

## 243 Covalent Activators Of K2p Channels

### ► Asset Overview

<b>Product Type</b>	Small molecule
<b>Indication</b>	Cardiovascular diseases
<b>Current Stage</b>	Lead Identification /optimization
<b>Target(MoA)</b>	Covalent Activators Of K2p Channels
<b>Brief Description</b>	The newly identified chemical probes consist of an aromatic region that specifically binds to a novel allosteric pocket unique to the TREK1 potassium ion channel, as well as an electrophilic moiety that binds to the channel. Treating cells expressing wild-type K2P or mutant channels with the appropriate electrophile results in 2-5-fold activation of the channel over baseline activity.
<b>Organization</b>	University of California, San Francisco

### ► Differentiation

#### □ Role of TREK-1 in Health and Disease

- TREK-1 is the most studied background K2P channel
- In the nervous system, TREK-1 is involved in many physiological and pathological processes such as depression, neuroprotection, pain, and anesthesia
- Despite recent advances poor pharmacological profiles of K2P channels limit mechanistic and biological studies

#### □ First Covalent Activators Of K2p Channels

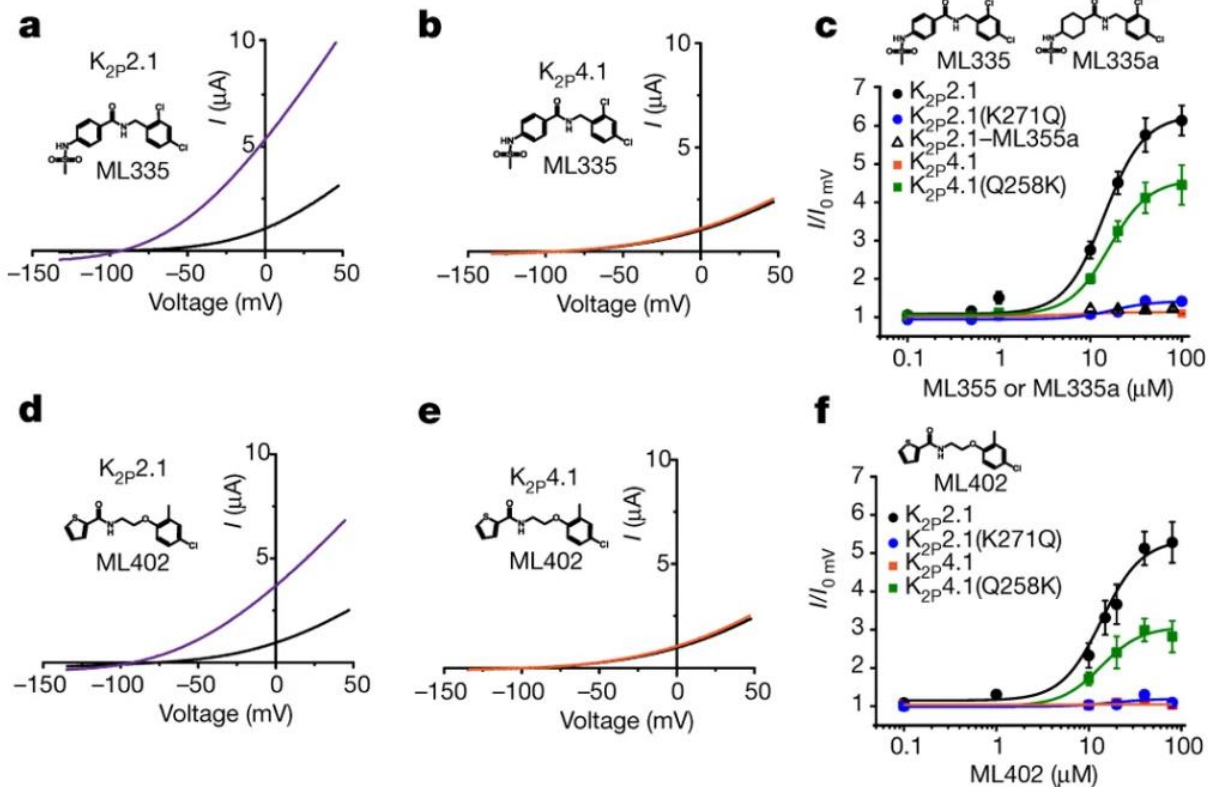
- Researchers at UCSF have identified a novel allosteric pocket unique to the TREK subfamily of potassium ion channels
- Developed a series of covalent small-molecule modulators that specifically target TREK1
- All members of the series increase TREK1 activity over channel baseline, and their covalence has been confirmed with x-ray crystallography and/or washout studies

#### □ Value Proposition

- UCSF products ML335 and ML402 bind and activate a cryptic binding pocket within the C-type gate selectivity filter of TREK-1 channel
- It activate also TREK-2 with no significant effect on TRAAK channels

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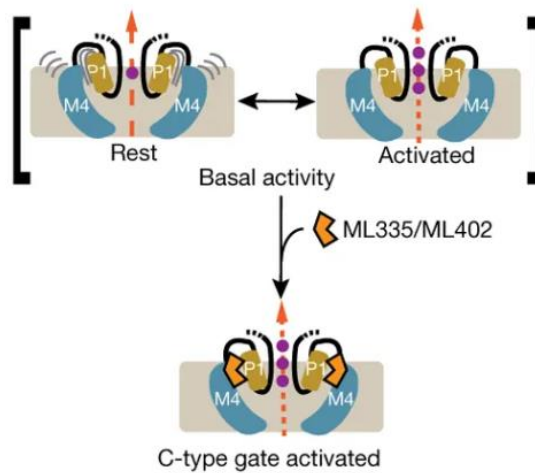
## ► Key Data

K<sub>2</sub>P2.1 activator function

a, b, Exemplar current traces for K<sub>2</sub>P2.1 (black) with 20 μM ML335 (purple) (a) and K<sub>2</sub>P4.1 (black) with 50 μM ML335 (orange) (b). c, ML335 dose-response curves for K<sub>2</sub>P2.1 (black), EC<sub>50</sub> = 14.3 ± 2.7 μM (n ≥ 5); K<sub>2</sub>P2.1(K271Q) (blue filled circles); K<sub>2</sub>P4.1 (orange); and K<sub>2</sub>P4.1(Q258K) (green), EC<sub>50</sub> = 16.2 ± 3.0 μM (n ≥ 4); and K<sub>2</sub>P2.1-ML335a (black open triangles). d, e, Exemplar current traces for K<sub>2</sub>P2.1 (black) with 20 μM ML402 (purple) (d) and K<sub>2</sub>P4.1 (black) with 50 μM ML335 (orange) (e). f, ML402 dose-response curves for K<sub>2</sub>P2.1 (black), EC<sub>50</sub> = 13.7 ± 7.0 μM (n ≥ 3); K<sub>2</sub>P2.1(K271Q) (blue); K<sub>2</sub>P2.1 (blue); K<sub>2</sub>P4.1 (orange); and K<sub>2</sub>P4.1(Q258K) (green), EC<sub>50</sub> = 13.6 ± 1.5 μM (n ≥ 3).

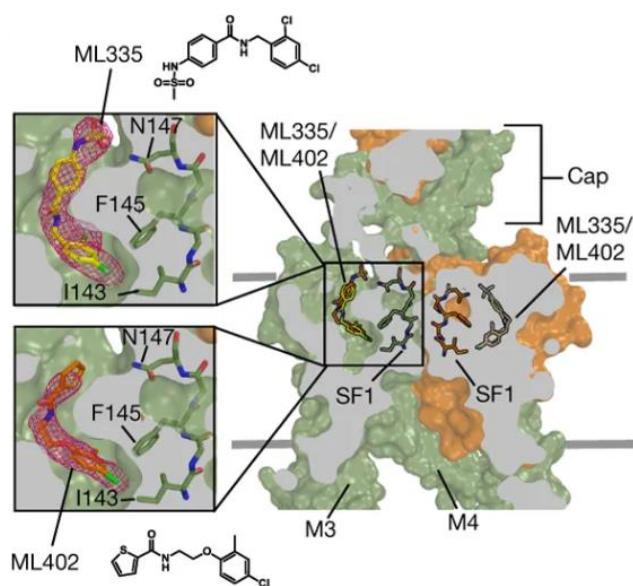
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## TREK activation model



Grey lines indicate mobile P1 (tan) and M4 (blue). C-type activators (orange) stabilize the selectivity filter and channel 'leak mode'. Potassium ions are purple. Gap in arrows indicates current flow intensity. Membrane is grey.

## K<sub>2</sub>P modulator pocket cutaway



Cut-outs display ML335 and ML402 Fo - Fc densities (3.0σ). ML335, ML402 and selectivity filter 1 (SF1) are sticks.

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## ► Intellectual Property

<b>Patent No.</b>	US 9862684 B2
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<b>Status</b>	Registered
<b>Country</b>	US, EP, JP

## ► Contact Information

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