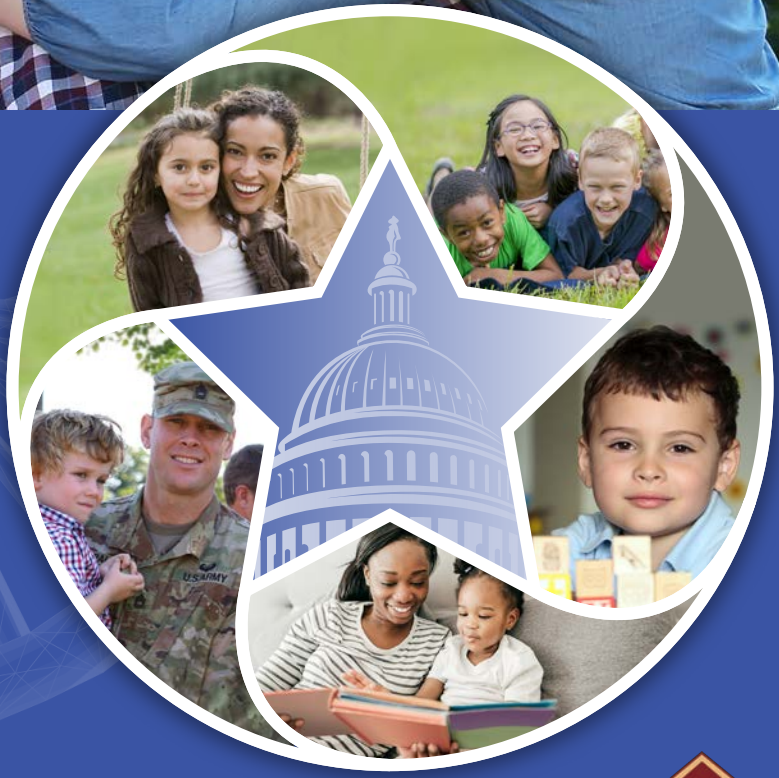
Tuberous Sclerosis Complex Research Program

Congressionally Directed Medical Research Programs

CDMRP

Department of Defense



U.S. Army Medical Research and Development Command

CONGRESSIONALLY DIRECTED MEDICAL RESEARCH PROGRAMS

HISTORY

The Congressionally Directed Medical Research Programs (CDMRP) was created in 1992 from a powerful grassroots effort led by the breast cancer advocacy community that resulted in a Congressional appropriation of funds for breast cancer research. This initiated a unique partnership among the public, Congress, and the military. Since then, the CDMRP has grown to encompass over 30 targeted programs and has received over $15 billion in appropriations from its inception through fiscal year 2020 (FY20). Funds for the CDMRP are added to the Department of Defense (DoD) budget, in which support for individual programs, such as the Tuberous Sclerosis Complex Research Program (TSCRP), 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, which is composed of leading scientists, clinicians, and TSC consumers. In this tier, the Programmatic Panel compares applications to each other and makes recommendations for funding based on scientific merit as determined in peer review, potential impact, portfolio balance, and relevance to overall program goals.

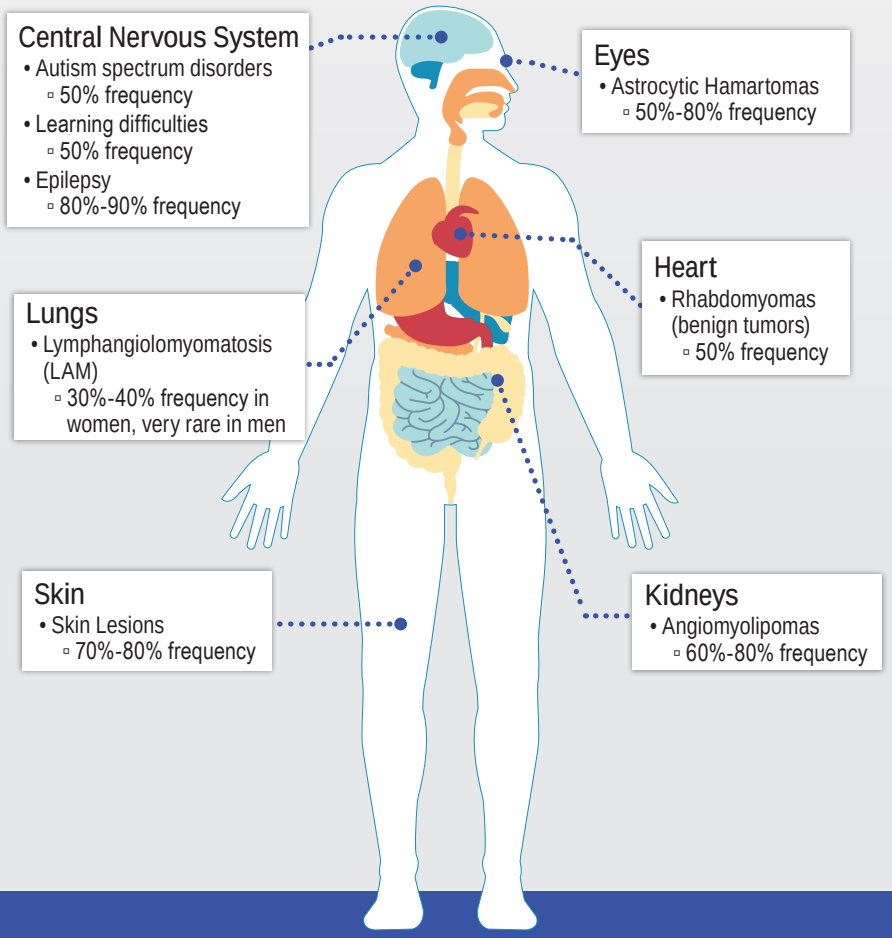
Tuberous Sclerosis Complex Research Program

ABOUT TSC AND THE PROGRAM

Tuberous sclerosis complex (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. It affects approximately 50,000 individuals in the United States and 1 to 2 million individuals worldwide.

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.

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

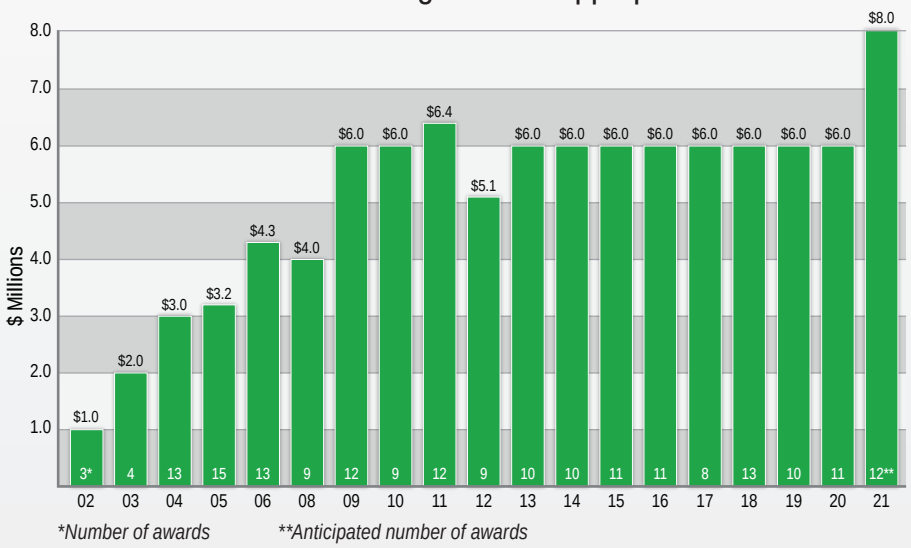


VISION: Improve prevention strategies and treatments to lessen the impact of TSC while striving for a cure

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 for the benefit of Service members, their beneficiaries, and the American public

The TSCRP was established in FY02 with a Congressional appropriation of $1M. Since then, a total of $97M has been appropriated to the program, including $8M in FY21. From FY02 to FY19, the TSCRP has funded 170 awards. Today, the TSCRP is the second largest government funding source for TSC research in the United States. Since its inception 18 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.

FY02–FY21 Congressional Appropriations



*Number of awards **Anticipated number of awards

Strategic Plan

In 2018, the TSCRP developed a Strategic Plan that sets forth the strategic goals and direction for the program. The TSCRP recognizes that a broad range of unanswered research questions are potentially critical to advancing prevention and treatment of the diverse manifestations of TSC with the ultimate goal to find a cure. The current overarching strategic goals for the TSCRP are: Tumor eradication, Epilepsy, and Neurodevelopmental features. To accomplish its strategic goals, TSCRP has identified Focus Areas for each of these goals and encourages the TSC scientific community to submit research proposals that address one of these areas:

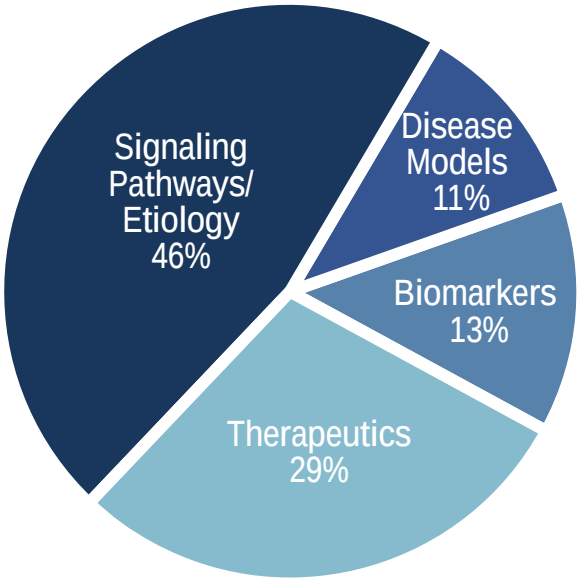
Strategic Goals	Focus Areas
Tumor Eradication	Eradicating tumors associated with TSC and TSC-associated lymphangioleiomyomatosis (LAM), including gaining a deeper mechanistic understanding of TSC signaling pathways
Epilepsy	Preventing epilepsy, improving treatment, and mitigating comorbidities associated with TSC-related seizures
Neurodevelopmental Features	Understanding the features of TSC-Associated Neuropsychiatric Disorders (TAND) and reducing their impact, including pharmacological and behavioral interventions

Portfolio Analysis

INVESTMENT BY DISEASE RESEARCH SPECTRUM

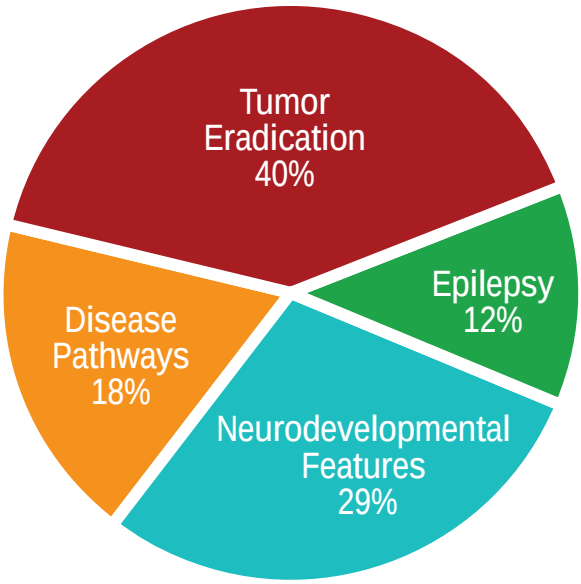
Since FY02, the TSCRP has funded research projects focused on understanding the underlying signaling pathways and disease etiology, developing disease models to further understand the disease and identify targets for treatment, identifying biomarkers, and developing new therapeutic approaches.

Analysis of the most recently funded research projects (FY14–FY19) is reflected in the pie chart on the right, indicating the percentage of the program's research investment in each area. As illustrated in the chart, approximately half of the TSCRP's funding has been invested in research understanding the basic biology underlying TSC (signaling pathways and etiology), while a quarter of the funding has focused on developing therapeutics.



INVESTMENT BY STRATEGIC GOALS

TSC is a complicated disease that manifests differently from person to person. The TSCRP strives to obtain a balanced research portfolio based on its recently established strategic goals, which reflect the current needs of the TSC Community. In addition, the TSCRP funds projects in broad scientific areas, including molecular pathways, cellular consequences of TSC deficiency, and phenotypic studies underlying all manifestations, that will inform and advance all 3 strategic goals. These projects make up the Disease Pathways category, which is included in the figure on the right showing the analysis of the portfolio from FY14 thru FY19.



The table below shows examples of funded projects in each strategic goal/priority.

Disease Pathways	Tumor Eradication	Epilepsy	Neurodevelopmental Features
• Structural Basis of TSC Assembly • Role of MicroRNA in Pathogenesis and Treatment of TSC • Mechanism of Cell Invasion in TSC/LAM	• Mechanisms of Initiation of LAM and AML tumors • Role of Microbiome in LAM • TSC Deficiency and SEGA Formation	• mTOR Targeted Inhibition of Neuronal Hyperexcitability • fMRI Directed Surgical Intervention and Optimization • Exosome Contribution to Seizure Severity	• Early Behavior Intervention to Improve Social Communication • Brain Region Specific Contribution to Autism-Relevant Behaviors • Remote Caregiver Training to Improve Social Engagement

Research Outcomes

The TSCRP has funded 170 awards, including 11 clinical awards, totaling $72.5M through FY19 to support high-impact, innovative research aimed at advancing knowledge of TSC and its clinical manifestations to the central nervous system, heart, skin, eyes, lungs, and kidneys. Importantly, the TSCRP aims to support new ideas and new investigators.

Research outcomes from these awards have led to 307 publications in peer-reviewed journals with over 38,975 citations. TSCRP-funded investigators have also received 140 additional grants which expanded upon their TSCRP-funded studies, totaling over $148M to further advance their research.

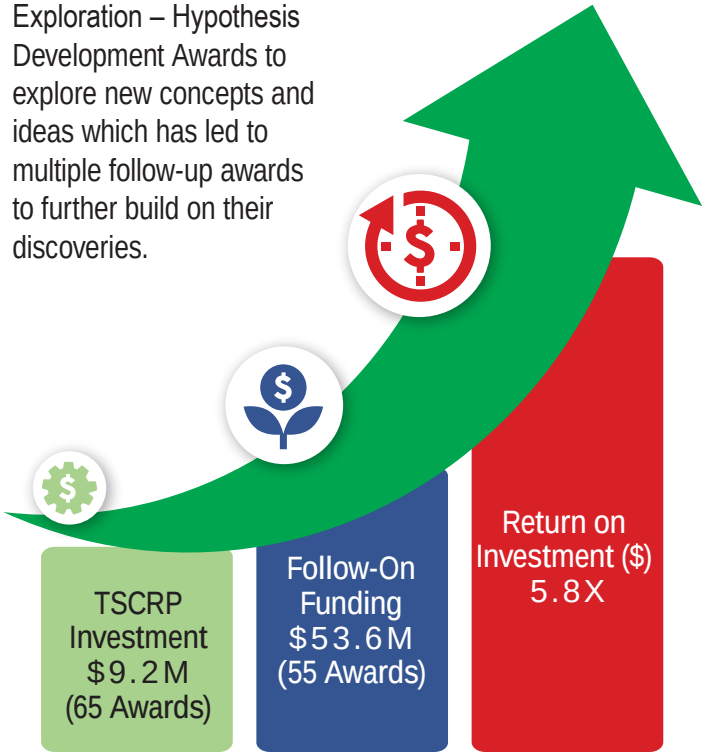
BEDSIDE IMPACT OF TSCRP CLINICAL TRIALS:

- 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. Newly funded award is an extension focused on using telemedicine.
- The Sirolimus and Autophagy Inhibition in LAM (SAIL): The combination of an autophagy inhibitor, hydroxychloroquine, with sirolimus is well-tolerated.

TSCRP Fosters New Ideas and Attracts New Investigators in the TSC Research Field

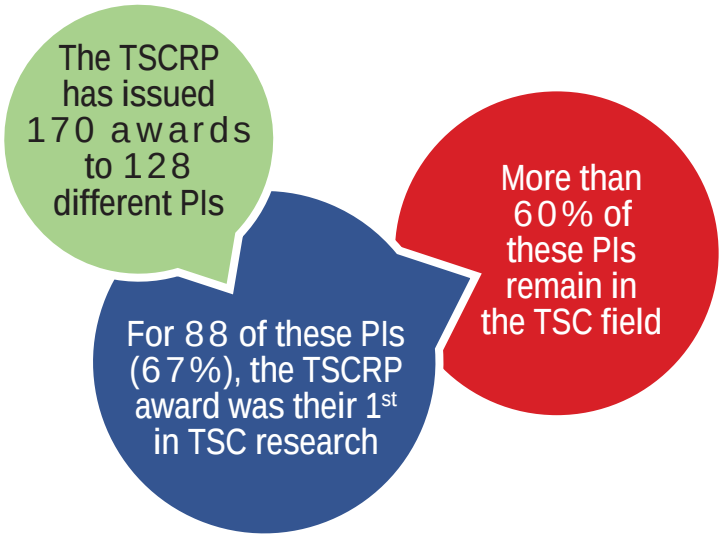
FUNDING THE EXPLORATION OF NEW CONCEPTS AND IDEAS

TSCRP has supported 65 Exploration – Hypothesis Development Awards to explore new concepts and ideas which has led to multiple follow-up awards to further build on their discoveries.



BRINGING NEW INVESTIGATORS TO THE TSC RESEARCH FIELD

Out of the 128 Principal Investigators funded by TSCRP, 88 have received their first TSC-related award from our Program, and the majority of them remain in the field.



Metabolic Imaging Biomarkers for TSC

Carmen Priolo, M.D., Ph.D., Brigham and Women's Hospital

BIOMARKERS

The majority of women with TSC develop lymphangioleiomyomatosis (LAM), a progressive disease in which muscle-like cells that line the lungs' airways and blood vessels begin to grow out of control and, over time, can destroy normal lung tissue. Clinical trials showed that the mTORC1 inhibitor rapamycin stabilizes pulmonary function; however, lung function declines and tumor growth resumes when the drug is discontinued. An important component of clinical trial design and implementation is having specific biomarkers of disease progression and response to therapy, which currently are not available in the TSC field. Dr. Carmen Priolo's long-term research goal is to address this need, as well as to understand the biochemical basis of TSC tumorigenesis.

With support from FY12 and FY15 Exploration - Hypothesis Development Awards, Dr. Priolo first sought to answer the following questions: What are the major nutrients used by TSC tumor cells to grow and proliferate? What are the major fuels of TSC tumors? How is utilization of these fuels impacted by rapamycin? To start, she used metabolic assays to identify nutrients that are preferentially processed by TSC2-deficient cells. She found that some of these nutrients are important for tumor cells to grow and double and are utilized by TSC tumors to make macromolecules or generate energy. Dr. Priolo then teamed up with the Gordon Center for Medical Imaging at Massachusetts General Hospital, Boston, to chemically modify specific nutrients (choline and acetate) to generate radioactively labeled derivatives [18F]fluorocholine (FCH) and [18F]fluoroacetate (FACE) to test their potential as biomarkers. Positron Emission Tomography (PET) imaging uses radiolabeled derivatives of nutrients to noninvasively detect body cells that have an increased uptake and consumption of these nutrients. Using PET imaging in preclinical models of TSC and LAM, Dr. Priolo and her team showed that TSC2-deficient tumors exhibited rapid uptake of [18F]FCH and [18F]FACE. These findings provide evidence for testing the potential of [18F]FCH and [18F]FACE as metabolic imaging biomarkers in TSC and LAM.

Referring to what has contributed to her success, Dr. Priolo has stated, "Funding from the DoD TSCRP has been truly critical to support our work. I believe that our strength resides in the multidisciplinarity of our team, which includes physician-scientists, molecular biologists, physicists, and chemists. We brainstormed together to find solutions and set up a platform to test TSC tumor metabolic features generating consistent and rigorous preclinical data that may serve as the first required step to move as quickly as possible to clinical studies. We will be able to use this platform for future studies not only to identify the best potential metabolic biomarkers of TSC, but also to increase our understanding of the molecular mechanisms involved in TSC tumorigenesis."

Targeting Autophagy for the Treatment of TSC and LAM

Elizabeth Henske, M.D., Brigham and Women's Hospital

THERAPEUTICS

BIOMARKERS

A common comorbidity of TSC is the lung disease lymphangioleiomyomatosis (LAM), which is caused by the overproliferation of smooth muscle cells and cysts in the lungs, leading to breathing problems and lung failure. The current standard of care treatment for LAM is management with Sirolimus (Rapamycin), which inhibits mTORC1 and triggers autophagy, a process which degrades and clears damaged cells and cellular components. Unfortunately, when Sirolimus treatment is discontinued, patients' lung function deteriorates; therefore, significant research efforts aim to identify a treatment for LAM with a sustained response.

Previous findings indicate that administration of autophagy inhibitor hydroxychloroquine in combination with Sirolimus decreased survival of TSC2-deficient cells and reduced the tumor size in mouse models.

Dr. Elizabeth Henske received an FY11 Clinical Trial Award to examine the safety, efficacy, and physiological impact of combining these two drugs, Sirolimus and hydroxychloroquine, in a Phase I clinical trial of patients with TSC-LAM. The study was designed to measure the tolerance and safety of administering Sirolimus and hydroxychloroquine in LAM patients (NCT 01687179). This study demonstrated that the combination of these drugs is well-tolerated, with no dose-limited adverse effects up to 48 weeks. To further examine the impact of this combination therapy, Dr. Henske, along with Dr. Carmen Priolo, investigated metabolic changes in response to treatment to determine the level of nutrient loss that could occur in LAM patients receiving this treatment. They observed that serum methylthioadenosine (MTA) levels (a tumor suppressor) increased in response to treatment, providing a potential biomarker for determining whether a LAM patient is responding positively to the treatment.

In follow-on work led by Dr. Souheil El-Chemaly, the Henske group further assessed Sirolimus and autophagy inhibition combination therapy, focusing on biomarker identification that could directly elucidate the process of disease progression and therapy response. The team found that serum soluble vascular endothelial growth factor receptor (VEGFR)-3 and C-C motif chemokine ligand 21 (CCL21) levels decreased in LAM patients treated with the combination therapy. Both VEGFR-3 and CCL21 are closely linked to VEGF-D, the only current diagnostic biomarker for LAM. Expression of these two proteins is also associated with lymphatic endothelial biology and is therefore believed to be linked to the pathology of LAM. This discovery and the resulting ability to diagnose LAM via confirmed biomarkers could provide more effective ways to diagnose, treat, and monitor LAM and TSC. In addition to continuing to evaluate biomarkers, Dr. Henske hopes to continue investigating the long-term effects and efficacy of Sirolimus and hydroxychloroquine combination therapy in larger Phase II/III clinical trials in order to improve quality of life for patients.

A New Therapeutic Strategy: Treating Seizures by Inhibiting Neuron Hyperexcitability in TSC

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

DISEASE MODELS

THERAPEUTICS

Tuberous Sclerosis Complex (TSC) is a rare genetic disorder characterized by non-malignant tumor growth in multiple organs which, when presented in the brain, can lead to epilepsy, developmental delays, intellectual disability, and autism. TSC is caused by mutations in either the TSC1 or TSC2 gene. When functioning properly, these genes code for proteins that bind together to form a complex that negatively regulates the mammalian target of rapamycin (mTOR) pathway. mTOR inhibitors have been successful in the past; however, it remains unknown which neuronal proteins mTOR regulates and how malfunctions in the TSC/mTOR pathway could result in the neurological symptoms observed in TSC.

Patients with TSC typically present with masses called tubers in their brain that interfere with normal brain development and often become a focus of seizures. Dr. Akira Yoshii and his team found that there are multiple critical windows for the mTOR inhibitor treatment to correct different aspects of structural abnormalities in TSC, and the responses depend on the stage of neuronal circuit formation. These results require an additional therapeutic (for example, treatment with Vigabatrin, a drug that blocks the degradation of the inhibitory neurotransmitter GABA, and reduces infantile spasms).

With support from an FY08 Career Development Award, Dr. Akira Yoshii and his team sought to find another therapeutic target by determining whether abnormal protein synthesis caused by malfunctions in the TSC/mTOR pathway triggers an imbalance in neuronal excitation and inhibition in the TSC brain. Using a mouse model with a mutation in the Tsc1 gene and gene sequencing approaches, Dr. Yoshii discovered dysregulation of more than 30 gene transcripts in the brain of mice with a deleted Tsc1 gene. For example, the Arc protein, which mediates synaptic transmission, was decreased in the brain of mice harboring the Tsc1 gene mutation compared to mice with normal Tsc1 gene function. Dr. Yoshii rationalized that an insufficient amount of the Arc protein results in a buildup of neurotransmitter receptors at the termini of neurons, leading to hyperexcitability in Tsc1-deleted neurons. To confirm this, Dr. Yoshii and his team measured neurotransmitter receptors at neuronal termini, which revealed that the ratio between excitatory AMPA and inhibitory GABA receptor subunits was biased toward hyperexcitability in Tsc1-deleted neurons. In agreement with the biochemical results, electrophysiological studies of the cortical neuronal circuit in Tsc1 mutant mice also showed evidence for hyperexcitability. To further define hyperexcitability in TSC1 mutant neurons, Dr. Yoshii is currently using image analysis, which indicates Tsc1-deleted neurons show an abnormal pattern, indicative of continual neuron activation, while non-mutant neurons exhibit both increases and decreases in calcium levels. To determine whether the observed hyperexcitability in Tsc1-deleted neurons can be corrected, Dr. Yoshii treated these neurons with an inhibitor of a neurotransmitter receptor, which returned abnormal calcium levels to those observed in normal neurons, thus highlighting the candidate molecule as a potential therapeutic to treat neurological symptoms of TSC.

Neurological manifestations of TSC dramatically affect a patient's quality of life and, through this work, the relationship between neuronal protein synthesis and neuron hyperexcitability in the TSC brain has helped identify potential therapeutics that reduce the burden of this disease. Dr. Yoshii continues to investigate novel compounds that inhibit neuron hyperexcitability in an effort to provide multiple treatment options for patients.

Neural Circuits Underlying Autism Relevant Behaviors in TSC

Peter Tsai, M.D., Ph.D., University of Texas, Southwestern Medical Center

SIGNALING PATHWAYS

THERAPEUTICS

Within the TSC community, there is a very high prevalence of autism spectrum disorders (ASDs) – often approaching 50%. ASDs are neuropsychiatric disorders characterized by social impairment and repetitive, restrictive, or inflexible behaviors. Despite the high prevalence in TSC and in the population at large, the underlying mechanisms remain poorly understood and, to date, no targeted therapies exist for this disorder. Clinical studies have implicated dysfunction of the cerebellum in the pathogenesis of autism, and Dr. Tsai and his team have generated a TSC model that demonstrates that cerebellar dysfunction is sufficient to generate ASD behaviors. They have additionally shown that inhibition of a specific cerebellar domain, RCrusI, also generates ASD behaviors, while stimulation of this domain rescues social behaviors in the TSC mouse model. However further research is needed to elucidate how this cerebellar domain regulates these behaviors.

With support from an FY16 Idea Development Award, Dr. Tsai and his team aimed to study how the RCrusI domain regulates autism-relevant behaviors in TSC. They hypothesized that the RCrusI domain regulates these behaviors via modulation of cerebellar output nuclei, the deep cerebellar nuclei (DCN), and downstream neural circuit connections. Through this work, they have identified that RCrusI largely targets the lateral, dentate nucleus (DN), with observations that activity in DN is increased in a PC-Tsc1 mouse model of TSC. Upon further evaluation of the anatomic pathways connecting these two regions, they found that the connections between RCrusI and the parietal association cortex are mediated via the DN cerebellar output nucleus. They also identified rescue of social behaviors in multiple paradigms, including social approach and social olfaction testing, in PC-Tsc1 mice upon inhibition of the DN. However, unlike with social behaviors, they observed no evidence for rescue of repetitive and inflexibility behaviors.

Together these findings support the hypothesis that the parietal association cortex is mediating cerebellar-regulated ASD behaviors in TSC and that modulation of parietal association cortex function is sufficient to rescue social behaviors in PC-Tsc1 mutant mice. These data point to the critical role of cerebellar-cortical circuits in the regulation of ASD relevant behaviors in TSC and the ability to modulate behaviors (specifically social behaviors) in mutant animals during adulthood. This raises the prospect that circuit modulation may provide a therapeutic opportunity for social behaviors and that this modulation might have potential benefit even into adulthood. Ultimately, Dr. Tsai's team hopes these translational studies will lead to a clinical benefit for individuals with TSC and potentially to individuals with ASD even outside of TSC.

In The Pipeline

Tumor Eradication

Disease Models | *Biomarkers*

A Subependymal Giant Cell Astrocytoma (SEGA) Mouse Model

Dr. David Feliciano of Clemson University received an Idea Development Award to study TSC signaling pathways and the cellular consequences of TSC deficiency in Subependymal Giant Cell Astrocytomas (SEGAs). Dr. Feliciano will determine how SEGAs form and how specific substrates of mTORC1 are altered within different cell types. The team will determine whether TSC SEGAs can be permanently destroyed using a class III mTORC1 inhibitor called Rapalink1 or ATRA.

Disease Models

An Innovative Model System of Cell Invasion in TSC/LAM to Uncover New Drug Targets and Therapies

Dr. Elaine Dunlop of Cardiff University received an Exploration - Hypothesis Development Award to develop a novel in vitro model of LAM to assess the core drivers of LAM cell invasion into the lung. Using this knowledge, Dr. Dunlop will design and test therapies to block invasion, as well as investigate circulating cells for potential biomarkers. This project will develop a key tool to study LAM cell invasion and potentially identify novel LAM biomarkers.

Epilepsy

Signaling Pathways/Etiology

Exosome Contribution to Social Deficits in TSC

Dr. Angelique Bordey of Yale University received an Idea Development Award to study the contribution of extracellular nano-sized vesicles, called exosomes, to the social deficits in TSC. Dr. Bordey's team is currently studying exosomes released from TSC mutant neurons and how those may lead to autistic traits and seizure worsening over time. This work will lay the foundation for future work on exosomes in TSC and other neurodevelopmental disorders.

Therapeutics

Using Resting State Functional MRI to Find the Correct Surgical Target to Stop Seizures in TSC

Dr. Varina Boerwinkle, M.D. at Phoenix Children's Hospital received a Clinical Translational Research Award to improve surgical outcomes in children with epilepsy due to TSC using resting state functional MRI (RS). Pre-surgery, RS will identify the specific brain area(s) in which the seizures arise. Post-surgery, RS will determine whether the area was surgically removed and seizure outcomes improved. This study will also enroll patients at the Cincinnati Children's Hospital, and Texas Children's Hospital.

Neurodevelopmental Features

Signaling Pathways/Etiology

Modeling TSC and Translating for Therapeutics with Human Cerebral Organoids

Dr. Zhexing Wen of Emory University received an Exploration - Hypothesis Development Award to develop patient-specific induced-pluripotent stem cells (iPSC)-derived 3-D cerebral organoids as a translational model to study the mechanisms underlying developmental deficits of TSC. Dr. Wen will investigate whether TSC mutations act through the mTOR pathway to impair neural development and function, and if mTOR-targeting therapeutics could rescue developmental deficits in TSC.

Therapeutics

Using a Remote Caregiver Training to Improve the Social Engagement and Social Communication in Children with TSC

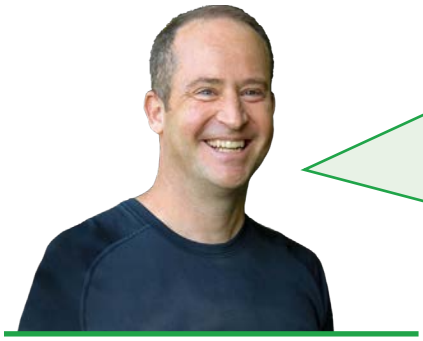
Dr. Connie Kasari at the University of California, Los Angeles, received a Clinical Translational Research Award to improve social engagement and communication in children with TSC. This study builds on a previously funded TSCRP pilot clinical trial and assesses the therapist- and parent-mediated intervention JASPER (Joint Attention; Symbolic Play, Engagement, and Regulation) using a remote training program. In the adapted version of JASPER, called TSC Remote Assessment and Intervention (TRAIN), all training, after an initial consultation, is via weekly teleconferences and video feedback.

Scientists and Consumers Working Together

The two-tier review process established by the CDMRP brings together the expertise of scientists with the perspective and experience of individuals living with TSC or the families of individuals with TSC. This innovative approach has proven to be an effective way to evaluate research applications for their potential to meet the program's goals for those impacted by TSC. Individuals with TSC and their family members have an equal voice in the research administration of setting the TSCRP's vison, reviewing applications, and making final funding recommendations. From their unique perspective gained through personal experience, consumers bring a sense of urgency and focus to each part of the program cycle. Consumers evaluate the impact of the research to individuals with TSC, as well as the needs of their family members and caregivers and the clinicians who treat them. Working together, TSC researchers, clinicians, and consumers ensure that the TSCRP funds the most relevant, groundbreaking, innovative, and high-risk/high-reward projects to end TSC.

"My first study in TSC was funded by the TSCRP, and it was focused on understanding the earliest underpinnings of autism in early infancy. This study has now paved the way for the first randomized clinical trial of early intervention for infants with TSC. This TSCRP funding is critical to launch careers, and it encourages 'outside the box' investigations that could lead to true breakthroughs. I feel honored to be able to give back to the TSCRP by serving on the Programmatic Panel with other advocates, clinicians and researchers, and we are all committed to funding research that will substantially improve outcomes for individuals with TSC."

Shafali Jeste, M.D., University of California, Los Angeles, Programmatic Panel Member



"There have been great leaps in the research and treatment options due to the work that we look to advance through the TSCRP. I am confident, when looking at what has been accomplished in this short time that we can and will have a significant, positive impact on those who struggle with the effects of TSC every day."

Matt Bolger, Tuberous Sclerosis Alliance, Consumer Peer Reviewer

"The TSCRP was one of the first sources of research support I was awarded when starting my independent research group. Receiving that grant was an incredible boost for a junior scientist, and the findings from that research fueled an enduring passion for studying TSC. Now, as an established investigator, I am honored to serve on the TSCRP scientific review committee and help encourage the next wave of researchers. This program is especially meaningful because it reflects many of the priorities of TSC patients, advocates, and families; working with the consumer reviewers from the TSC community reminds us of the greater purpose behind all those late nights in the lab!"

Rebecca Ihrie, Ph.D., Vanderbilt University School of Medicine, ***Scientific Peer Reviewer***

"I am proud to serve as a consumer reviewer. I encourage all who are involved with the Tuberous Sclerosis Alliance and March on the Hill to at least ask about the volunteer process to serve as a consumer reviewer. You can make a difference in ways one never thought."

Danielle Garcia-Clark Tuberous Sclerosis Alliance, Consumer Peer Reviewer

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