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(54) **TARGETED GENE THERAPIES FOR PAIN AND OTHER NEURO-RELATED DISORDERS**

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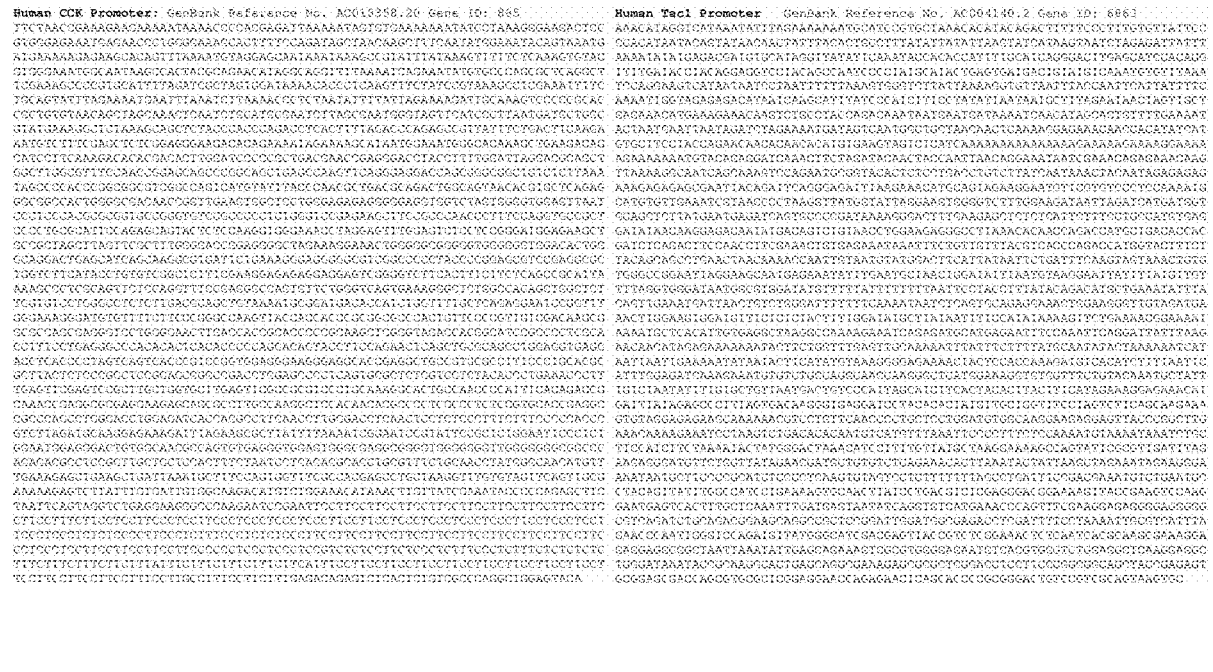
(57) **ABSTRACT**

Provided herein are nucleic acids for expressing modified ligand-gated ion channel proteins in excitable cells or secretory cells, such as nerves and neurons and optionally including viral sequences, such as Adeno-associated virus sequences, for delivery to excitable cells or secretory cells of a patient. Also provided herein are methods of modulating cell membrane potentials in an excitable cell or secretory cell, and for treatment of a disease or disorder associated with the nervous system in a patient, such as chronic pain or itch.

Specification includes a Sequence Listing.



Human CCK Promoter: GenBank Reference No. AC018358.20 Gene ID: 885

TTCTAACCGAAAGAAGAAAAATAAAACCCCACGAGATTAAAAATAGTGTGAAAAAAATATCCTAAAGGGAAGACTCC
GTGGGAGAAATGAGAACCCTGGGGAAAGCACTTTTCCAGATAGCTAACAAGCTTTCAATATGGAAATACAGTAAATG
ATGAAAAAGAGAAGCACAGTTTAAAATGTAGGAGCAATAAATAAAGCCGTATTTATAAAGTTTTTCTCAAAGTGTAC
GTGGGAAATGGCAATAAGCCACTACGCAGAACATAGGCAGGTTTTAAAATCAGAAATATGTGCCCAGCGCTCAGGCT
TCGAAAGCCCCGTGCATTTTAGATCGCTAGTGGATAAAACACCCTCAAGTTTCTATCCGTAAAGCCTCGAAATTTTC
TGCAGTATTTAGAAAATGAATTTAAATCTTAAAACCCTCTAATATTTTATTAGAAAAGATTGCAAAGTCCCCCGCAC
CGCTGTGTAACAGCTAGCAAACTCAATCTGCATGCGAATCTTAGCGAATGGGTAGTTCATCCCTTAATGATGCTGGC
GTATGAAAGGCTCTAAAGCAGCTCTACCCACCCAGACCTCACTTTTAGACCCAGAGCCGTTATTTCTGACTTCAAGA
AATGTCTTTCGAGCTCTCGGAGGGAAGACACAGAAAATAGAAAAGCATAATGGAAATGGGCACAAAGCTGAAGACAG
CATCCTTCAAAGACACACGACACTTGGATCCCCCGCTGACGAACCGAGGGACCTACCTTTTGGATTAGGACGCAGCT
GGCTTGGCGTTTCCAACCGGAGCAGCCCGGCAGCTGAGCCAAGTTCAGGGAGGACCAGCGGGCGGCTGTCTCTTAAA
TAGCCCCACCCGGCGGCGTCGGCCAGTCATGTATTTACCCAACGCTGACGCAGACTGGCAGTAACACGTGCTCAGAG
GGCGGCCACTGGGGCGACAACCGGTTGAAGTGGCTCCTGGGAGAGAGGGGGAGGTGGTCTAGTGGGGTGGAGTTAAT
CCCTCCCACGCGCGGTGCCGGGTGTCCGCCCCCTCTGGGTCCGAGAAGCTTCCGCCCAACCCTTTCCAGGTGCCGCT
CCCCTGCGCATTCCAGAGCAGTACTCTCCAAGGTGGGAAACCTAGGAGTTTGGAGTCTCCTCCGGGATGGAGAAGCT
GCCGCTAGCTTAGTTCGCTTTGGGGACCGGAGGGGCTAGAAAGGAAACTGGGGGCGGGGGTGGGGGGTGGACACTGG
GCAGGACTGAGCATCAGCAAGGCGTGATTCTGAAAGGGAGGGGGCGTCGGCCCCCTACCCCGGAGCGTCCGAGGCGC
TGGTCTTCATACCTGTGTCGGCTCTTTCGAAGGAGAGAGGAGGAGTCGGGGTCTTCACTTTCTTCTCAGCCGCATTA
AAAGCCCTCGCAGTTCTCCAGGTTTCCGAGGGCCAGTGTTCTGGGTCAGTGAAAGGGCTCTGGCCACAGCTGGCTCT
TGGTGTCCTGGGCCTCTCTTGACGCAGCTGTAAAATGCGGATGACACCATCTGGTTTTGCTCAGAGGAATCCGGTTT
GGGAAAGGGATGTGTTTTCTTCCCGGGCCAAGTTACCACCACCCGCGGCGCCCACTGTTCCCCGTTGTCGACAAGCG
GCGCCAGCGAGGGTCCTGGGGAACTTGACCACCGCACCCCCGCAAGCTCGGGTAGACCACGGCATCCGCCCCTCGCA
CCTTTCCTGAGGGCCCACACACTCACACCCCCAGGACAGTACCTTCCAGAACTCAGCTGCGCAGCCTGGAGGTGAGG
ACCTCACCCCTAGTCAGTCACCCGTCCGGTGGAGGGAAGGGAGGCACCGAGGCTGCCGTGCGCCTTTCCCTGCACGC
GGTTACTCTCCCGGCTCCGGAGCGGGCCGACCTGGAGCCCCTCAGTGCGCTCTGGTCGTCTACACCCTGAAACCCTT
TGAGTTCGAGTCCGCTTGCTGGTGCTTGAGTTCGCCGCGTCCCTGCAAAGGCACTGCCAACCCCATTTCACAGACCG
CAAACCGAGGCGCGAGGAAGAGCAGCGCCTTGCCAAGGCTCCACAACACGCCCCTCGCCCTCTCCGTGCACCGAGGC
CGCCCAGCCTGGGACCTGGAGATCACCAGGCCTTGAACCTTGGGACCTCAACTCCTCTCCCTTTCTTTCCCCCACCC
GTCTTAGATGCAAGGAGAAAGATTTAGAAGCGCTTATTTTAAAATCGGAATCCGTATTCCGCTCTGGAATTCCCTCT
GGAATGGAGGGACTGTGGCAACGCCAGTGTGAGGGTGGAGTGGGCGAGGCGGGGTGGGGGGGTTGGGGGGGCGGCCC
AGAGACGCCTCCGGTTGCTGCTCCACTTTCTAATCCTGAGAGGCAGCTGCGTTTCTGCAACCTATGGGCAACATGTT
TGAAAGAGCTGAAGCTGATTAAATGCTTTCCAGTGGTTTCGCCACGAGCCTGCTAAGGTTTGTGTAGTTCAGTTGCG
AAAAAGAGTCTTATTTGTGATTGTGGCAAGACATGTCTGGAAACATAAACTTGTTATCGAAATACCCCCAGAGCTTC
TAATTCAGTAGGTCTGAGGAAGGGCCCAAGAATCCGAATTCCTTCCTTCCTTCCTTCCTTCCTTCCTTCCTTCCTTC
CTTCCTTTCTTCCTCCTTCCCTCCTTCCCTCCCTCCCTCCCTTCCTTCCTCCCTCCCTCCCTCCCTTCCTCCCTCCT
TCCCTCCCTCTCTCCCCTTCCCTCTTTCCCTCTCTCCCTTCCTTCCTTCCTTCCTTCCTTCCTTCCTTCCTTCCTTC
CCTCCCTCCTTCCTTCCTTCCTTCCCCCCTCCCTCCCTCCGTCTCTCCTTCTCCCTCTTTCCCTCTTTCTCTCTCTC
TTTCTTTCTTTCTTCTTTATTTCTTTCTTTCTTTCTTCATTTCCTTCCTTCCTTCCTTCCTTCCTTCCTTCCTTCCT
TCCTTCCTTCCTTCCTTTCCTTGCCTTTCCTTCTTTGAGACAGAGTCTCACTCTGTCGCCCAGGCTGGAGTACA

Fig. 1A

Human Tac1 Promoter GenBank Reference No. AC004140.2 Gene ID: 6863

AAACATAGGTCATAAATATTTAGAAAAAAATGCATCCGTGCTAAACACATACAGACTTTTTCCCTTTGTGTTATTCC
CCACATAATACAGTATAACAACTATTTACACTGCCTTTATATTATATTAAGTATCATAAGTAATCTAGAGATTATTT
AAAATATATGAGACGATGTGCATAGGTTATATTCAAATACCACACCATTTTGCATCAGGGACTTGAGCATCCACAGG
TTTTGATACCTACAGGAGGTCCTACAGCCAATCCCCTATGCATACTGAGTGATGACTGTATGTCAAATGTGTTTAAA
TCCAGGAAGTCATAATAATCCTAATTTTTTAAAGTGGGTCTTATTAAAAGGTGTTAATTTACCAATTCATTATTTTC
AAAATTGGTAGAGAGACATAATCAAGCATTTATCCCATCTTTCCTATATTAATAATGCTTTAGAATAACTAGTTGCT
GAGAAACATGAAAGAAACAAGTCTGCCTACCAGACAAATAATGAATGATAAAATCAACATAGCACTGTTTTGAAAAT
ACTAATGAATTAATAGATCTAGAAAATGATAGTCAATGGCTGCTAACAACTCAAAAGGAGAAACAACCACATATCAT
GTGCTTCCTACCAGAACAACACAACACATGTGAAGTAGTCTCATCAAAAAAAAAAAAAAAAGAAAAAGAAAAGGAAAA
AGAAAAAAATGTACAGAGGATCAAACTTCTAGATACAACTACCAATTAACAGGAAATAATCGAAACAGAGAAACAAG
TTAAAAGGCAATCAGCAAAGTCCAGAATGCGGTACACTCTCCTGACCTGTCTTATCAATAAACTACAATAGAGAGAG
AAAGAGAGAGCGAATTACAGATTCAGGGAGATTTAAGAAACATGCAGTAGAAGGAATGTTCGTGTCCCTCCAAAATG
CATGTGTTGAAATCGTAACCCCTAAGGTTATGGTATTAGGAAGTGGGGTCTTTGGAAGATAATTAGATCATGATGGT
GCAGCTCTTATGAATGAGATCAGTGCCCCGATAAAAGGGACTTTGAAGAGCTCTCTCATTCTTTCCTGCCATGTGAG
GATATAACAAGGAGACAATATGACAGTCTGTAACCTGGAAGAGGGCCTTAAACACAACCAGACCATGCTGACACCAC
GATCTCAGACTTCCAACCTTCGAAACTGTGAGAAATAAATTTCTGTTGTTTACGTCACCCAGACCATGGTACTTTCT
TACAGCAGCCTGAACTAACAAAACCAATTGTAATGTATGGACTTCATTATAATTCTGATTTCAAGTAGTAAACTGTG
TGGGCCGGAATTAGGAAGCAATGAGAAATATTTGAATGCTAACTGGATATTTAATGTAAGGAATTATTTTATGTTGT
TTTAGGTGGGATAATGGCGTGGATATGTTTTTATTTTTTTTAATTCCTACCTTTATACAGACATGCTGAAATATTTA
CAGTTGAAATGATTAACTGTCTGGGATTTTTTTCAAAATAATCTCAGTGCAGAGGAAACTGGAAGGGTTGTAGATGA
AACTTGGAAGTGGATGTTTCTCTCTACTTTTGGATATGCTTATAATTTTCCATATAAAAGTTCTGAAAACGGAAAAT
AAAATGCTCACATTGTGAGGCTAAGGCCAAAAGAAATCAGAGATGCATGAGAATTTCCAAATTCAGGATTATTTAAG
AACAACATAGAGAAAAAAATACTTCTGGTTTGAGTTGCAAAAATTTATTTCTTTTATGCAATATACTAAAAAATCAT
AATTAATTGAAAAATATAATACTTCATATGTAAAGGGGAGAAAACTACTCCACCAAAGATGTCACATCTTTTAATTC
ATTTGGAGATCAAAGAAATGTGTCTGCCAGGCAACCAAGGGCTCATGGAAAGGTGTGGTTTCTGTACAAATGCTATT
TGTCTAATATTTTGTGCTGTTAATGACTGTCCCATTAGCATCTTCACTACACTTACTTTCATAGAAAGGAGAAACAT
GATTTATAGAGCCCTTTAGTGACAAGGGTGAGGATCCTACACACTATGTTGCTGGTTTCCTAGTCTTCAGCAAGAAA
GTGTAGGAGAGAAGCAAAAAACGTCCTGTTCAACCCCTGCTCCTGGATGTGGCAAGGAAGAGGAGTTACCCGGCTTG
AAACAAAAGAAATCCTAAGTCTGACACACAATGTCATGTTTAAATTCCCCTTTCTCCAAAATGTAAAATAAATCTGC
TTCCATCTTCTAAAATACTATGGGACTAAACATCCTTTTGTTATGCTAAGGAAAAGCCAGTATTCGCGTTGATTTAG
AAGAGGGATGTTCTGGTTATAGAACGATGCTGTGTCTCAGAAACACTTAAATACTATTAAGCTAGAAATAGAAGGGA
AAATAATGCTTCCCCGCATCTCCCCTCAAGTGTAGTCCTCTTTTTTTAGCCTGATTTCCGACGAAATGTCTGAATGC
CTACAGTTATTTGGCCATCCTGAAAAGTGCAACTTATCCTGACGTCTCGAGGGACGGAAAAGTTACCGAAGTCCAAG
GAATGAGTCACTTTGCTCAAATTTGATGAGTAATATCAGGTGTCATGAAACCCAGTTTCGAAGGAGAGGGGAGGGGG
CGTCAGATCTGCAGACGGAAGCAGGCCGCTCCGGATTGGATGGCGAGACCTCGATTTTCCTAAAATTGCGTCATTTA
GAACCCAATTGGGTCCAGATGTTATGGGCATCGACGAGTTACCGTCTCGGAAACTCTCAATCACGCAAGCGAAAGGA
GAGGAGGCGGCTAATTAAATATTGAGCAGAAAGTCGCGTGGGGAGAATGTCACGTGGGTCTGGAGGCTCAAGGAGGC
TGGGATAAATACCGCAAGGCACTGAGCAGGCGAAAGAGCGCGCTCGGACCTCCTTCCCGGCGGCAGCTACCGAGAGT
GCGGAGCGACCAGCGTGCGCTCGGAGGAACCAGAGAACTCAGCACCCCGCGGGACTGTCCGTCGCAGTAAGTGC

Fig. 1B

Human Nts Promoter GenBank Reference No. NG_047010.1 Gene ID: 4922

GATTATTTTCAGCAATTACCTAATAAAGGTCTGACATAAGTAACAGTACAAGCTTAGAAATCTACCTACTTTAGAGA
TGTTGTAATCAACAGGTACCTAACAGGTAACATCCACTTAAGAAGGCCAACACAGGAATATTATTAAAGGACAATGC
TTAAAATCTTTATCAGATATTTTAAGAACTAGGTAACCCTTAGAAGGATCTAAGGTATGCCGGGCATGGTGGCTCAC
GCCTGTAATCCCAGCACTTTGGGAGGCCGAGGTGGGCGGATCATGAGGTCAAGAGATCGAGACCATCCTGGCCAACA
TGGTGAAACCCCGTCTCTACTAAAAATACAAGAATTAGCTGGGCCTGGTGGTGTGCCTGTAGTCCCAGCTACTCGGG
GGGCTGAGGCAGGAGAGTTGCTTGAACCCAGGAGGTGGAGACTGCAGTGAGCCGAGATCACACCACTGCACTCCAGC
CTGGTGACAGAGAGAAGCTCCATCTCAAAAAAAAAAAAAAAGAAAAAAGAAAAAGGATCTGGGGTAAAAAGCCTTTA
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GGGTACTTTTTAAGTGGAAAAATACATACTTAACCTTTATCCCTACAACAAATTGTTTTATTGGTTTATGTGTAGCT
TGAAGGCATTAGATTAGAGCAAGAAACAAAAAGCCTAACACATTAAAGAAAATACCAATTAGAGGTCAAAGTTTATC
TACATCATAATTTTACCAAAGTTATACATCTTTTTTCCCCAAAAGAAAAGTAGCATATAGCATCTATTTGAATTTGA
ATTATTTGACATAACTTAATGTTTCCCCTATTCTTGAATATTTATCACATATCTCAATTTTCACATTAACAACTAAT
ATCCATGTTATATATTTAAAATGAATTTCCATTAATTCTTCTCCCCCTTTTTTCTAATTAATTAGGGATCAATTTTG
TCAACATATTGAAGAAATCATCTGAGGAAAATAAGAATCACATTTCCTTTTTACTATTAGACTGCTATCACACATTT
TAAAAGATCATTCTTTGTATTTGCAATTCAAAAGCAGAGAAAACAACTAATTTAATTATCATGCAAAGTATATATAA
TTTTCCCGATTTGTTAATCAAAGTGGCTTTAAGAGGATTCTGTCACAAAGATGCTCTGATAGTAACAGGAAAGTAAG
CACAAATCCTCACTGAGACTCTGTTAAGTGAAAACCAAGTGTTTCAAGCTTCCATTGCTCCCCCTAATGGTAGGAAA
GCAGAAAACATCTAGACGTATGTATTTCACATTTGTCAACTAAATACTTTACAGAAACCTTCCTCCATGTGAGTATG
TTCAATATTGTGTTTTATGTAAGTTCAGAAAACAAACTAAAAGTAATAAATATATCAGTTATTATTAAATTTCTGGT
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TGTTACTACATGATTGATTTATTTAAAAATTAAACAAGACTCAGACAACTTTACATTCAAATATTCACATCTCTAAC
AGCACTGACTTGTCAAATTACCCCATGTATCTTGAAATGCTTACTACAAGAAGAAAGTTTTACTCTAAAAGGCATTT
TGAACAATTTTCTTTTGAGAACTCAGACAAAGAATGGGTATCAGTGTAACTCATGAAATACATGAAGACTATCATAG
AAAAGTGACTTTGGTGAATGGTGGTTATTTAGGATTGTCTCCTTTCCAAAAGTACAATCTCTTTTTTTATGGTGAAA
AGAGTATTATAACAGGGAAAGAAAGCCGATGCAATAGTAAAAACTGTTGAGAAGGGAATTATACAAAGAGTGAGACA
TGGCATCAAGAATGAATTCAAAAAGAGCAGAAAAATATAGGCATAAAAAGAGATAATGTACAGAAAAAAAGTCAGTG
ATACAACAACACAAATTTTTACCTGCTAGAATGTAAGTAATTTAGAGCTGGATTTTATAAACATGAAATTGTTTTTC
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GGGCAAAGAGGGGAGGGATGGAGGTGAAGATAGGGCACATCCTGCAAAGATAATGTCTGTACAATCAATGACATCAT
CCTCCTGCTTATATATATAGGGGAATGGCCAGAGCACCTCTCATAGTTCACTCACTTTCAAAGCCAGCTGAAGGAAA
GAGGAAGTGCTAGAGAGAGCCCCCTTCAGTGTGCTTCTGACTTTTACGGACTTGGCTTGTTAGAAGGCTGAAAG

Fig. 1C

Human Nmu Promoter: GenBank Reference No. AC024243.8 Gene ID: 10874

GGATGTATTAGCTGGTGTCCTGGAAGAGGCTGCTTCCTGAACGTTTCCAATCAAGGAAATAAAGGAAAGTATAGAGA
TGGAAAGAGGGAGTCAGGTCACGGTAGAAATCAGGATGCAATAGCAGCAGAAATGCATAGAAAAAGGAGTTTCCTTA
GGCTTGGAAATCCGTAGGATAACCAGCGCTCCAGACCAGTTAGAAATGTGTGTGTGTGGTCAAGCCCCAGCAGTCCT
TTCTTCTTTGTCCTTTATTAACAGGCAACTGCATTTCCCTAAGGGGTCTGTGATTTTGCAGGAATTTGGGGGAGGGT
CGATAGCATCAACATCACAGTTGAACCAACACTGCCCTGATATGCACCAGGCATTGCGCTTGGAACTGGGGATAAAC
CGGGGAACAAAACAGAGGTGCTTCCACAGAGGTGCGTACTAGTGACTGCCGGAGCTCTGGAAGAGGTGAAGGAGAAA
GGGTGTCCCACGTAGACCCAGGACACCAGAGAGCGTCGCCACTACCAAGTTTAAAAACTCAGACGGCCTGGTTTGCC
ATCCACACCCTGTTCCCAGTCCAGTCCTTCCAAAGGTGGGAATGGTGCATTATTTAAATTCCATTCTCTTTATCCCA
GAGCGAAAATGCGTGGTACTCGGGTCAGAAACTCAGGCTAGGGGGCTCGGGTCCTGCTGCAGGGTGGGGCGCGGGCA
GGCAGCGGGGCGGGGTGAGGCGAGGTAGGCCGGGGGCGGCAGGCGGCGAGGTGACGCGCGGCGGGGACCGCGCAGCC
CAGCCCACTTGTGCGCGAGATTTAAAAGTTGGCGGCTCGCCGGGCGCTCAGTCCTGTGTCCGGGCCCCGAGGCACAG
CCAGGGCACCAGGTGGAGCACCAGCTACGCGTGGCGCAGCGCAGCGTCCCTAGCACCGAGCCTCCCGCAGCCGCCGA
GATGCTGCGAACAGAGAGCT

Human Calb1 Promoter: GenBank Reference No. AC123779.5 Gene ID: 793

ACAAATTGAAGCAAATAATTTGGAAATGTGTATTAAAATCTAAAATATGCATTCTATTAACTAAAAATACTGCTTTT
GGGACTCTGCCCTGTTGTATTCAGAAACATGTATAGCTAATATAAATGTATAAAGGTGTTTATTGCAGCATTGTGTG
TCACAGTGTACTACTAGAAATAGATCCGTATATCTGTAATTATAGTTAATTAATAAAATATTAAACTGTAAAAAGTA
TACATTAGATGTTGATGTTAATACTGGAGGGATGCCCTTGAATTAATAATAGAAAGTTGAAGGATAATATACAAAAC
ATAGTCCCTTTTCTGTAAAACCAGATAACAACAACAAAAAAAAAACCTTTAGATATGGATTTGTATATTTCCATAAG
CATGGCTCTTTTAGTGTTGATTACCTCATGGTAGGGGCAGCACTAAACTGCTTTAGAGCTCCATAATCTACATTAGT
TCCCTCAAAAGCCACTTCATATAAACATAAAAAGAACACACAAAAAAAACTATGTCCAAACTTGCTGTTTGGACATA
GTTCCAAGGAAGTCTCCCATTTATTTCTCACTCTCTCTCAAGTCACAGCACCTATACATTTCTAAATGGAAATTTGG
AAGTTGCCATAGCTTCAGGAAAGTGAATAAGAAAAAAGATTACTTTCATATAAATATTTTTAACTTTTACAAATTGT
CTTGTAATACTTTTGGAAGTTAAGATAAAATTCTAAAAAACCAACAAACAGATTATGGTGAAAATGTTTAGGAATTT
TTACCACAGTGTGTGGTCTCTTTTTAGGAAGAAAATTAATTTTAATTACTTTTTAAAATAGTAGAAATGTTGCTCTT
TTTTCATCAGTTTGTTCAGTCCATATTCCTACATACTTTTTCTAGCATTTTTCTTTGTCTCAGAACTGTATCCAAAG
TCTAGACATTGTTAGCTCTGTCAAGACTAGCAAGGGTCAGAGTGATTCTTCAAGTCATTCCTTAGTCACTGCATTCT
CACTCTCTCTTCAAAGTTTATTCTCTAGCGCTGGTCTCCAAGTTCACACACTATATTTTTCACACAGCGACCCTGGC
CACTAACATAGGACCAATAGGACCATCAGTGAGAATCAGATGAGGTATCATAAGTAAAAATAATGTATGAACTGGAA
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GCTCTGTCACCAGGCTGGAGTGCAGTGGCGTGATCTTGGCTCACTGCAACCTCCGCCTCCCAGGTTCAAGCCATTCT
CCTGCCTCAGCCTCCCAAGTAGTTCAGATTACAGGTGCCCACCCCCATGCCCAGCTAATTTTTGTATTTTTAGTAGA
GACGGGATTTCACCATGTTGGCCAGGATGGTCTCGATCTCGTGACCTTGTGATCTGCCTGCCTCGGCCTTCCAAAGT
GCTGGGATTACAGGCGTGAGCCACCGCGCCCGGCCGGTAAATTCATTTTAATTCACTTTAAGCTTATATTGGCTATG
TGTAGATTTTCTCTTGTTCCTTCATTTTGTTTTAGTACAATTGTAATTAGACTTTTGGGATACATTTTTAGTGGACT
TCAAGGTCCAAAAGACTCAAAGCCAAATACTCCAGAAGTACTTATGTAAATAAGAAATAATCCAAGTATATAATTAA
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TGATGGTGACTTCCAATTTCTGAAAAATTCTCCAGTAGGGGTTGCTTGAAACAGAAAGAAGGAGACGTGTGTGTTAA
GGCGACTGAATGGGGCTGTGGTGGTAGCACTAACGTACCTACTTATGAACCTGGTCAGATCCTTCCTTTCTCTTTGT
TTTAGTTTACTCACTCCTTCTAAACTGAAAGGCAGTAAACTCTAGTATCTGTAAGATGACTTCCTTATCTAAGATTT
TAAGGTTTTATAATTTAACTGTATTACTTTCCAATTATAATTCTACTTCATGCTGAAAAGAAATCCATAATCTAGCT
TTTTTCGTGTTGGCAAGGTTAGTTCATAGAAACCATCTTAAGAAACATTGACATGATGGCACAAAATAGAGTGATTA
TTGATAGCAATCAACTCATTGTATACATTAATCAAATTATTCTAATGCGTGCCAAGGTTTCACATGCTTTTTTTTTT
TCAAACAAATACTGAAAAGTCTTGGAGAAATCACACAAGAATATAATAATCTTTTATGTGATTTTACCCGTCATCAG
CTTTCCCCTTCTATCTGAACATTTAAACCTCTCTAGATAACAAGAGTTTTACTATAATATTCAGGAATAAGATTCTT
CCTGGACTAGGAGGATGTAGGGGGAAATGAGCCTCTGTTTTCAGCATCCAATCTCTGAGCAAAGGATCTCCCACCAC
CTGCTGCTTCCAACAAGCCCAAACTCCGCTCCAGCTAGCTTTCCTGGGAACAGAGCAGAAAACTGGAAGGGAGGGGA
AGAAGGCTGGTGAGAGCAAGAGGCGGGGGTGAGGAATGGGAGGCTGGAGGAGGCGTGGCCCGGCTTGGGGCCGTCGG
GAAAATACTGAGAACTGGGTGCGGGGTGTAGGGAGAGAACTCTGGAGGAACGCTAGCTGAGCAGCACCGAGGACAGC
GCCCGGCAGCGCCCGCGCCCAGGTCTCCTCCGCAGCCCTGACTCGCGCACACGCTGAGCTTTTGCTCACT

Fig. 1D

Human Parvalbumin Promoter: GenBank Reference No. Z82185.2 Gene ID: 5816

CCAAAGGACTTGGACCTGAAAGTTTGTAGCATTGCAGGGACAGCCATCTTGCCACCCTCAGGGGTCAACCAGTTTGA
GAGAGTGGCACAAGGTATTGCTGAGAAGTAAGAGAAACAGCATCTTCCTGACAGCATTTGAGTTCTGGATCAAACCA
TGCTTGAACCTTCGTGGACTTTTCAGTTGCACGAGTTAGCAAATCCCCCACTGTCTTAAGCCAGCCCAAGTCAGACT
TTCTCATCACTTACAGGCAAAAACAGACCTGACTGATAAACCCATTTTCTGGCATCAAGGCCCTTGTATAATTAACC
AAATTAATAAAATGAAGCCTGCTTCAATCAGCACAGATTCAGAGCAAAAAAACAAACAAACAAAAAAAAAAAAACT
AGATCATGTTTCCAGATATATGACTCGGGTTTTAGGACATCTCTACCCTACTTTAAGTATTGTAGGGGGAAAGATCC
TCCAGAATCAGAAGTGCTCAGTTTAAATCCTAGCTCTCCCACCTACTTCCTACCTGTGTGACCTTAGGTAAGTCACT
AAACCTCTCTGAGATTCTATTTCTTCGAACGTCTGAGATAAAGCACATAAAGCACTAGGTACGCAGTAGGTGCTCAA
TAAATGCACCCCCCCCCCAACACACACACACACACGATATGGTTCAGCCCATTCAGATTTGCTTAATTAGAGGTA
CATGAAGAAGACCTATGGGGACAAAGAGGAAGGCCATCTGGGCTCCTGAGAATTCACCCACAGTAGGTGCTGCTCCC
GTCTTCCGGTCTTATTCTGGAAGCAGGATAGTGTGGTAGAAAGGAGCAAGTGCTTTGGAGTCAGAGAACCGGGGCTG
AAATCCTACCTCCATTCTGTGATCTTAGGCAAGTTGCCCAATCTCTCTGAGCCTTGTTCTTCCATCATTAGTAAAAA
AGAGAGGGTTTTGCCTACCTCTTAAGGGGATACAAGAATCAAAGTGCGATGCTGTGCACACAGAACCCAGCACACTG
TTCAACAAACAAGTGTAATTATTTTCCCAGGCCCCAGCCAGCGATCTTCCTCAAGGGTTCATCCTCAAGGTTCTCCT
GCATCCCGGCTCCCTGAGCTCAGCCATGCCCACGACTTGACGAGATCAACTCCTTGACTTCTCTGATGACAAAGCCC
CCAGGGTCCAGCCCTGACCTCACTCCAGAGTTCAGACACATCTCCGCCAGGGTGTCCTTCAGGTCCCCTAAACCCAG
CATCAGCTCTTGGCTCTTCCACTACTCTCTGGGGGATTTGGGTAAGTCACCCTGGCCTTGGTTTCTTCATCTATAAC
ATGATGTCATTTGTAGAAGTTTGTAGCCGATCACCACGGAGGCTGTCCCAGCCCTAACATCCTAGGATTCAACACCA
CTTACTCTATCATCCCTTCGACTGAGCACTACCTCCTCCCTACACTCCCTGCCTTCAAAGTCAACACCTTCCTTCTT
CAGCAAACCCCACCTTGAATATTTAGGGTCAGCTTGGATTTGTCCCTCTTGTTCATGCCACAGCCCCAATTCTGGAA
GCTTCTCTCCAAGAGGTGCTCCCCTATCTGCACACTCCTTCCTGTTGCCACCACCAGCAACCTAGCTCAGGCCCCAG
CACCACACCTCAAGGAGGCCCCAGTCCCAGCTTCCCCCATGCAGCCTGCCCTCGGCCCTTTCTATCCATGGAGCTTC
CAAACAGCCTTTGCATGGAGCCTGGGATTCCTCGTGTCACTGTGAAGAACTAGACCCCACCATTGACAATCTTCGTG
CCCTGGAGATTCTTTTCAGGTTAGGGATGAGGAGAGGAACATTTCATGGTGGTCAGATTAGATATTCACTACGTATT
TATTGAATTCATTTGGTCATTCATGCTTCTCAAAACACATCCCTCAGCTGGTCCTCTCCAATCCAAAACAGACAATG
TCAGAGATCTCTTTGCAAATCATGAAGGGCTTGGGCCTTTGTGCCTCAATGTCACACGCATACAATTTCAGGGGGTC
CATCTTCCCCTCGCCCTAGACCATCTATAGGGCACAGTTTACCTCTGATTGAGCTCATGTTACAGGTGGAAAGACTG
AGAAAGAGAGAGGAAGGGACTTGTCTGAGAATATGCGGAACATTTCCTTCTACCAGGCACTAGATCCTCGCACAAAA
GTGCTGAGTCCGCTCCCAACCCCAGGCCCGTGGCTTTGAGCAGCAGGTCACTTAACATCTAACGTCTTTATGCTGTT
TCCTCATCTGTGCGAGAGCAGCTATGTCTACCTGGCAAGGCTGTAGTGAGAGATCATATCAGCATAGGAATGGGGCT
CAGCCCCATGCACAGAGGACAGTTCTTGTTTCATTCTTTTCCTTGCTGTTTCTCTTCCTTTCCTGGCAGAATATGGA
GGAAGGAAGCATCGCTGCCATCTACAGTGGTCACGGAAGGCTTCATGGAAGAGGCGAGCCCTGCCTGGGCCTCAATT
TTGGGTGCTGGAGGGAAGCAGGGGCCAAGAGTTATTAATAGTCTTGGCCTGATGGGCCCAGGGAGGCTGAATGTGAT
ACAGACACCCAGCACCACGGTTGGGGAGTACCTGACACCGGAAGGGGAGGGGGCCGGGGCTACGGGGAGTGCCACCT
CCCAAAATAGCCAGAGCAGAAGCCTATATAGGTGGCCATCCCACCTCCAGGCTCACTTCCCGACAGGACTTCCCACC
AGCCCAGCCTTTCAGTGCAGGCTCCAGCCCTCCACCCCCACCCGAGGTGAGTGGCAGCTACCGAGGTTGGAGGATAG
AGGGATGCAGCAGGATGAGCCAGCTGGAAGGGAGAGCTACATCTCCCCTGTCCGTAGTGACCCGGGGAGGGGGGTGC
GGTGGGGGTGCTGGAGGCAGGGCAGCTGTGGAATGTAGGGCTGAGAGCATGCATTCCTGCTTCTCCACCCAGACTCC
TGGTGTGGCCTGGGGCAAACTCCCCCCACCCACCGCCCCCCGTGGCTGGGCCTCAGATTCCCCAGCCTTAGAAC

Fig. 1E

Human Gal Promoter: GenBank Reference No. NG_052785.1 Gene ID: 51083

CTTGGCCTCCCAAAGTGCTGGGATTACAGGCATGAGCCACCGCACCCGGCCTGAAATTTATTTTTCTTTTTTTCCTT
TCTCTTTCCTCACTTTCCTTCCTTCTCTTTTCTTCTTCTCCTTCTCCTCCTCGTCCTCCTCCTTCTTCTTCTTTT
CTTCTTCTTCCCTTCTCTCTCTCTCTCTCTCTCTCTCCCTCCCTCCCTCCTTCTTTCTTTCTTGACAGAGACTTGCT
CTGTTGCCTATGCTGGAGTGCAGGCTTGATCGTGGCTCACTGTAGCCTCAACCTCCTGGGCTCAGGTGATCCTCCCA
CCTCAGCCTCCTGAGCTGAGTAGCTGGGACTACAGGCACGTGCCATCATGCTTGGCTGATTTTTAAAAAATATTTAT
TTATTTATTTTTAGTAGAGATGAGGCCTTGCTATGTTGCCCCAGCTGGTCTTGGACTCCAGGGCTCAAGTGATCTAT
CTACTCACCTCAGCCTCCCAAAATGCTGGGATTACAAGCGTGAGCCACTGCGCCCAGTCTGAAGTTTCTTTGAAAGC
AAAAAAGGAAACAAAAAGAGTACATAGGCCCAAATGAAGACAGCTGAAAGTTTAATGTACCTCAAATTCCAGCCCAT
GACTAAGGGATGGACTTTGAGTCTCTTTTCGAATCCATCTCAAGGATTTAGGTTTAGAGTTTGTGCTCCTTTAAACA
GACTAAGAGCCTCTGTGACAAAGTAAATAGAGAAAATAAGTGTAGTCAAGCTCTGGCAGGATTTGGAAGGGGGCCTA
ACGTGGAAGAAAGGAGAAGGCTGGAATTGACTAAGATGTGCTATGCACTGGGCTGGATTTGTTCTCAGCAGAAAGCA
AGAAAGAGCTCTGGGATGGTAGCAGGGCTCCCACTACCACCGGGGGCCAAAGGTTGCAGTATTTCTCAGGTAGCCAA
GAGGCACCCATGAGCCCAGCCCCTGCCCACTCCCTGATGTCATCTAGACACAAGGACATGGGGCATGAGAGGACATC
ATTGTCACTTCTCTGCAGAGTCACAGGAACGTGCCCTCTGCTCCTCCGCCTCTCGGCTGTCCTTCTGCCCACGGCTG
GCCCAGACTCTCATGGCGACTCACTGTCTCCCACGCCCCCACTCCCGGCAGGAAACCACTTCAGGGTTTACTGTGGG
CTCCGAAATCAGCCTGTGAGTCCTAGTTAGGGTCCCCTGTGCCTGACTCTCCTCTCCCCAGGCTGCAAGAAATAGGG
ATGACCAGAAGTCAAACTGTGCCCTTGGGAACACCCCACCCCTCACCACTGTCGTGCCAGGAGTCTGTTCCTAAGAC
CCCTCCCCAAGTCCTGTCTCCTCCTCTTCCTCCCATAAACCACAGCAGACACTCAGCCACCAGGCTGCAGCCCTGCA
CCTTCTCCAGCAGCCGCTGGCCTTCGCCAGAGTTCTTGAAAGCCCAGTTGTCCTTCCCCAGCCACGTGGAGGCAGAC
GGATCTCTCCTGGGGGCAGCCTGTAGCTGTCTGTGCAAAGGTTCCCAAGACTAAAGTGTAGAGGACAGGTAAGATGA
CACTGTCATGATCATCATTCGTCCTGTGCCCTGTGGACATCAACCCACAGATGTGACATCAACCCATCTGATATTGA
GCCCAGTGGGTGGGGAGATCCTAACCCAGCTGCTGCTGTTGAGGACTTGGGTGGTGTCTGGCCAGTGGGAGGGGAGG
TCAGGCGAGTTTTCAGCAGATGACCCCGTGCTCTTCGGAAGCCCGGAGGTGCCACACTGTACAAGTGTGATGCCTGG
GATCCTGTGCTCCCCTGATGCCTGGGAATGGGGTGAAGGAACAGCCTAGGCTTGGGTTCTCTCCTGGGTTGTTTCGG
GACTTGGCCCCAGCTCAGGAAGGGTTTGTGGAGGAGCCAAGGAGGGCCTTGTTCCTGTGGGATGTCTTTGCCTTGGG
CACAAGGACAGCCTCTTGCTGCTGCTCTGCCCACCGCCCACCCCTTGGCGGCCTCTGGGAGTCTGGGCTGCTCTCCC
TCTGGACCTAACCAGTTGCCCAATGGCTGGACCTGCTTAAGCTCCCTCTTACAACTGGACCAGGCAGCCAGGGGAGG
CACTGAGAGGCCGAGCTTCTGAGCTGGTGCCTGTGGATGCTCGACGGTCCCGCAGCTCCCACAATGGGATGGCCAAG
CAGACCCTGAGATCCACAGCCCCCCTTTAGTGAAACAGGAGGGAGGTCGCTGGGCACAGGGAGCCGGGAACGCCTGC
CCTCCCCGCCATCGACGGCTCCCGAGGCCTGAACCTTCGCTCCAGCCCCAGCACAAGCCGGCCAGGGCGCAGGGCCA
AGTGTTGCCCGCCATTCCCCGGGTACCCCATGACCTCCCAGCTGGGGCTGGCTCGGACTGAGGAGTCGTCCCTGCCC
GTCACCCTCTGGGGTCTCCAGTGCTGCGGAGCTCAGCTGGCTTTTGCAGCGGTAGGGGCTGGGAGGAGAAGCTGCAG
GGAGACCGCAGGCGTGGGACGTTGTGGGGGGTCAGGCTTGCTCTGGGGCTGGGACCCCGGGGGGAGCAGTGGGGTTG
ACGCCACAGCGATGACTTGGGCCACGGGTCTGGGGGCTCTCCCGCGGGGCGATTGGGCTCTGTCTTTCGGGATTAGG
GTCTCTCCCACAGGGTTTGGGGTTCTCTCTGCAGATTTGGGGGAGTCTCTCCCGCGGGATGAGGGGGGGCTCTCCGC
CGCACCCGCCTATGATGGCCCAGAGGACCCGAGCTCGGGTCACTCCCGTCGCCCTCGGGGCTCGGCGAGGGTGCAGG
AGGCGGGCGCTGAGCCGGTGACGCGACTCCGGGCGGCTCCCGGGTGCGCCGCATATATAGCAGCGGCGGCGGTGGCG
GCGGCCACACCGGGCGGCGGACACGTGGAGGGACCCGGCCCGCGCCTTCTGCCCCTGCTGCCGGCCGCGCCATGCGG
TGAGCGCCCCAGGCCGCCAGAGCCCACCCGACCCGGCCCGACGCCCGGACCTGCCGCCCAGACCCGCCACCGCA

Fig. 1F

Human NPY Promoter: GenBank Reference No. NG_016148.1 Gene ID: 4852

AGGTATAAGGTGCAAAATACACTGGATAGGATTGGCAGTAATCAGATATTACAGAAGAAAACATTAGTGAACTCACA
GACATAGCAATAGAGACTATCCAAAATAAAATATGAAGGAAAAAATGAGCAAAACAGAAGCAAAAACAGATCACCAA
CAAACTGTGGGCCAATATACACTCACCGTCTGACTCAGCCATTCTGGTTTTAAGTATTTTCCAAGAGAATTAAAGGC
TTTATGTCCATACAAAGACTTGCATATGAATGTCAAGGCAGCTTTATTCGTAAAAGTTTCAAGTGAAAATAACCAAA
AATTCATGAGCAGTAGAATTGATTAAAAATTTTGAAGTATATCATATAATGAAATACTGCCCAGCAATAAAAAAGAA
TAAACTATTGCTACATTTAACAATGTGAGTGGATTCAAAAATAATGATGCTAAGTGAAAGAAGTCAGACAAAGAGTA
CCTACCGTGGAACTATATTTATGTGCAATTCTAGAAAACGCAAACAAATCTCTAGTGATAGCAGATCAATGGAGGAG
GGGGTGAGGAAGAGGCAAAAGGAAGGAATTACAAAGGTACATGTGGAAATTTGGGGAAGTGATGTATAATCTTCATT
TTCTTGGTTTCAGTGATGGCTTCCTGAGCATATAACACACATGCATATGTGTAAGAATATATCCAATTGAATATTTT
ACACATTTGTAGCTTTGTATATATTCAGCAGTATCTATTCATTCCTTCTGCTTCTTTACCTTAGGTTTAGTCATGAA
ACCACTGGGTTTCATGTGGTCCAGGTTCTATCTGAATCAAGCTATGAACCTGCTATCAGTAAGACCTCCTAATTGCA
AACCACATGGACCTTTACCGGTTATTTGACTTCTCTCGGTCATTACCTTCTCTAGTCTCCACTGATTCACCTCCTTT
TGAATCTCAACAAGCTCAACAGTATCTCAATGTTATCTTAACAAAGCTGTTAGAAATAAACAACTTGACTTTGAAAC
AAAGGAGAGAAATGGCTCAGCAGCTAGGAGAAGATGCAGGGTTGAGTTGCCAACAGTTGGTTTTGTTTGTATTTTGG
CCAGGGGATGTGGCTTGGACTGGAGAGAAAGGAGATAAGGATGTAAGCACATGTAGGGCATATCACCCCCTATTTTT
TATTCTCTGAATCCTTAACCCTCAGAATAAGTTCTTATTCTTGAGAATCAATGACATTATCTTAAGCTAAATTAATC
AAGCCTCCACAGTGTTCTTCTCTCAATAGTGGTGTGGGCCTTCCTAGAAGTAATTTTTCCCAAATTCAGTGATACAT
TTTAAGTTCAGATTTTAATTGATATGAATCTGTGATACACTCTAAAATAAGATTATTTTATTGAAAAGTGGACTGTA
ACTTTCCCTTTATCTAGGAAGAGCTCTAAGTTAGAAGATGTTTTGCACTTTTACCGAAGGCTGTGTCTTGTAAGCAC
CCCCGAGCAACTCTGAGAGCCTTGATTTTTGTGTCCTCAGCATATGTTTGTGTAATACAGAAAGAGAAGCAGTTGCC
AAGTGAAAGGGATGTTGGTCTCCAAAATTATAGTTTGATCCCACAAACACACAAACACATACATGCAAAGGATTGTT
TGCTTCACGGTTTTTGATATTTAATTCAATGCTGTTGGAACAGCACAAAAACTAAGTGTCAGTTTAACAGAATCACT
TGTCCTTTTAGCATTAAAATAACATGGAACTTAATGCTTTAATTTCCCAACATGCCTTTTTATTTAGAAAGATTCAG
ACTTATATTTCATTTAGAAATAAAATGCCATTTTATTTAGAAAGATACAGGAGCATTCATTCACGGAACTTTCAGAT
CTCAGTCCACTGCATAAAATCTTGATCCTGTAATAATAGTTTCTGTATCTTGCATATTCATTCAACAGGTTTAACGC
GATGAGCAAATTAATGTTCATCGTTTTTAACATGTTTCATCTTAATCAGAACCCACATTCTCAACGTTAATTGAACG
TACATAGGACTATACAAGGGTTAGTAAATAAGACAGAAACTGTTGTTCATTTAACCACCGTCACTTTGGACCAAAAA
AGAAAAAATATATATTTTTAAAATTGAGCTTAAAAGAGTCTCTAGAAGCTGGAAGCGTGGCTCTTTTTCAGCAAACT
GGGGGAATAGGTTTACCGTGTTCCCCCTCTGGGGAATTTTGAGTCGCCACACTCATGTCTCGACCGAGCCTGGCTCG
CTGCGTCTGAGCGAGTACTTGAGGAAGGCTGATCTAGAAAAACCAGCTGAGAGAAGGGGCAGAAGCCCCTGAAACCA
CGGGCGGGGGTGGGGTGGGGAGCGCAGCTTTGGGACCCTCTAGCCGGAGACTTCCGGCAGCTGCCTCCGACTTGTTC
TAAGTACAGGAAAAATCTGTGCGCCCAGTTGCCTCACTCCAACAGCGCGCAGTTGTGCCCGGCGAGGATGCCGCGCT
AGTCGTGGAGATGCCCCACCACAAAGAGGATTCAGGTGCTTCCTACTCCGGCACCCAGTGGGTTGGTAGTCCTGTTG
GCAGGAGACAAGAATCGTCTGGGCTGCTCCTATCTCTGGCAGGACTAGACGGGGCGTGAAGGAAAGAAGGAAAGAAG
GAAAGCAGGGATCGGGCACTGCCCGAGGGCAGATACTTGGGCTTTGGTGTTGTCCAGCGCGCTCGGAGTGCGCTGCC
TCGCTCACGCGGTCCCAGGCCCCGCTTCTTCAGGCAGTGCCTGGGGCGGGAGGGTTGGGGTGTGGGTGGCTCCCTAA
GTCGACACTCGTGCGGCTGCGGTTCCAGCCCCCTCCCCCCGCCACTCAGGGGCGGGAAGTGGCGGGTGGGAGTCACC
CAAGCGTGACTGCCCGAGGCCCCTCCTGCCGCGGCGAGGAAGCTCCATAAAAGCCCTGTCGCGACCCGCTCTCTGCA
CCCCATCCGCTGGCTCTCACCCCTCGGAGACGCTCGCCCGACAGCATAGTACTTGCCGCCCAGCCACGCCCGCGCG

Fig. 1G

Human SST Promoter: GenBank Reference No. AC072022.19 Gene ID: 6750

CCTGCCTGTGTGCCCTCTTGTAAGGCACTGAAGGTCTCAGGACCTCAGTTTCCTCCTCTGTGAGGTGGGAATAGCAT
GCCCTGAAGTGTTGGATGAGAAAGTGTTTTGTGAGCAACAGAGGACTGGGTAAGGATTCCTAGTGAGTTTGGTTGGT
CTGGGCAATAGCGTCCCCAATACAACCACAAAACACTTTACCCTTCCAGCTTTGAGACTTGGGAGAGATGCCCTGGG
GGTTGATTACAGAAGGCTCAGGTTGGGAAAGTTTGAAGTGCTTCATGCTAAACCAACCTTTAAGCTATAACTGGCCA
TGGAGGGCTTAAGGGAGAATTTATGTCCCTTTTTGTCCTGGCTTCTCTGATAAGTGGTTCTCAGACTCATAACTCTC
CAGGAGTTATAAAACAACAAAAGCAAAACCCTTAAGTCATCTCATTTACAGCTTCAGCTCTTCAGCAGGGTATGAGG
GAAGCAACTGTTTACTATTCATAAGTAGATACTTAAACAGATAGACATCATGAGGTTTTTTGTTTGTTTGTTTTTGG
TGAGAAGCAGTTGAGGAGGGAAGAAGAAAGAAAAGAGGAGAGAAAAGAGAGGGAGAGATGTCTTGAGGCAGAGACTG
GGATAGGCACTGGCTAAGCAGGGTGAGAAGGCAGGGAAAGAGCCGGGCTGACCCAAACCAAAGTCAGAAAATGATTG
AGAAGAGCAAGAAAAACAAAGGAATGAGGATACAGAGTCAAGAGAGGAGACAAAAGAAGGATTGAGTGAGGAAAATT
CTGAAACATAAATTTGCAGAAAGGTTAAGGAAAAGGAGGAATAAGAAGGAGGAGAAAGTGTAGAGGGAGAGCACAAG
GATGTGGAAGGAGGGGAGCAAGCGTCTGGGGAAGGAGACAGAAGAGATCCTAGAGCACAGGGGAAGATGGGGAGCTG
CTATTTGTTCTTCGGCTGGCTCCTGCTTTGGAAAAATCCTCGTTTCCTACTCAGTGGGTATGCCAAAGACCACATCC
TGGGTACAGGAGATATGAGATCATTTGGAGGTACCTAGAGACAGTCACAGTGATAGAACTAAACTCTGAGTCCTTAG
AGGCCAGAGAGAGTTGCAAGATTTAGAGAATATAACATGTATTTCCTAGGACTGGGTTCCACAGCTCCAGATTCATT
GATCTCTTAGACTACTCCAACACATGTGAATGACTTTTTAATGCCCCACTTTGTGCTTAGTCTTGGCTGGCCTTGTC
AAGACCTGGAAACTTTAACACTTCTTGCTGTGCATTTCCGCTTTGCCTTGGATTACAAGCACAAAAAGAAATAGTGA
CAATTATTCAAGCCATTCAGGATACTTCCCAAACCCTTCTGCCTCTCAACACTGTGGTTCGGGTCTAAGTACTGAGA
ATATTTTAATACCTAATATGAGCTTCGCATGGTTTCCAGAGATGCAGCATATCTTTTTAGCTAATATTGGCTTTTTT
GAAGCTCATAAGATAACAGCTCTTAAAGATCCTGTAGGGATCATCTCGTCCATGCTAGGAAATTAGCTGGTCCTTCC
TCAGTAAGGAACTATTTAGATAAAAGCAGTCAGAACTCTGGCCTGAACAGTAAACATTTAACCAGAGTTCAATCAGA
ATTCAAGGACAGGTTTTCTTAAACTTTCTTTGTTTCTAGGAGATCAGGCAGAGCTGAATTTAACCAAGAATCTTTTG
ATCCTTTCCACATATAGATATACAATAGTGGTCACATATGTTCTGGGAGTTCCTAGACCTTATATGTCTAAACTGGG
GCTTCCTGACATAAAACTATGCTTACCGGCCAGGAATCTGTTAGAAAACTCAGAGCTCAGTAGAAGGAACACTGGCT
TTGGAATGTGGAGGTCTGGTTTTGCTCAAAGTGTGCAGTATGTGAAGGAGAACAATTTACTGACCATTACTCTGCCT
TACTGATTCAAATTCTGAGGTTTATTGAATAATTTCTTAGATTGCCTTCCAGCTCTAAATTTCTCAGCACCAAAATG
AAGTCCATTTCAATCTCTCTCTCTCTCTTTCCCTCCCGTACATATACACACACTCATACATATATATGGTCACAATA
GAAAGGCAGGTAGATCAGAAGTCTCAGTTGCTGAGAAAGAGGGAGGGAGGGTGAGCCAGAGGTACCTTCTCCCCCAT
TGTAGAGAAAAGTGAAGTTCTTTTAGAGCCCCGTTACATCTTCAAGGCTTTTTATGAGATAATGGAGGAAATAAAGA
GGGCTCAGTCCTTCTACTGTCCATATTTCATTCTCAAATCTGTTATTAGAGGAATGATTCTGATCTCCACCTACCAT
ACACATGCCCTGTTGCTTGTTGGGCCTTCCTAAAATGTTAGAGTATGATGACAGATGGAGTTGTCTGGGTACATTTG
TGTGCATTTAAGGGTGATAGTGTATTTGCTCTTTAAGAGCTGAGTGTTTGAGCCTCTGTTTGTGTGTAATTGAGTGT
GCATGTGTGGGAGTGAAATTGTGGAATGTGTATGCTCATAGCACTGAGTGAAAATAAAAGATTGTATAAATCGTGGG
GCATGTGGAATTGTGTGTGCCTGTGCGTGTGCAGTATTTTTTTTTTTTTAAGTAAGCCACTTTAGATCTTGTCACCT
CCCCTGTCTTCTGTGATTGATTTTGCGAGGCTAATGGTGCGTAAAAGGGCTGGTGAGATCTGGGGGCGCCTCCTAGC
CTGACGTCAGAGAGAGAGTTTAAAACAGAGGGAGACGGTTGAGAGCACACAAGCCGCTTTAGGAGCGAGGTTCGGAG
CCATCGCTGCTGCCTGCTGATCCGCGCCTAGAGTTTGACCAGCCACTCTCCAGCTCGGCTTTCGCGGCGCCGAGATG
CTGTCCTGCCGCCTCCAGTGCGCGCTGGCTGCGCTGTCCATCGTCCTGGCCCTGGGCTGTGTCACCGGCGCTCCCTC
GGACCCCAGACTCCGTCAGTTTCTGCAGAAGTCCCTGGCTGCTGCCGCGGGGAAGCAGGTAAGGAGACTCCCTC

Fig. 1H

Human GRPR Promoter: GenBank Reference No. NG_012512.1 Gene ID: 2925

GCCTGAAGCCAAATTCAGCCTTTCCCTCCAGAAGCTTCCCTTTTGACCTTGCTCATAGCCAGTGGGAAGAGGCTTTG
TCTCCACACTCTGTGGTCCCATTGAATCTACCTGTTCTCCTAAATTCTATCAAGTCACTGTTGCCCACCTCATGTTA
GAGCCCCACAGAAAATCCAGTCTTTTGGAAAGATGAAAAAGGTGACTCTATTGACTGAAATAGAAACAGAAGTGACA
ACCCTGTCCCAACACATAAGAAAAGATGCTGAGTCATACTCCAATTCTATTCAGAAATTGGACTCCCTGGGGACAGA
GATTTTATATTACATTTGTTCCATGTCATGTTCACATGTCAGAGGCATCTCATGTTCACCAGTAAATAAAAAGCTAA
GCAAATGTCTGAATACGTTTGGTGTTTGGTGTTCCGGCTCTGCCGGAAGGTGACACATAATGGTAGGGATGGAAAGA
GTCATTATAGTTAATTAGTTGAAATGACATAGAAATTATGGAATTAGCTTTTTTTTTTTTTTTTTTTTTTGAGAG
GGAGTCTTGCTCTGTCGCACAGGCTGGAGTGCAGTGGCACGATCTCGGCTCACTGCAAGCTCTGCCTCCTGGGTTCA
CGCCATTCTCCTGCCTCAGCCTCCCAAGTAGCTGGGACTACAGGTGCCCATCACCACGCTTGGTTAATTTTTTGTAT
TTTTAGTACAGACGGGGTTTCACTGTGTTAGCCAGGATGGTCTCGATCTCCTGACCTCATGATCCACCCGCCTCGGC
CTCCCAAAGTGCTGGGATTACATGCGTGAGCCACCGCACCTGGCCCGAATTAGCTTTTTAAAGCATCCTTGATCCCC
GAAAATATTAGATGTCAAACCTCAACGCACCTTTACTCCTAAAATACCATTAGAAGAATCTATAGTGCTGTGGAACA
CATAATGCTAACACCAGCTATGAGAAATCAATATCTATCAGCATCCCCTTAACTTACATTGGAAGAAACACTAACCA
CCCAATTAGATTTAAGTAGTGAGGCTGACTCAGCACACAGGGGTGTCTAAAGAAATAAAGGGAAACAACATCCAGAA
GTTCTCTTTGTGAACCAAAAATATGCCTTTTAGACCAAACTTCTTAGCAAGAATACAAGATCCATCACAATCTCACC
CAAACCTGCTTCTAGCTGCATTTCACGCTGTTCTTTTTCCACCCCTGTCTTCCAATCTGGGTGACCCTCTGGATTTA
TAGATGTCCCTCTGCTCAATGTCATGCTCTTTCCTTTATGCCTTGATCCTAGGCACATATGATTTTCTTCATTCAAA
AGACCTTGTCAACACTTAACCTTTAAAGATATCGTCTTTTCTGGAGAAAAGGTAGTTGCTTCACTCCAGAGAGGGGT
TGGGGTCTAAAGAGCTGTGAGAGTACACATCTTCATGCTATTTTTCTCAGCCTCTTGCTCAGTGCCTGGCAACTGGT
AGATGTTTGATAAATTTTTTTCAAGTAAATAAAGGAGTTGCTAATTCACTCGTATGAGTGCTTGCCTATTGATCTGA
GGTCAATCACTCTTCTGAACTCATTGGGCTTTTCCAAAGTAAGCCTTTCCCCCTCAATCTAATAATGATAATAATAA
TAAGTGCTAATATTAATTGAGCACTTACTATGTGCCAAATACTATGCAATCTTAACATGAATCATTTCATCTAACTT
CATAAGTTCTCCTCACCCTGCAGATGAGGAACCTGAAGCTTAAGACACTAAGTAACTTGCCATAATTATAAATGAGG
GAGCCAGGATTGAAGCAGAGCCTGTGTACTGTATCATTAAGCTATATTGCTGGCAACTAATCAACACCACTGGGCTC
ATGGCTATTGGCTGGTTACTGGTGCTACTGATCTCTGCCGAGAAGCTCTTCCACCTCTAGCCATGCAGCATCAGTCT
CCCTCCTGCTGGCAGAGAGGGGCGCTGAGCCTTTCATATTTACATAGAAAGCATGGCAGCAGCCTCAGTGTTGGAAC
CTGCCACTGGAAATGTCCATAACAACACAGTTGGGGGCTTTCTTTGTGGGCCCTGGCATGGTAAGTGCAAGTTTTGT
TATTCCTTATGGGTTCTGAAAAATGAGACTTCACCTGTTAGTGACTGGCTTCACGTCATGTACCTGGAGGAGCTGGC
TTCACATACGTCATAAAGATGCACTCTAATAATGTATTTAGAAGTTGTTGGCTAAAGGTCTAAGCCTGATTCTAATA
GCACTTCCTCAATTAAGCTTTTTCTAGCACTCCTTCAACGATAACTTACTTCTTTTACCACCCACTCAATTCCTCAG
TATTGTATCTATCACGCTTTTATAGTTCTTTATTTTCCACACAGGGCTATAAAGAGGATATTTGCTATAAAACATGG
CAAACATTCAATTAAAAATGCAAATAGCTGCATCAAAATGCCGATTCATAAAATTTTTAGATCAGATGAGAAAAGAC
CCATTTTTCTGGAAAAGACTATTGATCATTGAGAGTTAAGAATACAGCTGGTTCCCAATTTAATTTCTCCCTGGTAA
ACAGAATAGGAATGGCTTGGCAAATCTACAGGAAAGAACATGTGTGCATTGTGCTTCTGGCTTTTCCAGATGTCAGT
TGCTGAAGGTTTAAGGTGTGAGTCTGTGCATGTGTTTCTGAGGATCAGTCCCTGTTCAAAGAGGCAGTGGGAAGACT
GAGTGGGATAACTCACACATGGACACCCTGTGCATCAGTGTGCGTTTAATTCAAAGACAGACCTCATTTGATAGCAA
TATTGACATGTCATTCTAATGAATTAGAAAAAATGAGAAAATGGGATGTAAATCCCCATCTGGATTCATGGGGATAG
TATCAGAAAGATTTTCAGTGCCTTTGCAGAATGCTAGCAACATTTATTAAATACCTACCCTAGGTGCTATGTGCTTA
CATGAGAAGCCAAAGGTATCTGTTAAGCTAGGTAGGAACTGCAGTCGGCTGGTTGCTTCTCATCTGGAGAAAGCCTA
CACATGCTGCTGCCAGCGGCCAGCTGATCTCTAGGTGTTTAGGCCTAGAAGACCAACCAGCTCCAAATCACTTAAAG
CCTAAACGTTCCCTGTCTCTACTAAAAATACAAACATTAGCCACGCATGGTGGCGGGCGCCTGTAATCCCAGCTACT
TGGGAGGCTGAGGGAGGAGAATCGCTTGAACCTGGGAGGTGGAGGTTGCAGTGAGCAGAGATTGCCCCATTGCACTC
TAGTCTGGGCGACAGAGTGAGACACACAGACACACACACACACACACACACACACACACACACACACACACACAC
ACACACACGCCTAAACATTCAAGGCCAGGATGCTTGACAGATGTTGATTCATAAAAATGACAAAAAGCACAAAATCC
AAAATCTCGTATAAGCTCAGTGGCTGTGGCAGCGAGGTTGAAGAGCAAAGGCAGGCCGGGCACCTGGCTGATGATGT
GTGGACCCGTTGCACAGCAGGGCCCCGCAGTGCGGTGTGGGTGTGGGTGGGCCAGTCTCTGCCGCTCACCCTATTCC
AGGGACACAGTCTGCTTGGCTCTTCTGGACTGAGCCATCCTCATCACCGAGATCCTCCCTGAATTCAGCCCACGACA
GCCACCCCGGCCGTTTTCCTTGTTCTGTGTGGGGAGGGAGGCAGCGCGGTGGTTATCAACCTCACCCTGCAGAGGAG
GCACCTGAGGCCCAGAGACGAGGAGGGATGGGTCTAACCCAGAACCACAGATGGCTCTGAGCCGGGGGCCTGTCCAC
CCTCCCAGGCCGACGTCAGTGGCCGCAGGACTGCCTGGGCCCTGCTAGGCCTGCTCACCTCTGAGGCCTCTGGGGTG
AGAGGTTCAGTCCTGGAAACACTTCAGTTCTAGGGGGCTGGGGGCAGCAGCAAGTTGGAGTTTTGGGGTACCCTGCT
TCACAGGGCCCTTGGCAAGGAGGGCAGGTGGGGTCTAAGGACAAGCAGTCCTTACTTTGGGAGTCAACCCCGGCGTG
GTGGCTGCTGCAGGTTGCACACTGGGCCACAGAGGATCCAGCAAGG

Fig. 1I

Human PRKCG Promoter GenBank Reference No. NG_009114.1 Gene ID: 5582

CCCGCCCAGCCTCGCGGGGCACGCCGGGAGGCGGAGTTCTCGGTCGTGTCCCGAGAGTGGCTGGTCCGCAGGCTCGG
ACTACCAGTCCCAGAATGCACTGCGCCCGCAGCCCGGGGCGGGCCGTGGTTGCCCCTGGCAACAGAGAGGGCTCCCG
GGAGCGGGGACTGGGAAGCGCTCCCGAGCCGGGGAGGCGCAGAGCCCGACCAGAGAGAGGCGGGGACGCGGGTAGAG
CGACCAAGAGGTGTGGAGGCCGGAAGAGACTGACCGCGCCGGCCCTTGGAGAGACCCCTTTCCTGAGAGGGGGCGCA
CAGAGAGGATGCCGAAGCCAGCGAGATCTAGAGAGAGGGAGACAGGGATTGAATCACAGAGACACTTAGAGGGAGGG
AGAGACCTCAAAGACAGAGAGATTCACAGGGCCAGAGAGACACGTAGAGTGGGTCAGAGAAGAGGACAGAGGACAGA
GACATAGAAAAGACAGGAGGGAGAGAGACTGAATCACAGAGACACAGGGAGAGAGGGAGAGACCTCAGAGATGGAGA
GAGACTCACAGGGCCAGATAGACACATGGAGTGGGTCAGAGAAGGGGACAGAGAGAGAGACACAGAAAAGGGAAGAG
GGAGAGAGACTGAATCACAGAGACACAGAGAGGGAAGTCTCTATCTAGAGACCCTCGACAGAGATTCCTAGAGCCAG
AGACAGAGATTCAGAGAGCCAGAGACACAGAGAGATTCATAGAGACATATAGAGAGATTCAGAGAGCCTGAATCACA
GAGATTCACAGAGCCAACGAGACAAACAGAGAGATTCATAGAGCCAGAGACACAGATTCGGAGAGTCAGAGAGACAT
AGAAAGATTCATAGAGCCAGAGACACAGAGATTCAGAGAGTCAGAGAGACATAGAGAGACATTCATAGAGCCAGAGA
CACAGAGAGATTCATAGACATATAGAGAGATTCAGAGAGCCTGAATCACAGAGATTCACAGAGCCAAAGAGACAAAC
AGAGAGATTCATAGAGCCAGAGACACAGAGGGATTCGGAGAGTCAGAGAGACATAGAAAGAGATTCATAGAGCCAGA
GACACAGAGATTCATAGAGACATAGAGATTCATAGAGCCAGAGACACAGAGATTCAGAGAGTCAGAGAGACATAGAA
AGACATTCATAGAGCCAGAGACACAGAGAGATTCAGAGTCAGAGAAACATAGAGATTCATAGAGCCAGAGACACAGA
GAGATTCAGAGTCAGAGAGACATAGAGAGACATTCATAGAGCCGGAGACACAGAGAGATTCAGAGTCAGAGAGACAT
AGATTTATAGAGCCAGAGACACAGATTCAGGGAGTCAGAGAGACATAGAGAGACATTCATAGAGCCGGAGACACAGA
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AGAGCCAGAGACACAGGGAGAGTGAATCACAGACACAGAGGGACGGGGAGATCCCCAGAAACAGAAAGAGATTCATA
GAGCCAGAGAGACAAATAGAGATTGGGTCAGAGAGAAAGGGACAGAGACAGAGACAGAGAAGAGAAGAGGGAGAGAG
ATTGGGTCAGAGAGAAAGGGACAGAGACAGAGAAGAGAAGAGGGAGAGAGAGACTGAGTCATAGACAGGAGAGAGAC
CCCCCTAGCATCAGAGAGAGAGAGAGAGATCAACAGAGCCAGAGAGGGACAAGTACAGAGAAACAGATGGAACCAGA
GAGATATAGGAAGAGACAAACAAAAACAGAGACGGAGTTGCAGAACCGGAGGAAGGGAGAGAGACAGAGACAAAGGC
ATTTATAAAGACGGGTGGAGGTGAGGAGAGAGAGGGAGAGACAGGGGCAAGCATTTAGAGAGTGACTCCCAGAGAGG
AAGACAGAGACGGACTCCCAAAGAGATCAAGTTGCAGAGGGAGGGGGAGACAGAGTCACAGCCTGAGAGAGAATAGA
GATTCACAGAGCCAGAGAGACAAAGACAGGGAAAGAAACAAACTCAGGGAGACAGAGGCGGAAGAATTTATCAGACG
TAGAGGGAGAGACAGAGGGAGACTGATTCACAGTGAGGCAGACCAAGACCCCGAGAAGAACCACGACACCAAGACCC
AGAGATGGCGACAGATACAGATGGAGACACACAGCAGAGGAAATAGAGAAATAGAAAGAAATAGAAACAGCATTTCT
CGGAGACAGGGAAAAGAAAACAGATCCACTGAGAGGCAGAAACAGAGACACATCGAGAAAGCTCGCTCCAGGAATAG
AGGGAGAGGGACAGAGGTCACAAGAAAGACACACGCAGGCAGAGAGCTACACAAATAATGGAGAGGCCAGGGGAGGA
AATAAAGACTCAGCCGGCATCGGAGAAAGTGAGAACCTTAGCGCCCTGCCTGTCCACTGCTGGACCCCTAGCGTGGA
GCATAAAGTTTGTTGAAGGAAGGAGAGGGGCAGGGTCAGACACAGGGACCCCAGGGCGCCCACAGGACACACGAGGC
ACCCTAGTGGGGGAGGAACGCGGGGCAGGATGACAGATTGCAGGGTGGTGGGGGGGAGCCAGGCTCAGAGGATGCCC
CTCCCTCCAGCCAGCCCCCGGAGTGGGTGTGTGCACGTGTGGGGGGCGGGGAGGGAGGACATTTGTCCCGTGTCTCC
GGGAGGGGAGCGCCTTTAAGCCGAAACCCCGCCCTCTCGGTCGTCCTGGCAACGCCTCCCCCAACCCGGGGCTCCCA
CATTTCAGCAGGTGCCGGAGCTGGAGCTCCCACCGCCGCCGCCCGTGCCTCCGGCTGCCGGCGCCCCTGCCTTTGGC
TCTTCCTCCCCACTCGCCCGCTCCCCCTGGCGGAGCCGGCGCGCCCGGGGTGCCGCTCCCTGCCTGGCGCGCTCCGC
ACCTGGAGGTGCCTTGCCCCTCTCCTGCCCACCTCGGAATTTCCCTGTGGCTCCTTTGATCCTTCGAGTCTCC

Fig. 1J

Human Calb2 Promoter GenBank Reference No. AC106736.4 Gene ID: 794

CGCTCATGAGATCACTGTCGAGATACTTCCCTTCATTTCCTTCTCTGTGACCTTGAAGGGTCTGGGCTACATCATCT
CCATGTCTCCATCCCATTCCGATATTCTTGAAGATCAAGACCCTGGGTGGCCCATTAAAGGGGAATGGAAGGGAGGT
GGGTAGATTTTGATACGTCTTTGCAAAGAGGTTGACATTCCTGTTGTTGCAGGCTTGGCGGAAGTACGACACAGACA
GGAGTGGCTACATCGAAGCCAATGAGCTCAAGGTAGGATGGGCCTTGGGGAGGGTGTGAGGCCAGAGTGGCGGTGGG
CTTAAGGTGCCTGAGGAGGGAGGAGATGTTGGATGAGGGGCATGAGTTTGCGGGCTGCTTAGGAATACTCAGACCTG
GCACTGAATTGTTGGACTTGTTTAGAGAAGTCAGGGGAAATCAGTAACATAGAGCTGCCAGGCTGTAGATTTCAACG
AAACCCAGCTCTTCTGCACCTCCATGCTCGGGACAGGAGTCCTCCAGGCAATTCCAGAAGATTGGCCTCTGGCTCCT
AGGTCCACCTCCAAATTCCTCTGGCTATCACCCAGTGATTCCCCAGGCACTGCTTAGCTCCGTATACTGGTCTCCCA
GGAGGCAGAGCCAATCTCTAGCGCCTATTCTGTGAGGCAGGGTTGCACCACCAGCTAGTACAGCCTTAAAAGTCACT
CCCCAAGAGTTAGGAATTATGAGGGCCCTGAGTCATAGAACTGGTAGACCTGAAAAACACACACACACACATTGAGA
GACTGTCTGAATGAGCAAGTAAGGAAATGAATGAGGGACCGAATGCACGAGTCAGGAGTACTAAAGAGGCCTTTTGT
GTTGCAGGGATTCCTGTCAGACCTGCTGAAGAAGGCGAACCGGCCGTACGATGAGCCCAAGCTCCAGGAATACACCC
AAACCATAGTGAGTGAACAGAAGTGTCCCTCTCCCCCAGGGTGCAGGACTTGTGCCCCAAGCCACTTGGGCTCTGGT
GTGCAGGGTCCCTTGTTTGCTGATTCTTCAGGCCCAAGGGAAGTGATTCACAGTGGCAGCTGGCAAAAAGGGATGCT
ACTTCGTGGCTTCACATACCCTTTGAGGTCCTGGGTGTGAGCTGACTCGTGGGCCAATGTGATTGTCTGTCTCCATG
GCAACCTCTGCAGCTCTAGGAGAGGATGATCTTGGAGAGAGTGGGCCTTTAGTGCCGGCCTGCTGTGCCTCAGCTGC
CCCTGTCCCTGAGGAGGGGAGAGAGGAGCAGTGAACGAGTCCCTGTGGTCCACCCAGGGGACCCCCGTGACTGATTT
AGCCCATGTTGGTTCTTGGCCCCTACGGACCTCAGAGGAAGCATGAGCACGTGTCACCCGTCCTCCTTCCCATCCTC
TCCAGTAAAAGGGGATGTCAGGTCAGAGAAATTCACAGCAAATAACCCAGGCACCTTTCTGTCCCCAACAGCTACGG
ATGTTTGACTTGAACGGGGATGGCAAATTGGGCCTCTCAGAGATGTCCCGGTAAGCACCTCACCCCCGGGGTCACTG
ATACTGGCTCCCACAGGTCATTCCTGTGTTATCCGTCTCTGAGATCCATTGGTGGGAAAGTGACAGGTGCGGGTGTC
AAGAAGCTCAAGACAAAGCAAGATAGAATTGTGACCGTCAACACCTCACCTTGTCTGTCTCCCTCGTTTTTGAACTT
CCCACTGATTCATTATGTGTGAAGTGCTCAGAAATCATTTCTGTAACTGCAGGCACCGCCTCTGCCTTCCCCTCTCC
CGCTTGCCCTTGCCTGTGCAGTCTCCTCATCTCTGCTCTAACATTTTCTCCCCAGACTCCTGCCTGTCCAGGAAAAC
TTCCTGCTTAAATTTCAGGTAAAACTTTGCTTTCCTTCCTTCCCCCTTCCCTCATCCCTCTGAGCCTGGCCCTGCAC
CCTCCTTCCCCCAACGCACCACACACAACACACTACACACACCCACACACACCACACACACACAAAACACACCACAC
ACACAACACACACAGATCACACACACAAAACACACACAGACCACACACACCACATACACAACACACGCAGACCACAC
ACACTACATATCACACGCACACACCCCACATACACAGAGACATCACACACACCACACAGACCACACACCACACACAC
AACACACACATCACACATGCACACACCACACACATAAACACACACACACAAACGCACACCCACACACACACCACTGC
GCTTCTGCTTCTGTCTTTAATACCCTGGTTCTTGCAGGGCATGAAGCTGACCTCAGAGGAGTTTAACGCGATCTTCA
CATTTTACGACAAGGTAAGAGAGGGAGTTGGCATGGCAGGGAAAATCAGAAGCCCATCAGCCCGTCCAGAAGGGCTC
AGCTTCATCCCTGGGAAGAGACAGCTTTCCAGGGGTGGCCTGGGCCGTGTGGTTTCTTCCTGCCGCATCTTCTGCTG
TATGAGAAGGCAAATGTCATTCTCCACCGGTGGCCTATGGAGCCCAAGGGGTTGGTTTCTGCAGAGTGCAGCCGAGA
ATCGTTGGGGGAGGACTATGCTTAGAACTAGGGTGTGACCACGCTGTCGGGAGCCAAAGGGAAGAGACACTCAGAAC
TGCCCTGGTGCCAGATCACAATTCTGCCCAGGGCCAAGTCTTTCTCTGGGAAGTTGGAAGTTAGATGATCTCCATAC
CCACCCCTCCCTGGGCTGTCCCCTGCCCACATGACTCCGGTGGTTTTCTTCATAACCAGTGTTGGAGGTAAACTTTA
AATAGCCCCCGGACTCAGGGAGTTAACCAAATGCTTCTTGAATCTCACTTAAATTTTCAACGCACATGAAAAGCACC
ACAATGAAAGGCTACCCAAAGCTTGCACCCACTGCCACCTTCCTGCCATGACTGGTTAAGGCAGAAGGGACACATTA
TTTTGTCATTACACGATCTGAACACCCCCTTTTGCACAGAGTAATGGAGAGGCTAGACTCTTAGACATCCCTGG

Fig. 1K

Mouse CCK Promoter (2441 bp) (GenBank Reference No. AC131660.4 Gene ID: 12424
GAATTCCCAGGGAAGATCCCAGGGAAGATGAAGAAACCATGGCTACAATATTTTATTAAATAAAGAGTCCATTGTGC
CACCTTCTTCCAGCTTCTAACTGTCCTTGACACCTTTGGCTTCTCCTGGTGGCTTTTCTACTCTGGCCTTTGACCCT
GCCTGTGGTCAGGTGCTGGACCCTTCTCCCGTTCCTTCCTCTGGCTGTCACACCTGGGAATCTGGGCAGAGATGCCT
TTTCTCTTCCCTCGCTTCCCACCTTTTGAGTCTCTTCCTACAGCTTCCAGGTGGGAAGCCACCATCTACAGAAAGAG
TCTTGGGTTGTACCTCCAGTGTCCCTCTGTCCAGGACTTGAGATCACAACCTTCTCTAGCTGTCCACCCATAACCTG
GATTCATCCCCCACGCCCCGCCAGACACACACCAGTTGGTGTGTTTTCTTCTGAACTCCCCCTGTGGCCAATACACT
CCCACCCACCCTTGTCTCTCAGCCCAGAACTTCACAGTCAGCCCCAGACACGGAGTACCTTTGGGTTTCTTGAAGAG
CAAGATGCTGCTTCCATGCCTGGAAGTTTCTGCTTATGTCTACTGTTCTAGCTATTCGGATGTTCTATTGTAGGCAC
TTAGGACTCGTATAGTGTCTGCTACATTTCATGATAGTGAATAAATTTCACAAAAGCATATTAGGCTTCCTATAAAT
CTGTCCTCATTCCTCAATGGCCCTCCCATCTCCTGTCTTCCTAACCTGTCCTGGTCTCCCGTGTCTGCCCTAGGGAC
ACCTCCATGTCACCACCAGACTCAGTGGAAATCCTTACTCCGCCCTTGGCTATTAGTGCAGATCTGAACTCAGTTCC
TTGTACTTGCAGGCAAGCACTTCACTGGCTGAGCCGCCTCCCAGTTCCAGCTCCAGGCCCCCGGCTCCCAAAGGTGT
TTATTTGTGTGGGTATTTATTTTGTCCAGTCTTGGTCACACCGCATCCTCAGGGGCTGGGCACAGTTCATAAATCTT
GAGGCAAGCGATGGAGGGAAGGAGGCAGCTAAGCGTCCATATCTCAGCCACCGACCCAGGGAAGTCAGCGCCTGTGG
ATTCTGACCATATCGAACAGCCTTGTGCCCAGCTGCTTTATCCACAATTCCGGACATGCTCGATCTGTCACAGATAC
ATTCCCACAACCTGAGCTGTCTTGTGCGGGAAATCACCCCACAGCATTTAATCTGTTGCTGTTTAAAACATGTTGCC
TCTAGGTTGCAGACACCGCTAGAGCCACAACCATGAACCTAAACTCTTGGCATCACTTGCTGTTTCTCATAGTCCCC
CTCAGCCGGAAGTCCCCAAACTGTGTGCCTTTTCTATTTAGAAAGAGTTTCTAACCCTTTCTCCATTCACCCTAGCT
TGACAGGGTTGAGGGCATGGTTGCCCTGGCTGGTGGTGACCCCAAGTTACAAGCTAGCAGCAAGGAGGTTGCTGTGG
GGCTTCCTCAGTATGTGTTCTGTGGAATGGGGTTAGAGGGATTCAGCAAATTCTAGCACCCTGGGCATAGATAATCA
CTTTGTTATGTGAGAACTGGGGGTTGCAGGATTGTGCGCACTACAGCAGAGAGAGCCCCCTCTCTCCTTCTTGCTTG
GTAAGAGTCTTTTTCTCAGCCAAGATCCTCATCACCCAGCGAAATCCCATAACTTTAGAGGGACTAGACTGGAAAGG
GTGATCTGAGCTCTTGGGAAGGTGCGAGCCCAGCCCGCATGGCTCAGCCAGCCAGAGCTTGGGAGTGCCTGAGACAC
TCTCTGGCGCCACTTCACGACCAAAAGCATCAGTAGATGATAGGCCCCTGGGAAGTCGTCGTGGAAAGAAATTACAA
ATCTTTTTCCCAGAGGCTTTTCGCAGAAAGGCAGGAGCTGCACCCGATCTTACAATTGTGTAAGAATAGAATCCAGG
ATGCCAACTGCAATTGAGTTCTGAAAAATTGGGAGCCCGATTTCCCTCTCTTACTTGTGAGAGCCCACTCAGGTCTG
AGGTGGTCCCAGAGAACACACCAGGATTACATCTGCTGACACCCAGCCTGTGAGGGTCCCCCAGTTTCCTTGAAGGA
TTTGATCCCCAAAGCTCACTGAACTTGGTCAGCTTCTCCATTGCAGATAAACTCCTGTTTTTCACCGAGAGTGGAGG
TGGCACCCTCCCTGAGGTGGACTCTGCACAGGCGCCGAACAGGTGGGAAGGAAGCTCTTTAGATAAAGAGTAAGACC
CATGCAAAGTGCCCCCCTGGGAGGGGCTATCCTCATTCACTGGGACGCTTCCCTTCTCTCCGGAGGGCCACATCAAT
CGGTGGTCCCTCCAGTGGCTGCCTCTGAGCACGTGTCCTGCTGGACTGCGTCAGCACTGGGTAAACAGATGACTGGC
TGCGAACCGGGAGGAGCTATTTAAGAGCAGTCACCCTCCCGCCTGCCCTCACCT

Mouse Calb2 Promoter Region: Genbank Accession No. U34818.1 Gene ID: 12308
CCATGGCGATGGAAAGCTGACCAGTGCTCCCTCTGATCAAGGAATCCTTTCCAAGCTCACCAGAGAGCACAAGCATA
AAGGACAGGAACACAGACTCATGTAATCCCCAGAACAATCCAAGATGTCAATACCCACACACCCATTTTACAGACTC
GGAAAGCCAAGGCACAGACAGGCTGTGTAAGCCAAACAACGTTGTGGAGGTTTTGTTGTTGTTTGTTTAGGAACTAG
ACCCGAGGAGTTTGATTCTATTGCAACTGTTCTTTAGGACTGAGCCTTCTTGCCTTCTCGAAGGCAAGACTCAGGCT
GGGGGACTCTAGCTTAGTAATTTCTCAGCCCTGGCAGCAAGGAATGCTGGGTTACAGAAGCCCCAACAGTTAGCCTA
TTTTGCTGCGTCTTTCCCAGTCTGTTCTTGTAAACAACCTCAAACTGTGTGCCTGGGCAACACACCAGCAGTTTTGA
AACTTGGGCTCCATGTTGCCCTTTGAGGTTAGCTCCGAGCTACCTCAACCTGACCCCAGGAAACAGCCTGCTCTTCT
CCGCTCCCCCCCCTCCCCCCCACCCCACCCCGGGTTCTCCTCTCCCCTAGCGACCTGCTTTAGATTCTCACCTCCTT
CTCTTTTGCTCTCCCTTCGAAGGCAGCTCAGCTAACACTCATTAGCACATGTTAATGAGCAGCAATTCAAGTCTCTG
TCCTTCTTTTTTAGGGGCAGGGTGCTTGCTGTTGCTCTGAAGGTAAGGTGTCCAAGAAGCAAGCACACACTGCAGACC
TTTAGAGTAGGGAGGATATGGGACGGAGGCTGGCTCTCTGATTGAGGAGACCCCACGGTGTGCTGTGCTTGCTGTCT
GTTTTCTTTAACAGAAGTTCAGCACATCTTTGGGTCAGAGTTTACCGCCATCTACCTACGGGACTACGGGAGGCTCC
AGTCTGCTACTACCTGGATAAAGGTCTAAAAGTCTGCAGGATGTGACAGATACCGGAGGGAAGTGGGTTACTGAACA
GTGGAGTAGTTCCTCCATTCCCATCTGAATCCTCATTGCACCTTGTCGATTCCAGTTGTCCACCTACGGTAAAACCT
TGAGAACCCTGCTTTCCTGCAATCCTGGTACCCCTCGAGGGAGTCACAGGACAGGAAGAGTTCTGGGCTCAAATCTT
AGCTTTGCTACTTGTTAATAATGCTATTGCTGCGACTAGAAACTGGGTGTGCTCAAGATGGACAGAGGGAAGGGAAG
GCAGGAGCTGCCTCTCCCCATTTCCAGCTAAATACCTGCGGTGTCCCCGGAGGGCACCCAGAAGTCTCATTGAACAC
TCTCTCCCGGTCCCCAGGAACCCTGGCAGAGAAGAGCCCCCGCCCGTGCAGCGCCGCGCCCTGCGCGATTCCCTGAG
TGTGCGCGCCCCCTTCCGGCGGCCCGACGCGGCGCAGCTCCGGGCTGCATATAAAGGCAGCGTGGCGCGCAGCCCCA
GCGCGAGAACCAGAGCCAAGCGGCACCGAGTGACAGCGCGCTGAGAGAGAGGCTTAAGATCTCCGGAGCGGCTCGCC
ATGG

Fig. 1L

Mouse PRKCG Promoter Region: Genbank Accession No. AC245272.2, Gene ID: 18752

GGACTAGATCCTGGATCCCTGGGTATGAGGAAGGAGGGGAGTTGTGCCTAGATTCCTAGATCCTGAGAGACAAGGGA
CCTGGAGGAGTTCCAAAGGATAGAATCAGAGGCATCCATGTGTGTAAGAAGTTGTATCCAGAAGCTGGCTCCTGTGT
ACTTCGGGAGCTGTTCTGGGACAGTGTGAGCTTCCAGAGGTTAAAGCAAGCCCTTCTGTCTTTCCGTGGGCTTGACC
TTAGCACGACTTTTCTTCGGGGGAAAGTTATGAATAATTCTGTGTTCATCACAGAACACAGGATGATGGGCTGCCGC
GCGGTGGTGGCTACACCTTTAATTACAGCACTCCAAAGACAGAGGCAGGCAGATCTCTTTGAGTTCGAGGCCAGCCA
GCCTGATCTGCATAGTGAGTTCCAGTACAGCCACAACAGAACAAACAAACAAACAAAGATGCAAGGTCAAAGAGACC
AAAGTTAACCCAAGTGCACTGGGTGAGCCAGTGAGTGGACTGGAAATACTTGCAGGGGCATAGAGAAGCCCACCCCA
ACATGGAAGACTCATGGAAGACGCATTTCTGGGGTACACTGCTCAACTTGTAGTCAGCTGGGCAGAAGAGTCTTCCT
GTCCTCTCTTAATTGTTTGCTGCTCATATATTACTTCAGCTTTGGGAGGGGCCTCATAGCACAGCCCTGTAACTTTC
TGAGCCTTGGGGGTTCTATGGTTTGTCTTTCTAACATGTAATTATTGTGTGTGTGCATGTATGTGTACACCCCATAG
CCAGTGTATGGAGGTCAGAGGACAATTTGCAGAATTCCACATGGTCTATCCACCATGTGGGTCTTGGGGACAGAACT
CAGCTTATCATGCTCTGTTGTAAGTCTCTTTCTTTCTTTCTTTCTTTCTTTCTTTCTTTCTTTCAATTTATTTATTT
ATTTTCCATATATGAGTACATTGTAGCTATACAGATGGTTGTGAGCCATCATGTGGTTGCTGGGAATTGAACTCAGG
ACCTCTGCTTGCTCCAGCCCTGCTTGCTCCAGCCCAAAGATTTATTTATTATTATATGTACGCTGTACATATAATAA
TAAATACATACATAAGTAATATTATTATTATAATAATAAATAAGTACACTGTAGCTGTTTTCGGACCCACCAGAAGA
GGGTGTCAGATCTCATTACGGATGGTTGTGAGCCACCATGTGGTTGCTGGGATTTGAACTCAGGACCTTCAGAAGAG
CAATCAGTGCTCTTACCTGCTGAGTCATCTCAACAGCCCATGTTGTAAGTATCTTTACCCACTGAGCCATTTAGTTG
GCCCTTAGTCTCTATAGCTTTTGAGTTATTTGAGTCCCTCCCCTCCCTCTATCAGCTGATGTTCAATTCAGAAGAAA
TAACTACAGAACTGACAATAGTAATAAGAAAATTGGACCTGGAAACCACCTTCTCATATCTTTAGTGGCATCAGCCG
AGAGGTCAGACAGTTAACATCCTGAGAAGGGCTCTGGCATTTGGTCCTAGTTCTGAGCCTCTAGGACAAGGAGACAG
AAGCTGTGGTTTGCAGTGTAAAAAAAGAGATGTGGCTGGGCAGTGGTGGCACATGCCTTTAATCCCAGCACATGGAA
GGCAGAGGCAGGTGGATCTCTGAGTTCAAGGCCAGCCTGGTCTACAGAGTGAGTTCCAGGCCAGCCATGGCTACACA
GAGAAACCCCGTCTCGAAAAAACAAAACAAACAAAAAGATGTTAGTCCTTCCACTCACTTCCCATGTCAGGGTTACA
TGGTACACTAGAAGGCCGAGAGGCCTGTCCTGAGGTCTAGCCCTGCATGACTGATCTCGAAAACTAGAGATTTCAGT
GGACTGCTCAATGAGAATGGAGGGAGTTGAATTTTCCTGTACTTGAGGTACCTGTTAGCTGAGTCCCTGGAGGAAGT
GATAAGCTCAGAGATAAGAAAGCAGAAACTGAGCAGTCTTCAATTCTCCAGGTCTGAGGTAGGATTGGGGGTGGGGT
GGGTGAAGCTTGAAAGGAGGGGAGAAAGAAAGCATAATGTTCCTGGTCAGAGATCTCTGGAAGAGGAGTGAGAAGGA
TGCAGGTCCAGTACTCTGGTTAGATGTGGGAGGTGGAATAGAAGATGGAATTTTGAGTGGGTAGGGGCTGCTAAGGT
CTATGTTGCTCTTATGTACACGAAATCTTTTCACAGGGCATAAAGTATGAGGAAGTTAGAGTCTTGGCTATGGAGAA
GTTAGAGATGACTGAGTCGCTGTGGATAAAAGAGGGAACTTTGTACACAGGGCCTGGGGTAAAAAAAAAACCCTAGG
TCACACACAGGAGGAAGTGAAGTACAGGCTAGATCTTAGACCATATCTTTCATTGCTGGGTGGGTGGTTTTGTTGTT
TGTTATAAAACAGGGTTTGTTTGTTTGTTTGTTTGTTTGTAATAAAACAGAGTAGCCTTGACCATTCTGGAACTCAC
TCTGTAGACCAGGTTGGCTTTGTTTGTTTTAAAGGCAGAACCACATTCTGTAGCCCAAGCTAGCTTGGACTTTATTA
CAGAGCCGAGGCTGGTCTCCATCTCACAGTAGCCTTCCCACTTTAGCCTCCCAATTTCTAAGATCATGGGTGTGCCC
TTCTTGACTTGGTTTGCGTAGTGCAGGGTTCAGATCCAAGGCTTCCTGAATGATATAGACAAGCGTGTTACCAGCTA
AGCCACATCCCCACGGTCAAAGTTGTAGGTGTATGTTTGGGGTGAGTCTGTATGTGTTCGCATGGAGGTCAGAAGTT
GGTTTTTTCCTTCCAGGAGTTATGTCCCAGTAAGCCAGCTCTAGTTTTCCAGCATGGCAGCACACACTCCCGTGGAT
AGGATGCTGACTCCCTGGGAAAGGGAAGCAAGAAGTATAGCTTTGAGTGTTTGGATTTTGGGTTTTCTTATGGGTAG
GGCTAGGATGAGCCTAGAACCTAGATGACCAATTCATTTTTATAGTTTATAGACAAGTTCCATATATTAAGACACAT
CCTTTTCAGAA

Fig. 1M

Mouse Calb1 Promoter: GenBank Reference No. L42901.1 Gene ID: 12307

GATCTTTCAGGAAACACTAGTAGGTAACAGCATGAGTCTCTCCCCAAGAAGGCTTGACTAATCTATTAGAAATCCTA
TGTGTGGACATGTTCATAAGAGAGCATGATGGAATCCTTCATGTGCTTGAACCCATAGTAAAATATCTGAGCATTTT
CTTTTCCCCTTGAAGGCTAAGAAAGCATTCATTCAACCTGAAAGGTTCTGGTTCTCCCATATGCATAGTGATTTGAA
CTGCCATGTCTTAGTCAGGGTGTTTATTCCTGGACAAACATCATGACCAAGAAGCAAGTTGGGGAGGAAAGGGTTTA
TTTGGCTTACACTTCCAGACTGCTGTTATCACCAAGGAAGTCAGGACTGGAACTCAAGCAGGTCAGGAAGCAGGAGC
TGATGCAGAGGCCATGGAGGGATGTTCCTTACTGGCTTGCCTCCCCTGGCTTGCTTAGCCTGCTCTCTTATAGAACC
AAGATTACCAGCCCAGAGATGGTCCCACCCACAAGGGGCCTTTCCCCCTTGATCACTAATTGAGAAAATGCCTTACA
GCTGGATCTCATGGAGGCATTTCCCCAACTGAAGCTCCTTTCTCTGTGATAACTCCAGCTGTGTCAAGTTGACACAA
ACTAGCCAGTACATGCCAGTAGGGCCTAAGTCTAAATACAGATGCAATAATTCAGTAACATGAAATGGGAAAGAGTT
TAATTGTGCTGGAGATTTTTTTTCTCCTCTTATGACACGTGGGATCGTGAACCTGTTCACCTGAATGCTGTGTAATG
AGGCCTAAGAGGCAAGTCATAAGAGTGCTTTGCAATGCTTTTGGAAAGTTTAATCTTATGGAACAATCACAGTATTC
AAAGGGTGTGTACTTCTTCCAGAATCCTAGAAGGTGAGAGAGGTTCCTGAATATTTGAAAAATAACACCCTCCCAAT
CTTGGTTAATGAACTGAAAAATTCGGCAGGCAAAAGGCAGAAATAGTTCTTAAGTTACTTCAGAGCTGTAGAACTGA
AACACACACTTGTTTAGTGTCCTTAAACTCAATTTAATTTTGAAGTGACACCAAAAATGTCTAAAAAGAGATGTTGA
TTTTAAATGAGAGTCTAAGACTAATAGTTATTTAAGAGAAAAATGTATTTTATGAAGTTACATTTCTTCTGCTAAAA
AAAATTATCCAGGAAAAAATATTACCTTAGAAAATCAAAATGAAAAAAAAAAGAAAATCAAAATGTAAATTGAAGAA
ATTGAAGACTATAACATTCAAAGATGTTGAGGATGCCATGTTTACAGCTTGTTAATCTGAGTTGATACAAACTAAAA
GAACTAATCTAGAAATGTTCTTTAAATTTTAAATTATATATGCTTTTGTACTAACAATAGTACCCCTATGACCAGGA
AAAAATGTATATCTAAAATAAATATCTGAAGATATTTGTTGCAGCTGTTTGTCACAGTAGAACACTAAAAAAGATGG
AATGTCTACAATTAGGATGGAAAACTATGTTATGTAAACATGGGCTAATGGAGGAAGTGTCTACCGAGGAACAAACT
TTTGTATGAGGATGTGACTTGGGTAGGCTGAGATTCAGTTTTCCCTGGAAATTAAGAGGTATATGAACAAAAGTAAC
TGACGTGTATTGGGTCAAATGCCCCTTTACCTTTGTAAGCCACAGAAGGTAAGGTTAATACGTTTTATTGCACTACT
TGCAGGACCTAGCAAAGTACCTGACCCAAAAGCTGTTGATAAGTGTTCACTGAATGGATGAAAATATAAACAACTGG
GCATGCACATAATCTTTTTAAGTAAAAACAATATCCTTGTTATCCTCTCAGAGTTTGGCTTGCTTTGTGTATAATAT
CAGTCTGAGATTTGTGTGAGAATCAGATAAGGTGATGAAAGTCAAAACTTACATCCATGAAAACTTTAGAGTATCAT
GGCTGCAGGACTTGTCTGGAGAAGACAATTGGTTGCCTCACAATCCCACTATTGGAGGAAACACAAATGTGGTGAAT
TCCATATTCTATGACACACGTGAAACCTGTGGCGCTTCATGAGCTCGTTTTGAAAGTTTATACCACACTGGTTTGCT
TTTGTTTACTGTAACCAGACACATAGGGTTCATTTTCAGCAGACCATAAGGTCTCAAAAGATGGACAATTAGATAAC
TTAGAAATACTTACGTAAAAGAAAACCTAAATACAGTATTTGTCATATTAAAATACCAATTGTAACATGTAGCCGGA
TATTTTTCCCACCTCTAATGATTTCCAGTTTCTGGAAAAAAATCCCTCACCTAGAGATAGAAGCAGCGCAGCTGTAA
AATCAGTGAGTGGGGCTGCTACGGAGTCACTGGTTAGCCTGGTGACATTTCTTTCAGTTTCTACTTTGTAAGATGCA
AGTAACTAATGGCATCGATAAAATCACTTCCTTCCTAACATCTTAAATTCTTATAAGTTAATTCTACTACATTCCAA
TAATTCTGCTTCAAGCTCAAAAAGTAACAACAGCAAGAGCAGCAGACTCCTGCATTCTGCTGTCTCTAAGCATAGCT
CACATCTTAAACAGCCACGTGATGGTCTCCATTAGCGCAATATGAAGCATTGTTACAATTAACCACAGCAACGTATG
CATTAATCAAATTAAACTAACACTTGACATCTGATTTTGTTCAAATACTCAACTGCCTCGATAAATACTAAGTAGAC
AAAATCTCCACTGACGTGGTTTATCAGTCAGCTTTCCCTTCCATCTGAAAAAAAATCAAACAATTCTAGGTATGTTG
CTTTACTCTAACATTCAGGAGTGAAAGCCTCCCTGAACCTGGGGGATGTGAGGAGAAATGAGTCTGAGCAAGGGATC
CCCACCACCTGCTGCTTCCTAGACTCCAAAACTCCAGCTCCAGCTATTTCCTGGGAAGAGAGAAATCGGAGGGGAGG
GGAAGAAGGTTGGTGAGAGCAAGAGGCGGGAGCTAGGAAAAGGAGGCAGGAGGAGGCGTGGCCCGGCCTGGGGCCGG
CGGGATAAATACAGAGAACTGGGTGCGGGGTGCGGAGAACTCCGGAGGACGCCCGAACGGAGCAGCACCGCGGACAG
CGCCCCGCCGCGCCGCGCCCAGCTCAGCCTGCGCAGCCCTCTCGCCCGAGGTTCGCGCTCCGCGCACTCTCAAACTA
GCCGCTGCACCACG

Fig. 1N

Mouse Nmu Promoter Region: GenBank Reference No. AC133184.3 Gene ID: 56183

TAAAAATAGTAATGGTATTCTTTTAATTGATCTTCAGGGTTTCATTCCTACTACTCTCTGTATTTCCAGTAGCAGCC
CATTCTCCCTAGAACTGCGCAGCTCTTGGGTATGATTTGGCAGTACCTTACCTTTAGTTCCCTAAAGGAAATGCTCC
TCCTACTAAACTGTGATTCCCTCAAAGTACCTGTCTTGCTTATGTTATAGTGGGTCACACATTCATGCCAGATGCCA
GGAAACCGAGGCGAGGAAGAAACCTATGTCCGTGCTCCTTCCCAGGCTAGGTTGTCTGAAGAAAGATAGCAACAGTG
CACTCATATACATAAAATAAATAAATAAATCTAAAAAAAGAGAAAAGAAGGAAGGAAGGAAGGAAGGAAGGAAGGAAG
GAAGGAAGGAAGGAAGGAAGGAAGAAAAAGATGGAAGGAAGGGAAGAAAGAAAGAGAGAAAGGTTGCTAGGAATTGA
ACTCAGGACCTCAGGAAGAGCACTGACTGCTCTTAGCCGCTGAGCATCATTCCAGCCCCCTCTTTCTTTCTTTCTTT
CTTTCTTTCTTTCTTTCTTTCTTTCTTTCTTTCTTTCTTAAAAAGAACTTTACACTGCAGATATGTCATGAATATTA
AATGAAATTGCACGAGAAAGTCCGTGGCTACATGACCCCAAGATGCCCCGTTCAAAAACAGCAATGTGCTTCCGTCC
TGCCCTTTCCTCCGAGCTCCTCGCCTTTCAAAAGGAGGTTAAACAAGATCAGATGCCCTTTTTTTCTGCAGAAGGAA
ATTAGAATTGTATTTCTCAGTGTCCTGTTAAGAGGTTGGTTCCTGGAGTGTGGGAATAGCGGAAGTGAGGTTCCAAA
GTAAATTAGAGAGAAGAGCATCCTTCGGGCAGAATGGCCACCTGAGCCTTGGGTGCCCCACCTTCTAACCTCTGCAA
CTGCACCCAATCCCAAGCCCTCCCCATTCCTCAGCACCATTTTACTGCGTCTCTAGGAATGGATTCGGACTTTGCAG
GCATTTGGAGGTTTAGATGGTATCATCTTCACCCACATTGTGGTGGAAGTAGCATCACTCTGATGCCCTGGGCATTG
GGCGTTGTGTTTCCCAGGGAAAGAAGAGAAGTGTGCCTAGACAGCAGGGGGACAAATGGGCCGGCTGGGTATACTGT
GGCATCTCAGGCGACACAAGGGAGAGTGTGGCCACCTCTTCCAACTTGACCACCCTGATCTCAGGCTCTGGGAGGCT
GCTACCCCCTCCGGCTCCCACCCAAGTCCTTCCACAGGTGGGAGTGGACCGCCATGGTTTAATTCCATTCTCCAGCT
CAGAGCCAACTGCGTGGTGTCCTGAGTCAGACACTCGGCCAGGGAGCGCGTGTCCTGCGGGGGCGGCAGCAGGTCCG
GGTGACGCCAGGGAGCCAGGGGCGGCGAGGTCACGCGTGAAGACCACGCCAGCCCAGCCCACGTGTGCGCCAGATTT
AAAAGTTGGTGGCGCGCGGAGATGGTCACTTTGGTGTCTGAGCTCAGCAAGAGGAGGCGCACAGGACACGCTGAGGG
ACAGCTAAAACACCCGCACAACACAGGG

Fig. 10

MRCSPGGVWLALAASLLHVSLQGEFQRKLYKELVKNYNPLERPVANDSQP
LTVYFSLSLLQIMDVDEKNQVLTTNIWLQMSWTDHYLQWNVSEYPGVKTV
RFPDGQIWKPDILLYNSADERFDATFHTNVLVNSSGHCQYLPPGIFKSSC
YIDVRWFPFDVQHCKLKFGSWSYGGWSLDLQMQEADISGYIPNGEWDLVG
IPGKRSERFYECCKEPYPDVTFTV (SEQ ID NO: 18)

MRCSPGGVWLALAASLLHVSLQGEFQRKLYKELVKNYNPLERPVANDSQP
LTVYFSLSLLQIMDVDEKNQVLTTNIWLQMSWTDHYLQWNVSEYPGVKTV
RFPDGQIWKPDILLYNSADERFDATFHTNVLVNSSGHCQYLPPGIFKSSC
YIDVRWFPFDVQHCKLKFGSWSYGGWSLDLQMQEADISGYIPNGEWDLVG
IPGKRSERFYECCKEPYPDVTFTVTMRRR (SEQ ID NO: 19)

MRCSPGGVWLALAASLLHVSLQGEFQRKLYKELVKNYNPLERPVANDSQP
LTVYFSLSLLQIMDVDEKNQVLTTNIWLQMSWTDHYLQWNVSEYPGVKTV
RFPDGQIWKPDILLYNSADERFDATFHTNVLVNSSGHCQYLPPGIFKSSC
YIDVRWFPFDVQHCKLKFGSWSYGGWSLDLQMQEADISGYIPNGEWDLVG
IPGKRSERFYECCKEPYPDVTFTVTMRRRTLYY (SEQ ID NO: 20)

Fig 2.

MRCSPGGVWLALAASLLHVSLQGEFQRKLYKELVKNYNPLERPVANDSQPLTVYFSLSLL
QIMDVDEKNQVLTTNIWLQMSWTDHYLQWNVSEYPGVKTVRFPDGQIWKPDILLYNSADE
RFDATFHTNVLVNSSGHCQYLPPGIFKSSCYIDVRWFPFDVQHCKLKFGSWSYGGWSLDL
QMQEADISGYIPNGEWDLVGIPGKRSERFYECCKEPYPDVTFTVIIRRRPLFYAVSLLLP
SIFLMVVDIVGFCLPPDSGERVSFKITLLLGYSVFLIIVSDTLPATIGTPLIGVYFVVCM
ALLVISLAETIFIVRLVHKQDLQRPVPDWLRHLVLDRIAWILCLGEQPMAHRPPATFQAN
KTDDCSGSDLLPAMGNHCSHVGGPQDLEKTPRGRGSPLPPPREASLAVRGLLQELSSIRH
FLEKRDEMREVARDWLRVGYVLDRLLFRIYLLAVLAYSITLVTLWSIWHYS

Fig. 3A

MRCSPGGVWLALAASLLHVSLQGEFQRKLYKELVKNYNPLERPVANDSQPLTVYFSLSLL
QIMDVDEKNQVLTTNIWLQMSWTDHYLQWNVSEYPGVKTRFPDGQIWKPDILLYNSADER
FDATFHTNVLVNSSGHCQYLPPGIFKSSCYIDVRWFPFDVQHCKLKFGSWSYGGWSLDLQ
MQEADISGYIPNGEWDLVGIPGKRSERFYECCKEPYPDVTFTVTMRRRMGYYLIQMYIPS
LLIVILSWISFWINMDAAPARVGLGITTVLTMTTQSSGSRASLPKVSYVKAIDIWMAVCL
LFVFSALLEYAAVNFVSRQHKELLRFRRKRRHHKEDEAGEGRFNFSAYGMGPACLQAKDG
ISVKGANNSNTTNPPPAPSKSPEEMRKLFIQRAKKIDKISRIGFPMAFLIFNMFYWIIYK
IVRREDVHNQ

Fig. 3B

MRCSPGGVWLALAASLLHVSLQGEFQRKLYKELVKNYNPLERPVANDSQPLTVYFSLSLL
QIMDVDEKNQVLTTNIWLQMSWTDHYLQWNVSEYPGVKTVRFPDGQIWKPDILLYNSADE
RFDATFHTNVLVNSSGHCQYLPPGIFKSSCYIDVRWFPFDVQHCKLKFGSWSYGGWSLDL
QMQEADISGYIPNGEWDLVGIPGKRSERFYECCKEPYPDVTFTVIIRRRPLFYVVSLLLP
SIFLMVMDIVGFYLPPNSGERVSFKITLLLGYSVFLIIVSDTLPATAIGTPLIGVYFVVC
MALLVISLAETIFIVRLVHKQDLQQPVPAWLRHLVLERIAWLLCLREQSTSQRPPATSQA
TKTDDCSAMGNHCSHMGGPQDFEKSPRDRCSPPPPPREASLAVCGLLQELSSIRQFLEKR
DEIREVARDWLRVGSVLDKLLFHIYLLAVLAYSITLVMLWSIWQYA

Fig. 3C

MRCSPGGVWLALAASLLHVSLQGEFQRKLYKELVKNYNPLERPVANDSQPLTVYFSLSLL
QIMDVDEKNQVLTTNIWLQMSWTDHYLQWNVSEYPGVKTVRFPDGQIWKPDILLYNSADE
RFDATFHTNVLVNSSGHCQYLPPGIFKSSCYIDVRWFPFDVQHCKLKFGSWSYGGWSLDL
QMQEADISGYIPNGEWDLVGIPGKRSERFYECCKEPYPDVTFTVTMRRRTLYYLLQTYFP
ATLMVMLSWVSFWIDRRAVPARVPLGITTVLTMSTIITGVNASMPRVSYIKAVDIYLWVS
FVFVFLSVLEYAAVNYLTTVQERKEQKLREKLPCTSGLPPPRTAMLDGNYSDGEVNDLDN
YMPENGEKPDRMMVQLTLASERSSPQRKSQRSSYVSMRIDTHAIDKYSRIIFPAAYILFN
LIYWSIFS

Fig. 3D

MGGGRGGIWLALAAALLHVSLQGEFQRRLYKELVKNYNPLERPVANDSQPLTVYFSLSLL
QIMDVDEKNQVLTTNIWLQMSWTDHYLQWNMSEYPGVKNVRFPDGQIWKPDILLYNSADE
RFDATFHTNVLVNASGHCQYLPPGIFKSSCYIDVRWFPFDVQQCKLKFGSWSYGGWSLDL
QMQEADISSYIPNGEWDLMGIPGKRNEKFYECCKEPYPDVTYTVTMRRRTLYYGLNLLIP
CVLISALALLVFLLPADSGEKISLGITVLLSLTVFMLLVAEIMPATSDSVPLIAQYFAST
MIIVGLSVVVTVIVLRYHHHDPDGGKMPKWTRIILLNWCAWFLRMKRPGEDKVRPACQHK
PRRCSLASVELSAGAGPPTSNGNLLYIGFRGLEGMHCAPTPDSGVVCGRLACSPTHDEHL
MHGAHPSDGDPDLAKILEEVRYIANRNRCQDESEVICSEWKFAACVVDPLCLMAFSVFTI
ICTIGILMSAPNFVEAVSKDFA

Fig. 3E

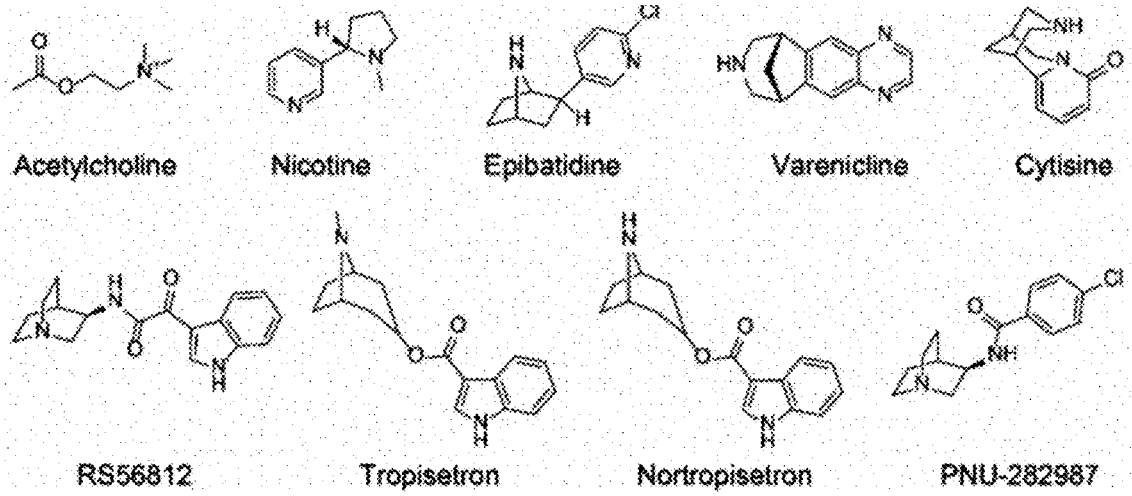
Acetylcholine
Nicotine
Epibatidine
Varenicline
Cytisine
RS56812
Tropisetron
Nortropisetron
PNU-282987

Fig. 4

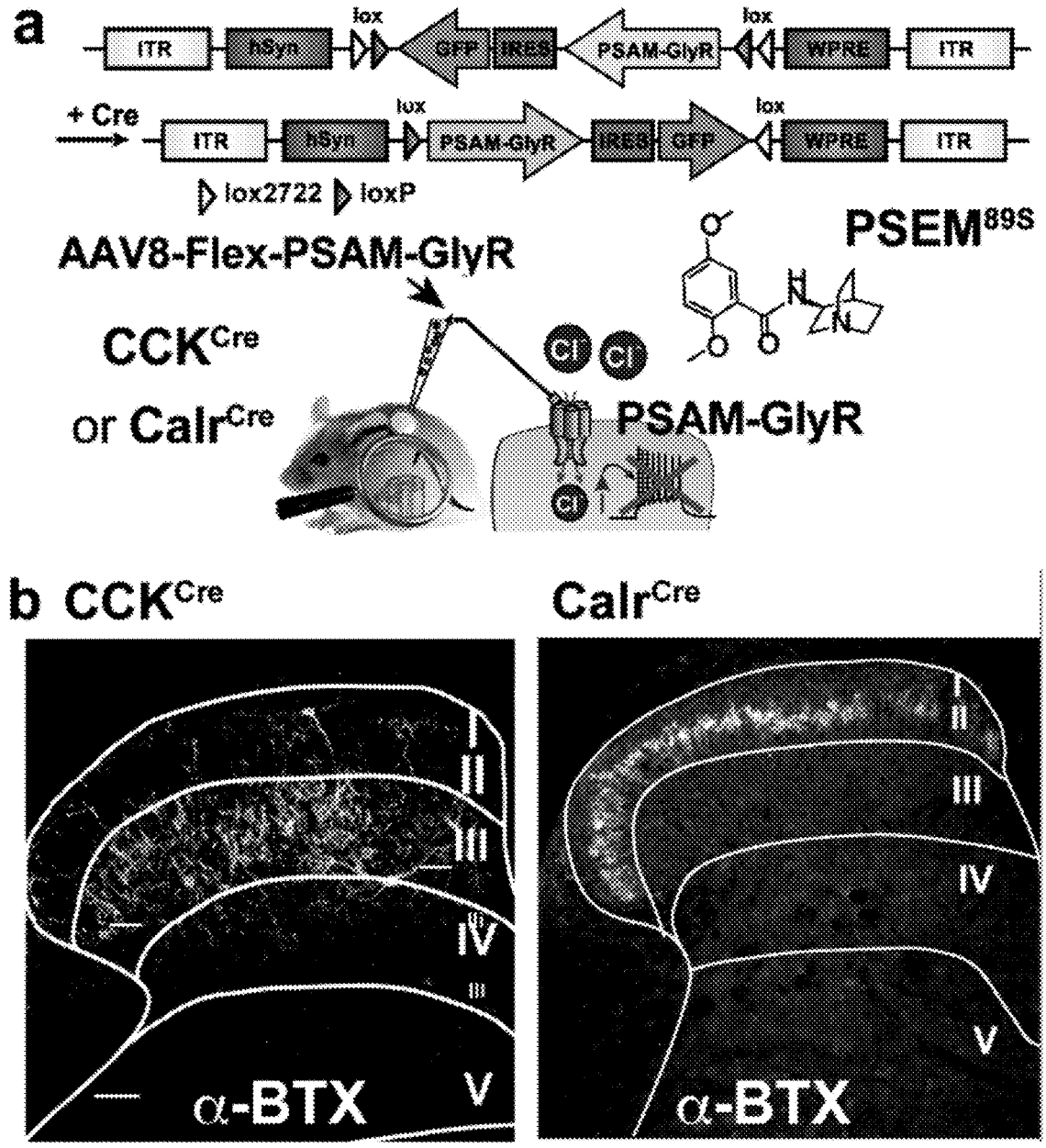
a
ITR
hSyn
lox
GFP
IRES
PSAM-GlyR
WPRE
+ Cre
lox2722
loxP
AAV8-Flex-PSAM-GlyR
CCKCre
or CalrCre
PSEM89S
PSAM-GlyR
b CCKCre
CalrCre
II
III
IV
V
α-BTX

Fig. 5

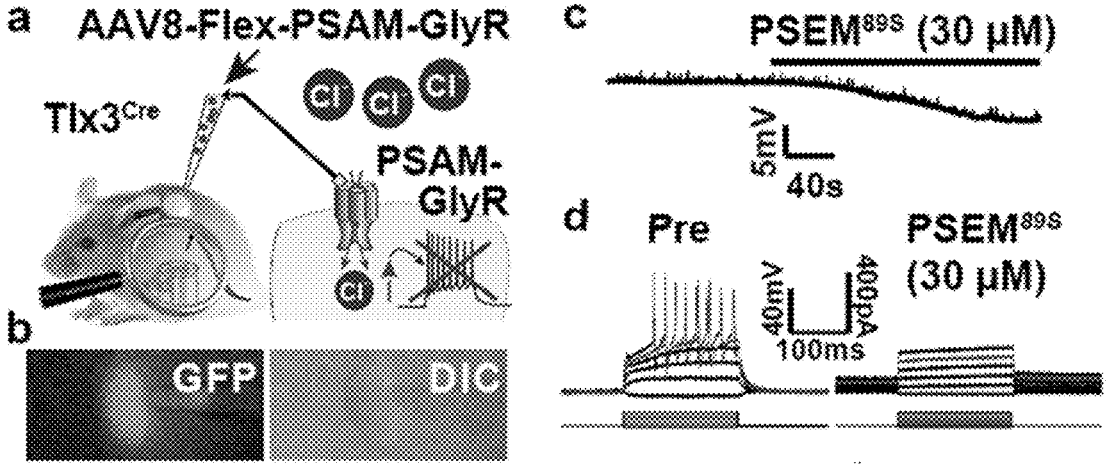
a
AAV8-Flex-PSAM-GlyR
Tlx3Cre
PSAM-GlyR
Cl
b
GFP
DIC
c
PSEM89S (30 μM)
5mV
40s
d
Pre
PSEM89S (30 μM)
40mV
400pA
100ms

Fig. 6A

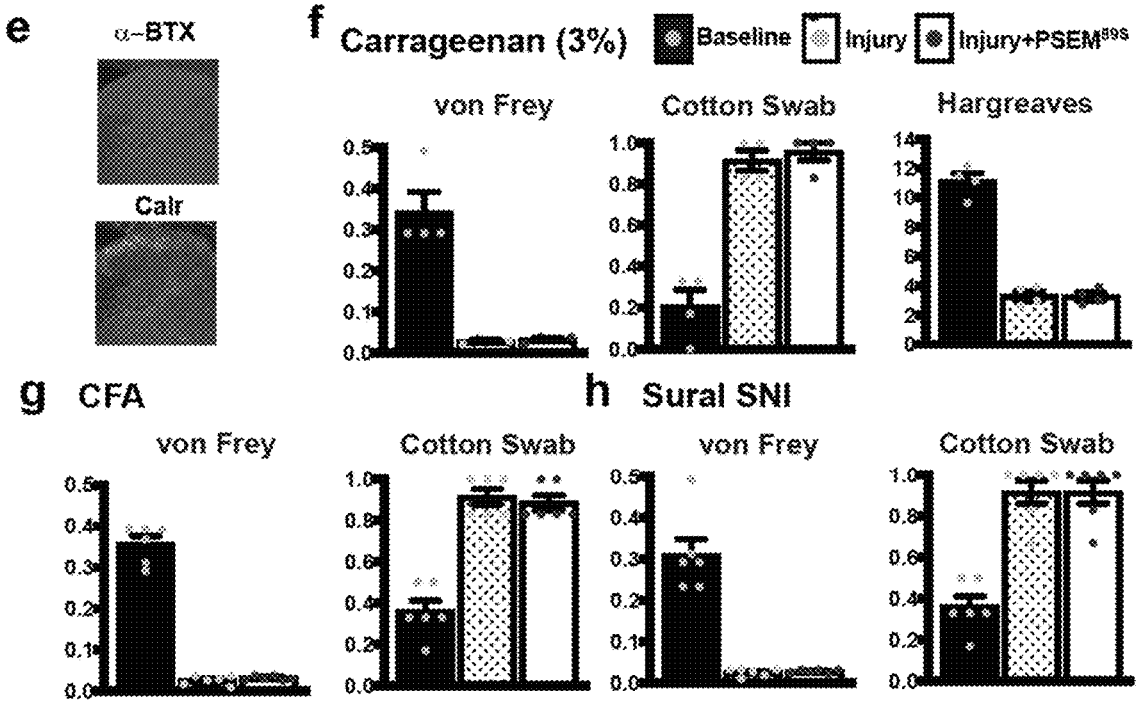
e
α-BTX
Calr
f
Carrageenan (3%)
Baseline
Injury
Injury+PSEM89S
von Frey
Cotton Swab
Hargreaves
g
CFA
von Frey
Cotton Swab
h
Sural SNI
von Frey
Cotton Swab

Fig. 6B

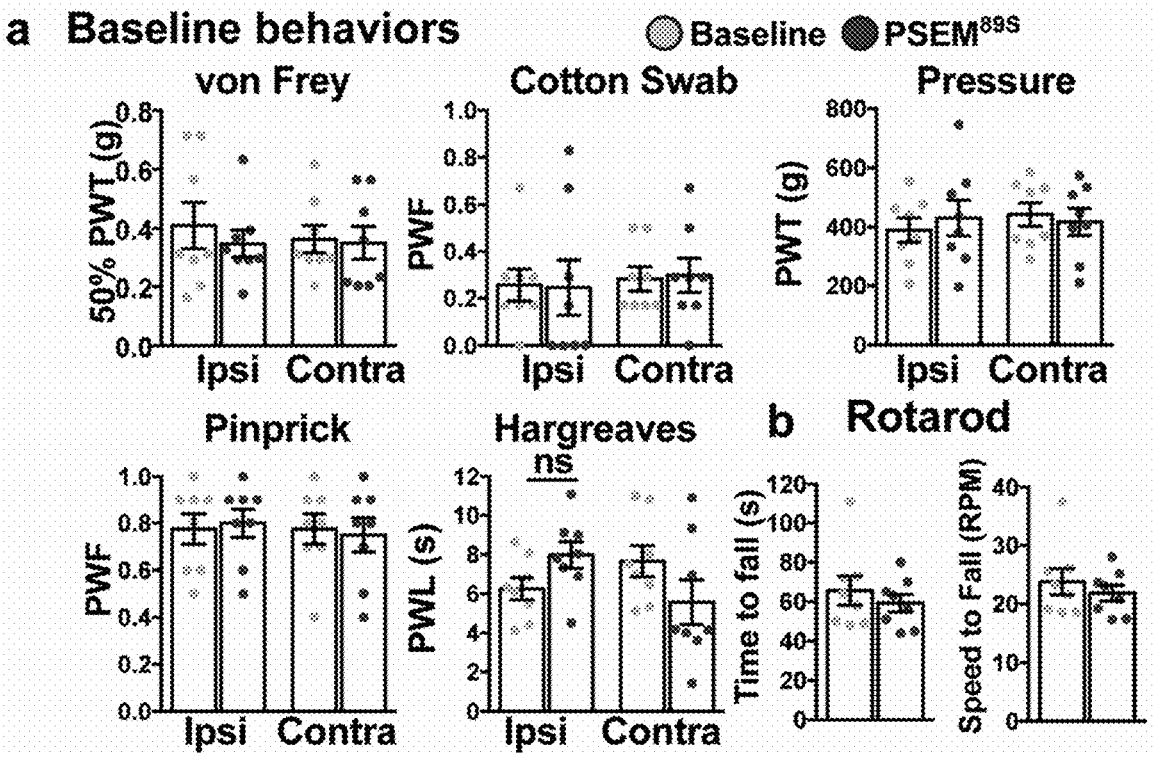
a Baseline behaviors
Baseline
PSEM89S
von Frey
50% PWT (g)
Ipsi
Contra
Cotton Swab
PWF
Pressure
PWT (g)
Pinprick
Hargreaves
ns
PWL (s)
b Rotarod
Time to fall (s)
Speed to Fall (RPM)

Fig. 7

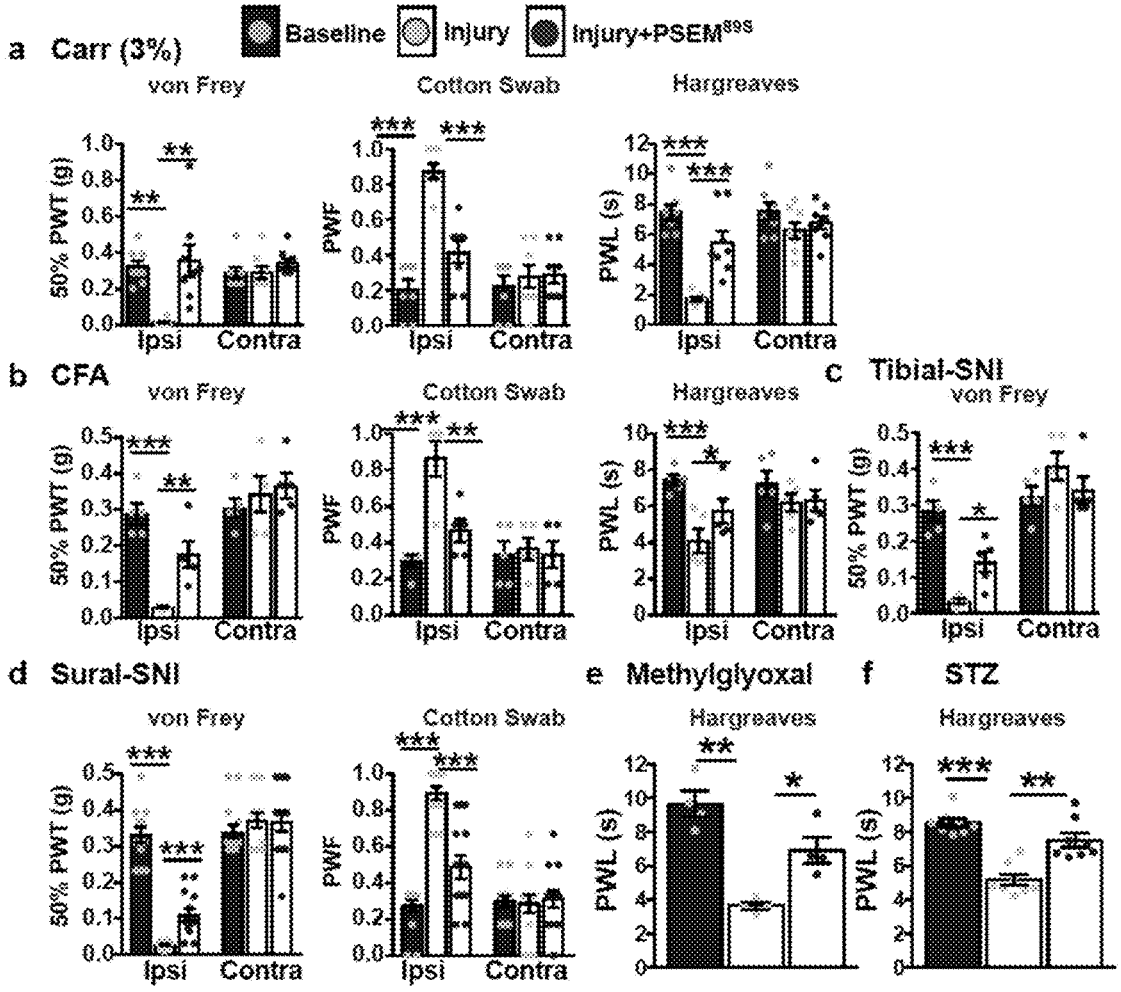
a Carr (3%)
Baseline
Injury
Injury+PSEM^{89S}
von Frey
Cotton Swab
Hargreaves
50% PWT (g)
PWF
PWL (s)
Ipsi
Contra
b CFA
c Tibial-SNI
d Sural-SNI
e Methylglyoxal
f STZ

Fig. 8

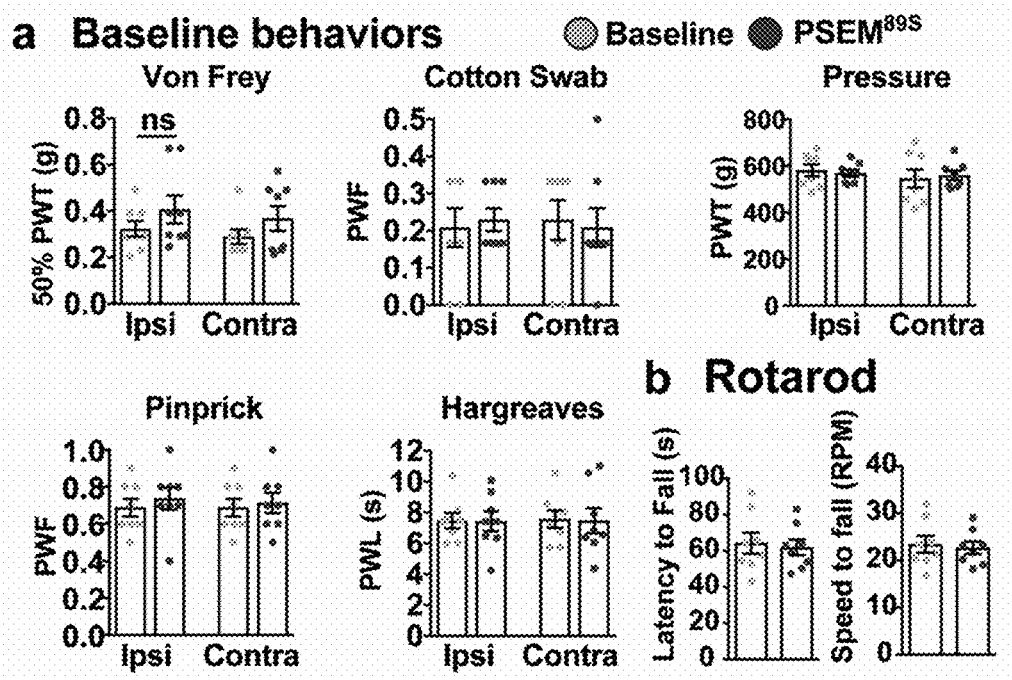
a Baseline behaviors
Baseline
PSEM89S
Von Frey
50% PWT (g)
ns
Ipsi
Contra
Cotton Swab
PWF
Pressure
PWT (g)
Pinprick
Hargreaves
PWL (s)
b Rotarod
Latency to Fall (s)
Speed to fall (RPM)

Figure 9

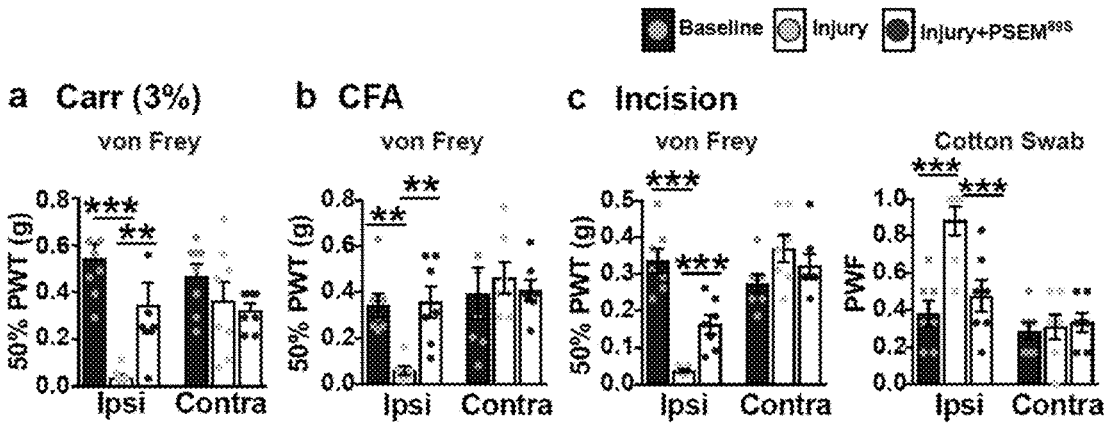
Baseline
Injury
Injury+PSEM89S
a Carr (3%)
von Frey
50% PWT (g)
0.8
0.6
0.4
0.2
0.0
***
**
Ipsi
Contra
b CFA
von Frey
50% PWT (g)
0.8
0.6
0.4
0.2
0.0
**
**
Ipsi
Contra
c Incision
von Frey
50% PWT (g)
0.5
0.4
0.3
0.2
0.1
0.0
***
***
Ipsi
Contra
Cotton Swab
PWF
1.0
0.8
0.6
0.4
0.2
0.0
***
***
**
Ipsi
Contra

Fig. 10

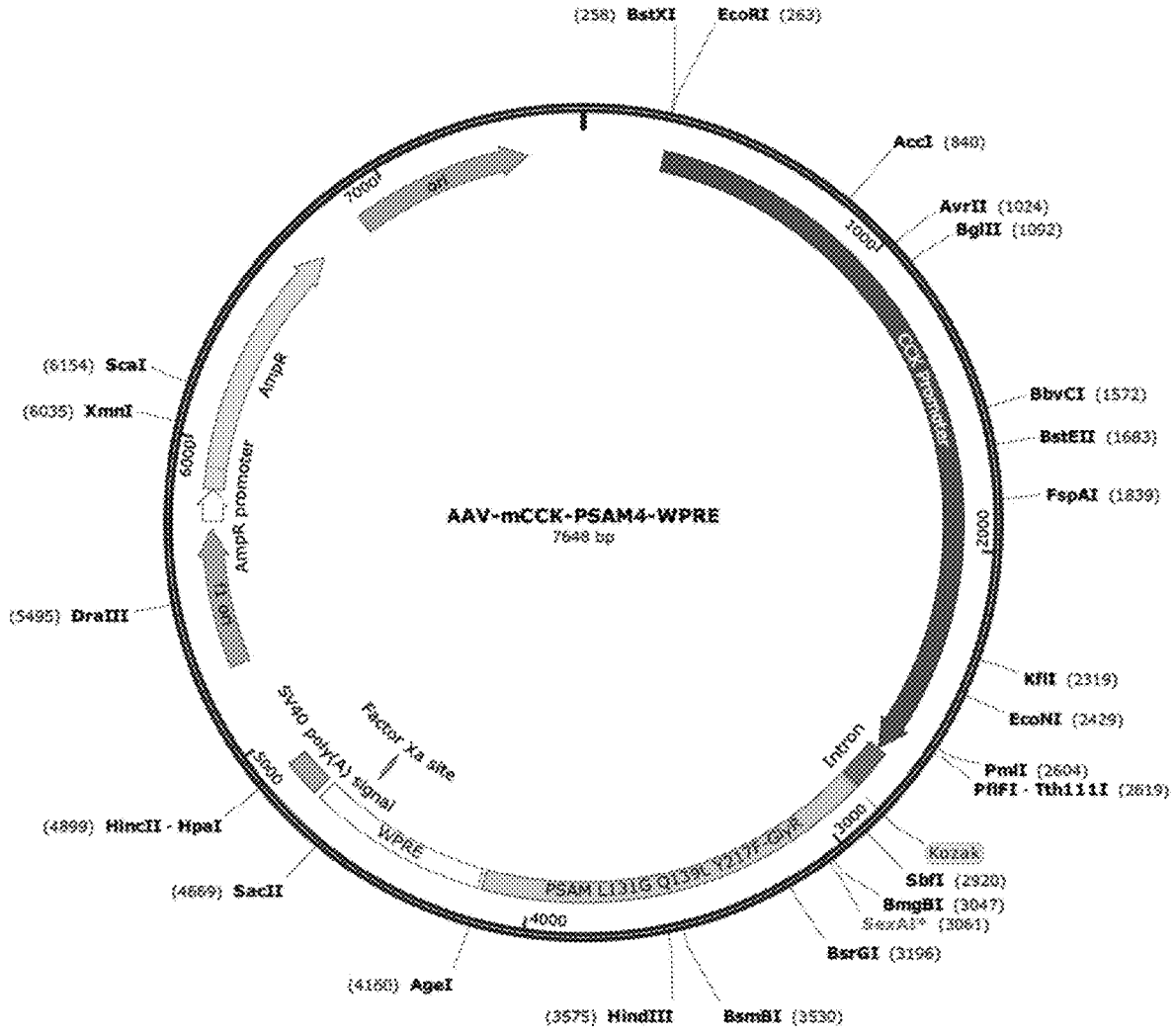
(258) BstXI
EcoRI (263)
AccI (848)
AvrII (1024)
SgfI (1092)
SbvCI (1572)
BstEII (1683)
FspAI (1839)
KflI (2319)
EcoNI (2429)
PmlI (2604)
PflFI - Tth111I (2819)
SbfI (2920)
BmgBI (3047)
SexAI* (3061)
BsrGI (3196)
BsmBI (3530)
HindIII (3575)
AgeI (4180)
SacII (4869)
HincII - HpaI (4899)
DraIII (5495)
XmnI (6035)
ScaI (6154)
AAV-mCCK-PSAM4-WPRE
7648 bp
5'ITR
CCK Enhancer
Intron
PSAM L131G Q133C Y119F Q76R
WPRE
Sv40 poly(A) signal
Factor Xa site
AmpR promoter
AmpR
1000
2000
3000
4000
5000
6000
7000

Fig. 11

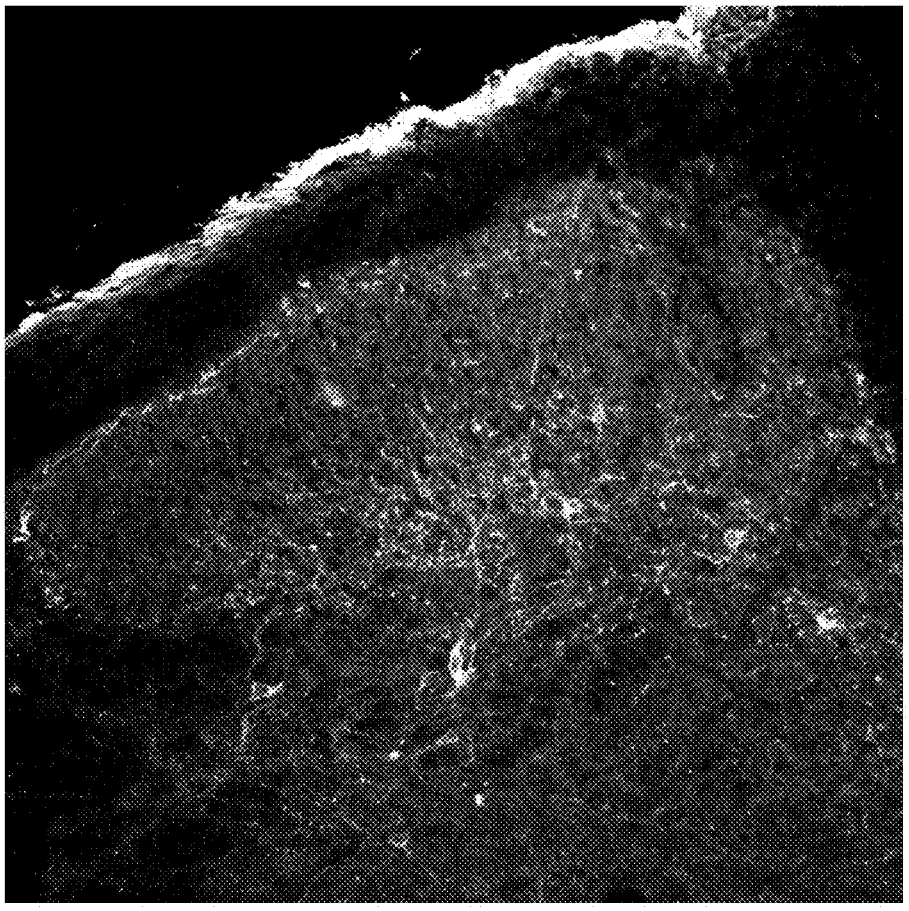

Fig. 12.

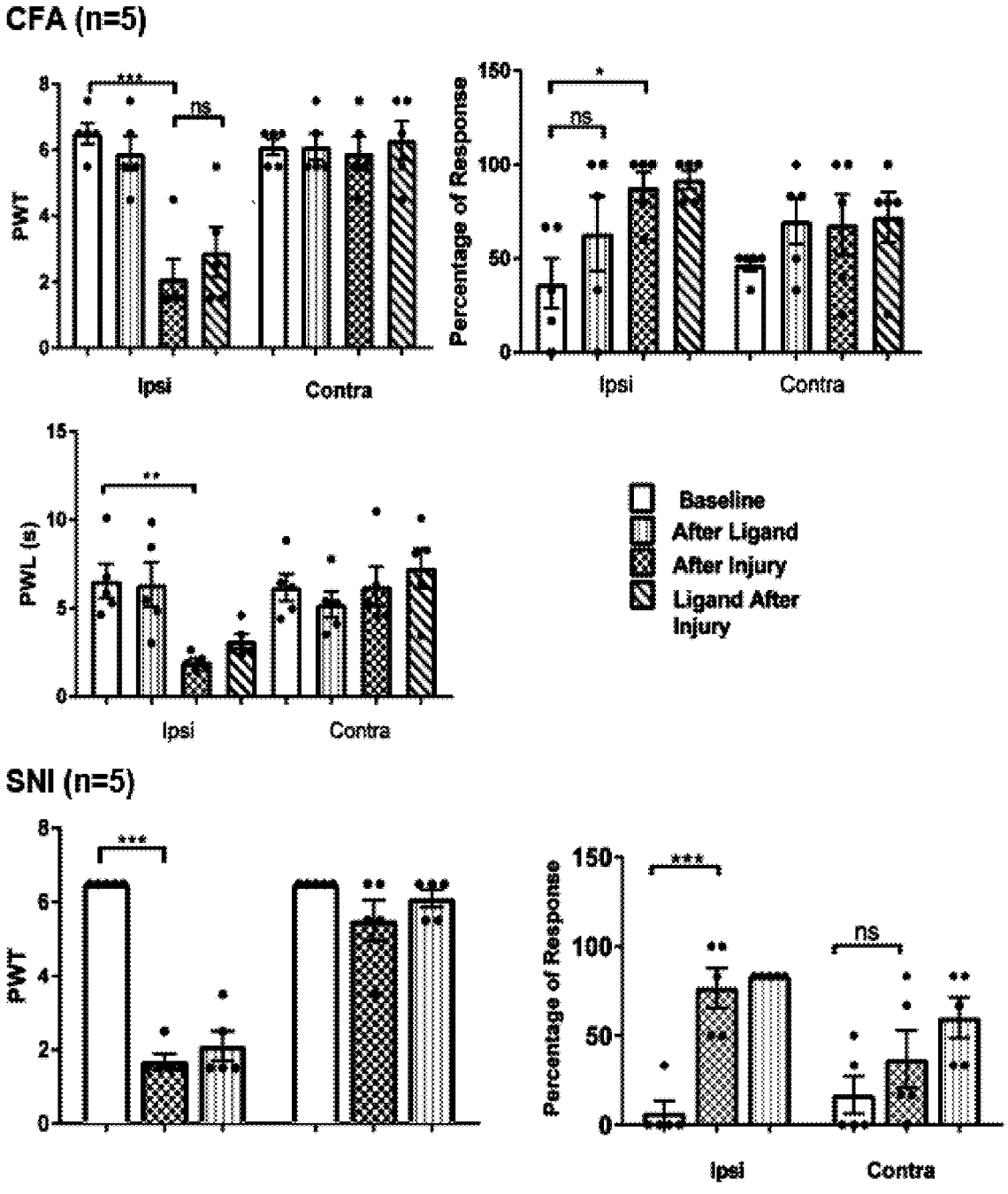
CFA (n=5)
PWT
***
ns
Ipsi
Contra
Percentage of Response
*
ns
Ipsi
Contra
PWL (s)
**
Ipsi
Contra
Baseline
After Ligand
After Injury
Ligand After Injury
SNI (n=5)
PWT
***
Percentage of Response
***
ns
Ipsi
Contra

Fig. 13

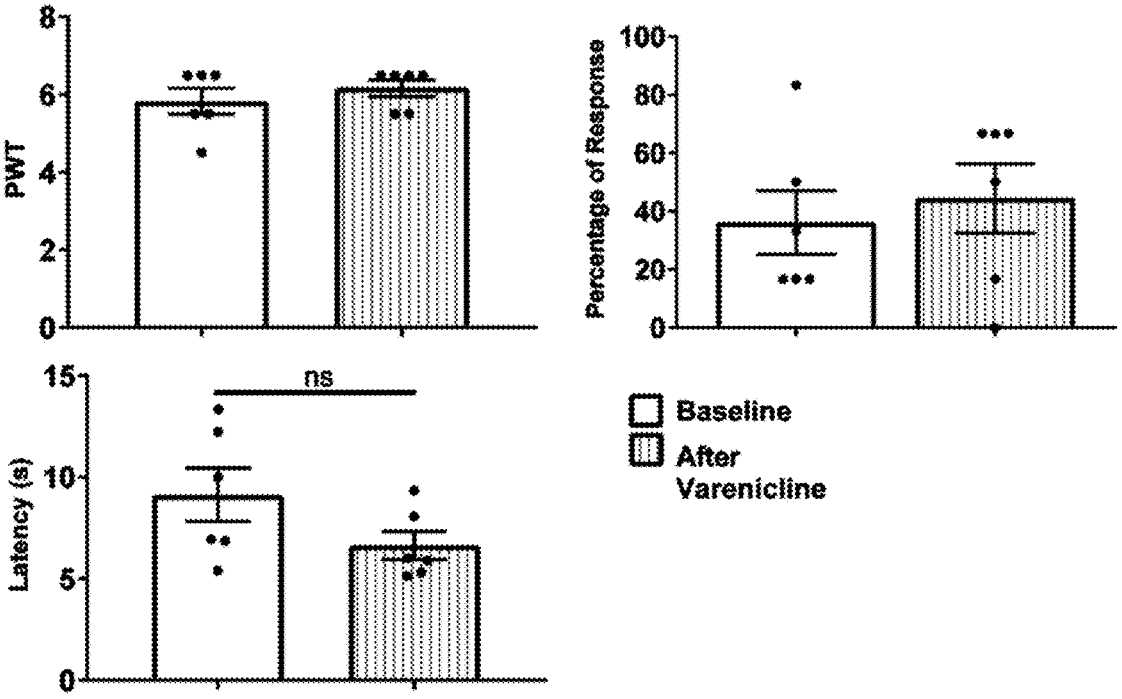
PWT
Latency (s)
ns
Percentage of Response
Baseline
After Varenicline

Fig. 14

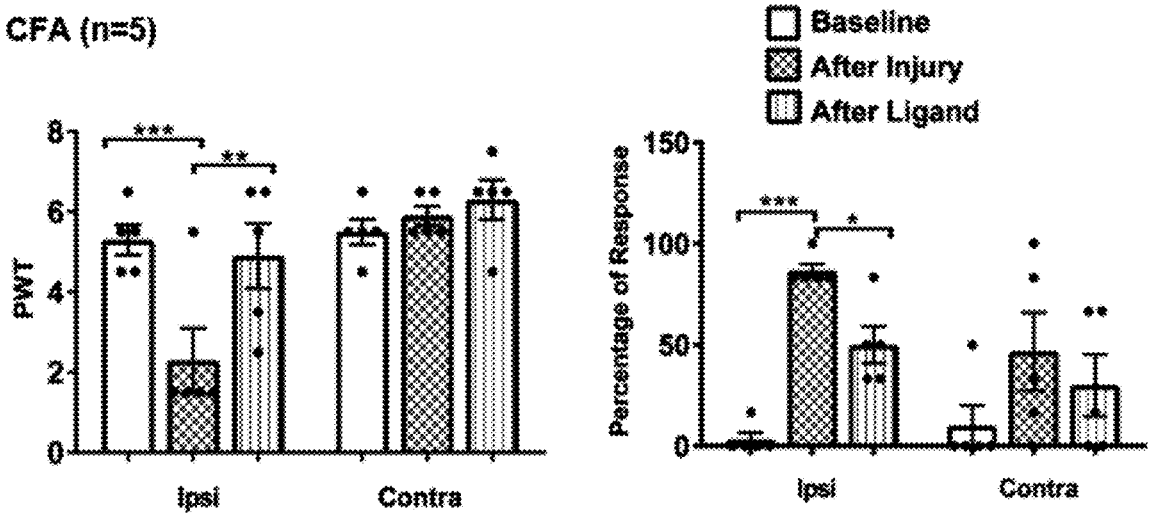
CFA (n=5)
PWT
Ipsi
Contra
Baseline
After Injury
After Ligand
Percentage of Response

Fig. 15

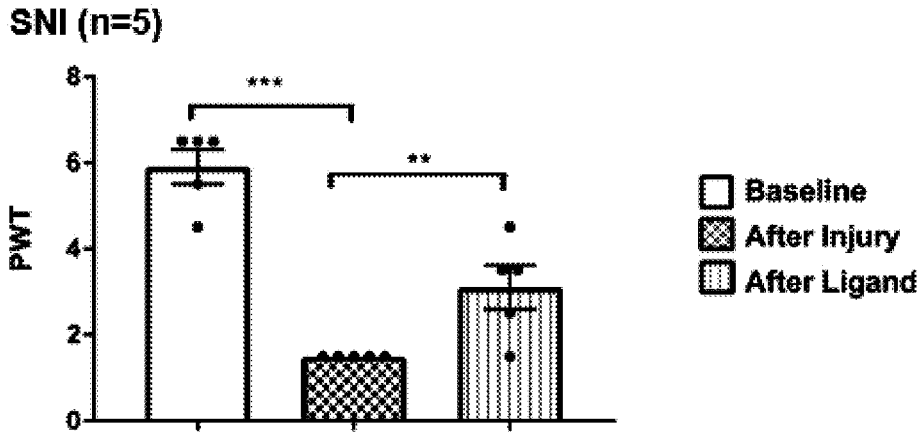

Fig. 16

TARGETED GENE THERAPIES FOR PAIN AND OTHER NEURO-RELATED DISORDERS

CROSS REFERENCE TO RELATED APPLICATIONS

[0001] This application is a divisional application of U.S. patent application Ser. No. 16/493,387, filed Mar. 20, 2018, which is the United States national phase of International Application No. PCT/US2018/023364 filed Mar. 20, 2018, and claims the benefit of U.S. Provisional Patent Application No. 62/473,630 filed Mar. 20, 2017, each of which is incorporated herein by reference in its entirety.

SEQUENCE LISTING

[0002] The Sequence Listing associated with this application is filed in electronic format via Patent Center and is hereby incorporated by reference into the specification in its entirety. The name of the file containing the Sequence Listing is 2304751.xml. The size of the file is 73,585 bytes, and the file was created on Jun. 1, 2023.

[0003] Provided herein are compositions and related methods useful for treatment of pain, especially chronic pain.

[0004] Over 100 million people in the U.S. suffer from debilitating pain caused by disease and trauma. Current therapies are focused on opioids and NSAIDs, but these treatments lose efficacy or produce serious side effects. Addiction to opioid-based prescription painkillers has led to an epidemic level rise in opioid-related overdose deaths. Because of the lack of adequate treatment options, pain continues to be a major clinical problem. Therapeutic solutions to the lack of adequate pain treatment, especially for chronic pain, are needed.

SUMMARY

[0005] Provided herein are nucleic acids for tissue-specific delivery of modified ligand-gated ion channels (LGICs) that can be selectively activated with tailored compound ligands. Such LGICs, once delivered to the neurons of interest by gene therapy methods, would render those neurons sensitive to a ligand selective for such novel LGICs and would obviate the need for local delivery of the ligand, since the tailored ligand would have no effect on native LGICs. Furthermore, selective activation of those tissue-targeted LGICs would eliminate the non-specific effects arising from activation of neighboring populations of neurons that inevitably occur due to the ubiquitous expression of native LGICs. This provides specificity for control of neuron activity that can be used therapeutically to treat neurological diseases and conditions, such as chronic pain or itch. Therefore, development of novel tissue-targeted LGICs with unique pharmacology has therapeutic utility. Related methods also are provided.

[0006] According to a first aspect of the invention, a nucleic acid is provided, comprising a gene for expressing a modified ligand-gated ion channel. The gene comprises an open reading frame encoding a modified ligand-gated ion channel under transcriptional control of transcriptional control elements governing cell-specific expression in CNS neurons, such as dorsal horn neurons, spinal cord cells, or brain cells, or in inhibitory neurons or nerve cells. Examples of transcription control elements include: a CCK promoter, a Tac1 promoter, an NTS promoter, an NMU promoter, a Calb1 promoter, an SST promoter, a GRPR promoter, a parvalbumin promoter, a Gal promoter, an NPY promoter, a PKCγ promoter, or a Calb2 promoter. The modified ligand-gated ion channel comprises a modified ligand binding domain activatable by an exogenous ligand, and optionally selective to the exogenous ligand, and an ion pore domain.

[0007] In another aspect of the invention, a method is provided of modulating (increasing or decreasing) the membrane potential of an excitable cell or a secretory cell. The method comprises expressing in the cell a genetic construct comprising a gene for expressing a modified ligand-gated ion channel, comprising an open reading frame encoding a modified ligand-gated ion channel under transcriptional control of transcriptional control elements governing cell-specific expression in CNS neurons, such as dorsal horn neurons, spinal cord cells, or brain cells, or in inhibitory neurons or nerve cells, such as a CCK promoter, a Tac1 promoter, an NTS promoter, an NMU promoter, a Calb1 promoter, an SST promoter, a GRPR promoter, a parvalbumin promoter, a Gal promoter, an NPY promoter, a PKCγ promoter, or Calb2 promoter and a modified ligand-gated ion channel comprising a modified ligand binding domain activatable by an exogenous ligand, and optionally selective to the exogenous ligand, and an ion pore domain, and contacting the cell with an amount of the exogenous ligand effective to activate the modified ligand gated ion channel thereby modulating the membrane potential of the cell.

[0008] In a further aspect of the invention, a method is provided of treating a disease or disorder associated with the nervous system in a patient. The method comprises delivering a nucleic acid as described below, and administering the exogenous ligand to the patient in an amount effective to activate a modified ligand gated ion channel in a patient thereby treating the disease or disorder associated with the nervous system in the patient. The nucleic acid comprises a gene for expressing the modified ligand-gated ion channel. The gene comprises an open reading frame encoding the modified ligand-gated ion channel under transcriptional control of transcriptional control elements governing cell-specific expression in CNS neurons, such as dorsal horn neurons, spinal cord cells, or brain cells, or in inhibitory neurons or nerve cells. Examples of transcription control elements include: a CCK promoter, a Tac1 promoter, an NTS promoter, an NMU promoter, a Calb1 promoter, an SST promoter, a GRPR promoter, a parvalbumin promoter, a Gal promoter, an NPY promoter, a PKCγ promoter, or a Calb2 promoter. The modified ligand-gated ion channel comprises a modified ligand binding domain activatable by an exogenous ligand, and optionally selective to the exogenous ligand, and an ion pore domain.

BRIEF DESCRIPTION OF THE DRAWINGS

[0009] FIGS. **1A-1** depict exemplary nucleic acid sequences, continuous over FIGS. **1A-10**, comprising promoter sequences useful in the genetic constructs described herein, as follows: Human CCK Promoter (SEQ ID NO: 1), Human Tac1 Promoter (SEQ ID NO: 2), Human Nts Promoter (SEQ ID NO: 3), Human Nmu Promoter (SEQ ID NO: 4), Human Calb1 Promoter (SEQ ID NO: 5), Human Parvalbumin Promoter (SEQ ID NO: 6), Human Gal Promoter (SEQ ID NO: 7), Human NPY Promoter (SEQ ID NO: 8), Human SST Promoter (SEQ ID NO: 9), Human GRPR Promoter (SEQ ID NO: 10), Human PRKCG Promoter (SEQ ID NO: 11), Human Calb2 Promoter (SEQ ID

NO: 12), Mouse CCK Promoter (SEQ ID NO: 13), Mouse Calb2 Promoter (SEQ ID NO: 14), Mouse PRKCG Promoter (SEQ ID NO: 15), Mouse Calb1 Promoter (SEQ ID NO: 16), and Mouse Nmu Promoter (SEQ ID NO: 17).

[0010] FIG. **2** provides amino acid sequences of exemplary a7-nicotinic acetylcholine receptor ligand binding domains (SEQ ID NOs: 18-20 as indicated in the figure).

[0011] FIGS. **3**A-**3**E provide exemplary amino acid sequences for chimeric LGICs. FIG. **3**A provides an exemplary amino acid sequence of an α7-5HT3 chimeric receptor (SEQ ID NO: 21), including a human α7 nAChR LBD and a murine 5HT3 IPD components. FIG. **3**B provides an exemplary amino acid sequence of α7-GIyR chimeric receptor (SEQ ID NO: 22) including a human α7 nAChR LBD) and a human GIyR IPD components. FIG. **3**C provides an exemplary amino acid sequence of α7-5HT3 chimeric receptor (SEQ ID NO: 23, including human α7 nAChR LBD and a human 5HT3 IPD components. FIG. **3**D provides an exemplary amino acid sequence of α7-GABAC chimeric receptor (SEQ ID NO: 24), including a human α7 nAChR LBD and a human GABAC IPD components. FIG. **3**E provides an exemplary amino acid sequence of rat nAChR sequence (SEQ ID NO: 25).

[0012] FIG. **4** provides exemplary exogenous ligands (U.S. 2018/0009862 A1).

[0013] FIG. **5**. (a) Cre-dependent construct for expressing PSAM-GIyR in neurons using AAV delivery. $PSEM^{89S}$ activates the PSAM-GIyR channel, preventing action potential firing of the cells expressing PSAM-GIyR. (b) Dorsal horns of CCK^{Cre} and $Calr^{Cre}$ mice injected intraspinally with AAV8-Flex-PSAM-GIyR virus shows binding of alpha-bungarotoxin-Alexa647 ((α-BTX-Alexa647) to PSAM-GIyR in patterns consistent with the distribution of these two genes.

[0014] FIGS. **6**A and **6**B. Positive and negative controls for PSAM-GIyR and $PSEM^{89S}$. (a) Schematic of PSAM-GIyR construct with GFP reporter used to make AAV8-hSyn-Flex-PSAM-GIyR. Virus was injected into $Tlx3^{Cre}$ mice for electrophysiological slice recordings. (b) Electrode impaling a GFP+ cell (also shown as DI, image) in a transverse slice of the dorsal horn from a $Tlx3^{Cre}$ mouse injected with AAV8-hSyn-Flex-PSAMGIyR virus. (c) Bath application of 30 μM $PSEM^{89S}$ induces a sustained hyperpolarization specifically in GFP-expressing cells. (d) Current injected into GFP+ cell produces action potentials (Pre) that are completely blocked after application of $PSEM^{89S}$ (30 μM) to the slice. (e) Control for the specificity of α-BTX-Alexa647. Contralateral dorsal horn lacks staining for α-BTX-Alexa647. Calretinin; PKCγ. Scale bar=50 μm. Box indicates area of inset. (f) In mice lacking PSAM-GIyR, mechanical allodynia and heat hypersensitivity induced by the carrageenan pain model are not altered by injection of $PSEM^{89S}$ (30 mg/kg, i.p.) ($p>0.999$, n=4) (g) Punctate and dynamic allodynia induced by CFA are also not altered by injection of $PSEM^{89S}$ ($p>0.999$, n=6). (h) In the mice lacking PSAM-GIyR, punctate and dynamic allodynia induced by the sural-SNI model are not altered by injection of $PSEM^{89S}$ (30 mg/kg, i.p.) ($n>0.999$, n=6). Data are mean±standard error of the mean (SEM). ***P<0.001; ns=not significant (i.e. $p>0.05$)

[0015] FIG. **7**. CCK^{+} excitatory neurons in the dorsal horn primarily lamina III-IV are not required for baseline somatosensory behavior or motor behavior on rotarod. (a) Injection of $PSEM^{89S}$ into CCK^{Cre} mice expressing PSAM-GIyR ipsilaterally in the dorsal horn has no effect on baseline von Frey threshold ($p=0.2192$, n=8), response to cotton swab ($p=0.7293$, n=8), pressure with calibrated calipers ($p=0.7450$, n=8) or pinprick ($p=0.5983$, n=8). Hargreaves latencies are unchanged ($p=0.9746$, n=8). (b) Performance on the rotarod is also not altered by injection of $PSEM^{89S}$. Data are mean±SEM. None are significantly different.

[0016] FIG. **8**. CCK+ excitatory dorsal horn neurons are required for the transmission of persistent forms of pain. Mice expressing PSAM-GIyR in CCK+ dorsal horn neurons were tested in persistent pain behaviors. (a) In the carrageenan pain model, injection of $PSEM^{89S}$ (30 mg/kg, i.p.) reversed punctate ($p=0.0017$, n=8) and dynamic allodynia ($p=0.0001$, n=8) as well as heat hypersensitivity ($p=0.0002$, n=8). (b) In the CFA model, $PSEM^{89S}$ injection also markedly reversed punctate ($p=0.0034$, n=5) and dynamic allodynia ($p=0.0016$, n=5) as well as heat hypersensitivity ($p=0.0368$, n=5). (c,d) Inhibiting the CCK population reversed punctate allodynia in the sural-SNI ($p=0.0003$, n=12) and tibial-SNI ($p=0.0054$, n=5) models. Dynamic allodynia in sural-SNI is also reversed ($p=0.0001$, n=12). (e,f) $PSEM^{89S}$ also reversed heat hypersensitivity induced by MG ($p=0.0272$, n=4) or multi-dose STZ ($p=0.010$, n=9). Data are mean±SEM. *p<0.05, **p<0.01, ***P<0.001.

[0017] FIG. **9**. $Calretinin^{+}$ excitatory neurons in the dorsal horn lamina II are not required for baseline somatosensory behavior or motor behavior on the rotarod. (a) Injection of $PSEM^{89S}$ (30 mg/kg, i.p.) into $Calr^{Cre}$ mice expressing PSAM-GIyR ipsilaterally in the dorsal horn has no effect on ipsilateral von Frey threshold ($p=0.3988$, n=8), response to cotton swab ($p=0.7963$, n=8), pressure with calibrated calipers ($p=0.8350$, n=8) sticky tape ($p=0.9346$, n=8) or pinprick ($p=0.7689$, n=8). Hargreaves latencies are also unchanged ($p=0.6125$, n=8). (b) Motor behavior measured by rotarod is not altered by inhibition of dorsal horn calretinin neurons with $PSEM^{89S}$. Data are mean±SEM. None are significantly different.

[0018] FIG. **10**. $Calretinin^{+}$ excitatory neurons in lamina II of the dorsal horn convey mechanical allodynia induced by inflammatory, but not neuropathic pain models. Inhibition of PSAM-GlyR expressing calretinin neurons in the dorsal horn lamina II by injection of $PSEM^{89S}$ (30 mg/kg, i.p.) reverses mechanical allodynia induced by models of inflammatory pain including (a) carrageenan ($p=0.0074$, n=8), (b) CFA ($p=0.0026$, n=8), (c) incision (punctate, $p=0.0028$, n=7; dynamic $p=0.0001$, n=7) Data are mean±SEM. **p<0.01, ***P<0.001.

[0019] FIG. **11**: AAV-mCCK-PSAM4-WPRE construct. A 2.5 kb fragment of the mouse CCK promoter was sub-cloned upstream of the PSAM (L131G Q139L Y217F)-GlyR (PSAM4) gene with a chimeric intron (135 bp) located in between the promoter and the PSAM4 gene.

[0020] FIG. **12**. Expression of PSAM4 in the dorsal horn of an adult wildtype C57Bl/6 mouse. α-bungarotoxin-Alexa647 (α-BTXAlexa-647) staining of the lumbar dorsal horn of a mouse unilaterally injected with the AAV8 mCCK-PSAM4-WPRE virus in the dorsal horn (1^{13} vg/ml, custom packaged).

[0021] FIG. **13**. Varenicline has no effect on baseline mechanical and heat sensitivity or CFA or sural SNI induced hypersensitivity in mice lacking PSAM4. PWT, frequency of response and PWL were tested in adult wildtype C57Bl/6 mice (not expressing PSAM4) before and after injection of varenicline (0.1 mpk, i.p) at baseline and 3 and 7 days after

injection of CFA or sural-SNI surgery, respectively. Data are mean±SEM. N=5 mice. *p<0.05, **p<0.01, ***P<0.001; ns=not significant (i.e. p>0.05).

[0022] FIG. **14**. Control showing effect of varenicline on mechanical and heat sensitivity at baseline in mice injected with mCCK-PSAM4 virus. The effect of varenicline (0.3 mpk, i.p) on baseline mechanical and heat hypersensitivity was tested 2 weeks after injection of AAV8 mCCK-PSAM4 unilaterally into the dorsal horn. Injection of varenicline had no effect on baseline PWT, percentage response or PWL (measured 30-60 minutes following injection of the drug) in mice expressing PSAM4 in dorsal horn CCK+ neurons. Data are mean±SEM. N=5-6 mice. **p<0.05, **p<0.01, ***P<0.001; ns=not significant (i.e. p>0.05).

[0023] FIG. **15**. Varenicline reverses mechanical allodynia induced by CFA in mice expressing mCCK-PSAM4 in the dorsal horn. Adult wildtype C57Bl/6 mice injected with AAV8 mCCK-PSAM4-WPRE virus unilaterally in the dorsal horn. PWT to von Frey filaments and percentage of response to cotton swab were measured before and 3 days after CFA injection in plantar hindpaw and after injection of varenicline (0.3 mpk, i.p). Injection of varenicline reversed both PWT and response frequency to cotton swab after CFA. Data are mean±SEM. N=5 mice. *p<0.05, **p<0.01, ***P<0.001.

[0024] FIG. **16**. Varenicline reverses mechanical allodynia induced by the sural model of SNI in mice expressing mCCK-PSAM4 in the dorsal horn. Adult wildtype C57Bl/6 mice injected with mCCK-PSAM4 unilaterally in the dorsal horn. Three weeks later, PWT to von Frey filaments was measured before and 7 days after sural-SNI surgery on the ipsilateral side and then again after injection of varenicline (0.3 mpk, i.p). Injection of varenicline reversed PWT after SNI. Data are mean±SEM. N=5 mice. **p<0.01, ***p<0.001.

DETAILED DESCRIPTION

[0025] The use of numerical values in the various ranges specified in this application, unless expressly indicated otherwise, are stated as approximations as though the minimum and maximum values within the stated ranges are both preceded by the word "about". In this manner, slight variations above and below the stated ranges can be used to achieve substantially the same results as values within the ranges. Also, unless indicated otherwise, the disclosure of ranges is intended as a continuous range including every value between the minimum and maximum values. As used herein "a" and "an" refer to one or more.

[0026] As used herein, the term "comprising" is open-ended and may be synonymous with "including", "containing", or "characterized by". The term "consisting essentially of" limits the scope of a claim to the specified materials or steps and those that do not materially affect the basic and novel characteristic(s) of the claimed invention. The term "consisting of" excludes any element, step, or ingredient not specified in the claim. As used herein, embodiments "comprising" one or more stated elements or steps also include, but are not limited to embodiments "consisting essentially of" and "consisting of" these stated elements or steps.

[0027] A "patient" is a human or animal, e.g., vertebrates or mammals, including rat, mouse, rabbit, pig, monkey, chimpanzee, cat, dog, horse, goat, guinea pig, and birds, and does not imply or require a doctor-patient or veterinarian-patient relationship.

[0028] The terms "transfect", "transfection", "transfected", and like terms refer to the introduction of a gene into a eukaryotic cell, such as a keratinocyte, and includes "transduction," which is viral-mediated gene transfer, for example, by use of recombinant AAV, adenovirus (Ad), retrovirus (e.g., lentivirus), or any other applicable viral-mediated gene transfer platform.

[0029] By "expression" or "gene expression," it is meant the overall flow of information from a gene. A "gene" is a functional genetic unit for producing a gene product, such as RNA or a protein in a cell, or other expression system encoded on a nucleic acid and generally comprising: a transcriptional control sequence, such as a promoter and other cis-acting elements, such as transcriptional response elements (TREs) and/or enhancers; an expressed sequence that typically encodes a protein (referred to as an open-reading frame or ORF) or functional/structural RNA; and a polyadenylation sequence). A gene produces a gene product (typically a protein, optionally post-translationally modified or a functional/structural RNA) when transcribed. By "expression of genes under transcriptional control of," or alternately "subject to control by," a designated sequence such as a promotor, it is meant gene expression from a gene containing the designated sequence operably linked (functionally attached, typically in cis) to the gene. A gene that is "under transcriptional control" of a promotor or transcription control element, is a gene that is transcribed at detectably different levels in the presence of a transcription factor, e.g., in specific cells, as further described below, and in the context of the present disclosure, produces a difference in transcription levels when expressed in a specific cell type (e.g., where the promoter is a CCK promoter, the gene is preferentially expressed in cells that express CCK natively. A "gene for expression of" a stated gene product is a gene capable of expressing that stated gene product when placed in a suitable environment, that is, for example, when transformed, transfected, transduced, etc. into a cell, and subjected to suitable conditions for expression. In the case of a constitutive promoter "suitable conditions" means that the gene typically need only be introduced into a host cell. In the case of an inducible promoter, such as the tissue specific promoters described herein, "suitable conditions" means when factors that regulate transcription, such as DNA-binding proteins, are present or absent, for example, an amount of the respective inducer is available to the expression system (e.g., cell), or factors causing suppression of a gene are unavailable or displaced—effective to cause expression of the gene.

[0030] Transcriptional control elements include promoters, enhancers, transcription factor-responsive elements (TREs, e.g., transcription factor binding sequences), suppressors, introns, etc., as are broadly-known. Additional transcription control elements, such as a WPRE (woodchuck hepatitis virus post-transcriptional regulatory element), or an intron, e.g., as shown below, which can increase expression from certain viral vectors, can be included in the gene.

[0031] Exemplary tissue specific promoters, specific to excitable cells or secretory cells, e.g. of the central nervous system (CNS), such as, without limitation, neurons, sensory neurons, dorsal horn cells, spinal cord cells, brain cells, and inhibitory neurons, include, for example and without limitation, those promoter sequences depicted in FIGS. **1A-1L**, and described in Table 1.

TABLE 1

Promoter	Location for Expression	Inhibitory or excitatory LGIC	Physiological Effect
Cholecystokinin (CCK)	Dorsal horn neuron	inhibitory	Blocks persistent pain
Tachykinin (Tac1)	Dorsal horn neuron	inhibitory	Blocks persistent pain
PKCγ (PRKCG)	Dorsal horn neuron	inhibitory	Blocks persistent pain
Neurotensin (NTS)	Dorsal horn neuron	inhibitory	Blocks persistent pain
Neuromedin U (NMU)	Dorsal horn neuron	inhibitory	Blocks persistent pain
Calbindin 1 (Calb1)	Dorsal horn neuron	inhibitory	Blocks persistent pain
Calbindin 2 (Calb2)	Dorsal horn neuron	inhibitory	Blocks persistent pain
Somatostatin (SST)	Dorsal horn neuron	inhibitory	Blocks persistent pain
Gastrin related peptide receptor (GRPR)	Dorsal horn neuron	inhibitory	Blocks itch
Galanin (GAL)	Dorsal horn neuron	Excitatory	Blocks persistent pain or itch
Neuropeptide Y (NPY)	Dorsal horn neuron	Excitatory	Blocks persistent pain or itch
Parvalbumin (PV)	Dorsal horn neuron	Excitatory	Blocks persistent pain or itch

[0032] A promoter is "specific" to specified excitable cells or secretory cells if it causes gene expression in those cells of a gene to a sufficient extent for production of useful or therapeutically effective amounts of the described modified LGICs described herein in the specified excitable cells or secretory cells, and insignificant expression elsewhere in the context of the use, e.g. therapeutic use.

[0033] Although these are human sequences and consensus sequences, there is conservation among species and many promoter sequences that function in human cells will also be expected to do so in mice, or any mammal or vertebrate, and many promoter sequences that function in mice, or any mammal or vertebrate will also be expected to do so in human cells. The sequences also may be modified, e.g., shortened, for virion packaging purposes and optimal expression, so long as tissue-specificity of the construct remains.

[0034] One of the advantages of using highly circumscribed cell-type specific promoters described herein, for example, Calb2 or CCK to drive expression of PSAM4 or another LGIC (e.g., an inhibitory LGIC in Calb2 or CCK expressing dorsal horn neurons), is that baseline mechanical or heat sensitivity are not affected (see, Examples 1 and 2, below) with exogenous ligand-mediated activation of the LGIC. These promoters provide an important advantage over pan neuronal or pan excitatory neuron or pan inhibitory neuron promoters, or also primary afferent promoters such as TRPV1 (those neurons fibers are required for all heat sensation), which will negatively impact acute pain or touch in the area innervated by the targeted neurons with exogenous ligand-mediated activation of the LGIC. The ability to feel acute pain is important to protect the patient from bodily harm.

[0035] Production of useful nucleic acid constructs, such as recombinant viral vectors for production of nucleic acids, such as the genetic constructs and recombinant viral genomes described herein, is routine, in that molecular cloning and gene assembly methods are routine. Further, a number of companies can custom-synthesize and verify multi-kilobase genes, making the production of genes or genomes as described herein, such as rAAV or scAAV genomes, routine (See, e.g., Gene Synthesis Handbook, 2d Edition, 2014, GenScript USA, Inc.).

[0036] AAV (adeno-associated virus), is a virus belonging to the genus Dependoparvovirus, and family Parvoviridae. The virus is a small replication-defective, non-enveloped virus. AAV is not currently known to cause any disease by itself. AAV requires a helper virus, such as adenovirus or herpes simplex virus, to facilitate productive infection and replication. In the absence of helper virus, AAVs establish a latent infection within the cell, either by site-specific integration into the host genome or by persisting in episomal forms. Gene therapy vectors using AAV can infect both dividing and quiescent cells. Furthermore, AAV serotypes have different tropism and can infect cells of multiple diverse tissue types. While eleven serotypes of AAV have been identified to date, AAV2 was among the first to be identified and has been consistently used for the generation of recombinant AAV vectors. Further certain natural or modified AAVs transduce specific organs or cell populations. In one example, AAV-PHP.eB and AAV-PHP.S, capsids efficiently transduce the central and peripheral nervous systems, respectively, when administered intravenously (Chan, K. Y., et al. Engineered AAVs for efficient noninvasive gene delivery to the central and peripheral nervous systems (2017) Nat. Neurosci 20(8):1172-1179). For example, compared to AAV9, AAV-PHP.B delivers genes to the brain and spinal cord at least 40 times more efficiently. See also, Tervo, D G, et al. A Designer AAV Variant Permits Efficient Retrograde Access to Projection Neurons (2016) *Neuron* 92, 372-382, describing engineered AAV variants, e.g., rAAV2-retro, which permit robust retrograde access to projection neurons with efficiency comparable to classical synthetic retrograde tracers, and enable sufficient sensor/effector expression for functional circuit interrogation and in vivo genome editing in targeted neuronal populations.

[0037] The AAV virion shell is approximately 25 nm in diameter and encapsulates a single-stranded DNA genome that consists of two large open reading frames (ORFs) flanked by inverted terminal repeats (ITR). The ITRs are the only cis-acting elements required for genome replication and packaging. In wild-type AAV, the left ORF encodes four replication proteins responsible for site-specific integration, nicking, and helicase activity, as well as regulation of promoters within the AAV genome. AAV possesses a 4.7 kb genome, and as such, efficient packaging of recombinant AAV (rAAV) vectors can be performed with constructs ranging from 4.1 kb to 4.9 kb in size (see, e.g., Samulski, R J, et al., AAV-Mediated Gene Therapy for Research and Therapeutic Purposes, *Annu. Rev. Virol.* 2014. 1:427-51).

[0038] Helper-free production of the rAAV requires transfection of the following components into host cells, typically 293 cells (HEK293 cells), which are broadly available, or similar cell lines: (1) an rAAV vector containing the transgene expression cassette flanked by the two ITRs; (2) expression of Rep and Cap proteins, typically provided by a helper plasmid in trans; and (3) adenovirus genes encoding E1, E2A, E4, and virus-associated RNA, also provided, at least in part by another helper plasmid in trans (293 cells produce the Ad E1 gene in trans). Rep and Cap proteins, which are necessary for viral packaging, are replication

proteins and capsid proteins, respectively. Rep proteins consist of rep 78, 68, 52 and 40. They specifically are involved with the replication of AAV. Cap proteins are comprised of three proteins, VP1, VP2 and VP3, with molecular weight of 87, 72 and 62 kDa, respectively. These capsid proteins assemble into a near-spherical protein shell of 60 subunits. Helper-free AAV packaging systems are broadly available, for example, from Clontech of Mountain View, California, from Cell Biolabs, Inc. of San Diego, CA, and see, e.g., U.S. Pat. Nos. 6,093,570, 6,458,587, 6,951,758, and 7,439,065. In scAAV (self-complementary AAV), the right ITR contains a deletion of D-sequence (the packaging signal) and a terminal resolution site mutation (Atrs), which prevent Rep-mediated nicking and force packaging of dimer or self-complementary genomes (see FIG. **8**). Making dsAAV from scAAV vector renders much improved transduction both in vitro and in vivo (see, e.g., pscAAV-MCS Expression vector, Product Data Sheet, Cell Biolabs, Inc., San Diego, California (2012-2016)).

[0039] Preparation of rAAV transducing particles, such as scAAV transducing particles is routine. Since the transfection method is often considered unsuitable for large-scale production, the infection of cell lines stably expressing Rep and Cap with adenovirus carrying a vector genome has afforded the ability to scale-up. Another option includes infection of proviral cell lines with adenovirus or herpes simplex virus vector carrying an AAV Rep and Cap expression cassette. These methods still require the complete elimination of adenovirus (or herpesvirus) during the production process. However, in baculovirus expression vector systems for rAAV vector production in insect SF9 cells, the components of AAV production, including Rep and Cap proteins, as well as vector genomes are provided by separate recombinant baculoviruses. Ayuso, E., "Manufacturing of recombinant adeno-associated viral vectors: new technologies are welcome", *Molecular Therapy—Methods & Clinical Development* (2016) 3, 15049; doi:10.1038/mtm.2015.49, and Merten, O-W, et al., describe numerous robust current rAAV production methods, though commercial scale-up and validation needs improvement. High viral titers ($\sim 10^{12}$~10^{13} vp/mL) may be required for certain uses described herein. Protocols are available in the literature for concentration and purification of AAV vectors, allowing production of virus at these high concentrations (see, e.g., Gray S J, et al. (2011) Production of recombinant adeno-associated viral vectors and use in in vitro and in vivo administration. *Curr Protoc Neurosci*. doi:10.1002/0471142301.ns0417s57 and Guo P, et al. (2012) Rapid and simplified purification of recombinant adeno-associated virus. *J Virol Methods* 183(2):139-146).

[0040] Once the virus has been produced in the, e.g., 293 cells, the cells are collected, lysed, and the resultant virus is purified. Density gradient ultracentrifugation, e.g., in cesium chloride or nonionic iodixanol (VISIPAQ™) gradients and column chromatography, such as ion-exchange, heparin-affinity, or mucin-affinity column chromatography, depending on the AAV serotype. Once the rAAV has been purified and concentrated to a suitable concentration, the virus can be used for in vitro cell transduction or for in vivo animal injection at an appropriate MOI (Multiplicity of Infection).

[0041] Numerous rAAV vectors have been made containing genes for expressing fluorescent proteins, and are commercially available. A "gene" is a genetic element for production of a gene product such as a protein or RNA. A gene for production of a protein product includes, from 5' to 3' according to convention: one or more regulatory elements (transcription control elements) such as promoters, transcription response elements (TREs), repressors, enhancers; an open-reading frame (ORF) encoding a protein or a sequence encoding a functional RNA; and a polyadenylation (pA) site. Due to size limitations, genes for use in rAAV vectors typically do not include introns. rAAV vectors also include the 5' ITR and 3' ITR flanking the gene, which is referred to as a transgene. Thus a typical rAAV genome has the following structure, in order from 5' to 3' on the sense strand: ITR—promoter—transgene ORF—pA—ITR, and in one aspect of the present invention, the promoter includes a TRE and the transgene ORF is that of a colorimetric, e.g., fluorescent protein. Methods of molecular cloning of rAAV transgene constructs, preparation of rAAV particles, and storage and use thereof are broadly-known and further technical details are unnecessary for one of ordinary skill in the art to be able to construct useful rAAV vectors, and produce and use rAAV particles as described herein. As indicated above, so long as the gene sequence is less than the packaging limit of rAAV or scAAV, it is useful for production of a transduction particle as described herein.

[0042] AAV is but one of many robust and well-characterized viral vectors suited for gene therapy, which also includes, without limitation, gammaretroviruses, lentiviruses, adenovirus, and herpes simplex virus. While AAV is likely preferred in many instances, other safe and effective viral transducing particles can be developed based on the genes described herein for use in the devices, systems and methods described herein.

[0043] Likewise, DNA, such as plasmid or other forms of DNA, optionally combined with suitable transfection reagents, such as liposomes.

[0044] In aspects, compositions and methods are provided for delivery of a gene to excitable cells or secretory cells, such as nerve cells or neurons, e.g., to sensory neurons, or inhibitory neurons or nerve cells, that encodes a protein comprising a ligand binding domain fused to a functional or effector domain (transmembrane ion channel or ion pore domain). As described in further detail below, the protein may be a mutated native (non-chimeric) protein, such as a mutated GIyR or a7-nicotinic acetylcholine receptor, or a chimeric protein, such as a protein comprising a mutated α7-nicotinic acetylcholine receptor ligand binding domain (LBD) and a GIyR transmembrane ion channel domain.

[0045] In all instances, ligand-gated ion channels and their respective LBDs and transmembrane domains, are broadly-known, and their nucleotide and amino acid sequences, including a large number of mutated sequences that selectively bind exogenous ligands, and transcription control elements, such as promoters, are broadly-available in the literature and free databases and sources, such as GenBank, UniProt, Addgene, EPD (eukaryotic promoter database), see, U.S. Pat. No. 8,435,762 and U.S. Patent Application Publication No. 2018/0009862, etc., among many other literature and on-line sources, and do not need to be recited herein. Likewise, methods of preparing genes encoding such proteins and for expressing such proteins in a tissue-specific manner is routine and need not be described beyond what is provided herein. Nevertheless, exemplary nucleic acid constructs, nucleic acid and amino acid sequences, recombinant

virus particles, and related methods and reagents are provided herein for illustrative purposes, and as proof of concept.

[0046] Excitable cells or secretory cells include, for example and without limitation, sensory nerves and neurons including, without limitation, CNS neurons, such as spinal cord cells, such as dorsal horn cells and/or brain cells, including and without limitation a brainstem, hindbrain, midbrain or forebrain excitatory or inhibitory cell population.

[0047] The functional domain of the modified LGICs described herein is a transmembrane ion channel that can be cationic-selective or anion-selective. Cationic-selective (e.g., Na^+—Ca^{2+}-, and K^+-selective) channels, such as that of the 5HT3 receptor (also, 5-HT3 receptor, or 5-hydroxytryptamine type 3 receptor), and the α7-nicotinic acetylcholine receptor, have an excitatory, depolarizing effect on a neuron, while anion-selective (e.g., Cl^--selective) channels, such as that of the glycine receptor (e.g., GIyR) or GABA A receptor, have an inhibitory, hyperpolarizing effect on the neuron. In one aspect, for pain management, the ion channel is hyperpolarizing, that is, when active, that is, when bound to the agonist ligand, the ion channel decreases a neuron's membrane potential to values more negative (e.g., −90 millivolts (mV)) than resting potential (e.g., −70 mV). In aspects, a hyperpolarizing ion channel is permeable to Cl^- or K^+ ions, and thereby decreases neuron membrane potential when active. GIyR is permeable to Cl^-, and therefore, when active, transfers Cl^- ions into the neuron. Suitable ion channels include transmembrane domains of members of the Cys-loop family of receptors. Non-limiting examples of suitable hyperpolarizing ion channels include: Glycine receptors; GABA receptors, such as $GABA_A$ and $GABA_C$ receptors; Glutamate-gated chloride receptors.

[0048] In another aspect, for pain management, the ion channel is depolarizing, and the cell is an inhibitory neuron. For example, as indicated in Table 1, NPPY, Gal, or PV promoters can be used to effectively target inhibitory neurons in the dorsal horn.

[0049] In one aspect, the protein is a mutated ligand-gated ion channel, such as GIyR, $GABA_A$, α7-nicotinic acetylcholine receptor, or 5HT3 receptor, having mutations in the protein causing enhanced selectivity of binding to exogenous ligands (ligands not naturally found in the cell in which the protein is expressed). In reference to binding of a ligand, by "selective to" it is meant either exclusive to or substantially or sufficiently exclusive binding to a ligand, such that the effect of the other ligand is insignificant or below a suitable or acceptable threshold level to achieve a desired purpose. For example, an LGIC having a mutated α7-nicotinic acetylcholine LBD can be selective to an exogenous small molecule compound, such as varenicline, such that the LGIC is activated by the exogenous small molecule compound, and not to any clinically-relevant or physiologically-relevant extent by acetylcholine. Selective binding to an exogenous ligand is, compared to binding to an endogenous ligand, at least about 4-fold to at least about 200-fold enhanced potency as an agonist to the LGIC, including increments there between (see, e.g., U.S. 2018/0009862). Optionally, though preferably in many instances, the LGIC exhibits reduced binding to endogenous ligands (native ligands), such as in the case of the α7-nicotinic acetylcholine ligand binding domain, reduced, negligible, or no binding to acetylcholine, but enhanced binding to exogenous ligands, such as, for example and without limitation, varenicline (e.g., CHANTIX©).

[0050] Methods of modification or mutation of ligand-gated ion channel proteins, including production of chimeric proteins, able to bind selectively to exogenous ligands, and examples of such proteins are broadly-known, and well within the skill of an ordinary artisan (see, e.g., U.S. Pat. No. 8,435,762; U.S. Patent Application Publication No. 2018/0009862; U.S. Pat. No. 8,957,036, incorporated herein by reference in its entirety; International Patent Publication No. 2017/049252, incorporated herein by reference for its description of additional modified LGICs; Weir et al., Using an engineered glutamate-gated chloride channel to silence sensory neurons and treat neuropathic pain at the source (2017) Brain 140; 2570-2585; Kynagh, T., et al., An Improved Ivermectin-activated Chloride Channel Receptor for Inhibiting Electrical Activity in Defined Neuronal Populations (2010) J. Biol. Chem. 285(20):14890-14897; and Sternson, S. M, et al. Chemogenetic Tools to Interrogate Brain Functions (2014) 37:387-407).

[0051] Chimeric ligand-gated ion channel proteins have ligand-binding domains and transmembrane ion channel domains from different proteins, either from the same or different species. In aspects, the protein is a chimeric protein comprising a LBD of a nicotinic acetylcholine receptor, such as a mutated ligand binding domain from the α7 nicotinic acetylcholine receptor. In one aspect, the chimeric protein is a chimeric protein described in one of U.S. Pat. No. 8,435,762, or U.S. Patent Application Publication No. 2018/0009862, or International Patent Publication No. 2017/049252, each of which is incorporated herein by reference in its entirety for its technical disclosure of suitable chimeric proteins (modified LGICs) e.g., comprising a mutated α7 nicotinic acetylcholine receptor binding domain (ligand binding domain, LBD) fused to an ion pore domain (IPD), e.g., from a 5HT3, a GIyR, or a $GABA_C$ receptor, as well as for disclosure of other modified LGICs. Non-limiting examples of LGICs include, without limitation, Cys-loop receptors, e.g., AChR such as a nAChR, e.g., a muscle-type nAChR or a neuronal-type nAChR, gamma-aminobutyric acid (GABA; such as $GABA_A$ and $GABA_{A-p}$ (also referred to as $GABA_C$) receptors, GIyR, GluCl receptors, and 5HT3 receptors), ionotropic glutamate receptors (iGluR; such as AMPA receptors, kainate receptors, NMDA receptors, and delta receptors), ATP-gated channels (e.g., P2X), and phosphatidylinositol 4,5-bisphosphate (PIP2)-gated channels, and the modified LGIC can comprise sequences of any appropriate combination of LBD and ion channel of the preceding, modified be selective for an exogenous ligand. LBD sequences and transmembrane ion channel sequences may be obtained from any species, such as human, mouse, rat, sheep, cow, pig, or simian species, so long as it is functional for the intended use, for example, in humans, when used to produce a modified LGIC. The LGIC may be homomeric, or multimeric, comprising one or more LGIC subunits that can be the same or different.

[0052] In some aspects, a modified LGIC subunit described herein can include a LBD from a α7 nAChR. Exemplary amino acid sequences for a7-nicotinic acetylcholine receptor LBDs are provided in FIG. **2** (obtained from U.S. Patent Application Publication No. 2018/0009862). In various aspects, an α7-nicotinic acetylcholine receptor LBD is a homolog, orthologue, or paralog of the human an α7-nicotinic acetylcholine receptor LBD set forth in SEQ ID

NO: 18, SEQ ID NO: 19, or SEQ ID NO: 20. In various aspects, an α7-nicotinic acetylcholine receptor LBD has at least 75 percent sequence identity (e.g., at least 80%, at least 82%, at least 85%, at least 88%, at least 90%, at least 93%, at least 95%, at least 97% or at least 99% sequence identity) to SEQ ID NO: 18, SEQ ID NO: 19, or SEQ ID NO: 20. Exemplary amino acid sequences for chimeric LGICs are provided in FIGS. **3**A-**3**E (obtained from U.S. Patent Application Publication No. 2018/0009862). In various aspects, a modified LGIC has a sequence set forth in SEQ ID NO: 21, SEQ ID NO: 22, SEQ ID NO: 23, or SEQ ID NO: 24. In aspects, a modified LGIC has an amino acid sequence having at least 75 percent sequence identity (e.g., at least 80%, at least 82%, at least 85%, at least 88%, at least 90%, at least 93%, at least 95%, at least 97% or at least 99% sequence identity) to SEQ ID NO: 21, SEQ ID NO: 22, SEQ ID NO: 23, or SEQ ID NO: 24.

[0053] For purposes of generating a genetic construct for expressing these, or any amino acids, the nucleotide sequence of the ORF used can have any suitable sequence that can be translated to the desired amino acid sequence. Due to codon degeneracy, the nucleotide sequence can vary greatly, but codon usage may be the same or different from the natural gene, and can be optimized for increased, or optimal, expression.

[0054] In calculating percent sequence identity, two sequences are aligned and the number of identical matches of amino acid residues between the two sequences is determined. The number of identical matches is divided by the length of the aligned region (i.e., the number of aligned amino acid residues) and multiplied by 100 to arrive at a percent sequence identity value. The length of the aligned region can be a portion of one or both sequences up to the full-length size of the shortest sequence. Alignment of two or more sequences to determine percent sequence identity can be performed using the computer program ClustalW2 (EMBL-EBI) and default parameters, which calculates the best match between a query and one or more subject sequences, and aligns them.

[0055] FIGS. **3**A-**3**E (excerpted from U.S. Patent Application Publication No. 2018/0009862) show exemplary amino acid sequences of chimeric LGICs. Mutation of amino acid residue 77 (e.g., W77F or W77Y) resulted in sensitivity to granisetron and tropisetron. Mutation of amino acid residue 79 (e.g., Q79G) was most effective for several agonists. Mutations of amino acid residue 131 (e.g., L131G, L131A, L131M, or L131N) altered sensitivity to varenicline, tropisetron, granisetron, and ACh. Potency was considerably enhanced when LBD mutations were combined with mutation at amino acid residue 298 in the GlyR or $GABA_C$ IPD. Potency was also enhanced when a7nAChR LBD mutations were combined with mutation at amino acid residue G175 and P216.

[0056] Specific, and non-limiting examples of modified LBDs of LGICs (relative to SEQ ID NOs: 18, 19, and 20) that change ligand binding specificity include, amino acid substitution at one or more of amino acid residues 77, 79, 115, 131, 139, 141, 175, 210, 216, 217, and 219, including, without limitation: W77F, W77Y, W77M, Q79A, Q79G, Q79C, Q79D, Q79E, Q79H, Q79L, Q79P, Q79R, Q79S, Q79T, Q79W, Y1 15F, Q1 39A, Q139C, Q139D, Q139F, Q139G, Q139H, Q1391, Q139K, Q139L, Q139M, Q139N, Q139R, Q139S, Q139V, Q139W, Q139Y, L141A, L141F, L141P, L141G, L141H, L1411, L141 M, L141 N, L141Q, L141S, L141 V, L141W, G175K, G175A, G175F, G175H, G175M, G175R, G175S, G175V, P2161, and Y217F. In one aspect, the modified LBDs has the following combinations of point mutations: L131G and Q139L; L131G, Q139L, and Y217F; Q79G and L131G; L131G and Y217F; Q79S and L131G; or Q79S, L131G, and Q139L.

[0057] Point mutations that reduce binding to acetylcholine include Y1 15F, Q79R, Q139G, Q139V, Q1 39W, Q139Y, L141A, L141 Q, L141S, can be combined with any of the selectivity-inducing mutations as described herein, such as Q79G and L141 F. These modifications can be combined with amino acid substitutions to the ion channel domain that can alter conductance (See, U.S. Pat. No. 8,435,762 and U.S. Patent Application Publication No. 2018/0009862).

[0058] Various synthetic ligands, and the modified LGICs they bind to and activate, e.g., LGICs including modified α7nAChR LBDs are provided in, see, U.S. Pat. No. 8,435,762 and U.S. Patent Application Publication No. 2018/0009862 A1, as well in the priority application to the present application, U.S. Provisional Patent Application No. 62/473,630 filed Mar. 20, 2017, which is incorporated herein by reference in its entirety.

[0059] The exogenous LGIC ligand can be a synthetic exogenous LGIC ligand selected from the group consisting of a quinuclidine, a tropane, a 9-azabicyclo[3.3.1]nonane, a 6,7,8,9-tetrahydro-6,10-methano-6H-pyrazino(2,3-h)benzazepine, and a 1,4-diazabicyclo[3.2.2]nonane. When the synthetic exogenous LGIC ligand is a tropane, the tropane can be tropisetron, pseudo-tropisetron, nortropisetron, compound 723, compound 725, compound 737, or compound 745. When the synthetic exogenous LGIC ligand is a quinuclidine, the quinuclidine can be PNU-282987, PHA-543613, compound 0456, compound 0434, compound 0436, compound 0354, compound 0353, compound 0295, compound 0296, compound 0536, compound 0676, or compound 702. When the synthetic exogenous LGIC ligand is a 6,7,8,9-tetrahydro-6,10-methano-6H-pyrazino(2,3-h)benzazepine, the ligand can be compound 765 or compound 770. When the synthetic exogenous LGIC ligand is a 1,4-diazabicyclo[3.2.2]nonane, the ligand can be compound 773 or compound 774 (U.S. Patent Application Publication No. 2018/0009862 A1).

[0060] Certain LGIC agonists associate increased potency with specific LBD substitutions in modified LGICs. FIG. **4**A (from U.S. Patent Application Publication No. 2018/0009862 A1) shows LGIC agonists that exhibit enhanced potency with substituted a7nAChR LBD having a Q79G amino acid substitution. Additional LGIC agonists are shown in FIG. **4**B (also excerpted from U.S. Patent Application Publication No. 2018/0009862 A1). For example, $\alpha7^{Q79G}$-$GlyR^{A298G}$ can be controlled by tropisetron, and $\alpha7^{L131G,Q139L,Y217F}$-GlyR can be controlled by varenicline. Further examples of modified LGICs include the ivermectin-responsive glutamate-gated chloride channels described in Weir et al., which were administered in AAV9 transducing particles intrathecally to mouse spinal cords (Weir et al., (2017) Brain 140; 2570-2585, see, also, Kynagh, T., et al., (2010) J. Biol. Chem. 285(20):14890-14897), and the ivermectin-responsive GIyR LGIC described in U.S. Pat. No. 8,957,036. Additional examples of the large number of known, specific modified LGICs and their specific agonists is beyond the scope of this disclosure, and is unnecessary.

[0061] According to one aspect of the invention, a method of modulating activity of excitable cells or secretory cells, such as nerve cells or neurons, e.g., to sensory neurons, e.g, depolarization or hyperpolarization of a neuron, in a patient is provided, comprising administering to an excitable cell or a secretory cell, such as a nerve cell or neuron of the patient a nucleic acid comprising a gene for expressing a modified LGIC that selectively binds, and is gated by an exogenous ligand to the cell, and where expression of the gene is under transcriptional control of a promoter specific to an excitable cell or a secretory cell, e.g., a sensory nerve cell or neuron, thereby expressing the modified LGIC in the cell, and administering the exogenous ligand to the patient, thereby activating the LGIC. The LGIC comprises an LBD and a transmembrane ion channel domain, for example and without limitation, according to any aspect described herein. Where hyperpolarization is desired, the modified LGIC comprises a transmembrane ion channel domain that is selective for Cl– or K+ ions, such as a GlyR or $GABA_A$ or $GABA_C$ ion channel domain. Where depolarization is desired, the modified LGIC comprises a transmembrane ion channel domain that is selective for Na^+ or Ca^{2+} ions. In aspects, the LBD is an α7-nicotinic acetylcholine receptor LBD according to any aspect provided herein.

[0062] According to another aspect of the invention, a method of treating a disease or disorder associated with the nervous system in a patient. In one aspect, the disease or disorder associated with the nervous system is pain, such as chronic pain. In another aspect, the disease or disorder associated with the nervous system is itch. The method comprises administering to an excitable cell or a secretory cell of the patient, such as a nerve cell or neuron, e.g., to CNS cells, such as spinal cord cells or brain cells, such as a dorsal horn cell or a supraspinal cell, a nucleic acid comprising a gene for expressing a modified LGIC that selectively binds, and is gated by an exogenous ligand to the cell, and where expression of the gene is under transcriptional control of a promoter specific to a sensory neuron, thereby expressing the modified LGIC in the sensory neuron, and administering the exogenous ligand to the patent, thereby activating the LGIC. The LGIC comprises an LBD and a hyperpolarizing transmembrane ion channel domain introduced into an excitatory cell, or a depolarizing, excitatory transmembrane ion channel domain that is administered to inhibitory neurons. For example and without limitation, inhibitory ion channel domains according to any aspect described herein, include a transmembrane ion channel domain that is selective for Cl^- or K^+ ions, such as a GlyR or $GABA_A$ or $GABA_C$ ion channel domain. For example and without limitation, excitatory ion channel domains according to any aspect described herein, include a transmembrane ion channel domain that is selective for Na^+ or Ca^{+2} ions, such as a 5HT3 ion channel domain. In aspects, the LBD is an α7-nicotinic acetylcholine receptor LBD according to any aspect provided herein. In aspects, the pain is localized chronic pain in a patient, such as from osteoarthritic conditions, surgical implants, wounds, scarring, fibrotic conditions, nerve damage, or disease, visceral pain, muscle or deep tissue damage, spinal cord injury, post herpetic neuralgia, metabolic disease such as diabetes, chemotherapeutic neuropathy, idiopathic peripheral neuropathy.

[0063] In methods of delivering nucleic acids encoding modified LGICs, according to any aspect described herein to a cell or to a patient, the nucleic acid may be delivered by any useful method, in any useful form, as is recognized by those of ordinary skill in the field of genetic therapies. The nucleic acid may be naked nucleic acid, such as a plasmid, deposited, for example and without limitation, by a colloidal drug delivery method, such as liposomes, e.g., cationic liposomes, or nanoparticles, or as part of a recombinant viral genome, as are broadly-known. In aspects, liposomes or nanoparticles comprising the nucleic acid are injected at a desired site, such as in or adjacent to specific neuronal tissue. In other aspects, a recombinant viral particle (transducing particle), is delivered, for example, injected, at a desired site, such as in or adjacent to, or otherwise targeting specific neuronal tissue. In one aspect, the nucleic acid comprising a gene for expressing the modified LGIC is an AAV (Adeno-Associated Virus) genome. In another aspect, the nucleic acid is injected into or adjacent to a tissue containing the target excitable or secretory cell, such as a CNS cell, e.g, a dorsal horn cell, a spinal cord cell, a brain cell, or a supraspinal cell. In another aspect, the nucleic acid is administered systemically, e.g., intravenously, and optionally in a delivery vehicle, such as an AAV particle that has a tropism to excitable or secretory cells, such as, for example and without limitation, AAV9, AAV-PHP.eB, AAV-PHP.S, or rAAV2-retro particles mentioned above, selective to brain, peripheral and/or spinal cord tissue. The nucleic acid may be injected once or more than once in order to establish sufficient expression of the modified LGIC in the target neuron cells. Suitable carriers or excipients for use in delivery of the nucleic acid, as are known in the related arts, may be included in the dosage form for delivery of the nucleic acid, such as in a liposomal or a recombinant viral transducing particle.

[0064] An "excipient" is an inactive substance used as a carrier for the active ingredients of a medication. Although "inactive," excipients may facilitate and aid in increasing the delivery, stability or bioavailability of an active ingredient in a drug product. Non-limiting examples of useful excipients include: antiadherents, binders, rheology modifiers, coatings, disintegrants, emulsifiers, oils, buffers, salts, acids, bases, fillers, diluents, solvents, flavors, colorants, glidants, lubricants, preservatives, antioxidants, sorbents, vitamins, sweeteners, etc., as are available in the pharmaceutical/compounding arts. For example, for delivery to a nerve cell by injection, a drug product might comprise the nucleic acid in the form of a viral particle, nanoparticle, or liposome, in a suitable solvent, such as saline or phosphate-buffered saline, and including a rheology modifier or thixotropic agent.

[0065] Suitable dosage forms for delivery of exogenous ligands as described herein, include, without limitation, oral, percutaneous, or inhaled dosage forms, the formulation of which is within the skill of an ordinary artisan (see, generally, Troy, DB, Editor, Remington: The Science and Practice of Pharmacy, 21st Ed., Lippincott Williams & Wilkins (2005), pp. 745-849, for descriptions of various compositions, solutions, and dosage forms useful for administration of the described compounds, as well as methods of making such compositions, solutions, and dosage forms). The exogenous ligand is delivered in an amount, and dosage regimen, effective to achieve a desired therapeutic end-point, such as lessening pain. Determination of safe and effective amounts of the exogenous ligand is routine, and within the skill of an ordinary artisan. Further, certain suitable exogenous ligands are approved for use for other indications, such as vareni-

cline, or tropisetron, and as such suitable safe dosage ranges are already established in humans.

Example 1—Calretinin^{+} and CCK^{+} Neurons in the Dorsal Horn are Required for Persistent Pain

[0066] Methods. Animals: All animals were kept on a standard 12:12 light/dark cycle in micro-isolator caging racks (Allentown Caging) with food and water provided ad libitum. Mouse strains obtained from Jackson Laboratories include C57Bl/6J (JAX #000664), Calr^{Cre} (JAX #010774) and CCK^{Cre} (JAX #012706). Adeno-associated viruses (AAV2/8) used in these experiments: hSyn-Flex-rev-PSAM^{L141F}-GIyR-IRES-eGFP (7^{12} vg/ml) and hSyn-Flex-rev-PSAM^{L}141F,Y115F-GyR-IRES-eGFP (1.7^{13} vg/ml) were custom made by UNC Vector core based on plasmid material developed by Scott Sternson and provided by Addgene. The hSyn-Flex-rev-PSAM^{L}141F-GlyR-IRES-eGFP (7^{12} vg/ml) was used in all experiments except FIG. **8** (*e,f*). For these experiments, hSyn-Flex-rev-PSAM^{L}141F, Y115F-GyR-IRES-eGFP (1.7^{13} vg/ml) was used. Methods including: intra-spinal virus injections, paw withdrawal threshold to von Frey filaments, to cotton swab, Hargreaves, pinprick and acute pain behaviors licking, guarding, flicking are all as previously described (Peirs, C. et al. Dorsal Horn Circuits for Persistent Mechanical Pain. Neuron 87, 797-812 (2015); Seal, R. P. et al. Injury-induced mechanical hypersensitivity requires C-low threshold mechanoreceptors. Nature 462, 651-655, (2009)); For paw withdrawal threshold to pressure: mice were lightly restrained by hand such that their rear legs were allowed to freely hang. Using a Pressure Application Measurement device (Ugo Basile) the hind paw was grasped between the experimenter's forefinger and thumb (with pressure transducer on the thumb), and force was slowly applied to the paw until the mouse struggled or flicked its limb (paw withdrawal threshold, PWT). The final force in grams was recorded. Each mouse was tested on the left and right paw for three trials with a ten-minute inter-trial interval between applications, and the three results averaged for each paw. Injury Models including incision, complete Freund's adjuvant, spared nerve injury tibial and sural models, carrageenan, methylglyoxal and multi-dose streptozotocin are as previously described (Peirs, C. et al. Dorsal Horn Circuits for Persistent Mechanical Pain. *Neuron* 87, 797-812 (2015); Seal, R. P. et al. Injury-induced mechanical hypersensitivity requires C-low threshold mechanoreceptors. Nature 462, 651-655, (2009); Decosterd, I. and Woolf, C. J. Spared nerve injury: an animal model of persistent peripheral neuropathic pain. Pain 87, 149-158 (2000); Bierhaus, A. et al. Methylglyoxal modification of Nav1.8 facilitates nociceptive neuron firing and causes hyperalgesia in diabetic neuropathy. Nat Med 18, 926-933 (2012); Cavanaugh, D. J. et al. Distinct subsets of unmyelinated primary sensory fibers mediate behavioral responses to noxious thermal and mechanical stimuli. Proc Natl Acad Sci U S A 106, 9075-9080, (2009)). Chemogenetic Activation of PSAM-GIyR Receptor: Behavior thresholds were performed as described above in AAV8-hSyn-DIO-PSAM-GIyR-IRES-GFP injected mice. PSEM^{89S} at 30 mg/kg was injected intraperitoneally 15 minutes prior to testing. Immunohistochemistry was performed as previously described (Peirs, C. et al. Dorsal Horn Circuits for Persistent Mechanical Pain. *Neuron* 87, 797-812 (2015); Seal, R. P. et al. Injury-induced mechanical hypersensitivity requires C-low threshold mechanoreceptors. Nature 462, 651-655 (2009)). α-bungarotoxin conjugated to Alexa-647 (1:1000; ThermoFisher B35450), α-bungarotoxin conjugated to Alexa-488 (1:1000; ThermoFisher B13422). Imaging: Spinal cord sections were imaged with a confocal laser-scanning microscope (Nikon A1R) and Nikon Elements software using 405-, 488-, 561- and 640 nm excitation laser light. In order to suppress emission crosstalk, the microscope was configured to perform all scanning in sequential mode. Z-series were scanned at 20× magnification with an oil immersion lens and a z-step of 5.0 μm. Quantification and Statistical Analysis: all data are reported as mean±SEM. For acute behaviors, a two-tailed Student's t-test was used. The effect of chemogenetic activation on persistent pain behavior was analyzed by one-way repeated measures ANOVA with Bonferroni's Post hoc test. Significance was considered $p<0.05$. (*$p<0.05$, **$p<0.01$, ***$p<0.001$.) All quantitative analysis, graphs and statistical tests were performed on GraphPad Prism 7.0 (GraphPad).

[0067] Results. To determine the role of calretinin and cholecystokinin (CCK) excitatory dorsal horn neurons in persistent pain and baseline somatosensory behavior, we used the designer ligand-gated anion channel, PSAM-GIyR (FIGS. **5**, **8**, and **10**), which allowed us to acutely and reversibly inhibit these specific populations of neurons. Somatosensory behavior was tested under chemogenetic control at baseline and after the induction of inflammatory and neuropathic pain models (FIGS. **8** and **10**). The inhibitory designer receptor, PSAM-GlyR[16], is engineered such that a mutated ligand-binding domain of the human α-7 nicotinic receptor is fused to the anion channel domain of the human glycine receptor (FIG. **5**(*a*), that is, FIG. **1**, panel (a)) (Magnus, C. J. et al. Chemical and genetic engineering of selective ion channel-ligand interactions. Science 333, 1292-1296, (2011)). This mutated receptor binding domain no longer recognizes physiological levels of acetylcholine, but instead binds the synthetic ligand PSEM^{89S} with high affinity. To selectively target the CCK and Calretinin neurons in the dorsal horn, a Cre-dependent adeno-associated virus (AAV) encoding PSAM-GIyR (AAV8-hSyn.FLEX.PSAM-GlyR.IRES.EGFP) was injected unilaterally into the dorsal horn of P21 CCK^{Cre} or Calretinin^{Cre} mice (FIG. **5**(*b*)). Four weeks later, receptor expression was examined by staining spinal cord slices with α-bungarotoxin conjugated to Alexa Fluor-647 (α-BTX-Alexa647), which specifically recognizes the ligand binding domain of α-7 nicotinic acetylcholine receptors, including the ligand binding domain of PSAM-GIyR (FIG. **5**(*b*)). Expression of PSAM-GIyR was largely limited to laminae III-IV (FIG. **5**(*b*)) and did not overlap with PKCγ (PKCγ staining not shown). Specificity of α-BTX-Alexa647 staining for the exogenously expressed PSAM-GIyR was demonstrated by the lack of staining observed in the contralateral dorsal horn (FIG. **6***e*).

[0068] In Vitro and In Vivo Controls for the Specific Actions of PSEM89S on PSAM-GIyR

[0069] Prior to assessing the role of the neurons in somatosensory behavior, the ability of PSAM-GIyR to inhibit excitatory interneurons in the dorsal horn was tested using electrophysiological recordings in spinal cord slices. AAV8-Flex-PSAM-GIyR was injected intraspinally into the dorsal horn of P16 Tlx3^{Cre} mice. In this mouse line, the recombinase is strictly expressed by excitatory neurons located throughout laminae 1-Ill. Three weeks later, neuronal excitability was measured using patch clamp electrophysiology in spinal cord slices in the presence and absence of PSEM^{89S}

(FIG. **6**(*a-d*)). To identify PSAM-GlyR^{+} neurons, we identified cells expressing green fluorescent protein (GFP), which is also encoded by the PSAM-GIyR viral construct (FIG. **6**(*a,b*)). Application of PSEM^{89S} (30 μM) to spinal cord slices significantly decreased the membrane potential (−7.3±3.4 mV, n=3 cells from 2 mice) and blocked action potentials generated by current injection in GFP+(FIG. **6**(*c,d*)), but not GFP^{-} neurons (data not shown). We also tested the effect of the ligand PSEM^{89S} on pain behavior in mice lacking the receptor (FIG. **6**(*f,h*)). PSEM^{89S} injection had no effect on mechanical allodynia or heat hypersensitivity in the carrageenan, complete Freund's adjuvant or SNI pain model, suggesting the drug alone has no unintended behavioral effects.

[0070] CCK+ Dorsal Horn Neurons are Required for Conveying Persistent Pain, but not Baseline Somatosensory Behavior.

[0071] Three weeks after unilateral injection of AAV8-hSyn-Flex-PSAM-GlyR in the dorsal horn of CCK^{Cre} mice, we tested the effect of inhibiting the dorsal horn CCK neurons on baseline somatosensory behavior using von Frey threshold, cotton swab assay, pinprick assay, pressure test and Hargreaves assay (FIG. **7**). We also tested motor behavior using rotarod (FIG. **7**). All behaviors were normal and similar to the contralateral hindpaw (FIG. **7**). We next tested the effect of inhibiting the dorsal horn CCK neurons on persistent pain in the carrageenan model of inflammatory pain. PSEM^{89S}injection significantly reversed punctate and dynamic mechanical allodynia as well as heat hypersensitivity (FIG. **8**(*a*)). Similarly, using the more chronic inflammatory model, complete Freund's adjuvant (CFA), PSEM^{89S} injection again significantly reversed both punctate and dynamic allodynia (FIG. **8**(*b*)) as well as heat hypersensitivity. Injection of PSEM^{89S} (30 mg/kg, i.p.) into mice lacking the receptor showed no effect on CFA-induced persistent pain (FIG. **6**(*g*)). In the sural-SNI model of neuropathic pain, PSEM^{89S}injection significantly reversed both punctate and dynamic allodynia (FIG. **8**(*c*)). Similarly, in the tibial-SNI model of neuropathic pain, PSEM^{89S} injection markedly reversed punctate allodynia (FIG. **8**(*d*)).

[0072] We have shown here that the CCK population is essential for the transmission of carrageenan and CFA-induced heat hypersensitivity, but is dispensable for normal heat sensibility. Because heat hypersensitivity also develops in diabetic neuropathic pain models, we tested whether the CCK neurons are also required in this type of pain. Indeed, acute inhibition of the CCK population markedly reversed the heat hypersensitivity induced by methylglyoxal (MG) treatment as well as the heat hypersensitivity induced by the multi-dose STZ model of diabetic neuropathy (FIG. **8**(*e,f*)). These data reveal for the first time an essential role for CCK excitatory dorsal horn neurons in conveying punctate and dynamic mechanical allodynia induced by inflammatory and neuropathic pain models. This population also has an important role in conveying heat hypersensitivity induced by inflammatory and polyneuropathic pain models.

[0073] Calretinin neurons in lamina II of the dorsal horn are required for conveying mechanical allodynia induced by inflammatory injuries. Here we show that calretinin expressing neurons in inner lamina II of the dorsal horn are required for conveying mechanical allodynia induced by inflammatory injury. We unilaterally injected Cre-dependent AAV8 PSAM-GIyR into the dorsal horn of Calr^{Cre} mice at P21 (FIGS. **5** and **10**). Similar to what was observed when expressing the excitatory designer receptor in this population, neurons expressing PSAM-GIyR were restricted to inner lamina II (FIG. **5**(*b*)) and co-localized with calretinin, but not PKCγ (not shown). Baseline measures of mechanical and heat sensitivity showed no change after injection of PSEM^{89}s at either the ipsilateral or contralateral hindpaw. Motor behavior was also normal after PSEM^{89S} injection (FIGS. **9**(*a,b*)). We next tested whether the calretinin neurons are required for conveying mechanical allodynia or heat hypersensitivity in the carrageenan model of inflammatory pain. Injection of PSEM^{89S} 24 hours after carrageenan injection significantly reversed punctate mechanical allodynia (FIG. **10**(*a*)). We also tested whether the neurons are required for mechanical allodynia in the CFA model. Measured 5 days after injection of the inflammatory agent, injection of PSEM^{89S}resulted in a complete reversal of punctate mechanical allodynia at the ipsilateral hindpaw (FIG. **10**(*b*)). To determine how generalizable the requirement for calretinin neurons is in conveying mechanical allodynia induced by inflammatory pain models, we tested the incision model of post-operative pain (FIG. **10**(*c*)). Inhibition of the calretinin neurons also significantly reversed mechanical allodynia in this model. The data collected from a number of inflammatory pain models show that dorsal horn neurons expressing calretinin are required for conveying mechanical allodynia induced by inflammatory injuries.

[0074] Discussion Work shown here demonstrates that targeting of a designer ligand-gated anion channel (in this case PSAM-GIyR) to neurons that express CCK^{+} or calretinin^{+} in the dorsal horn markedly attenuates mechanical allodynia and/or heat hypersensitivity caused by models of inflammatory and neuropathic pain when the receptor is activated by the designer ligand (in this case PSEM^{89S}). The data also demonstrate that PSEM^{89S} and PSAM-GIyR mediated inhibition of the neurons does not affect baseline mechanical or thermal sensitivity. Finally, the data demonstrate that the ligand alone (i.e. in the absence of the receptor) does not affect mechanical or thermal sensitivity either before or after inflammatory or neuropathic injury. Therefore, the data suggest that inhibition of these neurons is sufficient to block persistent mechanical and heat pain.

Example 2—Mechanical Allodynia Induced by Inflammatory and Neuropathic Pain Models is Attenuated by Injection of Varenicline in Mice with mCCK-PSAM4 Delivered to the Dorsal Horn

[0075] As further proof of concept, a varenicline-responsive PSAM-GIyR receptor mutant that was directly under the transcriptional control of a CCK promoter and delivered to the dorsal horn was shown to markedly attenuate mechanical allodynia in persistent pain models. The mouse cholecystokinin (CCK) promoter with an added chimeric intron to drive expression of $\alpha7^{L131G,\ Q139L,\ Y217F}$ GIyR (PSAM4) was packaged into AAV2/8 and injected into the dorsal horn of 3-week-old wildtype C57Bl/6 male and female mice. Injection of AAV into the dorsal horn was performed as described previously (Peirs, C. et al. Dorsal Horn Circuits for Persistent Mechanical Pain. Neuron 87, 797-812 (2015)). See FIG. **11** for a schematic of the plasmid used to produce these rAAV particles. Briefly, a 2.5 kb fragment of the mouse CCK promoter was subcloned upstream of the PSAM4 gene with the chimeric intron (135

bp) located in between. This construct expressed in AAV8 is sufficient to drive expression in neurons in the deep dorsal horn.

[0076] Expression of the PSAM4 in the dorsal horn was examined by immunostaining for α-BTX-Alexa647 (FIG. **12**). α-BTX-Alexa647 staining was observed in cells in the deep dorsal horn below the PKCγ layer (PKCγ staining not shown). This expression pattern is similar to the pattern for CCK mRNA in the dorsal horn detected by in situ hybridization (Allen Spinal Cord Atlas) and by injecting AAV8 hSyn-Flex-PSAM-GIyR virus in the dorsal horn of CCK^{Cre} mice (see FIG. **5**(*a*)).

[0077] Varenicline has no effect on mechanical or heat sensitivity at baseline or after CFA or sural-SNI in the absence of PSAM4. Mechanical and heat hypersensitivity was tested in adult wildtype male and female C57BI/6 mice (not injected with mCCK-PSAM4 virus) before and after intraperitoneal injection of (i.p) varenicline (0.1 milligram per kilogram (mpk) (FIG. **13**). We also tested these parameters before and 2-5 days after induction of the complete Freund's adjuvant (CFA)-model of inflammatory pain and 7 days after induction of the sural version of the spared nerve injury (SNI) model of neuropathic pain (FIG. **13**). Sensitivity to mechanical stimuli was tested by measuring the paw withdrawal threshold to von Frey filaments (PWT) and the paw withdrawal response to a cotton swab (percentage of response) as described previously (Peirs, C. et al. Dorsal Horn Circuits for Persistent Mechanical Pain. Neuron 87, 797-812 (2015)). Heat sensitivity was tested by measuring the withdrawal latency to a radiant heat source using the Hargreaves apparatus (PWL) as described previously (Peirs, C. et al. Dorsal Horn Circuits for Persistent Mechanical Pain. Neuron 87, 797-812 (2015)). As shown in FIG. **13**, injection of varenicline (0.1 mpk, i.p) had no effect on baseline PWT, response frequency or PWL in uninjured mice (measured 30-60 minutes after injection). Injection of varenicline also had no effect on mechanical or heat hypersensitivity 3 and 2 days, respectively, after induction of CFA or 7 days after induction of sural-SNI models. PSAM4 ligands have no effect on baseline mechanical or heat sensitivity, but reverse mechanical allodynia induced by CFA and SNI in mice with targeted expression of PSAM4 in CCK+ neurons of the dorsal horn.

[0078] Mice were injected unilaterally in the dorsal horn with AAV8 mCCK-PSAM4 virus and tested two weeks later. As shown in FIG. **14**, varenicline (0.3 mpk, i.p.) did not alter baseline PWTs, response frequencies or PWLs. Thus, inhibition of the dorsal horn CCK+ neurons does not alter mechanical or heat sensitivity. The ipsilateral plantar hindpaw of the mice was injected with CFA and PWTs and response frequencies tested 3 days later in the absence and presence of varenicline (0.3 mpk, i.p.). As shown in FIG. **15**, varenicline (0.3 mpk, i.p.) markedly reversed both PWT and response frequency after CFA. As shown in FIG. **16**, varenicline (0.3 mpk, i.p.) markedly reversed the PWT when measured 7 days following sural spared nerve injury. These results are similar to what we observed with $PSEM^{89S}$ and PSAM-GlyR in FIGS. **7** and **8**.

[0079] The following numbered clauses provide illustrative examples of aspects of the invention:

[0080] 1. A nucleic acid comprising a gene for expressing a modified ligand-gated ion channel, comprising an open reading frame encoding a modified ligand-gated ion channel under transcriptional control of transcriptional control elements governing cell-specific expression in CNS neurons, such as dorsal horn neurons, spinal cord cells, or brain cells, or in inhibitory neurons or nerve cells, such as a CCK promoter, a Tac1 promoter, an NTS promoter, an NMU promoter, a Calb1 promoter, an SST promoter, a GRPR promoter, a parvalbumin promoter, a Gal promoter, an NPY promoter, a PKCγ promoter or Calb2 promoter, wherein the modified ligand-gated ion channel comprises a modified ligand binding domain activatable by an exogenous ligand, and optionally selective to the exogenous ligand, and an ion pore domain.

[0081] 2. The nucleic acid of clause 1, wherein transcription of the modified ligand-gated ion channel is controlled at least in part by a CCK promoter, an SST promoter, a GRPR promoter, a Tac1 promoter, an NTS promoter, an NMU promoter, a Calb1 promoter, a parvalbumin promoter, a Gal promoter, an NPY promoter, a Calb2 promoter or a PKCγ promoter.

[0082] 3. The nucleic acid of clause 1, wherein transcription of the modified ligand-gated ion channel is controlled at least in part by a CCK promoter, a Calb2 promoter, or a PKCγ promoter.

[0083] 4. The nucleic acid of clause 1, wherein transcription of the modified ligand-gated ion channel is controlled at least in part by a CCK promoter.

[0084] 5. The nucleic acid of any one of clauses 1-3, wherein the transcription control element comprises a human promoter sequence.

[0085] 6. The nucleic acid of clause 5, wherein the transcription control element is a promoter having at least 75 percent sequence identity to a sequence set forth in SEQ ID NOs: 1-17.

[0086] 7. The nucleic acid of any one of clauses 1-6, wherein the modified ligand binding domain is a modified α7 nicotinic acetylcholine ligand binding domain. 8. The nucleic acid of clause 7, wherein the modified α7 nicotinic acetylcholine ligand binding domain comprises a sequence having at least 75 percent sequence identity to a sequence set forth in SEQ ID NO: 18, SEQ ID NO: 19, or SEQ ID NO: 20.

[0087] 9. The nucleic acid of clause 7, wherein the modified α7 nicotinic acetylcholine ligand binding domain comprises an amino acid substitution at one or more of amino acid residues 77, 79, 115, 131, 139, 141, 175, 210, 216, 217, and 219.

[0088] 10. The nucleic acid of clause 7, wherein the modified α7 nicotinic acetylcholine ligand binding domain comprises an amino acid substitution at one or more of amino acid residues 77, 79, 115, 139, and 141, such as Q79A, Q79G, L141A, L141 F, L141 P, W77F, W77Y, and W77M. 11. The nucleic acid of clause 7, wherein the modified α7 nicotinic acetylcholine ligand binding domain comprises:

[0089] a L131G amino acid substitution, a Q139L amino acid substitution, and a Y217F amino acid substitution;

[0090] a W77F amino acid substitution, a Q79G amino acid substitution, and a G175K amino acid substitution;

[0091] a Q79G amino acid substitution, a Y1.15F amino acid substitution, and a G175K amino acid substitution;

[0092] a Y115F amino acid substitution and a G175K amino acid substitution;

[0093] a Q79G amino acid substitution and a P2161 amino acid substitution; or

[0094] a R27D amino acid substitution and/or a E41R amino acid substitution.

[0095] 12. The nucleic acid of clause 7, wherein the modified α7 nicotinic acetylcholine ligand binding domain comprises a L131 G amino acid substitution, a Q139L amino acid substitution, and a Y217F amino acid substitution.

[0096] 13. The nucleic acid of clause 7, wherein the modified α7 nicotinic acetylcholine ligand binding domain has reduced binding with endogenous acetylcholine (ACh) as compared to unmodified α7-nAChR LBD.

[0097] 14. The nucleic acid of clause one of clauses 1-13, wherein the ion pore domain is anion-selective, or cation-selective, and optionally is an ion pore domain of an ionotropic nicotinic acetylcholine receptor, an ionotropic serotonin receptor, an ionotropic glycine receptor, or an ionotropic GABA receptor.

[0098] 15. The nucleic acid of any one of clauses 1-13, wherein the ion pore domain is an ion pore domain from a serotonin 3 receptor (5HT3) ion pore domain, a glycine receptor (GIyR) ion pore domain, a gamma-aminobutyric acid (GABA) receptor ion pore domain, or an α7 nicotinic acetylcholine receptor ion pore domain.

[0099] 16. The nucleic acid of clause 15, wherein the ion pore domain is a GIyR ion pore domain comprising an amino acid substitution at residue 298.

[0100] 17. The nucleic acid of clause 16, wherein the GIyR ion pore domain comprising an A298G amino acid substitution.

[0101] 18. The nucleic acid of clause 1, wherein the exogenous ligand is selected from the group consisting of a quinuclidine, a tropane, a 9-azabicyclo[3.3.1]nonane, a 6,7,8,9-tetrahydro-6,10-methano-6H-pyrazino(2,3-h)benzazepine, and a 1,4-diazabicyclo[3.2.2]nonane.

[0102] 19. The nucleic acid of any one of clauses 1-18, comprising a sequence of a packageable viral genome comprising the gene for expressing a modified ligand-gated ion channel.

[0103] 20. The nucleic acid of clause 19, comprising Adeno-associated virus ITR sequences flanking the gene for expressing a modified ligand-gated ion channel, producing a sequence of a packageable recombinant AAV genome or a self-complementary AAV genome comprising the gene for expressing a modified ligand-gated ion channel.

[0104] 21. A method of modulating (increasing or decreasing) the membrane potential of an excitable cell or a secretory cell, comprising expressing in the cell a genetic construct comprising a gene for expressing a modified ligand-gated ion channel, comprising an open reading frame encoding a modified ligand-gated ion channel under transcriptional control of transcriptional control elements governing cell-specific expression in CNS neurons, such as dorsal horn neurons, spinal cord cells, or brain cells, or in inhibitory neurons or nerve cells, such as a CCK promoter, a Tac1 promoter, an NTS promoter, an NMU promoter, a Calb1 promoter, an SST promoter, a GRPR promoter, a parvalbumin promoter, a Gal promoter, an NPY promoter, a PKCγ promoter, or Calb2 promoter and a modified ligand-gated ion channel comprising a modified ligand binding domain activatable by an exogenous ligand, and optionally selective to the exogenous ligand, and an ion pore domain, and contacting the cell with an amount of the exogenous ligand effective to activate the modified ligand gated ion channel thereby modulating the membrane potential of the cell.

[0105] 22. The method of clause 21, wherein transcription of the modified ligand-gated ion channel is controlled at least in part by a CCK promoter, an SST promoter, a GRPR promoter, a Tac1 promoter, an NTS promoter, an NMU promoter, a Calb1 promoter, a parvalbumin promoter, a Gal promoter, an NPY promoter, Calb2 promoter or a PKCγ promoter.

[0106] 23. The method of clause 21, wherein transcription of the modified ligand-gated ion channel is controlled at least in part by a CCK promoter, a Calb2 promoter, or a PKCγ promoter.

[0107] 24. The method of clause 21, wherein transcription of the modified ligand-gated ion channel is controlled at least in part by a CCK promoter.

[0108] 25. The method of any one of clauses 21-24, wherein the transcription control element comprises a human promoter sequence.

[0109] 26. The method of clause 25, wherein the transcription control element is a promoter having at least 75 percent sequence identity to a sequence set forth in SEQ ID NOs: 1-17.

[0110] 27. The method of any one of clauses 21-26, wherein the modified ligand binding domain is a modified α7 nicotinic acetylcholine ligand binding domain.

[0111] 28. The method of clause 27, wherein the modified α7 nicotinic acetylcholine ligand binding domain comprises a sequence having at least 75 percent sequence identity to a sequence set forth in SEQ ID NO: 18, SEQ ID NO: 19, or SEQ ID NO: 20.

[0112] 29. The method of clause 27, wherein the modified α7 nicotinic acetylcholine ligand binding domain comprises an amino acid substitution at one or more of amino acid residues 77, 79, 115, 131, 139, 141, 175, 210, 216, 217, and 219.

[0113] 30. The method of clause 27, wherein the modified α7 nicotinic acetylcholine ligand binding domain comprises an amino acid substitution at one or more of amino acid residues 77, 79, 115, 139, and 141, such as Q79A, Q79G, L141A, L141 F, L141 P, W77F, W77Y, and W77M.

[0114] 31. The method of clause 27, wherein the modified α7 nicotinic acetylcholine ligand binding domain comprises:

[0115] a L131G amino acid substitution, a Q139L amino acid substitution, and a Y217F amino acid substitution;

[0116] a W77F amino acid substitution, a Q79G amino acid substitution, and a G175K amino acid substitution;

[0117] a Q79G amino acid substitution, a Y1.15F amino acid substitution, and a G1.75K amino acid substitution;

[0118] a Y115F amino acid substitution and a G175K amino acid substitution;

[0119] a Q79G amino acid substitution and a P2161 amino acid substitution; or

[0120] a R27D amino acid substitution and/or a E41R amino acid substitution.

[0121] 32. The method of clause 27, wherein the modified α7 nicotinic acetylcholine ligand binding domain comprises a L131 G amino acid substitution, a Q139L amino acid substitution, and a Y217F amino acid substitution, and, optionally, the exogenous ligand is varenicline.

[0122] 33. The method of clause 27, wherein the modified α7 nicotinic acetylcholine ligand binding domain has reduced binding with endogenous acetylcholine (ACh) as compared to unmodified α7-nAChR LBD.

[0123] 34. The method of clause one of clauses 21-33, wherein the ion pore domain is an ion pore domain of an ionotropic nicotinic acetylcholine receptor, an ionotropic serotonin receptor, an ionotropic glycine receptor, or an ionotropic GABA receptor.

[0124] 35. The method of any one of clauses 21-33, wherein the ion pore domain is anion-selective, or cation-selective, and optionally is an ion pore domain from a serotonin 3 receptor (5HT3) ion pore domain, a glycine receptor (GlyR) ion pore domain, a gamma-aminobutyric acid (GABA) receptor ion pore domain, or an α7 nicotinic acetylcholine receptor ion pore domain.

[0125] 36. The method of clause 35, wherein the ion pore domain is a GIyR ion pore domain comprising an amino acid substitution at residue 298.

[0126] 37. The method of clause 36, wherein the GIyR ion pore domain comprising an A298G amino acid substitution.

[0127] 38. The method of clause 37, wherein the exogenous ligand-gated ion channel ligand is selected from the group consisting of a quinuclidine, a tropane, a 9-azabicyclo[3.3.1]nonane, a 6,7,8,9-tetrahydro-6,10-methano-6H-pyrazino(2,3-h)benzazepine, and a 1,4-diazabicyclo[3.2.2]nonane.

[0128] 39. The method of any one of clauses 21-38, comprising a sequence of a packageable viral genome comprising the gene for expressing a modified ligand-gated ion channel.

[0129] 40. A method of treating a disease or disorder associated with the nervous system in a patient comprising: delivering a nucleic acid according to any one of clauses 1-20 to the patient, and administering the exogenous ligand to the patient in an amount effective to activate the modified ligand gated ion channel in a patient thereby treating the disease or disorder associated with the nervous system in the patient.

[0130] 41. The method of clause 40, wherein the disease or disorder associated with the nervous system is itch.

[0131] 42. The method of clause 40, wherein the disease or disorder associated with the nervous system is chronic pain, and transcription of the modified ligand-gated ion channel is controlled at least in part by a CCK promoter, an SST promoter, a GRPR promoter, a Tac1 promoter, an NTS promoter, an NMU promoter, a Calb1 promoter, a parvalbumin promoter, a Gal promoter, an NPY promoter, a Calb2 promoter or a PKCγ promoter.

[0132] 43. The method of clause 25, wherein transcription of the modified ligand-gated ion channel is controlled at least in part by a CCK promoter, a calb2 promoter, or a PKCγ promoter.

[0133] 44. The method of any one of clauses 40-43, wherein the nucleic acid comprising the gene for expressing a modified ligand-gated ion channel is delivered to the patient as a recombinant AAV transducing particle.

[0134] 45. The method of any one of clauses 40-44, wherein the exogenous ligand is selected from the group consisting of a quinuclidine, a tropane, a 9-azabicyclo[3.3.1]nonane, a 6,7,8,9-tetrahydro-6,10-methano-6H-pyrazino(2,3-h)benzazepine, and a 1,4-diazabicyclo[3.2.2]nonane.

[0135] While the present invention is described with reference to several distinct aspects or embodiments, those skilled in the art may make modifications and alterations without departing from the scope and spirit. Accordingly, the above detailed description is intended to be illustrative rather than restrictive.

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FEATURE                Location/Qualifiers
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                       organism = Mus musculus
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                       organism = Mus musculus
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                       organism = Homo sapiens
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RFDATFHTNV LVNSSGHCQY LPPGIFKSSC YIDVRWFPFD VQHCKLKFGS WSYGGWSLDL  180
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                       mol_type = protein
                       organism = Homo sapiens
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SEQ ID NO: 20          moltype = AA  length = 233
FEATURE                Location/Qualifiers
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                       mol_type = protein
                       organism = Homo sapiens
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QIMDVDEKNQ VLTTNIWLQM SWTDHYLQWN VSEYPGVKTV RFPDGQIWKP DILLYNSADE  120
RFDATFHTNV LVNSSGHCQY LPPGIFKSSC YIDVRWFPFD VQHCKLKFGS WSYGGWSLDL  180
QMQEADISGY IPNGEWDLVG IPGKRSERFY ECCKEPYPDV TFTVTMRRRT LYY         233

SEQ ID NO: 21          moltype = AA  length = 471
FEATURE                Location/Qualifiers
REGION                 1..471
                       note = alpha7-5HT3 chimeric receptor
source                 1..471
                       mol_type = protein
                       organism = synthetic construct
SEQUENCE: 21
MRCSPGGVWL ALAASLLHVS LQGEFQRKLY KELVKNYNPL ERPVANDSQP LTVYFSLSLL  60
QIMDVDEKNQ VLTTNIWLQM SWTDHYLQWN VSEYPGVKTV RFPDGQIWKP DILLYNSADE  120
RFDATFHTNV LVNSSGHCQY LPPGIFKSSC YIDVRWFPFD VQHCKLKFGS WSYGGWSLDL  180
QMQEADISGY IPNGEWDLVG IPGKRSERFY ECCKEPYPDV TFTVIIRRRP LFYAVSLLLP  240
SIFLMVVDIV GFCLPPDSGE RVSFKITLLL GYSVFLIIVS DTLPATIGTP LIGVYFVVCM  300
ALLVISLAET IFIVRLVHKQ DLQRPVPDWL RHLVLDRIAW ILCLGEQPMA HRPPATFQAN  360
KTDDCSGSDL LPAMGNHCSH VGGPQDLEKT PRGRGSPLPP PREASLAVRG LLQELSSIRH  420
FLEKRDEMRE VARDWLRVGY VLDRLLFRIY LLAVLAYSIT LVTLWSIWHY S           471

SEQ ID NO: 22          moltype = AA  length = 430
FEATURE                Location/Qualifiers
REGION                 1..430
                       note = Alpha7-GlyR chimeric receptor
source                 1..430
                       mol_type = protein
                       organism = synthetic construct
SEQUENCE: 22
MRCSPGGVWL ALAASLLHVS LQGEFQRKLY KELVKNYNPL ERPVANDSQP LTVYFSLSLL  60
QIMDVDEKNQ VLTTNIWLQM SWTDHYLQWN VSEYPGVKTR FPDGQIWKPD ILLYNSADER  120
FDATFHTNVL VNSSGHCQYL PPGIFKSSCY IDVRWFPFDV QHCKLKFGSW SYGGWSLDLQ  180
MQEADISGYI PNGEWDLVGI PGKRSERFYE CCKEPYPDVT FTVTMRRRMG YYLIQMYIPS  240
LLIVILSWIS FWINMDAAPA RVGLGITTVL TMTTQSSGSR ASLPKVSYVK AIDIWMAVCL  300
LFVFSALLEY AAVNFVSRQH KELLRFRRKR RHHKEDEAGE GRFNFSAYGM GPACLQAKDG  360
ISVKGANNSN TTNPPPAPSK SPEEMRKLFI QRAKKIDKIS RIGFPMAFLI FNMFYWIIYK  420
IVRREDVHNQ                                                         430

SEQ ID NO: 23          moltype = AA  length = 466
FEATURE                Location/Qualifiers
REGION                 1..466
                       note = alpha7-5HT3 chimeric receptor
source                 1..466
                       mol_type = protein
                       organism = synthetic construct
SEQUENCE: 23
MRCSPGGVWL ALAASLLHVS LQGEFQRKLY KELVKNYNPL ERPVANDSQP LTVYFSLSLL  60
QIMDVDEKNQ VLTTNIWLQM SWTDHYLQWN VSEYPGVKTV RFPDGQIWKP DILLYNSADE  120
RFDATFHTNV LVNSSGHCQY LPPGIFKSSC YIDVRWFPFD VQHCKLKFGS WSYGGWSLDL  180
QMQEADISGY IPNGEWDLVG IPGKRSERFY ECCKEPYPDV TFTVIIRRRP LFYVVSLLLP  240
SIFLMVMDIV GFYLPPNSGE RVSFKITLLL GYSVFLIIVS DTLPATAIGT PLIGVYFVVC  300
MALLVISLAE TIFIVRLVHK QDLQQPVPAW LRHLVLERIA WLLCLREQST SQRPPATSQA  360
TKTDDCSAMG NHCSHMGGPQ DFEKSPRDRC SPPPPPREAS LAVCGLLQEL SSIRQFLEKR  420
DEIREVARDW LRVGSVLDKL LFHIYLLAVL AYSITLVMLW SIWQYA                 466

SEQ ID NO: 24          moltype = AA  length = 428
FEATURE                Location/Qualifiers
REGION                 1..428
                       note = alpha7-GABAc chimeric receptor
source                 1..428
                       mol_type = protein
                       organism = synthetic construct
SEQUENCE: 24
MRCSPGGVWL ALAASLLHVS LQGEFQRKLY KELVKNYNPL ERPVANDSQP LTVYFSLSLL  60
QIMDVDEKNQ VLTTNIWLQM SWTDHYLQWN VSEYPGVKTV RFPDGQIWKP DILLYNSADE  120
RFDATFHTNV LVNSSGHCQY LPPGIFKSSC YIDVRWFPFD VQHCKLKFGS WSYGGWSLDL  180
QMQEADISGY IPNGEWDLVG IPGKRSERFY ECCKEPYPDV TFTVTMRRRT LYYLLQTYFP  240
ATLMVMLSWV SFWIDRRAVP ARVPLGITTV LTMSTIITGV NASMPRVSYI KAVDIYLWVS  300
FVFVFLSVLE YAAVNYLTTV QERKEQKLRE KLPCTSGLPP PRTAMLDGNY SDGEVNDLDN  360
YMPENGEKPD RMMVQLTLAS ERSSPQRKSQ RSSYVSMRID THAIDKYSRI IFPAAYILFN  420
LIYWSIFS                                                           428

SEQ ID NO: 25          moltype = AA  length = 502
FEATURE                Location/Qualifiers
source                 1..502
                       mol_type = protein
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organism = Rattus norvegicus

SEQUENCE: 25

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MGGGRGGIWL ALAAALLHVS LQGEFQRRLY KELVKNYNPL ERPVANDSQP LTVYFSLSLL  60
QIMDVDEKNQ VLTTNIWLQM SWTDHYLQWN MSEYPGVKNV RFPDGQIWKP DILLYNSADE  120
RFDATFHTNV LVNASGHCQY LPPGIFKSSC YIDVRWFPFD VQQCKLKFGS WSYGGWSLDL  180
QMQEADISSY IPNGEWDLMG IPGKRNEKFY ECCKEPYPDV TYTVTMRRRT LYYGLNLLIP  240
CVLISALALL VFLLPADSGE KISLGITVLL SLTVFMLLVA EIMPATSDSV PLIAQYFAST  300
MIIVGLSVVV TVIVLRYHHH DPDGGKMPKW TRIILLNWCA WFLRMKRPGE DKVRPACQHK  360
PRRCSLASVE LSAGAGPPTS NGNLLYIGFR GLEGMHCAPT PDSGVVCGRL ACSPTHDEHL  420
MHGAHPSDGD PDLAKILEEV RYIANRNRCQ DESEVICSEW KFAACVVDPL CLMAFSVFTI  480
ICTIGILMSA PNFVEAVSKD FA                                           502
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What is claimed is:

1. A nucleic acid comprising a gene for expressing a modified ligand-gated ion channel, comprising an open reading frame encoding a modified ligand-gated ion channel under transcriptional control of a regulatory element governing cell-specific expression in dorsal horn neurons, wherein the modified ligand-gated ion channel comprises a modified ligand binding domain activatable by an exogenous ligand, and an ion pore domain,

wherein the modified ligand-gated ion channel is a modified α7 nicotinic acetylcholine ligand binding domain, and

wherein the ion pore domain is an ion pore domain of an ionotropic nicotinic acetylcholine receptor, an ionotropic serotonin receptor, an ionotropic glycine receptor, an ionotropic GABA receptor, a serotonin 3 receptor (5HT3) ion pore domain, a glycine receptor (GlyR) ion pore domain, a gamma-aminobutyric acid (GABA) receptor ion pore domain, or an α7 nicotinic acetylcholine receptor.

2. The nucleic acid of claim **1**, wherein the regulatory element is a promoter, a transcription response element, a repressor, and/or an enhancer.

3. The nucleic acid of claim **1**, wherein the modified ligand binding domain is a modified α7 nicotinic acetylcholine ligand binding domain.

4. The nucleic acid of claim **3**, wherein the modified α7 nicotinic acetylcholine ligand binding domain comprises a sequence having at least 75 percent sequence identity to a sequence set forth in SEQ ID NO: 18, SEQ ID NO: 19, or SEQ ID NO: 20.

5. The nucleic acid of claim **3**, wherein the modified α7 nicotinic acetylcholine ligand binding domain comprises an amino acid substitution at one or more of amino acid residues 77, 79, 115, 131, 139, 141, 175, 210, 216, 217, or 219 of SEQ ID NO: 18, SEQ ID NO: 19, or SEQ ID NO: 20, such as Q79A, Q79G, L141A, L141 F, L141 P, W77F, W77Y, or W77M.

6. The nucleic acid of claim **3**, wherein the modified α7 nicotinic acetylcholine ligand binding domain comprises:

a. a L131G amino acid substitution, a Q139L amino acid substitution, and a Y217F amino acid substitution;

b. a W77F amino acid substitution, a Q79G amino acid substitution, and a G175K amino acid substitution;

c. a Q79G amino acid substitution, a Y115F amino acid substitution, and a G175K amino acid substitution;

d. a Y115F amino acid substitution and a G175K amino acid substitution;

e. a Q79G amino acid substitution and a P2161 amino acid substitution; or

f. a R27D amino acid substitution and/or a E41R amino acid substitution.

7. The nucleic acid of claim **3**, wherein the modified α7 nicotinic acetylcholine ligand binding domain has reduced binding with endogenous acetylcholine (ACh) as compared to unmodified α7-nAChR LBD.

8. The nucleic acid of claim **1**, wherein the exogenous ligand is selected from the group consisting of a quinuclidine, a tropane, a 9-azabicyclo[3.3.1]nonane, a 6,7,8,9-tetrahydro-6,10-methano-6H-pyrazino(2,3-h)benzazepine, and a 1,4-diazabicyclo[3.2.2]nonane.

9. The nucleic acid of claim **1**, comprising a sequence of a packageable viral genome comprising the gene for expressing a modified ligand-gated ion channel.

10. The nucleic acid of claim **9**, comprising Adeno-associated virus ITR sequences flanking the gene for expressing a modified ligand-gated ion channel, producing a sequence of a packageable recombinant AAV genome or a self-complementary AAV genome comprising the gene for expressing a modified ligand-gated ion channel.

11. A method of preparing a patient for a treatment for relieving chronic pain, comprising:

delivering to the patient a nucleic acid comprising an open reading frame encoding a modified ligand-gated ion channel under transcriptional control of a regulatory element governing cell-specific expression in dorsal horn neurons, wherein the modified ligand-gated ion channel comprises a modified ligand binding domain activatable by an exogenous ligand, and an ion pore domain,

wherein the modified ligand-gated ion channel is a modified α7 nicotinic acetylcholine ligand binding domain, and

wherein the ion pore domain is an ion pore domain of an ionotropic nicotinic acetylcholine receptor, an ionotropic serotonin receptor, an ionotropic glycine receptor, an ionotropic GABA receptor, a serotonin 3 receptor (5HT3) ion pore domain, a glycine receptor (GlyR) ion pore domain, a gamma-aminobutyric acid (GABA) receptor ion pore domain, or an α7 nicotinic acetylcholine receptor.

12. The method of claim **11**, wherein the nucleic acid is delivered to the dorsal horn of the spinal cord of the patient.

13. The method of claim **11**, wherein the regulatory element is a promoter, a transcription response element, a repressor, and/or an enhancer.

14. The method of claim **11**, wherein the modified ligand binding domain is a modified α7 nicotinic acetylcholine ligand binding domain.

15. The method of claim **14**, wherein the modified α7 nicotinic acetylcholine ligand binding domain comprises a

sequence having at least 75 percent sequence identity to a sequence set forth in SEQ ID NO: 18, SEQ ID NO: 19, or SEQ ID NO: 20.

16. The method of claim **14**, wherein the modified α7 nicotinic acetylcholine ligand binding domain comprises an amino acid substitution at one or more of amino acid residues 77, 79, 115, 131, 139, 141, 175, 210, 216, 217, or 219 of SEQ ID NO: 18, SEQ ID NO: 19, or SEQ ID NO: 20, such as Q79A, Q79G, L141A, L141 F, L141 P, W77F, W77Y, or W77M.

17. The method of claim **14**, wherein the modified α7 nicotinic acetylcholine ligand binding domain comprises:

a. a L131G amino acid substitution, a Q139L amino acid substitution, and a Y217F amino acid substitution;

b. a W77F amino acid substitution, a Q79G amino acid substitution, and a G175K amino acid substitution;

c. a Q79G amino acid substitution, a Y115F amino acid substitution, and a G175K amino acid substitution;

d. a Y115F amino acid substitution and a G175K amino acid substitution;

e. a Q79G amino acid substitution and a P2161 amino acid substitution; or

f. a R27D amino acid substitution and/or a E41R amino acid substitution.

18. The method of claim **14**, wherein the modified α7 nicotinic acetylcholine ligand binding domain has reduced binding with endogenous acetylcholine (ACh) as compared to unmodified α7-nAChR LBD.

19. The method of claim **11**, further comprising administering the exogenous ligand to the patient in an amount effective to activate the modified ligand gated ion channel, thereby treating the chronic pain in the patient.

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