

27. HUMAN PARAOXONASE AS A CATALYTIC SCAVENGER AGAINST CW ORGANOPHOSPHATES.

Josse, Denis¹, Vigue, Nathalie¹, Renault, Frédéric¹, Bartels, Cynthia², Lockridge Oksana² and Masson, Patrick¹.

¹Unité d'Enzymologie, Centre de Recherches du Service de Santé des Armées, 24 avenue des Maquis du Grésivaudan, BP 87, 38702 La Tronche cedex, France.

²Eppley Institute, University of Nebraska Medical Center, Omaha, NE, USA.

During the past 10 years, various OP hydrolases have been explored as potential antidotes against OP poisoning. Hence, it has recently been demonstrated that the administration of the bacterial phosphotriesterase (PTE) to mice could improve the classical treatment of sarin poisoning. Furthermore, it is well established that the presence of endogenous scavengers in plasma plays an important role in determining the susceptibility to OPs. We currently study human paraoxonase (PON1, E.C. 3.1.8.1), a naturally-occurring serum catalytic scavenger. Human PON1 is a HDL-associated enzyme which exhibits a calcium-dependent organophosphatase activity toward various substrates, including the nerve agents sarin, soman and VX. Our main objective is to modify human PON1 to increase its catalytic efficiency by a 100-fold factor toward sarin, soman and VX. Rational design of PON1 mutants with an improved catalytic efficiency toward OPs first requires to identify the PON1 active site components and to solve its 3D structure. Recombinant human PON1 wild-type and mutants can be expressed in CHO cells. Another important issue is to produce human PON1 as a soluble and active enzyme in *Escherichia coli*.

Keywords: paraoxonase, organophosphate, scavenger, engineering