TUBEROUS SCLEROSIS COMPLEX RESEARCH PROGRAM:

A Competitive, Peer-Reviewed Department of Defense Grant Program

"My 16-year-old daughter Katie was diagnosed with TSC at 11 months old while I was stationed at Fort Leonard Wood, MO. At age 4, Katie had brain surgery to remove a subependymal giant cell astrocytoma (SEGA). Katie has epilepsy that has been a challenge but is currently controlled with medication. She also has facial angiofibromas and other TSC skin conditions; a topical cream helps with those. Katie is a gifted student at school, taking several AP courses and playing the violin and piano, but she struggles with anxiety, social situations and making friends. At about the time of Katie's brain surgery, mTOR inhibitors were introduced, and have been life changing for many, preventing some brain surgeries and keeping kidneys, lungs and skin issues manageable for others. The CDMRP's TSC Research Program (TSCRP) is critically important to help Katie and others with TSC so all, not just some, can thrive."

SCOTT HOWE, GYSGT USMC RETIRED

The Howe Family

FY26 Request: Support the continuation of the Tuberous Sclerosis Complex Research Program (TSCRP) at the Department of Defense (DoD).

For FY25 the TSCRP had tremendous bipartisan support in the House (185 Dear Colleague Letter signers) and Senate (41 Dear Colleague Letter signers).

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

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

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

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

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

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

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

- **Hallmark achievement:** TSCRP-supported research that examined the role TSC genes play in cell growth and proliferation—specifically in controlling the mechanistic Target of Rapamycin (mTOR) signaling pathway in cells. This research rapidly led to clinical trials, resulting in the first drug approved by the FDA specifically for treatment of individuals with TSC.
- **Discovery of inflammation in the brain** in mice with mutations in TSC genes by an FY2011 award. This finding opens up potential new ways of treating TSC. Also, brain inflammation occurs in other disorders such as traumatic brain injury and Alzheimer's disease, enabling research impact to be shared among many disorders.
- **Effectiveness of a behavioral intervention strategy, JASPER, to improve outcomes in children with autism** is being tested in a large, NIH-funded clinical trial. This breakthrough trial would not be possible without data obtained from an FY2010 TSCRP clinical research award to define early autism predictors in TSC and an FY2014 TSCRP award for a pilot clinical trial.
- **Two TSCRP awards in FY2012 and FY2015** enabled generation of a potential approach for gene therapy of TSC, which has shown promising results in a mouse model of TSC tumors in the brain. Multiple companies are now working on TSC gene therapy because of the success of these early studies.
- **In 2022, the first rapamycin topical gel was FDA-approved** for treatment of facial angiofibromas in TSC. TSCRP funding in FY2010 funded a clinical trial of topical rapamycin which demonstrated effectiveness of this approach.
- **Two FY2023 awards address near-term needs of the TSC community,** one to understand the impact of caregiver wellbeing on behavioral and other neuropsychiatric issues in those with TSC for whom they are caring, and another to measure the risk and impact of lung and renal complications in women with TSC of child-bearing age and the impact of pregnancy. The occurrence of lung and kidney issues during pregnancy have been observed, but no quantitative data exists to guide healthcare at this critical point for mother and baby.
- **Creation of the first comprehensive natural history clinical database for TSC,** designed to understand how TSC progresses throughout a lifetime. To date 2,795 participants are enrolled at 22 sites. The database has helped recruit individuals for clinical trials and has been used to answer research questions.

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

FY2026 Request Summary: Funding for more innovative research is needed to prevent the manifestations of TSC and improve diagnosis and treatment of TSC and related diseases to reduce the healthcare burden imposed by this multi-organ disorder.

Increased TSCRP funding will enable the establishment of a TSC Clinical Trial Consortium. The TSCRP's Strategic Plan calls for early investments in (1) hypothesis-generating research and (2) development of the resulting new ideas into novel candidate therapeutics for treating TSC. The Strategic Plan also calls for (3) translation of these new ideas into the clinic through necessary research in animal models and into (4) clinical trials. Levels of TSCRP funding from FY02-FY24 have been demonstrably effective for the first three parts of the Strategic Plan and have funded pilot studies toward the fourth part. However, the current level of TSCRP funding is not sufficient for large clinical trials required to demonstrate conclusively the effectiveness of new candidate therapeutics.

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