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Development and Characterization of a Bispecific Antibody Targeting EGFR and AXL

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Abstract

Traditional cancer therapies often overlook the dynamic nature of cancer by utilizing single targets, considering only homogenous tumors, not considering the tumor microenvironment, and failing to overcome common issues such as induced and acquired resistance to therapy. The development of new therapies that address all these concerns remains a challenge in oncology today, and there is a need for single low-dose therapies that can specifically address heterogenous and complex populations. We propose a bispecific antibody targeting EGFR and AXL can address this gap, while considering cytotoxicity and avoiding off-target effects.

EGFR is a receptor commonly overexpressed in many tumors and a known target in cancer therapy, however, many anti-EGFR treatments have detrimental off-target side effects for healthy cells. Additionally, resistance to anti-EGFR drugs is a common occurrence after prolonged treatment. One known mechanism of anti-EGFR resistance involves cross-talk between EGFR and the AXL receptor, a member of the TAM family of tyrosine kinase receptors which is also overexpressed in many tumors as well as in their immunosuppressive tumor microenvironments. AXL expression in oral cancers is known to mediate epithelial-mesenchymal transition through the PI3K pathway and has been shown to be associated with poor prognosis. New data from spatial tumor analysis of human patient derived xenografts shows huge diversity of expression of EGFR and AXL, both between tumors and within different cells of the same tumor where the expression levels of the two receptors appear to complement each other.

This research includes the development and characterization of an IgG-like bispecific antibody targeting both EGFR and AXL receptors which we hypothesize can not only eliminate the immunosuppressive tumor microenvironment and tumors with heterogenous expression of the two targets, but could also prevent the common complication of acquired resistance as well as improve specificity and biodistribution of the therapy to reduce off-target effects.