

**Boston
Children's
Hospital**

Rosamund Stone Zander
Translational
Neuroscience Center

SUPPORT HEALTH EQUITY END RACISM



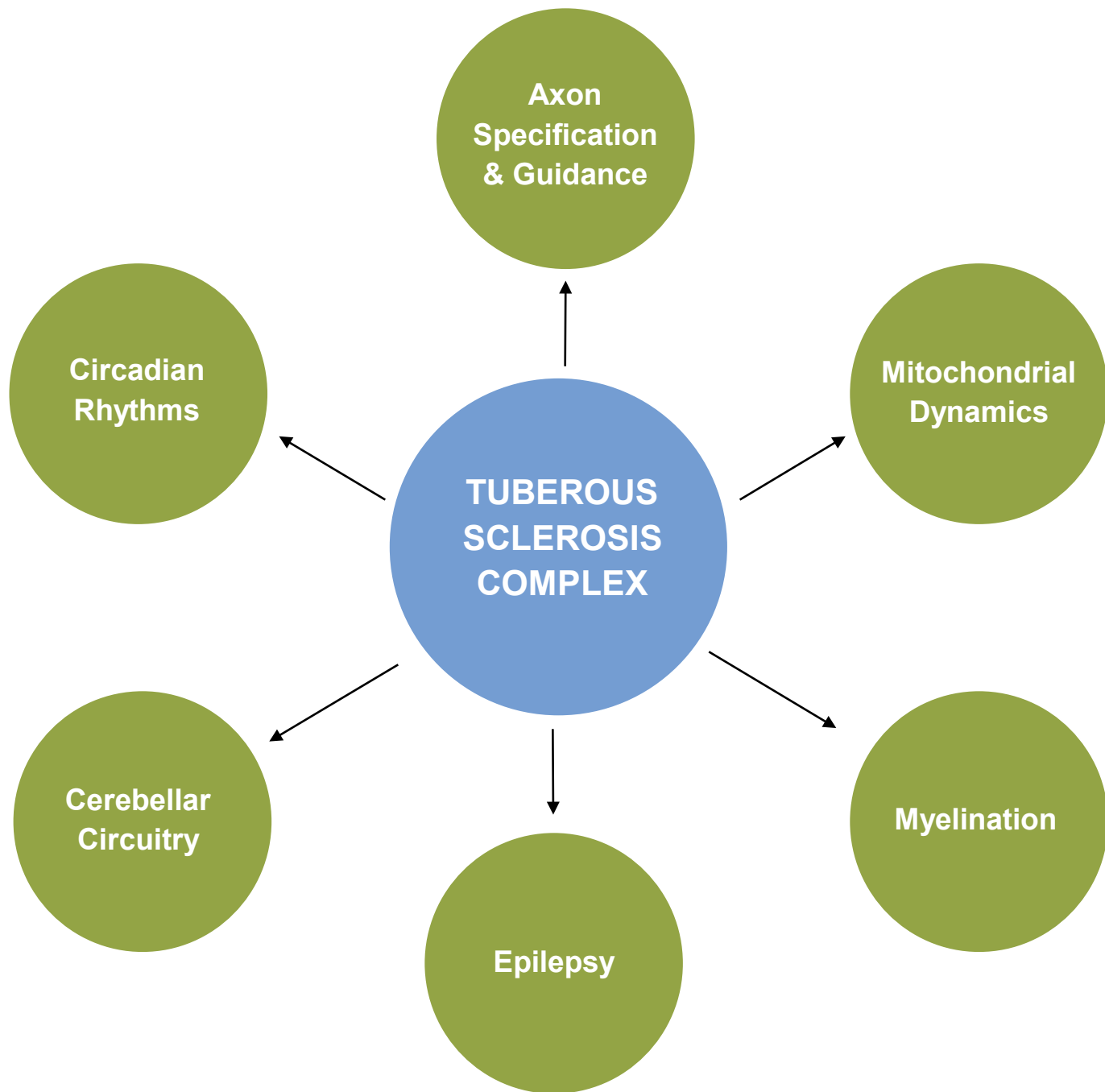
Testing mGluR5 modulation for epilepsy in TSC

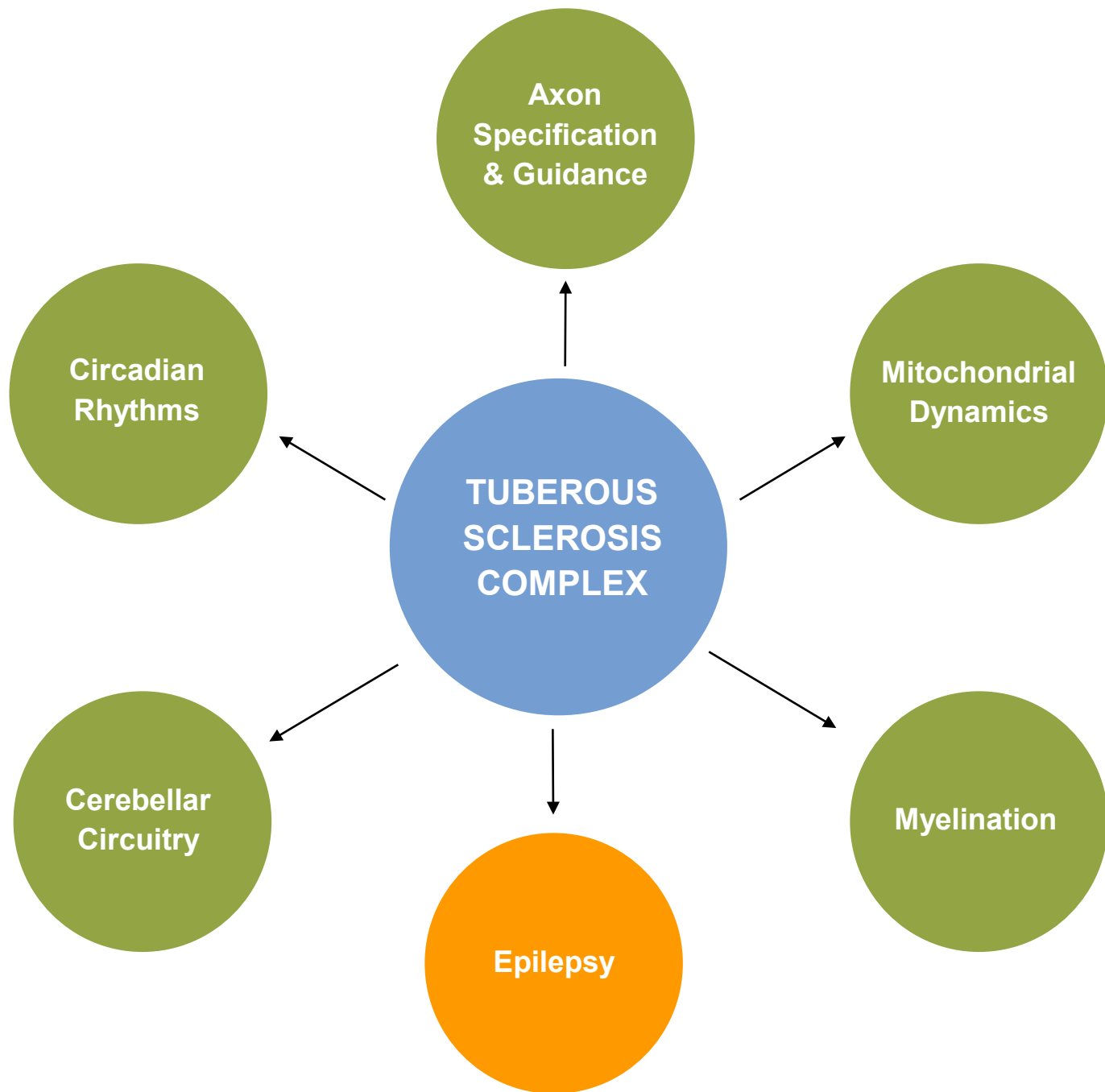
Mustafa Sahin, MD, PhD

Director, Translational Neuroscience Center

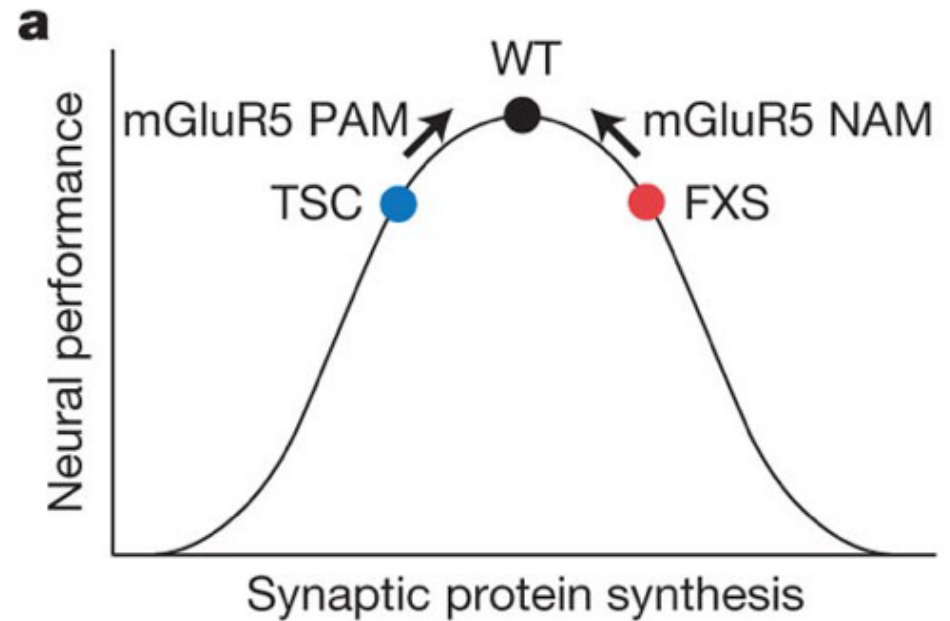
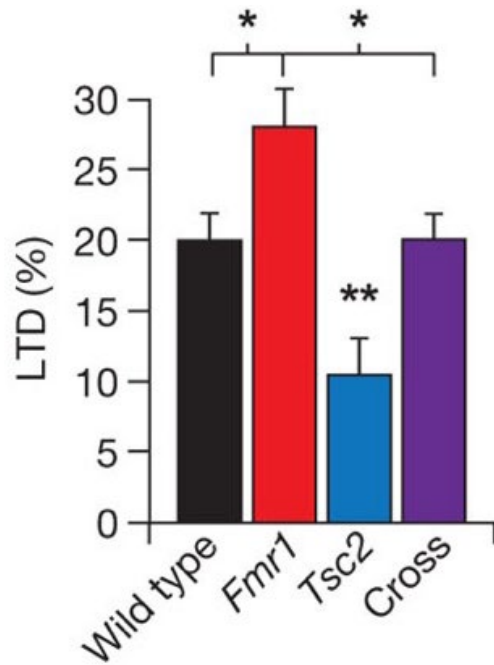
Rosamund Stone Zander Chair, Boston Children's Hospital

Professor, Neurology, Harvard Medical School



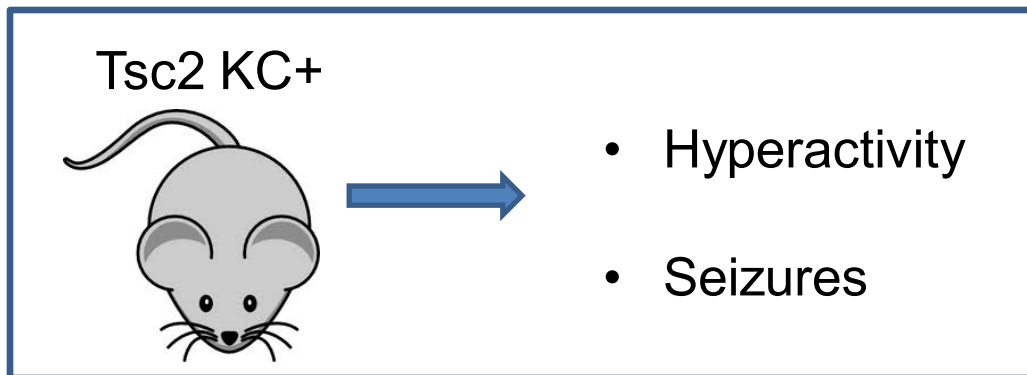


Tsc2^{+/-} and *Fmr1*^{-/-} mice show opposite phenotypes



An Epilepsy Model for Translational Studies

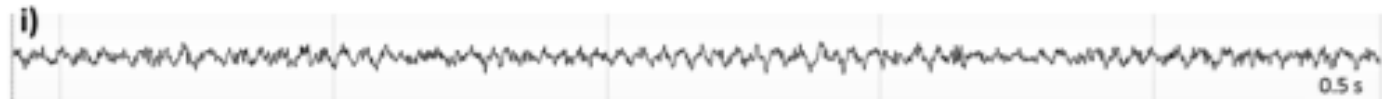
- Spontaneous seizures
- 100% penetrant
- Able to survive electrode placement
- Enable long-term EEG monitoring
- Phenotype modulated by small molecules



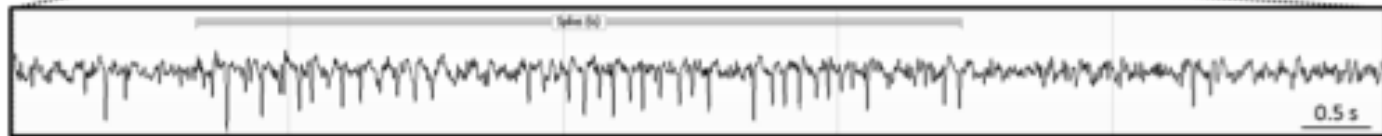
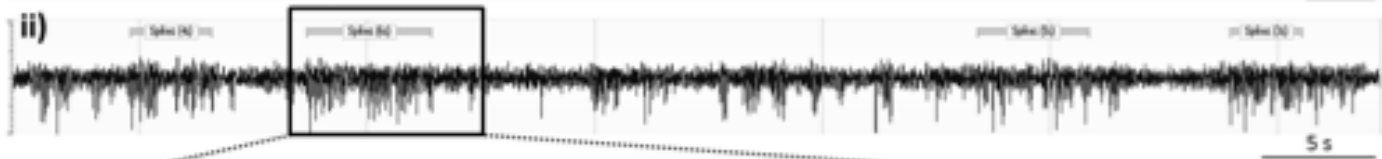
- Removal of exon 3 near N-terminus of *Tsc2*
- Encodes for a functional TSC2 protein
- 8% neuronal TSC2 expression

Seizure phenotype of Tsc2 hypomorph mice

Control



Tsc2 KO



Neuropsychopharmacology (2018), 1–9

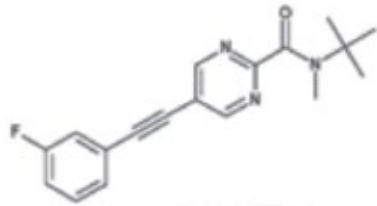
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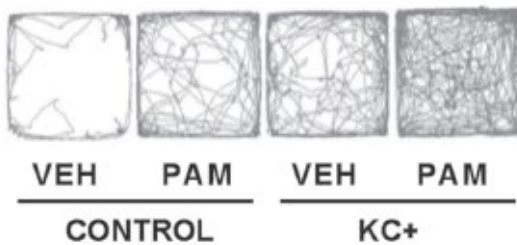
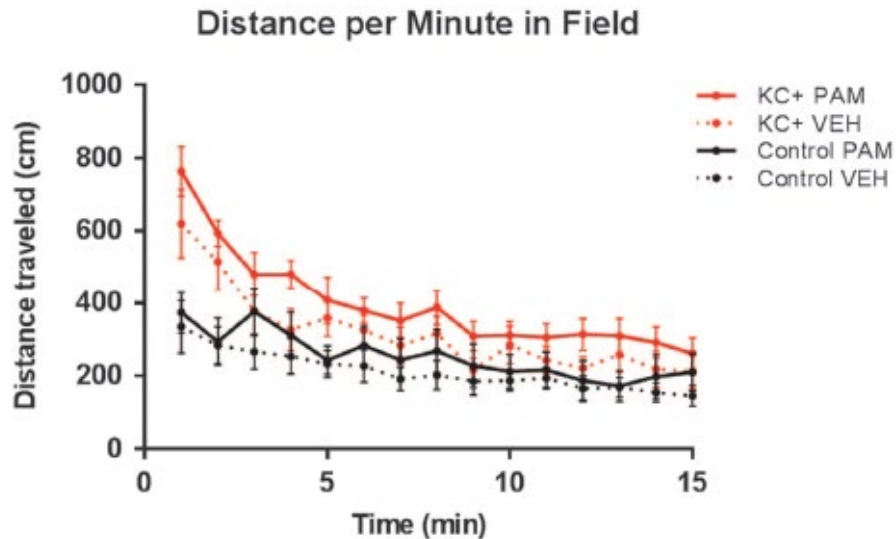
mGluR5 Modulation of Behavioral and Epileptic Phenotypes in a Mouse Model of Tuberous Sclerosis Complex

Elyza Kelly^{1,2,9}, Samantha M Schaeffer^{1,9}, Sameer C Dhamne¹, Jonathan O Lipton^{1,3}, Lothar Lindemann⁴, Michael Honer⁵, Georg Jaeschke⁶, Chloe E Super¹, Stephen HT Lammers¹, Meera E Modi¹, Jill L Silverman⁷, John R Dreier⁸, David J Kwiatkowski⁸, Alexander Rotenberg¹ and Mustafa Sahin^{*,1}

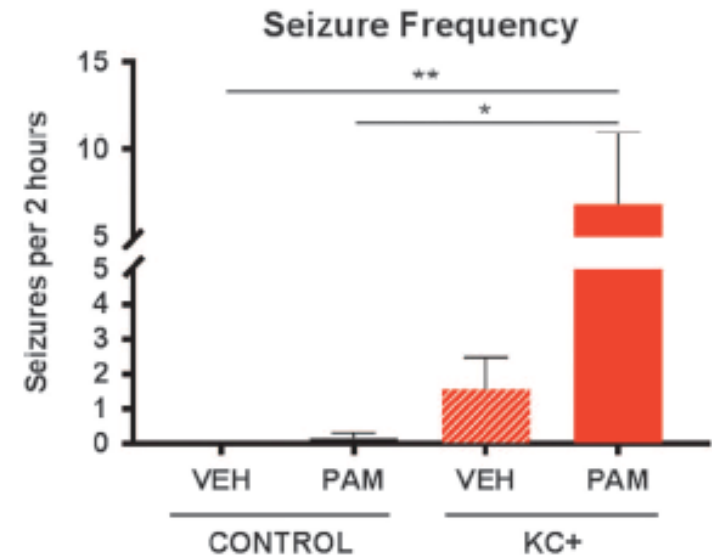
mGluR5 PAM worsens



RO6807794
 $C_{17}H_{18}FN_3O$, M_w 311.35



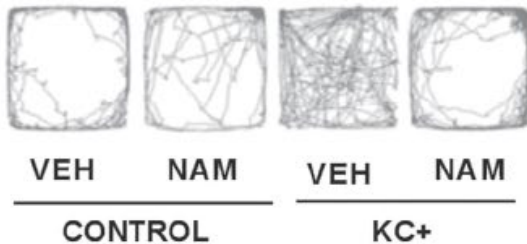
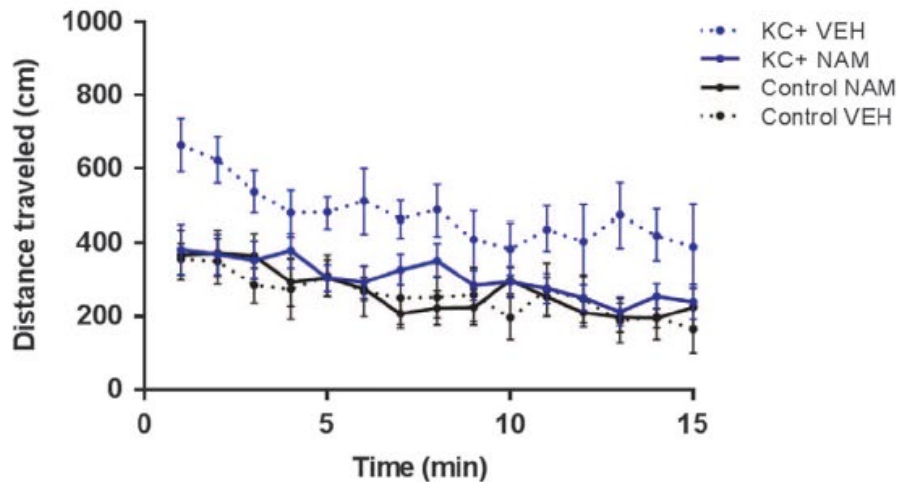
Acute PAM Treatment



mGluR5 NAM (CTEP) improves

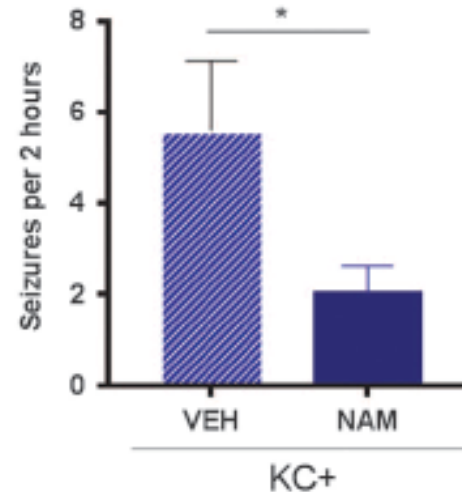
Chronic NAM Treatment

(i) Distance per Minute in Field



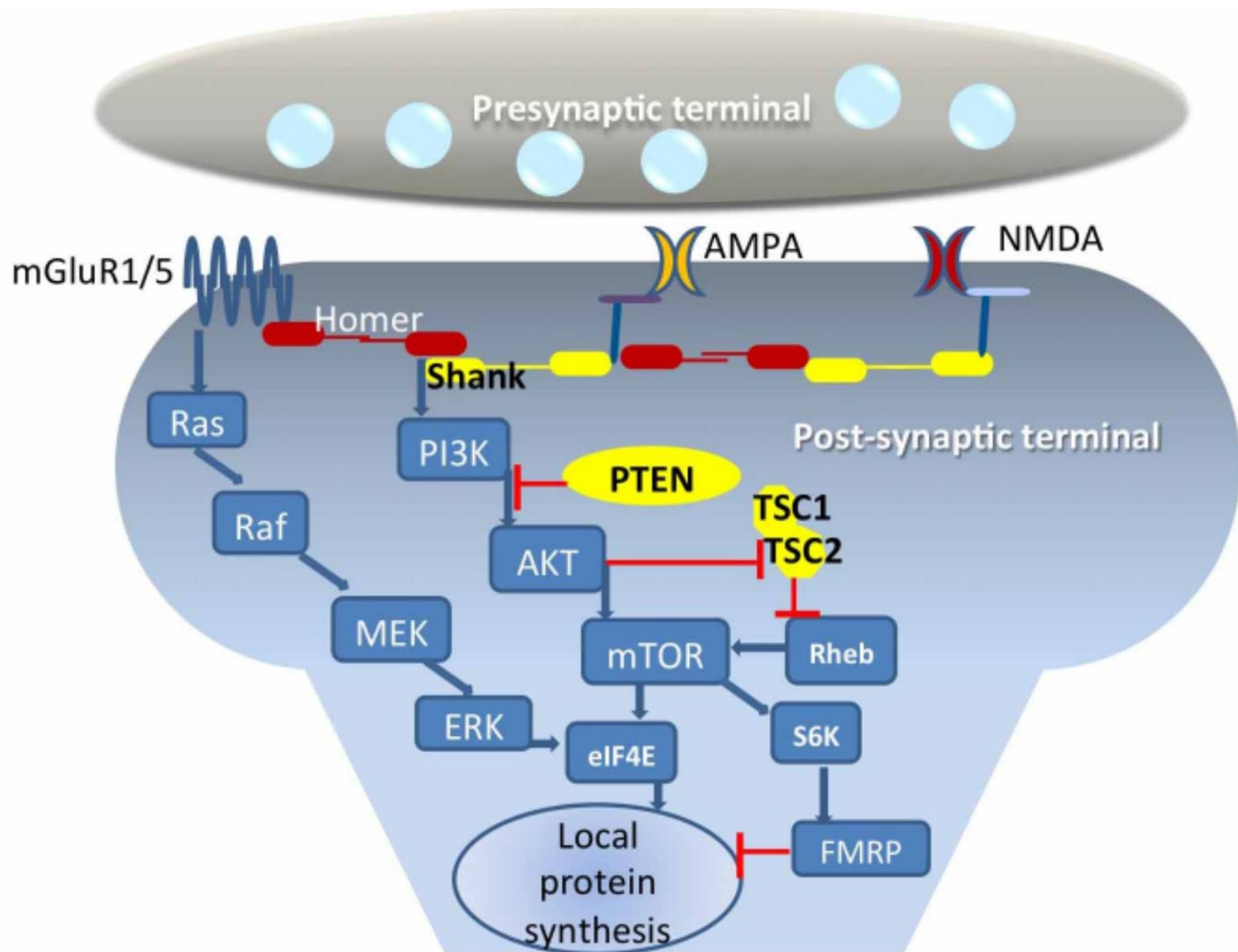
Chronic NAM Treatment

(i) Seizure Frequency



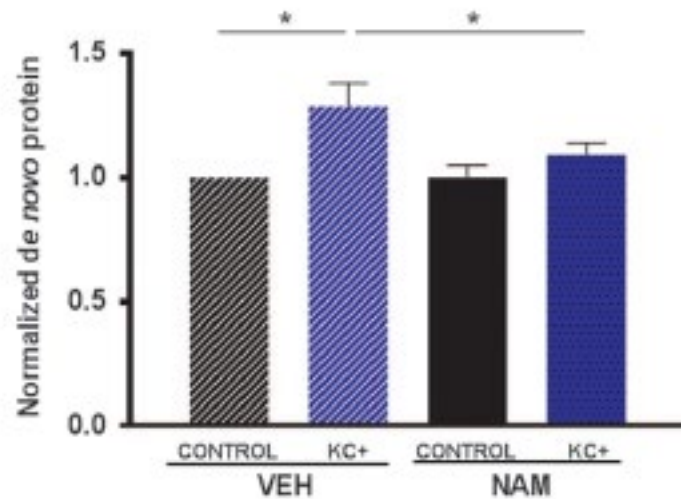
**Clinical trial with an
mGluR5 NAM
(basimglurant) has now
started**

Developmental Synaptopathies: the mTOR Pathway



mGluR5 NAM reduces protein synthesis

(ii) Anti-biotin *de novo* protein synthesis



(ii) Puromycin *de novo* protein synthesis

