Biomimetic responsive antigen-delivery vehicles for therapeutic and preventive vaccines against hereditary triple-negative breast cancer

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Abstract:

This project aims to revolutionize the prevention and treatment of hereditary triple-negative breast cancer (TNBC) associated with BRCA1/2 mutations through the development of a personalized therapeutic and preventive vaccine. The proposed vaccine employs biomimetic lipid nanoparticles (BLNPs) coated with a tumour-derived membrane obtained from a resected tumour. This membrane provides a comprehensive antigenic profile tailored to TNBC's unique ligand expression. The nanoparticle core encapsulates immunostimulatory adjuvants and/or mRNA encoding antigens to activate a robust and targeted immune response. A key objective is to evaluate the vaccine's dual role in treatment and prevention. By promoting durable immune memory, it aims to prevent tumour recurrence in patients and reduce cancer incidence in descendants with a high genetic predisposition to TNBC.
BLNPs will be designed for dual delivery routes: intramuscular injection for systemic immune activation and oral administration using gastro-resistant pellets for enhanced patient compliance and accessibility. Upon administration, BLNPs interact with immature dendritic cells, ensuring efficient cytosolic release of antigens and adjuvants to drive MHC-I antigen cross-presentation and dendritic cell maturation. This results in the activation of $CD8^+$ cytotoxic T-cells and T-helper cells, augmented by co-administration of immune checkpoint inhibitors, such as anti-PD-L1 antibodies, to overcome tumour-induced immunosuppression and enhance immune infiltration into the tumour microenvironment. To validate the vaccine, a preclinical model using BRCA-deficient murine 4T1 TNBC cells will be employed to produce tumour-derived membranes and establish an orthotopic TNBC model in mice.

This innovative approach integrates nanotechnology and cutting-edge immunotherapy to offer a transformative solution for a highly aggressive genetic cancer, improving patient outcomes and providing preventive care for at-risk individuals.