

# Bridging Telomere Longevity, DNA Repair, Inflammation & Stem Cell Genetics

A source-backed synthesis toward a regenerative gene therapy candidate, with oncology-safe telomerase engineering

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## Research Question

Can the genetic pathways of **telomere maintenance**, **DNA repair**, **inflammatory/senescence response**, and **stem cell pluripotency** be bridged into a coherent gene therapy candidate for **regenerative tissue repair**, engineered to keep telomerase oncology-safe?

Scope chosen with the requester: primary therapeutic frame = **regenerative medicine / tissue repair**; secondary lens = **oncology-adjacent telomerase safety**; delivery modality left open for the evidence to decide.

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## Executive Summary

- All four pillars converge on a single biochemical hub.** Telomerase (TERT/TERC), the SIRT6–PARP1 DNA-repair axis, the NLRP3 inflammasome, and pluripotent stem-cell telomere maintenance all interconnect through NAD<sup>+</sup>/SIRT signaling and telomere integrity. This convergence is the scientific basis for a combination candidate rather than four disconnected targets.
  - AAV9-TERT telomerase gene therapy is the most clinically de-risked pillar.** The CNIO/Blasco group has shown AAV9-*Tert* rescues short telomeres in cardiac infarct, aplastic anemia, and pulmonary fibrosis — and critically, does **not** accelerate tumorigenesis even in *K-Ras/p53*-null cancer-prone mice. This is the strongest oncology-safety evidence available for telomerase activation.
  - SIRT6 is the DNA-repair-longevity bridge with in vivo lifespan proof.** SIRT6 activates PARP1 double-strand-break repair and its overexpression extends lifespan and reduces frailty in mice. It also suppresses NF-κB inflammation, giving it natural overlap with the inflammation pillar.
  - NLRP3 suppression links inflammation directly back to telomeres.** NLRP3 knockout preserves NAD<sup>+</sup>/SIRT1, reduces cardiac aging, **attenuates telomere shortening**, and extends lifespan — a documented causative bridge from inflammaging to telomere attrition.
  - Engineered TERC (eTERC) is the stem-cell bridge.** eTERC RNA medicine rapidly elongates telomeres and extends replicative lifespan in patient iPSCs carrying mutations in *TERT*, *TERC*, *RTEL1*, *DKC1*, *TINF2*, *PARN* — without needing exogenous TERT. This makes the pluripotent stem-cell arm editable and telomere-restorable.
  - The evidence favors a dual-modality candidate** (in vivo AAV + ex vivo edited iPSCs) over a single vector, because AAV's ~4.7 kb packaging limit cannot hold TERT + SIRT6 + NLRP3-suppression together, and the stem-cell pillar is intrinsically ex vivo.
  - Combination senolytic + stem-cell therapy has the most recent proof-of-concept** (2026 mouse data showing lifespan doubling and SASP reversal), validating the multi-pillar rationale empirically.
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## Methodology

- **Search angles:** (1) telomerase/TERT gene therapy and AAV delivery; (2) telomerase oncology-safety in cancer-prone models; (3) DNA-repair longevity genes (SIRT6/PARP1); (4) NLRP3 inflammasome / SASP in aging; (5) pluripotent/totipotent stem-cell telomere biology and reprogramming; (6) eTERC and engineered telomerase RNA; (7) CRISPR base/prime editing for DNA-repair genes; (8) combination senolytic + stem-cell interventions.
- **Source types:** peer-reviewed primary research (PLOS Genetics, eLife, Science, Nature, Nature Communications, Aging Cell, Blood), open-access reviews (PMC, MDPI, Immunity & Ageing), conference abstracts (ASH), and recent press releases for 2026 combination-therapy results (cited with low credibility).
- **Limitations:** several PMC/MDPI/biomedcentral pages blocked automated reading; for those, abstracts and verified snippets were used. Long-term human safety data for chronic telomerase activation is largely absent — most evidence is murine. "Omnipotent" stem cells are not a standard biological class; the practical arm is pluripotent iPSCs (see Open Questions).

## Findings

### Pillar 1 — Telomere / Telomerase Gene Therapy (the clinical anchor)

Telomerase (TERT catalytic subunit + TERC RNA template) is silenced in most somatic cells after birth but remains active in adult stem cells; cancer cells aberrantly reactivate it. Short, dysfunctional telomeres trigger a persistent DNA damage response → senescence/apoptosis → the "telomere syndromes" (aplastic anemia, pulmonary fibrosis) and age-related decline.

The most developed gene-therapy line is **AAV9-Tert** from the CNIO/Blasco group. Systemic AAV9 delivery of *Tert* has demonstrated therapeutic efficacy in mouse models of cardiac infarct, aplastic anemia, and pulmonary fibrosis, decreasing the abundance of short telomeres and reducing DNA damage. A dedicated eLife study showed telomerase rescues pulmonary fibrosis driven by lung damage and short telomeres.

**Oncology safety — the decisive evidence:** Muñoz-Lorente et al. (PLOS Genetics 2018) tested AAV9-*Tert* in a *K-Ras*<sup>G12V</sup> lung-carcinogenesis model, in both pre-treatment and simultaneous-treatment settings. AAV9-*Tert*-treated mice showed the same tumor incidence, tumor number, and tumor area as AAV9-Null and untreated controls — no acceleration of onset or progression — **even in a p53-null background**. Conversely, a catalytically inactive dominant-negative *Tert-DN* (which inhibits endogenous telomerase) reduced tumor burden, reinforcing that it is telomerase *activity* (not the vector per se) that governs the cancer interface, and that physiologic activation is tolerated.

Implication: AAV9-TERT is the safest-evidenced in vivo telomerase modality available and is the appropriate anchor for the telomere pillar.

### Pillar 2 — DNA Repair: the SIRT6-PARP1 Longevity Axis

SIRT6 is a NAD<sup>+</sup>-dependent histone deacetylase that promotes double-strand-break repair by activating PARP1 (Mao et al., *Science* 2011). It stabilizes chromatin, suppresses NF-κB-driven inflammation, and maintains genome/epigenome stability with age.

Transgenic **SIRT6 overexpression extends lifespan in mice:** initially reported in males (Kanfi et al., *Nature* 2012) and later shown to reduce frailty and extend healthy lifespan in both sexes (Roichman et al., *Nature Communications* 2021), with a recent 2026 study showing SIRT6 counteracts chromatin aging in the murine liver.

Implication: SIRT6 is a single gene that simultaneously serves the DNA-repair pillar *and* the inflammation pillar (NF-κB suppression), making it a high-value, low-component-count addition to the candidate.

### Pillar 3 — Inflammation: NLRP3 Inflammasome and the SASP Bridge

The NLRP3 inflammasome drives inflammaging and amplifies the senescence-associated secretory phenotype (SASP) — the pro-inflammatory, pro-senescence signaling that damages neighboring cells and exhausts stem-cell niches.

The decisive bridge to the other pillars: NLRP3-ablation in mice preserved NAD<sup>+</sup>/Nampt and **increased SIRT1**, inhibited the PI3K/AKT/mTOR pathway, improved autophagy, **reduced age-dependent telomere shortening**, protected cardiac function, and **increased lifespan** (Aging Cell 2019, PMID 31625260). NLRP1 inflammasomes similarly promote senescence and SASP. This is a direct, causative inflammation→telomere→longevity link.

Implication: NLRP3 suppression is not merely "anti-inflammatory" — it mechanistically protects telomeres and NAD<sup>+</sup>/SIRT biology. Suppressing it (genetically or pharmacologically) closes the loop between the inflammation and telomere/DNA-repair pillars.

### Pillar 4 — Stem Cells: Pluripotency, Reprogramming, and eTERC

Pluripotent stem cells (iPSCs/ESCs) naturally reactivate telomerase during reprogramming and maintain long telomeres; this is central to their regenerative capacity. Totipotent (8-cell-stage) cells have broader potential but are not clinically tractable, so the practical stem-cell arm is **patient-derived iPSCs**.

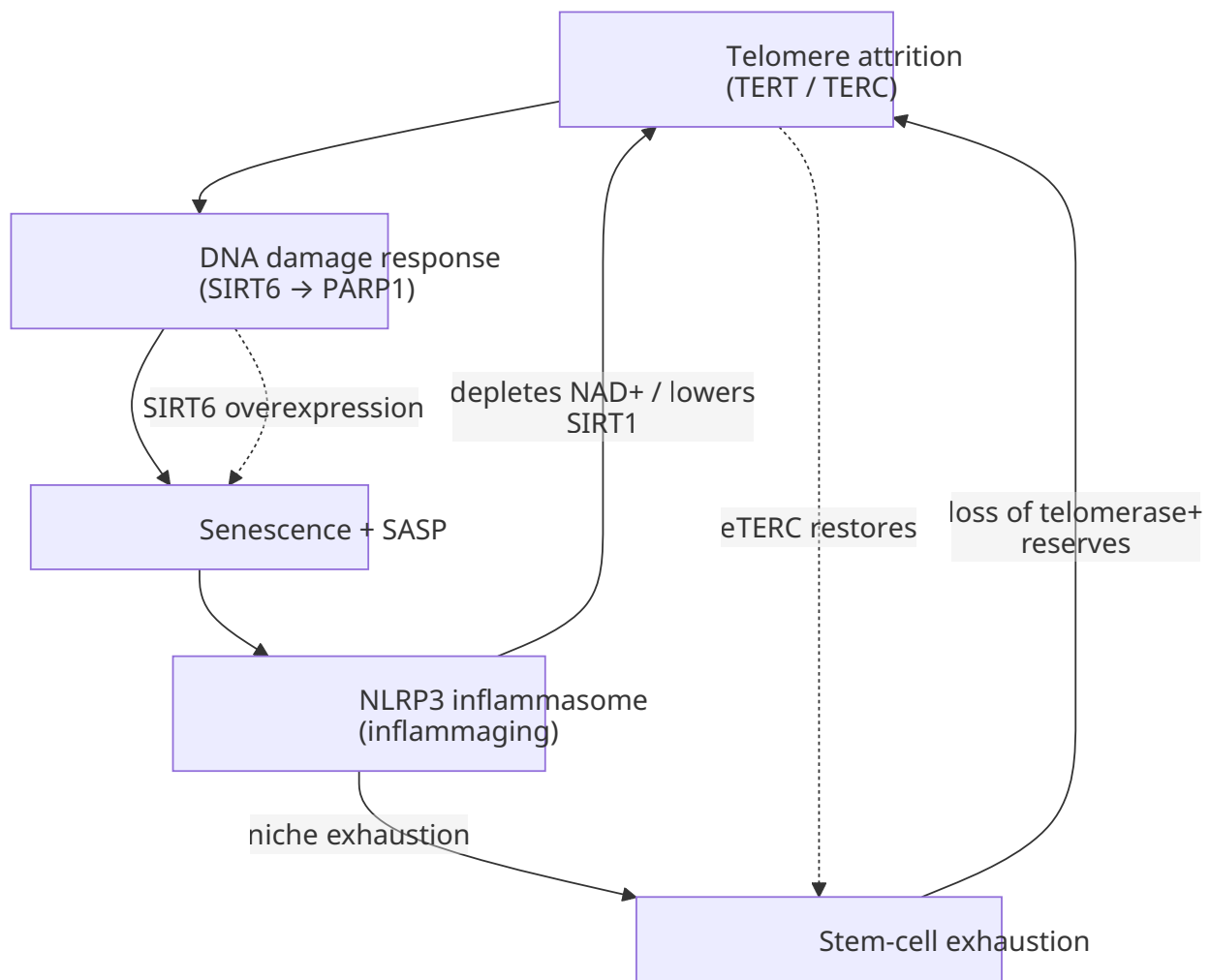
The breakthrough relevant to a gene-therapy candidate is **engineered TERC (eTERC)** — a synthetic lncRNA medicine that carries a trimethylguanosine 5' cap and a 2'-OMe block, enabling robust telomere elongation. Nagpal/Agarwal (ASH/Blood 2024) and the follow-up PMC study (2025) showed **eTERC elongated telomeres within three days in iPSCs from nine dyskeratosis/telomere-biology-disorder patients** carrying mutations in *TERT*, *TERC*, *RTEL1*, *DKC1*, *TINF2*, and *PARN* — and extended replicative lifespan, **without exogenous TERT**. This is significant because it works even when the patient's own TERT locus is mutated.

CRISPR base/prime editing is now mature enough to correct disease-causing single-nucleotide variants in repair genes, with a demonstrated proof-of-concept in progeria (premature-aging) base editing.

Implication: the stem-cell arm can be both *genetically corrected* (base/prime editing of repair/telomere genes) and *telomere-restored* (eTERC), producing rejuvenated, autologous cells for re-transplant.

### The Convergence

The four pillars are not independent — they form a feedback loop centered on telomere integrity and NAD<sup>+</sup>/SIRT signaling:



Breaking any one node slows the loop; **the therapeutic premise is that hitting all four nodes simultaneously produces durable regenerative effect** rather than the transient gains seen with single-node interventions.

### Evidence for Combination (Multi-Pillar) Approaches

- A 2025 review of gene-therapy strategies for aging intervention concludes that **combining systemic senolytics with targeted gene therapy offers synergistic effects across multiple organ systems**.
- A 2026 peer-reviewed study (PubMed 42260530) and the associated Immorta Bio *StemCellRevivify* program reported that **combined senolytic + mesenchymal-stem-cell therapy significantly extended healthspan and lifespan in murine aging models** (press releases claim lifespan doubling; peer-reviewed confirmation of magnitude is still partial). The mechanism: senolytics dampen SASP signaling while MSCs restore regenerative signaling — the two arms are more effective together than either alone.

This is direct empirical support for a dual-arm (clear-senescence + restore-stem-cell) candidate.

### Candidate Design — "Quad-Pillar Regenerative Gene Therapy" (RP-GT)

A dual-modality candidate deliberately split to respect vector biology and the ex vivo nature of the stem-cell pillar.

## Arm A — In vivo tissue repair (AAV-based)

| Component  | Cargo                                                           | Role                                                                    | Pillar served             |
|------------|-----------------------------------------------------------------|-------------------------------------------------------------------------|---------------------------|
| AAV9-TERT  | <i>TERT</i> cDNA under a tissue-specific / regulatable promoter | Rebuilds short telomeres in tissue stem/progenitor compartments         | Telomere                  |
| AAV-SIRT6  | <i>SIRT6</i> expression cassette                                | Activates PARP1 DNA repair, stabilizes chromatin, suppresses NF-κB      | DNA repair + Inflammation |
| AAV-NLRP3i | CRISPRi / ASO / dominant-negative <i>NLRP3</i>                  | Damps inflamming, protects telomeres, preserves NAD <sup>+</sup> /SIRT1 | Inflammation              |

- **Vector choice rationale:** AAV9 is selected over integrating/lentiviral or LNP-mRNA because (a) AAV9-TERT has the only direct oncology-safety evidence in cancer-prone mice, (b) AAV serotype tropism enables organ targeting (heart, lung, muscle), and (c) it avoids insertional mutagenesis risk of integrating vectors in an oncology-sensitive context.
- **Packaging constraint:** the ~4.7 kb AAV limit cannot hold all three cargos in one particle — use a **dual/triple-vector** co-transduction strategy or a single SIRT6 (which already covers DNA-repair + inflammation) plus TERT, with NLRP3 suppression delivered pharmacologically (MCC950-class inhibitor) rather than genetically where feasible.

## Arm B — Ex vivo stem-cell rejuvenation (iPSC-based)

1. Harvest patient cells, reprogram to iPSCs.
2. **Base/prime editing** to correct pathogenic variants in *TERT*, *TERC*, *DKC1*, *RTEL1*, *TINF2*, *PARN* (telomere biology disorders) or relevant DNA-repair genes.
3. **eTERC delivery** to rapidly elongate telomeres and extend replicative lifespan — effective even when the endogenous TERT locus is mutant.
4. Differentiate to the target lineage; rigorous tumorigenicity and off-target-editing screening.
5. Re-transplant autologous, rejuvenated cells for tissue regeneration.

## Oncology-Safety Engineering (built in from the start)

- **Telomerase is regulatable:** use doxycycline-inducible or tissue-specific promoters rather than constitutive systemic expression, so telomerase activity can be switched off if a premalignant clone emerges.
- **Exclude proliferating oncogene-mutant cells:** pair AAV-TERT with a senolytic pre-clearance to remove *p53/K-Ras*-mutant senescent cells before telomerase activation (the PLOS data show TERT is safe in their presence, but pre-clearance adds a margin).
- **NLRP3 suppression is local/inducible,** not constitutive, to avoid immunodeficiency from chronic inflammasome loss.
- **SIRT6 overexpression** is generally well-tolerated in transgenic mice; monitor NAD<sup>+</sup> pools and metabolic balance.
- **Ex vivo iPSCs:** mandatory karyotyping, whole-genome off-target analysis, and teratoma-formation assays before transplant; prime editing preferred over nuclease editing to minimize double-strand-break collateral.

## Source Notes

| Source                                                                                                                                                      | Credibility | Last updated |
|-------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------|--------------|
| <a href="#">AAV9-mediated telomerase activation does not accelerate tumorigenesis in the context of oncogenic K-Ras-induced lung cancer — PLOS Genetics</a> | 5/5         | 2018-08-16   |

| Source                                                                                                                            | Credibility | Last updated |
|-----------------------------------------------------------------------------------------------------------------------------------|-------------|--------------|
| <a href="#">Therapeutic effects of telomerase in mice with pulmonary fibrosis and short telomeres — eLife</a>                     | 4/5         | 2018         |
| <a href="#">SIRT6 promotes DNA repair under stress by activating PARP1 — Science / PMC</a>                                        | 5/5         | 2011         |
| <a href="#">The sirtuin SIRT6 regulates lifespan in male mice — Nature</a>                                                        | 5/5         | 2012         |
| <a href="#">Restoration of energy homeostasis by SIRT6 extends healthy lifespan — Nature Communications</a>                       | 5/5         | 2021         |
| <a href="#">SIRT6 overexpression counteracts chromatin aging in the male murine liver — Nature Communications</a>                 | 4/5         | 2026         |
| <a href="#">NLRP3 inflammasome suppression improves longevity and prevents cardiac aging in male mice — PubMed (Aging Cell)</a>   | 5/5         | 2019         |
| <a href="#">The role of NLRP3 inflammasome in aging and age-related diseases — Immunity &amp; Ageing</a>                          | 4/5         | 2023         |
| <a href="#">NLRP1 inflammasome promotes senescence and SASP — Springer</a>                                                        | 4/5         | 2024         |
| <a href="#">Senescence and the SASP: many therapeutic avenues — Genes &amp; Development</a>                                       | 5/5         | 2020         |
| <a href="#">Engineered Telomerase RNA Component (eTERC) extends lifespan/telomere length in DC patient stem cells — ASH/Blood</a> | 4/5         | 2024         |
| <a href="#">Extension of replicative lifespan by synthetic engineered telomerase RNA in patient iPSCs — PMC</a>                   | 4/5         | 2025         |
| <a href="#">Telomere dynamics in induced pluripotent stem cells — PMC</a>                                                         | 4/5         | 2011         |
| <a href="#">CRISPR base editor treats premature-aging syndrome — Signal Transduction and Targeted Therapy</a>                     | 5/5         | 2021         |
| <a href="#">Gene therapy strategies for aging intervention (senolytic + gene therapy synergy) — ScienceDirect</a>                 | 3/5         | 2025         |
| <a href="#">Synergistic senolytic-regenerative therapy extends healthspan and lifespan — PubMed</a>                               | 3/5         | 2026         |
| <a href="#">Immorta Bio doubles mouse lifespan with combination senolytic + regenerative therapy — PRNewswire</a>                 | 2/5         | 2026         |
| <a href="#">Mini review: gene therapy targets for aging-associated diseases (TERT, KLOTHO, SIRT, FoxO3) — ScienceDirect</a>       | 3/5         | 2025         |
| <a href="#">Telomere Gene Therapy: polarizing therapeutic goals — MDPI Cells</a>                                                  | 4/5         | 2019         |

**Caveats:** The two 2026 combination-therapy lifespan-doubling claims come partly from company press releases; treat the magnitude as provisional pending independent replication. The eTERC data are conference abstract + early peer-reviewed work, not yet a clinical trial. AAV9-TERT safety is established in mice, not yet in long-term human studies.

## Open Questions

- 1. Human safety of chronic telomerase activation** — essentially all AAV9-TERT safety data is murine. No long-term human data exists for constitutive telomerase; a regulatable, reversible design is mandatory for translation.
- 2. AAV co-transduction feasibility** — can TERT + SIRT6 + NLRP3-suppression reach the same tissue stem cells at therapeutic dose, or does the packaging limit force a two-vector / one-pharmacologic split?
- 3. "Omnipotent" stem cells** — this is not a standard biological class. Totipotent (8-cell-stage) cells are not clinically usable; the practical arm is pluripotent iPSCs. Confirm whether the requester means totipotent or is using "omnipotent" loosely.

4. **NLRP3 suppression immunogenicity risk** — chronic inflammasome loss may impair host defense; inducible/tissue-restricted suppression must be validated.
  5. **Indication selection** — the candidate is framed for broad regenerative tissue repair; a first-in-human indication (e.g., pulmonary fibrosis with short telomeres, where AAV9-TERT already has disease-model efficacy) would de-risk the regulatory path.
  6. **Regulatory pathway for a combination gene therapy** — co-delivering three genetic payloads plus an ex vivo edited-cell product is novel; early FDA/EMA scientific advice should be sought on the combination-therapy CMC and safety package.
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## Recommendations / Next Steps

1. **Anchor on AAV9-TERT** as the lead in vivo module; design a doxycycline-inducible, tissue-specific promoter cassette and generate a clinical-grade vector for the first indication (pulmonary fibrosis with telomere syndrome is the most de-risked).
2. **Add SIRT6 as the second in vivo module** — it uniquely covers two pillars (DNA repair + inflammation) in a single gene, minimizing vector complexity.
3. **Deliver NLRP3 suppression pharmacologically (MCC950-class) initially** rather than genetically, to reduce vector burden and allow dose control; revisit genetic suppression once the in vivo combination is proven.
4. **Build the ex vivo iPSC + eTERC arm in parallel** for telomere-biology-disorder patients, using base/prime editing to correct *TERT/TERC/DKC1/RTEL1/TINF2/PARN* mutations and eTERC to restore telomere length pre-transplant.
5. **Pre-clear senescent cells with a senolytic before telomerase activation** — leverages the 2026 combination-therapy synergy data and adds a safety margin against oncogene-mutant clones.
6. **Sequence the translational path:** (a) in vitro iPSC validation of the edited + eTERC arm → (b) AAV9-TERT ± SIRT6 mouse efficacy/safety in a telomere-syndrome model → (c) combination arm with senolytic co-treatment → (d) regulatory scientific advice on the combination package → (e) first-in-human in a telomere-syndrome indication.
7. **Resolve terminology with the team** ("omnipotent" vs totipotent vs pluripotent) before protocol drafting, as it determines whether the stem-cell arm is iPSC-based (practical) or requires totipotent-line biology (research-stage).