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166 MUCOSAL-ASSOCIATED INVARIANT T-CELLS (MAIT) IN PANCREATIC CANCER

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Background Immunotherapy has changed the standard of care for multiple cancers; however, its efficacy is limited. Chemo-therapy and radiation had little effect in pancreatic ductal adenocarcinoma (PDAC) outcome in patients with metastatic disease, hence the urgency for new effective courses of treatment. Increasing evidence suggests mucosal-associated invariant T-cells (MAIT) play a role in anti-cancer T-cell responses, by recognizing transformed cells or bacterial products. MAIT respond towards microbial antigens and vitamin derivatives, produce pro-inflammatory cytokines and have been found present in primary and metastatic cancer lesions. Long-term survival PDAC patients present a unique microbiome pattern. In contrast, some microbial species may promote oncogenesis. The focus of this project is the characterization of MAIT as immune effector cells in PDAC specimens.

Methods We performed a retrospective analysis of long-term survivors (LTS) and short-term survivors (STS) patients with pancreatic cancer associating clinical endpoints with the presence of MAIT infiltration in the tumor tissue using immuno-fluorescence staining for MR1 (MHC class I-related gene, a MAIT ligand receptor), CD3 and TCR Vγ9Vδ2 (frequently reported chain in MAIT). Tumor infiltrating lymphocytes (TILs) were expanded and tested for recognition of microbial products presented to TILs or to PBMCs defined by cytokine production (ELISA), cytotoxicity (CD107a induction assay), production (TNFalpha). This allows to explore MAIT TCRs for adoptive therapies or distinct microbial species that drive clinically relevant responses.

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Ethics Approval This study was approved by the Champalimaud Foundation Ethics Committee and by Ethics Research Committee of NOVA Medical School of NOVA University of Lisbon.

Consent For each patient, written informed consent and approval by the Ethical Committee of the Champalimaud Foundation will be obtained. The study will be in compliance with the Declaration of Helsinki.

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167 B-CELL-BASED VACCINATION ELICIT POTENT IMMUNITY AGAINST GliOBLASTOMA

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Background Despite the tremendous effort in basic, translational and clinical research, the standard-of-care of patients with glioblastoma (GBM) has been virtually unchanged for the past two decades, aside from tumor-treating fields. GBM is one of the immunologically ‘coldest tumors’ where T-cell exclusion is at its maximum, and myeloid infiltration predominates. This is due to profound immunosuppression, the metabolically hostile microenvironment, and the low mutational burden of these tumors. Together, these barriers have hindered the development of effective immunotherapies. With the goal of exploring ways to boost anti-GBM immunity, we developed a B-cell-based vaccine (BVax) that consists of 4-1BBL+ B cells activated with CD40 agonism and IFNgamma stimulation.

Methods Studies on B-cell-driven inflammation have identified a subset of B cells expressing the co-stimulatory marker 4-1BBL (or CD137L) capable of enhancing CD8+ T-cell anti-tumor cytotoxicity. Such activation was achieved through multiple mechanisms, including antigen presenta-tion, T-cell co-stimulation (4-1BBL and CD86), and cytokine production (TNFalpha). Thus, 4-1BBL+ B cells could be utilized to boost anti-tumor CD8+ T-cell response. In order to stabilize their antigen presentation function in-vivo and avoid potential immunosuppressive functions, we activated 4-1BBL+ B cells using CD40 and IFNgamma receptor (IFNgR) ligation (designated as BVax, figure 1A). Both of which were effective to enhance B-cell-mediated antigen presentation (figure 1B-E). In the present study, we explored the ability of BVax to inhibit GBM growth by promoting tumor-specific CD8+ T-cell immunity and production of tumor-reactive antibodies. BVax’s therapeutic effectiveness was examined both alone and in combination with radiation and checkpoint blockade.

Results BVax migrate to key secondary lymphoid organs and are proficient at antigen cross-presentation (figure 2A), which...