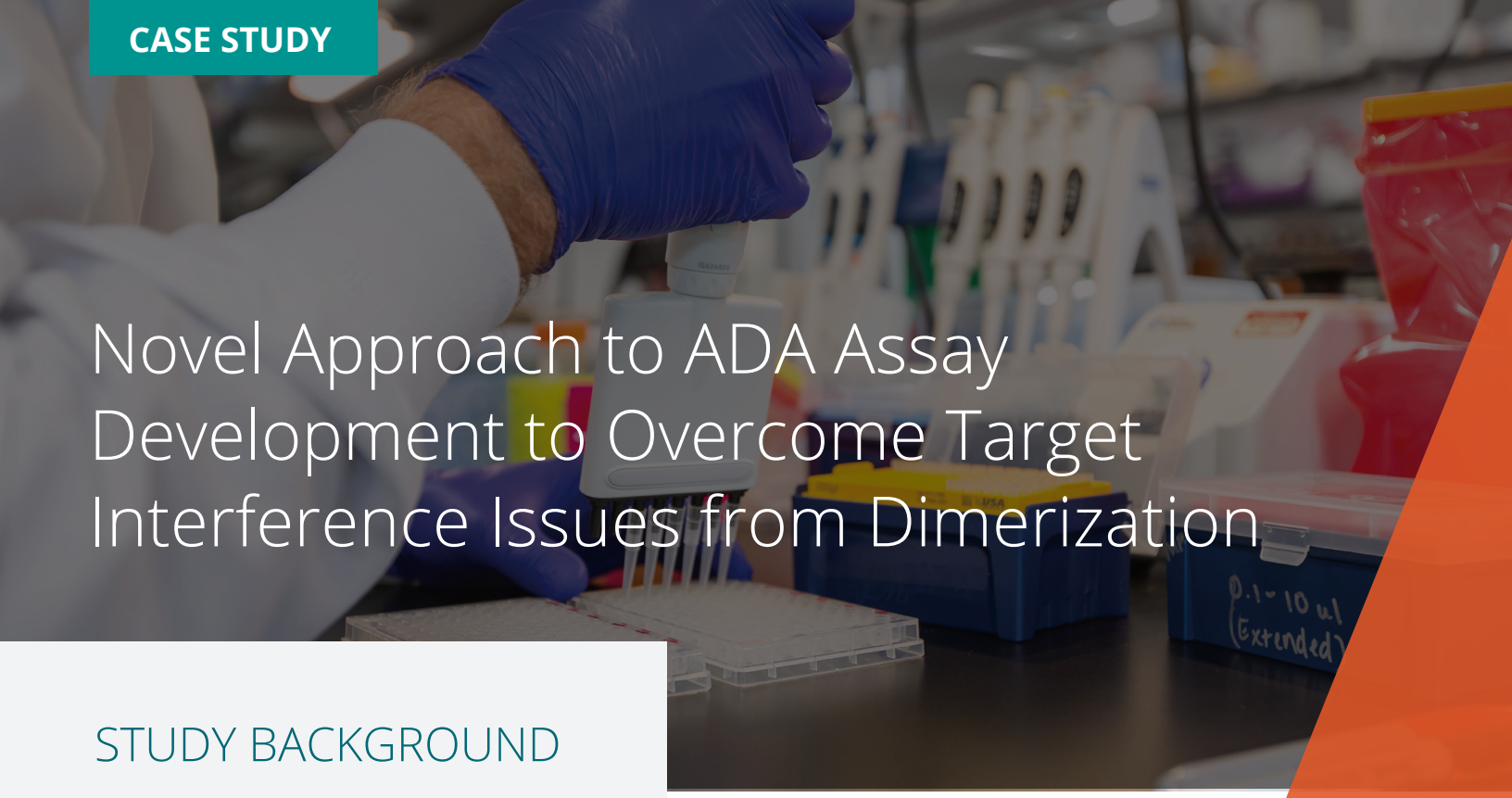
CASE STUDY



Novel Approach to ADA Assay Development to Overcome Target Interference Issues from Dimerization

STUDY BACKGROUND

TYPE OF STUDY

Phase II clinical development and validation of an antidrug antibody (ADA) assay for a monoclonal antibody (mAb) binding to a soluble target which contained the dimerization interface.

REGULATORY PARAMETERS

GCP study evaluating the drug for multiple indications.

OBJECTIVE

Develop the assay to achieve the necessary levels of drug tolerance and sensitivity and minimize target interference.

CHALLENGE

Dimerization of soluble targets is a known issue in the field of immunogenicity, as these compounds have the ability to bridge the labeled capture and detection drugs in the ADA assay system. This may lead to false positive ADA assay results.

Such was the case when a large biopharmaceutical company approached BioAgilytix with a rescue project requiring expedited timelines. The objective was to develop an ADA assay for a mAb binding to a target protein which contained the dimerization interface. Prior attempts to develop an ADA assay resulted in ADA prevalence of 80% due to the use of a simple bridging assay. A second attempt at managing the target interference resulted in sensitivity and drug tolerance results that were insufficient to meet regulatory requirements. The entire drug development program was at risk.

The project was brought to BioAgilytix with very tight timelines. A strategic plan had to be made to overcome the challenge of target interference and validate if the high rate of immunogenicity was due to target dimerization rather than the drug candidate itself.

BioAgilytix

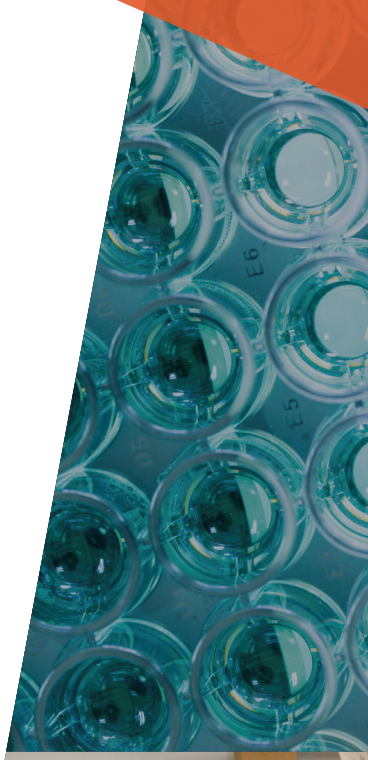
SOLUTION

In close collaboration with the sponsor's internal scientific team, BioAgilytix was able to develop a robust ADA assay using a novel method: heat treatment minimized target interference, while acid dissociation improved the drug tolerance of the assay.

Although heat treatment has been used in a number of different assays to mitigate interference, it had never been tested in a target dimerization issue before. The technique was one that the BioAgilytix team had ideated previously but was now given the opportunity to apply in practice, and the creative approach gave the study the turnaround it needed.

Samples were first diluted into buffer containing a chelate and the optimal time and temperature of sample treatment was determined in collaboration with the sponsor. Target interference was tested by adding up to 2000 ng/mL of target in both monomer and dimer forms with no observed interference. To achieve drug tolerance of at least 100 µg/mL in clinical samples, the heat-treated samples were incorporated into an acid capture elution (ACE) method. The assay was able to detect anti-drug antibodies at 100 ng/mL in the presence of greater than 100 µg/mL of added drug for multiple indications.

In less than 30 days, the BioAgilytix team was able to develop the assay to the required levels of drug tolerance and sensitivity. Immediately following the assay was qualified and validated for use to analyze samples for multiple indications, including gastric cancer, cystic fibrosis, Crohn's disease, ulcerative colitis, and rheumatoid arthritis. Samples were tested for several clinical studies, where the prevalence of immunogenicity was closer to 5%-10%—a significant improvement from the inflated 80% prevalence experienced with a previous method.



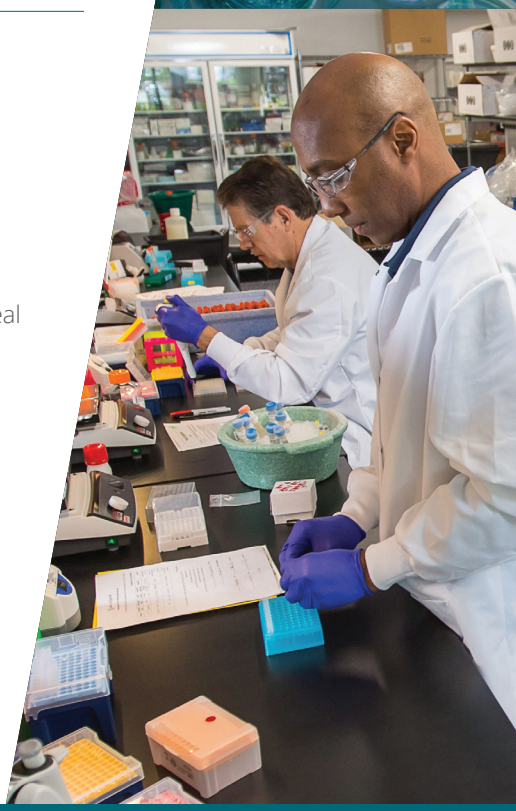
OUTCOME

BioAgilytix was able to progress a sinking program to Phase II clinical trials through the rapid development of an ADA assay to maximize drug tolerance and sensitivity and minimize target interference.

By showing that the prevalence of immunogenicity was significantly lower than the original estimates, a study that was on the verge of cancellation has now progressed to multiple clinical studies.

This novel solution for target interference in ADA assays can also be applied in other projects. Recently, the same heat treatment method was applied to a project involving the HER2 gene—a potential breast cancer indication. Once again, lower immunogenicity rates were observed with BioAgilytix's assays in comparison with other programs involving HER2.

The heat pre-treatment may not be ideal for all situations of target interference, as some targets may be stable under these conditions. This novel sample pre-treatment and subsequent assay design is something that must be evaluated empirically by scientists who understand the complex biology of antibody therapeutics and their binding partners.



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