Background Immune modulatory vaccines (IMVs) are a novel therapeutic treatment modality that aims to activate anti-regulatory T cells (anti-Tregs).1 Anti-Tregs recognize HLA-restricted epitopes derived from proteins like IDO, PD-L1, Arginase and TGFβ, expressed by regulatory cells.2 TGFβ is a key molecule involved in immunosuppression and fibrosis, which is elevated in the tumor microenvironment (TME) of e.g. pancreatic cancer (PC). TGFβ may thus prevent the clinical response to immune checkpoint inhibitors (ICI). In the present study, we are investigating the effect and mode of action of TGFβ-based IMVs in murine models and in patients with PC.3–5

Methods The characterization of immune responses against TGFβ was performed by cytokine release assays, flow cytometry, gene expression analysis of blood samples and biopsies from pancreatic cancer patients before and during application of immunotherapeutic approaches. Specific T-cells were isolated from blood. The therapeutic effects and the TME modulation of TGFβ-based IMVs were examined in murine models of cancer and in an ongoing clinical trial at Herlev and Gentofte Hospital, Denmark (EudraCT 2022–002734-13).

Results TGFβ-specific T cells reacted towards cancer cells of different origin as well as autologous, regulatory immune cells in a TGFβ-dependent manner. Patients with a strong TGFβ-specific immune response at ICI/radiotherapy treatment initiation had longer progression-free and overall survival, compared to patients with a weak or no TGFβ-specific immune response. Mimicking a TGFβ-vaccination in vitro, we showed that repeated stimulations with the TGFβ epitope expanded specific T cells. In a murine model, TGFβ-based IMVs control tumor-growth of PC by polarizing its cellular composition towards a more pro-inflammatory phenotype. This polarization is mediated by different kind of modulation of cells of the TME; direct (by specific T-cell recognition) and indirect (by change in microenvironment). Clinical and immunological monitoring of patients with PC vaccinated with a TGFβ-based IMV in combination with ICI/radiotherapy are ongoing.

Conclusions Our data illustrate the ability of a TGFβ-based IMVs to elicit antigen-specific immunosurveillance in PC. We show that the TGFβ-based IMV targets immunosuppression and fibrosis in the TME by polarizing the cellular composition towards a more pro-inflammatory phenotype. TGFβ-specific proinflammatory T-cells was associated with clinical benefit and improved survival after ICI/radiotherapy for patients with PC. Our data suggest that combining TGFβ-based vaccination in combination with ICI/radiotherapy will be beneficial for patients with PC.

REFERENCES


Ethics Approval Buffy coats from healthy donors were attained anonymously from the blood bank at Rigshospitalet, Copenhagen, Denmark. The usage of anonymized biological material does not require approval from an ethics committee according to Danish Law. Patients were included in the Danish BIOPAC study ‘Biomarkers in Patients with Pancreatic Cancer’ (ClinicalTrials.gov identifier: NCT03311776). The Protocol and informed consent form were approved by an independent ethics committee before the study commenced. Both written and verbal informed consent were obtained from all participants. This study followed the CONSORT reporting guidelines. Animal experimental procedures were conducted according to Federation of European Laboratory Animal Science Association (FELASA) guidelines and under licenses issued by the Danish Animal Experimentation Inspectorate.