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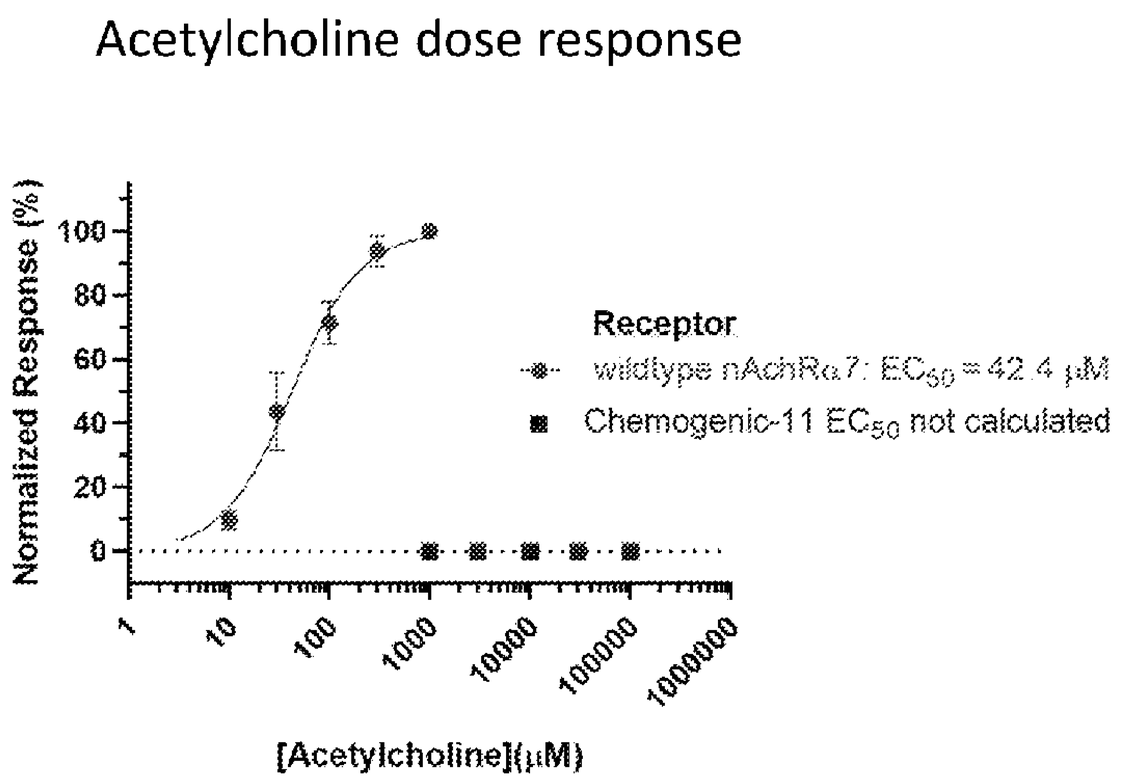
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(54) **Title:** COMPOSITIONS AND METHODS FOR NEUROLOGICAL DISEASES

FIG. 2A



Chemogenic-11 (CR-11):
SEQ ID NO:33 with amino acid substitutions Y115D+L131Q

(57) **Abstract:** Compositions and methods are provided for modulating the activity of cells using engineered receptors, polynucleotide encoded engineered receptors, and gene therapy vectors comprising polynucleotides encoding engineered receptors. These compositions and methods find particular use in modulating the activity of neurons, for example in the treatment of disease or in the study of neuronal circuits.

[Continued on next page]

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COMPOSITIONS AND METHODS FOR NEUROLOGICAL DISEASES

CROSS-REFERENCE TO RELATED APPLICATIONS

[0001] This application claims the benefit of U.S. Provisional Application No. 63/068,890, filed August 21, 2020, the content of which is herein incorporated by reference in its entirety.

DESCRIPTION OF THE TEXT FILE SUBMITTED ELECTRONICALLY

[0002] The sequence listing associated with this application is provided in text format in lieu of a paper copy, and is hereby incorporated by reference into the specification. The name of the text file containing the sequence listing is SWCH_034_01WO_SeqList_ST25.txt. The text file is about 297 kb in size, was created on August 19, 2021, and is being submitted electronically via EFS-Web.

FIELD

[0003] This disclosure pertains to engineered receptors and the use of engineered receptors and small molecule ligands to modulate the activity of cells and treat diseases.

BACKGROUND

[0004] Intractable neurological disease is often associated with aberrantly acting neurons. Attempts to develop therapies to treat these conditions have been hampered by a lack of tractable target proteins associated with the disease. For example, unrelieved chronic pain is a critical health problem in the US and worldwide. A report by the Institute of Medicine estimated that 116 million Americans suffer from pain that persists for weeks to years, with resulting annual costs exceeding $560 billion. There are no adequate long-term therapies for chronic pain sufferers, leading to significant cost for both society and the individual. Pain often results in disability and, even when not disabling, it has a profound effect on the quality of life. Pain treatment frequently fails even when the circumstances of care delivery are optimal, such as attentive, well-trained physicians; ready access to opioids; use of adjuvant analgesics; availability of patient-controlled analgesia; and evidence-based use of procedures like nerve blocks and IT pumps.

[0005] The most commonly used therapy for chronic pain is the application of opioid analgesics and nonsteroidal anti-inflammatory drugs, but these drugs can lead to addiction and may cause side effects, such as drug dependence, tolerance, respiratory depression, sedation, cognitive failure, hallucinations, and other systemic side effects. Despite the wide usage of pharmaceuticals, there is a strikingly low success rate for its effectiveness in pain relief. A large randomized study with various medications found only one out of every two or three patients achieving at least 50% pain relief (Finnerup *et al.*, 2005). A follow-up study using the most developed pharmacological treatments found the same results, indicating that there was no improvement in the efficacy of medications for pain (Finnerup *et al.*, *Pain*, 150(3):573-81, 2010).

[0006] More invasive options for the treatment of pain include nerve blocks and electrical stimulation. A nerve block is a local anesthetic injection usually in the spinal cord to interrupt pain signals to the brain, the effect of which only lasts from weeks to months. Nerve blocks are not the recommended treatment option in most cases (Mailis and Taenzer, *Pain Res Manag*. 17(3):150–158, 2012). Electrical stimulation involves providing electric currents to block pain signals. Although the effect may last longer than a nerve block, complications arise with the electrical leads itself: dislocation, infection, breakage, or the battery dying. One review found that 40% of patients treated with electrical stimulation for neuropathy experienced one or more of these issues with the device (Wolter, 2014).

[0007] The most invasive, and least preferred, method for managing pain is complete surgical removal of the nerve or section thereof that is causing the pain. This option is only recommended when the patient has exhausted the former and other less invasive, treatments and found them ineffective. Radiofrequency nerve ablation uses heat to destroy problematic nerves and provides a longer pain relief than a nerve block. However, one study found no difference between the control and treatment groups in partial radiofrequency lesioning of the DRG for chronic lumbosacral radicular pain (Geurts *et al.*, 2003). Other surgical methods for surgically removing the pain nerves suffer from similar shortcomings and have serious side effects long-term, including sensory or motor deficits, or cause pain elsewhere.

[0008] Methods for treating neurological disorders should be safe, efficient and cost-effective. Gene therapy could provide non-invasive treatment options for a variety of neurological diseases, including managing pain. However, to date, gene therapy methods have not found widespread use in the treatment of neurological diseases. The present disclosure addresses these needs.

BRIEF DESCRIPTION OF THE DRAWINGS

[0009] The disclosure is best understood from the following detailed description when read in conjunction with the accompanying drawings. The patent or application file contains at least one drawing executed in color. It is emphasized that, according to common practice, the various features of the drawings are not to-scale. On the contrary, the dimensions of the various features are arbitrarily expanded or reduced for clarity. Included in the drawings are the following figures:

[0010] **FIG. 1A – FIG. 1J** show the heat maps of the percent quench of YFP fluorescence in the mutants of the engineered chimeric receptor SEQ ID NO: 33 that comprise the indicated amino acid substitutions following stimulation by various doses of either acetylcholine or the indicated non-native ligand. Ligand doses are written across the top of each chart. Numbers in the boxes indicate the relative amount of quench observed. Higher level of quench indicates higher level of receptor activation by the ligand at the indicated dose. Quench level is also indicated by color gradient. Dark color = more than 70% of maximal quench of YFP reporter (*i.e.*, most of the engineered receptors are activated). White = less than 10% quench (*i.e.*, few of the engineered receptors are activated). Negative values represent non-responders that have a negative quench due to a stimulation artifact. SEQ ID NO: 29 is a non-responding chimera used as a negative control. CODA283 contains an extra N379K mutation introduced during cloning, which is located outside the ligand binding domain and therefore does not affect ligand binding. **FIG. 1A** shows the YFP fluorescence quenching using acetylcholine; **FIG. 1B** shows the YFP fluorescence quenching using CNL001; **FIG. 1C** shows the YFP fluorescence quenching using TC-6683; **FIG. 1D** shows the YFP fluorescence quenching using TC-5619/Bradanicline; **FIG. 1E** shows the YFP fluorescence quenching using CNL002; **FIG. 1F** shows the YFP fluorescence quenching using ABT-126; **FIG. 1G** shows the YFP fluorescence quenching using AZD-0328; **FIG. 1H** shows the YFP fluorescence quenching using Facinicline; **FIG. 1I** shows the YFP fluorescence quenching using TC-6987; **FIG. 1J** shows the YFP fluorescence quenching using Varenicline. Abbreviations for non-native ligand names: abt: ABT-126; ach: acetylcholine; azd: AZD-0328; brd: TC-5619 (Bradanicline); fac: RG3487 (Facinicline); tc6: TC-6987; var: Varenicline.

[0011] **FIG. 2A – FIG. 2B** show the concentration-response curves of CR-11 (Chemogenic receptor-11, an engineered receptor comprising an amino acid sequence having the amino acid substitutions of Y115D and L131Q in SEQ ID NO: 33) expressed in HEK 293 cells to acetylcholine as well as to non-native ligands RG-3487 (SA-2, Synthetic Agonist-2). The responses were evaluated using manual patch clamp electrophysiology. Currents were

normalized to unity for the maximal response. The continuous line through the data points is the best fit obtained with the Hill equation, and EC_{50}s for each ligand are estimated from the concentration-response curves. **FIG. 2A** shows the concentration-response curves of wild type and CR-11 receptors to acetylcholine. **FIG. 2B** shows the concentration-response curves of wild type and CR-11 receptors to RG-3487 (SA-2).

[0012] **FIG. 3** shows exemplary chloride currents induced by RG-3487 (SA-2) in adult rat DRG neurons transduced with a Lentivirus expressing CR-11 (Chemogenic receptor-11, an engineered receptor comprising an amino acid sequence having the amino acid substitutions of Y115D and L131Q in SEQ ID NO: 33).

[0013] **FIG. 4A** shows the evoked action potential of transduced DRG neurons expressing CR-11 (an engineered receptor comprising an amino acid sequence having the amino acid substitutions of Y115D and L131Q in SEQ ID NO: 33) or control DRG neurons (without CR-11 expression) at different current injections (50 pA to 700 pA). The upper panel shows the evoked action potential of a control DGF neuron. The lower left panel shows the evoked action potential of a transduced DRG neuron expressing CR-11 in the presence of 3 μM RG-3487 (SA-2). The lower right panel shows the evoked action potential of a transduced DRG neuron expressing CR-11 after RG-3487 (SA-2) is washed away. **FIG. 4B** shows the rheobase value (current required to elicit action potentials) for the control DRG neurons and transduced DRG neurons expressing CR-11 in the absence or presence of indicated ligand.

[0014] **FIG. 5** shows the % of HA-tag positive cells that are expressing the engineered receptors, normalized to control cells expressing the amino acid sequence of SEQ ID NO: 33 ("Normalized HA %"); and the % of α-bungarotoxin positive cells that are expressing the engineered receptors, normalized to control cells expressing the amino acid sequence of SEQ ID NO: 33 ("Normalized AB %"). **FIG. 5** also shows the median fluorescent intensity (MFI) of a cell expressing the engineered receptors, normalized to control cells expressing the amino acid sequence of SEQ ID NO: 33, as evaluated using anti-HA antibodies ("Normalized HA MFI") or fluorescently labeled α-bungarotoxin conjugated to Alexa Fluor 647 ("Normalized AB MFI").

[0015] **FIG. 6A** shows the relative surface and total expression of the indicated engineered receptors in cultured DRG neurons or in the HEK cells. **FIG. 6B** shows the relative surface and total expression of the indicated engineered receptors in cultured hippocampal neurons.

SUMMARY

[0016] The disclosure provides engineered receptors comprising a ligand binding domain derived from human α7 nicotinic acetylcholine receptor (α7-nAChR), wherein the ligand binding domain comprises an amino acid mutation at an amino acid residue corresponding to W77, R101, Y115, L131, Q139, Y140, S170, S172 or Y210 of SEQ ID NO: 4. In some embodiments, the ligand binding domain comprises an amino acid sequence having at least 85% identity to amino acid residues 23-220 of SEQ ID NO: 4. In some embodiments, the ligand binding domain comprises the amino acid mutation at two or more amino acid residues selected from those corresponding to W77, R101, Y115, L131, Q139, Y140, S170, S172 and Y210 of SEQ ID NO: 4. In some embodiments, the ligand binding domain comprises a mutation at the amino acid residue(s) corresponding to the indicated position of SEQ ID NO: 4:

a) Y140;

b) R101 and L131;

c) Y115 and Y210;

d) R101 and Y210;

e) R101, Y115 and Y210;

f) W77, R101 and L131;

g) R101, L131 and S172;

h) Q139 and S172D;

i) S172 and Y210

j) L131 and S172;

k) Y115 and S170; or

l) Y115 and L131.

[0017] In some embodiments, the mutation is amino acid substitution. In some embodiments, the ligand binding domain comprises the amino acid substitutions(s) corresponding to the indicated position of SEQ ID NO: 4:

a) Y140I ;

b) R101F and L131G;

c) R101F and L131D;

d) Y115E and Y210W;

e) R101W and Y210V;

f) R101F and Y210V;

g) R101F and Y210F;

h) R101M and L131A;

i) R101M and L131F;

j) R101W, Y115E and Y210W;

k) R101F, Y115E and Y210W;

l) W77F, R101F and L131D;

m) R101F, L131N and S172D;

n) Q139E and S172D;

o) S172D and Y210W;

p) L131S and S172D;

q) L131T and S172D;

r) L131D and S172D;

s) Y115D and S170T;

t) Y115D and L131Q;

u) Y115D and L131E;

v) L131E;

w) Y140C;

x) R101W;

y) Y210V; or

z) Q139E.

[0018] In some embodiments, the engineered receptor is a chimeric ligand gated ion channel (LGIC) receptor comprising an ion pore domain derived from a human Glycine receptor. In some embodiments, the human Glycine receptor is human Glycine receptor α1, human Glycine receptor α2, or human Glycine receptor α3. In some embodiments, the ion pore domain comprises an amino acid sequence having at least 85% identity to amino acids 255-457 of SEQ ID NO: 2, 260-452 of SEQ ID NO: 83, amino acids 259-464 of SEQ ID NO: 85, or amino acids 259-449 of SEQ ID NO: 87. In some embodiments, the ligand binding domain of the engineered receptor comprises a Cys-loop domain derived from the human Glycine receptor. In some embodiments, the Cys-loop domain comprises amino acids 166-172 of SEQ ID NO: 2. In some embodiments, the Cys-loop domain comprises amino acids 166-180 of SEQ ID NO: 2. In some embodiments, the ligand binding domain of the engineered receptor comprises a β1-2 loop domain from the human Glycine receptor α1 subunit. In some embodiments, the β1-2 loop domain comprises amino acids 81-84 of SEQ ID NO:2. In some

embodiments, the engineered receptor comprises an amino acid sequence according to any one of SEQ ID NOs. 58-78 and 88.

[0019] The disclosure provides engineered chimeric ligand gated ion channel (LGIC) comprising a ligand binding domain derived from a first LGIC and an ion pore domain derived from a second LGIC, wherein the first LGIC is the human α7 nicotinic acetylcholine receptor (α7-nAChR) and comprises an amino acid mutation at an amino acid residue corresponding to W77, R101, Y115, L131, Q139, Y140, S170, S172 or Y210 of SEQ ID NO: 4.

[0020] In some embodiments, the ligand binding domain comprises a mutation at the amino acid residue(s) corresponding to the indicated position of SEQ ID NO: 4:

a. Y140;
b. R101 and L131;
c. Y115 and Y210;
d. R101 and Y210;
e. R101, Y115 and Y210;
f. W77, R101 and L131;
g. R101, L131 and S172;
h. Q139 and S172D;
i. S172 and Y210
j. L131 and S172;
k. Y115 and S170; or
l. Y115 and L131

[0021] In some embodiments, the ligand binding domain comprises the amino acid substitutions(s) corresponding to the indicated position of SEQ ID NO: 4:

a. Y140I;
b. R101F and L131G;
c. R101F and L131D;
d. Y115E and Y210W;
e. R101W and Y210V;
f. R101F and Y210V;
g. R101F and Y210F;
h. R101M and L131A;
i. R101M and L131F;
j. R101W, Y115E and Y210W;

k. R101F, Y115E and Y210W;
l. W77F, R101F and L131D;
m. R101F, L131N and S172D;
n. Q139E and S172D;
o. S172D and Y210W;
p. L131S and S172D;
q. L131T and S172D;
r. L131D and S172D;
s. Y115D and S170T;
t. Y115D and L131Q;
u. Y115D and L131E;
v. L131E;
w. Y140C;
x. R101W;
y. Y210V; or
z. Q139E.

[0022] In some embodiments, the second LGIC is a human Glycine receptor. In some embodiments, the human Glycine receptor is human Glycine receptor α1. In some embodiments, the engineered chimeric LGIC comprises a polypeptide sequence having at least 85% sequence identity to SEQ ID NO: 33.

[0023] In some embodiments, the potency of the engineered receptor to acetylcholine is lower than the potency of the human α7 nicotinic acetylcholine receptor (α7-nAChR), or a control receptor, to acetylcholine. In some embodiments, the potency of the engineered receptor to acetylcholine is at least 2-fold lower than the potency of the human α7 nicotinic acetylcholine receptor (α7-nAChR), or a control receptor, to acetylcholine. In some embodiments, the potency of the engineered receptor to a non-native ligand is about the same as the potency of the human α7 nicotinic acetylcholine receptor (α7-nAChR), or a control receptor, to the non-native ligand. In some embodiments, the potency of the engineered receptor to a non-native ligand is higher than the potency of the human α7 nicotinic acetylcholine receptor (α7-nAChR), or a control receptor, to the non-native ligand. In some embodiments, the potency of the engineered receptor to the non-native ligand is at least 2-fold higher than the potency of the human α7 nicotinic acetylcholine receptor (α7-nAChR), or a control receptor, to the non-native ligand. In some embodiments, the potency of the engineered

receptor to a ligand is determined by the EC50 of the receptor for the ligand according to the YFP fluorescence quenching assay using Lenti-X 293T cells.

[0024] In some embodiments, the efficacy of the engineered receptor in the presence of a non-native ligand is higher than the efficacy the human α7 nicotinic acetylcholine receptor (α7-nAChR), or a control receptor, in presence of the non-native ligand. In some embodiments, the efficacy of the engineered receptor in the presence of a non-native ligand is at least 2-fold higher than the efficacy the human α7 nicotinic acetylcholine receptor (α7-nAChR), or a control receptor, in presence of the non-native ligand. In some embodiments, determining the efficacy comprises determining the amount of current passed through the engineered receptor in vitro in the presence of the non-native ligand.

[0025] In some embodiments, the non-native ligand is selected from the group consisting of AZD-0328, TC-6987, ABT-126, CNL002, TC-5619, CNL001, TC-6683, Varenicline, and Facinicline/RG3487. In some embodiments, the non-native ligand is selected from the group consisting of ABT-126, RG3487, and CNL002. In some embodiments, the non-native ligand is TC-5619.

[0026] The disclosure provides polynucleotides encoding an engineered receptor of the disclosure. In some embodiments, the polynucleotide encodes an engineered receptor comprising an amino acid sequence of any one of SEQ ID NOs: 58-78 and 88. In some embodiments, the polynucleotide comprises a promoter operably linked to the nucleic acid encoding the engineered receptor. In some embodiments, the promoter is a regulatable promoter. In some embodiments, the regulatable promoter is active in an excitable cell. In some embodiments, the excitable cell is a neuron or a myocyte. In some embodiments, the excitable cell is a neuron.

[0027] The disclosure provides vectors comprising any one of the polynucleotides disclosed herein. In some embodiments, the vector is a plasmid, or a viral vector. In some embodiments, the vector is a viral vector selected from the group consisting of an adenoviral vector, a retroviral vector, an adeno-associated viral (AAV) vector, and a herpes simplex-1 viral vector (HSV-1). In some embodiments, the viral vector is an AVV vector, and wherein the AAV vector is AAV5 or a variant thereof, AAV6 or a variant thereof or AAV9 or a variant thereof.

[0028] The disclosure provides compositions comprising any one of the engineered receptors disclosed herein, any one of the polynucleotides disclosed herein, or any one of the vectors disclosed herein. The disclosure further provides pharmaceutical compositions comprising any one of the engineered receptors disclosed herein, any one of the

polynucleotides disclosed herein, or any one of the vectors disclosed herein; and a pharmaceutically acceptable carrier.

[0029] The disclosure provides methods of expressing an engineered receptor in a neuron, comprising contacting the neuron with any one of the polynucleotides disclosed herein, any one of the vectors disclosed herein, any one of the compositions disclosed herein, or any one of the pharmaceutical compositions disclosed herein. In some embodiments, the neuron is a neuron of the peripheral nervous system. In some embodiments, the neuron is a neuron of the central nervous system. In some embodiments, the neuron is a nociceptive neuron. In some embodiments, the neuron is a non-nociceptive neuron. In some embodiments, the neuron is a dorsal root ganglion (DRG) neuron, a trigeminal ganglion (TG) neuron, a motor neuron, an excitatory neuron, an inhibitory neuron, or a sensory neuron. In some embodiments, the neuron is an Aδ afferent fiber, a C fiber or an Aβ afferent fiber. In some embodiments, the neuron is Aβ afferent fiber. In some embodiments, the Aβ afferent fiber is an injured Aβ afferent fiber. In some embodiments, the Aβ afferent fiber is an uninjured Aβ afferent fiber. In some embodiments, wherein the neuron expresses neurofilament 200 (NF200), piezo 2, and TLR-5. In some embodiments, the neuron does not express TrpV1, prostatic acid phosphatase, NaV1.1.

[0030] In some embodiments, the contacting step is performed *in vitro*, *ex vivo*, or *in vivo*. In some embodiments, the contacting step is performed *in vivo* in a subject. In some embodiments, the contacting step comprises administering the polynucleotide, the vector, the composition, or the pharmaceutical composition to the subject. In some embodiments, the contacting step is performed *in vitro* or *ex vivo*. In some embodiments, the contacting step comprises lipofection, nanoparticle delivery, particle bombardment, electroporation, sonication, or microinjection. In some embodiments, the engineered receptor is capable of localizing to the cell surface of the neuron.

[0031] The disclosure provides methods of inhibiting the activity of a neuron, comprising (a) contacting the neuron with any one of the engineered receptors disclosed herein, any one of the polynucleotides disclosed herein, any one of the vectors disclosed herein, any one of the compositions disclosed herein, or any one of the pharmaceutical compositions disclosed herein, and (b) contacting the neuron with a non-native ligand of the engineered receptor. In some embodiments, the neuron is a neuron of the peripheral nervous system. In some embodiments, the neuron is a neuron of the central nervous system. In some embodiments, the neuron is a nociceptive neuron. In some embodiments, the neuron is a non-nociceptive neuron. In some embodiments, the neuron is a dorsal root ganglion (DRG) neuron, a trigeminal ganglion (TG) neuron, a motor neuron, an excitatory neuron, an inhibitory neuron,

or a sensory neuron. In some embodiments, the neuron is an Aδ afferent fiber, a C fiber or an Aβ afferent fiber. In some embodiments, the neuron is Aβ afferent fiber. In some embodiments, the Aβ afferent fiber is an injured Aβ afferent fiber. In some embodiments, the Aβ afferent fiber is an uninjured Aβ afferent fiber. In some embodiments, the neuron expresses neurofilament 200 (NF200), piezo 2, and TLR-5. In some embodiments, the neuron does not express TrpV1, prostatic acid phosphatase, NaV1.1.

[0032] In some embodiments, the contacting step (a) is performed *in vitro*, *ex vivo*, or *in vivo*. In some embodiments, the contacting step (b) is performed *in vitro*, *ex vivo*, or *in vivo*. In some embodiments, the contacting steps (a) and/or (b) are performed *in vivo* in a subject. In some embodiments, the contacting step (a) comprises administering the engineered receptor, the polynucleotide, the vector, or the pharmaceutical composition to the subject; and/or the contacting step (b) comprises administering the non-native ligand to the subject. In some embodiments, the contacting step (a) and/or (b) comprises lipofection, nanoparticle delivery, particle bombardment, electroporation, sonication, or microinjection. In some embodiments, the engineered receptor is capable of localizing to the cell surface of the neuron.

[0033] The disclosure provides methods of treating and/or delaying the onset of a neurological disorder in a subject, in need thereof, comprising: administering to the subject, a therapeutically effective amount of any one of the engineered receptors disclosed herein, any one of the polynucleotides disclosed herein, any one of the vectors disclosed herein, any one of the compositions disclosed herein, or any one of the pharmaceutical compositions disclosed herein, and administering to the subject a non-native ligand of the engineered receptor. In some embodiments, the subject is administered the non-native ligand after step (a). In some embodiments, the subject is administered the non-native ligand concurrently with step (a).

[0034] In some embodiments, the neurological disorder is a seizure disorder, a movement disorder, an eating disorder, a spinal cord injury, neurogenic bladder, allodynia, a spasticity disorder, pruritus, Alzheimer's disease, Parkinson's disease, post-traumatic stress disorder (PTSD), gastroesophageal reflux disease (GERD), addiction, anxiety, depression, memory loss, dementia, sleep apnea, stroke, narcolepsy, urinary incontinence, essential tremor, trigeminal neuralgia, burning mouth syndrome, or atrial fibrillation. In some embodiments, the neurological disorder is allodynia. In some embodiments, the non-native ligand is selected from the group consisting of AZD-0328, ABT-126, TC6987, CNL002, TC-5619, CNL001, TC-6683, Varenicline, and Facinicline/RG3487.

[0035] In some embodiments, the non-native ligand is administered orally, subcutaneously, topically, or intravenously. In some embodiments, the non-native ligand is

administered orally. In some embodiments, the engineered receptor, the polynucleotide, the vector, the composition, or the pharmaceutical composition is administered subcutaneously, orally, intrathecally, topically, intravenously, intraganglioncally, intraneurally, intracranially, intraspinally, or to the cisterna magna. In some embodiments, the engineered receptor, the polynucleotide, the vector, the composition, or the pharmaceutical composition is administered by transforaminal injection or intrathecally. In some embodiments, the subject suffers from trigeminal neuralgia, and wherein the engineered receptor, the polynucleotide, the vector, the composition, or the pharmaceutical composition is administered to the trigeminal ganglion (TG) of the subject. In some embodiments, the subject suffers from neuropathic pain, and wherein the engineered receptor, the polynucleotide, the vector, the composition, or the pharmaceutical composition is administered to the dorsal root ganglion (DRG) of the subject. In some embodiments, the subject is a human.

[0036] In some embodiments, the therapeutically effectively amount diminishes the severity of a sign and/or or a symptom of the neurological disorder. In some embodiments, the therapeutically effectively amount delays the onset of a sign and/or or a symptom of the neurological disorder. In some embodiments, the therapeutically effectively amount eliminates a sign and/or or a symptom of the neurological disorder. In some embodiments, the sign of the neurological disorder is nerve damage, nerve atrophy, and/or seizure. In some embodiments, the nerve damage is peripheral nerve damage. In some embodiments, the symptom of the neurological disorder is pain.

[0037] The disclosure provides methods of treating and/or delaying the onset of pain in a subject, in need thereof, comprising: administering to the subject, a therapeutically effective amount of any one of the engineered receptors disclosed herein, any one of the polynucleotides disclosed herein, any one of the vectors disclosed herein, any one of the compositions disclosed herein, or any one of the pharmaceutical compositions disclosed herein, and administering to the subject a non-native ligand of the engineered receptor. In some embodiments, the subject is administered the non-native ligand after step (a). In some embodiments, the subject is administered the non-native ligand concurrently with step (a). In some embodiments, the non-native ligand is selected from the group consisting of AZD-0328, ABT-126, TC6987, CNL002, TC-5619, CNL001, TC-6683, Varenicline, and Facinicline/RG3487.

[0038] In some embodiments, the non-native ligand is administered orally, subcutaneously, topically, or intravenously. In some embodiments, the non-native ligand is administered orally. In some embodiments, the engineered receptor, the polynucleotide, the

vector, the composition, or the pharmaceutical composition is administered subcutaneously, orally, intrathecally, topically, intravenously, intraganglioncally, intraneurally, intracranially, intraspinally, or to the cisterna magna. In some embodiments, the engineered receptor, the polynucleotide, the vector, the composition, or the pharmaceutical composition is administered by transforaminal injection or intrathecally.

[0039] In some embodiments, the subject suffers from trigeminal neuralgia, and wherein the engineered receptor, the polynucleotide, the vector, the composition, or the pharmaceutical composition is administered to the trigeminal ganglion (TG) of the subject. In some embodiments, the subject suffers from neuropathic pain, and wherein the engineered receptor, the polynucleotide, the vector, the composition, or the pharmaceutical composition is administered to the dorsal root ganglion (DRG) of the subject.

[0040] In some embodiments, the subject is a human. In some embodiments, the pain is neuropathic pain. In some embodiments, the pain is associated with, caused by, or resulting from chemotherapy. In some embodiments, the pain is associated with, caused by, or resulting from trauma. In some embodiments, the subject suffers from allodynia. In some embodiments, the pain manifests after a medical procedure. In some embodiments, the pain is associated with, is caused by, or resulting from childbirth or Caesarean section. In some embodiments, the pain is associated with, is caused by, or resulting from migraine. In some embodiments, the therapeutically effectively amount diminishes pain in the subject transiently, diminishes pain in the subject permanently, prevents the onset of pain in the subject, and/or eliminates pain in the subject. In some embodiments, steps (a) and (b) are performed before the manifestation of pain in the subject.

[0041] The disclosure provides kits comprising (a) a vector of the disclosure and (b) a non-native ligand of the engineered receptor encoded by the vector. The disclosure provides kits comprising (a) the engineered receptor of the disclosure, and (b) a non-native ligand of the engineered receptor. In some embodiments, the combination of engineered receptor and the non-native ligand is according to any one the combinations provided in Table 29. In some embodiments, the kit comprises a device adapted to administration of the vector.

DETAILED DESCRIPTION

A. Overview

[0042] Compositions and methods are provided for modulating the activity of cells using engineered ligand gated ion channel (LGIC) receptors, polynucleotide encoded engineered LGIC receptors, and gene therapy vectors comprising polynucleotides encoding engineered LGIC receptors. These compositions and methods find particular use in modulating the activity of neurons, for example in the treatment of disease or in the study of neuronal circuits. In addition, reagents, devices and kits thereof that find use in practicing the subject methods are provided.

[0043] In particular, the present disclosure provides engineered receptors that bind to and signal in response to ligands. In some embodiments, the ligand is a drug. In some embodiments, the ligand is referred to as "binding agent". In some embodiments, the engineered receptors described herein demonstrate increased affinity for a known agonist ligand. In some embodiments, the engineered receptors described herein demonstrate an affinity for an antagonist or modulator ligand and respond to the antagonist and/or modulator ligands as if they were agonist ligands. The present disclosure further provides for methods of treating neurological diseases in subjects in need thereof. The present disclosure increases the number of clinical indications that a known drug may be used for by utilizing engineered receptors that respond to a known drug in a manner that is distinct from the wild-type endogenous receptor.

[0044] Before the present methods and compositions are described, it is to be understood that this disclosure is not limited to particular method or composition described, as such may, of course, vary. It is also to be understood that the terminology used herein is for the purpose of describing particular embodiments only, and is not intended to be limiting, since the scope of the present disclosure will be limited only by the appended claims.

[0045] Where a range of values is provided, it is understood that each intervening value, to the tenth of the unit of the lower limit unless the context clearly dictates otherwise, between the upper and lower limits of that range is also specifically disclosed. Each smaller range between any stated value or intervening value in a stated range and any other stated or intervening value in that stated range is encompassed within the disclosure. The upper and lower limits of these smaller ranges may independently be included or excluded in the range, and each range where either, neither or both limits are included in the smaller ranges is also encompassed within the disclosure, subject to any specifically excluded limit in the stated

range. Where the stated range includes one or both of the limits, ranges excluding either or both of those included limits are also included in the disclosure.

[0046] Unless defined otherwise, all technical and scientific terms used herein have the same meaning as commonly understood by one of ordinary skill in the art to which this disclosure belongs. Although any methods and materials similar or equivalent to those described herein can be used in the practice or testing of the present disclosure, some potential and preferred methods and materials are now described. All publications mentioned herein are incorporated herein by reference to disclose and describe the methods and/or materials in connection with which the publications are cited. It is understood that the present disclosure supersedes any disclosure of an incorporated publication to the extent there is a contradiction.

[0047] As will be apparent to those of skill in the art upon reading this disclosure, each of the individual embodiments described and illustrated herein has discrete components and features which may be readily separated from or combined with the features of any of the other several embodiments without departing from the scope or spirit of the present disclosure. Any recited method can be carried out in the order of events recited or in any other order which is logically possible.

[0048] The publications discussed herein are provided solely for their disclosure prior to the filing date of the present application. Nothing herein is to be construed as an admission that the present disclosure is not entitled to antedate such publication by virtue of prior disclosure. Further, the dates of publication provided may be different from the actual publication dates which may need to be independently confirmed.

B. Definitions

[0049] As used in this specification and the appended claims, the singular forms "a," "an" and "the" include plural references unless the content clearly dictates otherwise. Thus, for example, reference to "a cell" includes a plurality of such cells and reference to "the peptide" includes reference to one or more peptides and equivalents thereof, *e.g.* polypeptides, known to those skilled in the art, and so forth.

[0050] As used in this specification, the term "and/or" is used in this disclosure to either "and" or "or" unless indicated otherwise.

[0051] Throughout this specification, unless the context requires otherwise, the word "comprise", or variations such as "comprises" or "comprising" refers to the inclusion of a stated element or integer or group of elements or integers but not the exclusion of any other element

or integer or group of elements or integers. Further, the statement of numerical ranges throughout this specification specifically includes all integers and decimal points in between.

[0052] Throughout this specification, unless the context requires otherwise, the phrase "consisting essentially of" refers to a limitation of the scope of composition, method, or kit described to the specified materials or steps that do not materially affect the basic and novel characteristic(s) of the subject disclosure. For example, a ligand binding domain "consisting essentially of" a disclosed sequence has the amino acid sequence of the disclosed sequence plus or minus about 5 amino acid residues at the boundaries of the sequence, *e.g.* about 5 residues, 4 residues, 3 residues, 2 residues or about 1 residue less than the recited bounding amino acid residue, or about 1 residue, 2 residues, 3 residues, 4 residues, or 5 residues more than the recited bounding amino acid residue.

[0053] Throughout this specification, unless the context requires otherwise, the phrase "consisting of" refers to the exclusion from the composition, method, or kit of any element, step, or ingredient not specified in the claim. For example, a ligand binding domain "consisting of" a disclosed sequence consists only of the disclosed amino acid sequence.

[0054] As used in this application, the terms "about" and "approximately" are used as equivalents. Any numerals used in this application with or without about/approximately are meant to cover any normal fluctuations appreciated by one of ordinary skill in the relevant art. In certain embodiments, the term "approximately" or "about" refers to a range of values that fall within 25%, 20%, 19%, 18%, 17%, 16%, 15%, 14%, 13%, 12%, 11%, 10%, 9%, 8%, 7%, 6%, 5%, 4%, 3%, 2%, 1%, or less in either direction (greater than or less than) of the stated reference value unless otherwise stated or otherwise evident from the context (except where such number would exceed 100% of a possible value).

[0055] As used herein, the term "isolated" means material that is substantially or essentially free from components that normally accompany is as found in its native state. In some embodiments, the terms "obtained" or "derived" are used synonymously with isolated.

[0056] The terms "subject," "individual," and "patient" are used interchangeably herein to refer to a vertebrate, such as a mammal. The mammal may be, for example, a mouse, a rat, a rabbit, a cat, a dog, a pig, a sheep, a horse, a non-human primate (e.g., cynomolgus monkey, chimpanzee), or a human. A subject's tissues, cells, or derivatives thereof, obtained in vivo or cultured in vitro are also encompassed. A human subject may be an adult, a teenager, a child (2 years to 14 years of age), an infant (1 month to 24 months), or a neonate (up to 1 month). In some embodiments, the adults are seniors about 65 years or older, or about 60 years

or older. In some embodiments, the subject is a pregnant woman or a woman intending to become pregnant.

[0057] The term "sample" refers to a volume and/or mass of biological material that is subjected to analysis. In some embodiments, a sample comprises a tissue sample, cell sample, a fluid sample, and the like. In some embodiments, a sample is taken from or provided by a subject (*e.g.*, a human subject). In some embodiments, a sample comprises a portion of tissue taken from any internal organ, a cancerous, pre-cancerous, or non-cancerous tumor, brain, skin, hair (including roots), eye, muscle, bone marrow, cartilage, white adipose tissue, and/or brown adipose tissue. In some embodiments, a fluid sample comprises buccal swabs, blood, cord blood, saliva, semen, urine, ascites fluid, pleural fluid, spinal fluid, pulmonary lavage, tears, sweat, and the like. Those of ordinary skill in the art will appreciate that, in some embodiments, a "sample" is a "primary sample" in that it is obtained directly from a source (*e.g.*, a subject). In some embodiments, a "sample" is the result of processing of a primary sample, for example to remove certain potentially contaminating components, to isolate certain components, and/or to purify certain components of interest. In some embodiments, a sample is a cell or population of cells (*e.g.*, a neuronal cell). A cell sample may be derived directly from a subject (*e.g.*, a primary sample) or may be a cell line. Cell lines may include non-mammalian cells (*e.g.*, insect cells, yeast cells, and/or bacterial cells) or mammalian cells (*e.g.*, immortalized cell lines).

[0058] "Treating" or "treatment" as used herein refers to delivering a composition (*e.g.*, an engineered receptor and/or a ligand) to a subject and/or population of cells to affect a physiologic outcome. In particular embodiments, treatment results in an improvement (*e.g.*, reduction, amelioration, or remediation) of one or more disease symptoms. The improvement may be an observable or measurable improvement, or may be an improvement in the general feeling of well-being of the subject. Treatment of a disease can refer to a reduction in the severity of disease symptoms. In some embodiments, treatment can refer to a reduction in the severity of disease symptoms to levels comparable to those prior to disease onset. In some embodiments, treatment may refer to a short-term (*e.g.*, temporary or acute) and/or a long-term (*e.g.*, sustained or chronic) reduction in disease symptoms. In some embodiments, treatment may refer to a remission of disease symptoms. In some embodiments, treatment may refer to the prophylactic treatment of a subject at risk of developing a particular disease in order to prevent disease development. Prevention of disease development can refer to complete prevention of the disease symptoms, a delay in disease onset, a lessening of the severity of the symptoms in a subsequently developed disease, or reducing the likelihood of disease development.

[0059] As used herein, "management" or "controlling" refers to the use of the compositions or methods contemplated herein, to improve the quality of life for an individual suffering from a particular disease. In certain embodiments, the compositions and methods described herein provide analgesia to a subject suffering from pain.

[0060] A "therapeutically effective amount" is an amount of a composition required to achieve a desired therapeutic outcome. The therapeutically effective amount may vary according to factors such as, but not limited to, disease state and age, sex, and weight of the subject. Generally, a therapeutically effective amount is also one in which any toxic or detrimental effects of a composition are outweighed by the therapeutically beneficial effects. A "therapeutically effective amount" includes an amount of a composition that is effective to treat a subject.

[0061] An "increase" refers to an increase in a value (*e.g.*, increased binding affinity, increased physiologic response, increased therapeutic effect, etc.) of at least 5% as compared to a reference or control level. For example, an increase may include a 5, 6, 7, 8, 9, 10, 15, 20, 25, 30, 35, 40, 45, 50, 60, 70, 80, 90, 100, 150, 200, 250, 500, 1000% or more increase. Increase also means an increase that is 1.1, 1.2, 1.5, 2, 3, 4, 5, 6, 7, 8, 9, 10, 15, 20, 30 or more times (*e.g.*, 500, 1000 times) higher than a reference or control level.

[0062] A "decrease", "reduce", "diminish" or synonyms thereof refers to a decrease in a value (*e.g.*, decreased binding affinity, decreased physiologic response, decreased therapeutic effect, decrease in pain in a subject etc.) of at least 5% as compared to a reference or control level. For example, a decrease may include a 5, 6, 7, 8, 9, 10, 15, 20, 25, 30, 35, 40, 45, 50, 60, 70, 80, 90, 100, 150, 200, 250, 500, 1000% or more decrease. Decrease also means a decrease that is 1.1, 1.2, 1.5, 2, 3, 4, 5, 6, 7, 8, 9, 10, 15, 20, 30 or more times (*e.g.*, 500, 1000 times) lower than a reference or control level.

[0063] By "maintain," or "preserve," or "maintenance," or "no change," or "no substantial change," or "no substantial decrease" refers generally to a physiologic and/or therapeutic effect that is comparable to an effect caused by either vehicle, or a control molecule/composition. A comparable response is one that is not significantly different or measurable different from the reference response

[0064] The terms "reference" or "control" level are used interchangeably herein and refer the value of a particular physiologic and/or therapeutic effect in a subject or sample that has not been treated with a composition described herein, or a subject or sample that has been treated with a vehicle control. In some embodiments, a reference level refers to a value of a

particular physiologic and/or therapeutic effect that is measure in a subject or sample prior to the administration of a composition described herein (*e.g.*, a baseline level).

[0065] As used herein, "ligand" refers to a molecule that binds to another, larger molecule. In some embodiments, the ligand binds to a receptor. In some embodiments, the binding of the ligand to the receptor alters the function of the receptor – to activate or repress its function. In some embodiments, the binding of the ligand to a receptor such a ligand gated ion channel (LGIC) leads to the opening or closing of the ion channel.

[0066] "Receptor-ligand binding" and "ligand binding" are used interchangeably herein and refer to the physical interaction between a receptor (*e.g.*, a LGIC) and a ligand. The term "ligand" as used herein may refer to an endogenous or naturally occurring ligand. For example, in some embodiments, a ligand refers to a neurotransmitter (*e.g.*, λ-aminobutyric acid (GABA), acetylcholine, serotonin, and others) and signaling intermediate (*e.g.*, phosphatidylinositol 4,5-bisphosphate (PIP_2)), amino acids (*e.g.*, glycine), or nucleotides (*e.g.*, ATP). In some embodiments, a ligand may refer to a non-native, i.e. synthetic or non-naturally occurring, ligand. For example, in some embodiments, a ligand refers to a small molecule. Ligand binding can be measured by a variety of methods known in the art (*e.g.*, detection of association with a radioactively labeled ligand).

[0067] "Binding affinity" generally refers to the strength of the sum total of noncovalent interactions between a single binding site of a receptor and a ligand. Unless indicated otherwise, as used herein, "binding affinity" refers to intrinsic binding affinity which reflects a 1:1 interaction between members of a binding pair (*e.g.,* receptor and ligand). The affinity of a molecule X for its partner Y can generally be represented by the dissociation constant (K_d). Affinity can be measured by common methods known in the art, including those described herein.

[0068] The terms "specific binding affinity" or "specific binding" are used interchangeably throughout the specification and claims and refer to binding which occurs between a paired species of molecules, *e.g.,* receptor and ligand. When the interaction of the two species produces a non-covalently bound complex, the binding which occurs is typically electrostatic, hydrogen-bonding, or the result of lipophilic interactions. In various embodiments, the specific binding between one or more species is direct. In one embodiment, the affinity of specific binding is about 2 times greater than background binding (non-specific binding), about 5 times greater than background binding, about 10 times greater than background binding, about 20 times greater than background binding, about 50 times greater

than background binding, about 100 times greater than background binding, or about 1000 times greater than background binding or more.

[0069] "Signaling" refers to the generation of a biochemical or physiological response as a result of ligand binding to a receptor.

[0070] The term "wild type" or "native" is a term of the art understood by skilled persons and means the typical form of an organism, strain, gene, protein, or characteristic as it occurs in nature as distinguished from mutant or variant forms. For example, a wild type protein is the typical form of that protein as it occurs in nature.

[0071] The terms "non-native", "variant", and "mutant" are used interchangeably throughout the specification and the claims to refer to a mutant of a native, or wild type, composition, for example a variant polypeptide having less than 100% sequence identity with the native, or wild type, sequence.

[0072] "Amino acid modifications" or "amino acid mutations" may be amino acid substitutions, amino acid deletions and/or amino acid insertions. Amino acid substitutions may be conservative amino acid substitutions or non-conservative amino acid substitutions. A conservative replacement (also called a conservative mutation, a conservative substitution or a conservative variation) is an amino acid replacement in a protein that changes a given amino acid to a different amino acid with similar biochemical properties (e.g. charge, hydrophobicity and size). As used herein, "conservative variations" refer to the replacement of an amino acid residue by another, biologically similar residue. Examples of conservative variations include the substitution of one hydrophobic residue such as isoleucine, valine, leucine or methionine for another; or the substitution of one polar residue for another, such as the substitution of arginine for lysine, glutamic for aspartic acids, or glutamine for asparagine, and the like. Other illustrative examples of conservative substitutions include the changes of: alanine to serine; arginine to lysine; asparagine to glutamine or histidine; aspartate to glutamate; cysteine to serine; glutamine to asparagine; glutamate to aspartate; glycine to praline; histidine to asparagine or glutamine; isoleucine to leucine or valine; leucine to valine or isoleucine; lysine to arginine, glutamine, or glutamate; methionine to leucine or isoleucine; phenylalanine to tyrosine, leucine or methionine; serine to threonine; threonine to serine; tryptophan to tyrosine; tyrosine to tryptophan or phenylalanine; valine to isoleucine or leucine, and the like.

[0073] The term "parental" or "starter" are used interchangeably throughout the specification and claims to refer to an initial composition, or protein that is mutated, modified, or derivatized, to create an engineered composition having novel properties. In some embodiments, the parental protein is a chimeric protein.

[0074] The term "engineered" is used throughout the specification and claims to refer to a non-naturally occurring composition, or protein having properties that are distinct from the parental composition, or protein from which it was derivatized.

[0075] In general, "sequence identity" or "sequence homology" refers to the nucleotide-to-nucleotide or amino acid-to-amino acid correspondence of two polynucleotides or polypeptide sequences, respectively. Typically, techniques for determining sequence identity include determining the nucleotide sequence of a polynucleotide and/or determining the amino acid sequence encoded thereby, and comparing these sequences to a second nucleotide or amino acid sequence. Two or more sequences (polynucleotide or amino acid) can be compared by determining their "percent identity." The percent identity of two sequences, whether nucleic acid or amino acid sequences, is the number of exact matches between two aligned sequences divided by the length of the shorter sequences and multiplied by 100. Percent identity may also be determined, for example, by comparing sequence information using the advanced BLAST computer program, including version 2.2.9, available from the National Institutes of Health. The BLAST program is based on the alignment method of Karlin and Altschul, Proc. Natl. Acad. Sci. USA 87:2264-2268 (1990) and as discussed in Altschul, et al., J. Mol. Biol. 215:403-410 (1990); Karlin And Altschul, Proc. Natl. Acad. Sci. USA 90:5873-5877 (1993); and Altschul et al., Nucleic Acids Res. 25:3389-3402 (1997). Briefly, the BLAST program defines identity as the number of identical aligned symbols (generally nucleotides or amino acids), divided by the total number of symbols in the shorter of the two sequences. The program may be used to determine percent identity over the entire length of the proteins being compared. Default parameters are provided to optimize searches with short query sequences in, for example, with the blastp program. The program also allows use of an SEG filter to mask-off segments of the query sequences as determined by the SEG program of Wootton and Federhen, Computers and Chemistry 17:149-163 (1993). Ranges of desired degrees of sequence identity are approximately 80% to 100% and intervening integer values. Typically, the percent identities between a disclosed sequence and a claimed sequence are at least 80%, at least 85%, at least 90%, at least 95%, or at least 98%.

[0076] As used herein, "substantially identical" refers to having a sequence identity that is 85% or more, for example 90% or more, *e.g.* 95%, 96%, 97%, 98%, 99%, 99.5%, 99.9%, or 100%, wherein the activity of the composition is unaltered by the modifications in the sequence that result in the difference in sequence identity.

[0077] As used herein in relation to the position of an amino acid or a nucleotide, the terms "corresponding to" or "correspond to" refer to an amino acid in a first polypeptide

sequence that aligns with a given amino acid in a reference polypeptide sequence when the first polypeptide and reference polypeptide sequences are aligned, or a nucleotide in a first polynucleotide sequence that aligns with a given nucleotide in a reference polynucleotide sequence when the first polynucleotide and reference polynucleotide sequences are aligned. Alignment is performed by one of skill in the art using software designed for this purpose, for example, BLAST program version 2.2.9 with the default parameters for that version.

[0078] As used herein, the term "promoter" refers to one or more nucleic acid control sequences that direct transcription of an operably linked nucleic acid. Promoters may include nucleic acid sequences near the start site of transcription, such as a TATA element. Promoters may also include cis-acting polynucleotide sequences that can be bound by transcription factors. A "constitutive" promoter is a promoter that is active under most environmental and developmental conditions. An "inducible" promoter is a promoter that is active under environmental or developmental regulation. The term "operably linked" refers to a functional linkage between a nucleic acid expression control sequence (such as a promoter, or array of transcription factor binding sites) and a second nucleic acid sequence, wherein the expression control sequence directs transcription of the nucleic acid corresponding to the second sequence.

[0079] As used herein, the terms “virus vector,” “viral vector,” or “gene delivery vector” refer to a virus particle that functions as a nucleic acid delivery vehicle, and which comprises a nucleic acid (e.g., an AAV expression cassette) packaged within a virion. Exemplary virus vectors of the disclosure include adenovirus vectors, adeno-associated virus vectors (AAVs), lentivirus vectors, and retrovirus vectors.

[0080] As used herein, “neuronal activity”, “activity of a neuron”, “neuronal firing” and variations and synonyms thereof, refer to the electrical activity resulting from the stimulation or excitation of a neuron. In some embodiments, neuronal activity is measured using automated or manual patch clamp techniques. In some embodiments, determining the activity of a neuron comprises determining the excitatory postsynaptic potential (EPSP), inhibitory postsynaptic potential (IPSP), and/or action potential of the neuron. In some embodiments, the level of activity of a neuron depends on, or is affected by, the excitatory postsynaptic potential (EPSP), inhibitory postsynaptic potential (IPSP), and/or action potential.

[0081] As used herein, a “neurological disease” or “neurological disorder” refers to a disease or disorder of the nervous system. In some embodiments, the neurological disease is associated with, caused by, or results from structural, biochemical, and/or electrical abnormalities in the brain, spinal cord, a nerve or any component of the nervous system.

[0082] As used herein, a "sign" of a disease refers to a physical or mental feature which is regarded as indicating a condition of disease. In some embodiments, a sign is an objective indication of the disease. In some embodiments, a sign is evaluated, examined, observed or measured objectively by a person other than the patient, such as a doctor.

[0083] As used herein, a "symptom" of a disease refers to a physical or mental feature which is regarded as indicating a condition of disease, particularly such a feature that is apparent to the patient. In some embodiments, the symptom is subjectively evaluated by the patient. For example, in some embodiments, the symptom is pain.

[0084] As used herein, "potency" refers to the ability of a receptor described herein to respond to a particular ligand. An increase in potency therefore refers to an increase in the responsiveness of the receptor for a particular ligand. A decrease in potency therefore refers to a decrease in the responsiveness of the receptor for a particular ligand. The potency of a receptor is generally determined herein by the half maximal effective concentration (EC50) for a particular ligand of a particular receptor. The EC50 refers to the concentration of the ligand which induces a response halfway between the baseline and maximum after a specific exposure time. In some embodiments, the response is the opening or closing of the ion channel in the receptor.

[0085] As used herein, "substantially retaining the potency" for a ligand refers to an engineered receptor having an EC50 for a particular ligand that is unchanged, or changed by and increase or decrease of less than 2-fold, compared to a parental or control receptor..

[0086] As used herein, "efficacy" of a receptor in relation to a ligand refers to a measure of the activity of the receptor in the presence of a ligand. In some embodiments, the efficacy refers to the amount of current passed through the receptor under specific conditions, such as in the presence of a specific concentration of the ligand. In some embodiments, determining the efficacy comprises determining the amount of current passed through the receptor, and/or the rheobase of the receptor.

C. Engineered Receptors

[0087] The present disclosure is directed to engineered receptors, engineered receptor mutants, and methods for their use. The term "receptor" as used herein refers to any protein that is situated on the surface of a cell and that can mediate signaling to and/or from the cell. The term "engineered receptor" is used herein to refer to a receptor that has been experimentally altered such that it is physically and/or functionally distinct from a corresponding parental receptor. In some embodiments, the parental receptor is a wild-type

receptor. The term "wild-type receptor" is used herein to refer to a receptor having a polypeptide sequence that is identical to the polypeptide sequence of a protein found in nature. Wild-type receptors include receptors that naturally occur in humans as well as orthologs that naturally occur in other eukaryotes, *e.g.* protist, fungi, plants or animals, for example yeast, insects, nematodes, sponge, mammals, non-mammalian vertebrates. In some embodiments, the parental receptor is a non-native receptor; that is, it is a receptor that does not occur in nature, for example, a receptor that is engineered from a wild type receptor. For example, a parental receptor may be an engineered receptor comprising one or more subunits from one wild-type receptor with one or more subunits from a second wild-type receptor. The resulting proteins are therefore comprised of subunits from two or more wild-type receptors. Therefore, in some embodiments, the parental receptor is a chimeric receptor. Engineered receptors of the present disclosure include, for example, parental receptor mutants, and switch receptors.

[0088] In some aspects, an engineered receptor of the present disclosure comprises at least one amino acid mutation relative to the corresponding parental receptor, *e.g.* one or more mutations in one or more domains of a wild-type receptor. In some embodiments, the mutation is an amino acid substitution. In some embodiments, the engineered receptor shares a sequence identity of about 99%, about 98%, about 95%, about 90%, about 85%, about 80%, about 70%, about 60%, about 50%, or less with the corresponding parental receptor, inclusive of all values and subranges that lie therebetween. In some embodiments, the parental receptor mutant has a sequence identity of 85% or more with the corresponding parental receptor, *e.g.* 90% or more or 95% or more, for example, about 96%, about 97%, about 98% or about 99% identity with the corresponding parental receptor, inclusive of all values and subranges that lie therebetween. In some embodiments, an engineered receptor (*e.g.*, a parental receptor mutant) is generated by error prone PCR.

[0089] In some embodiments, the ligand binding domain (LBD) of the engineered receptor of the disclosure comprises at least one amino acid mutation relative to the corresponding ligand binding domain of the parental receptor, e.g. one or more mutations in the ligand binding domain of a wild-type receptor. In some embodiments, the mutation is an amino acid substitution. In some embodiments, the ligand binding domain of the engineered receptor has a sequence identity of 85% or more with the corresponding ligand binding domain of the parental receptor, e.g. 90% or more or 95% or more, for example, about 85%, about 90%, about 95%, about 96%, about 97%, about 98%, about 99% identity, or 100% identity with the corresponding ligand binding domain of the parental receptor, inclusive of all values and subranges that lie therebetween. In some embodiments, the ligand binding domain of the

engineered receptor shares a sequence identity of at least 85%, at least 90%, at least 95%, at least 96%, at least 97%, at least 98% or at least 99% identity with the corresponding ligand binding domain of the parental receptor, inclusive of all values and subranges that lie therebetween.

[0090] In some embodiments, the ion pore domain (IPD) of the engineered receptor of the disclosure comprises at least one amino acid mutation relative to the corresponding ion pore domain of the parental receptor, e.g. one or more mutations in the ion pore domain of a wild-type receptor. In some embodiments, the mutation is an amino acid substitution. In some embodiments, the ion pore domain of the engineered receptor has a sequence identity of 85% or more with the corresponding ion pore domain of the parental receptor, e.g. 90% or more or 95% or more, for example, about 85%, about 90%, about 95%, about 96%, about 97%, about 98%, about 99% identity, or 100% identity with the corresponding ion pore domain of the parental receptor, inclusive of all values and subranges that lie therebetween. In some embodiments, the ion pore domain of the engineered receptor shares a sequence identity of at least 85%, at least 90%, at least 95%, at least 96%, at least 97%, at least 98% or at least 99% identity with the corresponding ion pore domain of the parental receptor, inclusive of all values and subranges that lie therebetween.

[0091] In some embodiments, the amino acid mutation is a loss-of-function amino acid mutation relative to a corresponding parental receptor. "Loss-of-function" amino acid mutations refer to one or more mutations that reduce, substantially decrease, or abolish the function of the engineered receptor relative to the parental receptor, for example by reducing the binding of an endogenous ligand to an engineered receptor relative to the binding of endogenous ligand to the parental receptor, or by reducing the activity of signaling pathway(s) downstream of the engineered receptor that are typically activated in response to the binding of a ligand to the corresponding parental receptor. In some embodiments, the mutation is an amino acid substitution.

[0092] In some embodiments, the amino acid mutation is a gain-of-function amino acid mutation relative to a corresponding parental receptor. "Gain-of-function" amino acid mutations refer to one or more mutations that modify the function of the engineered receptor relative to the parental receptor, for example by altering or enhancing the affinity of an engineered receptor for a ligand relative to the binding of endogenous ligand to the parental receptor, or by altering or enhancing the activity of the signaling pathways that are activated in response to the binding of a ligand to an engineered receptor relative to the binding of the endogenous ligand to the corresponding parental receptor. In some embodiments, a gain-of-

function mutation results in an increased affinity of the engineered receptor for a ligand. In particular embodiments, a gain-of-function mutation results in an increased affinity of the engineered receptor for an agonist ligand. In some embodiments, a gain-of-function mutation results in an antagonist ligand acting as an agonist ligand upon binding to the engineered receptor (*e.g.*, results in the activation of agonist signaling pathways instead of antagonist signaling pathways). In some embodiments, a gain-of-function mutation results in a modulator ligand acting as an agonist ligand upon binding to the engineered receptor. In some embodiments, the mutation is an amino acid substitution.

[0093] In some embodiments, the subject engineered receptor of the present disclosure, or the ligand binding domain and/or the ion pore domain thereof, comprises one or more loss-of-function amino acid mutations and one or more gain-of-function amino acid mutations relative to a corresponding parental receptor. In some embodiments, the mutation is an amino acid substitution.

[0094] In some embodiments, the loss of function mutation and the gain of function mutation are at the same residue, i.e. they are the same mutation. In other embodiments, the loss of function mutation and the gain of function mutation are mutations at different amino acid residues. In some embodiments, the mutation is an amino acid substitution. In some embodiments, the subject engineered receptor (or the ligand binding domain and/or the ion pore domain thereof) comprising the loss of function mutation and/or gain of function mutation shares a sequence identity of about 99%, about 98%, about 95%, about 90%, about 85%, about 80%, about 70%, about 60%, about 50%, including all ranges and subranges therebetween, or less with the corresponding parental receptor, *e.g.* wild type receptor or non-native receptor (or the ligand binding domain and/or the ion pore domain thereof). In some embodiments, the subject engineered receptor (or the ligand binding domain and/or the ion pore domain thereof) shares a sequence identity of 85% or more with the corresponding parental receptor (or the ligand binding domain and/or the ion pore domain thereof) , for example 85%, 90%, or 95% or more sequence identity, in some instances 96%, 97%, 98% or more sequence identity, *e.g.* 99% or 99.5% or more sequence identity, inclusive of all values and subranges that lie therebetween.

[0095] In some aspects, engineered receptors of the present disclosure include receptors produced by the combination of one or more amino acid sequences, *e.g.* subunits, derived from one wild-type receptor with one or more amino acid sequences, *e.g.* subunits, derived from a second wild-type receptor. In other words, the engineered receptor comprises amino acid sequences that are heterologous to one another, where by "heterologous", it is

meant not occurring together in nature. Such receptors are referred to herein as "chimeric receptors". In some embodiments, chimeric receptors serve as parental receptors from which an engineered receptor of the present disclosure is generated.

[0096] In some embodiments, a parental receptor mutant demonstrates increased affinity for an agonist ligand. In some embodiments, a ligand that functions as an antagonist or modulator when binding to a wild type receptor functions as an agonist when binding to a parental receptor mutant.

[0097] In some embodiments, the engineered receptor is a "ligand-gated ion channel" or LGIC. An LGIC refers to a large group of transmembrane proteins that allow passage of ions upon activation by a specific ligand. LGIC are composed of at least two domains: a ligand binding domain and a transmembrane ion pore domain. Ligand binding to an LGIC results in activation of the LGIC and opening of the ion pore. Ligand binding causes a drastic change in the permeability of the channel to a specific ion or ions; effectively no ions can pass through the channel when it is inactive or closed but up to 10^7 ions/second can pass through upon ligand binding. In some embodiments, LGICs respond to extracellular ligands (*e.g.*, neurotransmitters) and facilitate an influx of ions into the cytosol. In some embodiments, LGICs respond to intracellular ligands (*e.g.*, nucleotides such at ATP and signaling intermediates such as PIP_2) and facilitate an efflux of ions from the cytosol into the extracellular environment. Importantly, activation of LGIC results in the transport of ions across the cellular membrane (*e.g.*, Ca^{2+}, Na^+, K^+, Cl^-, etc.) and does not result in the transport of the ligand itself.

[0098] LGIC receptors are comprised of multiple subunits and can be either homomeric receptors or heteromeric receptors. A homomeric receptor is comprised of subunits that are all the same type. A heteromeric receptor is comprised of subunits wherein at least one subunit is different from at least one other subunit comprised within the receptor. For example, the glycine receptor is comprised of 5 subunits of which there are two types: α-subunits, of which there are four isoforms ($\alpha_1 - \alpha_4$) and β-subunits, of which there is a single known isoform. An exemplary homomeric GlyR is a GlyR comprised of 5 α_1-GlyR subunits. Similarly, a homomeric $GABA_A$ receptor may be comprised of β_3-$GABA_A$ subunits, and an nAchR receptor may be comprised of α_7-nAchR subunits. An exemplary heteromeric GlyR may be comprised of one or more α-subunits and one or more of β-subunits (*e.g.*, an $\alpha_1\beta$-GlyR). Subunits of example LGIC receptors are shown in **Table 1**.

Table 1: LGIC Receptors and Subunits

Receptor	Subunits	Subunit Isoforms
GlyR	GLRA1	
	GLRA2	
	GLRA3	
	GLRA4	
	GLRB	
$5HT_3$	5-HT3A	
	5-HT3B	
	5-HT3C	
	5-HT3D	
	5-HT3E	
nAChR	α	α1
		α2
		α3
		α4
		α5
		α6
		α7
		α8
		α9
		α10
	β	β1
		β2
		β3
		β4
	γ	γ
	δ	δ
	ε	ε
$GABA_A$	α	α1
		α2
		α3
		α4
		α5
$GABA_A$	α	α6
	β	β1
		β2
		β3
	γ	γ1
		γ2
		γ3
	δ	δ
	ε	ε
	π	π
	ρ	ρ1
		ρ2
		ρ3
P2X	P2X1	

Receptor	Subunits	Subunit Isoforms
	P2X2	
	P2X3	
	P2X4	
	P2X5	
	P2X6	
	P2X7	
KCNQ	α	$K_v\alpha1$
		$K_v\alpha2$
		$K_v\alpha3$
		$K_v\alpha4$
		$K_v\alpha5$
		$K_v\alpha6$
		$K_v\alpha7$
		$K_v\alpha8$
		$K_v\alpha9$
		$K_v\alpha10$
		$K_v\alpha11$
		$K_v\alpha12$
	β	$K_v\beta1$
		$K_v\beta2$
		$K_v\beta3$
		minK
		MiRP1
		MiRP2
		MiRP3
		KCNE1-like
		KCNIP1
		KCNIP2
		KCNIP3
		KCNIP4

[0099] Illustrative examples of families of LGICs suitable for use in particular embodiments include, but are not limited to Cys-loop receptors such as Glycine receptors (GlyR), serotonin receptors (*e.g.*, 5-HT3 receptors), λ-Aminobutyric Acid A (GABA-A) receptors, and Nicotinic acetylcholine receptors (nAchR); as well as Acid-sensing (proton-gated) ion channels (ASICs), Epithelial sodium channels (ENaC), Ionotropic glutamate receptors, IP3 receptor, P2X receptors, the Ryanodine receptor, and Zinc activated channels (ZAC).

[0100] Specific non-limiting examples of LGICs that are suitable for use with the methods described herein include: HTR3A; HTR3B; HTR3C; HTR3D; HTR3E; ASIC1; ASIC2; ASIC3; SCNN1A; SCNN1B; SCNN1D; SCNN1G; GABRA1; GABRA2; GABRA3; GABRA4; GABRA5; GABRA6; GABRB1; GABRB2; GABRB3; GABRG1; GABRG2; GABRG3; GABRD; GABRE; GABRQ; GABRP; GABRR1; GABRR2; GABRR3; GLRA1;

GLRA2; GLRA3; GLRA4; GLRB; GRIA1; GRIA2; GRIA3; GRIA4; GRID1; GRID2; GRIK1; GRIK2; GRIK3; GRIK4; GRIK5; GRIN1; GRIN2A; GRIN2B; GRIN2C; GRIN2D; GRIN3A; GRIN3B; ITPR1; ITPR2; ITPR3; CHRNA1; CHRNA2; CHRNA3; CHRNA4; CHRNA5; CHRNA6; CHRNA7; CHRNA9; CHRNA10; CHRNB1; CHRNB2; CHRNB3; CHRNB4; CHRNG; CHRND; CHRNE; P2RX1; P2RX2; P2RX3; P2RX4; P2RX5; P2RX6; P2RX7; RYR1; RYR2; RYR3; and ZACN.

[0101] TRPV1, TRPM8 and $P2X_2$ are members of large LGIC families that share structural features as well as gating principles. For example TRPV4, similar to TRPV1, is also triggered by heat, but not by capsaicin; and $P2X_3$, is triggered by ATP, but desensitizes more rapidly than $P2X_2$. TRPV1, TRPM8 and $P2X_2$ are, therefore, non-limiting examples of LGIC suitable for use in particular embodiments.

[0102] In one embodiment, the engineered receptor is a TRPV1 or TRPM8 receptor or a mutein thereof. TRPV1 and TRPM8, are vanilloid and menthol receptors expressed by nociceptive neurons of the peripheral nervous system. Both channels are thought to function as non-selective, sodium- and calcium-permeable homotetramers. In addition, both channels and their principal agonists--capsaicin and cooling compounds, such as menthol, respectively--are virtually absent from the central nervous system. Capsaicin and some cooling compounds, including menthol and icilin, contain potential acceptor sites for photolabile blocking groups. Association of a photolabile blocking group with such an acceptor would result in a ligand-gated ion channel in which light acts as an indirect trigger by releasing the active ligand.

[0103] In one embodiment, the engineered receptor is a $P2X_2$ receptor or a mutein thereof. $P2X_2$ is an ATP-gated non-selective cation channel distinguished by its slow rate of desensitization. $P2X_2$ may be used as a selectively addressable source of depolarizing current and present a platform for the generation of engineered channel-ligand combinations that lack natural agonists altogether.

[0104] Non-limiting examples of sequences of wild-type LGIC receptor that find use in the generation of engineered receptors of the present disclosure include the following. In the sequences, the signal peptide is italicized, the ligand binding domain is bolded, and the ion pore domain is underlined:

[0105] In some embodiments, the wild-type LGIC receptor is a human alpha 1 glycine receptor (GlyRα1) (GenBank Accession No. NP_001139512.1, SEQ ID NO:2), encoded by the *GLRA1* gene (GenBank Accession No. NM_001146040.1 (SEQ ID NO:1):

```
    10        20        30        40        50        60
MYSFNTLRLY LWETIVFFSL AASKEAEAAR SAPKPMSPSD FLDKLMGRTS GYDARIRPNF
```

```
    70      80      90     100     110     120
KGPPVNVSCN IFINSFGSIA ETTMDYRVNI FLRQQWNDPR LAYNEYPDDS LDLDPSMLDS
    130     140     150     160     170     180
IWKPDLFFAN EKGAHFHEIT TDNKLLRISR NGNVLYSIRI TLTLACPMDL KNFPMDVQTC
    190     200     210     220     230     240
IMQLESFGYT MNDLIFEWQE QGAVQVADGL TLPQFILKEE KDLRYCTKHY NTGKFTCIEA
    250     260     270     280     290     300
RFHLERQMGY YLIQMYIPSL LIVILSWISF WINMDAAPAR VGLGITTVLT MTTQSSGSRA
    310     320     330     340     350     360
SLPKVSYVKA IDIWMAVCLL FVFSALLEYA AVNFVSRQHK ELLRFRRKRR HHKSPMLNLF
    370     380     390     400     410     420
QEDEAGEGRF NFSAYGMGPA CLQAKDGISV KGANNSNTTN PPPAPSKSPE EMRKLFIQRA
    430     440     450     457
KKIDKISRIG FPMAFLIFNM FYWIIYKIVR REDVHNQ
```

(SEQ ID NO: 2).

[0106] In some embodiments, the wild-type LGIC receptor is a human alpha 2 glycine receptor (GlyRα2) (GenBank Accession No. NP_001112357.1, SEQ ID NO: 83), encoded by the *GLRA2* gene (GenBank Accession No. NM_001118885.1, SEQ ID NO: 82):

```
    10      20      30      40      50      60
MNRQLVNILT ALFAFFLETN HFRTAFCKDH DSRSGKQPSQ TLSPSDFLDK LMGRTSGYDA
    70      80      90     100     110     120
RIRPNFKGPP VNVTCNIFIN SFGSVTETTM DYRVNIFLRQ QWNDSRLAYS EYPDDSLDLD
    130     140     150     160     170     180
PSMLDSIWKP DLFFANEKGA NFHDVTTDNK LLRISKNGKV LYSIRLTLTL SCPMDLKNFP
    190     200     210     220     230     240
MDVQTCTMQL ESFGYTMNDL IFEWLSDGPV QVAEGLTLPQ FILKEEKELG YCTKHYNTGK
    250     260     270     280     290     300
FTCIEVKFHL ERQMGYYLIQ MYIPSLLIVI LSWVSFWINM DAAPARVALG ITTVLTMTTQ
    310     320     330     340     350     360
SSGSRASLPK VSYVKAIDIW MAVCLLFVFA ALLEYAAVNF VSRQHKEFLR LRRRQKRQNK
    370     380     390     400     410     420
EEDVTRESRF NFSGYGMGHC LQVKDGTAVK ATPANPLPQP PKDGDAIKKK FVDRAKRIDT
    430     440     450  452
ISRAAFPLAF LIFNIFYWIT YKIIRHEDVH KK
```

(SEQ ID NO: 83).

[0107] In some embodiments, the wild-type LGIC receptor is a human alpha 3 glycine receptor (GlyRα3) isoform L (GenBank Accession No. NP_006520.2, SEQ ID NO: 85), encoded by the *GLRA3* gene (GenBank Accession No. NM_006529.3, SEQ ID NO: 84):

```
    10      20      30      40      50      60
MAHVRHFRTL VSGFYFWEAA LLLSLVATKE TDSARSRSAP MSPSDFLDKL MGRTSGYDAR
    70      80      90     100     110     120
IRPNFKGPPV NVTCNIFINS FGSIAETTMD YRVNIFLRQK WNDPRLAYSE YPDDSLDLDP
    130     140     150     160     170     180
SMLDSIWKPD LFFANEKGAN FHEVTTDNKL LRIFKNGNVL YSIRLTLTLS CPMDLKNFPM
    190     200     210     220     230     240
DVQTCIMQLE SFGYTMNDLI FEWQDEAPVQ VAEGLTLPQF LLKEEKDLRY CTKHYNTGKF
    250     260     270     280     290     300
```

TCIEVRFHLE RQMGYYLIQM YIPSLLIVIL SWVSFWINMD AAPARVALGI TTVLTMTTQS
310 320 330 340 350 360
SGSRASLPKV SYVKAIDIWM AVCLLFVFSA LLEYAAVNFV SRQHKELLRF RRKRKNKTEA
370 380 390 400 410 420
FALEKFYRFS DMDDEVRESR FSFTAYGMGP CLQAKDGMTP KGPNHPVQVM PKSPDEMRKV
430 440 450 460 464
FIDRAKKIDT ISRACFPLAF LIFNIFYWVI YKILRHEDIH QQQD

(SEQ ID NO: 85).

[0108] In some embodiments, the wild-type LGIC receptor is a human alpha 3 glycine receptor (GlyRα3) isoform K (GenBank Accession No. NP_001036008.1, SEQ ID NO: 87), encoded by the *GLRA3* gene (GenBank Accession No. NM_001042543.3, SEQ ID NO: 86):

10 20 30 40 50
*MAHVRHFRTL VSGFYFWEAA LLLSLVATKE TDS***ARSRSAP MSPSDFLDKL**
60 70 80 90 100
MGRTSGYDAR IRPNFKGPPV NVTCNIFINS FGSIAETTMD YRVNIFLRQK
110 120 130 140 150
WNDPRLAYSE YPDDSLDLDP SMLDSIWKPD LFFANEKGAN FHEVTTDNKL
160 170 180 190 200
LRIFKNGNVL YSIRLTLTLS CPMDLKNFPM DVQTCIMQLE SFGYTMNDLI
210 220 230 240 250
FEWQDEAPVQ VAEGLTLPQF LLKEEKDLRY CTKHYNTGKF TCIEVRFHLE
260 270 280 290 300
RQMGYYLIQM YIPSLLIVIL SWVSFWINMD AAPARVALGI TTVLTMTTQS
310 320 330 340 350
SGSRASLPKV SYVKAIDIWM AVCLLFVFSA LLEYAAVNFV SRQHKELLRF
360 370 380 390 400
RRKRKNKDDE VRESRFSFTA YGMGPCLQAK DGMTPKGPNH PVQVMPKSPD
410 420 430 440
EMRKVFIDRA KKIDTISRAC FPLAFLIFNI FYWVIYKILR HEDIHQQQD
(SEQ ID NO: 87).

[0109] In some embodiments, the wild-type LGIC receptor is a human nicotinic cholinergic receptor alpha 7 subunit (α7-nAchR) (GenBank Accession No. NP_000737.1, SEQ ID NO:4), encoded by the *CHRNA7* gene (GenBank Accession No. NM_000746.5 (SEQ ID NO:3):

10 20 30 40 50 60
*MRCSPGGVWL ALAASLLHVS LQ***GEFQRKLY KELVKNYNPL ERPVANDSQP LTVYFSLSLL**
70 80 90 100 110 120
QIMDVDEKNQ VLTTNIWLQM SWTDHYLQWN VSEYPGVKTV RFPDGQIWKP DILLYNSADE
130 140 150 160 170 180
RFDATFHTNV LVNSSGHCQY LPPGIFKSSC YIDVRWFPFD VQHCKLKFGS WSYGGWSLDL
190 200 210 220 230 240
QMQEADISGY IPNGEWDLVG IPGKRSERFY ECCKEPYPDV TFTVTMRRRT LYYGLNLLIP
250 260 270 280 290 300
CVLISALALL VFLLPADSGE KISLGITVLL SLTVFMLLVA EIMPATSDSV PLIAQYFAST
310 320 330 340 350 360
MIIVGLSVVV TVIVLQYHHH DPDGGKMPKW TRVILLNWCA WFLRMKRPGE DKVRPACQHK
370 380 390 400 410 420

QRRCSLASVE MSAVAPPPAS NGNLLYIGFR GLDGVHCVPT PDSGVVCGRM ACSPTHDEHL
430 440 450 460 470 480
LHGGQPPEGD PDLAKILEEV RYIANRFRCQ DESEAVCSEW KFAACVVDRL CLMAFSVFTI
490 500 502
ICTIGILMSA PNFVEAVSKD FA

(SEQ ID NO:4).

[0110] In some embodiments, the wild-type LGIC receptor is a human 5-hydroxytryptamine receptor 3A (5HT3A, GenBank Accession No. NP_998786.2, SEQ ID NO:6), encoded by the *HTR3A* gene (GenBank Accession No. NM_213621.3, SEQ ID NO:5):

(a) *MLGKLAMLLWVQQALLALLLPTL***LAQGEARRSRNTTRPALLRLSDYL LTNYRKGVRPVRDWRKPTTVSIDVIVYAILNVDEKNQVLTTYIWYRQYWTDEF LQWNPEDFDNITKLSIPTDSIWVPDILINEFVDVGKSPNIPYVYIRHQGEVQNYKP LQVVTACSLDIYNFPFDVQNCSLTFTSWLHTIQDINISLWRLPEKVKSDRSVFMN QGEWELLGVLPYFREFSMESSNYYAEMKFYVVIRRR**PLFYVVSLLLPSIFLMVMD IVGFYLPPNSGERVSFKITLLLGYSVFLIIVSDTLPATAIGTPLIGKAPPGSRAQSGEKPA PSHLLHVSLASALGCTGVYFVVCMALLVISLAETIFIVRLVHKQDLQQPVPAWLRHL VLERIAWLLCLREQSTSQRPPATSQATKTDDCSAMGNHCSHMGGPQDFEKSPRDRC SPPPPPREASLAVCGLLQELSSIRQFLEKRDEIREVARDWLRVGSVLDKLLFHIYLLAV LAYSITLVMLWSIWQYA (SEQ ID NO:6).

[0111] In some embodiments, the wild-type LGIC receptor is a human 5-hydroxytryptamine receptor 3B (5HT3B GenBank Accession No. NP_006019.1, SEQ ID NO:57), encoded by the *HTR3B* gene (GenBank Accession No. NM_006028.4, SEQ ID NO:56):

(a) *MLSSVMAPLWACILVAAGILA***TDTHHPQDSALYHLSKQLLQKYHKEV RPVYNWTKATTVYLDLFVHAILDVDAENQILKTSVWYQEVWNDEFLSWNSSMF DEIREISLPLSAIWAPDIIINEFVDIERYPDLPYVYYVNSSGTIENYKPIQVVSACSLE TYAFPFDVQNCSLTFKSILHTVEDVDLAFLRSPEDIQHDKKAFLNDSEWELLSVS STYSILQSSAGGFAQIQFNVVMRRHP**LVYYVVSLLIPSIFLMLVDLGSFYLPPNCRARI VFKTSVLVGYTVFRVNMSNQVPRSVGSTPLIGHFFTICMAFLVLSLAKSIVLVKFLHD EQRGGQEQPFLCLRGDTDADRPRVEPRAQRAVVTESSLYGEHLAQPGTLKEVWSQL QSISNYLQTQDQTDQQEAEWLVLLSRFDRLLFQSYLFMLGIYTITLCSLWALWGGV (SEQ ID NO:57).

[0112] In some embodiments, the wild-type LGIC receptor is a human Gamma-aminobutyric acid receptor A (GABA-A), subunit beta-3 (GABA-A β3) (GenBank Accession

No. NP_000805.1, SEQ ID NO:8), encoded by the *GABRB3* gene (GenBank Accession No. NM_000814.5, SEQ ID NO:7):

(a) *MWGLAGGRLFGIFSAPVLVAVVCCA***QSVNDPGNMSFVKETVDKLLKG YDIRLRPDFGGPPVCVGMNIDIASIDMVSEVNMDYTLTMYFQQYWRDKRLAYS GIPLNLTLDNRVADQLWVPDTYFLNDKKSFVHGVTVKNRMIRLHPDGTVLYGL RITTTAACMMDLRRYPLDEQNCTLEIESYGYTTDDIEFYWRGGDKAVTGVERIE LPQFSIVEHRLVSRNVVFATGAYPRLSLSFRLKRNIGY**FILQTYMPSILITILSWVSF WINYDASAARVALGITTVLTMTTINTHLRETLPKIPYVKAIDMYLMGCFVFVFLALL EYAFVNYIFFGRGPQRQKKLAEKTAKAKNDRSKSESNRVDAHGNILLTSLEVHNEM NEVSGGIGDTRNSAISFDNSGIQYRKQSMPREGHGRFLGDRSLPHKKTHLRRRSSQLK IKIPDLTDVNAIDRWSRIVFPFTFSLFNLVYWLYYVN (SEQ ID NO:8).

[0113] In some embodiments, the wild-type LGIC receptor is a human GABA-A, subunit rho1 (ρ1) (GABA-A ρ1) (GenBank Accession No. NP_002033.2, SEQ ID NO:10), encoded by the *GABRR1* gene (GenBank Accession No. NM_002042.4, SEQ ID NO:9):

(a) *MLAVPNMRFGIFLLWWGWVLA***TESRMHWPGREVHEMSKKGRPQRQ RREVHEDAHKQVSPILRRSPDITKSPLTKSEQLLRIDDHDFSMRPGFGGPAIPVG VDVQVESLDSISEVDMDFTMTLYLRHYWKDERLSFPSTNNLSMTFDGRLVKKI WVPDMFFVHSKRSFIHDTTTDNVMLRVQPDGKVLYSLRVTVTAMCNMDFSRFP LDTQTCSLEIESYAYTEDDLMLYWKKGNDSLKTDERISLSQFLIQEFHTTTKLAF YSSTGWYNRLYINFTLRRHIFF**FLLQTYFPATLMVMLSWVSFWIDRRAVPARVPLG ITTVLTMSTIITGVNASMPRVSYIKAVDIYLWVSFVFVFLSVLEYAAVNYLTTVQERK EQKLREKLPCTSGLPPPRTAMLDGNYSDGEVNDLDNYMPENGEKPDRMMVQLTLA SERSSPQRKSQRSSYVSMRIDTHAIDKYSRIIFPAAYILFNLIYWSIFS (SEQ ID NO:10).

[0114] In some embodiments, the wild-type LGIC receptor is a human GABA-A, subunit rho2 (ρ2) (GABA-A ρ2) (GenBank Accession No. NP_002034.3, SEQ ID NO:12), encoded by the GABRR2 gene (GenBank Accession No. NM_002043.4, SEQ ID NO:11):

(a) *MPYFTRLILFLFCLMVLVES***RKPKRKRWTGQVEMPKPSHLYKKNLD VTKIRKGKPQQLLRVDEHDFSMRPAFGGPAIPVGVDVQVESLDSISEVDMDFTM TLYLRHYWKDERLAFSSASNKSMTFDGRLVKKIWVPDVFFVHSKRSFTHDTTT DNIMLRVFPDGHVLYSMRITVTAMCNMDFSHFPLDSQTCSLELESYAYTDEDLM LYWKNGDESLKTDEKISLSQFLIQKFHTTSRLAFYSSTGWYNRLYINFTLRRHIF FFLLQTYFPATLMVMLSWVSFWIDRRAVPARVSLGITTVLTMTTIITGVNASMPRVS YVKAVDIYLWVSFVFVFLSVLEYAAVNYLTTVQERKERKLREKFPCMCGMLHSKT**

MMLDGSYSESEANSLAGYPRSHILTEEERQDKIVVHLGLSGEANAARKKGLLKGQT GFRIFQNTHAIDKYSRLIFPASYIFFNLIYWSVFS (SEQ ID NO:12).

[0115] In some embodiments, the wild-type LGIC receptor is a human GABA-A, subunit rho3 (ρ3) (GABA-A ρ3) (GenBank Accession No. NP_001099050.1, SEQ ID NO: 14), encoded by the GABRR3 gene (GenBank Accession No. NM_001105580.2, SEQ ID NO:13):

(a) *MVLAFQLVSFTYIWIILKPNVCA***ASNIKMTHQRCSSSMKQTCKQETRM KKDDSTKARPQKYEQLLHIEDNDFAMRPGFGGSPVPVGIDVHVESIDSISETNMD FTMTFYLRHYWKDERLSFPSTANKSMTFDHRLTRKIWVPDIFFVHSKRSFIHDT TMENIMLRVHPDGNVLLSLRITVSAMCFMDFSRFPLDTQNCSLELESYAYNEDD LMLYWKHGNKSLNTEEHMSLSQFFIEDFSASSGLAFYSSTGWYNRLFINFVLRR HVFF**FVLQTYFPAILMVMLSWVSFWIDRRAVPARVSLGITTVLTMSTIITAVSASMPQ VSYLKAVDVYLWVSSLFVFLSVIEYAAVNYLTTVEERKQFKKTGKISRMYNIDAVQ AMAFDGCYHDSEIDMDQTSLSLNSEDFMRRKSICSPSTDSSRIKRRKSLGGHVGRIILE NNHVIDTYSRILFPIVYILFNLFYWGVYV (SEQ ID NO:14).

[0116] In some aspects, the engineered receptor is a chimeric LGIC receptor. In some embodiments, the chimeric receptor comprises a ligand binding domain sequence derived from at least a first LGIC and an ion pore conduction domain sequence, or more simply, "ion pore domain sequence" derived from at least a second LGIC. In some embodiments, the derived amino acid sequence is identical to the corresponding region of the LGIC from which it was derived. In some embodiments, the derived amino acid sequence may contain alterations in at least one amino acid position compared to the corresponding region of the LGIC from which it was derived. In some embodiments, an amino acid sequence derived from an LGIC sequence differs by up to 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10 amino acid residues from the corresponding region of the original amino acid sequence. In some embodiments, a derived amino acid sequence has at least 85%, at least 90%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or at least 99.5% (including all ranges and subranges therebetween) sequence identity to the corresponding region of the LGIC amino acid sequence.

[0117] In some embodiments, the first and second LGIC are Cys-loop receptors. Ligand binding domain sequences and ion pore domain sequences of the Cys-loop receptors are well known in the art and can be readily identified from the literature by use of publicly available software, *e.g.* PubMed, Genbank, Uniprot, and the like. In some embodiments, the ligand binding domain of the chimeric receptor has at least 85%, at least 90%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, at least 99.5%, or 100% sequence identity

to the ligand binding domain of the first LGIC. In some embodiments, the ion pore domain of the chimeric receptor has at least 85%, at least 90%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, at least 99.5%, or 100% sequence identity to the ion pore domain of the second LGIC. In the sequences described above, the ligand binding domain is bolded, and the ion pore domain is underlined.

[0118] In some embodiments, the ligand binding domain of the chimeric receptor is derived from the ligand binding domain sequence of a human glycine receptor. In some embodiments, the human glycine receptor is human GlyRα1 (SEQ ID NO:2). In some embodiments, the ligand binding domain comprises an amino acid sequence having at least 85%, at least 90%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, at least 99.5%, or 100% sequence identity to about amino acids 29-235 of GlyRα1, *e.g.* amino acids 29-235, amino acids 29-240, amino acids 29-246, amino acids 29-248, amino acids 29-250, or amino acids 29-252 of SEQ ID NO:2. In certain such embodiments, the ligand binding domain consists essentially of amino acids 29-235 of SEQ ID NO:2, consists essentially of amino acids 29-240 of SEQ ID NO:2, consists essentially of amino acids 29-246 of SEQ ID NO:2, consists essentially of amino acids 29-248 of SEQ ID NO:2, consists essentially of amino acids 29-250 of SEQ ID NO:2, consists essentially of amino acids 29-252 of SEQ ID NO:2. In some embodiments, the ion pore domain sequence is derived from a Cys-loop receptor other than the human GlyRα1.

[0119] In some embodiments, the ligand binding domain of the chimeric receptor comprises the ligand binding domain sequence of a human nicotinic cholinergic receptor. In some embodiments, the human nicotinic cholinergic receptor is human α7-nAChR. In some embodiments, the ligand binding domain comprises about amino acids 23-220 of human α7-nAChR (SEQ ID NO:4), *e.g.* amino acids 23-220, amino acids 23-221, amino acids 23-222, amino acids 23-223, amino acids 23-224, amino acids 23-225, amino acids 23-226, amino acids 23-227, amino acids 23-228, amino acids 23-229, amino acids 23-230, or amino acids 23-231 of SEQ ID NO:4. In some embodiments, the ligand binding domain consists essentially of amino acids 23-220, amino acids 23-221, amino acids 23-222, amino acids 23-223, amino acids 23-224, amino acids 23-225, amino acids 23-226, amino acids 23-227, amino acids 23-228, amino acids 23-229, amino acids 23-230, or amino acids 23-231 of SEQ ID NO: 4. In some embodiments, the ion pore domain sequence is derived from a Cys-loop receptor other than the human α7-nAChR.

[0120] In some embodiments, the ligand binding domain of the chimeric receptor is derived from the ligand binding domain sequence of a human nicotinic cholinergic receptor. In

some embodiments, the human nicotinic cholinergic receptor is human α7-nAChR. In some embodiments, the ligand binding domain comprises an amino acid sequence having at least 85%, at least 90%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, at least 99.5%, or 100% sequence identity to about amino acids 23-220 of human α7-nAChR (SEQ ID NO: 4), e.g. amino acids 23-220, amino acids 23-221, amino acids 23-222, amino acids 23-223, amino acids 23-224, amino acids 23-225, amino acids 23-226, amino acids 23-227, amino acids 23-228, amino acids 23-229, amino acids 23-230, or amino acids 23-231 of SEQ ID NO: 4. In some embodiments, the ion pore domain sequence is derived from a Cys-loop receptor other than the human α7-nAChR.

[0121] In some embodiments, the ligand binding domain of the chimeric receptor is derived from the ligand binding domain sequence of a human serotonin receptor. In some embodiments, the human serotonin receptor is human 5HT3A or 5HT3B. In some such embodiments, the ligand binding domain comprises about amino acids 23-247 of 5HT3A (SEQ ID NO:6), *e.g.* amino acids 23-240, amino acids 30-245, amino acids 23-247, amino acids 23-250, in some instances amino acids 30-255 of SEQ ID NO:6. In certain embodiments, the ligand binding domain consists essentially of amino acids 23-240 of SEQ ID NO:6, consists essentially of amino acids 23-245 of SEQ ID NO:6, consists essentially of amino acids 30-247 of SEQ ID NO:6, consists essentially of amino acids 23-250 of SEQ ID NO:6, consists essentially of amino acids 23-255 of SEQ ID NO:6. In some such embodiments, the ligand binding domain comprises about amino acids 21-239 of 5HT3B (SEQ ID NO:57), *e.g.* amino acids 21-232, amino acids 21-235, amino acids 21-240, amino acids 21-245, in some instances amino acids 21-247 of SEQ ID NO:57. In certain embodiments, the ligand binding domain consists essentially of amino acids 21-239 of SEQ ID NO:57, consists essentially of amino acids 21-232 of SEQ ID NO:57, consists essentially of amino acids 21-235 of SEQ ID NO:57, consists essentially of amino acids 21-240 of SEQ ID NO:57, consists essentially of amino acids 21-245 of SEQ ID NO:57. In some embodiments, the ion pore domain sequence is derived from a Cys-loop receptor other than the human 5-hydroxytryptamine receptor 3.

[0122] In some embodiments, the ligand binding domain of the chimeric receptor is derived from the ligand binding domain sequence of a human GABA receptor. In some embodiments, the human GABA receptor is human GABA-A β3. In some such embodiments, the ligand binding domain comprises about amino acids 26-245 of GABA-A β3 (SEQ ID NO:8), *e.g.* amino acids 26-240, amino acids 26-245, amino acids 26-248, amino acids 26-250, in some instances amino acids 26-255 of SEQ ID NO:8. In certain such embodiments, the ligand binding domain consists essentially of amino acids 26-240 of SEQ ID NO:8, consists

essentially of amino acids 26-245 of SEQ ID NO:8, consists essentially of amino acids 26-248 of SEQ ID NO:8, consists essentially of amino acids 26-250 of SEQ ID NO:8, or consists essentially of amino acids 26-255 of SEQ ID NO:8. In some embodiments, the ion pore domain sequence is derived from a Cys-loop receptor other than the human GABA-A receptor.

[0123] In some embodiments, the ion pore domain to which the ligand binding domain is fused conducts anions, *e.g.* it comprises an ion pore domain sequence of a human glycine receptor or a human serotonin receptor. In other embodiments, the ion conduction pore domain to which the ligand binding domain is fused conducts cations, *e.g.* it comprises an ion pore domain sequence of a human acetylcholine receptor or a human gamma-aminobutyric acid receptor A.

[0124] In some embodiments, the ion pore domain of the engineered receptor is derived from the ion pore domain sequence of a human glycine receptor. In some embodiments, the human glycine receptor is human GlyRα1. In some embodiments, the ion pore domain comprises an amino acid sequence having at least 85%, at least 90%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, at least 99.5%, or 100% sequence identity to about amino acids 245-457 of GlyRα1 (SEQ ID NO:2), *e.g.* amino acids 240-457, amino acids 245-457, amino acids 248-457, amino acids 249-457, amino acids 250-457, amino acids 255-457, or amino acids 260-457 of SEQ ID NO:2. In some embodiments, the ion pore domain consists essentially of amino acids 245-457 of SEQ ID NO:2, consists essentially of amino acids 248-457 of SEQ ID NO:2, consists essentially of amino acids 249-457 of SEQ ID NO:2, or consists essentially of amino acids 250-457 of SEQ ID NO:2.

[0125] In some embodiments, the ion pore domain of the chimeric receptor comprises the ion pore domain sequence of human GlyRα2 (SEQ ID NO: 83). In some embodiments, the ion pore domain of the chimeric receptor comprises, consists essentially of, or consists of an amino acid sequence derived from the ion pore domain sequence of human GlyRα2 (SEQ ID NO: 83). In some embodiments, the ion pore domain of the chimeric receptor comprises, consists essentially of, or consists of an amino acid sequence having at least 85%, at least 90%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or at least 99.5% sequence identity to the ion pore domain sequence of human GlyRα2 (SEQ ID NO: 83). In some embodiments, the ion pore domain of the chimeric receptor comprises, consists essentially of, or consists of an amino acid sequence identical to the ion pore domain sequence of human GlyRα2 (SEQ ID NO: 83). In some embodiments, the ion pore domain sequence of human GlyRα2 comprises, consists essentially of, or consists of amino acids 254-452 of SEQ ID NO: 83. In some embodiments, the ion pore domain sequence of human GlyRα2 comprises, consists

essentially of, or consists of amino acids 254-452 of SEQ ID NO: 83. In some embodiments, the ion pore domain sequence of human GlyRα2 comprises, consists essentially of, or consists of amino acids 258-452 of SEQ ID NO: 83. In some embodiments, the ion pore domain sequence of human GlyRα2 comprises, consists essentially of, or consists of amino acids 260-452 of SEQ ID NO: 83.

[0126] In some embodiments, the ion pore domain of the chimeric receptor comprises the ion pore domain sequence of human GlyRα3 isoform L (SEQ ID NO: 85). In some embodiments, the ion pore domain of the chimeric receptor comprises, consists essentially of, or consists of an amino acid sequence derived from the ion pore domain sequence of human GlyRα3 isoform L (SEQ ID NO: 85). In some embodiments, the ion pore domain of the chimeric receptor comprises, consists essentially of, or consists of an amino acid sequence having at least 85%, at least 90%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or at least 99.5% sequence identity to the ion pore domain sequence of human GlyRα3 isoform L (SEQ ID NO: 85). In some embodiments, the ion pore domain of the chimeric receptor comprises, consists essentially of, or consists of an amino acid sequence identical to the ion pore domain sequence of human GlyRα3 isoform L (SEQ ID NO: 85). In some embodiments, the ion pore domain sequence of human GlyRα3 isoform L comprises, consists essentially of, or consists of amino acids 253-464 of SEQ ID NO: 85. In some embodiments, the ion pore domain sequence of human GlyRα3 isoform L comprises, consists essentially of, or consists of amino acids 257-464 of SEQ ID NO: 85. In some embodiments, the ion pore domain sequence of human GlyRα3 isoform L comprises, consists essentially of, or consists of amino acids 259-464 of SEQ ID NO: 85.

[0127] In some embodiments, the ion pore domain of the chimeric receptor comprises the ion pore domain sequence of human GlyRα3 isoform K (SEQ ID NO: 87). In some embodiments, the ion pore domain of the chimeric receptor comprises, consists essentially of, or consists of an amino acid sequence derived from the ion pore domain sequence of human GlyRα3 isoform K (SEQ ID NO: 87). In some embodiments, the ion pore domain of the chimeric receptor comprises, consists essentially of, or consists of an amino acid sequence having at least 85%, at least 90%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or at least 99.5% sequence identity to the ion pore domain sequence of human GlyRα3 isoform K (SEQ ID NO: 87). In some embodiments, the ion pore domain of the chimeric receptor comprises, consists essentially of, or consists of an amino acid sequence identical to the ion pore domain sequence of human GlyRα3 isoform K (SEQ ID NO: 87). In some embodiments, the ion pore domain sequence of human GlyRα3 isoform K comprises, consists

essentially of, or consists of amino acids 253-449 of SEQ ID NO: 87. In some embodiments, the ion pore domain sequence of human GlyRα3 isoform K comprises, consists essentially of, or consists of amino acids 257-449 of SEQ ID NO: 87. In some embodiments, the ion pore domain sequence of human GlyRα3 isoform K comprises, consists essentially of, or consists of amino acids 259-449 of SEQ ID NO: 87.

[0128] In some embodiments, the ion pore domain is derived from the ion pore domain sequence of a human nicotinic cholinergic receptor. In some embodiments, the human nicotinic cholinergic receptor is human α7-nAChR. In some embodiments, the ion pore domain comprises an amino acid sequence having at least 85%, at least 90%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, at least 99.5%, or 100% sequence identity to about amino acids 230-502 of α7-nAChR (SEQ ID NO:4), *e.g.* amino acids 227-502, amino acids 230-502, amino acids 231-502, amino acids 232-502, or amino acids 235-502. In certain such embodiments, the ion pore domain consists essentially of amino acids 227-502 of SEQ ID NO:4, consists essentially of amino acids 230-502 of SEQ ID NO:4, consists essentially of amino acids 231-502 of SEQ ID NO:4, consists essentially of amino acids 232-502 of SEQ ID NO:4, or consists essentially of amino acids 235-502 of SEQ ID NO:4.

[0129] In some embodiments, the ion pore domain is derived from the ion pore domain sequence of a human serotonin receptor. In some embodiments, the human serotonin receptor is human 5HT3A or 5HT3B. In some such embodiments, the ion pore domain comprises an amino acid sequence having at least 85%, at least 90%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, at least 99.5%, or 100% sequence identity to about amino acids 248-516 of 5HT3A (SEQ ID NO:6), *e.g.* amino acids 240-516, amino acids 245-516, amino acids 248-516, amino acids 250-516, or amino acids 255-516 of SEQ ID NO:6. In certain such embodiments, the ion pore domain consists essentially of amino acids 240-516 of SEQ ID NO:6, consists essentially of amino acids 245-516 of SEQ ID NO:6, consists essentially of amino acids 248-516 of SEQ ID NO:6, consists essentially of amino acids 250-516 of SEQ ID NO:6, or consists essentially of amino acids 253-516. In some embodiments, the ion pore domain comprises an amino acid sequence having at least 85%, at least 90%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, at least 99.5%, or 100% sequence identity to about amino acids 240-441 of 5HT3B (SEQ ID NO:57), *e.g.* amino acids 230-441, amino acids 235-441, amino acids 240-441, amino acids 245-441, or amino acids 250-441 of SEQ ID NO:57. In certain such embodiments, the ion pore domain consists essentially of amino acids 230-441 of SEQ ID NO:57, consists essentially of amino acids 235-441 of SEQ ID NO:57,

consists essentially of amino acids 240-441 of SEQ ID NO:57, consists essentially of amino acids 245-441 of SEQ ID NO:57, or consists essentially of amino acids 250-441.

[0130] In some embodiments, the ion pore domain is derived from the ion pore domain sequence of a human GABA receptor. In some embodiments, the human GABA receptor is human GABA-A β3. In some embodiments, the ion pore domain comprises an amino acid sequence having at least 85%, at least 90%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, at least 99.5%, or 100% sequence identity to about amino acids 246-473 of GABA-A β3 (SEQ ID NO:8), *e.g.* amino acids 240-473, amino acids 245-473, amino acids 247-473, amino acids 250-473, or amino acids 253-473 of SEQ ID NO:8. In certain such embodiments, the ion pore domain consists essentially of amino acids 240-473 of SEQ ID NO:8, amino acids 245-473 of SEQ ID NO:8, amino acids 247-473 of SEQ ID NO:8, amino acids 250-473 of SEQ ID NO:8, or amino acids 253-473 of SEQ ID NO:8.

[0131] In some embodiments, the ion pore domain of the chimeric receptor comprises the ion pore domain sequence of human GABA-A ρ1 (GABRR1, SEQ ID NO: 10). In some embodiments, the ion pore domain of the chimeric receptor comprises, consists essentially of, or consists of an amino acid sequence derived from the ion pore domain sequence of human GABA-A ρ1 (SEQ ID NO: 10). In some embodiments, the ion pore domain of the chimeric receptor comprises, consists essentially of, or consists of an amino acid sequence having at least 85%, at least 90%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or at least 99.5% sequence identity to the ion pore domain sequence of human GABA-A ρ1 (SEQ ID NO: 10). In some embodiments, the ion pore domain of the chimeric receptor comprises, consists essentially of, or consists of an amino acid sequence identical to the ion pore domain sequence of human GABA-A ρ1 (SEQ ID NO: 10). In some embodiments, the ion pore domain sequence of human GABA-A ρ1 comprises, consists essentially of, or consists of amino acids 284-479 of SEQ ID NO: 10. In some embodiments, the ion pore domain sequence of human GABA-A ρ1 comprises, consists essentially of, or consists of amino acids 288-479 of SEQ ID NO: 10. In some embodiments, the ion pore domain sequence of human GABA-A ρ1 comprises, consists essentially of, or consists of amino acids 290-479 of SEQ ID NO: 10.

[0132] In some embodiments, the ion pore domain of the chimeric receptor comprises the ion pore domain sequence of human GABA-A ρ2 (GABRR2, SEQ ID NO: 12). In some embodiments, the ion pore domain of the chimeric receptor comprises, consists essentially of, or consists of an amino acid sequence derived from the ion pore domain sequence of human GABA-A ρ2 (SEQ ID NO: 12). In some embodiments, the ion pore domain of the chimeric receptor comprises, consists essentially of, or consists of an amino acid sequence having at

least 85%, at least 90%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or at least 99.5% sequence identity to the ion pore domain sequence of human GABA-A ρ2 (SEQ ID NO: 12). In some embodiments, the ion pore domain of the chimeric receptor comprises, consists essentially of, or consists of an amino acid sequence identical to the ion pore domain sequence of human GABA-A ρ2 (SEQ ID NO: 12). In some embodiments, the ion pore domain sequence of human GABA-A ρ2 comprises, consists essentially of, or consists of amino acids 265-466 of SEQ ID NO: 12. In some embodiments, the ion pore domain sequence of human GABA-A ρ2 comprises, consists essentially of, or consists of amino acids 269-466 of SEQ ID NO: 12. In some embodiments, the ion pore domain sequence of human GABA-A ρ2 comprises, consists essentially of, or consists of amino acids 271-466 of SEQ ID NO: 12.

[0133] In some embodiments, the ion pore domain of the chimeric receptor comprises the ion pore domain sequence of human GABA-A ρ3 (GABRR3, SEQ ID NO: 14). In some embodiments, the ion pore domain of the chimeric receptor comprises, consists essentially of, or consists of an amino acid sequence derived from the ion pore domain sequence of human GABA-A ρ3 (SEQ ID NO: 14). In some embodiments, the ion pore domain of the chimeric receptor comprises, consists essentially of, or consists of an amino acid sequence having at least 85%, at least 90%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or at least 99.5% sequence identity to the ion pore domain sequence of human GABA-A ρ3 (SEQ ID NO: 14). In some embodiments, the ion pore domain of the chimeric receptor comprises, consists essentially of, or consists of an amino acid sequence identical to the ion pore domain sequence of human GABA-A ρ3 (SEQ ID NO: 14). In some embodiments, the ion pore domain sequence of human GABA-A ρ3 comprises, consists essentially of, or consists of amino acids 271-468 of SEQ ID NO: 14. In some embodiments, the ion pore domain sequence of human GABA-A ρ3 comprises, consists essentially of, or consists of amino acids 275-468 of SEQ ID NO: 14. In some embodiments, the ion pore domain sequence of human GABA-A ρ3 comprises, consists essentially of, or consists of amino acids 277-467 of SEQ ID NO: 14.

[0134] In some embodiments, the ion pore domain of the subject chimeric ligand-gated ion channel comprises an M2-M3 linker domain that is heterologous to the M2-M3 linker domain of the ion pore domain. By an "M2-M3 linker domain", or "M2-M3 linker", it is meant the sequence within an ion pore domain of a LGIC that is flanked at its amino (N) terminus by the C-terminal end of transmembrane domain 2 (M2) of the receptor and at its carboxy (C) terminus by the N-terminal end of transmembrane domain 3 (M3) of the receptor. The M2-M3 linker of a LGIC may be readily determined from the art and/or by using any publicly available protein analysis tool, *e.g.* Expasy, uniProt, etc. In some embodiments,, when the ion pore

domain of a chimeric receptor comprises a heterologous M2-M3 linker, the M2-M3 linker is derived from the same receptor as the ligand binding domain of the chimeric receptor. For example, when the subject ligand-gated ion channel comprises a ligand binding domain from an AChR and an ion pore domain from a GlyR, its ion pore domain sequence may comprise a M2-M3 linker sequence derived from the AChR. In some embodiments, the ion pore domain is derived from GlyRα1 and the M2-M3 linker is derived from α7-nAChR. In some embodiments, the native M2-M3 linker sequence that is removed from the ion pore domain corresponds to about amino acids 293-313, of GlyRα1 (SEQ ID NO:2), *e.g.* amino acids 304-310, 293-306, 298-310, 305-311, 302-313, etc. In some such embodiments, the M2-M3 linker that is inserted is derived from about amino acids 281-295 of α7-nAChR (SEQ ID NO:4), *e.g.* amino acids 290-295, 281-290, 281-295, 283-295, 287-292, etc. or a sequence at least 50%, at least 55%, at least 60%, at least 65%, at least 70%, at least 75%, at least 80%, at least 85%, at least 90%, at least 95% , or 100% identical to amino acids 281-295 or 283-295 of α7-nAChR.

[0135] In some embodiments, the ligand binding domain of the subject chimeric ligand-gated ion channel comprises a Cys-loop domain sequence that is heterologous to the Cys-loop sequence of the ligand binding domain. By a "Cys-loop domain sequence", or "Cys-loop sequence", it is meant the domain within a ligand binding domain of a Cys-loop LGIC that forms a loop structure flanked by a cysteine at the N-terminus and the C-terminus. Without wishing to be bound by theory, it is believed that upon binding of the ligand to the ligand binding domain, the Cys-loop structurally moves to be in close proximity to the M2-M3 loop, this movement mediating the biophysical translation of ligand binding in the extracellular domain to signal transduction in the ion pore domain (as reviewed in Miller and Smart, Trends in Pharmacological Sci 2009:31(4)). The substitution of an endogenous Cys-loop sequence with a heterologous Cys-loop sequence may increase the conductivity of the LGIC by 1.5-fold or more, *e.g.* at least 2-fold, 3-fold or 4-fold, in some instances at least 5-fold or 6-fold, and at certain doses, at least 7-fold, 8-fold, 9-fold or 10-fold. The Cys-loop domain of a Cys-loop receptor may be readily determined from the art and/or by using any publicly available protein analysis tool, *e.g.* Expasy, uniProt, etc. Typically, when the ligand binding domain of a chimeric receptor comprises a heterologous Cys-loop sequence, the Cys-loop sequence is derived from the same receptor as the ion pore domain of the chimeric receptor. For example, when the subject chimeric ligand-gated ion channel comprises a ligand binding domain from an AChR and an ion pore domain from a GlyR, the subject ligand-gated ion channel may comprise ligand binding domain sequence from an AChR except for the sequence of the Cys-loop domain, which is instead derived from a GlyR. In some embodiments, the ligand binding

domain is derived from α7-nAChR and the Cys-loop sequence is derived from a GLyR. In some embodiments, the Cys-loop sequence that is removed from the ligand binding domain corresponds to about amino acids 150-164 of α7-nAChR (SEQ ID NO:4), *e.g.* amino acids 150-157 of α7-nAChR. In some embodiments, the Cys loop sequence that is inserted is derived from about amino acids 166-180 of GlyRα1 (SEQ ID NO:2), *e.g.* amino acids 166-172 of GlyRα1, or a sequence at least 80%, at least 85%, at least 90%, or at least 95% identical to amino acids 166-180 of GlyRα1.

[0136] In some embodiments, the Cys loop sequence that is inserted is derived from about amino acids 172-186 of GlyRα2 (SEQ ID NO:83), e.g. amino acids 172-178 of GlyRα2, or a sequence at least 80%, at least 85%, at least 90%, or at least 95% identical to amino acids 172-186 of GlyRα2. In some embodiments, the Cys loop sequence that is inserted is derived from about amino acids 171-185 of GlyRα3 (SEQ ID NO:85 or 87), e.g. amino acids 171-177 of GlyRα3, or a sequence at least 80%, at least 85%, at least 90%, or at least 95% identical to amino acids 171-185 of GlyRα3. In some embodiments, the Cys loop sequence that is inserted is derived from about amino acids 198-212 of GABA-A ρ1 (SEQ ID NO:10), e.g. amino acids 198-204 of GABA-A ρ1, or a sequence at least 80%, at least 85%, at least 90%, or at least 95% identical to amino acids 198-212 of GABA-A ρ1. In some embodiments, the Cys loop sequence that is inserted is derived from about amino acids 178-192 of GABA-A ρ2 (SEQ ID NO:12), e.g. amino acids 178-184 of GABA-A ρ2, or a sequence at least 80%, at least 85%, at least 90%, or at least 95% identical to amino acids 178-192 of GABA-A ρ2. In some embodiments, the Cys loop sequence that is inserted is derived from about amino acids 184-198 of GABA-A ρ3 (SEQ ID NO:14), e.g. amino acids 184-190 of GABA-A ρ3, or a sequence at least 80%, at least 85%, at least 90%, or at least 95% identical to amino acids 184-198 of GABA-A ρ3.

[0137] In some embodiments, the ligand binding domain of the subject chimeric ligand-gated ion channel comprises a β1-2 loop domain sequence that is heterologous to the β1-2 loop domain sequence of the ligand binding domain. By a "β1-2 loop domain sequence", or "β1-2 loop, or β1- β2 loop", it is meant the domain within a ligand binding domain of a Cys-loop LGIC that is flanked at its N-terminus by the C-terminus of the β1 sheet and, at its C-terminus, by the N-terminus of the β2 sheet. Without wishing to be bound by theory, it is believed that the β1-2 loop helps to mediate biophysical translation of ligand binding in the extracellular domain to the ion pore domain and subsequent signal transduction (i.e. chloride influx in case of GlyR). It is believed that upon binding of ligand, the β1-2 loop, together with the Cys-loop, come in close proximity to the M2-M3 loop to mediate the biophysical translation of ligand binding in the extracellular domain to signal transduction in the ion pore domain

where the M2-M3 loop resides (as reviewed in Miller and Smart, *supra*). The substitution of an endogenous β1-2 loop sequence with a heterologous β1-2 loop sequence may increase the conductivity of the LGIC by 1.5-fold or more, *e.g.* at least 2-fold, 3-fold or 4-fold, in some instances at least 5-fold or 6-fold, and at certain doses, at least 7-fold, 8-fold, 9-fold or 10-fold. The β1-2 loop of a Cys-loop receptor may be readily determined from the art and/or by using any publicly available protein analysis tool, *e.g.* Expasy, uniProt, etc. Typically, when the ligand binding domain of a chimeric receptor comprises a heterologous β1-2 loop sequence, the β1-2 loop sequence is derived from the same receptor as the ion pore domain of the chimeric receptor. For example, when the subject chimeric ligand-gated ion channel comprises a ligand binding domain derived from an AChR and an ion pore domain derived from a GlyR, the sequence of the β1-2 loop domain of the ligand binding domain may be derived from a GlyR. In some embodiments, the ligand binding domain is derived from α7-nAChR. In some embodiments, the β1-2 loop sequence that is removed from the ligand binding domain corresponds to about amino acids 64-72 or 67-70 of α7-nAChR (SEQ ID NO:4), *e.g.* amino acids 67-70, 66-71 or 64-72 of α7-nAChR. In some embodiments, the β1-2 loop sequence that is inserted is about amino acids 79-85 of GlyRα1 (SEQ ID NO:2), *e.g.* amino acids 80-85, 81-84, 79-85, or 81-84 of GlyRα1, with at most 3, at most 2, at most 1, or no amino acid mutations. In some embodiments, the ion pore domain is derived from GlyRα2 and the β1-2 loop that is inserted corresponds to about amino acids 86-91 of GlyRα2 (SEQ ID NO:83) with at most 3, at most 2, at most 1, or no amino acid mutations. In some embodiments, the ion pore domain is derived from GlyRα3 and the β1-2 loop that is inserted corresponds to about amino acids 85-90 of GlyRα3 (SEQ ID NO:85 or 87) with at most 3, at most 2, at most 1, or no amino acid mutations. In some embodiments, the ion pore domain is derived from GABA-A ρ1 and the β1-2 loop that is inserted corresponds to about amino acids 112-117 of GABA-A ρ1 (SEQ ID NO:10) with at most 3, at most 2, at most 1, or no amino acid mutations. In some embodiments, the ion pore domain is derived from GABA-A ρ2 and the β1-2 loop that is inserted corresponds to about amino acids 92-97 of GABA-A ρ2 (SEQ ID NO:12) with at most 3, at most 2, at most 1, or no amino acid mutations. In some embodiments, the ion pore domain is derived from GABA-A ρ3 and the β1-2 loop that is inserted corresponds to about amino acids 98-103 of GABA-A ρ3 (SEQ ID NO:14) with at most 3, at most 2, at most 1, or no amino acid mutations. In some embodiments, the mutation is an amino acid substitution.

[0138] In some embodiments, the disclosure provides chimeric LGIC receptors comprising a ligand binding domain derived from human α7-nAChR, wherein the ligand binding domain comprises one or more amino acid substitutions of the disclosure, and an ion

pore domain derived from a human Glycine receptor. In some embodiments, the human Glycine receptor is human Glycine receptor α1, human Glycine receptor α2, or human Glycine receptor α3. In some embodiments, the ligand binding domain comprises a Cys-loop domain derived from the human Glycine receptor. In some embodiments, the ligand binding domain comprises a β1-2 loop domain derived from the human Glycine receptor.

[0139] In some embodiments, the disclosure provides chimeric LGIC receptors comprising a ligand binding domain derived from human α7-nAChR, wherein the ligand binding domain comprises one or more amino acid substitutions of the disclosure, and an ion pore domain derived from a human GABA receptor. In some embodiments, the human GABA receptor is human GABA-A ρ1, human GABA-A ρ2, or human GABA-A ρ3. In some embodiments, the ligand binding domain comprises a Cys-loop domain derived from the human GABA receptor. In some embodiments, the ligand binding domain comprises a β1-2 loop domain derived from the human GABA receptor.

[0140] Non-limiting examples of sequences of chimeric LGIC receptors of the present disclosure include the sequences disclosed herein as SEQ ID NO:15 – SEQ ID NO:52. In some embodiments, the chimeric LGIC receptor or the polynucleotide that encodes it has a sequence identity of 85% or more to a sequence provided in SEQ ID NO:15 – SEQ ID NO:52 herein, e.g. a sequence identity of 90% or more, 93% or more, or 95% or more, i.e. about 96%, about 97%, about 98%, about 99% or about 100% to a sequence provided in SEQ ID NO:15 - SEQ ID NO:52. In the sequences, the signal peptide is italicized, the ligand binding domain is bolded, and the ion pore domain is underlined.

[0141] In some embodiments, the chimeric LGIC receptor is a CHRNA7/GLRA1 chimera (R229 junction), comprising the human α7-nAChR signal peptide (italics) and ligand binding domain (bold), fused to the human GlyRα1 ion pore domain (underlined):

*MRCSPGGVWLALAASLLHVSLQ***GEFQRKLYKELVKNYNPLERPVANDSQPL TVYFSLSLLQIMDVDEKNQVLTTNIWLQMSWTDHYLQWNVSEYPGVKT VRFPDGQIWKPDILLYNSADERFDATFHTNVLVNSSGHCQYLPPGIFKSSC YIDVRWFPFDVQHCKLKFGSWSYGGWSLDLQMQEADISGYIPNGEWDL VGIPGKRSERFYECCKEPYPDVTFTVTMRRR**MGYYLIQMYIPSLLIVILSWI SFWINMDAAPARVGLGITTVLTMTTQSSGSRASLPKVSYVKAIDIWMAVCLL FVFSALLEYAAVNFVSRQHKELLRFRRKRRHHKSPMLNLFQEDEAGEGRFNF SAYGMGPACLQAKDGISVKGANNSNTTNPPPAPSKSPEEMRKLFIQRAKKID KISRIGFPMAFLIFNMFYWIIYKIVRREDVHNQ (SEQ ID NO:16, encoded by SEQ ID NO:15).

[0142] In some embodiments, the chimeric LGIC receptor is a CHRNA7/GLRA1 (R228 junction) chimera, comprising the human α7-nAChR signal peptide (italics) and ligand binding domain (bold), fused to the human GlyRα1 ion pore domain (underlined):

*MRCSPGGVWLALAASLLHVSLQ***GEFQRKLYKELVKNYNPLERPVANDSQPL TVYFSLSLLQIMDVDEKNQVLTTNIWLQMSWTDHYLQWNVSEYPGVKT VRFPDGQIWKPDILLYNSADERFDATFHTNVLVNSSGHCQYLPPGIFKSSC YIDVRWFPFDVQHCKLKFGSWSYGGWSLDLQMQEADISGYIPNGEWDL VGIPGKRSERFYECCKEPYPDVTFTVTMRR**QMGYYLIQMYIPSLLIVILSWI SFWINMDAAPARVGLGITTVLTMTTQSSGSRASLPKVSYVKAIDIWMAVCLL FVFSALLEYAAVNFVSRQHKELLRFRRKRRHHKSPMLNLFQEDEAGEGRFNF SAYGMGPACLQAKDGISVKGANNSNTTNPPPAPSKSPEEMRKLFIQRAKKID KISRIGFPMAFLIFNMFYWIIYKIVRREDVHNQ (SEQ ID NO:17).

[0143] In some embodiments, the chimeric LGIC receptor is a CHRNA7/GLRA1 (V224 junction) chimera, comprising the human α7-nAChR signal peptide (italics) and ligand binding domain (bold), fused to the human GlyRα1 ion pore domain (underlined):

*MRCSPGGVWLALAASLLHVSLQ***GEFQRKLYKELVKNYNPLERPVANDSQPL TVYFSLSLLQIMDVDEKNQVLTTNIWLQMSWTDHYLQWNVSEYPGVKT VRFPDGQIWKPDILLYNSADERFDATFHTNVLVNSSGHCQYLPPGIFKSSC YIDVRWFPFDVQHCKLKFGSWSYGGWSLDLQMQEADISGYIPNGEWDL VGIPGKRSERFYECCKEPYPDVTFTV**HLERQMGYYLIQMYIPSLLIVILSWIS FWINMDAAPARVGLGITTVLTMTTQSSGSRASLPKVSYVKAIDIWMAVCLLF VFSALLEYAAVNFVSRQHKELLRFRRKRRHHKSPMLNLFQEDEAGEGRFNFS AYGMGPACLQAKDGISVKGANNSNTTNPPPAPSKSPEEMRKLFIQRAKKIDKI SRIGFPMAFLIFNMFYWIIYKIVRREDVHNQ (SEQ ID NO:18).

[0144] In some embodiments, the chimeric LGIC receptor is a CHRNA7/GLRA1 (Y233 junction) chimera, comprising the human α7-nAChR signal peptide (italics) and ligand binding domain (bold), fused to the human GlyRα1 ion pore domain (underlined):

*MRCSPGGVWLALAASLLHVSLQ***GEFQRKLYKELVKNYNPLERPVANDSQPL TVYFSLSLLQIMDVDEKNQVLTTNIWLQMSWTDHYLQWNVSEYPGVKT VRFPDGQIWKPDILLYNSADERFDATFHTNVLVNSSGHCQYLPPGIFKSSC YIDVRWFPFDVQHCKLKFGSWSYGGWSLDLQMQEADISGYIPNGEWDL VGIPGKRSERFYECCKEPYPDVTFTVTMRRRTLYY**LIQMYIPSLLIVILSWIS FWINMDAAPARVGLGITTVLTMTTQSSGSRASLPKVSYVKAIDIWMAVCLLF

VFSALLEYAAVNFVSRQHKELLRFRRKRRHHKSPMLNLFQEDEAGEGRFNFS AYGMGPACLQAKDGISVKGANNSNTTNPPPAPSKSPEEMRKLFIQRAKKIDKI SRIGFPMAFLIFNMFYWIIYKIVRREDVHNQ (SEQ ID NO:19).

[0145] In some embodiments, the chimeric LGIC receptor is a CHRNA7/GLRA1 chimera (R229 junction), comprising the human α7-nAChR signal peptide (italics) and ligand binding domain (bold), fused to the human GlyRα1 ion pore domain (underlined) comprising an α7-nAChR M2-M3 linker (lowercase):

(a) *MRCSPGGVWLALAASLLHVSLQ***GEFQRKLYKELVKNYNPLERPVAND SQPLTVYFSLSLLQIMDVDEKNQVLTTNIWLQMSWTDHYLQWNVSEYPGVKTV RFPDGQIWKPDILLYNSADERFDATFHTNVLVNSSGHCQYLPPGIFKSSCYIDVR WFPFDVQHCKLKFGSWSYGGWSLDLQMQEADISGYIPNGEWDLVGIPGKRSER FYECCKEPYPDVTFTVTMRRR**MGYYLIQMYIPSLLIVILSWISFWINMDAAPARVG LGITTVLTMTTQSSGSeimpatsdsvSYVKAIDIWMAVCLLFVFSALLEYAAVNFVSRQH KELLRFRRKRRHHKSPMLNLFQEDEAGEGRFNFSAYGMGPACLQAKDGISVKGANN SNTTNPPPAPSKSPEEMRKLFIQRAKKIDKISRIGFPMAFLIFNMFYWIIYKIVRREDVH NQ (SEQ ID NO:21, encoded by SEQ ID NO:20);

(b) *MRCSPGGVWLALAASLLHVSLQ***GEFQRKLYKELVKNYNPLERPVAND SQPLTVYFSLSLLQIMDVDEKNQVLTTNIWLQMSWTDHYLQWNVSEYPGVKTV RFPDGQIWKPDILLYNSADERFDATFHTNVLVNSSGHCQYLPPGIFKSSCYIDVR WFPFDVQHCKLKFGSWSYGGWSLDLQMQEADISGYIPNGEWDLVGIPGKRSER FYECCKEPYPDVTFTVTMRRR**MGYYLIQMYIPSLLIVILSWISFWINMDAAPARVG LGITTVLTMTTQSSGSeimpatsdsvpliaqAIDIWMAVCLLFVFSALLEYAAVNFVSRQHK ELLRFRRKRRHHKSPMLNLFQEDEAGEGRFNFSAYGMGPACLQAKDGISVKGANNS NTTNPPPAPSKSPEEMRKLFIQRAKKIDKISRIGFPMAFLIFNMFYWIIYKIVRREDVHN Q (SEQ ID NO:23, encoded by SEQ ID NO:22);

(c) *MRCSPGGVWLALAASLLHVSLQ***GEFQRKLYKELVKNYNPLERPVAND SQPLTVYFSLSLLQIMDVDEKNQVLTTNIWLQMSWTDHYLQWNVSEYPGVKTV RFPDGQIWKPDILLYNSADERFDATFHTNVLVNSSGHCQYLPPGIFKSSCYIDVR WFPFDVQHCKLKFGSWSYGGWSLDLQMQEADISGYIPNGEWDLVGIPGKRSER FYECCKEPYPDVTFTVTMRRR**MGYYLIQMYIPSLLIVILSWISFWINMDAAPARVG LGITTVLTMTTQSSGSRASLPKVsdsvplIDIWMAVCLLFVFSALLEYAAVNFVSRQHKE LLRFRRKRRHHKSPMLNLFQEDEAGEGRFNFSAYGMGPACLQAKDGISVKGANNSN

TTNPPPAPSKSPEEMRKLFIQRAKKIDKISRIGFPMAFLIFNMFYWIIYKIVRREDVHNQ (SEQ ID NO:25, encoded by SEQ ID NO:24);

(d) *MRCSPGGVWLALAASLLHVSLQ***GEFQRKLYKELVKNYNPLERPVAND SQPLTVYFSLSLLQIMDVDEKNQVLTTNIWLQMSWTDHYLQWNVSEYPGVKTV RFPDGQIWKPDILLYNSADERFDATFHTNVLVNSSGHCQYLPPGIFKSSCYIDVR WFPFDVQHCKLKFGSWSYGGWSLDLQMQEADISGYIPNGEWDLVGIPGKRSER FYECCKEPYPDVTFTVTM**ERQMGYYLIQMYIPSLLIVILSWISFWINMDAAPARVGL GITTVLTMTTQSSGSeimpatsdsvpliaqAIDIWMAVCLLFVFSALLEYAAVNFVSRQHKE LLRFRRKRRHHKSPMLNLFQEDEAGEGRFNFSAYGMGPACLQAKDGISVKGANNSN TTNPPPAPSKSPEEMRKLFIQRAKKIDKISRIGFPMAFLIFNMFYWIIYKIVRREDVHNQ (SEQ ID NO:27, encoded by SEQ ID NO:26);

(e) *MRCSPGGVWLALAASLLHVSLQ***GEFQRKLYKELVKNYNPLERPVAND SQPLTVYFSLSLLQIMDVDEKNQVLTTNIWLQMSWTDHYLQWNVSEYPGVKTV RFPDGQIWKPDILLYNSADERFDATFHTNVLVNSSGHCQYLPPGIFKSSCYIDVR WFPFDVQHCKLKFGSWSYGGWSLDLQMQEADISGYIPNGEWDLVGIPGKRSER FYECCKEPYPDVTFTVTMRRRT**GYYLIQMYIPSLLIVILSWISFWINMDAAPARVGL GITTVLTMTTQSSGSeimpatsdsvpliaqAIDIWMAVCLLFVFSALLEYAAVNFVSRQHKE LLRFRRKRRHHKSPMLNLFQEDEAGEGRFNFSAYGMGPACLQAKDGISVKGANNSN TTNPPPAPSKSPEEMRKLFIQRAKKIDKISRIGFPMAFLIFNMFYWIIYKIVRREDVHNQ (SEQ ID NO: 29, encoded by SEQ ID NO: 28); or

(f) *MRCSPGGVWLALAASLLHVSLQ***GEFQRKLYKELVKNYNPLERPVAND SQPLTVYFSLSLLQIMDVDEKNQVLTTNIWLQMSWTDHYLQWNVSEYPGVKTV RFPDGQIWKPDILLYNSADERFDATFHTNVLVNSSGHCQYLPPGIFKSSCYIDVR WFPFDVQHCKLKFGSWSYGGWSLDLQMQEADISGYIPNGEWDLVGIPGKRSER FYECCKEPYPDVTFTVTMRRRTL**YYLIQMYIPSLLIVILSWISFWINMDAAPARVGL GITTVLTMTTQSSGSeimpatsdsvpliaqAIDIWMAVCLLFVFSALLEYAAVNFVSRQHKE LLRFRRKRRHHKSPMLNLFQEDEAGEGRFNFSAYGMGPACLQAKDGISVKGANNSN TTNPPPAPSKSPEEMRKLFIQRAKKIDKISRIGFPMAFLIFNMFYWIIYKIVRREDVHNQ (SEQ ID NO:31, encoded by SEQ ID NO:30).

[0146] In some embodiments, the chimeric LGIC receptor is a CHRNA7/GLRA1 chimera comprising the human α7-nAChR signal peptide (italics) and ligand binding domain (bold) comprising an GlyRα1 Cys-loop sequence (lowercase); fused to the human GlyRα1 ion

pore domain (underlined). In some embodiments, the chimeric LGIC receptor comprises an amino acid sequence having a sequence identity of 80% or more, 85% or more, 90% or more, 95% or more, 97% or more, 98% or more, 99% or more, or 100%, to SEQ ID NO: 33:

```
    10        20        30        40        50        60
MRCSPGGVWL ALAASLLHVS LQGEFQRKLY KELVKNYNPL ERPVANDSQP LTVYFSLSLL
    70        80        90       100       110       120
QIMDVDEKNQ VLTTNIWLQM SWTDHYLQWN VSEYPGVKTV RFPDGQIWKP DILLYNSADE
    130       140       150       160       170       180
RFDATFHTNV LVNSSGHCQY LPPGIFKSSc pmdlknfpmd vqtcKLKFGS WSYGGWSLDL
    190       200       210       220       230       240
QMQEADISGY IPNGEWDLVG IPGKRSERFY ECCKEPYPDV TFTVTMRRRM GYYLIQMYIP
    250       260       270       280       290       300
SLLIVILSWI SFWINMDAAP ARVGLGITTV LTMTTQSSGS RASLPKVSYV KAIDIWMAVC
    310       320       330       340       350       360
LLFVFSALLE YAAVNFVSRQ HKELLRFRRK RRHHKSPMLN LFQEDEAGEG RFNFSAYGMG
    370       380       390       400       410       420
PACLQAKDGI SVKGANNSNT TNPPPAPSKS PEEMRKLFIQ RAKKIDKISR IGFPMAFLIF
    430       439
NMFYWIIYKI VRREDVHNQ
```

(SEQ ID NO: 33, encoded by SEQ ID NO: 32).

(a)

*MRCSPGGVWLALAASLLHVSLQ***GEFQRKLYKELVKNYNPLERPVANDSQPLTVYFS**

LSLLQIMDVDEKNQVLTTNIWLQMSWTDHYLQWNVSEYPGVKTVRFPDGQIW

KPDILLYNSADERFDATFHTNVLVNSSGHCQYLPPGIFKSScpmdlknFPFDVQHCK

LKFGSWSYGGWSLDLQMQEADISGYIPNGEWDLVGIPGKRSERFYECCKEPYP

DVTFTVTMRRRMGYYLIQMYIPSLLIVILSWISFWINMDAAPARVGLGITTVLTMTT

QSSGSRASLPKVSYVKAIDIWMAVCLLFVFSALLEYAAVNFVSRQHKELLRFRRKRR

HHKSPMLNLFQEDEAGEGRFNFSAYGMGPACLQAKDGISVKGANNSNTTNPPPAPS

KSPEEMRKLFIQRAKKIDKISRIGFPMAFLIFNMFYWIIYKIVRREDVHNQ (SEQ ID NO:35, encoded by SEQ ID NO:34).

[0147] In some embodiments, the chimeric LGIC receptor is a CHRNA7/GLRA1 chimera comprising the human α7-nAChR signal peptide (italics) and ligand binding domain (bold) comprising an GlyRα1 β1-2 loop sequence (lowercase); fused to the human GlyRα1 ion pore domain (underlined):

(a) *MRCSPGGVWLALAASLLHVSLQ***GEFQRKLYKELVKNYNPLERPVAND**

SQPLTVYFSLSLLQIMDVDettmVLTTNIWLQMSWTDHYLQWNVSEYPGVKTVR

FPDGQIWKPDILLYNSADERFDATFHTNVLVNSSGHCQYLPPGIFKSSCYIDVRW

FPFDVQHCKLKFGSWSYGGWSLDLQMQEADISGYIPNGEWDLVGIPGKRSERF

YECCKEPYPDVTFTVTMRRRMGYYLIQMYIPSLLIVILSWISFWINMDAAPARVGL

GITTVLTMTTQSSGSRASLPKVSYVKAIDIWMAVCLLFVFSALLEYAAVNFVSRQHK
ELLRFRRKRRHHKSPMLNLFQEDEAGEGRFNFSAYGMGPACLQAKDGISVKGANNS
NTTNPPPAPSKSPEEMRKLFIQRAKKIDKISRIGFPMAFLIFNMFYWIIYKIVRREDVHN
Q (SEQ ID NO:37, encoded by SEQ ID NO:36).

[0148] In some embodiments, the chimeric LGIC receptor is a CHRNA7/GLRA1 chimera comprising the human α7-nAChR signal peptide (italics) and ligand binding domain (bold) comprising an GlyRα1 β1-2 loop sequence (lowercase) and Cys-loop sequence (lowercase); fused to the human GlyRα1 ion pore domain (underlined):

(a) *MRCSPGGVWLALAASLLHVSLQ***GEFQRKLYKELVKNYNPLERPVAND**
SQPLTVYFSLSLLQIMDiaettmdLTTNIWLQMSWTDHYLQWNVSEYPGVKTVRFP
DGQIWKPDILLYNSADERFDATFHTNVLVNSSGHCQYLPPGIFKSScpmdlknfpmd
vqtcKLKFGSWSYGGWSLDLQMQEADISGYIPNGEWDLVGIPGKRSERFYECCK
EPYPDVTFTVTMRRRMGYYLIQMYIPSLLIVILSWISFWINMDAAPARVGLGITTVL
TMTTQSSGSRASLPKVSYVKAIDIWMAVCLLFVFSALLEYAAVNFVSRQHKELLRFR
RKRRHHKSPMLNLFQEDEAGEGRFNFSAYGMGPACLQAKDGISVKGANNSNTTNPP
PAPSKSPEEMRKLFIQRAKKIDKISRIGFPMAFLIFNMFYWIIYKIVRREDVHNQ (SEQ ID NO:39, encoded by SEQ ID NO:38).

(b) *MRCSPGGVWLALAASLLHVSLQ***GEFQRKLYKELVKNYNPLERPVAND**
SQPLTVYFSLSLLQIMDVDettmVLTTNIWLQMSWTDHYLQWNVSEYPGVKTVR
FPDGQIWKPDILLYNSADERFDATFHTNVLVNSSGHCQYLPPGIFKSScpmdlknfp
mdvqtcKLKFGSWSYGGWSLDLQMQEADISGYIPNGEWDLVGIPGKRSERFYEC
CKEPYPDVTFTVTMRRRMGYYLIQMYIPSLLIVILSWISFWINMDAAPARVGLGITT
VLTMTTQSSGSRASLPKVSYVKAIDIWMAVCLLFVFSALLEYAAVNFVSRQHKELLR
FRRKRRHHKSPMLNLFQEDEAGEGRFNFSAYGMGPACLQAKDGISVKGANNSNTTN
PPPAPSKSPEEMRKLFIQRAKKIDKISRIGFPMAFLIFNMFYWIIYKIVRREDVHNQ
(SEQ ID NO:41, encoded by SEQ ID NO:40).

(c) *MRCSPGGVWLALAASLLHVSLQ***GEFQRKLYKELVKNYNPLERPVAND**
SQPLTVYFSLSLLQIMDVDettmVLTTNIWLQMSWTDHYLQWNVSEYPGVKTVR
FPDGQIWKPDILLYNSADERFDATFHTNVLVNSSGHCQYLPPGIFKSScpmdlknfp
mdvqtcKLKFGSWSYGGWSLDLQMQEADISGYIPNGEWDLVGIPGKRSERFYEC
CKEPYPDVTFTVTMERQMGYYLIQMYIPSLLIVILSWISFWINMDAAPARVGLGITT
VLTMTTQSSGSRASLPKVSYVKAIDIWMAVCLLFVFSALLEYAAVNFVSRQHKELLR
FRRKRRHHKSPMLNLFQEDEAGEGRFNFSAYGMGPACLQAKDGISVKGANNSNTTN

PPPAPSKSPEEMRKLFIQRAKKIDKISRIGFPMAFLIFNMFYWIIYKIVRREDVHNQ (SEQ ID NO:43, encoded by SEQ ID NO:42).

(d) *MRCSPGGVWLALAASLLHVSLQ***GEFQRKLYKELVKNYNPLERPVANDSQPLTVYFSLSLLQIMDiaettmdLTTNIWLQMSWTDHYLQWNVSEYPGVKTVRFPDGQIWKPDILLYNSADERFDATFHTNVLVNSSGHCQYLPPGIFKSScpmdlknfpmdvqtcKLKFGSWSYGGWSLDLQMQEADISGYIPNGEWDLVGIPGKRSERFYECCKEPYPDVTFTVTM**ERQMGYYLIQMYIPSLLIVILSWISFWINMDAAPARVGLGITTVLTMTTQSSGSRASLPKVSYVKAIDIWMAVCLLFVFSALLEYAAVNFVSRQHKELLRFRRKRRHHKSPMLNLFQEDEAGEGRFNFSAYGMGPACLQAKDGISVKGANNSNTTNPPPAPSKSPEEMRKLFIQRAKKIDKISRIGFPMAFLIFNMFYWIIYKIVRREDVHNQ (SEQ ID NO:45, encoded by SEQ ID NO:44).

[0149] In some embodiments, the chimeric LGIC receptor is a CHRNA7/GLRA1 chimera comprising the human α7-nAChR signal peptide (italics) and ligand binding domain (bold) comprising an GlyRα1 β1-2 loop sequence (lowercase); fused to the human GlyRα1 ion pore domain (underlined) comprising human α7-nAChR M2-M3 linker (lowercase):

(a) *MRCSPGGVWLALAASLLHVSLQ***GEFQRKLYKELVKNYNPLERPVANDSQPLTVYFSLSLLQIMDVDettmVLTTNIWLQMSWTDHYLQWNVSEYPGVKTVRFPDGQIWKPDILLYNSADERFDATFHTNVLVNSSGHCQYLPPGIFKSSCYIDVRWFPFDVQHCKLKFGSWSYGGWSLDLQMQEADISGYIPNGEWDLVGIPGKRSERFYECCKEPYPDVTFTVTMRRR**MGYYLIQMYIPSLLIVILSWISFWINMDAAPARVGLGITTVLTMTTQSSGSeimpatsdsvpliaqAIDIWMAVCLLFVFSALLEYAAVNFVSRQHKELLRFRRKRRHHKSPMLNLFQEDEAGEGRFNFSAYGMGPACLQAKDGISVKGANNSNTTNPPPAPSKSPEEMRKLFIQRAKKIDKISRIGFPMAFLIFNMFYWIIYKIVRREDVHNQ (SEQ ID NO:47, encoded by SEQ ID NO:46).

[0150] In some embodiments, the chimeric LGIC receptor is a CHRNA7/GLRA1 chimera comprising the human α7-nAChR signal peptide (italics) and ligand binding domain (bold) comprising a GlyRα1 Cys-loop sequence (lowercase); fused to the human GlyRα1 ion pore domain (underlined) comprising a human α7-nAChR M2-M3 linker (lowercase):

(a) *MRCSPGGVWLALAASLLHVSLQ***GEFQRKLYKELVKNYNPLERPVANDSQPLTVYFSLSLLQIMDVDEKNQVLTTNIWLQMSWTDHYLQWNVSEYPGVKTVRFPDGQIWKPDILLYNSADERFDATFHTNVLVNSSGHCQYLPPGIFKSScpmdlknfpmdvqtcKLKFGSWSYGGWSLDLQMQEADISGYIPNGEWDLVGIPGKRSERFYECCKEPYPDVTFTVTMRRR**MGYYLIQMYIPSLLIVILSWISFWINMDAAPARVGLGITT

VLTMTTQSSGSeimpatsdsvpliaqAIDIWMAVCLLFVFSALLEYAAVNFVSRQHKELLRF RRKRRHHKSPMLNLFQEDEAGEGRFNFSAYGMGPACLQAKDGISVKGANNSNTTNP PPAPSKSPEEMRKLFIQRAKKIDKISRIGFPMAFLIFNMFYWIIYKIVRREDVHNQ (SEQ ID NO:49, encoded by SEQ ID NO:48).

[0151] In some embodiments, the chimeric LGIC receptor is a HTR3A/GLRA1 chimera (R241 junction), comprising the human 5HT3A serotonin receptor signal peptide (italics) and ligand binding domain (bold), fused to the human GlyRα1 ion pore domain (underlined):

(a) *MLLWVQQALLALLLPTLLAQGEA***RRSRNTTRPALLRLSDYLLTNYRK GVRPVRDWRKPTTVSIDVIVYAILNVDEKNQVLTTYIWYRQYWTDEFLQWNPE DFDNITKLSIPTDSIWVPDILINEFVDVGKSPNIPYVYIRHQGEVQNYKPLQVVTA CSLDIYNFPFDVQNCSLTFTSWLHTIQDINISLWRLPEKVKSDRSVFMNQGEWEL LGVLPYFREFSMESSNYYAEMKFYVVIRRR**MGYYLIQMYIPSLLIVILSWISFWINM DAAPARVGLGITTVLTMTTQSSGSRASLPKVSYVKAIDIWMAVCLLFVFSALLEYAA VNFVSRQHKELLRFRRKRRHHKSPMLNLFQEDEAGEGRFNFSAYGMGPACLQAKD GISVKGANNSNTTNPPPAPSKSPEEMRKLFIQRAKKIDKISRIGFPMAFLIFNMFYWIIY KIVRREDVHNQ (SEQ ID NO:50).

[0152] In some embodiments, the chimeric LGIC receptor is a HTR3A/GLRA1 chimera (V236 junction) comprising the human 5HT3A serotonin receptor signal peptide (italics) and ligand binding domain (bold), fused to the human GlyRα1 ion pore domain (underlined):

(a) *MLLWVQQALLALLLPTLLAQGEA***RRSRNTTRPALLRLSDYLLTNYRK GVRPVRDWRKPTTVSIDVIVYAILNVDEKNQVLTTYIWYRQYWTDEFLQWNPE DFDNITKLSIPTDSIWVPDILINEFVDVGKSPNIPYVYIRHQGEVQNYKPLQVVTA CSLDIYNFPFDVQNCSLTFTSWLHTIQDINISLWRLPEKVKSDRSVFMNQGEWEL LGVLPYFREFSMESSNYYAEMKFYV**HLERQMGYYLIQMYIPSLLIVILSWISFWINM DAAPARVGLGITTVLTMTTQSSGSRASLPKVSYVKAIDIWMAVCLLFVFSALLEYAA VNFVSRQHKELLRFRRKRRHHKSPMLNLFQEDEAGEGRFNFSAYGMGPACLQAKD GISVKGANNSNTTNPPPAPSKSPEEMRKLFIQRAKKIDKISRIGFPMAFLIFNMFYWIIY KIVRREDVHNQ (SEQ ID NO:51).

[0153] In some embodiments, the chimeric LGIC receptor is a GABRB3/GLRA1 chimera (Y245 junction), comprising the human GABA-A β3 signal peptide (italics) and ligand binding domain (bold), fused to the human GlyRα1 ion pore domain (underlined):

(a) *MWGLAGGRLFGIFSAPVLVAVVCCA***QSVNDPGNMSFVKETVDKLLKG YDIRLRPDFGGPPVCVGMNIDIASIDMVSEVNMDYTLTMYFQQYWRDKRLAYS GIPLNLTLDNRVADQLWVPDTYFLNDKKSFVHGVTVKNRMIRLHPDGTVLYGL RITTTAACMMDLRRYPLDEQNCTLEIESYGYTTDDIEFYWRGGDKAVTGVERIE LPQFSIVEHRLVSRNVVFATGAYPRLSLSFRLKRNIGY**MGYYLIQMYIPSLLIVILS WISFWINMDAAPARVGLGITTVLTMTTQSSGSRASLPKVSYVKAIDIWMAVCLLFVF SALLEYAAVNFVSRQHKELLRFRRKRRHHKSPMLNLFQEDEAGEGRFNFSAYGMGP ACLQAKDGISVKGANNSNTTNPPPAPSKSPEEMRKLFIQRAKKIDKISRIGFPMAFLIF NMFYWIIYKIVRREDVHNQ (SEQ ID NO:52).

C1. Amino Acid Mutations

[0154] As discussed above, in some aspects, the subject engineered receptor comprises at least one amino acid mutation that alters the potency of a ligand on the engineered receptor relative to its potency on the unmutated parental receptor. Put another way, the one or more amino acid mutations, *e.g.* a loss-of-function mutations or a gain-of-function mutations, shift the potency of the engineered receptor to the ligand relative to the potency of the unmutated parental receptor. In some embodiments, the mutation is an amino acid substitution. In some embodiments, the one or more mutations is in the ligand binding domain of the engineered receptor. In some embodiments, as when the ligand binding domain of the engineered receptor is a Cys-loop receptor protein, the one or more amino acid mutations is a substitution at a residue corresponding to a residue of α7-nAChR (SEQ ID NO:4) selected from the group consisting of W77, Y94, R101, W108, Y115, T128, N129, V130, L131, Q139, L141, Y151, S170, W171, S172, S188, Y190, Y210, C212, C213 and Y217. In some embodiments, one residue is substituted. In some embodiments, 2, 3, 4, or 5 or more residues are substituted, *e.g.* 6, 7, 8, 9 or 10 residues are substituted. In certain embodiments, the residue corresponds to a residue of α7-nAChR (SEQ ID NO:4) that is selected from the group consisting of W77, R101, Y115, N129, L131, S170, S172, and S188. In certain embodiments, the one or more substitutions is within an α7-nAChR sequence.

[0155] In some embodiments, the one or more substitutions decreases, *e.g.* 2-fold or more, 3-fold or more, 4-fold or more. 5-fold or more, 10-fold or more, 20-fold or more, 30-fold or more, 50-fold or more, or 100-fold, the potency of an engineered receptor to acetylcholine and a non-native ligand. In certain embodiments, the one or more substitutions is a substitution corresponding to R101I, R101S, R101D, Y115L, Y115M, Y115D, Y115T, T128M, T128R, T128I, N129I, N129V, N129P, N129W, N129T, N129D, N129E, L131E,

L131P, L131T, L131D, L131S, L141S, L141R, W171F, W171H, S172F, S172Y, S172R, S172D, C212A, C212L, or C213P of α7-nAChR. In other instances, the one or more substitutions decreases the potency of acetylcholine on the engineered receptor selectively. In other words, the one or more substitutions decreases the potency of the engineered receptor to acetylcholine while essentially maintaining potency to non-native ligand or otherwise decreasing the potency of the engineered receptor to acetylcholine 2-fold or more, *e.g.* 3-fold, 4-fold, 5-fold or more, in some instances 10-fold, 20-fold, 50-fold, or 100-fold or more, than it decreases the potency of the engineered receptor to non-native ligand. In some embodiments, the substitution corresponds to L131E, L131S, L131T, L131D, or S172D of α7-nAChR. In yet other embodiments, the one or more substitutions decreases the potency of a non-native ligand on the engineered receptor selectively. In other words, the one or more substitutions decreases the potency of the engineered receptor to non-native ligand while essentially maintaining potency to acetylcholine or otherwise decreasing the potency of the engineered receptor to non-native ligand 2-fold or more, *e.g.* 3-fold, 5-fold or more, in some instances 10-fold, 20-fold or 50-fold or more, than it decreases the potency of the engineered receptor to acetylcholine. In some embodiments, the substitution corresponds to W77M, Y115W, S172T, or S172C of α7-nAChR. In certain embodiments, the one or more substitutions is within an α7-nAChR sequence. In certain embodiments, the non-native ligand is selected from AZD-0328, TC6987, ABT-126, and Facinicline/RG3487.

[0156] In other embodiments, the one or more substitutions increases, *e.g.* 2-fold or more, 3-fold or more, 4-fold or more. 5-fold or more, 10-fold or more, 20-fold or more, 30-fold or more, 50-fold or more, or 100-fold, the potency of the engineered receptor to acetylcholine and/or non-native ligand. In some embodiments, the substitution corresponds to L131N, L141W, S170G, S170A, S170L, S170I, S170V, S170P, S170F, S170M, S170T, S170C, S172T, S172C, S188I, S188V, S188F, S188M, S188Q, S188T, S188P or S188W. In some embodiments. the one or more substitutions increases potency of both acetylcholine and non-native ligand. In some embodiments, the substitution corresponds to L131N, S170G, S170A, S170L, S170I, S170V, S170P, S170F, S170M, S170T, S170C, S172T, S188I, S188V, S188F, S188M, S188Q or S188T of α7-nAChR. In other instances, the one or more substitutions increases the potency of acetylcholine on the engineered receptor selectively. In other words, the one or more substitutions increases the potency of the engineered receptor to acetylcholine 2-fold or more, *e.g.* 3-fold, 4-fold, or 5-fold or more, in some instances 10-fold, 20-fold, 50-fold, or 100-fold, than it increases the potency of the engineered receptor to non-native ligand. In some embodiments, the substitution corresponds to L141W, S172T, S172C,

S188P or S188W, of α7-nAChR. In certain embodiments, the one or more substitutions is within an α7-nAChR sequence. In certain embodiments, the non-native ligand is selected from AZD-0328, TC6987, ABT-126 and Facinicline/RG3487. In yet other instances, the one or more substitutions increases the potency of the non-native ligand on the engineered receptor selectively. In other words, the one or more substitutions increases the potency of the engineered receptor to non-native ligand 2-fold or more, *e.g.* 3-fold, 5-fold or more, in some instances 10-fold, 20-fold or 50-fold or more, than it increases the potency of the engineered receptor to acetylcholine.

[0157] In some embodiments, the amino acid residue that is mutated in the subject engineered receptor is not an amino acid corresponding to R27, E41, Q79, Q139, L141, G175, Y210, P216, Y217, or D219 of wild type a7 nAChR (SEQ ID NO:4). In some embodiments, the mutation is an amino acid substitution. In some embodiments, the amino acid residue that is mutated in the subject engineered receptor is an amino acid corresponding to R27, E41, Q79, Q139, L141, G175, Y210, P216, Y217, or D219 of wild type a7 nAChR (SEQ ID NO:4). In some embodiments, the substitution is not a substitution corresponding to W77F, W77Y, W77M, Q79A, Q79Q, Q79S, Q79G, Y115F, L131A, L131G, L131M, L131N, L131Q, L131V, L131F, Q139G, Q139L, G175K, G175A, G175F, G175H, G175M, G175R, G175S, G175V, Y210F, P216I, Y217F, or D219A in wild type α7 nAChR. In some embodiments, the substitution is a substitution corresponding to W77F, W77Y, W77M, Q79A, Q79Q, Q79S, Q79G, Y115F, L131A, L131G, L131M, L131N, L131Q, L131V, L131F, Q139G, Q139L, G175K, G175A, G175F, G175H, G175M, G175R, G175S, G175V, Y210F, P216I, Y217F, or D219A in wild type α7 nAChR. In some embodiments, when such a substitution exists within the engineered receptor, it exists in combination with one or more of the amino acid mutations described herein.

[0158] In some embodiments, residues Y94, Y115, Y151, and Y190 of α7-nAChR (SEQ ID NO:4) mediate binding of the native ligand acetylcholine. In some embodiments, mutations at these residues may reduce binding of acetylcholine and hence be considered loss of function mutations. In some embodiments, residues W77, Y115, N129, V130, L131, Q139, L141, S170, Y210, C212, C213 and Y217 of the α7-nAChR may mediate the binding of non-native ligand AZD0328 to this receptor, and mutation of these residues may increase the affinity of AZD0328 and/or other ligands for this receptor and hence be considered gain-of-function mutations. In some embodiments, the subject engineered receptor comprises a mutation in one or more amino acid residues of the ligand binding domain region of α7-nAChR (SEQ ID NO:4) or the ligand binding domain of a chimeric receptor that comprises the ligand

binding domain region of α7-nAChR, wherein the one or more amino acid residues is selected from the group consisting of W77, Y94, Y115, N129, V130, L131, Q139, L141, Y151, S170, Y190, Y210, C212, C213 and Y217. In some embodiments, the mutation is an amino acid substitution. In certain embodiments, the mutation in the one or more amino acid residues of the ligand binding domain region of α7-nAChR (SEQ ID NO:4) or the ligand binding domain of a chimeric receptor that comprises the ligand binding domain region of α7-nAChR is a substitution at one or more amino acid residues selected from the group consisting of W77, Y94, Y115, N129, V130, L131, Q139, L141, Y151, S170, Y190, Y210, C212, C213 and Y217.

[0159] In some embodiments, residues Y115, L131, L141, S170, W171, S172, C212, and Y217 of α7-nAChR (SEQ ID NO:4) may mediate binding of acetylcholine and/or nicotine, and mutations at one or more of these residues may reduce binding of acetylcholine and/or nicotine. In some embodiments, R101, Y115, L131, L141, W171, S172, S188, Y210, and Y217 of α7-nAChR may mediate binding of the non-native ligand ABT126, and mutation of one or more of these residues may increase the affinity of ABT126 and/or other ligands for α7-nAChR. In some embodiments, the mutation is an amino acid substitution. In some embodiments, R101, Y115, T128, N129, L131, L141, W171, S172, Y210, C212, C213 and Y217 of α7-nAChR may mediate binding of the non-native ligand TC6987, and mutation of one or more of these residues may increase the affinity of TC6987 and/or other ligands for α7-nAChR. In some embodiments, R101, N120, L131, L141, S170, W171, S172, Y210, and Y217 of α7-nAChR may mediate binding of the non-native ligand Facinicline/RG3487, and mutation of one or more of these residues may increase the affinity of Facinicline/RG3487and/or other ligands for α7-nAChR. In some embodiments, the subject engineered receptor comprises a mutation in one or more amino acid residues of the ligand binding domain region of α7-nAChR or the ligand binding domain of a chimeric receptor that comprises the ligand binding domain region of α7-nAChR, where the one or more amino acid residues is selected from the group consisting of R101, Y115, T128, N120, N129, L131, L141, S170, W171, S172, S188, Y210, C212, C213 and Y217. In some embodiments, the one or more amino acid residues alters the binding of acetylcholine and/or nicotine to α7-nAChR, wherein the amino acid is selected from the group consisting of Y115, L131, L141, S170, W171, S172, C212 and Y217 of α7-nAChR. In certain such embodiments, the amino acid is selected from C212 and S170. In some embodiments, the mutation in the one or more amino acid residues alters the binding of ABT126 to α7-nAChR, wherein one or more amino acid residues is selected from the group consisting of R101, Y115, L131, L141, W171, S172, S188, Y210, and Y217 of α7-nAChR. In certain such embodiments, the amino acid is selected from R101, S188, and Y210. In some

embodiments, the mutation in the one or more amino acid residues alters the binding of TC6987 to α7-nAChR, wherein one or more amino acid residues is selected from the group consisting of R101, Y115, T128, N129, L131, L141, W171, S172, Y210, C212, C213 and Y217 of α7-nAChR. In certain such embodiments, the amino acid is selected from R101, T128, N129, Y210 and C213. In some embodiments, the mutation in the one or more amino acid residues alters the binding of Facinicline/RG3487 to α7-nAChR, wherein one or more amino acid residues is selected from the group consisting R101, N120, L131, L141, S170, W171, S172, Y210, and Y217 of α7-nAChR. In certain such embodiments, the amino acid is selected from Y210, R101, and N129.

[0160] In some embodiments, residues W85, R87, Y136, Y138, G146, N147, Y148, K149, S177, S178, L179, Y228, and Y229 of 5HT3 (SEQ ID NO:6) may mediate binding of serotonin, and mutations at one or more of these residues may reduce binding of serotonin to 5HT3. D64, I66, W85, R87, Y89, N123, G146, Y148, T176, S177, S178, W190, R191, F221, E224, Y228, Y229 and E231 of 5HT3 mediate binding of the non-native ligand Cilansetron, and mutation of one or more of these residues may increase the affinity of Cilansetron and/or other ligands for 5HT3. In some embodiments, the mutation is an amino acid substitution. In some embodiments, the subject engineered receptor comprises a mutation in one or more amino acid residues of the ligand binding domain region 5HT3A or the ligand binding domain of a chimeric receptor that comprises the ligand binding domain region of 5HT3, where the one or more amino acid residues is selected from the group consisting of D64, I66, W85, R87, Y89, N123, Y136, Y138, G146, N147, Y148, K149, T176, S177, S178, L179, W190, R191, F221, E224, Y228, Y229, and E231. In some embodiments, the mutation in the one or more amino acid residues alters the binding of serotonin to 5HT3, wherein the amino acid is selected from the group consisting of W85, R87, Y136, Y138, G146, N147, Y148, K149, S177, S178, L179, Y228, and Y229 of 5HT3A. In certain such embodiments, the amino acid is selected from Y136, Y138, N147, K149, and L179. In some embodiments, the mutation in the one or more amino acid residues alters the binding of Cilansetron to 5HT3 wherein one or more amino acid residues is selected from the group consisting of D64, I66, W85, R87, Y89, N123, G146, Y148, T176, S177, S178, W190, R191, F221, E224, Y228, Y229 and E231 of 5HT3A. In certain such embodiments, the amino acid is selected from D64, I66, Y89, N123, T176, W190, R191, F221, E224, and E231.

[0161] In some embodiment, the one or more mutations that affects the ability of a ligand to modulate the activity of the LGIC is located in the ion pore domain of the LGIC. In some embodiments, the mutation is an amino acid substitution. For example, residue T279 of

the serotonin receptor 5HT3A mediates the way in which the ligand modulates the activity of the channel, such that mutation of this residue to, *e.g.* serine (T279S), converts the effect from being antagonistic (i.e., reducing the activity of the LGIC) to agonistic (i.e. promoting the activity of the channel). In some embodiments, the subject ligand gated ion channel comprises a mutation in one or more amino acid residues of the ion pore domain of the human 5HT3A (SEQ ID NO:6) or the ion pore domain of a chimeric LGIC receptor that comprises the ion pore domain of 5HT3A, where the substitution is in an amino acid corresponding to 279 of SEQ ID NO:6. In certain embodiments, the substitution is a T279S substitution relative to SEQ ID NO:6.

[0162] The disclosure provides engineered receptors having two or more mutations, such as amino acid substitutions, as compared to the parental receptor. In some embodiments, the parental receptor comprises a ligand binding domain derived from human α7 nicotinic acetylcholine receptor (α7-nAChR). In some embodiments, the parental receptor is a chimeric receptor. In some embodiments, the parental receptor comprises an ion pore domain derived from a human Glycine receptor. In some embodiments, the human Glycine receptor is human Glycine receptor α1, human Glycine receptor α2, or human Glycine receptor α3. In some embodiments, the ligand binding domain of the engineered receptor comprises a Cys-loop domain derived from the human Glycine receptor. In some embodiments, the parental receptor comprises an amino acid sequence of SEQ ID NO: 33. In some embodiments, the engineered receptors comprise two amino acid substitutions as compared to the parental receptor comprising an amino acid sequence of SEQ ID NO: 33. In some embodiments, the ligand binding domain of the engineered receptor comprises a β1-2 loop domain from the human Glycine receptor α1 subunit.

[0163] In some embodiments, the ligand binding domain of the engineered receptor comprises amino acid substitutions at two or more amino acid residues selected from those corresponding to W77, R101, Y115, L131, Q139, Y140, S170, S172 and Y210 of human α7-nAChR (SEQ ID NO: 4).

[0164] In some embodiments, the two amino acid substitutions are at a pair of amino acid residues selected from the group consisting of L131 and S172, Y115 and S170, and Y115 and L131. In some embodiments, the ligand binding domain comprises two amino acid substitutions at a pair of amino acids residues selected from the group consisting of L131 and S172, Y115 and S170, and Y115 and L131. In some embodiments, the ligand binding domain comprises an amino acid substitution at residue L131 and the amino acid substitution of S172D. In some embodiments, the ligand binding domain comprises an amino acid substitution at

residue L131 and the amino acid substitution of Y115D. In some embodiments, the ligand binding domain comprises a pair of amino acid substitutions selected from the group consisting of L131S and S172D, L131T and S172D, L131D and S172D, Y115D and S170T, Y115D and L131Q, and Y115D and L131E. In some embodiments, the ligand binding domain comprises an amino acid substitution of L131E.

[0165] In some embodiments, the ligand binding domain comprises one or more amino acid substitutions at amino acids residues selected from the group consisting of Y140, R101, L131, Y115, and Y210, wherein the amino acid residues correspond to the amino acid residues of α7-nAChR. In some embodiments, the ligand binding domain comprises an amino acid substitution of R101W and/or Y210V. In some embodiments, the ligand binding domain comprises two or more amino acid substitutions at amino acid residues selected from the group consisting of R101, L131, Y115, Y210, and Y140. In some embodiments, the ligand binding domain comprises two amino acid substitutions at amino acid residues selected from the group consisting of R101, L131, Y115, Y210, and Y140. In some embodiments, the ligand binding domain comprises two amino acid substitutions at a pair of amino acid residues selected from the group consisting of: R101 and L131, Y115 and Y210, R101 and Y210. In some embodiments, the ligand binding domain comprises a pair of amino acid substitutions selected from the group consisting of R101F and L131G, R101F and L131D, Y115E and Y210W, R101W and Y210V, R101F and Y210V, R101F and Y210F, R101M and L131A, and R101M and L131F. In some embodiments, the ligand binding domain comprises three amino acid substitutions at the amino acid residues R101, Y115, and Y210. In some embodiments, the ligand binding domain comprises amino acid substitutions R101W, Y115E, and Y210W, or the amino acid substitutions R101F, Y115E, and Y210W.

[0166] In some embodiments, the ligand binding domain comprises an amino acid substitution at residue L131 and the amino acid substitution of R101F or R101M. In some embodiments, the amino acid substitution at residue L131 is L131G, L131D, L131A, L131F, or L131N.

[0167] In some embodiments, the ligand binding domain comprises a hydrophobic amino acid substitution at residue Y210 and the amino acid substitution of R101W or R101F. In some embodiments, the amino acid substitution at residue Y210 is Y210V, Y210F, or Y210W.

[0168] A person skilled in the art will readily recognize proper control receptor for comparison with the engineered receptor of the disclosure. In some embodiments, the control receptor is identical in sequence to the engineered receptor except for the one or more

distinguishing amino acid mutations (e.g., substitutions). In all cases, references to a control receptor is meant to indicate that the recited change of property (e.g., potency to a ligand) is the result of the amino acid mutation(s) of the engineered receptor of the disclosure.

[0169] The disclosure provides engineered receptors, wherein the engineered receptor is a chimeric ligand gated ion channel (LGIC) receptor and comprises: (a) a ligand binding domain derived from the human α7 nicotinic acetylcholine receptor (α7-nAChR) and comprising a Cys-loop domain from the human Glycine receptor α1 subunit; and (b) an ion pore domain derived from the human Glycine receptor α1 subunit. In some embodiments, the engineered receptor is derived from a parental engineered receptor comprising or consisting of an amino acid sequence of SEQ ID NO: 33, and further comprises one or more amino acid substitutions based on the parental engineered receptor.

[0170] In some embodiments, the potency of the engineered receptor to acetylcholine is lower than the potency of the human α7 nicotinic acetylcholine receptor (α7-nAChR) to acetylcholine. In some embodiments, the potency of the engineered receptor to acetylcholine is at least about 1.5-fold (for example, about 2-fold lower, about 3-fold, about 4-fold, about 5-fold, about 6-fold, about 7-fold, about 8-fold, about 9-fold, about 10-fold, about 12-fold, about 15-fold, about 20-fold, about 30-fold, about 40-fold, about 50-fold, about 60-fold, about 70-fold, about 80-fold, about 90-fold, or about 100-fold, including all subranges and values that lie therebetween) lower than the potency of the human α7 nicotinic acetylcholine receptor (α7-nAChR) to acetylcholine. In some embodiments, the potency of the engineered receptor to acetylcholine is evaluated by its EC50 for acetylcholine based on a cell reporter assay using YFP fluorescence quenching as described in Example 2 of the disclosure. In some embodiments, the EC50 of the engineered receptor to acetylcholine is at least 100 uM, at least 200 uM, at least 300 uM, at least 500 uM, at least 700 uM, at least 1 mM, at least 2 mM, at least 3 mM, at least 4 mM, at least 5 mM, at least 6 mM, at least 7 mM, at least 8 mM, at least 9 mM, or at least 10 mM. In some embodiments, the EC50 of the engineered receptor to acetylcholine is at least 1 mM. In some embodiments, the EC50 of the engineered receptor to acetylcholine is at least 3 mM. In some embodiments, having a higher EC50 for acetylcholine permits higher expression level of the engineered receptor in the cell or on the cell surface, without passing significant amount of current into the cell at the presence of physiological concentration of acetylcholine.

[0171] In some embodiments, the potency of the engineered receptor to a non-native ligand is about the same as the potency of the human α7 nicotinic acetylcholine receptor (α7-nAChR) to the non-native ligand. In some embodiments, the potency of the engineered receptor

to a non-native ligand is higher than the potency of the human α7 nicotinic acetylcholine receptor (α7-nAChR) to the non-native ligand. In some embodiments, the potency of the engineered receptor to the non-native ligand is at least about 1.5-fold (for example, about 2-fold lower, about 3-fold, about 4-fold, about 5-fold, about 6-fold, about 7-fold, about 8-fold, about 9-fold, about 10-fold, about 12-fold, about 15-fold, about 20-fold, about 30-fold, about 40-fold, about 50-fold, about 60-fold, about 70-fold, about 80-fold, about 90-fold, or about 100-fold, including all subranges and values that lie therebetween) higher than the potency of the human α7 nicotinic acetylcholine receptor (α7-nAChR) to the non-native ligand. In some embodiments, determining the potency comprises determining the EC50 based on a cell reporter assay using YFP fluorescence quenching as described in Example 2 of the disclosure. In some embodiments, the EC50 of the engineered receptor to a non-native ligand is less than 1 nM, less than 2 nM, less than 3 nM, less than 4 nM, less than 5 nM, less than 6 nM, less than 7 nM, less than 8 nM, less than 9 nM, less than 10 nM, less than 15 nM, less than 20 nM, less than 30 nM, less than 40 nM, less than 50 nM, less than 60 nM, less than 70 nM, less than 80 nM, less than 90 nM, less than 100 nM, less than 150 nM, less than 200 nM, less than 300 nM, less than 400 nM, less than 500 nM, less than 600 nM, less than 700 nM, less than 800 nM, less than 900 nM, less than 1 uM, less than 2 uM, less than 3 uM, less than 4 uM, less than 5 uM, less than 6 uM, less than 7 uM, less than 8 uM, less than 9 uM, or less than 10 uM. In some embodiments, the EC50 of the engineered receptor to a non-native ligand is less than 10 nM. In some embodiments, the EC50 of the engineered receptor to a non-native ligand is less than 100 nM. In some embodiments, the EC50 of the engineered receptor to a non-native ligand is less than 1 uM.

[0172] In some embodiments, the efficacy of the engineered receptor in the presence of a non-native ligand is higher than the efficacy the human α7 nicotinic acetylcholine receptor (α7-nAChR) in presence of the non-native ligand. In some embodiments, the efficacy of the engineered receptor in the presence of a non-native ligand is at least about 1.5-fold (for example, about 2-fold lower, about 3-fold, about 4-fold, about 5-fold, about 6-fold, about 7-fold, about 8-fold, about 9-fold, about 10-fold, about 12-fold, about 15-fold, about 20-fold, about 30-fold, about 40-fold, about 50-fold, about 60-fold, about 70-fold, about 80-fold, about 90-fold, or about 100-fold, including all subranges and values that lie therebetween) higher than the efficacy the human α7 nicotinic acetylcholine receptor (α7-nAChR) in presence of the non-native ligand. In some embodiments, determining the efficacy comprises determining the amount of current passed through the engineered receptor *in vitro* in the presence of the non-native ligand.

[0173] In some aspects, the subject ligand-gated ion channel comprises one or more non-desensitizing mutations. In some embodiments, the mutation is an amino acid substitution. When used in the context of a ligand-gated ion channel, "desensitization" refers to the progressive reduction in ionic flux in the prolonged presence of agonist. This results in a progressive loss of potency of the neuron to the ligand. By a non-desensitizing mutation, it is meant an amino acid mutation that prevents the LGIC from becoming desensitized to ligand, thereby preventing the neuron from becoming less responsive or nonresponsive to ligand. Non-desensitizing mutations can be readily identified by introducing the LGIC carrying the mutation into a neuron and analyzing the current flux over time during prolonged exposure to ligand. If the LGIC does not comprise a non-desensitizing mutation, the current will restore from peak to steady state during prolonged exposure, whereas if the LGIC comprises a non-desensitizing mutation, the current will remain at peak flux for the duration of exposure to ligand. Exemplary amino acid mutations that result in desensitization include a V322L mutation in the human GlyRα1 (V294L post-processing of the pro-protein to remove the signal peptide) and a L321V mutation in human GABA-A receptor GABRB3 (L296V post-processing of the pro-protein to remove the signal peptide). In some embodiments, the desensitizing mutation is the replacement of amino acid residues at or near the C-terminus of the LGIC with a desensitizing sequence, for example, a sequence having 90% identity or more to IDRLSRIAFPLLFGIFNLVYWATYLNREPQL (SEQ ID NO:53) derived from the C terminus of the protein encoded by GABAR1, *e.g.* the replacement of residues 455-479 in GABRR1 with IDRLSRIAFPLLFGIFNLVYWATYLNREPQL (SEQ ID NO:53). LGIC desensitization, methods for measuring desensitization of LGICs, and mutations that are non-desensitizing are well known in the art; see, *e.g.* Gielen et al. Nat Commun 2015 Apr 20, 6:6829, and Keramidas et al. Cell Mol Life Sci. 2013 Apr;70(7):1241-53, the full disclosures of which are incorporated herein by reference.

[0174] In some aspects, the subject ligand-gated ion channel comprises one or more conversion mutations. In some embodiments, the mutation is an amino acid substitution. By a conversion mutation, it is meant a mutation that changes the permeability of the ion pore domain of the LGIC such that it becomes permissive to the conductance of a non-native ion, i.e. an ion that does not naturally allow to pass through. In some cases, the mutation converts the permeability from cation to anion, for example the replacement of amino acid residues 260-281 in human α7-nAChR (CHRNA7) (EKISLGITVLLSLTVFMLLVAE, SEQ ID NO:54) or the corresponding amino acids in another cation-permeable LGIC with the peptide sequence PAKIGLGITVLLSLTTFMSGVAN (SEQ ID NO:55). In some cases, the mutation converts

the permeability from anion to cation, for example, the substitution of amino acid residue 279 of GLRA1 or the corresponding amino acid in another anion-permeable LGIC to glutamic acid (E), (which, as an A293E substitution in GLRA1 converts the LGIC from being anion-permissive to calcium-permissive), or the deletion of amino acid residue 278 of GLRA1 or the corresponding amino acid in another anion-permeable LGIC, the substitution of amino acid residue 279 of GLRA1 or the corresponding amino acid in another anion-permeable LGIC to glutamic acid (E), and the substitution of amino acid residue 293 of GLRA1 or the corresponding amino acid in another anion-permeable LGIC to valine (V) (which, as a P278Δ, A279E, T293V in GLRA1 converts the LGIC from being anion-permissive to cation-permissive).

[0175] Additional engineered receptors beyond those described herein can be readily identified by *in vitro* screening and validation methods. In some embodiments, a library of parental receptor mutants is generated from a limited number of parental receptors. The parental receptors can be mutated using methods known in the art, including error prone PCR. In some embodiments, the library of parental receptor mutants is then transfected into yeast or mammalian cells and screened in high throughput to identify functional receptors (*e.g.*, to identify parental receptor mutants that are capable of signaling in response to a ligand). In some embodiments, the functional parental receptor mutants identified in this primary screen is then expressed in mammalian cells and screened for potency to ligands, *e.g.* by the plate reader and/or electrophysiology assays described herein. The parental receptor mutants that demonstrate either increased binding affinity for agonist ligands, or that enable the use of antagonist or modulator ligands as agonists in the secondary screen can then be selected and carried though further *in vitro* and/or *in vivo* validation and characterization assays. Such screening assays are known in the art, for example Armbruster, B.N. *et al.* (2007) PNAS, 104, 5163–5168; Nichols, C.D. and Roth, B.L. (2009) Front. Mol. Neurosci. 2, 16; Dong, S. *et al.* (2010) Nat. Protoc. 5, 561–573; Alexander, G.M. *et al.* (2009) Neuron 63, 27–39; Guettier, J.M. *et al.* (2009) PNAS 106, 19197–19202; Ellefson J.W. *et al.* (2014) Nat Biotechnol. 32(1):97-101; Maranhao AC and Ellington AD. (2017) ACS Synth Biol. 20;6(1):108-119; Talwar S *et al.* (2013) PLoS One;8(3):e58479; Gilbert D.F. *et al.* (2009) Front Mol Neurosci. 30;2:17; Lynagh and Lynch, (2010), Biol Chem. 14:285(20), 14890–14897; Islam R. *et al.* (2016) ACS Chem Neurosci. 21;7(12):1647-1657; and Myers *et al.* (2008) Neuron. 8:58(3): 362–373.

C2. Exemplary chimeric LGICs

[0176] In some embodiments, the engineered receptor comprises a ligand binding domain derived from human α7-nAChR and the amino acid substitutions corresponding to L131S and S172D in the LBD of human α7-nAChR. In some embodiments, such an engineered receptor has a lower potency (*e.g.*, as determined by a higher EC50) for acetylcholine as compared to a control receptor without the substitutions or with only one of such substitutions. In some embodiments, such an engineered receptor substantially retains the potency (or has a higher potency) for a non-native ligand as compared to a control receptor without such substitutions or with only one of such substitutions. In some embodiments, the non-native ligand is CNL001. In some embodiments, the engineered receptor is a chimeric LGIC comprising a ligand binding domain derived from human α7-nAChR and an ion pore domain derived from human GlyRα1. In some embodiments, the engineered receptor is CODA534 (SEQ ID NO: 59), and the control receptor is CODA71, CODA333, or CODA377.

[0177] In some embodiments, the engineered receptor comprises a ligand binding domain derived from human α7-nAChR and the amino acid substitutions corresponding to L131T and S172D in the LBD of human α7-nAChR. In some embodiments, such an engineered receptor has a lower potency (*e.g.*, as determined by a higher EC50) for acetylcholine as compared to a control receptor without the substitutions or with only one of such substitutions. In some embodiments, such an engineered receptor has an EC50 for acetylcholine of >3 mM. In some embodiments, such an engineered receptor substantially retains the potency (or has a higher potency) for a non-native ligand as compared to a control receptor without such substitutions or with only one of such substitutions. In some embodiments, the non-native ligand is CNL001. In some embodiments, the engineered receptor is a chimeric LGIC comprising a ligand binding domain derived from human α7-nAChR and an ion pore domain derived from human GlyRα1. In some embodiments, the engineered receptor is CODA535 (SEQ ID NO: 60), and the control receptor is CODA71, CODA335, or CODA377.

[0178] In some embodiments, the engineered receptor comprises a ligand binding domain derived from human α7-nAChR and the amino acid substitutions corresponding to L131D and S172D in the LBD of human α7-nAChR. In some embodiments, such an engineered receptor has a lower potency (*e.g.*, as determined by a higher EC50) for acetylcholine as compared to a control receptor without such substitutions or with only one of such substitutions. In some embodiments, such an engineered receptor substantially retains the potency (or has a higher potency) for a non-native ligand as compared to a control receptor without such substitutions or with only one of such substitutions. In some embodiments, such

an engineered receptor has a higher potency (lower EC50) for CNL002 as compared to to a control receptor without such substitutions and/or with only one of such substitutions. In some embodiments, the non-native ligand for such an engineered receptor is CNL002, AZD-0328 or Facinicline. In some embodiments, the non-native ligand is Facinicline. In some embodiments, the non-native ligand is AZD-0328. In some embodiments, the non-native ligand is CNL002. In some embodiments, the engineered receptor is a chimeric LGIC comprising a ligand binding domain derived from human α7-nAChR and an ion pore domain derived from human GlyRα1. In some embodiments, the engineered receptor is CODA536 (SEQ ID NO: 58), and the control receptor is CODA71, CODA339, or CODA377.

[0179] In some embodiments, the engineered receptor comprises a ligand binding domain derived from human α7-nAChR and the amino acid substitutions corresponding to Y115D and S170T in the LBD of human α7-nAChR. In some embodiments, such an engineered receptor has a lower potency (*e.g.*, as determined by a higher EC50) for acetylcholine as compared to a control receptor without such substitutions and/or with only one of such substitutions (e.g., S170T only). In some embodiments, such an engineered receptor has an EC50 for acetylcholine of >3 mM. In some embodiments, such an engineered receptor substantially retains the potency (or has a higher potency) for a non-native ligand as compared to a control receptor without such substitutions or with only one of such substitutions (e.g., S170T only). In some embodiments, the non-native ligand for such an engineered receptor is Facinicline or TC-6987. In some embodiments, the non-native ligand is Facinicline. In some embodiments, the non-native ligand is TC-6987. In some embodiments, the engineered receptor is a chimeric LGIC comprising a ligand binding domain derived from human α7-nAChR and an ion pore domain derived from human GlyRα1. In some embodiments, the engineered receptor is CODA805 (SEQ ID NO: 63), and the control receptor is CODA71, CODA282, or CODA109.

[0180] In some embodiments, the engineered receptor comprises a ligand binding domain derived from human α7-nAChR and the amino acid substitutions corresponding to Y115D and L131Q in the LBD of human α7-nAChR. In some embodiments, such an engineered receptor has a lower potency (*e.g.*, as determined by a higher EC50) for acetylcholine as compared to a control receptor without such substitutions or with only one of such substitutions (e.g., L131Q only). In some embodiments, such an engineered receptor has an EC50 for acetylcholine of >3 mM. In some embodiments, such an engineered receptor substantially retains the potency (or has a higher potency) for a non-native ligand as compared to a control receptor without such substitutions or with only one of such substitutions. In some

embodiments, the non-native ligand for such an engineered receptor is AZD-0328, Facinicline, or TC-6987. In some embodiments, the non-native ligand is Facinicline. In some embodiments, the non-native ligand is AZD-0328. In some embodiments, the non-native ligand is TC-6987. In some embodiments, the engineered receptor is a chimeric LGIC comprising a ligand binding domain derived from human α7-nAChR and an ion pore domain derived from human GlyRα1. In some embodiments, the engineered receptor is CODA806 (SEQ ID NO: 62), and the control receptor is CODA71, CODA282, or CODA334.

[0181] In some embodiments, the engineered receptor comprises a ligand binding domain derived from human α7-nAChR and the amino acid substitutions corresponding to Y115D and L131E in the LBD of human α7-nAChR. In some embodiments, such an engineered receptor has a lower potency (*e.g.*, as determined by a higher EC50) for acetylcholine as compared to a control receptor without such substitutions or with only one of such substitutions. In some embodiments, such an engineered receptor substantially retains the potency (or has a higher potency) for a non-native ligand as compared to a control receptor without such substitutions or with only one of such substitutions. In some embodiments, the non-native ligand ligand for such an engineered receptor is TC-5619, AZD-0328, Facinicline or TC-6987. In some embodiments, the non-native ligand is TC-5619. In some embodiments, the non-native ligand is Facinicline. In some embodiments, the non-native ligand is AZD-0328. In some embodiments, the non-native ligand is TC-6987. In some embodiments, the engineered receptor is a chimeric LGIC comprising a ligand binding domain derived from human α7-nAChR and an ion pore domain derived from human GlyRα1. In some embodiments, the engineered receptor is CODA807 (SEQ ID NO: 61), and the control receptor is CODA71, CODA282, or CODA340.

[0182] In some embodiments, the engineered receptor comprises a ligand binding domain derived from human α7-nAChR and the amino acid substitutions corresponding to R101F and L131G in the LBD of human α7-nAChR. In some embodiments, such an engineered receptor has a lower potency (*e.g.*, as determined by a higher EC50) for acetylcholine as compared to a control receptor without such substitutions or with only one of such substitutions. In some embodiments, such an engineered receptor substantially retains the potency (or has a higher potency) for a non-native ligand as compared to a control receptor without such substitutions or with only one of such substitutions. In some embodiments, the non-native ligands for such an engineered receptor is CNL001, TC-5619, CNL002, AZD-0328, TC-6987, or Varenicline. In some embodiments, the non-native ligand is CNL001. In some embodiments, the non-native ligand is TC-5619. In some embodiments, the non-native ligand

is CNL002. In some embodiments, the non-native ligand is AZD-0328. In some embodiments, the non-native ligand is TC-6987. In some embodiments, the non-native ligand is Varenicline. In some embodiments, the engineered receptor is a chimeric LGIC comprising a ligand binding domain derived from human α7-nAChR and an ion pore domain derived from human GlyRα1. In some embodiments, the engineered receptor is CODA1025 (SEQ ID NO: 65), and the control receptor is CODA71, CODA236, or CODA325.

[0183] In some embodiments, the engineered receptor comprises a ligand binding domain derived from human α7-nAChR and the amino acid substitutions corresponding to R101F and L131D in the LBD of human α7-nAChR. In some embodiments, such an engineered receptor has a lower potency (*e.g.*, as determined by a higher EC50) for acetylcholine as compared to a control receptor without such substitutions or with only one of such substitutions. In some embodiments, such an engineered receptor substantially retains the potency (or has a higher potency) for a non-native ligand as compared to a control receptor without such substitutions or with only one of such substitutions. In some embodiments, the non-native ligands for such an engineered receptor is CNL001, TC-5619, CNL002, or TC-6987. In some embodiments, the non-native ligand is CNL001. In some embodiments, the non-native ligand is TC-5619. In some embodiments, the non-native ligand is CNL002. In some embodiments, the non-native ligand is TC-6987. In some embodiments, the engineered receptor is a chimeric LGIC comprising a ligand binding domain derived from human α7-nAChR and an ion pore domain derived from human GlyRα1. In some embodiments, the engineered receptor is CODA1027 (SEQ ID NO: 66), and the control receptor is CODA71, CODA236, or CODA339.

[0184] In some embodiments, the engineered receptor comprises a ligand binding domain derived from human α7-nAChR and the amino acid substitutions corresponding to Y115E and Y210W in the LBD of human α7-nAChR. In some embodiments, such an engineered receptor has a lower potency (*e.g.*, as determined by a higher EC50) for acetylcholine as compared to a control receptor without such substitutions or with only one of such substitutions. In some embodiments, such an engineered receptor substantially retains the potency (or has a higher potency) for a non-native ligand as compared to a control receptor without such substitutions or with only one of such substitutions. In some embodiments, the non-native ligand for such an engineered receptor is TC-5619, ABT-0126 or CNL002. In some embodiments, the non-native ligand is TC5619/Bradanicline. In some embodiments, the non-native ligand is ABT-0126. In some embodiments, the non-native ligand is CNL002. In some embodiments, the engineered receptor is a chimeric LGIC comprising a ligand binding domain

derived from human α7-nAChR and an ion pore domain derived from human GlyRα1. In some embodiments, the engineered receptor is CODA1039 (SEQ ID NO: 67), and the control receptor is CODA71, CODA283, or CODA409.

[0185] In some embodiments, the engineered receptor comprises a ligand binding domain derived from human α7-nAChR and the amino acid substitutions corresponding to R101W and Y210V in the LBD of human α7-nAChR. In some embodiments, such an engineered receptor has a lower potency (*e.g.*, as determined by a higher EC50) for acetylcholine as compared to a control receptor without such substitutions or with only one of such substitutions. In some embodiments, such an engineered receptor has an EC50 for acetylcholine of >3 mM. In some embodiments, such an engineered receptor substantially retains the potency (or has a higher potency) for a non-native ligand as compared to a control receptor without such substitutions or with only one of such substitutions. In some embodiments, the non-native ligand is TC-5619/bradanicline. In some embodiments, the engineered receptor is a chimeric LGIC comprising a ligand binding domain derived from human α7-nAChR and an ion pore domain derived from human GlyRα1. In some embodiments, the engineered receptor is CODA1045 (SEQ ID NO: 68), and the control receptor is CODA71, CODA238, or CODA405.

[0186] In some embodiments, the engineered receptor comprises a ligand binding domain derived from human α7-nAChR and the amino acid substitutions corresponding to R101F and Y210V in the LBD of human α7-nAChR. In some embodiments, such an engineered receptor has a lower potency (*e.g.*, as determined by a higher EC50) for acetylcholine as compared to a control receptor without such substitutions or with only one of such substitutions (e.g., R101F). In some embodiments, such an engineered receptor has an EC50 for acetylcholine of >3 mM. In some embodiments, such an engineered receptor substantially retains the potency (or has a higher potency) for a non-native ligand as compared to a control receptor without such substitutions or with only one of such substitutions (e.g., Y210V). In some embodiments, the non-native ligand is TC-5619/Bradanicline. In some embodiments, the engineered receptor is a chimeric LGIC comprising a ligand binding domain derived from human α7-nAChR and an ion pore domain derived from human GlyRα1. In some embodiments, the engineered receptor is CODA1047 (SEQ ID NO: 69), and the control receptor is CODA71, CODA236, or CODA405.

[0187] In some embodiments, the engineered receptor comprises a ligand binding domain derived from human α7-nAChR and the amino acid substitutions corresponding to R101F and Y210F in the LBD of human α7-nAChR. In some embodiments, such an engineered

receptor has a lower potency (*e.g.*, as determined by a higher EC50) for acetylcholine as compared to a control receptor without such substitutions or with only one of such substitutions. In some embodiments, such an engineered receptor has an EC50 for acetylcholine of >1 mM. In some embodiments, such an engineered receptor substantially retains the potency (or has a higher potency) for a non-native ligand as compared to a control receptor without such substitutions or with only one of such substitutions. In some embodiments, such an engineered receptor has an EC50 of <= about 10 nM for CNL001 and/or an EC50 of <= about 30 nM for TC5619/Bradanicline. In some embodiments, the non-native ligand for such an engineered receptor is CNL001 or TC5619/Bradanicline. In some embodiments, the non-native ligand is CNL001. In some embodiments, the non-native ligand is TC5619/Bradanicline. In some embodiments, the engineered receptor is a chimeric LGIC comprising a ligand binding domain derived from human α7-nAChR and an ion pore domain derived from human GlyRα1. In some embodiments, the engineered receptor is CODA1048 (SEQ ID NO: 70), and the control receptor is CODA71, CODA236, or CODA407.

[0188] In some embodiments, the engineered receptor comprises a ligand binding domain derived from human α7-nAChR and the amino acid substitutions corresponding to R101M and L131A in the LBD of human α7-nAChR. In some embodiments, such an engineered receptor has a lower potency (*e.g.*, as determined by a higher EC50) for acetylcholine as compared to a control receptor without such substitutions or with only one of such substitutions. In some embodiments, such an engineered receptor has an EC50 for acetylcholine of >1 mM. In some embodiments, such an engineered receptor substantially retains the potency (or has a higher potency) for a non-native ligand as compared to a control receptor without such substitutions or with only one of such substitutions. In some embodiments, such an engineered receptor has an EC50 of <= about 10 nM for CNL001, an EC50 of <= about 3 nM for TC5619/Bradanicline, and/or an EC50 of <= about 3 nM for Varenicline. In some embodiments, the non-native ligand for such an engineered receptor is CNL001, TC5619/Bradanicline, or Varenicline. In some embodiments, the non-native ligand is CNL001. In some embodiments, the non-native ligand is TC5619/Bradanicline. In some embodiments, the non-native ligand is Varenicline. In some embodiments, the engineered receptor is a chimeric LGIC comprising a ligand binding domain derived from human α7-nAChR and an ion pore domain derived from human GlyRα1. In some embodiments, the engineered receptor is CODA1053 (SEQ ID NO: 71), and the control receptor is CODA71, CODA237, or CODA326.

[0189] In some embodiments, the engineered receptor comprises a ligand binding domain derived from human α7-nAChR and the amino acid substitutions corresponding to R101M and L131F in the LBD of human α7-nAChR. In some embodiments, such an engineered receptor has a lower potency (*e.g.*, as determined by a higher EC50) for acetylcholine as compared to a control receptor without such substitutions or with only one of such substitutions. In some embodiments, such an engineered receptor has an EC50 for acetylcholine of >1 mM or >3 mM. In some embodiments, such an engineered receptor substantially retains the potency (or has a higher potency) for a non-native ligand as compared to a control receptor without such substitutions or with only one of such substitutions In some embodiments, such an engineered receptor has an EC50 of <= about 1 nM for CNL001, and/or an EC50 of <= about 3 nM for Varenicline. . In some embodiments, the non-native ligand is CNL001, TC5619/Bradanicline, or Varenicline. In some embodiments, the non-native ligand is CNL001. In some embodiments, the non-native ligand is TC5619/Bradanicline. In some embodiments, the non-native ligand is Varenicline. In some embodiments, the engineered receptor is a chimeric LGIC comprising a ligand binding domain derived from human α7-nAChR and an ion pore domain derived from human GlyRα1. In some embodiments, the engineered receptor is CODA1054 (SEQ ID NO: 72), and the control receptor is CODA71, CODA237, or CODA330.

[0190] In some embodiments, the engineered receptor comprises a ligand binding domain derived from human α7-nAChR and the amino acid substitutions corresponding to R101W, Y115E and Y210W in the LBD of human α7-nAChR. In some embodiments, such an engineered receptor has a lower potency (*e.g.*, as determined by a higher EC50) for acetylcholine as compared to a control receptor without such substitutions or with only one or two of such substitutions. In some embodiments, such an engineered receptor has an EC50 for acetylcholine of >3 mM or >10 mM. In some embodiments, such an engineered receptor substantially retains the potency (or has a higher potency) for a non-native ligand as compared to a control receptor without such substitutions or with only one or two of such substitutions. In some embodiments, the non-native ligand is TC-5619/Bradanicline. In some embodiments, such an engineered receptor has an EC50 of <= about 1 nM for TC-5619/Bradanicline. In some embodiments, the engineered receptor is a chimeric LGIC comprising a ligand binding domain derived from human α7-nAChR and an ion pore domain derived from human GlyRα1. In some embodiments, the engineered receptor is CODA1055 (SEQ ID NO: 73), and the control receptor is CODA71, CODA238, CODA283, or CODA409.

[0191] In some embodiments, the engineered receptor comprises a ligand binding domain derived from human α7-nAChR and the amino acid substitutions corresponding to R101F, Y115E and Y210W in the LBD of human α7-nAChR. In some embodiments, such an engineered receptor has a lower potency (*e.g.*, as determined by a higher EC50) for acetylcholine as compared to a control receptor without such substitutions or with only one or two of such substitutions. In some embodiments, such an engineered receptor has an EC50 for acetylcholine of >3 mM or >10 mM. In some embodiments, such an engineered receptor substantially retains the potency (or has a higher potency) for a non-native ligand as compared to a control receptor without such substitutions or with only one or two of such substitutions. In some embodiments, the non-native ligand is TC-5619/Bradanicline. In some embodiments, such an engineered receptor has an EC50 of <= about 10 nM for TC-5619/Bradanicline. In some embodiments, the engineered receptor is a chimeric LGIC comprising a ligand binding domain derived from human α7-nAChR and an ion pore domain derived from human GlyRα1. In some embodiments, the engineered receptor is CODA1056 (SEQ ID NO: 74), and the control receptor is CODA71, CODA236, CODA283, or CODA409.

[0192] In some embodiments, the engineered receptor comprises a ligand binding domain derived from human α7-nAChR and the amino acid substitutions corresponding to W77F, R101F and L131D in the LBD of human α7-nAChR. In some embodiments, such an engineered receptor has a lower potency (*e.g.*, as determined by a higher EC50) for acetylcholine as compared to a control receptor without such substitutions or with only one or two of such substitutions. In some embodiments, such an engineered receptor has an EC50 for acetylcholine of >1 mM or >3 mM. In some embodiments, such an engineered receptor substantially retains the potency (or has a higher potency) for a non-native ligand as compared to a control receptor without such substitutions or with only one or two of such substitutions. In some embodiments, such an engineered receptor has an EC50 of <= about 10 nM for CNL002. In some embodiments, the non-native ligand is CNL001, CNL002, or ABT-126. In some embodiments, the non-native ligand is CNL001. In some embodiments, the non-native ligand is CNL002. In some embodiments, the non-native ligand is ABT-126. In some embodiments, the engineered receptor is a chimeric LGIC comprising a ligand binding domain derived from human α7-nAChR and an ion pore domain derived from human GlyRα1. In some embodiments, the engineered receptor is CODA1138 (SEQ ID NO: 75), and the control receptor is CODA71, CODA217, CODA236, or CODA339.

[0193] In some embodiments, the engineered receptor comprises a ligand binding domain derived from human α7-nAChR and the amino acid substitutions corresponding to

R101F, L131N, and S172D in the LBD of human α7-nAChR. In some embodiments, such an engineered receptor has a lower potency (*e.g.*, as determined by a higher EC50) for acetylcholine as compared to a control receptor without such substitutions or with only one or two of such substitutions. In some embodiments, such an engineered receptor has an EC50 for acetylcholine of >1 mM or >3 mM. In some embodiments, such an engineered receptor substantially retains the potency (or has a higher potency) for a non-native ligand as compared to a control receptor without such substitutions or with only one or two of such substitutions. In some embodiments, such an engineered receptor has an EC50 of <= about 1 nM for CNL001, or an EC50 of <= about 10 nM for CNL002. In some embodiments, the non-native ligand is CNL001 or CNL002. In some embodiments, the non-native ligand is CNL001. In some embodiments, the non-native ligand is CNL002. In some embodiments, the engineered receptor is a chimeric LGIC comprising a ligand binding domain derived from human α7-nAChR and an ion pore domain derived from human GlyRα1. In some embodiments, the engineered receptor is CODA1140 (SEQ ID NO: 76), and the control receptor is CODA71, CODA236, CODA337, or CODA377.

[0194] In some embodiments, the engineered receptor comprises a ligand binding domain derived from human α7-nAChR and the amino acid substitutions corresponding to Q139E and S172D in the LBD of human α7-nAChR. In some embodiments, such an engineered receptor has a lower potency (*e.g.*, as determined by a higher EC50) for acetylcholine as compared to a control receptor without such substitutions or with only one of such substitutions (e.g., S172D). In some embodiments, such an engineered receptor substantially retains the potency (or has a higher potency) for a non-native ligand as compared to a control receptor without such substitutions or with only one of such substitutions. In some embodiments, the non-native ligand is CNL001 or CNL002. In some embodiments, the non-native ligand is CNL001. In some embodiments, the non-native ligand is CNL002. In some embodiments, the engineered receptor is a chimeric LGIC comprising a ligand binding domain derived from human α7-nAChR and an ion pore domain derived from human GlyRα1. In some embodiments, the engineered receptor is CODA1157 (SEQ ID NO: 77), and the control receptor is CODA71, CODA945, or CODA377.

[0195] In some embodiments, the engineered receptor comprises a ligand binding domain derived from human α7-nAChR and the amino acid substitutions corresponding to S172D and Y210W in the LBD of human α7-nAChR. In some embodiments, such an engineered receptor has a lower potency (*e.g.*, as determined by a higher EC50) for acetylcholine as compared to a control receptor without such substitutions or with only one of

such substitutions. In some embodiments, such an engineered receptor has an EC50 for acetylcholine of >3 mM or >10 mM. In some embodiments, such an engineered receptor substantially retains the potency (or hasa higher potency) for a non-native ligand as compared to a control receptor without such substitutions or with only one of such substitutions. In some embodiments, such an engineered receptor has an EC50 of <= about 10 nM for CNL001. In some embodiments, the non-native ligand for such an engineered receptor is CNL001, CNL002, or ABT-126. In some embodiments, the non-native ligand is CNL001. In some embodiments, the non-native ligand is CNL002. In some embodiments, the non-native ligand is ABT-126. In some embodiments, the engineered receptor is a chimeric LGIC comprising a ligand binding domain derived from human α7-nAChR and an ion pore domain derived from human GlyRα1. In some embodiments, the engineered receptor is CODA1173 (SEQ ID NO: 78), and the control receptor is CODA71, CODA377, or CODA409.

[0196] In some embodiments, the engineered receptor comprises a ligand binding domain derived from human α7-nAChR and an amino acid substitution at the amino acid residue corresponding to Y140 of human α7-nAChR. In some embodiments, the amino acid substitution is Y140I. In some embodiments, such an engineered receptor has a lower potency (*e.g.*, as determined by a higher EC50) for acetylcholine as compared to a control receptor without such a substitution. In some embodiments, the engineered receptor is a chimeric LGIC comprising a ligand binding domain derived from human α7-nAChR and an ion pore domain derived from human GlyRα1 (e.g., CODA952, SEQ ID NO: 64) and the control receptor is CODA71 (SEQ ID NO: 33). In some embodiments, such an engineered receptor substantially retains the potency (or has a higher potency) for a non-native ligand as compared to a control receptor without such a substitution. In some embodiments, the non-native ligand for such an engineered receptor is CNL001, TC-5619/Bradanicline, CNL002, or Facinicline. In some embodiments, the non-native ligand is CNL001. In some embodiments, the non-native ligand is TC-5619/Bradanicline. In some embodiments, the non-native ligand is CNL002. In some embodiments, the non-native ligand is Facinicline.

[0197] In some embodiments, the engineered receptor comprises a ligand binding domain derived from human α7-nAChR and an amino acid substitution at the amino acid residue corresponding to Y140 of human α7-nAChR. In some embodiments, the amino acid substitution is Y140C. In some embodiments, such an engineered receptor has a lower potency (*e.g.*, as determined by a higher EC50) for acetylcholine as compared to a control receptor without such a substitution. In some embodiments, the engineered receptor is a chimeric LGIC comprising a ligand binding domain derived from human α7-nAChR and an ion pore domain

derived from human GlyRα1 (e.g., CODA965, SEQ ID NO: 88) and the control receptor is CODA71 (SEQ ID NO: 33). In some embodiments, such an engineered receptor substantially retains the potency (or has a higher potency) for a non-native ligand as compared to a control receptor without such a substitution. In some embodiments, the non-native ligand for such an engineered receptor is CNL001, TC-5619/Bradanicline, CNL002, ABT-126, or TC-6987. In some embodiments, the non-native ligand is CNL001. In some embodiments, the non-native ligand is TC-5619/Bradanicline. In some embodiments, the non-native ligand is CNL002. In some embodiments, the non-native ligand is ABT-126. In some embodiments, the non-native ligand is TC-6987.

[0198] A summary of these exemplary engineered receptors is provided below in Table 10.

Table 10: Exemplary Engineered Receptors

SEQ ID NO:	**Name**	**Sequence**
SEQ ID NO: 58	CODA536	L131D, S172D in SEQ ID NO: 33
SEQ ID NO: 59	CODA534	L131S, S172D in SEQ ID NO: 33
SEQ ID NO: 60	CODA535	L131T, S172D in SEQ ID NO: 33
SEQ ID NO: 61	CODA807	Y115D, L131E in SEQ ID NO: 33
SEQ ID NO: 62	CODA806	Y115D, L131Q in SEQ ID NO: 33
SEQ ID NO: 63	CODA805	Y115D, S170T in SEQ ID NO: 33
SEQ ID NO: 64	CODA952	Y140I in SEQ ID NO: 33
SEQ ID NO: 65	CODA1025	R101F, L131G in SEQ ID NO: 33
SEQ ID NO: 66	CODA1027	R101F, L131D in SEQ ID NO: 33
SEQ ID NO: 67	CODA1039	Y115E, Y210W in SEQ ID NO: 33
SEQ ID NO: 68	CODA1045	R101W, Y210V in SEQ ID NO: 33
SEQ ID NO: 69	CODA1047	R101F, Y210V in SEQ ID NO: 33
SEQ ID NO: 70	CODA1048	R101F, Y210F in SEQ ID NO: 33
SEQ ID NO: 71	CODA1053	R101M, L131A in SEQ ID NO: 33
SEQ ID NO: 72	CODA1054	R101M, L131F in SEQ ID NO: 33
SEQ ID NO: 73	CODA1055	R101W, Y115E, Y210W in SEQ ID NO: 33
SEQ ID NO: 74	CODA1056	R101F, Y115E, Y210W in SEQ ID NO: 33
SEQ ID NO: 75	CODA1138	W77F, R101F, L131D in SEQ ID NO: 33
SEQ ID NO: 76	CODA1140	R101F, L131N, S172D in SEQ ID NO: 33

SEQ ID NO:	Name	Sequence
SEQ ID NO: 77	CODA1157	Q139E, S172D in SEQ ID NO: 33
SEQ ID NO: 78	CODA1173	S172D, Y210W in SEQ ID NO: 33
SEQ ID NO: 88	CODA965	Y140C in SEQ ID NO: 33

D. Ligands

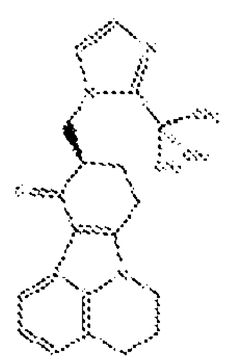
[0199] In some embodiments, the ligands of the disclosure refer to exogenous drugs or compounds with a known mechanism of action on a mammalian cell (*e.g.*, are known to act as an agonist, antagonist, or modulator of a receptor). Such ligands may also be referred to as "binding agents". Ligands of the disclosure can include proteins, lipids, nucleic acids, and/or small molecules. In some embodiments, ligands include drugs or compounds that have been approved by the US Food and Drug Administration (FDA) for clinical use in the treatment of a particular disease (*e.g.*, a neurological disease). In some embodiments, ligands include drugs or compounds that have not been approved by the FDA for clinical use, but have been tested in one or more clinical trials, are currently being tested in one or more clinical trials, and/or are anticipated to be tested in one or more clinical trials. In some embodiments, ligands include drugs or compounds that have not been approved by the FDA for clinical use, but are routinely used in laboratory research. In some embodiments, the ligand is an analog of one of the aforementioned ligands. In particular embodiments, a ligand is selected from any one of the ligands in **Tables 2 – 9** below. In some embodiments, the ligand is selected from the group consisting of AZD0328, ABT-126, AQW-051, Cannabidiol, Cilansetron, PH-399733, FACINICLINE/RG3487/MEM-3454, TC-6987, CNL002, and TC-5619/AT-101. In some embodiments, the ligand is selected from the group consisting of ABT-126, AZD-0328, CNL002, RG3487, TC-6987, CNL001, TC-6683, Varenicline, and TC-5619.

[0200] In particular embodiments, the ligand is an analog of Cilansetron, *e.g.* as described by one of the compound formulas 2-7 below in either its R or S enantiomer:

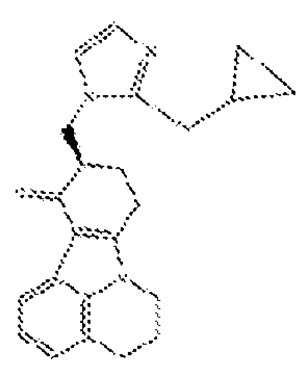
Compound 1 = cilansetron
(-CH3)



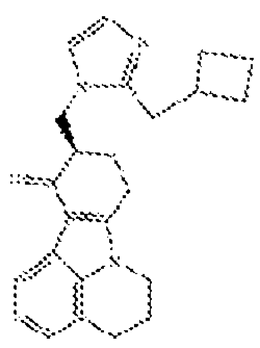
Compound 2
(-tBu)



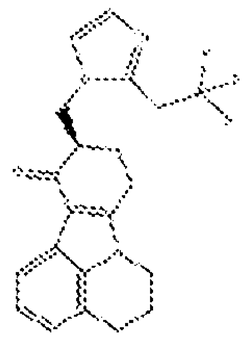
Compound 3
(-CH2-cyclopropyl)



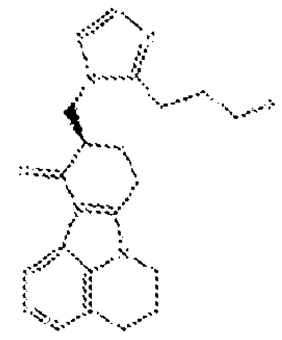
Compound 4
(-CH2-cyclobutyl)



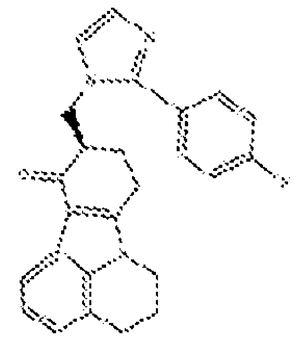
Compound 5
(-CH2CF3)



Compound 6
(-Ch2Ch2Ch2F)

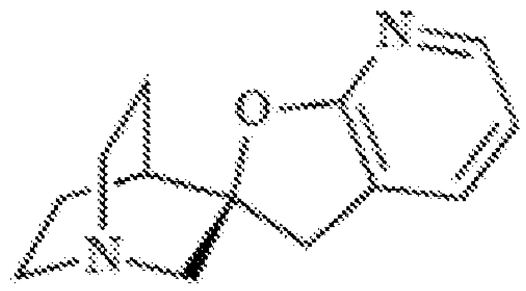


Compound 7
(-p-F-Phenyl)



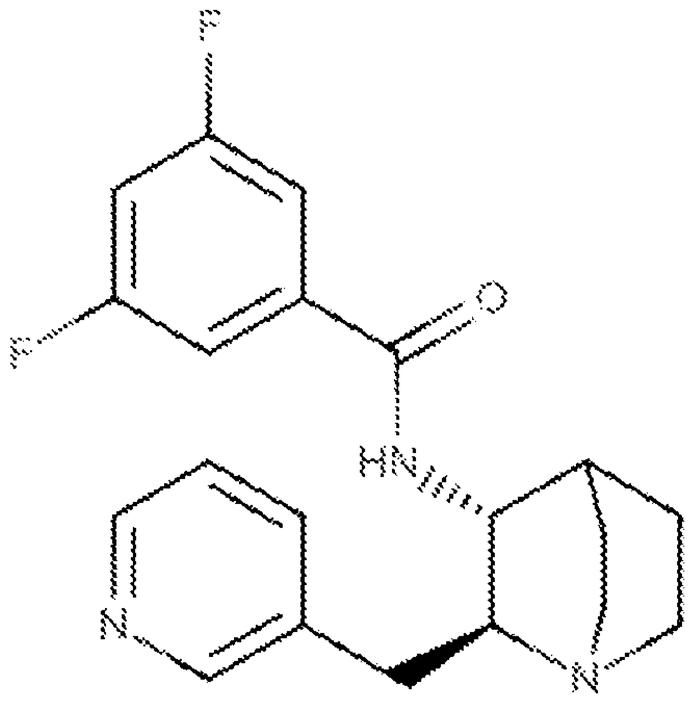
[0201] In some embodiments, the ligand acts as an agonist. The term "agonist" as used herein refers to a ligand that induces a signaling response. In some embodiments, the ligand acts as an antagonist. The term antagonist is used herein to refer to a ligand that inhibits a signaling response.

[0202] In some embodiments, the ligand is AZD-0328 according to the formula below:

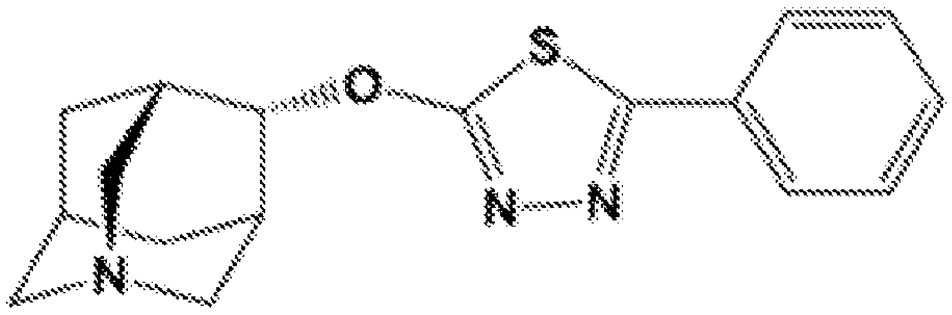


AZD0328

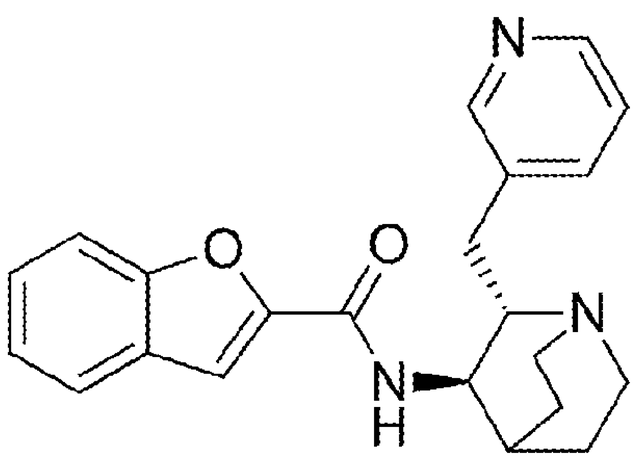
[0203] In some embodiments, the ligand is TC-6987 according to the formula below:



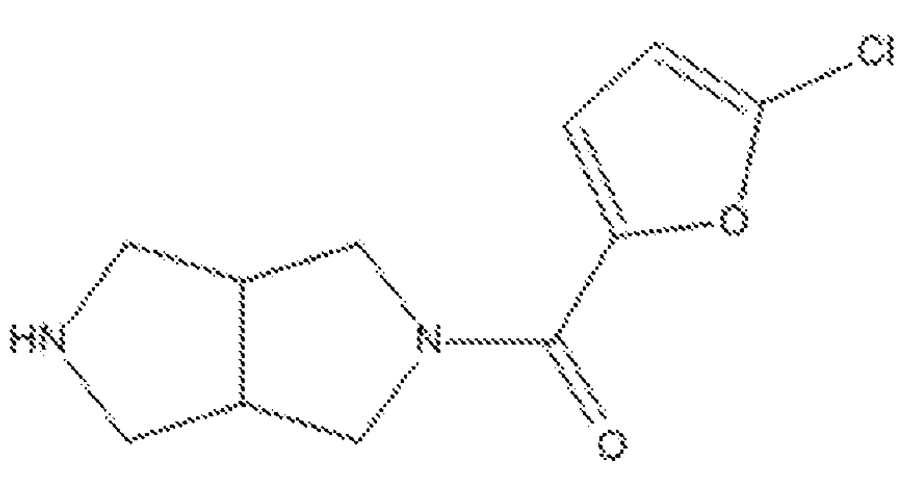
[0204] In some embodiments, the ligand is ABT-126 according to the formula below:



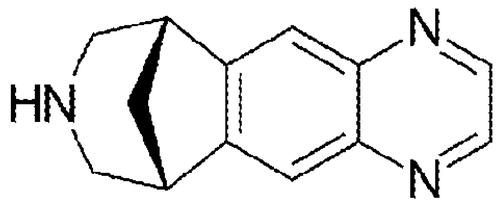
[0205] In some embodiments, the ligand is TC-5619/Bradanicline according to the formula below:



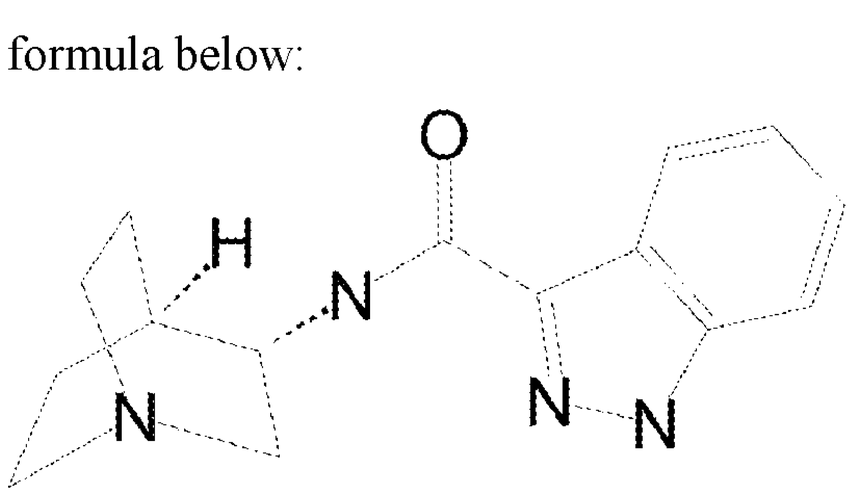
[0206] In some embodiments, the ligand is TC-6683 according to the formula below:



[0207] In some embodiments, the ligand is Varenicline according to the formula below:



[0208] In some embodiments, the ligand is Facinicline/RG3487 according to the formula below:



[0209] In some embodiments, the ligand is CNL001.

[0210] In some embodiments, the ligand is CNL002.

[0211] In some embodiments, the ligand is an anxiolytic, anticonvulsant, antidepressant, antipsychotic, antiemetic, nootropic, antibiotic, antifungal, antiviral, or an antiparasitic.

Table 2: Ligands for Glycine Receptor (GlyR)

Agonists		**Modulators/Binders**	**Antagonists**	
Bilobalide	L-Serine	Gavestinel	468816	Lindane
Cannabidiol	MDL-27531	Halothane	ACEA-2085	MDL-100748
D-Alanine	Methoxyflurane		Bicuculline	MDL-102288
D-Serine	Milacemide		Brucine	MDL-105519
Desflurane	Moxidectin		Caffeine	PD-165650
Doramectin	NRX-1050		Gavestinel	Picrotoxin
Emamectin	NRX-1060		Ginkgo biloba	Strychnine
Eprinomectin	P-9939		GV-196771	Thiocolchicoside
Ethanol	Quisqualamine		GW 468816	Tutin
Glycine	Rapastinel		HMR-2371	UK-315716
Hypotaurine	S-18841		L-695902	ZD-9379
Isoflurane	Sarcosine		L-701324	
Ivermectin	Sevoflurane			
L-Alanine	Taurine			
L-Proline	β-Alanine			

Table 3: Ligands for λ-Aminobutyric Acid A Receptor (GABA-A)

Agonists	**Modulators/Binders**			**Antagonists**
3-acyl-4-quinolone	(−)Epigallo-catechin-3-Gallate	Etifoxine	Pentobarbital	(±)-cis-(3-Aminocyclopentyl) butylphosphinic acid
Acamprosate	10-Methoxy-yangonin	Etizolam	Petrichloral	(S)-(4-Aminocyclopent-1-enyl)butylphosphinic acid
Alfadolone	11-Hydroxy-yangonin	Etomidate	PF-4480682	Amoxapine
Bamaluzole	11-Methoxy-12-Hydroxy-dehydrokavain	Evt-201	Phenazepam	Bicuculline
Basmisanil	11-Methoxy-yangonin	Fasiplon	Phenobarbital	CGP-36742 (3-aminopropyl-n-butyl-phosphinic acid)
Bretazenil	123i-Iomazenil	Fg-8205	Pinazepam	Flumazenil
CACA	2-Oxoquazepam	Fletazepam	Pipequaline	Gabazine
CAMP	3-Hydroxy-phenazepam	Flubromazepam	Pivoxazepam	Ginkgo biloba
CP-409092	5-Hydroxykavain	Flubromazolam	Potassium Bromide	Lindane

Agonists	Modulators/Binders			Antagonists
Doramectin	5,6-Dehydro-methysticin	Fludiazepam	Prazepam	Methohexital
Emamectin	5,6-Dihydro-yangonin	Flumazenil	Premazepam	Picrotoxin
Eprinomectin	5,6,7,8-Tetrahydro-yangonin	Flunitrazepam	Primidone	SKF-97541 (3-Aminopropyl (methyl)phosphinic acid)
Eszopiclone	7,8-Dihydrokavain	Flurazepam	Proflazepam	TPMPA
Ethanol	7,8-Dihydro-methysticin	Flutazolam	Propanidid	ZAPA ((Z)-3-[(Aminoiminomethyl)thio]prop-2-enoic acid)
Etomidate	7,8-Dihydro-yangonin	Flutemazepam	Propofol	
Flunitrazepam	Abecarnil	Flutoprazepam	PWZ-007A	
GABA	Adinazolam	Fosazepam	PWZ-009A1	
Gabamide	Allobarbital	Fospropofol	Pwz-029	
GABOB	Allo-pregnanolone	Ganaxolone	Pyrazolam	
Gaboxadol	Alphaxolone	Gbld-345	PZ-II-028	
Gamma Hydroxybutyric Acid	Alphenal	Gedocarnil	PZ-II-029	
Glutethimide	Alpidem	Gidazepam	Qh-Ii-66	
Ibotenic acid	Alprazolam	Girisopam	Quazepam	
Imidazenil	Amentoflavone	Glutethimide	Quinidine Barbiturate	
Isoflurane	Amobarbital	Gyki-52466	Reclazepam	
Isoguvacine	Apigenin	Gyki-52895	Remimazolam	
Isonipecotic acid	Aprobarbital	Halazepam	Rilmazafone	
Ivermectin	Arfendazam	Haloxazolam	Ripazepam	
L-830982	Avizafone	Heptabarbital	Ro15-4513	
Meprobamate	AZD7325	Hexobarbital	Ro48-6791	
Methoxyflurane	Baicalein	Iclazepam	Ro48-8684	
MK-0777/L83098	Baicalin	Imidazenil	Ro4938581	
Methyprylon	Barbital	Indiplon	Rwj-51204	
Moxidectin	Barbituric Acid Derivative	Irazepine	Saripidem	
Muscimol	Bentazepam	Kavain	Sarmazenil	
N4-Chloroacetyl-cytosine arabinoside	Brallobarbital	Kenazepine	Sb-205,384	
Pagoclone	Bretazenil	Ketazolam	Scutellarein	
Phenibut	Bromazepam	L-655708	Secobarbital	
Picamilon	Brotizolam	L-838,417	Sevoflurane	

Agonists	Modulators/Binders			Antagonists
Piperazine	Butalbital	Lanthanum	Sh-053-R-Ch3-2′F	
Piperidine-4-sulfonic acid	Butethal	LAU 156	Skull-capflavone II	
Progabide	Butobarbital	LAU 157	Sl-651,498	
QH-ii-066	Camazepam	LAU 159	Sodium Amytal	
Quisqualamine	Carburazepam	LAU 161	Sodium Pentothal	
Sevoflurane	Carisoprodol	LAU 162	Stiripentol	
SL 75102	CGS 20625	LAU 163	Sulazepam	
SL-651,498	CGS 20625	LAU 176	Sulfonmethane	
Thiamylal	CGS 8216	LAU 177	Suproclone	
Thiomuscimol	CGS 9895	LAU 206	Suriclone	
Tolgabide	CGS 9896	Lofendazam	Sx-3228	
Topiramate	Chloral Hydrate	Lopirazepam	Talampanel	
Zolpidem	Chloralose	Loprazolam	Talbutal	
α5IA	Chlordiazepoxide	Lorazepam	Taniplon	
	Chlormezanone	Lorbamate	Temazepam	
	Chloroform	Loreclezole	Tetrazepam	
	Ciclotizolam	Lorediplon	Tetronal	
	Cinazepam	Lormetazepam	Thdoc	
	Cinolazepam	Meclonazepam	Theanine	
	Cl-218,872	Medazepam	Thiamylal	
	Clazolam	Menitrazepam	Thieno-diazepine	
	Climazolam	Mephobarbital	Thiopental	
	Clobazam	Meprobamate	Tofisopam	
	Clomethiazole	Metaclazepam	Tolufazepam	
	Clonazepam	Methaqualone	Tp-003	
	Clonazolam	Metharbital	Tp-13	
	Clorazepate	Methohexital	Tpa-023	
	Clotiazepam	Methyl-phenobarbital	Triazolam	
	Cloxazolam	Methyprylon	Triflubazam	
	Cp-1414s	Methysticin	Triflunor-dazepam	
	CTP-354	Metizolam	Trional	
	Cyclobarbital	Mexazolam	Tuclazepam	
	Cyprazepam	Midazolam	Uldazepam	
	Delorazepam	Motrazepam	Valerenic Acid	
	Demoxepam	N-Desalkyl-flurazepam	Valeric Acid	
	Deschloro-etizolam	Necopidem	Wogonin	
	Desmethoxy-yangonin	Nerisopam	XHe-II-006	

Agonists	Modulators/Binders			Antagonists
	Desmethyl-flunitrazepam	Niacin	XHe-II-019	
	Diazepam	Niacinamide	XHe-II-087c	
	Diclazepam	Nifoxipam	XHe-II-094	
	Diethyl Ether	Nimetazepam	XHe-II-098b	
	Dihydro-ergotoxine	Nitrazepam	XHe-II-17	
	Dihydroquinidine Barbiturate	Nitrazepate	XHe-III-006c	
	Diproqualone	Nitrazolam	XHe-III-063	
	Divaplon	Nordazepam	XHe-III-24	
	Doxefazepam	Nortetrazepam	XHe/ON-I	
	Elb-139	Ns-2664	Y-23684	
	Elfazepam	Ns-2710	Yangonin	
	Estazolam	Ocinaplon	Zaleplon	
	Eszopiclone	Oroxylin A	Zapizolam	
	Etaqualone	Oxazepam	Zinc	
	Etazepine	Oxazolam	Zk-93423	
	Etazolate	Pagoclone	Zolazepam	
	Ethyl Carfluzepate	Panadiplon	Zolpidem	
	Ethyl Dirazepate	Pazinaclone	Zomebazam	
	Ethyl Loflazepate	PB-XHe	Zopiclone	

Table 4: Ligands for 5-Hydroxytryptamine Receptor (5-HT3)

Agonists	Modulators/ Binders	Antagonists	
2-methyl-5-HT	5-chloroindole	3-Tropanyl indole-3-carboxylate	Mianserin
Alpha-Methyltryptamine	Trimipramine	Adr-851	Mirisetron Maleate
Bufotenin		Adr-882	Mirtazapine
Chlorophenyl-biguanide		Alosetron	Ml-1035
Cisapride		Amoxapine	Mm-218
DDP733		Anpirtoline	N-3256
Ethanol		Aripiprazole	Netupitant
Ethanol		AS-8112	Olanzapine
Ibogaine		Azasetron	Ondansetron
Metoclopramide		Batanopride	Org-4419
Phenylbiguanide		Bimu-1	Org-4419-2
Quipazine		Chloroprocaine	Palonosetron
RS-56812		Cilansetron	Pancopride
SR-57227		Clozapine	Procaine
Tapentadol		Cp-81386	Quetiapine
Varenicline		Cp-93318	R-093777

Agonists	Modulators/ Binders	Antagonists	
YM-31636		Cr-3124	R-Zacopride
		DA-9701	Ramosetron
		Daizac	Renzapride
		Dat-582	Rg-12915
		Dau-6285	Ricasetron
		Ddp-225	Rocuronium
		Dolasetron	Rs-16566
		E-3620	Rs-33800
		Fabesetron	Rs-56532
		Facinicline/RG3487 Hydrochloride	Rs-56812
		Galdansetron	S-21007
		Gastroprokinetics	Sc-50410
		Gk-128	Sc-52150
		Gr-65630	Sc-52246
		Granisetron	Sc-52491
		Gyki-46903	Sc-54750
		Itasetron	Sdz-Icm-567
		Kb-6806	Sep-226332
		Kf-18259	Srss-021
		Kf-20170	Tedatioxetine
		Kga-0941	Thujone
		L-683877	Topiramate
		Lamotrigine	Tropisetron
		Lerisetron	Tubocurarine
		Lintopride	Tzb-30878
		Litoxetine	Va-21B7
		Loxapine	Vi-0134
		Lurosetron	Vortioxetine
		Ly-278584	Vortioxetine Hydrobromide
		M1, the major active metabolite of mosapride	Way-100289
		Mci-225	Ym-114
		Mci-225	Ym-26103-2
		Memantine	Ym-26308-2
		Menthol	Zacopride
		Methadone	Zatosetron
		Metoclopramide	Ziprasidone

Table 5: Ligands for Nicotinic Acetylcholine Receptor (nAchR)

Agonists	Modulators/Binders	Antagonists
(+)-N-(1-azabicyclo[2.2.2]oct-3-yl)benzo[b]furan- 2-carboxamide	A-867744	(−)-7-methyl-2-exo-[3'-(6-[18F]fluoropyridin-2-yl)-5'-pyridinyl]-7-azabicyclo[2.2.1]heptane
3-Bromocytisine	AQW-051	2-fluoro-3-(4-nitro-phenyl)deschloroepibatidine
A-366,833	AVL-3288	Acv-1
A-582941	Desformylflustrabromine	ACVx
A-82695	Ethanol	Amobarbital
A-84,543	Galantamine	Anandamide
ABT-089	Ivermectin	Anq-9040
ABT-126	Nefiracetam	Aprobarbital
Abt-202	NS-1738	ATG-001
ABT-418	NS-9283	ATG003
Abt-418	PNU-120,596	Atracurium besylate
Abt-560	Tetraethylammonium	Barbital
ABT-894		Barbituric acid derivative
Acetylcholine		Biperiden
Altinicline		Bupropion
Altinicline		Butabarbital
Aminoethoxypyridine		Butalbital
Anabasine		Butethal
AR-R17779		Chloroprocaine
Asm-024		Cisatracurium Besilate
AZD-0328		Cisatracurium besylate
Bupropion Hydrochloride		Coclaurine
Carbachol		Dehydronorketamine
Choline		Deuterated Bupropion
Cm-2433		Dextromethorphan
CP-601927		Doxacurium chloride
CP-601932		Ethanol
Cp-810123		Gallamine Triethiodide
Cytisine		Heptabarbital
DBO-83		Hexobarbital
Decamethonium		Hydroxybupropion
Dianicline		Hydroxynorketamine
Dianicline		Inaperisone
Encenicline		Iptakalim
Epibatidine		Isoflurane
EVP-6124		Ketamine
Evp-6124		Kynurenic acid
Galantamine		Levomethadyl Acetate

Agonists	Modulators/Binders	Antagonists
GTS-21		Lobeline
Gts-21		Mecamylamine
ICH-3		Mecamylamine
Ispronicline		Memantine
Levamisole		Methadone
Lobeline		Metharbital
Lobeline Sulphate		Methyllycaconitine
Mem-3454		Methylphenobarbital
MEM-63908		Metocurine
Mem-63908		Metocurine Iodide
N-(3-pyridinyl)-bridged bicyclic diamine		Mivacurium
Nicotine		Neramexane
PH-399733		Nic-002
Ph-399733		Nitrous oxide
PHA-543,613		Norketamine
Pha-543613		Org-9991
PHA-709829		Pancuronium
PNU-282,987		Pentobarbital
Pnu-282987		Pentolinium
Pozanicline		Phenobarbital
Pozanicline		Pipecuronium
Rivanicline		Pipecuronium
Rivanicline		PNU-120,596
Rjr-1401		Primidone
Sar-130479		Procaine
Sazetidine A		Quinolizidine (–)-1-epi-207I
Sib-1663		RJR-2531
Sib-1765f		Rocuronium
Sib-3182		RPI-78M
Sofinicline		Secobarbital
SSR-180,711		Talbutal
Succinylcholine		Thiopental
Suvn-F90101		Trimethaphan
Suvn-F91201		Tubocurarine
Tacrine-huperzine A		U-2902
TC-1698		Vecuronium
TC-1827		α-Bungarotoxin
Tc-2216		α-Conotoxin
Tc-2403		
Tc-2429		

Agonists	Modulators/Binders	Antagonists
Tc-2559		
Tc-2696		
TC-5619		
Tebanicline		
Tropisetron		
Ub-165		
Varenicline		
WAY-317,538		
CNL001		
CNL002		

Table 6: Ligands for ATP-Gated P2X Receptor Cation Channel (P2X)

Agonists	Modulators /Binders	Antagonists	
ATP	Ivermectin	4-benzoyl-1-substituted-piperazin-2-ones	MK-801
BzATP		5-methyl-6,7-dihydro-5Hcyclopentapyrazine	MRS2159
α,β-meATP		5-oxo-3-pyrrolidinecarboxamides	NF023
		5,6,7,8-tetrahydropyrido[4,3,d]-pyrimidines	NF279
		A-317491	NF449
		Amitriptyline	Nortriptyline
		Azaindole-3-carboxamides	Oxoisoquinoline carboxamides
		AZD-9056	Paroxetine
		Benzamide 6	Piperazines
		Benzofuro-1,4-diazepin-2-ones	Polycyclic guanines
		Benzoimidazoles	PPADS
		Biaryl benzamides	PPNDS
		Carboxamides	Pyrazolo-[1,5,a]-pyridine carboxamides
		CE-224535	Pyridazinones
		Desipramine	Pyridoxal-5-phosphate
		Diaminopyridines	Pyrrolinones
		Doxepin	Pyrrolo-[2,3,b]-pyridine carboxamides
		Eslicarbazepine acetate	Pyrrolopyrimidin-7-ones
		EVT-401	Quinoline carboxamides
		Fluoxetine	RO-3
		Hyaluronic acid derivatives	RO-4
		Imipramine	RO-51
		Indole carboxamides	Spinorphins
		Indole-3-carboxamides	Suramin
		Ip5I	Tetrahydro-2H-1,2-thiazine 1,1-dioxides

Agonists	Modulators /Binders	Antagonists	
		Isoquinoline carboxamides	TNP-ATP
		Isothiazolidine 1,1-dioxides	

Table 7: Ligands for Inwardly Rectifying Potassium Channel (Kir)

Agonists	Modulators / Binders	Antagonists
Diazoxide		Acetohexamide
Iptakalim		Carbutamide
Minoxidil		Chlorpropamide
Nicorandil		Glibenclamide
Phosphatidylinositol 4,5-Bisphosphate		Glibenclamide
Pinacidil		Glibornuride
		Gliclazide
		Glimepiride
		Glipizide
		Gliquidone
		Glisoxepide
		Glyburide
		Glyclopyramide
		Glycyclamide
		Metahexamide
		Tolazamide
		Tolbutamide
		Tolhexamide

Table 8: Ligands for Voltage Dependent Potassium Channel (KCNQ/Kv7)

Agonists	Modulators / Binders	Antagonists
Diazoxide		Azimilide
Flupirtine		Amiodarone
Minoxidil		Bretylium
Nicorandil		Clofilium
Pinacidil		Dalfampridine
Retigabine		Dofetilide
		E-4031
		Ibutilide
		Nifekalant
		Sematilide
		Sotalol
		Sulfonylureas
		Tedisamil

Table 9: Ligands for Cystic Fibrosis Transmembrane Conductance Regulator (CFTR)

Agonists	Modulators / Binders	Antagonists
	8-cyclopentyl-1,3-dipropylxanthine	Bumetanide
	8-methoxypsoralen	Crofelemer
	Apigenin	Glyburide
	CTP-656	Ibuprofen
	Genistein	
	IBMX	
	Ivacaftor	
	Lumacaftor	

E. Polynucleotides

[0212] In various illustrative embodiments, the present disclosure contemplates, in part, polynucleotides, polynucleotides encoding engineered receptor polypeptides including LGICs, and subunits and muteins thereof, and fusion polypeptides, viral vector polynucleotides, and compositions comprising the same.

[0213] As used herein, the terms "polynucleotide," "nucleotide," "nucleotide sequence" or "nucleic acid" are used interchangeably. They refer to a polymeric form of nucleotides of any length, either deoxyribonucleotides or ribonucleotides, or analogs thereof. Polynucleotides may have any three dimensional structure, and may perform any function, known or unknown. The following are non-limiting examples of polynucleotides: coding or non-coding regions of a gene or gene fragment, loci (locus) defined from linkage analysis, exons, introns, messenger RNA (mRNA), transfer RNA (tRNA), ribosomal RNA (rRNA), short interfering RNA (siRNA), short-hairpin RNA (shRNA), micro-RNA (miRNA), ribozymes, cDNA, recombinant polynucleotides, branched polynucleotides, plasmids, vectors, isolated DNA of any sequence, isolated RNA of any sequence, nucleic acid probes, and primers. A polynucleotide may comprise one or more modified nucleotides, such as methylated nucleotides and nucleotide analogs. If present, modifications to the nucleotide structure may be imparted before or after assembly of the polymer. The sequence of nucleotides may be interrupted by non-nucleotide components. A polynucleotide may be further modified after polymerization, such as by conjugation with a labeling component. Polynucleotides may be deoxyribonucleic acid (DNA), ribonucleic acid (RNA) or DNA/RNA hybrids. Polynucleotides may be single-stranded or double-stranded. Polynucleotides include, but are not limited to: pre-messenger RNA (pre-mRNA), messenger RNA (mRNA), RNA, short interfering RNA (siRNA), short hairpin RNA (shRNA), microRNA (miRNA), ribozymes, synthetic RNA, genomic RNA (gRNA), plus strand RNA (RNA(+)), minus strand RNA (RNA(-)), synthetic RNA, genomic DNA (gDNA), PCR amplified DNA, complementary DNA (cDNA), synthetic

DNA, or recombinant DNA. Polynucleotides refer to a polymeric form of nucleotides of at least 5, at least 10, at least 15, at least 20, at least 25, at least 30, at least 40, at least 50, at least 100, at least 200, at least 300, at least 400, at least 500, at least 1000, at least 5000, at least 10000, or at least 15000 (including all ranges and subranges therebetween) or more nucleotides in length, either ribonucleotides or deoxynucleotides or a modified form of either type of nucleotide, as well as all intermediate lengths. It will be readily understood that "intermediate lengths" in this context, means any length between the quoted values, such as 6, 7, 8, 9, *etc.*, 101, 102, 103, *etc.*; 151, 152, 153, *etc.*; 201, 202, 203, *etc.* In particular embodiments, polynucleotides or variants have at least or about 50%, 55%, 60%, 65%, 70%, 71%, 72%, 73%, 74%, 75%,76%, 77%, 78%, 79%, 80%, 81%, 82%, 83%, 84%,85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% or 100% (including all ranges and subranges therebetween) sequence identity to a reference sequence described herein or known in the art, typically where the variant maintains at least one biological activity of the reference sequence unless otherwise stated.

[0214] As used herein, the term "gene" may refer to a polynucleotide sequence comprising enhancers, promoters, introns, exons, and the like. In particular embodiments, the term "gene" refers to a polynucleotide sequence encoding a polypeptide, regardless of whether the polynucleotide sequence is identical to the genomic sequence encoding the polypeptide.

[0215] As used herein, a "cis-acting sequence, "cis-acting regulatory sequence", or "cis-acting nucleotide sequence" or equivalents refers to a polynucleotide sequence that is associated with the expression, e.g. transcription and/or translation, of a gene. In one embodiment, the cis-acting sequence regulates transcription because it is a binding site for a polypeptide that represses or decreases transcription or a polynucleotide sequence associated with a transcription factor binding site that contributes to transcriptional repression. Examples of cis-acting sequences that regulate the expression of polynucleotide sequences and that may be operably linked to the polynucleotides of the present disclosure to regulate the expression of the subject engineered receptors are well known in the art and include such elements as promoter sequences (e.g CAG, CMV, SYN, CamKII, TRPV1), Kozak sequences, enhancers, posttranscriptional regulatory elements, miRNA binding elements, and polyadenylation sequences.

[0216] As one non-limiting example, a promoter sequence is a DNA regulatory region capable of binding RNA polymerase in a cell and initiating transcription of a downstream (3' direction) coding sequence. For purposes of defining the present invention, the promoter sequence is bounded at its 3' terminus by the transcription initiation site and extends upstream

(5' direction) to include the minimum number of bases or elements necessary to initiate transcription at levels detectable above background. Within the promoter sequence will be found a transcription initiation site, as well as protein binding domains responsible for the binding of RNA polymerase. Eukaryotic promoters will often, but not always, contain "TATA" boxes and "CAT" boxes. Various promoters may be used to drive the various vectors of the present invention. For example, the promoter may be a constitutively active promoter, i.e. a promoter that is active in the absence externally applied ligands, e.g. the CMV IE1 promoter, the SV40 promoter, GAPDH promoter, Actin promoter. The promoter may be an inducible promoter, i.e. a promoter whose activity is regulated upon the application of an ligand to the cell, e.g. doxycycline, the tet-on or tet-off promoter, the estrogen receptor promoter, etc. The promoter may be a tissue-specific promoter, i.e. a promoter that is active on certain types of cells.

[0217] In some embodiments, the promoter is active in an excitable cell. By an "excitable cell", it is meant a cell that is activated by a change in membrane potential, e.g. a neuron or myocyte, e.g. a dorsal root ganglion neuron, a motor neuron, an excitatory neuron, an inhibitory neuron, or a sensory neuron. Promoters that are active in an excitable cell that would find use in the present polynucleotide compositions would include neuronal promoters, for example, the synapsin (SYN), TRPV1, $Na_v1.7$, $Na_v1.8$, $Na_v1.9$, CamKII, NSE, and Advillin promoters; myocyte promoters, e.g. the desmin (Des), alpha-myosin heavy chain (α-MHC), myosin light chain 2 (MLC-2) and cardiac troponin C (cTnC) promoters; and ubiquitous acting promoters, e.g. CAG, CBA, E1Fa, Ubc, CMV, and SV40 promoters.

[0218] As used herein, a "regulatory element for inducible expression" refers to a polynucleotide sequence that is a promoter, enhancer, or functional fragment thereof that is operably linked to a polynucleotide to be expressed and that responds to the presence or absence of a molecule that binds the element to increase (turn-on) or decrease (turn-off) the expression of the polynucleotide operably linked thereto. Illustrative regulatory elements for inducible expression include, but are not limited to, a tetracycline responsive promoter, an ecdysone responsive promoter, a cumate responsive promoter, a glucocorticoid responsive promoter, an estrogen responsive promoter, an RU-486 responsive promoter, a PPAR-γ promoter, and a peroxide inducible promoter.

[0219] A "regulatory element for transient expression" refers to a polynucleotide sequence that can be used to briefly or temporarily express a polynucleotide nucleotide sequence. In particular embodiments, one or more regulatory elements for transient expression

can be used to limit the duration of a polynucleotide. In certain embodiments, the preferred duration of polynucleotide expression is on the order of minutes, hours, or days. Illustrative regulatory elements for transient expression include, but are not limited to, nuclease target sites, recombinase recognition sites, and inhibitory RNA target sites. In addition, to some extent, in particular embodiments, a regulatory element for inducible expression may also contribute to controlling the duration of polynucleotide expression.

[0220] As used herein, the terms "polynucleotide variant" and "variant" and the like refer to polynucleotides displaying substantial sequence identity with a reference polynucleotide sequence or polynucleotides that hybridize with a reference sequence under stringent conditions that are defined hereinafter. These terms also encompass polynucleotides that are distinguished from a reference polynucleotide by the addition, deletion, substitution, or modification of at least one nucleotide. Accordingly, the terms "polynucleotide variant" and "variant" include polynucleotides in which one or more nucleotides have been added or deleted, or modified, or replaced with different nucleotides. In this regard, it is well understood in the art that certain alterations inclusive of mutations, additions, deletions and substitutions can be made to a reference polynucleotide whereby the altered polynucleotide retains the biological function or activity of the reference polynucleotide. In particular embodiments, polynucleotides or variants have at least or about 50%, 55%, 60%, 65%, 70%, 71%, 72%, 73%, 74%, 75%,76%, 77%, 78%, 79%, 80%, 81%, 82%, 83%, 84%,85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% or 100% (including all ranges and subranges therebetween) sequence identity to a reference sequence described herein or known in the art, typically where the variant maintains at least one biological activity of the reference sequence unless otherwise stated.

[0221] In one embodiment, a polynucleotide comprises a nucleotide sequence that hybridizes to a target nucleic acid sequence under stringent conditions. To hybridize under "stringent conditions" describes hybridization protocols in which nucleotide sequences at least 60% identical to each other remain hybridized. Generally, stringent conditions are selected to be about 5°C lower than the thermal melting point (Tm) for the specific sequence at a defined ionic strength and pH. The Tm is the temperature (under defined ionic strength, pH and nucleic acid concentration) at which 50% of the probes complementary to the target sequence hybridize to the target sequence at equilibrium. Since the target sequences are generally present at excess, at Tm, 50% of the probes are occupied at equilibrium.

[0222] The recitations "sequence identity" or, for example, comprising a "sequence 50% identical to," as used herein, refer to the extent that sequences are identical on a

nucleotide-by-nucleotide basis or an amino acid-by-amino acid basis over a window of comparison. Thus, a "percentage of sequence identity" may be calculated by comparing two optimally aligned sequences over the window of comparison, determining the number of positions at which the identical nucleic acid base (*e.g.*, A, T, C, G, I) or the identical amino acid residue (*e.g.*, Ala, Pro, Ser, Thr, Gly, Val, Leu, Ile, Phe, Tyr, Trp, Lys, Arg, His, Asp, Glu, Asn, Gln, Cys and Met) occurs in both sequences to yield the number of matched positions, dividing the number of matched positions by the total number of positions in the window of comparison (*i.e.*, the window size), and multiplying the result by 100 to yield the percentage of sequence identity. Terms used to describe sequence relationships between two or more polynucleotides or polypeptides include "reference sequence," "comparison window," "sequence identity," "percentage of sequence identity," and "substantial identity." A "reference sequence" is at least 12 but frequently 15 to 18 and often at least 25 monomer units, inclusive of nucleotides and amino acid residues, in length. Because two polynucleotides may each comprise (1) a sequence (*i.e.*, only a portion of the complete polynucleotide sequence) that is similar between the two polynucleotides, and (2) a sequence that is divergent between the two polynucleotides, sequence comparisons between two (or more) polynucleotides are typically performed by comparing sequences of the two polynucleotides over a "comparison window" to identify and compare local regions of sequence similarity. A "comparison window" refers to a conceptual segment of at least 6 contiguous positions, usually about 50 to about 100, more usually about 100 to about 150 in which a sequence is compared to a reference sequence of the same number of contiguous positions after the two sequences are optimally aligned. The comparison window may comprise additions or deletions (*i.e.*, gaps) of about 20% or less as compared to the reference sequence (which does not comprise additions or deletions) for optimal alignment of the two sequences. Optimal alignment of sequences for aligning a comparison window may be conducted by computerized implementations of algorithms (GAP, BESTFIT, FASTA, and TFASTA in the Wisconsin Genetics Software Package Release 7.0, Genetics Computer Group, 575 Science Drive Madison, WI, USA) or by inspection and the best alignment (*i.e.*, resulting in the highest percentage homology over the comparison window) generated by any of the various methods selected. Reference also may be made to the BLAST family of programs as for example disclosed by Altschul *et al.*, 1997, *Nucl. Acids Res.* 25:3389. A detailed discussion of sequence analysis can be found in Unit 19.3 of Ausubel *et al.*, *Current Protocols in Molecular Biology*, John Wiley & Sons Inc, 1994-1998, Chapter 15.

[0223] An "isolated polynucleotide," as used herein, refers to a polynucleotide that has been purified from the sequences which flank it in a naturally-occurring state, *e.g.*, a DNA

fragment that has been removed from the sequences that are normally adjacent to the fragment. In particular embodiments, an "isolated polynucleotide" refers to a complementary DNA (cDNA), a recombinant DNA, or other polynucleotide that does not exist in nature and that has been made by the hand of man.

[0224] Terms that describe the orientation of polynucleotides include: 5' (normally the end of the polynucleotide having a free phosphate group) and 3' (normally the end of the polynucleotide having a free hydroxyl (OH) group). Polynucleotide sequences can be annotated in the 5' to 3' orientation or the 3' to 5' orientation. For DNA and mRNA, the 5' to 3' strand is designated the "sense," "plus," or "coding" strand because its sequence is identical to the sequence of the pre-messenger (premRNA) [except for uracil (U) in RNA, instead of thymine (T) in DNA]. For DNA and mRNA, the complementary 3' to 5' strand which is the strand transcribed by the RNA polymerase is designated as "template," "antisense," "minus," or "non-coding" strand. As used herein, the term "reverse orientation" refers to a 5' to 3' sequence written in the 3' to 5' orientation or a 3' to 5' sequence written in the 5' to 3' orientation.

[0225] The term "flanked" refers to a polynucleotide sequence that is in between an upstream polynucleotide sequence and/or a downstream polynucleotide sequence, *i.e.*, 5' and/or 3', relative to the sequence. For example, a sequence that is "flanked" by two other elements (*e.g.*, ITRs), indicates that one element is located 5' to the sequence and the other is located 3' to the sequence; however, there may be intervening sequences therebetween.

[0226] The terms "complementary" and "complementarity" refer to polynucleotides (*i.e.*, a sequence of nucleotides) related by the base-pairing rules. For example, the complementary strand of the DNA sequence 5' A G T C A T G 3' is 3' T C A G T A C 5'. The latter sequence is often written as the reverse complement with the 5' end on the left and the 3' end on the right, 5' C A T G A C T 3'. A sequence that is equal to its reverse complement is said to be a palindromic sequence. Complementarity can be "partial," in which only some of the nucleic acids' bases are matched according to the base pairing rules. Or, there can be "complete" or "total" complementarity between the nucleic acids.

[0227] The terms "nucleic acid cassette" or "expression cassette" as used herein refers to polynucleotide sequences within a larger polynucleotide, such as a vector, which are sufficient to express one or more RNAs from a polynucleotide. The expressed RNAs may be translated into proteins, may function as guide RNAs or inhibitory RNAs to target other polynucleotide sequences for cleavage and/or degradation. In one embodiment, the nucleic acid cassette contains one or more polynucleotide(s)-of-interest. In another embodiment, the nucleic

acid cassette contains one or more expression control sequences operably linked to one or more polynucleotide(s)-of-interest. Polynucleotides include polynucleotide(s)-of-interest. As used herein, the term "polynucleotide-of-interest" refers to a polynucleotide encoding a polypeptide or fusion polypeptide or a polynucleotide that serves as a template for the transcription of an inhibitory polynucleotide, *e.g.,* LGICs, and subunits and muteins thereof, as contemplated herein. In a particular embodiment, a polynucleotide-of-interest encodes a polypeptide or fusion polypeptide having one or more enzymatic activities, such as a nuclease activity and/or chromatin remodeling or epigenetic modification activities.

[0228] Vectors may comprise 1, 2, 3, 4, 5, 6, 7, 8, 9 or 10 or more nucleic acid cassettes. In a preferred embodiment of the disclosure, a nucleic acid cassette comprises one or more expression control sequences (*e.g.,* a promoter or enhancer operable in a neuronal cell) operably linked to a polynucleotide encoding a engineered receptor, *e.g.,* an LGIC, or subunit or muteins thereof. The cassette can be removed from or inserted into other polynucleotide sequences, *e.g.,* a plasmid or viral vector, as a single unit.

[0229] In one embodiment, a polynucleotide contemplated herein comprises 1, 2, 3, 4, 5, 6, 7, 8, 9, or more nucleic acid cassettes any number or combination of which may be in the same or opposite orientations.

[0230] Moreover, it will be appreciated by those of ordinary skill in the art that, as a result of the degeneracy of the genetic code, there are many nucleotide sequences that may encode a polypeptide, or fragment of variant thereof, as contemplated herein. Some of these polynucleotides bear minimal homology to the nucleotide sequence of any native gene. Nonetheless, polynucleotides that vary due to differences in codon usage are specifically contemplated by the present disclosure, for example polynucleotides that are optimized for human and/or primate codon selection. In one embodiment, polynucleotides comprising particular allelic sequences are provided. Alleles are endogenous polynucleotide sequences that are altered as a result of one or more mutations, such as deletions, additions and/or substitutions of nucleotides.

[0231] In some embodiments, the present disclosure provides a polynucleotide encoding an engineered receptor described herein. In some embodiments, the present disclosure provides a polynucleotide encoding a chimeric engineered LGIC receptor described herein.

[0232] In some embodiments, the present disclosure provides a polynucleotide encoding an engineered receptor comprising an amino acid sequence that is at least 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identical to the amino acid sequence of

one of SEQ ID NOs: 58-78 and 88. In some embodiments, the present disclosure provides a polynucleotide encoding an engineered receptor comprising an amino acid sequence of one of SEQ ID NOs: 58-78 and 88. In some embodiments, the present disclosure provides a polynucleotide encoding an engineered receptor consisting of an amino acid sequence of one of SEQ ID NOs: 58-78 and 88.

F. Vectors

[0233] In some aspects of the disclosure, a nucleic acid molecule, i.e., a polynucleotide encoding an engineered receptor is delivered to a subject. In some cases, the nucleic acid molecule encoding the engineered receptor is delivered to a subject by a vector. In various embodiments, a vector comprises a one or more polynucleotide sequences contemplated herein. The term "vector" is used herein to refer to a nucleic acid molecule capable of transferring or transporting another nucleic acid molecule. The transferred polynucleotide is generally linked to, *e.g.*, inserted into, the vector nucleic acid molecule. A vector may include sequences that direct autonomous replication in a cell, or may include sequences sufficient to allow integration into host cell DNA. A vector can deliver a target polynucleotide to an organism, a cell or a cellular component. In some cases, the vector is an expression vector. An "expression vector" as used herein refers to a vector, for example, a plasmid, that is capable of promoting expression, as well as replication of a polynucleotide incorporated therein. Typically, the nucleic acid sequence to be expressed is operably linked to cis-acting regulatory sequence, e.g. a promoter and/or enhancer sequence, and is subject to transcription regulatory control by the promoter and/or enhancer. In particular cases, a vector is used to deliver a nucleic acid molecule encoding an engineered receptor of the disclosure to a subject.

[0234] In particular embodiments, any vector suitable for introducing an expression cassette or polynucleotide encoding an engineered receptor into a neuronal cell can be employed. Illustrative examples of suitable vectors include plasmids (*e.g.*, DNA plasmids or RNA plasmids), transposons, cosmids, bacterial artificial chromosomes, and viral vectors. In some cases, the vector is a circular nucleic acid, for *e.g.*, a plasmid, a BAC, a PAC, a YAC, a cosmid, a fosmid, and the like. In some cases, circular nucleic acid molecules can be utilized to deliver a nucleic acid molecule encoding an engineered receptor to a subject. For example, a plasmid DNA molecule encoding an engineered receptor can be introduced into a cell of a subject whereby the DNA sequence encoding the engineered receptor is transcribed into mRNA and the mRNA "message" is translated into a protein product. The circular nucleic acid vector will generally include regulatory elements that regulate the expression of the target

protein. For example, the circular nucleic acid vector may include any number of promoters, enhancers, terminators, splice signals, origins of replication, initiation signals, and the like.

[0235] In some cases, the vector can include a replicon. A replicon may be any nucleic acid molecule capable of self-replication. In some cases, the replicon is an RNA replicon derived from a virus. A variety of suitable viruses (*e.g.* RNA viruses) are available, including, but not limited to, alphavirus, picornavirus, flavivirus, coronavirus, pestivirus, rubivirus, calcivirus, and hepacivirus.

[0236] In some embodiments, the vector is a non-viral vector. By a "non-viral vector", it is meant any delivery vehicle that does not comprise a viral capsid or envelope, *e.g.* lipid nanoparticles (anionic (negatively charged), neutral, or cationic (positively charged)), heavy metal nanoparticles, polymer-based particles, plasmid DNA, minicircle DNA, minivector DNA, ccDNA, synthetic RNA, exosomes, and the like. Non-viral vectors may be delivered by any suitable method as would be well understood in the art, including, *e.g.*, nanoparticle delivery, particle bombardment, electroporation, sonication, or microinjection. See, *e.g.* Chen et al. Mol. Therapy, Methods and Clinical Development. 2016 Jan; Vol 3, issue 1; and Hardy, CE et al. Genes (Basel). 2017 Feb; 8(2): 65

[0237] In other embodiments, the vector is a viral vector. By a "viral vector" it is meant a delivery vehicle that comprises a viral capsid or envelop surrounding a polynucleotide encoding an RNA or polypeptide of interest. In some cases, the viral vector is derived from a replication-deficient virus. Non-limiting examples of viral vectors suitable for delivering a nucleic acid molecule of the disclosure to a subject include those derived from adenovirus, retrovirus (*e.g.*, lentivirus), adeno-associated virus (AAV), and herpes simplex-1 (HSV-1). Illustrative examples of suitable viral vectors include, but are not limited to, retroviral vectors (*e.g.,* lentiviral vectors), herpes virus based vectors and parvovirus based vectors (*e.g.*, adeno-associated virus (AAV) based vectors, AAV-adenoviral chimeric vectors, and adenovirus-based vectors).

[0238] The term "parvovirus" as used herein encompasses all parvoviruses, including autonomously-replicating parvoviruses and dependoviruses. The autonomous parvoviruses include members of the genera *Parvovirus, Erythrovirus, Densovirus, Iteravirus*, and *Contravirus*. Exemplary autonomous parvoviruses include, but are not limited to, mouse minute virus, bovine parvovirus, canine parvovirus, chicken parvovirus, feline panleukopenia virus, feline parvovirus, goose parvovirus, and B19 virus. Other autonomous parvoviruses are known to those skilled in the art. *See, e.g.*, Fields *et al.*, 1996 *Virology*, volume 2, chapter 69 (3d ed., Lippincott-Raven Publishers).

[0239] The genus *Dependovirus* contains the adeno-associated viruses (AAV), including but not limited to, AAV type 1, AAV type 2, AAV type 3, AAV type 4, AAV type 5, AAV type 6, AAV type 7, AAV type 8, AAV type 9, AAV type rh10, avian AAV, bovine AAV, canine AAV, equine AAV, and ovine AAV.

[0240] In a preferred embodiment, the vector is an AAV vector. In particular cases, the viral vector is an AAV5, AAV-6 or AAV-9 vector.

[0241] The genomic organization of all known AAV serotypes is similar. The genome of AAV is a linear, single-stranded DNA molecule that is less than about 5,000 nucleotides (nt) in length. Inverted terminal repeats (ITRs) flank the unique coding nucleotide sequences for the non-structural replication (Rep) proteins and the structural (VP) proteins. The VP proteins (VPl, -2 and -3) form the capsid and contribute to the tropism of the virus. The terminal 145 nt ITRs are self-complementary and are organized so that an energetically stable intramolecular duplex forming a T-shaped hairpin may be formed. These hairpin structures function as an origin for viral DNA replication, serving as primers for the cellular DNA polymerase complex. Following wild-type (wt) AAV infection in mammalian cells the Rep genes are expressed and function in the replication of the viral genome.

[0242] In some cases, the outer protein "capsid" of the viral vector occurs in nature, *e.g.* AAV1, AAV2, AAV3, AAV4, AAV5, AAV6, AAV7, AAV8, AAV9, or AAV10. In particular cases, the capsid is synthetically engineered (*e.g.* through directed evolution or rational design) to possess certain unique characteristics not present in nature such as altered tropism, increased transduction efficiency, or immune evasion. An example of a rationally designed capsid is the mutation of one or more surface-exposed tyrosine (Y), serine (S), threonine (T), and lysine (K) residues on the VP3 viral capsid protein. Non-limiting examples of viral vectors whose VP3 capsid proteins have been synthetically engineered and are amenable for use with the compositions and methods provided herein include: AAV1(Y705+731F+T492V), AAV2(Y444+500+730F+T491V), AAV3(Y705+731F), AAV5(Y436+693+719F), AAV6(Y705+731F+T492V), AAV8(Y733F), AAV9(Y731F), and AAV10(Y733F). Non-limiting examples of viral vectors that have been engineered through directed evolution and are amenable for use with the compositions and methods provided herein include AAV-7m8 and AAV-ShH10. In some embodiments, the viral vector comprises an AAV capsid protein comprising amino acid mutation at one or more positions corresponding to T492, Y705, Y731, or any combination thereof, of AAV6 capsid protein, wherein the AAV capsid protein is of serotype AAV1, AAV2, AAV3, AAV4, AAV5, AAV6, AAV7, AAV8, AAV9, AAV10, or another AAV serotype. In some embodiments, the one or more positions

are two or more positions, two positions, or three positions. In some embodiments, the viral vector comprises an AAV capsid protein comprising one or more amino acid substitutions corresponding to T492V, Y705F or Y731F, or any combination thereof, of AAV6 capsid protein, wherein the AAV capsid protein is of serotype AAV1, AAV2, AAV3, AAV4, AAV5, AAV6, AAV7, AAV8, AAV9, AAV10, or another AAV serotype. In some embodiments, the one or more substitutions are two or more substitutions, two substitutions, or three substitutions.

[0243] In some embodiments, the viral vector comprises an AAV5 capsid protein comprising a mutation at one or more amino acid positions selected from Y693 and Y719. In some embodiments, the viral vector comprises an AAV5 capsid protein comprising one or more mutations selected from Y693F and Y719F. In some embodiments, the viral vector comprises an AAV5 capsid protein comprising the amino acid mutation Y693F+Y719F. In some embodiments, the AAV5 capsid protein comprises or consists of an amino acid sequence having at least 85%, at least 90%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or 100 % sequence identity to SEQ ID NO: 79.

[0244] In some embodiments, the viral vector comprises an AAV6 capsid protein comprising a mutation at one or more amino acid positions selected from T492, Y705 and Y731. In some embodiments, the viral vector comprises an AAV6 capsid protein comprising one or more mutations selected from T492V, Y705F, and Y731F. In some embodiments, the viral vector comprises an AAV6 capsid protein comprising the amino acid mutation T492V+Y705F+Y731F. In some embodiments, the AAV6 capsid protein comprises or consists of an amino acid sequence having at least 85%, at least 90%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or 100 % sequence identity to SEQ ID NO: 80.

[0245] In some embodiments, the viral vector comprises an AAV9 capsid protein comprising a mutation at one or more amino acid positions selected from T492, Y705 and Y731. In some embodiments, the viral vector comprises an AAV9 capsid protein comprising one or more mutations selected from T492V, Y705F, and Y731F. In some embodiments, the viral vector comprises an AAV9 capsid protein comprising the amino acid mutation T492V+Y705F+Y731F. In some embodiments, the AAV9 capsid protein comprises or consists of an amino acid sequence having at least 85%, at least 90%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or 100 % sequence identity to SEQ ID NO: 81.

[0246] In some embodiments, the viral vector comprising the AAV capsid protein (or a mutant of the disclosure) contributes to targeted expression of an engineered receptor to a

sub-population of cells or neurons in a subject. In some embodiments, the neurons are nociceptors.

[0247] A "recombinant parvoviral or AAV vector" (or "rAAV vector") herein refers to a vector comprising one or more polynucleotides contemplated herein that are flanked by one or more AAV ITRs. Such polynucleotides are said to be "heterologous" to the ITRs, as such combinations do not ordinarily occur in nature. Such rAAV vectors can be replicated and packaged into infectious viral particles when present in an insect host cell that is expressing AAV rep and cap gene products (*i.e.*, AAV Rep and Cap proteins). When an rAAV vector is incorporated into a larger nucleic acid construct (*e.g.*, in a chromosome or in another vector such as a plasmid or baculovirus used for cloning or transfection), then the rAAV vector is typically referred to as a "pro-vector" which can be "rescued" by replication and encapsidation in the presence of AAV packaging functions and necessary helper functions.

[0248] In particular embodiments, any AAV ITR may be used in the AAV vectors, including ITRs from AAV1, AAV2, AAV3, AAV4, AAV5, AAV6, AAV7, AAV8, AAV9, AAV10, AAV11, AAV12, AAV13, AAV14, AAV15, and AAV16. In one preferred embodiment, an AAV vector contemplated herein comprises one or more AAV2 ITRs.

[0249] rAAV vectors comprising two ITRs have a payload capacity of about 4.4 kB. Self-complementary rAAV vectors contain a third ITR and package two strands of the recombinant portion of the vector leaving only about 2.1 kB for the polynucleotides contemplated herein. In one embodiment, the AAV vector is an scAAV vector.

[0250] Extended packaging capacities that are roughly double the packaging capacity of an rAAV (about 9kB) have been achieved using dual rAAV vector strategies. Dual vector strategies useful in producing rAAV contemplated herein include, but are not limited to splicing (trans-splicing), homologous recombination (overlapping), or a combination of the two (hybrid). In the dual AAV trans-splicing strategy, a splice donor (SD) signal is placed at the 3′ end of the 5′-half vector and a splice acceptor (SA) signal is placed at the 5′ end of the 3′-half vector. Upon co-infection of the same cell by the dual AAV vectors and inverted terminal repeat (ITR)-mediated head-to-tail concatemerization of the two halves, trans-splicing results in the production of a mature mRNA and full-size protein (Yan *et al.*, 2000). Trans-splicing has been successfully used to express large genes in muscle and retina (Reich *et al.*, 2003; Lai *et al.*, 2005). Alternatively, the two halves of a large transgene expression cassette contained in dual AAV vectors may contain homologous overlapping sequences (at the 3′ end of the 5′-half vector and at the 5′ end of the 3′-half vector, dual AAV overlapping), which will mediate reconstitution of a single large genome by homologous recombination (Duan *et al.*,

2001). This strategy depends on the recombinogenic properties of the transgene overlapping sequences (Ghosh *et al.*, 2006). A third dual AAV strategy (hybrid) is based on adding a highly recombinogenic region from an exogenous gene (*i.e.,* alkaline phosphatase; Ghosh *et al.*, 2008, Ghosh *et al.*, 2011)) to the trans-splicing vectors. The added region is placed downstream of the SD signal in the 5′-half vector and upstream of the SA signal in the 3′-half vector in order to increase recombination between the dual AAVs.

[0251] A "hybrid AAV" or "hybrid rAAV" refers to an rAAV genome packaged with a capsid of a different AAV serotype (and preferably, of a different serotype from the one or more AAV ITRs), and may otherwise be referred to as a pseudotyped rAAV. For example, an rAAV type 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, or 16 genome may be encapsidated within an AAV type 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, or 16 capsid or variants thereof, provided that the AAV capsid and genome (and preferably, the one or more AAV ITRs) are of different serotypes. In certain embodiments, a pseudotyped rAAV particle may be referred to as being of the type "x/y ", where "x" indicates the source of ITRs and "y" indicates the serotype of capsid, for example a 2/5 rAAV particle has ITRs from AAV2 and a capsid from AAV6.

[0252] A "host cell" includes cells transfected, infected, or transduced *in vivo, ex vivo,* or *in vitro* with a recombinant vector or a polynucleotide of the disclosure. Host cells may include virus producing cells and cells infected with viral vectors. In particular embodiments, host cells *in vivo* are infected with viral vector contemplated herein. In certain embodiments, the term "target cell" is used interchangeably with host cell and refers to infected cells of a desired cell type.

[0253] High titer AAV preparations can be produced using techniques known in the art, *e.g.*, as described in U.S. Pat. Nos. 5,658,776; 6,566,118; 6,989,264; and 6,995,006; U.S. 2006/0188484; WO98/22607; WO2005/072364; and WO/1999/011764; and Viral Vectors for Gene Therapy: Methods and Protocols, ed. Machida, Humana Press, 2003; Samulski et al., (1989) J. Virology 63, 3822 ; Xiao et al., (1998) J. Virology 72, 2224 ; lnoue et al., (1998) J. Virol. 72, 7024. Methods of producing pseudotyped AAV vectors have also been reported (*e.g.*, WO 00/28004), as well as various modifications or formulations of AAV vectors, to reduce their immunogenicity upon in vivo administration (*see e.g.*, WO 01/23001; WO 00/73316; WO 04/1 12727; WO 05/005610; WO 99/06562).

G. Pharmaceutical compositions

[0254] In some embodiments, the present disclosure provides compositions comprising a polynucleotide encoding an engineered receptor described herein, or a vector comprising a polynucleotide encoding an engineered receptor described herein. In some embodiments, the compositions further comprise a ligand described here. Pharmaceutical preparations include the subject polynucleotide (RNA or DNA) encoding an engineered receptor, vector carrying a polynucleotide (RNA or DNA) encoding a subject engineered receptor, or ligand present in a pharmaceutically acceptable vehicle. In some embodiments, the present disclosure provides a first composition comprising a polynucleotide encoding an engineered receptor described herein, or a vector comprising a polynucleotide encoding an engineered receptor described herein, and a second composition comprising a ligand described here.

[0255] "Pharmaceutically acceptable vehicles" may be vehicles approved by a regulatory agency of the Federal or a state government or listed in the U.S. Pharmacopeia or other generally recognized pharmacopeia for use in mammals, such as humans. The term "vehicle" refers to a diluent, adjuvant, excipient, or carrier with which a compound of the disclosure is formulated for administration to a mammal. Such pharmaceutical vehicles can be liquids, such as water and oils, including those of petroleum, animal, vegetable or synthetic origin, such as peanut oil, soybean oil, mineral oil, sesame oil and the like. The pharmaceutical vehicles can be saline, gum acacia, gelatin, starch paste, talc, keratin, colloidal silica, urea, and the like. In addition, auxiliary, stabilizing, thickening, lubricating and coloring agents may be used. When administered to a mammal, the compounds and compositions of the disclosure and pharmaceutically acceptable vehicles, excipients, or diluents may be sterile. In some instances, an aqueous medium is employed as a vehicle when the compound of the disclosure is administered intravenously, such as water, saline solutions, and aqueous dextrose and glycerol solutions.

[0256] Pharmaceutical compositions can take the form of capsules, tablets, pills, pellets, lozenges, powders, granules, syrups, elixirs, solutions, suspensions, emulsions, suppositories, or sustained-release formulations thereof, or any other form suitable for administration to a mammal. In some instances, the pharmaceutical compositions are formulated for administration in accordance with routine procedures as a pharmaceutical composition adapted for oral or intravenous administration to humans. Examples of suitable pharmaceutical vehicles and methods for formulation thereof are described in Remington: The Science and Practice of Pharmacy, Alfonso R. Gennaro ed., Mack Publishing Co. Easton, Pa., 19th ed., 1995, Chapters 86, 87, 88, 91, and 92, incorporated herein by reference.

[0257] The choice of excipient will be determined in part by the particular vector, as well as by the particular method used to administer the composition. Accordingly, there is a wide variety of suitable formulations of the pharmaceutical composition of the present disclosure.

[0258] In some embodiments, the pharmaceutical composition is formulated for subcutaneous administration. In some embodiments, the pharmaceutical composition is formulated for parenteral administration. In some embodiments, the pharmaceutical composition is formulated for intravenous administration. In some embodiments, the pharmaceutical composition is formulated for intramuscular administration. In some embodiments, the pharmaceutical composition is formulated for intradermal administration. In some embodiments, the pharmaceutical composition is formulated for intraperitoneal administration. In some embodiments, the pharmaceutical composition is formulated for oral administration. In some embodiments, the pharmaceutical composition is formulated for infusion. In some embodiments, the pharmaceutical composition is formulated for intracranial administration. In some embodiments, the pharmaceutical composition is formulated for intrathecal administration. In some embodiments, the pharmaceutical composition is formulated for intranasal administration. In some embodiments, the pharmaceutical composition is formulated for intraganglionic administration. In some embodiments, the pharmaceutical composition is formulated for intraspinal administration. In some embodiments, the pharmaceutical composition is formulated for intraventricular administration. In some embodiments, the pharmaceutical composition is formulated for cisterna magna administration. In some embodiments, the pharmaceutical composition is formulated for intraneural administration. In some embodiments, the pharmaceutical composition is formulated for delivery into a neuronal cell.

[0259] For example, the vector may be formulated into preparations for injection by dissolving, suspending or emulsifying them in an aqueous or nonaqueous solvent, such as vegetable or other similar oils, synthetic aliphatic acid glycerides, esters of higher aliphatic acids or propylene glycol; and if desired, with conventional additives such as solubilizers, isotonic agents, suspending agents, emulsifying agents, stabilizers and preservatives.

[0260] As another example, the vector may be formulated into a preparation suitable for oral administration, including (a) liquid solutions, such as an effective amount of the compound dissolved in diluents, such as water, or saline; (b) capsules, sachets or tablets, each containing a predetermined amount of the active ingredient, as solids or granules; (c) suspensions in an appropriate liquid; and (d) suitable emulsions. Tablet forms can include one

or more of lactose, mannitol, corn starch, potato starch, microcrystalline cellulose, acacia, gelatin, colloidal silicon dioxide, croscarmellose sodium, talc, magnesium stearate, stearic acid, and other excipients, colorants, diluents, buffering agents, moistening agents, preservatives, flavoring agents, and pharmacologically compatible excipients. Lozenge forms can include the active ingredient in a flavor, usually sucrose and acacia or tragacanth, as well as pastilles including the active ingredient in an inert base, such as gelatin and glycerin, or sucrose and acacia, emulsions, gels, and the like containing, in addition to the active ingredient, such excipients as are described herein.

[0261] As another example, the subject formulations of the present disclosure can be made into aerosol formulations to be administered via inhalation. These aerosol formulations can be placed into pressurized acceptable propellants, such as dichlorodifluoromethane, propane, nitrogen, and the like. They may also be formulated as pharmaceuticals for non-pressured preparations such as for use in a nebulizer or an atomizer.

[0262] In some embodiments, formulations suitable for parenteral administration include aqueous and non-aqueous, isotonic sterile injection solutions, which can contain anti-oxidants, buffers, bacteriostats, and solutes that render the formulation isotonic with the blood of the intended recipient, and aqueous and non-aqueous sterile suspensions that can include suspending agents, solubilizers, thickening agents, stabilizers, and preservatives. The formulations can be presented in unit-dose or multi-dose sealed containers, such as ampules and vials, and can be stored in a freeze-dried (lyophilized) condition requiring only the addition of the sterile liquid excipient, for example, water, for injections, immediately prior to use. Extemporaneous injection solutions and suspensions can be prepared from sterile powders, granules, and tablets of the kind previously described.

[0263] Formulations suitable for topical administration may be presented as creams, gels, pastes, or foams, containing, in addition to the active ingredient, such carriers as are appropriate. In some embodiments the topical formulation contains one or more components selected from a structuring agent, a thickener or gelling agent, and an emollient or lubricant. Frequently employed structuring agents include long chain alcohols, such as stearyl alcohol, and glyceryl ethers or esters and oligo(ethylene oxide) ethers or esters thereof. Thickeners and gelling agents include, for example, polymers of acrylic or methacrylic acid and esters thereof, polyacrylamides, and naturally occurring thickeners such as agar, carrageenan, gelatin, and guar gum. Examples of emollients include triglyceride esters, fatty acid esters and amides, waxes such as beeswax, spermaceti, or carnauba wax, phospholipids such as lecithin, and sterols and fatty acid esters thereof. The topical formulations may further include other

components, *e.g.*, astringents, fragrances, pigments, skin penetration enhancing agents, sunscreens (i.e., sunblocking agents), etc.

[0264] A compound of the disclosure may be formulated for topical administration. The vehicle for topical application may be in one of various forms, *e.g.* a lotion, cream, gel, ointment, stick, spray, or paste. They may contain various types of carriers, including, but not limited to, solutions, aerosols, emulsions, gels, and liposomes. The carrier may be formulated, for example, as an emulsion, having an oil-in-water or water-in-oil base. Suitable hydrophobic (oily) components employed in emulsions include, for example, vegetable oils, animal fats and oils, synthetic hydrocarbons, and esters and alcohols thereof, including polyesters, as well as organopolysiloxane oils. Such emulsions also include an emulsifier and/or surfactant, *e.g.* a nonionic surfactant to disperse and suspend the discontinuous phase within the continuous phase.

[0265] Suppository formulations are also provided by mixing with a variety of bases such as emulsifying bases or water-soluble bases. Formulations suitable for vaginal administration may be presented as pessaries, tampons, creams, gels, pastes, foams.

[0266] Unit dosage forms for oral or rectal administration such as syrups, elixirs, and suspensions may be provided wherein each dosage unit, for example, teaspoonful, tablespoonful, tablet or suppository, contains a predetermined amount of the composition containing one or more inhibitors. Similarly, unit dosage forms for injection or intravenous administration may include the inhibitor(s) in a composition as a solution in sterile water, normal saline or another pharmaceutically acceptable carrier.

[0267] The term "unit dosage form," as used herein, refers to physically discrete units suitable as unitary dosages for human and animal subjects, each unit containing a predetermined quantity of compounds of the present disclosure calculated in an amount sufficient to produce the desired effect in association with a pharmaceutically acceptable diluent, carrier or vehicle. The specifications for the novel unit dosage forms of the present disclosure depend on the particular compound employed and the effect to be achieved, and the pharmacodynamics associated with each compound in the host.

[0268] Dose levels can vary as a function of the specific compound, the nature of the delivery vehicle, and the like. Desired dosages for a given compound are readily determinable by a variety of means.

[0269] The dose administered to an animal, particularly a human, in the context of the present disclosure should be sufficient to affect a prophylactic or therapeutic response in the animal over a reasonable time frame, *e.g.*, as described in greater detail below. Dosage will

depend on a variety of factors including the strength of the particular compound employed, the condition of the animal, and the body weight of the animal, as well as the severity of the illness and the stage of the disease. The size of the dose will also be determined by the existence, nature, and extent of any adverse side-effects that might accompany the administration of a particular compound.

[0270] In pharmaceutical dosage forms, the compound(s) may be administered in the form of a free base, their pharmaceutically acceptable salts, or they may also be used alone or in appropriate association, as well as in combination, with other pharmaceutically active compounds.

H. Clinical Applications and Methods of Treatment

[0271] The compositions and methods disclosed herein can be utilized to treat a neurological disease or disorder. In some aspects of the disclosure, a method of treating a neurological disease or disorder in a subject is provided, the method comprising the introducing an engineered receptor into a neuronal cell and providing a ligand that activates the engineered receptor in an effective amount to control the activity of the cell, thereby relieving pain in the subject. In some aspects, vectors or compositions disclosed herein are used in the manufacture of a medicament for treating a neurological disease or disorder.

[0272] In some cases, the methods and compositions of the disclosure are utilized to treat epilepsy. Compositions described herein may be used to prevent or control epileptic seizures. Epileptic seizures may be classified as tonic-clonic, tonic, clonic, myoclonic, absence or atonic seizures. In some cases, the compositions and methods herein may prevent or reduce the number of epileptic seizures experienced by a subject by about 5%, about 10%, about 10%, about 15%, about 20%, about 25%, about 30%, about 35%, about 40%, about 45%, about 50%, about 55%, about 60%, about 65%, about 70%, about 75%, about 80%, about 85%, about 90%, about 95%, about 99% or 100%, including all ranges and subranges therebetween.

[0273] In some cases, the methods and compositions of the disclosure are utilized to treat an eating disorder. An eating disorder may be a mental disorder defined by abnormal eating behaviors that negatively affect a subject's physical or mental health. In some cases, the eating disorder is anorexia nervosa. In other cases, the eating disorder is bulimia nervosa. In some cases, the eating disorder is pica, rumination disorder, avoidant/restrictive food intake disorder, binge eating disorder (BED), other specified feeding and eating disorder (OSFED), compulsive overeating, diabulimia, orthorexia nervosa, selective eating disorder, drunkorexia, pregorexia, or Gourmand syndrome. In some cases, the composition includes a G-protein

coupled receptor that increases or decreases the production of one or more molecules associated with an eating disorder. In other cases, the composition includes a ligand-gated ion channel that alters the production of one or more molecules associated with an eating disorder. The one or more molecules associated with an eating disorder may include, without limitation, a molecule of the hypothalamus-pituitary-adrenal (HPA) axis, including vasopressin, corticotropin-releasing hormone (CRH), adrenocorticotropic hormone (ACTH), cortisol, epinephrine, or norepinephrine; as well as serotonin, dopamine, neuropeptide Y, leptin, or ghrelin.

[0274] In some cases, the compositions and methods are utilized to treat post-traumatic stress disorder (PTSD), gastroesophageal reflex disease (GERD), addiction (*e.g.*, alcohol, drugs), anxiety, depression, memory loss, dementia, sleep apnea, stroke, urinary incontinence, narcolepsy, essential tremor, movement disorder, atrial fibrillation, cancer (*e.g.*, brain tumors), Parkinson's disease, or Alzheimer's disease. Other non-limiting examples of neurological diseases or disorders that can be treated by the compositions and methods herein include: Abulia, Agraphia, Alcoholism, Alexia, Aneurysm, Amaurosis fugax, Amnesia, Amyotrophic lateral sclerosis (ALS), Angelman syndrome, Aphasia, Apraxia, Arachnoiditis, Arnold-Chiari malformation, Asperger syndrome, Ataxia, Ataxia-telangiectasia, Attention deficit hyperactivity disorder, Auditory processing disorder, Autism spectrum, Bipolar disorder, Bell's palsy, Brachial plexus injury, Brain damage, Brain injury, Brain tumor, Canavan disease, Capgras delusion, Carpal tunnel syndrome, Causalgia, Central pain syndrome, Central pontine myelinolysis, Centronuclear myopathy, Cephalic disorder, Cerebral aneurysm, Cerebral arteriosclerosis, Cerebral atrophy, Cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL), Cerebral gigantism, Cerebral palsy, Cerebral vasculitis, Cervical spinal stenosis, Charcot-Marie-Tooth disease, Chiari malformation, Chorea, Chronic fatigue syndrome, Chronic inflammatory demyelinating polyneuropathy (CIDP), Chronic pain, Coffin–Lowry syndrome, Coma, Complex regional pain syndrome, Compression neuropathy, Congenital facial diplegia, Corticobasal degeneration, Cranial arteritis, Craniosynostosis, Creutzfeldt-Jakob disease, Cumulative trauma disorders, Cushing's syndrome, Cyclothymic disorder, Cytomegalic inclusion body disease (CIBD), Cytomegalovirus Infection, Dandy-Walker syndrome, Dawson disease, De Morsier's syndrome, Dejerine-Klumpke palsy, Dejerine-Sottas disease, Delayed sleep phase syndrome, Dementia, Dermatomyositis, Developmental coordination disorder, Diabetic neuropathy, Diffuse sclerosis, Diplopia, Down syndrome, Dravet syndrome, Duchenne muscular dystrophy, Dysarthria, Dysautonomia, Dyscalculia, Dysgraphia, Dyskinesia, Dyslexia,

Dystonia, Empty sella syndrome, Encephalitis, Encephalocele, Encephalotrigeminal angiomatosis, Encopresis, Enuresis, Epilepsy, Epilepsy-intellectual disability in females, Erb's palsy, Erythromelalgia, Exploding head syndrome, Fabry's disease, Fahr's syndrome, Fainting, Familial spastic paralysis, Febrile seizures, Fisher syndrome, Friedreich's ataxia, Fibromyalgia, Foville's syndrome, Fetal alcohol syndrome, Fragile X syndrome, Fragile X-associated tremor/ataxia syndrome (FXTAS), Gaucher's disease, Generalized epilepsy with febrile seizures plus, Gerstmann's syndrome, Giant cell arteritis, Giant cell inclusion disease, Globoid Cell Leukodystrophy, Gray matter heterotopia, Guillain-Barré syndrome, Generalized anxiety disorder, HTLV-1 associated myelopathy, Hallervorden-Spatz disease, Head injury, Headache, Hemifacial Spasm, Hereditary Spastic Paraplegia, Heredopathia atactica polyneuritiformis, Herpes zoster oticus, Herpes zoster, Hirayama syndrome, Hirschsprung's disease, Holmes-Adie syndrome, Holoprosencephaly, Huntington's disease, Hydranencephaly, Hydrocephalus, Hypercortisolism, Hypoxia, Immune-Mediated encephalomyelitis, Inclusion body myositis, Incontinentia pigmenti, Infantile Refsum disease, Infantile spasms, Inflammatory myopathy, Intracranial cyst, Intracranial hypertension, Isodicentric 15, Joubert syndrome, Karak syndrome, Kearns-Sayre syndrome, Kinsbourne syndrome, Kleine-Levin Syndrome, Klippel Feil syndrome, Krabbe disease, Lafora disease, Lambert-Eaton myasthenic syndrome, Landau-Kleffner syndrome, Lateral medullary (Wallenberg) syndrome, Learning disabilities, Leigh's disease, Lennox-Gastaut syndrome, Lesch-Nyhan syndrome, Leukodystrophy, Leukoencephalopathy with vanishing white matter, Lewy body dementia, Lissencephaly, Locked-In syndrome, Lumbar disc disease, Lumbar spinal stenosis, Lyme disease - Neurological Sequelae, Machado-Joseph disease (Spinocerebellar ataxia type 3), Macrencephaly, Macropsia, Mal de debarquement, Megalencephalic leukoencephalopathy with subcortical cysts, Megalencephaly, Melkersson-Rosenthal syndrome, Menieres disease, Meningitis, Menkes disease, Metachromatic leukodystrophy, Microcephaly, Micropsia, Migraine, Miller Fisher syndrome, Mini-stroke (transient ischemic attack), Misophonia, Mitochondrial myopathy, Mobius syndrome, Monomelic amyotrophy, Motor skills disorder, Moyamoya disease, Mucopolysaccharidoses, Multi-infarct dementia, Multifocal motor neuropathy, Multiple sclerosis, Multiple system atrophy, Muscular dystrophy, Myalgic encephalomyelitis, Myasthenia gravis, Myelinoclastic diffuse sclerosis, Myoclonic Encephalopathy of infants, Myoclonus, Myopathy, Myotubular myopathy, Myotonia congenita, Narcolepsy, Neuro-Behçet's disease, Neurofibromatosis, Neuroleptic malignant syndrome, Neurological manifestations of AIDS, Neurological sequelae of lupus, Neuromyotonia, Neuronal ceroid lipofuscinosis, Neuronal migration disorders, Neuropathy,

Neurosis, Niemann-Pick disease, Non-24-hour sleep–wake disorder, Nonverbal learning disorder, O'Sullivan-McLeod syndrome, Occipital Neuralgia, Occult Spinal Dysraphism Sequence, Ohtahara syndrome, Olivopontocerebellar atrophy, Opsoclonus myoclonus syndrome, Optic neuritis, Orthostatic Hypotension, Otosclerosis, Overuse syndrome, Palinopsia, Paresthesia, Parkinson's disease, Paramyotonia Congenita, Paraneoplastic diseases, Paroxysmal attacks, Parry-Romberg syndrome, PANDAS, Pelizaeus-Merzbacher disease, Periodic Paralyses, Peripheral neuropathy, Pervasive developmental disorders, Photic sneeze reflex, Phytanic acid storage disease, Pick's disease, Pinched nerve, Pituitary tumors, PMG, Polyneuropathy, Polio, Polymicrogyria, Polymyositis, Porencephaly, Post-Polio syndrome, Postherpetic Neuralgia (PHN), Postural Hypotension, Prader-Willi syndrome, Primary Lateral Sclerosis, Prion diseases, Progressive hemifacial atrophy, Progressive multifocal leukoencephalopathy, Progressive Supranuclear Palsy, Prosopagnosia, Pseudotumor cerebri, Quadrantanopia, Quadriplegia, Rabies, Radiculopathy, Ramsay Hunt syndrome type I, Ramsay Hunt syndrome type II, Ramsay Hunt syndrome type III, Rasmussen encephalitis, Reflex neurovascular dystrophy, Refsum disease, REM sleep behavior disorder, Repetitive stress injury, Restless legs syndrome, Retrovirus-associated myelopathy, Rett syndrome, Reye's syndrome, Rhythmic Movement Disorder, Romberg syndrome, Saint Vitus dance, Sandhoff disease, Schilder's disease, Schizencephaly, Sensory processing disorder, Septo-optic dysplasia, Shaken baby syndrome, Shingles, Shy-Drager syndrome, Sjögren's syndrome, Sleep apnea, Sleeping sickness, Snatiation, Sotos syndrome, Spasticity, Spina bifida, Spinal cord injury, Spinal cord tumors, Spinal muscular atrophy, Spinal and bulbar muscular atrophy, Spinocerebellar ataxia, Split-brain, Steele-Richardson-Olszewski syndrome, Stiff-person syndrome, Stroke, Sturge-Weber syndrome, Stuttering, Subacute sclerosing panencephalitis, Subcortical arteriosclerotic encephalopathy, Superficial siderosis, Sydenham's chorea, Syncope, Synesthesia, Syringomyelia, Tarsal tunnel syndrome, Tardive dyskinesia, Tardive dysphrenia, Tarlov cyst, Tay-Sachs disease, Temporal arteritis, Temporal lobe epilepsy, Tetanus, Tethered spinal cord syndrome, Thomsen disease, Thoracic outlet syndrome, Tic Douloureux, Todd's paralysis, Tourette syndrome, Toxic encephalopathy, Transient ischemic attack, Transmissible spongiform encephalopathies, Transverse myelitis, Traumatic brain injury, Tremor, Trichotillomania, Trigeminal neuralgia, Tropical spastic paraparesis, Trypanosomiasis, Tuberous sclerosis, Unverricht-Lundborg disease, Von Hippel-Lindau disease (VHL), Viliuisk Encephalomyelitis (VE), Wallenberg's syndrome, West syndrome, Whiplash, Williams syndrome, Wilson's disease, or Zellweger syndrome.

[0275] In some cases, the compositions and methods disclosed herein can be used to treat brain cancer or brain tumors. Non-limiting examples of brain cancers or tumors that may be amenable to treatment with vectors and compositions described herein include: gliomas including anaplastic astrocytoma (grade III glioma), astrocytoma (grade II glioma), brainstem glioma, ependymoma, ganglioglioma, ganglioneuroma, glioblastoma (grade IV glioma), glioma, juvenile pilocytic astrocytoma (JPA), low-grade astrocytoma (LGA), medullablastoma, mixed glioma, oligodendroglioma, optic nerve glioma, pilocytic astrocytoma (grade I glioma), and primitive neuroectodermal (PNET); skull base tumors including acoustic neuroma (vestibular schwannoma), acromegaly, adenoma, chondrosarcoma, chordoma, craniopharyngioma, epidermoid tumor, glomus jugulare tumor, infratentorial meningioma, meningioma, pituitary adenoma, pituitary tumor, Rathke's cleft cyst; metastatic cancer including brain metastasis, metastatic brain tumor; other brain tumors including brain cyst, choroid plexus papilloma, CNS lymphoma, colloid cyst, cystic tumor, dermoid tumor, germinoma, lymphoma, nasal carcinoma, naso-pharyngeal tumor, pineal tumor, pineoblastoma, pineocytoma, supratentorial meningioma, and vascular tumor; spinal cord tumors including astrocytoma, ependymoma, meningioma, and schwannoma.

[0276] The present disclosure contemplates, in part, compositions and methods for controlling, managing, preventing, or treating pain in a subject. "Pain" refers to an uncomfortable feeling and/or an unpleasant sensation in the body of a subject. Feelings of pain can range from mild and occasional to severe and constant. Pain can be classified as acute pain or chronic pain. Pain can be nociceptive pain (i.e., pain caused by tissue damage), neuropathic pain or psychogenic pain. In some cases, the pain is caused by or associated with a disease (*e.g.*, cancer, arthritis, diabetes). In other cases, the pain is caused by injury (*e.g.*, sports injury, trauma). Non-limiting examples of pain that are amenable to treatment with the compositions and methods herein include: neuropathic pain including peripheral neuropathy, diabetic neuropathy, post herpetic neuralgia, trigeminal neuralgia, back pain, neuropathy associated with cancer, neuropathy associated with HIV/AIDS, phantom limb pain, carpal tunnel syndrome, central post-stroke pain, pain associated with chronic alcoholism, hypothyroidism, uremia, pain associated with multiple sclerosis, pain associated with spinal cord injury, pain associated with Parkinson's disease, epilepsy, osteoarthritic pain, rheumatoid arthritic pain, visceral pain, and pain associated with vitamin deficiency; and nociceptive pain including pain associated with central nervous system trauma, strains/sprains, and burns; myocardial infarction, acute pancreatitis, post-operative pain, posttraumatic pain, renal colic, pain

associated with cancer, pain associated with fibromyalgia, pain associated with carpal tunnel syndrome, and back pain.

[0277] The compositions and methods herein may be utilized to ameliorate a level of pain in a subject. In some cases, a level of pain in a subject is ameliorated by at least about 5%, at least about 10%, at least about 15%, at least about 20%, at least about 25%, at least about 30%, at least about 35%, at least about 40%, at least about 45%, at least about 50%, at least about 55%, at least about 60%, at least about 65%, at least about 70%, at least about 75%, at least about 80%, at least about 85%, at least about 90%, at least about 95%, at least 99% or about 100%, including all ranges and subranges therebetween. A level of pain in a subject can be assessed by a variety of methods. In some cases, a level of pain is assessed by self-reporting (i.e., a human subject expresses a verbal report of the level of pain he/she is experiencing). In some cases, a level of pain is assessed by behavioral indicators of pain, for example, facial expressions, limb movements, vocalization, restlessness and guarding. These types of assessments may be useful for example when a subject is unable to self-report (*e.g.*, an infant, an unconscious subject, a non-human subject). A level of pain may be assessed after treatment with a composition of the disclosure as compared to the level of pain the subject was experiencing prior to treatment with the composition.

[0278] In various embodiments, a method for controlling, managing, preventing, or treating pain in a subject comprises administering to the subject an effective amount of an engineered receptor contemplated herein. Without wishing to be bound by any particular theory, the present disclosure contemplates using the vectors disclosed herein to modulate neuronal activity to alleviate pain in the subject.

[0279] In various embodiments, a vector encoding an engineered receptor that activates or depolarizes neuronal cells is administered to (or introduced into) one or more neuronal cells that decrease pain sensation, *e.g.,* inhibitory interneurons. In the presence of ligand, the neuronal cell expressing the engineered receptor, is activated and decreases the sensitivity to pain potentiating the analgesic effect of stimulating these neuronal cells.

[0280] In various embodiments, a vector encoding an engineered receptor that deactivates or hyperpolarizes neuronal cells is administered to (or introduced into) one or more neuronal cells that increase pain sensation or sensitivity to pain, *e.g.,* nociceptor, peripheral sensory neurons, C-fibers, Aδ fibers, Aβ fibers, DRG neurons, TGG neurons, and the like. In the presence of ligand, the neuronal cell expressing the engineered receptor, is deactivated and decreases the sensitivity to pain and potentiating an analgesic effect.

[0281] Targeting expression of an engineered receptor to a sub-population of nociceptors can be achieved by one or more of: selection of the vector (*e.g.*, AAV1, AAV1(Y705+731F+T492V), AAV2(Y444+500+730F+T491V), AAV3(Y705+731F), AAV5, AAV5(Y436+693+719F), AAV6, AAV6 (VP3 variant Y705F/Y731F/T492V), AAV-7m8, AAV8, AAV8(Y733F), AAV9, AAV9 (VP3 variant Y731F), AAV10(Y733F), and AAV-ShH10); selection of a promoter; and delivery means.

[0282] In particular embodiments, the compositions and methods contemplated herein are effective in reducing pain. Illustrative examples of pain that are amenable to treatment with the vectors, compositions, and methods contemplated herein, include but are not limited to acute pain, chronic pain, neuropathic pain, nociceptive pain, allodynia, inflammatory pain, inflammatory hyperalgesia, neuropathies, neuralgia, diabetic neuropathy, human immunodeficiency virus-related neuropathy, nerve injury, rheumatoid arthritic pain, osteoarthritic pain, burns, back pain, eye pain, visceral pain, cancer pain (*e.g.*, bone cancer pain), dental pain, headache, migraine, carpal tunnel syndrome, fibromyalgia, neuritis, sciatica, pelvic hypersensitivity, pelvic pain, post herpetic neuralgia, post-operative pain, post stroke pain, and menstrual pain.

[0283] Pain can be classified as acute or chronic. "Acute pain" refers to pain that begins suddenly and is usually sharp in quality. Acute pain might be mild and last just a moment, or it might be severe and last for weeks or months. In most cases, acute pain does not last longer than three months, and it disappears when the underlying cause of pain has been treated or has healed. Unrelieved acute pain, however, may lead to chronic pain. "Chronic pain" refers to ongoing or recurrent pain, lasting beyond the usual course of acute illness or injury or lasting for more than three to six months, and which adversely affects the individual's well-being. In particular embodiments, the term "chronic pain" refers to pain that continues when it should not. Chronic pain can be nociceptive pain or neuropathic pain.

[0284] In some embodiments, the pain is expected or anticipated to develop in association with or as a result of an injury, an infection, or a medical intervention. In some embodiments, the infection causes nerve damage. In some embodiments, the medical intervention is a surgery, such as surgery to the central core of the body. In some embodiments, the medical intervention is a surgery to remove parts or whole of one or more tissues, tumors or organs in the body. In some embodiments, the medical intervention is an amputation. In particular embodiments, the compositions and methods contemplated herein are effective in reducing acute pain. In particular embodiments, the compositions and methods contemplated herein are effective in reducing chronic pain.

[0285] Clinical pain is present when discomfort and abnormal sensitivity feature among the patient's symptoms. Individuals can present with various pain symptoms. Such symptoms include: 1) spontaneous pain which may be dull, burning, or stabbing; 2) exaggerated pain responses to noxious stimuli (hyperalgesia); and 3) pain produced by normally innocuous stimuli (allodynia-Meyer et al., 1994, Textbook of Pain, 13-44). Although patients suffering from various forms of acute and chronic pain may have similar symptoms, the underlying mechanisms may be different and may, therefore, require different treatment strategies. Pain can also therefore be divided into a number of different subtypes according to differing pathophysiology, including nociceptive pain, inflammatory pain, and neuropathic pain.

[0286] In particular embodiments, the compositions and methods contemplated herein are effective in reducing nociceptive pain. In particular embodiments, the compositions and methods contemplated herein are effective in reducing inflammatory pain. In particular embodiments, the compositions and methods contemplated herein are effective in reducing neuropathic pain.

[0287] Nociceptive pain is induced by tissue injury or by intense stimuli with the potential to cause injury. Moderate to severe acute nociceptive pain is a prominent feature of pain from central nervous system trauma, strains/sprains, burns, myocardial infarction and acute pancreatitis, post-operative pain (pain following any type of surgical procedure), posttraumatic pain, renal colic, cancer pain and back pain. Cancer pain may be chronic pain such as tumor related pain (*e.g.*, bone pain, headache, facial pain or visceral pain) or pain associated with cancer therapy (*e.g.*, post chemotherapy syndrome, chronic postsurgical pain syndrome or post radiation syndrome). Cancer pain may also occur in response to chemotherapy, immunotherapy, hormonal therapy or radiotherapy. Back pain may be due to herniated or ruptured intervertebral discs or abnormalities of the lumber facet joints, sacroiliac joints, paraspinal muscles or the posterior longitudinal ligament. Back pain may resolve naturally but in some patients, where it lasts over 12 weeks, it becomes a chronic condition which can be particularly debilitating.

[0288] Neuropathic pain can be defined as pain initiated or caused by a primary lesion or dysfunction in the nervous system. Etiologies of neuropathic pain include, *e.g.*, peripheral neuropathy, diabetic neuropathy, post herpetic neuralgia, trigeminal neuralgia, back pain, cancer neuropathy, HIV neuropathy, phantom limb pain, carpal tunnel syndrome, central post-stroke pain and pain associated with chronic alcoholism, hypothyroidism, uremia, multiple sclerosis, spinal cord injury, Parkinson's disease, epilepsy, and vitamin deficiency.

[0289] Neuropathic pain can be related to a pain disorder, a term referring to a disease, disorder or condition associated with or caused by pain. Illustrative examples of pain disorders include arthritis, allodynia, a typical trigeminal neuralgia, trigeminal neuralgia, somatoform disorder, hypoesthesis, hypealgesia, neuralgia, neuritis, neurogenic pain, analgesia, anesthesia dolorosa, causlagia, sciatic nerve pain disorder, degenerative joint disorder, fibromyalgia, visceral disease, chronic pain disorders, migraine/headache pain, chronic fatigue syndrome, complex regional pain syndrome, neurodystrophy, plantar fasciitis or pain associated with cancer.

[0290] The inflammatory process is a complex series of biochemical and cellular events, activated in response to tissue injury or the presence of foreign substances, which results in swelling and pain. Arthritic pain is a common inflammatory pain.

[0291] Other types of pain that are amenable to treatment with the vectors, compositions, and methods contemplated herein, include but are not limited to pain resulting from musculoskeletal disorders, including myalgia, fibromyalgia, spondylitis, sero-negative (non-rheumatoid) arthropathies, non-articular rheumatism, dystrophinopathy, glycogenolysis, polymyositis and pyomyositis; heart and vascular pain, including pain caused by angina, myocardical infarction, mitral stenosis, pericarditis, Raynaud's phenomenon, scleredoma and skeletal muscle ischemia; head pain, such as migraine (including migraine with aura and migraine without aura), cluster headache, tension-type headache mixed headache and headache associated with vascular disorders; and orofacial pain, including dental pain, otic pain, burning mouth syndrome, and temporomandibular myofascial pain.

[0292] The effective amount of the compositions and methods contemplated herein to reduce the amount of pain experienced by a human subject can be determined using a variety of pain scales. Patient self-reporting can be used to assess whether pain is reduced; see, *e.g.*, Katz and Melzack (1999) Surg. Clin. North Am. 79:231. Alternatively, an observational pain scale can be used. The LANSS Pain Scale can be used to assess whether pain is reduced; see, *e.g.*, Bennett (2001) Pain 92:147. A visual analog pain scale can be used; see, *e.g.*, Schmader (2002) Clin. J. Pain 18:350. The Likert pain scale can be used; *e.g.*, where 0 is no pain, 5 is moderate pain, and 10 is the worst pain possible. Self -report pain scales for children include, *e.g.*, Faces Pain Scale; Wong-Baker FACES Pain Rating Scale; and Colored Analog Scale. Self-report pain scales for adults include, *e.g.*, Visual Analog Scale; Verbal Numerical Rating Scale; Verbal Descriptor Scale; and Brief Pain Inventory. Pain measurement scales include, *e.g.*, Alder Hey Triage Pain Score (Stewart et al. (2004) Arch. Dis. Child. 89:625); Behavioral Pain Scale (Payen et al. (2001) Critical Care Medicine 29:2258); Brief Pain Inventory

(Cleeland and Ryan (1994) Ann. Acad. Med. Singapore 23: 129); Checklist of Nonverbal Pain Indicators (Feldt (2000) Pain Manag. Nurs. 1 : 13); Critical-Care Pain Observation Tool (Gelinas et al. (2006) Am. J. Crit. Care 15:420); COMFORT scale (Ambuel et al. (1992) J. Pediatric Psychol. 17:95); Dallas Pain Questionnaire (Ozguler et al. (2002) Spine 27:1783); Dolorimeter Pain Index (Hardy et al. (1952) Pain Sensations and Reactions Baltimore: The Williams & Wilkins Co.); Faces Pain Scale - Revised (Hicks et al. (2001) Pain 93:173); Face Legs Activity Cry Consolability Scale; McGill Pain Questionnaire (Melzack (1975) Pain 1 :277); Descriptor Differential Scale (Gracely and Kwilosz (1988) Pain 35:279); Numerical 1 1 point Box (Jensen et al. (1989) Clin. J. Pain 5: 153); Numeric Rating Scale (Hartrick et al. (2003) Pain Pract. 3:310); Wong-Baker FACES Pain Rating Scale; and Visual Analog Scale (Huskisson (1982) J. Rheumatol. 9:768).

[0293] In particular embodiments, a method of relieving pain in a subject is provided, the method comprising introducing an engineered receptor into a neuronal cell and controlling the activity of the cell by providing an effective amount of a ligand that activates the engineered receptor, thereby relieving pain in the subject. The method provides significant analgesia for pain without off-target effects, such as general central nervous system depression. In certain embodiments, the method provides a 1%, 5%, 10%, 15%, 20%, 25%, 30%, 35%, 40%, 45%, 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or more including all ranges and subranges therebetween) reduction in the neuropathic pain in a subject compared to an untreated subject. In some embodiments, the method comprises the step of measuring pain in the subject before and after the administration of the ligand, wherein the pain in the subject is reduced 1%, 5%, 10%, 15%, 20%, 25%, 30%, 35%, 40%, 45%, 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% or more, including all ranges and subranges therebetween. In such instances, the measuring may occur 4 hours or more after administration of the ligand, e.g. 8 hours 12 hours, 16 hours, 24 hours, 36 hours, 48 hours, 3 days, or 4 days or more after administration of the ligand.

[0294] In particular embodiments, the vectors contemplated herein are administered or introduced into one or more neuronal cells. The neuronal cells may be the same type of neuronal cells, or a mixed population of different types of neuronal cells. In one embodiment, the neuronal cell is a nociceptor or peripheral sensory neuron. Illustrative examples of sensory neurons include, but are not limited to, dorsal root ganglion (DRG) neurons and trigeminal ganglion (TGG) neurons. In one embodiment, the neuronal cell is an inhibitory interneuron involved in the neuronal pain circuit.

[0295] In some cases, a vector encoding an engineered receptor is administered to a subject in need thereof. Non-limiting examples of methods of administration include subcutaneous administration, intravenous administration, intramuscular administration, intradermal administration, intraperitoneal administration, oral administration, infusion, intracranial administration, intrathecal administration, intranasal administration, intraganglionic administration, intraspinal administration, cisterna magna administration and intraneural administration. In some cases, administration can involve injection of a liquid formulation of the vector. In other cases, administration can involve oral delivery of a solid formulation of the vector. In some cases, the oral formulation can be administered with food. In particular embodiments, a vector is parenterally, intravenously, intramuscularly, intraperitoneally, intrathecally, intraneurally, intraganglionicly, intraspinally, or intraventricularly administered to a subject in order to introduce the vector into one or more neuronal cells. In various embodiments, the vector is rAAV.

[0296] In one embodiment, AAV is administered to sensory neuron or nociceptor, *e.g.*, DRG neurons, TGG neurons, etc. by intrathecal (IT) or intraganglionic (IG) administration. The IT route delivers AAV to the cerebrospinal fluid (CSF). This route of administration may be suitable for the treatment of *e.g.*, chronic pain or other peripheral nervous system (PNS) or central nervous system (CNS) indications. In animals, IT administration has been achieved by inserting an IT catheter through the *cisterna magna* and advancing it caudally to the lumbar level. In humans, IT delivery can be easily performed by lumbar puncture (LP), a routine bedside procedure with excellent safety profile.

[0297] In a particular case, a vector may be administered to a subject by intraganglionic administration. Intraganglionic administration may involve an injection directly into one or more ganglia. The IG route may deliver AAV directly into the DRG or TGG parenchyma. In animals, IG administration to the DRG is performed by an open neurosurgical procedure that is not desirable in humans because it would require a complicated and invasive procedure. In humans, a minimally invasive, CT imaging-guided technique to safely target the DRG can be used. A customized needle assembly for convection enhanced delivery (CED) can be used to deliver AAV into the DRG parenchyma. In a non-limiting example, a vector of the disclosure may be delivered to one or more dorsal root ganglia and/or trigeminal ganglia for the treatment of chronic pain. In another non-limiting example, a vector of the disclosure may be delivered to the nodose ganglion (vagus nerve) to treat epilepsy.

[0298] In yet another particular case, a vector may be administered to the subject by intracranial administration (i.e., directly into the brain). In non-limiting examples of

intracranial administration, a vector of the disclosure may be delivered into the cortex of the brain to treat *e.g.*, an epileptic seizure focus, into the paraventricular hypothalamus to treat *e.g.*, a satiety disorder, or into the amygdala central nucleus to treat *e.g.*, a satiety disorder. In another particular case, a vector may be administered to a subject by intraneural injection (i.e., directly into a nerve). The nerve may be selected based on the indication to be treated, for example, injection into the sciatic nerve to treat chronic pain or injection into the vagal nerve to treat epilepsy or a satiety disorder. In yet another particular case, a vector may be administered to a subject by subcutaneous injection, for example, into the sensory nerve terminals to treat chronic pain.

[0299] A vector dose may be expressed as the number of vector genome units delivered to a subject. A "vector genome unit" as used herein refers to the number of individual vector genomes administered in a dose. The size of an individual vector genome will generally depend on the type of viral vector used. Vector genomes of the disclosure may be from about 1.0 kilobase, 1.5 kilobases, 2.0 kilobases, 2.5 kilobases, 3.0 kilobases, 3.5 kilobases, 4.0 kilobases, 4.5 kilobases, 5.0 kilobases, 5.5 kilobases, 6.0 kilobases, 6.5 kilobases, 7.0 kilobases, 7.5 kilobases, 8.0 kilobases, 8.5 kilobases, 9.0 kilobases, 9.5 kilobases, 10.0 kilobases, to more than 10.0 kilobases. Therefore, a single vector genome may include up to or greater than 10,000 base pairs of nucleotides. In some cases, a vector dose may be about 1×10^6, 2×10^6, 3×10^6, 4×10^6, 5×10^6, 6×10^6, 7×10^6, 8×10^6, 9×10^6, 1×10^7, 2×10^7, 3×10^7, 4×10^7, 5×10^7, 6×10^7, 7×10^7, 8×10^7, 9×10^7, 1×10^8, 2×10^8, 3×10^8, 4×10^8, 5×10^8, 6×10^8, 7×10^8, 8×10^8, 9×10^8, 1×10^9, 2×10^9, 3×10^9, 4×10^9, 5×10^9, 6×10^9, 7×10^9, 8×10^9, 9×10^9, 1×10^{10}, 2×10^{10}, 3×10^{10}, 4×10^{10}, 5×10^{10}, 6×10^{10}, 7×10^{10}, 8×10^{10}, 9×10^{10}, 1×10^{11}, 2×10^{11}, 3×10^{11}, 4×10^{11}, 5×10^{11}, 6×10^{11}, 7×10^{11}, 8×10^{11}, 9×10^{11}, 1×10^{12}, 2×10^{12}, 3×10^{12}, 4×10^{12}, 5×10^{12}, 6×10^{12}, 7×10^{12}, 8×10^{12}, 9×10^{12}, 1×10^{13}, 2×10^{13}, 3×10^{13}, 4×10^{13}, 5×10^{13}, 6×10^{13}, 7×10^{13}, 8×10^{13}, 9×10^{13}, 1×10^{14}, 2×10^{14}, 3×10^{14}, 4×10^{14}, 5×10^{14}, 6×10^{14}, 7×10^{14}, 8×10^{14}, 9×10^{14}, 1×10^{15}, 2×10^{15}, 3×10^{15}, 4×10^{15}, 5×10^{15}, 6×10^{15}, 7×10^{15}, 8×10^{15}, 9×10^{15}, 1×10^{16}, 2×10^{16}, 3×10^{16}, 4×10^{16}, 5×10^{16}, 6×10^{16}, 7×10^{16}, 8×10^{16}, 9×10^{16}, 1×10^{17}, 2×10^{17}, 3×10^{17}, 4×10^{17}, 5×10^{17}, 6×10^{17}, 7×10^{17}, 8×10^{17}, 9×10^{17}, 1×10^{18}, 2×10^{18}, 3×10^{18}, 4×10^{18}, 5×10^{18}, 6×10^{18}, 7×10^{18}, 8×10^{18}, 9×10^{18}, 1×10^{19}, 2×10^{19}, 3×10^{19}, 4×10^{19}, 5×10^{19}, 6×10^{19}, 7×10^{19}, 8×10^{19}, 9×10^{19}, 1×10^{20}, 2×10^{20}, 3×10^{20}, 4×10^{20}, 5×10^{20}, 6×10^{20}, 7×10^{20}, 8×10^{20}, 9×10^{20} or more vector genome units.

[0300] In particular embodiments, a vector contemplated herein is administered to a subject at a titer of at least about 1×10^9 genome particles/mL, at least about 1×10^{10} genome

particles/mL, at least about 5 x 10^{10} genome particles/mL, at least about 1 x 10^{11} genome particles/mL, at least about 5 x 10^{11} genome particles/mL, at least about 1 x 10^{12} genome particles/mL, at least about 5 x 10^{12} genome particles/mL, at least about 6 x 10^{12} genome particles/mL, at least about 7 x 10^{12} genome particles/mL, at least about 8 x 10^{12} genome particles/mL, at least about 9 x 10^{12} genome particles/mL, at least about 10 x 10^{12} genome particles/mL, at least about 15 x 10^{12} genome particles/mL, at least about 20 x 10^{12} genome particles/mL, at least about 25 x 10^{12} genome particles/mL, at least about 50 x 10^{12} genome particles/mL, or at least about 100 x 10^{12} genome particles/mL. The terms "genome particles (gp)" or "genome equivalents" or "genome copies" (gc) as used in reference to a viral titer, refer to the number of virions containing the recombinant AAV DNA genome, regardless of infectivity or functionality. The number of genome particles in a particular vector preparation can be measured by well understood methods in the art, for example, quantitative PCR of genomic DNA or for example, in Clark et al. (1999) Hum. Gene Ther., 10:1031-1039; Veldwijk et al. (2002) Mol. Ther., 6:272-278.

[0301] A vector of the disclosure may be administered in a volume of fluid. In some cases, a vector may be administered in a volume of about 0.1mL, 0.2mL, 0.3mL, 0.4mL, 0.5mL, 0.6mL, 0.7mL, 0.8mL, 0.9mL, 1.0mL, 2.0mL, 3.0mL, 4.0mL, 5.0mL, 6.0mL, 7.0mL, 8.0mL, 9.0mL, 10.0mL, 11.0mL, 12.0mL, 13.0mL, 14.0mL, 15.0mL, 16.0mL, 17.0mL, 18.0mL, 19.0mL, 20.0mL or greater than 20.0mL. In some cases, a vector dose may be expressed as a concentration or titer of vector administered to a subject. In this case, a vector dose may be expressed as the number of vector genome units per volume (i.e., genome units/volume).

[0302] In particular embodiments, a vector contemplated herein is administered to a subject at a titer of at least about 5 x 10^9 infectious units/mL, at least about 6 x 10^9 infectious units/mL, at least about 7 x 10^9 infectious units/mL, at least about 8 x 10^9 infectious units/mL, at least about 9 x 10^9 infectious units/mL, at least about 1 x 10^{10} infectious units/mL, at least about 1.5 x 10^{10} infectious units/mL, at least about 2 x 10^{10} infectious units/mL, at least about 2.5 x 10^{10} infectious units/mL, at least about 5 x 10^{10} infectious units/mL, at least about 1 x 10^{11} infectious units/mL, at least about 2.5 x 10^{11} infectious units/mL, at least about 5 x 10^{11} infectious units/mL, at least about 1 x 10^{12} infectious units/mL, at least about 2.5 x 10^{12} infectious units/mL, at least about 5 x 10^{12} infectious units/mL, at least about 1 x 10^{13} infectious units/mL, at least about 5 x 10^{13} infectious units/mL, at least about 1 x 10^{14} infectious units/mL. The terms "infection unit (iu)," "infectious particle," or "replication unit," as used in reference to a viral titer, refer to the number of infectious and replication-competent recombinant AAV

vector particles as measured by the infectious center assay, also known as replication center assay, as described, for example, in McLaughlin et al. (1988) J. Virol., 62:1963-1973.

[0303] In particular embodiments, a vector contemplated herein is administered to a subject at a titer of at least about 5 x 10^{10} transducing units/mL, at least about 1 x 10^{11} transducing units/mL, at least about 2.5 x 10^{11} transducing units/mL, at least about 5 x 10^{11} transducing units/mL, at least about 1 x 10^{12} transducing units/mL, at least about 2.5 x 10^{12} transducing units/mL, at least about 5 x 10^{12} transducing units/mL, at least about 1 x 10^{13} transducing units/mL, at least about 5 x 10^{13} transducing units/mL, at least about 1 x 10^{14} transducing units/mL. The term "transducing unit" (tu)" as used in reference to a viral titer, refers to the number of infectious recombinant AAV vector particles that result in the production of a functional transgene product as measured in functional assays such as described in, for example, in Xiao et al. (1997) Exp. Neurobiol., 144:113-124; or in Fisher et al. (1996) J. Virol., 70:520-532 (LFU assay).

[0304] The vector dose will generally be determined by the route of administration. In a particular example, an intraganglionic injection may include from about 1 x 10^{9} to about 1 x 10^{13} vector genomes in a volume from about 0.1mL to about 1.0mL. In another particular case, an intrathecal injection may include from about 1 x 10^{10} to about 1 x 10^{15} vector genomes in a volume from about 1.0 mL to about 12.0 mL. In yet another particular case, an intracranial injection may include from about 1 x 10^{9} to about 1 x 10^{13} vector genomes in a volume from about 0.1 mL to about 1.0 mL. In another particular case, an intraneural injection may include from about 1 x 10^{9} to about 1 x 10^{13} vector genomes in a volume from about 0.1 mL to about 1.0 mL. In another particular example, an intraspinal injection may include from about 1 x 10^{9} to about 1 x 10^{13} vector genomes in a volume from about 0.1 mL to about 1.0 mL. In yet another particular case, a cisterna magna infusion may include from about 5 x 10^{9} to about 5 x 10^{13} vector genomes in a volume from about 0.5 mL to about 5.0 mL. In yet another particular case, a subcutaneous injection may include from about 1 x 10^{9} to about 1 x 10^{13} vector genomes in a volume from about 0.1mL to about 1.0mL.

[0305] In some cases, a vector is delivered to a subject by infusion. A vector dose delivered to a subject by infusion can be measured as a vector infusion rate. Non-limiting examples of vector infusion rates include: 1-10 μL/min for intraganglionic, intraspinal, intracranial or intraneural administration; and 10-1000 μL/min for intrathecal or cisterna magna administration. In some cases, the vector is delivered to a subject by MRI-guided Convection Enhanced Delivery (CED). This technique enables increased viral spread and

transduction distributed throughout large volumes of the brain, as well as reduces reflux of the vector along the needle path.

[0306] In various embodiments, a method is provided comprising administering a vector encoding a engineered receptor, that deactivates or hyperpolarizes neuronal cells, to one or more neuronal cells that increase pain sensation or sensitivity to pain, and administering a ligand that specifically binds the neuronal cell expressing the engineered receptor to the subject, thereby deactivating the cell, decreasing the sensitivity to pain and potentiating an analgesic effect.

[0307] In various embodiments, a method is provided comprising administering a vector encoding a engineered receptor, that activates or polarizes neuronal cells, to one or more neuronal cells that decrease pain sensation or sensitivity to pain, and administering a ligand that specifically binds the neuronal cell expressing the engineered receptor to the subject, thereby activating the cell, decreasing the sensitivity to pain and potentiating an analgesic effect.

[0308] Formulations of ligands may be administered to a subject by various routes. Non-limiting examples of methods of administration include subcutaneous administration, intravenous administration, intramuscular administration, transdermal administration, intradermal administration, intraperitoneal administration, oral administration, infusion, intracranial administration, intrathecal administration, intranasal administration, intraganglionic administration, and intraneural administration. In some cases, administration can involve injection of a liquid formulation of the ligand. In other cases, administration can involve oral delivery of a solid formulation of the ligand. In a particular case, a ligand is administered by oral administration (*e.g.*, a pill, tablet, capsule and the like). In some cases, the oral composition can be administered with food. In another particular case, a ligand is administered by intrathecal injection (i.e., into the subarachnoid space of the spinal cord) for delivery to the cerebrospinal fluid (CSF) of the subject. In another particular case, a ligand is administered topically (*e.g.*, dermal patch, cream, lotion, ointment and the like).

[0309] The dosages of the ligands administered to a subject are not subject to absolute limits, but will depend on the nature of the composition and its active ingredients and its unwanted side effects (*e.g.,* immune response against the antibody), the subject being treated and the type of condition being treated and the manner of administration. Generally, the dose will be a therapeutically effective amount, such as an amount sufficient to achieve a desired biological effect, for example an amount that is effective to decrease or attenuate the level of pain experienced by the subject. In particular embodiments, the dose can also be a prophylactic

amount or an effective amount. A therapeutically effective amount of ligand may depend on the route of administration, the indication being treated, and/or the ligand selected for use.

[0310] In one embodiment, the ligand is first administered to the subject prior to administration of the vector. A therapeutically effective amount of ligand may be administered to a subject at some time after delivery of a vector. Generally, after delivery of a vector, there will be a period of time required for one or more cells of the subject to generate a protein (i.e., engineered receptor) encoded by the vector. During this period of time, administration of a ligand to the subject may not be beneficial to the subject. In this situation, it may be suitable to administer the ligand after an amount of engineered receptor has been produced by one or more cells of the subject.

[0311] In one embodiment, the ligand is first administered to the subject at about the same time that the vector is administered to the subject.

[0312] In one embodiment, the ligand is first administered 1, 2, 3, 4, 5, 6, 7, 8, 9, 11, or 12 hours, days, weeks, months, or years after administration of the vector to the subject. In some cases, a therapeutically effective amount of a ligand may be administered to a subject at least one day, two days, three days, four days, five days, six days, seven days, eight days, nine days, 10 days, 11 days, 12 days, 13 days, 14 days, 15 days, 16 days, 17 days, 18 days, 19 days, 20 days, 21 days, 22 days, 23 days, 24 days, 25 days, 26 days, 27 days, 28 days, 29 days, 30 days or more than 30 days after delivery of the vector. In a particular example, a therapeutically effective amount of a ligand is administered to a subject at least one week after delivery of a vector. In a further example, the therapeutically effective amount of ligand is administered to the subject daily for at least three consecutive days.

[0313] A therapeutically effective amount or dose of a ligand of the disclosure can be expressed as mg or μg of the ligand per kg of subject body mass. In some instances, a therapeutically effective amount of a ligand may be about 0.001 μg/kg, about 0.005 μg/kg, about 0.01 μg/kg, about 0.05 μg/kg, about 0.1 μg/kg, about 0.5 μg/kg, about 1 μg/kg, about 2 μg/kg, about 3 μg/kg, about 4 μg/kg, about 5 μg/kg, about 6 μg/kg, about 7 μg/kg, about 8 μg/kg, about 9 μg/kg, about 10 μg/kg, about 20 μg/kg, about 30 μg/kg, about 40 μg/kg, about 50 μg/kg, about 60 μg/kg, about 70 μg/kg, about 80 μg/kg, about 90 μg/kg, about 100 μg/kg, about 120 μg/kg, about 140 μg/kg, about 160 μg/kg, about 180 μg/kg, about 200 μg/kg, about 220 μg/kg, about 240 μg/kg, about 260 μg/kg, about 280 μg/kg, about 300 μg/kg, about 320 μg/kg, about 340 μg/kg, about 360 μg/kg, about 380 μg/kg, about 400 μg/kg, about 420 μg/kg, about 440 μg/kg, about 460 μg/kg, about 480 μg/kg, about 500 μg/kg, about 520 μg/kg, about

540 μg/kg, about 560 μg/kg, about 580 μg/kg, about 600 μg/kg, about 620 μg/kg, about 640 μg/kg, about 660 μg/kg, about 680 μg/kg, about 700 μg/kg, about 720 μg/kg, about 740 μg/kg, about 760 μg/kg, about 780 μg/kg, about 800 μg/kg, about 820 μg/kg, about 840 μg/kg, about 860 μg/kg, about 880 μg/kg, about 900 μg/kg, about 920 μg/kg, about 940 μg/kg, about 960 μg/kg, about 980 μg/kg, about 1 mg/kg, about 2 mg/kg, about 3 mg/kg, about 4 mg/kg, about 5 mg/kg, about 6 mg/kg, about 7 mg/kg, about 8 mg/kg, about 9 mg/kg, about 10 mg/kg, or greater than 10 mg/kg.

[0314] In particular embodiments, the dose of ligand administered to a subject is at least about 0.001 micrograms per kilogram (μg/kg), at least about 0.005 μg/kg, at least about 0.01 μg/kg, at least about 0.05 μg/kg, at least about 0.1 μg/kg, at least about 0.5 μg/kg, 0.001 milligrams per kilogram (mg/kg), at least about 0.005 mg/kg, at least about 0.01 mg/kg, at least about 0.05 mg/kg, at least about 0.1 mg/kg, at least about 0.5 mg/kg , at least about 1 mg/kg, at least about 2 mg/kg, at least about 3 mg/kg, at least about 4 mg/kg, at least about 5 mg/kg, at least about 5 mg/kg, at least about 6 mg/kg, at least about 7 mg/kg, at least about 8 mg/kg, at least about 8 mg/kg, at least about 9 mg/kg, or at least about 10 or more mg/kg.

[0315] In particular embodiments, the dose of ligand administered to a subject is at least about 0.001 μg/kg to at least about 10 mg/kg, at least about 0.01 μg/kg to at least about 10 mg/kg, at least about 0.1 μg/kg to at least about 10 mg/kg, at least about 1 μg/kg to at least about 10 mg/kg, at least about 0.01 mg/kg to at least about 10 mg/kg, at least about 0.1 mg/kg to at least about 10 mg/kg, or at least about 1 mg/kg to at least about 10 mg/kg, or any intervening range thereof.

[0316] In some aspects, a therapeutically effective amount of a ligand can be expressed as a molar concentration (i.e., M or mol/L). In some cases, a therapeutically effective amount of a ligand can be about 1nM, 2nM, 3nM, 4nM, 5nM, 6nM, 7nM, 8nM, 9nM, 10nM, 20nM, 30nM, 40nM, 50nM, 60nM, 70nM, 80nM, 90nM, 100nM, 200nM, 300nM, 400nM, 500nM, 600nM, 700nM, 800nM, 900nM, 1mM, 2mM, 3mM, 4mM, 5mM, 6mM, 7mM, 8mM, 9mM, 10mM, 20mM, 30mM, 40mM, 50mM, 60mM, 70mM, 80mM, 90mM, 100mM, 200mM, 300mM, 400mM, 500mM, 600mM, 700mM, 800mM, 900mM, 1000mM or greater.

[0317] A therapeutically effective amount of a ligand can be administered once or more than once each day. In some cases, a therapeutically effective amount of a ligand is administered as needed (*e.g.*, when pain relief is needed). The ligand may be administered serially (*e.g.*, every day without a break for the duration of the treatment regimen). In some cases, the treatment regimen can be less than a week, a week, two weeks, three weeks, a month,

or greater than a month. In some cases, a therapeutically effective amount of a ligand is administered for a day, at least two consecutive days, at least three consecutive days, at least four consecutive days, at least five consecutive days, at least six consecutive days, at least seven consecutive days, at least eight consecutive days, at least nine consecutive days, at least ten consecutive days, or at least greater than ten consecutive days. In a particular case, a therapeutically effective amount of a ligand is administered for three consecutive days. In some cases, a therapeutically effective amount of a ligand can be administered one time per week, two times per week, three times per week, four times per week, five times per week, six times per week, seven times per week, eight times per week, nine times per week, 10 times per week, 11 times per week, 12 times per week, 13 times per week, 14 times per week, 15 times per week, 16 times per week, 17 times per week, 18 times per week, 19 times per week, 20 times per week, 25 times per week, 30 times per week, 35 times per week, 40 times per week, or greater than 40 times per week. In some cases, a therapeutically effective amount of a ligand can be administered one time per day, two times per day, three times per day, four times per day, five times per day, six times per day, seven times per day, eight times per day, nine times per day, 10 times per day, or greater than 10 times per day. In some cases, a therapeutically effective amount of a ligand is administered at least every hour, at least every two hours, at least every three hours, at least every four hours, at least every five hours, at least every six hours, at least every seven hours, at least every eight hours, at least every nine hours, at least every 10 hours, at least every 11 hours, at least every 12 hours, at least every 13 hours, at least every 14 hours, at least every 15 hours, at least every 16 hours, at least every 17 hours, at least every 18 hours, at least every 19 hours, at least every 20 hours, at least every 21 hours, at least every 22 hours, at least every 23 hours, or at least every day. The dose of ligand may be administered to the subject continuously, or 1, 2, 3, 4, or 5 times a day; 1, 2, 3, 4, 5, 6, or 7 times a week, 1, 2, 3, or 4 times a month, once every 2, 3, 4, 5, or 6 months, or once a year, or at even longer intervals. The duration of treatment can last a day, 1, 2, or 3 weeks, 1, 2, 3, 4, 5, 7, 8, 9, 10, or 11 months, 1, 2, 3, 4, 5, or more years, or longer.

[0318] A subject treated by methods and compositions disclosed herein can be a human, or can be a non-human animal. The term “treat” and its grammatical equivalents used herein generally refer to the use of a composition or method to reduce, eliminate, or prevent symptoms of a disease and includes achieving a therapeutic benefit and/or a prophylactic benefit. By therapeutic benefit is meant slowing the progression of, halting the progression of, reversing the progression of, or eradication or amelioration of the symptoms of the disorder or condition being treated. A prophylactic benefit of treatment includes reducing the risk of a

condition, retarding the progress of a condition, or decreasing the likelihood of occurrence of a condition.

[0319] Non-limiting examples of non-human animals include a non-human primate, a livestock animal, a domestic pet, and a laboratory animal. For example, a non-human animal can be an ape (*e.g.*, a chimpanzee, a baboon, a gorilla, or an orangutan), an old world monkey (*e.g.*, a rhesus monkey), a new world monkey, a dog, a cat, a bison, a camel, a cow, a deer, a pig, a donkey, a horse, a mule, a lama, a sheep, a goat, a buffalo, a reindeer, a yak, a mouse, a rat, a rabbit, or any other non-human animal. The compositions and methods as described herein are amenable to the treatment of a veterinary animal. A veterinary animal can include, without limitation, a dog, a cat, a horse, a cow, a sheep, a mouse, a rat, a guinea pig, a hamster, a rabbit, a snake, a turtle, and a lizard. In some aspects, contacting the tissue or cell population with a composition comprises administering the composition to a cell population or subject. In some embodiments, administration occurs *in vitro*, for example by adding the composition to a cell culture system. In some aspects, administration occurs *in vivo*, for example by administration through a particular route. Wherein more than one composition is to be administered, the compositions may be administered via the same route at the same time (*e.g.*, on the same day), or via the same route at different times. Alternatively, the compositions may be administered via different routes at the same time (*e.g.*, on the same day) or via different routes at different times.

[0320] The number of times a composition is administered to a subject in need thereof depends on the discretion of a medical professional, the disorder, the severity of the disorder, and the subject's response to the formulation. In some aspects, administration of a composition occurs at least once. In further aspects, administration occurs more than once, for example 2, 3, 4, 5, 6, 7, 8, 9, 10 or more times in a given period. The dosage of each administration and/or frequency of administrations may be adjusted as necessary based on the patient's condition and physiologically responses.

[0321] In some embodiments, compositions may be administered a sufficient amount of times to achieve a desired physiologic effect or improvement in a subject's condition. In the case wherein the subject's condition does not improve, upon the doctor's discretion the composition may be administered chronically, that is, for an extended period of time, including throughout the duration of the subject's life in order to ameliorate or otherwise control or limit the symptoms of the subject's disease or condition. In the case wherein the subject's status does improve, upon the doctor's discretion the composition may administered continuously; alternatively, the dose of drug being administered may be temporarily reduced or temporarily

suspended for a certain length of time (*i.e.*, a "drug holiday"). The length of the drug holiday varies between 2 days and 1 year, including by way of example only, 2 days, 3 days, 4 days, 5 days, 6 days, 7 days, 10 days, 12 days, 15 days, 20 days, 28 days, 35 days, 50 days, 70 days, 100 days, 120 days, 150 days, 180 days, 200 days, 250 days, 280 days, 300 days, 320 days, 350 days, and 365 days. The dose reduction during a drug holiday may be from 10%- 100%, including by way of example only 10%, 15%, 20%, 25%, 30%, 35%, 40%, 45%, 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, and 100%.

[0322] Where compositions are administered more than once, each administration may be performed by the same actor and/or in the same geographical location. Alternatively, each administration may be performed by a different actor and/or in a different geographical location.

With regard to human and veterinary treatment, the amount of a particular ligand(s) that is administered may be dependent on a variety of factors, including the disorder being treated and the severity of the disorder; activity of the specific ligand(s) employed; the age, body weight, general health, sex and diet of the patient; the time of administration, route of administration, and rate of excretion of the specific ligand(s) employed; the duration of the treatment; drugs used in combination or coincidental with the specific ligand(s) employed; the judgment of the prescribing physician or veterinarian; and like factors known in the medical and veterinary arts. Similarly, the effective concentration of a given composition may be dependent on a variety of factors including the age, sex, weight, genetic status, and overall health of the patient or subject.

Kits

[0323] In one aspect, the present disclosure provides kits comprising a vector comprising a polynucleotide encoding an engineered receptor of the disclosure. In one aspect, the present disclosure provides kits comprising the engineered receptor of the disclosure.

[0324] In some embodiments, the kit comprises (a) a vector comprising a polynucleotide encoding an engineered receptor of the disclosure; and (b) a non-native ligand of the disclosure. In some embodiments, the vector is a viral vector. In some embodiments, the vector is an AAV vector. In some embodiments, the kit comprises instructions for administering the vector. In some embodiments, the kit comprises a device adapted to administration of the vector.

[0325] In some embodiments, the kit comprises (a) an engineered receptor of the disclosure; and (b) a non-native ligand of the disclosure.

[0326] Exemplary combinations of engineered receptors described herein and non-native ligands that can comprise the kits of the present disclosure are provided in Table 29 below. Each of the engineered receptors in Table 29 may be present as a protein, a polynucleotide encoding the protein, or a vector comprising the polynucleotide encoding the protein. In some embodiments, the engineered receptor comprises a ligand binding domain derived from human α7-nAChR. In some embodiments, the engineered receptor comprises an ion pore domain derived from human Glycine receptor. In some embodiments, the human Glycine receptor is human Glycine receptor α1. In some embodiments, the engineered receptor comprises a polypeptide sequence having at least 85%, at least 90%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, at least 99.5%, or 100% identical to SEQ ID NO: 33 except for the indicated mutation in Table 29.

Table 29: Exemplary Kits

Engineered Receptor with Amino Acid Substitution(s) Corresponding to the Indicated Position(s) in SEQ ID NO: 4	Non-native ligand	Non-limiting Example of the Engineered Receptor
L131S_S172D	CNL001	CODA534
L131T_S172D	CNL001	CODA535
L131D_S172D	CNL002	CODA536
L131D_S172D	AZD-0328	CODA536
L131D_S172D	Facinicline	CODA536
Y115D_S170T	Facinicline	CODA805
Y115D_S170T	TC-6987	CODA805
Y115D_L131Q	AZD-0328	CODA806
Y115D_L131Q	Facinicline	CODA806
Y115D_L131Q	TC-6987	CODA806
Y115D_L131E	TC-5619	CODA807
Y115D_L131E	AZD-0328	CODA807
Y115D_L131E	Facinicline	CODA807
Y115D_L131E	TC-6987	CODA807
Y140I	CNL001	CODA952
Y140I	TC-5619	CODA952
Y140I	CNL002	CODA952
Y140I	Facinicline	CODA952
Y140C	CNL001	CODA965
Y140C	TC-5619	CODA965
Y140C	CNL002	CODA965
Y140C	ABT-126	CODA965
Y140C	TC-6987	CODA965
R101F_L131G	CNL001	CODA1025
R101F_L131G	TC-5619	CODA1025
R101F_L131G	CNL002	CODA1025
R101F_L131G	AZD-0328	CODA1025
R101F_L131G	TC-6987	CODA1025
R101F_L131G	Varenicline	CODA1025
R101F_L131D	CNL001	CODA1027

Engineered Receptor with Amino Acid Substitution(s) Corresponding to the Indicated Position(s) in SEQ ID NO: 4	Non-native ligand	Non-limiting Example of the Engineered Receptor
R101F_L131D	TC-5619	CODA1027
R101F_L131D	CNL002	CODA1027
R101F_L131D	TC-6987	CODA1027
Y115E_Y210W	TC-5619	CODA1039
Y115E_Y210W	CNL002	CODA1039
Y115E_Y210W	ABT-126	CODA1039
R101W_Y210V	TC-5619	CODA1045
R101F_Y210V	TC-5619	CODA1047
R101F_Y210F	CNL001	CODA1048
R101F_Y210F	TC-5619	CODA1048
R101M_L131A	CNL001	CODA1053
R101M_L131A	TC-5619	CODA1053
R101M_L131A	Varenicline	CODA1053
R101M_L131F	CNL001	CODA1054
R101M_L131F	TC-5619	CODA1054
R101M_L131F	Varenicline	CODA1054
R101W_Y115E_Y210W	TC-5619	CODA1055
R101F_Y115E_Y210W	TC-5619	CODA1056
W77F_R101F_L131D	CNL001	CODA1138
W77F_R101F_L131D	CNL002	CODA1138
W77F_R101F_L131D	ABT-126	CODA1138
R101F_L131N_S172D	CNL001	CODA1140
R101F_L131N_S172D	CNL002	CODA1140
Q139E_S172D	CNL001	CODA1157
Q139E_S172D	CNL002	CODA1157
S172D_Y210W	CNL001	CODA1173
S172D_Y210W	CNL002	CODA1173
S172D_Y210W	ABT-126	CODA1173
L131S_S172D	CNL001	CODA534
L131T_S172D	CNL001	CODA535
L131D_S172D	CNL002	CODA536

[0327] In some embodiments, the kit further comprises packaging material and one or more components therein. A kit may include a label or packaging insert including a description of the components or instructions for use in vitro, in vivo, or ex vivo, of the components therein.

[0328] Labels or inserts can include identifying information of one or more components therein, dose amounts, clinical pharmacology of the active ingredient(s) including mechanism of action, pharmacokinetics and pharmacodynamics. Labels or inserts can include information identifying the manufacturer, lot numbers, manufacturer location and date, expiration dates. Labels or inserts can include information identifying manufacturer information, lot numbers, manufacturer location and date. Labels or inserts can include information on a disease a kit component may be used for. Labels or inserts can include instructions for the clinician or subject for using one or more of the kit components in a method,

use, or treatment protocol or therapeutic regimen. Instructions can include dosage amounts, frequency or duration, and instructions for practicing any of the methods, uses, treatment protocols or prophylactic or therapeutic regimes described herein.

[0329] Labels or inserts can include information on any benefit that a component may provide, such as a prophylactic or therapeutic benefit. Labels or inserts can include information on potential adverse side effects, complications or reactions, such as warnings to the subject or clinician regarding situations where it would not be appropriate to use a particular composition. Adverse side effects or complications could also occur when the subject has, will be or is currently taking one or more other medications that may be incompatible with the composition, or the subject has, will be or is currently undergoing another incompatible treatment protocol or therapeutic regimen and, therefore, instructions could include information regarding such incompatibilities.

[0330] All papers, publications and patents cited in this specification are herein incorporated by reference as if each individual paper, publication or patent were specifically and individually indicated to be incorporated by reference and are incorporated herein by reference to disclose and describe the methods and/or materials in connection with which the publications are cited. However, mention of any reference, article, publication, patent, patent publication, and patent application cited herein is not, and should not be taken as an acknowledgment or any form of suggestion that they constitute valid prior art or form part of the common general knowledge in any country in the world.

[0331] Unless the context indicates otherwise, it is specifically intended that the various features described herein can be used in any combination.

[0332] 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 disclosure belongs.

[0333] It is to be understood that the description above as well as the examples that follow are intended to illustrate, and not limit, the scope of the invention. Other aspects, advantages and modifications within the scope of the invention will be apparent to those skilled in the art to which the invention pertains.

EXAMPLES

Example 1. Discovery of Engineered Receptors Comprising Mutations in the Ligand Binding Domain

[0334] To generate LGICs that conduct anion current following exposure to non-native small molecule agonists of the human α7-nAChR, chimeric ligand gated ion channel (LGIC) receptors comprising the ligand binding domain derived from the human α7 nicotinic acetylcholine receptor (α7-nAChR) and the chloride-conducting ion pore domain derived from the human GlyR1α were genetically engineered. An engineered receptor with an amino acid sequence of SEQ ID NO: 33 (CODA71) was identified, which was approximately as sensitive to acetylcholine, ABT-126 and TC-6987 as wild type α7-nAChR, with TC-6987 showing partial agonist activity on SEQ ID NO:33 similar to wild type. SEQ ID NO:33 was approximate 2-fold less sensitive to nicotine and approximately 3-fold and 10-fold more sensitive to AZD-0328 and Facinicline/RG3487, respectively, than wild type. CODA71 is described in detail in WO2019104307 and WO2021035179, which are incorporated herein in their entireties.

[0335] Amino acid substitutions were introduced into the ligand binding domain of the engineered receptor with the amino acid sequence of SEQ ID NO: 33. The binding pocket for each ligand in the α7-nAChR was modeled, and the amino acid residues that form the binding pocket were mapped. Libraries of single, double, and triple mutant chimeric LGICs were then generated, each mutant chimeric LGIC comprising substitutions in one or more amino acids of the ligand binding pocket of SEQ ID NO: 33. The parental chimera receptor (SEQ ID NO: 33) was cloned into pcDNA3.1(+) (Invitrogen) using BamHI and EcoRI sites by standard molecular biology techniques. Amino acid substitutions were introduced by site-directed mutagenesis. A list of the mutants generated is provided above in Table 20.

[0336] All of the resulting engineered receptors were analyzed for their potency to the native ligand, acetylcholine (Ach), and non-native ligands such as, AZD-0328 (adisinsight.springer.com/drugs/800018503), TC-6987 (drugbank.ca/drugs/DB14854), ABT-126 (medchemexpress.com/Nelonicline.html), TC-5619 (en.wikipedia.org/wiki/Bradanicline), TC-6683 (pubchem.ncbi.nlm.nih.gov/compound/TC-6683_-Azd1446), Varenicline (en.wikipedia.org/wiki/Varenicline), Facinicline/RG3487 (researchgate.net/figure/Molecular-structure-of-RG3487_fig1_47499934), CNL001, and CNL002.

Example 2: Characterization of the Engineered Receptors using High Throughput Fluorescence Based Plate Screening

[0337] To screen these mutant LGICs for those having novel response profiles to ligands, an anion reporter assay was developed to assess the function of the LGICs in a high throughput format. In this assay, cells expressing a YFP reporter whose fluorescence is quenched in the presence of anion are transfected with DNA encoding the channel of interest. Upon exposure to ligand, channels that are activated will flux anion, resulting in a dose-dependent quench of the YFP that can be detected on a plate reader. The greater the quench signal (*i.e.*, the more positive the value), the higher the ligand activity on the receptor is.

[0338] Lenti-X 293T cells (LX293T, Clontech) were maintained in DMEM containing 10% FBS and 1% penicillin/streptomycin (Invitrogen). For plate reader assays, LX293T cells were infected with a lentivirus to create cells that stably express a mutant YFP (H148Q/I152L) reporter, which displays enhanced sensitivity to anions. Two days before assay, cells were split at a density of 20,000 cells/well in a 96-well tissue culture plate coated with poly-d lysine (Thermo Scientific). The next day, the cells were transiently transfected with 0.1 μg of DNA per well using standard Fugene protocol (Promega). On the day of assay, cells were washed 2 times in 1X extracellular solution (1X ECS: 140 mM NaCl, 5 mM KCl, 1 mM MgCl2, 2 mM CaCl2, 10 mM HEPES, 10 mM glucose, pH 7.2, mOsms 300). After the last wash, 100 μL of 1X ECS was added to the wells and the plate was incubated at 37°C for 30 min. While incubating the plate, the drugs were diluted to a 2X concentration in 1X ECS-NaI (same components as 1X ECS except the 140 mM NaCl was replaced by 140 mM NaI). The plates were then read on a Flexstation3 (Molecular Devices). Each well, 8 wells at a time, of the plate is read for 2 min using a Flexstation3 (Molecular Devices) as follows: 1) a baseline YFP fluorescence is read for 17 sec, 2) 100 μL of ligand is added, and 3) the changes in YFP fluorescence are then measured every 1.3 sec for 1 minute and 43 seconds. The percent quench is calculated from the average fluorescence of the last 10 seconds of the read divided by the baseline average of the first 15 seconds prior to the ligand addition.

[0339] **FIGs. 1A-1J** provide heat maps of the percent quench of YFP fluorescence following stimulation by various doses of either acetylcholine or the non-native ligand as indicated in the Figures. CODA71 (SEQ ID NO: 33) was used as a control, and CODA75 (SEQ ID NO: 29, a non-responding chimeric engineered receptor) was used as the negative control. Quenching of the fluorescence signal, as indicated by blue shaded cells, indicate the level of engineered receptor activation by the non-native ligand at that concentration. The results

indicate that the engineered receptors have varying potency towards acetylcholine and the non-native ligands tested (see also Section C1 "Amino Acid Mutations" of the disclosure above).

[0340] The numeric values in these heat maps can be found in **Tables 11-20** below.

Table 11: YFP fluorescence quenching using acetylcholine

Name	Amino Acid Mutation(s) in SEQ ID NO: 33	10 uM ach	30 uM ach	50 uM ach	100 uM ach	300 uM ach	500 uM ach	1 mM ach	3 mM ach	5 mM ach	10 mM ach
CODA71	-	15.61	63.31	73.16	74.94	65.94	62.78	74.24	76.27	77.15	77.96
CODA75	SEQ ID NO: 29	-12.88	-18.67	-0.29	-14.46	-16.31	-17.41	-16.46	-12.38	-20.88	-8.69
CODA217	W77F	-5.86			70.06			68.71	73.45		
CODA109	S170T	82.91	82.53	82.11	83.68			69.89	78.12		
CODA236	R101F	-18.24			60			66.07	71.38		
CODA237	R101M	-16.79			-18.63			46.28	69.31		
CODA238	R101W	-16.58			75.18			78.99	75.74		
CODA282	Y115D	6.81			1.19			-14.05	2.37		
CODA283	Y115E_N379K	-6.16			-11.12			-2.74	53.61		
CODA325	L131G	5.66			74.07			62.65	69.49		
CODA326	L131A	7.43			73.57			71.8	74.49		
CODA330	L131F	11.07			43.34			77.52	74.89		
CODA333	L131S	-10.11			-10.05			32.11	57.37		
CODA334	L131Q	-2.63	30.06		71.27			79.66	74.9		
CODA335	L131T	-9.13			-9.29			0.57	35.37		
CODA339	L131D	4.56			10.19			77.34	77.79		
CODA340	L131E	15.29	66.56		81.31			80.77	77.31		
CODA342	L131R	-2.57			-3.18			78.98	75.75		
CODA337	L131N	28.32			81.8			71.22	73.7		
CODA945	Q139E	-1.25			71.21			71.79	76.04		
CODA377	S172D	-3.19			0.07			71.7	76.95		

Name	Amino Acid Mutation(s) in SEQ ID NO: 33	10 uM ach	30 uM ach	50 uM ach	100 uM ach	300 uM ach	500 uM ach	1 mM ach	3 mM ach	5 mM ach	10 mM ach
CODA405	Y210V	-6.31			-14.48			-2.82	1.06		
CODA407	Y210F	-3.75			-1.6			71.65	79.09		
CODA409	Y210W	-5.43			17.14			78.84	78.55		
CODA534	L131S_S172D	-11.3			-27.53			2.84	14.65		
CODA535	L131T_S172D	-12.24			-26.23			-1.16	2.97		
CODA536	L131D_S172D	-12.91			-20.88			79.85	79.98		
CODA805	Y115D_S170T	-0.46			-4.93			-11.18	-3.53		
CODA806	Y115D_L131Q	9.47			6.12			-1.56	17.57		
CODA807	Y115D_L131E	15.45			13.77			27.42	53.62		
CODA952	Y140I	-1.97			2.79			58.81	66.9		
CODA965	Y140C	-21.71			3.49			63.34	51.92		
CODA1025	R101F_L131G	12.57		-3.46	12.65	-6.96	-6.77	19.42	65.06		
CODA1027	R101F_L131D	-1.62		-1.6	-2.62	-6.12	-7.71	-5.73	33.69		
CODA1039	Y115E_Y210W	-2.97		-3.94	0.35	-4.13	-5.18	1.21	26.69		
CODA1045	R101W_Y210V	-2.52			-11.98	-16.71	-12.87	-14.41	-7.4		-1.5
CODA1047	R101F_Y210V	-4.26			-13.05	-11.73	-10.75	-8.81	-6.77		-1.03
CODA1048	R101F_Y210F				-17.31	-13.7	-10.1	5.53	68.61		78.22
CODA1053	R101M_L131A	-3.98			-11	-7.92	7.36	57.28	60.54		79.46
CODA1054	R101M_L131F	-3.98			-10.34	-10.25	-11.46	1.77	36.81		74.02
CODA1055	R101W_Y115E_Y210W				-15.63	-12.05	-12.87	-11.55	12.68		37.58
CODA1056	R101F_Y115E_Y210W				-20.55	-19.32	-19.75	-14.08	14.07		25.7
CODA1138	W77F_R101F_L131D	-12.92	-15.36		-19.35	-14.79		37.5	61.73		
CODA1140	R101F_L131N_S172D	-20.07	-16.92		-25.8	-11.21		9.02	45		

Name	Amino Acid Mutation(s) in SEQ ID NO: 33	10 uM ach	30 uM ach	50 uM ach	100 uM ach	300 uM ach	500 uM ach	1 mM ach	3 mM ach	5 mM ach	10 mM ach
CODA1157	Q139E_S172D	-36.89	-37.78		-25.67	-18.94		16.38	45.71		
CODA1173	S172D_Y210W							-6.12	11.31		

Table 12: YFP fluorescence quenching using CNL001

Name	Amino Acid Mutation(s) in SEQ ID NO: 33	1nM CNL001	1nM CNL001	10nM CNL001	10nM CNL001	50nM CNL001	50nM CNL001	100nM CNL001	100nM CNL001	1uM CNL001	1uM CNL001
CODA71	-	3.727	20.231	81.096	82.368	83.62	84.482	84.297	85.368	85.647	86.358
CODA75	SEQ ID NO: 29	-8.496	-2.266	1.816	-4.649	-5.922	-5.597	-8.159	-5.058	-4.272	-1.281
CODA217	W77F	-22.273	-19.415	-9.563	6.398	61.938	66.837	79.791	80.908	83.444	83.905
CODA109	S170T	19.755	65.484	79.024	81.563	81.926	83.092	83	83.811	81.834	83.858
CODA236	R101F	9.048	26.601	71.533	72.948	75.895	74.238	76	75.861	76.367	76.162
CODA237	R101M	-2.114	-5.079	15.096	50.554	66.585	74.462	78	77.411	79.06	79.162
CODA238	R101W	32.42	54.768	75.149	75.339	75.881	77.844	78	78.575	81.126	79.482
CODA282	Y115D	-15.837	-6.519	-4.862	-8.244	-3.807	-2.871	-7.924	2.11	11.047	8.04
CODA283	Y115E_N379K	-0.713	-0.621	7.739	15.277	19.489	33.703	56.886	60.171	69.836	73.855
CODA325	L131G	74.429	78.715	79.033	79.322	79.966	80.091	81	79.701	79.289	80.581
CODA326	L131A	76.424	80.567	80.284	81.232	81.575	82.544	81	81.718	82.334	81.539
CODA330	L131F	76.289	78.896	79.339	80.245	80.831	80.605	81	80.663	81.293	81.428
CODA333	L131S	76.165	78.463	79.349	78.238	80.221	81.789	81.855	80.766	81.707	82.665
CODA334	L131Q	76.165	78.463	79.349	78.238	80.221	81.789	82	80.766	81.707	82.665
CODA335	L131T	-9.942	-0.475	17.889	38.46	61.741	69.159	73.635	76.092	80.633	79.637
CODA339	L131D	73.711	76.44	77.049	77.76	77.882	78.708	79.567	79.273	79.992	79.927
CODA340	L131E	76.413	77.144	78.258	78.763	79.757	79.327	79.011	79.948	79.855	80.618

Name	Amino Acid Mutation(s) in SEQ ID NO: 33	1nM CNL001	1nM CNL001	10nM CNL001	10nM CNL001	50nM CNL001	50nM CNL001	100nM CNL001	100nM CNL001	1uM CNL001	1uM CNL001
CODA342	L131R	23.532	26.054	43.69	54.016	59.955	56.091	64.536	58.987	65.987	64.312
CODA337	L131N	76.917	79.554	79.479	79.506	81.465	81.297	82.619	81.722	81.96	81.773
CODA945	Q139E	6.65	13.512	78.678	82.723	84.91	84.849	85.046	84.642	85.493	86.071
CODA377	S172D	67.544	74.209	74.346	75.816	77.068	76.99	79.352	77.865	80.272	79.432
CODA405	Y210V	-16.246	-4.217	-6.142	-10.003	-11.054	-10.06	-3.832	-3.784	1.129	7.1
CODA407	Y210F	-10.845	-2.629	4.66	12.246	29.307	41.78	50.654	62.054	81.742	81.304
CODA409	Y210W	-8.914	-14.319	-1.444	4.393	11.897	11.434	12.719	16.053	14.077	15.495
CODA534	L131S_S172D	23.438	28.59	56.882	56.777	65.044	67.373	68.666	70.357	73.019	73.527
CODA535	L131T_S172D	8.736	24.572	60.552	63.09	73.242	73.889	76.147	76.21	78.988	78.818
CODA536	L131D_S172D										
CODA805	Y115D_S170T	-10.729	-15.278	-20.403	-14.905	-14.303	-15.741	-12.637	-10.606	-13.535	-11.335
CODA806	Y115D_L131Q	6.587	-5.179	-2.366	-1.272	2.763	1.995	3.091	1.45	7.331	9.103
CODA807	Y115D_L131E	0.885	-1.707	-0.567	0.043	5.141	9.409	9.796	11.009	27.914	29.109
CODA952	Y140I	0.368	-1.976	-3.923	4.348	74.107	75.866	80.323	81.996	83.489	82.208
CODA965	Y140C	-12.765	-12.608	68.134	71.394	80.298	82.159	82.404	82.14	82.34	80.649
CODA1025	R101F_L131G	-18.527	-21.577	14.063	49.818	77.765	79.23	80.544	80.695	81.191	82.385
CODA1027	R101F_L131D	24.049	36.755	52.927	61.449	67.308	68.77	69.049	71.613	71.811	69.907
CODA1039	Y115E_Y210W	-1.12	-3.941	6.275	11.943	12.949	18.635	17.576	18.319	19.329	20.672
CODA1045	R101W_Y210V	0.804	11.275	15.843	16.619	15.205	18.771	9.332	18.218	35.294	36.542
CODA1047	R101F_Y210V	-7.82	-8.382	-5.381	-1.431	-0.999	3.909	-0.823	-5.885	1.638	3.483
CODA1048	R101F_Y210F	9.114	0.845	28.944	53.629	68.581	74.379	80.541	80.774	83.143	81.751
CODA1053	R101M_L131A	-8.554	-13.711	39.631	66.809	82.122	82.031	83.312	83.986	84.363	83.877
CODA1054	R101M_L131F	21.932	39.689	54.192	64.111	71.409	70.989	74.148	71.722	71.378	71.411

Name	Amino Acid Mutation(s) in SEQ ID NO: 33	1nM CNL001	1nM CNL001	10nM CNL001	10nM CNL001	50nM CNL001	50nM CNL001	100nM CNL001	100nM CNL001	1uM CNL001	1uM CNL001
CODA1055	R101W_Y115E_Y210W	-12.889	-13.295	-10.401	-7.981	-1.972	-1.661	0.277	4.325	2.88	3.259
CODA1056	R101F_Y115E_Y210W	-8.104	-12.153	-10.462	-4.735	-8.617	-1.606	-1.243	1.838	-0.567	4.663
CODA1138	W77F_R101F_L131D	-6.175	5.89	-2.032	7.601	9.263	4.423	24	30.448	73.823	73.271
CODA1140	R101F_L131N_S172D	52.592	61.248	71.678	71.881	73.807	75.649	76	76.329	76.168	74.076
CODA1157	Q139E_S172D	68.362	69.495	75.078	74.193	77.481	77.205	77	77.042	78.2	76.244
CODA1173	S172D_Y210W	16.321	30.264	61.978	65.343	73.006	74.903	76	76.759	76.928	76.619

Table 13: YFP fluorescence quenching using TC-6683

Name	Amino Acid Mutation(s) in SEQ ID NO: 33	30nM TC-6683	300nM TC-6683	3uM TC-6683	30uM TC-6683	100uM TC-6683
CODA71	-	-14.43	-13.08	-13.71	-14.02	-8.77
CODA282	Y115D	0.365	-6.865	-4.927	-11.259	-11.894
CODA325	L131G	-21.27	-18.33	-7.03	56.84	64.51
CODA326	L131A	-16.28	-11.73	-2.38	-9.77	0.97
CODA330	L131F	-22.26	-18.89	-9.45	-9.23	-10.75
CODA333	L131S	-23.88	-21.46	-21.07	-16.15	-18.96
CODA334	L131Q	-17.99	-23.26	-18.84	-16.92	-15.59
CODA335	L131T	-13.84	-20.66	-17.86	-18.91	-16.88
CODA339	L131D	-18.32	-17.25	-10	-8.51	-9.77
CODA340	L131E	30.14	33.02	41.68	35.75	24.32
CODA342	L131R	-16.26	-22.45	-13.48	-12.68	-10.33
CODA337	L131N	-11.51	-13.17	-5.46	8.53	14.41
CODA945	Q139E	-26.47	-18.62	-13.39	-16.6	-12.89
CODA377	S172D	-20.23	-13.94	-14.17	1.86	43.61
CODA534	L131S_S172D	-22.464	-23.976	-24.897	-20.474	-22.253
CODA535	L131T_S172D	-29.362	-28.954	-23.708	-23.431	-18.324
CODA536	L131D_S172D	-22.285	-23.926	-20.514	-3.078	7.37
CODA807	Y115D_L131E	-26.801	-25.363	-23.651	-26.235	-24.182
CODA952	Y140I	-27.7	-26.87	-31.2	-33.12	-24.67
CODA965	Y140C	-8.21	-16.37	-19.48	-24.32	-24.99
CODA1025	R101F_L131G	-1.645	3.043	0.082	2.449	10.437
CODA1027	R101F_L131D	1.189	0.939	1.327	-0.845	-3.136
CODA1039	Y115E_Y210W	-1.608	-3.491	-6.153	-9.263	-9.19
CODA1045	R101W_Y210V	1.735	0.642	2.403	6.006	-4.277
CODA1047	R101F_Y210V	-24.195	-24.234	-21.291	-16.363	-24.9
CODA1048	R101F_Y210F	-29.055	-33.935	-24.613	-21.752	-22.815
CODA1054	R101M_L131F	-22.996	-27.055	-18.611	-13.879	-21.521
CODA1055	R101W_Y115E_Y210W	-30.056	-30.801	-25.558	-18.295	-17.554
CODA1056	R101F_Y115E_Y210W	-19.889	-22.443	-12.623	-10.728	-10.959

Table 14: YFP fluorescence quenching using TC-5619/Bradanicline

Name	Amino Acid Mutation(s) in SEQ ID NO: 33	1 nM brd	3 nM brd	10 nM brd	30 nM brd	100 nM brd	300 nM brd	1 uM brd
CODA71	-	9.41	44.38	76.61	70.23	78.62	75.51	
CODA75	SEQ ID NO: 29	-13.39	-15.78	-13.47	-16.41		-17.56	
CODA217	W77F		-12.1		-14.72		-6.3	
CODA109	S170T		70.58		80.71		80.66	
CODA236	R101F		49.33		77.38		77.51	
CODA237	R101M		-14.87		69.93		76.57	
CODA238	R101W		74.7		76.78		77.01	
CODA282	Y115D	-0.54	-7.22	-2.82	-16.67	-0.02	-12.37	31.23
CODA283	Y115E_N379K	0.59	-6.41	-1.58	-14.24	33.36	43.81	75.39
CODA325	L131G		68.45		76.95		77.1	
CODA326	L131A		72.24		77.4		78.02	
CODA330	L131F	-12.4	25.12	72.19	76.35	78.94	77.06	78.61
CODA333	L131S	-0.85	-2.05	-2.8	-2.07	30.34	50.56	72.42
CODA334	L131Q		41.92		63.65		64.85	
CODA335	L131T	-2.39	-4.08	-3.3	-9.69	-1.05	10.53	34.72
CODA339	L131D	4.12	19.15	68.98	77.29	81.41	75.79	82.26
CODA340	L131E		68.57		76.85		78.49	
CODA342	L131R	-7.83	-12.89	-10.47	59.48	70.19	75.11	77.42
CODA337	L131N		71.02		78.43		77.12	
CODA945	Q139E		14.15		78.18		76.8	
CODA377	S172D	0.77	-4.59	0.06	-10.48	0.25	-10.61	3.82
CODA405	Y210V		9.92		4.37		59	
CODA407	Y210F		-0.53		8.71		76.26	
CODA409	Y210W	-13.45	-0.64	37.3	76.36	72.72	75.47	78.73
CODA534	L131S_S172D	-1.13	-3.83	-3.78		-2.03		1.68
CODA536	L131D_S172D	-1.24	0.25	-2.57	0.78	4.51	30.97	44.41
CODA805	Y115D_S170T	-9.78	-12.06	-9.02	-16.3	-7.44	-10.93	-4.55
CODA806	Y115D_L131Q	0.92	-4.65	0.38	-8.96	12.18	-0.3	45.47
CODA807	Y115D_L131E	-1.52	-5.35	-3.49	-2.16	4.18	70.2	43.11
CODA952	Y140I		-2.45		66.97		78.48	
CODA965	Y140C		-18.49		22.66		38.02	
CODA1025	R101F_L131G	-10.61	2.63	17.71	68.48		75.12	
CODA1027	R101F_L131D	-10.07	-0.8	1.74	53.95		76.74	
CODA1039	Y115E_Y210W	-5.55	6.78	-2.7	34.43		70.05	
CODA1045	R101W_Y210V	-1.431	-14.993	-5.52	15.49	72.105	71.411	

Name	Amino Acid Mutation(s) in SEQ ID NO: 33	1 nM brd	3 nM brd	10 nM brd	30 nM brd	100 nM brd	300 nM brd	1 uM brd
CODA1047	R101F_Y210V	-5.548	-9.432	-3.068	2.368	47.529	74.413	
CODA1048	R101F_Y210F	-2.084	-9.098	-2.587	55.818	76.957	74.268	
CODA1053	R101M_L131A	0.008	43.21	77.672	76.277	76.856	75.32	
CODA1054	R101M_L131F	6.609	-7.635	4.459	69.782	77.633	72.933	
CODA1055	R101W_Y115E_Y210W	-8.113	-11.136	38.755	39.111	61.378	52.398	
CODA1056	R101F_Y115E_Y210W	-7.894	-11.812	36.211	40.624	65.869	59.661	

Table 15: YFP fluorescence quenching using CNL002

Name	Amino Acid Mutation(s) in SEQ ID NO: 33	1nM CNL002	10nM CNL002	50nM CNL002	100 nM CNL002	1 uM CNL002	30 uM CNL002
CODA71	-				49.61	74.15	75.21
CODA75	SEQ ID NO: 29				-7.94	-9.81	-15.27
CODA217	W77F				67.81	69.42	73.64
CODA109	S170T				73.48	70.03	
CODA236	R101F				-9.56	56.9	70.28
CODA237	R101M				-8.68	-2.24	66.99
CODA238	R101W				2.95	67.93	73.02
CODA282	Y115D				-9.7	-8.37	3.4
CODA283	Y115E_N379K				-5.81	9.69	-12.85
CODA325	L131G				45.62	74.72	77.4
CODA326	L131A				27.88	73.79	75.89
CODA330	L131F				-3.76	68.51	77.77
CODA333	L131S				-15.44	15.21	
CODA334	L131Q				49.9	80.72	80.97
CODA335	L131T				-14.53	6.45	57.43
CODA339	L131D				12.83	77.73	80.58
CODA340	L131E				49.97	67.8	64.58
CODA342	L131R				-17.2	8.12	57.24
CODA337	L131N				76.37	80.18	80.93
CODA945	Q139E				60.5	75.41	77.46
CODA377	S172D				59.35	79.26	79.96
CODA405	Y210V				-14.3	-7.56	-2.02
CODA407	Y210F				-12.47	-3.93	80.97
CODA409	Y210W				-14.92	-0.85	29.62
CODA534	L131S_S172D				14.26	45.55	64.93
CODA535	L131T_S172D				1.23	35.77	68.29

Name	Amino Acid Mutation(s) in SEQ ID NO: 33	1nM CNL002	10nM CNL002	50nM CNL002	100 nM CNL002	1 uM CNL002	30 uM CNL002
CODA536	L131D_S172D				71.72	77.26	77.5
CODA805	Y115D_S170T				-18.17	-15.2	-14
CODA806	Y115D_L131Q				-10.03	-3.33	6.96
CODA807	Y115D_L131E				-5.71	13.03	25.2
CODA952	Y140I				32.58	69.08	73.28
CODA965	Y140C				43.24	42.72	51.43
CODA1025	R101F_L131G				12.48	46.04	39.82
CODA1027	R101F_L131D				7.75	61.97	65.77
CODA1039	Y115E_Y210W				21.85	47.37	59.97
CODA1138	W77F_R101F_L131D	-2.209	43.044	73.418	81.66	81.69	
CODA1140	R101F_L131N_S172D	0.337	59.894	76.501	79.03	82.85	
CODA1157	Q139E_S172D				80.62	81.32	
CODA1173	S172D_Y210W				70.15	77.33	

Table 16: YFP fluorescence quenching using ABT-126

Name	Amino Acid Mutation(s) in SEQ ID NO: 33	50 nM abt	100 nM abt	300 nM abt	500 nM abt	1 uM abt	3 uM abt	10 uM abt	30 uM abt	50 uM abt	100 uM abt
CODA71	-	-1.98	24.27	56.8	76.28	73.16	70.98	72.62	77.49	77.96	77.81
CODA75	SEQ ID NO: 29	-17.07	-16.76	-16.76	-14.68	-16	-14.11	-13.98	-21.05	-21.35	-24.12
CODA217	W77F	37.81	57.31	12.61		66.05					
CODA109	S170T	55.83	68.89	72.52		70.96					
CODA236	R101F	-18.69	-23.01	-20.92		4.99					
CODA237	R101M	-24.34	-20.22	-20.57		-19.55					
CODA238	R101W	-14.97	-14.66	-16.35		50.02					
CODA282	Y115D	-21.22	-19.7	-15.55		-14.31					
CODA283	Y115E_N379K	-22.65	-20.55	-12.93		1.71					
CODA325	L131G	-17.39	6.89	38.65		45.82					
CODA326	L131A	-21.91	-0.5	34.86		56.66					
CODA330	L131F	-16.22	-11.89	39.23		66.5					
CODA333	L131S	-20.99	-16.21	-13.34		4.96					
CODA334	L131Q	23.65	61.83	76.44		77.68					
CODA335	L131T	-18	-16.39	-15.05		-5.56					
CODA339	L131D	-16.65	-12.3	18.5		59.09					
CODA340	L131E	2.2	25.39	36.48		50.76					
CODA342	L131R	-18.14	-18.14	-0.81	23.29	45.76	53.03	64.08	71.98	73.98	73.51
CODA337	L131N	-11.64	34.79	60.08		65.99					
CODA945	Q139E	-8.27	4.76	30.88		60.66					
CODA377	S172D	-1.53	18.18	59.15		72.28					

Name	Amino Acid Mutation(s) in SEQ ID NO: 33	50 nM abt	100 nM abt	300 nM abt	500 nM abt	1 uM abt	3 uM abt	10 uM abt	30 uM abt	50 uM abt	100 uM abt
CODA405	Y210V	-2.9	-2.06	-0.19		-3.64					
CODA407	Y210F	-13.07	0.1	5.97		50.23					
CODA409	Y210W	8.23	55.53	74.82	77.39	77.77	69.33	74.79	75.61	75.72	78.52
CODA534	L131S_S172D	-11.96	-10.72	11.65		-3.06					
CODA535	L131T_S172D	-11.09	-10.37	-4		4.05					
CODA536	L131D_S172D	-3.19	7.58	-1.65		31.29					
CODA805	Y115D_S170T	-11.83	-11.5	-8.01		-9.34					
CODA806	Y115D_L131Q	-1.81	-2.61	-3.78		-2.6					
CODA807	Y115D_L131E	-1.68	-2.25	-2.37		3.68					
CODA952	Y140I	-12.34	-11.57	-5.21		3.93					
CODA965	Y140C	-10.75	-4.11	18.93		52.64					
CODA1025	R101F_L131G	-11.53	-7.61	6.55		25.08					
CODA1027	R101F_L131D	-11.89	-16.07	-11.21		-9.38					
CODA1039	Y115E_Y210W	-17.32	-13.93	9.9	36.97	48.37	50.5	58.13	64.1	66.67	68.63
CODA1045	R101W_Y210V	-24.16	-24.7	-16.09		-11.61					
CODA1047	R101F_Y210V	-14.1	-11.72	-12.98		-15.09					
CODA1048	R101F_Y210F	-23.28	-21.78	-19.35		-16.33					
CODA1053	R101M_L131A	-27.01	-18.76	-17.8		-6.55					
CODA1054	R101M_L131F	-19.54	-18.28	-16.87		-11.77					
CODA1055	R101W_Y115E_Y210W	-21.36	-22.28	-14.63		-7.34					
CODA1056	R101F_Y115E_Y210W	-20.96	-21.95	-10.96		10.79					
CODA1138	W77F_R101F_L131D	-11.71	-5.13	15.09		56.63		75.93			
CODA1140	R101F_L131N_S172D	-7.87	-5.35	-3.67		3.64		5.91			

Name	Amino Acid Mutation(s) in SEQ ID NO: 33	50 nM abt	100 nM abt	300 nM abt	500 nM abt	1 uM abt	3 uM abt	10 uM abt	30 uM abt	50 uM abt	100 uM abt
CODA1157	Q139E_S172D	-26.77	-24.64	-10.64		19.57		55.64			
CODA1173	S172D_Y210W	5.15	25.08	66.86		66.94		78.67			

Table 17: YFP fluorescence quenching using AZD-0328

Name	Amino Acid Mutation(s) in SEQ ID NO: 33	100 nM azd0328	300 nM azd0328	1 uM azd0328	10 uM azd0328	30 uM azd0328
CODA71	-	73.59	78.09			79.05
CODA75	SEQ ID NO: 29	-8.83	-11.15			-11.92
CODA217	W77F	-7.57	7.08			81.59
CODA109	S170T	84.01	87.08			87.27
CODA236	R101F	-9.78	49.64			81.14
CODA237	R101M	-17.84	-11.98			81.2
CODA238	R101W	22.94	75.38			81.8
CODA282	Y115D	3.19	4.79			76.78
CODA283	Y115E_N379K	-2.1	38.2			79.44
CODA325	L131G	79.75	80.62			80.19
CODA326	L131A	80.39	82.07			82.23
CODA330	L131F	27.56	73.35			77.14
CODA333	L131S	38.49	67.13			80.61
CODA334	L131Q	80.55	83.15			82.53
CODA335	L131T	11.33	44.15			80.96
CODA339	L131D	62.87	77.03			78.63
CODA340	L131E	82.48	82.04			81.8
CODA342	L131R	1.79	66.58			80.55
CODA337	L131N	82.1	82.52			82.32
CODA945	Q139E	-5.79	58.47			66.57
CODA377	S172D	65.04	81.73			82.3
CODA405	Y210V	-8.13	-3.35			-2.86
CODA407	Y210F	0.85	1.25			82.08
CODA409	Y210W	-6.57	-4.84			81.64
CODA534	L131S_S172D	-9.32	4.94			60.61
CODA535	L131T_S172D	-7.02	-0.48			70.16
CODA536	L131D_S172D	51.44	77.12			79.26
CODA805	Y115D_S170T	-0.71	-1.73			47.39
CODA806	Y115D_L131Q	12.15	30.92			68.65
CODA807	Y115D_L131E	24.49	45.34			71.21
CODA952	Y140I	-12.96	-13.21			68.5
CODA965	Y140C	-16.69	1.3			21.78
CODA1025	R101F_L131G	6.26	37.98			79.31
CODA1027	R101F_L131D	-4.76	-7.52			74.9
CODA1039	Y115E_Y210W	-10.45	-13			30.76

Table 18: YFP fluorescence quenching using Facinicline

Name	Amino Acid Mutation(s) in SEQ ID NO: 33	30 nM fac	50 nM fac	100 nM fac	300 nM fac	1 uM fac	10 uM fac	30 uM fac
CODA71	-	53.42		83.6	77.44			79.62
CODA75	SEQ ID NO: 29	-11.68		4.35	-10.55			-5.25
CODA217	W77F	-10.14			68.29			87.35
CODA109	S170T	76.45		82.45	71.09			69.41
CODA236	R101F	-28.54			72.98			87.6
CODA237	R101M	-24.14			-14.38			88.78
CODA238	R101W	-19.61			76.54			87.94
CODA282	Y115D	10.17		24.77	51.04		79.76	81.7
CODA283	Y115E_N379K	6.39			78.36		81.93	78.63
CODA325	L131G	75.75			78.01			76.61
CODA326	L131A	69.94			80.07			78.32
CODA330	L131F	2.9			74.96		81.97	78.31
CODA333	L131S	6.27			69.8		80.07	81.35
CODA334	L131Q	83.07		85.36	84.19			82.75
CODA335	L131T	1.24			46.92		79.06	81.06
CODA339	L131D	12.67			80.4		82.18	82.14
CODA340	L131E	82.51		83.6	82.92			82.68
CODA342	L131R	-6.2			76.75		82.16	81.71
CODA337	L131N	82.25			83.59			82.82
CODA945	Q139E	-7.16			71.17			72.14
CODA377	S172D	4.93			84.13		66.96	85.29
CODA405	Y210V	-26.25			-23.52			0.83
CODA407	Y210F	-21.94			-22.46			82.63
CODA409	Y210W	-10.93			-5.82		60.97	57.77
CODA534	L131S_S172D	-23.44			2.75		69.71	61.44
CODA535	L131T_S172D	-21.36			4.17			65.94
CODA536	L131D_S172D	24.15			80.17		81.34	79.9
CODA805	Y115D_S170T	38.08		-14.37	19.41		67.33	79.67
CODA806	Y115D_L131Q	41.32		59.51	74.86		78.53	84.45
CODA807	Y115D_L131E	45.76		63.92	79.43		80.1	84.91
CODA952	Y140I	-8.83			51.6			71.01
CODA965	Y140C	-12.29			20.11			37.62

Name	Amino Acid Mutation(s) in SEQ ID NO: 33	30 nM fac	50 nM fac	100 nM fac	300 nM fac	1 uM fac	10 uM fac	30 uM fac
CODA1025	R101F_L131G	-8.99			10.21			78.24
CODA1027	R101F_L131D	-10.05			-12.54			70.96
CODA1039	Y115E_Y210W	-13.46			5.43			49.06

Table 19: YFP fluorescence quenching using TC-6987

Name	Amino Acid Mutation(s) in SEQ ID NO: 33	1 uM tc6987	3 uM tc6987	5 uM tc6987	10 uM tc6987	30 uM tc6987	50 uM tc6987	100 uM tc6987	300 uM tc6987	500 uM tc6987
CODA71	-	31.56	31.82	30.75	56.68	51.46	61.26	43.21	7.79	51.58
CODA75	SEQ ID NO: 29	-11.79			-14.31					-19.65
CODA217	W77F	-10.35			-13.93					-7.54
CODA109	S170T	71.45			71.04					66.2
CODA236	R101F	45.34			70.04					75.86
CODA237	R101M	-21.62			21.52					60.33
CODA238	R101W	72.47			72.04					76.56
CODA282	Y115D	13.01			14.73					14.29
CODA283	Y115E_N379K	-9.54			-7.06					-15.15
CODA325	L131G	64.59			76.28					70.95
CODA326	L131A	73.37			78.18					75.42
CODA330	L131F	53.37			74.23					72.25
CODA333	L131S	-3.87	-20.2	-15.25	4.92	14.75	21.33	29.7	20.79	44.37
CODA334	L131Q	74.1			81.7					80.18
CODA335	L131T	-0.14	-8.32	-2.13	0.13	-6.86	-9.5	-10.98	-12.16	-2.41
CODA339	L131D	50	80.39	79.93	80.99	83.11	83.18	82.16	64.58	76.77
CODA340	L131E	80.13			81.29					79.6
CODA342	L131R	2.51			46.22					68.33
CODA337	L131N	79.06			82.36					80.19
CODA945	Q139E	-0.97			21.53					7.39
CODA377	S172D	-9.74	-14.04	-0.95	-7.41	-16.12	-12.79	-11.77	-19.68	-17.02

Name	Amino Acid Mutation(s) in SEQ ID NO: 33	1 uM tc6987	3 uM tc6987	5 uM tc6987	10 uM tc6987	30 uM tc6987	50 uM tc6987	100 uM tc6987	300 uM tc6987	500 uM tc6987
CODA405	Y210V	-22.63			-23.03					-40.88
CODA407	Y210F	-15.22			-19.89					-33.32
CODA409	Y210W	62.82			78.66					70.35
CODA534	L131S_S172D	-20.99			-27.62					-24.22
CODA535	L131T_S172D	-21.8			-27.08					-21.56
CODA536	L131D_S172D	-18.24			-23.06					-19.3
CODA805	Y115D_S170T	31.9			25.54					21.13
CODA806	Y115D_L131Q	38.83			31.59					29.83
CODA807	Y115D_L131E	36.07			31.35					28.18
CODA952	Y140I	6.03			2.25					-0.24
CODA965	Y140C	2.73			30.37					33.07
CODA1025	R101F_L131G	-13.32			43.71					53.98
CODA1027	R101F_L131D	0.88			56.27					71.3
CODA1039	Y115E_Y210W	7.26			11					7.97

Table 20: YFP fluorescence quenching using Varenicline

Name	Amino Acid Mutation(s) in SEQ ID NO: 33	3nM var	3nM var	30nM var	30nM var	300nM var	300nM var	500nM var	500nM var	1uM var	1uM var
CODA71	-	-2.36	-3.522	-4.255	-3.636	46.195	45.522	69.253	71.705	79.254	79.244
CODA75	SEQ ID NO: 29	4.161	-6.216	-5.173	-6.593	-5.733	-7.312	-10.35	-7.586	-5.637	-3.757
CODA217	W77F	5.662	7.57	13.968	19.079	16.183	18.025	23.366	19.206	34.69	30.504
CODA109	S170T	-20.96	-19.953	-16.094	-21.502	64.373	71.198	71.892	73.53	75.461	78.578
CODA236	R101F	19.949	22.334	15.764	16.213	23.135	22.987	35.048	34.188	71.031	71.005
CODA237	R101M	18.429	16.83	23.07	15.868	18.819	19.155	19.117	22.593	24.525	23.383
CODA238	R101W	17.896	12.564	16.263	22.117	77.492	79.056	80.186	80.065	81.263	80.702
CODA282	Y115D	2.111	-12.265	-4.433	-6.153	-0.861	-1.308	0.733	-4.633	-4.512	0.02
CODA283	Y115E_N379K										
CODA325	L131G	-12.241	-9.415	75.334	72.278	78.305	77.83	75.936	76.788	77.805	77.352
CODA326	L131A	-5.939	-2.294	68.663	70.718	79.88	79.742	79.311	80.029	80.952	79.329
CODA330	L131F	-3.016	-1.452	-0.193	-1.853	6.915	6.513	27.593	29.863	67.499	65.57
CODA333	L131S	-4.782	1.048	2.084	5.022	12.162	12.979	29.238	25.614	43.863	39.346
CODA334	L131Q	-5.192	-4.327	-0.688	0.672	75.189	74.923	79.048	80.337	79.766	76.836
CODA335	L131T	0.398	3.947	5.31	7.666	4.327	3.275	1.835	4.863	9.471	7.505
CODA339	L131D	-0.902	-7.62	-6.009	-3.447	49.328	47.685	66.7	64.798	70.85	69.038
CODA340	L131E	-4.061	-0.568	62.964	63.631	74.912	75.084	76.346	75.876	75.805	74.856
CODA342	L131R	0.271	-3.613	-4.935	-4.363	0.282	2.32	23.777	18.376	66.17	66.088
CODA337	L131N	3.093	12.327	77.097	77.653	79.446	79.998	80.691	80.309	80.258	79.509
CODA945	Q139E	8.207	7.835	9.509	10.204	9.818	12.539	16.762	15.21	48.292	54.096
CODA377	S172D	-3.433	-5.737	-5.319	-6.175	-4.135	-8.614	-6.062	-6.125	-14.134	-15.373
CODA405	Y210V	7.317	7.643	9.457	9.134	15.503	11.954	13.427	10.784	9.032	11.591

Name	Amino Acid Mutation(s) in SEQ ID NO: 33	3nM var	3nM var	30nM var	30nM var	300nM var	300nM var	500nM var	500nM var	1uM var	1uM var
CODA407	Y210F	2.441	7.326	1.275	12.96	13.119	2.355	11.539	6.571	8.397	7.309
CODA409	Y210W	7.776	-2.964	-5.568	3.024	2.815	3.06	1.766	2.819	1.844	-4.059
CODA952	Y140I	-22.522	-18.173	-15.306	-12.832	-14.671	-17.016	-16.713	-18.893	-15.847	-16.236
CODA965	Y140C	-17.716	-23.019	-14.993	-12.182	-11.731	-10.13	-12.518	-15.043	-13.385	-17.022
CODA1025	R101F_L131G	48.074	60.978	70.023	69.433	78.989	79.21	79.212	79.771	79.538	80.577
CODA1027	R101F_L131D	-3.367	-0.431	-0.761	2.989	2.966	10.211	15.278	20.84	37.104	42.439
CODA1039	Y115E_Y210W	-10.926	-7.395	-5.661	-1.244	-4.555	1.081	9.172	12.561	7.139	12.664
CODA1045	R101W_Y210V	6.745	8.397	14.1	19.095	16.83	21.507	21.586	23.131	31.591	26.479
CODA1047	R101F_Y210V	-3.035	-0.786	-5.181	0.669	-2.748	-6.708	-9.123	-9.869	-6.702	-7.26
CODA1048	R101F_Y210F	-17.119	-13.234	-7.747	4.193	4.149	1.512	-1.572	3.71	8.414	4.091
CODA1053	R101M_L131A	74.835	76.119	77.608	79.015	80.71	79.002	78.709	78.884	79.688	80
CODA1054	R101M_L131F	34.923	28.944	42.214	43.015	47.059	52.768	59.542	62.641	71.449	69.145
CODA1055	R101W_Y115E_Y210W	0.468	-10.015	-15.532	-14.462	-17.027	-15.59	-13.343	-10.702	-6.604	-7.612
CODA1056	R101F_Y115E_Y210W										
CODA1138	W77F_R101F_L131D	3.893	1.107	0.972	0.872	2.282	-0.288	3.637	-1.804	-1.84	6.36
CODA1140	R101F_L131N_S172D	-6.169	-10.445	-9.679	-10.878	-9.572	-8.873	-14.656	-11.304	-13.996	-16.128
CODA1157	Q139E_S172D	-0.225	-1.954	1.269	5.972	6.84	5.943	8.717	6.41	5.635	7.068
CODA1173	S172D_Y210W	9.211	7.193	7.821	9.078	6.933	8.36	5.501	7.04	7.174	5.185

[0341] **Table 21** below lists the EC50 values from one set of experiments for the indicated mutants, in which the EC50 values to Ach and TC-5619 as determined from the YFP fluorescence plate reader experiments are compared with the EC50 values from the electrophysiology studies as described in Example 3 below. The results in **Table 21** demonstrate that the EC50 values derived from the YFP fluorescence plate reader experiments are in excellent agreement with those derived from high throughput electrophysiology (ephys) studies as described in Example 3 below.

Table 21: EC50 values of the engineered receptors to either acetylcholine or TC-5619

	Acetylcholine		TC-5619	
Name	**EC50 (plate reader)**	**EC50 (ephys)**	**EC50 (plate reader)**	**EC50 (ephys)**
CODA536	359 μM		757 nM	
CODA534	>3mM		>1μM	
CODA535	>3mM			
CODA1027	>3mM	3.88 mM	23.5 nM	25 nM
CODA1025	1.28 mM	993 uM	14 nM	17 nM
COAD1056	>3mM	4.18 mM	25.1 nM	42.1 nM
CODA1048	1.39 mM	4.78 mM	21.5 nM	41.2 nM
CODA1047	>3mM	14.4 mM	77 nM	159 nM
CODA1053	650 uM	1.74 mM	2.62 nM	3.58 nM
CODA1054	2.88 mM	4.74 mM	18.3 nM	21.8 nM
COAD1055	>3mM	3.86 mM	23.5 nM	10.6 nM
CODA1045	>3mM	11.8 mM	60.5 nM	70.4 nM
CODA807	1.74 mM		149 nM	
CODA806	4.61 mM		968 nM	
CODA805	>3mM		>1 μM	
CODA1039	>3mM	4.82 mM	30.1 nM	99.3 nM
CODA952	575 μM	1.74 mM	19.3 nM	

Example 3: Characterization of the Engineered Receptors using High Throughput Electrophysiology

[0342] To confirm the EC_{50}s determined by plate reader as well as develop a better understanding of maximum current flow, the engineered receptors were subjected to high throughput electrophysiology system, as described below. For HEK293T studies, cDNAs encoding ion channels were cloned into pcDNA3.1 using standard recombination techniques. HEK293T cells from Clontech (Lenti-X™ 293T Cell Line) were cultured in DMEM

supplemented with 10% FBS and 1% Pen/Strep to 40-50% confluence using standard cell culture protocols, transfected with ion channel plasmids at a concentration of 18 µg per 15 cm dish using Fugene 6, and grown for an additional 24 hours. Cells were then assayed on an electrophysiological system (IonFluxHT and/or Mercury, Fluxion Biosciences) in which dose-response relationships may be assessed through a microfluidics-based platform for establishing whole cell configurations. Ensemble plates were primed with extracellular buffer (140 mM NaCl, 5 mM KCl, 2 mM $CaCl_2$, 1 mM $MgCl_2$, 10 mM HEPES, and 10 mM glucose, pH 7.2 with NaOH, mOsm 310), intracellular buffer (145 mM CsCl, 2 mM CaCl2, 2 mM MgCl2, 10 mM HEPES, and 10 mM EGTA, pH 7.2 with CsOH, mOsm 305), as adapted from Lynagh and Lynch, and test compounds (stocks prepared fresh) diluted in extracellular buffer. Cells were then released from the plate with Accutase, centrifuged, resuspended in extracellular buffer, and loaded into Ensemble plates. Cells were then subjected to a standard protocol for priming, trapping, breaking, and establishing whole cell configuration, with cells held at -60 mV throughout the recording. After recording baseline, progressive doses of test compounds were applied using the IonFlux software to assess dose response relationships. Data were then analyzed off-line using custom Python scripts to convert data to .csv format, re-plot traces, and apply QC measurements to reject unstable recordings (i.e. thresholding based on access resistance and/or standard deviation in baseline, as well as artifact rejection). Peak currents were then calculated, and population data were fit using a 4-parameter logistic equation as described by the Hill Equation. Currents were measured on an automated patch clamp system (Fluxion Biosciences) following 1 second addition of drug and the EC50 values calculated are tabulated below in **Table 22** below and **Table 21** above (in Example 2).

Table 22: EC50 from high throughput electrophysiology

		High-throughput Ephys EC50 (uM)					
		HEK293 Cell Line					
Name	**Amino Acid Mutation(s) in SEQ ID NO: 33**	**Acetyl-choline**	**TC-5619**	**CNL002**	**Facini-cline**	***TC-6987***	***AZD-0328***
Wild type nAchRa7	n/a	47.9			2.2	3.5	1.2
CODA71	-	74.1	0.04	0.132	0.24		
CODA282	Y115D	26887			0.7		
CODA283	Y115E	2295			0.1		
CODA333	L131S	1759			0.73	26.5	0.45
CODA335	L131T	6015			1.76		2.92

		High-throughput Ephys EC50 (uM)					
		HEK293 Cell Line					
Name	**Amino Acid Mutation(s) in SEQ ID NO: 33**	**Acetyl-choline**	**TC-5619**	**CNL002**	**Facini-cline**	***TC-6987***	***AZD-0328***
CODA339	L131D	532			0.41	5.42	0.33
CODA377	S172D	1037			0.39		0.3
CODA536	L131D, S172D	345		-	0.132		
CODA534	L131S, S172D	1410	-	-	0.193		3.89
CODA535	L131T, S172D	3850	-	-	2.65		5.5
CODA805	Y115D, S170T	30000			2.47		
CODA806	Y115D, L131Q	28000			0.145		
CODA807	Y115D, L131E	1790			0.095		
CODA952	Y140I	1740	0.311				
CODA1025	R101F, L131G	993 μM	0.017				
CODA1027	R101F, L131D	3880	0.025				
CODA1039	Y115E, Y210W	4820	0.099				
CODA1045	R101W, Y210V	11800	0.0704				
CODA1047	R101F, Y210V	14400	0.159				
CODA1048	R101F, Y210F	4780	0.041				
CODA1053	R101M, L131A	1740	0.0036				
CODA1054	R101M, L131F	4740	0.0218				
COAD1055	R101W,Y115E, Y210W	3860	0.0106				
COAD1056	R101F,Y115E, Y210W	4180	0.042				
CODA1138	W77F,R101F, L131D	1900		0.041			
CODA1140	R101F,L131N, S172D	3640		0.019			
CODA1157	Q139E,S172D	7000		0.011			
CODA1173	S172D,Y210W	14000		0.027			

[0343] These results show that all the mutant engineered receptors have reduced potency to acetylcholine as compared to wild type nAchRa7 or SEQ ID NO: 33 control. For instance, some of the engineered receptors have EC50 values that are several orders of

magnitudes higher than the EC50 of wild type nAchRa7. Furthermore, the results show that some of the engineered receptors have increased potency to certain non-native ligands, as compared to the wild type receptor. For instance, the engineered receptor comprising the amino acid sequence of L131D, S172D in SEQ ID NO: 33 shows at least 10-fold increased potency towards AZD-0328 and RG-3487, as compared to the wild type control receptor. These results demonstrate that the engineered receptors may be used to decrease potency to acetylcholine, while simultaneously retaining or increasing the potency to synthetic small molecule nAChα7 receptor agonists, which have been recognized as being safe and well tolerated in humans.

[0344] These results from electrophysiological methods provide confirmation of the EC50 values from the plate reader, and further confirm the decoupling of acetylcholine and non-native ligand responses of the engineered receptors disclosed herein.

Example 4: Characterization of the Engineered Receptors using Manual Patch Clamp Electrophysiology

[0345] Using whole cell manual patch clamp electrophysiology in HEK293 cells, rat DRG neurons and rat hippocampal neurons, the EC50 of the various engineered receptors disclosed herein to Ach and non-native ligands was measured using the Hill equation with peak current measurements from escalating doses of ligand. The rheobase shift was also measured in rat DRG neurons, which reflects the efficacy of the receptors. To calculate the rheobase, first, the amount of current that can produce an action potential was determined. Then the ligand was added, followed by a step wise increase in the current injected up to 700 pA.

[0346] For manual patch clamp experiments, Cells plated on coverslips were visualized at 10x and 40x on an inverted fluorescence microscope (Olympus). Recordings were made with an Axopatch 200B amplifier and Digidata 1550B (Molecular Devices) at RT using 3-6 MOhm glass patch electrodes (Sutter, BF150-86-10). Unless otherwise stated, recordings were made in extracellular solution (ECS) containing: 140 mM sodium chloride, 4 mM potassium chloride, 1 mM magnesium chloride, 2 mM calcium chloride, 10 mM HEPES, and 10 mM D-(+)-glucose (pH = 7.3 with sodium hydroxide, osmolarity = 305-315 mOsm). An 8-line reservoir (AutoMate Scientific) in combination with an 8-channel zero-dead-volume perfusion pencil (AutoMate Scientific) was used for perfusion. Data was acquired using pClamp software (Molecular Devices). Traces were either analyzed in Clampfit (Molecular Devices) or using custom Python code. Plotting and statistics were performed in GraphPad Prism.

[0347] For dose-response, ligand-induced currents were recorded in voltage clamp mode. For HEK cell experiments, recordings took place in the normal ECS with a cesium-

based internal solution containing: 140 mM cesium chloride, 5 mM potassium fluoride, 2 mM Calcium chloride, 2 mM magnesium chloride, 10 mM HEPES, and 10 mM EGTA (pH = 7.2 with cesium hydroxide, osmolarity = 290-295 mOsm). For DRG neuron experiments, cells were patched in normal ECS and then switched to an NMDG-based ECS to prevent endogenous cation currents, containing: 145 mM N-methyl-D-glucamine, 4 mM potassium chloride, 0.5 mM magnesium chloride, 0.5 mM calcium chloride, 10 mM HEPES, and 10 mM D-(+)-glucose (pH = 7.4 with hydrochloric acid, osmolarity = 305-315mOsm). Internal solution for DRG neurons contained: 145 mM cesium chloride, 1 mM magnesium chloride, 5 mM magnesium ATP, 10 mM HEPES, and 1 mM EGTA (pH = 7.2 with cesium hydroxide, osmolarity = 290-295 mOsm) Cells were held at -60mV and current across the membrane was recorded in gapfree mode at 3 kHz sampling rate, with Bessel filter at 1 kHz. Capacitance and series resistance were compensated. Drugs tested include acetycholine chloride and other synthetic compounds. Drug doses were applied for 1-10 sec until the peak of the current was observed, and washes occurred for at least 2 min between dose applications. The holding current was subtracted from the peak to find the current amplitude.

[0348] DRG rheobase experiments were performed in current clamp mode using a potassium-based internal solution containing: 100 mM potassium D-gluconate, 28 mM potassium chloride, 1 mM magnesium chloride hexahydrate, 5mM magnesium ATP, 10 mM HEPES , and 0.5 mM EGTA (pH = 7.2 with potassium hydroxide, osmolarity = 290-295 mOsm, calculated liquid junction potential = -13.5 mV). To measure DRG input resistance and rheobase, 500 ms current steps (-200 pA to 700 pA) were applied the membrane in the presence and absence of a compound. No holding current was applied to the membrane for cells included in the final datasets. Data were acquired at 10 kHz, with Bessel filter at 2 kHz and series resistance compensation at 100%. Rheobase was defined as the smallest depolarizing current injection required to cause an action potential to fire in the cell. In a subset of cells, the rheobase was ambiguous, since the action potential appeared to be graded in amplitude. In these cases, a polar plot of the trace clarified the rheobase. Input resistance was measured from the negative current injections, calculated as the difference in membrane potential at steady state divided by the current injection amplitude and then averaged across the four negative current steps for each recording. Resting membrane potential was measured from the first 100ms of each sweep, averaged for each recording, and corrected for liquid junction potential. One-way ANOVA with multiple comparisons was used to test for significance of difference in rheobase and input resistance between baseline, drug, and wash conditions.

[0349] Hippocampal rheobase experiments were performed in current clamp mode using a potassium-based internal solution containing: 115 mM potassium D-gluconate, 13 mM potassium chloride, 1 mM magnesium chloride hexahydrate, 5 mM magnesium ATP, 10 mM HEPES, and 0.5 EGTA mM (pH = 7.2 with potassium hydroxide, osmolarity = 290-295 mOsm, calculated liquid junction potential = -14.9 mV. NBQX (10 μM) and AP5 (50 μM) were included in the bath to block excitatory synaptic transmission. To measure HC input resistance and rheobase, 500 ms current steps (-200pA to 700pA) were applied the membrane in the presence and absence of a compound. No holding current was applied to the membrane for cells included in the final datasets. Data acquisition settings and analysis methods were the same as for the DRG rheobase experiments.

[0350] Hippocampal spontaneous action potentials were recorded in current clamp mode using a potassium-based internal solution containing: 115 mM potassium D-gluconate, 13 mM potassium chloride, 1 mM magnesium chloride hexahydrate, 5 mM magnesium ATP, 10 mM HEPES, and 0.5 mM EGTA (pH = 7.2, osmolarity = 290-295 mOsm, calculated liquid junction potential = -14.9 mV). Spontaneous activity was recorded in gapfree mode, in the presence and absence of a compound. Data were acquired at 10 kHz, with Bessel filter at 2 kHz and series resistance compensation at 100%. No holding current was applied to the membrane. Data were analyzed using Clampfit as well as custom Python code (within-cell comparisons of the two methods did not reveal differences in results). For Clampfit, threshold-based event detection was run separately for each epoch to detect action potentials. For the custom Python code, a peak-finding package was used to automatically detect action potentials (SciPy). For both methods, minimum height, average height, maximum height were measured and frequency was calculated as the number of events in the epoch divided by the length of time of the epoch. For Clampfit, the resting membrane potential was measured at 3 points between events and averaged for each epoch. For resting membrane potential in Python, a median filter was applied to the trace and averaged for each epoch. For both methods, membrane potential was corrected for the calculated liquid junction potential. One-way ANOVA with multiple comparisons was used to test for significance between baseline, drug, and wash conditions.

[0351] The results are tabulated below in **Tables 23 - 27**. These results confirm that the engineered receptors disclosed herein have very low potency to Ach, but higher potency and efficacy to non-native ligands such as RG3487 and TC5619. *See* also, Example 6.

Table 23: Manual patch clamp based EC50 values using HEK293 cell line

	EC50			
Name	***TC-5619***	***CNL002***	***Facinicline/RG-3487***	***Acetylcholine***
CODA71	0.03 μM		0.20 μM	65 uM
CODA952				1740 μM
CODA806			0.29 μM	>30,000 μM
CODA807			0.23 μM	2200 μM
CODA1025	0.041 μM			3853 μM
CODA1027	0.095 μM			6412 μM
CODA1039	0.201 μM			5400 μM
CODA1045	0.253 μM			>100,000 μM
CODA1048	0.156 μM			7341 μM
CODA1054	0.040 μM			7426 μM
COAD1055	0.016 μM			3899 μM
COAD1056	0.096 μM			4460 μM
CODA1138		0.033 μM		1963 μM
CODA1140		0.018 μM		3134 μM
CODA1157		0.032 μM		2521 μM
CODA1173		0.039 μM		2782 μM

Table 24: Manual patch clamp based EC50 values using Rat DRG Neurons

	EC50		
Name	**TC-5619**	**Facinicline/RG-3487**	**Acetylcholine**
CODA806		0.29 μM	>30,000 μM
CODA1025	0.107 μM		9700 μM
CODA1027	0.377 μM		>100,000 μM
CODA1039	0.649 μM		>100,000 μM
CODA1045	0.268 μM		>100,000 μM
CODA1048	0.203 μM		8552 μM
CODA1054	0.150 μM		11070 μM
COAD1055	0.056 μM		6825 μM
COAD1056	0.116 μM		7449 μM

Table 25: Manual patch clamp based EC50 values using Rat Hippocampal Neurons

	EC50	
Name	**CNL002**	**Acetylcholine**
CODA1138	0.139 μM	3369 μM
CODA1140	0.031 μM	
CODA1157	0.095 μM	4669 μM
CODA1173	0.121 μM	8461 μM

Table 26: Rheobase shift of rat DRG neurons using indicated ligand at EC90

	Rheobase Shift; Rat DRG Neurons		
Name	**Baseline**	**+TC-5619 @ EC90**	**Facinicline/RG-3487 @ EC90**
CODA806	163 ± 28 pA		625 ± 35 pA
CODA1025	140 ± 19 pA	560 ± 72 pA	
CODA1027	100 ± 23 pA	638 ± 63 pA	
CODA1039	88 ± 9 pA	453 ± 58 pA	
CODA1045	141 ± 22 pA	700 ± 0 pA	
CODA1048	120 ± 19 pA	590 ± 46 pA	
CODA1054	105 ± 13 pA	673 ± 27 pA	
COAD1055	83 ± 7 pA	562 ± 35 pA	
COAD1056	114 ± 12 pA	632 ± 43 pA	

Table 27: Spontaneous Firing Rate and Evoked Rheobase Shift of Rat Hippocampal Neurons at EC90

Firing Rate Spontaneous; Rat Hippocampal Neurons		
Sequence of the engineered receptor	***Baseline***	***+CNL002 @ EC90***
R101F_L131N_S172D in SEQ ID NO: 33 (CODA1140)	3.29 ± 0.75 Hz	0.71 ± 0.29 Hz
Rheobase Shift Evoked; Rat Hippocampal Neurons		
Sequence of the engineered receptor	***Baseline***	***+CNL002 @ EC90***
R101F_L131N_S172D in SEQ ID NO: 33 (CODA1140)	40.63 ± 10.50 pA	296.9 ± 72.65 pA

Example 5: Characterization of the Localization of the Engineered Receptors

[0352] The efficiency with which the engineered receptors disclosed herein are localized to the surface of the cells was evaluated using multiple methods. First, HA-tagged engineered receptors were expressed in HEK293T cells and their surface expression was monitored using fluorescently tagged HA antibodies. Second, fluorescently labelled α-bungarotoxin, which specifically binds to amino acids on the engineered receptors comprising LBD derived from nAchRa7, was used to bind to the engineered receptors. The use of both these methods, followed by flow cytometry, allowed corroboration of the surface localization of the engineered receptors.

[0353] Monoclonal antibodies anti-HA-PeCy7 (16B12) were purchased from Biolegend (San Diego, CA). The monoclonal antibody clone name is listed in parentheses. alpha-bungarotoxin conjugated to biotin, Alexa Fluor 647 were all purchased from Thermo/Fisher (Waltham MA). Briefly, HEK-293T were plated at 200,00 cells per well and

transfected with Fugene 6 the next day at a 1:3 ratio of DNA to Fugene. Cells were analyzed the day after transfection using flow cytometry. For flow cytometry analysis, transfected HEK293T cells were lifted using 0.05% Trypsin and 0.02% EDTA (Thermo/Fisher), washed and incubated in antibody (30min, 1:100) or α-bungarotoxin at (1 hour. 1:1000) in FACS Buffer (2% BSA, 1X PBS without Ca+ and Mg+, and 1X Penicillin Streptomycin). Cells were then washed in FACS buffer and then analyzed on a Sony SH800 FACS sorter (San Jose, CA). Subsequent analysis was done using FlowJo (San Jose, CA). Data presented are normalized to the % of cells positive for HA-tag fluorescence or α-bungarotoxin staining; and the median fluorescent intensity of the parental chimeric receptor comprising the amino acid sequence of SEQ ID NO: 33.

[0354] **FIG. 5** and **Table 28** show % of HA-tag positive cells that are expressing the engineered receptors, normalized to control cells expressing the amino acid sequence of SEQ ID NO: 33 ("Normalized HA %"); and the % of α-bungarotoxin positive cells that are expressing the engineered receptors, normalized to control cells expressing the amino acid sequence of SEQ ID NO: 33 ("Normalized AB %"). They also show the median fluorescent intensity (MFI) of a cell expressing the engineered receptors, normalized to control cells expressing the amino acid sequence of SEQ ID NO: 33, as evaluated using anti-HA antibodies ("Normalized HA MFI") or fluorescently labeled α-bungarotoxin conjugated to Alexa Fluor 647 ("Normalized AB MFI"). The different point mutations can influence the detection of both HA and alpha-bungarotoxin by flow cytometry.

Table 28: Surface Localization of the Engineered Receptors

Name	Normalized HA %	Normalized HA MFI	N	Normalized AB %	Normalized AB MFI	N
CODA282	0.91	0.74	2	1.23	1.04	2
CODA283	1.16	1.00	2	1.24	1.31	2
CODA333	1.42	0.76	2	1.28	1.20	2
CODA335	2.00	0.88	2	1.65	1.32	3
CODA339	1.59	0.79	2	0.84	1.41	3
CODA342	1.83	0.74	2	0.61	1.24	3
CODA377	0.36	0.61	2	0.50	0.90	4
CODA409	0.96	1.09	2	0.88	0.62	4
CODA534	0.47	1.10	8	0.44	0.91	3
CODA535	0.33	0.86	9	0.43	0.72	2
CODA536	0.40	0.87	9	0.48	0.87	2

Name	Normalized HA %	Normalized HA MFI	N	Normalized AB %	Normalized AB MFI	N
CODA805	0.70	0.94	4	0.56	0.93	4
CODA806	0.36	0.83	4	0.33	2.04	5
CODA807	0.91	1.00	4	0.78	1.14	4
CODA952	1.41	1.53	2	0.54	2.64	2
CODA1025	0.98	0.63	2	0.46	0.90	2
CODA1027	0.61	0.49	2	0.50	0.68	2
CODA1058	1.44	0.68	2	0.34	1.08	2
CODA1045	1.09	0.87	11	0.03	0.35	12
CODA1047	1.13	0.65	4	0.03	0.38	4
CODA1048	1.05	0.61	4	0.55	0.57	4
CODA1053	1.31	0.97	10	0.91	0.90	10
CODA1054	0.96	0.88	11	0.82	0.82	12
CODA1072	1.07	0.78	9	0.51	0.69	9
CODA1073	1.22	0.56	4	0.44	0.70	4

*Abbreviations: MFI- Mean Fluorescence Intensity; AB- α-bungarotoxin

[0355] The results show that the mutations in the engineered receptors disclosed herein affect the localization to the surface of the cell. While the localization of some double mutants is comparable to that of the parental chimera (SEQ ID NO: 33), others have diminished cell surface localization compared to the parental chimera (SEQ ID NO: 33). For instance, the engineered receptor CODA409 shows comparable localization to the parental chimera as evaluated by the HA tag. Moreover, the majority of the engineered receptors show comparable localization to the parental chimera by both techniques, that is, as evaluated by the HA tag as well as the α-bungarotoxin. On the other hand, certain mutations may affect the binding to α-bungarotoxin.

Localization of the Engineered Receptors in Neuron Cells

[0356] To determine the efficiency with which the engineered receptors disclosed herein are localized to the surface of the neuron cells, immunocytochemistry was used in rat DRG neurons and rat hippocampal neurons.

[0357] *Primary neuron culture:* For dorsal root ganglion (DRG) neuron experiments, adult rat lumbar ganglia were harvested and dissociated according to standard protocols, cultured on glass coverslips coated with poly-L-lysine and mouse laminin, transduced with

human synapsin-driven, ires-GFP-containing lentiviral vectors, and processed for immunocytochemistry. For hippocampal neuron experiments, hippocampi were harvested from embryonic day 18 rat pups and dissociated according to standard protocols, cultured on glass coverslips coated with poly-L-lysine, transduced with human synapsin-driven, ires-GFP-containing lentiviral or AAV6 vectors, and processed for immunocytochemistry. 5-fluoro-deoxyuridine was added to hippocampal cultures to inhibit glial growth. The ires-GFP-containing lentiviral vectors either encoded for HA tagged engineered receptors with the indicated sequence, or were empty control ires-GFP vectors.

[0358] *Immunocytochemistry and quantification:* Coverslips were rinsed in protein-free HEPES-based extracellular buffer, and non-viable cells stained with Live-or-Dye 350/448 (Biotium) at room temperature. After rinsing, cells were stained for surface HA tag with rabbit anti-HA antibody at 4C. Cells were fixed at room temperature in 4% paraformaldehyde, blocked and permeabilized with 5% normal goat serum / 0.1% triton X-100, and stained overnight at 4C for total HA tag (mouse anti-HA antibody) and GFP. After washing, cells were incubated with appropriate fluorescent secondary goat or donkey antibodies, washed, mounted and imaged via 4-color fluorescence microscopy. Images were analyzed with custom scripts (ImageJ) to identify viable neuronal soma and axon / dendritic compartments, and to quantify surface and total HA immunoreactivity present in these structures. All data are expressed as mean +/- SEM of individual coverslips, from multiple independent cultures as indicated. For results of DRG neurons transduced with lentiviral vectors, the values for cells transduced with empty vector are listed. For all other results, the values for cells transduced with empty vector are subtracted from all measurements as part of experimental background correction.

[0359] The results are provided in **FIG. 6A** and **FIG. 6B**. The fluorescence signal from the HA tagged engineered receptor in the soma of the neuron, or in the processes (including pseudo-axons, and dendrites) is presented as a fraction of the corresponding fluorescence signal from that of the wild type GLRA1 receptor. The “total” value indicates the fluorescence signal of the engineered receptor as a fraction of the corresponding fluorescence signal from that of the wild type GLRA1 obtained from the whole cell after permeabilization. The “surface” value indicates the fluorescence signal of the engineered receptor as a fraction of the corresponding fluorescence signal from that of the wild type GLRA1 obtained from just the cell surface in cells without permeabilization. Blank cells indicate data not yet available; (0) indicates that the value is below assay detection threshold.

[0360] These results indicate that the engineered receptors are capable of being expressed in neurons and localize to the cell surface. And some of the engineered receptors are more effectively expressed and localized to the soma.

Example 6: Characterization of the CR-11 engineered receptor

[0361] The high throughput electrophysiology platform indicated that the potency of the engineered receptor comprising an amino acid sequence with amino acid substitutions of Y115D and L131Q in SEQ ID NO: 33, named CR-11, to acetylcholine is over 500 fold reduced as compared to the wild type receptor, while its potency to RG-3487 is increased by over 10-fold.

[0362] Using whole cell manual patch clamp electrophysiology, in both HEK293 cells and cultured rat dorsal root ganglion (DRG) sensory neurons, it was confirmed the engineered receptor comprising an amino acid sequence with amino acid substitutions of Y115D and L131Q in SEQ ID NO: 33 is essentially insensitive to acetylcholine, but way more sensitive to RG-3487, as compared to the wildtype nAchRα7 receptor. See **FIG. 2A – FIG. 2B**.

[0363] In HEK293 cells, the EC_{50} of the engineered receptor comprising an amino acid sequence with amino acid substitutions of Y115D and L131Q in SEQ ID NO: 33 to ACh could not be determined because almost no current could be generated, even at concentration of Ach up to 100 mM. In contrast, the EC_{50} of the wildtype nAchRα7 receptor to ACh is 42.4 μM (**FIG. 2A**). Further confirming the high throughput data, the manual patch clamp electrophysiology results also shows that the engineered receptor comprising an amino acid sequence with amino acid substitutions of Y115D and L131Q in SEQ ID NO: 33 is more sensitive to RG-3487 (SA-2) (with an EC_{50} = 0.3 μM), as compared to the wildtype nAchα7 receptor (EC_{50} =2.9 μM) (**FIG. 2B**).

[0364] In cultured adult rat DRG neurons expressing the engineered receptor comprising an amino acid sequence with amino acid substitutions of Y115D and L131Q in SEQ ID NO: 33, application of RG-3487 (SA-2) generated chloride current in a dose dependent manner (**FIG. 3**), although such a current is not observed in non-transduced cells.

[0365] Additionally, aactivation of the engineered receptor comprising an amino acid sequence with amino acid substitutions of Y115D and L131Q in SEQ ID NO: 33 with RG-3487 (SA-2) at 3 μM concentration in transduced rat DRG neurons reversibly inhibits current injection evoked action potentials (**FIG. 4A**) with an approximate 3x increase in the current required to elicit action potentials (n=7). Acetylcholine at 3.0 mM had no effect on evoked

action potentials in transduced neurons (n=4) (**FIG. 4B**). These results show that expression of the engineered receptor comprising an amino acid sequence with amino acid substitutions of Y115D and L131Q in SEQ ID NO: 33 in DRG neurons can inhibit evoked action potential.

Example 7. Characterization of engineered receptors in IPSC-derived neurons

[0366] Differentiation protocols to generate IPSC-derived Aβ neurons are developed. The following markers are used to define the cells as Aβ neurons; expression of Neurofilament 200 (NF200), which delineates myelinated primary afferent neurons (Basbaum et al, 2009), Piezo 2, a marker of Low Threshold Mechanoreceptor sensory neurons (LTMRs) (Ranade et al., 2014) and TLR5, a toll-like receptor that reportedly also marks Aβ fibers (Xu et al., 2015). The characterization will also include evaluation for absence of the nociceptor specific marker TrpV1, which is expressed in many C and Aβ fibers (Caterina et al., 1997), prostatic acid phosphatase, which delineates non-peptidergic unmyelinated afferents (Zylka et al., 2009), and NaV1.1, a marker of Aβ nociceptive neurons. IPSC-derived neurons that meet the above criteria will be further characterized as either rapidly adapting LTMRs, based on expression of c-Ret and MafA/C-Maf, or slowly adapting LTMRs, based on expression of TrkB and Shox2, in the absence of c-Ret expression (Koch et al., 2018).

[0367] (1) Confirm that cells meeting the above expression marker criteria of Aβ neurons have electrophysiology properties characteristic of non-nociceptive sensory neurons. These properties include generation of current in response to ligand and that direct current injection evokes action potentials.

[0368] (2) Confirm presence of chloride currents in neurons transduced with select chemogenetic receptors (engineered receptors). Cells are transduced with a lentivirus vector encoding an HA-tagged chemogenetic receptor(s) with an IRES GFP to identify transduced cells via GFP fluorescence. Chloride currents in response to Synthetic Agonists are detected in voltage clamp mode with NMGD+ as the internal/external fluid cation. As NMDG+ is impermeable to cation channels, its inclusion eliminates any endogenous nAchRα7 cation currents in response to the Synthetic Agonists studied. The EC50 for Chemogenetic Receptor-Synthetic Agonist pairs is then determined. Following recordings, expression and cell surface localization of the receptor(s) are evaluated by fluorescence microscopy in permeabilized and non-permeabilized cells using antibodies directed at the HA tag.

[0369] (3) Assess ability to inhibit current injection evoked action potentials. Cells are transduced with a lentivirus vector encoding an HA-tagged chemogenetic receptor(s) with an IRES GFP to identify transduced cells via GFP fluorescence. In current clamp mode, by

escalating application of current until the cell membranes depolarizes, the rheobase in the presence and absence of the synthetic agonist is determined. Results are compared to cells that are transduced with GFP only.

[0370] (4) Assess impact on input resistance. Cells are transduced with a lentivirus vector encoding an HA-tagged chemogenetic receptor(s) with an IRES GFP to identify cells via GFP fluorescence. In current clamp mode, to calculate the input resistance, sub threshold current is injected and resulting change in membrane voltage is determined. Results are compared to cells that are transduced with GFP only.

[0371] (5) Assess impact on resting membrane potential in the presence and absence of synthetic agonist. Cells are transduced with a lentivirus vectors encoding an HA-tagged chemogenetic receptor(s) with an IRES GFP to identify transduced cells via GFP fluorescence. In voltage clamp mode the resting membrane potential is determined in the presence and absence of the synthetic agonist. Results are compared to cells that are transduced with GFP only.

[0372] The above electrophysiology properties in the IPSC-derived Aβ neurons are compared with those in IPSC-derived C-fiber neurons as well as adult rat DRG neurons. In addition, as biochemical changes in the injured Aβ fiber afferents can contribute to spontaneous pain in neuropathic states, the electrophysiological properties of the IPSC derived Aβ neurons is investigated following injury in vitro. To produce the injuries *in vitro,* cells are harvested and re-plated after processes have been extended in culture. The re-plating process severs the processes, mimicking an axonal injury. At various time point post injury the cells are evaluated for various electrophysiology properties including: generation of spontaneous action potentials, changes in resting membrane potentials and changes in the rheobase. The effect of the chemogenetic receptors are evaluated in the injured state as well.

Example 8. Assessing the efficacy of engineered receptors to treat disease in animal models

[0373] The engineered receptors disclosed herein are assessed for their ability to provide analgesia in a rat model of neuropathic pain following administration of a small molecule ligand. AAV expression cassettes containing a human synapsin-1 (hSYN) promoter linked to polynucleotides encoding either a wild type α7-nAChR, or any one of the engineered chimeric receptors disclosed herein are constructed using standard molecular biology techniques.

[0374] These AAV expression cassettes are subcloned into AAV bacmids, purified, transfected into Sf9 insect cells to produce recombinant baculovirus, and then amplified. Sf9 cells are double infected with the amplified recombinant baculovirus containing with either the wild type α7-nAChR, or any one of the engineered chimeric receptors cassettes described above, and another recombinant baculovirus containing the Rep and AAV6 (Y705+731F+T492V) Cap genes to produce recombinant AAV vectors. The viral vectors are purified, viral titer determined using qPCR, and SDS-PAGE used to verify the purity of AAV vectors.

[0375] *Behavioral experiments and pain models:* To produce mechanical hypersensitivity in a model that mimics a neuropathic pain condition, the spared nerve injury (SNI) model (a validated model of mechanical allodynia) is used (Shields et al., 2003, The Journal of Pain, 4, 465-470). This model is produced by the sectioning of the common peroneal and the sural nerves and isolating the tibial branch. Mechanical withdrawal threshold is assessed by placing rats on an elevated wire-mesh grid and stimulating the plantar surface of the hind paw with von Frey filaments.

[0376] *AAV injection into the spinal cord of rats:* A dorsal hemilaminectomy is made at the level of the lumbar enlargement to expose two segments (about 1.5–2 mm) of lumbar spinal cord, after which the dura mater is incised and reflected. The viral solution is loaded into a glass micropipette (prefilled with mineral oil). The micropipette is connected to a manual micro-injector mounted on a stereotactic apparatus. The viral solution is targeted to the dorsal horn (left side). Along the rostro-caudal axis within the exposed region, 6 injections of 240 nl each are performed, in an equidistant linear fashion. After each injection, 1 min of resting time is observed and then the muscle layer is sutured, the skin closed with staples, and the animals were allowed to recover with heated-pad before they were returned to their home cages. Animals are perfused for histological analysis after the last behavior test.

[0377] *AAV intraganglionic injections into the dorsal root ganglion (DRG) of rats:* The injection is performed with a borosilicate glass capillary (0.78/1 mm internal/external diameters) pulled to a fine point, attached by polyethylene tubing (0.4/0.8 mm internal/ external diameters) to a syringe mounted in a microinjection pump. The needle is mounted on an extended arm of a stereotaxic frame swung to the outside (used to hold and manipulate the needle only). Tubing, syringe, and needle are all filled with water. One microliter air is taken up into the needle followed by 3 μL of the viral vector solution. The needle is loaded separately with this volume for each injection. Animals are anesthetized prior to surgery. Following an incision along the dorsal midline, the L4 and L5 DRG are exposed by removal of the lateral

processes of the vertebrae. The epineurium lying over the DRG is opened, and the glass needle inserted into the ganglion, to a depth of 400 μm from the surface of the exposed ganglion. After a 3-minute delay to allow sealing of the tissue around the glass capillary tip, 1.1 μL virus solution was injected at a rate of 0.2 μL/minute. After a further delay of 2 minutes, the needle is removed. The L4 ganglion is injected first followed by the L5 ganglion. The muscles overlying the spinal cord are loosely sutured together with a 5-0 suture and the wound closed. Animals are allowed to recover at 37 °C and received postoperative analgesia.

[0378] *AAV intrathecal injections in rats:* Rats are first anesthetized and then placed vertically with their head fixed in a stereotaxic frame. An incision is made in the base of the neck to expose the groove in the nuchal crest. An incision is made (1-2 mm) in the cisternal membrane to a depth such that cerebrospinal fluid leaks out. A 4 cm 32 G intrathecal catheter is then slowly inserted in the direction of the lumbar spinal cord and skin is closed by suture around the catheter. The rats are then allowed to recover. Rats are then anesthetized and the vector (6 μL) is administered. The catheter is flushed with 6 μL of PBS and then removed and rats allowed to recover.

[0379] *Effects of administration:* This SNI model is produced by the sectioning of the common peroneal and the sural nerves and isolating the tibial branch of the rat. The up-down method of Chaplan & Yaksh is used to determine mechanical thresholds before the injection of the AAV.hSYN-α7-nAChR/GlyRα1 into the spinal cord, DRG, or intrathecal space. Three weeks after unilateral vector injection, animals are tested again to verify that their mechanical withdrawal thresholds do not change. Motor coordination is also tested before and after injection, using an accelerating rotarod (Stoelting, USA) at a maximum speed of 33 rpm. The duration that the rat spends on the rotarod is recorded, with a cut-off at 300 sec. Each rat goes through three training trials and is tested two hours later.

[0380] Subsequently, half of the rats in each chimera cohort are administered a single IP injection of AZD-0328 or Facinicline and mechanical thresholds tested using the up-down method at 1, 2, 5, 7, and 13 days post IP injection. On the third day, when the thresholds has returned to post-injury baseline, AZD-0328 is again injected IP and again a recovery to non-injury baseline thresholds is observed. These animals are followed for 48 hours. Animals are then perfused for histology.

Example 9: Treatment of a patient suffering from chronic pain

[0381] In a non-limiting example, a patient suffering from chronic radicular pain is treated using the compositions and methods disclosed herein. The patient is treated on Day One

with 10^{13} vector genomes of AAV.hSYN operably linked to a polynucleotide encoding any one of the engineered receptors disclosed herein in a volume of 1.0 mL delivered directly into one or more dorsal root ganglia (i.e., intraganglionic convection-enhanced delivery into lumbar, cervical, or thoracic DRGs). In this example, the AAV vector encodes any one of the engineered receptors disclosed herein under the control of the human Synapsin-1 (SYN1) promoter for selective neuronal expression. Two weeks post-injection, the patient returns to the clinic for a prescription for AZD-0328 or another non-native ligand. The patient self-administers 0.1 mg/kg AZD-0328 or another non-native ligand orally as needed (i.e., during a pain episode).

Example 10. Treatment of a patient suffering from chronic pain

[0382] In a non-limiting example, a patient suffering from chronic craniofacial pain (*e.g.* trigeminal neuralgia or termporomandibular joint dysfunction) is treated using the compositions and methods disclosed herein. The patient is treated on Day One with 10^{13} vector genomes of AAV.hSYN operably linked to a polynucleotide encoding any one of the engineered receptors disclosed herein in a volume of 0.150 mL delivered directly into the trigeminal ganglion (i.e., intraganglionic convection enhanced delivery). In this example, the AAV vector encodes any one of the engineered receptors disclosed herein under the control of the human Synapsin-1 (SYN1) promoter for selective neuronal expression. Two weeks post-injection, the patient returns to the clinic for a prescription for AZD-0328 or another non-native ligand. The patient self-administers 0.1 mg/kg AZD-0328 or another non-native ligand orally as needed (i.e., during a pain episode).

Example 11. Treatment of a patient suffering from obesity

[0383] In a non-limiting example, a patient suffering from obesity is treated using the compositions and methods disclosed herein. The patient is treated on Day One with 10^{13} vector genomes of AAV. Ghrelin operably linked to a polynucleotide encoding any one of the engineered receptors disclosed herein in a volume of 1.0 mL delivered directly into the gastric branch of the vagus nerve (i.e., intraneural). In this example, the AAV vector encodes the engineered receptor under the control of the human Ghrelin promoter for selective neuronal expression. Two weeks post-injection, the patient returns to the clinic for a prescription for AZD-0328 or another non-native ligand. The patient self-administers 0.1 mg/kg AZD-0328 or another non-native ligand orally daily for excess weight loss (i.e. for apetitite suppression).

Example 12. Treatment of a patient suffering from obesity

[0384] In a non-limiting example, a patient suffering from obesity is treated using the compositions and methods disclosed herein. The patient is treated on Day One with 10^{13} vector genomes of AAV-TRPV1 operably linked to a polynucleotide encoding any one of the engineered receptors disclosed herein in a volume of 1.0 mL delivered directly into the dorsal root ganglia innervating the pancreas (i.e., intragangionic). In this example, the AAV vector encodes the engineered receptor under the control of the human TRPV1 promoter for selective neuronal expression in nociceptors. Two weeks post-injection, the patient returns to the clinic for a prescription for AZD-0328 or another non-native ligand. The patient self-administers 0.1 mg/kg AZD-0328 or another non-native ligand orally daily for excess weight loss.

Example 13. Treatment of a patient suffering from obesity

[0385] In a non-limiting example, a patient suffering from obesity is treated using the compositions and methods disclosed herein. The patient is treated on Day One with 10^{13} vector genomes of AAV-SIM1 operably linked to a polynucleotide encoding any one of the engineered receptors disclosed herein in a volume of 1.0 mL delivered directly into the paraventricular nucleus (PVH) in the hypothalamus (i.e., intracranial, convection enhanced delivery). In this example, the AAV vector encodes the engineered channel under the control of the human Single-Minded Family BHLH Transcription Factor 1 (SIM1) promoter for selective neuronal expression in pro-opiomelanocortin (POMC) neurons and ultimately stimulation of the anorexigenic pathway. Two weeks post-injection, the patient returns to the clinic for a prescription for AZD-0328 or another non-native ligand. The patient self-administers 0.15 mg/kg AZD-0328 or another non-native ligand orally daily for excess weight loss (i.e. for apetitite suppression).

Example 14. Treatment of a patient suffering from PTSD

[0386] In a non-limiting example, a patient suffering from post-traumatic stress disorder (PTSD) is treated using the compositions and methods disclosed herein. The patient is treated on Day One with 10^{13} vector genomes of AAV-hSYN1 operably linked to a polynucleotide encoding any one of the engineered receptors disclosed herein in a volume of 1.0 mL delivered directly into the C6 stellate ganglion, (i.e., intraganglionic). In this example, the AAV vector encodes the engineered receptor under the control of the human Synapsin-1 (hSYN1) promoter for selective neuronal expression. Two weeks post-injection, the patient returns to the clinic for a prescription for AZD-0328 or another non-native ligand. The patient

self-administers 0.15 mg/kg AZD-0328 or another non-native ligand orally daily for PTSD symptoms (i.e. for anxiety).

Example 15. Treatment of a patient suffering from depression

[0387] In a non-limiting example, a patient suffering from treatment-resistant depression (TRD) is treated using the compositions and methods disclosed herein. The patient is treated on Day One with 10^{13} vector genomes of AAV-hSYN1 operably linked to a polynucleotide encoding any one of the engineered receptors disclosed herein in a volume of 1.0 mL delivered directly into the vagus nerve, (i.e., intraneural). In this example, the AAV vector encodes the engineered receptor under the control of the human Synapsin-1 (hSYN1) promoter for selective neuronal expression. Two weeks post-injection, the patient returns to the clinic for a prescription for AZD-0328 or another non-native ligand. The patient self-administers 0.1 mg/kg AZD-0328 or another non-native ligand orally daily for depression symptoms.

Example 16. Treatment of a patient suffering from GERD

[0388] In a non-limiting example, a patient suffering from gastroesophageal reflux disease (GERD) is treated using the compositions and methods disclosed herein. The patient is treated on Day One with 10^{13} vector genomes of AAV-hSYN1 operably linked to a polynucleotide encoding any one of the engineered receptors disclosed herein or AAV-CAG operably linked to a polynucleotide encoding any one of the engineered receptors disclosed herein in a volume of 1.0 mL delivered directly into the lower esophageal sphincter (LES) vagus nerve and myenteric plexus (i.e., intraneural) or smooth muscle (intramuscular), respectively. In this example, the AAV vector encodes the engineered receptor under the control of the human Synapsin-1 (hSYN1) promoter for selective neuronal expression or the CAG promoter for expression in LES myocytes. Two weeks post-injection, the patient returns to the clinic for a prescription for AZD-0328 or another non-native ligand. The patient self-administers 0.15 mg/kg AD-0328 or another non-native ligand orally daily for symptoms of GERD (i.e. acid reflux).

Example 17. Treatment of a patient suffering from epilepsy

[0389] In a non-limiting example, a patient suffering from seizures associated with epilepsy is treated using the compositions and methods disclosed herein. The patient is treated on Day One with 10^{13} vector genomes of AAV-CamKIIα operably linked to a polynucleotide encoding any one of the engineered receptors disclosed herein in a volume of 1.0 mL delivered

directly into a pre-determined seizure focus such as the motor cortex (i.e., intracranial). In this example, the AAV vector encodes the engineered receptor under the control of the human Calcium/calmodulin-dependent protein kinase II α (CamKIIα) promoter for selective neuronal expression in excitatory neurons. Two weeks post-injection, the patient returns to the clinic for a prescription for AZD-0328. The patient self-administers 0.1 mg/kg AZD-0328 orally daily for epileptic symptoms (i.e. seizures).

Example 18. Treatment of a patient suffering from a movement disorder

[0390] In a non-limiting example, a patient suffering from a movement disorder (*e.g.* Parkinsonian tremor) is treated using the compositions and methods disclosed herein. The patient is treated on Day One with 10^{13} vector genomes of AAV-CamKIIα operably linked to a polynucleotide encoding any one of the engineered receptors disclosed herein in a volume of 1.0 mL delivered directly into the subthalamic nucleus (i.e., intracranial STN). In this example, the AAV vector encodes the engineered receptor under the control of the human Calcium/calmodulin-dependent protein kinase II α (CamKIIα) promoter for selective neuronal expression in excitatory neurons. Two weeks post-injection, the patient returns to the clinic for a prescription forAZD-0328. The patient self-administers 0.1 mg/kg AZD-0328 orally daily for movement disorder symptoms (i.e. tremor).

FURTHER NUMBERED EMBODIMENTS

[0391] Further embodiments of the instant invention are provided in the numbered embodiments below:

[0392] Embodiment 1. An engineered receptor, comprising a ligand binding domain derived from human α7 nicotinic acetylcholine receptor (α7-nAChR), wherein the ligand binding domain comprises an amino acid mutation at an amino acid residue corresponding to W77, R101, Y115, L131, Q139, Y140, S170, S172 or Y210 of SEQ ID NO: 4.

[0393] Embodiment 2. The engineered receptor of Embodiment 1, wherein the ligand binding domain comprises an amino acid sequence having at least 85% identity to amino acid residues 23-220 of SEQ ID NO: 4.

[0394] Embodiment 3. The engineered receptor of Embodiment 1 or 2, wherein the ligand binding domain comprises the amino acid mutation at two or more amino acid residues selected from those corresponding to W77, R101, Y115, L131, Q139, Y140, S170, S172 and Y210 of SEQ ID NO: 4.

[0395] Embodiment 4. The engineered receptor of any one of Embodiments 1-3, wherein the ligand binding domain comprises a mutation at the amino acid residue(s) corresponding to the indicated position of SEQ ID NO: 4:

a) Y140;

b) R101 and L131;

c) Y115 and Y210;

d) R101 and Y210;

e) R101, Y115 and Y210;

f) W77, R101 and L131;

g) R101, L131 and S172;

h) Q139 and S172D;

i) S172 and Y210

j) L131 and S172;

k) Y115 and S170; or

l) Y115 and L131.

[0396] Embodiment 5. The engineered receptor of any one of Embodiments 1-4, wherein the mutation is amino acid substitution.

[0397] Embodiment 6. The engineered receptor of Embodiment 4, wherein the ligand binding domain comprises the amino acid substitutions(s) corresponding to the indicated position of SEQ ID NO: 4:

a) Y140I ;

b) R101F and L131G;

c) R101F and L131D;

d) Y115E and Y210W;

e) R101W and Y210V;

f) R101F and Y210V;

g) R101F and Y210F;

h) R101M and L131A;

i) R101M and L131F;

j) R101W, Y115E and Y210W;

k) R101F, Y115E and Y210W;

l) W77F, R101F and L131D;

m) R101F, L131N and S172D;

n) Q139E and S172D;

o) S172D and Y210W;

p) L131S and S172D;

q) L131T and S172D;

r) L131D and S172D;

s) Y115D and S170T;

t) Y115D and L131Q;

u) Y115D and L131E;

v) L131E;

w) Y140C;

x) R101W;

y) Y210V; or

z) Q139E.

[0398] Embodiment 7. The engineered receptor of any one of Embodiments 1-6, wherein the engineered receptor is a chimeric ligand gated ion channel (LGIC) receptor comprising an ion pore domain derived from a human Glycine receptor.

[0399] Embodiment 8. The engineered receptor of Embodiment 7, wherein the human Glycine receptor is human Glycine receptor α1, human Glycine receptor α2, or human Glycine receptor α3.

[0400] Embodiment 9. The engineered receptor of Embodiment 7, wherein the ion pore domain comprises an amino acid sequence having at least 85% identity to amino acids 255-457 of SEQ ID NO: 2, 260-452 of SEQ ID NO: 83, amino acids 259-464 of SEQ ID NO: 85, or amino acids 259-449 of SEQ ID NO: 87.

[0401] Embodiment 10. The engineered receptor of any one of Embodiments 7-9, wherein the ligand binding domain of the engineered receptor comprises a Cys-loop domain derived from the human Glycine receptor.

[0402] Embodiment 11. The engineered receptor of Embodiment 10, wherein the Cys-loop domain comprises amino acids 166-172 of SEQ ID NO: 2.

[0403] Embodiment 12. The engineered receptor of Embodiment 10, wherein the Cys-loop domain comprises amino acids 166-180 of SEQ ID NO: 2.

[0404] Embodiment 13. The engineered receptor of any one of Embodiments 1-12, wherein the ligand binding domain of the engineered receptor comprises a β1-2 loop domain from the human Glycine receptor α1 subunit.

[0405] Embodiment 14. The engineered receptor of Embodiment 13, wherein the β1-2 loop domain comprises amino acids 81-84 of SEQ ID NO:2.

[0406] Embodiment 15. The engineered receptor of any one of Embodiments 1-14, wherein the engineered receptor comprises an amino acid sequence according to any one of SEQ ID NOs. 58-78 and 88.

[0407] Embodiment 16. An engineered chimeric ligand gated ion channel (LGIC) comprising a ligand binding domain from a first LGIC and an ion pore domain from a second LGIC, wherein the first LGIC is the human α7 nicotinic acetylcholine receptor (α7-nAChR) and comprises an amino acid mutation at an amino acid residue corresponding to W77, R101, Y115, L131, Q139, Y140, S170, S172 or Y210 of SEQ ID NO: 4.

[0408] Embodiment 17. The engineered chimeric LGIC of Embodiment 16, wherein the ligand binding domain comprises a mutation at the amino acid residue(s) corresponding to the indicated position of SEQ ID NO: 4:

a. Y140;

b. R101 and L131;

c. Y115 and Y210;

d. R101 and Y210;

e. R101, Y115 and Y210;

f. W77, R101 and L131;

g. R101, L131 and S172;

h. Q139 and S172D;

i. S172 and Y210

j. L131 and S172;

k. Y115 and S170; or

l. Y115 and L131

[0409] Embodiment 18. The engineered chimeric LGIC of Embodiment 16, wherein the ligand binding domain comprises the amino acid substitutions(s) corresponding to the indicated position of SEQ ID NO: 4:

a. Y140I;

b. R101F and L131G;

c. R101F and L131D;

d. Y115E and Y210W;

e. R101W and Y210V;

f. R101F and Y210V;

g. R101F and Y210F;

h. R101M and L131A;

i. R101M and L131F;

j. R101W, Y115E and Y210W;

k. R101F, Y115E and Y210W;

l. W77F, R101F and L131D;

m. R101F, L131N and S172D;

n. Q139E and S172D;

o. S172D and Y210W;

p. L131S and S172D;

q. L131T and S172D;

r. L131D and S172D;

s. Y115D and S170T;

t. Y115D and L131Q;

u. Y115D and L131E;

v. L131E;

w. Y140C;

x. R101W;

y. Y210V; or

z. Q139E.

[0410] Embodiment 19. The engineered chimeric LGIC of any one of Embodiments 16-18, wherein the second LGIC is a human Glycine receptor.

[0411] Embodiment 20. The engineered chimeric LGIC of Embodiment 19, wherein the human Glycine receptor is human Glycine receptor α1.

[0412] Embodiment 21. The engineered chimeric LGIC of Embodiment 20, comprising a polypeptide sequence having at least 85% sequence identity to SEQ ID NO: 33.

[0413] Embodiment 22. The engineered receptor of any one of Embodiments 1-21, wherein the potency of the engineered receptor to acetylcholine is lower than the potency of the human α7 nicotinic acetylcholine receptor (α7-nAChR), or a control receptor, to acetylcholine.

[0414] Embodiment 23. The engineered receptor of Embodiment 22, wherein the potency of the engineered receptor to acetylcholine is at least 2-fold lower than the potency of the human α7 nicotinic acetylcholine receptor (α7-nAChR), or a control receptor, to acetylcholine.

[0415] Embodiment 24. The engineered receptor of any one of Embodiments 1-23, wherein the potency of the engineered receptor to a non-native ligand is about the same as the

potency of the human α7 nicotinic acetylcholine receptor (α7-nAChR), or a control receptor, to the non-native ligand.

[0416] Embodiment 25. The engineered receptor of any one of Embodiments 1-24, wherein the potency of the engineered receptor to a non-native ligand is higher than the potency of the human α7 nicotinic acetylcholine receptor (α7-nAChR), or a control receptor, to the non-native ligand.

[0417] Embodiment 26. The engineered receptor of Embodiment 25, wherein the potency of the engineered receptor to the non-native ligand is at least 2-fold higher than the potency of the human α7 nicotinic acetylcholine receptor (α7-nAChR), or a control receptor, to the non-native ligand.

[0418] Embodiment 27. The engineered receptor of any one of Embodiments 22-26, wherein the potency of the engineered receptor to a ligand is determined by the EC50 of the receptor for the ligand according to the YFP fluorescence quenching assay using Lenti-X 293T cells.

[0419] Embodiment 28. The engineered receptor of any one of Embodiments 1-27, wherein the efficacy of the engineered receptor in the presence of a non-native ligand is higher than the efficacy the human α7 nicotinic acetylcholine receptor (α7-nAChR), or a control receptor, in presence of the non-native ligand.

[0420] Embodiment 29. The engineered receptor of any one of Embodiments 1-28, wherein the efficacy of the engineered receptor in the presence of a non-native ligand is at least 2-fold higher than the efficacy the human α7 nicotinic acetylcholine receptor (α7-nAChR), or a control receptor, in presence of the non-native ligand.

[0421] Embodiment 30. The engineered receptor of any one of Embodiments 28-29, wherein determining the efficacy comprises determining the amount of current passed through the engineered receptor in vitro in the presence of the non-native ligand.

[0422] Embodiment 31. The engineered receptor of any one of Embodiments 24-30, wherein the non-native ligand is selected from the group consisting of AZD-0328, TC-6987, ABT-126, CNL002, TC-5619, CNL001, TC-6683, Varenicline, and Facinicline/RG3487.

[0423] Embodiment 32. The engineered receptor of Embodiment 31, wherein the non-native ligand is selected from the group consisting of ABT-126, RG3487, and CNL002.

[0424] Embodiment 33. The engineered receptor of Embodiment 31, wherein the non-native ligand is TC-5619.

[0425] Embodiment 34. A polynucleotide encoding the engineered receptor of any one of Embodiments 1-33.

[0426] Embodiment 35. A polynucleotide encoding an engineered receptor comprising an amino acid sequence of any one of SEQ ID NOs: 58-78 and 88.

[0427] Embodiment 36. The polynucleotide of Embodiment 34 or 35, wherein the polynucleotide comprises a promoter operably linked to the nucleic acid encoding the engineered receptor.

[0428] Embodiment 37. The polynucleotide of Embodiment 36, wherein the promoter is a regulatable promoter.

[0429] Embodiment 38. The polynucleotide of Embodiment 37, wherein the regulatable promoter is active in an excitable cell.

[0430] Embodiment 39. The polynucleotide of Embodiment 38, wherein the excitable cell is a neuron or a myocyte.

[0431] Embodiment 40. The polynucleotide of Embodiment 39, wherein the excitable cell is a neuron.

[0432] Embodiment 41. A vector comprising the polynucleotide of any one of Embodiments 34-40.

[0433] Embodiment 42. The vector of Embodiment 41, wherein the vector is a plasmid, or a viral vector.

[0434] Embodiment 43. The vector of Embodiment 42, wherein the vector is a viral vector selected from the group consisting of an adenoviral vector, a retroviral vector, an adeno-associated viral (AAV) vector, and a herpes simplex-1 viral vector (HSV-1).

[0435] Embodiment 44. The vector of Embodiment 43, wherein the viral vector is an AVV vector, and wherein the AAV vector is AAV5 or a variant thereof, AAV6 or a variant thereof or AAV9 or a variant thereof.

[0436] Embodiment 45. A composition comprising the engineered receptor of any one of Embodiments 1-33, the polynucleotide of any one of Embodiments 34-40, or the vector of any one of Embodiments 41-44.

[0437] Embodiment 46. A pharmaceutical composition comprising the engineered receptor of any one of Embodiments 1-33, the polynucleotide of any one of Embodiments 34-40, or the vector of any one of Embodiments 41-44. and a pharmaceutically acceptable carrier.

[0438] Embodiment 47. A method of expressing an engineered receptor in a neuron, comprising contacting the neuron with the polynucleotide of any one of Embodiments 34-40, the vector of any one of Embodiments 41-44, the composition of Embodiment 45, or the pharmaceutical composition of Embodiment 46.

[0439] Embodiment 48. The method of Embodiment 47 or the polynucleotide of Embodiment 40, wherein the neuron is a neuron of the peripheral nervous system.

[0440] Embodiment 49. The method of Embodiment 47 or 48, or the polynucleotide of Embodiment 40, wherein the neuron is a neuron of the central nervous system.

[0441] Embodiment 50. The method of any one of Embodiments 47-49 or the polynucleotide of Embodiment 40, wherein the neuron is a nociceptive neuron.

[0442] Embodiment 51. The method of any one of Embodiments 47-50 or the polynucleotide of Embodiment 40, wherein the neuron is a non-nociceptive neuron.

[0443] Embodiment 52. The method of any one of Embodiments 47-51 or the polynucleotide of Embodiment 40, wherein the neuron is a dorsal root ganglion (DRG) neuron, a trigeminal ganglion (TG) neuron, a motor neuron, an excitatory neuron, an inhibitory neuron, or a sensory neuron.

[0444] Embodiment 53. The method of any one of Embodiments 47-52 or the polynucleotide of Embodiment 40, wherein the neuron is an Aδ afferent fiber, a C fiber or an Aβ afferent fiber.

[0445] Embodiment 54. The method of Embodiment 53 or the polynucleotide of Embodiment 40, wherein the neuron is Aβ afferent fiber.

[0446] Embodiment 55. The method of Embodiment 54 or the polynucleotide of Embodiment 40, wherein Aβ afferent fiber is an injured Aβ afferent fiber.

[0447] Embodiment 56. The method of Embodiment 54 or the polynucleotide of Embodiment 40, wherein Aβ afferent fiber is an uninjured Aβ afferent fiber.

[0448] Embodiment 57. The method of any one of Embodiments 47-56 or the polynucleotide of Embodiment 40, wherein the neuron expresses neurofilament 200 (NF200), piezo 2, and TLR-5.

[0449] Embodiment 58. The method of any one of Embodiments 47-57 or the polynucleotide of Embodiment 40, wherein the neuron does not express TrpV1, prostatic acid phosphatase, NaV1.1.

[0450] Embodiment 59. The method of any one of Embodiments 47-58, wherein the contacting step is performed in vitro, ex vivo, or in vivo.

[0451] Embodiment 60. The method of Embodiment 59, wherein the contacting step is performed in vivo in a subject.

[0452] Embodiment 61. The method of Embodiment 60, wherein the contacting step comprises administering the polynucleotide, the vector, the composition, or the pharmaceutical composition to the subject.

[0453] Embodiment 62. The method of Embodiment 61, wherein the contacting step is performed in vitro or ex vivo.

[0454] Embodiment 63. The method of Embodiment 62, wherein the contacting step comprises lipofection, nanoparticle delivery, particle bombardment, electroporation, sonication, or microinjection.

[0455] Embodiment 64. The method of any one of Embodiments 47-63, wherein the engineered receptor is capable of localizing to the cell surface of the neuron.

[0456] Embodiment 65. A method of inhibiting the activity of a neuron, comprising (a) contacting the neuron with the engineered receptor of any one of Embodiments 1-33, the polynucleotide of any one of Embodiments 34-40, or the vector of any one of Embodiments 41-44, the composition of Embodiment 45, or the pharmaceutical composition of Embodiment 46, and (b) contacting the neuron with a non-native ligand of the engineered receptor.

[0457] Embodiment 66. The method of Embodiment 65, wherein the neuron is a neuron of the peripheral nervous system.

[0458] Embodiment 67. The method of Embodiment 65, wherein the neuron is a neuron of the central nervous system.

[0459] Embodiment 68. The method of any of the Embodiments 65-67, wherein the neuron is a nociceptive neuron.

[0460] Embodiment 69. The method of any of the Embodiments 65-67, wherein the neuron is a non-nociceptive neuron.

[0461] Embodiment 70. The method of any one of Embodiments 65-69, wherein the neuron is a dorsal root ganglion (DRG) neuron, a trigeminal ganglion (TG) neuron, a motor neuron, an excitatory neuron, an inhibitory neuron, or a sensory neuron.

[0462] Embodiment 71. The method of any one of Embodiments 65-70, wherein the neuron is an Aδ afferent fiber, a C fiber or an Aβ afferent fiber.

[0463] Embodiment 72. The method of Embodiment 71, wherein the neuron is Aβ afferent fiber.

[0464] Embodiment 73. The method of Embodiment 72, wherein Aβ afferent fiber is an injured Aβ afferent fiber.

[0465] Embodiment 74. The method of Embodiment 72, wherein Aβ afferent fiber is an uninjured Aβ afferent fiber.

[0466] Embodiment 75. The method of any one of Embodiments 65-74, wherein the neuron expresses neurofilament 200 (NF200), piezo 2, and TLR-5.

[0467] Embodiment 76. The method of any one of Embodiments 65-75, wherein the neuron does not express TrpV1, prostatic acid phosphatase, NaV1.1.

[0468] Embodiment 77. The method of any one of Embodiments 65-76, wherein the contacting step (a) is performed in vitro, ex vivo, or in vivo.

[0469] Embodiment 78. The method of any one of Embodiments 65-77, wherein the contacting step (b) is performed in vitro, ex vivo, or in vivo.

[0470] Embodiment 79. The method of any one of Embodiments 65-78, wherein the contacting steps (a) and/or (b) are performed in vivo in a subject.

[0471] Embodiment 80. The method of Embodiment 79, wherein the contacting step (a) comprises administering the engineered receptor, the polynucleotide, the vector, or the pharmaceutical composition to the subject; and/or the contacting step (b) comprises administering the non-native ligand to the subject.

[0472] Embodiment 81. The method of any one of Embodiments 65-80, wherein the contacting step (a) and/or (b) comprises lipofection, nanoparticle delivery, particle bombardment, electroporation, sonication, or microinjection.

[0473] Embodiment 82. The method of any one of Embodiments 65-81, wherein the engineered receptor is capable of localizing to the cell surface of the neuron.

[0474] Embodiment 83. A method of treating and/or delaying the onset of a neurological disorder in a subject, in need thereof, comprising:

a. administering to the subject, a therapeutically effective amount of the engineered receptor of any one of Embodiments 1-33, the polynucleotide of any one of Embodiments 34-40, or the vector of any one of Embodiments 41-44, the composition of Embodiment 45, or the pharmaceutical composition of Embodiment 46, and

b. administering to the subject a non-native ligand of the engineered receptor.

[0475] Embodiment 84. The method of Embodiment 83, wherein the subject is administered the non-native ligand after step (a).

[0476] Embodiment 85. The method of Embodiment 83, wherein the subject is administered the non-native ligand concurrently with step (a).

[0477] Embodiment 86. The method of any one of Embodiments 83-85, wherein the neurological disorder is a seizure disorder, a movement disorder, an eating disorder, a spinal cord injury, neurogenic bladder, allodynia, a spasticity disorder, pruritus, Alzheimer's disease, Parkinson's disease, post-traumatic stress disorder (PTSD), gastroesophageal reflux disease (GERD), addiction, anxiety, depression, memory loss, dementia, sleep apnea, stroke,

narcolepsy, urinary incontinence, essential tremor, trigeminal neuralgia, burning mouth syndrome, or atrial fibrillation.

[0478] Embodiment 87. The method of Embodiment 86, wherein the neurological disorder is allodynia.

[0479] Embodiment 88. The method of any one of Embodiments 83-87, wherein the non-native ligand is selected from the group consisting of AZD-0328, ABT-126, TC6987, CNL002, TC-5619, CNL001, TC-6683, Varenicline, and Facinicline/RG3487.

[0480] Embodiment 89. The method of any one of Embodiments 83-88, wherein the non-native ligand is administered orally, subcutaneously, topically, or intravenously.

[0481] Embodiment 90. The method of Embodiment 89, wherein the non-native ligand is administered orally.

[0482] Embodiment 91. The method of any one of Embodiments 83-90, wherein the engineered receptor, the polynucleotide, the vector, the composition, or the pharmaceutical composition is administered subcutaneously, orally, intrathecally, topically, intravenously, intraganglioncally, intraneurally, intracranially, intraspinally, or to the cisterna magna.

[0483] Embodiment 92. The method of any one of Embodiments 83-91, wherein the engineered receptor, the polynucleotide, the vector, the composition, or the pharmaceutical composition is administered by transforaminal injection or intrathecally.

[0484] Embodiment 93. The method of any one of Embodiments 83-92, wherein the subject suffers from trigeminal neuralgia, and wherein the engineered receptor, the polynucleotide, the vector, the composition, or the pharmaceutical composition is administered to the trigeminal ganglion (TG) of the subject.

[0485] Embodiment 94. The method of any one of Embodiments 83-92, wherein the subject suffers from neuropathic pain, and wherein the engineered receptor, the polynucleotide, the vector, the composition, or the pharmaceutical composition is administered to the dorsal root ganglion (DRG) of the subject.

[0486] Embodiment 95. The method of any one of Embodiments 83-94, wherein the subject is a human.

[0487] Embodiment 96. The method of any one of Embodiments 83-95, wherein the therapeutically effectively amount diminishes the severity of a sign and/or or a symptom of the neurological disorder.

[0488] Embodiment 97. The method of any one of Embodiments 83-96, wherein the therapeutically effectively amount delays the onset of a sign and/or or a symptom of the neurological disorder.

[0489] Embodiment 98. The method of any one of Embodiments 83-97, wherein the therapeutically effectively amount eliminates a sign and/or or a symptom of the neurological disorder.

[0490] Embodiment 99. The method of any one of Embodiments 96-98, wherein the sign of the neurological disorder is nerve damage, nerve atrophy, and/or seizure.

[0491] Embodiment 100. The method of Embodiment 99, wherein the nerve damage is peripheral nerve damage.

[0492] Embodiment 101. The method of any one of Embodiments 96-100, wherein the symptom of the neurological disorder is pain.

[0493] Embodiment 102. A method of treating and/or delaying the onset of pain in a subject, in need thereof, comprising:

a. administering to the subject, a therapeutically effective amount of the engineered receptor of any one of Embodiments 1-33, the polynucleotide of any one of Embodiments 34-40, or the vector of any one of Embodiments 41-44, the composition of Embodiment 45, or the pharmaceutical composition of Embodiment 46, and

b. administering to the subject a non-native ligand of the engineered receptor.

[0494] Embodiment 103. The method of Embodiment 102, wherein the subject is administered the non-native ligand after step (a).

[0495] Embodiment 104. The method of Embodiment 102, wherein the subject is administered the non-native ligand concurrently with step (a).

[0496] Embodiment 105. The method of any one of Embodiments 102-104, wherein the non-native ligand is selected from the group consisting of AZD-0328, ABT-126, TC6987, CNL002, TC-5619, CNL001, TC-6683, Varenicline, and Facinicline/RG3487.

[0497] Embodiment 106. The method of any one of Embodiments 102-105, wherein the non-native ligand is administered orally, subcutaneously, topically, or intravenously.

[0498] Embodiment 107. The method of Embodiment 106, wherein the non-native ligand is administered orally.

[0499] Embodiment 108. The method of any one of Embodiments 102-107, wherein the engineered receptor, the polynucleotide, the vector, the composition, or the pharmaceutical composition is administered subcutaneously, orally, intrathecally, topically, intravenously, intraganglioncally, intraneurally, intracranially, intraspinally, or to the cisterna magna.

[0500] Embodiment 109. The method of any one of Embodiments 102-108, wherein the engineered receptor, the polynucleotide, the vector, the composition, or the pharmaceutical composition is administered by transforaminal injection or intrathecally.

[0501] Embodiment 110. The method of any one of Embodiments 102-109, wherein the subject suffers from trigeminal neuralgia, and wherein the engineered receptor, the polynucleotide, the vector, the composition, or the pharmaceutical composition is administered to the trigeminal ganglion (TG) of the subject.

[0502] Embodiment 111. The method of any one of Embodiments 102-110, wherein the subject suffers from neuropathic pain, and wherein the engineered receptor, the polynucleotide, the vector, the composition, or the pharmaceutical composition is administered to the dorsal root ganglion (DRG) of the subject.

[0503] Embodiment 112. The method of any one of Embodiments 102-111, wherein the subject is a human.

[0504] Embodiment 113. The method of any one of Embodiments 101-112, wherein the pain is neuropathic pain.

[0505] Embodiment 114. The method of any one of Embodiments 101-113, wherein the pain is associated with, caused by, or resulting from chemotherapy.

[0506] Embodiment 115. The method of any one of Embodiments 101-114, wherein the pain is associated with, caused by, or resulting from trauma.

[0507] Embodiment 116. The method of any of Embodiments 101-115, wherein the subject suffers from allodynia.

[0508] Embodiment 117. The method of any one of Embodiments 101-116, wherein the pain manifests after a medical procedure.

[0509] Embodiment 118. The method of any one of Embodiments 101-117, wherein the pain is associated with, is caused by, or resulting from childbirth or Caesarean section.

[0510] Embodiment 119. The method of any one of Embodiments 101-118, wherein the pain is associated with, is caused by, or resulting from migraine.

[0511] Embodiment 120. The method of any one of Embodiments 101-119, wherein the therapeutically effectively amount diminishes pain in the subject transiently, diminishes pain in the subject permanently, prevents the onset of pain in the subject, and/or eliminates pain in the subject.

[0512] Embodiment 121. The method of any one of Embodiments 101-120, wherein steps (a) and (b) are performed before the manifestation of pain in the subject.

[0513] Embodiment 122. A kit, comprising (a) the vector of any one of Embodiments 41-44, and (b) a non-native ligand of the engineered receptor.

[0514] Embodiment 123. A kit, comprising (a) the engineered receptor of any one of Embodiments 1-33, and (b) a non-native ligand of the engineered receptor.

[0515] Embodiment 124. The kit of Embodiment 122 or 123, wherein the engineered receptor and the non-native ligand is according to any one the combinations provided in Table 29.

[0516] Embodiment 125. The kit of Embodiment 122 or 124, comprising a device adapted to administration of the vector.

[0517] The preceding merely illustrates the principles of the disclosure. It will be appreciated that those skilled in the art will be able to devise various arrangements which, although not explicitly described or shown herein, embody the principles of the disclosure and are included within its spirit and scope. Furthermore, all examples and conditional language recited herein are principally intended to aid the reader in understanding the principles of the disclosure and the concepts contributed by the inventors to furthering the art, and are to be construed as being without limitation to such specifically recited examples and conditions. Moreover, all statements herein reciting principles, aspects, and embodiments of the disclosure as well as specific examples thereof, are intended to encompass both structural and functional equivalents thereof. Additionally, it is intended that such equivalents include both currently known equivalents and equivalents developed in the future, i.e., any elements developed that perform the same function, regardless of structure. The scope of the present disclosure, therefore, is not intended to be limited to the exemplary embodiments shown and described herein. Rather, the scope and spirit of the present disclosure is embodied by the appended claims.

CLAIMS

What is claimed is:

1. An engineered receptor, comprising a ligand binding domain derived from human α7 nicotinic acetylcholine receptor (α7-nAChR), wherein the ligand binding domain comprises an amino acid mutation at an amino acid residue corresponding to W77, R101, Y115, L131, Q139, Y140, S170, S172 or Y210 of SEQ ID NO: 4.

2. The engineered receptor of claim 1, wherein the ligand binding domain comprises an amino acid sequence having at least 85% identity to amino acid residues 23-220 of SEQ ID NO: 4.

3. The engineered receptor of claim 1 or 2, wherein the ligand binding domain comprises the amino acid mutation at two or more amino acid residues selected from those corresponding to W77, R101, Y115, L131, Q139, Y140, S170, S172 and Y210 of SEQ ID NO: 4.

4. The engineered receptor of any one of claims 1-3, wherein the ligand binding domain comprises a mutation at the amino acid residue(s) corresponding to the indicated position of SEQ ID NO: 4:

a) Y140;

b) R101 and L131;

c) Y115 and Y210;

d) R101 and Y210;

e) R101, Y115 and Y210;

f) W77, R101 and L131;

g) R101, L131 and S172;

h) Q139 and S172D;

i) S172 and Y210

j) L131 and S172;

k) Y115 and S170; or

l) Y115 and L131.

5. The engineered receptor of any one of claims 1-4, wherein the mutation is amino acid substitution.

6. The engineered receptor of claim 4, wherein the ligand binding domain comprises the amino acid substitutions(s) corresponding to the indicated position of SEQ ID NO: 4:

a) Y140I ;

b) R101F and L131G;

c) R101F and L131D;

d) Y115E and Y210W;

e) R101W and Y210V;

f) R101F and Y210V;

g) R101F and Y210F;

h) R101M and L131A;

i) R101M and L131F;

j) R101W, Y115E and Y210W;

k) R101F, Y115E and Y210W;

l) W77F, R101F and L131D;

m) R101F, L131N and S172D;

n) Q139E and S172D;

o) S172D and Y210W;

p) L131S and S172D;

q) L131T and S172D;

r) L131D and S172D;

s) Y115D and S170T;

t) Y115D and L131Q;

u) Y115D and L131E;

v) L131E;

w) Y140C;

x) R101W;

y) Y210V; or

z) Q139E.

7. The engineered receptor of any one of claims 1-6, wherein the engineered receptor is a chimeric ligand gated ion channel (LGIC) receptor comprising an ion pore domain derived from a human Glycine receptor.

8. The engineered receptor of claim 7, wherein the human Glycine receptor is human Glycine receptor α1, human Glycine receptor α2, or human Glycine receptor α3.

9. The engineered receptor of claim 7, wherein the ion pore domain comprises an amino acid sequence having at least 85% identity to amino acids 255-457 of SEQ ID NO: 2, 260-452 of SEQ ID NO: 83, amino acids 259-464 of SEQ ID NO: 85, or amino acids 259-449 of SEQ ID NO: 87.

10. The engineered receptor of any one of claims 7-9, wherein the ligand binding domain of the engineered receptor comprises a Cys-loop domain derived from the human Glycine receptor.

11. The engineered receptor of claim 10, wherein the Cys-loop domain comprises amino acids 166-172 of SEQ ID NO: 2.

12. The engineered receptor of claim 10, wherein the Cys-loop domain comprises amino acids 166-180 of SEQ ID NO: 2.

13. The engineered receptor of any one of claims 1-12, wherein the ligand binding domain of the engineered receptor comprises a β1-2 loop domain from the human Glycine receptor α1 subunit.

14. The engineered receptor of claim 13, wherein the β1-2 loop domain comprises amino acids 81-84 of SEQ ID NO:2.

15. The engineered receptor of any one of claims 1-14, wherein the engineered receptor comprises an amino acid sequence according to any one of SEQ ID NOs. 58-78 and 88.

16. An engineered chimeric ligand gated ion channel (LGIC) comprising a ligand binding domain derived from a first LGIC and an ion pore domain derived from a second LGIC, wherein the first LGIC is the human α7 nicotinic acetylcholine receptor (α7-nAChR) and comprises an amino acid mutation at an amino acid residue corresponding to W77, R101, Y115, L131, Q139, Y140, S170, S172 or Y210 of SEQ ID NO: 4.

17. The engineered chimeric LGIC of claim 16, wherein the ligand binding domain comprises a mutation at the amino acid residue(s) corresponding to the indicated position of SEQ ID NO: 4:

a. Y140;
b. R101 and L131;
c. Y115 and Y210;
d. R101 and Y210;
e. R101, Y115 and Y210;
f. W77, R101 and L131;
g. R101, L131 and S172;
h. Q139 and S172D;
i. S172 and Y210
j. L131 and S172;
k. Y115 and S170; or
l. Y115 and L131

18. The engineered chimeric LGIC of claim 16, wherein the ligand binding domain comprises the amino acid substitutions(s) corresponding to the indicated position of SEQ ID NO: 4:

a. Y140I;
b. R101F and L131G;
c. R101F and L131D;
d. Y115E and Y210W;
e. R101W and Y210V;
f. R101F and Y210V;
g. R101F and Y210F;
h. R101M and L131A;
i. R101M and L131F;
j. R101W, Y115E and Y210W;
k. R101F, Y115E and Y210W;
l. W77F, R101F and L131D;
m. R101F, L131N and S172D;
n. Q139E and S172D;
o. S172D and Y210W;

p. L131S and S172D;
q. L131T and S172D;
r. L131D and S172D;
s. Y115D and S170T;
t. Y115D and L131Q;
u. Y115D and L131E;
v. L131E;
w. Y140C;
x. R101W;
y. Y210V; or
z. Q139E.

19. The engineered chimeric LGIC of any one of claims 16-18, wherein the second LGIC is a human Glycine receptor.

20. The engineered chimeric LGIC of claim 19, wherein the human Glycine receptor is human Glycine receptor α1.

21. The engineered chimeric LGIC of claim 20, comprising a polypeptide sequence having at least 85% sequence identity to SEQ ID NO: 33.

22. The engineered receptor of any one of claims 1-21, wherein the potency of the engineered receptor to acetylcholine is lower than the potency of the human α7 nicotinic acetylcholine receptor (α7-nAChR), or a control receptor, to acetylcholine.

23. The engineered receptor of claim 22, wherein the potency of the engineered receptor to acetylcholine is at least 2-fold lower than the potency of the human α7 nicotinic acetylcholine receptor (α7-nAChR), or a control receptor, to acetylcholine.

24. The engineered receptor of any one of claims 1-23, wherein the potency of the engineered receptor to a non-native ligand is about the same as the potency of the human α7 nicotinic acetylcholine receptor (α7-nAChR), or a control receptor, to the non-native ligand.

25. The engineered receptor of any one of claims 1-24, wherein the potency of the engineered receptor to a non-native ligand is higher than the potency of the human α7

nicotinic acetylcholine receptor (α7-nAChR), or a control receptor, to the non-native ligand.

26. The engineered receptor of claim 25, wherein the potency of the engineered receptor to the non-native ligand is at least 2-fold higher than the potency of the human α7 nicotinic acetylcholine receptor (α7-nAChR), or a control receptor, to the non-native ligand.

27. The engineered receptor of any one of claims 22-26, wherein the potency of the engineered receptor to a ligand is determined by the EC50 of the receptor for the ligand according to the YFP fluorescence quenching assay using Lenti-X 293T cells.

28. The engineered receptor of any one of claims 1-27, wherein the efficacy of the engineered receptor in the presence of a non-native ligand is higher than the efficacy the human α7 nicotinic acetylcholine receptor (α7-nAChR), or a control receptor, in presence of the non-native ligand.

29. The engineered receptor of any one of claims 1-28, wherein the efficacy of the engineered receptor in the presence of a non-native ligand is at least 2-fold higher than the efficacy the human α7 nicotinic acetylcholine receptor (α7-nAChR), or a control receptor, in presence of the non-native ligand.

30. The engineered receptor of any one of claims 28-29, wherein determining the efficacy comprises determining the amount of current passed through the engineered receptor *in vitro* in the presence of the non-native ligand.

31. The engineered receptor of any one of claims 24-30, wherein the non-native ligand is selected from the group consisting of AZD-0328, TC-6987, ABT-126, CNL002, TC-5619, CNL001, TC-6683, Varenicline, and Facinicline/RG3487.

32. The engineered receptor of claim 31, wherein the non-native ligand is selected from the group consisting of ABT-126, RG3487, and CNL002.

33. The engineered receptor of claim 31, wherein the non-native ligand is TC-5619.

34. A polynucleotide encoding the engineered receptor of any one of claims 1-33.

35. A polynucleotide encoding an engineered receptor comprising an amino acid sequence of any one of SEQ ID NOs: 58-78 and 88.

36. The polynucleotide of claim 34 or 35, wherein the polynucleotide comprises a promoter operably linked to the nucleic acid encoding the engineered receptor.

37. The polynucleotide of claim 36, wherein the promoter is a regulatable promoter.

38. The polynucleotide of claim 37, wherein the regulatable promoter is active in an excitable cell.

39. The polynucleotide of claim 38, wherein the excitable cell is a neuron or a myocyte.

40. The polynucleotide of claim 39, wherein the excitable cell is a neuron.

41. A vector comprising the polynucleotide of any one of claims 34-40.

42. The vector of claim 41, wherein the vector is a plasmid, or a viral vector.

43. The vector of claim 42, wherein the vector is a viral vector selected from the group consisting of an adenoviral vector, a retroviral vector, an adeno-associated viral (AAV) vector, and a herpes simplex-1 viral vector (HSV-1).

44. The vector of claim 43, wherein the viral vector is an AVV vector, and wherein the AAV vector is AAV5 or a variant thereof, AAV6 or a variant thereof or AAV9 or a variant thereof.

45. A composition comprising the engineered receptor of any one of claims 1-33, the polynucleotide of any one of claims 34-40, or the vector of any one of claims 41-44.

46. A pharmaceutical composition comprising the engineered receptor of any one of claims 1-33, the polynucleotide of any one of claims 34-40, or the vector of any one of claims 41-44. and a pharmaceutically acceptable carrier.

47. A method of expressing an engineered receptor in a neuron, comprising contacting the neuron with the polynucleotide of any one of claims 34-40, the vector of any one of claims 41-44, the composition of claim 45, or the pharmaceutical composition of claim 46.

48. The method of claim 47 or the polynucleotide of claim 40, wherein the neuron is a neuron of the peripheral nervous system.

49. The method of claim 47 or 48, or the polynucleotide of claim 40, wherein the neuron is a neuron of the central nervous system.

50. The method of any one of claims 47-49 or the polynucleotide of claim 40, wherein the neuron is a nociceptive neuron.

51. The method of any one of claims 47-50 or the polynucleotide of claim 40, wherein the neuron is a non-nociceptive neuron.

52. The method of any one of claims 47-51 or the polynucleotide of claim 40, wherein the neuron is a dorsal root ganglion (DRG) neuron, a trigeminal ganglion (TG) neuron, a motor neuron, an excitatory neuron, an inhibitory neuron, or a sensory neuron.

53. The method of any one of claims 47-52 or the polynucleotide of claim 40, wherein the neuron is an Aδ afferent fiber, a C fiber or an Aβ afferent fiber.

54. The method of claim 53 or the polynucleotide of claim 40, wherein the neuron is Aβ afferent fiber.

55. The method of claim 54 or the polynucleotide of claim 40, wherein Aβ afferent fiber is an injured Aβ afferent fiber.

56. The method of claim 54 or the polynucleotide of claim 40, wherein Aβ afferent fiber is an uninjured Aβ afferent fiber.

57. The method of any one of claims 47-56 or the polynucleotide of claim 40, wherein the neuron expresses neurofilament 200 (NF200), piezo 2, and TLR-5.

58. The method of any one of claims 47-57 or the polynucleotide of claim 40, wherein the neuron does not express TrpV1, prostatic acid phosphatase, NaV1.1.

59. The method of any one of claims 47-58, wherein the contacting step is performed *in vitro*, *ex vivo*, or *in vivo*.

60. The method of claim 59, wherein the contacting step is performed *in vivo* in a subject.

61. The method of claim 60, wherein the contacting step comprises administering the polynucleotide, the vector, the composition, or the pharmaceutical composition to the subject.

62. The method of claim 61, wherein the contacting step is performed *in vitro* or *ex vivo*.

63. The method of claim 62, wherein the contacting step comprises lipofection, nanoparticle delivery, particle bombardment, electroporation, sonication, or microinjection.

64. The method of any one of claims 47-63, wherein the engineered receptor is capable of localizing to the cell surface of the neuron.

65. A method of inhibiting the activity of a neuron, comprising (a) contacting the neuron with the engineered receptor of any one of claims 1-33, the polynucleotide of any one of claims 34-40, or the vector of any one of claims 41-44, the composition of claim 45, or the pharmaceutical composition of claim 46, and (b) contacting the neuron with a non-native ligand of the engineered receptor.

66. The method of claim 65, wherein the neuron is a neuron of the peripheral nervous system.

67. The method of claim 65, wherein the neuron is a neuron of the central nervous system.

68. The method of any of the claims 65-67, wherein the neuron is a nociceptive neuron.

69. The method of any of the claims 65-67, wherein the neuron is a non-nociceptive neuron.

70. The method of any one of claims 65-69, wherein the neuron is a dorsal root ganglion (DRG) neuron, a trigeminal ganglion (TG) neuron, a motor neuron, an excitatory neuron, an inhibitory neuron, or a sensory neuron.

71. The method of any one of claims 65-70, wherein the neuron is an Aδ afferent fiber, a C fiber or an Aβ afferent fiber.

72. The method of claim 71, wherein the neuron is Aβ afferent fiber.

73. The method of claim 72, wherein Aβ afferent fiber is an injured Aβ afferent fiber.

74. The method of claim 72, wherein Aβ afferent fiber is an uninjured Aβ afferent fiber.

75. The method of any one of claims 65-74, wherein the neuron expresses neurofilament 200 (NF200), piezo 2, and TLR-5.

76. The method of any one of claims 65-75, wherein the neuron does not express TrpV1, prostatic acid phosphatase, NaV1.1.

77. The method of any one of claims 65-76, wherein the contacting step (a) is performed *in vitro*, *ex vivo*, or *in vivo*.

78. The method of any one of claims 65-77, wherein the contacting step (b) is performed *in vitro*, *ex vivo*, or *in vivo*.

79. The method of any one of claims 65-78, wherein the contacting steps (a) and/or (b) are performed *in vivo* in a subject.

80. The method of claim 79, wherein the contacting step (a) comprises administering the engineered receptor, the polynucleotide, the vector, or the pharmaceutical composition to the subject; and/or the contacting step (b) comprises administering the non-native ligand to the subject.

81. The method of any one of claims 65-80, wherein the contacting step (a) and/or (b) comprises lipofection, nanoparticle delivery, particle bombardment, electroporation, sonication, or microinjection.

82. The method of any one of claims 65-81, wherein the engineered receptor is capable of localizing to the cell surface of the neuron.

83. A method of treating and/or delaying the onset of a neurological disorder in a subject, in need thereof, comprising:

    a. administering to the subject, a therapeutically effective amount of the engineered receptor of any one of claims 1-33, the polynucleotide of any one of claims 34-40, or the vector of any one of claims 41-44, the composition of claim 45, or the pharmaceutical composition of claim 46, and

    b. administering to the subject a non-native ligand of the engineered receptor.

84. The method of claim 83, wherein the subject is administered the non-native ligand after step (a).

85. The method of claim 83, wherein the subject is administered the non-native ligand concurrently with step (a).

86. The method of any one of claims 83-85, wherein the neurological disorder is a seizure disorder, a movement disorder, an eating disorder, a spinal cord injury, neurogenic bladder, allodynia, a spasticity disorder, pruritus, Alzheimer's disease, Parkinson's disease, post-traumatic stress disorder (PTSD), gastroesophageal reflux disease (GERD), addiction, anxiety, depression, memory loss, dementia, sleep apnea, stroke, narcolepsy, urinary incontinence, essential tremor, trigeminal neuralgia, burning mouth syndrome, or atrial fibrillation.

87. The method of claim 86, wherein the neurological disorder is allodynia.

88. The method of any one of claims 83-87, wherein the non-native ligand is selected from the group consisting of AZD-0328, ABT-126, TC6987, CNL002, TC-5619, CNL001, TC-6683, Varenicline, and Facinicline/RG3487.

89. The method of any one of claims 83-88, wherein the non-native ligand is administered orally, subcutaneously, topically, or intravenously.

90. The method of claim 89, wherein the non-native ligand is administered orally.

91. The method of any one of claims 83-90, wherein the engineered receptor, the polynucleotide, the vector, the composition, or the pharmaceutical composition is administered subcutaneously, orally, intrathecally, topically, intravenously, intraganglioncally, intraneurally, intracranially, intraspinally, or to the cisterna magna.

92. The method of any one of claims 83-91, wherein the engineered receptor, the polynucleotide, the vector, the composition, or the pharmaceutical composition is administered by transforaminal injection or intrathecally.

93. The method of any one of claims 83-92, wherein the subject suffers from trigeminal neuralgia, and wherein the engineered receptor, the polynucleotide, the vector, the composition, or the pharmaceutical composition is administered to the trigeminal ganglion (TG) of the subject.

94. The method of any one of claims 83-92, wherein the subject suffers from neuropathic pain, and wherein the engineered receptor, the polynucleotide, the vector, the composition, or the pharmaceutical composition is administered to the dorsal root ganglion (DRG) of the subject.

95. The method of any one of claims 83-94, wherein the subject is a human.

96. The method of any one of claims 83-95, wherein the therapeutically effectively amount diminishes the severity of a sign and/or or a symptom of the neurological disorder.

97. The method of any one of claims 83-96, wherein the therapeutically effectively amount delays the onset of a sign and/or or a symptom of the neurological disorder.

98. The method of any one of claims 83-97, wherein the therapeutically effectively amount eliminates a sign and/or or a symptom of the neurological disorder.

99. The method of any one of claims 96-98, wherein the sign of the neurological disorder is nerve damage, nerve atrophy, and/or seizure.

100. The method of claim 99, wherein the nerve damage is peripheral nerve damage.

101. The method of any one of claims 96-100, wherein the symptom of the neurological disorder is pain.

102. A method of treating and/or delaying the onset of pain in a subject, in need thereof, comprising:

a. administering to the subject, a therapeutically effective amount of the engineered receptor of any one of claims 1-33, the polynucleotide of any one of claims 34-40, or the vector of any one of claims 41-44, the composition of claim 45, or the pharmaceutical composition of claim 46, and
b. administering to the subject a non-native ligand of the engineered receptor.

103. The method of claim 102, wherein the subject is administered the non-native ligand after step (a).

104. The method of claim 102, wherein the subject is administered the non-native ligand concurrently with step (a).

105. The method of any one of claims 102-104, wherein the non-native ligand is selected from the group consisting of AZD-0328, ABT-126, TC6987, CNL002, TC-5619, CNL001, TC-6683, Varenicline, and Facinicline/RG3487.

106. The method of any one of claims 102-105, wherein the non-native ligand is administered orally, subcutaneously, topically, or intravenously.

107. The method of claim 106, wherein the non-native ligand is administered orally.

108. The method of any one of claims 102-107, wherein the engineered receptor, the polynucleotide, the vector, the composition, or the pharmaceutical composition is administered subcutaneously, orally, intrathecally, topically, intravenously, intraganglioncally, intraneurally, intracranially, intraspinally, or to the cisterna magna.

109. The method of any one of claims 102-108, wherein the engineered receptor, the polynucleotide, the vector, the composition, or the pharmaceutical composition is administered by transforaminal injection or intrathecally.

110. The method of any one of claims 102-109, wherein the subject suffers from trigeminal neuralgia, and wherein the engineered receptor, the polynucleotide, the vector, the composition, or the pharmaceutical composition is administered to the trigeminal ganglion (TG) of the subject.

111. The method of any one of claims 102-110, wherein the subject suffers from neuropathic pain, and wherein the engineered receptor, the polynucleotide, the vector, the composition, or the pharmaceutical composition is administered to the dorsal root ganglion (DRG) of the subject.

112. The method of any one of claims 102-111, wherein the subject is a human.

113. The method of any one of claims 101-112, wherein the pain is neuropathic pain.

114. The method of any one of claims 101-113, wherein the pain is associated with, caused by, or resulting from chemotherapy.

115. The method of any one of claims 101-114, wherein the pain is associated with, caused by, or resulting from trauma.

116. The method of any of claims 101-115, wherein the subject suffers from allodynia.

117. The method of any one of claims 101-116, wherein the pain manifests after a medical procedure.

118. The method of any one of claims 101-117, wherein the pain is associated with, is caused by, or resulting from childbirth or Caesarean section.

119. The method of any one of claims 101-118, wherein the pain is associated with, is caused by, or resulting from migraine.

120. The method of any one of claims 101-119, wherein the therapeutically effectively amount diminishes pain in the subject transiently, diminishes pain in the subject permanently, prevents the onset of pain in the subject, and/or eliminates pain in the subject.

121. The method of any one of claims 101-120, wherein steps (a) and (b) are performed before the manifestation of pain in the subject.

122. A kit, comprising (a) the vector of any one of claims 41-44, and (b) a non-native ligand of the engineered receptor.

123. A kit, comprising (a) the engineered receptor of any one of claims 1-33, and (b) a non-native ligand of the engineered receptor.

124. The kit of claim 122 or 123, wherein the engineered receptor and the non-native ligand is according to any one the combinations provided in Table 29.

125. The kit of claim 122 or 124, comprising a device adapted to administration of the vector.

SEQUENCE LISTING

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Keifer, Orion P.
Makinson, Stefanie
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<120> COMPOSITIONS AND METHODS FOR NEUROLOGICAL DISEASES

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35 40 45

Gln Pro Leu Thr Val Tyr Phe Ser Leu Ser Leu Leu Gln Ile Met Asp
50 55 60

Val Asp Glu Lys Asn Gln Val Leu Thr Thr Asn Ile Trp Leu Gln Met
65 70 75 80

Ser Trp Thr Asp His Tyr Leu Gln Trp Asn Val Ser Glu Tyr Pro Gly
85 90 95

Val Lys Thr Val Arg Phe Pro Asp Gly Gln Ile Trp Lys Pro Asp Ile
100 105 110

Leu Leu Tyr Asn Ser Ala Asp Glu Arg Phe Asp Ala Thr Phe His Thr
115 120 125

Asn Val Leu Val Asn Ser Ser Gly His Cys Gln Tyr Leu Pro Pro Gly
130 135 140

Ile Phe Lys Ser Ser Cys Tyr Ile Asp Val Arg Trp Phe Pro Phe Asp
145 150 155 160

Val Gln His Cys Lys Leu Lys Phe Gly Ser Trp Ser Tyr Gly Gly Trp

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                165                 170                 175

Ser Leu Asp Leu Gln Met Gln Glu Ala Asp Ile Ser Gly Tyr Ile Pro
            180                 185                 190

Asn Gly Glu Trp Asp Leu Val Gly Ile Pro Gly Lys Arg Ser Glu Arg
        195                 200                 205

Phe Tyr Glu Cys Cys Lys Glu Pro Tyr Pro Asp Val Thr Phe Thr Val
    210                 215                 220

Thr Met Arg Arg Arg Thr Leu Tyr Tyr Gly Leu Asn Leu Leu Ile Pro
225                 230                 235                 240

Cys Val Leu Ile Ser Ala Leu Ala Leu Leu Val Phe Leu Leu Pro Ala
                245                 250                 255

Asp Ser Gly Glu Lys Ile Ser Leu Gly Ile Thr Val Leu Leu Ser Leu
            260                 265                 270

Thr Val Phe Met Leu Leu Val Ala Glu Ile Met Pro Ala Thr Ser Asp
        275                 280                 285

Ser Val Pro Leu Ile Ala Gln Tyr Phe Ala Ser Thr Met Ile Ile Val
    290                 295                 300

Gly Leu Ser Val Val Val Thr Val Ile Val Leu Gln Tyr His His His
305                 310                 315                 320

Asp Pro Asp Gly Gly Lys Met Pro Lys Trp Thr Arg Val Ile Leu Leu
                325                 330                 335

Asn Trp Cys Ala Trp Phe Leu Arg Met Lys Arg Pro Gly Glu Asp Lys
            340                 345                 350

Val Arg Pro Ala Cys Gln His Lys Gln Arg Arg Cys Ser Leu Ala Ser
        355                 360                 365

Val Glu Met Ser Ala Val Ala Pro Pro Pro Ala Ser Asn Gly Asn Leu
    370                 375                 380
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Leu Tyr Ile Gly Phe Arg Gly Leu Asp Gly Val His Cys Val Pro Thr
385                 390                 395                 400

Pro Asp Ser Gly Val Val Cys Gly Arg Met Ala Cys Ser Pro Thr His
                405                 410                 415

Asp Glu His Leu Leu His Gly Gly Gln Pro Pro Glu Gly Asp Pro Asp
            420                 425                 430

Leu Ala Lys Ile Leu Glu Glu Val Arg Tyr Ile Ala Asn Arg Phe Arg
        435                 440                 445

Cys Gln Asp Glu Ser Glu Ala Val Cys Ser Glu Trp Lys Phe Ala Ala
    450                 455                 460

Cys Val Val Asp Arg Leu Cys Leu Met Ala Phe Ser Val Phe Thr Ile
465                 470                 475                 480

Ile Cys Thr Ile Gly Ile Leu Met Ser Ala Pro Asn Phe Val Glu Ala
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Val Ser Lys Asp Phe Ala
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<212> DNA
<213> Homo sapiens

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tgtcggatta ccttttgacc aactacagga agggtgtgcg ccccgtgagg gactggagga      420

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<212> PRT
<213> Homo sapiens

<400> 6

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20 25 30

Arg Asn Thr Thr Arg Pro Ala Leu Leu Arg Leu Ser Asp Tyr Leu Leu
35 40 45

Thr Asn Tyr Arg Lys Gly Val Arg Pro Val Arg Asp Trp Arg Lys Pro
50 55 60

Thr Thr Val Ser Ile Asp Val Ile Val Tyr Ala Ile Leu Asn Val Asp
65 70 75 80

Glu Lys Asn Gln Val Leu Thr Thr Tyr Ile Trp Tyr Arg Gln Tyr Trp
85 90 95

Thr Asp Glu Phe Leu Gln Trp Asn Pro Glu Asp Phe Asp Asn Ile Thr
100 105 110

Lys Leu Ser Ile Pro Thr Asp Ser Ile Trp Val Pro Asp Ile Leu Ile
115 120 125

Asn Glu Phe Val Asp Val Gly Lys Ser Pro Asn Ile Pro Tyr Val Tyr
130 135 140

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Ile Arg His Gln Gly Glu Val Gln Asn Tyr Lys Pro Leu Gln Val Val
145                 150                 155                 160


Thr Ala Cys Ser Leu Asp Ile Tyr Asn Phe Pro Phe Asp Val Gln Asn
                165                 170                 175


Cys Ser Leu Thr Phe Thr Ser Trp Leu His Thr Ile Gln Asp Ile Asn
            180                 185                 190


Ile Ser Leu Trp Arg Leu Pro Glu Lys Val Lys Ser Asp Arg Ser Val
        195                 200                 205


Phe Met Asn Gln Gly Glu Trp Glu Leu Leu Gly Val Leu Pro Tyr Phe
    210                 215                 220


Arg Glu Phe Ser Met Glu Ser Ser Asn Tyr Tyr Ala Glu Met Lys Phe
225                 230                 235                 240


Tyr Val Val Ile Arg Arg Arg Pro Leu Phe Tyr Val Val Ser Leu Leu
                245                 250                 255


Leu Pro Ser Ile Phe Leu Met Val Met Asp Ile Val Gly Phe Tyr Leu
            260                 265                 270


Pro Pro Asn Ser Gly Glu Arg Val Ser Phe Lys Ile Thr Leu Leu Leu
        275                 280                 285


Gly Tyr Ser Val Phe Leu Ile Ile Val Ser Asp Thr Leu Pro Ala Thr
    290                 295                 300


Ala Ile Gly Thr Pro Leu Ile Gly Lys Ala Pro Pro Gly Ser Arg Ala
305                 310                 315                 320


Gln Ser Gly Glu Lys Pro Ala Pro Ser His Leu Leu His Val Ser Leu
                325                 330                 335


Ala Ser Ala Leu Gly Cys Thr Gly Val Tyr Phe Val Val Cys Met Ala
            340                 345                 350


Leu Leu Val Ile Ser Leu Ala Glu Thr Ile Phe Ile Val Arg Leu Val
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        355                 360                 365

His Lys Gln Asp Leu Gln Gln Pro Val Pro Ala Trp Leu Arg His Leu
    370                 375                 380

Val Leu Glu Arg Ile Ala Trp Leu Leu Cys Leu Arg Glu Gln Ser Thr
385                 390                 395                 400

Ser Gln Arg Pro Pro Ala Thr Ser Gln Ala Thr Lys Thr Asp Asp Cys
                405                 410                 415

Ser Ala Met Gly Asn His Cys Ser His Met Gly Gly Pro Gln Asp Phe
            420                 425                 430

Glu Lys Ser Pro Arg Asp Arg Cys Ser Pro Pro Pro Pro Pro Arg Glu
        435                 440                 445

Ala Ser Leu Ala Val Cys Gly Leu Leu Gln Glu Leu Ser Ser Ile Arg
    450                 455                 460

Gln Phe Leu Glu Lys Arg Asp Glu Ile Arg Glu Val Ala Arg Asp Trp
465                 470                 475                 480

Leu Arg Val Gly Ser Val Leu Asp Lys Leu Leu Phe His Ile Tyr Leu
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Trp Gln Tyr Ala
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<212> PRT
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<400> 8

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Asn Met Ser Phe Val Lys Glu Thr Val Asp Lys Leu Leu Lys Gly Tyr
35 40 45

Asp Ile Arg Leu Arg Pro Asp Phe Gly Gly Pro Pro Val Cys Val Gly
50 55 60

Met Asn Ile Asp Ile Ala Ser Ile Asp Met Val Ser Glu Val Asn Met
65 70 75 80

Asp Tyr Thr Leu Thr Met Tyr Phe Gln Gln Tyr Trp Arg Asp Lys Arg

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Leu Ala Tyr Ser Gly Ile Pro Leu Asn Leu Thr Leu Asp Asn Arg Val
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Ala Asp Gln Leu Trp Val Pro Asp Thr Tyr Phe Leu Asn Asp Lys Lys
        115                 120                 125

Ser Phe Val His Gly Val Thr Val Lys Asn Arg Met Ile Arg Leu His
    130                 135                 140

Pro Asp Gly Thr Val Leu Tyr Gly Leu Arg Ile Thr Thr Thr Ala Ala
145                 150                 155                 160

Cys Met Met Asp Leu Arg Arg Tyr Pro Leu Asp Glu Gln Asn Cys Thr
                165                 170                 175

Leu Glu Ile Glu Ser Tyr Gly Tyr Thr Thr Asp Asp Ile Glu Phe Tyr
            180                 185                 190

Trp Arg Gly Gly Asp Lys Ala Val Thr Gly Val Glu Arg Ile Glu Leu
        195                 200                 205

Pro Gln Phe Ser Ile Val Glu His Arg Leu Val Ser Arg Asn Val Val
    210                 215                 220

Phe Ala Thr Gly Ala Tyr Pro Arg Leu Ser Leu Ser Phe Arg Leu Lys
225                 230                 235                 240

Arg Asn Ile Gly Tyr Phe Ile Leu Gln Thr Tyr Met Pro Ser Ile Leu
                245                 250                 255

Ile Thr Ile Leu Ser Trp Val Ser Phe Trp Ile Asn Tyr Asp Ala Ser
            260                 265                 270

Ala Ala Arg Val Ala Leu Gly Ile Thr Thr Val Leu Thr Met Thr Thr
        275                 280                 285

Ile Asn Thr His Leu Arg Glu Thr Leu Pro Lys Ile Pro Tyr Val Lys
    290                 295                 300
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Ala Ile Asp Met Tyr Leu Met Gly Cys Phe Val Phe Val Phe Leu Ala
305                 310                 315                 320

Leu Leu Glu Tyr Ala Phe Val Asn Tyr Ile Phe Phe Gly Arg Gly Pro
                325                 330                 335

Gln Arg Gln Lys Lys Leu Ala Glu Lys Thr Ala Lys Ala Lys Asn Asp
            340                 345                 350

Arg Ser Lys Ser Glu Ser Asn Arg Val Asp Ala His Gly Asn Ile Leu
        355                 360                 365

Leu Thr Ser Leu Glu Val His Asn Glu Met Asn Glu Val Ser Gly Gly
    370                 375                 380

Ile Gly Asp Thr Arg Asn Ser Ala Ile Ser Phe Asp Asn Ser Gly Ile
385                 390                 395                 400

Gln Tyr Arg Lys Gln Ser Met Pro Arg Glu Gly His Gly Arg Phe Leu
                405                 410                 415

Gly Asp Arg Ser Leu Pro His Lys Lys Thr His Leu Arg Arg Arg Ser
            420                 425                 430

Ser Gln Leu Lys Ile Lys Ile Pro Asp Leu Thr Asp Val Asn Ala Ile
        435                 440                 445

Asp Arg Trp Ser Arg Ile Val Phe Pro Phe Thr Phe Ser Leu Phe Asn
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Leu Val Tyr Trp Leu Tyr Tyr Val Asn
465                 470
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gaactaattt agaccggcta aaataattgt tccactggga cacaggaatt caacctcagt 240

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<212> PRT
<213> Homo sapiens

<400> 10

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Gly Trp Val Leu Ala Thr Glu Ser Arg Met His Trp Pro Gly Arg Glu
            20                  25                  30

Val His Glu Met Ser Lys Lys Gly Arg Pro Gln Arg Gln Arg Arg Glu
        35                  40                  45

Val His Glu Asp Ala His Lys Gln Val Ser Pro Ile Leu Arg Arg Ser
    50                  55                  60

Pro Asp Ile Thr Lys Ser Pro Leu Thr Lys Ser Glu Gln Leu Leu Arg
65                  70                  75                  80

Ile Asp Asp His Asp Phe Ser Met Arg Pro Gly Phe Gly Gly Pro Ala
                85                  90                  95

Ile Pro Val Gly Val Asp Val Gln Val Glu Ser Leu Asp Ser Ile Ser
            100                 105                 110

Glu Val Asp Met Asp Phe Thr Met Thr Leu Tyr Leu Arg His Tyr Trp
        115                 120                 125

Lys Asp Glu Arg Leu Ser Phe Pro Ser Thr Asn Asn Leu Ser Met Thr
    130                 135                 140

Phe Asp Gly Arg Leu Val Lys Lys Ile Trp Val Pro Asp Met Phe Phe
145                 150                 155                 160

Val His Ser Lys Arg Ser Phe Ile His Asp Thr Thr Thr Asp Asn Val
                165                 170                 175

Met Leu Arg Val Gln Pro Asp Gly Lys Val Leu Tyr Ser Leu Arg Val
            180                 185                 190

Thr Val Thr Ala Met Cys Asn Met Asp Phe Ser Arg Phe Pro Leu Asp
        195                 200                 205
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Thr Gln Thr Cys Ser Leu Glu Ile Glu Ser Tyr Ala Tyr Thr Glu Asp
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Asp Leu Met Leu Tyr Trp Lys Lys Gly Asn Asp Ser Leu Lys Thr Asp
225                 230                 235                 240

Glu Arg Ile Ser Leu Ser Gln Phe Leu Ile Gln Glu Phe His Thr Thr
                245                 250                 255

Thr Lys Leu Ala Phe Tyr Ser Ser Thr Gly Trp Tyr Asn Arg Leu Tyr
            260                 265                 270

Ile Asn Phe Thr Leu Arg Arg His Ile Phe Phe Phe Leu Leu Gln Thr
        275                 280                 285

Tyr Phe Pro Ala Thr Leu Met Val Met Leu Ser Trp Val Ser Phe Trp
    290                 295                 300

Ile Asp Arg Arg Ala Val Pro Ala Arg Val Pro Leu Gly Ile Thr Thr
305                 310                 315                 320

Val Leu Thr Met Ser Thr Ile Ile Thr Gly Val Asn Ala Ser Met Pro
                325                 330                 335

Arg Val Ser Tyr Ile Lys Ala Val Asp Ile Tyr Leu Trp Val Ser Phe
            340                 345                 350

Val Phe Val Phe Leu Ser Val Leu Glu Tyr Ala Ala Val Asn Tyr Leu
        355                 360                 365

Thr Thr Val Gln Glu Arg Lys Glu Gln Lys Leu Arg Glu Lys Leu Pro
    370                 375                 380

Cys Thr Ser Gly Leu Pro Pro Pro Arg Thr Ala Met Leu Asp Gly Asn
385                 390                 395                 400

Tyr Ser Asp Gly Glu Val Asn Asp Leu Asp Asn Tyr Met Pro Glu Asn
                405                 410                 415

Gly Glu Lys Pro Asp Arg Met Met Val Gln Leu Thr Leu Ala Ser Glu
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420 425 430

Arg Ser Ser Pro Gln Arg Lys Ser Gln Arg Ser Ser Tyr Val Ser Met
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<212> PRT
<213> Homo sapiens

<400> 12

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Leu Val Glu Ser Arg Lys Pro Lys Arg Lys Arg Trp Thr Gly Gln Val
20 25 30

Glu Met Pro Lys Pro Ser His Leu Tyr Lys Lys Asn Leu Asp Val Thr
35 40 45

Lys Ile Arg Lys Gly Lys Pro Gln Gln Leu Leu Arg Val Asp Glu His
50 55 60

Asp Phe Ser Met Arg Pro Ala Phe Gly Gly Pro Ala Ile Pro Val Gly
65 70 75 80

Val Asp Val Gln Val Glu Ser Leu Asp Ser Ile Ser Glu Val Asp Met
85 90 95

Asp Phe Thr Met Thr Leu Tyr Leu Arg His Tyr Trp Lys Asp Glu Arg
100 105 110

Leu Ala Phe Ser Ser Ala Ser Asn Lys Ser Met Thr Phe Asp Gly Arg
115 120 125

Leu Val Lys Lys Ile Trp Val Pro Asp Val Phe Phe Val His Ser Lys

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    130                 135                 140

Arg Ser Phe Thr His Asp Thr Thr Thr Asp Asn Ile Met Leu Arg Val
145                 150                 155                 160

Phe Pro Asp Gly His Val Leu Tyr Ser Met Arg Ile Thr Val Thr Ala
                165                 170                 175

Met Cys Asn Met Asp Phe Ser His Phe Pro Leu Asp Ser Gln Thr Cys
            180                 185                 190

Ser Leu Glu Leu Glu Ser Tyr Ala Tyr Thr Asp Glu Asp Leu Met Leu
        195                 200                 205

Tyr Trp Lys Asn Gly Asp Glu Ser Leu Lys Thr Asp Glu Lys Ile Ser
    210                 215                 220

Leu Ser Gln Phe Leu Ile Gln Lys Phe His Thr Thr Ser Arg Leu Ala
225                 230                 235                 240

Phe Tyr Ser Ser Thr Gly Trp Tyr Asn Arg Leu Tyr Ile Asn Phe Thr
                245                 250                 255

Leu Arg Arg His Ile Phe Phe Phe Leu Leu Gln Thr Tyr Phe Pro Ala
            260                 265                 270

Thr Leu Met Val Met Leu Ser Trp Val Ser Phe Trp Ile Asp Arg Arg
        275                 280                 285

Ala Val Pro Ala Arg Val Ser Leu Gly Ile Thr Thr Val Leu Thr Met
    290                 295                 300

Thr Thr Ile Ile Thr Gly Val Asn Ala Ser Met Pro Arg Val Ser Tyr
305                 310                 315                 320

Val Lys Ala Val Asp Ile Tyr Leu Trp Val Ser Phe Val Phe Val Phe
                325                 330                 335

Leu Ser Val Leu Glu Tyr Ala Ala Val Asn Tyr Leu Thr Thr Val Gln
            340                 345                 350
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Glu Arg Lys Glu Arg Lys Leu Arg Glu Lys Phe Pro Cys Met Cys Gly
        355                 360                 365

Met Leu His Ser Lys Thr Met Met Leu Asp Gly Ser Tyr Ser Glu Ser
    370                 375                 380

Glu Ala Asn Ser Leu Ala Gly Tyr Pro Arg Ser His Ile Leu Thr Glu
385                 390                 395                 400

Glu Glu Arg Gln Asp Lys Ile Val Val His Leu Gly Leu Ser Gly Glu
                405                 410                 415

Ala Asn Ala Ala Arg Lys Lys Gly Leu Leu Lys Gly Gln Thr Gly Phe
            420                 425                 430

Arg Ile Phe Gln Asn Thr His Ala Ile Asp Lys Tyr Ser Arg Leu Ile
        435                 440                 445

Phe Pro Ala Ser Tyr Ile Phe Phe Asn Leu Ile Tyr Trp Ser Val Phe
    450                 455                 460

Ser
465
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aacatggact ttacaatgac tttttatctc aggcattact ggaaagacga gaggctctcc      360

tttcctagca cagcaaacaa aagcatgaca tttgatcata gattgaccag aaagatctgg      420

gtgcctgata tctttttttgt ccactctaaa agatccttca tccatgatac aactatggag      480
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Leu Lys Pro Asn Val Cys Ala Ala Ser Asn Ile Lys Met Thr His Gln
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Arg Cys Ser Ser Ser Met Lys Gln Thr Cys Lys Gln Glu Thr Arg Met
35 40 45

Lys Lys Asp Asp Ser Thr Lys Ala Arg Pro Gln Lys Tyr Glu Gln Leu

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    50                  55                  60

Leu His Ile Glu Asp Asn Asp Phe Ala Met Arg Pro Gly Phe Gly Gly
65                  70                  75                  80

Ser Pro Val Pro Val Gly Ile Asp Val His Val Glu Ser Ile Asp Ser
                85                  90                  95

Ile Ser Glu Thr Asn Met Asp Phe Thr Met Thr Phe Tyr Leu Arg His
            100                 105                 110

Tyr Trp Lys Asp Glu Arg Leu Ser Phe Pro Ser Thr Ala Asn Lys Ser
        115                 120                 125

Met Thr Phe Asp His Arg Leu Thr Arg Lys Ile Trp Val Pro Asp Ile
    130                 135                 140

Phe Phe Val His Ser Lys Arg Ser Phe Ile His Asp Thr Thr Met Glu
145                 150                 155                 160

Asn Ile Met Leu Arg Val His Pro Asp Gly Asn Val Leu Leu Ser Leu
                165                 170                 175

Arg Ile Thr Val Ser Ala Met Cys Phe Met Asp Phe Ser Arg Phe Pro
            180                 185                 190

Leu Asp Thr Gln Asn Cys Ser Leu Glu Leu Glu Ser Tyr Ala Tyr Asn
        195                 200                 205

Glu Asp Asp Leu Met Leu Tyr Trp Lys His Gly Asn Lys Ser Leu Asn
    210                 215                 220

Thr Glu Glu His Met Ser Leu Ser Gln Phe Phe Ile Glu Asp Phe Ser
225                 230                 235                 240

Ala Ser Ser Gly Leu Ala Phe Tyr Ser Ser Thr Gly Trp Tyr Asn Arg
                245                 250                 255

Leu Phe Ile Asn Phe Val Leu Arg Arg His Val Phe Phe Phe Val Leu
            260                 265                 270
```

```
Gln Thr Tyr Phe Pro Ala Ile Leu Met Val Met Leu Ser Trp Val Ser
        275                 280                 285

Phe Trp Ile Asp Arg Arg Ala Val Pro Ala Arg Val Ser Leu Gly Ile
    290                 295                 300

Thr Thr Val Leu Thr Met Ser Thr Ile Ile Thr Ala Val Ser Ala Ser
305                 310                 315                 320

Met Pro Gln Val Ser Tyr Leu Lys Ala Val Asp Val Tyr Leu Trp Val
                325                 330                 335

Ser Ser Leu Phe Val Phe Leu Ser Val Ile Glu Tyr Ala Ala Val Asn
            340                 345                 350

Tyr Leu Thr Thr Val Glu Glu Arg Lys Gln Phe Lys Lys Thr Gly Lys
        355                 360                 365

Ile Ser Arg Met Tyr Asn Ile Asp Ala Val Gln Ala Met Ala Phe Asp
    370                 375                 380

Gly Cys Tyr His Asp Ser Glu Ile Asp Met Asp Gln Thr Ser Leu Ser
385                 390                 395                 400

Leu Asn Ser Glu Asp Phe Met Arg Arg Lys Ser Ile Cys Ser Pro Ser
                405                 410                 415

Thr Asp Ser Ser Arg Ile Lys Arg Arg Lys Ser Leu Gly Gly His Val
            420                 425                 430

Gly Arg Ile Ile Leu Glu Asn Asn His Val Ile Asp Thr Tyr Ser Arg
        435                 440                 445

Ile Leu Phe Pro Ile Val Tyr Ile Leu Phe Asn Leu Phe Tyr Trp Gly
    450                 455                 460

Val Tyr Val
465
```

<210> 15

<211> 1320
<212> DNA
<213> Artificial Sequence

<220>
<223> synthetic sequence of chimeric LGIC

<400> 15
atgcgctgct cgccgggagg cgtctggctg gcgctggccg cgtcgctcct gcacgtgtcc 60

ctgcaaggcg agttccagag gaagctttac aaggagctgg tcaagaacta caatcccttg 120

gagaggcccg tggccaatga ctcgcaacca ctcaccgtct acttctccct gagcctcctg 180

cagatcatgg acgtggatga gaagaaccaa gttttaacca ccaacatttg gctgcaaatg 240

tcttggacag atcactattt acagtggaat gtgtcagaat atccaggggt gaagactgtt 300

cgtttcccag atggccagat ttggaaacca gacattcttc tctataacag tgctgatgag 360

cgctttgacg ccacattcca cactaacgtg ttggtgaact cttctgggca ttgccagtac 420

ctgcctccag gcatattcaa gagttcctgc tacatcgatg tacgctggtt tccctttgat 480

gtgcagcact gcaaactgaa gtttgggtcc tggtcttacg gaggctggtc cttggatctg 540

cagatgcagg aggcagatat cagtggctat atccccaatg gagaatggga cctagtggga 600

atccccggca agaggagtga aaggttctat gagtgctgca aagagcccta ccccgatgtc 660

accttcacag tgaccatgcg ccgcaggatg ggttactacc tgattcagat gtatattccc 720

agcctgctca ttgtcatcct ctcatggatc tccttctgga tcaacatgga tgctgcacct 780

gctcgtgtgg gcctaggcat caccactgtg ctcaccatga ccacccagag ctccggctct 840

cgagcatctc tgcccaaggt gtcctatgtg aaagccattg acatttggat ggcagtttgc 900

ctgctctttg tgttctcagc cctattagaa tatgctgccg ttaactttgt gtctcggcaa 960

cataaggagc tgctccgatt caggaggaag cggagacatc acaagagccc catgttgaat 1020

ctattccagg aggatgaagc tggagaaggc cgctttaact tctctgccta tgggatgggc 1080

ccagcctgtc tacaggccaa ggatggcatc tcagtcaagg gcgccaacaa cagtaacacc 1140

accaaccccc ctcctgcacc atctaagtcc ccagaggaga tgcgaaaact cttcatccag 1200

agggccaaga agatcgacaa aatatcccgc attggcttcc ccatggcctt cctcattttc 1260

aacatgttct actggatcat ctacaagatt gtccgtagag aggacgtcca caaccagtga 1320

<210> 16

<211> 439
<212> PRT
<213> Artificial Sequence

<220>
<223> synthetic sequence of chimeric LGIC

<400> 16

Met Arg Cys Ser Pro Gly Gly Val Trp Leu Ala Leu Ala Ala Ser Leu
1 5 10 15

Leu His Val Ser Leu Gln Gly Glu Phe Gln Arg Lys Leu Tyr Lys Glu
20 25 30

Leu Val Lys Asn Tyr Asn Pro Leu Glu Arg Pro Val Ala Asn Asp Ser
35 40 45

Gln Pro Leu Thr Val Tyr Phe Ser Leu Ser Leu Leu Gln Ile Met Asp
50 55 60

Val Asp Glu Lys Asn Gln Val Leu Thr Thr Asn Ile Trp Leu Gln Met
65 70 75 80

Ser Trp Thr Asp His Tyr Leu Gln Trp Asn Val Ser Glu Tyr Pro Gly
85 90 95

Val Lys Thr Val Arg Phe Pro Asp Gly Gln Ile Trp Lys Pro Asp Ile
100 105 110

Leu Leu Tyr Asn Ser Ala Asp Glu Arg Phe Asp Ala Thr Phe His Thr
115 120 125

Asn Val Leu Val Asn Ser Ser Gly His Cys Gln Tyr Leu Pro Pro Gly
130 135 140

Ile Phe Lys Ser Ser Cys Tyr Ile Asp Val Arg Trp Phe Pro Phe Asp
145 150 155 160

Val Gln His Cys Lys Leu Lys Phe Gly Ser Trp Ser Tyr Gly Gly Trp
165 170 175

Ser Leu Asp Leu Gln Met Gln Glu Ala Asp Ile Ser Gly Tyr Ile Pro

```
            180                 185                 190

Asn Gly Glu Trp Asp Leu Val Gly Ile Pro Gly Lys Arg Ser Glu Arg
        195                 200                 205

Phe Tyr Glu Cys Cys Lys Glu Pro Tyr Pro Asp Val Thr Phe Thr Val
    210                 215                 220

Thr Met Arg Arg Arg Met Gly Tyr Tyr Leu Ile Gln Met Tyr Ile Pro
225                 230                 235                 240

Ser Leu Leu Ile Val Ile Leu Ser Trp Ile Ser Phe Trp Ile Asn Met
                245                 250                 255

Asp Ala Ala Pro Ala Arg Val Gly Leu Gly Ile Thr Thr Val Leu Thr
            260                 265                 270

Met Thr Thr Gln Ser Ser Gly Ser Arg Ala Ser Leu Pro Lys Val Ser
        275                 280                 285

Tyr Val Lys Ala Ile Asp Ile Trp Met Ala Val Cys Leu Leu Phe Val
    290                 295                 300

Phe Ser Ala Leu Leu Glu Tyr Ala Ala Val Asn Phe Val Ser Arg Gln
305                 310                 315                 320

His Lys Glu Leu Leu Arg Phe Arg Arg Lys Arg Arg His His Lys Ser
                325                 330                 335

Pro Met Leu Asn Leu Phe Gln Glu Asp Glu Ala Gly Glu Gly Arg Phe
            340                 345                 350

Asn Phe Ser Ala Tyr Gly Met Gly Pro Ala Cys Leu Gln Ala Lys Asp
        355                 360                 365

Gly Ile Ser Val Lys Gly Ala Asn Asn Ser Asn Thr Thr Asn Pro Pro
    370                 375                 380

Pro Ala Pro Ser Lys Ser Pro Glu Glu Met Arg Lys Leu Phe Ile Gln
385                 390                 395                 400
```

Arg Ala Lys Lys Ile Asp Lys Ile Ser Arg Ile Gly Phe Pro Met Ala
405 410 415

Phe Leu Ile Phe Asn Met Phe Tyr Trp Ile Ile Tyr Lys Ile Val Arg
420 425 430

Arg Glu Asp Val His Asn Gln
435

<210> 17
<211> 439
<212> PRT
<213> Artificial Sequence

<220>
<223> synthetic sequence of chimeric LGIC

<400> 17

Met Arg Cys Ser Pro Gly Gly Val Trp Leu Ala Leu Ala Ala Ser Leu
1 5 10 15

Leu His Val Ser Leu Gln Gly Glu Phe Gln Arg Lys Leu Tyr Lys Glu
20 25 30

Leu Val Lys Asn Tyr Asn Pro Leu Glu Arg Pro Val Ala Asn Asp Ser
35 40 45

Gln Pro Leu Thr Val Tyr Phe Ser Leu Ser Leu Leu Gln Ile Met Asp
50 55 60

Val Asp Glu Lys Asn Gln Val Leu Thr Thr Asn Ile Trp Leu Gln Met
65 70 75 80

Ser Trp Thr Asp His Tyr Leu Gln Trp Asn Val Ser Glu Tyr Pro Gly
85 90 95

Val Lys Thr Val Arg Phe Pro Asp Gly Gln Ile Trp Lys Pro Asp Ile
100 105 110

Leu Leu Tyr Asn Ser Ala Asp Glu Arg Phe Asp Ala Thr Phe His Thr
115 120 125

```
Asn Val Leu Val Asn Ser Ser Gly His Cys Gln Tyr Leu Pro Pro Gly
    130                 135                 140

Ile Phe Lys Ser Ser Cys Tyr Ile Asp Val Arg Trp Phe Pro Phe Asp
145                 150                 155                 160

Val Gln His Cys Lys Leu Lys Phe Gly Ser Trp Ser Tyr Gly Gly Trp
                165                 170                 175

Ser Leu Asp Leu Gln Met Gln Glu Ala Asp Ile Ser Gly Tyr Ile Pro
            180                 185                 190

Asn Gly Glu Trp Asp Leu Val Gly Ile Pro Gly Lys Arg Ser Glu Arg
        195                 200                 205

Phe Tyr Glu Cys Cys Lys Glu Pro Tyr Pro Asp Val Thr Phe Thr Val
    210                 215                 220

Thr Met Arg Arg Gln Met Gly Tyr Tyr Leu Ile Gln Met Tyr Ile Pro
225                 230                 235                 240

Ser Leu Leu Ile Val Ile Leu Ser Trp Ile Ser Phe Trp Ile Asn Met
                245                 250                 255

Asp Ala Ala Pro Ala Arg Val Gly Leu Gly Ile Thr Thr Val Leu Thr
            260                 265                 270

Met Thr Thr Gln Ser Ser Gly Ser Arg Ala Ser Leu Pro Lys Val Ser
        275                 280                 285

Tyr Val Lys Ala Ile Asp Ile Trp Met Ala Val Cys Leu Leu Phe Val
    290                 295                 300

Phe Ser Ala Leu Leu Glu Tyr Ala Ala Val Asn Phe Val Ser Arg Gln
305                 310                 315                 320

His Lys Glu Leu Leu Arg Phe Arg Arg Lys Arg Arg His His Lys Ser
                325                 330                 335

Pro Met Leu Asn Leu Phe Gln Glu Asp Glu Ala Gly Glu Gly Arg Phe
```

```
            340                 345                 350

Asn Phe Ser Ala Tyr Gly Met Gly Pro Ala Cys Leu Gln Ala Lys Asp
        355                 360                 365

Gly Ile Ser Val Lys Gly Ala Asn Asn Ser Asn Thr Thr Asn Pro Pro
    370                 375                 380

Pro Ala Pro Ser Lys Ser Pro Glu Glu Met Arg Lys Leu Phe Ile Gln
385                 390                 395                 400

Arg Ala Lys Lys Ile Asp Lys Ile Ser Arg Ile Gly Phe Pro Met Ala
                405                 410                 415

Phe Leu Ile Phe Asn Met Phe Tyr Trp Ile Ile Tyr Lys Ile Val Arg
            420                 425                 430

Arg Glu Asp Val His Asn Gln
        435


<210>  18
<211>  439
<212>  PRT
<213>  Artificial Sequence

<220>
<223>  synthetic sequence of chimeric LGIC

<400>  18

Met Arg Cys Ser Pro Gly Gly Val Trp Leu Ala Leu Ala Ala Ser Leu
1               5                   10                  15

Leu His Val Ser Leu Gln Gly Glu Phe Gln Arg Lys Leu Tyr Lys Glu
            20                  25                  30

Leu Val Lys Asn Tyr Asn Pro Leu Glu Arg Pro Val Ala Asn Asp Ser
        35                  40                  45

Gln Pro Leu Thr Val Tyr Phe Ser Leu Ser Leu Leu Gln Ile Met Asp
    50                  55                  60

Val Asp Glu Lys Asn Gln Val Leu Thr Thr Asn Ile Trp Leu Gln Met
```

```
65                  70                  75                  80

Ser Trp Thr Asp His Tyr Leu Gln Trp Asn Val Ser Glu Tyr Pro Gly
                85                  90                  95

Val Lys Thr Val Arg Phe Pro Asp Gly Gln Ile Trp Lys Pro Asp Ile
            100                 105                 110

Leu Leu Tyr Asn Ser Ala Asp Glu Arg Phe Asp Ala Thr Phe His Thr
        115                 120                 125

Asn Val Leu Val Asn Ser Ser Gly His Cys Gln Tyr Leu Pro Pro Gly
    130                 135                 140

Ile Phe Lys Ser Ser Cys Tyr Ile Asp Val Arg Trp Phe Pro Phe Asp
145                 150                 155                 160

Val Gln His Cys Lys Leu Lys Phe Gly Ser Trp Ser Tyr Gly Gly Trp
                165                 170                 175

Ser Leu Asp Leu Gln Met Gln Glu Ala Asp Ile Ser Gly Tyr Ile Pro
            180                 185                 190

Asn Gly Glu Trp Asp Leu Val Gly Ile Pro Gly Lys Arg Ser Glu Arg
        195                 200                 205

Phe Tyr Glu Cys Cys Lys Glu Pro Tyr Pro Asp Val Thr Phe Thr Val
    210                 215                 220

His Leu Glu Arg Gln Met Gly Tyr Tyr Leu Ile Gln Met Tyr Ile Pro
225                 230                 235                 240

Ser Leu Leu Ile Val Ile Leu Ser Trp Ile Ser Phe Trp Ile Asn Met
                245                 250                 255

Asp Ala Ala Pro Ala Arg Val Gly Leu Gly Ile Thr Thr Val Leu Thr
            260                 265                 270

Met Thr Thr Gln Ser Ser Gly Ser Arg Ala Ser Leu Pro Lys Val Ser
        275                 280                 285
```

```
Tyr Val Lys Ala Ile Asp Ile Trp Met Ala Val Cys Leu Leu Phe Val
    290                 295                 300

Phe Ser Ala Leu Leu Glu Tyr Ala Ala Val Asn Phe Val Ser Arg Gln
305                 310                 315                 320

His Lys Glu Leu Leu Arg Phe Arg Arg Lys Arg Arg His His Lys Ser
                325                 330                 335

Pro Met Leu Asn Leu Phe Gln Glu Asp Glu Ala Gly Glu Gly Arg Phe
            340                 345                 350

Asn Phe Ser Ala Tyr Gly Met Gly Pro Ala Cys Leu Gln Ala Lys Asp
        355                 360                 365

Gly Ile Ser Val Lys Gly Ala Asn Asn Ser Asn Thr Thr Asn Pro Pro
    370                 375                 380

Pro Ala Pro Ser Lys Ser Pro Glu Glu Met Arg Lys Leu Phe Ile Gln
385                 390                 395                 400

Arg Ala Lys Lys Ile Asp Lys Ile Ser Arg Ile Gly Phe Pro Met Ala
                405                 410                 415

Phe Leu Ile Phe Asn Met Phe Tyr Trp Ile Ile Tyr Lys Ile Val Arg
            420                 425                 430

Arg Glu Asp Val His Asn Gln
        435
```

<210> 19
<211> 439
<212> PRT
<213> Artificial Sequence

<220>
<223> synthetic sequence of chimeric LGIC

<400> 19

```
Met Arg Cys Ser Pro Gly Gly Val Trp Leu Ala Leu Ala Ala Ser Leu
1               5                   10                  15
```

```
Leu His Val Ser Leu Gln Gly Glu Phe Gln Arg Lys Leu Tyr Lys Glu
            20                  25                  30

Leu Val Lys Asn Tyr Asn Pro Leu Glu Arg Pro Val Ala Asn Asp Ser
        35                  40                  45

Gln Pro Leu Thr Val Tyr Phe Ser Leu Ser Leu Leu Gln Ile Met Asp
    50                  55                  60

Val Asp Glu Lys Asn Gln Val Leu Thr Thr Asn Ile Trp Leu Gln Met
65                  70                  75                  80

Ser Trp Thr Asp His Tyr Leu Gln Trp Asn Val Ser Glu Tyr Pro Gly
                85                  90                  95

Val Lys Thr Val Arg Phe Pro Asp Gly Gln Ile Trp Lys Pro Asp Ile
            100                 105                 110

Leu Leu Tyr Asn Ser Ala Asp Glu Arg Phe Asp Ala Thr Phe His Thr
        115                 120                 125

Asn Val Leu Val Asn Ser Ser Gly His Cys Gln Tyr Leu Pro Pro Gly
    130                 135                 140

Ile Phe Lys Ser Ser Cys Tyr Ile Asp Val Arg Trp Phe Pro Phe Asp
145                 150                 155                 160

Val Gln His Cys Lys Leu Lys Phe Gly Ser Trp Ser Tyr Gly Gly Trp
                165                 170                 175

Ser Leu Asp Leu Gln Met Gln Glu Ala Asp Ile Ser Gly Tyr Ile Pro
            180                 185                 190

Asn Gly Glu Trp Asp Leu Val Gly Ile Pro Gly Lys Arg Ser Glu Arg
        195                 200                 205

Phe Tyr Glu Cys Cys Lys Glu Pro Tyr Pro Asp Val Thr Phe Thr Val
    210                 215                 220

Thr Met Arg Arg Arg Thr Leu Tyr Tyr Leu Ile Gln Met Tyr Ile Pro
```

```
225                 230                 235                 240

Ser Leu Leu Ile Val Ile Leu Ser Trp Ile Ser Phe Trp Ile Asn Met
                245                 250                 255

Asp Ala Ala Pro Ala Arg Val Gly Leu Gly Ile Thr Thr Val Leu Thr
            260                 265                 270

Met Thr Thr Gln Ser Ser Gly Ser Arg Ala Ser Leu Pro Lys Val Ser
        275                 280                 285

Tyr Val Lys Ala Ile Asp Ile Trp Met Ala Val Cys Leu Leu Phe Val
    290                 295                 300

Phe Ser Ala Leu Leu Glu Tyr Ala Ala Val Asn Phe Val Ser Arg Gln
305                 310                 315                 320

His Lys Glu Leu Leu Arg Phe Arg Arg Lys Arg Arg His His Lys Ser
                325                 330                 335

Pro Met Leu Asn Leu Phe Gln Glu Asp Glu Ala Gly Glu Gly Arg Phe
            340                 345                 350

Asn Phe Ser Ala Tyr Gly Met Gly Pro Ala Cys Leu Gln Ala Lys Asp
        355                 360                 365

Gly Ile Ser Val Lys Gly Ala Asn Asn Ser Asn Thr Thr Asn Pro Pro
    370                 375                 380

Pro Ala Pro Ser Lys Ser Pro Glu Glu Met Arg Lys Leu Phe Ile Gln
385                 390                 395                 400

Arg Ala Lys Lys Ile Asp Lys Ile Ser Arg Ile Gly Phe Pro Met Ala
                405                 410                 415

Phe Leu Ile Phe Asn Met Phe Tyr Trp Ile Ile Tyr Lys Ile Val Arg
            420                 425                 430

Arg Glu Asp Val His Asn Gln
        435
```

<210> 20
<211> 1329
<212> DNA
<213> Artificial Sequence

<220>
<223> synthetic sequence of chimeric LGIC

<400> 20
atgcgctgct cgccgggagg cgtctggctg gcgctggccg cgtcgctcct gcacgtgtcc 60

ctgcaaggcg agttccagag gaagctttac aaggagctgg tcaagaacta caatcccttg 120

gagaggcccg tggccaatga ctcgcaacca ctcaccgtct acttctccct gagcctcctg 180

cagatcatgg acgtggatga gaagaaccaa gttttaacca ccaacatttg gctgcaaatg 240

tcttggacag atcactattt acagtggaat gtgtcagaat atccaggggt gaagactgtt 300

cgtttcccag atggccagat ttggaaacca gacattcttc tctataacag tgctgatgag 360

cgctttgacg ccacattcca cactaacgtg ttggtgaact cttctgggca ttgccagtac 420

ctgcctccag gcatattcaa gagttcctgc tacatcgatg tacgctggtt tccctttgat 480

gtgcagcact gcaaactgaa gtttgggtcc tggtcttacg gaggctggtc cttggatctg 540

cagatgcagg aggcagatat cagtggctat atccccaatg gagaatggga cctagtggga 600

atccccggca agaggagtga aaggttctat gagtgctgca aagagcccta ccccgatgtc 660

accttcacag tgaccatgcg ccgcaggatg ggttactacc tgattcagat gtatattccc 720

agcctgctca ttgtcatcct ctcatggatc tccttctgga tcaacatgga tgctgcacct 780

gctcgtgtgg gcctaggcat caccactgtg ctcaccatga ccacccagag ctccggctct 840

gagatcatgc ccgcaacatc cgattcggta tcctatgtga aagccattga catttggatg 900

gcagtttgcc tgctctttgt gttctcagcc ctattagaat atgctgccgt taactttgtg 960

tctcggcaac ataaggagct gctccgattc aggaggaagc ggagacatca caagagcccc 1020

atgttgaatc tattccagga ggatgaagct ggagaaggcc gctttaactt ctctgcctat 1080

gggatgggcc cagcctgtct acaggccaag gatggcatct cagtcaaggg cgccaacaac 1140

agtaacacca ccaacccccc tcctgcacca tctaagtccc cagaggagat gcgaaaactc 1200

ttcatccaga gggccaagaa gatcgacaaa atatcccgca ttggcttccc catggccttc 1260

ctcattttca acatgttcta ctggatcatc tacaagattg tccgtagaga ggacgtccac 1320

aaccagtga 1329

<210> 21
<211> 442
<212> PRT
<213> Artificial Sequence

<220>
<223> synthetic sequence of chimeric LGIC

<400> 21

Met Arg Cys Ser Pro Gly Gly Val Trp Leu Ala Leu Ala Ala Ser Leu
1 5 10 15

Leu His Val Ser Leu Gln Gly Glu Phe Gln Arg Lys Leu Tyr Lys Glu
20 25 30

Leu Val Lys Asn Tyr Asn Pro Leu Glu Arg Pro Val Ala Asn Asp Ser
35 40 45

Gln Pro Leu Thr Val Tyr Phe Ser Leu Ser Leu Leu Gln Ile Met Asp
50 55 60

Val Asp Glu Lys Asn Gln Val Leu Thr Thr Asn Ile Trp Leu Gln Met
65 70 75 80

Ser Trp Thr Asp His Tyr Leu Gln Trp Asn Val Ser Glu Tyr Pro Gly
85 90 95

Val Lys Thr Val Arg Phe Pro Asp Gly Gln Ile Trp Lys Pro Asp Ile
100 105 110

Leu Leu Tyr Asn Ser Ala Asp Glu Arg Phe Asp Ala Thr Phe His Thr
115 120 125

Asn Val Leu Val Asn Ser Ser Gly His Cys Gln Tyr Leu Pro Pro Gly
130 135 140

Ile Phe Lys Ser Ser Cys Tyr Ile Asp Val Arg Trp Phe Pro Phe Asp
145 150 155 160

Val Gln His Cys Lys Leu Lys Phe Gly Ser Trp Ser Tyr Gly Gly Trp

```
                165                 170                 175

Ser Leu Asp Leu Gln Met Gln Glu Ala Asp Ile Ser Gly Tyr Ile Pro
            180                 185                 190

Asn Gly Glu Trp Asp Leu Val Gly Ile Pro Gly Lys Arg Ser Glu Arg
        195                 200                 205

Phe Tyr Glu Cys Cys Lys Glu Pro Tyr Pro Asp Val Thr Phe Thr Val
    210                 215                 220

Thr Met Arg Arg Arg Met Gly Tyr Tyr Leu Ile Gln Met Tyr Ile Pro
225                 230                 235                 240

Ser Leu Leu Ile Val Ile Leu Ser Trp Ile Ser Phe Trp Ile Asn Met
                245                 250                 255

Asp Ala Ala Pro Ala Arg Val Gly Leu Gly Ile Thr Thr Val Leu Thr
            260                 265                 270

Met Thr Thr Gln Ser Ser Gly Ser Glu Ile Met Pro Ala Thr Ser Asp
        275                 280                 285

Ser Val Ser Tyr Val Lys Ala Ile Asp Ile Trp Met Ala Val Cys Leu
    290                 295                 300

Leu Phe Val Phe Ser Ala Leu Leu Glu Tyr Ala Ala Val Asn Phe Val
305                 310                 315                 320

Ser Arg Gln His Lys Glu Leu Leu Arg Phe Arg Arg Lys Arg Arg His
                325                 330                 335

His Lys Ser Pro Met Leu Asn Leu Phe Gln Glu Asp Glu Ala Gly Glu
            340                 345                 350

Gly Arg Phe Asn Phe Ser Ala Tyr Gly Met Gly Pro Ala Cys Leu Gln
        355                 360                 365

Ala Lys Asp Gly Ile Ser Val Lys Gly Ala Asn Asn Ser Asn Thr Thr
    370                 375                 380
```

```
Asn Pro Pro Pro Ala Pro Ser Lys Ser Pro Glu Glu Met Arg Lys Leu
385                 390                 395                 400

Phe Ile Gln Arg Ala Lys Lys Ile Asp Lys Ile Ser Arg Ile Gly Phe
                405                 410                 415

Pro Met Ala Phe Leu Ile Phe Asn Met Phe Tyr Trp Ile Ile Tyr Lys
            420                 425                 430

Ile Val Arg Arg Glu Asp Val His Asn Gln
        435                 440
```

<210> 22
<211> 1332
<212> DNA
<213> Artificial Sequence

<220>
<223> synthetic sequence of chimeric LGIC

<400> 22

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atgcgctgct cgccgggagg cgtctggctg gcgctggccg cgtcgctcct gcacgtgtcc       60

ctgcaaggcg agttccagag gaagctttac aaggagctgg tcaagaacta caatcccttg      120

gagaggcccg tggccaatga ctcgcaacca ctcaccgtct acttctccct gagcctcctg      180

cagatcatgg acgtggatga gaagaaccaa gttttaacca ccaacatttg gctgcaaatg      240

tcttggacag atcactattt acagtggaat gtgtcagaat atccaggggt gaagactgtt      300

cgtttcccag atggccagat ttggaaacca gacattcttc tctataacag tgctgatgag      360

cgctttgacg ccacattcca cactaacgtg ttggtgaact cttctgggca ttgccagtac      420

ctgcctccag gcatattcaa gagttcctgc tacatcgatg tacgctggtt tccctttgat      480

gtgcagcact gcaaactgaa gtttgggtcc tggtcttacg gaggctggtc cttggatctg      540

cagatgcagg aggcagatat cagtggctat atccccaatg gagaatggga cctagtggga      600

atccccggca agaggagtga aaggttctat gagtgctgca aagagcccta ccccgatgtc      660

accttcacag tgaccatgcg ccgcaggatg ggttactacc tgattcagat gtatattccc      720

agcctgctca ttgtcatcct ctcatggatc tccttctgga tcaacatgga tgctgcacct      780

gctcgtgtgg gcctaggcat caccactgtg ctcaccatga ccacccagag ctccggctct      840
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gagatcatgc ccgcaacatc cgattcggta ccattgatag cccaggccat tgacatttgg 900

atggcagttt gcctgctctt tgtgttctca gccctattag aatatgctgc cgttaacttt 960

gtgtctcggc aacataagga gctgctccga ttcaggagga agcggagaca tcacaagagc 1020

cccatgttga atctattcca ggaggatgaa gctggagaag gccgctttaa cttctctgcc 1080

tatgggatgg gcccagcctg tctacaggcc aaggatggca tctcagtcaa gggcgccaac 1140

aacagtaaca ccaccaaccc ccctcctgca ccatctaagt ccccagagga gatgcgaaaa 1200

ctcttcatcc agagggccaa gaagatcgac aaaatatccc gcattggctt ccccatggcc 1260

ttcctcattt tcaacatgtt ctactggatc atctacaaga ttgtccgtag agaggacgtc 1320

cacaaccagt ga 1332

<210> 23
<211> 443
<212> PRT
<213> Artificial Sequence

<220>
<223> synthetic sequence of chimeric LGIC

<400> 23

Met Arg Cys Ser Pro Gly Gly Val Trp Leu Ala Leu Ala Ala Ser Leu
1 5 10 15

Leu His Val Ser Leu Gln Gly Glu Phe Gln Arg Lys Leu Tyr Lys Glu
20 25 30

Leu Val Lys Asn Tyr Asn Pro Leu Glu Arg Pro Val Ala Asn Asp Ser
35 40 45

Gln Pro Leu Thr Val Tyr Phe Ser Leu Ser Leu Leu Gln Ile Met Asp
50 55 60

Val Asp Glu Lys Asn Gln Val Leu Thr Thr Asn Ile Trp Leu Gln Met
65 70 75 80

Ser Trp Thr Asp His Tyr Leu Gln Trp Asn Val Ser Glu Tyr Pro Gly
85 90 95

Val Lys Thr Val Arg Phe Pro Asp Gly Gln Ile Trp Lys Pro Asp Ile

```
            100                 105                 110

Leu Leu Tyr Asn Ser Ala Asp Glu Arg Phe Asp Ala Thr Phe His Thr
        115                 120                 125

Asn Val Leu Val Asn Ser Ser Gly His Cys Gln Tyr Leu Pro Pro Gly
    130                 135                 140

Ile Phe Lys Ser Ser Cys Tyr Ile Asp Val Arg Trp Phe Pro Phe Asp
145                 150                 155                 160

Val Gln His Cys Lys Leu Lys Phe Gly Ser Trp Ser Tyr Gly Gly Trp
                165                 170                 175

Ser Leu Asp Leu Gln Met Gln Glu Ala Asp Ile Ser Gly Tyr Ile Pro
            180                 185                 190

Asn Gly Glu Trp Asp Leu Val Gly Ile Pro Gly Lys Arg Ser Glu Arg
        195                 200                 205

Phe Tyr Glu Cys Cys Lys Glu Pro Tyr Pro Asp Val Thr Phe Thr Val
    210                 215                 220

Thr Met Arg Arg Arg Met Gly Tyr Tyr Leu Ile Gln Met Tyr Ile Pro
225                 230                 235                 240

Ser Leu Leu Ile Val Ile Leu Ser Trp Ile Ser Phe Trp Ile Asn Met
                245                 250                 255

Asp Ala Ala Pro Ala Arg Val Gly Leu Gly Ile Thr Thr Val Leu Thr
            260                 265                 270

Met Thr Thr Gln Ser Ser Gly Ser Glu Ile Met Pro Ala Thr Ser Asp
        275                 280                 285

Ser Val Pro Leu Ile Ala Gln Ala Ile Asp Ile Trp Met Ala Val Cys
    290                 295                 300

Leu Leu Phe Val Phe Ser Ala Leu Leu Glu Tyr Ala Ala Val Asn Phe
305                 310                 315                 320
```

Val Ser Arg Gln His Lys Glu Leu Leu Arg Phe Arg Arg Lys Arg Arg
325 330 335

His His Lys Ser Pro Met Leu Asn Leu Phe Gln Glu Asp Glu Ala Gly
340 345 350

Glu Gly Arg Phe Asn Phe Ser Ala Tyr Gly Met Gly Pro Ala Cys Leu
355 360 365

Gln Ala Lys Asp Gly Ile Ser Val Lys Gly Ala Asn Asn Ser Asn Thr
370 375 380

Thr Asn Pro Pro Pro Ala Pro Ser Lys Ser Pro Glu Glu Met Arg Lys
385 390 395 400

Leu Phe Ile Gln Arg Ala Lys Lys Ile Asp Lys Ile Ser Arg Ile Gly
405 410 415

Phe Pro Met Ala Phe Leu Ile Phe Asn Met Phe Tyr Trp Ile Ile Tyr
420 425 430

Lys Ile Val Arg Arg Glu Asp Val His Asn Gln
435 440

<210> 24
<211> 1323
<212> DNA
<213> Artificial Sequence

<220>
<223> synthetic sequence of chimeric LGIC

<400> 24
atgcgctgct cgccgggagg cgtctggctg gcgctggccg cgtcgctcct gcacgtgtcc 60

ctgcaaggcg agttccagag gaagctttac aaggagctgg tcaagaacta caatcccttg 120

gagaggcccg tggccaatga ctcgcaacca ctcaccgtct acttctccct gagcctcctg 180

cagatcatgg acgtggatga gaagaaccaa gttttaacca ccaacatttg gctgcaaatg 240

tcttggacag atcactattt acagtggaat gtgtcagaat atccaggggt gaagactgtt 300

cgtttcccag atggccagat ttggaaacca gacattcttc tctataacag tgctgatgag 360

cgctttgacg ccacattcca cactaacgtg ttggtgaact cttctgggca ttgccagtac 420

ctgcctccag gcatattcaa gagttcctgc tacatcgatg tacgctggtt tccctttgat 480

gtgcagcact gcaaactgaa gtttgggtcc tggtcttacg gaggctggtc cttggatctg 540

cagatgcagg aggcagatat cagtggctat atccccaatg gagaatggga cctagtggga 600

atccccggca agaggagtga aaggttctat gagtgctgca aagagcccta ccccgatgtc 660

accttcacag tgaccatgcg ccgcaggatg ggttactacc tgattcagat gtatattccc 720

agcctgctca ttgtcatcct ctcatggatc tccttctgga tcaacatgga tgctgcacct 780

gctcgtgtgg gcctaggcat caccactgtg ctcaccatga ccacccagag ctccggctct 840

cgagcatctc tgcccaaggt gtccgattcg gtaccattga ttgacatttg gatggcagtt 900

tgcctgctct ttgtgttctc agccctatta gaatatgctg ccgttaactt tgtgtctcgg 960

caacataagg agctgctccg attcaggagg aagcggagac atcacaagag ccccatgttg 1020

aatctattcc aggaggatga agctggagaa ggccgcttta acttctctgc ctatgggatg 1080

ggcccagcct gtctacaggc caaggatggc atctcagtca agggcgccaa caacagtaac 1140

accaccaacc cccctcctgc accatctaag tccccagagg agatgcgaaa actcttcatc 1200

cagagggcca agaagatcga caaaatatcc cgcattggct tccccatggc cttcctcatt 1260

ttcaacatgt tctactggat catctacaag attgtccgta gagaggacgt ccacaaccag 1320

tga 1323

<210> 25
<211> 440
<212> PRT
<213> Artificial Sequence

<220>
<223> synthetic sequence of chimeric LGIC

<400> 25

Met Arg Cys Ser Pro Gly Gly Val Trp Leu Ala Leu Ala Ala Ser Leu
1 5 10 15

Leu His Val Ser Leu Gln Gly Glu Phe Gln Arg Lys Leu Tyr Lys Glu
20 25 30

Leu Val Lys Asn Tyr Asn Pro Leu Glu Arg Pro Val Ala Asn Asp Ser

```
        35                  40                  45

Gln Pro Leu Thr Val Tyr Phe Ser Leu Ser Leu Leu Gln Ile Met Asp
    50                  55                  60

Val Asp Glu Lys Asn Gln Val Leu Thr Thr Asn Ile Trp Leu Gln Met
65                  70                  75                  80

Ser Trp Thr Asp His Tyr Leu Gln Trp Asn Val Ser Glu Tyr Pro Gly
                85                  90                  95

Val Lys Thr Val Arg Phe Pro Asp Gly Gln Ile Trp Lys Pro Asp Ile
            100                 105                 110

Leu Leu Tyr Asn Ser Ala Asp Glu Arg Phe Asp Ala Thr Phe His Thr
        115                 120                 125

Asn Val Leu Val Asn Ser Ser Gly His Cys Gln Tyr Leu Pro Pro Gly
    130                 135                 140

Ile Phe Lys Ser Ser Cys Tyr Ile Asp Val Arg Trp Phe Pro Phe Asp
145                 150                 155                 160

Val Gln His Cys Lys Leu Lys Phe Gly Ser Trp Ser Tyr Gly Gly Trp
                165                 170                 175

Ser Leu Asp Leu Gln Met Gln Glu Ala Asp Ile Ser Gly Tyr Ile Pro
            180                 185                 190

Asn Gly Glu Trp Asp Leu Val Gly Ile Pro Gly Lys Arg Ser Glu Arg
        195                 200                 205

Phe Tyr Glu Cys Cys Lys Glu Pro Tyr Pro Asp Val Thr Phe Thr Val
    210                 215                 220

Thr Met Arg Arg Arg Met Gly Tyr Tyr Leu Ile Gln Met Tyr Ile Pro
225                 230                 235                 240

Ser Leu Leu Ile Val Ile Leu Ser Trp Ile Ser Phe Trp Ile Asn Met
                245                 250                 255
```

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Asp Ala Ala Pro Ala Arg Val Gly Leu Gly Ile Thr Thr Val Leu Thr
            260                 265                 270

Met Thr Thr Gln Ser Ser Gly Ser Arg Ala Ser Leu Pro Lys Val Ser
        275                 280                 285

Asp Ser Val Pro Leu Ile Asp Ile Trp Met Ala Val Cys Leu Leu Phe
    290                 295                 300

Val Phe Ser Ala Leu Leu Glu Tyr Ala Ala Val Asn Phe Val Ser Arg
305                 310                 315                 320

Gln His Lys Glu Leu Leu Arg Phe Arg Arg Lys Arg Arg His His Lys
                325                 330                 335

Ser Pro Met Leu Asn Leu Phe Gln Glu Asp Glu Ala Gly Glu Gly Arg
            340                 345                 350

Phe Asn Phe Ser Ala Tyr Gly Met Gly Pro Ala Cys Leu Gln Ala Lys
        355                 360                 365

Asp Gly Ile Ser Val Lys Gly Ala Asn Asn Ser Asn Thr Thr Asn Pro
    370                 375                 380

Pro Pro Ala Pro Ser Lys Ser Pro Glu Glu Met Arg Lys Leu Phe Ile
385                 390                 395                 400

Gln Arg Ala Lys Lys Ile Asp Lys Ile Ser Arg Ile Gly Phe Pro Met
                405                 410                 415

Ala Phe Leu Ile Phe Asn Met Phe Tyr Trp Ile Ile Tyr Lys Ile Val
            420                 425                 430

Arg Arg Glu Asp Val His Asn Gln
        435                 440
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<210> 26
<211> 1332
<212> DNA
<213> Artificial Sequence

<220>
<223> synthetic sequence of chimeric LGIC

<400> 26
atgcgctgct cgccgggagg cgtctggctg gcgctggccg cgtcgctcct gcacgtgtcc 60

ctgcaaggcg agttccagag gaagctttac aaggagctgg tcaagaacta caatcccttg 120

gagaggcccg tggccaatga ctcgcaacca ctcaccgtct acttctccct gagcctcctg 180

cagatcatgg acgtggatga gaagaaccaa gttttaacca ccaacatttg gctgcaaatg 240

tcttggacag atcactattt acagtggaat gtgtcagaat atccaggggt gaagactgtt 300

cgtttcccag atggccagat ttggaaacca gacattcttc tctataacag tgctgatgag 360

cgctttgacg ccacattcca cactaacgtg ttggtgaact cttctgggca ttgccagtac 420

ctgcctccag gcatattcaa gagttcctgc tacatcgatg tacgctggtt tccctttgat 480

gtgcagcact gcaaactgaa gtttgggtcc tggtcttacg gaggctggtc cttggatctg 540

cagatgcagg aggcagatat cagtggctat atccccaatg gagaatggga cctagtggga 600

atccccggca agaggagtga aaggttctat gagtgctgca aagagcccta ccccgatgtc 660

accttcacag tgaccatgga gcggcagatg ggttactacc tgattcagat gtatattccc 720

agcctgctca ttgtcatcct ctcatggatc tccttctgga tcaacatgga tgctgcacct 780

gctcgtgtgg gcctaggcat caccactgtg ctcaccatga ccacccagag ctccggctct 840

gagatcatgc ccgcaacatc cgattcggta ccattgatag cccaggccat tgacatttgg 900

atggcagttt gcctgctctt tgtgttctca gccctattag aatatgctgc cgttaacttt 960

gtgtctcggc aacataagga gctgctccga ttcaggagga agcggagaca tcacaagagc 1020

cccatgttga atctattcca ggaggatgaa gctggagaag gccgctttaa cttctctgcc 1080

tatgggatgg gcccagcctg tctacaggcc aaggatggca tctcagtcaa gggcgccaac 1140

aacagtaaca ccaccaaccc ccctcctgca ccatctaagt ccccagagga gatgcgaaaa 1200

ctcttcatcc agagggccaa gaagatcgac aaaatatccc gcattggctt ccccatggcc 1260

ttcctcattt tcaacatgtt ctactggatc atctacaaga ttgtccgtag agaggacgtc 1320

cacaaccagt ga 1332

<210> 27
<211> 443
<212> PRT

<213> Artificial Sequence

<220>
<223> synthetic sequence of chimeric LGIC

<400> 27

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Met Arg Cys Ser Pro Gly Gly Val Trp Leu Ala Leu Ala Ala Ser Leu
1               5                  10                  15


Leu His Val Ser Leu Gln Gly Glu Phe Gln Arg Lys Leu Tyr Lys Glu
            20                  25                  30


Leu Val Lys Asn Tyr Asn Pro Leu Glu Arg Pro Val Ala Asn Asp Ser
        35                  40                  45


Gln Pro Leu Thr Val Tyr Phe Ser Leu Ser Leu Leu Gln Ile Met Asp
    50                  55                  60


Val Asp Glu Lys Asn Gln Val Leu Thr Thr Asn Ile Trp Leu Gln Met
65                  70                  75                  80


Ser Trp Thr Asp His Tyr Leu Gln Trp Asn Val Ser Glu Tyr Pro Gly
                85                  90                  95


Val Lys Thr Val Arg Phe Pro Asp Gly Gln Ile Trp Lys Pro Asp Ile
            100                 105                 110


Leu Leu Tyr Asn Ser Ala Asp Glu Arg Phe Asp Ala Thr Phe His Thr
        115                 120                 125


Asn Val Leu Val Asn Ser Ser Gly His Cys Gln Tyr Leu Pro Pro Gly
    130                 135                 140


Ile Phe Lys Ser Ser Cys Tyr Ile Asp Val Arg Trp Phe Pro Phe Asp
145                 150                 155                 160


Val Gln His Cys Lys Leu Lys Phe Gly Ser Trp Ser Tyr Gly Gly Trp
                165                 170                 175


Ser Leu Asp Leu Gln Met Gln Glu Ala Asp Ile Ser Gly Tyr Ile Pro
            180                 185                 190
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```
Asn Gly Glu Trp Asp Leu Val Gly Ile Pro Gly Lys Arg Ser Glu Arg
        195                 200                 205

Phe Tyr Glu Cys Cys Lys Glu Pro Tyr Pro Asp Val Thr Phe Thr Val
    210                 215                 220

Thr Met Glu Arg Gln Met Gly Tyr Tyr Leu Ile Gln Met Tyr Ile Pro
225                 230                 235                 240

Ser Leu Leu Ile Val Ile Leu Ser Trp Ile Ser Phe Trp Ile Asn Met
                245                 250                 255

Asp Ala Ala Pro Ala Arg Val Gly Leu Gly Ile Thr Thr Val Leu Thr
            260                 265                 270

Met Thr Thr Gln Ser Ser Gly Ser Glu Ile Met Pro Ala Thr Ser Asp
        275                 280                 285

Ser Val Pro Leu Ile Ala Gln Ala Ile Asp Ile Trp Met Ala Val Cys
    290                 295                 300

Leu Leu Phe Val Phe Ser Ala Leu Leu Glu Tyr Ala Ala Val Asn Phe
305                 310                 315                 320

Val Ser Arg Gln His Lys Glu Leu Leu Arg Phe Arg Arg Lys Arg Arg
                325                 330                 335

His His Lys Ser Pro Met Leu Asn Leu Phe Gln Glu Asp Glu Ala Gly
            340                 345                 350

Glu Gly Arg Phe Asn Phe Ser Ala Tyr Gly Met Gly Pro Ala Cys Leu
        355                 360                 365

Gln Ala Lys Asp Gly Ile Ser Val Lys Gly Ala Asn Asn Ser Asn Thr
    370                 375                 380

Thr Asn Pro Pro Pro Ala Pro Ser Lys Ser Pro Glu Glu Met Arg Lys
385                 390                 395                 400

Leu Phe Ile Gln Arg Ala Lys Lys Ile Asp Lys Ile Ser Arg Ile Gly
```

405 410 415

Phe Pro Met Ala Phe Leu Ile Phe Asn Met Phe Tyr Trp Ile Ile Tyr
420 425 430

Lys Ile Val Arg Arg Glu Asp Val His Asn Gln
435 440

<210> 28
<211> 1332
<212> DNA
<213> Artificial Sequence

<220>
<223> synthetic sequence of chimeric LGIC

<400> 28
atgcgctgct cgccgggagg cgtctggctg gcgctggccg cgtcgctcct gcacgtgtcc 60

ctgcaaggcg agttccagag gaagctttac aaggagctgg tcaagaacta caatcccttg 120

gagaggcccg tggccaatga ctcgcaacca ctcaccgtct acttctccct gagcctcctg 180

cagatcatgg acgtggatga gaagaaccaa gttttaacca ccaacatttg gctgcaaatg 240

tcttggacag atcactattt acagtggaat gtgtcagaat atccaggggt gaagactgtt 300

cgtttcccag atggccagat ttggaaacca gacattcttc tctataacag tgctgatgag 360

cgctttgacg ccacattcca cactaacgtg ttggtgaact cttctgggca ttgccagtac 420

ctgcctccag gcatattcaa gagttcctgc tacatcgatg tacgctggtt tccctttgat 480

gtgcagcact gcaaactgaa gtttgggtcc tggtcttacg gaggctggtc cttggatctg 540

cagatgcagg aggcagatat cagtggctat atccccaatg gagaatggga cctagtggga 600

atccccggca agaggagtga aaggttctat gagtgctgca aagagcccta ccccgatgtc 660

accttcacag tgaccatgcg ccgcaggacg ggttactacc tgattcagat gtatattccc 720

agcctgctca ttgtcatcct ctcatggatc tccttctgga tcaacatgga tgctgcacct 780

gctcgtgtgg gcctaggcat caccactgtg ctcaccatga ccacccagag ctccggctct 840

gagatcatgc ccgcaacatc cgattcggta ccattgatag cccaggccat tgacatttgg 900

atggcagttt gcctgctctt tgtgttctca gccctattag aatatgctgc cgttaacttt 960

gtgtctcggc aacataagga gctgctccga ttcaggagga agcggagaca tcacaagagc 1020

cccatgttga atctattcca ggaggatgaa gctggagaag gccgctttaa cttctctgcc 1080

tatgggatgg gcccagcctg tctacaggcc aaggatggca tctcagtcaa gggcgccaac 1140

aacagtaaca ccaccaaccc ccctcctgca ccatctaagt ccccagagga gatgcgaaaa 1200

ctcttcatcc agagggccaa gaagatcgac aaaatatccc gcattggctt ccccatggcc 1260

ttcctcattt tcaacatgtt ctactggatc atctacaaga ttgtccgtag agaggacgtc 1320

cacaaccagt ga 1332

<210> 29
<211> 443
<212> PRT
<213> Artificial Sequence

<220>
<223> synthetic sequence of chimeric LGIC

<400> 29

Met Arg Cys Ser Pro Gly Gly Val Trp Leu Ala Leu Ala Ala Ser Leu
1 5 10 15

Leu His Val Ser Leu Gln Gly Glu Phe Gln Arg Lys Leu Tyr Lys Glu
20 25 30

Leu Val Lys Asn Tyr Asn Pro Leu Glu Arg Pro Val Ala Asn Asp Ser
35 40 45

Gln Pro Leu Thr Val Tyr Phe Ser Leu Ser Leu Leu Gln Ile Met Asp
50 55 60

Val Asp Glu Lys Asn Gln Val Leu Thr Thr Asn Ile Trp Leu Gln Met
65 70 75 80

Ser Trp Thr Asp His Tyr Leu Gln Trp Asn Val Ser Glu Tyr Pro Gly
85 90 95

Val Lys Thr Val Arg Phe Pro Asp Gly Gln Ile Trp Lys Pro Asp Ile
100 105 110

Leu Leu Tyr Asn Ser Ala Asp Glu Arg Phe Asp Ala Thr Phe His Thr
115 120 125

```
Asn Val Leu Val Asn Ser Ser Gly His Cys Gln Tyr Leu Pro Pro Gly
    130                 135                 140

Ile Phe Lys Ser Ser Cys Tyr Ile Asp Val Arg Trp Phe Pro Phe Asp
145                 150                 155                 160

Val Gln His Cys Lys Leu Lys Phe Gly Ser Trp Ser Tyr Gly Gly Trp
                165                 170                 175

Ser Leu Asp Leu Gln Met Gln Glu Ala Asp Ile Ser Gly Tyr Ile Pro
            180                 185                 190

Asn Gly Glu Trp Asp Leu Val Gly Ile Pro Gly Lys Arg Ser Glu Arg
        195                 200                 205

Phe Tyr Glu Cys Cys Lys Glu Pro Tyr Pro Asp Val Thr Phe Thr Val
    210                 215                 220

Thr Met Arg Arg Arg Thr Gly Tyr Tyr Leu Ile Gln Met Tyr Ile Pro
225                 230                 235                 240

Ser Leu Leu Ile Val Ile Leu Ser Trp Ile Ser Phe Trp Ile Asn Met
                245                 250                 255

Asp Ala Ala Pro Ala Arg Val Gly Leu Gly Ile Thr Thr Val Leu Thr
            260                 265                 270

Met Thr Thr Gln Ser Ser Gly Ser Glu Ile Met Pro Ala Thr Ser Asp
        275                 280                 285

Ser Val Pro Leu Ile Ala Gln Ala Ile Asp Ile Trp Met Ala Val Cys
    290                 295                 300

Leu Leu Phe Val Phe Ser Ala Leu Leu Glu Tyr Ala Ala Val Asn Phe
305                 310                 315                 320

Val Ser Arg Gln His Lys Glu Leu Leu Arg Phe Arg Arg Lys Arg Arg
                325                 330                 335

His His Lys Ser Pro Met Leu Asn Leu Phe Gln Glu Asp Glu Ala Gly
```

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            340                 345                 350

Glu Gly Arg Phe Asn Phe Ser Ala Tyr Gly Met Gly Pro Ala Cys Leu
        355                 360                 365

Gln Ala Lys Asp Gly Ile Ser Val Lys Gly Ala Asn Asn Ser Asn Thr
    370                 375                 380

Thr Asn Pro Pro Pro Ala Pro Ser Lys Ser Pro Glu Glu Met Arg Lys
385                 390                 395                 400

Leu Phe Ile Gln Arg Ala Lys Lys Ile Asp Lys Ile Ser Arg Ile Gly
                405                 410                 415

Phe Pro Met Ala Phe Leu Ile Phe Asn Met Phe Tyr Trp Ile Ile Tyr
            420                 425                 430

Lys Ile Val Arg Arg Glu Asp Val His Asn Gln
        435                 440


<210>  30
<211>  1332
<212>  DNA
<213>  Artificial Sequence

<220>
<223>  synthetic sequence of chimeric LGIC

<400>  30
atgcgctgct cgccgggagg cgtctggctg gcgctggccg cgtcgctcct gcacgtgtcc       60

ctgcaaggcg agttccagag gaagctttac aaggagctgg tcaagaacta caatcccttg      120

gagaggcccg tggccaatga ctcgcaacca ctcaccgtct acttctccct gagcctcctg      180

cagatcatgg acgtggatga gaagaaccaa gttttaacca ccaacatttg gctgcaaatg      240

tcttggacag atcactattt acagtggaat gtgtcagaat atccaggggt gaagactgtt      300

cgtttcccag atggccagat ttggaaacca gacattcttc tctataacag tgctgatgag      360

cgctttgacg ccacattcca cactaacgtg ttggtgaact cttctgggca ttgccagtac      420

ctgcctccag gcatattcaa gagttcctgc tacatcgatg tacgctggtt tccctttgat      480

gtgcagcact gcaaactgaa gtttgggtcc tggtcttacg gaggctggtc cttggatctg      540
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cagatgcagg aggcagatat cagtggctat atccccaatg gagaatggga cctagtggga 600

atccccggca agaggagtga aaggttctat gagtgctgca aagagcccta ccccgatgtc 660

accttcacag tgaccatgcg ccgcaggacg ctctactacc tgattcagat gtatattccc 720

agcctgctca ttgtcatcct ctcatggatc tccttctgga tcaacatgga tgctgcacct 780

gctcgtgtgg gcctaggcat caccactgtg ctcaccatga ccacccagag ctccggctct 840

gagatcatgc ccgcaacatc cgattcggta ccattgatag cccaggccat tgacatttgg 900

atggcagttt gcctgctctt tgtgttctca gccctattag aatatgctgc cgttaacttt 960

gtgtctcggc aacataagga gctgctccga ttcaggagga agcggagaca tcacaagagc 1020

cccatgttga atctattcca ggaggatgaa gctggagaag gccgctttaa cttctctgcc 1080

tatgggatgg gcccagcctg tctacaggcc aaggatggca tctcagtcaa gggcgccaac 1140

aacagtaaca ccaccaaccc ccctcctgca ccatctaagt ccccagagga gatgcgaaaa 1200

ctcttcatcc agagggccaa gaagatcgac aaaatatccc gcattggctt ccccatggcc 1260

ttcctcattt tcaacatgtt ctactggatc atctacaaga ttgtccgtag agaggacgtc 1320

cacaaccagt ga 1332

<210> 31
<211> 443
<212> PRT
<213> Artificial Sequence

<220>
<223> synthetic sequence of chimeric LGIC

<400> 31

Met Arg Cys Ser Pro Gly Gly Val Trp Leu Ala Leu Ala Ala Ser Leu
1 5 10 15

Leu His Val Ser Leu Gln Gly Glu Phe Gln Arg Lys Leu Tyr Lys Glu
20 25 30

Leu Val Lys Asn Tyr Asn Pro Leu Glu Arg Pro Val Ala Asn Asp Ser
35 40 45

Gln Pro Leu Thr Val Tyr Phe Ser Leu Ser Leu Leu Gln Ile Met Asp
50 55 60

```
Val Asp Glu Lys Asn Gln Val Leu Thr Thr Asn Ile Trp Leu Gln Met
65                  70                  75                  80

Ser Trp Thr Asp His Tyr Leu Gln Trp Asn Val Ser Glu Tyr Pro Gly
                85                  90                  95

Val Lys Thr Val Arg Phe Pro Asp Gly Gln Ile Trp Lys Pro Asp Ile
            100                 105                 110

Leu Leu Tyr Asn Ser Ala Asp Glu Arg Phe Asp Ala Thr Phe His Thr
        115                 120                 125

Asn Val Leu Val Asn Ser Ser Gly His Cys Gln Tyr Leu Pro Pro Gly
    130                 135                 140

Ile Phe Lys Ser Ser Cys Tyr Ile Asp Val Arg Trp Phe Pro Phe Asp
145                 150                 155                 160

Val Gln His Cys Lys Leu Lys Phe Gly Ser Trp Ser Tyr Gly Gly Trp
                165                 170                 175

Ser Leu Asp Leu Gln Met Gln Glu Ala Asp Ile Ser Gly Tyr Ile Pro
            180                 185                 190

Asn Gly Glu Trp Asp Leu Val Gly Ile Pro Gly Lys Arg Ser Glu Arg
        195                 200                 205

Phe Tyr Glu Cys Cys Lys Glu Pro Tyr Pro Asp Val Thr Phe Thr Val
    210                 215                 220

Thr Met Arg Arg Arg Thr Leu Tyr Tyr Leu Ile Gln Met Tyr Ile Pro
225                 230                 235                 240

Ser Leu Leu Ile Val Ile Leu Ser Trp Ile Ser Phe Trp Ile Asn Met
                245                 250                 255

Asp Ala Ala Pro Ala Arg Val Gly Leu Gly Ile Thr Thr Val Leu Thr
            260                 265                 270

Met Thr Thr Gln Ser Ser Gly Ser Glu Ile Met Pro Ala Thr Ser Asp
```

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        275                 280                 285

Ser Val Pro Leu Ile Ala Gln Ala Ile Asp Ile Trp Met Ala Val Cys
    290                 295                 300

Leu Leu Phe Val Phe Ser Ala Leu Leu Glu Tyr Ala Ala Val Asn Phe
305                 310                 315                 320

Val Ser Arg Gln His Lys Glu Leu Leu Arg Phe Arg Arg Lys Arg Arg
                325                 330                 335

His His Lys Ser Pro Met Leu Asn Leu Phe Gln Glu Asp Glu Ala Gly
            340                 345                 350

Glu Gly Arg Phe Asn Phe Ser Ala Tyr Gly Met Gly Pro Ala Cys Leu
        355                 360                 365

Gln Ala Lys Asp Gly Ile Ser Val Lys Gly Ala Asn Asn Ser Asn Thr
    370                 375                 380

Thr Asn Pro Pro Pro Ala Pro Ser Lys Ser Pro Glu Glu Met Arg Lys
385                 390                 395                 400

Leu Phe Ile Gln Arg Ala Lys Lys Ile Asp Lys Ile Ser Arg Ile Gly
                405                 410                 415

Phe Pro Met Ala Phe Leu Ile Phe Asn Met Phe Tyr Trp Ile Ile Tyr
            420                 425                 430

Lys Ile Val Arg Arg Glu Asp Val His Asn Gln
        435                 440


<210>  32
<211>  1320
<212>  DNA
<213>  Artificial Sequence

<220>
<223>  synthetic sequence of chimeric LGIC

<400>  32
atgcgctgct cgccgggagg cgtctggctg gcgctggccg cgtcgctcct gcacgtgtcc       60
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ctgcaaggcg agttccagag gaagctttac aaggagctgg tcaagaacta caatcccttg 120

gagaggcccg tggccaatga ctcgcaacca ctcaccgtct acttctccct gagcctcctg 180

cagatcatgg acgtggatga gaagaaccaa gttttaacca ccaacatttg gctgcaaatg 240

tcttggacag atcactattt acagtggaat gtgtcagaat atccaggggt gaagactgtt 300

cgtttcccag atggccagat ttggaaacca gacattcttc tctataacag tgctgatgag 360

cgctttgacg ccacattcca cactaacgtg ttggtgaact cttctgggca ttgccagtac 420

ctgcctccag gcatattcaa gagttcctgc cccatggact tgaagaattt ccccatggat 480

gtccagacat gcaaactgaa gtttgggtcc tggtcttacg gaggctggtc cttggatctg 540

cagatgcagg aggcagatat cagtggctat atccccaatg gagaatggga cctagtggga 600

atccccggca agaggagtga aaggttctat gagtgctgca aagagcccta ccccgatgtc 660

accttcacag tgaccatgcg ccgcaggatg ggttactacc tgattcagat gtatattccc 720

agcctgctca ttgtcatcct ctcatggatc tccttctgga tcaacatgga tgctgcacct 780

gctcgtgtgg gcctaggcat caccactgtg ctcaccatga ccacccagag ctccggctct 840

cgagcatctc tgcccaaggt gtcctatgtg aaagccattg acatttggat ggcagtttgc 900

ctgctctttg tgttctcagc cctattagaa tatgctgccg ttaactttgt gtctcggcaa 960

cataaggagc tgctccgatt caggaggaag cggagacatc acaagagccc catgttgaat 1020

ctattccagg aggatgaagc tggagaaggc cgctttaact tctctgccta tgggatgggc 1080

ccagcctgtc tacaggccaa ggatggcatc tcagtcaagg gcgccaacaa cagtaacacc 1140

accaaccccc ctcctgcacc atctaagtcc ccagaggaga tgcgaaaact cttcatccag 1200

agggccaaga agatcgacaa aatatcccgc attggcttcc ccatggcctt cctcattttc 1260

aacatgttct actggatcat ctacaagatt gtccgtagag aggacgtcca caaccagtga 1320

<210> 33
<211> 439
<212> PRT
<213> Artificial Sequence

<220>
<223> synthetic sequence of chimeric LGIC

<400> 33

Met Arg Cys Ser Pro Gly Gly Val Trp Leu Ala Leu Ala Ala Ser Leu

```
1               5                   10                  15

Leu His Val Ser Leu Gln Gly Glu Phe Gln Arg Lys Leu Tyr Lys Glu
            20                  25                  30

Leu Val Lys Asn Tyr Asn Pro Leu Glu Arg Pro Val Ala Asn Asp Ser
        35                  40                  45

Gln Pro Leu Thr Val Tyr Phe Ser Leu Ser Leu Leu Gln Ile Met Asp
    50                  55                  60

Val Asp Glu Lys Asn Gln Val Leu Thr Thr Asn Ile Trp Leu Gln Met
65                  70                  75                  80

Ser Trp Thr Asp His Tyr Leu Gln Trp Asn Val Ser Glu Tyr Pro Gly
                85                  90                  95

Val Lys Thr Val Arg Phe Pro Asp Gly Gln Ile Trp Lys Pro Asp Ile
            100                 105                 110

Leu Leu Tyr Asn Ser Ala Asp Glu Arg Phe Asp Ala Thr Phe His Thr
        115                 120                 125

Asn Val Leu Val Asn Ser Ser Gly His Cys Gln Tyr Leu Pro Pro Gly
    130                 135                 140

Ile Phe Lys Ser Ser Cys Pro Met Asp Leu Lys Asn Phe Pro Met Asp
145                 150                 155                 160

Val Gln Thr Cys Lys Leu Lys Phe Gly Ser Trp Ser Tyr Gly Gly Trp
                165                 170                 175

Ser Leu Asp Leu Gln Met Gln Glu Ala Asp Ile Ser Gly Tyr Ile Pro
            180                 185                 190

Asn Gly Glu Trp Asp Leu Val Gly Ile Pro Gly Lys Arg Ser Glu Arg
        195                 200                 205

Phe Tyr Glu Cys Cys Lys Glu Pro Tyr Pro Asp Val Thr Phe Thr Val
    210                 215                 220
```

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Thr Met Arg Arg Arg Met Gly Tyr Tyr Leu Ile Gln Met Tyr Ile Pro
225                 230                 235                 240

Ser Leu Leu Ile Val Ile Leu Ser Trp Ile Ser Phe Trp Ile Asn Met
                245                 250                 255

Asp Ala Ala Pro Ala Arg Val Gly Leu Gly Ile Thr Thr Val Leu Thr
            260                 265                 270

Met Thr Thr Gln Ser Ser Gly Ser Arg Ala Ser Leu Pro Lys Val Ser
        275                 280                 285

Tyr Val Lys Ala Ile Asp Ile Trp Met Ala Val Cys Leu Leu Phe Val
    290                 295                 300

Phe Ser Ala Leu Leu Glu Tyr Ala Ala Val Asn Phe Val Ser Arg Gln
305                 310                 315                 320

His Lys Glu Leu Leu Arg Phe Arg Arg Lys Arg Arg His His Lys Ser
                325                 330                 335

Pro Met Leu Asn Leu Phe Gln Glu Asp Glu Ala Gly Glu Gly Arg Phe
            340                 345                 350

Asn Phe Ser Ala Tyr Gly Met Gly Pro Ala Cys Leu Gln Ala Lys Asp
        355                 360                 365

Gly Ile Ser Val Lys Gly Ala Asn Asn Ser Asn Thr Thr Asn Pro Pro
    370                 375                 380

Pro Ala Pro Ser Lys Ser Pro Glu Glu Met Arg Lys Leu Phe Ile Gln
385                 390                 395                 400

Arg Ala Lys Lys Ile Asp Lys Ile Ser Arg Ile Gly Phe Pro Met Ala
                405                 410                 415

Phe Leu Ile Phe Asn Met Phe Tyr Trp Ile Ile Tyr Lys Ile Val Arg
            420                 425                 430

Arg Glu Asp Val His Asn Gln
```

<210> 34
<211> 1320
<212> DNA
<213> Artificial Sequence

<220>
<223> synthetic sequence of chimeric LGIC

<400> 34
atgcgctgct cgccgggagg cgtctggctg gcgctggccg cgtcgctcct gcacgtgtcc 60

ctgcaaggcg agttccagag gaagctttac aaggagctgg tcaagaacta caatcccttg 120

gagaggcccg tggccaatga ctcgcaacca ctcaccgtct acttctccct gagcctcctg 180

cagatcatgg acgtggatga gaagaaccaa gttttaacca ccaacatttg gctgcaaatg 240

tcttggacag atcactattt acagtggaat gtgtcagaat atccaggggt gaagactgtt 300

cgtttcccag atggccagat ttggaaacca gacattcttc tctataacag tgctgatgag 360

cgctttgacg ccacattcca cactaacgtg ttggtgaact cttctgggca ttgccagtac 420

ctgcctccag gcatattcaa gagttcctgc cccatggact tgaagaattt tccctttgat 480

gtgcagcact gcaaactgaa gtttgggtcc tggtcttacg gaggctggtc cttggatctg 540

cagatgcagg aggcagatat cagtggctat atccccaatg gagaatggga cctagtggga 600

atccccggca agaggagtga aaggttctat gagtgctgca aagagcccta ccccgatgtc 660

accttcacag tgaccatgcg ccgcaggatg ggttactacc tgattcagat gtatattccc 720

agcctgctca ttgtcatcct ctcatggatc tccttctgga tcaacatgga tgctgcacct 780

gctcgtgtgg gcctaggcat caccactgtg ctcaccatga ccacccagag ctccggctct 840

cgagcatctc tgcccaaggt gtcctatgtg aaagccattg acatttggat ggcagtttgc 900

ctgctctttg tgttctcagc cctattagaa tatgctgccg ttaactttgt gtctcggcaa 960

cataaggagc tgctccgatt caggaggaag cggagacatc acaagagccc catgttgaat 1020

ctattccagg aggatgaagc tggagaaggc cgctttaact tctctgccta tgggatgggc 1080

ccagcctgtc tacaggccaa ggatggcatc tcagtcaagg gcgccaacaa cagtaacacc 1140

accaaccccc ctcctgcacc atctaagtcc ccagaggaga tgcgaaaact cttcatccag 1200

agggccaaga agatcgacaa aatatcccgc attggcttcc ccatggcctt cctcattttc 1260

aacatgttct actggatcat ctacaagatt gtccgtagag aggacgtcca caaccagtga 1320

<210> 35
<211> 439
<212> PRT
<213> Artificial Sequence

<220>
<223> synthetic sequence of chimeric LGIC

<400> 35

Met Arg Cys Ser Pro Gly Gly Val Trp Leu Ala Leu Ala Ala Ser Leu
1 5 10 15

Leu His Val Ser Leu Gln Gly Glu Phe Gln Arg Lys Leu Tyr Lys Glu
20 25 30

Leu Val Lys Asn Tyr Asn Pro Leu Glu Arg Pro Val Ala Asn Asp Ser
35 40 45

Gln Pro Leu Thr Val Tyr Phe Ser Leu Ser Leu Leu Gln Ile Met Asp
50 55 60

Val Asp Glu Lys Asn Gln Val Leu Thr Thr Asn Ile Trp Leu Gln Met
65 70 75 80

Ser Trp Thr Asp His Tyr Leu Gln Trp Asn Val Ser Glu Tyr Pro Gly
85 90 95

Val Lys Thr Val Arg Phe Pro Asp Gly Gln Ile Trp Lys Pro Asp Ile
100 105 110

Leu Leu Tyr Asn Ser Ala Asp Glu Arg Phe Asp Ala Thr Phe His Thr
115 120 125

Asn Val Leu Val Asn Ser Ser Gly His Cys Gln Tyr Leu Pro Pro Gly
130 135 140

Ile Phe Lys Ser Ser Cys Pro Met Asp Leu Lys Asn Phe Pro Phe Asp
145 150 155 160

Val Gln His Cys Lys Leu Lys Phe Gly Ser Trp Ser Tyr Gly Gly Trp

```
                165                 170                 175

Ser Leu Asp Leu Gln Met Gln Glu Ala Asp Ile Ser Gly Tyr Ile Pro
            180                 185                 190

Asn Gly Glu Trp Asp Leu Val Gly Ile Pro Gly Lys Arg Ser Glu Arg
        195                 200                 205

Phe Tyr Glu Cys Cys Lys Glu Pro Tyr Pro Asp Val Thr Phe Thr Val
    210                 215                 220

Thr Met Arg Arg Arg Met Gly Tyr Tyr Leu Ile Gln Met Tyr Ile Pro
225                 230                 235                 240

Ser Leu Leu Ile Val Ile Leu Ser Trp Ile Ser Phe Trp Ile Asn Met
                245                 250                 255

Asp Ala Ala Pro Ala Arg Val Gly Leu Gly Ile Thr Thr Val Leu Thr
            260                 265                 270

Met Thr Thr Gln Ser Ser Gly Ser Arg Ala Ser Leu Pro Lys Val Ser
        275                 280                 285

Tyr Val Lys Ala Ile Asp Ile Trp Met Ala Val Cys Leu Leu Phe Val
    290                 295                 300

Phe Ser Ala Leu Leu Glu Tyr Ala Ala Val Asn Phe Val Ser Arg Gln
305                 310                 315                 320

His Lys Glu Leu Leu Arg Phe Arg Arg Lys Arg Arg His His Lys Ser
                325                 330                 335

Pro Met Leu Asn Leu Phe Gln Glu Asp Glu Ala Gly Glu Gly Arg Phe
            340                 345                 350

Asn Phe Ser Ala Tyr Gly Met Gly Pro Ala Cys Leu Gln Ala Lys Asp
        355                 360                 365

Gly Ile Ser Val Lys Gly Ala Asn Asn Ser Asn Thr Thr Asn Pro Pro
    370                 375                 380
```

Pro Ala Pro Ser Lys Ser Pro Glu Glu Met Arg Lys Leu Phe Ile Gln
385 390 395 400

Arg Ala Lys Lys Ile Asp Lys Ile Ser Arg Ile Gly Phe Pro Met Ala
405 410 415

Phe Leu Ile Phe Asn Met Phe Tyr Trp Ile Ile Tyr Lys Ile Val Arg
420 425 430

Arg Glu Asp Val His Asn Gln
435

<210> 36
<211> 1320
<212> DNA
<213> Artificial Sequence

<220>
<223> synthetic sequence of chimeric LGIC

<400> 36
atgcgctgct cgccgggagg cgtctggctg gcgctggccg cgtcgctcct gcacgtgtcc 60

ctgcaaggcg agttccagag gaagctttac aaggagctgg tcaagaacta caatcccttg 120

gagaggcccg tggccaatga ctcgcaacca ctcaccgtct acttctccct gagcctcctg 180

cagatcatgg acgtggatga gacaaccatg gttttaacca ccaacatttg gctgcaaatg 240

tcttggacag atcactattt acagtggaat gtgtcagaat atccaggggt gaagactgtt 300

cgtttcccag atggccagat ttggaaacca gacattcttc tctataacag tgctgatgag 360

cgctttgacg ccacattcca cactaacgtg ttggtgaact cttctgggca ttgccagtac 420

ctgcctccag gcatattcaa gagttcctgc tacatcgatg tacgctggtt tccctttgat 480

gtgcagcact gcaaactgaa gtttgggtcc tggtcttacg gaggctggtc cttggatctg 540

cagatgcagg aggcagatat cagtggctat atccccaatg gagaatggga cctagtggga 600

atccccggca agaggagtga aaggttctat gagtgctgca aagagcccta ccccgatgtc 660

accttcacag tgaccatgcg ccgcaggatg ggttactacc tgattcagat gtatattccc 720

agcctgctca ttgtcatcct ctcatggatc tccttctgga tcaacatgga tgctgcacct 780

gctcgtgtgg gcctaggcat caccactgtg ctcaccatga ccacccagag ctccggctct 840

cgagcatctc tgcccaaggt gtcctatgtg aaagccattg acatttggat ggcagtttgc 900

ctgctctttg tgttctcagc cctattagaa tatgctgccg ttaactttgt gtctcggcaa 960

cataaggagc tgctccgatt caggaggaag cggagacatc acaagagccc catgttgaat 1020

ctattccagg aggatgaagc tggagaaggc cgctttaact tctctgccta tgggatgggc 1080

ccagcctgtc tacaggccaa ggatggcatc tcagtcaagg gcgccaacaa cagtaacacc 1140

accaaccccc ctcctgcacc atctaagtcc ccagaggaga tgcgaaaact cttcatccag 1200

agggccaaga agatcgacaa aatatcccgc attggcttcc ccatggcctt cctcattttc 1260

aacatgttct actggatcat ctacaagatt gtccgtagag aggacgtcca caaccagtga 1320

<210> 37
<211> 439
<212> PRT
<213> Artificial Sequence

<220>
<223> synthetic sequence of chimeric LGIC

<400> 37

Met Arg Cys Ser Pro Gly Gly Val Trp Leu Ala Leu Ala Ala Ser Leu
1 5 10 15

Leu His Val Ser Leu Gln Gly Glu Phe Gln Arg Lys Leu Tyr Lys Glu
20 25 30

Leu Val Lys Asn Tyr Asn Pro Leu Glu Arg Pro Val Ala Asn Asp Ser
35 40 45

Gln Pro Leu Thr Val Tyr Phe Ser Leu Ser Leu Leu Gln Ile Met Asp
50 55 60

Val Asp Glu Thr Thr Met Val Leu Thr Thr Asn Ile Trp Leu Gln Met
65 70 75 80

Ser Trp Thr Asp His Tyr Leu Gln Trp Asn Val Ser Glu Tyr Pro Gly
85 90 95

Val Lys Thr Val Arg Phe Pro Asp Gly Gln Ile Trp Lys Pro Asp Ile
100 105 110

```
Leu Leu Tyr Asn Ser Ala Asp Glu Arg Phe Asp Ala Thr Phe His Thr
        115                 120                 125

Asn Val Leu Val Asn Ser Ser Gly His Cys Gln Tyr Leu Pro Pro Gly
    130                 135                 140

Ile Phe Lys Ser Ser Cys Tyr Ile Asp Val Arg Trp Phe Pro Phe Asp
145                 150                 155                 160

Val Gln His Cys Lys Leu Lys Phe Gly Ser Trp Ser Tyr Gly Gly Trp
                165                 170                 175

Ser Leu Asp Leu Gln Met Gln Glu Ala Asp Ile Ser Gly Tyr Ile Pro
            180                 185                 190

Asn Gly Glu Trp Asp Leu Val Gly Ile Pro Gly Lys Arg Ser Glu Arg
        195                 200                 205

Phe Tyr Glu Cys Cys Lys Glu Pro Tyr Pro Asp Val Thr Phe Thr Val
    210                 215                 220

Thr Met Arg Arg Arg Met Gly Tyr Tyr Leu Ile Gln Met Tyr Ile Pro
225                 230                 235                 240

Ser Leu Leu Ile Val Ile Leu Ser Trp Ile Ser Phe Trp Ile Asn Met
                245                 250                 255

Asp Ala Ala Pro Ala Arg Val Gly Leu Gly Ile Thr Thr Val Leu Thr
            260                 265                 270

Met Thr Thr Gln Ser Ser Gly Ser Arg Ala Ser Leu Pro Lys Val Ser
        275                 280                 285

Tyr Val Lys Ala Ile Asp Ile Trp Met Ala Val Cys Leu Leu Phe Val
    290                 295                 300

Phe Ser Ala Leu Leu Glu Tyr Ala Ala Val Asn Phe Val Ser Arg Gln
305                 310                 315                 320

His Lys Glu Leu Leu Arg Phe Arg Arg Lys Arg Arg His His Lys Ser
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                325                 330                 335

Pro Met Leu Asn Leu Phe Gln Glu Asp Glu Ala Gly Glu Gly Arg Phe
            340                 345                 350

Asn Phe Ser Ala Tyr Gly Met Gly Pro Ala Cys Leu Gln Ala Lys Asp
        355                 360                 365

Gly Ile Ser Val Lys Gly Ala Asn Asn Ser Asn Thr Thr Asn Pro Pro
    370                 375                 380

Pro Ala Pro Ser Lys Ser Pro Glu Glu Met Arg Lys Leu Phe Ile Gln
385                 390                 395                 400

Arg Ala Lys Lys Ile Asp Lys Ile Ser Arg Ile Gly Phe Pro Met Ala
                405                 410                 415

Phe Leu Ile Phe Asn Met Phe Tyr Trp Ile Ile Tyr Lys Ile Val Arg
            420                 425                 430

Arg Glu Asp Val His Asn Gln
        435
```

<210> 38
<211> 1320
<212> DNA
<213> Artificial Sequence

<220>
<223> synthetic sequence of chimeric LGIC

<400> 38

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atgcgctgct cgccgggagg cgtctggctg gcgctggccg cgtcgctcct gcacgtgtcc       60

ctgcaaggcg agttccagag gaagctttac aaggagctgg tcaagaacta caatcccttg      120

gagaggcccg tggccaatga ctcgcaacca ctcaccgtct acttctccct gagcctcctg      180

cagatcatgg acattgctga gacaaccatg gacttaacca ccaacatttg gctgcaaatg      240

tcttggacag atcactattt acagtggaat gtgtcagaat atccaggggt gaagactgtt      300

cgtttcccag atggccagat ttggaaacca gacattcttc tctataacag tgctgatgag      360

cgctttgacg ccacattcca cactaacgtg ttggtgaact cttctgggca ttgccagtac      420
```

ctgcctccag gcatattcaa gagttcctgc cccatggact tgaagaattt ccccatggat 480

gtccagacat gcaaactgaa gtttgggtcc tggtcttacg gaggctggtc cttggatctg 540

cagatgcagg aggcagatat cagtggctat atccccaatg gagaatggga cctagtggga 600

atccccggca agaggagtga aaggttctat gagtgctgca aagagcccta ccccgatgtc 660

accttcacag tgaccatgcg ccgcaggatg ggttactacc tgattcagat gtatattccc 720

agcctgctca ttgtcatcct ctcatggatc tccttctgga tcaacatgga tgctgcacct 780

gctcgtgtgg gcctaggcat caccactgtg ctcaccatga ccacccagag ctccggctct 840

cgagcatctc tgcccaaggt gtcctatgtg aaagccattg acatttggat ggcagtttgc 900

ctgctctttg tgttctcagc cctattagaa tatgctgccg ttaactttgt gtctcggcaa 960

cataaggagc tgctccgatt caggaggaag cggagacatc acaagagccc catgttgaat 1020

ctattccagg aggatgaagc tggagaaggc cgctttaact tctctgccta tgggatgggc 1080

ccagcctgtc tacaggccaa ggatggcatc tcagtcaagg gcgccaacaa cagtaacacc 1140

accaaccccc ctcctgcacc atctaagtcc ccagaggaga tgcgaaaact cttcatccag 1200

agggccaaga agatcgacaa aatatcccgc attggcttcc ccatggcctt cctcattttc 1260

aacatgttct actggatcat ctacaagatt gtccgtagag aggacgtcca caaccagtga 1320

<210> 39
<211> 439
<212> PRT
<213> Artificial Sequence

<220>
<223> synthetic sequence of chimeric LGIC

<400> 39

Met Arg Cys Ser Pro Gly Gly Val Trp Leu Ala Leu Ala Ala Ser Leu
1 5 10 15

Leu His Val Ser Leu Gln Gly Glu Phe Gln Arg Lys Leu Tyr Lys Glu
20 25 30

Leu Val Lys Asn Tyr Asn Pro Leu Glu Arg Pro Val Ala Asn Asp Ser
35 40 45

Gln Pro Leu Thr Val Tyr Phe Ser Leu Ser Leu Leu Gln Ile Met Asp

```
    50                  55                  60

Ile Ala Glu Thr Thr Met Asp Leu Thr Thr Asn Ile Trp Leu Gln Met
65                  70                  75                  80

Ser Trp Thr Asp His Tyr Leu Gln Trp Asn Val Ser Glu Tyr Pro Gly
                85                  90                  95

Val Lys Thr Val Arg Phe Pro Asp Gly Gln Ile Trp Lys Pro Asp Ile
            100                 105                 110

Leu Leu Tyr Asn Ser Ala Asp Glu Arg Phe Asp Ala Thr Phe His Thr
        115                 120                 125

Asn Val Leu Val Asn Ser Ser Gly His Cys Gln Tyr Leu Pro Pro Gly
    130                 135                 140

Ile Phe Lys Ser Ser Cys Pro Met Asp Leu Lys Asn Phe Pro Met Asp
145                 150                 155                 160

Val Gln Thr Cys Lys Leu Lys Phe Gly Ser Trp Ser Tyr Gly Gly Trp
                165                 170                 175

Ser Leu Asp Leu Gln Met Gln Glu Ala Asp Ile Ser Gly Tyr Ile Pro
            180                 185                 190

Asn Gly Glu Trp Asp Leu Val Gly Ile Pro Gly Lys Arg Ser Glu Arg
        195                 200                 205

Phe Tyr Glu Cys Cys Lys Glu Pro Tyr Pro Asp Val Thr Phe Thr Val
    210                 215                 220

Thr Met Arg Arg Arg Met Gly Tyr Tyr Leu Ile Gln Met Tyr Ile Pro
225                 230                 235                 240

Ser Leu Leu Ile Val Ile Leu Ser Trp Ile Ser Phe Trp Ile Asn Met
                245                 250                 255

Asp Ala Ala Pro Ala Arg Val Gly Leu Gly Ile Thr Thr Val Leu Thr
            260                 265                 270
```

```
Met Thr Thr Gln Ser Ser Gly Ser Arg Ala Ser Leu Pro Lys Val Ser
        275                 280                 285

Tyr Val Lys Ala Ile Asp Ile Trp Met Ala Val Cys Leu Leu Phe Val
    290                 295                 300

Phe Ser Ala Leu Leu Glu Tyr Ala Ala Val Asn Phe Val Ser Arg Gln
305                 310                 315                 320

His Lys Glu Leu Leu Arg Phe Arg Arg Lys Arg Arg His His Lys Ser
                325                 330                 335

Pro Met Leu Asn Leu Phe Gln Glu Asp Glu Ala Gly Glu Gly Arg Phe
            340                 345                 350

Asn Phe Ser Ala Tyr Gly Met Gly Pro Ala Cys Leu Gln Ala Lys Asp
        355                 360                 365

Gly Ile Ser Val Lys Gly Ala Asn Asn Ser Asn Thr Thr Asn Pro Pro
    370                 375                 380

Pro Ala Pro Ser Lys Ser Pro Glu Glu Met Arg Lys Leu Phe Ile Gln
385                 390                 395                 400

Arg Ala Lys Lys Ile Asp Lys Ile Ser Arg Ile Gly Phe Pro Met Ala
                405                 410                 415

Phe Leu Ile Phe Asn Met Phe Tyr Trp Ile Ile Tyr Lys Ile Val Arg
            420                 425                 430

Arg Glu Asp Val His Asn Gln
        435
```

<210> 40
<211> 1320
<212> DNA
<213> Artificial Sequence

<220>
<223> synthetic sequence of chimeric LGIC

<400> 40

atgcgctgct cgccgggagg cgtctggctg gcgctggccg cgtcgctcct gcacgtgtcc 60

ctgcaaggcg agttccagag gaagctttac aaggagctgg tcaagaacta caatcccttg 120

gagaggcccg tggccaatga ctcgcaacca ctcaccgtct acttctccct gagcctcctg 180

cagatcatgg acgtggatga gacaaccatg gttttaacca ccaacatttg gctgcaaatg 240

tcttggacag atcactattt acagtggaat gtgtcagaat atccaggggt gaagactgtt 300

cgtttcccag atggccagat ttggaaacca gacattcttc tctataacag tgctgatgag 360

cgctttgacg ccacattcca cactaacgtg ttggtgaact cttctgggca ttgccagtac 420

ctgcctccag gcatattcaa gagttcctgc cccatggact tgaagaattt ccccatggat 480

gtccagacat gcaaactgaa gtttgggtcc tggtcttacg gaggctggtc cttggatctg 540

cagatgcagg aggcagatat cagtggctat atccccaatg gagaatggga cctagtggga 600

atccccggca agaggagtga aaggttctat gagtgctgca aagagcccta ccccgatgtc 660

accttcacag tgaccatgcg ccgcaggatg ggttactacc tgattcagat gtatattccc 720

agcctgctca ttgtcatcct ctcatggatc tccttctgga tcaacatgga tgctgcacct 780

gctcgtgtgg gcctaggcat caccactgtg ctcaccatga ccacccagag ctccggctct 840

cgagcatctc tgcccaaggt gtcctatgtg aaagccattg acatttggat ggcagtttgc 900

ctgctctttg tgttctcagc cctattagaa tatgctgccg ttaactttgt gtctcggcaa 960

cataaggagc tgctccgatt caggaggaag cggagacatc acaagagccc catgttgaat 1020

ctattccagg aggatgaagc tggagaaggc cgctttaact tctctgccta tgggatgggc 1080

ccagcctgtc tacaggccaa ggatggcatc tcagtcaagg gcgccaacaa cagtaacacc 1140

accaaccccc ctcctgcacc atctaagtcc ccagaggaga tgcgaaaact cttcatccag 1200

agggccaaga agatcgacaa aatatcccgc attggcttcc ccatggcctt cctcattttc 1260

aacatgttct actggatcat ctacaagatt gtccgtagag aggacgtcca caaccagtga 1320

<210> 41
<211> 439
<212> PRT
<213> Artificial Sequence

<220>
<223> synthetic sequence of chimeric LGIC

<400> 41

```
Met Arg Cys Ser Pro Gly Gly Val Trp Leu Ala Leu Ala Ala Ser Leu
1               5                  10                  15

Leu His Val Ser Leu Gln Gly Glu Phe Gln Arg Lys Leu Tyr Lys Glu
            20                  25                  30

Leu Val Lys Asn Tyr Asn Pro Leu Glu Arg Pro Val Ala Asn Asp Ser
        35                  40                  45

Gln Pro Leu Thr Val Tyr Phe Ser Leu Ser Leu Leu Gln Ile Met Asp
    50                  55                  60

Val Asp Glu Thr Thr Met Val Leu Thr Thr Asn Ile Trp Leu Gln Met
65                  70                  75                  80

Ser Trp Thr Asp His Tyr Leu Gln Trp Asn Val Ser Glu Tyr Pro Gly
                85                  90                  95

Val Lys Thr Val Arg Phe Pro Asp Gly Gln Ile Trp Lys Pro Asp Ile
            100                 105                 110

Leu Leu Tyr Asn Ser Ala Asp Glu Arg Phe Asp Ala Thr Phe His Thr
        115                 120                 125

Asn Val Leu Val Asn Ser Ser Gly His Cys Gln Tyr Leu Pro Pro Gly
    130                 135                 140

Ile Phe Lys Ser Ser Cys Pro Met Asp Leu Lys Asn Phe Pro Met Asp
145                 150                 155                 160

Val Gln Thr Cys Lys Leu Lys Phe Gly Ser Trp Ser Tyr Gly Gly Trp
                165                 170                 175

Ser Leu Asp Leu Gln Met Gln Glu Ala Asp Ile Ser Gly Tyr Ile Pro
            180                 185                 190

Asn Gly Glu Trp Asp Leu Val Gly Ile Pro Gly Lys Arg Ser Glu Arg
        195                 200                 205

Phe Tyr Glu Cys Cys Lys Glu Pro Tyr Pro Asp Val Thr Phe Thr Val
```

```
    210                 215                 220

Thr Met Arg Arg Arg Met Gly Tyr Tyr Leu Ile Gln Met Tyr Ile Pro
225                 230                 235                 240

Ser Leu Leu Ile Val Ile Leu Ser Trp Ile Ser Phe Trp Ile Asn Met
                245                 250                 255

Asp Ala Ala Pro Ala Arg Val Gly Leu Gly Ile Thr Thr Val Leu Thr
            260                 265                 270

Met Thr Thr Gln Ser Ser Gly Ser Arg Ala Ser Leu Pro Lys Val Ser
        275                 280                 285

Tyr Val Lys Ala Ile Asp Ile Trp Met Ala Val Cys Leu Leu Phe Val
    290                 295                 300

Phe Ser Ala Leu Leu Glu Tyr Ala Ala Val Asn Phe Val Ser Arg Gln
305                 310                 315                 320

His Lys Glu Leu Leu Arg Phe Arg Arg Lys Arg Arg His His Lys Ser
                325                 330                 335

Pro Met Leu Asn Leu Phe Gln Glu Asp Glu Ala Gly Glu Gly Arg Phe
            340                 345                 350

Asn Phe Ser Ala Tyr Gly Met Gly Pro Ala Cys Leu Gln Ala Lys Asp
        355                 360                 365

Gly Ile Ser Val Lys Gly Ala Asn Asn Ser Asn Thr Thr Asn Pro Pro
    370                 375                 380

Pro Ala Pro Ser Lys Ser Pro Glu Glu Met Arg Lys Leu Phe Ile Gln
385                 390                 395                 400

Arg Ala Lys Lys Ile Asp Lys Ile Ser Arg Ile Gly Phe Pro Met Ala
                405                 410                 415

Phe Leu Ile Phe Asn Met Phe Tyr Trp Ile Ile Tyr Lys Ile Val Arg
            420                 425                 430
```

Arg Glu Asp Val His Asn Gln
435

<210> 42
<211> 1317
<212> DNA
<213> Artificial Sequence

<220>
<223> synthetic sequence of chimeric LGIC

<400> 42
atgcgctgct cgccgggagg cgtctggctg gcgctggccg cgtcgctcct gcacgtgtcc 60

ctgcaaggcg agttccagag gaagctttac aaggagctgg tcaagaacta caatcccttg 120

gagaggcccg tggccaatga ctcgcaacca ctcaccgtct acttctccct gagcctcctg 180

cagatcatgg acgtggatga gacaaccatg gttttaacca ccaacatttg gctgcaaatg 240

tcttggacag atcactattt acagtggaat gtgtcagaat atccaggggt gaagactgtt 300

cgtttcccag atggccagat ttggaaacca gacattcttc tctataacag tgctgatgag 360

cgctttgacg ccacattcca cactaacgtg ttggtgaact cttctgggca ttgccagtac 420

ctgcctccag gcatattcaa gagttcctgc cccatggact tgaagaattt ccccatggat 480

gtccagacat gcaaactgaa gtttgggtcc tggtcttacg gaggctggtc cttggatctg 540

cagatgcagg aggcagatat cagtggctat atccccaatg gagaatggga cctagtggga 600

atccccggca agaggagtga aaggttctat gagtgctgca aagagcccta ccccgatgtc 660

accttcacag tgaccatgga gcggcagatg ggttactacc tgattcagat gtatattccc 720

agcctgctca ttgtcatcct ctcatggatc tccttctgga tcaacatgga tgctgcacct 780

gctcgtgtgg gcctaggcat caccactgtg ctcaccatga ccacccagag ctccggctct 840

cgagcatctc tgcccaaggt gtcctatgtg aaagccattg acatttggat ggcagtttgc 900

ctgctctttg tgttctcagc cctattagaa tatgctgccg ttaactttgt gtctcggcaa 960

cataaggagc tgctccgatt caggaggaag cggagacatc acaagagccc catgttgaat 1020

ctattccagg aggatgaagc tggagaaggc cgctttaact tctctgccta tgggatgggc 1080

ccagcctgtc tacaggccaa ggatggcatc tcagtcaagg gcgccaacaa cagtaacacc 1140

accaaccccc ctcctgcacc atctaagtcc ccagaggaga tgcgaaaact cttcatccag 1200

agggccaaga agatcgacaa aatatcccgc attggcttcc ccatggcctt cctcattttc 1260

aacatgttct actggatcat ctacaagatt gtccgtagag aggacgtcca caaccag 1317

<210> 43
<211> 439
<212> PRT
<213> Artificial Sequence

<220>
<223> synthetic sequence of chimeric LGIC

<400> 43

Met Arg Cys Ser Pro Gly Gly Val Trp Leu Ala Leu Ala Ala Ser Leu
1 5 10 15

Leu His Val Ser Leu Gln Gly Glu Phe Gln Arg Lys Leu Tyr Lys Glu
20 25 30

Leu Val Lys Asn Tyr Asn Pro Leu Glu Arg Pro Val Ala Asn Asp Ser
35 40 45

Gln Pro Leu Thr Val Tyr Phe Ser Leu Ser Leu Leu Gln Ile Met Asp
50 55 60

Val Asp Glu Thr Thr Met Val Leu Thr Thr Asn Ile Trp Leu Gln Met
65 70 75 80

Ser Trp Thr Asp His Tyr Leu Gln Trp Asn Val Ser Glu Tyr Pro Gly
85 90 95

Val Lys Thr Val Arg Phe Pro Asp Gly Gln Ile Trp Lys Pro Asp Ile
100 105 110

Leu Leu Tyr Asn Ser Ala Asp Glu Arg Phe Asp Ala Thr Phe His Thr
115 120 125

Asn Val Leu Val Asn Ser Ser Gly His Cys Gln Tyr Leu Pro Pro Gly
130 135 140

Ile Phe Lys Ser Ser Cys Pro Met Asp Leu Lys Asn Phe Pro Met Asp
145 150 155 160

```
Val Gln Thr Cys Lys Leu Lys Phe Gly Ser Trp Ser Tyr Gly Gly Trp
                165                 170                 175

Ser Leu Asp Leu Gln Met Gln Glu Ala Asp Ile Ser Gly Tyr Ile Pro
            180                 185                 190

Asn Gly Glu Trp Asp Leu Val Gly Ile Pro Gly Lys Arg Ser Glu Arg
        195                 200                 205

Phe Tyr Glu Cys Cys Lys Glu Pro Tyr Pro Asp Val Thr Phe Thr Val
    210                 215                 220

Thr Met Glu Arg Gln Met Gly Tyr Tyr Leu Ile Gln Met Tyr Ile Pro
225                 230                 235                 240

Ser Leu Leu Ile Val Ile Leu Ser Trp Ile Ser Phe Trp Ile Asn Met
                245                 250                 255

Asp Ala Ala Pro Ala Arg Val Gly Leu Gly Ile Thr Thr Val Leu Thr
            260                 265                 270

Met Thr Thr Gln Ser Ser Gly Ser Arg Ala Ser Leu Pro Lys Val Ser
        275                 280                 285

Tyr Val Lys Ala Ile Asp Ile Trp Met Ala Val Cys Leu Leu Phe Val
    290                 295                 300

Phe Ser Ala Leu Leu Glu Tyr Ala Ala Val Asn Phe Val Ser Arg Gln
305                 310                 315                 320

His Lys Glu Leu Leu Arg Phe Arg Arg Lys Arg Arg His His Lys Ser
                325                 330                 335

Pro Met Leu Asn Leu Phe Gln Glu Asp Glu Ala Gly Glu Gly Arg Phe
            340                 345                 350

Asn Phe Ser Ala Tyr Gly Met Gly Pro Ala Cys Leu Gln Ala Lys Asp
        355                 360                 365

Gly Ile Ser Val Lys Gly Ala Asn Asn Ser Asn Thr Thr Asn Pro Pro
```

```
    370                 375                 380

Pro Ala Pro Ser Lys Ser Pro Glu Glu Met Arg Lys Leu Phe Ile Gln
385                 390                 395                 400

Arg Ala Lys Lys Ile Asp Lys Ile Ser Arg Ile Gly Phe Pro Met Ala
                405                 410                 415

Phe Leu Ile Phe Asn Met Phe Tyr Trp Ile Ile Tyr Lys Ile Val Arg
            420                 425                 430

Arg Glu Asp Val His Asn Gln
        435
```

<210> 44
<211> 1317
<212> DNA
<213> Artificial Sequence

<220>
<223> synthetic sequence of chimeric LGIC

<400> 44

```
atgcgctgct cgccgggagg cgtctggctg gcgctggccg cgtcgctcct gcacgtgtcc       60

ctgcaaggcg agttccagag gaagctttac aaggagctgg tcaagaacta caatcccttg      120

gagaggcccg tggccaatga ctcgcaacca ctcaccgtct acttctccct gagcctcctg      180

cagatcatgg acattgctga gacaaccatg gacttaacca ccaacatttg gctgcaaatg      240

tcttggacag atcactattt acagtggaat gtgtcagaat atccaggggt gaagactgtt      300

cgtttcccag atggccagat ttggaaacca gacattcttc tctataacag tgctgatgag      360

cgctttgacg ccacattcca cactaacgtg ttggtgaact cttctgggca ttgccagtac      420

ctgcctccag gcatattcaa gagttcctgc cccatggact tgaagaattt ccccatggat      480

gtccagacat gcaaactgaa gtttgggtcc tggtcttacg gaggctggtc cttggatctg      540

cagatgcagg aggcagatat cagtggctat atccccaatg gagaatggga cctagtggga      600

atccccggca agaggagtga aaggttctat gagtgctgca aagagcccta ccccgatgtc      660

accttcacag tgaccatgga gcggcagatg ggttactacc tgattcagat gtatattccc      720

agcctgctca ttgtcatcct ctcatggatc tccttctgga tcaacatgga tgctgcacct      780
```

gctcgtgtgg gcctaggcat caccactgtg ctcaccatga ccacccagag ctccggctct 840

cgagcatctc tgcccaaggt gtcctatgtg aaagccattg acatttggat ggcagtttgc 900

ctgctctttg tgttctcagc cctattagaa tatgctgccg ttaactttgt gtctcggcaa 960

cataaggagc tgctccgatt caggaggaag cggagacatc acaagagccc catgttgaat 1020

ctattccagg aggatgaagc tggagaaggc cgctttaact tctctgccta tgggatgggc 1080

ccagcctgtc tacaggccaa ggatggcatc tcagtcaagg gcgccaacaa cagtaacacc 1140

accaaccccc ctcctgcacc atctaagtcc ccagaggaga tgcgaaaact cttcatccag 1200

agggccaaga agatcgacaa aatatcccgc attggcttcc ccatggcctt cctcattttc 1260

aacatgttct actggatcat ctacaagatt gtccgtagag aggacgtcca caaccag 1317

<210> 45
<211> 439
<212> PRT
<213> Artificial Sequence

<220>
<223> synthetic sequence of chimeric LGIC

<400> 45

Met Arg Cys Ser Pro Gly Gly Val Trp Leu Ala Leu Ala Ala Ser Leu
1 5 10 15

Leu His Val Ser Leu Gln Gly Glu Phe Gln Arg Lys Leu Tyr Lys Glu
20 25 30

Leu Val Lys Asn Tyr Asn Pro Leu Glu Arg Pro Val Ala Asn Asp Ser
35 40 45

Gln Pro Leu Thr Val Tyr Phe Ser Leu Ser Leu Leu Gln Ile Met Asp
50 55 60

Ile Ala Glu Thr Thr Met Asp Leu Thr Thr Asn Ile Trp Leu Gln Met
65 70 75 80

Ser Trp Thr Asp His Tyr Leu Gln Trp Asn Val Ser Glu Tyr Pro Gly
85 90 95

Val Lys Thr Val Arg Phe Pro Asp Gly Gln Ile Trp Lys Pro Asp Ile

```
            100                 105                 110

Leu Leu Tyr Asn Ser Ala Asp Glu Arg Phe Asp Ala Thr Phe His Thr
        115                 120                 125

Asn Val Leu Val Asn Ser Ser Gly His Cys Gln Tyr Leu Pro Pro Gly
    130                 135                 140

Ile Phe Lys Ser Ser Cys Pro Met Asp Leu Lys Asn Phe Pro Met Asp
145                 150                 155                 160

Val Gln Thr Cys Lys Leu Lys Phe Gly Ser Trp Ser Tyr Gly Gly Trp
                165                 170                 175

Ser Leu Asp Leu Gln Met Gln Glu Ala Asp Ile Ser Gly Tyr Ile Pro
            180                 185                 190

Asn Gly Glu Trp Asp Leu Val Gly Ile Pro Gly Lys Arg Ser Glu Arg
        195                 200                 205

Phe Tyr Glu Cys Cys Lys Glu Pro Tyr Pro Asp Val Thr Phe Thr Val
    210                 215                 220

Thr Met Glu Arg Gln Met Gly Tyr Tyr Leu Ile Gln Met Tyr Ile Pro
225                 230                 235                 240

Ser Leu Leu Ile Val Ile Leu Ser Trp Ile Ser Phe Trp Ile Asn Met
                245                 250                 255

Asp Ala Ala Pro Ala Arg Val Gly Leu Gly Ile Thr Thr Val Leu Thr
            260                 265                 270

Met Thr Thr Gln Ser Ser Gly Ser Arg Ala Ser Leu Pro Lys Val Ser
        275                 280                 285

Tyr Val Lys Ala Ile Asp Ile Trp Met Ala Val Cys Leu Leu Phe Val
    290                 295                 300

Phe Ser Ala Leu Leu Glu Tyr Ala Ala Val Asn Phe Val Ser Arg Gln
305                 310                 315                 320
```

```
His Lys Glu Leu Leu Arg Phe Arg Arg Lys Arg Arg His His Lys Ser
                325                 330                 335

Pro Met Leu Asn Leu Phe Gln Glu Asp Glu Ala Gly Glu Gly Arg Phe
            340                 345                 350

Asn Phe Ser Ala Tyr Gly Met Gly Pro Ala Cys Leu Gln Ala Lys Asp
        355                 360                 365

Gly Ile Ser Val Lys Gly Ala Asn Asn Ser Asn Thr Thr Asn Pro Pro
    370                 375                 380

Pro Ala Pro Ser Lys Ser Pro Glu Glu Met Arg Lys Leu Phe Ile Gln
385                 390                 395                 400

Arg Ala Lys Lys Ile Asp Lys Ile Ser Arg Ile Gly Phe Pro Met Ala
                405                 410                 415

Phe Leu Ile Phe Asn Met Phe Tyr Trp Ile Ile Tyr Lys Ile Val Arg
            420                 425                 430

Arg Glu Asp Val His Asn Gln
        435
```

<210> 46
<211> 1329
<212> DNA
<213> Artificial Sequence

<220>
<223> synthetic sequence of chimeric LGIC

<400> 46

```
atgcgctgct cgccgggagg cgtctggctg gcgctggccg cgtcgctcct gcacgtgtcc       60

ctgcaaggcg agttccagag gaagctttac aaggagctgg tcaagaacta caatcccttg      120

gagaggcccg tggccaatga ctcgcaacca ctcaccgtct acttctccct gagcctcctg      180

cagatcatgg acgtggatga gacaaccatg gttttaacca ccaacatttg gctgcaaatg      240

tcttggacag atcactattt acagtggaat gtgtcagaat atccaggggt gaagactgtt      300

cgtttcccag atggccagat ttggaaacca gacattcttc tctataacag tgctgatgag      360
```

cgctttgacg ccacattcca cactaacgtg ttggtgaact cttctgggca ttgccagtac 420

ctgcctccag gcatattcaa gagttcctgc tacatcgatg tacgctggtt tccctttgat 480

gtgcagcact gcaaactgaa gtttgggtcc tggtcttacg gaggctggtc cttggatctg 540

cagatgcagg aggcagatat cagtggctat atccccaatg gagaatggga cctagtggga 600

atccccggca agaggagtga aaggttctat gagtgctgca aagagcccta ccccgatgtc 660

accttcacag tgaccatgcg ccgcaggatg ggttactacc tgattcagat gtatattccc 720

agcctgctca ttgtcatcct ctcatggatc tccttctgga tcaacatgga tgctgcacct 780

gctcgtgtgg gcctaggcat caccactgtg ctcaccatga ccacccagag ctccggctct 840

gagatcatgc ccgcaacatc cgattcggta ccattgatag cccaggccat tgacatttgg 900

atggcagttt gcctgctctt tgtgttctca gccctattag aatatgctgc cgttaacttt 960

gtgtctcggc aacataagga gctgctccga ttcaggagga agcggagaca tcacaagagc 1020

cccatgttga atctattcca ggaggatgaa gctggagaag gccgctttaa cttctctgcc 1080

tatgggatgg gcccagcctg tctacaggcc aaggatggca tctcagtcaa gggcgccaac 1140

aacagtaaca ccaccaaccc ccctcctgca ccatctaagt ccccagagga gatgcgaaaa 1200

ctcttcatcc agagggccaa gaagatcgac aaaatatccc gcattggctt ccccatggcc 1260

ttcctcattt tcaacatgtt ctactggatc atctacaaga ttgtccgtag agaggacgtc 1320

cacaaccag 1329

<210> 47
<211> 443
<212> PRT
<213> Artificial Sequence

<220>
<223> synthetic sequence of chimeric LGIC

<400> 47

Met Arg Cys Ser Pro Gly Gly Val Trp Leu Ala Leu Ala Ala Ser Leu
1 5 10 15

Leu His Val Ser Leu Gln Gly Glu Phe Gln Arg Lys Leu Tyr Lys Glu
20 25 30

Leu Val Lys Asn Tyr Asn Pro Leu Glu Arg Pro Val Ala Asn Asp Ser

```
        35                  40                  45

Gln Pro Leu Thr Val Tyr Phe Ser Leu Ser Leu Leu Gln Ile Met Asp
    50                  55                  60

Val Asp Glu Thr Thr Met Val Leu Thr Thr Asn Ile Trp Leu Gln Met
65                  70                  75                  80

Ser Trp Thr Asp His Tyr Leu Gln Trp Asn Val Ser Glu Tyr Pro Gly
                85                  90                  95

Val Lys Thr Val Arg Phe Pro Asp Gly Gln Ile Trp Lys Pro Asp Ile
            100                 105                 110

Leu Leu Tyr Asn Ser Ala Asp Glu Arg Phe Asp Ala Thr Phe His Thr
        115                 120                 125

Asn Val Leu Val Asn Ser Ser Gly His Cys Gln Tyr Leu Pro Pro Gly
    130                 135                 140

Ile Phe Lys Ser Ser Cys Tyr Ile Asp Val Arg Trp Phe Pro Phe Asp
145                 150                 155                 160

Val Gln His Cys Lys Leu Lys Phe Gly Ser Trp Ser Tyr Gly Gly Trp
                165                 170                 175

Ser Leu Asp Leu Gln Met Gln Glu Ala Asp Ile Ser Gly Tyr Ile Pro
            180                 185                 190

Asn Gly Glu Trp Asp Leu Val Gly Ile Pro Gly Lys Arg Ser Glu Arg
        195                 200                 205

Phe Tyr Glu Cys Cys Lys Glu Pro Tyr Pro Asp Val Thr Phe Thr Val
    210                 215                 220

Thr Met Arg Arg Arg Met Gly Tyr Tyr Leu Ile Gln Met Tyr Ile Pro
225                 230                 235                 240

Ser Leu Leu Ile Val Ile Leu Ser Trp Ile Ser Phe Trp Ile Asn Met
                245                 250                 255
```

```
Asp Ala Ala Pro Ala Arg Val Gly Leu Gly Ile Thr Thr Val Leu Thr
            260                 265                 270

Met Thr Thr Gln Ser Ser Gly Ser Glu Ile Met Pro Ala Thr Ser Asp
        275                 280                 285

Ser Val Pro Leu Ile Ala Gln Ala Ile Asp Ile Trp Met Ala Val Cys
    290                 295                 300

Leu Leu Phe Val Phe Ser Ala Leu Leu Glu Tyr Ala Ala Val Asn Phe
305                 310                 315                 320

Val Ser Arg Gln His Lys Glu Leu Leu Arg Phe Arg Arg Lys Arg Arg
                325                 330                 335

His His Lys Ser Pro Met Leu Asn Leu Phe Gln Glu Asp Glu Ala Gly
            340                 345                 350

Glu Gly Arg Phe Asn Phe Ser Ala Tyr Gly Met Gly Pro Ala Cys Leu
        355                 360                 365

Gln Ala Lys Asp Gly Ile Ser Val Lys Gly Ala Asn Asn Ser Asn Thr
    370                 375                 380

Thr Asn Pro Pro Pro Ala Pro Ser Lys Ser Pro Glu Glu Met Arg Lys
385                 390                 395                 400

Leu Phe Ile Gln Arg Ala Lys Lys Ile Asp Lys Ile Ser Arg Ile Gly
                405                 410                 415

Phe Pro Met Ala Phe Leu Ile Phe Asn Met Phe Tyr Trp Ile Ile Tyr
            420                 425                 430

Lys Ile Val Arg Arg Glu Asp Val His Asn Gln
        435                 440
```

<210> 48
<211> 1332
<212> DNA
<213> Artificial Sequence

<220>
<223> synthetic sequence of chimeric LGIC

<400> 48
atgcgctgct cgccgggagg cgtctggctg gcgctggccg cgtcgctcct gcacgtgtcc 60

ctgcaaggcg agttccagag gaagctttac aaggagctgg tcaagaacta caatcccttg 120

gagaggcccg tggccaatga ctcgcaacca ctcaccgtct acttctccct gagcctcctg 180

cagatcatgg acgtggatga gaagaaccaa gttttaacca ccaacatttg gctgcaaatg 240

tcttggacag atcactattt acagtggaat gtgtcagaat atccaggggt gaagactgtt 300

cgtttcccag atggccagat ttggaaacca gacattcttc tctataacag tgctgatgag 360

cgctttgacg ccacattcca cactaacgtg ttggtgaact cttctgggca ttgccagtac 420

ctgcctccag gcatattcaa gagttcctgc cccatggact tgaagaattt ccccatggat 480

gtccagacat gcaaactgaa gtttgggtcc tggtcttacg gaggctggtc cttggatctg 540

cagatgcagg aggcagatat cagtggctat atccccaatg gagaatggga cctagtggga 600

atccccggca agaggagtga aaggttctat gagtgctgca aagagcccta ccccgatgtc 660

accttcacag tgaccatgcg ccgcaggatg ggttactacc tgattcagat gtatattccc 720

agcctgctca ttgtcatcct ctcatggatc tccttctgga tcaacatgga tgctgcacct 780

gctcgtgtgg gcctaggcat caccactgtg ctcaccatga ccacccagag ctccggctct 840

gagatcatgc ccgcaacatc cgattcggta ccattgatag cccaggccat tgacatttgg 900

atggcagttt gcctgctctt tgtgttctca gccctattag aatatgctgc cgttaacttt 960

gtgtctcggc aacataagga gctgctccga ttcaggagga agcggagaca tcacaagagc 1020

cccatgttga atctattcca ggaggatgaa gctggagaag gccgctttaa cttctctgcc 1080

tatgggatgg gcccagcctg tctacaggcc aaggatggca tctcagtcaa gggcgccaac 1140

aacagtaaca ccaccaaccc ccctcctgca ccatctaagt ccccagagga gatgcgaaaa 1200

ctcttcatcc agagggccaa gaagatcgac aaaatatccc gcattggctt ccccatggcc 1260

ttcctcattt tcaacatgtt ctactggatc atctacaaga ttgtccgtag agaggacgtc 1320

cacaaccagt ga 1332

<210> 49
<211> 443
<212> PRT

<213> Artificial Sequence

<220>
<223> synthetic sequence of chimeric LGIC

<400> 49

```
Met Arg Cys Ser Pro Gly Gly Val Trp Leu Ala Leu Ala Ala Ser Leu
1               5                  10                  15


Leu His Val Ser Leu Gln Gly Glu Phe Gln Arg Lys Leu Tyr Lys Glu
            20                  25                  30


Leu Val Lys Asn Tyr Asn Pro Leu Glu Arg Pro Val Ala Asn Asp Ser
        35                  40                  45


Gln Pro Leu Thr Val Tyr Phe Ser Leu Ser Leu Leu Gln Ile Met Asp
    50                  55                  60


Val Asp Glu Lys Asn Gln Val Leu Thr Thr Asn Ile Trp Leu Gln Met
65                  70                  75                  80


Ser Trp Thr Asp His Tyr Leu Gln Trp Asn Val Ser Glu Tyr Pro Gly
                85                  90                  95


Val Lys Thr Val Arg Phe Pro Asp Gly Gln Ile Trp Lys Pro Asp Ile
            100                 105                 110


Leu Leu Tyr Asn Ser Ala Asp Glu Arg Phe Asp Ala Thr Phe His Thr
        115                 120                 125


Asn Val Leu Val Asn Ser Ser Gly His Cys Gln Tyr Leu Pro Pro Gly
    130                 135                 140


Ile Phe Lys Ser Ser Cys Pro Met Asp Leu Lys Asn Phe Pro Met Asp
145                 150                 155                 160


Val Gln Thr Cys Lys Leu Lys Phe Gly Ser Trp Ser Tyr Gly Gly Trp
                165                 170                 175


Ser Leu Asp Leu Gln Met Gln Glu Ala Asp Ile Ser Gly Tyr Ile Pro
            180                 185                 190
```

```
Asn Gly Glu Trp Asp Leu Val Gly Ile Pro Gly Lys Arg Ser Glu Arg
        195                 200                 205

Phe Tyr Glu Cys Cys Lys Glu Pro Tyr Pro Asp Val Thr Phe Thr Val
    210                 215                 220

Thr Met Arg Arg Arg Met Gly Tyr Tyr Leu Ile Gln Met Tyr Ile Pro
225                 230                 235                 240

Ser Leu Leu Ile Val Ile Leu Ser Trp Ile Ser Phe Trp Ile Asn Met
                245                 250                 255

Asp Ala Ala Pro Ala Arg Val Gly Leu Gly Ile Thr Thr Val Leu Thr
            260                 265                 270

Met Thr Thr Gln Ser Ser Gly Ser Glu Ile Met Pro Ala Thr Ser Asp
        275                 280                 285

Ser Val Pro Leu Ile Ala Gln Ala Ile Asp Ile Trp Met Ala Val Cys
    290                 295                 300

Leu Leu Phe Val Phe Ser Ala Leu Leu Glu Tyr Ala Ala Val Asn Phe
305                 310                 315                 320

Val Ser Arg Gln His Lys Glu Leu Leu Arg Phe Arg Arg Lys Arg Arg
                325                 330                 335

His His Lys Ser Pro Met Leu Asn Leu Phe Gln Glu Asp Glu Ala Gly
            340                 345                 350

Glu Gly Arg Phe Asn Phe Ser Ala Tyr Gly Met Gly Pro Ala Cys Leu
        355                 360                 365

Gln Ala Lys Asp Gly Ile Ser Val Lys Gly Ala Asn Asn Ser Asn Thr
    370                 375                 380

Thr Asn Pro Pro Pro Ala Pro Ser Lys Ser Pro Glu Glu Met Arg Lys
385                 390                 395                 400

Leu Phe Ile Gln Arg Ala Lys Lys Ile Asp Lys Ile Ser Arg Ile Gly
```

405 410 415

Phe Pro Met Ala Phe Leu Ile Phe Asn Met Phe Tyr Trp Ile Ile Tyr
420 425 430

Lys Ile Val Arg Arg Glu Asp Val His Asn Gln
435 440

<210> 50
<211> 451
<212> PRT
<213> Artificial Sequence

<220>
<223> synthetic sequence of chimeric LGIC

<400> 50

Met Leu Leu Trp Val Gln Gln Ala Leu Leu Ala Leu Leu Leu Pro Thr
1 5 10 15

Leu Leu Ala Gln Gly Glu Ala Arg Arg Ser Arg Asn Thr Thr Arg Pro
20 25 30

Ala Leu Leu Arg Leu Ser Asp Tyr Leu Leu Thr Asn Tyr Arg Lys Gly
35 40 45

Val Arg Pro Val Arg Asp Trp Arg Lys Pro Thr Thr Val Ser Ile Asp
50 55 60

Val Ile Val Tyr Ala Ile Leu Asn Val Asp Glu Lys Asn Gln Val Leu
65 70 75 80

Thr Thr Tyr Ile Trp Tyr Arg Gln Tyr Trp Thr Asp Glu Phe Leu Gln
85 90 95

Trp Asn Pro Glu Asp Phe Asp Asn Ile Thr Lys Leu Ser Ile Pro Thr
100 105 110

Asp Ser Ile Trp Val Pro Asp Ile Leu Ile Asn Glu Phe Val Asp Val
115 120 125

Gly Lys Ser Pro Asn Ile Pro Tyr Val Tyr Ile Arg His Gln Gly Glu

```
    130                 135                 140

Val Gln Asn Tyr Lys Pro Leu Gln Val Val Thr Ala Cys Ser Leu Asp
145                 150                 155                 160

Ile Tyr Asn Phe Pro Phe Asp Val Gln Asn Cys Ser Leu Thr Phe Thr
                165                 170                 175

Ser Trp Leu His Thr Ile Gln Asp Ile Asn Ile Ser Leu Trp Arg Leu
            180                 185                 190

Pro Glu Lys Val Lys Ser Asp Arg Ser Val Phe Met Asn Gln Gly Glu
        195                 200                 205

Trp Glu Leu Leu Gly Val Leu Pro Tyr Phe Arg Glu Phe Ser Met Glu
    210                 215                 220

Ser Ser Asn Tyr Tyr Ala Glu Met Lys Phe Tyr Val Val Ile Arg Arg
225                 230                 235                 240

Arg Met Gly Tyr Tyr Leu Ile Gln Met Tyr Ile Pro Ser Leu Leu Ile
                245                 250                 255

Val Ile Leu Ser Trp Ile Ser Phe Trp Ile Asn Met Asp Ala Ala Pro
            260                 265                 270

Ala Arg Val Gly Leu Gly Ile Thr Thr Val Leu Thr Met Thr Thr Gln
        275                 280                 285

Ser Ser Gly Ser Arg Ala Ser Leu Pro Lys Val Ser Tyr Val Lys Ala
    290                 295                 300

Ile Asp Ile Trp Met Ala Val Cys Leu Leu Phe Val Phe Ser Ala Leu
305                 310                 315                 320

Leu Glu Tyr Ala Ala Val Asn Phe Val Ser Arg Gln His Lys Glu Leu
                325                 330                 335

Leu Arg Phe Arg Arg Lys Arg Arg His His Lys Ser Pro Met Leu Asn
            340                 345                 350
```

```
Leu Phe Gln Glu Asp Glu Ala Gly Glu Gly Arg Phe Asn Phe Ser Ala
        355                 360                 365

Tyr Gly Met Gly Pro Ala Cys Leu Gln Ala Lys Asp Gly Ile Ser Val
    370                 375                 380

Lys Gly Ala Asn Asn Ser Asn Thr Thr Asn Pro Pro Pro Ala Pro Ser
385                 390                 395                 400

Lys Ser Pro Glu Glu Met Arg Lys Leu Phe Ile Gln Arg Ala Lys Lys
                405                 410                 415

Ile Asp Lys Ile Ser Arg Ile Gly Phe Pro Met Ala Phe Leu Ile Phe
            420                 425                 430

Asn Met Phe Tyr Trp Ile Ile Tyr Lys Ile Val Arg Arg Glu Asp Val
        435                 440                 445

His Asn Gln
    450
```

<210> 51
<211> 451
<212> PRT
<213> Artificial Sequence

<220>
<223> synthetic sequence of chimeric LGIC

<400> 51

```
Met Leu Leu Trp Val Gln Gln Ala Leu Leu Ala Leu Leu Leu Pro Thr
1               5                   10                  15

Leu Leu Ala Gln Gly Glu Ala Arg Arg Ser Arg Asn Thr Thr Arg Pro
            20                  25                  30

Ala Leu Leu Arg Leu Ser Asp Tyr Leu Leu Thr Asn Tyr Arg Lys Gly
        35                  40                  45

Val Arg Pro Val Arg Asp Trp Arg Lys Pro Thr Thr Val Ser Ile Asp
    50                  55                  60
```

```
Val Ile Val Tyr Ala Ile Leu Asn Val Asp Glu Lys Asn Gln Val Leu
65                  70                  75                  80

Thr Thr Tyr Ile Trp Tyr Arg Gln Tyr Trp Thr Asp Glu Phe Leu Gln
                85                  90                  95

Trp Asn Pro Glu Asp Phe Asp Asn Ile Thr Lys Leu Ser Ile Pro Thr
            100                 105                 110

Asp Ser Ile Trp Val Pro Asp Ile Leu Ile Asn Glu Phe Val Asp Val
        115                 120                 125

Gly Lys Ser Pro Asn Ile Pro Tyr Val Tyr Ile Arg His Gln Gly Glu
    130                 135                 140

Val Gln Asn Tyr Lys Pro Leu Gln Val Val Thr Ala Cys Ser Leu Asp
145                 150                 155                 160

Ile Tyr Asn Phe Pro Phe Asp Val Gln Asn Cys Ser Leu Thr Phe Thr
                165                 170                 175

Ser Trp Leu His Thr Ile Gln Asp Ile Asn Ile Ser Leu Trp Arg Leu
            180                 185                 190

Pro Glu Lys Val Lys Ser Asp Arg Ser Val Phe Met Asn Gln Gly Glu
        195                 200                 205

Trp Glu Leu Leu Gly Val Leu Pro Tyr Phe Arg Glu Phe Ser Met Glu
    210                 215                 220

Ser Ser Asn Tyr Tyr Ala Glu Met Lys Phe Tyr Val His Leu Glu Arg
225                 230                 235                 240

Gln Met Gly Tyr Tyr Leu Ile Gln Met Tyr Ile Pro Ser Leu Leu Ile
                245                 250                 255

Val Ile Leu Ser Trp Ile Ser Phe Trp Ile Asn Met Asp Ala Ala Pro
            260                 265                 270

Ala Arg Val Gly Leu Gly Ile Thr Thr Val Leu Thr Met Thr Thr Gln
```

```
        275                 280                 285

Ser Ser Gly Ser Arg Ala Ser Leu Pro Lys Val Ser Tyr Val Lys Ala
    290                 295                 300

Ile Asp Ile Trp Met Ala Val Cys Leu Leu Phe Val Phe Ser Ala Leu
305                 310                 315                 320

Leu Glu Tyr Ala Ala Val Asn Phe Val Ser Arg Gln His Lys Glu Leu
                325                 330                 335

Leu Arg Phe Arg Arg Lys Arg Arg His His Lys Ser Pro Met Leu Asn
            340                 345                 350

Leu Phe Gln Glu Asp Glu Ala Gly Glu Gly Arg Phe Asn Phe Ser Ala
        355                 360                 365

Tyr Gly Met Gly Pro Ala Cys Leu Gln Ala Lys Asp Gly Ile Ser Val
    370                 375                 380

Lys Gly Ala Asn Asn Ser Asn Thr Thr Asn Pro Pro Pro Ala Pro Ser
385                 390                 395                 400

Lys Ser Pro Glu Glu Met Arg Lys Leu Phe Ile Gln Arg Ala Lys Lys
                405                 410                 415

Ile Asp Lys Ile Ser Arg Ile Gly Phe Pro Met Ala Phe Leu Ile Phe
            420                 425                 430

Asn Met Phe Tyr Trp Ile Ile Tyr Lys Ile Val Arg Arg Glu Asp Val
        435                 440                 445

His Asn Gln
    450
```

<210> 52
<211> 455
<212> PRT
<213> Artificial Sequence

<220>
<223> synthetic sequence of chimeric LGIC

<400> 52

```
Met Trp Gly Leu Ala Gly Gly Arg Leu Phe Gly Ile Phe Ser Ala Pro
1               5                  10                  15

Val Leu Val Ala Val Val Cys Cys Ala Gln Ser Val Asn Asp Pro Gly
            20                  25                  30

Asn Met Ser Phe Val Lys Glu Thr Val Asp Lys Leu Leu Lys Gly Tyr
        35                  40                  45

Asp Ile Arg Leu Arg Pro Asp Phe Gly Gly Pro Pro Val Cys Val Gly
    50                  55                  60

Met Asn Ile Asp Ile Ala Ser Ile Asp Met Val Ser Glu Val Asn Met
65                  70                  75                  80

Asp Tyr Thr Leu Thr Met Tyr Phe Gln Gln Tyr Trp Arg Asp Lys Arg
                85                  90                  95

Leu Ala Tyr Ser Gly Ile Pro Leu Asn Leu Thr Leu Asp Asn Arg Val
            100                 105                 110

Ala Asp Gln Leu Trp Val Pro Asp Thr Tyr Phe Leu Asn Asp Lys Lys
        115                 120                 125

Ser Phe Val His Gly Val Thr Val Lys Asn Arg Met Ile Arg Leu His
    130                 135                 140

Pro Asp Gly Thr Val Leu Tyr Gly Leu Arg Ile Thr Thr Thr Ala Ala
145                 150                 155                 160

Cys Met Met Asp Leu Arg Arg Tyr Pro Leu Asp Glu Gln Asn Cys Thr
                165                 170                 175

Leu Glu Ile Glu Ser Tyr Gly Tyr Thr Thr Asp Asp Ile Glu Phe Tyr
            180                 185                 190

Trp Arg Gly Gly Asp Lys Ala Val Thr Gly Val Glu Arg Ile Glu Leu
        195                 200                 205
```

```
Pro Gln Phe Ser Ile Val Glu His Arg Leu Val Ser Arg Asn Val Val
    210                 215                 220

Phe Ala Thr Gly Ala Tyr Pro Arg Leu Ser Leu Ser Phe Arg Leu Lys
225                 230                 235                 240

Arg Asn Ile Gly Tyr Met Gly Tyr Tyr Leu Ile Gln Met Tyr Ile Pro
                245                 250                 255

Ser Leu Leu Ile Val Ile Leu Ser Trp Ile Ser Phe Trp Ile Asn Met
            260                 265                 270

Asp Ala Ala Pro Ala Arg Val Gly Leu Gly Ile Thr Thr Val Leu Thr
        275                 280                 285

Met Thr Thr Gln Ser Ser Gly Ser Arg Ala Ser Leu Pro Lys Val Ser
    290                 295                 300

Tyr Val Lys Ala Ile Asp Ile Trp Met Ala Val Cys Leu Leu Phe Val
305                 310                 315                 320

Phe Ser Ala Leu Leu Glu Tyr Ala Ala Val Asn Phe Val Ser Arg Gln
                325                 330                 335

His Lys Glu Leu Leu Arg Phe Arg Arg Lys Arg Arg His His Lys Ser
            340                 345                 350

Pro Met Leu Asn Leu Phe Gln Glu Asp Glu Ala Gly Glu Gly Arg Phe
        355                 360                 365

Asn Phe Ser Ala Tyr Gly Met Gly Pro Ala Cys Leu Gln Ala Lys Asp
    370                 375                 380

Gly Ile Ser Val Lys Gly Ala Asn Asn Ser Asn Thr Thr Asn Pro Pro
385                 390                 395                 400

Pro Ala Pro Ser Lys Ser Pro Glu Glu Met Arg Lys Leu Phe Ile Gln
                405                 410                 415

Arg Ala Lys Lys Ile Asp Lys Ile Ser Arg Ile Gly Phe Pro Met Ala
```

420 425 430

Phe Leu Ile Phe Asn Met Phe Tyr Trp Ile Ile Tyr Lys Ile Val Arg
435 440 445

Arg Glu Asp Val His Asn Gln
450 455

<210> 53
<211> 31
<212> PRT
<213> Artificial Sequence

<220>
<223> C-terminal amino acids of GABAR1

<400> 53

Ile Asp Arg Leu Ser Arg Ile Ala Phe Pro Leu Leu Phe Gly Ile Phe
1 5 10 15

Asn Leu Val Tyr Trp Ala Thr Tyr Leu Asn Arg Glu Pro Gln Leu
20 25 30

<210> 54
<211> 22
<212> PRT
<213> Artificial Sequence

<220>
<223> Amino acid residues 260-281 of human CHRNA7

<400> 54

Glu Lys Ile Ser Leu Gly Ile Thr Val Leu Leu Ser Leu Thr Val Phe
1 5 10 15

Met Leu Leu Val Ala Glu
20

<210> 55
<211> 23
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic polypeptide sequence

<400> 55

Pro Ala Lys Ile Gly Leu Gly Ile Thr Val Leu Leu Ser Leu Thr Thr
1 5 10 15

Phe Met Ser Gly Val Ala Asn
20

<210> 56
<211> 1780
<212> DNA
<213> Homo sapiens

<400> 56
atgttgtcaa gtgtaatggc tcccctgtgg gcctgcatcc tggtggctgc aggaattcta 60

gccacagata cacatcatcc ccaggattct gctctgtatc atctcagcaa gcagctatta 120

cagaaatatc ataaagaagt gagacctgtt tacaactgga ccaaggccac cacagtctac 180

ctggacctgt tcgtccatgc tatattggat gtggatgcag agaatcaaat attaaagaca 240

agtgtatggt accaagaggt ctggaatgat gaatttttat cctggaactc cagcatgttt 300

gatgagatta gagagatctc cctacctcta agtgccatct gggcccccga tatcatcatc 360

aatgagtttg tggacattga aagataccct gaccttccct atgtttatgt gaactcatct 420

gggaccattg agaactataa gcccatccag gtggtctctg cgtgcagttt agagacatat 480

gcttttccat ttgatgtcca gaattgcagc ctgaccttca agagcattct gcatacagtg 540

gaagacgtag acctggcctt tctgaggagc ccagaagaca ttcagcatga caaaaaggcg 600

tttttgaatg acagtgagtg ggaacttcta tctgtgtcct ccacatacag catcctgcag 660

agcagcgctg gaggatttgc acagattcag tttaatgtgg tgatgcgcag gcacccccctg 720

gtctatgtcg tgagtctgct gattcctagc atctttctca tgctggtgga cctggggagc 780

ttctacctgc cacccaactg ccgagccagg attgtgttca agaccagtgt gctggtgggc 840

tacaccgtct tcagggtcaa catgtccaac caggtgccac ggagtgtagg gagcacccct 900

ctgattgggc acttcttcac catctgcatg gccttcttgg ttctcagctt agctaagtcc 960

atcgtgttgg tcaaattcct ccatgatgag cagcgtggtg gacaggagca gcccttcttg 1020

tgccttcgag gggacaccga tgctgacagg cctagagtgg aacccagggc ccaacgtgct 1080

gtggtaacag agtcctcgct gtatggagag cacctggccc agccaggaac cctgaaggaa 1140

gtctggtcgc agcttcaatc tatcagcaac tacctccaaa ctcaggacca gacagaccaa 1200

caggaggcag agtggctggt cctcctgtcc cgctttgacc gactgctctt ccaaagctac 1260

cttttcatgc tggggatcta caccatcact ctgtgctccc tctgggcact gtggggcggc 1320

gtgtgaagac tgaagtgttc ttcagtaatt gtgctggcac ttaggagaga gaggaggggg 1380

aataatagtg ggttaaaaag ctttctgggt cgggtgtggt ggttcttgcc tatagtccca 1440

gtgctttggg aggccatagc aggaggattg cttgagccca ggagttcgag accagccaga 1500

gcaacatagt gagaccacat ctctaccagt aaataaataa ataaataaat aaataaataa 1560

ataaataaat agctgggcat agtggctcat gcctgtactc tcagctactt gggaggttga 1620

ggtgggagga ttgcttgagc ccaggatttc aaggctgcag tgagccatga ttgcaccact 1680

gcaccccagc ctgggtgaca gagcaagacc ctgtctcaaa aaaaataaaa taaaaggctt 1740

tctgccttca aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa 1780

<210> 57
<211> 441
<212> PRT
<213> Homo sapiens

<400> 57

Met Leu Ser Ser Val Met Ala Pro Leu Trp Ala Cys Ile Leu Val Ala
1 5 10 15

Ala Gly Ile Leu Ala Thr Asp Thr His His Pro Gln Asp Ser Ala Leu
20 25 30

Tyr His Leu Ser Lys Gln Leu Leu Gln Lys Tyr His Lys Glu Val Arg
35 40 45

Pro Val Tyr Asn Trp Thr Lys Ala Thr Thr Val Tyr Leu Asp Leu Phe
50 55 60

Val His Ala Ile Leu Asp Val Asp Ala Glu Asn Gln Ile Leu Lys Thr
65 70 75 80

Ser Val Trp Tyr Gln Glu Val Trp Asn Asp Glu Phe Leu Ser Trp Asn
85 90 95

```
Ser Ser Met Phe Asp Glu Ile Arg Glu Ile Ser Leu Pro Leu Ser Ala
            100                 105                 110

Ile Trp Ala Pro Asp Ile Ile Ile Asn Glu Phe Val Asp Ile Glu Arg
        115                 120                 125

Tyr Pro Asp Leu Pro Tyr Val Tyr Val Asn Ser Ser Gly Thr Ile Glu
    130                 135                 140

Asn Tyr Lys Pro Ile Gln Val Val Ser Ala Cys Ser Leu Glu Thr Tyr
145                 150                 155                 160

Ala Phe Pro Phe Asp Val Gln Asn Cys Ser Leu Thr Phe Lys Ser Ile
                165                 170                 175

Leu His Thr Val Glu Asp Val Asp Leu Ala Phe Leu Arg Ser Pro Glu
            180                 185                 190

Asp Ile Gln His Asp Lys Lys Ala Phe Leu Asn Asp Ser Glu Trp Glu
        195                 200                 205

Leu Leu Ser Val Ser Ser Thr Tyr Ser Ile Leu Gln Ser Ser Ala Gly
    210                 215                 220

Gly Phe Ala Gln Ile Gln Phe Asn Val Val Met Arg Arg His Pro Leu
225                 230                 235                 240

Val Tyr Val Val Ser Leu Leu Ile Pro Ser Ile Phe Leu Met Leu Val
                245                 250                 255

Asp Leu Gly Ser Phe Tyr Leu Pro Pro Asn Cys Arg Ala Arg Ile Val
            260                 265                 270

Phe Lys Thr Ser Val Leu Val Gly Tyr Thr Val Phe Arg Val Asn Met
        275                 280                 285

Ser Asn Gln Val Pro Arg Ser Val Gly Ser Thr Pro Leu Ile Gly His
    290                 295                 300

Phe Phe Thr Ile Cys Met Ala Phe Leu Val Leu Ser Leu Ala Lys Ser
```

305 310 315 320

Ile Val Leu Val Lys Phe Leu His Asp Glu Gln Arg Gly Gly Gln Glu
325 330 335

Gln Pro Phe Leu Cys Leu Arg Gly Asp Thr Asp Ala Asp Arg Pro Arg
340 345 350

Val Glu Pro Arg Ala Gln Arg Ala Val Val Thr Glu Ser Ser Leu Tyr
355 360 365

Gly Glu His Leu Ala Gln Pro Gly Thr Leu Lys Glu Val Trp Ser Gln
370 375 380

Leu Gln Ser Ile Ser Asn Tyr Leu Gln Thr Gln Asp Gln Thr Asp Gln
385 390 395 400

Gln Glu Ala Glu Trp Leu Val Leu Leu Ser Arg Phe Asp Arg Leu Leu
405 410 415

Phe Gln Ser Tyr Leu Phe Met Leu Gly Ile Tyr Thr Ile Thr Leu Cys
420 425 430

Ser Leu Trp Ala Leu Trp Gly Gly Val
435 440

<210> 58
<211> 439
<212> PRT
<213> Artificial Sequence

<220>
<223> synthetic sequence of chimeric LGIC

<400> 58

Met Arg Cys Ser Pro Gly Gly Val Trp Leu Ala Leu Ala Ala Ser Leu
1 5 10 15

Leu His Val Ser Leu Gln Gly Glu Phe Gln Arg Lys Leu Tyr Lys Glu
20 25 30

Leu Val Lys Asn Tyr Asn Pro Leu Glu Arg Pro Val Ala Asn Asp Ser

```
        35                  40                  45

Gln Pro Leu Thr Val Tyr Phe Ser Leu Ser Leu Leu Gln Ile Met Asp
    50                  55                  60

Val Asp Glu Lys Asn Gln Val Leu Thr Thr Asn Ile Trp Leu Gln Met
65                  70                  75                  80

Ser Trp Thr Asp His Tyr Leu Gln Trp Asn Val Ser Glu Tyr Pro Gly
                85                  90                  95

Val Lys Thr Val Arg Phe Pro Asp Gly Gln Ile Trp Lys Pro Asp Ile
            100                 105                 110

Leu Leu Tyr Asn Ser Ala Asp Glu Arg Phe Asp Ala Thr Phe His Thr
        115                 120                 125

Asn Val Asp Val Asn Ser Ser Gly His Cys Gln Tyr Leu Pro Pro Gly
    130                 135                 140

Ile Phe Lys Ser Ser Cys Pro Met Asp Leu Lys Asn Phe Pro Met Asp
145                 150                 155                 160

Val Gln Thr Cys Lys Leu Lys Phe Gly Ser Trp Asp Tyr Gly Gly Trp
                165                 170                 175

Ser Leu Asp Leu Gln Met Gln Glu Ala Asp Ile Ser Gly Tyr Ile Pro
            180                 185                 190

Asn Gly Glu Trp Asp Leu Val Gly Ile Pro Gly Lys Arg Ser Glu Arg
        195                 200                 205

Phe Tyr Glu Cys Cys Lys Glu Pro Tyr Pro Asp Val Thr Phe Thr Val
    210                 215                 220

Thr Met Arg Arg Arg Met Gly Tyr Tyr Leu Ile Gln Met Tyr Ile Pro
225                 230                 235                 240

Ser Leu Leu Ile Val Ile Leu Ser Trp Ile Ser Phe Trp Ile Asn Met
                245                 250                 255
```

```
Asp Ala Ala Pro Ala Arg Val Gly Leu Gly Ile Thr Thr Val Leu Thr
            260                 265                 270

Met Thr Thr Gln Ser Ser Gly Ser Arg Ala Ser Leu Pro Lys Val Ser
        275                 280                 285

Tyr Val Lys Ala Ile Asp Ile Trp Met Ala Val Cys Leu Leu Phe Val
    290                 295                 300

Phe Ser Ala Leu Leu Glu Tyr Ala Ala Val Asn Phe Val Ser Arg Gln
305                 310                 315                 320

His Lys Glu Leu Leu Arg Phe Arg Arg Lys Arg Arg His His Lys Ser
                325                 330                 335

Pro Met Leu Asn Leu Phe Gln Glu Asp Glu Ala Gly Glu Gly Arg Phe
            340                 345                 350

Asn Phe Ser Ala Tyr Gly Met Gly Pro Ala Cys Leu Gln Ala Lys Asp
        355                 360                 365

Gly Ile Ser Val Lys Gly Ala Asn Asn Ser Asn Thr Thr Asn Pro Pro
    370                 375                 380

Pro Ala Pro Ser Lys Ser Pro Glu Glu Met Arg Lys Leu Phe Ile Gln
385                 390                 395                 400

Arg Ala Lys Lys Ile Asp Lys Ile Ser Arg Ile Gly Phe Pro Met Ala
                405                 410                 415

Phe Leu Ile Phe Asn Met Phe Tyr Trp Ile Ile Tyr Lys Ile Val Arg
            420                 425                 430

Arg Glu Asp Val His Asn Gln
        435
```

<210> 59
<211> 439
<212> PRT
<213> Artificial Sequence

<220>
<223> synthetic sequence of chimeric LGIC

<400> 59

Met Arg Cys Ser Pro Gly Gly Val Trp Leu Ala Leu Ala Ala Ser Leu
1   5   10   15

Leu His Val Ser Leu Gln Gly Glu Phe Gln Arg Lys Leu Tyr Lys Glu
            20   25   30

Leu Val Lys Asn Tyr Asn Pro Leu Glu Arg Pro Val Ala Asn Asp Ser
        35   40   45

Gln Pro Leu Thr Val Tyr Phe Ser Leu Ser Leu Leu Gln Ile Met Asp
    50   55   60

Val Asp Glu Lys Asn Gln Val Leu Thr Thr Asn Ile Trp Leu Gln Met
65   70   75   80

Ser Trp Thr Asp His Tyr Leu Gln Trp Asn Val Ser Glu Tyr Pro Gly
                85   90   95

Val Lys Thr Val Arg Phe Pro Asp Gly Gln Ile Trp Lys Pro Asp Ile
            100   105   110

Leu Leu Tyr Asn Ser Ala Asp Glu Arg Phe Asp Ala Thr Phe His Thr
        115   120   125

Asn Val Ser Val Asn Ser Ser Gly His Cys Gln Tyr Leu Pro Pro Gly
    130   135   140

Ile Phe Lys Ser Ser Cys Pro Met Asp Leu Lys Asn Phe Pro Met Asp
145   150   155   160

Val Gln Thr Cys Lys Leu Lys Phe Gly Ser Trp Asp Tyr Gly Gly Trp
                165   170   175

Ser Leu Asp Leu Gln Met Gln Glu Ala Asp Ile Ser Gly Tyr Ile Pro
            180   185   190

Asn Gly Glu Trp Asp Leu Val Gly Ile Pro Gly Lys Arg Ser Glu Arg

```
        195                 200                 205

Phe Tyr Glu Cys Cys Lys Glu Pro Tyr Pro Asp Val Thr Phe Thr Val
    210                 215                 220

Thr Met Arg Arg Arg Met Gly Tyr Tyr Leu Ile Gln Met Tyr Ile Pro
225                 230                 235                 240

Ser Leu Leu Ile Val Ile Leu Ser Trp Ile Ser Phe Trp Ile Asn Met
                245                 250                 255

Asp Ala Ala Pro Ala Arg Val Gly Leu Gly Ile Thr Thr Val Leu Thr
            260                 265                 270

Met Thr Thr Gln Ser Ser Gly Ser Arg Ala Ser Leu Pro Lys Val Ser
        275                 280                 285

Tyr Val Lys Ala Ile Asp Ile Trp Met Ala Val Cys Leu Leu Phe Val
    290                 295                 300

Phe Ser Ala Leu Leu Glu Tyr Ala Ala Val Asn Phe Val Ser Arg Gln
305                 310                 315                 320

His Lys Glu Leu Leu Arg Phe Arg Arg Lys Arg Arg His His Lys Ser
                325                 330                 335

Pro Met Leu Asn Leu Phe Gln Glu Asp Glu Ala Gly Glu Gly Arg Phe
            340                 345                 350

Asn Phe Ser Ala Tyr Gly Met Gly Pro Ala Cys Leu Gln Ala Lys Asp
        355                 360                 365

Gly Ile Ser Val Lys Gly Ala Asn Asn Ser Asn Thr Thr Asn Pro Pro
    370                 375                 380

Pro Ala Pro Ser Lys Ser Pro Glu Glu Met Arg Lys Leu Phe Ile Gln
385                 390                 395                 400

Arg Ala Lys Lys Ile Asp Lys Ile Ser Arg Ile Gly Phe Pro Met Ala
                405                 410                 415
```

Phe Leu Ile Phe Asn Met Phe Tyr Trp Ile Ile Tyr Lys Ile Val Arg
420 425 430

Arg Glu Asp Val His Asn Gln
435

<210> 60
<211> 439
<212> PRT
<213> Artificial Sequence

<220>
<223> synthetic sequence of chimeric LGIC

<400> 60

Met Arg Cys Ser Pro Gly Gly Val Trp Leu Ala Leu Ala Ala Ser Leu
1 5 10 15

Leu His Val Ser Leu Gln Gly Glu Phe Gln Arg Lys Leu Tyr Lys Glu
20 25 30

Leu Val Lys Asn Tyr Asn Pro Leu Glu Arg Pro Val Ala Asn Asp Ser
35 40 45

Gln Pro Leu Thr Val Tyr Phe Ser Leu Ser Leu Leu Gln Ile Met Asp
50 55 60

Val Asp Glu Lys Asn Gln Val Leu Thr Thr Asn Ile Trp Leu Gln Met
65 70 75 80

Ser Trp Thr Asp His Tyr Leu Gln Trp Asn Val Ser Glu Tyr Pro Gly
85 90 95

Val Lys Thr Val Arg Phe Pro Asp Gly Gln Ile Trp Lys Pro Asp Ile
100 105 110

Leu Leu Tyr Asn Ser Ala Asp Glu Arg Phe Asp Ala Thr Phe His Thr
115 120 125

Asn Val Thr Val Asn Ser Ser Gly His Cys Gln Tyr Leu Pro Pro Gly
130 135 140

```
Ile Phe Lys Ser Ser Cys Pro Met Asp Leu Lys Asn Phe Pro Met Asp
145                 150                 155                 160

Val Gln Thr Cys Lys Leu Lys Phe Gly Ser Trp Asp Tyr Gly Gly Trp
                165                 170                 175

Ser Leu Asp Leu Gln Met Gln Glu Ala Asp Ile Ser Gly Tyr Ile Pro
            180                 185                 190

Asn Gly Glu Trp Asp Leu Val Gly Ile Pro Gly Lys Arg Ser Glu Arg
        195                 200                 205

Phe Tyr Glu Cys Cys Lys Glu Pro Tyr Pro Asp Val Thr Phe Thr Val
    210                 215                 220

Thr Met Arg Arg Arg Met Gly Tyr Tyr Leu Ile Gln Met Tyr Ile Pro
225                 230                 235                 240

Ser Leu Leu Ile Val Ile Leu Ser Trp Ile Ser Phe Trp Ile Asn Met
                245                 250                 255

Asp Ala Ala Pro Ala Arg Val Gly Leu Gly Ile Thr Thr Val Leu Thr
            260                 265                 270

Met Thr Thr Gln Ser Ser Gly Ser Arg Ala Ser Leu Pro Lys Val Ser
        275                 280                 285

Tyr Val Lys Ala Ile Asp Ile Trp Met Ala Val Cys Leu Leu Phe Val
    290                 295                 300

Phe Ser Ala Leu Leu Glu Tyr Ala Ala Val Asn Phe Val Ser Arg Gln
305                 310                 315                 320

His Lys Glu Leu Leu Arg Phe Arg Arg Lys Arg Arg His His Lys Ser
                325                 330                 335

Pro Met Leu Asn Leu Phe Gln Glu Asp Glu Ala Gly Glu Gly Arg Phe
            340                 345                 350

Asn Phe Ser Ala Tyr Gly Met Gly Pro Ala Cys Leu Gln Ala Lys Asp
```

355 360 365

Gly Ile Ser Val Lys Gly Ala Asn Asn Ser Asn Thr Thr Asn Pro Pro
370 375 380

Pro Ala Pro Ser Lys Ser Pro Glu Glu Met Arg Lys Leu Phe Ile Gln
385 390 395 400

Arg Ala Lys Lys Ile Asp Lys Ile Ser Arg Ile Gly Phe Pro Met Ala
405 410 415

Phe Leu Ile Phe Asn Met Phe Tyr Trp Ile Ile Tyr Lys Ile Val Arg
420 425 430

Arg Glu Asp Val His Asn Gln
435

<210> 61
<211> 439
<212> PRT
<213> Artificial Sequence

<220>
<223> synthetic sequence of chimeric LGIC

<400> 61

Met Arg Cys Ser Pro Gly Gly Val Trp Leu Ala Leu Ala Ala Ser Leu
1 5 10 15

Leu His Val Ser Leu Gln Gly Glu Phe Gln Arg Lys Leu Tyr Lys Glu
20 25 30

Leu Val Lys Asn Tyr Asn Pro Leu Glu Arg Pro Val Ala Asn Asp Ser
35 40 45

Gln Pro Leu Thr Val Tyr Phe Ser Leu Ser Leu Leu Gln Ile Met Asp
50 55 60

Val Asp Glu Lys Asn Gln Val Leu Thr Thr Asn Ile Trp Leu Gln Met
65 70 75 80

Ser Trp Thr Asp His Tyr Leu Gln Trp Asn Val Ser Glu Tyr Pro Gly

```
                85                  90                  95

Val Lys Thr Val Arg Phe Pro Asp Gly Gln Ile Trp Lys Pro Asp Ile
            100                 105                 110

Leu Leu Asp Asn Ser Ala Asp Glu Arg Phe Asp Ala Thr Phe His Thr
        115                 120                 125

Asn Val Glu Val Asn Ser Ser Gly His Cys Gln Tyr Leu Pro Pro Gly
    130                 135                 140

Ile Phe Lys Ser Ser Cys Pro Met Asp Leu Lys Asn Phe Pro Met Asp
145                 150                 155                 160

Val Gln Thr Cys Lys Leu Lys Phe Gly Ser Trp Ser Tyr Gly Gly Trp
                165                 170                 175

Ser Leu Asp Leu Gln Met Gln Glu Ala Asp Ile Ser Gly Tyr Ile Pro
            180                 185                 190

Asn Gly Glu Trp Asp Leu Val Gly Ile Pro Gly Lys Arg Ser Glu Arg
        195                 200                 205

Phe Tyr Glu Cys Cys Lys Glu Pro Tyr Pro Asp Val Thr Phe Thr Val
    210                 215                 220

Thr Met Arg Arg Arg Met Gly Tyr Tyr Leu Ile Gln Met Tyr Ile Pro
225                 230                 235                 240

Ser Leu Leu Ile Val Ile Leu Ser Trp Ile Ser Phe Trp Ile Asn Met
                245                 250                 255

Asp Ala Ala Pro Ala Arg Val Gly Leu Gly Ile Thr Thr Val Leu Thr
            260                 265                 270

Met Thr Thr Gln Ser Ser Gly Ser Arg Ala Ser Leu Pro Lys Val Ser
        275                 280                 285

Tyr Val Lys Ala Ile Asp Ile Trp Met Ala Val Cys Leu Leu Phe Val
    290                 295                 300
```

```
Phe Ser Ala Leu Leu Glu Tyr Ala Ala Val Asn Phe Val Ser Arg Gln
305                 310                 315                 320


His Lys Glu Leu Leu Arg Phe Arg Arg Lys Arg Arg His His Lys Ser
                325                 330                 335


Pro Met Leu Asn Leu Phe Gln Glu Asp Glu Ala Gly Glu Gly Arg Phe
            340                 345                 350


Asn Phe Ser Ala Tyr Gly Met Gly Pro Ala Cys Leu Gln Ala Lys Asp
        355                 360                 365


Gly Ile Ser Val Lys Gly Ala Asn Asn Ser Asn Thr Thr Asn Pro Pro
    370                 375                 380


Pro Ala Pro Ser Lys Ser Pro Glu Glu Met Arg Lys Leu Phe Ile Gln
385                 390                 395                 400


Arg Ala Lys Lys Ile Asp Lys Ile Ser Arg Ile Gly Phe Pro Met Ala
                405                 410                 415


Phe Leu Ile Phe Asn Met Phe Tyr Trp Ile Ile Tyr Lys Ile Val Arg
            420                 425                 430


Arg Glu Asp Val His Asn Gln
        435


<210>  62
<211>  439
<212>  PRT
<213>  Artificial Sequence

<220>
<223>  synthetic sequence of chimeric LGIC

<400>  62

Met Arg Cys Ser Pro Gly Gly Val Trp Leu Ala Leu Ala Ala Ser Leu
1               5                   10                  15


Leu His Val Ser Leu Gln Gly Glu Phe Gln Arg Lys Leu Tyr Lys Glu
            20                  25                  30
```

```
Leu Val Lys Asn Tyr Asn Pro Leu Glu Arg Pro Val Ala Asn Asp Ser
        35                  40                  45

Gln Pro Leu Thr Val Tyr Phe Ser Leu Ser Leu Leu Gln Ile Met Asp
    50                  55                  60

Val Asp Glu Lys Asn Gln Val Leu Thr Thr Asn Ile Trp Leu Gln Met
65                  70                  75                  80

Ser Trp Thr Asp His Tyr Leu Gln Trp Asn Val Ser Glu Tyr Pro Gly
                85                  90                  95

Val Lys Thr Val Arg Phe Pro Asp Gly Gln Ile Trp Lys Pro Asp Ile
            100                 105                 110

Leu Leu Asp Asn Ser Ala Asp Glu Arg Phe Asp Ala Thr Phe His Thr
        115                 120                 125

Asn Val Gln Val Asn Ser Ser Gly His Cys Gln Tyr Leu Pro Pro Gly
    130                 135                 140

Ile Phe Lys Ser Ser Cys Pro Met Asp Leu Lys Asn Phe Pro Met Asp
145                 150                 155                 160

Val Gln Thr Cys Lys Leu Lys Phe Gly Ser Trp Ser Tyr Gly Gly Trp
                165                 170                 175

Ser Leu Asp Leu Gln Met Gln Glu Ala Asp Ile Ser Gly Tyr Ile Pro
            180                 185                 190

Asn Gly Glu Trp Asp Leu Val Gly Ile Pro Gly Lys Arg Ser Glu Arg
        195                 200                 205

Phe Tyr Glu Cys Cys Lys Glu Pro Tyr Pro Asp Val Thr Phe Thr Val
    210                 215                 220

Thr Met Arg Arg Arg Met Gly Tyr Tyr Leu Ile Gln Met Tyr Ile Pro
225                 230                 235                 240

Ser Leu Leu Ile Val Ile Leu Ser Trp Ile Ser Phe Trp Ile Asn Met
```

```
                245                 250                 255

Asp Ala Ala Pro Ala Arg Val Gly Leu Gly Ile Thr Thr Val Leu Thr
            260                 265                 270

Met Thr Thr Gln Ser Ser Gly Ser Arg Ala Ser Leu Pro Lys Val Ser
        275                 280                 285

Tyr Val Lys Ala Ile Asp Ile Trp Met Ala Val Cys Leu Leu Phe Val
    290                 295                 300

Phe Ser Ala Leu Leu Glu Tyr Ala Ala Val Asn Phe Val Ser Arg Gln
305                 310                 315                 320

His Lys Glu Leu Leu Arg Phe Arg Arg Lys Arg Arg His His Lys Ser
                325                 330                 335

Pro Met Leu Asn Leu Phe Gln Glu Asp Glu Ala Gly Glu Gly Arg Phe
            340                 345                 350

Asn Phe Ser Ala Tyr Gly Met Gly Pro Ala Cys Leu Gln Ala Lys Asp
        355                 360                 365

Gly Ile Ser Val Lys Gly Ala Asn Asn Ser Asn Thr Thr Asn Pro Pro
    370                 375                 380

Pro Ala Pro Ser Lys Ser Pro Glu Glu Met Arg Lys Leu Phe Ile Gln
385                 390                 395                 400

Arg Ala Lys Lys Ile Asp Lys Ile Ser Arg Ile Gly Phe Pro Met Ala
                405                 410                 415

Phe Leu Ile Phe Asn Met Phe Tyr Trp Ile Ile Tyr Lys Ile Val Arg
            420                 425                 430

Arg Glu Asp Val His Asn Gln
        435

<210>  63
<211>  439
<212>  PRT
```

<213> Artificial Sequence

<220>
<223> synthetic sequence of chimeric LGIC

<400> 63

```
Met Arg Cys Ser Pro Gly Gly Val Trp Leu Ala Leu Ala Ala Ser Leu
1               5                  10                  15


Leu His Val Ser Leu Gln Gly Glu Phe Gln Arg Lys Leu Tyr Lys Glu
            20                  25                  30


Leu Val Lys Asn Tyr Asn Pro Leu Glu Arg Pro Val Ala Asn Asp Ser
        35                  40                  45


Gln Pro Leu Thr Val Tyr Phe Ser Leu Ser Leu Leu Gln Ile Met Asp
    50                  55                  60


Val Asp Glu Lys Asn Gln Val Leu Thr Thr Asn Ile Trp Leu Gln Met
65                  70                  75                  80


Ser Trp Thr Asp His Tyr Leu Gln Trp Asn Val Ser Glu Tyr Pro Gly
                85                  90                  95


Val Lys Thr Val Arg Phe Pro Asp Gly Gln Ile Trp Lys Pro Asp Ile
            100                 105                 110


Leu Leu Asp Asn Ser Ala Asp Glu Arg Phe Asp Ala Thr Phe His Thr
        115                 120                 125


Asn Val Leu Val Asn Ser Ser Gly His Cys Gln Tyr Leu Pro Pro Gly
    130                 135                 140


Ile Phe Lys Ser Ser Cys Pro Met Asp Leu Lys Asn Phe Pro Met Asp
145                 150                 155                 160


Val Gln Thr Cys Lys Leu Lys Phe Gly Thr Trp Ser Tyr Gly Gly Trp
                165                 170                 175


Ser Leu Asp Leu Gln Met Gln Glu Ala Asp Ile Ser Gly Tyr Ile Pro
            180                 185                 190
```

```
Asn Gly Glu Trp Asp Leu Val Gly Ile Pro Gly Lys Arg Ser Glu Arg
        195                 200                 205

Phe Tyr Glu Cys Cys Lys Glu Pro Tyr Pro Asp Val Thr Phe Thr Val
    210                 215                 220

Thr Met Arg Arg Arg Met Gly Tyr Tyr Leu Ile Gln Met Tyr Ile Pro
225                 230                 235                 240

Ser Leu Leu Ile Val Ile Leu Ser Trp Ile Ser Phe Trp Ile Asn Met
                245                 250                 255

Asp Ala Ala Pro Ala Arg Val Gly Leu Gly Ile Thr Thr Val Leu Thr
            260                 265                 270

Met Thr Thr Gln Ser Ser Gly Ser Arg Ala Ser Leu Pro Lys Val Ser
        275                 280                 285

Tyr Val Lys Ala Ile Asp Ile Trp Met Ala Val Cys Leu Leu Phe Val
    290                 295                 300

Phe Ser Ala Leu Leu Glu Tyr Ala Ala Val Asn Phe Val Ser Arg Gln
305                 310                 315                 320

His Lys Glu Leu Leu Arg Phe Arg Arg Lys Arg Arg His His Lys Ser
                325                 330                 335

Pro Met Leu Asn Leu Phe Gln Glu Asp Glu Ala Gly Glu Gly Arg Phe
            340                 345                 350

Asn Phe Ser Ala Tyr Gly Met Gly Pro Ala Cys Leu Gln Ala Lys Asp
        355                 360                 365

Gly Ile Ser Val Lys Gly Ala Asn Asn Ser Asn Thr Thr Asn Pro Pro
    370                 375                 380

Pro Ala Pro Ser Lys Ser Pro Glu Glu Met Arg Lys Leu Phe Ile Gln
385                 390                 395                 400

Arg Ala Lys Lys Ile Asp Lys Ile Ser Arg Ile Gly Phe Pro Met Ala
```

405 410 415

Phe Leu Ile Phe Asn Met Phe Tyr Trp Ile Ile Tyr Lys Ile Val Arg
420 425 430

Arg Glu Asp Val His Asn Gln
435

<210> 64
<211> 439
<212> PRT
<213> Artificial Sequence

<220>
<223> synthetic sequence of chimeric LGIC

<400> 64

Met Arg Cys Ser Pro Gly Gly Val Trp Leu Ala Leu Ala Ala Ser Leu
1 5 10 15

Leu His Val Ser Leu Gln Gly Glu Phe Gln Arg Lys Leu Tyr Lys Glu
20 25 30

Leu Val Lys Asn Tyr Asn Pro Leu Glu Arg Pro Val Ala Asn Asp Ser
35 40 45

Gln Pro Leu Thr Val Tyr Phe Ser Leu Ser Leu Leu Gln Ile Met Asp
50 55 60

Val Asp Glu Lys Asn Gln Val Leu Thr Thr Asn Ile Trp Leu Gln Met
65 70 75 80

Ser Trp Thr Asp His Tyr Leu Gln Trp Asn Val Ser Glu Tyr Pro Gly
85 90 95

Val Lys Thr Val Arg Phe Pro Asp Gly Gln Ile Trp Lys Pro Asp Ile
100 105 110

Leu Leu Tyr Asn Ser Ala Asp Glu Arg Phe Asp Ala Thr Phe His Thr
115 120 125

Asn Val Leu Val Asn Ser Ser Gly His Cys Gln Ile Leu Pro Pro Gly

```
    130                 135                 140

Ile Phe Lys Ser Ser Cys Pro Met Asp Leu Lys Asn Phe Pro Met Asp
145                 150                 155                 160

Val Gln Thr Cys Lys Leu Lys Phe Gly Ser Trp Ser Tyr Gly Gly Trp
                165                 170                 175

Ser Leu Asp Leu Gln Met Gln Glu Ala Asp Ile Ser Gly Tyr Ile Pro
            180                 185                 190

Asn Gly Glu Trp Asp Leu Val Gly Ile Pro Gly Lys Arg Ser Glu Arg
        195                 200                 205

Phe Tyr Glu Cys Cys Lys Glu Pro Tyr Pro Asp Val Thr Phe Thr Val
    210                 215                 220

Thr Met Arg Arg Arg Met Gly Tyr Tyr Leu Ile Gln Met Tyr Ile Pro
225                 230                 235                 240

Ser Leu Leu Ile Val Ile Leu Ser Trp Ile Ser Phe Trp Ile Asn Met
                245                 250                 255

Asp Ala Ala Pro Ala Arg Val Gly Leu Gly Ile Thr Thr Val Leu Thr
            260                 265                 270

Met Thr Thr Gln Ser Ser Gly Ser Arg Ala Ser Leu Pro Lys Val Ser
        275                 280                 285

Tyr Val Lys Ala Ile Asp Ile Trp Met Ala Val Cys Leu Leu Phe Val
    290                 295                 300

Phe Ser Ala Leu Leu Glu Tyr Ala Ala Val Asn Phe Val Ser Arg Gln
305                 310                 315                 320

His Lys Glu Leu Leu Arg Phe Arg Arg Lys Arg Arg His His Lys Ser
                325                 330                 335

Pro Met Leu Asn Leu Phe Gln Glu Asp Glu Ala Gly Glu Gly Arg Phe
            340                 345                 350
```

Asn Phe Ser Ala Tyr Gly Met Gly Pro Ala Cys Leu Gln Ala Lys Asp
355 360 365

Gly Ile Ser Val Lys Gly Ala Asn Asn Ser Asn Thr Thr Asn Pro Pro
370 375 380

Pro Ala Pro Ser Lys Ser Pro Glu Glu Met Arg Lys Leu Phe Ile Gln
385 390 395 400

Arg Ala Lys Lys Ile Asp Lys Ile Ser Arg Ile Gly Phe Pro Met Ala
405 410 415

Phe Leu Ile Phe Asn Met Phe Tyr Trp Ile Ile Tyr Lys Ile Val Arg
420 425 430

Arg Glu Asp Val His Asn Gln
435

<210> 65
<211> 439
<212> PRT
<213> Artificial Sequence

<220>
<223> synthetic sequence of chimeric LGIC

<400> 65

Met Arg Cys Ser Pro Gly Gly Val Trp Leu Ala Leu Ala Ala Ser Leu
1 5 10 15

Leu His Val Ser Leu Gln Gly Glu Phe Gln Arg Lys Leu Tyr Lys Glu
20 25 30

Leu Val Lys Asn Tyr Asn Pro Leu Glu Arg Pro Val Ala Asn Asp Ser
35 40 45

Gln Pro Leu Thr Val Tyr Phe Ser Leu Ser Leu Leu Gln Ile Met Asp
50 55 60

Val Asp Glu Lys Asn Gln Val Leu Thr Thr Asn Ile Trp Leu Gln Met
65 70 75 80

```
Ser Trp Thr Asp His Tyr Leu Gln Trp Asn Val Ser Glu Tyr Pro Gly
                85                  90                  95

Val Lys Thr Val Phe Phe Pro Asp Gly Gln Ile Trp Lys Pro Asp Ile
            100                 105                 110

Leu Leu Tyr Asn Ser Ala Asp Glu Arg Phe Asp Ala Thr Phe His Thr
        115                 120                 125

Asn Val Gly Val Asn Ser Ser Gly His Cys Gln Tyr Leu Pro Pro Gly
    130                 135                 140

Ile Phe Lys Ser Ser Cys Pro Met Asp Leu Lys Asn Phe Pro Met Asp
145                 150                 155                 160

Val Gln Thr Cys Lys Leu Lys Phe Gly Ser Trp Ser Tyr Gly Gly Trp
                165                 170                 175

Ser Leu Asp Leu Gln Met Gln Glu Ala Asp Ile Ser Gly Tyr Ile Pro
            180                 185                 190

Asn Gly Glu Trp Asp Leu Val Gly Ile Pro Gly Lys Arg Ser Glu Arg
        195                 200                 205

Phe Tyr Glu Cys Cys Lys Glu Pro Tyr Pro Asp Val Thr Phe Thr Val
    210                 215                 220

Thr Met Arg Arg Arg Met Gly Tyr Tyr Leu Ile Gln Met Tyr Ile Pro
225                 230                 235                 240

Ser Leu Leu Ile Val Ile Leu Ser Trp Ile Ser Phe Trp Ile Asn Met
                245                 250                 255

Asp Ala Ala Pro Ala Arg Val Gly Leu Gly Ile Thr Thr Val Leu Thr
            260                 265                 270

Met Thr Thr Gln Ser Ser Gly Ser Arg Ala Ser Leu Pro Lys Val Ser
        275                 280                 285

Tyr Val Lys Ala Ile Asp Ile Trp Met Ala Val Cys Leu Leu Phe Val
```

290 295 300

Phe Ser Ala Leu Leu Glu Tyr Ala Ala Val Asn Phe Val Ser Arg Gln
305 310 315 320

His Lys Glu Leu Leu Arg Phe Arg Arg Lys Arg Arg His His Lys Ser
325 330 335

Pro Met Leu Asn Leu Phe Gln Glu Asp Glu Ala Gly Glu Gly Arg Phe
340 345 350

Asn Phe Ser Ala Tyr Gly Met Gly Pro Ala Cys Leu Gln Ala Lys Asp
355 360 365

Gly Ile Ser Val Lys Gly Ala Asn Asn Ser Asn Thr Thr Asn Pro Pro
370 375 380

Pro Ala Pro Ser Lys Ser Pro Glu Glu Met Arg Lys Leu Phe Ile Gln
385 390 395 400

Arg Ala Lys Lys Ile Asp Lys Ile Ser Arg Ile Gly Phe Pro Met Ala
405 410 415

Phe Leu Ile Phe Asn Met Phe Tyr Trp Ile Ile Tyr Lys Ile Val Arg
420 425 430

Arg Glu Asp Val His Asn Gln
435

<210> 66
<211> 439
<212> PRT
<213> Artificial Sequence

<220>
<223> synthetic sequence of chimeric LGIC

<400> 66

Met Arg Cys Ser Pro Gly Gly Val Trp Leu Ala Leu Ala Ala Ser Leu
1 5 10 15

Leu His Val Ser Leu Gln Gly Glu Phe Gln Arg Lys Leu Tyr Lys Glu

```
            20                  25                  30

Leu Val Lys Asn Tyr Asn Pro Leu Glu Arg Pro Val Ala Asn Asp Ser
        35                  40                  45

Gln Pro Leu Thr Val Tyr Phe Ser Leu Ser Leu Leu Gln Ile Met Asp
    50                  55                  60

Val Asp Glu Lys Asn Gln Val Leu Thr Thr Asn Ile Trp Leu Gln Met
65                  70                  75                  80

Ser Trp Thr Asp His Tyr Leu Gln Trp Asn Val Ser Glu Tyr Pro Gly
                85                  90                  95

Val Lys Thr Val Phe Phe Pro Asp Gly Gln Ile Trp Lys Pro Asp Ile
            100                 105                 110

Leu Leu Tyr Asn Ser Ala Asp Glu Arg Phe Asp Ala Thr Phe His Thr
        115                 120                 125

Asn Val Asp Val Asn Ser Ser Gly His Cys Gln Tyr Leu Pro Pro Gly
    130                 135                 140

Ile Phe Lys Ser Ser Cys Pro Met Asp Leu Lys Asn Phe Pro Met Asp
145                 150                 155                 160

Val Gln Thr Cys Lys Leu Lys Phe Gly Ser Trp Ser Tyr Gly Gly Trp
                165                 170                 175

Ser Leu Asp Leu Gln Met Gln Glu Ala Asp Ile Ser Gly Tyr Ile Pro
            180                 185                 190

Asn Gly Glu Trp Asp Leu Val Gly Ile Pro Gly Lys Arg Ser Glu Arg
        195                 200                 205

Phe Tyr Glu Cys Cys Lys Glu Pro Tyr Pro Asp Val Thr Phe Thr Val
    210                 215                 220

Thr Met Arg Arg Arg Met Gly Tyr Tyr Leu Ile Gln Met Tyr Ile Pro
225                 230                 235                 240
```

```
Ser Leu Leu Ile Val Ile Leu Ser Trp Ile Ser Phe Trp Ile Asn Met
                245                 250                 255

Asp Ala Ala Pro Ala Arg Val Gly Leu Gly Ile Thr Thr Val Leu Thr
            260                 265                 270

Met Thr Thr Gln Ser Ser Gly Ser Arg Ala Ser Leu Pro Lys Val Ser
        275                 280                 285

Tyr Val Lys Ala Ile Asp Ile Trp Met Ala Val Cys Leu Leu Phe Val
    290                 295                 300

Phe Ser Ala Leu Leu Glu Tyr Ala Ala Val Asn Phe Val Ser Arg Gln
305                 310                 315                 320

His Lys Glu Leu Leu Arg Phe Arg Arg Lys Arg Arg His His Lys Ser
                325                 330                 335

Pro Met Leu Asn Leu Phe Gln Glu Asp Glu Ala Gly Glu Gly Arg Phe
            340                 345                 350

Asn Phe Ser Ala Tyr Gly Met Gly Pro Ala Cys Leu Gln Ala Lys Asp
        355                 360                 365

Gly Ile Ser Val Lys Gly Ala Asn Asn Ser Asn Thr Thr Asn Pro Pro
    370                 375                 380

Pro Ala Pro Ser Lys Ser Pro Glu Glu Met Arg Lys Leu Phe Ile Gln
385                 390                 395                 400

Arg Ala Lys Lys Ile Asp Lys Ile Ser Arg Ile Gly Phe Pro Met Ala
                405                 410                 415

Phe Leu Ile Phe Asn Met Phe Tyr Trp Ile Ile Tyr Lys Ile Val Arg
            420                 425                 430

Arg Glu Asp Val His Asn Gln
        435
```

<210> 67

<211> 439
<212> PRT
<213> Artificial Sequence

<220>
<223> synthetic sequence of chimeric LGIC

<400> 67

Met Arg Cys Ser Pro Gly Gly Val Trp Leu Ala Leu Ala Ala Ser Leu
1 5 10 15

Leu His Val Ser Leu Gln Gly Glu Phe Gln Arg Lys Leu Tyr Lys Glu
20 25 30

Leu Val Lys Asn Tyr Asn Pro Leu Glu Arg Pro Val Ala Asn Asp Ser
35 40 45

Gln Pro Leu Thr Val Tyr Phe Ser Leu Ser Leu Leu Gln Ile Met Asp
50 55 60

Val Asp Glu Lys Asn Gln Val Leu Thr Thr Asn Ile Trp Leu Gln Met
65 70 75 80

Ser Trp Thr Asp His Tyr Leu Gln Trp Asn Val Ser Glu Tyr Pro Gly
85 90 95

Val Lys Thr Val Arg Phe Pro Asp Gly Gln Ile Trp Lys Pro Asp Ile
100 105 110

Leu Leu Glu Asn Ser Ala Asp Glu Arg Phe Asp Ala Thr Phe His Thr
115 120 125

Asn Val Leu Val Asn Ser Ser Gly His Cys Gln Tyr Leu Pro Pro Gly
130 135 140

Ile Phe Lys Ser Ser Cys Pro Met Asp Leu Lys Asn Phe Pro Met Asp
145 150 155 160

Val Gln Thr Cys Lys Leu Lys Phe Gly Ser Trp Ser Tyr Gly Gly Trp
165 170 175

Ser Leu Asp Leu Gln Met Gln Glu Ala Asp Ile Ser Gly Tyr Ile Pro

```
            180                 185                 190

Asn Gly Glu Trp Asp Leu Val Gly Ile Pro Gly Lys Arg Ser Glu Arg
        195                 200                 205

Phe Trp Glu Cys Cys Lys Glu Pro Tyr Pro Asp Val Thr Phe Thr Val
    210                 215                 220

Thr Met Arg Arg Arg Met Gly Tyr Tyr Leu Ile Gln Met Tyr Ile Pro
225                 230                 235                 240

Ser Leu Leu Ile Val Ile Leu Ser Trp Ile Ser Phe Trp Ile Asn Met
                245                 250                 255

Asp Ala Ala Pro Ala Arg Val Gly Leu Gly Ile Thr Thr Val Leu Thr
            260                 265                 270

Met Thr Thr Gln Ser Ser Gly Ser Arg Ala Ser Leu Pro Lys Val Ser
        275                 280                 285

Tyr Val Lys Ala Ile Asp Ile Trp Met Ala Val Cys Leu Leu Phe Val
    290                 295                 300

Phe Ser Ala Leu Leu Glu Tyr Ala Ala Val Asn Phe Val Ser Arg Gln
305                 310                 315                 320

His Lys Glu Leu Leu Arg Phe Arg Arg Lys Arg Arg His His Lys Ser
                325                 330                 335

Pro Met Leu Asn Leu Phe Gln Glu Asp Glu Ala Gly Glu Gly Arg Phe
            340                 345                 350

Asn Phe Ser Ala Tyr Gly Met Gly Pro Ala Cys Leu Gln Ala Lys Asp
        355                 360                 365

Gly Ile Ser Val Lys Gly Ala Asn Asn Ser Asn Thr Thr Asn Pro Pro
    370                 375                 380

Pro Ala Pro Ser Lys Ser Pro Glu Glu Met Arg Lys Leu Phe Ile Gln
385                 390                 395                 400
```

Arg Ala Lys Lys Ile Asp Lys Ile Ser Arg Ile Gly Phe Pro Met Ala
405 410 415

Phe Leu Ile Phe Asn Met Phe Tyr Trp Ile Ile Tyr Lys Ile Val Arg
420 425 430

Arg Glu Asp Val His Asn Gln
435

<210> 68
<211> 439
<212> PRT
<213> Artificial Sequence

<220>
<223> synthetic sequence of chimeric LGIC

<400> 68

Met Arg Cys Ser Pro Gly Gly Val Trp Leu Ala Leu Ala Ala Ser Leu
1 5 10 15

Leu His Val Ser Leu Gln Gly Glu Phe Gln Arg Lys Leu Tyr Lys Glu
20 25 30

Leu Val Lys Asn Tyr Asn Pro Leu Glu Arg Pro Val Ala Asn Asp Ser
35 40 45

Gln Pro Leu Thr Val Tyr Phe Ser Leu Ser Leu Leu Gln Ile Met Asp
50 55 60

Val Asp Glu Lys Asn Gln Val Leu Thr Thr Asn Ile Trp Leu Gln Met
65 70 75 80

Ser Trp Thr Asp His Tyr Leu Gln Trp Asn Val Ser Glu Tyr Pro Gly
85 90 95

Val Lys Thr Val Trp Phe Pro Asp Gly Gln Ile Trp Lys Pro Asp Ile
100 105 110

Leu Leu Tyr Asn Ser Ala Asp Glu Arg Phe Asp Ala Thr Phe His Thr
115 120 125

```
Asn Val Leu Val Asn Ser Ser Gly His Cys Gln Tyr Leu Pro Pro Gly
    130                 135                 140

Ile Phe Lys Ser Ser Cys Pro Met Asp Leu Lys Asn Phe Pro Met Asp
145                 150                 155                 160

Val Gln Thr Cys Lys Leu Lys Phe Gly Ser Trp Ser Tyr Gly Gly Trp
                165                 170                 175

Ser Leu Asp Leu Gln Met Gln Glu Ala Asp Ile Ser Gly Tyr Ile Pro
            180                 185                 190

Asn Gly Glu Trp Asp Leu Val Gly Ile Pro Gly Lys Arg Ser Glu Arg
        195                 200                 205

Phe Val Glu Cys Cys Lys Glu Pro Tyr Pro Asp Val Thr Phe Thr Val
    210                 215                 220

Thr Met Arg Arg Arg Met Gly Tyr Tyr Leu Ile Gln Met Tyr Ile Pro
225                 230                 235                 240

Ser Leu Leu Ile Val Ile Leu Ser Trp Ile Ser Phe Trp Ile Asn Met
                245                 250                 255

Asp Ala Ala Pro Ala Arg Val Gly Leu Gly Ile Thr Thr Val Leu Thr
            260                 265                 270

Met Thr Thr Gln Ser Ser Gly Ser Arg Ala Ser Leu Pro Lys Val Ser
        275                 280                 285

Tyr Val Lys Ala Ile Asp Ile Trp Met Ala Val Cys Leu Leu Phe Val
    290                 295                 300

Phe Ser Ala Leu Leu Glu Tyr Ala Ala Val Asn Phe Val Ser Arg Gln
305                 310                 315                 320

His Lys Glu Leu Leu Arg Phe Arg Arg Lys Arg Arg His His Lys Ser
                325                 330                 335

Pro Met Leu Asn Leu Phe Gln Glu Asp Glu Ala Gly Glu Gly Arg Phe
```

```
            340                 345                 350

Asn Phe Ser Ala Tyr Gly Met Gly Pro Ala Cys Leu Gln Ala Lys Asp
        355                 360                 365

Gly Ile Ser Val Lys Gly Ala Asn Asn Ser Asn Thr Thr Asn Pro Pro
    370                 375                 380

Pro Ala Pro Ser Lys Ser Pro Glu Glu Met Arg Lys Leu Phe Ile Gln
385                 390                 395                 400

Arg Ala Lys Lys Ile Asp Lys Ile Ser Arg Ile Gly Phe Pro Met Ala
                405                 410                 415

Phe Leu Ile Phe Asn Met Phe Tyr Trp Ile Ile Tyr Lys Ile Val Arg
            420                 425                 430

Arg Glu Asp Val His Asn Gln
        435


<210>  69
<211>  439
<212>  PRT
<213>  Artificial Sequence

<220>
<223>  synthetic sequence of chimeric LGIC

<400>  69

Met Arg Cys Ser Pro Gly Gly Val Trp Leu Ala Leu Ala Ala Ser Leu
1               5                   10                  15

Leu His Val Ser Leu Gln Gly Glu Phe Gln Arg Lys Leu Tyr Lys Glu
            20                  25                  30

Leu Val Lys Asn Tyr Asn Pro Leu Glu Arg Pro Val Ala Asn Asp Ser
        35                  40                  45

Gln Pro Leu Thr Val Tyr Phe Ser Leu Ser Leu Leu Gln Ile Met Asp
    50                  55                  60

Val Asp Glu Lys Asn Gln Val Leu Thr Thr Asn Ile Trp Leu Gln Met
```

```
65                  70                  75                  80

Ser Trp Thr Asp His Tyr Leu Gln Trp Asn Val Ser Glu Tyr Pro Gly
                85                  90                  95

Val Lys Thr Val Phe Phe Pro Asp Gly Gln Ile Trp Lys Pro Asp Ile
            100                 105                 110

Leu Leu Tyr Asn Ser Ala Asp Glu Arg Phe Asp Ala Thr Phe His Thr
        115                 120                 125

Asn Val Leu Val Asn Ser Ser Gly His Cys Gln Tyr Leu Pro Pro Gly
    130                 135                 140

Ile Phe Lys Ser Ser Cys Pro Met Asp Leu Lys Asn Phe Pro Met Asp
145                 150                 155                 160

Val Gln Thr Cys Lys Leu Lys Phe Gly Ser Trp Ser Tyr Gly Gly Trp
                165                 170                 175

Ser Leu Asp Leu Gln Met Gln Glu Ala Asp Ile Ser Gly Tyr Ile Pro
            180                 185                 190

Asn Gly Glu Trp Asp Leu Val Gly Ile Pro Gly Lys Arg Ser Glu Arg
        195                 200                 205

Phe Val Glu Cys Cys Lys Glu Pro Tyr Pro Asp Val Thr Phe Thr Val
    210                 215                 220

Thr Met Arg Arg Arg Met Gly Tyr Tyr Leu Ile Gln Met Tyr Ile Pro
225                 230                 235                 240

Ser Leu Leu Ile Val Ile Leu Ser Trp Ile Ser Phe Trp Ile Asn Met
                245                 250                 255

Asp Ala Ala Pro Ala Arg Val Gly Leu Gly Ile Thr Thr Val Leu Thr
            260                 265                 270

Met Thr Thr Gln Ser Ser Gly Ser Arg Ala Ser Leu Pro Lys Val Ser
        275                 280                 285
```

```
Tyr Val Lys Ala Ile Asp Ile Trp Met Ala Val Cys Leu Leu Phe Val
    290                 295                 300

Phe Ser Ala Leu Leu Glu Tyr Ala Ala Val Asn Phe Val Ser Arg Gln
305                 310                 315                 320

His Lys Glu Leu Leu Arg Phe Arg Arg Lys Arg Arg His His Lys Ser
                325                 330                 335

Pro Met Leu Asn Leu Phe Gln Glu Asp Glu Ala Gly Glu Gly Arg Phe
            340                 345                 350

Asn Phe Ser Ala Tyr Gly Met Gly Pro Ala Cys Leu Gln Ala Lys Asp
        355                 360                 365

Gly Ile Ser Val Lys Gly Ala Asn Asn Ser Asn Thr Thr Asn Pro Pro
    370                 375                 380

Pro Ala Pro Ser Lys Ser Pro Glu Glu Met Arg Lys Leu Phe Ile Gln
385                 390                 395                 400

Arg Ala Lys Lys Ile Asp Lys Ile Ser Arg Ile Gly Phe Pro Met Ala
                405                 410                 415

Phe Leu Ile Phe Asn Met Phe Tyr Trp Ile Ile Tyr Lys Ile Val Arg
            420                 425                 430

Arg Glu Asp Val His Asn Gln
        435
```

<210> 70
<211> 439
<212> PRT
<213> Artificial Sequence

<220>
<223> synthetic sequence of chimeric LGIC

<400> 70

```
Met Arg Cys Ser Pro Gly Gly Val Trp Leu Ala Leu Ala Ala Ser Leu
1               5                   10                  15
```

```
Leu His Val Ser Leu Gln Gly Glu Phe Gln Arg Lys Leu Tyr Lys Glu
            20                  25                  30

Leu Val Lys Asn Tyr Asn Pro Leu Glu Arg Pro Val Ala Asn Asp Ser
        35                  40                  45

Gln Pro Leu Thr Val Tyr Phe Ser Leu Ser Leu Leu Gln Ile Met Asp
    50                  55                  60

Val Asp Glu Lys Asn Gln Val Leu Thr Thr Asn Ile Trp Leu Gln Met
65                  70                  75                  80

Ser Trp Thr Asp His Tyr Leu Gln Trp Asn Val Ser Glu Tyr Pro Gly
                85                  90                  95

Val Lys Thr Val Phe Phe Pro Asp Gly Gln Ile Trp Lys Pro Asp Ile
            100                 105                 110

Leu Leu Tyr Asn Ser Ala Asp Glu Arg Phe Asp Ala Thr Phe His Thr
        115                 120                 125

Asn Val Leu Val Asn Ser Ser Gly His Cys Gln Tyr Leu Pro Pro Gly
    130                 135                 140

Ile Phe Lys Ser Ser Cys Pro Met Asp Leu Lys Asn Phe Pro Met Asp
145                 150                 155                 160

Val Gln Thr Cys Lys Leu Lys Phe Gly Ser Trp Ser Tyr Gly Gly Trp
                165                 170                 175

Ser Leu Asp Leu Gln Met Gln Glu Ala Asp Ile Ser Gly Tyr Ile Pro
            180                 185                 190

Asn Gly Glu Trp Asp Leu Val Gly Ile Pro Gly Lys Arg Ser Glu Arg
        195                 200                 205

Phe Phe Glu Cys Cys Lys Glu Pro Tyr Pro Asp Val Thr Phe Thr Val
    210                 215                 220

Thr Met Arg Arg Arg Met Gly Tyr Tyr Leu Ile Gln Met Tyr Ile Pro
```

```
225                 230                 235                 240

Ser Leu Leu Ile Val Ile Leu Ser Trp Ile Ser Phe Trp Ile Asn Met
                245                 250                 255

Asp Ala Ala Pro Ala Arg Val Gly Leu Gly Ile Thr Thr Val Leu Thr
            260                 265                 270

Met Thr Thr Gln Ser Ser Gly Ser Arg Ala Ser Leu Pro Lys Val Ser
        275                 280                 285

Tyr Val Lys Ala Ile Asp Ile Trp Met Ala Val Cys Leu Leu Phe Val
    290                 295                 300

Phe Ser Ala Leu Leu Glu Tyr Ala Ala Val Asn Phe Val Ser Arg Gln
305                 310                 315                 320

His Lys Glu Leu Leu Arg Phe Arg Arg Lys Arg Arg His His Lys Ser
                325                 330                 335

Pro Met Leu Asn Leu Phe Gln Glu Asp Glu Ala Gly Glu Gly Arg Phe
            340                 345                 350

Asn Phe Ser Ala Tyr Gly Met Gly Pro Ala Cys Leu Gln Ala Lys Asp
        355                 360                 365

Gly Ile Ser Val Lys Gly Ala Asn Asn Ser Asn Thr Thr Asn Pro Pro
    370                 375                 380

Pro Ala Pro Ser Lys Ser Pro Glu Glu Met Arg Lys Leu Phe Ile Gln
385                 390                 395                 400

Arg Ala Lys Lys Ile Asp Lys Ile Ser Arg Ile Gly Phe Pro Met Ala
                405                 410                 415

Phe Leu Ile Phe Asn Met Phe Tyr Trp Ile Ile Tyr Lys Ile Val Arg
            420                 425                 430

Arg Glu Asp Val His Asn Gln
        435
```

<210> 71
<211> 439
<212> PRT
<213> Artificial Sequence

<220>
<223> synthetic sequence of chimeric LGIC

<400> 71

Met Arg Cys Ser Pro Gly Gly Val Trp Leu Ala Leu Ala Ala Ser Leu
1 5 10 15

Leu His Val Ser Leu Gln Gly Glu Phe Gln Arg Lys Leu Tyr Lys Glu
20 25 30

Leu Val Lys Asn Tyr Asn Pro Leu Glu Arg Pro Val Ala Asn Asp Ser
35 40 45

Gln Pro Leu Thr Val Tyr Phe Ser Leu Ser Leu Leu Gln Ile Met Asp
50 55 60

Val Asp Glu Lys Asn Gln Val Leu Thr Thr Asn Ile Trp Leu Gln Met
65 70 75 80

Ser Trp Thr Asp His Tyr Leu Gln Trp Asn Val Ser Glu Tyr Pro Gly
85 90 95

Val Lys Thr Val Met Phe Pro Asp Gly Gln Ile Trp Lys Pro Asp Ile
100 105 110

Leu Leu Tyr Asn Ser Ala Asp Glu Arg Phe Asp Ala Thr Phe His Thr
115 120 125

Asn Val Ala Val Asn Ser Ser Gly His Cys Gln Tyr Leu Pro Pro Gly
130 135 140

Ile Phe Lys Ser Ser Cys Pro Met Asp Leu Lys Asn Phe Pro Met Asp
145 150 155 160

Val Gln Thr Cys Lys Leu Lys Phe Gly Ser Trp Ser Tyr Gly Gly Trp
165 170 175

```
Ser Leu Asp Leu Gln Met Gln Glu Ala Asp Ile Ser Gly Tyr Ile Pro
            180                 185                 190

Asn Gly Glu Trp Asp Leu Val Gly Ile Pro Gly Lys Arg Ser Glu Arg
        195                 200                 205

Phe Tyr Glu Cys Cys Lys Glu Pro Tyr Pro Asp Val Thr Phe Thr Val
    210                 215                 220

Thr Met Arg Arg Arg Met Gly Tyr Tyr Leu Ile Gln Met Tyr Ile Pro
225                 230                 235                 240

Ser Leu Leu Ile Val Ile Leu Ser Trp Ile Ser Phe Trp Ile Asn Met
                245                 250                 255

Asp Ala Ala Pro Ala Arg Val Gly Leu Gly Ile Thr Thr Val Leu Thr
            260                 265                 270

Met Thr Thr Gln Ser Ser Gly Ser Arg Ala Ser Leu Pro Lys Val Ser
        275                 280                 285

Tyr Val Lys Ala Ile Asp Ile Trp Met Ala Val Cys Leu Leu Phe Val
    290                 295                 300

Phe Ser Ala Leu Leu Glu Tyr Ala Ala Val Asn Phe Val Ser Arg Gln
305                 310                 315                 320

His Lys Glu Leu Leu Arg Phe Arg Arg Lys Arg Arg His His Lys Ser
                325                 330                 335

Pro Met Leu Asn Leu Phe Gln Glu Asp Glu Ala Gly Glu Gly Arg Phe
            340                 345                 350

Asn Phe Ser Ala Tyr Gly Met Gly Pro Ala Cys Leu Gln Ala Lys Asp
        355                 360                 365

Gly Ile Ser Val Lys Gly Ala Asn Asn Ser Asn Thr Thr Asn Pro Pro
    370                 375                 380

Pro Ala Pro Ser Lys Ser Pro Glu Glu Met Arg Lys Leu Phe Ile Gln
```

385 390 395 400

Arg Ala Lys Lys Ile Asp Lys Ile Ser Arg Ile Gly Phe Pro Met Ala
405 410 415

Phe Leu Ile Phe Asn Met Phe Tyr Trp Ile Ile Tyr Lys Ile Val Arg
420 425 430

Arg Glu Asp Val His Asn Gln
435

<210> 72
<211> 439
<212> PRT
<213> Artificial Sequence

<220>
<223> synthetic sequence of chimeric LGIC

<400> 72

Met Arg Cys Ser Pro Gly Gly Val Trp Leu Ala Leu Ala Ala Ser Leu
1 5 10 15

Leu His Val Ser Leu Gln Gly Glu Phe Gln Arg Lys Leu Tyr Lys Glu
20 25 30

Leu Val Lys Asn Tyr Asn Pro Leu Glu Arg Pro Val Ala Asn Asp Ser
35 40 45

Gln Pro Leu Thr Val Tyr Phe Ser Leu Ser Leu Leu Gln Ile Met Asp
50 55 60

Val Asp Glu Lys Asn Gln Val Leu Thr Thr Asn Ile Trp Leu Gln Met
65 70 75 80

Ser Trp Thr Asp His Tyr Leu Gln Trp Asn Val Ser Glu Tyr Pro Gly
85 90 95

Val Lys Thr Val Met Phe Pro Asp Gly Gln Ile Trp Lys Pro Asp Ile
100 105 110

Leu Leu Tyr Asn Ser Ala Asp Glu Arg Phe Asp Ala Thr Phe His Thr

```
        115                 120                 125

Asn Val Phe Val Asn Ser Ser Gly His Cys Gln Tyr Leu Pro Pro Gly
    130                 135                 140

Ile Phe Lys Ser Ser Cys Pro Met Asp Leu Lys Asn Phe Pro Met Asp
145                 150                 155                 160

Val Gln Thr Cys Lys Leu Lys Phe Gly Ser Trp Ser Tyr Gly Gly Trp
                165                 170                 175

Ser Leu Asp Leu Gln Met Gln Glu Ala Asp Ile Ser Gly Tyr Ile Pro
            180                 185                 190

Asn Gly Glu Trp Asp Leu Val Gly Ile Pro Gly Lys Arg Ser Glu Arg
        195                 200                 205

Phe Tyr Glu Cys Cys Lys Glu Pro Tyr Pro Asp Val Thr Phe Thr Val
    210                 215                 220

Thr Met Arg Arg Arg Met Gly Tyr Tyr Leu Ile Gln Met Tyr Ile Pro
225                 230                 235                 240

Ser Leu Leu Ile Val Ile Leu Ser Trp Ile Ser Phe Trp Ile Asn Met
                245                 250                 255

Asp Ala Ala Pro Ala Arg Val Gly Leu Gly Ile Thr Thr Val Leu Thr
            260                 265                 270

Met Thr Thr Gln Ser Ser Gly Ser Arg Ala Ser Leu Pro Lys Val Ser
        275                 280                 285

Tyr Val Lys Ala Ile Asp Ile Trp Met Ala Val Cys Leu Leu Phe Val
    290                 295                 300

Phe Ser Ala Leu Leu Glu Tyr Ala Ala Val Asn Phe Val Ser Arg Gln
305                 310                 315                 320

His Lys Glu Leu Leu Arg Phe Arg Arg Lys Arg Arg His His Lys Ser
                325                 330                 335
```

```
Pro Met Leu Asn Leu Phe Gln Glu Asp Glu Ala Gly Glu Gly Arg Phe
            340                 345                 350

Asn Phe Ser Ala Tyr Gly Met Gly Pro Ala Cys Leu Gln Ala Lys Asp
        355                 360                 365

Gly Ile Ser Val Lys Gly Ala Asn Asn Ser Asn Thr Thr Asn Pro Pro
    370                 375                 380

Pro Ala Pro Ser Lys Ser Pro Glu Glu Met Arg Lys Leu Phe Ile Gln
385                 390                 395                 400

Arg Ala Lys Lys Ile Asp Lys Ile Ser Arg Ile Gly Phe Pro Met Ala
                405                 410                 415

Phe Leu Ile Phe Asn Met Phe Tyr Trp Ile Ile Tyr Lys Ile Val Arg
            420                 425                 430

Arg Glu Asp Val His Asn Gln
        435
```

<210> 73
<211> 439
<212> PRT
<213> Artificial Sequence

<220>
<223> synthetic sequence of chimeric LGIC

<400> 73

```
Met Arg Cys Ser Pro Gly Gly Val Trp Leu Ala Leu Ala Ala Ser Leu
1               5                   10                  15

Leu His Val Ser Leu Gln Gly Glu Phe Gln Arg Lys Leu Tyr Lys Glu
            20                  25                  30

Leu Val Lys Asn Tyr Asn Pro Leu Glu Arg Pro Val Ala Asn Asp Ser
        35                  40                  45

Gln Pro Leu Thr Val Tyr Phe Ser Leu Ser Leu Leu Gln Ile Met Asp
    50                  55                  60
```

```
Val Asp Glu Lys Asn Gln Val Leu Thr Thr Asn Ile Trp Leu Gln Met
65                  70                  75                  80

Ser Trp Thr Asp His Tyr Leu Gln Trp Asn Val Ser Glu Tyr Pro Gly
                85                  90                  95

Val Lys Thr Val Trp Phe Pro Asp Gly Gln Ile Trp Lys Pro Asp Ile
            100                 105                 110

Leu Leu Glu Asn Ser Ala Asp Glu Arg Phe Asp Ala Thr Phe His Thr
        115                 120                 125

Asn Val Leu Val Asn Ser Ser Gly His Cys Gln Tyr Leu Pro Pro Gly
    130                 135                 140

Ile Phe Lys Ser Ser Cys Pro Met Asp Leu Lys Asn Phe Pro Met Asp
145                 150                 155                 160

Val Gln Thr Cys Lys Leu Lys Phe Gly Ser Trp Ser Tyr Gly Gly Trp
                165                 170                 175

Ser Leu Asp Leu Gln Met Gln Glu Ala Asp Ile Ser Gly Tyr Ile Pro
            180                 185                 190

Asn Gly Glu Trp Asp Leu Val Gly Ile Pro Gly Lys Arg Ser Glu Arg
        195                 200                 205

Phe Trp Glu Cys Cys Lys Glu Pro Tyr Pro Asp Val Thr Phe Thr Val
    210                 215                 220

Thr Met Arg Arg Arg Met Gly Tyr Tyr Leu Ile Gln Met Tyr Ile Pro
225                 230                 235                 240

Ser Leu Leu Ile Val Ile Leu Ser Trp Ile Ser Phe Trp Ile Asn Met
                245                 250                 255

Asp Ala Ala Pro Ala Arg Val Gly Leu Gly Ile Thr Thr Val Leu Thr
            260                 265                 270

Met Thr Thr Gln Ser Ser Gly Ser Arg Ala Ser Leu Pro Lys Val Ser
```

```
        275                 280                 285

Tyr Val Lys Ala Ile Asp Ile Trp Met Ala Val Cys Leu Leu Phe Val
    290                 295                 300

Phe Ser Ala Leu Leu Glu Tyr Ala Ala Val Asn Phe Val Ser Arg Gln
305                 310                 315                 320

His Lys Glu Leu Leu Arg Phe Arg Arg Lys Arg Arg His His Lys Ser
                325                 330                 335

Pro Met Leu Asn Leu Phe Gln Glu Asp Glu Ala Gly Glu Gly Arg Phe
            340                 345                 350

Asn Phe Ser Ala Tyr Gly Met Gly Pro Ala Cys Leu Gln Ala Lys Asp
        355                 360                 365

Gly Ile Ser Val Lys Gly Ala Asn Asn Ser Asn Thr Thr Asn Pro Pro
    370                 375                 380

Pro Ala Pro Ser Lys Ser Pro Glu Glu Met Arg Lys Leu Phe Ile Gln
385                 390                 395                 400

Arg Ala Lys Lys Ile Asp Lys Ile Ser Arg Ile Gly Phe Pro Met Ala
                405                 410                 415

Phe Leu Ile Phe Asn Met Phe Tyr Trp Ile Ile Tyr Lys Ile Val Arg
            420                 425                 430

Arg Glu Asp Val His Asn Gln
        435
```

<210> 74
<211> 439
<212> PRT
<213> Artificial Sequence

<220>
<223> synthetic sequence of chimeric LGIC

<400> 74

```
Met Arg Cys Ser Pro Gly Gly Val Trp Leu Ala Leu Ala Ala Ser Leu
```

```
1               5                   10                  15

Leu His Val Ser Leu Gln Gly Glu Phe Gln Arg Lys Leu Tyr Lys Glu
            20                  25                  30

Leu Val Lys Asn Tyr Asn Pro Leu Glu Arg Pro Val Ala Asn Asp Ser
        35                  40                  45

Gln Pro Leu Thr Val Tyr Phe Ser Leu Ser Leu Leu Gln Ile Met Asp
    50                  55                  60

Val Asp Glu Lys Asn Gln Val Leu Thr Thr Asn Ile Trp Leu Gln Met
65                  70                  75                  80

Ser Trp Thr Asp His Tyr Leu Gln Trp Asn Val Ser Glu Tyr Pro Gly
                85                  90                  95

Val Lys Thr Val Phe Phe Pro Asp Gly Gln Ile Trp Lys Pro Asp Ile
            100                 105                 110

Leu Leu Glu Asn Ser Ala Asp Glu Arg Phe Asp Ala Thr Phe His Thr
        115                 120                 125

Asn Val Leu Val Asn Ser Ser Gly His Cys Gln Tyr Leu Pro Pro Gly
    130                 135                 140

Ile Phe Lys Ser Ser Cys Pro Met Asp Leu Lys Asn Phe Pro Met Asp
145                 150                 155                 160

Val Gln Thr Cys Lys Leu Lys Phe Gly Ser Trp Ser Tyr Gly Gly Trp
                165                 170                 175

Ser Leu Asp Leu Gln Met Gln Glu Ala Asp Ile Ser Gly Tyr Ile Pro
            180                 185                 190

Asn Gly Glu Trp Asp Leu Val Gly Ile Pro Gly Lys Arg Ser Glu Arg
        195                 200                 205

Phe Trp Glu Cys Cys Lys Glu Pro Tyr Pro Asp Val Thr Phe Thr Val
    210                 215                 220
```

```
Thr Met Arg Arg Arg Met Gly Tyr Tyr Leu Ile Gln Met Tyr Ile Pro
225                 230                 235                 240

Ser Leu Leu Ile Val Ile Leu Ser Trp Ile Ser Phe Trp Ile Asn Met
                245                 250                 255

Asp Ala Ala Pro Ala Arg Val Gly Leu Gly Ile Thr Thr Val Leu Thr
            260                 265                 270

Met Thr Thr Gln Ser Ser Gly Ser Arg Ala Ser Leu Pro Lys Val Ser
        275                 280                 285

Tyr Val Lys Ala Ile Asp Ile Trp Met Ala Val Cys Leu Leu Phe Val
    290                 295                 300

Phe Ser Ala Leu Leu Glu Tyr Ala Ala Val Asn Phe Val Ser Arg Gln
305                 310                 315                 320

His Lys Glu Leu Leu Arg Phe Arg Arg Lys Arg Arg His His Lys Ser
                325                 330                 335

Pro Met Leu Asn Leu Phe Gln Glu Asp Glu Ala Gly Glu Gly Arg Phe
            340                 345                 350

Asn Phe Ser Ala Tyr Gly Met Gly Pro Ala Cys Leu Gln Ala Lys Asp
        355                 360                 365

Gly Ile Ser Val Lys Gly Ala Asn Asn Ser Asn Thr Thr Asn Pro Pro
    370                 375                 380

Pro Ala Pro Ser Lys Ser Pro Glu Glu Met Arg Lys Leu Phe Ile Gln
385                 390                 395                 400

Arg Ala Lys Lys Ile Asp Lys Ile Ser Arg Ile Gly Phe Pro Met Ala
                405                 410                 415

Phe Leu Ile Phe Asn Met Phe Tyr Trp Ile Ile Tyr Lys Ile Val Arg
            420                 425                 430

Arg Glu Asp Val His Asn Gln
```

435

<210> 75
<211> 439
<212> PRT
<213> Artificial Sequence

<220>
<223> synthetic sequence of chimeric LGIC

<400> 75

Met Arg Cys Ser Pro Gly Gly Val Trp Leu Ala Leu Ala Ala Ser Leu
1 5 10 15

Leu His Val Ser Leu Gln Gly Glu Phe Gln Arg Lys Leu Tyr Lys Glu
20 25 30

Leu Val Lys Asn Tyr Asn Pro Leu Glu Arg Pro Val Ala Asn Asp Ser
35 40 45

Gln Pro Leu Thr Val Tyr Phe Ser Leu Ser Leu Leu Gln Ile Met Asp
50 55 60

Val Asp Glu Lys Asn Gln Val Leu Thr Thr Asn Ile Phe Leu Gln Met
65 70 75 80

Ser Trp Thr Asp His Tyr Leu Gln Trp Asn Val Ser Glu Tyr Pro Gly
85 90 95

Val Lys Thr Val Phe Phe Pro Asp Gly Gln Ile Trp Lys Pro Asp Ile
100 105 110

Leu Leu Tyr Asn Ser Ala Asp Glu Arg Phe Asp Ala Thr Phe His Thr
115 120 125

Asn Val Asp Val Asn Ser Ser Gly His Cys Gln Tyr Leu Pro Pro Gly
130 135 140

Ile Phe Lys Ser Ser Cys Pro Met Asp Leu Lys Asn Phe Pro Met Asp
145 150 155 160

Val Gln Thr Cys Lys Leu Lys Phe Gly Ser Trp Ser Tyr Gly Gly Trp

```
                165                 170                 175

Ser Leu Asp Leu Gln Met Gln Glu Ala Asp Ile Ser Gly Tyr Ile Pro
            180                 185                 190

Asn Gly Glu Trp Asp Leu Val Gly Ile Pro Gly Lys Arg Ser Glu Arg
        195                 200                 205

Phe Tyr Glu Cys Cys Lys Glu Pro Tyr Pro Asp Val Thr Phe Thr Val
    210                 215                 220

Thr Met Arg Arg Arg Met Gly Tyr Tyr Leu Ile Gln Met Tyr Ile Pro
225                 230                 235                 240

Ser Leu Leu Ile Val Ile Leu Ser Trp Ile Ser Phe Trp Ile Asn Met
                245                 250                 255

Asp Ala Ala Pro Ala Arg Val Gly Leu Gly Ile Thr Thr Val Leu Thr
            260                 265                 270

Met Thr Thr Gln Ser Ser Gly Ser Arg Ala Ser Leu Pro Lys Val Ser
        275                 280                 285

Tyr Val Lys Ala Ile Asp Ile Trp Met Ala Val Cys Leu Leu Phe Val
    290                 295                 300

Phe Ser Ala Leu Leu Glu Tyr Ala Ala Val Asn Phe Val Ser Arg Gln
305                 310                 315                 320

His Lys Glu Leu Leu Arg Phe Arg Arg Lys Arg Arg His His Lys Ser
                325                 330                 335

Pro Met Leu Asn Leu Phe Gln Glu Asp Glu Ala Gly Glu Gly Arg Phe
            340                 345                 350

Asn Phe Ser Ala Tyr Gly Met Gly Pro Ala Cys Leu Gln Ala Lys Asp
        355                 360                 365

Gly Ile Ser Val Lys Gly Ala Asn Asn Ser Asn Thr Thr Asn Pro Pro
    370                 375                 380
```

```
Pro Ala Pro Ser Lys Ser Pro Glu Glu Met Arg Lys Leu Phe Ile Gln
385                 390                 395                 400


Arg Ala Lys Lys Ile Asp Lys Ile Ser Arg Ile Gly Phe Pro Met Ala
                405                 410                 415


Phe Leu Ile Phe Asn Met Phe Tyr Trp Ile Ile Tyr Lys Ile Val Arg
            420                 425                 430


Arg Glu Asp Val His Asn Gln
        435


<210>  76
<211>  439
<212>  PRT
<213>  Artificial Sequence

<220>
<223>  synthetic sequence of chimeric LGIC

<400>  76

Met Arg Cys Ser Pro Gly Gly Val Trp Leu Ala Leu Ala Ala Ser Leu
1               5                   10                  15


Leu His Val Ser Leu Gln Gly Glu Phe Gln Arg Lys Leu Tyr Lys Glu
            20                  25                  30


Leu Val Lys Asn Tyr Asn Pro Leu Glu Arg Pro Val Ala Asn Asp Ser
        35                  40                  45


Gln Pro Leu Thr Val Tyr Phe Ser Leu Ser Leu Leu Gln Ile Met Asp
    50                  55                  60


Val Asp Glu Lys Asn Gln Val Leu Thr Thr Asn Ile Trp Leu Gln Met
65                  70                  75                  80


Ser Trp Thr Asp His Tyr Leu Gln Trp Asn Val Ser Glu Tyr Pro Gly
                85                  90                  95


Val Lys Thr Val Phe Phe Pro Asp Gly Gln Ile Trp Lys Pro Asp Ile
            100                 105                 110
```

```
Leu Leu Tyr Asn Ser Ala Asp Glu Arg Phe Asp Ala Thr Phe His Thr
        115                 120                 125

Asn Val Asn Val Asn Ser Ser Gly His Cys Gln Tyr Leu Pro Pro Gly
    130                 135                 140

Ile Phe Lys Ser Ser Cys Pro Met Asp Leu Lys Asn Phe Pro Met Asp
145                 150                 155                 160

Val Gln Thr Cys Lys Leu Lys Phe Gly Ser Trp Asp Tyr Gly Gly Trp
                165                 170                 175

Ser Leu Asp Leu Gln Met Gln Glu Ala Asp Ile Ser Gly Tyr Ile Pro
            180                 185                 190

Asn Gly Glu Trp Asp Leu Val Gly Ile Pro Gly Lys Arg Ser Glu Arg
        195                 200                 205

Phe Tyr Glu Cys Cys Lys Glu Pro Tyr Pro Asp Val Thr Phe Thr Val
    210                 215                 220

Thr Met Arg Arg Arg Met Gly Tyr Tyr Leu Ile Gln Met Tyr Ile Pro
225                 230                 235                 240

Ser Leu Leu Ile Val Ile Leu Ser Trp Ile Ser Phe Trp Ile Asn Met
                245                 250                 255

Asp Ala Ala Pro Ala Arg Val Gly Leu Gly Ile Thr Thr Val Leu Thr
            260                 265                 270

Met Thr Thr Gln Ser Ser Gly Ser Arg Ala Ser Leu Pro Lys Val Ser
        275                 280                 285

Tyr Val Lys Ala Ile Asp Ile Trp Met Ala Val Cys Leu Leu Phe Val
    290                 295                 300

Phe Ser Ala Leu Leu Glu Tyr Ala Ala Val Asn Phe Val Ser Arg Gln
305                 310                 315                 320

His Lys Glu Leu Leu Arg Phe Arg Arg Lys Arg Arg His His Lys Ser
```

```
                325                 330                 335

Pro Met Leu Asn Leu Phe Gln Glu Asp Glu Ala Gly Glu Gly Arg Phe
            340                 345                 350

Asn Phe Ser Ala Tyr Gly Met Gly Pro Ala Cys Leu Gln Ala Lys Asp
        355                 360                 365

Gly Ile Ser Val Lys Gly Ala Asn Asn Ser Asn Thr Thr Asn Pro Pro
    370                 375                 380

Pro Ala Pro Ser Lys Ser Pro Glu Glu Met Arg Lys Leu Phe Ile Gln
385                 390                 395                 400

Arg Ala Lys Lys Ile Asp Lys Ile Ser Arg Ile Gly Phe Pro Met Ala
                405                 410                 415

Phe Leu Ile Phe Asn Met Phe Tyr Trp Ile Ile Tyr Lys Ile Val Arg
            420                 425                 430

Arg Glu Asp Val His Asn Gln
        435
```

<210> 77
<211> 439
<212> PRT
<213> Artificial Sequence

<220>
<223> synthetic sequence of chimeric LGIC

<400> 77

```
Met Arg Cys Ser Pro Gly Gly Val Trp Leu Ala Leu Ala Ala Ser Leu
1               5                   10                  15

Leu His Val Ser Leu Gln Gly Glu Phe Gln Arg Lys Leu Tyr Lys Glu
            20                  25                  30

Leu Val Lys Asn Tyr Asn Pro Leu Glu Arg Pro Val Ala Asn Asp Ser
        35                  40                  45

Gln Pro Leu Thr Val Tyr Phe Ser Leu Ser Leu Leu Gln Ile Met Asp
```

```
    50                  55                  60

Val Asp Glu Lys Asn Gln Val Leu Thr Thr Asn Ile Trp Leu Gln Met
65                  70                  75                  80

Ser Trp Thr Asp His Tyr Leu Gln Trp Asn Val Ser Glu Tyr Pro Gly
                85                  90                  95

Val Lys Thr Val Arg Phe Pro Asp Gly Gln Ile Trp Lys Pro Asp Ile
            100                 105                 110

Leu Leu Tyr Asn Ser Ala Asp Glu Arg Phe Asp Ala Thr Phe His Thr
        115                 120                 125

Asn Val Leu Val Asn Ser Ser Gly His Cys Glu Tyr Leu Pro Pro Gly
    130                 135                 140

Ile Phe Lys Ser Ser Cys Pro Met Asp Leu Lys Asn Phe Pro Met Asp
145                 150                 155                 160

Val Gln Thr Cys Lys Leu Lys Phe Gly Ser Trp Asp Tyr Gly Gly Trp
                165                 170                 175

Ser Leu Asp Leu Gln Met Gln Glu Ala Asp Ile Ser Gly Tyr Ile Pro
            180                 185                 190

Asn Gly Glu Trp Asp Leu Val Gly Ile Pro Gly Lys Arg Ser Glu Arg
        195                 200                 205

Phe Tyr Glu Cys Cys Lys Glu Pro Tyr Pro Asp Val Thr Phe Thr Val
    210                 215                 220

Thr Met Arg Arg Arg Met Gly Tyr Tyr Leu Ile Gln Met Tyr Ile Pro
225                 230                 235                 240

Ser Leu Leu Ile Val Ile Leu Ser Trp Ile Ser Phe Trp Ile Asn Met
                245                 250                 255

Asp Ala Ala Pro Ala Arg Val Gly Leu Gly Ile Thr Thr Val Leu Thr
            260                 265                 270
```

```
Met Thr Thr Gln Ser Ser Gly Ser Arg Ala Ser Leu Pro Lys Val Ser
        275                 280                 285

Tyr Val Lys Ala Ile Asp Ile Trp Met Ala Val Cys Leu Leu Phe Val
    290                 295                 300

Phe Ser Ala Leu Leu Glu Tyr Ala Ala Val Asn Phe Val Ser Arg Gln
305                 310                 315                 320

His Lys Glu Leu Leu Arg Phe Arg Arg Lys Arg Arg His His Lys Ser
                325                 330                 335

Pro Met Leu Asn Leu Phe Gln Glu Asp Glu Ala Gly Glu Gly Arg Phe
            340                 345                 350

Asn Phe Ser Ala Tyr Gly Met Gly Pro Ala Cys Leu Gln Ala Lys Asp
        355                 360                 365

Gly Ile Ser Val Lys Gly Ala Asn Asn Ser Asn Thr Thr Asn Pro Pro
    370                 375                 380

Pro Ala Pro Ser Lys Ser Pro Glu Glu Met Arg Lys Leu Phe Ile Gln
385                 390                 395                 400

Arg Ala Lys Lys Ile Asp Lys Ile Ser Arg Ile Gly Phe Pro Met Ala
                405                 410                 415

Phe Leu Ile Phe Asn Met Phe Tyr Trp Ile Ile Tyr Lys Ile Val Arg
            420                 425                 430

Arg Glu Asp Val His Asn Gln
        435
```

<210> 78
<211> 439
<212> PRT
<213> Artificial Sequence

<220>
<223> synthetic sequence of chimeric LGIC

<400> 78

```
Met Arg Cys Ser Pro Gly Gly Val Trp Leu Ala Leu Ala Ala Ser Leu
1               5                  10                  15

Leu His Val Ser Leu Gln Gly Glu Phe Gln Arg Lys Leu Tyr Lys Glu
            20                  25                  30

Leu Val Lys Asn Tyr Asn Pro Leu Glu Arg Pro Val Ala Asn Asp Ser
        35                  40                  45

Gln Pro Leu Thr Val Tyr Phe Ser Leu Ser Leu Leu Gln Ile Met Asp
    50                  55                  60

Val Asp Glu Lys Asn Gln Val Leu Thr Thr Asn Ile Trp Leu Gln Met
65                  70                  75                  80

Ser Trp Thr Asp His Tyr Leu Gln Trp Asn Val Ser Glu Tyr Pro Gly
                85                  90                  95

Val Lys Thr Val Arg Phe Pro Asp Gly Gln Ile Trp Lys Pro Asp Ile
            100                 105                 110

Leu Leu Tyr Asn Ser Ala Asp Glu Arg Phe Asp Ala Thr Phe His Thr
        115                 120                 125

Asn Val Leu Val Asn Ser Ser Gly His Cys Gln Tyr Leu Pro Pro Gly
    130                 135                 140

Ile Phe Lys Ser Ser Cys Pro Met Asp Leu Lys Asn Phe Pro Met Asp
145                 150                 155                 160

Val Gln Thr Cys Lys Leu Lys Phe Gly Ser Trp Asp Tyr Gly Gly Trp
                165                 170                 175

Ser Leu Asp Leu Gln Met Gln Glu Ala Asp Ile Ser Gly Tyr Ile Pro
            180                 185                 190

Asn Gly Glu Trp Asp Leu Val Gly Ile Pro Gly Lys Arg Ser Glu Arg
        195                 200                 205

Phe Trp Glu Cys Cys Lys Glu Pro Tyr Pro Asp Val Thr Phe Thr Val
```

```
    210                 215                 220

Thr Met Arg Arg Arg Met Gly Tyr Tyr Leu Ile Gln Met Tyr Ile Pro
225                 230                 235                 240

Ser Leu Leu Ile Val Ile Leu Ser Trp Ile Ser Phe Trp Ile Asn Met
                245                 250                 255

Asp Ala Ala Pro Ala Arg Val Gly Leu Gly Ile Thr Thr Val Leu Thr
            260                 265                 270

Met Thr Thr Gln Ser Ser Gly Ser Arg Ala Ser Leu Pro Lys Val Ser
        275                 280                 285

Tyr Val Lys Ala Ile Asp Ile Trp Met Ala Val Cys Leu Leu Phe Val
    290                 295                 300

Phe Ser Ala Leu Leu Glu Tyr Ala Ala Val Asn Phe Val Ser Arg Gln
305                 310                 315                 320

His Lys Glu Leu Leu Arg Phe Arg Arg Lys Arg Arg His His Lys Ser
                325                 330                 335

Pro Met Leu Asn Leu Phe Gln Glu Asp Glu Ala Gly Glu Gly Arg Phe
            340                 345                 350

Asn Phe Ser Ala Tyr Gly Met Gly Pro Ala Cys Leu Gln Ala Lys Asp
        355                 360                 365

Gly Ile Ser Val Lys Gly Ala Asn Asn Ser Asn Thr Thr Asn Pro Pro
    370                 375                 380

Pro Ala Pro Ser Lys Ser Pro Glu Glu Met Arg Lys Leu Phe Ile Gln
385                 390                 395                 400

Arg Ala Lys Lys Ile Asp Lys Ile Ser Arg Ile Gly Phe Pro Met Ala
                405                 410                 415

Phe Leu Ile Phe Asn Met Phe Tyr Trp Ile Ile Tyr Lys Ile Val Arg
            420                 425                 430
```

Arg Glu Asp Val His Asn Gln
        435

<210> 79
<211> 724
<212> PRT
<213> Artificial Sequence

<220>
<223> AAV5 capsid protein

<400> 79

Met Ser Phe Val Asp His Pro Pro Asp Trp Leu Glu Glu Val Gly Glu
1   5   10   15

Gly Leu Arg Glu Phe Leu Gly Leu Glu Ala Gly Pro Pro Lys Pro Lys
            20   25   30

Pro Asn Gln Gln His Gln Asp Gln Ala Arg Gly Leu Val Leu Pro Gly
        35   40   45

Tyr Asn Tyr Leu Gly Pro Gly Asn Gly Leu Asp Arg Gly Glu Pro Val
    50   55   60

Asn Arg Ala Asp Glu Val Ala Arg Glu His Asp Ile Ser Tyr Asn Glu
65   70   75   80

Gln Leu Glu Ala Gly Asp Asn Pro Tyr Leu Lys Tyr Asn His Ala Asp
                85   90   95

Ala Glu Phe Gln Glu Lys Leu Ala Asp Asp Thr Ser Phe Gly Gly Asn
            100   105   110

Leu Gly Lys Ala Val Phe Gln Ala Lys Lys Arg Val Leu Glu Pro Phe
        115   120   125

Gly Leu Val Glu Glu Gly Ala Lys Thr Ala Pro Thr Gly Lys Arg Ile
    130   135   140

Asp Asp His Phe Pro Lys Arg Lys Lys Ala Arg Thr Glu Glu Asp Ser
145   150   155   160

```
Lys Pro Ser Thr Ser Ser Asp Ala Glu Ala Gly Pro Ser Gly Ser Gln
                165                 170                 175

Gln Leu Gln Ile Pro Ala Gln Pro Ala Ser Ser Leu Gly Ala Asp Thr
            180                 185                 190

Met Ser Ala Gly Gly Gly Gly Pro Leu Gly Asp Asn Asn Gln Gly Ala
        195                 200                 205

Asp Gly Val Gly Asn Ala Ser Gly Asp Trp His Cys Asp Ser Thr Trp
    210                 215                 220

Met Gly Asp Arg Val Val Thr Lys Ser Thr Arg Thr Trp Val Leu Pro
225                 230                 235                 240

Ser Tyr Asn Asn His Gln Tyr Arg Glu Ile Lys Ser Gly Ser Val Asp
                245                 250                 255

Gly Ser Asn Ala Asn Ala Tyr Phe Gly Tyr Ser Thr Pro Trp Gly Tyr
            260                 265                 270

Phe Asp Phe Asn Arg Phe His Ser His Trp Ser Pro Arg Asp Trp Gln
        275                 280                 285

Arg Leu Ile Asn Asn Tyr Trp Gly Phe Arg Pro Arg Ser Leu Arg Val
    290                 295                 300

Lys Ile Phe Asn Ile Gln Val Lys Glu Val Thr Val Gln Asp Ser Thr
305                 310                 315                 320

Thr Thr Ile Ala Asn Asn Leu Thr Ser Thr Val Gln Val Phe Thr Asp
                325                 330                 335

Asp Asp Tyr Gln Leu Pro Tyr Val Val Gly Asn Gly Thr Glu Gly Cys
            340                 345                 350

Leu Pro Ala Phe Pro Pro Gln Val Phe Thr Leu Pro Gln Tyr Gly Tyr
        355                 360                 365

Ala Thr Leu Asn Arg Asp Asn Thr Glu Asn Pro Thr Glu Arg Ser Ser
```

```
    370                 375                 380

Phe Phe Cys Leu Glu Tyr Phe Pro Ser Lys Met Leu Arg Thr Gly Asn
385                 390                 395                 400

Asn Phe Glu Phe Thr Tyr Asn Phe Glu Glu Val Pro Phe His Ser Ser
                405                 410                 415

Phe Ala Pro Ser Gln Asn Leu Phe Lys Leu Ala Asn Pro Leu Val Asp
            420                 425                 430

Gln Tyr Leu Tyr Arg Phe Val Ser Thr Asn Asn Thr Gly Gly Val Gln
        435                 440                 445

Phe Asn Lys Asn Leu Ala Gly Arg Tyr Ala Asn Thr Tyr Lys Asn Trp
    450                 455                 460

Phe Pro Gly Pro Met Gly Arg Thr Gln Gly Trp Asn Leu Gly Ser Gly
465                 470                 475                 480

Val Asn Arg Ala Ser Val Ser Ala Phe Ala Thr Thr Asn Arg Met Glu
                485                 490                 495

Leu Glu Gly Ala Ser Tyr Gln Val Pro Pro Gln Pro Asn Gly Met Thr
            500                 505                 510

Asn Asn Leu Gln Gly Ser Asn Thr Tyr Ala Leu Glu Asn Thr Met Ile
        515                 520                 525

Phe Asn Ser Gln Pro Ala Asn Pro Gly Thr Thr Ala Thr Tyr Leu Glu
    530                 535                 540

Gly Asn Met Leu Ile Thr Ser Glu Ser Glu Thr Gln Pro Val Asn Arg
545                 550                 555                 560

Val Ala Tyr Asn Val Gly Gly Gln Met Ala Thr Asn Asn Gln Ser Ser
                565                 570                 575

Thr Thr Ala Pro Ala Thr Gly Thr Tyr Asn Leu Gln Glu Ile Val Pro
            580                 585                 590
```

Gly Ser Val Trp Met Glu Arg Asp Val Tyr Leu Gln Gly Pro Ile Trp
595 600 605

Ala Lys Ile Pro Glu Thr Gly Ala His Phe His Pro Ser Pro Ala Met
610 615 620

Gly Gly Phe Gly Leu Lys His Pro Pro Pro Met Met Leu Ile Lys Asn
625 630 635 640

Thr Pro Val Pro Gly Asn Ile Thr Ser Phe Ser Asp Val Pro Val Ser
645 650 655

Ser Phe Ile Thr Gln Tyr Ser Thr Gly Gln Val Thr Val Glu Met Glu
660 665 670

Trp Glu Leu Lys Lys Glu Asn Ser Lys Arg Trp Asn Pro Glu Ile Gln
675 680 685

Tyr Thr Asn Asn Tyr Asn Asp Pro Gln Phe Val Asp Phe Ala Pro Asp
690 695 700

Ser Thr Gly Glu Tyr Arg Thr Thr Arg Pro Ile Gly Thr Arg Tyr Leu
705 710 715 720

Thr Arg Pro Leu

<210> 80
<211> 736
<212> PRT
<213> Artificial Sequence

<220>
<223> AAV6 capsid protein

<400> 80

Met Ala Ala Asp Gly Tyr Leu Pro Asp Trp Leu Glu Asp Asn Leu Ser
1 5 10 15

Glu Gly Ile Arg Glu Trp Trp Asp Leu Lys Pro Gly Ala Pro Lys Pro
20 25 30

```
Lys Ala Asn Gln Gln Lys Gln Asp Asp Gly Arg Gly Leu Val Leu Pro
        35                  40                  45

Gly Tyr Lys Tyr Leu Gly Pro Phe Asn Gly Leu Asp Lys Gly Glu Pro
    50                  55                  60

Val Asn Ala Ala Asp Ala Ala Ala Leu Glu His Asp Lys Ala Tyr Asp
65                  70                  75                  80

Gln Gln Leu Lys Ala Gly Asp Asn Pro Tyr Leu Arg Tyr Asn His Ala
                85                  90                  95

Asp Ala Glu Phe Gln Glu Arg Leu Gln Glu Asp Thr Ser Phe Gly Gly
            100                 105                 110

Asn Leu Gly Arg Ala Val Phe Gln Ala Lys Lys Arg Val Leu Glu Pro
        115                 120                 125

Phe Gly Leu Val Glu Glu Gly Ala Lys Thr Ala Pro Gly Lys Lys Arg
    130                 135                 140

Pro Val Glu Gln Ser Pro Gln Glu Pro Asp Ser Ser Ser Gly Ile Gly
145                 150                 155                 160

Lys Thr Gly Gln Gln Pro Ala Lys Lys Arg Leu Asn Phe Gly Gln Thr
                165                 170                 175

Gly Asp Ser Glu Ser Val Pro Asp Pro Gln Pro Leu Gly Glu Pro Pro
            180                 185                 190

Ala Thr Pro Ala Ala Val Gly Pro Thr Thr Met Ala Ser Gly Gly Gly
        195                 200                 205

Ala Pro Met Ala Asp Asn Asn Glu Gly Ala Asp Gly Val Gly Asn Ala
    210                 215                 220

Ser Gly Asn Trp His Cys Asp Ser Thr Trp Leu Gly Asp Arg Val Ile
225                 230                 235                 240

Thr Thr Ser Thr Arg Thr Trp Ala Leu Pro Thr Tyr Asn Asn His Leu
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                245                 250                 255

Tyr Lys Gln Ile Ser Ser Ala Ser Thr Gly Ala Ser Asn Asp Asn His
            260                 265                 270

Tyr Phe Gly Tyr Ser Thr Pro Trp Gly Tyr Phe Asp Phe Asn Arg Phe
        275                 280                 285

His Cys His Phe Ser Pro Arg Asp Trp Gln Arg Leu Ile Asn Asn Asn
    290                 295                 300

Trp Gly Phe Arg Pro Lys Arg Leu Asn Phe Lys Leu Phe Asn Ile Gln
305                 310                 315                 320

Val Lys Glu Val Thr Thr Asn Asp Gly Val Thr Thr Ile Ala Asn Asn
                325                 330                 335

Leu Thr Ser Thr Val Gln Val Phe Ser Asp Ser Glu Tyr Gln Leu Pro
            340                 345                 350

Tyr Val Leu Gly Ser Ala His Gln Gly Cys Leu Pro Pro Phe Pro Ala
        355                 360                 365

Asp Val Phe Met Ile Pro Gln Tyr Gly Tyr Leu Thr Leu Asn Asn Gly
    370                 375                 380

Ser Gln Ala Val Gly Arg Ser Ser Phe Tyr Cys Leu Glu Tyr Phe Pro
385                 390                 395                 400

Ser Gln Met Leu Arg Thr Gly Asn Asn Phe Thr Phe Ser Tyr Thr Phe
                405                 410                 415

Glu Asp Val Pro Phe His Ser Ser Tyr Ala His Ser Gln Ser Leu Asp
            420                 425                 430

Arg Leu Met Asn Pro Leu Ile Asp Gln Tyr Leu Tyr Tyr Leu Asn Arg
        435                 440                 445

Thr Gln Asn Gln Ser Gly Ser Ala Gln Asn Lys Asp Leu Leu Phe Ser
    450                 455                 460
```

```
Arg Gly Ser Pro Ala Gly Met Ser Val Gln Pro Lys Asn Trp Leu Pro
465                 470                 475                 480

Gly Pro Cys Tyr Arg Gln Gln Arg Val Ser Lys Thr Lys Thr Asp Asn
                485                 490                 495

Asn Asn Ser Asn Phe Thr Trp Thr Gly Ala Ser Lys Tyr Asn Leu Asn
            500                 505                 510

Gly Arg Glu Ser Ile Ile Asn Pro Gly Thr Ala Met Ala Ser His Lys
        515                 520                 525

Asp Asp Lys Asp Lys Phe Phe Pro Met Ser Gly Val Met Ile Phe Gly
    530                 535                 540

Lys Glu Ser Ala Gly Ala Ser Asn Thr Ala Leu Asp Asn Val Met Ile
545                 550                 555                 560

Thr Asp Glu Glu Glu Ile Lys Ala Thr Asn Pro Val Ala Thr Glu Arg
                565                 570                 575

Phe Gly Thr Val Ala Val Asn Leu Gln Ser Ser Ser Thr Asp Pro Ala
            580                 585                 590

Thr Gly Asp Val His Val Met Gly Ala Leu Pro Gly Met Val Trp Gln
        595                 600                 605

Asp Arg Asp Val Tyr Leu Gln Gly Pro Ile Trp Ala Lys Ile Pro His
    610                 615                 620

Thr Asp Gly His Phe His Pro Ser Pro Leu Met Gly Gly Phe Gly Leu
625                 630                 635                 640

Lys His Pro Pro Pro Gln Ile Leu Ile Lys Asn Thr Pro Val Pro Ala
                645                 650                 655

Asn Pro Pro Ala Glu Phe Ser Ala Thr Lys Phe Ala Ser Phe Ile Thr
            660                 665                 670

Gln Tyr Ser Thr Gly Gln Val Ser Val Glu Ile Glu Trp Glu Leu Gln
```

675 680 685

Lys Glu Asn Ser Lys Arg Trp Asn Pro Glu Val Gln Tyr Thr Ser Asn
690 695 700

Tyr Ala Lys Ser Ala Asn Val Asp Phe Thr Val Asp Asn Asn Gly Leu
705 710 715 720

Tyr Thr Glu Pro Arg Pro Ile Gly Thr Arg Tyr Leu Thr Arg Pro Leu
725 730 735

<210> 81
<211> 736
<212> PRT
<213> Artificial Sequence

<220>
<223> AAV9 capsid protein

<400> 81

Met Ala Ala Asp Gly Tyr Leu Pro Asp Trp Leu Glu Asp Asn Leu Ser
1 5 10 15

Glu Gly Ile Arg Glu Trp Trp Ala Leu Lys Pro Gly Ala Pro Gln Pro
20 25 30

Lys Ala Asn Gln Gln His Gln Asp Asn Ala Arg Gly Leu Val Leu Pro
35 40 45

Gly Tyr Lys Tyr Leu Gly Pro Gly Asn Gly Leu Asp Lys Gly Glu Pro
50 55 60

Val Asn Ala Ala Asp Ala Ala Ala Leu Glu His Asp Lys Ala Tyr Asp
65 70 75 80

Gln Gln Leu Lys Ala Gly Asp Asn Pro Tyr Leu Lys Tyr Asn His Ala
85 90 95

Asp Ala Glu Phe Gln Glu Arg Leu Lys Glu Asp Thr Ser Phe Gly Gly
100 105 110

Asn Leu Gly Arg Ala Val Phe Gln Ala Lys Lys Arg Leu Leu Glu Pro

```
        115                 120                 125

Leu Gly Leu Val Glu Glu Ala Ala Lys Thr Ala Pro Gly Lys Lys Arg
    130                 135                 140

Pro Val Glu Gln Ser Pro Gln Glu Pro Asp Ser Ser Ala Gly Ile Gly
145                 150                 155                 160

Lys Ser Gly Ala Gln Pro Ala Lys Lys Arg Leu Asn Phe Gly Gln Thr
                165                 170                 175

Gly Asp Thr Glu Ser Val Pro Asp Pro Gln Pro Ile Gly Glu Pro Pro
            180                 185                 190

Ala Ala Pro Ser Gly Val Gly Ser Leu Thr Met Ala Ser Gly Gly Gly
        195                 200                 205

Ala Pro Val Ala Asp Asn Asn Glu Gly Ala Asp Gly Val Gly Ser Ser
    210                 215                 220

Ser Gly Asn Trp His Cys Asp Ser Gln Trp Leu Gly Asp Arg Val Ile
225                 230                 235                 240

Thr Thr Ser Thr Arg Thr Trp Ala Leu Pro Thr Tyr Asn Asn His Leu
                245                 250                 255

Tyr Lys Gln Ile Ser Asn Ser Thr Ser Gly Gly Ser Ser Asn Asp Asn
            260                 265                 270

Ala Tyr Phe Gly Tyr Ser Thr Pro Trp Gly Tyr Phe Asp Phe Asn Arg
        275                 280                 285

Phe His Cys His Phe Ser Pro Arg Asp Trp Gln Arg Leu Ile Asn Asn
    290                 295                 300

Asn Trp Gly Phe Arg Pro Lys Arg Leu Asn Phe Lys Leu Phe Asn Ile
305                 310                 315                 320

Gln Val Lys Glu Val Thr Asp Asn Asn Gly Val Lys Thr Ile Ala Asn
                325                 330                 335
```

```
Asn Leu Thr Ser Thr Val Gln Val Phe Thr Asp Ser Asp Tyr Gln Leu
            340                 345                 350

Pro Tyr Val Leu Gly Ser Ala His Glu Gly Cys Leu Pro Pro Phe Pro
        355                 360                 365

Ala Asp Val Phe Met Ile Pro Gln Tyr Gly Tyr Leu Thr Leu Asn Asp
    370                 375                 380

Gly Ser Gln Ala Val Gly Arg Ser Ser Phe Tyr Cys Leu Glu Tyr Phe
385                 390                 395                 400

Pro Ser Gln Met Leu Arg Thr Gly Asn Asn Phe Gln Phe Ser Tyr Glu
                405                 410                 415

Phe Glu Asn Val Pro Phe His Ser Ser Tyr Ala His Ser Gln Ser Leu
            420                 425                 430

Asp Arg Leu Met Asn Pro Leu Ile Asp Gln Tyr Leu Tyr Tyr Leu Ser
        435                 440                 445

Lys Thr Ile Asn Gly Ser Gly Gln Asn Gln Gln Thr Leu Lys Phe Ser
    450                 455                 460

Val Ala Gly Pro Ser Asn Met Ala Val Gln Gly Arg Asn Tyr Ile Pro
465                 470                 475                 480

Gly Pro Ser Tyr Arg Gln Gln Arg Val Ser Thr Thr Val Thr Gln Asn
                485                 490                 495

Asn Asn Ser Glu Phe Ala Trp Pro Gly Ala Ser Ser Trp Ala Leu Asn
            500                 505                 510

Gly Arg Asn Ser Leu Met Asn Pro Gly Pro Ala Met Ala Ser His Lys
        515                 520                 525

Glu Gly Glu Asp Arg Phe Phe Pro Leu Ser Gly Ser Leu Ile Phe Gly
    530                 535                 540

Lys Gln Gly Thr Gly Arg Asp Asn Val Asp Ala Asp Lys Val Met Ile
```

545 550 555 560

Thr Asn Glu Glu Glu Ile Lys Thr Thr Asn Pro Val Ala Thr Glu Ser
565 570 575

Tyr Gly Gln Val Ala Thr Asn His Gln Ser Ala Gln Ala Gln Ala Gln
580 585 590

Thr Gly Trp Val Gln Asn Gln Gly Ile Leu Pro Gly Met Val Trp Gln
595 600 605

Asp Arg Asp Val Tyr Leu Gln Gly Pro Ile Trp Ala Lys Ile Pro His
610 615 620

Thr Asp Gly Asn Phe His Pro Ser Pro Leu Met Gly Gly Phe Gly Met
625 630 635 640

Lys His Pro Pro Pro Gln Ile Leu Ile Lys Asn Thr Pro Val Pro Ala
645 650 655

Asp Pro Pro Thr Ala Phe Asn Lys Asp Lys Leu Asn Ser Phe Ile Thr
660 665 670

Gln Tyr Ser Thr Gly Gln Val Ser Val Glu Ile Glu Trp Glu Leu Gln
675 680 685

Lys Glu Asn Ser Lys Arg Trp Asn Pro Glu Ile Gln Tyr Thr Ser Asn
690 695 700

Tyr Tyr Lys Ser Asn Asn Val Glu Phe Ala Val Asn Thr Glu Gly Val
705 710 715 720

Tyr Ser Glu Pro Arg Pro Ile Gly Thr Arg Tyr Leu Thr Arg Asn Leu
725 730 735

<210> 82
<211> 1359
<212> DNA
<213> Homo sapiens

<400> 82
atgaaccggc agctagtgaa cattttgaca gccttgtttg cattttttctt agagacaaac 60

cacttcagga cggctttctg caaagaccat gactccaggt ctggaaaaca accttcacag 120

accctatctc cttcagattt cttggacaag ttaatgggaa ggacatcagg atatgatgca 180

agaatcaggc caaattttaa aggtcctcca gtaaacgtta cttgcaatat ttttatcaac 240

agttttggat cagtcacaga aacgaccatg gactaccgag tgaatatttt tctgagacaa 300

cagtggaatg attcacggct ggcgtacagt gagtacccag atgactccct ggacttggac 360

ccatccatgc tagactccat ttggaaacca gatttgttct ttgccaatga gaagggtgcc 420

aacttccacg atgtcaccac tgacaacaaa ttgctacgga tttcgaaaaa tggcaaagtg 480

ctctacagta tcagactcac cttgacctta tcctgtccca tggacttgaa gaactttccg 540

atggatgtcc agacctgtac aatgcagctg gagagttttg ggtacacgat gaatgacctg 600

atatttgagt ggttaagtga tggtccagtg caagttgctg aaggattgac cctgccccag 660

tttattttga aagaagagaa ggaacttggc tactgtacaa agcactacaa cactggaaag 720

tttacctgca ttgaggtcaa gtttcatctg gaacgccaaa tgggatatta tttgatccag 780

atgtacatcc caagcctgct tatagtaatt ttgtcctggg tttccttttg gataaatatg 840

gatgcagccc ctgccagggt cgcactgggc atcaccacag tcttaacgat gaccacccag 900

agttcaggct ccagggcatc tctgccaaag gtctcctatg taaaagcgat tgacatctgg 960

atggcggtgt gccttctgtt tgtgtttgct gccttactgg aatacgcagc ggtgaacttc 1020

gtctccaggc aacacaagga gttcctgcgc ctccgaagaa gacagaagag gcagaataag 1080

gaagaagacg ttactcgtga aagtcgtttt aattttagcg gttatgggat gggtcactgc 1140

ctccaagtga aagatggaac agctgtcaag gccacacctg ccaacccact cccacaaccg 1200

ccaaaagatg gagatgctat caagaagaag tttgtggacc gggcaaaaag gattgacacg 1260

atatctcgag ctgccttccc attggccttc ctcattttca acatctttta ctggatcaca 1320

tacaagatca ttcggcatga agatgtccac aagaaatag 1359

<210> 83
<211> 452
<212> PRT
<213> Homo sapiens

<400> 83

Met Asn Arg Gln Leu Val Asn Ile Leu Thr Ala Leu Phe Ala Phe Phe

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1               5                   10                  15

Leu Glu Thr Asn His Phe Arg Thr Ala Phe Cys Lys Asp His Asp Ser
            20                  25                  30

Arg Ser Gly Lys Gln Pro Ser Gln Thr Leu Ser Pro Ser Asp Phe Leu
        35                  40                  45

Asp Lys Leu Met Gly Arg Thr Ser Gly Tyr Asp Ala Arg Ile Arg Pro
    50                  55                  60

Asn Phe Lys Gly Pro Pro Val Asn Val Thr Cys Asn Ile Phe Ile Asn
65                  70                  75                  80

Ser Phe Gly Ser Val Thr Glu Thr Thr Met Asp Tyr Arg Val Asn Ile
                85                  90                  95

Phe Leu Arg Gln Gln Trp Asn Asp Ser Arg Leu Ala Tyr Ser Glu Tyr
            100                 105                 110

Pro Asp Asp Ser Leu Asp Leu Asp Pro Ser Met Leu Asp Ser Ile Trp
        115                 120                 125

Lys Pro Asp Leu Phe Phe Ala Asn Glu Lys Gly Ala Asn Phe His Asp
    130                 135                 140

Val Thr Thr Asp Asn Lys Leu Leu Arg Ile Ser Lys Asn Gly Lys Val
145                 150                 155                 160

Leu Tyr Ser Ile Arg Leu Thr Leu Thr Leu Ser Cys Pro Met Asp Leu
                165                 170                 175

Lys Asn Phe Pro Met Asp Val Gln Thr Cys Thr Met Gln Leu Glu Ser
            180                 185                 190

Phe Gly Tyr Thr Met Asn Asp Leu Ile Phe Glu Trp Leu Ser Asp Gly
        195                 200                 205

Pro Val Gln Val Ala Glu Gly Leu Thr Leu Pro Gln Phe Ile Leu Lys
    210                 215                 220
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Glu Glu Lys Glu Leu Gly Tyr Cys Thr Lys His Tyr Asn Thr Gly Lys
225                 230                 235                 240


Phe Thr Cys Ile Glu Val Lys Phe His Leu Glu Arg Gln Met Gly Tyr
                245                 250                 255


Tyr Leu Ile Gln Met Tyr Ile Pro Ser Leu Leu Ile Val Ile Leu Ser
            260                 265                 270


Trp Val Ser Phe Trp Ile Asn Met Asp Ala Ala Pro Ala Arg Val Ala
        275                 280                 285


Leu Gly Ile Thr Thr Val Leu Thr Met Thr Thr Gln Ser Ser Gly Ser
    290                 295                 300


Arg Ala Ser Leu Pro Lys Val Ser Tyr Val Lys Ala Ile Asp Ile Trp
305                 310                 315                 320


Met Ala Val Cys Leu Leu Phe Val Phe Ala Ala Leu Leu Glu Tyr Ala
                325                 330                 335


Ala Val Asn Phe Val Ser Arg Gln His Lys Glu Phe Leu Arg Leu Arg
            340                 345                 350


Arg Arg Gln Lys Arg Gln Asn Lys Glu Glu Asp Val Thr Arg Glu Ser
        355                 360                 365


Arg Phe Asn Phe Ser Gly Tyr Gly Met Gly His Cys Leu Gln Val Lys
    370                 375                 380


Asp Gly Thr Ala Val Lys Ala Thr Pro Ala Asn Pro Leu Pro Gln Pro
385                 390                 395                 400


Pro Lys Asp Gly Asp Ala Ile Lys Lys Lys Phe Val Asp Arg Ala Lys
                405                 410                 415


Arg Ile Asp Thr Ile Ser Arg Ala Ala Phe Pro Leu Ala Phe Leu Ile
            420                 425                 430


Phe Asn Ile Phe Tyr Trp Ile Thr Tyr Lys Ile Ile Arg His Glu Asp
```

435 440 445

Val His Lys Lys
450

<210> 84
<211> 1395
<212> DNA
<213> Homo sapiens

<400> 84
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ctgttactca gtttggttgc cacaaaggaa acagacagtg caagatctcg aagtgctcca 120

atgtcacctt ctgattttct ggataaatta atgggcagga catcaggata tgatgcaaga 180

atcagaccca attttaaagg ccctccagtt aatgtcacat gcaacatatt catcaacagc 240

tttggctcta tcgcagagac gaccatggat tacagagtga atatctttct tcgtcagaaa 300

tggaatgatc cccgcctcgc gtacagtgaa tatcctgacg actctttaga cctcgacccc 360

tccatgttgg actccatttg gaaacctgat ttgttctttg ccaatgaaaa gggtgccaac 420

tttcatgaag tcactacaga caacaaattg ctaagaattt tcaaaaatgg aaatgttctt 480

tattcaataa gattaacatt aacactttcc tgtccaatgg atctcaagaa ttttcccatg 540

gatgtacaaa catgtataat gcaactggaa agctttgggt acacaatgaa tgatctcatt 600

tttgaatggc aagatgaggc acccgtacaa gtggcagaag gactcacttt gccccagttt 660

ctgttgaaag aagaaaaaga tttacgatac tgcactaaac attacaatac aggaaagttt 720

acgtgtatag aagtgcgatt ccatctggag cgacaaatgg gatactatct gatccagatg 780

tacattccca gtctcctgat tgttattcta tcctgggttt cattctggat caacatggat 840

gcagcaccgg ccagggtagc tctggggata accactgtgc taacgatgac tacacagagt 900

tcaggatcac gagcttcctt gccaaaagtt tcatatgtca aagctattga tatttggatg 960

gcagtatgcc tccttttgt gttttcagca cttctggagt atgcagctgt aaattttgta 1020

tcaagacaac acaaagaact tctgagattt cgacgaaaga gaaagaataa gacagaagct 1080

tttgcactgg agaagtttta ccgtttctca gatatggatg atgaggtaag ggaaagccga 1140

ttcagcttca cagcctatgg aatgggacca tgtctacaag caaaggatgg catgactcca 1200

aagggcccca accaccctgt ccaggtaatg ccaaaaagtc ctgatgaaat gaggaaggtc 1260

tttatcgacc gggccaagaa gattgatacc atctcccgag cctgcttccc attagctttt 1320

ttgattttta atattttcta ctgggttatc tataaaattc ttaggcatga ggatattcat 1380

cagcagcaag attaa 1395

<210> 85
<211> 464
<212> PRT
<213> Homo sapiens

<400> 85

Met Ala His Val Arg His Phe Arg Thr Leu Val Ser Gly Phe Tyr Phe
1 5 10 15

Trp Glu Ala Ala Leu Leu Leu Ser Leu Val Ala Thr Lys Glu Thr Asp
20 25 30

Ser Ala Arg Ser Arg Ser Ala Pro Met Ser Pro Ser Asp Phe Leu Asp
35 40 45

Lys Leu Met Gly Arg Thr Ser Gly Tyr Asp Ala Arg Ile Arg Pro Asn
50 55 60

Phe Lys Gly Pro Pro Val Asn Val Thr Cys Asn Ile Phe Ile Asn Ser
65 70 75 80

Phe Gly Ser Ile Ala Glu Thr Thr Met Asp Tyr Arg Val Asn Ile Phe
85 90 95

Leu Arg Gln Lys Trp Asn Asp Pro Arg Leu Ala Tyr Ser Glu Tyr Pro
100 105 110

Asp Asp Ser Leu Asp Leu Asp Pro Ser Met Leu Asp Ser Ile Trp Lys
115 120 125

Pro Asp Leu Phe Phe Ala Asn Glu Lys Gly Ala Asn Phe His Glu Val
130 135 140

Thr Thr Asp Asn Lys Leu Leu Arg Ile Phe Lys Asn Gly Asn Val Leu
145 150 155 160

```
Tyr Ser Ile Arg Leu Thr Leu Thr Leu Ser Cys Pro Met Asp Leu Lys
                165                 170                 175

Asn Phe Pro Met Asp Val Gln Thr Cys Ile Met Gln Leu Glu Ser Phe
            180                 185                 190

Gly Tyr Thr Met Asn Asp Leu Ile Phe Glu Trp Gln Asp Glu Ala Pro
        195                 200                 205

Val Gln Val Ala Glu Gly Leu Thr Leu Pro Gln Phe Leu Leu Lys Glu
    210                 215                 220

Glu Lys Asp Leu Arg Tyr Cys Thr Lys His Tyr Asn Thr Gly Lys Phe
225                 230                 235                 240

Thr Cys Ile Glu Val Arg Phe His Leu Glu Arg Gln Met Gly Tyr Tyr
                245                 250                 255

Leu Ile Gln Met Tyr Ile Pro Ser Leu Leu Ile Val Ile Leu Ser Trp
            260                 265                 270

Val Ser Phe Trp Ile Asn Met Asp Ala Ala Pro Ala Arg Val Ala Leu
        275                 280                 285

Gly Ile Thr Thr Val Leu Thr Met Thr Thr Gln Ser Ser Gly Ser Arg
    290                 295                 300

Ala Ser Leu Pro Lys Val Ser Tyr Val Lys Ala Ile Asp Ile Trp Met
305                 310                 315                 320

Ala Val Cys Leu Leu Phe Val Phe Ser Ala Leu Leu Glu Tyr Ala Ala
                325                 330                 335

Val Asn Phe Val Ser Arg Gln His Lys Glu Leu Leu Arg Phe Arg Arg
            340                 345                 350

Lys Arg Lys Asn Lys Thr Glu Ala Phe Ala Leu Glu Lys Phe Tyr Arg
        355                 360                 365

Phe Ser Asp Met Asp Asp Glu Val Arg Glu Ser Arg Phe Ser Phe Thr
```

```
    370                 375                 380

Ala Tyr Gly Met Gly Pro Cys Leu Gln Ala Lys Asp Gly Met Thr Pro
385                 390                 395                 400

Lys Gly Pro Asn His Pro Val Gln Val Met Pro Lys Ser Pro Asp Glu
                405                 410                 415

Met Arg Lys Val Phe Ile Asp Arg Ala Lys Lys Ile Asp Thr Ile Ser
            420                 425                 430

Arg Ala Cys Phe Pro Leu Ala Phe Leu Ile Phe Asn Ile Phe Tyr Trp
        435                 440                 445

Val Ile Tyr Lys Ile Leu Arg His Glu Asp Ile His Gln Gln Gln Asp
    450                 455                 460
```

<210> 86
<211> 1350
<212> DNA
<213> Homo sapiens

<400> 86

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atggcccacg tgagacactt tcggacatta gtttcgggat tttacttctg ggaagcagca       60

ctgttactca gtttggttgc cacaaaggaa acagacagtg caagatctcg aagtgctcca      120

atgtcacctt ctgattttct ggataaatta atgggcagga catcaggata tgatgcaaga      180

atcagaccca attttaaagg ccctccagtt aatgtcacat gcaacatatt catcaacagc      240

tttggctcta tcgcagagac gaccatggat tacagagtga atatctttct tcgtcagaaa      300

tggaatgatc cccgcctcgc gtacagtgaa tatcctgacg actctttaga cctcgacccc      360

tccatgttgg actccatttg gaaacctgat ttgttctttg ccaatgaaaa gggtgccaac      420

tttcatgaag tcactacaga caacaaattg ctaagaattt tcaaaaatgg aaatgttctt      480

tattcaataa gattaacatt aacactttcc tgtccaatgg atctcaagaa ttttcccatg      540

gatgtacaaa catgtataat gcaactggaa agctttgggt acacaatgaa tgatctcatt      600

tttgaatggc aagatgaggc acccgtacaa gtggcagaag gactcacttt gccccagttt      660

ctgttgaaag aagaaaaaga tttacgatac tgcactaaac attacaatac aggaaagttt      720

acgtgtatag aagtgcgatt ccatctggag cgacaaatgg gatactatct gatccagatg      780
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tacattccca gtctcctgat tgttattcta tcctgggttt cattctggat caacatggat 840

gcagcaccgg ccagggtagc tctggggata accactgtgc taacgatgac tacacagagt 900

tcaggatcac gagcttcctt gccaaaagtt tcatatgtca aagctattga tatttggatg 960

gcagtatgcc tccttttgt gttttcagca cttctggagt atgcagctgt aaattttgta 1020

tcaagacaac acaaagaact tctgagattt cgacgaaaga gaaagaataa ggatgatgag 1080

gtaagggaaa gccgattcag cttcacagcc tatggaatgg gaccatgtct acaagcaaag 1140

gatggcatga ctccaaaggg ccccaaccac cctgtccagg taatgccaaa aagtcctgat 1200

gaaatgagga aggtctttat cgaccgggcc aagaagattg ataccatctc ccgagcctgc 1260

ttcccattag ctttttgat ttttaatatt ttctactggg ttatctataa aattcttagg 1320

catgaggata ttcatcagca gcaagattaa 1350

<210> 87
<211> 449
<212> PRT
<213> Homo sapiens

<400> 87

Met Ala His Val Arg His Phe Arg Thr Leu Val Ser Gly Phe Tyr Phe
1 5 10 15

Trp Glu Ala Ala Leu Leu Leu Ser Leu Val Ala Thr Lys Glu Thr Asp
20 25 30

Ser Ala Arg Ser Arg Ser Ala Pro Met Ser Pro Ser Asp Phe Leu Asp
35 40 45

Lys Leu Met Gly Arg Thr Ser Gly Tyr Asp Ala Arg Ile Arg Pro Asn
50 55 60

Phe Lys Gly Pro Pro Val Asn Val Thr Cys Asn Ile Phe Ile Asn Ser
65 70 75 80

Phe Gly Ser Ile Ala Glu Thr Thr Met Asp Tyr Arg Val Asn Ile Phe
85 90 95

Leu Arg Gln Lys Trp Asn Asp Pro Arg Leu Ala Tyr Ser Glu Tyr Pro

```
            100                 105                 110

Asp Asp Ser Leu Asp Leu Asp Pro Ser Met Leu Asp Ser Ile Trp Lys
        115                 120                 125

Pro Asp Leu Phe Phe Ala Asn Glu Lys Gly Ala Asn Phe His Glu Val
    130                 135                 140

Thr Thr Asp Asn Lys Leu Leu Arg Ile Phe Lys Asn Gly Asn Val Leu
145                 150                 155                 160

Tyr Ser Ile Arg Leu Thr Leu Thr Leu Ser Cys Pro Met Asp Leu Lys
                165                 170                 175

Asn Phe Pro Met Asp Val Gln Thr Cys Ile Met Gln Leu Glu Ser Phe
            180                 185                 190

Gly Tyr Thr Met Asn Asp Leu Ile Phe Glu Trp Gln Asp Glu Ala Pro
        195                 200                 205

Val Gln Val Ala Glu Gly Leu Thr Leu Pro Gln Phe Leu Leu Lys Glu
    210                 215                 220

Glu Lys Asp Leu Arg Tyr Cys Thr Lys His Tyr Asn Thr Gly Lys Phe
225                 230                 235                 240

Thr Cys Ile Glu Val Arg Phe His Leu Glu Arg Gln Met Gly Tyr Tyr
                245                 250                 255

Leu Ile Gln Met Tyr Ile Pro Ser Leu Leu Ile Val Ile Leu Ser Trp
            260                 265                 270

Val Ser Phe Trp Ile Asn Met Asp Ala Ala Pro Ala Arg Val Ala Leu
        275                 280                 285

Gly Ile Thr Thr Val Leu Thr Met Thr Thr Gln Ser Ser Gly Ser Arg
    290                 295                 300

Ala Ser Leu Pro Lys Val Ser Tyr Val Lys Ala Ile Asp Ile Trp Met
305                 310                 315                 320
```

```
Ala Val Cys Leu Leu Phe Val Phe Ser Ala Leu Leu Glu Tyr Ala Ala
                325                 330                 335

Val Asn Phe Val Ser Arg Gln His Lys Glu Leu Leu Arg Phe Arg Arg
            340                 345                 350

Lys Arg Lys Asn Lys Asp Asp Glu Val Arg Glu Ser Arg Phe Ser Phe
        355                 360                 365

Thr Ala Tyr Gly Met Gly Pro Cys Leu Gln Ala Lys Asp Gly Met Thr
    370                 375                 380

Pro Lys Gly Pro Asn His Pro Val Gln Val Met Pro Lys Ser Pro Asp
385                 390                 395                 400

Glu Met Arg Lys Val Phe Ile Asp Arg Ala Lys Lys Ile Asp Thr Ile
                405                 410                 415

Ser Arg Ala Cys Phe Pro Leu Ala Phe Leu Ile Phe Asn Ile Phe Tyr
            420                 425                 430

Trp Val Ile Tyr Lys Ile Leu Arg His Glu Asp Ile His Gln Gln Gln
        435                 440                 445

Asp
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<210> 88
<211> 439
<212> PRT
<213> Artificial Sequence

<220>
<223> synthetic sequence of chimeric LGIC

<400> 88

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Met Arg Cys Ser Pro Gly Gly Val Trp Leu Ala Leu Ala Ala Ser Leu
1               5                   10                  15

Leu His Val Ser Leu Gln Gly Glu Phe Gln Arg Lys Leu Tyr Lys Glu
            20                  25                  30
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Leu Val Lys Asn Tyr Asn Pro Leu Glu Arg Pro Val Ala Asn Asp Ser
        35                  40                  45

Gln Pro Leu Thr Val Tyr Phe Ser Leu Ser Leu Leu Gln Ile Met Asp
    50                  55                  60

Val Asp Glu Lys Asn Gln Val Leu Thr Thr Asn Ile Trp Leu Gln Met
65                  70                  75                  80

Ser Trp Thr Asp His Tyr Leu Gln Trp Asn Val Ser Glu Tyr Pro Gly
                85                  90                  95

Val Lys Thr Val Arg Phe Pro Asp Gly Gln Ile Trp Lys Pro Asp Ile
            100                 105                 110

Leu Leu Tyr Asn Ser Ala Asp Glu Arg Phe Asp Ala Thr Phe His Thr
        115                 120                 125

Asn Val Leu Val Asn Ser Ser Gly His Cys Gln Cys Leu Pro Pro Gly
    130                 135                 140

Ile Phe Lys Ser Ser Cys Pro Met Asp Leu Lys Asn Phe Pro Met Asp
145                 150                 155                 160

Val Gln Thr Cys Lys Leu Lys Phe Gly Ser Trp Ser Tyr Gly Gly Trp
                165                 170                 175

Ser Leu Asp Leu Gln Met Gln Glu Ala Asp Ile Ser Gly Tyr Ile Pro
            180                 185                 190

Asn Gly Glu Trp Asp Leu Val Gly Ile Pro Gly Lys Arg Ser Glu Arg
        195                 200                 205

Phe Tyr Glu Cys Cys Lys Glu Pro Tyr Pro Asp Val Thr Phe Thr Val
    210                 215                 220

Thr Met Arg Arg Arg Met Gly Tyr Tyr Leu Ile Gln Met Tyr Ile Pro
225                 230                 235                 240

Ser Leu Leu Ile Val Ile Leu Ser Trp Ile Ser Phe Trp Ile Asn Met
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                245                 250                 255

Asp Ala Ala Pro Ala Arg Val Gly Leu Gly Ile Thr Thr Val Leu Thr
            260                 265                 270

Met Thr Thr Gln Ser Ser Gly Ser Arg Ala Ser Leu Pro Lys Val Ser
        275                 280                 285

Tyr Val Lys Ala Ile Asp Ile Trp Met Ala Val Cys Leu Leu Phe Val
    290                 295                 300

Phe Ser Ala Leu Leu Glu Tyr Ala Ala Val Asn Phe Val Ser Arg Gln
305                 310                 315                 320

His Lys Glu Leu Leu Arg Phe Arg Arg Lys Arg Arg His His Lys Ser
                325                 330                 335

Pro Met Leu Asn Leu Phe Gln Glu Asp Glu Ala Gly Glu Gly Arg Phe
            340                 345                 350

Asn Phe Ser Ala Tyr Gly Met Gly Pro Ala Cys Leu Gln Ala Lys Asp
        355                 360                 365

Gly Ile Ser Val Lys Gly Ala Asn Asn Ser Asn Thr Thr Asn Pro Pro
    370                 375                 380

Pro Ala Pro Ser Lys Ser Pro Glu Glu Met Arg Lys Leu Phe Ile Gln
385                 390                 395                 400

Arg Ala Lys Lys Ile Asp Lys Ile Ser Arg Ile Gly Phe Pro Met Ala
                405                 410                 415

Phe Leu Ile Phe Asn Met Phe Tyr Trp Ile Ile Tyr Lys Ile Val Arg
            420                 425                 430

Arg Glu Asp Val His Asn Gln
        435
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