**Author:** Monivan CHHOUR

**Title:** Study of intracellular metabolism of quinones, generated oxidative stress and associated detoxification processes

**DIRECTOR OF THESIS:** Pr. Karine REYBIER

**Abstract:**

Quinones are ubiquitous compounds in nature. They are also one of the essential elements in living organisms. However, their metabolisms are considered as toxic because there are highly reactive. Their structure is easily reduced by one or two electrons. The intracellular metabolism of these quinones via one-electron reduction such as cytochrome P450 reductase or others flavoproteins generates an unstable semiquinones which leads to a burst of free radical production that results in oxidative stress. On the other hand, quinone reductases 1 and 2 (QR1 and QR2) catalyze quinone reduction via two electrons to form hydroquinones that chemically more stable. This property is well-known as the detoxifying character of quinone-reductase enzymes. However, previous analyses have shown that this detoxifying effect was appeared only for certain types of quinones and depended, in particular, on the type of cells. Thus, in order to better understand the mechanisms leading to the generation of reactive species and in consideration to those links that were mentioned in the literature between QR2 and neurodegeneration, studies were conducted on primary neurons and neuroblastoma cells genetically modified to overexpress in QR2. These studies have shown, by various analytical techniques such as electron paramagnetic resonance or LC-MS, an increase in the toxicity of menadione but also of adrenochrome in the presence of quinone- reductase 2. In order to explain the contradictory characteristics of QR2 from one cell to another, we proposed a hypothesis that a cooperation with another conjugating enzyme, which could react with the unstable reduced form that prevent its reoxidation, is needed to effectively detoxify quinones. Additional analyses (RPE, LCMS, fluorescence) conducted on neuroblastoma cells overexpressing both QR2 and a para-hydroquinone specific conjugation enzyme (UGT) have shown a decrease in oxidative stress when both enzymes are co-expressed.

**Keywords:** quinone-reductase 2, menadione, oxidative stress, neurodegeneration, quinones, free radical, EPR, neuroblastoma.