Integrative Multi-Omic Data Profiling of Pancreatic Ductal Adenocarcinoma for Identification of Oncofetal Targets and Designing a Novel Bispecific Antibody-Drug Conjugate

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Pancreatic ductal adenocarcinoma (PDAC) is a highly lethal cancer with a 90% mortality rate. Standard treatments such as surgery and chemotherapy show high recurrence rates of ~85% due to PDAC's extensive tumor heterogeneity, high metastatic potential, and dense stromal microenvironment that limit drug penetration and increase off-target toxicity. This study proposes a targeted therapeutic strategy using bispecific antibody-drug conjugates (ADCs). Bispecific ADCs require co-expression of two target surface proteins, increasing precision and reducing off-target toxicity. Oncofetal antigens, which are used in fetal development, are minimally expressed in healthy adult tissue and re-expressed in cancer, making them ideal targets. Multi-omic single-cell analysis identified TSPAN8 and CD24 as highly overexpressed oncofetal antigens in PDAC, with average patient cancer cell co-expression exceeding the 50% ADC research threshold, enabling targeting across heterogeneous populations. Furthermore, both are associated with EMT and cancer stemness, making them ideal targets for reducing metastatic potential in PDAC tumors. Novel antibodies targeting TSPAN8 and CD24 were computationally designed using RFDiffusion and evaluated for stability and efficacy using AlphaFold and PBPK modeling. Results demonstrated high structural confidence (mean pLDDT ~85) and stable internalization, supporting the design's potential for tumor-specific targeting. PDAC has no approved ADCs due to premature drug release concerns, so a liposome carrier design was proposed to improve circulation time and stroma penetration. Thus, this work presents novel target PDAC genes and bispecific ADC designs targeting oncofetal antigens, offering a potential strategy to overcome key therapeutic barriers in PDAC.

Awards Won:
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