Tuberous Sclerosis Complex

A successful transition from the bench to the bedside

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Bench to Bedside

The process by which the results of research done in a laboratory are directly used to develop new ways to treat patients.
TSC

- Genetic disorder
- Benign tumors in multiple organ systems
- Abnormal skin pigmentation
- Affects 1 in 6000 individuals
TSC Non-Neurologic Manifestations

- **Eye (40-50%)**
  - Retinal hamartoma

- **Heart (50-70%)**
  - Rhabdomyoma

- **Lungs (25-40%)**
  - Lymphangioleiomyomatosis

- **Kidney (55-75%)**
  - Renal angiomyolipoma
  - Cysts
  - Renal cell carcinoma

- **Skin (>90%)**
  - Hypopigmented macules
  - Periungual fibromas
  - Facial angiofibromas

Organ Involvement in TSC
Skin

Hypomelanotic macules
Skin

Confetti Lesions

Fibrous Facial Plaque
Skin

Shagreen Patch
Skin

Periungual Fibromas
Skin

Facial Angiofibromas
Eye

Retinal hamartoma
Cardiac Rhabdomyoma
Lung

Lymphangioleiomyomatosis (LAM)
Kidney

Cysts

Angiomyolipomas (AML)
Clinical Manifestations: Neurologic

- **Epilepsy**
  - Infantile spasms (30%)
  - Partial onset seizures (90%)
  - Intractable in >50%

- **Tuberous Sclerosis Associated Neuropsychiatric Disorders (TAND)**
  - Cognitive impairment (50%)
  - Learning Disabilities
  - Autism (50%)
  - Psychiatric (50%)
  - Sleep disorders
Structural Brain Findings in TSC

- **Tubers**
  - Occur in 80% to 90% of patients
  - Manifest as early as 20 weeks of gestation
  - Vary in size and number (1 to >30 lesions)

- **Subependymal Nodules (SEN)**
  - Occur in up to 90% of patients
  - Develop during fetal life
  - Asymptomatic
Sub-Ependymal Nodules
Structural Brain Findings in TSC

- **Sub-ependymal Giant Cell Astrocytoma (SEGA)**
  - Occur in up to 20% of patients with TSC
  - Tumor is present prior to the age of 24 years
  - Can lead to obstruction of cerebrospinal fluid (CSF) flow and possibly sudden death
Subependymal Giant Cell Astrocytoma

Brain
Onset of Symptoms With Age

- Cardiac
- Renal
- Cerebral
- Skin
- Lung

Age (Yrs)
0 20 40 60 80
Surveillance of Patients With TSC

- Skin – Physical examination annually
- Eyes - Fundoscopic exam annually (if able)
- Renal – Renal MRI annually
- Heart – EKG every 1-3 years
- Lungs – Chest CT > 18 years; PFTs symptomatically
- Brain –
  - If no SEGA is present: MRI brain every 1-3 years until 24 years of age
  - Current or history of SEGA: ongoing MRI surveillance for life
The Timeline of TSC
French dermatologist Pierre Francois Olive Rayer published an atlas of skin diseases. Included a drawing entitled ‘vegetations vasculaires’ that is considered the 1st description of tuberous sclerosis.
1862

- German physician Friedrich Daniel von Recklinghausen presented a case of an infant who died from cardiac tumors.
- Also noted a ‘great number of scleroses’ in the brain.
1880

- French neurologist Desire-Magloire Bourneville described a 15 year old girl with psychomotor retardation, a vascular-papuluous eruption of the nose, cheeks, and forehead; and worsening seizures.

- The child died from her condition and post-mortem evaluation demonstrated hard, dense, tubers in the brain and kidneys.

- He titled the disease ‘Sclerose tubereuse des circonvolutions cerebrales’
  
  [tuberous sclerosis of the brain convolutions]
1908

- German pediatric neurologist Heinrich Vogt established the diagnostic criteria for TSC defining a triad of symptoms required for diagnosis:
  - Epilepsy
  - Idiocy
  - Adenoma Sebaceum
Dr. Manuel Gomez refuted Vogt’s triad for TSC publishing a review of 79 patients with TSC, of which 1/3 had normal intelligence.

In 1979 he published a textbook on TSC establishing comprehensive diagnostic criteria that remains the basis of our current criteria.
Linkage analysis of 19 families with TSC identified a probable gene on chromosome 9 (named TSC1)

LINKAGE OF TUBEROUS SCLEROSIS TO ABO BLOOD GROUP

THE LANCET, OCTOBER 3, 1987

HOPE NORTHROP
ARTHUR L. BEAUDET
WILLIAM E. O’BRIEN
GAIL E. HERMAN
RICHARD A. LEWIS
MARILYN S. POLLACK
Linkage analysis located the 2nd gene for TSC on chromosome 16 (named TSC2)

Linkage of an important gene locus for tuberous sclerosis to a chromosome 16 marker for polycystic kidney disease

R. S. Kandt¹, J. L. Haines², M. Smith³, H. Northrup⁴, R. J. M. Gardner⁵, M. P. Short², K. Dumars³, E. S. Roach⁶, S. Steingold¹, S. Wall⁷, S. H. Blanton⁸, P. Flodman³, D. J. Kwiatkowski³, A. Jewell², J. L. Weber¹⁰, A. D. Roses⁷ & M. A. Pericak-Vance⁷

*nature genetics  volume 2  september 1992*
1993

- TSC2 gene located and characterized
- Protein product named ‘tuberin’

Identification and Characterization of the Tuberous Sclerosis Gene on Chromosome 16

The European Chromosome 16 Tuberous Sclerosis Consortium*
1997

- TSC1 gene located and characterized
- Protein product named ‘hamartin’
1998

Complex formation of TSC1 & TSC2 confirmed

**Hamartin, the Product of the Tuberous Sclerosis 1 (TSCI) Gene, Interacts with Tuberin and Appears to Be Localized to Cytoplasmic Vesicles¹**

Tracey L. Plank, Raymond S. Yeung, and Elizabeth Petri Henske²

Department of Medical Oncology, Fox Chase Cancer Center, Philadelphia Pennsylvania 19111 (T. L. P.; E. P. H.); and Department of Surgery, University of Washington, Seattle, Washington (E. P. Y.)

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**Interaction between hamartin and tuberin, the TSC1 and TSC2 gene products**

Marjon van Siegenhorst*, Mark Nellist*, Bas Nagelkerken¹, Jeremy Cheadle², Russell Snell², Ans van den Ouweland, Arnold Reuser, Julian Sampson², Dicky Halley* and Peter van der Sluijs¹

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TSC inhibits mTOR in mammalian cells

Phosphatidylinositol 3-Kinase/Akt Pathway Regulates Tuberous Sclerosis TumorSuppressor Complex by Phosphorylation of Tuberin*


Identification of the Tuberous Sclerosis Complex-2 Tumor Suppressor Gene Product Tuberin as a Target of the Phosphoinositide 3-Kinase/Akt Pathway

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of these kinases is blocked by PI3K-specific inhibitors (Burgering and Coffer, 1995; Chung et al., 1994; Franke et al., 1995). Akt contains a PH domain that is specific to PtdIns-3,4P2 and PtdIns-3,4,5P3 (Franke et al., 1997). Akt is thereby recruited to these PI3K-generated second messengers and to the PDK1 protein kinase, which also specifically binds to these lipids (Stokoe et al., 1997). PDK1 then phosphorylates and activates Akt (Aleksi et al., 1997).

The regulation of S6K1 is much more complex, with both PI3K-dependent and -independent signaling path-

TSC2 is phosphorylated and inhibited by Akt and suppresses mTOR signalling

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The mTOR Pathway in TSC

- Mammalian target of rapamycin (mTOR) is a serine/threonine kinase that regulates cellular metabolism, growth, and proliferation.

- **Defects in TSC1 or TSC2** result in a release of inhibition on mTOR leading to the formation of the solid tumors seen in multiple organ systems in patients with TSC.
TSC Signaling Pathways
The Era of Treatment
Rapalogs
Rapamycin

- The macrolide rapamycin (sirolimus) was discovered in 1975 on Easter Island.
- Initially used as an anti-fungal, its immunosuppressant and anticancer properties were soon recognized.
- In 1990 the mechanism of action was found to be inhibition of cellular proliferation and cell cycle progression via inhibition of mTOR.
Rapalogs

- Designed to enhance pharmacokinetics and reduce immunosuppression
  - Temsirolimus
  - Everolimus
  - Ridaforolimus
- Used as monotherapy and combination therapy for many cancer types
- Cytostatic – do not kill cells, only inhibit growth
TSC-Associated Sub-Ependymal Giant Cell Astrocytoma (SEGA)
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, MD1,6

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
1st report of use of rapamycin in 4 TSC patients
Showed regression of astrocytomas with low dose rapamycin
Everolimus for Subependymal Giant-Cell Astrocitaryomas in Tuberous Sclerosis

Darcy A. Krueger, M.D., Ph.D., Marguerite M. Care, M.D., Katherine Holland, M.D., Ph.D., Karen Agricola, F.N.P., Cynthia Tudor, P.N.P., Prajakta Mangeshkar, M.S., Kimberly A. Wilson, M.S., Anna Byars, Ph.D., Tarek Sahmoud, M.D., Ph.D., and David Neal Franz, M.D.

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Results following 6 months of treatment

Reduction in the volume of the SEGA of at least:

- 30% in 21/28 (75%) patients
- 50% in 9/28 (32%) patients
FDA approval

- Approved for treatment of SEGA in TSC
  October 29, 2010
  - 175 years after the 1st description of TSC
  - 23 years after identification of the 1st gene
  - 8 years after discovery of the gene function

*Everolimus is indicated for the treatment of SEGA associated with TSC in patients requiring therapeutic intervention but who are not candidates for curative surgical resection*
TSC Associated Lymphangioleiomyomatosis (LAM) & Renal Angiomyolipoma (AML)
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*
MILES Trial

- 12 month randomized, double-blind comparison of sirolimus with placebo followed by a 12 month observation period
- 89 LAM patients with moderate lung impairment
- Sirolimus stabilized lung function and reduced symptoms
FDA approval

- Approved for treatment of angiomyolipoma (AML) in TSC April 26, 2012

*Everolimus is indicated for the treatment of AML associated with TSC in patients requiring therapeutic intervention but who do not require immediate surgery*
FDA approval

- Approved for the treatment of lymphangioleiomyomatosis (LAM) in TSC May 28, 2015

Sirolimus is indicated for the treatment of Lymphangioleiomyomatosis
Prospective, multi-center, open-label trial

Treated 20 patients with TSC & refractory epilepsy for 12 weeks

Seizure frequency was reduced by ≥50% in 12 of 20 (60%) subjects

Overall, seizures were reduced in 17 of the 20 (85%) by a median reduction of 73%
EXIST-3

- A placebo-controlled study of efficacy & safety of everolimus as adjunctive therapy in patients with TSC & refractory partial-onset seizures
- 102 international study locations
- 326 subjects
Prospective, randomized, double-blind, placebo controlled study

23 subjects with 6 months of treatment

73% percent of subjects in the treatment arms versus 38% of subjects in the placebo arm reported a subjective improvement in the appearance of their facial angiofibromas
TREATMENT Trial

- Multi-center, international, prospective, double-blind, placebo-controlled trial investigating the efficacy of topical rapamycin for the treatment of facial angiofibromas
- 10 study sites
- 177 subjects
- Data analysis pending
Ongoing trials of everolimus and neurocognition in TSC

- **Boston & Cincinnati**
  - Placebo controlled study of children aged 6-21 years with TSC to assess changes in cognitive status with 6 months of everolimus therapy

- **Cardiff (England)**
  - Randomized, placebo-controlled study of adults to assess changes in memory and executive function with 6 months of everolimus therapy

- **Erasmus (Netherlands)**
  - Randomized, placebo-controlled study of children aged 4-15 years to assess learning and development with 12 months of everolimus therapy
Thank You

Clinical & Research Team:
- Alejandro Carrillo, RN
- Hope Northrup, MD
- Adelaide Hebert, MD
- Elida Salazar
- Joshua Samuels, MD, MPH
- John Slopis, MD
- Patti Tate, RT

UT Tuberous Sclerosis Complex Center of Excellence