790 DSP502 — A NOVEL APPROACH FOR TARGETING TIGIT AND PD1 PATHWAYS FOR CANCER IMMUNOTHERAPY

[1]Ayelet Chajut*, [1]Shirley Greenwald, [2]Matthew Weber, [1]Ami Tamir, [1]Iris Pecker, [1]Rinat Tabakman, [1]Lucy Ganthous, [1]Liat Tamir, [1]Roy Kahn, [1]Jasmine Avichzer, [1]Alexandra Aronin, [3]Elina Zorde-Khvalevsky, [3]Amnon Peled, [4]Michal Michal Elhalel Dranitzki, [1]Adam Foley-Comer, [2]Mark Tykocinski. *[1]Kahr Medical Ltd., Jerusalem, Israel; [2]Thomas Jefferson University, Philadelphia, PA, United States; [3]Hebrew University Hospital, Jerusalem, AZ, Israel; [4]Hadassah Medical Center, Jerusalem, Israel*

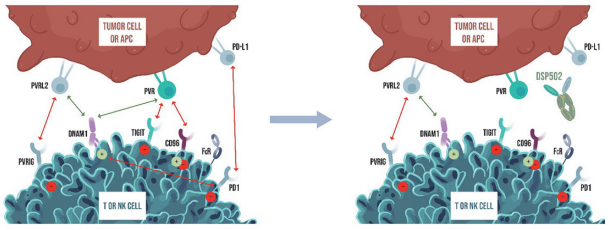
Background TIGIT, an inhibitory immune checkpoint, is a target of interest for immuno-oncology combination therapies. TIGIT is part of a complex molecular network containing four receptors (DNAM1, TIGIT, PVRIG and CD96) and two ligands (PVR and PVRL2). Here we describe Dual Signaling Protein 502 (DSP502), a novel, multi-functional IgG1-Fc-fusion protein targeting this molecular pathway in a unique way. DSP502, comprising the extracellular domains of TIGIT and PD1, is designed to simultaneously bind its two respective ligands, PVR and PD-L1, overexpressed on cancer and myeloid cells in the tumor microenvironment. DSP502 binds PVR preventing inhibitory signaling through TIGIT and CD96 and promoting DNAM1 costimulatory signaling on activated T- and NK-cells. DSP502's PD1 arm binds PD-L1 to unleash effector T-cells through checkpoint inhibition. In parallel, DSP502's IgG1-Fc delivers an immune-activating signal via Fc receptors. The net effect is enhanced anti-tumor immunity (figure 1).

Methods DSP502 heterodimer was successfully produced in a mammalian expression system. DSP502 was evaluated for binding to its cognate ligands on cells and in ELISA-based assays, with and without competing antibodies. NK and PBMC killing activity were evaluated against human K562 CML cells overexpressing PVR. Simultaneous binding of DSP502 to fluorescently-labeled tumor and NK-cells was evaluated by FACS. In vivo activity of DSP502 was evaluated in a humanized NSG A549 NSCLC xenograft mouse model.

Results Both DSP502 arms were shown to bind their cognate ligands in ELISA and on cell surface. DSP502 binding was dependent on the presence of both ligands on cells and was abolished by competing antibodies to the respective targets, demonstrating binding specificity and the 'AND-gate' phenomenon. Overexpression of PVR reduced the sensitivity of K562 cells to NK-cell mediated killing, while DSP502 treatment restored it as measured by target cell killing and granzyme-B secretion. Increased, dose-dependent, complexation of NK- and tumor cells was observed following DSP502 treatment and was abolished by both PVR and FcR antibodies. Treatment with DSP502 markedly inhibited tumor growth of A549-NSCLC xenograft in a humanized NSG mouse model, with all mice being tumor-free at the end of the experiment, compared to control PBMC-injected mice.

Conclusions Here we report the design and function of a novel immunotherapeutic fusion protein, DSP502, that offers multiple functionalities that can coordinately and synergistically drive anti-tumor immunity. Beyond targeting PVR and PDL1, DSP502 has the potential to additionally impact the TIGIT pathway through its effects on CD96 and DNAM1. DSP502 is currently in IND-enabling studies and CMC development.

Ethics Approval The study was conducted at the Authority of Biological and Preclinical Models, the Hebrew University of Jerusalem, Ein Kerem, Sharet Specific Pathogen-Free (SPF) Unit under the Hebrew university ethic committee board approval (number MD-19-15815-5).



Abstract 790 Figure 1

http://dx.doi.org/10.1136/jitc-2021-SITC2021.790