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Topical Review

Advances and Future Directions for Tuberous Sclerosis Complex Research: Recommendations From the 2015 Strategic Planning Conference

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ABSTRACT

On March 10 to March 12, 2015, the National Institute of Neurological Disorders and Stroke and the Tuberous Sclerosis Alliance sponsored a workshop in Bethesda, Maryland, to assess progress and new opportunities for research in tuberous sclerosis complex with the goal of updating the 2003 Research Plan for Tuberous Sclerosis (http://www.ninds.nih.gov/about_ninds/plans/tscler_research_plan.htm). In addition to the National Institute of Neurological Disorders and Stroke and Tuberous Sclerosis Alliance, participants in the strategic planning effort and workshop included representatives from six other Institutes of the National Institutes of Health, the Department of Defense Tuberous Sclerosis Complex Research Program, and a broad cross-section of basic scientists and clinicians with expertise in tuberous sclerosis complex along with representatives from the pharmaceutical industry. Here we summarize the outcomes from the extensive premeeting deliberations and final workshop recommendations, including (1) progress in the field since publication of the initial 2003 research plan for tuberous sclerosis complex, (2) the key gaps, needs, and challenges that hinder progress in tuberous sclerosis complex research, and (3) a new set of research priorities along with specific recommendations for addressing the major challenges in each priority

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area. The new research plan is organized around both short-term and long-term goals with the expectation that progress toward specific objectives can be achieved within a five to ten year time frame.

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Introduction

Tuberous sclerosis complex (TSC) is a rare genetic disorder (~1:6000 live births) caused by inactivating mutations in either *TSC1* or *TSC2*.[1,2] The proteins encoded by *TSC1* and *TSC2*, hamartin and tuberin, form a complex that negatively regulates the mechanistic target of rapamycin complex 1 (mTORC1).[3] mTORC1 is a kinase that regulates cell growth and anabolic processes in response to nutrient and growth factor stimulation.[3] Clinically, TSC individuals bearing *TSC1* or *TSC2* (*TSC1/2*) mutations develop nonmalignant tumors in multiple organs including the brain, eyes, heart, kidney, skin, and lungs, following a classic tumor suppressor paradigm.[1] However, for many individuals with TSC, the symptoms that most strongly impact quality of life are due to brain involvement, including seizures, intellectual disability, and autism, by mechanisms that are not well understood.[4]

The incidence and severity of TSC manifestations vary widely between individuals, and even between identical twins.[5] This phenotypic heterogeneity is likely due to differences in mutations occurring in *TSC1* versus *TSC2* and other poorly defined factors. TSC is inherited in an autosomal dominant pattern with approximately two thirds of cases arising from *de novo* mutations.[1] In addition, many cases result from genetic mosaicism in which a somatic mutation in *TSC1/2* occurs during early embryonic development.[6,7] In somatic cells, a second-hit event causing complete loss of either *TSC1/2* is typically required to cause unregulated mTORC1 activation and tumor development[1]; heterogeneity arises from stochastic factors that affect the number and distribution of these second hits. Other potential contributors to the heterogeneity include cell-specific responses to the mutation, genetic modifying loci, and developmental and environmental factors, to name a few. This heterogeneity has posed major challenges in identifying effective treatments for TSC.

In 2001, Congress stated its support for the improved detection and treatment of TSC and directed the National Institutes of Health (NIH) to develop a long-range research plan for TSC (S.Con.Res.69, H.Con.Res.25). To assist in developing the first strategic plan for TSC research, the National Institute of Neurological Disorders and Stroke (NINDS), the Tuberous Sclerosis Alliance (TS Alliance), and the NIH Office of Rare Diseases Research convened an international symposium in Chantilly, Virginia, in September 2002 leading to a comprehensive 5- to 10-year research plan for TSC that was published in 2003 (http://www.ninds.nih.gov/about_ninds/plans/tscler_research_plan.htm).

In the Spring of 2014, the NIH, the Department of Defense Tuberous Sclerosis Complex Research Program (DOD TSCRP), and the TS Alliance initiated a new strategic planning effort for TSC that culminated in a workshop on March 10 to 12, 2015, entitled "Unlocking Treatments for TSC: 2015 Strategic Plan" (held in Bethesda, Maryland; Supplementary Data: Appendix 1: Methods; Appendix 2: Workshop Organizing Committee and Working Groups; Appendix 3: Agenda and list of meeting participants). The conference brought together 82 participants including investigators and clinicians with diverse expertise, industry representatives, patient advocates and TSC family members, and representatives from seven NIH Institutes and Centers, the DOD TSCRP, and the TS Alliance. The conference goals included reviewing the state of the TSC research field and progress in reaching the original 2003 research objectives. A major goal was to update the 2003 Research Plan for TSC by identifying critical priorities and new opportunities for the field. Here, we summarize the major workshop outcomes and recommendations to update the TSC Research Plan.

Results

Progress in understanding and treating TSC

The workshop outcomes, described here, included reviewing the state of the TSC field and research progress since publication of the 2003 Research Plan (http://www.ninds.nih.gov/about_ninds/plans/tscler_research_plan.htm).

Elucidation of signaling pathways

Since 2003, tremendous progress has been made in understanding the functions of *TSC1* and *TSC2*, and the molecular and cellular consequences of loss-of-function mutations in these genes. This progress was initiated by seminal findings in *Drosophila* followed by cell culture, and mouse genetic studies indicating that *TSC1* and *TSC2* inhibited cell and tissue growth.[8-11] These studies led to the recognition that TSC1 (also referred to as hamartin), TSC2 (tuberin), and a third protein TBC1D7 form a protein complex (the TSC complex) which acts as a sensor of cellular growth conditions and is an essential negative regulator of mTORC1 (reviewed in the studies[3,12,13]). The TSC complex lies at the heart of a signaling network in which multiple different signaling pathways converge to regulate its function through direct phosphorylation of TSC2. In short, growth-promoting signals from growth factors, hormones, cytokines, nutrients, and cellular energy inhibit the TSC complex, leading to the activation of mTORC1. In contrast, poor growth conditions, such as growth factor or nutrient withdrawal or cellular stress, activate the TSC complex to turn off mTORC1. The TSC complex regulates mTORC1 by acting as a GTPase-activating protein for the Ras-related protein, Rheb, which in its GTP-bound form is an essential activator of mTORC1. Thus, in response to poor growth conditions, the TSC complex, through a GTPase-activating