The clinical features of LAM have been well described, but the clinical course of LAM varies considerably. Uncovering biomarkers with prognostic and target value could help to rectify the clinical course of LAM. LAM lesions and angiomyolipomas in the kidney contain increased levels of the enzyme called urokinase plasminogen activator (uPA). uPA is the proteolytic enzyme which initiates activation of the cascade of the multiple tissue-degrading enzymes and therefore mediates metastasis and tumor angiogenesis. High levels of uPA in tumor tissues and plasma are strong indicators of poor prognosis and metastasis in various common cancers. We propose that up-regulation of uPA facilitates destruction of lung tissue by LAM cells and their spread to other organs.

Our pilot data indicate the increase in uPA is a direct consequence of TSC inactivation. We found that Sirolimus, despite its cytostatic effect, further augments expression of uPA in TSC-compromised cells, which might confer higher propensity to metastasize and cause local tissue destruction by LAM cells in some patients. Our data suggest that uPA may emerge as target to delay the growth and dissemination of LAM and other TSC-related tumors. We posit that measurement of uPA levels in LAM lesions, plasma and urine may be of diagnostic and prognostic value. These studies may also suggest that addition of specific inhibitors of uPA (Mesupron, Midamor), now in clinical studies, to Sirolimus might further attenuate lung tissue destruction and dissemination of LAM cells.