**Curebound Targeted Grant Fall 2022**

**Targeting the Proteostasis Network in Acute Myeloid Leukemia**

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**Scientific Abstract:**

Leukemia stem cells (LSCs) are self-renewing leukemia cells that propagate malignant disease. Failure to eradicate LSCs in acute myeloid leukemia (AML) leads to patients relapsing with advanced disease, and the 5-year survival rate is just 29%. Identifying strategies to target LSCs can have immense clinical significance by leading to the development of curative therapies. LSCs typically arise from transformation of hematopoietic stem cells (HSCs), which are particularly dependent on the maintenance of proteostasis. This raises the possibility that LSCs may also depend on proteostasis maintenance and that interventions that disrupt proteostasis could impair/eradicate LSCs. However, proteostasis has not been studied in LSCs. Proteasome inhibitors are approved to treat myeloma, and their effectiveness is tied to their ability to disrupt proteostasis. However, proteasome inhibitors exhibit little efficacy for AML. In preliminary studies, we determined that proteasome inhibition is insufficient to disrupt proteostasis in AML cells due to compensatory activation of autophagy and HSF1. This raises the possibility that the integrated nature of the proteostasis network confers resistance to proteasome inhibition, and that concurrent targeting of multiple mechanisms is required to disrupt proteostasis. We generated data demonstrating that when combined with autophagy or HSF1 disruption, proteasome inhibition results in a synergistic decline in AML cell viability. The goal of our studies is to test if disrupting proteostasis can impair AML stem cells in vivo. These studies will unravel how the proteostasis network is configured in AML and could reveal coordinated targeting of the proteostasis network as a novel approach for eliminating LSCs.

**Lay Abstract:**

Acute myeloid leukemia (AML) is an aggressive and deadly cancer of white blood cells. Traditional chemotherapy has been used to treat AML for the past 50 years, and the survival rate is just 29%. Thus, identifying new strategies to treat AML could have a profound impact on patient survival and quality of life. Our strategy is to target the machinery that degrades proteins. Proteins are the products of genes and perform virtually all specialized tasks within cells. Sometimes proteins are produced incorrectly or get damaged. Damaged proteins are a cell’s version of trash, and if that trash is allowed to buildup, it can cause cells to die. To prevent this from happening, cells have machines called proteasomes that destroy protein trash. There was great hope that drugs that block proteasomes would cause protein trash to buildup and kill cancer cells, but unfortunately those drugs are ineffective in AML. We discovered that when the proteasome is blocked, cells activate a recycling pathway to compensate for the lack of trash removal and this keeps the cells healthy. In our preliminary research, we found that when we block both the trash removal and recycling pathways at the same time, it causes AML cells to rapidly fill up with protein trash, resulting in death of these cancer cells. Our goal is to expand these studies to test if this is a tractable approach for eliminating AML inside the body. These studies could ultimately lead to new therapies for AML and other cancer patients.