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

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-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-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.
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: