ANTIGEN: P-glycoprotein (MDR1)

ANTISERUM: Signet laboratories (8720-01). Mouse monoclonal antibody. Clone: C494. isotype: IgG\textsubscript{2a}

IMMUNOGEN:

PRESENTATION:

PROTEIN CONCENTRATION (mg/ml):

IMMUNOGLOBULIN CONCENTRATION (µg/ml): 120

REACTIVITY ACCORDING TO MANUFACTURER:

P-glycoprotein, the product of MDR1 gene, is expressed in distinct non-malignant cells, typically with secretory and excretory functions. It is assumed to function as an ATP-dependent drug efflux pump with broad substrate specificity. The highest expression of P-glycoprotein has been observed in kidney (proximal tubules), liver (bile canaliculi), adrenal gland and intestine, suggesting that the primary role of P-glycoprotein is in the normal secretion of physiological metabolites and ingested chemicals into bile, urine and the lumen of the intestinal tract. Elevated levels of P-glycoprotein have also been reported in multidrug-resistant cell lines and in colon, endometrial, ovarian, and breast tumors, as well as in sarcomas and leukemias/lymphomas.

C494 detects a gene-specific, internal cellular epitope present only in the Mdr1 isoform of P-glycoprotein. This antibody does not cross-react with Mdr3. It does cross-react with pyruvate carboxylase (PC), an abundant mitochondrial enzyme, on both immunoblots and immunohistochemical tests. Unequivocal plasma membrane patterns of immunostaining represent true P-glycoprotein expression. Weak, homogeneous, cytoplasmic, or granular patterns of reactivity may represent staining of the PC cross-reactive epitope rather than positive staining for P-glycoprotein.

MULTIPLE DRUG RESISTANCE IN NEOPLASTIC DISEASES

Many drugs that are either natural products or their derivatives share common mechanisms of resistance. Many of these drugs are substrates for membrane-based proteins that act to pump out of cells. P-glycoprotein (P = pleiotropic) is one of those membrane proteins and is encoded by the multiple drug-resistance (mdr) genes. P-glycoprotein is one of the components of the family of ATP-binding cassette (ABC) molecules that include the cystic fibrosis transmembrane conductance regulator, and the multidrug resistance protein (MRP). The lung resistance protein (LRP) belongs to a different family but it is also associated with resistance to multiple drugs and probably causes export of drugs from cells by sequestering them into intracellular organelles. There are other substances involved in multidrug resistance such as topoisomerase II, glutathione, etc.
Causes of multiple drug resistance and their specificity for individual cancer drug groups

<table>
<thead>
<tr>
<th>P-glycoprotein</th>
<th>Multidrug-resistance Protein (MRP)</th>
<th>Lung-resistance protein (LRP)</th>
<th>Decreased topoisomerase II activity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anthracyclines</td>
<td>Anthracyclines</td>
<td>Anthracyclines</td>
<td>Anthracyclines</td>
</tr>
<tr>
<td>Mitoxantrone</td>
<td>Mitoxantrone</td>
<td>Mitoxantrone</td>
<td>Mitoxantrone</td>
</tr>
<tr>
<td>Vinca alkaloids</td>
<td>Vinca alkaloids</td>
<td>? Cisplatin</td>
<td>? Cisplatin</td>
</tr>
<tr>
<td>Etoposide</td>
<td>Etoposide</td>
<td>? Alkylating agents</td>
<td>? Alkylating agents</td>
</tr>
<tr>
<td>Taxanes</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Actinomycin D</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Modified from Tannock and Goldenberg, 1998

STAINING PROCEDURE ACCORDING TO MANUFACTURER:
- Formalin-fixed, paraffin-embedded tissue sections. Use the antibody at a concentration of 3 μg/ml for Streptavidin detection system or 12 μg/ml for a PAP detection system.


METHOD: EnVision+/PO. 1h. RT.

SPECIES CROSS-REACTIVITY: Only dog tested.

CELLS/TISSUES STAINED (canine tissues unless specified):
- **Liver**: Distinct staining of the cytoplasmic membrane of hepatocytes and much weaker staining of the cytoplasm (inconstant). The endothelium is positive. Bile duct epithelium is weakly positive (mainly apical membrane).
- **Lung**: Mainly respiratory and alveolar epithelium.
- **Kidney**: Apical border and diffuse cytoplasmic in tubular epithelium. Pars recta epithelium of cortical and medullary tubules has a distinct membrane pattern similar to that seen in the liver. Glomerular tufts are also positive.
- **Skin**: Diffuse cytoplasmic and moderate in hair follicle epithelium and diffuse cytoplasmic and more intense in the apical border of apocrine glands.

NOTE.
- P-glycoprotein is responsible for part of the resistance to chemotherapy. Tumors originating from organs heavily expressing this protein are more prone to express it also. However, changes in the expression of this protein can happen in a given tumor before and after a round of chemotherapy.

REFERENCES:


