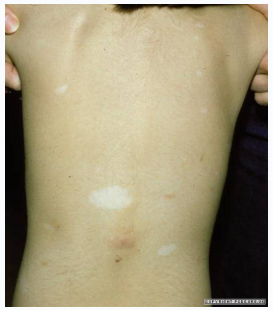
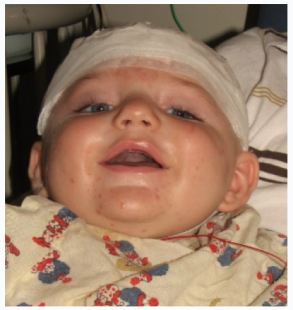
Treating Epilepsy in an Orphan Genetically-defined Seizure Disorder, Tuberous Sclerosis Complex (TSC)

Tuberous Sclerosis Complex, a genetically-defined (*TSC1/TSC2*) life-long epilepsy disorder

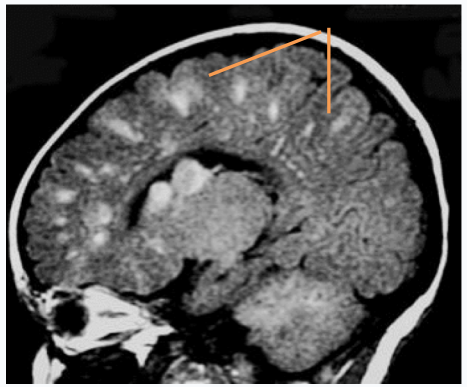




TSC diagnosis: First by pediatricians, referred to specialists

- 1-100 Daily Seizures: 85% of all patients (neurologists)
- Median age of seizure onset: 3 months
- Skin patches (dermatologists)

Brain malformations



Characteristics	Current SOC	Efficacy	Comorbidities
• Brain Malformations • Childhood onset seizures • Life-long epilepsy • AED resistant	• Brain surgery • Everolimus	• Limited efficacy • Side-effects	• Insomnia • Learning disabilities • Behavior issues (e.g., anxiety)

- High burden on care givers and patients: We need new drugs to treat seizures and comorbidities

TSC is an orphan disorder with a high societal cost

Incidence: 1/6,000 new births
50,000 TSC pts with epilepsy in the US
30,000-40,000 TSC pts with drug-resistant epilepsy (60-80% all pts)

Cost of Everolimus (SOC): $16K/mo/pt, $192K/year/pt
For 30,000 patients this represents **a US market opportunity of $5-6B/year**

TEAM

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Inadequate SOC - Established clinical trial design

Brain surgery: In only 10-15% of pts
Seizures remain in ~40% of operated pts
Seizures return in 50% of seizure-free pts post-op

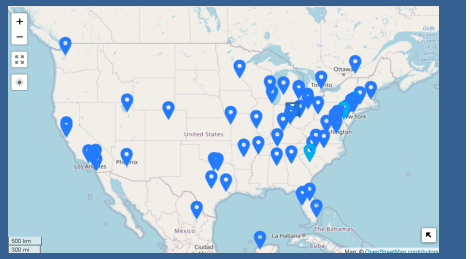
Everolimus: (Afinitor)
Limited efficacy (40% of pts respond at high dose)
Major side-effects

We will use everolimus trial's design and clinical endpoints

Primary endpoint Phase III: Percent change in seizure frequency [core phase (18 wks) vs baseline (8 wks)]

Secondary endpoints: Impact on behavior and quality of life (and more)

TSC clinics



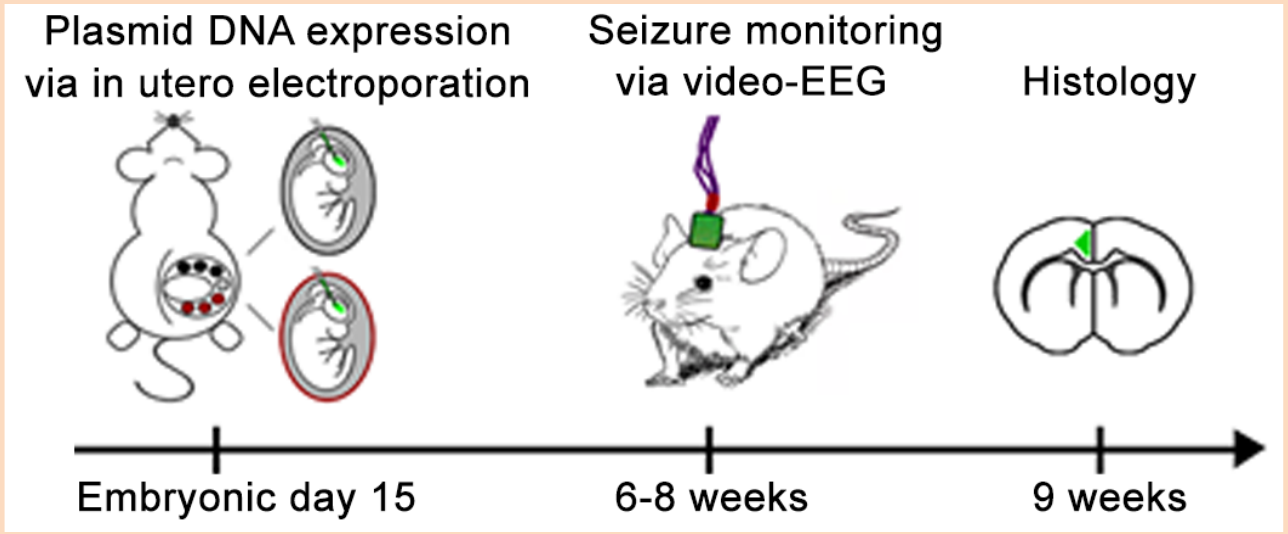
68 Centers of Excellence

Competition

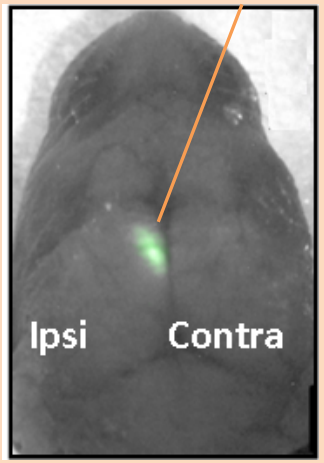
Drugs	Efficacity	Formulation	Side-effects	Mode of action	Company
Conventional AED	Seizure reduction in 30-40% pts	Liquid, pill, suppository	e.g., Sleepiness, nausea depending on the drug		several
Everolimus (SOC) (Afinitor)	40% pts with >50% seizures reductions	Liquid suspension	Many and serious: e.g., stomatitis, diarrhea, infections (bone loss)	mTOR inhibitor	Novartis
Under development	Unknown (failed phase II for Fragile X syndrome)	unknown	Unknown but widespread expression	mGluR5 antagonist	Noema Pharma
Epidiolex (cannabidiol)	Age 1-57 years, 201 pts 20% reduction (vs placebo)	Liquid solution, twice daily	serious: e.g. diarrhea, suicidal thoughts, elevated liver enzymes, sleepiness, fever, vomiting, rash	Cannabinoid receptor mTOR inhibition	Greenwich Biosciences Inc.

Our Mouse Model: Competitive Advantage for Drug Discovery

Using in utero electroporation to model human brain malformation in TSC



Brain malformation



Our mouse model: Definitive and only model for TSC seizures

- Hsieh, Bordey 2016
- Validated through collaborations with Biotechs

Three New Validated Targets & Four Yale Solutions – Three patents

Mutant TSC1/TSC2

Increased Rheb

Increased mTOR

Increased MEK

Decreased 4EBP1 activity
Increased EIF4E activity

Abnormal HCN4

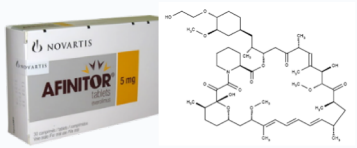
Enhanced excitability

Cell overgrowth, brain malformations

Seizures

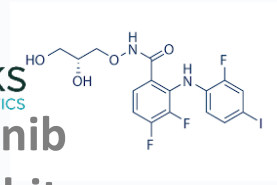
Increased Filamin A

Yale 4EBP Gene Therapy and/or EIF4E RNAi
Patent Filed



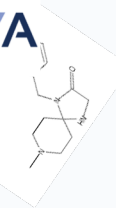
Everolimus

SpringWorks THERAPEUTICS



Mirdametinib
MEK1/2 Inhibitor
(Ph 2 Solid Tumors)

CASSAVA sciences



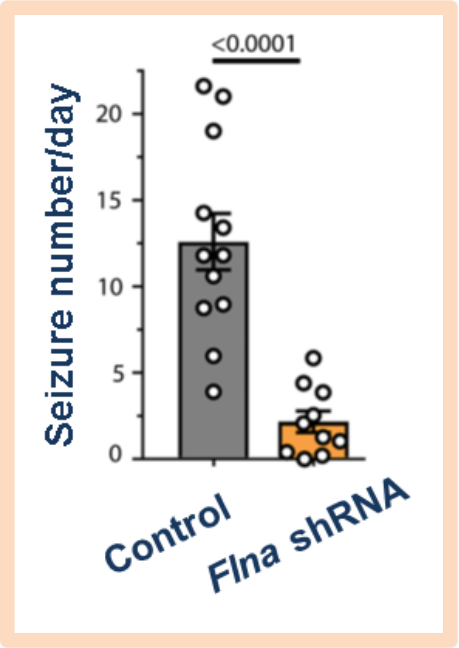
PTI-125
(Ph 3 AD)

Yale HCN4 Gene Therapy
Patent Filed

Yale FLNA NCE and RNAi
Patent Filed

Solution 1: Targeting Filamin A (FLNA) for seizure reduction is validated in adult mice

- FLNA is an actin-binding molecule that is increased in TSC patients and mouse models.
- Normalizing (shRNA) or blocking (drug) FLNA shrinks cell size and brain malformation and reduces seizure activity in the most relevant and accepted mouse model (Yale generated).



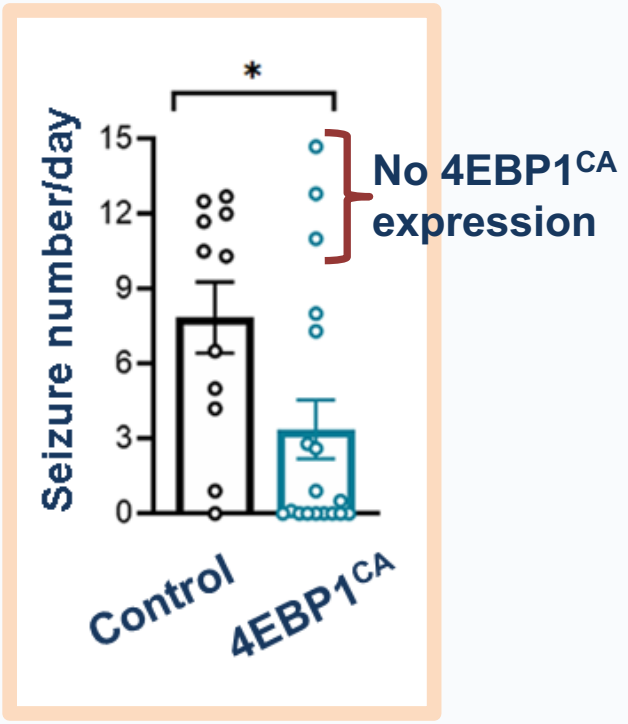
Flna shRNA decreases seizure activity

Goal: CNS Injection of *Flna* siRNA

Neuron 2014
Science Translational Medicine 2020

Solution 2: Overexpressing 4EBP1 for seizure reduction is validated in adult mice

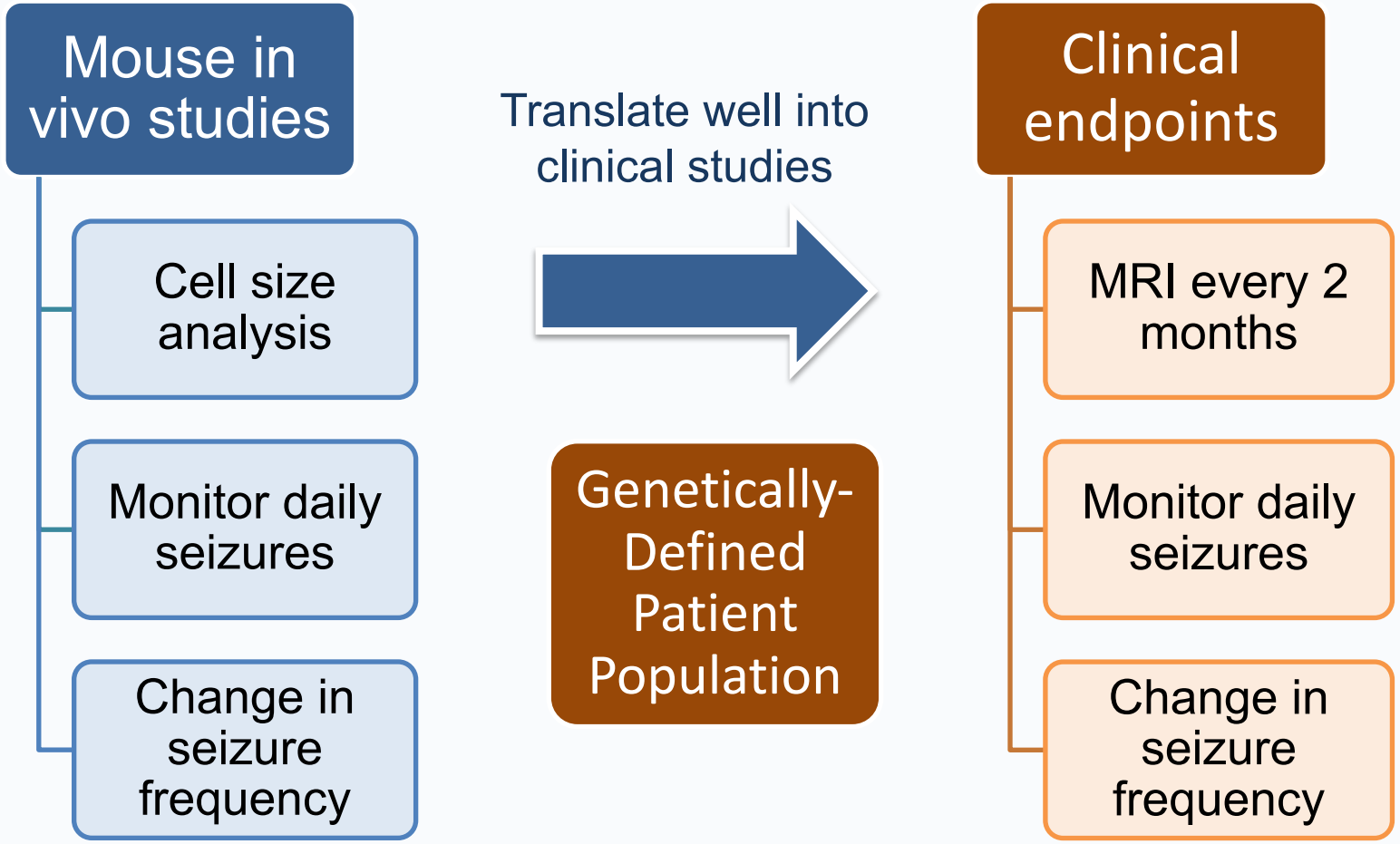
- 4EBP1 activity is decreased in TSC patients and mouse models
- Decreased 4EBP1 activity results in increased protein synthesis, cell overgrowth, and brain malformation.
- Overexpression a constitutively active 4EBP1 shrunk brain malformation and reduced seizures.



Goal: Focal delivery of 4EBP1-AAV Gene Therapy

Brain 2021 (for 4EBP1)

Mouse *in vivo* efficacy studies of RNAi and AAV will enable our IND application



RNAi and AAV efficacy on seizures is gating to pre-IND meeting

Completed

- ✓ Target validation FLNA and 4EBP1
- ✓ Clinical collaboration
- ✓ Animal model
- ✓ Clinical endpoints established

Flna RNAi solution - $70K

Deliverables — **Q4 2022**

- RNAi being generated (commercial source)
- Efficacy on seizures via CNS injections in Yale Model
- Validation of knockdown in human neurons

4EBP1 AAV solution - $70K

Deliverables — **Q3 2022**

- 4EBP1-AAV being produced (commercial source)
- Efficacy on seizures via CNS injection in Yale Model

Partnership - $5M Seed

Q2 2023

- Efficacy on seizures via second model
- Final Tox study
- Pre-IND package