Augmenting the efficacy of chemotherapies by inhibiting the GAS6/AXL pathway

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The AXL receptor and its activating ligand, growth arrest–specific 6 (GAS6), are important drivers of metastasis and therapeutic resistance in human cancers. The strong picomolar binding affinity between GAS6 and AXL and the promiscuity of small molecule inhibitors represent important challenges faced by current anti-AXL therapeutics. Here, we present an engineered high-affinity AXL decoy receptor with an apparent affinity of 93 femtomolar to GAS6. The structural study revealed long range interactions that stabilized the binding interface. The decoy receptor profoundly inhibited disease progression in aggressive preclinical models of human cancers and induced cell killing in leukemia cells. When directly compared with the most advanced anti-AXL small molecules in the clinic, the decoy receptor achieved superior antitumor efficacy while displaying no toxicity. The decoy receptor lead to improvements upon the therapeutic index of current standard-of-care chemotherapies in preclinical models of advanced pancreatic and ovarian cancer.

References

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