

Tuberous Sclerosis Complex Research Program

Decreasing the Global Impact of TSC



Congressionally Directed Medical Research Programs



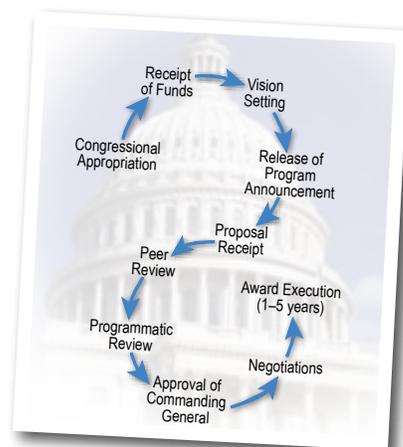
HISTORY The Office of the Congressionally Directed Medical Research Programs (CDMRP) was created in 1992 from a powerful grassroots effort led by the breast cancer advocacy community that resulted in a congressional appropriation of funds for breast cancer research.

This initiated a unique partnership among the public, Congress, and the military. The success in managing the initial congressional appropriations in breast cancer research combined with additional advocacy movements and the need for focused biomedical research catapulted the CDMRP into a global funding organization for cancer research, military medical research, and other disease-specific research.

The CDMRP has grown to encompass multiple targeted programs and has received over \$8 billion in appropriations from its inception through fiscal year 2014 (FY14). Funds for the CDMRP are added to the Department of Defense (DoD) budget in which support for individual programs, such as the Tuberous Sclerosis Complex Research Program (TSCR), is allocated via specific guidance from Congress.

Application Review Process

The CDMRP uses a two-tier review process for application evaluation with both steps involving dynamic interaction between scientists and clinicians and consumer advocates. The first tier of evaluation is a scientific peer review of applications measured against established criteria for determining scientific merit. The second tier is a programmatic review, conducted by the Integration Panel (IP), which is composed of leading scientists, clinicians, and consumer advocates. The IP compares applications to each other and makes recommendations for funding based on scientific merit, portfolio composition, and relevance to program goals.



Consumer Advocacy Participation

A unique aspect of the CDMRP is the active participation of consumer advocates or patient representatives, throughout the program's annual cycle. Individuals with TSC and their family members have an equal voice in the research administration process of setting the TSCR's vision, reviewing applications, and making final funding recommendations. From the unique perspective gained through personal experience, the consumer brings a sense of urgency and focus to each part of the program cycle. Consumers evaluate the impact of the research to individuals with TSC, as well as the needs of their family members, caregivers, and clinicians.

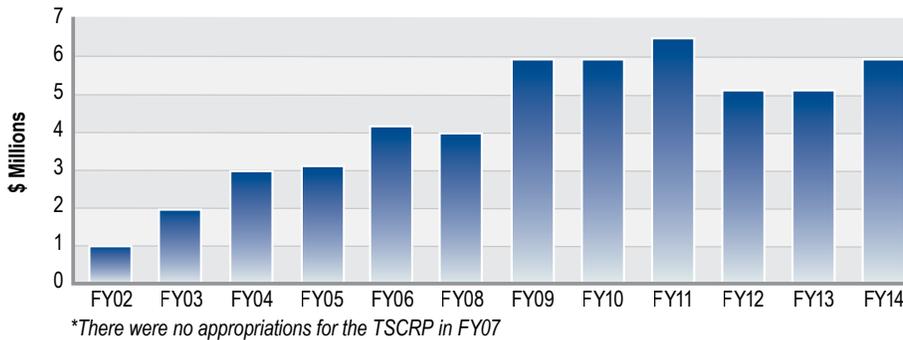
Tuberous Sclerosis Complex Research Program

Tuberous Sclerosis Complex (TSC) is a genetic disorder that causes non-malignant tumors to form in many different organs, and it presents itself in a variety of clinical manifestations. TSC can be inherited as an autosomal dominant trait; however, two-thirds of cases are the result of a spontaneous genetic change on one of two genes, TSC1 or TSC2. It is estimated that TSC affects **25,000 to 50,000** individuals in the United States and **1 to 2** million individuals worldwide.

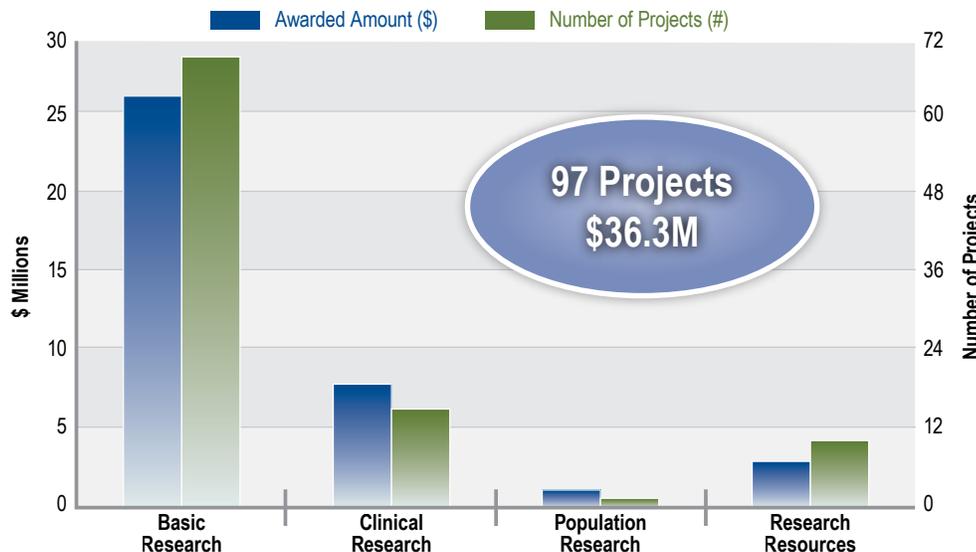
History of the TSCRCP

The TSCRCP was first funded in FY02 when the efforts of TSC advocates led to a congressional appropriation of \$1 million (M). Since then, a total of \$53M has been appropriated to the program, including \$6M in FY14. Today, the TSCRCP is one of the leading sources of extramural TSC research funding in the United States.

FY02–FY14 TSCRCP Appropriations*



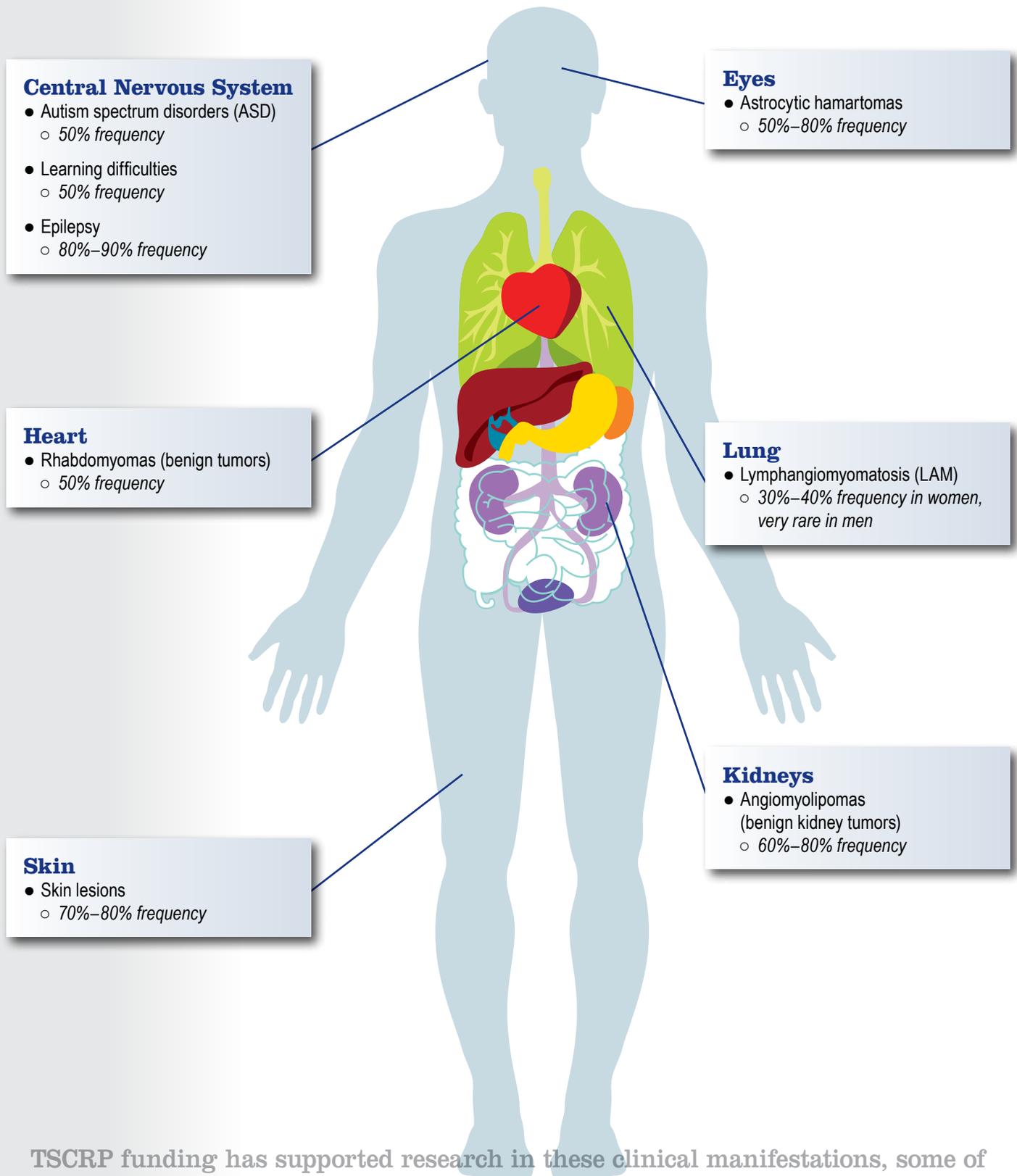
FY02–FY12 TSCRCP Portfolio



Program Goals

- **Support** high impact, innovative research.
- **Foster** the development of research resources and tools.
- **Promote** the translation of new research findings to patient care.
- **Advance** the knowledge of TSC and its clinical manifestations.

TSC Clinical Manifestations



TSCRP funding has supported research in these clinical manifestations, some of which are highlighted on the following pages.

Research Highlights



Targeting Estrogen-Induced COX-2 Activity in Lymphangi leiomyomatosis (LAM)

Jane Yu, Ph.D., Brigham and Women's Hospital

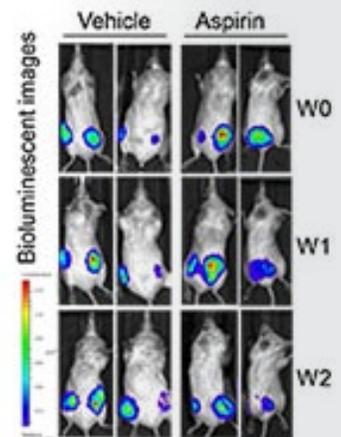
LAM is a rare lung disease that leads to lung destruction and respiratory failure, primarily in women. LAM cells are histologically benign smooth muscle cells carrying Tuberous Sclerosis Complex 2 (TSC2) gene mutations that are believed to metastasize to the lungs. Many end-stage LAM patients may require lung transplantation; however, the tumors may return in the transplanted lungs after a year. In LAM patients, the mammalian target of rapamycin complex 1 (mTORC1) inhibitor rapamycin stabilizes lung function and improves symptoms; however, not all patients respond to this therapy, and lung function declines when rapamycin is discontinued. Dr. Jane Yu at Brigham and Women's Hospital is investigating the role of estrogen in the pathogenesis of LAM. She has observed that the female hormone, 17-beta estradiol (E2), promotes the survival and lung metastasis of TSC2-null cells as well as increased levels of prostaglandin production, including PGE₂, in these tumors.

With funding from an FY11 TSCRP Exploration-Hypothesis Development Award, Dr. Yu is testing her hypothesis that E2 induces cyclooxygenase-2 (COX-2) activity, the rate-limiting enzyme in the biosynthesis of prostaglandins. She believes that these elevated COX-2 levels will result in increased prostaglandin biosynthesis, which, in turn, will promote the survival and lung metastasis of TSC2-null cells. A corollary of this hypothesis is that COX-2 suppression will block E2-promoted lung metastasis and will induce regression of lung lesions.

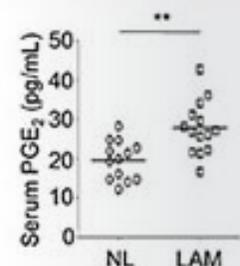
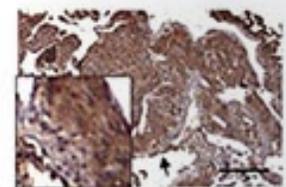
Dr. Yu and her research team, in collaboration with Drs. Kwiatkowski, Levy, Henske, Xu, and Blenis, found that, in TSC2-null cells, E2 increases COX-2 activity and enhances prostaglandin production in an mTORC1-independent way. Treatment of TSC2-null cells with aspirin, a COX-2 inhibitor, resulted in decreased PGE₂ production and decreased cell proliferation. Moreover, aspirin treatment of a TSC2 xenograft model resulted in decreased tumor size, decreased levels of COX-2 in the tumors, and decreased urinary PGE₂ levels. Furthermore, COX-2 was abundant in LAM lesions, and PGE₂ serum levels were elevated in LAM patients.

Dr. Yu and her team believe that aspirin and/or other COX-1/COX-2 inhibitors may be effective in slowing the clinical progression of LAM. It is worth noting that aspirin and other COX-1/COX-2 inhibitors' side effects and toxicity profiles are well characterized, making them promising candidates for long-term LAM therapy.

Inhibition of COX-2 in mouse models



COX-2 in pulmonary LAM



Publication:

Li C, Lee P-S, Sun Y, et al. 2014. Estradiol and mTORC2 cooperate to enhance prostaglandin biosynthesis and tumorigenesis in TSC2-deficient LAM cells. *Journal of Experimental Medicine* 211(1):15-28.



Defining Early Markers of Autism in Infants with TSC

Charles A. Nelson III, Ph.D., Boston Children's Hospital

Nearly 60% of all children with TSC also exhibit autism spectrum disorder (ASD), a range of neurodevelopmental disorders characterized by impairments in social interaction and communication, repetitive behaviors and interests, and possible cognitive delays. Because the prevalence of ASD in the general population is significantly lower, it is clear that there is an association between TSC and ASD. Although evidence suggests that the abnormalities in brain development present in children with TSC might interfere with areas important for social communication, the precise link between TSC and ASD is largely unknown. The diagnosis of ASD at a young age is crucial for early intervention strategies, which can dramatically improve developmental outcomes. However, the developmental disabilities associated with TSC often confound the diagnosis of ASD, which typically relies on evidence-based assessment of ASD symptoms.

Dr. Charles Nelson of Boston Children's Hospital is the recipient of an FY10 Clinical Research Award from the TSCRP, working in collaboration with Dr. Shafali Jeste of the University of California, Los Angeles. Through this award, Dr. Nelson has sought to better define the phenotype of children with TSC and ASD in order to identify markers of ASD that could be used to predict neurocognitive and behavioral outcomes before clinical diagnosis. In one study with children under age four, Dr. Nelson used electroencephalography (EEG), a non-invasive technique that involves the placement of small sensors on the surface of the scalp to measure brain waves, to look at differences in neural correlates of face processing, which is thought to serve as a biomarker of ASD. Interestingly, he found that children with TSC had slower face processing than typically developing children, and face processing was particularly slow in the subset of TSC children with ASD diagnoses. In a second study, Dr. Nelson used high-density scalp EEG to compare brain rhythms in infants with and without TSC. Through these analyses, he discovered that there were significant differences in EEG frequencies between the two groups as early as 20-24 months of age, and he hypothesizes that frequency differences may distinguish ASD in infants with TSC. These studies, along with additional work being done by Dr. Nelson, may provide early markers of ASD in children with TSC prior to clinical diagnosis, and may allow for effective intervention strategies to improve the child's developmental outcomes and future well-being.

Publications:

Jeste SS, Wu JY, Denturk D, et al. 2014. Early developmental trajectories associated with ASD in infants with tuberous sclerosis complex. *Neurology* (Accepted).
Stamoulis C, Vogel-Farley V, Degregorio G, et al. 2013. Resting and task modulated high-frequency brain measured by scalp encephalograms in infants with tuberous sclerosis complex. *Journal of Autism and Developmental Disorders* (Epub ahead of print).
Jeste SS, Hirsch S, Vogel-Farley V, et al. 2012. Atypical face processing in children with tuberous sclerosis complex. *Journal of Child Neurology* (12):1569-1576.



"My son Bao was born with TSC and associated early infantile spasms – 60-80 clusters per day. He endured four brain surgeries before his 2nd birthday. I have participated in the TSCRP program as a consumer reviewer for several years, and it is the single most important thing I can do for my son. This program is extremely well-run and has already resulted in clinical interventions that are vastly improving the health and quality of life of my son and so many others across the world."

Ron Heffron, P.E.,
Consumer IP Member

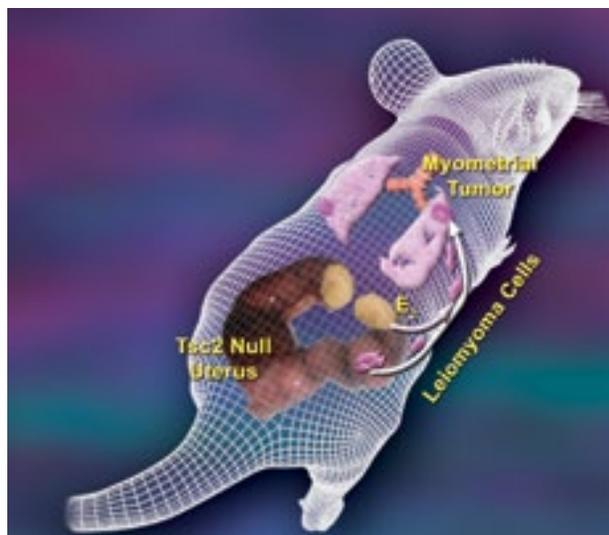


A Mouse Model for Lymphangi leiomyomatosis (LAM)

Stephen R. Hammes, M.D., Ph.D., University of Rochester

Lymphangi leiomyomatosis (LAM) is a rare lung disease in which abnormal smooth muscle cells proliferate out of control, leading to the loss of lung function. As a result of these tumors, approximately 50% of LAM patients will have at least one lung collapse, and over 30% will develop fluid in their lungs. Many LAM patients will require a lung transplant; however, the tumors may return. Genetic studies have shown that LAM cells contain mutations in one of the two tuberous sclerosis complex (TSC) genes, Tsc1 or Tsc2, and as many as 30%–40% of women with TSC may be affected by LAM in their lifetime. LAM is found almost exclusively in women and has similarities with uterine leiomyomas, benign tumors of myometrial cells, such as hormone sensitivity and exacerbation during pregnancy and hormonal contraception. Moreover, LAM tumors may recur after transplantation, suggesting that they may be the result of metastasis of another tumor in the body.

Supported by an FY11 TSCRP Exploration–Hypothesis Development Award, Dr. Stephen Hammes tested the hypothesis that LAM tumors, similar to uterine leiomyomas, originate from the uterine myometrium and that Tsc mutations provide the “additional hit” necessary to promote tumor growth and lymphatic spread to the lungs. To test this hypothesis, Dr. Hammes’ team at the University of Rochester, led by graduate student Hen Prizant, created a mouse model



for uterine leiomyomas and LAM by deleting the Tsc2 gene primarily in uterine cells. All of these mice developed uterine leiomyomas, recapitulating the condition observed in humans. Moreover, uterine cell proliferation was promoted by estrogen but not progesterone in ovariectomized Tsc2 null mice, mirroring the higher risk for LAM observed during pregnancy. Finally, analysis of lung tissue in older Tsc2 null mice revealed an infiltration of LAM-like, smooth muscle tumors in some of the animals, offering support for the hypothesis that LAM tumors might originate from tumors in the uterus. This new mouse model has the potential to improve our understanding of LAM and leiomyomas, and it may lead to novel therapeutic strategies for both diseases.

The figure was provided by the Endocrine Society.

Publication:

Prizant H, Sen A, Light A, et al. 2013. Uterine-specific loss of Tsc2 leads to myometrial tumors in both the uterus and lungs. *Molecular Endocrinology* 27:1403-1417.



“Being part of the TSCRP program has allowed me to review many exciting ideas and projects in the field of Tuberous Sclerosis. Each year, these projects cement my enthusiasm as a researcher focusing on this disease. I am honored to be a participant and am grateful to be involved in this unfolding area of research. The TSCRP program is a true example of funding ‘bench-to-bedside’ medicine! I can’t wait to see what the future holds.”

Mary Kay Koenig, M.D., University of Texas Health Science Center at Houston,
IP Member



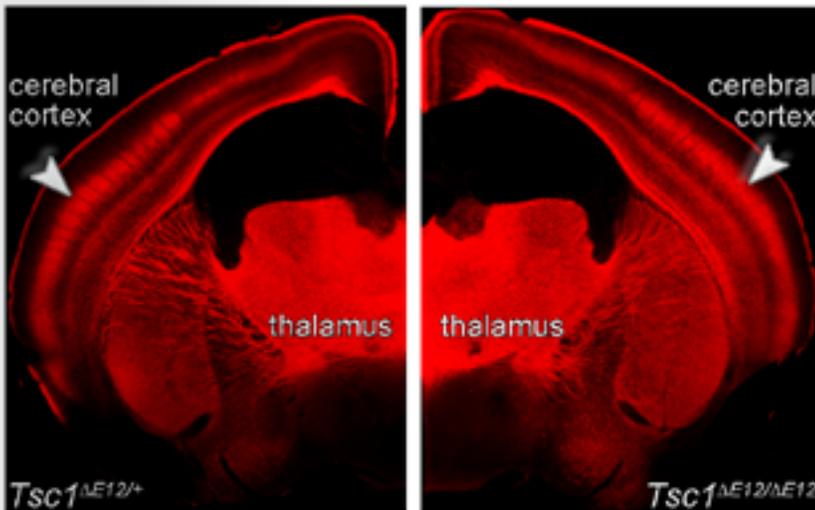
Loss of Tsc1 in Neurons in the Developing Thalamus Leads to Brain Abnormalities and Behavioral Symptoms

Mark Zervas, Ph.D., Brown University

TSC is an inherited disorder characterized by a variety of symptoms that may range from relatively mild to severe, including benign tumors throughout the body, seizures, developmental delay, and autism. TSC results from the loss of both alleles of the TSC1 or TSC2 gene, where one bad allele is often inherited from a parent and the other allele develops a mutation during embryonic development. The timing of TSC mutations during development and the effect on disease severity are not known. Dr. Mark Zervas received funding from the TSCRP to investigate the effects of Tsc1 loss in the mouse brain at different points during embryonic development. Specifically, his team is studying the loss of Tsc1 in neurons of the developing thalamus, a relay center of the brain that provides sensory and motor inputs to the cortex.

Dr. Zervas' team used a novel mouse model to delete both Tsc1 alleles specifically in thalamic neurons at different time points in embryonic development. Overall, they found that mice with Tsc1 deletion on the 12th day of gestation (E12) had many more behavioral symptoms, such as self-grooming and seizures, than mice with Tsc1 deletion on 18th day of gestation (E18), which is just before birth. They also compared the brains of mice with Tsc1 deletion on E12 and E18 with normal mice and, consistent with the behavioral findings, found that the abnormalities resulting from Tsc1 deletion at E12 were more severe than at E18. In addition to disorganization of the thalamic projections to parts of the cortex in mice with Tsc1 deletion on E12, Dr. Zervas' team observed enlarged size and altered physiological properties of neurons lacking Tsc1. Further, the growth-regulating mTOR pathway was disrupted in 70% of neurons in mice with the Tsc1 deletion on E12 compared to only 29% in mice with the deletion on E18. The mTOR pathway is overactive in patients in TSC, and these findings may indicate a previously unknown temporal role of the mTOR pathway in brain development.

Dr. Zervas' work has demonstrated that deletion of Tsc1 in the developing thalamus leads to both behavioral symptoms and anatomical changes in the brain. He also demonstrated that the severity of this phenotype depends on the timing and distribution of neurons with Tsc1 loss during development. Dr. Zervas will continue these studies to better define the developmental window during which Tsc1 loss is the most damaging, and to test the use of the mTOR inhibitor rapamycin to ameliorate the effects of Tsc1 loss in the developing thalamus.



Publication:

Norman EA, Crandall SR, Thorn CA, et al. 2013. Temporal and mosaic Tsc1 deletion in the developing thalamus disrupts thalamocortical circuitry, neural function, and behavior. *Neuron* (78)895-909.

TSC-Related Epilepsy Research

Epilepsy, a disorder involving repeated and spontaneous seizures, is a common manifestation of TSC that is estimated to affect up to 80%–90% of individuals with TSC at some point during their lifetime. Seizures result from abnormal electrical impulses in the brain and, in TSC, they are thought to be related to the presence of cortical tubers. Seizures can also result from an increase in pressure in the brain due to the presence and growth of a subependymal giant cell astrocytoma, or SEGA, which occurs in about 15% of TSC patients. There are many different seizure types associated with TSC including simple partial, complex partial, and generalized tonic-clonic seizures. Infantile spasms, severe single or clustered seizures that begin in infancy, are common in TSC but adult-onset seizures also occur. There is a variety of medications available to treat seizures, although not all seizures will respond well to all medications and some may remain intractable, or unresponsive, to medication. Alternative treatment options include dietary changes, vagus nerve stimulation, and surgery.

The TSCRP has funded a number of studies investigating epilepsy and seizures in the context of TSC. Following are brief descriptions of some of the current TSCRP awards addressing this important topic:



Novel Strategies for Treatment and Prevention

Stuart Lipton, M.D., Ph.D., Sanford-Burnham Medical Research Institute

Supported by an FY12 TSCRP Exploration–Hypothesis Development Award, Dr. Lipton is evaluating the efficacy of the FDA-approved drug Memantine in correcting the neurological and behavioral abnormalities in a mouse model of TSC, including electrophysiological abnormalities. Memantine is currently approved for use in Alzheimer’s disease and is under investigation in clinical trials for children with autism, intellectual disabilities, and epilepsy. Dr. Lipton also plans to evaluate a novel class of Memantine derivatives called NitroMemantines.



Altered Astrocyte-Neuron Interactions and Epileptogenesis in Tuberous Sclerosis Complex Disorder

David Sulzer, Ph.D., Columbia University

Dr. Sulzer hypothesizes that the development of epilepsy in TSC results from a failure of astrocytes to remove, or prune, excess excitatory synapses in the brain. Funded by an FY11 TSCRP Idea Development Award, he is evaluating the effect of TSC1 and TSC2 mutations in astrocytes on synaptic function in mice, and whether astrocyte dysfunction results in a deficit in pruning. He also plans to analyze human brain tissue for biomarkers of astrocyte function.



Studying Protein Synthesis-Dependent Synaptic Changes in Tuberous Sclerosis

Akira Yoshii, M.D., Ph.D., University of Illinois at Chicago

Dr. Yoshii is investigating whether the imbalance in excitatory and inhibitory neuronal signals in TSC is caused by altered synaptic protein synthesis. Specifically, he is testing whether the balance between excitatory and inhibitory synaptic proteins is altered in TSC mutant mice and whether this imbalance can be corrected by treatment with the mTOR inhibitor rapamycin. He also plans to identify synaptic proteins with enhanced synthesis in TSC and characterize their functions in TSC neurons.

TSCRП Perspectives



Cristy Wade: A Mother's Efforts to Defeat TSC

When my son was diagnosed with TSC in 2008, I felt as though my family and I had been thrown “through the looking glass” into a strange and frightening world. I joined the Tuberous Sclerosis Alliance, the only national advocacy group for TSC in the United States, to get support and help in finding treatment options. I became a volunteer for the group not only to help other families, but also to attempt to exert some control over a world that now seemed to be turned upside down. I wanted to take steps to try to understand and defeat this disease.

I first learned of the TSCRП through my government advocacy work with the Tuberous Sclerosis Alliance. Adults with TSC, parents of children with TSC, and other volunteers come together once a year to advocate in Congress for medical research funding. We share with Congressional offices our personal TSC stories and the great advances that have been made in TSC research in the past several years. Much of this progress has come from TSCRП-funded research. So when a consumer reviewer for the TSCRП suggested that I apply to become a reviewer, I jumped at the chance to be a part of this valuable program. While my primary job is that of a homeschooling mother to two teenage boys, my background of a biology degree and part-time work as a clinical research coordinator led me to believe that I could make a unique contribution in this role.

I was very proud to go back to the Congressional offices this year and tell them of my consumer reviewer experience with the TSCRП. I could testify to the excellent quality of grant proposals submitted to the panel and the highly competitive process to fund the very best. I feel honored to be given a chance to represent the TSC community on the selection panels to help choose the research that could have the greatest impact on our community. As a parent and volunteer, I have seen the end results of the research in the form of new treatments for the disease that have made significant impacts on the lives of those who suffer. My experience as a consumer reviewer has been educational, empowering, and very fulfilling.

Cristy Wade and family on the front cover. Left in brown shirt is Ryan, age 15, with TSC; center is Christy; right in blue shirt is Kyle, age 17; smaller dog on lap is Jackie, larger dog is Terra.



“The recent research advances in the TSC field are enormous, yet much work is needed to get to the finish line and provide TSC patients with the best therapeutics and sensitive diagnostics. To meet this mission, the TSCRП promotes a very competitive review process based on scientific rigor, transparency, and care to the translational relevance of the proposals. I feel fortunate to have had the opportunity to be part of this process serving as a peer review panel member for the TSCRП and contribute, together with wonderful colleagues, consumer advocates, and TSCRП members, to the identification of studies that may impact the lives of children and adults affected by TSC. I look forward to seeing results from these studies and even more amazing progress in the TSC field.”

**Carmen Priolo, M.D., Ph.D.,
Brigham and Women's Hospital/Harvard Medical School,
Scientific Peer Reviewer**



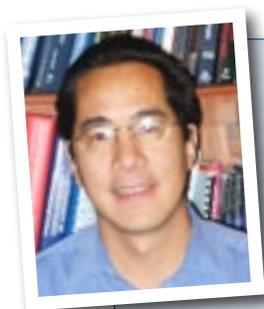
Reiko Donato: A Mother's Involvement in Helping Those Afflicted with TSC

Reiko Donato's daughter, Alex, was diagnosed with TSC at 12 months of age. Since that day, thirteen years ago, Reiko has been steadfast in her role as an advocate, both for individuals with the disease and for the family members and loved ones who struggle to help those with TSC.

A volunteer for the Tuberous Sclerosis Alliance (TS Alliance) for many years, Reiko is currently in her fifth year as a member of the organization's Board of Directors. She has chaired the local chapter, Atlanta Area Community Alliance, and directed a major fundraising event, Atlanta Step Forward to Cure TSC, a walkathon that has raised nearly \$1 million in the last 10 years. She has also served as the clinic ambassador at the Atlanta TSC Clinic at the Scottish Rite Children's Hospital. Every March for the past several years, Reiko has traveled with other TS Alliance members to Capitol Hill to visit members of the U.S. Senate and House of Representatives to ask for their support of the CDMRP's TSCRP, so she was familiar with the program long before she was nominated and invited to serve on the TSCRP's peer review panel. Reiko says it was wonderful to join the peer review panel and to experience the high regard consumers enjoy working alongside scientists and clinicians who want to hear the perspective of those who are directly affected by TSC. Reiko applauds the researchers and clinicians who are involved with TSC research and the treatment of individuals affected by TSC. However, she also attests to the wealth of information that consumers can bring to the table in terms of personal experience and knowledge, adding significantly to a more complete picture of the disease. Consumers find themselves not only asking questions of the researchers but sharing what they know with the researchers—describing the clinical manifestations of TSC, for example, or explaining the kinds of challenges faced daily by individuals with TSC and their families.

It is fitting that Reiko's leisure time is spent training for and competing in sprint, Olympic, and half-Ironman distance triathlons. Traits essential to Reiko's triathlon performance are also fundamental to advancing scientific research: perseverance, determination, and risk-taking, among others. In no small measure, these traits have been central to Reiko's role as an advocate, heightening awareness of TSC and promoting research to lessen its impact.

Reiko Donato and daughter Alex on the back cover.



"It's been rewarding to experience the TSCRP review process from both sides, as a grant applicant and a reviewer. Having a specialized review panel dedicated to the TSCRP represents a unique opportunity to learn about, evaluate, and promote research on multiple aspects of this rare, but important, disease. The consumer advocates have been an invaluable part of the TSCRP review process. They provide the most relevant, first-hand insights into the impact and priorities of research for TSC patients, which scientists may sometimes lack. The TSCRP has been an outstanding mechanism for promoting understanding and new discoveries for TSC. Research supported by the TSCRP has not only helped lead directly to the development of new treatments for TSC patients, particularly mTOR inhibitors, but also may have therapeutic applications for many other diseases as well."

**Michael Wong, M.D., Ph.D., Washington University School of Medicine,
Scientific Peer Reviewer**



**Encouraging Innovative
Research to Improve the Lives
of Individuals with TSC**

For more information, visit

<http://cdmrp.army.mil>

or contact us at:

usarmy.detrick.medcom-cdmrp.mbx.cdmrp-public-affairs@mail.mil

(301) 619-7071

