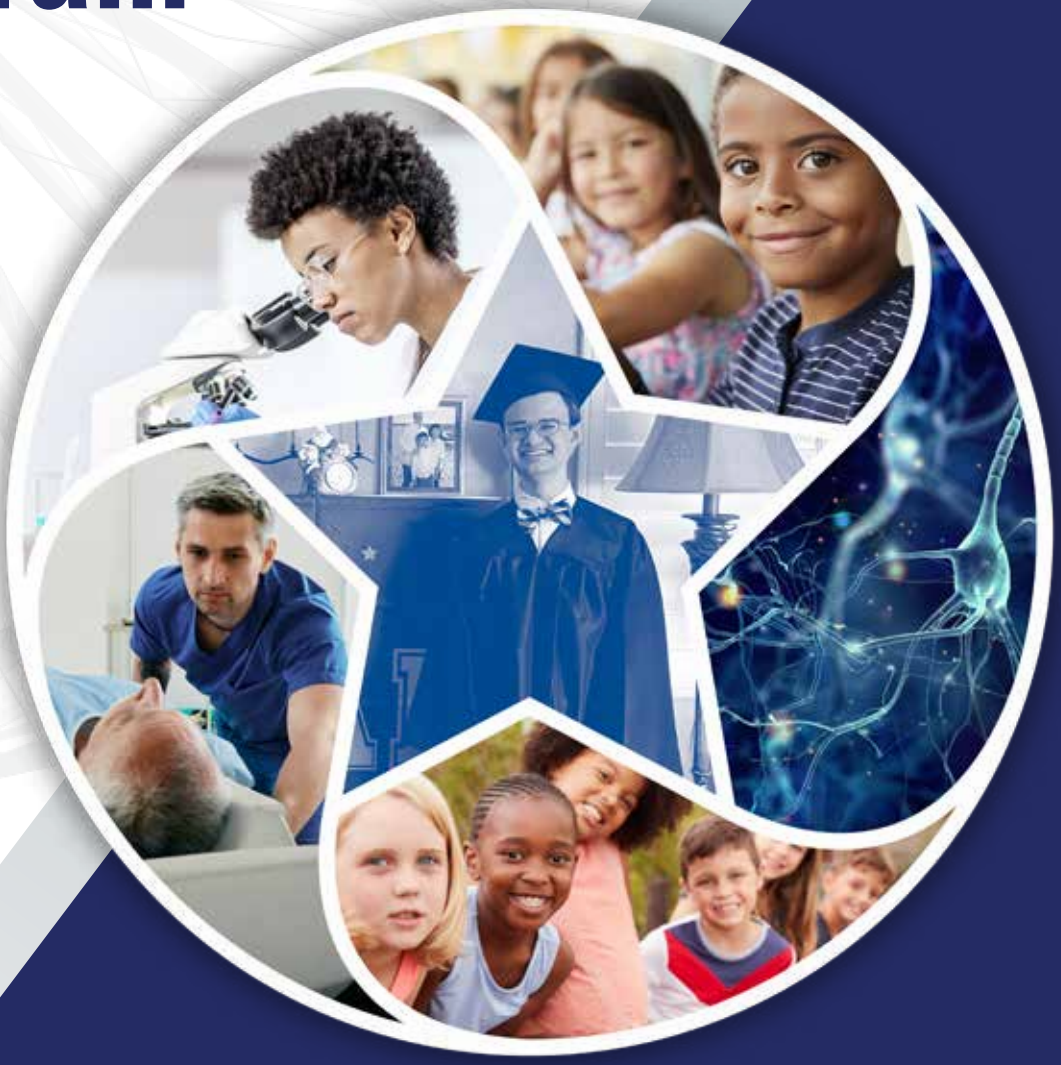
CDMRP
DEPARTMENT OF DEFENSE
CONGRESSIONALLY DIRECTED
MEDICAL RESEARCH PROGRAMS

Tuberous Sclerosis Complex Research Program



Accelerating TSC Research Toward a Cure

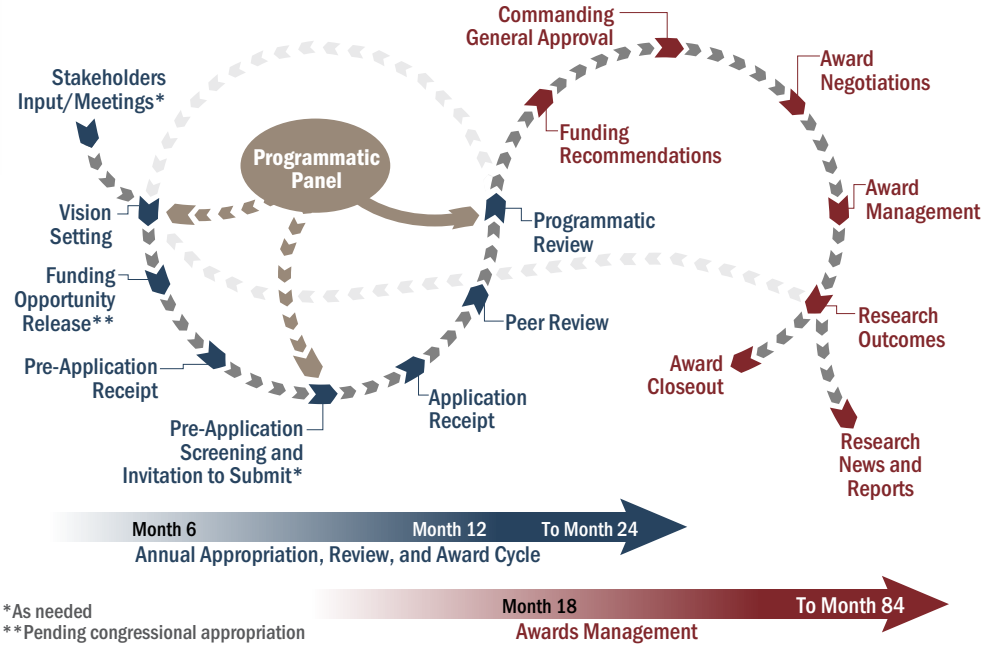
For more information, please visit
cdmrp.health.mil/tscrp

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

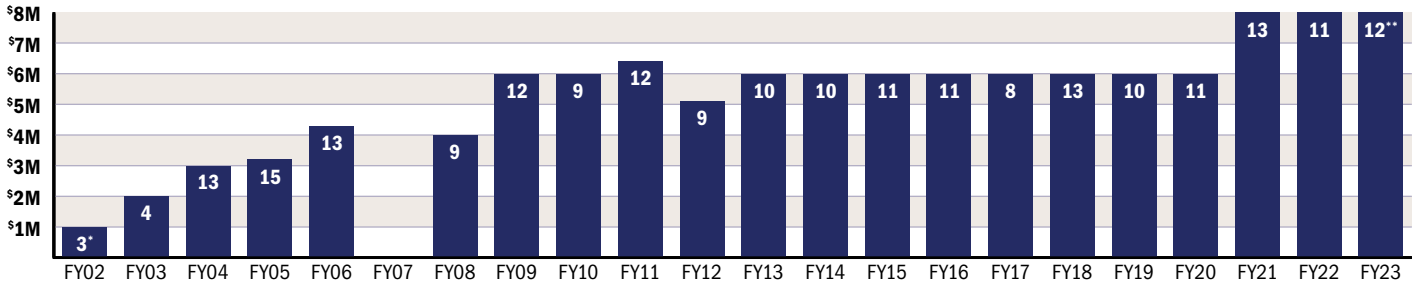
SUMMARY OF TSC AND OUR HISTORY

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.

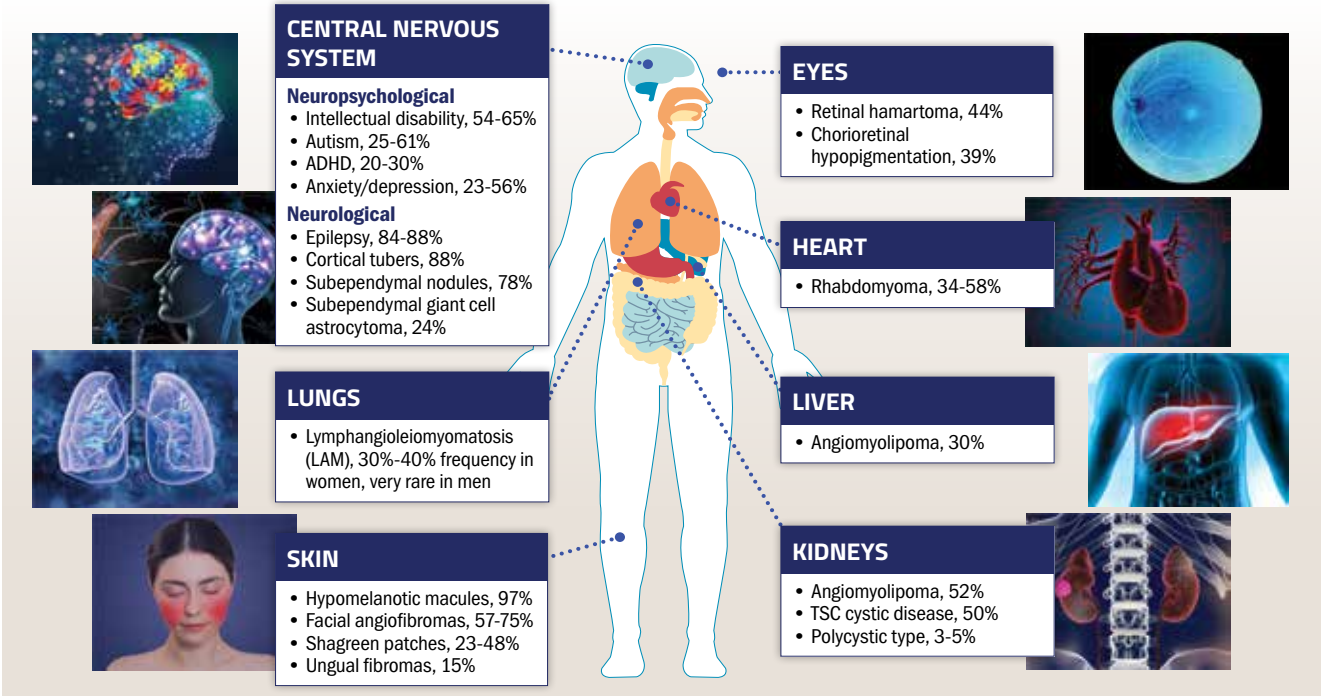
The TSCRP was established in FY02 with a congressional appropriation of $1 million (M). Since then, a total of **$113M** has been appropriated to the program, including $8M in FY23. From FY02 to FY22, the TSCRP has funded **205** awards. Today, the TSCRP is the second largest government funding source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

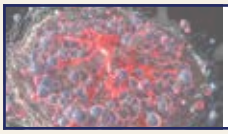
ACCELERATING TSC TOWARD A CURE

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



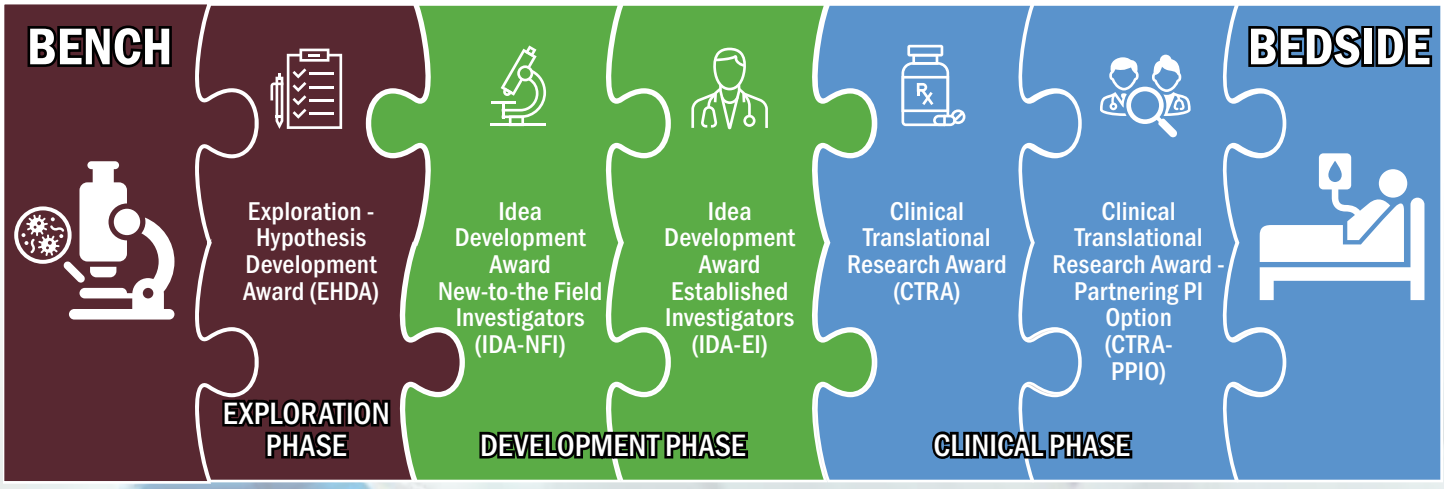
Strategies for **eradicating tumors** associated with TSC and TSC-associated **LAM**, including gaining a deeper mechanistic understanding of the tumor microenvironment, TSC signaling, and mTOR-independent pathways

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)

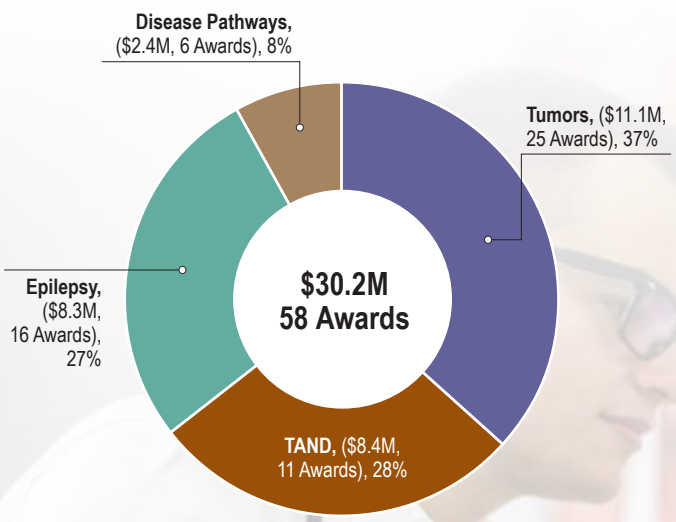
EXPLORATION PHASE	DEVELOPMENT PHASE	CLINICAL PHASE
$15.2M (17%) 93 Awards (45%)	$61.5M (67%) 97 Awards (47%)	$15.2M (17%) 15 Awards (7%)
• Exploration - Hypothesis Development Award (EHDA)* • Concept Award (CA)	• Idea Development Award (IDA)* • Career Transition Award (CARTA) • Natural History Development 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.*

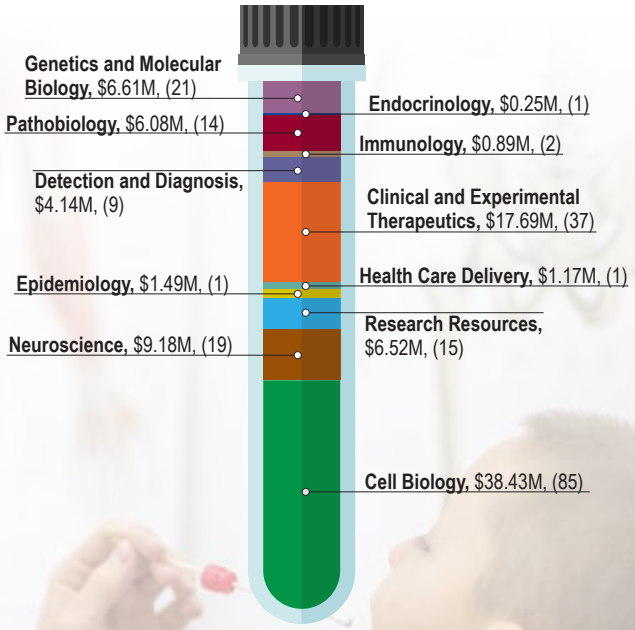
Investment by Focus Areas and Research Areas

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.

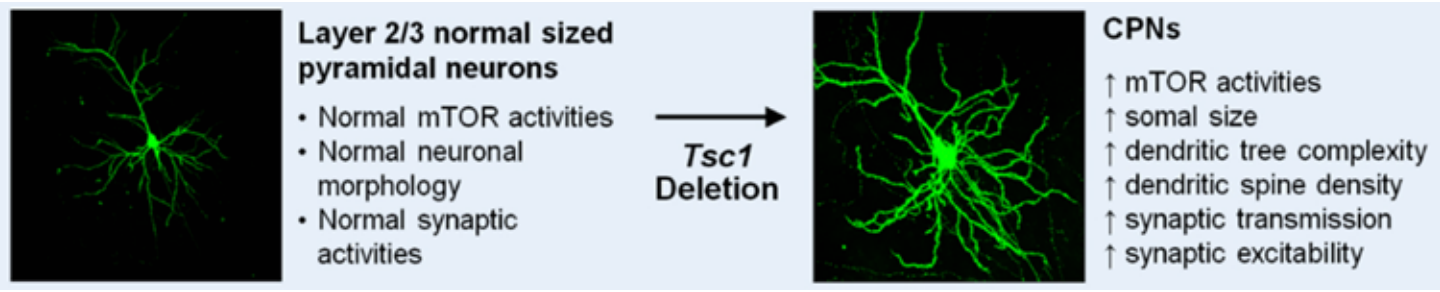
Dr. Goldman's FY14 IDA further studied the molecular mechanisms underlying epileptogenesis and seizure progression in *Tsc1*-deficient mouse models. Using systems biology/gene expression profiling and electrophysiological, biochemical, immunohistochemical, and behavioral studies, Dr. Goldman's group 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.

RESEARCH HIGHLIGHTS

Dr. Michael Hall

Dr. Stefan Imseng

Dr. Asier Gonzalez

Developing Novel mTORC1 Inhibitors to Treat TSC

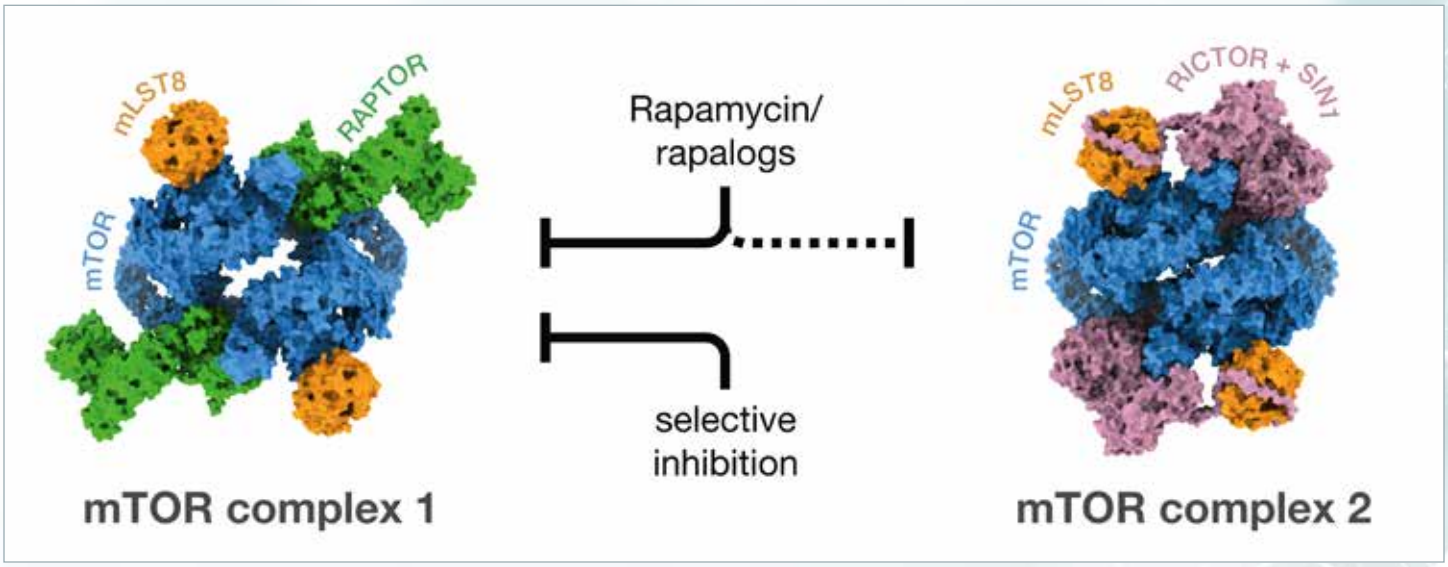
Dr. Michael Hall, Dr. Stefan Imseng, and Dr. Asier Gonzalez, University of Basel, Switzerland

In FY19, Dr. Michael Hall, at the University of Basel in Switzerland, received an Exploration - Hypothesis Award from the TSCRP to investigate novel mTORC1 inhibitors to treat TSC. Over the course of this award, Dr. Hall's group, spearheaded by Drs. Imseng and Gonzalez, identified a novel, rapalog-unrelated, druggable site on mTORC1 and that perturbing this novel site reduces mTORC1's ability to phosphorylate substrates in cultured cells. The group has continued the development of a novel class of selective mTORC1 inhibitors and has identified six compounds that selectively inhibit mTORC1 in vitro. These compounds are potential selective mTORC1 inhibitors and are promising candidates for chemical and pharmaceutical development. This groundwork may lead to a new generation of selective mTORC1 inhibitors that could lead to novel treatment options for TSC, as well as other diseases characterized by mTORC1 hyperactivation that have not been addressable by the previous generations of mTORC1 inhibitors.

Dr. Hall will continue to build on this work with additional support from the TSCRP in the form of a new FY21 IDA, titled "Selective mTORC1 Inhibitors to Treat TSC." The aims of this study are to determine the efficacy of selective mTORC1 inhibitors on mTORC1 activity and to determine whether the optimized compounds selectively inhibit mTORC1 and exhibit tumor-reducing abilities in mice.

Dr. Hall said, "The clinical potential of these novel compounds is immense and readily testable. We believe our approach could be an important development, as we predict it to be more effective, selective, and safer in the treatment of TSC symptoms. Innovative treatments with better efficacy and safety will ameliorate TSC symptoms. Novel mTORC1-targeted drugs with reduced mTORC2-associated side effects would greatly improve the health and quality of life of TSC patients."

Exploring and developing novel mechanisms for selective mTORC1 inhibition by targeting mTORC1-specific functions have allowed Hall's group to gain fundamental insights into the TSC-mTOR signaling pathway. Understanding the cellular pathways that drive different TSC manifestations will lead to innovative treatments with better efficacy and safety to ameliorate TSC symptoms.



Overview of mTOR complex 1 (left) and mTOR complex 2 (right) architecture with emphasis on the kinase active site in mTOR.

Dr. Krinio Giannikou

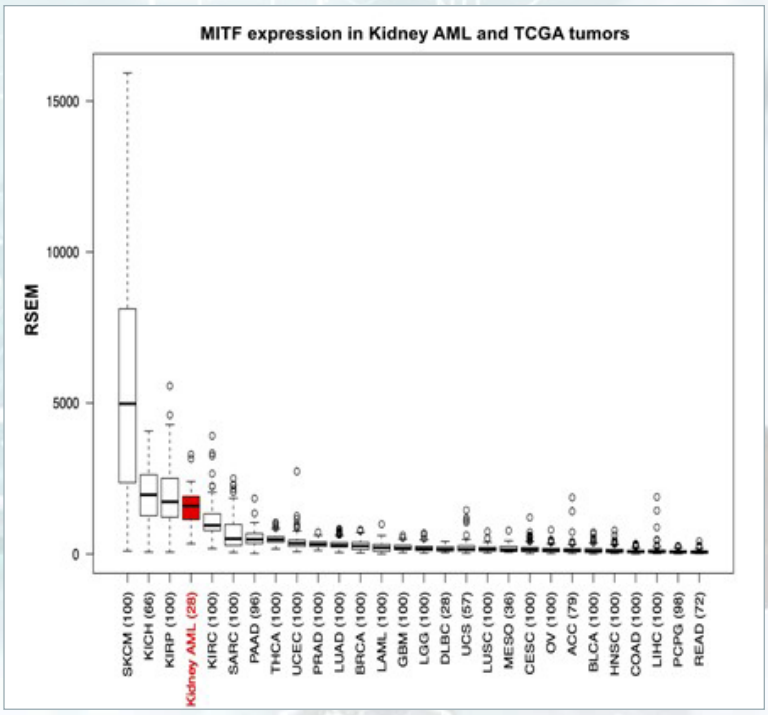
Dr. Mahsa Zarei

Genetic Analysis of TSC Tumors Identifies Novel Therapeutic Targets

Krinio Giannikou, Ph.D., Brigham and Women's Hospital; Mahsa Zarei, Ph.D., Texas A&M University

With support from an FY16 TSCRP Postdoctoral Development Award, Dr. Krinio Giannikou explored the transcriptomic and epigenetic profile of kidney angiomyolipoma AML and LAM tumors to identify active enhancer/super-enhancers (cis-regulatory regions of open chromatin highly marked by H3K27ac histone mark) and master transcription factors that drive expression of multiple genes and may play a critical role in kidney AML/LAM tumor development and progression. Giannikou worked closely with Dr. Mahsa Zarei, who was supported by funding from an FY17 TSCRP Exploration - Hypothesis Award. Zarei investigated the transcriptional and metabolic mechanisms that cause selective cell death of TSC-deficient cells with the long-term goal of identifying strategies that selectively kill TSC2-deficient cells, thereby decreasing the need for continuous anti-tumor therapy in TSC.

The researchers found that kidney AML/LAM tumors have a unique transcriptional and epigenetic landscape that is distinct from other malignancies and normal tissues. Through innovative cutting-edge multi-omics approaches , they identified a set of candidate transcriptional driver genes that are highly expressed in kidney AML in comparison to other cancers that might drive tumor growth. Integrative analyses of RNA-Seq and H3K27ac ChIP-Seq of renal AMLs from TSC subjects in an unbiased genome-wide manner for the first time identified a set of novel transcription factors as super-enhancers, which are highly expressed in kidney AMLs, that might drive tumor growth. These genome wide studies, in combination with functional studies in cellular and animal TSC models, demonstrated that MITF is a driver oncogene and potential therapeutic target in kidney AML tumors through transcriptional regulation of CYR61. Dr. Zarei has also demonstrated that targeting specific tumor cell essential genes will selectively induce cell death of TSC2-null cells and that inhibition of transcription regulators is a promising therapeutic approach for treatment of TSC-associated tumors. These studies were performed in collaboration with other TSCRP-supported researchers including Drs. Elizabeth Henske, Heng-Jia Liu, and David Kwiatkowski. This work was published in the journals *Journal of Experimental Medicine* in 2019 and *Oncogene* in 2021.



RNA-seq data showing MITF expression in 28 kidney angiomyolipomas compared to 2463 tumors of 27 different histologic types (Cancer Genome Atlas [TCGA] dataset).

Abbreviations for all TCGA tumor types are available here: https://gdc.cancer.gov/resources-tcga-users/tcga-code-tables/tcga-study-abbreviations.
Gene expression is shown in RNA-Seq by Expectation – Maximization values.

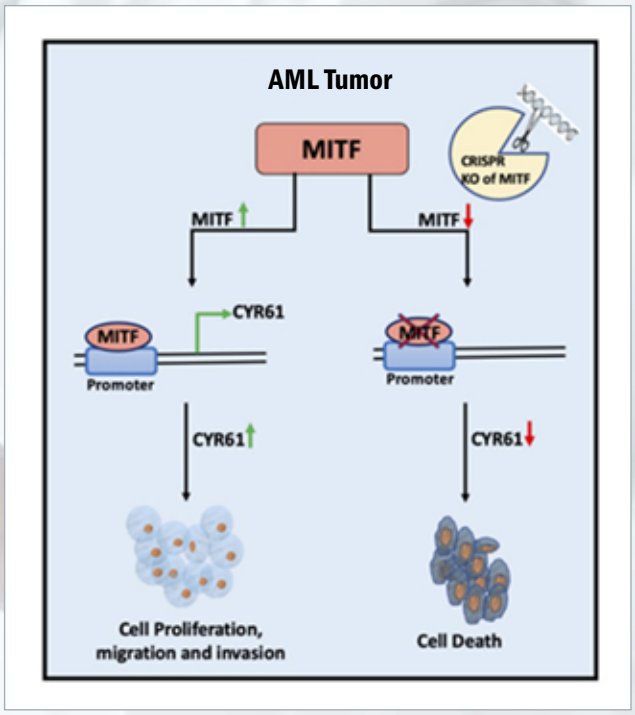


Diagram showing how MITF regulates AML growth and development through transcriptional regulation of CYR61, suggesting that these two genes form a regulatory axis, and may be an actionable therapeutic target in AML.

Zarei M, Giannikou K, et.al, Oncogene. 2021 Jan; 40(1): 112–126. Published online 2020 Oct 20. doi: 10.1038/s41388-020-01504-8

TSCRP ACCOMPLISHMENTS: PROD

$92.0M INVESTMENT

205 AWARDS

411 PUBLICATIONS

66,191 CITATIONS

$194.4M FOLLOW-UP FUNDING

159 FOLLOW-UP AWARDS

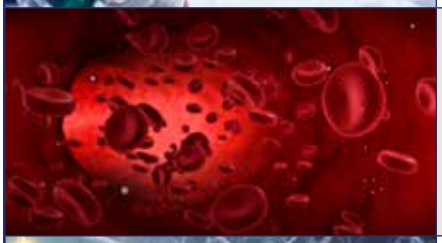
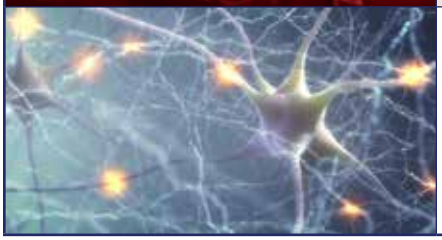
4 PATENTS

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."

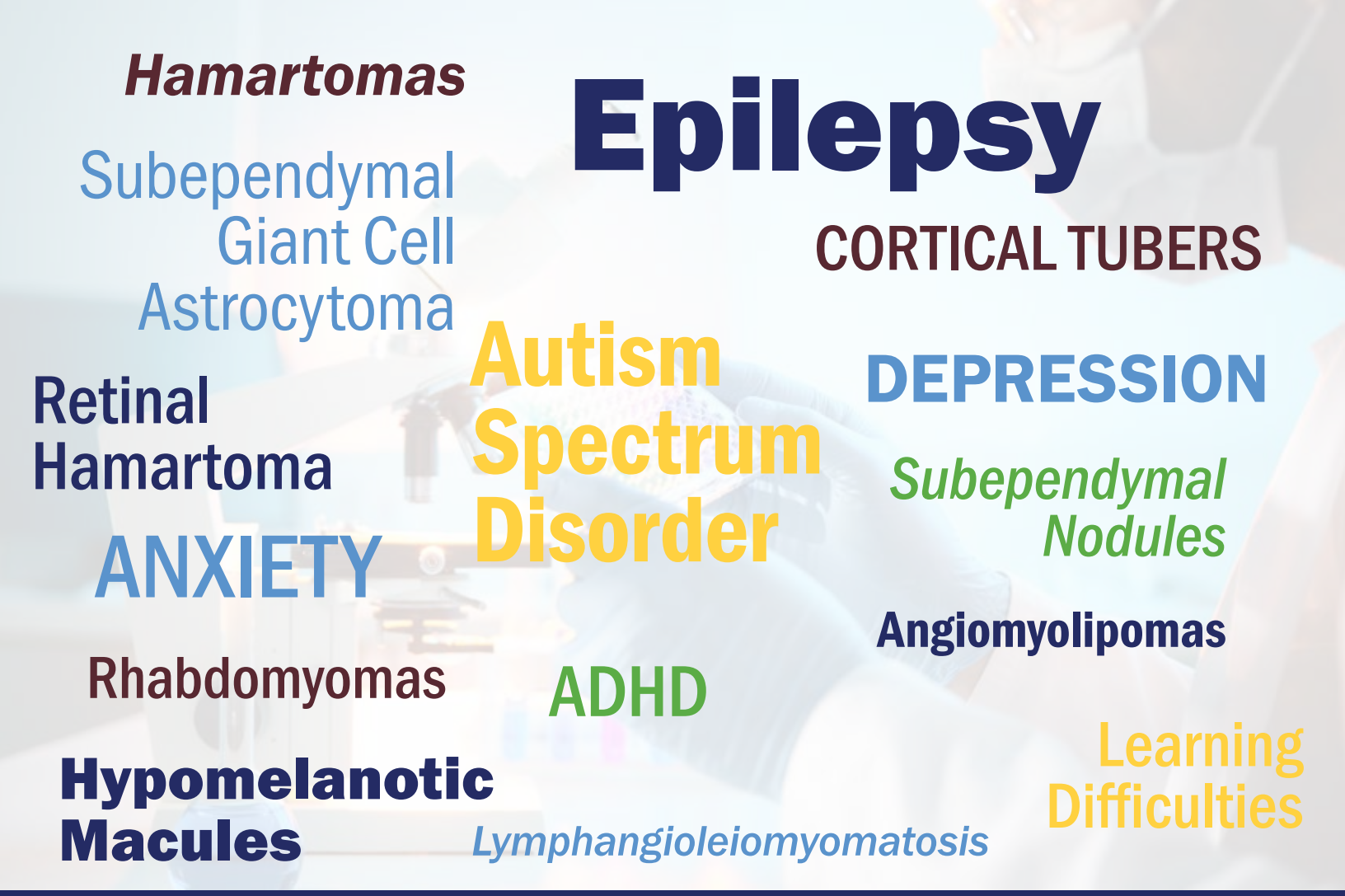
Ron Heffron, P.E., TSC Alliance
Programmatic Panel Member

"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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