Modelling the Tuberous Sclerosis-related neoplasm Lymphangioleiomyomatosis (LAM)

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Lymphangioleiomyomatosis (LAM) is a Tuberous Sclerosis-related lesion of the lung, similar to a cancer, which only affects women. LAM cells produce enzymes that destroy the lungs of the patients. The only treatment is the drug Rapamycin that slows down the progression of the disease until the patient can receive a double lung transplant, which carries a lot of risk. A major obstacle for LAM research and the development of new LAM treatments has been the difficulty in isolation of LAM cells from patients to study LAM or to perform drug screens. When LAM cells have been isolated, these cells don't behave like LAM in the culture dish or they stop growing. To solve these problems we have made LAM-like cells from both female and male human stem cells and we have developed a gel that has many of the properties of a human lung so that we can grow LAM or LAM-like cells in a 3D lung-like environment. We found that TSC deficient, LAM-like cells behave differently in 2D (normal) and 3D culture. In this proposal we will use our LAM-like cell lines and our 3D lung tissue like culture system to tease apart why Rapamycin only slows down LAM but does not stop it and to explore why mutations in TSC2 predispose a woman LAM more than mutations in TSC1. In addition, we will perform a drug screen of nearly 1300 FDA-approved drugs to identify drugs that can work alone or in concert with Rapamycin to preferentially kill LAM cells or to stop their production of MMPs, which destroy the lungs of LAM patients. In addition, since we are using both male and female cells, we may learn why LAM only strikes women.