Breton CS, Aubry D, Ginet V, Puyal J, Heulot M, Widmann C, Duchosal MA, Nahimana A. (2015). Combinative effects of β-Lapachone and APO866 on pancreatic cancer cell death through reactive oxygen species production and PARP-1 activation. *Biochimie*. 116:141-53.

Pancreatic cancer (PC) is one of the most lethal human malignancies and a major health problem. Patients diagnosed with PC and treated with conventional approaches have an overall 5-year survival rate of less than 5%. Novel strategies are needed to treat this disease. Herein, we propose a combinatorial strategy that targets two unrelated metabolic enzymes overexpressed in PC cells:

NAD(P)H: quinone oxidoreductase-1 (NQO1) and nicotinamide phosphoribosyl transferase (NAMPT) using β-lapachone (BL) and APO866, respectively. We show that BL tremendously enhances the antitumor activity of APO866 on various PC cell lines without affecting normal cells, in a PARP-1 dependent manner. The chemopotentiation of APO866 with BL was characterized by the following: (i) nicotinamide adenine dinucleotide (NAD) depletion; (ii) catalase (CAT) degradation; (iii) excessive H2O2 production; (iv) dramatic drop of mitochondrial membrane potential (MMP); and finally (v) autophagic-associated cell death. H2O2 production, loss of MMP and cell death (but not NAD depletion) were abrogated by exogenous supplementation with CAT or pharmacological or genetic inhibition of PARP-1. Our data demonstrates that the combination of a non-lethal dose of BL and low dose of APO866 optimizes significantly cell death on various PC lines over both compounds given separately and open new and promising combination in PC therapy.