CDMRP

Department of Defense

Tuberous Sclerosis Complex Research Program

U.S. Army Medical Research and Materiel Command

Congressionally Directed Medical Research Programs (CDMRP)

HISTORY

The CDMRP was established in 1992 through 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. Since then, the CDMRP has grown to encompass multiple targeted programs and has received over $12.6 billion in appropriations from its inception through fiscal year 2018 (FY18).

APPLICATION REVIEW PROCESS

The CDMRP uses a two-tier review process for proposal evaluation, with both tiers involving dynamic interaction among scientists and consumers. The first tier of evaluation is a scientific peer review of proposals, measuring them against established criteria for determining their scientific merit. The second tier is a programmatic review, conducted by a Programmatic Panel composed of leading scientists, clinicians, and consumers. The Programmatic Panel compares proposals to each other and makes recommendations for funding based on scientific merit, portfolio balance, and relevance to overall program goals.

Tuberous Sclerosis Complex Research Program

VISION

Accelerate high-impact research to improve prevention strategies and treatments and to find a cure for TSC

MISSION

Fund exploratory, pioneering and transformative science that promotes discoveries in TSC, from mechanistic insights to clinical application, by supporting new ideas and investigators for the benefit of Service members, their beneficiaries, and the American public

ABOUT TSC AND THE PROGRAM

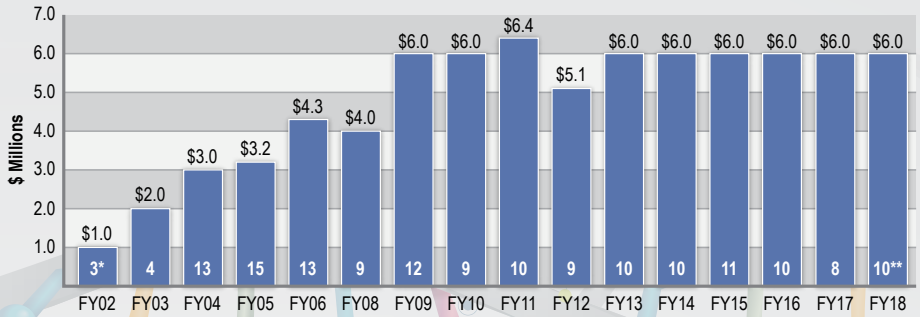
Tuberous Sclerosis Complex (TSC) is a rare genetic disorder that affects approximately 50,000 individuals in the United States and 1 million to 2 million (M) individuals worldwide.

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.

While there is no cure yet for TSC, earlier diagnosis and better treatments are helping those with TSC live healthier and fuller lives.

The TSCRP was established in FY02 when the efforts of TSC advocates led to a Congressional appropriation of $1M. Since then, a total of $77M has been appropriated to the program, including $6M in FY18. Today, the TSCRP is one of the leading sources of TSC research funding in the United States.

FY02-FY18 Congressional Appropriations



*Number of awards
**Anticipated number of awards

Strategic Plan

In 2018 the TSCRP developed a Strategic Plan that specifies the mission of the program, coordination activities with other organizations, goals and how those goals will be addressed by future award mechanisms, how research outcomes will be tracked, and how outcomes will inform future research initiatives.

Details of the Strategic Plan can be found here:
http://cdmrp.army.mil/tscrp/pdfs/TSCRP%20Strategic%20Plan.pdf

Taking into consideration the funding provided by other federal and non-federal organizations, the state of TSC research, and the needs of the scientific community, the TSCRP will continue its efforts to improve prevention and treatment of TSC while working toward the ultimate goal of finding a cure, all for the benefit of Service members, their beneficiaries, and the American public.

STRATEGIC GOALS

- Eradicate tumors associated with TSC
- Prevent epilepsy, improve treatment, and mitigate co-morbidities associated with TSC-related seizures
- Understand the neurodevelopmental features of TSC and reduce their impact

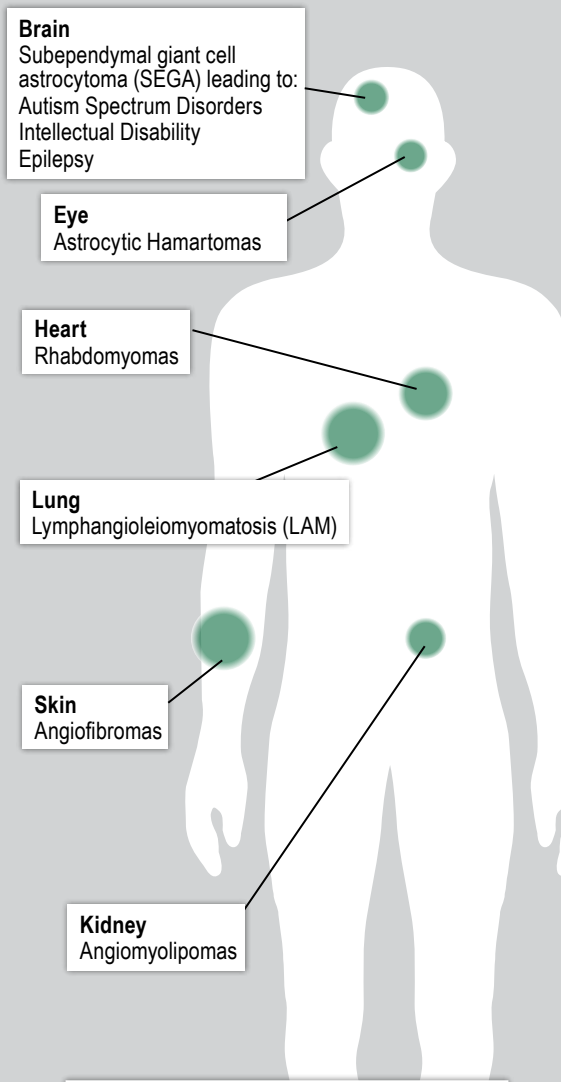
These three strategic goals offer the greatest promise to advancing care and leading to a cure for TSC while responding to the most pressing needs and concerns expressed by patients and families affected by TSC. More detail regarding the range of research areas to be supported by the TSCRP is provided in the table below.

Range of Research Areas

Research Area	Tumor Eradication	Epilepsy Prevention, Treatment, Mitigation	Neurodevelopmental Features of TSC
Mechanisms	• Cells of origin • Roles of the microenvironment • Mechanisms of tumor development	• Mechanisms of epileptogenesis in TSC	• Mechanisms underlying neurodevelopmental disorders • Causes of heterogeneity
Models	• Preclinical models to understand biology and test treatments	• Preclinical models to understand biology and test treatments	• Preclinical models to understand biology and test treatments
Treatments	• Novel treatment targets	• Use of existing therapies • Novel pharmacological agents • Optimal timing for surgery and therapy	• Effective treatments to optimize outcomes - Cognitive - Behavioral - Pharmacological - Biologic
Diagnostic Tools	• Tools to assess treatment response	• Tools to predict onset, severity, and treatment outcomes	• Tools to predict and measure neurodevelopmental outcomes

Disease Manifestations

TSC causes non-malignant tumors in many different organs, primarily in the brain, eyes, heart, kidney, skin, and lungs. It presents itself in a variety of clinical manifestations; however, the aspects of TSC that most strongly impact quality of life are generally associated with the brain—seizures, developmental delay, intellectual disability, and autism.



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

Program Overview

RESEARCH OUTCOMES

From FY02 to FY17, the TSCRP funded 147 awards, totaling $61.7M, with the goal of understanding the causes of the disease, improving prevention strategies and treatment, and finding a cure for TSC. TSCRP-funded research projects have resulted in numerous impactful achievements from basic research to therapeutics, including treatments of various TSC manifestations. Among the outcomes stemming from these awards are 217 publications in high-impact peer-reviewed journals and data sharing at many scientific and patient-focused conferences.

Many TSCRP grants are exploratory in nature, supporting the initial exploration of innovative, high-risk/high-gain, and potentially groundbreaking concepts in the TSC research field with the goal to generate preliminary data for future avenues of scientific investigation. TSCRP-funded investigators have been awarded 113 follow-up research grants from other federal and non-federal funding agencies, including the National Institutes of Health (NIH), the Tuberous Sclerosis Alliance (TS Alliance), the LAM Foundation, and other non-profit organizations totaling over $102M to build on and advance knowledge gained from their TSCRP-funded studies.

TSCRP-funded research resulted in numerous publications and follow-up funding

147
Awards Through FY17

217
Publications

113
Additional Grants

$102M
Additional Funding

TSCRP-FUNDED CLINICAL TRIALS THAT SIGNIFICANTLY REDUCED THE IMPACT OF VARIOUS MANIFESTATIONS OF TSC:

- Topical Rapamycin Therapy to Alleviate Cutaneous Manifestations of TSC: Topical rapamycin was shown to be effective and safe for treatment of TSC-related facial angiofibromas; the treatment significantly improved the appearance of facial lesions.
- JASPER (Joint Attention; Symbolic Play, Engagement, and Regulation) Early Behavioral Intervention in infants with TSC: JASPER treatment showed improvements in the developmental skills of TSC infants.
- The Sirolimus and Autophagy Inhibition in LAM (SAIL): The combination of an autophagy inhibitor, hydroxychloroquine, with sirolimus is well tolerated.

Because TSC is a rare disease, the scientific community focusing on TSC-related research is very small, and early on TSCRP recognized the need to bring new investigators into the field. Although the TSCRP does not offer a funding opportunity for career development, the program has funded a significant number of early-career investigators.

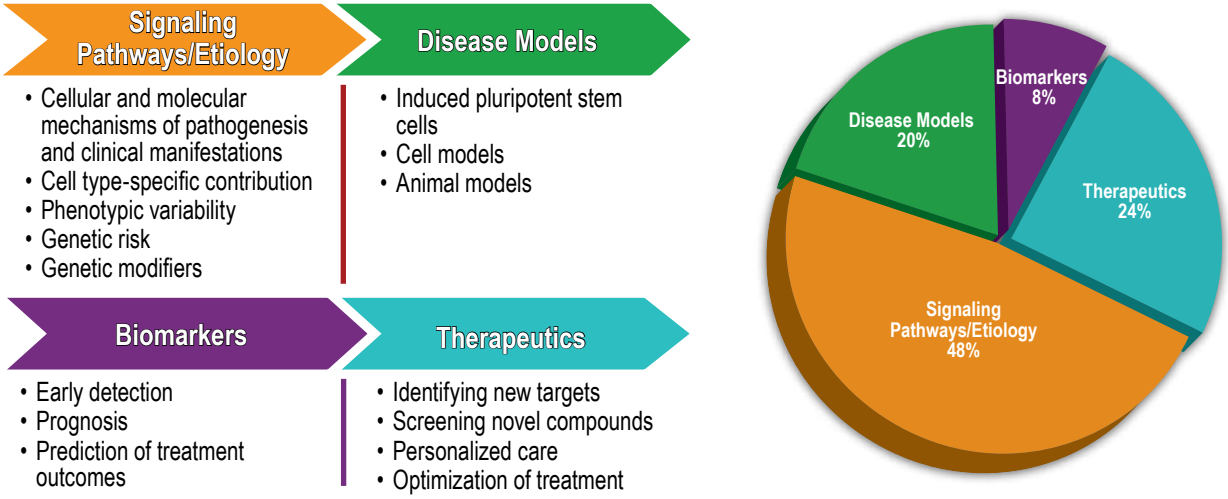
Notably, **56%** of the TSCRP-funded investigators did not have previous funding in TSC research and they received their first such grant from TSCRP.

TSCRP FUNDED RESEARCH AREAS

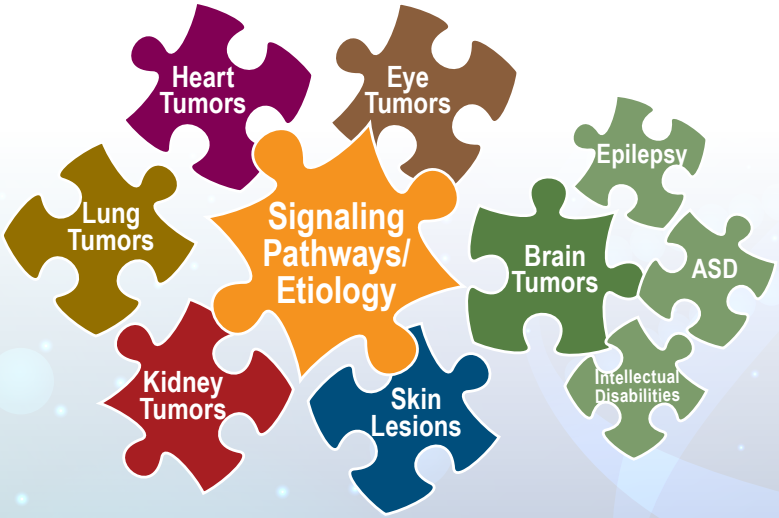
Since its inception in FY02, the TSCRP has supported research along the disease spectrum with the goals of improving TSC prevention and treatments and of finding a cure. This includes research from understanding the signaling pathways and etiology, to developing disease models, to biomarkers, and finally to therapeutics.

Analysis of the most recently funded research projects (FY13-FY17) is reflected in the graph below, indicating the percentage of TSCRP's research investment in each area. Approximately half of the TSCRP funding has been invested in research focused on the most basic biology underlying TSC (signaling pathways and etiology), while a quarter of the funding has focused on developing therapeutics.

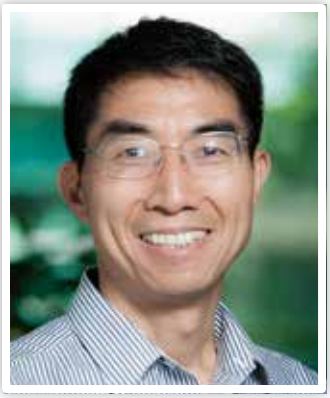
Program Priorities Along the Disease Research Spectrum



Although research in the area of signaling pathways and etiology does not immediately produce or test new treatments, these investigations are critically important pieces of the TSC puzzle because they may reveal molecular targets that can lead to new treatments. Notably, the current first-line treatment for TSC, based on the mammalian target to rapamycin (mTOR) inhibitor rapamycin, stemmed from a TSCRP-funded study to understand the basic mechanisms of this pathway.



TSCRP-funded studies to understand the mechanisms that lead to the various clinical manifestations of TSC, and to develop models to further understand the causes of the disease and test potential treatments, have led to significant advances in the field and to major improvements in patient care. They have identified biomarkers that have led to early treatment of clinical manifestations. Moreover, they have driven the development of new therapeutic approaches to address previously untreatable manifestations of the disease. Examples of successful TSCRP efforts in each of the research areas are presented in the next pages.



Elucidating the Role of the mTOR Pathway in Tuberous Sclerosis

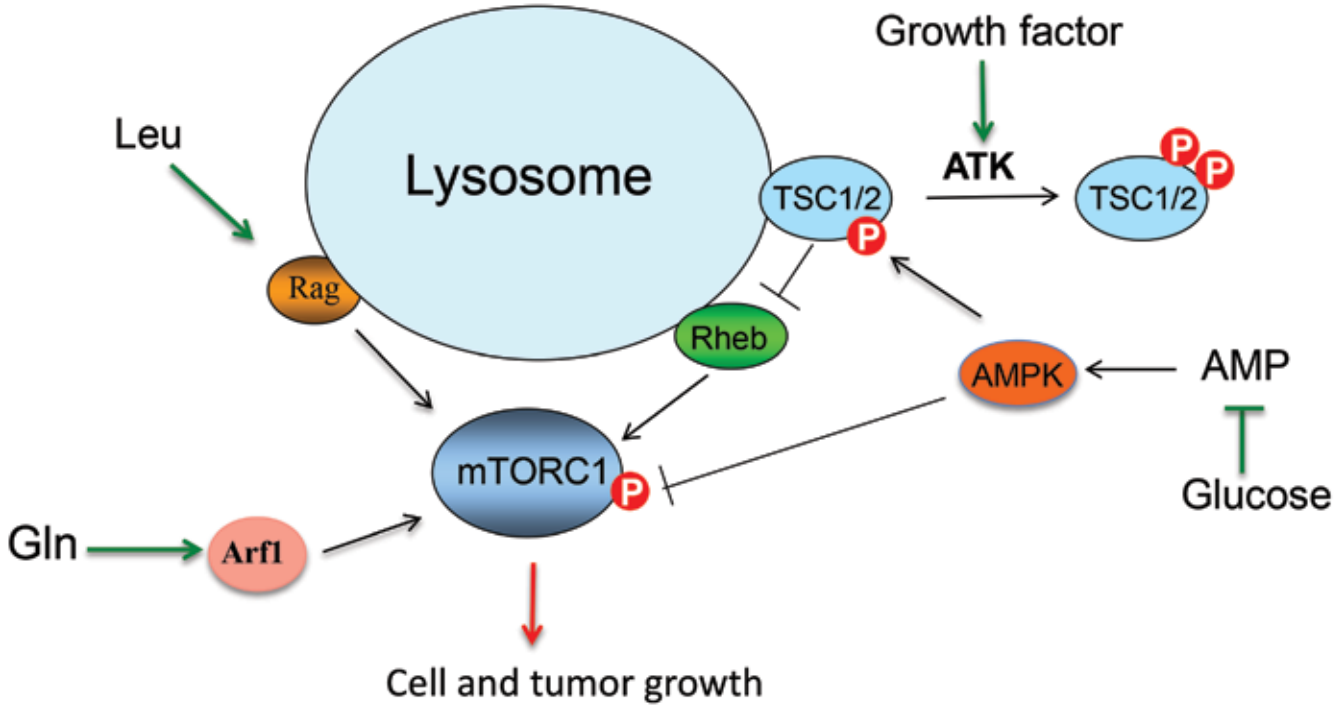
Kun-Liang Guan, Ph.D., University of California, San Diego

Over the span of a decade, Dr. Guan has received six awards from the TSCRP to study the relationship between TSC and the mTOR. The results of his research have significantly advanced the field of TSC, defining TSC1 and TSC2 as the key upstream regulators of mTOR, and have helped identify potential drug targets for the treatment of TSC.

With funding from an FY04 Concept Award, Dr. Guan showed that functional TSC proteins work together to affect mTOR signaling, leading to significant consequences when one of these proteins was rendered inactive by mutation as can be the case in TSC disease.

Dr. Guan received two FY05 Concept Awards, the first of which led him to realize that TSC1 regulates TOR complex 2 (TORC2) indirectly through the TORC1/S6k pathway. This research was among the earliest to show TSC1 regulation of TORC2, which then led to a new direction in mTOR research aimed at understanding the role and mechanisms by which TSC1 regulates TORC2. His second project determined that, in a cell experiencing metabolic starvation, AMPK phosphorylates TSC2 to inhibit the mTOR pathway, thus preventing unregulated cell growth. Dr. Guan demonstrated that AMPK stabilizes p53, another protein required for programmed cell death in cells lacking functional TSC2 proteins. These results explained why TSC-deficient cells were more susceptible to misregulated p53 activation, causing the increased likelihood of tumor growth in patients with TSC disease.

Regulation of mTORC1 by Upstream Signals



Dr. Guan also established that the Bnip3 protein directly binds Rheb, inhibiting its ability to activate TORC1. This interaction mediates the inhibitory effect of hypoxia (low oxygen levels) on mTOR signaling. This research, a result of Dr. Guan's FY06 Concept Award, identified Bnip3 as a tumor suppressor that inhibits the mTOR pathway, leading to the inhibition of cell growth in hypoxic conditions.

Continuing his studies with the support of an FY08 Idea Development Award, Dr. Guan identified the mechanism by which recombination-activating gene (Rag) GTPase regulates both TORC1 activation and the crosstalk between the mTOR and cAMP-PKA pathways. This project also produced the first three-dimensional structure of a GTPase dimer. Structural analysis resulting from this finding has led to further investigations by others in the field into the role of Rag proteins in cellular signaling.

His FY12 Idea Development Award allowed Dr. Guan to build on the findings from his FY08 Award. Here his findings showed that glutamine activates mTORC1 in a Rag-independent mechanism, with the Arf1 GTPase protein playing a key role. Furthermore, he showed that a nemo-like kinase disrupts Rag GTPase activity, thereby inhibiting mTORC1 lysosomal localization and activation during osmotic and oxidative stress.

Supported by TSCRP funding, Dr. Guan has identified and characterized many of the key regulators in the mTOR pathway, significantly advancing our understanding of TSC's role in this pathway. We are optimistic that this work lays the foundation for new therapeutic targets that will be used in the treatment of TSC.

http://cdmrp.army.mil/tscrp/research_highlights/15guan_highlight

IN THE PIPELINE

Genetic Contributors to TSC Severity

Vinodh Narayanan, M.D., Translational Genomics Research Institute (TGen)

Variations in phenotype within a family are known as intra-familial phenotypic variability (IPV). In TSC, it is not uncommon to see families wherein different individuals carrying the same TSC gene mutation exhibit varying levels of phenotypic severity. Dr. Narayanan believes that IPV in TSC may occur when there are variations in modifier genes, which impact the TSC gene mutation's effects on the mTOR pathway, or when there are quantitative differences in gene expression in this study. He is studying parent-child pairs with the same TSC gene mutation, but in which the parent is mildly affected and the child severely affected. This allows him to identify the other genetic changes that account for the differences in disease severity. The ultimate goal is to develop a blood-based molecular profile that will help predict disease severity in a given patient and help select patients for pre-symptomatic treatment.

Modeling TSC and LAM Using Patient-Derived Induced Pluripotent Stem Cells

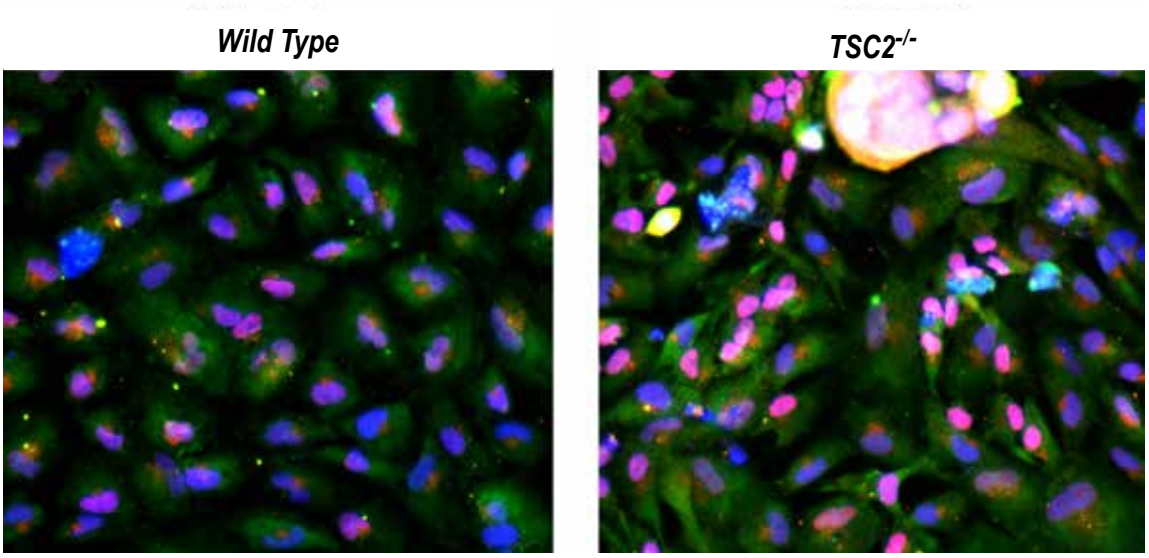
William L. Stanford, Ph.D., Ottawa Hospital Research Institute and University of Ottawa, Ottawa

Scientists often study disease by growing cells isolated from patient tissue biopsies. These cells often contribute to our understanding of the basic mechanisms of disease initiation and progression. However, a major limitation in better understanding TSC and its associated tumors is that tissue biopsies from TSC patients are rare, particularly from the brain or lung. Moreover, when biopsies are isolated from TSC patient tumors, scientists have generally been unable to grow the patient cells in culture.

With support from an FY13 Idea Development Award, Dr. Stanford overcame this limitation using a two-pronged approach: Deriving stem cells from TSC patient skin cells and engineering TSC patient mutations into the TSC2 gene in normal stem cells. Using this strategy, he and his team have studied models of the TSC-related lung disease LAM and the cells that contribute to the neurological manifestations of TSC.

Dr. Stanford used pluripotent stem cells, which can differentiate into any cell types in our body, for his project. Since LAM cells are smooth muscle-like cells, he allowed the TSC2 mutant stem cells to become smooth muscle cells. These engineered cells expressed the same proteins that LAM cells have been shown to express in lung biopsies, demonstrating that they are a good model for LAM cells. Similarly, he allowed the TSC2 mutant stem cells to differentiate into neural stem cells, which then differentiated into the three main cell types in the brain. These TSC2 mutant neurons exhibited abnormal shapes and electrical activity, similar to that found in epilepsy.

Dr. Stanford's work showed that both the lung and neural manifestations of TSC can be modeled. These models can now serve as a launchpad for further research into possible treatments for both LAM and TSC.



Neural stem cell cultures: TSC2 wild type (left) versus TSC2-/- (right). In the TSC2 null cultures, "giant cells" form (yellow image, top of the photo), reminiscent of subependymal giant cell astrocytomas (SEGAs), one of the neural tumors in TSC patients. GFAP is stained green, Sox2 red, with the nuclei in blue.

http://cdmrp.army.mil/tscrp/research_highlights/18stanford_highlight

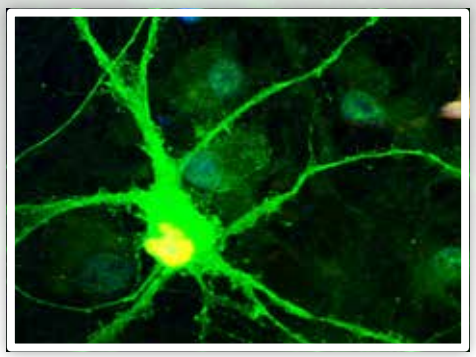
A Novel Model Provides Insight into TSC

Mustafa Sahin, M.D., Ph.D., Boston Children's Hospital, Boston

While an increased likelihood of developing autism spectrum disorder (ASD) is associated with a TSC diagnosis, the underlying molecular mechanisms linking TSC and ASD are poorly understood. TSC is the result of mutations in the TSC1 or TSC2 genes, but multiple factors, including developmental cerebellar abnormalities, have been implicated in the increased incidence of ASD among TSC patients. The absence of critical tools, such as an in-vitro model of TSC, has prevented in-depth mechanistic studies that could lead to a better understanding of the relationship between TSC and ASD and potential novel therapeutics for both.

Dr. Sahin was awarded an FY14 Idea Development Award to develop an in-vitro system for neurodevelopmental diseases such as TSC. The Sahin lab had previously shown that mutation of TSC1 in Purkinje cells in the mouse brain resulted in autism-like behaviors in mice. With this preliminary evidence, Dr. Sahin used induced pluripotent stem cells (iPSCs) from TSC patients, with or without ASD, to generate the first human TSC patient-derived Purkinje cell model. During the course of these studies, Dr. Sahin's team detected downregulation of fragile X mental retardation protein (FMRP) as well as synaptic dysfunction and hypoexcitability in cells derived from TSC patients with ASD.

TSC is a regulator of the mTOR pathway, which is known to play a role in neural stem cell proliferation. Based on this connection, Dr. Sahin decided to investigate the mTOR in depth in his new in-vitro model. His results showed the mTORC1 pathway was hyperactivated in TSC patient-derived Purkinje cells. He went on to show that rapamycin, an inhibitor of the mTOR pathway, could partially rescue the TSC patient-derived Purkinje cells' deficits in differentiation, synaptic dysfunction, hypoexcitability, and the downregulation of FMRP.



Human Purkinje cell in culture

The limited accessibility to human nervous system tissues has been a major barrier to TSC and ASD research. Dr. Sahin's in-vitro model utilizing human iPSCs will help to eliminate that barrier and may help to identify and validate novel therapeutic targets for TSC and TSC-associated ASD.

http://cdmrp.army.mil/tscrp/research_highlights/18sahin_highlight

IN THE PIPELINE

Daniel Vogt, Ph.D

John Rubenstein, M.D., Ph.D

A Mouse Model of TSC1 Mutations' Role in Neuronal Development

John Rubenstein, M.D., Ph.D., University of California, San Francisco

Dr. Rubenstein and his team are creating a mouse model with the same TSC1 mutations found in TSC patients to elucidate the role of TSC1 in the development and function of subtypes of cortical neurons. Studying this model has the potential to provide insight into the variability of neurological problems across the spectrum of patients with TSC and may allow for a more thorough understanding of how mutations in this gene may lead to tumors, seizure disorders, and ASD.

Defining Early Markers of Autism in Infants with TSC

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

Nearly 60% of all children with TSC also exhibit 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.

With support from an FY10 Clinical Research Award, Dr. Nelson, in collaboration with Dr. Shafali Jeste (featured on page 13), 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 4, they 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. They found that children with TSC had slower face processing than typically developing children, and face processing was particularly slow in the subset of those children with both TSC and ASD diagnoses. These findings are consistent with what might be expected among children with impairments in social communication. In a second study, they used high-density scalp EEG to compare brain rhythms in infants with and without TSC. Through these analyses, they discovered that there were significant differences in EEG frequencies between the two groups as early as 20 to 24 months of age, and they hypothesized that frequency differences may distinguish ASD in infants with TSC. These studies led to the identification of early markers of ASD in children with TSC prior to clinical diagnosis and allowed for effective intervention strategies to improve the child's developmental outcomes and future well-being.

http://cdmrp.army.mil/tscrp/research_highlights/14nelson_highlight

http://cdmrp.army.mil/tscrp/research_highlights/18jeste_highlight

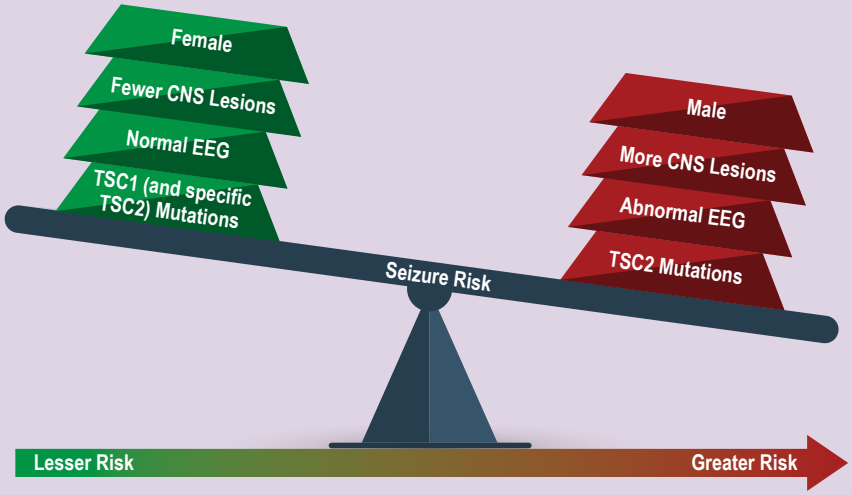
EEG sensors on the scalp of a young child affected by TSC.

IN THE PIPELINE

Scoring Epilepsy Risk in TSC

Laura Farach, M.D., University of Texas, Houston

Even though epilepsy occurs in 80% to 90% of individuals with TSC, we currently cannot predict which individuals will develop seizures. Clinical biomarkers that identify who will develop seizures are necessary for early treatment and prevention. Dr. Farach is developing an epilepsy risk prediction model based on known clinical, demographic, and genetic risk factors for epilepsy in TSC. To accomplish this goal, she will evaluate genetic differences (modifiers) that put patients with TSC at high or low risk of developing seizures. This project has the potential to lead to the development of a predictive model that can provide a personalized risk of seizures.



IN THE PIPELINE

A Non-Invasive Method for Classifying Malignant Kidney Tumors

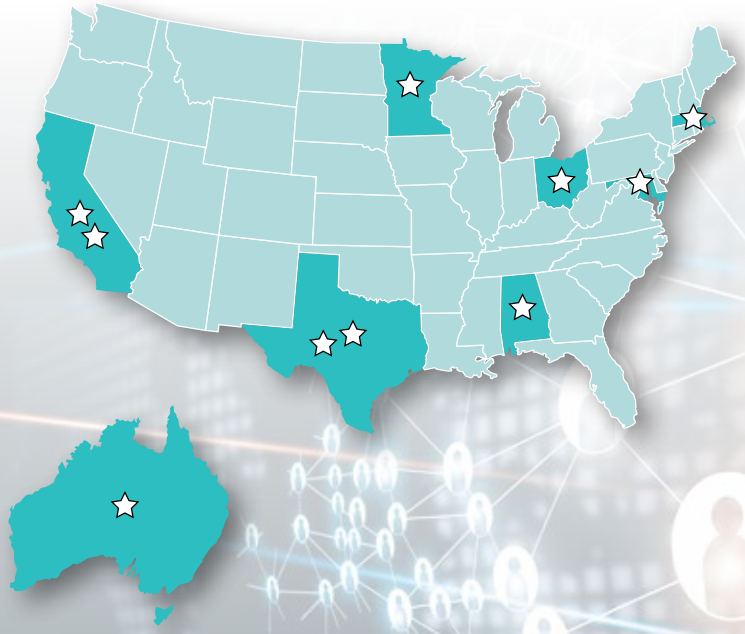
Adam S. Feldman, M.D., M.P.H., Massachusetts General Hospital, Boston

One of the symptoms of TSC is an increased risk of tumor growth (both cancerous and non-cancerous) in the kidneys. Non-cancerous tumors, called angiomyolipomas, can sometimes look exactly like cancerous tumors on imaging of the kidneys, resulting in unnecessary biopsies and/or surgeries. Dr. Feldman is investigating magnetic resonance spectroscopy, a non-invasive technique used to evaluate metabolites in tissues, as a novel method to evaluate suspicious kidney tumors in patients with TSC. This research may provide the tools to make a non-invasive distinction between cancerous and non-cancerous kidney tumors and has potential to significantly impact TSC patient care by decreasing the use of invasive procedures such as renal mass biopsy and/or surgery.

Topical Rapamycin Therapy to Alleviate Cutaneous Manifestations of TSC

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

One of the many manifestations of TSC is the development of angiofibromas (red bumps on the face, especially on the nose and cheeks) that can slowly enlarge and cause significant textural changes to the skin. Although not life-threatening, they cause notable disfigurement and are one of the most significant features to impact the life of people with TSC. Currently, there is no effective method for preventing or permanently removing the angiofibromas. mTOR inhibitors, such as rapamycin, are used as a first line of treatment for TSC. However, oral delivery of rapamycin has side effects that inhibit its usefulness in treating the skin symptoms of TSC. Knowing how beneficial mTOR inhibitors have been in TSC therapeutics, Dr. Koenig developed a topical rapamycin therapy that could be used in patients who were not candidates for oral therapy or could be combined with oral therapy to improve efficacy. With support from an FY10 Clinical Research Award, Dr. Koenig established a multicenter clinical trial with 10 sites*, including one in Australia, allowing her team to successfully formulate and optimize the drug and controls and test them. The formula was well-tolerated by patients and shown to be efficacious, with dose-dependent improvement of symptoms. Since angiofibromas in individuals with TSC represent a major quality-of-life concern, the impact of this study is considerable. Dr. Koenig plans to perform a follow-up study to confirm these exciting results with the ultimate goal of petitioning the U.S. Food and Drug Administration (FDA) for a formal indication for the treatment of facial angiofibromas.



*(1) University of Texas Health Science Center at Houston
(2) Clinic Without Walls, Minnesota Epilepsy Group
(3) University of Alabama Birmingham
(4) Texas Scottish Rite Hospital for Children and University of Texas Southwestern Medical Center
(5) Massachusetts General Hospital
(6) Cincinnati Children's Hospital
(7) Kennedy Krieger Institute and Johns Hopkins University
(8) Children's Hospital University of California Los Angeles
(9) Children's Hospital and Research Center at Oakland
(10) Sydney Children's Hospital

http://cdmrp.army.mil/tscrp/research_highlights/18koenig_highlight

A Promising Early Intervention for TSC-Linked Autism in Infants

Shafali Jeste, M.D., University of California, Los Angeles

Autism occurs in approximately one-half of children with TSC but is often diagnosed late due to the frequency of other medical and neurodevelopmental challenges early in infancy, making early interventions a significant challenge. However, because infants are diagnosed with TSC before the onset of autism, there is tremendous opportunity in studying signs of autism early in infancy to guide early interventions.

Dr. Jeste received an FY13 Pilot Clinical Trial Award to follow up on a previous TSCRP-funded trial, which demonstrated that infants with TSC who develop autism show delays in social and communication skills as early as 6 months of age. Dr. Jeste designed the pilot clinical trial to improve social skills in infants with TSC before they develop autism. The study investigators used a well-validated behavioral intervention, JASPER (Joint Attention, Symbolic Play, Engagement, and Regulation), developed by Dr. Connie Kasari, a collaborator and expert in behavioral intervention for autism. The team examined the effects of this intervention on various behavioral outcomes, as well as brain function in infants with TSC, to determine if brain changes might predict changes in behavior. They found that infants showed improvements in their developmental skills after JASPER and made substantial gains in their development over that seen in infants not receiving this targeted early intervention. This pilot clinical trial was the first study of early intervention in TSC, and its successes have since led to a large NIH-funded, randomized control trial of JASPER in infants with TSC. (NICHD R01, PI Jeste, www.JETSstudy.org)

http://cdmrp.army.mil/tscrp/research_highlights/18jeste_highlight

IN THE PIPELINE

Supporting the Immune System to Fight Tumors

Caroline Le Poole, Ph.D., Northwestern University, Chicago

Dr. Le Poole plans to apply concepts used in the cancer field to use the body's own immune cells to eliminate tumors that develop in TSC. This project aims to test genetically modified T cells (white blood cells that are involved in protecting the body against foreign invaders and eliminating abnormal cells) in mice to confirm whether they are a safe and effective treatment of TSC tumors. Dr. Le Poole plans to confirm whether T cell treatment is effective even in advanced stages of disease, and in combination with rapamycin treatment. Upon completion of this project, Dr. Le Poole and her team will submit an Investigational New Drug application to the FDA for approval of a clinical trial to apply a patient's own genetically modified immune cells so that they will recognize and kill tumor cells in TSC.

A Perspective of Strength and Optimism on the Treatment and Care of TSC Patients

Shelly Meitzler, TS Alliance, Consumer Peer Reviewer

As the parent of three children, two with TSC, it is my responsibility to educate and foster a better understanding of TSC and the ongoing challenges we face daily. I am the voice for my daughter, who, due to significant developmental delays resulting from TSC, does not have a voice of her own. I am my son's voice, for he is too young to speak. I have no control over what tomorrow will bring, but I can be an active part of our future. TSC is a significant part of our life but does not define my family.

I first learned of the TSCRP in 2006, when advocating for research in Washington, DC. My children, as well as many other families, have benefited from the outcomes of the research funded by TSCRP. I was nominated by the TS Alliance to serve as a consumer reviewer on the TSCRP peer review panel in 2016. My experience with the TSCRP has been rewarding, enlightening, and empowering. On-site review meetings have been a particular representation of how dedicated the research community is to TSC research. My voice and experience representing the community were appreciated and respected, and it has been an honor to be afforded this opportunity. I wish to express my deepest gratitude for the passion and dedication from the CDMRP's staff who devote their time to this cause. The TSC community is fortunate that there is a dedicated commitment from the scientific community to understanding the pathogenesis and manifestations of TSC, with the goal of improving the lives of individuals with TSC. This relationship has reinforced my determination and passion to continue to advocate for vital funding for TSC.

"By participating in the panel, I help ensure the TSCRP funding strategy is complementary with, and not duplicative of, the TS Alliance's research strategy, and vice versa. Along with TSC consumers on the Programmatic Panel, I also help ensure the focus and priorities of the TSCRP are driven by the needs of individuals affected by TSC. Because tuberous sclerosis complex causes tumors, autism, and epilepsy, among other things, what researchers learn from their TSCRP-funded work will help us understand and find treatments for related disorders. The TSCRP has already impacted the lives of those living with TSC by funding development of animal models and clinical studies for new therapies. The potential impact of the TSCRP is almost limitless, and I'm fortunate to help contribute to this important program."

Steven Roberds, Ph.D., TS Alliance, Programmatic Panel Member

"Now looking back after serving on multiple study panels, my observations are that TSCRP has helped galvanize the TSC research community. The topics selected for emphasis in the Program Announcements tend to capture the more relevant issues in TSC clinical care. The TSCRP has been invaluable both in the implementation of basic biology to the clinic and recruiting junior investigators to the field. The willingness of the TSCRP to explore various grant mechanisms along with the commitment of the consumers, basic scientists, and clinicians are what make this program so special."

Dave Viskochil, M.D., Ph.D., University of Utah, Scientific Peer Reviewer

and Consumers Working Together

"My early research, funded by TSCRP, led to discovery of a novel mechanism deregulated in TSC-LAM and paved the way toward a clinical trial. I am honored and delighted to serve on the TSCRP Programmatic Panel together with distinct experts in the field and representatives from TSC patients' families. Each year TSCRP advances high-impact research and brings us closer toward finding a cure for TSC."

Vera Krymskaya, Ph.D., University of Pennsylvania, Perelman School of Medicine, Programmatic Panel Member

"The TSCRP has been invaluable for promoting research and clinical advances in TSC. My own research on epilepsy in TSC benefited immensely from a TSCRP grant almost 10 years ago. Having now served on the Scientific Peer Review and Programmatic Panels, I have further witnessed how the TSCRP has directly driven scientific progress in the field, leading to new clinical approaches and treatments for TSC patients."

Michael Wong, M.D., Ph.D., Washington University in St. Louis, Programmatic Panel Member

In Memory of Keith Hall: Making a Difference in TSC

As an individual with TSC, Keith Hall dedicated his life to helping others living with the same disorder. He was diagnosed at the age of 12 when his doctor determined that his facial angiofibromas were caused by TSC. In 1996, he began volunteering with what is now known as the Tuberous Sclerosis (TS) Alliance and went on to become a leading advocate for the TSC community. As a participant in the TS Alliance's annual "March on Capitol Hill," Keith learned about the role of the TSCRP in providing research funding dedicated to understanding the disorder and developing prevention and treatment strategies in the hopes of finding a cure. He advocated for continued funding for the TSCRP and later served as a Consumer Peer Reviewer for the program.

In July 2017, Keith passed away after a battle with cancer. As described in the TS Alliance's *Perspective* magazine, he left behind "a legacy of caring for others and inspiring hundreds of children, teens, and adults with TSC to embrace life and live it to the fullest, despite any challenges they may face." It was his personal experience with these challenges that gave him a unique perspective when reviewing grant applications – a perspective that he was able to share with other reviewers and which served as a reminder of the individuals living with TSC who are hoping for meaningful discoveries to help understand, treat, and one day cure the disorder affecting their lives.

Keith encouraged individuals affected by TSC to become involved. Everyone can help make a difference. Keith's major goals included addressing the needs of adults with TSC and increasing participation in the TSC Natural History Database – an effort initiated with funding from the TSCRP and now sponsored by the TS Alliance to document the impact of the disease on a person's health over his or her lifetime.

In the months since his passing, Keith has been remembered for his compassion and his caring for others, his kindness, and his tireless efforts, even in his last weeks, advocating for the TSC community. He offered encouragement to others living with TSC and their loved ones, and he served as an inspiration to so many of those affected by this disorder. Those fortunate enough to have known him lost a committed friend and passionate supporter. His impact on the TSC community will not be forgotten.

Encouraging innovative research to improve the lives of individuals with TSC

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