

The genetic causes underlying the development and progression of uterine leiomyosarcoma (ULMS) and, in general, leiomyosarcoma (LMS), remain largely unknown. Much work has been done to describe the expression of patterns of genes expressed by these tumors once they have grown and spread. Importantly, this is providing insight into the fact that major subtypes exist and this may explain differences in tumor behaviour and response to treatment. Despite these findings, no single gene has been identified as an initiator of the disease. Finding this gene will be important to better understand what initiates the cascade of events which result in tumorigenesis and spread and hopefully provide a powerful target for treatment.

Our studies have identified the first LMS initiator gene. Funding from the National Leiomyosarcoma Foundation, including a generous contribution from the Ellen McCullough Golf Classic, have allowed us to move these studies forward. Specifically, we recently demonstrated that female mice genetically engineered to overexpress the KLF6-SV1 gene result in mice which develop uterine leiomyosarcomas. We knew that the KLF6-SV1 gene is an oncogene and it is excessively produced in a number of other cancers. When tumor cells make KLF6-SV1, they can grow, spread and metastasize more efficiently. To our knowledge, this mouse represents the first animal model for uterine leiomyosarcoma. This suggests two immediate consequences.

Therefore, and with the funding provided by the NLMSF, we explored this important first question: "If high-levels of KLF6-SV1 causes leiomyosarcomas to develop in mice, can it do the same in humans?" To answer this question, Dr. Analisa DiFeo an Instructor in my laboratory and Dr. Fei Huang, first examined uterine LMS tumors samples from our own pathology department. In each case, and in agreement with our hypothesis, we found that the KLF6-SV1 gene was more highly expressed in these patient-derived tumors than in adjacent normal tissue. Based on these findings, we then sought a larger collection of tissues to strengthen our results. In collaboration with Dr. Matt van de Rijn's group at Stanford University Medical Center and Dr. Douglas Levine's group at Memorial Sloan-Kettering Cancer Center we obtained additional tumor samples for analysis. Again, the KLF6-SV1 gene and protein were found to be more prevalent in tumor than normal tissues. Based on these human tumor findings, we believe that KLF6-SV1 is involved in the development of human LMS. These findings, along with the mouse model of LMS, are currently being prepared for submission for publication. The generous funding of the NLMSF and the important role it played in allowing us to pursue these studies will be gratefully acknowledged.

The second and next important question for us to pursue in the future will be how to leverage these findings into an even better molecular and clinical understanding of LMS. For example: "Can KLF6-SV1 levels in a tumor sample predict the disease outcome or sensitivity to a particular drug regimen?" or "Can KLF6-SV1 be a predictor of disease in families with a history of LMS?" Finally, if high levels of KLF6-SV1 can initiate the growth and spread of LMS can we find a way to inactivate this gene and shut off tumor growth. In this regard, some of our work suggests that this may be achievable. We recently published our findings that a new class of drug molecule known as siRNA, that can shut-down or "silence" a gene, can be injected into mice which are burdened with ovarian cancer and by specifically and efficiently shutting-down the KLF6-SV1 gene, mouse survival was greatly increased.