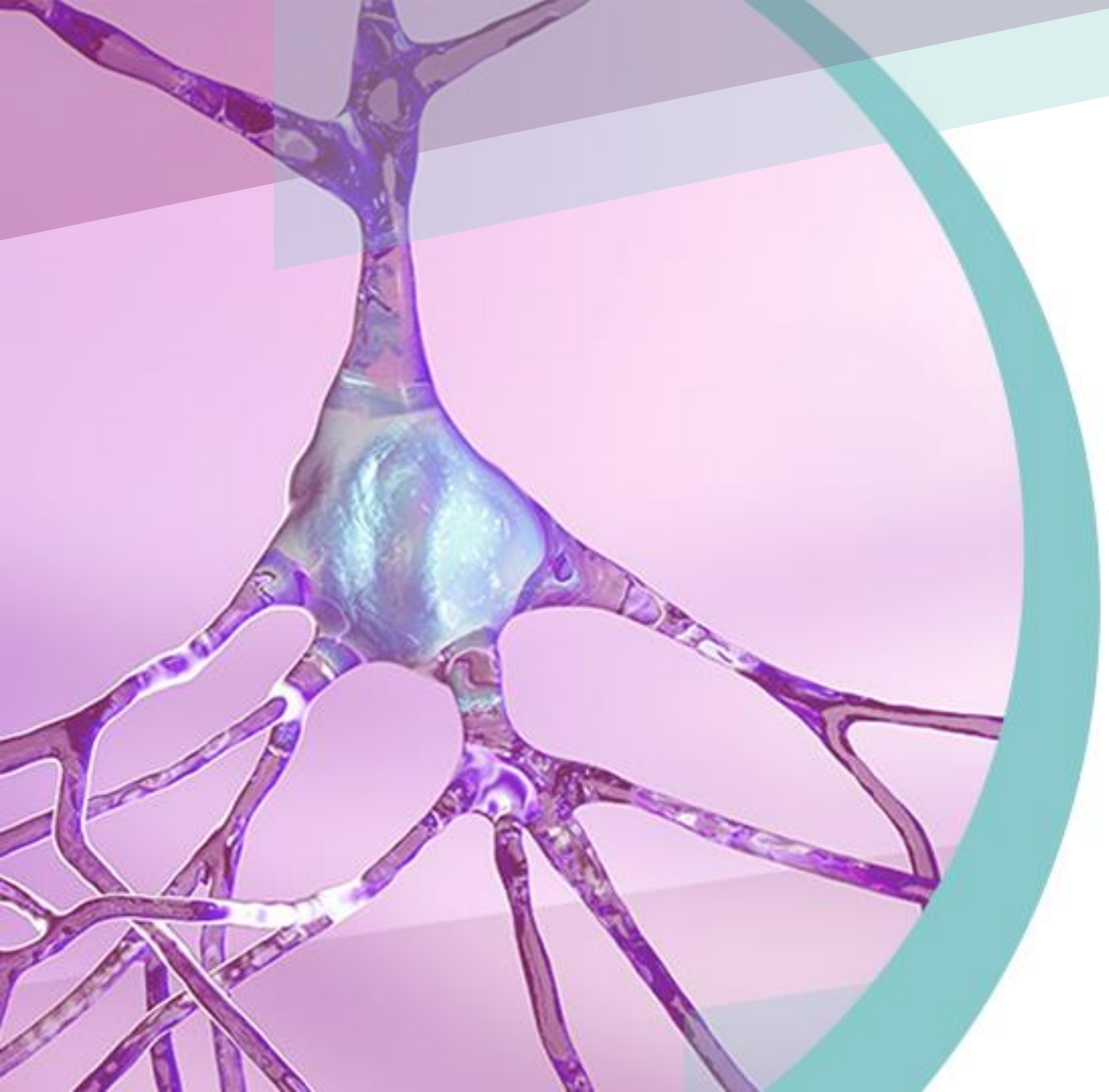

Discovery and characterisation of ETX-123: a novel Kv7.2/Kv7.3 activator

7th RSC/SCI - Ion Channel Meeting

Manuela Cerina, PhD

Eliem Therapeutics

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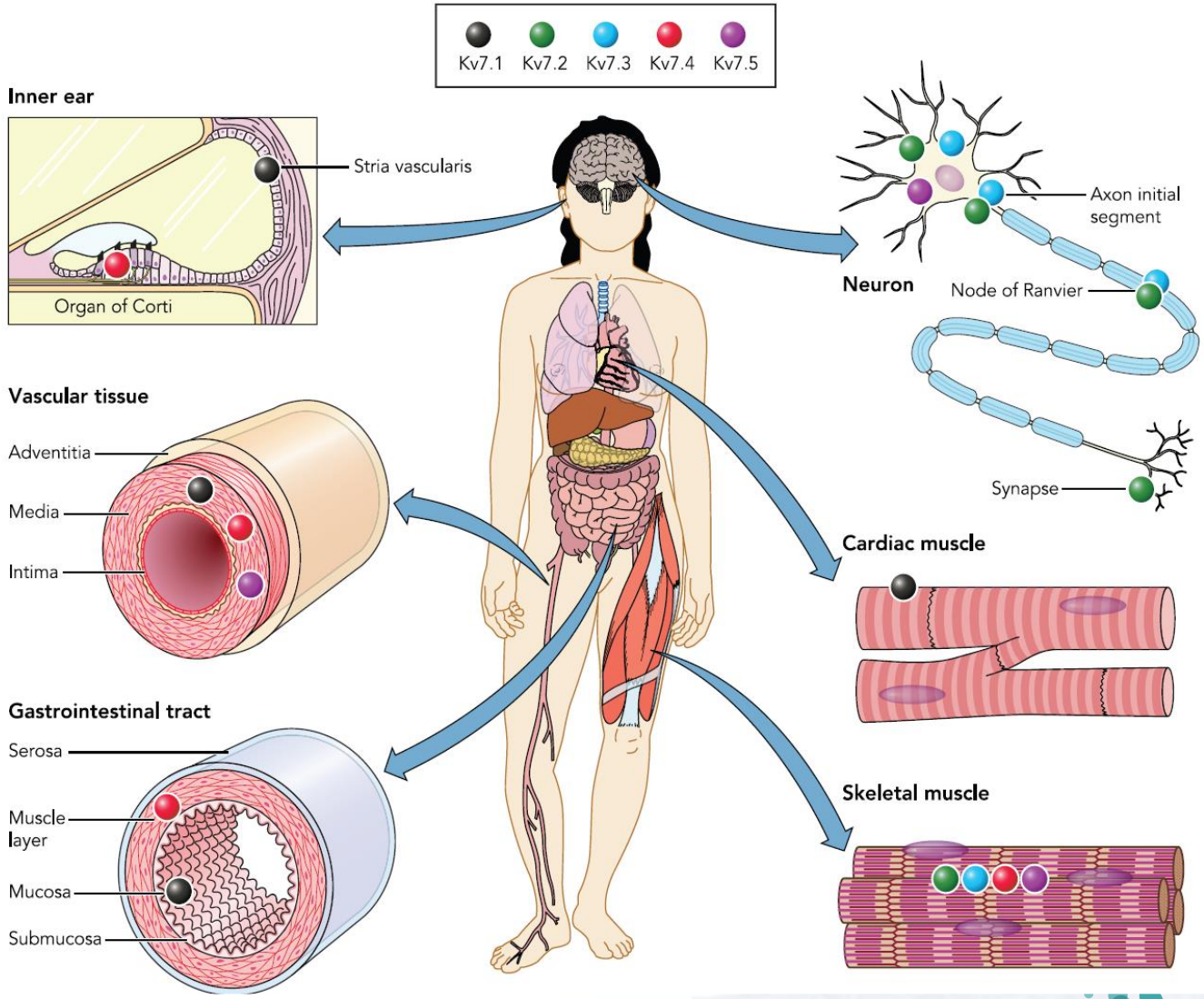
Tissue-specific expression of Kv7 channels

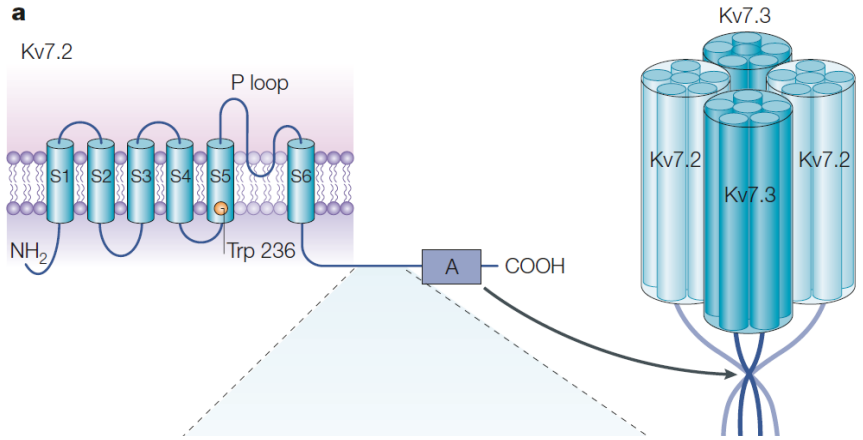
The Kv7 family consists of 5 different subtypes which differ for electrophysiological properties and tissue expression:

- Kv7.1 = cardiac tissue
- Kv7.2 and Kv7.3 = CNS and PNS (all brain resident cells)
- Kv7.4 = smooth muscles and inner ear
- Kv7.5 = CNS, smooth and skeletal muscles



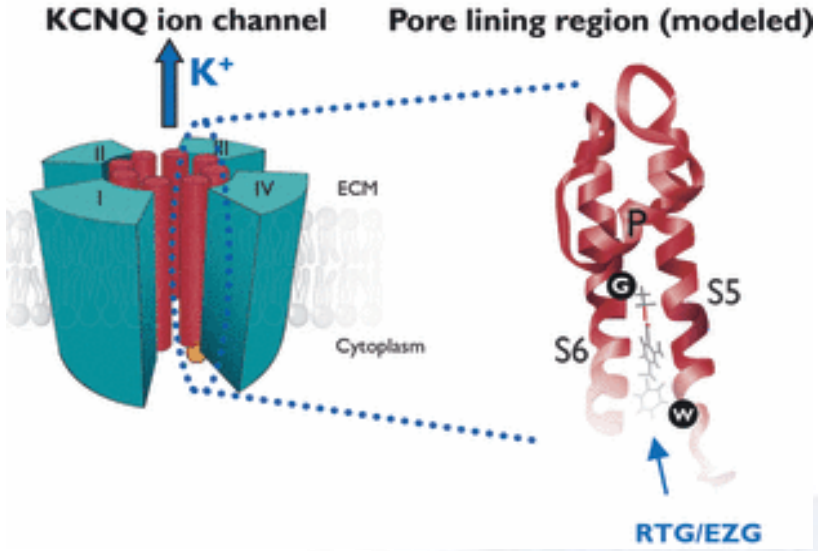
Source: Soldovieri et al., 2011

Functional properties and modulation of Kv7 channels

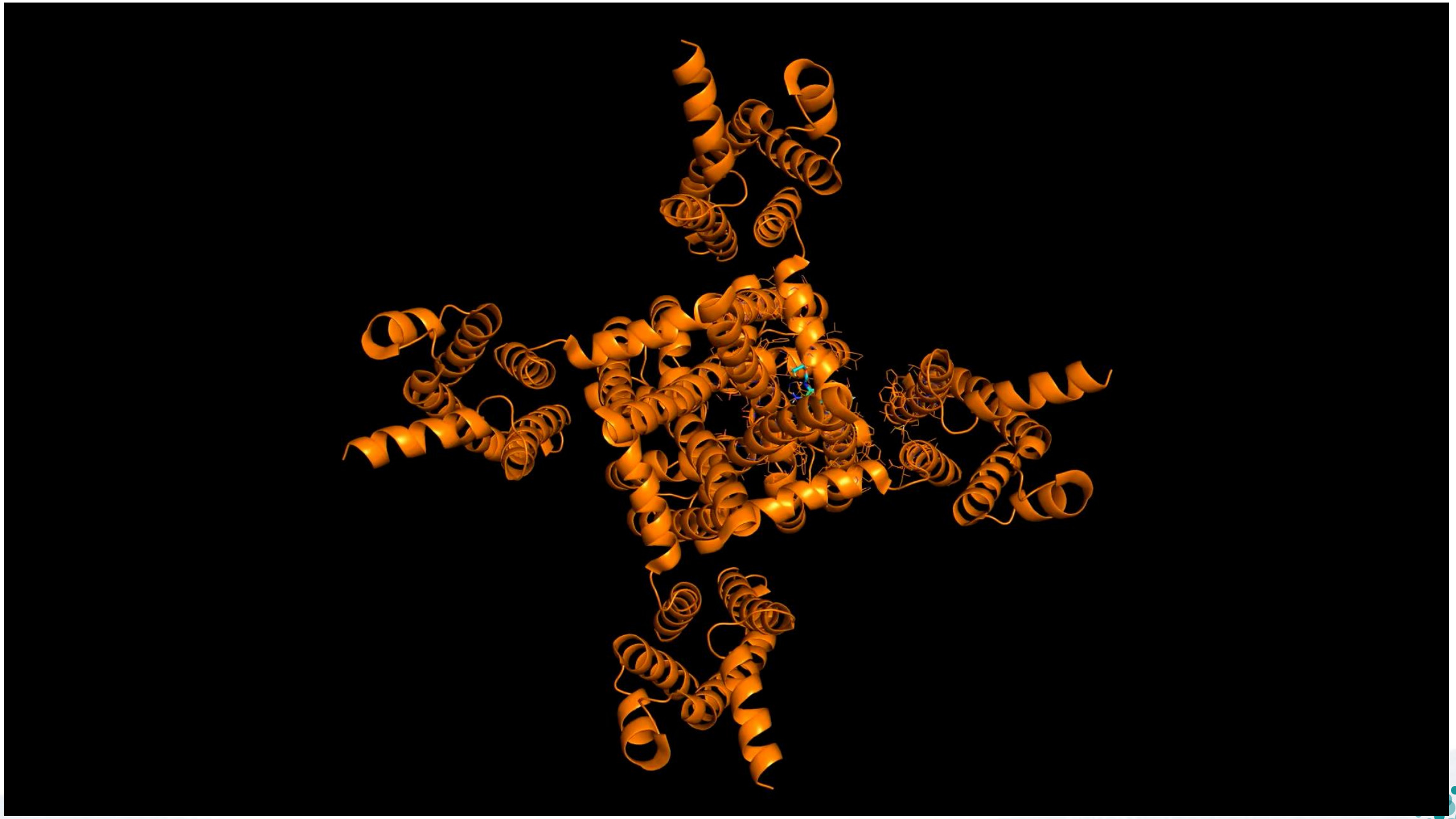


- Loss of function mutation of KCNQ2 and 3 have been associated to the onset of epilepsy syndromes and encephalopathies
- Functional properties of these channels have been validated using endogenous- (e.g. muscarine) and exogenous activators like Retigabine

- K^+ voltage-activated channels
- As homo- or heteromeric channels mediate a slow activating, non-inactivating K^+ current called M-current
- Set and maintain the resting membrane potential
- Dampen neuronal excitability by reducing neuronal firing and prolongating the after-hyperpolarisation phase in excitable cells

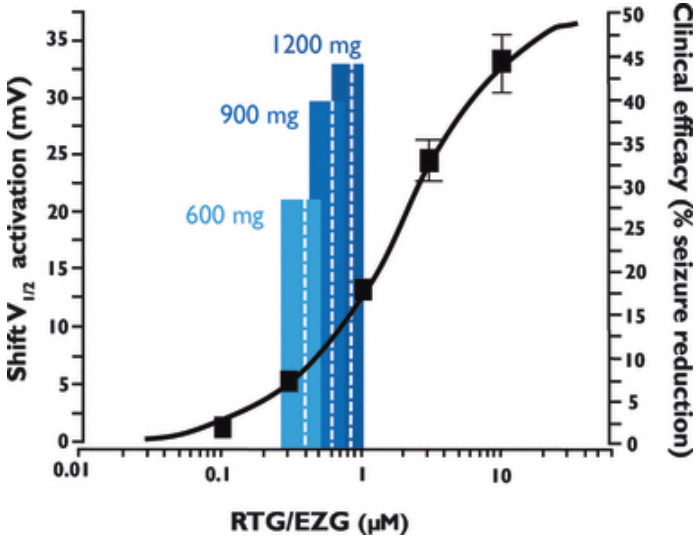


Source: Demas and Brown, 2005, Gunthorpe et al., 2012



Source: Cambridge Structural database - entry 7CR2

Kv7 channels: an ideal target in the treatment of epilepsy

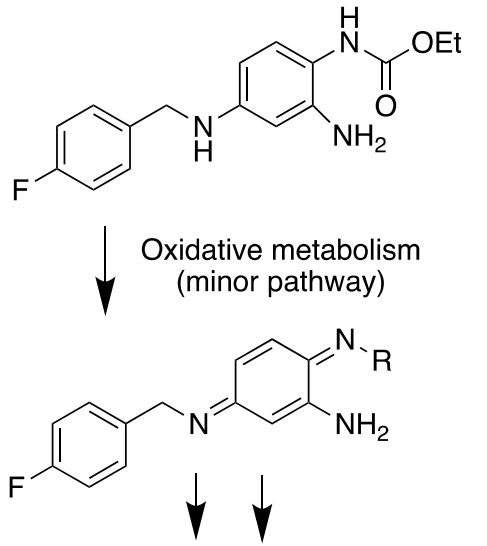


Proven clinical validation of Retigabine/Ezogabine in the treatment of Refractory Partial Onset Epilepsy

Poor CNS tolerability

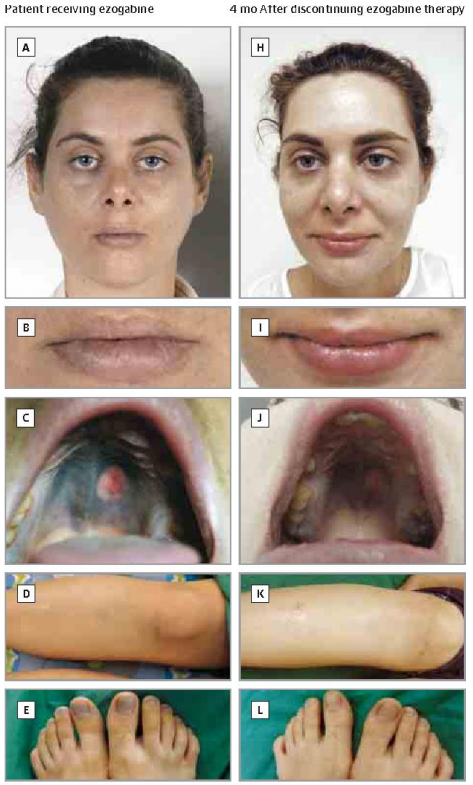
Occurrence of retinal abnormalities, vision loss, skin discoloration, over-pigmentation and urinary retention lead to label warnings first and then complete discontinuation in 2017

Retigabine metabolic issue



Dimerisation to blue anthraquinones

Potential for other nucleophilic trapping



Source: modified from Shkolnik et al., 2014

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Rationale for the Kv7.2/Kv7.3 program: Developing a differentiated opener for neuronal excitability indications

Kv7 opportunity

Human genetic validation

Strong preclinical validation in pain and epilepsy
(retigabine, flupirtine, XEN1101)

Metabolic/safety liabilities with first generation molecules

Clear translational path to clinical efficacy

Eliem Kv7 Program Goal

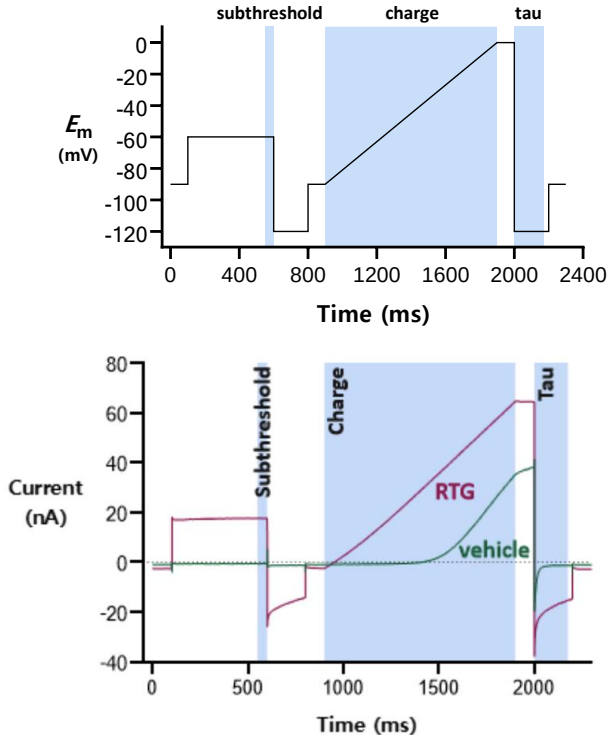
Maintain efficacy with improved tolerability and safety

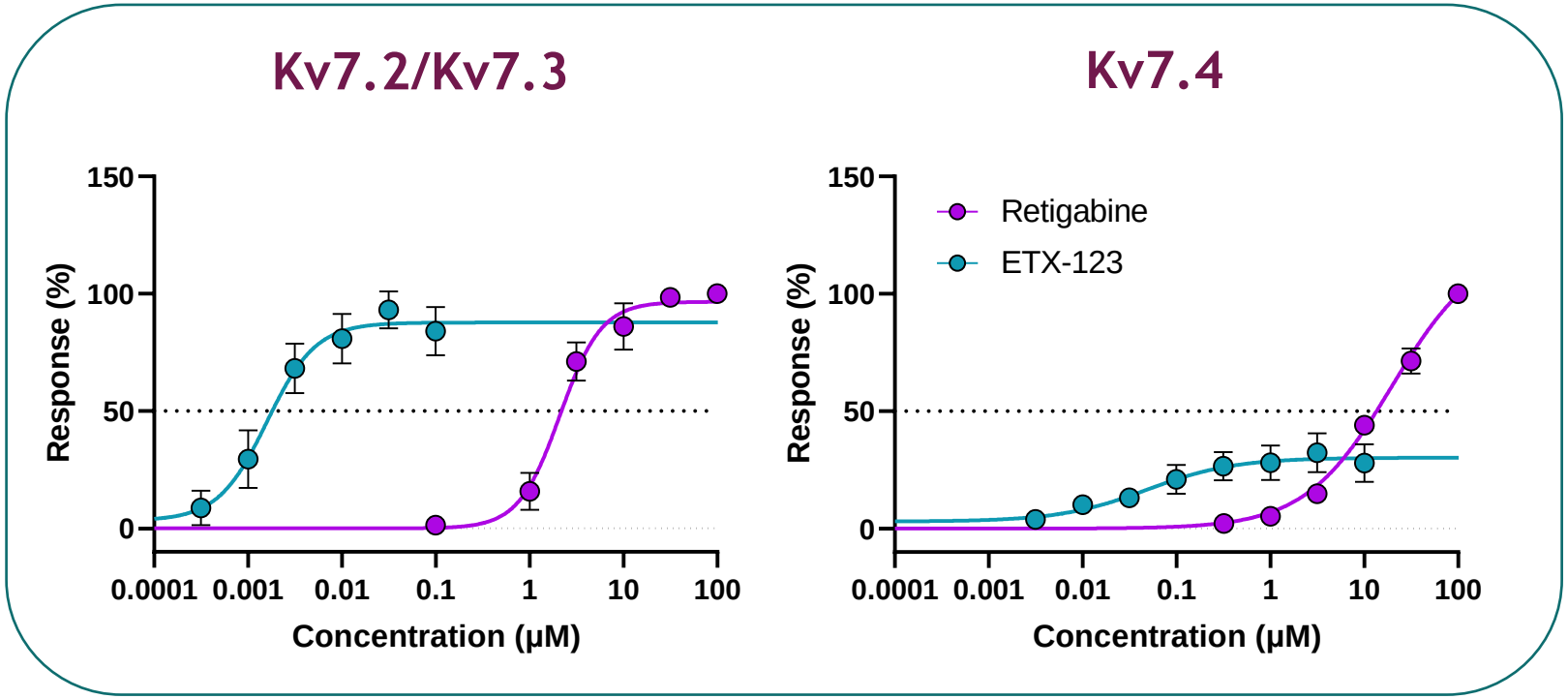
Program Status

- IP filed
- Lead candidate selected with backup candidate in novel chemical space
- Metabolic stability by design
- Potent at Kv7.2/3, selective vs Kv7.1/4, active in MES model, with encouraging therapeutic index
- No $GABA_A$, hERG or other off target liabilities

IND-enabling studies ongoing; Phase 1 anticipated in 1H2024

Activation of Kv7.2/Kv7.3 – high potency of ETX-123

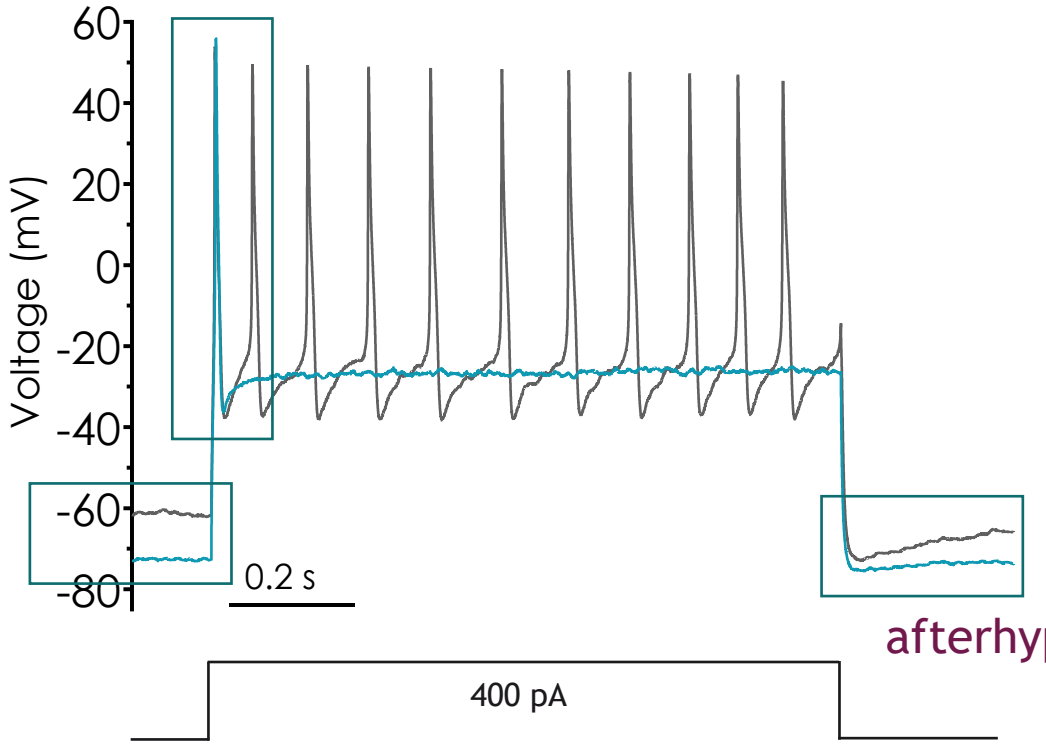




In vitro, ETX-123 is significantly more potent and selective than Retigabine on Kv7.2/Kv7.3 but not on Kv7.4

Proposed MoA for the modulation of Kv7 channels

Decreased firing and
potential firing pattern change



Baseline
Kv7 channel activator

Hyperpolarisation and
decrease of RMP

afterhyperpolarisation

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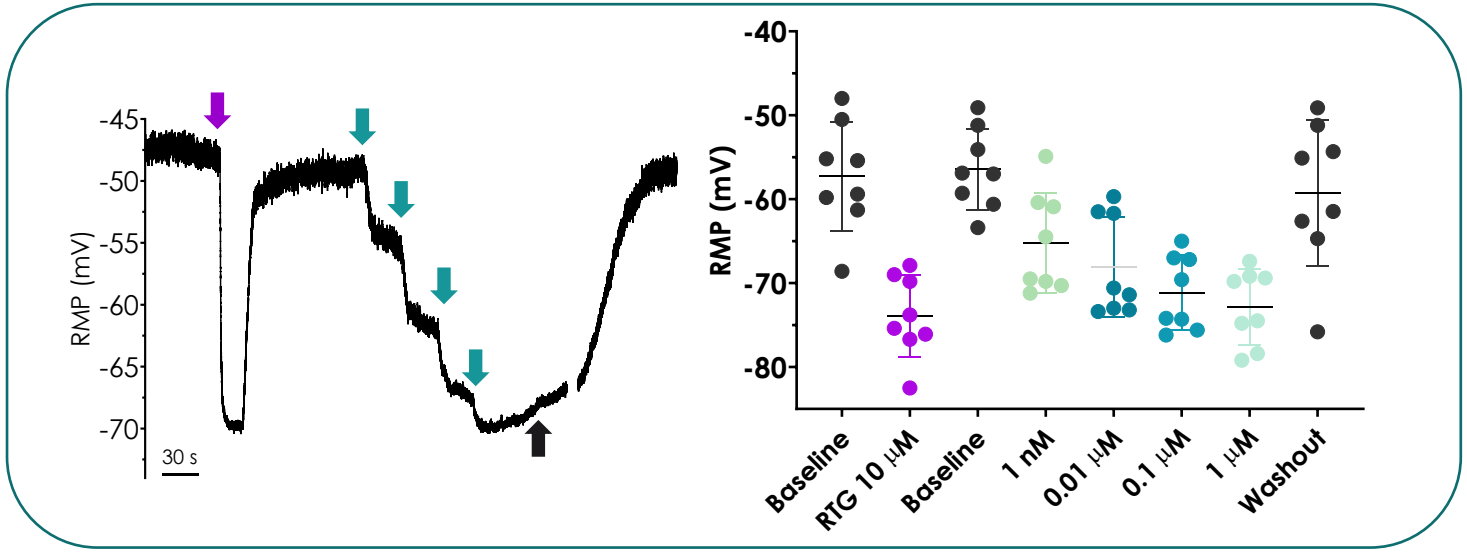
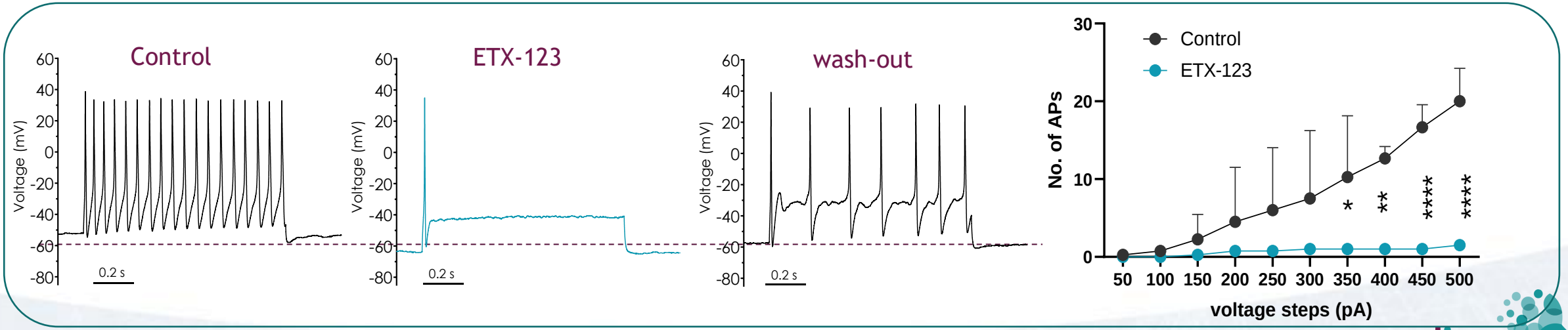
Translational Pharmacology – effect of ETX-123 on rat DRG functionality



ETX-123 hyperpolarizes the cells and significantly inhibits repeat firing of action potentials



****p < 0.0001, **p < 0.01 and *p <0.05 - comparisons all groups vs. the control group

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ETX-123 is efficacious in a rat maximal electroshock model

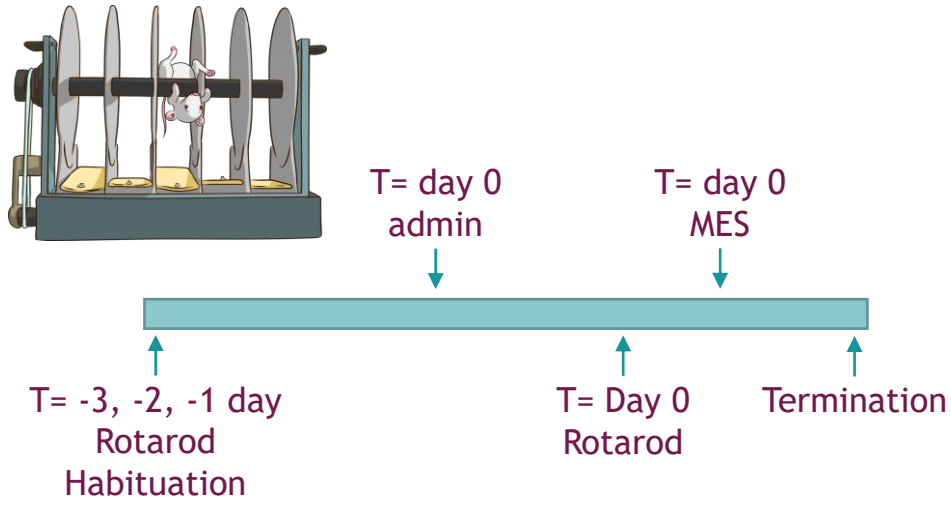
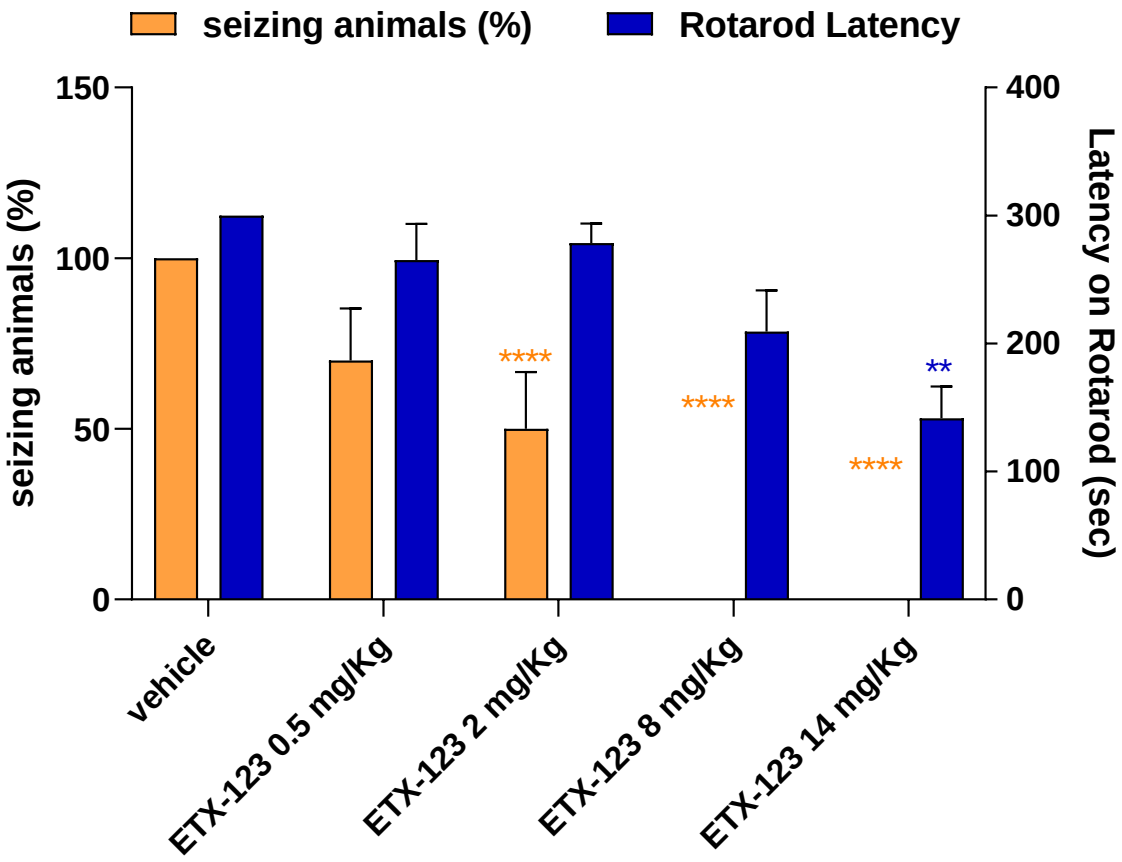


Image Source: https://conductscience.com/maze/maze-basics-rotarod-test-for-mice/



ETX-123 has demonstrated a favorable in vivo efficacy in a highly translatable model of epilepsy in association with a favorable tolerability profile

****p < 0.0001 and **p < 0.01 – comparisons all groups vs. vehicle for each variable

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Summary

	ETX-123	Retigabine
In vitro profile		
Potency at Kv7.2/3	+++ (0.7-2 nM)	+ (2-14 µM)
Selectivity over Kv7.4	++++ (14,000-fold)	+ (7.8-fold)
Selectivity over Kv7.1	+++	+++
Safety profile and cross-reactivity	+++	-
In vivo profile		
Rat MES/Rotarod	++++ (2 mg/Kg oral)	+++
Oral bioavailability (rat)	+	+++
Chemistry		
Structural features	Novel Scaffold (non-disclosed)	Substitute aniline

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Thank you.