Support Funding for the
Tuberous Sclerosis Complex Research Program (TSCRCP)

** THIS IS A PROGRAMMATIC REQUEST. **
Members are required to submit the request online.

Dear Colleague:

Please join us in requesting a continuation of funding for the Tuberous Sclerosis Complex (TSC) research program in the fiscal year 2019 Department of Defense (DOD) Appropriations Act.

TSC is a genetic condition that affects an estimated 50,000 Americans, causing tumors in the kidneys, lungs, liver, heart, eyes, skin, and brain. Researchers have linked TSC to seizures, autism spectrum disorder and severe intellectual disability. Research on TSC is also having a significant impact on our understanding of traumatic brain injury and other medical conditions like cancer and diabetes, and the TSC program at DOD is critical to ongoing progress.

From fiscal years 2002 to 2017, Congress appropriated an aggregate of $71 million for the Tuberous Sclerosis Complex Research Program (TSCRCP) at DOD. This program has greatly benefited from significant bipartisan support from Congress and has competitively awarded 139 grants to TSC researchers. While this investment represents an important step toward gaining a better understanding of TSC, more must be done to expand research toward finding a cure. In fiscal year 2017, only 18.6% of applications were funded by the TSCRCP. A continuation of funding for the TSCRCP is needed to support clinical studies to validate biomarkers and outcome measurements necessary to accelerate development of new therapeutic agents, understand the biology underlying the wide variation in severity of manifestations among individuals with TSC, attract new researchers into this field of study, develop assays and animal models necessary for translating basic scientific discoveries into clinical treatments -- and to ensure that strong scientific proposals are not left unfunded.

This is a programmatic request. Members are required to submit the request online to ensure the Appropriations Committee recognizes your support for the TSCRCP.

If you would like to sign on to the below letter to Chairwoman Granger and Ranking Member Visclosky or if you have any additional questions, please contact Henry Yaniz (Rep. Ros-Lehtinen) at 5-3931 or henry.yaniz@mail.house.gov, or Katie Murray (Rep. Loebssack) at 5-6576 or katie.murray@mail.house.gov by COB Tuesday March 13th.

Sincerely,

ILEANA ROS-LEHTINEN
Member of Congress

DAVE LOEBSSACK
Member of Congress
March 1, 2018

The Honorable Kay Granger
Chairman
Subcommittee on Defense
Committee on Appropriations
H-405 Capitol Building
Washington, DC 20515

The Honorable Pete Visclosky
Ranking Member
Subcommittee on Defense
Committee on Appropriations
1016 Longworth House Office Building
Washington, DC 20515

Dear Chairwoman Granger and Ranking Member Visclosky:

We are writing to support a continuation of funding for Tuberous Sclerosis Complex Research Program (TSCRP) at the Department of Defense (DoD) in the fiscal year 2019 Defense Appropriations Act.

Tuberous sclerosis complex (TSC) is a genetic condition that afflicts an estimated 50,000 Americans, causing tumors in the kidneys, lungs, liver, heart, eyes, skin, and brain. Researchers have linked TSC to seizures, autism spectrum disorder and severe intellectual disability. Research on TSC is also having a significant impact on our understanding of traumatic brain injury and other medical conditions like cancer and diabetes, and research at the TSCRP is critical to ongoing progress.

From fiscal years 2002 to 2017, Congress appropriated an aggregate of $71 million to the TSCRP. This well-established program, which has enjoyed bipartisan support from Congress, awards grants competitively to cutting edge research proposals aimed at gaining a better understanding of this complex disorder. Research at the TSCRP complements – and does not duplicate – ongoing studies on TSC supported by the National Institutes of Health (NIH). Coordination between NIH and DoD is managed by a trans-NIH working group, led by the National Institute of Neurological Disorders and Stroke, with participation from eight separate Institutes, DoD and the Tuberous Sclerosis Alliance, representing the patient community.

While this research has led to significant breakthroughs, far more is needed if we hope to find ways to more effectively treat those who suffer with TSC and prevent its occurrence in future generations. In fiscal year 2017, there was only enough research funding available to fund 18.6 percent of the research proposals received by the TSCRP. Continued funding is required to support clinical studies to validate biomarkers and outcome measurements necessary to accelerate development of new therapeutic agents, understand the biology underlying the wide variation in severity of manifestations among individuals with TSC, attract new researchers into this field of study, and develop assays and animal models necessary for translating basic scientific discoveries into clinical treatments.

To date, patient organizations have invested more than $20.3 million in privately raised resources to the research effort. Ongoing support is necessary to move this research closer to ultimately finding a cure for tuberous sclerosis complex.

We firmly believe that Congress should match these private sector commitments, and we urge you to appropriate funding necessary to continue the TSCRP in fiscal year 2019.
February 27, 2018

The Honorable John McCain
Chairman
Senate Committee on Armed Services
Russell Senate Building, Room 228
Washington, DC 20510

The Honorable Mac Thornberry
Chairman
House Committee on Armed Services
2216 Rayburn House Office Building
Washington, DC 20515

The Honorable Jack Reed
Ranking Member
Senate Committee on Armed Services
Russell Senate Building, Room 228
Washington, DC 20510

The Honorable Adam Smith
Ranking Member
House Committee on Armed Services
2216 Rayburn House Office Building
Washington, DC 20515

Dear Chairmen McCain and Thornberry and Ranking Members Reed and Smith:

As you work to develop your respective versions of the fiscal year 2019 National Defense Authorization Act (NDAA), we encourage you to refrain from including any language that would have a detrimental impact on research at the Congressionally-Directed Medical Research Program (CDMRP) and other medical research conducted by the U.S. Department of Defense (DoD).

Last year, the fiscal year 2018 NDAA reported by the Senate Committee on Armed Services and ultimately approved by the Senate included provisions that would have individually and collectively restricted, if not outright prohibited, medical research on diseases and disorders that affect our nation’s men and women who serve or have served in the U.S. Armed Services. These provisions (sections 733, 891, 892, and 893 of the Senate bill) would have restricted the types of research that could be funded, and added burdensome contracting and auditing requirements designed for large weapons system contracts. Moreover, one of these provisions (Section 733) would have affected all medical research at DoD, not just the CDMRP.

In response to the inclusion of this language last year, the U.S. Army’s Medical Research and Materiel Command issued a memorandum that stated:

“This language will impact force readiness and medical providers’ readiness…. Impacts on military medical training programs will negatively affect the readiness of our military health care providers.”

Because the Senate version of the bill is not marked-up in public, our organizations did not have a chance to respond to this language until after the bill was reported from committee. Furthermore, an amendment to remove this language was filed in the Senate and cosponsored by more than half of the Senate, but was not given a vote on
the Senate floor. After passage of the bill, “Dear Colleague” letters asking for removal of this language in the House-Senate conference were circulated and signed by 54 Senators and 180 Representatives.

Thankfully, the final version of the FY18 NDAA did not include this language. This result was due in large part to an arduous four-month advocacy campaign by your constituents, who expended an enormous amount of time and energy to defeat language that a clear Majority in Congress opposed from the outset.

The strong level of bipartisan Congressional support for the defense health research programs is a beacon of hope to the military families, retirees, veterans and civilians who must cope with these diseases and disorders. We urge you to honor their concerns and refrain from including in this year's NDAA any language that would restrict medical research at DoD.

We appreciate your prompt and urgent consideration of our request.

Sincerely,

AcademyHealth
Action to Cure Kidney Cancer
Adult Congenital Heart Association
ALS Association
American Academy of Dermatology Association
American Academy of Ophthalmology
American Association of Clinical Urologists
American Brain Tumor Association
American College of Rheumatology
American Gastroenterological Association
American Liver Foundation
American Psychological Association
American Urological Association
Aplastic Anemia and MDS International Foundation
Arthritis Foundation
Association of American Cancer Institutes
Association of Public and Land-grant Universities
The Asthma and Allergy Foundation of America
Lymphoma Research Foundation
Malaria No More
Malecare Cancer Support
Marfan Foundation
METAvisor
The Michael J. Fox Foundation for Parkinson's Research
Muscular Dystrophy Association
National Alliance for Eye and Vision Research
National Alliance of State Prostate Cancer Coalitions
National Autism Association
National Brain Tumor Society
National Fragile X Foundation
National Kidney Foundation
National Multiple Sclerosis Society
National Organization for Rare Disorders (NORD)
NephCure Kidney International
Neurofibromatosis Midwest
Neurofibromatosis Network
Oncology Nursing Society
Ovarian Cancer Research Fund Alliance
Pancreatic Cancer Action Network
Parent Project Muscular Dystrophy
Penn State University
Prostate Cancer Foundation
Pulmonary Hypertension Association
Research!America
Restless Legs Syndrome Foundation
Scleroderma Foundation
The Sergeant Sullivan Circle
Sleep Research Society
Society of Gynecologic Oncology
Stony Brook University
Susan G. Komen
TB Alliance
Texas NF Foundation
Theresa’s Research Foundation
Tuberous Sclerosis Alliance
University of California System
University of Hawaii
Letter to Chairs/Ranking Members
House and Senate Armed Services Committees
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University of Iowa
University of New Mexico Health Sciences Center
University of Pittsburgh
University of Virginia School of Medicine
US Hereditary Angioedema Foundation
Us TOO International Prostate Cancer Education & Support
Vanderbilt University
Vanderbilt University Medical Center
Veterans for Common Sense
The Veterans Health Council
Vietnam Veterans of America
Wayne State University
Weill Cornell Medicine
ZERO-The End of Prostate Cancer

cc: Members of the House and Senate
We are visiting your office today in conjunction with the Tuberous Sclerosis Alliance’s “March on Capitol Hill” during the week of March 4. As members of the tuberous sclerosis complex (TSC) community, we respectfully urge you take action over the next few weeks to assure the continuation of the Tuberous Sclerosis Complex Research Program.

Tuberous sclerosis complex (TSC) is a genetic disorder that can affect the body’s vital organs including the brain, heart, kidneys, lungs, liver, eyes and skin. The hallmark of this disorder is uncontrollable tumor growth in all of the organs, possible kidney failure and lesions of the central nervous system that can result in seizures, behavioral disorders, autism spectrum disorder and severe learning disabilities. The cellular pathways involved in TSC are also activated in traumatic brain injury, a common occurrence in military personnel and TSC research may have implications for treating epilepsy in returning troops. The Tuberous Sclerosis Alliance is the only national voluntary nonprofit organization dedicated to finding a cure for TSC while improving the lives of those affected.

The Tuberous Sclerosis Complex Research Program (TSCRP) – administered by the Department of Defense (DoD) – is a peer-reviewed program that awards grants competitively to cutting edge research proposals aimed at gaining a better understanding of this complex disorder. It has enjoyed bipartisan support from Members of the House and the Senate. Since fiscal year 2002, Congress has appropriated an aggregate of $71 million for the TSCRP. In fiscal year 2017, the program received an appropriation of $6 million.

We urge Congress to support a continuation of funding for the TSCRP in fiscal year 2019 to build on the investments that it has already made in the TSCRP. Continued funding is essential to support a robust level of grant awards for basic, translational and clinical research to truly provide hope for improved quality of life for all those living with TSC.

The enclosed packet of information provides detailed information about TSC, the TSCRP, and the justification for continuing this important federal investment. Thanks to Congressional efforts over the past decade, we have taken significant steps toward improving the quality of life for those impacted by TSC. For more information, please contact Katie Smith at the Tuberous Sclerosis Alliance at ksmith@tsalliance.org or 301-562-9890. We hope to count on you to bring us one step closer to a cure!

We appreciate your consideration of this request.
After my son’s birth and diagnosis, I was diagnosed with tuberous sclerosis complex (TSC) at the age of 43, just three months after I retired from my 23-year Naval career. The complexity of this disease means that it remains to be seen whether my young son will be able to live the "typical" life that I have been fortunate to live. Because of research conducted through the TSCRP, my son has effective treatment options available to him that were not available even just a decade ago. But there is still so much to learn and discover, and the TSCRP is essential in getting us to where we need to be: a cure.

- William R. Tuttle, Jr., AMC(AW), USN, Retired
  Adult with TSC and father to Billy, 2 years old with TSC

FY2019 Request: Support the continuation of the Tuberous Sclerosis Complex Research Program (TSCRP) at the Department of Defense (DoD).

TSC Facts: Tuberous sclerosis complex (TSC) is a genetic disorder that can cause tumor growth in all 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. TSC is considered a linchpin disease because critical cellular pathways disrupted in TSC are shared with other diseases, including cancer, lymphangioleiomyomatosis (LAM), and diabetes. Research breakthroughs in TSC may also have an impact on future treatments for epilepsy, autism, cancer and LAM. 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 caused by mutations in a TSC gene that results in cystic destruction of the lung.

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.¹
- Seizures often result from traumatic brain injury in military personnel, and approximately 85% of individuals with TSC experience seizures during their lifetimes.
- TSC research may lead to new interventions for preventing the development of seizures in high-risk military and civilian individuals.²

TSCRP-funded studies are also relevant to autism spectrum disorder, diabetes, cancer and other disorders that affect service personnel and their families.³

¹ Wong, Michael. The Role of Brain Inflammation in Epileptogenesis in TSC, #W81XWH-12-1-0190
² Raab-Graham, Kimberley. Molecular Studies Investigating the Link Between Dendritic mRNA Translation and Repression Leading to Epilepsy in TSC, #W81XWH-14-1-0061
Competitive Awards with No Duplication of NIH Funding: All TSCRP grants are awarded on a competitive basis. An NIH program officer participates in the prioritization of TSCRP awards 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 TSCRP and NIH funds go to distinct, non-overlapping research projects.

More than a Decade of Progress: Since its inception in fiscal year 2002, 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 uncovered 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 only drug approved by the FDA specifically for treatment of individuals with TSC.

- **Two clinical trials for treatment of LAM:** one funded in FY2012 to test a combination of two drugs to treat LAM and another funded in FY2013 to determine if imatinib, an FDA-approved drug for cancer treatment, can safely improve blood levels of VEGF-D, a biomarker of LAM.

- **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.

- **Linking cognitive impairments in TSC to autism, anxiety, and other mental disorders through FY2010-funded research on glutamate receptors (mGluR5),** which may lead to new drug therapies.

- **Based on data from TSCRP-funded animal models of TSC that have seizures and share pathology related to that of traumatic brain injury,** an industry-sponsored clinical trial demonstrated in 2016 the effectiveness the mTOR inhibitor, everolimus, at treating epilepsy in many individuals with TSC.

- **Creation of the first comprehensive natural history clinical database for TSC,** designed to understand how TSC progresses throughout a lifetime. To date, 2,124 participants are enrolled at 18 U.S. sites. The database has helped recruit individuals for clinical trials and has been used to answer research questions.

- **Development of an innovative cream to treat disfiguring facial tumors caused by TSC.** A FY2010-funded multi-site clinical trial to test the efficacy of topical rapamycin on facial angiofibromas was completed in 2014.

None of this progress would have been possible without the financial support provided through the TSCRP.

FY2019 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. The FY2017 appropriation of $6 million funded only 18.6% of grant applications. A continuation of funding for the TSCRP is needed to understand the biology underlying the wide variation in severity of manifestations among individuals with TSC and LAM, to support clinical studies to validate biomarkers and outcome measurements necessary to accelerate development of new therapies, and to attract new researchers into this field to develop innovative approaches for translating basic scientific discoveries into clinical treatments.
The tuberous sclerosis complex (TSC) genes lie at the heart of a biochemical network that is disrupted in a diverse array of common human diseases and health concerns.

Research on tuberous sclerosis complex has revealed insights and therapeutic targets for numerous human diseases. The genes mutated in TSC result in a loss of function in two key proteins, TSC1 and TSC2. These proteins are present in all human cells as they play a modulating role in a large signaling cascade of other proteins that together form the “mTOR Pathway.” This biochemical pathway translates external cell stimuli (such as insulin or stress hormones) into a signal that dictates mTOR’s activity. One of many cell growth controllers, mTOR is particularly important as its dysfunction is a common driver of several forms of cancer.

Because the mTOR pathway reacts in response to insulin, TSC mutations can lead to metabolic disorders. Similarly, because the mTOR pathway is sensitive to certain stress hormones, loss of TSC function can interrupt cells’ normal stress response, which may lead to certain autoimmune and inflammatory diseases. Studying the tuberous sclerosis protein complex may help unlock better understanding of a diverse array of diseases because of its direct role in modulating mTOR.

Tuberous Sclerosis Complex

Tuberous sclerosis complex (TSC) is a multisystem genetic disorder that causes non-malignant tumors to form in vital organs including the brain, eyes, heart, kidneys, liver, skin, and lungs. TSC is caused by a mutation in either the TSC1 or TSC2 gene. Two-thirds of individuals with TSC have a sporadic genetic mutation, and one third inherit TSC from one of their parents. Individuals with TSC have a 50% chance of passing the condition on to each child.

In addition to multi-organ tumor growth, medical issues associated with TSC include varying degrees of neurological and behavioral issues. These medical problems not only vary between individual cases of TSC but are often complicated by the interdependent nature of behavior and neurology. As a result, the medical problems due
to TSC may vary even between two family members (such as siblings) with TSC.

The incidence of TSC is estimated to be 1 in 6,000 live births. At least two children born each day in the United States will have TSC. Approximately 50,000 Americans and 1 million individuals worldwide have TSC, making TSC as common as ALS (Lou Gehrig’s Disease) or Duchenne’s Muscular Dystrophy.

**TSC and Epilepsy/Seizure Disorders**
Seizures remain one of the most common neurological features of TSC, occurring in approximately 85% of individuals with TSC. Infants are often diagnosed with TSC after they begin having a very serious type of seizure called infantile spasms. Some children appear to develop normally until the onset of seizures, when their progress slows or they actually lose developmental milestones. Older children and adults may develop multiple types of seizures including generalized, complex partial and other focal seizures. More than 50% of individuals with TSC who have epilepsy will not respond to standard antiepileptic medications and have intractable epilepsy, thus increasing the likelihood of intellectual impairment.

**TSC and Autism Spectrum Disorders (ASD)**
TSC leads to more cases of autism spectrum disorder (ASD) than any other single–gene disorder. Approximately 50% of all children with TSC will be diagnosed with ASD. The rate of ASD in the general population is substantially lower (approximately 1 in 68, or 1.5%, of the total population), so there is a much higher rate of ASD in children with TSC. ASD is usually diagnosed in young children between the ages of 2 and 4 years, but in individuals with TSC, the diagnosis of ASD may go unrecognized or be delayed due to other developmental disabilities. It is believed the abnormalities in brain development that occur in TSC and the inability for normal connections to be formed in the brain interfere with the proper development of brain areas that are important for the development of social communication skills. Recent animal studies indicate that it may be possible to prevent or reverse intellectual disabilities and ASD if treated early.

**TSC and Cancer**
The proteins produced by TSC genes participate in the mTOR Pathway, an important biochemical network that is involved in the control of cell growth. Therefore, loss of function of these proteins in TSC is associated with uncontrolled growth leading to the development of widespread tumors. Importantly, the biochemical pathway affected by TSC genes is also rendered dysfunctional in over 50% of human cancers, across nearly all lineages, and underlies tumor development in these settings. The study of TSC is improving our understanding and treatment of cancer.

**Tuberous Sclerosis Alliance**
The Tuberous Sclerosis Alliance (TS Alliance) is the only national organization dedicated to finding a cure for TSC while improving the lives of those affected.

The TS Alliance acts as a clearinghouse for individuals with TSC, their families, caregivers, educators and healthcare providers seeking the most up-to-date information about TSC. The TS Alliance also provides resource information on many aspects of healthcare, treatment, education and other challenges that may be encountered by individuals with TSC. The organization serves to connect individuals throughout the nation and beyond, creating a network of informed constituents, educators and healthcare providers.

The TS Alliance is the only organization able to rally the financial resources, the research, the partnerships, and the sheer will of families impacted by TSC to break the back of this linchpin disease. TSC research truly creates a domino effect: Every dollar spent finding cures and treatments for TSC can bring about quantum leaps forward in the cures for ASD, epilepsy and cancer - diseases that touch many people we know and love.
The Tuberous Sclerosis Alliance invites you to our 7th annual National Walk on the Mall Step Forward to Cure TSC event!

Contact: Gail Saunders, Senior Regional Manager, South at 240.638.4652 or gsaunders@tsalliance.org for more details.

SUNDAY, MAY 6
National Mall, Constitution Gardens
20th NW and Constitution Ave
Washington, DC 20024

9:00 am Registration
10:00 am Walk Begins

Register today at www.stepforwardtocuretsc.org

On this day, individuals and families affected by TSC will join together to increase public awareness of the rare disease and share their stories of hope for the future.

Contact: Gail Saunders, Senior Regional Manager, South at 240.638.4652 or gsaunders@tsalliance.org for more details.
Tuberous Sclerosis Complex Research Program

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

Mission
Fund pioneering and transformative science that promotes new discoveries in TSC, from mechanistic insights to clinical application, for the benefit of Service Members, their beneficiaries, and the American public

Program History
Tuberous sclerosis complex (TSC) is a genetic disorder that causes non-malignant tumors in many different organs, primarily in the brain, eyes, heart, kidney, skin, and lungs. It has several clinical manifestations; however, seizures, developmental delay, intellectual disability, and autism have the greatest impact on quality of life. The incidence and severity of the various aspects of TSC vary widely between individuals—even between identical twins. TSC can be inherited as an autosomal dominant trait or can be the result of a spontaneous genetic change on the TSC1 (hamartin) or TSC2 (tuberin) gene. The TSC1 and TSC2 genes are located on chromosome 9 and chromosome 16, respectively. 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. The Tuberous Sclerosis Complex Research Program (TSCRP) was first funded in FY02, when the efforts of TSC advocates led to a congressional appropriation of $1M. Since then, a total of $71M has been appropriated to the program, including $6M in FY17. Today, TSCRP is one of the leading sources of extramural TSC research funding in the United States.

Program Portfolio
TSCRP funded 139 awards through FY16 to support high-impact, innovative research; foster the development of research resources and tools; promote the translation of new research findings to patient care; and advance the knowledge of TSC and its clinical manifestations.
Targeting Amino Acid-mTORC1 Signaling for Treatment of TSC

Do-Hyung Kim, Ph.D.,
University of Minnesota,
Twin Cities

The mechanistic target of mTORC1 plays a key role in the cell growth response to amino acid availability. Dr. Do-Hyung Kim was awarded an FY12 Idea Development Award to study amino acid-mTORC1 signaling in TSC, focusing on the protein SH3BP4, a negative regulator of amino acid-mTORC1 signaling that may be involved in endosomal trafficking. His laboratory found that mTORC1 binds to and phosphorylates the endosomal protein UVRAG, attenuating endosome maturation and lysosomal degradation of growth factor receptors. Furthermore, his group observed that TSC null mouse cells expressed high levels of several growth factor receptors that are often found overexpressed in tumor cells, indicating that amino acid/SH3BP4/mTORC1 signaling, through UVRAG, can increase levels of cell surface growth factor receptors in TSC cells. In looking for mediators of amino acid-mTORC1 signaling, Dr. Kim and colleagues found that mTORC1 promotes immunoproteasome formation in a manner dependent upon amino acids and mTORC1 activity, and that immunoproteasome activity is increased in TSC mutant mouse cells. This suggests that TSC cells might degrade unnecessary proteins at a greater rate than normal cells by up-regulating the immunoproteasome, as a result of a response to an inflammatory reaction. These studies have uncovered new pathways mediated by mTORC1 signaling that have resulted in novel potential targets for therapy in TSC.

Identifying the Roots of Myelin Dysfunction in the TSC Brain

Mustafa Sahin, M.D., Ph.D.,
Boston Children’s Hospital

Hypomyelination, which occurs when glial cells in the brain are unable to generate the myelin sheath that surrounds nerve fibers and facilitates efficient transmission of nerve impulses, is a key feature of TSC and contributes to the neurological symptoms of TSC, including autism, developmental delays, and epilepsy. Dr. Mustafa Sahin has recently shown that neurons in TSC brains express increased levels of connective tissue growth factor (CTGF), a protein that is secreted by neurons and prevents proper myelination of oligodendrocytes. With funding from an FY12 Idea Development Award, Dr. Sahin investigated the role of CTGF in hypomyelination in the TSC brain. He found that deleting CTGF in neuronal cells that also lack TSC1 improves the ability of oligodendrocytes to produce myelin and develop normally. He also observed that the protein serum response factor, SRF, a repressor of CTGF gene transcription, is expressed at decreased levels in neurons lacking TSC2 and in TSC1 mouse model brains indicating that CTGF up-regulation, and the resultant hypomyelination may be due to the down-regulation of SRF. Dr. Sahin hopes that, by understanding the basis of the neurological symptoms in TSC, it will be possible to develop therapies to block the impact of CTGF expression and restore myelination to normal levels. In addition to patients with TSC, such a therapy would also impact patients suffering from similar myelination deficit disorders, including multiple sclerosis and cerebral palsy.

"The Tuberous Sclerosis Complex Research Program serves to fill gaps in the field of tuberous sclerosis research. This program brings experts in the field together to help fund exciting new ideas. This program has allowed me to work with others researching tuberous sclerosis to both share and expand my knowledge."

Mary Kay Koenig, M.D., University of Texas Health Science Center at Houston, FY13-FY17 Programmatic Panel Member (FY17 Chair)

"My experience with the TSCRP has been rewarding, enlightening, and empowering. My voice and experience representing the community was appreciated and respected, and it has been an honor to be afforded this opportunity. I wish to express my deepest gratitude for the passion and dedication from the CDMRP’s staff, who devote their time to this cause. The TSC community is fortunate that there is a dedicated commitment from the scientific community to understanding the pathogenesis and manifestations of TSC with the goal of improving the lives of individuals with TSC."

Shelly Meitzler, FY16 Consumer Peer Reviewer

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Tuberous Sclerosis Complex Research Program

U.S. Army Medical Research and Materiel Command
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 (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 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 – Koenig, 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.
A wide variety of research resources were developed by several TSCR-funded projects* and shared with the Research Community.

<table>
<thead>
<tr>
<th>Resources</th>
<th>Number</th>
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<tbody>
<tr>
<td>Mouse Models</td>
<td>21*</td>
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<td>Drosophila Models</td>
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<td>3D TSC1 Structure</td>
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<td>Antibodies</td>
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*The number represents the number of projects that produced the resource indicated.

TSC Training

- Undergraduate Students: 19
- Post-Doctoral Fellows: 38
- Residents/Medical Students: 3
- University Research Professors: 2
- Clinicians: 8
- Researchers: 46
- MD/PhD Students: 26
- Clinical Research Program Managers: 4
- Other/Not Specified: 61

Over 200 researchers and/or clinicians were trained with TSCR awards.

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

<table>
<thead>
<tr>
<th>Category</th>
<th>Project/Year</th>
<th>Description</th>
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<tbody>
<tr>
<td>DATABASE</td>
<td>FY04 – Sparagana, S</td>
<td>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.</td>
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<tr>
<td>SOFTWARE</td>
<td>FY04 – Sabatini, D</td>
<td>Developed the CellProfiler software package for cell-image analysis.</td>
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<td>SCREENING TOOL</td>
<td>FY05 – Su, TT</td>
<td>Led to improving the methods for using <em>Drosophila</em> as a screening tool.</td>
</tr>
<tr>
<td>NETWORK</td>
<td>FY09 – McCormack, F</td>
<td>Developed the LAM Clinic Network, linked by a repository and registry.</td>
</tr>
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</table>
Understanding TSC Pathogenesis

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.

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.

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.

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 autphagic death.

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

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

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.
**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.

**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 Rbe, 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 TSC deletion in the oligodendrocyte lineage.

**Perrimon, N:** Identified three genes, mRNA-cap, Pitsf1e, and CycT, which when mutated in the background of TSC1 or 2 mutations cause cells to die, providing potential TSC therapeutics.

**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.

**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.

**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.

**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.

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**Wood, T:** Established mouse model with inducible TSC deletion in the oligodendrocyte lineage.
Studying Clinical Manifestations

**CENTRAL NERVOUS SYSTEM**

- Autism
- Epilepsy

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

- **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.

- **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.

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

- **Tamanoi, F:** Showed that activation of inflammatory pathways in the TSC brain and the role of mTOR signaling in lesion formation.

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

- **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 – Lymphangioleiomyomatosis (LAM)**
- **Kidneys – Angiomyolipomas**
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.

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.

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.

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.

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.

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.

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.

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.

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

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.

Yoshii, A: Showed 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.

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

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

It was during the first of these “Marches” that Keith really came to understand the critical role that the TSCRPs 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 TSCRPs 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.”

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.
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.

Ron Heffron, Consumer Programmatic Panel Member

“I 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.”

Steven Sparagana, M.D., Texas Scottish Rite Hospital for Children, 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.”

For more consumer stories, visit http://cdmrp.army.mil/cwg/stories/tsc_stories
Encouraging innovative research to improve the lives of individuals with TSC.

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