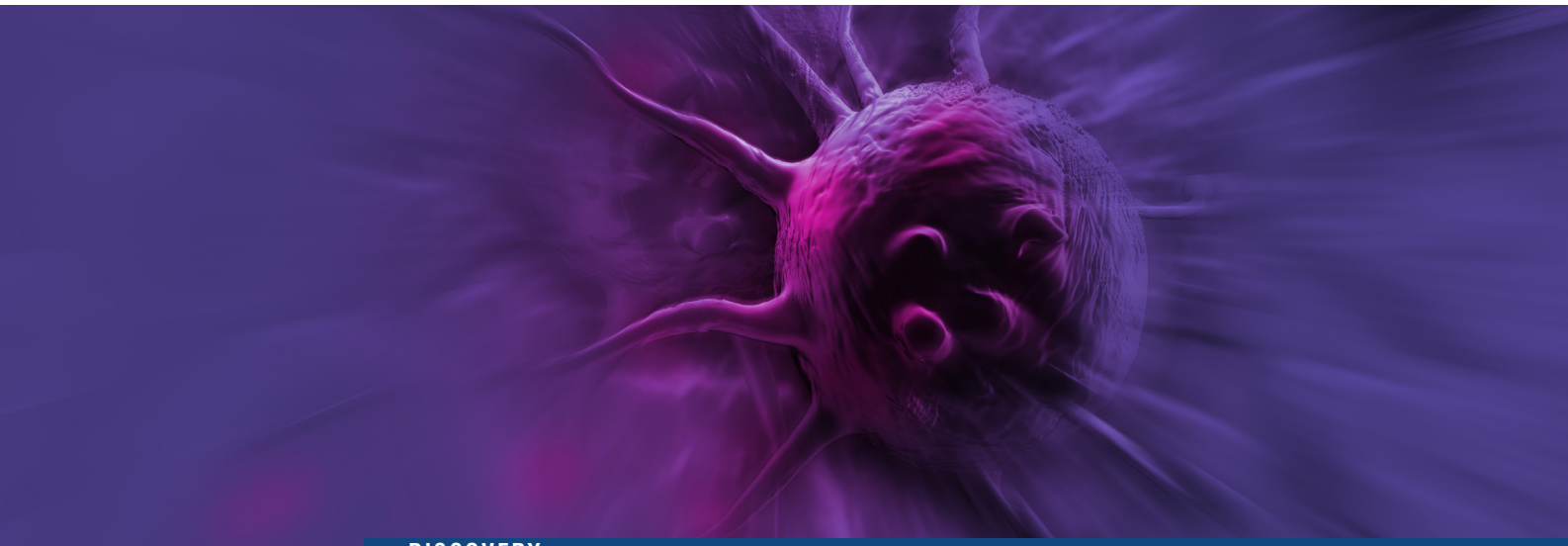
charles river



DISCOVERY

Oncology Drug Discovery Capabilities

Charles River's experience with oncology drug discovery and development spans all phases, from target identification to IND. Utilizing the most effective combination of tools available to identify promising compounds, our broad range of models and support services allows clients to choose the most appropriate study design and screening method to identify promising compounds and optimize lead candidates. We work with clients through every step of the process to streamline preclinical programs, determine the optimal outsourcing strategy and provide data in real time via secure online client portals.

Services and Tools for Oncology Drug Discovery:

- Target identification
- Hit finding
- Lead optimization
- Xenografts
- Syngeneic models
- Patient-derived tumor models
- Humanized models
- Orthotopic models
- Single mouse trials
- Imaging
- Flow cytometry
- Biomarkers and bioinformatics
- 2D and 3D screening
- Safety assessment
- Study management

EVERY STEP OF THE WAY

Target Discovery

Charles River's target discovery group has delivered novel validated drug targets in oncology for over a decade. Efficient target identification results from high-throughput screening of disease-relevant cell lines (PhenoFocus™), including patient-derived disease and normal cells, primary cell lines and stem cell-derived cells. Our current cell line portfolio includes over 100 cell-based assays to screen targets in over 20 disease areas. In addition to the latest screening methods such as CRISPR genome editing technology, adenoviral-based gene overexpression and RNA interference (SilenceSelect™) knockdown, we offer custom assay development and multi-parametric screening readouts, including FACS, bead-based assays (e.g., Luminex®) and plate-based assays (e.g., Meso Scale Discovery).

Hit Finding

Charles River offers state-of-the-art screening platforms for the identification of hit compounds across the spectrum of gene and target classes. We supplement our high-throughput screening platforms with virtual screening approaches for hit enrichment; this expansion process is a cost-effective way to enlarge the pool of active compounds following a screen and gain early structure-activity relationship (SAR) data. By examining chemical structures that were found to have activity in the primary screen, related compounds are selected from the in-house library for follow-on screening. Fragment-based screening includes a high-quality fragment library, screening methods and in-house structural biology support. In addition to the use of our in-house libraries, we also provide compound screening services for client libraries.

Lead Optimization

Charles River's lead optimization services are designed to demonstrate *in vivo* efficacy and identify possible safety concerns early in the drug discovery process. This allows clients to focus on candidate compounds that are most likely to succeed in subsequent testing. We tailor individual lead optimization programs according to the client's therapeutic target and lead compound type. Charles River has a wide array of areas of expertise, including biomarker identification and testing, *in vitro* and *in vivo* drug metabolism and pharmacokinetics (ADME), non-GLP toxicology and *in vivo* pharmacology.

Xenografts

Our broad range of tumor lines ensures a wide variety of testing options for each compound. We offer over 400 cell lines for *in vitro* studies, with over 200 models validated for *in vivo* growth. When required, our team can work with clients to develop custom models. We routinely evaluate our portfolio of xenograft models for Short Tandem Repeat (STR) analysis and response to standards of care and use this data to guide study design.

Syngeneic Models

Cancer immunotherapies are designed to work in conjunction with a patient's immune system to increase native anti-tumor responses. Our syngeneic mouse portfolio provides an effective approach for studying how cancer therapies perform in the presence of a functional immune system. We offer a broad range of syngeneic tumor models with well-characterized responses to known immune checkpoint inhibitors (e.g., anti-PDL-1, anti-PD-1 and anti-CTLA-4), as well as baseline tumor infiltrate flow data to inform model selection. Whole exome sequencing data enhances our ability to leverage these models in predicting sensitivity to targeted therapies.

Flow Cytometry

Our in-house multiplex flow cytometry enables a comprehensive analysis of the immune system, allowing identification of various cell populations and deep interrogation of an immune response elicited from novel therapeutics. With a streamlined process for tissue dissociation, cell isolation, staining and acquisition, systemic and tumor-infiltrating immune cells can be processed rapidly to give clients the flexibility of reviewing data and making quick decisions about compounds and studies.

Patient-Derived Tumor Models

Our portfolio consists hundreds of fully characterized, proprietary patient-derived xenografts (PDXs) which represent all major histotypes and tumors, and provide extensive background and characterization.

Our PDX portfolio includes:

- Subcutaneous, orthotopic and disseminated models
- Extensive molecular and pharmacological characterization
- Integrated approach using the same PDX models and/or the corresponding cell line
- Identification of biomarkers, which help identify target patient populations and predict tumor sensitivity of compounds
- Constant addition of new models established through international collaborations with research hospitals and universities

Single Mouse Trials

The single mouse trial (SMT) format for *in vivo* PDX studies addresses the need for compound testing in larger, more diverse tumor populations. This format employs a single mouse per PDX model and treatment arm, thereby enabling a cost-effective investigation of *in vivo* efficacy in large panels of PDX models. The SMT format reliably identifies compounds that are strongly active (or inactive) across a panel of tumor models, and can be used to investigate the most promising compounds, new indications or optimal drug combinations.

Humanized Models

Humanized mouse models are a unique tool to assess the anti-tumor response of the human immune system to checkpoint inhibitors. We offer studies on both PDX and traditional xenograft mouse models in this test system for evaluating the response to immune checkpoint inhibitors in humanized mouse models.

Orthotopic Models

Orthotopic implantation of tumor models supports assessment of tumor development in a complimentary environment and provides efficacy evaluation in a preclinical tumor model mimicking the disease process in humans. This allows for a more representative strategy of primary tumor growth, metastatic activity, and response to therapy scenarios to be more accurately captured. We evaluate disease progress through a variety of methods, including clinical signs, survival study design and our imaging platform utilizing both *in vivo* and *ex vivo* capabilities. We have refined our technique and surgical skills to offer a selection of orthotopic models across many organ systems, including bladder, intracranial, intratibial, mammary resection, spleen, pancreas, prostate, liver, and ovarian.

Imaging

Our team has validated the use of 2D and 3D *in vivo* optical imaging (bioluminescence and fluorescence) for applications such as examining biodistribution of antibodies or immune cells in tumor-bearing animals, and those that quantify cancer-related biomarkers. Imaging data can help researchers optimize dose and delivery strategies, which ultimately improves a therapy's translation to the clinic. More complex studies use a combination of luciferase and fluorescence imaging to track two differently radiolabeled tumors and therapies within a precise anatomical microenvironment to reveal new options to improve treatment outcomes.

Biomarkers, Bioinformatics and Online Tumor Model Database

Our extensive background data and data generated from studies can be used for a wide variety of biomarker and bioinformatics analyses, such as:

- Identification of a large number of compounds in diverse tumor populations
- Efficient and reliable identification of treatments with broad anti-tumor activity
- Identification of resistance mechanisms
- Strategic exploration of new drug combinations
- Comprehensive exploration of one histotype
- Screening of a particular molecular characteristic
- Generation of data for biomarker analysis and identification

Our online compendium of tumor models allows clients to search by features of interest to facilitate model selection, whether it be for cell line screening, 3D culture assays or an *in vivo* study. Search parameters include histologies, gene expression, copy number variation and whole exome sequencing data, or a combination search across several molecular properties.

2D and 3D Screening

Our extensive *in vitro* portfolio provides the foundation for a comprehensive screening approach. With over 400 publicly available cell lines and more than 80 proprietary cell lines derived from our portfolio of PDX models, as well as over 300 PDX-derived explants, we can design the best strategy for assessing a molecule based on any combination of tumor histotypes, molecular subtypes and drug sensitivity.

Safety Assessment

Charles River has the experience, range of services and expertise to help clients 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 collaborate with clients to develop and execute individual studies or customized testing programs to ensure that safety and efficacy assessments are conducted in the most efficient manner.

Study Management

A dedicated team consisting of scientists, technical personnel and a project manager is assigned at project initiation to manage the study, from design through execution. Weekly verified data updates and secure 24/7 online data access support interim decision-making. Upon study completion, our scientists apply their drug development industry experience to deliver timely statistical analysis of final results and a summary report suitable for regulatory submission. In life study decisions can be flexible and altered throughout the study based on previous results.