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MEETING ABSTRACTS

A PARADIGM SHIFT IN UNDERSTANDING THE MECHANISMS OF ANTHRACYCLINE CARDIOTOXICITY AND OPPORTUNITIES FOR EFFECTIVE PHARMACOLOGICAL CARDIOPROTECTION

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Anthracycline (ANT) anticancer drugs (e.g., doxorubicin and daunorubicin) are known for their cardiotoxic effects which are associated with degenerative changes in cardiomyocytes, programmed and non-programmed cell death, pathological remodeling of the myocardium and cardiomyopathy development. Historically, the predominant hypothesis of ANT cardiotoxicity development emphasized redox cycling of ANT molecule in the heart with or without participation of free iron resulting to ROS production and direct oxidative damage to the heart. However, different antioxidants and selective biocompatible iron chelators largely failed in clinically relevant experimental models and few clinical trials performed so far. Although many theories were proposed over decades none of them yielded a druggable target for effective cardioprotection against ANT cardiotoxicity. This has been changed in last decade when ANT cardiotoxicity has been proposed to be topoisomerase II beta (TOP2B)-dependent with subsequent induction of DNA damage with apoptosis and failure of mitochondrial biogenesis. Our network of laboratories in Hradec Kralove has brought several important experimental and translational insights into pharmacological cardioprotection against ANT cardiotoxicity which further develop this paradigm changing hypothesis. In this contribution, the complicated pathway to new TOP2B targeting cardioprotective drugs will be described together with possible future research directions.

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