

118P The role of asunercept as a selective CD95L inhibitor in cutaneous melanoma: Rationale and results from an enhanced TiRP model

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Background: CD95/CD95L signalling plays an important role in cancer cells resistant to CD95-mediated apoptosis and CD95L inhibition can overcome this mechanism. Several mechanisms related to apoptosis induction or dysfunction of effector T-cells via CD95L in the tumour microenvironment (TME) have also been investigated, with supporting evidence from preclinical melanoma models.

Methods: An autochthonous mouse model of melanoma (TiRP), genetically engineered to express P1A (defined MAGE-type antigen) mimics the T-cell suppressive effects of the TME through CD95L, which normal transplantation models cannot replicate. An advanced version of this murine melanoma TiRP model has been recently developed. This model can generate synchronized tumours in multiple mice in which treatments can be compared simultaneously while maintaining the advantages of the previous model regarding the role of CD95L in the TME interaction. This enhanced TiRP model was used to verify the effect of CD95L inhibition on apoptosis of tumour specific TILs using asunercept.

Results: In this novel synchronized in vivo melanoma model, asunercept decreased intra-tumour apoptosis among tumour-specific T cells by 67% vs controls (9% vs 28%, $p = 0.04$). This validates the immune-suppressive interaction between the TME and infiltrating tumour-specific T cells in this model. Furthermore, cross-species specific asunercept prevents T cell apoptosis triggered by the tumour microenvironment, highlighting a rationale for potential application of CD95L inhibition in immuno-oncology for other solid tumours.

Conclusion: Selective CD95L inhibition by asunercept might have potential clinical implications in different tumours beyond recurrent glioblastoma, including cutaneous melanoma. To date, asunercept has demonstrated clinical efficacy and safety in patients with recurrent glioblastoma and myelodysplastic syndromes and may warrant further investigation in clinical trials.

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