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Longevity Horizon
ISSN:3088-4063

2026

Vol.2 No.2:6

Centrosome Transplantation

Conceptual Breakthrough and a Technical Challenge

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Citation: Tkemaladze, J. (2026). Centrosome Transplantation. Longevity Horizon, 2(2). DOI : https://doi.org/10.65649/rz3mb206

Abstract

The centrosome, a key microtubule-organizing center, has long been implicated in fundamental cellular processes such as division, polarity, and ciliogenesis. Observations linking centrosomal aberrations to specific cellular states, including senescence and aging, raise a pivotal question: is the centrosome merely a structural casualty of these states, or does it actively encode and transmit information dictating cellular phenotype? This article explores the conceptual framework, methodology, and profound implications of centrosome transplantation, an experimental paradigm designed to answer this question by directly testing causality. We review the historical context of organelle transplantation, detail a comprehensive technical protocol encompassing centrosome isolation, microinjection, and phenotypic analysis, and discuss the significant challenges and alternative approaches. A meta-analysis of pioneering and preliminary data highlights the potential of this method to demonstrate the transfer of age-related traits. We argue that a successful transplantation experiment would constitute a revolution in cell biology, providing definitive proof of non-genetic, organelle-based inheritance of cellular age. This would position the centriole as a strategic custodian of cellular time and open transformative therapeutic avenues focused on rejuvenating the centrosomal machinery in stem cells, thereby offering a novel paradigm for intervening in the aging process.

Keywords: Centrosome, Transplantation, Cellular Aging, Structural Inheritance, Organelle Rejuvenation, Non-Genetic Memory, Phenotypic Transfer.

Introduction

The centrosome, long recognized as the primary microtubule-organizing center of animal cells, orchestrates critical processes from cell division to polarity establishment. For over a century, its structural and numerical integrity has been correlated with cellular states such as proliferation, quiescence, differentiation, and senescence. However, establishing definitive causality—whether the centrosome is a passive indicator or an active regulator of cellular fate—has remained a formidable challenge in cell biology. Centrosome transplantation emerges as an elegant, albeit technically extreme, methodology designed to directly test this causality by physically transferring the organelle from a donor to a recipient cell. The core hypothesis is provocative: if cellular "age" or "youth" is encoded, even in part, within the centrosome's structure and associated molecular milieu, then transplanting this organelle should confer the corresponding phenotypic state onto the recipient (Brito & Rieder, 2009; Palazzo et al., 2000).

This premise is rooted in the conceptual framework of non-genetic, structural inheritance. Classical experiments in developmental biology, most famously the nuclear transfer studies by Gurdon (Gurdon, 1962), demonstrated that the nucleus contains information sufficient to direct embryonic development, establishing the primacy of genetic material. Subsequent research on mitochondrial transplantation extended this logic to cytoplasmic inheritance, showing that the transfer of mitochondria could alter metabolic phenotypes (King & Attardi, 1989; McCully et al., 2009). The centrosome transplantation experiment represents a logical, yet more radical, extension of this paradigm. It probes a form of inheritance that is not based on DNA sequence but on the self-perpetuating structure and composition of an organelle complex. Unlike the nucleus, the centrosome duplicates via a templated assembly process, and its abnormalities can propagate through cell generations, influencing spindle geometry and, consequently, genomic stability (Nigg & Holland, 2018; Gonczy, 2012). This positions it as a potential carrier of "cellular memory" independent of the genome.

The technical hurdles, however, are monumental. The centrosome is not a membrane-bound organelle but a dense, proteinaceous matrix—the pericentriolar material (PCM)—organized around a core of centrioles. Its integrity is exquisitely sensitive to biochemical perturbations. Early attempts to isolate functional centrosomes relied on protocols using high concentrations of KI or other salts, which, while yielding structurally recognizable particles, often stripped away essential regulatory components (Mitchison & Kirschner, 1986). Modern transplantation strategies must therefore balance the need for biochemical "purity" to ensure specific transfer with the imperative of preserving the native supramolecular architecture and the elusive "state" it purportedly encodes. Pioneering work by La Terra et al. (2005) demonstrated that microinjection of isolated centrosomes could induce microtubule aster formation in Xenopus eggs, proving the principle of functional transfer into a large, amenable system. Translating this to somatic mammalian cells, with their smaller size and more complex cell cycle regulation, requires nanoscale precision.

The central question driving this methodology is: Can an "old" centrosome from a senescent cell, characterized by amplified PCM, disorganized microtubules, and altered protein composition (such as elevated levels of p53 and senescence-associated proteins), induce

senescence in a young, proliferative cell? Conversely, can a "young" centrosome from a cycling cell rejuvenate or stimulate proliferation in a quiescent or senescent recipient? Answering these questions would fundamentally reshape our understanding of centrosome biology, moving it from a cytoskeletal orchestrator to a central signaling hub that integrates and transmits information about cellular history and state (Arquint & Nigg, 2014; Fry et al., 2017).

Furthermore, this approach has profound implications for understanding disease. Centrosome amplification is a hallmark of many cancers and is linked to invasion and genomic instability (Godinho & Pellman, 2014; Chan, 2011). Could the transplantation of an amplified centrosome from a cancer cell into a normal cell initiate a path toward transformation? Similarly, in aging, where centrosomal aberrations accumulate, does the organelle actively drive the aging phenotype? By providing a direct tool for causal testing, centrosome transplantation offers a unique path to dissect these long-standing correlations. It represents not just a technical feat but a conceptual gateway to exploring the role of self-perpetuating organelle states in development, homeostasis, and disease, firmly placing the centrosome at the heart of epigenetic cellular regulation.

Detailed Method Protocol: From Isolation to Analysis

The success of a centrosome transplantation experiment hinges on a meticulously optimized, multi-stage protocol designed to preserve the structural and functional integrity of the donor organelle while ensuring its precise delivery and subsequent analysis in a permissive recipient cell. This section details the critical steps, from the isolation of intact centrosomes to their microinjection and the subsequent phenotypic validation.

Stage 1: Isolation and Purification of Intact Centrosomes

Source Material:
The choice of donor cells is paramount and depends on the experimental hypothesis. For studies on aging, donors are classified as: "Old": primary stem/progenitor cells from aged animals (e.g., mouse, 24+ months) or cells subjected to extensive replicative senescence in vitro (e.g., beyond passage 40) (Shao et al., 2021). "Young": analogous cells from young animals (e.g., 2-3 months) or early passages. Crucial genetic controls include cells with defined centriolar defects, such as Plk4 or CEP164 knockouts, which produce aberrant or no centrioles, respectively (Bettencourt-Dias et al., 2005; Sillibourne et al., 2010).

Isolation Method (The Gold Standard – Bornens' Protocol with Modifications):
The cornerstone of centrosome isolation is the method developed by Bornens and colleagues, which relies on cell lysis in a low-ionic-strength, microtubule-stabilizing buffer (Bornens et al., 1987). The modern adaptation proceeds as follows:

1. Cell Lysis: Cells are swollen in a hypotonic lysis buffer (e.g., 1 mM Tris-HCl, pH 8.0, 0.5% IGEPAL CA-630 or NP-40, 0.1% β-mercaptoethanol) supplemented with

protease/phosphatase inhibitors, 1 mM ATP, and 5–20 μM taxol (paclitaxel) to stabilize microtubule-nucleated centrosomes. This osmotic shock, performed on ice, is critical for preserving the centrosome-microtubule complex, which acts as a handle for subsequent purification (Klotz et al., 1990).

2. Differential Centrifugation: The lysate is gently homogenized and subjected to low-speed centrifugation (800–1,000 × g for 5–10 min) to pellet nuclei and large debris. The centrosomes remain in the supernatant.

3. Sucrose Gradient Fractionation: The supernatant is layered onto a discontinuous sucrose density gradient (typically 40%, 50%, and 70% sucrose in 10 mM PIPES, pH 7.2, with 0.1% IGEPAL CA-630). After ultracentrifugation (e.g., 10,000–25,000 × g for 1 hour), intact centrosomes, due to their high density, sediment at the 50%/70% sucrose interface (Mitchison & Kirschner, 1986).

4. Percoll Gradient Purification: To achieve higher purity by removing contaminating membranes, ribosomes, and protein aggregates, the centrosome-enriched fraction can be further purified on an isotonic Percoll gradient, where centrosomes migrate as a distinct band (Paintrand et al., 1992).

Verification and Quality Control: The structural integrity of the isolated centrosomes must be confirmed before transplantation. This is typically done via immunofluorescence staining for core markers like γ-tubulin (PCM) and centrin (centrioles) spotted onto coverslips. The gold standard for ultrastructural validation is negative staining and transmission electron microscopy (TEM), which confirms the presence of an intact mother-daughter centriole pair and associated PCM (Tournier et al., 1991).

Challenges and Solutions:

- Low Yield: A major limitation is the low yield, often only ~10^4–10^5 centrosomes from 10^8 cells. A solution is to use cell lines engineered to overexpress centriolar proteins like SAS-6 or PLK4, which leads to enlarged PCM or centriole amplification, thereby increasing the physical mass and yield of isolated organelles (Kleylein-Sohn et al., 2007).

- Loss of Associated Factors: Harsh isolation can strip away critical centrosome-associated filamentous structures (CAFS) and signaling complexes. To mitigate this, a cross-linking step can be introduced prior to lysis. Treating intact cells with a membrane-permeable, reversible cross-linker like dithiobis(succinimidyl propionate) (DSP) helps stabilize the native centrosome interactome before detergent exposure (Müller et al., 2010).

Stage 2: Microinjection of Centrosomes into Recipient Cells

Recipient Cell Preparation: Recipient cells (e.g., young mesenchymal stem cells) must be rendered temporarily acentrosomal to prevent competition with the endogenous organelle and

to clearly attribute any phenotypic effect to the transplanted one. Cells are synchronized in G1 or early S-phase using serum starvation or a CDK4/6 inhibitor.

- Centrosome Depletion: The most effective method is pharmacological inhibition of centriole duplication and function. A combined treatment with a PLK4 inhibitor (e.g., Centrinone B, 100 nM) to block new centriole assembly and a PLK1 inhibitor (e.g., BI 2536, 100 nM) to inactivate the existing centrosome's microtubule-organizing capacity for 4–6 hours prior to injection is employed (Wong et al., 2015; Lénárt et al., 2007). As an alternative, laser ablation can be used to specifically destroy the resident centrosome, though this is lower throughput.

Microinjection Technique:

- Instrumentation: The procedure requires an inverted microscope equipped with high-precision hydraulic or pneumatic micromanipulators and a microinjection system (e.g., Eppendorf InjectMan).
- Injection Needles: Glass capillaries are pulled to an ultra-fine tip diameter of <0.5 µm.
- Injection Solution: Isolated centrosomes are gently resuspended in an injection buffer (e.g., 120 mM KCl, 20 mM NaCl, 10 mM HEPES, pH 7.4) supplemented with 0.1% bovine serum albumin to prevent adhesion to the glass.
- Procedure: The needle is advanced into the cytoplasm of a target cell, near the nucleus but avoiding it. A precisely controlled volume of 2–5 fl, estimated to contain 1–3 intact centrosomes, is injected. The process is monitored in real-time using phase-contrast or, if centrosomes are fluorescently labeled (e.g., via a tagged centriolar protein in donor cells), weak fluorescence optics.

Critical Injection Controls:

- Negative Control: Injection of centrosome isolation/injection buffer alone to account for mechanical and volumetric stress.
- Damage Control: Injection of inert latex beads of comparable size to the centrosome pellet to control for the physical disruption caused by introducing a particulate object.
- Specificity Control: Injection of centrosomes that have been functionally inactivated, for example, by pre-incubation with function-blocking antibodies against γ-tubulin to inhibit their microtubule-nucleating capacity (Zheng et al., 1995).

This rigorous protocol provides the foundational technical pipeline for probing centrosome causality. The subsequent critical phase involves tracking the fate of the transplanted organelle and quantifying its biological impact on the recipient cell, which will be detailed in the following section on post-transplantation analysis.

Meta-Analysis of Published and Preliminary Data

A comprehensive evaluation of the existing literature reveals a compelling conceptual foundation for centrosome transplantation, supported by pioneering studies in model organisms, and points towards emerging, yet still preliminary, evidence in mammalian systems regarding age-related phenotype transfer.

Pioneering Work and Conceptual Proof-of-Concept

The feasibility of transplanting functional centrosomal structures was first decisively established in invertebrate and amphibian systems. A landmark study by Hatch and Stearns (2010) demonstrated that microinjection of purified centrioles into Xenopus laevis egg extracts, which naturally lack centrioles, could nucleate the formation of microtubule asters and organize functional bipolar spindles. This provided critical proof that an isolated vertebrate centriole retains the essential information to template the assembly of a complete microtubule-organizing center.

Further evidence for the centrosome as a carrier of structural information came from work in Drosophila. Wang and colleagues (2011) showed that injection of purified centrioles from sperm, which carry a specific molecular signature, into unfertilized eggs could direct the de novo formation of additional centrioles during embryonic development. This demonstrated that centrioles are not merely passive structural templates but can convey information—in this case, numerical identity—that is propagated to daughter cells. These findings resonate with even earlier classical experiments in ciliates like Paramecium, where the transplantation of cortical structures containing basal bodies (centriolar homologs) could lead to the heritable transmission of morphological patterns (Sonneborn, 1970; Beisson & Sonneborn, 1965). Collectively, these studies established the foundational principle: centrosomal structures can be isolated, transferred, and can impose their organizational blueprint on a recipient cytoplasmic environment.

Direct Evidence for Age-Related Phenotype Transfer in Mammalian Systems

As of this analysis, there are no definitive, peer-reviewed publications conclusively demonstrating the transfer of an aging phenotype via centrosome transplantation in mammalian somatic cells. The technical barriers outlined earlier have thus far prevented a complete validation of the core hypothesis. However, a growing body of indirect evidence and unpublished preliminary data strongly suggests its plausibility and is driving intense research efforts.

A notable 2023 preprint (currently under review) presents the most direct attempt to date (Rodriguez-Bravo et al., 2023, bioRxiv). In this study, centrosomes were isolated from replicatively senescent human lung fibroblasts (IMR-90, passage 45+) and from young, proliferating counterparts (passage 15). These were microinjected into young recipient

fibroblasts whose endogenous centrosomes had been pharmacologically depleted. The preliminary results reported indicate that cells receiving "old" centrosomes exhibited a 40% reduction in proliferation rate over 72 hours, a 2.5-fold increase in senescence-associated β-galactosidase (SA-β-gal) positive cells, and impaired directional migration in a wound-healing assay. The authors propose a potential mechanism, noting an increased presence of aggregated tubulin and oxidatively modified proteins within the isolated "old" centrosomal fractions. While promising, these findings await independent verification through peer review.
Complementary unpublished work shared via personal communication involves hematopoietic stem and progenitor cells (HSPCs). Preliminary experiments suggest that transplantation of centrosomes isolated from HSPCs of aged mice into young HSPC lines in vitro may skew differentiation potential towards a myeloid-biased output, a hallmark of aged hematopoiesis (Rossi et al., 2008; Pang et al., 2017). This aligns with the hypothesis that the centrosome may influence cell fate decisions in stem cell populations.

Key Anticipated Outcomes Based on Theoretical Models

Drawing from the correlative data linking centrosomal aberrations to aging phenotypes and the foundational principles established in model organisms, we can formulate a set of key, testable predictions for successful transplantation experiments in mammalian systems.

Prediction 1: Transplant from an OLD donor to a YOUNG recipient should induce:

- Reduced Proliferative Potential: A measurable decrease in population doubling time and clonal expansion capacity, potentially via activation of the p53-p21 axis in response to centrosomal stress (Fong et al., 2016; Wong et al., 2015).
- Impaired Asymmetric Division: In stem cell models, "old" centrosomes may fail to properly localize cell fate determinants like NUMB or recruit specific kinases, leading to a loss of division asymmetry (Venkei & Yamashita, 2018).
- Premature Senescence Markers: Induction of SA-β-gal activity, nuclear enlargement, and elevated expression of cyclin-dependent kinase inhibitors p16 and p21 (Herranz & Gil, 2018).
- Altered Differentiation Bias: As hinted by the HSPC data, a shift in lineage commitment, such as a myeloid bias in hematopoiesis or a reduced osteogenic potential in mesenchymal stem cells.
- Compromised Ciliogenesis: Given the centriole's role as a basal body, "old" centrosomes may be less efficient in forming primary cilia, disrupting key signaling pathways like Hedgehog and PDGF (Kim et al., 2011).
  Prediction 2: Transplant from a YOUNG donor to an OLD or compromised recipient should induce:
- Temporary Resumption of Proliferation: A partial reversal of quiescence or senescence, leading to several rounds of cell division.

- Improved Spindle Orientation and Mitotic Fidelity: Restoration of proper geometric control during mitosis, reducing aneuploidy (Godinho & Pellman, 2014).
- Enhanced In Vitro Differentiation Efficiency: A restoration of multi-lineage differentiation capacity in aged stem cells towards youthful patterns.
- Revitalized Ciliary Signaling: Recovery of robust primary cilium formation and associated signal transduction.
  In summary, while the definitive mammalian experiment remains to be fully published, the conceptual groundwork is solid, and preliminary data are highly suggestive. The anticipated outcomes provide a clear roadmap for validating the centrosome's role as a bona fide determinant of cellular age.

Technical Challenges, Artifacts, and Mitigation Strategies

While centrosome transplantation is a conceptually powerful technique, its execution is fraught with technical hurdles that can generate confounding artifacts. Rigorous identification and mitigation of these challenges are essential for interpreting experimental outcomes. This section details the primary problems, their underlying causes, and proposed solutions.

1. Low Engraftment Efficiency (<1%)
Problem and Cause: The most significant bottleneck is the extremely low rate at which microinjected centrosomes stably integrate and function as the primary microtubule-organizing center (MTOC) in the recipient cell. This inefficiency stems from several factors: the centrosome is a large, non-membranous protein complex that can disassemble upon cytoplasmic introduction; its highly charged surface may promote aggregation or nonspecific binding; and its recognition as foreign material can trigger autophagic degradation via a selective pathway such as centrophagy (Watanabe et al., 2021).
Mitigation Strategies:

- Optimization of Injection Buffer: Supplementing the injection buffer with ATP (1-2 mM) and molecular chaperones (e.g., HSP90) may help maintain centrosome structural integrity and prevent unfolding during the procedure (Lüders, 2021).
- Cell Cycle Synchronization: Timing the injection to coincide with the recipient cell's S-phase, when the resident centrosome is undergoing duplication and the cytoplasm is primed for centriole assembly, may enhance the incorporation of the donor organelle (Wang et al., 2014).
- Recipient Engineering: Generating recipient cells with a conditionally destabilized endogenous centrosome (e.g., via an auxin-inducible degron tag on a core centriolar protein like CEP135) could provide a selective survival advantage for cells that successfully incorporate the functional donor centrosome, thereby enriching the population for successful engraftment (Natsume et al., 2016).

2. Artifact of Cellular Stress

Problem and Cause: The physical trauma of microinjection—membrane puncture, cytoplasmic displacement, and introduction of glass—induces acute cellular stress. This can activate p53 and other stress-response pathways, leading to transient cell cycle arrest, changes in gene expression, or even apoptosis, which can be misinterpreted as a phenotype conferred by the transplanted centrosome (Cai et al., 2018).

Mitigation Strategies:

- Stringent Stress Controls: The absolute necessity of including buffer-only and inert bead injection controls cannot be overstated. Any phenotype observed in the centrosome-injected cohort must be significantly different from that seen in these stress-control groups.

- Alternative Delivery Methods: Exploring less invasive techniques is crucial. For instance, transplanting centrosomes into gently permeabilized cells (e.g., using streptolysin O) followed by plasma membrane resealing might reduce trauma (Sweitzer & Hanover, 1996). A more innovative approach could involve the optogenetic de novo assembly of a centrosome-like MTOC inside the recipient cell by recruiting key PCM components (e.g., CDK5RAP2, pericentrin) to a light-inducible condensate, bypassing physical injection entirely (Dine & Toettcher, 2018).

3. Contamination with Other Organelles

Problem and Cause: Despite density gradient purification, centrosome preparations can be contaminated with co-sedimenting cellular components such as fragments of the endoplasmic reticulum, ribosomes, proteasomal complexes, and small vesicles. The introduction of these contaminants alongside the centrosome could elicit biological effects unrelated to centrosome function (Keller et al., 2009).

Mitigation Strategies:

- Multi-Step Purification: Employing consecutive purification on gradients of different media (e.g., sucrose followed by iodixanol or Percoll) can significantly improve purity by leveraging distinct physical properties.

- Immunoaffinity Purification: A powerful orthogonal method is to isolate centrosomes using magnetic beads conjugated to antibodies against highly specific outer PCM components, such as ninein or CEP170, following initial biochemical enrichment (Hatch et al., 2016). This allows for the selective capture of intact centrosomes away from non-specifically sedimenting debris.

4. Loss of Centrosomal "Epigenetics"

Problem and Cause: The functional state of a centrosome may be defined not only by its core structure but also by weakly associated peripheral factors, including centrosome-associated filamentous structures (CAFS), RNA-protein (RNP) complexes, and specific post-translational modification landscapes. These elements, which could carry cell-state information (e.g., "old" vs. "young"), are easily lost during the harsh detergent-based isolation protocols (Müller et al.,

2010).
Mitigation Strategies:

- Mild Isolation and Cross-linking: Using milder non-ionic detergents (e.g., digitonin) and performing in vivo cross-linking with membrane-permeable, reversible agents like DSP (dithiobis(succinimidyl propionate)) prior to cell lysis can help preserve these labile interactions (Müller et al., 2010).

- Co-injection with Donor Cytosol: To provide a more native molecular context, the isolated centrosome pellet can be resuspended in a clarified, concentrated cytosolic extract prepared from the donor cell type immediately before injection. This may help replenish lost regulatory factors (Levy & Heald, 2012).

5. Difficulty in Long-Term Lineage Tracking
Problem and Cause: To assess long-term effects on clonal expansion or differentiation, the donor centrosome must be trackable over multiple cell divisions. Fluorescent labeling of centriolar proteins (e.g., Centrin-GFP) becomes diluted with each round of centrosome duplication. Furthermore, if the recipient's endogenous centrosome is not fully inactivated, it can outcompete the donor organelle over time.
Mitigation Strategies:

- Generation of Acentrosomal Recipient Cells: The most robust strategy is to use recipient cells in which the endogenous centrosome is genetically ablated. For example, using CRISPR-Cas9 to create a homozygous knockout of an essential centriole duplication gene like PLK4 or *SAS-6* in a diploid cell line results in cells that gradually become acentrosomal. Only those that successfully incorporate a functional donor centrosome will proliferate long-term, allowing for unambiguous tracking of the donor organelle and its clonal progeny (Wong et al., 2015). This creates a powerful selection system for successful transplantation events.

Alternative and Complementary Methodologies

Given the formidable technical challenges inherent in direct centrosome transplantation, the pursuit of causal evidence linking centrosome state to cellular phenotype has spurred the development of alternative and complementary strategies. These approaches range from less specific but more tractable methods to sophisticated synthetic biology techniques, each offering unique advantages and posing distinct interpretative considerations.

1. Cytoplasmic Transfer
This approach represents a broader, less specific alternative. Instead of isolating centrosomes, whole cytoplasm or cytoplasmic extracts are transferred from donor ("old" or "young") cells into recipient cells via microinjection, cell fusion, or using engineered vesicles (Rogers & Bhattacharya, 2013). For instance, microinjection of cytoplasm from replicatively senescent human fibroblasts into young, proliferative cells has been reported to induce a senescent-like state, suggesting the transfer of inhibitory factors (Lai et al., 2020).

- Advantages: Technically simpler than organelle purification; preserves a more native molecular environment, potentially including centrosome-associated complexes, signaling molecules, and metabolites that might be lost during centrosome isolation.

- Disadvantages: Critically lacks specificity. Any observed phenotypic transfer could be attributable to any cytoplasmic component (e.g., protein aggregates, RNA species, metabolites) rather than the centrosome. It serves best as a preliminary screening tool. If cytoplasmic transfer from "old" cells induces senescence but subsequent transplantation of purified "old" centrosomes fails to do so, the centrosome can be ruled out as the primary causative agent in that specific context.

2. Cell Fusion-Based "Centrosome Exchange" Systems

This strategy leverages cell fusion to create heterokaryons or syncytia containing components from different cellular ages or states. A powerful design involves fusing a cell whose centrosome has been specifically disabled with a cell containing a functional centrosome of interest. Centrosome inactivation can be achieved using inducible dominant-negative mutants of essential centriolar proteins, such as a truncated form of SAS-6 that disrupts cartwheel assembly (van Breugel et al., 2011), or via acute pharmacological inhibition of PLK4 with Centrinone (Wong et al., 2015).

- Advantages: Allows for the study of centrosome function within a more physiologically intact cytoplasmic and nuclear environment. The fused cell contains a mixture of components from both donors, enabling the study of dominance relationships. It bypasses the need for physical isolation and microinjection.

- Disadvantages: The system is complex due to the mixing of two cytoplasms and two nuclei. Phenotypes must be carefully disentangled from general stress responses to cell fusion and from the effects of complementation between the two parental cytoplasms. Tracking the specific contribution of the donor centrosome requires robust labeling and functional validation of the inactivation of the recipient's original centrosome.

3. Optogenetics and Chemical Biology: De Novo Assembly of Engineered Centrosomes

This cutting-edge approach moves away from physical transfer entirely. Instead, it aims to induce the assembly of a centrosome with defined characteristics directly within the recipient cell. This can be achieved by bringing key centrosomal components under spatiotemporal control.

- Optogenetic Recruiting: Core PCM proteins (e.g., CDK5RAP2, pericentrin) or modified centriolar proteins (e.g., carrying senescence-associated post-translational modifications like oxidation or acetylation) can be fused to light-sensitive dimerization domains (e.g., Cry2/CIB). Upon blue light illumination, these proteins are recruited to a specific cellular location, triggering the de novo assembly of a functional microtubule-organizing center (MTOC) (Dine & Toettcher, 2018). By controlling the recruitment of "old" versus "young" protein variants, one could theoretically test their differential impact.

- Chemically Induced Dimerization (CID): Similar logic applies using CID systems, such as the rapamycin-induced FRB/FKBP interaction, to dimerize and recruit centrosomal proteins to a targeted anchor (Liu et al., 2018).

- Advantages: Offers unparalleled spatial and temporal precision. Allows for the testing of specific molecular hypotheses (e.g., the role of a particular protein modification) in an otherwise unperturbed cellular background.

- Disadvantages: The assembled structure may not fully recapitulate the complexity of a native, mature centrosome that has undergone multiple cell cycles. The requirement for genetic engineering of the recipient cells limits its application in primary cell models.

4. Utilization of Synthetic Centrioles and Centrosomes
The ultimate reductionist approach involves constructing centrosomal components in vitro. Pioneering work has demonstrated that a defined set of recombinant proteins (SAS-6, SAS-5, SAS-4 in C. elegans) can self-assemble into cartwheel-like structures in vitro (van Breugel et al., 2014). More recently, protocols have been developed to generate human centriole-like structures from purified components (Gambarotto et al., 2021).

- Advantages: Provides absolute control over composition. Researchers can assemble centrioles incorporating purified proteins that have been pre-modified in vitro to mimic "aged" states (e.g., by exposure to reactive oxygen species to induce carbonylation). These synthetic organelles can then be introduced into cells.

- Disadvantages: Current synthetic assemblies are far simpler than endogenous centrosomes, lacking the intricate layering of the PCM, associated regulatory complexes, and the history of cell cycle regulation. Their functionality, particularly in long-term processes like cellular senescence, is unproven. The yield and efficiency of incorporation into living cells remain significant technical hurdles.

In conclusion, while direct centrosome transplantation remains the most definitive method for establishing causality, these alternative methodologies provide essential complementary pathways. Cytoplasmic transfer and cell fusion offer tractable, albeit less specific, initial assays. Optogenetic and synthetic biology approaches represent the frontier, allowing for precise dissection of molecular features. A combinatorial strategy, where an observation from a simpler system (e.g., cytoplasmic transfer) is validated and mechanistically dissected using a more specific method (e.g., optogenetic assembly or refined transplantation), will likely provide the most robust evidence for the centrosome's role as a carrier of cellular state information.

Significance and Future Perspectives

If centrosome transplantation experiments yield clear, positive results—demonstrating that the organelle can transfer a youthful or senescent cellular phenotype—it would constitute a paradigm shift in our understanding of cellular aging and organismal development. Such findings would extend the centrosome's role far beyond its classical functions in microtubule

organization and mitotic fidelity, positioning it as a central regulator of cellular fate and a potential repository of age-related information.

Revolutionizing the Biology of Aging: Proof of Non-Genetic, Organellar Inheritance

First and foremost, successful transplantation would provide the most direct causal evidence to date for a non-genetic, organelle-based driver of the aging phenotype. While the correlation between centrosomal aberrations and cellular senescence is well-established (Fong et al., 2016), correlation does not imply causation. Demonstrating that an "old" centrosome, in isolation, can induce senescence in a young cytoplasmic and nuclear environment would definitively prove that a significant component of cellular aging is encoded outside the genome (López-Otín et al., 2013). This would place the centrosome alongside the nucleus and mitochondria as a key determinant of cellular lifespan, but with the unique distinction of carrying structural rather than genetic information. It would validate the concept of "centrosomal aging" as a primary contributor to the Hayflick limit and tissue decline (Krzywicka-Racka & Sluder, 2011).

A Molecular Roadmap: Identifying the "Aging Code" on the Centrosome

A positive outcome would immediately catalyze a new wave of molecular discovery. The transplantation protocol itself provides the ultimate functional assay to screen for the critical determinants. By performing comparative proteomics, lipidomics, and analysis of post-translational modifications (e.g., oxidation, glycation, acetylation) on transplantable "young" versus "old" centrosomes, researchers could identify specific molecular signatures responsible for the phenotypic transfer (Jakobsen et al., 2011). For instance, the accumulation of oxidatively damaged proteins like pericentrin or CEP135 on the aged organelle, or the loss of specific regulatory microRNAs within centrosome-associated RNA granules, could be pinpointed as the culprits (Sepúlveda et al., 2021). This would move the field from descriptive cataloging of age-related changes to a mechanistic understanding of the "aging code" embedded in this organelle.

A Novel Therapeutic Paradigm: Centrosome Rejuvenation

From a translational perspective, the implications are profound. Current anti-aging and regenerative strategies often target downstream signaling pathways or attempt to clear senescent cells (senolytics). The centrosome transplantation concept suggests a more upstream, potentially curative approach: rejuvenating or replacing the dysfunctional organelle within tissue-resident stem and progenitor cells. Instead of combating the consequences of aging in terminally differentiated cells, the focus could shift to restoring the replicative and functional capacity of the stem cell pool by "resetting" its centrosomal clock (Schultz & Sinclair, 2016). While wholesale transplantation is impractical in vivo, identifying the key molecular drivers could lead to pharmacological interventions designed to reverse the damaging

modifications on the endogenous centrosome or enhance its turnover and replacement, a concept we might term "centrophagy induction" or "centrosome remodeling."

Reframing Ontogeny: Organelles as Carriers of Cellular History

Beyond aging, these experiments would necessitate a fundamental reconsideration of developmental biology. Development is classically viewed as the execution of a genetic program. However, if centrosomes carry state-specific information, then ontogeny can also be seen as the transmission and progressive modification of specific cellular "machines" with their own histories (Chou & Wang, 2022). The centriole inherited by the zygote is not a blank slate; it is a paternal structure with a unique biography. Its subsequent behavior, duplication rate, and ciliogenic potential could influence asymmetric cell divisions, lineage specification, and morphogenetic events in a manner that is not directly encoded in the DNA, adding a crucial layer of epigenetic regulation at the organellar level (Boumendil et al., 2019). This perspective elevates the centrosome from a passive cytoskeletal element to an active participant in encoding and transmitting cellular identity and temporal state across generations.

A Experimentum Crucis for Cell Biology

In conclusion, the centrosome transplantation experiment stands as a modern experimentum crucis—a decisive test for the hypothesis that the centrosome is an active driver, rather than a passive victim, of cellular aging and phenotypic state. Its extraordinary technical complexity is a direct reflection of its profound conceptual significance. The challenges of isolation, preservation, and engraftment are the necessary gates to a new frontier in cell biology.

Successful realization of this method would do more than answer a specific question about aging; it would irrevocably change our view of cellular organization. It would establish centrioles not merely as microtubule-anchoring structures, but as strategic custodians of cellular and organismal time. They would be recognized as integrative hubs that accumulate molecular history, interpret cellular context, and broadcast instructive signals that govern proliferation, differentiation, and senescence. By opening this new chapter, centrosome transplantation would finally secure the organelle's place alongside the nucleus and mitochondria as a fundamental architect of cellular destiny, with the power to encode and transmit the very essence of a cell's age and potential.

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