THE HARTWELL FOUNDATION

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Targeted Protein Degradation for the Treatment of Ewing Sarcoma

Pediatric sarcomas, most notably Ewing sarcoma (EWS), are bone malignancies that affect over 1000 American children, adolescents, and young adults every year. For patients with localized EWS, the 5-year survival rate exceeds 80%, but for those patients whose tumors have metastasized or have recurred after years of remission, survival decreases to <15%. Toxic chemotherapy or radiation therapy are the only treatment options of choice, leading to adverse side effects including severe weight loss, chronic nausea and vomiting, fatigue, hair loss, and increased chances of infection or follow-on cancer. Similar to many pediatric cancers, the molecular features of EWS involve a genetic fusion of two genes that code for a stable tumorigenic fusion protein, EWS-FLI1, which is pathognomonic for cancer (found in 90% of all EWS tumors) and notoriously difficult to target with standard chemotherapy. An enzyme known as E3 ubiquitin ligase or TRIM8, controls the levels of EWS-FLI1 by tagging it for degradation in the cell's natural waste disposal system, allowing the tumor to persist. By contrast, removal of TRIM8 results in EWS-FLI1-mediated oncogene overdose, driving DNA damage and tumor cell death. To remove disease-causing proteins like TRIM8, targeted protein degradation occurs in the ubiquitin-proteasome pathway, where protein complexes called proteosomes form to degrade unneeded or damaged proteins by a chemical reaction called enzymatic proteolysis. Harnessing the cell's natural waste disposal system to selectively eliminate cancer-causing protein requires bringing a target protein into close proximity with the ubiquitin ligase that flags the protein for rapid degradation by adding a "disposal tag". Unfortunately, E3 ubiquitin ligases, such as TRIM8, are notoriously difficult to target. In part, no clinically approved degrader exists because standard small molecule or chemical-based degradation systems suffer from specificity constraints, complex design restrictions with long lead times, and drug side effects. Based upon my early proof-of-concept, I propose to develop a new generation of safe and effective degraders for those proteins that directly regulate tumorigenicity in EWS. Using computational methods that take advantage of machine learning-based design, I will design synthetic protein chimeras called "ubiquibodies" (uAbs), which will combine the activity of a E3 ubiquitin ligase with a designer binding protein to direct the cancer target protein for degradation. My preliminary data suggests that uAbs can be encapsulated within lipid nanoparticles for efficient delivery in cell culture and mouse test systems. To achieve selective and controllable depletion of TRIM8, I will demonstrate effective delivery, degradation, and tumor regression in mouse tumor models. If I am successful, clinical translation will provide a much-needed safe and effective therapy for children suffering from EWS, as well as other pediatric cancers that are currently untreatable by standard chemotherapies.