Selecting a Laboratory to Support Your Clinical Trial

Highlights

- **Clinical trials are integral to the development of new treatments for patients with a variety of diseases, including cancer**
- **Oncology clinical trials frequently use histological techniques to analyze patient biopsies**
- **New tests may be developed to characterize results of novel biomarkers and the effect of therapeutic antibodies**
- **CLIA-certification ensures clinical trial samples are processed according to similar quality standards required for diagnostic tests**

Introduction

Immunotherapy is one of the most promising approaches to cancer treatment that works by harnessing the body's own immune system to fight cancer. The market for immunotherapies has recently exploded, and new drugs have been approved to treat a variety of cancers. But before a new therapy can be used by the general population, it must first undergo extensive testing for safety and efficacy in a clinical trial. Clinical trials are integral to the development of novel therapies for cancer patients. Each trial must be carefully designed to include tests to determine the appropriate dosage, side effects, and therapeutic benefit of the investigational drug. Selecting the right laboratory to support both your clinical trial and pre-clinical research can improve the success rate of drug development.

Tip: Select a laboratory that specializes in histology.

Histological Stains are Essential in Oncology Clinical Trials

Histological techniques like hematoxylin and eosin (H&E) and immunohistochemistry (IHC) staining are essential in oncology clinical trials. Tissue sections of patient biopsies are stained and analyzed to:

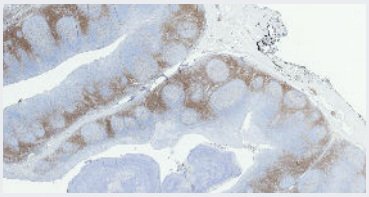
- Evaluate therapeutic efficacy
- Assess pharmacodynamic effects
- Enroll and place patients in trial arms
- Monitor key cell populations

H&E staining is a diagnostic tool that reveals cell morphology and the broader tissue architecture. Pathologists interpret tissue patterns to make cancer diagnoses and characterize underlying pathology (e.g., neoplasia, angiogenesis, necrosis, etc.). IHC staining reveals the localization and expression levels of specific cellular proteins. IHC tests also assist with diagnosis and accurate tumor classification. Patients who meet the diagnostic criteria are matched with clinical trials and trial arms to test new therapies.

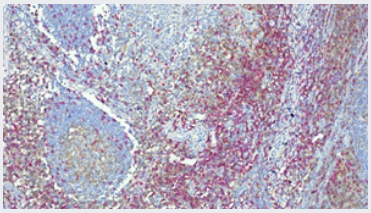
These techniques are also frequently used to monitor patients on treatment, since molecular changes in post-treatment biopsies are indicative of the effectiveness of the investigational drug. The results help make decisions on whether individual patients should continue in the clinical trial and, more broadly, determine whether the trial is effective. Select a laboratory that specializes in histology to run your precious clinical trial samples.

Pre-Validated IHC Tests

CD3	Ki67
CD4	p21
CD8	p53
CD20	Pax-5
CD21	PCNA
CD45	PD-1
CD57	PD-L1
CD163	pEGFR
c-Myc	PTEN
EGFR	Rb
FoxP3	Sox-2
HER2	ZAP-70
HSP70	& more



A. IHC stain for CD8+ cells in tonsil.



B. Multiplex IHC stain for CD4+ and CD8+ cells.

Authors: MADISON TYLER, JESSICA RUNYON, VIJAY BAICHWAL

Tests for Novel Biomarkers Must Be Thoroughly Validated

Identifying relevant biological markers or "biomarkers" of disease is integral to drug development. Biomarkers may be signs of normal or abnormal processes and may be used to see how well the body responds to treatment as an early indication of drug effectiveness or toxicity. Validated IHC and fluorescence in situ hybridization (FISH) tests exist for a variety of protein and genetic biomarkers relevant to cancer research.

New tests must be validated for clinical trials investigating novel biomarkers or developing therapeutic antibodies. Canopy Biosciences® uses an orthogonal strategy for assay validation which involves cross-referencing results obtained by one assay with data obtained using an independent method. For example, the specificity of an antibody is verified when the protein signal in the IHC assay correlates to the levels of the genetic signal in a FISH assay. This strategy is critical to identify any artifacts that are directly related to the antibody in question. Partnering with a laboratory that has experience in assay development can improve the success rate of drug development.

A Board-Certified Pathologist Creates Opportunities for Deeper Analysis

Laboratories that analyze clinical trial biopsies for non-diagnostic purposes are not required to work with a pathologist. Yet, selecting a laboratory with a board-certified pathologist ensures that morphological and molecular data for analysis is performed to a consistently high standard. Pathologists are trained to analyze stained tissue to identify tumor, non-tumor, and immune regions. This is useful for pathologist-guided macrodissections of tissue for nucleic acid isolation to conduct additional analyses, such as gene expression analysis with NanoString® nCounter® or qPCR.

Pathologists can also provide semi-quantitative analyses for IHC assays, as they do when they make diagnoses in the clinic. This may mean using a traditional tiered score or H-score, which represents the percent of positive cells based on intensity read-out, indicative of the level of protein expression. Access to a pathologist also creates an opportunity to develop new scoring criteria and guidelines for a particular biomarker for which the current scoring criteria is ineffective or nonexistent, as when developing tests for novel biomarkers. Overall, working with a board-certified pathologist expands opportunities and enhances the credibility of your results.

TIP: Select a laboratory with a board-certified pathologist and experience in assay development.

MET IHC Test for Potential Diagnostic Tool:
Using an Orthogonal Strategy for Assay Development

Case Study

Initial clinical studies evaluating molecules targeting the MET signaling pathway have demonstrated patients with MET+ tumors benefit from the therapeutic antibody onartuzumab. A MET IHC test and scoring criteria using biopsies from patients with non-small cell lung cancer was used to evaluate MET expression as a predictor of patient benefit. Canopy Biosciences scientists were involved in employing an orthogonal strategy using a FISH test to verify that gene copy number levels corresponded to MET protein levels in the IHC test. The results showed that the IHC test to detect tumor MET levels was the best predictor of benefit (Koeppen et al., 2014). These results have guided the phase III clinical development strategy of onartuzumab and the development of a MET IHC test as a potential diagnostic tool.

CLIA-Certification Ensures Quality Laboratory Testing and Enhances Credibility of Results

Clinical trials should be designed to anticipate necessary analyses, but additional unplanned tests are often warranted based on initial results. Samples may additionally be analyzed with enzyme histochemistry (EHC), sequencing, or gene expression platforms like NanoString® nCounter®. Selecting a laboratory that specializes in histology and offers additional services commonly used to molecularly characterize tumor samples will minimize time to ship samples between sites and increase efficiency.

For all analyses, the laboratory should have good laboratory practices to ensure quality laboratory testing. The Clinical Laboratory Improvement Amendments (CLIA) regulate laboratory testing and require clinical laboratories to be certified to perform diagnostic testing on patient samples. CLIA-certification is not always required for laboratories performing tests for clinical trials. Yet, clinical trial teams may want to work with a laboratory with CLIA-certification to ensure their clinical trial samples are processed according the highest quality standards, especially those outlined in their trial requirements.

CLIA-certification provides data reviewers with confidence that the results are valid and not influenced by artifacts that may arise due to poor laboratory practices. This includes FDA reviewers who evaluate the clinical benefit and risk information submitted by the drug maker, considering any uncertainties that may result from imperfect data.

Tip: Select CLIA-certified laboratory that offers a variety of services.

Case Study

Therapeutic Antibody Development:
Pre-Clinical Research In a CLIA-Certified Lab

The market for therapeutic antibody drugs has exploded as new drugs have been approved for treating various human diseases including many cancers. The therapeutic antibody TTX-030 is being developed in phase I/Ib clinical trials as a monotherapy and in combination with anti-PD-1 immunotherapy and standard chemotherapy in adults with advanced cancer (Moesta et al., 2020). Early work on TTX-030 was conducted in a Canopy Biosciences' CLIA-certified laboratory using a variety of techniques including H&E staining, enzyme histochemistry (EHC), and gene expression analysis with NanoString® nCounter®.

Oncology Clinical Trials May Require a Suite of Services

Canopy Biosciences® offers a number of services to support clinical trial work, from sample preparation to custom assay development:

- Specimen fixation and embedding, tissue sectioning onto glass slides
- Tissue procurement
- Histological staining
- Pre-validated single or multiplexed IHC tests and FISH tests
- Custom IHC or FISH test development
- Analysis of IHC test results and scoring by a board-certified pathologist
- Development of new scoring criteria
- Pathologist-guided macrodissections and microdissections

and additional services such gene expression analysis with NanoString® nCounter® or qPCR, etc.

Conclusion

Bringing a drug to market can be a lengthy and complicated process. Partnering with an experienced CLIA-certified laboratory can improve the success rate of drug development by improving efficiency and enhancing credibility of results. Canopy Biosciences® offers the knowledge that comes with years of experience and a suite of services including specimen preparation, routine histology staining, assay development, and pathologist-guided analyses to support clinical trials.

References

Koeppen, H., Yu, W., Zha, J., Pandita, A., Penuel, E., Rangell, L., Raja, R., … Yauch, R. L. (2014). Biomarker Analyses from a Placebo-Controlled Phase II Study Evaluating Erlotinib ± Onartuzumab in Advanced Non–Small Cell Lung Cancer: MET Expression Levels Are Predictive of Patient Benefit. Clinical Cancer Research, 20(17), 4488–4498. https://doi.org/10.1158/1078-0432.CCR-13-1836

Moesta, A. K., Li, X.-Y., & Smyth, M. J. (2020). Targeting CD39 in cancer. Nature Reviews Immunology, 20(12), 739–755. https://doi.org/10.1038/s41577-020-0376-4.

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Canopy Biosciences
4340 Duncan Avenue
Suite 220
Saint Louis, Missouri 63110