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“New Therapies for Myeloid Leukemia”

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SCIENTIFIC ABSTRACT

Current therapies for Acute Myelogenous Leukemia (AML) are often not effective, with therapy-resistant cancer cells leading to relapse and death in many patients. AML often arises from early stage myeloid disorders such as myelodysplastic syndrome (MDS) or myeloproliferative neoplasms (MPN); thus targeting the indolent diseases could provide a unique opportunity to block progression into a therapy resistant state. Here we propose to develop a new therapeutic against these myeloid neoplasms, in both their indolent and progressed states.

To identify new targets in myeloid leukemia, we focused on identifying programs downstream of the stem cell signal Musashi2 (Msi2), which we and others have shown is required for growth of aggressive myeloid leukemias. Specifically, we focused on cell surface molecules that may be more readily targeted to mimic Msi2 loss and block myeloid leukemia. This led us to identifying Tetraspanin 3 (Tspan3) as a key regulator of myeloid leukemia; our work demonstrated a strong impact upon Tspan3 loss in mouse models as well as in primary patient samples *in vitro* and xenografts *in vivo*.

These studies provided a strong rationale for developing mAbs against human Tspan3 as a potential therapeutic. Here, we propose to define the breadth and impact of the inhibitory Tspan3 mAbs we generated against diverse types of indolent and aggressive human myeloid disease, including MDS, MPN and AML, and identify biomarkers predictive of response to Tspan3 inhibition. If successful, these exciting studies could lead to clinical trials to test the impact of Tspan3 mAbs as therapy for myeloid leukemia.

LAY ABSTRACT

Acute Myelogenous Leukemia (AML) is a cancer marked by rapid and uncontrolled growth of immature cells of the myeloid lineage. Although it is the most common acute leukemia in adults, current treatments, which include chemotherapy and bone marrow transplantation, are largely ineffective, leading to relapse and death in most patients. AML also occurs in children, and pediatric AML has a much poorer outcome than other childhood leukemias. In light of these issues, AML represents a disease with a significant unmet medical need. Given that there have been no new therapies

for AML in the last 30-40 years, identifying new approaches to target AML is critically important. At a cellular level, AML is heterogeneous and has been shown to be driven by cancer stem cells. Thus strategies aimed at inhibiting cancer stem cell growth and renewal may target the fundamental propagative abilities of the tumor and allow development of a more targeted therapy. Importantly, AML can often arise from early stage myeloid disorders such as myelodysplastic syndrome (MDS) or myeloproliferative neoplasms (MPN), thus also providing an opportunity to block its progression at earlier stages. Our goal is to develop a new therapeutic agent that can block growth and progression of these myeloid disorders. To this end we have developed antibodies that target a protein required for AML growth. We will test whether these antibodies can block progression of MDS/MPN to AML and improve outcomes. If successful, these exciting studies could lead to a new treatment strategy for myeloid leukemia.