**Abstract (lay version) of project**

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**"The role of the tumor microenvironment in S45F desmoid tumor chemotherapeutic resistance."**

Desmoid tumors are a locally aggressive tumor type that can cause remarkable debility and even mortality in afflicted patients. While the antitumor activity of sorafenib has been clinically demonstrated in DT patients to the best of our knowledge, sorafenib mechanism of action has not been elucidated, which makes it more difficult to identify the patients who may derive benefit from this drug. Our preliminary studies have shown that desmoids harboring the CTNNB1 S45F mutation appeared to be more tolerant of sorafenib as compared to DTs harboring T41A/S45P or wild-type CTNNB1 and that the mechanism of cell death in response to sorafenib differs between desmoids harboring the CTNNB1 S45F mutation and the desmoid harboring T41A/S45P or the wild-type CTNNB1. The TME describes the non-cancer cells that surround tumor cells. In desmoid patients, βcatenin S45F mutation correlates with a poor prognosis as compared to the T41A mutation. In the first aim of this grant, we propose to investigate the differences between desmoids harboring different CTNNB1 mutations and their response to sorafenib. Several studies have correlated drug resistance to the tissue microenvironment (TME). While much is already known about the TME conferring drug resistance in other type of cancer, little is currently known about the role of TME in the resistance to therapy in desmoid tumor cells. Therefore, it is important to investigate if the TME cells separated from different mutated desmoids possess diverse behaviors. In the second aim of this study, we propose to analyze the role of the TME in the resistance of S45F-mutated desmoid tumors to therapy. Our preliminary studies have shown that the separation of TME cells from desmoid tumor cells is feasible. Moreover, our preliminary data showed that TME cells separated from S45Fmutated desmoid cells are more resistant to doxorubicin, suggesting that TME cells may play a role in the resistance to drugs observed in some DT cells. Interestingly, the S45F-mutated desmoid cells cultured in the absence of TME cells did not show resistance to doxorubicin, as opposed to previous results from our group in which S45F-mutated DT cells cultured in the presence of TME are resistant to doxorubicin. Lastly, our results showed that the pure population of T41A-mutated desmoids cultured with media collected from TME sorted from S45F-mutated desmoid tumors are more tolerant to doxorubicin treatment, as oppose to the sensitivity seen in the mixed population, suggesting that the TME releases factors that may play a critical role in the therapeutic resistance of desmoid tumors harboring the S45F mutation. These preliminary results are promising; however, these findings are in need of further investigation to identify the molecular mechanisms driving the role of the TME in desmoid resistance to drugs. We hope that this study plan will result in important findings that can positively impact the management of patients burdened by desmoid tumors.