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Novel CEAxCD3 (NILK-2301) and CEAxCD28 (NILK-3301) κλ bispecific antibodies for next generation immunotherapy of CEA-expressing cancer

Anja Seckinger[1], Sara Majocchi[2], Valéry Moine[2], Lise Nouveau[2], Bruno Daubeuf[2], Vanessa Buatois[2], Franck Gueneau[2], Ulla Ravn[2], Krzysztof Masternak[2], Yves Poitevin[2], Giovanni Magistrelli[2], Pauline Malinge[2], Limin Shang[2], Nicolas Fischer[2], Klaus Strein[1], Walter Ferlin[2], Dirk Hose[1]

[1]LamKap Bio AG, Bahnhofstrasse 1, 8808 Pfäffikon SZ, Switzerland; [2]Light Chain Bioscience (LCB), Chemin du Pré-Fleuri 15, 1228 Plan-les-Ouates, Geneva, Switzerland

LamKap Bio
HELPING THE BODY TO FIGHT CANCER

BACKGROUND

- Coupling carcinoembryonic antigen-related cell adhesion molecule 5 (CEA or CEACAM5) on tumor cells and CD3 on T-cells by CEAxCD3 bispecific antibodies (bsAbs) activates the latter to destroy CEA-positive cancer cells.
- Clinical activity is, however, limited, in part by insufficient T-cell activation, dose-limiting toxicities (e.g., cytokine release syndrome (CRS), or immunogenicity).

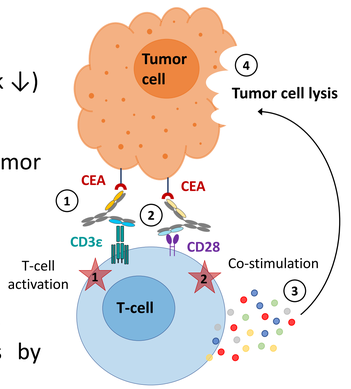
AIMS & MECHANISM OF ACTION

Strategy & aims:
Combination of CEAxCD3 bsAb with CEA-targeted CD28-costimulation shall

- T-cell activity & tumor cell killing ↑
- Duration of response ↑
- Better controllable dose response (CRS risk ↓)

Mechanism of action (MoA):

1) Mediates co-engagement of CEA on tumor cells and CD3 & CD28 on T-cells.
2) TCR/CD3 cross-linking leading to T-cell activation (Signal 1) & co-stimulation via CD28 engagement (Signal 2).
3) Release of cytokines & cytolytic enzymes.
4) Redirected killing of CEA⁺ tumor cells by effector T-cells.



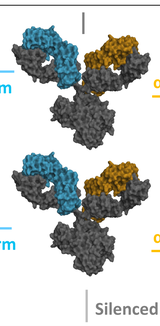
NILK-2301 & NILK-3301 BsAbs

One tumor-associated target, one complementary MoA:

- CEA is (over-) expressed in tumors of epithelial origin, including but not limited to colorectal, gastric, lung, and pancreatic carcinomas.

CD3 or CD28 — CEA: unbalanced affinity

Based on LCB's fully human κλ-body platform:
- 2 identical heavy chains
- 2 different light chains, i.e., one kappa (**κ**) and one lambda (**λ**)



NILK-2301
- Binds specifically to **CD3 on T-cells**
- Triggers **T-cell activation** (Signal 1)

NILK-3301
- Binds specifically to **CD28 on T-cells**
- **Agonist arm:** Delivers T-cell co-stimulatory Signal 2

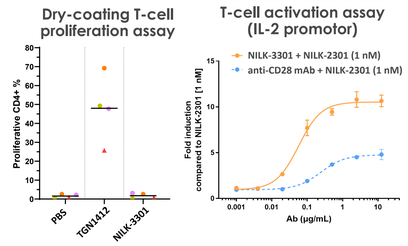
- Bind specifically to **CEA positive** cells
- High affinity, **drives the specificity**

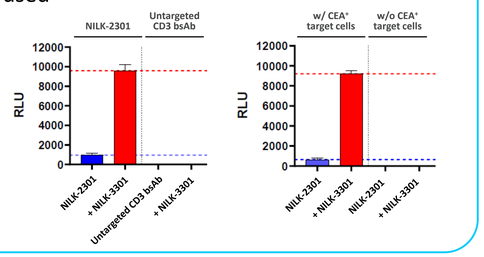
- Bind specifically to **CEA positive** cells (different epitopes, i.e., non-competing)
- High affinity, **drives the specificity**

- Modified to **avoid FcγR-binding** whilst **maintaining FcRn engagement**
- **Fully human** IgG1

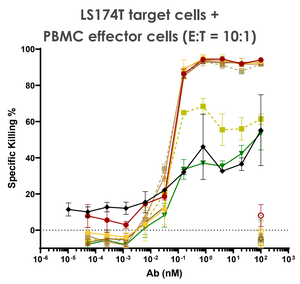
NILK-3301 IS NOT SUPERAGONISTIC

- Superagonistic activity of NILK-3301 was excluded in *in vitro* T-cell proliferation, for both CD4⁺ (left panel) and CD8⁺ (not shown) T-cells, as well as activation assays (right panel).
- The superagonistic monoclonal anti-human CD28 antibody (IgG4κ) TGN1412 (Theralizumab) was used as comparator.
- NILK-3301 activates T-cells only in the presence of primary T-cell stimulation (Signal 1; left panel) and CEA-expressing target cells (right panel).





IN VITRO FUNCTIONAL CHARACTERIZATION



- NILK-2301 DR

NILK-2301 DR + NILK-3301 FD:
- + NILK-3301 2 µg/mL
- + NILK-3301 1 µg/mL
- + NILK-3301 0.5 µg/mL
- + NILK-3301 0.1 µg/mL
- + NILK-3301 0.05 µg/mL
- + NILK-3301 0.01 µg/mL
- + NILK-3301 0.005 µg/mL

NILK-3301 FD:
- NILK-3301 2 µg/mL
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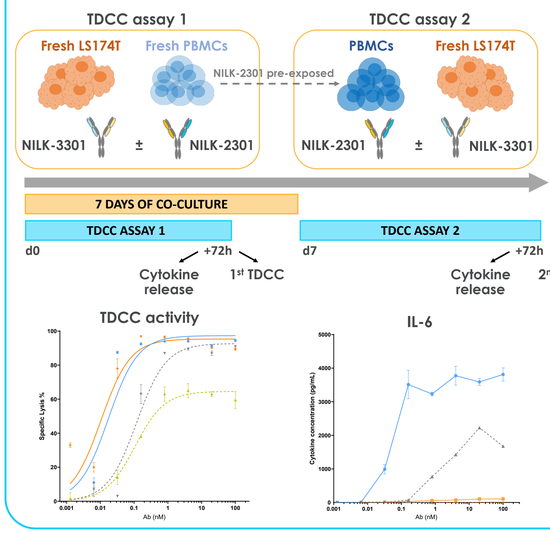
- NILK-3301 0.1 µg/mL
- NILK-3301 0.05 µg/mL
- NILK-3301 0.01 µg/mL
- NILK-3301 0.005 µg/mL

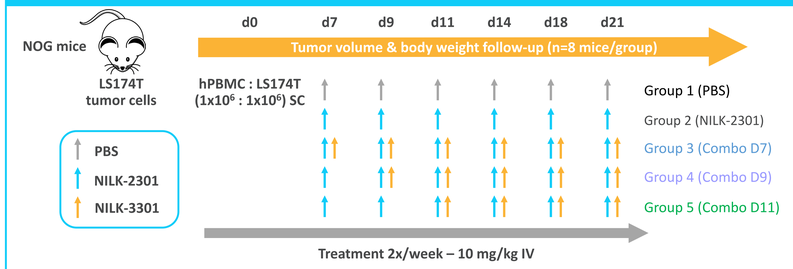
- Maximal cytotoxicity is achieved with NILK-2301 concentrations ≥ 0.8 nM, combined with as little as 0.05 µg/mL [0.33 nM] of NILK-3301.
- Cytotoxicity is reflected by T-cell activation data.

DR, dose range; FD, fixed dose.

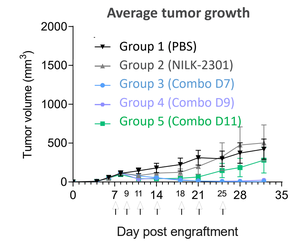


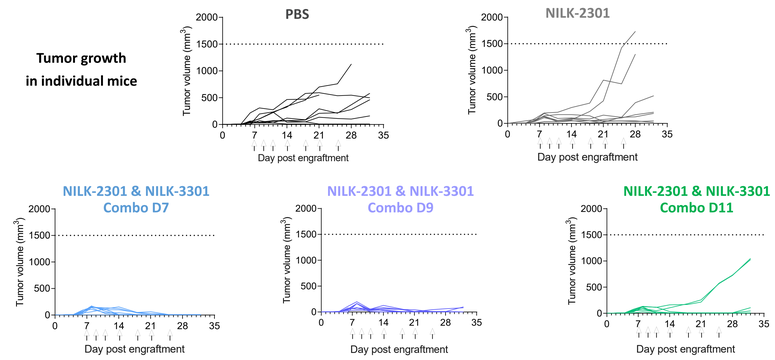
Two-dose assay:
Sequential (NILK-2301 pre-exposed PBMCs) vs. simultaneous NILK-2301 plus NILK-3301 dosing has equal activity at reduced cytokine release.

IN VIVO ACTIVITY



- Simultaneous (Combo D7) and sequential (d+2 [Combo D9] or d+4 [Combo D11]) combination treatment of NILK-2301 plus NILK-3301 induces markedly improved activity and tumor regression in 8/8 (Combo D7), 8/8 (Combo D9), and 6/8 (Combo D11) mice, respectively.





- No signs of toxicity were observed in any of the groups.

Activity was also seen in CD34⁺ humanized BRGSF mice (genOway).

CONCLUSIONS

- NILK-2301 is active as single agent.
- NILK-2301 + NILK-3301 combination treatment significantly increases activity already at low NILK-2301 doses with reduced cytokine release when given sequentially.
- IND-filing for NILK-2301 is expected in Q1/2023.

CONTACT

- https://www.lamkapbio.com/
- dh@lamkapbio.com or as@lamkapbio.com
- Our partner: https://www.lightchainbio.com/

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