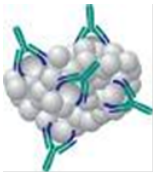
CYP450-GP



CYP ImmunoInhibit Kit

PRODUCT Hu-A011A, Hu-A011B+

Inhibitory Antibodies to CYP1A2, CYP2C8, CYP2C9, CYP2C19, CYP2D6 & CYP3A4
Developed in Rabbits and Mice, IgG Fraction

The *CYP ImmunoInhibit Kit* from CYP450-GP is designed for performing P450 reaction phenotyping studies with human liver microsomes (HLMx). P450 reaction phenotyping is a regulatory agency requirement for experimental therapeutics to assess their potential to become a "victim" drug, or one whose bioavailability is markedly influenced by: a) co-administration with enzyme inducers and/or inhibitors (i.e., drug-drug interactions); b) metabolism by P450 enzymes known to exhibit genetic polymorphisms or; c) metabolism by P450 enzymes whose hepatic (and extrahepatic) levels display marked interindividual variation. The inhibitory polyclonal and monoclonal antibodies that comprise the *CYP ImmunoInhibit Kit* are potent tools for identifying which of the major drug-metabolizing P450s catalyzes the hepatic metabolism of the test therapeutic. This panel of highly-specific P450 antibodies, upon binding to their cognate enzyme, markedly decreases (up to 90%) that enzyme's metabolic activity; in each case, optimal catalytic inhibition attained with the six different kit antibodies is at least 80%, thus enabling the description of P450s that contribute $\geq$ 25% to an investigational drug's catabolism. The inhibitory IgGs are effective not only against P450s found in native HLMx but can also be used with purified, reconstituted P450 enzymes and heterologously-expressed P450s (e.g., Supersomes and Bactosomes).

- Evidence now suggests that specific inhibitory P450 antibodies, such as those comprising the *CYP ImmunoInhibit Kit*, may be superior to CYP-selective chemical inhibitors, especially in the case of newer experimental therapeutics that possess increased metabolic stability. These agents require prolonged incubation times with high concentrations of HLMx in order to accurately measure parent depletion and/or metabolite formation. Under these conditions, many chemical inhibitors are consumed, thereby losing their inhibitory properties whereas P450 antibodies, which are non-competitive irreversible inhibitors, do not undergo this process.

- *CYP ImmunoInhibit Kit* antibodies can be employed in metabolite formation studies as well as in substrate depletion experiments with HLMx when labeled substrate and/or authentic metabolite standards are not available. The kit can also be adapted to various high-throughput formats.

- Since assay conditions used with *CYP ImmunoInhibit Kit* antibodies employ saturating drug substrate concentrations, the maximum metabolic contribution of each target P450 can be ascertained. The results obtained are easily interpreted and do not

require extrapolation (e.g., ISEF or RAF) to assess the contribution of a given P450 enzyme to lead compound metabolism in liver microsomes.

- The *CYP ImmunoInhibit Kit* enables the identification of investigational drugs that are metabolized by two or more P450s, partner drugs metabolized by a common P450 enzyme and, importantly, drugs that are metabolized by P450s (e.g., CYP2D6) that exhibit functional genetic polymorphisms.

- Ongoing studies with *CYP ImmunoInhibit Kit* antibodies and MetMax™ human hepatocytes are leading to the successful deployment of these P450 antibodies in a phenotyping system that utilizes human hepatocytes rather than liver microsomes. Hepatocytes are usually considered the "gold standard" with regards to models of human liver drug metabolism *in vitro*, and the MetMax™ cell membranes have been permeabilized to allow antibodies to reach their intracellular targets.

+Please see the associated Hu-A011 specification sheet for further details.