

# Abstract 133: NEO-201-recognized truncated Core 1 O-glycans represent a new target for CAR-NK therapy in AML. **FREE**

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## Abstract

### Introduction:

Acute myeloid leukemia (AML) continues to have poor long-term outcomes, particularly in high-risk and relapsed/refractory disease. Progress in AML immunotherapy has been hindered by the scarcity of antigens selectively expressed on leukemic cells while sparing hematopoietic stem/progenitor cells (HSPCs). AML-restricted surface glycans represent an underexplored class of targets. NEO-201 is a humanized IgG1 monoclonal antibody that binds truncated Core 1 O-glycans expressed by several solid tumors, circulating neutrophils, and select leukemia cell lines, with limited reactivity to most normal tissues and an acceptable safety profile in a phase I solid tumor trial (NCT03476681). We evaluated the NEO-201-recognized truncated O-glycan antigen as an AML-associated antigen, characterized its expression across AML subtypes, and developed a CAR NK cell therapy directed against this target.

### Methods:

Ten AML cell lines representing diverse molecular subtypes were analyzed for NEO-201 binding by flow cytometry. NK cells from healthy donors were expanded *ex vivo* using lymphoblastoid feeder cells and IL-2. CAR NK cells were generated via retroviral transduction with a second-generation CAR, incorporating a NEO-201-binding domain, CD8 $\alpha$  transmembrane region, 4-1BB co-stimulation and CD3 $\zeta$  signaling domains, and a truncated CD34 (tCD34) marker. Cytotoxicity was assessed in co-culture assays using calcein-AM-labeled AML targets at varying effector-to-target ratios. Antigen expression across hematopoietic maturation stages was evaluated by flow cytometry in G-CSF-mobilized peripheral blood to assess potential on-target/off-tumor toxicity.

### Results:

The NEO-201-recognized antigen was expressed at >40% in 6 of 10 AML cell lines, spanning FLT3-ITD-mutated, MLL-rearranged, biphenotypic, and core-binding factor leukemias. Expression ranged from 41-100% in positive lines: THP-1 (100%), MOLM-14 (88%), MV4-11 (60%), U-937 (45%), HL-60 (44%), and ME-1 (41%). NEO-201-based CAR NK cells demonstrated potent antigen-dependent cytotoxicity, including against lines with lower antigen density. At a 10:1 E:T ratio, CAR NK cells lysed 61% of THP-1, 45% of HL-60, and 40% of MOLM-14 targets. Antigen expression was minimal or absent on CD34<sup>+</sup> HSCs (0-1%), low on early myeloid progenitors (10-15%), and enriched in mature neutrophils (~99%), consistent with restricted expression during late myeloid maturation.

### Conclusion:

This study identifies Core 1 O-glycans recognized by NEO-201 as a novel AML-associated antigen present across multiple subtypes and largely absent from early hematopoietic progenitors. The potent antileukemic activity of NEO-201CAR NK cells in preclinical systems highlights the promise of this approach and sets the stage for advancing O-glycan-directed CAR NK therapy into translational and clinical development.

### Citation Format:

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