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(54) **DEVICES, SYSTEMS AND METHODS FOR
OPTOGENETIC MODULATION OF ACTION
POTENTIALS IN TARGET CELLS**

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C07K 14/705 (2006.01)

A61N 5/06 (2006.01)

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(52) **U.S. Cl.**

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2830/15 (2013.01); *A01K 2207/05* (2013.01);
A01K 2227/105 (2013.01); *A01K 2267/0393*
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2830/002 (2013.01)

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(DE)

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(57)

ABSTRACT

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(51) **Int. Cl.**

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Aspects of the disclosure include devices, systems and methods for optogenetic modulation of action potentials in target cells. The subject devices include light-generating devices, control devices, and delivery devices for delivering vectors to target cells. The subject systems include light-activated proteins, response proteins, nucleic acids comprising nucleotide sequences encoding these proteins, as well as expression systems that facilitate expression of these proteins in target cells. Also provided are methods of using the subject devices and systems to optogenetically inhibit and intercept action potentials in target cells, e.g., to treat a neurological or psychiatric condition in a human or non-human animal subject.

Specification includes a Sequence Listing.

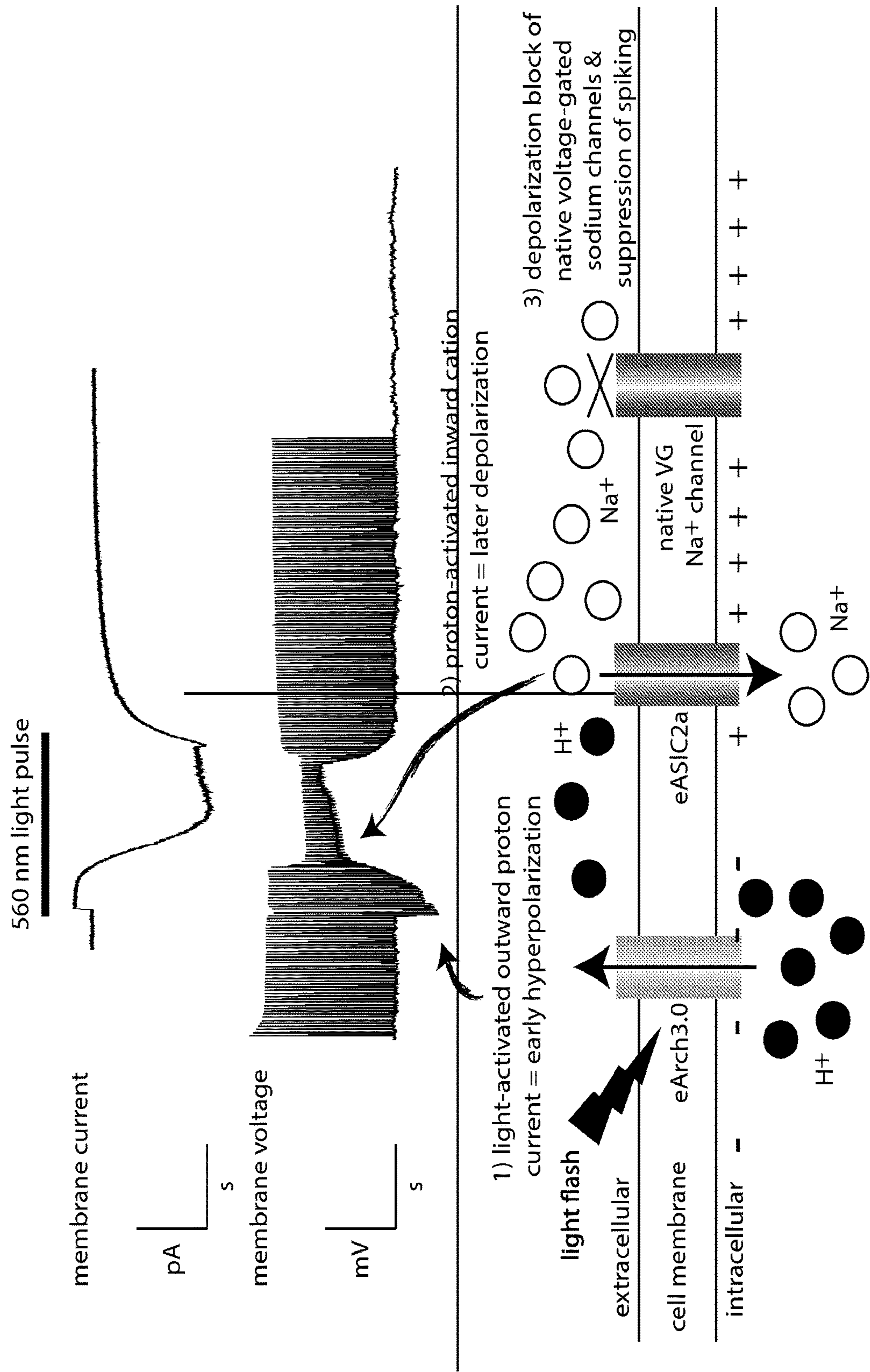
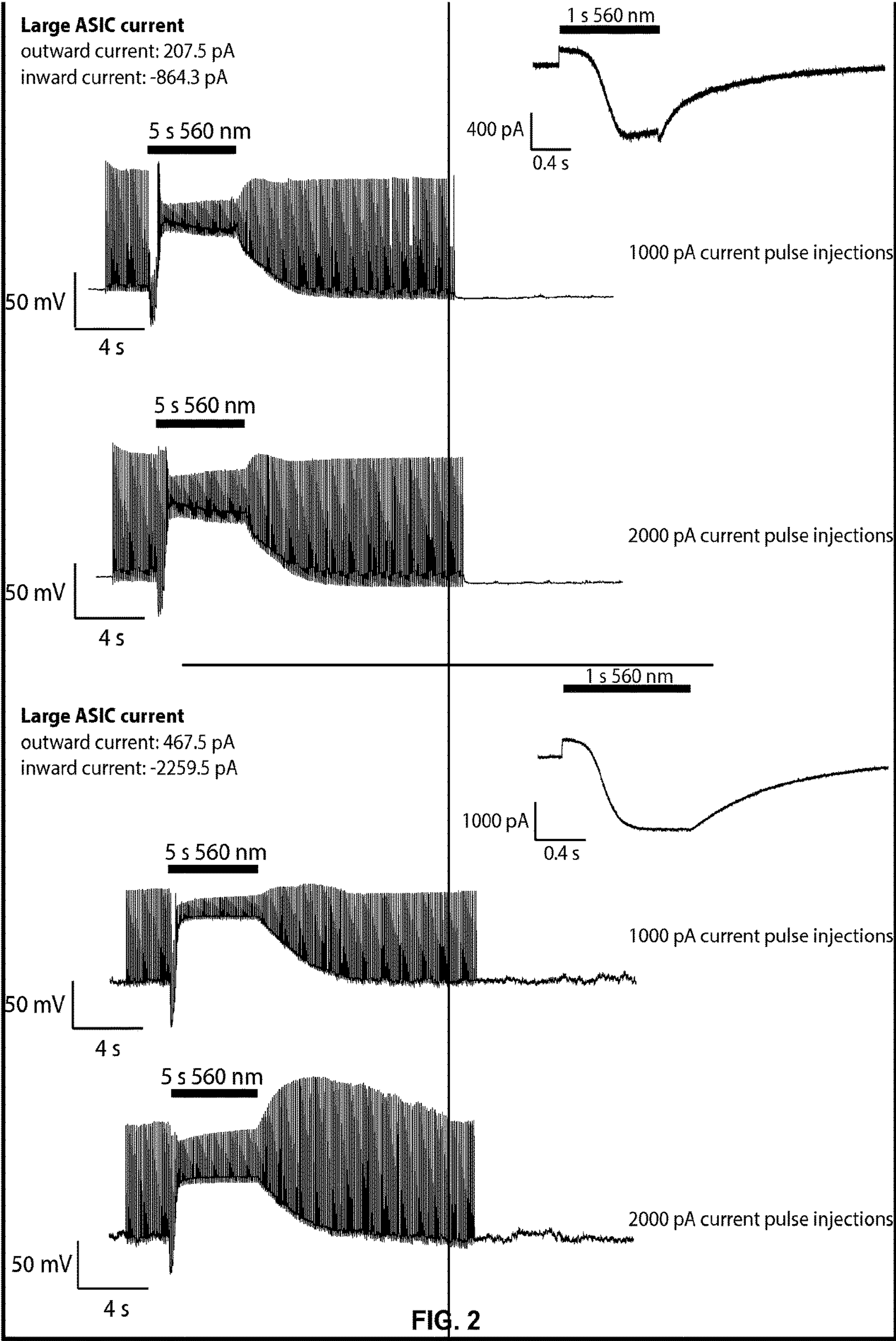


FIG. 1



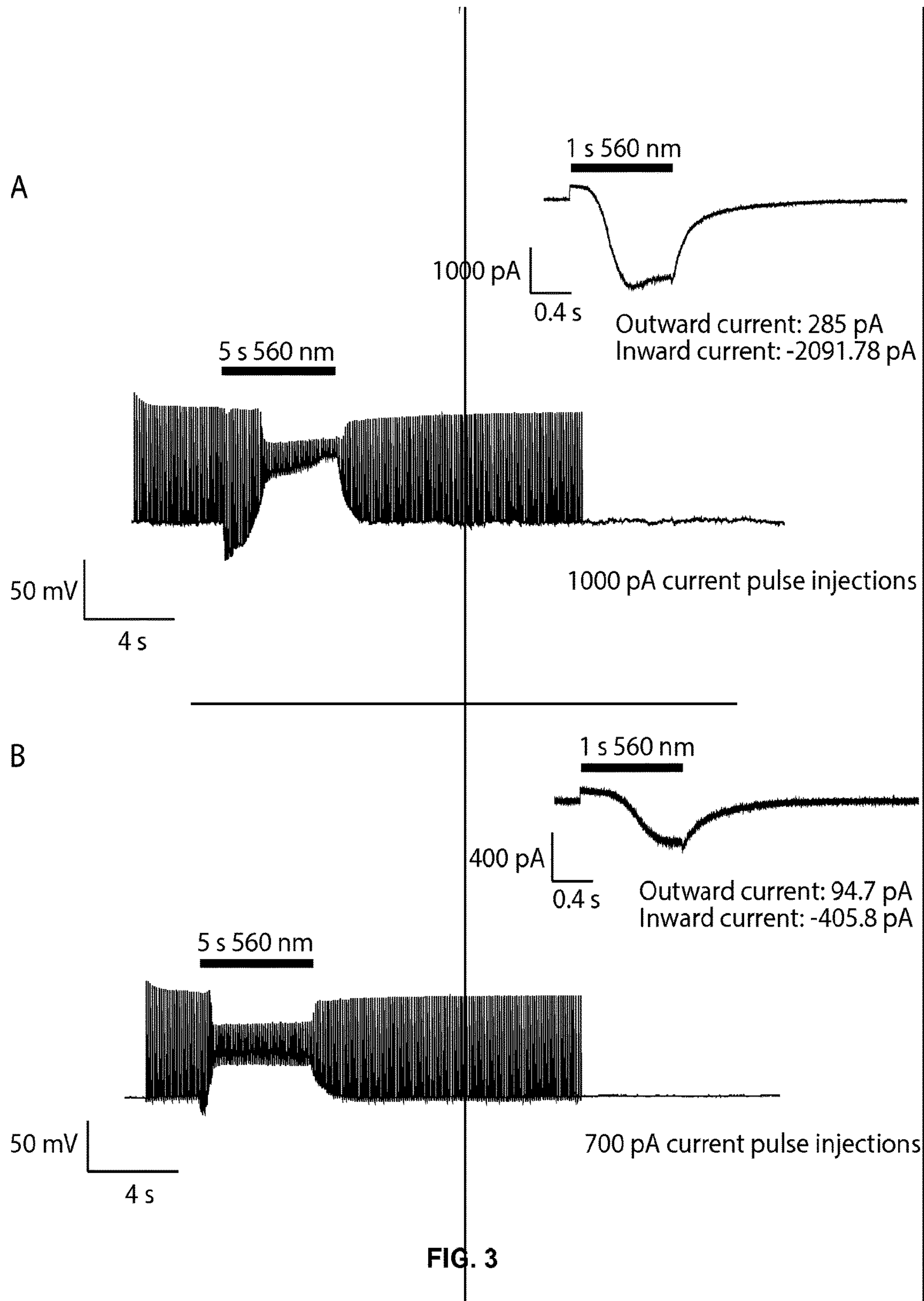


FIG. 3

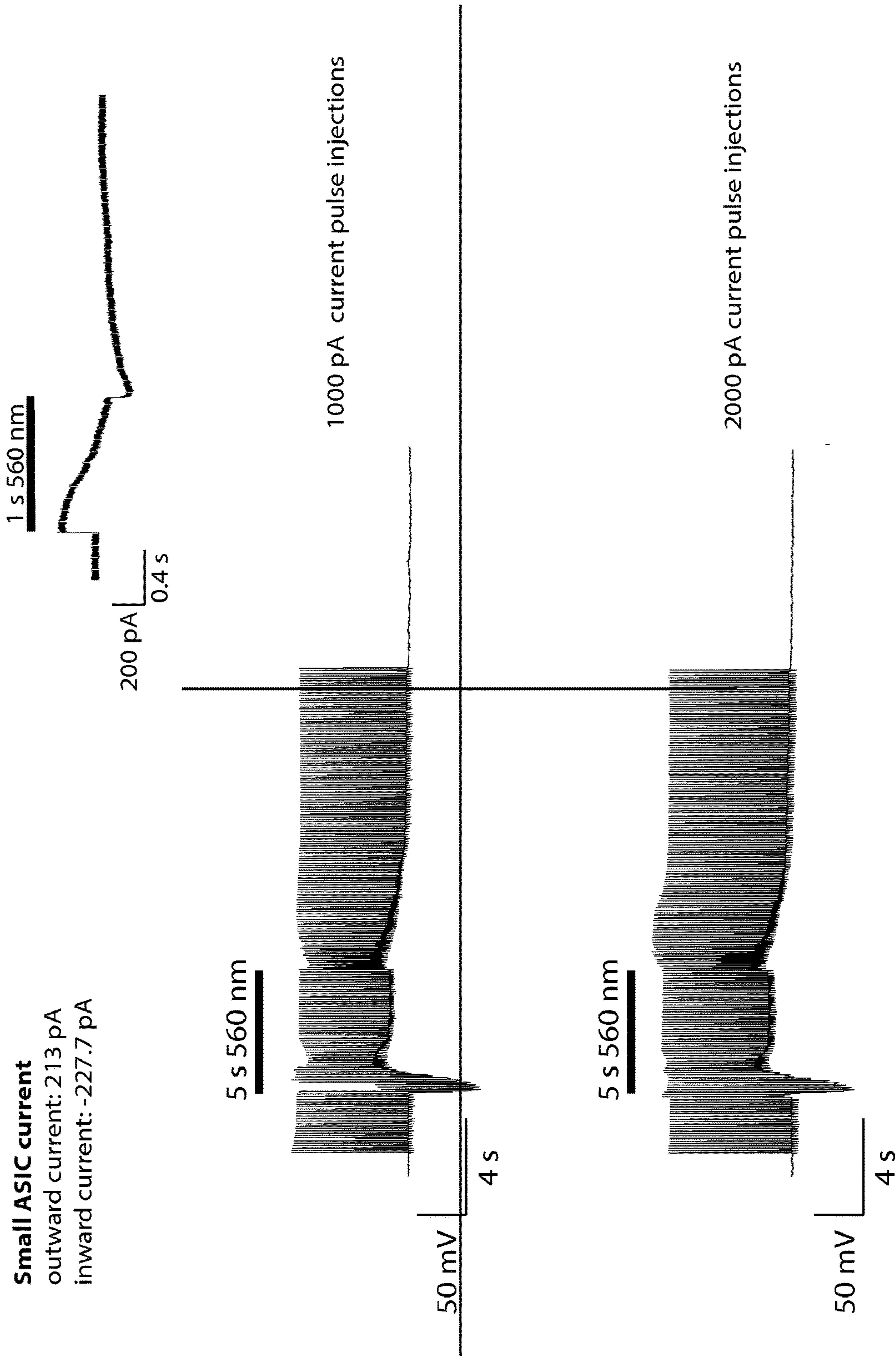


FIG. 4

Arch-TS-p2A-ASIC2a-EYFP

atggaccccatcgctctgcaggctggttacgacctgctgggtgacggcagacctgaaactctgtggctgggcacatcggcactctgctgatgctg
attggaaccttctactttctggtccgcggatggggaqtcaccgataagcatgcccgggaattaccgctgtgactatcctggtgcccggaatcg
catccgcccatatctgtctatgttctttggtatcggtctactgaggtgacctgcccgggcgaaatgttgatctattatgccaggtacgcc
gactggctgtttacacccccacttctgctgctggatctggcccttctcctaagggtggatcggtgacatcggcaccctggtgggtgtggacg
ccctgatgatcgctcactggcctcatcggaagccttgagccacacggccatagccagatacagttggtgggtgttctctacaattgcatgatagt
gtgctctatttctggctacatccctgcatctgctgcaaaaggagcggggcccccggaggtggcatctaccttaacaccctgacagctctggtctt
gggtgctgtggacccgttacctatcctgtggatcataggcactgagggcgctggcgtgtgggctgggcacatcgaaactctgctgtttatggt
gttggacgtgactgccaaggctggctttggctttatcctgttgagatccccgggctattctgggcgacaccgagggcaccagaaccagtgccgg
tgcctgtgcatgctgcccgcgacaagagcaggatcaccagcgaggggcgagtfacatccccctggaccagatcgacatcaacgtgggcgcgcc
cggtctccggagcgcaagaaacttctctctgttaagcaagcgaggagcggtggagaaaaaccccggtcccatggacctgaaggatcaccaagc
gagggatcactgcagccatcaagcattcagattttcgctaatacagcacactgcacggcatccggcatatcttcgtgtacggcccactgacct
tcggaagatcctgtgtggcagtgccctttgtcggaagcctgggactgctgctggtggagagctccgaaaagatcagttactatttctcatatca
gcacgtgactaagggtggacgaggtggtcgtcagtcctggtgtttcccgacgtcaccctgtgcaacctgaatgggttcaggttttctgcctg
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cattcaggaactgggattggagtgaccaggattccagacatttgcgtactcaggagcagcgccctgacctatctgccacccccctggggc
gagtgccgactctagtgaatgggctggacttttctgtgtactctatcaccgcctgcccgaattgattgtgagacacggtatatctgtgaaaa
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ggctgagaaggatagtaactactgctgtgtagaacacctgtaacctgactaggataataaggaactgagcatggtgaagatcccttccaa
aacatctgcaaaqtacctggagaagaagttcaacaagtctgagaagfacatcagtgaaaacattctggtgctggacatcttctttgaagctctga
attacgagaccattgaacagaagaaagcatatgaggtggccgctctgctgggggatattggagggcagatgggactgttcatcgccgccaq
cctgctgacaattctggagctgtttgactacatctatgagctgattaaggaaaaactgctggaictgctggggaaggaggaaggaaggaagat
cacacgacgaaaacatgagcacttgcgataccatgcctaatacacagcgagaccatctccatacagtgaaatgtccactgcagactgcactgg
gcacctggaggaaaattgcctgtgcggccgcccgtgagcaaggggcgaggagctgttcacgggggtgggtgcccattcctggctgagctggacg
gcgacgtaaaacggccacaagttcagcgtgtccggcgagggcgaggggcgatgccacctacggcaagctgacctgaagttcactgcaccac
cggaagctgcccgtgcccggcccacctcgtgaccaccttcggctacggcctgcagtgcttgcggcgctaccccggaccacatgaagcagca
cgacttctcaagtcggcctgcccgaaggctacgtccaggagcgcaccaatcttctcaaggacgacgggaactacaagacctgcggcgagg
tgaagttcgaggggcgacacctgggtgaaccgcatcgagctgaaggggcatcgacttcaggaggagcggaacatctggggcacaagctgg
agtacaactacaacagccacaacgtctatatcatggccgacaagcagaagaaggcatcaagggtgaacttcaagatccgccacaacatcgag
gacggcagcgtgcagctgcggaccactaccagcagaacacccccctcgggcgacggccccgtgctgctgcccgacaaccactacctgagct
accagtcggccctgagcaaaagaccccaacgagaagcgcgatcacatggtctgtggagttcgtgaccgcggccgggatcactctcggcatg
gacgagctgtacaagtaa

Arch = underlinedTS = *italic*p2A = white-on-blackASIC2a = *italic underlined*EYFP = italic white-on-black

FIG. 5

Arch-TS-p2A-ASIC2a-TS-EYFP-ER

atggaccccatcgctctgcaggctgggttacgacctgctgggtgacggcagacctgaaactctgtggctgggcacatcgccactctgctgatgctg
attggaaccttctactttctggtccgcggatggggagtcaccgataaggatgcccgggaatattacgctgtgactatcctgggtgcccggaaatcg
catccgcgcataatctgtctatgtttcttgggtatcgggcttactgaggtgaccgtcgggggcqaaatgttggatactattatgccaggtacgcc
gactggctgtttaccaccccaacttctgctgctggaatctggcccttctcgctaagggtggatcgggtgaccatcgccacccctggtgggtgtggacg
ccctgatgatcgtcactggcctcatcgagcccttgagccacacggccatagccagatacaagttggtggtgtttctctacaatttgcagtagatg
gtgctctattttctggctacatccctgcgactgctgcaaaaggagcggggccccgaggtggcatctaccttaacacccctgacagctctggtctt
ggtgctgtggaccgcttaccctatcctgtggtataggaactgagggcgctggcggtgggctgggcacatcgaaactctgctgtttatggt
gttggacgtgactgccaaaggctggctttggctttatcctgttgagatcccgggctattctgggcgacaccgaggcaccagaacccagtgcccg
tgccgatgtcagtgccggcgacaagagcaggatcaccagcgaggggcgagtfacatccccctggaccagatcgacatcaacgtgggcgcgcc
cggtctcgggagccacgaacttctctgtttaaagcaagcaggagacgltggaagaaaacccccggltcccatagacactgaaggagtcaccaagc
gagggatcactgcagccatcaagcattcagaatttctgctaatacaagcacactgcacggcatccggcatatcttctgtgtacggcccactgacat
tcggagagtcctgtgtggcagtgccctttgtcggaaqcctgggactgctgctggtggagagctccgaaagagtcagttactatttctcatatca
gcacgtgactaaaggtggacgaaggtgtgctgctcagtcctgtgtttcccgagtcaccctgtgcaacctgaatgggttcaggttttctcgccctg
accacaaacgacctgtaccacggcggagagctgctggctctgctggatgtgaatctgcagatcccagacccccatctggccgatccaaccgtg
ctggaagcactgaggcagaaaggccaacttcaaacactacaagcccaaacagttcagcatgctggagtttctgcaccgcgtgggacatgacct
gaaagatatgatgctgtattgcaagttcaaaggccaggagtggtggcatcaggacttactaccgtgtttacaaagtcaggcaaatgttacatg
ttcaactccggggaagatggaaaacctctgctgacaactgtgaaggcgggacaggggaatggactggagatcatgctggacattcagcag
gatgagtcacctgccaatctggggagaaactgaggaaccacattcgaggccggcggtgaaggtccagatccactcacagagcgagccccctt
cattcaggaactgggatttggagtgccaccaggattccagacatttgcgtactcaggagcagcgccctgacctatctgccaccccccttggggc
gagtgccgatctagtgaatggggctggacttcttctgtgtactctatcacccgctgccgaattgattgtgagacacgggtatatctgtgaaaa
ctgcaattgtaggaatgttccacatgcttggcgacgccccattctgcactcccgaacagcataaaagagtgctgtgaacctgcactggggctgt
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gcaccctggagggaaattgcctgtgcggccgccaagagcaggatcaccagcgaggggcgagtfacatccccctggaccagatcgacatcaacgt
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cagcagaacacccccatcgggcgacggccccgtgctgctgcccgacaaccactacctgagctaccagtcggccctgagcaaaagaccccaacga
gaagcgcgatcacatggtctgtggagttcgtgacggccggccggatcactctcggcagtgacgagctgtacaagttctgctacgagaacg
aggtgtaa

Arch = underline

TS = *italic*

p2A = white-on-black

ASIC2a = *italic underline*

TS = double underline

EYFP = *italic white-on-black*

ER = *italic double underline*

FIG. 6

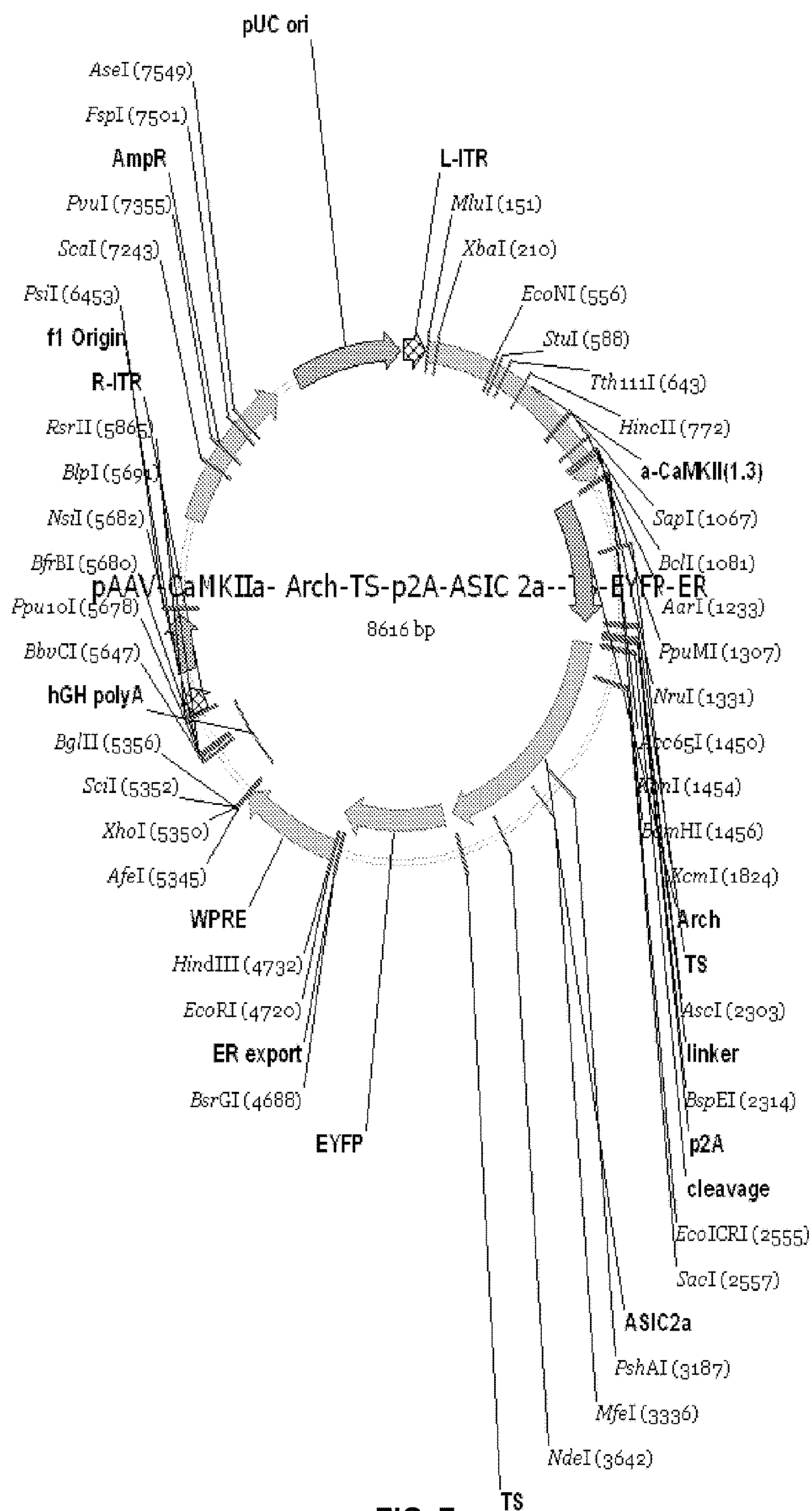


FIG. 7

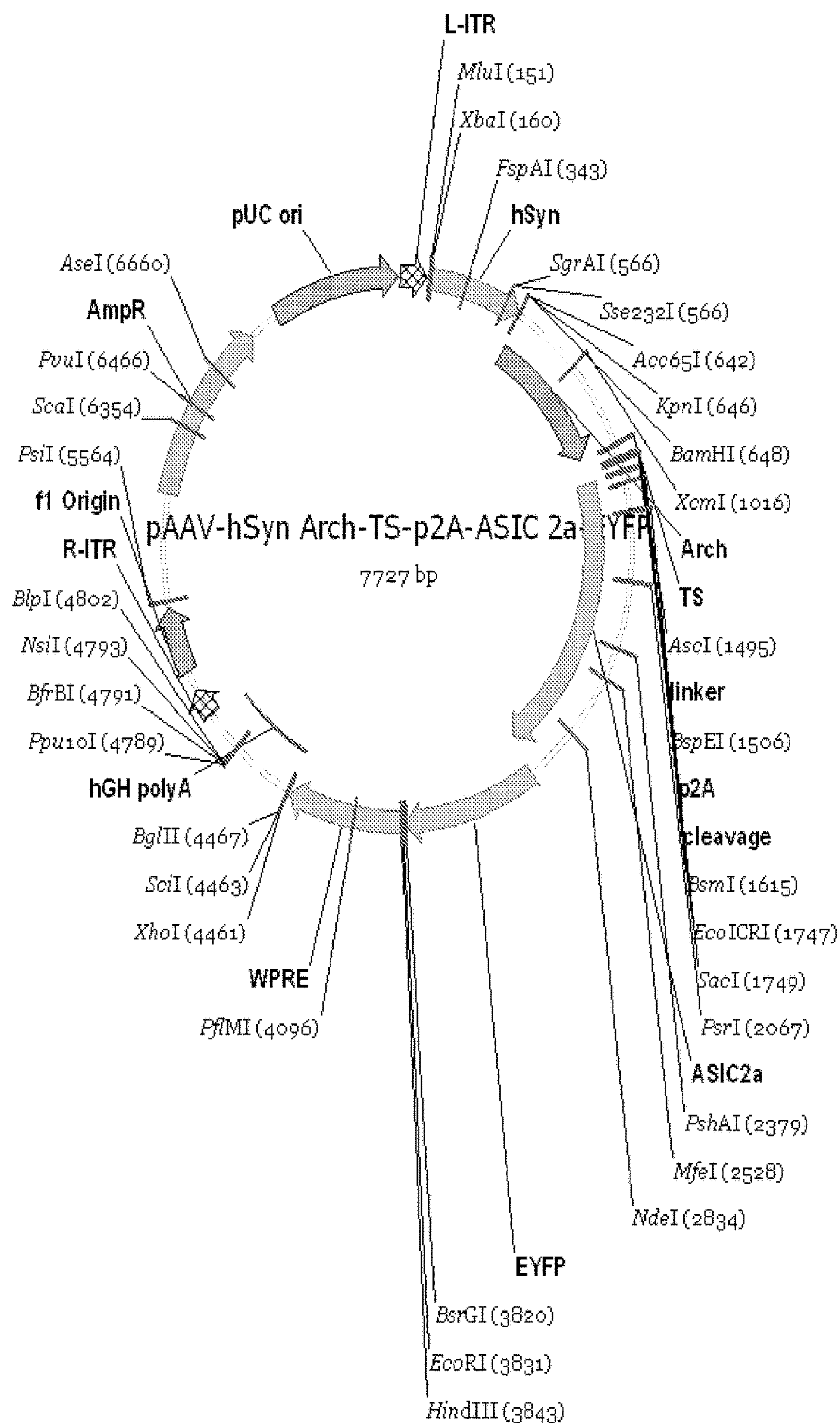


FIG. 8

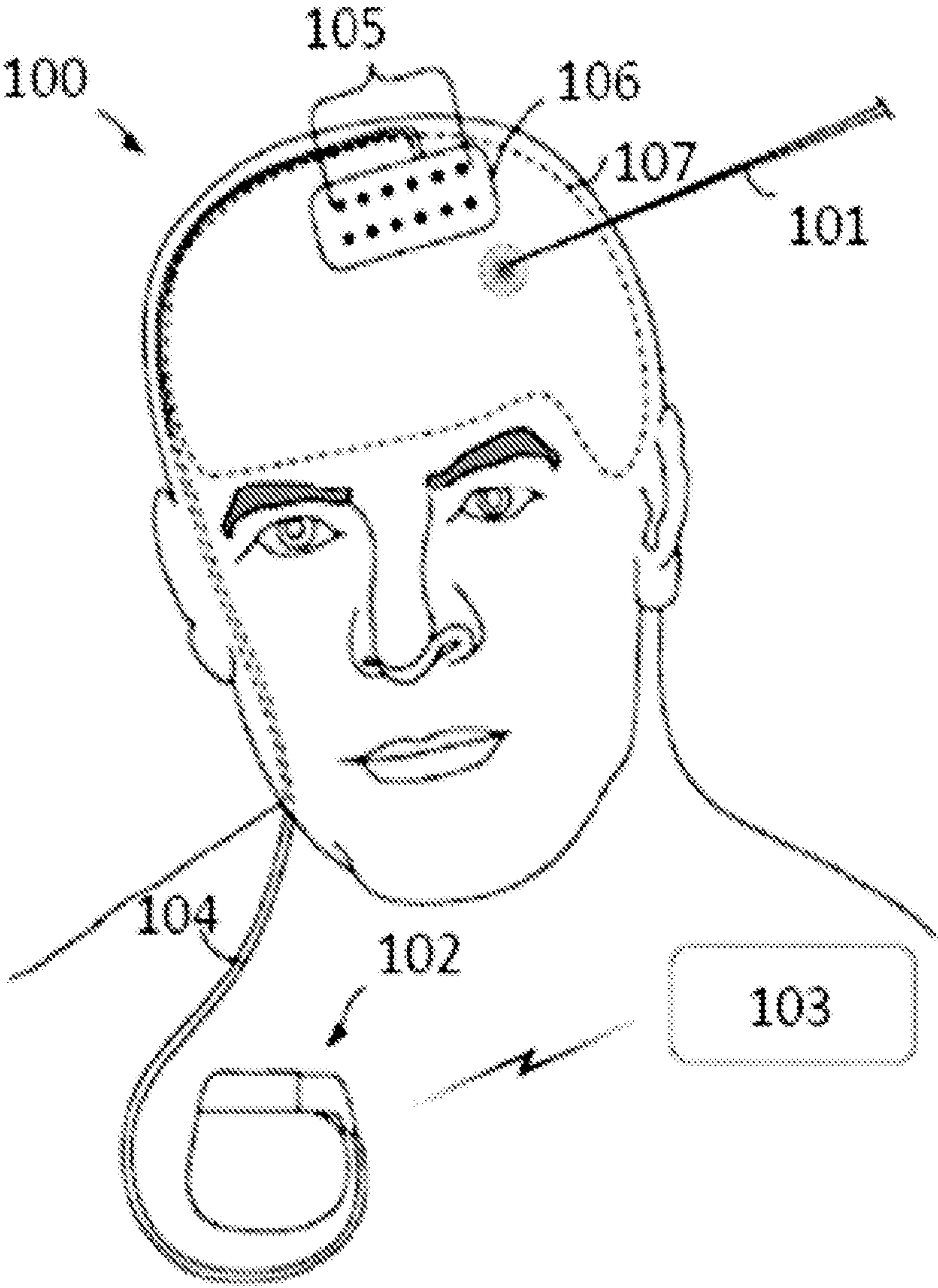


FIG. 9

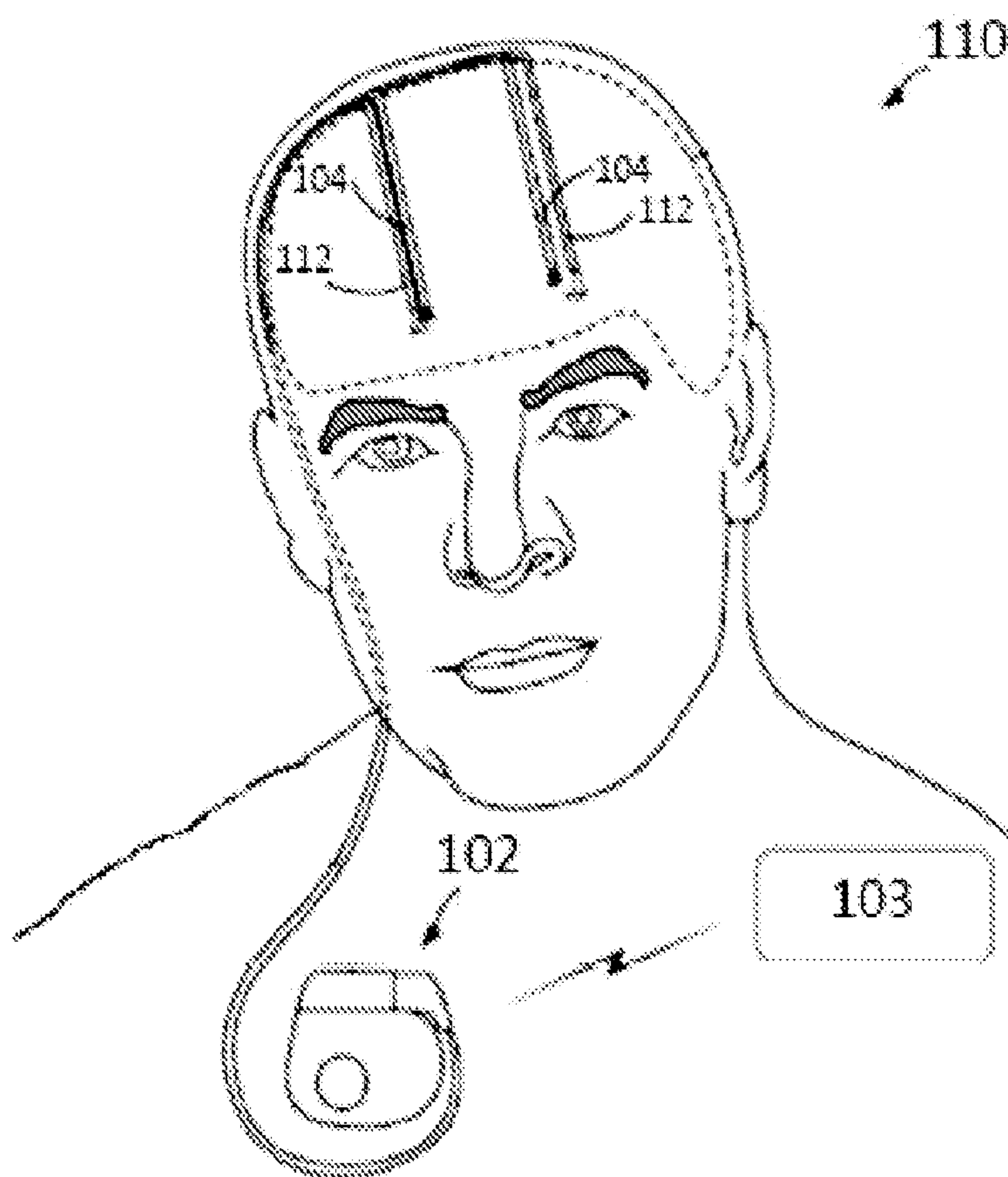


FIG 10

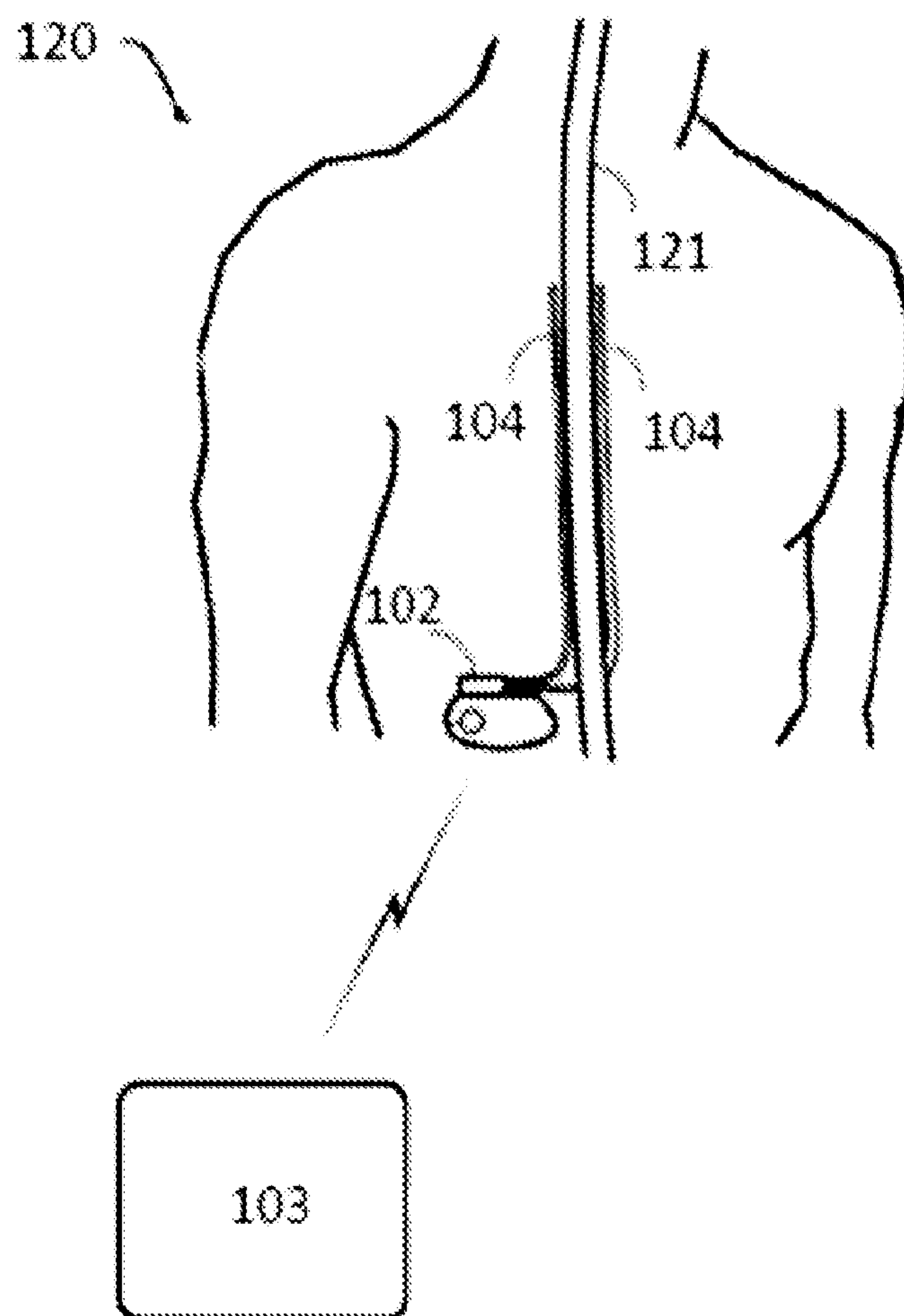


FIG. 11

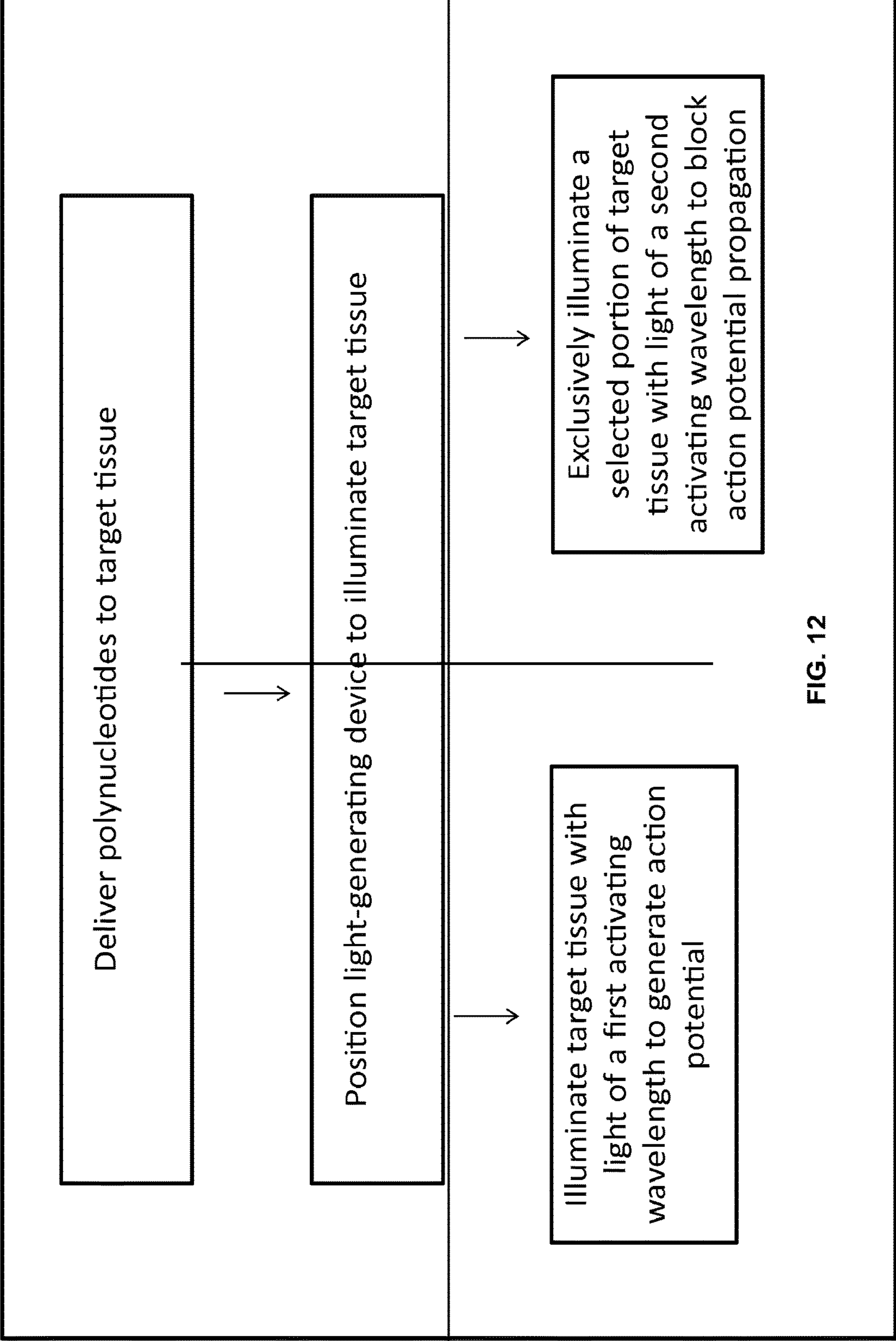


FIG. 12

amino acid sequence of eArch:

MDPIALQAGYDLLGDGRPETLWLGIGTLLMLIGTFYFLVRGWGVTDKDAREYYAVTIL
VPGIASAAYLSMFFGIGLTEVTVGGEMLDIYYARYADWLFTTPLLALLDLALLAKVDRV
TIGTLVGVDALMIVTGLIGALSHTAIARYSWWLFSTICMIVVLYFLATSLRSAAKERGPE
VASTFNTLTALVLVLWTAYPILWIIGTEGAGVVGLGIETLLFMVLDVTAKVGFGFILLR
SRAILGDTEAPEPSAGADVSAAD (SEQ ID NO:1).

amino acid sequence of eArch3.0-EYFP:

MDPIALQAGYDLLGDGRPETLWLGIGTLLMLIGTFYFLVRGWGVTDKDAREYYAVTIL
VPGIASAAYLSMFFGIGLTEVTVGGEMLDIYYARYADWLFTTPLLALLDLALLAKVDRV
TIGTLVGVDALMIVTGLIGALSHTAIARYSWWLFSTICMIVVLYFLATSLRSAAKERGPE
VASTFNTLTALVLVLWTAYPILWIIGTEGAGVVGLGIETLLFMVLDVTAKVGFGFILLR
SRAILGDTEAPEPSAGADVSAADRPVVAVSKAAAKSRITSEGEYIPLDQIDINVVSKGEE
LFTGVVPILVELDGDVNGHKFSVSgegeG DATYGKLTCLKFICTTGKLPVPWPTLVTTFG
YGLQCFARYPDHMKQHDFFKSAMPEGYVQERTIFFKDDGNYKTRAEVKFEGDTLVNR
IELKGIDFKEDGNILGHKLEYNYNshNVYIMADKQKNGIKVNFKIRHNIEDGSVQLADH
YQQNTPIGDGPVLLPDNHYSYQSALS KDPNEKRDHMLLEFVTAAGITLGMDELYKF
CYENEV (SEQ ID NO:2).

ArchT 3.0

MDPIALQAGYDLLGDGRPETLWLGIGTLLMLIGTFYFLVRGWGVTDKEAREYYSTITLVP
GIASAAYLSMFFGIGLTEVTVAGEVLDIYYARYADWLFTTPLLALLDLALLAKVDRVSIGT
LVGVDALMIVTGLIGALSHTPLARYSWWLFSTICMIVVLYFLATSLRAAAKERGPEVAST
FNTLTALVLVLWTAYPILWIIGTEGAGVVGLGIETLLFMVLDVTAKVGFGFILLRSRAIL
GDTEAPEP (SEQ ID NO:3)

amino acid sequence of GtR3:

ASSFGKALLEFVFIVFACITLLLGINAAKSKAASRVLFPATFVTGIASIAYFSMASGGGWVI
APDCRQLFVARYLDWLITPLLIDLGLVAGVSRWDIMALCLSDVLMIAATGAFGSLTVG
NVKWWWWFFGMCWFLHIIFALGKSWAEAAKAKGGDSASVYSKIAGITVITWFCYPVV
WVFAEGFGNFSVTFEVLIYGVLDVISKAVFGLILMSGAAATGYESI (SEQ ID NO:4).

Amino acid sequence of a *Oxyrrhis marina* proton pump (rhodopsin type II)

maplaqdwty aewsavynal sfgiagmgsa tiffwlqlpn vtknyrtalt itgivtliat
yhyfrifnsw vaafnvglgv ngayevtvsg tpfndayryv dwlltvplll velilvmklp
aketvclawt lgiasavmva lgypgeiqdd lsvrwwac amvpfvvyvg tlvvglgaat
akqpegvdl vsaaryltnv swltypfvyi vkniglagst atmyeqigys aadvtakavf
gvliwaiana ksrleeegkl ra (SEQ ID NO:5)

FIG. 13A

Amino acid sequence of *L. maculans* rhodopsin

mivdqfeevl mktsqlfplp tatqsaqpth vapvptvlpd tpiyetvgds gsktlwvvfv
lmliasaافت alswwkipvnr rlyhvittii tltaalsyfa matghgvaln kivirtqhdh
vpdtyetvyr qvyyaryidw aittplllld lgllagmsga hifmaivadl imvltglfaa
fgsegtpqkw gwytiaciay ifvwwhlvln gganarvkge klrsffvaig aytlilwtay
pivwgladga rkigvdgeii ayavldvlak gvfgawllvt hanlresdve lngfwangln
regairiged dga (SEQ ID NO:6)

Mac 3.0

MIVDQFEEVLMKTSQLFPLPTATQSAQPTHVAPVPTVLPDTPITYETVGDSGSKTLWVVFV
LMLIASAافتTALSWKIPVNRRLYHVITTTIITLTAALSYFAMATGHGVALNKIVIRTQHDH
VPDTYETVYRQVYYARYIDWAITTPLLLLDLGLLAGMSGAHIFMAIVADLIMVLTGLFAA
FGSEGTPQKWGWYTIACIAYIFVWWHLVLNGGANARVKGEKLRSFFVAIGAYTLILWTAY
PIVWGLADGARKIGVDGEIIAYAVLDVLAKGVFGAWLLVTHANLRESDELNGFWANGLN
REGAIRIGEDDGARPVVAVSK (SEQ ID NO:7)

FIG. 13B

Amino acid sequence of ChR2:

MDYGGALSAVGRELLFVTNPVVVNGSVLVPEDQCYCAGWIESRGTNGAQTASNVLQWLAAGFSIL
LLMFYAYQTWKSTCGWEEIYVCAIEMVKVILEFFFEFKNPSMLYLATGHRVQWLRYAEWLLTCPV
ILIHLSNLTGLSNDYSRRTMGLLVSDIGTIVWGATSAMATGYVKVIFFCGLGLCYGANTFFHAAKA
YIEGYHTVPKGRRCRQVVTGMAWLFFVSWGMFPILFILGPEGFGVLSVYGSTVGHTIIDLMSKNCW
GLLGHYLRVLIHEHILIHGDIRKTTKLNIGGTEIEVETLVEDEAEAGAVP (SEQ ID NO:8).

amino acid sequence of a SFO:

MDYGGALSAVGRELLFVTNPVVVNGSVLVPEDQCYCAGWIESRGTNGAQTASNVLQW
LAAGFSILLMFYAYQTWKSTCGWEEIYVCAIEMVKVILEFFFEFKNPSMLYLATGHRVQ
WLRYAEWLLTSPVILIHLSNLTGLSNDYSRRTMGLLVSDIGTIVWGATSAMATGYVKVIF
FCLGLCYGANTFFHAAKAYIEGYHTVPKGRRCRQVVTGMAWLFFVSWGMFPILFILGPEG
FGVLSVYGSTVGHTIIDLMSKNCWGLLGHYLRVLIHEHILIHGDIRKTTKLNIGGTEIEVET
LVEDEAEAGAVP (SEQ ID NO:9).

amino acid sequence of an SSFO:

MDYGGALSAVGRELLFVTNPVVVNGSVLVPEDQCYCAGWIESRGTNGAQTASNVLQW
LAAGFSILLMFYAYQTWKSTCGWEEIYVCAIEMVKVILEFFFEFKNPSMLYLATGHRVQ
WLRYAEWLLTSPVILIHLSNLTGLSNDYSRRTMGLLVSAIGTIVWGATSAMATGYVKVIF
FCLGLCYGANTFFHAAKAYIEGYHTVPKGRRCRQVVTGMAWLFFVSWGMFPILFILGPEG
FGVLSVYGSTVGHTIIDLMSKNCWGLLGHYLRVLIHEHILIHGDIRKTTKLNIGGTEIEVET
LVEDEAEAGAVP (SEQ ID NO:10).

amino acid sequence of C1V1:

MSRRPWLLALALAVALAAGSAGASTGSDATVPVATQDGPDYVFHRAHERMLFQTSY
TLENNGSVICIPNNGQCFCLAWLKSNGTNAEKLAANILQWITFALSALCLMFYGYQTW
KSTCGWEEIYVATIEMIKFIIIEYFHEFDEPAVIYSSNGNKTWLRYAEWLLTCPVLLIHL
SNLTGLKDDYSKRTMGLLVSDVGCIVWGATSAMCTGWTKILFFLISLSYGMITYFHA
AKVYIEAFHTVPKGICRELVRVMAWTFVAVWGMFPVLFLLGTEGFGHISPYGSAIGHSI
LDLIAKNMWGVLGNYLRVKIHEHILLYGDIRKKQKITIAGQEMEVEVETLVAEEED (SEQ
ID NO:11).

amino acid sequence of C1V1 (E122T):

MSRRPWLLALALAVALAAGSAGASTGSDATVPVATQDGPDYVFHRAHERMLFQTSYTL
ENNGSVICIPNNGQCFCLAWLKSNGTNAEKLAANILQWITFALSALCLMFYGYQTWKST
CGWETIYVATIEMIKFIIIEYFHEFDEPAVIYSSNGNKTWLRYAEWLLTCPVLLIHLNLT
GLKDDYSKRTMGLLVSDVGCIVWGATSAMCTGWTKILFFLISLSYGMITYFHA
AKVYIEAFHTVPKGICRELVRVMAWTFVAVWGMFPVLFLLGTEGFGHISPYGSAIGHSI
LDLIAKNMWGVLGNYLRVKIHEHILLYGDIRKKQKITIAGQEMEVEVETLVAEEED (SEQ ID NO:12).

FIG. 13C

amino acid sequence of CIV1 (E162T):

MSRRPWLLALALAVALAAGSAGASTGSDATVPVATQDGPDYVFHRAHERMLFQTSY
 TLENNGSVICIPNNGQCFCCLAWLKSNGTNAEKLAANILQWITFALSALCLMFYGYQTW
 KSTCGWEEIYVATIEMIKFIEYFHEFDEPAVIYSSNGNKTVWRLRYATWLLTCPVLLIHL
 SNLTGLKDDYSKRTMGLLVSDVGCIVWGA TSAMCTGWT KILFFLISLSYGM TYFHA
 AKVYIEAFHTV PKGICRELVRVMAW TFFVA WGMFPVL FLLGTEGFGHISPYGSAIGHSI
 LDLIAKNMWGV LGNYLRVKIHEHILLYGDIRKKQKITIAGQEMEVE TLVAEEED (SEQ
 ID NO:13).

amino acid sequence of CIV1 (E122T/E162T):

MSRRPWLLALALAVALAAGSAGASTGSDATVPVATQDGPDYVFHRAHERMLFQTSY
 TLENNGSVICIPNNGQCFCCLAWLKSNGTNAEKLAANILQWITFALSALCLMFYGYQTW
 KSTCGWETIYVATIEMIKFIEYFHEFDEPAVIYSSNGNKTVWRLRYATWLLTCPVLLIHL
 SNLTGLKDDYSKRTMGLLVSDVGCIVWGA TSAMCTGWT KILFFLISLSYGM TYFHA
 AKVYIEAFHTV PKGICRELVRVMAW TFFVA WGMFPVL FLLGTEGFGHISPYGSAIGHSI
 LDLIAKNMWGV LGNYLRVKIHEHILLYGDIRKKQKITIAGQEMEVE TLVAEEED (SEQ
 ID NO:14).

Amino acid sequence of *Dunaliella salina* channelrhodopsin

mrrresqlay lclfvliagw aprltesapd laerrppser ntpyanikkv pnitepnanv
 qldgwalyqd fyylagsdke wvvgpsdqcy crawskshgt dregeaavvw ayivfaiciv
 qlvyfmfaaw katvgweevy vniielvhia lviwvefdkp amlylndgqm vpwlrysawl
 lscpvilihl snltglkgdy skrtmglivs digtivfgts aalappnhvk vilftiglly
 glftfftaak vyieayhtvp kgqcrnlvra mawtyfvswa mfpilfilgr egfghityfg
 ssighfilei fsknlwsllg hglryrirqh iiihgnltkk nkiniagdnv eveeyvdsnd
 kdsdv (SEQ ID NO:15)

FIG. 13D

amino acid sequence of NpHR without the (native) signal peptide:

VTQRELFEFVLNDPLLASSLYINIALAGLSILLFVFMTRGLDDPRAKLIIVSTILVPVVSIA
YTGLASGLTISVLEMPAGHFAEGSSVMLGGEEVDGVVTMWGRYLTWALSTPMILLALG
LLAGSNATKLFTAITFDIAMCVTGLAAALTTSSHLMRWFWY AISCACFLVVLYILLVEW
AQDAKAAGTADMFTLKLTVVMWLGYPVWALGVEGIAVLPVGVTSWGYSFLDIVA
KYIFAFLLLNYLTSNESVVSIGSILDVPSASGTPADD (SEQ ID NO:16).

amino acid sequence of eYFP-NpHR3.0:

MTETLPPVTESAVALQAEVTQRELFEFVLNDPLLASSLYINIALAGLSILLFVFMTRGLDD
PRAKLIIVSTILVPVVSIA SYTGLASGLTISVLEMPAGHFAEGSSVMLGGEEVDGVVTMW
GRYLTWALSTPMILLALG LLAGSNATKLFTAITFDIAMCVTGLAAALTTSSHLMRWFWY
AISCACFLVVLYILLVEWAQDAKAAGTADMFTLKLTVVMWLGYPVWALGVEGIAV
LPVGVTSWGYSFLDIVAKYIFAFLLLNYLTSNESVVSIGSILDVPSASGTPADDAAAKSRIT
SEGEYIPLDQIDINVVSKGEELFTGVVPILVELDGDVNGHKFSVSGEGEGDATYGKLTCLKF
ICTTGKLPVPWPTLVTTFGYGLQCFARYPDHMKQHDFFKSAMPEGYVQERTIFFKDDGN
YKTRAEVKFEGDTLVNRIELKGIDFKEDGNILGHKLEYNYN SHNVYIMADKQKNGIKVN
FKIRHNIEDGSVQLADHYQQNTPIGDGPVLLPDNHYLSYQSALS KDPNEKRDHMLLEF
VTAAGITLGMDELYKFCYENEV (SEQ ID NO:17).

amino acid sequence of eYFP-NpHR3.1:

MVTQRELFEFVLNDPLLASSLYINIALAGLSILLFVFMTRGLDDPRAKLIIVSTILVPVVS
ASYTGLASGLTISVLEMPAGHFAEGSSVMLGGEEVDGVVTMWGRYLTWALSTPMILLA
LGLLAGSNATKLFTAITFDIAMCVTGLAAALTTSSHLMRWFWY AISCACFLVVLYILLVE
WAQDAKAAGTADMFTLKLTVVMWLGYPVWALGVEGIAVLPVGVTSWGYSFLDIV
AKYIFAFLLLNYLTSNESVVSIGSILDVPSASGTPADDAAAKSRITSEGEYIPLDQIDINVV
KGEELFTGVVPILVELDGDVNGHKFSVSGEGEGDATYGKLTCLKFICTTGKLPVPWPTLV
TFGYGLQCFARYPDHMKQHDFFKSAMPEGYVQERTIFFKDDGN YKTRAEVKFEGDTLV
NRIELKGIDFKEDGNILGHKLEYNYN SHNVYIMADKQKNGIKVNFKIRHNIEDGSVQLAD
HYQQNTPIGDGPVLLPDNHYLSYQSALS KDPNEKRDHMLLEFVTAAGITLGMDELYKF
CYENEV (SEQ ID NO:18).

Amino acid sequence of C1C2

MSRRPWLLALALAVALAAGSAGASTGSDATVPVATQDGPDYVFHRAHERMLFQTSYTL
NNGSVICIPNNGQCFCLAWLKSNGTNAEKLAANILQWITFALSALCLMFYGYQTWKSTC
GWEEIYVATIEMIKFIIIEYFHEFDEPAVIYSSNGNKTWVLRYAEWLLTCPVILIHLSNL
TGLANDYNKRTMGLLVSDIGTIVWGTTAALSKGYVRVIFFLMGLCYGIYTFFNAAKVYI
EAYHTVPGKRCRQVVTGMAWLFFVSWGMFPILFILGPEGFGVLSVYGSTVGHTIIDLMS
KNCWGLLGHYLRVLIHEHILIHGDIRKTTKLNIGGTEIEVETLVEDEAEAGAV (SEQ
ID NO:29)

FIG. 13E

Amino acid sequence of ReaChR

MVSRRPWLLALALAVALAAGSAGASTGSDATVPVATQDGPDYVFHRAHERMLFQTSYTL
 ENNGSVICIPNNGQCFCLAWLKSNGTNAEKLAANILQWVTFALSVACLGWYAYQAWRAT
 CGWEEVYVALIEMMKSIIEAFHEFDSPATLWLSSGNGVVMRYGEWLLTCPVILIHLSN
 LTGLKDDYSKRTMGLLVSDVGCIVWGATSAMCTGWTKILFFLISLSYGMITYFHAAKVY
 IEAFHTVPKGLCRQLVRAMAWLFFVSWGMPVLFLLGPEGFGHISPYGSAIGHSIIDLI
 AKNMWGVLGNYLRVKIHEHILLYGDIRKKOKITIAGQEMEVETLVAEEDDKYESS
 (SEQ ID NO:30)

FIG. 13F

Champ 1.0:

MDPIALQAGYDLLGDGRPETLWLIGITLLMLIGTFYFLVRGWGVTDKDAREYYAVTILV
PGIASAAYLSMFFGIGLTEVTVGGEMLDIYYARYADWLFTTPLLLDLALLAKVDRVITIG
TLVGVDALMIVTGLIGALSHTAIARYSWWLFSTICMIVVLYFLATSLRSAAKERGPPEVAS
TFNTLTALVLVLWTAYPILWIIIGTEGAGVVGLGIETLLFMVLDVTAKVGFGFILLRSRAIL
GDTEAPEPSAGADVSAADKSRTSEGEYIPLDQIDINVGAPGSGATNFSLLKQAGDVEENP
 MDLKESPSEGLQPSIQIFANTSTLHGIRHIFVYGPLTIRRVLWAVAFVGSGLLLVESSERSY
 YFSYQHVTKVDEVVAQSLVFPVATLCNLNGFRFSRLTTNDLYHAGELLALLDVNLQIPDPHLA
 DPTVLEALRQKANFKHYKPKQFSMLEFLHRVGHDLKDMMLYCKFKGQECGHQDFTTVFTK
 YGKCYMFNSGEDGKPLLTIVKGGTGNGLEIMLDIQQDEYLPWGETEETTFEAGVKVQIHSQS
 EPPFIQELGFGVAPGFQTFVATQEQRLTYLPPPWGECRSSEMGLDFFPVYSITACRIDCETRYI
 VENCNCRMVHMPGDAPFCTPEQHKECAEPALGLLAEKDSNYCLCRTPCNLTRYNKELSMVKI
 PSKTSAKYLEKKFNKSEKYISENVLVDIFFEALNYETIEQKKAYEVAALLGDIGGQMGLFIGASL
 LTILELFDYIELIKEKLLDLLGKEEEEGSHDENMSTCDTMPNHSETISHTVNVPLQTALGTLEE
 IACAAVSKGEELFTGVVPILVELDGDVNGHKFSVSGEGEGDATYGKLTCLKFICTTGKLPVPW
 PTLVTTFGYGLQCFARYPDHMKQHDFFKSAMPEGYVQERTIFFKDDGNYKTRAEVKFEGDT
 LVNRIELKGIDFREDGNILGHKLEYNYNSHNVIYIMADKQKNGIKVNFKIRHNIEDGSVQLADHY
 QQNTPIGDGPVLLPDNHYLSYQSALS KDPNEKRDMHVLLEFVTAAGITLGMDELYKFCYENEV
 ** (SEQ ID NO:31)

KEY:

Arch = underline

ASIC2a = *italic*

TS = **white-on-black**

ER = ***italic white-on-black***

eYFP = *italic underline*

p2A = double underline

FIG. 13G

Champ 2.0:

MDPIALQAGYDLLGDGRPETLWLIGIGTLLMLIGTFYFLVRGWGVTDKDAREYYAVTILV
PGIASAAYLSMFFGIGLTEVTVGGEMLDIYYARYADWLFTTPLLLLDLALLAKVDRVTIG
TLVGVDALMIVTGLIGALSHTAIARYSWWLFSTICMIVVLYFLATSLRSAAKERGP EVAS
TFNTLTALVLVLWTAYPILWIIGTEGAGVVGLGIETLLFMVLDVTAKVGFGFILLRSRAIL
GDTEAPEPSAGADVSAADKSRITSEGEYIPLDQIDINVGAPGSGATNFSLLKQAGDVEENP
MDLKESPSSEGLQPSSIQIFANTSTLHGIRHIFVYGPLTIRRVLWAVAFVGSGLLLVESSERSY
YFSYQHVTKVDEVVAQSLVFPVAVTLCNLNGFRFSRLTTNDLYHAGELLALLDVNLQIPDPHLA
DPTVLEALRQKANFKHYKPKQFSMLEFLHRVGHDLKDMMLYCKFKGQECGHQDFTTVFTK
YGKCYMFNSGEDGKPLLTVKGGTGNGLEIMLDIQQDEYLPWGETEETTFEAGVKVQIHSQS
EPPFIQELGFGVAPGFQTFVATQEQRLTYLPPPWGECRSSEMGLDFFPVYSITACRIDCETRYI
VENCNCRMVHMPGDAPFCTPEQHKECAEPALGLLAEKDSNYCLCRTPCNLTRYNKELSMVKI
PSKTSAKYLEKKFNKSEKYISENILVLDIFFEADNYETIEQKKAYEVAALLGDIGGQMGLFIGASL
LTILELFDYIYELIKEKLLDLLGKEEEEGSHDENMSTCDTMPNHSETISHTVNVPLQTALGTLEE
IACAAAKSRITSEGEYIPLDQIDINVVSKGEELFTGVVPILVELDGDVNGHKFSVSGEGEGDA
TYGKLTLFICTTGKLPVPWPTLVTTFGYGLOCFARYPDHMKOHDFFKSAMPEGYVOERTIF
FKDDGNYKTRAEVKFEGDTLVNRIELKGIDFREDGNILGHKLEYNYNSHNVYIMADKQKNGIK
VNFKIRHNIEDGSVQLADHYQONTPIGDGPVLLPDNHYSYQSALSKDPNEKRDHMLLEFVT
AAGITLGMDELYKFCYENEV** (SEQ ID NO:32)

KEY: _____

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ER = ***italic white-on-black***

eYFP = *italic underline*

p2A = double underline

FIG. 13H

Champ 3.0

MDPIALQAGYDLLGDGRPETLWLGIGTLLMLIGTFYFLVRGWGVTDKDAREYYAVTILV
PGIASAAYLSMFFGIGLTEVTVGGEMLDIYYARYADWLFTTPLLLLDLALLAKVDRVTIG
TLVGVDALMIVTGLIGALSHTAIARYSWWLFSTICMIVVLYFLATSLRSAAKERGPEVAS
TFNTLTALVLVLTAYPILWIIGTEGAGVVGLGIETLLFMVLDVTAKVGFGFILLRSRAIL
GDTEAPEPSAGADVSAADKSRITSEGEYIPLDQIDINVGAPMDLKESPSEGSLQPSSIQIFAN
TSTLHGIRHIFVYGPLTIRRVLWAVAFVGSLGLLVESSERVSYFSYQHVTKVDEVVAQSLVFPA
VTLCNLNGFRFSRLTTNDLYHAGELLALLDVNLQIPDPHLADPTVLEALRQKANFKHYKPKQF
SMLEFLHRVGHDLKDMMLYCKFKGQECGHQDFTTVFTKYGKCYMFNSGEDGKPLLTTVKG
GTGNGLEIMLDIQQDEYLPIWGETEETTFEAGVKVQIHSQSEPPFIQELGFGVAPGFQTFVAT
QEQRLTYLPPPWGECRSSEMGLDFFPVYSITACRIDCETRYIVENCNCRMVHMPGDAPFCTPE
QHKECAEPALGLLAEKDSNYCLCRTPCNLTRYNKELSMVKIPSKTSAKYLEKKFNKSEKYISENI
LVLDIFFEALNYETIEQKKAYEVAALLGDIGGQMGLFIGASLLTILELFDYIYELIKEKLLDLLGK
EEEEGSHDENMSTCDTMPNHSETISHTVNVPLQTALGTLEEIACAAAKSRITSEGEYIPLDQI
DINVVSKGEELFTGVVPILVELDGDVNGHKFSVSGEGEGDATYGKLTLKFICTTGKLPVPWPT
LVTTFGYGLQCFARYPDHMKOHDFFKSAMPEGYVOERTIFFKDDGNYKTRAEVKFEGDTLV
NRIELKGIDFREDGNILGHKLEYNYNSHNVYIMADKOKNGIKVNFKIRHNIEDGSVOLADHYO
QNTPIGDGPVLLPDNHLYSYQSALSKDPNEKRDHMLLEFVTAAGITLGMDELYKFCYENEV*
(SEQ ID NO:33)

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ER = ***white-on-black***

eYFP = *italic underline*

p2A = double underline

FIG. 13I

Champ 4.0:

<u>MDPIALQAGYDLLGDGRPETLWL</u> <u>GIGTLLML</u> <u>LIGTFYFLVRGWGVTDKDAREYYAVTILV</u>	
<u>PGIASAAYLSMFFGIGLTEVT</u> <u>VGGEMLDIYY</u> <u>ARYADWLFTTPLLLDLALLAKVDRV</u> <u>TIG</u>	
<u>TLVGVDALMIVTGLIGALSHTAI</u> <u>ARYSWW</u> <u>L</u> <u>FSTICMIVVLYFLATSLRSAAKERGPEVAS</u>	
<u>TFNTLTALVVLWTA</u> <u>YPILWIIGTEGAGVV</u> <u>GLGIETLLFMVLDVTAKVGFGFILLRSRAIL</u>	
<u>GDTEAPEPSAGADVSAAD</u> <u>KS</u> <u>RITSEGEYIPLDQIDINV</u> <u>GAPGSGATNFSLLKQAGDVEENP</u>	
<u>GPMDLKESPSEGS</u> <u>LQPSSIQIFANTSTLHGIRH</u> <u>IFVYGPLTIRRVLWAVAFVGS</u> <u>LGLLLVESSERV</u>	
<u>SYFYSYQHVT</u> <u>KVDEVVAQSLVFP</u> <u>AVTLCNLNGFRFSRLTTNDLYHAGELLALLDVNLQIPD</u> <u>PHL</u>	
<u>ADPTVLEALRQKANFKHYKPKQ</u> <u>FSMLEFLHRVGHDLKDMMLYCKFKGQECGHQDFTTVFT</u>	
<u>KYGKCYMFNSGEDGKPLLTTV</u> <u>KGGTGNGLE</u> <u>MLDIQQDEYLPIWGETEETTFEAGVKVQIHS</u>	
<u>QSEPPFIQELGFGVAPGFQTF</u> <u>VATQEQR</u> <u>LTYP</u> <u>PPWGECSRSEMGLDFFPVYSITACRIDCETR</u>	
<u>YIVENCNCRMVHMPGDAPFCT</u> <u>PEQHKECAEPALG</u> <u>LLAEKDSNYCLCRTPCNLTRYNKELSMV</u>	
<u>KIPSKTSAKYLEKKFNKSEKYISE</u> <u>NILVLDIFFEALNYETIEQKKAYEVAALLGDIGGQMGLFIGA</u>	
<u>SLLTILELFDYIYELIKEKLLD</u> <u>LLGKEEEEGSHDENMSTCDTMPNHSETISHTVNVPLQTALGTL</u>	
<u>EEIACAAAKS</u> <u>RITSEGEYIPLDQIDINV</u> <u>VSKGEELFTGVVPILVELDGDVNGHKFSVS</u> <u>GEGEG</u>	
<u>DATYGKLT</u> <u>LKFICTTGKLPVPWPTLV</u> <u>TTFGYGLQCFARYPDHMKQHDF</u> <u>FKSAMPEGYVQERT</u>	
<u>IFFKDDGNYKTRAEVKFEGD</u> <u>TLVNRIELKGIDFREDGNILGHKLEYNYN</u> <u>SHNVYIMADKQKNG</u>	
<u>IKVNFKIRHNIEDGSVOLADHYQ</u> <u>ONTPIGDGPVLLPDNHLYSYQSALS</u> <u>KDPNEKRDHMLLEF</u>	
<u>VTAAGITLGMDELYK</u> <u>FCYENEV</u> * (SEQ ID NO:34)	

KEY:

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TS = **white-on-black**

ER = ***italic white-on-black***

eYFP = *italic underline*

p2A = double underline

FIG. 13J

Amino acid Sequence of *Coccomyxa subellipsoidea* (*Chlorella vulgaris*) C-169 Rhodopsin

MAVHQIGEGGLVMYWVTFGLMAFSALAF	AVMTFTRPLNKRSHGYITLAIVTIAA	IYYAMAAS
GGKALVSNPDGNLRDIYYARYIDWFF	TTPLLLDIILLTGIPIGVTLWIVLADV	AMIMLGLFGALS
TNSYRWGYYGVS	CAFFVVLWGLFFPGAKGARARGGQV	PGLYFGLAGYLALLWFGYPIVWGL
AEGSDYISVTAEAA	SYAGLDIAAKVVFGWAVMLSHPLIARN	QTDGSLLINSTNDPFVASTTHIPE
RQGGIFGGLMGKKRGAGT	PLATNEGVP	PKAAPTAAATTAGNPATAAEVRTPRELMARL (SEQ ID NO:62)

FIG. 13K

ASIC

1 mdlkespseg slqpssiqif antstlhgir hifvygplti rrvlwavafv gslgl llves
61 servsyysy qhvtkvdevv aqslvfpavt lcnlngfrfs rlttndlyha gellalldvn
121 lqipdphlad ptvlealrqk anfkhykpkq fsmleflhrv ghdlkdmnly ckfkqgecgh
181 qdfttvftky gkcymfnsge dgkpllttvk ggtnggleim ldiqqdeylyp iwgeteettf
241 eagvkvqihs qseppfiqel gfgvapgfft fvatqeqlt ylpwpwgecr ssemgl dffp
301 vysitacrid cetryivenc ncrmvhmpgd apfctpeqh ecaepalgll aekdsnyc lc
361 rtpcnltryn kelsmvkips ktsakylekk fnksekyise nilvldiffe alnyetieqk
421 kayevaallg digggmg lfi gaslltiel fdyiyelike klldllgkee eegshdenms
481 tcdtmpnhse tishtvnpvl qtalgtleei ac (SEQ ID NO:19)

Helicobacter pylori potassium channel

1 mfe klkffki kddedqpev nlnseyeqf kvfrlplili qlvl lgtlg yfale nyslm
61 qaffqttytm tatfgalne sqfgpisifl tsilmfcgtg iiafsvailv svvnkg tltr
121 likekgmiyk iarlkdhvyi cyhneytiel skqfrsaqip fvvvdndpsf eeeai khkyp
181 yyiigdphtn lamlkthlss argvvalski lpvnvalmvs vrlfekelkr kpyyiasah
241 sdegleklkk lgadmvspt klmaqrvsam avrpdmenil erfinkkdtl ldleevi vpk
301 tswlvlrklk eahfreiaka fvigitqkdg kyipmpdget iiasesklm vgtsegvatc
361 kqlitshqkp kevdylsl (SEQ ID NO:20)

FIG. 14A

Sodium-calcium exchanger SLC24

GenBank NP_065077

Homo sapiens

1 mdlqqsttit slekwcldes lsgcrrhysv kkkklirvl glfmglvais tvfsisafs

61 etdtqstgea svvsgprvaq gyhqrtdlldl ndkildytpq pplskegese nstdhaqgdy

121 pkdifsleer rkgaiilhvi gmiymfiala ivcdeffvps ltviteklgi sddvagatfm

181 aaggsapelf tsligvfiah snvgigtivg savfnilfvi gmcalfsrei lnltwvplfr

241 dvsfyivdli mliiffldnv imwveslllll tayfcyvvmf kfnvqvekvw kqminrnkvv

301 kvtapeaqak psardkdep tlpakprlqr ggssaslhns lmrnsifqlm ihtldplae

361 lgsyggklky dtmteegrfr ekasilhkia kkkchvdene rqngaanhve kielpnstst

421 dvemtpssda sepvqngnls hniegaeaqt adeeedqpls lawpsetrkq vtflivfpiv

481 fplwitlpdv rkpssrkffp itffgsitwi avfsylmvww ahqvgetigi seeimglti

541 aagtsipdli tsvivarkgl gdmavsssvg snifdittvgl plpwlllytvi hrfaqpvavss

601 nglfcaivll fimllfvils ialckwrmnk ilgfmfgly fvflvvsvll edrlt

661 1 (SEQ ID NO:21) cpvs

FIG. 14B

Sodium-calcium exchanger SCL8A3

GenBank CAC40984

Homo sapiens

1	mawlr1qplt	saf1hf9lvt	fvlflnglra	eaggsgdvps	tgqnnescsg	ssdckegvil
61	piwypenpsl	gdkiarvivy	fvaliymflg	vsiiadrfma	sievitsqer	evtikkpnge
121	tstttirvwn	etvsnltlma	lgssapeill	slievchgfh	iagdlgpsti	vgsaafnmfi
181	iigicvyvip	dgetrkikh1	rvffitaaws	ifayiwlymi	lavfspgvvq	vwegllt1ff
241	fpvcvllawv	adkrllfyky	mhkkyrtldkh	rgi1ietegd	hpkgiemdgk	mmnshfldgn
301	lvplegkevd	esrremiril	kdlkqkhppek	dldqlveman	yyalshqqks	rafyriqatr
361	mmtgagnilk	khaaeqakka	ssmsevh1tde	pedfiskvff	dpcsyqc1en	cgavlltvvr
421	kggdmsktmy	vdyktedgsa	nagadyefte	gtvvlkpget	qkefsvgiid	ddifeedehf
481	fvrlsnvrie	eeqpee9mpp	aifnslplpr	avlaspcvat	vt1lddd1ag	iftfecdtih
541	vsesigvmev	kv1rtsgarg	tvivpf1tve	gtakgggedf	edtygelef1k	ndetvktihi
601	kviddeayek	nknyfiemm9	prmvdm\$fqk	alllspdrkl	tmeeeeakri	aemgkpv1ge
661	hpkleviiee	syefkttvd1k	likktn1alv	vgthswrdqf	meaitvsaag	dededesgee
721	rlpscfdyvm	hfltvfwkv1	facvppte1yc	hgwacfavsi	liigmltaii	gd1ashfgct
781	iglkdsvtav	vfvaft9tsvp	dtfaskaaal	qdv1yadasig	nvtgsnavnv	flg1glawsv
841	aaiywalq9q	efhvsagtla	fsvtlftifa	fvcisvll1yr	rrphlggelg	gprgcklatt
901	wlfvslwll1y	ilfatleayc	yikgf	(SEQ ID NO:22)		

FIG. 14C

Sodium-hydrogen exchanger (NhaA)
GenBank ZP_16216900
Moraxella catarrhalis

1 mfaqfkrfle leaaggivla aaallamia nspldemyha fihapvvvqi gtfqiakdah
61 hwindglmai ffflvglelk realigelsd vkqilmpala avggmimpal iyaaafnqsnp
121 eqlagwaipa atdiafalgv lsllgnrvpn alkvlvsia ifddlgaivi ialfytsdls
181 lsslavagvc fpflfilnkm nvvrtpyll iglvmwaaf1 ksgvhatlag vllaaffiplr
241 nksdpehspl eeledlhnt vafgvlp1fa fanagiglag tgidsllhsv plgiaag1fi
301 gkqigvmtav flclklglas lpkgttikql ygvsl1cgig ftmsl1fisgl afgntpkdfd
361 prlgiilgsi isgvigymil rgnipnadh1p vlakdtgegf iptqhdaqa (SEQ ID NO:23)

KVLQT1 (KCNQ1)
GenBank AAC51776
Homo sapiens

1 maaassppra erkrgwgrl pgarrgsagl akkcpfslel aeggpaggal yapiapgagp
61 pappaspaap aappvasdlg prppvsldpr vsiystrrpv larthvqgrv ynflerptgw
121 kcfvyhfavf livlvclifs vlstieqyaa latgt1fwme ivlvvffgte yvvr1wsagc
181 rskyvglwgr lrfarkpisi idlivvvasm v1cvgskgq vfatsairgi rflqilrmlh
241 vdrqgggtwrl lgsvvfihrq elit1lyigf lg1ifssyfv ylaekdavne sgrvefgsya
301 dalwwgvvtv ttigygd1kvp qtwvgktias cfsvfaisff alpagilgsg falkvqqkqr
361 qkhfnrqipa aasliqtawr cyaaenpdss twkiyirkap rsh1tllspsp kpksv1v1kk
421 kkfkldkdng vtpgekm1tv phitcdppee rrldhfsvdg ydssvrkspt 1levsmp1hf1m
481 rtnsf1aedld leget1ltpi thisqlrehh ratikvirrm qyfvakkkfq qar1kpydvrd
541 vieqysqghl nlmvrikelq rrldqsigkp slfisvseks kdr1gsntiga rlnrvedkvt
601 qldqrlalit dmlhqlslsh ggstpgsggp preggahitq pcgsggsvdp elf1psnt1lp
661 tyeqltvpr1r gpdeg1s (SEQ ID NO:24)

FIG. 14D

HERG (KCNH2)
GenBank AAA62473
Homo sapiens

1	mpvrrghvap	qntfldtiir	kfegqsrkfi	ianarvenca	viycndgfce	lcygsraevm
61	grpctcdfllh	gprtqrraaa	qiaqallgae	erkveiafyr	kdgscflclv	dvvpvknedg
121	avimfilnfe	vvmekdmvgs	pahdtnhrgp	ptswlapgra	ktfrlklpal	laltaressv
181	rsggaggaga	pgavvvvdvdl	tpaapssesl	aldevtamdn	hvaglgpaee	rralvgpgsp
241	prsapgqlps	prahslnpda	sgsscsliart	rsrescasvr	rassaddiea	mragslppppp
301	rhastgamhp	lrsgllnsts	dsdlvryrti	skipqitlnf	vdllkgdpfla	sptsdreilia
361	pkikerthnv	tekvtqvlsl	gadvlpeykl	qaprihrwti	lhyspfkavw	dwlilllviiy
421	tavftpysaa	fllketeeegp	patecgvacq	plavvdlivd	imfivdiln	frttyvnane
481	evvshpgria	vhyfkqwfli	dmvaaipfdl	lifgsgseel	igllktarl	rlvrvarkl
541	ryseygaavl	fllmctfali	ahwlaciwya	ignmeqphmd	srigwlhnl	g
601	glgppsikdk	yvtalyftfs	sltsvgtgnv	spntnsekif	sicvmligs	myasifgnvs
661	aiiqrlysgt	aryhtqmlrv	refirfhqip	nplqrleey	fqhawsytng	idmnavlkgf
721	peclqadicl	hlnrslqhc	kpfrgatkgc	lralamkft	thappgdtlv	hagdlltaly
781	fisrgsieil	rgdvvvailg	kndifgepln	lyarpgksng	dvraltycdl	hkihrddlle
841	vldmypefsd	hfwssleitf	nldrtnnpg	spgstelegg	fsrqrkrkls	frrtdkdte
901	qpgevsalgp	gragagpssr	grpaggpwges	pssgpsspes	sedegpgrss	splrlvpfss
961	prppgeppgg	eplmedceks	sdtcnplsga	fsgvsnifsf	wgdsrgrqyq	elprcpaptp
1021	sllniplssp	grprgrdves	rldalqrqln	rletrlsadm	atvlqlqrq	mtlvppaysa
1081	vttpgpgpts	tspllpvspl	ptltldslsq	vsqfmaceel	ppgapelpqe	gprrlslpg
1141	qlgaltsqpl	hrhgsdpgs	(SEQ ID NO:25)			

FIG. 14E

KCNJ2/Kir2.1
Homo sapiens
GenBank NP_000882

1 mgsvrtnrys ivsseedgmklatmavangfgngkskvhtrqqcrsrfvkkdghcnvqfin
61 vgekqqryla dfftctvdirwrwmlvlfclafvlswlffgcvfwliallhglddaskegk
121 acvsevnst aafsfstetqttigygrcvtdecpiavfmvfvqsivgciidafiigavm
181 akmakpkkrnetlvfshnaviamrdgklclmwrvgnlrkshlveahvraqllksritseg
241 eyipldqidi nvgsdgidriflvspitvheidedsplydlskqidna dfeivvileg
301 mveatamtq crssylaneilwghryepvlfeekhykvdysrfhktyev pntplcsard
361 laekkyilsn ansfcyenevaltskeedds engvpestst dtpddidlnqasvpleprp
421 lrresei (SEQ ID NO:26)

FIG. 14F

GenBank AAH35294
SLC34A1 sodium-phosphate co-transporter
Homo sapiens

1 mlsygerlgs pavsplpvrghvmrgtafayvpspqvlhr ipgtsayaftp slgpvalaeh
61 tcpcgevrler heplpaklal eeeqkesrlypklrqagamllkvpmltflylfvcsldm
121 lssafqlagg kvagdifkdn ailsnpvagl vvgilvtvlv qssststsiivsmvssglle
181 vssaipling snigtsvtnt ivalmqagdr tdfrr (SEQ ID NO:27)

FIG. 14G

GenBank AAL32454
Sodium-potassium-chloride cotransporter
Homo sapiens

1 vivlglyiyv tykkpdrvng sstqaltyln alqhsirlsg vedhvkfrp qclvmtgapn
61 srpallhlvh dftknvglmi cghvhmgprp gamkemsidq akyqrwlkn kmkafyapvh
121 addlregaqy lmqaaglgm kpntlvlgfk kdwlqadmrd vdmyinlfhd afdiqygvvv
181 irlkegl dis hlqqqeells sqekspgtdk vvsvveyskk sldtskpls ekpithkesk
241 gpivplnvad qllleastqf qkkqgkntid vwlfdgggl tllipylltt kkkwdckir
301 vfiggkinri d (SEQ ID NO:28)

FIG. 14H

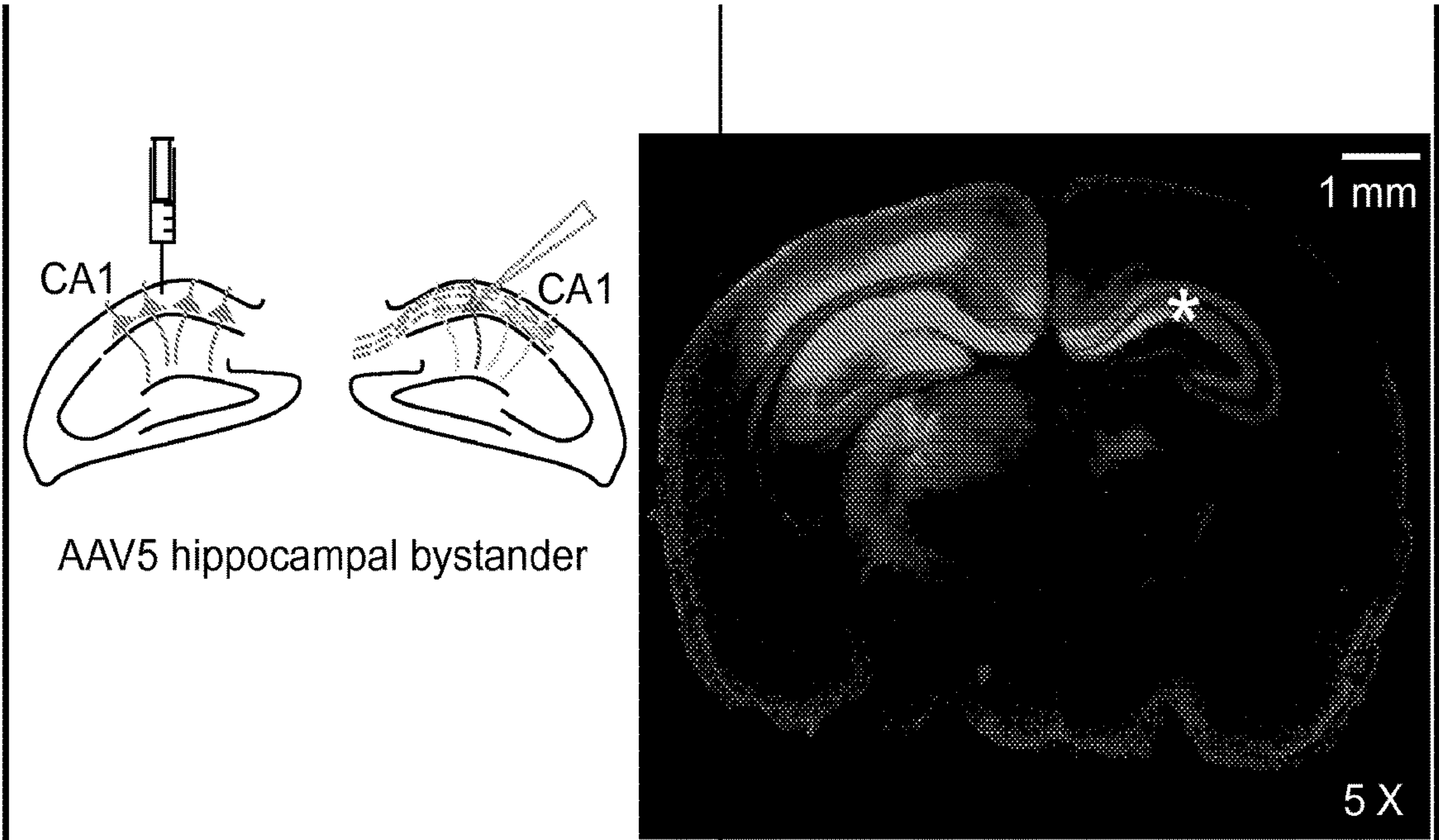


FIG. 15A

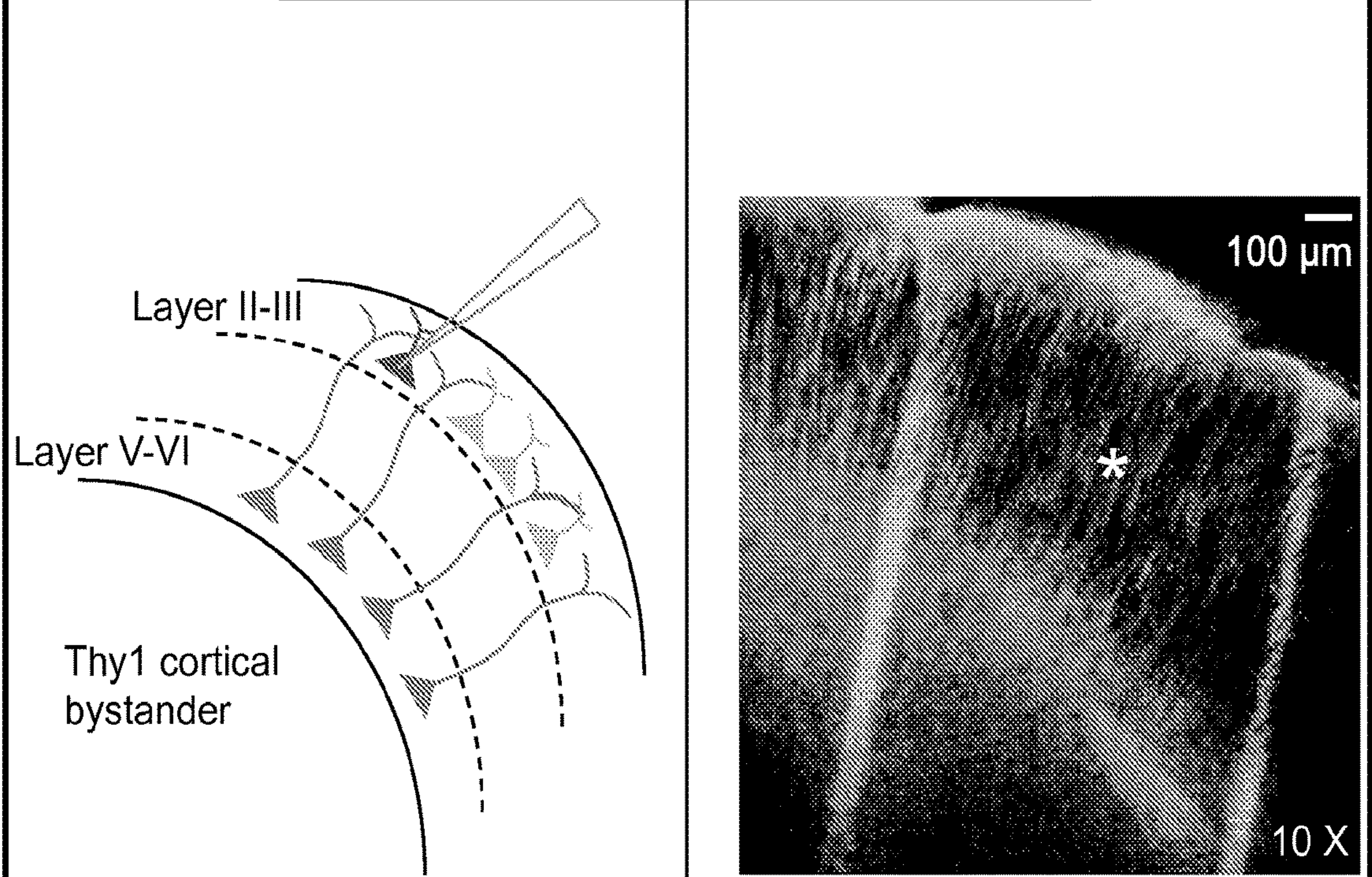


FIG. 15B

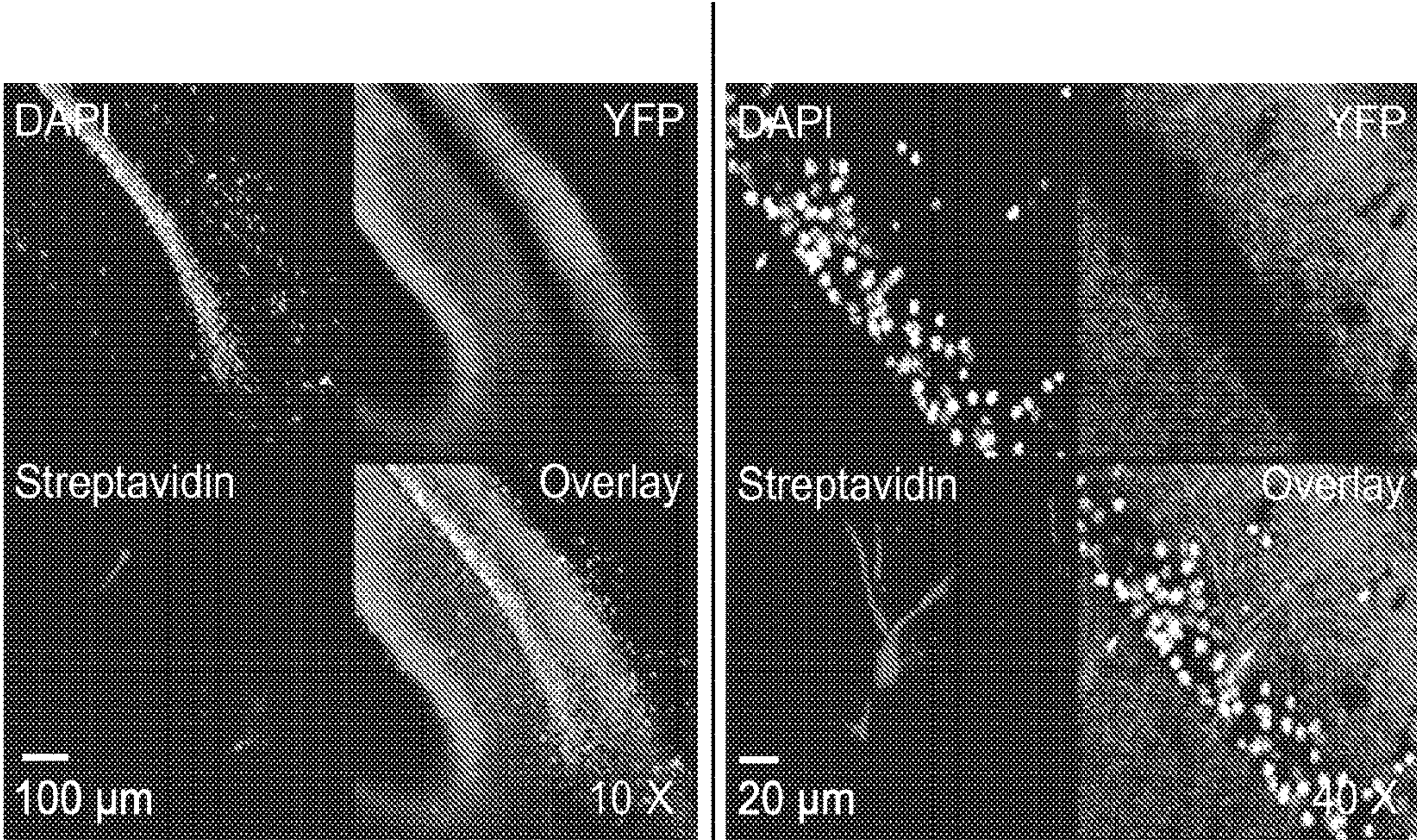


FIG. 15C

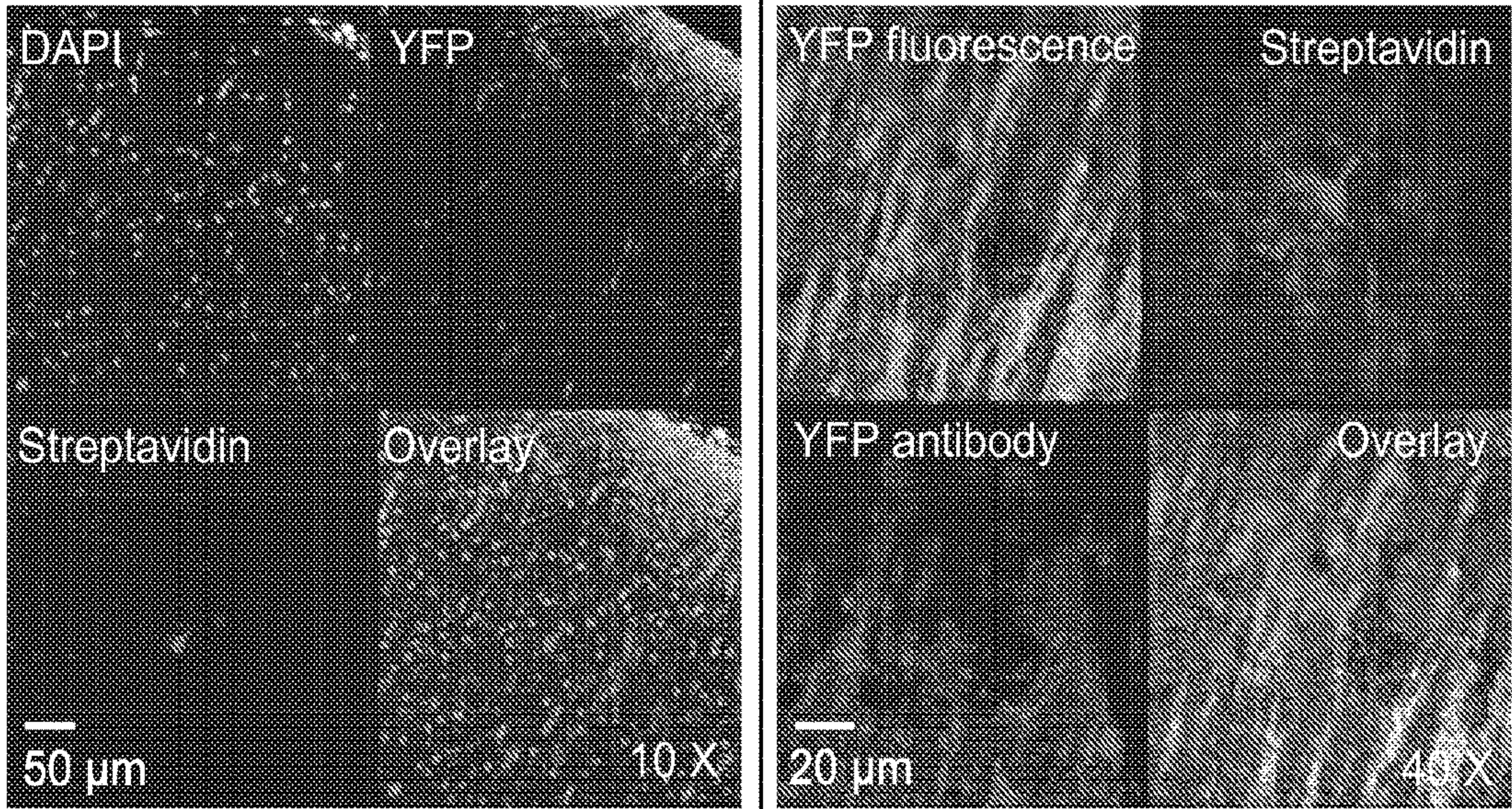


FIG. 15D

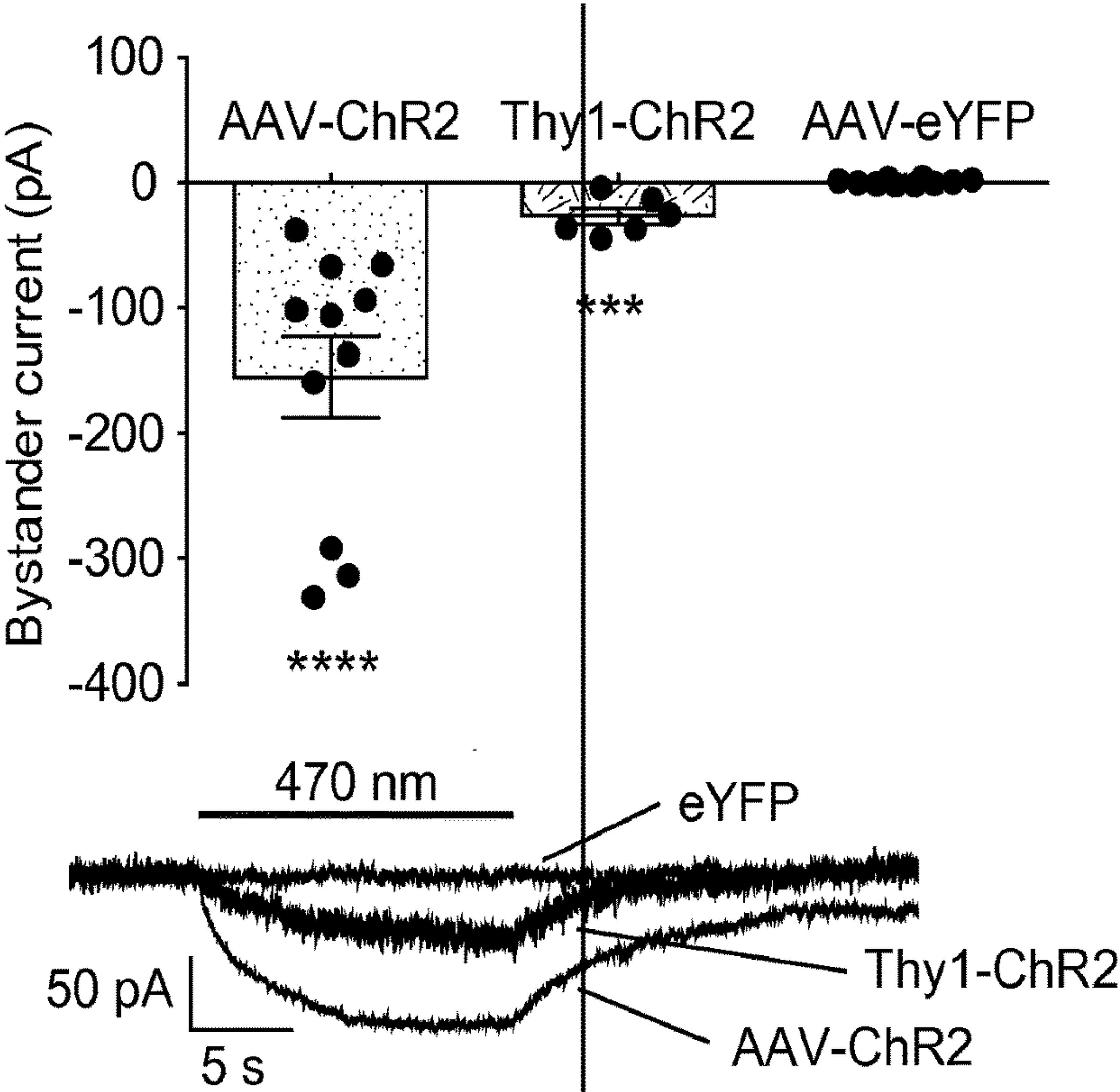


FIG. 15E

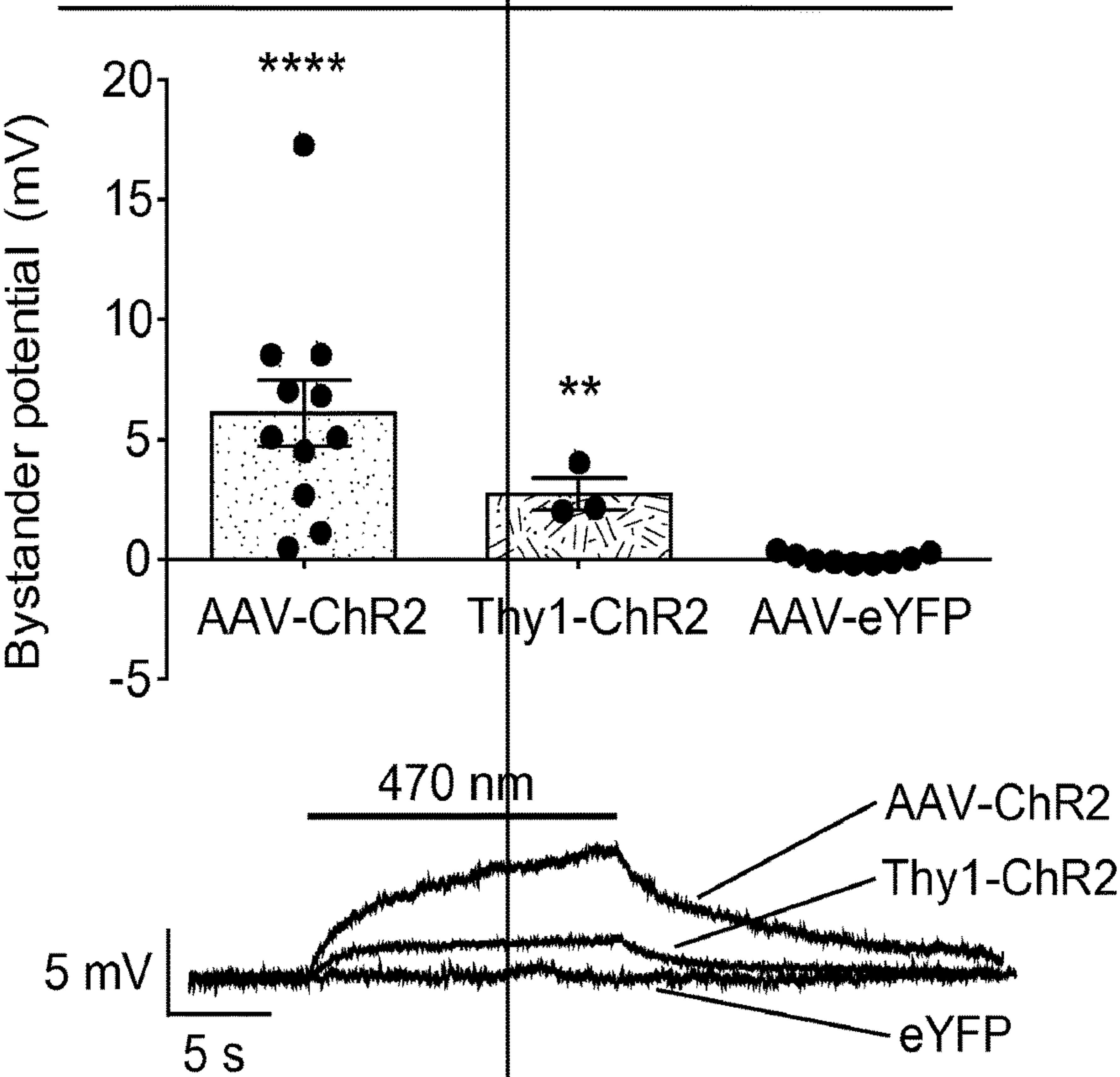


FIG. 15F

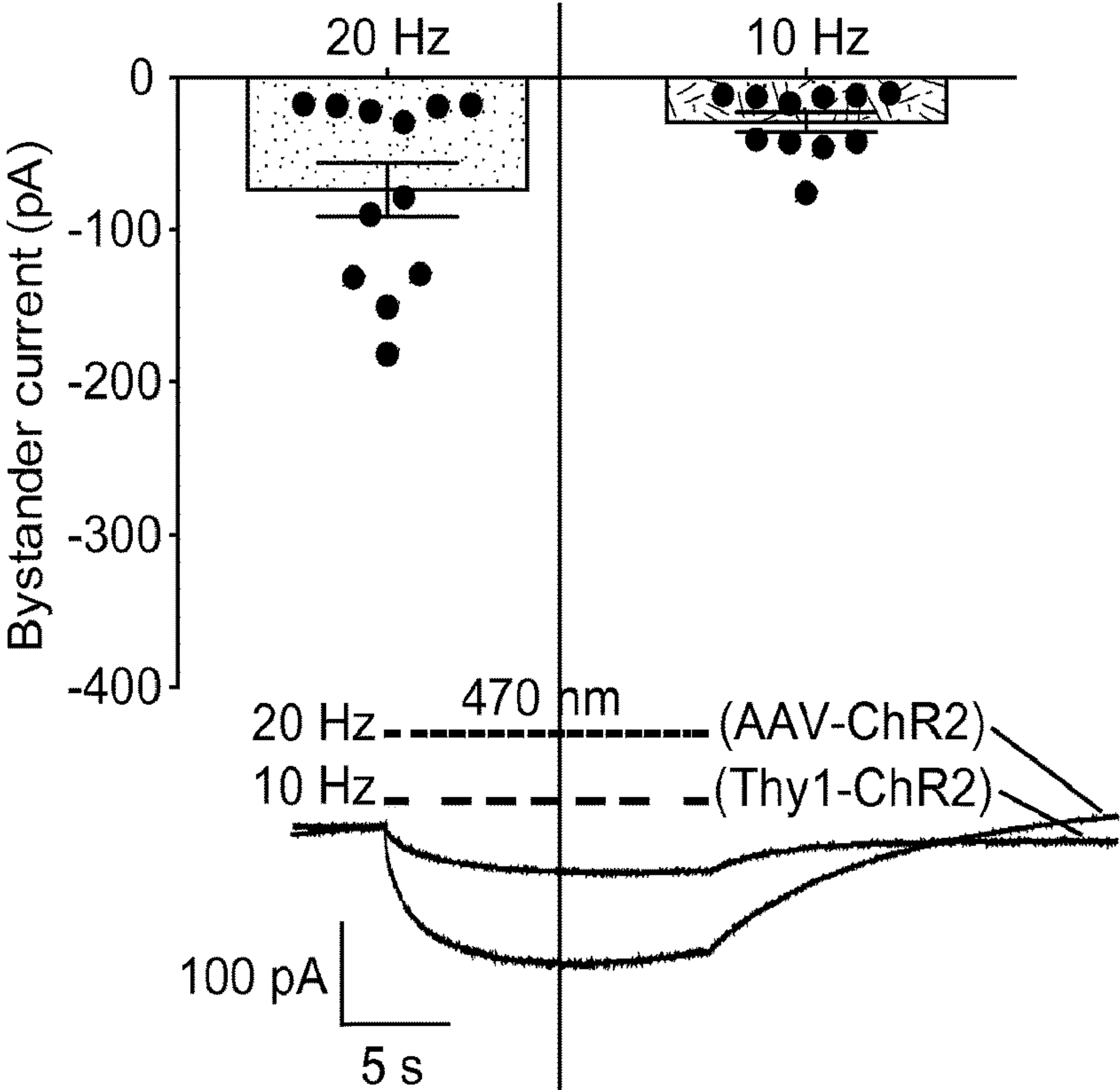


FIG. 15G

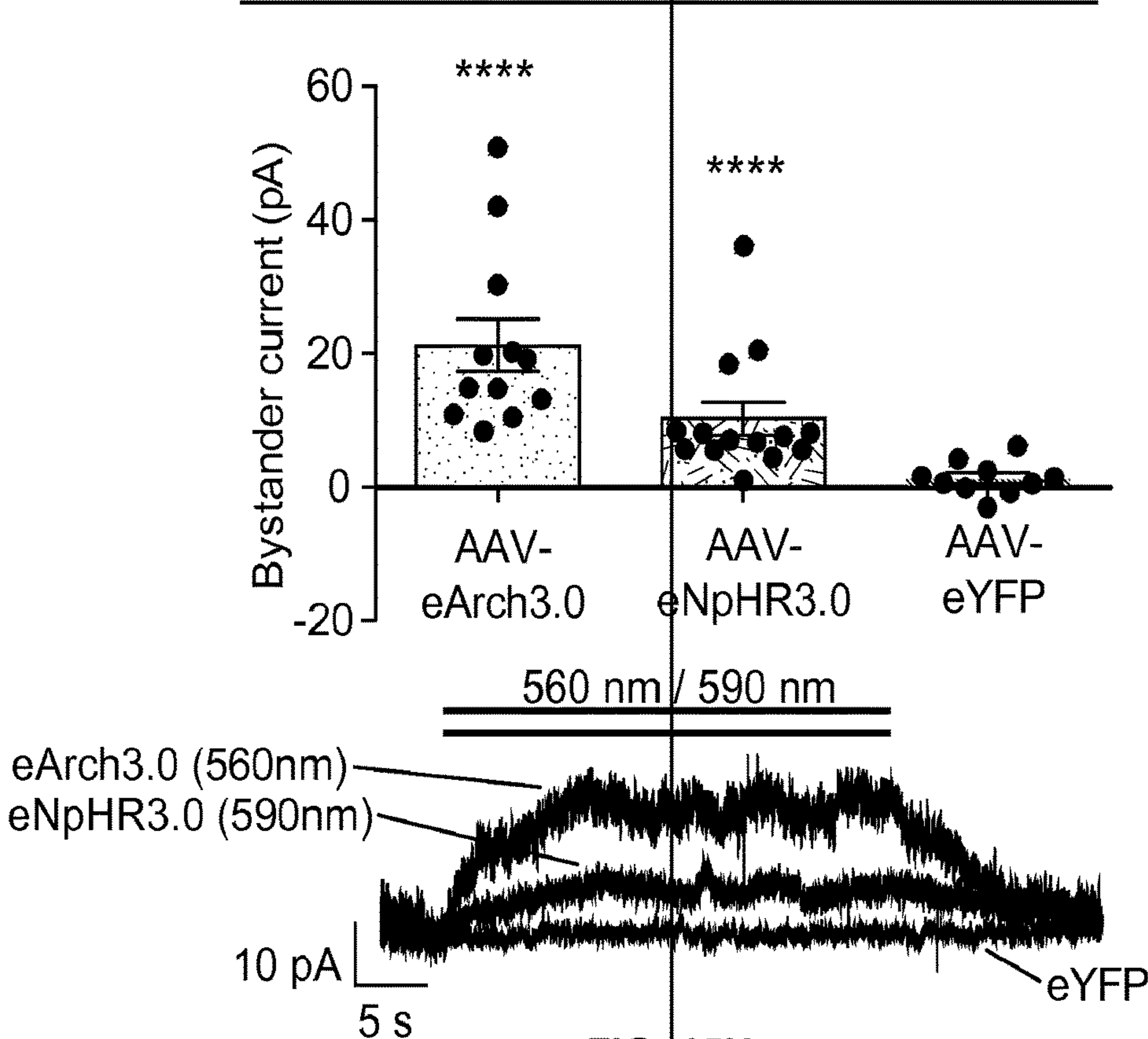


FIG. 15H

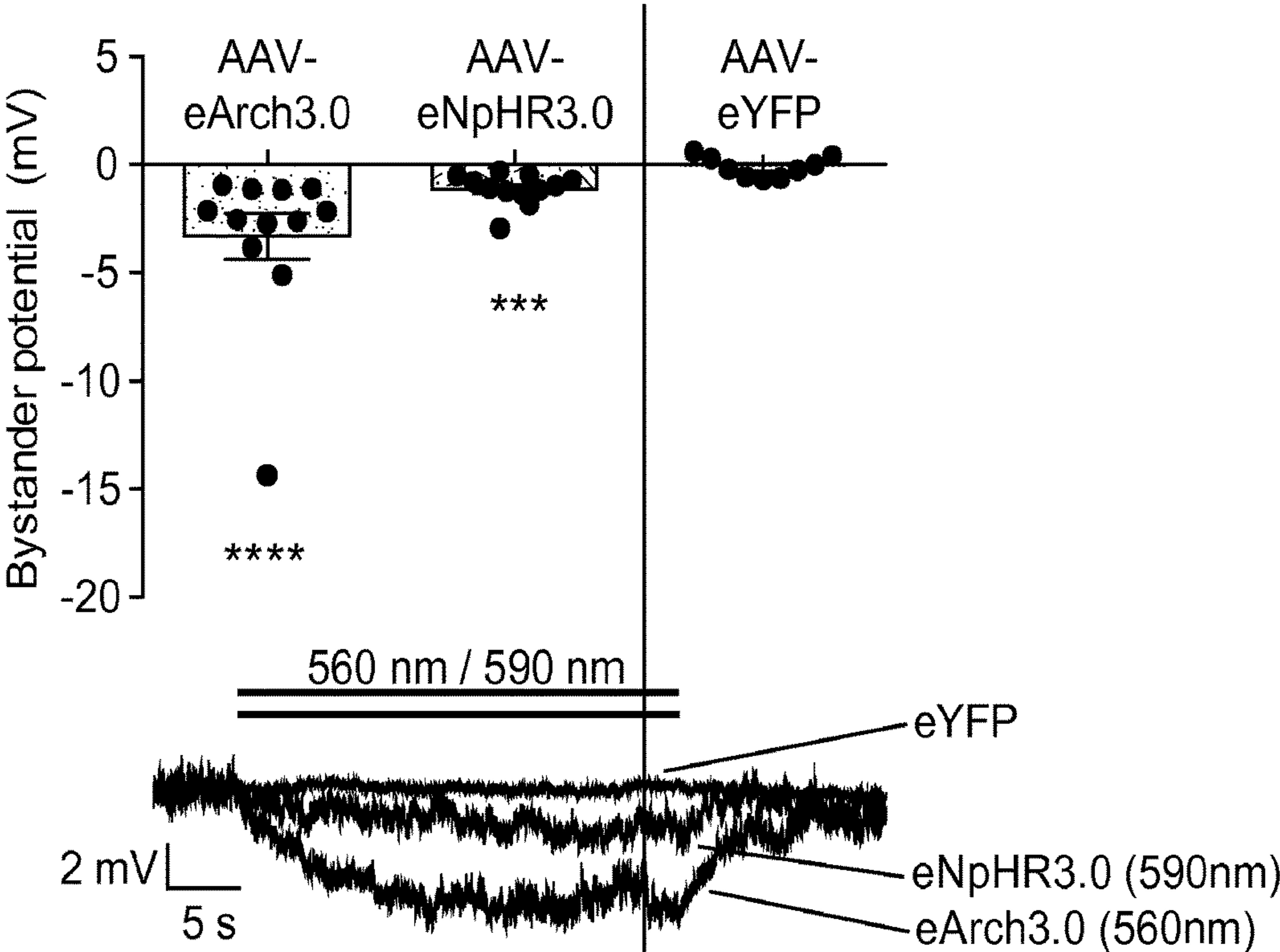


FIG. 15I

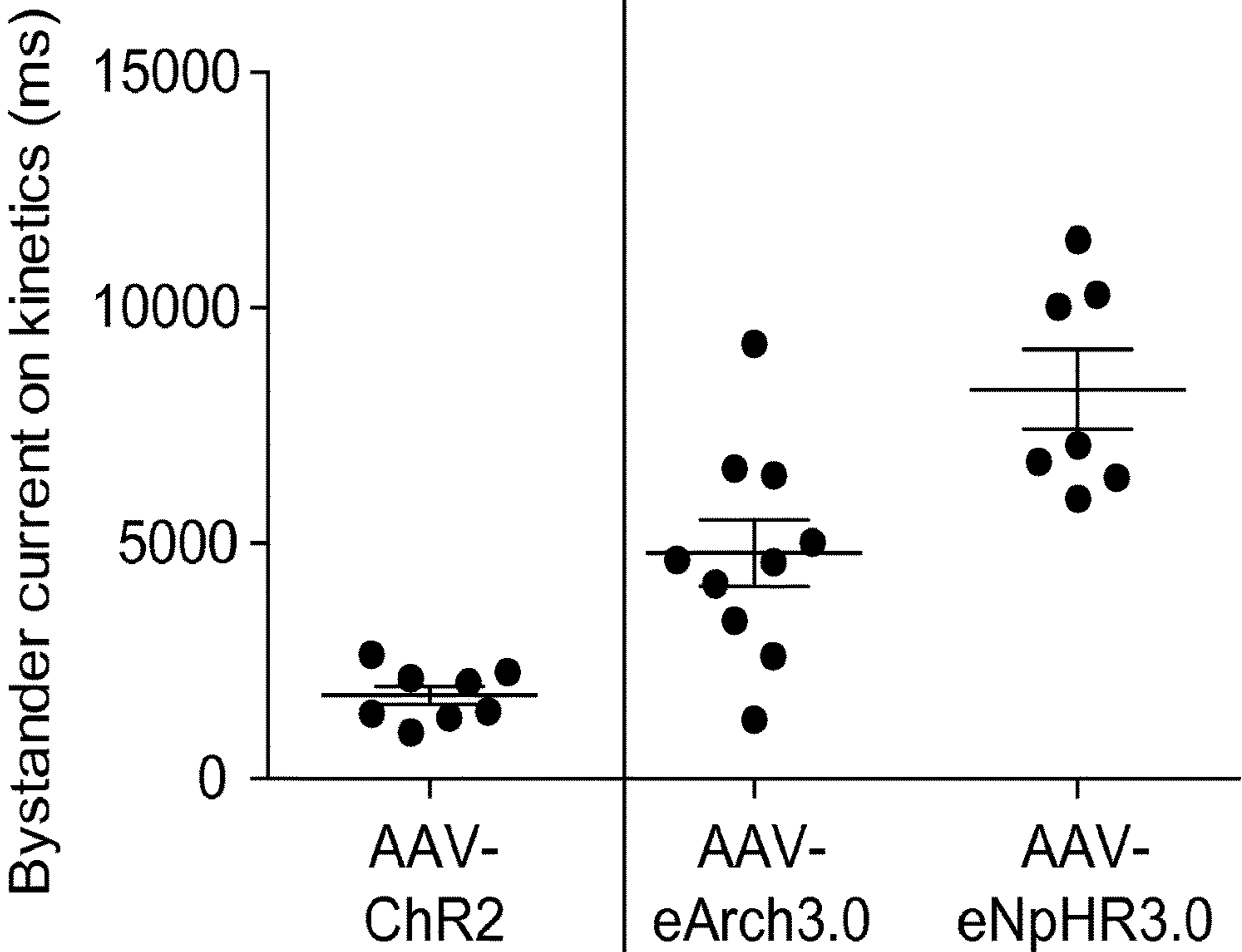


FIG. 15J

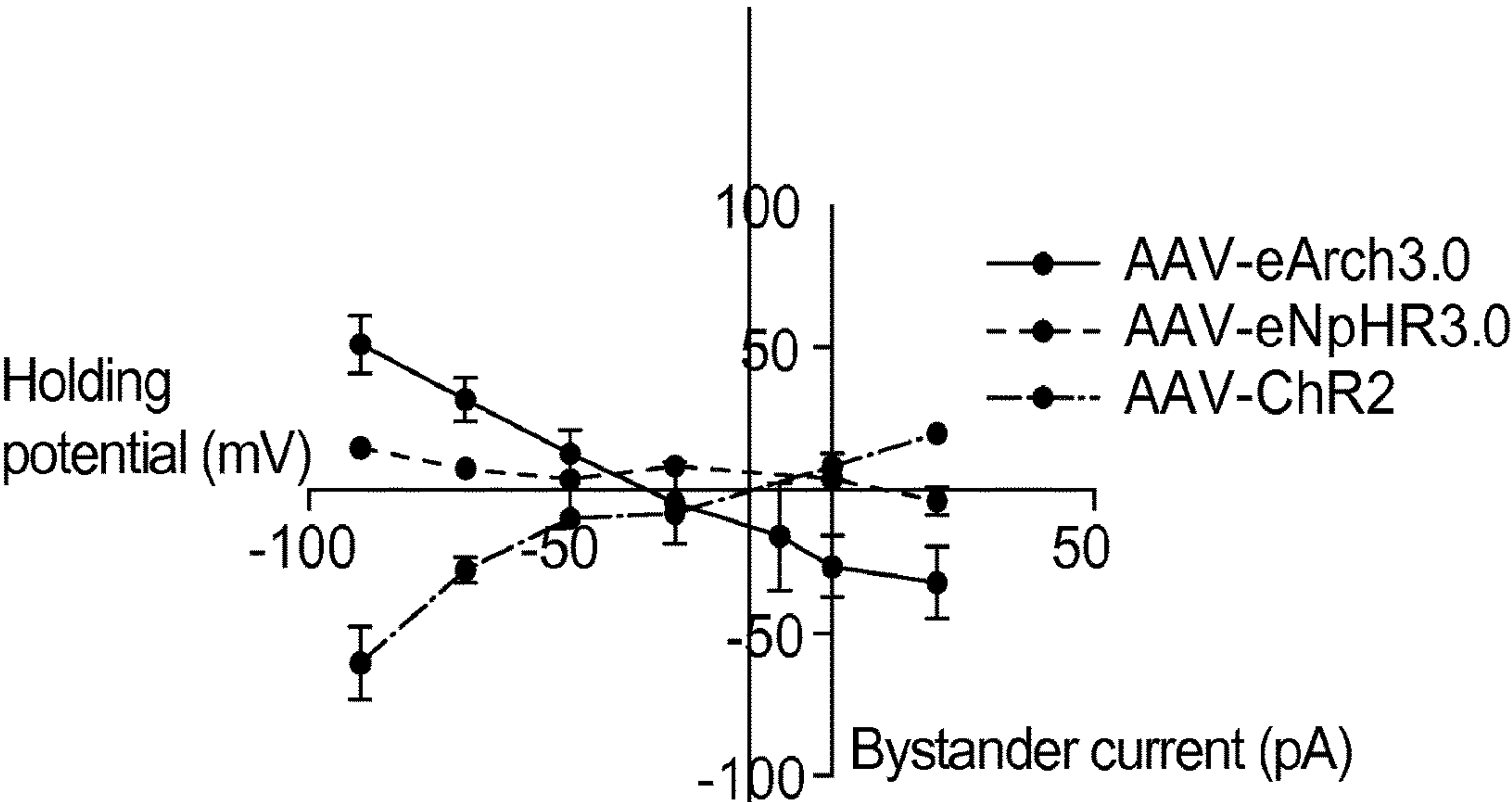


FIG. 15K

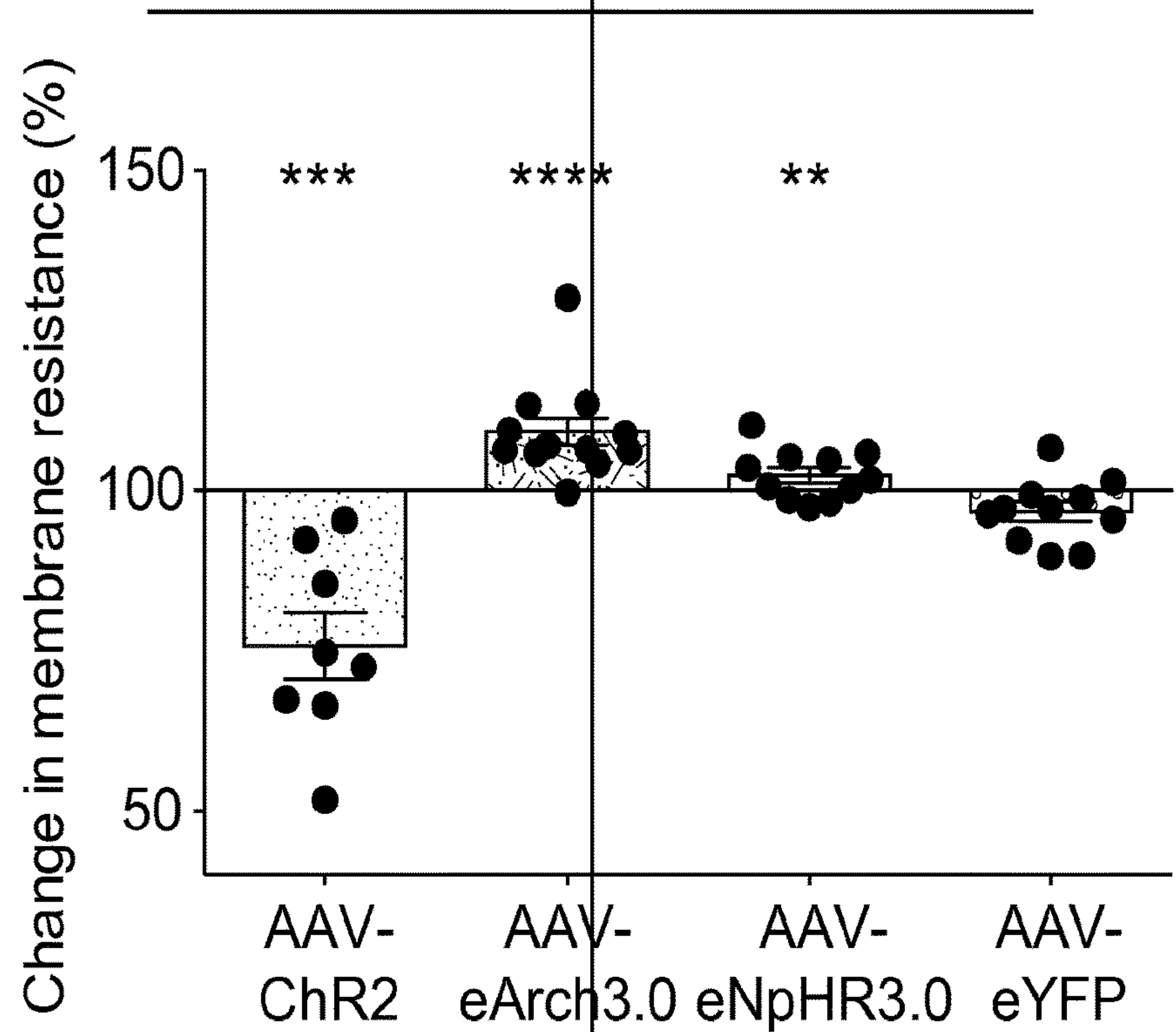


FIG. 15L

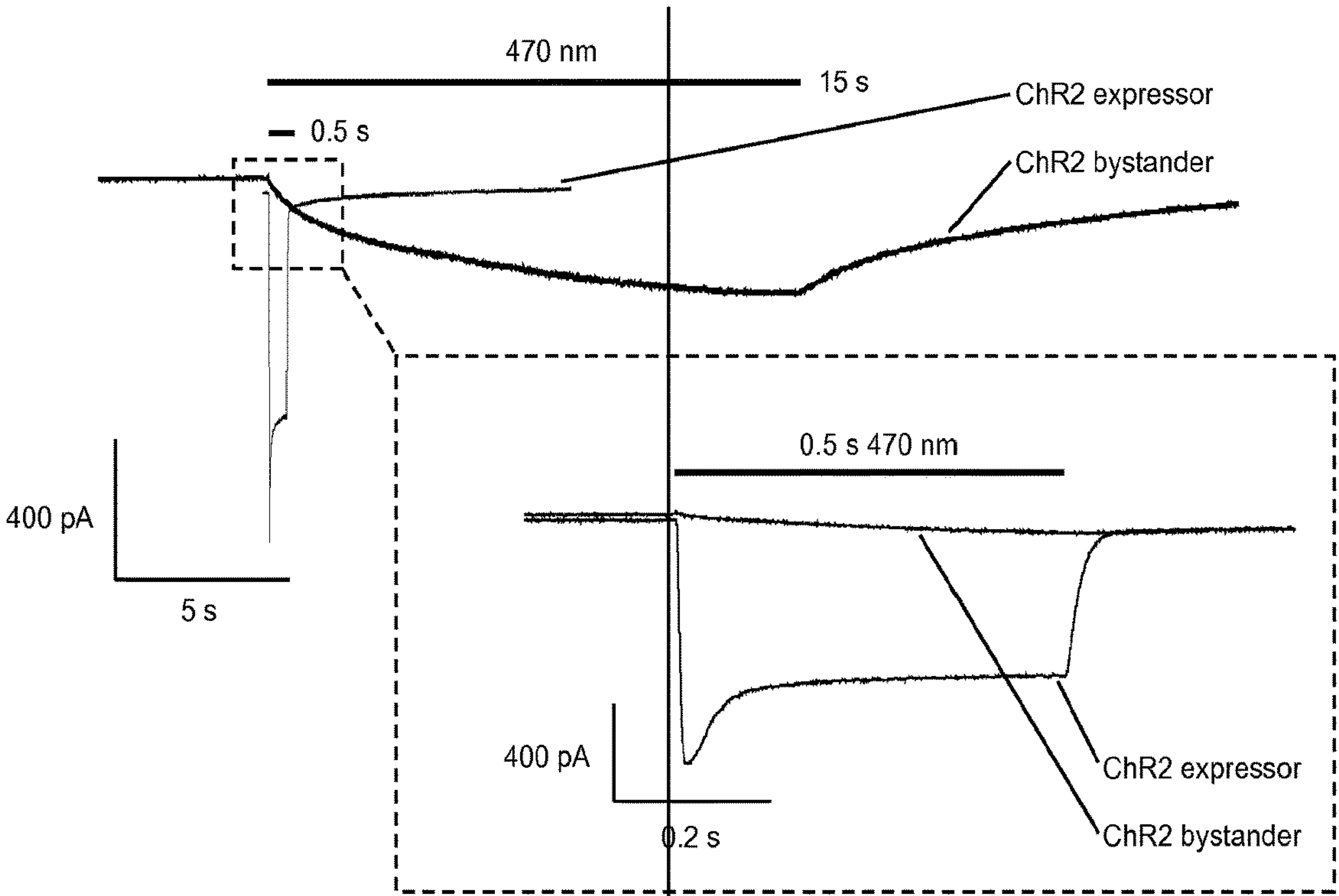


FIG. 16

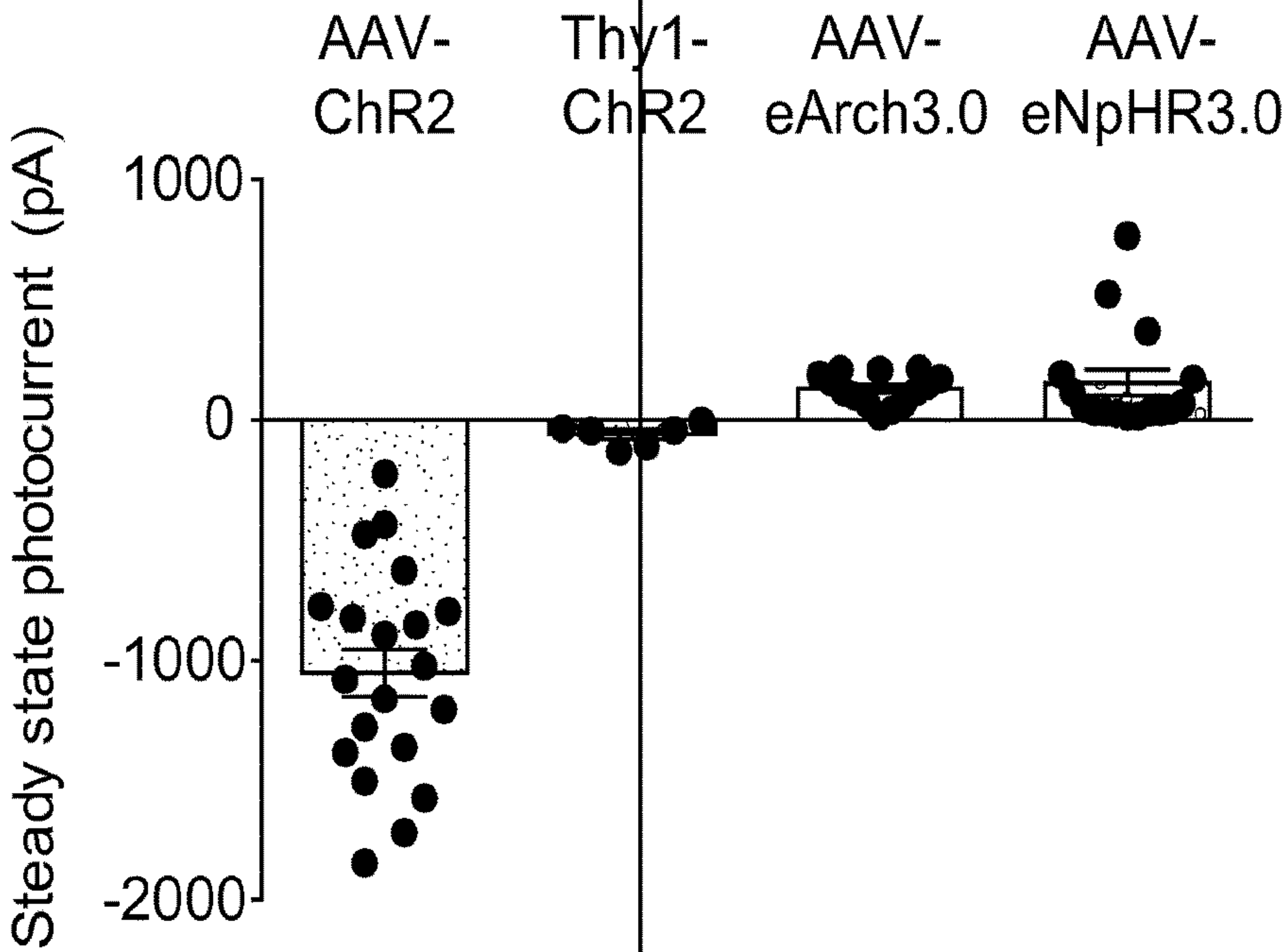


FIG. 17A

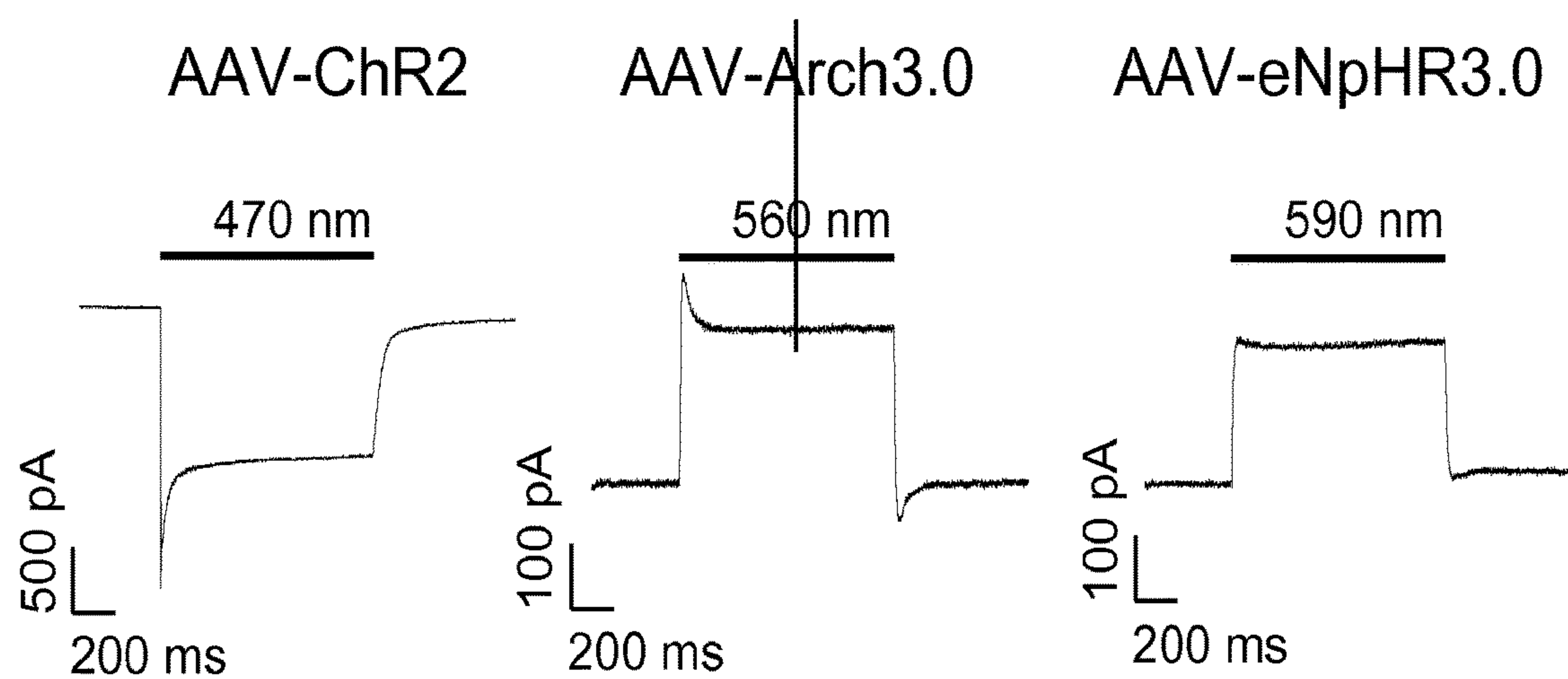


FIG. 17B

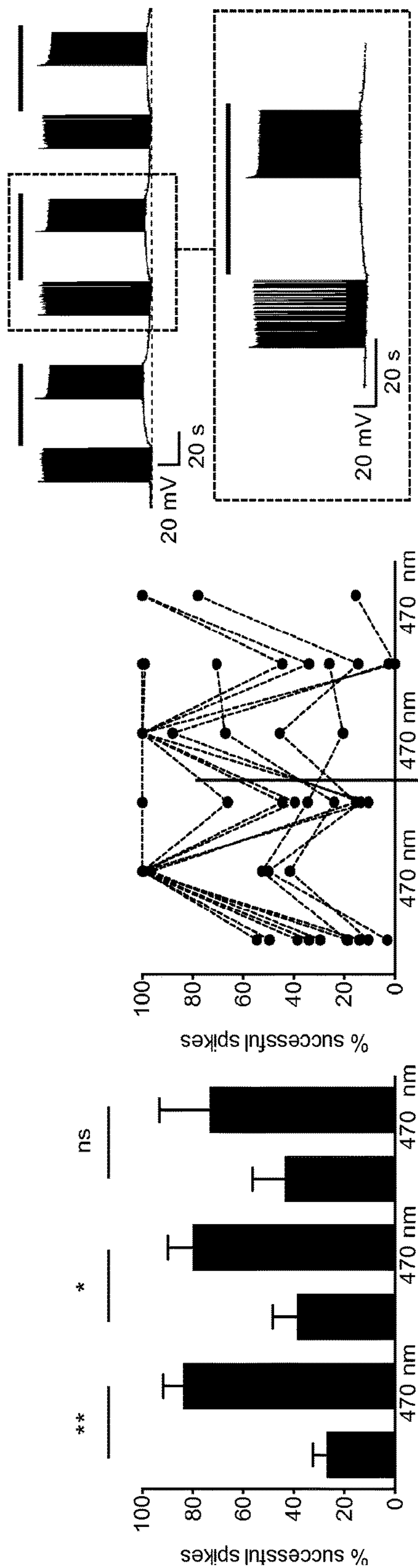


FIG. 18A

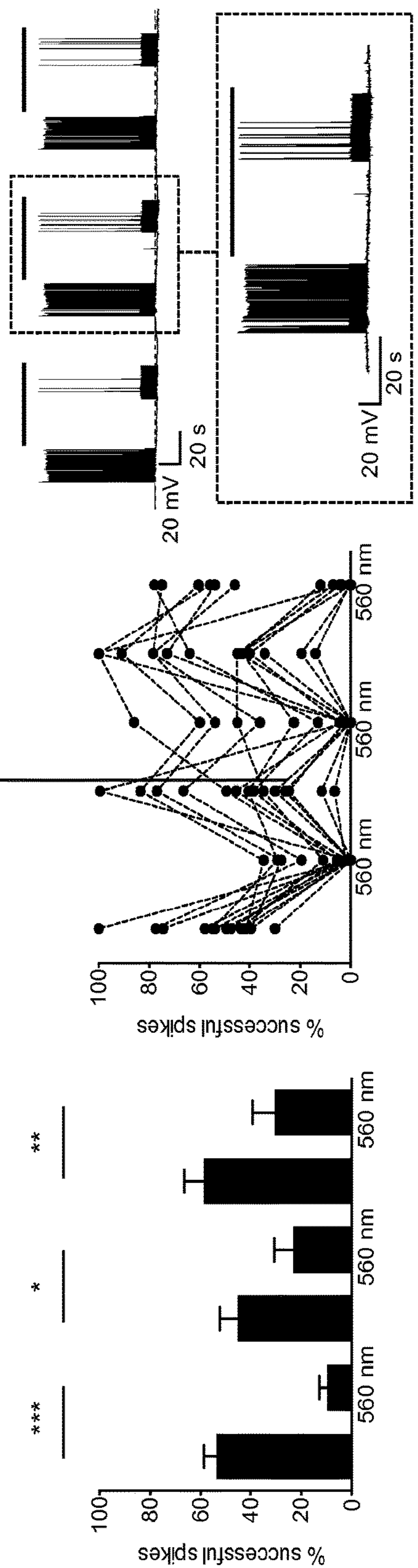


FIG. 18B

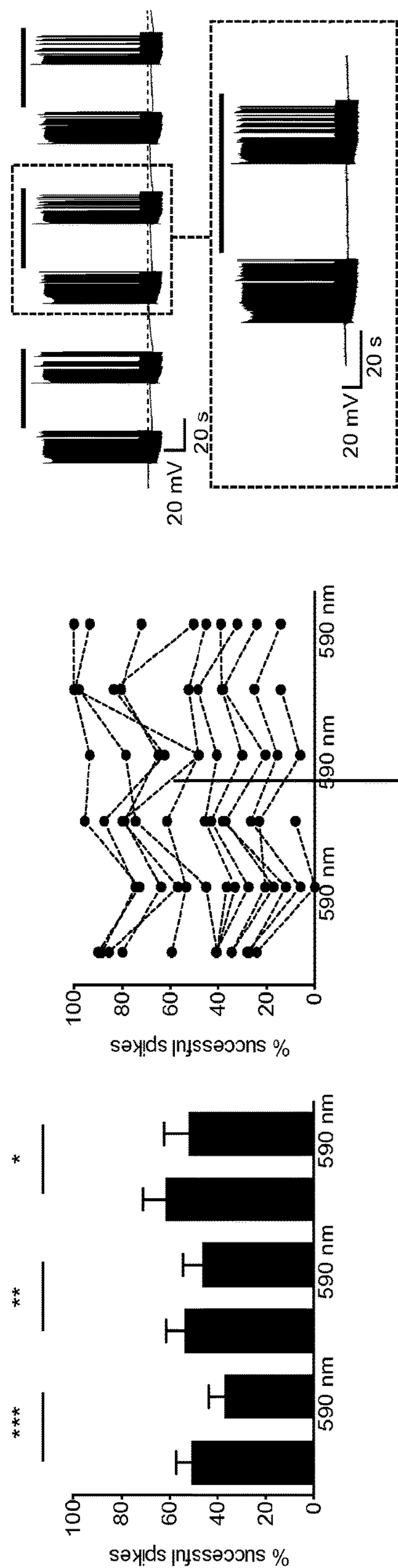


FIG. 18C

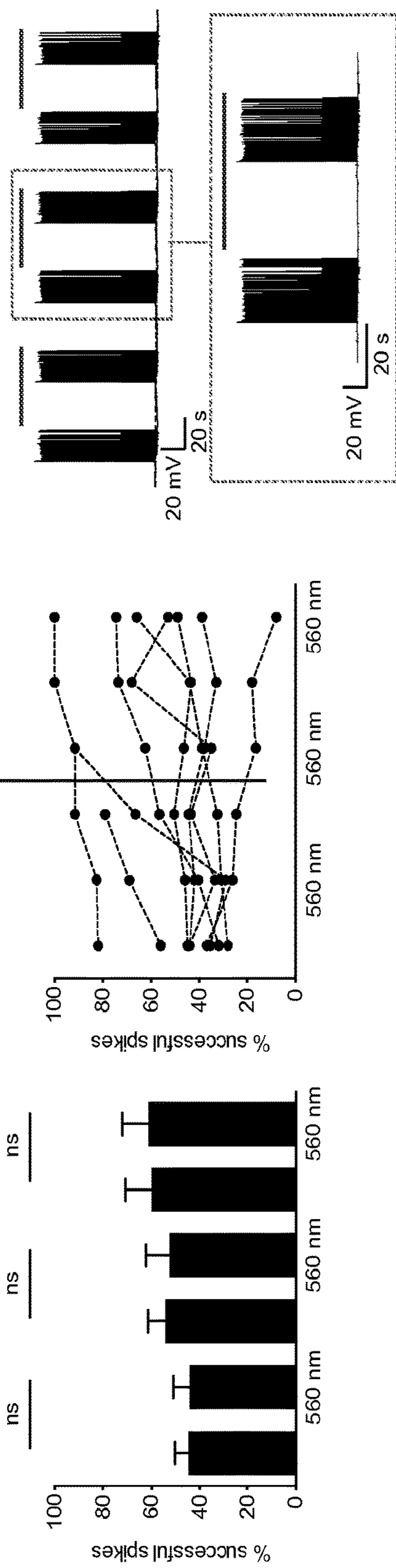


FIG. 18D

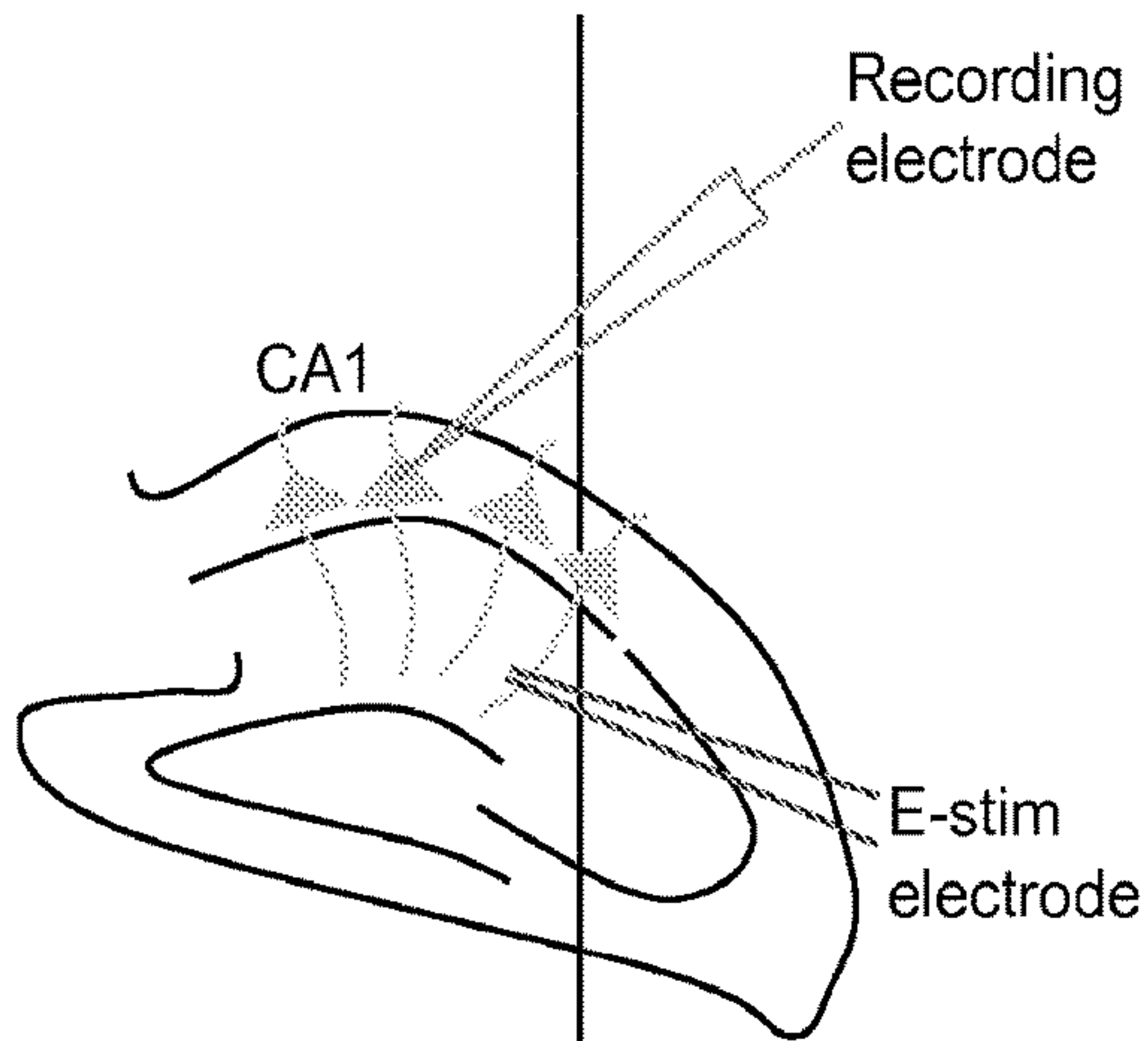


FIG. 19A

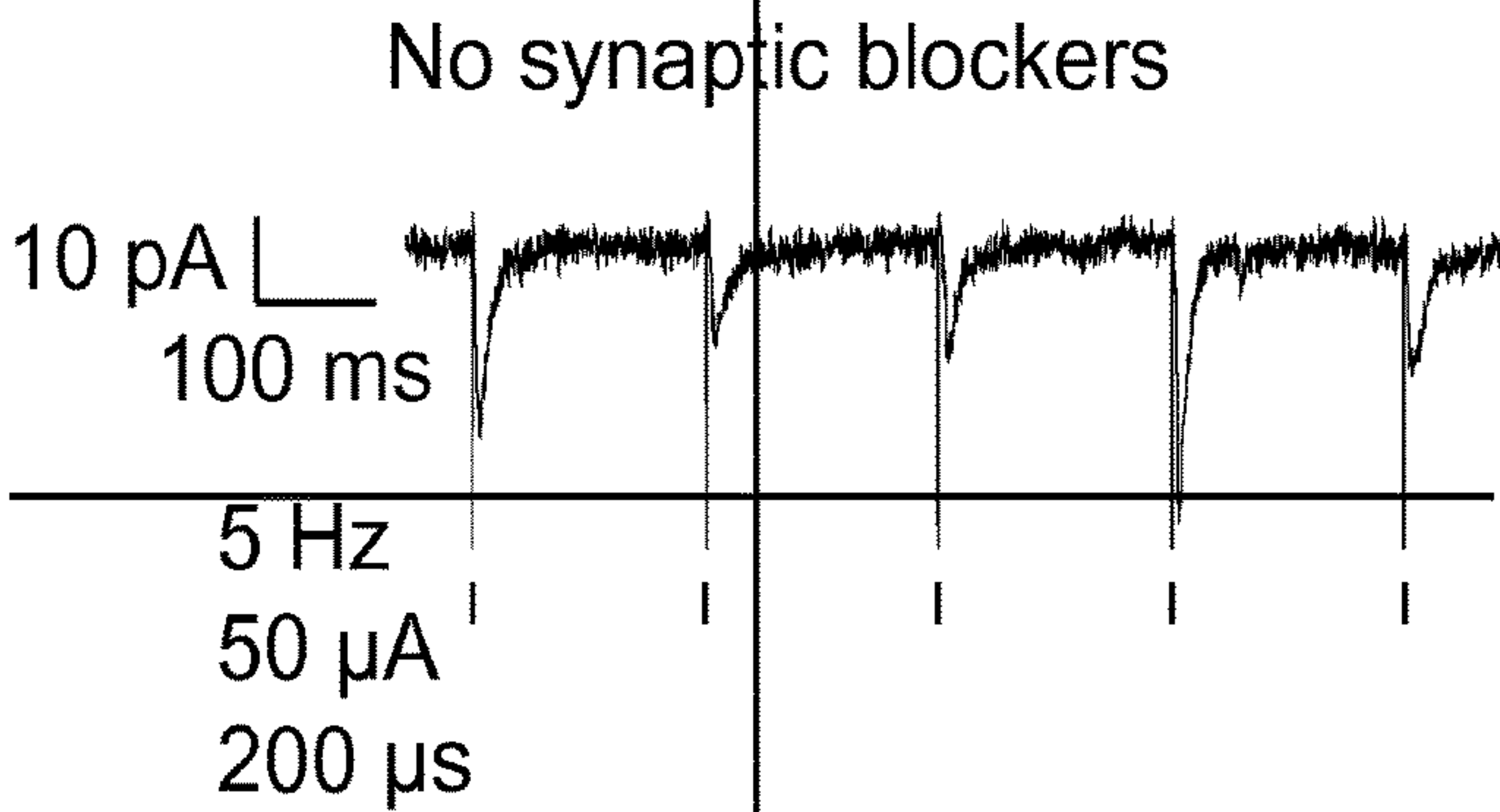


FIG. 19B

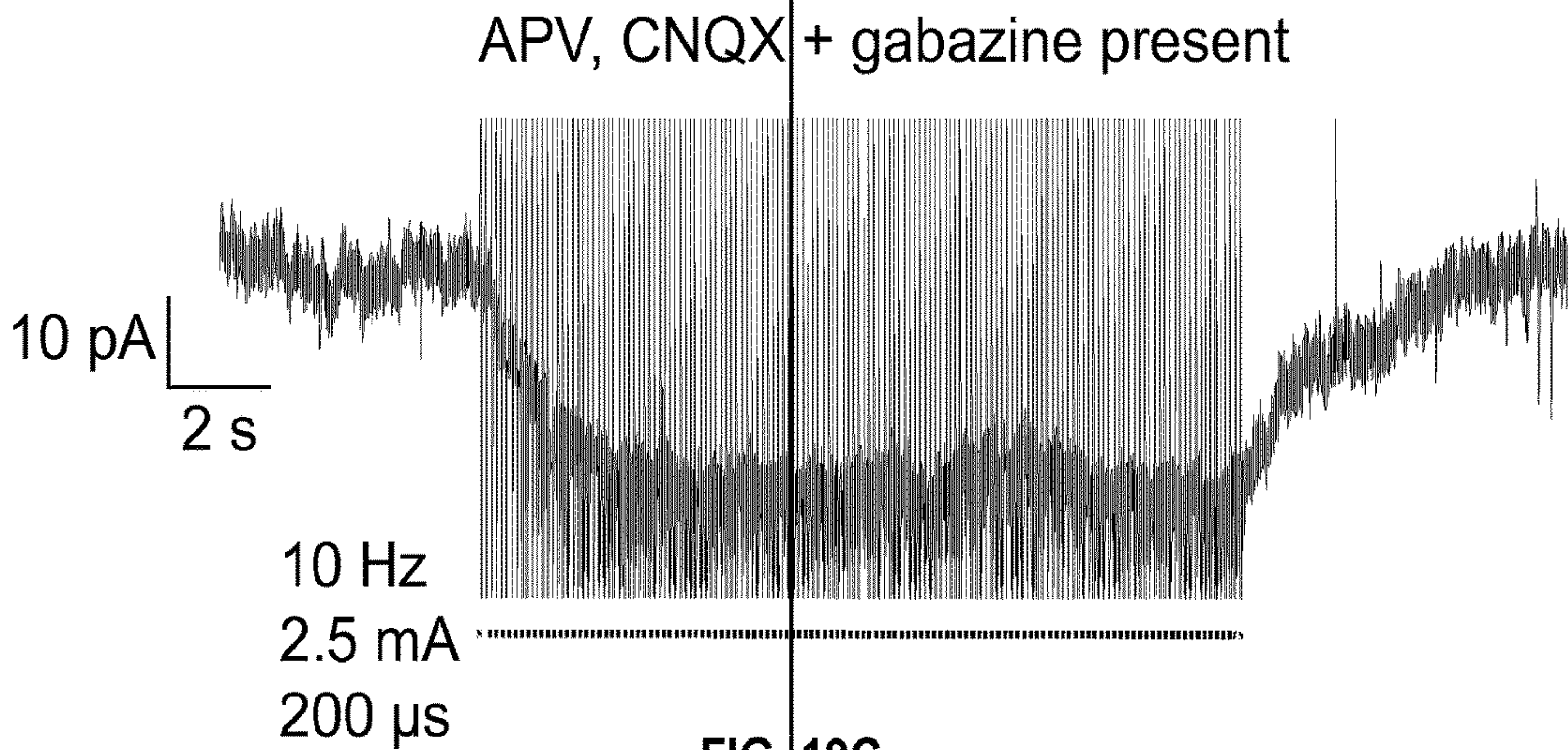


FIG. 19C

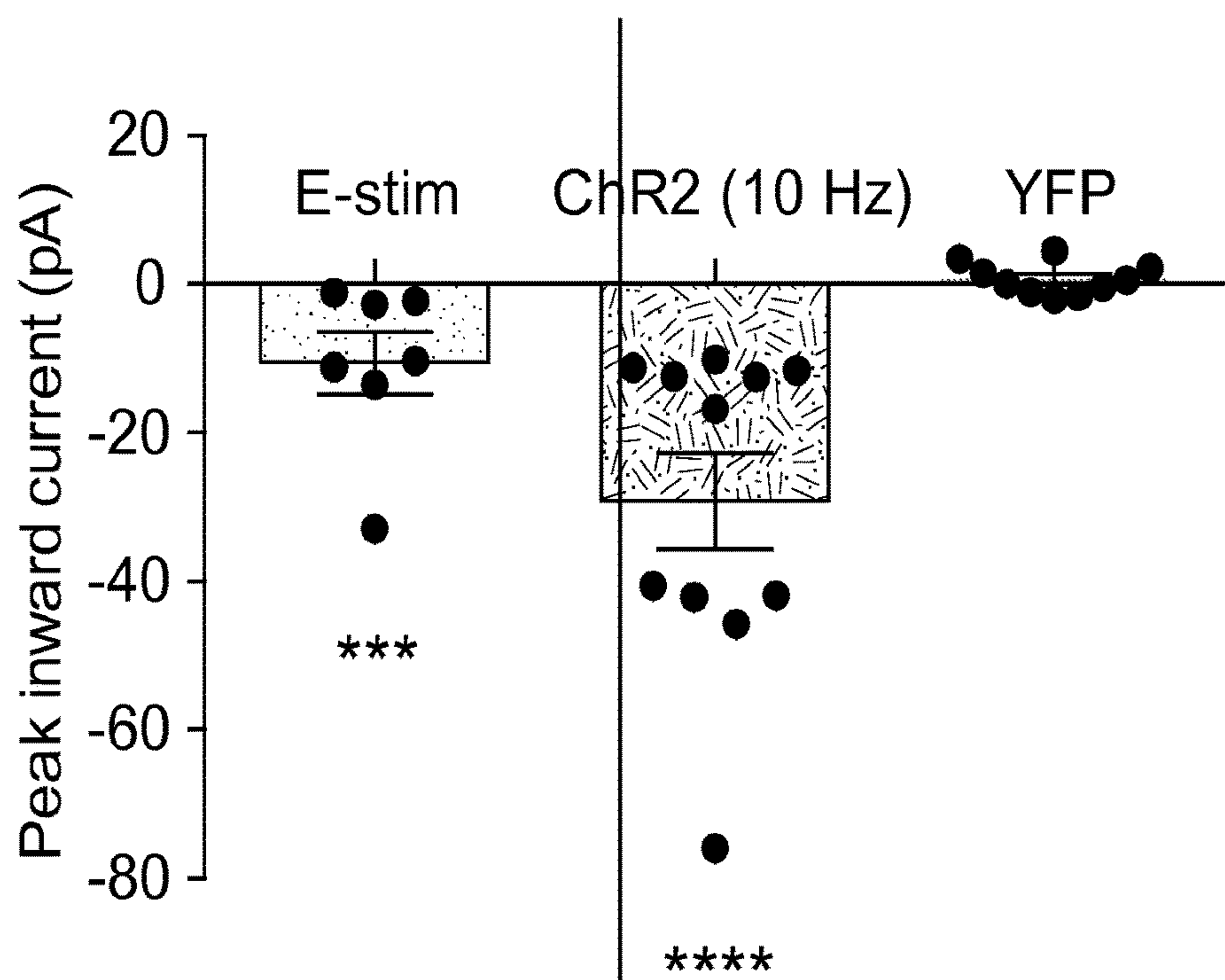


FIG. 19D

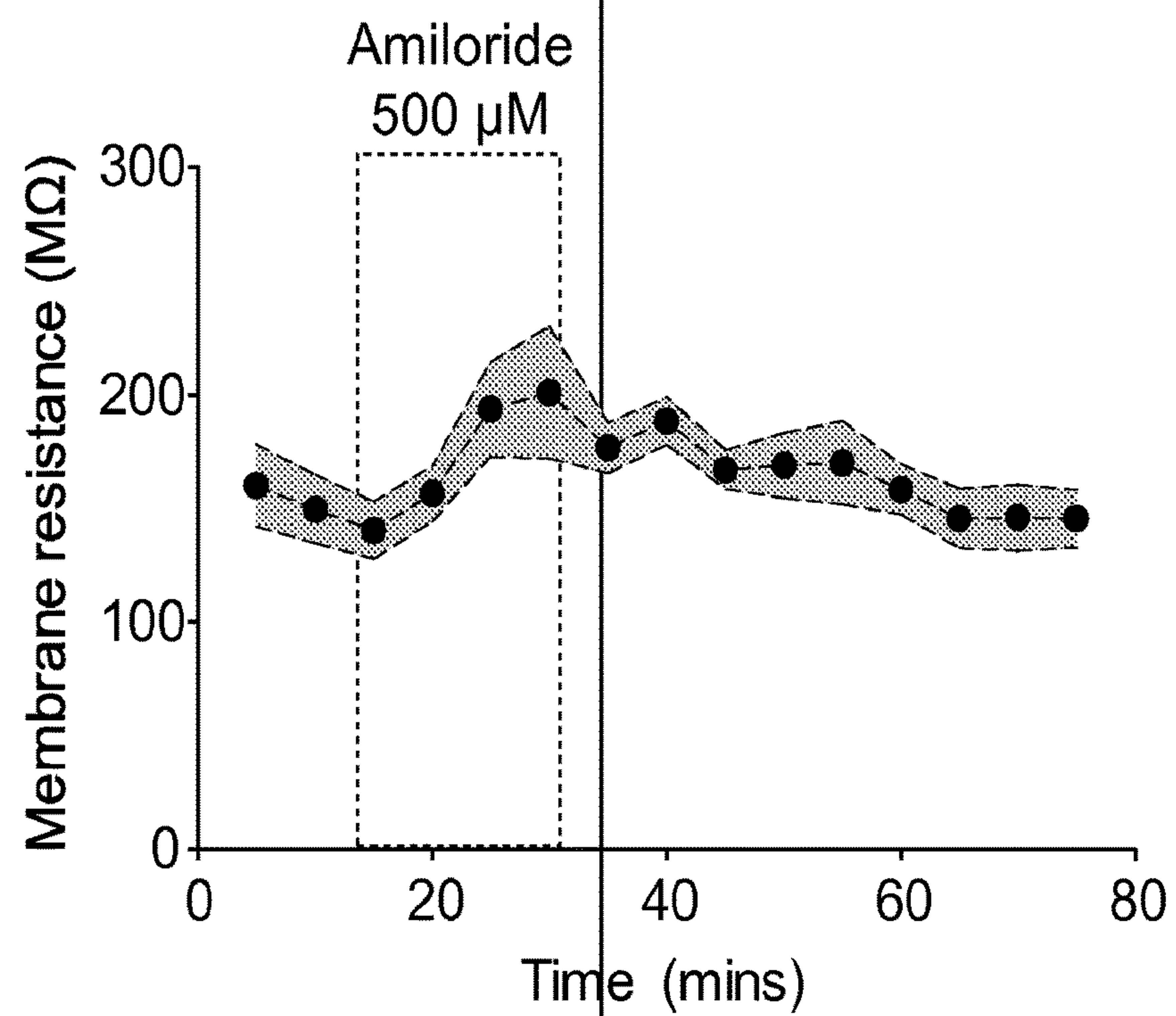


FIG. 19E

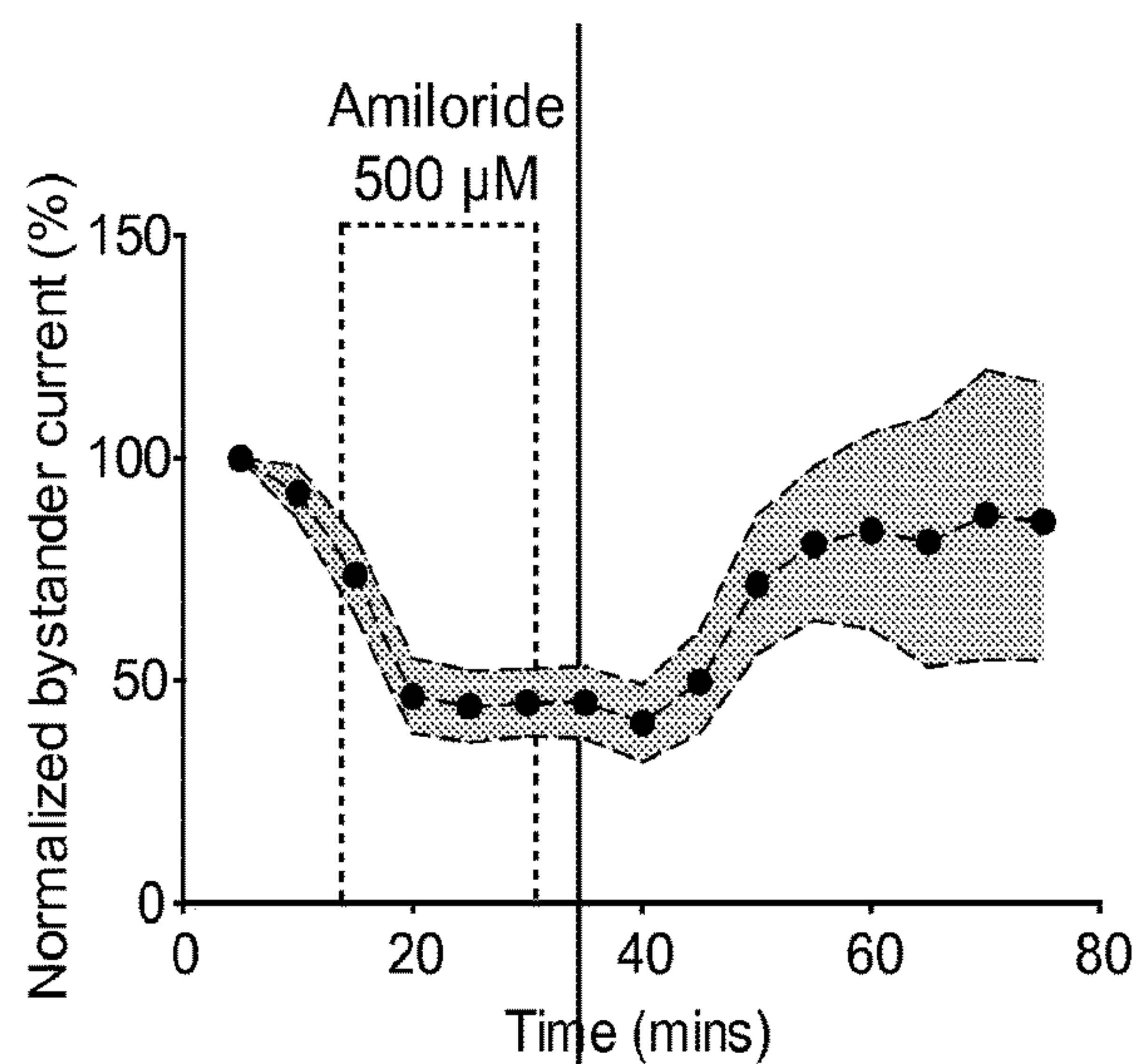


FIG. 19F

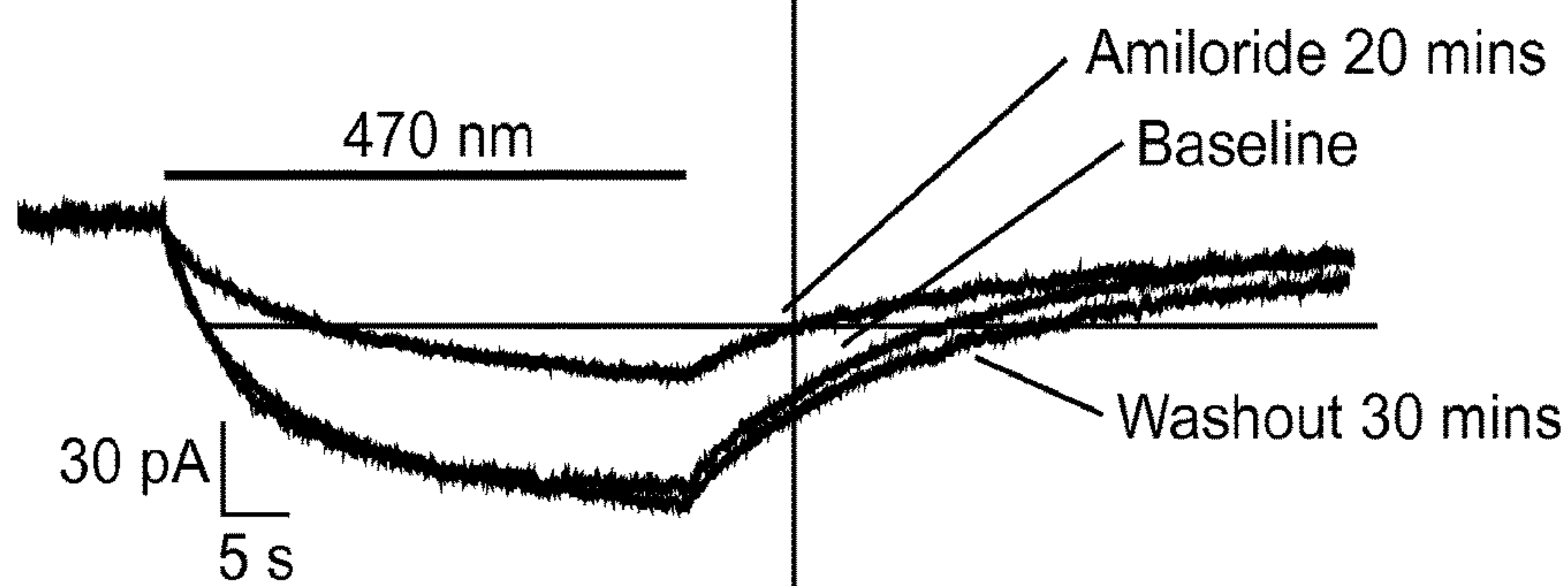


FIG. 19G

Electrical stimulation with tungsten bipolar concentric electrode.

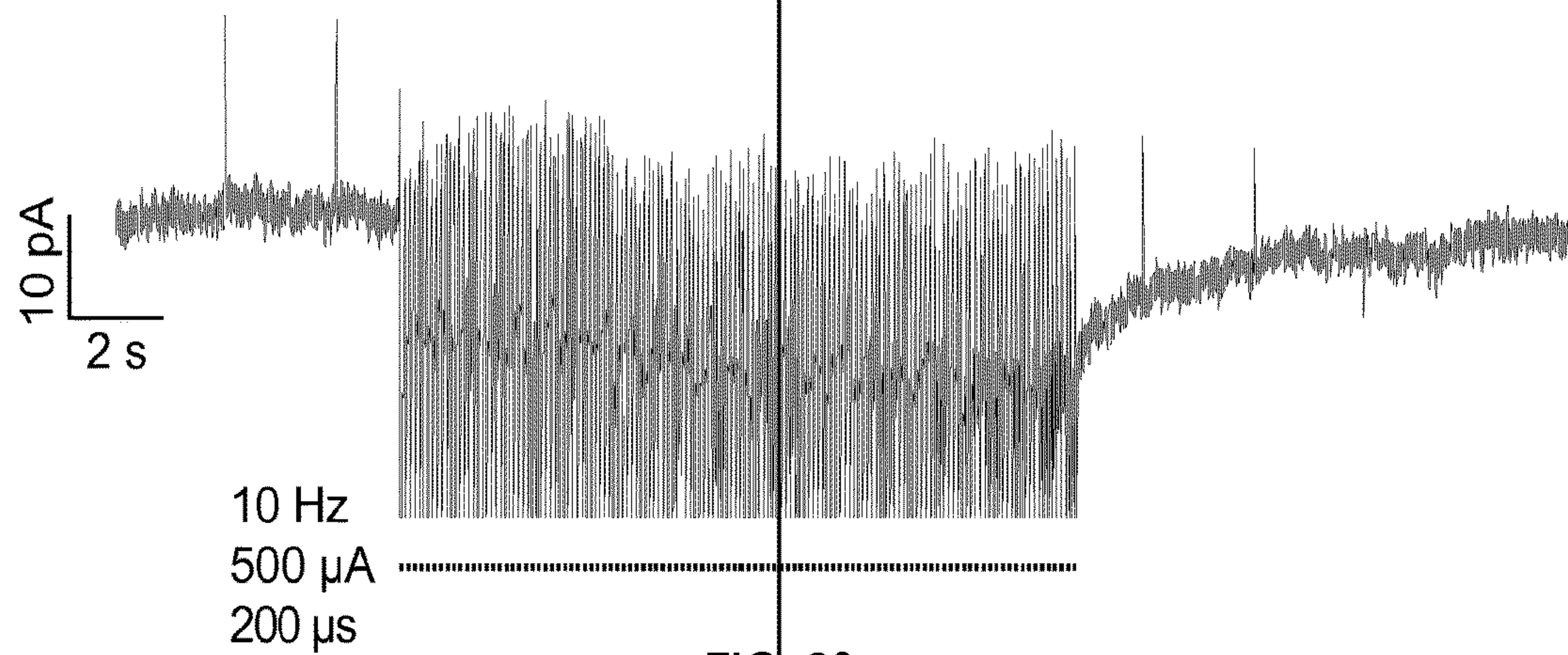


FIG. 20

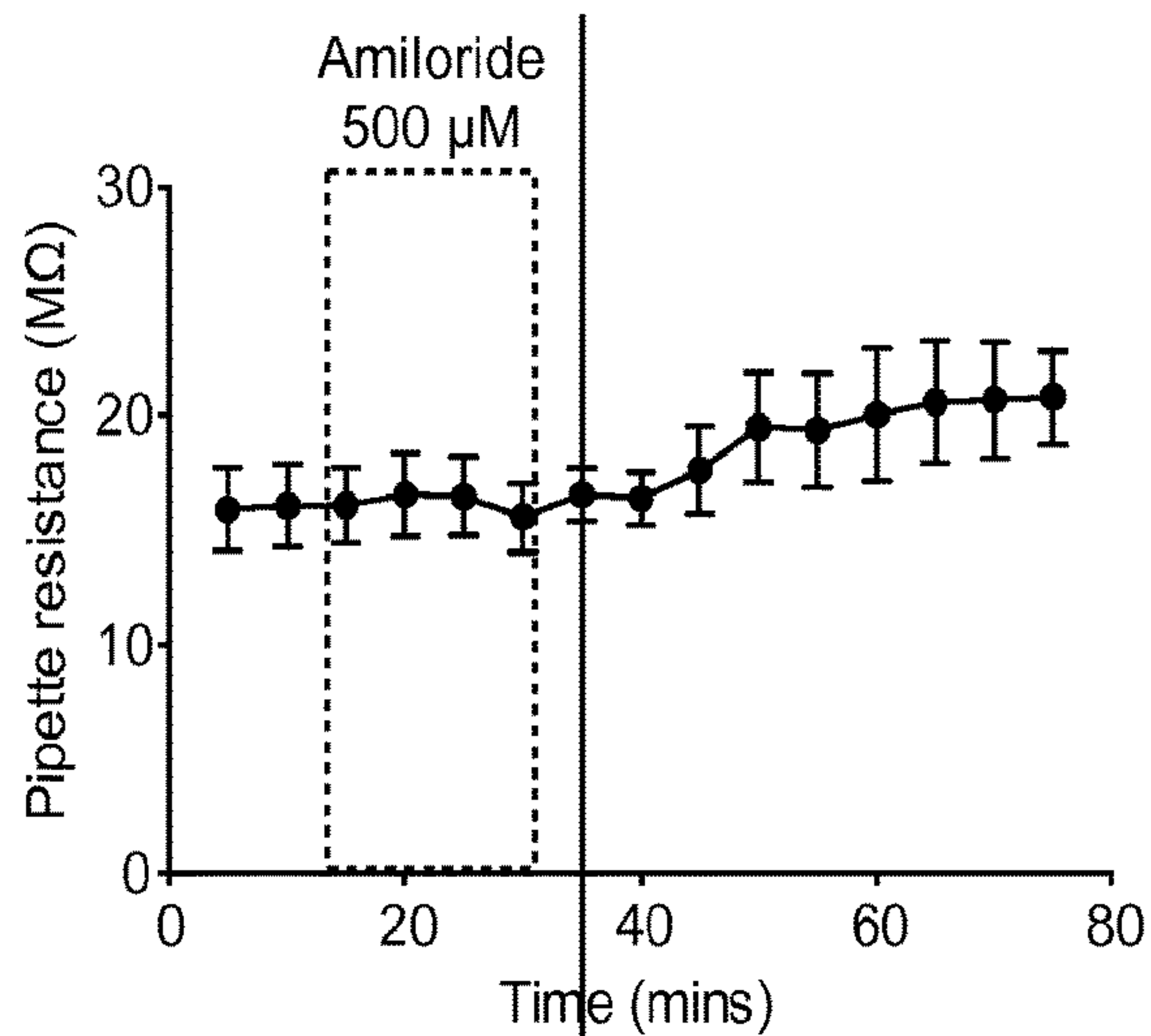


FIG. 21A

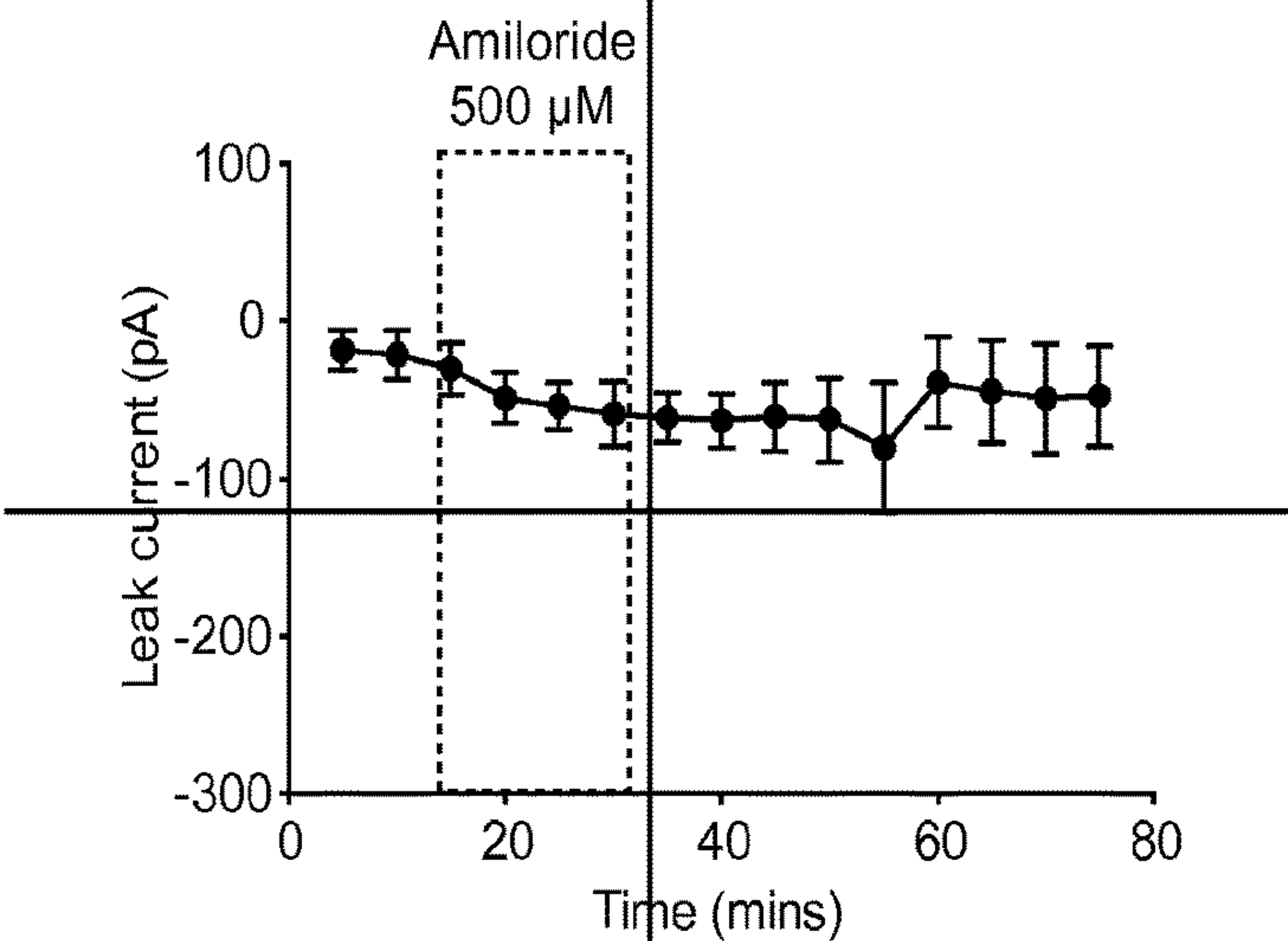


FIG. 21B

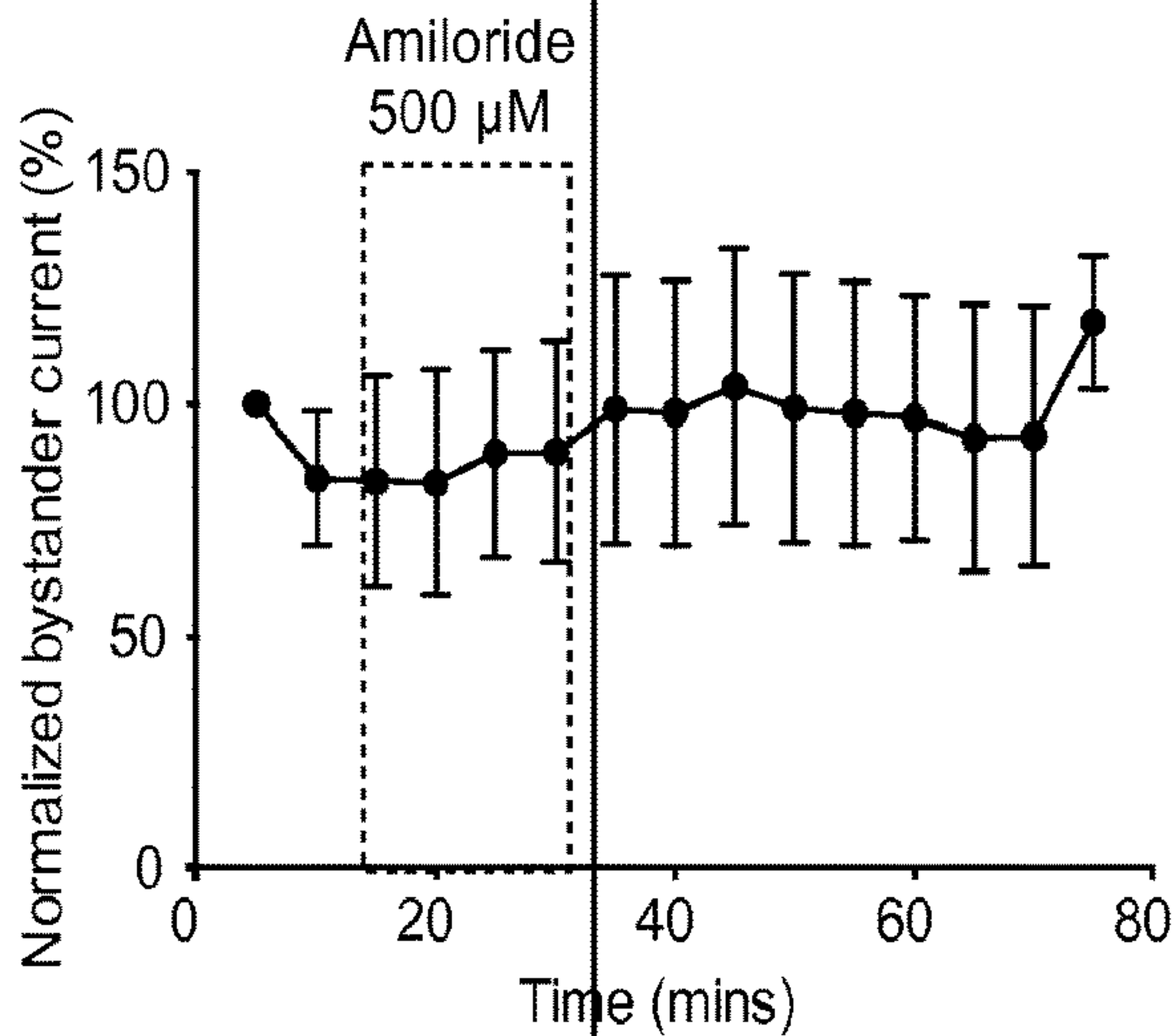


FIG. 21C

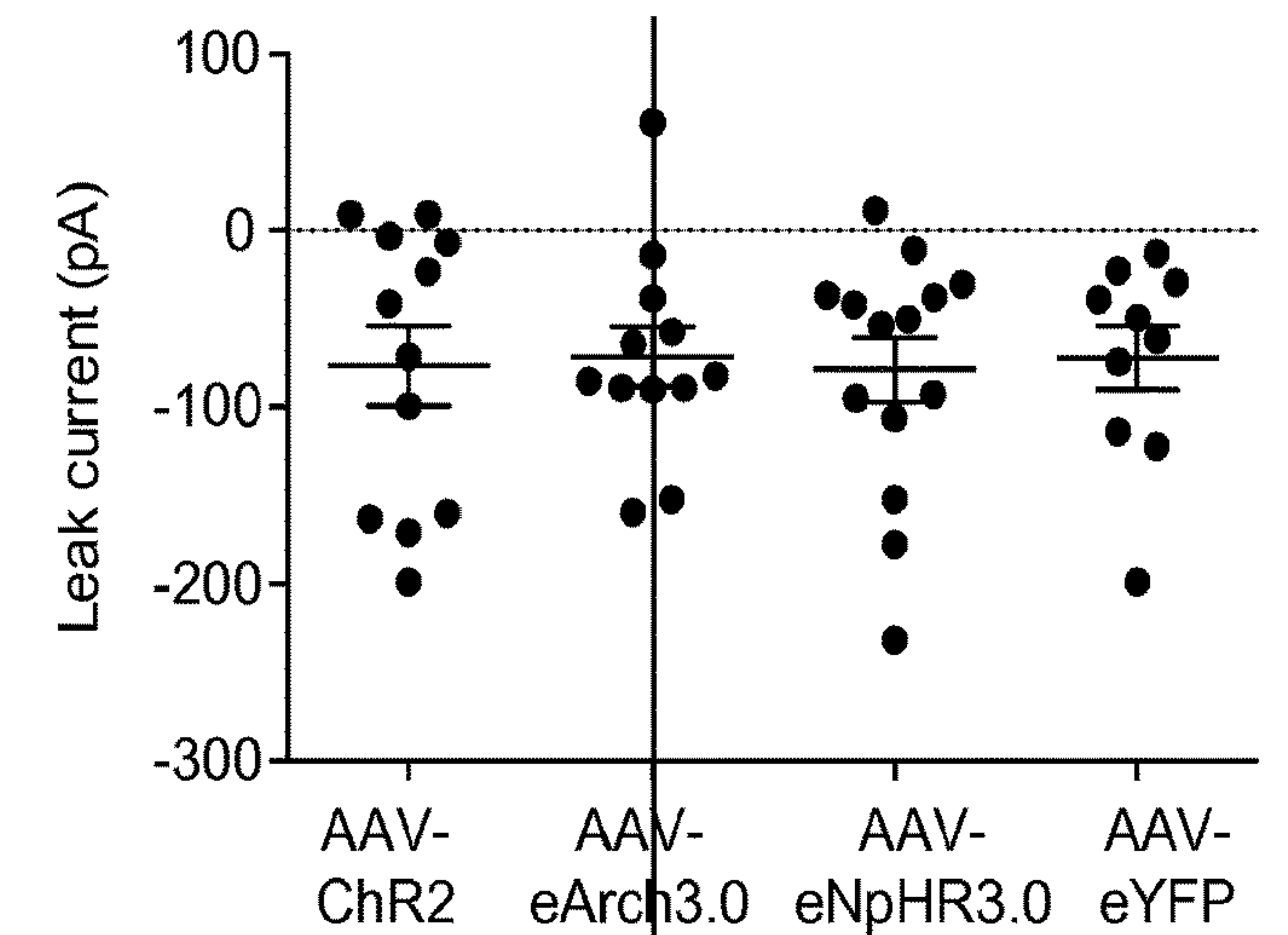


FIG. 22A

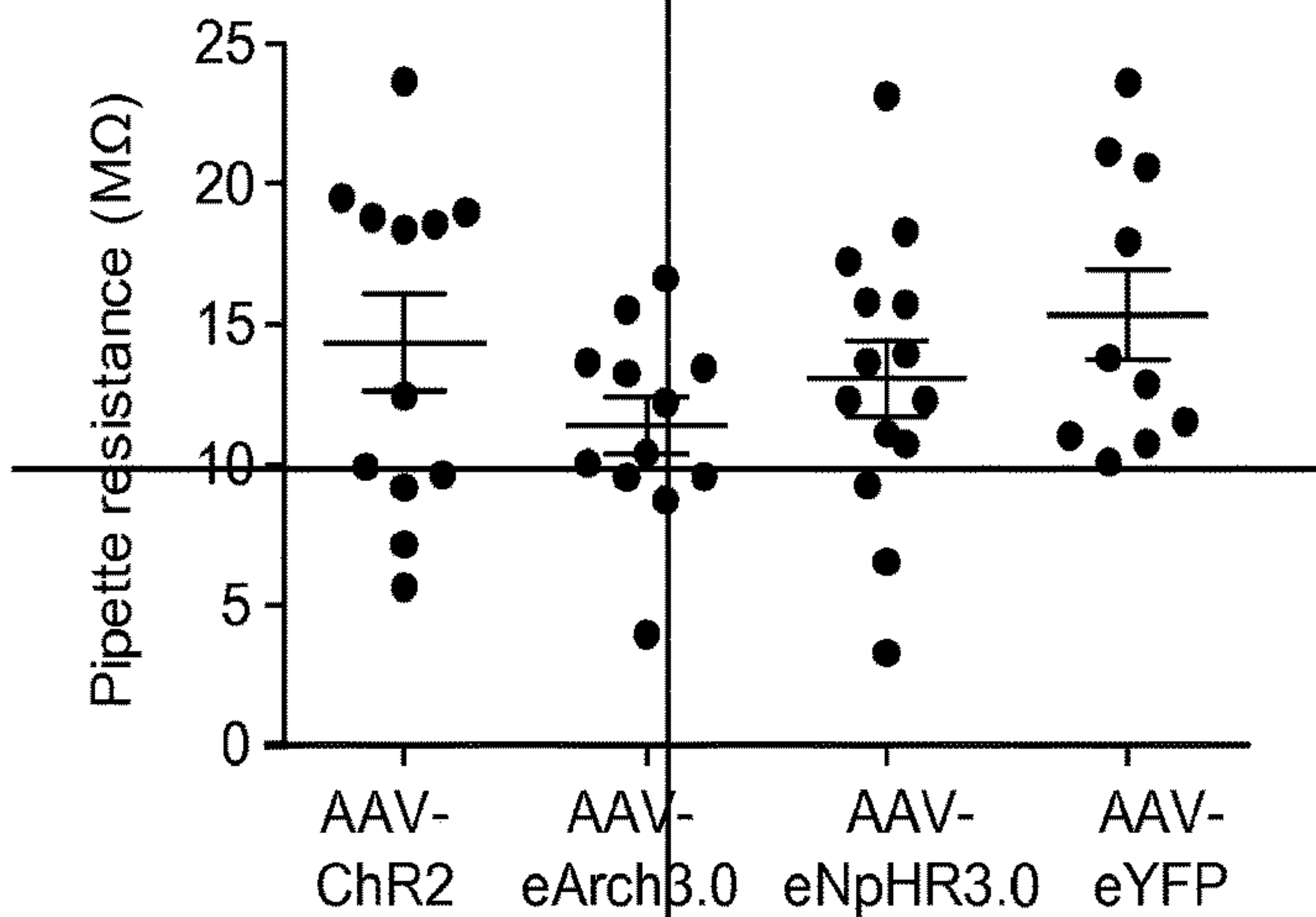


FIG. 22B

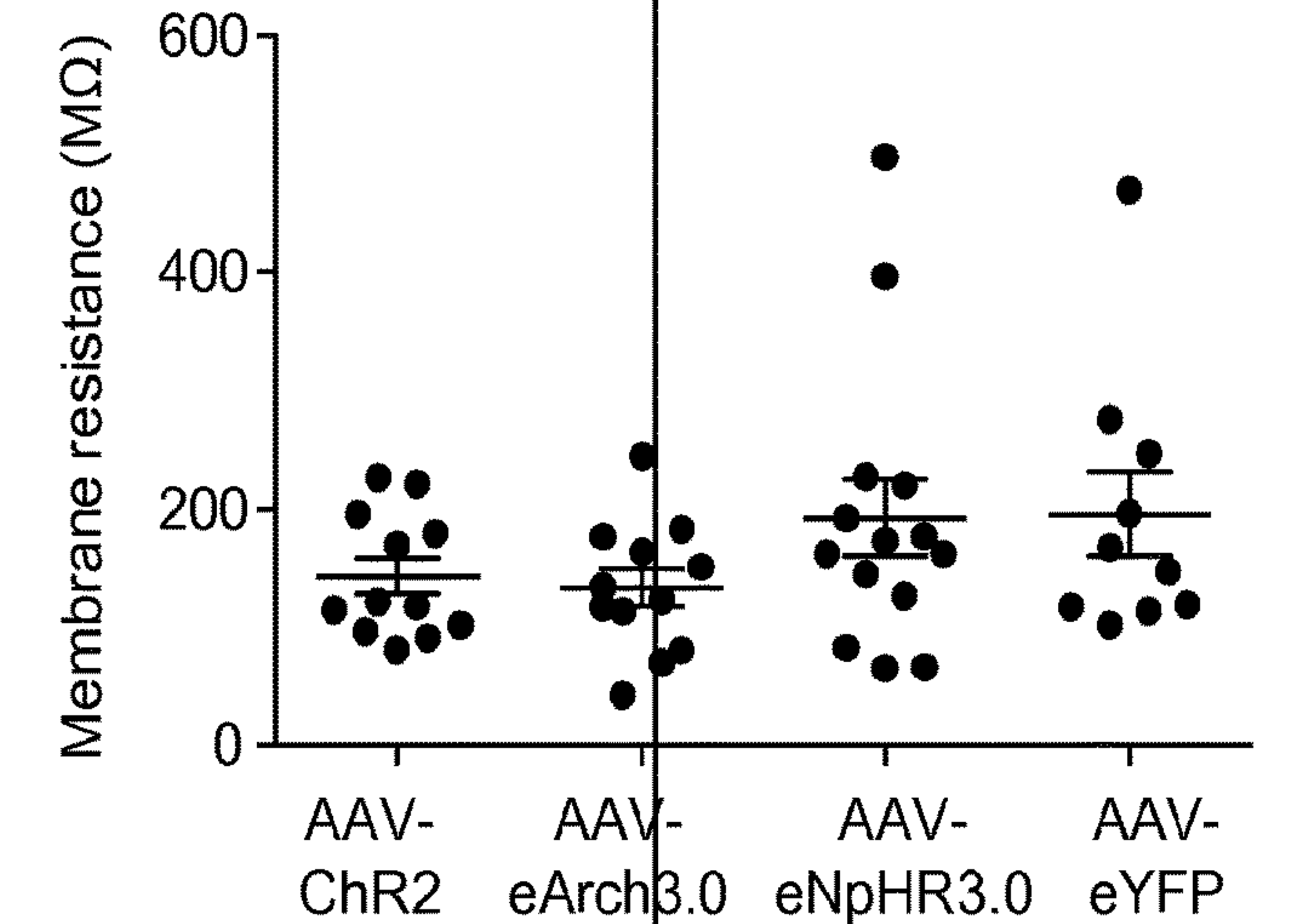


FIG. 22C

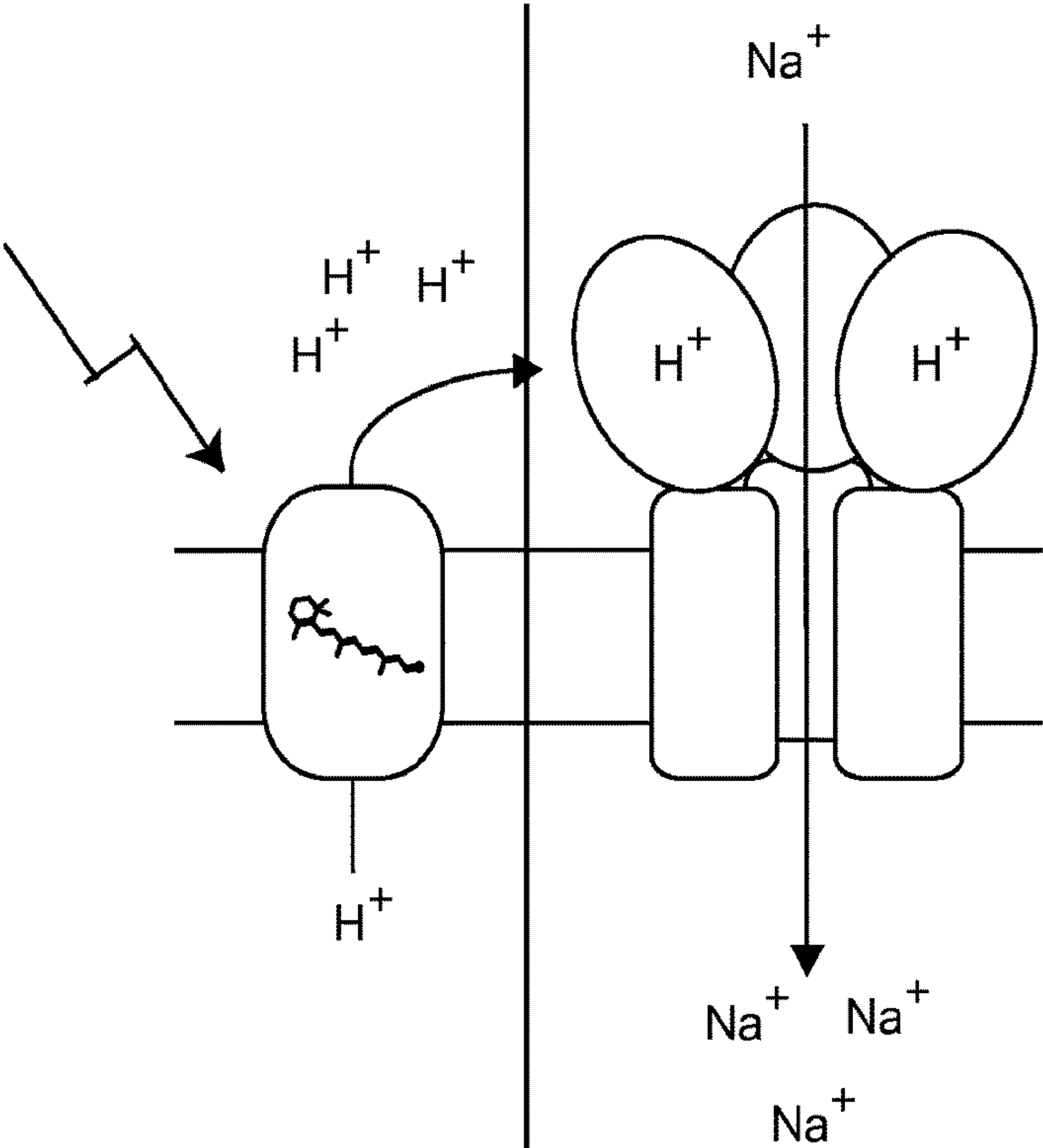


FIG. 23A

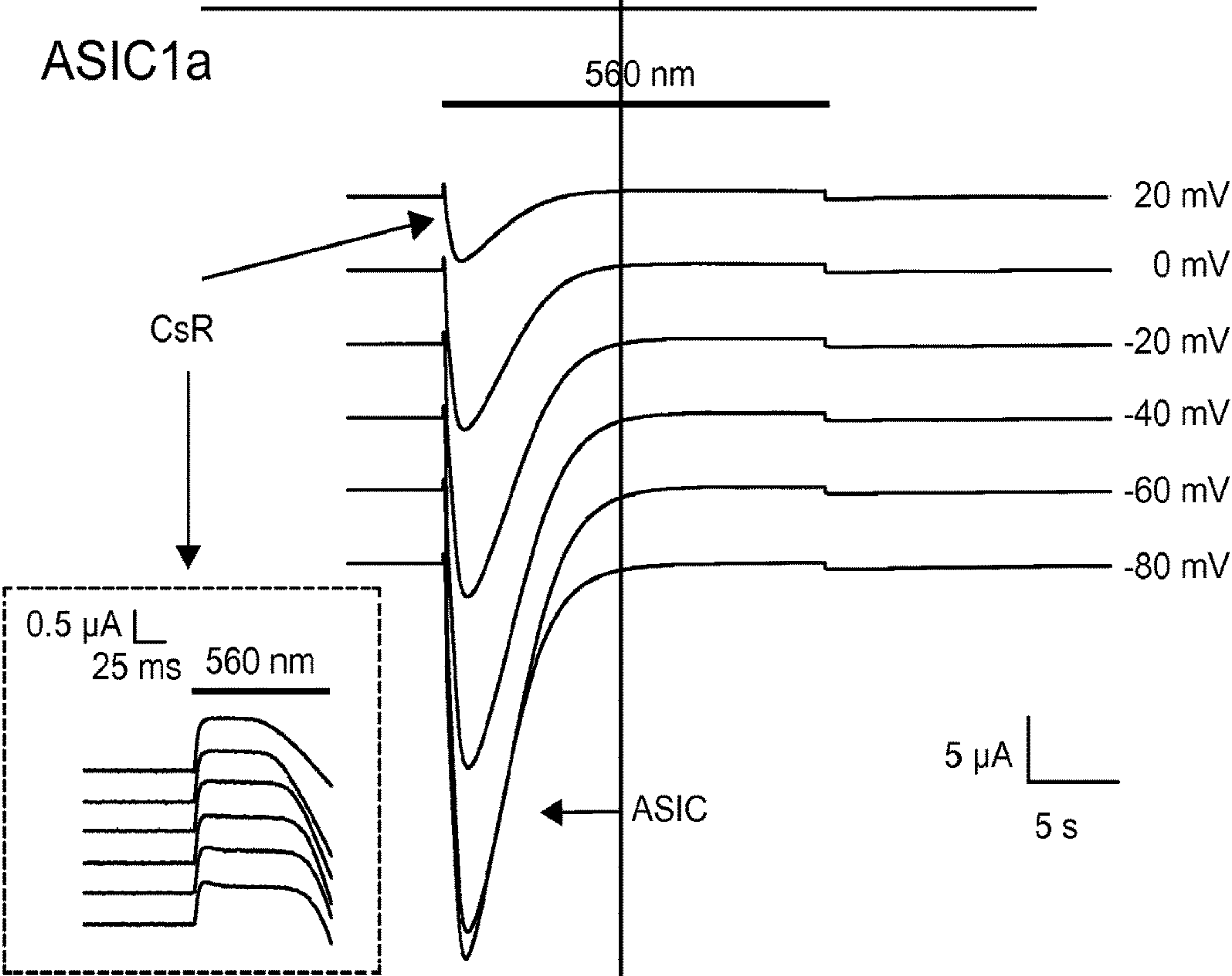


FIG. 23B

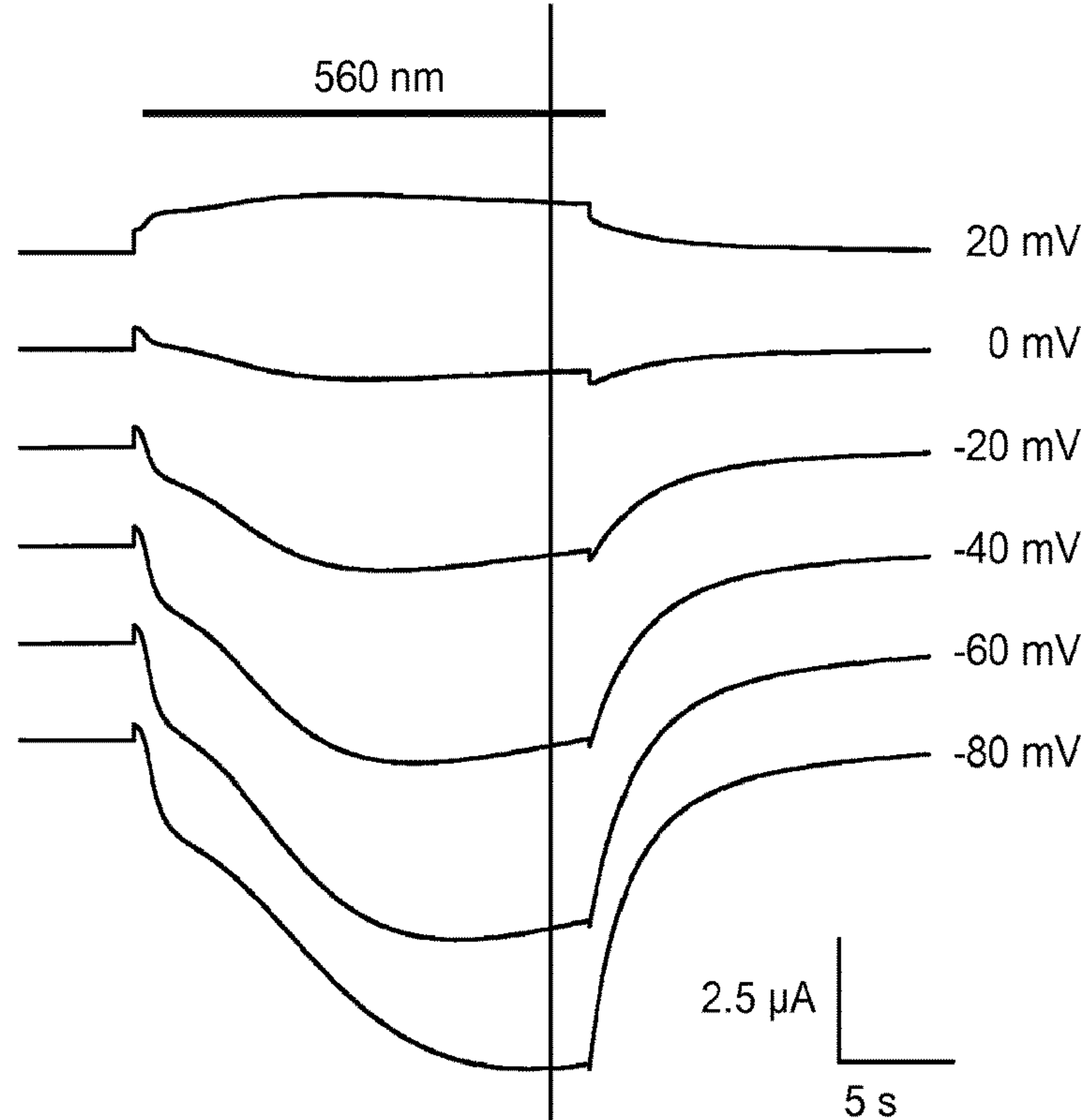


FIG. 23C

ASIC3

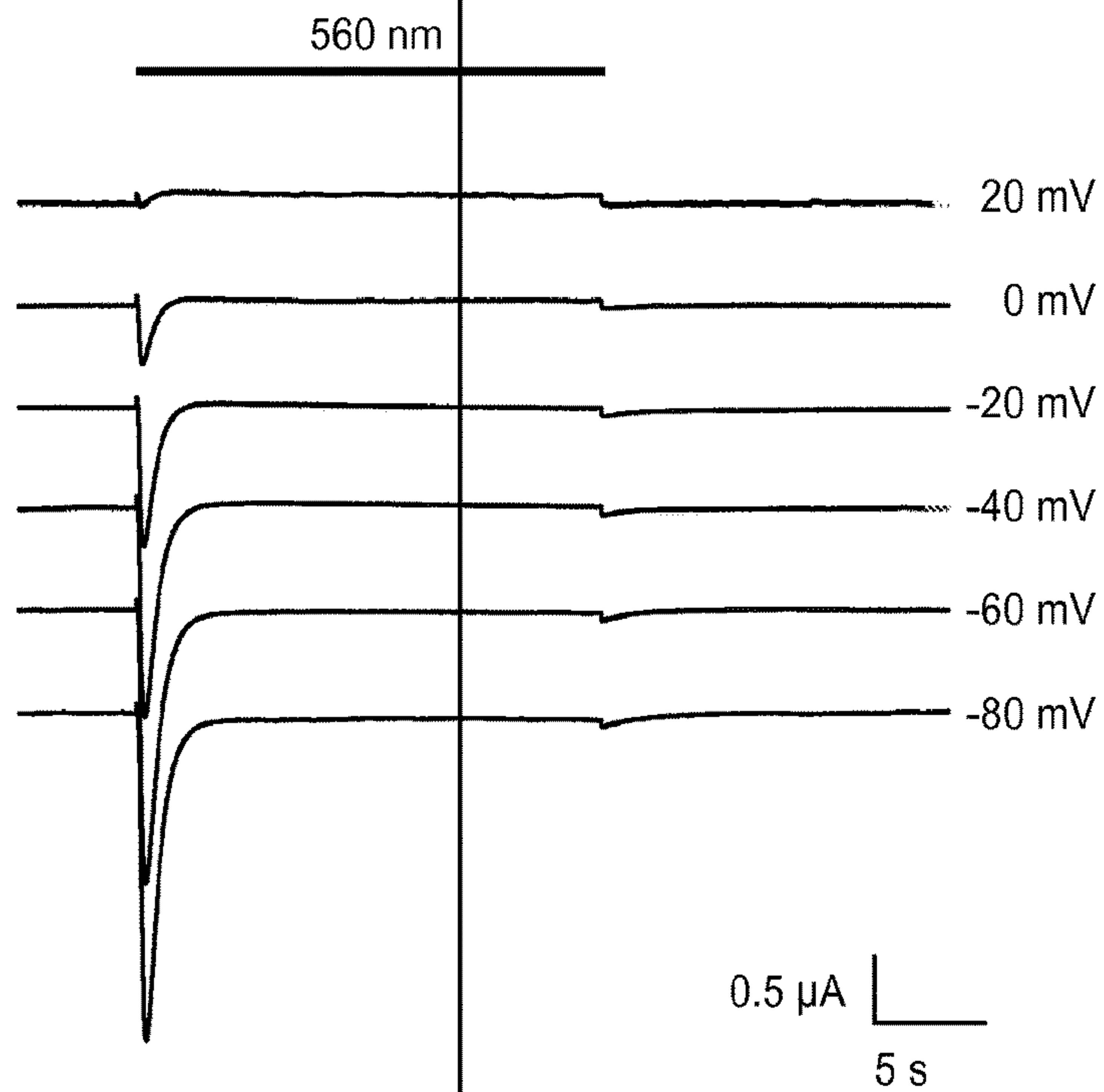
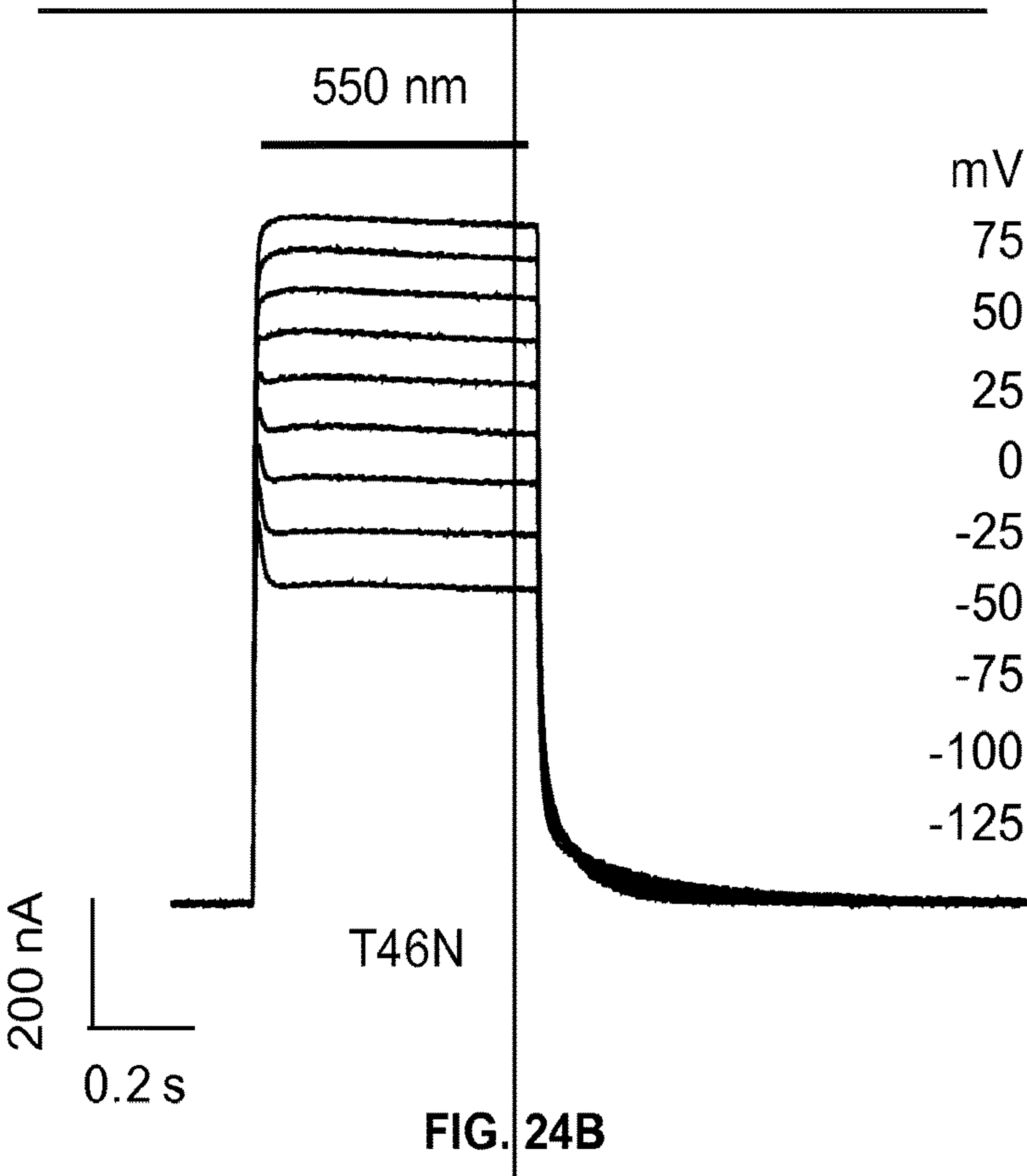
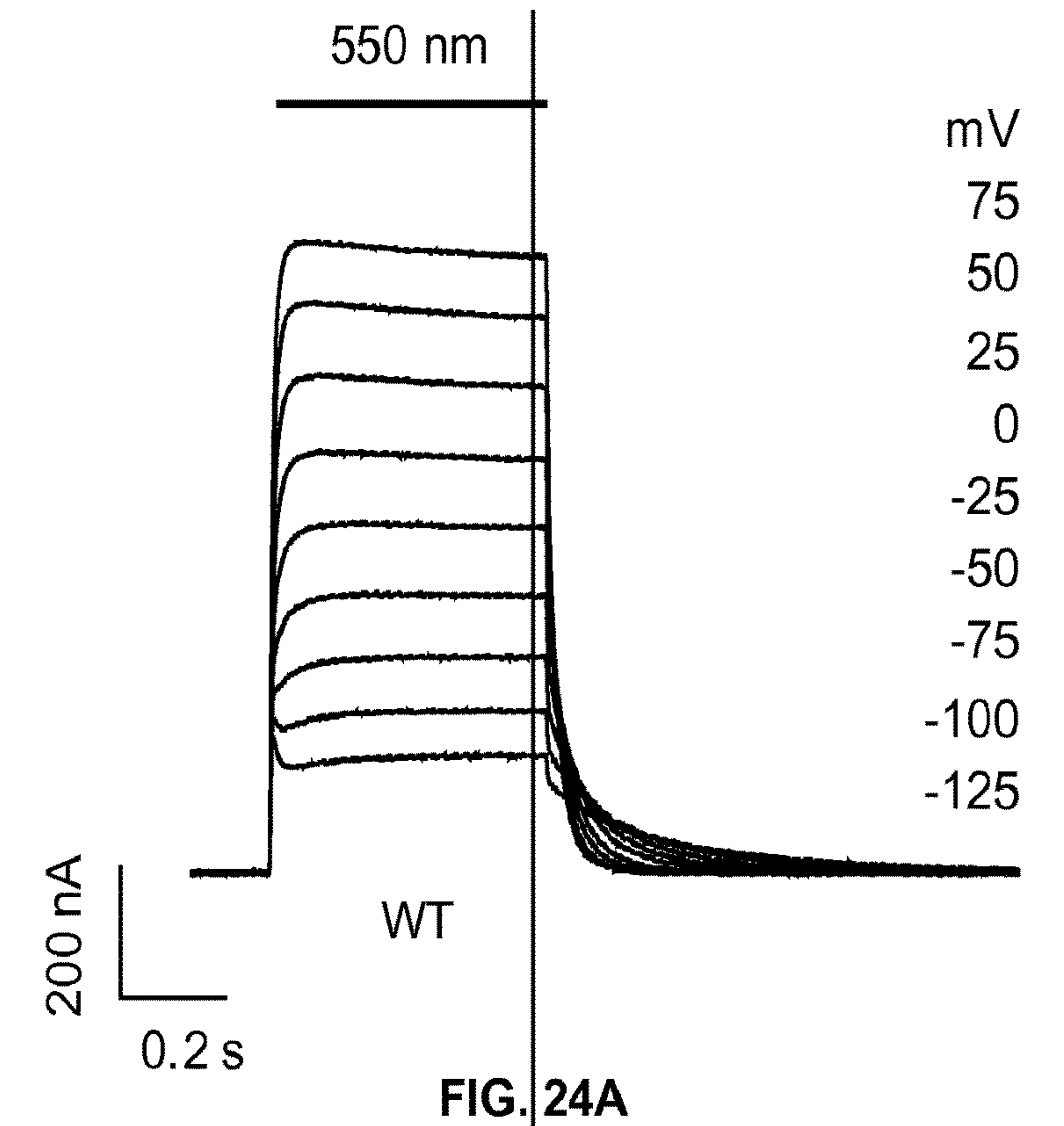


FIG. 23D



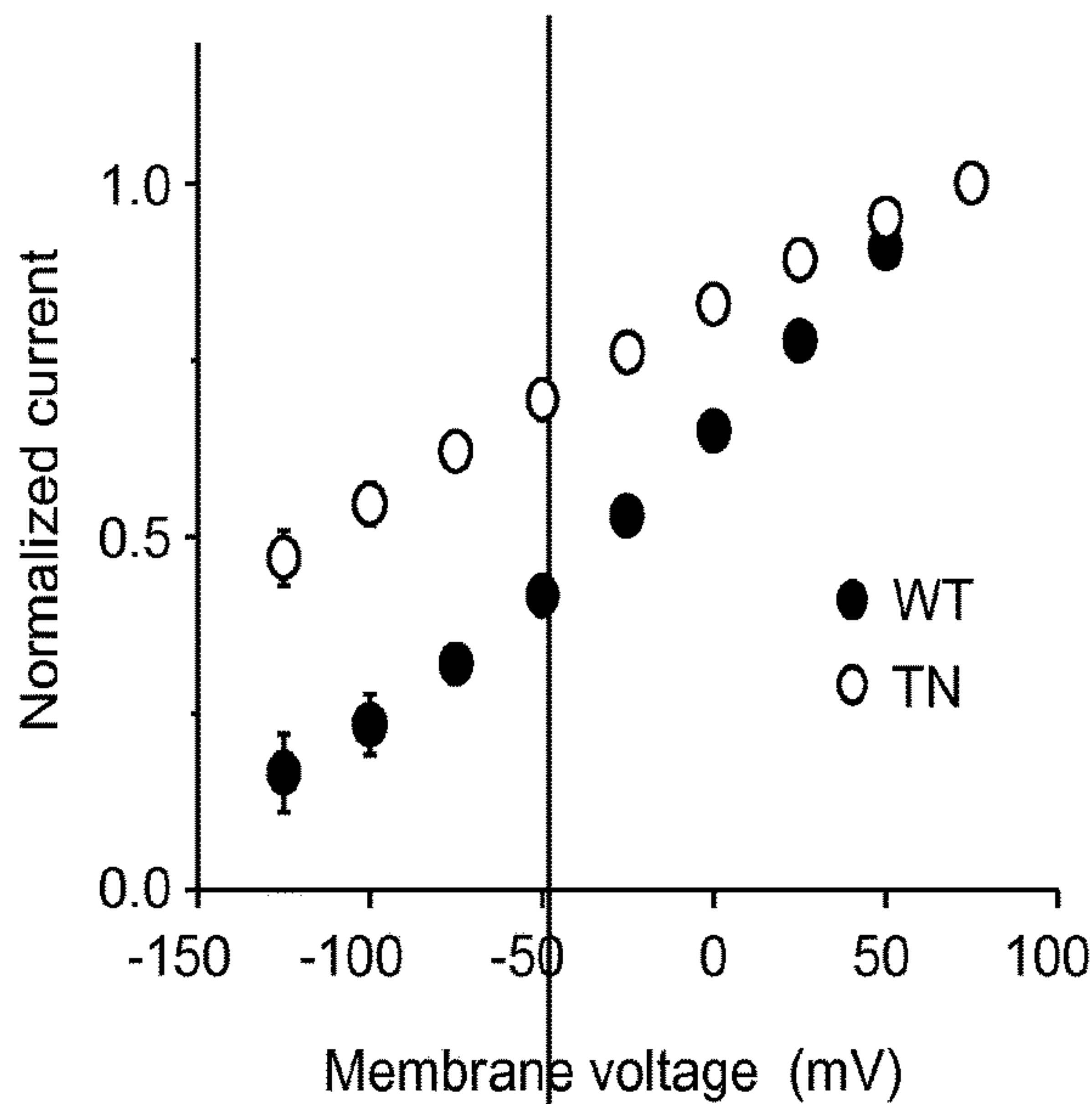


FIG. 24C

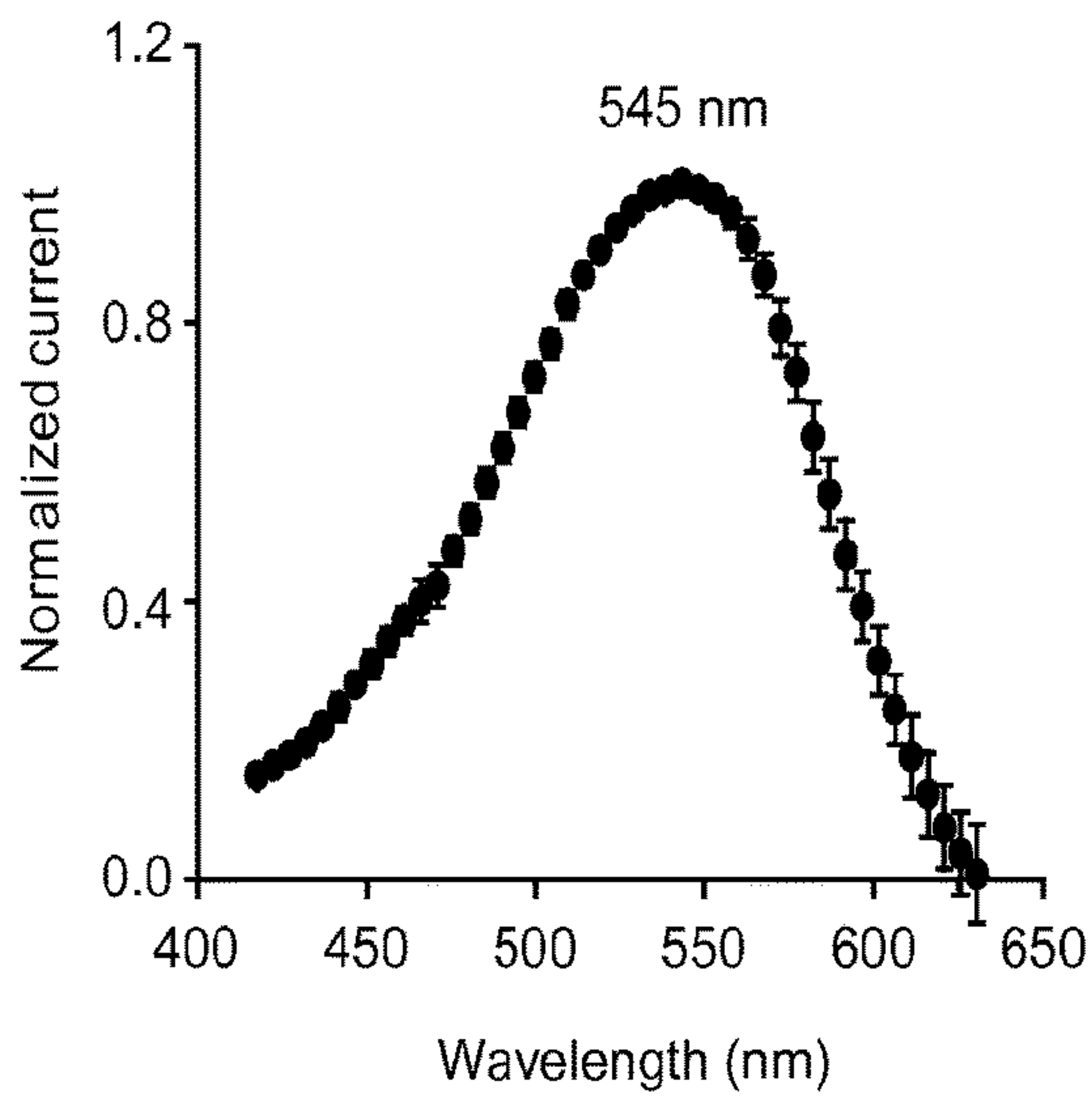


FIG. 24D

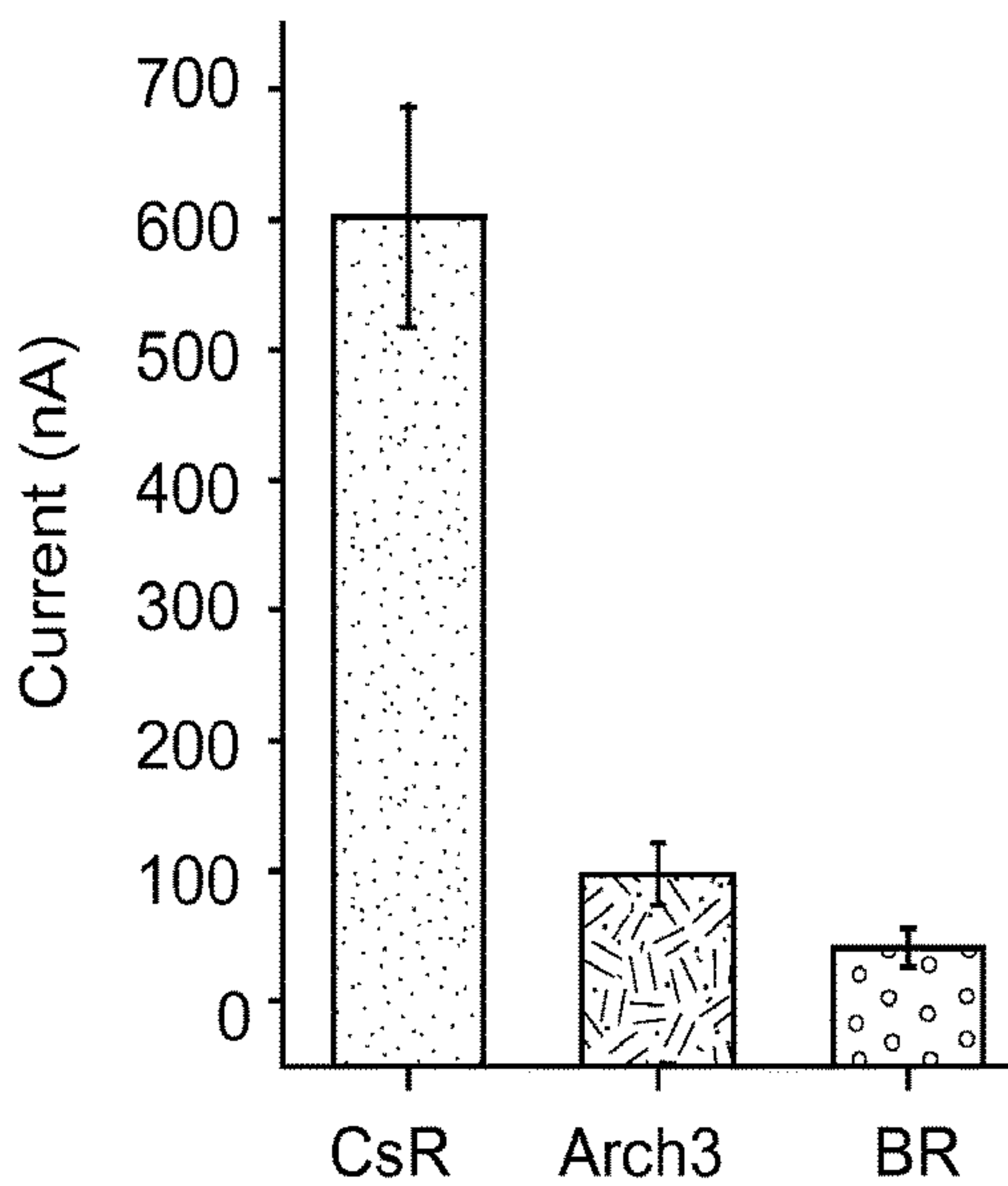
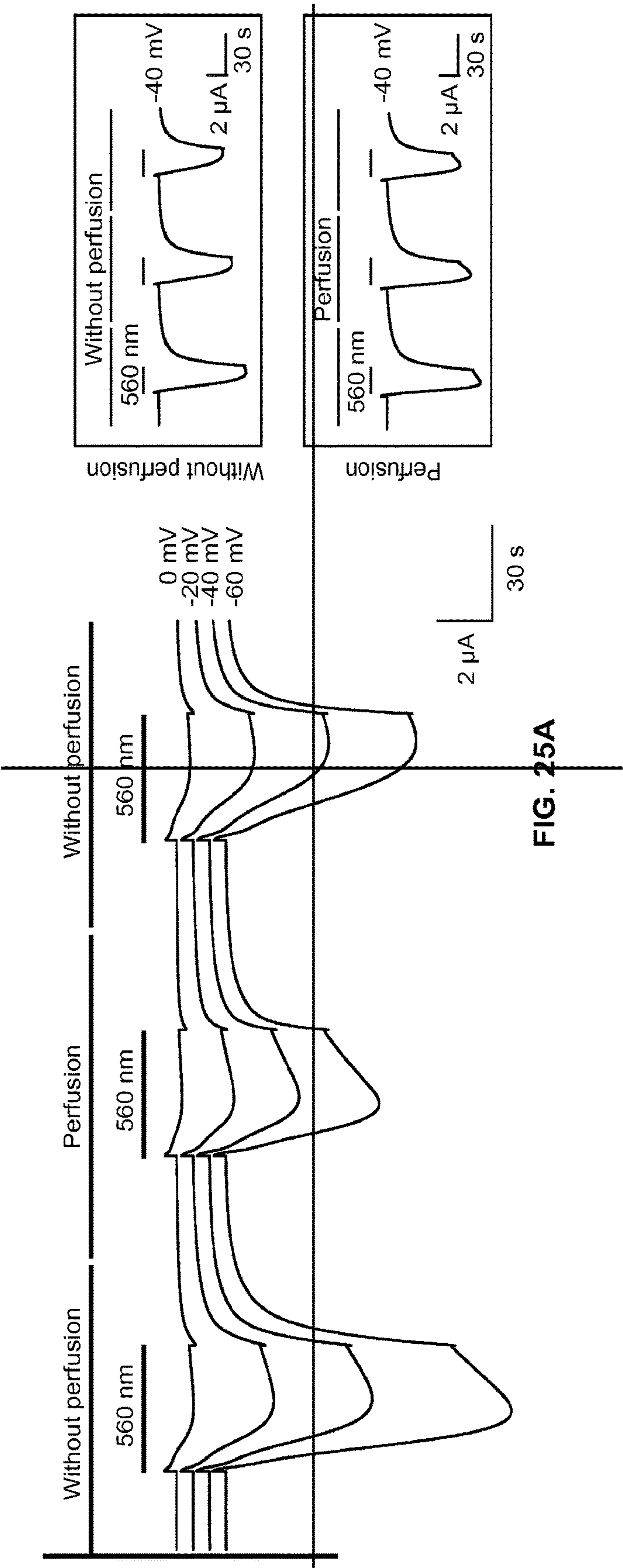


FIG. 24E



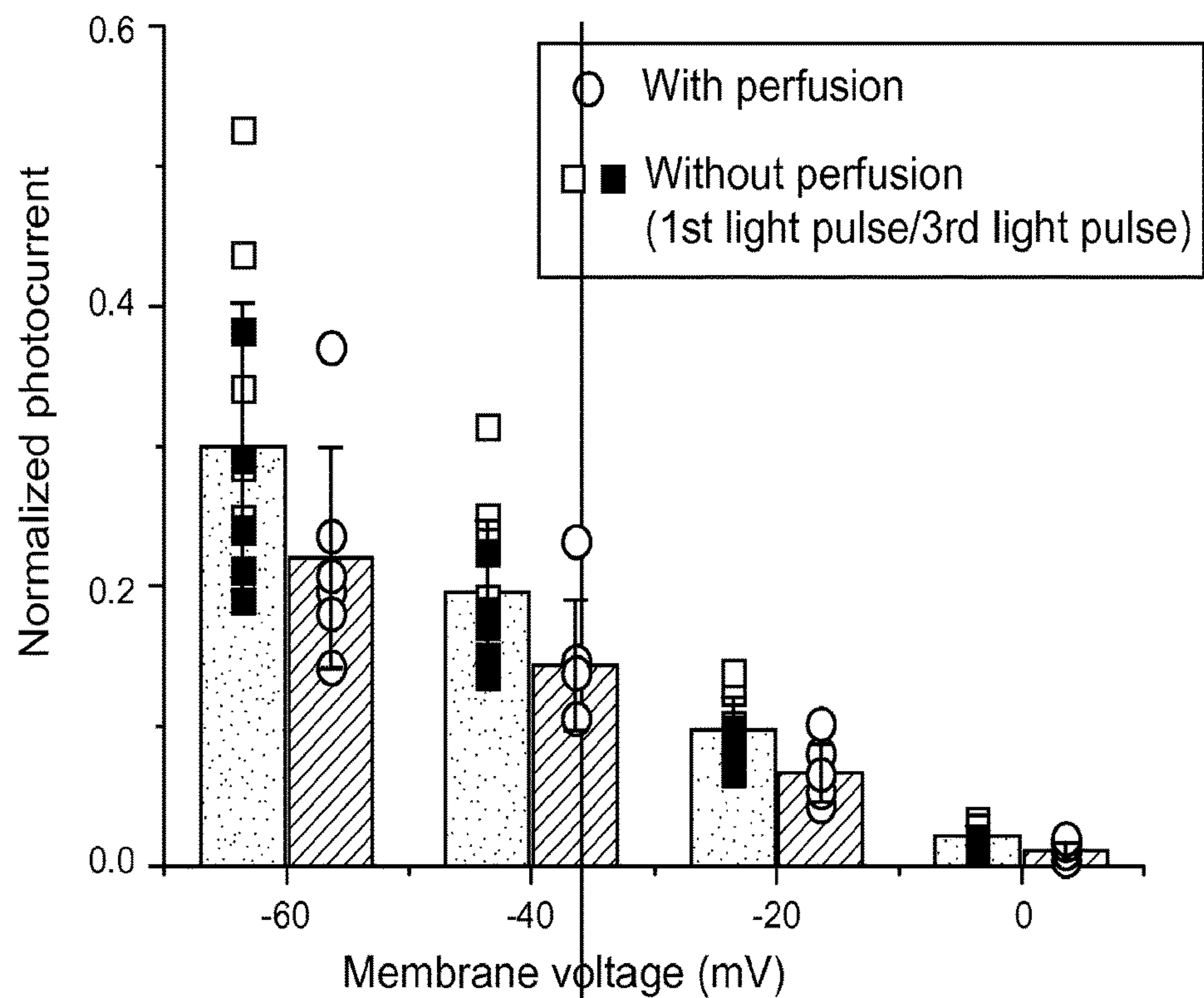


FIG. 25B

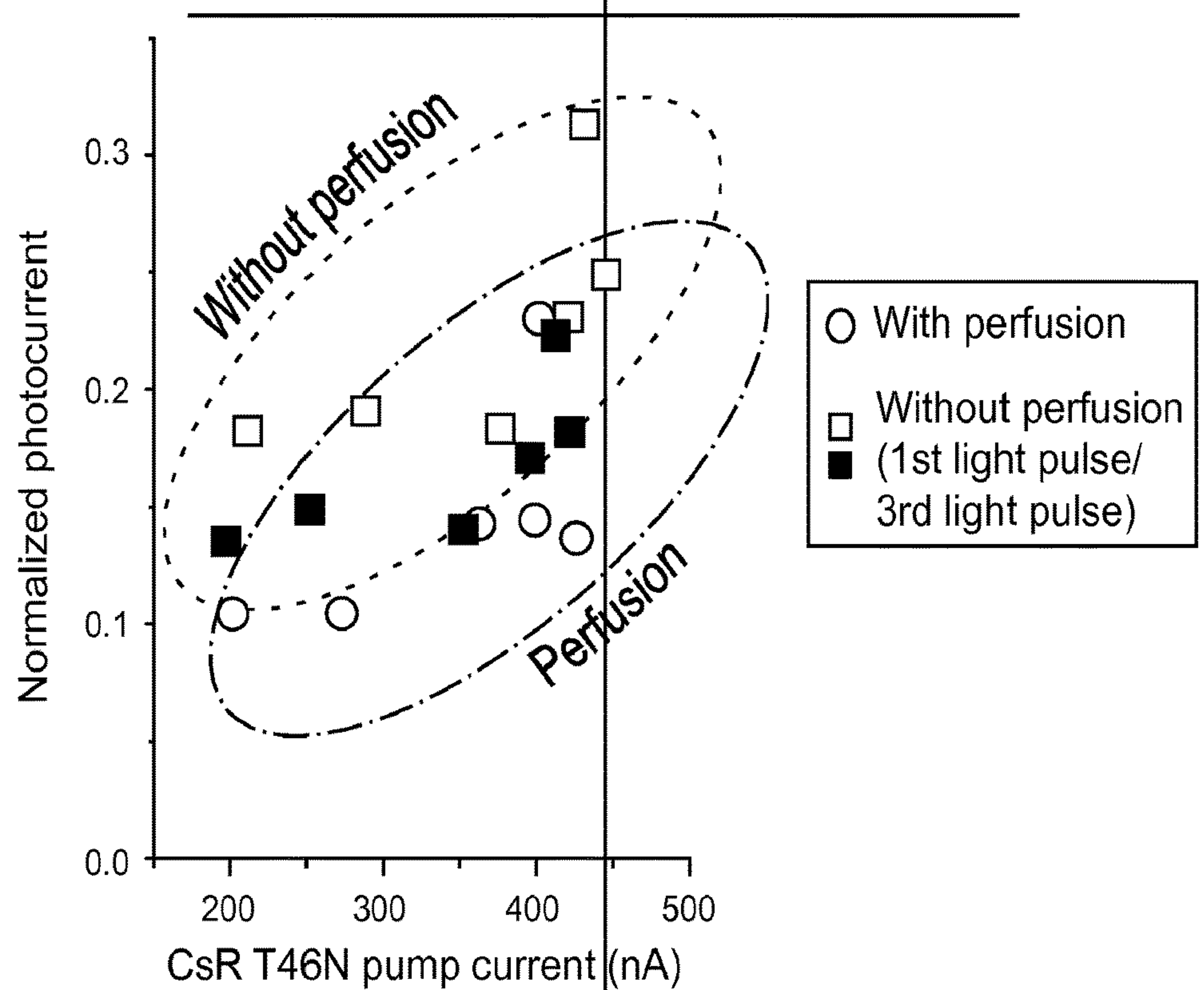


FIG. 25C

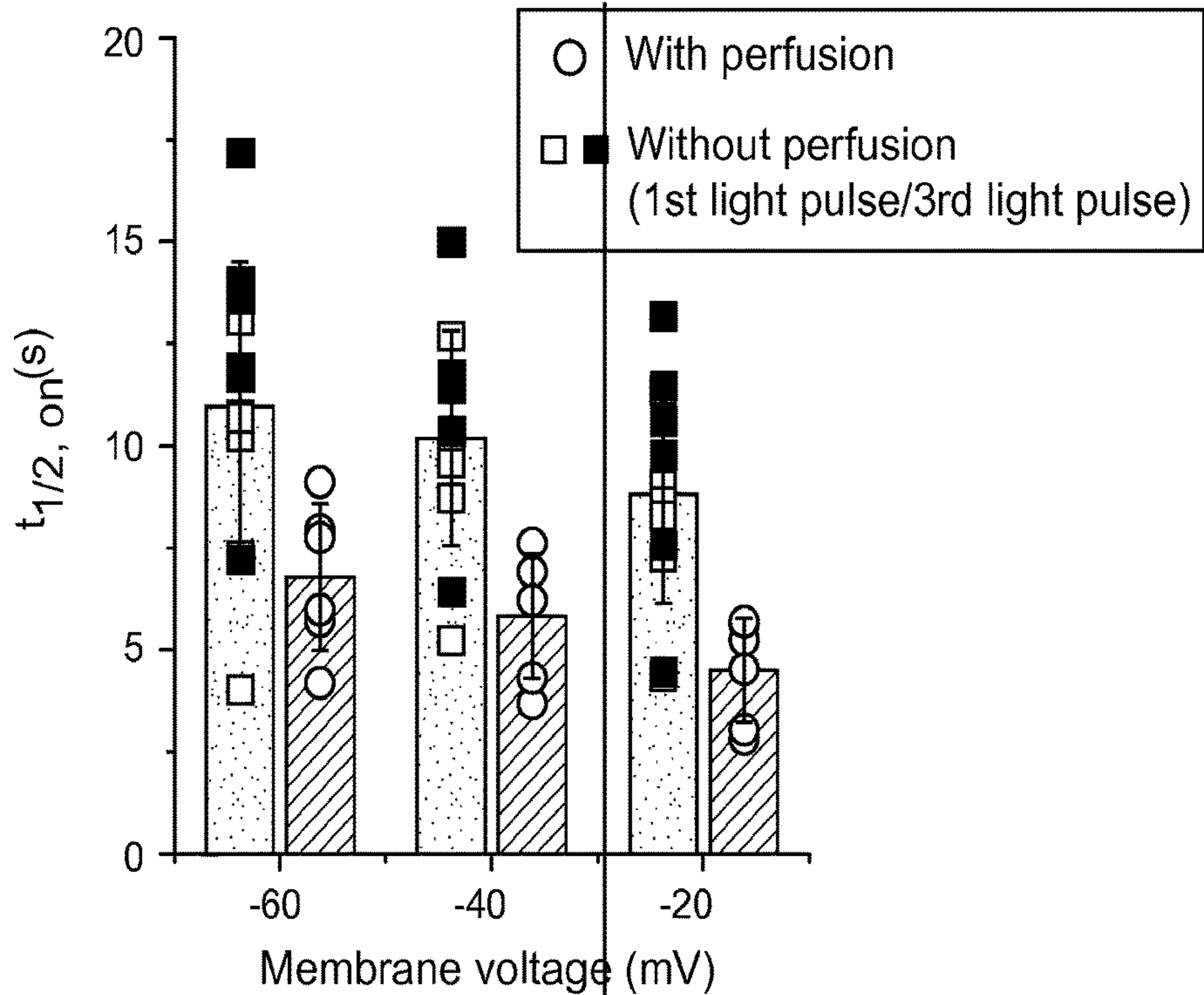


FIG. 25D

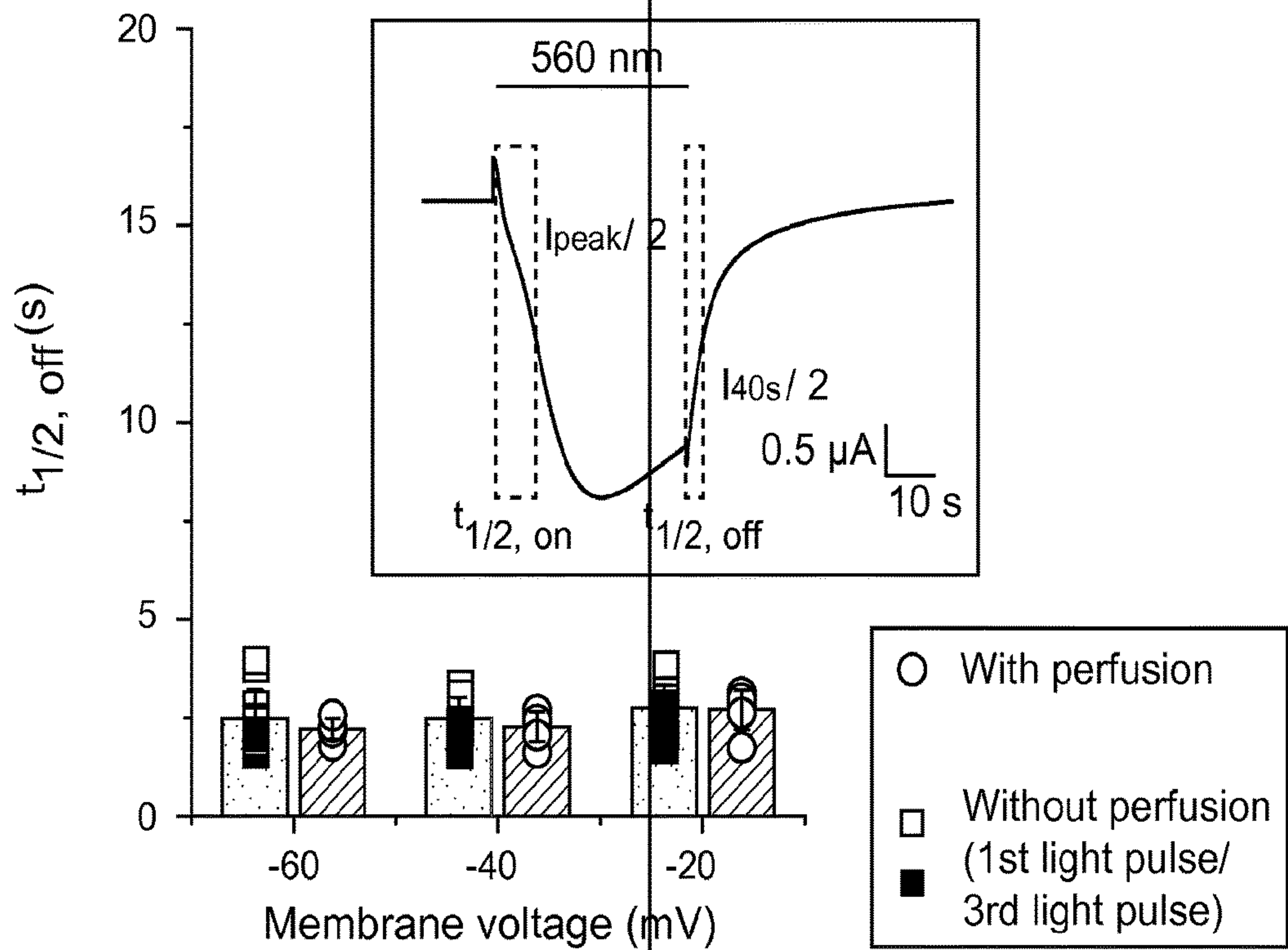


FIG. 25E

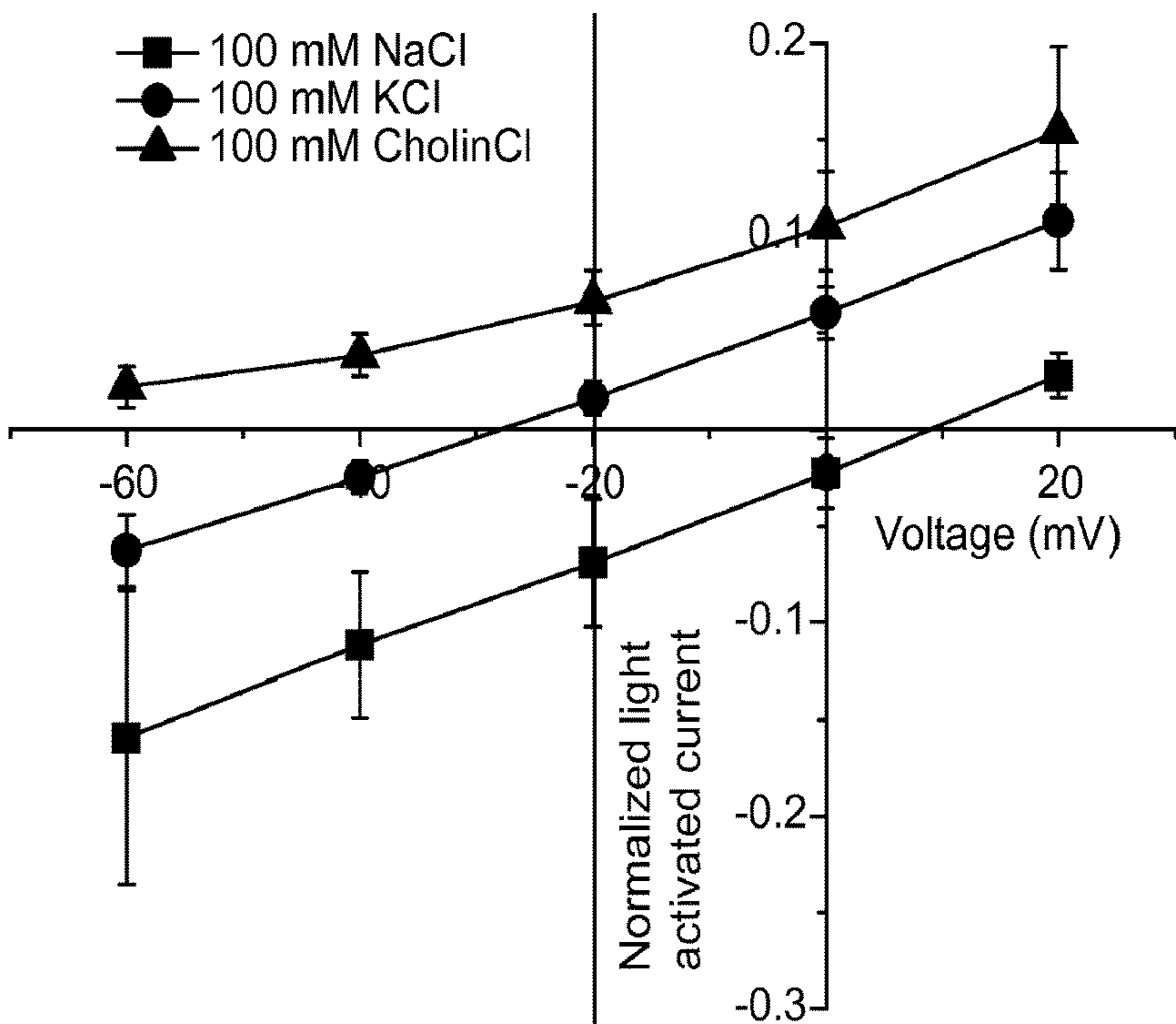


FIG. 26A

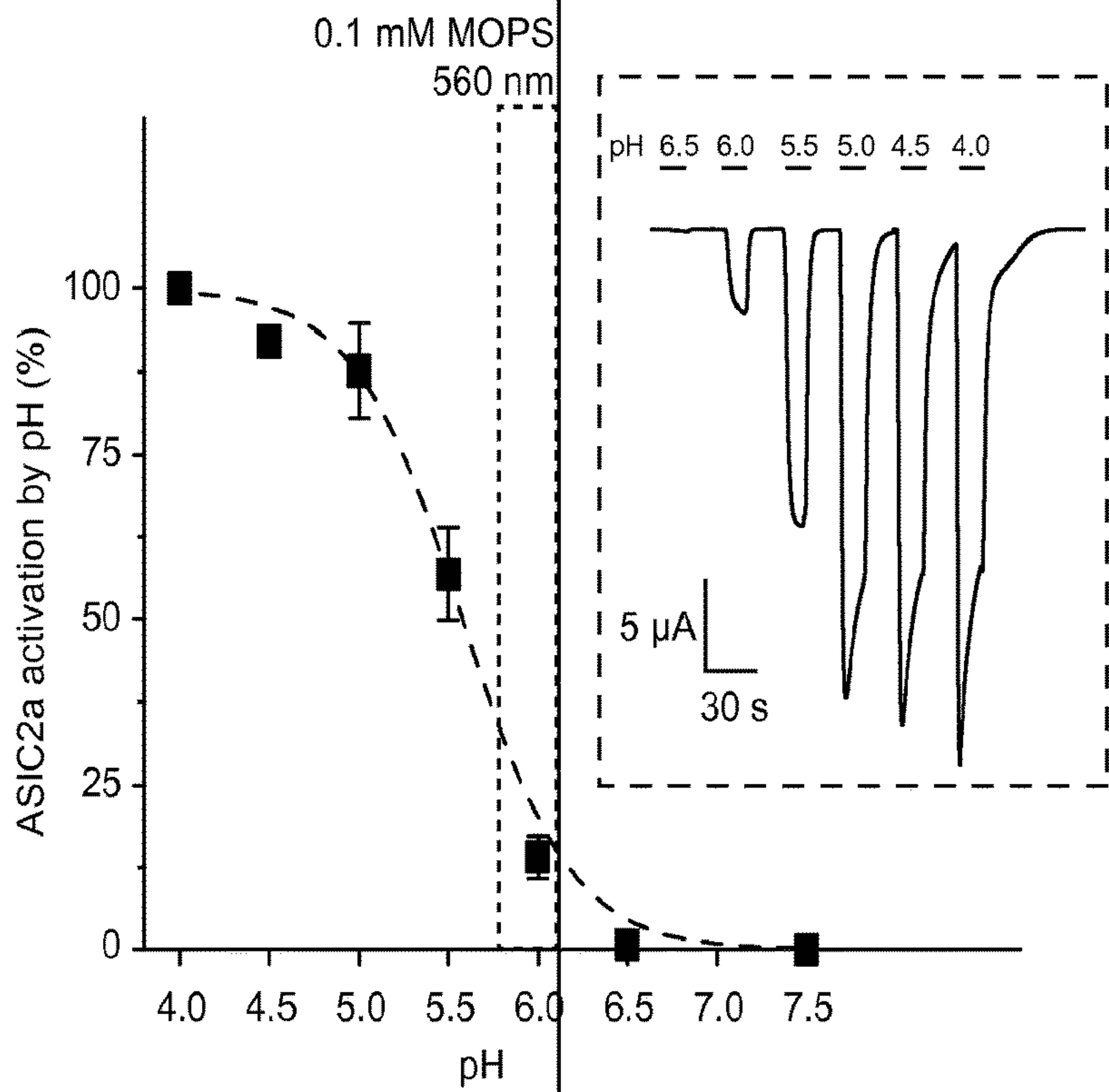


FIG. 26B

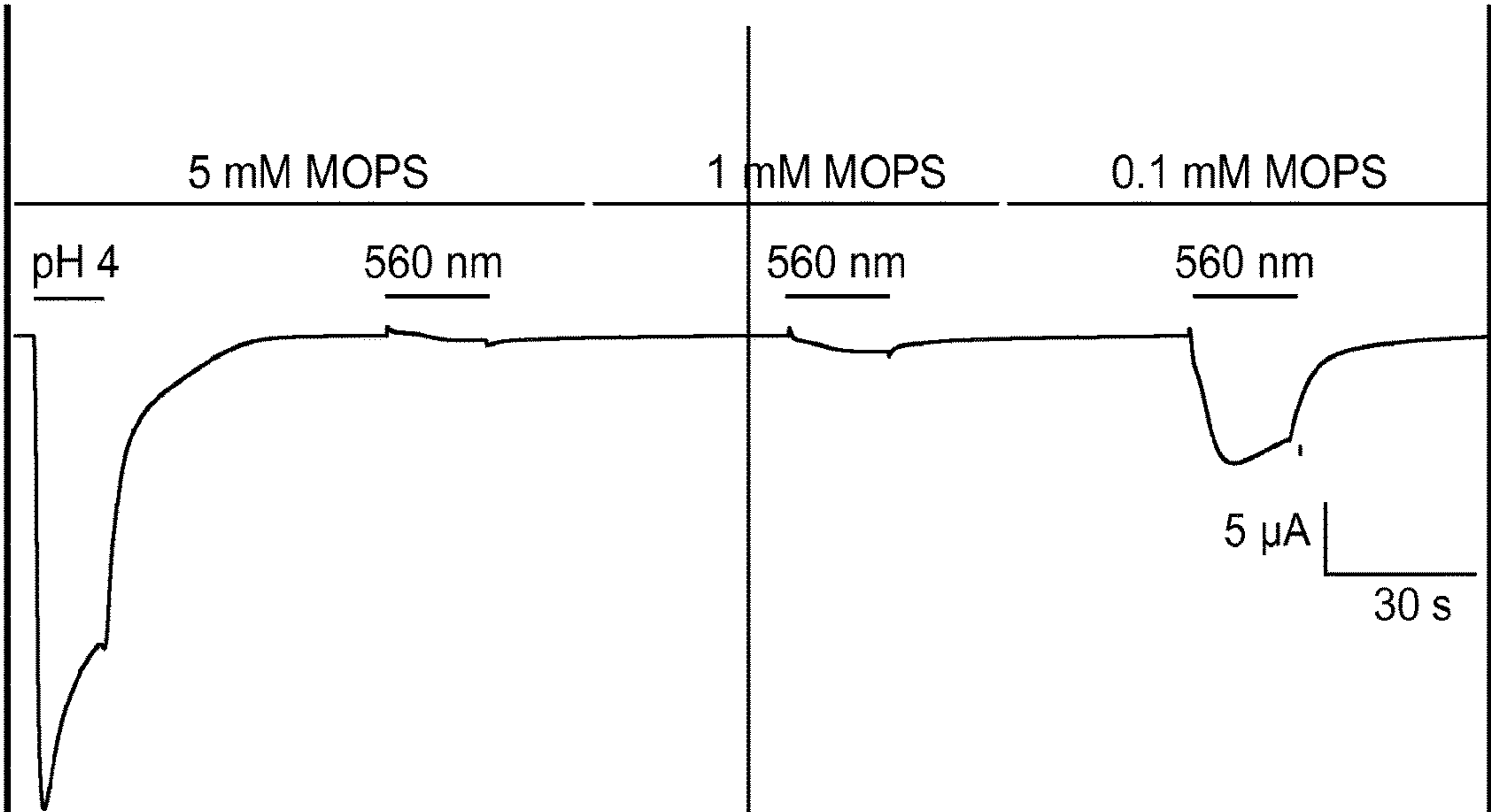


FIG. 26C

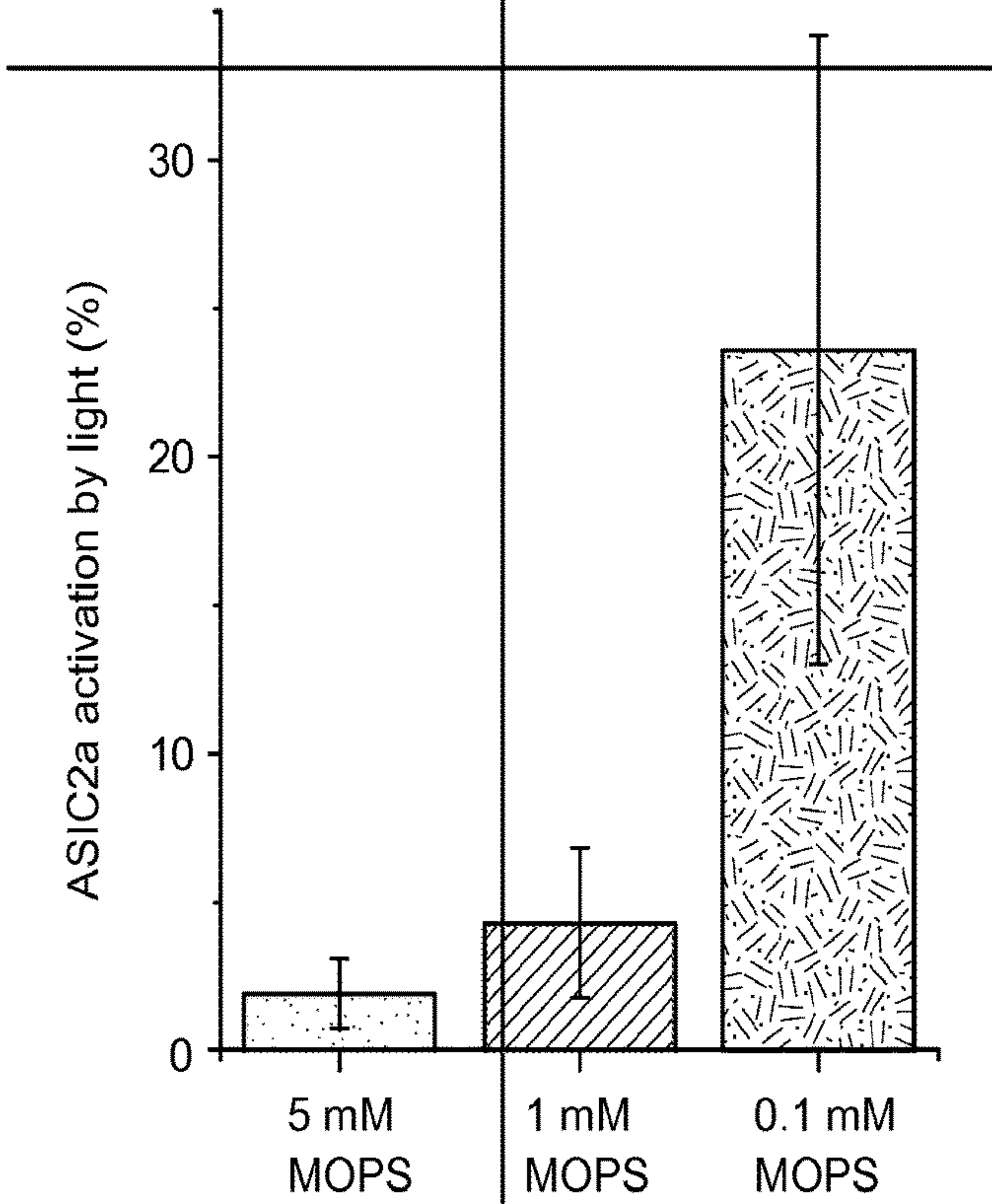


FIG. 26D

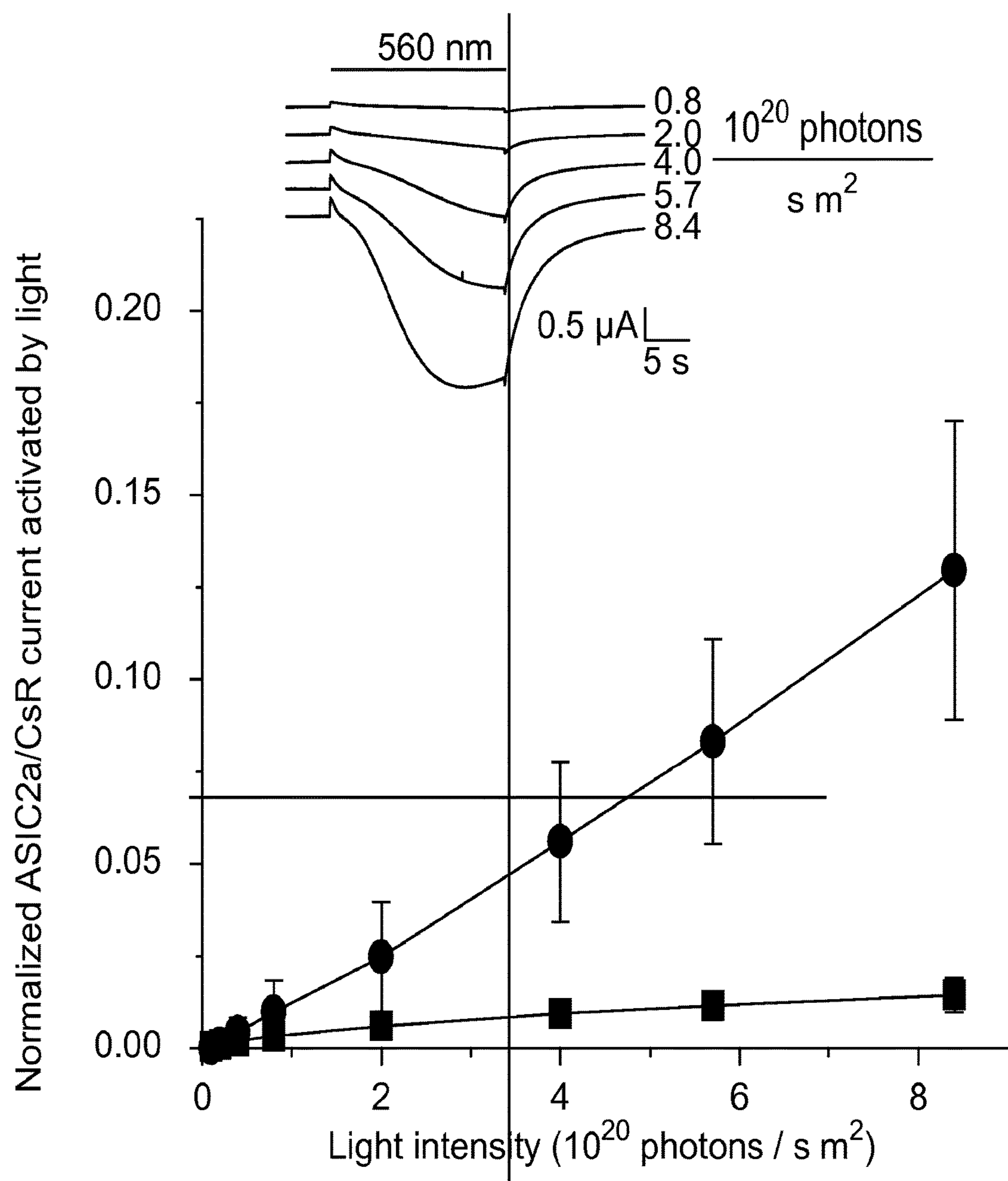


FIG. 26E

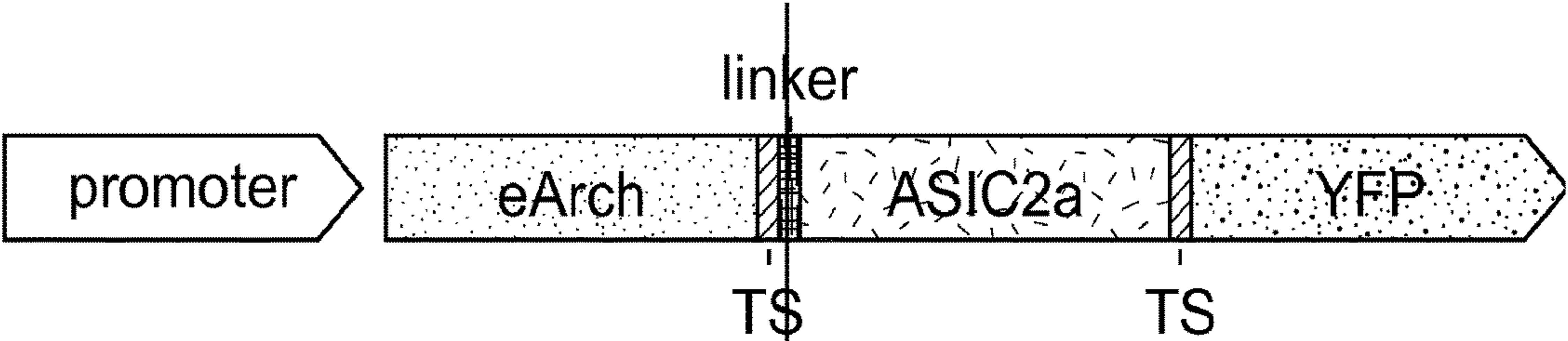
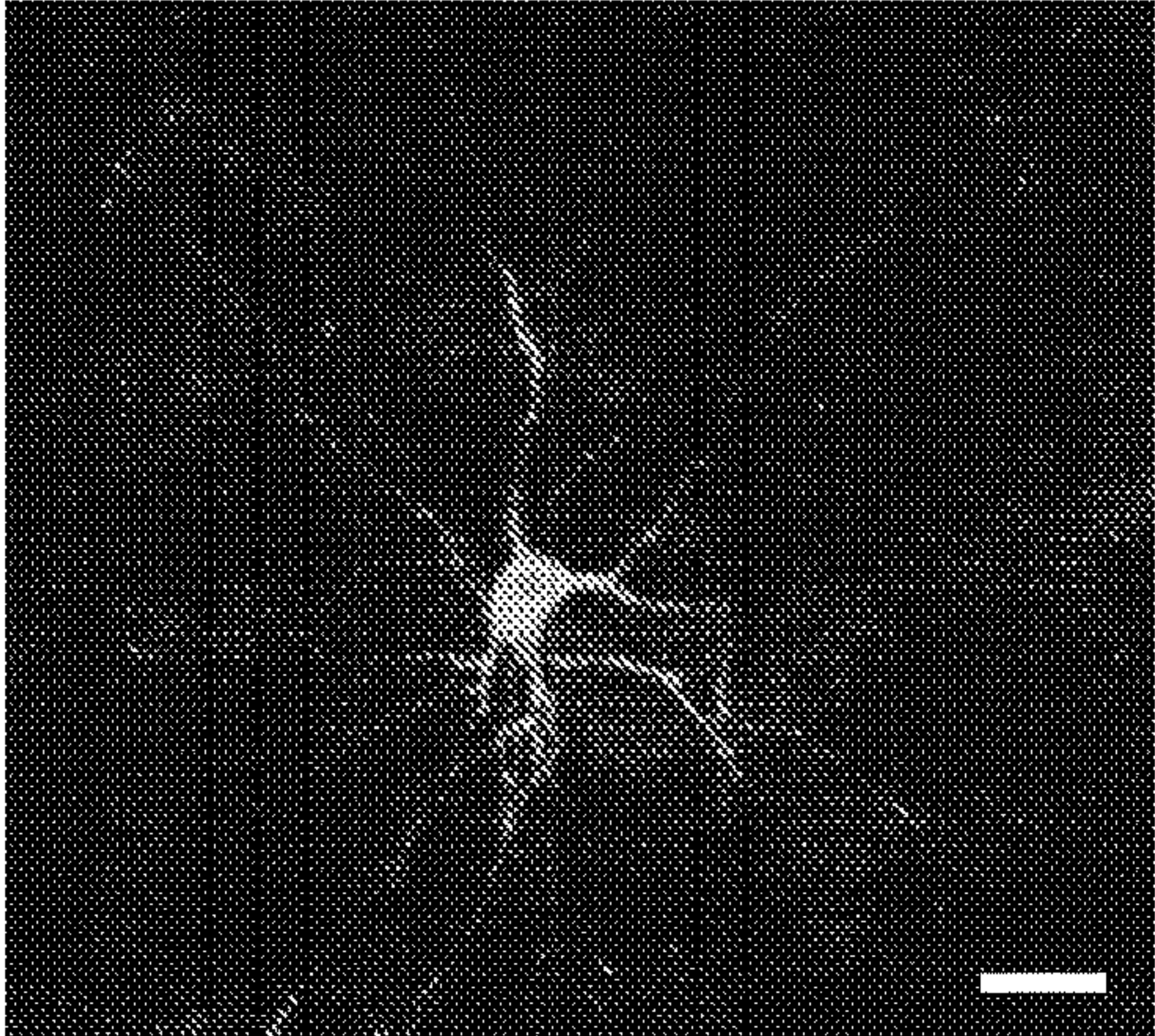


FIG. 27A

CamKII α -eArch-linker-ASIC2a-eYFP



hSyn-eArch-linker-ASICa-YFP

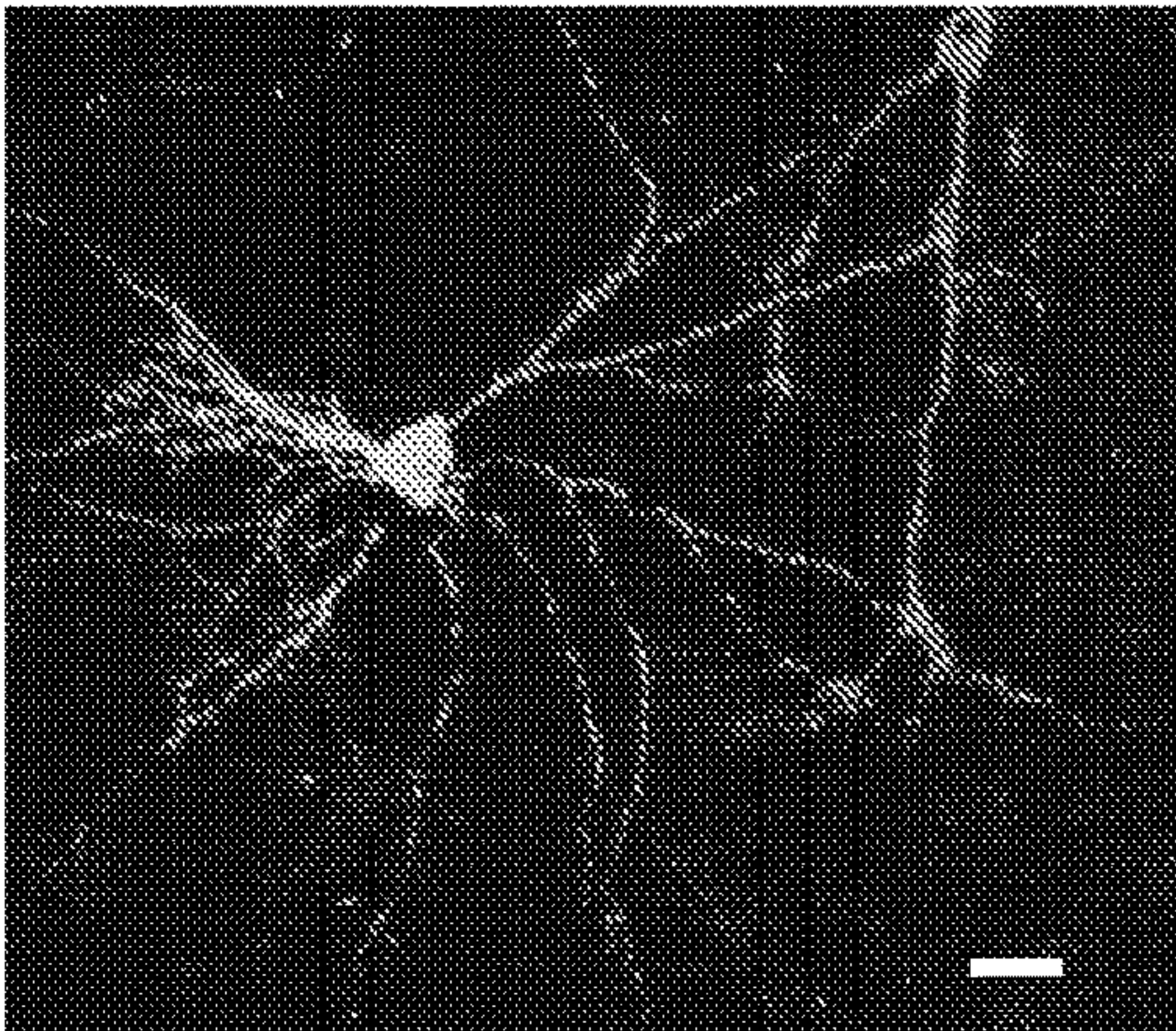


FIG. 27B

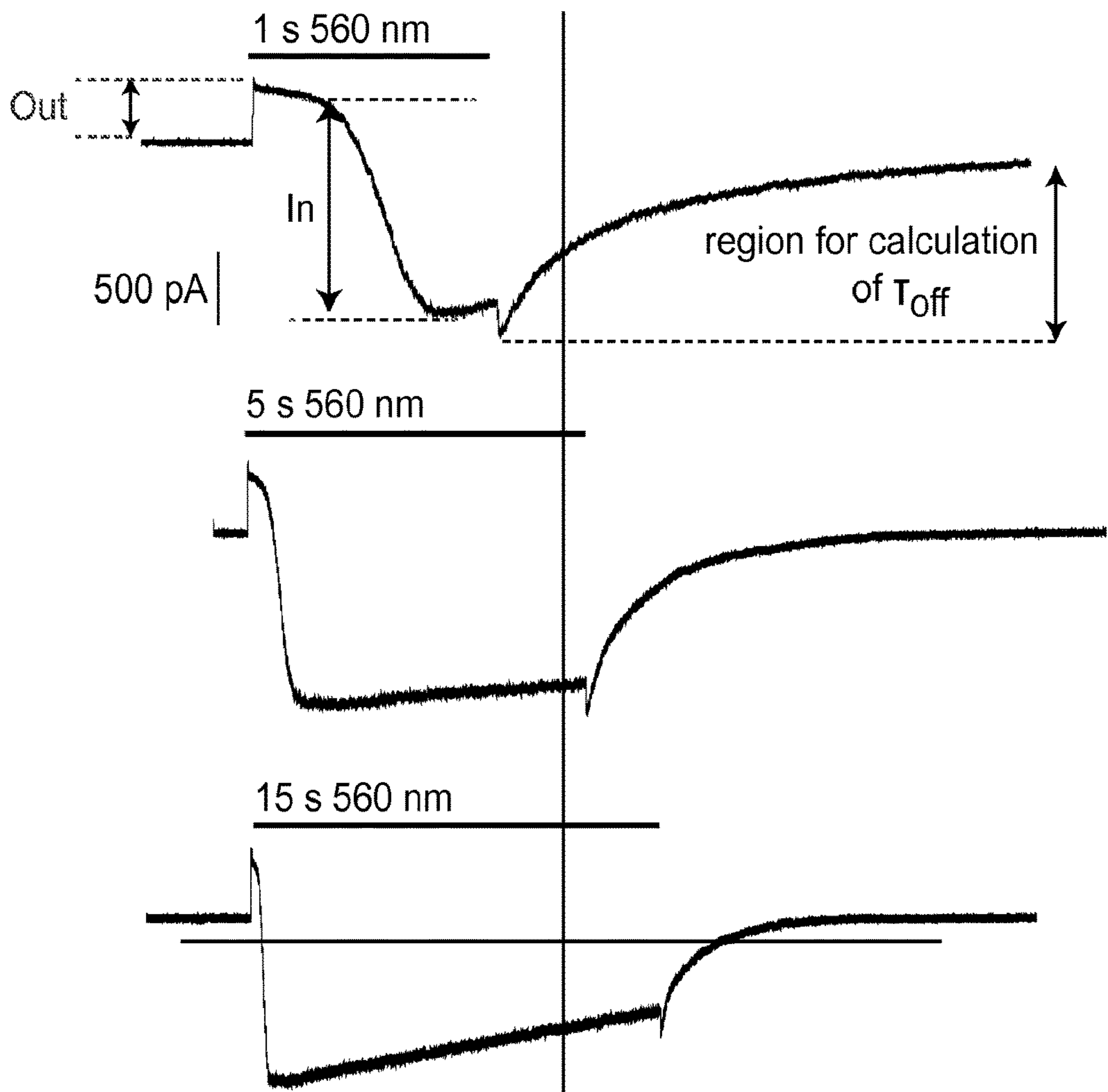


FIG. 27C

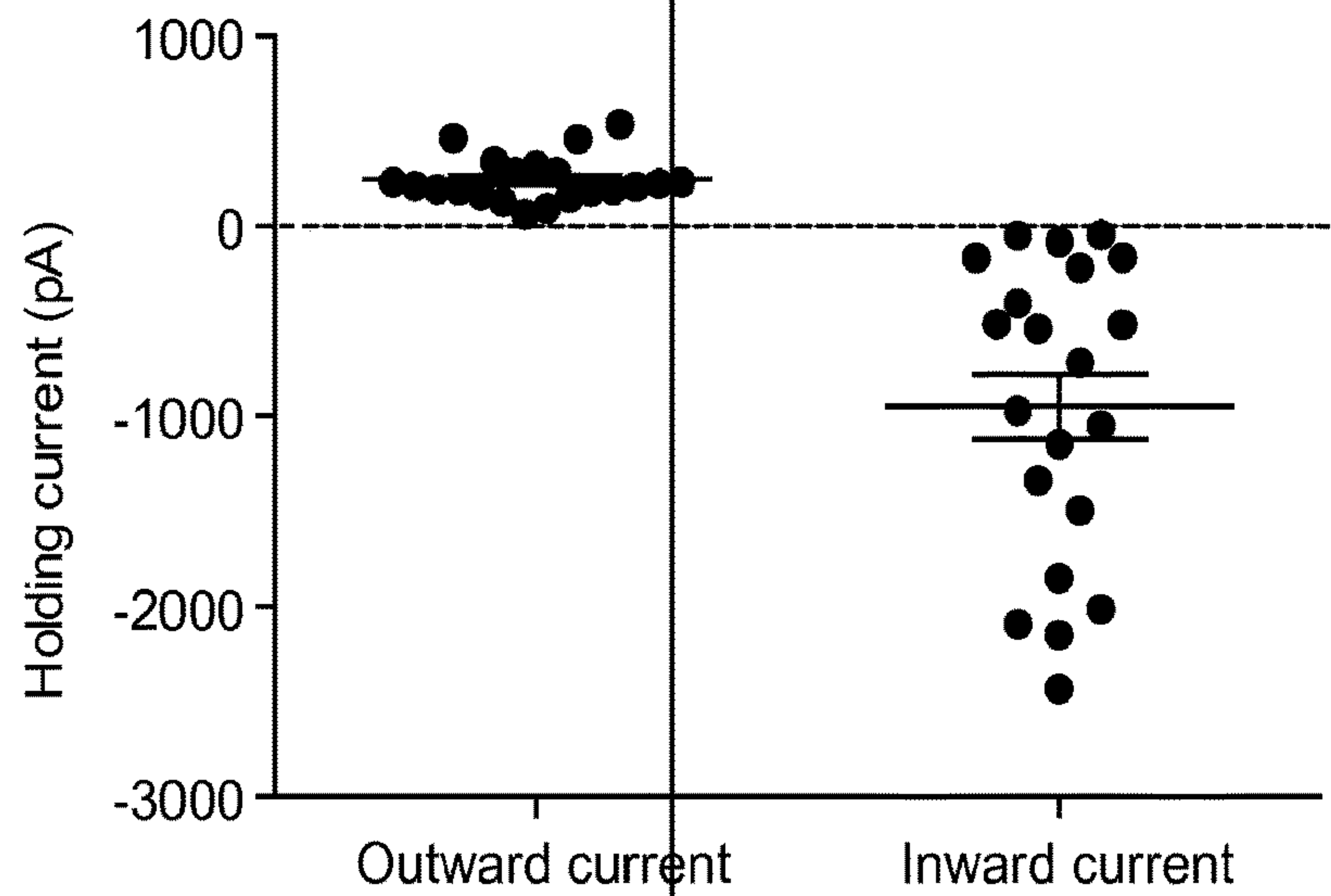


FIG. 27D

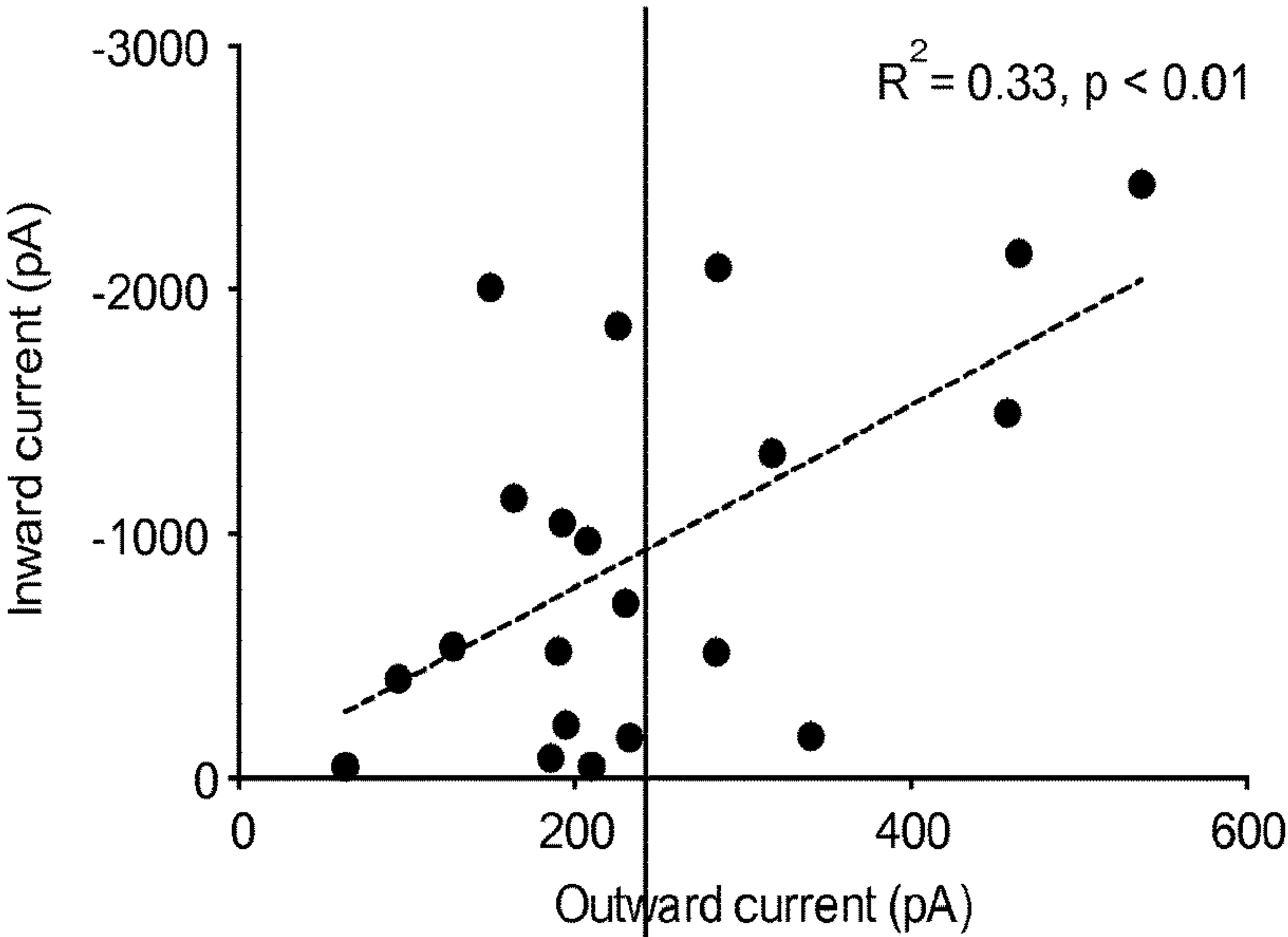


FIG. 27E

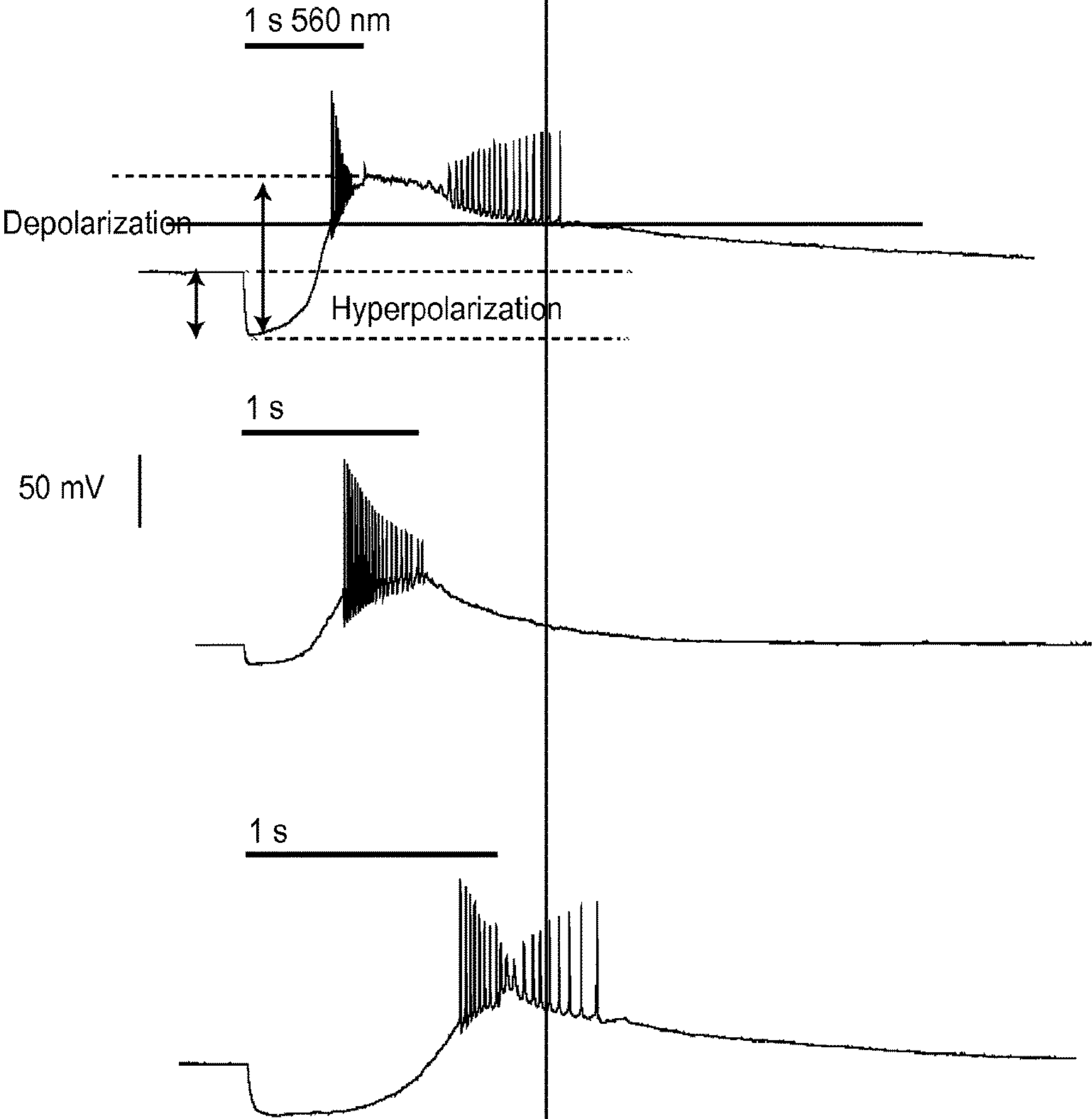


FIG. 27F

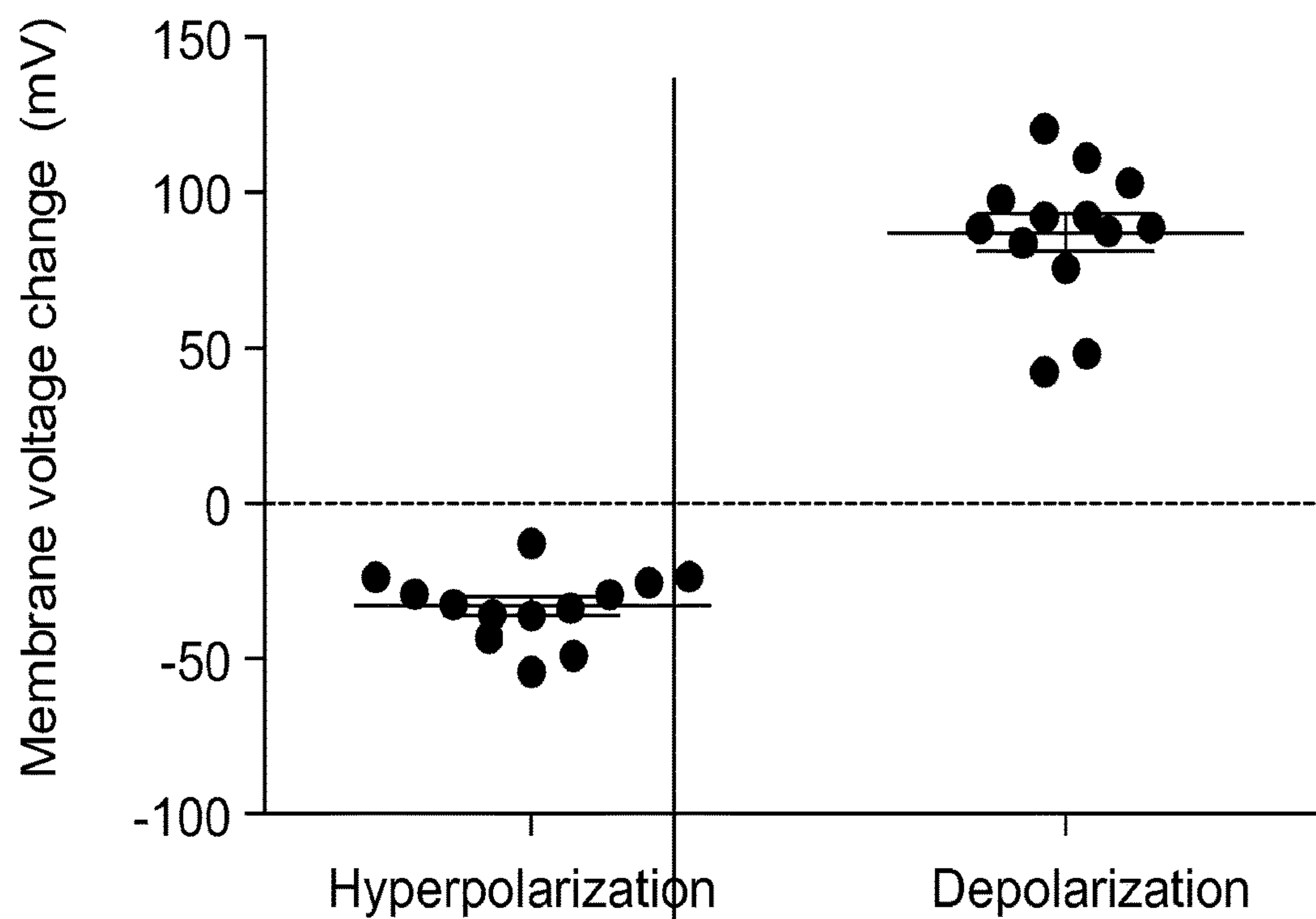


FIG. 27G

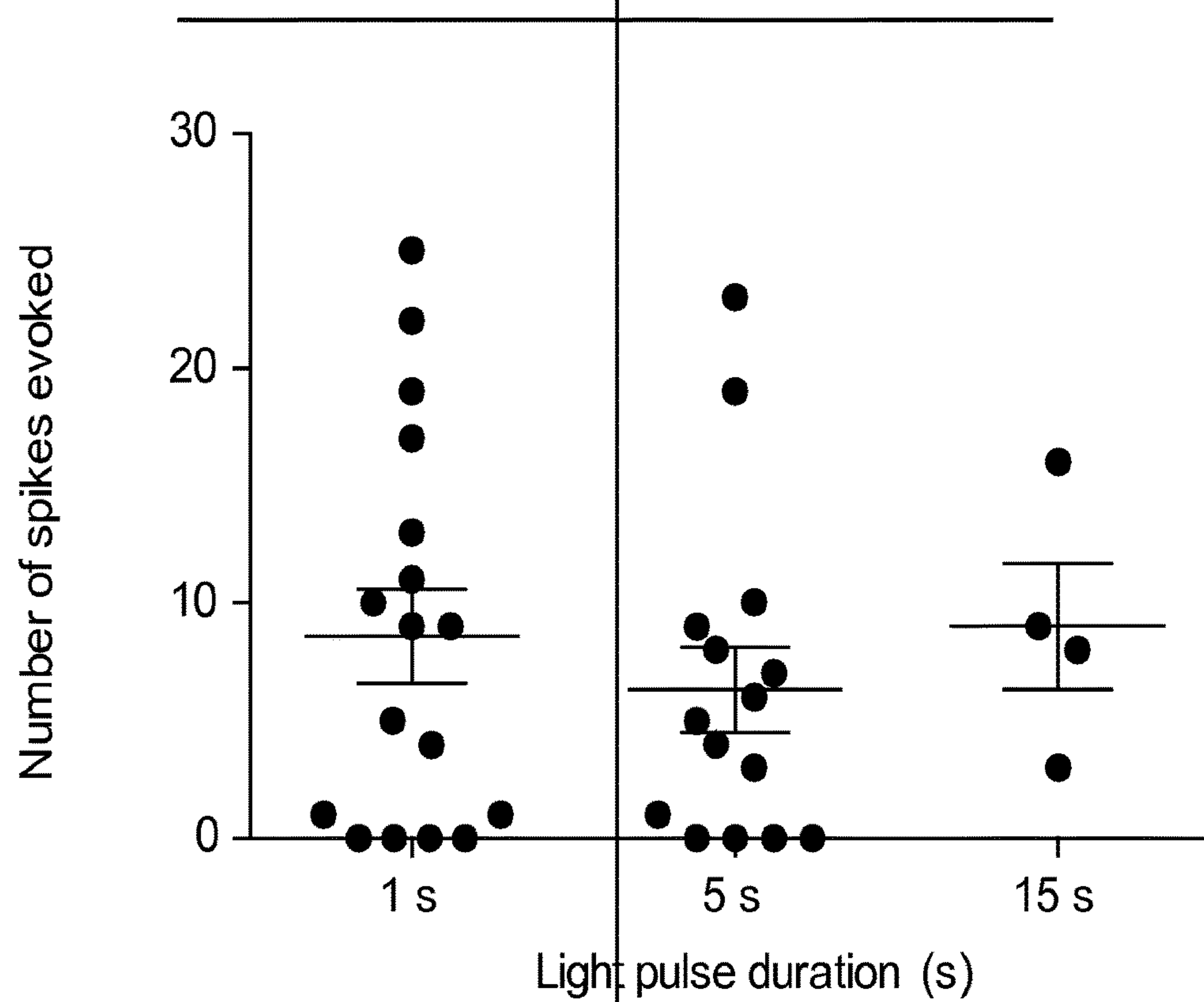


FIG. 27H

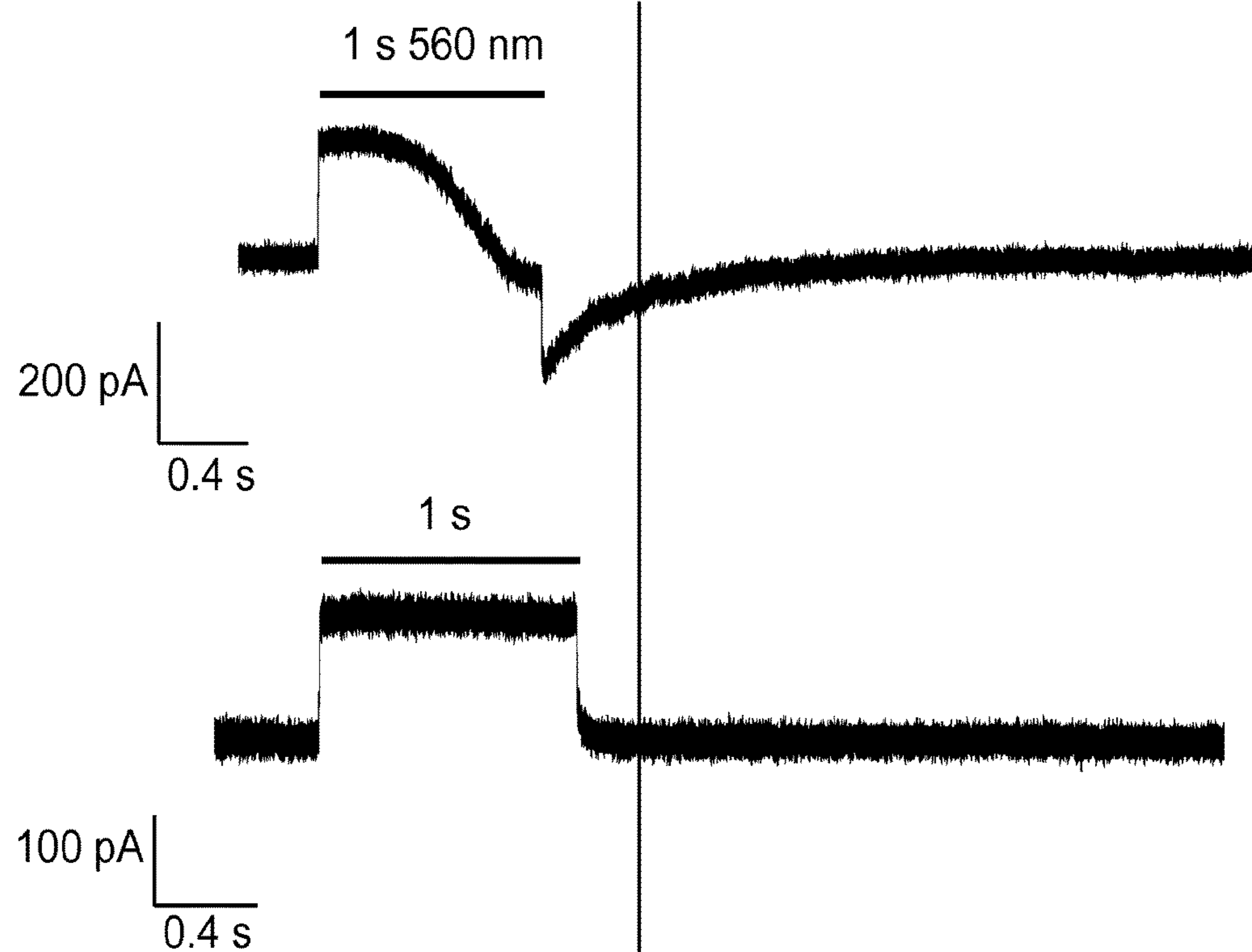


FIG. 28A

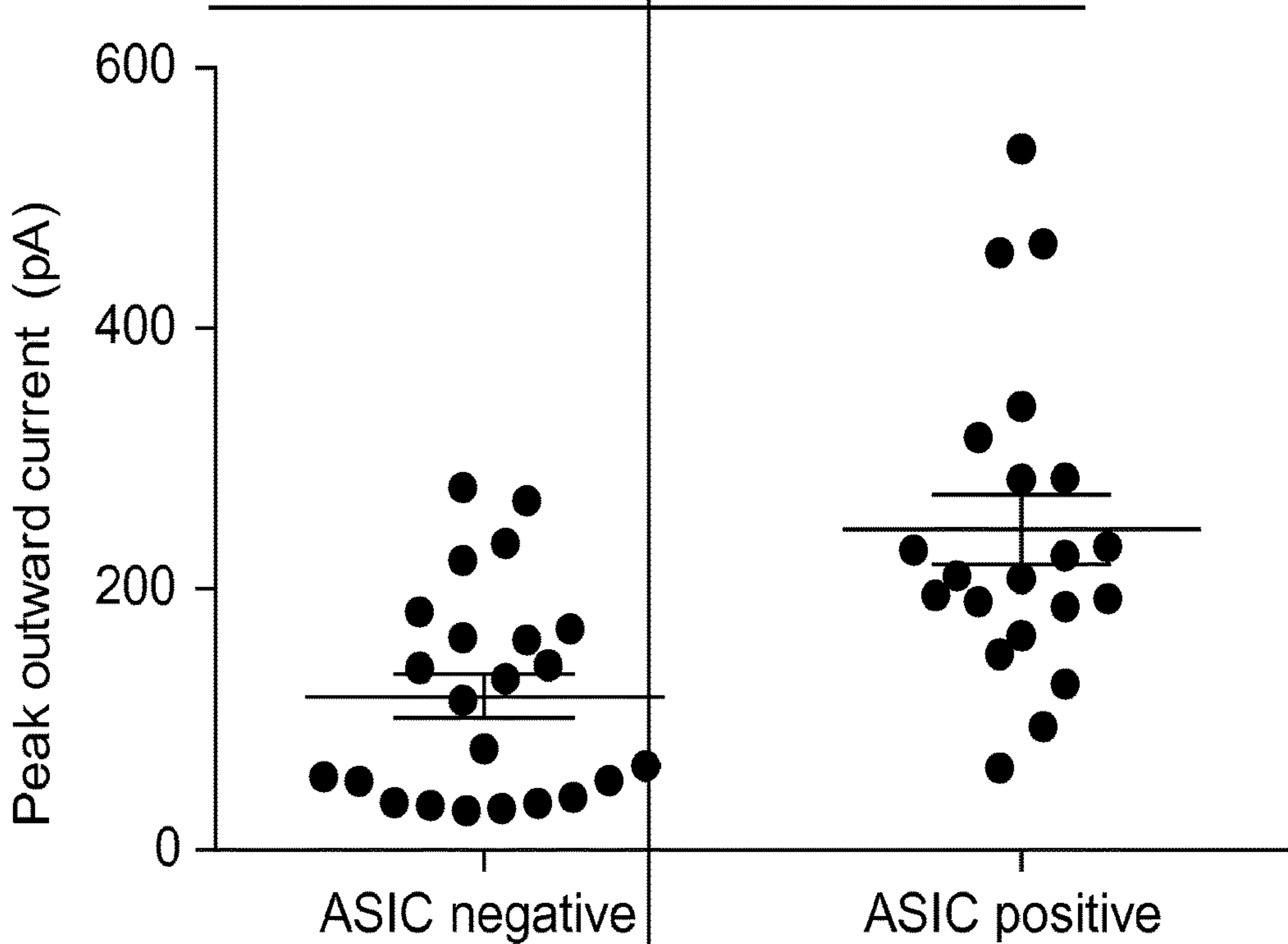


FIG. 28B

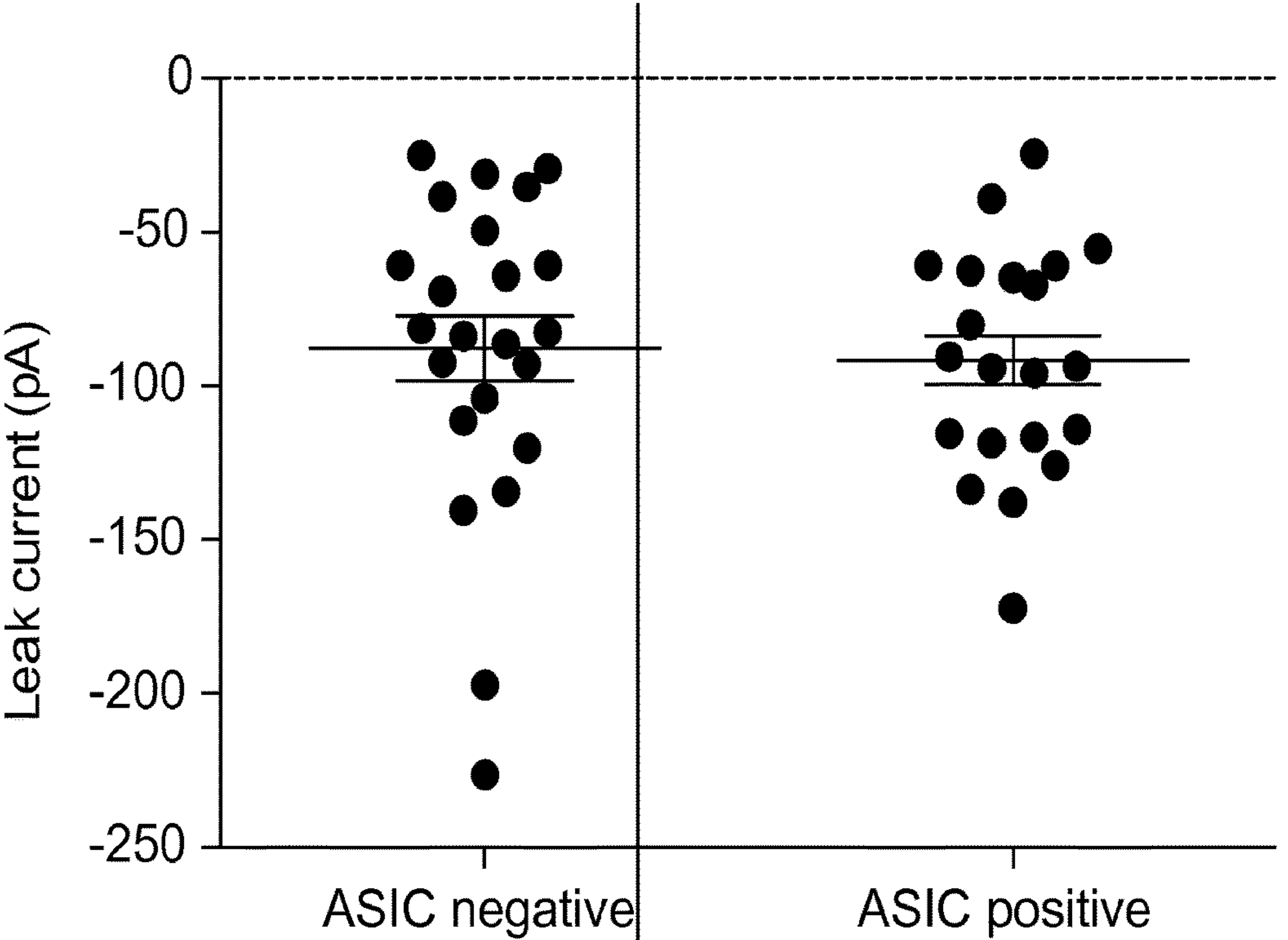


FIG. 28C

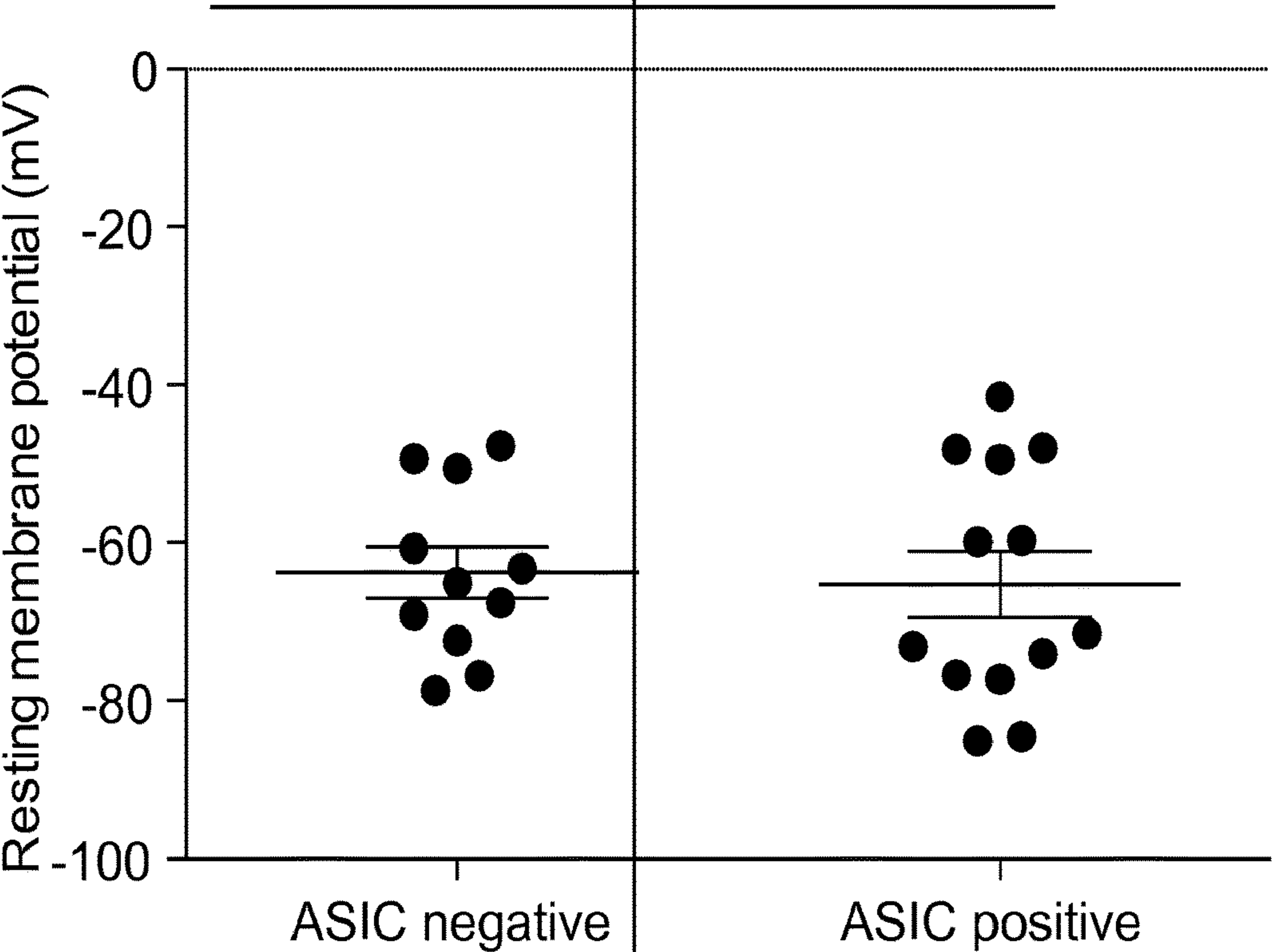


FIG. 28D

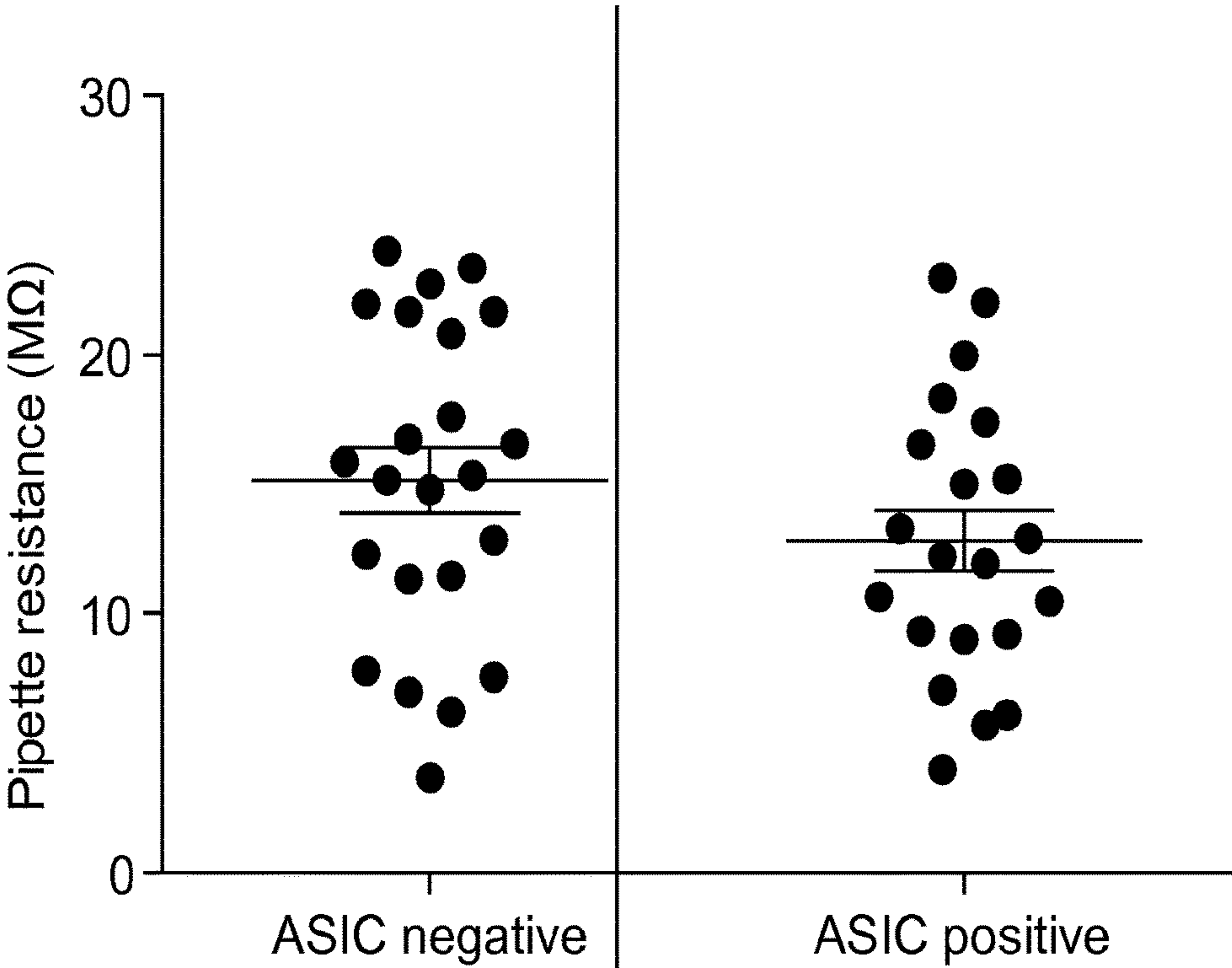


FIG. 28E

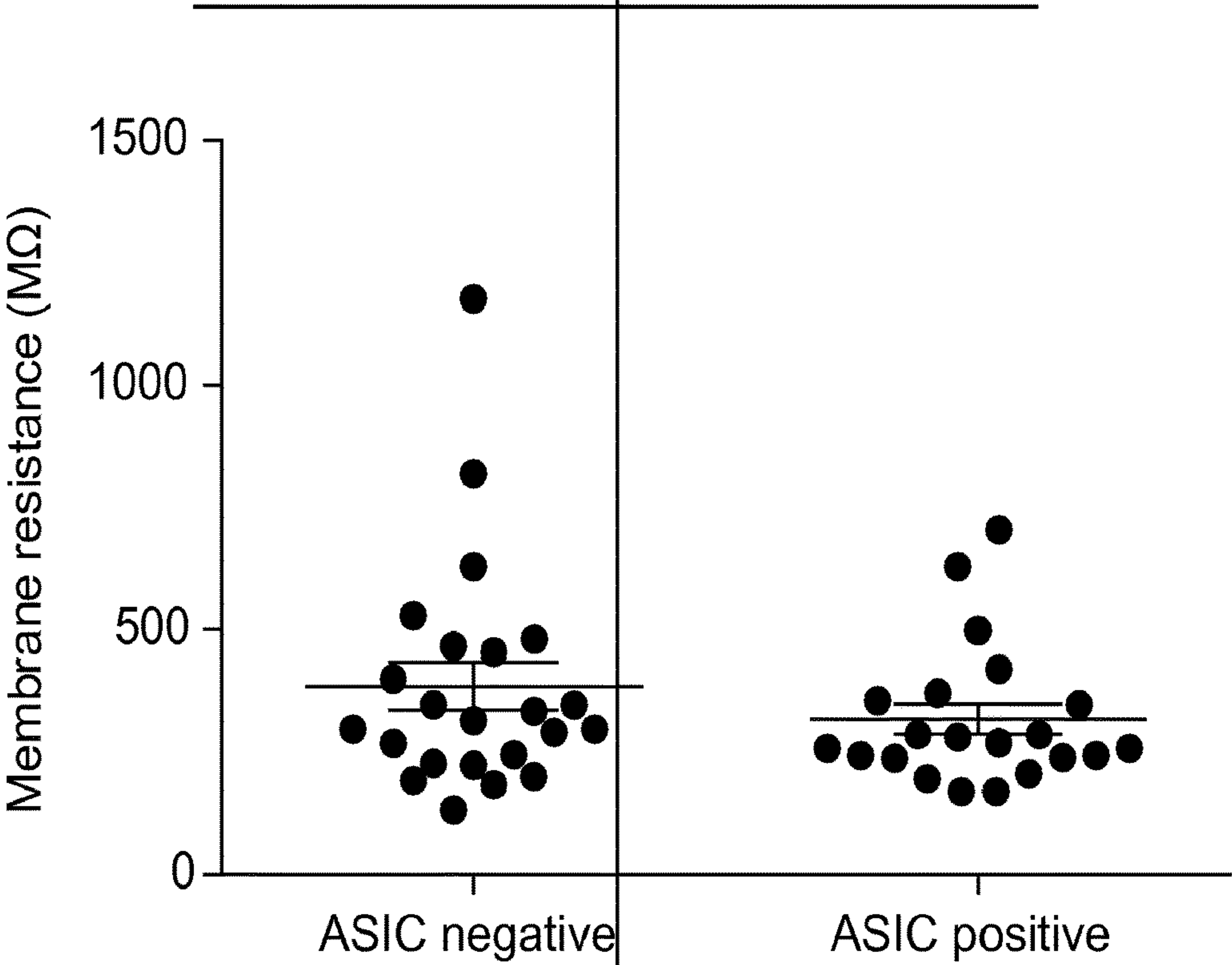


FIG. 28F

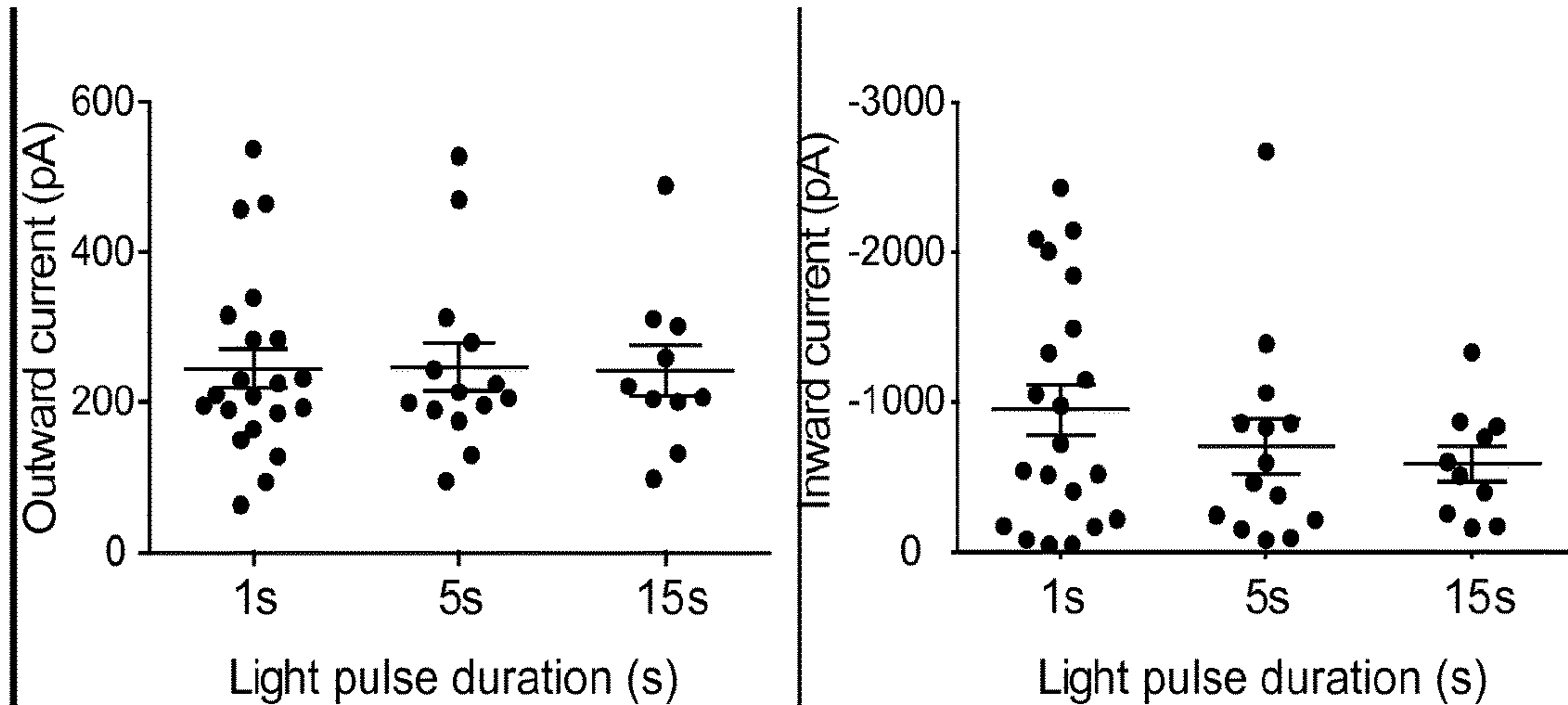


FIG. 29A

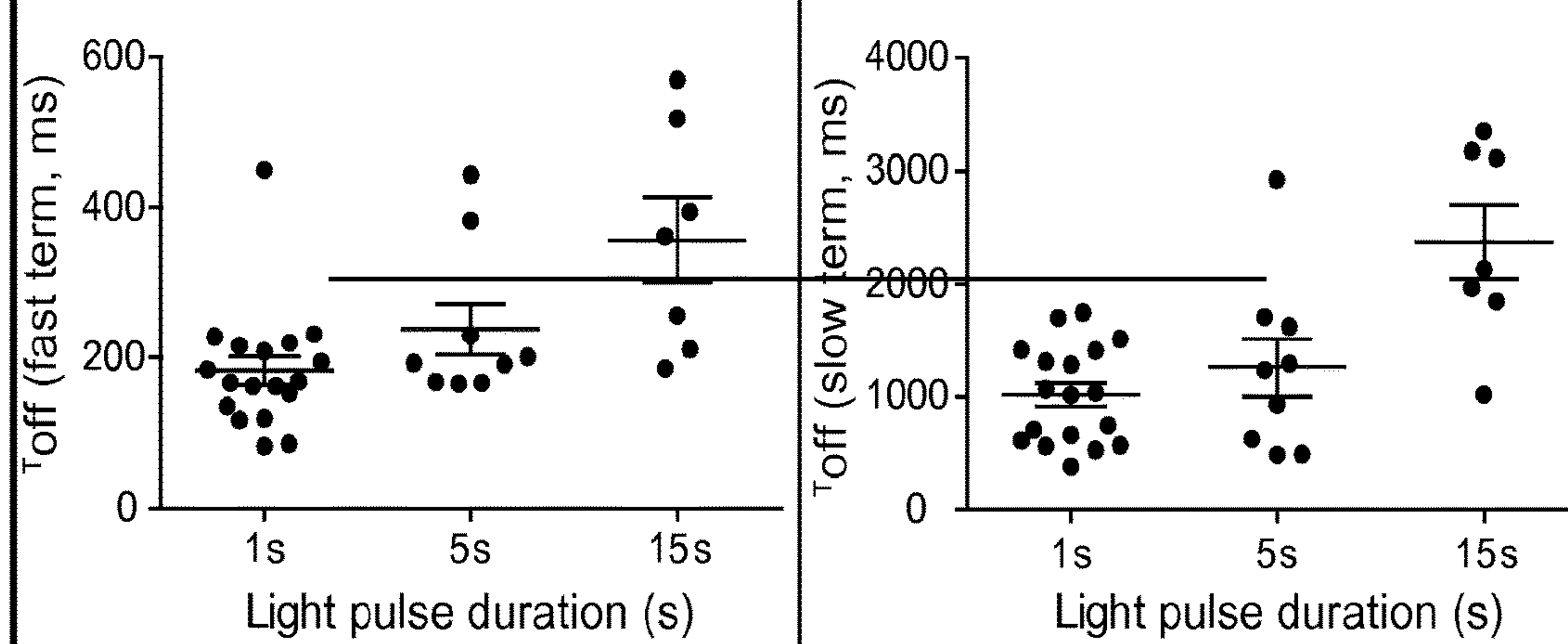


FIG. 29B

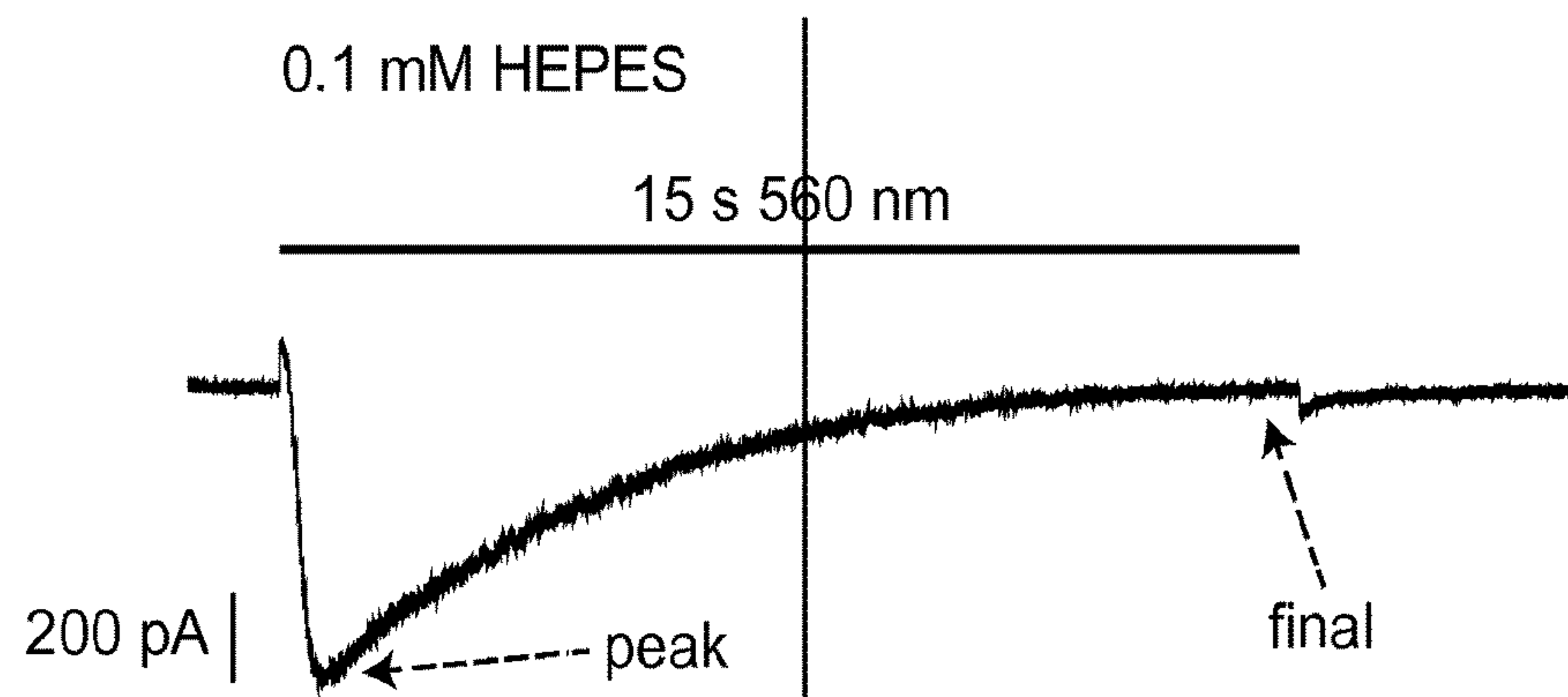


FIG. 30A

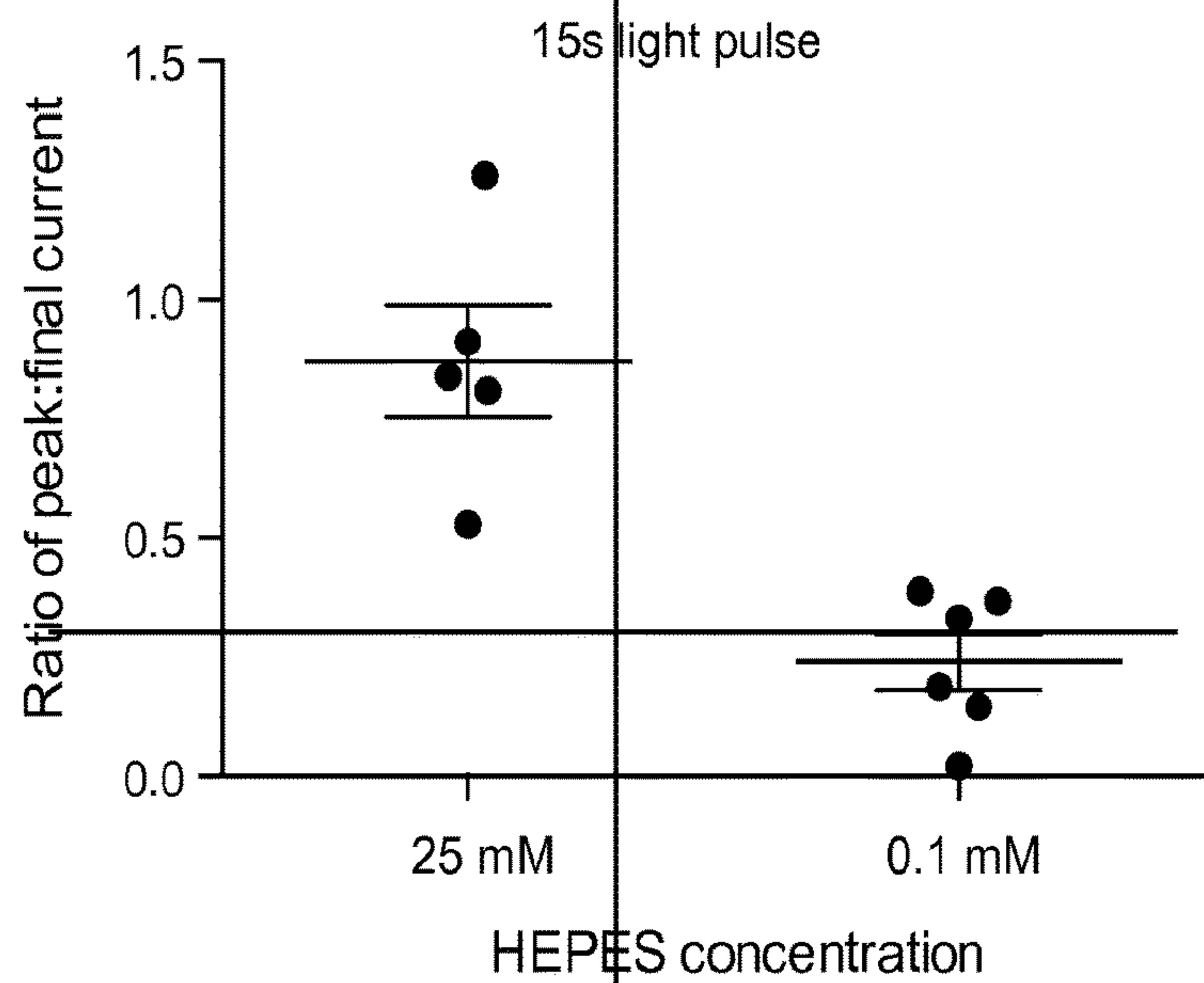


FIG. 30B

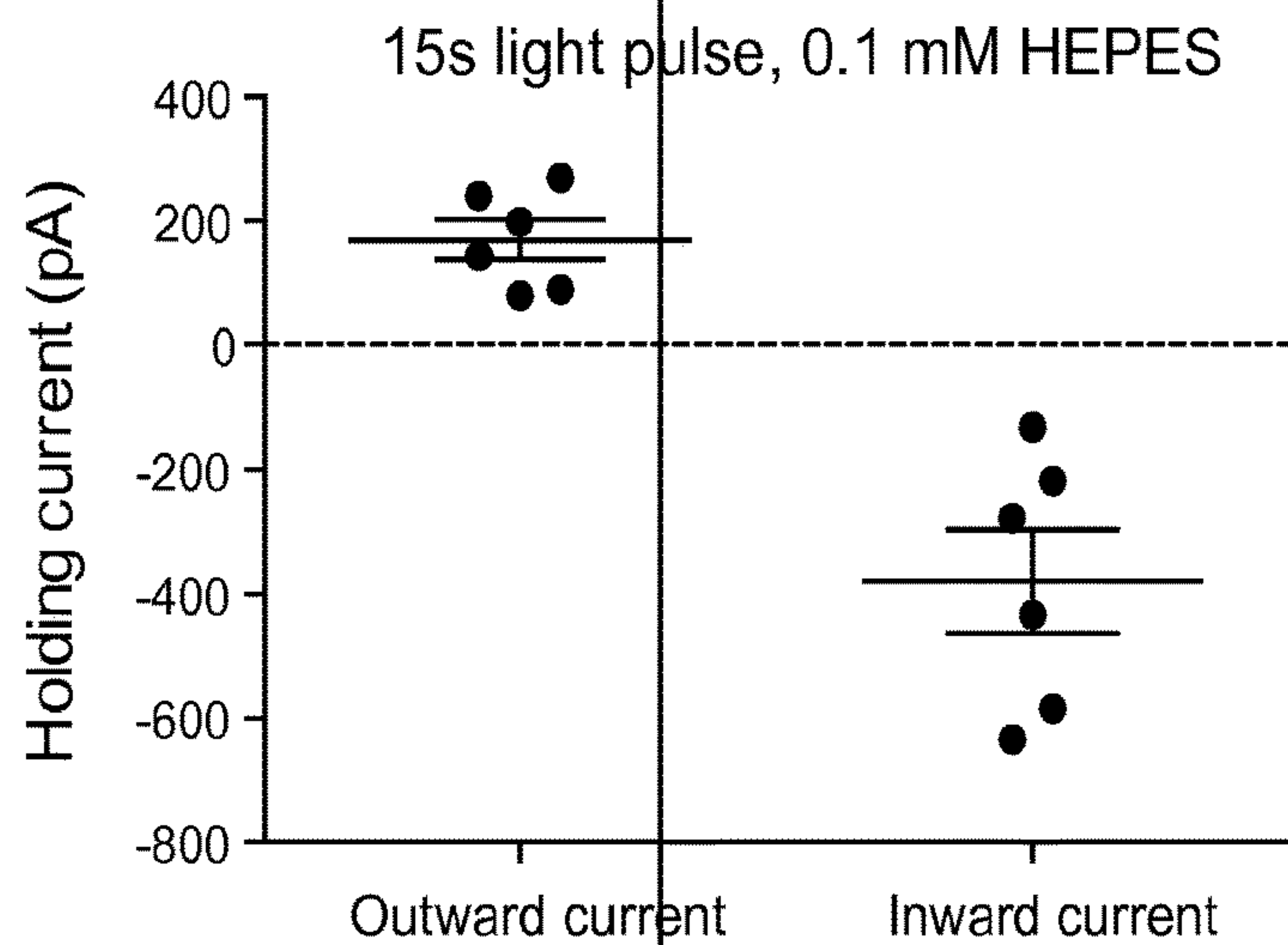


FIG. 30C

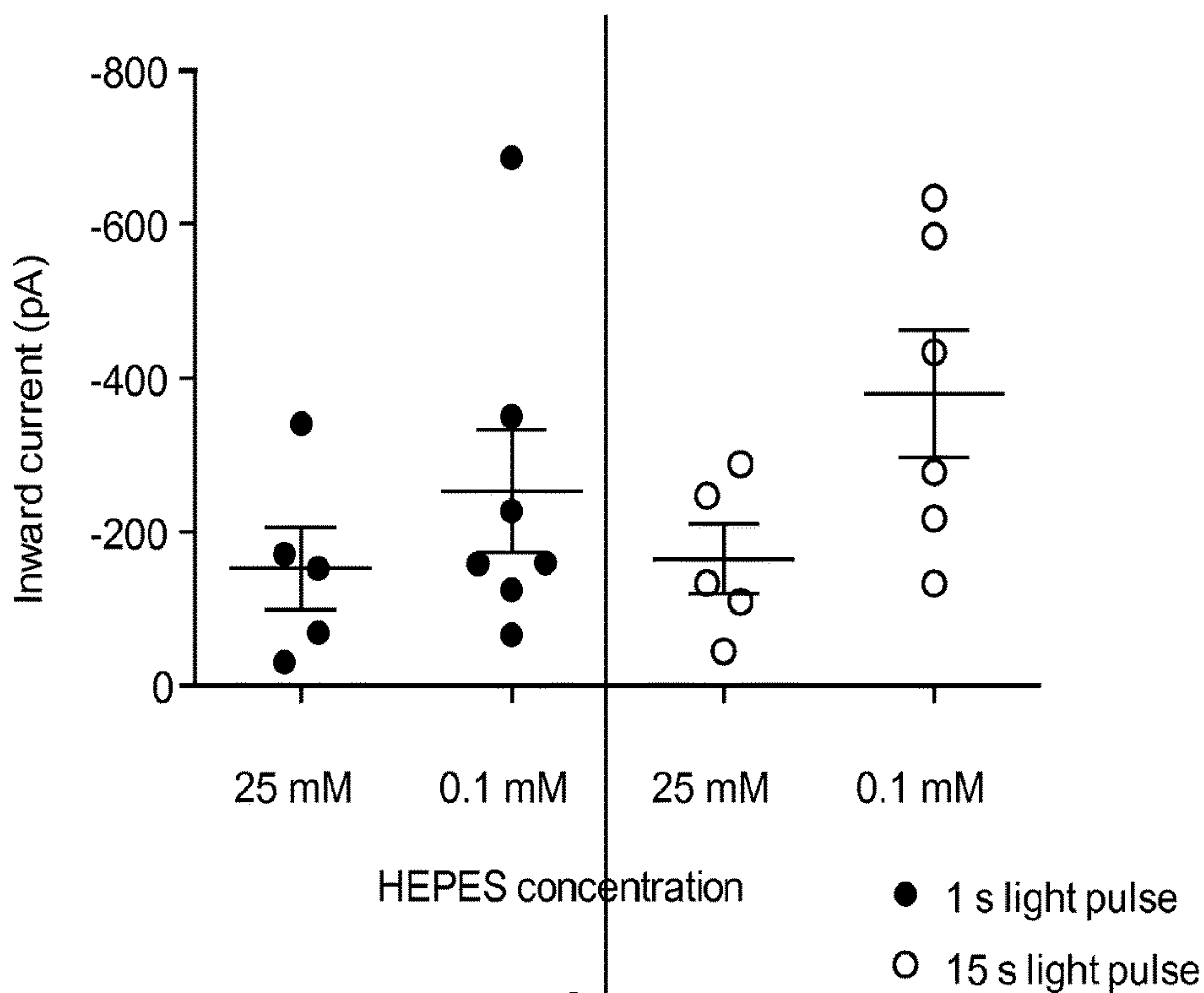


FIG. 30D

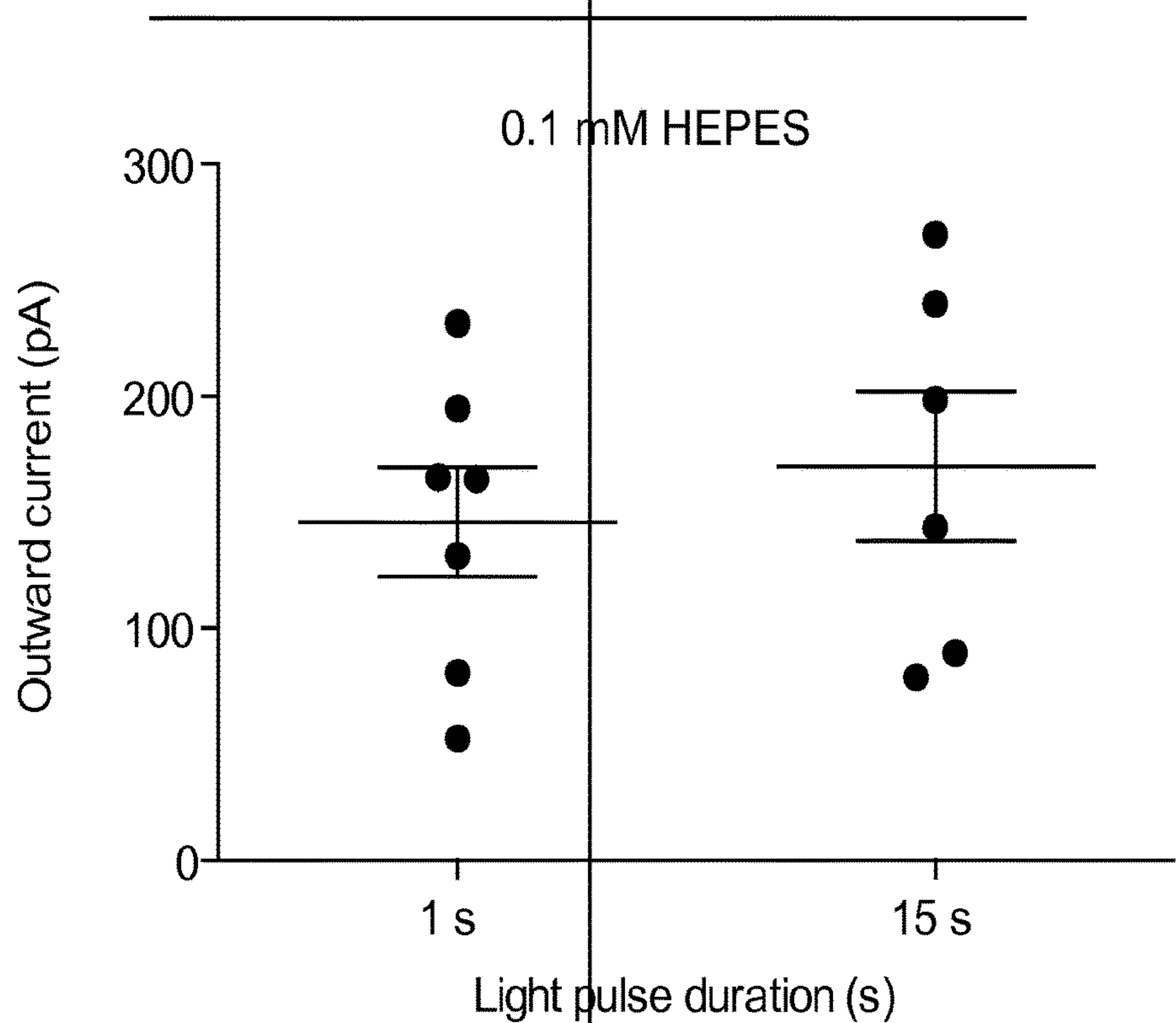


FIG. 30E

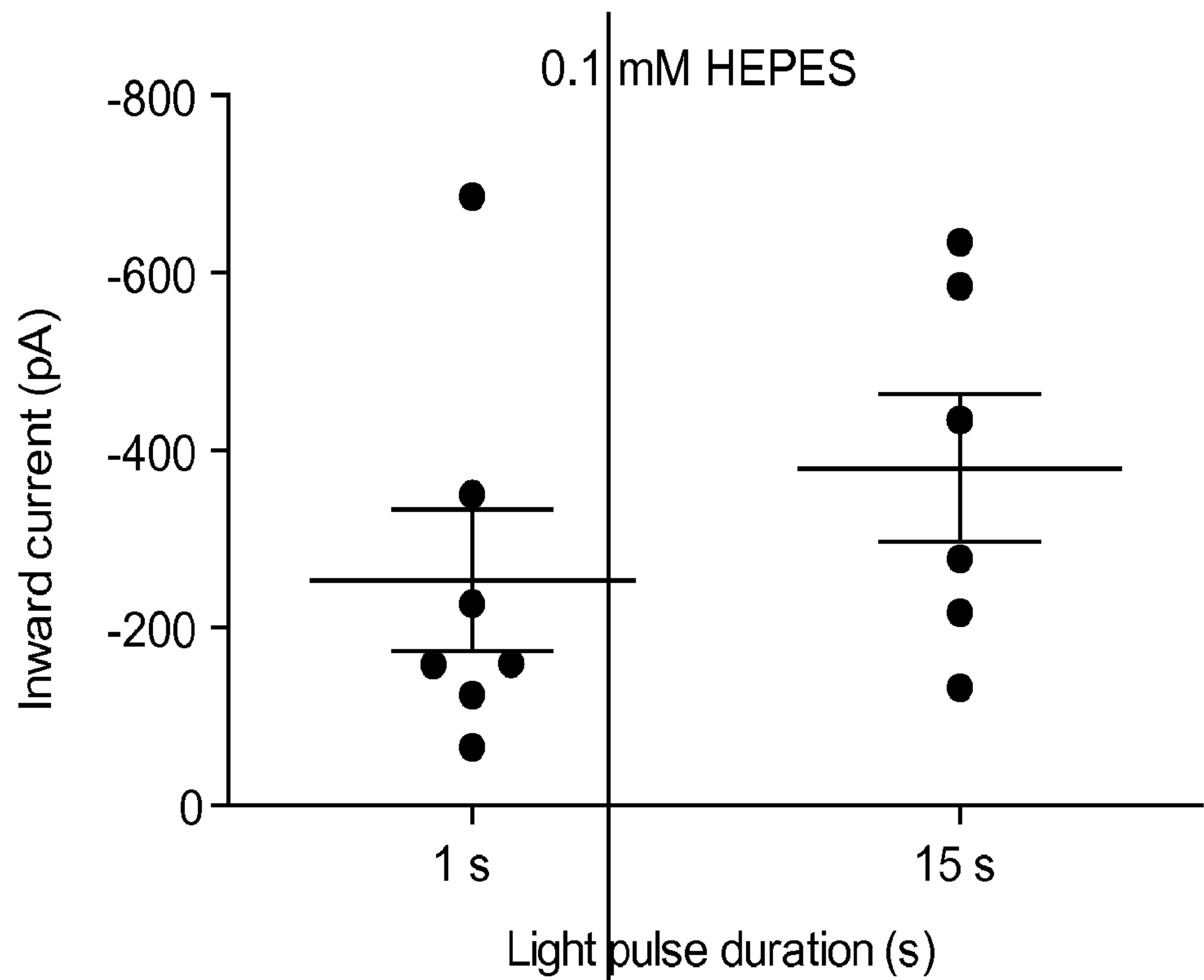
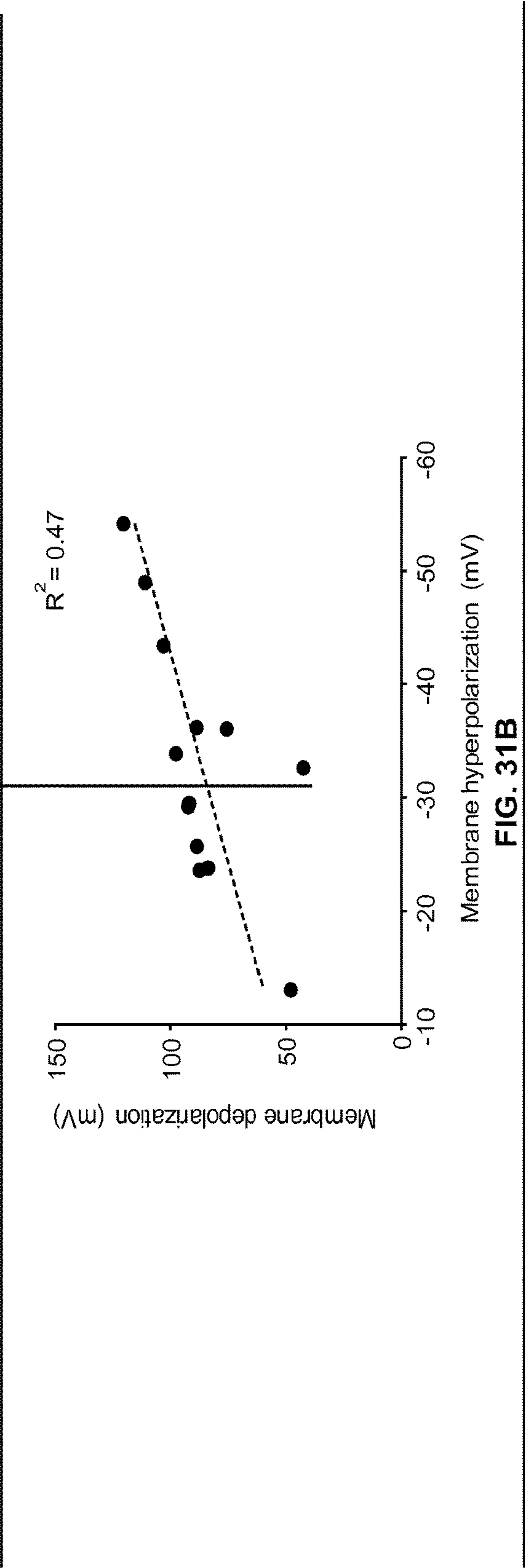
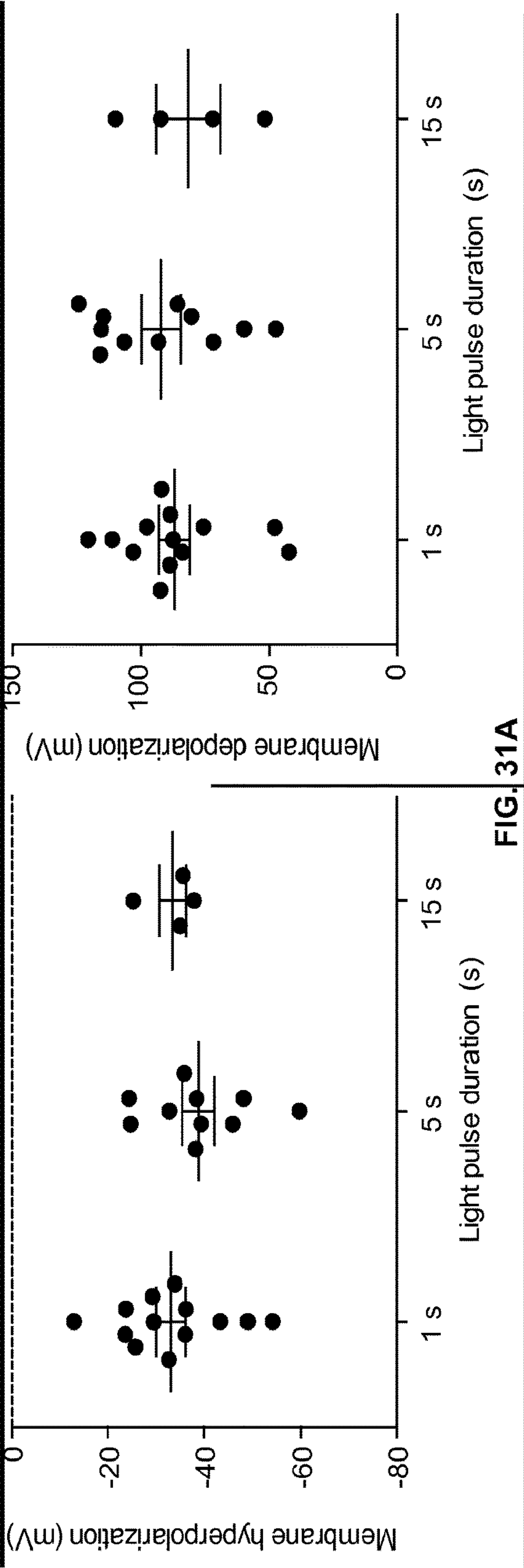
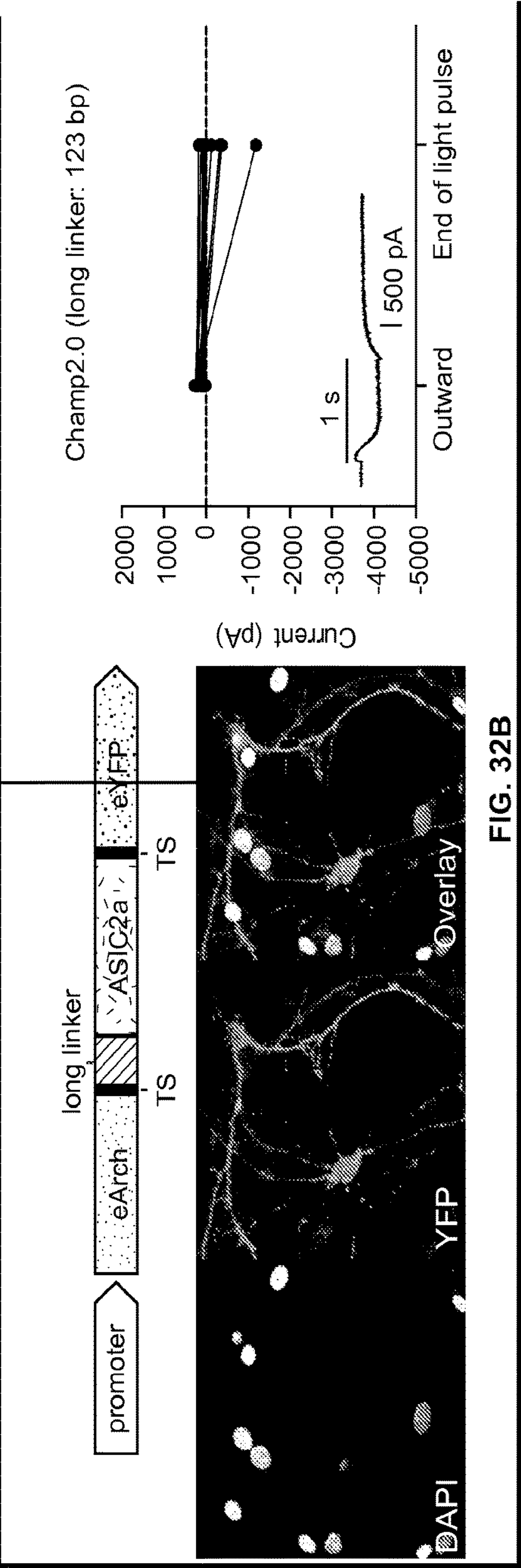
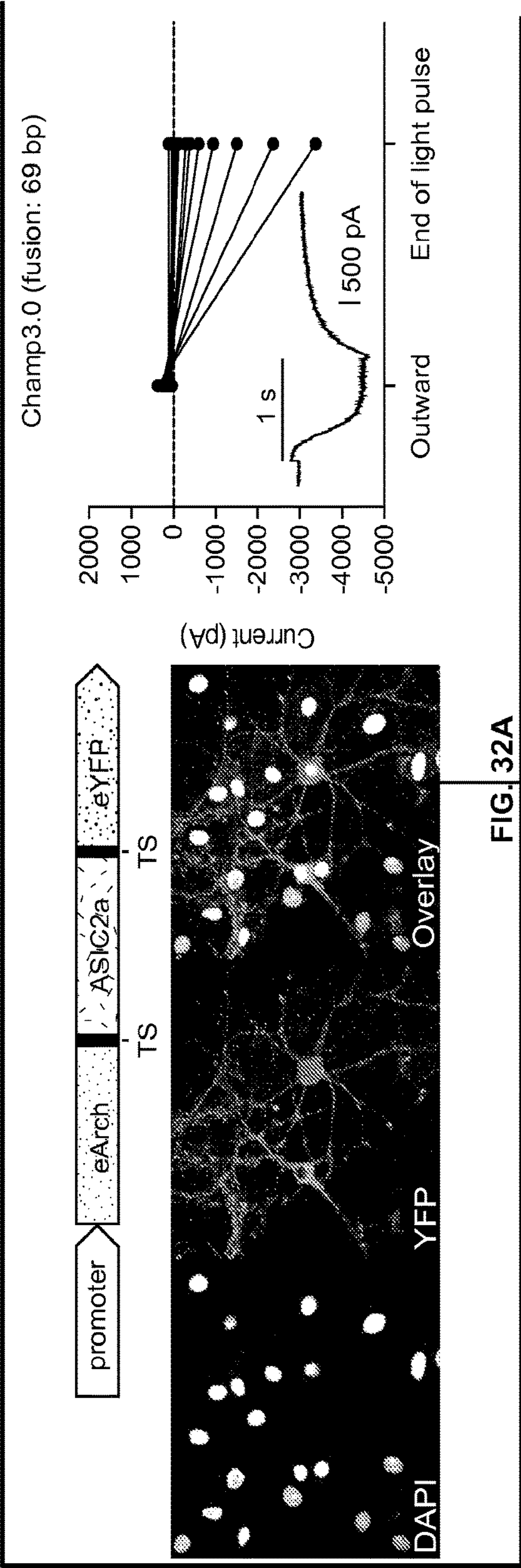


FIG. 30F





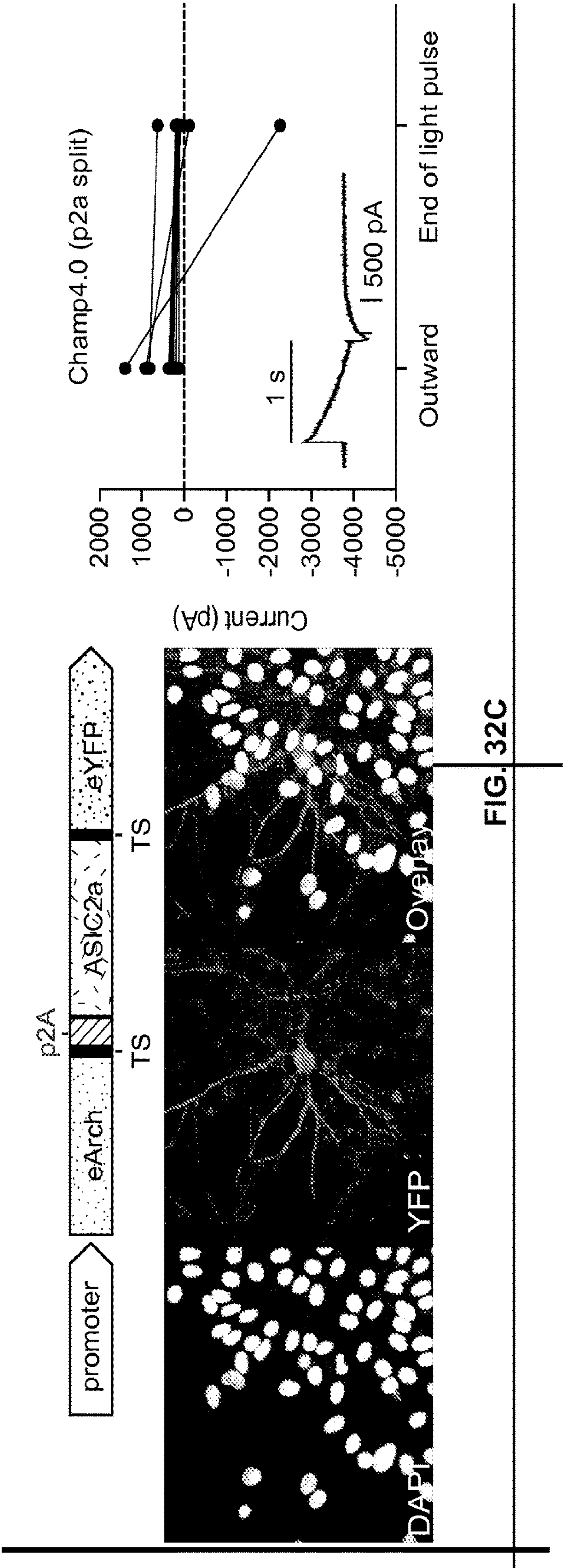


FIG. 32C

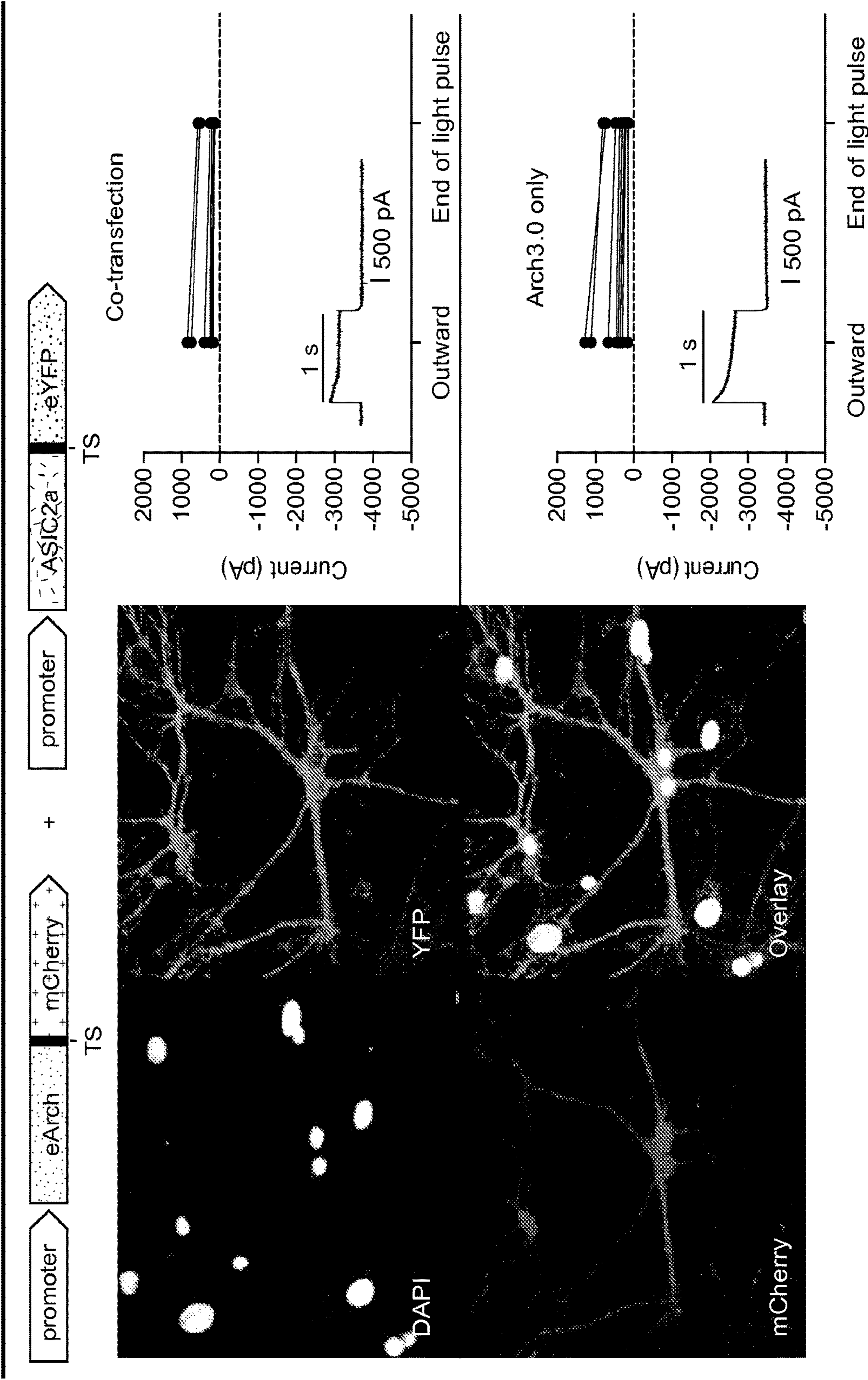


FIG. 32D

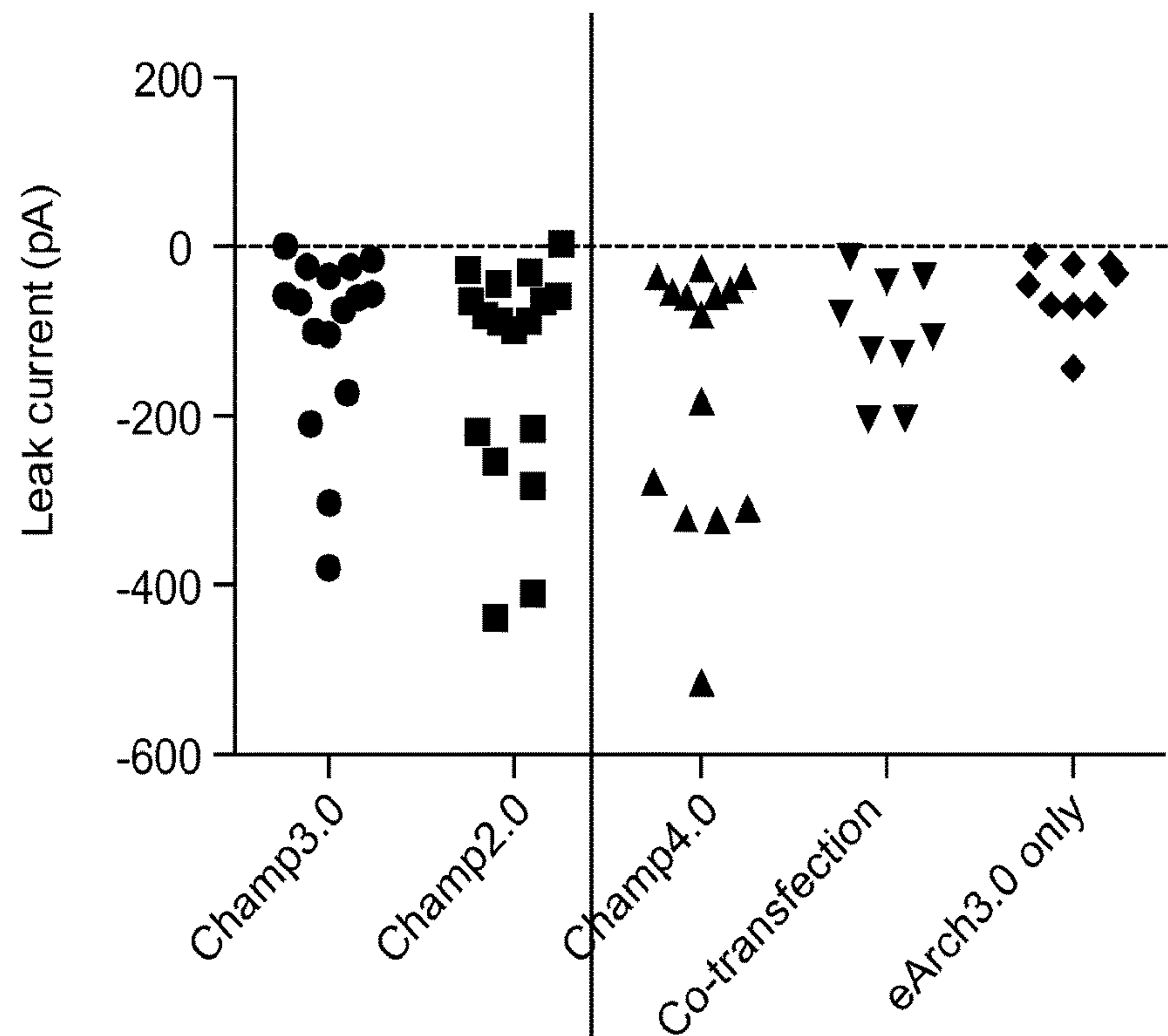


FIG. 33A

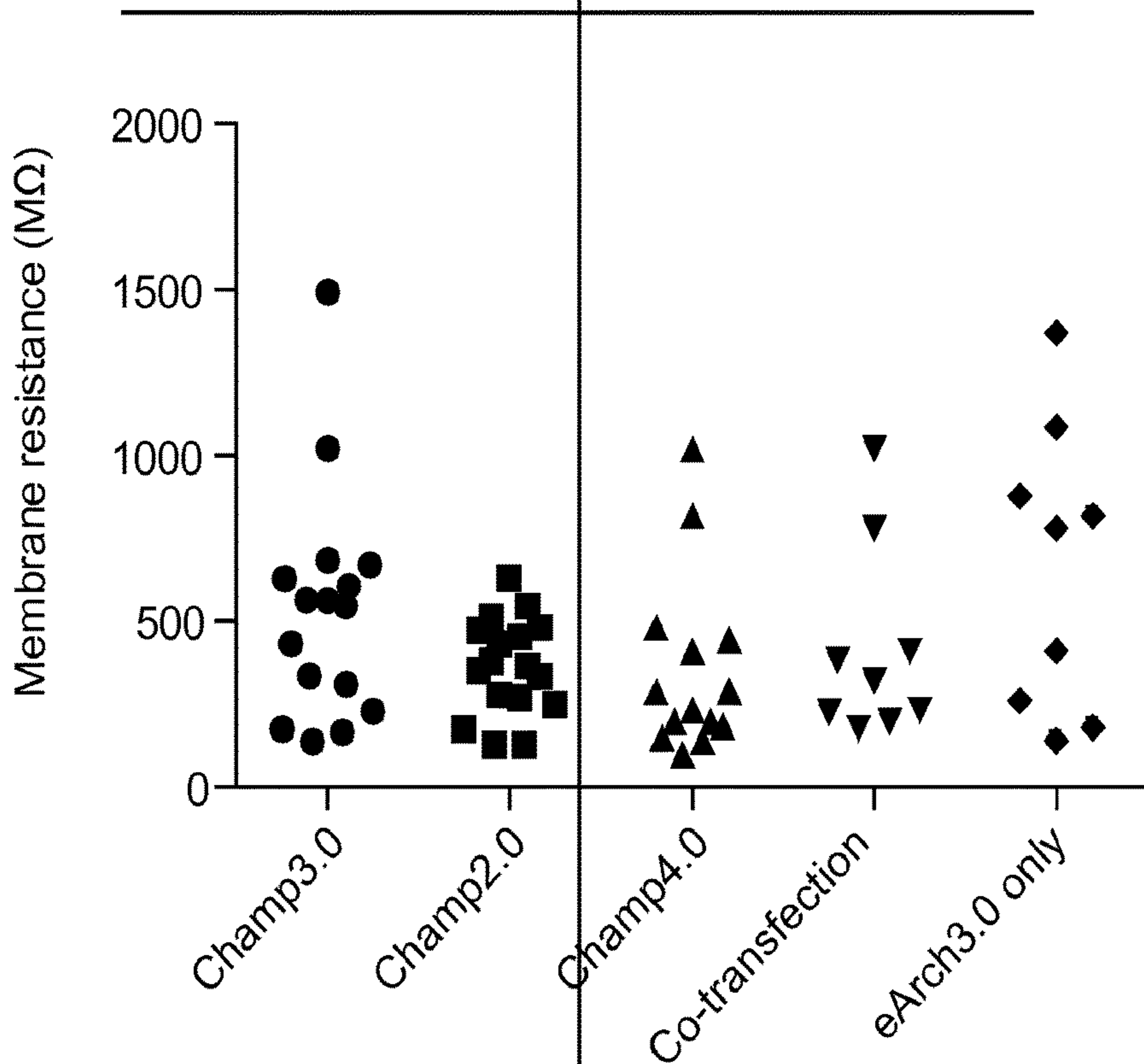


FIG. 33B

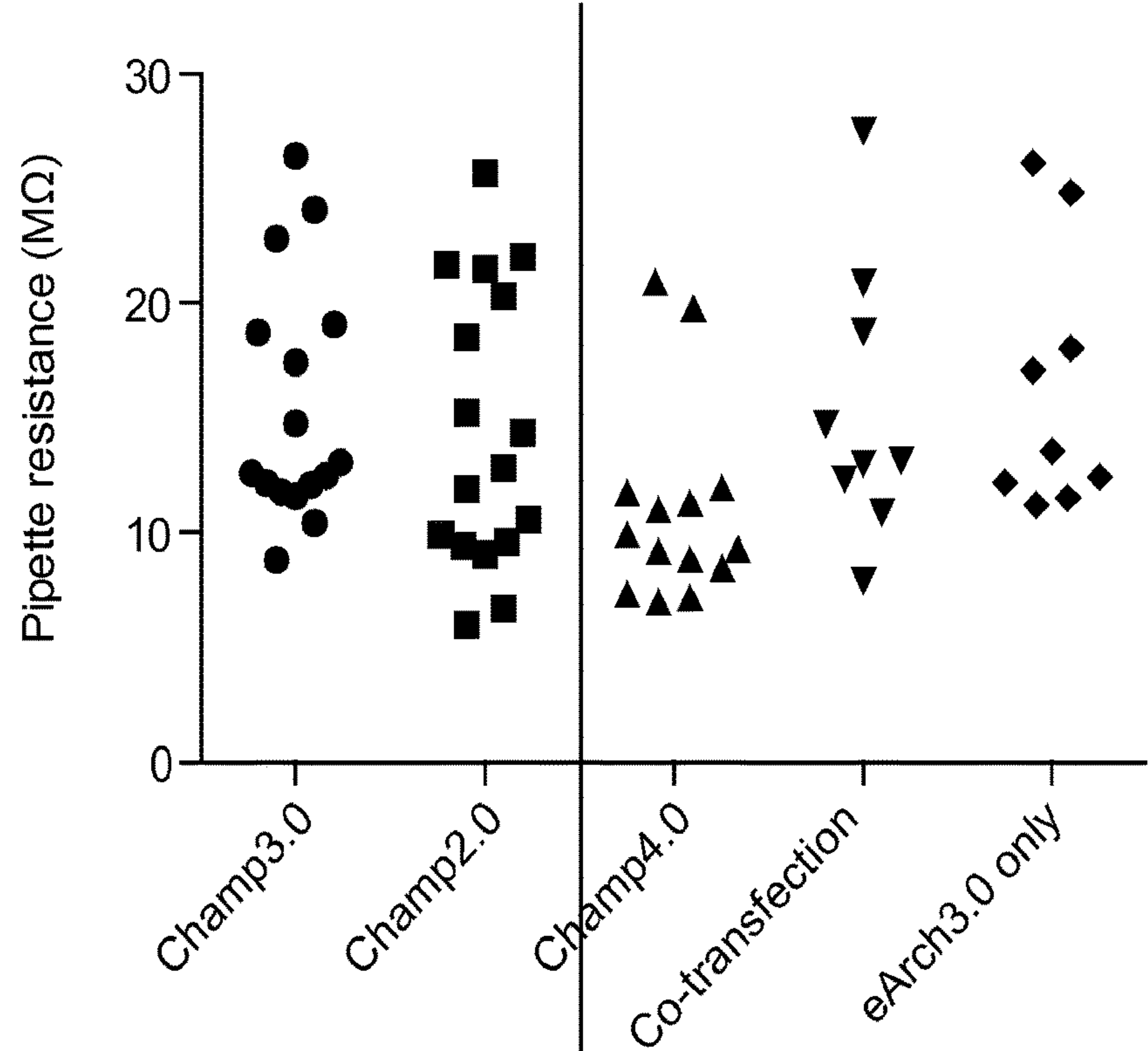


FIG. 33C

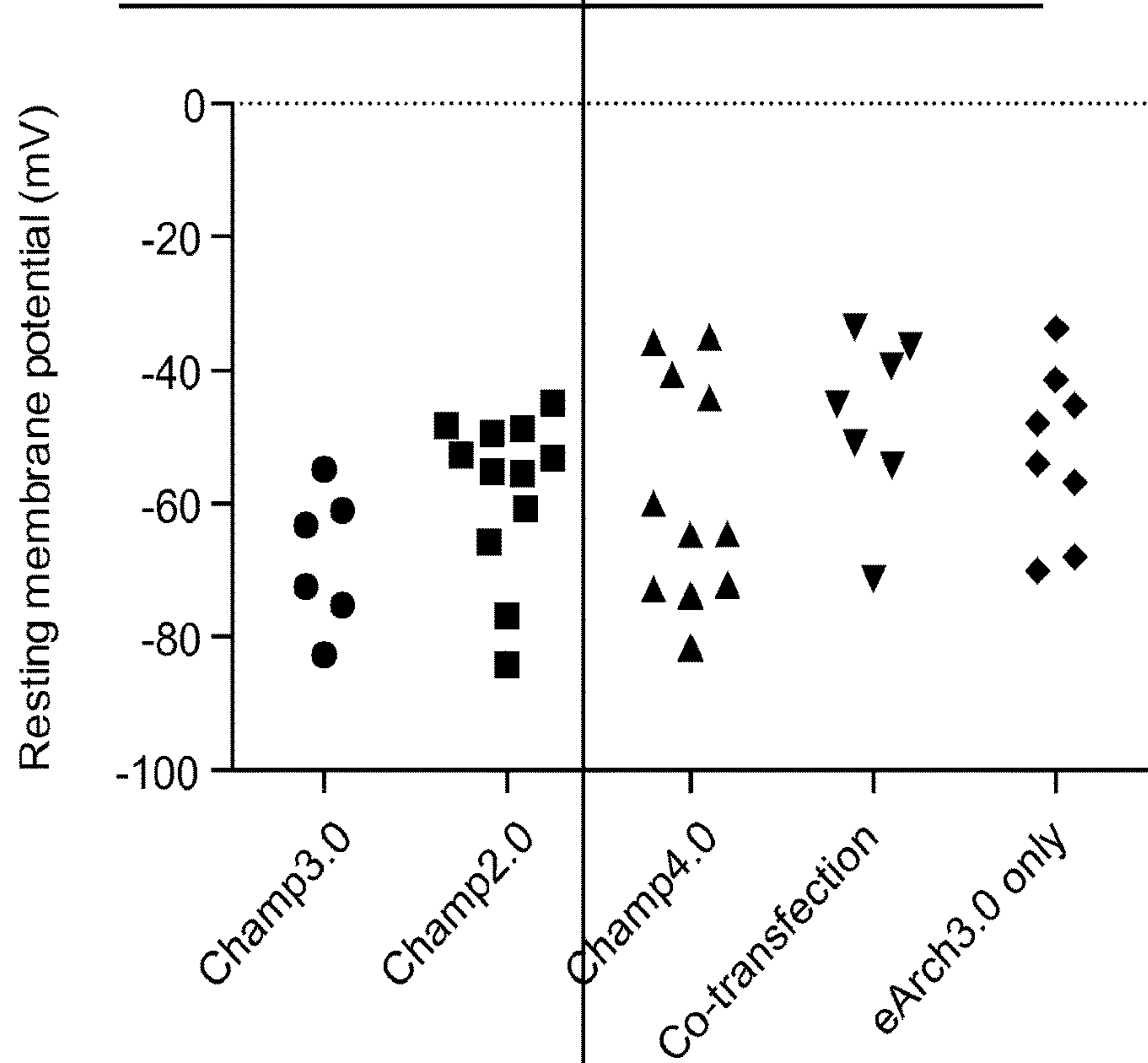


FIG. 33D

DEVICES, SYSTEMS AND METHODS FOR OPTOGENETIC MODULATION OF ACTION POTENTIALS IN TARGET CELLS

CROSS-REFERENCE

[0001] This application claims the benefit of U.S. Provisional Patent Application No. 61/817,221, filed Apr. 29, 2013, which application is incorporated herein by reference in its entirety.

INCORPORATION BY REFERENCE OF SEQUENCE LISTING PROVIDED AS A TEXT FILE

[0002] A Sequence Listing is provided herewith as a text file, "STAN-1030WO SeqList_ST25.txt" created on Apr. 29, 2014 and having a size of 208 KB. The contents of the text file are incorporated by reference herein in their entirety.

INTRODUCTION

[0003] Optogenetics refers to the combination of genetic and optical methods used to control specific events in target cells with the temporal precision (millisecond-timescale) needed to keep pace with functioning intact biological systems. Optogenetics involves the introduction of fast light-responsive ion channel or pump proteins into the plasma membranes of target cells to allow temporally precise manipulation of membrane potentials while maintaining cell-type resolution through the use of specific targeting mechanisms, such as tissue-specific promoters.

[0004] A major limiting step in optogenetic electrical inhibition is that the existing tools do not cause input resistance changes, and only generate relatively weak photocurrents because the existing ion pump proteins only move one ion per photon. Conversely, a major limiting step in optogenetic excitation is that when exciting a projection of a target cell, such as an axon, retrograde propagating action potentials can return to the cell body and proceed down collateral cell projections, thereby reducing specificity. As such, there is a need for devices, systems and methods that can be used to inhibit and/or intercept action potentials in target cells, thereby expanding the potential uses of optogenetic technology.

SUMMARY

[0005] Aspects of the disclosure include devices, systems and methods for optogenetic modulation of action potentials in target cells. The subject devices include light-generating devices, control devices, and delivery devices for delivering vectors to target cells. The subject systems include light-activated proteins, response proteins, nucleic acids comprising nucleotide sequences encoding these proteins, as well as expression systems that facilitate expression of these proteins in target cells. Also provided are methods of using the subject devices and systems to optogenetically inhibit and intercept action potentials in target cells, e.g., to treat a neurological or psychiatric condition in a human or non-human animal subject.

BRIEF DESCRIPTION OF THE DRAWINGS

[0006] FIG. 1 is a schematic representation of a subject optogenetic system, showing a light-activated protein (eArch3.0) and a response protein (eASIC2a or ASIC2a)

present in the membrane of a nerve cell. Also depicted are the membrane current as a function of time after the cell is illuminated with light of the indicated wavelength and the influence of light on evoked action potential spiking (membrane voltage) as a function of time.

[0007] FIG. 2 shows several graphs that depict the influence of light on evoked action potential firing when ASIC2a currents are large. The graphs show examples of membrane voltage of an eArch-ASIC2a expressing nerve cell as a function of time when the nerve cell is illuminated with light of the indicated wavelength, during electrically-evoked action potential spiking.

[0008] FIG. 3 shows several graphs that depict the influence of light on evoked action potential firing when ASIC2a currents are large. The graphs show examples of membrane voltage of an eArch-eASIC2a-expressing nerve cell as a function of time when the nerve cell is illuminated with light of the indicated wavelength, during electrically-evoked action potential spiking.

[0009] FIG. 4 shows several graphs that depict the influence of light on evoked action potential firing when the ASIC2a current is small. The graphs show examples of membrane voltage of an eArch-eASIC2a-expressing nerve cell as a function of time when the nerve cell is illuminated with light of the indicated wavelength, during electrically-evoked action potential spiking.

[0010] FIG. 5 shows the nucleotide sequence of an example polynucleotide containing an Arch sequence (Arch), a trafficking sequence (TS), a ribosomal skip sequence (p2A), an ASIC2a sequence (ASIC2a), and a yellow fluorescent protein sequence (EYFP).

[0011] FIG. 6 shows the nucleotide sequence of an example polynucleotide containing an Arch sequence (Arch), a trafficking sequence (TS), a ribosomal skip sequence (p2A), an ASIC2a sequence (ASIC2a), a trafficking sequence (TS), a yellow fluorescent protein sequence (EYFP), and an endoplasmic reticulum export sequence (ER).

[0012] FIG. 7 shows a map of an example vector containing an Arch sequence and an ASIC2a sequence, as well as additional components, such as a CaMKIIa promoter.

[0013] FIG. 8 shows a map of an example vector containing an Arch sequence and an ASIC2a sequence, as well as additional components, such as an hSyn promoter.

[0014] FIG. 9 shows a first example of an optical stimulation system in accordance with embodiments of the present disclosure.

[0015] FIG. 10 shows a second example of an optical stimulation system in accordance with embodiments of the present disclosure.

[0016] FIG. 11 shows a third example of an optical stimulation system in accordance with embodiments of the present disclosure.

[0017] FIG. 12 shows a flow diagram that illustrates the steps of an example method in accordance with embodiments of the present disclosure.

[0018] FIGS. 13A-K provide amino acid sequences of various light-responsive proteins.

[0019] FIGS. 14A-H provide amino acid sequences of exemplary response proteins.

[0020] FIGS. 15A-L depicts the identification and delineation of the bystander effect.

[0021] FIG. 16 depicts traces illustrating the difference in on-kinetics between a Chr2 expressing-cell photocurrent

and a ChR2 bystander current (dashed box shows a zoom-in of the first 0.5 s of both traces).

[0022] FIGS. 17A-B depict photocurrent magnitudes and traces for opsin-expressing neurons.

[0023] FIGS. 18A-D depict the functional impact of bystander currents on action potential firing measured as a percentage of successfully evoked spikes during repeated light-off and light-on epochs.

[0024] FIGS. 19A-G depict electrical stimulation-elicited bystander effects and the effects of ASIC antagonist amiloride administration.

[0025] FIG. 20 depicts an exemplary bystander current in response to electrical stimulation of Schaffer collaterals to CA1 region of hippocampus using a tungsten concentric bipolar electrode.

[0026] FIGS. 21A-C depict control experiments pertaining to amiloride administration.

[0027] FIGS. 22A-C depict measures of cell health for bystander neurons.

[0028] FIGS. 23A-D depict optical activation of three acid-sensitive ion channels using the Two Component Optogenetic (TCO) approach.

[0029] FIGS. 24A-E depict photocurrents of Chlorellarhodopsin (CsR) and related current quantification.

[0030] FIGS. 25A-E depict CsR-ASIC1a photocurrents with and without permanent perfusion in *Xenopus laevis* oocytes and related quantification.

[0031] FIGS. 26A-E depict the effects of various parameters (pH, buffer, light intensity, etc.) on CsR-ASIC2a photocurrents measured by two-electrode voltage clamp (TEVC) in oocytes.

[0032] FIGS. 27A-H depict expression of eArch3.0-ASIC2a (Champ) in hippocampal neurons, photocurrents in such neurons, and related quantification.

[0033] FIGS. 28A-F depict various measures of the variable presence of the ASIC2a component in cultured hippocampal neurons.

[0034] FIGS. 29A-B depict the effects of light pulse duration on Champ currents and kinetics.

[0035] FIGS. 30A-F depict the effects of HEPES concentration in Tyrode's solution on Champ photocurrents

[0036] FIGS. 31A-B depict Champ-mediated membrane hyperpolarization and depolarization in response to light pulses of increasing duration.

[0037] FIGS. 32A-D depict the effects of increasing molecular distance between components in a head-to-head comparison of four Champ constructs.

[0038] FIGS. 33A-D depict various measures of cell health across 4 different Champ constructs with increasing molecular separation between proton pump and ASIC.

DEFINITIONS

[0039] As used herein, an “individual,” “subject,” or “patient” can be a mammal, including a human. Mammals include, but are not limited to, ungulates, canines, felines, bovines, ovines, non-human primates, lagomorphs (e.g., rabbits), and rodents (e.g., mice and rats). In one aspect, an individual is a human. In another aspect, an individual is a non-human mammal.

[0040] Amino acid substitutions in a native protein sequence may be “conservative” or “non-conservative” and such substituted amino acid residues may or may not be one encoded by the genetic code. A “conservative amino acid substitution” is one in which the amino acid residue is

replaced with an amino acid residue having a chemically similar side chain (i.e., replacing an amino acid possessing a basic side chain with another amino acid with a basic side chain). A “non-conservative amino acid substitution” is one in which the amino acid residue is replaced with an amino acid residue having a chemically different side chain (i.e., replacing an amino acid having a basic side chain with an amino acid having an aromatic side chain). The standard twenty amino acid “alphabet” is divided into chemical families based on chemical properties of their side chains. These families include amino acids with basic side chains (e.g., lysine, arginine, histidine), acidic side chains (e.g., aspartic acid, glutamic acid), uncharged polar side chains (e.g., glycine, asparagine, glutamine, serine, threonine, tyrosine, cysteine), nonpolar side chains (e.g., alanine, valine, leucine, isoleucine, proline, phenylalanine, methionine, tryptophan), beta-branched side chains (e.g., threonine, valine, isoleucine) and side chains having aromatic groups (e.g., tyrosine, phenylalanine, tryptophan, histidine).

[0041] As used herein, an “effective dosage” or “effective amount” of drug, compound, or pharmaceutical composition is an amount sufficient to effect beneficial or desired results. For prophylactic use, beneficial or desired results include results such as eliminating or reducing the risk, lessening the severity, or delaying the onset of the disease, including biochemical, histological and/or behavioral symptoms of the disease, its complications and intermediate pathological phenotypes presenting during development of the disease. For therapeutic use, beneficial or desired results include clinical results such as decreasing one or more symptoms resulting from the disease, increasing the quality of life of those suffering from the disease, decreasing the dose of other medications required to treat the disease, enhancing effect of another medication such as via targeting, delaying the progression of the disease, and/or prolonging survival. An effective dosage can be administered in one or more administrations. For purposes of this disclosure, an effective dosage of drug, compound, or pharmaceutical composition is an amount sufficient to accomplish prophylactic or therapeutic treatment either directly or indirectly. As is understood in the clinical context, an effective dosage of a drug, compound, or pharmaceutical composition may or may not be achieved in conjunction with another drug, compound, or pharmaceutical composition. Thus, an “effective dosage” may be considered in the context of administering one or more therapeutic agents, and a single agent may be considered to be given in an effective amount if, in conjunction with one or more other agents, a desirable result may be or is achieved.

[0042] As used herein, “treatment” or “treating” is an approach for obtaining beneficial or desired results including clinical results. For purposes of this disclosure, beneficial or desired clinical results include, but are not limited to, one or more of the following: decreasing symptoms resulting from the disease, increasing the quality of life of those suffering from the disease, decreasing the dose of other medications required to treat the disease, delaying the progression of the disease, and/or prolonging survival of individuals.

[0043] Before the present invention is described in greater detail, it is to be understood that this invention is not limited to particular embodiments described, as such may, of course, vary. It is also to be understood that the terminology used herein is for the purpose of describing particular embodi-

ments only, and is not intended to be limiting, since the scope of the present invention will be limited only by the appended claims.

[0044] Where a range of values is provided, it is understood that each intervening value, to the tenth of the unit of the lower limit unless the context clearly dictates otherwise, between the upper and lower limit of that range and any other stated or intervening value in that stated range, is encompassed within the invention. The upper and lower limits of these smaller ranges may independently be included in the smaller ranges and are also encompassed within the invention, subject to any specifically excluded limit in the stated range. Where the stated range includes one or both of the limits, ranges excluding either or both of those included limits are also included in the invention.

[0045] Certain ranges are presented herein with numerical values being preceded by the term “about.” The term “about” is used herein to provide literal support for the exact number that it precedes, as well as a number that is near to or approximately the number that the term precedes. In determining whether a number is near to or approximately a specifically recited number, the near or approximating unre-cited number may be a number which, in the context in which it is presented, provides the substantial equivalent of the specifically recited number.

[0046] Unless defined otherwise, all technical and scientific terms used herein have the same meaning as commonly understood by one of ordinary skill in the art to which this invention belongs. Although any methods and materials similar or equivalent to those described herein can also be used in the practice or testing of the present invention, representative illustrative methods and materials are now described.

[0047] All publications and patents cited in this specification are herein incorporated by reference as if each individual publication or patent were specifically and individually indicated to be incorporated by reference and are incorporated herein by reference to disclose and describe the methods and/or materials in connection with which the publications are cited. The citation of any publication is for its disclosure prior to the filing date and should not be construed as an admission that the present invention is not entitled to antedate such publication by virtue of prior invention. Further, the dates of publication provided may be different from the actual publication dates which may need to be independently confirmed.

[0048] It is noted that, as used herein and in the appended claims, the singular forms “a”, “an”, and “the” include plural referents unless the context clearly dictates otherwise. It is further noted that the claims may be drafted to exclude any optional element. As such, this statement is intended to serve as antecedent basis for use of such exclusive terminology as “solely,” “only” and the like in connection with the recitation of claim elements, or use of a “negative” limitation.

[0049] As will be apparent to those of skill in the art upon reading this disclosure, each of the individual embodiments described and illustrated herein has discrete components and features which may be readily separated from or combined with the features of any of the other several embodiments without departing from the scope or spirit of the present invention. Any recited method can be carried out in the order of events recited or in any other order which is logically possible.

[0050] In further describing various aspects of embodiments of the invention in greater detail, aspects of the systems and devices of various embodiments are reviewed first in greater detail, followed by a discussion of methods and kits according to certain embodiments of the invention.

DETAILED DESCRIPTION

[0051] Aspects of the disclosure include devices, systems and methods for optogenetic modulation of action potentials in target cells. The subject devices include light-generating devices, control devices, and delivery devices for delivering vectors to target cells. The subject systems include light-activated proteins, response proteins, nucleic acids comprising nucleotide sequences encoding these proteins, as well as expression systems that facilitate expression of these proteins in target cells. Also provided are methods of using the subject devices and systems to optogenetically inhibit and intercept action potentials in target cells, e.g., to treat a neurological or psychiatric condition in a human or animal subject.

Systems and Devices

[0052] Aspects of the present disclosure include systems and devices configured for optogenetically modulating action potentials in target cells. The subject systems generally include a light-activated protein, a response protein, and one or more devices for delivering light of an activating wavelength to a target cell. The subject systems further include nucleic acids comprising nucleotide sequences encoding the subject proteins, as well as additional components, such as transcriptional control elements (e.g., promoter sequences, such as tissue-specific or cell type-specific promoter sequences), trafficking sequences, signal sequences, endoplasmic reticulum export sequences, and the like. Also provided are devices for delivering the subject nucleic acids to target cells, and devices for controlling the delivery of light to the target cells. Each of these components is now further described in greater detail.

Light-Activated Proteins

[0053] As summarized above, aspects of the present disclosure include light-activated proteins that allow one or more ions to pass through the plasma membrane of a target cell when the protein is illuminated with light of an activating wavelength. Light-activated proteins may be characterized as ion pump proteins, which facilitate the passage of a small number of ions through the plasma membrane per photon of light, or as ion channel proteins, which allow a stream of ions to freely flow through the plasma membrane when the channel is open. The subject light-activated proteins are in some embodiments specific to a particular species of ion, meaning that the subject light-activated proteins only allow ions of a particular species to pass through the membrane.

[0054] Examples of suitable light-responsive polypeptides include, e.g., the Halorhodopsin family of light-responsive chloride pumps (e.g., NpHR, NpHR2.0, NpHR3.0, NpHR3.1). As another example, the GtR3 proton pump can be used to promote neural cell membrane hyperpolarization in response to light. As another example, eArch (a proton pump) can be used to promote neural cell membrane hyperpolarization in response to light. As another example, an

ArchT opsin protein or a Mac opsin protein can be used to promote neural cell membrane hyperpolarization in response to light.

[0055] Examples of suitable light-responsive polypeptides include, e.g., members of the Channelrhodopsin family of light-responsive cation channel proteins (e.g., ChR2, SFOs, SSFOs, C1V1s), which can be used to promote neural cell membrane depolarization or depolarization-induced synaptic depletion in response to a light stimulus.

Enhanced Intracellular Transport Amino Acid Motifs

[0056] The present disclosure provides for the modification of light-responsive opsin proteins expressed in a cell by the addition of one or more amino acid sequence motifs which enhance transport to the plasma membranes of mammalian cells. Light-responsive opsin proteins having components derived from evolutionarily simpler organisms may not be expressed or tolerated by mammalian cells or may exhibit impaired subcellular localization when expressed at high levels in mammalian cells. Consequently, in some embodiments, the light-responsive opsin proteins expressed in a cell can be fused to one or more amino acid sequence motifs selected from the group consisting of a signal peptide, an endoplasmic reticulum (ER) export signal, a membrane trafficking signal, and/or an N-terminal golgi export signal. The one or more amino acid sequence motifs which enhance light-responsive protein transport to the plasma membranes of mammalian cells can be fused to the N-terminus, the C-terminus, or to both the N- and C-terminal ends of the light-responsive protein. Optionally, the light-responsive protein and the one or more amino acid sequence motifs may be separated by a linker. In some embodiments, the light-responsive protein can be modified by the addition of a trafficking signal (ts) which enhances transport of the protein to the cell plasma membrane. In some embodiments, the trafficking signal can be derived from the amino acid sequence of the human inward rectifier potassium channel Kir2.1. In other embodiments, the trafficking signal can comprise the amino acid sequence KSRITSEGEYIPLDQIDINV (SEQ ID NO:37).

[0057] Trafficking sequences that are suitable for use can comprise an amino acid sequence having 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%, amino acid sequence identity to an amino acid sequence such as a trafficking sequence of human inward rectifier potassium channel Kir2.1 (e.g., KSRITSEGEYIPLDQIDINV (SEQ ID NO:37)).

[0058] A trafficking sequence can have a length of from about 10 amino acids to about 50 amino acids, e.g., from about 10 amino acids to about 20 amino acids, from about 20 amino acids to about 30 amino acids, from about 30 amino acids to about 40 amino acids, or from about 40 amino acids to about 50 amino acids.

[0059] Signal sequences that are suitable for use can comprise an amino acid sequence having 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%, amino acid sequence identity to an amino acid sequence such as one of the following:

1) the signal peptide of hChR2 (e.g., MDYGGALSAVGRELLFVTNPVVVNGS (SEQ ID NO:38))

2) the $\beta 2$ subunit signal peptide of the neuronal nicotinic acetylcholine receptor (e.g., MAGHSNSMALFSFSLWLCSGVLGTEF (SEQ ID NO:39));

3) a nicotinic acetylcholine receptor signal sequence (e.g., MGLRALMLWLLAAAGLVRESLQG (SEQ ID NO:40)); and

4) a nicotinic acetylcholine receptor signal sequence (e.g., MRGTPLLLVVSLSLLQD (SEQ ID NO:41)).

[0060] A signal sequence can have a length of from about 10 amino acids to about 50 amino acids, e.g., from about 10 amino acids to about 20 amino acids, from about 20 amino acids to about 30 amino acids, from about 30 amino acids to about 40 amino acids, or from about 40 amino acids to about 50 amino acids.

[0061] Endoplasmic reticulum (ER) export sequences that are suitable for use in a modified opsin of the present disclosure include, e.g., VXXSL (where X is any amino acid) (SEQ ID NO:42) (e.g., VKESL (SEQ ID NO:43); VLGS (SEQ ID NO:44); etc.); NANSFCYENEVALTSK (SEQ ID NO:45); FXYENE (SEQ ID NO:46) (where X is any amino acid), e.g., FCYENEV (SEQ ID NO:47); and the like. An ER export sequence can have a length of from about 5 amino acids to about 25 amino acids, e.g., from about 5 amino acids to about 10 amino acids, from about 10 amino acids to about 15 amino acids, from about 15 amino acids to about 20 amino acids, or from about 20 amino acids to about 25 amino acids.

[0062] In some embodiments, the signal peptide sequence in the protein can be deleted or substituted with a signal peptide sequence from a different protein.

Proton Pump Proteins

[0063] In some embodiments, a light-activated protein is an Archaeorhodopsin (Arch) proton pump that can transport one or more protons across the plasma membrane of a cell when the cell is illuminated with light. The light can have a wavelength between about 530 and about 595 nm or can have a wavelength of about 560 nm. In some embodiments, the Arch protein can comprise an amino acid sequence that is at least about 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identical to the sequence shown in SEQ ID NO:1 (Arch). The Arch protein can additionally comprise substitutions, deletions, and/or insertions introduced into a native amino acid sequence to increase or decrease sensitivity to light, increase or decrease sensitivity to particular wavelengths of light, and/or increase or decrease the ability of the Arch protein to transport ions across the plasma membrane of a target cell. Additionally, the Arch protein can contain one or more conservative amino acid substitutions and/or one or more non-conservative amino acid substitutions. The Arch protein comprising substitutions, deletions, and/or insertions introduced into the native amino acid sequence suitably retains the ability to transport ions across the plasma membrane of a target cell in response to light.

[0064] In some embodiments, an Arch protein comprises at least one (such as one, two, three, or more) amino acid sequence motifs that enhance transport to the plasma membranes of target cells selected from the group consisting of a signal peptide, an ER export signal, and a membrane trafficking signal. In some embodiments, the Arch protein comprises an N-terminal signal peptide and a C-terminal ER export signal. In some embodiments, the Arch protein comprises an N-terminal signal peptide and a C-terminal trafficking signal. In some embodiments, the Arch protein comprises an N-terminal signal peptide, a C-terminal ER export signal, and a C-terminal trafficking signal. In some

embodiments, the Arch protein comprises a C-terminal ER export signal and a C-terminal trafficking signal. In some embodiments, the C-terminal ER export signal and the C-terminal trafficking signal are linked by a linker. The linker can comprise any of about 5, 10, 20, 30, 40, 50, 75, 100, 125, 150, 175, 200, 225, 250, 275, 300, 400, or 500 amino acids in length. The linker may further comprise a fluorescent protein, for example, but not limited to, a yellow fluorescent protein, a red fluorescent protein, a green fluorescent protein, or a cyan fluorescent protein. In some embodiments the ER export signal is more C-terminally located than the trafficking signal. In some embodiments the trafficking signal is more C-terminally located than the ER Export signal.

[0065] In some embodiments, the light-responsive proton pump protein can be responsive to blue light and can be derived from *Guillardia theta*, wherein the proton pump protein can be capable of mediating a hyperpolarizing current in the cell when the cell is illuminated with blue light. The light can have a wavelength between about 450 and about 495 nm or can have a wavelength of about 490 nm. In another embodiment, the light-responsive proton pump protein can comprise an amino acid sequence at least about 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identical to the sequence shown in SEQ ID NO:4 (GtR3). The light-responsive proton pump protein can additionally comprise substitutions, deletions, and/or insertions introduced into a native amino acid sequence to increase or decrease sensitivity to light, increase or decrease sensitivity to particular wavelengths of light, and/or increase or decrease the ability of the light-responsive proton pump protein to regulate the polarization state of the plasma membrane of the cell. Additionally, the light-responsive proton pump protein can contain one or more conservative amino acid substitutions and/or one or more non-conservative amino acid substitutions. The light-responsive proton pump protein comprising substitutions, deletions, and/or insertions introduced into the native amino acid sequence suitably retains the ability to hyperpolarize the plasma membrane of a neuronal cell in response to light.

[0066] In other aspects of the methods disclosed herein, the light-responsive proton pump protein can comprise a core amino acid sequence at least about 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identical to the sequence shown in SEQ ID NO:4 and at least one (such as one, two, three, or more) amino acid sequence motifs which enhance transport to the plasma membranes of mammalian cells selected from the group consisting of a signal peptide, an ER export signal, and a membrane trafficking signal. In some embodiments, the light-responsive proton pump protein comprises an N-terminal signal peptide and a C-terminal ER export signal. In some embodiments, the light-responsive proton pump protein comprises an N-terminal signal peptide and a C-terminal trafficking signal. In some embodiments, the light-responsive proton pump protein comprises an N-terminal signal peptide, a C-terminal ER Export signal, and a C-terminal trafficking signal. In some embodiments, the light-responsive proton pump protein comprises a C-terminal ER Export signal and a C-terminal trafficking signal. In some embodiments, the C-terminal ER Export signal and the C-terminal trafficking signal are linked by a linker. The linker can comprise any of about 5, 10, 20, 30, 40, 50, 75, 100, 125, 150, 175, 200, 225, 250, 275, 300, 400, or 500 amino acids in length. The linker

may further comprise a fluorescent protein, for example, but not limited to, a yellow fluorescent protein, a red fluorescent protein, a green fluorescent protein, or a cyan fluorescent protein. In some embodiments the ER Export signal is more C-terminally located than the trafficking signal. In some embodiments the trafficking signal is more C-terminally located than the ER Export signal.

[0067] Also provided herein are isolated polynucleotides encoding any of the light-responsive proton pump proteins described herein, such as a light-responsive proton pump protein comprising a core amino acid sequence at least about 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identical to the sequence shown in SEQ ID NO:4. Also provided herein are expression vectors (such as a viral vector described herein) comprising a polynucleotide encoding the proteins described herein, such as a light-responsive proton pump protein comprising a core amino acid sequence at least about 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identical to the sequence shown in SEQ ID NO:4.

[0068] In some embodiments, a light-activated protein is an *Oxyrrhis marina* (Oxy) proton pump that can transport one or more protons across the plasma membrane of a cell when the cell is illuminated with light. The light can have a wavelength between about 500 and about 560 nm or can have a wavelength of about 530 nm. In some embodiments, the Oxy protein can comprise an amino acid sequence that is at least about 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identical to the sequence shown in SEQ ID NO:5. The Oxy protein can additionally comprise substitutions, deletions, and/or insertions introduced into a native amino acid sequence to increase or decrease sensitivity to light, increase or decrease sensitivity to particular wavelengths of light, and/or increase or decrease the ability of the Oxy protein to transport ions across the plasma membrane of a target cell. Additionally, the Oxy protein can contain one or more conservative amino acid substitutions and/or one or more non-conservative amino acid substitutions. The Oxy protein comprising substitutions, deletions, and/or insertions introduced into the native amino acid sequence suitably retains the ability to transport ions across the plasma membrane of a target cell in response to light.

[0069] In some embodiments, an Oxy protein comprises at least one (such as one, two, three, or more) amino acid sequence motifs that enhance transport to the plasma membranes of target cells selected from the group consisting of a signal peptide, an ER export signal, and a membrane trafficking signal. In some embodiments, the Oxy protein comprises an N-terminal signal peptide and a C-terminal ER export signal. In some embodiments, the Oxy protein comprises an N-terminal signal peptide and a C-terminal trafficking signal. In some embodiments, the Oxy protein comprises an N-terminal signal peptide, a C-terminal ER export signal, and a C-terminal trafficking signal. In some embodiments, the Oxy protein comprises a C-terminal ER export signal and a C-terminal trafficking signal. In some embodiments, the C-terminal ER export signal and the C-terminal trafficking signal are linked by a linker. The linker can comprise any of about 5, 10, 20, 30, 40, 50, 75, 100, 125, 150, 175, 200, 225, 250, 275, 300, 400, or 500 amino acids in length. The linker may further comprise a fluorescent protein, for example, but not limited to, a yellow fluorescent protein, a red fluorescent protein, a green fluorescent protein, or a cyan fluorescent protein. In some embodiments the ER

export signal is more C-terminally located than the trafficking signal. In some embodiments the trafficking signal is more C-terminally located than the ER Export signal.

[0070] In some embodiments, the light-responsive proton pump protein can be responsive to light and can be derived from *Leptosphaeria maculans*, wherein the proton pump protein can be capable of pumping protons across the membrane of a cell when the cell is illuminated with 520 nm to 560 nm light. The light can have a wavelength between about 520 nm to about 560 nm. In another embodiment, the light-responsive proton pump protein can comprise an amino acid sequence at least about 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identical to the sequence shown in SEQ ID NO:6 or SEQ ID NO:7 (Mac; Mac 3.0). The light-responsive proton pump protein can additionally comprise substitutions, deletions, and/or insertions introduced into a native amino acid sequence to increase or decrease sensitivity to light, increase or decrease sensitivity to particular wavelengths of light, and/or increase or decrease the ability of the light-responsive proton pump protein to regulate the polarization state of the plasma membrane of the cell. Additionally, the light-responsive proton pump protein can contain one or more conservative amino acid substitutions and/or one or more non-conservative amino acid substitutions. The light-responsive proton pump protein comprising substitutions, deletions, and/or insertions introduced into the native amino acid sequence suitably retains the ability to pump protons across the plasma membrane of a neuronal cell in response to light.

[0071] In other aspects of the methods disclosed herein, the light-responsive proton pump protein can comprise a core amino acid sequence at least about 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identical to the sequence shown in SEQ ID NO:6 and at least one (such as one, two, three, or more) amino acid sequence motifs which enhance transport to the plasma membranes of mammalian cells selected from the group consisting of a signal peptide, an ER export signal, and a membrane trafficking signal. In some embodiments, the light-responsive proton pump protein comprises an N-terminal signal peptide and a C-terminal ER export signal. In some embodiments, the light-responsive proton pump protein comprises an N-terminal signal peptide and a C-terminal trafficking signal. In some embodiments, the light-responsive proton pump protein comprises an N-terminal signal peptide, a C-terminal ER Export signal, and a C-terminal trafficking signal. In some embodiments, the light-responsive proton pump protein comprises a C-terminal ER Export signal and a C-terminal trafficking signal. In some embodiments, the C-terminal ER Export signal and the C-terminal trafficking signal are linked by a linker. The linker can comprise any of about 5, 10, 20, 30, 40, 50, 75, 100, 125, 150, 175, 200, 225, 250, 275, 300, 400, or 500 amino acids in length. The linker may further comprise a fluorescent protein, for example, but not limited to, a yellow fluorescent protein, a red fluorescent protein, a green fluorescent protein, or a cyan fluorescent protein. In some embodiments the ER Export signal is more C-terminally located than the trafficking signal. In some embodiments the trafficking signal is more C-terminally located than the ER Export signal.

[0072] Also provided herein are isolated polynucleotides encoding any of the light-responsive proton pump proteins described herein, such as a light-responsive proton pump protein comprising a core amino acid sequence at least about

90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identical to the sequence shown in SEQ ID NO:6. Also provided herein are expression vectors (such as a viral vector described herein) comprising a polynucleotide encoding the proteins described herein, such as a light-responsive proton pump protein comprising a core amino acid sequence at least about 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identical to the sequence shown in SEQ ID NO:6.

[0073] Further disclosure related to light-activated proton pump proteins can be found in International Patent Application No. PCT/US2011/028893, the disclosure of which is hereby incorporated by reference in its entirety.

Cation Channel Proteins

[0074] In some aspects, the light-responsive cation channel protein can be derived from *Chlamydomonas reinhardtii*, wherein the cation channel protein can be capable of transporting cations across a cell membrane when the cell is illuminated with light. In another embodiment, the light-responsive cation channel protein can comprise an amino acid sequence at least about 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identical to the sequence shown in SEQ ID NO:8. The light used to activate the light-responsive cation channel protein derived from *Chlamydomonas reinhardtii* can have a wavelength between about 460 and about 495 nm or can have a wavelength of about 480 nm. Additionally, light pulses having a temporal frequency of about 100 Hz can be used to activate the light-responsive protein. In some embodiments, activation of the light-responsive cation channel derived from *Chlamydomonas reinhardtii* with light pulses having a temporal frequency of about 100 Hz can cause depolarization-induced synaptic depletion of the neurons expressing the light-responsive cation channel. The light-responsive cation channel protein can additionally comprise substitutions, deletions, and/or insertions introduced into a native amino acid sequence to increase or decrease sensitivity to light, increase or decrease sensitivity to particular wavelengths of light, and/or increase or decrease the ability of the light-responsive cation channel protein to regulate the polarization state of the plasma membrane of the cell. Additionally, the light-responsive cation channel protein can contain one or more conservative amino acid substitutions and/or one or more non-conservative amino acid substitutions. The light-responsive proton pump protein comprising substitutions, deletions, and/or insertions introduced into the native amino acid sequence suitably retains the ability to transport cations across a cell membrane. In another embodiment, the light-responsive cation channel protein can comprise an amino acid sequence at least about 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identical to the C1C2 amino sequence shown in FIG. 13E, and set forth in SEQ ID NO:29. A crystal structure of C1C2 is presented in Kato et al. (2012) Nature 482:369. In another embodiment, the light-responsive cation channel protein can comprise an amino acid sequence at least about 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identical to the ReaChR amino sequence shown in FIG. 13F, and set forth in SEQ ID NO:30.

[0075] In some embodiments, the light-responsive cation channel comprises a T159C substitution of the amino acid sequence set forth in SEQ ID NO:8. In some embodiments, the light-responsive cation channel comprises a L132C

substitution of the amino acid sequence set forth in SEQ ID NO:8. In some embodiments, the light-responsive cation channel comprises an E123T substitution of the amino acid sequence set forth in SEQ ID NO:8. In some embodiments, the light-responsive cation channel comprises an E123A substitution of the amino acid sequence set forth in SEQ ID NO:8. In some embodiments, the light-responsive cation channel comprises a T159C substitution and an E123T substitution of the amino acid sequence set forth in SEQ ID NO:8. In some embodiments, the light-responsive cation channel comprises a T159C substitution and an E123A substitution of the amino acid sequence set forth in SEQ ID NO:8. In some embodiments, the light-responsive cation channel comprises a T159C substitution, an L132C substitution, and an E123T substitution of the amino acid sequence set forth in SEQ ID NO:8. In some embodiments, the light-responsive cation channel comprises a T159C substitution, an L132C substitution, and an E123A substitution of the amino acid sequence set forth in SEQ ID NO:8. In some embodiments, the light-responsive cation channel comprises an L132C substitution and an E123T substitution of the amino acid sequence set forth in SEQ ID NO:8. In some embodiments, the light-responsive cation channel comprises an L132C substitution and an E123A substitution of the amino acid sequence set forth in SEQ ID NO:8. In some embodiments, the light-responsive cation channel comprises an H143R amino acid substitution of the amino acid sequence set forth in SEQ ID NO:8.

[0076] In some embodiments, a Chr2 protein comprises at least one (such as one, two, three, or more) amino acid sequence motifs that enhance transport to the plasma membranes of target cells selected from the group consisting of a signal peptide, an ER export signal, and a membrane trafficking signal. In some embodiments, the Chr2 protein comprises an N-terminal signal peptide and a C-terminal ER export signal. In some embodiments, the Chr2 protein comprises an N-terminal signal peptide and a C-terminal trafficking signal. In some embodiments, the Chr2 protein comprises an N-terminal signal peptide, a C-terminal ER export signal, and a C-terminal trafficking signal. In some embodiments, the Chr2 protein comprises a C-terminal ER export signal and a C-terminal trafficking signal. In some embodiments, the C-terminal ER export signal and the C-terminal trafficking signal are linked by a linker. The linker can comprise any of about 5, 10, 20, 30, 40, 50, 75, 100, 125, 150, 175, 200, 225, 250, 275, 300, 400, or 500 amino acids in length. The linker may further comprise a fluorescent protein, for example, but not limited to, a yellow fluorescent protein, a red fluorescent protein, a green fluorescent protein, or a cyan fluorescent protein. In some embodiments the ER export signal is more C-terminally located than the trafficking signal. In some embodiments the trafficking signal is more C-terminally located than the ER Export signal.

Step Function Opsins and Stabilized Step Function Opsins

[0077] In other embodiments, the light-responsive cation channel protein can be a step function opsin (SFO) protein or a stabilized step function opsin (SSFO) protein that can have specific amino acid substitutions at key positions throughout the retinal binding pocket of the protein. In some embodiments, the SFO protein can have a mutation at amino acid residue C128 of SEQ ID NO:8. In other embodiments, the SFO protein has a C128A mutation in SEQ ID NO:5. In

other embodiments, the SFO protein has a C128S mutation in SEQ ID NO:8. In another embodiment, the SFO protein has a C128T mutation in SEQ ID NO:8. In some embodiments, the SFO protein can comprise an amino acid sequence at least about 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identical to the sequence shown in SEQ ID NO:9.

[0078] In some embodiments, the SSFO protein can have a mutation at amino acid residue D156 of SEQ ID NO:8. In other embodiments, the SSFO protein can have a mutation at both amino acid residues C128 and D156 of SEQ ID NO:8. In one embodiment, the SSFO protein has an C128S and a D156A mutation in SEQ ID NO:8. In another embodiment, the SSFO protein can comprise an amino acid sequence at least about 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identical to the sequence shown in SEQ ID NO:10. In another embodiment, the SSFO protein can comprise a C128T mutation in SEQ ID NO:8. In some embodiments, the SSFO protein comprises C128T and D156A mutations in SEQ ID NO:8.

[0079] In some embodiments the SFO or SSFO proteins provided herein can be capable of mediating a depolarizing current in the cell when the cell is illuminated with blue light. In other embodiments, the light can have a wavelength of about 445 nm. Additionally, in some embodiments the light can be delivered as a single pulse of light or as spaced pulses of light due to the prolonged stability of SFO and SSFO photocurrents. In some embodiments, activation of the SFO or SSFO protein with single pulses or spaced pulses of light can cause depolarization-induced synaptic depletion of the neurons expressing the SFO or SSFO protein. In some embodiments, each of the disclosed step function opsin and stabilized step function opsin proteins can have specific properties and characteristics for use in depolarizing the membrane of a neuronal cell in response to light.

[0080] Further disclosure related to SFO or SSFO proteins can be found in International Patent Application Publication No. WO 2010/056970, the disclosure of which is hereby incorporated by reference in its entirety.

C1V1 Chimeric Cation Channels

[0081] In other embodiments, the light-responsive cation channel protein can be a C1V1 chimeric protein derived from the VChR1 protein of *Volvox carteri* and the ChR1 protein from *Chlamydomonas reinhardtii*, wherein the protein comprises the amino acid sequence of VChR1 having at least the first and second transmembrane helices replaced by the first and second transmembrane helices of ChR1; is responsive to light; and is capable of mediating a depolarizing current in the cell when the cell is illuminated with light. In some embodiments, the C1V1 protein can further comprise a replacement within the intracellular loop domain located between the second and third transmembrane helices of the chimeric light responsive protein, wherein at least a portion of the intracellular loop domain is replaced by the corresponding portion from ChR1. In another embodiment, the portion of the intracellular loop domain of the C1V1 chimeric protein can be replaced with the corresponding portion from ChR1 extending to amino acid residue A145 of the ChR1. In other embodiments, the C1V1 chimeric protein can further comprise a replacement within the third transmembrane helix of the chimeric light responsive protein, wherein at least a portion of the third transmembrane helix is replaced by the corresponding sequence of ChR1. In yet

another embodiment, the portion of the intracellular loop domain of the C1V1 chimeric protein can be replaced with the corresponding portion from ChR1 extending to amino acid residue W163 of the ChR1. In other embodiments, the C1V1 chimeric protein can comprise an amino acid sequence at least about 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identical to the sequence shown in SEQ ID NO:11.

[0082] In some embodiments, the C1V1 protein can mediate a depolarizing current in the cell when the cell is illuminated with green light. In other embodiments, the light can have a wavelength of between about 540 nm to about 560 nm. In some embodiments, the light can have a wavelength of about 542 nm. In some embodiments, the C1V1 chimeric protein is not capable of mediating a depolarizing current in the cell when the cell is illuminated with violet light. In some embodiments, the chimeric protein is not capable of mediating a depolarizing current in the cell when the cell is illuminated with light having a wavelength of about 405 nm. Additionally, in some embodiments, light pulses having a temporal frequency of about 100 Hz can be used to activate the C1V1 protein.

C1V1 Chimeric Mutant Variants

[0083] In some aspects, the present disclosure provides polypeptides comprising substituted or mutated amino acid sequences, wherein the mutant polypeptide retains the characteristic light-activatable nature of the precursor C1V1 chimeric polypeptide but may also possess altered properties in some specific aspects. For example, the mutant light-responsive C1V1 chimeric proteins described herein can exhibit an increased level of expression both within an animal cell or on the animal cell plasma membrane; an altered responsiveness when exposed to different wavelengths of light, particularly red light; and/or a combination of traits whereby the chimeric C1V1 polypeptide possess the properties of low desensitization, fast deactivation, low violet-light activation for minimal cross-activation with other light-responsive cation channels, and/or strong expression in animal cells.

[0084] Accordingly, provided herein are C1V1 chimeric light-responsive opsin proteins that can have specific amino acid substitutions at key positions throughout the retinal binding pocket of the VChR1 portion of the chimeric polypeptide. In some embodiments, the C1V1 protein can have a mutation at amino acid residue E122 of SEQ ID NO:11. In some embodiments, the C1V1 protein can have a mutation at amino acid residue E162 of SEQ ID NO:11. In other embodiments, the C1V1 protein can have a mutation at both amino acid residues E162 and E122 of SEQ ID NO:11. In other embodiments, the C1V1 protein can comprise an amino acid sequence at least about 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identical to the sequence shown in SEQ ID NO:12, SEQ ID NO:13, or SEQ ID NO:14.

[0085] In some aspects, the C1V1-E122 mutant chimeric protein is capable of mediating a depolarizing current in the cell when the cell is illuminated with light. In some embodiments the light can be green light. In other embodiments, the light can have a wavelength of between about 540 nm to about 560 nm. In some embodiments, the light can have a wavelength of about 546 nm. In other embodiments, the C1V1-E122 mutant chimeric protein can mediate a depolarizing current in the cell when the cell is illuminated with

red light. In some embodiments, the red light can have a wavelength of about 630 nm. In some embodiments, the C1V1-E122 mutant chimeric protein does not mediate a depolarizing current in the cell when the cell is illuminated with violet light. In some embodiments, the chimeric protein does not mediate a depolarizing current in the cell when the cell is illuminated with light having a wavelength of about 405 nm. Additionally, in some embodiments, light pulses having a temporal frequency of about 100 Hz can be used to activate the C1V1-E122 mutant chimeric protein. In some embodiments, activation of the C1V1-E122 mutant chimeric protein with light pulses having a frequency of 100 Hz can cause depolarization-induced synaptic depletion of the neurons expressing the C1V1-E122 mutant chimeric protein.

[0086] In other aspects, the C1V1-E162 mutant chimeric protein is capable of mediating a depolarizing current in the cell when the cell is illuminated with light. In some embodiments the light can be green light. In other embodiments, the light can have a wavelength of between about 535 nm to about 540 nm. In some embodiments, the light can have a wavelength of about 542 nm. In other embodiments, the light can have a wavelength of about 530 nm. In some embodiments, the C1V1-E162 mutant chimeric protein does not mediate a depolarizing current in the cell when the cell is illuminated with violet light. In some embodiments, the chimeric protein does not mediate a depolarizing current in the cell when the cell is illuminated with light having a wavelength of about 405 nm. Additionally, in some embodiments, light pulses having a temporal frequency of about 100 Hz can be used to activate the C1V1-E162 mutant chimeric protein. In some embodiments, activation of the C1V1-E162 mutant chimeric protein with light pulses having a frequency of 100 Hz can cause depolarization-induced synaptic depletion of the neurons expressing the C1V1-E162 mutant chimeric protein.

[0087] In yet other aspects, the C1V1-E122/E162 mutant chimeric protein is capable of mediating a depolarizing current in the cell when the cell is illuminated with light. In some embodiments the light can be green light. In other embodiments, the light can have a wavelength of between about 540 nm to about 560 nm. In some embodiments, the light can have a wavelength of about 546 nm. In some embodiments, the C1V1-E122/E162 mutant chimeric protein does not mediate a depolarizing current in the cell when the cell is illuminated with violet light. In some embodiments, the chimeric protein does not mediate a depolarizing current in the cell when the cell is illuminated with light having a wavelength of about 405 nm. In some embodiments, the C1V1-E122/E162 mutant chimeric protein can exhibit less activation when exposed to violet light relative to C1V1 chimeric proteins lacking mutations at E122/E162 or relative to other light-responsive cation channel proteins. Additionally, in some embodiments, light pulses having a temporal frequency of about 100 Hz can be used to activate the C1V1-E122/E162 mutant chimeric protein. In some embodiments, activation of the C1V1-E122/E162 mutant chimeric protein with light pulses having a frequency of 100 Hz can cause depolarization-induced synaptic depletion of the neurons expressing the C1V1-E122/E162 mutant chimeric protein.

Dunaliella salina Light-Responsive Proteins

[0088] In some embodiments, the light-responsive ion channel protein can be responsive to 470 nm-510 nm light and can be derived from *Dunaliella salina*, wherein the ion

channel protein can be capable of mediating a hyperpolarizing current in the cell when the cell is illuminated with light. The light can have a wavelength between about 470 nm and about 510 nm or can have a wavelength of about 490 nm. In another embodiment, the light-responsive ion channel protein can comprise an amino acid sequence at least about 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identical to the sequence shown in SEQ ID NO:15. The light-responsive ion channel protein can additionally comprise substitutions, deletions, and/or insertions introduced into a native amino acid sequence to increase or decrease sensitivity to light, increase or decrease sensitivity to particular wavelengths of light, and/or increase or decrease the ability of the light-responsive ion channel protein to regulate the polarization state of the plasma membrane of the cell. Additionally, the light-responsive ion channel protein can contain one or more conservative amino acid substitutions and/or one or more non-conservative amino acid substitutions. The light-responsive ion channel protein comprising substitutions, deletions, and/or insertions introduced into the native amino acid sequence suitably retains the ability to transport ions across the plasma membrane of a neuronal cell in response to light.

[0089] In other aspects of the methods disclosed herein, the light-responsive ion channel protein can comprise a core amino acid sequence at least about 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identical to the sequence shown in SEQ ID NO:15 and at least one (such as one, two, three, or more) amino acid sequence motifs which enhance transport to the plasma membranes of mammalian cells selected from the group consisting of a signal peptide, an ER export signal, and a membrane trafficking signal. In some embodiments, the light-responsive proton ion channel comprises an N-terminal signal peptide and a C-terminal ER export signal. In some embodiments, the light-responsive ion channel protein comprises an N-terminal signal peptide and a C-terminal trafficking signal. In some embodiments, the light-responsive ion channel protein comprises an N-terminal signal peptide, a C-terminal ER Export signal, and a C-terminal trafficking signal. In some embodiments, the light-responsive ion channel protein comprises a C-terminal ER Export signal and a C-terminal trafficking signal. In some embodiments, the C-terminal ER Export signal and the C-terminal trafficking signal are linked by a linker. The linker can comprise any of about 5, 10, 20, 30, 40, 50, 75, 100, 125, 150, 175, 200, 225, 250, 275, 300, 400, or 500 amino acids in length. The linker may further comprise a fluorescent protein, for example, but not limited to, a yellow fluorescent protein, a red fluorescent protein, a green fluorescent protein, or a cyan fluorescent protein. In some embodiments the ER Export signal is more C-terminally located than the trafficking signal. In some embodiments the trafficking signal is more C-terminally located than the ER Export signal.

[0090] Also provided herein are isolated polynucleotides encoding any of the light-responsive channel proteins described herein, such as a light-responsive ion channel protein comprising a core amino acid sequence at least about 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identical to the sequence shown in SEQ ID NO:15. Also provided herein are expression vectors (such as a viral vector described herein) comprising a polynucleotide encoding the proteins described herein, such as a light-responsive channel protein comprising a core amino acid sequence at

least about 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identical to the sequence shown in SEQ ID NO:15.

Chloride Ion Pumps

[0091] In some aspects, said one or more light-responsive chloride pump proteins expressed on the plasma membranes of the neurons described above can be derived from *Natronomonas pharaonis*. In some embodiments, the light-responsive chloride pump proteins can be responsive to amber light as well as red light and can mediate a hyperpolarizing current in the neuron when the light-responsive chloride pump proteins are illuminated with amber or red light. The wavelength of light which can activate the light-responsive chloride pumps can be between about 580 and 630 nm. In some embodiments, the light can be at a wavelength of about 589 nm or the light can have a wavelength greater than about 630 nm (e.g. less than about 740 nm). In another embodiment, the light has a wavelength of around 630 nm. In some embodiments, the light-responsive chloride pump protein can hyperpolarize a neural membrane for at least about 90 minutes when exposed to a continuous pulse of light. In some embodiments, the light-responsive chloride pump protein can comprise an amino acid sequence at least about 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identical to the sequence shown in SEQ ID NO:16. Additionally, the light-responsive chloride pump protein can comprise substitutions, deletions, and/or insertions introduced into a native amino acid sequence to increase or decrease sensitivity to light, increase or decrease sensitivity to particular wavelengths of light, and/or increase or decrease the ability of the light-responsive protein to regulate the polarization state of the plasma membrane of the cell. In some embodiments, the light-responsive chloride pump protein contains one or more conservative amino acid substitutions. In some embodiments, the light-responsive protein contains one or more non-conservative amino acid substitutions. The light-responsive protein comprising substitutions, deletions, and/or insertions introduced into the native amino acid sequence suitably retains the ability to hyperpolarize the plasma membrane of a neuronal cell in response to light.

[0092] Additionally, in other aspects, the light-responsive chloride pump protein can comprise a core amino acid sequence at least about 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identical to the sequence shown in SEQ ID NO:16 and an endoplasmic reticulum (ER) export signal. This ER export signal can be fused to the C-terminus of the core amino acid sequence or can be fused to the N-terminus of the core amino acid sequence. In some embodiments, the ER export signal is linked to the core amino acid sequence by a linker. The linker can comprise any of about 5, 10, 20, 30, 40, 50, 75, 100, 125, 150, 175, 200, 225, 250, 275, 300, 400, or 500 amino acids in length. The linker may further comprise a fluorescent protein, for example, but not limited to, a yellow fluorescent protein, a red fluorescent protein, a green fluorescent protein, or a cyan fluorescent protein. In some embodiments, the ER export signal can comprise the amino acid sequence FXYENE (SEQ ID NO:46), where X can be any amino acid. In another embodiment, the ER export signal can comprise the amino acid sequence VXXSL (SEQ ID NO:42), where X can be any amino acid. In some

embodiments, the ER export signal can comprise the amino acid sequence FCYENEV (SEQ ID NO:47).

[0093] Endoplasmic reticulum (ER) export sequences that are suitable for use in a modified opsin of the present disclosure include, e.g., VXXSL (where X is any amino acid) (SEQ ID NO:42) (e.g., VKESL (SEQ ID NO:43); VLGSL (SEQ ID NO:44); etc.); NANSFCYENEVALTSK (SEQ ID NO:45); FXYENE (where X is any amino acid) (SEQ ID NO:46), e.g., FCYENEV (SEQ ID NO:47); and the like. An ER export sequence can have a length of from about 5 amino acids to about 25 amino acids, e.g., from about 5 amino acids to about 10 amino acids, from about 10 amino acids to about 15 amino acids, from about 15 amino acids to about 20 amino acids, or from about 20 amino acids to about 25 amino acids.

[0094] In other aspects, the light-responsive chloride pump proteins described herein can comprise a light-responsive protein expressed on the cell membrane, wherein the protein comprises a core amino acid sequence at least about 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identical to the sequence shown in SEQ ID NO:16 and a trafficking signal (e.g., which can enhance transport of the light-responsive chloride pump protein to the plasma membrane). The trafficking signal may be fused to the C-terminus of the core amino acid sequence or may be fused to the N-terminus of the core amino acid sequence. In some embodiments, the trafficking signal can be linked to the core amino acid sequence by a linker which can comprise any of about 5, 10, 20, 30, 40, 50, 75, 100, 125, 150, 175, 200, 225, 250, 275, 300, 400, or 500 amino acids in length. The linker may further comprise a fluorescent protein, for example, but not limited to, a yellow fluorescent protein, a red fluorescent protein, a green fluorescent protein, or a cyan fluorescent protein. In some embodiments, the trafficking signal can be derived from the amino acid sequence of the human inward rectifier potassium channel Kir2.1. In other embodiments, the trafficking signal can comprise the amino acid sequence KSRITSEGEYIPLDQIDINV (SEQ ID NO:37).

[0095] In some aspects, the light-responsive chloride pump protein can comprise a core amino acid sequence at least about 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identical to the sequence shown in SEQ ID NO:16 and at least one (such as one, two, three, or more) amino acid sequence motifs which enhance transport to the plasma membranes of mammalian cells selected from the group consisting of an ER export signal, a signal peptide, and a membrane trafficking signal. In some embodiments, the light-responsive chloride pump protein comprises an N-terminal signal peptide, a C-terminal ER Export signal, and a C-terminal trafficking signal. In some embodiments, the C-terminal ER Export signal and the C-terminal trafficking signal can be linked by a linker. The linker can comprise any of about 5, 10, 20, 30, 40, 50, 75, 100, 125, 150, 175, 200, 225, 250, 275, 300, 400, or 500 amino acids in length. The linker can also further comprise a fluorescent protein, for example, but not limited to, a yellow fluorescent protein, a red fluorescent protein, a green fluorescent protein, or a cyan fluorescent protein. In some embodiments the ER Export signal can be more C-terminally located than the trafficking signal. In other embodiments the trafficking signal is more C-terminally located than the ER Export signal. In some embodiments, the signal peptide comprises the amino acid sequence MTETLPPVTESAVALQAE (SEQ ID NO:48). In another embodiment, the light-responsive chlo-

ride pump protein comprises an amino acid sequence at least 95% identical to SEQ ID NO:17.

[0096] Moreover, in other aspects, the light-responsive chloride pump proteins can comprise a core amino acid sequence at least about 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identical to the sequence shown in SEQ ID NO:16, wherein the N-terminal signal peptide of SEQ ID NO:16 is deleted or substituted. In some embodiments, other signal peptides (such as signal peptides from other opsins) can be used. The light-responsive protein can further comprise an ER transport signal and/or a membrane trafficking signal described herein. In some embodiments, the light-responsive chloride pump protein comprises an amino acid sequence at least 95% identical to SEQ ID NO:18.

[0097] In some embodiments, the light-responsive opsin protein is a NpHR opsin protein comprising an amino acid sequence at least 95%, at least 96%, at least 97%, at least 98%, at least 99% or 100% identical to the sequence shown in SEQ ID NO:16. In some embodiments, the NpHR opsin protein further comprises an endoplasmic reticulum (ER) export signal and/or a membrane trafficking signal. For example, the NpHR opsin protein comprises an amino acid sequence at least 95% identical to the sequence shown in SEQ ID NO:16 and an endoplasmic reticulum (ER) export signal. In some embodiments, the amino acid sequence at least 95% identical to the sequence shown in SEQ ID NO:16 is linked to the ER export signal through a linker. In some embodiments, the ER export signal comprises the amino acid sequence FXYENE (SEQ ID NO:46), where X can be any amino acid. In another embodiment, the ER export signal comprises the amino acid sequence VXXSL (SEQ ID NO:42), where X can be any amino acid. In some embodiments, the ER export signal comprises the amino acid sequence FCYENEV (SEQ ID NO:47). In some embodiments, the NpHR opsin protein comprises an amino acid sequence at least 95% identical to the sequence shown in SEQ ID NO:16, an ER export signal, and a membrane trafficking signal. In other embodiments, the NpHR opsin protein comprises, from the N-terminus to the C-terminus, the amino acid sequence at least 95% identical to the sequence shown in SEQ ID NO:16, the ER export signal, and the membrane trafficking signal. In other embodiments, the NpHR opsin protein comprises, from the N-terminus to the C-terminus, the amino acid sequence at least 95% identical to the sequence shown in SEQ ID NO:16, the membrane trafficking signal, and the ER export signal. In some embodiments, the membrane trafficking signal is derived from the amino acid sequence of the human inward rectifier potassium channel Kir2.1. In some embodiments, the membrane trafficking signal comprises the amino acid sequence KSRITSEGEYIPLDQIDINV (SEQ ID NO:37). In some embodiments, the membrane trafficking signal is linked to the amino acid sequence at least 95% identical to the sequence shown in SEQ ID NO:16 by a linker. In some embodiments, the membrane trafficking signal is linked to the ER export signal through a linker. The linker may comprise any of 5, 10, 20, 30, 40, 50, 75, 100, 125, 150, 175, 200, 225, 250, 275, 300, 400, or 500 amino acids in length. The linker may further comprise a fluorescent protein, for example, but not limited to, a yellow fluorescent protein, a red fluorescent protein, a green fluorescent protein, or a cyan fluorescent protein. In some embodiments, the light-responsive opsin protein further comprises an N-terminal signal

peptide. In some embodiments, the light-responsive opsin protein comprises the amino acid sequence of SEQ ID NO:17. In some embodiments, the light-responsive opsin protein comprises the amino acid sequence of SEQ ID NO:18.

[0098] Also provided herein are polynucleotides encoding any of the light-responsive chloride ion pump proteins described herein, such as a light-responsive protein comprising a core amino acid sequence at least about 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identical to the sequence shown in SEQ ID NO:16, an ER export signal, and a membrane trafficking signal. In another embodiment, the polynucleotides comprise a sequence which encodes an amino acid at least 95% identical to SEQ ID NO:17 and SEQ ID NO:18. The polynucleotides may be in an expression vector (such as, but not limited to, a viral vector described herein). The polynucleotides may be used for expression of the light-responsive chloride ion pump proteins.

[0099] Further disclosure related to light-responsive chloride pump proteins can be found in U.S. Patent Application Publication Nos: 2009/0093403 and 2010/0145418 as well as in International Patent Application No: PCT/US2011/028893, the disclosures of each of which are hereby incorporated by reference in their entireties.

Chlorella vulgaris Type 1 Rhodopsin

[0100] In some embodiments, a suitable light-responsive polypeptide is a rhodopsin from *Coccomyxa subellipsoidea* (*Chlorella vulgaris*). In some embodiments, a suitable light-responsive polypeptide comprises an amino acid sequence that is at least about 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identical to the sequence shown in SEQ ID NO:62. Additionally, the light-responsive polypeptide can comprise substitutions, deletions, and/or insertions introduced into a native amino acid sequence to increase or decrease sensitivity to light, increase or decrease sensitivity to particular wavelengths of light, and/or increase or decrease the ability of the light-responsive protein to regulate the polarization state of the plasma membrane of the cell. In some embodiments, the light-responsive polypeptide contains one or more conservative amino acid substitutions. In some embodiments, the light-responsive polypeptide contains one or more non-conservative amino acid substitutions. The light-responsive polypeptide comprising substitutions, deletions, and/or insertions introduced into the native amino acid sequence suitably retains the ability to hyperpolarize the plasma membrane of a neuronal cell in response to light.

[0101] In some cases, a suitable light-responsive polypeptide comprises an amino acid sequence that is at least about 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identical to the sequence shown in SEQ ID NO:62; and comprises an ER export signal (e.g., FCYENEV (SEQ ID NO:47)). In some cases, a suitable light-responsive polypeptide comprises an amino acid sequence that is at least about 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identical to the sequence shown in SEQ ID NO:62; and comprises a membrane trafficking signal (e.g., KSRITSEGEYIPLDQIDINV (SEQ ID NO:37)). In some cases, a suitable light-responsive polypeptide comprises an amino acid sequence that is at least about 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identical to the sequence shown in SEQ ID NO:62; and comprises a membrane trafficking signal

(e.g., KSRITSEGEYIPLDQIDINV (SEQ ID NO:37)) and an ER export signal (e.g., FCYENEV (SEQ ID NO:47)).

(SEQ ID NO: 62)
 MAVHQIGEGGLVMYVWTFGLMAFSALAFVMTFTRPLNKRSHGYITLAIV
 TIAAIAYYAMAASGGKALVSNPDGNLRDIYYARYIDWFFTTPLLLLDIIL
 LTGIPIGVTLWIVLADVAMIMLGLFGALSTNSYRWGYGVSCAFFFVVLW
 GLFFPGAKGARARGGQVPGLYFGLAGYLALLWFGYPIVWGLAEGSDYISV
 TAEAASYAGLDIAAKVVFVGWAVMLSHPLIARNQTDGSLINSTNDPFVAS
 TTHIPERQGGIFGGLMGKKRGAGTPLATNEGVPKKAAPTAAATTAGNPAT
 AAEVRTPRELMARL.

Response Proteins

[0102] As summarized above, aspects of the present disclosure include response proteins that allow one or more ions to pass through a membrane when the response protein detects the presence of one or more ions that have passed through a subject light-activated protein. Response proteins may be characterized as ion pump proteins, which facilitate the passage of a small number of ions through the membrane per action cycle, or as ion channel proteins, which allow a stream of ions to freely flow through the membrane. The subject response proteins are specific to a particular species of ion or to a particular group of ions (e.g., cations) meaning that the subject response proteins only allow ions of a particular species or group to pass through the membrane. In some cases, the response protein is a heterologous protein for a given cell, e.g., the response protein is one that is not normally expressed in the cell. In other cases, the response protein is native to a given cell, e.g., the response protein is one that is normally expressed in the cell. A response protein can be a mammalian protein (e.g., a human protein, a non-human protein), a bacterial protein, an archael protein, etc.

[0103] In some embodiments, the response protein is an ion channel. In some cases, the response protein is a cation channel, e.g., a potassium channel or a calcium channel. In some cases, the response protein is an anion channel, e.g., a chloride ion channel or a sodium channel. In other instances, the response protein is a proton pump. Response proteins can be voltage-gated or ligand-gated.

[0104] Non-limiting examples of suitable response proteins include, e.g., a voltage-gated potassium channel (e.g., KVLQT1); a potassium channel (e.g., HERG); an inward rectifier K⁺ channel (e.g., Kir2.1); an acid sensing sodium ion channel; and the like. In some cases, the response protein is an ion exchanger (antiporter), e.g. the sodium-calcium exchanger (NCX), the potassium-dependent sodium-calcium exchanger (SLC24) or the sodium-hydrogen exchanger (NhaA). In some cases, the response protein is an ion co-transporter of the symport variety, e.g. the sodium-potassium-chloride co-transporter (NKCC1 and NKCC2) or the sodium-phosphate co-transporter (SLC34A1).

[0105] For example, a suitable response protein can comprise an amino acid sequence having at least about 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% amino acid sequence identity to a contiguous stretch of from about 100 amino acid (aa) to about 200 aa, from about 200 aa to about 300 aa, from about 300 aa to about 400 aa, from

about 400 aa to about 500 aa, from about 500 aa to about 600 aa, from about 600 aa to about 700 aa, from about 700 aa to about 800 aa, from about 800 aa to about 900 aa, from 900 aa to about 1000 aa, from about 1000 aa to about 1100 aa, up to the full length, of the amino acid sequence shown in one of FIGS. 14A-H (SEQ ID NOs:19-28).

Acid Sensing Ion Channel Variant 2a (ASIC2a)

[0106] In some embodiments, a response protein is an Acid Sensing Ion Channel variant 2a (ASIC2a) sodium ion channel protein that allows a plurality of sodium ions to flow across the plasma membrane of a target cell when the ASIC2a protein detects acidic conditions, such as the presence of a plurality of hydrogen ions on or near the external surface of the plasma membrane. In some embodiments, the ASIC2a protein can comprise an amino acid sequence that is at least about 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identical to the sequence shown in SEQ ID NO:19. The ASIC2a protein can additionally comprise substitutions, deletions, and/or insertions introduced into a native amino acid sequence to increase or decrease sensitivity to acidic conditions, and/or increase or decrease the ability of the ASIC2a protein to regulate the flow of sodium ions across the plasma membrane of a target cell. Additionally, the ASIC2a protein can contain one or more conservative amino acid substitutions and/or one or more non-conservative amino acid substitutions. The ASIC2a protein comprising substitutions, deletions, and/or insertions introduced into the native amino acid sequence suitably retains the functionality of the ASIC2a protein.

[0107] In some embodiments, an ASIC2a protein comprises at least one (such as one, two, three, or more) amino acid sequence motifs that enhance transport to the plasma membranes of target cells selected from the group consisting of a signal peptide, an ER export signal, and a membrane trafficking signal. In some embodiments, the ASIC2a protein comprises an N-terminal signal peptide and a C-terminal ER export signal. In some embodiments, the ASIC2a protein comprises an N-terminal signal peptide and a C-terminal trafficking signal. In some embodiments, the ASIC2a protein comprises an N-terminal signal peptide, a C-terminal ER export signal, and a C-terminal trafficking signal. In some embodiments, the ASIC2a protein comprises a C-terminal ER export signal and a C-terminal trafficking signal. In some embodiments, the C-terminal ER export signal and the C-terminal trafficking signal are linked by a linker. The linker can comprise any of about 5, 10, 20, 30, 40, 50, 75, 100, 125, 150, 175, 200, 225, 250, 275, 300, 400, or 500 amino acids in length. The linker may further comprise a fluorescent protein, for example, but not limited to, a yellow fluorescent protein, a red fluorescent protein, a green fluorescent protein, or a cyan fluorescent protein. In some embodiments the ER export signal is more C-terminally located than the trafficking signal. In some embodiments the trafficking signal is more C-terminally located than the ER Export signal.

Helicobacter pylori Potassium Channel (HpKchA)

[0108] In some embodiments, a response protein is a *Helicobacter pylori* potassium ion channel protein (HpKchA) that allows a plurality of potassium ions to flow across the plasma membrane of a target cell when the HpKchA protein detects acidic conditions, such as the presence of a plurality of hydrogen ions on or near the external surface of the plasma membrane. In some embodiments, the HpKchA

protein can comprise an amino acid sequence that is at least about 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identical to the sequence shown in SEQ ID NO:20. The HpKchA protein can additionally comprise substitutions, deletions, and/or insertions introduced into a native amino acid sequence to increase or decrease sensitivity to acidic conditions, and/or increase or decrease the ability of the HpKchA protein to regulate the flow of potassium ions across the plasma membrane of a target cell. Additionally, the HpKchA protein can contain one or more conservative amino acid substitutions and/or one or more non-conservative amino acid substitutions. The HpKchA protein comprising substitutions, deletions, and/or insertions introduced into the native amino acid sequence suitably retains the functionality of the HpKchA protein.

[0109] In some embodiments, an HpKchA protein comprises at least one (such as one, two, three, or more) amino acid sequence motifs that enhance transport to the plasma membranes of target cells selected from the group consisting of a signal peptide, an ER export signal, and a membrane trafficking signal. In some embodiments, the HpKchA protein comprises an N-terminal signal peptide and a C-terminal ER export signal. In some embodiments, the HpKchA protein comprises an N-terminal signal peptide and a C-terminal trafficking signal. In some embodiments, the HpKchA protein comprises an N-terminal signal peptide, a C-terminal ER export signal, and a C-terminal trafficking signal. In some embodiments, the HpKchA protein comprises a C-terminal ER export signal and a C-terminal trafficking signal. In some embodiments, the C-terminal ER export signal and the C-terminal trafficking signal are linked by a linker. The linker can comprise any of about 5, 10, 20, 30, 40, 50, 75, 100, 125, 150, 175, 200, 225, 250, 275, 300, 400, or 500 amino acids in length. The linker may further comprise a fluorescent protein, for example, but not limited to, a yellow fluorescent protein, a red fluorescent protein, a green fluorescent protein, or a cyan fluorescent protein. In some embodiments the ER export signal is more C-terminally located than the trafficking signal. In some embodiments the trafficking signal is more C-terminally located than the ER Export signal.

Fusion Proteins

[0110] In some cases, the light-responsive protein and the response protein are present together in a single polypeptide chain, e.g., the light-responsive protein and the response protein are a fusion protein. The present disclosure provides a two-component optogenetic fusion polypeptide comprising a light-responsive polypeptide and a response polypeptide.

[0111] In some embodiments, a subject two-component optogenetic fusion polypeptide comprises, in order from amino terminus to carboxyl terminus: a) a light-responsive polypeptide (as described above); and b) a response protein (as described above). In some embodiments, a subject two-component optogenetic fusion polypeptide comprises, in order from amino terminus to carboxyl terminus: a) a light-responsive polypeptide; b) a linker peptide; and c) a response protein. In some embodiments, a subject two-component optogenetic fusion polypeptide comprises, in order from amino terminus to carboxyl

terminus: a) a light-responsive polypeptide; b) a membrane trafficking signal; and c) a response protein. In some embodiments, a subject two-component optogenetic fusion polypeptide comprises, in order from amino terminus to carboxyl terminus: a) a light-responsive polypeptide; b) a membrane trafficking signal; c) a response protein; and d) a membrane trafficking signal. In some embodiments, a subject two-component optogenetic fusion polypeptide comprises, in order from amino terminus to carboxyl terminus: a) a light-responsive polypeptide; b) a membrane trafficking signal; c) a self-cleaving polypeptide; d) a response protein; and e) a membrane trafficking signal.

[0112] In some embodiments, a subject two-component optogenetic fusion polypeptide comprises, in order from amino terminus to carboxyl terminus: a) a light-responsive polypeptide; b) a membrane trafficking signal; c) a spacer polypeptide; d) a response protein; and e) an ER export signal. In some embodiments, a subject two-component optogenetic fusion polypeptide comprises, in order from amino terminus to carboxyl terminus: a) a light-responsive polypeptide; b) a membrane trafficking signal; c) a spacer polypeptide; d) a response protein; e) a membrane trafficking signal; and f) an ER export signal. In some embodiments, a subject two-component optogenetic fusion polypeptide comprises, in order from amino terminus to carboxyl terminus: a) a light-responsive polypeptide; b) a membrane trafficking signal; c) a response protein; d) a membrane trafficking signal; and e) an ER export signal. In some embodiments, a subject two-component optogenetic fusion polypeptide comprises, in order from amino terminus to carboxyl terminus: a) a light-responsive polypeptide; b) a membrane trafficking signal; c) a self-cleaving polypeptide; d) a response protein; e) a membrane trafficking signal; and f) an ER export signal.

[0113] Suitable self-cleaving polypeptides include, e.g., a 2A peptide such as a P2A peptide: ATNFSLLKQAGDVEENPGP (SEQ ID NO:49); a T2A peptide: EGRG-SLLTCGDVEENPGP (SEQ ID NO:50); an E2A peptide: QCTNYALLKLAGDVESNPGP (SEQ ID NO:51); an F2A peptide: VKQTLNFDLLKLAGDVESNPGP (SEQ ID NO:52); and the like. In some cases, the self-cleaving peptide is a P2A peptide: ATNFSLLKQAGDVEENPGP (SEQ ID NO:49). In some cases, a P2A peptide comprises the amino acid sequence GSGATNFSLLKQAGDVEENPGP (SEQ ID NO:61).

[0114] In some embodiments, a subject two-component optogenetic fusion polypeptide comprises, in order from amino terminus to carboxyl terminus: a) an eArch polypeptide comprising an amino acid sequence having at least 80%, at least 85%, at least 90%, at least 95%, at least 98%, at least 99%, or 100%, amino acid sequence identity to the eArch polypeptide amino acid sequence set forth in SEQ ID NO:1; b) a membrane trafficking signal; c) an ASIC2a polypeptide comprising an amino acid sequence having at least 80%, at least 85%, at least 90%, at least 95%, at least 98%, at least 99%, or 100%, amino acid sequence identity to the ASIC2a polypeptide amino acid sequence set forth in SEQ ID NO:19; and d) a membrane trafficking signal. In some cases, the membrane trafficking signal is: KSRITSEGEYIPLDQIDINV (SEQ ID NO:37). In some of these embodiments, the two-component optogenetic fusion polypeptide further comprises an ER export signal (e.g., FCYENEV (SEQ ID NO:47)).

[0115] In some embodiments, a subject two-component optogenetic fusion polypeptide comprises, in order from amino terminus to carboxyl terminus: a) an eArch polypeptide comprising an amino acid sequence having at least 80%, at least 85%, at least 90%, at least 95%, at least 98%, at least 99%, or 100%, amino acid sequence identity to the eArch polypeptide amino acid sequence set forth in SEQ ID NO:1; b) a membrane trafficking signal (e.g., KSRITSEGEYIPLDQIDINV (SEQ ID NO:37)); c) a polypeptide linker of from about 5 amino acids to about 100 amino acids, e.g., a polypeptide linker of from about 20 amino acids to about 25 amino acids in length; d) an ASIC2a polypeptide comprising an amino acid sequence having at least 80%, at least 85%, at least 90%, at least 95%, at least 98%, at least 99%, or 100%, amino acid sequence identity to the ASIC2a polypeptide amino acid sequence set forth in SEQ ID NO:19; and e) a membrane trafficking signal (e.g., KSRITSEGEYIPLDQIDINV (SEQ ID NO:37)). In some of these embodiments, the two-component optogenetic fusion polypeptide further comprises an ER export signal (e.g., FCYENEV (SEQ ID NO:47)).

[0116] In some embodiments, a subject two-component optogenetic fusion polypeptide comprises, in order from amino terminus to carboxyl terminus: a) an eArch polypeptide comprising an amino acid sequence having at least 80%, at least 85%, at least 90%, at least 95%, at least 98%, at least 99%, or 100%, amino acid sequence identity to the eArch polypeptide amino acid sequence set forth in SEQ ID NO:1; b) a membrane trafficking signal (e.g., KSRITSEGEYIPLDQIDINV (SEQ ID NO:37)); c) a polypeptide linker of from about 5 amino acids to about 100 amino acids, e.g., a polypeptide linker of from about 40 amino acids to about 45 amino acids in length; d) an ASIC2a polypeptide comprising an amino acid sequence having at least 80%, at least 85%, at least 90%, at least 95%, at least 98%, at least 99%, or 100%, amino acid sequence identity to the ASIC2a polypeptide amino acid sequence set forth in SEQ ID NO:19; and e) a membrane trafficking signal (e.g., KSRITSEGEYIPLDQIDINV (SEQ ID NO:37)). In some of these embodiments, the two-component optogenetic fusion polypeptide further comprises an ER export signal (e.g., FCYENEV (SEQ ID NO:47)).

[0117] In some embodiments, a subject two-component optogenetic fusion polypeptide comprises, in order from amino terminus to carboxyl terminus: a) an eArch polypeptide comprising an amino acid sequence having at least 80%, at least 85%, at least 90%, at least 95%, at least 98%, at least 99%, or 100%, amino acid sequence identity to the eArch polypeptide amino acid sequence set forth in SEQ ID NO:1; b) a membrane trafficking signal; c) a self-cleaving peptide (e.g., ATNFSLLKQAGDVEENPGP (SEQ ID NO:49)); d) an ASIC2a polypeptide comprising an amino acid sequence having at least 80%, at least 85%, at least 90%, at least 95%, at least 98%, at least 99%, or 100%, amino acid sequence identity to the ASIC2a polypeptide amino acid sequence set forth in SEQ ID NO:19; and e) a membrane trafficking signal. In some cases, the membrane trafficking signal is: KSRITSEGEYIPLDQIDINV (SEQ ID NO:37). In some of these embodiments, the two-component optogenetic fusion polypeptide further comprises an ER export signal (e.g., FCYENEV (SEQ ID NO:47)).

[0118] Suitable linkers include “flexible linkers”. If present, the linker polypeptide is generally of sufficient length to allow some flexible movement between the polypeptides

connected by the linker. Suitable linkers can be readily selected and can be of any of a suitable of different lengths, such as from 5 amino acids to 100 amino acids, e.g., from 5 amino acids (aa) to 10 aa, from 10 aa to 15 aa, from 15 aa to 25 aa, from 25 aa to 40 aa, from 40 aa to 60 aa, from 60 aa to 80 aa, or from 80 aa to 100 aa. In some cases, the polypeptide linker, if present, is from 20 aa to 25 aa in length. In some cases, the polypeptide linker, if present, is from 40 aa to 45 aa in length.

[0119] Exemplary polypeptide linkers include glycine polymers (G)_n, glycine-serine polymers (including, for example, (GS)_n, (GSGGS)_n (SEQ ID NO:53) and (GGGS)_n (SEQ ID NO:54), where n is an integer of at least one, e.g., 1, 2, 3, 4, 5, or from 5 to 10), glycine-alanine polymers, alanine-serine polymers, and other polypeptide linkers known in the art. Exemplary flexible linkers include, but are not limited GSGG (SEQ ID NO:55), GGS GG (SEQ ID NO:56), GSGSG (SEQ ID NO:57), GSGGG (SEQ ID NO:58), GGGSG (SEQ ID NO:59), GSSSG (SEQ ID NO:60), and the like. The ordinarily skilled artisan will recognize that design of a linker polypeptide can include linkers that are all or partially flexible, such that the linker can include a flexible linker as well as one or more portions that confer less flexible structure.

[0120] In some cases, a subject two-component optogenetic fusion polypeptide comprises an amino acid sequence having at least 85%, at least 85%, at least 90%, at least 95%, at least 98%, at least 99%, or 100%, amino acid sequence identity to the amino acid sequence set forth in SEQ ID NO:31 (Champ 1.0). In some cases, a subject two-component optogenetic fusion polypeptide comprises an amino acid sequence having at least 85%, at least 85%, at least 90%, at least 95%, at least 98%, at least 99%, or 100%, amino acid sequence identity to the amino acid sequence set forth in SEQ ID NO:32 (Champ 2.0). In some cases, a subject two-component optogenetic fusion polypeptide comprises an amino acid sequence having at least 85%, at least 85%, at least 90%, at least 95%, at least 98%, at least 99%, or 100%, amino acid sequence identity to the amino acid sequence set forth in SEQ ID NO:33 (Champ 3.0). In some cases, a subject two-component optogenetic fusion polypeptide comprises an amino acid sequence having at least 85%, at least 85%, at least 90%, at least 95%, at least 98%, at least 99%, or 100%, amino acid sequence identity to the amino acid sequence set forth in SEQ ID NO:34 (Champ 4.0).

[0121] In some cases, a subject two-component optogenetic fusion polypeptide comprises an amino acid sequence having at least 85%, at least 85%, at least 90%, at least 95%, at least 98%, at least 99%, or 100%, amino acid sequence identity to the amino acid sequence set forth in SEQ ID NO:31 (Champ 1.0) without the yellow fluorescent protein (eYFP) sequence. In some cases, a subject two-component optogenetic fusion polypeptide comprises an amino acid sequence having at least 85%, at least 85%, at least 90%, at least 95%, at least 98%, at least 99%, or 100%, amino acid sequence identity to the amino acid sequence set forth in SEQ ID NO:32 (Champ 2.0) without the yellow fluorescent protein (eYFP) sequence. In some cases, a subject two-component optogenetic fusion polypeptide comprises an amino acid sequence having at least 85%, at least 85%, at least 90%, at least 95%, at least 98%, at least 99%, or 100%, amino acid sequence identity to the amino acid sequence set forth in SEQ ID NO:33 (Champ 3.0) without the yellow

fluorescent protein (eYFP) sequence. In some cases, a subject two-component optogenetic fusion polypeptide comprises an amino acid sequence having at least 85%, at least 85%, at least 90%, at least 95%, at least 98%, at least 99%, or 100%, amino acid sequence identity to the amino acid sequence set forth in SEQ ID NO:34 (Champ 4.0) without the yellow fluorescent protein (eYFP) sequence.

[0122] The present disclosure provides a nucleic acid comprising a nucleotide sequence encoding a fusion polypeptide as described above. The present disclosure provides a recombinant expression vector comprising a nucleic acid comprising a nucleotide sequence encoding a fusion polypeptide as described above. In some cases, the nucleotide sequence encoding the fusion polypeptide is operably linked to a neuron-specific transcriptional control element. Suitable expression vectors and neuron-specific transcriptional control elements are described herein. The present disclosure provides a cell genetically modified with a recombinant expression vector comprising a nucleic acid comprising a nucleotide sequence encoding a fusion polypeptide as described above. In some embodiments, the cell is a neuron.

Exemplary Systems

[0123] The present disclosure provides various compositions, which include, but are not limited to, the following:

[0124] a) a composition comprising: i) a nucleic acid comprising a nucleotide sequence encoding a light-responsive polypeptide, where the light-responsive polypeptide is a proton pump; and ii) a nucleic acid comprising a nucleotide sequence encoding a response protein, wherein the response protein is an ion channel, e.g., an anion channel;

[0125] b) a composition comprising: i) a nucleic acid comprising a nucleotide sequence encoding a light-responsive polypeptide, where the light-responsive polypeptide is a proton pump; and ii) a nucleic acid comprising a nucleotide sequence encoding a response protein, wherein the response protein is a chloride ion channel;

[0126] c) a composition comprising: i) a nucleic acid comprising a nucleotide sequence encoding a light-responsive polypeptide, where the light-responsive polypeptide is a proton pump; and ii) a nucleic acid comprising a nucleotide sequence encoding a response protein, wherein the response protein is an ion channel, e.g., a cation channel;

[0127] d) a composition comprising: i) a nucleic acid comprising a nucleotide sequence encoding a light-responsive polypeptide, where the light-responsive polypeptide is a proton pump; and ii) a nucleic acid comprising a nucleotide sequence encoding a response protein, wherein the response protein is a potassium ion channel;

[0128] e) a composition comprising: i) a nucleic acid comprising a nucleotide sequence encoding a light-responsive polypeptide, where the light-responsive polypeptide is a proton pump; and ii) a nucleic acid comprising a nucleotide sequence encoding a response protein, wherein the response protein is a sodium ion channel;

[0129] f) a composition comprising: i) a nucleic acid comprising a nucleotide sequence encoding a light-responsive polypeptide, where the light-responsive polypeptide is a channelrhodopsin; and ii) a nucleic acid comprising a nucleotide sequence encoding a response protein, wherein the response protein is an ion channel, e.g., an anion channel;

[0130] g) a composition comprising: i) a nucleic acid comprising a nucleotide sequence encoding a light-respon-

sive polypeptide, where the light-responsive polypeptide is a channelrhodopsin; and ii) a nucleic acid comprising a nucleotide sequence encoding a response protein, wherein the response protein is a chloride ion channel;

[0131] h) a composition comprising: i) a nucleic acid comprising a nucleotide sequence encoding a light-responsive polypeptide, where the light-responsive polypeptide is a channelrhodopsin; and ii) a nucleic acid comprising a nucleotide sequence encoding a response protein, wherein the response protein is an ion channel, e.g., a cation channel;

[0132] i) a composition comprising: i) a nucleic acid comprising a nucleotide sequence encoding a light-responsive polypeptide, where the light-responsive polypeptide is a channelrhodopsin; and ii) a nucleic acid comprising a nucleotide sequence encoding a response protein, wherein the response protein is a potassium channel;

[0133] j) a composition comprising: i) a nucleic acid comprising a nucleotide sequence encoding a light-responsive polypeptide, where the light-responsive polypeptide is a channelrhodopsin; and ii) a nucleic acid comprising a nucleotide sequence encoding a response protein, wherein the response protein is a sodium channel;

[0134] k) a composition comprising: i) a nucleic acid comprising a nucleotide sequence encoding a light-responsive polypeptide, where the light-responsive polypeptide is a channelrhodopsin; and ii) a nucleic acid comprising a nucleotide sequence encoding a response protein, wherein the response protein is a proton pump;

[0135] l) a composition comprising: i) a nucleic acid comprising a nucleotide sequence encoding a light-responsive polypeptide, where the light-responsive polypeptide is a proton pump; and ii) a nucleic acid comprising a nucleotide sequence encoding a response protein, wherein the response protein is a proton pump;

[0136] m) a composition comprising: i) a nucleic acid comprising a nucleotide sequence encoding a light-responsive polypeptide, where the light-responsive polypeptide is a chloride ion pump; and ii) a nucleic acid comprising a nucleotide sequence encoding a response protein, wherein the response protein is an anion channel;

[0137] n) a composition comprising: i) a nucleic acid comprising a nucleotide sequence encoding a light-responsive polypeptide, where the light-responsive polypeptide is a chloride ion pump; and ii) a nucleic acid comprising a nucleotide sequence encoding a response protein, wherein the response protein is a cation channel;

[0138] o) a composition comprising: i) a nucleic acid comprising a nucleotide sequence encoding a light-responsive polypeptide, where the light-responsive polypeptide is a chloride ion pump; and ii) a nucleic acid comprising a nucleotide sequence encoding a response protein, wherein the response protein is a potassium channel;

[0139] p) a composition comprising: i) a nucleic acid comprising a nucleotide sequence encoding a light-responsive polypeptide, where the light-responsive polypeptide is a chloride ion pump; and ii) a nucleic acid comprising a nucleotide sequence encoding a response protein, wherein the response protein is a sodium channel; and

[0140] q) a composition comprising: i) a nucleic acid comprising a nucleotide sequence encoding a light-responsive polypeptide, where the light-responsive polypeptide is a chloride ion pump; and ii) a nucleic acid comprising a nucleotide sequence encoding a response protein, wherein the response protein is a proton pump.

[0141] The present disclosure provides various compositions, which include, but are not limited to, the following:

[0142] a) a composition comprising i) a nucleic acid comprising a nucleotide sequence encoding a light-responsive polypeptide, where the light responsive polypeptide is a ion pump or channel, and ii) a nucleic acid comprising a nucleotide sequence encoding a response protein wherein the response protein an ion exchanger, transporter, antiporter, or symport co-transporter;

[0143] b) a composition comprising: i) a nucleic acid comprising a nucleotide sequence encoding a light-responsive polypeptide, where the light-responsive polypeptide is a proton pump; and ii) a nucleic acid comprising a nucleotide sequence encoding a response protein, wherein the response protein is a sodium-phosphate co-transporter;

[0144] c) a composition comprising: i) a nucleic acid comprising a nucleotide sequence encoding a light-responsive polypeptide, where the light-responsive polypeptide is a proton pump; and ii) a nucleic acid comprising a nucleotide sequence encoding a response protein, wherein the response protein is a sodium-potassium-chloride co-transporter;

[0145] d) a composition comprising: i) a nucleic acid comprising a nucleotide sequence encoding a light-responsive polypeptide, where the light-responsive polypeptide is a proton pump; and ii) a nucleic acid comprising a nucleotide sequence encoding a response protein, wherein the response protein is an ion exchanger (antiporter), e.g. a sodium-calcium exchanger, a potassium-dependent sodium-calcium exchanger, or a sodium-hydrogen exchanger;

[0146] e) a composition comprising: i) a nucleic acid comprising a nucleotide sequence encoding a light-responsive polypeptide, where the light-responsive polypeptide is a channelrhodopsin; and ii) a nucleic acid comprising a nucleotide sequence encoding a response protein, wherein the response protein is a sodium-phosphate co-transporter;

[0147] f) a composition comprising: i) a nucleic acid comprising a nucleotide sequence encoding a light-responsive polypeptide, where the light-responsive polypeptide is a channelrhodopsin; and ii) a nucleic acid comprising a nucleotide sequence encoding a response protein, wherein the response protein is a sodium-potassium-chloride co-transporter;

[0148] g) a composition comprising: i) a nucleic acid comprising a nucleotide sequence encoding a light-responsive polypeptide, where the light-responsive polypeptide is a channelrhodopsin; and ii) a nucleic acid comprising a nucleotide sequence encoding a response protein, wherein the response protein is an ion exchanger (antiporter), e.g. a sodium-calcium exchanger, a potassium-dependent sodium-calcium exchanger, or a sodium-hydrogen exchanger.

[0149] The present disclosure provides various compositions, which include, but are not limited to, the following:

[0150] a) a composition comprising a nucleic acid comprising a nucleotide sequence encoding a two-component optogenetic fusion polypeptide, as described above;

[0151] b) a composition comprising a nucleic acid comprising a two-component optogenetic fusion polypeptide that comprises, in order from amino terminus to carboxyl terminus: i) a light-responsive polypeptide (as described above); and ii) a response protein (as described above).

[0152] c) a composition comprising a nucleic acid comprising a two-component optogenetic fusion polypeptide

that comprises, in order from amino terminus to carboxyl terminus: i) a response protein; and ii) a light-responsive polypeptide.

[0153] d) a composition comprising a nucleic acid comprising a two-component optogenetic fusion polypeptide that comprises, in order from amino terminus to carboxyl terminus: i) a light-responsive polypeptide; ii) a linker peptide; and iii) a response protein.

[0154] e) a composition comprising a nucleic acid comprising a two-component optogenetic fusion polypeptide that comprises, in order from amino terminus to carboxyl terminus: i) a light-responsive polypeptide; ii) a membrane trafficking signal; and iii) a response protein.

[0155] f) a composition comprising a nucleic acid comprising a two-component optogenetic fusion polypeptide that comprises, in order from amino terminus to carboxyl terminus: i) a light-responsive polypeptide; ii) a membrane trafficking signal; iii) a response protein; and iv) a membrane trafficking signal.

[0156] g) a composition comprising a nucleic acid comprising a two-component optogenetic fusion polypeptide that comprises, in order from amino terminus to carboxyl terminus: i) a light-responsive polypeptide; ii) a membrane trafficking signal; iii) a self-cleaving polypeptide; iv) a response protein; and v) a membrane trafficking signal.

[0157] h) a composition comprising a nucleic acid comprising a two-component optogenetic fusion polypeptide that comprises, in order from amino terminus to carboxyl terminus: i) an eArch polypeptide comprising an amino acid sequence having at least 80%, at least 85%, at least 90%, at least 95%, at least 98%, at least 99%, or 100%, amino acid sequence identity to the eArch polypeptide amino acid sequence set forth in SEQ ID NO:1; ii) a membrane trafficking signal; iii) an ASIC2a polypeptide comprising an amino acid sequence having at least 80%, at least 85%, at least 90%, at least 95%, at least 98%, at least 99%, or 100%, amino acid sequence identity to the ASIC2a polypeptide amino acid sequence set forth in SEQ ID NO:19; and iv) a membrane trafficking signal. In some cases, the membrane trafficking signal is: KSRITSEGEYIPLDQIDINV (SEQ ID NO:37). In some of these embodiments, the two-component optogenetic fusion polypeptide further comprises an ER export signal (e.g., FCYENEV (SEQ ID NO:47)).

[0158] i) a composition comprising a nucleic acid comprising a two-component optogenetic fusion polypeptide that comprises, in order from amino terminus to carboxyl terminus: i) an eArch polypeptide comprising an amino acid sequence having at least 80%, at least 85%, at least 90%, at least 95%, at least 98%, at least 99%, or 100%, amino acid sequence identity to the eArch polypeptide amino acid sequence set forth in SEQ ID NO:1; ii) a membrane trafficking signal (e.g., KSRITSEGEYIPLDQIDINV (SEQ ID NO:37)); iii) a polypeptide linker of from about 5 amino acids to about 100 amino acids, e.g., a polypeptide linker of from about 20 amino acids to about 25 amino acids in length; iv) an ASIC2a polypeptide comprising an amino acid sequence having at least 80%, at least 85%, at least 90%, at least 95%, at least 98%, at least 99%, or 100%, amino acid sequence identity to the ASIC2a polypeptide amino acid sequence set forth in SEQ ID NO:19; and v) a membrane trafficking signal (e.g., KSRITSEGEYIPLDQIDINV (SEQ ID NO:37)). In some of these embodiments, the two-

component optogenetic fusion polypeptide further comprises an ER export signal (e.g., FCYENEV (SEQ ID NO:47)).

[0159] j) a composition comprising a nucleic acid comprising a two-component optogenetic fusion polypeptide that comprises, in order from amino terminus to carboxyl terminus: i) an eArch polypeptide comprising an amino acid sequence having at least 80%, at least 85%, at least 90%, at least 95%, at least 98%, at least 99%, or 100%, amino acid sequence identity to the eArch polypeptide amino acid sequence set forth in SEQ ID NO:1; ii) a membrane trafficking signal (e.g., KSRITSEGEYIPLDQIDINV (SEQ ID NO:37)); iii) a polypeptide linker of from about 5 amino acids to about 100 amino acids, e.g., a polypeptide linker of from about 40 amino acids to about 45 amino acids in length; iv) an ASIC2a polypeptide comprising an amino acid sequence having at least 80%, at least 85%, at least 90%, at least 95%, at least 98%, at least 99%, or 100%, amino acid sequence identity to the ASIC2a polypeptide amino acid sequence set forth in SEQ ID NO:19; and v) a membrane trafficking signal (e.g., KSRITSEGEYIPLDQIDINV (SEQ ID NO:37)). In some of these embodiments, the two-component optogenetic fusion polypeptide further comprises an ER export signal (e.g., FCYENEV (SEQ ID NO:47)).

[0160] k) a composition comprising a nucleic acid comprising a two-component optogenetic fusion polypeptide that comprises, in order from amino terminus to carboxyl terminus: i) an eArch polypeptide comprising an amino acid sequence having at least 80%, at least 85%, at least 90%, at least 95%, at least 98%, at least 99%, or 100%, amino acid sequence identity to the eArch polypeptide amino acid sequence set forth in SEQ ID NO:1; ii) a membrane trafficking signal; iii) a self-cleaving peptide (e.g., ATNF-SLLKQAGDVEENPGP (SEQ ID NO:49)); iv) an ASIC2a polypeptide comprising an amino acid sequence having at least 80%, at least 85%, at least 90%, at least 95%, at least 98%, at least 99%, or 100%, amino acid sequence identity to the ASIC2a polypeptide amino acid sequence set forth in SEQ ID NO:19; and v) a membrane trafficking signal. In some cases, the membrane trafficking signal is: KSRITSEGEYIPLDQIDINV (SEQ ID NO:37). In some of these embodiments, the two-component optogenetic fusion polypeptide further comprises an ER export signal (e.g., FCYENEV (SEQ ID NO:47)).

[0161] In some cases, the above-noted nucleic acids are expression vectors comprising a nucleotide sequence encoding a light-responsive protein and/or a response protein. In some cases, a subject composition comprises a first expression vector that comprises a nucleotide sequence encoding a light-responsive protein; and a second expression vector that comprises a nucleotide sequence encoding a response protein. In some cases, a subject composition comprises a single expression vector that includes a nucleotide sequence encoding a light-responsive protein and a nucleotide sequence encoding a response protein. Where the composition comprises a single expression vector, in some cases, the nucleotide sequence encoding the light-responsive protein and the nucleotide sequence encoding the response protein are under transcriptional control (operably linked) to the same transcriptional control element (e.g., promoter). Where the composition comprises a single expression vector, in some cases, the nucleotide sequence encoding the light-responsive pro-

tein and the nucleotide sequence encoding the response protein are under transcriptional control (operably linked) to two different promoters.

[0162] The present disclosure provides a system for modulating the membrane potential of a cell, the system comprising: i) a first nucleic acid comprising a nucleotide sequence encoding a light-activated protein that is adapted to allow a first ion to pass through a cell membrane in response to light; ii) a second nucleic acid comprising a nucleotide sequence encoding a response protein that responds to the passage of the first ion through the cell membrane by allowing a second ion to pass through the cell membrane; and iii) a device configured to illuminate a target location with a light. Any of the above-noted combinations of nucleic acids can be included in a subject system.

Polynucleotides and Vectors

[0163] Aspects of the present disclosure include nucleic acids, such as polynucleotides, that comprise a nucleotide sequence that encodes one or more of the subject proteins described herein (e.g., one or more light-activated proteins or response proteins as described above). In some embodiments, a subject polynucleotide comprises an expression cassette, wherein the expression cassette contains a plurality of components (e.g., a plurality of coding sequences) that are utilized to express one or more proteins encoded by the polynucleotide in a target cell.

[0164] In some embodiments, a portion of a polynucleotide encoding a subject protein is operably linked to a promoter sequence. Any suitable promoter that functions in a target cell can be used for expression of the subject polynucleotides. In certain embodiments, a promoter sequence can be a promoter that is specific to a particular target cell type or to a particular tissue type, such as a particular neuron or a pan-neuronal promoter. Initiation control regions of promoters, which are useful to drive expression of polynucleotides in a specific animal cell, are numerous and familiar to those skilled in the art. Virtually any promoter capable of driving expression of the subject polynucleotides can be used. In some embodiments, the promoter used to drive expression of a subject protein can be the Thy1 promoter (See, e.g., Llewellyn, et al., 2010, *Nat. Med.*, 16(10):1161-1166). In some embodiments, the promoter used to drive expression of a subject protein can be a human synapsin (hSyn) promoter, a human elongation factor 1- α (EF1 α) promoter, a cytomegalovirus (CMV) promoter, a CMV early enhancer/chicken β actin (CAG) promoter, a synapsin-I promoter (e.g., a human synapsin-I promoter), a human synuclein 1 promoter, a human Thy1 promoter, a calcium/calmodulin-dependent kinase II alpha (CAMKII α) promoter, or any other promoter capable of driving expression of the a subject nucleic acid sequence in a target cell.

[0165] In some embodiments, a promoter may be an inducible promoter. For example, the promoter may be induced by a trans-acting factor that responds to an exogenously administered drug. Examples of inducible promoters include, but are not limited to, tetracycline-on or tetracycline-off promoters, or tamoxifen-inducible CreER.

[0166] In some embodiments, a subject polynucleotide may comprise a ribosomal skip sequence that can be used to generate two separate proteins from the same transcript. In such embodiments, a subject polynucleotide will typically include a coding sequence that encodes a light-activated protein as well as a response protein. In these embodiments,

a ribosomal skip sequence may be placed between the two coding sequences to produce two distinct proteins (namely, the light-activated protein and the response protein) from the same transcript.

[0167] Also provided herein are vectors comprising the subject polynucleotides or any variant thereof as described herein. Vectors according to the present disclosure also include vectors comprising a nucleotide sequence that encodes an RNA (e.g., an mRNA) that when transcribed from the polynucleotides of the vector will result in the accumulation of a subject protein on the plasma membranes of target cells. Vectors which may be used include, without limitation, lentiviral, HSV, adenoviral, and adeno-associated viral (AAV) vectors. Lentiviruses include, but are not limited to HIV-1, HIV-2, SIV, FIV and EIAV. Lentiviruses may be pseudotyped with the envelope proteins of other viruses, including, but not limited to VSV, rabies, Mo-MLV, baculovirus and Ebola. Such vectors may be prepared using standard methods in the art.

[0168] In some embodiments, a vector may be a recombinant AAV vector. AAV vectors are DNA viruses of relatively small size that can integrate, in a stable and site-specific manner, into the genome of the cells that they infect. They are able to infect a wide spectrum of cells without inducing any effects on cellular growth, morphology or differentiation, and they do not appear to be involved in human pathologies. The AAV genome has been cloned, sequenced and characterized. It encompasses approximately 4700 bases and contains an inverted terminal repeat (ITR) region of approximately 145 bases at each end, which serves as an origin of replication for the virus. The remainder of the genome is divided into two essential regions that carry the encapsidation functions: the left-hand part of the genome that contains the rep gene involved in viral replication and expression of the viral genes; and the right-hand part of the genome that contains the cap gene encoding the capsid proteins of the virus.

[0169] AAV vectors may be prepared using standard methods in the art. Adeno-associated viruses of any serotype are suitable (see, e.g., Blacklow, pp. 165-174 of "Parvoviruses and Human Disease" J. R. Pattison, ed. (1988); Rose, *Comprehensive Virology* 3:1, 1974; P. Tattersall "The Evolution of Parvovirus Taxonomy" In Parvoviruses (J R Kerr, S F Cotmore. M E Bloom, R M Linden, C R Parrish, Eds.) p 5-14, Hudder Arnold, London, U K (2006); and D E Bowles, J E Rabinowitz, R J Samulski "The Genus Dependovirus" (J R Kerr, S F Cotmore. M E Bloom, R M Linden, C R Parrish, Eds.) p 15-23, Hudder Arnold, London, UK (2006), the disclosures of each of which are hereby incorporated by reference herein in their entireties). Methods for purifying for vectors may be found in, for example, U.S. Pat. Nos. 6,566,118, 6,989,264, and 6,995,006 and WO/1999/011764 titled "Methods for Generating High Titer Helper-free Preparation of Recombinant AAV Vectors", the disclosures of which are herein incorporated by reference in their entirety. Methods of preparing AAV vectors in a baculovirus system are described in, e.g., WO 2008/024998. AAV vectors can be self-complementary or single-stranded. Preparation of hybrid vectors is described in, for example, PCT Application No. PCT/US2005/027091, the disclosure of which is herein incorporated by reference in its entirety. The use of vectors derived from the AAVs for transferring genes in vitro and in vivo has been described (See e.g., International Patent Application Publication Nos.: 91/18088 and

WO 93/09239; U.S. Pat. Nos. 4,797,368, 6,596,535, and 5,139,941; and European Patent No.: 0488528, all of which are hereby incorporated by reference herein in their entireties). These publications describe various AAV-derived constructs in which the rep and/or cap genes are deleted and replaced by a gene of interest, and the use of these constructs for transferring the gene of interest in vitro (into cultured cells) or in vivo (directly into an organism). The replication-defective recombinant AAVs according to the present disclosure can be prepared by co-transfecting a plasmid containing the nucleic acid sequence of interest flanked by two AAV inverted terminal repeat (ITR) regions, and a plasmid carrying the AAV encapsidation genes (rep and cap genes), into a cell line that is infected with a human helper virus (for example an adenovirus). The AAV recombinants that are produced are then purified by standard techniques.

[0170] In some embodiments, the vector(s) for use in the methods of the present disclosure are encapsidated into a virus particle (e.g. AAV virus particle including, but not limited to, AAV1, AAV2, AAV3, AAV4, AAV5, AAV6, AAV7, AAV8, AAV9, AAV10, AAV11, AAV12, AAV13, AAV14, AAV15, and AAV16). Accordingly, the present disclosure includes a recombinant virus particle (recombinant because it contains a recombinant polynucleotide) comprising any of the vectors described herein. Methods of producing such particles are known in the art and are described in U.S. Pat. No. 6,596,535, the disclosure of which is hereby incorporated by reference in its entirety.

[0171] FIG. 5 provides an example of a subject polynucleotide. The depicted polynucleotide, from 5' to 3', comprises a light-activated protein sequence (Arch), a trafficking sequence (ts), a ribosomal skip sequence (p2A), a response protein sequence (ASIC2a), and a yellow fluorescent protein sequence (EYFP). FIG. 6 provides an different example of a subject polynucleotide. The depicted polynucleotide, from 5' to 3', comprises a light-activated protein sequence (Arch), a trafficking sequence (ts), a ribosomal skip sequence (p2A), a response protein sequence (ASIC2a), a trafficking sequence (ts), a yellow fluorescent protein sequence (EYFP), and an endoplasmic reticulum export sequence (ER).

[0172] FIG. 7 provides an example of a subject vector. The depicted vector includes, from 5' to 3', a CamKII promoter sequence, an Arch coding sequence, a trafficking sequence (ts), a ribosomal skip sequence (p2A), an ASIC2a coding sequence, a trafficking sequence (ts), a yellow fluorescent protein sequence (EYFP), and an endoplasmic reticulum export sequence (ER). FIG. 8 provides another example of a subject vector. The depicted vector includes, from 5' to 3', an hSyn promoter sequence, an Arch coding sequence, a trafficking sequence (ts), a ribosomal skip sequence (p2A), an ASIC2a coding sequence, and a yellow fluorescent protein sequence (EYFP).

Pharmaceutical Compositions

[0173] Aspects of the present disclosure include pharmaceutical compositions that comprise the subject polynucleotides, vectors, or components thereof. The subject pharmaceutical compositions may be administered to a subject for purposes genetically modifying a target cell so that the target cell expresses one or more subject proteins. A subject pharmaceutical composition may, in some embodiments, comprise a pharmaceutically acceptable excipient. In some embodiments, a pharmaceutical composition may comprise

components to facilitate delivery of the subject polynucleotides or vectors to a target cell, including but not limited to transfection reagents or components thereof, such as lipids, polymers, and the like.

[0174] In some embodiments, a subject pharmaceutical composition will be suitable for injection into a subject, e.g., will be sterile. For example, in some embodiments, a subject pharmaceutical composition will be suitable for injection into a subject, e.g., where the composition is sterile and is free of detectable pyrogens and/or other toxins.

[0175] Pharmaceutically acceptable excipients, such as vehicles, adjuvants, carriers or diluents, are readily available to the public. Moreover, pharmaceutically acceptable auxiliary substances, such as pH adjusting and buffering agents, tonicity adjusting agents, stabilizers, wetting agents and the like, are readily available to the public as well, and may be incorporated into the pharmaceutical compositions of the present disclosure without limitation.

Target Cells and Tissues

[0176] As summarized above, aspects of the present disclosure include delivering the subject polynucleotides, or components thereof, to target cells. Target cells are generally cells that carry or transmit electrical impulses, such as nerve cells. In some embodiments, a target cell may be, e.g., a sensory neuron, a motor neuron, or an interneuron. Target cells of the disclosure may include cells of the central nervous system and/or cells of the peripheral nervous system. In some embodiments, a target tissue may include a plurality of nerve fibers, a nerve, a nerve cell ganglion, a neuromuscular junction, a tissue that is innervated by nerves, including but not limited to muscle, skin, or endocrine tissue, or an anatomical region, such as a portion or sub-portion of the brain or spinal cord. In some embodiments, a target tissue may be a portion of an individual cell, such as specific axon of a nerve cell.

[0177] Once the subject polynucleotides have been delivered to a target cell or tissue, the polynucleotides enter the target cells and are expressed. In some embodiments, the subject polynucleotides may contain tissue-specific promoters so that expression only occurs in target cells wherein the tissue-specific promoter is active. In this way, if a subject polynucleotide is delivered to cells other than a target cell, the polynucleotide will not be expressed in the non-target cells because the tissue-specific promoter will be inactive in those cells. In some embodiments, a subject polynucleotide may contain an inducible promoter, such that expression of the polynucleotide only takes place when an exogenously administered drug is present in a sufficient concentration within the cell to activate the promoter.

[0178] In some cases, the present disclosure provides methods for modulating activity of a target cell that expresses a light-responsive protein and a response protein, as described above, where the method involves activating the light-responsive protein with light. In some cases, the present disclosure provides methods for modulating activity of a target cell that is proximal to a cell that expresses a light-responsive protein and a response protein, as described above, where the method involves activating the light-responsive protein with light. Thus, the target cell may not express the light-responsive protein and the response protein, but the activity of the target cell is modulated upon activating with light the light-responsive protein in a cell proximal to the target cell. A target cell that is "proximal" to

a cell that expresses a light-responsive protein and a response protein, as described above, includes a cell that is in direct physical contact with the cell that expresses a light-responsive protein and a response protein, as described above. A target cell that is “proximal” to a cell that expresses a light-responsive protein and a response protein, as described above, includes a cell that is not in direct physical contact with the cell that expresses a light-responsive protein and a response protein, as described above, but whose activity is modulated by the cell that expresses a light-responsive protein and a response protein, as described above, e.g., modulated by neurotransmitter produced by the cell that expresses a light-responsive protein and a response protein, as described above; etc.

Devices

[0179] As summarized above, aspects of the present disclosure include various devices that can be used to carry out aspects of the subject methods. Devices that find use in the subject methods include delivery devices that can be used to deliver the subject polynucleotides to target cells and tissues, light-generating devices that can be used to illuminate target cells that express the subject light-activated proteins, and control devices that can be used to control the delivery of light to specific target cells or tissues. Each of these devices is further described below.

Delivery Devices

[0180] Aspects of the present disclosure include delivery devices that can be used to deliver a subject pharmaceutical composition to a target cell. The subject delivery devices may provide regular, irregular, programmed, or clinician- or patient-activated doses of the subject pharmaceutical compositions to one or more target cells to ensure that the target cells continue to express the subject proteins.

[0181] The subject delivery devices may generally include various components, such as reservoirs, pumps, actuators, tubing components, needles, catheters, and any other suitable components for delivering the subject pharmaceutical compositions to a target cell or tissue of a patient. Delivery devices may also include components that facilitate computerized operation, such as a power source, a processor comprising a memory, a user input device, and/or a graphical user interface. In some embodiments, a delivery device may be completely or partially implantable within a patient. In some embodiments, a delivery device may be operated by a caregiver, wherein the device is introduced into a portion of the patient’s body, e.g., into the patient’s brain, and a subject pharmaceutical composition is delivered to a target tissue, e.g., a portion of the patient’s brain. In some embodiments, following delivery of the pharmaceutical composition, the device may be removed. In other embodiments, the device may be kept in place for later delivery of additional pharmaceutical compositions.

Light-Generating Devices

[0182] Aspects of the present disclosure include light-generating devices that can be used to deliver light to target cells that express one or more of the subject proteins. Light-generating devices in accordance with embodiments of the present disclosure can generally produce light of a variety of different wavelengths from one or more light sources on the device. In some embodiments, a light-

generating device may include a light cuff or sleeve that can be placed around or near target cells expressing one or more subject proteins. In some embodiments, a portion of the light source or the entire light source may be implantable. The subject light-generating devices may be of any useful configuration for stimulating the light-activated proteins disclosed herein. In some embodiments, for example, a light-generating device may comprise components that facilitate exclusive illumination of a target cell or tissue. For example, in some embodiments, a light-generating device may exclusively direct light to a target cell, a portion of a target cell, e.g., a particular axon of a nerve cell, or a specific anatomical structure, such as, e.g. a bundle of nerve fibers, a target tissue, or a portion of the spinal cord. By “exclusively direct light” is meant that the light-generating device only delivers light to the specific target structure, and does not illuminate other structures. For examples, in some embodiments, a light-generating device may be configured to illuminate an axon of a nerve cell, but not illuminate any other portion of the nerve cell. In this way, the light from the light-generating device only affects light-activated proteins in the specific target structure that is illuminated.

[0183] In some embodiments, a light-generating device may not completely surround the region containing a target cell expressing a light-activated protein, but, rather, can have a U-shape. In some embodiments, a light-generating device can have an attachment arm that can be used to guide the light-generating device to a specific region or target structure, e.g., a specific neuronal region. The attachment arm can be removed following implantation of the light-generating device or can be left in place to fix the position of the light-generating device in proximity to the target cells of interest.

[0184] In some embodiments, the subject light-generating devices may comprise an inner body, the inner body having at least one means for generating light which is connected to a power source. In some embodiments, the power source can be an internal battery for powering the light-generating device. In some embodiments, an implantable light-generating device may comprise an external antenna for receiving wirelessly transmitted electromagnetic energy from an external source for powering device. The wirelessly transmitted electromagnetic energy can be a radio wave, a microwave, or any other electromagnetic energy source that can be transmitted from an external source to power the light-generating device. In some embodiments, the light-generating device is controlled by, e.g., an integrated circuit produced using semiconductor or other processes known in the art.

[0185] In some embodiments, the light-generating device may comprise a light emitting diode (LED). In some embodiments, the LED can generate blue and/or green light. In other embodiments, the LED can generate amber and/or yellow light. In some embodiments, several micro LEDs are embedded into the inner body of the light-generating device. In other embodiments, the light-generating device is a solid state laser diode or any other means capable of generating light. The light-generating device can generate light having a wavelength and intensity sufficient to activate a subject light-activated protein. In some embodiments, a light-generating device produces light having an intensity of any of about 0.05 mW/mm², 0.1 mW/mm², 0.2 mW/mm², 0.3 mW/mm², 0.4 mW/mm², 0.5 mW/mm², about 0.6 mW/mm², about 0.7 mW/mm², about 0.8 mW/mm², about

0.9 mW/mm², about 1.0 mW/mm², about 1.1 mW/mm², about 1.2 mW/mm², about 1.3 mW/mm², about 1.4 mW/mm², about 1.5 mW/mm², about 1.6 mW/mm², about 1.7 mW/mm², about 1.8 mW/mm², about 1.9 mW/mm², about 2.0 mW/mm², about 2.1 mW/mm², about 2.2 mW/mm², about 2.3 mW/mm², about 2.4 mW/mm², about 2.5 mW/mm², about 3 mW/mm², about 3.5 mW/mm², about 4 mW/mm², about 4.5 mW/mm², about 5 mW/mm², about 5.5 mW/mm², about 6 mW/mm², about 7 mW/mm², about 8 mW/mm², about 9 mW/mm², or about 10 mW/mm², inclusive, including values in between these numbers. In some embodiments, the light-generating device produces light having an intensity of at least about 10 Hz, such as up to about 25 Hz, such as up to about 50 Hz, such as up to about 75 Hz, such as up to about 100 Hz.

[0186] The subject light-generating devices are generally capable of generating light having a wavelength ranging from about 350 nm, up to about 360 nm, up to about 370 nm, up to about 380 nm, up to about 390 nm, up to about 400 nm, up to about 410 nm, up to about 420 nm, up to about 430 nm, up to about 440 nm, up to about 450 nm, up to about 460 nm, up to about 470 nm, up to about 480 nm, up to about 490 nm, up to about 500 nm, up to about 510 nm, up to about 520 nm, up to about 530 nm, up to about 540 nm, up to about 550 nm, up to about 560 nm, up to about 570 nm, up to about 580 nm, up to about 590 nm, up to about 600 nm, up to about 610 nm, up to about 620 nm, up to about 630 nm, up to about 640 nm, up to about 650 nm, up to about 660 nm, up to about 670 nm, up to about 680 nm, up to about 690 nm, up to about 700 nm, up to about 710 nm, up to about 720 nm, up to about 730 nm, up to about 740 nm, and/or up to about 750 nm.

[0187] In some embodiments, a subject light-generating device may include one or more optical fibers that can transmit light from a light source and deliver the light to a target structure. The optical fibers may comprise plastic or glass materials, and in some embodiments may be suitably flexible to facilitate placement of the light-generating device in locations that could not be accommodated by rigid structures. For example, in some embodiments, a light-generating device may comprise a light source that generates light, as well as one or more optical fibers that can be placed in various locations on or in the patient's body. Light from the light source can pass through the optical fiber, passing around corners and bends in the optical fiber, and emerge at the end of the optical fiber to deliver light to a target structure.

[0188] In some embodiments, the subject light-generating devices may comprise a plurality of light sources that can be used to illuminate a target tissue with different wavelengths of light. For example, in some embodiments, a light-generating device may comprise a first light source that generates light of a first wavelength, e.g., red light, and a second light source that generates light of a second wavelength, e.g., green light. Such light-generating devices may be used to simultaneously illuminate the same target tissue with light of both wavelengths, or may alternately illuminate the target tissue with light of the first wavelength and light of the second wavelength. In some embodiments, such light generating devices may be used to deliver light from the same light source different target tissues. For example, in some embodiments a light-generating device may deliver light of a first wavelength to a first target tissue, and may deliver light of a second wavelength to a different target tissue.

Control Devices

[0189] Aspects of the present disclosure include control devices that can control, or modulate, the amount of light that is emitted from the subject light-generating devices. In some embodiments, a control device may be configured to modulate the wavelength and/or the intensity of light that is delivered to a target tissue from a light-generating device. In some embodiments, a control device may be configured to modulate the frequency and/or duration of light that is delivered to a target tissue from a light-generating device. For example, in some embodiments, a control device may be configured to deliver pulses of light from the light-generating device to a target tissue. The control device can modulate the frequency and/or duration of the light pulses such that the target tissue is illuminated with light from the light-generating device, e.g., at a regular or irregular rate, according to a user input, etc. In some embodiments, a control device can produce pulses of light from the light-generating device that have a duration ranging from about 1 millisecond or less, up to about 1 second, up to about 10 seconds, up to about 20 seconds, up to about 30 seconds, up to about 40 seconds, up to about 50 seconds, up to about 60 seconds or more. In some embodiments, a control device can produce pulses of light from the light-generating device that have a frequency of 1 pulse per millisecond, up to about 1 pulse per second, up to about 1 pulse per minute, up to about 1 pulse per 10 minutes, up to about 1 pulse per 20 minutes, up to about 1 pulse per 30 minutes.

[0190] In some embodiments, a subject control device may comprise a power source that can be mounted to a transmitting coil. In some embodiments, a battery can be connected to the power source for providing power thereto. A switch can be connected to the power source, allowing an operator (e.g., a patient or caregiver) to manually activate or deactivate the power source. In some embodiments, upon activation of the switch, the power source can provide power to the light-generating device through electromagnetic coupling between the transmitting coil on the control device and an external antenna of an implantable light-generating device (such as a light cuff or sleeve). The transmitting coil can establish an electromagnetic coupling with the external antenna of the implantable light-generating device when in proximity thereof, for supplying power to the light-generating device and for transmitting one or more control signals to the light-generating device. In some embodiments, the electromagnetic coupling between the transmitting coil of the control device and the external antenna of the implantable light-generating device can be radio-frequency magnetic inductance coupling. When radio-frequency magnetic inductance coupling is used, the operational frequency of the radio wave can be between about 1 and 20 MHz, inclusive, including any values in between these numbers (for example, about 1 MHz, about 2 MHz, about 3 MHz, about 4 MHz, about 5 MHz, about 6 MHz, about 7 MHz, about 8 MHz, about 9 MHz, about 10 MHz, about 11 MHz, about 12 MHz, about 13 MHz, about 14 MHz, about 15 MHz, about 16 MHz, about 17 MHz, about 18 MHz, about 19 MHz, or about 20 MHz). However, other coupling techniques may be used, such as an optical receiver, infrared, or a biomedical telemetry system (See, e.g., Kiourti, "Biomedical Telemetry: Communication between Implanted Devices and the External World, Opticon1826, (8): Spring, 2010).

[0191] Turning now to FIG. 9, a first example of an optical stimulation system **100** is depicted. The optical stimulation

system **100** comprises a delivery device **101** for delivering a subject polynucleotide to a target tissue, e.g., brain tissue **107** of a patient. Also provided are a light-generating device **102**, a control device **103**, and optical fibers **104** for conveying light generated by the light-generating device **102** to a light array **105** positioned on a light cuff **106**.

[0192] Turning now to FIG. **10**, a second example of an optical stimulation system **110** is depicted. The optical stimulation system **110** comprises a catheter **112** for delivering a subject polynucleotide to a target tissue, e.g., brain tissue **107** of a patient. Also provided are a light-generating device **102**, a control device **103**, and optical fibers **104** for conveying light generated by the light-generating device **102** to the end of the optical fibers **104**.

[0193] Turning now to FIG. **11**, a third example of an optical stimulation system **120** is depicted. The optical stimulation system **120** comprises a light-generating device **102**, a control device **103**, and optical fibers **104** for conveying light generated by the light-generating device **102** to various positions along the spinal cord **121** of the patient.

Methods

[0194] Aspects of the present disclosure include methods for optogenetic modulation of action potentials in target cells. The subject methods generally involve introducing a light-activated protein and a response protein into a target cell and illuminating the target cell with light of an activating wavelength. Illumination of the target cell with light of an activating wavelength causes the light-activated protein to allow one or more of a first species of ions to pass through the plasma membrane of the target cell. The presence of the first species of ions that passed through the light-activated protein causes the response protein to allow a second species of ions to pass through the plasma membrane of the target cell. The passage of the second species of ions through the plasma membrane of the target cell has a desired effect, such as, e.g., modulating the membrane potential of the plasma membrane, activating or inactivating an ion channel, etc. In some embodiments, the passage of the second ion species through the plasma membrane may be used to modulate one or more neurological responses or processes in a patient, and may therefore be used to treat a disease or condition in the patient. As such, in some embodiments, the subject methods involve treating a patient for a condition, such as a neurological condition, using the systems and devices provided herein. The subject methods are now described in greater detail below.

[0195] As discussed above, in some cases, a target cell does not express the light-responsive protein and the response protein, but the activity of the target cell is modulated upon activating with light the light-responsive protein in a cell proximal to the target cell. A target cell that is “proximal” to a cell that expresses a light-responsive protein and a response protein, as described above, includes a cell that is in direct physical contact with the cell that expresses a light-responsive protein and a response protein, as described above. A target cell that is “proximal” to a cell that expresses a light-responsive protein and a response protein, as described above, includes a cell that is not in direct physical contact with the cell that expresses a light-responsive protein and a response protein, as described above, but whose activity is modulated by the cell that expresses a light-responsive protein and a response protein, as described above, e.g., modulated by neurotransmitter produced by the

cell that expresses a light-responsive protein and a response protein, as described above; etc.

Modulating Membrane Potentials in Target Cells

[0196] In some embodiments, the subject methods involve modulating membrane potentials in target cells using the subject systems and devices. In some embodiments, a nucleic acid encoding a subject light-activated protein and a subject response protein is introduced into a target cell such that the target cell expresses both the light-activated protein and the response protein. The target cell is then illuminated with light of an activating wavelength using a light-generating device. Illumination of the light-activated protein results in the movement of one or more ions of a first species through the plasma membrane of the cell in response to light. In some embodiments, for example, the light-activated protein is a proton pump, and in response to light moves proteins from the internal side of the plasma membrane to the external side of the plasma membrane.

[0197] Once the first ion species has been moved across the plasma membrane of the target cell, the response protein responds to the presence of the first ion species by transporting a second ion species across the plasma membrane of the target cell. In some embodiments, for example, the response protein is an acid sensing ion channel, such as, e.g., ASIC2a, which detects the presence of acidic conditions, such as the presence of protons on the external side of the plasma membrane, and responds by opening an ion channel, such as a sodium ion channel, that allows ions of a second species to pass through the plasma membrane. The passage of the second species of ions through the plasma membrane modulates the membrane potential of the cell by changing the charge distribution across the plasma membrane. For example, in some embodiments, the passage of the second species of ions through the plasma membrane results in a build-up of positive charge inside the cell, which modulates the membrane potential of the cell. As such, using the subject light-activated proteins in combination with the subject response proteins, the methods of the present disclosure can be used to modulate the membrane potential of a target cell in response to light of an activating wavelength.

Inhibiting Activity of Voltage-Gated Ion Channels

[0198] In some embodiments, the subject methods involve inhibiting the activity of voltage-gated sodium channels (VGSCs) that may be present in a nerve cell. VGSCs are a class of ion channels that are activated by changes in the membrane potential of nerve cells, and are generally involved with rapid, coordinated depolarization of nerve cell membranes in response to a given stimulus. For example, VGSCs are frequently found along the axons of nerve cells, and generally facilitate propagation of an action potential along the axon.

[0199] VGSCs function by allowing sodium ions to flow into the nerve cell from outside the plasma membrane. The flow of positively-charged sodium ions into the nerve cell changes the membrane potential and thereby propagates an action potential along the length of the nerve cell. Following activation, the VGSCs inactivate in a time-dependent manner. Once inactivated, the VGSC remains in a refractory inactivated state until the cell membrane potential repolarizes. As such, inactivation of VGSCs is a powerful technique

for controlling nerve cell activity because, once inactivated, the VGSCs cannot regain activity until the nerve cell has repolarized.

[0200] In some embodiments, the subject methods involve inhibiting the activity of VGSCs by introducing into a nerve cell a light-activated protein, such as a light-activated proton pump (e.g., Arch), and a response protein, such as an acid sensing sodium ion channel (e.g., ASIC2a). Polynucleotides encoding these proteins are introduced into the nerve cell, and the proteins are expressed by the nerve cell and inserted into the plasma membrane of the nerve cell. Next, the nerve cell is illuminated with light of an activating wavelength from a light-generating device to cause the light-activated proton pump to transport protons through the plasma membrane from inside the cell to the outside of the cell. When the protons are present on or near the external surface of the plasma membrane, the response protein detects the presence of the protons and responds by opening a sodium ion channel. The sodium ion channel allows sodium ions to pass through the plasma membrane from outside the cell to the inside of the cell.

[0201] Once inside the nerve cell, the sodium ions depolarize the membrane sufficiently to inactivate one or more VGSCs in the plasma membrane. The inactivation of the VGSCs prevents the VGSCs from generating further action potentials in the nerve cell until the membrane repolarizes, which is facilitated by the cessation of light and decay of the response protein current, and the refractory period ends. As such, the propagation of action potentials along the nerve cell is blocked for the duration of the light pulse, the response protein current decay, and the refractory period. Accordingly, the subject methods may be used to block the propagation of an action potential along a nerve cell by introducing the subject proteins into the nerve cell plasma membrane and illuminating the cell with light of an activating wavelength from a light-generating device to inactivate one or more VGSCs in the nerve cell. Since the duration of action potential blockade outlasts the duration of the light pulse, inhibition of action potentials may be achieved using pulsed light delivery, rather than continuous light delivery.

[0202] In some embodiments, the subject methods involve inhibiting the activity of one or more voltage-gated calcium channels (VGCCs) that may be present in a target tissue. For example, in some cells and tissues, voltage-gated calcium channels (VGCCs) play analogous roles to those described above regarding voltage-gated sodium channels (VGSCs), and also exhibit voltage-dependent inactivation. Moreover, VGCCs also mediate neurotransmitter release, modulator and hormone release, and muscle contraction. Accordingly, in some embodiments, the subject methods involve inhibiting the activity of VGCCs by introducing into a target cell a light-activated protein, such as a light-activated proton pump (e.g., Arch), and a response protein, such as an acid sensing sodium ion channel (e.g., ASIC2a). Polynucleotides encoding these proteins are introduced into the target cell, and the proteins are expressed by the target cell and inserted into the plasma membrane of the target cell. Next, the target cell is illuminated with light of an activating wavelength from a light-generating device to cause the light-activated proton pump to transport protons through the plasma membrane from inside the cell to the outside of the cell. When the protons are present on or near the external surface of the plasma membrane, the response protein detects the presence of the protons and responds by opening a sodium ion

channel. The sodium ion channel allows sodium ions to pass through the plasma membrane from outside the cell to the inside of the cell.

[0203] Once inside the target cell, the sodium ions depolarize the membrane sufficiently to inactivate one or more VGCCs in the plasma membrane. The inactivation of the VGCCs prevents the VGCCs from, e.g., generating further action potentials in the target cell; mediating the release of neurotransmitters, modulators, or hormones; mediating muscle contraction; and the like until the membrane repolarizes, which is facilitated by the cessation of light and decay of the response protein current, and the refractory period ends. As such, various functions of the VGCCs in the target cell are blocked for the duration of the light pulse, the response protein current decay, and the refractory period. Accordingly, the subject methods may be used to block various functions of VGCCs in a target cell by introducing the subject proteins into the target cell plasma membrane and illuminating the cell with light of an activating wavelength from a light-generating device to inactivate one or more VGCCs in the target cell. Since the duration of the VGCC blockade outlasts the duration of the light pulse, inhibition of VGCCs may be achieved using pulsed light delivery, rather than continuous light delivery.

Inhibiting and/or Blocking Retrograde Action Potentials in Nerve Cells

[0204] In some embodiments, the subject methods involve inhibiting and/or blocking the propagation of a retrograde action potential along a portion of a nerve cell (e.g., along an axon of a nerve cell) using the subject systems and devices. For example, in some embodiments, the subject methods involve introducing into a nerve cell a light-activated protein, such as a light-activated proton pump (e.g., Arch), and a response protein, such as an acid sensing sodium ion channel (e.g., ASIC2a). Polynucleotides encoding the proteins are introduced into the nerve cell, and the proteins are expressed by the nerve cell and inserted into the plasma membrane of the nerve cell.

[0205] Next, a light-generating device is positioned such that only a target portion of the nerve cell (e.g., only the axon, or only a portion of the axon, of the nerve cell) is illuminated with light of an activating wavelength when the light-generating device is activated. Next, the light-generating device is activated to deliver light to the desired portion of the nerve cell to cause the light-activated proton pump to transport protons through the plasma membrane from inside the cell to the outside of the cell. When the protons are present on or near the external surface of the plasma membrane, the response protein detects the presence of the protons and responds by opening a sodium ion channel. The sodium ion channel allows sodium ions to pass through the plasma membrane from outside the cell to the inside of the cell.

[0206] Once inside the cell, the sodium ions depolarize the membrane sufficiently to inactivate one or more VGSCs in the plasma membrane in the portion of the cell that is illuminated with light from the light-generating device. The inactivation of the VGSCs in the designated area of the nerve cell prevents the VGSCs from generating further action potentials in the nerve cell until the membrane repolarizes, which is facilitated by the cessation of light and decay of the response protein current, and the refractory period ends. As such, the propagation of action potentials along the nerve cell in the illuminated area is blocked for the

duration of the light pulse, the response protein current decay and the refractory period. Accordingly, the subject methods may be used to block the propagation of an action potential along a particular portion of a nerve cell by introducing the subject proteins into the nerve cell plasma membrane and illuminating only a specific portion of the nerve cell with light of an activating wavelength from a light-generating device to inactivate one or more VGSCs in the illuminated portion of nerve cell or axon. Since the duration of action blockade outlasts the duration of the light pulse, inhibition of action potentials may be achieved using pulsed light delivery, rather than continuous light delivery. Accordingly, the subject methods may be used to block or inhibit the propagation of action potentials along a particular portion of a nerve cell or axon by delivering light of an activating wavelength to the specific portion of the nerve cell. Importantly, action potentials may still propagate through other portions of the nerve cell or axon that are not illuminated with light of a wavelength that activates the subject light-activated protein. In this way, specificity is achieved for restricting action potential propagation (anterograde and/or orthograde, and elicited naturally, optically, or electrically) to subdomains of the axonal arborization or cell.

Methods of Treatment

[0207] In some embodiments, the subject methods may be used to treat a patient for a condition or disorder, such as a neurological condition or disorder, by optogenetically modulating the action potentials of target cells within the patient. In some embodiments, the subject methods involve introducing a light-activated protein, such as a light-activated proton pump (e.g., Arch), and a response protein, such as an acid sensing sodium ion channel (e.g., ASIC2a) in a target tissue within the patient. In some embodiments, introduction of the subject proteins into the target tissue is accomplished using a subject delivery device. The polynucleotides encoding the subject proteins are introduced into the target tissue, and the proteins are expressed by nerve cells in the target tissue and inserted into the plasma membrane of the nerve cells.

[0208] Next, a light-generating device is positioned to illuminate the target tissue with light of an activating wavelength when the light-generating device is activated. The light-generating device is activated (either by the patient or by a caregiver) to deliver light to the target tissue to cause the light-activated proton pump to transport protons through the plasma membrane from inside a cell in the target tissue to the outside of the cell. When the protons are present on or near the external surface of the plasma membrane, the response protein detects the presence of the protons and responds by opening a sodium ion channel. The sodium ion channel allows sodium ions to pass through the plasma membrane from outside the cell to the inside of the cell.

[0209] Once inside the cell, the sodium ions depolarize the membrane sufficiently to inactivate one or more VGSCs in the plasma membrane in the portion of the cell that is illuminated with light from the light-generating device. The inactivation of the VGSCs in the designated area of the nerve cell prevents the VGSCs from generating further action potentials in the nerve cell until the membrane repolarizes, which is facilitated by the cessation of light and decay of the response protein current, and the refractory period ends. As such, the propagation of action potentials along the nerve cell is blocked for the duration of the light

pulse, the response protein current decay and the refractory period. Accordingly, the subject methods may be used to block the propagation of an action potential in a nerve cell by introducing the subject proteins into the nerve cell plasma membrane and illuminating the nerve cell with light of an activating wavelength from a light-generating device to inactivate one or more VGSCs in the illuminated portion of nerve cell. As the duration of action blockade outlasts the duration of the light pulse, inhibition of action potentials may be achieved using pulsed light delivery, rather than continuous light delivery.

[0210] In some embodiments, the subject methods involve treating a subject for a disorder by inhibiting the activity of one or more voltage-gated calcium channels (VGCCs) that may be present in a target tissue. For example, in some cells and tissues, voltage-gated calcium channels (VGCCs) play analogous roles to those described above regarding voltage-gated sodium channels (VGSCs), and also exhibit voltage-dependent inactivation. Moreover, VGCCs also mediate neurotransmitter release, modulator and hormone release, and muscle contraction. Accordingly, in some embodiments, the subject methods involve treating a subject by inhibiting the activity of VGCCs by introducing into a target cell a light-activated protein, such as a light-activated proton pump (e.g., Arch), and a response protein, such as an acid sensing sodium ion channel (e.g., ASIC2a). Polynucleotides encoding these proteins are introduced into the target cell, and the proteins are expressed by the target cell and inserted into the plasma membrane of the target cell. Next, the target cell is illuminated with light of an activating wavelength from a light-generating device to cause the light-activated proton pump to transport protons through the plasma membrane from inside the cell to the outside of the cell. When the protons are present on or near the external surface of the plasma membrane, the response protein detects the presence of the protons and responds by opening a sodium ion channel. The sodium ion channel allows sodium ions to pass through the plasma membrane from outside the cell to the inside of the cell.

[0211] Once inside the target cell, the sodium ions depolarize the membrane sufficiently to inactivate one or more VGCCs in the plasma membrane. The inactivation of the VGCCs prevents the VGCCs from, e.g., generating further action potentials in the target cell; mediating the release of neurotransmitters, modulators, or hormones; mediating muscle contraction; and the like until the membrane repolarizes, which is facilitated by the cessation of light and decay of the response protein current, and the refractory period ends. As such, various functions of the VGCCs in the target cell are blocked for the duration of the light pulse, the response protein current decay, and the refractory period. Accordingly, the subject methods may be used to treat a subject for a disorder by blocking various functions of VGCCs in a target cell by introducing the subject proteins into the target cell plasma membrane and illuminating the cell with light of an activating wavelength from a light-generating device to inactivate one or more VGCCs in the target cell. Since the duration of the VGCC blockade outlasts the duration of the light pulse, inhibition of VGCCs may be achieved using pulsed light delivery, rather than continuous light delivery.

[0212] Accordingly, the subject methods may be used to treat any disease or condition in which blocking or inhibiting the propagation of an action potential along an excitable or

nerve cell, or along a particular portion of an excitable or nerve cell, would have a therapeutic effect for the patient, or wherein blocking the function of a VGCC would have a therapeutic effect for the patient. Examples of therapeutic applications of the subject methods include, without limitation, therapy for cardiac rhythm disorders, such as pacing, cardioversion, defibrillation, resynchronization, or other cardiac-related conditions; gastrointestinal therapy, such as therapy to address obesity, motility disorders (e.g., gastroparesis), dyspepsia, or other therapies, therapy for pelvic floor tissue (e.g., sacral or pudendal nerve tissue) to support pelvic floor therapy such as pain therapy, urinary or fecal incontinence therapy, sexual dysfunction, or other therapies; cranial nerve therapy, such as therapy to relieve occipital neuralgia, trigeminal neuralgia, facial pain, migraine headaches; therapy for the treatment of pain, such as nociceptive pain or neuropathic pain; therapy for neurological and/or psychiatric conditions; therapy for endocrine conditions; or the like.

[0213] Specificity can be achieved as above for restricting action potential propagation (anterograde and/or orthograde, and elicited naturally, optically, or electrically) to subdomains of the axonal arborization or cell.

Combination Treatment Methods

[0214] In some embodiments, the subject methods involve combination treatments that involve activating or initiating an action potential in a first tissue, and also involve blocking or inhibiting the propagation of an action potential within a second tissue. For example, in some embodiments, the subject methods involve introducing a first light-activated protein into a first tissue, such as a nerve cell, by introducing into the cell a polynucleotide that encodes a first light-activated protein. The first light-activated protein is capable of transporting one or more ions across the plasma membrane of cells in the target tissue to trigger an action potential in the first tissue in response to light of an activating wavelength.

[0215] Simultaneously, a second light-activated protein, such as a light-activated proton pump (e.g., Arch), and a response protein, such as an acid sensing sodium ion channel (e.g., ASIC2a) are also introduced into the tissue. Next, a light-generating device is positioned near the target tissue to illuminate the target tissue. The light-generating device comprises a plurality of light sources, such that the target tissue, or portions thereof, can be illuminated with light of different wavelengths. A portion of the light-generating device is positioned to exclusively illuminate a portion of the target tissue in which it is desirable to block or inhibit action potentials. For example, a portion of the light-generating device, such as a particular light cuff or sleeve, may be positioned to exclusively illuminate, e.g., a particular portion of a nerve cell, such as an axon of the nerve cell, with a particular wavelength of light.

[0216] Next, the light-generating device is activated to deliver light of a wavelength that activates the first light-activated protein in the target tissue. This illumination generates an action potential in the target tissue that propagates through nerve cells in the target tissue. Simultaneously, the light-generating device is activated to deliver light of a wavelength that activates the second light-activated protein to the specific portion of the target tissue in which it is desirable to block or inhibit action potentials. This illumination causes the light-activated proton pump to transport

protons through the plasma membrane from inside the cell to the outside of the cell. When the protons are present on or near the external surface of the plasma membrane, the response protein detects the presence of the protons and responds by opening a sodium ion channel. The sodium ion channel allows sodium ions to pass through the plasma membrane from outside the cell to the inside of the cell depolarizing the cell sufficiently to render native voltage-gated sodium channels inactive, a phenomenon known as depolarization block.

[0217] The voltage-dependent inactivation of the VGSCs in the designated portion of the target tissue prevents the VGSCs from generating further action potentials in the nerve cell until the membrane repolarizes, which is facilitated by the cessation of light and decay of the response protein current, and the refractory period ends. As such, the propagation of action potentials along the nerve cell in the specified area is profoundly blocked for the duration of the light pulse, the decay of the response protein current, and the refractory period. Accordingly, the subject methods may be used to control the flow of action potentials through a target tissue by initiating an action potential in a target tissue using light of a first activating wavelength, and simultaneously blocking or inhibiting the propagation of the action potential through a specific portion of the target tissue by inactivating VGSCs in the specific portion of the target tissue. Additionally, since the duration of action blockade outlasts the duration of the light pulse, inhibition of action potentials may be achieved using pulsed light delivery, rather than continuous light delivery. In this way, the subject methods provide for directing and controlling the flow of action potentials through a target tissue using the subject systems and devices. FIG. 12 provides a flow diagram that illustrates the steps of an example of the subject methods.

Kits

[0218] Also provided are kits that at least include the subject systems and devices or components thereof, e.g., as described above, and instructions for how to use the subject systems and/or devices to optogenetically modulate action potentials in a target tissue. In some embodiments, a kit may include one or more of the subject polynucleotides, vectors, or pharmaceutical compositions. Kits in accordance with embodiments of the present disclosure may also include one or more devices, such as one or more delivery devices, one or more light-generating device, and/or one or more control devices.

[0219] The instructions for using the systems and devices as discussed above are generally recorded on a suitable recording medium. For example, the instructions may be printed on a substrate, such as paper or plastic, etc. As such, the instructions may be present in the kits as a package insert, in the labeling of the container of the kit or components thereof (i.e. associated with the packaging or sub-packaging) etc. In other embodiments, the instructions are present as an electronic storage data file present on a suitable computer-readable storage medium, e.g., a digital storage medium, e.g., a CD-ROM, diskette, etc. The instructions may take any form, including complete instructions for how to use the systems and devices or as a website address with which instructions posted on the Internet may be accessed.

EXAMPLES

Example 1: Inhibition of Action Potentials Using eArch3.0 and ASIC2a in a Nerve Cell

[0220] A nerve cell was transfected with a polynucleotide that encodes a light-activated proton pump protein (eArch3.0) and an acid sensing sodium ion channel response protein (ASIC2a). The proteins were expressed in the nerve cell and were present in the plasma membrane of the nerve cell. A pulse of 560 nm light activated eArch3.0, causing a fast outward proton current, resulting in early hyperpolarization of the plasma membrane. The extracellular protons then activated an inward cation current carried by ASIC2a resulting in sustained membrane depolarization and subsequent inactivation of native voltage-gated sodium channels, causing depolarization block and suppression of evoked spiking. Results are shown in FIG. 1.

Example 2: Strong Inhibition of Action Potentials Using ASIC2a

[0221] A hippocampal cultured neuron was transfected with a polynucleotide that encodes an acid sensing sodium ion channel response protein (ASIC2a). The protein was expressed in the nerve cell and was present in the plasma membrane of the nerve cell. A 1000 pA current was injected into the cell at 10 Hz, and whole cell patch clamp recordings were collected. In response to the 1000 pA current pulse injections, the outward current component inhibited spiking. During 2000 pA current pulse injections, however, only the depolarization block caused by the ASIC component was sufficient to inhibit spiking. The results are shown in FIG. 2. Insets show the voltage-clamp trace of each cell in response to a 1 second green light pulse.

Example 3: ASIC2a-Mediated Inhibition of Action Potentials

[0222] A nerve cell was transfected with a polynucleotide that encodes a light-activated proton pump protein (eArch3.0) and an acid sensing sodium ion channel response protein (ASIC2a). The proteins were expressed in the nerve cell and were present in the plasma membrane of the nerve cell. Spikes were evoked at baseline using suprathreshold (high reliability spiking) current pulse injections at 10 Hz. When light was applied, the eArch3.0-mediated hyperpolarization was insufficient to inhibit spiking, whereas the ASIC2a-mediated depolarization strongly suppressed spiking throughout the remainder of the light pulse, due to depolarization block. The insets to the right show the voltage-clamp response of the same neurons to a 1 second pulse of 560 nm light, with the amplitude of outward and inward currents provided. Results are shown in FIG. 3.

Example 4: Weak ASIC2a-Mediated Inhibition of Action Potentials

[0223] A nerve cell was transfected with a polynucleotide that encodes a light-activated proton pump protein (eArch3.0) and an acid sensing sodium ion channel response protein (ASIC2a). The proteins were expressed in the nerve cell and were present in the plasma membrane of the nerve cell. In this example, the inward:outward current ratio was small (≈ 1), therefore the depolarization caused by the ASIC component was insufficient to cause depolarization block and overcome the evoked spiking. Results are shown in FIG. 4.

Example 5: Volumetric Modulation of Excitability by Extracellular Protons

[0224] In this example, it is described how extracellular ions, in particular protons, can influence local neural activity in non-cell-autonomous fashion through activation of acid-sensitive membrane proteins. An approach for manipulating cellular function, which couples light-sensitive proton pumps to acid-sensitive ion channels, permitting longer lasting, ion-specific regulation of transmembrane currents with many possible permutations for flexible neural control, is described.

Methods

Bystander Experiments

[0225] All experiments were conducted under protocols approved by the Stanford Administrative Panel on Laboratory Animal Care.

[0226] Stereotactic Injections:

[0227] For expression of ChR2(H134R), eArch3.0 or eNpHR3.0 in CamKII-positive neurons, adeno-associated virus (AAV) serotype 2/5 was produced by the University of North Carolina Chapel Hill Vector Core at a genomic titer of $\sim 4\text{-}16 \times 10^{12}$ pfu mL^{-1} . 1 μL of virus was stereotactically injected at two sites unilaterally into the CA1 region of the hippocampus of 3-4 week-old mice. Coordinates for all animals at injection site #1 were -2.2 anteroposterior, 1.5 mediolateral (left side) and -1.3 dorsoventral (in mm from bregma) and for injection site #2 were -1.7 anteroposterior, 1.25 mediolateral (left side) and -1.5 dorsoventral (in mm from bregma). For cortical bystander experiments, Thy1::ChR2 (line 18) mice (Arenkiel et al, 2007) were used (bred in-house).

[0228] Acute Slice Electrophysiology Recordings:

[0229] Acute brain slices were prepared from mice at 4-8 weeks post virus injection, or at 4 weeks of age for transgenic mice. After lethal anesthesia, transcardial perfusion was performed prior to decapitation, followed by rapid brain extraction and submersion of the brain in ice-cold sucrose-based slicing solution (234 mM sucrose, 11 mM glucose, 10 mM $\text{MgSO}_4 \cdot 7\text{H}_2\text{O}$, 2.5 KCl, 1.25 mM $\text{NaH}_2\text{PO}_4 \cdot \text{H}_2\text{O}$, 0.5 mM $\text{CaCl}_2 \cdot 2\text{H}_2\text{O}$). 300 μm thick slices of hippocampus were cut on a Leica vibratome (Leica VT1000S). After cutting, slices were submerged in a hypertonic recovery solution (artificial cerebrospinal fluid (ACSF) at an 8% increased concentration) at 33°C . for 15 mins before being transferred to standard ACSF (123 mM NaCl, 26 mM NaHCO_3 , 11 mM glucose, 3 mM KCl, 2 mM $\text{CaCl}_2 \cdot 2\text{H}_2\text{O}$, 1.25 mM $\text{NaH}_2\text{PO}_4 \cdot \text{H}_2\text{O}$, 1 mM $\text{MgCl}_2 \cdot 6\text{H}_2\text{O}$) for a further 45 mins at 33°C ., at which point they were transferred to room temperature.

[0230] Whole cell patch clamp recordings on cortical and hippocampus neurons were performed on an upright Leica DM-LFSA microscope. Slices were continually perfused in warmed (33°C .) ACSF at a rate of 7 ml min^{-1} . Patching was performed in the presence of synaptic transmission blockers 6-cyano-7-nitroquinoxaline-2,3-dione (CNQX, 50 μM) and D(-)-2-amino-5-phosphonovaleric acid (APV, 25 μM) and gabazine (25 μM) (Tocris Bioscience) except for during testing of electrically-evoked synaptic responses. For amiloride experiments, amiloride was added to the ACSF at a concentration of 500 μM (Tocris). Borosilicate glass (Sutter Instruments) pipette resistances were pulled to 3-6

MΩ and filled with potassium gluconate intracellular solution (130 mM K Gluconate, 10 mM KCl, 10 mM HEPES, 10 mM EGTA, 2 mM MgCl₂, pH adjusted with KOH to 7.3). Voltage and current clamp electrophysiological recordings and manipulations were performed using pClamp (Axon Instruments). Cells were held at -70 mV for all experiments. Cells with leak current greater than -300 pA or pipette resistance greater than 30 MΩ were excluded. Light (full-field illumination) was emitted from a 300 W DG-4 lamp (Sutter Instruments, Novato, Calif., USA) fitted with a Lambda 10-3 filter wheel (Sutter Instruments) with a 10-position wheel for filters of different wavelengths, or external filters (wavelength in nm/bandwidth in nm: 470/20; 560/25; 590/20). Light pulses were delivered through a 40×, 0.8 NA water-immersion objective at 4-7 mW/mm² light power density. Extracellular electrical stimulation was performed using a concentric bipolar electrode of platinum iridium (FHC, Bowdoin, ME, USA) or tungsten (World Precision Instruments, Sarasota, Fla. USA). Electrical pulses were delivered using a stimulus isolator (ISO-Flex, A.M.P.I) controlled by pClamp to deliver 200 μs square pulses at intensities ranging from 500 μA-2.5 mA and frequencies of 5-10 Hz.

[0231] Immunohistochemistry:

[0232] For identification of bystanders in slice preparations, 0.3% biocytin was added to the intracellular pipette solution and following recording slices were fixed in 4% paraformaldehyde perfusion fix solution (Electron Microscopy Services, Hatfield, Pa., USA) for 24 hours then transferred to 1× phosphate buffered saline (Gibco, Life Technologies). Biocytin was stained with fluorescent streptavidin (Alexa Fluor 546 conjugate, Invitrogen, over 3 hours. For YFP staining, slices were incubated in anti-GFP primary antibody (Invitrogen, 1:500 dilution) for 24 hours. Cy5 secondary antibody (Jackson Laboratories, West Grove, Pa., 1:500 dilution) was applied in 2% NDS for 1 hour at room temperature for 3 hours followed by DAPI (1:50,000) for 30 mins, then mounted, and coverslipped with PVA-DABCO (Sigma). Images were obtained on a Leica confocal microscope (DM600B) at 1024×1024 pixel resolution using 5× and 10× dry objectives and 20×, 40× and 63× oil objectives.

[0233] Data Analysis:

[0234] Analysis of all of physiological results was performed using Clampfit software (Axon Instruments). Pipette (access) resistance (R_a) and membrane resistance (R_m) were monitored at 5 minute intervals to ensure stability of the recording and data was only included when leak current was less than 300 pA and R_a less than 30 MΩ with less than 25% change in R_a for the duration of periods of drug application and between sequential membrane tests. Reversal potentials were corrected for an estimated liquid junction potential of 14 mV. Statistical analysis was performed using GraphPad Prism 6.0 for Mac OS X. For comparisons between YFP controls and opsin or electrical stimulation groups we performed non-parametric unpaired 2-tailed Mann Whitney tests to compare mean ranks between groups, without assuming a Gaussian distribution. For comparison of the functional impact of light on bystander neuron spiking, we compared successive light-on vs light-off epochs for each opsin, using a non-parametric, paired Wilcoxin signed rank test, again without assuming a Gaussian distribution. Significance thresholds were set at $p < 0.05$ (*), $p < 0.01$ (**), $p < 0.001$ (***) and $p < 0.0001$ (****).

[0235] Two-Component Optogenetics Experiments.

[0236] Construct design and expression in *Xenopus laevis* oocytes: The coding sequences for rat ASICs (in pRSSP6009) were provided by Stefan Grander (Aachen). The pRSSP6009 plasmid coding for ASICs and the pGEM plasmid coding for *Coccomyxa subellipsoidea* C-169 Rhodopsin CsR_{T46N} were linearized by Mull site in pRSSP 6009 and by NheI in pGEM. After transcription into RNA using T7 (pGEM) or SP6 (pRSSP6009) mMessage mMachine Kit (Ambion Inc, Texas, USA) 32 ng of capped RNA encoding CsR pump and one type of ASIC were co-injected into *Xenopus laevis* oocytes with a molar ratio of 1:1 pump: channel for ASIC1 and ASIC2a and a molar ratio of 1:2 for ASIC3. Oocytes were incubated for 3 days at 18° C. in ORI solution with 1 μM all-trans retinal (Tsunoda & Hegemann, 2009).

[0237] Two-Electrode Voltage Clamp Measurements:

[0238] TEVC measurements on *X. laevis* oocytes were performed using a GeneClamp 500 amplifier (Axon Instruments, Union City). Data acquisition, buffer exchange and light triggering were controlled with pClamp software via a Digidata 1322A interface (Molecular Devices, Sunnyvale). The light supplied by a 75 W Xenon lamp (Jena-Instruments, Jena, Germany) was passed through a K55 filter (Balzers, Liechtenstein) and applied to the oocytes using a light guide (diameter of 2 mm). The light intensity was 8.5×10^{20} photons s⁻¹ m⁻² at the surface of the oocyte. The bulk buffer (chamber volume 300 μl) was continuously perfused at a flow rate of 1.8 ± 0.2 ml min⁻¹. Data was acquired at 1 kHz and filtered at 0.5 kHz. If not otherwise specified the extracellular buffer was composed of 100 mM NaCl, 1 mM KCl, 1 mM MgCl₂, 0.1 mM CaCl₂ and 0.1 to 5 mM MOPS at pH 7.5. For pH titration, buffer solutions were adjusted with 5 mM MOPS/MES/Citrate over the range of pH 8.0 to 4.0, and were subsequently compared with photocurrents measured at 0.1 mM MOPS at pH 7.5.

[0239] Construct Design for Hippocampal Neurons:

[0240] The protein sequence of rat ASIC2a (Genbank accession number NM 001034014.1) was human codon optimized and synthesized by Genscript. eArch3.0 and ASIC-YFP fusions were cloned into an AAV2 backbone either under a CaMKIIα or human synapsin promoter. The trafficking signal (TS) and endoplasmic reticulum export signal (ER) sequences were appropriately added to enhance membrane trafficking. All maps and sequence details are on the website: [www\(dot\)optogenetics\(dot\)org](http://www(dot)optogenetics(dot)org).

[0241] Hippocampal Neuron Culture and Calcium Phosphate Transfection (as Per Mattis et al. (Nat Methods 2011; 9: 159-72)).

[0242] Primary cultured hippocampal neurons were prepared from P0 Sprague-Dawley rat pups (Charles River). CA1 and CA3 were isolated, digested with 0.4 mg ml⁻¹ papain (Worthington), and plated onto glass coverslips pre-coated with 1:30 Matrigel (Becton Dickinson Labware). Cultures were maintained in a 5% CO₂ humid incubator with Neurobasal-A medium (Invitrogen) containing 1.25% FBS (HyClone), 4% B-27 supplement (Gibco), 2 mM Glutamax (Gibco) and 2 mg ml⁻¹ fluorodeoxyuridine (FUDR) (Sigma), and grown on coverslips in a 24-well plate at a density of 65,000 cells per well. For each well, a DNA-CaCl₂ mix was prepared with 2 μg DNA (Qiagen endotoxin-free preparation) and 1.875 μl 2 M CaCl₂ (final Ca²⁺ concentration 250 mM) in 15 μl H₂O. To DNA-CaCl₂ was added 15 μl of 2×HEPES-buffered saline (pH 7.05). After 20 min at room temperature (20-22° C.), the mix was added

dropwise into each well (from which the growth medium had been removed and replaced with pre-warmed minimal essential medium (MEM)) and transfection proceeded for 45-60 min at 37° C., after which each well was washed with 3×1 ml warm MEM before the original growth medium was returned.

[0243] Electrophysiological Recordings in Cultured Hippocampal Neurons:

[0244] Whole cell patch clamp recordings were performed on cultured hippocampal neurons 4-8 days post-transfection on an upright Leica DM-LFSA microscope (Mattis et al, 2011). Cells were continuously perfused in standard extracellular Tyrode's solution (NaCl: 125 mM, KCl 2 mM, CaCl₂ 2 mM, MgCl₂ 2 mM, glucose 30 mM, HEPES 25 mM, titrated to pH 7.3-7.4 with NaOH, 320 mOsm) or in low HEPES Tyrode's solution (NaCl: 125 mM, KCl 2 mM, CaCl₂ 2 mM, MgCl₂ 2 mM, glucose 55 mM, HEPES 0.1 mM, titrated to pH 7.3-7.4, 320 mOsm) at a rate of 1-2 ml min⁻¹, in the presence of synaptic transmission blockers 6-cyano-7-nitroquinoxaline-2,3-dione (CNQX), D(-)-2-amino-5-phosphonovaleric acid (APV) and gabazine (25 μM; Tocris Bioscience). Patch pipette borosilicate glass electrodes (Sutter Instruments) with tip resistance of 3-6 MΩ were filled with a potassium gluconate intracellular solution (K-gluconate 130 mM, KCl 10 mM, HEPES 10 mM, EGTA 10 mM, MgCl₂ 2 mM, titrated to pH 7.3 with KOH, 300 mOsm). Data acquisition, current and light manipulations were controlled using pClamp (Axon Instruments) via a Digidata 1440A interface and analyzed using ClampFit software (Axon Instruments). Cells were held at -70 mV for all voltage-clamp experiments. Resting membrane potentials were corrected for an estimated liquid junction potential of 16 mV. Full-field illumination for activation of optogenetic tools was delivered by a 300 W DG-4 lamp (Sutter instruments) via a 40×, 0.8 numerical aperture (NA) water-immersion objective. The light was first passed through a 560/25 nm filter within a Lambda 10-3 filter wheel (Sutter Instruments). Light power density was ~5 mWmm⁻² for all experiments. All experiments were performed at room temperature (24-25° C.).

[0245] Confocal Images of Cultured Neurons:

[0246] Confocal images were obtained by staining glass coverslips of transfected neurons with DAPI (1:50,000) which were then imaged using a Leica confocal microscope (DM600B) as 1,025×1,024 pixel resolution, at 40× magnification, 1.25 NA (oil). Excitation/emission wavelengths for eYFP were 488 nm/500-545 nm.

Results

Electrophysiological Characterization of the Bystander Effect

[0247] The existence of "bystander neurons", defined here as neurons indirectly exposed to, but not direct expressors of, optogenetically-mediated changes in neural activity was tested. Two optogenetic targeting strategies were employed: first, an optogenetic construct containing one of CHR2 (H134R), eArch3.0, eNpHR3.0 or a YFP control, driven by the calmodulin kinase IIα promoter (AAV5-CamKII-(opsin)-eYFP), was injected unilaterally in the CA1 region of hippocampus. Due to the contralateral axonal projections of these neurons, one could then record from non-expressing neurons (bystander neurons) surrounded by opsin-expressing axons in the contralateral CAL (FIGS. 15A and 15C).

Bystander responses to the depolarizing opsin CHR2 (H134R) (from now on referred to as ChR2), two hyperpolarizing opsins (enhanced for membrane targeted expression)—the proton pump archeorhodopsin (eArch3.0) and the chloride pump halorhodopsin (eNpHR3.0), and a YFP-control were compared in the hippocampal preparation, under matched experimental conditions. A second category of bystander neuron was identified using the transgenic mouse strain Thy1-ChR2 (line 18), where ChR2 is expressed in layer V cortical neurons and bystander neurons are located in superficial cortical layers, where they are surrounded by ChR2-expressing membrane processes but not expressing ChR2 themselves (FIGS. 15B and 15D).

[0248] Whole cell recordings from bystander neurons in the presence of ionotropic synaptic transmission blockers were performed in acute brain slices. In response to a 15 s blue light pulse, hippocampal ChR2 bystander neurons exhibited a depolarizing membrane current (mean=-155 pA) (FIG. 15E) with onset-kinetics several orders of magnitude slower (~2 s) than a direct ChR2 photocurrent (FIG. 15J and FIG. 16). Cortical Thy1-ChR2 bystander neurons displayed a smaller inward current (mean=-27 pA) consistent with the smaller direct ChR2 photocurrent magnitude in Thy1-ChR2-expressing neurons (FIG. 17). These inward currents corresponded to a mean membrane depolarization of 6.1 mV for hippocampal ChR2 bystanders and 2.7 mV for cortical Thy1-ChR2 bystanders (FIG. 15F). AAV5-YFP control bystanders did not exhibit a change in membrane current or voltage. Given that pulsed-light paradigms are commonly used for depolarizing optogenetic applications, we examined bystander responses to 20 and 10 Hz light pulse trains, and again observed similar slow inward currents (mean=-73 pA for 20 Hz and -29 pA for 10 Hz) (FIG. 15G).

[0249] We next examined the impact of hyperpolarizing optogenetic tools on hippocampal bystander neurons. During a 30 s light pulse, AAV5-eArch3.0 bystanders exhibited a slow (~5 s) hyperpolarizing current (mean=21 pA), several orders of magnitude slower than a direct eArch3.0 photocurrent and AAV5-eNpHR3.0 bystanders exhibited a smaller (mean=10 pA) and even slower (~8 s) hyperpolarizing current (FIGS. 15H and 15J). These outward currents corresponded to a small mean membrane hyperpolarization of -3.3 mV for eArch3.0 and -1.1 mV for eNpHR3.0 whereas no change in membrane current or voltage was observed for AAV5-YFP control bystanders under matched experimental conditions (FIG. 15I).

[0250] During the application of light, ChR2 bystander neurons experienced a 24% mean decrease in membrane resistance, whereas eArch3.0-bystander neurons experienced a 9% increase in membrane resistance and eNpHR3.0 a 2% increase. YFP controls showed a 3% decrease in membrane resistance (FIG. 15L). Current-voltage relationships demonstrated a significantly positive slope for depolarizing bystanders and significantly negative slope for hyperpolarizing bystanders converging at a reversal potential between -10 to -40 mV (FIG. 15K). Functional and mechanistic investigation of the bystander effect.

[0251] FIGS. 15A-L. Identification and delineation of the bystander effect. A Unilateral injection of AAV5-CamKII-(opsin)-eYFP into CA1 of hippocampus yielded non-expressing bystander neurons in the contralateral hippocampus. Confocal image showing YFP expression and location of bystander neurons (star) (5×, scale bar 1 mm). B Cortical

bystander neurons in superficial layers of cortex of Thy1-ChR2 (line 18) transgenic mice. Confocal image showing YFP expression and location of bystander neurons (star) (10 $\times$, scale bar 100 μ m). C Biocytin-filled hippocampal bystander neurons labeled with streptavidin in CA1 (scale bars 100 μ m and 20 μ m). D Biocytin-filled cortical bystander neuron labeled with streptavidin, surrounded by but not overlapping with YFP fluorescence confirmed by anti-YFP antibody staining (scale bars 50 μ m and 20 μ m). E Depolarizing bystander currents in response to 15 s 470 nm light pulses for AAV5-ChR2 hippocampal bystanders (mean $\pm$ SEM=-155 $\pm$ 32 pA, n=11, p<0.0001 compared to YFP), Thy1-ChR2 cortical bystanders (-27 $\pm$ 6 pA, n=6, p<0.001 compared to AAV5-YFP) and AAV5-YFP controls (0.7 $\pm$ 0.7 pA, n=10). Example voltage clamp traces shown below summary plot. F Depolarizing bystander potentials for AAV5-ChR2 hippocampal bystanders (6.1 $\pm$ 1.4 mV, n=11, p<0.0001), Thy1-ChR2 bystanders (2.7 $\pm$ 0.6 mV, n=3, p<0.01) and AAV5-YFP controls (0.02 $\pm$ 0.07 mV, n=9). Example current clamp traces shown below summary plot. G Bystander currents in response to 470 nm light pulse trains at 20 Hz (-73 $\pm$ 18 pA, n=12) and 10 Hz (-29 $\pm$ 6 pA, n=11). Example voltage clamp traces shown below summary plot. H Hyperpolarizing bystander currents in response to 30 s 560 nm light for AAV5-eArch3.0 (21 $\pm$ 4 pA, n=12, p<0.0001), 590 nm for AAV5-eNpHR3.0 (10 $\pm$ 2 pA, n=14, p<0.0001) and AAV5-YFP controls (1.3 $\pm$ 0.8 pA, n=10, 560 nm light). Example voltage clamp traces shown below summary plot. I Hyperpolarizing bystander potentials for AAV5-eArch3.0 (-3.3 $\pm$ 1.1 mV, n=12, p<0.0001), AAV5-eNpHR3.0 (-1.1 $\pm$ 0.2 mV, n=12, p<0.001) and AAV5-YFP controls (-0.1 $\pm$ 0.2 mV, n=9). Example current clamp traces shown below the summary plot. J Onset kinetics (τ_{on}) for depolarizing (ChR2: 1800 $\pm$ 200 ms, n=8) and hyperpolarizing (eArch3.0: 4800 $\pm$ 710 ms n=10, eNpHR3.0: 8300 $\pm$ 850 ms, n=7) bystanders. K Current-voltage relationships for depolarizing ChR2 bystander currents (R^2 for slope (difference from 0)=0.71, p<0.0001) and hyperpolarizing bystander currents (eArch3.0: R^2 for slope=0.43, p<0.0001, eNpHR3.0: R^2 for slope=0.26, p=0.0001) (n=5-12). L Change in membrane resistance from baseline in response to 30 s pulse of light for ChR2 (470 nm, 24% decrease in membrane resistance, n=8, p<0.001), eArch3.0 (560 nm, 9% increase in membrane resistance, n=12, p<0.0001) eNpHR3.0 (590 nm, 2% increase in membrane resistance, n=11, p<0.01) and YFP control bystanders (560 nm, 3% decrease in membrane resistance, n=11). All bar charts indicate mean values and error bars represent standard error of the mean (SEM). Individual data points indicate results from single cells. All statistical comparisons are between test (opsin) groups and YFP controls using the Mann Whitney (non-parametric) paired t-test.

[0252] FIG. 16: Kinetics of Photocurrents and Bystanders.

[0253] Example traces illustrating the difference in on-kinetics between a ChR2 expressing-cell photocurrent and a ChR2 bystander current in response to a 470 nm light pulse (0.5 s and 15 s respectively). Dashed box shows a zoom-in of the first 0.5 s of both traces.

[0254] FIGS. 17A and 17B: Photocurrent Magnitudes.

[0255] A Steady state photocurrent magnitudes (in response to 1 s light) for opsin-expressing neurons present in same preparations as bystander neurons: AAV-ChR2 (n=20, 470 nm), Thy1-ChR2 (n=6, 470 nm), AAV-eArch3.0 (n=14, 560 nm), AAV-eNpHR3.0 (n=16, 590 nm). Bars indicate

mean and SEM, filled circles indicate individual cell photocurrents. B Example photocurrent traces for AAV5-ChR2 (blue), AAV-eArch3.0 (green) and AAV-eNpHR3.0 (amber) expressing neurons.

[0256] The influence of the bystander effect on evoked action potential firing was investigated (FIG. 18). During epochs of illumination (470 nm, 560 nm or 590 nm), the proportion of action potentials evoked in bystander neurons was modulated in a bidirectional manner, approximately doubling in the case of AAV5-ChR2 bystanders and halving in the case of AAV5-eArch3.0 bystanders (FIGS. 18A and 18B). AAV5-eNpHR3.0 bystanders also experienced a modest but significant reduction in spiking success during illumination whereas no modulation by light epochs was observed in AAV5-YFP controls (FIGS. 18C and 18D).

[0257] FIGS. 18A-D.

[0258] Functional impact of bystander currents on action potential firing. Spikes were evoked in the bystander neuron by intracellular injection of electrical current pulses at 10 Hz titrated to achieve a ~50% success rate at baseline. Light pulses were applied and the change in evoked spiking was recorded. Plots show percentage of successfully evoked spikes during repeated light-off and light-on epochs for A AAV-ChR2 (n=4-10), B AAV-eArch3.0 (n=13-14), C AAV-eNpHR3.0 (n=9-14) and D AAV-YFP control bystander neurons. Summary plots and individual cell data are shown with example traces. Dashed box shows zoom-in of the center light-off/light-on epochs. Bar charts indicate mean values and error bars represent SEM. All statistical comparisons (Wilcoxon matched pairs signed rank test) are between the light-on epoch and the preceding light-off epoch.

[0259] Having observed that the bystander effect tracked the direction of change in local neural activity we questioned whether the effect could be observed during manipulation of neural activity using electrical stimulation. Although electrical stimulation is not constrained to a genetically specified cell type or projection, we endeavored to create “electrical bystanders” by stimulating axonal inputs (Schaffer collaterals) to the CA1 region of hippocampus (FIG. 19A). The ability of the stimulation paradigm to induce synaptic release (FIG. 19B) was confirmed, then ionotropic synaptic transmission blockers were applied to isolate the impact of electrical axonal stimulation on the extracellular milieu. To mimic the intensity of the optogenetic manipulations, high amplitude (0.5-2.5 mA) extracellular current pulses at a frequency of 10 Hz for a period of 20 s were used (FIG. 19C). Electrical artifacts challenged the assessment of whole-cell current responses during stimulation, however the mean change in holding current immediately post-stimulation compared to baseline was significantly more negative than the YFP control group (-11 pA) (FIG. 19D), displaying a slow recovery comparable to the ChR2 optogenetic bystander currents. The possibility of a unique electrochemical reaction between the electrode metal and the extracellular fluid was controlled for by performing the experiments using both tungsten and platinum-iridium electrodes; similar effects were found with both electrode-types (FIG. 20).

[0260] It was hypothesized that the bystander effect could be driven by changes in local extracellular pH. Neural activity and synaptic release can modulate extracellular pH and many membrane proteins are modulated by extracellular protons such as acid-sensing ion channels (ASICs), which

may be partially open at rest and are plentiful in the brain. The contribution of ASICs to the ChR2 bystander current was tested by using pharmacological blockade by the ASIC inhibitor, amiloride. A bystander current (15 s light pulse) was evoked in hippocampal ChR2 bystander neurons every 5 minutes for up to 75 minutes. Following two baseline measurements, 500 μ M amiloride was applied for 20 minutes, then returned to ACSF alone for a “washout” period. During amiloride application, an increase in membrane resistance (in the absence of any illumination) (FIG. 15E) was observed, with a concurrent reduction in the magnitude of the light-evoked bystander current to ~50% of the baseline value, which slowly recovered during the washout period (FIGS. 15F and 15G). To control for the effect of holding cells in whole-cell patch clamp configuration for long periods, the experiment was repeated in the absence of amiloride application and no consistent reduction in bystander current magnitude over time was seen (FIG. 21C). Measures of cell health confirmed the integrity of the pipette access and cell membrane for the duration of the recordings (FIGS. 22A and 22B).

Coupling Proton Pumps to Acid-Sensing Ion Channels

[0261] The response of acid-sensing ion channels to extracellular protons was exploited through a concept that we term “two-component optogenetics” (TCO). A modular system was devised, in which a light-sensitive protein such as a proton pump (e.g. *Coccomyxa subellipsoidea* C-169 (CsR) or Archaeorhodopsin (Arch)) is co-expressed with a secondary-coupled ion channel, such as an acid-sensing ion channel (ASIC), to evoke a light-triggered secondary current carried by a specific ionic species, as illustrated in FIG. 23A.

[0262] Oocytes: To test this approach in *Xenopus laevis* oocytes, we chose a light-driven proton pump of the arctic green alga *Coccomyxa subellipsoidea* C-169 (CsR) (Blanc et al, 2012), which has improved expression in oocytes compared to the well-characterized bacteriorhodopsin or archaeorhodopsin, used for hyperpolarization of neurons. The CsR mutant T46N was used, which exhibits less voltage dependence than the wild type, with large photocurrents at negative voltages (FIG. 24).

[0263] In *Xenopus laevis* oocytes we co-expressed CsR with each of three different rat acid-sensing ion channels ASIC1a, ASIC2a or ASIC3. These channels are characterized by a steep pH-dependence of the proton-activated currents, more or less below the physiological pH. Immediately after light onset a small outward current carried by proton pumping of CsR was observed, followed by a large inward current carried by the co-expressed acid-sensing ion channel (FIGS. 23B-D). For both ASIC1 α and ASIC3, the secondary activated inward current peaked within 1-2 s after light onset then rapidly decayed to the initial pump current, due to the high proton sensitivity and fast desensitization of ASIC1 α and ASIC3 as described previously (Zhang & Canessa, 2002) (FIGS. 23B and 23D). In contrast ASIC2a mediated a long-lasting light activated inward current (FIG. 23C). The rise of the ASIC2a current was multiphasic at all voltages, a property not observed in previous studies in which the channel was directly activated by acidification of the bulk solution. This is possibly due to the indirect activation of the channel by the proton pump. In accordance with a low pH₅₀ of 5 and the reported slow and incomplete desensitization of ASIC2a (Zhang & Canessa 2002), the light-induced currents decayed only very slowly during

illumination. Following light offset the current decayed to zero within ~20 seconds and could be reactivated by illumination any time (FIG. 25A).

[0264] FIGS. 23A-D.

[0265] Optical activation of three acid-sensitive ion channels. A Principle of the Two Component Optogenetic (TCO) approach. Upon illumination the light-activated proton pump may moderately acidify the local extracellular medium and activate acid-sensitive ion channels, ASICs, via their proton-sensing domain. This results in a remote but large sodium influx that can be used for sustained cell depolarization at moderate light intensities. In *Xenopus* oocytes, a light-driven proton pump of *Coccomyxa subellipsoidea* (CsR) was used. B-D Macroscopic currents of CsR_{T46N} coexpressed with rat ASIC1a, rat ASIC2a or rat ASIC3 in oocytes at a molar RNA ratio of 1:1 (for ASIC3 of 2:1). Cells were illuminated with 560 nm light at different holding voltages at 0.1 mM MOPS and pH 7.5 under constant perfusion. The small outward directed pump currents (CsR) triggers large inward sodium currents (ASIC). Inset zooming to the initial pump activity directly after starting to illuminate CsR_{T46N}-ASIC1a with green light. Note that ASIC1a and ASIC3 show strong inactivation in sustained light, whereas ASIC2a shows moderate to no inactivation at all.

[0266] FIGS. 24A-E. Photocurrents of Chlorellarhodopsin (CsR).

[0267] A, B Light induced pump currents of CsR WT (A) and T46N (B) in *Xenopus* oocytes. The T46N mutant exhibits greater currents at negative membrane voltage compared to WT. C Current-voltage relationships, I(E), and D action spectra with maxima at 545 nm. E Comparison of CsR photocurrents (545 nm excitation) with those of bacteriorhodopsin (BR, 570 nm excitation) expressed under identical conditions. Current amplitudes of CsR are on average 10 fold greater than those of BR.

[0268] FIGS. 25A-D. Characterization of CsR-ASIC1a with and without Permanent Perfusion in *Xenopus laevis* Oocytes.

[0269] In “perfusion” conditions a measuring chamber of 300 μ l was continuously perfused with 1.8 ± 0.2 ml/min of standard measuring buffer containing 100 mM NaCl, 1 mM KCl, 1 mM MgCl₂, 0.1 mM CaCl₂, 0.1 mM MOPS (pH 7.5). In measurements “without perfusion” the buffer supply was disconnected and the peristaltic pump switched off. A Representative CsR_{T46N}-ASIC2a photocurrents at 40 s light pulses of 560 nm in a succession of conditions “without perfusion”, with continuous “perfusion” and “without perfusion” at different voltages. Insets: Repetitive photocurrent “without perfusion” and with “continuous perfusion” at -40 mV. B Comparison of normalized peak photocurrent with “perfusion” (open circles) and “without perfusion” (squares). Empty squares describe the response to the first light pulse and filled squares to the third light pulse (see A). C Normalized peak photocurrent at -40 mV in dependence on the initial CsR_{T46N} pump current in “perfusion” condition and “without perfusion” for 1st light pulse empty for 3rd light pulse (see A and B)). All currents were normalized to ASIC2a current at pH4 and -40 mV (see FIG. 5). D CsR_{T46N}-ASIC2a on-kinetics quantified by the time to reach the half maximal photocurrent $t_{1/2,on}$ with perfusion (circles) and without perfusion (filled and empty squares, see B and C) E CsR_{T46N}-ASIC2a off-kinetics quantified by the time to reduce the photocurrent by half after light switched off $t_{1/2,off}$

with perfusion (circles) and without perfusion (filled and empty squares, see B and C). Inset: Description of $t_{1/2,on}$ and $t_{1/2,off}$ (red) on a representative photocurrent at -40 mV.

[0270] The observed light activated inward currents were inversely proportional to the membrane voltage due to the increased driving force for Na^+ at negative voltages and voltage independent gating and permeability of ASIC2a (Zhang & Canessa, 2002) (FIG. 23A; FIG. 26A). Changing the concentration of the major extracellular cation from Na^+ to K^+ or choline shifted the reversal potential and greatly decreased the magnitude of the inward current component, confirming the Na^+ selectivity of the ASIC2a response as a major feature of the TCO pair (FIG. 26A).

[0271] To determine the fraction of ASIC2a channels that are activated by light, we titrated the ASIC2a currents by rapid buffer exchange. It was found that the maximal current (when holding the membrane potential at -60 mV) was only reached at pH 4 (FIG. 26B). Normalization of light-activated currents to this value revealed that approximately 25% of ASICs are activated by CsR-mediated acidification (FIGS. 26B-D) and allowed an approximation of the acidification sensed by ASICs at the cell surface (FIG. 26B green bar). It was also noticed that at pH values of 5.5 or below, ASIC2a inactivates more severely than at pH 6. Thus for neuronal applications, the degree of inactivation may serve as a useful indicator for the external pH value that may have been reached.

[0272] ASIC activation strongly depended on the number of active proton pumps as probed by application of light at different intensities (FIG. 26E). Furthermore efficient activation was expected to depend on the external buffering capacity for protons, namely buffer strength and extracellular volume. Indeed increasing the buffer strength from 0.1 mM to 5 mM strongly decreased the ASIC2a mediated inward current (FIG. 26C) and correspondingly the fraction of light activated ASIC2a channels from $\sim 25\%$ at 0.1 mM MOPS to $\sim 2\%$ at 5 mM MOPS (FIG. 26D). In contrast the extracellular bulk volume seemed of low importance. Consecutive exchange of the bulk medium during illumination by continuous perfusion only slightly decreased the light activated ASIC2a current compared to conditions with a constant bulk phase (FIG. 25).

[0273] FIG. 26A-E. Characterization of CsR-ASIC2a by two-electrode voltage clamp (TEVC) in oocytes. A Current-voltage dependency of normalized photocurrents in 100 mM NaCl, 100 mM KCl or 100 mM CholineCl extracellular medium (all media contained additionally 1 mM NaCl/KCl, 1 mM MgCl_2 , 0.1 mM CaCl_2 and 0.1 mM MOPS, pH 7.5, $n=5$, normalized to ASIC2a current activated by pH 4). B ASIC2a currents measured during pH titration in darkness and comparison with photocurrents measured at pH 7.5. The boxed region highlights the percent activation of ASIC2a by illumination with green light at 0.1 mM MOPS (data shown in FIG. 5B). Inset: representative pH activated current trace of ASIC2a at -40 mV. C Macroscopic currents of CsR_{T46N}-ASIC2a activated by pH 4 or green light at different buffer concentrations (5 mM MOPS, 1 mM MOPS and 0.1 mM MOPS, -40 mV, constant perfusion) D Percent activation of ASIC2a by the light driven proton pump CsR_{T46N} in different buffer concentrations (5 mM MOPS, 1 mM MOPS and 0.1 mM MOPS, -40 mV, $n=9$, 100% activation taken as the peak ASIC current produced by pH 4). E Normalized ASIC2a and CsR_{T46N} photocurrents measured at different

light intensities (0.1 mM MOPS, -40 mV, $n=5$, normalized to ASIC2a current activated by pH 4). Inset: representative current traces at -40 mV.

[0274] Neurons:

[0275] For application to neuroscience, ASIC2a was tested in cultured hippocampal neurons. The channels were co-expressed with the light-driven proton pump eArch3.0, one of the highest-expressing pumps in neurons (Chow et al, 2010, Mattis et al, 2011). A single eArch3.0-ASIC2a construct was developed, termed Champ (Channel/pump), fusing the proton pump and ASIC2a channel at the DNA level, separating the two genes only by a linker sequence (FIG. 27A). The combination of eArch3.0-ASIC2a (Champ1.0) was enhanced for better membrane localization (Champ2.0) via trafficking signal (TS) and endoplasmic reticulum (ER) export motifs (Gradinaru et al, 2010) (FIGS. 27A and 27B). We performed whole-cell patch clamp recordings from cultured hippocampal pyramidal neurons, expressing the constructs under the human synapsin (hSyn) or calmodulin kinase II α (CamKII α) promoters and saw a characteristic biphasic membrane current in response to 560 nm light in voltage-clamp recordings (FIG. 27C). The mean current magnitudes were 246 pA for the outward proton pump-mediated component and -950 pA for the inward ASIC-mediated component (FIG. 27D). The biphasic current was observed in 48% of YFP-positive neurons (FIGS. 28A and 28B) and there was no evidence of adverse effects on cell health in neurons expressing the dual component construct (FIGS. 28C-F). The inward current magnitude was linearly related to the magnitude of the outward proton pump current (FIG. 27E). Peak inward and outward current magnitude did not vary significantly with the duration of light pulses (1 s to 15 s) in a HEPES buffered solution (FIGS. 29A and 29B), suggesting that maximal currents were achievable within 1 s, however off-kinetics, as fitted by a two-term exponential, increased with increasing light pulse duration (FIGS. 29C and 29D). For longer light pulses (15 s), a clear decay in the inward current magnitude over the course of the light pulse to approximately 80% of the initial value was observed (FIG. 27C and FIG. 30B), which may be explained by increases in extracellular acidity under sustained light conditions.

[0276] In a separate experiment we tested the effect of decreasing the concentration of HEPES buffer in the extracellular Tyrode's solution (from 25 mM to 0.1 mM) on the magnitude of the currents (FIG. 30). In a low (0.1 mM) HEPES solution, 7/11 ($\sim 60\%$) neurons exhibited the characteristic biphasic membrane response (compared to 5/10 (50%) neurons in standard (25 mM) Tyrode's under otherwise matched conditions). There was a trend towards an increase in current magnitude in low HEPES solution, particularly during longer light pulses (15 s) (FIG. 30D-F) however this was accompanied by a decrease in the stability of the response with greater decay of the peak inward current over the duration of the light pulse (FIGS. 30A and 30B), likely due to the larger drop in extracellular pH in the weakly buffered solution.

[0277] Current clamp recordings of membrane potential responses of TCO-expressing neurons revealed that 560 nm light evoked an initial hyperpolarization (-33 mV) of the membrane potential, followed by a subsequent depolarization (87 mV) (FIGS. 27F and 27G) which was sufficient to generate action potentials (~ 9 spikes) and persisted beyond the termination of the light pulse (FIGS. 27F and 27H). The

extent of ASIC-mediated depolarization was proportional to the initial pump-mediated hyperpolarization (FIG. 31B), echoing the linear relationship between the inward and outward current components seen in voltage-clamp recordings. The light pulse duration did not significantly alter the magnitude of membrane potential change beyond 1 s light (FIG. 31).

[0278] FIGS. 27A-H. eArch3.0-ASIC2a (Champ) expression in hippocampal neurons. A Confocal images of yellow fluorescent protein (YFP) fluorescence from cultured hippocampal neurons expressing ASIC2a labeled with YFP in combination with the enhanced light-driven proton pump Arch3.0 at 40 $\times$ magnification. Scale bars represent 30 μ m. The construct expressed well under both the CamKII α and human synapsin (hSyn) promoter. B Cartoon illustration of the two-component construct containing eArch (enhanced by trafficking sequence, TS) and ASIC2a, separated by a linker sequence and labeled with YFP. C Representative voltage clamp traces of the Champ current (eArch3.0-ASIC2a current in response to 1 s, 5 s and 15 s pulses of 560 nm light (timing of light pulse is indicated by horizontal line). Regions of the trace used to measure outward and inward current components and off-kinetics are indicated by dashed lines and arrows. D Magnitude of outward (mean $\pm$ SEM=246 $\pm$ 27 pA) and inward (-950 $\pm$ 172 pA) components of the Champ current in response to a 1 s pulse of 560 nm light (n=21). E Relationship between the inward and outward components of the current response to 1 s pulse of 560 nm light (n=21). Linear regression analysis yields $R^2=0.33$, $p<0.01$ for difference of slope from zero. F Examples of a variety of membrane potential responses to 1 s pulses of 560 nm light (light pulse timing indicated by horizontal lines) from 4 different eArch-ASIC2a (Champ) expressing cells recorded in current clamp. Regions of the trace used to measure hyperpolarizing and depolarizing components of the response are indicated. G Magnitude of hyperpolarizing (eArch3.0-mediated, -33 $\pm$ 3 mV) and depolarizing (ASIC2a-mediated, 87 $\pm$ 6 mV) components of the light response (n=13) H Number of spikes evoked in response to 1 s (n=17), 5 s (n=15) and 15 s (n=4) light pulses.

[0279] FIGS. 28A-F. Variable presence of the ASIC2a component in cultured hippocampal neurons. A Example of an eArch3.0-ASIC2a current when the ASIC2a component is small (upper trace) and example of an ASIC negative current, in which only the eArch3.0 (outward) component is present, with no inward ASIC2a component (lower trace). B Magnitude of outward current components for ASIC negative cells (eArch3.0 component present only, n=23) and ASIC positive cells (both outward (eArch3.0) and inward (ASIC2a) components present, n=21). C Leak current for all ASIC negative (n=23) and ASIC positive (n=21) cells. D Resting membrane potential for all ASIC negative (n=11) and ASIC positive (n=13) cells. E Pipette (access) resistance for all ASIC negative (n=23) and ASIC positive (n=21) cells. F Membrane resistance for all ASIC negative (n=23) and ASIC positive (n=21) cells.

[0280] FIGS. 29A and 29B.

[0281] Champ currents and kinetics in response to light pulses of increasing duration. A Magnitude of outward and inward current components in response to 1 s (n=21), 5 s (n=14) and 15 s (n=10) light pulses. B Off-kinetics of Champ current in response to 1 s (n=18), 5 s (n=9) and 15 s (n=7) light pulses. The off-response is fitted by an exponential with a fast and slow term.

[0282] FIGS. 30A-F.

[0283] Champ currents in low HEPES Tyrode's solution. A Example of an eArch3.0-ASIC2a (Champ) photocurrent in 0.1 mM HEPES, illustrating the rapid decay of the peak current over the duration of the 15 s light pulse. Regions of the trace used for measurement of peak and final currents are indicated. B Ratio of the peak: final current for cells patched in 25 mM HEPES (n=5) and 0.1 mM HEPES (n=6) in response to 15 s light pulses. C Magnitude of inward and outward current components in response to 15 s light pulses in 0.1 mM HEPES (n=6). D Inward current magnitude in 25 mM and 0.1 mM HEPES during 1 s and 15 s light pulses (n=5-7) under otherwise matched conditions. E & F Outward and inward membrane currents during 1 s and 15 s light pulses in 0.1 mM HEPES.

[0284] FIGS. 31A and 31B.

[0285] Champ potentials in response to light pulses of increasing duration and relationship between Champ-mediated hyperpolarization and depolarization. A Magnitude of membrane hyperpolarization and depolarization in response to 1 s (n=13), 5 s, (n=10) and 15 s (n=4) light pulses. B Linear regression analysis for the relationship between Champ-mediated membrane hyperpolarization and depolarization yields $R^2=0.47$, $p<0.01$ for difference of slope from zero.

[0286] The impact of the proximity of the proton pump and ASIC components in generating the characteristic biphasic TCO response was explored. The molecular separation of the two components was systematically increased by interspersing a linker sequence of DNA of increasing length between the two genes: first, a short linker consisting of a 69 base pair trafficking sequence which closely fuses the two proteins (Champ3.0), second, a long (123 base pair) linker sequence that still tethers the two proteins but with a longer intervening peptide chain (Champ2.0), third, a ribosomal p2a skip sequence which cleaves the two proteins during translation (Szymczak-Workman et al. (Cold Spring Harbor Protocols 2012; 2012: 199-204); Prakash et al. (Nat Methods 2012; 9: 1171-1179)). Finally, the neurons were transfected simultaneously using two separate constructs (CamKII-Arch3.0-mCherry and CamKII-ASIC2a-YFP) co-expressing them but without generating a fusion construct. The 4 constructs and a CamKII-eArch3.0-YFP control were tested in a head-to-head comparison under matched experimental conditions (FIG. 32).

[0287] It was found that all four approaches resulted in good YFP expression, indicating successful expression of the ASIC construct. In the co-expression experiment good co-localization of mCherry fluorescence was observed, confirming expression of both constructs within single cells (FIGS. 32A-D). It was found that increasing the molecular separation between the constructs resulted in a lower probability of observing the inward current component of the TCO response, with the short linker sequence (TS) construct (Champ3.0) exhibiting the most reliable and largest inward ASIC-mediated currents at 0.1 mM buffer (mean inward current=-599 pA, mean outward current=150 pA) (FIG. 32A). We occasionally saw large ASIC currents with the separated (p2a split) construct; however these occurred less reliably (FIG. 32D). The co-expressed constructs generated eArch3.0 photocurrents (outward component) only, which were closer in magnitude (mean=377 pA) to the Arch3.0 control (mean=575 pA) than the fusion or p2a split constructs. The observed dependence of TCO function on the

physical proximity of the proton pump and ASIC channel highlights the importance of nano-environment ion sensing in the interaction between the two components on the membrane.

[0288] FIGS. 32A-D. Head-to-head comparison of four Champ constructs: effect of increasing molecular distance. All electrophysiological recordings were performed in low HEPES (0.1 mM) Tyrode's solution. For each construct: a cartoon illustrates the structure of the two-component construct, confocal images demonstrate fluorescence expression in culture and graphs show the relative magnitude of the peak outward current and the current at the end of the light pulse. A more negative current at the end of the light pulse indicates a larger ASIC component. Insets: representative traces of the current responses to a 1 s pulse of 560 nm light for each two-component construct (timing of light pulse indicated by horizontal line). A Champ3.0: eArch3.0 and ASIC2a are fused by a short linker sequence consisting of a 69 base pair membrane trafficking signal (TS) (n=16). B Champ2.0: eArch3.0 and ASIC2a are fused by a longer (123 base pair) sequence (n=17). C Champ4.0: eArch3.0 and ASIC2a are separated during protein translation by the ribosomal skip sequence, p2A (n=14). D Co-transfection of eArch3.0 and ASIC2a: eArch3.0 is labeled with mCherry and ASIC2a is labeled with YFP to allow identification of both components in a single cell. Electrophysiological characterization of outward and end-of-light pulse currents for the co-transfected construct and an eArch3.0-only control (n=9 and n=9 respectively).

[0289] FIGS. 33A-D. Measures of cell health across 4 different Champ constructs with increasing molecular separation between proton pump and ASIC. There were no significant differences in any cell health measures across the 5 groups: Champ3.0, Champ2.0, Champ4.0, co-transfection of eArch3.0 and ASIC2a and eArch3.0 only (one-way ANOVA, $F=1.56-2.27$, $p>0.05$, $n=9-17$) A Leak current B Membrane resistance C Pipette resistance D Resting membrane potential.

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- [0356] Although the foregoing invention has been described in some detail by way of illustration and example for purposes of clarity of understanding, it is readily apparent to those of ordinary skill in the art in light of the teachings of this invention that certain changes and modifications may be made thereto without departing from the spirit or scope of the appended claims.
- [0357] Accordingly, the preceding merely illustrates the principles of the invention. It will be appreciated that those skilled in the art will be able to devise various arrangements which, although not explicitly described or shown herein, embody the principles of the invention and are included within its spirit and scope. Furthermore, all examples and conditional language recited herein are principally intended to aid the reader in understanding the principles of the invention and the concepts contributed by the inventors to furthering the art, and are to be construed as being without limitation to such specifically recited examples and conditions. Moreover, all statements herein reciting principles, aspects, and embodiments of the invention as well as specific examples thereof, are intended to encompass both structural and functional equivalents thereof. Additionally, it is intended that such equivalents include both currently known equivalents and equivalents developed in the future, i.e., any elements developed that perform the same function, regardless of structure. The scope of the present invention, therefore, is not intended to be limited to the exemplary embodiments shown and described herein. Rather, the scope and spirit of present invention is embodied by the appended claims.

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-continued

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		195					200					205				
Val	Gly	Leu	Gly	Ile	Glu	Thr	Leu	Leu	Phe	Met	Val	Leu	Asp	Val	Thr	
	210					215					220					
Ala	Lys	Val	Gly	Phe	Gly	Phe	Ile	Leu	Leu	Arg	Ser	Arg	Ala	Ile	Leu	
225					230					235					240	
Gly	Asp	Thr	Glu	Ala	Pro	Glu	Pro	Ser	Ala	Gly	Ala	Asp	Val	Ser	Ala	
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Ala	Asp															
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<220> FEATURE:																
<223> OTHER INFORMATION: synthetic amino acid sequence																
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1				5					10					15		
Arg	Pro	Glu	Thr	Leu	Trp	Leu	Gly	Ile	Gly	Thr	Leu	Leu	Met	Leu	Ile	
			20					25					30			
Gly	Thr	Phe	Tyr	Phe	Leu	Val	Arg	Gly	Trp	Gly	Val	Thr	Asp	Lys	Asp	
		35					40					45				
Ala	Arg	Glu	Tyr	Tyr	Ala	Val	Thr	Ile	Leu	Val	Pro	Gly	Ile	Ala	Ser	
	50					55					60					
Ala	Ala	Tyr	Leu	Ser	Met	Phe	Phe	Gly	Ile	Gly	Leu	Thr	Glu	Val	Thr	
65					70					75					80	
Val	Gly	Gly	Glu	Met	Leu	Asp	Ile	Tyr	Tyr	Ala	Arg	Tyr	Ala	Asp	Trp	
				85					90					95		
Leu	Phe	Thr	Thr	Pro	Leu	Leu	Leu	Leu	Asp	Leu	Ala	Leu	Leu	Ala	Lys	
		100						105					110			
Val	Asp	Arg	Val	Thr	Ile	Gly	Thr	Leu	Val	Gly	Val	Asp	Ala	Leu	Met	
		115					120					125				
Ile	Val	Thr	Gly	Leu	Ile	Gly	Ala	Leu	Ser	His	Thr	Ala	Ile	Ala	Arg	
	130					135					140					
Tyr	Ser	Trp	Trp	Leu	Phe	Ser	Thr	Ile	Cys	Met	Ile	Val	Val	Leu	Tyr	
145					150					155					160	
Phe	Leu	Ala	Thr	Ser	Leu	Arg	Ser	Ala	Ala	Lys	Glu	Arg	Gly	Pro	Glu	
				165					170					175		
Val	Ala	Ser	Thr	Phe	Asn	Thr	Leu	Thr	Ala	Leu	Val	Leu	Val	Leu	Trp	
			180					185					190			

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Thr	Ala	Tyr	Pro	Ile	Leu	Trp	Ile	Ile	Gly	Thr	Glu	Gly	Ala	Gly	Val	
	195						200					205				
Val	Gly	Leu	Gly	Ile	Glu	Thr	Leu	Leu	Phe	Met	Val	Leu	Asp	Val	Thr	
	210					215					220					
Ala	Lys	Val	Gly	Phe	Gly	Phe	Ile	Leu	Leu	Arg	Ser	Arg	Ala	Ile	Leu	
225					230					235					240	
Gly	Asp	Thr	Glu	Ala	Pro	Glu	Pro	Ser	Ala	Gly	Ala	Asp	Val	Ser	Ala	
				245					250					255		
Ala	Asp	Arg	Pro	Val	Val	Ala	Val	Ser	Lys	Ala	Ala	Ala	Lys	Ser	Arg	
			260					265					270			
Ile	Thr	Ser	Glu	Gly	Glu	Tyr	Ile	Pro	Leu	Asp	Gln	Ile	Asp	Ile	Asn	
		275					280					285				
Val	Val	Ser	Lys	Gly	Glu	Glu	Leu	Phe	Thr	Gly	Val	Val	Pro	Ile	Leu	
	290					295					300					
Val	Glu	Leu	Asp	Gly	Asp	Val	Asn	Gly	His	Lys	Phe	Ser	Val	Ser	Gly	
305					310					315					320	
Glu	Gly	Glu	Gly	Asp	Ala	Thr	Tyr	Gly	Lys	Leu	Thr	Leu	Lys	Phe	Ile	
				325					330					335		
Cys	Thr	Thr	Gly	Lys	Leu	Pro	Val	Pro	Trp	Pro	Thr	Leu	Val	Thr	Thr	
			340					345					350			
Phe	Gly	Tyr	Gly	Leu	Gln	Cys	Phe	Ala	Arg	Tyr	Pro	Asp	His	Met	Lys	
		355					360					365				
Gln	His	Asp	Phe	Phe	Lys	Ser	Ala	Met	Pro	Glu	Gly	Tyr	Val	Gln	Glu	
	370					375					380					
Arg	Thr	Ile	Phe	Phe	Lys	Asp	Asp	Gly	Asn	Tyr	Lys	Thr	Arg	Ala	Glu	
385					390					395					400	
Val	Lys	Phe	Glu	Gly	Asp	Thr	Leu	Val	Asn	Arg	Ile	Glu	Leu	Lys	Gly	
			405						410					415		
Ile	Asp	Phe	Lys	Glu	Asp	Gly	Asn	Ile	Leu	Gly	His	Lys	Leu	Glu	Tyr	
		420					425						430			
Asn	Tyr	Asn	Ser	His	Asn	Val	Tyr	Ile	Met	Ala	Asp	Lys	Gln	Lys	Asn	
	435						440					445				
Gly	Ile	Lys	Val	Asn	Phe	Lys	Ile	Arg	His	Asn	Ile	Glu	Asp	Gly	Ser	
	450					455					460					
Val	Gln	Leu	Ala	Asp	His	Tyr	Gln	Gln	Asn	Thr	Pro	Ile	Gly	Asp	Gly	
465					470					475					480	
Pro	Val	Leu	Leu	Pro	Asp	Asn	His	Tyr	Leu	Ser	Tyr	Gln	Ser	Ala	Leu	
				485					490					495		
Ser	Lys	Asp	Pro	Asn	Glu	Lys	Arg	Asp	His	Met	Val	Leu	Leu	Glu	Phe	
			500					505					510			
Val	Thr	Ala	Ala	Gly	Ile	Thr	Leu	Gly	Met	Asp	Glu	Leu	Tyr	Lys	Phe	
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<210> SEQ ID NO 3
<211> LENGTH: 248
<212> TYPE: PRT
<213> ORGANISM: Artificial sequence
<220> FEATURE:
<223> OTHER INFORMATION: synthetic amino acid sequence

<400> SEQUENCE: 3

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Met	Asp	Pro	Ile	Ala	Leu	Gln	Ala	Gly	Tyr	Asp	Leu	Leu	Gly	Asp	Gly	
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Arg	Pro	Glu	Thr	Leu	Trp	Leu	Gly	Ile	Gly	Thr	Leu	Leu	Met	Leu	Ile	
			20					25					30			
Gly	Thr	Phe	Tyr	Phe	Ile	Val	Lys	Gly	Trp	Gly	Val	Thr	Asp	Lys	Glu	
		35					40					45				
Ala	Arg	Glu	Tyr	Tyr	Ser	Ile	Thr	Ile	Leu	Val	Pro	Gly	Ile	Ala	Ser	
	50					55					60					
Ala	Ala	Tyr	Leu	Ser	Met	Phe	Phe	Gly	Ile	Gly	Leu	Thr	Glu	Val	Thr	
65					70					75					80	
Val	Ala	Gly	Glu	Val	Leu	Asp	Ile	Tyr	Tyr	Ala	Arg	Tyr	Ala	Asp	Trp	
				85					90					95		
Leu	Phe	Thr	Thr	Pro	Leu	Leu	Leu	Leu	Asp	Leu	Ala	Leu	Leu	Ala	Lys	
			100					105						110		
Val	Asp	Arg	Val	Ser	Ile	Gly	Thr	Leu	Val	Gly	Val	Asp	Ala	Leu	Met	
		115					120					125				
Ile	Val	Thr	Gly	Leu	Ile	Gly	Ala	Leu	Ser	His	Thr	Pro	Leu	Ala	Arg	
	130					135					140					
Tyr	Ser	Trp	Trp	Leu	Phe	Ser	Thr	Ile	Cys	Met	Ile	Val	Val	Leu	Tyr	
145					150					155					160	
Phe	Leu	Ala	Thr	Ser	Leu	Arg	Ala	Ala	Ala	Lys	Glu	Arg	Gly	Pro	Glu	
				165					170					175		
Val	Ala	Ser	Thr	Phe	Asn	Thr	Leu	Thr	Ala	Leu	Val	Leu	Val	Leu	Trp	
			180					185					190			
Thr	Ala	Tyr	Pro	Ile	Leu	Trp	Ile	Ile	Gly	Thr	Glu	Gly	Ala	Gly	Val	
	195					200						205				
Val	Gly	Leu	Gly	Ile	Glu	Thr	Leu	Leu	Phe	Met	Val	Leu	Asp	Val	Thr	
	210					215					220					
Ala	Lys	Val	Gly	Phe	Gly	Phe	Ile	Leu	Leu	Arg	Ser	Arg	Ala	Ile	Leu	
225					230					235					240	
Gly	Asp	Thr	Glu	Ala	Pro	Glu	Pro									
				245												
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<211> LENGTH: 223																
<212> TYPE: PRT																
<213> ORGANISM: Artificial sequence																
<220> FEATURE:																
<223> OTHER INFORMATION: synthetic amino acid sequence																
<400> SEQUENCE: 4																
Ala	Ser	Ser	Phe	Gly	Lys	Ala	Leu	Leu	Glu	Phe	Val	Phe	Ile	Val	Phe	
1				5					10					15		
Ala	Cys	Ile	Thr	Leu	Leu	Leu	Gly	Ile	Asn	Ala	Ala	Lys	Ser	Lys	Ala	
			20					25					30			
Ala	Ser	Arg	Val	Leu	Phe	Pro	Ala	Thr	Phe	Val	Thr	Gly	Ile	Ala	Ser	
		35					40					45				
Ile	Ala	Tyr	Phe	Ser	Met	Ala	Ser	Gly	Gly	Gly	Trp	Val	Ile	Ala	Pro	
	50					55					60					
Asp	Cys	Arg	Gln	Leu	Phe	Val	Ala	Arg	Tyr	Leu	Asp	Trp	Leu	Ile	Thr	
65					70					75					80	
Thr	Pro	Leu	Leu	Leu	Ile	Asp	Leu	Gly	Leu	Val	Ala	Gly	Val	Ser	Arg	
				85					90					95		

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Trp	Asp	Ile	Met	Ala	Leu	Cys	Leu	Ser	Asp	Val	Leu	Met	Ile	Ala	Thr	
			100					105					110			
Gly	Ala	Phe	Gly	Ser	Leu	Thr	Val	Gly	Asn	Val	Lys	Trp	Val	Trp	Trp	
		115					120					125				
Phe	Phe	Gly	Met	Cys	Trp	Phe	Leu	His	Ile	Ile	Phe	Ala	Leu	Gly	Lys	
	130					135					140					
Ser	Trp	Ala	Glu	Ala	Ala	Lys	Ala	Lys	Gly	Gly	Asp	Ser	Ala	Ser	Val	
145					150					155					160	
Tyr	Ser	Lys	Ile	Ala	Gly	Ile	Thr	Val	Ile	Thr	Trp	Phe	Cys	Tyr	Pro	
				165					170					175		
Val	Val	Trp	Val	Phe	Ala	Glu	Gly	Phe	Gly	Asn	Phe	Ser	Val	Thr	Phe	
			180					185					190			
Glu	Val	Leu	Ile	Tyr	Gly	Val	Leu	Asp	Val	Ile	Ser	Lys	Ala	Val	Phe	
		195					200					205				
Gly	Leu	Ile	Leu	Met	Ser	Gly	Ala	Ala	Thr	Gly	Tyr	Glu	Ser	Ile		
	210					215					220					
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<211> LENGTH: 262																
<212> TYPE: PRT																
<213> ORGANISM: Oxyrrhis marina																
<400> SEQUENCE: 5																
Met	Ala	Pro	Leu	Ala	Gln	Asp	Trp	Thr	Tyr	Ala	Glu	Trp	Ser	Ala	Val	
1				5					10					15		
Tyr	Asn	Ala	Leu	Ser	Phe	Gly	Ile	Ala	Gly	Met	Gly	Ser	Ala	Thr	Ile	
			20					25					30			
Phe	Phe	Trp	Leu	Gln	Leu	Pro	Asn	Val	Thr	Lys	Asn	Tyr	Arg	Thr	Ala	
		35					40					45				
Leu	Thr	Ile	Thr	Gly	Ile	Val	Thr	Leu	Ile	Ala	Thr	Tyr	His	Tyr	Phe	
		50				55					60					
Arg	Ile	Phe	Asn	Ser	Trp	Val	Ala	Ala	Phe	Asn	Val	Gly	Leu	Gly	Val	
65				70					75						80	
Asn	Gly	Ala	Tyr	Glu	Val	Thr	Val	Ser	Gly	Thr	Pro	Phe	Asn	Asp	Ala	
				85					90					95		
Tyr	Arg	Tyr	Val	Asp	Trp	Leu	Leu	Thr	Val	Pro	Leu	Leu	Leu	Val	Glu	
			100					105					110			
Leu	Ile	Leu	Val	Met	Lys	Leu	Pro	Ala	Lys	Glu	Thr	Val	Cys	Leu	Ala	
		115					120					125				
Trp	Thr	Leu	Gly	Ile	Ala	Ser	Ala	Val	Met	Val	Ala	Leu	Gly	Tyr	Pro	
						135					140					
Gly	Glu	Ile	Gln	Asp	Asp	Leu	Ser	Val	Arg	Trp	Phe	Trp	Trp	Ala	Cys	
145				150						155					160	
Ala	Met	Val	Pro	Phe	Val	Tyr	Val	Val	Gly	Thr	Leu	Val	Val	Gly	Leu	
				165					170					175		
Gly	Ala	Ala	Thr	Ala	Lys	Gln	Pro	Glu	Gly	Val	Val	Asp	Leu	Val	Ser	
			180					185					190			
Ala	Ala	Arg	Tyr	Leu	Thr	Val	Val	Ser	Trp	Leu	Thr	Tyr	Pro	Phe	Val	
		195					200					205				
Tyr	Ile	Val	Lys	Asn	Ile	Gly	Leu	Ala	Gly	Ser	Thr	Ala	Thr	Met	Tyr	
	210					215					220					
Glu	Gln	Ile	Gly	Tyr	Ser	Ala	Ala	Asp	Val	Thr	Ala	Lys	Ala	Val	Phe	
225					230					235					240	

Glu Gly Lys Leu Arg Ala
260

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<210> SEQ ID NO 6
<211> LENGTH: 313
<212> TYPE: PRT
<213> ORGANISM: Leptosphaeria maculans
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<400> SEQUENCE: 6

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Phe Pro Leu Pro Thr Ala Thr Gln Ser Ala Gln Pro Thr His Val Ala
20 25 30

Pro Val Pro Thr Val Leu Pro Asp Thr Pro Ile Tyr Glu Thr Val Gly
35 40 45

Asp Ser Gly Ser Lys Thr Leu Trp Val Val Phe Val Leu Met Leu Ile
50 55 60

Ala Ser Ala Ala Phe Thr Ala Leu Ser Trp Lys Ile Pro Val Asn Arg
65 70 75 80

Arg Leu Tyr His Val Ile Thr Thr Ile Ile Thr Leu Thr Ala Ala Leu
85 90 95

Ser Tyr Phe Ala Met Ala Thr Gly His Gly Val Ala Leu Asn Lys Ile
100 105 110

Val Ile Arg Thr Gln His Asp His Val Pro Asp Thr Tyr Glu Thr Val
115 120 125

Tyr Arg Gln Val Tyr Tyr Ala Arg Tyr Ile Asp Trp Ala Ile Thr Thr
130 135 140

Pro Leu Leu Leu Leu Asp Leu Gly Leu Leu Ala Gly Met Ser Gly Ala
145 150 155 160

His Ile Phe Met Ala Ile Val Ala Asp Leu Ile Met Val Leu Thr Gly
165 170 175

Leu Phe Ala Ala Phe Gly Ser Glu Gly Thr Pro Gln Lys Trp Gly Trp
180 185 190

Tyr Thr Ile Ala Cys Ile Ala Tyr Ile Phe Val Val Trp His Leu Val
195 200 205

Leu Asn Gly Gly Ala Asn Ala Arg Val Lys Gly Glu Lys Leu Arg Ser
210 215 220

Phe Phe Val Ala Ile Gly Ala Tyr Thr Leu Ile Leu Trp Thr Ala Tyr
235 239 235 241

Pro Ile Val Trp Gly Leu Ala Asp Gly Ala Arg Lys Ile Gly Val Asp

Gly Glu Ile Ile Ala Tyr Ala Val Leu Asp Val Leu Ala Lys Gly Val

Phe Gly Ala Trp Leu Leu Val Thr His Ala Asn Leu Arg Glu Ser Asp

Val Glu Leu Asn Gly Phe Trp Ala Asn Gly Leu Asn Arg Glu Gly Ala

Ile Arg Ile Gly Glu Asp Asp Gly Ala

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<210> SEQ ID NO 8
<211> LENGTH: 310
<212> TYPE: PRT
<213> ORGANISM: Chlamydomonas reinhardtii
<400> SEQUENCE: 8
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<210> SEQ ID NO 8
<211> LENGTH: 310
<212> TYPE: PRT
<213> ORGANISM: Chlamydomonas reinhardtii
<400> SEQUENCE: 8
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Met	Asp	Tyr	Gly	Gly	Ala	Leu	Ser	Ala	Val	Gly	Arg	Glu	Leu	Leu	Phe	
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Val	Thr	Asn	Pro	Val	Val	Val	Asn	Gly	Ser	Val	Leu	Val	Pro	Glu	Asp	
			20					25					30			
Gln	Cys	Tyr	Cys	Ala	Gly	Trp	Ile	Glu	Ser	Arg	Gly	Thr	Asn	Gly	Ala	
		35					40					45				
Gln	Thr	Ala	Ser	Asn	Val	Leu	Gln	Trp	Leu	Ala	Ala	Gly	Phe	Ser	Ile	
	50					55					60					
Leu	Leu	Leu	Met	Phe	Tyr	Ala	Tyr	Gln	Thr	Trp	Lys	Ser	Thr	Cys	Gly	
65					70					75					80	
Trp	Glu	Glu	Ile	Tyr	Val	Cys	Ala	Ile	Glu	Met	Val	Lys	Val	Ile	Leu	
				85					90					95		
Glu	Phe	Phe	Phe	Glu	Phe	Lys	Asn	Pro	Ser	Met	Leu	Tyr	Leu	Ala	Thr	
			100					105					110			
Gly	His	Arg	Val	Gln	Trp	Leu	Arg	Tyr	Ala	Glu	Trp	Leu	Leu	Thr	Cys	
	115					120						125				
Pro	Val	Ile	Leu	Ile	His	Leu	Ser	Asn	Leu	Thr	Gly	Leu	Ser	Asn	Asp	
	130					135					140					
Tyr	Ser	Arg	Arg	Thr	Met	Gly	Leu	Leu	Val	Ser	Asp	Ile	Gly	Thr	Ile	
145					150					155					160	
Val	Trp	Gly	Ala	Thr	Ser	Ala	Met	Ala	Thr	Gly	Tyr	Val	Lys	Val	Ile	
				165					170					175		
Phe	Phe	Cys	Leu	Gly	Leu	Cys	Tyr	Gly	Ala	Asn	Thr	Phe	Phe	His	Ala	
			180					185					190			
Ala	Lys	Ala	Tyr	Ile	Glu	Gly	Tyr	His	Thr	Val	Pro	Lys	Gly	Arg	Cys	
	195						200					205				
Arg	Gln	Val	Val	Thr	Gly	Met	Ala	Trp	Leu	Phe	Phe	Val	Ser	Trp	Gly	
	210					215					220					
Met	Phe	Pro	Ile	Leu	Phe	Ile	Leu	Gly	Pro	Glu	Gly	Phe	Gly	Val	Leu	
225					230					235					240	
Ser	Val	Tyr	Gly	Ser	Thr	Val	Gly	His	Thr	Ile	Ile	Asp	Leu	Met	Ser	
				245					250					255		
Lys	Asn	Cys	Trp	Gly	Leu	Leu	Gly	His	Tyr	Leu	Arg	Val	Leu	Ile	His	
		260						265					270			
Glu	His	Ile	Leu	Ile	His	Gly	Asp	Ile	Arg	Lys	Thr	Thr	Lys	Leu	Asn	
	275						280					285				
Ile	Gly	Gly	Thr	Glu	Ile	Glu	Val	Glu	Thr	Leu	Val	Glu	Asp	Glu	Ala	
	290					295					300					
Glu	Ala	Gly	Ala	Val	Pro											
305					310											
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<212> TYPE: PRT																
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<220> FEATURE:																
<223> OTHER INFORMATION: synthetic amino acid sequence																
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1				5					10					15		
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			20					25					30			

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Gln	Cys	Tyr	Cys	Ala	Gly	Trp	Ile	Glu	Ser	Arg	Gly	Thr	Asn	Gly	Ala	
	35						40					45				
Gln	Thr	Ala	Ser	Asn	Val	Leu	Gln	Trp	Leu	Ala	Ala	Gly	Phe	Ser	Ile	
	50					55					60					
Leu	Leu	Leu	Met	Phe	Tyr	Ala	Tyr	Gln	Thr	Trp	Lys	Ser	Thr	Cys	Gly	
65					70					75					80	
Trp	Glu	Glu	Ile	Tyr	Val	Cys	Ala	Ile	Glu	Met	Val	Lys	Val	Ile	Leu	
				85					90					95		
Glu	Phe	Phe	Phe	Glu	Phe	Lys	Asn	Pro	Ser	Met	Leu	Tyr	Leu	Ala	Thr	
				100				105					110			
Gly	His	Arg	Val	Gln	Trp	Leu	Arg	Tyr	Ala	Glu	Trp	Leu	Leu	Thr	Ser	
		115					120					125				
Pro	Val	Ile	Leu	Ile	His	Leu	Ser	Asn	Leu	Thr	Gly	Leu	Ser	Asn	Asp	
	130					135					140					
Tyr	Ser	Arg	Arg	Thr	Met	Gly	Leu	Leu	Val	Ser	Asp	Ile	Gly	Thr	Ile	
145					150					155					160	
Val	Trp	Gly	Ala	Thr	Ser	Ala	Met	Ala	Thr	Gly	Tyr	Val	Lys	Val	Ile	
				165					170					175		
Phe	Phe	Cys	Leu	Gly	Leu	Cys	Tyr	Gly	Ala	Asn	Thr	Phe	Phe	His	Ala	
			180					185					190			
Ala	Lys	Ala	Tyr	Ile	Glu	Gly	Tyr	His	Thr	Val	Pro	Lys	Gly	Arg	Cys	
	195						200					205				
Arg	Gln	Val	Val	Thr	Gly	Met	Ala	Trp	Leu	Phe	Phe	Val	Ser	Trp	Gly	
	210					215					220					
Met	Phe	Pro	Ile	Leu	Phe	Ile	Leu	Gly	Pro	Glu	Gly	Phe	Gly	Val	Leu	
225				230						235				240		
Ser	Val	Tyr	Gly	Ser	Thr	Val	Gly	His	Thr	Ile	Ile	Asp	Leu	Met	Ser	
				245					250					255		
Lys	Asn	Cys	Trp	Gly	Leu	Leu	Gly	His	Tyr	Leu	Arg	Val	Leu	Ile	His	
			260					265					270			
Glu	His	Ile	Leu	Ile	His	Gly	Asp	Ile	Arg	Lys	Thr	Thr	Lys	Leu	Asn	
		275					280					285				
Ile	Gly	Gly	Thr	Glu	Ile	Glu	Val	Glu	Thr	Leu	Val	Glu	Asp	Glu	Ala	
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Glu	Ala	Gly	Ala	Val	Pro											
305					310											
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<212> TYPE: PRT																
<213> ORGANISM: Artificial sequence																
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<223> OTHER INFORMATION: synthetic amino acid sequence																
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Val	Thr	Asn	Pro	Val	Val	Val	Asn	Gly	Ser	Val	Leu	Val	Pro	Glu	Asp	
			20					25					30			
Gln	Cys	Tyr	Cys	Ala	Gly	Trp	Ile	Glu	Ser	Arg	Gly	Thr	Asn	Gly	Ala	
	35						40					45				
Gln	Thr	Ala	Ser	Asn	Val	Leu	Gln	Trp	Leu	Ala	Ala	Gly	Phe	Ser	Ile	
	50					55					60					

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Leu	Leu	Leu	Met	Phe	Tyr	Ala	Tyr	Gln	Thr	Trp	Lys	Ser	Thr	Cys	Gly
65				70						75				80	
Trp	Glu	Glu	Ile	Tyr	Val	Cys	Ala	Ile	Glu	Met	Val	Lys	Val	Ile	Leu
			85						90					95	
Glu	Phe	Phe	Phe	Glu	Phe	Lys	Asn	Pro	Ser	Met	Leu	Tyr	Leu	Ala	Thr
			100					105					110		
Gly	His	Arg	Val	Gln	Trp	Leu	Arg	Tyr	Ala	Glu	Trp	Leu	Leu	Thr	Ser
		115					120					125			
Pro	Val	Ile	Leu	Ile	His	Leu	Ser	Asn	Leu	Thr	Gly	Leu	Ser	Asn	Asp
	130					135					140				
Tyr	Ser	Arg	Arg	Thr	Met	Gly	Leu	Leu	Val	Ser	Ala	Ile	Gly	Thr	Ile
145					150					155					160
Val	Trp	Gly	Ala	Thr	Ser	Ala	Met	Ala	Thr	Gly	Tyr	Val	Lys	Val	Ile
				165					170					175	
Phe	Phe	Cys	Leu	Gly	Leu	Cys	Tyr	Gly	Ala	Asn	Thr	Phe	Phe	His	Ala
		180						185					190		
Ala	Lys	Ala	Tyr	Ile	Glu	Gly	Tyr	His	Thr	Val	Pro	Lys	Gly	Arg	Cys
	195						200					205			
Arg	Gln	Val	Val	Thr	Gly	Met	Ala	Trp	Leu	Phe	Phe	Val	Ser	Trp	Gly
	210					215					220				
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225					230					235					240
Ser	Val	Tyr	Gly	Ser	Thr	Val	Gly	His	Thr	Ile	Ile	Asp	Leu	Met	Ser
			245						250					255	
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		260						265					270		
Glu	His	Ile	Leu	Ile	His	Gly	Asp	Ile	Arg	Lys	Thr	Thr	Lys	Leu	Asn
	275						280					285			
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Ser	Asn	Gly	Thr	Asn	Ala	Glu	Lys	Leu	Ala	Ala	Asn	Ile	Leu	Gln	Trp
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	130					135					140					
Ala	Val	Ile	Tyr	Ser	Ser	Asn	Gly	Asn	Lys	Thr	Val	Trp	Leu	Arg	Tyr	
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Ala	Glu	Trp	Leu	Leu	Thr	Cys	Pro	Val	Leu	Leu	Ile	His	Leu	Ser	Asn	
				165					170					175		
Leu	Thr	Gly	Leu	Lys	Asp	Asp	Tyr	Ser	Lys	Arg	Thr	Met	Gly	Leu	Leu	
		180						185					190			
Val	Ser	Asp	Val	Gly	Cys	Ile	Val	Trp	Gly	Ala	Thr	Ser	Ala	Met	Cys	
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	210					215					220					
Met	Tyr	Thr	Tyr	Phe	His	Ala	Ala	Lys	Val	Tyr	Ile	Glu	Ala	Phe	His	
225					230					235					240	
Thr	Val	Pro	Lys	Gly	Ile	Cys	Arg	Glu	Leu	Val	Arg	Val	Met	Ala	Trp	
			245						250					255		
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			260					265					270			
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	275						280					285				
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	290					295					300					
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Ala	Glu	Trp	Leu	Leu	Thr	Cys	Pro	Val	Leu	Leu	Ile	His	Leu	Ser	Asn	
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Leu	Thr	Gly	Leu	Lys	Asp	Asp	Tyr	Ser	Lys	Arg	Thr	Met	Gly	Leu	Leu	
		180						185					190			
Val	Ser	Asp	Val	Gly	Cys	Ile	Val	Trp	Gly	Ala	Thr	Ser	Ala	Met	Cys	
		195					200					205				
Thr	Gly	Trp	Thr	Lys	Ile	Leu	Phe	Phe	Leu	Ile	Ser	Leu	Ser	Tyr	Gly	
	210					215					220					
Met	Tyr	Thr	Tyr	Phe	His	Ala	Ala	Lys	Val	Tyr	Ile	Glu	Ala	Phe	His	
225					230					235					240	
Thr	Val	Pro	Lys	Gly	Ile	Cys	Arg	Glu	Leu	Val	Arg	Val	Met	Ala	Trp	
			245						250					255		
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		260						265					270			
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	275						280					285				
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	290					295					300					
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Arg	Lys	Lys	Gln	Lys	Ile	Thr	Ile	Ala	Gly	Gln	Glu	Met	Glu	Val	Glu	
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		20						25					30			
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Ala	Thr	Trp	Leu	Leu	Thr	Cys	Pro	Val	Leu	Leu	Ile	His	Leu	Ser	Asn	
			165					170						175		
Leu	Thr	Gly	Leu	Lys	Asp	Asp	Tyr	Ser	Lys	Arg	Thr	Met	Gly	Leu	Leu	
		180						185					190			
Val	Ser	Asp	Val	Gly	Cys	Ile	Val	Trp	Gly	Ala	Thr	Ser	Ala	Met	Cys	
		195					200					205				
Thr	Gly	Trp	Thr	Lys	Ile	Leu	Phe	Phe	Leu	Ile	Ser	Leu	Ser	Tyr	Gly	
	210					215					220					
Met	Tyr	Thr	Tyr	Phe	His	Ala	Ala	Lys	Val	Tyr	Ile	Glu	Ala	Phe	His	
225					230					235					240	
Thr	Val	Pro	Lys	Gly	Ile	Cys	Arg	Glu	Leu	Val	Arg	Val	Met	Ala	Trp	
			245						250					255		
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		260						265					270			
Thr	Glu	Gly	Phe	Gly	His	Ile	Ser	Pro	Tyr	Gly	Ser	Ala	Ile	Gly	His	
	275						280					285				
Ser	Ile	Leu	Asp	Leu	Ile	Ala	Lys	Asn	Met	Trp	Gly	Val	Leu	Gly	Asn	
	290					295					300					
Tyr	Leu	Arg	Val	Lys	Ile	His	Glu	His	Ile	Leu	Leu	Tyr	Gly	Asp	Ile	
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Arg	Lys	Lys	Gln	Lys	Ile	Thr	Ile	Ala	Gly	Gln	Glu	Met	Glu	Val	Glu	
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Val	Ala	Thr	Gln	Asp	Gly	Pro	Asp	Tyr	Val	Phe	His	Arg	Ala	His	Glu	
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Arg	Met	Leu	Phe	Gln	Thr	Ser	Tyr	Thr	Leu	Glu	Asn	Asn	Gly	Ser	Val	
	50					55					60					
Ile	Cys	Ile	Pro	Asn	Asn	Gly	Gln	Cys	Phe	Cys	Leu	Ala	Trp	Leu	Lys	
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Thr	Trp	Lys	Ser	Thr	Cys	Gly	Trp	Glu	Thr	Ile	Tyr	Val	Ala	Thr	Ile	
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	130					135					140					
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Ala	Thr	Trp	Leu	Leu	Thr	Cys	Pro	Val	Leu	Leu	Ile	His	Leu	Ser	Asn	
				165					170						175	
Leu	Thr	Gly	Leu	Lys	Asp	Asp	Tyr	Ser	Lys	Arg	Thr	Met	Gly	Leu	Leu	
		180						185					190			
Val	Ser	Asp	Val	Gly	Cys	Ile	Val	Trp	Gly	Ala	Thr	Ser	Ala	Met	Cys	
		195					200					205				
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	210					215					220					
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225					230					235					240	
Thr	Val	Pro	Lys	Gly	Ile	Cys	Arg	Glu	Leu	Val	Arg	Val	Met	Ala	Trp	
			245						250					255		
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			260					265					270			
Thr	Glu	Gly	Phe	Gly	His	Ile	Ser	Pro	Tyr	Gly	Ser	Ala	Ile	Gly	His	
	275						280					285				
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	290					295					300					
Tyr	Leu	Arg	Val	Lys	Ile	His	Glu	His	Ile	Leu	Leu	Tyr	Gly	Asp	Ile	
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Arg	Lys	Lys	Gln	Lys	Ile	Thr	Ile	Ala	Gly	Gln	Glu	Met	Glu	Val	Glu	
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Glu	Arg	Arg	Pro	Pro	Ser	Glu	Arg	Asn	Thr	Pro	Tyr	Ala	Asn	Ile	Lys	
	35						40					45				
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Trp	Val	Val	Gly	Pro	Ser	Asp	Gln	Cys	Tyr	Cys	Arg	Ala	Trp	Ser	Lys	
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Ser	His	Gly	Thr	Asp	Arg	Glu	Gly	Glu	Ala	Ala	Val	Val	Trp	Ala	Tyr	

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130						135						140					
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Ala	Met	Leu	Tyr	Leu	Asn	Asp	Gly	Gln	Met	Val	Pro	Trp	Leu	Arg	Tyr		
165						170						175					
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Val	Ser	Asp	Ile	Gly	Thr	Ile	Val	Phe	Gly	Thr	Ser	Ala	Ala	Leu	Ala		
210						215						220					
Pro	Pro	Asn	His	Val	Lys	Val	Ile	Leu	Phe	Thr	Ile	Gly	Leu	Leu	Tyr		
225						230						235					
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245						250						255					
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Trp	Thr	Tyr	Phe	Val	Ser	Trp	Ala	Met	Phe	Pro	Ile	Leu	Phe	Ile	Leu		
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325						330						335					
Leu	Thr	Lys	Lys	Asn	Lys	Ile	Asn	Ile	Ala	Gly	Asp	Asn	Val	Glu	Val		
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35						40						45					
Ile	Ala	Val	Ser	Thr	Ile	Leu	Val	Pro	Val	Val	Ser	Ile	Ala	Ser	Tyr		
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Thr	Gly	Leu	Ala	Ser	Gly	Leu	Thr	Ile	Ser	Val	Leu	Glu	Met	Pro	Ala		
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Gly	His	Phe	Ala	Glu	Gly	Ser	Ser	Val	Met	Leu	Gly	Gly	Glu	Glu	Val		
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Asp	Gly	Val	Val	Thr	Met	Trp	Gly	Arg	Tyr	Leu	Thr	Trp	Ala	Leu	Ser	
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Thr	Lys	Leu	Phe	Thr	Ala	Ile	Thr	Phe	Asp	Ile	Ala	Met	Cys	Val	Thr	
	130					135					140					
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Trp	Tyr	Ala	Ile	Ser	Cys	Ala	Cys	Phe	Leu	Val	Val	Leu	Tyr	Ile	Leu	
				165					170					175		
Leu	Val	Glu	Trp	Ala	Gln	Asp	Ala	Lys	Ala	Ala	Gly	Thr	Ala	Asp	Met	
		180						185					190			
Phe	Asn	Thr	Leu	Lys	Leu	Leu	Thr	Val	Val	Met	Trp	Leu	Gly	Tyr	Pro	
		195					200					205				
Ile	Val	Trp	Ala	Leu	Gly	Val	Glu	Gly	Ile	Ala	Val	Leu	Pro	Val	Gly	
	210					215					220					
Val	Thr	Ser	Trp	Gly	Tyr	Ser	Phe	Leu	Asp	Ile	Val	Ala	Lys	Tyr	Ile	
225					230					235					240	
Phe	Ala	Phe	Leu	Leu	Leu	Asn	Tyr	Leu	Thr	Ser	Asn	Glu	Ser	Val	Val	
			245						250					255		
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Leu	Leu	Ala	Ser	Ser	Leu	Tyr	Ile	Asn	Ile	Ala	Leu	Ala	Gly	Leu	Ser	
		35				40						45				
Ile	Leu	Leu	Phe	Val	Phe	Met	Thr	Arg	Gly	Leu	Asp	Asp	Pro	Arg	Ala	
50					55						60					
Lys	Leu	Ile	Ala	Val	Ser	Thr	Ile	Leu	Val	Pro	Val	Val	Ser	Ile	Ala	
65					70				75					80		
Ser	Tyr	Thr	Gly	Leu	Ala	Ser	Gly	Leu	Thr	Ile	Ser	Val	Leu	Glu	Met	
			85					90					95			
Pro	Ala	Gly	His	Phe	Ala	Glu	Gly	Ser	Ser	Val	Met	Leu	Gly	Gly	Glu	
		100					105						110			
Glu	Val	Asp	Gly	Val	Val	Thr	Met	Trp	Gly	Arg	Tyr	Leu	Thr	Trp	Ala	
	115						120					125				
Leu	Ser	Thr	Pro	Met	Ile	Leu	Leu	Ala	Leu	Gly	Leu	Leu	Ala	Gly	Ser	
	130					135					140					
Asn	Ala	Thr	Lys	Leu	Phe	Thr	Ala	Ile	Thr	Phe	Asp	Ile	Ala	Met	Cys	
145				150						155				160		
Val	Thr	Gly	Leu	Ala	Ala	Ala	Leu	Thr	Thr	Ser	Ser	His	Leu	Met	Arg	

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165							170					175				
Trp	Phe	Trp	Tyr	Ala	Ile	Ser	Cys	Ala	Cys	Phe	Leu	Val	Val	Leu	Tyr	
			180					185					190			
Ile	Leu	Leu	Val	Glu	Trp	Ala	Gln	Asp	Ala	Lys	Ala	Ala	Gly	Thr	Ala	
		195					200					205				
Asp	Met	Phe	Asn	Thr	Leu	Lys	Leu	Leu	Thr	Val	Val	Met	Trp	Leu	Gly	
	210					215					220					
Tyr	Pro	Ile	Val	Trp	Ala	Leu	Gly	Val	Glu	Gly	Ile	Ala	Val	Leu	Pro	
225					230					235					240	
Val	Gly	Val	Thr	Ser	Trp	Gly	Tyr	Ser	Phe	Leu	Asp	Ile	Val	Ala	Lys	
				245					250					255		
Tyr	Ile	Phe	Ala	Phe	Leu	Leu	Leu	Asn	Tyr	Leu	Thr	Ser	Asn	Glu	Ser	
			260					265					270			
Val	Val	Ser	Gly	Ser	Ile	Leu	Asp	Val	Pro	Ser	Ala	Ser	Gly	Thr	Pro	
		275					280					285				
Ala	Asp	Asp	Ala	Ala	Ala	Lys	Ser	Arg	Ile	Thr	Ser	Glu	Gly	Glu	Tyr	
	290					295					300					
Ile	Pro	Leu	Asp	Gln	Ile	Asp	Ile	Asn	Val	Val	Ser	Lys	Gly	Glu	Glu	
305					310					315					320	
Leu	Phe	Thr	Gly	Val	Val	Pro	Ile	Leu	Val	Glu	Leu	Asp	Gly	Asp	Val	
				325					330					335		
Asn	Gly	His	Lys	Phe	Ser	Val	Ser	Gly	Glu	Gly	Glu	Gly	Asp	Ala	Thr	
			340					345					350			
Tyr	Gly	Lys	Leu	Thr	Leu	Lys	Phe	Ile	Cys	Thr	Thr	Gly	Lys	Leu	Pro	
		355					360					365				
Val	Pro	Trp	Pro	Thr	Leu	Val	Thr	Thr	Phe	Gly	Tyr	Gly	Leu	Gln	Cys	
	370					375					380					
Phe	Ala	Arg	Tyr	Pro	Asp	His	Met	Lys	Gln	His	Asp	Phe	Phe	Lys	Ser	
385					390					395					400	
Ala	Met	Pro	Glu	Gly	Tyr	Val	Gln	Glu	Arg	Thr	Ile	Phe	Phe	Lys	Asp	
				405					410					415		
Asp	Gly	Asn	Tyr	Lys	Thr	Arg	Ala	Glu	Val	Lys	Phe	Glu	Gly	Asp	Thr	
			420					425					430			
Leu	Val	Asn	Arg	Ile	Glu	Leu	Lys	Gly	Ile	Asp	Phe	Lys	Glu	Asp	Gly	
		435					440					445				
Asn	Ile	Leu	Gly	His	Lys	Leu	Glu	Tyr	Asn	Tyr	Asn	Ser	His	Asn	Val	
	450					455					460					
Tyr	Ile	Met	Ala	Asp	Lys	Gln	Lys	Asn	Gly	Ile	Lys	Val	Asn	Phe	Lys	
465					470					475					480	
Ile	Arg	His	Asn	Ile	Glu	Asp	Gly	Ser	Val	Gln	Leu	Ala	Asp	His	Tyr	
				485					490					495		
Gln	Gln	Asn	Thr	Pro	Ile	Gly	Asp	Gly	Pro	Val	Leu	Leu	Pro	Asp	Asn	
			500					505					510			
His	Tyr	Leu	Ser	Tyr	Gln	Ser	Ala	Leu	Ser	Lys	Asp	Pro	Asn	Glu	Lys	
		515					520					525				
Arg	Asp	His	Met	Val	Leu	Leu	Glu	Phe	Val	Thr	Ala	Ala	Gly	Ile	Thr	
	530					535					540					
Leu	Gly	Met	Asp	Glu	Leu	Tyr	Lys	Phe	Cys	Tyr	Glu	Asn	Glu	Val		
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Leu	Ala	Ser	Ser	Leu	Tyr	Ile	Asn	Ile	Ala	Leu	Ala	Gly	Leu	Ser	Ile		
			20					25					30				
Leu	Leu	Phe	Val	Phe	Met	Thr	Arg	Gly	Leu	Asp	Asp	Pro	Arg	Ala	Lys		
		35					40					45					
Leu	Ile	Ala	Val	Ser	Thr	Ile	Leu	Val	Pro	Val	Val	Ser	Ile	Ala	Ser		
	50					55					60						
Tyr	Thr	Gly	Leu	Ala	Ser	Gly	Leu	Thr	Ile	Ser	Val	Leu	Glu	Met	Pro		
65					70					75					80		
Ala	Gly	His	Phe	Ala	Glu	Gly	Ser	Ser	Val	Met	Leu	Gly	Gly	Glu	Glu		
				85					90					95			
Val	Asp	Gly	Val	Val	Thr	Met	Trp	Gly	Arg	Tyr	Leu	Thr	Trp	Ala	Leu		
			100					105					110				
Ser	Thr	Pro	Met	Ile	Leu	Leu	Ala	Leu	Gly	Leu	Leu	Ala	Gly	Ser	Asn		
		115					120					125					
Ala	Thr	Lys	Leu	Phe	Thr	Ala	Ile	Thr	Phe	Asp	Ile	Ala	Met	Cys	Val		
	130					135					140						
Thr	Gly	Leu	Ala	Ala	Ala	Leu	Thr	Thr	Ser	Ser	His	Leu	Met	Arg	Trp		
145					150					155					160		
Phe	Trp	Tyr	Ala	Ile	Ser	Cys	Ala	Cys	Phe	Leu	Val	Val	Leu	Tyr	Ile		
			165						170					175			
Leu	Leu	Val	Glu	Trp	Ala	Gln	Asp	Ala	Lys	Ala	Ala	Gly	Thr	Ala	Asp		
		180					185						190				
Met	Phe	Asn	Thr	Leu	Lys	Leu	Leu	Thr	Val	Val	Met	Trp	Leu	Gly	Tyr		
		195					200					205					
Pro	Ile	Val	Trp	Ala	Leu	Gly	Val	Glu	Gly	Ile	Ala	Val	Leu	Pro	Val		
	210					215					220						
Gly	Val	Thr	Ser	Trp	Gly	Tyr	Ser	Phe	Leu	Asp	Ile	Val	Ala	Lys	Tyr		
225					230					235					240		
Ile	Phe	Ala	Phe	Leu	Leu	Leu	Asn	Tyr	Leu	Thr	Ser	Asn	Glu	Ser	Val		
			245						250					255			
Val	Ser	Gly	Ser	Ile	Leu	Asp	Val	Pro	Ser	Ala	Ser	Gly	Thr	Pro	Ala		
			260					265					270				
Asp	Asp	Ala	Ala	Ala	Lys	Ser	Arg	Ile	Thr	Ser	Glu	Gly	Glu	Tyr	Ile		
		275					280					285					
Pro	Leu	Asp	Gln	Ile	Asp	Ile	Asn	Val	Val	Ser	Lys	Gly	Glu	Glu	Leu		
	290					295					300						
Phe	Thr	Gly	Val	Val	Pro	Ile	Leu	Val	Glu	Leu	Asp	Gly	Asp	Val	Asn		
305					310					315					320		
Gly	His	Lys	Phe	Ser	Val	Ser	Gly	Glu	Gly	Glu	Gly	Asp	Ala	Thr	Tyr		
			325						330					335			
Gly	Lys	Leu	Thr	Leu	Lys	Phe	Ile	Cys	Thr	Thr	Gly	Lys	Leu	Pro	Val		
		340						345					350				
Pro	Trp	Pro	Thr	Leu	Val	Thr	Thr	Phe	Gly	Tyr	Gly	Leu	Gln	Cys	Phe		
		355					360					365					

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Ala	Arg	Tyr	Pro	Asp	His	Met	Lys	Gln	His	Asp	Phe	Phe	Lys	Ser	Ala	
370						375					380					
Met	Pro	Glu	Gly	Tyr	Val	Gln	Glu	Arg	Thr	Ile	Phe	Phe	Lys	Asp	Asp	
385					390					395					400	
Gly	Asn	Tyr	Lys	Thr	Arg	Ala	Glu	Val	Lys	Phe	Glu	Gly	Asp	Thr	Leu	
				405					410					415		
Val	Asn	Arg	Ile	Glu	Leu	Lys	Gly	Ile	Asp	Phe	Lys	Glu	Asp	Gly	Asn	
			420					425					430			
Ile	Leu	Gly	His	Lys	Leu	Glu	Tyr	Asn	Tyr	Asn	Ser	His	Asn	Val	Tyr	
		435					440					445				
Ile	Met	Ala	Asp	Lys	Gln	Lys	Asn	Gly	Ile	Lys	Val	Asn	Phe	Lys	Ile	
	450					455					460					
Arg	His	Asn	Ile	Glu	Asp	Gly	Ser	Val	Gln	Leu	Ala	Asp	His	Tyr	Gln	
465					470					475					480	
Gln	Asn	Thr	Pro	Ile	Gly	Asp	Gly	Pro	Val	Leu	Leu	Pro	Asp	Asn	His	
				485					490					495		
Tyr	Leu	Ser	Tyr	Gln	Ser	Ala	Leu	Ser	Lys	Asp	Pro	Asn	Glu	Lys	Arg	
			500					505					510			
Asp	His	Met	Val	Leu	Leu	Glu	Phe	Val	Thr	Ala	Ala	Gly	Ile	Thr	Leu	
		515					520					525				
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Ile	Gln	Ile	Phe	Ala	Asn	Thr	Ser	Thr	Leu	His	Gly	Ile	Arg	His	Ile	
			20					25					30			
Phe	Val	Tyr	Gly	Pro	Leu	Thr	Ile	Arg	Arg	Val	Leu	Trp	Ala	Val	Ala	
		35					40					45				
Phe	Val	Gly	Ser	Leu	Gly	Leu	Leu	Leu	Val	Glu	Ser	Ser	Glu	Arg	Val	
	50					55					60					
Ser	Tyr	Tyr	Phe	Ser	Tyr	Gln	His	Val	Thr	Lys	Val	Asp	Glu	Val	Val	
65					70					75					80	
Ala	Gln	Ser	Leu	Val	Phe	Pro	Ala	Val	Thr	Leu	Cys	Asn	Leu	Asn	Gly	
			85						90					95		
Phe	Arg	Phe	Ser	Arg	Leu	Thr	Thr	Asn	Asp	Leu	Tyr	His	Ala	Gly	Glu	
			100					105					110			
Leu	Leu	Ala	Leu	Leu	Asp	Val	Asn	Leu	Gln	Ile	Pro	Asp	Pro	His	Leu	
		115					120					125				
Ala	Asp	Pro	Thr	Val	Leu	Glu	Ala	Leu	Arg	Gln	Lys	Ala	Asn	Phe	Lys	
	130						135					140				
His	Tyr	Lys	Pro	Lys	Gln	Phe	Ser	Met	Leu	Glu	Phe	Leu	His	Arg	Val	
145					150					155					160	
Gly	His	Asp	Leu	Lys	Asp	Met	Met	Leu	Tyr	Cys	Lys	Phe	Lys	Gly	Gln	
			165						170					175		
Glu	Cys	Gly	His	Gln	Asp	Phe	Thr	Thr	Val	Phe	Thr	Lys	Tyr	Gly	Lys	

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Phe	Arg	Leu	Pro	Leu	Ile	Leu	Ile	Gln	Leu	Leu	Val	Leu	Leu	Gly	Thr	
	35						40					45				
Leu	Gly	Tyr	Phe	Ala	Leu	Glu	Asn	Tyr	Ser	Leu	Met	Gln	Ala	Phe	Phe	
	50					55				60						
Gln	Thr	Thr	Tyr	Thr	Met	Thr	Ala	Thr	Gly	Phe	Gly	Ala	Leu	Asn	Glu	
65					70					75					80	
Ser	Gln	Phe	Gly	Pro	Ile	Ser	Ile	Phe	Leu	Thr	Ser	Ile	Leu	Met	Phe	
				85					90					95		
Cys	Gly	Thr	Gly	Ile	Ile	Ala	Phe	Ser	Val	Ala	Ile	Leu	Val	Ser	Val	
			100					105					110			
Val	Asn	Lys	Gly	Thr	Leu	Thr	Arg	Leu	Ile	Lys	Glu	Lys	Gly	Met	Ile	
		115					120					125				
Tyr	Lys	Ile	Ala	Arg	Leu	Lys	Asp	His	Tyr	Val	Ile	Cys	Tyr	His	Asn	
	130					135					140					
Glu	Tyr	Thr	Ile	Glu	Leu	Ser	Lys	Gln	Phe	Arg	Ser	Ala	Gln	Ile	Pro	
145					150					155					160	
Phe	Val	Val	Val	Asp	Asn	Asp	Pro	Ser	Phe	Glu	Glu	Glu	Ala	Ile	Lys	
				165					170					175		
His	Lys	Tyr	Pro	Tyr	Tyr	Ile	Ile	Gly	Asp	Pro	His	Thr	Asn	Leu	Ala	
			180					185					190			
Met	Leu	Lys	Thr	His	Leu	Ser	Ser	Ala	Arg	Gly	Val	Val	Ala	Leu	Ser	
	195						200					205				
Lys	Ile	Leu	Pro	Val	Asn	Val	Ala	Leu	Met	Val	Ser	Val	Arg	Leu	Phe	
	210					215					220					
Glu	Lys	Glu	Leu	Lys	Arg	Lys	Pro	Tyr	Tyr	Ile	Ile	Ala	Ser	Ala	His	
225					230					235					240	
Ser	Asp	Glu	Gly	Leu	Glu	Lys	Leu	Lys	Lys	Leu	Gly	Ala	Asp	Met	Val	
				245					250					255		
Val	Ser	Pro	Thr	Lys	Leu	Met	Ala	Gln	Arg	Val	Ser	Ala	Met	Ala	Val	
			260					265					270			
Arg	Pro	Asp	Met	Glu	Asn	Ile	Leu	Glu	Arg	Phe	Ile	Asn	Lys	Lys	Asp	
		275					280					285				
Thr	Leu	Leu	Asp	Leu	Glu	Glu	Val	Ile	Val	Pro	Lys	Thr	Ser	Trp	Leu	
	290					295					300					
Val	Leu	Arg	Lys	Leu	Lys	Glu	Ala	His	Phe	Arg	Glu	Ile	Ala	Lys	Ala	
305					310					315					320	
Phe	Val	Ile	Gly	Ile	Thr	Gln	Lys	Asp	Gly	Lys	Tyr	Ile	Pro	Met	Pro	
				325					330					335		
Asp	Gly	Glu	Thr	Ile	Ile	Ala	Ser	Glu	Ser	Lys	Leu	Leu	Met	Val	Gly	
			340					345					350			
Thr	Ser	Glu	Gly	Val	Ala	Thr	Cys	Lys	Gln	Leu	Ile	Thr	Ser	His	Gln	
		355					360					365				
Lys	Pro	Lys	Glu	Val	Asp	Tyr	Ile	Ser	Leu							
	370					375										
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<211> LENGTH: 661																
<212> TYPE: PRT																
<213> ORGANISM: Homo sapiens																
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Met	Asp	Leu	Gln	Gln	Ser	Thr	Thr	Ile	Thr	Ser	Leu	Glu	Lys	Trp	Cys	
1				5					10					15		

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Leu	Asp	Glu	Ser	Leu	Ser	Gly	Cys	Arg	Arg	His	Tyr	Ser	Val	Lys	Lys	
			20					25					30			
Lys	Leu	Lys	Leu	Ile	Arg	Val	Leu	Gly	Leu	Phe	Met	Gly	Leu	Val	Ala	
		35					40					45				
Ile	Ser	Thr	Val	Ser	Phe	Ser	Ile	Ser	Ala	Phe	Ser	Glu	Thr	Asp	Thr	
	50					55					60					
Gln	Ser	Thr	Gly	Glu	Ala	Ser	Val	Val	Ser	Gly	Pro	Arg	Val	Ala	Gln	
65					70					75					80	
Gly	Tyr	His	Gln	Arg	Thr	Leu	Leu	Asp	Leu	Asn	Asp	Lys	Ile	Leu	Asp	
			85						90					95		
Tyr	Thr	Pro	Gln	Pro	Pro	Leu	Ser	Lys	Glu	Gly	Glu	Ser	Glu	Asn	Ser	
			100					105						110		
Thr	Asp	His	Ala	Gln	Gly	Asp	Tyr	Pro	Lys	Asp	Ile	Phe	Ser	Leu	Glu	
		115					120					125				
Glu	Arg	Arg	Lys	Gly	Ala	Ile	Ile	Leu	His	Val	Ile	Gly	Met	Ile	Tyr	
	130					135					140					
Met	Phe	Ile	Ala	Leu	Ala	Ile	Val	Cys	Asp	Glu	Phe	Phe	Val	Pro	Ser	
145					150					155					160	
Leu	Thr	Val	Ile	Thr	Glu	Lys	Leu	Gly	Ile	Ser	Asp	Asp	Val	Ala	Gly	
			165						170					175		
Ala	Thr	Phe	Met	Ala	Ala	Gly	Gly	Ser	Ala	Pro	Glu	Leu	Phe	Thr	Ser	
			180					185					190			
Leu	Ile	Gly	Val	Phe	Ile	Ala	His	Ser	Asn	Val	Gly	Ile	Gly	Thr	Ile	
		195					200					205				
Val	Gly	Ser	Ala	Val	Phe	Asn	Ile	Leu	Phe	Val	Ile	Gly	Met	Cys	Ala	
	210					215					220					
Leu	Phe	Ser	Arg	Glu	Ile	Leu	Asn	Leu	Thr	Trp	Trp	Pro	Leu	Phe	Arg	
225					230					235					240	
Asp	Val	Ser	Phe	Tyr	Ile	Val	Asp	Leu	Ile	Met	Leu	Ile	Ile	Phe	Phe	
			245						250					255		
Leu	Asp	Asn	Val	Ile	Met	Trp	Trp	Glu	Ser	Leu	Leu	Leu	Leu	Thr	Ala	
			260					265						270		
Tyr	Phe	Cys	Tyr	Val	Val	Phe	Met	Lys	Phe	Asn	Val	Gln	Val	Glu	Lys	
		275					280					285				
Trp	Val	Lys	Gln	Met	Ile	Asn	Arg	Asn	Lys	Val	Val	Lys	Val	Thr	Ala	
	290					295					300					
Pro	Glu	Ala	Gln	Ala	Lys	Pro	Ser	Ala	Ala	Arg	Asp	Lys	Asp	Glu	Pro	
305					310					315					320	
Thr	Leu	Pro	Ala	Lys	Pro	Arg	Leu	Gln	Arg	Gly	Gly	Ser	Ser	Ala	Ser	
			325						330					335		
Leu	His	Asn	Ser	Leu	Met	Arg	Asn	Ser	Ile	Phe	Gln	Leu	Met	Ile	His	
			340					345					350			
Thr	Leu	Asp	Pro	Leu	Ala	Glu	Glu	Leu	Gly	Ser	Tyr	Gly	Lys	Leu	Lys	
		355					360					365				
Tyr	Tyr	Asp	Thr	Met	Thr	Glu	Glu	Gly	Arg	Phe	Arg	Glu	Lys	Ala	Ser	
	370					375					380					
Ile	Leu	His	Lys	Ile	Ala	Lys	Lys	Lys	Cys	His	Val	Asp	Glu	Asn	Glu	
385					390					395					400	
Arg	Gln	Asn	Gly	Ala	Ala	Asn	His	Val	Glu	Lys	Ile	Glu	Leu	Pro	Asn	
			405						410					415		

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Ser	Thr	Ser	Thr	Asp	Val	Glu	Met	Thr	Pro	Ser	Ser	Asp	Ala	Ser	Glu	
			420					425					430			
Pro	Val	Gln	Asn	Gly	Asn	Leu	Ser	His	Asn	Ile	Glu	Gly	Ala	Glu	Ala	
		435					440					445				
Gln	Thr	Ala	Asp	Glu	Glu	Glu	Asp	Gln	Pro	Leu	Ser	Leu	Ala	Trp	Pro	
	450						455				460					
Ser	Glu	Thr	Arg	Lys	Gln	Val	Thr	Phe	Leu	Ile	Val	Phe	Pro	Ile	Val	
465					470					475					480	
Phe	Pro	Leu	Trp	Ile	Thr	Leu	Pro	Asp	Val	Arg	Lys	Pro	Ser	Ser	Arg	
				485					490						495	
Lys	Phe	Phe	Pro	Ile	Thr	Phe	Phe	Gly	Ser	Ile	Thr	Trp	Ile	Ala	Val	
			500					505					510			
Phe	Ser	Tyr	Leu	Met	Val	Trp	Trp	Ala	His	Gln	Val	Gly	Glu	Thr	Ile	
		515					520					525				
Gly	Ile	Ser	Glu	Glu	Ile	Met	Gly	Leu	Thr	Ile	Leu	Ala	Ala	Gly	Thr	
	530					535					540					
Ser	Ile	Pro	Asp	Leu	Ile	Thr	Ser	Val	Ile	Val	Ala	Arg	Lys	Gly	Leu	
545					550					555					560	
Gly	Asp	Met	Ala	Val	Ser	Ser	Ser	Val	Gly	Ser	Asn	Ile	Phe	Asp	Ile	
				565					570					575		
Thr	Val	Gly	Leu	Pro	Leu	Pro	Trp	Leu	Leu	Tyr	Thr	Val	Ile	His	Arg	
			580					585					590			
Phe	Gln	Pro	Val	Ala	Val	Ser	Ser	Asn	Gly	Leu	Phe	Cys	Ala	Ile	Val	
		595					600					605				
Leu	Leu	Phe	Ile	Met	Leu	Leu	Phe	Val	Ile	Leu	Ser	Ile	Ala	Leu	Cys	
	610					615					620					
Lys	Trp	Arg	Met	Asn	Lys	Ile	Leu	Gly	Phe	Ile	Met	Phe	Gly	Leu	Tyr	
625					630					635					640	
Phe	Val	Phe	Leu	Val	Val	Ser	Val	Leu	Leu	Glu	Asp	Arg	Ile	Leu	Thr	
				645					650					655		
Cys	Pro	Val	Ser	Ile												
			660													
<210> SEQ ID NO 22																
<211> LENGTH: 925																
<212> TYPE: PRT																
<213> ORGANISM: Homo sapiens																
<400> SEQUENCE: 22																
Met	Ala	Trp	Leu	Arg	Leu	Gln	Pro	Leu	Thr	Ser	Ala	Phe	Leu	His	Phe	
1				5					10					15		
Gly	Leu	Val	Thr	Phe	Val	Leu	Phe	Leu	Asn	Gly	Leu	Arg	Ala	Glu	Ala	
			20					25					30			
Gly	Gly	Ser	Gly	Asp	Val	Pro	Ser	Thr	Gly	Gln	Asn	Asn	Glu	Ser	Cys	
		35					40					45				
Ser	Gly	Ser	Ser	Asp	Cys	Lys	Glu	Gly	Val	Ile	Leu	Pro	Ile	Trp	Tyr	
	50					55				60						
Pro	Glu	Asn	Pro	Ser	Leu	Gly	Asp	Lys	Ile	Ala	Arg	Val	Ile	Val	Tyr	
65					70				75					80		
Phe	Val	Ala	Leu	Ile	Tyr	Met	Phe	Leu	Gly	Val	Ser	Ile	Ile	Ala	Asp	
			85					90					95			
Arg	Phe	Met	Ala	Ser	Ile	Glu	Val	Ile	Thr	Ser	Gln	Glu	Arg	Glu	Val	
			100				105						110			

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Thr	Ile	Lys	Lys	Pro	Asn	Gly	Glu	Thr	Ser	Thr	Thr	Thr	Ile	Arg	Val	
		115					120						125			
Trp	Asn	Glu	Thr	Val	Ser	Asn	Leu	Thr	Leu	Met	Ala	Leu	Gly	Ser	Ser	
	130					135					140					
Ala	Pro	Glu	Ile	Leu	Leu	Ser	Leu	Ile	Glu	Val	Cys	Gly	His	Gly	Phe	
145					150					155					160	
Ile	Ala	Gly	Asp	Leu	Gly	Pro	Ser	Thr	Ile	Val	Gly	Ser	Ala	Ala	Phe	
				165					170					175		
Asn	Met	Phe	Ile	Ile	Ile	Gly	Ile	Cys	Val	Tyr	Val	Ile	Pro	Asp	Gly	
		180						185					190			
Glu	Thr	Arg	Lys	Ile	Lys	His	Leu	Arg	Val	Phe	Phe	Ile	Thr	Ala	Ala	
		195					200					205				
Trp	Ser	Ile	Phe	Ala	Tyr	Ile	Trp	Leu	Tyr	Met	Ile	Leu	Ala	Val	Phe	
	210					215					220					
Ser	Pro	Gly	Val	Val	Gln	Val	Trp	Glu	Gly	Leu	Leu	Thr	Leu	Phe	Phe	
225					230					235					240	
Phe	Pro	Val	Cys	Val	Leu	Leu	Ala	Trp	Val	Ala	Asp	Lys	Arg	Leu	Leu	
				245					250					255		
Phe	Tyr	Lys	Tyr	Met	His	Lys	Lys	Tyr	Arg	Thr	Asp	Lys	His	Arg	Gly	
			260					265					270			
Ile	Ile	Ile	Glu	Thr	Glu	Gly	Asp	His	Pro	Lys	Gly	Ile	Glu	Met	Asp	
		275					280					285				
Gly	Lys	Met	Met	Asn	Ser	His	Phe	Leu	Asp	Gly	Asn	Leu	Val	Pro	Leu	
	290					295					300					
Glu	Gly	Lys	Glu	Val	Asp	Glu	Ser	Arg	Arg	Glu	Met	Ile	Arg	Ile	Leu	
305					310					315					320	
Lys	Asp	Leu	Lys	Gln	Lys	His	Pro	Glu	Lys	Asp	Leu	Asp	Gln	Leu	Val	
				325					330					335		
Glu	Met	Ala	Asn	Tyr	Tyr	Ala	Leu	Ser	His	Gln	Gln	Lys	Ser	Arg	Ala	
			340					345					350			
Phe	Tyr	Arg	Ile	Gln	Ala	Thr	Arg	Met	Met	Thr	Gly	Ala	Gly	Asn	Ile	
		355					360					365				
Leu	Lys	Lys	His	Ala	Ala	Glu	Gln	Ala	Lys	Lys	Ala	Ser	Ser	Met	Ser	
	370					375					380					
Glu	Val	His	Thr	Asp	Glu	Pro	Glu	Asp	Phe	Ile	Ser	Lys	Val	Phe	Phe	
385					390					395					400	
Asp	Pro	Cys	Ser	Tyr	Gln	Cys	Leu	Glu	Asn	Cys	Gly	Ala	Val	Leu	Leu	
				405					410					415		
Thr	Val	Val	Arg	Lys	Gly	Gly	Asp	Met	Ser	Lys	Thr	Met	Tyr	Val	Asp	
			420					425					430			
Tyr	Lys	Thr	Glu	Asp	Gly	Ser	Ala	Asn	Ala	Gly	Ala	Asp	Tyr	Glu	Phe	
		435					440					445				
Thr	Glu	Gly	Thr	Val	Val	Leu	Lys	Pro	Gly	Glu	Thr	Gln	Lys	Glu	Phe	
	450					455					460					
Ser	Val	Gly	Ile	Ile	Asp	Asp	Asp	Ile	Phe	Glu	Glu	Asp	Glu	His	Phe	
465					470					475					480	
Phe	Val	Arg	Leu	Ser	Asn	Val	Arg	Ile	Glu	Glu	Glu	Gln	Pro	Glu	Glu	
				485					490					495		
Gly	Met	Pro	Pro	Ala	Ile	Phe	Asn	Ser	Leu	Pro	Leu	Pro	Arg	Ala	Val	
			500					505					510			

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Leu	Ala	Ser	Pro	Cys	Val	Ala	Thr	Val	Thr	Ile	Leu	Asp	Asp	Asp	His
		515					520					525			
Ala	Gly	Ile	Phe	Thr	Phe	Glu	Cys	Asp	Thr	Ile	His	Val	Ser	Glu	Ser
	530					535					540				
Ile	Gly	Val	Met	Glu	Val	Lys	Val	Leu	Arg	Thr	Ser	Gly	Ala	Arg	Gly
545					550					555					560
Thr	Val	Ile	Val	Pro	Phe	Arg	Thr	Val	Glu	Gly	Thr	Ala	Lys	Gly	Gly
				565					570					575	
Gly	Glu	Asp	Phe	Glu	Asp	Thr	Tyr	Gly	Glu	Leu	Glu	Phe	Lys	Asn	Asp
			580					585					590		
Glu	Thr	Val	Lys	Thr	Ile	His	Ile	Lys	Val	Ile	Asp	Asp	Glu	Ala	Tyr
		595					600					605			
Glu	Lys	Asn	Lys	Asn	Tyr	Phe	Ile	Glu	Met	Met	Gly	Pro	Arg	Met	Val
	610					615					620				
Asp	Met	Ser	Phe	Gln	Lys	Ala	Leu	Leu	Leu	Ser	Pro	Asp	Arg	Lys	Leu
625					630					635					640
Thr	Met	Glu	Glu	Glu	Glu	Ala	Lys	Arg	Ile	Ala	Glu	Met	Gly	Lys	Pro
				645					650					655	
Val	Leu	Gly	Glu	His	Pro	Lys	Leu	Glu	Val	Ile	Ile	Glu	Glu	Ser	Tyr
			660					665					670		
Glu	Phe	Lys	Thr	Thr	Val	Asp	Lys	Leu	Ile	Lys	Lys	Thr	Asn	Leu	Ala
		675					680					685			
Leu	Val	Val	Gly	Thr	His	Ser	Trp	Arg	Asp	Gln	Phe	Met	Glu	Ala	Ile
	690					695					700				
Thr	Val	Ser	Ala	Ala	Gly	Asp	Glu	Asp	Glu	Asp	Glu	Ser	Gly	Glu	Glu
705					710					715					720
Arg	Leu	Pro	Ser	Cys	Phe	Asp	Tyr	Val	Met	His	Phe	Leu	Thr	Val	Phe
				725					730					735	
Trp	Lys	Val	Leu	Phe	Ala	Cys	Val	Pro	Pro	Thr	Glu	Tyr	Cys	His	Gly
			740					745					750		
Trp	Ala	Cys	Phe	Ala	Val	Ser	Ile	Leu	Ile	Ile	Gly	Met	Leu	Thr	Ala
		755					760					765			
Ile	Ile	Gly	Asp	Leu	Ala	Ser	His	Phe	Gly	Cys	Thr	Ile	Gly	Leu	Lys
	770					775					780				
Asp	Ser	Val	Thr	Ala	Val	Val	Phe	Val	Ala	Phe	Gly	Thr	Ser	Val	Pro
785					790					795					800
Asp	Thr	Phe	Ala	Ser	Lys	Ala	Ala	Ala	Leu	Gln	Asp	Val	Tyr	Ala	Asp
				805					810					815	
Ala	Ser	Ile	Gly	Asn	Val	Thr	Gly	Ser	Asn	Ala	Val	Asn	Val	Phe	Leu
			820					825					830		
Gly	Ile	Gly	Leu	Ala	Trp	Ser	Val	Ala	Ala	Ile	Tyr	Trp	Ala	Leu	Gln
		835					840					845			
Gly	Gln	Glu	Phe	His	Val	Ser	Ala	Gly	Thr	Leu	Ala	Phe	Ser	Val	Thr
	850						855				860				
Leu	Phe	Thr	Ile	Phe	Ala	Phe	Val	Cys	Ile	Ser	Val	Leu	Leu	Tyr	Arg
865					870					875					880
Arg	Arg	Pro	His	Leu	Gly	Gly	Glu	Leu	Gly	Gly	Pro	Arg	Gly	Cys	Lys
				885					890					895	
Leu	Ala	Thr	Thr	Trp	Leu	Phe	Val	Ser	Leu	Trp	Leu	Leu	Tyr	Ile	Leu
			900					905					910		
Phe	Ala	Thr	Leu	Glu	Ala	Tyr	Cys	Tyr	Ile	Lys	Gly	Phe			

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915	920	925
<210> SEQ ID NO 23		
<211> LENGTH: 409		
<212> TYPE: PRT		
<213> ORGANISM: Moraxella catarrhalis		
<400> SEQUENCE: 23		
Met Phe Ala Gln Phe Lys Arg Phe Leu Glu Leu Glu Ala Ala Gly Gly		
1 5 10 15		
Ile Val Leu Ala Ala Ala Ala Leu Leu Ala Met Ile Ile Ala Asn Ser		
20 25 30		
Pro Leu Asp Glu Met Tyr His Ala Phe Ile His Ala Pro Val Val Val		
35 40 45		
Gln Ile Gly Thr Phe Gln Ile Ala Lys Asp Ala His His Trp Ile Asn		
50 55 60		
Asp Gly Leu Met Ala Ile Phe Phe Phe Leu Val Gly Leu Glu Leu Lys		
65 70 75 80		
Arg Glu Ala Leu Ile Gly Glu Leu Ser Asp Val Lys Gln Ile Leu Met		
85 90 95		
Pro Ala Leu Ala Ala Val Gly Gly Met Ile Met Pro Ala Leu Ile Tyr		
100 105 110		
Ala Ala Phe Asn Gln Ser Asn Pro Glu Gln Leu Ala Gly Trp Ala Ile		
115 120 125		
Pro Ala Ala Thr Asp Ile Ala Phe Ala Leu Gly Val Leu Ser Leu Leu		
130 135 140		
Gly Asn Arg Val Pro Asn Ala Leu Lys Val Phe Leu Val Ser Ile Ala		
145 150 155 160		
Ile Phe Asp Asp Leu Gly Ala Ile Val Ile Ile Ala Leu Phe Tyr Thr		
165 170 175		
Ser Asp Leu Ser Leu Ser Ser Leu Ala Val Ala Gly Val Cys Phe Pro		
180 185 190		
Phe Leu Phe Ile Leu Asn Lys Met Asn Val Val Arg Leu Thr Pro Tyr		
195 200 205		
Leu Leu Ile Gly Leu Val Met Trp Ala Ala Phe Leu Lys Ser Gly Val		
210 215 220		
His Ala Thr Leu Ala Gly Val Leu Leu Ala Phe Phe Ile Pro Leu Arg		
225 230 235 240		
Asn Lys Ser Asp Pro Glu His Ser Pro Leu Glu Glu Leu Glu His Asp		
245 250 255		
Leu His Asn Thr Val Ala Phe Gly Val Leu Pro Leu Phe Ala Phe Ala		
260 265 270		
Asn Ala Gly Ile Gly Leu Ala Gly Thr Gly Ile Asp Ser Leu Leu His		
275 280 285		
Ser Val Pro Leu Gly Ile Ala Ala Gly Leu Phe Ile Gly Lys Gln Ile		
290 295 300		
Gly Val Met Thr Ala Val Phe Leu Cys Leu Lys Leu Gly Leu Ala Ser		
305 310 315 320		
Leu Pro Lys Gly Thr Thr Ile Lys Gln Leu Tyr Gly Val Ser Leu Leu		
325 330 335		
Cys Gly Ile Gly Phe Thr Met Ser Leu Phe Ile Ser Gly Leu Ala Phe		
340 345 350		

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Gly	Asn	Thr	Pro	Lys	Asp	Phe	Asp	Pro	Arg	Leu	Gly	Ile	Ile	Leu	Gly	
	355						360					365				
Ser	Ile	Ile	Ser	Gly	Val	Ile	Gly	Tyr	Met	Ile	Leu	Arg	Gly	Asn	Ile	
	370					375					380					
Pro	Asn	Ala	Asp	His	Pro	Val	Leu	Ala	Lys	Asp	Thr	Gly	Glu	Gly	Phe	
385					390					395					400	
Ile	Pro	Thr	Gln	His	Asp	Ala	Gln	Ala								
				405												
<210> SEQ ID NO 24																
<211> LENGTH: 676																
<212> TYPE: PRT																
<213> ORGANISM: Homo sapiens																
<400> SEQUENCE: 24																
Met	Ala	Ala	Ala	Ser	Ser	Pro	Pro	Arg	Ala	Glu	Arg	Lys	Arg	Trp	Gly	
1				5				10						15		
Trp	Gly	Arg	Leu	Pro	Gly	Ala	Arg	Arg	Gly	Ser	Ala	Gly	Leu	Ala	Lys	
			20					25					30			
Lys	Cys	Pro	Phe	Ser	Leu	Glu	Leu	Ala	Glu	Gly	Gly	Pro	Ala	Gly	Gly	
		35					40					45				
Ala	Leu	Tyr	Ala	Pro	Ile	Ala	Pro	Gly	Ala	Pro	Gly	Pro	Ala	Pro	Pro	
	50					55					60					
Ala	Ser	Pro	Ala	Ala	Pro	Ala	Ala	Pro	Pro	Val	Ala	Ser	Asp	Leu	Gly	
65					70					75					80	
Pro	Arg	Pro	Pro	Val	Ser	Leu	Asp	Pro	Arg	Val	Ser	Ile	Tyr	Ser	Thr	
				85					90					95		
Arg	Arg	Pro	Val	Leu	Ala	Arg	Thr	His	Val	Gln	Gly	Arg	Val	Tyr	Asn	
			100					105					110			
Phe	Leu	Glu	Arg	Pro	Thr	Gly	Trp	Lys	Cys	Phe	Val	Tyr	His	Phe	Ala	
	115						120					125				
Val	Phe	Leu	Ile	Val	Leu	Val	Cys	Leu	Ile	Phe	Ser	Val	Leu	Ser	Thr	
	130					135						140				
Ile	Glu	Gln	Tyr	Ala	Ala	Leu	Ala	Thr	Gly	Thr	Leu	Phe	Trp	Met	Glu	
145					150					155					160	
Ile	Val	Leu	Val	Val	Phe	Phe	Gly	Thr	Glu	Tyr	Val	Val	Arg	Leu	Trp	
			165						170					175		
Ser	Ala	Gly	Cys	Arg	Ser	Lys	Tyr	Val	Gly	Leu	Trp	Gly	Arg	Leu	Arg	
			180					185					190			
Phe	Ala	Arg	Lys	Pro	Ile	Ser	Ile	Ile	Asp	Leu	Ile	Val	Val	Val	Ala	
	195						200					205				
Ser	Met	Val	Val	Leu	Cys	Val	Gly	Ser	Lys	Gly	Gln	Val	Phe	Ala	Thr	
	210					215					220					
Ser	Ala	Ile	Arg	Gly	Ile	Arg	Phe	Leu	Gln	Ile	Leu	Arg	Met	Leu	His	
225					230					235					240	
Val	Asp	Arg	Gln	Gly	Gly	Thr	Trp	Arg	Leu	Leu	Gly	Ser	Val	Val	Phe	
			245						250					255		
Ile	His	Arg	Gln	Glu	Leu	Ile	Thr	Thr	Leu	Tyr	Ile	Gly	Phe	Leu	Gly	
			260					265					270			
Leu	Ile	Phe	Ser	Ser	Tyr	Phe	Val	Tyr	Leu	Ala	Glu	Lys	Asp	Ala	Val	
	275						280					285				
Asn	Glu	Ser	Gly	Arg	Val	Glu	Phe	Gly	Ser	Tyr	Ala	Asp	Ala	Leu	Trp	
	290					295					300					

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Trp	Gly	Val	Val	Thr	Val	Thr	Thr	Ile	Gly	Tyr	Gly	Asp	Lys	Val	Pro	
305					310					315					320	
Gln	Thr	Trp	Val	Gly	Lys	Thr	Ile	Ala	Ser	Cys	Phe	Ser	Val	Phe	Ala	
				325					330					335		
Ile	Ser	Phe	Phe	Ala	Leu	Pro	Ala	Gly	Ile	Leu	Gly	Ser	Gly	Phe	Ala	
				340				345					350			
Leu	Lys	Val	Gln	Gln	Lys	Gln	Arg	Gln	Lys	His	Phe	Asn	Arg	Gln	Ile	
		355					360					365				
Pro	Ala	Ala	Ala	Ser	Leu	Ile	Gln	Thr	Ala	Trp	Arg	Cys	Tyr	Ala	Ala	
	370					375					380					
Glu	Asn	Pro	Asp	Ser	Ser	Thr	Trp	Lys	Ile	Tyr	Ile	Arg	Lys	Ala	Pro	
385					390					395					400	
Arg	Ser	His	Thr	Leu	Leu	Ser	Pro	Ser	Pro	Lys	Pro	Lys	Lys	Ser	Val	
				405					410					415		
Val	Val	Lys	Lys	Lys	Lys	Phe	Lys	Leu	Asp	Lys	Asp	Asn	Gly	Val	Thr	
			420					425					430			
Pro	Gly	Glu	Lys	Met	Leu	Thr	Val	Pro	His	Ile	Thr	Cys	Asp	Pro	Pro	
		435					440					445				
Glu	Glu	Arg	Arg	Leu	Asp	His	Phe	Ser	Val	Asp	Gly	Tyr	Asp	Ser	Ser	
	450					455					460					
Val	Arg	Lys	Ser	Pro	Thr	Leu	Leu	Glu	Val	Ser	Met	Pro	His	Phe	Met	
465					470					475					480	
Arg	Thr	Asn	Ser	Phe	Ala	Glu	Asp	Leu	Asp	Leu	Glu	Gly	Glu	Thr	Leu	
				485					490					495		
Leu	Thr	Pro	Ile	Thr	His	Ile	Ser	Gln	Leu	Arg	Glu	His	His	Arg	Ala	
			500					505					510			
Thr	Ile	Lys	Val	Ile	Arg	Arg	Met	Gln	Tyr	Phe	Val	Ala	Lys	Lys	Lys	
		515					520					525				
Phe	Gln	Gln	Ala	Arg	Lys	Pro	Tyr	Asp	Val	Arg	Asp	Val	Ile	Glu	Gln	
	530					535					540					
Tyr	Ser	Gln	Gly	His	Leu	Asn	Leu	Met	Val	Arg	Ile	Lys	Glu	Leu	Gln	
545					550					555					560	
Arg	Arg	Leu	Asp	Gln	Ser	Ile	Gly	Lys	Pro	Ser	Leu	Phe	Ile	Ser	Val	
				565					570					575		
Ser	Glu	Lys	Ser	Lys	Asp	Arg	Gly	Ser	Asn	Thr	Ile	Gly	Ala	Arg	Leu	
			580					585					590			
Asn	Arg	Val	Glu	Asp	Lys	Val	Thr	Gln	Leu	Asp	Gln	Arg	Leu	Ala	Leu	
		595					600					605				
Ile	Thr	Asp	Met	Leu	His	Gln	Leu	Leu	Ser	Leu	His	Gly	Gly	Ser	Thr	
	610					615					620					
Pro	Gly	Ser	Gly	Gly	Pro	Pro	Arg	Glu	Gly	Gly	Ala	His	Ile	Thr	Gln	
625					630					635					640	
Pro	Cys	Gly	Ser	Gly	Gly	Ser	Val	Asp	Pro	Glu	Leu	Phe	Leu	Pro	Ser	
				645					650					655		
Asn	Thr	Leu	Pro	Thr	Tyr	Glu	Gln	Leu	Thr	Val	Pro	Arg	Arg	Gly	Pro	
			660					665					670			
Asp	Glu	Gly	Ser													
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<212> TYPE: PRT															
<213> ORGANISM: Homo sapiens															
<400> SEQUENCE: 25															
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			20					25					30		
Asn	Ala	Arg	Val	Glu	Asn	Cys	Ala	Val	Ile	Tyr	Cys	Asn	Asp	Gly	Phe
		35					40					45			
Cys	Glu	Leu	Cys	Gly	Tyr	Ser	Arg	Ala	Glu	Val	Met	Gln	Arg	Pro	Cys
	50					55					60				
Thr	Cys	Asp	Phe	Leu	His	Gly	Pro	Arg	Thr	Gln	Arg	Arg	Ala	Ala	Ala
65					70					75					80
Gln	Ile	Ala	Gln	Ala	Leu	Leu	Gly	Ala	Glu	Glu	Arg	Lys	Val	Glu	Ile
				85					90					95	
Ala	Phe	Tyr	Arg	Lys	Asp	Gly	Ser	Cys	Phe	Leu	Cys	Leu	Val	Asp	Val
			100					105					110		
Val	Pro	Val	Lys	Asn	Glu	Asp	Gly	Ala	Val	Ile	Met	Phe	Ile	Leu	Asn
		115					120					125			
Phe	Glu	Val	Val	Met	Glu	Lys	Asp	Met	Val	Gly	Ser	Pro	Ala	His	Asp
	130						135				140				
Thr	Asn	His	Arg	Gly	Pro	Pro	Thr	Ser	Trp	Leu	Ala	Pro	Gly	Arg	Ala
145					150					155					160
Lys	Thr	Phe	Arg	Leu	Lys	Leu	Pro	Ala	Leu	Leu	Ala	Leu	Thr	Ala	Arg
				165					170					175	
Glu	Ser	Ser	Val	Arg	Ser	Gly	Gly	Ala	Gly	Gly	Ala	Gly	Ala	Pro	Gly
			180					185					190		
Ala	Val	Val	Val	Asp	Val	Asp	Leu	Thr	Pro	Ala	Ala	Pro	Ser	Ser	Glu
		195					200					205			
Ser	Leu	Ala	Leu	Asp	Glu	Val	Thr	Ala	Met	Asp	Asn	His	Val	Ala	Gly
	210					215					220				
Leu	Gly	Pro	Ala	Glu	Glu	Arg	Arg	Ala	Leu	Val	Gly	Pro	Gly	Ser	Pro
225					230					235					240
Pro	Arg	Ser	Ala	Pro	Gly	Gln	Leu	Pro	Ser	Pro	Arg	Ala	His	Ser	Leu
			245						250					255	
Asn	Pro	Asp	Ala	Ser	Gly	Ser	Ser	Cys	Ser	Leu	Ala	Arg	Thr	Arg	Ser
			260					265					270		
Arg	Glu	Ser	Cys	Ala	Ser	Val	Arg	Arg	Ala	Ser	Ser	Ala	Asp	Asp	Ile
		275					280					285			
Glu	Ala	Met	Arg	Ala	Gly	Val	Leu	Pro	Pro	Pro	Pro	Arg	His	Ala	Ser
	290					295					300				
Thr	Gly	Ala	Met	His	Pro	Leu	Arg	Ser	Gly	Leu	Leu	Asn	Ser	Thr	Ser
305					310					315					320
Asp	Ser	Asp	Leu	Val	Arg	Tyr	Arg	Thr	Ile	Ser	Lys	Ile	Pro	Gln	Ile
			325						330					335	
Thr	Leu	Asn	Phe	Val	Asp	Leu	Lys	Gly	Asp	Pro	Phe	Leu	Ala	Ser	Pro
			340					345					350		
Thr	Ser	Asp	Arg	Glu	Ile	Ile	Ala	Pro	Lys	Ile	Lys	Glu	Arg	Thr	His
		355					360					365			
Asn	Val	Thr	Glu	Lys	Val	Thr	Gln	Val	Leu	Ser	Leu	Gly	Ala	Asp	Val
		370				375					380				

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Leu	Pro	Glu	Tyr	Lys	Leu	Gln	Ala	Pro	Arg	Ile	His	Arg	Trp	Thr	Ile	
385					390					395					400	
Leu	His	Tyr	Ser	Pro	Phe	Lys	Ala	Val	Trp	Asp	Trp	Leu	Ile	Leu	Leu	
				405					410					415		
Leu	Val	Ile	Tyr	Thr	Ala	Val	Phe	Thr	Pro	Tyr	Ser	Ala	Ala	Phe	Leu	
			420					425					430			
Leu	Lys	Glu	Thr	Glu	Glu	Gly	Pro	Pro	Ala	Thr	Glu	Cys	Gly	Tyr	Ala	
		435					440					445				
Cys	Gln	Pro	Leu	Ala	Val	Val	Asp	Leu	Ile	Val	Asp	Ile	Met	Phe	Ile	
	450					455					460					
Val	Asp	Ile	Leu	Ile	Asn	Phe	Arg	Thr	Thr	Tyr	Val	Asn	Ala	Asn	Glu	
465					470					475					480	
Glu	Val	Val	Ser	His	Pro	Gly	Arg	Ile	Ala	Val	His	Tyr	Phe	Lys	Gly	
				485					490					495		
Trp	Phe	Leu	Ile	Asp	Met	Val	Ala	Ala	Ile	Pro	Phe	Asp	Leu	Leu	Ile	
		500						505					510			
Phe	Gly	Ser	Gly	Ser	Glu	Glu	Leu	Ile	Gly	Leu	Leu	Lys	Thr	Ala	Arg	
		515					520					525				
Leu	Leu	Arg	Leu	Val	Arg	Val	Ala	Arg	Lys	Leu	Asp	Arg	Tyr	Ser	Glu	
	530					535					540					
Tyr	Gly	Ala	Ala	Val	Leu	Phe	Leu	Leu	Met	Cys	Thr	Phe	Ala	Leu	Ile	
545					550					555					560	
Ala	His	Trp	Leu	Ala	Cys	Ile	Trp	Tyr	Ala	Ile	Gly	Asn	Met	Glu	Gln	
			565						570					575		
Pro	His	Met	Asp	Ser	Arg	Ile	Gly	Trp	Leu	His	Asn	Leu	Gly	Asp	Gln	
			580					585					590			
Ile	Gly	Lys	Pro	Tyr	Asn	Ser	Ser	Gly	Leu	Gly	Gly	Pro	Ser	Ile	Lys	
		595					600					605				
Asp	Lys	Tyr	Val	Thr	Ala	Leu	Tyr	Phe	Thr	Phe	Ser	Ser	Leu	Thr	Ser	
	610					615					620					
Val	Gly	Phe	Gly	Asn	Val	Ser	Pro	Asn	Thr	Asn	Ser	Glu	Lys	Ile	Phe	
625					630					635					640	
Ser	Ile	Cys	Val	Met	Leu	Ile	Gly	Ser	Leu	Met	Tyr	Ala	Ser	Ile	Phe	
			645						650					655		
Gly	Asn	Val	Ser	Ala	Ile	Ile	Gln	Arg	Leu	Tyr	Ser	Gly	Thr	Ala	Arg	
		660						665					670			
Tyr	His	Thr	Gln	Met	Leu	Arg	Val	Arg	Glu	Phe	Ile	Arg	Phe	His	Gln	
		675					680					685				
Ile	Pro	Asn	Pro	Leu	Arg	Gln	Arg	Leu	Glu	Glu	Tyr	Phe	Gln	His	Ala	
	690					695					700					
Trp	Ser	Tyr	Thr	Asn	Gly	Ile	Asp	Met	Asn	Ala	Val	Leu	Lys	Gly	Phe	
705					710					715					720	
Pro	Glu	Cys	Leu	Gln	Ala	Asp	Ile	Cys	Leu	His	Leu	Asn	Arg	Ser	Leu	
			725						730					735		
Leu	Gln	His	Cys	Lys	Pro	Phe	Arg	Gly	Ala	Thr	Lys	Gly	Cys	Leu	Arg	
		740						745					750			
Ala	Leu	Ala	Met	Lys	Phe	Lys	Thr	Thr	His	Ala	Pro	Pro	Gly	Asp	Thr	
	755						760					765				
Leu	Val	His	Ala	Gly	Asp	Leu	Leu	Thr	Ala	Leu	Tyr	Phe	Ile	Ser	Arg	
	770					775					780					

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Gly	Ser	Ile	Glu	Ile	Leu	Arg	Gly	Asp	Val	Val	Val	Ala	Ile	Leu	Gly
785					790				795					800	
Lys	Asn	Asp	Ile	Phe	Gly	Glu	Pro	Leu	Asn	Leu	Tyr	Ala	Arg	Pro	Gly
			805					810						815	
Lys	Ser	Asn	Gly	Asp	Val	Arg	Ala	Leu	Thr	Tyr	Cys	Asp	Leu	His	Lys
			820					825					830		
Ile	His	Arg	Asp	Asp	Leu	Leu	Glu	Val	Leu	Asp	Met	Tyr	Pro	Glu	Phe
		835					840					845			
Ser	Asp	His	Phe	Trp	Ser	Ser	Leu	Glu	Ile	Thr	Phe	Asn	Leu	Arg	Asp
	850					855					860				
Thr	Asn	Met	Ile	Pro	Gly	Ser	Pro	Gly	Ser	Thr	Glu	Leu	Glu	Gly	Gly
865					870					875				880	
Phe	Ser	Arg	Gln	Arg	Lys	Arg	Lys	Leu	Ser	Phe	Arg	Arg	Arg	Thr	Asp
			885					890						895	
Lys	Asp	Thr	Glu	Gln	Pro	Gly	Glu	Val	Ser	Ala	Leu	Gly	Pro	Gly	Arg
			900					905					910		
Ala	Gly	Ala	Gly	Pro	Ser	Ser	Arg	Gly	Arg	Pro	Gly	Gly	Pro	Trp	Gly
		915					920					925			
Glu	Ser	Pro	Ser	Ser	Gly	Pro	Ser	Ser	Pro	Glu	Ser	Ser	Glu	Asp	Glu
	930					935					940				
Gly	Pro	Gly	Arg	Ser	Ser	Ser	Pro	Leu	Arg	Leu	Val	Pro	Phe	Ser	Ser
945					950					955				960	
Pro	Arg	Pro	Pro	Gly	Glu	Pro	Pro	Gly	Gly	Glu	Pro	Leu	Met	Glu	Asp
				965					970					975	
Cys	Glu	Lys	Ser	Ser	Asp	Thr	Cys	Asn	Pro	Leu	Ser	Gly	Ala	Phe	Ser
			980					985					990		
Gly	Val	Ser	Asn	Ile	Phe	Ser	Phe	Trp	Gly	Asp	Ser	Arg	Gly	Arg	Gln
			995				1000					1005			
Tyr	Gln	Glu	Leu	Pro	Arg	Cys	Pro	Ala	Pro	Thr	Pro	Ser	Leu	Leu	
	1010					1015						1020			
Asn	Ile	Pro	Leu	Ser	Ser	Pro	Gly	Arg	Arg	Pro	Arg	Gly	Asp	Val	
	1025					1030						1035			
Glu	Ser	Arg	Leu	Asp	Ala	Leu	Gln	Arg	Gln	Leu	Asn	Arg	Leu	Glu	
	1040					1045					1050				
Thr	Arg	Leu	Ser	Ala	Asp	Met	Ala	Thr	Val	Leu	Gln	Leu	Leu	Gln	
	1055					1060					1065				
Arg	Gln	Met	Thr	Leu	Val	Pro	Pro	Ala	Tyr	Ser	Ala	Val	Thr	Thr	
	1070					1075					1080				
Pro	Gly	Pro	Gly	Pro	Thr	Ser	Thr	Ser	Pro	Leu	Leu	Pro	Val	Ser	
	1085					1090					1095				
Pro	Leu	Pro	Thr	Leu	Thr	Leu	Asp	Ser	Leu	Ser	Gln	Val	Ser	Gln	
	1100					1105					1110				
Phe	Met	Ala	Cys	Glu	Glu	Leu	Pro	Pro	Gly	Ala	Pro	Glu	Leu	Pro	
	1115					1120					1125				
Gln	Glu	Gly	Pro	Thr	Arg	Arg	Leu	Ser	Leu	Pro	Gly	Gln	Leu	Gly	
	1130					1135					1140				
Ala	Leu	Thr	Ser	Gln	Pro	Leu	His	Arg	His	Gly	Ser	Asp	Pro	Gly	
	1145					1150					1155				
Ser															

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<211> LENGTH: 427															
<212> TYPE: PRT															
<213> ORGANISM: Homo sapiens															
<400> SEQUENCE: 26															
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Asp	Gly	Met	Lys	Leu	Ala	Thr	Met	Ala	Val	Ala	Asn	Gly	Phe	Gly	Asn
			20					25					30		
Gly	Lys	Ser	Lys	Val	His	Thr	Arg	Gln	Gln	Cys	Arg	Ser	Arg	Phe	Val
		35					40					45			
Lys	Lys	Asp	Gly	His	Cys	Asn	Val	Gln	Phe	Ile	Asn	Val	Gly	Glu	Lys
	50					55					60				
Gly	Gln	Arg	Tyr	Leu	Ala	Asp	Ile	Phe	Thr	Thr	Cys	Val	Asp	Ile	Arg
65					70					75					80
Trp	Arg	Trp	Met	Leu	Val	Ile	Phe	Cys	Leu	Ala	Phe	Val	Leu	Ser	Trp
				85					90					95	
Leu	Phe	Phe	Gly	Cys	Val	Phe	Trp	Leu	Ile	Ala	Leu	Leu	His	Gly	Asp
			100					105					110		
Leu	Asp	Ala	Ser	Lys	Glu	Gly	Lys	Ala	Cys	Val	Ser	Glu	Val	Asn	Ser
		115					120					125			
Phe	Thr	Ala	Ala	Phe	Leu	Phe	Ser	Ile	Glu	Thr	Gln	Thr	Thr	Ile	Gly
		130					135					140			
Tyr	Gly	Phe	Arg	Cys	Val	Thr	Asp	Glu	Cys	Pro	Ile	Ala	Val	Phe	Met
145					150					155					160
Val	Val	Phe	Gln	Ser	Ile	Val	Gly	Cys	Ile	Ile	Asp	Ala	Phe	Ile	Ile
				165					170					175	
Gly	Ala	Val	Met	Ala	Lys	Met	Ala	Lys	Pro	Lys	Lys	Arg	Asn	Glu	Thr
			180					185					190		
Leu	Val	Phe	Ser	His	Asn	Ala	Val	Ile	Ala	Met	Arg	Asp	Gly	Lys	Leu
		195					200					205			
Cys	Leu	Met	Trp	Arg	Val	Gly	Asn	Leu	Arg	Lys	Ser	His	Leu	Val	Glu
	210					215					220				
Ala	His	Val	Arg	Ala	Gln	Leu	Leu	Lys	Ser	Arg	Ile	Thr	Ser	Glu	Gly
225					230					235					240
Glu	Tyr	Ile	Pro	Leu	Asp	Gln	Ile	Asp	Ile	Asn	Val	Gly	Phe	Asp	Ser
				245					250					255	
Gly	Ile	Asp	Arg	Ile	Phe	Leu	Val	Ser	Pro	Ile	Thr	Ile	Val	His	Glu
		260						265					270		
Ile	Asp	Glu	Asp	Ser	Pro	Leu	Tyr	Asp	Leu	Ser	Lys	Gln	Asp	Ile	Asp
	275						280					285			
Asn	Ala	Asp	Phe	Glu	Ile	Val	Val	Ile	Leu	Glu	Gly	Met	Val	Glu	Ala
	290					295					300				
Thr	Ala	Met	Thr	Thr	Gln	Cys	Arg	Ser	Ser	Tyr	Leu	Ala	Asn	Glu	Ile
305					310					315					320
Leu	Trp	Gly	His	Arg	Tyr	Glu	Pro	Val	Leu	Phe	Glu	Glu	Lys	His	Tyr
			325						330					335	
Tyr	Lys	Val	Asp	Tyr	Ser	Arg	Phe	His	Lys	Thr	Tyr	Glu	Val	Pro	Asn
		340					345						350		
Thr	Pro	Leu	Cys	Ser	Ala	Arg	Asp	Leu	Ala	Glu	Lys	Lys	Tyr	Ile	Leu
		355					360					365			
Ser	Asn	Ala	Asn	Ser	Phe	Cys	Tyr	Glu	Asn	Glu	Val	Ala	Leu	Thr	Ser

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370						375						380					
Lys	Glu	Glu	Asp	Asp	Ser	Glu	Asn	Gly	Val	Pro	Glu	Ser	Thr	Ser	Thr		
385					390					395					400		
Asp	Thr	Pro	Pro	Asp	Ile	Asp	Leu	His	Asn	Gln	Ala	Ser	Val	Pro	Leu		
				405					410					415			
Glu	Pro	Arg	Pro	Leu	Arg	Arg	Glu	Ser	Glu	Ile							
			420					425									
<210> SEQ ID NO 27																	
<211> LENGTH: 215																	
<212> TYPE: PRT																	
<213> ORGANISM: Homo sapiens																	
<400> SEQUENCE: 27																	
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Pro	Val	Arg	Gly	Gly	His	Val	Met	Arg	Gly	Thr	Ala	Phe	Ala	Tyr	Val		
			20					25					30				
Pro	Ser	Pro	Gln	Val	Leu	His	Arg	Ile	Pro	Gly	Thr	Ser	Ala	Tyr	Ala		
		35					40					45					
Phe	Pro	Ser	Leu	Gly	Pro	Val	Ala	Leu	Ala	Glu	His	Thr	Cys	Pro	Cys		
50						55				60							
Gly	Glu	Val	Leu	Glu	Arg	His	Glu	Pro	Leu	Pro	Ala	Lys	Leu	Ala	Leu		
65					70				75						80		
Glu	Glu	Glu	Gln	Lys	Pro	Glu	Ser	Arg	Leu	Val	Pro	Lys	Leu	Arg	Gln		
			85						90					95			
Ala	Gly	Ala	Met	Leu	Leu	Lys	Val	Pro	Leu	Met	Leu	Thr	Phe	Leu	Tyr		
			100					105					110				
Leu	Phe	Val	Cys	Ser	Leu	Asp	Met	Leu	Ser	Ser	Ala	Phe	Gln	Leu	Ala		
		115					120					125					
Gly	Gly	Lys	Val	Ala	Gly	Asp	Ile	Phe	Lys	Asp	Asn	Ala	Ile	Leu	Ser		
	130					135					140						
Asn	Pro	Val	Ala	Gly	Leu	Val	Val	Gly	Ile	Leu	Val	Thr	Val	Leu	Val		
145					150					155					160		
Gln	Ser	Ser	Ser	Thr	Ser	Thr	Ser	Ile	Ile	Val	Ser	Met	Val	Ser	Ser		
				165					170					175			
Gly	Leu	Leu	Glu	Val	Ser	Ser	Ala	Ile	Pro	Ile	Ile	Met	Gly	Ser	Asn		
			180					185					190				
Ile	Gly	Thr	Ser	Val	Thr	Asn	Thr	Ile	Val	Ala	Leu	Met	Gln	Ala	Gly		
		195					200					205					
Asp	Arg	Thr	Asp	Phe	Arg	Arg											
	210					215											
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<211> LENGTH: 311																	
<212> TYPE: PRT																	
<213> ORGANISM: Homo sapiens																	
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1				5					10					15			
Val	Asn	Trp	Gly	Ser	Ser	Thr	Gln	Ala	Leu	Thr	Tyr	Leu	Asn	Ala	Leu		
			20					25					30				
Gln	His	Ser	Ile	Arg	Leu	Ser	Gly	Val	Glu	Asp	His	Val	Lys	Asn	Phe		

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35						40						45					
Arg	Pro	Gln	Cys	Leu	Val	Met	Thr	Gly	Ala	Pro	Asn	Ser	Arg	Pro	Ala		
50						55						60					
Leu	Leu	His	Leu	Val	His	Asp	Phe	Thr	Lys	Asn	Val	Gly	Leu	Met	Ile		
65						70						75					
Cys	Gly	His	Val	His	Met	Gly	Pro	Arg	Arg	Gln	Ala	Met	Lys	Glu	Met		
85						90						95					
Ser	Ile	Asp	Gln	Ala	Lys	Tyr	Gln	Arg	Trp	Leu	Ile	Lys	Asn	Lys	Met		
100						105						110					
Lys	Ala	Phe	Tyr	Ala	Pro	Val	His	Ala	Asp	Asp	Leu	Arg	Glu	Gly	Ala		
115						120						125					
Gln	Tyr	Leu	Met	Gln	Ala	Ala	Gly	Leu	Gly	Arg	Met	Lys	Pro	Asn	Thr		
130						135						140					
Leu	Val	Leu	Gly	Phe	Lys	Lys	Asp	Trp	Leu	Gln	Ala	Asp	Met	Arg	Asp		
145						150						155					
Val	Asp	Met	Tyr	Ile	Asn	Leu	Phe	His	Asp	Ala	Phe	Asp	Ile	Gln	Tyr		
165						170						175					
Gly	Val	Val	Val	Ile	Arg	Leu	Lys	Glu	Gly	Leu	Asp	Ile	Ser	His	Leu		
180						185						190					
Gln	Gly	Gln	Glu	Glu	Leu	Leu	Ser	Ser	Gln	Glu	Lys	Ser	Pro	Gly	Thr		
195						200						205					
Lys	Asp	Val	Val	Val	Ser	Val	Glu	Tyr	Ser	Lys	Lys	Ser	Asp	Leu	Asp		
210						215						220					
Thr	Ser	Lys	Pro	Leu	Ser	Glu	Lys	Pro	Ile	Thr	His	Lys	Glu	Ser	Lys		
225						230						235					
Gly	Pro	Ile	Val	Pro	Leu	Asn	Val	Ala	Asp	Gln	Lys	Leu	Leu	Glu	Ala		
245						250						255					
Ser	Thr	Gln	Phe	Gln	Lys	Lys	Gln	Gly	Lys	Asn	Thr	Ile	Asp	Val	Trp		
260						265						270					
Trp	Leu	Phe	Asp	Asp	Gly	Gly	Leu	Thr	Leu	Leu	Ile	Pro	Tyr	Leu	Leu		
275						280						285					
Thr	Thr	Lys	Lys	Lys	Trp	Lys	Asp	Cys	Lys	Ile	Arg	Val	Phe	Ile	Gly		
290						295						300					
Gly	Lys	Ile	Asn	Arg	Ile	Asp											
305						310											
<210> SEQ ID NO 29																	
<211> LENGTH: 353																	
<212> TYPE: PRT																	
<213> ORGANISM: Artificial sequence																	
<220> FEATURE:																	
<223> OTHER INFORMATION: synthetic amino acid sequence																	
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Met	Ser	Arg	Arg	Pro	Trp	Leu	Leu	Ala	Leu	Ala	Leu	Ala	Val	Ala	Leu		
1				5				10				15					
Ala	Ala	Gly	Ser	Ala	Gly	Ala	Ser	Thr	Gly	Ser	Asp	Ala	Thr	Val	Pro		
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Val	Ala	Thr	Gln	Asp	Gly	Pro	Asp	Tyr	Val	Phe	His	Arg	Ala	His	Glu		
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Arg	Met	Leu	Phe	Gln	Thr	Ser	Tyr	Thr	Leu	Glu	Asn	Asn	Gly	Ser	Val		
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Ile	Cys	Ile	Pro	Asn	Asn	Gly	Gln	Cys	Phe	Cys	Leu	Ala	Trp	Leu	Lys		

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Ile	Thr	Phe	Ala	Leu	Ser	Ala	Leu	Cys	Leu	Met	Phe	Tyr	Gly	Tyr	Gln	
			100					105					110			
Thr	Trp	Lys	Ser	Thr	Cys	Gly	Trp	Glu	Glu	Ile	Tyr	Val	Ala	Thr	Ile	
		115					120					125				
Glu	Met	Ile	Lys	Phe	Ile	Ile	Glu	Tyr	Phe	His	Glu	Phe	Asp	Glu	Pro	
	130					135					140					
Ala	Val	Ile	Tyr	Ser	Ser	Asn	Gly	Asn	Lys	Thr	Val	Trp	Leu	Arg	Tyr	
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Ala	Glu	Trp	Leu	Leu	Thr	Cys	Pro	Val	Ile	Leu	Ile	His	Leu	Ser	Asn	
				165					170					175		
Leu	Thr	Gly	Leu	Ala	Asn	Asp	Tyr	Asn	Lys	Arg	Thr	Met	Gly	Leu	Leu	
			180					185					190			
Val	Ser	Asp	Ile	Gly	Thr	Ile	Val	Trp	Gly	Thr	Thr	Ala	Ala	Leu	Ser	
		195					200					205				
Lys	Gly	Tyr	Val	Arg	Val	Ile	Phe	Phe	Leu	Met	Gly	Leu	Cys	Tyr	Gly	
	210					215					220					
Ile	Tyr	Thr	Phe	Phe	Asn	Ala	Ala	Lys	Val	Tyr	Ile	Glu	Ala	Tyr	His	
225					230					235					240	
Thr	Val	Pro	Lys	Gly	Arg	Cys	Arg	Gln	Val	Val	Thr	Gly	Met	Ala	Trp	
				245					250					255		
Leu	Phe	Phe	Val	Ser	Trp	Gly	Met	Phe	Pro	Ile	Leu	Phe	Ile	Leu	Gly	
			260					265					270			
Pro	Glu	Gly	Phe	Gly	Val	Leu	Ser	Val	Tyr	Gly	Ser	Thr	Val	Gly	His	
		275					280					285				
Thr	Ile	Ile	Asp	Leu	Met	Ser	Lys	Asn	Cys	Trp	Gly	Leu	Leu	Gly	His	
	290					295					300					
Tyr	Leu	Arg	Val	Leu	Ile	His	Glu	His	Ile	Leu	Ile	His	Gly	Asp	Ile	
305					310					315					320	
Arg	Lys	Thr	Thr	Lys	Leu	Asn	Ile	Gly	Gly	Thr	Glu	Ile	Glu	Val	Glu	
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Pro	Val	Ala	Thr	Gln	Asp	Gly	Pro	Asp	Tyr	Val	Phe	His	Arg	Ala	His	
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Val	Ile	Cys	Ile	Pro	Asn	Asn	Gly	Gln	Cys	Phe	Cys	Leu	Ala	Trp	Leu	
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Lys	Ser	Asn	Gly	Thr	Asn	Ala	Glu	Lys	Leu	Ala	Ala	Asn	Ile	Leu	Gln	
			85						90					95		
Trp	Val	Thr	Phe	Ala	Leu	Ser	Val	Ala	Cys	Leu	Gly	Trp	Tyr	Ala	Tyr	
			100					105					110			
Gln	Ala	Trp	Arg	Ala	Thr	Cys	Gly	Trp	Glu	Glu	Val	Tyr	Val	Ala	Leu	
		115					120					125				
Ile	Glu	Met	Met	Lys	Ser	Ile	Ile	Glu	Ala	Phe	His	Glu	Phe	Asp	Ser	
	130					135					140					
Pro	Ala	Thr	Leu	Trp	Leu	Ser	Ser	Gly	Asn	Gly	Val	Val	Trp	Met	Arg	
145					150					155					160	
Tyr	Gly	Glu	Trp	Leu	Leu	Thr	Cys	Pro	Val	Ile	Leu	Ile	His	Leu	Ser	
			165						170					175		
Asn	Leu	Thr	Gly	Leu	Lys	Asp	Asp	Tyr	Ser	Lys	Arg	Thr	Met	Gly	Leu	
		180						185					190			
Leu	Val	Ser	Asp	Val	Gly	Cys	Ile	Val	Trp	Gly	Ala	Thr	Ser	Ala	Met	
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Cys	Thr	Gly	Trp	Thr	Lys	Ile	Leu	Phe	Phe	Leu	Ile	Ser	Leu	Ser	Tyr	
	210					215					220					
Gly	Met	Tyr	Thr	Tyr	Phe	His	Ala	Ala	Lys	Val	Tyr	Ile	Glu	Ala	Phe	
225					230					235					240	
His	Thr	Val	Pro	Lys	Gly	Leu	Cys	Arg	Gln	Leu	Val	Arg	Ala	Met	Ala	
			245						250					255		
Trp	Leu	Phe	Phe	Val	Ser	Trp	Gly	Met	Phe	Pro	Val	Leu	Phe	Leu	Leu	
		260						265					270			
Gly	Pro	Glu	Gly	Phe	Gly	His	Ile	Ser	Pro	Tyr	Gly	Ser	Ala	Ile	Gly	
	275						280					285				
His	Ser	Ile	Leu	Asp	Leu	Ile	Ala	Lys	Asn	Met	Trp	Gly	Val	Leu	Gly	
	290					295					300					
Asn	Tyr	Leu	Arg	Val	Lys	Ile	His	Glu	His	Ile	Leu	Leu	Tyr	Gly	Asp	
305					310					315					320	
Ile	Arg	Lys	Lys	Gln	Lys	Ile	Thr	Ile	Ala	Gly	Gln	Glu	Met	Glu	Val	
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			20					25					30			
Gly	Thr	Phe	Tyr	Phe	Leu	Val	Arg	Gly	Trp	Gly	Val	Thr	Asp	Lys	Asp	
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Ala	Arg	Glu	Tyr	Tyr	Ala	Val	Thr	Ile	Leu	Val	Pro	Gly	Ile	Ala	Ser	
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Ala	Ala	Tyr	Leu	Ser	Met	Phe	Phe	Gly	Ile	Gly	Leu	Thr	Glu	Val	Thr	
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Val	Gly	Gly	Glu	Met	Leu	Asp	Ile	Tyr	Tyr	Ala	Arg	Tyr	Ala	Asp	Trp	
				85					90					95		
Leu	Phe	Thr	Thr	Pro	Leu	Leu	Leu	Leu	Asp	Leu	Ala	Leu	Leu	Ala	Lys	
			100					105					110			
Val	Asp	Arg	Val	Thr	Ile	Gly	Thr	Leu	Val	Gly	Val	Asp	Ala	Leu	Met	
		115					120					125				
Ile	Val	Thr	Gly	Leu	Ile	Gly	Ala	Leu	Ser	His	Thr	Ala	Ile	Ala	Arg	
	130					135					140					
Tyr	Ser	Trp	Trp	Leu	Phe	Ser	Thr	Ile	Cys	Met	Ile	Val	Val	Leu	Tyr	
145					150					155					160	
Phe	Leu	Ala	Thr	Ser	Leu	Arg	Ser	Ala	Ala	Lys	Glu	Arg	Gly	Pro	Glu	
				165					170					175		
Val	Ala	Ser	Thr	Phe	Asn	Thr	Leu	Thr	Ala	Leu	Val	Leu	Val	Leu	Trp	
			180					185					190			
Thr	Ala	Tyr	Pro	Ile	Leu	Trp	Ile	Ile	Gly	Thr	Glu	Gly	Ala	Gly	Val	
		195					200					205				
Val	Gly	Leu	Gly	Ile	Glu	Thr	Leu	Leu	Phe	Met	Val	Leu	Asp	Val	Thr	
	210					215					220					
Ala	Lys	Val	Gly	Phe	Gly	Phe	Ile	Leu	Leu	Arg	Ser	Arg	Ala	Ile	Leu	
225					230					235					240	
Gly	Asp	Thr	Glu	Ala	Pro	Glu	Pro	Ser	Ala	Gly	Ala	Asp	Val	Ser	Ala	
				245					250					255		
Ala	Asp	Lys	Ser	Arg	Ile	Thr	Ser	Glu	Gly	Glu	Tyr	Ile	Pro	Leu	Asp	
			260					265					270			
Gln	Ile	Asp	Ile	Asn	Val	Gly	Ala	Pro	Gly	Ser	Gly	Ala	Thr	Asn	Phe	
		275					280					285				
Ser	Leu	Leu	Lys	Gln	Ala	Gly	Asp	Val	Glu	Glu	Asn	Pro	Met	Asp	Leu	
	290					295					300					
Lys	Glu	Ser	Pro	Ser	Glu	Gly	Ser	Leu	Gln	Pro	Ser	Ser	Ile	Gln	Ile	
305					310					315					320	
Phe	Ala	Asn	Thr	Ser	Thr	Leu	His	Gly	Ile	Arg	His	Ile	Phe	Val	Tyr	
				325					330					335		
Gly	Pro	Leu	Thr	Ile	Arg	Arg	Val	Leu	Trp	Ala	Val	Ala	Phe	Val	Gly	
			340					345					350			
Ser	Leu	Gly	Leu	Leu	Leu	Val	Glu	Ser	Ser	Glu	Arg	Val	Ser	Tyr	Tyr	
		355					360					365				
Phe	Ser	Tyr	Gln	His	Val	Thr	Lys	Val	Asp	Glu	Val	Val	Ala	Gln	Ser	
	370					375					380					
Leu	Val	Phe	Pro	Ala	Val	Thr	Leu	Cys	Asn	Leu	Asn	Gly	Phe	Arg	Phe	
385					390					395					400	
Ser	Arg	Leu	Thr	Thr	Asn	Asp	Leu	Tyr	His	Ala	Gly	Glu	Leu	Leu	Ala	
				405					410					415		
Leu	Leu	Asp	Val	Asn	Leu	Gln	Ile	Pro	Asp	Pro	His	Leu	Ala	Asp	Pro	
			420					425					430			
Thr	Val	Leu	Glu	Ala	Leu	Arg	Gln	Lys	Ala	Asn	Phe	Lys	His	Tyr	Lys	
		435					440					445				
Pro	Lys	Gln	Phe	Ser	Met	Leu	Glu	Phe	Leu	His	Arg	Val	Gly	His	Asp	
	450					455					460					

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Leu	Lys	Asp	Met	Met	Leu	Tyr	Cys	Lys	Phe	Lys	Gly	Gln	Glu	Cys	Gly	
465					470					475					480	
His	Gln	Asp	Phe	Thr	Thr	Val	Phe	Thr	Lys	Tyr	Gly	Lys	Cys	Tyr	Met	
				485					490					495		
Phe	Asn	Ser	Gly	Glu	Asp	Gly	Lys	Pro	Leu	Leu	Thr	Thr	Val	Lys	Gly	
			500					505					510			
Gly	Thr	Gly	Asn	Gly	Leu	Glu	Ile	Met	Leu	Asp	Ile	Gln	Gln	Asp	Glu	
		515					520					525				
Tyr	Leu	Pro	Ile	Trp	Gly	Glu	Thr	Glu	Glu	Thr	Thr	Phe	Glu	Ala	Gly	
	530					535					540					
Val	Lys	Val	Gln	Ile	His	Ser	Gln	Ser	Glu	Pro	Pro	Phe	Ile	Gln	Glu	
545					550					555					560	
Leu	Gly	Phe	Gly	Val	Ala	Pro	Gly	Phe	Gln	Thr	Phe	Val	Ala	Thr	Gln	
				565					570					575		
Glu	Gln	Arg	Leu	Thr	Tyr	Leu	Pro	Pro	Pro	Trp	Gly	Glu	Cys	Arg	Ser	
			580					585					590			
Ser	Glu	Met	Gly	Leu	Asp	Phe	Phe	Pro	Val	Tyr	Ser	Ile	Thr	Ala	Cys	
		595					600					605				
Arg	Ile	Asp	Cys	Glu	Thr	Arg	Tyr	Ile	Val	Glu	Asn	Cys	Asn	Cys	Arg	
	610					615					620					
Met	Val	His	Met	Pro	Gly	Asp	Ala	Pro	Phe	Cys	Thr	Pro	Glu	Gln	His	
625					630					635					640	
Lys	Glu	Cys	Ala	Glu	Pro	Ala	Leu	Gly	Leu	Leu	Ala	Glu	Lys	Asp	Ser	
				645					650					655		
Asn	Tyr	Cys	Leu	Cys	Arg	Thr	Pro	Cys	Asn	Leu	Thr	Arg	Tyr	Asn	Lys	
			660					665					670			
Glu	Leu	Ser	Met	Val	Lys	Ile	Pro	Ser	Lys	Thr	Ser	Ala	Lys	Tyr	Leu	
		675					680					685				
Glu	Lys	Lys	Phe	Asn	Lys	Ser	Glu	Lys	Tyr	Ile	Ser	Glu	Asn	Ile	Leu	
	690					695					700					
Val	Leu	Asp	Ile	Phe	Phe	Glu	Ala	Leu	Asn	Tyr	Glu	Thr	Ile	Glu	Gln	
705					710					715					720	
Lys	Lys	Ala	Tyr	Glu	Val	Ala	Ala	Leu	Leu	Gly	Asp	Ile	Gly	Gly	Gln	
				725					730					735		
Met	Gly	Leu	Phe	Ile	Gly	Ala	Ser	Leu	Leu	Thr	Ile	Leu	Glu	Leu	Phe	
			740					745					750			
Asp	Tyr	Ile	Tyr	Glu	Leu	Ile	Lys	Glu	Lys	Leu	Leu	Asp	Leu	Leu	Gly	
		755					760					765				
Lys	Glu	Glu	Glu	Glu	Gly	Ser	His	Asp	Glu	Asn	Met	Ser	Thr	Cys	Asp	
	770					775					780					
Thr	Met	Pro	Asn	His	Ser	Glu	Thr	Ile	Ser	His	Thr	Val	Asn	Val	Pro	
785					790					795					800	
Leu	Gln	Thr	Ala	Leu	Gly	Thr	Leu	Glu	Glu	Ile	Ala	Cys	Ala	Ala	Ala	
				805					810					815		
Val	Ser	Lys	Gly	Glu	Glu	Leu	Phe	Thr	Gly	Val	Val	Pro	Ile	Leu	Val	
			820					825					830			
Glu	Leu	Asp	Gly	Asp	Val	Asn	Gly	His	Lys	Phe	Ser	Val	Ser	Gly	Glu	
		835					840					845				
Gly	Glu	Gly	Asp	Ala	Thr	Tyr	Gly	Lys	Leu	Thr	Leu	Lys	Phe	Ile	Cys	
	850					855					860					
Thr	Thr	Gly	Lys	Leu	Pro	Val	Pro	Trp	Pro	Thr	Leu	Val	Thr	Thr	Phe	

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865				870				875					880		
Gly	Tyr	Gly	Leu	Gln	Cys	Phe	Ala	Arg	Tyr	Pro	Asp	His	Met	Lys	Gln
				885					890					895	
His	Asp	Phe	Phe	Lys	Ser	Ala	Met	Pro	Glu	Gly	Tyr	Val	Gln	Glu	Arg
				900				905					910		
Thr	Ile	Phe	Phe	Lys	Asp	Asp	Gly	Asn	Tyr	Lys	Thr	Arg	Ala	Glu	Val
				915				920				925			
Lys	Phe	Glu	Gly	Asp	Thr	Leu	Val	Asn	Arg	Ile	Glu	Leu	Lys	Gly	Ile
				930				935				940			
Asp	Phe	Arg	Glu	Asp	Gly	Asn	Ile	Leu	Gly	His	Lys	Leu	Glu	Tyr	Asn
945					950					955					960
Tyr	Asn	Ser	His	Asn	Val	Tyr	Ile	Met	Ala	Asp	Lys	Gln	Lys	Asn	Gly
				965					970					975	
Ile	Lys	Val	Asn	Phe	Lys	Ile	Arg	His	Asn	Ile	Glu	Asp	Gly	Ser	Val
				980					985				990		
Gln	Leu	Ala	Asp	His	Tyr	Gln	Gln	Asn	Thr	Pro	Ile	Gly	Asp	Gly	Pro
				995				1000					1005		
Val	Leu	Leu	Pro	Asp	Asn	His	Tyr	Leu	Ser	Tyr	Gln	Ser	Ala	Leu	
				1010				1015				1020			
Ser	Lys	Asp	Pro	Asn	Glu	Lys	Arg	Asp	His	Met	Val	Leu	Leu	Glu	
				1025				1030				1035			
Phe	Val	Thr	Ala	Ala	Gly	Ile	Thr	Leu	Gly	Met	Asp	Glu	Leu	Tyr	
				1040				1045				1050			
Lys	Phe	Cys	Tyr	Glu	Asn	Glu	Val								
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				20				25					30		
Gly	Thr	Phe	Tyr	Phe	Leu	Val	Arg	Gly	Trp	Gly	Val	Thr	Asp	Lys	Asp
				35				40				45			
Ala	Arg	Glu	Tyr	Tyr	Ala	Val	Thr	Ile	Leu	Val	Pro	Gly	Ile	Ala	Ser
				50				55				60			
Ala	Ala	Tyr	Leu	Ser	Met	Phe	Phe	Gly	Ile	Gly	Leu	Thr	Glu	Val	Thr
65					70				75					80	
Val	Gly	Gly	Glu	Met	Leu	Asp	Ile	Tyr	Tyr	Ala	Arg	Tyr	Ala	Asp	Trp
				85				90						95	
Leu	Phe	Thr	Thr	Pro	Leu	Leu	Leu	Leu	Asp	Leu	Ala	Leu	Leu	Ala	Lys
				100				105					110		
Val	Asp	Arg	Val	Thr	Ile	Gly	Thr	Leu	Val	Gly	Val	Asp	Ala	Leu	Met
				115				120				125			
Ile	Val	Thr	Gly	Leu	Ile	Gly	Ala	Leu	Ser	His	Thr	Ala	Ile	Ala	Arg
				130				135				140			
Tyr	Ser	Trp	Trp	Leu	Phe	Ser	Thr	Ile	Cys	Met	Ile	Val	Val	Leu	Tyr

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145					150					155					160
Phe	Leu	Ala	Thr	Ser	Leu	Arg	Ser	Ala	Ala	Lys	Glu	Arg	Gly	Pro	Glu
				165					170					175	
Val	Ala	Ser	Thr	Phe	Asn	Thr	Leu	Thr	Ala	Leu	Val	Leu	Val	Leu	Trp
			180					185					190		
Thr	Ala	Tyr	Pro	Ile	Leu	Trp	Ile	Ile	Gly	Thr	Glu	Gly	Ala	Gly	Val
		195					200					205			
Val	Gly	Leu	Gly	Ile	Glu	Thr	Leu	Leu	Phe	Met	Val	Leu	Asp	Val	Thr
	210					215					220				
Ala	Lys	Val	Gly	Phe	Gly	Phe	Ile	Leu	Leu	Arg	Ser	Arg	Ala	Ile	Leu
225					230					235					240
Gly	Asp	Thr	Glu	Ala	Pro	Glu	Pro	Ser	Ala	Gly	Ala	Asp	Val	Ser	Ala
				245					250					255	
Ala	Asp	Lys	Ser	Arg	Ile	Thr	Ser	Glu	Gly	Glu	Tyr	Ile	Pro	Leu	Asp
			260					265					270		
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	275						280					285			
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	290					295					300				
Lys	Glu	Ser	Pro	Ser	Glu	Gly	Ser	Leu	Gln	Pro	Ser	Ser	Ile	Gln	Ile
305					310					315					320
Phe	Ala	Asn	Thr	Ser	Thr	Leu	His	Gly	Ile	Arg	His	Ile	Phe	Val	Tyr
				325					330					335	
Gly	Pro	Leu	Thr	Ile	Arg	Arg	Val	Leu	Trp	Ala	Val	Ala	Phe	Val	Gly
			340					345					350		
Ser	Leu	Gly	Leu	Leu	Leu	Val	Glu	Ser	Ser	Glu	Arg	Val	Ser	Tyr	Tyr
		355					360					365			
Phe	Ser	Tyr	Gln	His	Val	Thr	Lys	Val	Asp	Glu	Val	Val	Ala	Gln	Ser
	370					375				380					
Leu	Val	Phe	Pro	Ala	Val	Thr	Leu	Cys	Asn	Leu	Asn	Gly	Phe	Arg	Phe
385					390					395					400
Ser	Arg	Leu	Thr	Thr	Asn	Asp	Leu	Tyr	His	Ala	Gly	Glu	Leu	Leu	Ala
				405					410					415	
Leu	Leu	Asp	Val	Asn	Leu	Gln	Ile	Pro	Asp	Pro	His	Leu	Ala	Asp	Pro
		420						425					430		
Thr	Val	Leu	Glu	Ala	Leu	Arg	Gln	Lys	Ala	Asn	Phe	Lys	His	Tyr	Lys
		435					440					445			
Pro	Lys	Gln	Phe	Ser	Met	Leu	Glu	Phe	Leu	His	Arg	Val	Gly	His	Asp
	450					455					460				
Leu	Lys	Asp	Met	Met	Leu	Tyr	Cys	Lys	Phe	Lys	Gly	Gln	Glu	Cys	Gly
465					470					475					480
His	Gln	Asp	Phe	Thr	Thr	Val	Phe	Thr	Lys	Tyr	Gly	Lys	Cys	Tyr	Met
				485					490					495	
Phe	Asn	Ser	Gly	Glu	Asp	Gly	Lys	Pro	Leu	Leu	Thr	Thr	Val	Lys	Gly
			500					505					510		
Gly	Thr	Gly	Asn	Gly	Leu	Glu	Ile	Met	Leu	Asp	Ile	Gln	Gln	Asp	Glu
	515						520					525			
Tyr	Leu	Pro	Ile	Trp	Gly	Glu	Thr	Glu	Glu	Thr	Thr	Phe	Glu	Ala	Gly
	530					535					540				
Val	Lys	Val	Gln	Ile	His	Ser	Gln	Ser	Glu	Pro	Pro	Phe	Ile	Gln	Glu
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Leu	Gly	Phe	Gly	Val	Ala	Pro	Gly	Phe	Gln	Thr	Phe	Val	Ala	Thr	Gln	
				565					570					575		
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			580					585					590			
Ser	Glu	Met	Gly	Leu	Asp	Phe	Phe	Pro	Val	Tyr	Ser	Ile	Thr	Ala	Cys	
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Met	Val	His	Met	Pro	Gly	Asp	Ala	Pro	Phe	Cys	Thr	Pro	Glu	Gln	His	
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Lys	Glu	Cys	Ala	Glu	Pro	Ala	Leu	Gly	Leu	Leu	Ala	Glu	Lys	Asp	Ser	
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Asn	Tyr	Cys	Leu	Cys	Arg	Thr	Pro	Cys	Asn	Leu	Thr	Arg	Tyr	Asn	Lys	
			660					665					670			
Glu	Leu	Ser	Met	Val	Lys	Ile	Pro	Ser	Lys	Thr	Ser	Ala	Lys	Tyr	Leu	
		675				680					685					
Glu	Lys	Lys	Phe	Asn	Lys	Ser	Glu	Lys	Tyr	Ile	Ser	Glu	Asn	Ile	Leu	
	690					695					700					
Val	Leu	Asp	Ile	Phe	Phe	Glu	Ala	Leu	Asn	Tyr	Glu	Thr	Ile	Glu	Gln	
705					710				715					720		
Lys	Lys	Ala	Tyr	Glu	Val	Ala	Ala	Leu	Leu	Gly	Asp	Ile	Gly	Gly	Gln	
			725					730					735			
Met	Gly	Leu	Phe	Ile	Gly	Ala	Ser	Leu	Leu	Thr	Ile	Leu	Glu	Leu	Phe	
		740						745					750			
Asp	Tyr	Ile	Tyr	Glu	Leu	Ile	Lys	Glu	Lys	Leu	Leu	Asp	Leu	Leu	Gly	
		755					760					765				
Lys	Glu	Glu	Glu	Glu	Gly	Ser	His	Asp	Glu	Asn	Met	Ser	Thr	Cys	Asp	
	770					775					780					
Thr	Met	Pro	Asn	His	Ser	Glu	Thr	Ile	Ser	His	Thr	Val	Asn	Val	Pro	
785					790					795					800	
Leu	Gln	Thr	Ala	Leu	Gly	Thr	Leu	Glu	Glu	Ile	Ala	Cys	Ala	Ala	Ala	
				805				810						815		
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Pro	Ile	Leu	Val	Glu	Leu	Asp	Gly	Asp	Val	Asn	Gly	His	Lys	Phe	Ser	
	850					855					860					
Val	Ser	Gly	Glu	Gly	Glu	Gly	Asp	Ala	Thr	Tyr	Gly	Lys	Leu	Thr	Leu	
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Lys	Phe	Ile	Cys	Thr	Thr	Gly	Lys	Leu	Pro	Val	Pro	Trp	Pro	Thr	Leu	
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Val	Thr	Thr	Phe	Gly	Tyr	Gly	Leu	Gln	Cys	Phe	Ala	Arg	Tyr	Pro	Asp	
			900					905					910			
His	Met	Lys	Gln	His	Asp	Phe	Phe	Lys	Ser	Ala	Met	Pro	Glu	Gly	Tyr	
		915					920					925				
Val	Gln	Glu	Arg	Thr	Ile	Phe	Phe	Lys	Asp	Asp	Gly	Asn	Tyr	Lys	Thr	
	930					935					940					
Arg	Ala	Glu	Val	Lys	Phe	Glu	Gly	Asp	Thr	Leu	Val	Asn	Arg	Ile	Glu	
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Leu	Lys	Gly	Ile	Asp	Phe	Arg	Glu	Asp	Gly	Asn	Ile	Leu	Gly	His	Lys	
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Leu	Glu	Tyr	Asn	Tyr	Asn	Ser	His	Asn	Val	Tyr	Ile	Met	Ala	Asp	Lys	
			980					985					990			
Gln	Lys	Asn	Gly	Ile	Lys	Val	Asn	Phe	Lys	Ile	Arg	His	Asn	Ile	Glu	
		995					1000					1005				
Asp	Gly	Ser	Val	Gln	Leu	Ala	Asp	His	Tyr	Gln	Gln	Asn	Thr	Pro		
	1010					1015					1020					
Ile	Gly	Asp	Gly	Pro	Val	Leu	Leu	Pro	Asp	Asn	His	Tyr	Leu	Ser		
	1025					1030					1035					
Tyr	Gln	Ser	Ala	Leu	Ser	Lys	Asp	Pro	Asn	Glu	Lys	Arg	Asp	His		
	1040					1045					1050					
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Gly	Thr	Phe	Tyr	Phe	Leu	Val	Arg	Gly	Trp	Gly	Val	Thr	Asp	Lys	Asp	
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Ala	Ala	Tyr	Leu	Ser	Met	Phe	Phe	Gly	Ile	Gly	Leu	Thr	Glu	Val	Thr	
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Val	Gly	Gly	Glu	Met	Leu	Asp	Ile	Tyr	Tyr	Ala	Arg	Tyr	Ala	Asp	Trp	
			85					90					95			
Leu	Phe	Thr	Thr	Pro	Leu	Leu	Leu	Leu	Asp	Leu	Ala	Leu	Leu	Ala	Lys	
			100					105					110			
Val	Asp	Arg	Val	Thr	Ile	Gly	Thr	Leu	Val	Gly	Val	Asp	Ala	Leu	Met	
		115					120					125				
Ile	Val	Thr	Gly	Leu	Ile	Gly	Ala	Leu	Ser	His	Thr	Ala	Ile	Ala	Arg	
	130					135					140					
Tyr	Ser	Trp	Trp	Leu	Phe	Ser	Thr	Ile	Cys	Met	Ile	Val	Val	Leu	Tyr	
145				150					155					160		
Phe	Leu	Ala	Thr	Ser	Leu	Arg	Ser	Ala	Ala	Lys	Glu	Arg	Gly	Pro	Glu	
			165					170					175			
Val	Ala	Ser	Thr	Phe	Asn	Thr	Leu	Thr	Ala	Leu	Val	Leu	Val	Leu	Trp	
			180				185					190				
Thr	Ala	Tyr	Pro	Ile	Leu	Trp	Ile	Ile	Gly	Thr	Glu	Gly	Ala	Gly	Val	
	195					200						205				
Val	Gly	Leu	Gly	Ile	Glu	Thr	Leu	Leu	Phe	Met	Val	Leu	Asp	Val	Thr	
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Ala	Lys	Val	Gly	Phe	Gly	Phe	Ile	Leu	Leu	Arg	Ser	Arg	Ala	Ile	Leu
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Gly	Asp	Thr	Glu	Ala	Pro	Glu	Pro	Ser	Ala	Gly	Ala	Asp	Val	Ser	Ala
				245					250					255	
Ala	Asp	Lys	Ser	Arg	Ile	Thr	Ser	Glu	Gly	Glu	Tyr	Ile	Pro	Leu	Asp
			260					265					270		
Gln	Ile	Asp	Ile	Asn	Val	Gly	Ala	Pro	Met	Asp	Leu	Lys	Glu	Ser	Pro
		275					280					285			
Ser	Glu	Gly	Ser	Leu	Gln	Pro	Ser	Ser	Ile	Gln	Ile	Phe	Ala	Asn	Thr
	290					295					300				
Ser	Thr	Leu	His	Gly	Ile	Arg	His	Ile	Phe	Val	Tyr	Gly	Pro	Leu	Thr
305					310					315					320
Ile	Arg	Arg	Val	Leu	Trp	Ala	Val	Ala	Phe	Val	Gly	Ser	Leu	Gly	Leu
				325					330					335	
Leu	Leu	Val	Glu	Ser	Ser	Glu	Arg	Val	Ser	Tyr	Tyr	Phe	Ser	Tyr	Gln
			340					345					350		
His	Val	Thr	Lys	Val	Asp	Glu	Val	Val	Ala	Gln	Ser	Leu	Val	Phe	Pro
		355					360					365			
Ala	Val	Thr	Leu	Cys	Asn	Leu	Asn	Gly	Phe	Arg	Phe	Ser	Arg	Leu	Thr
		370				375					380				
Thr	Asn	Asp	Leu	Tyr	His	Ala	Gly	Glu	Leu	Leu	Ala	Leu	Leu	Asp	Val
385					390					395					400
Asn	Leu	Gln	Ile	Pro	Asp	Pro	His	Leu	Ala	Asp	Pro	Thr	Val	Leu	Glu
			405						410					415	
Ala	Leu	Arg	Gln	Lys	Ala	Asn	Phe	Lys	His	Tyr	Lys	Pro	Lys	Gln	Phe
			420					425					430		
Ser	Met	Leu	Glu	Phe	Leu	His	Arg	Val	Gly	His	Asp	Leu	Lys	Asp	Met
		435					440					445			
Met	Leu	Tyr	Cys	Lys	Phe	Lys	Gly	Gln	Glu	Cys	Gly	His	Gln	Asp	Phe
	450					455					460				
Thr	Thr	Val	Phe	Thr	Lys	Tyr	Gly	Lys	Cys	Tyr	Met	Phe	Asn	Ser	Gly
465					470					475					480
Glu	Asp	Gly	Lys	Pro	Leu	Leu	Thr	Thr	Val	Lys	Gly	Gly	Thr	Gly	Asn
			485						490					495	
Gly	Leu	Glu	Ile	Met	Leu	Asp	Ile	Gln	Gln	Asp	Glu	Tyr	Leu	Pro	Ile
			500					505					510		
Trp	Gly	Glu	Thr	Glu	Glu	Thr	Thr	Phe	Glu	Ala	Gly	Val	Lys	Val	Gln
		515					520					525			
Ile	His	Ser	Gln	Ser	Glu	Pro	Pro	Phe	Ile	Gln	Glu	Leu	Gly	Phe	Gly
	530					535					540				
Val	Ala	Pro	Gly	Phe	Gln	Thr	Phe	Val	Ala	Thr	Gln	Glu	Gln	Arg	Leu
545					550					555					560
Thr	Tyr	Leu	Pro	Pro	Pro	Trp	Gly	Glu	Cys	Arg	Ser	Ser	Glu	Met	Gly
			565					570						575	
Leu	Asp	Phe	Phe	Pro	Val	Tyr	Ser	Ile	Thr	Ala	Cys	Arg	Ile	Asp	Cys
			580					585					590		
Glu	Thr	Arg	Tyr	Ile	Val	Glu	Asn	Cys	Asn	Cys	Arg	Met	Val	His	Met
		595					600					605			
Pro	Gly	Asp	Ala	Pro	Phe	Cys	Thr	Pro	Glu	Gln	His	Lys	Glu	Cys	Ala
	610					615					620				
Glu	Pro	Ala	Leu	Gly	Leu	Leu	Ala	Glu	Lys	Asp	Ser	Asn	Tyr	Cys	Leu

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Cys	Arg	Thr	Pro	Cys	Asn	Leu	Thr	Arg	Tyr	Asn	Lys	Glu	Leu	Ser	Met	
				645					650					655		
Val	Lys	Ile	Pro	Ser	Lys	Thr	Ser	Ala	Lys	Tyr	Leu	Glu	Lys	Lys	Phe	
			660					665					670			
Asn	Lys	Ser	Glu	Lys	Tyr	Ile	Ser	Glu	Asn	Ile	Leu	Val	Leu	Asp	Ile	
		675					680					685				
Phe	Phe	Glu	Ala	Leu	Asn	Tyr	Glu	Thr	Ile	Glu	Gln	Lys	Lys	Ala	Tyr	
	690					695					700					
Glu	Val	Ala	Ala	Leu	Leu	Gly	Asp	Ile	Gly	Gly	Gln	Met	Gly	Leu	Phe	
705					710					715					720	
Ile	Gly	Ala	Ser	Leu	Leu	Thr	Ile	Leu	Glu	Leu	Phe	Asp	Tyr	Ile	Tyr	
				725					730					735		
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			740					745					750			
Glu	Gly	Ser	His	Asp	Glu	Asn	Met	Ser	Thr	Cys	Asp	Thr	Met	Pro	Asn	
		755					760					765				
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	770					775					780					
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785					790					795					800	
Thr	Ser	Glu	Gly	Glu	Tyr	Ile	Pro	Leu	Asp	Gln	Ile	Asp	Ile	Asn	Val	
			805						810					815		
Val	Ser	Lys	Gly	Glu	Glu	Leu	Phe	Thr	Gly	Val	Val	Pro	Ile	Leu	Val	
			820					825					830			
Glu	Leu	Asp	Gly	Asp	Val	Asn	Gly	His	Lys	Phe	Ser	Val	Ser	Gly	Glu	
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Gly	Glu	Gly	Asp	Ala	Thr	Tyr	Gly	Lys	Leu	Thr	Leu	Lys	Phe	Ile	Cys	
	850					855					860					
Thr	Thr	Gly	Lys	Leu	Pro	Val	Pro	Trp	Pro	Thr	Leu	Val	Thr	Thr	Phe	
865					870					875					880	
Gly	Tyr	Gly	Leu	Gln	Cys	Phe	Ala	Arg	Tyr	Pro	Asp	His	Met	Lys	Gln	
			885						890				895			
His	Asp	Phe	Phe	Lys	Ser	Ala	Met	Pro	Glu	Gly	Tyr	Val	Gln	Glu	Arg	
		900						905					910			
Thr	Ile	Phe	Phe	Lys	Asp	Asp	Gly	Asn	Tyr	Lys	Thr	Arg	Ala	Glu	Val	
		915					920					925				
Lys	Phe	Glu	Gly	Asp	Thr	Leu	Val	Asn	Arg	Ile	Glu	Leu	Lys	Gly	Ile	
	930					935					940					
Asp	Phe	Arg	Glu	Asp	Gly	Asn	Ile	Leu	Gly	His	Lys	Leu	Glu	Tyr	Asn	
945					950					955					960	
Tyr	Asn	Ser	His	Asn	Val	Tyr	Ile	Met	Ala	Asp	Lys	Gln	Lys	Asn	Gly	
			965						970					975		
Ile	Lys	Val	Asn	Phe	Lys	Ile	Arg	His	Asn	Ile	Glu	Asp	Gly	Ser	Val	
		980					985						990			
Gln	Leu	Ala	Asp	His	Tyr	Gln	Gln	Asn	Thr	Pro	Ile	Gly	Asp	Gly	Pro	
	995						1000						1005			
Val	Leu	Leu	Pro	Asp	Asn	His	Tyr	Leu	Ser	Tyr	Gln	Ser	Ala	Leu		
	1010					1015					1020					
Ser	Lys	Asp	Pro	Asn	Glu	Lys	Arg	Asp	His	Met	Val	Leu	Leu	Glu		
	1025					1030					1035					

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Phe	Val	Thr	Ala	Ala	Gly	Ile	Thr	Leu	Gly	Met	Asp	Glu	Leu	Tyr	
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			20					25					30		
Gly	Thr	Phe	Tyr	Phe	Leu	Val	Arg	Gly	Trp	Gly	Val	Thr	Asp	Lys	Asp
		35					40					45			
Ala	Arg	Glu	Tyr	Tyr	Ala	Val	Thr	Ile	Leu	Val	Pro	Gly	Ile	Ala	Ser
	50					55					60				
Ala	Ala	Tyr	Leu	Ser	Met	Phe	Phe	Gly	Ile	Gly	Leu	Thr	Glu	Val	Thr
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Val	Gly	Gly	Glu	Met	Leu	Asp	Ile	Tyr	Tyr	Ala	Arg	Tyr	Ala	Asp	Trp
				85					90					95	
Leu	Phe	Thr	Thr	Pro	Leu	Leu	Leu	Leu	Asp	Leu	Ala	Leu	Leu	Ala	Lys
			100					105					110		
Val	Asp	Arg	Val	Thr	Ile	Gly	Thr	Leu	Val	Gly	Val	Asp	Ala	Leu	Met
		115					120					125			
Ile	Val	Thr	Gly	Leu	Ile	Gly	Ala	Leu	Ser	His	Thr	Ala	Ile	Ala	Arg
	130					135					140				
Tyr	Ser	Trp	Trp	Leu	Phe	Ser	Thr	Ile	Cys	Met	Ile	Val	Val	Leu	Tyr
145					150					155					160
Phe	Leu	Ala	Thr	Ser	Leu	Arg	Ser	Ala	Ala	Lys	Glu	Arg	Gly	Pro	Glu
				165					170					175	
Val	Ala	Ser	Thr	Phe	Asn	Thr	Leu	Thr	Ala	Leu	Val	Leu	Val	Leu	Trp
			180					185					190		
Thr	Ala	Tyr	Pro	Ile	Leu	Trp	Ile	Ile	Gly	Thr	Glu	Gly	Ala	Gly	Val
		195				200						205			
Val	Gly	Leu	Gly	Ile	Glu	Thr	Leu	Leu	Phe	Met	Val	Leu	Asp	Val	Thr
	210					215					220				
Ala	Lys	Val	Gly	Phe	Gly	Phe	Ile	Leu	Leu	Arg	Ser	Arg	Ala	Ile	Leu
225					230					235					240
Gly	Asp	Thr	Glu	Ala	Pro	Glu	Pro	Ser	Ala	Gly	Ala	Asp	Val	Ser	Ala
				245					250					255	
Ala	Asp	Lys	Ser	Arg	Ile	Thr	Ser	Glu	Gly	Glu	Tyr	Ile	Pro	Leu	Asp
		260						265					270		
Gln	Ile	Asp	Ile	Asn	Val	Gly	Ala	Pro	Gly	Ser	Gly	Ala	Thr	Asn	Phe
		275					280					285			
Ser	Leu	Leu	Lys	Gln	Ala	Gly	Asp	Val	Glu	Glu	Asn	Pro	Gly	Pro	Met
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			340					345					350			
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		355					360					365				
Tyr	Tyr	Phe	Ser	Tyr	Gln	His	Val	Thr	Lys	Val	Asp	Glu	Val	Val	Ala	
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				405					410					415		
Leu	Ala	Leu	Leu	Asp	Val	Asn	Leu	Gln	Ile	Pro	Asp	Pro	His	Leu	Ala	
			420					425					430			
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		435					440					445				
Tyr	Lys	Pro	Lys	Gln	Phe	Ser	Met	Leu	Glu	Phe	Leu	His	Arg	Val	Gly	
	450					455					460					
His	Asp	Leu	Lys	Asp	Met	Met	Leu	Tyr	Cys	Lys	Phe	Lys	Gly	Gln	Glu	
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Cys	Gly	His	Gln	Asp	Phe	Thr	Thr	Val	Phe	Thr	Lys	Tyr	Gly	Lys	Cys	
				485					490					495		
Tyr	Met	Phe	Asn	Ser	Gly	Glu	Asp	Gly	Lys	Pro	Leu	Leu	Thr	Thr	Val	
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Lys	Gly	Gly	Thr	Gly	Asn	Gly	Leu	Glu	Ile	Met	Leu	Asp	Ile	Gln	Gln	
		515					520					525				
Asp	Glu	Tyr	Leu	Pro	Ile	Trp	Gly	Glu	Thr	Glu	Glu	Thr	Thr	Phe	Glu	
	530					535					540					
Ala	Gly	Val	Lys	Val	Gln	Ile	His	Ser	Gln	Ser	Glu	Pro	Pro	Phe	Ile	
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Thr	Gln	Glu	Gln	Arg	Leu	Thr	Tyr	Leu	Pro	Pro	Pro	Trp	Gly	Glu	Cys	
			580					585					590			
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		595					600					605				
Ala	Cys	Arg	Ile	Asp	Cys	Glu	Thr	Arg	Tyr	Ile	Val	Glu	Asn	Cys	Asn	
	610					615					620					
Cys	Arg	Met	Val	His	Met	Pro	Gly	Asp	Ala	Pro	Phe	Cys	Thr	Pro	Glu	
625					630				635						640	
Gln	His	Lys	Glu	Cys	Ala	Glu	Pro	Ala	Leu	Gly	Leu	Leu	Ala	Glu	Lys	
				645					650					655		
Asp	Ser	Asn	Tyr	Cys	Leu	Cys	Arg	Thr	Pro	Cys	Asn	Leu	Thr	Arg	Tyr	
			660					665					670			
Asn	Lys	Glu	Leu	Ser	Met	Val	Lys	Ile	Pro	Ser	Lys	Thr	Ser	Ala	Lys	
		675					680					685				
Tyr	Leu	Glu	Lys	Lys	Phe	Asn	Lys	Ser	Glu	Lys	Tyr	Ile	Ser	Glu	Asn	
	690					695					700					
Ile	Leu	Val	Leu	Asp	Ile	Phe	Phe	Glu	Ala	Leu	Asn	Tyr	Glu	Thr	Ile	
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Glu	Gln	Lys	Lys	Ala	Tyr	Glu	Val	Ala	Ala	Leu	Leu	Gly	Asp	Ile	Gly	
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			740					745					750			
Leu	Phe	Asp	Tyr	Ile	Tyr	Glu	Leu	Ile	Lys	Glu	Lys	Leu	Leu	Asp	Leu	
		755					760					765				
Leu	Gly	Lys	Glu	Glu	Glu	Glu	Gly	Ser	His	Asp	Glu	Asn	Met	Ser	Thr	
	770					775					780					
Cys	Asp	Thr	Met	Pro	Asn	His	Ser	Glu	Thr	Ile	Ser	His	Thr	Val	Asn	
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Val	Pro	Leu	Gln	Thr	Ala	Leu	Gly	Thr	Leu	Glu	Glu	Ile	Ala	Cys	Ala	
				805					810					815		
Ala	Ala	Lys	Ser	Arg	Ile	Thr	Ser	Glu	Gly	Glu	Tyr	Ile	Pro	Leu	Asp	
			820					825					830			
Gln	Ile	Asp	Ile	Asn	Val	Val	Ser	Lys	Gly	Glu	Glu	Leu	Phe	Thr	Gly	
		835					840					845				
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	850					855					860					
Phe	Ser	Val	Ser	Gly	Glu	Gly	Glu	Gly	Asp	Ala	Thr	Tyr	Gly	Lys	Leu	
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Thr	Leu	Lys	Phe	Ile	Cys	Thr	Thr	Gly	Lys	Leu	Pro	Val	Pro	Trp	Pro	
			885						890					895		
Thr	Leu	Val	Thr	Thr	Phe	Gly	Tyr	Gly	Leu	Gln	Cys	Phe	Ala	Arg	Tyr	
			900					905					910			
Pro	Asp	His	Met	Lys	Gln	His	Asp	Phe	Phe	Lys	Ser	Ala	Met	Pro	Glu	
		915					920					925				
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	930					935					940					
Lys	Thr	Arg	Ala	Glu	Val	Lys	Phe	Glu	Gly	Asp	Thr	Leu	Val	Asn	Arg	
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Ile	Glu	Leu	Lys	Gly	Ile	Asp	Phe	Arg	Glu	Asp	Gly	Asn	Ile	Leu	Gly	
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His	Lys	Leu	Glu	Tyr	Asn	Tyr	Asn	Ser	His	Asn	Val	Tyr	Ile	Met	Ala	
			980				985					990				
Asp	Lys	Gln	Lys	Asn	Gly	Ile	Lys	Val	Asn	Phe	Lys	Ile	Arg	His	Asn	
		995					1000					1005				
Ile	Glu	Asp	Gly	Ser	Val	Gln	Leu	Ala	Asp	His	Tyr	Gln	Gln	Asn		
	1010					1015					1020					
Thr	Pro	Ile	Gly	Asp	Gly	Pro	Val	Leu	Leu	Pro	Asp	Asn	His	Tyr		
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Leu	Ser	Tyr	Gln	Ser	Ala	Leu	Ser	Lys	Asp	Pro	Asn	Glu	Lys	Arg		
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Asp	His	Met	Val	Leu	Leu	Glu	Phe	Val	Thr	Ala	Ala	Gly	Ile	Thr		
	1055					1060					1065					
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<220> FEATURE:
<223> OTHER INFORMATION: synthetic amino acid sequence

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	50					55					60					
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Thr	Gly	Gly	Thr	Cys	Cys	Gly	Cys	Gly	Gly	Ala	Thr	Gly	Gly	Gly	Gly	
		115					120					125				
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	130					135					140					
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Cys	Thr	Gly	Thr	Gly	Ala	Cys	Thr	Ala	Thr	Cys	Cys	Thr	Gly	Gly	Thr	
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			180					185					190			
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		195					200					205				
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	210					215					220					
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225					230					235					240	
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			245						250					255		
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			260					265					270			
Cys	Ala	Gly	Gly	Thr	Ala	Cys	Gly	Cys	Cys	Gly	Ala	Cys	Thr	Gly	Gly	
		275					280					285				
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	290						295				300					
Thr	Thr	Cys	Thr	Gly	Cys	Thr	Gly	Cys	Thr	Gly	Gly	Ala	Thr	Cys	Thr	
305					310					315					320	
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Thr	Cys	Gly	Gly	Cys	Ala	Cys	Cys	Cys	Thr	Gly	Gly	Thr	Gly	Gly	Gly	
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Thr	Gly	Thr	Gly	Gly	Ala	Cys	Gly	Cys	Cys	Cys	Thr	Gly	Ala	Thr	Gly	
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Cys	Ala	Cys	Gly	Gly	Cys	Cys	Ala	Thr	Ala	Gly	Cys	Cys	Ala	Gly	Ala
			420					425					430		
Thr	Ala	Cys	Ala	Gly	Thr	Thr	Gly	Gly	Thr	Gly	Gly	Thr	Thr	Gly	Thr
		435					440					445			
Thr	Cys	Thr	Cys	Thr	Ala	Cys	Ala	Ala	Thr	Thr	Thr	Gly	Cys	Ala	Thr
	450					455					460				
Gly	Ala	Thr	Ala	Gly	Thr	Gly	Gly	Thr	Gly	Cys	Thr	Cys	Thr	Ala	Thr
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Thr	Thr	Thr	Cys	Thr	Gly	Gly	Cys	Thr	Ala	Cys	Ala	Thr	Cys	Cys	Cys
			485						490					495	
Thr	Gly	Cys	Gly	Ala	Thr	Cys	Thr	Gly	Cys	Thr	Gly	Cys	Ala	Ala	Ala
			500					505					510		
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		515					520					525			
Gly	Thr	Gly	Gly	Cys	Ala	Thr	Cys	Thr	Ala	Cys	Cys	Thr	Thr	Thr	Ala
	530					535					540				
Ala	Cys	Ala	Cys	Cys	Cys	Thr	Gly	Ala	Cys	Ala	Gly	Cys	Thr	Cys	Thr
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Gly	Gly	Thr	Cys	Thr	Thr	Gly	Gly	Thr	Gly	Cys	Thr	Gly	Thr	Gly	Gly
			565						570					575	
Ala	Cys	Cys	Gly	Cys	Thr	Thr	Ala	Cys	Cys	Cys	Thr	Ala	Thr	Cys	Cys
			580				585						590		
Thr	Gly	Thr	Gly	Gly	Ala	Thr	Cys	Ala	Thr	Ala	Gly	Gly	Cys	Ala	Cys
		595					600					605			
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	610					615					620				
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			660					665					670		
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		675					680					685			
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	690					695					700				
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Gly	Gly	Cys	Gly	Ala	Cys	Ala	Cys	Cys	Gly	Ala	Gly	Gly	Cys	Ala	Cys
			725						730					735	
Cys	Ala	Gly	Ala	Ala	Cys	Cys	Cys	Ala	Gly	Thr	Gly	Cys	Cys	Gly	Gly
			740					745					750		
Thr	Gly	Cys	Cys	Gly	Ala	Thr	Gly	Thr	Cys	Ala	Gly	Thr	Gly	Cys	Cys
		755					760					765			
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				820					825					830		
Thr	Gly	Gly	Gly	Cys	Gly	Cys	Gly	Cys	Cys	Cys	Gly	Gly	Cys	Thr	Cys	
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Cys	Gly	Gly	Ala	Gly	Cys	Cys	Ala	Cys	Gly	Ala	Ala	Cys	Thr	Thr	Cys	
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Cys	Ala	Gly	Gly	Ala	Gly	Ala	Cys	Gly	Thr	Gly	Gly	Ala	Ala	Gly	Ala	
					885					890					895	
Ala	Ala	Ala	Cys	Cys	Cys	Cys	Gly	Gly	Thr	Cys	Cys	Cys	Ala	Thr	Gly	
				900					905					910		
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				915					920				925			
Cys	Ala	Ala	Gly	Cys	Gly	Ala	Gly	Gly	Gly	Ala	Thr	Cys	Ala	Cys	Thr	
				930					935				940			
Gly	Cys	Ala	Gly	Cys	Cys	Ala	Thr	Cys	Ala	Ala	Gly	Cys	Ala	Thr	Thr	
						950				955					960	
Cys	Ala	Gly	Ala	Thr	Thr	Thr	Thr	Cys	Gly	Cys	Thr	Ala	Ala	Thr	Ala	
					965					970					975	
Cys	Ala	Ala	Gly	Cys	Ala	Cys	Ala	Cys	Thr	Gly	Cys	Ala	Cys	Gly	Gly	
				980					985					990		
Cys	Ala	Thr	Cys	Cys	Gly	Gly	Cys	Ala	Thr	Ala	Thr	Cys	Thr	Thr	Cys	
				995					1000				1005			
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Ala	Cys	Cys	Ala	Thr	Thr	Cys	Gly	Gly	Ala	Gly	Ala	Gly	Thr	Cys		
							1030					1035				
Cys	Thr	Gly	Thr	Gly	Gly	Gly	Cys	Ala	Gly	Thr	Gly	Gly	Cys	Cys		
							1045					1050				
Thr	Thr	Thr	Gly	Thr	Cys	Gly	Gly	Ala	Ala	Gly	Cys	Cys	Thr	Gly		
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							1075					1080				
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							1090					1095				
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Thr	Cys	Ala	Thr	Ala	Thr	Cys	Ala	Gly	Cys	Ala	Cys	Gly	Thr	Gly		
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Ala	Cys	Thr	Ala	Ala	Gly	Gly	Thr	Gly	Gly	Ala	Cys	Gly	Ala	Gly		
							1135					1140				
Gly	Thr	Gly	Gly	Thr	Cys	Gly	Cys	Thr	Cys	Ala	Gly	Thr	Cys	Cys		
							1150					1155				
Cys	Thr	Gly	Gly	Thr	Gly	Thr	Thr	Thr	Cys	Cys	Cys	Gly	Cys	Ala		
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Gly	Thr	Cys	Ala	Cys	Cys	Cys	Thr	Gly	Thr	Gly	Cys	Ala	Ala	Cys		
							1180					1185				

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Cys	Thr	Gly	Ala	Ala	Thr	Gly	Gly	Gly	Thr	Thr	Cys	Ala	Gly	Gly
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Thr	Thr	Thr	Thr	Cys	Thr	Cys	Gly	Cys	Cys	Thr	Gly	Ala	Cys	Cys
1205						1210					1215			
Ala	Cys	Ala	Ala	Ala	Cys	Gly	Ala	Cys	Cys	Thr	Gly	Thr	Ala	Cys
1220						1225					1230			
Cys	Ala	Cys	Gly	Cys	Cys	Gly	Gly	Ala	Gly	Ala	Gly	Cys	Thr	Gly
1235						1240					1245			
Cys	Thr	Gly	Gly	Cys	Thr	Cys	Thr	Gly	Cys	Thr	Gly	Gly	Ala	Thr
1250						1255					1260			
Gly	Thr	Gly	Ala	Ala	Thr	Cys	Thr	Gly	Cys	Ala	Gly	Ala	Thr	Cys
1265						1270					1275			
Cys	Cys	Ala	Gly	Ala	Cys	Cys	Cys	Cys	Cys	Ala	Thr	Cys	Thr	Gly
1280						1285					1290			
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1295						1300					1305			
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1310						1315					1320			
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1325						1330					1335			
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1340						1345					1350			
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1355						1360					1365			
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1370						1375					1380			
Cys	Gly	Cys	Gly	Thr	Gly	Gly	Gly	Ala	Cys	Ala	Thr	Gly	Ala	Cys
1385						1390					1395			
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1400						1405					1410			
Cys	Thr	Gly	Thr	Ala	Thr	Thr	Gly	Cys	Ala	Ala	Gly	Thr	Thr	Cys
1415						1420					1425			
Ala	Ala	Ala	Gly	Gly	Cys	Cys	Ala	Gly	Gly	Ala	Gly	Thr	Gly	Thr
1430						1435					1440			
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1445						1450					1455			
Ala	Cys	Thr	Ala	Cys	Cys	Gly	Thr	Gly	Thr	Thr	Thr	Ala	Cys	Ala
1460						1465					1470			
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1475						1480					1485			
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1505						1510					1515			
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1520						1525					1530			
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1535						1540					1545			
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1550						1555					1560			
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Ala Cys Ala Thr Thr Cys 1625	Gly Ala Gly Gly Cys 1630	Cys Gly Gly Cys 1635
Gly Thr Gly Ala Ala Gly 1640	Gly Thr Cys Cys Ala 1645	Gly Ala Thr Cys 1650
Cys Ala Cys Thr Cys Ala 1655	Cys Ala Gly Ala Gly 1660	Cys Gly Ala Gly 1665
Cys Cys Cys Cys Cys Thr 1670	Thr Thr Cys Ala Thr 1675	Thr Cys Ala Gly 1680
Gly Ala Ala Cys Thr Gly 1685	Gly Gly Ala Thr Thr 1690	Thr Gly Gly Ala 1695
Gly Thr Gly Gly Cys Ala 1700	Cys Cys Ala Gly Gly 1705	Ala Thr Thr Cys 1710
Cys Ala Gly Ala Cys Ala 1715	Thr Thr Gly Thr 1720	Cys Gly Cys Thr 1725
Ala Cys Thr Cys Ala Gly 1730	Gly Ala Gly Cys Ala 1735	Gly Cys Gly Cys 1740
Cys Thr Gly Ala Cys Cys 1745	Thr Ala Thr Cys Thr 1750	Gly Cys Cys Ala 1755
Cys Cys Cys Cys Cys Thr 1760	Thr Gly Gly Gly Gly 1765	Cys Gly Ala Gly 1770
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Ala Thr Gly Gly Gly Gly 1790	Cys Thr Gly Gly Ala 1795	Cys Thr Thr Cys 1800
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Ala Thr Cys Ala Cys Cys 1820	Gly Cys Cys Thr Gly 1825	Cys Cys Gly Ala 1830
Ala Thr Thr Gly Ala Thr 1835	Thr Gly Thr Gly Ala 1840	Gly Ala Cys Ala 1845
Cys Gly Gly Thr Ala Thr 1850	Ala Thr Cys Gly Thr 1855	Gly Gly Ala Ala 1860
Ala Ala Cys Thr Gly Cys 1865	Ala Thr Thr Gly 1870	Thr Ala Gly Gly 1875
Ala Thr Gly Gly Thr Cys 1880	Cys Ala Cys Ala Thr 1885	Gly Cys Cys Thr 1890
Gly Gly Cys Gly Ala Cys 1895	Gly Cys Cys Cys Cys 1900	Ala Thr Thr Cys 1905
Thr Gly Cys Ala Cys Thr 1910	Cys Cys Gly Ala 1915	Ala Cys Ala Gly 1920
Cys Ala Thr Ala Ala Ala 1925	Gly Ala Gly Thr Gly 1930	Thr Gly Cys Thr 1935
Gly Ala Ala Cys Cys Thr 1940	Gly Cys Ala Cys Thr 1945	Gly Gly Gly Gly 1950

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1970						1975					1980			
Cys	Thr	Gly	Thr	Gly	Thr	Ala	Gly	Ala	Ala	Cys	Ala	Cys	Cys	Cys
1985						1990					1995			
Thr	Gly	Thr	Ala	Ala	Cys	Cys	Thr	Gly	Ala	Cys	Thr	Ala	Gly	Gly
2000						2005					2010			
Thr	Ala	Thr	Ala	Ala	Thr	Ala	Ala	Gly	Gly	Ala	Ala	Cys	Thr	Gly
2015						2020					2025			
Ala	Gly	Cys	Ala	Thr	Gly	Gly	Thr	Gly	Ala	Ala	Gly	Ala	Thr	Cys
2030						2035					2040			
Cys	Cys	Thr	Thr	Cys	Cys	Ala	Ala	Ala	Ala	Cys	Ala	Thr	Cys	Thr
2045						2050					2055			
Gly	Cys	Ala	Ala	Ala	Gly	Thr	Ala	Cys	Cys	Thr	Gly	Gly	Ala	Gly
2060						2065					2070			
Ala	Ala	Gly	Ala	Ala	Gly	Thr	Thr	Cys	Ala	Ala	Cys	Ala	Ala	Gly
2075						2080					2085			
Thr	Cys	Thr	Gly	Ala	Gly	Ala	Ala	Gly	Thr	Ala	Cys	Ala	Thr	Cys
2090						2095					2100			
Ala	Gly	Thr	Gly	Ala	Ala	Ala	Ala	Cys	Ala	Thr	Thr	Cys	Thr	Gly
2105						2110					2115			
Gly	Thr	Gly	Cys	Thr	Gly	Gly	Ala	Cys	Ala	Thr	Cys	Thr	Thr	Cys
2120						2125					2130			
Thr	Thr	Thr	Gly	Ala	Ala	Gly	Cys	Thr	Cys	Thr	Gly	Ala	Ala	Thr
2135						2140					2145			
Thr	Ala	Cys	Gly	Ala	Gly	Ala	Cys	Cys	Ala	Thr	Thr	Gly	Ala	Ala
2150						2155					2160			
Cys	Ala	Gly	Ala	Ala	Gly	Ala	Ala	Ala	Gly	Cys	Ala	Thr	Ala	Thr
2165						2170					2175			
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2180						2185					2190			
Cys	Thr	Gly	Gly	Gly	Gly	Gly	Ala	Thr	Ala	Thr	Thr	Gly	Gly	Ala
2195						2200					2205			
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2210						2215					2220			
Thr	Thr	Cys	Ala	Thr	Cys	Gly	Gly	Cys	Gly	Cys	Cys	Ala	Gly	Cys
2225						2230					2235			
Cys	Thr	Gly	Cys	Thr	Gly	Ala	Cys	Ala	Ala	Thr	Thr	Cys	Thr	Gly
2240						2245					2250			
Gly	Ala	Gly	Cys	Thr	Gly	Thr	Thr	Thr	Gly	Ala	Cys	Thr	Ala	Cys
2255						2260					2265			
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						215					220			Gly
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	610					615					620					
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1700						1705					1710			
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1715						1720					1725			
Ala	Cys	Thr	Cys	Ala	Gly	Gly	Ala	Gly	Cys	Ala	Gly	Cys	Gly	Cys
1730						1735					1740			
Cys	Thr	Gly	Ala	Cys	Cys	Thr	Ala	Thr	Cys	Thr	Gly	Cys	Cys	Ala
1745						1750					1755			
Cys	Cys	Cys	Cys	Cys	Thr	Thr	Gly	Gly	Gly	Gly	Cys	Gly	Ala	Gly
1760						1765					1770			
Thr	Gly	Cys	Cys	Gly	Ala	Thr	Cys	Thr	Ala	Gly	Thr	Gly	Ala	Ala
1775						1780					1785			
Ala	Thr	Gly	Gly	Gly	Gly	Cys	Thr	Gly	Gly	Ala	Cys	Thr	Thr	Cys
1790						1795					1800			
Thr	Thr	Thr	Cys	Cys	Thr	Gly	Thr	Gly	Thr	Ala	Cys	Thr	Cys	Thr
1805						1810					1815			

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Ala	Thr	Cys	Ala	Cys	Cys	Gly	Cys	Cys	Thr	Gly	Cys	Cys	Gly	Ala
1820						1825					1830			
Ala	Thr	Thr	Gly	Ala	Thr	Thr	Gly	Thr	Gly	Ala	Gly	Ala	Cys	Ala
1835						1840					1845			
Cys	Gly	Gly	Thr	Ala	Thr	Ala	Thr	Cys	Gly	Thr	Gly	Gly	Ala	Ala
1850						1855					1860			
Ala	Ala	Cys	Thr	Gly	Cys	Ala	Ala	Thr	Thr	Gly	Thr	Ala	Gly	Gly
1865						1870					1875			
Ala	Thr	Gly	Gly	Thr	Cys	Cys	Ala	Cys	Ala	Thr	Gly	Cys	Cys	Thr
1880						1885					1890			
Gly	Gly	Cys	Gly	Ala	Cys	Gly	Cys	Cys	Cys	Cys	Ala	Thr	Thr	Cys
1895						1900					1905			
Thr	Gly	Cys	Ala	Cys	Thr	Cys	Cys	Cys	Gly	Ala	Ala	Cys	Ala	Gly
1910						1915					1920			
Cys	Ala	Thr	Ala	Ala	Ala	Gly	Ala	Gly	Thr	Gly	Thr	Gly	Cys	Thr
1925						1930					1935			
Gly	Ala	Ala	Cys	Cys	Thr	Gly	Cys	Ala	Cys	Thr	Gly	Gly	Gly	Gly
1940						1945					1950			
Cys	Thr	Gly	Cys	Thr	Gly	Gly	Cys	Thr	Gly	Ala	Gly	Ala	Ala	Gly
1955						1960					1965			
Gly	Ala	Thr	Ala	Gly	Thr	Ala	Ala	Cys	Thr	Ala	Cys	Thr	Gly	Cys
1970						1975					1980			
Cys	Thr	Gly	Thr	Gly	Thr	Ala	Gly	Ala	Ala	Cys	Ala	Cys	Cys	Cys
1985						1990					1995			
Thr	Gly	Thr	Ala	Ala	Cys	Cys	Thr	Gly	Ala	Cys	Thr	Ala	Gly	Gly
2000						2005					2010			
Thr	Ala	Thr	Ala	Ala	Thr	Ala	Ala	Gly	Gly	Ala	Ala	Cys	Thr	Gly
2015						2020					2025			
Ala	Gly	Cys	Ala	Thr	Gly	Gly	Thr	Gly	Ala	Ala	Gly	Ala	Thr	Cys
2030						2035					2040			
Cys	Cys	Thr	Thr	Cys	Cys	Ala	Ala	Ala	Ala	Cys	Ala	Thr	Cys	Thr
2045						2050					2055			
Gly	Cys	Ala	Ala	Ala	Gly	Thr	Ala	Cys	Cys	Thr	Gly	Gly	Ala	Gly
2060						2065					2070			
Ala	Ala	Gly	Ala	Ala	Gly	Thr	Thr	Cys	Ala	Ala	Cys	Ala	Ala	Gly
2075						2080					2085			
Thr	Cys	Thr	Gly	Ala	Gly	Ala	Ala	Gly	Thr	Ala	Cys	Ala	Thr	Cys
2090						2095					2100			
Ala	Gly	Thr	Gly	Ala	Ala	Ala	Ala	Cys	Ala	Thr	Thr	Cys	Thr	Gly
2105						2110					2115			
Gly	Thr	Gly	Cys	Thr	Gly	Gly	Ala	Cys	Ala	Thr	Cys	Thr	Thr	Cys
2120						2125					2130			
Thr	Thr	Thr	Gly	Ala	Ala	Gly	Cys	Thr	Cys	Thr	Gly	Ala	Ala	Thr
2135						2140					2145			
Thr	Ala	Cys	Gly	Ala	Gly	Ala	Cys	Cys	Ala	Thr	Thr	Gly	Ala	Ala
2150						2155					2160			
Cys	Ala	Gly	Ala	Ala	Gly	Ala	Ala	Ala	Gly	Cys	Ala	Thr	Ala	Thr
2165						2170					2175			
Gly	Ala	Gly	Gly	Thr	Gly	Gly	Cys	Cys	Gly	Cys	Thr	Cys	Thr	Gly
2180						2185					2190			
Cys	Thr	Gly	Gly	Gly	Gly	Gly	Ala	Thr	Ala	Thr	Thr	Gly	Gly	Ala

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2195					2200					2205				
Gly	Gly	Cys	Cys	Ala	Gly	Ala	Thr	Gly	Gly	Gly	Ala	Cys	Thr	Gly
2210						2215					2220			
Thr	Thr	Cys	Ala	Thr	Cys	Gly	Gly	Cys	Gly	Cys	Cys	Ala	Gly	Cys
2225						2230					2235			
Cys	Thr	Gly	Cys	Thr	Gly	Ala	Cys	Ala	Ala	Thr	Thr	Cys	Thr	Gly
2240						2245					2250			
Gly	Ala	Gly	Cys	Thr	Gly	Thr	Thr	Thr	Gly	Ala	Cys	Thr	Ala	Cys
2255						2260					2265			
Ala	Thr	Cys	Thr	Ala	Thr	Gly	Ala	Gly	Cys	Thr	Gly	Ala	Thr	Thr
2270						2275					2280			
Ala	Ala	Gly	Gly	Ala	Ala	Ala	Ala	Ala	Cys	Thr	Gly	Cys	Thr	Gly
2285						2290					2295			
Gly	Ala	Thr	Cys	Thr	Gly	Cys	Thr	Gly	Gly	Gly	Gly	Ala	Ala	Gly
2300						2305					2310			
Gly	Ala	Gly	Gly	Ala	Ala	Gly	Ala	Gly	Gly	Ala	Ala	Gly	Gly	Ala
2315						2320					2325			
Thr	Cys	Ala	Cys	Ala	Cys	Gly	Ala	Cys	Gly	Ala	Ala	Ala	Ala	Cys
2330						2335					2340			
Ala	Thr	Gly	Ala	Gly	Cys	Ala	Cys	Thr	Thr	Gly	Cys	Gly	Ala	Thr
2345						2350					2355			
Ala	Cys	Cys	Ala	Thr	Gly	Cys	Cys	Thr	Ala	Ala	Thr	Cys	Ala	Cys
2360						2365					2370			
Ala	Gly	Cys	Gly	Ala	Gly	Ala	Cys	Cys	Ala	Thr	Cys	Thr	Cys	Cys
2375						2380					2385			
Cys	Ala	Thr	Ala	Cys	Ala	Gly	Thr	Gly	Ala	Ala	Thr	Gly	Thr	Cys
2390						2395					2400			
Cys	Cys	Ala	Cys	Thr	Gly	Cys	Ala	Gly	Ala	Cys	Thr	Gly	Cys	Ala
2405						2410					2415			
Cys	Thr	Gly	Gly	Gly	Cys	Ala	Cys	Cys	Cys	Thr	Gly	Gly	Ala	Gly
2420						2425					2430			
Gly	Ala	Ala	Ala	Thr	Thr	Gly	Cys	Cys	Thr	Gly	Thr	Gly	Cys	Gly
2435						2440					2445			
Gly	Cys	Cys	Gly	Cys	Cys	Ala	Ala	Gly	Ala	Gly	Cys	Ala	Gly	Gly
2450						2455					2460			
Ala	Thr	Cys	Ala	Cys	Cys	Ala	Gly	Cys	Gly	Ala	Gly	Gly	Gly	Cys
2465						2470					2475			
Gly	Ala	Gly	Thr	Ala	Cys	Ala	Thr	Cys	Cys	Cys	Cys	Cys	Thr	Gly
2480						2485					2490			
Gly	Ala	Cys	Cys	Ala	Gly	Ala	Thr	Cys	Gly	Ala	Cys	Ala	Thr	Cys
2495						2500					2505			
Ala	Ala	Cys	Gly	Thr	Gly	Gly	Thr	Gly	Ala	Gly	Cys	Ala	Ala	Gly
2510						2515					2520			
Gly	Gly	Cys	Gly	Ala	Gly	Gly	Ala	Gly	Cys	Thr	Gly	Thr	Thr	Cys
2525						2530					2535			
Ala	Cys	Cys	Gly	Gly	Gly	Gly	Thr	Gly	Gly	Thr	Gly	Cys	Cys	Cys
2540						2545					2550			
Ala	Thr	Cys	Cys	Thr	Gly	Gly	Thr	Cys	Gly	Ala	Gly	Cys	Thr	Gly
2555						2560					2565			
Gly	Ala	Cys	Gly	Gly	Cys	Gly	Ala	Cys	Gly	Thr	Ala	Ala	Ala	Cys
2570						2575					2580			

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Gly	Gly	Cys	Cys	Ala	Cys	Ala	Ala	Gly	Thr	Thr	Cys	Ala	Gly	Cys
2585						2590					2595			
Gly	Thr	Gly	Thr	Cys	Cys	Gly	Gly	Cys	Gly	Ala	Gly	Gly	Gly	Cys
2600						2605					2610			
Gly	Ala	Gly	Gly	Gly	Cys	Gly	Ala	Thr	Gly	Cys	Cys	Ala	Cys	Cys
2615						2620					2625			
Thr	Ala	Cys	Gly	Gly	Cys	Ala	Ala	Gly	Cys	Thr	Gly	Ala	Cys	Cys
2630						2635					2640			
Cys	Thr	Gly	Ala	Ala	Gly	Thr	Thr	Cys	Ala	Thr	Cys	Thr	Gly	Cys
2645						2650					2655			
Ala	Cys	Cys	Ala	Cys	Cys	Gly	Gly	Cys	Ala	Ala	Gly	Cys	Thr	Gly
2660						2665					2670			
Cys	Cys	Cys	Gly	Thr	Gly	Cys	Cys	Cys	Thr	Gly	Gly	Cys	Cys	Cys
2675						2680					2685			
Ala	Cys	Cys	Cys	Thr	Cys	Gly	Thr	Gly	Ala	Cys	Cys	Ala	Cys	Cys
2690						2695					2700			
Thr	Thr	Cys	Gly	Gly	Cys	Thr	Ala	Cys	Gly	Gly	Cys	Cys	Thr	Gly
2705						2710					2715			
Cys	Ala	Gly	Thr	Gly	Cys	Thr	Thr	Cys	Gly	Cys	Cys	Cys	Gly	Cys
2720						2725					2730			
Thr	Ala	Cys	Cys	Cys	Cys	Gly	Ala	Cys	Cys	Ala	Cys	Ala	Thr	Gly
2735						2740					2745			
Ala	Ala	Gly	Cys	Ala	Gly	Cys	Ala	Cys	Gly	Ala	Cys	Thr	Thr	Cys
2750						2755					2760			
Thr	Thr	Cys	Ala	Ala	Gly	Thr	Cys	Cys	Gly	Cys	Cys	Ala	Thr	Gly
2765						2770					2775			
Cys	Cys	Cys	Gly	Ala	Ala	Gly	Gly	Cys	Thr	Ala	Cys	Gly	Thr	Cys
2780						2785					2790			
Cys	Ala	Gly	Gly	Ala	Gly	Cys	Gly	Cys	Ala	Cys	Cys	Ala	Thr	Cys
2795						2800					2805			
Thr	Thr	Cys	Thr	Thr	Cys	Ala	Ala	Gly	Gly	Ala	Cys	Gly	Ala	Cys
2810						2815					2820			
Gly	Gly	Cys	Ala	Ala	Cys	Thr	Ala	Cys	Ala	Ala	Gly	Ala	Cys	Cys
2825						2830					2835			
Cys	Gly	Cys	Gly	Cys	Cys	Gly	Ala	Gly	Gly	Thr	Gly	Ala	Ala	Gly
2840						2845					2850			
Thr	Thr	Cys	Gly	Ala	Gly	Gly	Gly	Cys	Gly	Ala	Cys	Ala	Cys	Cys
2855						2860					2865			
Cys	Thr	Gly	Gly	Thr	Gly	Ala	Ala	Cys	Cys	Gly	Cys	Ala	Thr	Cys
2870						2875					2880			
Gly	Ala	Gly	Cys	Thr	Gly	Ala	Ala	Gly	Gly	Gly	Cys	Ala	Thr	Cys
2885						2890					2895			
Gly	Ala	Cys	Thr	Thr	Cys	Ala	Gly	Gly	Gly	Ala	Gly	Gly	Ala	Cys
2900						2905					2910			
Gly	Gly	Cys	Ala	Ala	Cys	Ala	Thr	Cys	Cys	Thr	Gly	Gly	Gly	Gly
2915						2920					2925			
Cys	Ala	Cys	Ala	Ala	Gly	Cys	Thr	Gly	Gly	Ala	Gly	Thr	Ala	Cys
2930						2935					2940			
Ala	Ala	Cys	Thr	Ala	Cys	Ala	Ala	Cys	Ala	Gly	Cys	Cys	Ala	Cys
2945						2950					2955			

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Ala	Ala	Cys	Gly	Thr	Cys	Thr	Ala	Thr	Ala	Thr	Cys	Ala	Thr	Gly
2960						2965					2970			
Gly	Cys	Cys	Gly	Ala	Cys	Ala	Ala	Gly	Cys	Ala	Gly	Ala	Ala	Gly
2975						2980					2985			
Ala	Ala	Cys	Gly	Gly	Cys	Ala	Thr	Cys	Ala	Ala	Gly	Gly	Thr	Gly
2990						2995					3000			
Ala	Ala	Cys	Thr	Thr	Cys	Ala	Ala	Gly	Ala	Thr	Cys	Cys	Gly	Cys
3005						3010					3015			
Cys	Ala	Cys	Ala	Ala	Cys	Ala	Thr	Cys	Gly	Ala	Gly	Gly	Ala	Cys
3020						3025					3030			
Gly	Gly	Cys	Ala	Gly	Cys	Gly	Thr	Gly	Cys	Ala	Gly	Cys	Thr	Cys
3035						3040					3045			
Gly	Cys	Cys	Gly	Ala	Cys	Cys	Ala	Cys	Thr	Ala	Cys	Cys	Ala	Gly
3050						3055					3060			
Cys	Ala	Gly	Ala	Ala	Cys	Ala	Cys	Cys	Cys	Cys	Cys	Ala	Thr	Cys
3065						3070					3075			
Gly	Gly	Cys	Gly	Ala	Cys	Gly	Gly	Cys	Cys	Cys	Cys	Gly	Thr	Gly
3080						3085					3090			
Cys	Thr	Gly	Cys	Thr	Gly	Cys	Cys	Cys	Gly	Ala	Cys	Ala	Ala	Cys
3095						3100					3105			
Cys	Ala	Cys	Thr	Ala	Cys	Cys	Thr	Gly	Ala	Gly	Cys	Thr	Ala	Cys
3110						3115					3120			
Cys	Ala	Gly	Thr	Cys	Cys	Gly	Cys	Cys	Cys	Thr	Gly	Ala	Gly	Cys
3125						3130					3135			
Ala	Ala	Ala	Gly	Ala	Cys	Cys	Cys	Cys	Ala	Ala	Cys	Gly	Ala	Gly
3140						3145					3150			
Ala	Ala	Gly	Cys	Gly	Cys	Gly	Ala	Thr	Cys	Ala	Cys	Ala	Thr	Gly
3155						3160					3165			
Gly	Thr	Cys	Cys	Thr	Gly	Cys	Thr	Gly	Gly	Ala	Gly	Thr	Thr	Cys
3170						3175					3180			
Gly	Thr	Gly	Ala	Cys	Cys	Gly	Cys	Cys	Gly	Cys	Cys	Gly	Gly	Gly
3185						3190					3195			
Ala	Thr	Cys	Ala	Cys	Thr	Cys	Thr	Cys	Gly	Gly	Cys	Ala	Thr	Gly
3200						3205					3210			
Gly	Ala	Cys	Gly	Ala	Gly	Cys	Thr	Gly	Thr	Ala	Cys	Ala	Ala	Gly
3215						3220					3225			
Thr	Thr	Cys	Thr	Gly	Cys	Thr	Ala	Cys	Gly	Ala	Gly	Ala	Ala	Cys
3230						3235					3240			
Gly	Ala	Gly	Gly	Thr	Gly	Thr	Ala	Ala						
3245						3250								

<210> SEQ ID NO 37
<211> LENGTH: 20
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 37

Lys Ser Arg Ile Thr Ser Glu Gly Glu Tyr Ile Pro Leu Asp Gln Ile
1 5 10 15

Asp Ile Asn Val
20

<210> SEQ ID NO 38

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<211> LENGTH: 26
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 38

Met Asp Tyr Gly Gly Ala Leu Ser Ala Val Gly Arg Glu Leu Leu Phe
1          5          10          15

Val Thr Asn Pro Val Val Val Asn Gly Ser
          20          25

<210> SEQ ID NO 39
<211> LENGTH: 27
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 39

Met Ala Gly His Ser Asn Ser Met Ala Leu Phe Ser Phe Ser Leu Leu
1          5          10          15

Trp Leu Cys Ser Gly Val Leu Gly Thr Glu Phe
          20          25

<210> SEQ ID NO 40
<211> LENGTH: 23
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 40

Met Gly Leu Arg Ala Leu Met Leu Trp Leu Leu Ala Ala Ala Gly Leu
1          5          10          15

Val Arg Glu Ser Leu Gln Gly
          20

<210> SEQ ID NO 41
<211> LENGTH: 18
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 41

Met Arg Gly Thr Pro Leu Leu Leu Val Val Ser Leu Phe Ser Leu Leu
1          5          10          15

Gln Asp

<210> SEQ ID NO 42
<211> LENGTH: 5
<212> TYPE: PRT
<213> ORGANISM: Artificial sequence
<220> FEATURE:
<223> OTHER INFORMATION: synthetic amino acid sequence
<220> FEATURE:
<221> NAME/KEY: MISC_FEATURE
<222> LOCATION: (2)..(3)
<223> OTHER INFORMATION: X may be any amino acid

<400> SEQUENCE: 42

Val Xaa Xaa Ser Leu
1          5

<210> SEQ ID NO 43
<211> LENGTH: 5
<212> TYPE: PRT
<213> ORGANISM: Artificial sequence
<220> FEATURE:

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<223> OTHER INFORMATION: synthetic amino acid sequence														
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Val	Lys	Glu	Ser	Leu										
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<211> LENGTH: 5														
<212> TYPE: PRT														
<213> ORGANISM: Artificial sequence														
<220> FEATURE:														
<223> OTHER INFORMATION: synthetic amino acid sequence														
<400> SEQUENCE: 44														
Val	Leu	Gly	Ser	Leu										
1				5										
<210> SEQ ID NO 45														
<211> LENGTH: 16														
<212> TYPE: PRT														
<213> ORGANISM: Artificial sequence														
<220> FEATURE:														
<223> OTHER INFORMATION: synthetic amino acid sequence														
<400> SEQUENCE: 45														
Asn	Ala	Asn	Ser	Phe	Cys	Tyr	Glu	Asn	Glu	Val	Ala	Leu	Thr	Ser Lys
1				5				10						15
<210> SEQ ID NO 46														
<211> LENGTH: 6														
<212> TYPE: PRT														
<213> ORGANISM: Artificial sequence														
<220> FEATURE:														
<223> OTHER INFORMATION: synthetic amino acid sequence														
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<221> NAME/KEY: MISC_FEATURE														
<222> LOCATION: (2)..(2)														
<223> OTHER INFORMATION: X may be any amino acid														
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Phe	Xaa	Tyr	Glu	Asn	Glu									
1				5										
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<211> LENGTH: 7														
<212> TYPE: PRT														
<213> ORGANISM: Artificial sequence														
<220> FEATURE:														
<223> OTHER INFORMATION: synthetic amino acid sequence														
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Phe	Cys	Tyr	Glu	Asn	Glu	Val								
1				5										
<210> SEQ ID NO 48														
<211> LENGTH: 18														
<212> TYPE: PRT														
<213> ORGANISM: Artificial sequence														
<220> FEATURE:														
<223> OTHER INFORMATION: synthetic amino acid sequence														
<400> SEQUENCE: 48														
Met	Thr	Glu	Thr	Leu	Pro	Pro	Val	Thr	Glu	Ser	Ala	Val	Ala	Leu Gln
1				5					10					15

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Ala Glu

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<210> SEQ ID NO 49
<211> LENGTH: 19
<212> TYPE: PRT
<213> ORGANISM: Artificial sequence
<220> FEATURE:
<223> OTHER INFORMATION: synthetic amino acid sequence
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<400> SEQUENCE: 49

Ala Thr Asn Phe Ser Leu Leu Lys Gln Ala Gly Asp Val Glu Glu Asn
1 5 10 15

Pro Gly Pro

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<210> SEQ ID NO 50
<211> LENGTH: 18
<212> TYPE: PRT
<213> ORGANISM: Artificial sequence
<220> FEATURE:
<223> OTHER INFORMATION: synthetic amino acid sequence
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<400> SEQUENCE: 50

Glu Gly Arg Gly Ser Leu Leu Thr Cys Gly Asp Val Glu Glu Asn Pro
1 5 10 15

Gly Pro

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<210> SEQ ID NO 51
<211> LENGTH: 20
<212> TYPE: PRT
<213> ORGANISM: Artificial sequence
<220> FEATURE:
<223> OTHER INFORMATION: synthetic amino acid sequence
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<400> SEQUENCE: 51

Gln Cys Thr Asn Tyr Ala Leu Leu Lys Leu Ala Gly Asp Val Glu Ser
1 5 10 15

Asn Pro Gly Pro
20

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<210> SEQ ID NO 52
<211> LENGTH: 22
<212> TYPE: PRT
<213> ORGANISM: Artificial sequence
<220> FEATURE:
<223> OTHER INFORMATION: synthetic amino acid sequence
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<400> SEQUENCE: 52

Val Lys Gln Thr Leu Asn Phe Asp Leu Leu Lys Leu Ala Gly Asp Val
1 5 10 15

Glu Ser Asn Pro Gly Pro
20

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<210> SEQ ID NO 53
<211> LENGTH: 5
<212> TYPE: PRT
<213> ORGANISM: Artificial sequence
<220> FEATURE:
<223> OTHER INFORMATION: synthetic amino acid sequence
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<400> SEQUENCE: 53

Gly Ser Gly Gly Ser
1 5

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<210> SEQ ID NO 54
<211> LENGTH: 4
<212> TYPE: PRT
<213> ORGANISM: Artificial sequence
<220> FEATURE:
<223> OTHER INFORMATION: synthetic amino acid sequence

<400> SEQUENCE: 54

Gly Gly Gly Ser
1

<210> SEQ ID NO 55
<211> LENGTH: 4
<212> TYPE: PRT
<213> ORGANISM: Artificial sequence
<220> FEATURE:
<223> OTHER INFORMATION: synthetic amino acid sequence

<400> SEQUENCE: 55

Gly Gly Ser Gly
1

<210> SEQ ID NO 56
<211> LENGTH: 5
<212> TYPE: PRT
<213> ORGANISM: Artificial sequence
<220> FEATURE:
<223> OTHER INFORMATION: synthetic amino acid sequence

<400> SEQUENCE: 56

Gly Gly Ser Gly Gly
1 5

<210> SEQ ID NO 57
<211> LENGTH: 5
<212> TYPE: PRT
<213> ORGANISM: Artificial sequence
<220> FEATURE:
<223> OTHER INFORMATION: synthetic amino acid sequence

<400> SEQUENCE: 57

Gly Ser Gly Ser Gly
1 5

<210> SEQ ID NO 58
<211> LENGTH: 5
<212> TYPE: PRT
<213> ORGANISM: Artificial sequence
<220> FEATURE:
<223> OTHER INFORMATION: synthetic amino acid sequence

<400> SEQUENCE: 58

Gly Ser Gly Gly Gly
1 5

<210> SEQ ID NO 59
<211> LENGTH: 5
<212> TYPE: PRT
<213> ORGANISM: Artificial sequence
<220> FEATURE:
<223> OTHER INFORMATION: synthetic amino acid sequence

<400> SEQUENCE: 59

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Gly Gly Gly Ser Gly															
1	5														
<210> SEQ ID NO 60															
<211> LENGTH: 5															
<212> TYPE: PRT															
<213> ORGANISM: Artificial sequence															
<220> FEATURE:															
<223> OTHER INFORMATION: synthetic amino acid sequence															
<400> SEQUENCE: 60															
Gly Ser Ser Ser Gly															
1	5														
<210> SEQ ID NO 61															
<211> LENGTH: 22															
<212> TYPE: PRT															
<213> ORGANISM: Artificial sequence															
<220> FEATURE:															
<223> OTHER INFORMATION: synthetic amino acid sequence															
<400> SEQUENCE: 61															
Gly Ser Gly Ala Thr Asn Phe Ser Leu Leu Lys Gln Ala Gly Asp Val															
1	5				10				15						
Glu Glu Asn Pro Gly Pro															
20															
<210> SEQ ID NO 62															
<211> LENGTH: 314															
<212> TYPE: PRT															
<213> ORGANISM: Coccomyxa subellipsoidea															
<400> SEQUENCE: 62															
Met Ala Val His Gln Ile Gly Glu Gly Gly Leu Val Met Tyr Trp Val															
1	5				10				15						
Thr Phe Gly Leu Met Ala Phe Ser Ala Leu Ala Phe Ala Val Met Thr															
20				25				30							
Phe Thr Arg Pro Leu Asn Lys Arg Ser His Gly Tyr Ile Thr Leu Ala															
35				40				45							
Ile Val Thr Ile Ala Ala Ile Ala Tyr Tyr Ala Met Ala Ala Ser Gly															
50				55				60							
Gly Lys Ala Leu Val Ser Asn Pro Asp Gly Asn Leu Arg Asp Ile Tyr															
65				70				75				80			
Tyr Ala Arg Tyr Ile Asp Trp Phe Phe Thr Thr Pro Leu Leu Leu Leu															
85				90				95							
Asp Ile Ile Leu Leu Thr Gly Ile Pro Ile Gly Val Thr Leu Trp Ile															
100				105				110							
Val Leu Ala Asp Val Ala Met Ile Met Leu Gly Leu Phe Gly Ala Leu															
115				120				125							
Ser Thr Asn Ser Tyr Arg Trp Gly Tyr Tyr Gly Val Ser Cys Ala Phe															
130				135				140							
Phe Phe Val Val Leu Trp Gly Leu Phe Phe Pro Gly Ala Lys Gly Ala															
145				150				155				160			
Arg Ala Arg Gly Gly Gln Val Pro Gly Leu Tyr Phe Gly Leu Ala Gly															
165				170				175							
Tyr Leu Ala Leu Leu Trp Phe Gly Tyr Pro Ile Val Trp Gly Leu Ala															
180				185				190							

-continued

Glu	Gly	Ser	Asp	Tyr	Ile	Ser	Val	Thr	Ala	Glu	Ala	Ala	Ser	Tyr	Ala
		195					200					205			
Gly	Leu	Asp	Ile	Ala	Ala	Lys	Val	Val	Phe	Gly	Trp	Ala	Val	Met	Leu
	210					215					220				
Ser	His	Pro	Leu	Ile	Ala	Arg	Asn	Gln	Thr	Asp	Gly	Ser	Leu	Leu	Ile
225					230					235					240
Asn	Ser	Thr	Asn	Asp	Pro	Phe	Val	Ala	Ser	Thr	Thr	His	Ile	Pro	Glu
				245					250					255	
Arg	Gln	Gly	Gly	Ile	Phe	Gly	Gly	Leu	Met	Gly	Lys	Lys	Arg	Gly	Ala
			260					265					270		
Gly	Thr	Pro	Leu	Ala	Thr	Asn	Glu	Gly	Val	Pro	Arg	Lys	Ala	Ala	Pro
		275					280					285			
Thr	Ala	Ala	Thr	Thr	Thr	Ala	Gly	Asn	Pro	Ala	Thr	Ala	Ala	Glu	Val
	290					295					300				
Arg	Thr	Pro	Arg	Glu	Leu	Met	Ala	Arg	Leu						
305					310										

What is claimed is:

1. A system for modulating the membrane potential of a cell, the system comprising:

a first nucleic acid comprising a nucleotide sequence encoding a light-activated protein that is adapted to allow a first ion to pass through a cell membrane in response to light;

a second nucleic acid comprising a nucleotide sequence encoding a response protein that responds to the passage of the first ion through the cell membrane by allowing a second ion to pass through the cell membrane; and

a device configured to illuminate a target location with a light.

2. The system according to claim 1, wherein the light-activated protein is an ion pump.

3. The system according to claim 2, wherein the ion pump is a hydrogen ion pump, a sodium ion pump, a potassium ion pump, a chloride ion pump, or a calcium ion pump.

4. The system according to claim 1, wherein the light-activated protein is an ion channel.

5. The system according to claim 4, wherein the ion channel is a hydrogen ion channel, a sodium ion channel, a potassium ion channel, a chloride ion channel, or a calcium ion channel.

6. The system according to claim 1, wherein the response protein is an ion pump.

7. The system according to claim 6, wherein the ion pump is a hydrogen ion pump, a sodium ion pump, a potassium ion pump, a chloride ion pump, or a calcium ion pump.

8. The system according to claim 1, wherein the response protein is an ion channel, an ion exchange protein, or an ion co-transporter.

9. The system according to claim 8, wherein the ion channel is a hydrogen ion channel, a sodium ion channel, a potassium ion channel, a chloride ion channel, a calcium ion channel, or a cation channel.

10. The system according to claim 1, wherein the device is configured to illuminate the target location with light having a wavelength ranging from about 350 to about 750 nm.

11. The system according to claim 10, wherein the device is configured to illuminate the target location with light having a wavelength ranging from about 530 up to about 560 nm.

12. The system according to claim 1, wherein the device is configured to constantly illuminate the target location with a light.

13. The system according to claim 1, wherein the device is configured to illuminate the target location with pulses of light.

14. The system according to claim 12 or 13, wherein the device is configured to modulate the wavelength and/or the intensity of the light.

15. The system according to claim 13, wherein the device is configured to modulate the frequency and/or the duration of the pulses of light.

16. The system according to 12 or 13, wherein the device is configured to illuminate the target location in response to a user input.

17. The system according to 16, wherein the user input comprises: the wavelength of light, the intensity of light, the duration of a light pulse, the frequency of a light pulse, and/or the target location.

18. The system according to claim 1, wherein the device is adapted to be implanted in a subject.

19. The system according to claim 1, wherein the target location is: a cell, a portion of a cell, a plurality of cells, a bundle of nerve fibers, a neuromuscular junction, a central nervous system (CNS) tissue, a peripheral nervous system (PNS) tissue, or an anatomical region.

20. The system according to claim 1, wherein the first nucleic acid and the second nucleic acid are present within a single expression vector.

21. The system according to claim 1, wherein the nucleotide sequence encoding a light-activated protein that is adapted to allow a first ion to pass through a cell membrane in response to light is operably linked to a neuron-specific transcription control element.

22. The system according to claim 1, wherein the second nucleic acid comprising a nucleotide sequence encoding a response protein that responds to the passage of the first ion

through the cell membrane by allowing a second ion to pass through the cell membrane is operably linked to a neuron-specific transcription control element.

23. A pharmaceutical composition comprising:

a first nucleic acid comprising a nucleotide sequence encoding a light-activated protein that is adapted to allow a first ion to pass through a cell membrane in response to light;

a second nucleic acid comprising a nucleotide sequence encoding a response protein that responds to the passage of the first ion through the cell membrane by allowing a second ion to pass through the cell membrane.

24. The composition according to claim **23**, wherein the light-activated protein is an ion pump.

25. The composition according to claim **24**, wherein the ion pump is a hydrogen ion pump, a sodium ion pump, a potassium ion pump, a chloride ion pump, or a calcium ion pump.

26. The composition according to claim **21**, wherein the light-activated protein is an ion channel.

27. The composition according to claim **26**, wherein the ion channel is a hydrogen ion channel, a sodium ion channel, a potassium ion channel, a chloride ion channel, or a calcium ion channel.

28. The composition according to claim **23**, wherein the response protein is an ion pump.

29. The composition according to claim **28**, wherein the ion pump is a hydrogen ion pump, a sodium ion pump, a potassium ion pump, a chloride ion pump, or a calcium ion pump.

30. The composition according to claim **23**, wherein the response protein is an ion channel, an ion-exchange protein, or an ion co-transporter.

31. The composition according to claim **30**, wherein the ion channel is a hydrogen ion channel, a sodium ion channel, a potassium ion channel, a chloride ion channel, a calcium ion channel, or a cation channel.

32. The composition according to claim **23**, wherein the first nucleic acid and the second nucleic acid are present within a single expression vector.

33. The composition according to claim **23**, wherein the nucleotide sequence encoding a light-activated protein that is adapted to allow a first ion to pass through a cell membrane in response to light is operably linked to a neuron-specific transcription control element.

34. The composition according to claim **23**, wherein the second nucleic acid comprising a nucleotide sequence encoding a response protein that responds to the passage of the first ion through the cell membrane by allowing a second ion to pass through the cell membrane is operably linked to a neuron-specific transcription control element.

35. A cell comprising:

a first nucleic acid comprising a nucleotide sequence encoding a light-activated protein that is adapted to allow a first ion to pass through a cell membrane in response to light;

a second nucleic acid comprising a nucleotide sequence encoding a response protein that responds to the passage of the first ion through the cell membrane by allowing a second ion to pass through the cell membrane.

36. The cell according to claim **35**, wherein the light-activated protein is an ion pump.

37. The cell according to claim **36**, wherein the ion pump is a hydrogen ion pump, a sodium ion pump, a potassium ion pump, a chloride ion pump, or a calcium ion pump.

38. The cell according to claim **35**, wherein the light-activated protein is an ion channel.

39. The cell according to claim **38**, wherein the ion channel is a hydrogen ion channel, a sodium ion channel, a potassium ion channel, a chloride ion channel, or a calcium ion channel.

40. The cell according to claim **35**, wherein the response protein is an ion pump.

41. The cell according to claim **40**, wherein the ion pump is a hydrogen ion pump, a sodium ion pump, a potassium ion pump, a chloride ion pump, or a calcium ion pump.

42. The cell according to claim **35**, wherein the response protein is an ion channel, an ion exchange protein, or an ion co-transporter.

43. The cell according to claim **42**, wherein the ion channel is a hydrogen ion channel, a sodium ion channel, a potassium ion channel, a chloride ion channel, a calcium ion channel, or a cation channel.

44. The cell according to claim **35**, wherein the first nucleic acid and the second nucleic acid are present within a single expression vector.

45. The cell according to claim **35**, wherein the nucleotide sequence encoding a light-activated protein that is adapted to allow a first ion to pass through a cell membrane in response to light is operably linked to a neuron-specific transcription control element.

46. The cell according to claim **35**, wherein the second nucleic acid comprising a nucleotide sequence encoding a response protein that responds to the passage of the first ion through the cell membrane by allowing a second ion to pass through the cell membrane is operably linked to a neuron-specific transcription control element.

47. A method for modulating the membrane potential of a cell in response to light, the method comprising exposing a cell to light of an activating wavelength, wherein the cell is genetically modified with:

a) a first nucleic acid comprising a nucleotide sequence encoding a light-activated protein that is adapted to allow a first ion to pass through a cell membrane in response to light; and

b) a second nucleic acid comprising a nucleotide sequence encoding a response protein that responds to the passage of the first ion through the cell membrane by allowing a second ion to pass through the cell membrane.

48. The method according to claim **47**, wherein the light-activated protein is an ion pump.

49. The method according to claim **48**, wherein the ion pump is a hydrogen ion pump, a sodium ion pump, a potassium ion pump, a chloride ion pump, or a calcium ion pump.

50. The method according to claim **47**, wherein the light-activated protein is an ion channel.

51. The method according to claim **50**, wherein the ion channel is a hydrogen ion channel, a sodium ion channel, a potassium ion channel, a chloride ion channel, or a calcium ion channel.

52. The method according to claim **47**, wherein the response protein is an ion pump.

53. The method according to claim **52**, wherein the ion pump is a hydrogen ion pump, a sodium ion pump, a potassium ion pump, a chloride ion pump, or a calcium ion pump.

54. The method according to claim **47**, wherein the response protein is an ion channel, an ion exchange protein, or an ion co-transporter.

55. The method according to claim **54**, wherein the ion channel is a hydrogen ion channel, a sodium ion channel, a potassium ion channel, a chloride ion channel, a calcium ion channel, or a cation channel.

56. The method according to claim **47**, wherein exposing the cell to light of an activating wavelength inhibits retrograde propagating action potentials within the cell.

57. A method for inhibiting the activity of a voltage-gated sodium channel in a cell in response to light, the method comprising exposing the cell to light of an activating wavelength, wherein the cell is genetically modified with:

- a) a first nucleic acid comprising a nucleotide sequence encoding a light-activated protein that is adapted to allow a plurality of hydrogen ions to pass through a cell membrane in an outward direction in response to light; and
- b) a second nucleic acid comprising a nucleotide sequence encoding a response protein that responds to the presence of the hydrogen ions on or near the external surface of the cell membrane by allowing a plurality of sodium ions to pass through the cell membrane in an inward direction, causing sustained depolarization of the cell membrane, thereby inactivating the voltage-gated sodium ion channel and inhibiting its activity.

58. The method according to claim **57**, wherein the light-activated protein is an ion pump.

59. The method according to claim **58**, wherein the ion pump is a hydrogen ion pump, a sodium ion pump, a potassium ion pump, a chloride ion pump, or a calcium ion pump.

60. The method according to claim **57**, wherein the light-activated protein is an ion channel.

61. The method according to claim **60**, wherein the ion channel is a hydrogen ion channel, a sodium ion channel, a potassium ion channel, a chloride ion channel, or a calcium ion channel.

62. The method according to claim **57**, wherein the response protein is an ion pump.

63. The method according to claim **62**, wherein the ion pump is a hydrogen ion pump, a sodium ion pump, a potassium ion pump, a chloride ion pump, or a calcium ion pump.

64. The method according to claim **57**, wherein the response protein is an ion channel, an ion exchange protein, or an ion co-transporter.

65. The method according to claim **64**, wherein the ion channel is a hydrogen ion channel, a sodium ion channel, a potassium ion channel, a chloride ion channel, a calcium ion channel, or a cation channel.

66. The method according to claim **57**, wherein exposing the cell to light of an activating wavelength inhibits retrograde or anterograde propagating action potentials within the cell.

67. A method of treating a condition in a subject, the method comprising:

genetically modifying a target cell of the subject with:

- a) a first nucleic acid comprising a nucleotide sequence encoding a light-activated protein that is adapted to allow a first ion to pass through a membrane of the target cell in response to light; and
- b) a second nucleic acid comprising a nucleotide sequence encoding a response protein that responds to the passage of the first ion through the membrane of the target cell by allowing a second ion to pass through the membrane, wherein passage of the second ion through the membrane treats the condition; and

exposing the target cell to light of an activating wavelength to treat the subject for the condition.

68. The method according to claim **67**, wherein the light-activated protein is an ion pump.

69. The method according to claim **68**, wherein the ion pump is a hydrogen ion pump, a sodium ion pump, a potassium ion pump, a chloride ion pump, or a calcium ion pump.

70. The method according to claim **67**, wherein the light-activated protein is an ion channel.

71. The method according to claim **70**, wherein the ion channel is a hydrogen ion channel, a sodium ion channel, a potassium ion channel, a chloride ion channel, or a calcium ion channel.

72. The method according to claim **67**, wherein the response protein is an ion pump.

73. The method according to claim **72**, wherein the ion pump is a hydrogen ion pump, a sodium ion pump, a potassium ion pump, a chloride ion pump, or a calcium ion pump.

74. The method according to claim **67**, wherein the response protein is an ion channel, an ion exchange protein, or an ion co-transporter.

75. The method according to claim **74**, wherein the ion channel is a hydrogen ion channel, a sodium ion channel, a potassium ion channel, a chloride ion channel, a calcium ion channel, or a cation channel.

76. The method according to claim **67**, wherein exposing the cell to light of an activating wavelength inhibits retrograde or anterograde propagating action potentials within the cell.

77. The method according to claim **67**, wherein the condition is a cardiac condition, a gastrointestinal condition, an endocrine condition, a neurological condition, or a psychiatric condition.

78. A method for treating a condition in a subject, the method comprising:

genetically modifying a nerve cell of the subject with:

- a) a first nucleic acid comprising a nucleotide sequence encoding a light-activated protein that is adapted to allow a plurality of hydrogen ions to pass through a membrane of the nerve cell in an outward direction in response to light; and
- b) a second nucleic acid comprising a nucleotide sequence encoding a response protein that responds to the passage of the plurality of hydrogen ions through the membrane of the nerve cell by allowing a plurality of sodium ions to pass through the membrane in an inward direction, wherein passage of the plurality of sodium ions through the membrane depolarizes the membrane and inactivates a voltage-

gated sodium channel in the membrane of the nerve cell, and thereby treats the neurological condition; and

exposing the nerve cell to light of an activating wavelength to treat the subject for the condition.

79. The method according to claim **78**, wherein the light-activated protein is a hydrogen ion pump.

80. The method according to claim **78**, wherein the light-activated protein is a hydrogen ion channel.

81. The method according to claim **78**, wherein the response protein is a sodium ion pump.

82. The method according to claim **78**, wherein the response protein is a sodium ion channel, a sodium ion exchange protein, or a sodium ion-cotransporter.

83. The method according to claim **78**, wherein exposing the cell to light of an activating wavelength inhibits retrograde or anterograde propagating action potentials within the cell.

84. The method according to claim **78**, wherein the condition is a cardiac condition, a gastrointestinal condition, or a neurological condition.

85. A method of selectively inhibiting retrograde propagating action potentials within a nerve cell or a portion thereof, the method comprising:

genetically modifying the nerve cell with:

- a) a first nucleic acid comprising a nucleotide sequence encoding a light-activated protein that is adapted to allow a plurality of hydrogen ions to pass through a membrane of the nerve cell in response to light; and
- b) a second nucleic acid comprising a nucleotide sequence encoding a response protein that responds to the passage of the hydrogen ions through the membrane of the nerve cell by allowing a plurality of sodium ions to pass through the membrane, wherein passage of the sodium ions through the membrane depolarizes the membrane and inactivates a plurality of voltage-gated sodium channels in the membrane of the nerve cell that cause retrograde propagating action potentials; and

exposing the nerve cell, or a portion thereof, to light of an activating wavelength to inhibit retrograde propagating action potentials therein.

86. The method according to claim **85**, wherein the light-activated protein is a hydrogen ion pump.

87. The method according to claim **85**, wherein the light-activated protein is a hydrogen ion channel.

88. The method according to claim **85**, wherein the response protein is a sodium ion pump.

89. The method according to claim **85**, wherein the response protein is a sodium ion channel, a sodium ion exchange protein, or a sodium ion co-transporter.

90. A kit comprising:

- a first nucleic acid comprising a nucleotide sequence encoding a light-activated protein that is adapted to allow a first ion to pass through a cell membrane in response to light; and
- a second nucleic acid comprising a nucleotide sequence encoding a response protein that responds to the passage of the first ion through the cell membrane by allowing a second ion to pass through the cell membrane.

91. The kit according to claim **90**, wherein the light-activated protein is an ion pump.

92. The kit according to claim **91**, wherein the ion pump is a hydrogen ion pump, a sodium ion pump, a potassium ion pump, a chloride ion pump, or a calcium ion pump.

93. The kit according to claim **90**, wherein the light-activated protein is an ion channel, an ion exchange protein, or an ion co-transporter.

94. The kit according to claim **93**, wherein the ion channel is a hydrogen ion channel, a sodium ion channel, a potassium ion channel, a chloride ion channel, a calcium ion channel, or a cation channel.

95. The kit according to claim **90**, wherein the response protein is an ion pump.

96. The kit according to claim **95**, wherein the ion pump is a hydrogen ion pump, a sodium ion pump, a potassium ion pump, a chloride ion pump, or a calcium ion pump.

97. The kit according to claim **90**, wherein the response protein is an ion channel.

98. The kit according to claim **97**, wherein the ion channel is a hydrogen ion channel, a sodium ion channel, a potassium ion channel, a chloride ion channel, or a calcium ion channel.

99. The kit according to claim **90**, further comprising a device configured to illuminate a target location with a light.

100. The kit according to claim **99**, wherein the device is configured to illuminate the target location with light having a wavelength ranging from about 350 to about 750 nm.

101. The kit according to claim **99**, wherein the device is configured to illuminate the target location with light having a wavelength ranging from about 530 up to about 560 nm.

102. The kit according to claim **99**, wherein the device is configured to constantly illuminate the target location with a light.

103. The kit according to claim **99**, wherein the device is configured to illuminate the target location with pulses of light.

104. The kit according to claim **102** or **103**, wherein the device is configured to modulate the wavelength and/or the intensity of the light.

105. The kit according to claim **103**, wherein the device is configured to modulate the frequency and/or duration of the pulses of light.

106. The kit according to claim **102** or **103**, wherein the device is configured to illuminate the target location in response to a user input.

107. The kit according to claim **106**, wherein the user input comprises: the wavelength of light, the intensity of light, the duration of a light pulse, the frequency of a light pulse, and/or the target location.

108. The kit according to claim **90**, wherein the device is adapted to be implanted in a subject.

109. The kit according to claim **90**, wherein the target location is: a cell, a portion of a cell, a plurality of cells, a bundle of nerve fibers, a neuromuscular junction, a central nervous system (CNS) tissue, a peripheral nervous system (PNS) tissue, or an anatomical region.

110. A fusion polypeptide comprising:

- a) a light-responsive protein that is adapted to allow a first ion to pass through a cell membrane in response to light; and
- b) a response protein that responds to the passage of the first ion through the cell membrane by allowing a second ion to pass through the cell membrane.

111. The fusion polypeptide according to claim **110**, wherein the fusion polypeptide comprises, in order from amino terminus to carboxyl terminus:

- a) a light-responsive protein that is adapted to allow a first ion to pass through a cell membrane in response to light;
- b) a membrane trafficking signal;
- c) a response protein that responds to the passage of the first ion through the cell membrane by allowing a second ion to pass through the cell membrane; and
- d) a membrane trafficking signal.

112. The fusion polypeptide according to claim **110** or **111**, wherein the response protein comprises an amino acid sequence having at least 80%, at least 85%, at least 90%, at least 95%, at least 98%, at least 99%, or 100%, amino acid sequence identity to the ASIC2a polypeptide amino acid sequence set forth in SEQ ID NO:19.

113. The fusion polypeptide according to claim **111**, wherein the membrane trafficking signal comprises the amino acid sequence KSRITSEGEYIPLDQIDINV (SEQ ID NO:37).

114. The fusion polypeptide according to any one of claims **110-113**, further comprising an endoplasmic reticulum (ER) export signal.

115. The fusion polypeptide according to claim **114**, wherein the ER export signal comprises the amino acid sequence FCYENEV (SEQ ID NO:47)

116. The fusion polypeptide according to any one of claims **110-115**, wherein the fusion polypeptide comprises, interposed between the light-responsive polypeptide and the response protein, a self-cleaving polypeptide.

117. The fusion polypeptide according to claim **116**, wherein the self-cleaving polypeptide comprises the amino acid sequence ATNFSLLKQAGDVEENPGP (SEQ ID NO:49).

118. A nucleic acid comprising a nucleotide sequence encoding the fusion polypeptide according to any one of claims **110-117**.

119. A recombinant expression vector comprising the nucleic acid according to claim **118**.

120. The recombinant expression vector according to claim **119**, wherein the nucleotide sequence encoding the fusion polypeptide is operably linked to a neuron-specific transcriptional control element.

121. A cell genetically modified with the recombinant expression vector according to claim **119**.

122. The cell according to claim **121**, wherein the cell is a neuron.

* * * * *