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4-1BB as an immune target

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Preclinical update on anti-CD137 Mab and Trastuzumab stimulation of natural killer cells with an anti-CD137 antibody enhances the efficacy of Trastuzumab, Cetuximab, and Rituximab in HER2-expressing breast cancer, EGFR+ head and neck cancer, and CD20+ lymphoma. My focus is on NK cells and translational research work that led from an initial *in vitro* observation to Phase 1 clinical studies. The starting observation was that primary human NK cells in the presence of a CD20-positive cell line and rituximab for 24 h upregulated CD137 (4-1BB) at their cell surface, and this upregulation was dependent on effective ADCC. The same observation was made with trastuzumab and cetuximab in the presence of HER-positive and EGFR-positive tumors, respectively. Using an agonistic anti-CD137 antibody, we demonstrate that triggering CD137 on NK cells enhanced the anti-tumor activity of rituximab, trastuzumab and cetuximab *in vitro* and *in vivo*. I will present various additional means to enhance ADCC by blocking inhibitory signals, such as CD47 on macrophages, IL-15 on monocytes or DCs, KIR or PD-1 on NK cells.

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Palm tocotrienols inhibit proliferation of murine mammary cancer cells, enhance immune response and induce expression of IL-24 mRNA

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Several mechanisms have been postulated for the anti-cancer effects of tocotrienols. In this study, the anti-cancer mechanism of tocotrienols is for the first time linked to increased expression of interleukin-24 (IL-24) mRNA, a cytokine reported to have anti-tumor effects in many cancer models. The anti-proliferative effects of tocotrienol-rich fraction (TRF) from palm oil, γ- and δ-tocotrienol (γ-T3 and δ-T3) and α-tocopherol (α-T) were studied on 4T1 murine mammary cancer cells. TRF, γ-T3 and δ-T3 significantly inhibited the growth of the 4T1 cells with IC50 values of 8.99, 4.79 and 3.73 μg/ml respectively. Tumor incidence and tumor load in BALB/c mice were decreased by 57.1% and 93.6% respectively ($p<0.05$) with TRF supplementation. Tumourigenesis was examined and compared against control in both nude and BALB/c mice models. The mice were injected with MDA-MB-231 and 4T1 cells respectively for the different models and were fed with TRF by oral gavage. This study shows that palm tocotrienols have strong inhibitory effects on the growth of both MDA-MB-231 and 4T1 cells both *in vitro* and *in vivo*. In addition the immune modulatory effects of tocotrienols were also investigated and it was found that TRF enhanced production of NK cells ($P<0.05$) as well as IFN-γ ($P<0.05$), which in turn regulate the immune protection against cancer cells. These observations were recorded in both mice models. The 4T1 cells treated with TRF, δ-T3 and α-T exhibited highest levels of IL-24 mRNA in δ-T3 treated cells, followed by TRF and α-T. The IL-24 mRNA levels in tumor tissues of BALB/c mice supplemented with TRF increased two-fold as compared to control mice. Increased levels of IL-24 have been associated with inhibition of tumor growth and angiogenesis. TRF and δ-T3 treated 4T1 cells significantly decreased IL-8 and vascular endothelial growth factor (VEGF) mRNA levels. We hereby report that the anti-tumor including the anti-angiogenic effects of tocotrienols are associated with increased levels of IL-24 mRNA.

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