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Summary of Hwang Lab Proposal for Ann's Hope Foundation

Title: Improving immunotherapy for melanoma through novel chemokine receptor antagonists

New treatments for metastatic melanoma are desperately needed because even the most effective current therapy for advanced melanoma (i.e., adoptive immunotherapy), is only partially effective. Chemokine receptors are cellular proteins that direct movement of cells through attraction to their ligands, termed chemokines. Recent data show that the chemokine receptor, CXCR4, is produced by human melanoma tumor cells and that CXCR4 expression predicts poor outcome in those patients where it is detected. Furthermore, CXCR4 enhances lung metastasis in murine melanoma models and upregulates cellular pathways, including Akt, that make cancer cells more resistant to cell death. We have previously shown in the laboratory that blocking the CXCR4 chemokine receptor on malignant melanoma cells makes these cells sensitive to killing by immune cells called T cells, raising the possibility that chemokine receptor antagonists can potentially synergize with immunotherapy (which also depends on T cells) to more effectively treat melanoma. The goals of this proposal are: 1) to conclusively demonstrate in mouse models that CXCR4 blockade can synergize with targeted immunotherapy treatment protocols to more effectively treat established melanoma lung metastases 2) to use a novel inducible model of CXCR4 expression to better understand the role of CXCR4 in melanoma metastases and 3) to identify new CXCR4 antagonists which may have better safety and efficacy profiles than current antagonists.