1440 ARGINASE-1 PEPTIDE-BASED VACCINE IS AN EXCITING APPROACH TO MODULATE THE TUMOR MICROENVIRONMENT AND DRIVE EFFICACY IN PRECLINICAL TUMOR MODELS

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Background Arginase-1 (ARG1) regulates tumor cells immune escape through various mechanisms in the tumor microenvironment (TME) and is being targeted experimentally in the clinic. However, selective and efficacious inhibitors of ARG1 remain elusive. Vaccination against TME targets have shown to be an exciting therapeutic approach where an IDO1/PD-L1 dual vaccine has shown substantial activity in early trials in melanoma[1] (and confirmatory Ph3 trial underway NCT05155254). We previously showed that vaccination against ARG1 increases anti-tumor activity preclinically.[2] Here we set out to develop a biological rationale for an ARG1 vaccine as a monotherapy or in combination with other immune therapies and understand the underlying mode of action of the treatment.

Methods ARG1 expression was examined by multiplex immunofluorescence in a tumor microarray (TMA) panel of cancer indications with a hyperplexed visualization of multiple markers on a single section. Vaccination was evaluated in mouse models expressing ARG1. Mice were inoculated with tumor cells and treated with ARG1 peptides. Tumor growth was monitored, organs and tumor samples were collected. Histopathological examination was performed on multiple tissues. Vaccine activity was determined per IFNgamma Elispot assay on splenocytes. Tumor samples were processed, RNA sequencing and flow cytometry analysis of the immune infiltrate were conducted.

Results The TMA analysis confirmed ARG1 expression in the TME and revealed that a distinct immune suppressive population of cells in the TME expresses it independently of IDO1/PD-L1 providing a rationale for combining the vaccines. ARG1 surrogate peptides of 20 amino acids ($ARG1_{261-280}$, $ARG1_{191-210}$) were identified and selected based on the induction of ARG1-specific IFNgamma recall responses in BALB/c or C57BL/6 animals. Both peptides demonstrated anti-tumor activity in vivo. This was associated with increased infiltration of CD45+cells, CD3+ and CD4+ T-cells at tumor site. The anti-tumor effect was enhanced when ARG1 treatment was combined with anti-PD-1 mAb, and/or in combination with a the dual IDO1/PD-L1 vaccine. Detailed efficacy results in the models will be discussed in addition to the cellular and molecular analysis of the tumors in the various cohorts and treatments elucidating the mode of action of the treatment.

Conclusions ARG1 is an attractive TME target and vaccination against it drove efficacy in vivo by increasing the recruitment of immune cells at tumor site thus changing from an immunosuppressive to a pro-inflammatory microenvironment. These data support the preclinical development of an ARG1 vaccine for the treatment of multiple solid tumors.

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Ethics Approval All animal experiments were reviewed and approved by the Danish Animal Experimentation Council and performed under license number 2018-15-0201-01395.

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