CDMRP

Department of Defense

Tuberous Sclerosis Complex Research Program

U.S. Army Medical Research and Materiel Command

Congressionally Directed Medical Research Programs

HISTORY The office of the Congressionally Directed Medical Research Programs (CDMRP) was created in 1992 from a powerful grassroots effort led by the breast cancer advocacy community that resulted in a congressional appropriation of funds for breast cancer research. This initiated a unique partnership among the public, Congress, and the military. 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 research, military medical research, and other disease-specific research. The CDMRP has grown to encompass multiple targeted programs and has received nearly $7 billion in appropriations from its inception through fiscal year 2012 (FY12). Funds for the CDMRP are added to the Department of Defense (DoD) budget in which support for individual programs, such as the Tuberous Sclerosis Complex Research Program (TSCRP), is allocated via specific guidance from Congress.

Application Review Process

The CDMRP uses a two-tier review process for application evaluation with both steps involving dynamic interaction between scientists and clinicians—subject matter experts—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 Integration Panel (IP), which compares applications to each other and makes funding recommendations based on scientific merit, portfolio composition, and relevance to program goals.

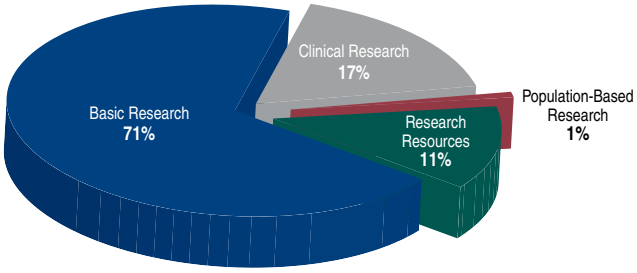
Consumer Advocacy Participation

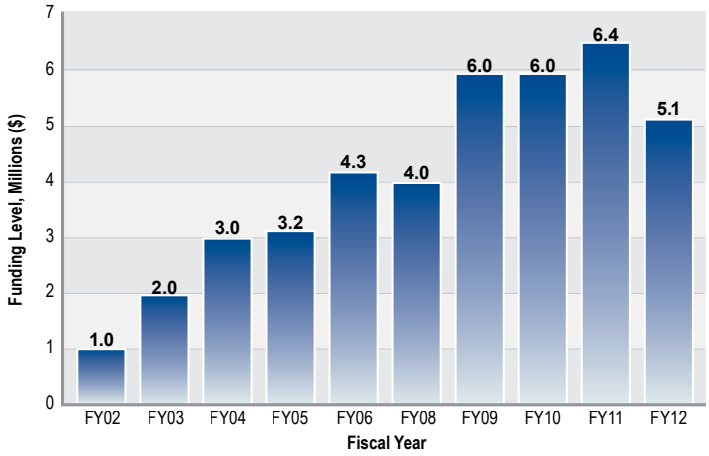
A unique aspect of the CDMRP is the active participation of consumer advocates or patient representatives, throughout the program's annual cycle. Individuals with TSC and their family members have an equal voice in the research administration process of setting the TSCRP's vision, reviewing applications, and making final funding recommendations. From the unique perspective gained through personal experience, the consumer brings 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.

Tuberous Sclerosis Complex Research Program

History of the DoD 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 $41M has been appropriated to the program, including $5.1M in FY12. Today, the TSCRP is one of the leading sources of extramural TSC research funding in the United States. The program's investment strategy is adapted yearly to facilitate rapid change and to better target funding to the most critical TSC research areas, thus ensuring that the program remains responsive to current needs and future opportunities. In total, 88 awards have been made through FY11, bridging basic, clinical, and population-based research, as shown below.





The TSCRP is dedicated to addressing the critical research needs of the TSC community by:

- Supporting high-impact, innovative research
- Fostering the development of research resources and tools for TSC researchers
- Promoting the translation of new research findings to patient care
- Advancing the knowledge of TSC and its clinical manifestations

TSCRP

VISION

To lessen the impact of TSC.

MISSION

To encourage innovative research aimed at understanding the pathogenesis and manifestations of TSC to improve the lives of individuals with TSC.

"This is an exciting time to be involved in tuberous sclerosis complex research. Excellent research proposals are coming to the TSCRP and, as reviewers, we get to see new ideas for advancements in understanding of the basic science of TSC and translational work to improve care of patients with TSC. Patients with TSC and their families have good reasons to be optimistic."

David Dunn, M.D., Indiana University School of Medicine
IP Chair

Research Highlights

LAM Clinical Research Network

Francis McCormack, M.D., University of Cincinnati

Tuberous sclerosis complex (TSC) is a rare genetic disorder, affecting approximately one million people worldwide, that may result in seizures, cognitive impairment, and benign tumors of the skin, eyes, brain, and other organs. Lymphangioleiomyomatosis (LAM), a life-threatening progressive lung manifestation of TSC, affects approximately 40% of women with TSC. Although a significant number of molecular targets have been identified as potential therapeutics for LAM, the design and implementation of clinical trials have been limited due to the rare occurrence of the disease. Dr. Francis McCormack at the University of Cincinnati received an FY09 Clinical and Translational Research Award from the TSCRP to develop a novel paradigm for conducting clinical trials in rare diseases more quickly and more conveniently to patients by bringing clinical trials to local LAM treatment sites. To this end, Dr. McCormack established the LAM Clinical Research Network (LCRN), a collaboration of 24 LAM clinics throughout the United States. LAM clinic directors are in the process of developing a longitudinal dataset that would be collected from all consenting participants to build a natural history database and maintain a list of prospective subjects for future clinical trials. The LCRN will allow patients to enroll in studies at their local LAM clinics with their physician, rather than traveling, sometimes long distances, to gain entry into cutting-edge clinical trials.

One of the initial LCRN aims is to develop and validate a biomarker for diagnosis of LAM using vascular endothelial growth factor-D (VEGF-D). Preliminary results suggest that serum VEGF-D levels can be utilized to diagnosis LAM in women with TSC. A second project of the LCRN is a Phase I/II trial of letrozole, an oral nonsteroidal aromatase inhibitor, in postmenopausal women with LAM (Trial of Aromatase Inhibition in LAM, or TRAIL), which is expected to begin enrollment at six LCRN clinics in 2012.

Dr. McCormack and the LCRN are in a unique position to increase access to clinical trials for individuals with LAM and, in turn, facilitate the delivery of novel LAM treatment options to patients.

Identification of Small Molecule Suppressors of *Tsc* Mutant Phenotypes in *Drosophila*

Tin Tin Su, Ph.D., University of Colorado, Boulder

The genes responsible for TSC, *Tsc1* and *Tsc2*, normally act to suppress cellular growth, but loss of these proteins due to mutations can result in excessive cell growth leading to tumor formation. *Drosophila melanogaster* (fruit fly) models of TSC have been particularly useful in studying the function of normal and mutant *Tsc1/2*. Dr. Tin Tin Su, with funding from an FY09 Exploration–Hypothesis Development Award, used the *Drosophila* model to screen for small molecules that may reverse the effects of *Tsc1/2* mutations. This work led to the identification of two small molecules that reliably inhibit the effects of mutant *Tsc1* in *Drosophila*. The next steps in this work involve validating the activity of these candidate small molecules using the *Drosophila* model and characterizing their mechanism of action.

Understanding the Etiology of Tuberous Sclerosis Complex

Angelique Bordey, Ph.D., Yale University

Individuals with TSC have mutations in the Tsc1 or Tsc2 genes and suffer from the formation of lesions on multiple organs. TSC patients also develop neurological symptoms including seizures, mental retardation, and autism. Cortical tuber lesions that form during embryonic development are associated with the occurrence of seizures in TSC patients. The mechanisms involved in TSC lesion formation and seizure generation are not well understood and validated animal models to investigate the etiology or cause of TSC lesions and subsequent development of neurological disorders are currently unavailable. Through funding from a fiscal year 2009 Idea Development Award, Dr. Angelique Bordey, at Yale University, has generated and validated a mouse model to bridge this gap in knowledge. Dr. Bordey and her research team have determined that deletion of Tsc1 in this mouse model leads to formation of lesions that contain many of the hallmark characteristics associated with human cortical tubers in TSC. This animal model will now allow TSC researchers to study the formation of cortical tuber lesions at specific time points during embryonic development.

Role of Altered mGluR Activity in Cognitive Impairments in TSC: Implications for a Novel Method of Treatment

Mark Bear, Ph.D., Massachusetts Institute of Technology

Patients with TSC develop benign tumors and suffer from cognitive deficiencies including mental retardation, epilepsy, autism, anxiety, and mental disorders. TSC is a genetic disorder resulting from the mutation of either the *Tsc1* or *Tsc2* gene. In healthy cells, the TSC proteins function to modulate protein synthesis by suppressing mTOR (mammalian target of rapamycin) signaling. Interestingly, maintenance of synaptic plasticity, critical for learning, memory, and cognition, requires precise regulation of protein synthesis. Based on these observations, Dr. Mark Bear hypothesized that dysregulation of synaptic protein synthesis may contribute to TSC-associated learning and cognitive deficiencies. Dr. Bear's research team, with funding from an FY10 TSCRP Idea Development Award, demonstrated that loss of *Tsc2* resulted in unregulated mTOR activity and suppressed hippocampal protein synthesis. In addition, the team also determined that treatment with an mGluR5 positive allosteric modulator (PAM) restored hippocampal protein synthesis. Additionally, treatment with mGluR5 PAM also reversed hippocampal-dependent behavioral deficits in *Tsc2*+/- mice. These exciting results suggest that mGluR5 PAM may be a novel therapeutic intervention for TSC-associated cognitive deficiencies.

TSCRP Perspectives

"The Tuberous Sclerosis Complex Research Program has funded research that has fundamentally altered our understanding of the clinical manifestations and molecular biology of tuberous sclerosis complex. Based on this new knowledge, we now have two drugs that should help to alleviate many of the manifestations of the disease."

Steve Roach, M.D., The Ohio State University
IP Member

"As the parent of a child with Tuberous Sclerosis Complex (TSC), it has been an honor to serve as a member of the CDMRP integration panel. The TSC community has made great strides in basic and clinical research in a relatively short time frame. This would not have been possible without the commitment of researchers funded through the CDMRP. My family and the Tuberous Sclerosis community as a whole have benefited greatly from the dedication of these researchers."

Rob Moss, Tuberous Sclerosis Alliance
Consumer IP Member

"This marked my first year participating in this activity as a consumer reviewer. As a parent of a child with tuberous sclerosis, I have lived with this disease for over eight years, but it was very gratifying to see and observe this process first hand. First, I was very impressed with the organization and flow of the entire review process, including all the logistics support which made the jobs of the reviewers much easier. The entire team who worked behind the scenes to support the on-site review process was extremely dedicated and professional. I was also touched by the moment of silence that kicked off the review process on the first day. This provided a personal insight and link to what may seem to be a purely antiseptic or medical, physical condition that may not include the emotional ties to actual people and families. I felt extremely honored and humbled to be representing the entire TSC community during this review process. I hope that my inputs will help researchers better understand the clinical, bedside impact on TSC families."

Maj David Long
Consumer Peer Reviewer

Please visit the TSCRP Research Resources page for the most up-to-date listing of research resources and tools from TSCRP-funded investigators.

http://cdmrp.army.mil/tscrp/resources/tscresources

"As both a parent of an adult child who is profoundly affected by TSC, and as a nurse and clinician/researcher who works with TSC and neurofibromatosis patients, I can attest to the vital role the CDMRP plays against these devastating disorders. The program not only draws the most talented and focused researchers from around the world, but provides an avenue for patient and other consumer input that is sorely lacking from other research programs. It has been both personally and professionally rewarding to serve as a consumer reviewer. I also cannot commend highly enough the positive, productive, and cost-effective manner in which the program staff—both DoD and contractor personnel—operate the program."

Nancy Elling
Consumer Peer Reviewer

"There is a quote by Richard Evans that states, 'It is often in the darkest skies that we see the brightest stars;' which reflects my soul as a mother dealing with my children's tuberous sclerosis complex diagnosis but yet has hope because of research. TSC research rescued me from the darkness that was replaced with an intense passion for TSC advocacy that includes fundraising, supporting TSC families, and lobbying for the continued funding of the TSCRP through the Department of Defense. The TSCRP that focuses on gaps in crucial TSC research to lessen the impact of TSC is one of the brightest stars in my constellation simply because it provides hope to me and all other TSC families. Without hope, there is no light. My role as a TSCRP Consumer Panelist had a tremendous impact because it was empowering and uplifting to be in the presence of scientists and doctors who are working together for TSC research as well as being able to review quality grant applications submitted by researchers with the goal of enhancing TSC research. This priceless experience through the TSCRP has fueled my soul to continue shooting toward the stars for TSC research."

Carole Pitard
Consumer Peer Reviewer

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