TSC Preclinical Consortium

Facilitating Drug Development Through Collaboration of Patient Advocacy, Industry and Academia

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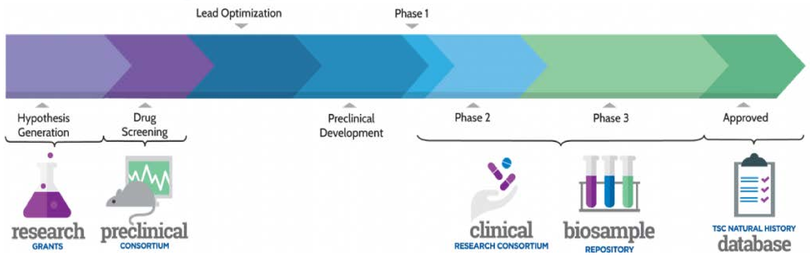
Overview

The Tuberous Sclerosis Alliance (TS Alliance) established the Tuberous Sclerosis Complex (TSC) Preclinical Consortium to:

- grow opportunities for clinical trials in TSC tumors, epilepsy and neuropsychiatric disorders (TAND)
- provide a forum for collaboration with academia and industry
- standardize models, tests and assays for preclinical drug development
  - repurpose drugs
  - evaluate analogs with improved safety
  - investigate novel compounds and mechanisms of action
- ensure transparency, robustness, replication and rigor of research

Accelerating Drug Development



The Consortium complements our other research programs by providing preclinical proof of concept for potential new treatments.

Both preclinical and clinical biosamples are available to evaluate mechanism of action and test hypotheses between mice and humans.

Data Sharing and Exclusivity

Consortium is open to any investigator or company.

Public Screening

Bucket A
Reference compounds with results released to consortium
Consortium covers cost of experiment

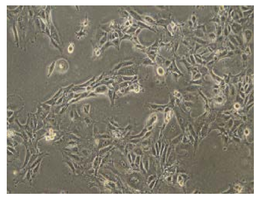
Private Screening

Bucket B
Company's compound with results released to consortium
Escrow period to protect IP

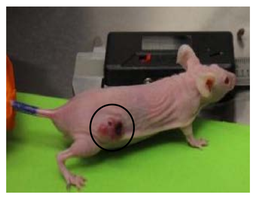
Bucket C
Company's compound - results not released to consortium
No strings attached

TSC Tumor Mouse Models

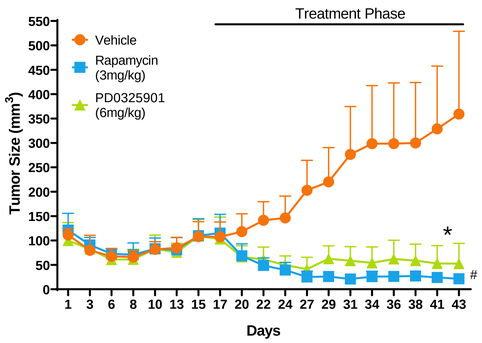
105K (Tsc2-null) cell graft



105K Cells in Culture
2x10⁶ cells/mouse
subcutaneous



Day 41 Tumor
Tumor volume
(length x width²)/2



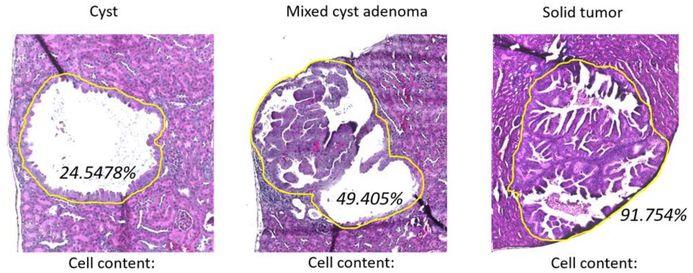
MEK1 Inhibitor PD-0325901

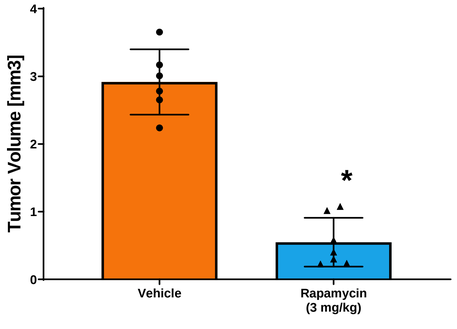
- MEK1 inhibitor shrunk tumors comparably to rapamycin when administered beginning at day 16 (~100mm³)

Asterisk indicates significant difference compared to vehicle-only group

**: p <0.0001; #: p<0.0001*

Tsc2$^{+/-}$ A/J mouse spontaneous renal cystadenoma





Validation with rapamycin

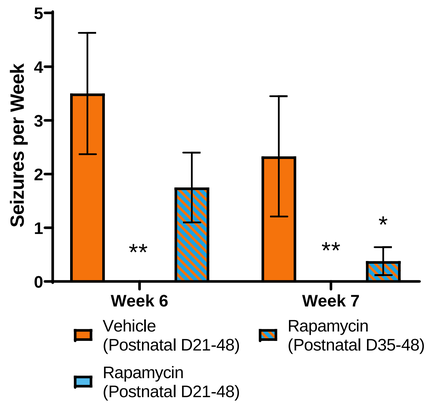
- Rapamycin decreased tumor growth with 30 days of treatment beginning at ~5mo. age

Asterisk indicates significant difference compared to vehicle-only group

**: p <0.0012*

TSC Epilepsy Mouse Models

TSC1-GFAP Conditional KO



Phenotype

- Tsc1$^{flox/flox}$;GFAP-Cre^{+} from crossing Tsc1$^{flox/flox}$ with Tsc1$^{flox/+}$;GFAP-Cre^{+}
- Develop spontaneous and robust epilepsy beginning at age 3-5 weeks

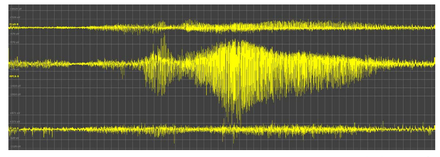
Validation with rapamycin

- Rapamycin completely prevented seizures when administered beginning at P21
- Strong reduction of seizures when administered beginning at P35

Asterisk indicates significant difference compared to vehicle-only group

**: p <0.05, **: p < 0.01*

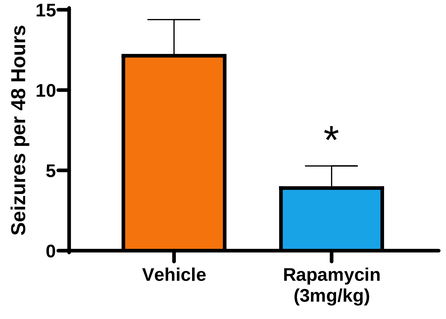
Rheb^{CA} – *in utero* electroporation in CD1 mice



60 Seconds

Phenotype

- Greater number of seizures per day compared to TSC1-GFAP CKO



Validation with rapamycin

- Rapamycin inhibited seizures when dosed at P115-132

Asterisk indicates significant difference compared to vehicle-only group

**: p <0.0219*

Nominations are Welcomed!

Thirty compounds or combinations of mechanisms of action tested to-date, e.g., mTOR, PI3K, MEK1, checkpoint kinase, PD-1, CTLA4, and more.

For more information, contact Dean Aguiar at daguiar@tsalliance.org.