Abstract (lay version) of project

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Next generation sequencing approach to desmoid tumors

Desmoid tumors are proliferations of relatively benign appearing fibroblasts. Despite their histologic bland appearance, a significant subset of these tumors recurs aggressively and requires often debilitating surgery. Currently there are no molecular markers that predict the behavior of desmoid tumors. The purpose of this study will be to perform a very broad molecular search for markers that can be used to address two clinically highly relevant questions.

First, it is well known that not all desmoid tumors behave in the same manner. Some are very aggressive, others have an indolent behavior. While attempts have been made to develop predictors for the behavior of desmoids, these rely only on clinical parameters such as tumor size, site and age of the patient and no molecular markers for recurrence risk have been identified. At this moment, it is impossible to tell with certainty which tumors require aggressive treatment and which can be followed by "watchful waiting". Through our ability to perform next generation sequencing on archival tumor samples we can now perform a very broad search for changes in the genetic material that can help us predict the behavior of desmoids. In addition to identifying markers that can be used to predict the behavior of desmoid tumors, we will also perform an in-depth search for markers that can be used by pathologists to distinguish scar from desmoid recurrence. During the first two years of this project we have identified multiple candidate markers that may address these two clinical questions. In the third year of this project we will validate these markers to develop novel assays that could be used in surgical pathology practice.

In the third year of this project we also plan to perform novel functional studies in an attempt to improve the existing cell culture models of desmoid tumors. The currently available cell cultures are composed of a mixture of normal cells (fibroblasts) and desmoid tumor cells carrying mutations in β-catenin. Experimental utility of these models is limited because fibroblasts usually tend to outgrowth the desmoid cells in these cultures. We plan to perform experiments that will selectively promote the proliferation of desmoid tumors cells and inhibit proliferation of fibroblasts. We expect that we will be able to derive pure desmoid cell cultures that eventually could be used for more efficient testing of novel therapies in desmoid tumors.