XENOTECH
A BioIVT Company

Why 3 Curves Matter

The importance of using 3-curve IC_{50} data to predict CYP Inhibition

Clinically relevant CYP inhibition can be caused by a drug candidate or by one of its metabolites, as was the case with Posicor® (mibefradil). This drug was withdrawn from the U.S. market after it was discovered to be a metabolism-dependent inhibitor of CYP3A4. As a result of this discovery, many companies now include a 30-minute preincubation of a drug with NADPH-fortified human liver microsomes during their in vitro experiments to evaluate inhibition of CYP enzymes by drug candidates and their potential metabolites (i.e., a 2-curve IC_{50} evaluation.)

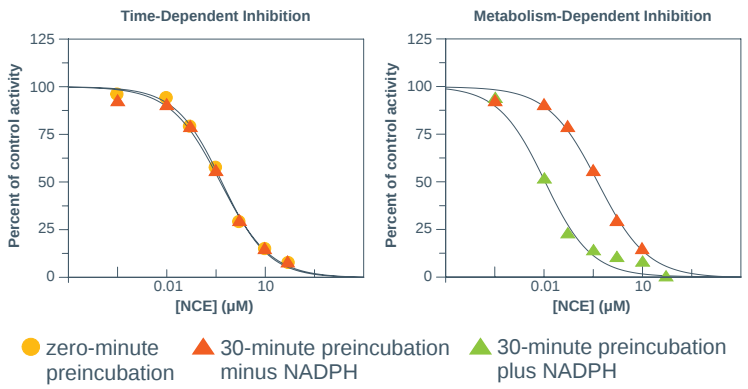
So why is XenoTech's 3-curve IC_{50} study better than a 2-curve IC_{50} study? The answer is that it gives you more information by distinguishing between metabolism-dependent inhibition and time-dependent inhibition.

The term 'metabolism-dependent inhibition' is often used synonymously with 'time-dependent inhibtion'. In the majority of cases this causes no confusion because the formation of inhibitory metabolites takes time, as is the case with mibefradil; therefore, all metabolism-dependent inhibitors are also time-dependent inhibitors. However, the converse is not true; not all time-dependent inhibitors are metabolism-dependent inhibitors.

Time-dependent inhibition can also be observed in vitro when inhibitors complex slowly with the enzyme they inhibit and when compounds degrade over time to products that are more inhibitory than the parent. At XenoTech, we use the term 'metabolism-dependent inhibition' to describe an increase in inhibitory potency that was observed when the test article was incubated with human liver microsomes in the presence of NADPH, and we use the term 'time-dependent inhibition' to describe an increase in inhibitory potency that was observed when the test article was incubated with human liver microsomes regardless of the presence of NADPH.

The figure below shows an example of metabolism-dependent inhibition from XenoTech's 3-curve IC_{50} study. By adding one additional curve to our study design (i.e., a 30-minute preincubation without NADPH), we are able to identify compounds that cause metabolism-dependent inhibition of CYP enzyme activity.

3-curve IC_{50} data predicts CYP inhibition by the test article and by its potential metabolites



A move into clinical trials represents a significant financial investment for a company. Knowing what to expect before you get into clinical trials can help you design your clinical studies, saving both time and money. By spending a little bit more in the early (and less expensive) in vitro studies, you can avoid these otherwise unnecessary and costly delays later.

If you have questions about IC_{50} studies or you would like more information, contact us at info@xenotechllc.com. Our experts are here and excited to talk to you and to help you get your compound ready for the clinic and through an IND approval.