Whether we’re helping you chart your course from bench to clinic or achieve a particular study milestone, Charles River is equipped to support your oncology research at any point along the drug discovery and development continuum. Dedicated to providing superior, flexible and tailored solutions, we provide a broad range of specialty oncology models and drug discovery and pharmacology services.

### Basic Research: Animal Models and Research Services

Advance your oncology research and development programs with our global portfolio of high-quality research animal models, including standard and disease-specific models.

#### Immunodeficient Models

<table>
<thead>
<tr>
<th>Strain</th>
<th>Hair</th>
<th>T-Cell-Deficient</th>
<th>B-Cell-Deficient</th>
<th>NK-Cell-Deficient</th>
</tr>
</thead>
<tbody>
<tr>
<td>Athymic Nude Mouse*</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>CD-1® Nude Mouse</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>NU/NU Mouse</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>BALB/c Nude Mouse</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>NIH III Nude Mouse</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
<td>Impaired</td>
</tr>
<tr>
<td>RNU Nude Rat</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>SCID Hairless Outbred (SHO®) Mouse</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>SCID Hairless Congenic (SHC™) Mouse</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>SCID/NcR Mouse (BALB/c Background)</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Fox Chase SCID® (C.B-17 SCID) Congenic Mouse*</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Fox Chase SCID® Beige Mouse*</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Impaired</td>
</tr>
<tr>
<td>NOD SCID Mouse</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Impaired</td>
</tr>
</tbody>
</table>

*Tumor growth data is available. For more information, please go to www.criver.com/immunodeficient.

#### Additional Oncology Models

Charles River offers additional models that support researchers as they investigate the biological, mechanistic and genetic basis of oncological 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.
Drug Discovery
Leveraging our broad portfolio and in-depth scientific expertise, Charles River Discovery Services work closely with you to support your complex discovery programs and expeditiously provide high-quality results.

Charles River offers target discovery to development candidate nomination capabilities as both standalone and fully integrated programs. In the last 15 years, integrated drug discovery projects performed at Charles River have delivered its partners 11 oncology development candidates (most advanced is in Phase III).

Clinically relevant cell models for screening, target discovery and validation
Discovery Services offers clients access to a portfolio of disease-relevant cell models and assays. In addition, our scientists have world-leading and proprietary expertise in adenoviral technologies to discover and validate novel drug targets in human primary cell systems. Readily available adenoviral shRNA (SilenceSelect® > 19,000 shRNAs) and cDNA (FLeXSelect®) libraries targeting the human druggable genome can be used for both target discovery, target validation and mode-of-action studies in human primary cell assays.

Assay Development and Screening
Our assay development and screening group is highly regarded and routinely employs high-throughput screening (HTS) technology to identify small molecules using both biochemical assays and cellular model systems, which modulate the activity of a wide range of target classes (including, proteases, kinases, GPCRs, ion channels, phosphatases, nuclear hormone receptors, epigenetic players and protein-protein interactions).

In Vitro Assay Services
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.

More than 300 human cell lines are available for standard assay platforms and custom development. These platforms and development programs include:
- Cell proliferation, IC50 determination
- Apoptosis assays
- Combination assays, Chou-Talalay
- Flow cytometry
- Biomarker analysis
- Multiplexed cytokine analysis
- Cytokine induction assays
- Custom assay design

Structural Biology and Biophysics
Our structural biology group has expertise in protein expression, protein purification, crystallization and structure determination by X-ray crystallography. We also provide a variety of biophysical orthogonal assay platforms that can be used to quantitatively measure small molecule and/or fragment binding to protein targets, including SPR, ITC, thermal shift, thermophoresis and native mass spectrometry.

Chemistry
Our chemistry department comprises over 130 chemists, with an additional 20 analytical and purification chemists and an 11-member computer-aided drug design (CADD) team. Collectively, this team provides highly effective fragment-to-lead, hit-to-lead and lead optimization capabilities and expertise and is responsible for delivering 11 oncology candidates over the last 15 years.

ADME/PK
We provide advanced capabilities for optimization of ADME and pharmacokinetics through a unique combination of technology and expertise. The capabilities of the ADME/PK group include a full panel of assays for in vitro and in vivo measurement of pharmacokinetic characteristics across a range of species. From an in vivo perspective, the group has a wealth of expertise across a wide range of dosing routes, including intramuscular, intravenous, intraperitoneal, oral, subcutaneous, minipump continuous infusion, intratracheal, intranasal, dry powder inhalation, suspension inhalation and whole-body aerosol.

In Vivo Services
Charles River applies a number of key technologies to the evaluation of anticancer activity and therapeutic effects. 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.

Coupling our in vitro capabilities 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.
# Human Tumor Xenografts in Nude Mice

**Models with Standard of Care In Vivo Profile Established**

<table>
<thead>
<tr>
<th>Histotype</th>
<th>Cell Line</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bladder</td>
<td>SW780</td>
</tr>
<tr>
<td>Brain</td>
<td>SK-N-AS, U87 MG, U-251, SF-295</td>
</tr>
<tr>
<td>Breast</td>
<td>BT474, HCC-1954, JIMT-1, MCF-7, MDA-MB-231, MX-1</td>
</tr>
<tr>
<td>Colon</td>
<td>CL-34, COLO 205, DLD-1, HCT 116, HCT-15, HT-29, LoVo, LS-174T, LS411N, RKO, SW-480, SW-620</td>
</tr>
<tr>
<td>Epithelial</td>
<td>A-431</td>
</tr>
<tr>
<td>Gastric</td>
<td>MKN-45, N87, SNU-5</td>
</tr>
<tr>
<td>Head and Neck</td>
<td>FaDu</td>
</tr>
<tr>
<td>Leukemia</td>
<td>HL-60, K-562, MOLT-4, MV4-11, SET2</td>
</tr>
<tr>
<td>Liver</td>
<td>Hep3B, SNU-398</td>
</tr>
<tr>
<td>Lung (small cell)</td>
<td>DMS 114, H69, H82, H211, H526, SHP-77</td>
</tr>
<tr>
<td>Lymphoma</td>
<td>Daudi, DoHH-2, Granta 519, Namalwa, Raji B, Ramos, REC-1, RL, SU-DHL-4, WSU-DLCL2</td>
</tr>
<tr>
<td>Melanoma</td>
<td>A2058, A375, IGR-37, SK-MEL-5</td>
</tr>
<tr>
<td>Mesothelioma</td>
<td>MSTD-211H</td>
</tr>
<tr>
<td>Multiple Myeloma</td>
<td>H929, OPM-2, RPMI 8226</td>
</tr>
<tr>
<td>Ovarian</td>
<td>A2170, IGR0V1, OVCAR-3, OVCAR-5, SK-OV-3, TOV-21G</td>
</tr>
<tr>
<td>Pancreas</td>
<td>BxPC-3, Capan-1, HPAC, KP4, Mia PaCa-2, Panc-1</td>
</tr>
<tr>
<td>Prostate</td>
<td>22Rv1, DU 145, MDA-PCa2B, PC3</td>
</tr>
<tr>
<td>Renal</td>
<td>786-0, Caki-1, Caki-2, G-401, G-402</td>
</tr>
<tr>
<td>Sarcoma</td>
<td>HT-1080, SJSA-1</td>
</tr>
<tr>
<td>Thyroid</td>
<td>8505C, FTC-238</td>
</tr>
<tr>
<td>Uterine</td>
<td>ECC-1, MFE-280</td>
</tr>
</tbody>
</table>

**In Vivo Established Models with Standard of Care Profile Not Yet Established**

<table>
<thead>
<tr>
<th>Histotype</th>
<th>Cell Line</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adrenal</td>
<td>H295R</td>
</tr>
<tr>
<td>Brain</td>
<td>SF-295, SK-N-MC</td>
</tr>
<tr>
<td>Breast</td>
<td>HCC70, HCC-1806</td>
</tr>
<tr>
<td>Leukemia</td>
<td>HEL92.1.7, RS4;11, THP-1</td>
</tr>
<tr>
<td>Liver</td>
<td>HuH-7</td>
</tr>
<tr>
<td>Lung</td>
<td>COR-L23, H1581, H1993</td>
</tr>
<tr>
<td>Melanoma</td>
<td>CHL-1, COLO 800, IGR-1, IGR-37, SK-MEL-24, UACC-62</td>
</tr>
<tr>
<td>Thyroid</td>
<td>K1</td>
</tr>
<tr>
<td>Uterine</td>
<td>HEC-1-A, HEC-1-B</td>
</tr>
</tbody>
</table>

## Human Tumor Xenografts in Nude Rats

### Histotype | Cell Line
--- | ---
Adrenal | H295R
Brain | U87MG
Breast | MDA-MB-231, MX-1
Colon | HCT116, HT29
Epidermoid | A431
Lung | H460, MV522
Melanoma | A2058, A375
Ovarian | A2780
Pancreatic | MiaPaCa-2
Prostate | PC3

### Murine Tumor Models

| Histotype | Cell Line
--- | ---
Breast | 4T1
Colon | Colon26, CT26, MC38
Fibrosarcoma | WEHI164
Glioma | GL261
Leukemia | L1210, P388
Lung | KLN 205, Lewis Lung
Lymphoma | A20, EL4, L5178-R
Melanoma | B16F0, CloudmanS91
Renal | Renca
Syngeneic Mouse Models and Flow Cytometry
Charles River offers a broad range of syngeneic mouse models in a number of histotypes, in both subcutaneous and systemic formats. Representative data describing the response to standards of care is available. In addition, multiple clones of known immunotherapeutic antibodies directed against targets such as CTLA-4, PD-1, and PDL-1 are being characterized to assist in proper selection for combination therapies. Initiation of treatment and clone selection has been determined to strongly dictate efficacy outcomes.

Our in-house flow cytometry enables validation of a functional immune system and allows us the ability to determine various cell populations. Evaluation of these cell populations then makes it possible to characterize an immune response elicited from novel therapeutics.

Methods for assessing immune cells such as CD4+ and CD8+ effector T cells, regulatory T cells and myeloid-derived suppressor cells in tumor-bearing animals have been validated. Custom panels are also available to meet your specific program needs.

Patient-Derived Human Tumor Grafts
Charles River defines patient-derived tumor grafts as explants established as models at low passage numbers (average mean of 6 passes removed from patient). They have not been grown in plastic or propagated as cell cultures.

Establishing xenograft tumor models from patient-derived tumor tissue (PDTT) at low passage is believed to conserve original tumor characteristics such as heterogeneous histology, clinical biomolecular signature, malignant phenotypes and genotypes, tumor architecture, and tumor vasculature. Based on this prevalent hypothesis, patient-derived tumor grafts are believed to offer relevant predictive insights into clinical outcomes when evaluating the efficacy of novel cancer therapies.

The models were established by implanting tissue obtained from clinical centers in the US into mice. After a minimal number of passages through NOD-SCID and nude mice, the models were banked and then profiled.

Profiling includes:
- Efficacy studies using Standards Of Care (SOC)
- Next-gen deep sequencing of 200+ cancer-related genes
- RNA expression
- DNA copy number
- Protein analysis (total and phospho-protein profiling)

Validated histotypes:
- Bladder
- Brain
- Breast
- Colon
- Gall bladder
- Kidney
- Liver
- Melanoma
- Non-small cell lung cancer
- Ovarian
- Pancreas
- Thyroid
- Uterine

Oncology Study Models
Our broad range of study models and support services allows clients to choose the most appropriate study design and screening method to identify promising compounds and optimize lead candidates.

- Orthotopic Tumor Models
  - Brain
  - Renal
  - Colon
  - Breast
  - Ovarian
- Angiogenesis – corneal micropocket assay
- Cachexia – Yoshica ascites hepatoma model
- Neurotoxicity – taxane-induced neurotoxicity

Efficacy evaluation can be combined with:
- Hematology (CBC/Diff) analysis
- Pharmacokinetic or bioavailability sampling and analysis
- Histopathology or tissue sampling
- Biomarker screening, sampling or evaluation
Combination Chemotherapy
Multiple therapeutic agents are often given together to treat cancer. Incorporating profiled chemotherapeutic effects 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 all 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.

Biomarkers
Identification and quantification 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.

Novel Biomarker Identification
Charles River has broad expertise in biomarker identification and assay development across a range of therapeutic areas, including oncology. Capabilities span the identification and validation of biomarkers and the development of quantitative assays in primary cells and disease tissue, pharmacodynamic and disease models, and as efficacy and translational medicine markers in the clinic.

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.

Safety Assessment
Charles River has the experience, range of services and expertise to help you successfully initiate and complete critical phases of preclinical oncology 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
- General toxicology
- Specialty toxicology
- Pathology
- Laboratory sciences