

Aptamer-Based GANAB Enzyme Blockade Guided by Artificial Intelligence for Therapeutic Intervention in Pancreatic Cancer

Anna Drabik1 , Przemyslaw Mielczarek 1 , Juseong Kim2 1 Department of Analytical Chemistry and Biochemistry, AGH University of Science and Technology, Krakow, Poland 2 Division of Artificial Intelligence, Pusan National University, Busan, Republic of Korea

Pancreatic cancer [PaCa] is among the most aggressive and lethal malignancies, characterized by rapid progression, early metastasis, and dismal prognosis, with a five-year survival rate. Aberrant glycosylation—a post-translational modification where sugar moieties are enzymatically attached to proteins—plays a critical role in pancreatic cancer pathophysiology. This modification profoundly influences protein folding, stability, cell adhesion, immune evasion, and signaling pathways. In particular, GANAB (Glucosidase II alpha subunit), a key enzyme in the N-linked glycosylation cascade, facilitates the formation of extensively glycosylated proteins that promote oncogenic processes such as tumor cell immune escape and invasiveness. This study investigates a novel therapeutic approach aimed at inhibiting GANAB enzyme activity in PaCa cells using aptamers—short, single-stranded nucleic acids designed for high affinity and specificity against target proteins. Employing an artificial intelligence (AI)-based framework, AptaTrans, we enhanced aptamer design through iterative optimization of sequence prediction, binding affinity, and molecular specificity, surpassing traditional methods. The efficacy of GANAB inhibition was evaluated by biochemical assays, fluorescence microscopy, and comprehensive proteomic profiling using mass spectrometry. Subsequent functional assays measured changes in pancreatic cancer cell proliferation, adhesion, and invasiveness, while toxicity studies assessed specificity on normal pancreatic cells. Our results demonstrate that AI-designed aptamers effectively reduced GANAB activity, disrupting glycan processing and significantly decreasing the abundance of glycosylated oncogenic proteins. This translated into reduced cancer cell adhesion and invasiveness, indicative of compromised metastatic potential. Crucially, aptamer treatment showed minimal cytotoxicity in normal pancreatic cells, underscoring therapeutic specificity. This study validates the feasibility and therapeutic promise of using AI-guided aptamer technology to inhibit GANAB enzymatic activity in PaCa. The integration of artificial intelligence in aptamer development offers a rapid, precise, and scalable modality to generate highly specific inhibitors for challenging molecular targets such as glycosylation enzymes, highlighting its potential for clinical translation.