CDMRP

Department of Defense

Tuberous Sclerosis Complex Research Program

U.S. Army Medical Research and Materiel Command

Congressionally Directed Medical Research Programs (CDMRP)

The CDMRP originated in 1992 via a Congressional appropriation to foster novel approaches to biomedical research in response to the expressed needs of its stakeholders—the American public, the military, and Congress.

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

The CDMRP has grown to encompass multiple targeted programs and has received over $11.2 billion in appropriations from its inception through fiscal year 2016 (FY16). 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.

Tuberous Sclerosis Complex Research Program

VISION
To lessen the impact of TSC

MISSION
To encourage innovative research aimed at understanding the pathogenesis, and preventing and treating the manifestations of TSC

PROGRAM GOALS

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

ABOUT THE DISEASE

Tuberous Sclerosis Complex (TSC) is a genetic disorder that causes non-malignant tumors to form in many different organs, primarily in the brain, eyes, heart, kidney, skin, and lungs. It presents itself in a variety of clinical manifestations; however, the aspects of TSC that most strongly impact quality of life are generally associated with the brain: seizures, developmental delay, intellectual disability, and autism. The incidence and severity of the various aspects of TSC can vary widely between individuals—even between identical twins.

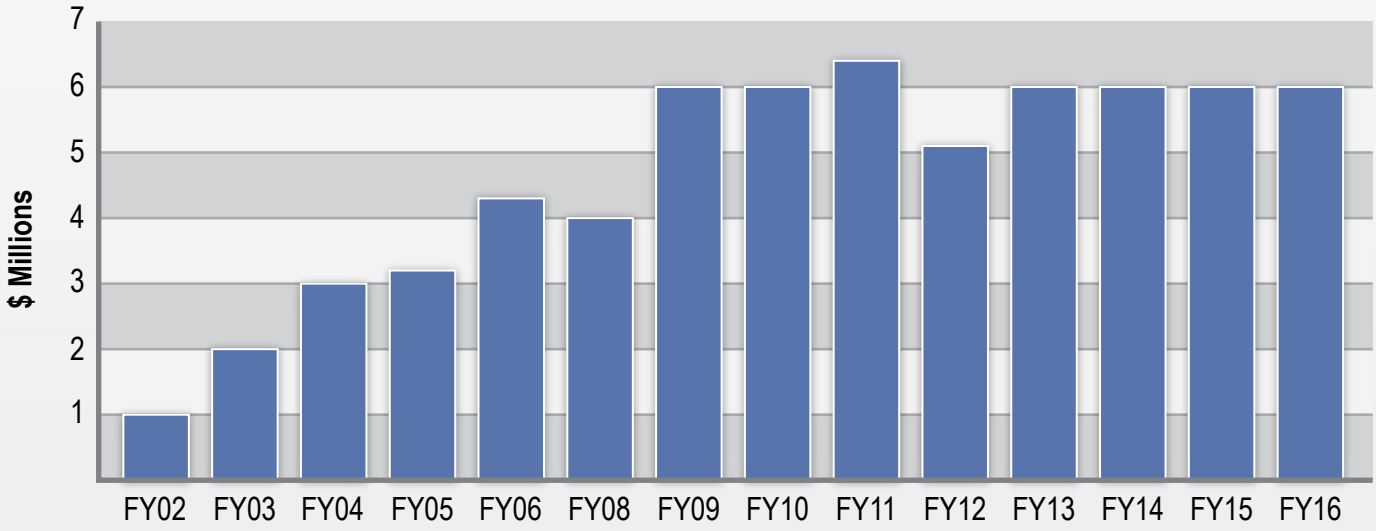
TSC can be inherited as an autosomal dominant trait; however two-thirds of cases are the result of a spontaneous genetic change on one of two genes: TSC1 or TSC2. The TSC1 gene is located on chromosome 9 and is called the hamartin gene. The other gene, TSC2, is located on chromosome 16 and is called the tuberin gene.

It is estimated that TSC affects approximately 50,000 individuals in the United States, and 1 to 2 million individuals worldwide. Many cases may remain undiagnosed for years or decades due to the relative obscurity of the disease and the mild form symptoms may take in some people.

History of the TSCRP

The TSCRP was first funded in FY02 when the efforts of TSC advocates led to a Congressional appropriation of $1 million (M). Since then, a total of $65M has been appropriated to the program, including $6M in FY16. Today, the TSCRP is one of the leading sources of extramural TSC research funding in the United States.

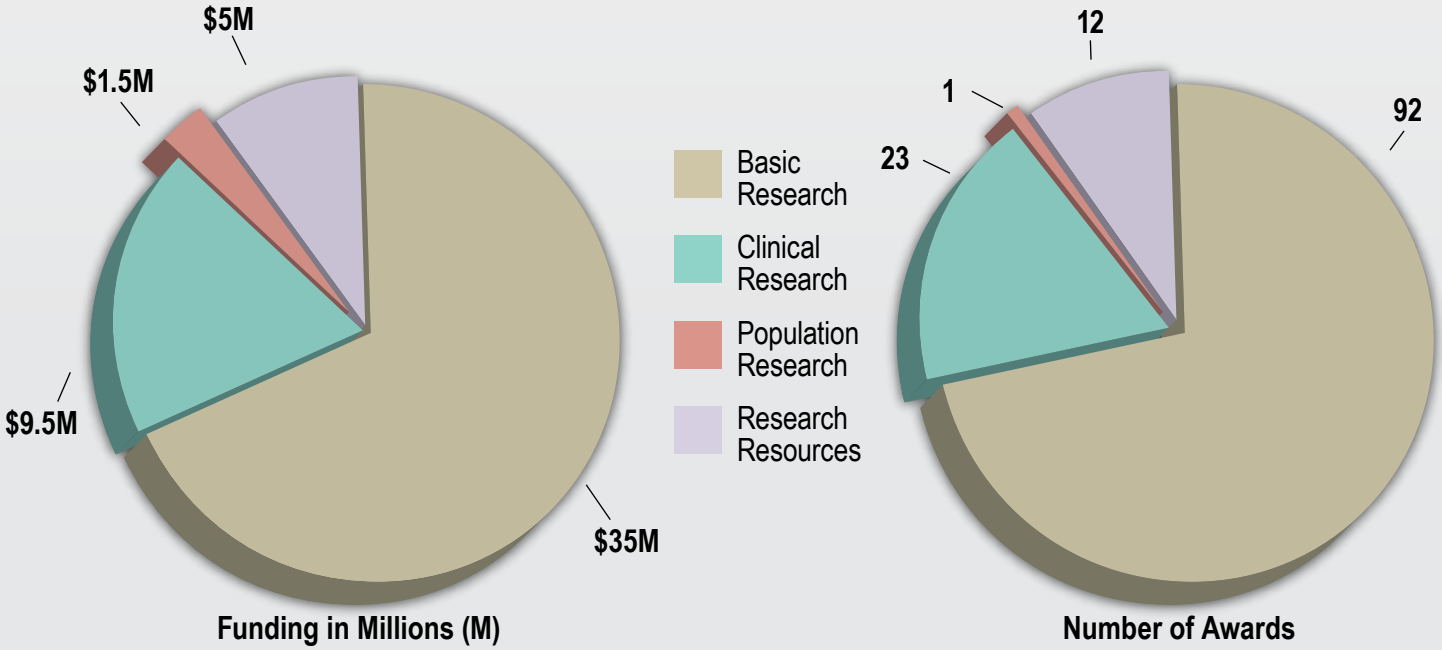
FY02–FY16 Appropriations*



**There were no appropriations for the TSCRP in FY07.*

FY02–FY15 Portfolio

The portfolio is displayed as funding in millions and number of awards for each research category.



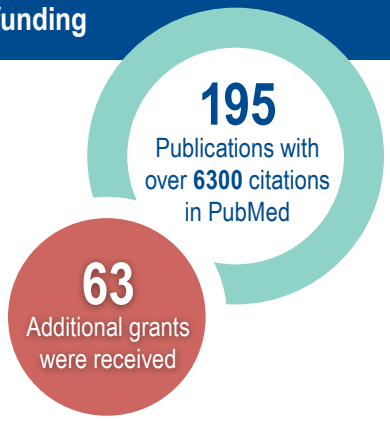
Research Outcomes

2015 Survey

In August 2015, the TSCRP surveyed the Principal Investigators (PIs) funded by the TSCRP (FY02–FY13) and requested that they provide information to assess research outcomes and the impact of their research on TSC and non-TSC diseases. The PIs were asked to report any **publications** directly related to their TSCRP projects, **additional funding** received to further advance their TSCRP-funded research, the research fields impacted, impact on patient care, resources developed and shared, and researchers and/or clinicians trained.

A total of 80 PIs of the 107 contacted responded to our survey, for a 75% response rate. Note that the majority of non-responders were funded between FY04 and FY06.

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



TSCRP-funded research has impacted clinical care by leading to effective, safe, inexpensive treatment, more accurate diagnostics, or disease prevention

Examples of projects that directly impacted patients

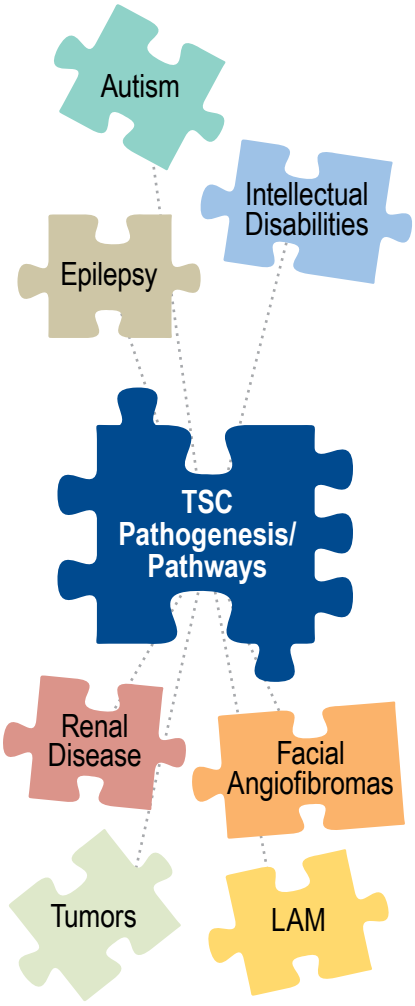
FY08 – Tsang, S: (1) Diagnostic procedure for TSC using infrared and SD-OCT will likely improve the accuracy of diagnosis. (2) Vigabatrin-intervention involves encouraging patients to decrease their light exposure to prevent, or at least decelerate, vision loss.

FY08 – Darling, T: Led to recommendations for sun protective measures in TSC patients.

FY09 – McCormack, F: Provided necessary evidence allowing doctors with patients who have cystic changes on CT scans to order a serum VEGF-D test to make the diagnosis of lymphangioleiomyomatosis (LAM) without biopsy.

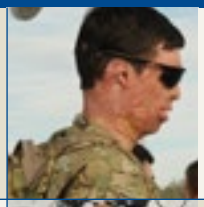
FY10 – Koening, MK: A new, safe, inexpensive, and effective treatment has been developed for facial angiofibromas. TSC patients are instructed to wash their face at bedtime and, once dry, to apply a small amount of topical rapamycin to the angiofibroma. It is becoming more accepted in the medical community and is sometimes covered by insurance companies, a great help to families.

TSCRP-funded research spans multiple research fields



TSCRP-funded research impacted several military-relevant conditions

Traumatic Brain Injury/Seizure/ Epilepsy



Skin Regeneration

Depression and Aggressiveness

Injury

Vision

Renal Cancer and Agent Orange

A wide variety of **research resources** were developed by several TSCRP-funded projects* and shared with the Research Community

21*	Mouse Models
11	Expression Plasmids
2	Zebrafish Models
2	Pharmacological Inhibitors
1	Drosophila Models
1	Proteomics Data
2	Yeast Lines
1	Serum Samples
15	Cell Lines
1	3D TSC1 Structure
3	Antibodies

**The number represents the number of projects that produced the resource indicated.*

TSC Training

TSCRP-funded projects led to development of several tools that enhance basic and clinical research

DATABASE	**FY04 – Sparagana, S:** Developed a central database (now utilizing Study Trax) of information about a large number of TSC individuals, such as the relationship between TSC genotype and phenotype; influence of biochemical changes, such as hormones or neurotransmitters on each manifestation of TSC; treatment outcomes for all of the medical complications of TSC.
SOFTWARE	**FY04 – Sabatini, D:** Developed the CellProfiler software package for cell-image analysis.
SCREENING TOOL	**FY05 – Su, TT:** Led to improving the methods for using *Drosophila* as a screening tool.
NETWORK	**FY09 – McCormack, F:** Developed the LAM Clinic Network, linked by a repository and registry.

Understanding TSC Pathogenesis

FY02

Henske, E: Discovered the *S. pombe* homologs of the TSC genes, and showed that they function as a protein complex.

FY03

Sabatini, B: Showed a cell-autonomous function of the TSC pathway in controlling the number, strength, and properties of excitatory synapses.

Kaelin, W: Showed that the TSC complex regulates VEGF in both mTOR-dependent and mTOR-independent ways, and that hypoxia regulates mTOR through TSC.

Krymskaya, V: Found that TSC2 modulates the actin dynamics and cell adhesion through the TSC1-binding domain and Rac1 GTPase.

FY04

Matsumoto, T: Using fission yeast demonstrated that an inhibitor of FTase (FTI) should be considered an anti-TSC drug and that a mutation in human Rheb may cause a symptom similar to that found in patients with TSC.

Chada, K: Identified an independent signaling pathway of the mTOR pathway; found that HMGA2 plays a role in LAM tumorigenesis.

Tamanoi, F: Established that Rheb activates mTOR and that the activation of mTOR is central to pathogenesis related to TSC deficiency.

Guan, K-L: Showed that TSC1 stabilizes TSC2 by inhibiting the interaction between TSC2 and the HERC1 ubiquitin ligase.

FY05

McNeill, H: Identified PntP2 as a novel target of TOR in regulating neuronal differentiation.

Kim, D-H: Identified PLD2 and PRAS40 as new components of TSC-mTOR signaling.

Stokoe, D: Showed that TSC1/TSC2 complex regulates protein translation through mTORC1-dependent and independent mechanisms, and implicates a discrete profile of deregulated mRNA translation in TSC pathology.

Guan, K-L: Discovered that TSC1 regulates TOR complex 2 (TORC2) indirectly through the TORC1/S6k pathway.

Guan, K-L: Showed that TSC mutant cells are easily killed by stress, particularly when p53 is activated.

FY06

Selleck, S: Found that Tsc1/2 affects signaling of molecular pathways that alter the development of the nervous system and function of mature synapses.

Sabatini, D: Discovered the Ragulator-Rag-v-ATPase complex that serves as an important amino acid-regulated docking site for mTORC1 on lysosomal membranes; elucidated the three-dimensional structure of human mTORC1; defined the mTOR-regulated phosphoproteome; deciphered the underlying mechanism of rapamycin resistance.

Gambello, M: Found that Tsc2 loss in Purkinje Cells causes increased cell size followed by autophagic death.

Guan, K-L: Connected mTOR regulation to cellular stress response via BNIP3.

Kim, D-H: Identified nuclear proteins, including those involved in DNA damage responses, that are regulated by mTOR.

Sun, Z: Showed reciprocal interaction between cilia and the Tor pathway.

Nellist, M: Improved classification of TSC-causing and benign TSC1 and TSC2 variants; provided insight into genotype-phenotype correlations in TSC; identified TSC1 and TSC2 functional domains; provided insight into structural features of the TSC complex.

Kriegstein, A: Showed that TSC can target the radial glial progenitor cell population and thereby cause both proliferation and migration phenotypes.

and Pathways

Guan, K-L: Identified the mechanism by which Rag GTPase regulates TORC1 activation, additional regulators of TORC1 in response to amino acids (protein building blocks), and the crosstalk between the mTOR and cAMP-PKA pathways.

Astrinidis, A: Showed that pharmacological inhibition of Polo-like kinase 1 (PLK1) by BI-2536 decreases the viability and survival of hamartin and tuberin-deficient cells via induction of apoptosis and attenuation of autophagy.

Zervas, M: Established a mouse model with both Tsc1 alleles specifically deleted in thalamic neurons and showed both behavioral symptoms and anatomical changes in the brain.

Qian, S-B: Found that mTOR/TSC signaling influences elongation speed, thereby affecting the quality of translational products.

Shaw, R: Showed that the ULK1 inhibitor, SBI-0206965, suppresses autophagy induced by mTOR inhibition and prevents ULK1-dependent cell survival following nutrient deprivation by

Breakefield, X: Developed a stochastic model of Tsc1 lesions in mouse brain.

Priolo, C: Revealed information on a novel metabolic pathway, lysophosphatidylcholine synthesis, altered in TSC.

Guan, K-L: Found new mechanisms of mTOR regulation involving the cAMP pathway, and showed that high mTOR activity is the major contributor to TSC pathology.

Xu, W: Provided the first three-dimensional structure of TSC1 and visualized the chemical details of TSC1-TBC1D7 interaction.

Sahin, M: Showed that loss of TSC1/2 genes results in myelination deficits via CTGF.

Kim, D-H: Connected the roles of mTORC1 in the endosomal trafficking process, with SH3BP4 involved as a potential target for TSC.

FY08 FY09 FY10 FY11 FY12 FY13

Manning, B: Revealed a novel pre-programmed adaptive response triggered by elevated mTORC1 signaling that counters the enhanced protein synthesis with the production of more proteasomes to help prevent proteotoxic stress.

Gan, B: Showed that under energy stress conditions, FoxO cooperates with the TSC1/TSC2 complex to inhibit mTORC1; also upregulates BNIP3, which then binds to and inhibits Rbeb, leading to mTORC1 inactivation in an AMPK-TSC-independent manner.

Ess, K: Generated and characterized a tsc2/p53 mutant zebrafish model; showed a high conservation of tsc2 gene function in zebrafish as compared to humans.

Wood, T: Established mouse model with inducible TSC1 deletion in the oligodendrocyte lineage.

Perrimon, N: Identified three genes, mRNA-cap, Pits1re, and CycT, which when mutated in the background of TSC1 or 2 mutations cause cells to die, providing potential TSC therapeutics.

Zervas, M: Elucidated the early developmental alterations and the developmental progression of TSC and resulting long lasting persistent changes in brain structure, function, and behavior.

Qian, S-B: Developed a high-resolution ribosome profiling approach to more accurately map start codon positions and corresponding initiation rates, and used it to show variations of start codon selection and also highlighted a dynamic range of initiation rates in response to nutrient starvation, which plays a key role in programmed cell death in TSC-deficient cells.

Studying Clinical Manifestations

CENTRAL NERVOUS SYSTEM

- Autism
- Epilepsy

FY02

Gutmann, D: Created the first genetically-engineered mouse strain with TSC-related epilepsy, and found that Rapamycin treatment can suppress seizure formation.

FY03

Sabatini, B: Showed a cell-autonomous function of the TSC pathway in controlling the number, strength, and properties of excitatory synapses; considered cellular defects in TSC and used it as a model of autism.

FY04

Chada, K: Showed that HMGA2 plays a central role in LAM.

Tamanoi, F: Showed that activation of Rheb is a central feature of LAM.

FY05

Crino, P: Performed the first comprehensive autopsy study in TSC and defined the presence of micropathology, which may account for autism and other intellectual disorders in TSC.

Crino, P: Showed activation of inflammatory pathways in the TSC brain and the role of mTOR signaling in lesion formation.

FY06

Nellist, M: Improved the classification of TSC-causing and benign TSC1 and TSC2 variants' role in non-TSC autism.

Nellist, M: Improved the classification of TSC-causing and benign TSC1 and TSC2 variants in non-TSC epilepsy; provided the functional characterization of DEPDC5 variants in focal epilepsy.

TUMORS

- Eyes – Astrocytomas
- Skin – Angiofibromas
- Lungs – Lymphangioleio myomatosis (LAM)
- Kidneys – Angiomyolipomas

Yoshii, A: Found that the balance between excitation and inhibition is altered in TSC, and the abnormal dendritic activity can be normalized by a serotonin receptor antagonist, leading to potential treatments.

Tsang, S: Showed that light exposure aggravates Vigabatrin (VGA)-toxicity in epileptic patients, which led to the recommendation that patients taking VGA decrease their exposure to light.

Yoshii, A: Found that the balance between excitation and inhibition is altered in TSC, and the abnormal dendritic activity can be normalized by a serotonin receptor antagonist, leading to potential treatments.

Bordey, A: Developed a unique novel model of focal cortical malformations that resemble cortical tubers in TSC; reported the activation of a novel molecular pathway that contributes to the TSC cortical tubers; showed that the cortical tubers are the causes of epilepsy.

Nelson, C: Identified early behavioral and electrophysiological markers of ASD; confirmed that the ASD diagnosis in TSC can reliably be made in the toddler years, and that many of the core social communication features of ASD in TSC are comparable to those in toddlers with non-syndromic ASD.

Bear, M: Demonstrated the efficacy of mGluR5 PAM treatment at both the synaptic and behavioral level. Found this is critical to determine a patient's spectrum of synaptic (dys) function in order to identify an appropriate therapeutic intervention.

Sulzer, D: Showed that normal TSC gene function is required for normal developmental pruning, and abnormal function is associated with autism.

Wong, M: Showed that specific inflammatory cytokines and chemokines are abnormally activated during epileptogenesis, and treatment with anti-inflammatory drugs specific to these inhibits pathological abnormalities, decreases seizures, and improves survival in a TSC mouse model.

FY08

Tsang, S: Determined optimal imaging techniques (infrared and SD-OCT) for detecting retinal astrocytic tumors at early stage.

Darling, T: Identified UV-signature mutations in TSC angiofibromas, prompting a recommendation that children with TSC use good sun protection.

FY09

McCormack, F: Showed that serum VEGF-D is potential biomarker for LAM diagnosis and prognosis.

Gan, B: Elucidated the molecular pathogenesis of TSC-related renal tumorigenesis, and provided novel insights of targeted therapies.

FY10

Koenig, M: Showed that topical rapamycin can reduce the size of facial angiofibroma without systemic absorption. This is a new, safe, inexpensive, and effective treatment, far less painful than removal with laser.

FY11

Hammes, S: Developed the first genetic and truly metastatic LAM mouse model and showed that LAM cells originate from the uterus, explaining the female sexual dimorphism of LAM.

Le Poole, I: Found that ganglioside D3 (GD3) overexpression is associated with LAM.

Yu, J: Found that TSC2 and estradiol regulate COX-2 expression and prostaglandin biosynthesis, and demonstrated that COX-2 is abundant in LAM lesions.

Yu, J: Showed that suppression of COX-2 with Celecoxib or aspirin inhibits tumor progression in a spontaneously arising renal cystadenoma tumor model of TSC.

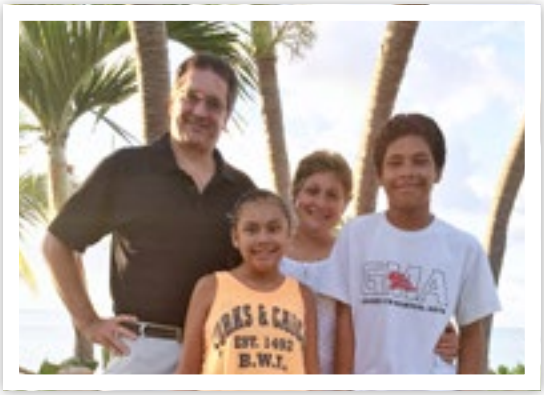
Application Review Process

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 vision and mission. Both steps involve dynamic interaction between scientists and clinicians and consumers. The first tier of evaluation is a scientific peer review of applications measured against established criteria for determining scientific merit. The second tier is a programmatic review, conducted by the Programmatic Panel, which is composed of leading scientists, clinicians, and consumers. In this tier of review, the Programmatic Panel compares applications to each other and makes recommendations for funding based on scientific merit as determined in peer review, relevance to program goals, and portfolio composition. The Commanding General of the USAMRMC issues the final approval for funding prior to award negotiations and execution.

Scientists, Clinicians, and Consumers Working Together

Consumer Involvement

The two-tier process established by the CDMRP brings together the expertise of scientists and clinicians with the perspective and experience of "consumers" (TSC patients or patient representatives). Individuals with TSC and their family members have an equal voice in the research administration process of setting the TSCRP's vision, reviewing applications, and making final funding recommendations. From the unique perspective gained through personal experience, the 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, caregivers, and clinicians.

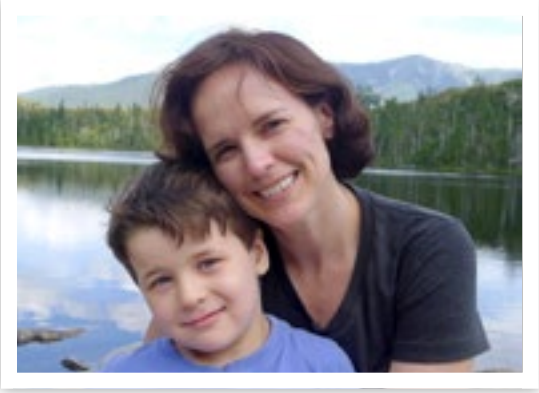


Never Stop Trying

Keith Hall,
Consumer Peer Reviewer

When Keith Hall was 12 years old, his doctor delivered life-changing news: his facial angiofibromas were caused by tuberous sclerosis complex (TSC). Today, over 30 years after his diagnosis, he is a leading advocate for the TSC community. Keith began volunteering with the now Tuberous Sclerosis (TS) Alliance in 1996, helping to find ways to better serve individuals living with TSC. Keith joined the TS Alliance Board of Directors in 2011, and each year since then he has participated in the TS Alliance's annual "March on Capitol Hill," meeting with U.S. Congress to advocate for continued funding for the TSCRP.

It was during the first of these "Marches" that Keith really came to understand the critical role that the TSCRP plays in providing the precious research dollars that scientists rely on to unlock the genetics and find cures for this disorder. He was honored to be offered the chance to serve on the TSCRP Peer Review Panel, where, as an adult living with TSC, he brings a unique and personal perspective. As a consumer reviewer, Keith says, "It was easy to feel like this group of experts had gathered to help you, or those you care about, solve the riddles behind the medical mysteries impacting your life. Listening to these motivated scientists provide thoughtful critiques really gave me hope that more meaningful discoveries are close, not only for TSC, but for other disorders this research will help unlock."



Everyone in the TSC Community Has Something to Give

Marlo Grolnic, Consumer Peer Reviewer

Marlo Grolnic had never heard the words "tuberous sclerosis complex" until she was expecting her son. Before he was even born, she was told that he may have TSC after a large rhabdomyoma was found in his heart. Marlo promptly launched her education in TSC and began volunteering for the TS Alliance. She became active in the community of individuals and families affected by TSC, and has served for over five years as the chair of her local chapter, the TS Alliance of New England. Marlo's advocacy work brought her into contact with the TSCRP, and she joined with others to advocate on Capitol Hill for continued Federal funding for the program.

Recently, the TS Alliance nominated Marlo to serve with the TSCRP, and she began her journey as a consumer reviewer of research applications submitted for future funding. Marlo found the review process "extremely well organized with plenty of resources to help understand how the program works and the steps involved in contributing as a consumer reviewer on a peer review panel." She remarks on how exciting it is to see projects funded for TSC research on so many fronts. Moreover, she continues to be impressed with, and grateful for, the commitment of the scientific community to find a cure for TSC. Marlo believes that everyone in the TSC community has something to offer to each other, even if it's just "a sympathetic ear." As Marlo says, there are so many ways to serve and give back to others who are living with TSC, whether it is service with others locally, in one's state, or nationally. She has seen the invaluable results of commitment and generous giving during her years of advocacy work and service with others.

For more consumer stories, visit http://cdmrp.army.mil/cwg/stories/tsc_stories.shtml

"As a father of a 12-year-old boy with TSC, I've had the honor of participating as a consumer reviewer in this well-run program for the past eight years, starting on the review panels and now on the Programmatic Panel. While never fast enough, the progress of the science in unlocking this complex puzzle of TSC is impressive! My son is living proof of how results of this research are being put into action to improve outcomes. Having a front-row seat in guiding the science in directions most relevant to TSC patients and families is the best thing I can do for my son, as well as the entire TSC-affected community."

Ron Heffron, Consumer Programmatic Panel Member

"I really enjoyed my experience of serving on the TSCRP review panel because the exciting science of proposals, fair and in-depth discussion, and high quality of the review panel."

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

"I have seen the benefits of the TSCRP from my service on both the Scientific Peer Review and the Programmatic Panels, and also from participating in clinical research trials funded by the TSCRP. From all of these perspectives, the program is a clear success. There have been tremendous gains in understanding of the knowledge and treatment of TSC arising from basic science research and clinical studies funded by this program. I am immensely proud of the works of the TSCRP."

Steven Sparagana, M.D., Texas Scottish Rite Hospital for Children, Programmatic Panel Member

Encouraging innovative research to improve the lives of individuals with TSC.

For more information, visit
http://cdmrp.army.mil/tscrp/default.shtml
or contact us at:
usarmy.detrick.medcom-cdmrp.mbx.cdmrp-public-affairs@mail.mil
(301) 619-7071

06-2016