Predictive *in vivo* evaluation of immunotherapy efficacy: tHIS is a reliable model

08/11/2021

Although working in different therapeutic areas, all researchers worldwide have a common goal: gather knowledge and data to ultimately help patients. One major difficulty–obstacle, even–encountered to reach this goal is the poor translatability of preclinical results to the clinic. To overcome this challenge, the development of optimized and reliable preclinical models is of utmost importance. In oncology, different labs are working on a specific approach: to create an avatar of a specific patient to test the efficacy of possible treatments.[1, 2] In the field of immuno-oncology, the translatability of preclinical models can be particularly tricky as, ideally, both the tumors and immune system should be faithfully represented to properly transpose to the clinic.

In 2020, Lang et al. showed that a patient-derived xenograft (PDX) in a human immune system (HIS) reconstituted mouse model can be used to test immunotherapy efficacy in adrenocortical cancer.[3] The preclinical model used in this study consisted of the xenograft of a patient-derived adrenocortical tumor into BRGS-HIS mice, i.e., mice with a reconstituted human immune system through human cord blood cells injection. Tumor-bearing mice were treated with pembrolizumab, a PD-1 checkpoint inhibitor, to assess its effect on tumor growth and human immune cells. Data showed that pembrolizumab significantly inhibited tumor growth (Fig.1A), correlating with an increased frequency of $CD8^+$ T cells in the tumor (Fig.1B), but not in peripheral lymph organs (not shown). Further analysis showed that these infiltrated $CD8^+$ T cells exhibited increased activation ($HLA\text{-}DR^+$ staining) and cytotoxic production of Granzyme B (GrB^+ staining; Fig.1C). Additionally, an increased frequency of $Tim3^+$ T cells was observed, together with

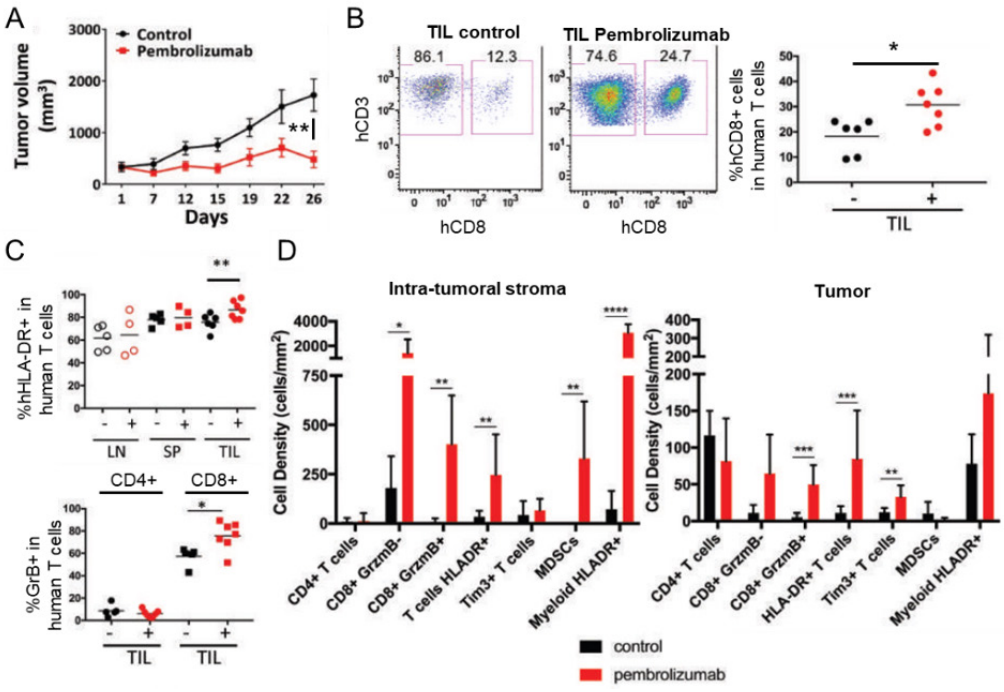

Figure 1: Pembrolizumab treatment reduced tumor growth with increased activated immune cells in tumors and intra-tumoral stroma. Tumor growth was impaired in pembrolizumab-treated mice (A). Frequency of $CD8^+$ T cells was increased in treated tumors (B), with a specific increase in $HLA\text{-}DR^+$ activated T-cells and cytotoxic GrB^+ T-cells (C). Using multispectral immunohistochemistry, the density of cells for each indicated cellular phenotype (D) was determined for intra-tumoral stroma regions (left) or tumor regions (right). LN: lymph nodes, SP: spleen, TIL: tumor infiltrating leukocytes. P values: *< 0.05, **< 0.01, ***< 0.001, ****< 0.0001. Adapted from Lang et al., *J Clin Endocrinol Metab*, 2020.

a decreased percentage of Tim3$^+$ myeloid cells in the tumor (data not shown). These data were confirmed by quantitative multispectral immunohistochemistry, further showing that PD-1 blockade increased immune infiltrate in the tumor microenvironment (Fig.1D). Indeed, most immune cells were found in the intra-tumoral stromal regions, with pembrolizumab treatment inducing increased CD8$^+$, myeloid-derived suppressor cells (MDSCs) and activated myeloid (HLA-DR$^+$) cells in the intra-tumoral stroma, together with increased CD8 cytotoxic cells (Granzyme B$^+$) and activated T cells (HLA-DR$^+$) in both intra-tumoral stroma and tumor.

In parallel to these analyses, and most interestingly, the patient from whom the initial tumor originated was treated with anti-PD-1 therapy on a compassionate basis. In pretreatment analyses by multispectral immunohistochemistry showed changes in immune markers similar to that observed in the animal model (Fig.2A). Two metastatic target lesions were followed over 16 months of pembrolizumab treatment and underwent significant decrease in size (Fig.2B), representing a remarkable response.

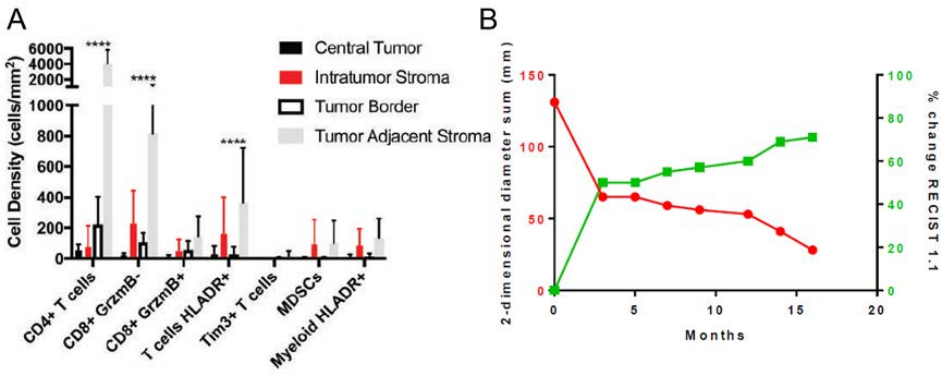

Figure 2: Corresponding patient responded to pembrolizumab treatment. Pretreatment multispectral immunohistochemistry of patient's lesion (A) showed similar changes in immune markers to that observed in the animal model. Target lesions were followed by CT imaging studies and measured per RECIST 1.1 criteria (B), showing a remarkable response. P values: ****< 0.0001. Adapted from Lang et al., *J Clin Endocrinol Metab*, 2020.

Taken together, these data showed that this preclinical model, a PDX-bearing HIS mouse, can be used as a predictive tool for immunotherapy treatment, i.e. as an avatar of the patient. This can be particularly useful to define and study the mechanisms and biomarkers associated with response and/or resistance to immunotherapies.

An optimized version of the mouse model used in this study, the BRGSF-HIS mouse, is available at genOway, designer and provider of multiple preclinical models in several research areas including immuno-oncology, metabolism, cardiovascular diseases, and neuroscience.

References:

1. Bousquet G, Feugeas JP, Ferreira I, Vercellino L, Jourdan N, Bertheau P, de Bazelaire C, Barranger E, Janin A. Individual xenograft as a personalized therapeutic resort for women with metastatic triple-negative breast carcinoma. *Breast Cancer Res*. 2014 Feb 11;16(1):401.
2. Weroha SJ, Becker MA, Enderica-Gonzalez S, Harrington SC, Oberg AL, Maurer MJ, Perkins SE, AlHilli M, Butler KA, McKinstry S, Fink S, Jenkins RB, Hou X, Kalli KR, Goodman KM, Sarkaria JN, Karlan BY, Kumar A, Kaufmann SH, Hartmann LC, Haluska P. Tumorgrafts as in vivo surrogates for women with ovarian cancer. *Clin Cancer Res*. 2014 Mar 1;20(5):1288-97.
3. Lang J, Capasso A, Jordan KR, French JD, Kar A, Bagby SM, Barbee J, Yacob BW, Head LS, Tompkins KD, Freed BM, Somerset H, Clark TJ, Pitts TM, Messersmith WA, Eckhardt SG, Wierman ME, Leong S, Kiseljak-Vassiliades K. Development of an Adrenocortical Cancer Humanized Mouse Model to Characterize Anti-PD1 Effects on Tumor Microenvironment. *J Clin Endocrinol Metab*. 2020 Jan 1;105(1):26–42.