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Tumour cell-specific death by non-death domain-containing TNF receptors

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The role of the tumour necrosis factor receptor (TNFR) family in regulating cell fate has been under extensive research. The ability of TNFRs to induce death in carcinoma cells renders them a promising target for cancer therapy. Yet, most studies have focused on death domain (DD)-containing receptors, such as Fas and TRAIL-R, due to their strong pro-apoptotic potential in malignant cells; however the ligands for such receptors can also induce toxicity to normal cells. Our research has focused on cell death that can be triggered via non DD-containing TNFRs. We were the first to show that such as a receptor, CD40 in particular, can induce tumour-specific death, as ligation by membrane-presented CD40L (mCD40L), but not soluble agonist, triggers apoptosis in carcinoma cells, whilst sparing their normal counterparts. We have recently identified the precise molecular nature of the CD40-signalling black-box and demonstrated using normal, para-malignant and tumour-derived cells that apoptotic susceptibility is dependent on cellular redox state, as well as understood the mechanistic differences in pro-apoptotic potential between soluble and membrane-bound agonists. Equally important, by exploiting a unique epithelial culture system that allowed us to monitor alterations in the redox state of cells at different stages of malignant transformation; we have shown how pro-apoptotic signals can elevate reactive oxygen species release past a previously hypothesized lethal pro-apoptotic threshold to induce tumour-specific death. By understanding these molecular pathways we have now designed a novel combinatorial therapeutic approach (ThanatoCure™) that demonstrates efficacy *in vivo*.

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