Neuroscience Drug Discovery

Innovative drug discovery for neurological and psychiatric diseases

Charles River provides innovative, flexible and efficient drug discovery services with a strong emphasis on acute and chronic neurological diseases. Deep expertise in both *in vitro* and *in vivo* disease models, combined with key technological capabilities including behavioral testing and imaging, gives our clients the partner they need to advance their research programs. Our scientists, veterinarians, study directors, project managers and client services teams are committed to supporting our clients' drug discovery programs from early target identification through *in vivo* pharmacology and safety assessment.

Multidisciplinary expertise allows us to deliver insight and data to progress discovery programs in major neurological and psychiatric indications, including depression, schizophrenia, Alzheimer's disease, Parkinson's disease, neuropathic pain, epilepsy, multiple sclerosis, stroke and ischemia. Additionally, we have a growing portfolio of innovative assays and models to advance research in rare and orphan diseases. Our scientific teams partner with each client to help identify the appropriate assay or disease model that will be used to identify targets and hit compounds as well as optimize lead compounds.

To further accelerate therapy development, we offer fully validated *in vitro* models and assays and a comprehensive portfolio of *in vivo* animal models (including rodents and large animals) to perform efficacy, toxicology, pharmacokinetic/pharmacodynamics and bioanalytical studies. Our wide range of cutting-edge *in vivo* imaging modalities, comprehensive behavioral and biomarker endpoints, and translational tools enables more effective decision-making in development and helps move clients' research forward.

Services and Tools for Neuroscience Drug Discovery:

- Target identification
- Hit finding
- Lead optimization
- Translational tools

- *In vitro* pharmacology and toxicology
  - Human primary cells and induced pluripotent stem cells (hIPSCs)
  - Patient-derived brain tissues
  - Rodent primary cells

- *In vivo* pharmacology and toxicology
  - Neurodegenerative diseases
  - Neuromuscular diseases
  - Psychiatric diseases
  - Pain and migraine

EVERY STEP OF THE WAY

Target Identification

Our target discovery group has delivered novel validated drug targets in multiple therapeutics areas for over a decade. Efficient target identification results from high-throughput screening of disease-relevant cell lines (PhenoFocus™), including patient-derived disease and normal lines, primary cell lines and stem cell derived cells. The current portfolio includes more than 100 cell-based assays to screen targets in over 20 disease areas. The screening technologies employed include CRISPR gene editing, adenoviral-based gene overexpression and RNA interference (SilenceSelect™) knockdown. We offer custom assay developments and multi-parametric screening readouts, including FACS, bead-based (e.g., Luminex®) and plate-based assays (e.g., Meso Scale Discovery). Additional resources such as chemogenomics and biophysical measures (chromatography, SPR and X-ray crystallography) are also available.

Hit Finding

Discovery from Charles River offers state-of-the-art screening platforms for the identification of hit compounds across the spectrum of gene and target classes. The high-throughput screening platforms are supplemented by virtual screening approaches for hit enrichment. Our hit expansion process is a cost-effective way to enlarge the pool of active compounds following a screen and to gain early structure-activity relationship (SAR) data. Fragment-based screening at Charles River 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 program is designed to demonstrate *in vivo* efficacy and to 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. Individual lead optimization programs are tailored based on the 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.

Translational Tools

Charles River's range of translational tools includes advanced imaging, behavioral, physiological and cognitive testing combined with biomarker endpoint assessment. Newly expanded capabilities include microdialysis with bioanalysis, EEG, and electrophysiology in single cells and brain slices. State-of-the-art imaging capabilities include anatomical and functional MRI and MRS cellular metabolite profiling, as well as PET/CT and SPECT/CT. *In vivo* pharmacology and early safety and efficacy testing is utilized to further understand novel drug candidates' off-target effects and mechanism of action.

In Vitro Pharmacology and Toxicology

Charles River has developed a comprehensive portfolio of neuronal cell lines for complex cell-based assays to evaluate neurotoxicity or neuroprotective effects of therapeutic compounds. Our portfolio includes human ES cells and fetal brain-derived neurons and we have the capability to characterize and differentiate induced pluripotent stem cells (iPSCs) into neurons. Patient-derived brain tissues are a unique alternative to stem-cell-derived neuronal cell lines. Multiple cell types are isolated from the postmortem tissues, including microglia, astrocytes and preoligodendrocytes, for customized assays.

In Vivo Pharmacology and Toxicology

Charles River offers early stage *in vivo* screening and proof-of-principle pharmacology studies in animal models of acute and chronic diseases. Our scientific team has extensive experience validating existing animal models as well as collaborating to design new models to meet specific project needs. The portfolio of *in vivo* models includes neurodegenerative diseases (e.g., Alzheimer's disease, Parkinson's disease), psychiatric disorders (e.g., depression, schizophrenia, anxiety), neuropathic pain, and injury models. Additionally, Charles River offers extensive neurotoxoicology, neuropathology and behavioral screening programs to move efficacious compounds into the clinic efficiently.

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