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Blood 142 (2023) 2060–2061

The 65th ASH Annual Meeting Abstracts

POSTER ABSTRACTS

703.CELLULAR IMMUNOTHERAPIES: BASIC AND TRANSLATIONAL

Engineering Superaffinity Antibody Dependent Cellular Cytotoxcity Receptors into iPSC-Derived NK Cells As Next-Generation Immunotherapies for Cancer

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Engineered immune cells have provided an important new approach to treating cancer. Most of the progress so far has focused on autologous CAR-T cell therapy, although this approach has been met with several limitations including high-cost and complexity of manufacturing, donor-to-donor variability, and severe toxicities in some patients. Allogenic natural killer (NK) cell therapies have also been shown to mount potent responses against hematologic malignancies but are less likely to cause high-grade toxicities and can be mass produced for off-the-shelf usage. We have developed an induced pluripotent stem cell (iPSC) derived NK (iNK) platform amenable to engineering multiple features in immune cells to improve efficacy against both solid and liquid tumors.

Our previous studies showed that knocking out the *CISH* gene, which encodes a key regulator of activation, in iNK cells significantly improves their anti-cancer activity, in vivo persistence, metabolic fitness, polyfunctional cytokine production, and resistance to cell exhaustion. In these *CISH* Knockout (KO) iNK cells, we have screened a library of CAR constructs containing domains from diverse immune cell signaling receptors including NK cell activating receptors, cytokine receptors, and integrins. Our screen identified SLNK12, a CAR signaling domains that performed better than both T cell CARs and previously reported NK cell CARs in the context of *CISH* KO iNK cells.

In this study, we describe the development of iNK cells with enhanced antibody dependent cellular cytotoxicity (ADCC) activity. NK cells normally bind antibodies via their CD16A receptor, which has medium-to-low affinity for the antibody Fc domain and is also typically expressed at a low level in unmodified iNKs. We have constructed a recombinant Fc-receptor that combines a high-affinity Fc-binding domain (to improve antibody binding) with our NK cell optimized SLNK12 CAR signaling domain to enhance ADCC-mediated killing. When co-cultured with multiple NC cell resistant tumor lines such as BT-474 (breast cancer) or FaDu (squamous cell carcinoma), these SuperAffinity ADCC receptor *CISH* KO iNK cells possess potent anti-cancer activity in combination with several different therapeutic monoclonal antibodies, including anti-EGFR (Cetuximab) and anti-HER2 (Trastuzumab) amongst others (Figure 1). We have assessed efficacy in a variety of different 2D and 3D spheroid cytotoxicity assays, as well as cytokine release and CAR activation assays. In addition, we demonstrate that our SuperAffinity receptor mediates tumor cell killing at lower antibody concentrations than do CD16A variants. Furthermore, introduction of serum IgG inhibits, but does not stop ADCC killing for both our SuperAffinity ADCC receptor and the CD16A receptor.

Taken together, our results show that engineering *CISH* KO iNK cells with NK-optimized CARs for enhanced ADCC improves anti-tumor activity against a variety of solid tumor target lines. Future work will focus on advancing the new cellular therapies into clinical development.

Disclosures Goodman: *Shoreline Biosciences:* Current Employment, Current holder of *stock options* in a privately-held company. **Lyon:** *Shoreline Biosciences:* Current Employment, Current holder of *stock options* in a privately-held company. **Hartwig:** *Shoreline Biosciences:* Current Employment, Current holder of *stock options* in a privately-held company. **Peng:** *Shoreline Biosciences:* Current Employment, Current holder of *stock options* in a privately-held company. **Li:** *Shoreline Biosciences:* Current Employment, Current holder of *stock options* in a privately-held company. **Murray:** *Shoreline Biosciences:* Current Employment, Current holder of *stock options* in a privately-held company. **Bernareggi:** *Shoreline Biosciences:* Current Employment, Current holder of *stock options* in a privately-held company. **Gonsalves:** *Shoreline Biosciences:* Current Employment, Current holder of *stock options* in a privately-held company. **Schabla:** *Shoreline Biosciences:* Current Employment, Current holder of *stock options* in a privately-held company. **Zhang:** *Shoreline Biosciences:* Current Employment, Current

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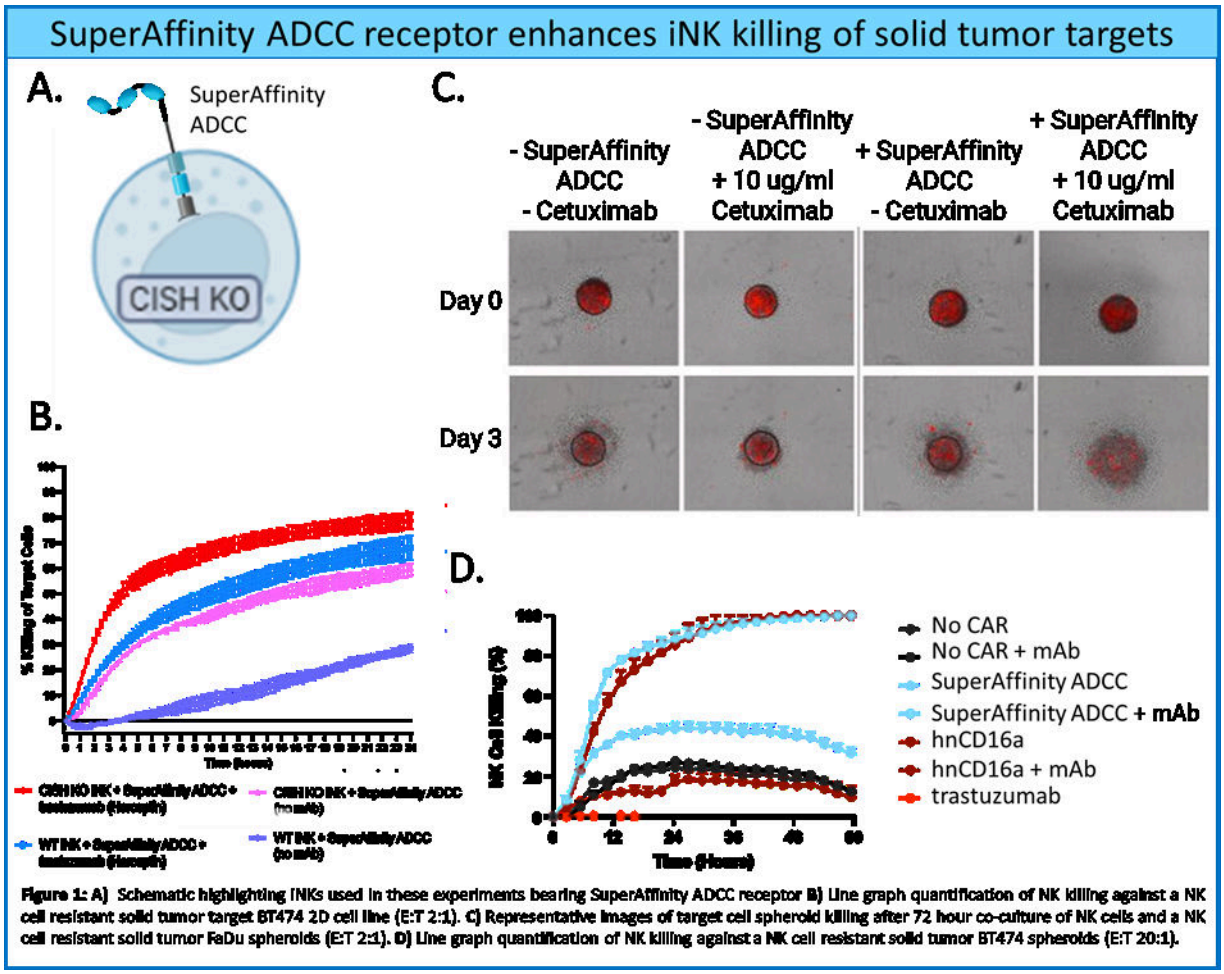

Figure 1

https://doi.org/10.1182/blood-2023-181261

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