

**Title:** Identifying the enzyme involved in Vacuolar ATPase acetylation during doxorubicin-induced cardiotoxicity

## **Abstract**

Doxorubicin is an established anticancer medication infamous for its bright colouration and extremely toxic side effects. Emerging studies support that the imbalance between acetylation and deacetylation disrupts the autophagic flux leading to doxorubicin-induced cardiotoxicity. Vacuolar ATPases are a family of electrogenic proton pumps present on the lysosomal membrane that create an acidic environment for proteases to degrade proteins. Our preliminary study found that acetylated Vacuolar ATPase subunit V<sub>0</sub> D1 levels increased in doxorubicin-injected mouse hearts. However, it is unknown how acetylation of subunit V<sub>0</sub> D1 is modulated and whether this modification plays a role in doxorubicin-induced cardiotoxicity.

The focus of the project is to identify the specific acetylase involved in acetylating Vacuolar ATPase subunit V<sub>0</sub> D1 using histone acetyltransferase (HAT) inhibitors and its potential role in doxorubicin-induced cardiotoxicity. For example, Garcinol is a p300 HAT inhibitor derived from a plant called *Garcinia Indica* and past studies revealed that Garcinol natural properties have cardioprotective effects. Cardiomyocytes will be used as a model and cell viability, apoptosis, lactate dehydrogenase release, autophagic flux, Vacuolar ATPase activity (lysosomal pH), and Vacuolar ATPase subunit V<sub>0</sub> D1 acetylation will be analyzed. It is hypothesized that selective HAT inhibition will prevent Vacuolar ATPase subunit V<sub>0</sub> D1 hyperacetylation and allow for regulated autophagic flux to restore cell viability during doxorubicin-induced cardiotoxicity.

## **Keywords**

Drug-induced cardiotoxicity, Doxorubicin, Vacuolar ATPase, Autophagy, Lysosome, Acetylation, Histone acetyltransferase inhibitors