

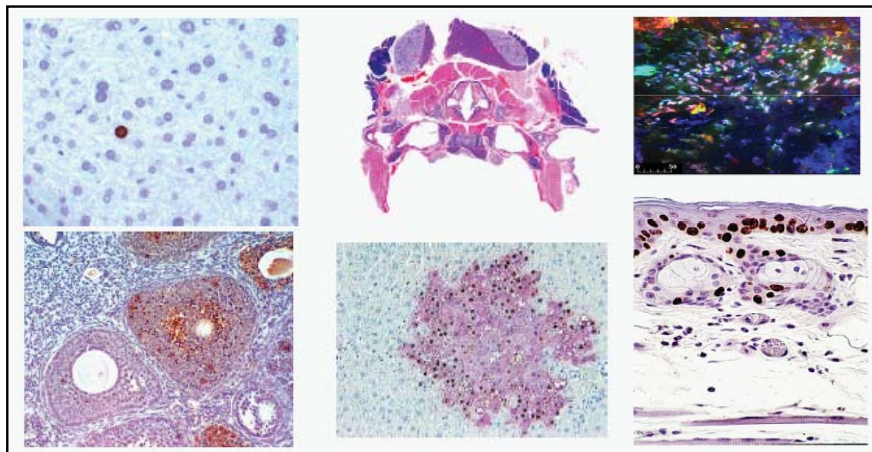
Tissue-Based Biomarkers

At Charles River we understand that biomarkers and surrogate end points are critical tools in the discovery and development of new drugs and therapies. Their measurements support target validation, proof of target, proof of mechanism, and proof of efficacy, and they are typically developed first in preclinical animal models of disease with translation to the clinic. Biomarkers are being applied clinically to identify patients at risk for disease, predict potential treatment responders or adverse event occurrences, and predict favorable clinical outcomes.

We offer biomarker services as part of our specialty pathology program, which involves immunohistochemical detection of marker proteins within target tissues. With a growing number of novel targeted drugs being developed against molecular sites controlling cell growth, cell death, and cell recruitment, the progress in understanding the molecular biology of disease is providing a growing range of targets for drug discovery. Key to this understanding is the pathology-based characterization of tissue changes at the cellular level, referred to as “phenotypic anchoring.”

The post-genomic era has yielded a wealth of new genes with unknown functions. Simultaneously, there is an increasing appreciation that gene expression profiling alone is not sufficient, and that protein expression and activity are needed to determine gene function and to define mechanisms underlying cell function and disease. With a plethora of antibodies available to target molecular sites that control cellular processes, we use antibodies of the highest possible quality to visualize protein expression at the cellular level by light and fluorescent microscopy within intact tissue.

Protein localization in tissues using immunohistochemistry with comprehensive histopathologic interpretation

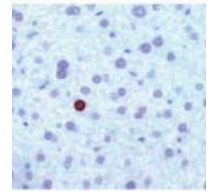


Biomarker Examples

- CD-31, CD-105 for angiogenesis
- PCNA, Ki-67 for cell proliferation
- TUNEL, caspase-3 for apoptosis
- Growth factors and receptors
- Lymphocyte markers

Applications

- Angiogenesis-based therapeutics
- Animal models of disease
- Apoptosis-based therapies
- Clinical trials for targeted cancer drugs
- Immunomodulation
- Medical devices
- Stem cell and cell-based therapies
- Tumor xenograft models

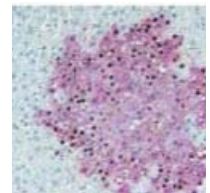


Preclinical to Clinical Biomarker Program

It is important to note that for clinical trials, the clinicians conducting the studies are responsible for diagnosis and assessing outcome for “go/no go” decisions. In contrast, we are providing correlative studies that are designed as an adjunct to the clinical trial. These studies assist in determining whether a drug is reaching the intended target and whether the drug works the same way in humans as it has in animals.



Our pathologists and scientists will work closely with you to identify which markers to assess, design a scientifically rigorous approach to sample testing, and provide a bridge between preclinical and clinical biomarker development.



| Biomarkers from Discovery Through Development | | |
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| Types of Biomarkers | Critical Questions | Key Outcome |
| Target Validation | <p>Is your gene or gene product of interest commonly expressed in target tissues?</p> <p>Does this target play an important role in the disease of interest?</p> | Determines whether your target is present in a variety of normal and disease tissues |
| Proof of Target | Does your drug modulate the target? | Measures activated (phosphorylated) vs. unactivated target using activation-state antibodies |
| Proof of Mechanism | What biological consequences are due to target modulation? | Evaluates modulation of cell proliferation, apoptosis, angiogenesis, and other key biological processes in target tissues |
| Proof of Efficacy | <p>Is your drug working?</p> <p>What markers correlate with favorable drug action?</p> | Identifies surrogate end points |