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Development of mRNA-Based Vaccination for BRCA1-Mutated Cancers

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We are still developing and optimizing this protocol

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Abstract

Title: *A Phase I/II Clinical Trial of mRNA-Encoded BRCA1 Therapy in BRCA1-Mutated Cancers: Assessing Safety, Efficacy, and Tumor Suppression*

Background: BRCA1 mutations are associated with a significantly increased risk of developing breast, ovarian, and other cancers due to defective DNA repair mechanisms. Current treatments, including PARP inhibitors, have shown limited long-term success, necessitating novel approaches. mRNA-based therapies represent a promising new frontier in cancer treatment, leveraging the body's cellular machinery to restore functional proteins and improve therapeutic outcomes.

Objective: This study aims to evaluate the safety, efficacy, and optimal dosing of an mRNA-based therapy encoding the **BRCA1 gene** in patients with advanced BRCA1-mutated cancers, including breast, ovarian, and glioblastoma. The therapy is designed to restore BRCA1 function, improve DNA repair capacity, and reduce tumor progression.

Methods: This is a randomized, open-label, Phase I/II clinical trial. Participants with confirmed germline or somatic BRCA1 mutations and advanced-stage cancers that have progressed despite standard treatments will be enrolled. The trial will compare the safety and efficacy of the mRNA BRCA1 therapy against standard-of-care treatments, such as chemotherapy and PARP inhibitors. Primary outcome measures include tumor response rate as assessed by RECIST criteria and DNA repair efficiency, while secondary outcomes include progression-free survival (PFS), overall survival (OS), and adverse events.

Expected Outcomes: We hypothesize that mRNA-encoded BRCA1 therapy will restore DNA repair functionality in BRCA1-mutated cells, leading to enhanced genomic stability and improved response to cancer treatment, ultimately reducing tumor growth and progression. If successful, this approach could offer a novel therapeutic option for patients with BRCA1-mutated cancers.

Conclusion: This trial represents a pioneering effort to explore the potential of mRNA-based gene therapy in cancer treatment, specifically targeting BRCA1 mutations. Positive outcomes from this study could revolutionize treatment strategies for hereditary cancers and other malignancies associated with BRCA1 mutations.

Headline

1 **Research Proposal: Development of mRNA-Based Vaccination for BRCA1-Mutated Cancers, Including BRCA1 Glioblastoma Cell Lines**

Introduction

2 BRCA1 is a critical tumor suppressor gene involved in homologous recombination (HR) repair of DNA double-strand breaks, with mutations leading to higher susceptibility to several cancers, including breast, ovarian, and more recently, certain glioblastomas. Glioblastomas (GBM), the most aggressive form of brain cancer, are generally resistant to treatment and characterized by high genomic instability. Emerging research shows that some glioblastomas may exhibit BRCA1/2 mutations or homologous recombination deficiencies (HRD), making them potential candidates for DNA repair-based therapies, including mRNA-based interventions. This proposal aims to develop an **mRNA vaccine** targeting **BRCA1-deficient cancers**, including those involving glioblastomas.

Objective

3 The primary objective of this research proposal is to develop and test an **mRNA vaccine** designed to transiently express the **BRCA1 protein** in cancer cells, focusing on both **BRCA1-mutated breast/ovarian cancers** and BRCA1-mutated **glioblastoma** cells. This strategy will be evaluated for its ability to:

- Restore BRCA1 function in cells with defective DNA repair mechanisms.
- Improve responses to DNA-damaging cancer treatments (e.g., radiation, chemotherapy).
- Reduce genomic instability, particularly in glioblastomas, where BRCA1 mutations or other homologous recombination defects contribute to poor prognosis.

Rationale

4 BRCA1 mutations impair homologous recombination repair, leading to increased reliance on alternative, error-prone DNA repair mechanisms. This increases the likelihood of cancer development and progression. **Glioblastoma**, a highly aggressive brain tumor, is generally resistant to conventional therapies. However, emerging data suggest that a subset of GBM tumors harbor **BRCA1/2 mutations** or related HR deficiencies, making them potential candidates for therapies targeting DNA repair mechanisms.
By delivering functional **BRCA1 mRNA**, we hypothesize that:

- Temporarily boosting BRCA1 expression in BRCA1-deficient glioblastoma cells will enhance DNA repair via homologous recombination, reducing DNA damage and genomic instability.
- The transient nature of mRNA expression will minimize risks associated with long-term overexpression of BRCA1.

Methodology

5 **mRNA Design**

mRNA Encoding BRCA1: We will design synthetic mRNA encoding the full-length BRCA1 protein, optimized for stability, translation efficiency, and minimal immunogenicity. The mRNA will be encapsulated in lipid nanoparticles (LNPs) for targeted delivery to glioblastoma cells. Modifications: mRNA will be modified with 5' capping, polyadenylation, and sequence optimization to enhance stability and prevent immune recognition.

6 **In Vitro Testing**

BRCA1-Mutated Cancer Cell Lines: The mRNA will be tested in both
BRCA1-deficient breast/ovarian cancer cell lines (e.g., MDA-MB-436) and BRCA1-mutated glioblastoma cell lines (e.g., U87-MG with BRCA1 knockdown or other established GBM lines exhibiting HRD).
Functional Assays: Homologous recombination efficiency will be assessed using assays such as the DR-GFP assay. DNA damage response will be monitored by quantifying γH2AX foci, a marker of DNA double-strand breaks.
Genomic Stability: The impact of BRCA1 restoration on genomic stability will be measured through karyotyping and DNA damage markers.

7 **In Vivo Testing**

Mouse Models: We will use both breast/ovarian cancer and glioblastoma mouse models with BRCA1 mutations. Tumor growth, DNA repair capacity, and overall survival will be measured.
Combination Therapy: The mRNA vaccine will be tested in combination with PARP inhibitors and radiation to evaluate whether BRCA1 restoration sensitizes tumors to DNA-damaging treatments.

8 **BRCA1 Glioblastoma Models**

BRCA1 Knockout GBM Models: We will create CRISPR-based BRCA1 knockout glioblastoma models to simulate the effects of BRCA1 deficiency in GBM. These models will be used to evaluate the effects of mRNA-induced BRCA1 expression.
Patient-Derived Xenografts (PDX): PDX models of glioblastoma with known BRCA1 mutations or HR deficiencies will be used to mimic clinical scenarios more accurately.

9 **Dosage and Safety**

Dose Optimization: A key focus will be on optimizing the mRNA dosage to achieve therapeutic BRCA1 expression without causing excessive repair activity that could lead to genomic instability.
Monitoring Homeostasis: Since mRNA vaccines are transient, BRCA1 levels and cellular responses will be monitored post-administration to ensure that homeostasis is quickly restored after mRNA degradation.

Expected Outcomes

10 **Improved DNA Repair:** BRCA1 mRNA vaccination should transiently restore DNA repair capability in BRCA1-deficient glioblastoma cells, resulting in reduced DNA damage and enhanced genomic stability.

11 **Increased Treatment Sensitivity:** By restoring BRCA1 function, tumor cells should become more sensitive to radiation and chemotherapy, both of which induce DNA damage that BRCA1 repairs.

12 **Controlled BRCA1 Expression:** The transient nature of mRNA expression should reduce the risks of overexpression-associated side effects, ensuring normal cell function resumes after treatment.

Challenges and Considerations

13 **Dosing for Glioblastoma**: Since glioblastomas are highly heterogeneous, dosing strategies may need to be tailored based on individual tumor characteristics. Additionally, overcoming the blood-brain barrier (BBB) will be a key challenge for delivering mRNA vaccines to brain tumors.

14 **Tumor Microenvironment:** The dense microenvironment of glioblastomas could limit the effectiveness of the vaccine. Strategies to enhance delivery to the tumor site, such as BBB-penetrating nanoparticles, will be explored.

15 **Immune Response:** Although mRNA vaccines are typically well-tolerated, immune responses specific to brain tissue may differ. Understanding and mitigating potential neuroinflammatory responses will be critical.

Significance

16 The development of an mRNA-based vaccine to restore **BRCA1 function in BRCA1-mutated glioblastomas** represents a novel approach to treating this deadly cancer. By temporarily boosting BRCA1 expression, this therapy could improve DNA repair and make tumors more vulnerable to existing treatments, potentially offering a new avenue for managing glioblastomas with DNA repair deficiencies.

Timeline

17 Year 1: mRNA design, in vitro testing in BRCA1-mutated breast/ovarian cancer and glioblastoma cell lines.

18 Year 2: In vivo testing in mouse models, including BRCA1-mutated glioblastomas.

19 Year 3: Preclinical safety assessments and preparation for clinical trial design.

Conclusion

20 This proposal outlines a novel strategy for using mRNA vaccination to transiently restore BRCA1 function in both BRCA1-mutated cancers and glioblastomas with homologous recombination deficiencies. By enhancing DNA repair mechanisms, this approach could sensitize tumors to existing therapies, improving patient outcomes in cancers with limited treatment options. If successful, this project could lead to the development of a new class of mRNA-based therapies for cancers caused by genetic mutations.