

Apoptosis Research Group Heart Foundation Research Centre
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Research Interests:

Anti-cancer activities of vitamin E analogues: The major thrust of our interest focuses on vitamin E (VE) analogues, epitomized by α -tocopheryl succinate (α -TOS), selective inducers of apoptosis and anti-cancer agents. We have shown that VE analogues induce apoptosis primarily by activating the intrinsic pathway and suppress cancer in pre-clinical models of colon and breast carcinomas as well as mesotheliomas, a fatal type of cancer. We study the molecular mechanism by which α -TOS induces apoptosis and by which it sensitizes resistant cancer cells to other apoptogens, such as the TNF family members. We are synthesizing novel analogues of α -TOS with higher apoptogenic activity and specificity for cancer cells, including specific adducts of the agents targeting malignant cells. We also investigate effects of VE analogues on signaling pathways that promote proliferation and/or survival of cancer cells, such as the FGF autocrine loop and the Akt pathway, including effects on transcriptional regulation of expression of key members. Further, we are interested in suppression of angiogenesis by VE analogues, since we found that α -TOS causes apoptosis of proliferating (angiogenic) endothelial cells but not normal, arrested endothelial cells. Another focus of our studies is to understand the reasons for selectivity of VE analogues for malignant cells. We believe that in near future, we will be in a position to commence testing of selected VE analogues in human patients. This project is supported by grants provided by ARC, QCF and NBCF.

Role of mitochondria in apoptosis of heart muscle cells during myocardial infarction: During myocardial infarction, muscle heart cells die by apoptosis. This leads to major complications associated with the heart muscle insufficiency. We are interested in furthering our understanding of the processes that underlie this process. Current data strongly suggest that mitochondria may be the major organelle modulating cardiomyocyte cell death, but the precise mechanism is not well understood. We are interested in the molecular mechanism of apoptosis of cardiomyocytes in situation like ischemia/reperfusion (I/R). To study this, we use several models of I/R, including cultured cells, isolated mouse hearts and whole animal models. Our major interest here is to extend the knowledge gained from cell culture studies to

the in situ heart model and to the whole animal. We are studying not only the mitochondrial pathways of cell death in cardiomyocytes but also the alternative/parallel signaling pathways that may play a significant role, including the Daxx pathway. At present, we are establishing a method that allows studying apoptosis on the beating heart in a mouse model of myocardial infarction on the level of single cells, which will make it possible to study intervention that may protect the heart muscle from infarction-induced death. We hope that results of these studies may be used in the future for human patients. This project is supported by grants provided by NHMRC and NHF.

Selected publications:

1. Neuzil J, Weber T, Schröder A, Lu M, Ostermann G, Gellert N, Mayne GC, Olejnicka B, Nègre-Salvayre A, Sticha M, Coffey RJ, Weber C (2001) Induction of apoptosis in cancer cells by α -tocopheryl succinate: Molecular pathways and structural requirements. *FASEB J* 15, 403-415.
2. Neuzil J, Schröder A, von Hundelshausen P, Zerneck A, Weber T, Gellert N, Weber C (2001) Inhibition of inflammatory endothelial responses by a pathway involving caspase activation and p65 cleavage. *Biochemistry* 40, 4686-4692.
3. Neuzil J, Kontush A, Weber C (2001) Vitamin E in atherosclerosis: Linking the chemical, biological and clinical aspects of the disease. *Atherosclerosis* 157, 257-283.
4. Weber T, Lu M, Andera L, Lahm H, Gellert N, Fariss MW, Korinek V, Sattler W, Ucker DS, Terman A, Schröder A, Erl W, Brunk U, Coffey RJ, Weber C, Neuzil J (2002) Vitamin E succinate is a potent novel anti-neoplastic agent with high tumor selectivity and cooperativity with tumor necrosis factor-related apoptosis-inducing ligand (TRAIL, Apo2L) *in vivo*. *Clin Cancer Res* 8, 863-869.
5. Neuzil J, Gellert N, Swettenham E (2004) Sensitisation of malignant mesothelioma to TRAIL apoptosis by inhibition of histone deacetylase: important role of Bcl-x_L down-regulation. *Biochem Biophys Res Commun* 314, 186-191.
6. Jostarndt K, Rubic T, Kühn H, Anthonen MW, Gellert N, Andera L, Trottmann M, Weber C, Johansen B, Hrboticky N, Neuzil J (2004) Enzymatically modified LDL upregulates CD36 expression in non-differentiated monocytic cells in a PPAR- γ -dependent mode. *Biochem Pharmacol* 67, 841-854.
7. Neuzil J, Massa H (2005) Hepatic processing determines dual activity of vitamin E succinate. *Biochem Biophys Res Commun* 327, 1024-1027.
8. Stapelberg M, Gellert N, Swettenham E, Tomasetti M, Witting PK, Procopio A, Neuzil J (2005) α -Tocopheryl succinate inhibits malignant mesothelioma by disruption of the FGF autocrine signaling loop: Mechanism and the role of oxidative stress. *J Biol Chem* (in press).