434 TARGETING THE EXPRESSION OF NEUROPILIN-1 BY LOCKED NUCLEIC ACID MODIFIED ANTISENSE OLIGONUCLEOTIDES RESULTS IN POTENT ANTI-TUMOR ACTIVITY IN VIVO

[1]Richard Klar*, [2]Clara Seger, [2]Nicole Kirchhammer, [1]André Maaske, [1]Julia Festag, [2]Laura Fernandez Rodriguez, [2]Mélanie Buchi, [1]Monika Schell, [1]Stefanie Raith, [1]Sven Michel, [2]Alfred Zippelius, [1]Frank Jaschinski. *[1]Secarna Pharmaceuticals GmbH & Co. KG, Planegg / Martinsried, Germany; [2]University Hospital Basel, Basel, Switzerland*

Background Despite the remarkable success of immune modulating cancer therapies, the majority of patients does not benefit from the currently available therapies. Therefore, there is a high need for the identification of novel therapies targeting cancer-induced immunosuppression.

The membrane-bound protein neuropilin-1 (NRP1) is a molecule with diverse functions and interaction partners that has been shown to contribute to tumor cell migration and survival as well as neoangiogenesis. Furthermore, NRP1 contributes to the suppressive capacity of immune cells like e.g. tumor associated macrophages and regulatory T cells. As the different functions of NRP1 are mediated by multiple domains of NRP1, there is a conceptual advantage to downregulate the expression of the whole protein over the functional or steric blockade of individual domains e.g. by monoclonal antibodies.

Methods We used our in-house Oligofyer™ bioinformatics system to design human and mouse Nrp1-specific antisense oligonucleotides (ASOs). The ASOs were modified in the flanks with locked nucleic acids to increase stability and affinity to the target RNA. RNA knockdown efficacy in vitro was investigated in different cells without the use of a transfection reagent. We furthermore investigated the anti-tumor activity of selected mouse Nrp1-specific ASOs in different syngeneic mouse tumor models after systemic administration of unformulated ASOs. In vivo target knockdown in different cell types was investigated by flow cytometry.

Results Treatment of different cell types with LNA-modified ASOs in vitro led to downregulation of NRP1 mRNA as well as protein expression by >85%. Systemic treatment of immune-competent tumor bearing mice with mouse Nrp1-specific ASOs without the use of a delivery reagent strongly delayed tumor growth or completely eradicated tumors. Furthermore, long-term anti-tumor immunity has been observed in immune-competent responder mice after re-challenge with tumor cells. The anti-tumor effects were almost completely absent in immune-compromised NSG mice.

Conclusions Our encouraging results indicate that downregulation of NRP1 with LNA-modified ASOs has the potential to become a promising treatment option for patients in the future. Currently, further studies are performed to investigate therapeutic activity in additional tumor models, combination therapies as well as to fully elucidate the mechanisms that underlie the observed anti-tumor efficacy of ASO-mediated NRP1 downregulation.

http://dx.doi.org/10.1136/jitc-2022-SITC2022.0434