TUBEROUS SCLEROSIS COMPLEX RESEARCH PROGRAM:

A Competitive, Peer-Reviewed Department of Defense Grant Program

"My son Jason has TSC and is now in his 50s. He started having grand mal seizures when he was 5 months old after we transferred to my Naval assignment in Guam. Later, it became clear he had cognitive challenges. Jason also suffered from disfiguring facial angiofibromas caused by TSC, which at the time required a painful skin-resurfacing procedure known as dermabrasion. In the 1990s he lost a kidney due to TSC and then had brain surgery to help control his seizures. All these are reasons why the DoD's TSC Research Program is so critically important for this community. In fact, this research recently led to the FDA's approval of a topical gel we can use to treat Jason's facial angiofibromas in the future, giving him a pain-free option. I have no doubt further research from the TSCRP will result in additional treatments that will also directly benefit Jason."

VAN STEWART, CDR, USN (RET)

The Stewart Family

FY2025 Request: Support the continuation of the Tuberous Sclerosis Complex Research Program (TSCRP) at the Department of Defense (DoD) at $10 million.

For FY2024 the TSCRP had tremendous bipartisan support in the House (191 Dear Colleague Letter signers) and Senate (41 Dear Colleague Letter signers).

TSC Facts: Tuberous sclerosis complex (TSC) is a genetic disorder that can cause tumor growth in all of the body's vital organs. Symptoms commonly include seizures, kidney failure, brain and lung tumors, autism spectrum disorder, and severe learning disabilities. TSC occurs in approximately 1:6000 live births. Because two-thirds of TSC cases result from a spontaneous genetic mutation, TSC can affect any family. Critical cellular pathways disrupted in TSC are shared with other diseases, including cancer, lymphangioleiomyomatosis (LAM), and diabetes. Approximately 40% of women with TSC will develop LAM, and many more may develop cysts without knowing they may progress to LAM. LAM is a systemic neoplasm that results in cystic destruction of the lung. The TSC Alliance has funded more than $37 million to further basic, clinical, and translational research as part of this private/public partnership.

Military Value: The cellular pathways involved in TSC are also activated by traumatic brain injury, an all-too-common occurrence in military personnel.

- TSCRP-funded research has led to the development of mouse models used in research on both TSC and traumatic brain injury.
- Seizures often result from traumatic brain injury in military personnel, and approximately 85% of individuals with TSC experience seizures during their lifetime.
- TSC research may lead to new interventions for preventing the development of seizures in high-risk military and civilian individuals.
- TSCRP-funded studies are also relevant to autism spectrum disorder, diabetes, cancer and other disorders that affect service personnel and their families.

Ensuring the health of military families improves the effectiveness of our fighting forces.

The TSC Alliance improves quality of life for everyone affected by tuberous sclerosis complex by catalyzing new treatments, driving research toward a cure and expanding access to lifelong support.

Competitive Awards with No Duplication of NIH Funding: All TSCRP grants are awarded on a competitive basis. An NIH program officer participates in the vision setting of TSCRP funding opportunities each year, and a DoD TSCRP officer participates in a trans-NIH meeting with program officers from all TSC-related NIH institutes. These practices ensure that TSCRP and NIH funds go to distinct, non-overlapping research projects.

More than Two Decades of Progress: Since its inception in FY2002, the TSCRP has supported research that is paving the way to cures and treatments for individuals with TSC and those with related disorders.

- **Hallmark achievement:** TSCRP-supported research that examined the role TSC genes play in cell growth and proliferation—specifically in controlling the mechanistic Target of Rapamycin (mTOR) signaling pathway in cells. This research rapidly led to clinical trials, resulting in the first drug approved by the FDA specifically for treatment of individuals with TSC.
- **Discovery of inflammation in the brain** in mice with mutations in TSC genes by an FY2011 award. This finding opens up potential new ways of treating TSC. Also, brain inflammation occurs in other disorders such as traumatic brain injury and Alzheimer's disease, enabling research impact to be shared among many disorders.
- **Effectiveness of a behavioral intervention strategy, JASPER, to improve outcomes in children with autism** is being tested in a large, NIH-funded clinical trial. This breakthrough trial would not be possible without data obtained from an FY2010 TSCRP clinical research award to define early autism predictors in TSC and an FY2014 TSCRP award for a pilot clinical trial.
- **Two TSCRP awards in FY2012 and FY2015** enabled generation of a potential approach for gene therapy of TSC, which has shown promising results in a mouse model of TSC tumors in the brain. Multiple companies are now working on TSC gene therapy because of the success of these early studies.
- **In 2022, the first rapamycin topical gel was FDA-approved** for treatment of facial angiofibromas in TSC. TSCRP funding in FY2010 funded a clinical trial of topical rapamycin which demonstrated effectiveness of this approach.
- **Two FY2023 awards address near-term needs of the TSC community,** one to understand the impact of caregiver wellbeing on behavioral and other neuropsychiatric issues in those with TSC for whom they are caring, and another to measure the risk and impact of lung and renal complications in women with TSC of child-bearing age and the impact of pregnancy. The occurrence of lung and kidney issues during pregnancy have been observed, but no quantitative data exists to guide healthcare at this critical point for mother and baby.
- **Creation of the first comprehensive natural history clinical database for TSC,** designed to understand how TSC progresses throughout a lifetime. To date 2,693 participants are enrolled at 22 sites. The database has helped recruit individuals for clinical trials and has been used to answer research questions.

None of this progress would have been possible without the financial support provided through the TSCRP, and quality research projects far outpace available funding.

FY2025 Request Summary: Funding for more innovative research is needed to prevent the manifestations of TSC and improve diagnosis and treatment of TSC and related diseases to reduce the healthcare burden imposed by this multi-organ disorder. In FY2023, 12 applications were selected for funding, but an additional 17 applications scored as Outstanding or Excellent were not funded (totaling $8.6 million in unfunded research). An appropriation of $10 million would enable funding of additional high-scoring applications.

A continuation of funding for the TSCRP is needed to accelerate development of new, targeted and more effective therapies, to understand the biology underlying the wide variation in severity of manifestations among individuals with TSC and LAM, to support discovery and validation of biomarkers needed to develop clinical trials for preventative treatments, to pilot a newborn screening assay, and to attract new researchers into this field to develop innovative approaches for translating basic scientific discoveries into clinical treatments.

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About tuberous sclerosis complex

TSC causes tumors to grow in different organs and can impair their function, primarily the brain, heart, kidneys, skin and lungs.

TSC is the leading genetic cause of epilepsy.

UP TO 1 MILLION PEOPLE WORLDWIDE HAVE TSC.

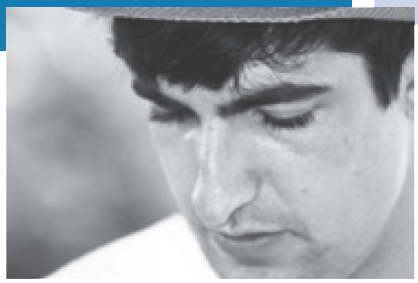
85%

OF PEOPLE WITH TSC EXPERIENCE SEIZURES, OF WHICH 40% HAVE MEDICINE RESISTANT EPILEPSY.

TSC occurs in all races and ethnic groups and in both males and females.

About 1/3 of people with TSC inherit the disease, while the other 2/3 result from a spontaneous mutation.

Approximately 50,000 in the United States have TSC.



TSC affects an estimated 1 in 6,000 live births.

Autism occurs in about 50% of people with TSC.

TSC impacts no two people in the same way – even identical twins.

Since 1984, the TSC Alliance has funded more than **$37 million** to further basic, translational and clinical research. But much more research is needed to identify new treatments and, one day, a cure.

Currently, there is no cure for TSC.

About the TSC Alliance

The TSC Alliance® is an internationally recognized nonprofit that does everything it takes to improve the lives of people with tuberous sclerosis complex (TSC). We improve quality of life for everyone affected by TSC by catalyzing new treatments, driving research toward a cure and expanding access to lifelong support.

Founded in 1974, the TSC Alliance will celebrate 50 years of progress and promise throughout 2024 by highlighting milestones and accomplishments from the past while also looking forward in our quest to create a future where everyone with TSC has what they need to live their fullest lives.

TSC is a rare genetic disease that causes tumors to grow in different organs, from the brain and heart to the lungs and kidneys to the skin and eyes. Nearly one million people worldwide have TSC. Some live independently with few symptoms while others require complex care.

We are a source of hope and connection for all affected by TSC. We drive research, increase care quality and access and advocate with and for people affected by the disease. Through our collaboration and partnerships, we've advanced FDA-approved treatments and created support systems around the world so no one has to navigate TSC alone.

The TSC community is our strongest ally. With the power of families and the support of donors, volunteers, researchers, educators, industry partners and more, we can create a future where everyone with TSC can realize their full potential—no matter how complex their journeys are to get there. **Join us at tscalliance.org or contact us at info@tscalliance.org.**

What differentiates the TSC Alliance

The TSC Alliance is a model nonprofit in the rare disease research and support sector. Here are some ways we have demonstrated our unique ability to reach our constituents and impact their quality of life.

Facilitated
4,278
peer-to-peer connections in 2023, helping to reduce the stress and anxiety of a TSC diagnosis and provide ongoing support.

Established and built the first TSC Natural History Database, as well as a TSC Biosample Repository, and brought together a consortium of researchers who completed the first preventative clinical trial in both TSC and epilepsy.

812
million
media impressions in 2023 dramatically increasing the visibility of TSC.

Raised
$29
million
from more than 1,000 engaged donors and community members since launching the Unlock the Cure research funding campaign in 2011, thereby advancing TSC research.

Galvanized the TSC community, and through their advocacy efforts, the Department of Defense Congressionally Directed Medical Research Program has appropriated
$113 million
toward TSC research since 2002.

Grew our volunteer base from
95 to more than **2,500**
volunteers, highlighting our community-building expertise.

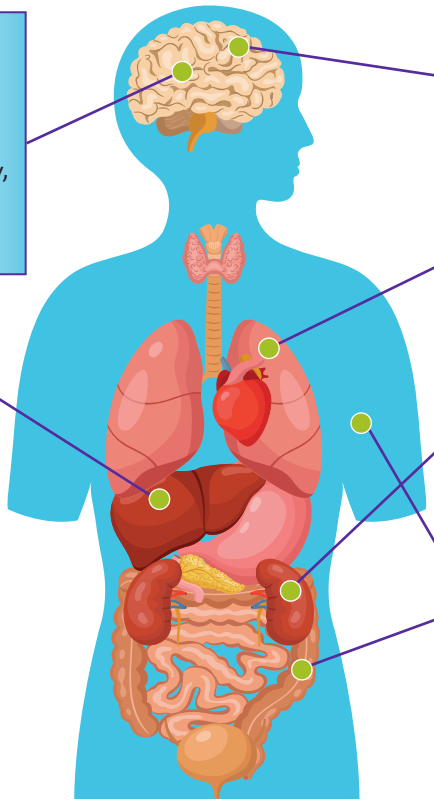
GreatNonprofits 2023 Top-Rated Nonprofit · Platinum Transparency 2023 Candid. · BBB Accredited Charity · Charity Navigator Four-Star

TSC Genes Lie at the Heart of a Network of Common Human Diseases

Neurology
Epilepsy, Infantile Spasms, Traumatic Brain Injury, Autism Spectrum Disorder, Aggression Disorders, Speech & Language Delay, Cognitive Impairment, Eating & Sleep Disorders, Communication Disorders, Anxiety, Depression, Attention Deficit Disorder, Alzheimer's Disease, Parkinson's Disease, Huntington's Disease

Metabolic Diseases
Non-Alcoholic Fatty Liver Syndrome, Cardiovascular Disease, Type II Diabetes

Oncology
Malignant & Non-Malignant Brain Tumors, Megalocephaly, Skin Growths, Non-Malignant Heart Tumors, Irregular Pulmonary Growths, Retinal Lesions, Renal Cell Carcinoma



mTORopathies
Focal Cortical Dysplasia, Polyhydramnios, Megalencephaly, Symptomatic Epilepsy Syndrome & Hemimegalencephaly

Pulmonology
Lymphangioleiomyomatosis (LAM)

Nephrology
Renal Cysts, Polycystic Kidney Disorder, Angiomyolipomas

Autoimmune & Inflammation
Arthritis, Inflammatory Bowel Disease, Colitis, Crohn's Disease

The tuberous sclerosis complex (TSC) genes lie at the heart of a biochemical network that is disrupted in a diverse array of common human diseases and health concerns.

Research on TSC has revealed insights and therapeutic targets for numerous other diseases. The genetic mutations that give rise to TSC result in a loss of function in two key proteins: TSC1 and TSC2. These proteins are present in all human cells and function together to inhibit a growth-promoting protein called the mechanistic target of rapamycin or mTOR.

Chronic inhibition of TSC1 and TSC2, for example, is very common in cancer. These defects can also contribute to the development of autoimmune and inflammatory diseases. As a biochemical pathway regulated by insulin and nutrients, the TSC-mTOR pathway is also disrupted in common metabolic diseases, such as obesity and diabetes. Thus, TSC research provides critical insights into a diverse array of other diseases.

Tuberous Sclerosis Complex

Tuberous sclerosis complex (TSC) is a multisystem genetic disorder that causes non-malignant tumors to form in vital organs including the brain, eyes, heart, kidneys, liver, skin, and lungs. TSC is caused by a mutation in either the TSC1 or TSC2 gene. Two-thirds of individuals with TSC have a sporadic genetic mutation, and one third inherit TSC from one of their parents. Individuals with TSC have a 50% chance of passing the condition on to each child.

In addition to multi-organ tumor growth, medical issues associated with TSC include varying degrees of neurological and behavioral issues. These medical problems not only vary between individual cases of TSC but are often complicated by the interdependent nature of behavior and neurology. As a result, the medical problems due to TSC may vary even between two family members (such as siblings) with TSC.

The incidence of TSC is estimated to be 1 in 6,000 live births. At least two children born each day in the United States will have TSC. Approximately 50,000 Americans and 1 million individuals worldwide have TSC, making TSC as common as ALS (Lou Gehrig's Disease) or Duchenne's Muscular Dystrophy.

The TSC Alliance improves quality of life for everyone affected by tuberous sclerosis complex (TSC) by catalyzing new treatments, driving research toward a cure and expanding access to lifelong support.

TSC and Epilepsy/Seizure Disorders

Seizures remain one of the most common neurological features of TSC, occurring in approximately 85% of individuals with TSC.

- Infants are often diagnosed with TSC after they begin having a very serious type of seizure called infantile spasms.
- Some children appear to develop normally until the onset of seizures, causing the loss of developmental milestones previously achieved.
- Older children and adults may develop multiple types of seizures including generalized, complex partial and other focal seizures.
- More than 50% of individuals with TSC who have epilepsy will not respond to standard antiepileptic medications, increasing the likelihood of intellectual impairment.

In addition to TSC-associated epilepsy, inconsistent control of mTOR is an underlying cause of the majority of familial epilepsies associated with focal cortical dysplasia, further demonstrating the importance of the TSC-mTOR pathway in epilepsy.

TSC and Autism Spectrum Disorders (ASD)

TSC leads to more cases of autism spectrum disorder (ASD) than any other single-gene disorder.

- An estimated 40-50% of individuals with TSC have ASD. The rate of ASD in the general population is substantially lower (approximately 1 in 59, or 1.7% of the total population).
- ASD is usually diagnosed in young children between the ages of 2 and 4 years. But in individuals with TSC, the diagnosis of ASD may go unrecognized due to other developmental disabilities.
- Physical abnormalities in brain development that occur in TSC are associated with impaired development of social communication skills.
- Recent animal studies indicate it may be possible to prevent or reverse intellectual disabilities and ASD if treated early.

Importantly, traits of ASD in TSC closely mimic ASD in the general population.

TSC and Cancer

Proteins produced by the TSC genes are key regulators of the mTOR pathway, an important biochemical network involved in the control of cell growth. Therefore, loss of function of these proteins in TSC is associated with uncontrolled growth leading to the development of widespread tumors.

The biochemical pathway affected by the TSC genes is also rendered dysfunctional in more than 50% of human cancers and underlies tumor development, progression and therapeutic resistance. The study of TSC is improving our understanding and revealing new treatment options in cancer.

Opportunities for Prevention of Epilepsy, Autism and Tumors

TSC is most frequently diagnosed in early childhood with the onset of seizures. However, heart tumors are often present in infants with TSC and are often detected by prenatal ultrasound, particularly in the third trimester. At birth, ash leaf-shaped spots on the skin are also a common feature of TSC. Increased recognition of these features has led to more frequent early diagnosis of TSC. Early diagnosis provides opportunities for timely interventions to prevent development of epilepsy, autism and other devastating childhood manifestations, as well as those occurring later in life, such as kidney tumors and LAM.

Biomarkers are needed to predict in advance those individuals with TSC at higher or lower risk of developing each manifestation. For instance, identification of an EEG biomarker before the onset of epilepsy in infants with TSC has led to a clinical trial to determine if a drug called vigabatrin can prevent the development and consequences of seizures.

Successful identification of additional biomarkers and preventative treatments for other features of TSC will undoubtedly spark research to determine if the same biomarkers are equally useful in the general population. This is yet another way in which research in TSC may provide a roadmap for the treatment and prevention of epilepsy, autism and cancer.

TSC Alliance

The TSC Alliance based in Silver Spring, Maryland is an internationally recognized nonprofit that does everything it takes to improve the lives of people with TSC. We drive research, improve quality care and access and advocate for all affected by the disease. The TSC community is our strongest ally. The collaboration of individuals and families, along with the partnership of other organizations, fuels our work to ensure people navigating TSC have support—and hope—every step of the way.

Together, we have raised awareness of TSC, accelerated discoveries that have led to new FDA-approved treatments and created support systems in the United States and around the world to improve TSC care and quality of life. Since 1984, the TSC Alliance has funded more than $37 million to further basic, translational and clinical research. But much more research is needed to identify new treatments and, one day, a cure.

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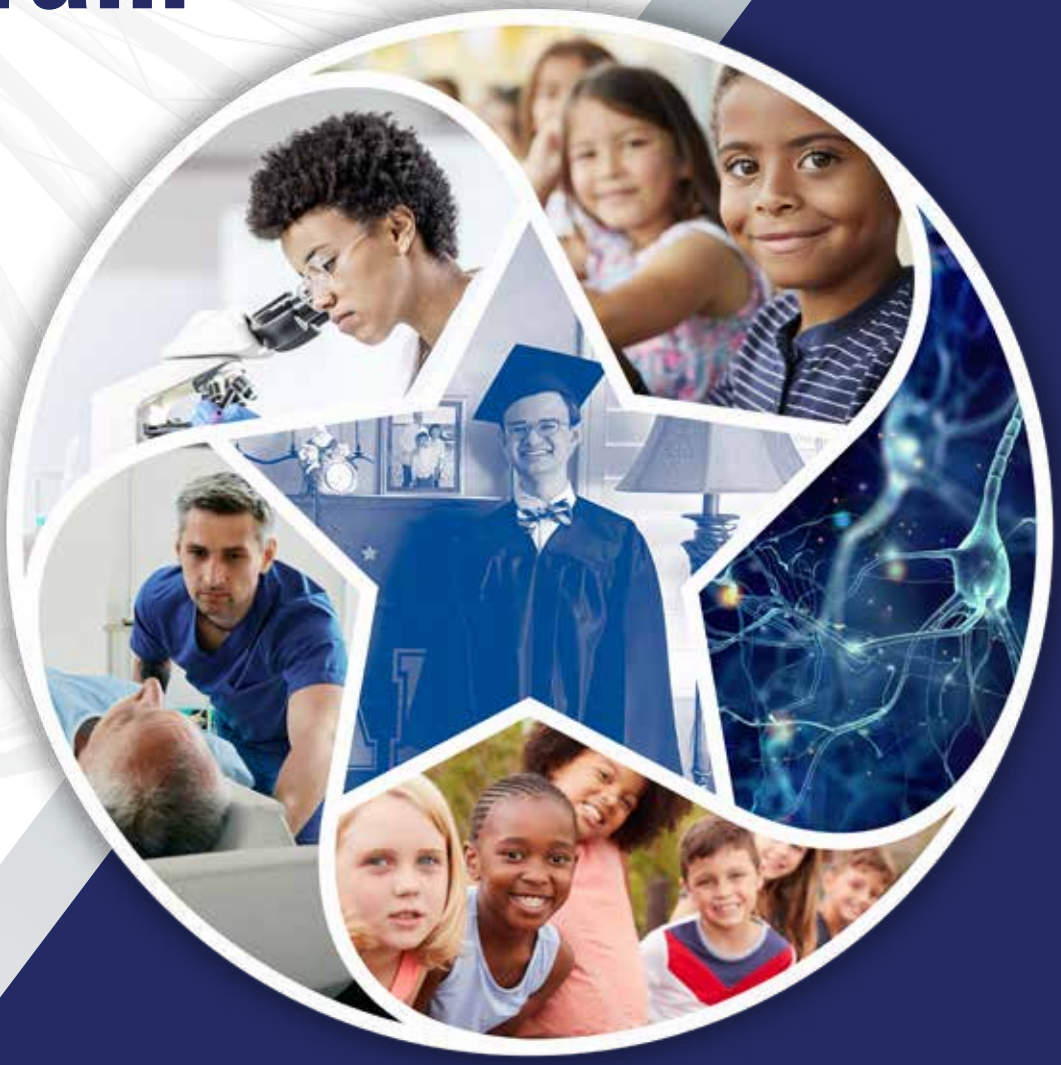
CDMRP
DEPARTMENT OF DEFENSE
CONGRESSIONALLY DIRECTED
MEDICAL RESEARCH PROGRAMS

Tuberous Sclerosis Complex Research Program



Accelerating TSC Research Toward a Cure

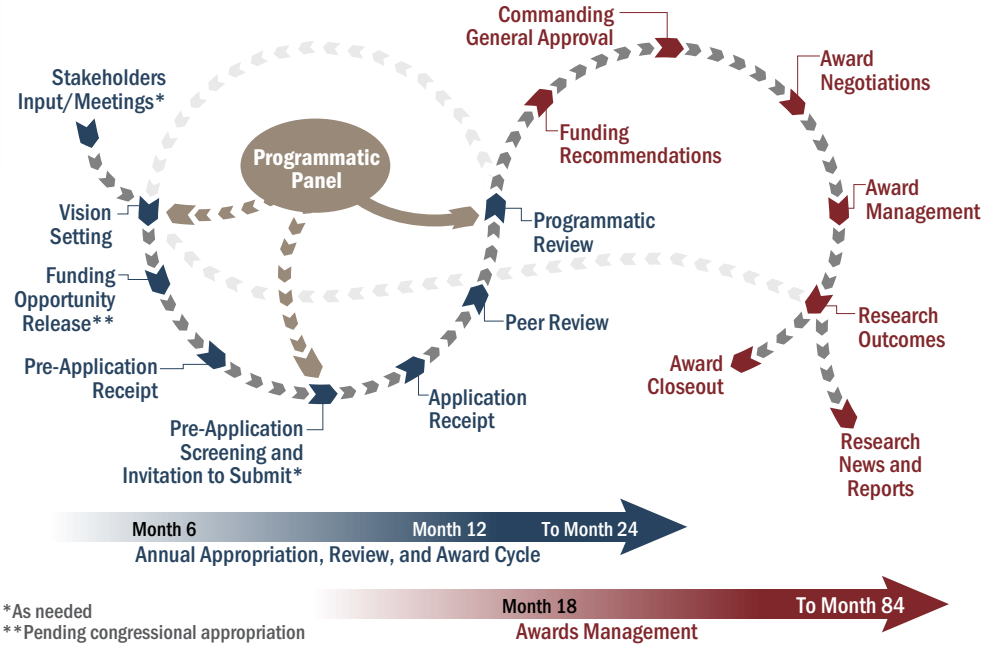
For more information, please visit
cdmrp.health.mil/tscrp

CONGRESSIONALLY DIRECTED MEDICAL RESEARCH PROGRAMS

The Congressionally Directed Medical Research Programs 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. Since then, the CDMRP has grown to encompass over 30 targeted programs and has received over $19.4 billion in appropriations from its inception through FY23. Funds for the CDMRP are added to the DOD budget, in which support for individual programs, such as the Tuberous Sclerosis Complex Research Program, is allocated via specific guidance from Congress.

APPLICATION REVIEW PROCESS

The CDMRP uses a two-tier review process for application evaluation, which is critical to ensuring that each of the research program portfolios reflects not only the most meritorious science, but also the research that best meets the program goals. The first tier of evaluation is a scientific peer review of applications, measured against established criteria determining their scientific merit. The second tier is a programmatic review conducted by a Programmatic Panel, composed of leading scientists, clinicians, and tuberous sclerosis complex consumers. In this tier, the Programmatic Panel compares applications to each other and makes recommendations for funding based on scientific merit as determined by peer review, potential impact, portfolio balance, and relevance to overall program goals.



*As needed
**Pending congressional appropriation

CDMRP Two-Tier Review Process

"The TSCRP plays a unique role in funding impactful TSC research. TSCRP's vision, mission, and focus areas are reviewed and updated annually to ensure the program is funding the most relevant and timely research. Individuals living with TSC, or their family members, are involved in annual vision setting and in prioritizing applications for funding. Additionally, the TSCRP includes representatives from the NIH and TSC Alliance in these processes, ensuring the types of research funded by TSCRP are distinct from other organizations."

Steve Roberds, Ph.D.,
TSC Alliance,
FY23 Programmatic Panel Member

TUBEROUS SCLEROSIS COMPLEX RESEARCH PROGRAM

Vision: Improve prevention strategies and treatments to lessen the impact of TSC while striving for a cure

Mission: Support innovative and high-impact research that promotes discoveries in TSC, from mechanistic insights to clinical application across all ages, by fostering new ideas and investigators to benefit Service Members, their families, and the public

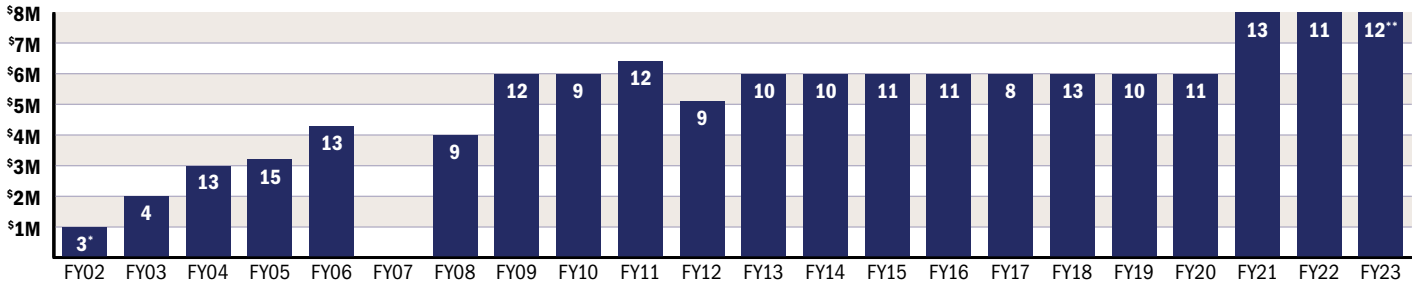
SUMMARY OF TSC AND OUR HISTORY

TSC is a rare genetic disorder that can be inherited from one parent with TSC or can result from a spontaneous genetic mutation during conception or very early development of the human embryo. TSC affects approximately 50,000 individuals in the United States and up to 2 million individuals worldwide.[1]

TSC causes non-malignant tumors in many different organs, primarily in the brain, eyes, heart, kidneys, 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. Research advances in earlier diagnosis and treatment options have led to significant improvements in the quality of life of those affected by TSC. However, to date, there is no cure for TSC.

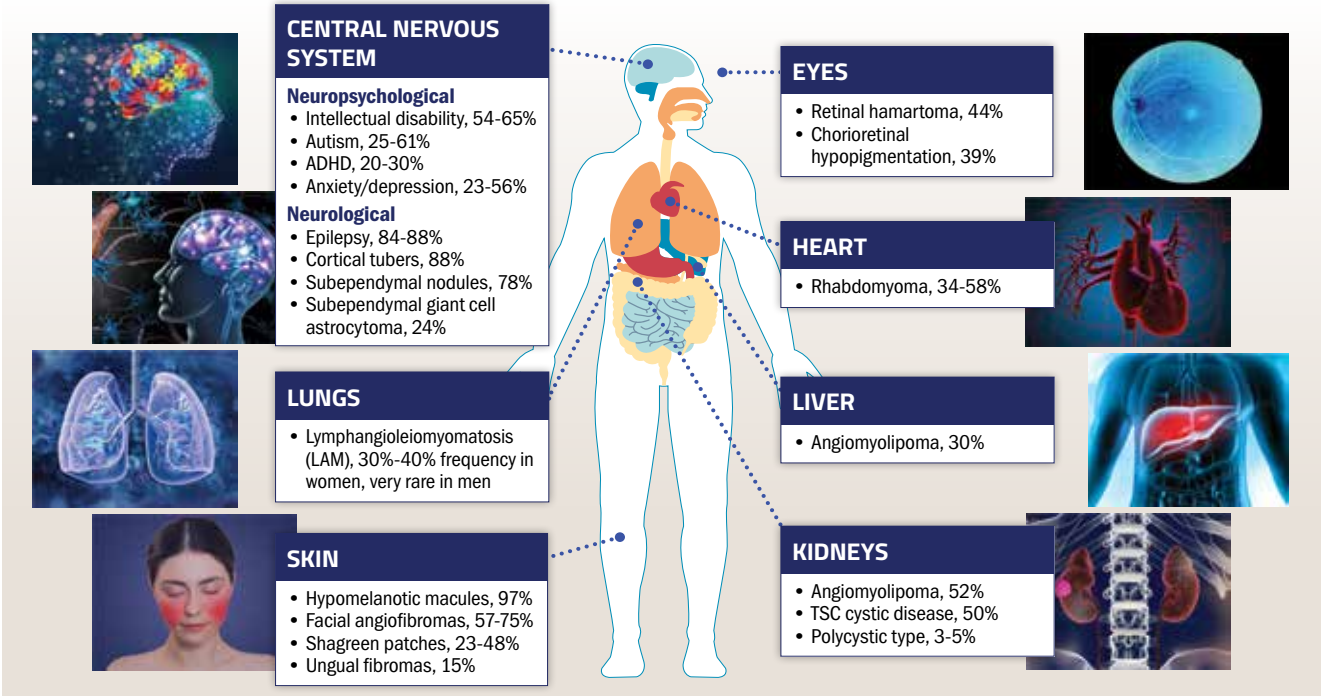
The TSCRP was established in FY02 with a congressional appropriation of $1 million (M). Since then, a total of **$113M** has been appropriated to the program, including $8M in FY23. From FY02 to FY22, the TSCRP has funded **205** awards. Today, the TSCRP is the second largest government funding source for TSC research in the United States.

FY02-FY23 Congressional Appropriations



** Number of Awards ** Anticipated number of awards*

TSC CLINICAL MANIFESTATIONS



[1] Uysal SP, Şahin M. Tuberous sclerosis: a review of the past, present, and future. Turk J Med Sci. 2020 Nov 3;50(SI-2):1665-1676. doi: 10.3906/sag-2002-133. PMID: 32222129; PMCID: PMC7672342.

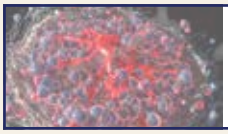
ACCELERATING TSC TOWARD A CURE

The TSCRP recognizes that a broad range of unanswered questions need to be answered to advance prevention and accelerate TSC toward a cure. The current overarching strategic goals for the TSCRP are focused on these clinical manifestations: **tumors**, **epilepsy**, and **neuropsychiatric disorders**. To accomplish these strategic goals, the TSCRP has identified four Focus Areas for each of these goals and requires research proposals to address one of these areas.

Investment Priority – Program Focus Areas

FY23 TSCRP Focus Areas

Understanding, **preventing**, and **treating** the features of **TSC-Associated Neuropsychiatric Disorders** (TAND) and reducing their impact, including pharmacological, behavioral, and surgical interventions



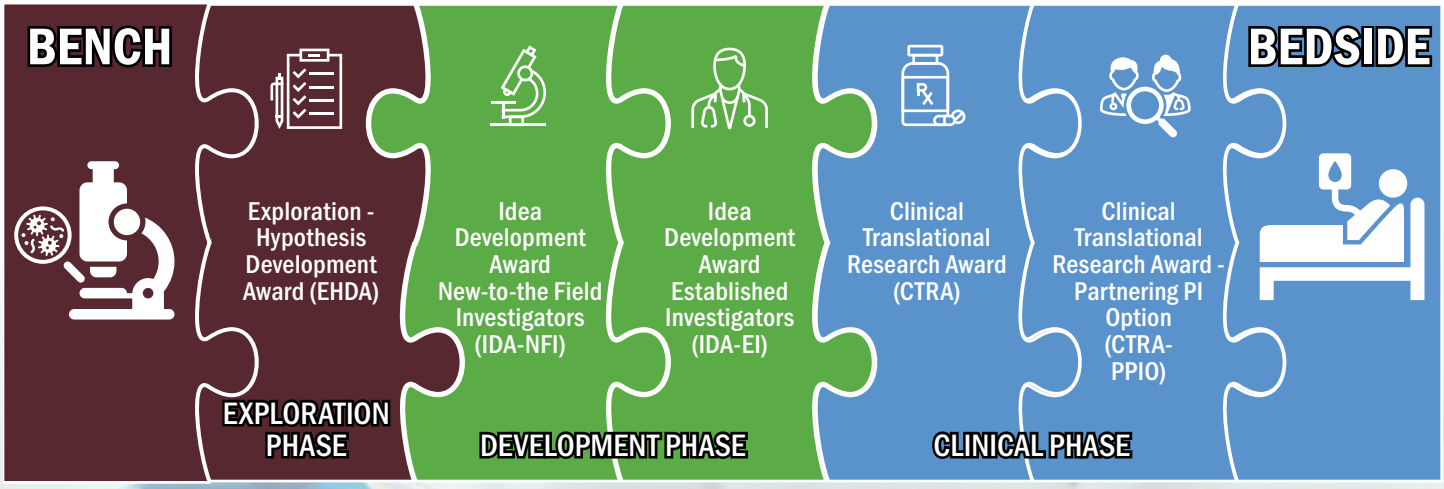
Strategies for **eradicating tumors** associated with TSC and TSC-associated **LAM**, including gaining a deeper mechanistic understanding of the tumor microenvironment, TSC signaling, and mTOR-independent pathways

Preventing epilepsy, **improving** treatment, and **mitigating** neurodevelopmental adverse outcomes associated with TSC-related seizures

Developing, **assessing**, and **testing** emerging technologies including imaging and molecular therapeutic strategies, such as **gene therapy**, to improve outcomes of TSC

To address the changing needs of the research and patient community, the TSCRP currently offers multiple award mechanisms across the research continuum to support ideas at various stages with the goal of bringing medical solutions to the patients.

Investment Approach – Award Mechanisms



PORTFOLIO ANALYSIS

The TSCRP supports a variety of award mechanisms along the research continuum. It supports ideas at the Exploration Phase, which encourages early stage, innovative, and high-risk/high reward concepts; all the way through ideas at the Clinical Phase, which emphasizes clinical impact to the patients.

Investment by Award Mechanisms

FY02-FY22 (205 Awards/$92.0M)

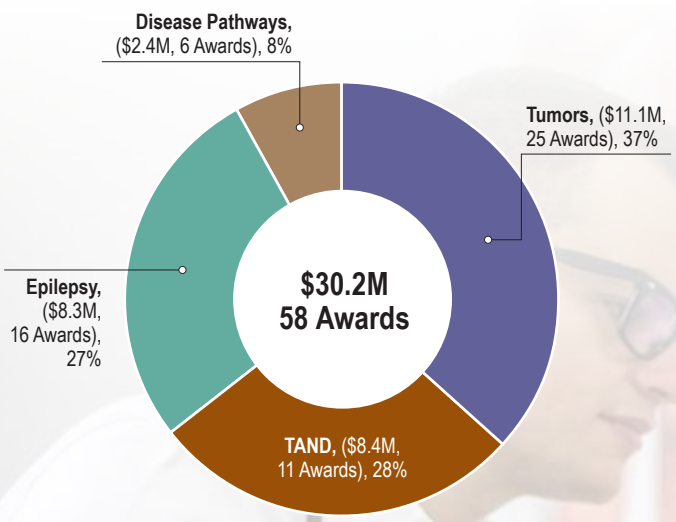
EXPLORATION PHASE	DEVELOPMENT PHASE	CLINICAL PHASE
$15.2M (17%) 93 Awards (45%)	$61.5M (67%) 97 Awards (47%)	$15.2M (17%) 15 Awards (7%)
• Exploration - Hypothesis Development Award (EHDA)* • Concept Award (CA)	• Idea Development Award (IDA)* • Career Transition Award (CARTA) • Natural History Development Award (NHDA) • Postdoctoral Development Award (PDA)	• Clinical Translational Research Award (CTRA)* • Clinical Resource Development Award (CRDA) • Clinical Trial Awar (CTA) • Pilot Clinical Trial Award (PCTA)

** Award mechanisms currently offered by the TSCRP.*

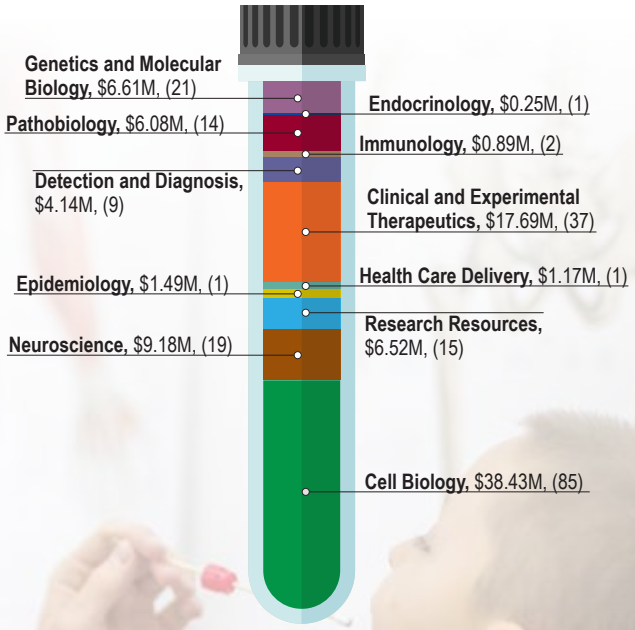
Investment by Focus Areas and Research Areas

TSC is a disease that manifests differently from person to person. As a result, the TSCRP strives to obtain a balanced research portfolio based on strategic goals, specific research areas, and ultimately the current need of the TSC community. Analyses of the most recently funded projects (FY18-FY22) by Focus Areas and Research Areas (FY02-FY22) are reflected below. Over half of the TSCRP investment is in the Focus Areas of neurodevelopment and epilepsy while over $38M is invested in cell biology-aimed research projects.

FY18-FY22 Investment by Focus Area



FY02-FY22 Investment by Research Area



RESEARCH HIGHLIGHTS

A Timeline for Success: The FDA Approves New Topical Treatment for Facial Tumors in TSC

Mary Kay Koenig, M.D., UTHealth Houston

The recent U.S. Food and Drug Administration (FDA) approval of HYFTOR™ to treat facial angiofibromas associated with TSC was great news to the TSC community, as there was previously no effective permanent treatment for this condition. The journey of developing a topical drug to target mTOR complex 1 (mTORC1) began over a decade ago with a clinical trial funded by the TSCRP.

Facial angiofibromas are benign skin tumors on the face, which are present in up to 80% of TSC patients.[2] These facial lesions create considerable cosmetic morbidity for patients with TSC. Although there are surgical procedures available to remove the tumors, the majority of these treatments are uncomfortable and lack long-term efficacy.

In **2009**, Dr. Mary Kay Koenig, M.D., with McGovern Medical School at UTHealth Houston, conducted the first small clinical trial using a topical rapamycin cream to treat cutaneous manifestations in TSC and neurofibromatosis 1 patients. Based on the preliminary results, in **2010**, Koenig received a TSCRP Clinical Research Award to pursue a phase 2 randomized clinical trial to study the safety and efficacy of topical rapamycin to treat TSC-related facial angiofibromas (named the TREATMENT trial). The TREATMENT trial started in **2011**. Patients were randomized at 1:1:1 ratio to 1% rapamycin, 0.1% rapamycin, or a control. The topical formulation was applied once to designated areas at bedtime for 6 months. The outcome measures included the angiofibromas grading scale (AGS) at baseline and 6 months by independent, masked dermatologists. The safety analysis included adverse events and serum rapamycin levels. In **2014**, the trial was successfully completed, enrolling 179 patients over 10 sites. At 6 months, the rapamycin treatment groups had significant AGS improvement compared to the control group. AGS results were improved by 16.7 points within the 1% rapamycin group and 11.2 points in the 0.1% rapamycin group, while the control group only had 2.1 points of improvement. Topical rapamycin was generally well tolerated with no measurable systemic absorption. The positive outcomes from the phase 2 trial laid the foundation for the next step of the drug development. In 2018, Dr. Koenig published the phase 2 clinical trial in *JAMA Dermatology* which demonstrated the safety and efficacy of the topical formulation of rapamycin in the treatment of TSC-related facial angiofibromas.

Koenig remarks, “Most people with TSC will develop facial angiofibromas. It can be very stigmatizing, disfiguring, and embarrassing.” Previously there was no effective method for treating this condition. Of the hard work and dedication that her team has shown over the lengthy process of bringing a therapeutic from bench top to bedside, Koenig said, “I have dedicated my life and my career to taking care of people with rare diseases. Everybody knows someone who has a rare disease. Collectively they are not rare.”

HYFTOR™
(sirolimus topical gel) 0.2%

2011

The TSCRP funded an early trial led by Dr. Mary Kay Koenig to study topical rapamycin (also known as sirolimus) to treat facial angiofibromas in TSC patients. The goal of the **TREATMENT** trial was to develop a form of rapamycin that could provide a safe, effective treatment for facial angiofibromas in patients with TSC.

2014

The **TREATMENT** trial was completed with a final enrollment of 179 patients.

2018

Dr. Koenig’s team published their results, “Efficacy and Safety of Topical Rapamycin in Patients with Facial Angiofibromas Secondary to Tuberous Sclerosis Complex: The **TREATMENT** Randomized Clinical Trial” in *JAMA Dermatology* in 2018.

2022

The FDA approved **HYFTOR™** for facial angiofibromas. **HYFTOR™** is the first FDA-approved topical treatment for facial angiofibromas in adults and children 6 years of age or older who have TSC.

[2] Northrup H, Krueger DA; International Tuberous Sclerosis Complex Consensus Group. Tuberous sclerosis complex diagnostic criteria update: recommendations of the 2012 Iinternational Tuberous Sclerosis Complex Consensus Conference. Pediatr Neurol. 2013 Oct;49(4):243-54. doi: 10.1016/j.pediatrneurol.2013.08.001. PMID: 24053982; PMCID: PMC4080684.

Dr. Wudu Lado

Dr. David Sulzer

Dr. James E. Goldman

Dr. Guomei Tang

A New Mouse Model Sheds Light on the Origination of Epilepsy in Tuberous Sclerosis Complex

Wudu Lado, Ph.D.; David Sulzer, Ph.D.; James E. Goldman, M.D., PhD; Guomei Tang, Ph.D., Columbia University

A key, unresolved issue is the cause of the neurological symptoms in TSC patients. A group of investigators at Columbia University recently published an article in *Cell Reports* on a new mouse model of TSC that sheds light on the cause of epilepsy in TSC patients. Among them, Drs. Tang, Sulzer, and Goldman have received Idea Development Awards (IDAs) in differing years from the TSCRP.

Dr. Sulzer was awarded an FY11 TSCRP IDA to investigate altered astrocyte-neuron interactions in TSC and a potential role for these pathological changes in the epileptogenesis observed in this disorder. This award supported the study of astrocytic mechanisms in pruning excessive excitatory synapse during development, which may produce neuronal hyperexcitability.

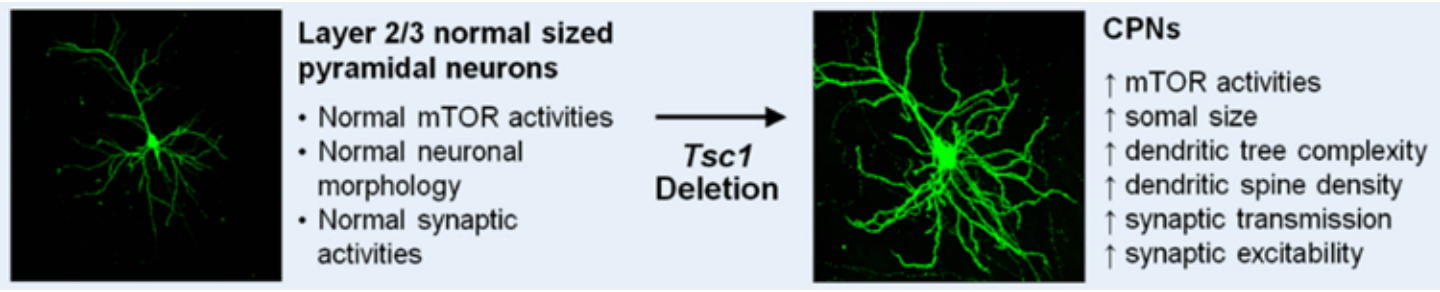
Dr. Goldman's FY14 IDA further studied the molecular mechanisms underlying epileptogenesis and seizure progression in *Tsc1*-deficient mouse models. Using systems biology/gene expression profiling and electrophysiological, biochemical, immunohistochemical, and behavioral studies, Dr. Goldman's group focused on the molecular signatures that are significantly changed during epileptogenesis in the model mice.

Dr. Tang's FY15 IDA delved into the altered mTOR-related macroautophagy and its role in TSC-associated neurocognitive deficits (mTOR is a kinase that is constitutively activated in TSC and, in turn, suppresses autophagy, a process by which cells can degrade their own components). The team also worked together to shed light on how epilepsy might originate in TSC.

The recent multi-laboratory collaborative publication titled, "Synaptic hyperexcitability of cytomegalic pyramidal neurons contributes to epileptogenesis in tuberous sclerosis complex," provides evidence that the new mouse model developed by this team is characterized by greatly enlarged cerebral cortical neurons and that those cells are epileptogenic. The team utilized a conditional knock-out system in which the *Tsc1* gene is inactivated only in specific embryonic cell types. In this new model, *Tsc1* deletion occurs in a subset of cortical neurons, leading to the development of enlarged ("cytomegalic") pyramidal neurons that mimic the neurons with abnormal morphological characteristics that are seen in human patients with TSC. These neurons show aberrant overgrowth of their cellular processes, enhanced excitatory synaptic transmission, and increased susceptibility to seizure-like activities. Heightened synaptic excitation contributes to the observed cortical hyperexcitability and epileptogenesis. As a result of these cortical alterations, the mice exhibited social and cognitive impairment and spontaneous seizures, that were akin to symptoms seen in TSC patients.

To follow up this study, the team received an FY20 Exploration - Hypothesis Development Award (Principal Investigator: Dr. Lado) to investigate whether the dysfunction of a neuronal-specific chloride transporter enhances the synaptic excitability of cytomegalic neurons in TSC. The team is also working on a follow-up article comparing the pathological characteristics of the enlarged mouse neurons to the dysplastic neurons found in human tubers, with the goal to identify common cellular and molecular changes that are involved in epileptogenesis.

"Our studies have given us new insights into the pathological and clinical features of TSC and opened up future studies to go deeper into molecular mechanisms. We are all grateful for the DOD support of our efforts." Dr. Goldman said.



The team developed a new Tsc1 conditional knockout (Tsc1CKO) mouse model. In this model, Cre-mediated gene deletion begins in cortical and hippocampal radial glial cells (RGCs) at embryonic day 18 (E18), leading to Tsc1 inactivation in the majority of astrocytes and a small number of layer 2/3 upper cortical pyramidal neurons. The mice develop enlarged "cytomegalic pyramidal neurons (CPNs)" that mimic dysplastic neurons in TSC human brains. These CPNs show elevated excitatory synaptic transmission, leading to cortical hyperexcitability and spontaneous seizures.

TSCRP ACCOMPLISHMENTS: PROD

$92.0M INVESTMENT

205 AWARDS

411 PUBLICATIONS

66,191 CITATIONS

$194.4M FOLLOW-UP FUNDING

159 FOLLOW-UP AWARDS

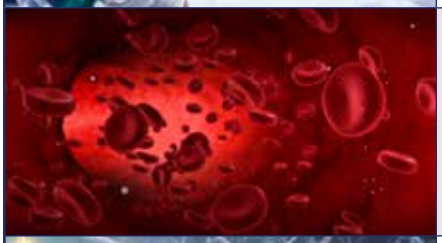
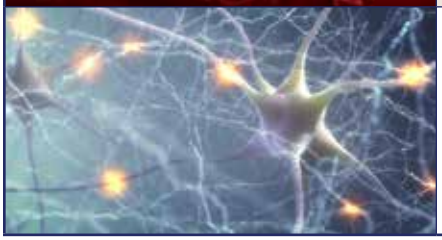
4 PATENTS

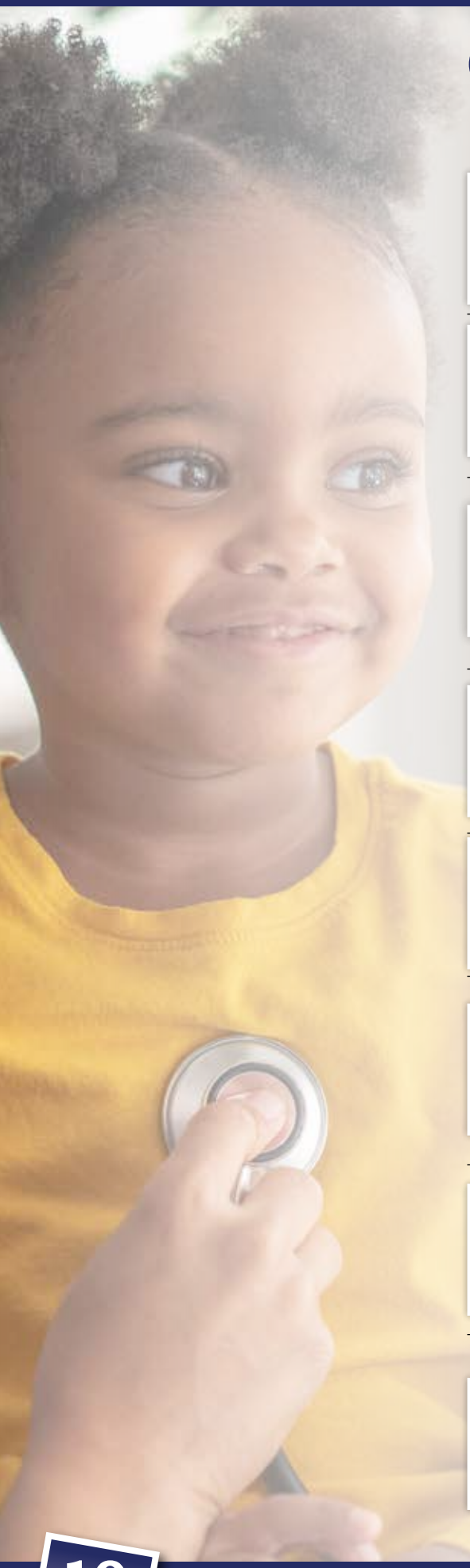
3 PATENT APPLICATIONS

10 CLINICAL TRIALS

1 FDA-APPROVED DRUG (HYFTOR™)

TSCRP-Funded Research Led to Three Patent Applications and Four Granted Patents

	Gray N, et al. 2013. Soluble mTOR Complexes and Modulators Thereof. **US8394818B2**. An invention to the synthesis of modulators of mTORC1 and mTORC2 and their applications to treat proliferative diseases and metabolic diseases. Supported by an FY06 TSCRP Idea Development Award (TS060023).
	Koenig MK, et al. 2018. Topical Rapamycin Therapy. **W02018031789A1**. An invention to use topical rapamycin for safe and effective treatment of various skin conditions, including angiofibromas in tuberous sclerosis complex. Supported by an FY10 TSCRP Clinical Research Award (TS100017).
	Prabhakar S, et al. 2018. Gene Therapy for Tuberous Sclerosis. **W0201821361 8A1**. An invention provides compositions and methods for treating tuberous sclerosis complex using gene therapy. Supported by an FY15 TSCRP Exploration – Hypothesis Development Award (TS150045).
	Yu J and Li CG. 2018. Treatment of Lymphangioleiomyomatosis. **US9925202B2**. An invention to use COX inhibitor and/or prostaglandin pathway inhibitors to treat LAM. Supported by an FY11 TSCRP Exploration – Hypothesis Development Award (TS110047).
	Sabatini DM. et al. 2019. Methods of Identifying Modulators of Sestrin-Gator-2 Interaction for Modulating Mtorc1 Activity. **US10168338B2**. An invention to identify modulators of mTORC1 based on their effect on GATOR2-Sestrin binding or Sestrin-leucine binding. Supported by an FY06 TSCRP Idea Development Award (TS060023).
	Shaw RJ, et al. 2019. ULK1 Inhibitors and Methods Using Same. **US10266549B2**. An invention to treat a disease (TSC) by co-administering ULK1-inhibitors and mTOR inhibitor. Supported by an FY12 I TSCRP Idea Development Award (TS120021).
	Bordey A, et al. 2020. Methods of Treating and Diagnosing Epilepsy. **W02020180990A2**. An invention to treat epilepsy using an HCN4 disrupting agent. Supported by an FY15 TSCRP Idea Development Award (TS150058).



CLINICAL INNOVATIONS MAKING A DIFFERENCE

Toward Chimeric Antigen Receptor Transgenic T Cell Therapy for Tuberous Sclerosis Complex, led by Dr. Isabelle Le Poole at Northwestern University. The project investigates whether immunotherapy can be used to treat TSC through the adoptive transfer of T cells. (FY17)

Resting State Functional MRI (RS fMRI) Finds Correct Surgical Target to Stop Seizures in Tuberous Sclerosis Complex, led by Dr. Varina Boerwinkle at Children's Hospital, Phoenix. This study evaluates whether RS fMRI can find where seizures are coming from in children with TSC and whether targeted removal improves their overall prognosis. (FY19)

Mapping of Brain GABA Levels in Tuberous Sclerosis Complex Using High-Resolution Proton MR Spectroscopic Imaging, led by Drs. Doris Da May Lin and Peter Baker at Johns Hopkins University. This is a pilot study to test the hypothesis that brain GABA levels are abnormal in patients with TSC, as well as related to severity of seizure activity. (FY19)

TSC Remote Assessment and Intervention (TRAIN), led by Dr. Connie Kasari at the University of California, Los Angeles. The primary goal is to determine whether joint engagement and social communication in children with TSC can be improved through a remotely administered caregiver training. (FY19)

LAM Pilot Study with Nilotinib LAMP-2, led by Dr. Jeanine D'Armiento at the Colombia University Medical Center. This project evaluates the safety and tolerability of nilotinib (tumoricidal therapeutic) in patients with LAM. (FY20)

Assessment and Treatment of Behavior Problems in TSC at Preschool Age: A Telehealth Approach, led by Dr. Nicole McDonald at the University of California, Los Angeles. Findings from this research will help us learn more about behavior problems in young children with TSC and have the potential to significantly broaden access to a treatment that promotes effective parent management skills and positive parent-child interactions. (FY20)

Optimizing Therapeutic Control of Epilepsy in Tuberous Sclerosis Complex: Using a Novel Biosensor, led by Dr. Edward Chaum at Vanderbilt University Medical Center. This study aims to validate the performance of a prototype handheld, plug-and-play biosensor platform for point-of-care testing of drug levels in biofluids. (FY22)

Regulating Together in Tuberous Sclerosis Complex: A Pilot Feasibility Study in Children and Adolescents with TSC-Associated Neuropsychiatric Disorder (TAND), led by Dr. Jamie Capal at University of North Carolina at Chapel Hill" Chapel Hill. This award aims to characterize Emotion Dysregulation (ED) in TSC children and adolescents with TAND and to evaluate the efficacy of a behavioral intervention, Regulating Together, for the treatment of ED in TSC. (FY22)

CELEBRATING OVER 20 YEARS OF ADVANCING TSC RESEARCH

Since its inception over 20 years ago, the TSCRP has played a critical role in helping **accelerate high-impact research, exploring new concepts, encouraging innovation, and bringing new investigators** into the TSC field. This aligns well with the goal of lessening the burden of TSC clinical manifestations and improving the quality of life for Service Members, their families, and the public.

"As a past Chair of the TSCRP Programmatic Panel and a former award recipient from the TSCRP, I am simply awed by the progress that has been possible because of the program. The TSCRP enables the fast-tracking of the highest impact research. Our knowledge about TSC is growing quickly and treatment options are improving steadily, thanks to TSCRP-supported research. TSC is often a devastating diagnosis, but thanks to the TSCRP, there is already a brighter future for individuals and families affected by TSC and tremendous optimism that the next breakthroughs will bring us even closer to a cure."

Elizabeth Henske, M.D., Harvard University
Former TSCRP Programmatic Panel Member and Award Recipient

"The discovery of dysregulated mTOR signaling as the fundamental cause of TSC has precipitated innovative research funded by TSCRP. Notably, mTOR's impact on bidirectional protein synthesis and degradation has catapulted the field of TSC research forward, providing pharmacological targets that are being developed as new therapies to treat TSC and other mTOR-related disorders."

Kim Raab-Graham, Ph.D.,
Wake Forest University School of Medicine
FY23 Programmatic Panel Chair

"Our vision to lessen the impact of TSC while striving for a cure is a shared vision between Department of Defense and civilian researchers, clinicians, families, and patients. We are one team, striving to support and promote innovative and clinically applicable research to benefit all of our patients. I am honored to contribute to the TSCRP in CDMRP and its 20-year legacy of funding research that has positively enhanced the quality of life for our patients with TSC and their families and is pushing us closer to a cure."

Col. David Hsleh, M.D., U.S. Air Force
Programmatic Panel Member

"It has been a true privilege serving on the TSCRP panels as a Consumer Reviewer. I started my involvement with this program when my TSC-afflicted son, Bao, was 5 years old; he's now graduated high school and attending college. The impact this TSCRP program has had over this period is nothing short of amazing! This is an extraordinarily well-managed and highly competitive grant process that delivers meaningful results for the TSC community. For me personally, participating in this program is the best thing I can do for my son."

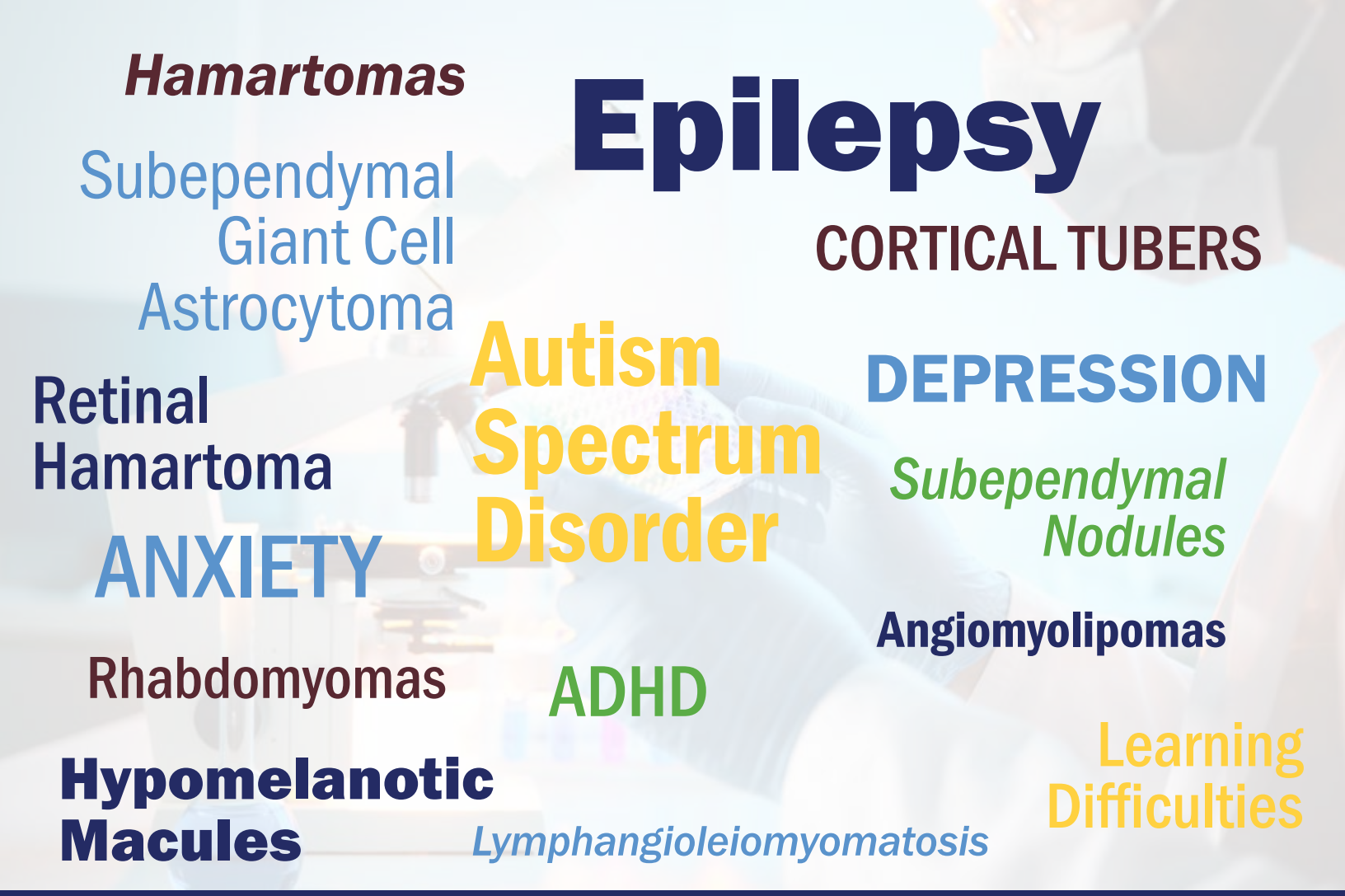
Ron Heffron, P.E., TSC Alliance
Programmatic Panel Member

"The research of the TSCRP has had a significant impact on our 9-year old daughter, Nell, recently. She was started on Hyftor, topical sirolimus, for her developing angiofibromas and a very early cephalic plaque. Within a month both disappeared! We are thankful for all research coming out of the TSCRP."

Heather Harden, TSC Alliance
Consumer Peer Reviewer

"TSCRP research has had a huge impact on my family and many others dealing daily with this rare disease. TSC patients, family, and caretakers deal with varying degrees of epilepsy (seizures), autism, and TSC-associated neurological psychiatric disorders affecting behaviors and mental health, including anxiety, aggression, depression, and more. My older brother Frank participated in two phases of TSCRP funded clinical trials, which led to USA FDA-approved Hyftor (mTOR inhibitor sirolimus) topical gel to treat facial angiofibromas. TSCRP-funded projects will have a significant impact on TSC challenges that could lead to a breakthrough in scientific advancement and possible cure for this rare disease."

Jocelyn Cenna, TSC Alliance
Consumer Peer Reviewer



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1/2024
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