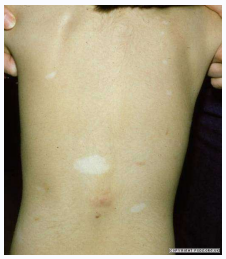
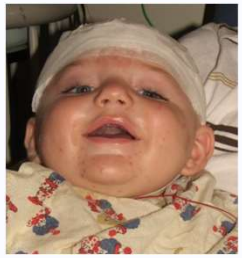
Treating Epilepsy in an Orphan Genetically-defined Seizure Disorder, Tuberous Sclerosis Complex (TSC)

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

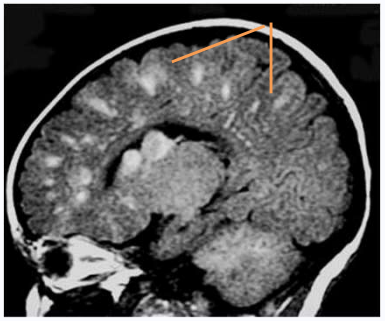




TSC diagnosis:

- 1-100 Daily Seizures: 85% of all patients
- 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

- **We need new options to treat seizures and comorbidities**

TSC is an orphan disorder with a high societal cost and inadequate SOC

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

SOC:

Brain surgery: In only 10-15% of pts with 50% becoming seixure free

Everolimus: (Afinitor)
Limited efficacy (40% seizure reduction)
Major side-effects

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

TEAM

Science

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Access to patients

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Liaison between TSCA and the **68 TSC Clinics**

Business

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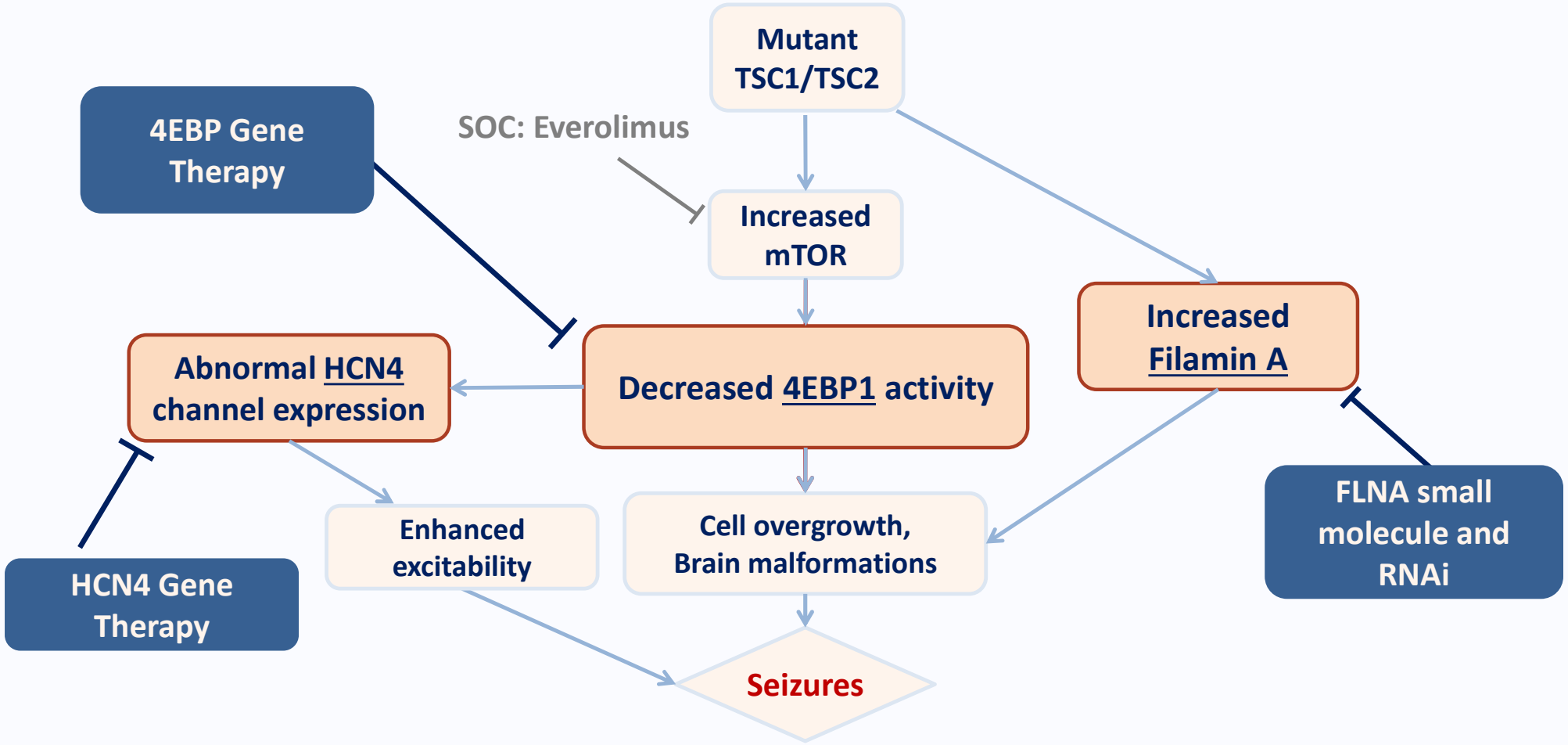
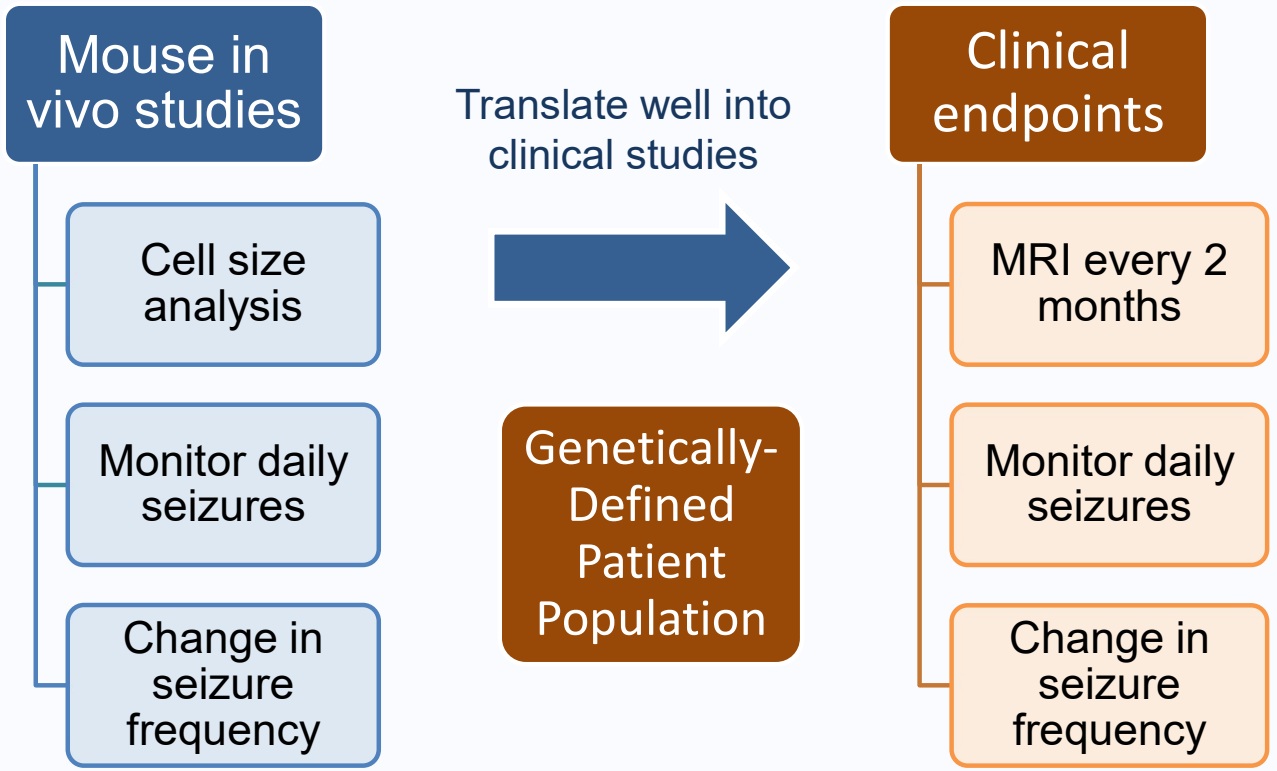
Competition

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.
Under development	MEK blocker	unknown	Serious side-effects expected	mTOR independent	Undisclosed

Three New Validated Targets & Three Yale Solutions



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 project – $500K

Q3 2023

Deliverables Part 1

- RNAi being generated by industry partner
- Efficacy on seizures via intraventricular injections in Yale Model

Q2 2024

Deliverables Part 2

- Human grade RNAi generation (industry partner)
- Validation of knockdown in human TSC neurons

4EBP1 AAV project - $500K

Deliverables Part 1

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

Q3 2024

- Final Tox study with partners
- Pre-IND package