interest has no known ligand.

156. A method for identifying a modulator of a protein of interest comprising the steps of:

a) contacting a cell according to any one of claims 1 to 74 with a test compound; and

b) detecting a change in the activity of the protein of interest in the cell contacted with the test compound compared to the activity of the protein in a cell not contacted by the test compound;

wherein a compound that produces a difference in the activity in the presence compared to in the absence is a modulator of the protein of interest.

157. A modulator identified by the method of claim 156.

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