SEKISUI XENOTECH

# *Drug-drug interactions between biologics and small molecule drugs*

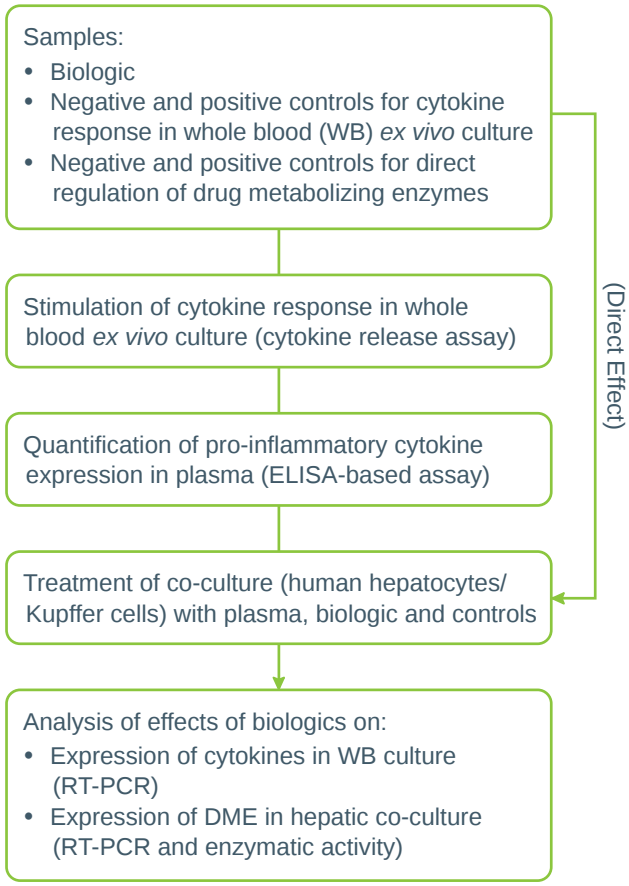
The most recent FDA Guidance for Industry on drug interactions recognizes the potential for therapeutic proteins that are cytokines or cytokine modulators, to change the plasma concentration of specific CYP substrate drugs. Therapeutic proteins, which typically are not cleared by metabolism or transport, can suppress drug metabolizing enzymes by evoking response of the pro-inflammatory cytokines.

An increasing number of large molecule drugs, otherwise known as biologics, are being introduced to the market. This broad category includes monoclonal antibodies, receptors, hormones, growth factors, immuno-modulators, enzymes, vaccines and oligonucleotides.

Biologics can trigger the release of pro-inflammatory cytokines (e.g. IL-1β, IL-6, INFγ and TNFα) from peripheral blood mononuclear cells. Extreme cases of cytokine release are known as a cytokine storm. *In vivo* cytokines released in response to certain biologic drugs, as well as, in response to inflammation or infection, regulate multiple physiological processes including drug transport and metabolism. Cytokine-mediated suppression of drug metabolizing enzymes can change the clearance of small molecule drugs and thereby precipitate a drug-drug interaction. Interactions between basiliximab and cyclosporin A and between basiliximab and tacrolimus were observed in the clinic. They exemplify significant effects of cytokine-mediated suppression of drug metabolizing enzymes, in these cases CYP3A4. The case of TGN1412, the anti-CD28 MAb that cased a life-threatening cytokine storm in a Phase I study despite all preclinical indications that the drug would be safe in humans, offers the most dramatic warning about the potential dangers of biologic drugs.

XenoTech offers an *in vitro* process by which biologics can be evaluated for direct and cytokine-mediated effect on cytochrome P450 enzymes expression. The cytokine release assay is the first step of the process, followed by examination of biologic-stimulated plasma in primary cultures of human hepatocytes. Consideration is given to the appropriate drug concentration that will yield the most relevant data on the release of cytokines. This *in vitro* method yields cytokine release information and detects the direct and cytokine-mediated effects of biologics on CYP expressions.

*In vitro system to evaluate the immune system-mediated and direct effects of biologics on drug metabolizing enzymes (DME)*




XenoTech is a global provider of strategic scientific solutions designed to offer pharma and biotech companies an efficient and expeditious path to an IND submission.

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