SELECTED OPPORTUNITIES IN NEUROSCIENCE

TREK1/TREK2 AS TARGETS FOR THE TREATMENT OF MIGRAINE (BIO17200)

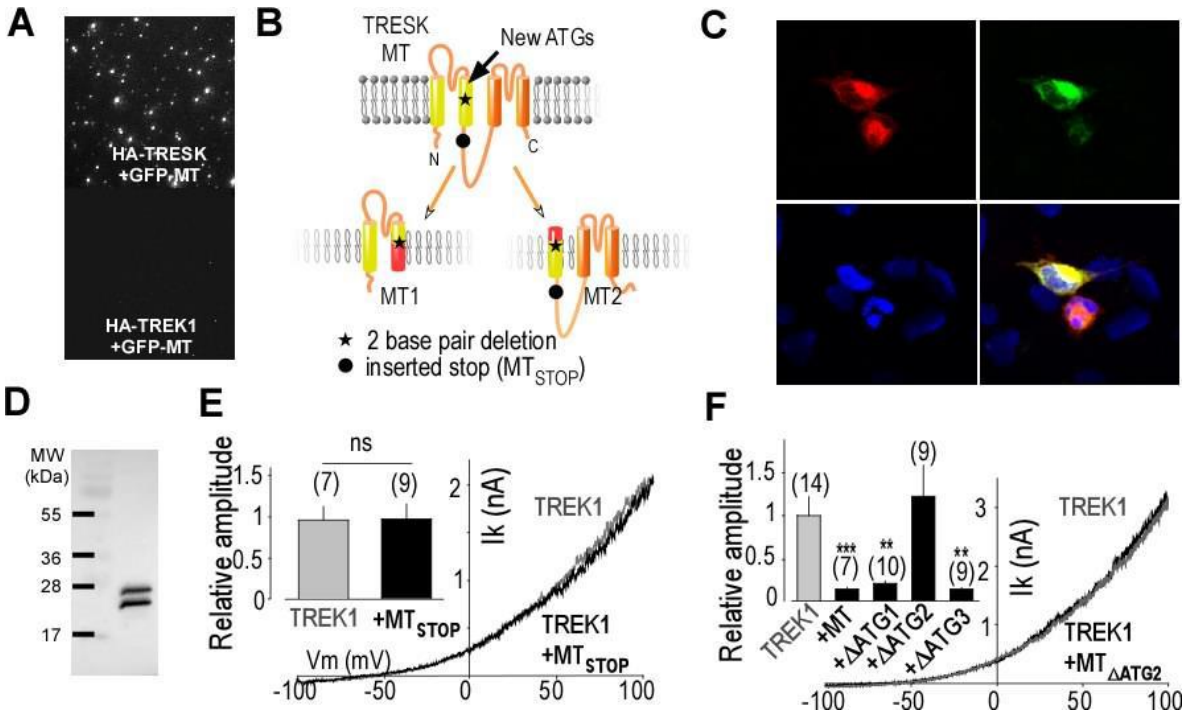
Product factsheet

Preclinical

- **Product:**
  - An agonist of TREK1 or TREK2
- **Rational / POC:**
  - Activation and sensitization of primary afferent neurons within the trigeminal (TG) sensory system is a key step in the initiation of migraine headache attacks
  - In humans, a mutation in a two-pore-domains K+ (K2P) channel (TRESK-MT) has been found to be strongly linked to migraine with Aura.
  - TRESK-MT induces the translation of a second protein , MT2, wich acts as a dominant negative on TREK1 and TREK2 channels leading to an increase of excitability of small TG neurons
- **Patent and publication:**
  - EP 17305813.2 : METHODS AND PREPARATIONS FOR TREATING MIGRAINE
  - Migraine-Associated TRESK Mutations Increase Neuronal Excitability through Alternative Translation Initiation and Inhibition of TREK, Royal et al., 2019, Neuron *101*, 1–14

Proof of concept

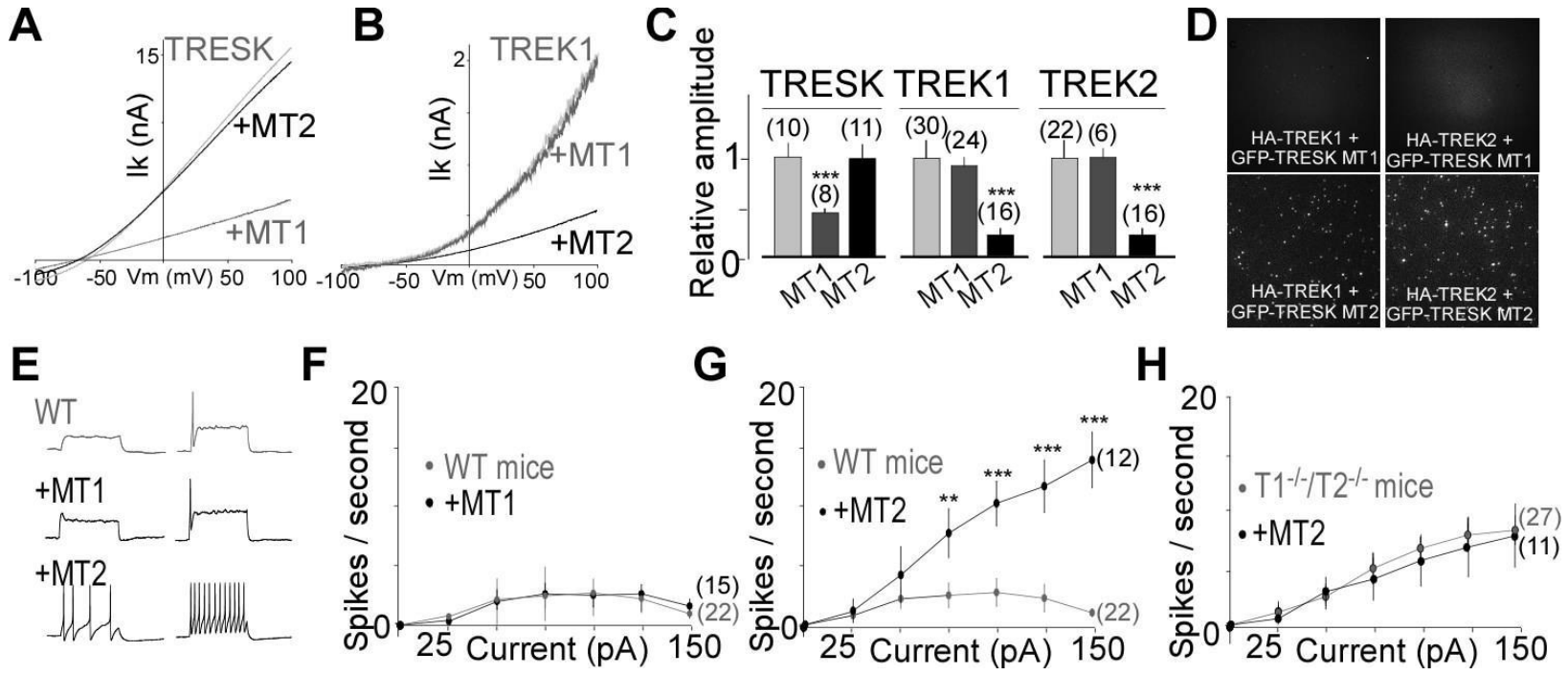
Preclinical



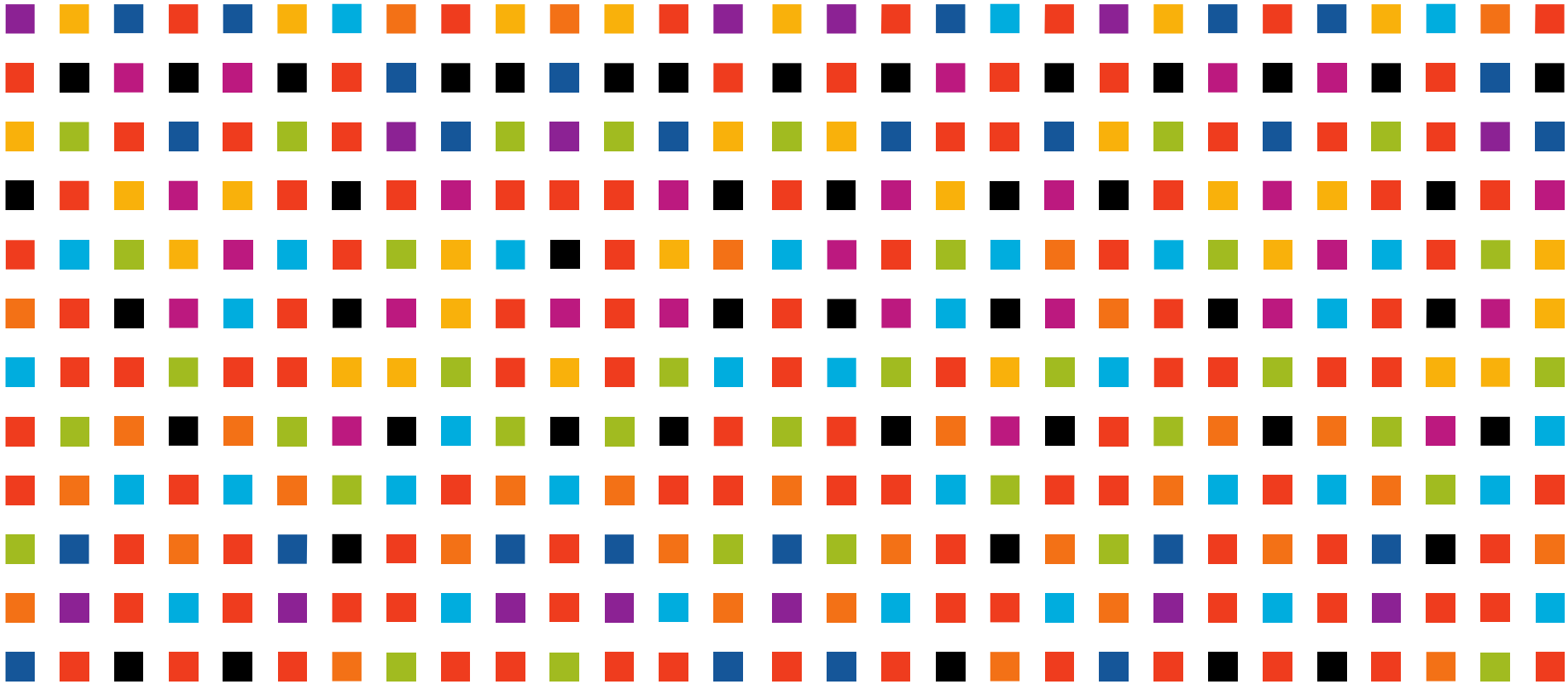
TRESK-MT induces the translation of a second protein, MT2, which mediates TREK1 inhibition. (**A**) Representative images from SiMPull experiments showing that GFP-TRESK can be pulled down by HA-TRESK but not by HA-TREK1. (**B**) Cartoon showing the membrane topology of TRESK and the expected products induced by ATI in the TRESK-MT mutation. (**C**) Co-synthesis of mCherry-MT1 and MT2-GFP product from the mCherry-TRESK-MT-GFP cDNA. (**D**) Western blot against HA-TRESK-MT-HA probed with anti-HA antibodies. (**E**) Representative traces showing the effect of introduction of a STOP codon at the beginning of the MT2 ORF within the 2-3 loop (TRESK-MTSTOP) on TREK1 current. Inset shows a summary of TREK1 relative current densities when TRESK-MTSTOP is coexpressed. (**F**) Representative traces and summary bar graph showing the effect of mutation of candidate alternative start codons (ΔATG1, ΔATG2, or ΔATG3) in TRESK-MT. Currents were elicited by voltage-ramps (from -100 to 100 mV, 1s duration). The numbers of cells tested are indicated in parentheses. Student's *t* test (**P< 0.01, ***P< 0.001) shows the difference between TREK1 and TREK1 co-expressed with different TRESK-MT constructs.

Proof of concept

Preclinical



MT2, but not MT1, by acting as a dominant negative on TREK1 and TREK2 channels, increases neuronal excitability of WT small TG neurons. (**A** and **B**) Representative traces showing the effect of TRESK-MT1 or TRESK-MT2 co-expression on TRESK (B) or TREK1 (B) currents. Currents were elicited by voltage-ramps (from -100 to 100 mV, 1s duration). (**C**) Bar graph summarizing the relative TRESK, TREK1 and TREK2 current amplitudes at 0 mV when MT1 or MT2 are co-expressed. Student's *t* test (***P< 0.001). (**D**) Representative images showing that GFP-MT2, but not GFP-MT1, can be pulled down by HA-TREK1 and HA-TREK2 via an anti-HA antibody in the SiMPull assay. (**E** to **G**) Representative traces and input-output plots of spikes generated by incremental depolarizing current injections in WT small-diameter TG neurns transfected with either GFP ("WT"), the GFP-tagged MT1 subunit ("MT1") or the GFP-tagged MT2 subunit ("MT2"). (**H**) Input-output plots of spike frequency show a lack of effect of GFP-MT2 expression on TG neurons from TREK1/TREK2 double KO mice (T1-/-/T2-/-). The numbers of cells tested are indicated in parentheses. Student's *t* test (**P< 0.01, ***P< 0.001).



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