Hera BioLabs

The SRG RAT® Displays More Human Tumor Characteristics and Interactions versus the NSG Mouse: Implications for Safety and Efficacy Testing

Immunodeficient mice are used for several study types including oncology zenograft studies, gene and cell therapy safety testing, and more. While immunodeficient mice have historically been the species of choice for efficacy and toxicology studies, they are not ideal due to small size, low blood volume, short plasma half-lives, and difficulty of surgical procedures.

The immunocompromised Sprague-Dawley rat (SRG RAT®; now commercially available) supports excellent growth of multiple human tissues and tumors (Noto 2020). The SRG rat is an ideal model for toxicity testing; compared to wild-type Sprague-Dawley rats commonly used for safety evaluations, SRG rats have similar background organ/tissue histology, serum chemistries, platelets and hematology, except for the expected lack of T, B, and NK cells and related lymphoid tissue, but with normal levels of monocytes and complement activity (Yong 2023, Walton 2024).

To compare the tumor growth in SRG rats versus NSG mice, we evaluated engraftment rates **(Table 1)** and tumor volume **(Figure 1)** following implantation of the same human tissue or cell preparations. SRG rats showed improved tumor growth and, for patient-derived xenografts (PDX), better engraftment rates versus NSG mice.

Table 1. Engraftment rates in SRG rats and NSG mice

PDX model	Engraftment Rate	
	SRG	NSG
J000096652 lung adenocarcinoma	2/2 (100%)	3/5 (60%)
PDX133 ovarian carcinosarcoma	2/2 (100%)	3/5 (60%)
PDX11 high-grade ovarian serous carcinoma	2/2 (100%)	1/5 (20%)

Next, we compared H&E images of primary patient tumors with those grown in NSG mice and SRG rats using a model PDX human tumor. Although neoplastic cell morphologies were comparable, fibrovascular stroma was denser and more extensively deposited in SRG rats versus NSG mice **(Figure 2)**, indicating SRG rats better model this human tumor morphology.

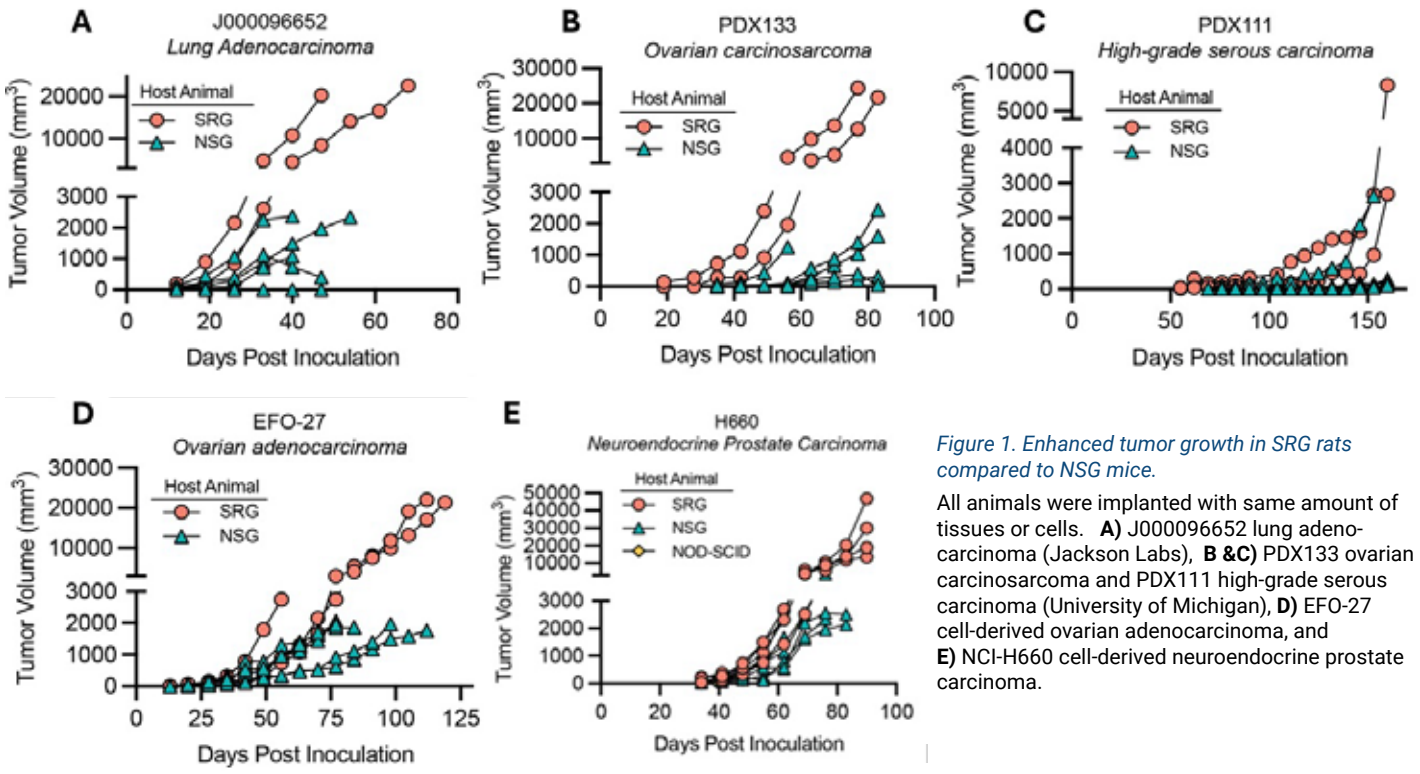

Figure 1. Enhanced tumor growth in SRG rats compared to NSG mice.

All animals were implanted with same amount of tissues or cells. **A)** J000096652 lung adenocarcinoma (Jackson Labs), **B &C)** PDX133 ovarian carcinosarcoma and PDX111 high-grade serous carcinoma (University of Michigan), **D)** EFO-27 cell-derived ovarian adenocarcinoma, and **E)** NCI-H660 cell-derived neuroendocrine prostate carcinoma.

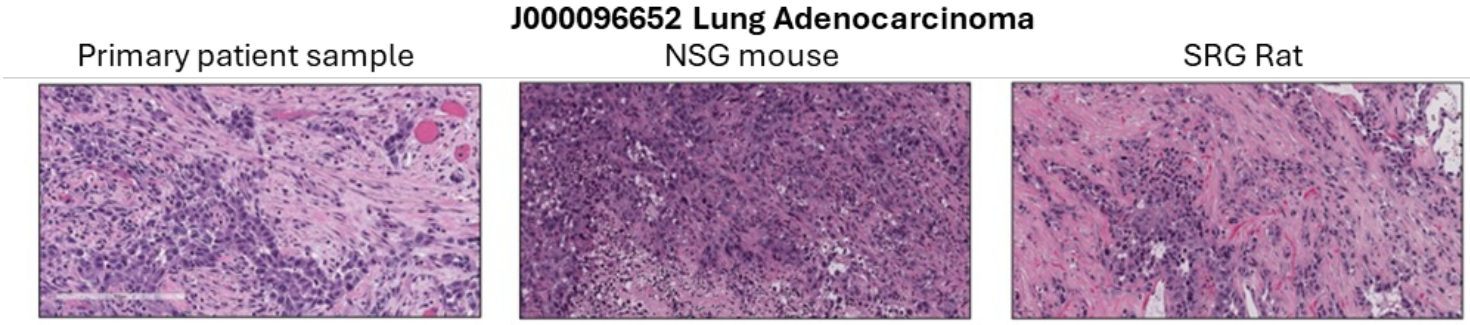

Figure 2: 20X H&E images from primary patient, mouse-grown tumor, and rat-grown tumor.
Compared to mice, PDX grown in SRG rats more closely represent the original patient tumor histology, with increased stromal infiltration (pink) relative to total nuclei (blue) in rats. Original patient tumor images are from Jackson Lab's Mouse Tumor Biology Database.

To understand differences in xenografts grown in SRG rats versus NSG mice, we measured gene expression in NCI-H660 human neuroendocrine prostate tumors. We used the 10x Genomics Xenium Human Multi-Tissue and Cancer panel, which provides spatially resolved expression patterns for 377 genes from tissue sections.

Top differentially expressed genes in SRG rats versus NSG mice from NCI-H660 xenografts are shown in **Table 2**. SRG rat tumors demonstrate higher expression of immune and stroma-related signaling genes along with marked increases in SRG rat macrophage infiltration in stromal regions (**Figure 3**), suggesting signaling between human tumors and SRG rat monocytes/macrophages may support both tumor growth and its morphology.

Table 2. Genes overexpressed in NCI-H660 tumors when grown in SRG rat versus NSG mouse

Gene	Log2Fc	Gene Function
CXCL2	8.23	Leukocyte and hematopoietic stem cell chemotaxis
CFB	5.43	Complement Factor B; alternative complement pathway activiation
TCIM	5.08	Positive regulator of Wnt/beta-catenin signaling
TNFRSF9	3.96	Peripheral monocyte proliferation;immune checkpoint
CAVIN2	3.18	Required for angiogenesis
CYP2B6	2.75	Androgen metabolism; associated with better prognosis
SCGN	2.37	Neuroendocrine marker; associated with relapse following prostatectomy
C15orf48	2.24	Upregulated in some aggressive tumors; macrophage infiltration
LIF	2.13	Inhibits differentiation;JAK/STAT3 activation; poor prognosis
RND1	2.1	Rho family of GTPases; growth factor signaling

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Combined, our data demonstrate that SRG rats support robust growth of multiple human tumor types, display more human-like characteristics, and have enhanced tumor microenvironment interactions relative to NSG mice. These results further highlight the SRG RAT® as a relevant immunocompromised model for safety and efficacy testing.

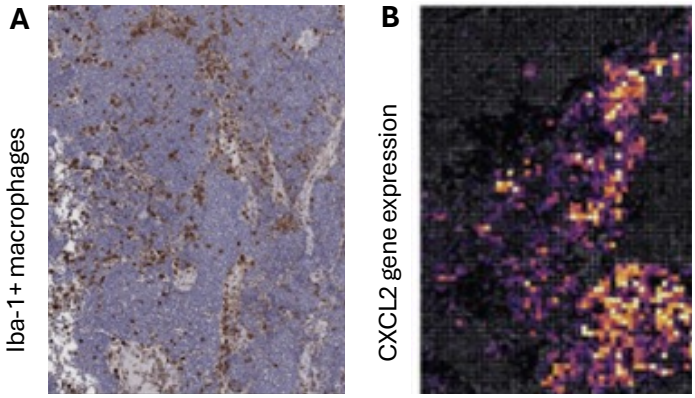

Figure 3. Abundant host animal macrophage infiltration in NCI-H660 tumors grown in the SRG rat.
A) Iba-1 immunohistochemistry stain of rat macrophages showing abundance in stroma-dense areas.
B) CXCL2 human tumor expression is highest in stromal areas with abundant macrophages (from 10x Genomics).

REFERENCES

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