



Oncology Research Products and Services

Because of the challenges inherent in oncology research, it is critical that you have the right tools and resources available to you. Charles River offers years of experience in providing high-quality animal models as well as unsurpassed expertise in testing a variety of anticancer agents in a broad spectrum of *in vitro* and *in vivo* models. These models include human tumor xenograft, syngeneic, orthotopic, angiogenic and genetically engineered.

Other services we offer to help you with the drug evaluation process include combination chemotherapeutic and radiation therapy, neurotoxicology, cachexia models, biomarker assessment, pharmacokinetics, pharmacodynamics, histopathology and immunohistochemistry. We regularly consult with you to develop detailed study protocols that meet your specific needs. Our global infrastructure, harmonized approach and commitment to quality allow us to provide unparalleled service in the field of cancer research.

Capabilities

- *In vitro* Efficacy Testing
- *In vivo* Efficacy Testing
- *In vivo* Imaging
- Research Animal Models
- Research Animal Diagnostic Services
- Genetically Engineered Models and Services
- Subcutaneous Syngeneic and Xenograft Tumor Models
- Combination Chemotherapy
- Combination Radiotherapy and Chemotherapy
- Orthotopic Tumor Models
- Genetically Engineered Mouse and Rat Models
- Corneal Micropocket Assay
- Biomarkers
- Maximum Tolerated Dose Determination
- Toxicity Range Finding
- Neurotoxicity
- Cachexia
- Fresh and Cryopreserved Hepatocytes
- Pharmacokinetics and Pharmacodynamics
- Carcinogenicity Studies
- Tumorigenicity Studies



Research Animal Models and Services

For more than 60 years, Charles River has provided the biomedical research community with high-quality research animal models and a full range of research animal services. With breeding and service centers around the globe, Charles River can provide you with the models and services required to advance your oncology research and development programs.

Our global portfolio of high-quality research animal models, which include standard and disease-specific (oncology, cardiovascular, metabolic and renal) models, helps ensure that you will have the right resources available to you in your chosen therapeutic area.

Immunodeficient Animals

Oncology is one of the leading areas of research into new therapeutics, and immunodeficient animal models play a critical role in that research. At Charles River, we utilize our decades of research model experience, our high level of scientific and technological expertise and our state-of-the-art facilities to ensure that only the highest quality immunodeficient research models are produced for our clients.

Table 1. Immunodeficient Models

Strain	Hair	T-Cell Deficient	B-Cell Deficient	NK Cell Deficient
Athymic Nude Mouse	No	Yes	No	No
CD-1® Mouse	No	Yes	No	No
NU/NU Mouse	No	Yes	No	No
BALB/c Nude Mouse	No	Yes	No	No
NIH III Mouse	No	Yes	Yes	Impaired
RNU Rat	No	Yes	No	No
SCID Hairless Outbred (SHO™) Mouse	No	Yes	Yes	No
SCID Hairless Congenic (SHC™) Mouse	No	Yes	Yes	No
Fox Chase SCID® Congenic Mouse	Yes	Yes	Yes	No
Fox Chase SCID® Beige Mouse	Yes	Yes	Yes	Impaired
NOD SCID Mouse	Yes	Yes	Yes	Impaired

Additional Oncology Models

Charles River offers additional models that support oncology researchers as they investigate the biological, mechanistic and genetic basis of this disease. Through the use of animal models with spontaneous or induced mutations, the effect of the mutation can be studied and approaches can be developed that link physiology, genetics, pathology and clinical phenotypes. These animals include reference inbred models, such as the AKR mouse and BDIX and Copenhagen rats, as well as breakthrough genetically engineered models, such as the p53 TGEM™ knockout rat which is available globally for the first time through Charles River.

View our oncology models brochure for a complete list of our oncology and immunodeficient models.

Research Animal Diagnostic Services

Proactive monitoring of your research animal colonies and facility is the best way to ensure that a health issue does not compromise the integrity of your research. To help you manage the potential risks, Charles River delivers sensitive and specific testing to screen your animal facility, research biologics and many research animal models, including mice, rats, rabbits, gerbils, hamsters, guinea pigs, ferrets and simian species.

- Research Biologics Screening: Any product of animal origin to be used in a facility or directly injected into animals (cells, tumor lines, viral stocks, mouse serum, etc.) should be screened for the presence of adventitious agents prior to use. These biological materials, which are often of unknown origin, can harbor both human and rodent infectious agents and may compromise the integrity of your *in vivo* research.
- Charles River provides TaqMan® PCR testing to identify human or rodent infectious agents in any of your research biologics. TaqMan® technology is 10 to 100 times more sensitive than traditional gel-based qualitative PCR, and the use of an internal probe provides incomparable specificity. This non-GLP service is available for research purposes only.

Genetically Engineered Models and Services

The use of genetically engineered rodent models carrying genetic alterations commonly found in human cancers allows preclinical validation of anticancer lead candidates. Targeted genetic mutations induce single or multiple tumor formation in various organs, providing an ideal model for proof-of-concept screening of compounds. These models are made more efficient and quantitative by the application of anatomical imaging technologies to follow tumor burden noninvasively over time.

Charles River also offers a comprehensive suite of services designed to help you better manage your research space, funds and animal care resources. Our world-class facilities are dedicated to the development, production, management and characterization of genetically engineered models.

- Breeding and Aging Services
 - Colony startup
 - Rapid colony expansion
 - Accelerated backcrossing
 - Colony maintenance and development
- Embryology Services
 - Rederivation
 - Cryopreservation and cryorecovery
 - Mouse Embryo Assay
 - BlastoKit®
 - ES cell injection
- Quarantine Services
- Genetic Testing Services
- Line Rescue Services
- Genetically Engineered Models and Model In-licensing

Discovery Services

The Discovery Services group provides extensive research and drug development services across multiple therapeutic areas. Leveraging our broad-based global portfolio and in-depth scientific expertise, we work closely with you to provide high-quality results within rapid timelines in support of your drug development program.

Experience

- Chemotherapeutics
- Chemopreventive Agents
- Blood Cell Factors
- Immunotherapy
- Targeted Therapies
- Supportive Care Therapies
- Mechanistic Studies
- Strategic Program and Study Design

In vitro Efficacy Testing

Through comprehensive and strategically planned assessments, our expert *in vitro* platform can support your *in vivo* program. With expertise in assay design and implementation, Charles River provides reproducible and consistent *in vitro* assay platforms for expansion of your in-life data and efficient, cost-effective early compound screening.

In vitro Assay Services

More than 300 human cell lines are available for standard assay platforms and custom development.

- Cell Proliferation, IC₅₀ Determination
- Apoptosis Assays
- Combination Assays, Chou-Talalay
- Flow Cytometry
- Biomarker Analysis
- Multiplexed Cytokine Analysis
- Cytokine Induction Assays
- Custom Assay Design

In vivo Services

Charles River applies a number of key technologies to the evaluation of anticancer activity and therapeutic effect. Traditional evaluation in syngeneic and human tumor xenografts remains a mainstay of our evaluation services. These traditional models are supplemented with orthotopic, neurotoxicity, bone resorption, cachexia, angiogenesis and genetically engineered mouse tumor models. The addition of functional imaging technologies provides an integrated and quantitative correlation of efficacy with mechanism of action.

Coupling our *in vitro* and imaging technologies with our selection of tumor models enables the validation of intended clinical biomarkers and the establishment of decision-making thresholds for the modulation of surrogate markers in Phase I and II clinical trials.

Subcutaneous Syngeneic and Xenograft Tumor Models

Charles River has over 300 cell lines available for *in vivo* and *in vitro* use. Some of the most frequently used lines are maintained through *in vivo* passage, enabling quick initiation of large-scale studies. Currently available validated tumor models and cell lines are listed in Table 2. In addition, our industry-recognized team extends their expertise to routinely validating new models in response to industry and client requests.

Table 2. Tumor Cell Lines: Tumor Xenograft Models

Tumor Type	Cell Line
Bladder	RT112, SW780
Brain	<u>D54</u> , <u>SF-295</u> , SK-N-AS, <u>U-87 MG</u>
Breast	BT474, JIMT-1, <u>MCF-7</u> , <u>MDA-MB-231</u> , MX-1, ZR-75-1 Murine: R320AC (intratibial), 13672 (sc, orthotopic or intratibial)
Colon	COLO 205, DLD-1, <u>HCT 116</u> , HCT-15, <u>HT-29</u> , LoVo, LS-174T, SW-480, SW-620 Murine: Colon 26
Fibrosarcoma	HT-1080
Gastric	MKN-45, NCI-N87, SNU-5
Head and Neck	FaDu, HONE-T-1
Hepacellular	SNU-398
Leukemia/Lymphoma	Daudi, DoHH2, <u>Granta 519</u> , HL-60, K-562, KG-1, <u>MOLT-4</u> , <u>MV4-11</u> , Namalwa, <u>Raji B</u> , Ramos, REC-1, RL, WSU-DLCL2 Murine: <u>L1210</u> , <u>P388</u>
Liver	Hep3B
Lung	A-427, <u>A549</u> , Calu-6, NCI-H125, H1975, NCI-H23, MV-522, NCI-H1299, NCI-H345, NCI-H460, NCI-H520, NCI-H522, NCI-H69, SK-MES-1 Murine: Madison109, <u>Lewis Lung</u>
Melanoma	A2058, A375, Malme 3M, SK-MEL-5, (Murine: <u>B16F10</u> , B16F1)
Multiple Myeloma	H929, OPM-2, RPMI 8226
Osteosarcoma	SJSA-1
Ovarian	<u>A2780</u> , <u>IGROV1</u> , OVCAR-3, SK-OV-3
Pancreas	BxPC-3, Capan-1, MIA PaCa-2, PANC-1
Prostate	<u>22Rv1</u> , DU 145, <u>PC3</u>
Renal	<u>786-O</u> , A498, <u>Caki-1</u> , Caki-2, G-401, G-402
Thyroid	8505C, FTC-238
Vulvar Epidermoid Carcinoma	A-431

Unless labeled otherwise, all cell lines are of human origin. Underlined cell lines are also available as orthotopic models.

Combination Chemotherapy

Multiple therapeutic agents are often given together to treat cancer. Incorporating profiled chemotherapeutic effect in characterized tumor models enables expanded translation of preclinical data to clinical trial design. Charles River has extensive expertise in combination efficacy studies to evaluate the therapeutic potential and effect of combinations of novel therapeutics with approved drugs.

Combination Radiotherapy and Chemotherapy

Over half of cancer patients are treated with radiation, often in combination with chemotherapeutic agents. Our experienced staff is well-published in the field of experimental radiation biology and utilizes state-of-the-art irradiation equipment. We can mimic clinical radiation therapy protocols and assess the interactions of drug treatment regimens with fractionated or bolus irradiation. In-depth expertise using animal data with combinations of drug therapies further drives clinical trial development.

Orthotopic Tumor Models

Charles River offers orthotopic models in the brain, liver, kidney, and breast. Orthotopic tumors are important because the environment of the tumor can affect its growth and response to treatment.

- **Brain:** We have vast experience using human and rat orthotopic glioma models. Tumor burden can be tracked over time using a luciferase-transfected cell line or MRI for virtually any model.
- **Liver:** We have developed methods for directly implanting liver tumor models. Current models utilize traditional or non-imaging endpoints.
- **Renal:** Orthotopic implantation of human tumors in the kidney of athymic nude mice allows for an assessment of tumor development in the host organ. At predetermined endpoints, renal tumors are measured with results based on tumor growth inhibition.
- **Breast:** With tumor cells implanted in the mammary fat pad, the breast orthotopic model can utilize traditional or non-imaging endpoints.

Angiogenesis – Corneal Micropocket Assay

The corneal micropocket assay is a quantitative assessment of vascularity conducted in a mouse cornea. This short-term assay provides an effective screening of your agent's angiogenic effects.

Cachexia

The Yoshida ascites hepatoma model is used to evaluate the anti-cachectic effects of therapy by inducing cachexia in rats and producing tissue wasting, particularly in skeletal muscle. Once injected with tumor cells intraperitoneally, animals are measured for heart, gastrocnemius and ascites for evaluation of therapeutic efficacy.

Neurotoxicity

Our taxane-induced neurotoxicity mouse model provides a useful assay in the evaluation of new strategies for chemoprevention drug combinations. Utilizing the mouse as the host maintains consistency with the more widely used model for efficacy assessment of cancer therapies. By combining toxicity and efficacy assessments in a single model, the use of an investigational agent is significantly minimized, while the evaluation of interactions of proposed protectant strategies for the disease and its treatment is obtained.

Bone Lysis

Utilizing intratibial injection of tumor cells, this intratibial bone model demonstrates tumor-induced bone resorption as affected by a testing agent. Quantified bone lysis is provided through Faxitron image analysis. Distant metastases are quantified by histopathology. Designs can incorporate treatment efficacy, histopathology, histomorphometry and immunohistochemistry.

Biomarkers

Quantitative analysis of biomarker expression can help define mechanism of action for targeted therapeutics and assess their safety and efficacy while providing strong support for *in vivo* efficacy and informed clinical trial designs.

- **Tissue Biomarker Analysis:** To further characterize your models following the *in vivo* portion of your study, we offer immunohistopathology, quantitative PCR-based expression testing and *in situ* hybridization to determine effects on key cellular and molecular processes, such as gene and protein expression, cell proliferation, cell death or angiogenesis.
- **Plasma Biomarker Testing:** Plasma biomarkers such as hormones, cytokines/chemokines, acute-phase reactants and other blood components can help you identify disease conditions as well as monitor progression and response to therapy.



Preclinical Services

Charles River has the experience, range of services, and expertise to help you successfully initiate and complete critical phases of preclinical drug development by designing, performing and documenting safety tests that meet the appropriate regulatory requirements before and after clinical trials begin.

Our scientific and regulatory staff works with you to develop and execute individual studies or customized testing programs to ensure that safety and efficacy assessments are conducted in the most efficient manner. We are proud to offer the following GLP services to support worldwide regulatory filings:

- Drug Metabolism and Pharmacokinetics
- Toxicology
- Pathology
- Laboratory Sciences



Carcinogenicity Studies

Carcinogenicity studies have been performed at multiple locations within Charles River since the 1970s, and, collectively, we typically perform over 20 studies per year. Our technical staff has in-depth understanding of the specific study requirements for pharmaceuticals, agrochemicals and food additives. We are able to advise on study design and are familiar with the reporting and interpretation of carcinogenicity study data. We offer full-service laboratory support to enable each client to perform all aspects of a carcinogenicity study at a single GLP-compliant facility. We also participated in the International Life Sciences Institute (ILSI) Alternatives to Carcinogenicity Testing program that began in 1997. Both the p53^{+/-} and the Tg.AC mouse models were validated at our facilities as part of this effort.

About Us

Charles River is a global provider of solutions that advance the drug discovery and development process. Our leading-edge products and services are designed to enable you to bring drugs to market faster and more efficiently. Backed by our rigorous, best-in-class procedures and our proven data collection, analysis and reporting capabilities, our products and services are organized into several categories spanning every step of the drug development pipeline: Research Models and Services, Discovery Services, Preclinical Services and Process Manufacturing Support.