Charles River is committed to developing a comprehensive portfolio of technologies and capabilities to support drug discovery and safety studies for therapies targeting neurological and psychiatric diseases. These experimental methodologies can be used for early discovery to identify drug targets and optimize lead compounds as well as for later pharmacology and toxicology studies. Each method is validated in relevant cell based assay systems and in vivo animal models of disease to generate predictive data that maximizes efficient translation from preclinical to clinical studies. Additionally, new technologies are added to the portfolio to improve sensitivity, efficacy and reproducibility at every stage of the drug discovery continuum. Our translational toolkit at Charles River encompasses biomarker development, pathology, behavioral and cognitive testing, electrophysiology, and state-of-the-art imaging methods. Robust preclinical testing in rodent and large animal models, combined with comprehensive pathology services and market-leading cardiac risk assessment services, helps shorten the time required to move a promising lead compound into the clinic.

Summary
Charles River offers neuroscience-specific translational tools which encompass biomarker development, behavioral and cognitive testing, electrophysiology, and state-of-the-art neuroimaging methods. These methods have been shown to dramatically increase the efficiency of lead candidate selection by providing earlier and more highly predictive data, compared with traditional measures.

Neuroscience Translational Tools:
Multimodal Technologies to Accelerate Pharmacology and Toxicology Studies

Services available:
• **Drug Discovery**
  - Biomarker development
  - Microdialysis with bioanalysis
  - Motor skills testing
  - Cognitive testing
  - Imaging
  - EEG

• **Safety Assessment**
  - Neurotoxicology
  - Cardiac risk assessment

Contact a neuroscience expert:
Visit criver.com/consult-pi-ds-cns-research

EVERY STEP OF THE WAY
Drug Discovery

Biomarker Development

Biomarkers are indispensable tools for drug discovery, as they are used extensively to assess the activity of novel therapeutic compounds, investigate the mechanism of action, and predict therapeutic efficacy. They are also critical endpoints to detect off-target effects and potential compound toxicity. Charles River’s expertise spans the identification of novel biomarkers across various disease areas, screening biomarkers to make critical go/no go decisions and translational biomarkers. Optimal translational biomarkers should be detectable, measurable, and translatable from animal models to man. Charles River’s expertise in biomarker identification and assay development in preclinical drug development is complemented by robust assay validation in a GLP-compliant environment for safety testing. Biomarker endpoints across neurological disease include behavioral assessments, physiological testing, imaging, and biological or chemical analytes.

Microdialysis

In support of our biomarker capabilities, we offer highly sensitive and specialized microdialysis techniques. With microdialysis, tiny probes are used to sample tissues and extracellular fluid in precise areas of the brain. This allows us to analyze the composition and amount of specific analytes, identify novel biomarkers, and assay known biomarkers such as PK/PD readouts. At Charles River, we offer multiple types of microdialysis services including conventional microdialysis, push-pull microdialysis and MetaQuant microdialysis. The push-pull method is used to sample high molecular analytes such as peptides, proteins, antibodies, protein aggregate, and interleukins, while the MetaQuant method is a proprietary method that uses customized probes to sample various tissues. Our deep experience with microdialysis enables a wide range of options for combining combining multiple probes probes across a broad array of applications. We can customize assays by combining PK or PD microdialysis techniques, and combining microdialysis with other methods such as behavior or EEG measurements.

Motor Skills Testing

Impairments in movement and gait, as well as in tasks requiring accuracy and coordination, are hallmarks of multiple neurological conditions, including Parkinson’s disease and ALS. Measurement of gross and fine motor phenotypic changes in response to a therapeutic modality or as a side effect of therapy are important clinical parameters in neurological disease drug development. Though used extensively to assess gross motor skill changes, the rotarod test is not considered a translational method. Our team has validated a robust kinematic method to assess fine motor impairment that translates from animal models to human patients. The experimental output is a high speed movie that is analyzed using proprietary algorithms to identify changes (mild or severe) in over 100 parameters. The MotoRater fine motor kinematic analysis reveals early changes in muscular or neuronal function in disease models to support the development of therapeutics that reverse or slow progressive degeneration and to test compounds that can cause fine motor impairment as a side effect.
Cognitive Testing
Cognitive decline is a hallmark of several neurodegenerative diseases and measurement of cognitive changes is integral to developing therapies targeting neurodegenerative diseases such as Alzheimer’s disease, Parkinson’s disease, etc. Cognitive testing has historically been performed using water mazes or contextual fear conditioning testing, but these methods do not directly translate to human conditions, and therefore cannot be compared directly with human cognitive assessment. To overcome this barrier, Charles River offers mouse behavior analysis via touchscreen-based tests and large animal cognitive analysis using CANTAB-based tasks and object retrieval tests. Offering distinct advantages over water maze or fear conditioning, touchscreen tests use images and actions similar to human assessments and are used to reliably test multiple neuropsychological parameters, including cognitive flexibility, learning, and memory.

Imaging
Neurological Imaging modalities help accelerate neurological drug discovery by providing predictive data that has more potential to translate to the clinic. Noninvasive imaging modalities (MRI, PET/CT, SPECT/CT, etc.) work well with in vivo pharmacology and safety projects that employ other experimental methods, and are ideally suited for longitudinal studies that include multiple milestones and endpoints. Our team has developed state-of-the-art imaging capabilities, including kinetic PET imaging, quantitative real-time autoradiography, autoradiography, Functional Ultrasound Imaging (FUS), nuclear imaging, and magnetic resonance spectroscopy (MRS) to noninvasively quantify metabolites in CNS tissues. We also offer MRI and SPECT imaging for rodents and large animal models.

EEG
Electroencephalogram (EEG) is a minimally invasive method to record electrical activity in the brain. It is used to assess changes in sleep state and seizures associated with brain trauma and dysfunction or neurological diseases. EEG patterns indicative of changes in underlying neuronal function show specific rhythms that can serve as translational biomarkers. Pharmaco-EEG is used to understand the effect of test compounds on brain activity and function when administered in an acute or chronic study paradigm. Noninvasive EEG measurements are easily combined with other techniques like behavior testing and microdialysis supporting a multi-modal approach to studying brain dysfunction. Understanding the effects of test compounds on the activity and function of the brain are essential in drug development and Charles River can perform continuous EEG following acute or chronic compound treatment in combination with PK/PD studies and behavioral testing.
Safety Assessment

Neurotoxicology
Charles River’s neurotoxicology program is well established and supported by a valuable historical control database for tests in developmental neurotoxicology. Our portfolio includes neurotoxicity screening tests for possible on- or off-target effects, specialized target tissue delivery, expanded investigative studies and developmental neurotoxicity. The assay areas include behavioral testing, chemical assays to quantify plasma biomarkers or neurotransmitter levels and comprehensive neuropathology services. Specific capabilities include:

- Neurobehavior, including locomotor assays, learning and memory testing, and observational batteries
- Neurochemistry, including quantification of endogenous levels of neurotransmitters
- Neuropathology, including qualitative neuropathological evaluations

Cardiac Risk Assessment

Charles River offers preclinical cardiac risk assessment services with industry-leading expertise. Our portfolio includes GLP-compliant hERG and action potential duration (ADP) assays, which are recommended for candidate selection and IND submissions. In vitro hERG patch clamp assays are the gold standard in cardiac safety evaluation for preclinical drug candidates, while ADP assays are useful to detect drug induced prolongation of action potentials and arrhythmia. We also offer cardiac channel panel tests using automated or manual patch clamp assays to evaluate multiple ion channels to assess cardiac risk associated with novel therapies.