and

November 2, 2019

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Disclosures

Research Funding

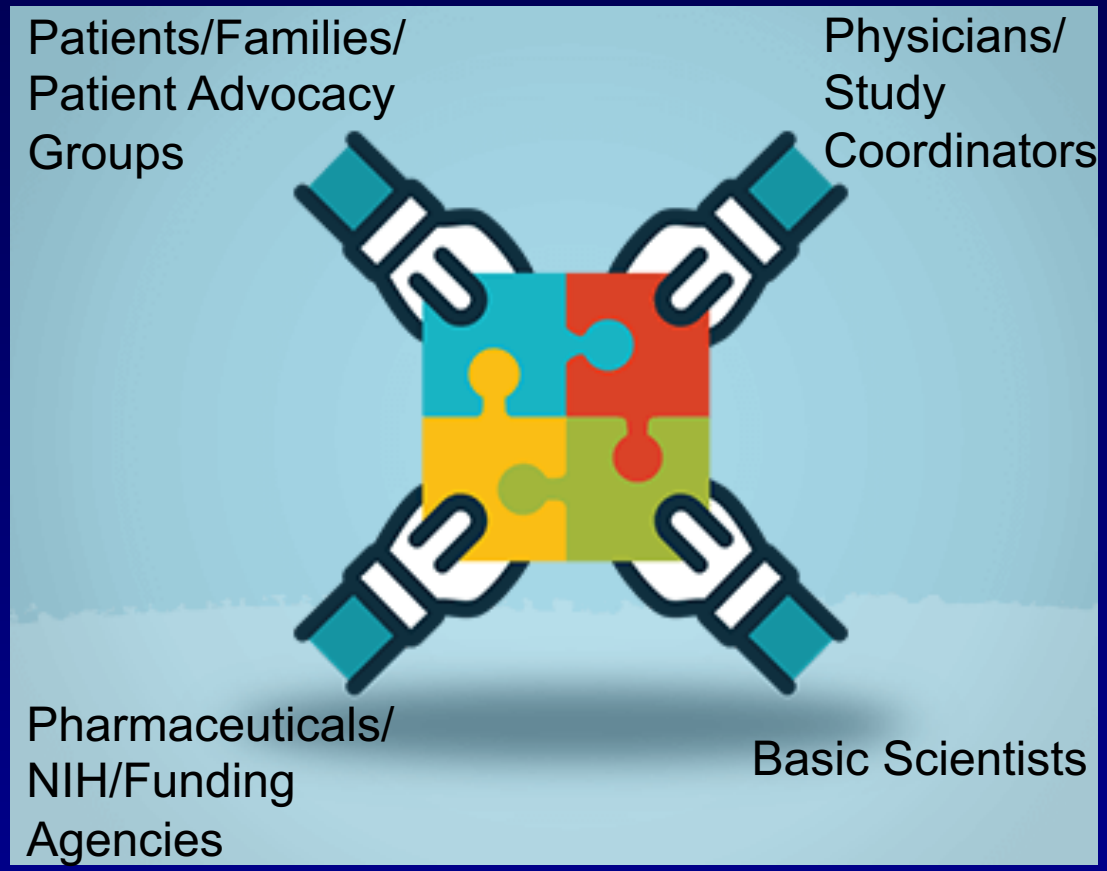
- National Institutes of Health
- Tuberous Sclerosis Alliance
- Novartis Pharmaceutical Inc.
- GW Pharmaceutical
- Today's and Tomorrow's Children Fund

Speaker's Bureau/Advisory Board

- Novartis Pharmaceutical Inc.
- GW Pharmaceutical

Helping one patient at a time, with compassion, teamwork, and innovation


KSB


Patients/Families/
Patient Advocacy
Groups
Physicians/
Study
Coordinators
Pharmaceuticals/
NIH/Funding
Agencies
Basic Scientists

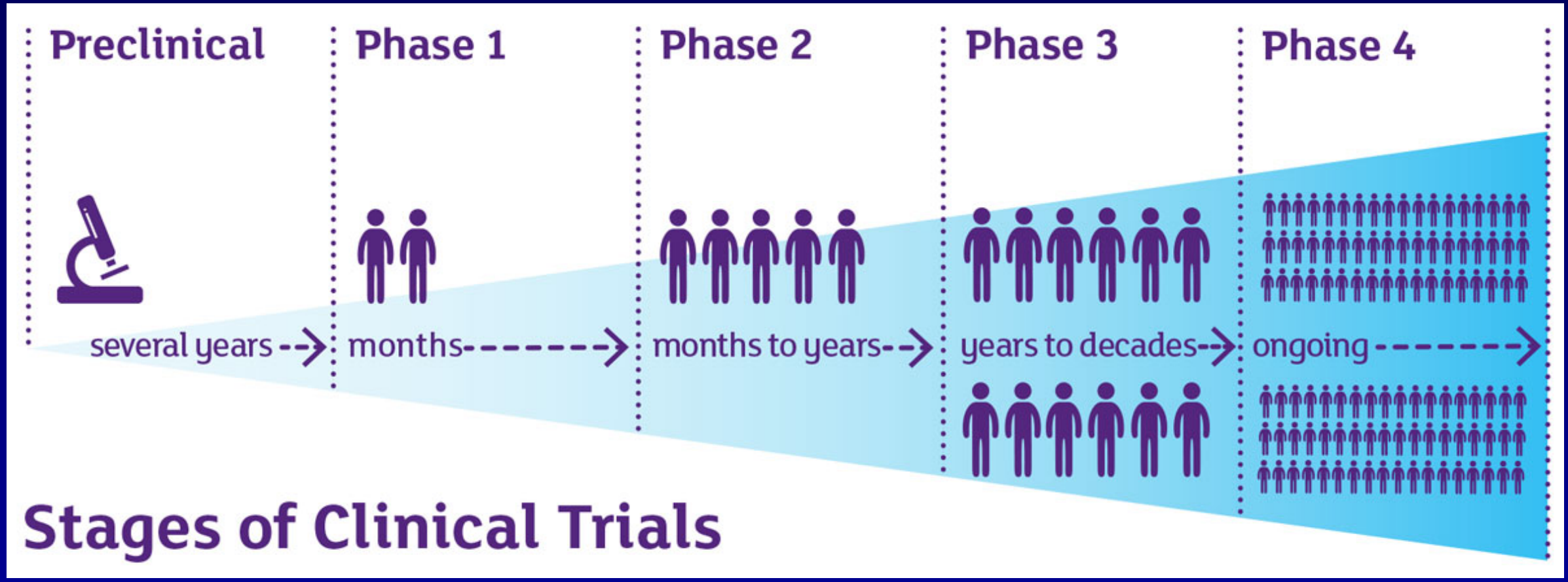
Lab Studies
Animal Studies

Human Safety

Efficacy at Treating Disease

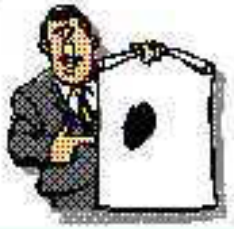
Large Scale Safety & Efficacy

Long Term Safety



Clinical Trials in a Nut Shell

Approved Protocol



Investigator selection

Approval Process

Patient recruitment and participation

Data Entered and reviewed

Statistical Analysis

Presentation and publication of report

Data filed and registration obtained

1993 – TSC2 gene identified as tuberin

1997 – TSC1 gene identified as hamartin

2002

Proc Natl Acad Sci U S A. 2002 October 15; 99(21): 13571–13576.
Published online 2002 September 23. doi: 10.1073/pnas.202476899.
PMCID: PMC129715

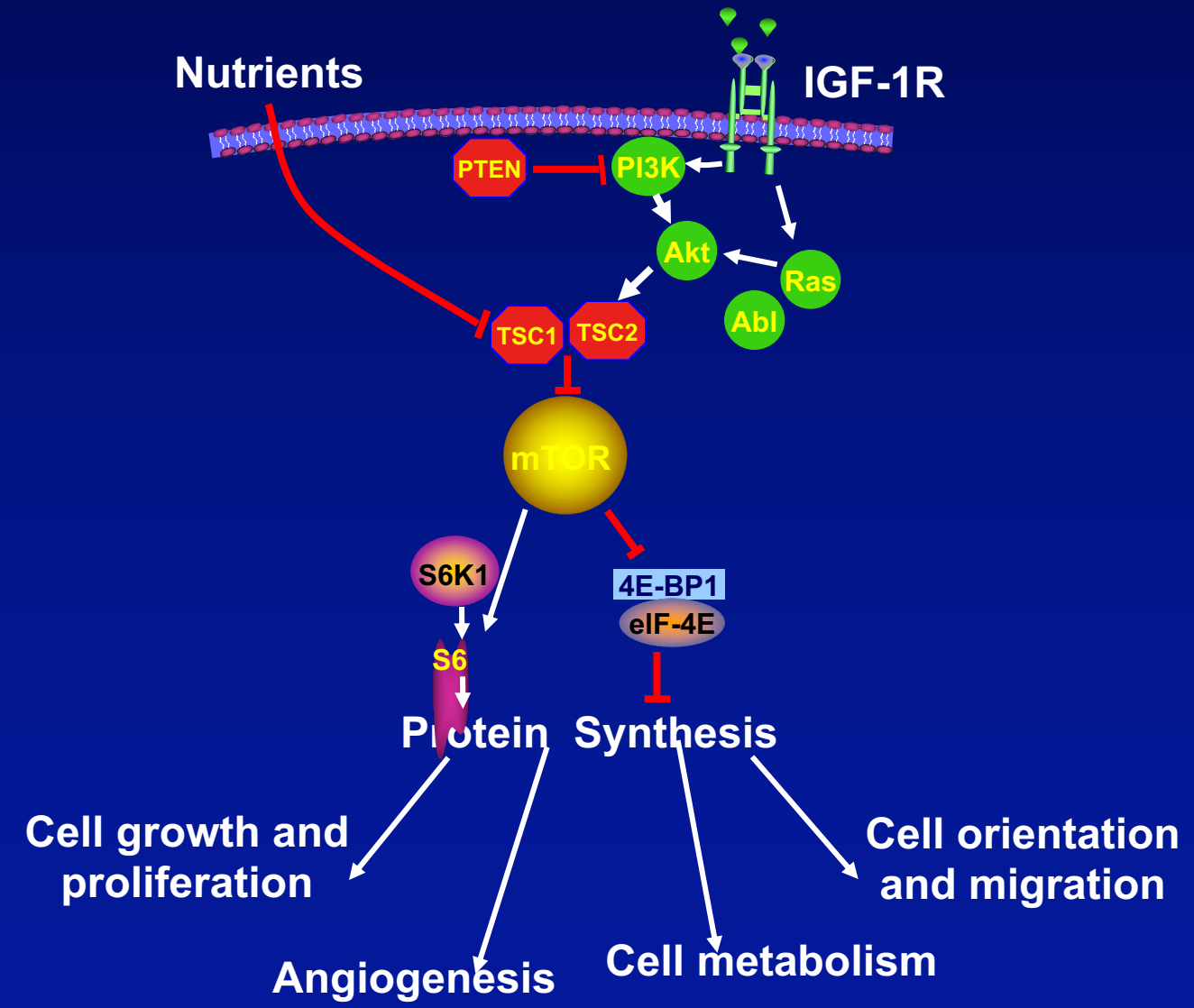
Cell Biology

Tuberous sclerosis complex-1 and -2 gene products function together to inhibit mammalian target of rapamycin (mTOR)-mediated downstream signaling

Andrew R. Tee,[*] Diane C. Fingar,[*] Brendan D. Manning,[*†] David J. Kwiatkowski,[‡] Lewis C. Cantley,[*†] and John Blenis[*§]

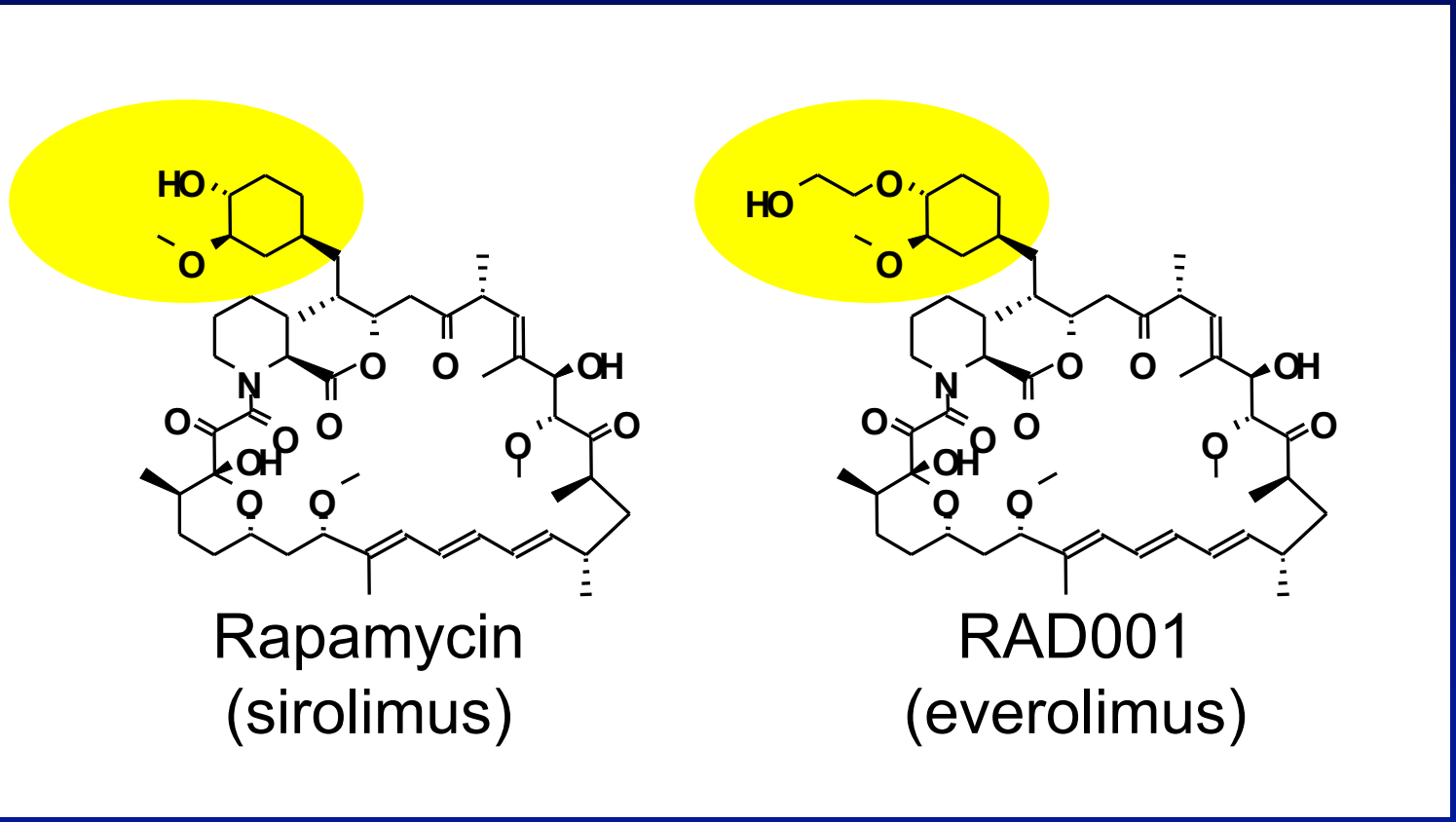
[*]Department of Cell Biology, Harvard Medical School, [†]Division of Signal Transduction, Beth Israel Deaconess Medical Center, and [‡]Genetics Laboratory, Hematology Division, Brigham and Woman's Hospital, Boston, MA

Molecular Biology of TSC



Franz. ASCO. 2010 (abstr 2004).

Rapamycin and Everolimus



Afinitor [package insert]. East Hanover, NJ: Novartis Pharmaceuticals Corporation; 2011; Rapamune [package insert]. New York, NY: Pfizer Inc.; 2010.

2006

Rapamycin Causes Regression of Astrocytomas in Tuberous Sclerosis Complex

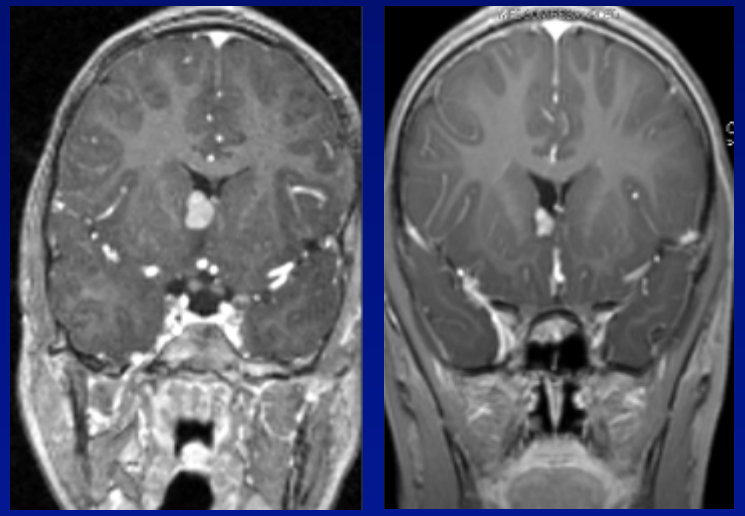
David Neal Franz, MD,[1,2] Jennifer Leonard, MSN, FNP,[1,2] Cynthia Tudor, MSN, PNP,[1,2] Gail Chuck, BS,[1,2] Marguerite Care, MD,[1,3] Gopalan Sethuraman, PhD,[4] Argirios Dinopoulos, MD,[1,2] George Thomas, PhD,[5] and Kerry R. Crone, MD[1,6]

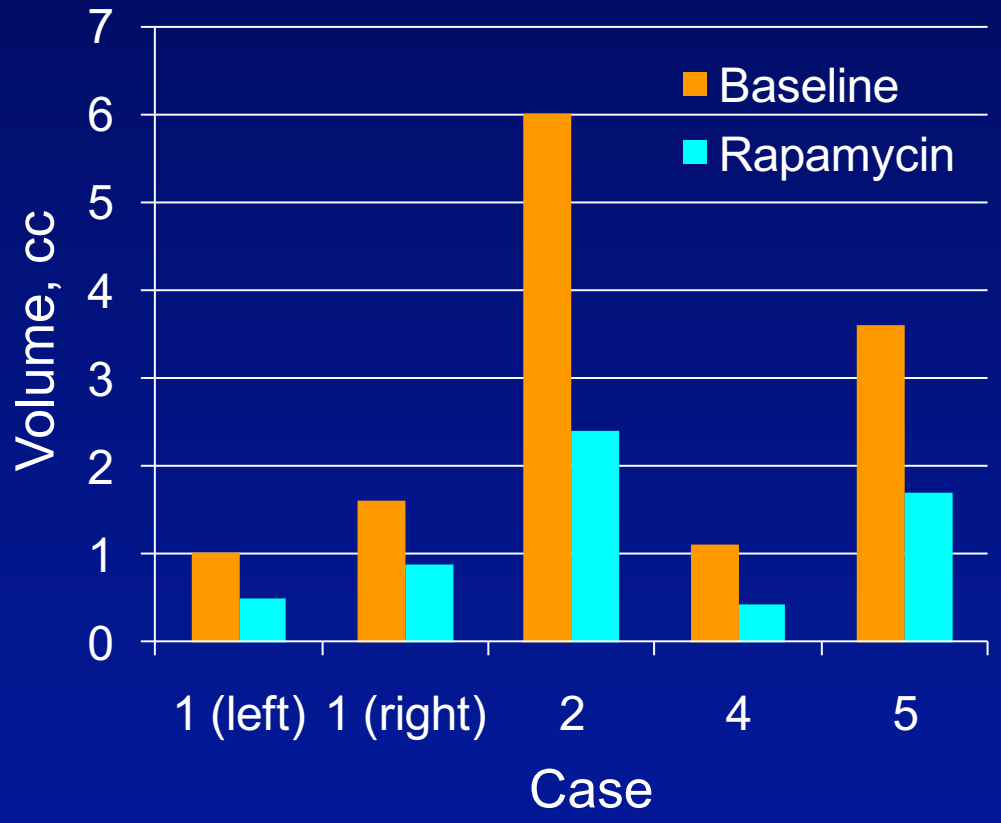
Objective: **Tuberous sclerosis complex (TSC) is a genetic disorder characterized by the formation of hamartomas in multiple organs. Five to 15% of affected individuals display subependymal giant cell astrocytomas, which can lead to substantial neurological and postoperative morbidity due to the production of hydrocephalus, mass effect, and their typical location adjacent to the foramen of Monro. We sought to see whether therapy with oral rapamycin could affect growth or induce regression in astrocytomas associated with TSC.** ***Methods:*** **Five subjects with clinically definite TSC and either subependymal giant cell astrocytomas (n = 4) or a pilocytic astrocytoma (n = 1) were treated with oral rapamycin at standard immunosuppressive doses (serum levels 5–15ng/ml) from 2.5 to 20 months. All lesions demonstrated growth on serial neuroimaging studies. Magnetic resonance imaging scans were performed before and at regular intervals following initiation of therapy.** ***Results:*** **All lesions exhibited regression and, in one case, necrosis. Interruption of therapy resulted in regrowth of subependymal giant cell astrocytomas in one patient. Resumption of therapy resulted in further regression. Treatment was well tolerated.** ***Interpretation:*** **Oral rapamycin therapy can induce regression of astrocytomas associated with TSC and may offer an alternative to operative therapy of these lesions.**

Ann Neurol 2006;59:490–498

Rapamycin for the Treatment of SEGA

Case 4





Reproduced with permission from Franz. *Ann Neurol*. 2006;59:490.

SEGA trial – EXIST-1 Trial

- Why – to reduce SEGA volume
- What - everolimus
- For Whom – TSC and SEGA
- Findings – Safe and efficacious for shrinking SEGA
- Status – FDA approved 2010

Efficacy and safety of everolimus for subependymal giant cell astrocytomas associated with tuberous sclerosis complex (EXIST-1): a multicentre, randomised, placebo-controlled phase 3 trial

David Neal Franz, Elena Belousova, Steven Sparagana, E Martina Bebin, Michael Frost, Rachel Kuperman, Olaf Witt, Michael H Kohrman, J Robert Flamini, Joyce Y Wu, Paolo Curatolo, Petrus J de Vries, Vicky H Whittemore, Elizabeth A Thiele, James P Ford, Gaurav Shah, Helene Cauwel, David Lebwohl, Tarek Sahmoud, Sergiusz Jozwiak

Nov 2012

Findings 117 patients were randomly assigned to everolimus (n=78) or placebo (n=39). 27 (35%) patients in the everolimus group had at least 50% reduction in the volume of subependymal giant cell astrocytomas versus none in the placebo group (difference 35%, 95% CI 15–52; one-sided exact Cochran-Mantel-Haenszel test, p<0·0001). Adverse events were mostly grade 1 or 2; no patients discontinued treatment because of adverse events. The most common adverse events were mouth ulceration (25 [32%] in the everolimus group *vs* two [5%] in the placebo group), stomatitis (24 [31%] *vs* eight [21%]), convulsion (18 [23%] *vs* ten [26%]), and pyrexia (17 [22%] *vs* six [15%]).

Interpretation These results support the use of everolimus for subependymal giant cell astrocytomas associated with tuberous sclerosis. Additionally, everolimus might represent a disease-modifying treatment for other aspects of tuberous sclerosis.

AML trial – EXIST-2 Trial

- Why – to reduce AML volume
- What - everolimus
- For Whom – TSC and AML
- Findings – Safe and efficacious for shrinking AML
- Status – FDA approved 2012

Everolimus for angiomyolipoma associated with tuberous sclerosis complex or sporadic lymphangioleiomyomatosis (EXIST-2): a multicentre, randomised, double-blind, placebo-controlled trial

John J Bissler, J Christopher Kingswood, Elżbieta Radzikowska, Bernard A Zonnenberg, Michael Frost, Elena Belousova, Matthias Sauter, Norio Nonomura, Susanne Brakemeier, Petrus J de Vries, Vicky H Whittemore, David Chen, Tarek Sahmoud, Gaurav Shah, Jeremie Lincy, David Lebwohl, Klemens Budde

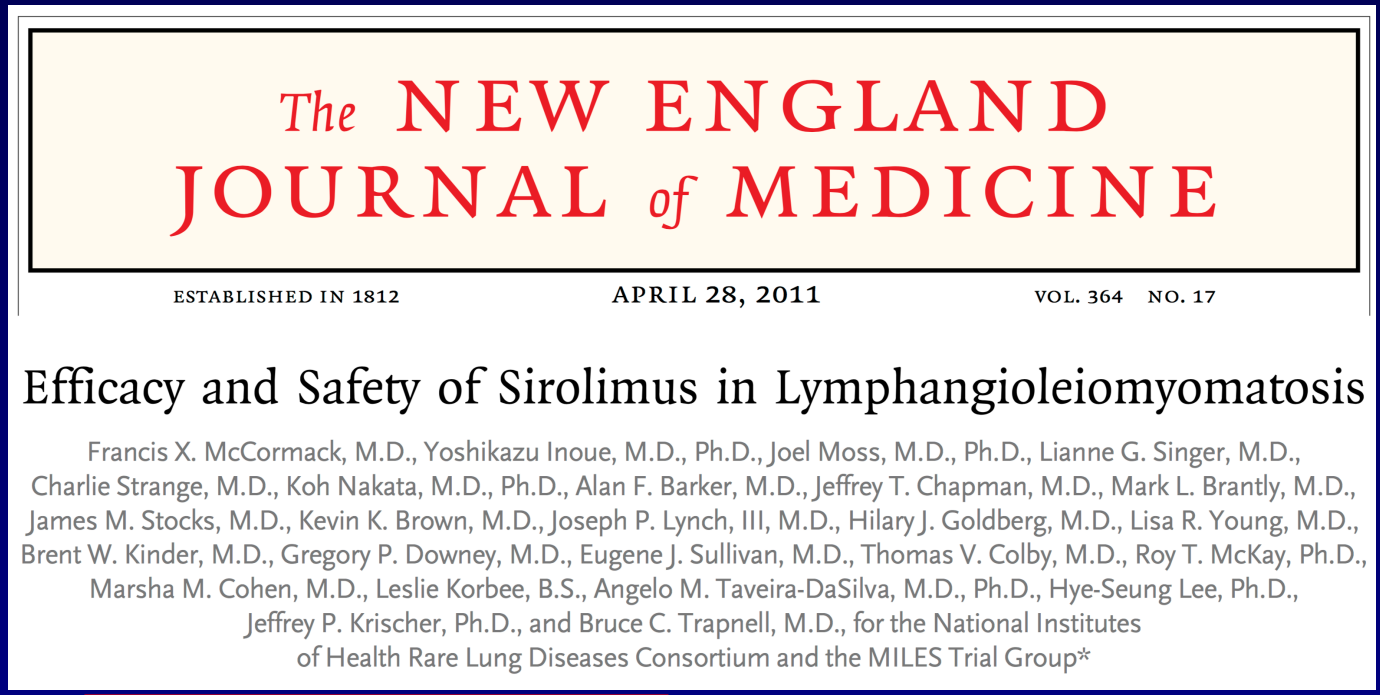
Mar 2013

Results 118 patients (median age 31·0 years; IQR 18·0–61·0) from 24 centres in 11 countries were randomly assigned to receive everolimus (n=79) or placebo (n=39). At the data cutoff, double-blind treatment was ongoing for 98 patients; two main reasons for discontination were disease progression (nine placebo patients) followed by adverse events (two everolimus patients; four placebo patients). The angiomyolipoma response rate was 42% (33 of 79 [95% CI 31–53%]) for everolimus and 0% (0 of 39 [0–9%]) for placebo (response rate difference 42% [24–58%]; one-sided Cochran-Mantel-Haenszel test p<0·0001). The most common adverse events in the everolimus and placebo groups were stomatitis (48% [38 of 79], 8% [3 of 39], respectively), nasopharyngitis (24% [19 of 79] and 31% [12 of 39]), and acne-like skin lesions (22% [17 of 79] and 5% [2 of 39]).

Interpretation Everolimus reduced angiomyolipoma volume with an acceptable safety profile, suggesting it could be a potential treatment for angiomyolipomas associated with tuberous sclerosis.

LAM trial

- Why – to improve LAM
- What - sirolimus
- For Whom – TSC and LAM
- Findings – Safe and efficacious for improving LAM
- Status – FDA approved 2012



The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 APRIL 28, 2011 VOL. 364 NO. 17

Efficacy and Safety of Sirolimus in Lymphangioleiomyomatosis

Francis X. McCormack, M.D., Yoshikazu Inoue, M.D., Ph.D., Joel Moss, M.D., Ph.D., Lianne G. Singer, M.D., Charlie Strange, M.D., Koh Nakata, M.D., Ph.D., Alan F. Barker, M.D., Jeffrey T. Chapman, M.D., Mark L. Brantly, M.D., James M. Stocks, M.D., Kevin K. Brown, M.D., Joseph P. Lynch, III, M.D., Hilary J. Goldberg, M.D., Lisa R. Young, M.D., Brent W. Kinder, M.D., Gregory P. Downey, M.D., Eugene J. Sullivan, M.D., Thomas V. Colby, M.D., Roy T. McKay, Ph.D., Marsha M. Cohen, M.D., Leslie Korbee, B.S., Angelo M. Taveira-DaSilva, M.D., Ph.D., Hye-Seung Lee, Ph.D., Jeffrey P. Krischer, Ph.D., and Bruce C. Trapnell, M.D., for the National Institutes of Health Rare Lung Diseases Consortium and the MILES Trial Group*

Epilepsy Trial – EXIST-3 Trial

- Why – to improve seizure
- What - everolimus
- For Whom – TSC and epilepsy
- Findings – Safe and efficacious for seizure reduction
- Status – FDA approved 2018

Adjunctive everolimus therapy for treatment-resistant focal-onset seizures associated with tuberous sclerosis (EXIST-3): a phase 3, randomised, double-blind, placebo-controlled study

Dr Prof Jacqueline A French MD [a], John A Lawson MD [b], Prof Zuhal Yapici MD [c], Hiroko Ikeda MD [d], Tilman Polster MD [e], Rima Nabbout MD [f], Prof Paolo Curatolo MD [g], Prof Petrus J de Vries PhD [h], Dennis J Dlugos MD [i], Noah Berkowitz MD [j], Maurizio Voi MD [j], Severine Peyrard MS [k], Diana Pelov MS [j], Prof David N Franz MD [l]

Lancet 2016

- Afinitor 1st adjunctive therapy in a randomized Phase III study to achieve clinically significant seizure control in TSC patients
- Low exposure (3-7 ng/mL; n=117), or high exposure (9-15 ng/mL; n =130), or placebo (n=119)
- Seizure response rate (>=50% reduction) significantly greater with low (28.2%, *P*=0.008; CI=95%) and high exposure (40.0%, *P*<0.001; CI=95%) vs placebo (15.1%; CI=95%).
- Seizure-free: 5 pts in high dose arm, 6 in low dose, 1 in placebo
- Safety profile similar to EXIST-1 and EXIST-2

Topical Rapamycin Trial

- Why – to improve facial angiofibroma
- What – topical rapamycin
- For Whom – TSC and facial angiofibroma
- Findings – safe and efficacious for improving angiofibroma
- Status – FDA submission

JAMA Dermatology | Original Investigation

Efficacy and Safety of Topical Rapamycin in Patients With Facial Angiofibromas Secondary to Tuberous Sclerosis Complex

The TREATMENT Randomized Clinical Trial

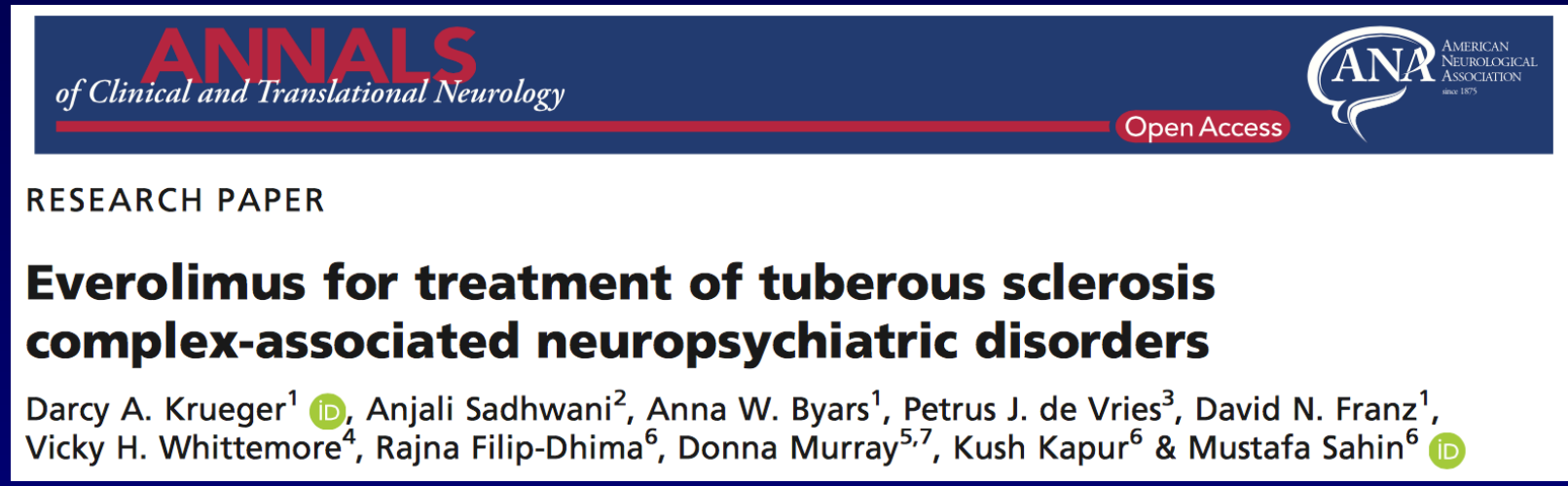
May 2018

Mary Kay Koenig, MD; Cynthia S. Bell, MS; Adelaide A. Hebert, MD; Joan Roberson, RN, BSN; Joshua A. Samuels, MD, MPH; John M. Slopis, MD; Patti Tate, RCP, CCRP; Hope Northrup, MD; for the TREATMENT Trial Collaborators

- multicenter, randomized, double-blind, vehicle-controlled, 2-dose trial
- 179 pt (59 in 1% rapamycin arm, 63 in 0.1% arm, 57 in vehicle-only arm)
- improvement for 81.8% of pt in 1% group, for 65.5% in 0.1% group, for 25.5% in vehicle-only group ($p < .001$, all 3 pairwise comparisons)
- well-tolerated, with no measurable systemic absorption
- drug-related adverse effects limited to ≤10% of application site discomfort and/or pain, pruritus, erythema, irritation
- nearly all adverse events were mild, with no drug-related moderate, severe, or serious events

Neurocognition Trial

- Why – to improve cognition
- What - everolimus
- For Whom – TSC and intellectual disability
- Findings – not efficacious
- Status –



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RESEARCH PAPER

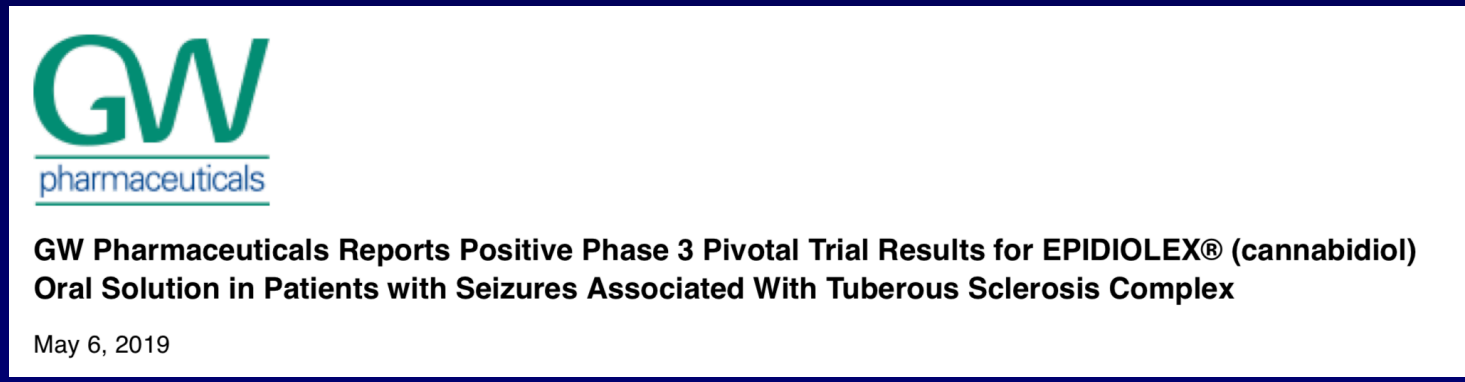
Everolimus for treatment of tuberous sclerosis complex-associated neuropsychiatric disorders

Darcy A. Krueger[1], Anjali Sadhwani[2], Anna W. Byars[1], Petrus J. de Vries[3], David N. Franz[1], Vicky H. Whittemore[4], Rajna Filip-Dhima[6], Donna Murray[5,7], Kush Kapur[6] & Mustafa Sahin[6]

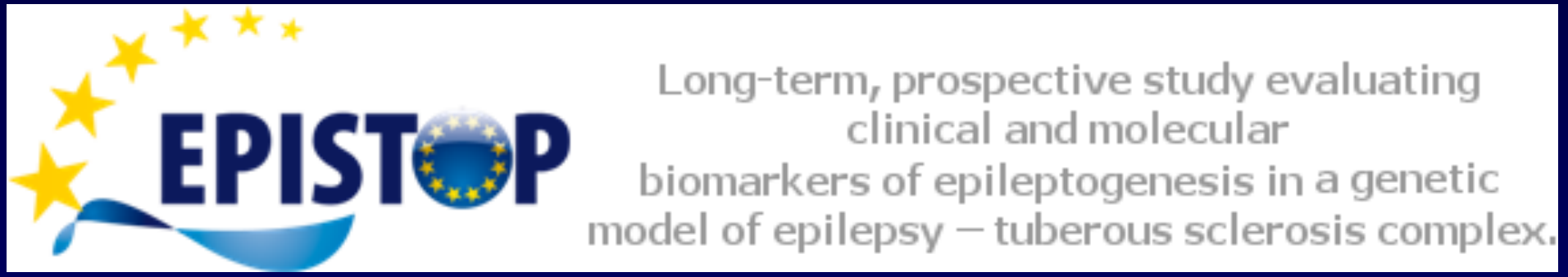
- double-blind, randomized, placebo-controlled, phase II trial
- 52 children age 6-21, randomized 2:1, with TSC and ID
- 74% also had epilepsy; 34% also had autism
- minimum IQ of 60 at enrollment
- NO significant improvement between everolimus (n=32) and placebo groups (n=15)

GW TSC trial

- Why – to improve seizures
- What - cannabidiol
- For Whom – TSC and epilepsy
- Findings – safe and efficacious in sz reduction
- Status – FDA submission



- double-blind, randomized, placebo-controlled, two-dose, phase III trial
- 224 patients, 1-65 years of age, 25 mg/kg/day (n=75), 50 mg/kg/day (n=73), placebo (n=76)
- seizure reductions in the 25 and 50 mg/kg/day groups of 48.6% and 47.5% from baseline respectively, vs 26.5% for placebo
- No new safety concerns from prior studies with Dravet or LGS



- Why – to prevent or delay sz onset
- What - vigabatrin
- For Whom – TSC, before sz onset, in EU
- Findings -
- Status – recruitment completed

- TSC infants
- < 4 months of age, before epilepsy onset
- Blinded, randomized to standard treatment vs pre-sz treatment with vigabatrin if EEG epileptiform discharges
- Separate control group
- Developmental testing
- Blood biomarkers

PREVeNT (Preventing Epilepsy with Vigabatrin in Infants with Tuberous Sclerosis Complex) Trial

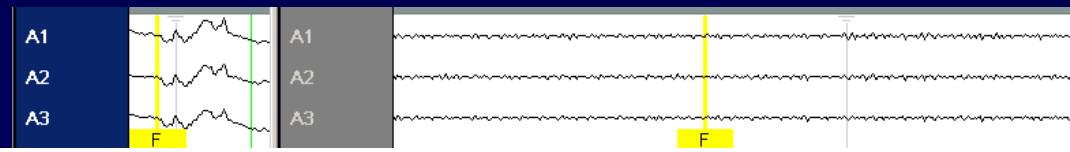
- Why – to prevent, delay, ameliorate sz course
- What - vigabatrin
- For Whom – TSC, before sz onset, in the US
- Findings -
- Status – Recruitment near completion

- TSC infants
- ≤ 6 months
- Never had sz, anti-seizure drugs, or mTOR inhibitors
- Developmental testing
- Blood biomarkers

Behavioral therapy trial

High Frequency Oscillation Surgical Trial

- Why – for best post-surgical seizure freedom
- What – Phase 3 tailored surgical resection trial
- For Whom – medically refractory epilepsy, including TSC
- Findings -
- Status – actively recruiting



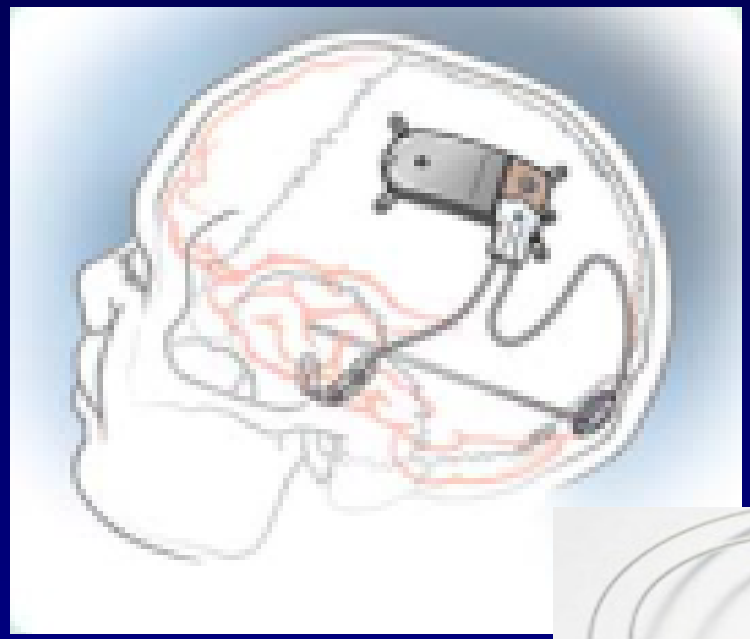
Intraoperative fast ripples independently predict postsurgical epilepsy outcome: Comparison with other electrocorticographic phenomena

Shaun A. Hussain[a,*], Gary W. Mathern[b,c], Phoebe Hung[a], Julius Weng[a], Raman Sankar[a,d], Joyce Y. Wu[a]

ECoG Abnormality	Prevalence(%)	Sens[g] (%)	Spec[h] (%)	PPV[i] (%)	NPV[j] (%)	Accuracy[k] (%)
FR[a] (n=48)	80.0	37.5	100.0	100.0	76.1	79.2
Slowing[b] (n=52)	86.7	33.3	91.9	62.5	77.2	75.0
Spikes[c] (n=45)	75.0	9.1	96.8	50.0	69.8	68.9
PFA[d] (n=29)	48.3	40.0	91.6	50.0	88.0	82.8
CEDs[e] (n=9)	15.0	0	75.0	0	37.5	33.3
Atten[f] (n=10)	16.7	0	80.0	0	44.4	40.0
Seizures (n=5)	8.3	0	100.0	N/A[l]	60.0	60.0

Pediatric Responsive Neurostimulation Trial

- Why – to reduce seizures in children (FDA approved for ≥ 18 years of age)
- What – Phase 3 neurostimulation device trial
- For Whom – medically refractory epilepsy, including TSC, 12-17 years of age
- Findings -
- Status – start date of ~ 2nd quarter, 2020



RaSuRE (Rapamycin for Surgically Refractory Epilepsy) Trial

- Why – to reduce seizures in children who have medically and surgically intractable epilepsy
- What – Phase 2 efficacy trial with ABI-009 (sirolimus albumin-bound nanoparticles for injectable suspension)
- For Whom – medically refractory epilepsy, after surgical failure, including TSC
- Findings -
- Status – start date of ~ 2nd half, 2020

STOP (Stopping TSC Onset and Progression) 2 Trial

- Why – epilepsy prevention
- What – Phase I/II sirolimus trial for safety and efficacy
- For Whom – TSC, ≤ 6 months, no prior sz, anti-seizure medications, ketogenic diet, surgery, or procedure
- Findings -
- Status – start ~ 2nd half, 2020

Summary of Clinical Trials

Trial Name	Indication	Status	FDA Approval
EXIST-1	Brain Subependymal Giant-cell Astrocytoma	Completed	Approved
EXIST-2	Renal Angiomyolipoma	Completed	Approved
LAM Trial	LAM	Completed	Approved
EXIST-3	Focal Epilepsy with TSC	Completed	Approved
Topical Rapamycin Trial	Facial Angiofibroma	Completed	Pending
TSC Epidiolex Trial	Focal Epilepsy with TSC	Active; not recruiting	Pending
EpiSTOP Trial	Epilepsy Prevention in TSC	Active; not recruiting	
PREVeNT Trial	Epilepsy Prevention in TSC	Active; recruiting	
Behavioral Therapy Trial	Behavioral Trial in TSC	Active; recruiting	
HFO Trial	Pediatric Epilepsy Surgery Trial	Active; recruiting	
Pediatric RNS Trial	Pediatric Neurostimulation Device Trial	Planning stages	
RaSuRE Trial	Focal Epilepsy after Surgical Failure	Planning stages	
STOP-2 Trial	Epilepsy Prevention in TSC	Planning stages	

clinicaltrials.gov

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Pediatric Epilepsy / TSC Program

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Ruby Escalante
Natalie Solis

Pediatric Neurosurgery

Aria Fallah, MD MS
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Brenda Porter, MD PhD
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Mustafa Sahin, MD PhD
(Boston Children's)

NIH National Institute of Neurological Disorders and Stroke

TACERN Tuberous Sclerosis Complex Autism Center of Excellence Research Network
Boston Cincinnati Birmingham Houston Los Angeles

Tuberous Sclerosis Alliance