Award ID:
RP180674

Project Title:
Predictive Biomarkers and Novel Therapies for High-Risk Pediatric Liver Cancers

Award Mechanism:
Multi-Investigator Research Awards (Version 2)

Principal Investigator:
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Entity:
Baylor College of Medicine

Lay Summary:

Hepatoblastoma (HB) and hepatocellular carcinoma (HCC) are the two most frequently diagnosed liver cancers in children. These cancers can be divided into smaller groups based on the look of the cells under the microscope and their molecular programming. Depending on which type of HB or HCC a child has, the prognosis can vary: some children with “low-risk” HBs are cured by surgical removal of the tumor, some children require additional chemotherapy while children with “high-risk” HBs and HCCs continue to have a dismal prognosis of 30-50% at 5 years despite maximal medical and surgical therapy. Treatments for these tumors include surgical resection or liver transplantation in combination with dose-intensive chemotherapy regimens which may cause low blood cell counts, hearing impairment, speech and cognitive delay and long-term damage to the heart. Therefore, it is critical to select the optimal chemotherapy for each group of patients and to develop new effective and safer therapies.

We propose three synergistic projects:

Project 1 will focus on validating and identifying molecules found in HBs and HCCs to better assign treatment groups. The validation of these molecules will enable improved diagnosis and better assignment of chemotherapy combination thereby maximizing antitumor effect and minimizing toxicity. Identifying new molecules or signaling pathways in the cancer cells that are responsible for the growth and spread of cancer cells can be the foundation for new therapies.

Project 2 will use already available preliminary data and findings from Project 1 to test new drugs to interfere with liver cancer associated molecules and signaling pathways. One promising molecule already identified by our team is called MDM4 and we will attempt to block this molecule in order to attack tumors. For HB to spread from the liver, it needs to invade the blood vessels. We will examine specifically those cells that are capable of invading the blood vessels and target them directly. We will use several models to test our new targeted therapies including a unique mouse model where tumor samples from patients are directly implanted and treated.

Project 3 will test a new promising form of cancer therapy called immunotherapy. This strategy relies on the body’s defense mechanism to fight cancer. We will target a

molecule called glypican-3 which can be found only in HB and HCC cells and not in healthy tissues. This molecule will be targeted by a special type of white blood cells called T cells, which will be genetically modified to recognize and kill liver cancer cells. In collaboration with Project 1 researchers, this Project will study the cancer cells to find out if they can produce molecules to stop these T cells. T cells will be monitored in patients as well to detect such blocking effect from the cancer cells. In addition, the researchers of Project 2 and 3 will test cancers and genetically modified T cells from the same patient in mice and study their genetic programming and behavior to improve the therapy.

Three cores will help these three projects to work together effectively and efficiently. The Administrative core will assist with patient material collection, tracking, and reporting. The Pathology core will be responsible for tissue processing, microscopic and molecular studies. Finally, the Technology and Statistics Core will provide expertise to examine cells on the single cell level and analyze the data with the appropriate statistical methods.

This comprehensive application has the potential to better assign currently available therapies to patients, evaluate new therapies in preclinical models for further clinical testing and establish immunotherapy as new effective and safe approach for children with liver cancers. With the support of the three well-defined cores, the projects will be well integrated and will function in a highly synergistic manner. The results of the research outlined in detail in our application may fundamentally change the way children with liver cancer are treated and the findings will likely be applicable to other pediatric and adult cancers.