mTOR inhibitors in TSC: Past, Present, and Future

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Objectives

• Discovery of mTOR and mTOR inhibitors
• Clinical trials leading to FDA approval to treat TSC
• What is next?
• Q&A
The Discovery of Rapamycin...
The Discovery of Rapamycin...Almost Lost

MAY 21, 2021

The Dirty Drug and the Ice Cream Tub

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Image credits: Sergio Rapu

This episode, a tale of a wonder drug that will make you wonder about way more than just drugs.
Finding the Target of Rapamycin

Kuntz, Hall. TIBS 18:334-338 (1993)
Genetic Basis of TSC

TSC1

TSC2

or

XX

XY
Linking TOR to TSC: *D. melanogaster*
Things are Smaller Than They Should Be

Loss of dTOR

Oldham et al. Genes & Development 2000
Loss of TSC 1
The mTOR Pathway (Simplified)

Growth Factors

Nutrients
(amino acids)

Energy
(AMP/ATP)

Protein Synthesis
Autophagy

Cell Growth
Cell Proliferation

Cell Survival
Cell Proliferation
mTOR Inhibitors Used in TSC

Sirolimus

Everolimus
The mTOR Pathway (Simplified)

Everolimus
Sirolimus
Normal
TSC1 and TSC2 regulate mTOR to limit its activity
Molecular Basis of TSC

TSC
Control of mTOR is lost when either TSC1 or TSC2 is missing or unable to perform its function
Molecular Basis of TSC

TSC + mTOR inhibitor

Control of mTOR is reestablished despite missing or nonfunctional TSC1 or TSC2

Sirolimus
Everolimus
Sirolimus to Treat SEGA (2006)

Everolimus to Treat SEGA (2010)

Baseline

24 months

Krueger et al., NEJM 2010
Krueger et al., Neurology 2013
Everolimus to Treat SEGA (2012)

EXIST-1

SEGA Progression

Change in SEGA Volume

<table>
<thead>
<tr>
<th></th>
<th>3 months</th>
<th>6 months</th>
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<tbody>
<tr>
<td><strong>Median</strong></td>
<td></td>
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<tr>
<td>Everolimus (n=78)</td>
<td>-39.1%</td>
<td>-47.7%</td>
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<tr>
<td>Placebo (n=39)</td>
<td>+0.9%</td>
<td>+1.6%</td>
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</tbody>
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Franz et al., Lancet 2012
Sirolimus to Treat Angiomyolipoma (2008)

Cincinnati Angiomyolipoma Sirolimus Trial (CAST)

Bissler et al., NEJM 2008
Everolimus to Treat Angiomyolipoma (2013)

EXIST-2

Bissler et al., Lancet 2012
Sirolimus to Treat LAM (2011)

Multicenter International Lymphangioleiomyomatosis Efficacy and Safety of Sirolimus Trial (MILES)

McCormack et al., NEJM 2011
Everolimus to Treat Epilepsy (2016)

EXIST-3

Sirolimus to Treat Angiofibromas (2018)

mTOR Inhibitors FDA-approved for the Treatment of TSC

2010 Subependymal Giant Cell Astrocytoma (SEGA)
2012 Renal Angiomyolipoma
2015 Lymphangioleiomyomatosis (LAM)
2018 Refractory Epilepsy
2022 Facial Angiofibroma

Everolimus
Everolimus
Sirolimus
Everolimus
Sirolimus
mTOR Inhibitors: Where Next?

**Ideal Approach**
- Diagnose TSC
- Identify ASD Risk
- Start treatment

**Conventional Approach**
- Diagnose TSC
- Wait for ASD symptoms
- Start treatment

**Symptom Onset**

**Presymptomatic Phase**
Windows of Opportunity

Kingswood et al. Orph J Rare Dis. (2014) 9:182
Kingswood et al. Orph J Rare Dis. (2017) 12:2
Targeting LAM: MILED Trial

Multicenter Interventional Lymphangioleiomyomatosis (LAM) Early Disease Trial (MILED)

- Primary objective: Determine if early, long-term (2 yr), low-dose sirolimus will prevent LAM progression to more advanced stages.
- Study design: N=60, randomized to blinded treatment with sirolimus vs. placebo.
- Eligibility: Adult female with confirmed diagnosis of LAM that is clinically mild and not in imminent clinically-indicated treatment with mTOR inhibitors.
- Funded through NIH (NHLBI and NCATS), the LAM foundation, and the University of Cincinnati.

For more information: susan.mcmahan@uc.edu
Targeting Angiomyolipoma: TBD

Targeting Epilepsy

Age When TSC Features First Detected/Recognized

Initial presentation
Cardiac rhabdomyoma
Tuber
Hypomelanotic macules
SEN
Seizures
Retinal hamartoma
Renal cyst
Facial angiofibroma
Shagreen patch
Renal angiomyolipoma
SEGA

Chu-Shore et al. Epilepsia 2010;51:1236-1241
Davis et al., Pediatrics. (2017) 140:e20164040
Targeting Epilepsy: TSC-STEPS

Clinicaltrials.gov: NCT05104983

Funding Sources
US FDA R01-FD007275-01
Clack Foundation
TSC Alliance
Targeting Epilepsy: TSC-STEPS

Randomized, double-blind, placebo-controlled clinical trial to assess the efficacy and safety of sirolimus in infants 0-12 months of age
Targeting Epilepsy: TSC-STEPS

Sites (Current):
• Cincinnati Children’s Hospital (Krueger)
• University of Alabama – Birmingham (Bebin)
• Boston Children’s Hospital (Sahin)
• University of North Carolina – Chapel Hill (Capal)
• Washington University – St. Louis (Wong)
• University of Texas – Houston (Northrup)
• Stanford University (Porter)
• University of California – Los Angeles (Rajaraman)
Targeting Epilepsy: TSC-STEPS

Eligibility:
• 0-6 months of age
• confirmed diagnosis of TSC
• no history of clinical seizures,
• no prior treatment with anti-seizure medication or therapy

For more information
Email: info@tscsteps.org
Phone: Molly Griffith (513-636-9669)
Web: clinicaltrials.gov/NCT05104983
Neste local foram obtidas em janeiro de 1965 as amostras de solo que permitiram obter a rapamicina, substância que inaugurou uma nova era para os pacientes submetidos a transplantes de órgãos.

Amonagem dos Investigadores brasileiros.
Novembro de 2005.

WYETH BRASIL