Congressionally Directed Medical Research Programs

CDMRP

Department of Defense

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Tuberous Sclerosis Complex Research Program

Tuberous sclerosis Complex (TSC) impacts U.S. Service members and their Families: Seizures often result from traumatic brain injury in military personnel, and according to the Defense Health Agency Medical Surveillance Monthly Report, 11,295 cases of epilepsy were reported among active duty Service members between 1998 and 2012.[1] In addition, in 2008, the Department of Defense (DoD) reported that 5,386 military dependents were diagnosed with autism spectrum disorder.[2] TSCRP-supported research is paving the way to finding cures and treatments for individuals with TSC and other neurological disorders that impact military Service members and their families.

VISION

Accelerate high-impact research to improve prevention strategies and treatment and to find a cure for TSC

MISSION

Fund exploratory, pioneering and transformative science that promotes discoveries in TSC, from mechanistic insights to clinical application, by supporting new ideas and investigators for the benefit of Service members, their beneficiaries, and the American public

PROGRAM HISTORY

Since its inception in 2002, with a Congressional appropriation totaling $77 million (M), the DoD Tuberous Sclerosis Complex Research Program (TSCRP), has supported high-risk, high-gain research that has led to significant advances in Tuberous Sclerosis Complex (TSC) research and major improvements in patient care.

TSC is a genetic disorder that causes tumors in various organs, primarily the brain, eyes, heart, kidneys, skin, and lungs. Seizures, developmental delay, intellectual disability, and autism, which are generally associated with the brain, are the aspects of TSC that most strongly impact quality of life.

"For all the TSC families that take Washington DC by storm every year to advocate for funding for this awesome research program, please know your hard work is making a difference. While it's never fast enough in the eyes of those affected, the science is advancing rapidly. Guided by a new Strategic Plan developed in 2018, this TSCRP is an extraordinarily effective program that achieves results! I am honored to be a participant in this process of finding a cure, and I always say it's the most important thing I can do to help my son, Bao, now and into the future."

Ron Heffron, P.E., Tuberous Sclerosis Alliance Programmatic Panel Member

Clinical Trials That Significantly Reduced the Impact of Various Manifestations of TSC	
Mary Kay Koenig, M.D., *University of Texas Health Science Center, Houston*	Topical rapamycin therapy was safe and effective for TSC-related facial angiofibromas and significantly improved the appearance of facial lesions.
Shafali Jeste, M.D., *University of California, Los Angeles*	Joint Attention, Symbolic Play, Engagement, and Regulation (JASPER) behavioral intervention in infants with TSC showed improvement in their developmental skills.
Elizabeth Henske, M.D., *Brigham and Women's Hospital, Boston*	A combination of an autophagy inhibitor, hydroxychloroquine, with sirolimus was well tolerated in TSC patients with LAM.

[1] Epilepsy in active component service members, 1998-2012. MSMR. 2013 May; 20(5): 19-22.
[2] https://health.mil/search-results?query=autism

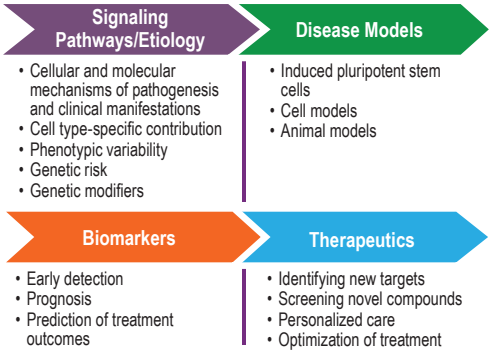
STRATEGIC GOALS

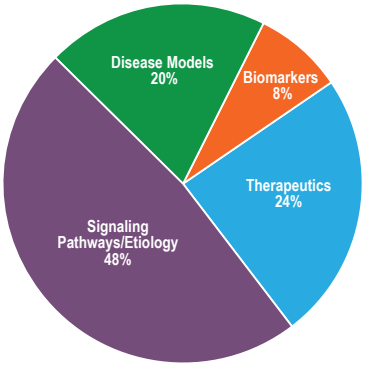
While working toward the goal of improving prevention strategies and treatments and finding a cure for TSC for the benefit of Service members, their beneficiaries, and the American public, TSCRP will continue its efforts to:

- Eradicate tumors associated with TSC
- Prevent epilepsy, improve treatment, and mitigate comorbidities associated with TSC-related seizures
- Understand the neurodevelopmental features of TSC and reduce their impact

PROGRAM PORTFOLIO

From fiscal years 2002 through 2017 (FY02-FY17), the TSCRP funded 147 awards to address the critical needs of TSC patients and scientific community. These studies have shed light on mechanisms underlying the clinical manifestations, developed disease models to test potential treatments, and identified biomarkers that have led to early treatment. Moreover, they have driven development of new therapeutic approaches to address previously untreatable manifestations of the disease. Notably, the current first-line treatment for TSC (based on rapamycin, an inhibitor of mTOR [mammalian target to rapamycin]) stemmed from a TSCRP-funded study to understand the basic mechanisms of this pathway. The 50 most recently funded projects (FY13-FY17) are reflected in the graph (percentage by research dollars).





RESEARCH IN THE PIPELINE

SCORING EPILEPSY RISK IN TSC

Laura Farach, M.D., University of Texas, Houston

Even though epilepsy occurs in 80% to 90% of individuals with TSC, we currently cannot predict which individuals will develop seizures. Clinical biomarkers that identify who will develop seizures are necessary for early treatment and prevention. Dr. Farach is developing an epilepsy risk prediction model based on known clinical, demographic, and genetic risk factors for epilepsy in TSC. To accomplish this goal, she will evaluate genetic differences (modifiers) that put patients with TSC at high or low risk of developing seizures. This project has the potential to lead to development of a predictive model that can provide a personalized risk of seizures.

SUPPORTING THE IMMUNE SYSTEM TO FIGHT TUMORS

Caroline Le Poole, Ph.D., Northwestern University, Chicago

Dr. Le Poole plans to apply concepts used in the cancer field to use the body's own immune cells to eliminate tumors that develop in TSC. This project aims to test genetically modified T cells (white blood cells that are involved in protecting the body against foreign invaders and eliminating abnormal cells) in mice to confirm whether they are a safe and effective treatment of TSC tumors. Dr. Le Poole plans to confirm whether T cell treatment is effective, even in advanced stages of disease and in combination with rapamycin treatment. Upon completion of this project, Dr. Le Poole and her team will submit an Investigational New Drug application to the Food and Drug Administration for approval of a clinical trial to apply a patient's own genetically modified immune cells so that they will recognize and kill tumor cells in TSC.

A NON-INVASIVE METHOD FOR CLASSIFYING MALIGNANT KIDNEY TUMORS

Adam S. Feldman, M.D., M.P.H., Massachusetts General Hospital, Boston

Non-cancerous tumors, called angiomyolipomas, can sometimes look exactly like cancerous tumors on imaging of the kidneys, resulting in unnecessary biopsies and/or surgeries. Dr. Feldman is investigating magnetic resonance spectroscopy, a non-invasive technique used to evaluate metabolites in tissues, as a novel method to evaluate suspicious kidney tumors in patients with TSC. This research may provide the tools to make a non-invasive distinction between cancerous and non-cancerous kidney tumors and has the potential to significantly impact TSC patient care by decreasing the use of invasive procedures such as renal mass biopsy and/or surgery.

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