charles river

Integrated Services for Cellular Therapeutic Development

The journey to market for a cellular therapy is challenging given the unique and high specialized nature of each individual program so it is crucial to choose a partner with proven experience developing these types of treatments and navigating the regulatory hurdles often associated with them. With over 70 years of experience, Charles River has a unique and comprehensive portfolio to support the development and execution of cellular therapy programs from animal model selection to discovery and safety testing through to clinical and CMC testing support. Our highly experienced scientific staff provides guidance every step of the way with sound strategies, working to mitigate common risk factors associated with the development of these types of products through protocols customized around the novel properties of each individual cellular therapy program. Our facilities in the United States, Canada, Britain, Finland, Netherlands, and Germany form a global scientific network, allowing us to provide our clients with flexible, comprehensive solutions to maximize resources and optimize results.

Areas of Expertise Include:

- Cell line characterization
- Animal model selection
- Proof of concept
- Biodistribution studies
- Imaging
- Molecular pathology & cell detection
- Toxicity evaluations
- GLP tumorgenicity studies
- Regulatory support & clinical translation
- Viral clearance testing
- Stability testing
- Cell banking
- Product & release testing

EVERY STEP OF THE WAY

Cell Line Characterization

In order to successfully develop a cellular therapy program that meets regulatory expectations, the cell source, type, and degree of manipulation must be considered to establish well-characterized cell product manufacturing practices and controls. This assures product quality and consistency, essential to safety studies. Charles River's characterization capabilities include identity and composition, viability and stability, as well as purity and sterility. To properly identify the cells, a series of translation biomarkers must be developed, including morphology, surface, and genetic markers. These are qualified and optimized for the cell target that reveal pharmacologic actions, are used for lot release, and later serve as tools for evaluating *in vivo* safety study results. GLP-compliant molecular pathology services at Charles River (as described below) allow exact identification of cells in tissues.

Animal Model Selection

Careful choice of a species is a must for cellular therapy programs. Models need to be appropriate for proof of concept studies as well as pharmacologically sensitive to serve as a progressive host for the therapeutic in development, keeping in mind the intended clinical route of administration. Multiple Charles River locations offer immunodeficient rodent models, large animal models, neonates, surgically altered models, and tumor/syngeneic models for both pilot and safety assessment studies. These are suitable for a range of therapeutic areas, including but not limited to inflammation, bone disease, neuroscience research, and metabolic disease. Our surgeons have vast experience in surgical cell implantation methods which mimic even the most specialized clinical routes of administration (e.g., injection into the brain or spinal cord using stereotaxic devices or intraocular instillations).

Proof of Concept

Pilot tolerability studies provide preliminary data on the maximum tolerated does, cell survival, and early testing of the cellular product. These are used to provide a strong proof of concept in the selected animal model, including elucidating the route of administration and dosing regimen, dose response, and onset as well as durability of effects.

Biodistribution Studies

Our non-GLP and GLP biodistribution studies use expansive molecular pathology immunophenotyping capabilities to track the distribution and fate of implanted cells. This allows us to understand where in an organism a cellular therapy goes, how long it stays, and how it engages with the targeted organ or tissue. With this data, we can then evaluate the cellular therapy product for survival, integration in non-target tissues, and the ability to endure in the animal model at the target site for durability, differentiation, and *in vivo* migration. Early biodistribution assessments can help guide the choice of animal model and the duration of toxicology studies. Later biodistribution studies can be built into ongoing toxicology work to conserve animals and reduce program costs.

Imaging

Noninvasive molecular imaging methods provide crucial data on the biodistribution of cellular therapies. At multiple sites globally, we conduct *in vivo* imaging using positron emission tomography (PET) and/or single-photon emission computerized tomography (SPECT), with repeated measures over several time points using a single animal subject. These are highly effective alternatives to traditional *ex vivo* biodistribution assessments which require a greater number of animal subjects assessed over multiple time points. Additional noninvasive imaging assessments include fluorescent imaging probes and/or magnetic resonance imaging (MRI). Tracking cell-based therapeutics through molecular imaging offers great advantages and insights into cell-based treatments, as well as applications beyond tracking biodistribution such as determining proof of concept for target engagement efficacy.

Molecular Pathology & Cell Detection

Reliable and robust markers for cell detection utilizing molecular or immunohistochemical techniques are essential for understanding the cell product biodistribution. Cell detection assessments can provide valuable information for selection of relevant animal models and study duration, as well as serve as the primary detection endpoints for the biodistribution evaluations. Morphological changes in cells are often accompanied by alterations in DNA, RNA, or protein molecules. A further understanding of these molecular changes can help to understand target distribution and pharmacology as well as the elucidation of mechanism(s) of toxicity and/or efficacy. Our team combines a strong background in molecular biology and histopathology to relate cell presence or gene expression to tissue histomorphology in both normal tissues and therapeutic models of disease. This provides valuable functional information and results in the best possible interpretation and troubleshooting of molecular-based tools, including in situ hybridization (ISH), immunohistochemistry (IHC), and various PCR-based methods.

Toxicity Evaluations

Our staff of toxicologists, pathologists, veterinary surgeons and support staff perform toxicological evaluations, including clinical observations, body weight and feed consumption measurements, ophthalmologic, and clinical pathology evaluations, as well as complete necropsy, organ weight, and histopathology assessments. Our scientists also evaluate immunogenicity and the irreversibility of engraftment – additional assessments crucial to a cell therapy program.

GLP Tumorigenicity Studies

The phenotypic stability (e.g., tumorigenic potential or ectopic tissue formation) of a cellular product is a serious concern for most cellular therapies and must be addressed. Our team of experts has extensive experience performing tumorgenicity studies to assess the potential for cell phenotypic stability or ectopic tissue formation by a cellular therapy product in an immunocompromised rodent through single subcutaneous or clinical route administration. Any masses or ectopic tissues identified are evaluated to identify the source of the mass, be it host (mouse) or graft (cell product).

Regulatory Support & Clinical Translation

Our scientific experts, including a former FDA reviewing pharmacologist at the Centers for Drug Evaluation and Biologics Evaluation (CDER & CBER), have a deep understanding of regulatory expectations to help design the best strategy to advance a cellular therapy program. Having this scientific support is particularly crucial for cell therapy, as reviewers at CBER/FDA highly encourage pre-IND meetings from the Office of Cell, Gene, and Tissue Therapy at the start of each program to discuss current standards of practice in relation to the specific cellular therapy being developed. Not only can they assist with IND filing, but they can also help to identify clinical trial risk mitigation steps, establish clinical biomarkers to address translation gaps, and prepare for BLA filing.

Viral Clearance Testing

All manufacturers of cellular therapy products are required to assess the ability of the manufacturing process to generate a product safe for human use. Therefore, a viral clearance study is performed to evaluate key steps of the manufacturing process to ensure that it is effective at removing or inactivating viruses. Our scientists have extensive experience in the design and performance of viral clearance studies, including transmissible spongiform encephalopathy (TSE) clearance for a wide range of products. We take a customized approach that includes advice and regulatory support in the selection of process steps and model viruses, scaling-down of purification processes, and subsequent design of study protocols to ensure a successful program is established and reported to meet timelines.

Stability Testing

Cellular therapy products have distinguishing characteristics and the quality of these products must be tested under a variety of environmental factors (e.g., temperature, humidity, light) to confirm their stability during the intended storage period. We provide drug substance and final product stability testing and storage services in compliance with current International Conference on Harmonization (ICH) guidelines to support clinical studies, license applications, and postmarketing commitments.

Cell Banking

Our team collaborates with clients to develop scientifically sound and cost-effective cell bank programs and can provide the appropriate cell storage services, all under Good Manufacturing Practice (GMP) guidelines. Our experienced technical staff can customize a project to create and characterize master cell banks, working cell banks, research cell banks, end-of-production cells, and cells at the limit of *in vitro* cell age, according to client specifications.

Product & Release Testing

To ensure that cell therapies are produced according to the strict requirements of Good Manufacturing Practice (GMP), we provide a full range of product release support, from addressing biosafety concerns and analyzing potency using suitable bioassays, to determining purity and other biochemical characteristics. Our commitment to providing rapid turnaround times for testing helps minimize the period between production and release.