VIII. Tuberous Sclerosis Complex Research Program
Vision
To lessen the impact of tuberous sclerosis complex.

Mission
To encourage innovative research, including natural history studies, aimed at improved detection, diagnosis, and treatment of tuberous sclerosis complex.
The Disease

Tuberous sclerosis complex (TSC) is a genetic disorder that can affect any or all systems of the body. TSC affects as many as 25,000 to 40,000 individuals in the United States and about 1 to 2 million individuals worldwide. Although this disorder can be inherited as an autosomal dominant trait, two-thirds of the 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 produces the protein hamartin. The TSC2 gene is located on chromosome 16 and produces the protein tuberin. Hamartin and tuberin are believed to act as tumor growth suppressors. Therefore, their dysfunction may underlie the appearance of tumors that characterize tuberous sclerosis.

There is currently no cure for this disease; however, surgical intervention and a number of treatments can help affected individuals.

1 National Institute of Neurological Disorders and Stroke Tuberous Sclerosis Fact Sheet.
Signs and Symptoms

Because TSC affects multiple organs, a variety of symptoms may be experienced. The disorder can cause benign tumors, called tubers, to grow in various organs, including the brain, skin, heart, kidneys, lungs, and eyes. However, in most individuals with TSC, only some of these organs are involved, and symptoms vary depending on which organs and systems are affected.

Other signs and symptoms of TSC include:

- seizures
- autism
- mental disabilities
- skin abnormalities
- behavioral problems
- kidney disease
- lung complications
Program Background

The Department of Defense (DOD) Tuberous Sclerosis Complex Research Program (TSCRP) was established in fiscal year 2002 (FY02) by Joint Appropriations Conference Committee Report No. 107-350, which provided $1 million (M) for TSC research. The TSCRP has managed $13.5M through FY06 to fund peer-reviewed TSC research (see Figure VIII-1 – TSCRP History). Thirty-five awards have been made through FY05 in an effort to advance progress in the field of tuberous sclerosis research. Key initiatives of the TSCRP include support for groundbreaking concepts and ideas and impacting patients’ lives.

![Figure VIII-1. TSCRP History](image)
The Program Today

Fiscal Year 2005 Summary

The TSCRP was continued through an FY05 congressional appropriation of $3.2M. The program retained the three award mechanisms offered in the previous fiscal year (Concept, Idea Development, and Natural History Development Awards). In addition, the program launched the Natural History Study Award to fund focused, hypothesis-driven natural history studies to elucidate the clinical course of TSC. A total of 60 proposals were received across award mechanisms, as shown in Table VIII-1, and 15 awards were made. As illustrated in Figure VIII-2, the FY05 TSCRP has developed a diverse research portfolio that encompasses basic and clinical research.

Table VIII-1. Funding Summary for the FY05 TSCRP

<table>
<thead>
<tr>
<th>Categories and Award Mechanisms</th>
<th>Proposals Received</th>
<th>Awards</th>
<th>Investment</th>
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<tr>
<td>Concept</td>
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<td>$814,065</td>
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<td><strong>TOTAL</strong></td>
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</tbody>
</table>

Clinical Research: 13%
Clinical and Experimental Therapeutics: 6.5%
Detection and Diagnosis: 6.5%

Basic Research: 87%
Cell Biology: 47%
Genetics and Molecular Biology: 40%

Figure VIII-2. FY05 TSCRP Portfolio by Research Area
Fiscal Year 2006 Summary

Congress appropriated $4.3M to continue the TSCRP in FY06. Three award mechanisms were offered to advance progress in the field of TSC, Concept Awards, Idea Development Awards, and Clinical Resource Development Awards, the last representing a new award mechanism for the program. As shown in Figure VIII-3, a total of 47 proposals were received, and approximately 16 awards are expected. The congressional appropriations and the investment strategy executed by the TSCRP for FY05 through FY06 are summarized in Appendix B, Table B-7.

Figure VIII-3. Award Mechanisms Offered and Proposals Received for the FY06 TSCRP
Advances and Progress in TSC Research

Recently there has been a tremendous amount of progress in TSC research. In the past 10 years, the causal genes (TSC1 and TSC2) have been identified, a commercial diagnostic test was made available to identify these gene mutations, functional studies of these genes have been performed, a drug (rapamycin) that mimics some TSC1 and TSC2 normal functions has been identified, clinical trials have been initiated, and natural history studies are under way.

The TSCRP aims to continue driving progress in TSC research by assembling the brainpower of outstanding people, funding groundbreaking ideas and technology, and funding the development of new research tools.
Advancing Progress through Outstanding People

The collective efforts of scientists, clinicians, research managers, and consumer advocates are making a difference in the advancement of progress in the field of TSC. The program recognizes the wisdom and dedication of these outstanding people who are working together to lessen the impact of the disease.
Consumer Advocate Participation

A unique feature of the TSCRP is that consumer advocates actively participate in setting program priorities and making funding decisions. Consumer advocates may be individuals with TSC or those who have family members with TSC (TSC initially manifests in childhood). Their firsthand experiences with TSC provide a unique perspective that helps scientists understand the human side of the disease and allows for funding decisions that reflect the concerns and needs of patients, their families, and clinicians. Consumer advocates also share what they have learned with their communities, resulting in increased awareness of the importance of research and a stronger relationship between the scientific and consumer advocate communities. The overwhelming success of the inclusion of consumer advocates in the review process for Congressionally Directed Medical Research Programs (CDMRP) such as the TSCRP has influenced other funding agencies to follow this precedent. Additional information about consumer participation can be found in Chapter I.

MS. LAURA JENSEN, FY06 TSCRP CONSUMER PEER REVIEW PANEL MEMBER

“There is a stereotype that government programs are bureaucratic and lack efficiency and accountability; however, the CDMRP proves that image wrong on all counts. I have never participated in a more thoughtfully designed or intelligently executed program. Although I have served on a variety of boards and committees, I have never seen one more inviting of feedback or more serious about improving each detail of the experience. As a result, every piece in place is efficient and effective, and the whole program really works to fulfill the mission of the CDMRP. As a consumer reviewer for the Tuberous Sclerosis Complex Research Program, I was thrilled to bring back to my local community news of the first-rate work being done. The program is a model, and it was an honor and an inspiration to participate.”
Integration Panel Members

The TSCRIP Integration Panel (IP) is composed of exceptional scientists, clinicians, and consumer advocates that use their expertise to create effective investment strategies, craft innovative research agendas, and develop broad-based research portfolios (for more information about the functions of the IP, see Chapter I). The program acknowledges past and current IP members whose commitment and active input are enabling the TSCRIP to drive progress in the field.

**Fiscal Year 2006 IP Members**

SANDRA DABORA, M.D., PH.D. (CHAIR), BRIGHAM AND WOMEN’S HOSPITAL
RAYMOND YEUNG, M.D. (CHAIR-ELECT), UNIVERSITY OF WASHINGTON
JANE FOUNTAIN, PH.D., NATIONAL INSTITUTE OF NEUROLOGICAL DISORDERS AND STROKE
JACKSON GIBBS, PH.D., ASTRA ZENECA
BRUCE KORF, M.D., PH.D., UNIVERSITY OF ALABAMA AT BIRMINGHAM
SUSAN LAMONT, PH.D., TUBEROUS SCLEROSIS ALLIANCE
ELIZABETH THIELE, M.D., PH.D., MASSACHUSETTS GENERAL HOSPITAL
TIAN XU, PH.D., YALE UNIVERSITY SCHOOL OF MEDICINE

DR. SANDRA DABORA, BRIGHAM AND WOMEN’S HOSPITAL, FY06 TSCRIP IP CHAIR

“I have enjoyed working together with members of the TSCRIP IP. The shared commitment to tuberous sclerosis research progress is apparent as the multidisciplinary TSCRIP IP considers each decision. The DOD TSCRIP is in an excellent position to facilitate the translation of laboratory research progress to clinically meaningful improvements in treatments for those with tuberous sclerosis in the coming years.”
Scientific Community

Renowned researchers from around the world are exploring the cutting edge of science to make a difference in the lives of patients affected with TSC. Selected TSCRP-supported investigators and their accomplishments are highlighted below.

**USING YEAST TO STUDY TSC**

Dr. Elizabeth Henske of Fox Chase Cancer Center received an FY02 Idea Development Award to learn new functions of the TSC1 and TSC2 proteins using yeast model systems. Understanding the functions of TSC1 and TSC2 will speed the development of new targeted therapeutics. Dr. Henske’s research team showed that deficiencies in TSC1 and TSC2 caused abnormal amino acid sensing, uptake, and metabolism. Diminished uptake of the amino acid glutamate is believed to contribute to seizure development, suggesting that the yeast model may provide a novel system for the study of TSC-related epilepsy and for preclinical screening of new therapeutics that may reduce seizures.

**STUDY OF TSC-RELATED EPILEPSY**

Dr. David Gutmann of the Washington University School of Medicine discovered new mechanisms by which TSC gene defects in the brain result in seizures. With support from an FY02 Idea Development Award, Dr. Gutmann (pictured right), Dr. Michael Wong (pictured left), and colleagues used mouse models to study molecular and cellular effects of decreased activity of TSC1 in the brain. The researchers discovered several genetic and cellular abnormalities that result from astrocyte-specific inactivation of TSC1, showed a role for astrocyte potassium homeostasis in influencing seizures, and developed a novel concept that the astrocyte may be centrally involved in the pathogenesis of neurological complications of TSC, including epilepsy. These findings suggest that astrocytes could provide targets for new innovative therapies against epilepsy.
VIII. Tuberous Sclerosis Complex Research Program
Advancing Progress through
Groundbreaking Ideas and Technology

The TSCRP has supported high-risk, high-reward research of exciting new ideas through two award mechanisms, Idea Development Awards and Concept Awards. Selected accomplishments from Idea Development Award recipients follow.

- **Idea Development Award:** Supports innovative research directed toward improving detection, diagnosis, and treatment of TSC

- **Concept Award:** Funds high-risk, high-reward research toward the exploration of novel theories or development of new preclinical tools
HYPOXIA AND THE TSC2 TUMOR SUPPRESSOR PROTEIN

FY03 Idea Development Award recipient Dr. William Kaelin of the Dana-Farber Cancer Institute studied how TSC2 mediates signaling pathways in response to hypoxia, or oxygen deprivation. Tumor hypoxia is associated with a negative prognosis in several types of cancers, including those associated with TSC. Dr. Kaelin’s research team dissected signaling pathways involving TSC2 and mTOR, a central regulator of protein synthesis and cell growth found at high levels in patients with TSC. They discovered that inhibition of mTOR in hypoxic cells requires a functional TSC1/TSC2 protein complex. Moreover, inactivation of TSC2 conferred a proliferative advantage to cells grown under hypoxic conditions. Improved understanding of the role of TSC2 in response to hypoxia could lead to better treatments for tumors associated with TSC.

CELL MOTILITY IN TSC PATIENTS WITH LUNG TUMORS

Dr. Vera Krymskaya of the University of Pennsylvania uncovered mechanisms by which TSC1 and TSC2 regulate cell adhesion and motility. Cell motility is particularly important in the correct positioning of neurons during brain development. Abnormal cell motility also leads to benign lung tumors, or lymphangioleiomyomatosis (LAM), in patients with TSC. With support from an FY03 Idea Development Award, Dr. Krymskaya and colleagues found that TSC2 modulates actin dynamics and cell adhesion and plays a critical role in modulating migration and invasiveness of LAM-derived cells. They also discovered that TSC1 and TSC2 regulate Rho and Rac, two proteins that are key regulators of cell shape and motility. Rho and Rac also play critical roles in tumor invasion and metastasis. These findings are important in developing new therapeutic strategies to treat neurological disorders and lung tumors in patients with TSC.
Advancing Progress by Impacting Patients’ Lives

The TSCRP is bringing new discoveries to patients through clinical research. Award mechanisms that have been supported by the program to directly lessen the impact of TSC include Natural History Awards (including Natural History Development Awards) and Clinical Resource Development Awards. The recipients of the Natural History Awards and their projects are profiled.

- **Natural History Award:** Funds focused, hypothesis-driven natural history studies to enhance the current knowledge of TSC manifestations and improve clinical management

- **Clinical Resource Development Award:** Supports the development and testing of breakthrough technologies for measuring TSC-relevant clinical or surrogate endpoints in clinical trials
TSC NATIONAL CLINICAL DATABASE

With support from an FY04 Natural History Development Award, Dr. Steven P. Sparagana of Texas Scottish Rite Hospital for Children and the University of Texas Southwestern Medical Center at Dallas, in collaboration with the Tuberous Sclerosis Alliance and other clinicians caring for patients with TSC, is developing a comprehensive clinical database of TSC that documents the natural history and variability of TSC over the lifespan of individuals with the disease. Understanding the clinical aspects of TSC could yield more accurate prognosis of disease course, help identify and develop targeted treatments, and help predict patient response to treatments.

NATURAL HISTORY STUDY OF TSC

FY05 Natural History Study Award recipient Dr. John Bissler of the University of Cincinnati is concentrating on the natural history of renal (kidney) complications from TSC. His research team is using imaging to study angiomyolipomata (abnormal growths consisting of blood vessels, muscle cells, and fat cells) found in 80 percent of patients with TSC. These lesions can cause severe pain and renal failure. Understanding the natural history of these lesions and which lesions are most likely to grow quickly or develop aneurysms will greatly assist in the clinical care of patients with TSC.
Advancing Progress through the Development of Research Tools

The design and testing of therapeutics for TSC present serious challenges because researchers do not fully understand how the loss of function of the TSC1 and TSC2 proteins leads to the disease state. However, investigators funded through the TSCRP are designing the tools needed to achieve breakthroughs in understanding the biological mechanisms of TSC and developing new treatments.
FRUITFLY AS A MODEL SYSTEM TO STUDY TSC

With funding from an FY02 Idea Development Award, Dr. Naoto Ito of Massachusetts General Hospital developed an animal model—using fruit flies (Drosophila melanogaster) that expressed mutated TSC1 or TSC2—to explore how such mutation affects the nervous system in the context of a living, developing animal.

MOUSE MODEL OF TSC

Taking a similar approach, Dr. James Shipley of Washington University, with support from an FY04 Idea Development Award, is developing a mouse model that either will delete the TSC1 gene or overexpress a mutated TSC2 gene in the smooth muscle of the mouse following the proper stimulus. This prototype, which may prove useful in the study of other tissues and cell types, will model a critical facet of the disease—the progressive lung disorder LAM that is a common corollary of TSC. As with TSC, no effective therapy currently exists for lymphangioleiomyomatosis (LAM).

GENERATION OF HUMAN LAM CELL LINES

While working at the Rothberg Institute of Childhood Diseases, Dr. Rachel Squillace, now at ARIAD Pharmaceuticals, Inc., received support from an FY04 Concept Award to derive a human TSC2-/- LAM cell line for the purpose of exploring both LAM and TSC and to test potential therapies. Dr. Squillace obtained two human LAM tissue samples that contained TSC2-negative cells and generated approximately 400 LAM cell lines. These lines are currently being characterized for TSC2 protein expression and activity.

The products from these and other projects funded by the TSCRP will provide the necessary means to study both TSC and LAM so that we may better understand the mechanisms through which the diseases develop and evaluate new potential treatments.