mTOR inhibitors in TSC: Past, Present, and Future

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TSC Alliance Research Webinar Series
23 June 2022

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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

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The Discovery of Rapamycin…

The Discovery of Rapamycin...Almost Lost

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MAY 21, 2021

The Dirty Drug and the Ice Cream Tub

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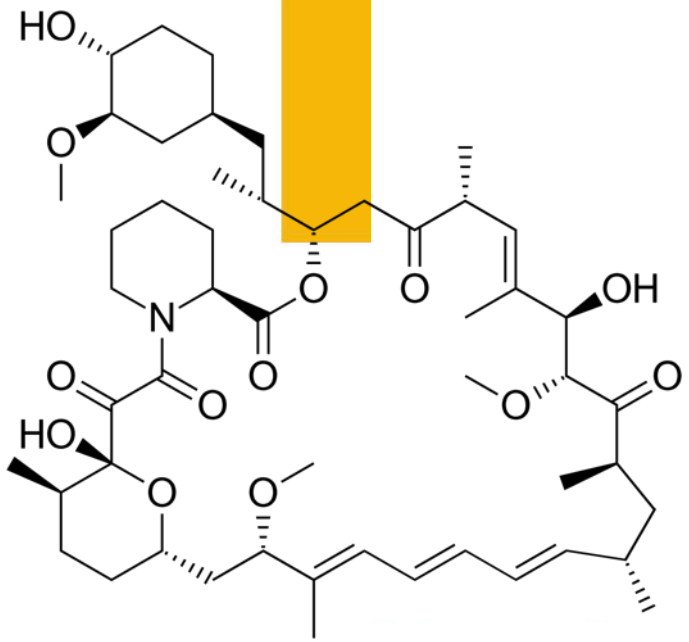
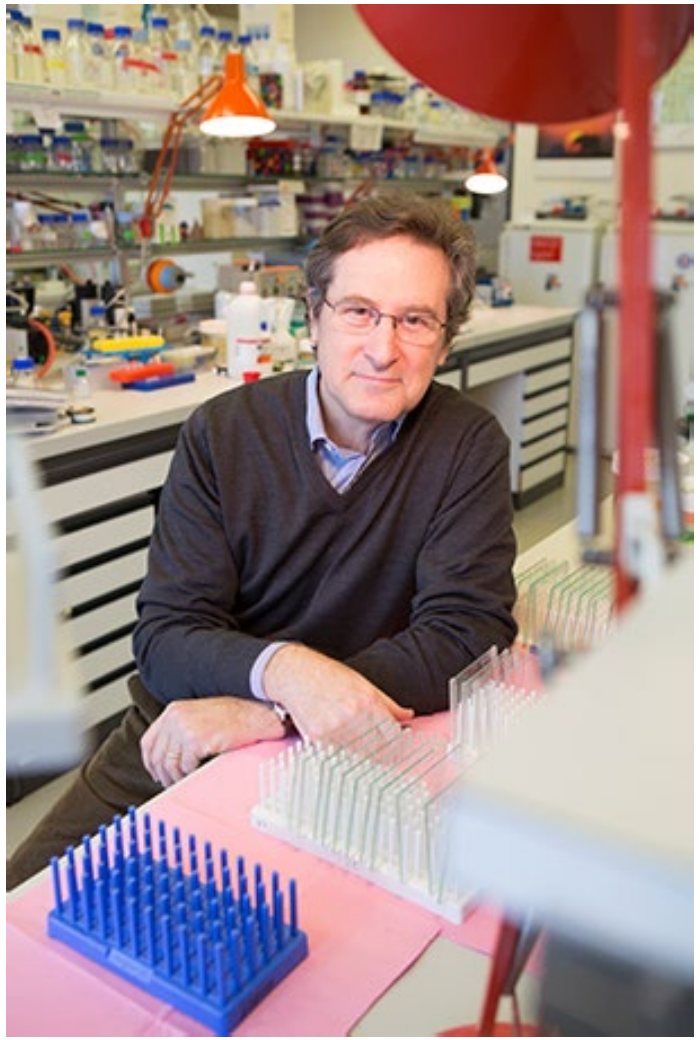
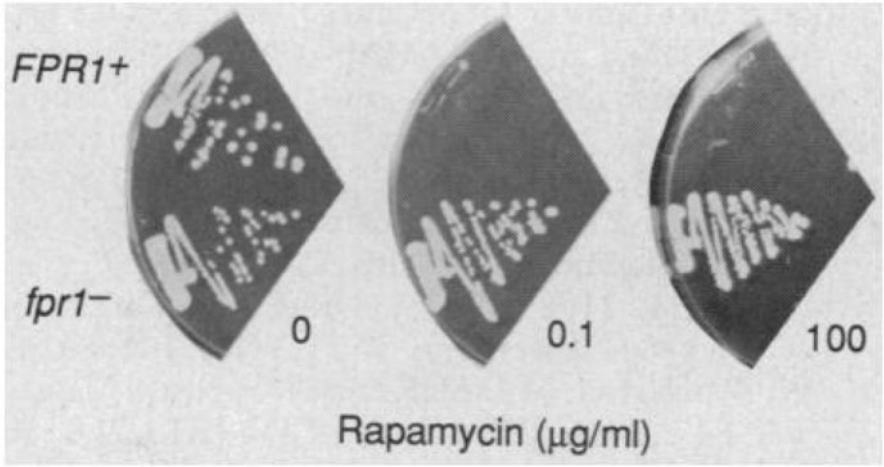
Image credits: Sergio Rapu

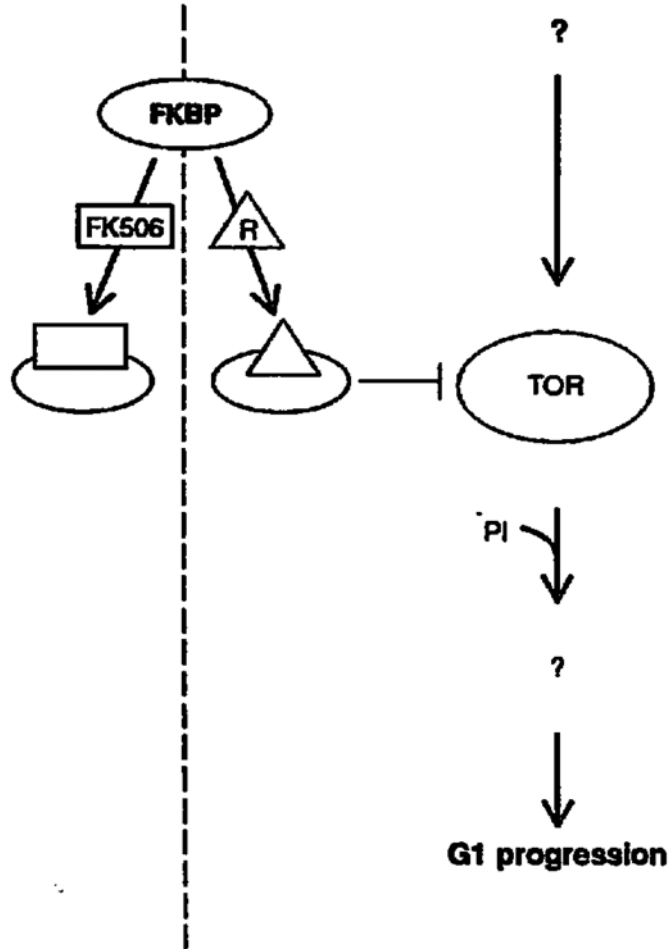
This episode, a tale of a wonder drug that will make you wonder about way more than just drugs.



Finding the Target of Rapamycin

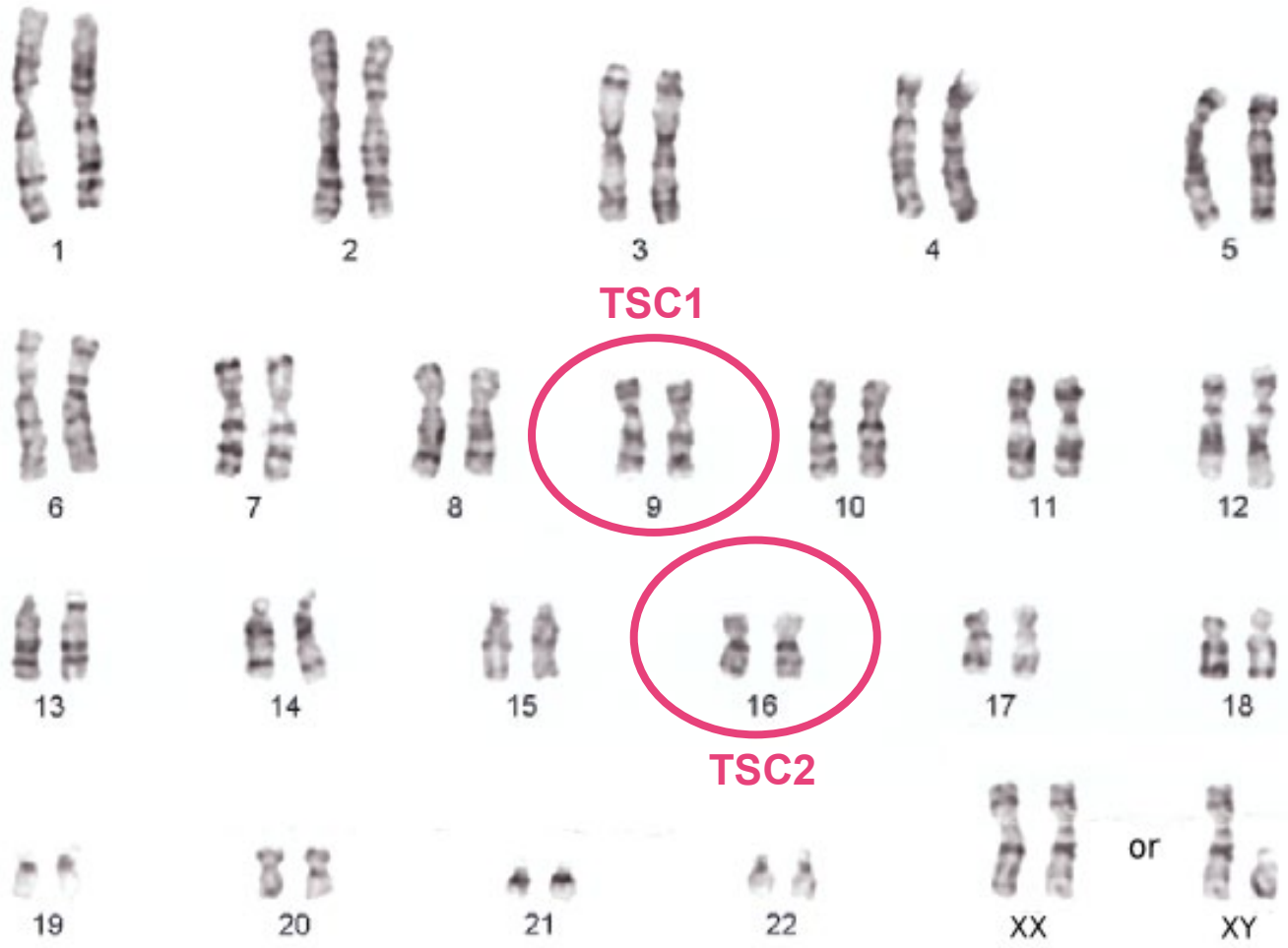






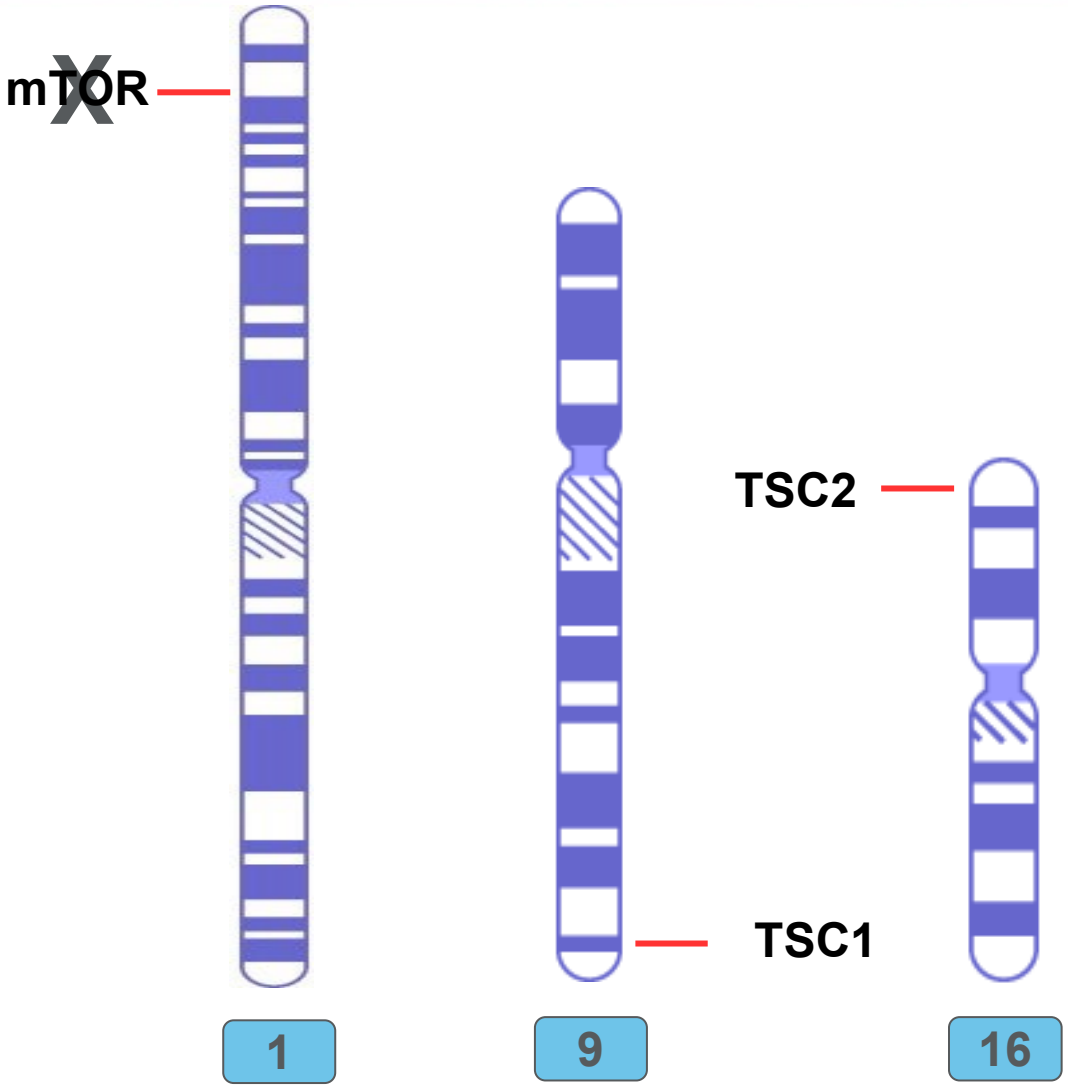
Heitman, Movva, Hall. Science 253:905-909 (1991)
Kuntz, Hall. TIBS 18:334-338 (1993)

Genetic Basis of TSC

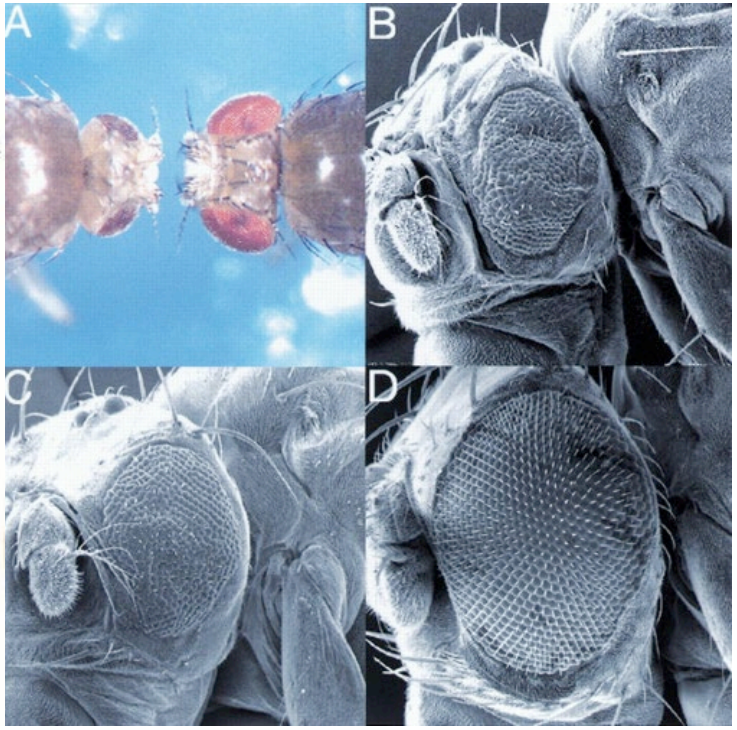


Linking TOR to TSC: *D. melanogaster*

Things are Smaller Than They Should Be

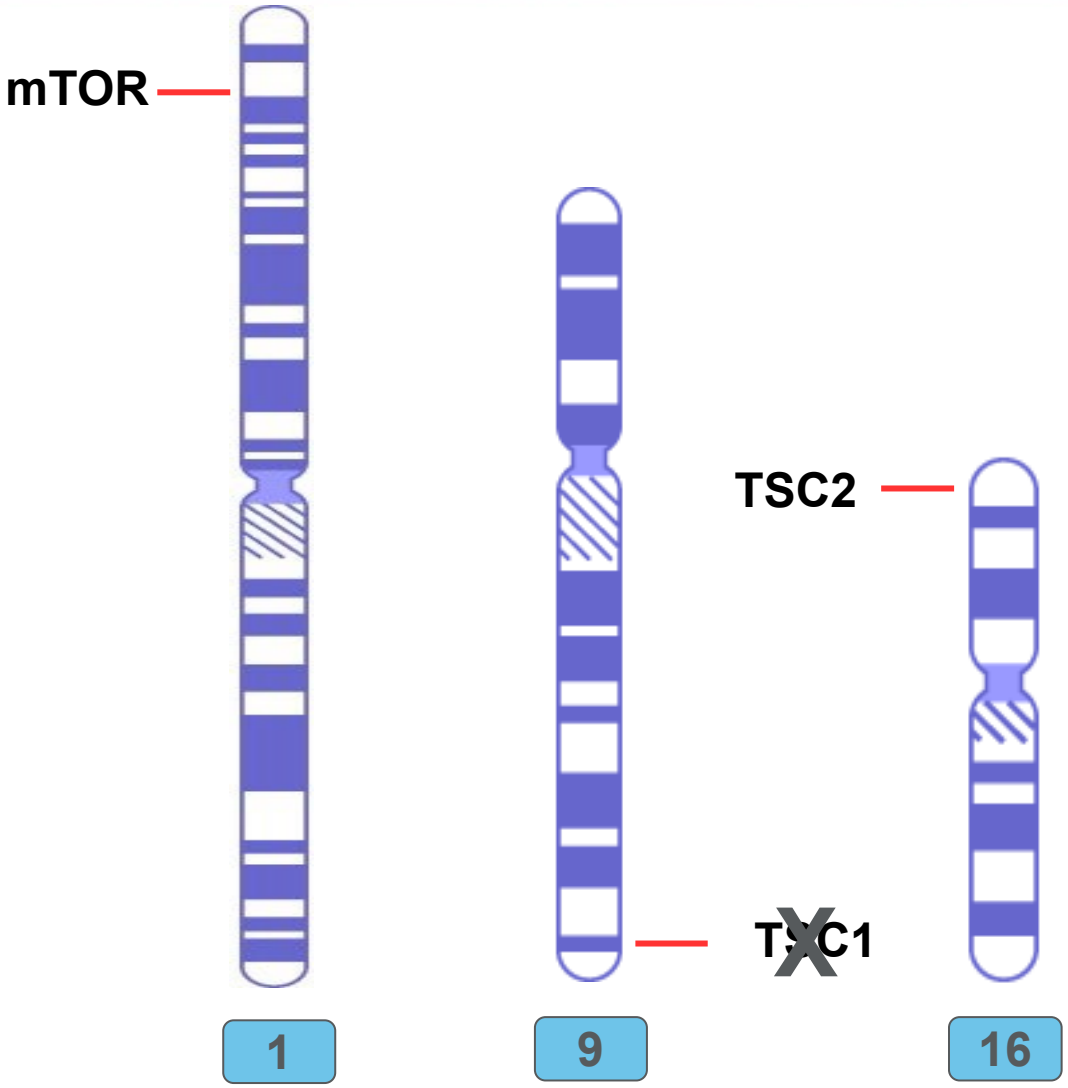


Loss of dTOR

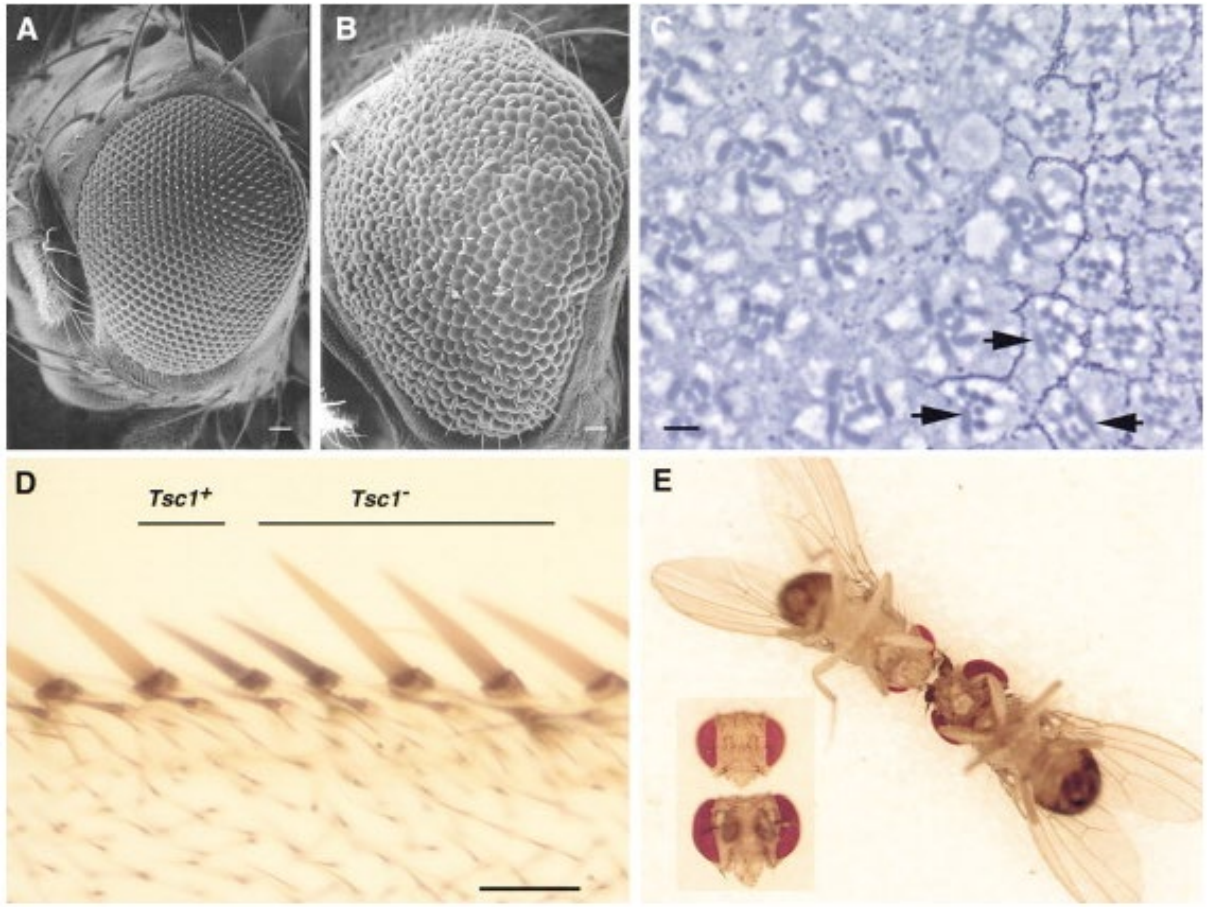


Oldham *et al.* Genes & Development 2000

Things are Bigger Than They Should Be

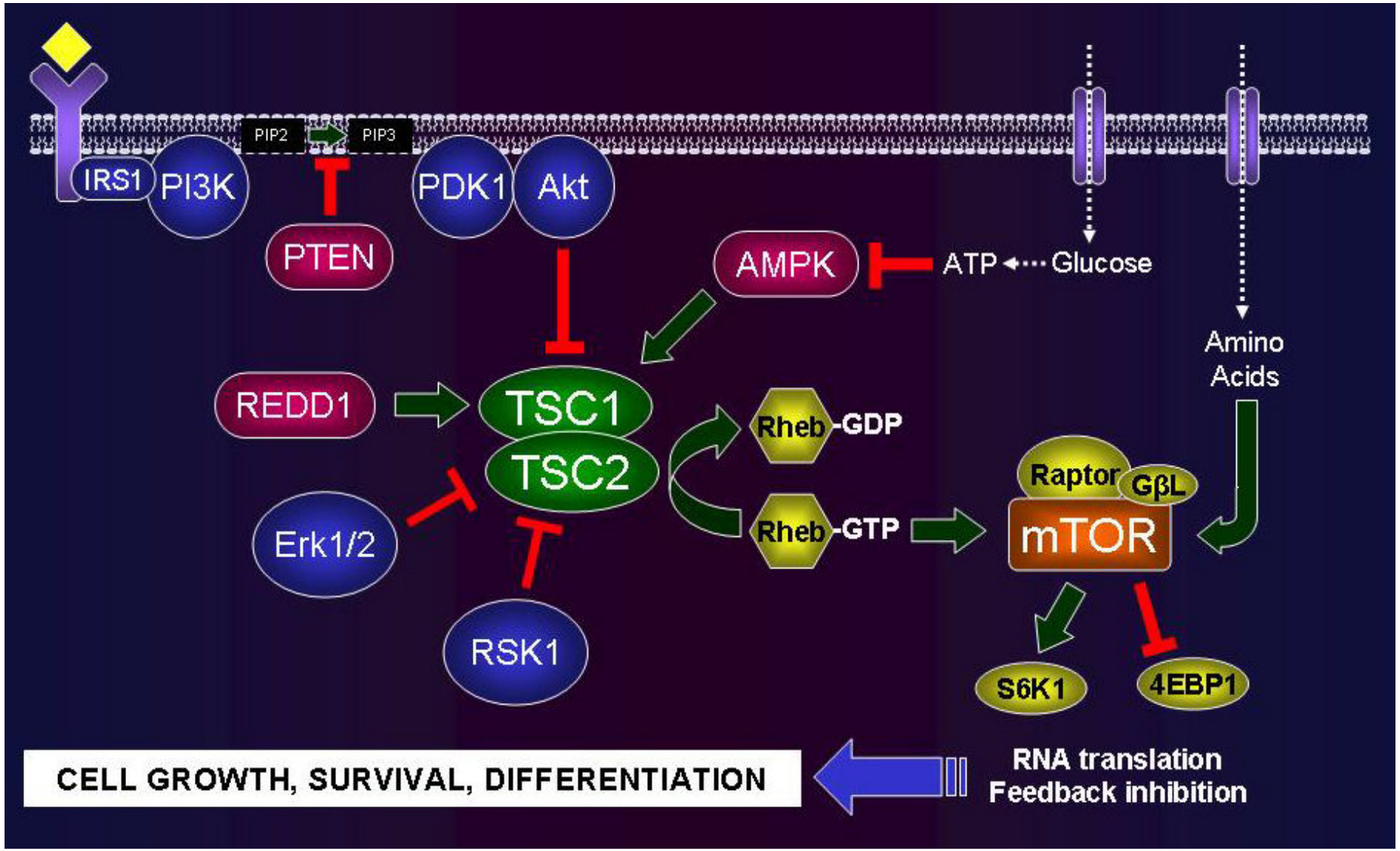


Loss of TSC 1

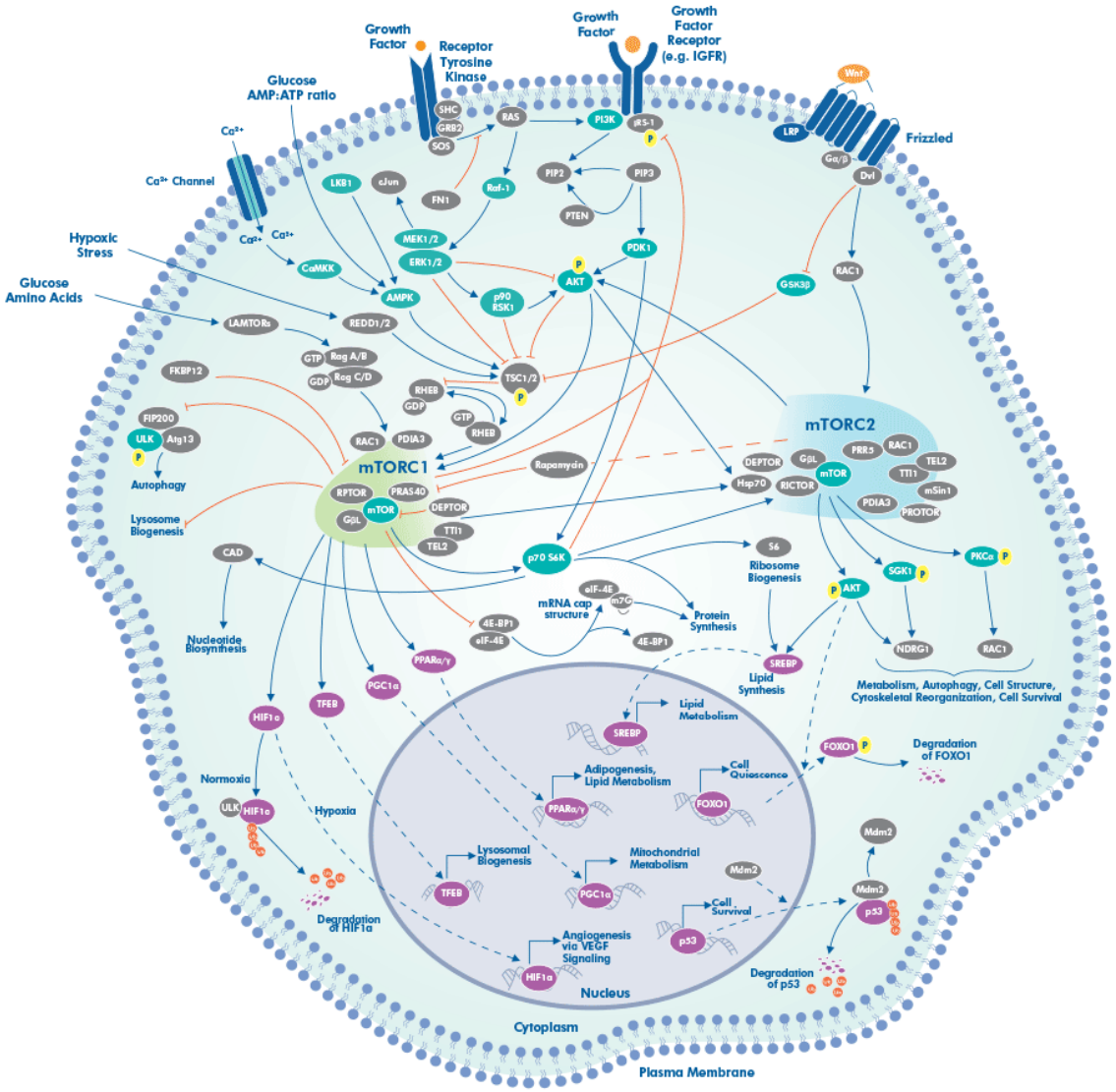


Potter *et al.* Cell 2001

The mTOR Pathway (2010)

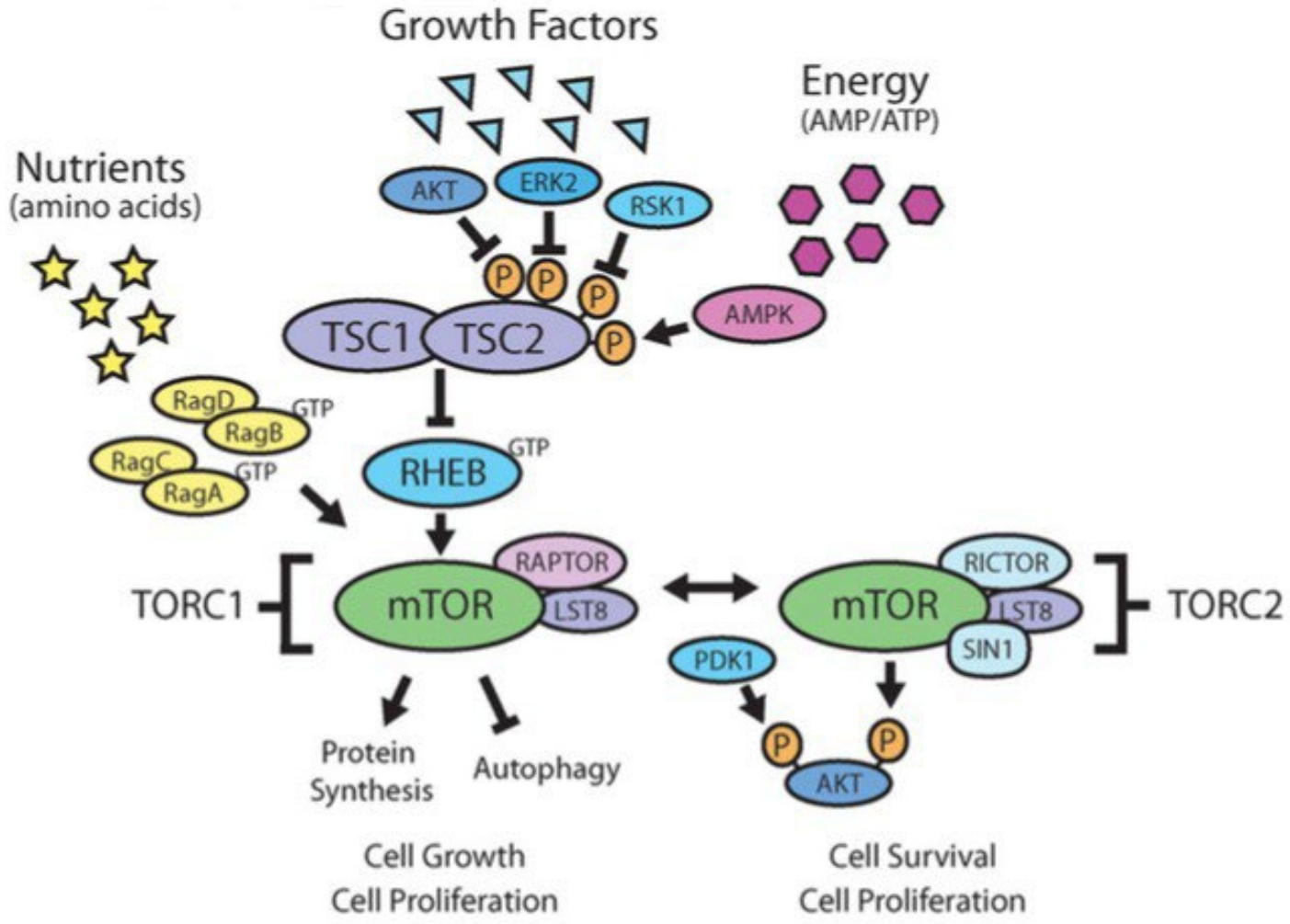


The mTOR Pathway (2020)

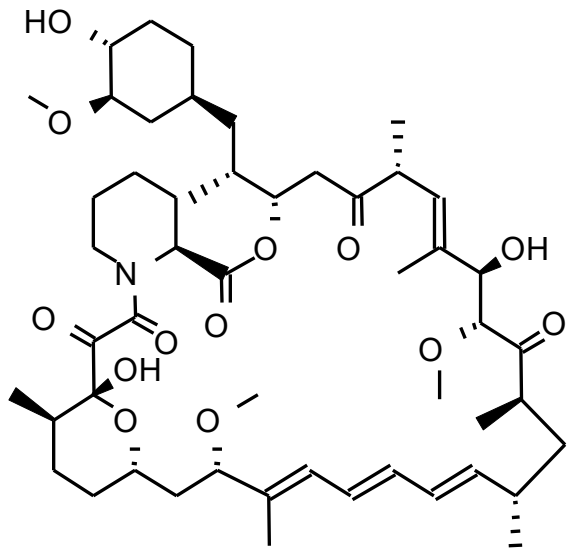


Novusbio.com

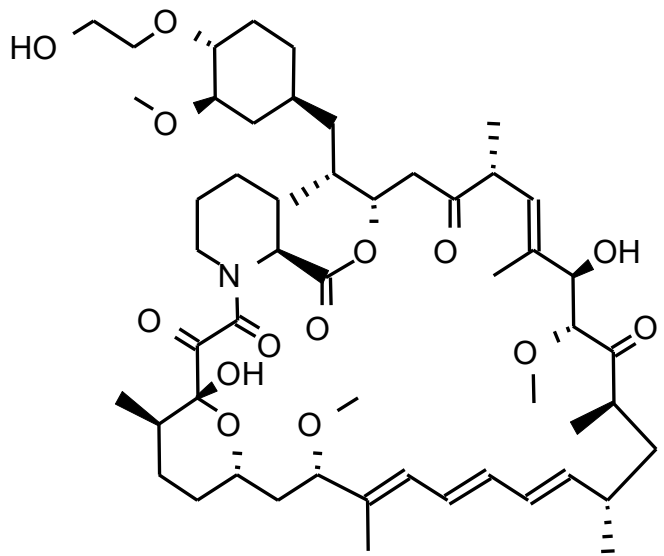
The mTOR Pathway (Simplified)



mTOR Inhibitors Used in TSC

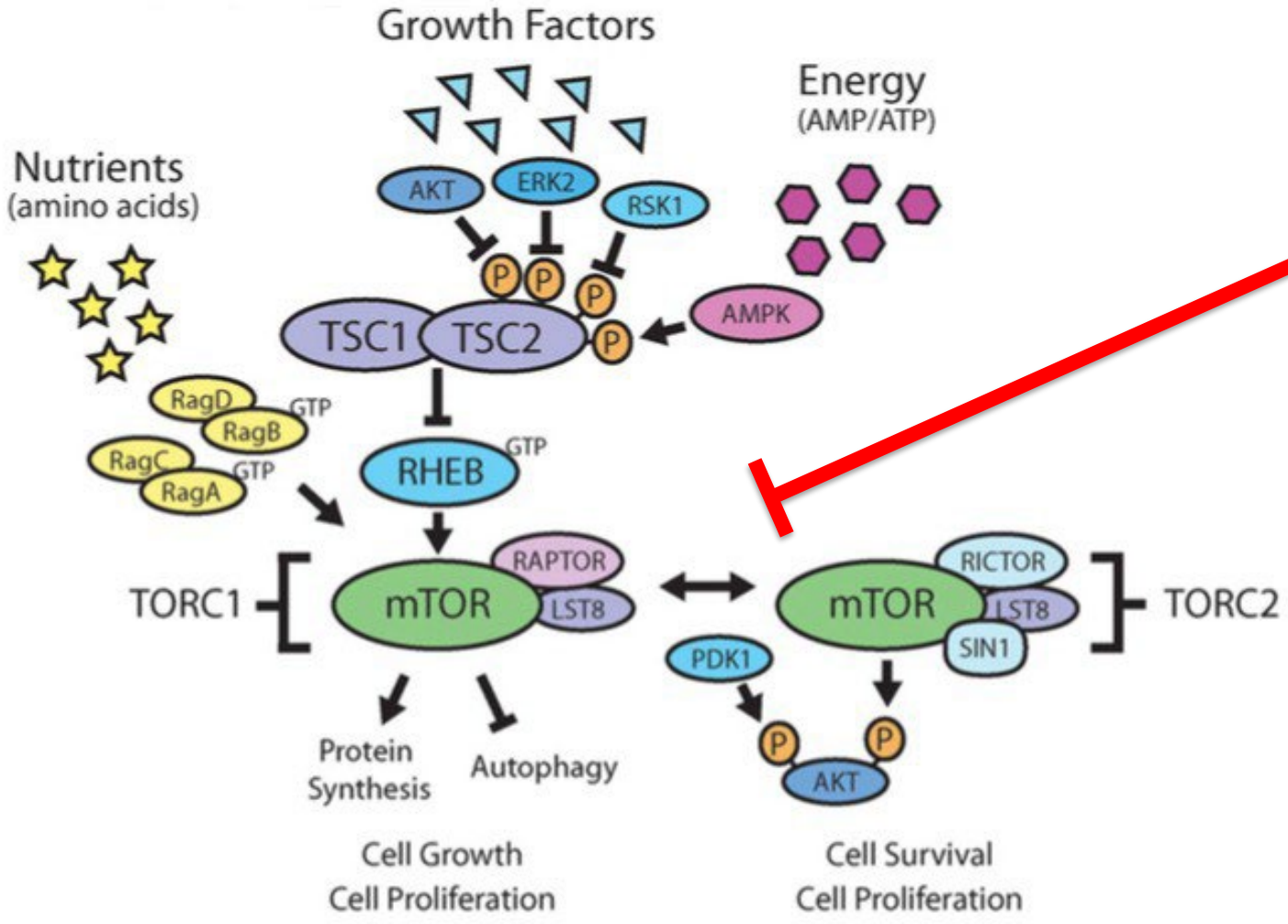


Sirolimus



Everolimus

The mTOR Pathway (Simplified)

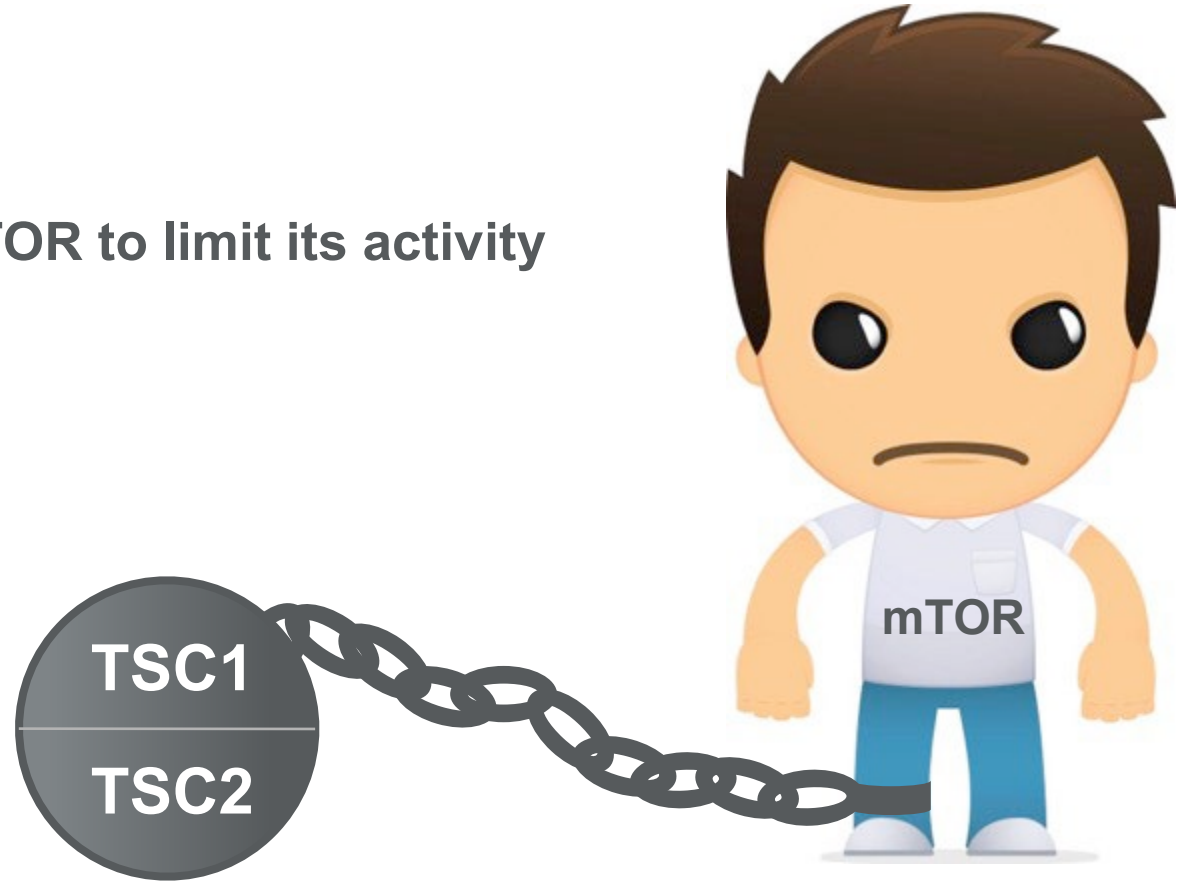


Everolimus
Sirolimus

Molecular Basis of TSC 101

Normal

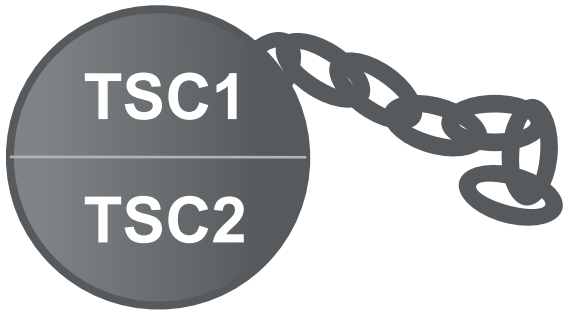
TSC1 and TSC2 regulate mTOR to limit its activity



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

Patient #1 (2003)

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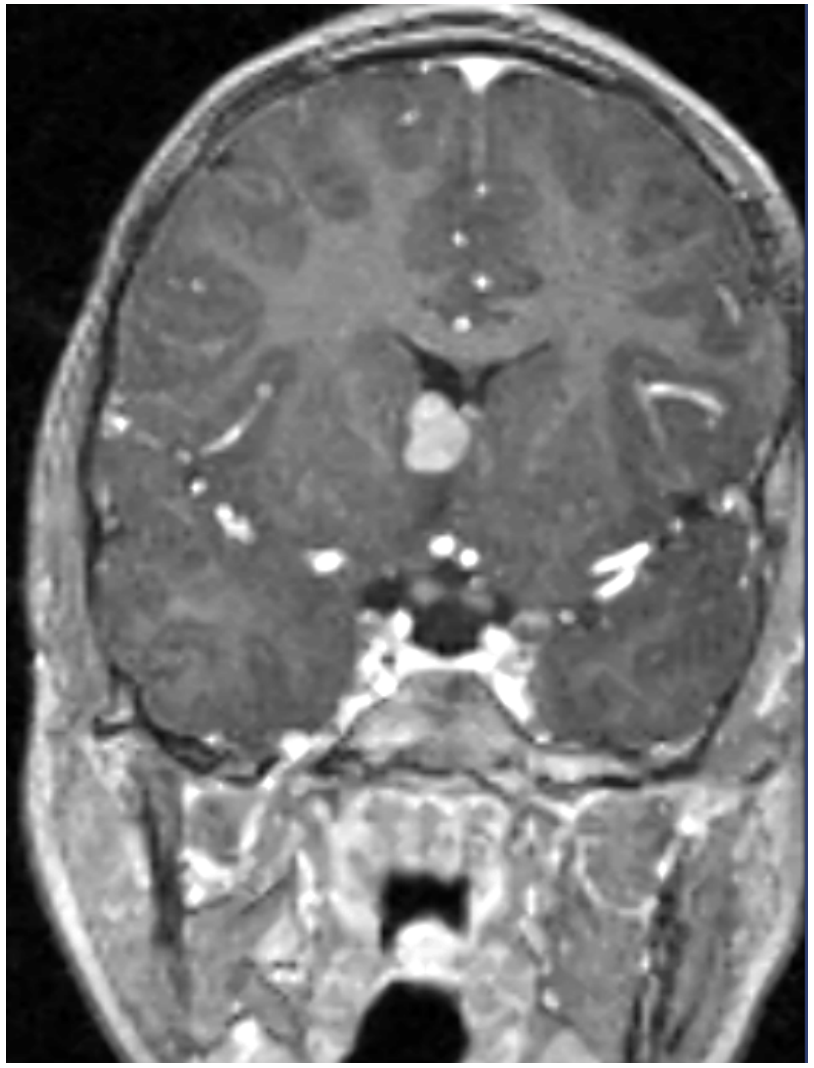
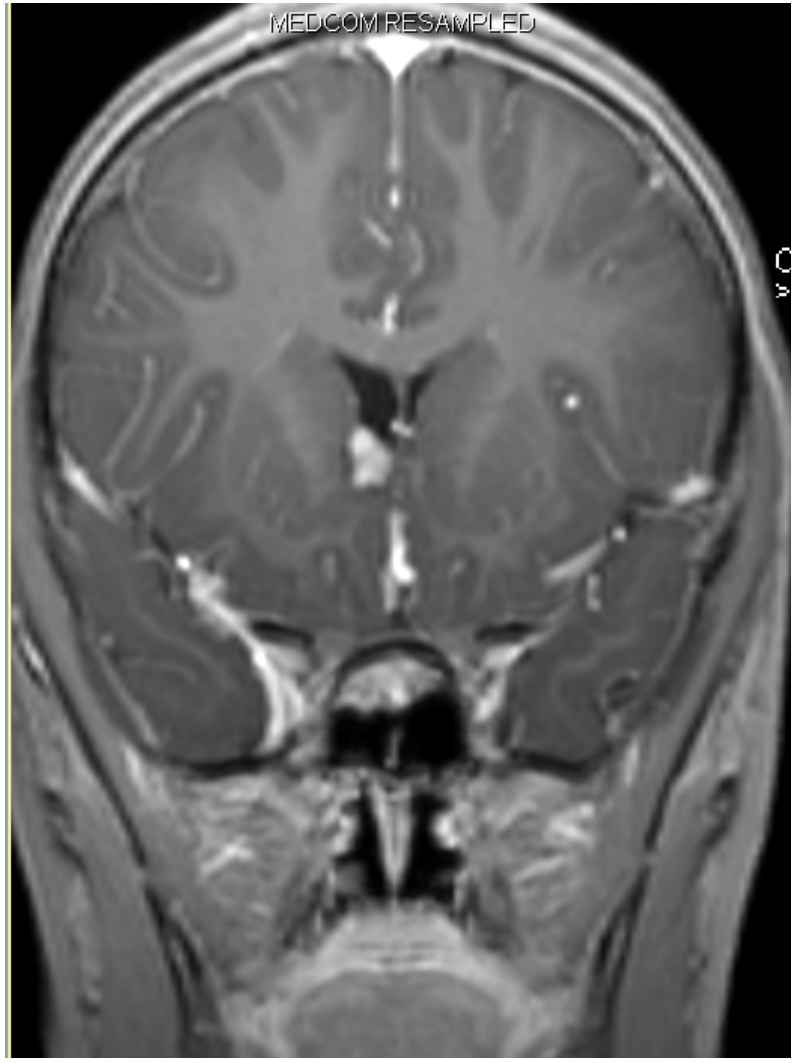
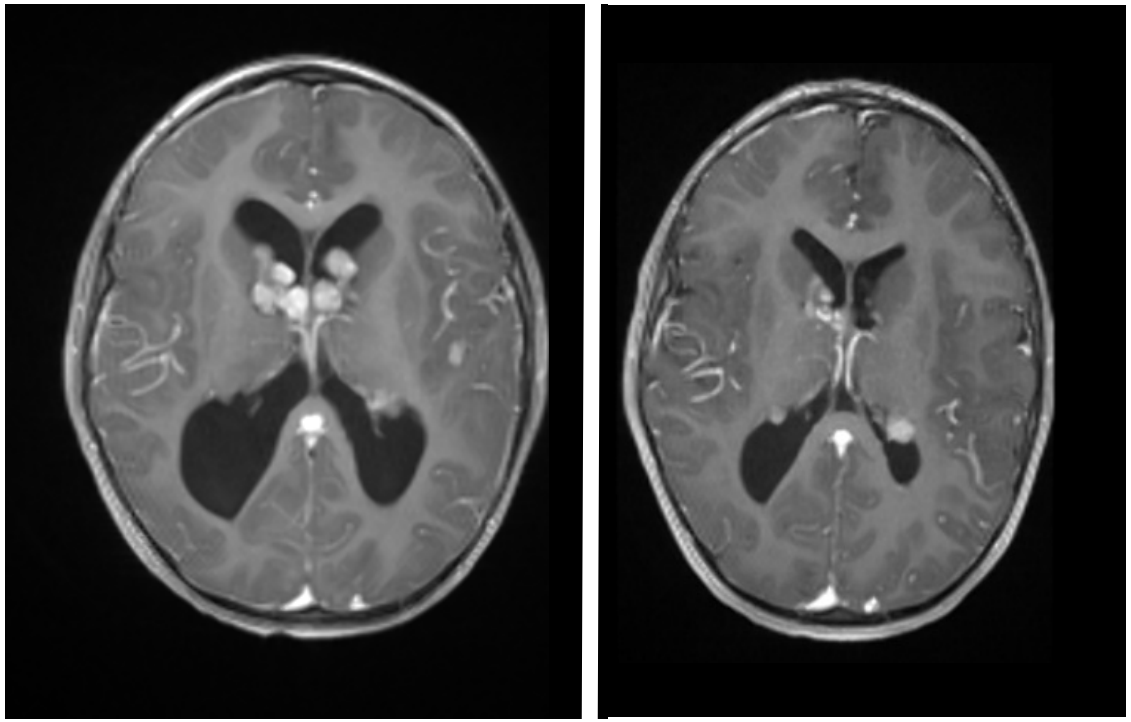
Sirolimus to Treat SEGA (2006)





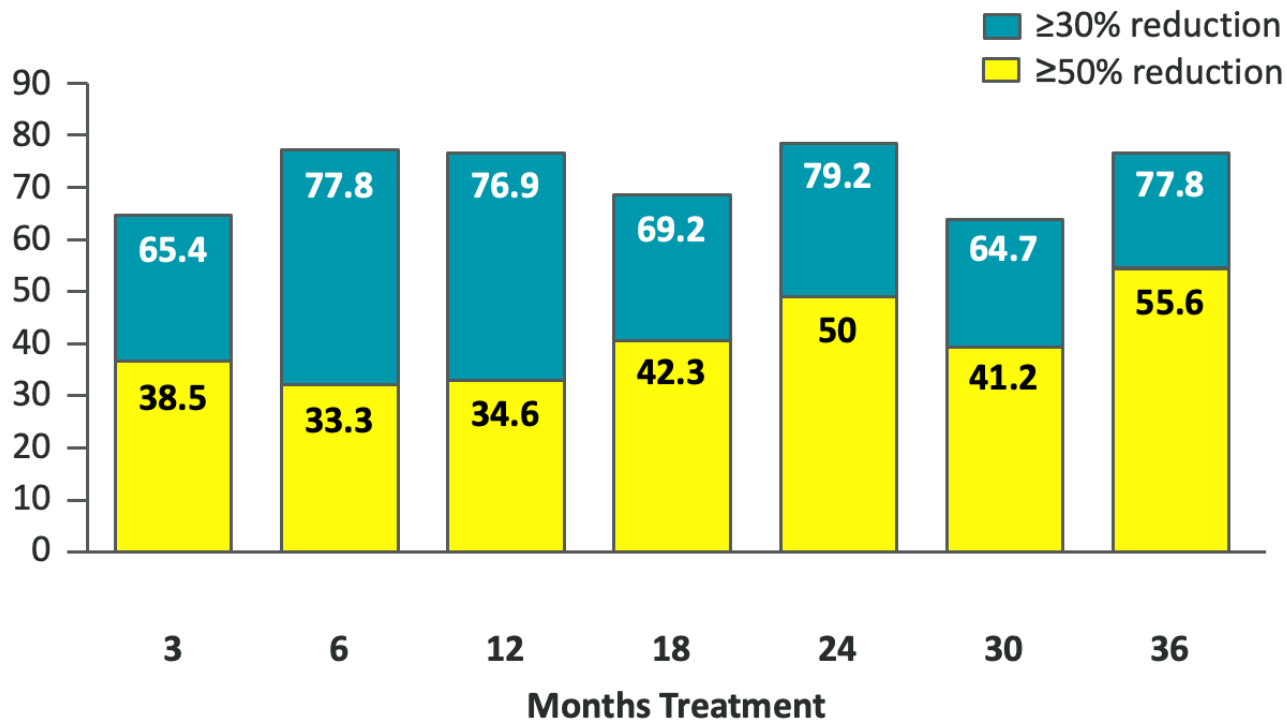
Franz et al. Ann Neurol, 2006

Everolimus to Treat SEGA (2010)



Baseline

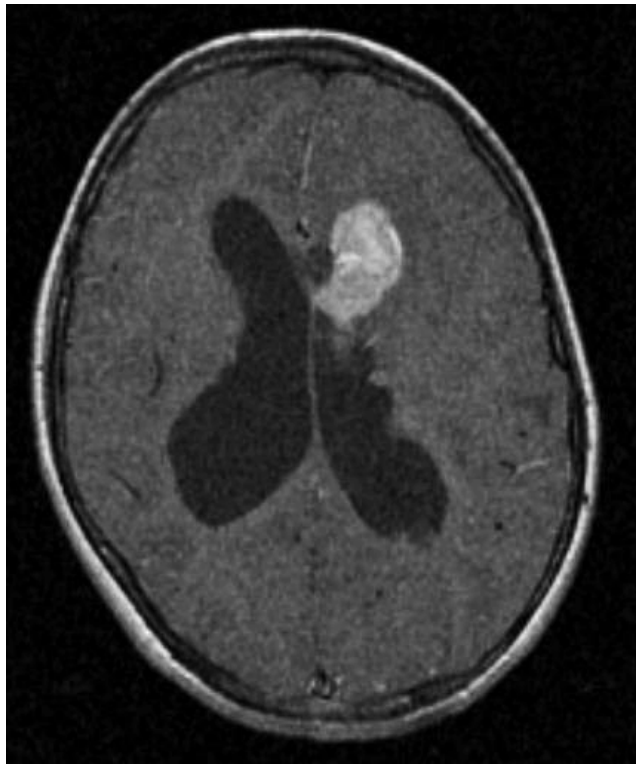
24 months



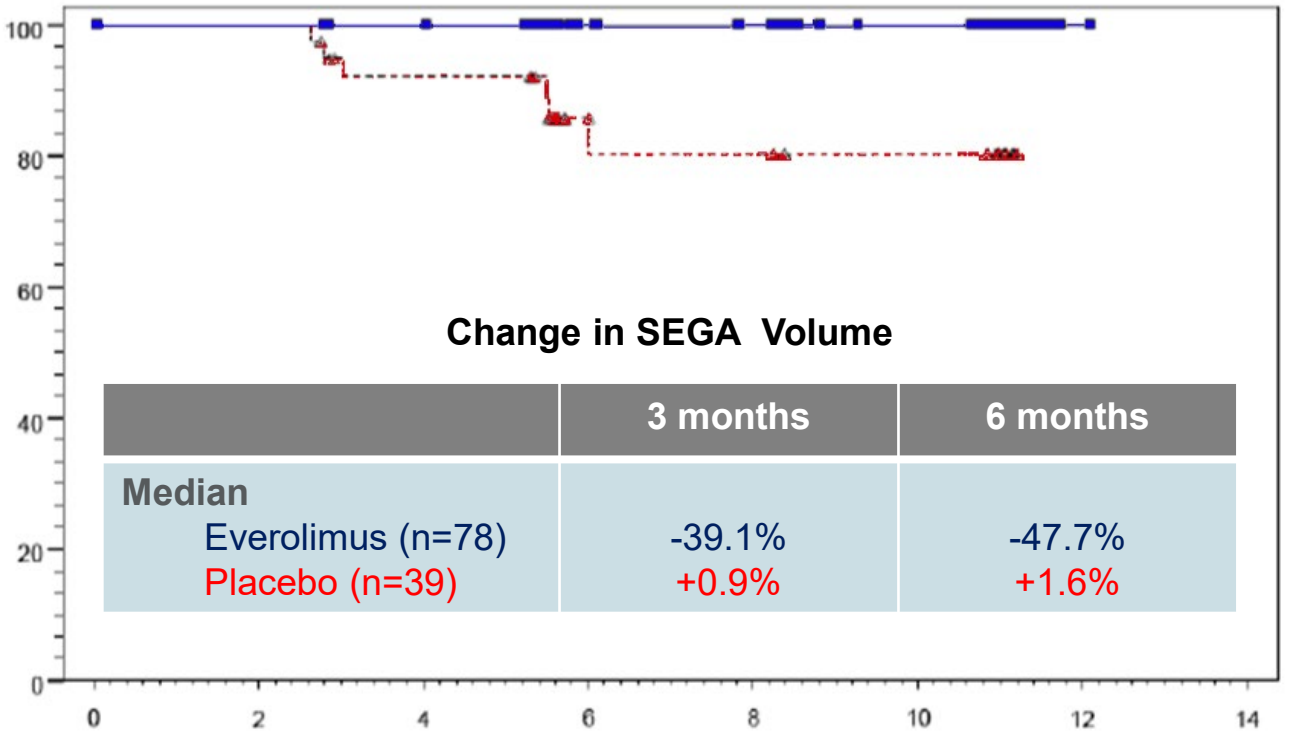
Krueger et al., NEJM 2010
Krueger et al., Neurology 2013

Everolimus to Treat SEGA (2012)

EXIST-1



SEGA Progression



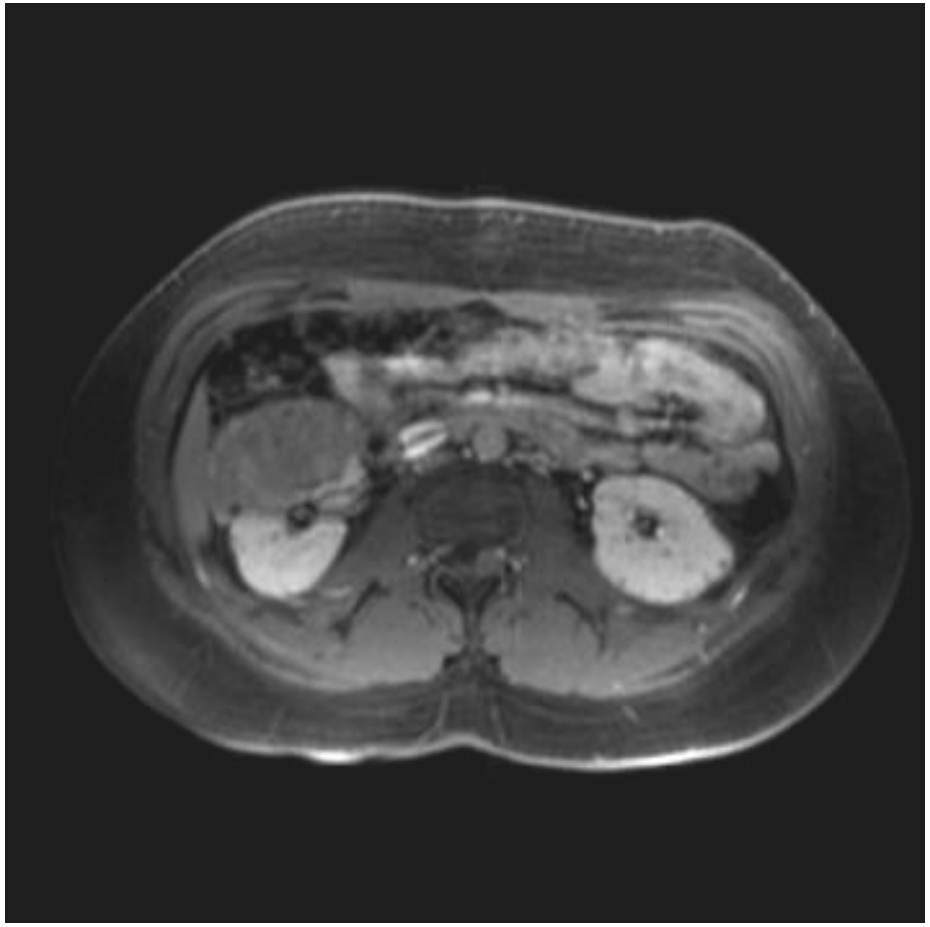
Change in SEGA Volume

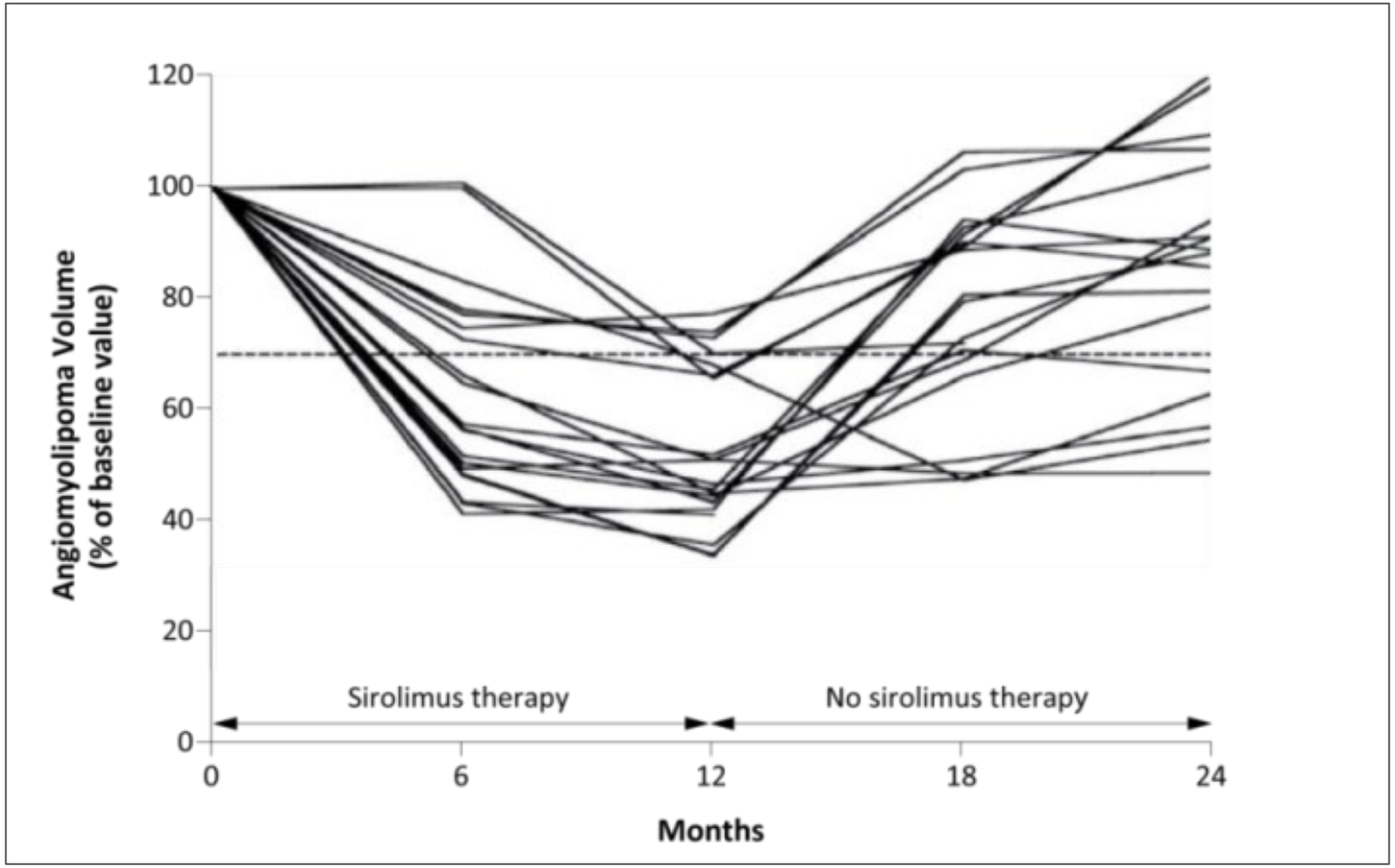
	3 months	6 months
Median		
Everolimus (n=78)	-39.1%	-47.7%
Placebo (n=39)	+0.9%	+1.6%

Franz et al., Lancet 2012

Sirolimus to Treat Angiomyolipoma (2008)

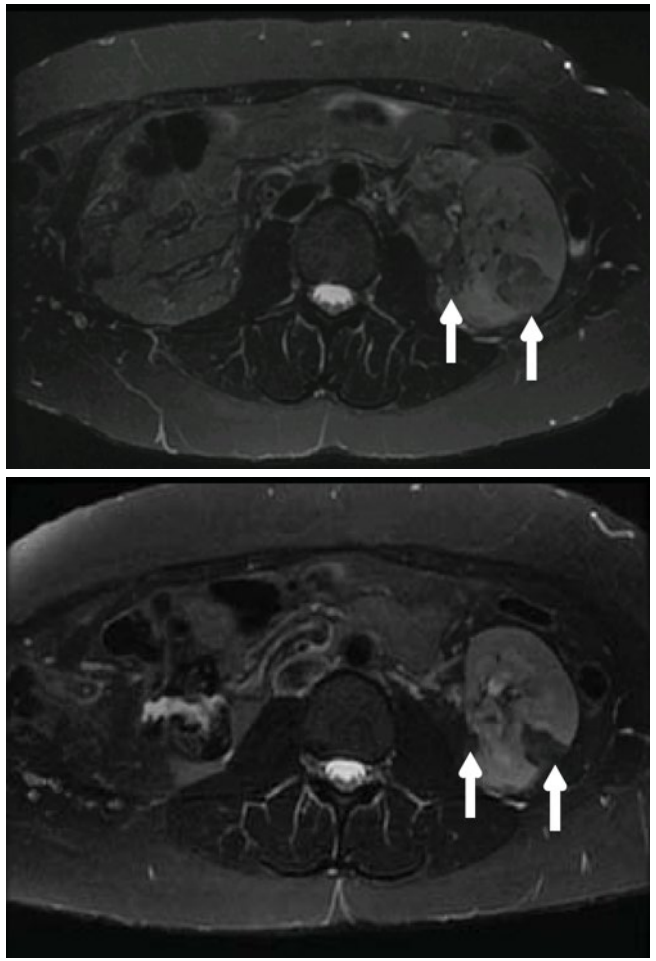
Cincinnati Angiomyolipoma Sirolimus Trial (CAST)



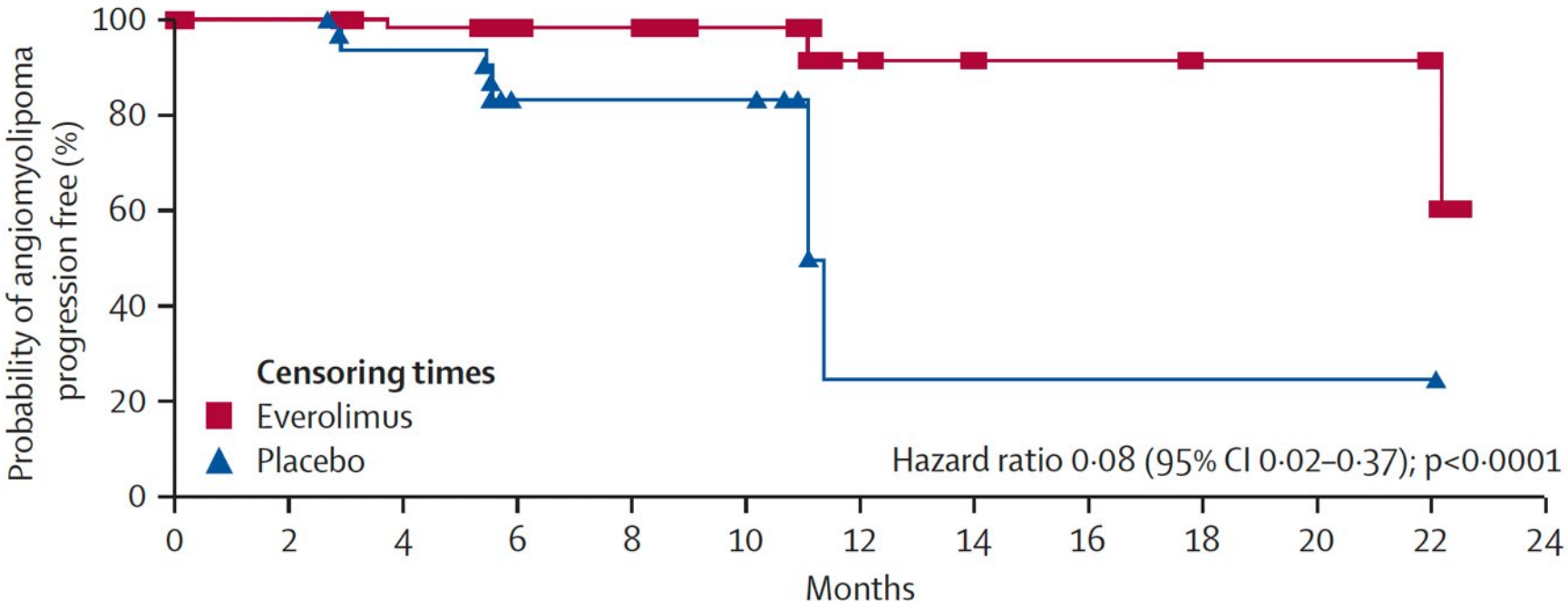


Bissler et al., NEJM 2008

Everolimus to Treat Angiomyolipoma (2013)



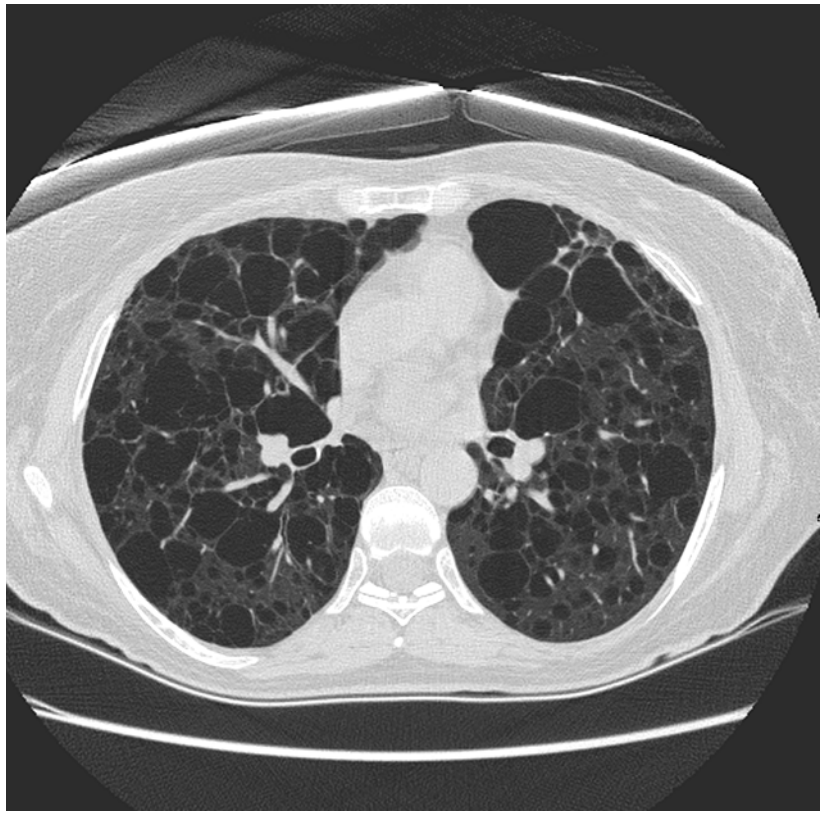
EXIST-2

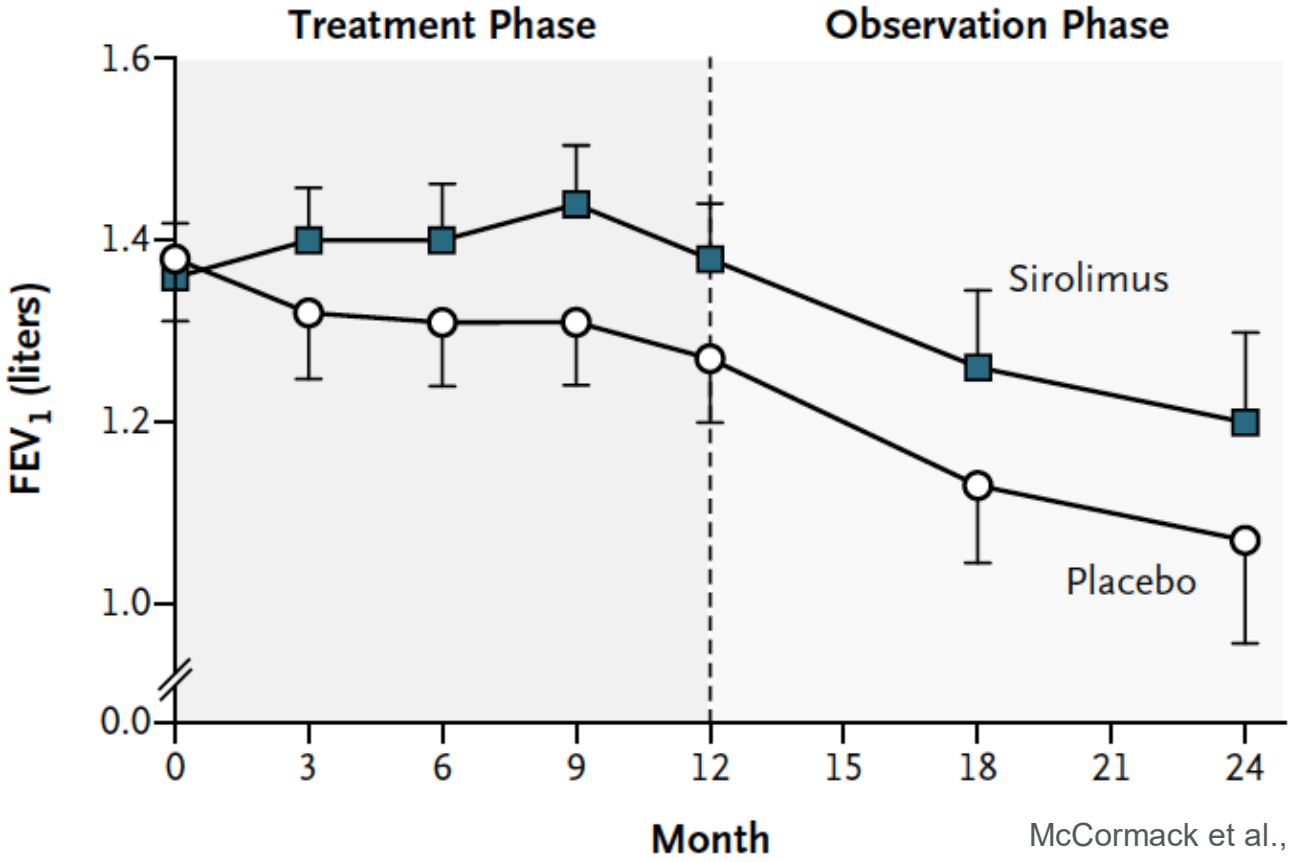


Bissler et al., Lancet 2012

Sirolimus to Treat LAM (2011)

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

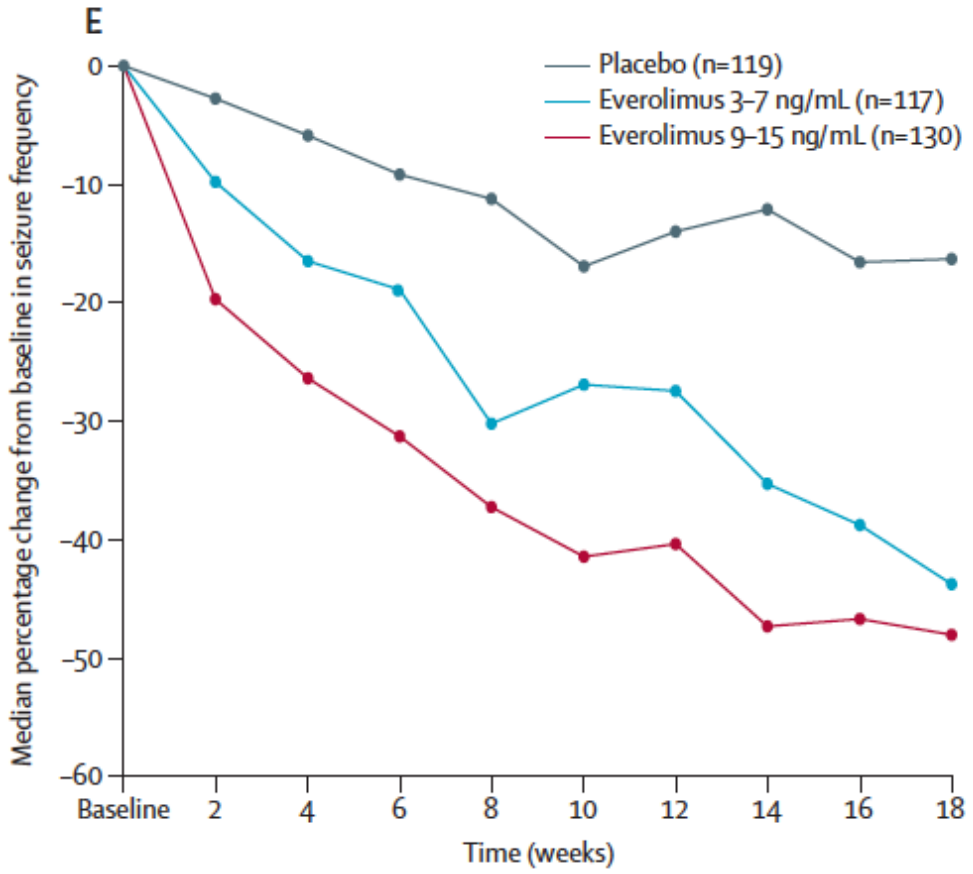


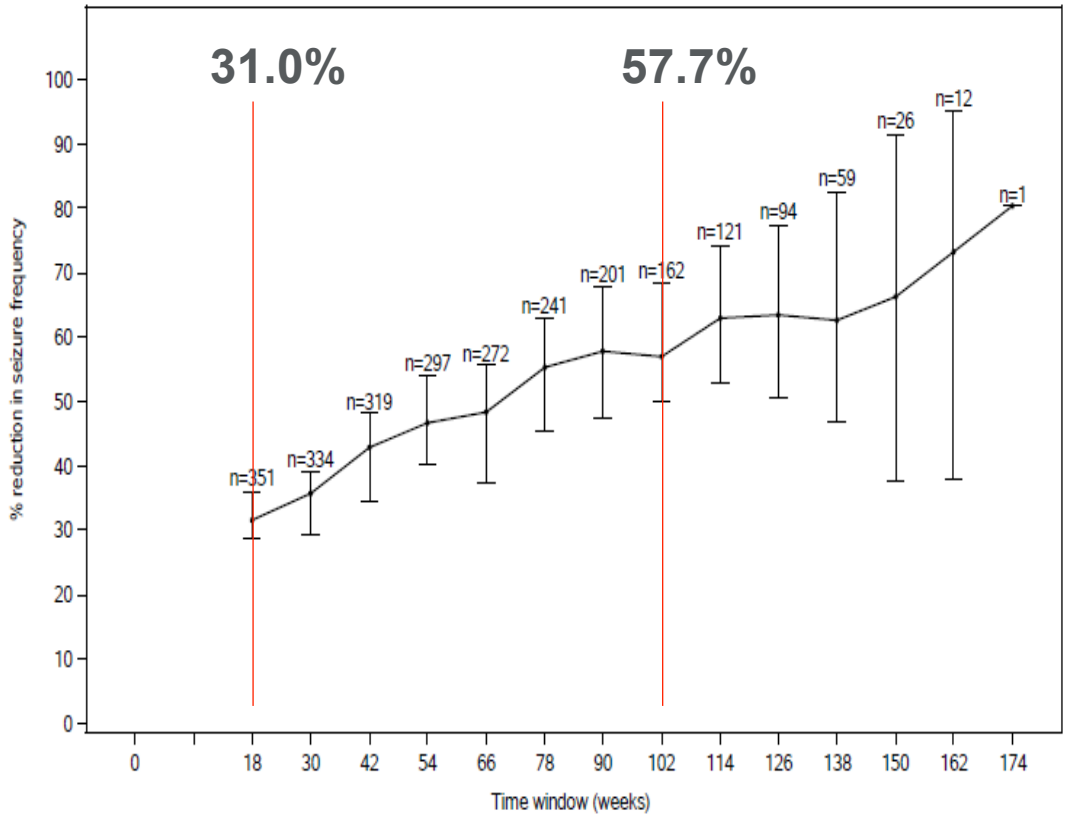


McCormack et al., NEJM 2011

Everolimus to Treat Epilepsy (2016)

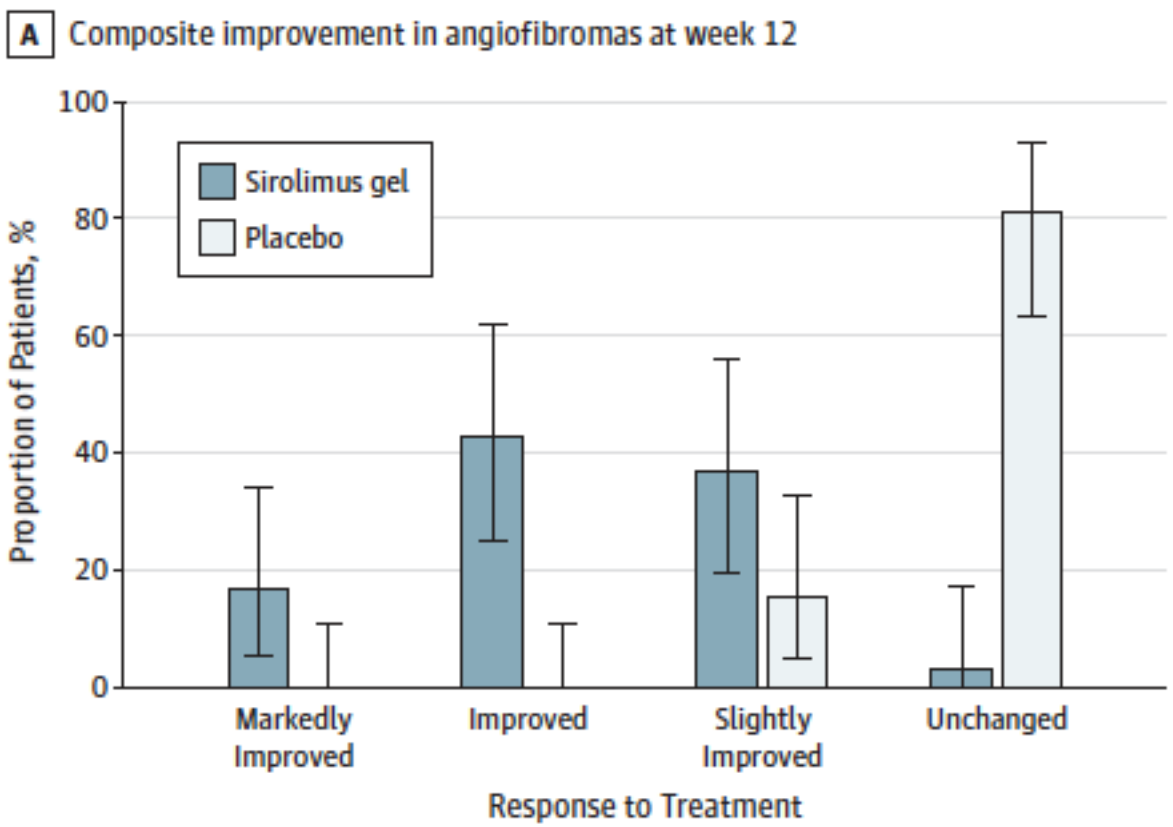
EXIST-3

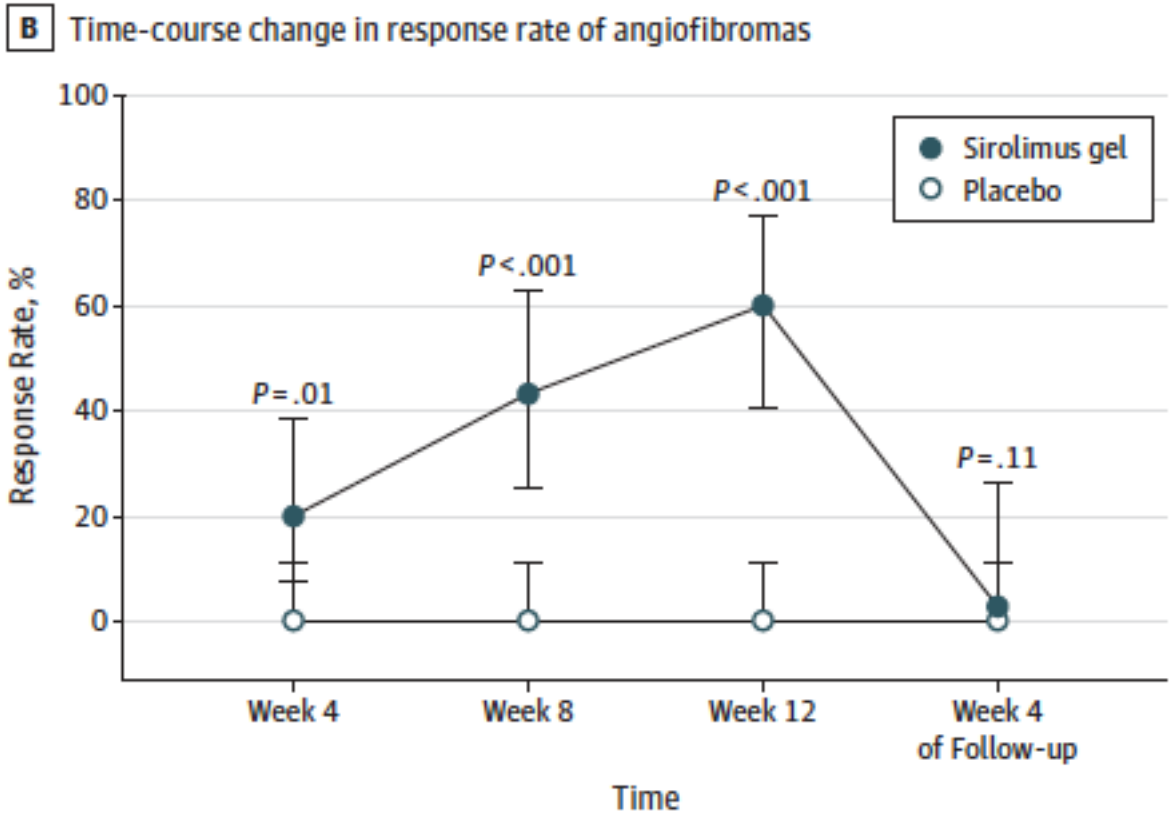




French JA et al. Lancet (2016). 388:2153-63.
Franz et al. Neurology Clin Pract. (2018). 8:412-420.

Sirolimus to Treat Angiofibromas (2018)

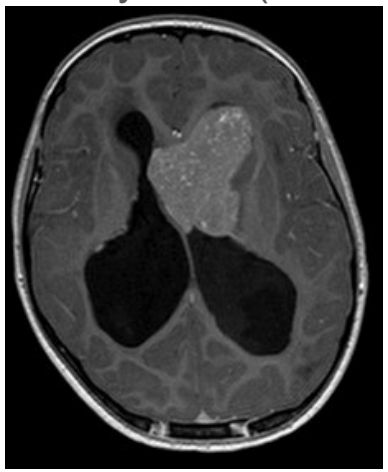




Wataya-Kaneda *et al.* (2018). *JAMA Dermatology 154:781-788*

mTOR Inhibitors FDA-approved for the Treatment of TSC

2010
Subependymal Giant Cell Astrocytoma (SEGA)



Everolimus

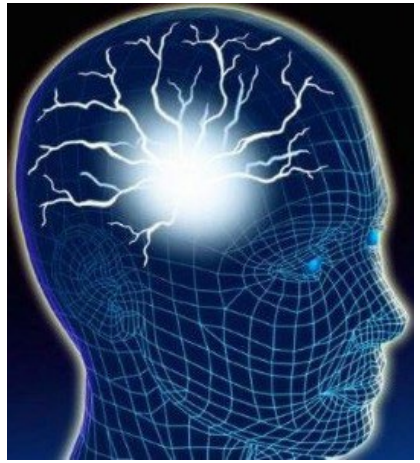
2012
Renal Angiomyolipoma

Everolimus

2015
Lymphangioleiomyomatosis (LAM)

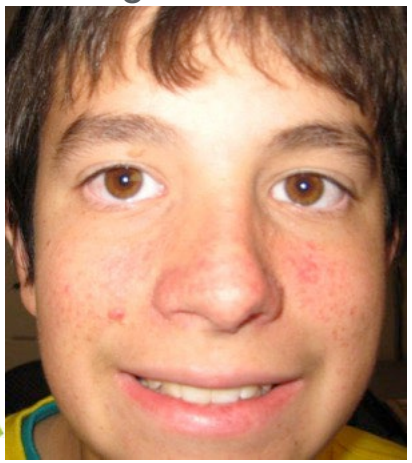
Sirolimus

2018
Refractory Epilepsy



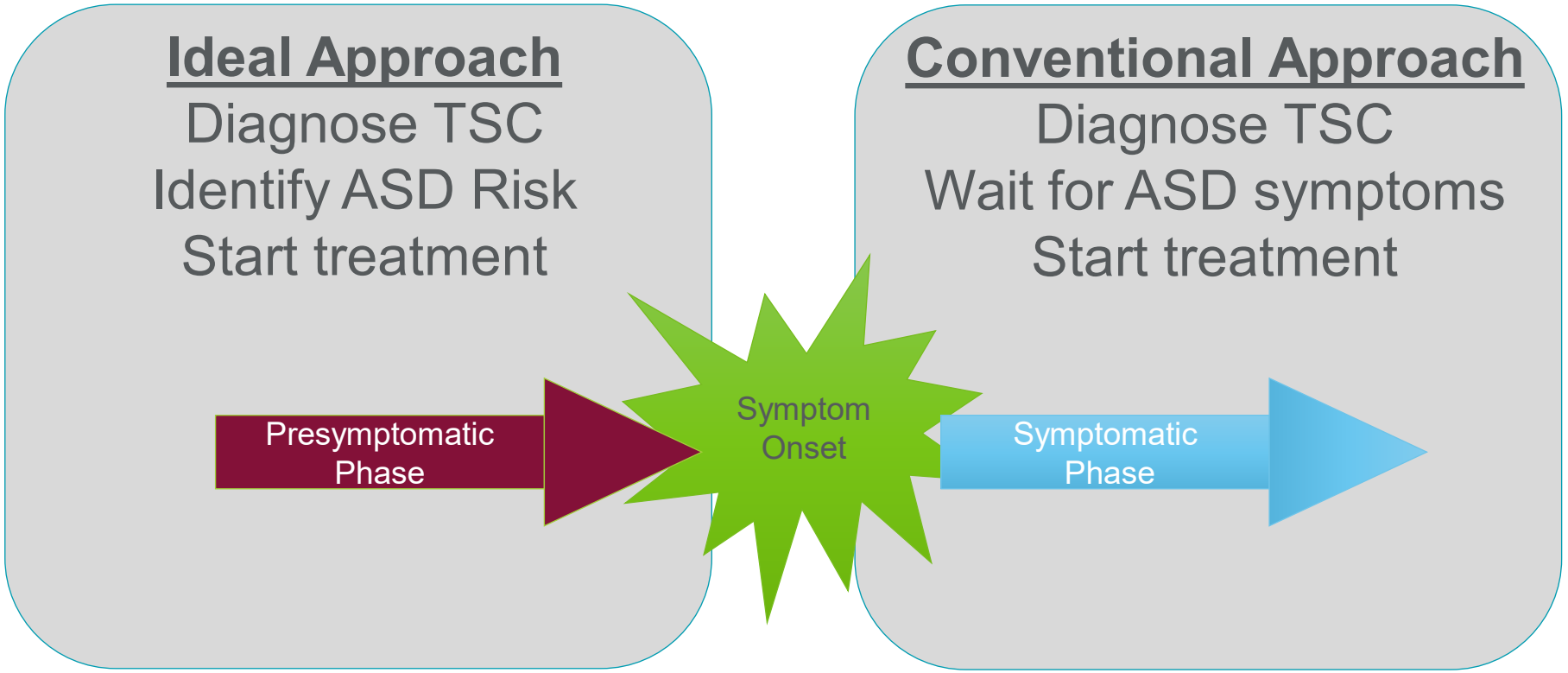
Everolimus

2022
Facial Angiofibroma



Sirolimus

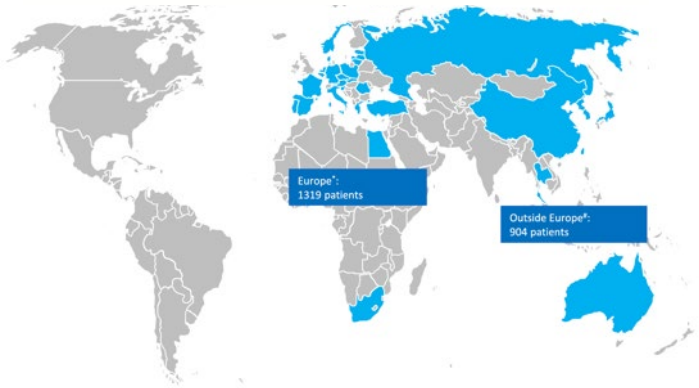
mTOR Inhibitors: Where Next?

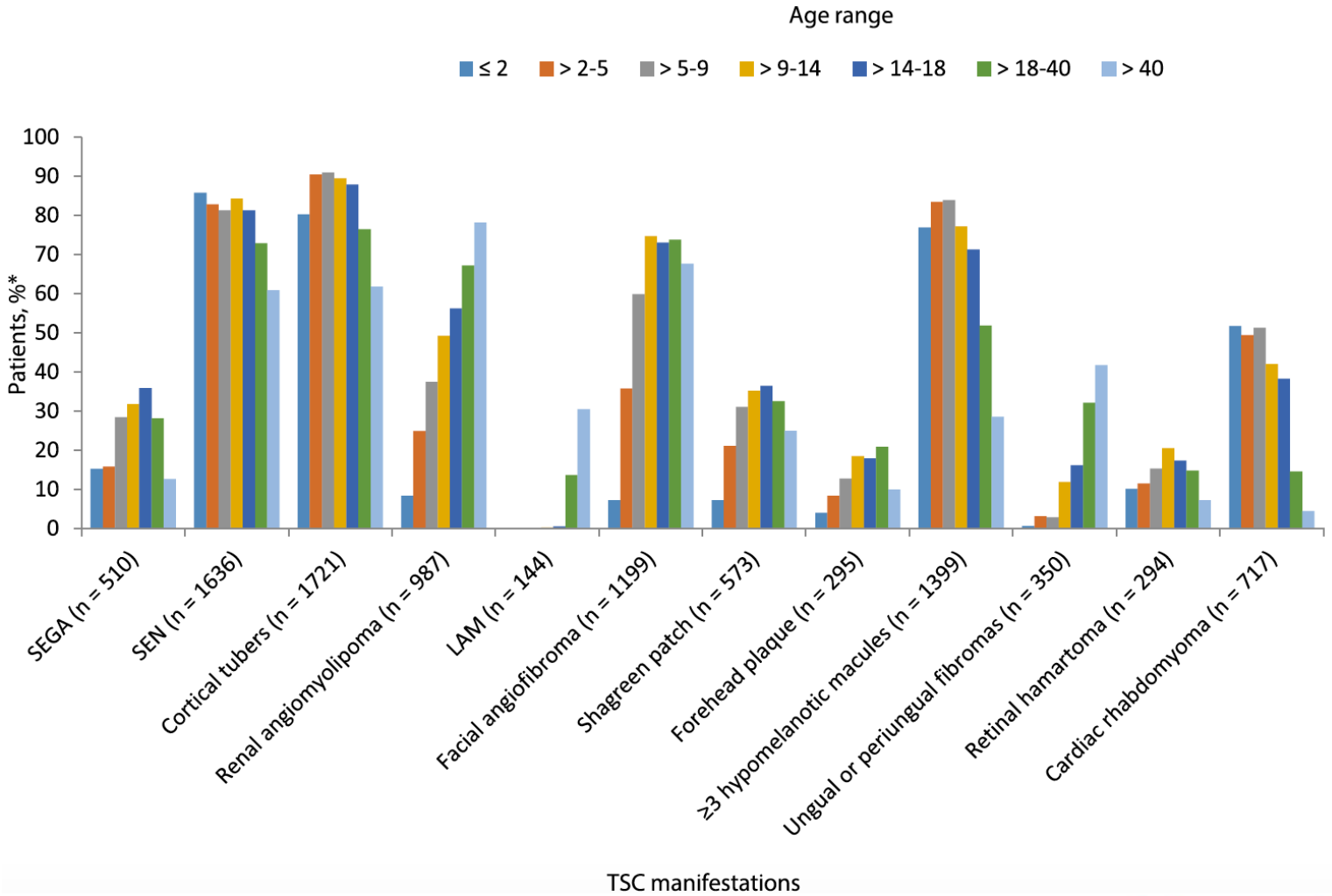


Windows of Opportunity

TOSCA

TuberOus SClerosis Registry to Increase disease Awareness





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)

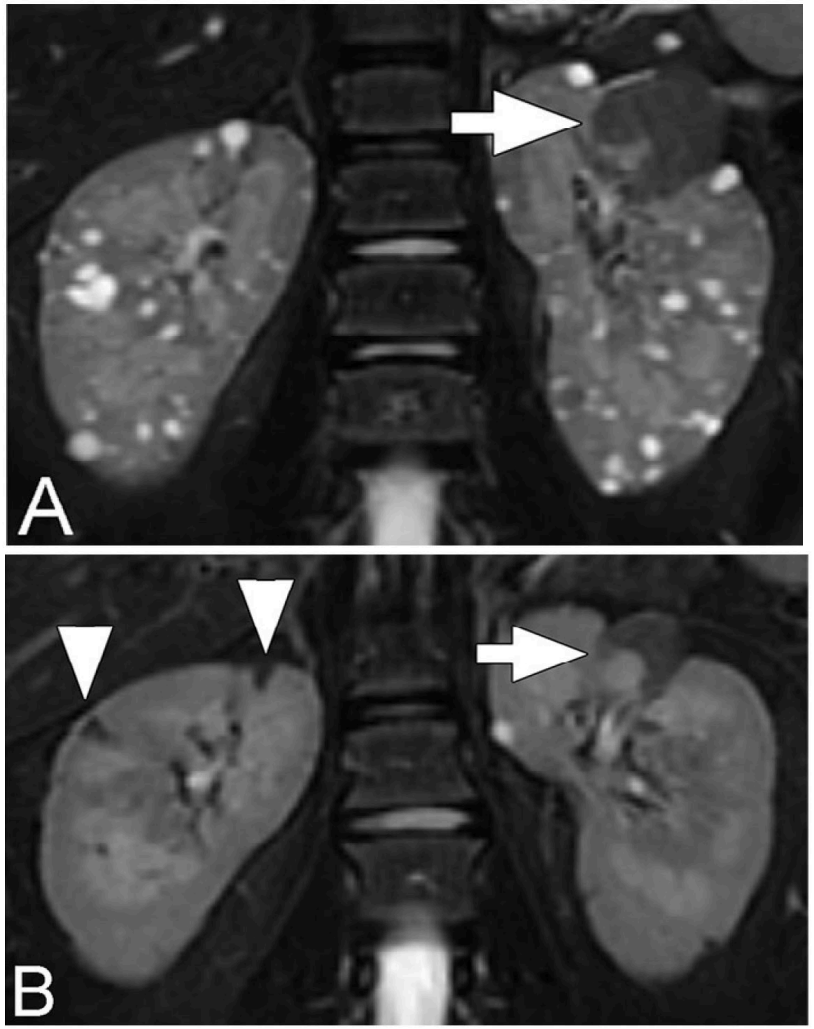
RARE LUNG DISEASES CONSORTIUM

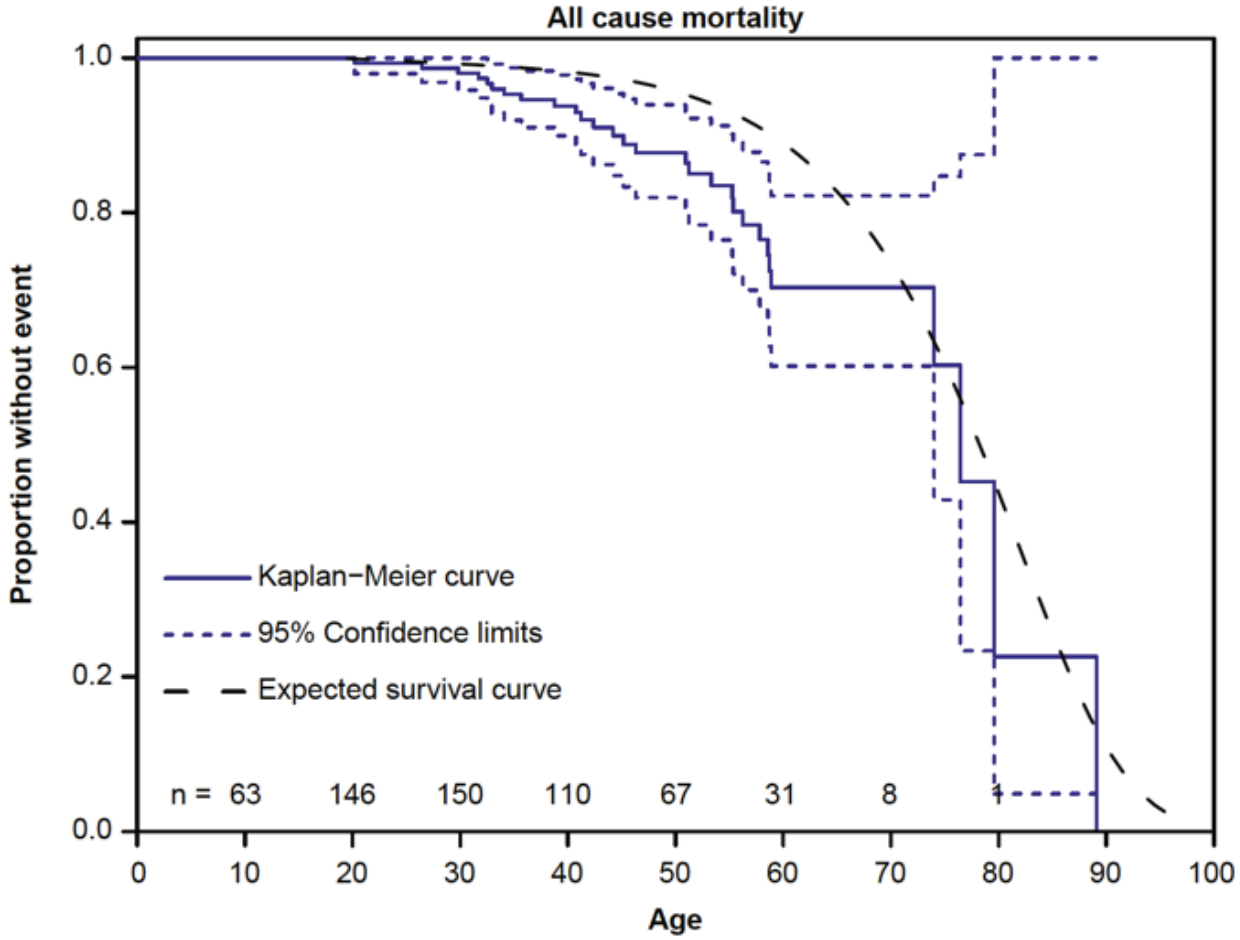
clinicaltrials.gov NCT03150914

- 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

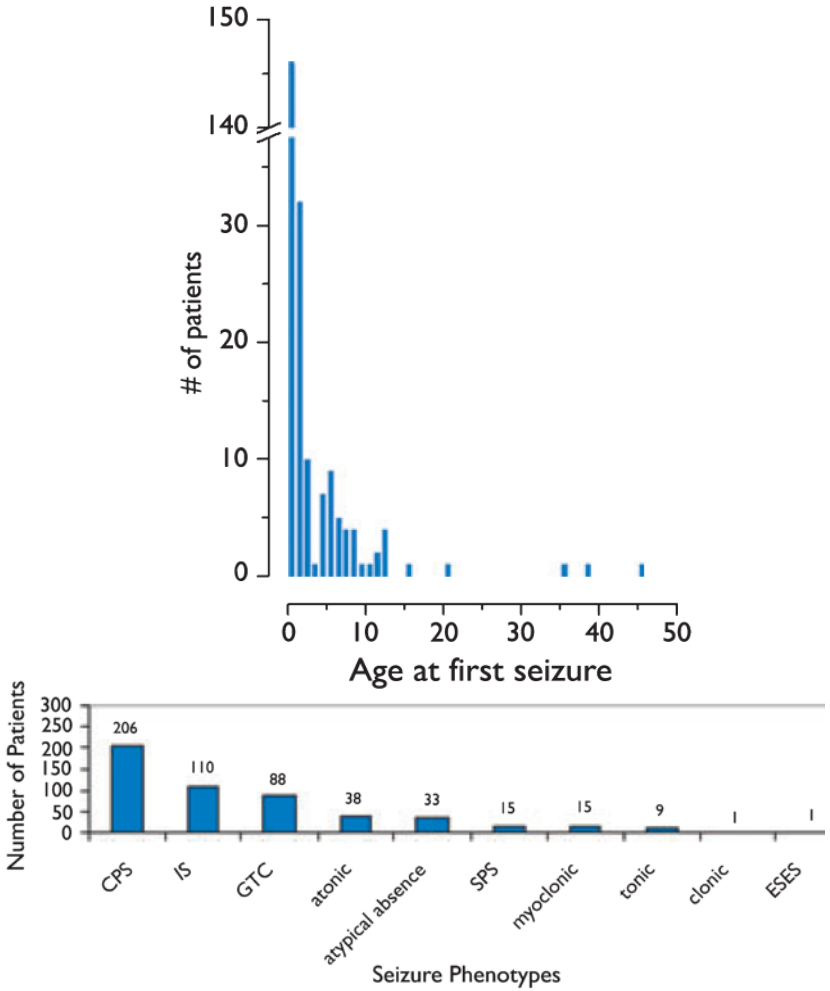
Targeting Angiomyolipoma: TBD



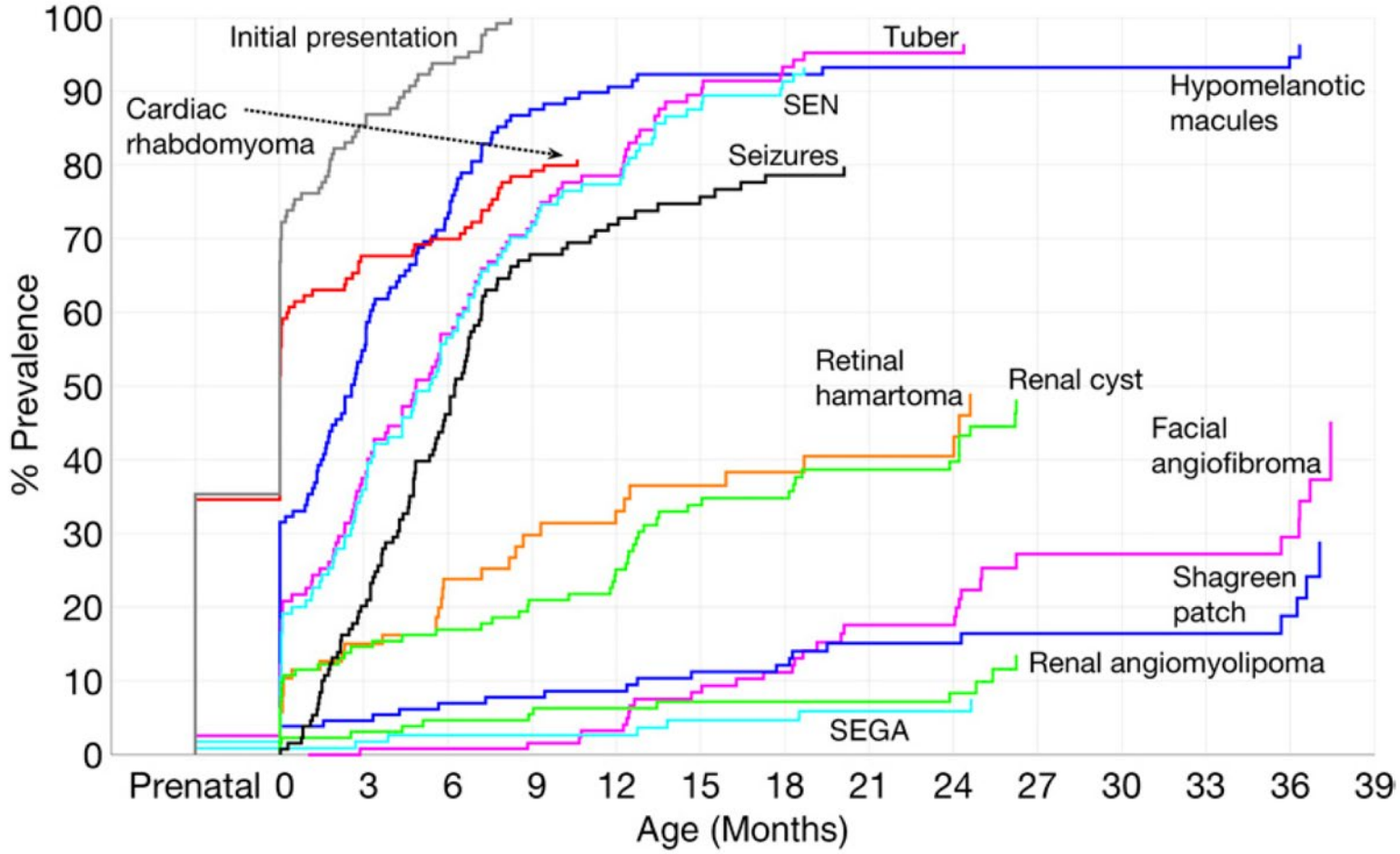


Eijkemans et al. AJKD. 66:638-645 (2015)
Siroky et al. J. Peds. 187:318-322 (2017)

Targeting Epilepsy



Age When TSC Features First Detected/Recognized



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

Targeting Epilepsy: TSC-STEPS

TSCSTEPS

SIROLIMUS TSC EPILEPSY PREVENTION STUDY

Clinicaltrials.gov:

NCT05104983

Funding Sources
US FDA R01-FD007275-01
Clack Foundation
TSC Alliance

Targeting Epilepsy: TSC-STEPS

TSCSTEPS

SIROLIMUS TSC EPILEPSY PREVENTION STUDY

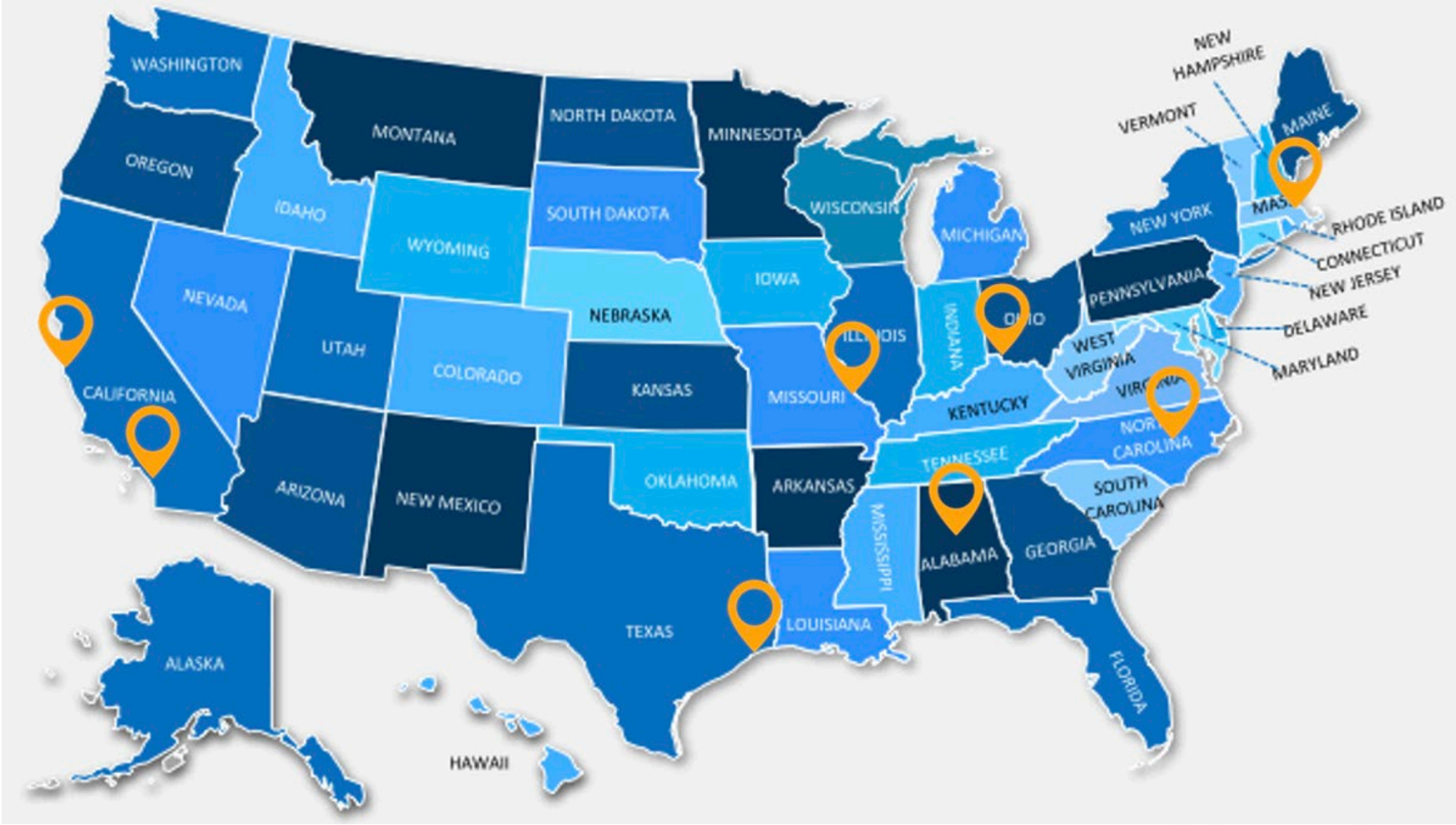
Randomized, double-blind, placebo-controlled clinical trial to assess the efficacy and safety of sirolimus in infants 0-12 months of age

Targeting Epilepsy: TSC-STEPS

TSCSTEPS
SIROLIMUS TSC EPILEPSY PREVENTION STUDY

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

TSCSTEPS
SIROLIMUS TSC EPILEPSY PREVENTION STUDY

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

Thank You


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.
Homenagem dos investigadores brasileiros.
Novembro de 2000.
WYETH BRASIL