

# Pharmacology Services

We understand how important it is to determine if your test article is efficacious for its intended use to avoid failures further down the development path. Charles River Discovery and Imaging Services offers early research and proof-of-principle pharmacology studies in relevant animal models of human diseases to assist your efficacy evaluations. Our scientific team has extensive experience helping clients with the selection of appropriate models and assays, as well as collaborating to design new models that are tailored to meet the specific needs of a particular compound or discovery program.

In parallel to your efficacy studies, Charles River can assist in your non-GLP pharmacokinetic and lead optimization toxicology screening. Once your drug has passed the discovery milestone, we provide a seamless transition to preclinical development and clinical trials, creating a more efficient program that can save you valuable time and accelerate your drug development, exactly.

## ONCOLOGY

<b>Human Subcutaneous Tumor Xenograft Models</b>	Antitumor efficacy studies in immunodeficient rodents inoculated with human tumor cells (experience with over 200 cell lines)
<b>Syngeneic Tumor Models</b>	Antitumor efficacy studies in immunocompetent rodents inoculated with tumor cells derived from the same species/strain
<b>Orthotopic Tumor Models</b>	Antitumor efficacy studies in orthotopic models including brain, breast, liver, lung, and prostate using imaging modalities to track tumor burden (PET, MRI, CT, and bioluminescence)
<b>Metastatic Tumor Models</b>	Antitumor efficacy studies in models of metastatic tumors using either luciferase-expressing breast, colon, melanoma, and prostate cancer cells imaged with bioluminescence alone or in conjunction with other imaging modalities to track metastases
<b>Genetically Engineered Models of Tumor</b>	Antitumor efficacy studies in genetically engineered mouse models of tumor combined with imaging
<b>Combination Chemotherapy</b>	Antitumor efficacy studies in multiple models using a combination of known/marketed and novel chemotherapeutic agents
<b>Combination Radio- and Chemotherapy</b>	Antitumor efficacy studies in multiple models using a combination of chemotherapy and irradiation
<b>Maximum Tolerated Dose Determination</b>	Determination of the maximum tolerated dose of test article prior to antitumor efficacy studies
<b>Angiogenesis – Matrigel Plug Assay</b>	Screening of anti-angiogenic compounds Models: subcutaneous implants of Matrigel impregnated with angiogenic factors, treated with test articles End points: new vessel formation observed by tissue biomarkers of angiogenesis or by dynamic contrast-enhanced MRI
<b>In Vitro IC<sub>50</sub> Determination</b>	Growth inhibition of cultured tumor cells in response to chemotherapy Models: tumor cell culture, MTT assay End points: cell growth inhibition and cell death

## METABOLIC DISEASES

<b>Diabetes Mellitus</b>	Efficacy screening of antidiabetic therapies in models of insulin resistance, hyperinsulinemia, hyperglycemia, and overt diabetes Models: The Pound Mouse™, ZDF rat, Zucker rat, ZSF1 rat, GK rat, diet-induced obese mouse/rat, db/db mouse, ob/ob mouse, STZ-induced diabetes, pancreatectomy, etc. End points: serum glucose and insulin levels, glucose/insulin tolerance test, renal function (proteinuria), biomarkers (HgbA1c), etc.
<b>Obesity</b>	Efficacy screening of antiobesity therapies in models of genetic and diet-induced obesity Models: diet-induced obese mouse/rat, The Pound Mouse™, OP-CD rat, SHROB rat, ZDF rat, Zucker rat, ZSF1 rat, GK rat, db/db mouse, ob/ob mouse, etc. End points: food consumption, DEXA scan, feeding bout behavior, energy expenditure, serum lipid profile, glucose and insulin levels, glucose/insulin tolerance test, biomarkers, etc.
<b>Hyperlipidemia</b>	Efficacy screening of lipid-lowering therapies Models: high-cholesterol diet fed hamster End points: serum lipid profile, glucose and insulin levels, food consumption, etc.
<b>Renal Diseases</b>	Efficacy screening of therapies in renal failure models Models: 5/6 nephrectomy in rats, PCK rat, diabetic nephropathy (ZDF rat, Zucker rat, GK rat, db/db mouse, STZ or pancreatectomy-induced diabetes), hypertensive nephropathy (SHROB rat, Dahl/SS rat) End points: creatinine clearance, blood urea nitrogen, complete blood count, serum chemistry, hormones, biomarkers, etc.
<b>Inflammatory Bowel Disease, Ulcerative Colitis</b>	Efficacy screening of anti-inflammatory therapies Models: chemically induced IBD (e.g., TNBS), T-cell induced IBD in SCID mouse, IL-10 knockout mouse End points: clinical observation, macroscopic scoring of colon (including weight), histopathology of colon for inflammation, etc.
<b>Additional Metabolic Disease Models</b>	Gastric emptying, GI transit Emesis Drug-induced ileus NSAID-induced gastric lesions

## CARDIOVASCULAR DISEASES

<b>Atherosclerosis</b>	Efficacy testing of anti-atherosclerosis therapies in genetically predisposed animals Models: ApoE knockout mouse End points: serum lipid profile, atherosclerotic plaque development by high-resolution ultrasound imaging, histopathology of aorta for atherosclerotic plaques and recruitment of inflammatory cells, etc.
<b>Hypertension</b>	Efficacy testing of antihypertensive therapies in hypertensive models Models: SHR rat, SHR/stroke prone rat, Dahl/SS rat, SHROB rat, ZSF1 rat, drug-induced hypertension End points: blood pressure and heart rate (tail-cuff, telemetry, invasive monitoring), nephropathy (creatinine clearance, proteinuria), biomarkers, etc.
<b>Myocardial Ischemia/ Reperfusion, Restenosis, Thrombosis</b>	Efficacy testing of thrombolytic and anti-ischemia therapies Models: ischemia/reperfusion, thrombosis/thrombolysis, restenosis/intimal hyperplasia animal models End points: assessment of cardiac function by echocardiography, invasive LV and arterial pressure monitoring, coagulation panel, histopathology, etc.
<b>Additional Cardiovascular Disease Models</b>	Pulmonary hypertension Chronic heart failure Hypovolemic shock Endotoxemia-induced hypotension

## INFLAMMATORY DISEASES

<b>Asthma, Airway Hyper-Responsiveness</b>	Efficacy screening of anti-asthma and anti-inflammatory therapies Models: ovalbumin sensitization/challenge in mouse, rat, and guinea pig End points: pulmonary resistance and compliance, inflammatory biomarkers, histopathology, etc.
<b>Experimental Allergic Encephalitis</b>	Efficacy testing of anti-inflammatory therapies (autoimmune disease of the central nervous system mimicking multiple sclerosis) Models: mouse inoculated with MOG35-55 in Complete Freund's Adjuvant and pertussis toxin End points: clinical scoring, cytokine response, histopathology evaluation for demyelination and perivascular inflammation, etc.
<b>TNP-OVA Immunization</b>	Efficacy screening of anti-inflammatory therapies Models: immunization by TNP-ovalbumin End points: T-cell dependent antibody response (IgM and IgG response)
<b>Thioglycollate-Induced Peritonitis</b>	Efficacy screening of anti-inflammatory therapies Models: intraperitoneal injection of thioglycollate End points: inflammatory cell recruitment in peritoneal lavage
<b>LPS-Induced Cytokine Release</b>	Efficacy screening of anti-inflammatory therapies Models: acute lipopolysaccharide challenge End points: pro-inflammatory cytokine response
<b>Delayed-Type Hypersensitivity</b>	Efficacy screening of anti-inflammatory therapies Models: carrageenan-induced footpad edema, DNFB-induced ear edema End points: paw/ear edema
<b>Rheumatoid Arthritis</b>	Efficacy screening of anti-arthritic and anti-inflammatory therapies Models: induction with type II collagen, collagen antibody (LPS synchronized), or adjuvant End points: clinical scoring, paw thickness, paw weight, X-ray scoring, micro-CT, pro-inflammatory cytokines, biochemical markers of bone and cartilage turnover, histopathology for inflammation, bone resorption, cartilage damage, etc.
<b>Inflammatory Bowel Disease, Ulcerative Colitis</b>	Efficacy screening of anti-inflammatory therapies. Models: chemically induced IBD (e.g., TNBS), T-cell induced IBD in SCID mouse, IL-10 knockout mouse End points: clinical observation, macroscopic scoring of colon (including weight), histopathology of colon for inflammation, etc.
<b>Additional Inflammatory Disease Models</b>	Acute and chronic sponge granuloma Atherosclerosis LPS-induced acute lung inflammation Ethanol-induced prostatitis Uveitis Topical irritation Multi-organ failure Dermal recruitment

## INFECTIOUS DISEASES

<b>Infectious Disease Models (Up to BSL-2 Organisms)</b>	Antibacterial efficacy testing (feasibility assessed upon request) Antiviral efficacy testing (feasibility assessed upon request) Antifungal efficacy testing (Candida; feasibility assessed upon request) Protozoa model (Trichinella; feasibility assessed upon request) Prion model (feasibility assessed upon request)
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## RESPIRATORY DISEASES

<b>Asthma, Airway Hyper-Responsiveness</b>	Efficacy screening of anti-asthma and anti-inflammatory therapies Models: ovalbumin sensitization/challenge in mouse, rat, and guinea pig End points: pulmonary resistance and compliance, inflammatory biomarkers, histopathology, etc.
<b>Chronic Obstructive Pulmonary Disease</b>	Efficacy testing of anti-inflammatory therapies Models: cigarette smoke-induced COPD in mouse End points: pulmonary resistance and compliance, inflammation by histopathology, biomarkers in bronchoalveolar lavage fluid, etc.
<b>Additional Respiratory Disease Models</b>	Bleomycin-induced pulmonary fibrosis LPS-induced acute lung inflammation Citric acid-induced cough in guinea pigs

## CENTRAL NERVOUS SYSTEM DISORDERS

<b>Experimental Allergic Encephalitis</b>	Efficacy testing of anti-inflammatory therapies (autoimmune disease of the central nervous system mimicking multiple sclerosis) Models: mouse inoculated with MOG35-55 in Complete Freund's Adjuvant and pertussis toxin End points: clinical scoring, cytokine response, histopathology evaluation for demyelination and perivascular inflammation, etc.
<b>Locomotor Disorders</b>	Compound efficacy/toxicity evaluation of spontaneous locomotor activity, exploratory behavior, locomotor coordination and balance in locomotor disorders Models: neurodegenerative diseases such as Parkinson's Disease, Huntington's Disease, and amyotrophic lateral sclerosis (ALS); attention deficit and hyperactivity disorder; neuromuscular disorders; etc. End points: clinical scoring, open field activity system, rotarod, gait analysis, grip strength, histopathology, etc.
<b>Cognitive Disorders</b>	Compound efficacy/toxicity evaluation in cognitive disorders Models: Alzheimer's Disease and other cognitive disorders End points: clinical scoring, learning and memory tests using mazes, histopathology, etc.
<b>Additional CNS Disorders</b>	Epilepsy Depression Stroke (rat middle cerebral artery occlusion) Migraine Orthotopic brain tumors
<b>Additional CNS Capabilities</b>	CNS imaging (MRI, CT, PET, bioluminescence, fluorescence) Visual function (ophthalmology) Auditory function (auditory startle reflex, cochlear histopathology) Electrophysiology (nerve conduction, evoked response, EEG) Neurochemistry Intrathecal and intracerebroventricular drug delivery

## PAIN MODELS

<b>Pain Models</b>	Acetic acid writhing Thermal and mechanical hyperalgesia Corneal hyperalgesia Inflammatory pain – carageenan-induced paw edema Streptozotocin- or neurotoxin-induced chronic neuropathy Chung spinal nerve ligation
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## OPHTHALMOLOGY

<b>Angiogenesis Models</b>	Laser-induced choroid neovascularization Corneal pouch model
<b>Additional Ocular Disease Models</b>	Streptozotocin-induced diabetic retinopathy Laser-induced choroid neovascularization (age-related macular degeneration) Keratoconjunctivitis Uveitis CMV retinitis Glaucoma Corneal epithelial wound healing
<b>Additional Ophthalmology Capabilities</b>	Ocular implants and dosing Slit lamp photography Fundoscopy Electroretinography (ERG) and Visual Evoked Potential (VEP) Angiography Tonometry Optical coherence tomography (OCT) Ultrasound Electron microscopy Histopathology

## BONE AND CARTILAGE DISEASES

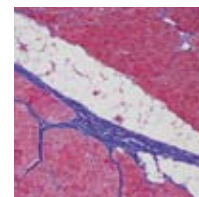
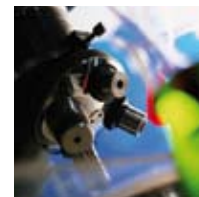
<b>Rheumatoid Arthritis</b>	Efficacy screening of anti-arthritic and anti-inflammatory therapies Models: induction with type II collagen, collagen antibody (LPS synchronized), or adjuvant End points: clinical scoring, paw thickness, paw weight, X-ray scoring, micro-CT, pro-inflammatory cytokines, biochemical markers of bone and cartilage turnover, histopathology for inflammation, bone resorption, cartilage damage, etc.
<b>Osteoarthritis</b>	Efficacy screening of anti-arthritic therapies Models: mono-iodoacetate-induced (MIA) osteoarthritis, anterior cruciate ligament transection (ACLT), partial meniscectomy End points: X-ray and DEXA scoring, micro-CT scanning, histopathology scoring, biochemical markers of bone and cartilage turnover, etc.
<b>Osteoporosis</b>	Efficacy screening of osteoporosis (anti-catabolic or anabolic) therapies, both prevention and treatment Models: gonadectomized models (ovariectomy or orchidectomy), Schenk weanling rat model (to test the effects of a compound on bone mineralization and growth), tibia periosteal injection in weanling rat (to test the effects of a compound on bone formation), thyroparathyroidectomy (TPTX) rat model (PTH-induced hypercalcemia model to test anti-catabolic compounds), 5/6 nephrectomized uremic rat model of renal osteodystrophy and secondary hyperparathyroidism End points: bone density and structure with DEXA scan, peripheral quantitative CT or micro-CT, biochemical markers of bone turnover, biomechanical bone strength testing, histomorphometry, serum calcium and hormone levels, etc.

## WOUND HEALING AND TISSUE REPAIR

<b>Wound Healing Models</b>	First and second intention wounds Partial and full-thickness blade wounds Partial and full-thickness burn wounds Abraded, punctate, surgical, infected, non-infected, diabetic skin and soft tissue lesions Histomorphometry and biomechanics strength testing of soft tissue
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## IMAGING SERVICES

<b>Magnetic Resonance Imaging (MRI)</b>	Anatomical and diffusion MRI of tumors Dynamic contrast-enhanced (DCE) MRI for quantification of anti-angiogenesis therapy <sup>19</sup> F MRI of macrophages in chronic inflammation
<b>Computed Tomography (CT)</b>	Soft tissue and bone imaging (e.g., rheumatoid arthritis) Evaluation of primary and metastatic tumor burden Imaging of blood flow and perfusion
<b>Positron Emission Tomography (PET)</b>	Applications in tumor, cardiovascular, neurological, and inflammatory diseases Glucose metabolism by <sup>18</sup> FDG PET Cellular proliferation by <sup>18</sup> FLT PET
<b>Bioluminescence and Fluorescence Imaging</b>	Visualization of luciferase-expressing orthotopic and metastatic tumor models Biodistribution of fluorescent-labeled test articles
<b>High-Resolution Ultrasound</b>	Assessment of embryonic viability, cardiac function and left ventricular mass (M-mode), cardiac outflow and valvular function (pulsed-wave Doppler), atherosclerotic plaque dimensions
<b>Dual-Energy X-Ray Absorptiometry (DEXA)</b>	DEXA scan is a noninvasive imaging modality that provides assessment of the fat vs. lean tissue ratio and bone mineral composition and density
<b>Digital X-Ray</b>	Assessment of organ size, bone density, and skeletal malformations



## PATHOLOGY, BIOMARKER, AND EXPRESSION TESTING SERVICES

<b>Necropsy</b>	Gross necropsy, organ collections, gross photographs
<b>Histopathology</b>	Routine H&E staining of tissues
<b>Specialty Pathology and Tissue Biomarkers</b>	Histomorphometry, immunohistochemistry, <i>in situ</i> hybridization to reveal tissue biomarker patterns
<b>Clinical Pathology</b>	Clinical chemistry, complete blood count (CBC) with differential, urinalysis
<b>Plasma Biomarkers</b>	Multi-analyte profiles (MAP) are comprehensive panels to evaluate multiple markers of infectious diseases, autoimmunity, metabolic and renal function, cardiovascular risk, as well as hormones, cytokines/chemokines, and acute phase reactants in 50 $\mu$ L of plasma
<b>Expression Testing</b>	Quantitative PCR to determine expression levels of target genes in efficacy/toxicity screening studies