CLINICAL CHARACTERIZATION OF THE PD PROFILE OF A MONOCLONAL ANTIBODY

WHAT DO ALL CANDIDATE IMMUNOTHERAPIES HAVE IN COMMON?

Whether in the preclinical or clinical stage, all immunotherapies need robust and reliable monitoring tools to characterize and track the immune response. ABL’s expertise lies in the monitoring of the immune response within a regulatory compliant setting. We have supported hundreds of preclinical and clinical studies evaluating the safety and efficacy of candidate Monoclonal Antibodies (mAbs), Antibody Drug Conjugates (ADCs), therapeutic vaccines, Chimeric Antigen Receptor T cells (CAR-T cells), and several other novel immunotherapies.

We invite you to discover our expertise through a series of real case studies:

- IMMUNOPHENOTYPING
- FUNCTIONAL ASSAYS
- SOLUBLE BIOMARKERS
- DRUG-TARGET INTERACTIONS

INTRODUCTION

One of the major challenges encountered during the preclinical and clinical development of a new drug is the characterization of its pharmacokinetic (PK) and pharmacodynamic (PD) properties. Preclinical PK/PD data issued from either in vitro or ex vivo animal studies, provide the basis for in silico modeling and simulation of the human PK/PD characteristics of the drug in humans, leading to determination of the minimum anticipated biological effect level (MABEL) and the selection of the first human dose for clinical trials.

Clinical PK/PD data from early phase clinical trials are highly valued in that they confirm or update current PK and PD models in addition to optimizing dosing regimens for subsequent efficacy and safety studies and later-stage clinical trials. Ligand binding assays are designed to quantify the binding of therapeutics to their targets, either by ELISA-based assays for circulating targets or by receptor occupancy assays for those located on the cell surface. When combined with the PK profile, the resulting data can establish PK/PD relationships and trends, which are essential for guiding dose decisions.

ASSSESSMENT OF DRUG-TARGET INTERACTIONS

Confirmation and evaluation of the binding of a biotherapeutic to its cellular target is mandatory in the early development phases as it helps to define the PD profile of that drug. To address those needs, ABL conducts several flow cytometry-based receptor occupancy (RO) assays to quantitatively assess the binding of a therapeutic agent to its target. To ensure that reliable and high quality results are generated from these RO assays, careful assay design and qualification, characterization of key reagents, data normalization and thorough planning for study implementation are of critical importance.

For more information on our ligand binding offerings, please contact us at: info@abl-immuno.com.
CASE STUDY

In the context of a phase II clinical study, ABL was requested to aid in the evaluation of a new therapeutic monoclonal antibody (phase II clinical study) targeting a receptor expressed on lymphocyte subsets. This was accomplished through characterization of the pharmacodynamic behavior of this investigational drug (i.e. the saturation level of its target on lymphocyte subsets) tested in two distinct dosing regimens.

After thorough method optimization and validation, we have developed a RO assay based on the detection of the drug bound to its cellular targets using a monoclonal antibody directed against the drug and measured directly in patients’ whole blood (see Figure 1).

This assay also included sample staining with other antibodies to identify unknown cell subsets of interest, i.e. those expressing the drug target. Specific molecules of equivalent soluble fluorochromes (i.e. MESF) beads representing multiple levels of fluorescence were run in parallel with study samples in order to normalize target expression through fluorescence intensity and to allow cross comparison.

Performance of the method, assessed using fit-for-purpose validation, demonstrated that this assay was suitable and robust enough to be run by multiple operators on multiple instruments with an inter-operator/inter-instrument variability below 10%.

ABL conducted this work on fresh whole blood samples from a clinical trial evaluation of two different dosing regimens (Dose A and Dose B). Samples were collected prior to dosing through day 28 post-dose. Overall results show that full saturation of the target is achieved with both doses but limited to 24h with Dose A while it lasted at least 4 weeks with Dose B (see Figure 2).

Figure 1: Receptor saturation assay
Evolution of the saturation level of cell surface receptors targeted by a therapeutic antibody before and after dosing. Corresponding flow cytometric histograms (gated on cells of interest, stained with anti-therapeutic drug) are presented.

CONCLUSION

ABL successfully validated and implemented a receptor occupancy assay on behalf of this phase II clinical trial. The pharmacodynamic profile of this monoclonal antibody, established from our high-quality data, when combined with additional PK and efficacy data, proved instrumental in informing decisions on dose selection for the following clinical trials.