Pharmacology Discovery Services

A Eurofins Discovery Partner Lab

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In Vivo Oncology Models for Drug Discovery

In Vivo and *Ex Vivo* Services to Expedite Preclinical Testing

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About Pharmacology Discovery Services (PDS)

Your Best *In Vivo* Partner to Establish Pre-Clinical Proof-of-Concept

Pharmacology Discovery Services (PDS), a partner lab of Eurofins Discovery, provides a comprehensive collection of validated *in vivo* oncology models to present key decision-making information for allowing test agents to move forward. Our services provide the data clients need to advance their preclinical development programs in a manner that is timely, flexible, and cost-effective. Each model can be customized to meet specific pharmacology needs.

Our *in vivo* oncology models include mouse tumor allografts (syngeneic models) and human xenografts from both cell line-derived (CDX) and patient-derived (PDX) samples. To assess new testing agents for their ability to promote anti-cancer responses, our CDX and PDX models, including subcutaneous and orthotopic formats, have been developed and validated for responses to known standard-of-care treatments. Thus, these models are suitable for the evaluation of efficacious treatment followed by *ex vivo* analysis with different platforms, including flow cytometry, RT-qPCR, ELISA, western blot, histopathology, and bioanalysis.

The carcinoma cell lines used for our CDX models are accessible from global cell banks, including the American Type Culture Collection (ATCC), the Japanese Collection of Research Bioresources Cell Bank (JCRB), and the RIKEN BRC Cell Bank. Through our Partner Lab, Eurofins Discovery, *in vitro* screening with these cell lines is available with OncoPanel™ cell-based screening and profiling, as well as test agents and combinations with BioMAP® Oncology and Immune Oncology Panels in modeling the human tumor microenvironment.

PDS has conducted *in vivo* pharmacology studies for both side-effect profiling and efficacy for over 50 years. We have the flexibility and expertise to develop custom models, and are experienced with small molecules, drug combinations, biologics, nucleic acids, liposomal formulations, nanoparticles, and vaccines.

Your Best *In Vivo* Partner to Establish Pre-Clinical Proof-of-Concept

We provide therapeutically focused disease efficacy models that incorporate biomarkers and outcome measures to enable greater prediction of success in the clinic.

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Overview of *In Vivo* Oncology Services

In Vivo Oncology Model Types

- Murine cell line-derived syngeneic models with immune-competent mice
- Human cell line-derived xenograft models with immune-deficient mice
- Human patient-derived xenograft models with immune-deficient mice
- Humanized mouse models with greater than 25% $hCD45^+$ cells

- Models are available with subcutaneous and orthotopic implantation
- Site-specific tumor implantation for metastatic evaluation is also available

Optimal Measurement Readouts Upon Selection

- Conventional caliper tumor measurements
- Conventional macroscopic metastatic nodules
- *In vivo* imaging with IVIS® Spectrum
- Survival analysis with humane endpoints
- Flow cytometry analysis with leukemia/lymphoma progression
- Histopathology, cytokine, flow cytometry, RT-qPCR, ELISA, and western blot
- Pharmacokinetics (PK) bioanalysis

Flexible Dosing Routes and Schedules

- Administration routes including but not limited to: oral (PO), subcutaneous (SC), intraperitoneal (IP), intravenous (IV), and intratumoral (Itu) injections
- Dosing frequencies include single or multiple doses per day (QD, BID, TID, and QID), per week (QWK, BIW, and TIW), or at a specific number of days for on-and-off dosing (i.e., 3 on/4 off per week)
- Formulation optimization services with customized vehicles
- Dose concentration and frequency optimizations with MTD and PK studies

Customized Models to Tailor Pharmacology Needs

- Collaborate with our technical staff to develop models specific to your needs

Our portfolio is expanding rapidly. To get started, speak to our expert:
ClientServicesPanlabsTaiwan@eurofinsasia.com for availability in your model of interest.

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In Vivo Syngeneic Mouse Models

Syngeneic mouse models with immune-competent mice provide a comprehensive, effective approach for *in vivo* efficacy studies. Our syngeneic mouse models (Table 1) include subcutaneous and orthotopic formats and have been developed and validated for responses to known chemotherapy and immunotherapy treatments, including immune checkpoint inhibitors.

Method Summary

Female immune-competent mice (tumor-originated mouse strain) are subcutaneously implanted with viable murine carcinoma cells at 0.1 mL per mouse. Vehicle and/or test articles are then administered starting on Day 1 when the mean tumor volume reaches 40-80 mm^3 upon randomization at the specified dose administration schedule. Prophylactic treatment can be implemented prior to tumor implantation or after a specified number of days (from 1 to 5) post-tumor implantation. The tumor volume and body weight are measured twice per week during the study period. The volume of the tumor is calculated according to the prolate ellipsoid formula, which is tumor volume = length x $(width)^2$ x 0.5. Once per week, interim data is provided for decision-making during the study progress.

Validated Syngeneic Models			
Model Name	Item Number	Cell Lines Used in Mouse Model	
Tumor, Syngeneic, Breast, 4T1	578590	ATCC	CRL-2539
Tumor, Syngeneic, Colon, CT26.WT	578600	ATCC	CRL-2638
Tumor, Syngeneic, Colon, MC-38	578620	Kerafast	ENH204-FP
Tumor, Syngeneic, Kidney, Renca	578630	ATCC	CRL-2947
Tumor, Syngeneic, Leukemia, L1210	578650	ATCC	CRL-219
Tumor, Syngeneic, Lung, KLN 205	578680	ATCC	CRL-1453
Tumor, Syngeneic, Lung, LL/2	578700	ATCC	CRL-1642
Tumor, Syngeneic, Lymphoma, A20	578900	ATCC	TIB-208
Tumor, Syngeneic, Melanoma, B16-F0	578800	ATCC	CRL-6322
Tumor, Syngeneic, Melanoma, B16-F10	578810	ATCC	CRL-6475

Table 1. Validated syngeneic models.

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In Vivo Syngeneic Mouse Models

4T1 Syngeneic Model

Triple-negative breast cancer (TNBC) is an invasive breast carcinoma that lacks estrogen receptor, progesterone receptor, and HER2 protein. TNBC is well known for its fast growth rate, high risk of metastasis, high recurrence risk, and difficulty to cure. Examples of therapeutic response data in our TNBC 4T1 models (syngeneic model #578590 and orthotopic model #578591) align with published immune checkpoint inhibitors and paclitaxel response profile (Figure 1). Immune profiling by flow cytometry demonstrates that high myeloid-derived suppressor cells (Figure 2) are found in the 4T1 model. The levels of differential immune cells are accessible with our syngeneic models when determining the host immune response with anti-tumor treatments.

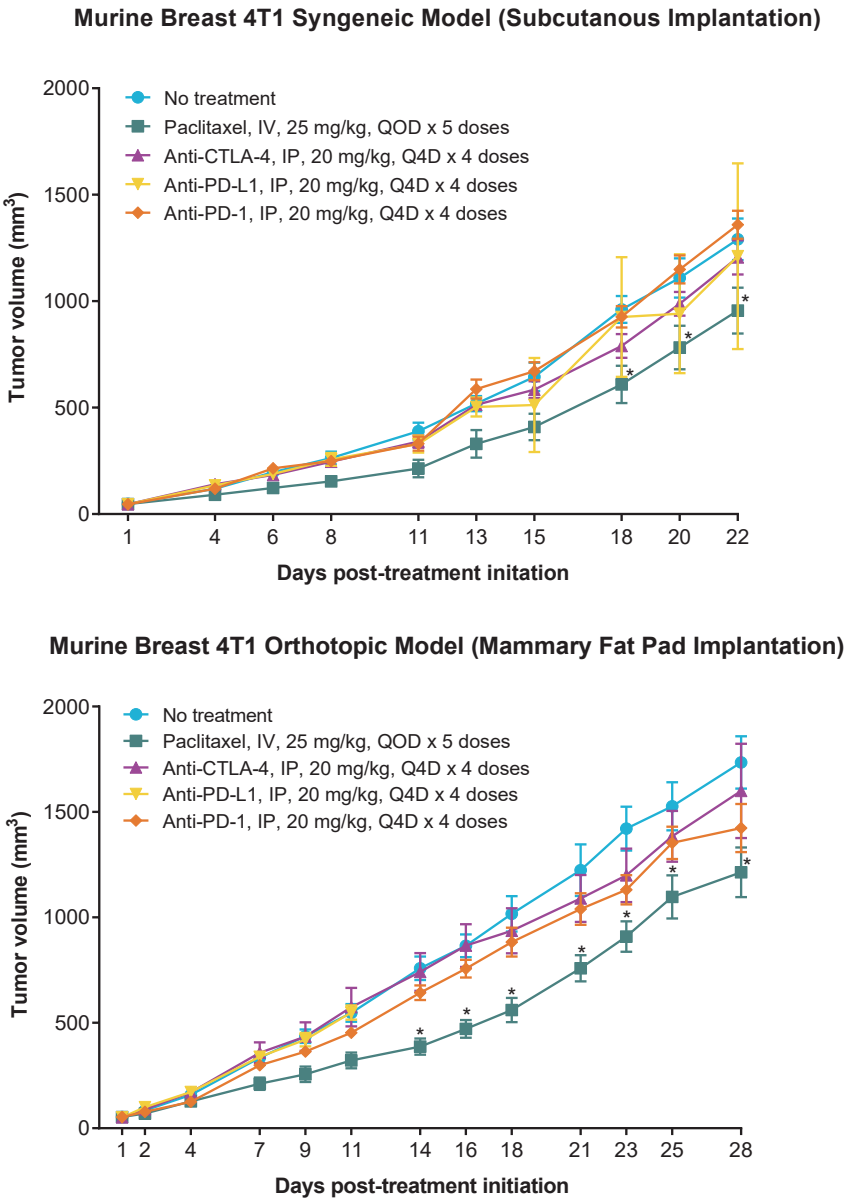

Figure 1. Syngeneic and orthotopic models of triple-negative breast carcinoma 4T1, tumor growth (mm^3) over time (Day). Murine TNBC 4T1 cells, at 1 x 10^5 cells/mouse, were subcutaneously (top panel, #578590) or orthotopically (bottom panel, #578591) implanted into female BALB/c mice. Treatment was initiated on Day 1 upon randomization when the mean tumor volume reached 40-80 mm^3. Chemotherapy, Paclitaxel at 25 mg/kg, was intravenously (IV) administered once every other day (QOD) for a total of five doses. Immune checkpoint inhibitors, mAnti-CTLA-4, mAnti-PD-L1, and mAnti-PD-1, each at 20 mg/kg was intraperitoneally (IP) administered once every four days (Q4D) for a total of four doses. Tumor growth, tumor volume by length x $(width)^2$ x 0.5, was measured thrice per week from Day 1 (treatment initiation) until the study end date. (*): Indicates a significant ($p < 0.05$) reduction in mean tumor volume compared to vehicle control as determined by two-way ANOVA followed by Bonferroni correction. Error bars are SEM values.

In Vivo Syngeneic Mouse Models

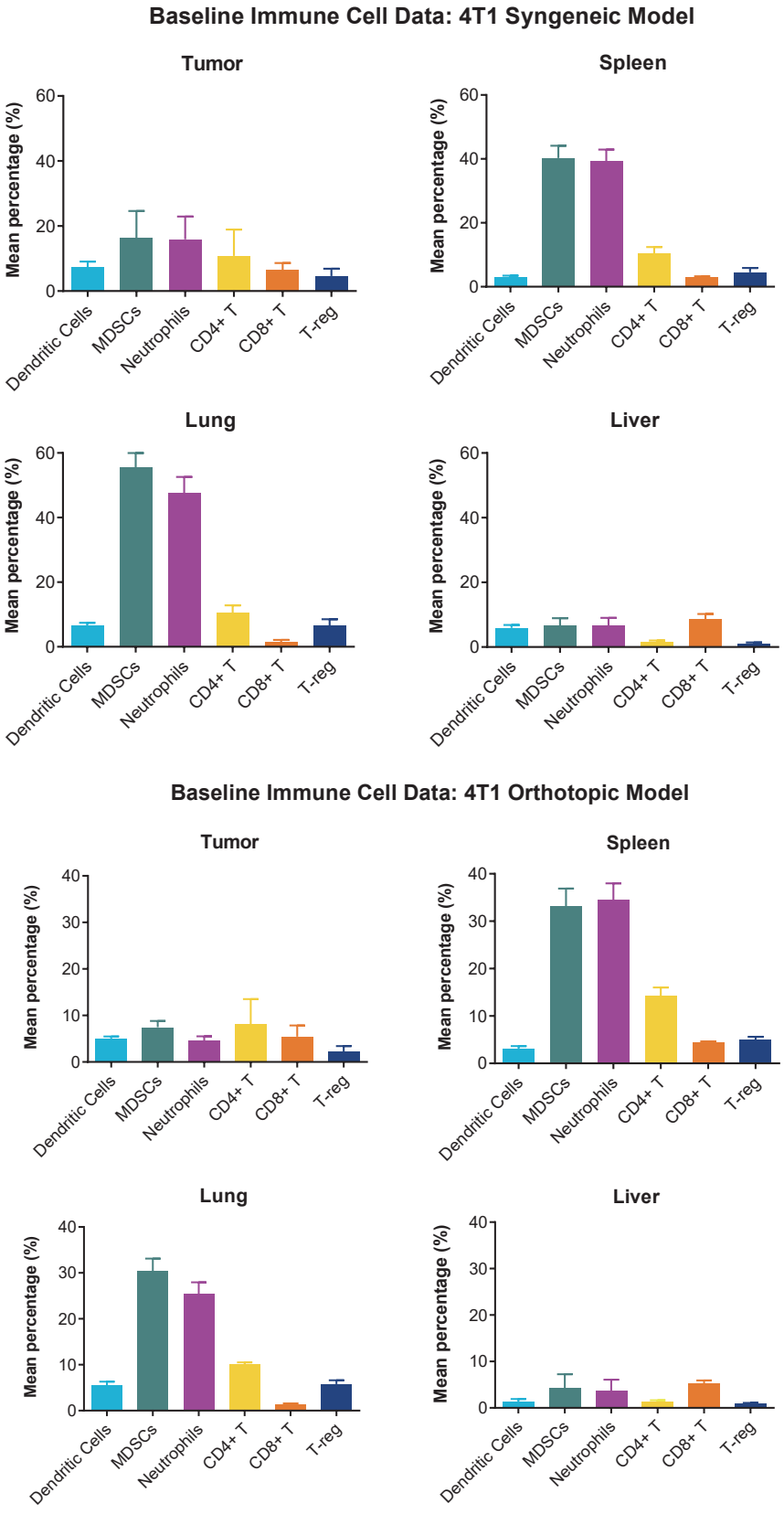

Figure 2. Immune profiling by flow cytometry in tumor, spleen, lung, and liver samples in the murine syngeneic and orthotopic 4T1 models. Murine TNBC 4T1 cells, at 1 x 10^5 cells/mouse, were subcutaneously or orthotopically implanted into female BALB/c mice. The tumor, spleen, lung, and liver tissues were harvested when the tumor volume reached 300 mm^3. No treatment was administered to the animals.

In Vivo Syngeneic Mouse Models

CT26 Syngeneic Model

In addition to different tumor implantation routes and accessible host immune levels, the treatment initiation time can be tailored to meet your pharmacology needs. Our colorectal CT26 syngeneic model (#578600) demonstrates different dose concentrations and efficacious levels when treatment is initiated upon disease establishment (tumor volume at 40-80 mm^3) or at one-day post-tumor implantation (Figure 3). Immune profiling is conducted to analyze tumor-infiltrating leukocytes (TILs) and correlates with prognosis and response to therapy (Figure 4 shows selective data only). Our team is experienced with a variety of single-cell dissociation methods and selection markers, and the procedures and staining panels are customized to meet client needs.

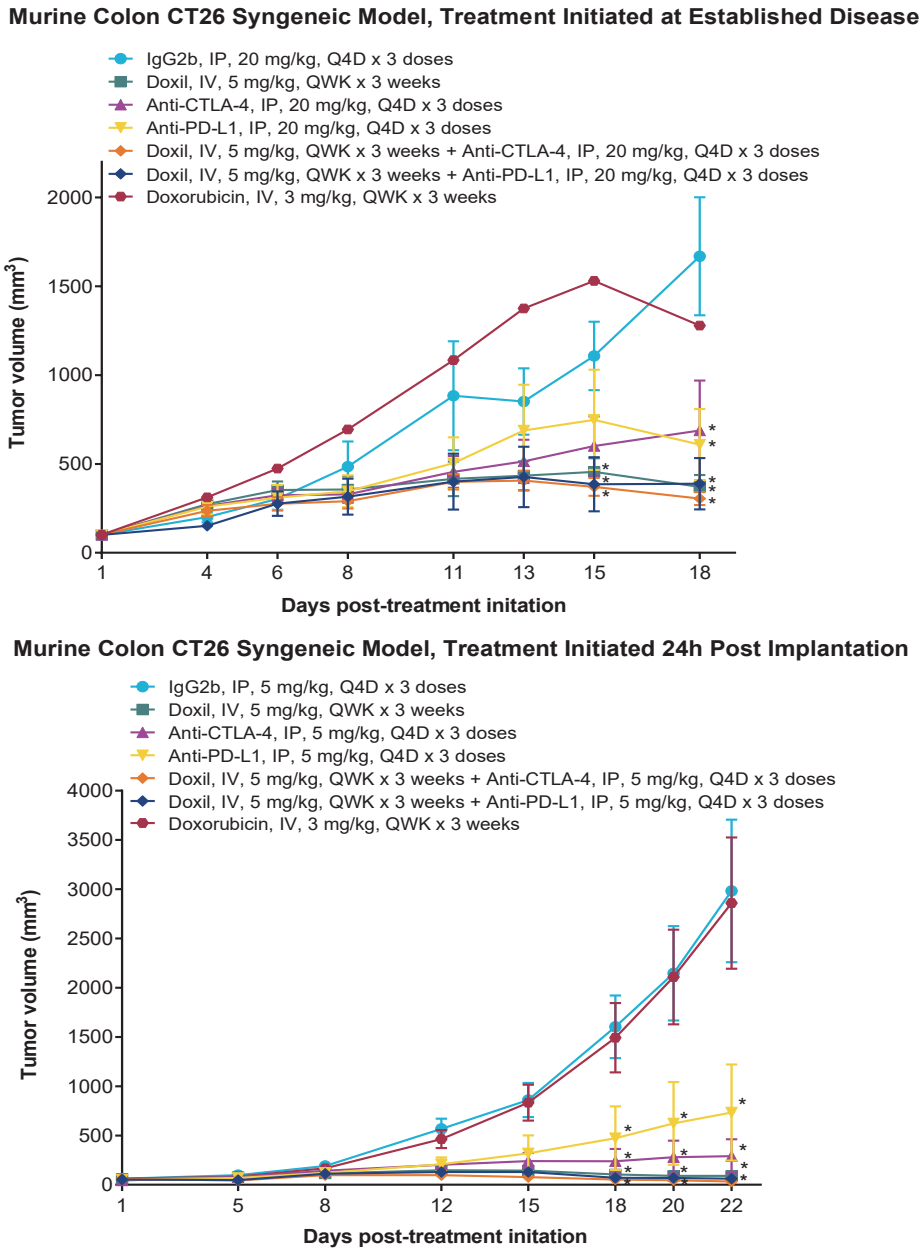

Figure 3. Syngeneic colorectal CT26 model (#578600), tumor growth (mm^3) over time (Day). Murine colorectal CT26 cells, at 1 x 10^6 cells/mouse, were subcutaneously implanted into female BALB/c mice. Treatment was initiated on Day 1 upon randomization when the mean tumor volumes reached 40-80 mm^3 (top panel) or one day post-tumor implantation (bottom panel). Chemotherapeutic compounds, Doxil and Doxorubicin, were intravenously (IV) administered once every week (QWK) in monotherapy or with an immune checkpoint inhibitor, mAnti-CTLA-4 by intraperitoneal (IP) injection. (*): Indicates a significant ($p < 0.05$) reduction in mean tumor volume compared to vehicle control as determined by two-way ANOVA followed by Bonferroni correction. Error bars are SEM values.

In Vivo Syngeneic Mouse Models

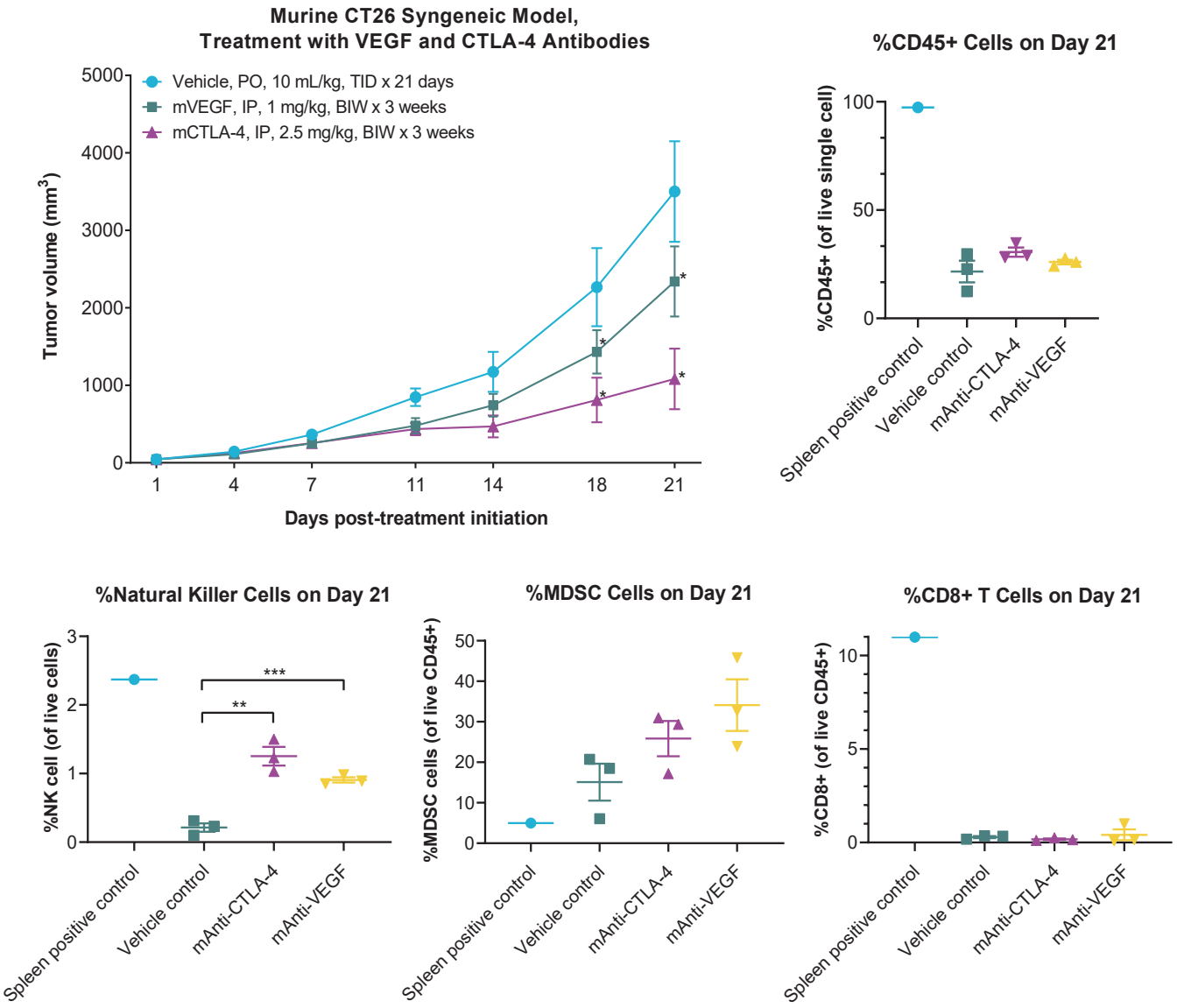

Figure 4. Syngeneic colorectal CT26 model (#578600), tumor growth (mm^3) over time (Day). Murine colorectal CT26 cells, at 5 x 10^5 cells/mouse, were subcutaneously implanted into female BALB/c mice. Treatment was initiated on Day 1 upon randomization when the mean tumor volume reached 40-80 mm^3. Murine anti-VEGF and CTLA-4 antibodies were intraperitoneally administered twice per week (top left panel), followed by TILs analysis on Day 21. The percentage of live and murine CD45 positive cell populations are plotted (top right panel). The percentage of murine natural killer (NK) cells, myeloid-derived suppressor cells (MDSC), and CD8 positive T-cells are plotted with respect to live CD45 positive cells for each group. (*): Indicates a significant ($p < 0.05$) reduction in the mean tumor volume compared to vehicle control as determined by two-way ANOVA followed by Bonferroni correction. Significant difference (**$p < 0.01$ and **$p < 0.001$) in the population of immune cells compared to vehicle control as determined by one-way ANOVA followed by Dunnett's test. Error bars are SEM values.

Testing novel cancer immunotherapies in predictive animal models is a key step for the development of innovative therapeutic approaches acting in conjunction with the host immune system to enhance anti-tumor responses. These models offer value for understanding the mechanism of action and safety profile of candidate immunotherapeutic in the presence of a functionally immunocompetent system.

In Vivo Xenograft Mouse Models

Xenograft mouse models with human cells play an important role in the screening and evaluation of novel anti-cancer test agents. The models can be derived from human tumor cell lines (CDX models) or patient tumors (PDX models) and are utilized to evaluate therapeutic efficacy and toxicity. The tumor cells are implanted subcutaneously (Table 2) or orthotopically (Table 3) in immune-deficient mice or mice with human immune cells (humanized mice). Therapeutic model performances with our xenograft models are demonstrated in Figure 5 with gastric carcinoma NCI-H87 (#582400) and Figure 6 with colorectal carcinoma SW480 (#580150) as examples. The therapeutic profile with standard-of-care drugs can be provided upon request for each model. Analysis of tumor infiltration is conducted by flow cytometry and is available with different tissues, an example with myelodysplasia SKM-1 xenograft model shown in Figure 7.

Method Summary

Female or male immune-deficient mice (nu/nu nude, BALB/c nude, SCID, NOD/SCID, NPG, or NSG) are subcutaneously implanted with viable human carcinoma cells with 50% Matrigel at 0.2 mL volume per mouse. Vehicle and/or test articles are then administered starting on Day 1 when the mean tumor volume reaches 100-150 mm^3 upon randomization at the specified dose administration schedule. The tumor volume and body weight are measured twice per week during the study progression. The volume of the tumor is calculated according to the prolate ellipsoid formula, which is tumor volume = length x $(width)^2$ x 0.5. Once per week, interim data is provided for decision-making during the study progress.

Xenograft Models			
Model Name	Item Number	Cell Lines Used in Mouse Model	
Tumor, Xenograft, Bladder, UM-UC-3	580500	ATCC	CRL-1749
Tumor, Xenograft, Brain, U-87 MG	579500	ATCC	HTB-14
Tumor, Xenograft, Breast, BT-474	579700	ATCC	HTB-20
Tumor, Xenograft, Breast, HCC1428	579800	ATCC	CRL-2327
Tumor, Xenograft, Breast, JIMT-1	579900	AddexBio	C0006005
Tumor, Xenograft, Breast, MCF7	580000	ATCC	HTB-22
Tumor, Xenograft, Breast, MDA-MB-231	580020	ATCC	HTB-26
Tumor, Xenograft, Breast, T-47D	580030	ATCC	HTB-133
Tumor, Xenograft, Bone, U-2 OS	580080	ATCC	HTB-96
Tumor, Xenograft, Colon, HCT 116	580090	ATCC	CCL-247
Tumor, Xenograft, Colon, HT-29	580100	ATCC	HTB-38
Tumor, Xenograft, Colon, SW480	580150	ATCC	CCL-228
Tumor, Xenograft, Gastric, NCI-N87	582400	ATCC	CRL-5822
Tumor, Xenograft, Melanoma, A-375	582100	ATCC	CRL-1619
Tumor, Xenograft, Melanoma, SK-MEL-5	582110	ATCC	HTB-70
Tumor, Xenograft, Myeloma, RPMI 8226	582200	ATCC	CCL-155
Tumor, Xenograft, Neuroblastoma, IMR-32	582300	ATCC	CCL-127
Tumor, Xenograft, Neuroblastoma, SK-N-AS	582310	ATCC	CRL-2137
Tumor, Xenograft, Head/Neck, SAS	580300	JCRB	JCRB0260
Tumor, Xenograft, Kidney, A-498	580400	ATCC	HTB-44
Tumor, Xenograft, Kidney, ACHN	580450	ATCC	CRL-1611
Tumor, Xenograft, Leukemia (PML/AML/M2), HL-60	580600	ATCC	CCL-240
Tumor, Xenograft, Leukemia (AML/M5), MV-4-11	580650	ATCC	CRL-9591
Tumor, Xenograft, Leukemia (AML/M5), SKM-1	580670	JCRB	JCRB0118

In Vivo Xenograft Mouse Models

Model Name	Item Number	Cell Lines Used in Mouse Model	
Tumor, Xenograft, Leukemia (AMoL/M5), THP-1	580680	ATCC	TIB-202
Tumor, Xenograft, Liver, Hep 3B2.1-7	580700	ATCC	HB-8064
Tumor, Xenograft, Liver, PLC/PRF/5	580730	ATCC	CRL-8024
Tumor, Xenograft, Lung (NSCLC), A549	580900	ATCC	CCL-185
Tumor, Xenograft, Lung (NSCLC), NCI-H1975	580910	ATCC	CRL-5908
Tumor, Xenograft, Lung (SCLC), NCI-H209	580940	ATCC	HTB-172
Tumor, Xenograft, Lung (NSCLC), NCI-H460	580950	ATCC	HTB-177
Tumor, Xenograft, Lung (SCLC), NCI-H526	580960	ATCC	CRL-5811
Tumor, Xenograft, Lung (NSCLC), PC-9	580970	Sigma Aldrich	90071810
Tumor, Xenograft, Lymphoma (AML/M5), U-937	581000	ATCC	CRL-1593.2
Tumor, Xenograft, Lymphoma, SU-DHL-5	581010	ATCC	CRL-2958
Tumor, Xenograft, Neuroepithelioma (Askin), SK-N-MC	581100	ATCC	HTB-10
Tumor, Xenograft, Ovary, SK-OV-3	581300	ATCC	HTB-77
Tumor, Xenograft, Ovary, OVCAR-3	581330	ATCC	HTB-161
Tumor, Xenograft, Pancreas, BxPC-3	581520	ATCC	CRL-1687
Tumor, Xenograft, Pancreas, MIA PaCa-2	581500	ATCC	CRL-1420
Tumor, Xenograft, Pancreas, PANC-1	581540	ATCC	CRL-1469
Tumor, Xenograft, Prostate, 22Rv1	581920	ATCC	CRL-2505
Tumor, Xenograft, Prostate, DU 145	581930	ATCC	HTB-81
Tumor, Xenograft, Prostate, LNCaP clone FGC	581950	ATCC	CRL-1740
Tumor, Xenograft, Prostate, PC-3	581900	ATCC	CRL-1435
Tumor, Xenograft, Skin, A-431	582000	ATCC	CRL-1555

Table 2. Validated cell line-derived xenografts (CDX).

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In Vivo Xenograft Mouse Models

NCI-N87 Gastric Xenograft Model

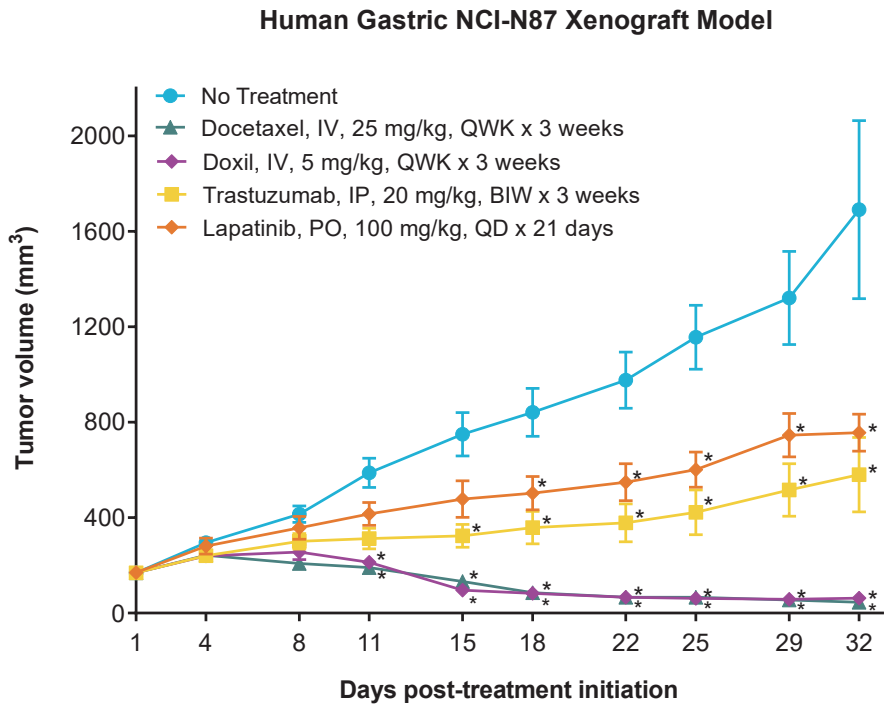


Figure 5. Xenograft model of human HER2 expressing gastric carcinoma NCI-N87 (#582400), tumor growth (mm^3) over time (Day). Female nu/nu mice, 6 weeks of age, were subcutaneously (SC) implanted with viable human gastric carcinoma NCI-N87 cells at 1 x 10^7 cells/mouse (0.2 mL/animal with 50% Matrigel). Treatment was initiated on Day 1 upon randomization when the mean tumor volume reached 100-150 mm^3. Docetaxel at 25 mg/kg and Doxil at 5 mg/kg were each intravenously (IV) administered once per week (QWK) for 3 consecutive weeks. Trastuzumab at 20 mg/kg was intraperitoneally (IP) administered twice per week (BIW) for 3 consecutive weeks. Lapatinib at 100 mg/kg was orally (PO) administered daily (QD) for 21 days. Tumor growth, tumor volume by length x $(width)^2$ x 0.5, was measured thrice per week from Day 1 (treatment initiation) till the study end date. Error bars are SEM values. (*): Indicates a significant ($p < 0.05$) reduction in mean tumor volume compared to vehicle control as determined by two-way ANOVA followed by Bonferroni correction. Error bars are SEM values.

In Vivo Xenograft Mouse Models

SW480 Colon Xenograft Model

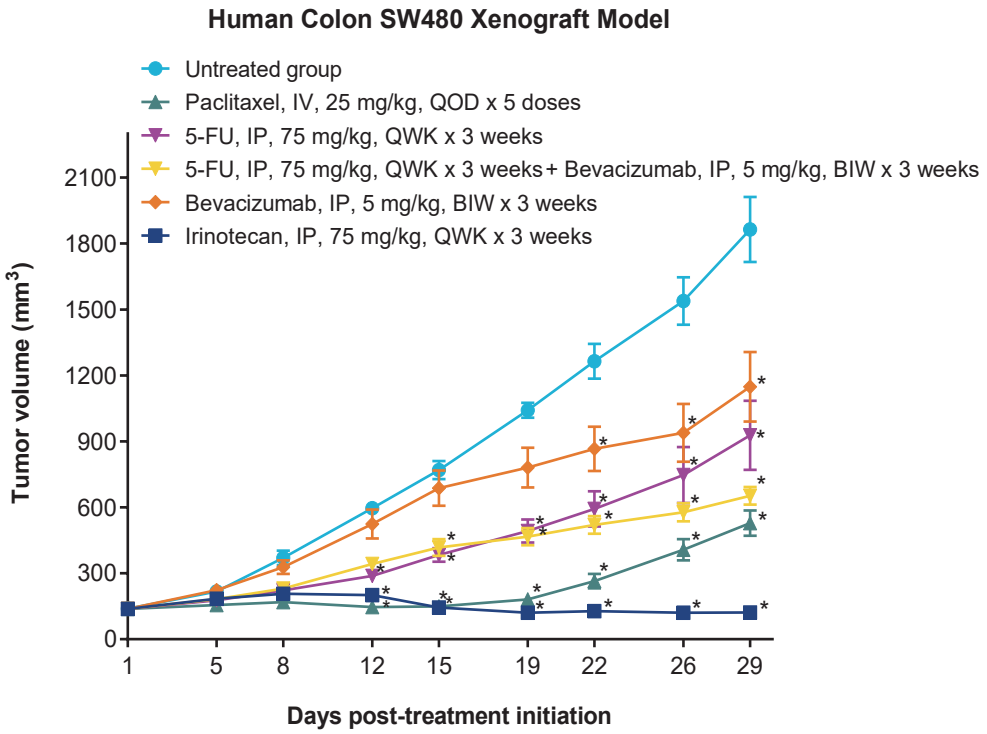


Figure 6. Xenograft model of human Duke's type B colorectal carcinoma SW480 (#580150), tumor growth (mm^3) over time (Day). Female nu/nu mice, 6 weeks of age, were subcutaneously (SC) implanted with viable human colorectal carcinoma SW480 cells at 5 x 10^6 cells/mouse (0.2 mL/animal with 50% Matrigel). Treatment was initiated on Day 1 upon randomization when the mean tumor volume reached 100-150 mm^3. Paclitaxel at 25 mg/kg was intravenously (IV) administered once every other day for a total of 5 doses (QOD x 5). Fluorouracil (5-FU) at 75 mg/kg and Bevacizumab at 5 mg/kg were each intraperitoneally (IP) administered with respect to once (QWK) and twice (BIW) per week for 3 consecutive weeks. A combination therapy of 5-FU and Bevacizumab was assessed to compare the effect with monotherapies. Irinotecan at 75 mg/kg IP administered QWK x 3 weeks. Tumor growth, tumor volume by length x $(width)^2$ x 0.5, was measured thrice per week from Day 1 (treatment initiation) till the study end date. Error bars are SEM values. (*): Indicates a significant ($p < 0.05$) reduction in mean tumor volume compared to vehicle control as determined by two-way ANOVA followed by Bonferroni correction. Error bars are SEM values.

In Vivo Xenograft Mouse Models

SKM-1 MDS/Leukemia Xenograft Model

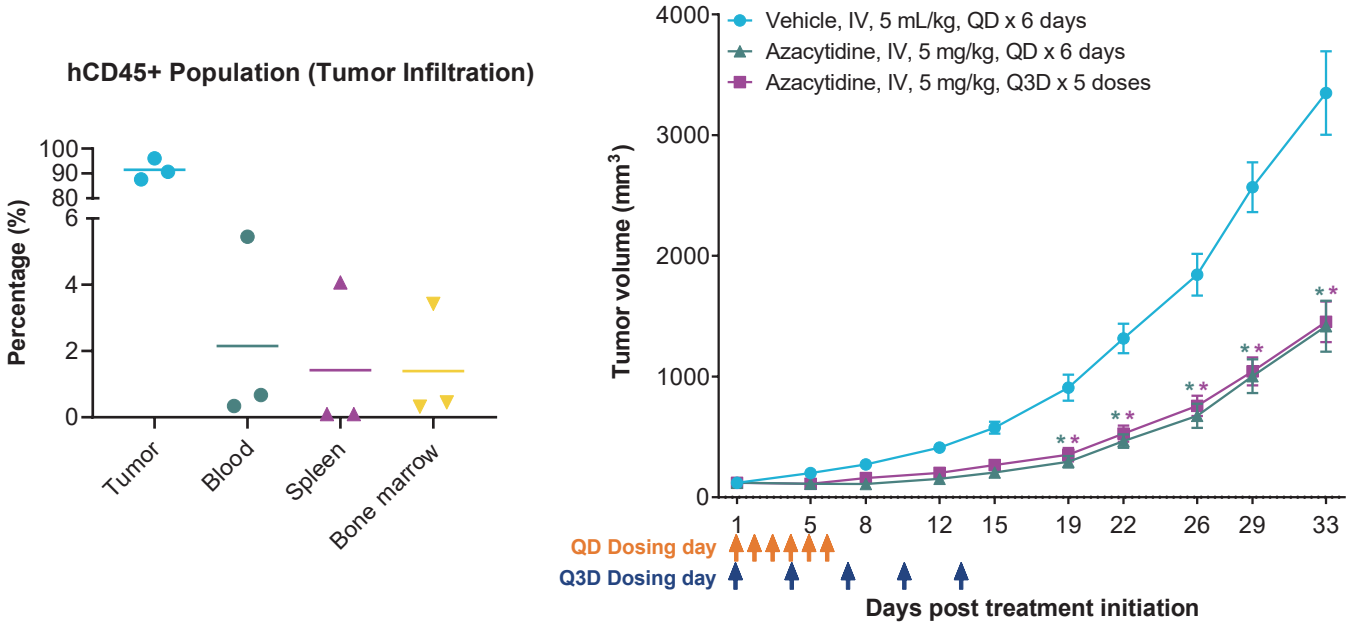


Figure 7. Example of tumor infiltration into the bloodstream, spleen tissue, and bone marrow in the myelodysplasia SKM-1 xenograft model (#580670). Female NOD/SCID mice, 6 weeks of age, were subcutaneously implanted with viable human myelodysplasia SKM-1 cells at 1 x 10^7 cells/mouse (0.2 mL/animal with 50% Matrigel) The efficacy evaluation with Azacytidine in the SKM-1 xenograft model, monitored by tumor, is shown in the right panel. Tumor growth, tumor volume by length x $(width)^2$ x 0.5, was measured thrice per week from Day 1 (treatment initiation) till the study end date. Error bars are SEM values. (*): Indicates a significant ($p < 0.05$) reduction in mean tumor volume compared to vehicle control as determined by two-way ANOVA followed by Bonferroni correction. Error bars are SEM values. Mice were sacrificed on Day 50 post-tumor implantation. Tumor, blood, spleen, and bone marrow were harvested followed by processing to single cells. Tumor infiltration was monitored by analyzing human CD45-positive cells by flow cytometry (left panel).

In Vivo Orthotopic Mouse Models

Orthotopic mouse models with murine and human cells play an important role in assessing tumor development in a relevant environment to evaluate the efficacy of therapeutic treatment that mimics the disease process in humans. The tumor cells are orthotopically implanted in the tissue of carcinoma origin. These models (Table 3) include the implantation of breast tumor cells into the mammary fat pad, pancreatic tumor cells into the pancreas, and by tail vein injection with leukemic cells (also known as disseminated models). Tumor cells that have metastatic potential will result in spontaneous metastasis that mimics the human disease progression as demonstrated with the highly metastatic TNBC murine 4T1 (Figure 8) and human MDA-MB-231 orthotopic models (Figure 9). In addition to the tracking of tumor cells with IVIS® Spectrum, flow cytometry can be applied for monitoring leukemic cells in the bloodstream as shown in Figure 10. If metastasis to a specific organ is of interest, our team is experienced with implantation via different injection routes, including directly into the pancreas (Figure 11), portal vein injection to reach liver tissues, and intracardiac injection for brain metastasis.

Method

Female or male immune-deficient mice are orthotopically implanted with viable murine or human carcinoma cells at the site of tumor origin. Vehicle and/or test articles are then administered starting on Day 1 when established tumor growth is observed with IVIS® Spectrum. For imaging, mice are simultaneously anesthetized with 4% isoflurane and d-luciferin potassium salt formulated at 15 mg/mL in DPBS, and intraperitoneally administered at a dose of 150 mg/kg. The images are taken 15 minutes post-luciferin injection. The regions of interest encompassing the implantation and metastatic areas are defined using IVIS Spectrum, and the total flux (photons per second) is recorded. Individual mouse photographs are provided.

Orthotopic Models			
Model Name	Item Number	Cell Lines Used in Mouse Model	
Tumor, Orthotopic, Breast, 4T1	578591	ATCC	CRL-2539
Tumor, Orthotopic, Breast, 4T1-Luc*	578592	JCRB	JCRB1447
Tumor, Orthotopic, Brain, U-87 MG-Luc*	579502	PerkinElmer	BW124577
Tumor, Orthotopic, Breast, MDA-MB-231	580021	ATCC	HTB-26
Tumor, Orthotopic, Breast, MDA-MB-231-Luc*	580022	JCRB	JCRB1559
Tumor, Orthotopic, Leukemia (AML/M5), MV-4-11	580651	ATCC	CRL-9591
Tumor, Orthotopic, Leukemia (PML/AML/M2), HL-60	580601	ATCC	CCL-240
Tumor, Orthotopic, Lymphoma, U-937	581001	ATCC	CRL-1593.2
Tumor, Orthotopic, Pancreas, BxPC-3	581521	ATCC	CRL-1687
Tumor, Orthotopic, Pancreas, BxPC-3-Luc*	581522	PerkinElmer	BW125058
Tumor, Orthotopic, Pancreas, MIA PaCa-2	581501	ATCC	CRL-1420
Tumor, Orthotopic, Pancreas, PANC-1	581541	ATCC	CRL-1469

* IVIS tracking and monitoring of luciferase-expressing cancer cells

Table 3. Cell line-derived orthotopic models.

In Vivo Orthotopic Mouse Models

4T1-Luc Orthotopic Model

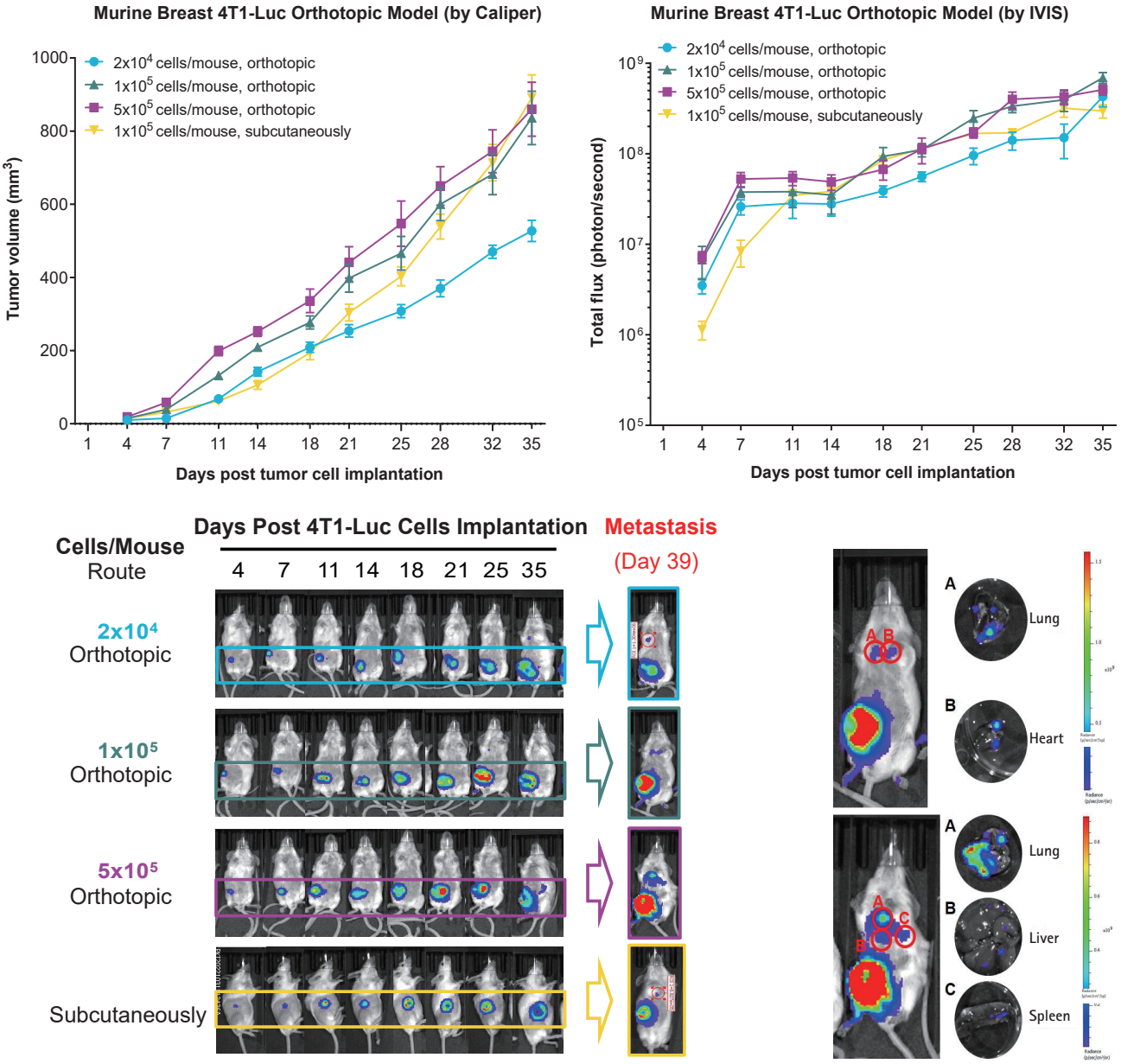


Figure 8. Orthotopic model of murine triple-negative breast carcinoma 4T1. Female BALB/c mice, 6 weeks of age, were orthotopically implanted with viable murine TNBC 4T1 cells at the selected target cell density into the mammary fat pad at 0.05 mL/animal. Tumor growth was measured by caliper and IVIS twice per week throughout the study progression. Both the caliper and IVIS versions with 4T1-Luc (luciferase labeled) cells are available (#578592). Representative luciferase signal in the bottom left panel throughout the course of the study. Multiple organ metastases are found, as shown in the bottom right panel. The orthotopic implantation with parental 4T1 cells is available under #578591, as shown in Figure 1.

In Vivo Orthotopic Mouse Models

MDA-MB-231-Luc Orthotopic Model

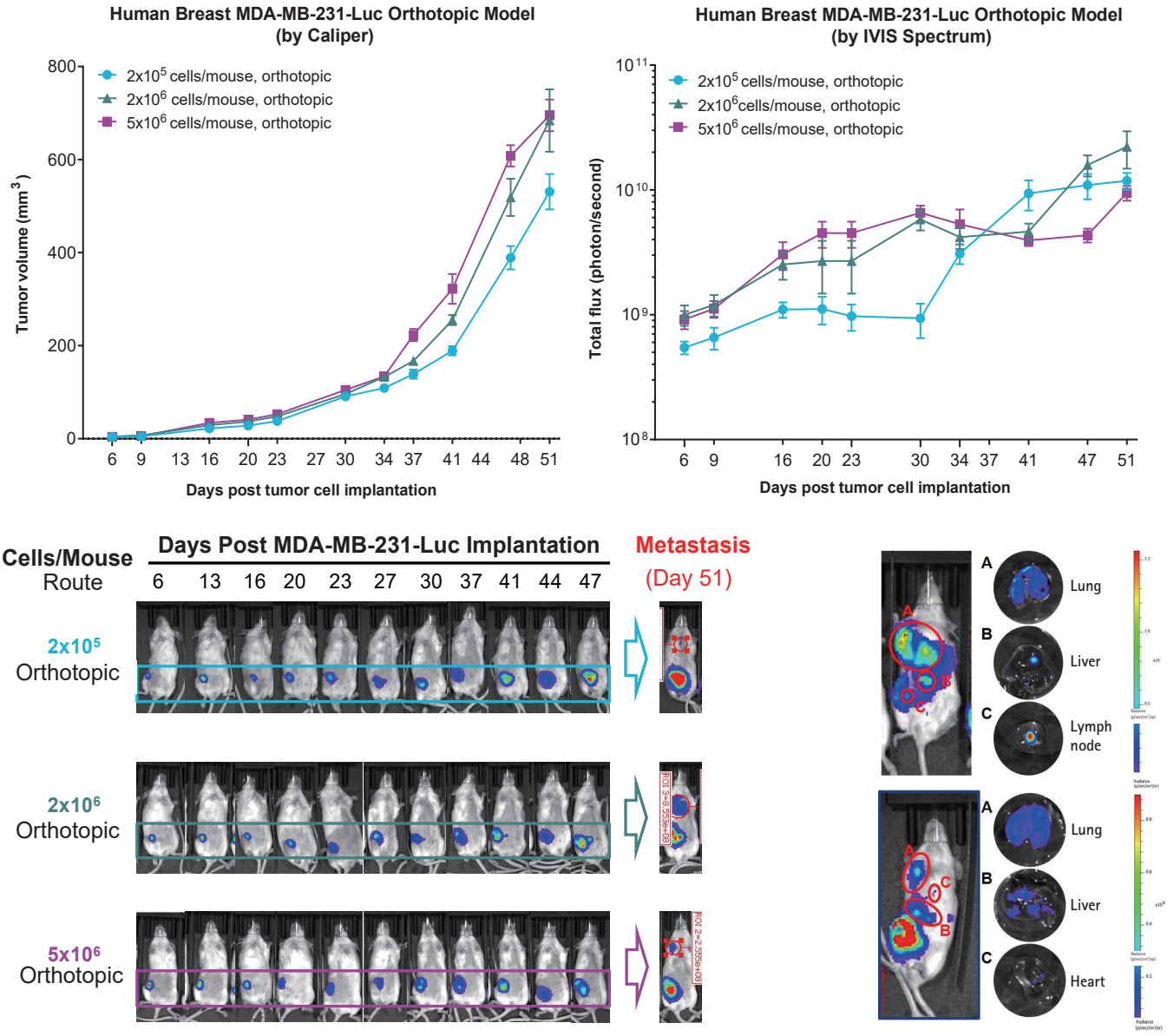


Figure 9. Orthotopic model of human triple-negative breast carcinoma MDA-MB-231. Female NPG mice, 6 weeks of age, were orthotopically implanted with viable human TNBC MDA-MB-231 cells at the selected target cell density into the mammary fat pad at 0.05 mL/animal. Tumor growth was measured by IVIS and caliper twice per week throughout the study progression. Both the caliper and IVIS versions with MDA-MB-231-Luc (luciferase labeled) cells are available (#580022). Representative luciferase signal in the bottom left panel throughout the course of the study. Multiple organ metastases are found, as shown in the bottom right panel. The xenograft (#580020) and orthotopic (#580021) models with the parental MDA-MB-231 (unlabeled cells) are also available for selection.

In Vivo Orthotopic Mouse Models

HL-60 Orthotopic Model

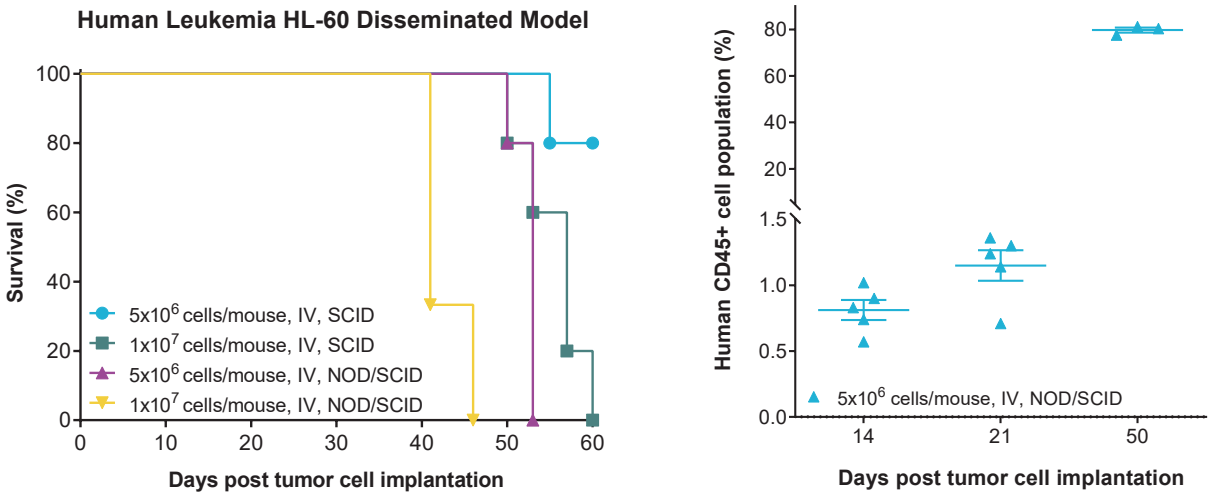


Figure 10. Disseminated model of human leukemia HL-60 (PML/AML, stage M2). Female SCID and NOD/SCID mice, 6 weeks of age, were orthotopically implanted with viable human leukemic HL-60 cells at 5 x 10^6 or 1 x 10^7 cells per mouse by tail vein intravenous injection at 0.2 mL/animal. Kaplan-Meier plot of 60-day survival in the HL-60 disseminated model (#580601). Tumor progression was monitored by analyzing human CD45-positive cells with flow cytometry (right panel, represented with 5 x 10^6 cells/mouse in NOD/SCID mice).

In Vivo Orthotopic Mouse Models

BxPC-3-Luc Orthotopic Model

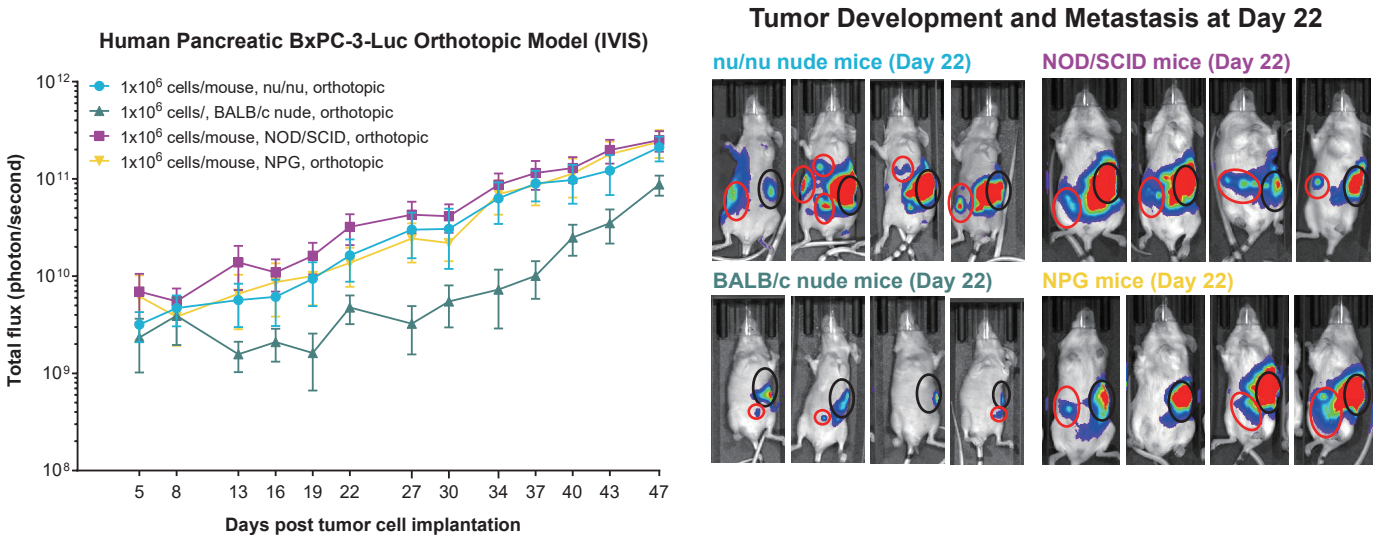


Figure 11. Orthotopic model of human pancreatic carcinoma BxPC3. Female nu/nu, BALB/c nude, NOD/SCID, and NPG mice, 6 weeks of age, were orthotopically implanted with viable human pancreatic carcinoma BxPC3-Luc cells at 1 x 10^6 cells per mouse at 0.05 mL/animal. IVIS monitoring is conducted throughout the study (left panel, #581522). Female nu/nu and NOD/SCID mice, 6 weeks of age, were orthotopically implanted with viable human pancreatic carcinoma BxPC3 cells at 1-5 x 10^6 cells per mouse at 0.05 mL/animal followed by endpoint weighing of the pancreatic tumors (right panel, #581521). Black circles denote primary tumor cell implantation site at the pancreas. Red circles denote metastatic sites.

Patient-Derived Xenografts (PDX Models)

Patient-derived tumor xenografts are developed by directly transplanting tumor fragments from surgically dissected cancer patients into immunodeficient or humanized mice. The model is useful for translational research by retention of the original tumor architecture and facilitating precision medicine. The susceptibility of a therapeutic compound that results in tumor reduction in PDX models is closely correlated with clinical data in patients from whom the PDX models were derived. This suggests that PDX models are highly effective in predicting the efficacy of both conventional and novel anti-cancer therapeutics.

Method Summary

Female or male immune-deficient mice are subcutaneously implanted with viable human tumor fragments at 2 mm each for width, length, and height. Vehicle and/or test articles are then administered starting on Day 1 when the mean tumor volumes reach 100-150 mm^3 upon randomization at the specified dose administration schedule. The tumor volume and body weight are measured twice per week during the study progression.

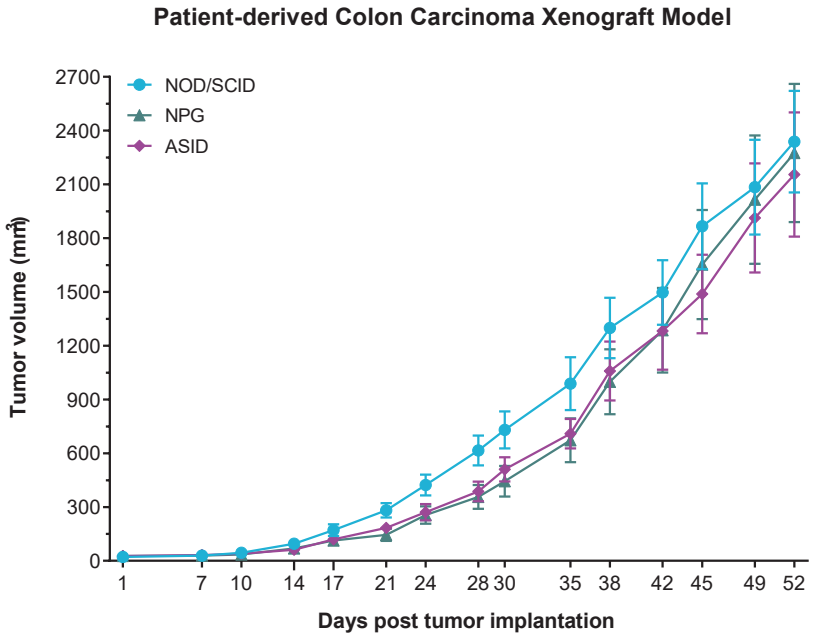


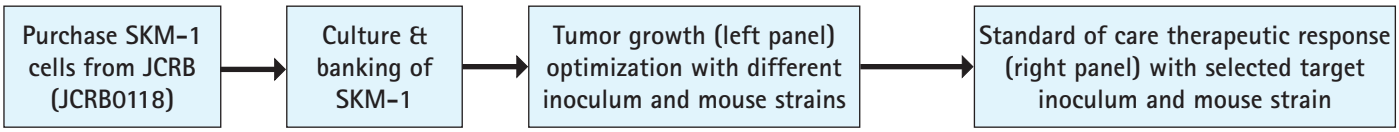
Figure 12. Patient-derived xenograft model with colorectal carcinoma, tumor growth (mm^3) over time (Day). Female ASID, NPG, and NOD/SCID mice, 8 weeks of age, were subcutaneously (SC) implanted with tumor fragments (passage number 3) obtained from an age 45 male patient with adenocarcinoma colorectal cancer at the upper rectum, stage IV A, poorly differentiated. Tumor growth, tumor volume by length x $(width)^2$ x 0.5, was measured twice per week during the study progression.

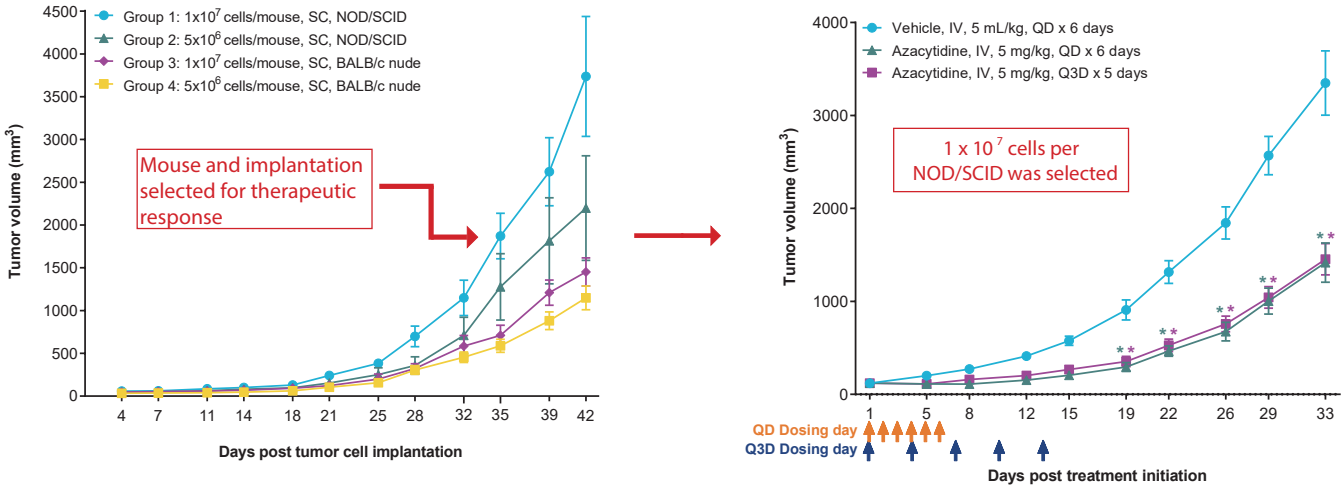
Customized New Models — Tailored to Meet Your Needs!

Pharmacology Discovery Services (PDS) routinely co-develops new *in vivo* models to tailor our clients' needs. We develop 5–8 new models annually with almost a 100% success rate. The target cell density and mouse strains for implantation are selected based on literature search for fast turnaround time and cost-effective model development. The main efficacy study is initiated once the implantation size (cell density) and mouse strain are selected halfway through the tumor growth optimization. The standard-of-care drug is selected to function with a similar mechanism to the test compound (if available and for head-to-head comparison) or with a benchmarked compound. Our clients prefer customized models for higher flexibility and allowance of selectivity for their preferred inoculum and/or mouse strain. Our clients enjoy working with our experts using their in-house genetically engineered or specific drug-resistant cell lines for these customized models. PDS also provides transient transfection and lentivirus infection services for genetic modifications of cell lines.

Custom models are developed in a 4-step process shown below:

1. Purchase a cell line from an available cell bank
2. *In vitro* cell culture and banking of the cell line
3. Tumor growth optimization with different implantation cell densities and mouse strains
4. Therapeutic response (main study) along with the standard-of-care drugs





Each model is developed and customized to meet our clients' expectations!

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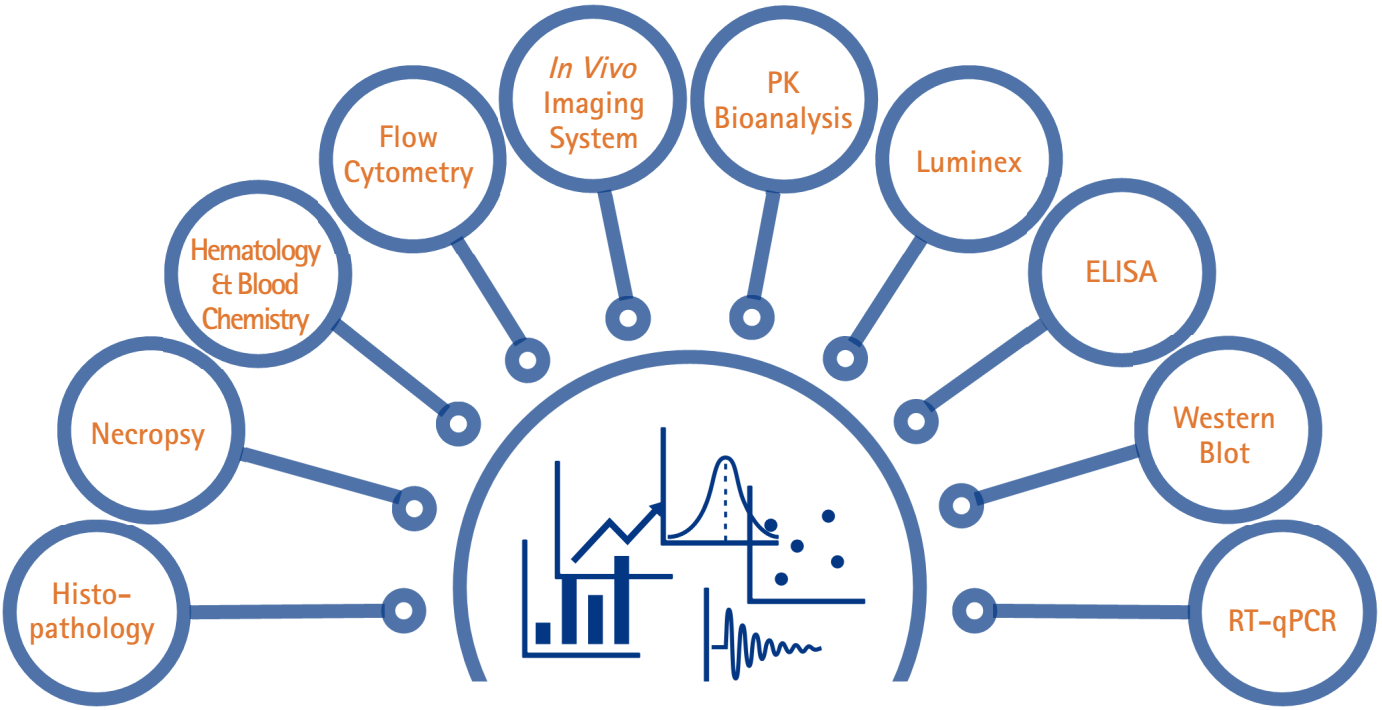
Comprehensive *Ex Vivo* Analyses

Pharmacology Discovery Services provides a full-service facility equipped for *in vitro*, *in vivo*, and *ex vivo* analyses. Supplemental *ex vivo* analysis during *in vivo* studies is often an important component of a complete preclinical program. These *ex vivo* analyses are important for understanding the function and mechanism of the *in vivo* effect of a test article, as well as for exploring the correlation between *in vivo* efficacy and biomarkers.

Our scientific team is experienced with cell culture, complex tissue digestion, cell enrichment, flow cytometry analysis, multiplex cytokine analysis (Luminex platform), ELISA analysis and other plate-based assays, RNA/DNA isolation, RT-qPCR, western blot, histopathology, bioanalysis, hematology, and blood chemistry. Whether these analyses are intended to complement an existing *in vivo* study or are indicated as standalone experiments, Pharmacology Discovery Services has the necessary tools and expertise to generate data that supports therapeutic efficacy and mechanism-of-action studies.



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Animal Facility and Accreditations

- AAALAC accredited vivarium
- Office of laboratory (OLAW) assurance
- In Compliance with EU Directive 2010/63/EU
- ISO 9001 certification
- Biosafety level 2 facility

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AN ACCREDITED ANIMAL CARE & USE PROGRAM SINCE 1971

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1669 m^2 vivarium plus 186 m^2 bioanalytical lab

- 50 years CRO business experience, formerly Panlabs Inc.
- 45 FTEs ; >10 year average tenure
- Biosafety Level 2 Facility
- 3,000+ rodent holding and 20 procedure rooms

Expert Provider of Non-GLP Safety, PK, and Efficacy Studies in Rodents with 350+ Validated Models

INFECTIOUS DISEASE
145+ validated models, CDC/WHO priority pathogens, *In vitro* antimicrobial assays and rodent infection models

NEUROSCIENCE
50+ validated models, CNS, pain, neurodegeneration, addiction, behavioral endpoints

GASTRO-INTESTINAL
20+ models, UC/Crohn's models, gut barrier function, FITC transport, DSS, TNBS, AKI, 5/6 SNx

350+
validated models across all major therapeutic areas

INFLAMMATION/IMMUNOLOGY
60+ validated models, comprehensive portfolio auto-immune, dermal inflammation, lung inflammation, liver injury and fibrosis, NASH, sepsis, miles assay, gout

METABOLIC/ENDROCRINE
20+ validated models, diabetes and obesity acute and chronic intake monitoring, taste aversion, IP/IV/oral glucose tolerance test

ONCOLOGY
60+ validated models, human cell-line derived xenografts (CDX) models, immortalized mouse cancer cell lines, custom in vivo development

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A Partner Lab of Eurofins Discovery

Providing Deep Technical Expertise from Discovery to Preclinical

Eurofins Discovery, a partner lab of PDS, has been supporting Drug Discovery research for over 40 years and offers thousands of assays to advance your oncology test agents from Target Validation to Pre-Clinical Development. Offerings include medicinal and synthetic chemistry, *in vitro* pharmacology, safety pharmacology, ADME-Toxicology, cell-based phenotypic assays, *in vivo* safety & efficacy, and custom proteins and assay development. The DiscoveryOne™ integrated drug discovery service is also available for clients to access all services, and it includes dedicated project management to drive the delivery of your preclinical candidates. With the combined expertise of our team, we deliver high-quality, actionable insights to solve drug discovery challenges.

For more information on *in vivo* Oncology, please visit: pharmacologydiscoveryservices.com/efficacy-models/oncology