B'SYS GmbH

CHO Na$_V$1.5 Duo Cell Line

Specification Sheet

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1   BACKGROUND

1.1   The cardiac INa is encoded by Na$_V$1.5

Around 20 different ionic currents can be divided into depolarizing and repolarizing currents involved in the generation of the cardiac action potential. The rapid depolarizing of the cell membrane at the beginning of the cardiac action potential is due to the activation of voltage-dependent sodium Na$_V$1.5 channels..

1.2   The Long QT Syndrome 3

Mutations in the SCNA5 gene result in persistent depolarizing current throughout action potential duration causing the Long QT Syndrome 3 phenotype.

1.3   B'SYS' CHO Na$_V$1.5 Duo cells

B'SYS has designed a CHO Na$_V$1.5-Duo cell line with constitutive coexpression of human Na$_V$1.5 sodium channels. The human Na$_V$1.5 cDNA was cloned and transfected twice (two different vectors) into CHO cells and then the functional properties of the Na$_V$1.5 channels suitable for manual and automated patch-clamping (cells were validated on Sophion Q-Patch ™ and Sophion Qube ™).

2 PRODUCT SHIPMENT

2.1 Product Format

CHO cells stably transfected with recombinant human Na$_V$1.5 channel:

- 1 x 0.5 mL aliquots of frozen cells at 1.2 E+06 cells/mL
- Cells are frozen in complete medium with 10% DMSO

2.2 Mycoplasma Certificate

B'SYS periodically tests cells for presence of mycoplasma by means of highly sensitive PCR based assays. All delivered cells are free of mycoplasma.

3   VALIDATION OF CHO NAV1.5-DUO CELLS

3.1   Manual Patch-clamp

B'SYS CHO Na$_V$1.5-Duo cell line was designed to increase current amplitudes and expression for more passages. A depolarization from -120 mV to 0 mV resulted in a peak current amplitude of 9.8 nA (n=50). The current amplitude was stable for over 30 passages. Biophysical parameters are comparable with the B'SYS CHO Na$_V$1.5 cell line.
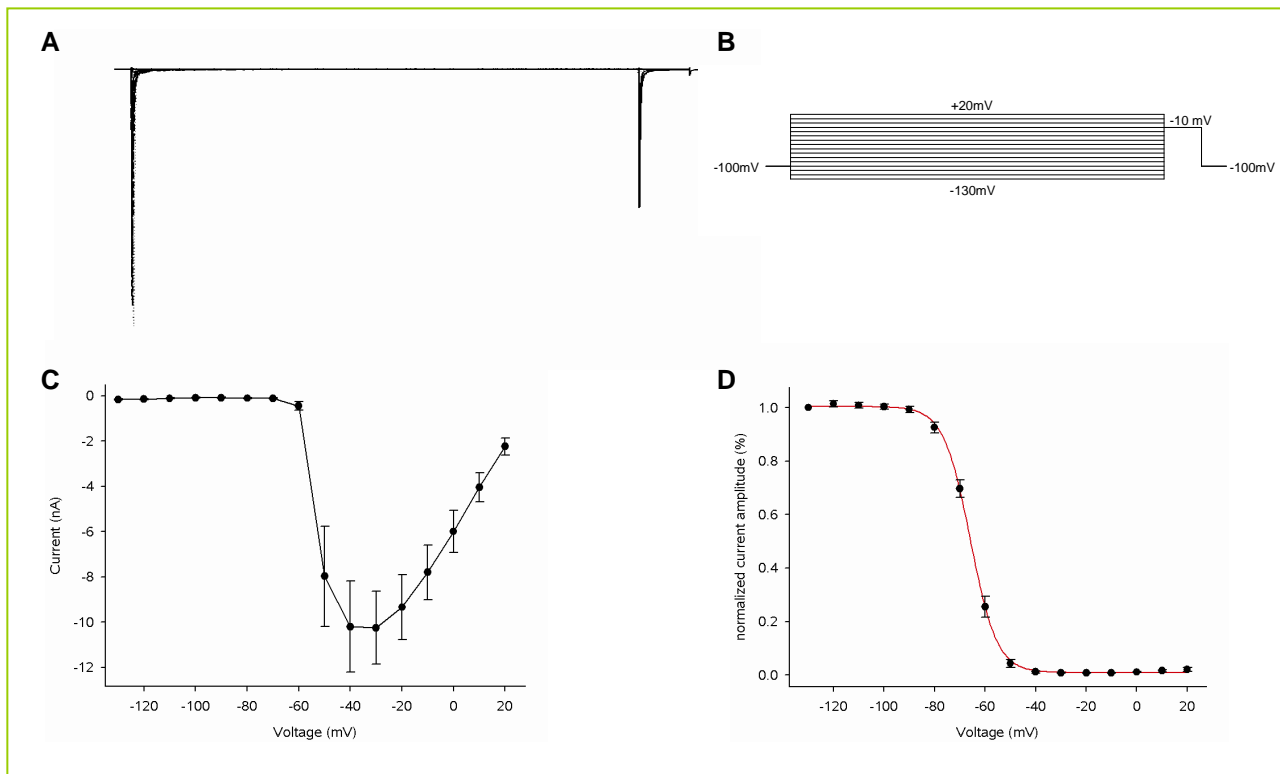
Fig. 1: Biophysical Characterization of stably transfected CHO Na$_V$1.5 cells. A) representative current recording. Cells were stimulated by the voltage protocol shown in b). C) IV curve if the Na$_V$1.5 channel. Peak current were measured at the beginning of the voltage pulse (n=11). D) Inactivation curve of the Na$_V$1.5 channel. The current amplitudes were measured at the beginning of the tail current. Data were fit by a Boltzmann equation. The V$_{0.5}$ value was 65.83 ± 0.88 mV (n=11). No currents were recorded in untransfected cells (data not shown).

Fig. 2: Dose response curves for Propafenone and Quinidine at stimulation frequencies of 1 and 3Hz.

The results can be summarized as follows.

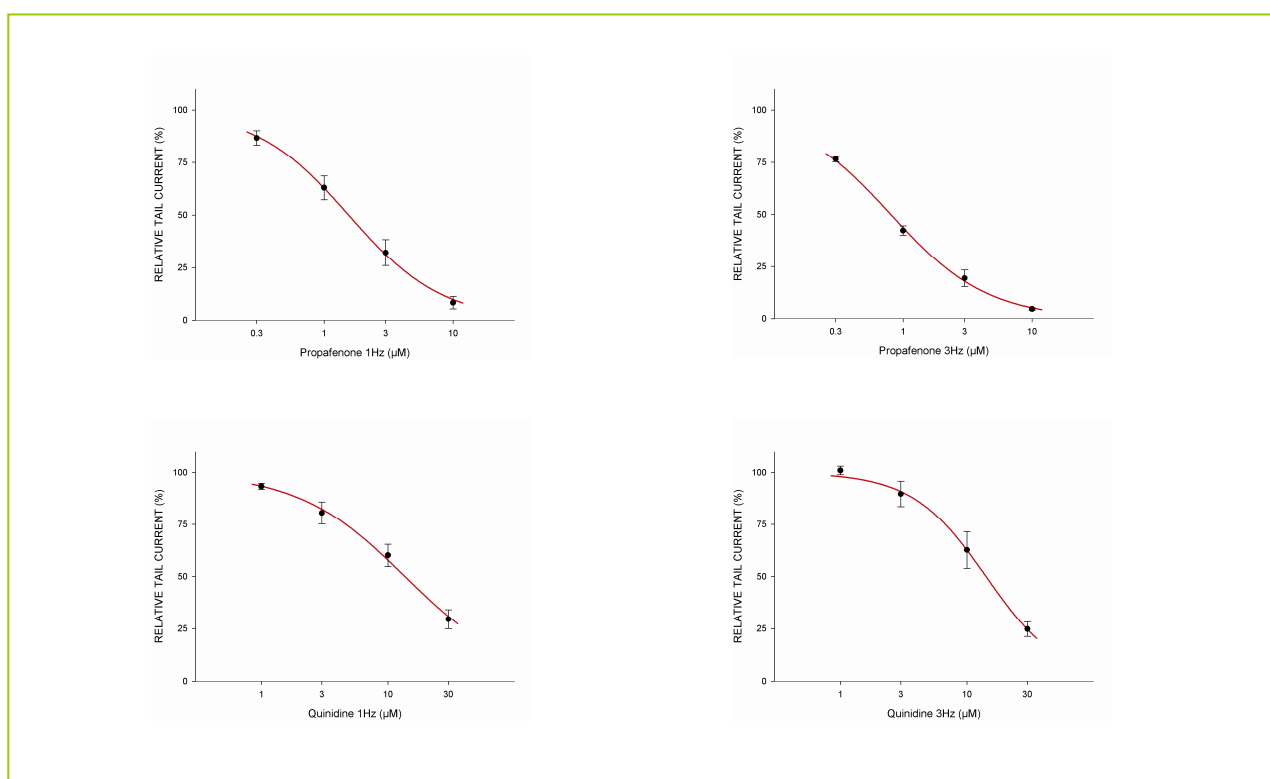| Application / stimulation frequency	IC$_{50}$ value (µM)	Hill coefficient
Propafenone / 1Hz	1.55	1.19
Propafenone / 3Hz	0.80	1.15
Quinidine / 1Hz	13.64	1.02
Quinidine / 3Hz	14.15	1.48

The observed inhibition of Na$_V$1.5 inward peak currents by Propafenone and Quinidine are in line with its known pharmacological profile (Persson et al. 2005, Harmer et al. 2008)

3.2 Automated Patch-clamp

The CHO Na$_V$1.5-Duo cell line was validated on the automated patch-clamp system Q-Patch 16.
The bath solution contained (in mM) NaCl 137 mM KCl 4 mM, CaCl$_2$ 1.8 mM, MgCl$_2$ 1 mM, HEPES 10 mM, D-Glucose 10 mM, pH (NaOH) 7.4. The intracellular solution consisted of (in mM) CsF 135 mM, NaCl 10 mM, HEPES 10 mM, EGTA 5 mM, pH (CsOH) 7.3.
To analyze the effect of the tested compound in the resting, fast and slow inactivated state the following voltage protocol was applied to the cells in the whole cell configuration.
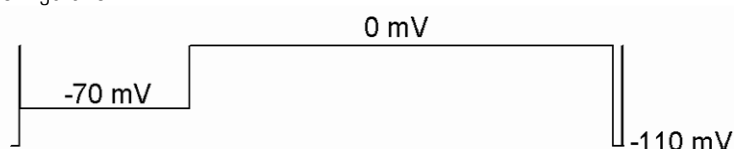
The cells were clamped at a holding potential of -110 mV. To test the channels in the resting state a first test pulse to 0 mV was applied (10 ms). Then the cells were clamped to -70 mV for 2 s followed by the second test pulse to 0 mV (10 ms duration). This test pulse results in the current values for the fast inactivated sodium channels. For the slow inactivation, channels were depolarized to 0 mV for a duration of 5 s. To recover the fast inactivated channels the cells were depolarized to -110 mV for 100 ms, followed by the third test pulse for the slow inactivated channels (0 mV, 10 ms). This voltage protocol was applied three times for each test concentration, after an incubation time of 90 s.

Fig. 1: Representative recordings of test pulses (0 mV) for the resting (A), fast (B) and slow (C) inactivated state at Lidocaine concentrations of 0.03, 0.3 and 3.0 mM

The effect of three Lidocaine concentrations on Na$_V$1.5 currents in the resting, fast and slow inactivated state was analyzed. Representative current recordings of the test pulses in the resting, fast and slow inactivated state are shown in Fig. 1.
The dose response curves of each state were generated and the IC$_{50}$ values and the Hill coefficients were calculated.

	resting	fast inactivated	slow inactivated
HillSlope	-1.190	-0.9866	-1.285
EC50 [mM]	1.646	0.2399	1.413
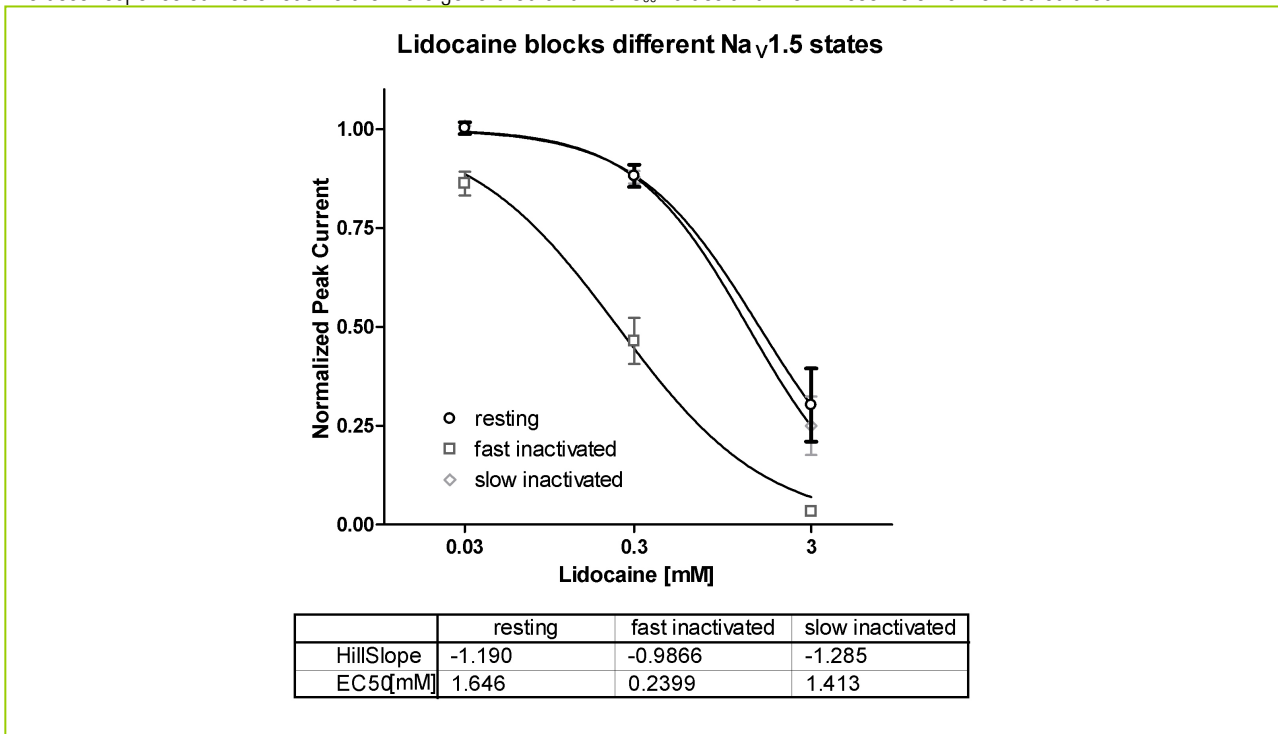
Fig. 2: Dose response curves for Lidocaine for the resting, fast and slow inactivated state.

Additionally, the effects of four Terfenadine concentrations were analyzed on Na$_V$1.5 currents in the three states. Representative current recordings of the test pulses and the corresponding dose response curves in the resting, fast and slow inactivated state are shown in Fig. 3.
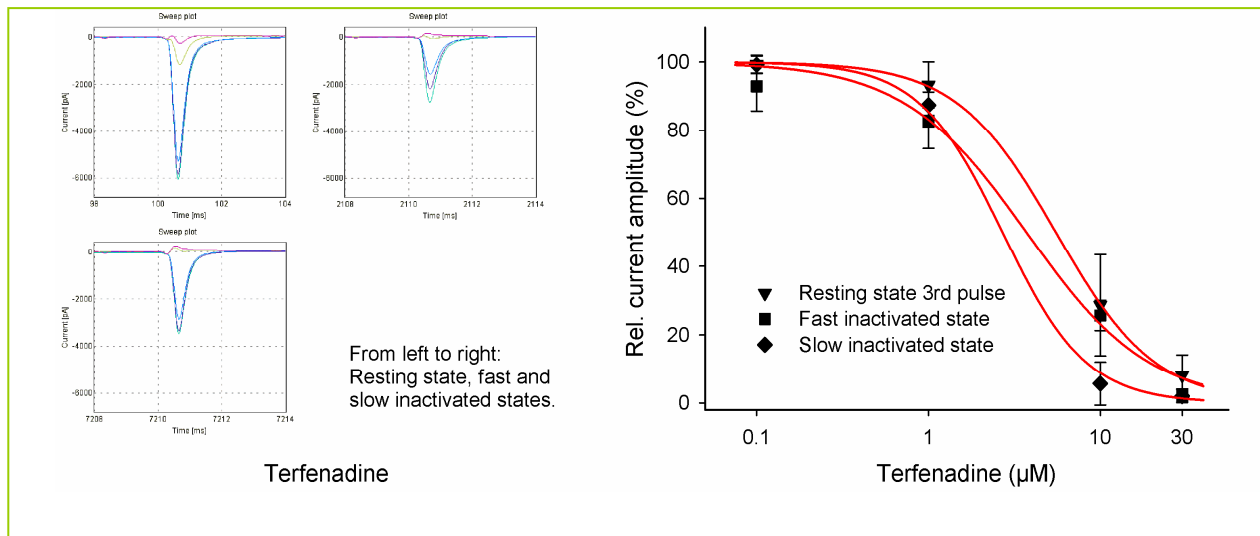
Fig. 3: Dose response curves for Terfenadine for the resting, fast and slow inactivated state.

The dose response curves of the four concentrations of Terfenadine generated the following IC$_{50}$ values.

Application / stimulation frequency	IC$_{50}$ value (µM)	Hill coefficient
Resting 3rd	5.5	1.5
Fast inactivated	3.7	1.2
Slow inactivated	2.7	1.8

A change in the kinetic of the channel in all three states was analyzed by application of Anthopleurin C.
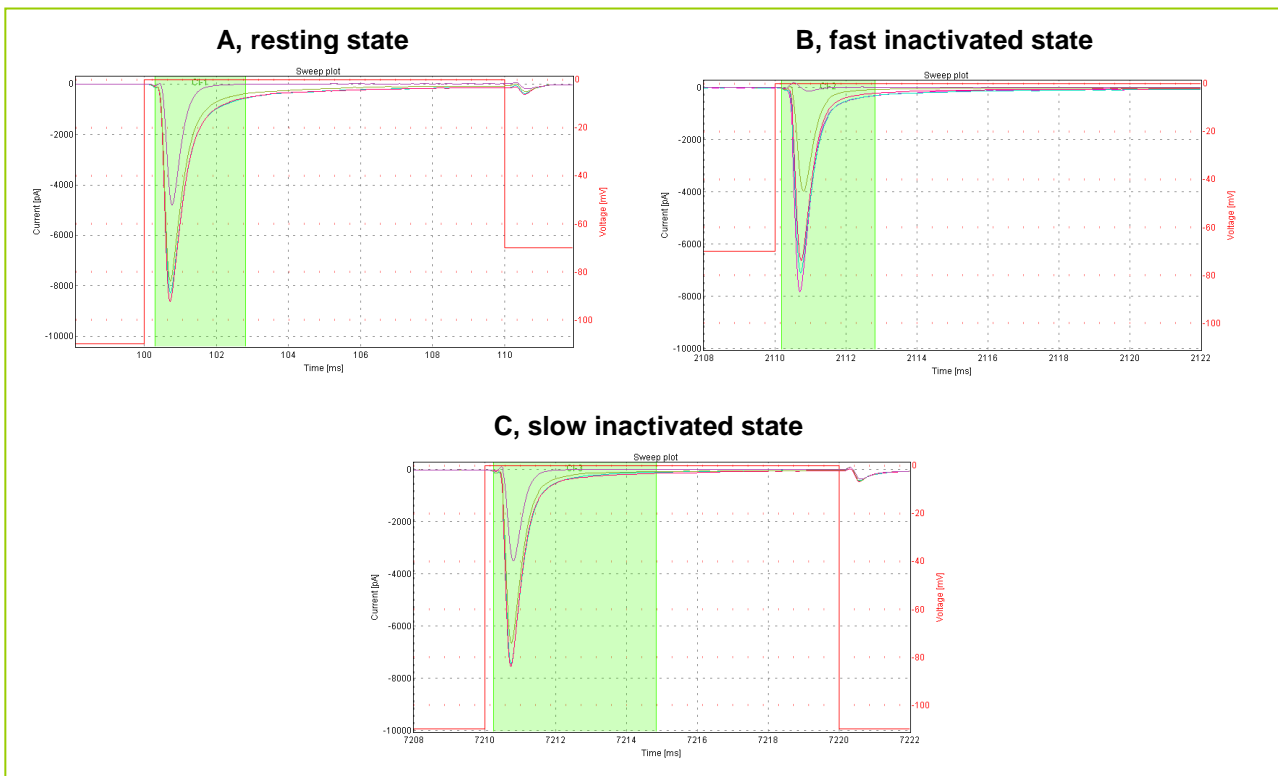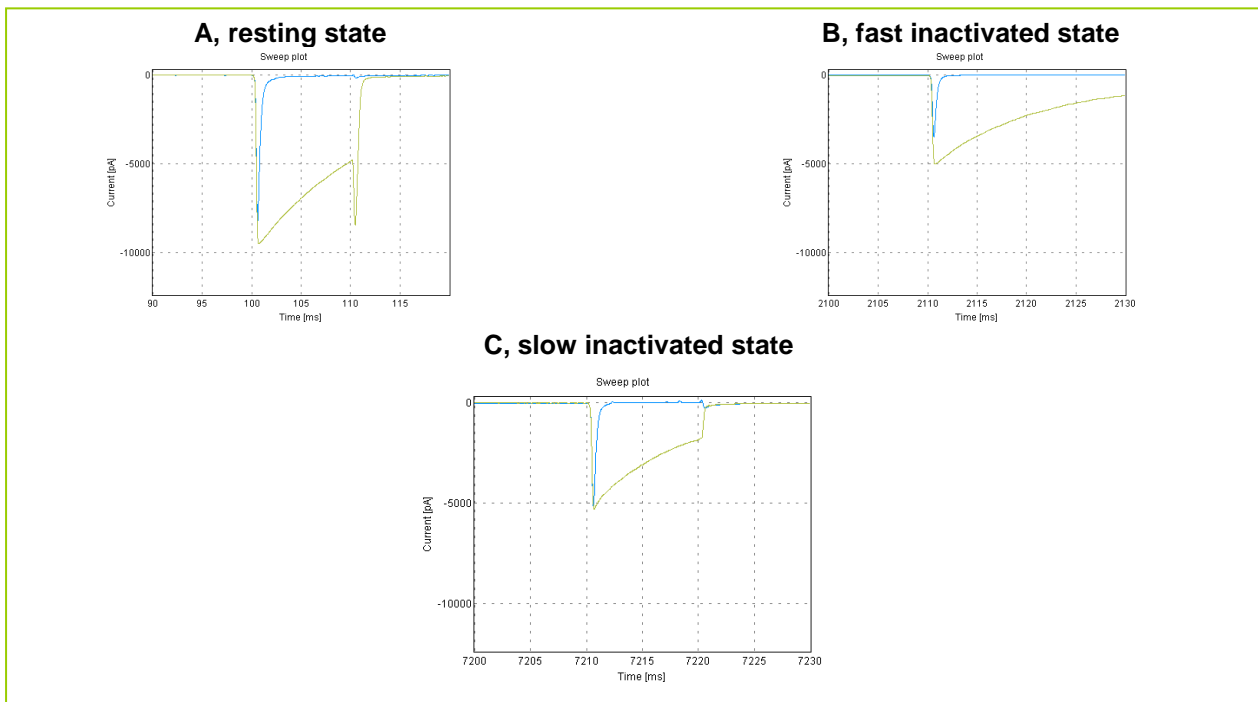

Fig. 4: Representative recordings of test pulses (0 mV) for the resting (A), fast (B) and slow (C) inactivated state at an Anthopleurin C concentration of 1nM.

Anthopleurin C increased the time course of inactivation resulting in increased current amplitudes at the end of the test pulse.

4   CELL CULTURE CONDITIONS

4.1   General

CHO Na$_V$1.5-Duo cells are incubated at 37°C in a humidified atmosphere with 5% CO$_2$ (rel. humidity > 95%). The cells are continuously maintained and passaged in sterile culture flasks containing F12 (HAM) medium supplemented with 9% fetal bovine serum, 0.9% Penicillin/Streptomycin solution and 250 µg/mL G-418 sulphate and 1 µg/mL Puromycine. The CHO Na$_V$1.5 cells are passaged at a confluence of about 80%. For manual electrophysiological measurements the cells are seeded onto e.g. 35 mm sterile culture dishes containing complete medium.

- All solutions and equipment coming in contact with the cells must be sterile.
- Use proper sterile technique and work in a laminar flow hood.
- Be sure to have frozen cell stocks at hand before starting experiments.
- Cells should be split every 2-3 days at 70% - 80% confluency at 1:3 to 1:5 ratio.

4.2   Recommended Complete Medium

- F12 (HAM) with L-Glutamine or GlutaMAX I
- 9% FBS
- 0.9% Penicillin/Streptomycin

4.3   Antibiotics

- CHO Na$_V$1.5-Duo clones were selected under 500 µg/mL G-418 sulphate and 2 µg/mL Puromycine antibiotic pressure.
- To cultivate CHO Na$_V$1.5-Duo cells, also a reduced antibiotic pressure (250µg/mL G-418 sulphate and 1 µg/mL Puromycine) can be used.

Remark: The permanent application of high antibiotic pressure has no effect on current density.

4.4   Thawing Cells

- Remove vial of cells from liquid nitrogen and thaw quickly at 37°C.
- Decontaminate outside of vial with 70% ethanol.
- Transfer cells to a T-75 culture flask containing 10 mL complete medium.
- Incubate cells at 37°C for 4-6 h to allow the cells to attach to the bottom of flask.
- Aspirate off the medium and replace with 10 mL complete medium & antibiotics.
- Antibiotics: 250 µg/mL G-418 sulphate and 1 µg/mL Puromycine
- Incubate cells and check them daily until 70% - 80% confluency is reached.

4.5   Splitting Cells

- When cells are 70% - 80% confluent remove medium.
- Wash cells once with 1x PBS to remove excess medium.
- Add 1x Trypsin/EDTA and incubate 30 s at room temperature.
- Remove Trypsin/EDTA quickly and incubate cells for 2 min at 37°C.
- Detach cells, add complete medium and pipet up and down to break clumps of cells.
- Passage cells into new flask with complete medium and antibiotics at 1:3 to 1:5 ratio.
- Use remaining suspension for counting the cells.

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4.6   Freezing Medium

- Mix 0.9 mL fresh complete medium and 0.1 mL DMSO for every 1 mL freezing medium.
- Sterilize freezing medium by means of appropriate micro filter (0.1 µm – 0.2 µm).

4.7   Freezing Cells

- Prepare fresh freezing medium and keep it on ice.
- Cells should have 80% - 90% confluency prior to freezing.
- Remove the complete medium.
- Wash cells once with 1x PBS to remove excess medium.
- Add 1x Trypsin/EDTA and incubate 30 sec at room temperature.
- Remove Trypsin/EDTA quickly and incubate cells for 2 min at 37°C.
- Detach cells, add complete medium and pipet up and down to break clumps of cells.
- Pellet cells with centrifuge and carefully aspirate off medium.
- Resuspend cells at a density of approximately 2.0 E+06 cells per mL with fresh freezing medium.
- Aliquot 0.5 mL of cell suspension into each cryovial.
- Overnight incubate cells in a styropor box at –80°C.
- The next morning transfer cryovial in liquid nitrogen tank for long-term storage.

5　　Na$_V$1.5 SEQUENCE

5.1　　　Human Na$_V$1.5 Accession Number NM_000335

Cloned cDNA sequence of human Na$_V$1.5 subunit was error-free and identical with NM_000335 sequence:

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aacctctttgcggggaagtttgggaggtgcatcaaccagacagagggagacttgcctttgaactacaccatcgtgaac
     N   L   F   A   G   K   F   G   R   C   I   N   Q   T   E   G   D   L   P   L   N   Y   T   I   V   N
aacaagagccagtgtgagtccttgaacttgaccggagaattgtactggaccaaggtgaaagtcaactttgacaacgtg
     N   K   S   Q   C   E   S   L   N   L   T   G   E   L   Y   W   T   K   V   K   V   N   F   D   N   V
ggggccgggtacctggccccttctgcaggtggcaacatttaaaggctggatggacattatgtatgcagctgtggactcc
```

```
 G   A   G   Y   L   A   L   L   Q   V   A   T   F   K   G   W   M   D   I   M   Y   A   A   V   D   S
aggggggtatgaagagcagcctcagtgggaatacaacctctacatgtacatctattttgtcattttcatcatctttggg
 R   G   Y   E   E   Q   P   Q   W   E   Y   N   L   Y   M   Y   I   Y   F   V   I   F   I   I   F   G
tctttcttcaccctgaacctctttattggtgtcatcattgacaacttcaaccaacagaagaaaaagttagggggccag
 S   F   F   T   L   N   L   F   I   G   V   I   I   D   N   F   N   Q   Q   K   K   K   L   G   G   Q
gacatcttcatgacagaggagcagaagaagtactacaatgccatgaagaagctgggctccaagaagccccagaagccc
 D   I   F   M   T   E   E   Q   K   K   Y   Y   N   A   M   K   K   L   G   S   K   K   P   Q   K   P
atcccacggcccctgaacaagtaccagggcttcatattcgacattgtgaccaagcaggcctttgacgtcaccatcatg
 I   P   R   P   L   N   K   Y   Q   G   F   I   F   D   I   V   T   K   Q   A   F   D   V   T   I   M
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 F   L   I   C   L   N   M   V   T   M   M   V   E   T   D   D   Q   S   P   E   K   I   N   I   L   A
aagatcaacctgctctttgtggccatcttcacaggcgagtgtattgtcaagctggctgccctgcgccactactacttc
 K   I   N   L   L   F   V   A   I   F   T   G   E   C   I   V   K   L   A   A   L   R   H   Y   Y   F
accaacagctggaatatcttcgacttcgtggttgtcatcctctccatcgtgggcactgtgctctcggacatcatccag
 T   N   S   W   N   I   F   D   F   V   V   V   I   L   S   I   V   G   T   V   L   S   D   I   I   Q
aagtacttcttctccccgacgctcttccgagtcatccgcctggcccgaataggccgcatcctcagactgatccgaggg
 K   Y   F   F   S   P   T   L   F   R   V   I   R   L   A   R   I   G   R   I   L   R   L   I   R   G
gccaaggggatccgcacgctgctctttgccctcatgatgtccctgcctgccctcttcaacatcgggctgctgctcttc
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ctcgtcatgttcatctactccatctttggcatggccaacttcgcttatgtcaagtgggaggctggcatcgacgacatg
 L   V   M   F   I   Y   S   I   F   G   M   A   N   F   A   Y   V   K   W   E   A   G   I   D   D   M
Ttcaacttccagaccttcgccaacagcatgctgtgcctcttccagatcaccacgtcggccggctgggatggcctcctc
 F   N   F   Q   T   F   A   N   S   M   L   C   L   F   Q   I   T   T   S   A   G   W   D   G   L   L
agccccatcctcaacactgggccgccctactgcgaccccactctgcccaacagcaatggctctcggggggactgcggg
 S   P   I   L   N   T   G   P   P   Y   C   D   P   T   L   P   N   S   N   G   S   R   G   D   C   G
aGcccagccgtgggcatcctcttcttcaccacctacatcatcatctccttcctcatcgtggtcaacatgtacattgcc
 S   P   A   V   G   I   L   F   F   T   T   Y   I   I   I   S   F   L   I   V   V   N   M   Y   I   A
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 I   I   L   E   N   F   S   V   A   T   E   E   S   T   E   P   L   S   E   D   D   F   D   M   F   Y
gagatctgggagaaatttgacccagaggccactcagtttattgagtattcggtcctgtctgactttgccgatgccctg
 E   I   W   E   K   F   D   P   E   A   T   Q   F   I   E   Y   S   V   L   S   D   F   A   D   A   L
tctgagccactccgtatcgccaagcccaaccagataagcctcatcaacatggacctgcccatggtgagtggggaccgc
 S   E   P   L   R   I   A   K   P   N   Q   I   S   L   I   N   M   D   L   P   M   V   S   G   D   R
atccattgcatggacattctctttgccttcaccaaaagggtcctgggggagtctggggagatggacgccctgaagatc
 I   H   C   M   D   I   L   F   A   F   T   K   R   V   L   G   E   S   G   E   M   D   A   L   K   I
cagatggaggagaagttcatggcagccaacccatccaagatctcctacgagcccatcaccaccacactccggcgcaag
 Q   M   E   E   K   F   M   A   A   N   P   S   K   I   S   Y   E   P   I   T   T   T   L   R   R   K
cacgaagaggtgtcggccatggttatccagagagccttccgcaggcacctgctgcaacgctcttttgaagcatgcctcc
 H   E   E   V   S   A   M   V   I   Q   R   A   F   R   R   H   L   L   Q   R   S   L   K   H   A   S
ttcctcttccgtcagcaggcgggcagcggcctctccgaagaggatgcccctgagcgagagggcctcatcgcctacgtg
 F   L   F   R   Q   Q   A   G   S   G   L   S   E   D   A   P   E   R   E   G   L   I   A   Y   V
atgagtgagaacttctcccgacccccttggcccaccctccagctcctccatctcctccacttccttcccaccctcctat
 M   S   E   N   F   S   R   P   L   G   P   P   S   S   S   I   S   S   T   S   F   P   P   S   Y
gacagtgtcactagagccaccagcgataacctccaggtgcgggggtctgactacagccacagtgaagatctcgccgac
 D   S   V   T   R   A   T   S   D   N   L   Q   V   R   G   S   D   Y   S   H   S   E   D   L   A   D
ttcccccccttctccggacagggaccgtgagtccatcgtg</span>tga
 F   P   P   S   P   D   R   D   R   E   S   I   V   -
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