GDA-501: ENGINEERED NAM-NK CELLS WITH HER2-CAR EXPRESSION DEMONSTRATE INCREASED CYTOTOXICITY AGAINST HER2-EXPRESSING SOLID TUMORS

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Background Natural killer (NK) cells have generated considerable interest as potential adoptive cell immunotherapy. Ex vivo expansion of allogeneic NK cells using our proprietary nicotinamide (NAM) platform enhances NK cell functionality by preventing cell exhaustion, enhancing cytotoxic activity, generating a protective effect against oxidative stress, and exhibiting improved homing to lymphoid tissues. These attributes provide opportunities to enhance the therapeutic potential of NK cells in the clinic.

The success of immunotherapy in solid tumors has been limited due to several barriers, including immunosuppressive tumor microenvironment, inefficient trafficking, and heterogeneity of tumor antigens. A number of therapeutic approaches to overcome these limitations have emerged.

Gene modification strategies of NK cells may further enhance their functionality and provide a promising next-generation immunotherapeutic tool. The use of chimeric antigen receptors (CARs) can target specific antigens on tumors. Human epidermal growth factor receptor 2 (HER2)-CAR may be used to target HER2+ solid tumors, such as breast, gastric, and ovarian carcinomas.

Methods HER2-CAR-NK cells were developed based on a single-chain variable fragment (scFv) of the widely used humanized monoclonal antibody trastuzumab. To construct our HER2-CAR-NK cells, we used the same binding domain present in trastuzumab, and designed different constructs in a modular way, optimized by modifying the hinge, transmembrane, and cytoplasmic domains with NK cell-related activating molecules to specifically enrich the cytotoxicity of NK cells.

Results Our engineered HER2-CAR NAM-NK cells (GDA-501) displayed significantly enhanced in vitro cytotoxicity when co-cultured with HER2+ target cells such as ovarian adenocarcinoma cell line SKOV3. Elevated levels of the degranulation marker CD107a and proinflammatory cytokines including interferon (IFN)-γ and tumor necrosis factor (TNF)-α were observed, signifying increased potency of GDA-501 compared with control cells. Furthermore, increased cytotoxicity and potency persisted for up to 5 days post electroporation.

The specificity of the cytotoxic effect was evaluated. No significant elevation of HER2-CAR NK cell activation was detected when cultured with HER2- tumor cell lines or normal lymphocytes.

Conclusions GDA-501 is a genetically modified NAM-NK targeting HER2. By optimizing downstream signaling, we were able to directly enhance NK cell activity. In vitro data demonstrated potent cytotoxicity against HER2-expressing cells. These results suggest that GDA-501 represents a unique allogeneic cell therapy potentially targeting HER2+ solid tumors.

Ethics Approval For the present study NK cells were collected from peripheral blood leukapheresis of individual donors. Ethics approval has been obtained from the local ethics committee (EC) at each of the sites (Hadassah Medical Center [0483-16-HMO], Rambam Medical Center [0641-18-RBM], Ichilov Sourasky Medical Center Tel-Aviv [0025-17-TLV]) prior to any study related activities.

The working procedures of the EC at the sites for conduct of clinical studies are in due compliance with local regulations (Israeli Ministry of Health) and provisions of Harmonized International Guidelines for Good Clinical Practice. Sites follow EC conditions & requirements in terms of submissions, notifications, and approval renewals. Participants gave informed consent (approved by the EC) before taking part in the study. Informed consent has been approved by the ECs. The Israeli template of informed consent is in used and it includes study specific information (e.g. study goal, design, method, duration, risks, etc.).