DoD Tuberous Sclerosis Complex Research Program (TSCRP)

Each year, the Department of Defense's office of the Congressionally Directed Medical Research Programs (CDMRP) assesses scientific opportunities to advance research in specific areas. The investigators supported by individual programs are making significant progress against targeted diseases, conditions, and injuries. This list is not intended to be a full representation of accomplishments, but rather a sampling of the broad portfolio of research and advances resulting from congressional appropriations.

Year	TSCRP Research Contributions	Additional Information and Hyperlinks
2002	Dr. Elizabeth Henske demonstrated that hamartin and tuberin play critical roles in amino acid sensing, uptake, and metabolism, and tuberous sclerosis symptoms may be linked to defects in these key cellular functions.	• TSCRP Research Highlight
2002	Dr. David Gutmann identified several genetic and cellular abnormalities resulting from astrocyte-specific inactivation of Tsc1, indicating that the astrocyte may be centrally involved in the pathogenesis of neurological complications of TSC, including epilepsy.	• TSCRP Research Highlight
2003	Dr. Bernardo Sabatini conducted studies that show that the TSC pathway regulates neuron soma size, the density and size of dendritic spines, and the properties of excitatory synapses in hippocampal pyramidal neurons both in cell culture and animal models.	• TSCRP Research Highlight
2003	Dr. Vera Krymskaya identified that a complex formed between TSC1 and TSC2 regulates cell adhesion and motility, and that dysregulation of the complex formation may contribute to the pathogenesis of TSC.	• TSCRP Research Highlight
2003	Dr. William Kaelin, Jr. showed that the intact TSC1/TSC2 protein complex is required for mTOR regulation by hypoxia. He also identified a novel component of this pathway, Redd1, that may act upstream of TSC1/TSC2 to downregulate mTOR in response to hypoxia.	• TSCRP Research Highlight
2004	Dr. Steven Sparagana developed a clinical database that documents the natural history and variability of TSC, which is currently managed by TS Alliance with 1,187 people enrolled as of March 2013.	• TSCRP Research Highlight
2004	Dr. Fuyuhiko Tamanoi found that activation of the TSC/Rheb/mTOR signaling pathway leads to constitutive activation of Cdk2 and blocks the translocation to the nucleus of p27. He also showed that mTOR forms a heterodimer in which heterozygous mutations could result in constitutive activation of mTOR and the constitutively active mTOR mutants can still be inhibited by rapamycin.	• TSCRP Research Highlight
2004	Dr. David Sabatini and Dr. Anne Carpenter developed a new image analysis software called CellProfiler, which is used to assay cell count, size, per-cell protein levels, cell/organelle shape, and subcellular localization of DNA or protein.	• TSCRP Research Highlight

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2005	Dr. Tin Tin Su developed a quantitative Drosophila-based assay to screen compounds and test their ability to rescue the larval lethality of TSC1 homozygous mutants.	• TSCRP Research Highlight
2005	Dr. Helen McNeill identified two genes, Pointed-P2 (PntP2) and S6K, that cooperate with TSC to regulate precocious neuronal differentiation. She showed that PntP2 activation was induced by either loss of TSC or growth factors such as insulin, and that loss of S6K blocked the neuronal differentiation in Drosophila lacking TSC.	• TSCRP Research Highlight
2005	Dr. Kun-Liang Guan showed that TSC mutant cells are easily killed by stress, particularly when p53 is activated.	• TSCRP Research Highlight
2006	Dr. David Sabatini found that binding of Rag GTPase to Raptor is necessary for amino acid signaling to mTORC1 and amino acid-induced relocalization of mTOR within the endomembrane system of the cell.	• TSCRP Research Highlight
2006	Dr. Mark Nellist identified the following regions as essential for TSC1 or TSC2 function: (1) N-terminal region (amino acids 1-200) of TSC1; substitutions destabilize TSC1, (2) Central region (amino acids 600-900) of TSC2; substitutions disrupt TSC1-TSC2 binding, (3) outside of the TSC2 GAP domain; substitutions inactivate the TSC1–TSC2 complex, and (4) TSC1 amino acids 50-224 are required for maintaining TSC1 at sufficient levels to form a stable TSC1-TSC2 complex and inhibit mTOR.	• TSCRP Research Highlight
2006	Dr. Kun-Liang Guan connected mTOR regulation to cellular stress response via BNIP3.	• TSCRP Research Highlight
2008	Dr. Thomas Darling showed that tranilast, an antiallergic and antifibrotic drug, has selective inhibitory effects on the viability of TSC skin tumor cells, indicating that it may be useful as an adjunctive agent for the treatment of TSC.	• TSCRP Research Highlight
2008	Dr. Kun-Liang Guan identified multiple regulators of the mTORC1 pathway and showed that cAMP elevation inhibits TORC1.	
2008	Dr. Aristotelis Astrinidis demonstrated that polo-like kinase 1 (PLK1) acts upstream of TSC1/TSC2 to positively regulate mTOR signaling in a TSC1-PLK1-dependent manner. Inhibition of PLK1 by BI-2536, which has already been investigated in clinical trials for several cancers, increased apoptosis and disrupted autophagy enhancing the cell death of Tsc1/Tsc2-null cells.	• TSCRP Research Highlight
2009	Dr. Angelique Bordey generated a mouse model to study the embryonic development of cortical tuber lesions, and she showed that upregulation of Hif1a transcriptional activity in newborn neurons promotes the growth and persistence of TSC lesions.	• TSCRP Research Highlight, 2012 • TSCRP Research Highlight, 2014
2009	Dr. Brendan Manning demonstrated that rapamycin treatment in combination with low-dose tunicamycin results in a cytotoxic response in Tsc2-null cells.	• TSCRP Research Highlight

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2009	Dr. Teresa Woods determined that TSC is a critical upstream regulator of mTORC1 and mTORC2 in oligodendrocyte lineage cells	
2009	Dr. Francis McCormack established the LAM Clinical Research Network (LCRN), a collaboration of 24 LAM clinics throughout the United States, to provide a natural history database and increase access to clinical trials of LAM patients and facilitate delivery of novel LAM treatment options.	• TSCRP Research Highlight
2009	Dr. Kevin Ess found that inactivating tsc2 in zebrafish alters the brain development, including increased cell size in the brain and disorganized gray and white matter, via cell autonomous and possibly non-cell autonomous mechanisms.	• TSCRP Research Highlight
2009	Dr. Boyi Gan elucidated the molecular pathogenesis of TSC-related renal tumorigenesis, and provided novel insights of targeted therapies against renal complications in TSC patients.	• TSCRP Research Highlight
2010	Dr. Mary Kay Koenig led a multi-center prospective, randomized, double-blind, placebo-controlled evaluation of the safety and efficacy of a topically applied formulation of rapamycin to treat cutaneous angiofibromas in individuals with TSC.	
2010	Dr. Mark Zervas generated TSC-like symptoms in mice and showed that the timing of Tsc1 deletion in neurons in developing thalamus impacted the extent of the disease in the brain, the degree of abnormality, and the severity of TSC-like symptoms.	• TSCRP Research Highlight
2010	Dr. Mark Bear demonstrated that loss of the TSC2 gene resulted in unregulated mTOR activity and decreased protein synthesis in the hippocampus, and treatment with an mGluR5-positive allosteric modulator (PAM) restored hippocampal protein synthesis and reversed hippocampal-dependent behavior deficits in Tsc2+/- mice.	• TSCRP Research Highlight
2010	Dr. Charles Nelson and Dr. Shafali Jeste found that children with tuberous sclerosis complex (TSC) had slower face processing than typically developing children, and this was particularly slow in the subset of TSC children with autism spectrum disorder (ASD) diagnosis. They also observed significant differences in electroencephalography (EEG) frequencies between the two groups as early as 20-24 months of age, and they speculate that frequency differences may provide early markers of ASD in children with TSC prior to clinical diagnosis and allow for effective intervention strategies.	• TSCRP Research Highlight
2010	Dr. Shu-Bing Qian found that mTOR/TSC signaling influences elongation speed, thereby affecting the quality of translational products, suggesting that mTOR/TSC inhibitors like rapamycin may increase protein homeostasis.	• TSCRP Research Highlight

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2011	Dr. Jane Yu found that aspirin, and other COX-1/COX-2 inhibitors, may slow the clinical progression of Lymphangioleiomyomatosis (LAM) in a rapamycin-independent manner.	• TSCRP Research Highlight
2011	Dr. Stephen R. Hammes developed a mouse model for uterine leiomyomas and lymphangioleiomyomatosis (LAM) and obtained evidence that LAM tumors might originate from tumors in the uterus.	• TSCRP Research Highlight
2011	Dr. Michael Wong found that anti-inflammatories inhibit pathological abnormalities, decrease seizures, and improve survival in a TSC mouse model.	• TSCRP Research Highlight
2011	Dr. Gabriella D'Arcangelo generated novel brain-specific Pten and Tsc2 conditional knock out mouse line, and found that NMDA receptor abnormalities do not play a central role in cognitive defects in TSC patients.	• TSCRP Research Highlight
2011	Dr. David Sulzer showed that normal TSC gene function is required for normal developmental pruning.	• TSCRP Research Highlight
2012	Dr. Reuben Shaw identified a novel inhibitor that may boost the effect of mTOR inhibitors.	• TSCRP Research Highlight
2012	Dr. Kun-Liang Guan found new mechanisms of mTOR regulation, and showed that high mTOR activity is the major contributor to TSC pathology.	• TSCRP Research Highlight
2012	Dr. Wenqing Xu provided the first three-dimensional structure of TSC1.	