

Gene Therapy for Tuberous Sclerosis Complex



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The Ramesh Laboratory has been investigating the pathophysiology of Neurofibromatosis 2 (NF2) and Tuberous Sclerosis Complex (TSC) for almost two decades. Our work on NF2 in human arachnoidal and meningioma cells discovered that NF2 protein merlin is a novel negative regulator of mTORC1 signaling. This work has been translated into clinical trials with RAD001 for NF2 and sporadic meningiomas. We have also established CRISPR-Cas genome editing technology in human arachnoidal cells, Schwann cells and iPSCs and have used this technique to create/correct mutations in NF1, NF2, TSC1 and TSC2 generating isogenic sets of human lines for drug screening.

TSC is a multisystem disorder that includes epilepsy, autism spectrum disorder (ASD), intellectual disability (ID), and hamartomas in many organs. TSC is caused by mutations in the TSC1 or TSC2 gene, encoding proteins hamartin (TSC1) and tuberin (TSC2), respectively. The TSC proteins act as a central hub relaying signals from diverse cellular pathways to control mammalian/mechanistic target of rapamycin complex 1 (mTORC1) activity, which regulates cell growth and proliferation. The aberrant activation of mTORC1 in TSC has led to treatment with mTORC1 inhibitor rapamycin analogs as a lifelong therapy since discontinuation leads to increase in growth of the TSC-associated lesions, and further treatment or lack of it can potentially compromise early brain development.

Therefore, there is a clear need to identify other therapeutic approaches for TSC. Toward this goal, gene therapy was evaluated in collaborative efforts between our laboratory and the Breakfield and Maguire laboratories at MGH, employing TSC2-patient-derived neural progenitor cell models (NPCs) and a mouse model of TSC2 using an AAV vector carrying a "condensed" form of tuberin (cTuberin). Functionality of cTuberin was first verified in human cellular models. A mouse model of TSC2 was generated by AAV-Cre recombinase disruption of Tsc2-floxed alleles at birth, leading to a shortened lifespan and brain pathology consistent with TSC. When these mice were injected intravenously on day 21 with AAV9-cTuberin, the mean survival was very significantly extended with reduction in brain pathology. This study demonstrates the preclinical efficacy of a single intravenous injection of AAV9-cTuberin, setting the stage for IND-enabling studies and clinical translation.

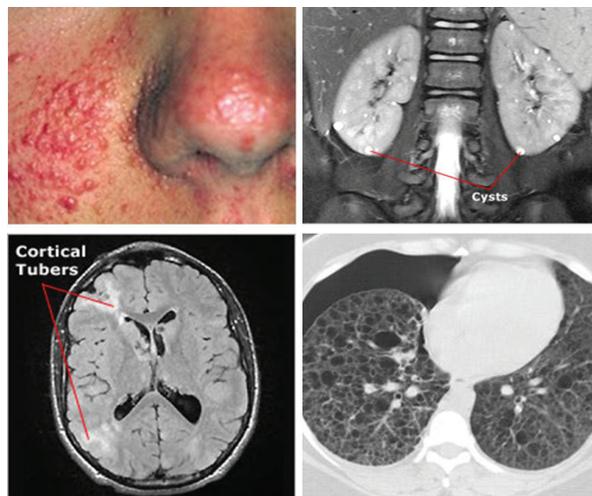


Figure 1. Tuberous Sclerosis Complex (TSC) is a multisystem disorder characterized by tumors affecting multiple organs as well as autism, epilepsy and intellectual disability.

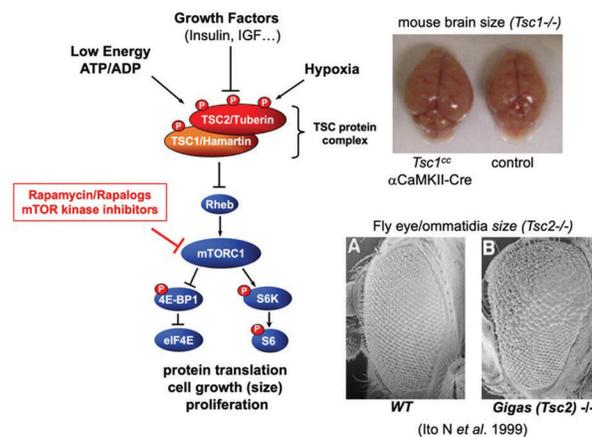


Figure 2. TSC protein complex is a master negative regulator of mTORC1 signaling, a key cellular sensor pathway integrating upstream external signals with downstream protein translation, cell size and proliferation.