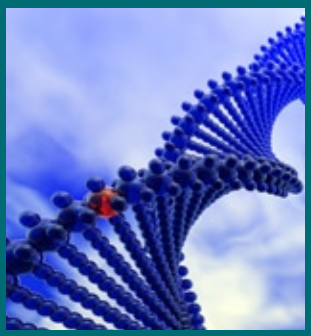
CDMRP

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) represents a unique partnership among the public, Congress, and the military. The CDMRP was established within the U.S. Army Medical Research and Materiel Command in 1992, when Congress, in response to grassroots advocacy efforts, tasked the Department of Defense (DOD) with developing and managing an innovative breast cancer research program. Since 1992, the CDMRP has grown to encompass multiple targeted programs and has received approximately $6 billion in appropriations. Funds for the CDMRP are added to the DOD budget, where support for individual programs such as the Tuberous Sclerosis Complex Research Program (TSCRP) is allocated via specific guidance from Congress.

Proposal Review Process

The TSCRP, like all CDMRP programs, is conducted according to the two-tier review model recommended by the National Academy of Sciences Institute of Medicine; this model has received high praise from the scientific community, advocacy groups, and Congress. The first tier is a peer review of proposals against established criteria for determining scientific and technical merit. Proposals are evaluated by scientific discipline, specialty area, or award mechanism by both scientific and consumer peer reviewers. The second tier is a programmatic review, conducted by members of the program's Integration Panel (an advisory board of leading scientists, clinicians, and consumer advocates). Programmatic review compares proposals against each other and recommends submissions for funding based on scientific merit, relative innovation and impact, portfolio balance, and overall program goals. Scientifically sound proposals that most effectively address the unique focus and goals of the program are subsequently recommended to the Commanding General, USAMRMC, for funding.

Tuberous Sclerosis Complex Research Program

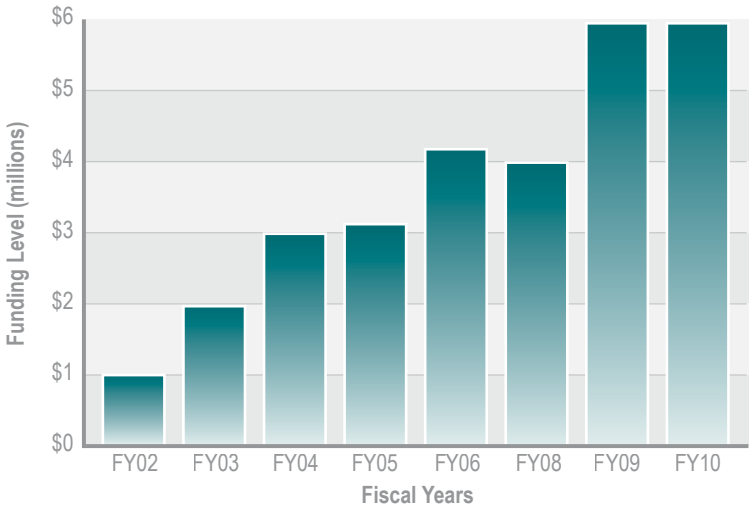
VISION

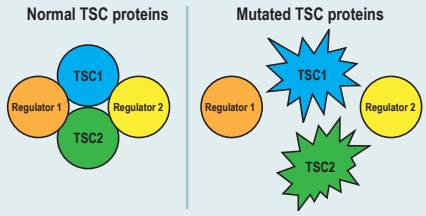
To lessen the impact of TSC.

MISSION

To encourage innovative research aimed at understanding the pathogenesis of TSC and to translate these findings to the care of individuals with TSC.

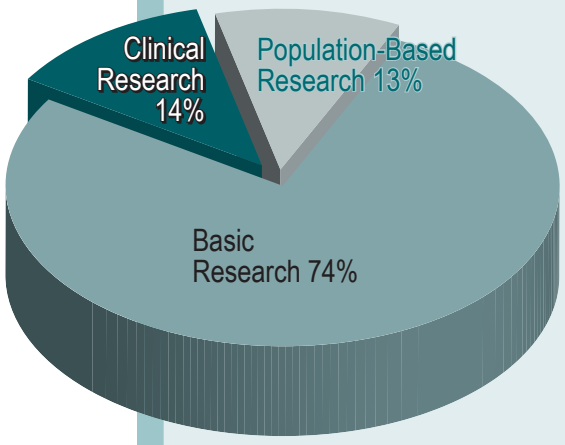
The TSCRP was established in fiscal year 2002 (FY02) when the efforts of TSC advocates led to a congressional appropriation of $1 million (M). Since then, a total of $29.5M has been appropriated, including $6M for FY10. This funding energized the development of a unique partnership among the public, Congress, and the military. The CDMRP within the U.S. Army Medical Research and Materiel Command (USAMRMC) manages the TSCRP. The TSCRP is conducted according to the two-tier review model recommended by the National Academy of Sciences Institute of Medicine; this model has received high praise from the scientific community, advocacy groups, and Congress. Today, the TSCRP is one of the leading sources of extramural TSC research funding in the United States. The TSCRP fills important gaps in TSC research not addressed by other funding agencies. The TSCRP vision 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.





The Disease:

TSC is a genetic disorder that affects as many as 50,000 individuals in the United States and about 1 to 2 million individuals worldwide. TSC causes tumors in many different organs, especially in the brain, eyes, heart, kidney, skin, and lungs. TSC is also characterized by seizures, developmental delays, behavioral problems, autism, and mental retardation. Major research breakthroughs have identified two genes, TSC1 and TSC2, whose dysfunction causes TSC. The TSC1 gene is located on chromosome 9 and produces a protein called TSC1 (hamartin). The TSC2 gene is located on chromosome 16 and produces a protein called TSC2 (tuberin). These proteins normally interact with each other and with important cell regulatory proteins. Mutations in TSC1 or TSC2 disrupt these communications. The discovery of the TSC1 and TSC2 genes is a giant step forward in the fight against TSC, as they provide excellent targets for the development of new diagnostic assays and therapies for TSC.



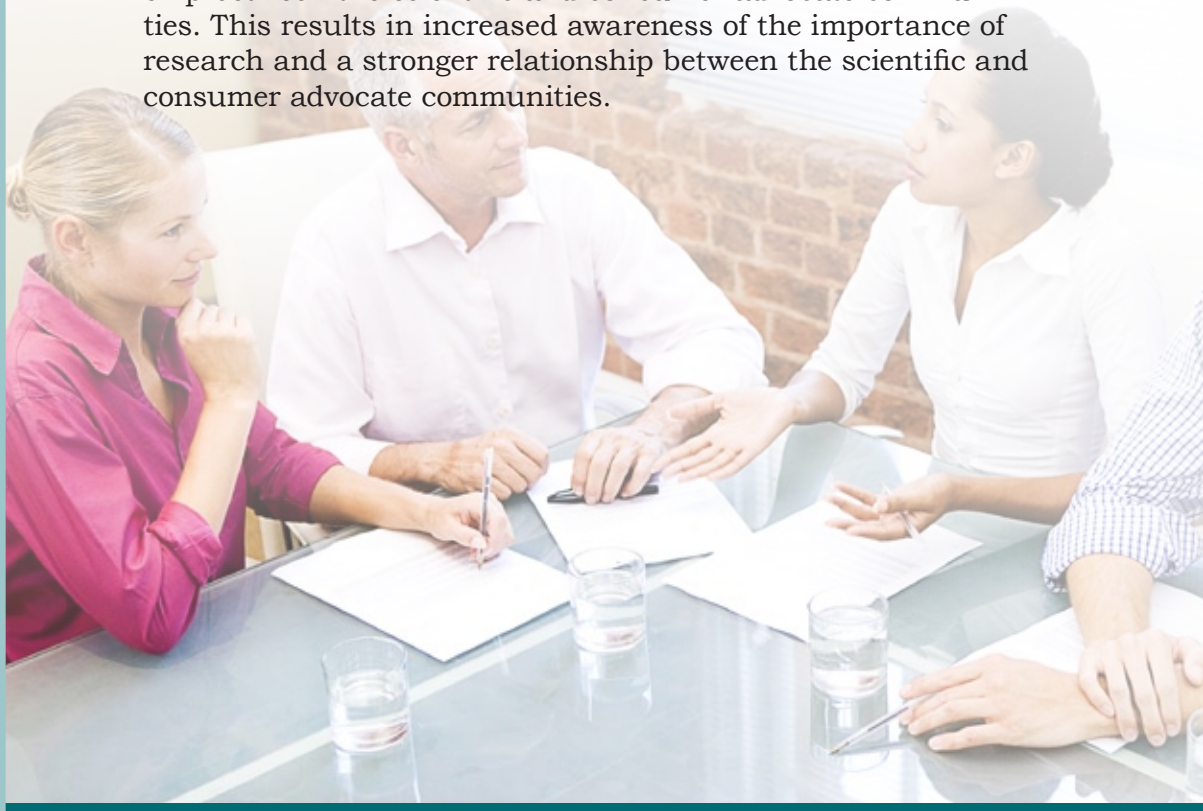
TSC FY02–09 Portfolio by Research Area

Building Partnerships

The successes of the TSCRP have and continue to be critically dependent on strong partnerships. Consumer advocates, peer review panel members, Integration Panel (IP) members, and the scientific community have worked synergistically to achieve the goal of lessening the impact of TSC. The combination of their diverse expertise has generated ideas that have hastened TSC research.

Consumer Advocates

Consumer advocates for the TSCRP may be individuals with TSC or those who have family members with TSC (TSC initially manifests in childhood). As active members of the TSCRP, consumer advocates participate in the peer review of proposals as well as in setting program priorities and making funding recommendations. Approximately 15 consumer advocates have contributed to both peer and programmatic review since 2002. Consumer advocates' firsthand experiences with TSC provide a unique perspective that is complementary to the expertise of the scientists and clinicians. This perspective keeps the urgency of lessening the impact of the disease at the forefront of research and helps scientists understand the human side of how research will impact the community. Equally important, consumer advocates 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. This results in increased awareness of the importance of research and a stronger relationship between the scientific and consumer advocate communities.



Ron Heffron's 6-year-old son, Bao, was diagnosed with TSC at 5 months of age. After coming to grips with this diagnosis, Ron and his wife, Ann, chose to fight back on Bao's behalf. Their mission in life has become a mission of love—giving Bao the best chance to lead as normal a life as possible, which by Ron's own admission has not been an easy task. The first thing he and Ann did was to research the disease and various treatments, knowing they had to find a way to stop Bao's infantile spasms as soon as possible. They attended international research conferences, met with at least a dozen neurologists and neurosurgeons, and read more medical journal papers than Ron cares to remember. They found the best neurosurgeons in the country, and Bao underwent a three-stage tuber resection process at 13 months old, which was followed by another surgery at 22 months old. Before his second surgery, Bao could not walk. As Ron exclaims, "Imagine the shock on his surgeon's face when Bao walked into his office 2 weeks after the surgery!" Although Bao still suffers occasional seizures, they remain milder than those he experienced prior to his surgery.

Ron, who has served as a consumer member on the peer review panel from FY08 through FY10, says, "Having now served for 3 years in this role, I have come to know two very important benefits from this experience. First, even though it is from a consumer reviewer's perspective, I have learned to ask much smarter questions on behalf of the TSC community and on behalf of Bao. By seeing what directions the science is taking, it helps me set expectations and chart a course for Bao, with realistic expectations. Second, I have learned that this is the single most important thing I can do for my son and for all those suffering from TSC. The CDMRP program is extraordinarily well organized and executed."

Scientific Peer Reviewers

Scientific peer review is conducted by panels of expert scientists, clinicians, and consumer advocates who provide unbiased, expert advice on the scientific and technical merit of proposals submitted to the TSCRP. Peer review panels are typically organized by scientific discipline and specialty areas. To date, over 90 scientists, clinicians, and consumer advocates have brought their expertise to the TSCRP.

Having served as a Scientific Peer Reviewer in FY06 and FY08 through FY10, **Dr. Daniel Noonan** first became involved in TSC research approximately 15 years ago. While attempting to clone modulators of steroid receptor-mediated gene regulation, his lab identified the TSC2 gene product tuberin as one of these regulators. These findings were relevant to the predominantly female-specific subset of TSC known as lymphangioleiomyomatosis (LAM), which is characterized by both mutations in the TSC2 gene and abnormal expression of the intracellular receptor for the steroid hormone estrogen. Currently, Dr Noonan's research is focused in two areas, with the first being an investigation of the mechanism by which the loss of normal TSC gene function might play a role in regulating estrogen receptor expression and activities. Second, Dr. Noonan is researching the biochemical mechanisms by which the loss of normal TSC gene function might be modulating fat synthesis, uptake, and storage, a universal parameter of TSC lesions and consequently a major contributor to tumor size and disease pathology.

Regarding his experience as a peer reviewer for the TSCRP, Dr. Noonan feels that this program is among the fairest and most comprehensive review panel on which he has served. He goes on to say, "As a scientist who fully understands the amount of work that goes into a grant submission, I truly appreciate the TSCRP's insistence on complete reviews and discussions of all submitted proposals. I also found the perspectives of the patient advocate reviewers to be refreshing and often highly enlightening."

During her pediatric neurology training at the Mayo Clinic, FY09 Scientific Peer Reviewer, **Dr. Martina Bebin**, had Dr. Manuel Gomez as a mentor. Spending time seeing TSC patients with him, she developed a keen interest in the condition and worked on several clinical research projects. Now nearly 20 years later, she works on new treatment options for patients with TSC and clinical research projects that broaden our understanding of the TSC phenotype-genotype. Of her experience as a peer reviewer, Dr. Bebin said, "It was a valuable experience to participate in the peer review process. I was very impressed with the investigators' scientific originality in the grant proposals and their ability to build on current scientific knowledge to advance the field of TSC research."

Integration Panel Members

The TSCRP IP is composed of 8 prominent scientists, clinicians, and consumer advocates with varied expertise in TSC. IP members use their knowledge and expertise to develop and recommend an annual vision and investment strategy for the TSCRP that focuses on innovative research aimed at understanding the pathogenesis of TSC and to translate these findings to the care of individuals with TSC. Additionally, IP members review proposals and suggest a broad-based research portfolio that best meets the program's vision and mission.

FY10 IP Members

David Kwiatkowski, M.D., Ph.D. (Chair) Brigham and Women's Hospital	**Jane Fountain, Ph.D.** National Institute of Neurological Disorders and Stroke	**Robert Moss** Tuberous Sclerosis Alliance	**E. Steve Roach, M.D.** The Ohio State University
David Dunn, M.D. Indiana University School of Medicine	**Vera P. Krymskaya, Ph.D.** University of Pennsylvania	**Hiroaki Onda, Ph.D.** Tuberous Sclerosis Alliance	**Mustafa Sahin, M.D., Ph.D.** Children's Hospital, Boston

Dr. David Kwiatkowski, FY09 Integration Panel (IP) Member and FY10 IP Chair, is a medical oncologist who became interested in TSC research about 20 years ago. He has focused on many aspects of TSC including: identification of the TSC1 gene; the human molecular genetics of TSC; mosaicism in TSC; development and analysis of mouse models of TSC; definition of the functions and signaling patterns of the TSC proteins TSC1 and TSC2; treatment approaches in TSC. Of his IP experience, he said, "I thought that it was an important forum in which consideration was given to the overall research support there is for TSC research, the balance of the overall portfolio (including NIH and foundations), as well the evaluation of each individual proposal."

Dr. Vera Krymskaya, FY10 Integration Panel (IP) Member, is an Associate Professor of Medicine at the University of Pennsylvania. Approximately 10 years ago, Dr. Krymskaya became interested in TSC research, specifically pulmonary manifestations of TSC characterized by the abnormal growth of smooth muscle-like cells and cystic destruction of the lung. Dr. Krymskaya's interest evolved to include another area of TSC research that focused on identifying signaling pathways that are dysregulated in TSC due to mutational inactivation of TSC1 and TSC2. Currently, Dr. Krymskaya is performing preclinical studies to identify novel targets for potential therapeutic intervention in TSC. Of her service on the IP, Dr. Krymskaya has said, "The TSC Research Program makes marked input into the advancement of basic, translational, and clinical research. I am honored to be a member of the Panel, where through constructive discussions, many important decisions are made including overall vision setting for TSC research, balancing the research portfolio, evaluating how each individual proposal can contribute to, and advance, TSC research, and therapeutic approaches in TSC."

Scientific Community

The TSCRP has funded 69 scientists and clinicians across the nation and abroad. TSCRP-supported investigators are engaged in cutting-edge work to find a cure for TSC. Through creative approaches and ideas, investigators are gaining momentum toward the goal of lessening the impact of TSC, as reflected in the success stories described in the remainder of this chapter.

The TSCRP has implemented research award mechanisms that are specifically aimed at minimizing the impact of TSC. To fill important research gaps, the TSCRP has focused on two broad areas:

- **Exploring Innovative, Groundbreaking Ideas and Technology:** Supporting high-risk and high reward research of exciting new ideas. Exploration–Hypothesis Development Awards fund research toward the exploration of novel theories and development of new preclinical tools. Idea Development Awards encourage innovative research directed toward the pathogenesis of TSC and improving its diagnosis and treatment.

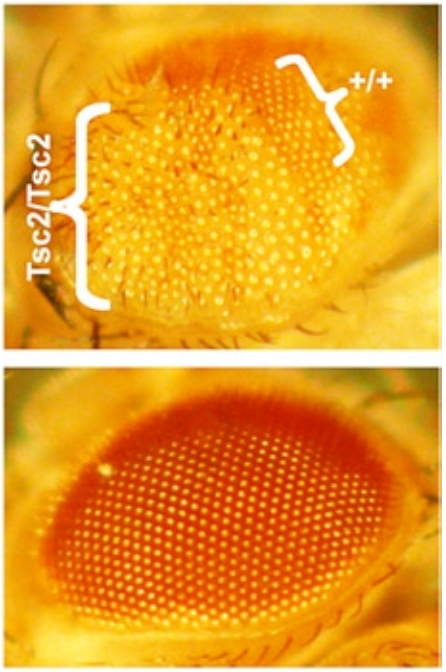
- **Retaining Young Scientists in TSC Research:** The Career Transition Award supports TSC researchers during the transition from postdoctoral training to an independent position. This award has the unique feature of funding up to 2 years of postdoctoral training followed by up to 2 years of a faculty-level position. The Career Transition Award addresses the important issue of retaining young scientists in TSC research and helps maintain the momentum and expansion of discoveries from a postdoctoral project into a new, independent TSC research laboratory.

Exploration–Hypothesis Development Awards and Idea Development Awards

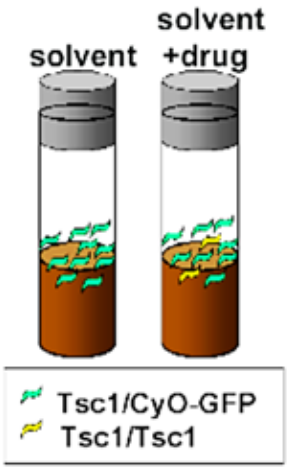
Identification of Small Molecule Suppressors of Tsc Mutant Phenotypes in Drosophila

Dr. Tin Tin Su, Ph.D.
University of Colorado
FY09 Exploration-Hypothesis Development Award Recipient

TSC is an autosomal dominant disorder characterized by the growth of benign tumors in many tissues including the brain, skin, kidney, and heart. TSC is due to mutations in one of two genes, Tsc1 and Tsc2. Under normal conditions, Tsc1/Tsc2 suppresses cellular growth, whereas constitutive loss of Tsc1 or Tsc2 due to mutations leads to excessive growth. Dr. Tin Tin Su will use *Drosophila melanogaster* (fruit flies) to screen small molecules that can potentially reverse the effects of Tsc1/Tsc2 mutations. *D. melanogaster* have been a useful animal model in the study of TSC and have been integral in elucidating the molecular pathway by which Tsc1 and Tsc2 mutations produce tumors. Prior studies have shown that Tsc mutant *Drosophila*, which die as larvae, exhibit overgrowth of Tsc-deficient tissue. Dr. Su will use these *Drosophila* mutants to screen 20,000 small molecules for their ability to rescue larvae from the lethality of Tsc mutations, and for their ability to reduce the overgrowth of Tsc mutant cells. Given the similarity in function between *Drosophila* Tsc and human Tsc genes, small molecules that are successful in suppressing overgrowth of Tsc mutant tumors have the potential to be potent anti-TS therapeutics in humans.



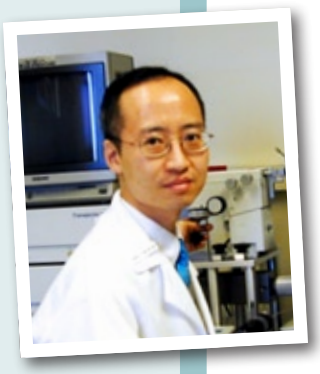
Tsc1 mutant clones (Tsc2/Tsc2) show overgrowth compared to wild-type sister clones (+/+). A wild-type eye is shown below for comparison.



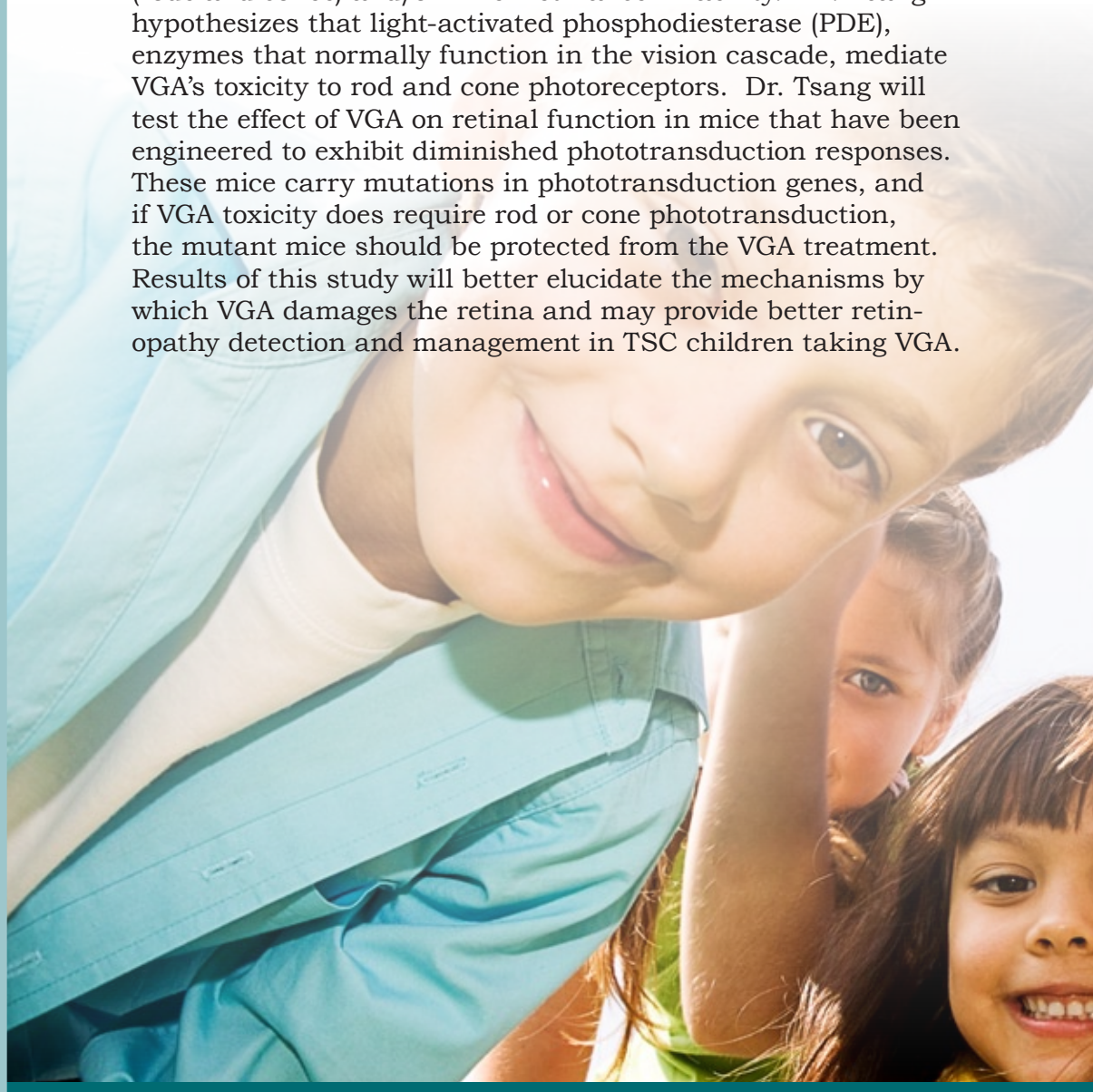
The rescue of Tsc1 homozygous larvae (GFP-; yellow) by added drug.

Preventing Visual Handicap in Children with Tuberous Sclerosis Complex

Dr. Stephen Tsang, M.D., Ph.D.
Columbia University
FY08 Idea Development Award Recipient



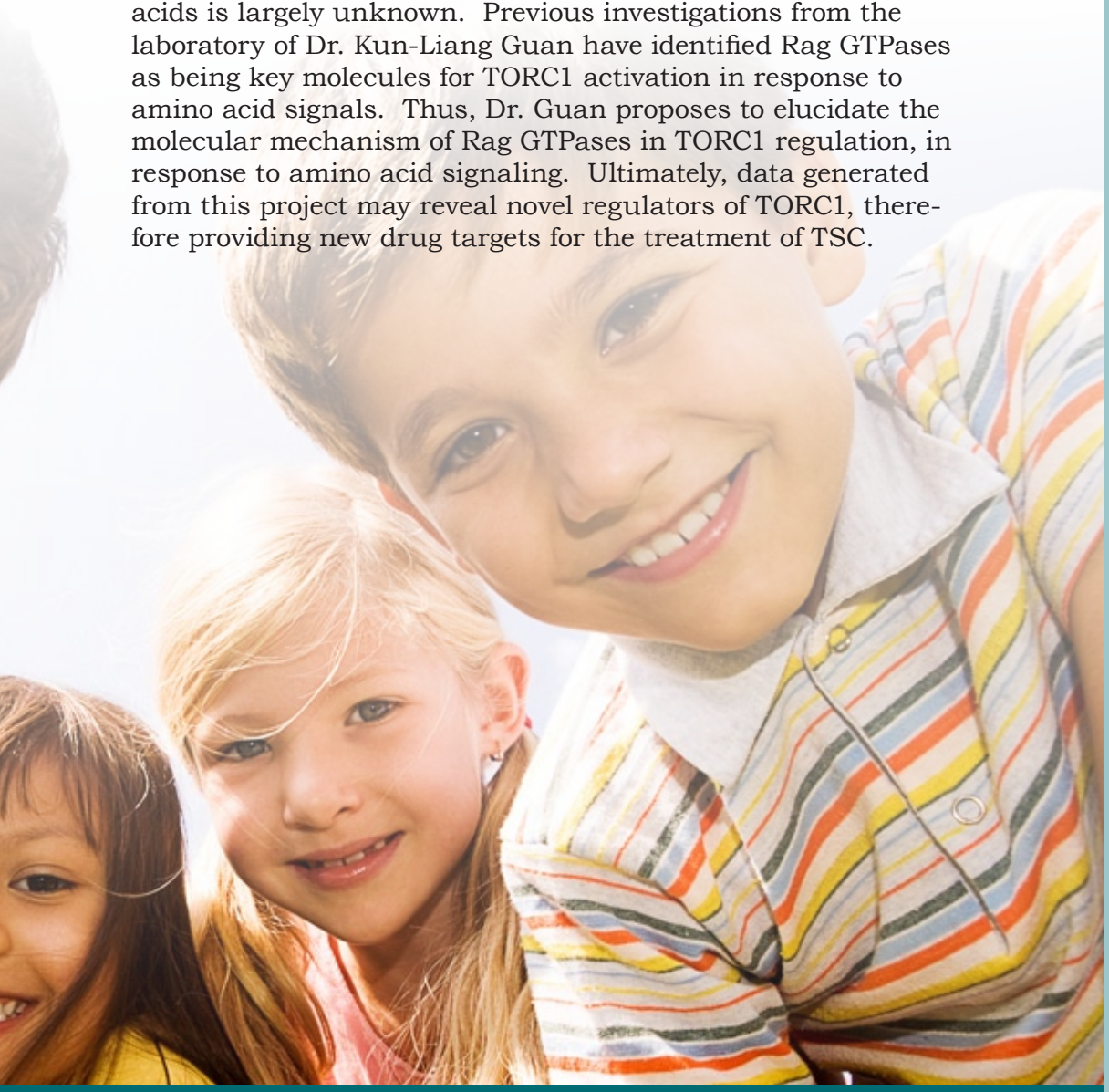
Epileptic seizures are one of the complications associated with TSC. Upwards of 90% of children and infants with TSC suffer from epileptic seizures. Treating these seizures can present a challenge. One treatment option that has become the standard for infantile spasms in the UK, Europe, and Canada is Vigabatrin (VGA). Approved by the U.S. Food and Drug Administration, in 2010 VGA is increasingly used in the United States as well. The use of this drug is limited by its retinal toxicity, causing irreversible peripheral vision loss in 30% to 50% of patients. As VGA-induced loss of peripheral vision is asymptomatic, it is often overlooked in children with TSC. Dr. Stephen Tsang is studying the mechanisms by which VGA damages the retina. Permanent visual loss from VGA treatment likely results from the drug's toxicity on photoreceptors (rods and cones) and/or inner retinal cell viability. Dr. Tsang hypothesizes that light-activated phosphodiesterase (PDE), enzymes that normally function in the vision cascade, mediate VGA's toxicity to rod and cone photoreceptors. Dr. Tsang will test the effect of VGA on retinal function in mice that have been engineered to exhibit diminished phototransduction responses. These mice carry mutations in phototransduction genes, and if VGA toxicity does require rod or cone phototransduction, the mutant mice should be protected from the VGA treatment. Results of this study will better elucidate the mechanisms by which VGA damages the retina and may provide better retinopathy detection and management in TSC children taking VGA.



Nutrient Regulation of mTOR

Kun-Liang Guan, Ph.D.
University of California, San Diego
FY08 Idea Development Award Recipient

The dominantly inherited syndrome TSC is caused by mutation of either the TSC1 or TSC2 tumor suppressor genes. TSC is characterized by the development of benign hamartomas throughout the body. Other potential clinical complications include seizures, kidney dysfunction, and mental retardation. The gene products of TSC1 and TSC2 form a tight complex and function as a GTPase activating enzyme toward the Rheb small GTPase, which binds to and activates the target of rapamycin complex 1 (TORC1). TORC1 stimulates protein synthesis, is a central cell growth controller, and is highly elevated in TSC mutant cells. As dysregulation of TORC1 is a major cellular consequence of TSC1 or TSC2 mutations and therefore contributing to TSC pathogenesis, understanding the regulation and function of TORC1 is critical. Although the mechanisms of TORC1 regulation by growth factors and energy levels have been identified, the mechanism of TORC1 activation by amino acids is largely unknown. Previous investigations from the laboratory of Dr. Kun-Liang Guan have identified Rag GTPases as being key molecules for TORC1 activation in response to amino acid signals. Thus, Dr. Guan proposes to elucidate the molecular mechanism of Rag GTPases in TORC1 regulation, in response to amino acid signaling. Ultimately, data generated from this project may reveal novel regulators of TORC1, therefore providing new drug targets for the treatment of TSC.

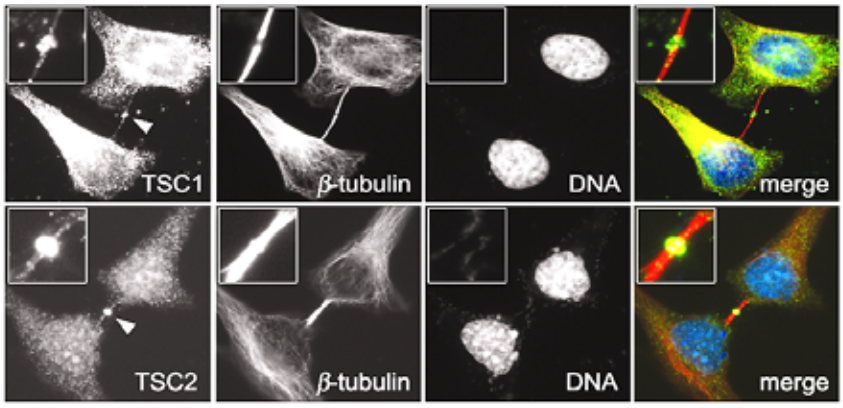


The Role of Plk1 in Tuberous Sclerosis Complex

Aristotelis Astrinidis, Ph.D.
Drexel University College of Medicine
FY09 Idea Development Award Recipient

TSC is an inherited disorder characterized by seizures, mental retardation, and benign tumors in multiple organs including the brain, kidney, heart, and skin. Worldwide, there are approximately 900,000 patients with TSC, 40,000 of whom are in the United States. TSC is caused by mutations in two genes: TSC1 and TSC2. The rare disorder LAM, which manifests primarily in the lungs and affects exclusively women, is another disease caused by TSC1 and TSC2 mutations.

Loss of TSC1 or TSC2 function leads to uncontrolled cell growth via activation of mTOR, a protein that is sensitive to the antibiotic rapamycin. Clinical trials are under way to determine rapamycin's potential for the treatment of TSC and LAM. Targeting multiple proteins in the TSC/mTOR pathway may provide additional TSC and LAM treatment options. Plk1, a protein regulating several aspects of cell division, including cytokinesis (the final stage of cell division), may serve as another protein target in TSC and LAM. Recent investigations in the laboratory of Dr. Aristotelis Astrinidis have identified Plk1 to be a new interacting partner of TSC1. His research team has also found that mTOR is activated by Plk1, that cells lacking TSC1 have abnormal cytokinesis, and that Plk1 expression is increased in cells without TSC1 or TSC2 and in samples from LAM patients. Dr. Astrinidis proposes to (1) define the pathway leading to mTOR activation by Plk1, (2) investigate the consequences of TSC1 or TSC2 loss in cell division, more specifically cytokinesis, and (3) determine whether targeting Plk1 by specific inhibitors causes death in cells without TSC1 or TSC2. This project will potentially lead to a new preclinical model for TSC treatment.

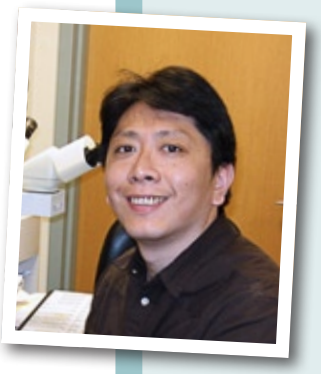


Indirect immunofluorescence staining of HeLa cells undergoing cytokinesis. TSC1 and TSC2 localize to cytokinetic structures (midbody, arrowheads). [courtesy Aristotelis Astrinidis, Drexel University College of Medicine]

Retaining Young Scientists in TSC Research Career Transition Award

TSC-FoxO Signaling Network in Kidney Cancer Development

Boyi Gan, Ph.D.
Dana-Farber Cancer Institute
FY09 Career Transition Award Recipient



The renal manifestations in TSC patients include the development of renal angiomyolipomas (AMLs), renal cell carcinomas (RCCs), and polycystic kidney disease (PKD). Although great progress has been made in the last decade in the field of TSC, little is known about TSC's role in renal cancer development, and the cooperative events in TSC-mediated renal tumorigenesis. Dr. Boyi Gan aims to elucidate the molecular pathogenesis of TSC-related renal tumorigenesis and to provide novel insights of targeted therapies against renal complications in TSC patients. Dr. Gan's central hypothesis is that FoxO transcriptional factors play a key role in the molecular pathogenesis of TSC-related renal tumorigenesis. Dr. Gan proposes to (1) determine the mechanism and role of FoxO activation in TSC-deficient cells and renal tumors, (2) investigate the underlying mechanisms by which FoxOs cooperate with the TSC1–TSC2 complex to inhibit mTORC1 signaling, and (3) identify direct FoxO transcriptional targets that contribute to TSC-mediated renal tumorigenesis. Dr. Gan's research has the potential to advance the understanding of TSC-mediated renal tumorigenesis and to expand drug development for those TSC patients with renal complications.

The Program Today

The Vision for FY10

In FY10, $6M was appropriated to the TSCRP for research by Congress. The TSCRP encourages innovative research aimed at understanding the pathogenesis of TSC and to translate these findings to the care of individuals with TSC. Four award mechanisms encompassing this overall mission were offered in FY10 to fill important gaps in TSC research and accelerate discoveries.

FOCUS	AWARD MECHANISM
Clinical Research 	*Clinical Research Award:* Supports either clinical/translational research studies or clinical trials. Multidisciplinary collaborations are encouraged to bring in new perspectives from other disciplines or bring new investigators into the field.
Innovative Research 	*Exploration–Hypothesis Development Award:* Supports the initial exploration of innovative, untested, high-risk, high-gain, and potentially groundbreaking concepts in TSC research.
	Idea Development Award: Supports high-impact, innovative research that will drive the TSC field forward.
Career Development 	*Career Transition Award:* Supports TSC researchers during the transition from postdoctoral training to an independent position.

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