Docket #: S02-267

KCNMA1 Knockout Mice (Jackson Labs stock no. 035902)

Dr. Andrea Meredith and Dr. Richard Aldrich have generated a viable mouse knockout KCNMA1, the gene encodes the pore-forming subunit of the BK large conductance calcium-activated potassium channel (also called KCa1.1, SLO1, and MaxiK). BK channels are prominent regulators of excitability in neurons, smooth muscle and neuroendocrine tissues. Loss of BK channel function disrupts many physiological processes and can cause cerebellar ataxia, tremor, urinary incontinence, disruption of circadian rhythms, bradycardia, hypertension, hyperaldosteronism, impaired neurovascular coupling, erectile dysfunction, impaired hearing, impaired glucose homeostasis, impaired neuro- and cardio-protection, and altered learning and memory. Recently, a new neuromuscular channelopathy was identified, stemming from mutations in KCNMA1 causing BK channel dysfunction (OMIM # 600150). KCNMA1 patient mutations are primarily associated with neurological conditions, including seizures, movement disorders, developmental delay, and intellectual disability. KCNMA1?/? (Slo?/?) mice provide an excellent model for drug development relevant to the human channelopathy disease, precision medicine, and investigations into the various physiological roles of BK channels. Dr. Meredith and the KCNMA1?/? (Slo?/?) mice are depicted in a 2019 Netflix documentary, featuring a patient with KCNMA1 channelopathy ('Diagnosis' episode 4, 'It takes a village': tinyurl.com/yxwdat23).

Stage of Research
Homozygous KCNMA1 knockouts KCNMA1?/? (Slo?/?) are viable and exhibit multiple phenotypes, including: ataxia, tremor, degraded circadian rhythms, reduced breeding efficiency (males and females), reduced body weight, smooth muscle hyper-contractility (leading to urinary incontinence, erectile dysfunction, and reduced cerebral vasodilation), altered olivo-cochlear inhibition, reduced adrenergic-stimulated K+ secretion in the colon, an impaired DHA-mediated blood pressure decrease, reduced cardio-protection in ischemia models, altered salivary secretion,

reduced cortical collecting duct flow-stimulated net K+ secretion in kidney, resistance to alcohol intoxication, and reduced sino-atrial node firing rate.

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Applications

- Drug development and design:
  - Generate new therapeutics for neuromuscular disease caused by BK channel dysfunction (OMIM # 609446 and 618729)
  - Evaluate drug and antibody specificity for KCNMA1
    - Precision medicine and isoform-selective pharmacology: study effects of human KCNMA1 mutations and alternative splice variants in knockout tissue/cell background
- Disease model for:
  - Seizure disorder
  - Movement disorder (ataxia and tremor)
  - Myogenic and neurogenic urinary incontinence
  - Erectile dysfunction
  - Primary circadian rhythm dysfunction
  - Learning and intellectual disability associated with autism, Fragile X, and Angelman's syndromes
- Research- study mechanistic role for BK channel in:
  - Neural excitability
  - Neuro-protection
  - Cardio-protection
  - Cardiac excitability
  - Tremor
  - Ataxia and movement disorder
  - Seizure
  - Familial hypokalemic periodic paralysis
  - Blood pressure and cardiovascular disease
  - Stroke
  - Vascular hypertension
  - Migraine and headache
  - Neuroendocrine regulation
  - Uterine contraction

- Asthma
- Sjogren's syndrome
- Alcoholism
- Diabetes
- Learning and memory
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Advantages

- Model for human neuromuscular disease (seizure and movement disorder)
- Live mice are available on the C57BL6/J background or cryopreserved sperm on the FVBN/J background.
- The mice have pleiotropic phenotypes making them a useful system to study multiple roles of the BK channel

Publications

- **Primary publication reporting the generation of the *Kcnma1*$^{-/-}$ mice:**
  - Meredith AL, Thorneloe KS, Werner ME, Nelson MT, Aldrich RW (2004). "KCNMA1-linked channelopathy" J. Gen Physiol. 2019, 151(10):1173-1189
  - **Additional publications using the *Kcnma1*$^{-/-}$ mice:**
    - **Hormonal:** Lovell PV, McCobb DP (2001). Pituitary control of BK potassium channel function and intrinsic firing properties of adrenal chromaffin cells. J. Neurosci. 21:3429-42.
    - Houamed KM, Sweet IR, Satin LS (2010). BK channels mediate a novel ionic mechanism that regulates glucose-dependent electrical activity and insulin section in mouse pancreatic beta cells J Physiol. 588(18):3511-23.
    - **Vascular Hypertension:** Brenner R1, Peréz GJ, Bonev AD, Eckman DM, Kosek JC, Wiler SW, Patterson AJ, Nelson MT, Aldrich RW (2000). Vasoregulation by the beta1 subunit of the calcium-activated potassium channel. Nature 407:870-6.
    - **Neuroprotection:** Gribkoff VK1, Starrett JE Jr, Dworetzky SI, Hewawasam P, Boissard CG, Cook DA, Frantz SW, Heman K, Hibbard JR, Huston K, Johnson G, Krishnan BS, Kinney GG, Lombardo LA, Meanwell NA, Molinoff PB, Myers RA, Moon SL, Ortiz A, Pajor L, Pieschl RL, Post-Munson DJ, Signor LJ, Srinivas N, Taber MT, Thalody G,

Trojnacki JT, Wiener H, Yeleswaram K, Yeola SW (2001). Targeting acute ischemic stroke with a calcium-sensitive opener of maxi-K potassium channels. Nat. Med. 7:471-7.

- **Bronchial:** Ise S1, Nishimura J, Hirano K, Hara N, Kanaide H (2003). Theophylline attenuates Ca2+ sensitivity and modulates BK channels in porcine tracheal smooth muscle. Br. J. Pharmacol. 140:939-47.
- **Uterine Contraction:** Khan RN, Smith SK, Ashford ML (1998). Contribution of calcium-sensitive potassium channels to NS1619-induced relaxation in human pregnant myometrium. Hum. Reprod. 13:208-13.
- **Learning & Memory:** Typlt M1, Mirkowski M, Azzopardi E, Ruettiger L, Ruth P, Schmid S (2013). Mice with deficient BK channel function show impaired prepulse inhibition and spatial learning, but normal working and spatial reference memory" PLoS One 8(11):e81270.
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- Montgomery, JM, Whitt, JP, Wright, BN, Lai, ML, and Meredith, AL (2013). Mis-expression of the BK K+ channel disrupts suprachiasmatic nucleus circuit rhythmicity and alters clock-controlled behavior. AJP-Cell Physiology 304(4):C299-C311.
- Hoshi, T, Wissuwa, B, Tian, Y, Tajima, T, Xu, R, Bauerb, M, Heinemann, S, and Hou, S (2013). Omega-3 fatty acids lower blood pressure by directly activating large-conductance Ca2+-dependent K+ channels. PNAS 110 (12): 4816–4821.

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