AN MHC CLASS II TARGETED IMMUNOTHERAPY FOR CD33-POSITIVE PEDIATRIC ACUTE MYELOID LEUKEMIA

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Background The treatment of pediatric acute myeloid leukemia (pAML) continues to be a challenge due to multiple subtypes and a wide variety of mutations. This heterogeneity undermines efforts to develop targeted therapeutics and conventional chemotherapy remains the standard of care (SOC). Sialic acid binding Ig-like lectin 3 (CD33) is a myeloid lineage cell surface glycoprotein that has emerged as a target for immunotherapy in AML. Gemtuzumab ozogamicin (GO), a CD33 specific antibody-drug conjugate (ADC), is FDA approved for the treatment of childhood AML. However, premature cleavage of the linker that connects the gemtuzumab monoclonal antibody to the cytotoxic calicheamicin payload can lead to undesirable off-target effects. Furthermore, while ~90% of AML cases exhibit CD33 expression, 50% of these patients express a single nucleotide polymorphism (SNP) in CD33 that eliminates the antibody binding epitope for GO, and clinical studies have failed to demonstrate an increase in overall survival in pAML patients treated with GO compared to SOC. These drawbacks highlight the critical need for a safer and more effective therapeutic that targets CD33-positive AML.

Methods Our lab has developed a novel immunotherapy platform that targets tumor associated antigens (TAAs) to MHC class II molecules on antigen presenting cells for enhanced presentation to immune effector cells. This MHC class II targeted platform, or M2T for short, consists of an optimized high affinity MHC class II binder linked to a TAA. CD33-M2T uses in silico optimized variants of full length and truncated versions of the CD33 protein to direct specific immune cell responses against full length and alternatively spliced CD33.

Results Our preliminary data show that CD33-M2T induces a robust polyclonal anti-CD33 humoral response that induces the full antibody repertoire in vivo, including all IgG subtypes and IgA. Additionally, CD33-M2T increases overall survival in a syngeneic mouse model of AML. CD33-M2T has demonstrated clear advantages over anti-CD33 monoclonal antibodies (e.g., gemtuzumab, lintuzumab), including the ability to bind to the truncated alternatively spliced version of CD33, long duration of action, and no overt toxicities in mice.

Conclusions These experiments demonstrate the preclinical potential of an innovative immunotherapy targeting CD33-positive childhood AML.

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