

# Tuberous Sclerosis Complex Research Program

## **Strategic Plan**

## **INTRODUCTION**

The Congressionally Directed Medical Research Programs (CDMRP) represents a unique partnership among the U.S. Congress, the military, and the public to fund innovative and impactful medical research in targeted program areas. In 2015, an ad hoc committee of the National Academies of Sciences, Engineering, and Medicine was assembled to evaluate the CDMRP's two-tier review process and its coordination of research priorities with the National Institutes of Health (NIH) and the Department of Veterans Affairs (VA). As part of their final report,<sup>1</sup> the committee recommended that each CDMRP program "... develop a strategic plan that identifies and evaluates research foci, benchmarks for success, and investment opportunities for 3-5 years into the future," and that these strategic plans "should specify the mission of the program, coordination activities with other organizations, research priorities, how those priorities will be addressed by future award mechanisms, how research outcomes will be tracked, and how outcomes will inform future research initiatives."

In response to these recommendations, this document presents the current strategy for the CDMRP's Tuberous Sclerosis Complex Research Program (TSCRP). The TSCRP Strategic Plan identifies the high-impact research goals most important to its stakeholders while providing a framework that is adaptable to changes in the medical research environment to address those goals. This plan has been formulated to provide greater clarity of the program's goals over time to the public and other stakeholders. Funding for the TSCRP is Congressionally appropriated on an annual basis; therefore, there is no guarantee of future funding. The TSCRP Strategic Plan will be reviewed during the program's annual Vision Setting meeting and updated as necessary.

## **TSCRP BACKGROUND AND OVERVIEW**

The TSCRP was established in fiscal year 2002 (FY02) to support innovative and impactful research that addresses fundamental issues and gaps in tuberous sclerosis complex (TSC). The overarching Vision and Mission of the TSCRP are as follows:

**VISION:** Accelerate high-impact research to improve prevention strategies and treatments and to find a cure for TSC

**MISSION:** Fund exploratory, pioneering and transformative science that promotes discoveries in TSC, from mechanistic insights to clinical application, by supporting new ideas and investigators for the benefit of Service members, their beneficiaries, and the American public

## **FUNDING HISTORY**

The TSCRP began in FY02 with an appropriation of \$1 million (M). Since then, a total of \$77M has been appropriated to the program, including \$6M in FY18. Since FY02, 684 applications have been submitted, and 139 awards were funded from FY02-FY16. Eight awards are currently under negotiation to fund projects submitted in FY17. FY02-FY18 appropriations and awards made per year are displayed in Figure 1 below.

#### Figure 1. TSCRP Appropriations and Number of Awards FY02-FY18



## **INVESTMENT HISTORY**

The TSCRP investment strategy has evolved over the history of the program to meet the needs of consumers and the scientific community. Since its inception, the program funded research projects along the continuum of research. Figure 2 summarizes the TSCRP's investment strategy from bench to bedside since FY02. The TSCRP has offered a variety of award mechanisms over the years to foster new ideas, encourage established scientists in the field, attract new scientific expertise, and encourage collaborations (Figure 2, top). To date 16 percent of the budget has been invested to support the exploration of new, untested concepts and ideas with very limited or minimum preliminary data, with the goal of providing a foundation for future new research (through the



Figure 2. TSCRP Investment Strategy FY02-FY17

Concept and Exploration Hypothesis – Development Awards). Approximately 72% has been invested in the development of more mature ideas leading toward clinical application (through the Idea Development, Career Transition, Postdoctoral Development, and Natural History Development Awards). The remaining 12 percent of the TSCRP's research investment is in clinical studies (through Clinical and Translational Research, Clinical Research, Clinical Trial, and Pilot Clinical Trial Awards). The bottom half of the figure shows the types and numbers (in parentheses) of awards supported each year.

## **RESEARCH PORTFOLIO**

More recently, between FY13 and FY17, 50 awards funded by the TSCRP supported research along the disease research spectrum: signaling pathways and etiology, disease models, biomarkers, and therapeutics (Figure 3). The pie chart in Figure 3 summarizes the number of awards addressing each research area (in parentheses) and the percentage of the TSCRP's research investment in each area. (Of note, some awards address two research areas, in which case the budget was evenly split between the categories.) Approximately half of TSCRP funding has been invested in research investigating signaling pathways and etiology, while a quarter of the funding is related to therapeutics. Although basic science investigations of signaling pathways and etiology do not directly produce or test new treatments, they are important nevertheless because they can reveal potential molecular targets for new treatments that can be tested in more advanced research.



#### Figure 3. Program Priorities along the Disease Research Spectrum FY13-FY17

## **RESEARCH ACCOMPLISHMENTS**

TSCRP research has resulted in a variety of impactful achievements in the areas of signaling pathways and etiology, disease models, biomarkers, and therapeutics. Examples of successful TSCRP efforts in each of the research areas are presented here.

#### **Signaling Pathways and Etiology**

Molecularly connected TSC and mTORC1; gained insight on the mechanism by which rapamycin inhibits mTORC1 functions, which led to clinical use of rapamycin and analogs (such as everolimus) to treat TSC

Showed activation of inflammatory pathways in the TSC brain and the role of mTOR signaling in lesion formation

Elucidated the molecular pathogenesis of TSC-related renal tumorigenesis

#### **Disease Models**

Created the first genetically engineered mouse strain with TSC-related epilepsy and found that rapamycin treatment can suppress seizure formation

Developed a unique novel model of focal cortical malformations that resemble cortical tubers in TSC; reported activation of a novel molecular pathway that contributes to the TSC cortical tubers; showed that the cortical tubers are the causes of epilepsy

Developed the first genetic and truly metastatic lymphangioleiomyomatosis (LAM) mouse model and showed that LAM cells originate from the uterus, explaining the female sexual dimorphism of LAM

#### **Biomarkers**

Developed early behavioral and electrophysiological predictors of autism, neurodevelopmental disabilities, and behavioral deficits in TSC

Showed that serum VEGF-D is potential biomarker for LAM diagnosis and prognosis

#### Therapeutics

Showed that suppression of COX-2 with Celecoxib or aspirin inhibits tumor progression in a spontaneously arising renal cystadenoma tumor model of TSC

Formulated and optimized topical rapamycin therapy to safely decrease the appearance of facial angiofibromas in patients with TSC

Provided evidence that treating infants with early interventions that are targeted, evidence-based, and effective will improve developmental outcomes, thereby attenuating symptoms that lead to the neurodevelopmental disabilities that impact so many infants and children with TSC

## **RESEARCH AND FUNDING ENVIRONMENT**

## **FUNDING LANDSCAPE**

Funding for TSC research comes from a variety of sources and through a variety of programs. In addition to the TSCRP, TSC researchers are funded by other federal agencies such as the NIH, as well as non-federal organizations, including the Tuberous Sclerosis (TS) Alliance and the LAM Foundation. Investments made by federal agencies and non-federal organizations in TSC-related research from FY13-FY17 are shown in Figure 4 (note that the funding amounts shown represent the research investment, not the funding appropriation).

In addition to the organizations noted above, the Center for LAM and Rare Lung Diseases at Columbia University, Cure

\$30.0 ■ NIH ■ TSCRP ■ TS Alliance ■ LAM Fdtn \$25.0 \$20.0 TSC Research Funding (Millions) \$15.0 \$10.0 \$6.0 \$4.0 \$2.0 \$0.0 2013 2014 2015 2016 2017

Epilepsy, Epilepsy Foundation, Epilepsy Society, Penn Medicine Orphan Disease Center, Simons Foundation, and multiple others also provide funding for TSC research.

#### Figure 4. Funding Landscape FY13-FY17



To enable the TSCRP to maximize its impact on TSC research and patient care, the program coordinates with other funding agencies to eliminate redundancy, maximize complementarity, and leverage collective efforts. To achieve this, representatives from the NIH and the TS Alliance serve on the TSCRP Programmatic Panel. Moreover, the NIH and TS Alliance meet regularly to assess the TSC research field and plan accordingly.

## STATE OF THE SCIENCE

The TSCRP monitors ongoing transformational efforts in TSC and/or biomedical research in general, as well as evolving technologies that could alter the scientific landscape and cause the TSCRP to reconsider and adjust is strategic direction, priorities, and goals. These strategic elements will be reviewed at future Vision Setting meetings to determine whether strategic adjustments are needed.

Ongoing transformational research efforts include the (1) TS Alliance Biorepository; (2) TS Alliance Natural History Database; (3) TS Alliance Preclinical Consortium; (4) Preventing Epilepsy Using Vigabatrin In Infants With Tuberous Sclerosis Complex (PREVeNT Trial) clinical trial; (5) Epilepsy - Tuberous Sclerosis Complex clinical trial; (6) Multicenter International LAM Efficacy of Sirolimus clinical trial; and (7) Tuberous Sclerosis Complex Autism Center of Excellence Research Network, as well as numerous other autism, biomarker, pharma-sponsored research, and rare disease research studies.

Evolving technologies that currently provide or can provide significant new tools to the TSCRP research community and offer new avenues of research to address important questions include (1) chemogenetics; (2) CRISPR-associated gene editing; (3) cryogenic electron microscopy; (4) eye tracking technology; (5) "omics" (genomics, proteomics, transcriptomics, and metabolomics); (6) next-generation sequencing; (7) stem cell technology; (8) molecular imaging; (9) quantitative imaging and electrophysiology; (10) signaling analysis; (11) single cell analysis; (12) technology for remote assessment; and (13) improved outcome measures.

## **STRATEGIC DIRECTION**

Considering the funding provided by other federal and non-federal organizations, the state of TSC research, and the needs of the scientific community, the TSCRP will continue its efforts to improve prevention and treatment of TSC while working toward the ultimate goal of finding a cure, all for the benefit of Service members, their beneficiaries, and the American public.

## STRATEGIC GOALS

To address its Strategic Direction, TSCRP identified the following strategic goals:

- 1. Eradicate tumors associated with TSC
- 2. Prevent epilepsy, improve treatment, and mitigate comorbidities associated with TSC-related seizures
- 3. Understand the neurodevelopmental features of TSC and reduce their impact

These three areas offer the greatest promise to advance care and lead to a cure for TSC while responding to the most pressing needs and concerns expressed by patients and families affected by TSC.

More detail regarding the range of research areas to be supported by the TSCRP is provided in Table 1 below.

Research Area	Tumor Eradication	Epilepsy Prevention, Treatment, Mitigation	Neurodevelopmental Features of TSC
Mechanisms	<ul> <li>Cells of origin</li> <li>Roles of the microenvironment</li> <li>Mechanisms of tumor development</li> </ul>	Mechanisms of epileptogenesis     in TSC	<ul> <li>Mechanisms underlying neurodevelopmental disorders</li> <li>Causes of heterogeneity</li> </ul>
Models	<ul> <li>Preclinical models to understand biology and test treatments</li> </ul>	<ul> <li>Preclinical models to understand biology and test treatments</li> </ul>	<ul> <li>Preclinical models to understand biology and test treatments</li> </ul>
Treatments	<ul> <li>Novel treatment targets</li> </ul>	<ul> <li>Use of existing therapies</li> <li>Novel pharmacological agents</li> <li>Optimal timing for surgery and therapy</li> </ul>	<ul> <li>Effective treatments to optimize outcomes <ul> <li>Cognitive</li> <li>Behavioral</li> <li>Pharmacological</li> <li>Biologic</li> </ul> </li> </ul>
Diagnostic Tools	Tools to assess treatment response	<ul> <li>Tools to predict onset, severity, and treatment outcomes</li> </ul>	<ul> <li>Tools to predict and measure neurodevelopmental outcomes</li> </ul>

## Table 1. Range of Research Areas

4



The TSCRP has identified three approaches to accomplish its strategic goals:

- 1. Fund projects distinct from the priorities and mechanisms of the NIH
  - The TSCRP has a unique opportunity to encourage and lend diversity to TSC research by focusing on gaps in the research landscape where other organizations have not prioritized funding.
- 2. Support higher-risk projects to generate new basic science ideas and understanding
  - In continuing to support basic science research, the TSCRP seeks to create an environment to nurture the identification of promising new approaches and breakthroughs.
- 3. Support projects that advance clinical readiness
  - The TSCRP will continue to support projects that have well-defined pathways to clinical use to accelerate the translation of novel ideas for the near-term benefit of the TSC community.

## **INVESTMENT STRATEGY**

During the next 5 years, the TSCRP will solicit research according to its scientific priorities to achieve its strategic goals by providing funding for the following:

- Exploring new ideas and untested concepts based on sound scientific rationale to generate preliminary data that will form the foundation of more robust hypothesis-driven research initiatives
  - o Exploration Hypothesis Development Award
- Conducting preclinical laboratory research that is based on a well-formulated, testable hypothesis derived from strong preliminary data and scientific rationale that can ultimately lead to critical discoveries in TSC research and/or improvements in patient care
  - o Idea Development Award
- Conducting clinical translational research that is based on sound preliminary data and rigorous scientific methodology and has the potential to make significant contributions to TSC research and patient care
  - o Clinical Translational Research Award
- Conducting pilot clinical trials involving small numbers of subjects to produce information on diagnostic or therapeutic effectiveness, safety, tolerability, or mechanisms of action, thus generating data for larger studies
  - o Pilot Clinical Trial Award

This investment strategy will be re-evaluated and updated as necessary during the program's annual Vision Setting meeting.

## **MEASURING PROGRESS**

Measurable outcomes over the next 1- to 5-years and beyond are used to gauge the TSCRP's progress toward accomplishing its strategic goals. The TSCRP will measure its success in the short term based on successful investments in areas important to the strategy. Medium- and long-term success will be evaluated based on the contributions to the scientific community and follow-on research that result from TSCRP-funded projects. Based on these outcomes, the TSCRP will adjust its strategic goals and priorities.

## **SHORT-TERM OUTCOMES (1-3 YEARS)**

- · Investment in research leading to eradication of tumors in TSC
- Investment in research leading to prevention and treatment of epilepsy associated with TSC
- · Investment in research leading to understanding of neurodevelopmental features of TSC and their outcomes

## **MEDIUM-TERM OUTCOMES (3-5 YEARS)**

- Contributions to the scientific community (publications, patents, etc.)
- · Follow-up federal and non-federal funding to expand on the knowledge gained from TSCRP-funded projects



## LONG-TERM OUTCOMES (6+ YEARS)

- Research outcomes leading to advancement in the areas outlined in the TSCRP strategic goals
- · Follow-up federal and non-federal funding to expand on the knowledge gained from TSCRP-funded projects
- · Food and Drug Administration submissions, approvals, or indications for prevention strategies and treatments

## REFERENCES

1. *Evaluation of the Congressionally Directed Medical Research Programs Review Process*. 2016. The National Academies of Sciences, Engineering, and Medicine. The National Academies Press. Washington, DC.