VIII. Tuberous Sclerosis Complex Research Program

BUILDING RESOURCES FOR THE FUTURE

Vision

To lessen the impact of tuberous sclerosis complex.

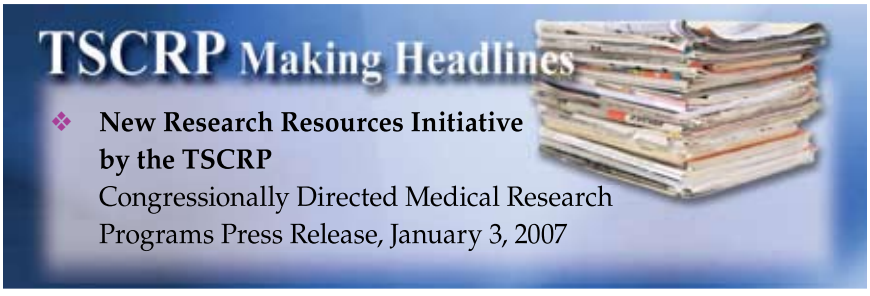
Mission

To encourage innovative research aimed at understanding the pathogenesis of TSC and improving its diagnosis and treatment.

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 50,000 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.



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
- mental disabilities
- skin abnormalities
- behavioral problems
- brain tumors
- autism
- kidney disease
- lung complications
- developmental delays

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 Funding History). A total of 48 awards have been made through FY06 in an effort to advance progress in the field of tuberous sclerosis research. Key initiatives of the TSCRP include support for building research resources for the future.

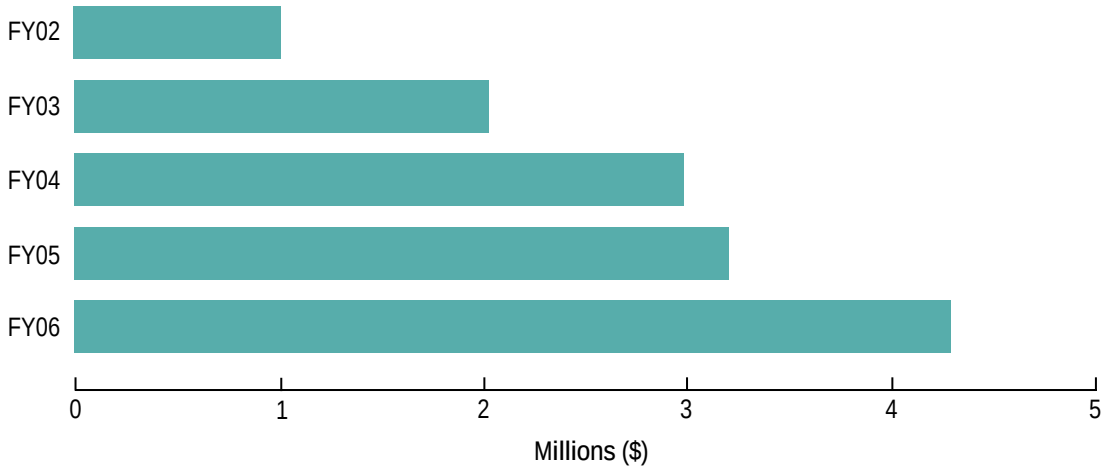


Figure VIII-1. TSCRP Funding History

Building a Network of Human Resources

The accomplishments of the TSCRP are only possible through the collective efforts and contribution of the best people working together to lessen the impact of TSC. From consumer advocates, research administrators, and the scientific community, many people have dedicated their time and effort to make the program a success. The TSCRP is grateful to all those who have been involved in the program.

Consumer Advocates

A unique feature of the TSCRP is that consumer advocates actively participate in recommending program priorities and 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 the 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 Section I, Overview.

Celia Mastbaum and her son Matthew
FY02–04 and FY06 Consumer Peer Review Panel Member

"As a parent of a teenage boy who is severely affected by tuberous sclerosis, I feel privileged to have served as a consumer reviewer in the Congressionally Directed Medical Research Programs. It has been extremely rewarding to see just how far TS research has come in just the past several years. Because of the efforts of the DOD's TSCRP, our community can now hope for a safe and effective therapy that will be able to treat the actual disease as opposed to trying, often unsuccessfully, to treat each of its many devastating symptoms. The CDMRP has been crucial in stimulating the much-needed research as well as providing a forum for discussion with some of the country's leading scientists. The program is well organized, efficient, and extremely conscientious. It also ensures that every viewpoint is heard by including the consumer perspective along with those of the experts. The TS community will never be able to fully express just how appreciative we are to this program for helping to improve the lives of so many affected people."

Peer Review Panel Members

The TSCRP peer review panels are composed of prominent TSC-focused scientists and clinicians and dedicated consumer advocates that provide unbiased, expert advice on the scientific and technical merit of the proposals. Scientific reviewers for this panel are selected for their subject matter expertise and experience with scientific peer review. Consumer reviewers are nominated by an advocacy or support organization and are chosen on the basis of their leadership skills, commitment to advocacy, support, and outreach as well as their interest in expanding their scientific knowledge. Approximately **60 scientists, clinicians, and consumer advocates** have contributed their expertise to peer review for the TSCRP. Further details about peer review can be found in Section I.

Vera Krymskaya, Ph.D.
University of Pennsylvania School of Medicine
FY05–06 Peer Review Panel Member

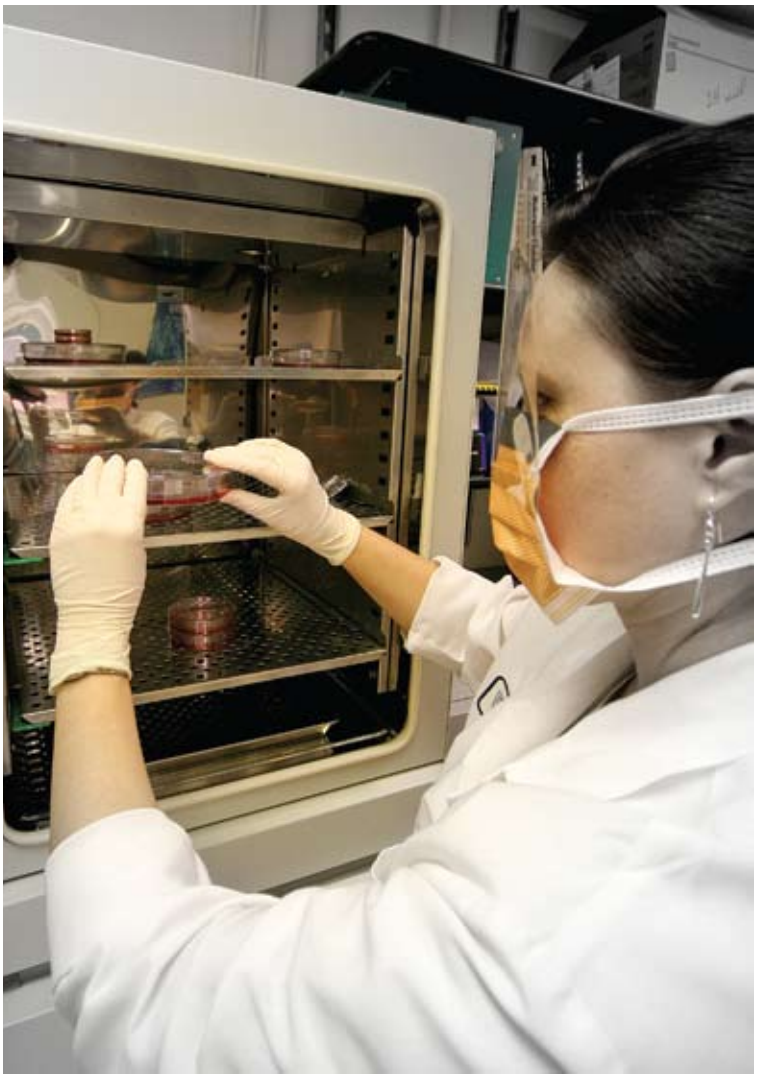
"Serving as a reviewer for DOD was a great experience for me. Professionally, I was glad to contribute my research expertise in evaluating research proposals that may advance not only our knowledge about this devastating disease, but also may bring us closer to finding a cure for TSC. Personally, it was great to work with DOD personnel involved in organizing the process, which was superb. I want to express my appreciation for all work done by DOD to support this vital research, which may help improve the quality of TSC patients' lives as well as save lives of patients who suffer from this disorder."

Integration Panel Members

Renowned scientists, clinicians, and consumer advocates comprise the TSCRP Integration Panel (IP). They have used their expertise to recommend strategies that meet the needs of the scientific and consumer advocate communities and recommend broad-based research portfolios to advance progress in the field (for more information about the functions of the IP, see Section I). The program acknowledges past and current IP members whose commitment and active input are enabling the TSCRP to drive progress in the field.

TSCRP IP Members

Name	Affiliation
FY06 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
Past Members	
Peter Adamson, M.D.	University of Pennsylvania School of Medicine
Peter Crino, M.D., Ph.D.	University of Pennsylvania School of Medicine
Robert Finkelstein, Ph.D.	National Institute of Neurological Disorders and Stroke
Elizebeth Petri Henske, M.D.	Fox Chase Cancer Center
William Johnson, M.D.	University of Medicine and Dentistry of New Jersey, Robert Wood Johnson Medical School
Eric Legius, M.D., Ph.D.	Catholic University of Leuven, Belgium
Judy Small, Ph.D.	The National Neurofibromatosis Foundation, Inc.
Vicky Holets Whittemore, Ph.D.	Tuberous Sclerosis Alliance



Scientific Community

Scientists and clinicians across the nation and abroad are dedicating their lives to find a cure for TSC. To date, the program has funded 41 researchers. The remainder of this section samples the wide-range and diversified efforts of TSCRP-supported investigators to lessen the impact of TSC.

Susan Lamont, Ph.D.
Tuberous Sclerosis Alliance
Integration Panel Member FY05–07
"The Integration Panel truly provides the forum to bring together consumer input and scientific expertise to identity the best scientific research to find answers that meet the needs of the TSC community."

Building Research Resources

The TSCRP began a groundbreaking research resource in
the disease by publicizing newly available resources supp
developed and posted on the TSCRP website that displays
Drosophila models, yeast models, cell lines, antibodies, dat
contact information for each resource. The goal of this in
research community and encourage resource sharing by
reference table can be accessed at http://cdmrp. army.mil

Tomohiro Matsumoto, Ph.D. (center) and colleagues Kyoto University, Japan

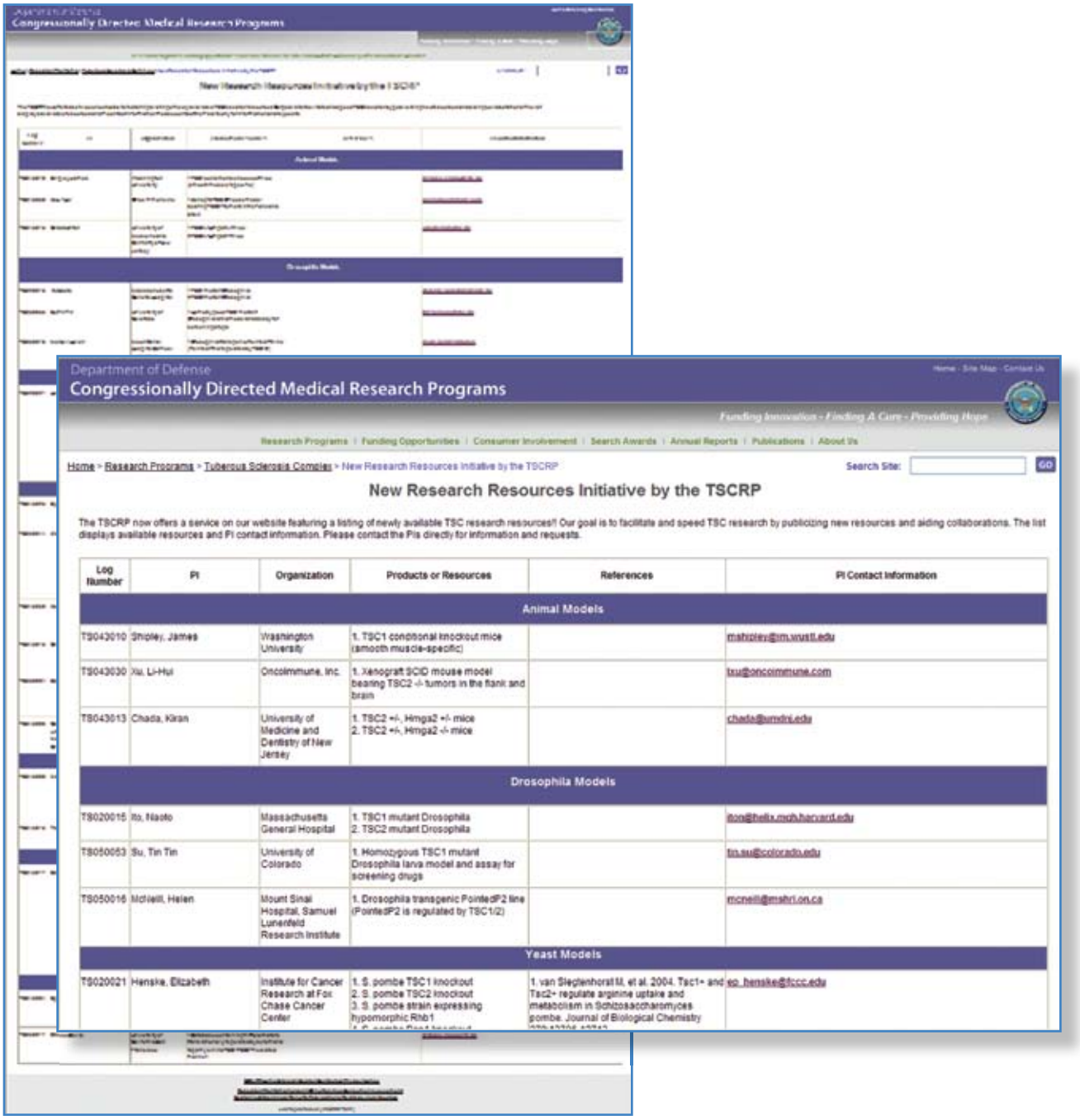
"We have received e-mails requesting antibodies and reagents for [TSC research]. Considering this is a relatively small research community, I think that the posting on the TSCRP website has had a great impact."

Although animal models, *Drosophila* models, and cell line
provide important model systems for studying the diseas
among many species. For example, there is over 90% ami
horse, dog, and primate TSC1 and TSC2 proteins. This su
functions in different species. These models can be used
of TSC1 and TSC2, thereby providing the foundation for t
also be used to test the potential efficacy and toxicity of candidate therapeutics so that the best drugs can be given to TSC patients.

The TSC1 and TSC2 proteins are part of the mTOR master regulatory pathway. Proteins in this signaling pathway play central roles in regulating nutrient uptake, metabolism, and energy, and this pathway has been implicated in diverse diseases including TSC, several cancers, diabetes, obesity, and metabolic disorders. Therefore, TSC1 and TSC2 may play important roles in a variety of diseases, and these model systems may be broadly applicable to studying these diseases.

There has been enthusiastic response from the community about this initiative. Several investigators have commented that the initiative is a great idea and will be extremely beneficial to the research community.

On the following pages are highlights of resources supported by the TSCRP. Additional information about these resources can be found on the TSCRP web page at http://cdmrp.army.mil/tscrp/tscresources



Department of Defense
Congressionally Directed Medical Research Programs

Funding Innovation - Finding A Cure - Providing Hope

Research Programs | Funding Opportunities | Consumer Involvement | Search Awards | Annual Reports | Publications | About Us

Home > Research Programs > Tuberous Sclerosis Complex > New Research Resources Initiative by the TSCRP

Search Site: GO

New Research Resources Initiative by the TSCRP

The TSCRP now offers a service on our website featuring a listing of newly available TSC research resources!! Our goal is to facilitate and speed TSC research by publicizing new resources and aiding collaborations. The list displays available resources and PI contact information. Please contact the PIs directly for information and requests.

Log Number	PI	Organization	Products or Resources	References	PI Contact Information
Animal Models					
TS043010	Shipley, James	Washington University	1. TSC1 conditional knockout mice (smooth muscle-specific)		mshipley@im.wustl.edu
TS043030	Xu, Li-Hui	Oncoimmune, Inc.	1. Xenograft SCID mouse model bearing TSC2 -/- tumors in the flank and brain		lxu@oncoimmune.com
TS043013	Chadia, Kiran	University of Medicine and Dentistry of New Jersey	1. TSC2 +/-, Hmga2 +/- mice 2. TSC2 +/-, Hmga2 -/- mice		chadia@umdnj.edu
Drosophila Models					
TS020015	Ito, Naoto	Massachusetts General Hospital	1. TSC1 mutant Drosophila 2. TSC2 mutant Drosophila		ito@helix.mgh.harvard.edu
TS050053	Su, Tin Tin	University of Colorado	1. Homozygous TSC1 mutant Drosophila larva model and assay for screening drugs		tin.su@colorado.edu
TS050016	McNeill, Helen	Mount Sinai Hospital, Samuel Lunenfeld Research Institute	1. Drosophila transgenic PointedP2 line (PointedP2 is regulated by TSC1/2)		mcneill@mshri.on.ca
Yeast Models					
TS020021	Henske, Elizabeth	Institute for Cancer Research at Fox Chase Cancer Center	1. S. pombe TSC1 knockout 2. S. pombe TSC2 knockout 3. S. pombe strain expressing hypomorphic Rhb1	1. van Slegtenhorst M, et al. 2004. Tsc1+ and Tsc2+ regulate arginine uptake and metabolism in Schizosaccharomyces pombe. Journal of Biological Chemistry	eo_henske@fccc.edu

Tin Tin Su, Ph.D.
University of Colorado

Drosophila Model System for Screening Drugs

Dr. Tin Tin Su of the University of Colorado is using *Drosophila* to screen new drugs. With support from an **FY05 Concept Award**, Dr. Su is using *Drosophila melanogaster* as a multicellular model to screen for small molecules that reverse the tissue overgrowth and larval lethality phenotypes of TSC1 mutants. This screening system could potentially yield novel therapeutics that are effective against TSC in humans. Dr. Su and her team are in the process of screening the mechanistic set small molecule library from the Developmental Therapeutics Program of the National Cancer Institute (http://dtp.nci.nih.gov/). This library consists of 879 molecules, each of which represents a group exhibiting similar growth inhibition patterns on 60 human cancer cell lines (NCI-60).

Dr. Su and her team have thus far found 11 promising candidates. Dr. Su's team also performed proof-of-concept screening with rapamycin using the model. The researchers showed that *Drosophila* can be used to rapidly screen for small molecules that potentially antagonize insulin-like growth factor (IGF) signaling. Altered IGF signaling has been implicated in aging and several human diseases, including cancers, growth disorders, diabetes, and Alzheimers.

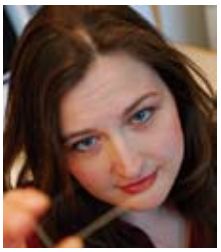
Kiran Chada, Ph.D.
University of Medicine and Dentistry of New Jersey

TSC2 and Hmga2 Mouse Model Systems

Dr. Kiran Chada of the University of Medicine and Dentistry of New Jersey developed new mouse models to study the interactions between TSC2 and the architectural transcription factor high mobility group A2 (HMGA2). HMGA2 is normally expressed specifically in undifferentiated mesenchymal cells but is misexpressed in TSC2-deficient cells, especially lymphangioleiomyomatosis and cardiac rhabdomyomas.

With support from an **FY04 Idea Development Award**, Dr. Chada and his team generated mice that were heterozygous for TSC2 and either heterozygous or null for Hmga2 (TSC2 +/-, Hmga2 +/- mice; TSC2+/-, Hmga2 -/- mice, respectively). Dr. Chada's group showed that an absence of Hmga2 caused a change in the diversity of tumor types in the mice. These findings have implications for many tumor types, as alterations in Hmga2 play important roles in uterine leiomyomas (fibroids), salivary gland tumors, neuroblastic tumors, and lipomas.

David Sabatini, M.D., Ph.D.
Whitehead Institute for Biomedical Research

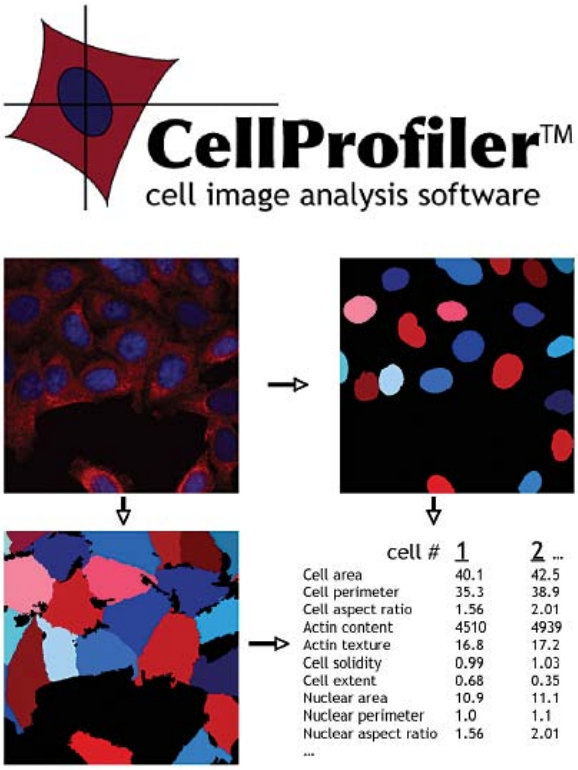


Anne Carpenter, Ph.D.
Whitehead Institute for Biomedical Research

New Software for Cell Image Analysis

Drs. David Sabatini and Anne Carpenter of the Whitehead Institute for Biomedical Research developed new image analysis software for identifying and quantifying cell phenotypes using funding from an **FY04 Concept Award**. CellProfiler™ is the first free, open-source system designed for flexible, high-throughput cell image analysis. CellProfiler can be used for assaying cell count, size, per-cell protein levels, cell/organelle shape, and subcellular localization of DNA or protein.

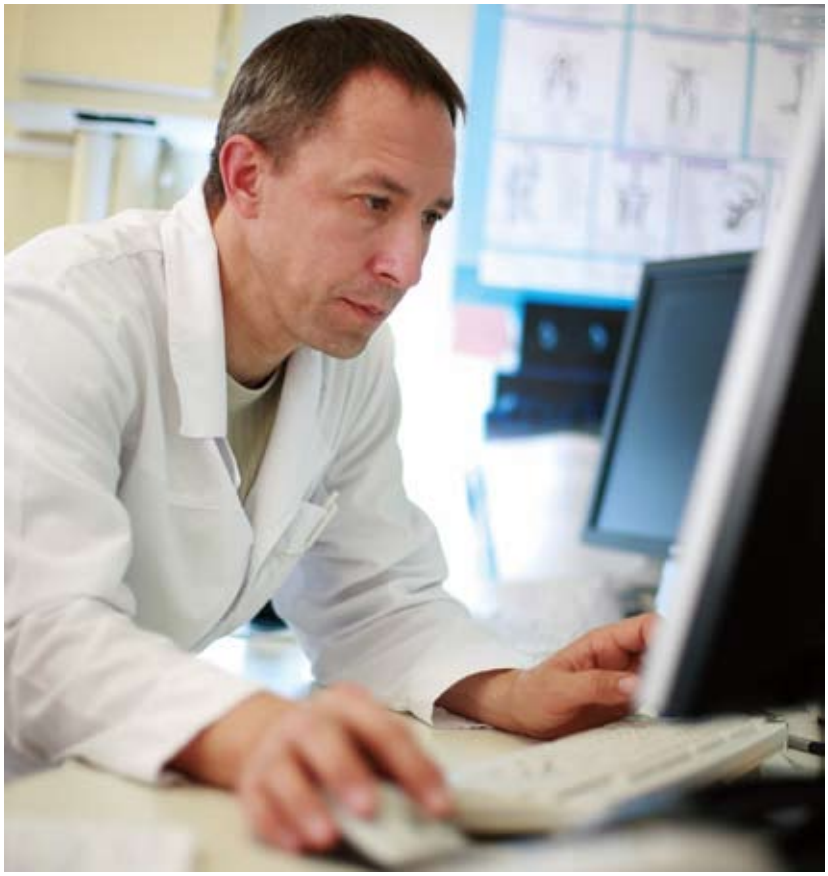
Dr. Sabatini's group is using CellProfiler as part of a high-throughput screen to identify new drug targets for treating TSC. The team is using cultured *Drosophila* cells as living cell microarrays and identifying all the genes in the genome whose RNAi-mediated reduction in expression (1) prevents growth and proliferation of TSC1- or TSC2-deficient cells without affecting normal cells, (2) induces apoptosis and cell death in TSC1- or TSC2-deficient cells without killing normal cells, or (3) reverts TSC1- or TSC2-deficient cells to a normal phenotype.



In addition to TSC research, CellProfiler has been used by several researchers for a variety of applications, including analysis of yeast, *Drosophila*, worm, and mammalian cells. CellProfiler has been used to count cells, identify tumors, and quantify wound healing (see www.cellprofiler.org for more information).

Database of mRNAs Regulated by TSC1/2

Dr. David Stokoe of the University of California, San Francisco, developed a database containing mRNAs that are translationally regulated by serum and rapamycin in a TSC1/TSC2-mediated manner. With funding from an **FY05 Concept Award**, Dr. Stokoe's team performed a systematic genome-wide screen and measured polyosomal and monosomal distribution of mRNAs in mouse embryo fibroblasts that were wild type, TSC1 null, or TSC2 null. The isolated differential mRNAs and their corresponding translated proteins represent new therapeutic targets for treating TSC. Using this innovative screen, Dr. Stokoe has identified over 100 potential targets. These targets may be applicable to other types of cancers, as rapamycin is currently being tested in clinical trials for breast, kidney, pancreatic, lung, prostate, leukemia, lymphoma, liver, and sarcoma tumors as well as for neurofibromatosis.



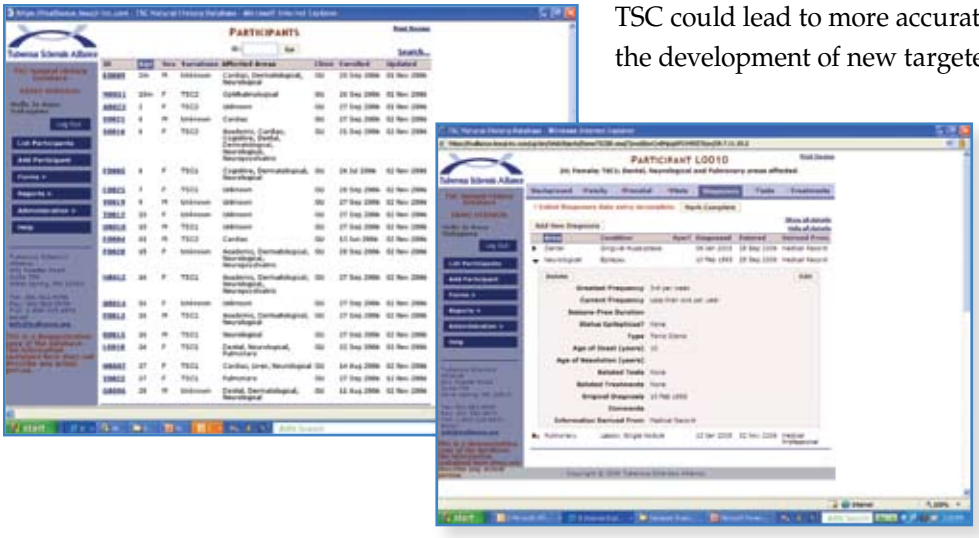
Leveraging Resources

Natural History Database

Dr. Steven Sparagana of Texas Scottish Rite Hospital for Children and the University of Texas Southwestern Medical Center at Dallas began development of a TSC Natural History Database using funds from an **FY04 Natural History Development Award**. The TS Alliance and a consortium of TSC clinics completed the development of this database. The database was piloted at two TSC clinics in 2006, six additional TSC clinics are being added in 2007, and all other TSC clinics are expected to be added in 2008. The TS Alliance is currently leading this project.

Phase I of the project was completed at the first two clinics (Minnesota Epilepsy Group, PA® and Texas Scottish Rite Hospital for Children) in April 2007. As of June 2007, these two clinics enrolled more than 80 individuals with TSC, 80 percent of whom were children. The database was optimized during Phase I. Phase II of the project was launched in 2007. In this phase, the following six clinics are being added: The Carol and James Herscot Center for Children and Adults with Tuberous Sclerosis Complex at Massachusetts General Hospital, The TS Center at New York University Medical Center, Washington Metro Area Tuberous Sclerosis Research Clinic, Chicago Corner Children's Hospital Neuorgenetic Clinic, The Jack and Julia Center for TSC at Children's Hospital and Research Center at Oakland, and the TSC Clinic at University of California, Los Angeles.

This comprehensive clinical database of TSC documents the natural history and variability of TSC over the lifespan of individuals with the disease. Patient information collected for the database includes demographics, enrollment in the database, initial TSC diagnosis, genotype, participation in investigational studies, mortality, family history, prenatal history, vital signs, TSC-related diagnoses, diagnostic tests, and treatments. Understanding the clinical aspects of TSC could lead to more accurate disease prognosis, the development of new targeted therapies, and the prediction of patient response to treatments.

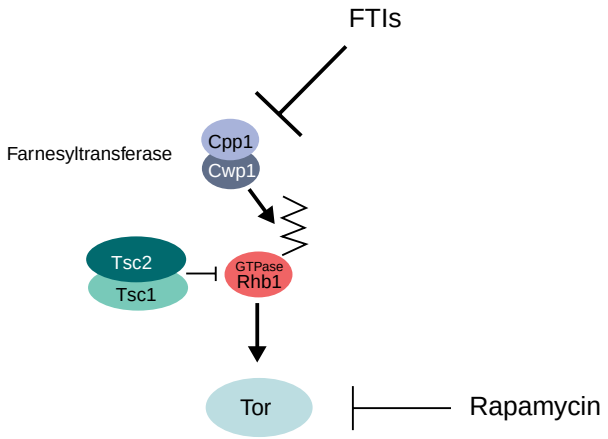


Trans-NIH TSC Working Group Meeting

The TSCRP participates in a yearly meeting with other agencies and organizations that fund TSC research, including the TS Alliance and National Institutes of Health (NIH). Representatives from these varied groups convene to discuss progress in TSC research in relation to the "5-year master plan," future research directions, and current TSC grants and collaborative initiatives between funding agencies.

Capitalizing on Resources

TSC researchers are capitalizing on existing models and using them to make key discoveries. Two TSCRP-funded researchers, Drs. Tomohiro Matsumoto of Kyoto University in Japan and Kun-Liang Guan of the University of Michigan, are using existing model systems to discover signal transduction pathways that may provide therapeutic targets for treating TSC.



Using Fission Yeast to Discover New Therapeutic Targets

Dr. Matsumoto performed a screen in a fission yeast model system to isolate genes that could suppress the defects found in TSC2-deficient yeast. With funding from an **FY04 Idea Development Award**, Dr. Matsumoto's team found that a mutated form of a protein called farnesyltransferase could suppress some, but not all, of the defects resulting from the mutated TSC2 protein. (Farneslytransferases are important regulators of cell growth, and they regulate proteins by farnesylation, or the addition of a fat-like farnesyl molecule.) Dr. Matsumoto's team found that deficient farneslyation of Rhb1, in particular, contributed to the suppression of cell defects.

Farnesyltransferase inhibitors (FTIs) are a new class of drugs that target farnesyltransferases and are currently in clinical trials to treat cancers and neurofibromatosis. The results of the research done by Dr. Matsumoto's team suggest that rapamycin may be a more effective treatment for TSC if used in combination with FTIs. These results also suggest that TSC1/2 and its signaling partners may play important roles in cancers and neurofibromatosis.

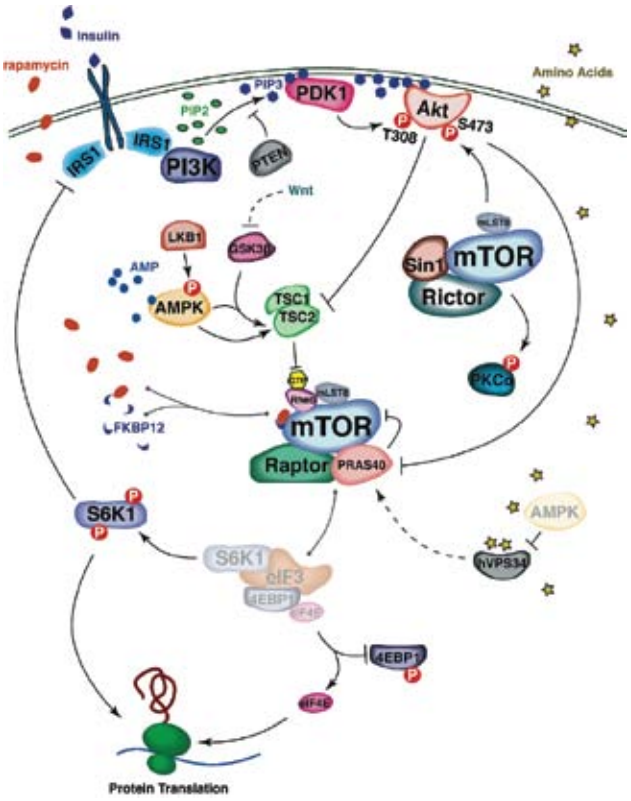
Kun-Liang Guan, Ph.D.
University of Michigan

Using *Drosophila*, Mouse Cell Lines, and Human Cell Lines to Discover New Therapeutic Targets

Dr. Guan investigated how TSC1/2 regulates the TORC1 and TORC2 pathways and searched for new components of the TORC2 complex. TORC1 is sensitive to rapamycin and regulates translation and cell growth while TORC2 is insensitive to rapamycin and regulates cell morphology and cell growth. With funding from an **FY05 Concept Award**, Dr. Guan's group studied TSC1/2 regulation of TORC1 and TORC2 in *Drosophila* cells (S2), human embryonic kidney cells (HEK293), and TSC mutant mouse embryonic fibroblast cells. Dr. Guan's team found that TSC1/2 negatively regulated TORC1 and positively regulated TORC2. Since TSC1/2 normally inhibits Rheb function in cells, these results suggest that in TSC patients with inactive TSC1/2, Rheb is no longer inhibited, and therefore there is positive regulation of TORC1 and negative regulation of TORC2.

Dr. Guan also explored components of TORC2. Dr. Guan's group identified hSin1 as an essential component of mTORC2 that was required for complex formation in HEK293 and HeLa cells under physiological conditions. However, hSin1 was not detected in mTORC1. Furthermore, hSin1 was required for TORC2 kinase activity in vitro. In yeast and mammalian cells, Sin1 has been implicated in the stress response, interactions with MAP kinase family proteins, and activating the JNK pathway.

These results suggest that hSin1 may be a new therapeutic target in rapamycin-insensitive TSC1/2 and mTOR-mediated pathways. Furthermore, therapeutics regulating the JNK and MAPK pathways may be useful in combination with rapamycin for simultaneously targeting mTORC1 and mTORC2 pathways in TSC patients.

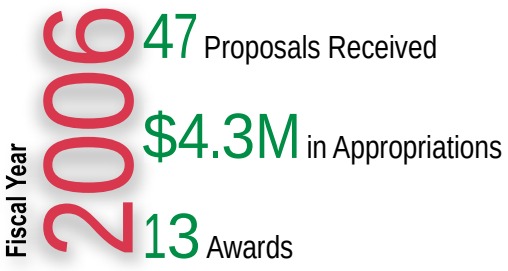


The Program Today

Fiscal Year 2006 Summary

A congressional appropriation of $4.3M was made 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 Table VIII-1, a total of 47 proposals were received in the Concept and Idea Development award mechanisms, and 13 awards were made. The portfolio developed by the FY06 TSCRP reflects the program's commitment to improve the detection, diagnosis, and treatment of TSC as reflected in Figure VIII-2. The congressional appropriations and the investment strategy executed by the TSCRP FY06 are summarized in Appendix B, Table B-7.

Although the TSC program did not receive appropriations in FY07, the program continues to support previously funded researchers by monitoring progress and capturing the most exciting findings. The TSCRP continues to evaluate the program and update the TSCRP website with research highlights, research resources, and consumer profiles.



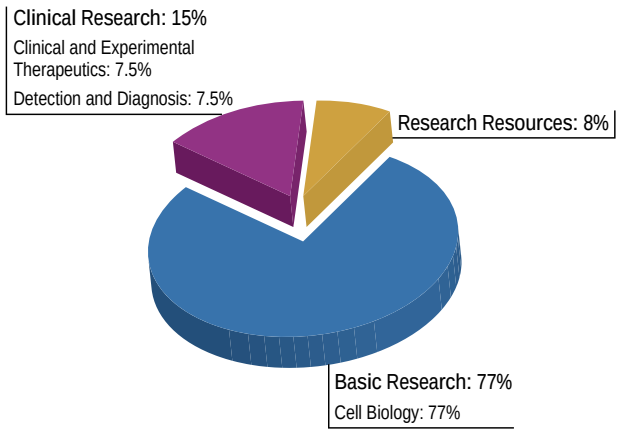


Figure VIII-2. FY06 TSCRP Portfolio by Research Area

Table VIII-1. Funding Summary for the FY06 TSCRP

Categories and Award Mechanisms	Proposals Received	Awards	Investment
Concept	22	8	$0.8M
Idea Development	25	5	$2.9M
TOTAL	47	13	$3.7M