Treating Epilepsy in an Orphan Genetically-defined Seizure Disorder, Tuberous Sclerosis Complex (TSC)
Tuberous Sclerosis Complex, a genetically-defined (\textit{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)

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Current SOC</th>
<th>Efficacy</th>
<th>Comorbidities</th>
</tr>
</thead>
<tbody>
<tr>
<td>Brain Malformations</td>
<td>Brain surgery</td>
<td>Limited efficacy</td>
<td>Insomnia</td>
</tr>
<tr>
<td>Childhood onset seizures</td>
<td>Everolimus</td>
<td>Side-effects</td>
<td>Learning disabilities</td>
</tr>
<tr>
<td>Life-long epilepsy</td>
<td></td>
<td></td>
<td>Behavior issues</td>
</tr>
<tr>
<td>AED resistant</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

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 seizure free

**Everolimus:** Limited efficacy (40% seizure reduction)
(Afinitor) 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

Angélique Bordey, PhD
Professor
Vice-Chair for Research Neurosurgery, Yale
Science Lead
angelique.bordey@yale.edu

Access to patients

Jo Anne Nakagawa
Director, Clinical Projects at the TSC Alliance (TSCA)
Liaison between TSCA and the 68 TSC Clinics

Business

David Lewin, PhD
Director Business Development, Yale, OCR
IP Management
david.lewin@yale.edu
## Competition

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

Yale Confidential and Proprietary - Copyright (c) 2021 by Bordey – All Rights reserved
Three New Validated Targets & Three Yale Solutions

- Mutant TSC1/TSC2
  - Increased mTOR
    - Cell overgrowth, Brain malformations
    - Seizures
  - Decreased 4EBP1 activity

- Increased Filamin A
  - FLNA small molecule and RNAi

- Abnormal HCN4 channel expression
  - Enhanced excitability
  - HCN4 Gene Therapy

- 4EBP Gene Therapy
  - SOC: Everolimus
Mouse *in vivo* efficacy studies of RNAi and AAV will enable our IND application.

**Mouse in vivo studies**
- Cell size analysis
- Monitor daily seizures
- Change in seizure frequency

**Clinical endpoints**
- MRI every 2 months
- Monitor daily seizures
- Change in seizure frequency

Translate well into clinical studies.

Genetically-Defined Patient Population
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

Deliverables Part 1
- RNAi being generated by industry partner
- Efficacy on seizures via intraventricular injections in Yale Model

Deliverables Part 2
- Human grade RNAi generation (industry partner)
- Validation of knockdown in human TSC neurons

Q3 2023

4EBP1 AAV project - $500K

Deliverables Part 1
- 4EBP1-AAV being produced (commercial source)
- Efficacy on seizures via intracerebral injection in Yale Model

Q3 2024

Q2 2024

- Final Tox study with partners
- Pre-IND package

Q3 2024