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TECHNOLOGY ABSTRACT

# Homologous Recombination (HR) Factors for Gene Editing in Non-Dividing Cells

## Description

Enables precise gene editing in non-dividing cells by activating homologous recombination outside S/G2 phases.

## Background

Precise genome modification has traditionally relied on homologous recombination (HR), a DNA repair mechanism that uses a donor template to introduce targeted genetic changes. While HR offers high fidelity, its naturally low activity in most eukaryotic cells—particularly non-dividing cells—has limited its practical use. Historically, efficient HR-based gene targeting was largely restricted to dividing cells in S/G2 phases of the cell cycle.

The introduction of programmable nucleases such as CRISPR/Cas systems dramatically improved gene editing efficiency by generating site-specific DNA double-strand breaks (DSBs). However, even with CRISPR, accurate gene correction via HR remains inefficient in cells arrested in G1 or G0, where non-homologous end joining (NHEJ) dominates. This limitation is especially relevant for therapeutic applications targeting terminally differentiated or dormant cells involved in cardiovascular, neurological, and chronic inflammatory diseases, as well as certain cancers characterized by HR defects.

## Technology Overview

This technology addresses a fundamental limitation of current gene editing platforms by enabling homologous recombination in cells that are not actively dividing. The invention identifies and manipulates key molecular regulators of HR—including BRCA1, PALB2, BRCA2, KEAP1, and the deubiquitylase USP11—to overcome the natural suppression of HR in G1-phase cells.

Under normal conditions, HR is inhibited in G1 due to the ubiquitylation of PALB2 by the CRL3-KEAP1 E3 ubiquitin ligase complex, which prevents the formation of the BRCA1-PALB2-BRCA2 repair complex. This technology demonstrates that restoring BRCA1-PALB2 interactions, combined with activation of DNA end resection, is sufficient to induce functional HR in G1-phase cells. The inhibition of KEAP1 or CRL3-KEAP1, stabilization or activation of USP11, or use of engineered PALB2 variants allows HR machinery to assemble outside its usual cell-cycle window.

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Importantly, this approach is compatible with existing gene editing tools, including CRISPR/Cas systems, and significantly expands their utility. By enabling precise, template-directed genome editing in non-dividing or quiescent cells, the technology opens new possibilities for therapeutic gene correction, functional genomics, and disease modeling. It also provides valuable biomarkers and screening platforms for agents that modulate HR, with additional relevance for enhancing or predicting responses to PARP inhibitor therapies.

**Benefits**

- Enables high-fidelity gene editing in non-dividing and G1-arrested cells
- Expands the therapeutic reach of CRISPR and other nuclease-based platforms
- Improves precision over error-prone NHEJ repair pathways
- Supports drug discovery and biomarker development for HR-related diseases
- Applicable to diseases with known homologous recombination defects

**Applications**

- Gene therapy for cardiovascular, neurological, and chronic inflammatory diseases
- Cancer therapeutics targeting HR-deficient tumors
- Genome editing in terminally differentiated or dormant cells
- Functional genomics and disease modeling
- Companion diagnostics and PARP inhibitor response prediction

**Commercial Opportunity**

Available for licensing or partnership

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