

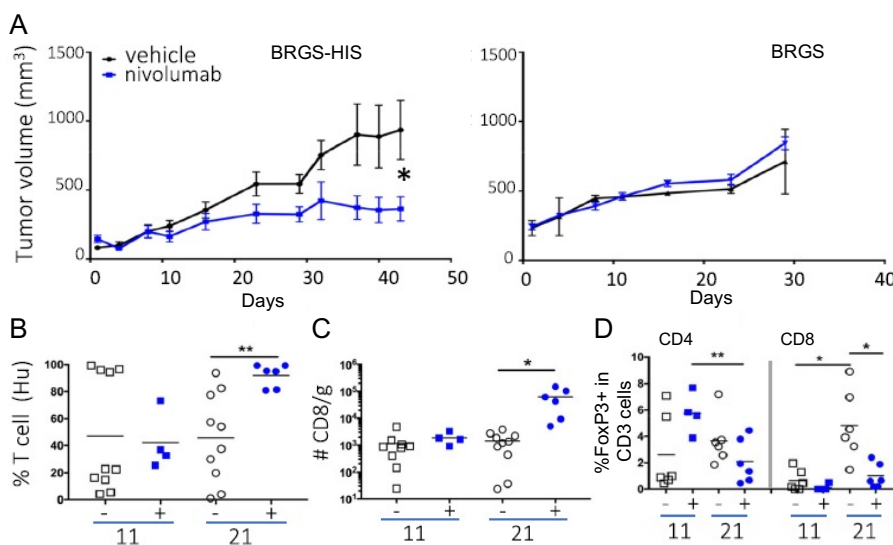
## Immunotherapy efficacy assessment and metastases studies: THIS model is highly permissive to engraftment

A commentary

24/11/2021

Immunodeficient mice reconstituted with a human immune system (HIS) have revolutionized cancer research, becoming the models of election to evaluate immunotherapies in preclinical studies. Compared to conventional murine xenograft models, HIS mice present several advantages, including the possibility to grow more diverse patient-derived tumors, and investigate human tumor-immune system interplay. However, despite the growing range of reconstituted HIS mice available, determining a standard of care for cancer treatment is still complex, illustrating the urgent need for reliable preclinical HIS models that truly recapitulate the anti-tumor immune response heterogeneity observed in clinics.

For example, as accumulating evidences suggests that only a small number of patients with triple-negative breast cancer (TNBC) respond to anti-PD-1 and anti-CTLA-4 immunotherapies, Tentler and colleagues investigated the ability of a novel  $\beta$ -catenin modulator to potentiate the anti-tumor efficacy of both checkpoint inhibitors in immunodeficient reconstituted BRGS-HIS mice engrafted with TNBC cell line xenografts (CDXs).<sup>1</sup> Capasso and colleagues used the same model to investigate the anti-tumor efficacy of anti-PD-1 therapies to TNBC CDXs and patient-derived colorectal cancer xenografts (PDXs).<sup>2</sup> Interestingly, both groups found that BRGS-HIS mice exhibit tumor-specific and reproducible responses, consistent with human clinical trials observations (Fig.1).

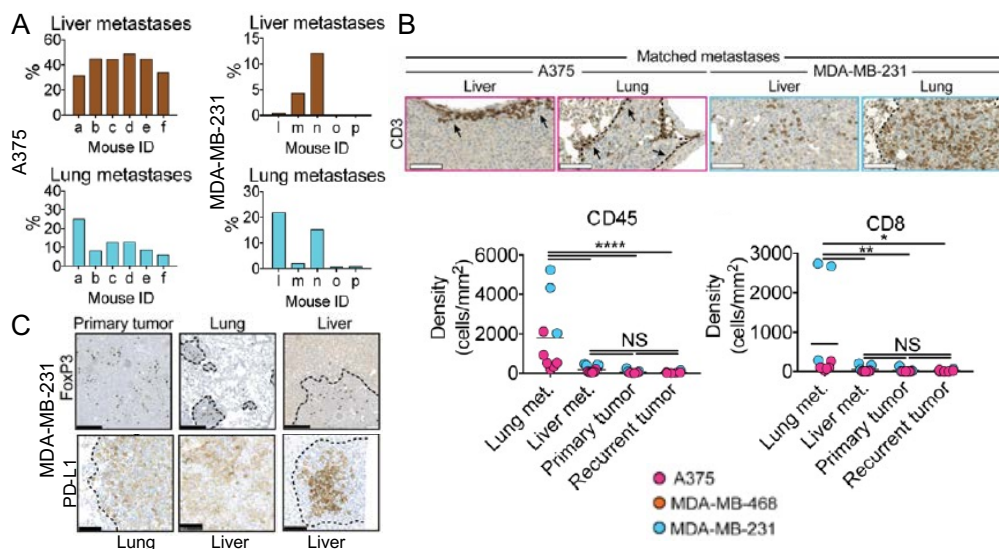


**Fig. 1)** Efficient engraftment of tumor cells for immunotherapy efficacy assessment in BRGS-HIS. A) Anti-PD-1 treatment, nivolumab, has an efficient anti-tumor effect on MDA-MB-231 tumors in reconstituted mice (left), but not in the immunodeficient recipient (right). Immunophenotyping of tumor infiltrates from individual BRGS-HIS mouse untreated (-, black) or treated with nivolumab (+, blue) for 11 or 21 days showed an increase in human T cell (B) and CD8 T cells (C) at D21 upon treatment. An increase in Treg over time was observed in untreated tumors, but abolished in treated mice (D). P-values: \* $< 0.05$ , \*\* $< 0.01$ . Adapted from Capasso et al. *J. immunotherapy cancer* 7, 37 (2019).

Another important advantage of these mice is their ability to exhibit the dynamic interactions between tumor, tumor microenvironment (TME), and human immune system: this is critical to study, predict and overcome potential immunotherapeutic resistance and side effects in clinical applications. In 2021, Marín-Jiménez and colleagues investigated immune infiltration in reconstituted BRGS-HIS mice engrafted with a great variety of tumors (e.g., breast, adrenocortical, lung, colorectal, pancreatic, melanoma and hematological malignancies) and treated with checkpoint blockade and/or other immunotherapies. Importantly, they demonstrated that the TME of engrafted HIS mice varies

by tumor type and combination treatments, mirroring what is observed in humans.<sup>3</sup> Moreover, they found that BRGS-HIS mice recapitulate TME in regard to immune infiltration, similar to what was previously observed using the same model.<sup>4</sup> Taken together, these findings suggest that the BRGS-HIS model represents a reliable tool to study TME complexity and heterogeneity, and its evolution during drug treatment.

Last but not least, BRGS-HIS mice were successfully used to study metastasis development. In 2018, Gammelgaard and colleagues demonstrated that BRGS-HIS mice consistently develop primary tumors that grow close to synchronous (unlike those reported in NSG-HIS animals), form spontaneous metastases (Fig.2A-B), and display immune escape mechanisms (Fig.2C), such as recruitment of Tregs and PDL1 expression by immune and cancer cells, similar to patients.<sup>4</sup>



**Fig. 2)** Metastases development in BRGS-HIS upon CDX engraftment. Primary tumors from A375 consistently yielded multiple large liver and lung metastases (A, left panel), which was occasionally observed with MDA-MB-231 primary tumors (right panel). Tumors derived from the A375 were largely immune-cell-excluding, whereas tumors derived from the MDA-MB-231 cell line were highly infiltrated by human T cells (B, top). Lung metastases from A375 and MDA-MB-231 were significantly more densely infiltrated by CD45<sup>+</sup> (B, bottom left), CD3<sup>+</sup> (not shown) and CD8<sup>+</sup> (B, bottom right) cells than matched primary tumors, liver metastases and recurrent tumors. MDA-MB-231 tumors presented high-density Treg infiltration (FoxP3<sup>+</sup>), but were absent in healthy parenchyma (C, top). MDA-MB-231 metastases contained higher numbers of PD-L1<sup>+</sup> cells than cancer cells, indicating PD-L1<sup>+</sup> immune cell recruitment (C, bottom). P-values: \* $< 0.05$ , \*\* $< 0.01$ , \*\*\*\* $< 0.0001$ . Adapted from Gammelgaard et al. *Mol Oncol* 12, 1797–1810 (2018).

Overall, these results demonstrate that BRGS-HIS mice allow to rapidly test multiple, immune-related therapeutics for tumors originating from unique clinical samples. In addition, this model is ideally suited to assess changes in tumor immunogenicity using different cancer cells and treatments, and to analyze their effects on a human immune response with data from multiple mice, prior to clinical trials. Interestingly, another study also showed that the same preclinical model can be used as a [predictive tool for immunotherapy treatment](#) when engrafted with a patient matched tumor, i.e. as an avatar of the patient.<sup>5</sup>

Taken together, these different publications show that the [BRGS-HIS model, and its upgrade BRGSF-HIS](#), are highly permissive to engraftment and thus represent an optimal model to study and predict human immune responses to immunotherapies *in vivo*.

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:

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